Harnessing Strained Systems: Arynes, Donor-Acceptor Cyclopropanes, and Bicyclobutanes in Annulations, Multicomponent Couplings and Insertion Reactions

A THESIS
SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN THE FACULTY OF SCIENCE

BY

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(Registration Number: 02-03-00-10-11-18-1-16141)

UNDER THE SUPERVISION OF

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July 2023

Dedicated to

My Family, Friends and Teachers

CERTIFICATE

Certified that the work contained in the thesis entitled **"Harnessing Strained Systems: Arynes, Donor-Acceptor Cyclopropanes, and Bicyclobutanes in Annulations, Multicomponent Couplings and Insertion Reactions"** has been carried out by **Mr. Avishek Guin** under my supervision at the Department of Organic Chemistry, Indian Institute of Science, Bangalore, India and that this has not been submitted elsewhere for the award of degree, diploma, membership, etc.

Prof. Akkattu T. Biju
Research Supervisor

DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"Harnessing Strained Systems: Arynes, Donor-Acceptor Cyclopropanes, and Bicyclobutanes in Annulations, Multicomponent Couplings and Insertion Reactions"** is the result of the investigations carried out by me at the Department of Organic Chemistry, Indian Institute of Science, Bangalore, India under the supervision of **Prof. Akkattu T. Biju** and this has not been submitted elsewhere for the award of degree, diploma, membership, etc. Any omissions that might have occurred due to oversight or error in judgment are regretted.

In keeping with the general practice of reporting scientific observations, due acknowledgment has been made whenever the work described is based on the findings of other investigators.

Avishek Guin

Avishek Guin

Acknowledgment

The journey to complete this doctoral work has been a wonderful experience. What makes this journey particularly captivating and exhilarating is the absence of a well-defined roadmap at the outset. The journey towards obtaining a doctorate is often filled with unexpected twists, challenges, and hurdles. Without the assistance of my advisor, colleagues, peers, friends, and family, reaching this milestone would have been impossible. I am filled with immense gratitude for the numerous individuals who have directly or indirectly contributed to the development of this work and have profoundly influenced my thinking, behavior, and actions throughout my doctoral study. Their help, kindness, encouragement, companionship, and unwavering support have played an integral role in my academic journey, and for that, I am incredibly thankful.

I am extremely delighted to convey my deep appreciation and admiration for Prof. Akkattu T. Biju, my teacher and research supervisor without whom all these works and the thesis would have been not possible. It has been a wonderful experience working with him. His vast knowledge and inspiring mentorship have brought me immense joy and gratitude. His passion and dedication towards science was always a inspiration for me. I am sincerely indebted to him for his enduring support, valuable suggestions, and constructive feedback throughout my research journey. I express my heartfelt thanks to him for equipping me with the necessary skills and guidance to progress in my future endeavors both professionally and personally.

I was privilaged to work with a fantastic group of colleagues in Prof. Biju's research group. Upon joining IISc in August 2018, I was incredibly fortunate to work alongside Dr. Tony Roy during the initial stages, and his profound influence greatly impacted me. His expertise in aryne chemistry served as a constant source of inspiration, motivating me to expand my knowledge in the field. In the early phases of my doctoral studies, I aspired to acquire a similar depth of understanding. Another individual who had a tremendous impact on me was my senior, Dr. Subrata Bhattacharjee. His profound grasp of organic chemistry stimulated me to explore new perspectives and approaches. Not only did I gain invaluable knowledge from him, but I also learned important life lessons. Interacting in discussions with him was consistently enjoyable, and his distinctive perspectives on various aspects had a profound and transformative impact on shaping me. Sukriyo, our ever-vibrant undergraduate project fellow, captivated me with his profound comprehension, not only in chemistry but across a wide range of subjects. I am an ardent admirer of his intellectual prowess and ideology.

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joy of playing badminton, which we all immensely enjoyed. I deeply admire Rohan's perspective on life and his approach towards it. While working alongside Shiksha, I noticed her knack for efficiently handling two columns simultaneously, which I found to be a time-saving approach. Inspired by her, I adopted this technique and, on occasion, even managed to handle three columns at once. I attribute my increased productivity in this aspect to Shiksha's influence. Spending more time in the lab, I often find myself resembling her, almost like a sister to me. I am grateful to Sowmya, our newly joined creative member, whose remarkable artistic skills have saved us on numerous occasions. Hearing Mahesh affectionately call me 'Avishek Dada' brings me great joy. His amiable nature and cheerful demeanor when interacting with others are always a delightful experience. Deeptanu, our energetic group member, brings a strong sense of vigor to the team. His passion for sports has a positive impact on all of us. My sincere thanks to all other lab mates as well Dr. S. Mondal, Dr. S. Mukherjee., Dr. T. K. Das, Dr. A. Ghosh, Dr. R. N. Gaykar, Kuruva Balanna, Anushree, Labeeb, Goutam, Anjali, Jaylaxmi, Johara, Priyanshu, Ganga and Sanjeevani for devoting their precious time and for providing many valuable suggestions which indeed helped me during this research work. It has been a great learning experience for me through our group seminars. A special thanks to Dr. T. Roy, Dr. R. N. Gaykar, Dr. S. Bhattacharjee, and Shiksha for their help in various projects.

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I would like to express my heartfelt gratitude to the exceptional teachers who have played a significant role in shaping my career and nurturing my love for academia. Prior to joining IISc,

their guidance and influence greatly impacted my journey. It was during my bachelor's degree in chemistry at Visva-Bharati University that my perspective on science underwent a transformative shift. I am particularly grateful to Prof. Bidhan Chandra Bag from Visva-Bharati University, who not only proved to be an exceptional teacher but also provided invaluable suggestions and advice that led me to pursue my MSc studies at IIT Kharagpur. I would like to extend my thanks to Prof. Pranab Sarkar, Prof. Asim Kumar Das, Prof. Goutam Brahmachari, and Prof. Alakananda Hajra for their inspirational guidance, which further fueled my desire to pursue a career in research. Additionally, I am grateful to my MSc supervisor, Prof. Madhu Sudan Maji, for introducing me to the captivating world of laboratory organic chemistry and inspiring me to pursue further studies at the doctoral level.

I express my gratitude to CSIR as well as MHRD (PMRF) for their support for the fellowship through out my whole Ph.D. tenure. Additionally, I extend my appreciation to the Indian Institute of Science for their contribution in terms of infrastructure.

I owe an immense debt of gratitude to my dearest friend Sangita, as without her, my journey from BSc to PhD would remain incomplete. I vividly recall our early days of studying BSc together and how she became a constant source of inspiration for me. She ignited a passion for chemistry research within me, much like the transformative effect of "Wings of Fire". I still remember the time when I considered deviating from a research career, she was genuinly disheartened by my decision. However, what I admire most about her is her compassionate and selfless nature towards every individual. I have strived to absorb as many of her admirable qualities as I can, within the confines of my own capacity. Above all, she has consistently provided me with unwavering support and love. Whether it was facing failures in reactions or dealing with rejected manuscripts, she always made it a point to remind me that these setbacks are an normal part of life. I feel incredibly fortunate and proud to be associated with her. Without her, I would be a completely different person from what I am today.

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I wish to thank the great scientific community whose achievements are a constant source of inspiration for me.

Avishek

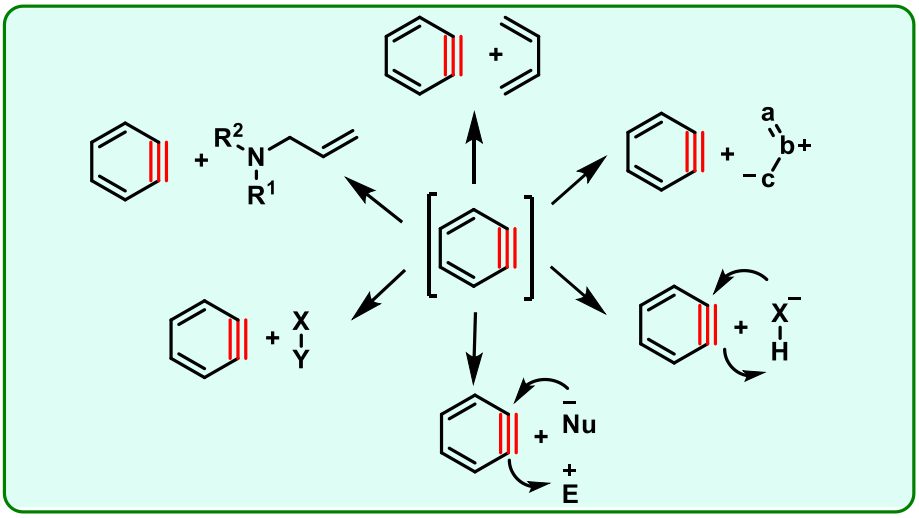
Table of Contents

Synopsis

The proposed thesis entitled "***Harnessing Strained Systems: Arynes, Donor-Acceptor Cyclopropanes, and Bicyclobutanes in Annulations, Multicomponent Couplings and Insertion Reactions***" is divided into two parts and each parts consists of four Chapters.

Chapter 1: Aryne Chemistry: A Brief Overview

More than a century ago, the discovery of aryne intermediates proved to be a valuable addition to the toolkit of organic chemists, enabling the synthesis of a diverse range of molecules using these electrophilic intermediates as building blocks. The intrinsic electrophilicity and kinetic instability of aryne intermediates arise from the presence of a carbon-carbon triple bond within a six-membered ring, leading to a strained structure, and this is the reason for the exceptional reactivity of arynes. In 1983, Kobayashi and co-workers developed a mild and efficient method to generate arynes from easily accessible 2-(trimethylsilyl)aryl triflates using fluoride-induced 1,2-elimination. This approach is mild and transition-metal-free, making it compatible with a wide range of functional groups. This Chapter provides a brief overview of historical developments in aryne chemistry, various generation methods, characterization, possible modes of reactivity, and other important developments.



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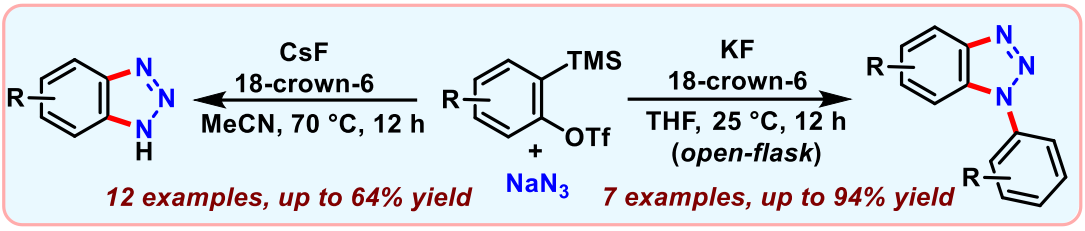
Chapter 2: Selective Synthesis of *N*-H and *N*-Aryl Benzotriazoles by the [3+2] Annulation of Sodium Azide with Arynes

The synthetic utility of NaN_3 as the inorganic azide component in the [3+2] annulation with arynes generated from 2-(trimethylsilyl)aryltriflates resulting in the transition-metal-free synthesis of *N*-H and *N*-aryl benzotriazoles has been demonstrated in this Chapter. Using CsF as the fluoride source in CH_3CN, the *N*-H benzotriazoles are formed in high selectivity instead of the expected azidobenzene. Interestingly, *N*-aryl benzotriazoles are formed using KF and THF as solvent in an open-flask reaction. Moreover, a method for the *N*1-arylation of benzotriazole has also been uncovered.



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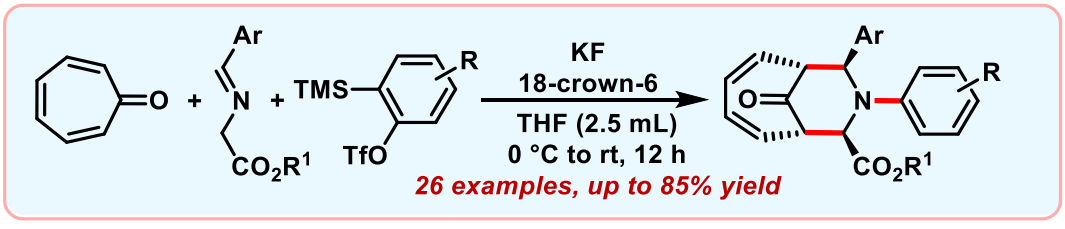
Chapter 3: Three-Component, Diastereoselective [6+3] Annulation of Tropone, Imino Esters and Arynes

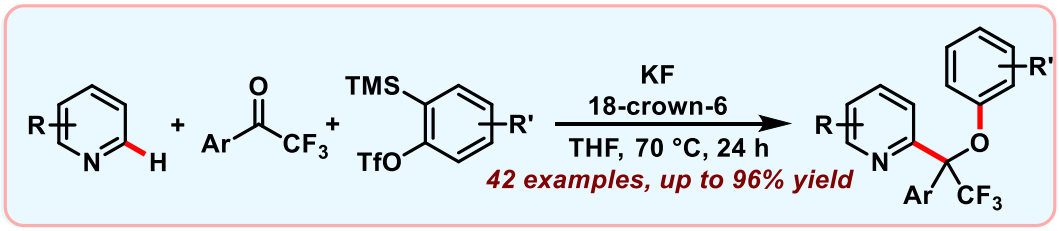
A transition-metal-free, three-component and diastereoselective [6+3] annulation reaction employing tropone, imino esters and arynes allowing the synthesis of bridged azabicyclo[4.3.1] decadienes is disclosed in this Chapter. The key nitrogen ylides for the [6+3] annulation was generated by the addition of imino esters to the arynes followed by a proton transfer. The nitrogen ylides undergo a regioselective addition to tropone to furnish the desired products in moderate to good yields with good functional group tolerance under mild conditions. The present reaction is operationally simple, advance smoothly under mild conditions and can tolerate various functional groups. Experiments were carried out to get insight into the possible course of the reaction and the product were transformed into other bridged azabicycles.



Reference: **Guin, A.** ; Gaykar, R. N.; Deswal, S.; Biju, A. T. *Org. Lett.* **2021**, *23*, 7456.

Chapter 4: Transition-Metal-Free C2-Functionalization of Pyridines via Aryne Three-Component Coupling

The direct C2-functionalization of pyridines via a transition-metal-free protocol using aryne multicomponent coupling is demonstrated in this Chapter. The reaction allowed a broad scope synthesis of C2 substituted pyridine derivatives bearing the -CF_3 group in good yields engaging α,α,α-trifluoroacetophenones as the third component. Activated keto esters could also be employed as the third component in this formal 1,2-di(hetero)arylation of ketones. Performing the reaction under dilute conditions inhibited the competing pyridine-aryne polymerization pathway. The nucleophilic pyridylidene intermediate generated from pyridine and aryne adds to the activated carbonyls in an S_NAr process (similar to the Smiles rearrangement) to afford the desired products. Detailed mechanistic studies were performed to get insight into the mechanism of the reaction. The present aryne coupling is not limited to -CF_3 containing ketones as electrophilic third components but instead α-ketoesters can also be used to intercept the pyridylidene intermediates generated from pyridine and aryne.



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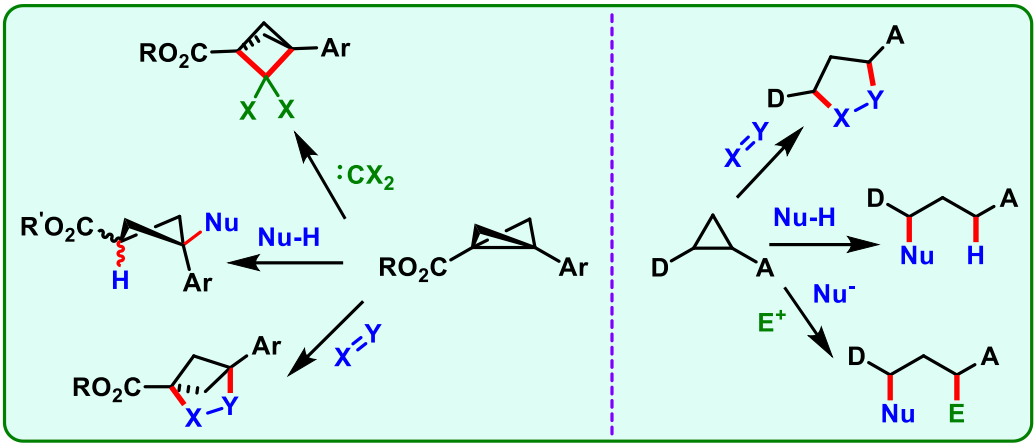
Chapter 5: Donor-Acceptor Cyclopropanes and Bicyclobutanes: An Overview

The advancement of novel reactive molecular entities plays a crucial role in enhancing the toolkit of synthetic organic chemists for constructing intricate architectures. Among these entities, donor-acceptor (D-A) cyclopropanes have emerged as particularly significant. This strained but kinetically stable intermediate can be further activated through various methods, including Lewis acid activation, organocatalysis, radical activation, and electrochemical activation. These activation processes enable a range of reactions, such as cycloaddition, ring-opening reactions, and 1,3-bisfunctionalization. This Chapter presents an overview of the progress in this field, the distinctive characteristics of D-A cyclopropanes, their potential modes of reactivity, and other notable advancements. Additionally, this Chapter also provides an introduction to highly strained bicyclobutane (BCB), which has gained popularity in recent years.



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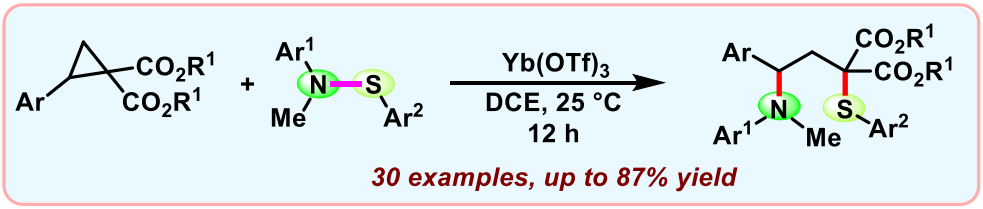
2. For selected reviews on bicyclobutanes, see: (a) Walczak, M. A. A.; Krainz T.; Wipf, P. *Acc. Chem. Res*. **2015**, *48*, 1149. (b) Kelly, C. B.; Milligan, J. A.; Tilley, L.; Sodano, T. M. *Chem. Sci*. **2022**, *13*, 11721.

Chapter 6: Lewis Acid-Catalyzed Ring-Opening 1,3-Aminothiolation of Donor-Acceptor Cyclopropanes Using Sulfenamides

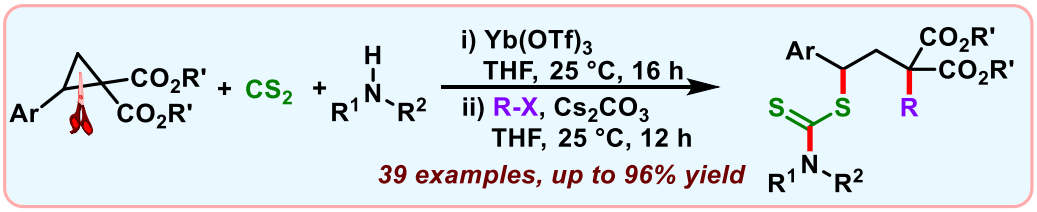
In this Chapter, the $Yb(OTf)_3$ catalyzed mild and regioselective ring-opening 1,3-aminothiolation of donor-acceptor (D-A) cyclopropanes using sulfenamides has been demonstrated. The insertion of the C-C σ-bond of D-A cyclopropanes into the S-N σ-bond of sulfenamides allows the synthesis of diverse γ-aminated α-thiolated malonic diesters in moderate to good yields (up to 87%) with good functional group compatibility. Complete regioselectivity was observed in the ring-opening of DACP with sulfonamides. The stereospecificity of the reaction was demonstrated using enantiopure D-A cyclopropanes.



Reference: **Guin, A.**; Rathod, T.; Gaykar, R. N.; Roy, T.; Biju, A. T. *Org. Lett*. **2020**, *22*, 2276.

Chapter 7: Ring-Opening 1,3-Carbothiolation of Donor-Acceptor Cyclopropanes Using Alkyl Halides and in Situ Generated Dithiocarbamates

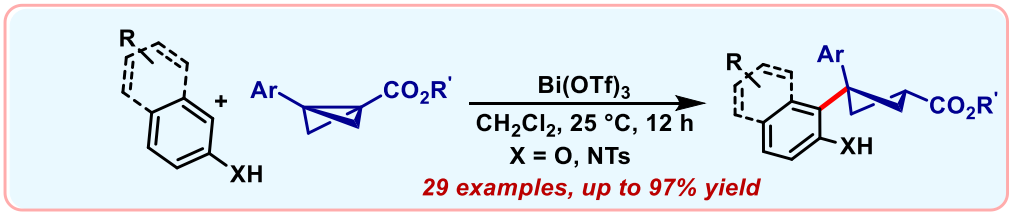
Ring-opening 1,3-carbothiolation of donor-acceptor (D-A) cyclopropanes employing alkyl halides and in situ generated dithiocarbamates (from amines and CS_2) has been demonstrated under mild conditions. The reaction is operationally simple and works with good functional group compatibility. Three new bonds including C-N, C-S and C-C are formed in this 1,3-bifunctionalization strategy. Electron-poor olefins can also be used as electrophiles instead of alkyl halides. The use of enantiomerically pure D-A cyclopropane afforded enantiopure 1,3-carbothiolated product thus demonstrating the stereospecificity of the reaction.



Reference: **Guin, A.**; Deswal, S.; Biju, A. T. *J. Org. Chem*. **2022**, *87*, 6504.

Chapter 8: Lewis Acid-Catalyzed Diastereoselective Carbofunctionalization of Bicyclobutanes Employing Naphthols

Traditional radical-mediated ring-opening of bicyclo[1.1.0]butanes (BCBs) for cyclobutane synthesis suffers from poor diastereoselectivity. Although few reports on BCB ring-opening via polar mechanisms are available, the Lewis acid-catalyzed diastereoselective ring-opening of BCBs using carbon nucleophiles is still underdeveloped. Herein, we report a mild and diastereoselective $Bi(OTf)_3$-catalyzed ring-opening of BCBs employing 2-naphthols. The anticipated carbofunctionalized trisubstituted cyclobutanes were obtained via the bicoordinated bismuth complex and the products are formed in good to excellent yields with high regio- and diastereoselectivity. The scope of the reaction was further extended using electron-rich phenols and naphthylamine. The functionalization of the synthesized trisubstituted cyclobutanes shows the synthetic utility of the present method.

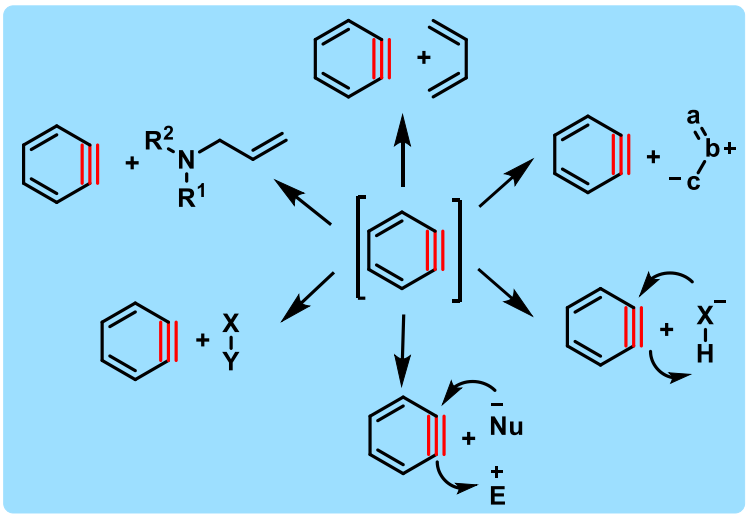


Reference: **Guin, A.** ; Bhattacharjee, S.; Harariya, M. S.; Biju, A. T. *Chem. Sci*. **2023**, *14*, 6585.

Chapter 1

Aryne Chemistry: A Brief Overview

More than a century ago, the discovery of aryne intermediates proved to be a valuable addition to the toolkit of organic chemists, enabling the synthesis of a diverse range of molecules using this electrophilic intermediate as building blocks. The intrinsic electrophilicity and kinetic instability of aryne intermediates arise from the presence of a carbon-carbon triple bond within a six-membered ring, leading to a strained structure. The central feature of aryne reaction's success can be attributed to this particular characteristic. Kobayashi and co-workers developed a mild and efficient method to generate arynes from easily accessible 2-(trimethylsilyl)aryl triflates using fluoride-induced 1,2-elimination in 1983. This approach is mild and transition-metal-free, making it compatible with a wide range of functional groups. This Chapter provides a brief overview of historical developments in aryne chemistry, various generation methods, characterization, possible modes of reactivity, and other important developments.

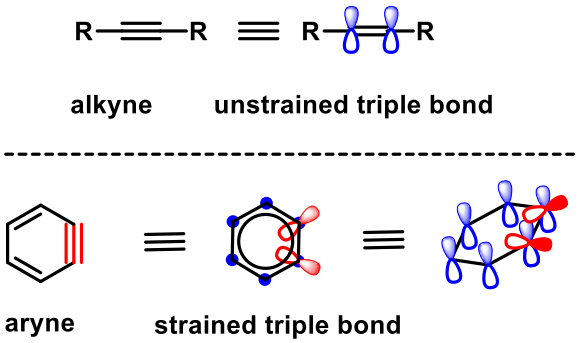


1.1. Introduction

Arynes are highly reactive intermediates that have recently experienced an unprecedented resurgence in popularity. Chemists have utilized these transient intermediates to synthesize various 1,2-disubstituted benzene derivatives, as well as benzo-fused carbocycles and heterocycles that are difficult to achieve using conventional methods.[1] Our focus has been on using arynes in transition metal-free carbon-carbon and carbon-heteroatom bond forming reactions. To provide context, this Chapter provides a brief overview of aryne chemistry, including its discovery, methods of generation, and recent advancements in aryne reactions.

Benzyne, also known as aryne or 1,2-dehydroarene, is an uncharged reactive intermediate formed by the removal of two vicinal substituents from an aromatic system, resulting in a highly strained C-C triple bond.[2] In contrast to unstrained parallel alkynes, the *p*-orbitals overlap is reduced, and they are no longer parallel to each other due to the geometric constraints on the C-C triple bond in a six-membered ring (Figure 1.1). This reduced *p*-orbital overlap leads to a significant decrease in the LUMO energy of arynes. The strained triple bond and the decreased energy gap between HOMO and LUMO in this kinetically unstable intermediate make it highly reactive towards various charged and uncharged electrophiles. As a result, a wide variety of anionic and uncharged nucleophiles can add to this intermediate.[3]

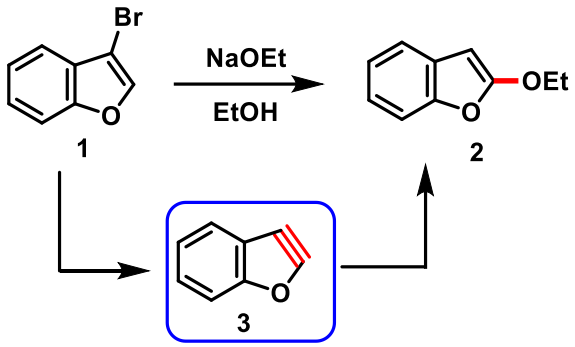
Figure 1.1. Geometry of Aryne



In 1902, Stoermer and Kahlert provided the initial suggestion of the existence of an aryne intermediate.[4] Their study involved the treatment of 3-bromobenzofuran **1** with sodium ethoxide in ethanol, which resulted in the formation of 2-ethoxybenzofuran **2**. They

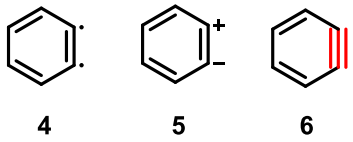
postulated that the involved reactive intermediate could be an aryne (Scheme 1.1). However, they were unable to present any direct experimental proof regarding the intermediate **3**.

Scheme 1.1. Stoermer and Kahlert Experiment



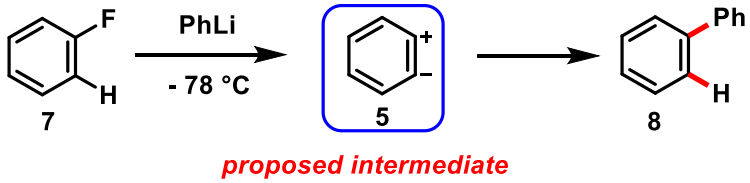
In 1927, Bachmann and Clarke from the Eastman Kodak Co. reported on the formation of triphenylene by the reaction of sodium with boiling chlorobenzene. They proposed benzyne as a reactive intermediate and considered it crucial in favor of the free radical explanation (Scheme 1.2).[5] Among the three proposed structures, diradical **4** was deemed to be the predominant structure. They also considered ylide structure **5**, as well as structure **6** with a carbon-carbon triple bond in a six-membered ring.

Scheme 1.2. Proposed Structures of Benzyne



Later, in 1942, Wittig proposed the zwitterionic structure **5** as the reactive intermediate for the generation of biphenyl **8** through the reaction of fluorobenzene **7** with phenyllithium (Scheme 1.3).[6]

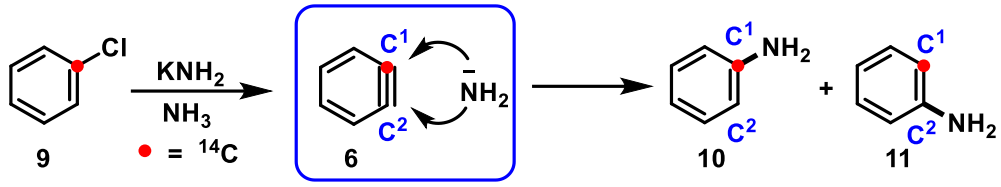
Scheme 1.3. Wittig's Experiment



A significant experiment in 1953 by Roberts and co-workers provided evidence for the existence of the reactive intermediate 'benzyne'. They treated isotopically labelled chlorobenzene-1-^{14}C **9** with potassium amide, which resulted in a mixture of labelled isomers

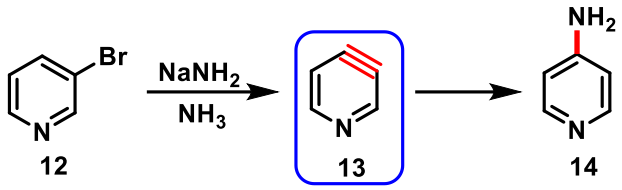
of aniline-1 **10** and aniline-2 **11**. The observed 1:1 product mixture demonstrated that the $\mathbf{C^1}$ and $\mathbf{C^2}$ positions are equivalent in the intermediate **6** (Scheme 1.4).[7]

Scheme 1.4. Roberts's Experiment



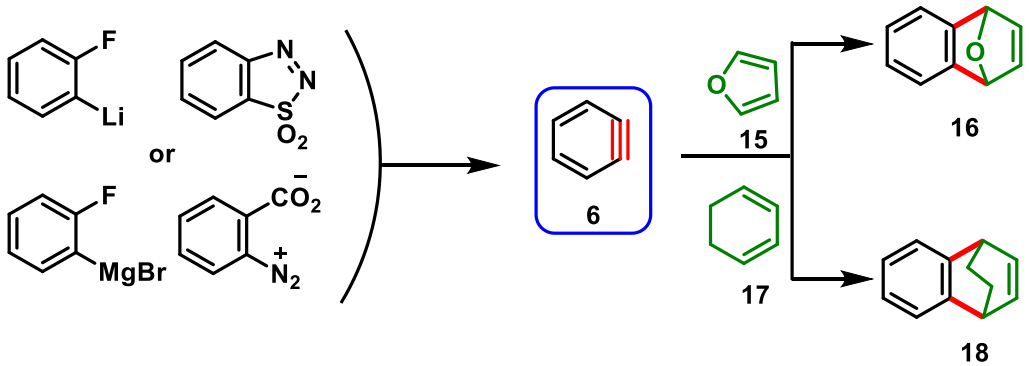
Levine and co-workers made a significant breakthrough when they successfully generated the first heteroaryne intermediate, pyridyne **13**, from pyridine **12**. Treatment of 3-bromo pyridine with excess sodamide led to the formation of 4-amino pyridine **14**, demonstrating the utility of the heteroaryne intermediate in organic synthesis (Scheme 1.5).[8]

Scheme 1.5. Heteroaryne Generation



Later on, Wittig and Pohmer were able to capture the aryne intermediate **6** through a [4+2] cycloaddition reaction with furan **15**, producing an epoxynaphthalene derivative **16** (Scheme 1.6).[9] Huisgen and Knorr independently demonstrated the utilization of aryne as an electrophilic dienophile by reacting aryne (generated from different precursors) with furan **15** or cyclohexadiene **17**.[10]

Scheme 1.6. Wittig and Huisgen's Aryne Trapping Experiment



1.2. Characterization of Aryne Intermediates

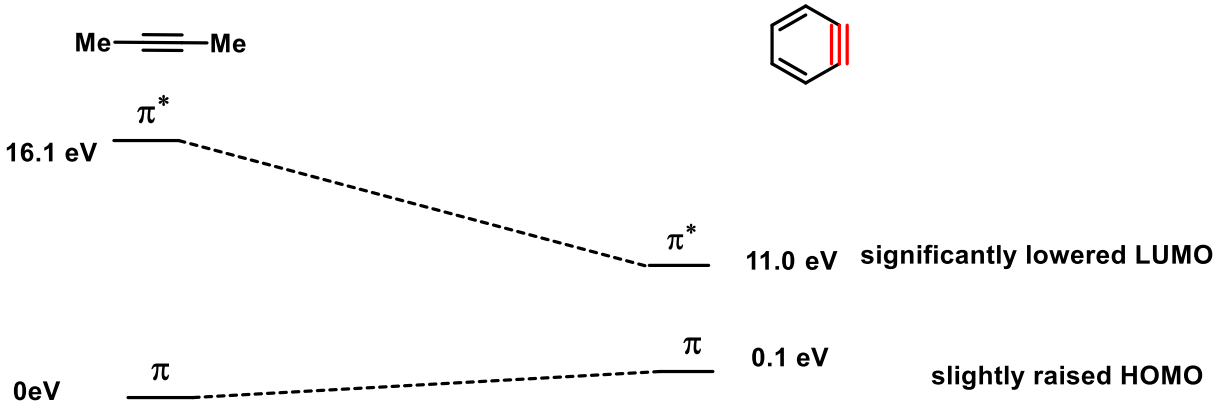
Fisher and Lossing investigated the structure of benzyne by carrying out the pyrolysis of diiodobenzenes (*ortho*, *meta*, and *para* isomers) and identified structure **6** based on the measured ionization potentials. The observation of mass 76 from the *o*-diiodobenzene by mass spectrometry also confirmed the structure of **6**.[11] Berry and co-workers further confirmed the structure of **6** by observing the mass 76 and other masses via the photo-initiated decomposition of benzene diazonium carboxylates in the gas phase.[12] They also employed UV spectra to explain the structure of **6** in the gaseous phase.[13] In 1992, Radziszewsk and co-workers measured the IR value of **6** obtained from different isotopomers of phthalic anhydride.[14] They found that the IR stretching frequency for the strained triple bond on aryne is 1846 cm^{-1}, indicating that the triple bond of benzyne is weaker than that of normal alkynes. In late 1996, Radziszewski and co-workers[15] measured the bond length of benzyne triple bond, which was 1.24 Å, using ^{13}C dipolar NMR spectrum of benzyne isolated in an argon matrix at a temperature of approximately 20 K. This value was in good agreement with that predicted by theoretical calculations.[16] These studies support that *o*-benzyne is better described as a strained alkyne rather than a biradical. The alkyne-type character of *o*-benzyne is also evident by Diels-Alder reactions. Wenthold and Squires measured the enthalpy of formation of structure **6** to be 103.6-109.6 kcal/mol.[17] Various properties of arynes, such as microwave,[18] mass spectroscopy, [19] photoelectron spectroscopy, [20] and NMR spectroscopy, [21] have been investigated. Warmuth was able to isolate aryne in a hemicarcerand, a molecular container, to measure the nuclear magnetic resonance spectrum in solution, which provided further evidence supporting the aryne structure.[21] The ^{13}C value of 182 ppm also supports the strained alkyne character of *o*-benzyne.

Hoffman established the electrophilic nature of aryne by validating the extended Hückel theory. According to this theory, the aryne LUMO is significantly reduced compared to dimethyl acetylene (5.1 eV), while the HOMO is higher in energy by 0.1 eV. This results in a highly electrophilic triple bond in aryne, making it more reactive towards various nucleophiles (Figure 1.2).[22]

The high reactivity of arynes can be attributed to their strained ring structure, which contains a carbon-carbon triple bond in a six-membered ring. Arynes display high reactivity

similar to highly reactive alkynes in cycloaddition reactions. Furthermore, the low-lying LUMO of aryne makes it a strong electrophile, facilitating the addition of nucleophiles.

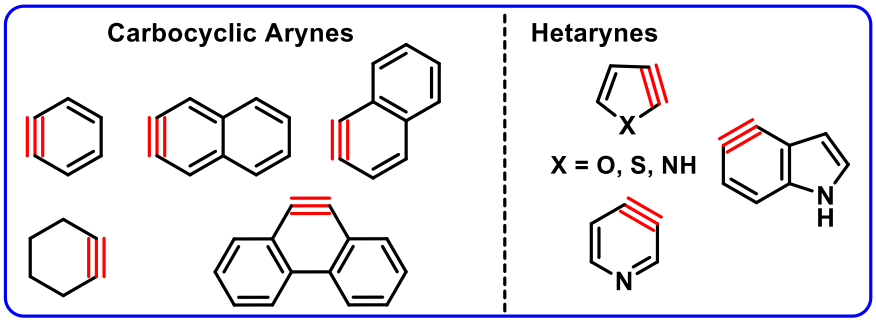
Figure 1.2. Energy Comparison of Dimethylacetylene and Aryne



1.3. Different Classes of Arynes

Over the past few decades, the field of aryne chemistry has experienced significant progress in organic synthesis, leading to the discovery of several novel arynes by different research groups (Figure 1.3). As with carbocyclic arynes, the remarkable reactivity of heterocyclic arynes can also be utilized for the construction of intricate structures that would be challenging to access through other synthetic approaches.[23]

Figure 1.3: Different Types of Arynes



1.4. Methods of Aryne Generation

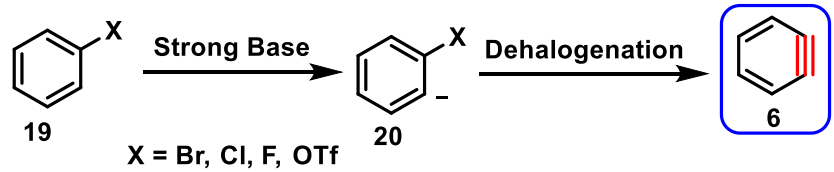
Because of their high reactivity and short lifespan, arynes cannot be isolated; rather, they are produced in situ in a solution. Since the identification of arynes, various research teams have developed different methods for generating arynes. In the following section, we will discuss some of the established methods for generating arynes.

1.4.1. Conventional Methods of Aryne Generation

1.4.1.1. Base-Induced 1,2-Elimination

The conventional approach for aryne generation involved deprotonating aryl halides or triflates **19** using strong bases like $NaNH_2$ or *n*-BuLi, leading to the dehalogenation of the resulting anionic intermediate **20**.[24] However, this method has limited applications as the strong basic conditions are not suitable for base-sensitive functional groups (Scheme 1.7).

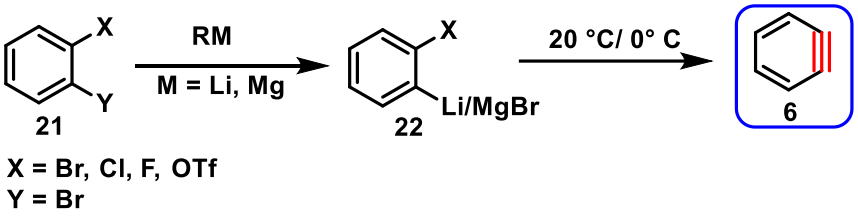
Scheme 1.7. Aryne from Halobenzene



1.4.1.2. Metal-Halogen Exchange/Elimination

An alternative method for aryne generation involves the exchange/elimination of halogens in 1,2-disubstituted haloarenes **21** or haloaryl triflates using metals (Mg or Li) or organometallic reagents derived from Li or Mg.[25] This approach is known as metal-halogen exchange/elimination. However, organometallic reagents can themselves act as nucleophiles towards the in situ generated arynes **6**, making this route less practical (Scheme 1.8).

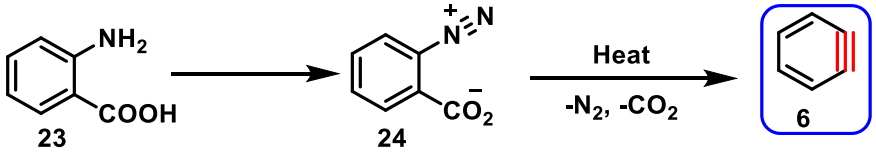
Scheme 1.8. Metal-halogen Exchange/Elimination



1.4.1.3. From Anthranilic Acids

Arynes can also be produced from anthranilic acids **23** through the conversion of the acids into the zwitterionic benzenediazonium 2-carboxylates **24** during the reaction. Upon heating, benzene diazonium 2-carboxylate decomposes to generate aryne, accompanied by

Scheme 1.9. Aryne from Anthranilic Acid

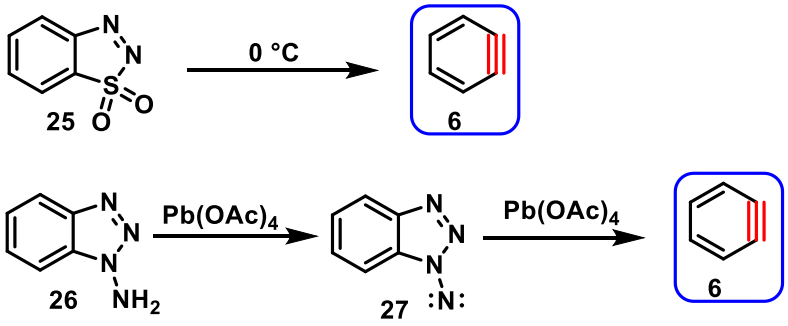


the release of nitrogen and carbon dioxide. However, the use of diazonium compounds poses a significant risk due to their explosive nature, which is a major drawback of this method (Scheme 1.9).[26]

1.4.1.4. Fragmentation of Aminotriazoles

Arynes **6** can also be generated through the fragmentation of benzo[*d*] [1,2,3]thiadiazole 1,1-dioxide **25** and aminotriazole **26**, resulting in the evolution of nitrogen gas. However, this method is explosive and requires the use of lead tetraacetate as oxidant, which leads to less functional group tolerance. As a result, it is not commonly used for generating arynes. (Scheme 1.10).[27]

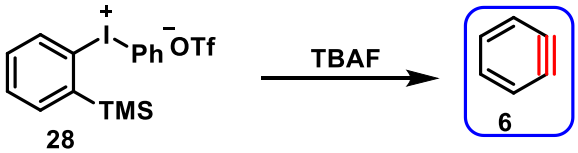
Scheme 1.10. Aryne from Benzothiadiazoledioxide and Aminotriazole



1.4.1.5. From Phenyl(2-(trimethylsilyl)phenyl)iodonium Triflate

Another method for generating aryne **6** is through the fluoride-induced elimination of the aryne precursor phenyl(2-(trimethylsilyl) phenyl)iodonium triflate **28**. However, the complicated procedure for preparing the starting material makes this method less appealing (Scheme 1.11).[28]

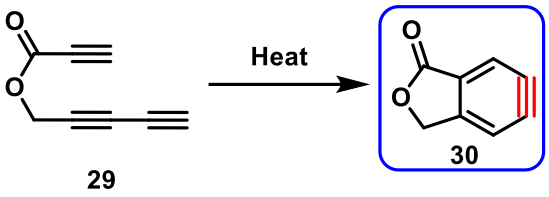
Scheme 1.11. Aryne from Phenyl(2-(trimethylsilyl)phenyl)iodonium Triflate



1.4.1.6. Using Hexadehydro Diels-Alder (HDDA) Reaction

A new approach for generating arynes has been reported by Hoye and co-workers, which involves the intramolecular hexadehydro Diels-Alder reaction (HDDA) of triynes **29**. This method allows the production of arynes **30** without the need for reagents or metals, but higher temperatures are required for aryne formation (Scheme 1.12).[29]

Scheme 1.12. Arynes Using HDDA Strategy

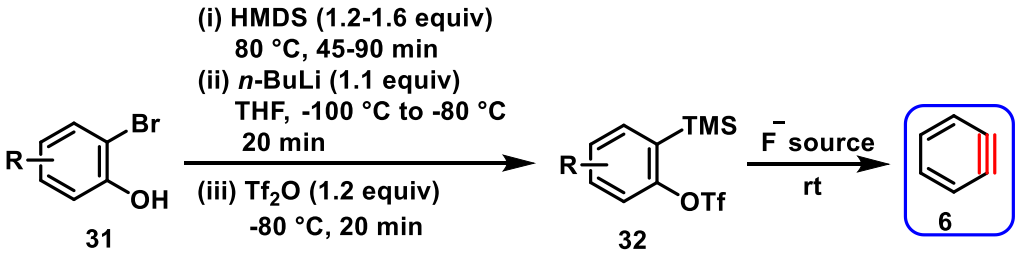


The utilization of metals, strong bases, and harsh reaction conditions in the previously discussed methods limited their applicability as they are not compatible with a wide range of functional groups. This, in turn, restricted the scope of aryne reactions in organic synthesis.

1.4.2. Kobayashi's Fluoride-Induced Generation of Aryne

Kobayashi and co-workers made a ground-breaking discovery in 1983, revealing a simple method for generating arynes in mild reaction conditions without the need for strong bases. The method involved fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates for aryne generation (Scheme 1.13).[30] This seminal discovery paved the way for the rapid development of aryne chemistry. The aryne precursor **32** could be easily synthesized from 2-bromophenol in just three steps.

Scheme 1.13. Kobayashi's Method of Aryne Generation



The generation of arynes from *o*-silylaryl triflates typically involves the use of various types of fluoride sources and solvents. Commonly used sources of fluoride include KF (with 18-crown-6 as an additive) in THF, CsF in CH_3CN, Tetrabutylammonium difluoro triphenylsilicate (TBAT) in THF or toluene, and tetrabutylammonium fluoride (TBAF) in THF. The careful selection of a fluoride source and solvent combination has been found to be crucial in controlling the rate of aryne generation. For instance, CsF has lower solubility in CH_3CN, which limits its ability to activate a significant proportion of *o*-silylaryl triflate **32** at any given reaction stage. DFT calculations have revealed that the fluoride-induced aryne generation process operates via a pseudo-S_N2 mechanism where the fluoride ion eliminates

the TMS group, forming a pentacoordinate silicon ate complex that is the rate-determining step.[31] This mechanism enables a steady supply of a sufficiently low concentration of aryne species. Consequently, Kobayashi's method has become a preferred choice for synthetic chemists over traditional methods for aryne generation. Furthermore, the mild reaction conditions make this method compatible with a wide range of functional groups, substrates, and reagents, including transition metal catalysts. As a result, chemists have revisited classical aryne reactions to broaden their scope and increase yield.

1.5. Different Modes of Reactivity of Arynes

The success of aryne reactions in organic synthesis, which enable the construction of a variety of compounds like 1,2-disubstituted arenes, benzo-fused heterocycles, and carbocycles, is due to the intrinsic electrophilicity and kinetic instability of arynes. This arises from the strain caused by the presence of a carbon-carbon triple bond in the six-membered ring. Aryne reactions can be divided into six main classes such as -

(a) Pericyclic reactions[32]

(b) Arylation reactions[33]

(c) Insertion reactions[34]

(d) Metal-catalyzed reactions[35]

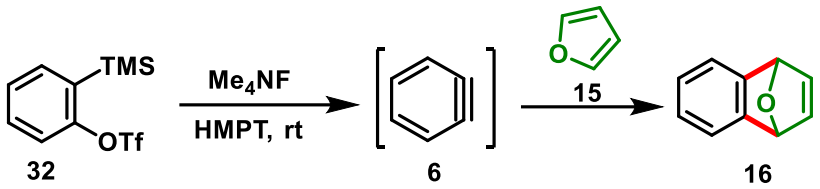
(e) Multicomponent coupling reactions (MCRs)[36]

(f) Molecular rearrangements[37]

1.5.1. Pericyclic Reactions

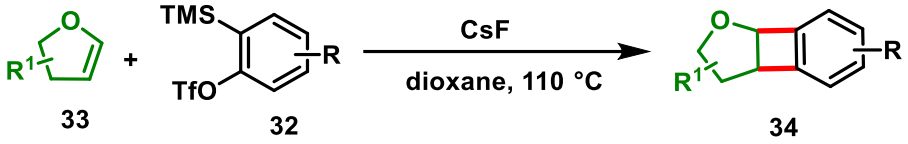
Arynes possess high electrophilic nature that makes them excellent dienophiles for a range of pericyclic reactions, including Diels-Alder, [2+2] cycloaddition and dipolar cycloaddition reactions. In many cases, pericyclic reactions of arynes are utilized to detect the generation of aryne intermediates in solution. Wittig and Pohmer successfully trapped the in situ generated aryne intermediate **6** via a [4+2] cycloaddition reaction with furan in a Diels-Alder reaction, leading to the formation of an epoxynaphthalene derivative (Scheme 1.6).[9] Kobayashi and co-workers also reported the Diels-Alder reaction of an aryne generated from 2-(trimethylsilyl)aryl triflates **32** with furan, yielding the cycloadduct 1,4-dihydro-1,4-epoxynaphthalene product **16** in almost quantitative yield in the presence of tetramethylammonium fluoride as a fluoride source in HMPT solvent (Scheme 1.14).[30a]

Scheme 1.14. Arynes Cycloaddition Reaction with Furan



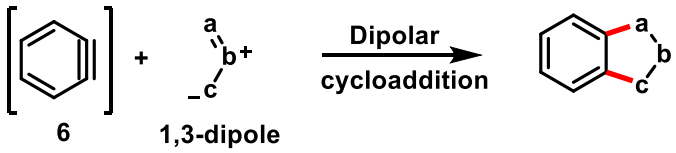
Due to high electrophilicity, arynes can take part in [2+2] cycloaddition reactions with electron-rich carbon-carbon double bonds. As a representative example, in 2015, Lakshman and co-workers demonstrated an aryne [2+2] cycloaddition reaction with cyclic enol etheres **33** for the synthesis of 1,2-disubstituted benzocyclobutenes **34** (Scheme 1.15).[38]

Scheme 1.15. [2+2] Cycloaddition Involving Arynes and Enol Ethers



In addition to [4+2] and [2+2] cycloaddition reactions, arynes can be employed in 1,3-dipolar cycloaddition reactions, allowing for the synthesis of benzo-fused five-membered rings (Scheme 1.16). Various 1,3-dipoles, including nitrones, nitrile oxides, nitrile imines, azomethine imines, azides, and diazo compounds, can easily add to arynes. The earliest study

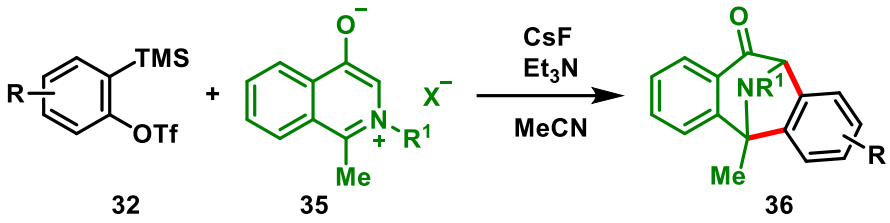
Scheme 1.16. 1,3-Dipolar Cycloaddition of Arynes



on the 1,3-dipolar cycloaddition reaction with *o*-silylaryl triflates was conducted by Carroll and co-workers. They developed a convenient approach for the synthesis of MK801, which is known to inhibit opioid tolerance and dependence. The reaction involved the participation of *N*-alkyl-4-hydroxy-1-methylisoquinolinium betaines **35** in the aryne 1,3-dipolar cycloaddition reaction, leading to the formation of *N*-alkyl-5-methyl-11-oxo-5*H*-dibenzo-[*a*,*d*]cyclohepten-5,10-imines **36** in high efficiency (Scheme 1.17),[39] which was then converted to MK801. The authors also explored the reactivity of **35** with two other benzyne precursors, namely, 1-aminobenzotriazole (generated via oxidation with lead tetraacetate) and anthranilic acid (generated via diazotization), both of which yielded either low amounts

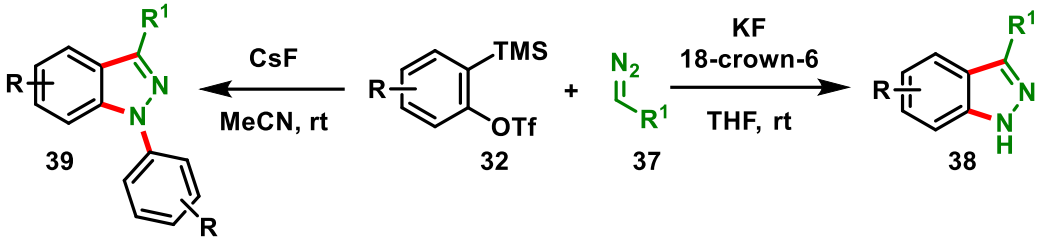
or no desired product at all. This approach demonstrates the effectiveness of Kobayashi's method compared to other methods of aryne generation.

Scheme 1.17. Aryne 1,3-Dipolar Cycloaddition Reactions with 4-Hydroxyisoquinolinium



In 2007, Yamamoto and co-workers also showed that diazo compounds **37** could be used to synthesize 1*H*-indazoles **38** and 1-arylated indazoles **39** in good to high yields, simply by adjusting the reaction conditions and the amount of *o*-silylaryl triflates used (Scheme 1.18).[40]

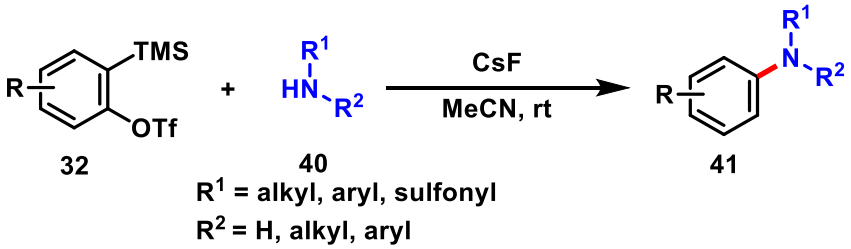
Scheme 1.18. Aryne 1,3-Dipolar Cycloaddition Reactions with Diazo Compounds



1.5.2. Arylation Reactions

Due to the electrophilic nature of arynes, aryne intermediates can effectively react with various charged and uncharged nucleophiles. Nucleophiles can add to the in situ formed aryne to produce aryl anions, which can then be protonated to enable efficient arylation reactions. This feature allows arynes to serve as aryl sources for the arylation of OH, SH, and NH bonds without the requirement of transition metals. In 2003, Larock and co-workers

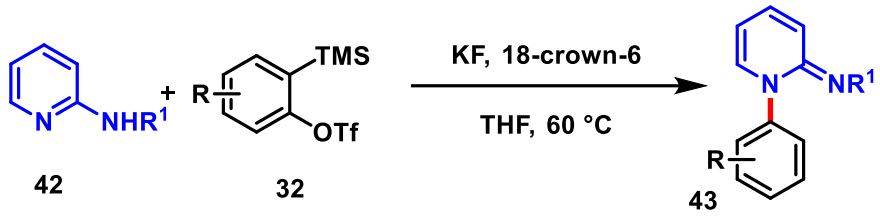
Scheme 1.19. *N*-Arylation of Amines



introduced a mild protocol for the *N*-arylation of primary and secondary amines **40** by utilizing the arylating property of arynes derived from the precursor **32**, resulting in the synthesis of diverse aniline derivatives **41** (Scheme 1.19).[41]

A chemoselective *N*-arylation reaction of 2-aminopyridine **42** derivatives with arynes was discovered by Zhai and co-workers in 2017. The resulting dearomatized pyridine products **43** can be conveniently employed to synthesize benzoisoquinuclidines and isoquinuclidines (Scheme 1.20).[42]

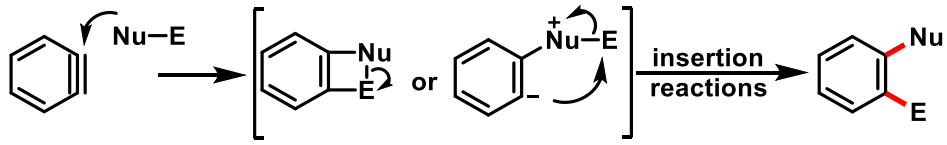
Scheme 1.20. *N*-Arylation of 2-Aminopyridines



1.5.3. Insertion Reactions

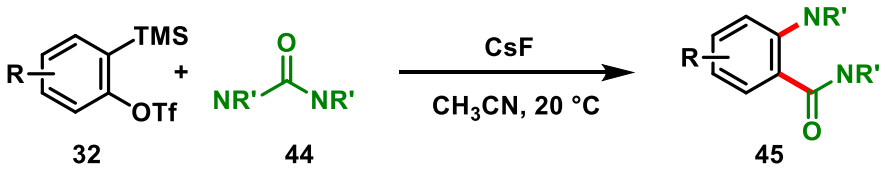
Arynes are significantly utilized in insertion reactions to several element-element σ-bonds and π-bonds for the construction of various functionalized 1,2-disubstituted arenes. After nucleophilic addition to the arynes, the insertion reaction can occur via a four-membered transition state or through direct 1,3-migration of the covalently bonded electrophile. (Scheme 1.21).[34]

Scheme 1.21. General Representation of Aryne Insertion Reactions



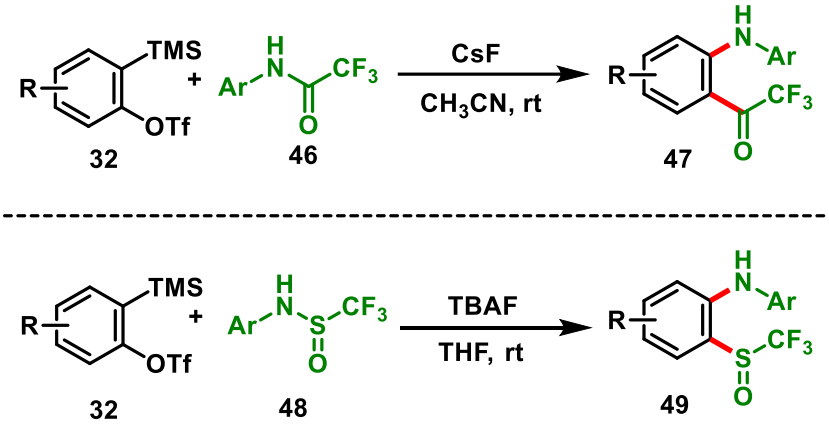
In 2002, Hiyama and co-workers reported one of the earliest examples of aryne insertion into a σ-bond. They used benzyne insertion to synthesize 2-aminobenzamides **45** by inserting a N-CO bond of urea's **44** (Scheme 1.22).[43] This method is noteworthy because these compounds are difficult to obtain using other conventional methods.

Scheme 1.22. Insertion of Arynes into the N-CO Bond in Urea's



Furthermore, Larock and co-workers uncovered an effective insertion of arynes to the C-N bond of amides **46** and S-N bond of sulfinamides **48** leading to a transition-metal-free access of 1,2-disubstituted arenes **47** and **49** respectively under mild reaction conditions with broad substrate scopes (Scheme 1.23).[44]

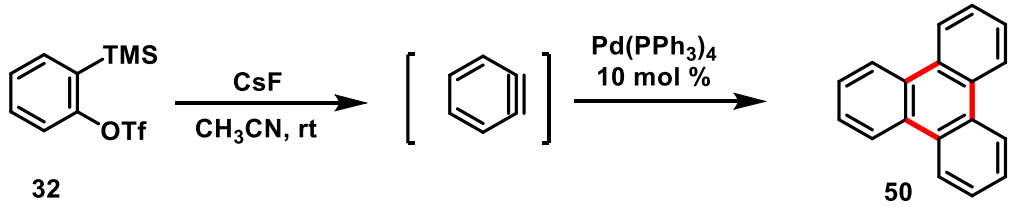
Scheme 1.23. Insertion of Arynes into C-N Bond of Amides and S-N Bond of Sulfinamides



1.5.4. Metal-Catalyzed Reactions

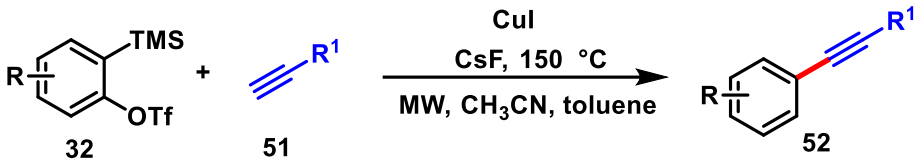
The discovery of *o*-(trimethylsilyl)aryl triflate by Kobayashi and co-workers enabled the exploration of new transition-metal-catalyzed reactions involving arynes. These reactions include metal-catalyzed aryne insertions, cyclotrimerizations, annulations, cycloadditions, and multicomponent couplings.[35,45] In 1998, Pérez, Guitián, and co-workers reported the use of Pd in metal-catalyzed aryne transformations using *o*-silylaryl triflates **32** as aryne precursors. They demonstrated a synthesis method for triphenylenes **50** through Pd-catalyzed [2 + 2 + 2] cyclotrimerization of arynes (Scheme 1.24).[46]

Scheme 1.24. Pd-Catalyzed [2+ 2 + 2] Cyclotrimerization of Arynes



In 2009, Biehl and co-workers disclosed a method utilizing CuI as a catalyst to synthesise phenyl acetylene derivatives **52**. The approach involved coupling of a terminal alkyne **51** with an aryne **32**. (Scheme 1.25).[47]

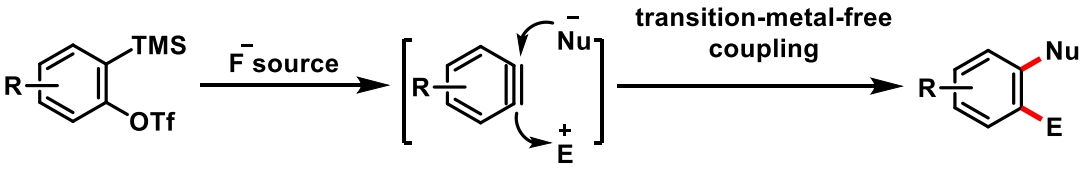
Scheme 1.25. Metal-Catalyzed Coupling Reaction of Arynes



1.5.5. Multicomponent Coupling Reactions

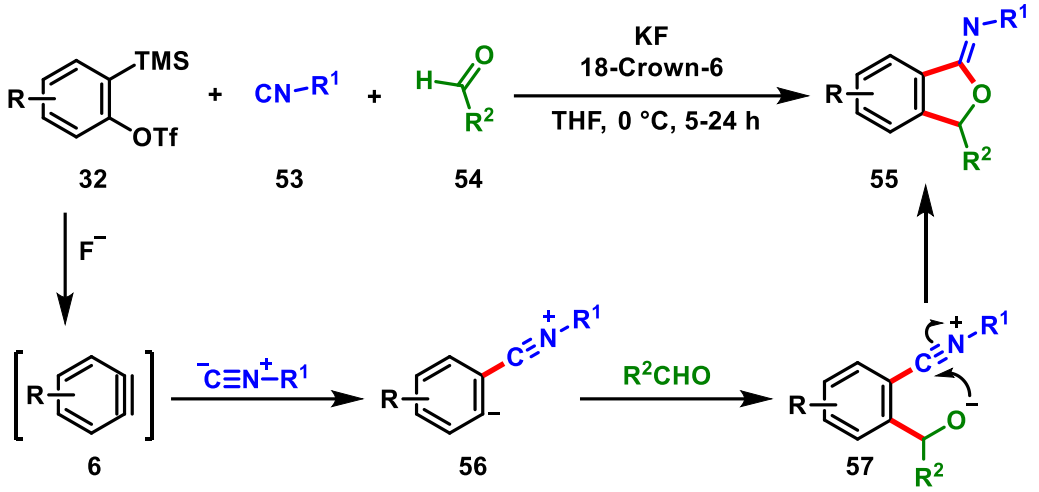
Recently, aryne-based reactions have been incredibly successful, especially in the domain of transition-metal-free multicomponent coupling reactions (MCRs). The success of aryne in MCRs can be attributed to the mild reaction conditions used in Kobayashi's method for aryne generation. This method allows the reactive intermediate to act as a connector between the nucleophilic and electrophilic coupling partners. In a typical aryne MCR, a nucleophile lacking acidic hydrogen atoms is added to the highly electrophilic aryne, resulting in the formation of an aryl anion intermediate. The electrophilic coupling partner subsequently intercepts this intermediate, resulting in the formation of 1,2-disubstituted arenes (as shown in Scheme 1.26).[36] Some representative examples of notable MCRs involving aryne will be discussed below.

Scheme 1.26. MCRs Involving Arynes



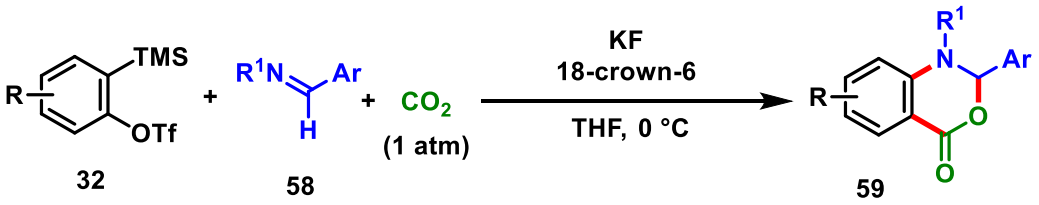
A facile three-component coupling of arynes with isocyanides **53** and aldehydes **54** was reported by Yoshida and co-workers in 2004. The reaction furnished iminoisobenzofuran **55** derivatives in good yields under mild reaction conditions (Scheme 1.27).[48] The reaction proceeds by the initial nucleophilic addition of isocyanides **53** to the aryne generated from *o*-silylaryl triflate **32**, to form a zwitterionic intermediate **56**. The aldehyde then captures the intermediate to afford the final products **55**. The same research group later discovered that imines[49] and activated ketones[50] could also serve as electrophilic third components instead of aldehydes in this three-component coupling.

Scheme 1.27. Aryne MCR Involving Isocyanides, and Aldehydes



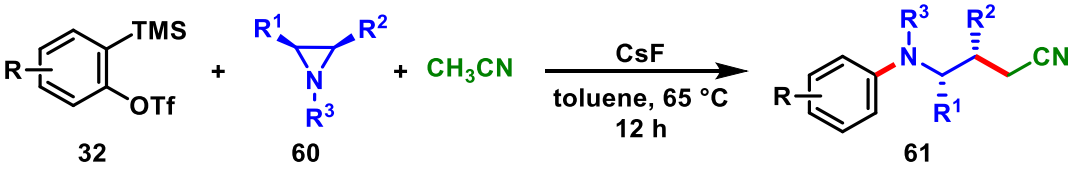
The utilization of carbon dioxide as the third component in an imine triggered multicomponent reaction was demonstrated by the Yoshida group in 2006. The reaction involves the nucleophilic addition of imines **58** to arynes, forming a zwitterion intermediate that is captured by CO_2 to yield benzoxazinone derivatives **59** (Scheme 1.28).[51]

Scheme 1.28. MCR Involving Arynes, Imines and CO_2



In 2013, Larionov and co-workers reported a stereospecific multicomponent reaction triggered by aziridines **60**. The present reaction utilized CH_3CN as the third component. This approach resulted in the synthesis of biologically relevant *N*-aryl γ-aminobutyronitriles **61** in moderate to good yields (Scheme 1.29).[52]

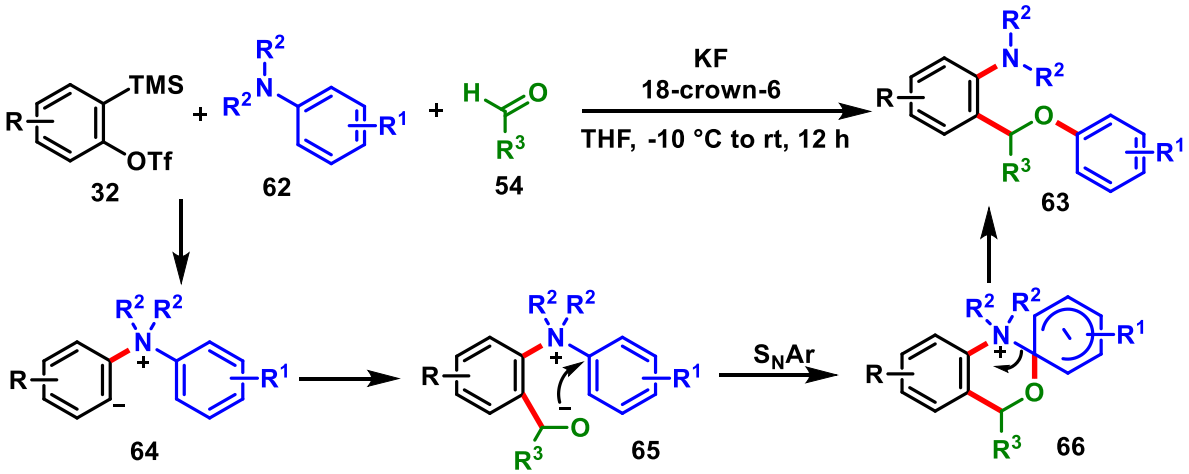
Scheme 1.29. Arynes MCR Involving CH_3CN



The rapid synthesis of 2-functionalized tertiary amines **63** was achieved by Biju and co-workers through the multicomponent coupling of arynes, aromatic tertiary amines **62**, and

aldehydes **54** in 2015. Under optimized conditions, activated carbonyls such as various isatins and phenyl ethyl glyoxylate also reacted efficiently to furnish the corresponding products in good yields (Scheme 1.30).[53] The reaction mechanism involves the initial nucleophilic attack of the tertiary amine on the aryne, resulting in the formation of zwitterionic intermediate **64**. The intermediate then adds to the aldehyde, forming the key tetrahedral intermediate **65**. The intermediate **65** subsequently undergoes an intramolecular nucleophilic aromatic substitution reaction (S_NAr) to yield the desired product **63** via the σ-complex **66**. The same group also disclosed the MCR involving aryne, tertiary amines and CO_2 and depending upon the electronics of the amine group the reaction outcome was different.[54]

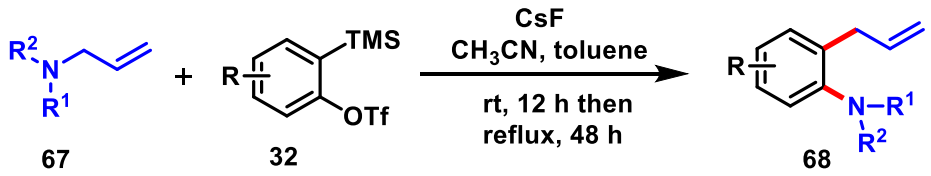
Scheme 1.30. Aryne MCR Involving Tertiary Amines, and Aldehydes



1.5.6. Molecular Rearrangements

In recent times, molecular rearrangements involving arynes have garnered significant attention due to their ease of operation and mild reaction conditions. These rearrangements have enabled the synthesis of several structurally significant motifs that would otherwise be difficult to access. Numerous classical molecular rearrangements have been adapted in aryne chemistry to make the aryne version of the same. For instance, Greaney and co-workers

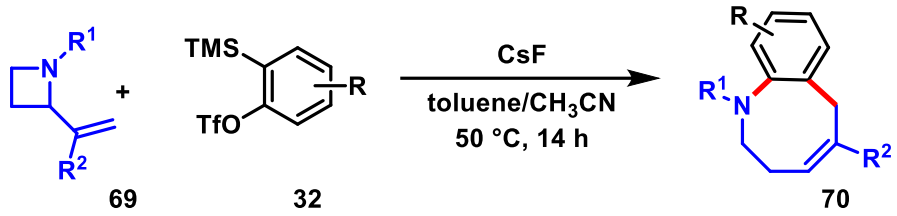
Scheme 1.31. Aryne Aza-Claisen Rearrangement



reported the development of an aza-Claisen rearrangement, utilizing various tertiary allylic amines **67** to synthesize functionalized aniline derivatives **68** (Scheme 1.31).[55]

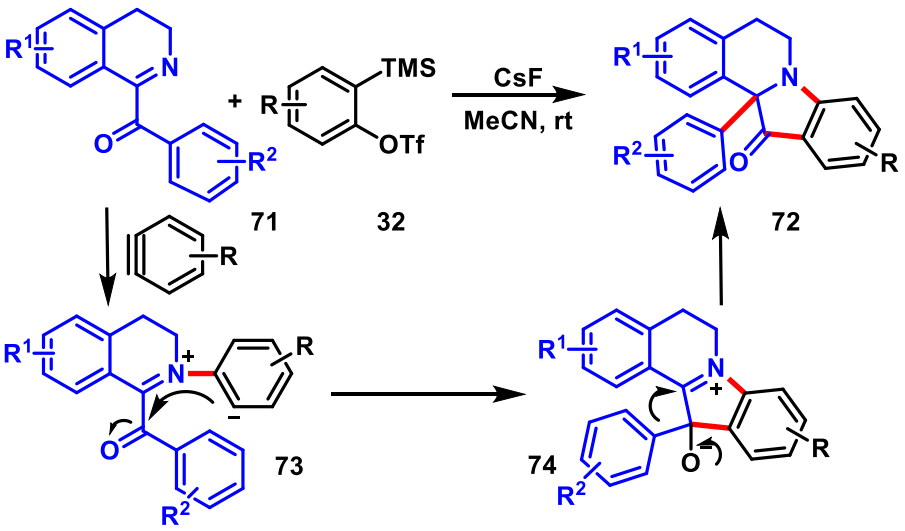
Following the Greaney group's work on the aryne aza-Claisen rearrangement, Saito and co-workers reported the smooth synthesis of 1-benzazocine derivatives **70** through the reaction of 2-vinylazetidines **69** with arynes (Scheme 1.32).[56] The reaction occurs through the nucleophilic addition of azetidine **69** to the aryne generated from **32**, followed by protonation of the aryl anion and a subsequent aza-Claisen rearrangement.

Scheme 1.32. Aryne Aza-Claisen Rearrangement



Voskressensky and co-workers reported the synthesis of indoxylisoquinolines **72** in 2016 by reacting 1-aryloxy substituted 3,4-dihydroisoquinolines **71** with arynes. This novel rearrangement reaction involving arynes provides a direct route to the synthesis of biologically significant indoxylisoquinoline cores (Scheme 1.33).

Scheme 1.33. Synthesis of Indoxylisoquinolines



Mechanistically, the reaction starts with the initial nucleophilic attack of dihydroisoquinoline **71** onto the aryne, resulting in the formation of the zwitterion **73**.

Subsequently, an intramolecular attack of the aryl anion to the carbonyl centre produces the intermediate **74**. The migration of the aryl substituent to the iminium carbon then leads to the formation of indoloisoquinolinones **72**. This migration is closely related to benzylic rearrangement and quasi-Favorskii rearrangements of α-haloarylketones.[57] Section 3.2.1 of Chapter 3 covers some of the more recent rearrangements.

1.6. Focal Theme of This Part of the Thesis

The central theme of this thesis is to utilize the strained intermediates in organic synthesis. The total dissertation is divided into two parts, each consisting of four Chapters. The first part investigates the aryne intermediates for diverse and distinctive transformations. As an introduction to aryne chemistry this Chapter has illustrated the brief history, methods of generation, characterization, and different modes of reactivity of arynes.[58]

Traditionally, inorganic salts were not considered as reacting partners in aryne cycloaddition chemistry mainly due to poor nucleophilicity and low solubility of inorganic salts. In this context, the synthetic potential of NaN_3 as the source of non-hazardous azide in contrast to organic azides in aryne 1,3-dipolar cycloaddition has been investigated. Selective synthesis of *N*-H and *N*-aryl benzotriazoles has been achieved by fine-tuning the choice of solvents and fluoride sources in aryne [3+2] cycloaddition reaction, which form the content in the 2nd Chapter.

Nitrogen ylide chemistry, although widely used in aryne chemistry but not well-explored for higher-order annulations. We employed aryne-triggered nitrogen ylide in a transition-metal-free, three-component, diastereoselective [6 + 3] annulation reaction. The diastereoselective synthesis of bridged azabicyclo[4.3.1] decadienes employing tropone, imino esters, and arynes has been discussed in detail in the 3rd Chapter.

Transition-metal-free direct C2 functionalization of pyridine is rare in organic synthesis, mainly due to the direct quenching of electrophiles by pyridine nitrogen. In Chapter 4, we reported an aryne three-component coupling reaction for pyridine C2 functionalization employing activated carbonyls as the electrophilic component. The nucleophilic pyridylidene intermediate generated from pyridine and aryne adds to the activated carbonyls in an S_NAr process to afford the desired products, which have been presented with detailed mechanistic studies in this Chapter.

1.7. References

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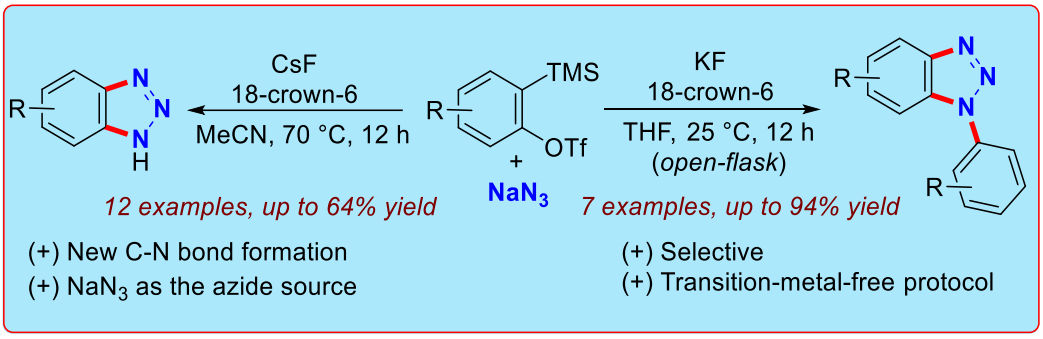
Chapter 2

Selective Synthesis of *N*-H and *N*-Aryl Benzotriazoles by the [3 + 2] Annulation of Sodium Azide with Arynes

The synthetic utility of NaN_3 as the inorganic azide component in the [3 + 2] annulation with arynes generated from 2-(trimethylsilyl)aryltriflates resulting in the transition-metal-free synthesis of *N*-H and *N*-aryl benzotriazoles has been demonstrated in this Chapter. Using CsF as the fluoride source in CH_3CN, the *N*-H benzotriazoles are formed in high selectivity instead of the expected azidobenzene. Interestingly, *N*-aryl benzotriazoles are formed using KF and THF as solvent in an open-flask reaction. Moreover, a method for the *N*1-arylation of benzotriazole is also presented.

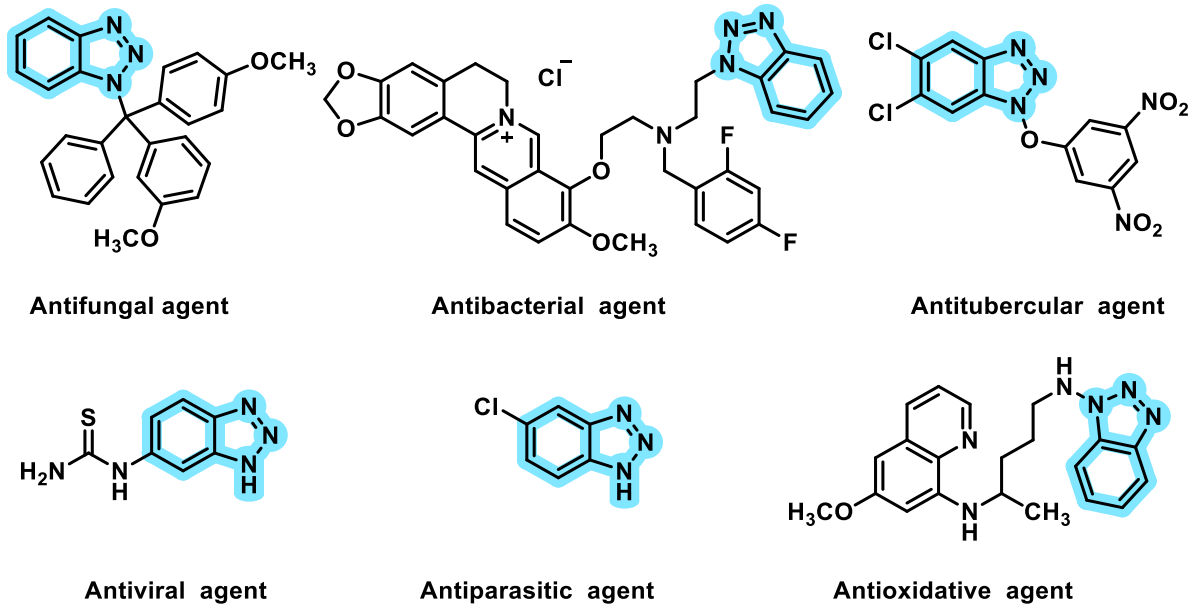


J. Org. Chem. **2019,** *84*, 12692.

2.1. Introduction

Benzotriazoles are a significant class of compounds with various applications in multiple fields.[1] For instance, they can serve as corrosion inhibitors and supramolecular ligands.[2] However, their primary importance lies in medicinal chemistry,[3] where benzotriazole derivatives find extensive use. The presence of a fused benzene ring in the benzotriazole nucleus results in a more extensive conjugated system that facilitates π-π stacking interactions. Additionally, its three nitrogen lone pairs allow for the easy formation of hydrogen and coordination bonds, enabling benzotriazole derivatives to interact with various enzymes and receptors in biological systems through non-covalent interactions.[4] Consequently, they exhibit various biological activities, including antifungal, antibacterial, antitubercular, antiviral, antiparasitic, and antioxidative properties (Figure 2.1). Furthermore, benzotriazole compounds can bind with different metal ions to produce benzotriazole-based metal complexes, which also exhibit bioactivities. As a result, some benzotriazole-based anticancer drugs have already entered clinical trials. The importance of benzotriazoles in drug discovery requires the development of practical and mild synthetic routes to this valuable core. This can improve the efficiency of drug discovery, reduce costs, and promote sustainability by reducing the use of harsh reagents and conditions.

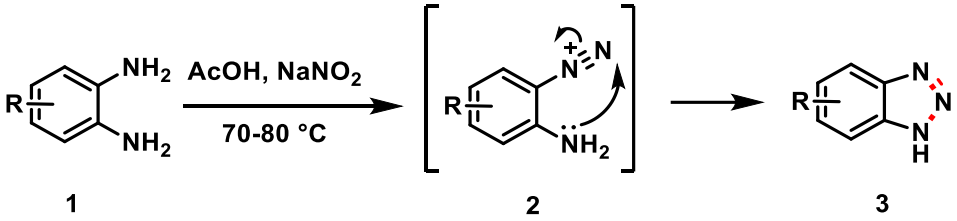
Figure 2.1. Representative Examples of Benzotriazole-Based Drugs



2.2. Different Routes for Synthesis of Benzotriazoles

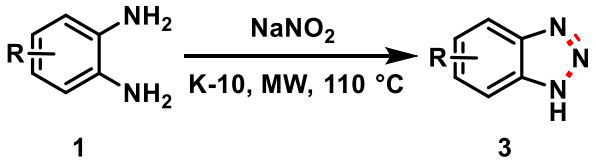
Diazotiaztion of benzene-1,2-diamine **1** is one of the most widely used methods to access benzotriazole derivatives **3**,[5] and this typically involves the use of sodium nitrite and acetic acid as reagents. During this reaction, the diazonium species **2** is generated in situ and then cyclized by the amine as a result of the intramolecular attack (Scheme 2.1). While this reaction has a broad scope, this classical approach suffers from the lack of tolerance for acid-sensitive functional groups.

Scheme 2.1. Classical Method for Benzotriazole Synthesis



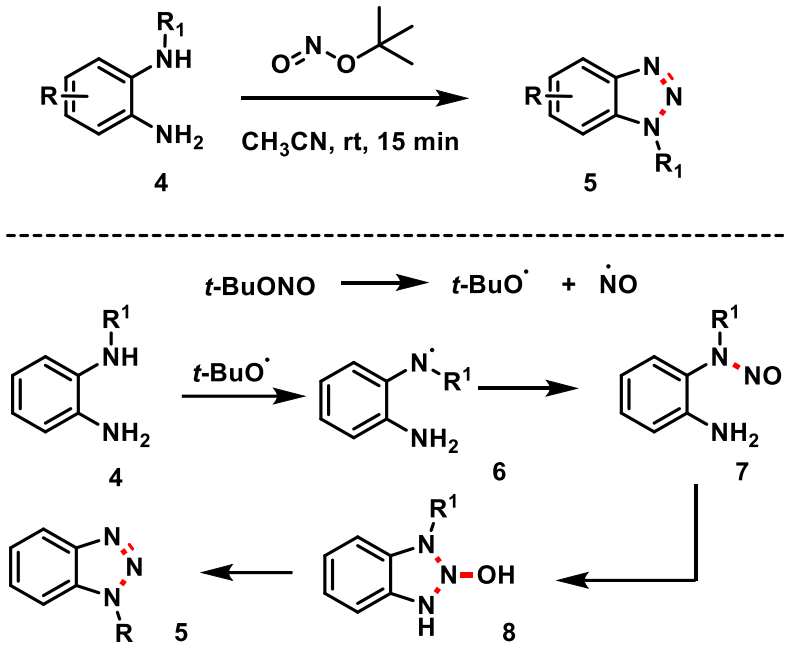
In addition to the classical method, several other protocols are available for synthesizing benzotriazoles. One such method is microwave-assisted solid-phase diazotization, discovered by Torok and co-workers in 2007 (Scheme 2.2).[6] This method offers an acid free alternative for benzotriazole synthesis and thus functional group tolerance is more than the classical method. K-10 Montmorillonite was utilized both as a catalyst and medium, making this approach environmentally friendly. The catalyst can be reused, and the reaction proceeds with high efficiency while producing no hazardous waste.

Scheme 2.2. Microwave-Assisted Benzotriazole Synthesis



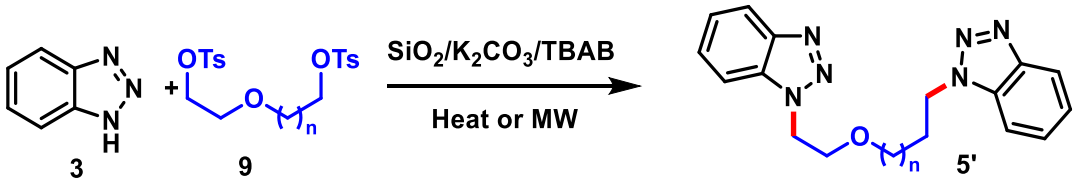
In 2018, Kandasamy and co-workers reported an alternative method for synthesizing benzotriazoles using *tert*-butyl nitrite-mediated nitrogen transfer reactions (Scheme 2.3).[7] This reaction occurs at room temperature and exhibits good functional group tolerance. The reaction occurs rapidly in a short amount of time. The reaction proceeds with the homolytic cleavage of *tert*-butyl nitrite, generating *tert*-butoxy and nitroso radicals. *O*-phenylenediamine **4** then undergoes radical mono-*N*-nitrosation **7**, followed by the elimination of water, resulting in the desired benzotriazole **5**.

Scheme 2.3. *tert*-Butyl Nitrite Mediated Benzotriazole Synthesis



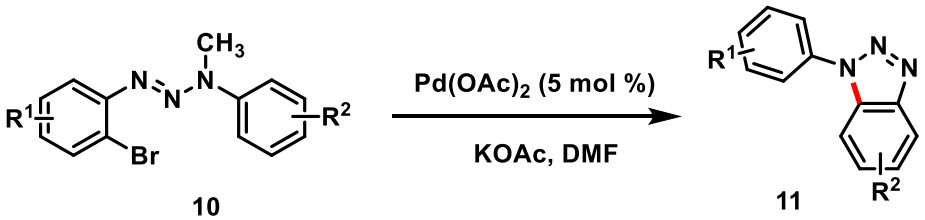
In 2007, Nezhat and co-workers reported a new method for the synthesis of alkylated benzotriazoles **5'**, which involved *N*-alkylation of benzotriazole **3** without the use of any solvents (Scheme 2.4). However, the authors observed a minor regioselectivity issue in the reaction, meaning that the alkyl group was added to both the 1- and 2- positions of the benzotriazole ring, resulting in a mixture of regioisomers.[8]

Scheme 2.4. Benzotriazole Synthesis via *N*-Alkylation



Ren and co-workers used a C-H activation strategy to construct benzotriazole core employing 1,3-diphenyltriazene **10** as the precursor (Scheme 2.5).[9] Mechanistically, the

Scheme 2.5. Benzotriazole Synthesis via C-H Activation



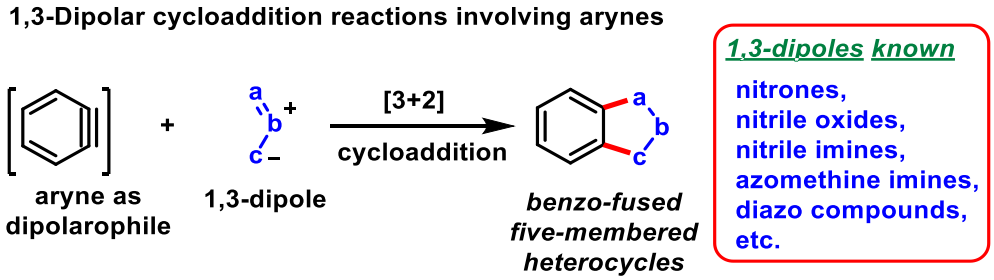
reaction proceeds via 1,7-palladium migration-cyclization-dealkylation sequences. These reactions occurred in excellent yields with high regioselectivities. However, a significant limitation of this approach is the use of expensive transition metal catalysts and the need for pre-functionalized 1,3-diphenyltriazene synthesis.

Despite the numerous available methodologies for benzotriazole synthesis, the use of sodium azide in a metal-free approach for this purpose has received limited attention. Moreover, it would be intriguing to explore the potential of utilizing sodium azide for the synthesis of benzotriazoles in a transition metal-free manner, as it would offer a straightforward route to access these compounds directly.

2.3. Arynes in [3+2] Cycloaddition Reactions

As mentioned in the previous Chapter, arynes have the ability to participate in multiple types of cycloaddition reactions, including [2+2], [3+2], [4+2], and [5+2], which can lead to the formation of diverse carbocycles and heterocycles.[10] This is due to the presence of a low-lying LUMO in arynes, making them highly susceptible to addition reactions with a variety of dipoles across the triple bond. The [3+2] cycloaddition of arynes with different 1,3-dipoles has been extensively studied as well. For instance, the 1,3-dipoles such as nitrones,[11] nitrile oxides,[12] nitrile imines,[13] azomethine imines,[14] diazo compounds,[15] are known to add to arynes resulting in the formation of benzo-fused five-membered heterocycles (Scheme 2.6).

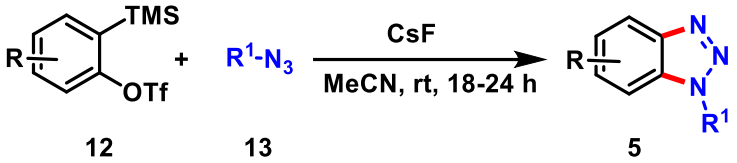
Scheme 2.6. General Representation for [3+2] Cycloaddition with Arynes



Previously, arynes also have been utilized for the synthesis of benzotriazoles. In 2008, Larock and co-workers developed an elegant approach for the formation of benzotriazoles through the [3+2] cycloaddition of alkyl azides with in situ generated arynes, employing a copper-free click reaction (Scheme 2.7).[16] During this dipolar cycloaddition reaction, organic azides react with arynes to produce the desired benzotriazole derivatives. The reaction was

carried out using CsF as a fluoride source and acetonitrile as a solvent. While this methodology is effective, it necessitates the preparation of organic azides, which are potentially hazardous compounds that can easily decompose upon exposure to even small amounts of external energy. Therefore, aryne mediated benzotriazole synthesis approach that does not require organic azides would be highly advantageous.

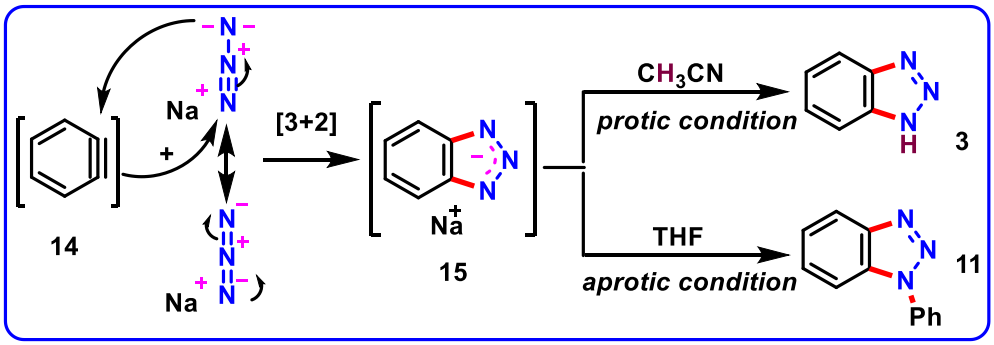
Scheme 2.7. Benzyne Click Chemistry



2.4. Statement of the Problem

Despite the availability of various methodologies for synthesizing benzotriazole derivatives, limitations such as the challenges involved in preparing pre-functionalized starting materials, the requirement of high temperatures, the use of explosive reagents, and concerns about regioselectivity have prompted synthetic chemists to seek out new and efficient methods for addressing these issues. Notable, our group[17] and Jiang group[18] independently disclosed the use of inorganic salts (KI, KBr, KCl) as nucleophilic triggers in aryne multicomponent coupling. This led us to envision whether inorganic salts could also be employed in aryne cycloaddition reactions. Sodium azide could potentially serve as a viable option in this regard. Our hypothesis suggests that when sodium azide is subjected to [3+2] cycloaddition with arynes,[19] it can yield benzotriazole **15** (Scheme 2.8). Depending on the abundance of the proton source, this reaction may result in the production of either *N*-H

Scheme 2.8. Employing NaN_3 for Aryne [3+2] Annulation (Working Hypothesis)



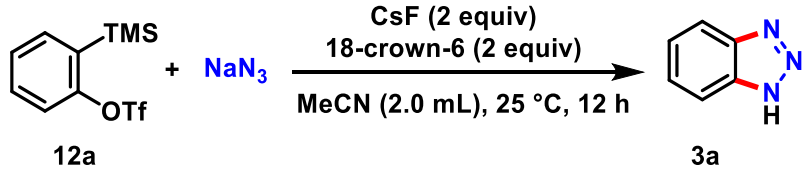
benzotriazole or *N*-aryl benzotriazole if there is an excess of arynes present. Given the usefulness of *N*-H and *N*-aryl benzotriazoles, it would be worthwhile to investigate a method for synthesizing them without the use of transition metals and using arynes as the aryl source.

2.5. Results and Discussion

2.5.1. Optimization Studies for *N*-H Benzotriazole

With a view to synthesize relevant benzotriazoles, the present study was initiated by the treatment of aryne generated from the triflate precursor **12a**[13] using CsF and 18-crown-6 with excess of NaN_3 in CH_3CN solvent. Interestingly, under these conditions, the *N*-H benzotriazole product **3a** was isolated in 32% yield (Table 2.1, entry 1). The 18-crown-6 was required for better conversion to **3a** as the reaction performed without 18-crown-6 provided inferior yield of **3a** (entry 2). The use of other fluoride sources such as KF and tetrabutyl ammonium fluoride (TBAF) were found to be not effective in this reaction (entries 3-4).

Table 2.1. Optimization of the Reaction Conditions[a]



12a 3a

entry	variation of the standard conditions	yield of 3a (%)[b]
1	none	32
2	without 18-crown-6	22
3[c]	KF instead of CsF	18
4	TBAF instead of CsF/ 18-crown-6	<5
5	70 °C instead of 25 °C	45
6	0 °C instead of 25 °C	<5
7	DME instead of MeCN	<5
8[d]	5.0 equiv CsF/18-crown-6	57
9[d]	4.0 equiv NaN_3	59
10[d,e]	4.0 equiv NaN_3 and 5.0 equiv CsF/18-crown-6	64

[a] Standard conditions: **12a** (0.50 mmol), NaN_3 (2 equiv), CsF (2 equiv), 18-crown-6 (2 equiv), MeCN (2.0 mL), 25 °C for 12 h. [b] Isolated yields are given. [c] Reaction was performed in THF. [d] Reaction performed at 70 °C. [e] Reaction performed at 70 °C in 3 mL MeCN.

Performing the reaction at 70 °C was helpful to improve the yield to 45% (entry 5) but lowering the reaction temperature did not improve the yield of product (entry 6). The reaction

was slow when carried out in DME instead of CH_3CN (entry 7). When the amount of CsF/18-crown-6 was increased, the product **3a** was formed in an improved yield of 57% (entry 8). The use of 4.0 equiv of NaN_3 also improved the yield of product (entry 9). Finally, when the reaction was carried out using 5.0 equiv of CsF/18-crown-6 and 4.0 equiv of NaN_3, the product **3a** was isolated in 64% yield (entry 10). This condition was used for the substrate scope analysis.

2.5.2. Substrate Scope of *N*-H Benzotriazole

After optimizing the reaction conditions for this inorganic azide mediated dipolar cycloaddition, we examined the scope and limitations of this reaction for synthesis of *N*-H benzotriazoles (Table 2.2). A series of symmetrical arynes generated from the corresponding precursors (**12a-12g**) readily underwent the [3+2] annulation under the present conditions to provide the *N*-H benzotriazole products in moderate to good yields (**3a-3g**). Interestingly, the phenanthrene-derived aryne afforded the desired product **3g** in 52% yield. Moreover, the naphthyl and the tetrahydro naphthyl derived unsymmetrical arynes generated from the starting triflates (**12h, 12i**) afforded the single regioisomeric product in moderate yields (**3h**, **3i**). In addition, the reaction using the unsymmetrical 4-methyl, 4-chloro, and 4-fluoro aryne derived from the respective precursors (**12j-12l**) also resulted in the formation of a single regioisomer in moderate yield (**3j-3l**). It is noted that, compound **3k** can be used as antiparasitic agent.

Moreover, aryne derived from pyridine moiety **12m** and domino aryne precursor **12n** were not ideal substrates for the present methodology (Scheme 2.9). Disappointingly, symmetrical difluoro aryne **12o** and methoxy aryne **12p** also failed to deliver the desired product.

Scheme 2.9. Unsuccessful Substrates

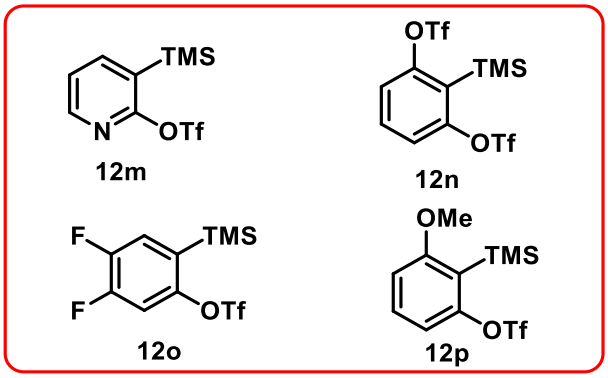
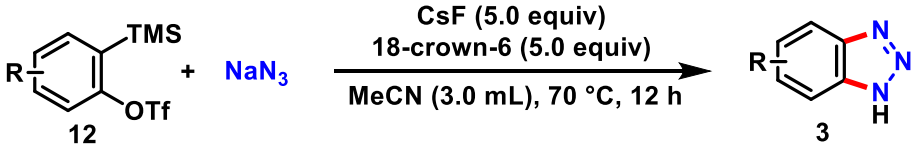
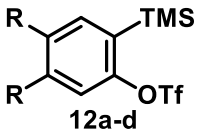
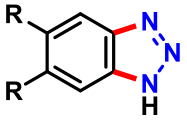
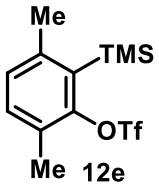
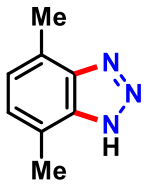
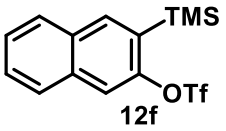
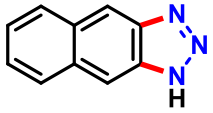
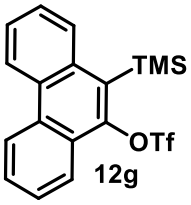
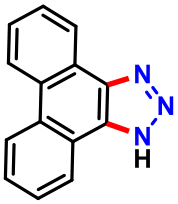
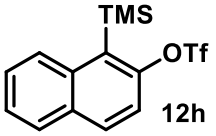
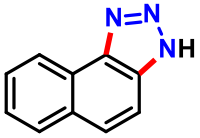
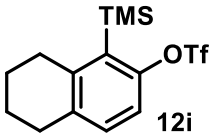
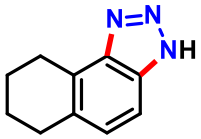
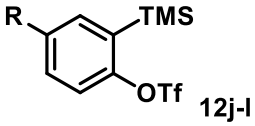
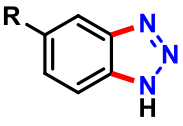


Table 2.2. Substrate Scope of *N*-H Benzotriazole[a]



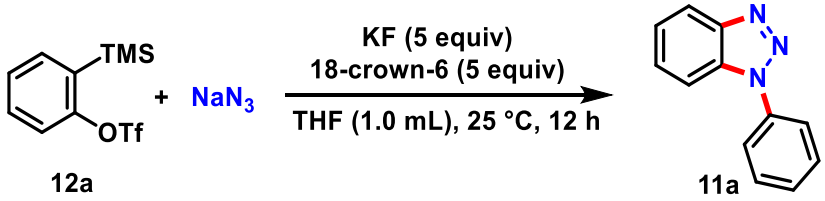
entry	aryne precursor	product	yield (%)[b]
1 2 3 4			3a, R = H, 64% (63%)[c] 3b, R = Me, 27% 3c, R = O(CH$_2$)O, 55% 3d, R = (CH$_2$)$_3$, 51%
5			3e, 41%
6			3f, 31%
7			3g, 52%
8			3h, 43%
9			3i, 43%
10 11 12			3j, R = Me, 51% 3k, R = Cl, 50% 3l, R = F, 50%

[a] General conditions: **12** (0.50 mmol), NaN_3 (2.0 mmol), CsF (5.0 equiv), 18-crown-6 (5.0 equiv), MeCN (3.0 mL), 70 °C, 12 h. [b] Yields of the isolated products are given. [c] Yield of **3a** in 1.0 mmol scale.

2.5.3. Optimization Studies for *N*-Aryl Benzotriazole

Interestingly, when the [3+2] annulation of NaN_3 was carried out using excess of arynes, the initially generated *N*-H benzotriazole underwent smoothly *N*-arylation with the additional arynes to produce the *N*-aryl benzotriazoles. Thus, treatment of NaN_3 with 2.5 equiv of **12a** and 5.0 equiv each of KF and 18-crown-6 afforded the *N*-phenyl benzotriazole **11a** in 80% isolated yield (Table 2.3, entry 1). Excess of aryne was important for this reaction as the reaction using less amount of aryne returned reduced yield of **11a** (entry 2). KF was found to be the best fluoride source and other fluoride sources such as CsF and tetrabutyl ammonium fluoride (TBAF) provided inferior results (entries 3,4). Moreover, the reactions performed at 60 °C or 0 °C did not improve the yield of **11a** further (entries 5,6). Surprisingly, performing the reaction under open-flask conditions further improved the yield of **11a** to 86% (entry 7). The open-flask conditions allow the smooth protonation of the generated aryl anion intermediate by the moisture from the atmosphere thus driving the reaction in forward.

Table 2.3. Optimization of *N*-Aryl Benzotriazole



entry	variation of the standard conditions	yield of 11a (%)[b]
1	none	80
2	1.5 equiv of 12a	18
3c	CsF instead of KF/18-crown-6	25
4	TBAF instead of KF/18-crown-6	53
5	60 °C instead of 25 °C	47
6	0 °C instead of 25 °C	39
7[d]	Open-flask reaction	86

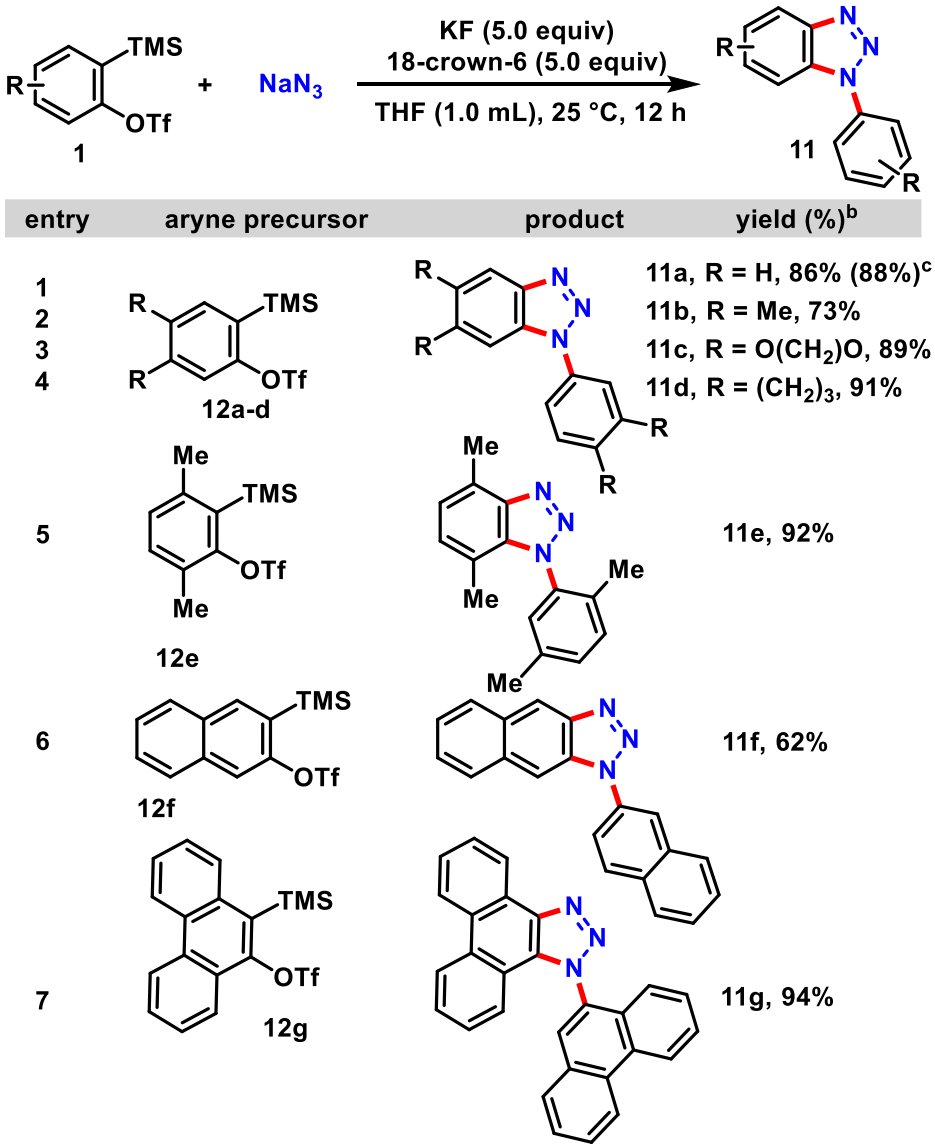
[a] Standard conditions: **12a** (0.625 mmol), NaN_3 (0.25 mmol), KF (5.0 equiv), 18-crown-6 (5.0 equiv), THF (1.0 mL), 25 °C for 12 h. [b] Isolated yields are provided. [c] Reaction was performed in CH_3CN. [d] Reaction performed in open air using commercial KF, 18-crown-6, and NaN_3.

2.5.4. Substrate Scope of *N*-Aryl Benzotriazole

This [3+2] annulation/*N*-arylation cascade using NaN_3 as the inorganic azide has been investigated with substituted arynes for synthesis of various substituted *N*-aryl benzotriazoles

(Table 2.4). The reaction carried out using electronically different symmetrically disubstituted arynes generated from the corresponding aryne precursors underwent facile cycloaddition to give different *N*-aryl benzotriazoles in moderate to excellent yield. For instance, electronically dissimilar 4,5-disubstituted symmetrical aryne precursors **12b-12e** furnished the corresponding *N*-aryl benzotriazole **11b-11e** in moderate to excellent yield (entry 1-4). However, the symmetric aryne derived from **12e** afforded the desired product **11e** in 92% yield (entry 5). Moreover, aryne generated from symmetrical naphthalene and phenanthrene (**12f-12g)** also underwent efficient cycloaddition, resulted in the formation of

Table 2.4. Substrate Scope of *N*-Aryl Benzotriazole



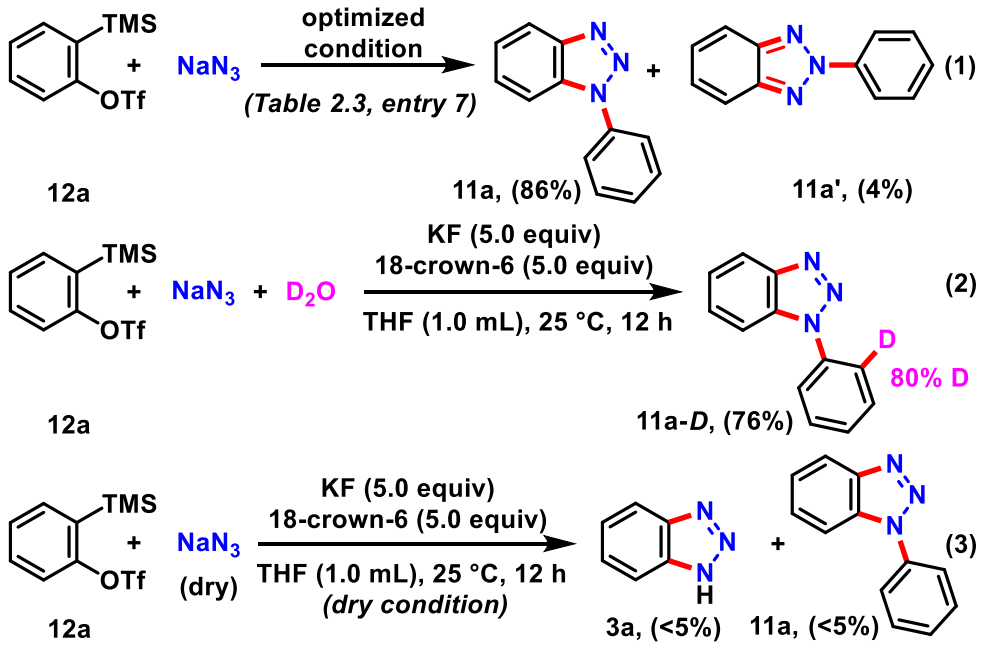
[a] General conditions: **12** (0.625 mmol), NaN_3 (0.25 mmol), KF (5.0 equiv), 18-crown-6 (5.0 equiv), THF (1.0 mL), 25 °C, 12 h. [b] Yields of the isolated products are given. [c] Yield of **11a** in 1.0 mmol scale.

11f and **11g** in 62% and 94% respectively (entry 6-7). Aryne derived from symmetrical 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate gave only trace yield of the product. Unlikely, the use of unsymmetrical aryne precursors was restricted as it leads to four inseparable regioisomers.

2.5.5 Mechanistic investigation

To get insight into the mechanism of the reaction, a few experiments were performed. The *N*-H benzotriazole can be formed only via the [3+2] annulation of NaN_3 with arynes and in this case, the azidobenzene formation was not observed. The *N*-aryl benzotriazole can be formed either via the [3+2] annulation-arylation cascade or via the initial formation of azidobenzene followed by the [3+2] cycloaddition with arynes. In the formation of *N*-phenyl benzotriazole, 4% of the 2-phenyl benzotriazole also was isolated (Scheme 2.10, eq 1). This is an indication that the initial [3+2] adduct can isomerize to the benzotriazole having negative charge at the *N*-2 position, which could be arylated to 2-aryl benzotriazole **11a'**. This experiment also rules out the initial formation of azidobenzene in the reaction. To shed light on the source of protonation of the aryl anion, an experiment was performed using D_2O

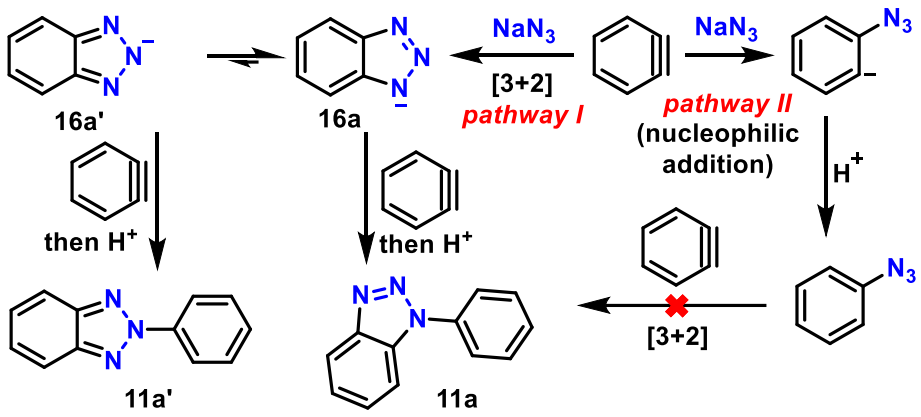
Scheme 2.10. Mechanistic Experiments



as an additive (eq 2). The formation of **11a**-*D* in 76% yield and 80% D incorporation at the 2-position of *N*-aryl ring indicates that the presence of moisture from the atmosphere as the source of proton in this open-flask reaction. This was also confirmed by performing a reaction using anhydrous NaN_3 under dry conditions, where only traces of **3a** and **11a** were observed (eq 3).

Based on these experiments, a plausible mechanism is presented in Scheme 2.11. The reaction proceeds via the initial [3+2] annulation of NaN_3 with in situ generated arynes leading to the formation of **16a** which could isomerize in trace amounts to **16a'** (pathway 1). The benzotriazole **16a** could be arylated using excess aryne leading to the formation of **11a**. The formation of **11a'** in traces could be via the *N*-arylation of **16a'**. Alternatively, the initial formation of azidobenzene by the nucleophilic addition of NaN_3 to aryne followed by protonation and a subsequent [3+2] with excess aryne could also result in **11a** (pathway II). However, based on our mechanistic experiments, pathway II via the azidobenzene is ruled out.

Scheme 2.11. Proposed Mechanism of the Reaction

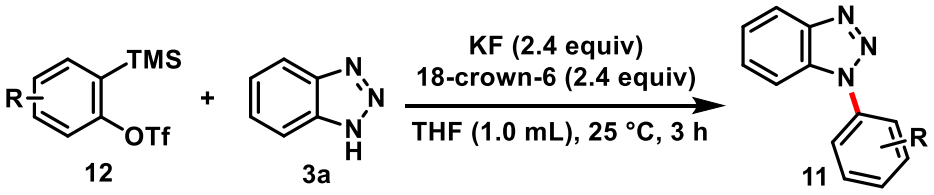


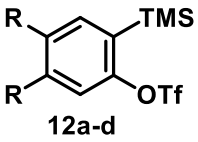
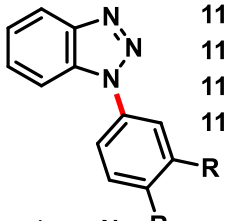
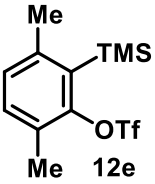
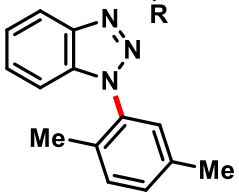
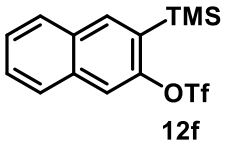
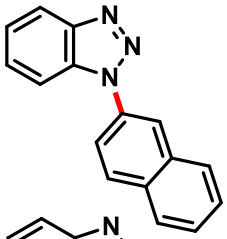
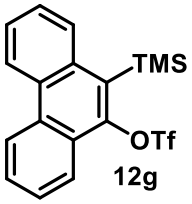
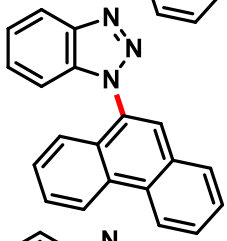
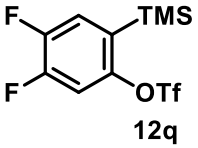
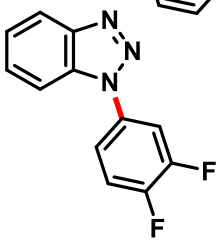
2.5.6. Synthesis of Differently Substituted *N*-Aryl Benzotriazoles

Given the fact that the *N*-arylation of *N*-H benzotriazole using arynes afforded the mixture of *N1* and *N2* arylated products demonstrated by the Larock group,[19] we envisioned the exclusive *N1*-arylation of benzotriazoles. Notably the use of *N*-H benzotriazoles for the *N*-arylation using different arynes is not well studied. The reaction of aryne generated from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12a** using KF and 18-crown-6 with the *N*-H benzotriazole **3a** resulted in the exclusively regioselective formation of the *N1*-aryl benzotriazole **11a** in 86% yield (Table 2.5, entry 1). Notably, the *N2*-arylation product **11a'**

was not observed under the present conditions. A series of various 4,5-disubstituted arynes generated from the triflate precursors are well tolerated under this condition and the *N1*-arylated benzotriazoles were formed in high yields and excellent *N1:N2* selectivity (entries 2-4). Moreover, the 3,6-dimethyl aryne generated from 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12e** afforded the expected product **11k** in

Table 2.5. Scope of Differently Substituted *N*-Aryl Benzotriazoles[a]



entry	aryne precursor	product	yield (%)[b]
1 2 3 4			11a, R= H, 86% 11h, R = Me, 97% 11i, R = $O(CH_2)O$, 92% 11j, R = $(CH_2)_3$, 92%
5			11k, 91%
6			11l, 74%
7			11m, 91%
8			11n, 85%

[a] General conditions: **12** (0.3 mmol), benzotriazole (0.25 mmol), KF (2.4 equiv), 18-crown-6 (2.4 equiv), THF (1.0 mL), 25 °C, 3 h. [b] Yields of the isolated products are given.

91% yield. Furthermore, the symmetrical naphthyl, phenanthryl and 4,5-difluoro arynes worked excellently under this conditions furnishing the *N1*-arylated products in good yields (**11l-11n**).

2.6. Conclusion

In conclusion, the use of NaN_3 as the azide component in the [3+2] annulation with arynes allowing the synthesis of *N*-H and *N*-aryl benzotriazoles with high selectivity has been demonstrated. Using CsF as the fluoride source and CH_3CN as solvent, *N*-H benzotriazoles were synthesized. Moreover, using KF as the fluoride source in aprotic medium, the *N*-aryl benzotriazoles are synthesized in good yields and selectivity. Moreover, a method for the exclusive *N*1-arylation of benzotriazole has been presented using arynes as the aryl source. The transition-metal-free methodology presented herein using NaN_3 for the synthesis of *N*-H as well as *N*-aryl benzotriazoles is likely to find potential applications.[21]

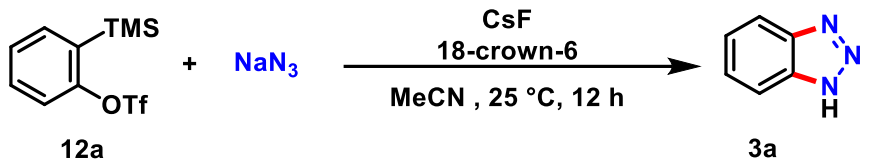
2.7. Experimental Details

2.7.1. General Information

Unless otherwise specified, synthesis of *N*-H benzotriazoles were carried out under an atmosphere of nitrogen in flame-dried reaction vessels with Teflon screw caps at 70 °C and synthesis of *N*-Aryl benzotriazoles were carried out under open flask at room temperature (25 °C). THF was freshly purified by distillation over Na-benzophenone and was transferred under nitrogen. 18-Crown-6 was recrystallized from dry CH_3CN and stored in nitrogen filled glove-box. Dry MeCN was purchased from commercial sources and was stored under argon over 4Å molecular sieves. CsF was dried by heating at 110 °C for 12 h and left to cool under argon. The NaN_3 was purchased from commercial sources and was used without further purification. The 2(trimethylsilyl)phenyl trifluoromethanesulfonate **12a** and the other symmetric and unsymmetrical aryne precursors were synthesized following literature procedure.[22] Analytical thin layer chromatography was performed on TLC Silica gel 60 F254. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system. All compounds

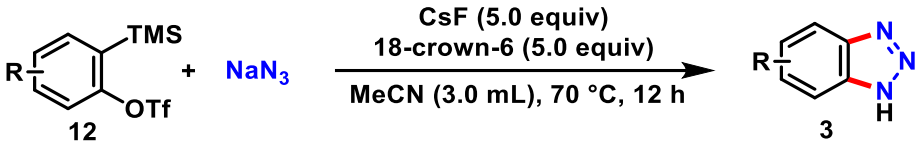
were fully characterized. ^{1}H and ^{13}C NMR spectra were recorded were recorded on Bruker Ultrashield spectrometer in $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $^{\delta}H$ = 7.26 ppm, $^{\delta}C$ = 77.16 ppm and DMSO-d_6: $^{\delta}H$ = 2.50 ppm, $^{\delta}C$ = 39.52 ppm). Infrared (FT-IR) spectra were recorded on a Bruker Alfa FT-IR, ν-max in cm^{-1}. HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument.

2.7.2. General Procedure for the Optimization of the *N*-H benzotriazole



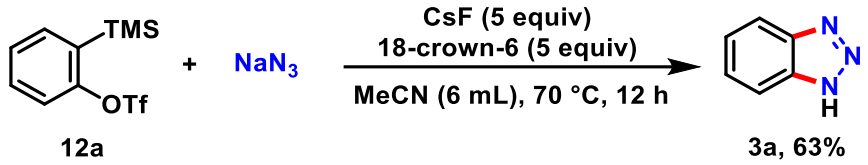
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the CsF and 18-crown-6 in a glove-box. Then NaN_3 was added outside the glove-box under nitrogen atmosphere followed by addition of MeCN. To the stirring solution, aryne precursor **12a** was added and reaction mixture was allowed to stir for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford the *N*-H benzotriazoles.

2.7.3. General Procedure for the Synthesis of *N*-H Benzotriazoles



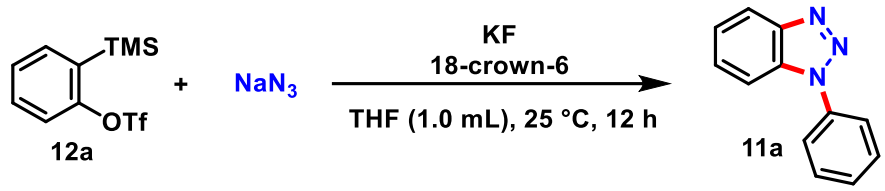
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in a glove-box. Then NaN_3 (0.130 g, 2.0 mmol) was added outside the glove-box under nitrogen atmosphere followed by addition of MeCN (3 mL). To the stirring solution, aryne precursor **12** (0.5 mmol) was added and reaction mixture was allowed to stir at 70 °C for 12 h. After 12 h, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 60/40) on silica gel to afford the corresponding *N*-H benzotriazole derivatives **3** in moderate to good yields.

Procedure for the 1.0 mmol scale reaction for the synthesis of 2a



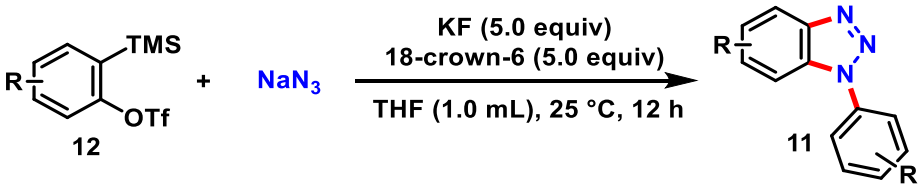
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the CsF (0.760 g, 5.0 mmol) and 18-crown-6 (1.320 g, 5.0 mmol) in a glove-box. Then NaN_3 (0.260 g, 4.0 mmol) was added outside the glove-box under nitrogen atmosphere followed by addition of MeCN (6 mL). To the stirring solution, aryne precursor 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12a** (0.298 g, 1.0 mmol) was added and reaction mixture was allowed to stir at 70 °C for 12 h. After 12 h, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 60/40) on silica gel to afford the 1*H*-benzo[*d*][1,2,3]triazole **3a** in 63% yield (0.075 g).

2.7.4. General Procedure for the Optimization of the *N*-Aryl benzotriazoles



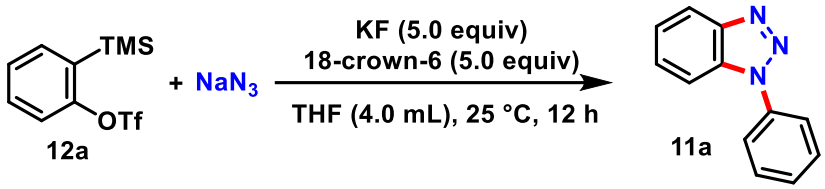
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF and 18-crown-6 in a glove-box. Then NaN_3 (0.25 mmol) was added outside the glove-box under nitrogen atmosphere followed by addition of THF. To the stirring solution, aryne precursor **12a** was added and reaction mixture was allowed to stir at rt for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford the *N*-phenyl benzotriazoles **11a**.

2.7.5. General Procedure for the Synthesis of *N*-Aryl Benzotriazoles



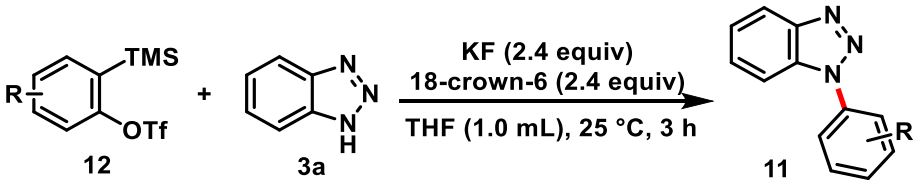
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF (0.73 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in an open atmosphere. Then NaN_3 (0.016g, 0.25 mmol) was added followed by addition of THF (1 mL). To the stirring solution, aryne precursor **12** (0.625 mmol) was added and reaction mixture was allowed to stir at 25 °C for 12 h. After 12 h the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 90/10) on silica gel to afford the corresponding *N*-aryl benzotriazole derivatives **11** in moderate to good yields.

Procedure for the 1.0 mmol scale reaction for the synthesis of 11a



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF (0.292 g, 5.0 mmol) and 18-crown-6 (1.320 g, 5.0 mmol) in an open atmosphere. Then NaN_3 (0.064g, 1.0 mmol) was added followed by addition of THF (4 mL). To the stirring solution, aryne precursor 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12a** (0.746 g, 2.5 mmol) was added and reaction mixture was allowed to stir at 25 °C for 12 h. After 12 h the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 90/10) on silica gel to afford the 1-phenyl-1*H*-benzo[*d*][1,2,3]triazole **11a** in 88 % yield (0.172 g).

2.7.6. Procedure for the Synthesis of *N*-Aryl benzotriazoles from *N*-H Benzotriazoles

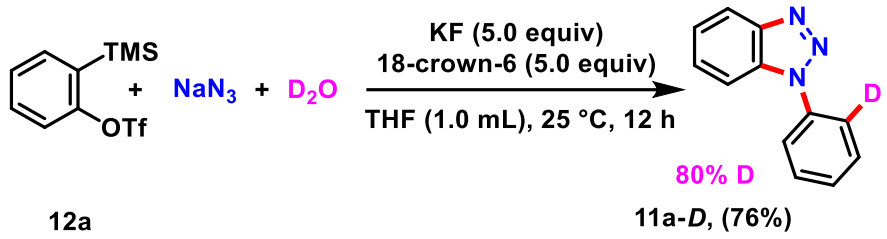


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF (0.035 g, 0.6 mmol) and 18-crown-6 (0.158 g, 0.6 mmol) in a glove-box. Then **3a**

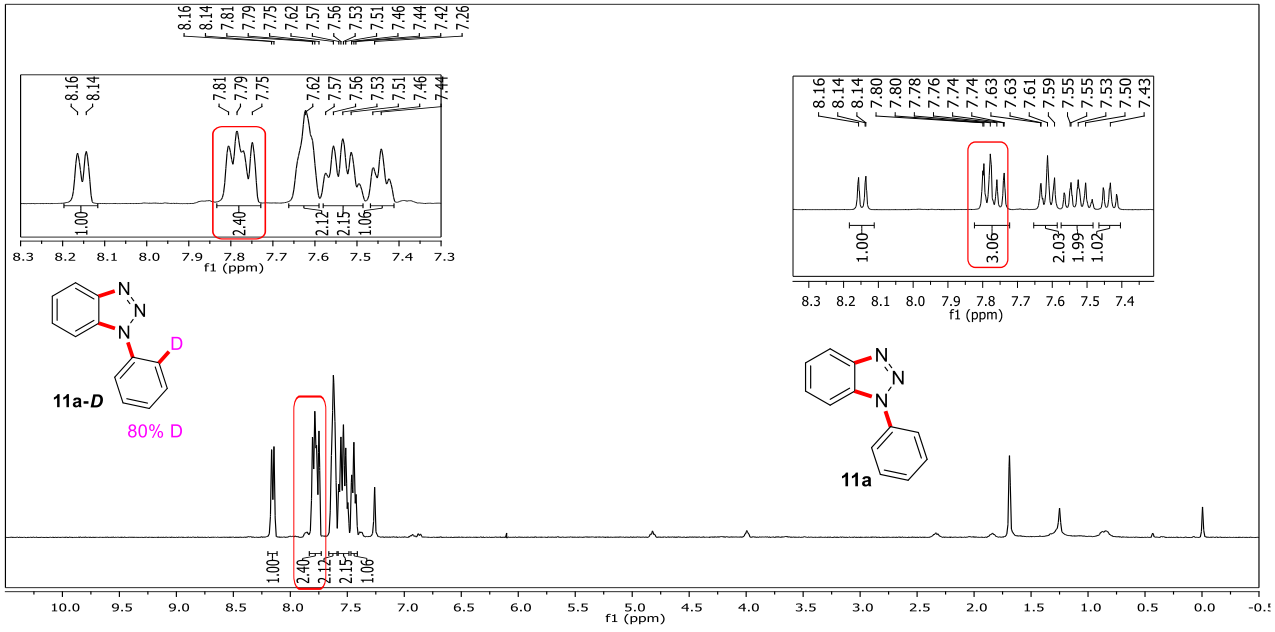
(0.030g, 0.25 mmol) was added outside the glove-box under nitrogen atmosphere followed by addition of THF (1 mL). To the stirring solution, aryne precursor **12** (0.3 mmol) was added and reaction mixture was allowed to stir at rt for 3 h. After 3 h the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether) on silica gel to afford *N*-aryl benzotriazoles derivatives **11** in excellent yields.

2.7.7. Mechanistic Experiment

Deuterium Labeling Experiment



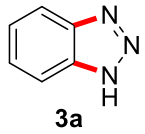
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the KF (0.073 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in a glove-box. Then NaN_3 (0.016g, 0.25 mmol) and D_2O (0.004 g, 4 µL, 0.25 mmol) was added outside the glove-box under nitrogen atmosphere followed by addition of THF (1 mL). To the stirring solution, aryne precursor **12a** (0.186 g, 152 µL, 0.625 mmol) was added and reaction mixture was



allowed to stir at rt for 12 h. After 12 h the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether) on silica gel to afford the **11a-*D*** in 76% yield with 80% D incorporation at the 2-position**.**

2.7.8. Synthesis and Characterization of *N*-H benzotriazoles

1*H*-Benzo[*d*][1,2,3]triazole (3a)

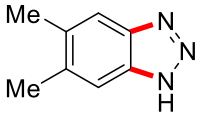


3a

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **12a** (0.149 g, 121 µL, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 1*H*-benzo[*d*][1,2,3]triazole **3a** as a white solid (0.038 g, 64% yield).

***R*f** (Pet. ether /EtOAc = 50/50): 0.32; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 11.54 (bs, 1H), 7.95 (dd, J_1 = 6.2 Hz, J_2 = 3.1 Hz, 2H), 7.44 (dd, J_1 = 6.3 Hz, J_2 = 2.9 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 138.97, 126.28, 115.13. **FTIR (cm^{-1})** 3347, 2757, 1919, 1460, 1204, 873, 774, 603.

5,6-Dimethyl-1*H*-benzo[*d*][1,2,3]triazole (3b)

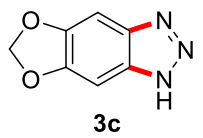


3b

Following the general procedure, treatment of 4,5-dimethyl-2-(trimethylsilyl) phenyl trifluoromethanesulfonate **12b** (0.163 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 60/40) of the crude reaction mixture afforded 5,6-dimethyl-1*H*-benzo[*d*][1,2,3]triazole **(3b)** as a white solid (0.020 g, 27% yield).

***R*f** (Pet. ether /EtOAc = 50/50): 0.36; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 (s, 2H), 2.35 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 137.93, 134.98, 113.88, 20.11. **HRMS (ESI)** calculated $[M+H]^+$ for $C_8H_{10}N_3$: 148.0869, found: 148.0878. **FTIR (cm^{-1})** 3438, 3277, 2383, 2241, 1588, 1206.

1*H*-[1,3]Dioxolo[4',5':4,5]benzo[1,2-*d*][1,2,3]triazole (3c)

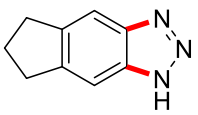


3c

Following the general procedure, treatment of 6-(trimethylsilyl)benzo[*d*] [1,3]dioxol-5-yl trifluoromethanesulfonate **12c** (0.171 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 1*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*][1,2,3]triazole **3c** as a white solid (0.045 g, 55% yield).

***R*f** (Pet. ether /EtOAc = 50/50): 0.29; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 15.38 (bs, 1H), 7.29 (s, 2H), 6.13 (s, 2H). **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 148.72, 146.64, 139.94, 129.64, 102.02, 95.66, 89.43. **HRMS (ESI)** calculated $[M+H]^+$ for $C_7H_6N_3O_2$: 164.0455, found: 164.0460. **FTIR (cm^{-1})** 3519, 3069, 2907, 1686, 1477, 1325, 1195, 771.

1,5,6,7-Tetrahydroindeno[5,6-*d*][1,2,3]triazole (3d)



3d

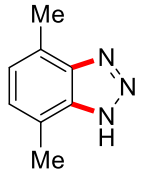
Following the general procedure, treatment of 6-(trimethylsilyl)-2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate **12d** (0.171 g, 0.5 mmol) and NaN_3 (0.170 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 1,5,6,7-tetrahydroindeno[5,6-*d*][1,2,3]triazole **3d** as a white solid (0.041 g, 51% yield).

***R*f** (Pet. ether /EtOAc = 50/50): 0.36; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 15.39 (s, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 2.95 (s, 4H), 2.11-2.01 (m, 2H). **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 144.86, 144.50, 140.78, 132.93, 112.74, 105.16, 31.95, 31.73, 26.31. **HRMS (ESI)** calculated $[M+H]^+$ for $C_9H_{10}N_3$: 160.0869, found: 160.0876. **FTIR (cm^{-1})** 3387, 2913, 2243, 1708, 1430, 1204, 993, 852.

4,7-Dimethyl-1*H*-benzo[*d*][1,2,3]triazole (3e)

Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12e** (0.163 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL)

at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 4,7-dimethyl-1*H*-benzo[*d*][1,2,3]triazole **(3e)** as a white solid (0.030 g, 41% yield).

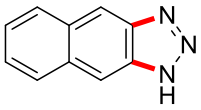


3e

***R*f** (Pet. ether /EtOAc = 50/50): 0.37; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.05 (s, 2H), 2.57 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 125.32 (broad), 16.67. **HRMS (ESI)** calculated $[M+H]^+$ for $C_8H_{10}N_3$: 148.0869, found: 148.0874. **FTIR (cm^{-1})** 3435, 2921, 2562, 1628, 1467, 1213, 1008, 869.

1*H*-Naphtho[2,3-*d*][1,2,3]triazole (3f)

Following the general procedure, treatment of 3-(trimethylsilyl)naphthalen-2-yl trifluoro methanesulfonate **12f** (0.174 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 1*H*-naphtho[2,3-*d*][1,2,3]triazole **(3f)** as a white solid (0.026 g, 31% yield).

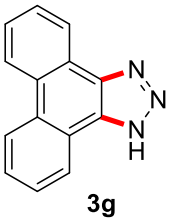


3f

***R*f** (Pet. ether /EtOAc = 50/50): 0.38; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.53 (s, 2H), 8.13-8.11 (m, 2H), 7.49-7.47 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 131.34 (broad), 128.64, 125.29. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{10}H_8N_3$: 170.0713, found: 170.0717. **FTIR (cm^{-1})** 3393, 2382, 2306, 1584, 1217, 849.

1*H*-Phenanthro[9,10-*d*][1,2,3]triazole (3g)

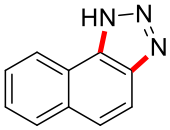
Following the general procedure, treatment of 10-(trimethylsilyl)phenanthren-9-yl trifluoro methanesulfonate **12g** (0.199 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 1*H*-phenanthro[9,10-*d*][1,2,3]triazole **3g** as a white solid (0.057 g, 52% yield).



3g

***R*f** (Pet. ether /EtOAc = 50/50): 0.40; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 8.84 (d, *J* = 7.9 Hz, 2H), 8.51 (d, *J* = 6.8 Hz, 2H), 7.79-7.72 (m, 4H). **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 129.29, 128.10, 127.66, 124.36, 123.00. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{14}H_{10}N_3$: 220.0869, found: 220.0876. **FTIR (cm^{-1})** 3423, 2985, 2373, 1618, 1430, 1194, 985, 751.

1*H*-Naphtho[1,2-*d*][1,2,3]triazole (3h)

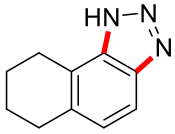


3h

Following the general procedure, treatment of 1-(trimethylsilyl)naphthalen-2-yl trifluoro methanesulfonate **12h** (0.174 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5mmol) and 18-crown-6 (0.660 g, 2.5mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification viasilica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixture afforded 1*H*-naphtho[1,2-*d*][1,2,3]triazole (**3h**) as a white solid (0.036 g, 43% yield).

***R*f** (Pet. ether /EtOAc = 50/50): 0.39; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 8.52 (d, *J* = 7.1 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.92-7.85 (m, 2H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 131.12, 129.04, 128.85, 128.64, 127.58, 126.67, 122.17. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{10}H_8N_3$: 170.0713, found: 170.0719. **FTIR (cm^{-1})** 3044, 2925, 2628, 2509, 1843, 1221, 803, 744.

6,7,8,9-Tetrahydro-1*H*-naphtho[1,2-d][1,2,3]triazole (3i)



3i

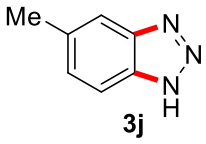
Following the general procedure, treatment of 1-(trimethylsilyl)-5,6,7,8-tetrahydro naphthalen-2-yl trifluoromethanesulfonate **12e** (0.177 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification viasilica gel flash column chromatography (Pet. ether /EtOAc = 50/50) of the crude reaction mixtureafforded6,7,8,9-tetrahydro-1*H*-naphtho[1,2-d][1,2,3]triazole **(3i)** as a white solid (0.037 g, 43% yield).

***R*f**(Pet. ether /EtOAc = 50/50): 0.38; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 2.97 (s, 2H), 2.79 (s, 2H), 1.81-1.80 (m, 4H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 137.35 (broad), 133.41, 127.04, 122.09 (broad), 112.80 (broad), 28.52, 24.38,

22.56, 21.77. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{10}H_{12}N_3$: 174.1026, found: 174.1030. **FTIR (cm^{-1})** 3420, 2922, 2382, 1225, 1115, 1036, 967.

5-methyl-1*H*-benzo[*d*][1,2,3]triazole (3j)

Following the general procedure, 4-methyl-2-(trimethylsilyl)phenyl trifluoro methanesulfonate **12j** (0.156 g,0.5 mmol) and NaN_3 (0.130 g, 2.0mmol) in the presence of CsF (0.380 g, 2.5mmol) and 18-crown-6 (0.660 g, 2.5mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification viasilica gel flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixtureafforded5-methyl-1*H*-benzo[*d*][1,2,3]triazole (**3j**) as a whitesolid(0.034 g, 51% yield).

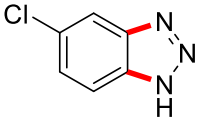


3j

***R*f** (Pet. ether /EtOAc = 50/50): 0.43;**^{1}H NMR (400 MHz, $CDCl_3$)**δ 10.74 (bs, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 2.47 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)**δ138.91, 138.23, 136.99, 128.08, 115.49, 113.08, 21.83.**HRMS (ESI)** calculated $[M+H]^+$ for $C_7H_8N_3$: 134.0713, found: 134.0718.**FTIR (cm^{-1})** 3745, 3164, 2919, 2810, 1629, 1454, 1205, 1014.

5-Chloro-1*H*-benzo[*d*][1,2,3]triazole (3k)

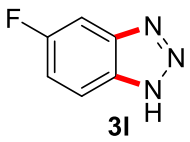
Following the general procedure, treatment of 4-chloro-2-(trimethylsilyl)phenyl trifluoro methanesulfonate **12k** (0.166 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 60/40) of the crude reaction mixture afforded 5-chloro-1*H*-benzo[*d*][1,2,3]triazole **3k** as a white solid (0.038 g, 50% yield).



3k

***R*f** (Pet. ether /EtOAc = 50/50): 0.51; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.03-8.03 (m, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.45 (dd, J_1 = 8.8, J_2 = 1.7 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-d_6)** δ 138.49, 130.27, 125.97, 116.78, 114.09. **HRMS (ESI)** calculated $[M+H]^+$ for $C_6H_5ClN_3$: 154.0167, found: 154.0181. **FTIR (cm^{-1})** 3055, 2920, 2644, 1592, 1496, 1275, 1051, 744.

5-fluoro-1*H*-benzo[*d*][1,2,3]triazole (3l)



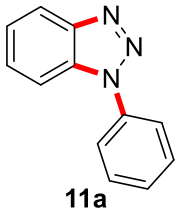
3l

Following the general procedure, treatment of 4-fluoro-2-(trimethylsilyl)phenyl trifluoro methanesulfonate **12l** (0.158 g, 0.5 mmol) and NaN_3 (0.130 g, 2.0 mmol) in the presence of CsF (0.380 g, 2.5 mmol) and 18-crown-6 (0.660 g, 2.5 mmol) in MeCN (3.0 mL) at 70 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 60/40) of the crude reaction mixture afforded 5-chloro-1*H*-benzo[*d*][1,2,3]triazole **3l** as a white solid (0.034 g, 50% yield).

***R*f** (Pet. ether /EtOAc = 50/50): 0.51; **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 15.89 (s, 1H), 8.00 (s, 1H) 7.72 (d, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H). **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 160.39 (d, *J* = 242 Hz), 137.78, 117.72, 114.75 (d, *J* = 27.0 Hz), 99.22. **HRMS (ESI)** calculated $[M+H]^+$ for $C_6H_5FN_3$: 138.0462, found: 138.0469 **FTIR (cm^{-1})** 3079, 2921, 2320, 1595, 1512, 1221, 1099, 773.

2.7.9. Synthesis and Characterization of *N*-Aryl benzotriazoles

1-Phenyl-1*H*-benzo[*d*][1,2,3]triazole (11a)



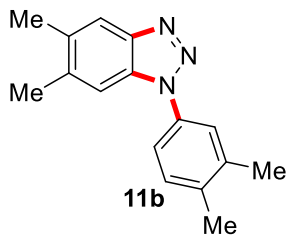
11a

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **12a** (0.186 g, 151 μL, 0.625 mmol) and NaN_3 (0.016 g, 0.025 mmol) in the presence of KF (0.072 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in THF (1.0 mL) at 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-phenyl-1*H*-benzo[*d*][1,2,3]triazole **11a** as a white solid (0.042 g, 86% yield).

***R*f** (Pet. ether /EtOAc = 85/15): 0.49; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.16-8.13 (m, 1H), 7.80-7.74 (m, 3H), 7.63-7.59 (m, 2H), 7.57-7.49 (m, 2H), 7.45-7.41 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 146.51, 136.99, 132.31, 129.90, 128.71, 128.27, 124.43, 122.90, 120.33, 110.39. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{12}H_{10}N_3$: 196.0869, found: 196.0877. **FTIR (cm^{-1})** 3448, 3058, 2332, 1596, 1501, 1277, 1187, 1057.

1-(3,4-Dimethylphenyl)-5,6-dimethyl-1*H*-benzo[*d*][1,2,3]triazole (11b)

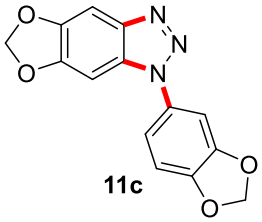
Following the general procedure, treatment of 4,5-dimethyl-2 (trimethylsilyl)phenyl trifluoro methanesulfonate **12b** (0.204 g, 0.625 mmol) and NaN_3 (0.016 g, 0.25 mmol) in the presence of KF (0.072 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in THF (1.0 mL) at 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(3,4-dimethylphenyl)-5,6-dimethyl-1*H*-benzo[*d*][1,2,3]triazole **(11b)** as a white solid (0.046 g, 73% yield).



***R*f** (Pet. ether /EtOAc = 85/15): 0.53; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.83 (s, 1H), 7.52 (s, 1H), 7.45-7.43 (m, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 2.41 (s, 6H), 2.37 (s, 3H), 2.35 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.71, 138.48, 138.45, 137.24, 135.07, 134.06, 131.54, 130.72, 124.07, 120.10, 119.27, 109.99, 21.08, 20.49, 20.04, 19.62. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{16}H_{18}N_3$: 252.1495, found: 252.1500. **FTIR (cm^{-1})** 3443, 2974, 1611, 1505,1063, 887.

1-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*][1,2,3]triazole (11c)

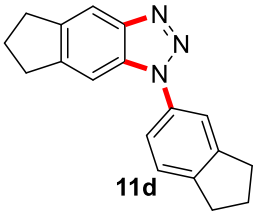
Following the general procedure, treatment of 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **12c** (0.213 g, 0.625 mmol) and NaN_3 (0.016 g, 0.025 mmol) in the presence of KF (0.072 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in THF (1.0 mL) at 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(benzo[*d*][1,3]dioxol-5-yl)-1*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*d*][1,2,3]triazole **11c** as a white solid (0.062 g, 86% yield).



***R*f** (Pet. ether /EtOAc = 85/15): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 (d, *J* = 1.4 Hz, 1H), 7.15 (d, *J* = 1.1 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.09-6.08 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.41, 148.79, 148.14, 147.23, 142.14, 130.98, 129.46, 116.83, 108.78, 105.03, 102.46, 102.23, 97.36, 89.11. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{14}H_{10}N_3O_4$: 284.0666, found: 284.0670. **FTIR (cm^{-1})** 3437, 2919, 2361, 1636, 1472, 1245, 1036, 948.

1-(2,3-Dihydro-1*H*-inden-5-yl)-1,5,6,7-tetrahydroindeno[5,6-*d*][1,2,3]triazole (11d)

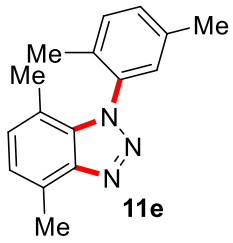
Following the general procedure, treatment of 6-(trimethylsilyl)-2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate **12d** (0.211 g, 0.625 mmol) and NaN_3 (0.016 g, 0.025 mmol) in the presence of KF (0.072 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in THF (1.0 mL) at 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(2,3-dihydro-1*H*-inden-5-yl)-1,5,6,7-tetrahydroindeno[5,6-*d*][1,2,3]triazole **11d** as a white solid (0.063 g, 91% yield).



***R*f** (Pet. ether /EtOAc = 85/15): 0.52; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 (s, 1H), 7.57 (s, 1H), 7.48-7.46 (m, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 3.02 (p, *J* = 8.4 Hz, 8H), 2.17 (p, *J* = 7.4 Hz, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 146.52, 146.50, 146.22, 144.93, 142.12, 135.48, 132.50, 125.30, 121.06, 119.34, 114.29, 105.13, 33.07, 32.95, 32.69, 32.34, 26.80, 25.75. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{18}H_{18}N_3$: 276.1495, found: 276.1503. **FTIR (cm^{-1})** 2955, 1615, 1499, 1433, 1300, 1244, 1054, 891.

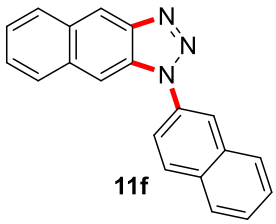
1-(2,5-Dimethylphenyl)-4,7-dimethyl-1*H*-benzo[*d*][1,2,3]triazole (11e)

Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12e** (0.204 g, 0.625 mmol) and NaN_3 (0.016 g, 0.25 mmol) in the presence of KF (0.072 g, 1.25mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in THF (1.0 mL) at 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(2,5-dimethylphenyl)-4,7-dimethyl-1*H*-benzo[*d*][1,2,3]triazole **(11e)** as a white solid (0.058 g, 92% yield).



***R*f** (Pet. ether /EtOAc = 85/15): 0.55; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33-7.24 (m, 2H), 7.20 (s, 1H), 7.13-7.01 (m, 2H), 2.84 (s, 3H), 2.41 (s, 3H), 2.02 (s, 3H), 1.94 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.68, 136.69, 136.55, 133.39, 133.16, 131.19, 130.57, 128.93, 128.84, 128.35, 124.07, 118.43, 20.86, 17.03, 16.91, 16.65. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{16}H_{18}N_3$: 252.1495, found: 252.1501. **FTIR (cm^{-1})** 3444, 2921, 1516, 1455, 1248, 1039.

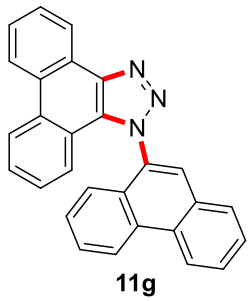
1-(Naphthalen-2-yl)-1*H*-naphtho[2,3-*d*][1,2,3]triazole (11f)



Following the general procedure, treatment of 3-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **12f** (0.218 g, 0.625 mmol) and NaN_3 (0.016 g, 0.25 mmol) in the presence of KF (0.072 g, 1.25mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in THF (1.0 mL) at 25 °C for 12 h followed by purification viasilica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(naphthalen-2-yl)-1*H*-naphtho[2,3-*d*][1,2,3]triazole **(11f)** as a yellow solid (0.045 g, 62% yield).

***R*f** (Pet. ether /EtOAc = 85/15): 0.47;**^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.72 (s, 1H), 8.31-8.30 (m, 1H), 8.27 (s, 1H), 8.12-8.08 (m, 2H), 8.04 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 1H), 8.01-7.95 (m, 3H), 7.64-7.57 (m, 2H), 7.55-7.51 (m, 1H), 7.50-7.46 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.87, 134.94, 133.60, 132.75, 130.92, 130.90, 130.23, 129.54, 128.32, 128.22, 128.12, 127.46, 127.08, 127.00, 125.15, 121.07, 120.32, 118.57, 106.42. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{20}H_{14}N_3$: 296.1182, found: 296.1187. **FTIR (cm^{-1})** 3443, 3054, 1510, 1399, 1058, 855.

1-(Phenanthren-9-yl)-1*H*-phenanthro[9,10-*d*][1,2,3]triazole (11g)



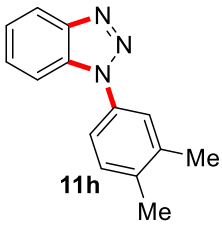
Following the general procedure, treatment of 10-(trimethylsilyl)phenanthren-9-yl trifluoromethanesulfonate **12g** (0.249 g, 0.625 mmol) and NaN_3 (0.016 g, 0.025 mmol) in the presence of KF (0.072 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in THF (1.0 mL) at 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(phenanthren-9-yl)-1*H*-phenanthro[9,10-*d*][1,2,3]triazole **11g** as a white solid (0.093 g, 94% yield).

***R*f** (Pet. ether /EtOAc = 85/15): 0.53; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.02 (d, *J* = 7.8 Hz, 1H), 8.83 (d, *J* = 8.3 Hz, 2H), 8.67 (t, *J* = 7.8 Hz, 2H), 8.12 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 7.5 Hz, 2H), 7.76-7.69 (m, 3H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.16 – 7.09 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** 13C NMR (101 MHz, CDCl3) δ 141.40, 133.19, 131.35, 131.28, 131.17, 130.69, 130.51, 129.70, 129.19,

128.75, 128.52, 128.39, 128.17, 128.07, 127.94, 127.74, 127.37, 127.33, 127.17, 125.10, 124.20, 123.55, 123.35, 123.33, 123.26, 123.08, 120.11. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{18}N_3$: 396.1495, found: 396.1502. **FTIR (cm^{-1})** 3456, 3295, 3065, 2922, 2554, 2364, 1454, 1134.

1-(3,4-Dimethylphenyl)-1*H*-benzo[*d*][1,2,3]triazole (11h)

Following the general procedure, 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoro methanesulfonate **12h** (0.098 g, 0.3 mmol) and 1*H*-benzo[*d*][1,2,3]triazole (0.030 g, 0.025 mmol) in the presence of KF (0.035 g, 0.6mmol) and 18-crown-6 (0.158 g, 0.6mmol) in THF (1.0 mL) at 25 °C for 3h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(3,4-dimethylphenyl)-1*H*-benzo[*d*][1,2,3]triazole **11h** as a white solid (0.053 g, 97% yield).

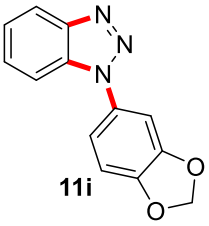


11h

***R*$_f$** (Pet. ether /EtOAc = 85/15): 0.50; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.54-7.45 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 146.50, 138.59, 137.58, 134.83, 132.54, 130.82, 128.07, 124.30, 124.20, 120.27, 110.57, 20.02, 19.62. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{14}H_{14}N_3$: 224.1182, found: 224.1189. **FTIR (cm^{-1})** 3064, 2920, 2858, 1611, 1508, 1453, 1279, 1064.

1-(Benzo[*d*][1,3]dioxol-5-yl)-1*H*-benzo[*d*][1,2,3]triazole (11i)

Following the general procedure, treatmentof 6-(trimethylsilyl)benzo[d] [1,3]dioxol-5-yl trifluoromethanesulfonate **12i** (0.103 g,0.3 mmol) and 1*H*-benzo[*d*][1,2,3]triazole (0.030 g, 0.025 mmol) in the presence of KF (0.035 g, 0.6mmol) and 18-crown-6 (0.158 g, 0.6mmol) in THF (1.0 mL) at 25 °C for 3h followed by purification viasilica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixtureafforded1-(benzo[*d*][1,3]dioxol-5-yl)-1*H*-benzo[*d*][1,2,3]triazole **11i** as a yellow solid (0.055 g, 92% yield).

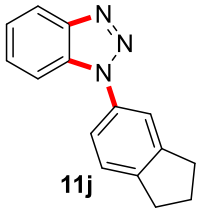


11i

***R*f**(Pet. ether /EtOAc = 85/15): 0.51;**^{1}H NMR (400 MHz, CDCl$_3$)**δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.54-7.50 (m, 1H),7.43-7.39 (m, 1H), 7.22-7.18 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.10 (s,2H).**^{13}C NMR (100 MHz, CDCl$_3$)**δ148.82, 148.13, 146.41, 132.66, 131.09, 128.26, 124.44, 120.36, 116.84, 110.36, 108.81, 105.02, 102.23. **HRMS (ESI)**calculated $[M+H]^+$ for $C_{13}H_{10}N_3O_2$: 240.0768, found: 240.0774. **FTIR (cm^{-1})** 3063, 2905, 2328, 1504, 1245, 1035, 931.

1-(2,3-Dihydro-1*H*-inden-5-yl)-1*H*-benzo[*d*][1,2,3]triazole (11j)

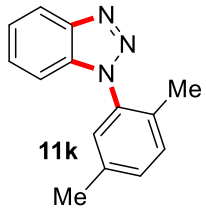
Following the general procedure, treatment of 6-(trimethylsilyl)-2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate **12j** (0.102 g, 0.3 mmol) and 1*H*-benzo[*d*][1,2,3]triazole (0.030 g, 0.25 mmol) in the presence of KF (0.035 g, 0.6 mmol) and 18-crown-6 (0.158 g, 0.6 mmol) in THF (1.0 mL) at 25 °C for 3h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(2,3-dihydro-1*H*-inden-5-yl)-1*H*-benzo[*d*][1,2,3]triazole **11j** as a white solid (0.054 g, 92% yield).



***R*f** (Pet. ether /EtOAc = 85/15): 0.52; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.59 (s, 1H), 7.53-7.47 (m, 2H), 7.42-7.38 (m, 2H), 3.01 (q, *J* = 7.7 Hz, 4H), 2.17 (p, *J* = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 146.48, 146.34, 145.24, 135.26, 132.62, 128.04, 125.40, 124.28, 121.09, 120.25, 119.37, 110.58, 33.07, 32.71, 25.73. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{15}H_{14}N_3$: 236.1182, found: 236.1186. **FTIR (cm^{-1})** 3064, 2923, 2324, 1903, 1611, 1495, 1282, 1071.

1-(2,5-Dimethylphenyl)-1*H*-benzo[*d*][1,2,3]triazole (11k)

Following the general procedure, treatment of 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12k** (0.098 g, 0.3 mmol) and 1*H*-benzo[*d*][1,2,3]triazole (0.030 g, 0.25 mmol) in the presence of KF (0.035 g, 0.6mmol) and 18-crown-6 (0.158 g, 0.6mmol) in THF (1.0 mL) at 25 °C for 3h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction

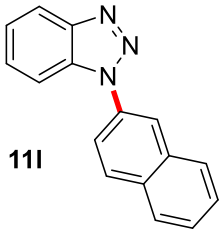


mixtureafforded1-(2,5-dimethylphenyl)-1*H*-benzo[*d*][1,2,3]triazole **11k** as a yellow oil (0.051 g, 91% yield).

***R*f**(Pet. ether /EtOAc = 85/15): 0.50;**^{1}H NMR (400 MHz, CDCl$_3$)**δ 8.13 (dd, J_1 = 8.4 Hz,J_2 = 0.6 Hz, 1H), 7.50-7.46 (m, 1H), 7.42-7.38 (m, 1H), 7.34-7.26 (m, 3H),7.19 (s, 1H), 2.39 (s, 3H), .06 (s, 3H).**^{13}C NMR (100 MHz, CDCl$_3$)**δ145.68, 137.05, 135.07, 133.98, 132.02, 131.49, 130.88, 128.00, 127.52, 124.14, 120.11, 110.29, 20.85, 17.37.**HRMS (ESI)**calculated $[M+H]^+$ for $C_{14}H_{14}N_3$: 224.1182, found: 224.1188.**FTIR (cm^{-1})** 3059, 2922, 2861, 1615, 1512, 1274, 1067.

1-(Naphthalen-2-yl)-1*H*-benzo[*d*][1,2,3]triazole (11l)

Following the general procedure, treatment of 3-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **12f** (0.104 g, 0.3 mmol) and 1*H*-benzo[*d*][1,2,3]triazole (0.030 g, 0.25 mmol) in the presence of KF (0.035 g, 0.6mmol) and 18-crown-6 (0.158 g, 0.6mmol) in THF (1.0 mL) at 25 °C for 3h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(naphthalen-2-yl)-1*H*-benzo[*d*][1,2,3]triazole **11l** as pale yellow oil (0.046 g, 74% yield).



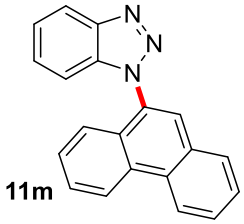
11l

***R*f** (Pet. ether /EtOAc = 85/15): 0.43; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.23-8.21 (m, 1H), 8.19-8.17 (m, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.97-7.91 (m, 3H), 7.84-7.82 (m, 1H), 7.63-7.55 (m, 3H), 7.48-7.42 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)** δ 146.7, 134.5, 133.5, 132.93, 132.6, 130.2, 128.5, 128.3, 128.1, 127.5, 127.2, 124.6, 121.2, 121.0, 120.5, 110.6. **HRMS (ESI)**calculated $[M+H]^+$ for $C_{16}H_{12}N_3$: 246.1026, found: 246.1032. **FTIR (cm^{-1})** 3059, 2923, 2853, 1629, 1593, 1361, 1205, 744.

1-(Phenanthren-9-yl)-1*H*-benzo[*d*][1,2,3]triazole (11m)

Following the general procedure, treatment of 10-(trimethylsilyl)phenanthren-9-yl trifluoromethanesulfonate **12g** (0.120 g, 0.3 mmol) and 1*H*-benzo[*d*][1,2,3]triazole (0.030 g, 0.25 mmol) in the presence of KF (0.035 g, 0.6mmol) and 18-crown-6 (0.158 g, 0.6mmol) in THF (1.0 mL) at 25 °C for 3h followed by purification via silica gel flash column

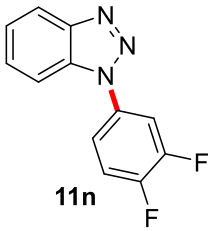
chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(phenanthren-9-yl)-1*H*-benzo[*d*][1,2,3]triazole **11m** as colorless solid (0.067 g, 91% yield).



***R*f** (Pet. ether /EtOAc = 85/15): 0.51; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.83-8.77 (m, 2H), 8.26-8.23 (m, 1H), 7.96-7.94 (m, 2H), 7.81-7.67 (m, 3H), 7.55-7.40 (m, 4H), 7.35-7.33 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.9, 135.0, 131.5, 131.5, 131.0, 130.8, 129.4, 128.4, 128.31, 128.1, 128.0, 127.7, 127.7, 126.1, 124.5, 123.6, 123.3, 123.0, 120.3, 110.5. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{20}H_{14}N_3$: 296.1182, found: 296.1189. **FTIR (cm^{-1})** 2922, 2851, 1605, 1453, 1063, 753.

1-(3,4-Difluorophenyl)-1*H*-benzo[*d*][1,2,3]triazole (11n)

Following the general procedure, treatment of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoro methanesulfonate **12m** (0.100 g, 0.3 mmol) and 1*H*-benzo[*d*][1,2,3]triazole (0.030 g, 0.25 mmol) in the presence of KF (0.035 g, 0.6mmol) and 18-crown-6 (0.158 g, 0.6mmol) in THF (1.0 mL) at 25 °C for 3h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded 1-(3,4-difluorophenyl)-1*H*-benzo[*d*][1,2,3]triazole **11n** as colorless solid (0.049 g, 85% yield).

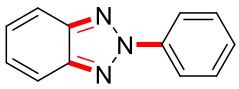


***R*f** (Pet. ether /EtOAc = 85/15): 0.31; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.73-7.66 (m, 2H), 7.61-7.55 (m, 2H), 7.49-7.42 (m, 2H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 150.9 (dd, J_1 = 251.6 Hz, J_2 = 14.1 Hz), 150.3 (dd, J_1 = 250.6 Hz, J_2 = 12.5 Hz), 146.6, 133.4 (dd, J_1 = 8.1 Hz, J_2 = 3.6 Hz), 132.2, 128.9, 124.9, 120.7, 118.9 (dd, J_1 = 6.6 Hz, J_2 = 3.8 Hz), 118.6 (dd, J_1 = 18.7 Hz, J_2 = 1.1 Hz), 112.8 (d, *J* = 21.1 Hz), 110.0. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{12}H_8F_2N_3$: 232.0681, found: 232.0688. **FTIR (cm^{-1})** 2960, 2920, 2329, 1649, 1524, 1458, 1377, 740.

2-Phenyl-2*H*-benzo[*d*][1,2,3]triazole (11a')

Following the general procedure, treatment of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **12a** (0.186 g, 151 μL, 0.625 mmol) and NaN_3 (0.016 g, 0.025 mmol) in the presence of KF (0.072 g, 1.25 mmol) and 18-crown-6 (0.330 g, 1.25 mmol) in

THF (1.0 mL) at 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-phenyl-2*H*-benzo[*d*][1,2,3]triazole **11a'** as a white solid (0.002 g, 4% yield).

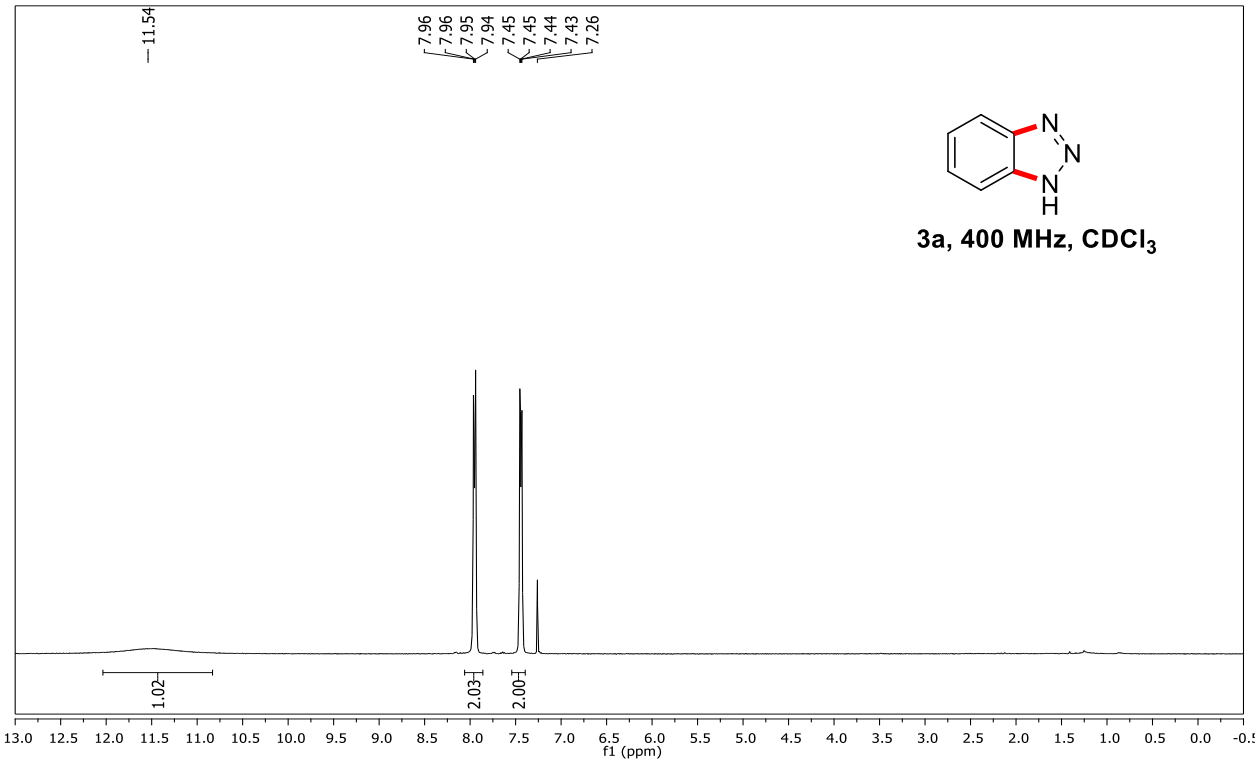


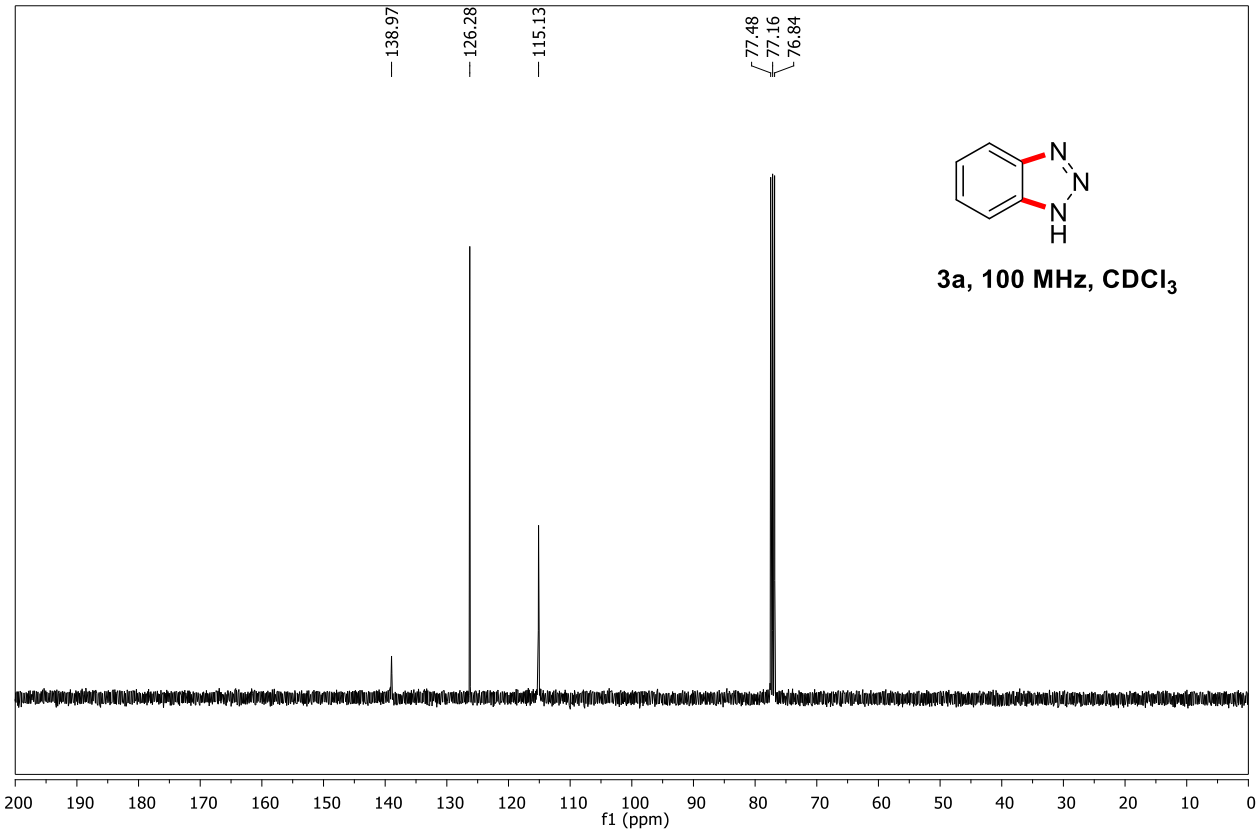
11a'

***R*f** (Pet. ether /EtOAc = 85/15): 0.63; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.36 (d, *J* = 7.7 Hz, 2H), 7.95-7.93 (m, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.47-7.42 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.18, 129.59, 129.14, 127.34, 120.79, 118.54. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{12}H_{10}N_3$: 196.0869, found: 196.0876. **FTIR (cm^{-1})** 3584, 3067, 2924, 2574, 1952, 1595, 1494, 1289.

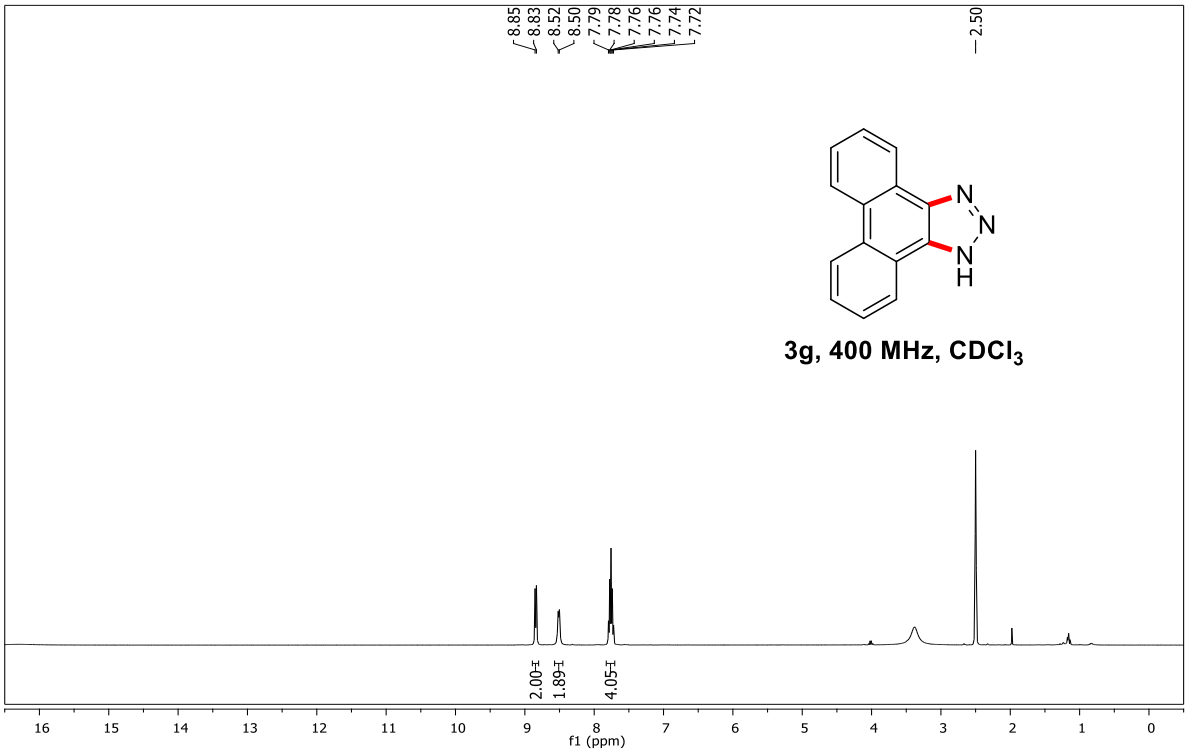
2.7.10. ^{1}H and ^{13}C NMR Spectra of Selected Compounds

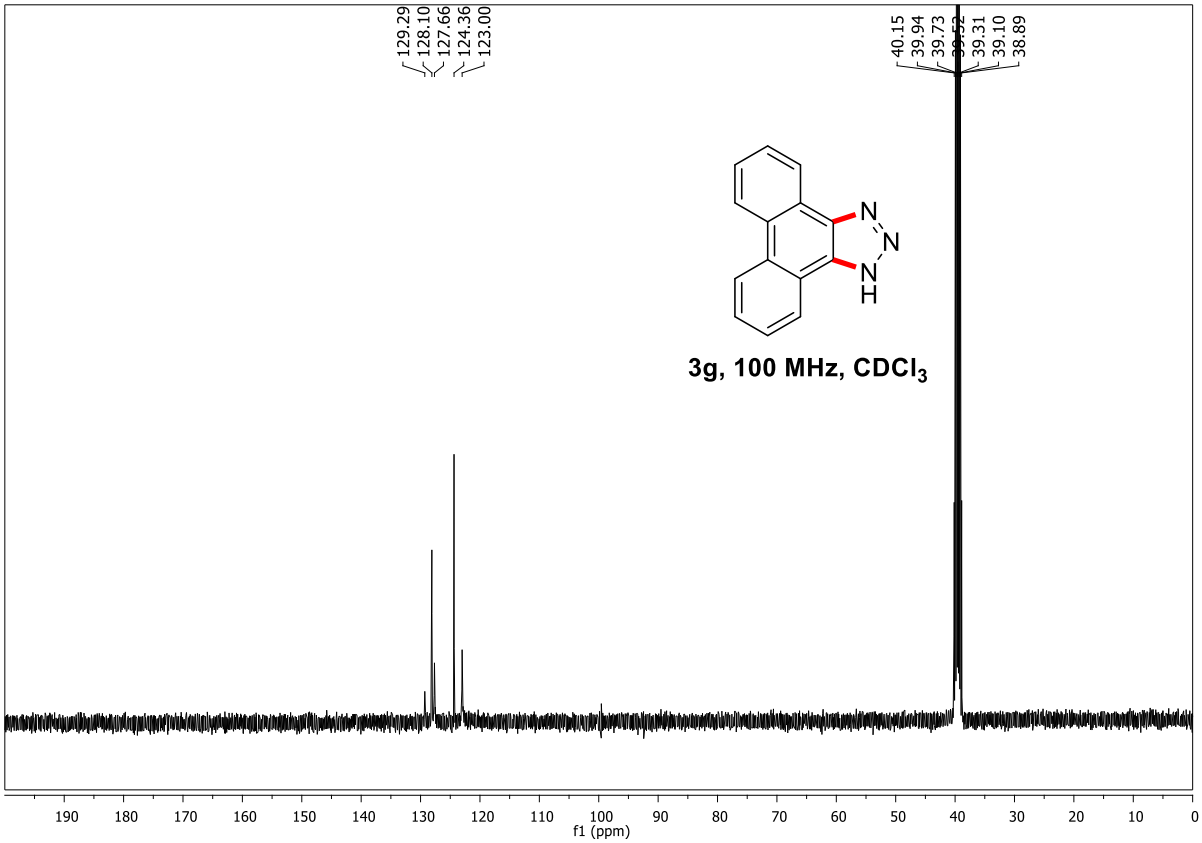
1*H*-Benzo[*d*][1,2,3]triazole (3a)



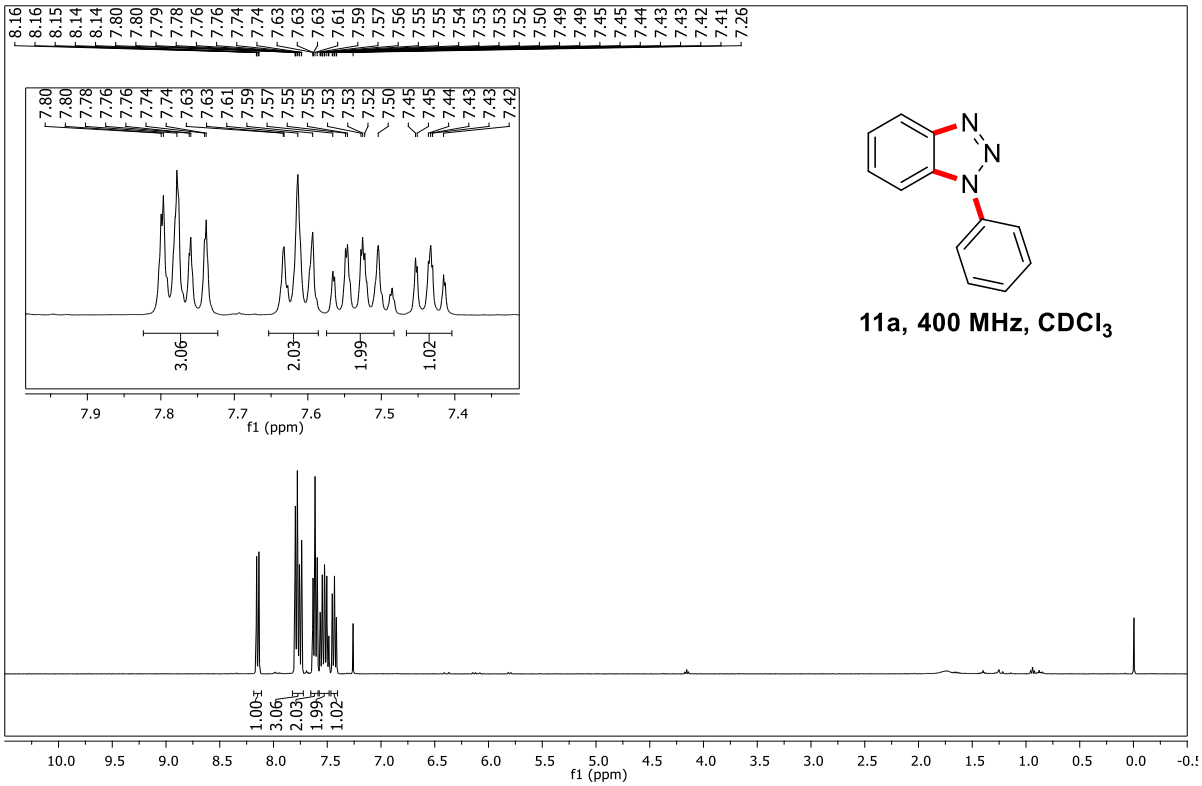


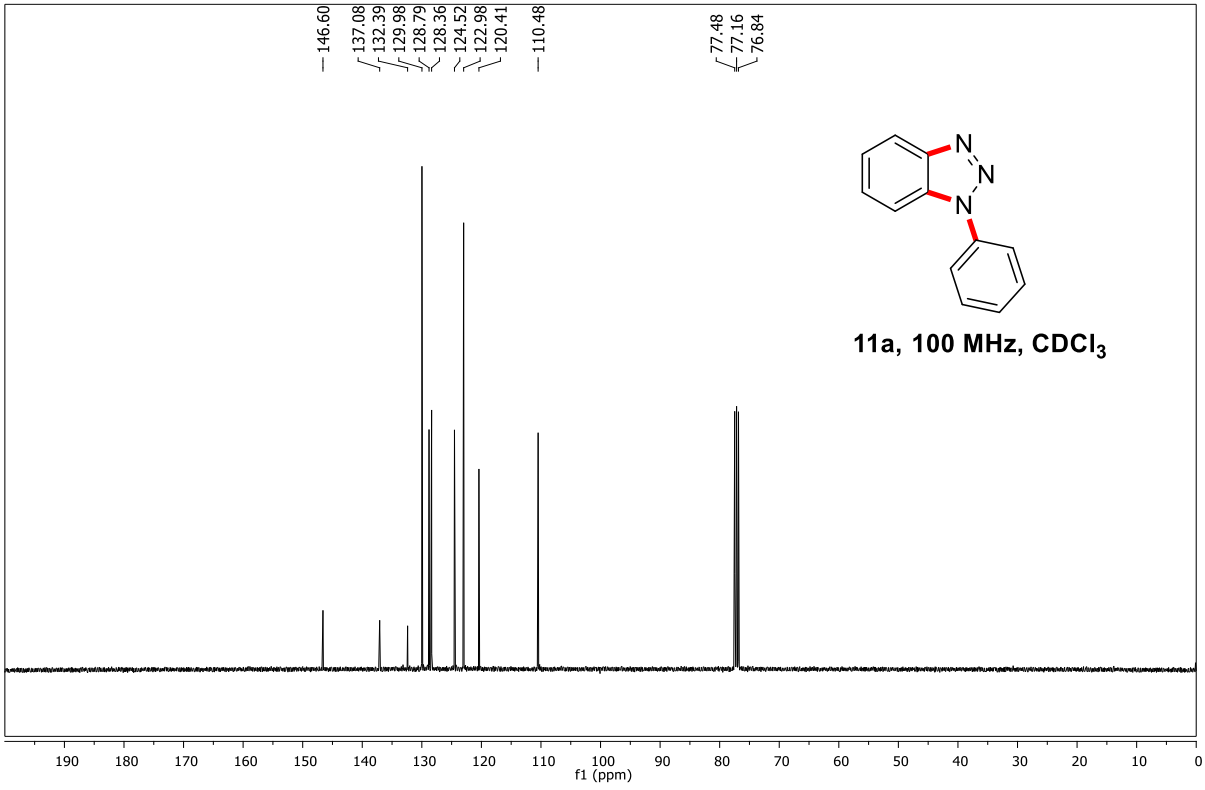
1*H*-Phenanthro[9,10-*d*][1,2,3]triazole (3g)



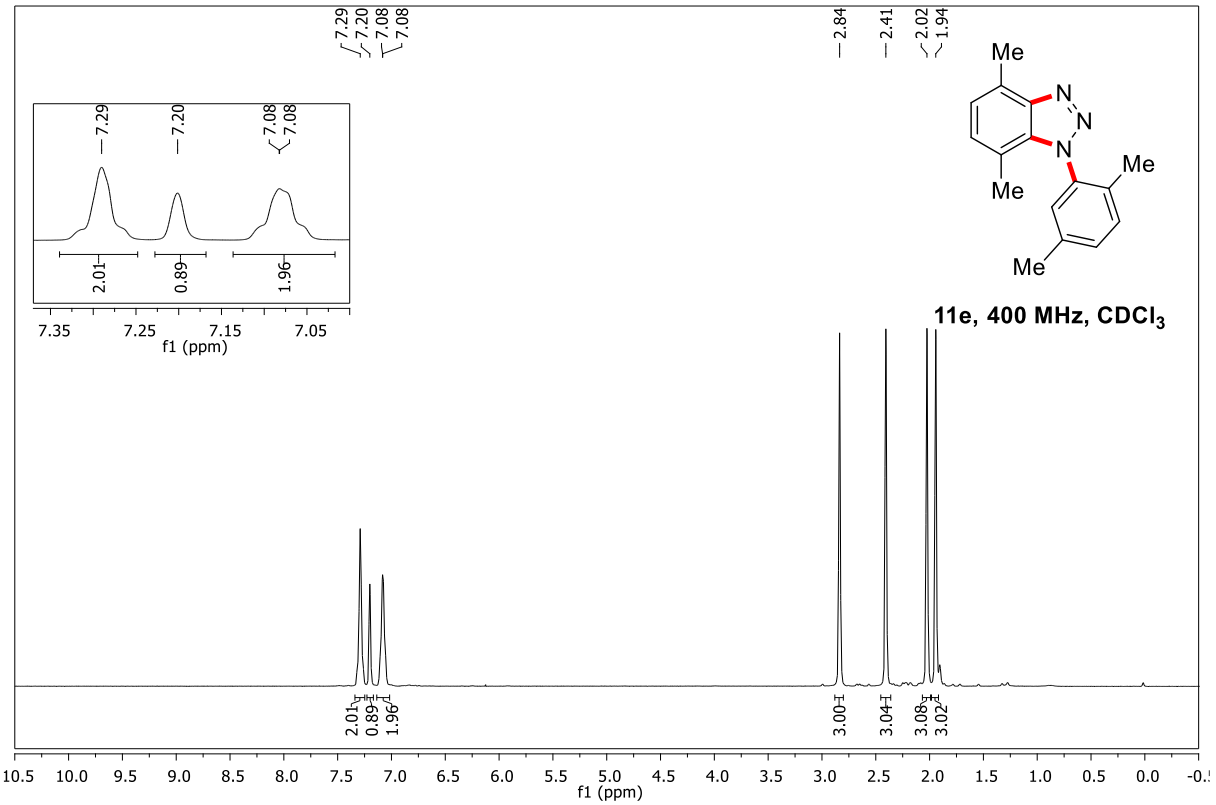


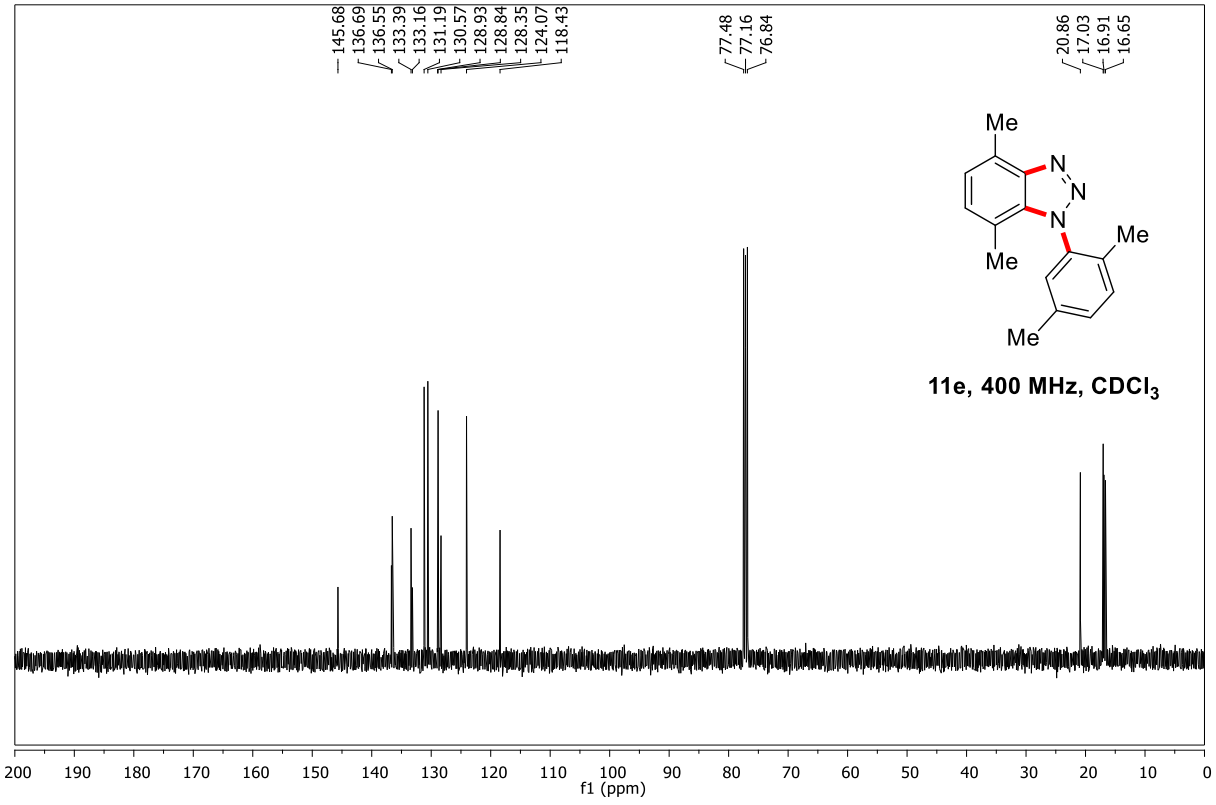
1-Phenyl-1*H*-benzo[*d*][1,2,3]triazole (11a)





1-(2,5-Dimethylphenyl)-4,7-dimethyl-1*H*-benzo[*d*][1,2,3]triazole (11e)





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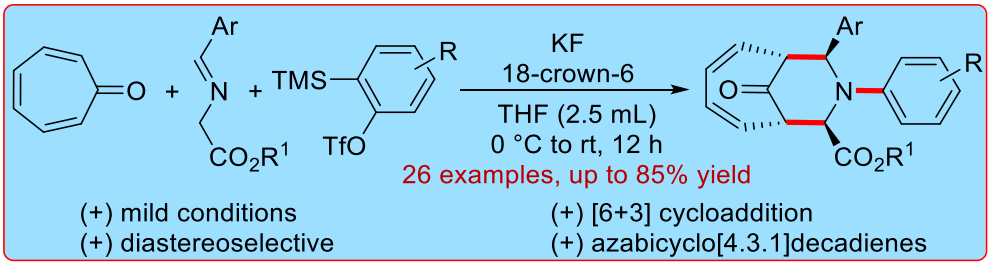
Chapter 3

Three-Component, Diastereoselective [6+3] Annulation of Tropone, Imino Esters and Arynes

A transition-metal-free, three-component and diastereoselective [6+3] annulation reaction employing tropone, imino esters and arynes allowing the synthesis of bridged azabicyclo[4.3.1]decadienes is demonstrated in this Chapter. The key nitrogen ylides for the [6+3] annulation was generated by the addition of imino esters to the arynes followed by a proton transfer. The nitrogen ylides undergo a regioselective addition to tropone to furnish the desired products in moderate to good yields with good functional group tolerance under mild conditions.

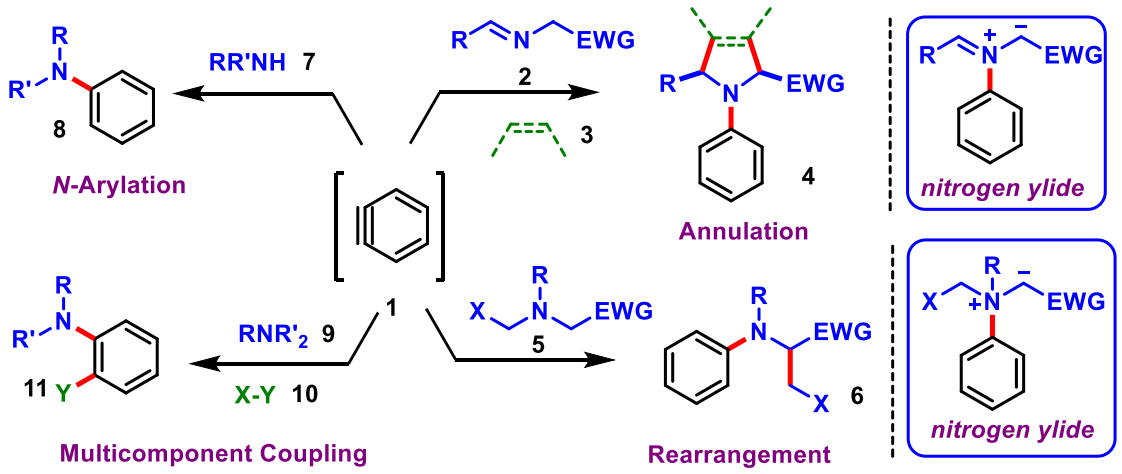


Org. Lett. **2021,** *23*, 7456.

3.1. Introduction

Arynes possess high electrophilicity, making them attractive to synthetic chemists for constructing complex and diverse 1,2-disubstituted arenes.[1] The strained carbon-carbon triple bond in arynes has been utilized in various reactions, such as pericyclic reactions, insertion reactions, multicomponent couplings, and molecular rearrangements.[2] Diverse nucleophiles can add to arynes, forging carbon-carbon or carbon-heteroatom bonds. The addition of nitrogen nucleophiles to arynes is a convenient method for carbon-nitrogen bond formation. Direct addition of nitrogen nucleophiles to arynes results in the synthesis of *N*-arylated products in high regioselectivity. Larock group has extensively employed this chemistry for the *N*-arylation of a diverse range of amines and sulfonamides **7**.[3] Biju group also developed a transition-metal-free monoarylation method for tertiary aromatic amines.[4] Furthermore, if the nitrogen nucleophiles bear an electron-withdrawing group at the appropriate position, their addition to arynes can lead to the formation of highly reactive nitrogen ylides.[5] This nitrogen ylide chemistry has been efficiently utilized for highly decorated heterocycle **4** synthesis when another dipole **3** is present or to produce the rearranged products **6** (Scheme 3.1). It is worth noting that in the absence of a proton source, interception of the aryl anion produced by the addition of a nitrogen nucleophile with another electrophile **10** can lead to the formation of a multicomponent coupling product **11**.[6] Despite the widespread use of aryne-triggered nitrogen ylide in various heterocycle syntheses, this chemistry has received limited attention for higher-order annulation reactions.

Scheme 3.1. Representative Examples of Nitrogen Nucleophiles Addition to Arynes

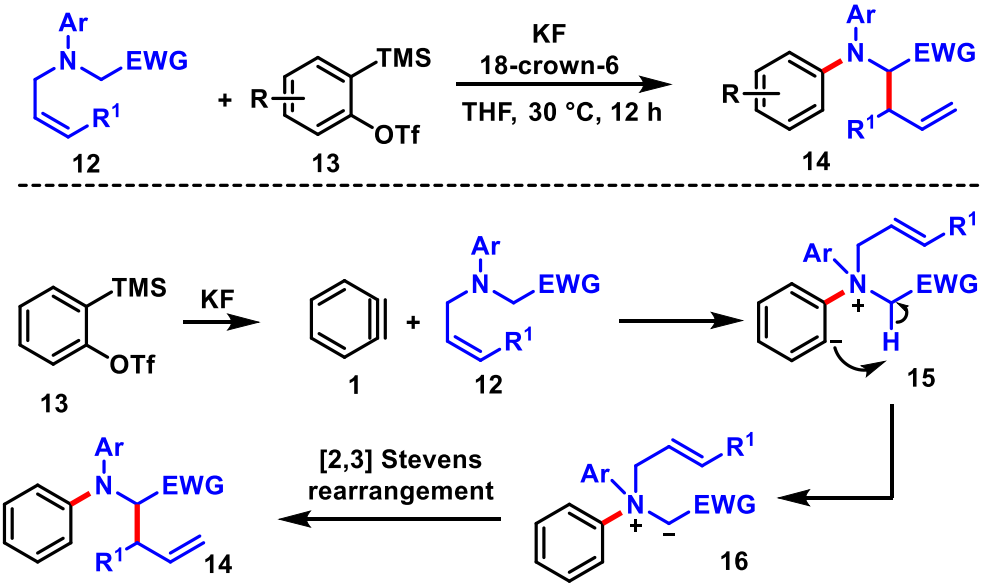


3.2. Reaction of Nitrogen Ylides with Arynes

3.2.1. Molecular Rearrangement Involving Nitrogen Ylides

The molecular rearrangement reactions of nitrogen ylides are highly efficient, and there are several well-known name reactions within the context of aryne-triggered nitrogen ylide chemistry. For instance, Tian and Biju research group independently demonstrated a mild and transition metal-free method for producing homoallylic amines **14** in good to moderate yield using the Stevens rearrangement of tertiary allylic amines **12** (Scheme 3.2).[7, 8] The reaction begins with the generation of 1,3-dipolar intermediate **15** through the addition of a tertiary allylic amine to an aryne generated in situ. Afterward, crucial nitrogen ylide intermediate **16** was formed through intramolecular proton transfer from intermediate **15**. The ylide **16** afforded the homoallylic amines **14** via [2,3] Stevens rearrangement.

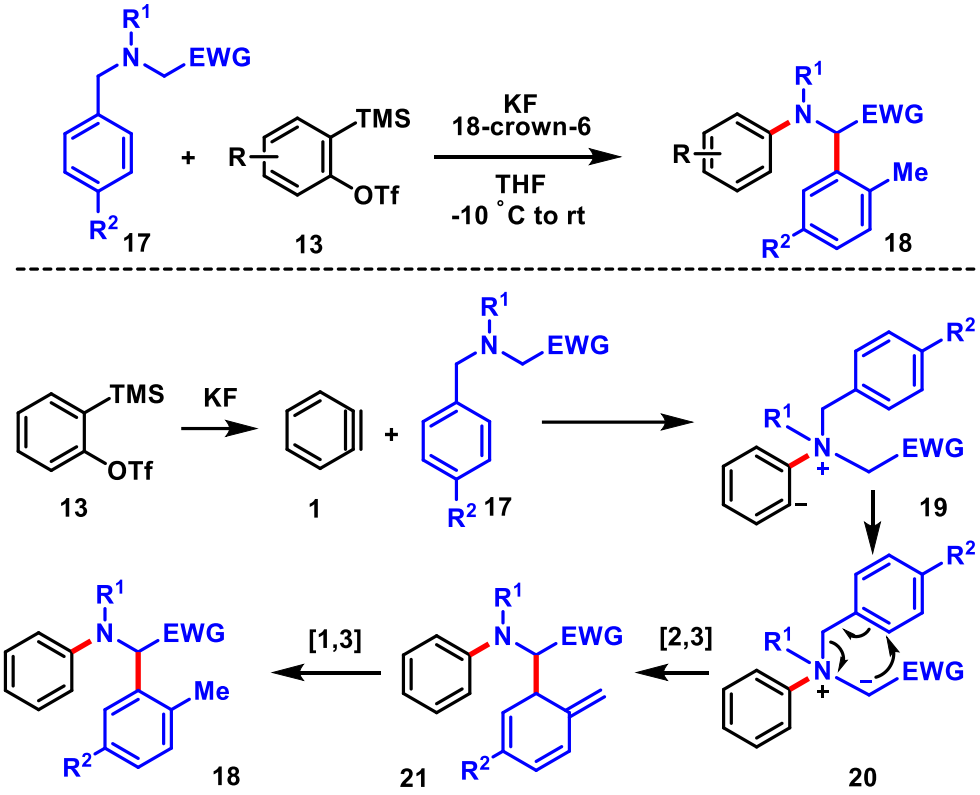
Scheme 3.2. [2,3]-Stevens Rearrangement of Tertiary Allylic Amines Using Arynes



In 2019, Biju and co-workers developed a method for constructing α-aryl tertiary amines **18** using the Sommelet-Hauser rearrangement of tertiary benzylic amines **17** possessing an electron-deficient group. Typically, the conventional Sommelet-Hauser rearrangement requires a strong base for the reaction, but the aryne pathway occurs under mild reaction conditions without the need of a base. The reaction begins with the formation of a 1,3-dipolar intermediate **19**, generated by the nucleophilic addition of an allylic tertiary amine **17** to the aryne **1** produced from the aryne precursor **13**. The key nitrogen ylide

intermediate **20** is formed through intramolecular proton transfer, which undergoes a [2,3] sigmatropic rearrangement to form the dearomatized intermediate **21**, followed by a [1,3]-H transfer to produce the desired aromatized product **18** (Scheme 3.3).[9]

Scheme 3.3. The Aryne Sommelet-Hauser Rearrangement

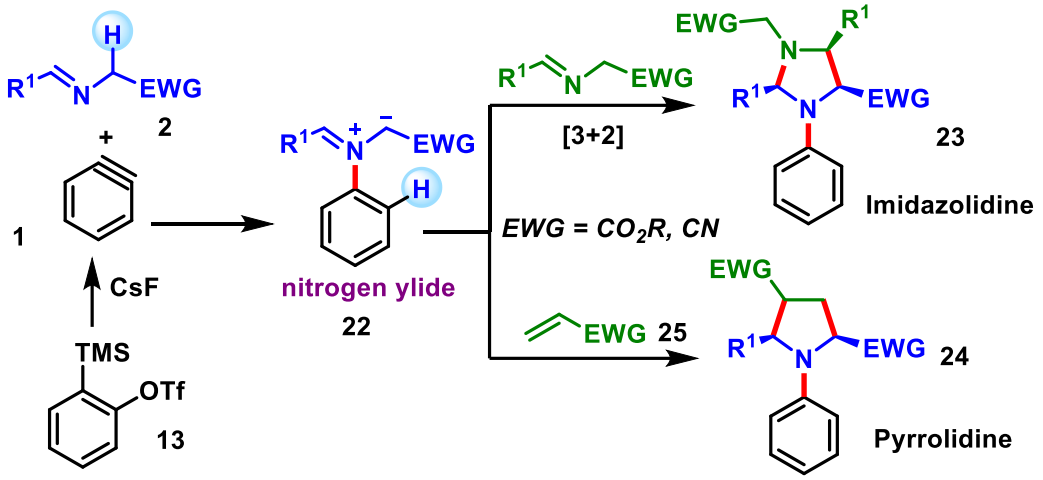


3.2.2. Three-Component Coupling Involving Arynes via Nitrogen Ylides

In 2015, Hwu and co-workers reported a protocol for synthesizing imidazolidines and pyrrolidines with high stereoselectivity using a 'single-flask' approach (Scheme 3.4).[10] The method involved three steps: First, an arylated Schiff base was generated by adding aryne. Second, an intramolecular proton transfer occurred from the methylene position to the anionic aryne ring. Third, the resulting ylide **22** reacted with either a second equivalent of the same Schiff base **2** in situ or an electron-deficient alkene **25** through a (3+2) cycloaddition. These sequential tandem 1,2-addition/ (3+2) cycloaddition reactions facilitated the formation of the desired heterocycles.

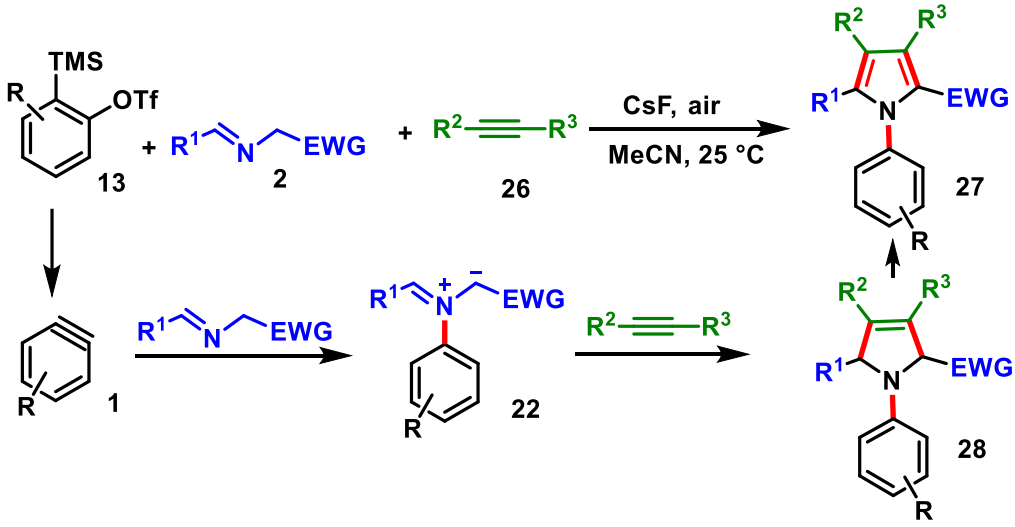
The same group also showcased the generation of polysubstituted pyrroles **27** by intercepting the in situ nitrogen ylides **22** with alkynes **26** (as shown in Scheme 3.5).[11] This reaction involved five consecutive steps in a single flask, including the formation of aryne

Scheme 3.4. Imidazolidines and Pyrrolidines Synthesis via Three Component Aryne Triggered Nitrogen Ylide



through 1,2-elimination, their alkylation by Schiff bases through 1,2-addition, 1,4-intramolecular proton transfer, Hüisgen 1,3-dipolar cycloaddition, and dehydrogenative aromatization. This approach was utilized to synthesize the natural product lamellarin R.

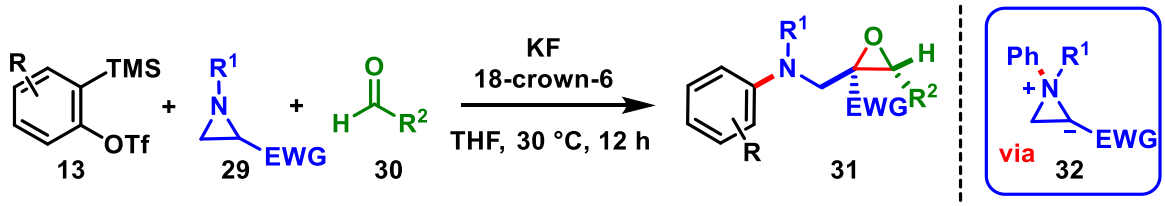
Scheme 3.5. Polysubstituted Pyrroles Synthesis via Aryne Triggered Nitrogen Ylide



The generation of nitrogen ylides is not restricted to imino esters as a substrate. Biju group has demonstrated that arynes can trigger ylide generation with strained aziridines if the aziridine ring contains an electron-stabilizing group. This results in the formation of a strained aziridinium ylide **32**, which can be used for the diastereoselective synthesis of 2-amino epoxides **31** when trapped with aldehydes **30** (Scheme 3.6).[12] Moreover, the reaction is not limited to aldehydes as the nucleophilic trigger. Activated ketones, such as isatins, are

also compatible with the optimized reaction conditions. This expands the applicability of the methodology and enhances its potential for synthesizing a diverse array of epoxide derivatives.

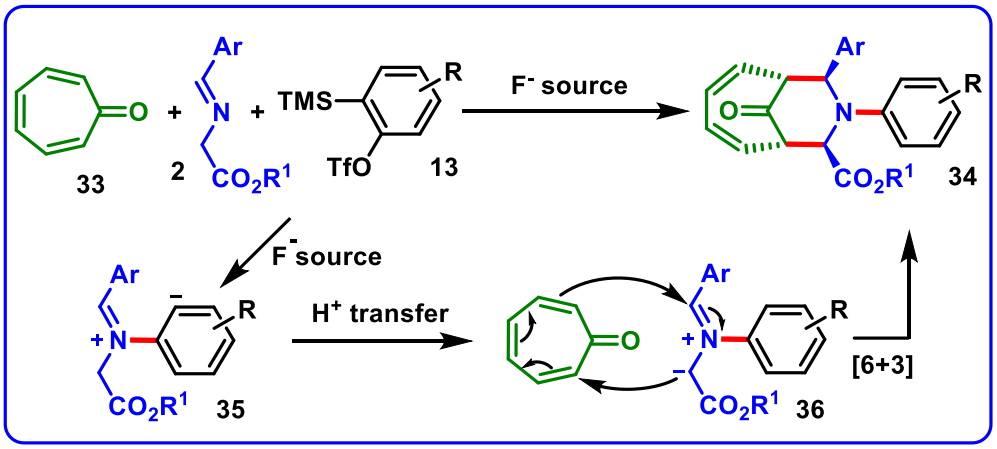
Scheme 3.6. Trapping of The Nitrogen Ylides with Aldehydes



3.3. Statement of the Problem

Although nitrogen ylides generated from aryne have been used in various rearrangement reactions and for the synthesis of functionalized heterocycles, their use in higher order annulation reactions was not previously known. Inspired by the work of Hwu and co-workers,[10] we envisioned that the nitrogen ylide generated from the Schiff base and aryne could react with tropone in a [6+3] annulation reaction, providing an easy pathway to synthesize azabicyclo[4.3.1]decadienes (Scheme 3.7). This three-component coupling is expected to proceed by forming the zwitterion **35** from the Schiff base **2** and aryne, followed by a proton transfer to create nitrogen ylide **36**, and finally resulting in the formation of bicyclic products **34** through a subsequent [6+3] annulation. It's worth noting that bridged bicyclic molecules similar to these are fundamental structures found in medicinally

Scheme 3.7. [6 + 3] Annulation of Tropone, Imino Esters, and Arynes (Working Hypothesis)



significant compounds and natural products.[13] However, the proposed [6+3] annulation reaction involving arynes faces two challenges. Firstly, an undesired 2:1 adduct of imino

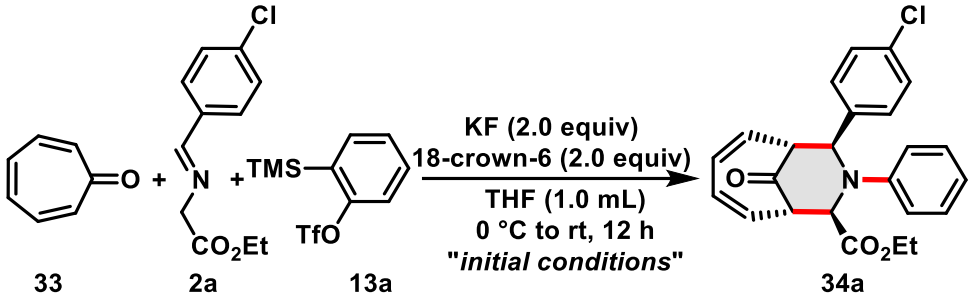
ester and aryne can form, leading to the production of imidazolidines instead of the desired three-component annulation product.[10] Secondly, tropone can undergo a competing Diels-Alder reaction with arynes, resulting in the formation of bicyclic products.[14] Herein, we present the three-component and diastereoselective [6+3] annulation of tropone, imino esters, and arynes leading to the transition-metal-free access to azabicyclo[4.3.1]decadienes as a consequence of the careful optimization studies.

3.4. Results and Discussion

3.4.1. Optimization Studies

The present studies were initiated by the treatment of tropone **33** and 4-chlorobenzaldehyde-derived imino ester **2a** with the aryne formed in situ from 2-(trimethylsilyl)aryl triflate **13a** using KF and 18-crown-6 in THF at 0 ° C to rt. To our delight, using these conditions, the anticipated azabicyclo[4.3.1]decadiene **34a** was formed in 47% yield as a single diastereomer (based on ^{1}H NMR, Table 3.1, entry 1). Interestingly, the possible side products originated from the 2:1 adduct of imino ester **2a** and aryne as well as the Diels-Alder adduct of tropone and aryne were not observed under these conditions. Increasing or decreasing the amount of imino ester **2a** did not enhance the yield of the product **34a** (entries 2, 3). Enhancing the tropone concentration was also not fruitful (entry 4). Reactions performed in other fluoride sources such as CsF or TBAF returned inferior results (entries 5, 6). Carrying out the reaction in other ether solvents such as DME or 1,4-dioxane returned the desired product in low yields (entries 7, 8). Moreover, product **34a** was formed in 39% yield when performed at 25 °C instead of 0 °C to rt (entry 9). Interestingly, carrying out our dilution experiments (0.125 M instead of 0.25 M) enhanced the yield of **34a** to 58% (entry 10). Further dilution to 0.1 M improved the yield of **34a** to 64% (entry 11). Performing additional dilution did not result in an improvement in the yield of **34a** (entry 12). Hence, entry 11 was chosen as the optimum condition for this three-component diastereoselective [6+3] annulation reaction employing imino ester, aryne and tropone and these conditions were used for further substrate scope analysis.

Table 3.1. Optimization of the Reaction Conditions[a]



33 2a 13a 34a

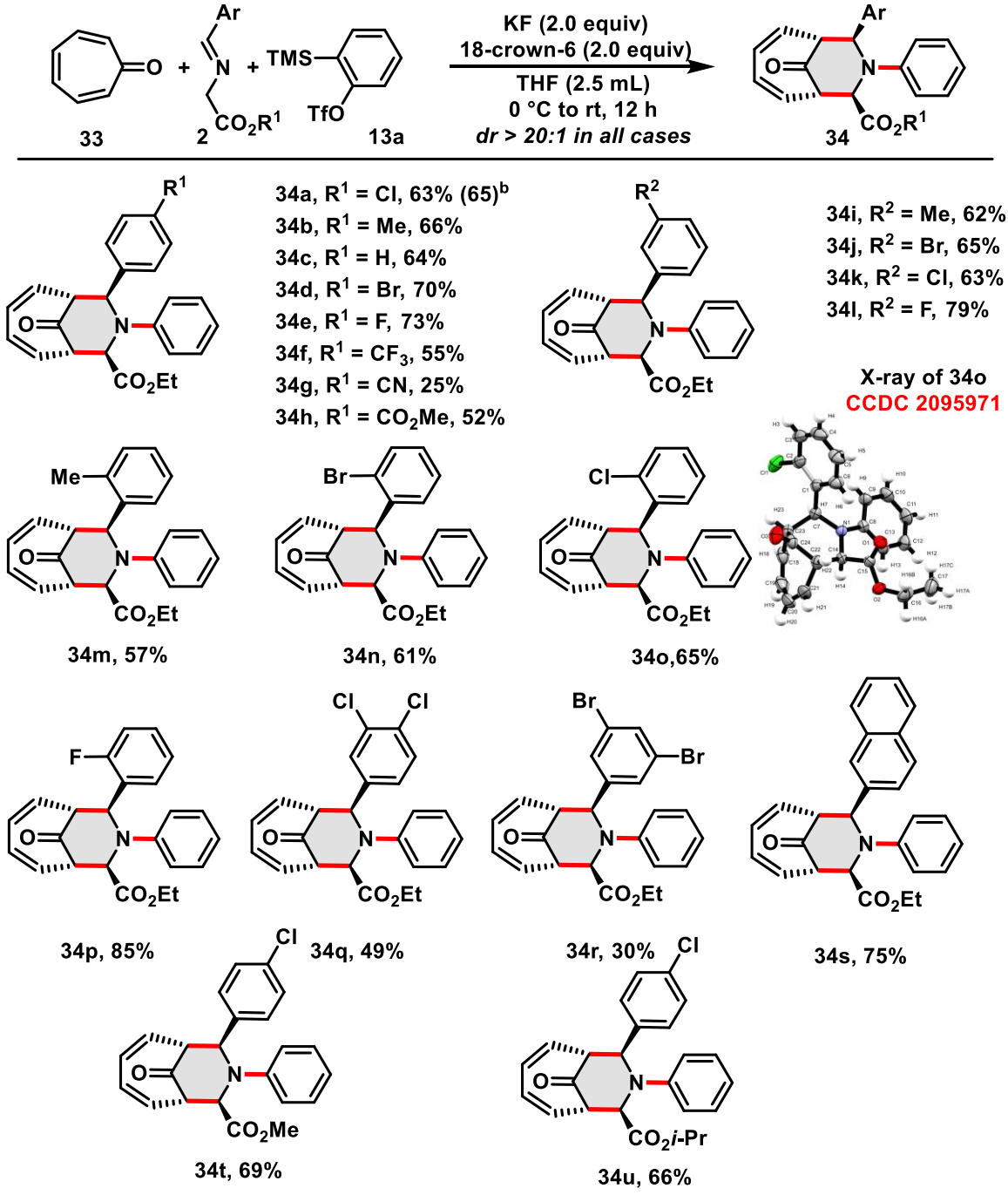
entry	variation of the initial conditions	yield of 34a (%)[b]
1	none	47
2	2.0 equiv of **2a** instead of 1.5 equiv	44
3	1.2 equiv of **2a** instead of 1.5 equiv	37
4	1.5 equiv of **33** instead of 1.2 equiv	45
5[c]	CsF instead of KF/18-crown-6	<5
6	TBAF instead of KF/18-crown-6	<5
7	DME instead of THF	41
8	1,4-dioxane instead of THF	27
9	25 °C instead of 0 °C to rt	39
10	0.125 M THF instead of 0.25 M	58
11	*0.1 M THF instead of 0.25 M*	*64 (63)*
12	0.083 M THF instead of 0.25 M	63

[a] Initial conditions: **33** (0.3 mmol), **2a** (0.375 mmol), **13a** (0.25 mmol), KF (2.0 equiv), 18-crown-6 (2.0 equiv), THF (1.0 mL), 0 °C to rt for 12 h. [b] The ^{1}H NMR yield of the crude products is provided where CH_2Br_2 was used as the internal standard and the isolated yield is given in parentheses. [c] Reaction was done in CH_3CN.

3.4.2. Substrate Scope of the Three-Component, Diastereoselective [6+3] Annulation Reaction: Scope of Imino Esters

With the identified optimal reaction conditions in hand, we evaluated the scope and drawbacks of this three-component coupling (Scheme 3.8). The variation on the imino esters was examined first. A variety of imino ester derivatives having electron-releasing, -neutral, or -withdrawing groups at the 4-position of the benzene ring underwent smooth three-component [6+3] annulation leading to the formation of the bridged azabicyclo[4.3.1]decadienes in low to good yields (**34a**-**34h**). When the reaction was carried out on a 2.0 mmol scale, **34a** was isolated in 65% yield signifying the scalable nature of the developed [6+3] annulation. Moreover, imino esters bearing substituents at the 3- position

Scheme 3.8. Substrate Scope: Variation of Imino Esters



[a] General conditions: **33** (0.3 mmol), **2** (0.375 mmol), **13a** (0.25 mmol), KF (2 equiv), 18-crown-6 (2 equiv), THF (2.5 mL), 0 °C to rt for 12 h. Provided are isolated yields of products. [b] Yield of the experiment conducted on a 2.0 mmol scale.

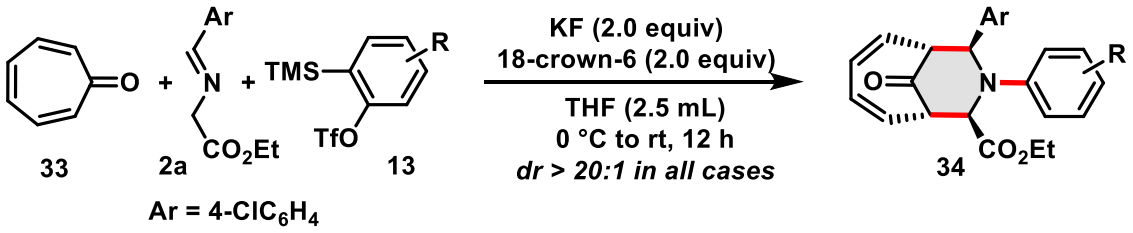
on the aryl ring were tolerated well under the present conditions resulting in the formation of the desired products in good yields (**34i**-**34l**). Furthermore, sterically congested 2-substitutions also furnished the three-component coupling product in good yields (**34m**-**34p**). The structure of the 2-chloro derivative **34o** was confirmed by X-ray analysis of the crystals. Notably, the 3,4-dichloro and 3,5-dibromo benzaldehyde derived imino esters worked well under the present conditions and the anticipated piperidine-fused bicycles were formed in moderate yields (**34q**-**34r**). In addition, imino ester bearing the 2-napthyl substitution was well suited in this present [6+3] annulation and the product **34s** was formed in 75% yield. Furthermore, this three-component coupling is not limited to ethyl ester derived imino esters but methyl and isopropyl substituted imino esters afforded the target products in good yields (**34t**-**34u**). It is worth mentioning that imino esters derived from aliphatic aldehydes failed to afford the desired [6+3] annulation reaction.

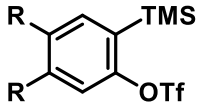
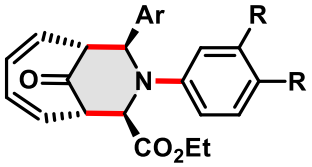
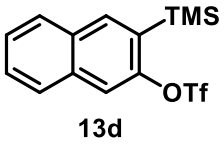
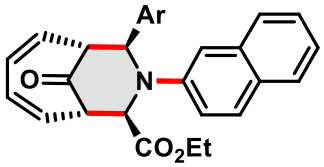
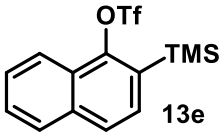
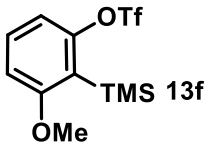
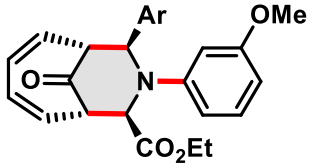
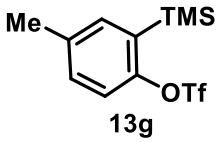
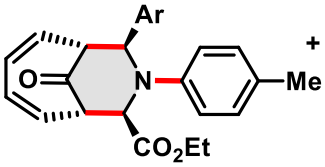
3.4.3. Substrate Scope of the Three-Component, Diastereoselective [6+3] Annulation Reaction: Scope of Arynes

The scope of the reaction has then been evaluated using differently substituted arynes (Table 3.2). The reaction conducted using 4,5-dimethyl substituted symmetrical aryne generated from **13b** furnished the desired product **34v** in 53% yield, and the sesamol derived aryne precursor formed from **13c** afforded the product **34w** in 71% yield. Interestingly, the symmetrical naphthyl aryne precursor **13d** and the unsymmetrical naphthyl aryne precursor **13e** delivered the piperidine-fused bicyclic product **34x** in 58% and 62% yield respectively. The formation of **34x** from **13e** is an indication of regioselective addition of imino ester to unsymmetrical arynes. Moreover, the reaction of 3-methoxy aryne generated from the precursor **13f** under the optimized conditions produced the single regioisomer **34y** in 56% yield. Finally, imino ester **2a** could add to unsymmetrical aryne produced from the precursor **13g** and tropone to provide the inseparable mixture of regioisomers **34z** and **34z'** in 73% yield and 1:1.1 ratio. It may be noted that the present [6+3] annulation is limited to tropone and the substituted tropone derivatives such as 2-methoxy, 2-tosylozy, 2-chloro and 2-phenyl tropones did not afford the desired [6+3] adduct under the optimized conditions. It is reasonable to assume that the steric hindrance created by the 2-substitution of the tropone moiety make this three-component coupling reaction unfeasible. We were unable to test the

feasibility of the [6+3] annulation reaction with other substituted tropones because accessing other substituents on the tropone ring proved difficult.

Table 3.2. Substrate Scope: Variation of Arynes



entry	aryne precursor	product	yield (%)[b]
1 2			34v, R = Me, 53% 34w, R = O(CH$_2$)O, 71%
3			34x, 58% from 13d 34x, 62% from 13e
4			
5			34y, 56%
6			34z, 34z' = 73% (1:1.1)[c]

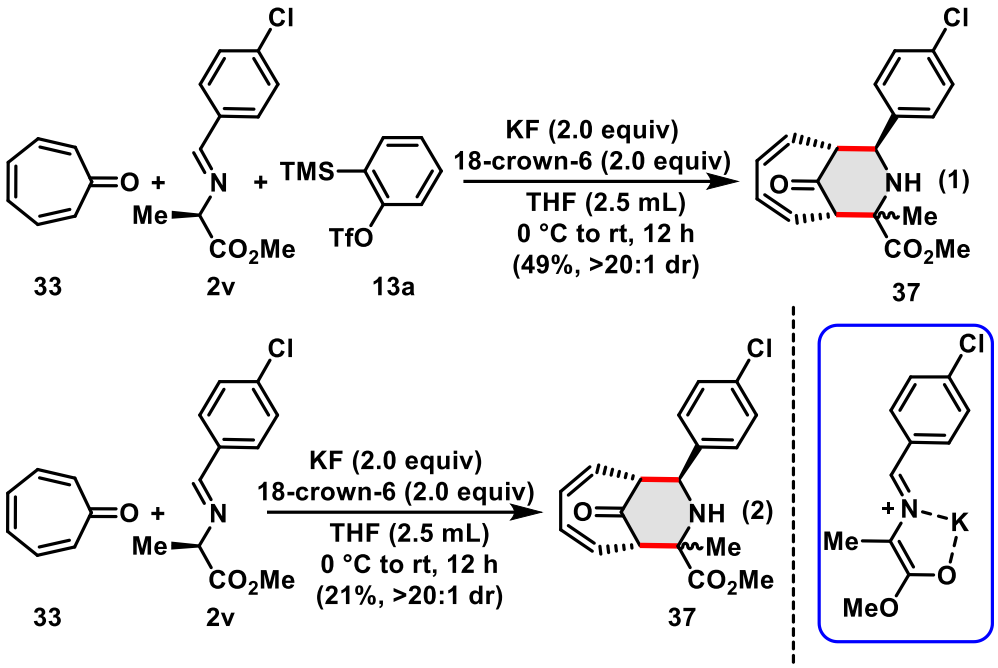
[a] General conditions: **33** (0.3 mmol), **2a** (0.375 mmol), **13** (0.25 mmol), KF (2 equiv), 18-crown-6 (2 equiv), THF (2.5 mL), 0 °C to rt for 12 h. [b] Provided are isolated yields of products. [c] Established by GC analysis.

3.4.4. [6+3] Annulation Reaction Using Alanine-Derived Imino Ester

Disappointingly, when enantiomerically pure alanine-derived imino ester **2v** was treated with tropone and aryne generated from **13a**, the desired three-component product was

not formed. Instead, the *N*-unsubstituted product **37** was obtained in 49% yield without the incorporation of the aryne moiety (Scheme 3.9, eq 1). Moreover, treatment of tropone with the imino ester **2v** in the absence of **13a** afforded **37** in low yields (eq 2). It is likely that in the reaction using **2v**, the initially formed azomethine ylide (in the presence of KF) is a more substituted ester enolate, which could easily complex with the potassium cation, and hence reduce the nucleophilicity of the imino ester nitrogen for addition to arynes.

Scheme 3.9. Reaction Using Alanine-Derived Imino Ester

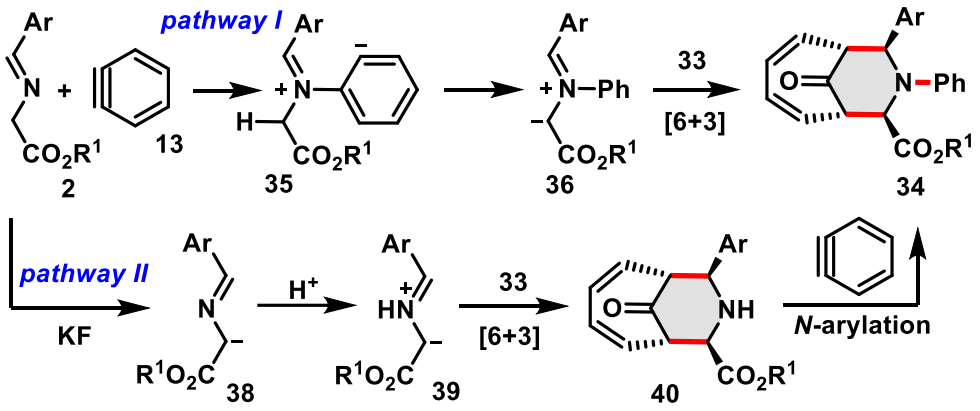


3.4.5. Mechanistic Investigation

It is reasonable to assume two mechanistic pathways leading to the formation of product **34**. In the first pathway, the nucleophilic addition of the imino ester **2** to aryne could generate the nitrogen ylide **36** via the zwitterion **35**, which could undergo a concerted [6+3] cycloaddition with tropone leading to the formation of **34** (Scheme 3.10).[15] This could also explain the diastereoselectivity observed in the process. Alternatively, in the presence of KF/18-crown-**6**, the imino ester could form the aza-allyl anion **38**, which could be protonated to form the azomethine ylide **39** (pathway 2). Subsequent [6+3] cycloaddition of **39** with tropone can form the adduct **40**, which can undergo *N*-arylation with aryne resulting in the formation of **34**.

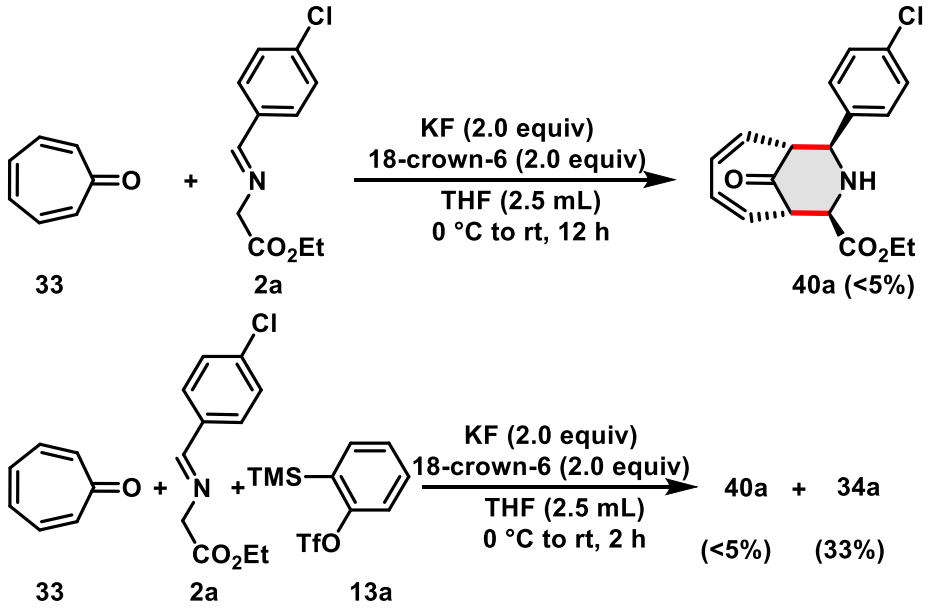
To shed light on the mechanism of this transformation, the reaction of tropone with imino ester was performed in the absence of aryne precursor **13a**. Interestingly, the [6+3] adduct **40a** was not formed under these conditions indicating that the pathway II is not

Scheme 3.10. Possible Mechanistic Pathways



operating in the present case (Scheme 3.11). Moreover, when the reaction between the three components were carried out under optimized conditions and quenched after 2 h, **34a** was obtained in 33% yield and **40a** was not observed. This experiment also rules out the pathway II and favors the generation of the nitrogen ylide **36** and a subsequent [6+3] cycloaddition with tropone.

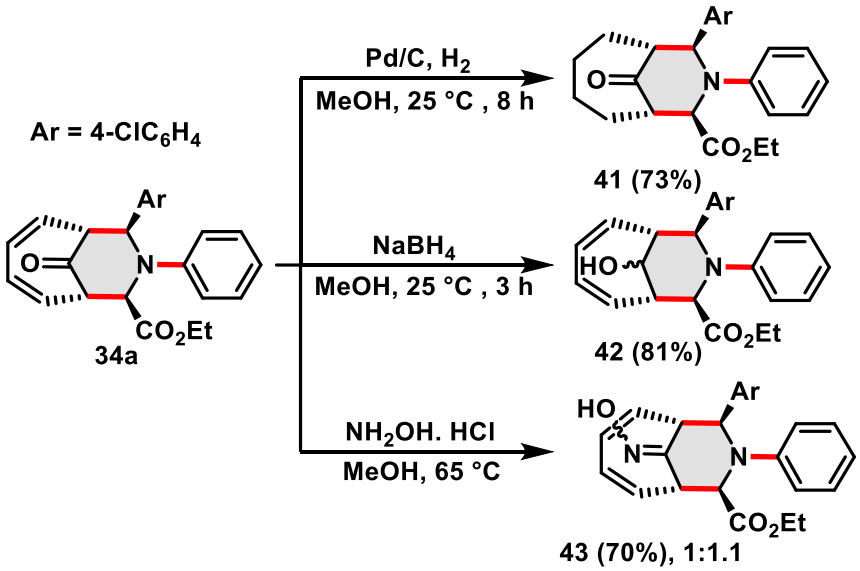
Scheme 3.11. Mechanistic Studies



3.4.6. Synthetic Utility of [6+3] Cycloadduct

The bridged-cycloadduct **34a** can be employed as a synthetically useful precursor for other bicyclo derivatives (Scheme 3.12). Hydrogenation of **34a** in the presence of Pd/C furnished **41** in 73% yield. The keto carbonyl in **34a** was selectively reduced by $NaBH_4$ in a diastereoselective manner and the expected product **42** was formed in 81% yield. In addition, the cycloadduct **34a** can be converted to the oxime **43** in 70% yield as inseparable mixture of cis/trans isomers in 1:1.1 ratio.

Scheme 3.12. Functionalization of the [6+3] Adduct



3.5. Conclusion

In conclusion, a transition-metal-free, three component and diastereoselective [6+3] annulation of tropone, imino esters and arynes for the facile synthesis of bridged azabicyclo[4.3.1]decadiene derivatives has been demonstrated. The key to the success of the reaction is the generation of nitrogen ylide from imino ester and aryne. The present reaction is operationally simple, advance smoothly under mild conditions and can tolerate various functional groups. The product were transformed into other bridged azabicycles.[16]

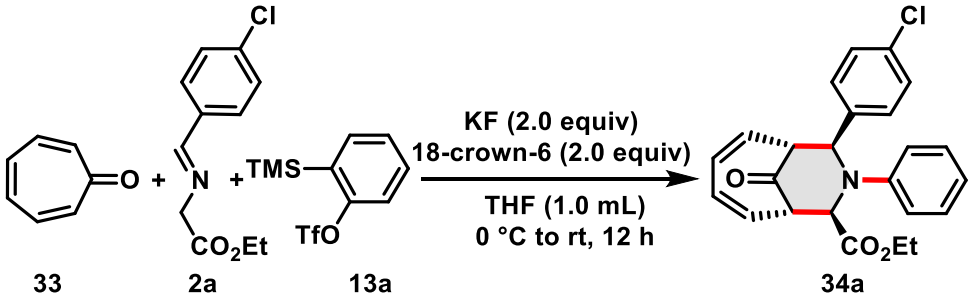
3.6. Experimental Details

3.6.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in oven-dried reaction vessels with Teflon screw caps. 25 °C Corresponds to the

room temperature (rt) of the lab when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under nitrogen. 18-Crown-6 was recrystallized from dry CH_3CN and KF was dried by heating at 110 °C for 12 h and left to cool under nitrogen and stored in nitrogen filled glove-box. Tropone, all the benzaldehyde derivatives, alanine and glycine ethyl ester hydrochloride were purchased from either Alfa Aesar, TCI or Sigma-Aldrich and were used as received. The imino esters **2a-2v** were synthesized following the literature procedure.[17] The 2(trimethylsilyl)phenyl trifluoromethane sulfonate **13a** and the other symmetric and unsymmetrical aryne precursors were synthesized following literature procedure.[18] Analytical thin layer chromatography was performed on TLC Silica gel 60 F254. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker Ultrashield spectrometer in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Infrared (FT-IR) spectra were recorded on a Bruker Alfa FT-IR, ν-max in cm^{-1}. HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument.

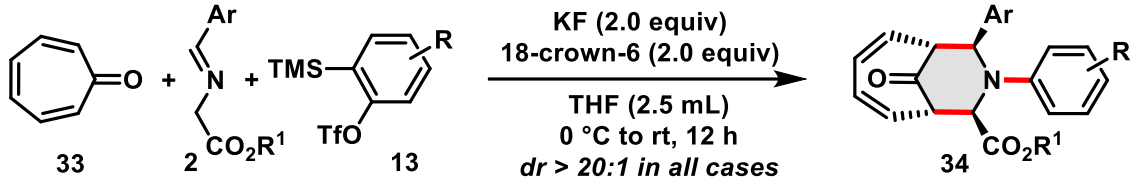
3.6.2. General Procedure for the Optimization of the Reaction Conditions



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in a nitrogen filled glove-box. After that solvent was added outside the glove-box under nitrogen atmosphere and then the mixture was cooled to 0 °C and kept stirring for five minutes. To the stirring solution, cyclohepta-2,4,6-trien-1-one **33**, ethyl (*E*)-2-((4-chlorobenzylidene)amino)acetate **2a** and 2-

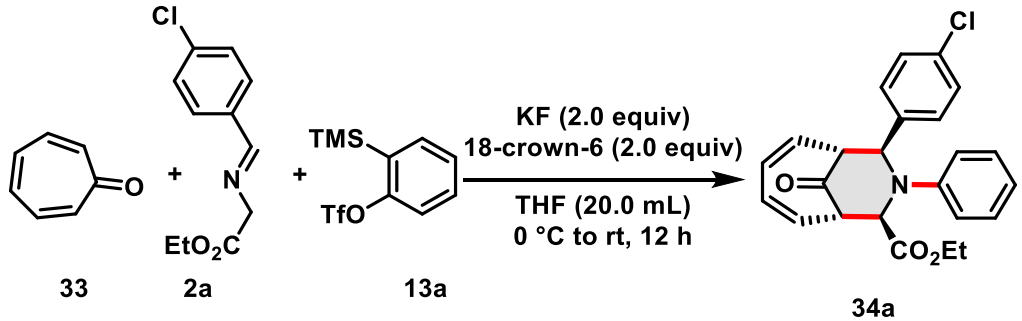
(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** were added. Then the reaction mixture was slowly warmed to rt and with maintained stirring for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude mixture was passed through a pad of silica gel and eluted with EtOAc (3x10 mL). The reaction mixture was concentrated under reduced pressure and then the yield of **34a** was determined by the ^{1}H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard.

3.6.3. General Procedure for the [6+3] Annulation of Tropone, Imino Esters and Arynes



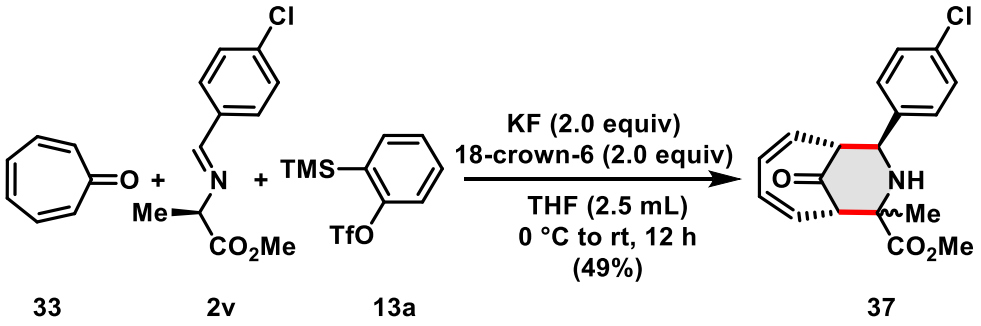
To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in a nitrogen filled glove-box. After that THF (2.5 mL) was added outside the glove-box under nitrogen atmosphere and then the mixture was cooled to 0 °C and kept stirring for five minutes. To the stirring solution, cyclohepta-2,4,6-trien-1-one **33** (0.3 mmol), imino esters **2** (0.375 mmol) and aryne precursor **13** (0.25 mmol) were added. Then the reaction mixture was slowly warmed to rt and with maintained stirring for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet.ether-EtOAc as eluent) to afford the corresponding azabicyclo[4.3.1]decadienes **34** in moderate to good yields.

Procedure for the 2.0 mmol Scale Reaction for the synthesis of 34a



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.232 g, 4.0 mmol) and 18-crown-6 (1.056 g, 4.0 mmol) in a nitrogen filled glove-box. After that THF (20.0 mL) was added outside the glove-box under nitrogen atmosphere and then the mixture was cooled to 0 °C and kept stirring for five minutes. To the stirring solution, cyclohepta-2,4,6-trien-1-one **33** (0.255 g, 2.4 mmol), imino esters **2a** (0.677 g, 3.0 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.597 g, 2.0 mmol) were added. Then the reaction mixture was slowly warmed to rt and with maintained stirring for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 90/10) to afford ethyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34a** as yellow oil (0.530 g, 65% yield).

3.6.4. Procedure for the [6+3] Annulation of Tropone, Alanine-Derived Imino Ester and Aryne

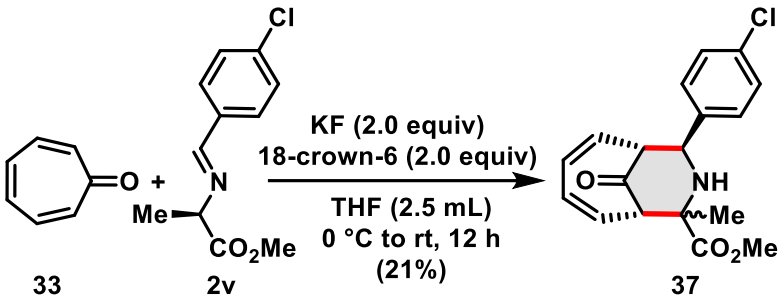


33 2v 13a 37

To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in a nitrogen filled glove-box. After that THF (2.5 mL) was added outside the glove-box under nitrogen atmosphere and then the mixture was cooled to 0 °C and kept stirring for five minutes. To the stirring solution, cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), methyl (*E*)-3-((4-chlorobenzylidene) amino)-2-methylpropanoate **2v** (0.085 g, 0.375 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) were added. Then the reaction mixture was slowly warmed to rt and with maintained stirring for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 80/20) to afford methyl-9-(4-chlorophenyl)-7-methyl-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-

carboxylate **37** as yellow oil (0.049 g, 49% yield) (tropone is considered as the limiting reagent).

3.6.5. Procedure for the [6+3] Annulation of Tropone and Alanine-Derived Imino Ester

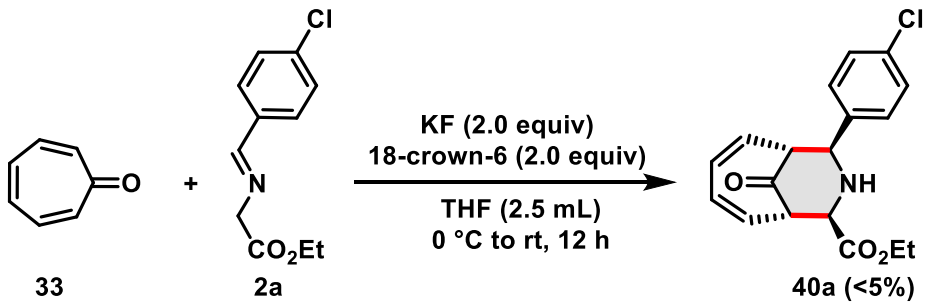


33 2v 37

To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in a nitrogen filled glove-box. After that THF (2.5 mL) was added outside the glove-box under nitrogen atmosphere and then the mixture was cooled to 0 °C and kept stirring for five minutes. To the stirring solution, cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol) and methyl (*E*)-3-((4-chlorobenzylidene)amino)-2-methylpropanoate **2v** (0.085 g, 0.375 mmol) were added. Then the reaction mixture was slowly warmed to rt and with maintained stirring for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 80/20) to afford methyl-9-(4-chlorophenyl)-7-methyl-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **37** as yellow oil (0.021 g, 21% yield) (tropone is considered as the limiting reagent).

3.6.6. Mechanistic Studies

(a) Reaction of Tropone with Imino ester 2a

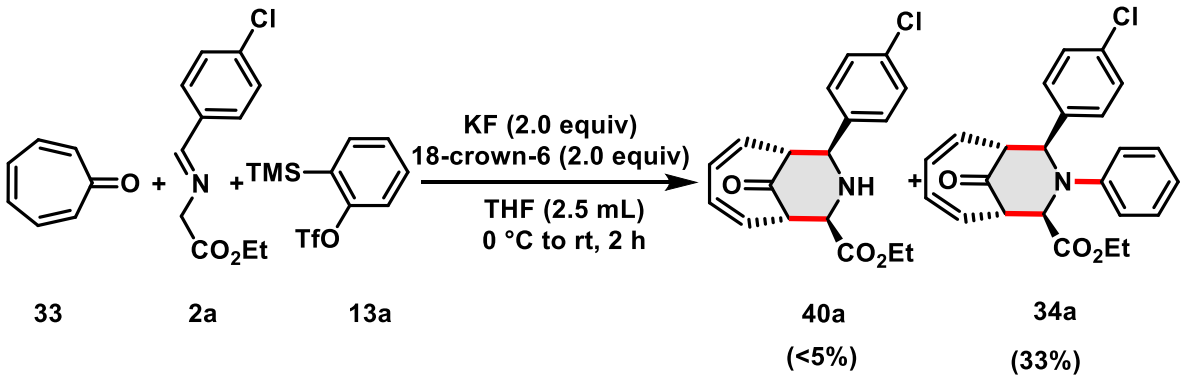


33 2a 40a (<5%)

To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in a nitrogen filled glove-box. After that THF (2.5 mL) was added outside the glove-box under nitrogen atmosphere and then the mixture was cooled to 0 °C and kept stirring for five minutes. To the stirring solution, cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol) and ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol) were added. Then the reaction mixture was slowly warmed to rt and with maintained stirring for 12 h. After 12 h, the reaction was stopped but in this case no product formation was observed (TLC and crude ^{1}H NMR analysis).

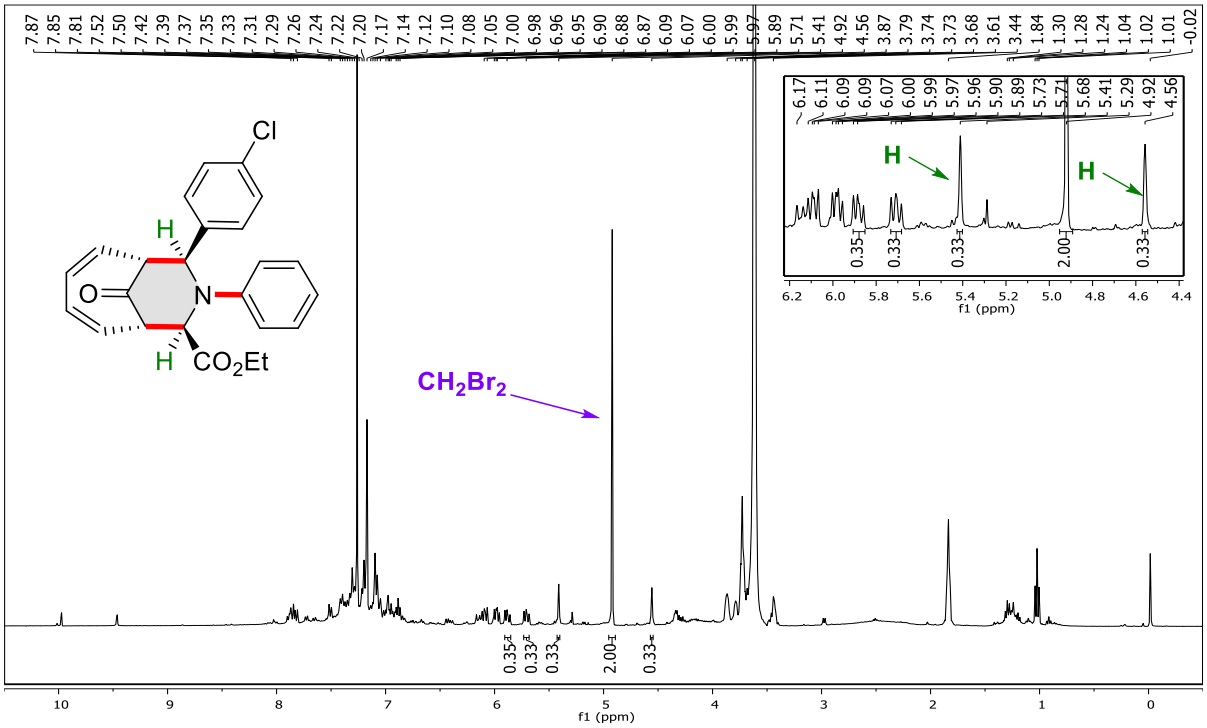
The [6+3] adduct 6a was not formed under these conditions indicating that the pathway II is not operating in the present case.

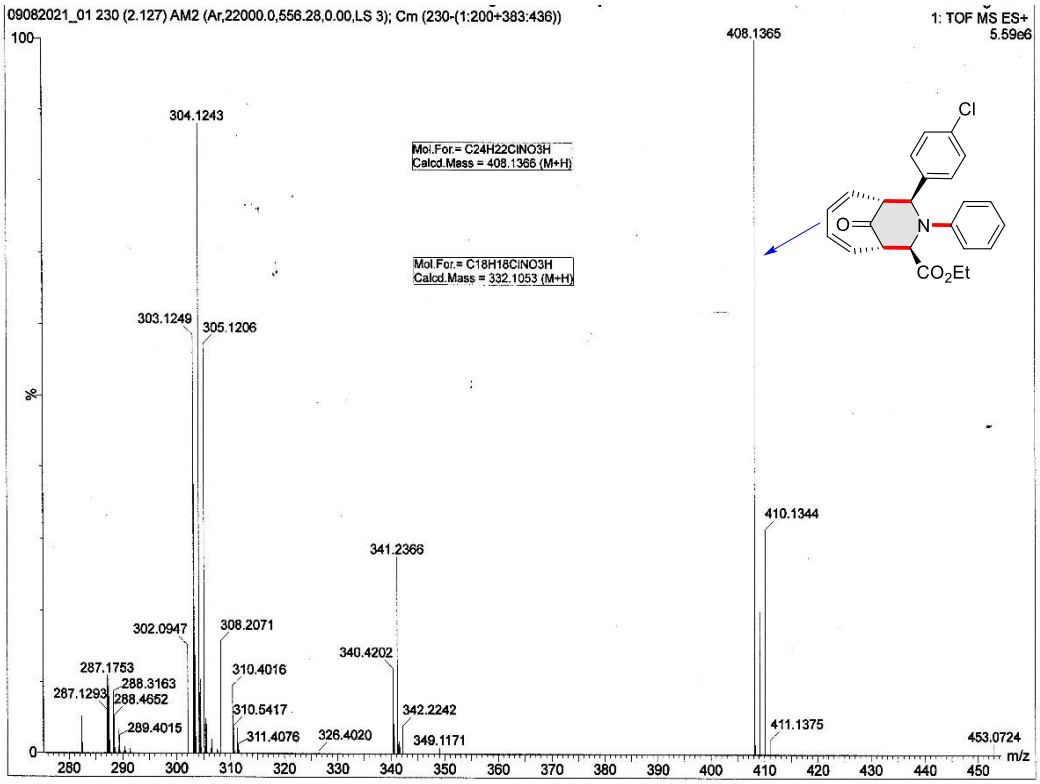
(b) Reaction of Tropone, Imino Ester 2a And Aryne Precursor 13a for 2 h



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in a nitrogen filled glove-box. After that THF (2.5 mL) was added outside the glove-box under nitrogen atmosphere and then the mixture was cooled to 0 °C and kept stirring for five minutes. To the stirring solution, cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol) and ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol) and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **13a** (0.074 g, 0.25 mmol) were added. Then the reaction mixture was slowly warmed to rt and with maintained stirring for 2 h. After 2 h, the reaction was stopped the solvent was evaporated and the crude mixture was passed through a pad of silica gel and eluted with EtOAc (3x10 mL). The reaction mixture was concentrated under reduced pressure and then the yield of 4a was determined by the ^{1}H NMR analysis of the crude

reaction products using CH_2Br_2 as the internal standard and the absence of **40a** was confirmed using HRMS analysis.

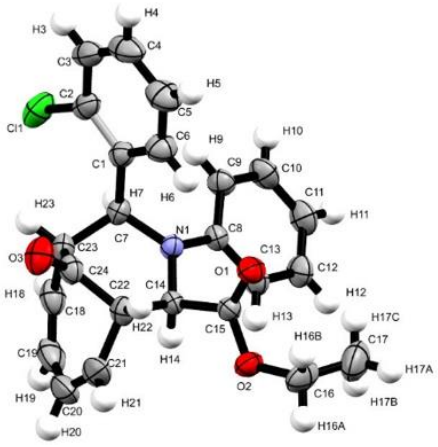




*These studies rule out the possibility of **40a** as the intermediate in this three-component [6+3] annulation reaction and favors the generation of the nitrogen ylide and a subsequent [6+3] cycloaddition with tropone.*

3.6.7. ORTEP Diagram of 34o

Single crystal of **34o** (recrystallized from $CDCl_3$/n-hexane at 25 °C) was mounted and the diffraction data was collected at 296 K on a Bruker APEX-II CCD diffractometer using SMART/SAINT software. Intensity data were collected using MoKα radiation (λ=0.71073 A°).

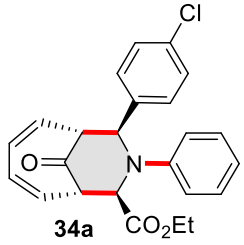


ORTEP Diagram of 34o

(CCDC 2095971, thermal ellipsoids are shown with 50% probability)

3.6.8. Synthesis and Characterization of Azabicyclo[4.3.1]decadienes

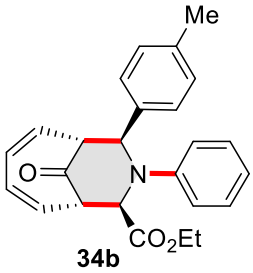
Ethyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7 carboxylate (34a)



Following the general procedure, treatment of ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded ethyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34a** as yellow oil (0.064 g, 63% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26-7.19 (m, 6H), 7.11-7.09 (m, 2H), 6.92-6.88 (m, 1H), 6.13-6.08 (m, 1H), 6.02-5.87 (m, 2H), 5.74-5.70 (m, 1H), 5.43 (s, 1H), 4.57 (s, 1H), 3.88 (s, 2H), 3.76-3.68 (m, 1H), 3.50-3.42 (m, 1H), 1.04 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.2, 171.4, 150.6, 139.8, 133.6, 129.3, 128.9, 128.4, 126.7, 126.4, 125.4, 125.0, 121.0, 117.7, 65.6, 64.4, 61.7, 55.9, 53.6, 13.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{23}ClNO_3$ 408.1361; found 408.1368. **FTIR (cm^{-1})** 2958, 1731, 1597, 1497, 1391, 1244.

Ethyl-10-oxo-8-phenyl-9-(*p*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34b)



34b

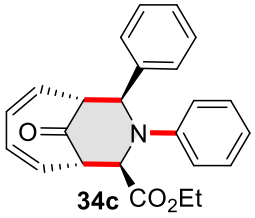
Following the general procedure, treatment of ethyl (*E*)-2-((4-methylbenzylidene) amino)acetate **2b** (0.077 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded ethyl-10-oxo-8-phenyl-9-(*p*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34b** as a yellow oil (0.064 g, 66% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.24-7.20 (m, 2H), 7.16-7.11 (m, 4H), 7.02 (d, *J* = 7.7 Hz, 2H), 6.90-6.87 (m, 1H), 6.09-6.05 (m, 1H), 5.98-5.87 (m, 2H), 5.73-5.68 (m, 1H), 5.48 (s, 1H), 4.57 (s, 1H), 3.97-3.89 (m, 2H), 3.67-3.59 (m, 1H), 3.37-3.29 (m, 1H), 2.27 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.8, 171.5, 151.0, 138.1, 137.4, 129.1, 128.9, 127.4, 126.6, 126.1, 125.6, 124.9, 120.4, 117.3, 65.6, 64.0, 61.5, 55.8, 53.5, 21.1, 13.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{25}H_{26}NO_3$ 388.1907; found 388.1912. **FTIR (cm^{-1})** 2924, 2364, 1730, 1597, 1500, 1389.

Ethyl-10-oxo-8,9-diphenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34c)

Following the general procedure, treatment of ethyl (*E*)-2-(benzylideneamino)acetate **2c** (0.072 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the

presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at

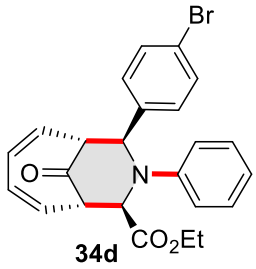


0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded ethyl-10-oxo-8,9-diphenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34c** as a yellow oil (0.060 g, 64% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.26-7.15 (m, 9H), 6.91-6.87 (m, 1H), 6.11-6.06 (m, 1H), 5.99-5.88 (m, 2H), 5.73-5.68 (m, 1H), 5.52 (s, 1H), 4.59 (s, 1H), 4.00-3.98 (m, 1H), 3.93-3.90 (m, 1H), 3.66-3.58 (m, 1H), 3.36-3.28 (m, 1H), 0.99 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.8, 171.4, 150.9, 141.0, 129.2, 128.3, 127.7, 127.5, 126.6, 126.2, 125.5, 124.8, 120.5, 117.4, 65.7, 64.0, 61.5, 55.6, 53.5, 13.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{24}NO_3$ 374.1751; found 374.1756. **FTIR (cm^{-1})** 3028, 2981, 1737, 1598, 1499, 1391.

Ethyl-9-(4-bromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34d)

Following the general procedure, treatment of ethyl (*E*)-2-((4-bromobenzylidene) amino)acetate **2d** (0.101 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded ethyl-9-(4-bromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34d** as a yellow oil (0.079 g, 70% yield).

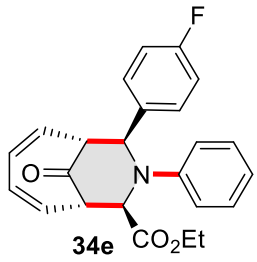


***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.23-7.19 (m, 2H), 7.13-7.09 (m, 4H), 6.92-6.88 (m, 1H), 6.13-6.08 (m, 1H), 6.02-5.97 (m, 1H), 5.92-5.87 (m, 1H), 5.74-5.70 (m, 1H), 5.41 (s, 1H), 4.57 (s, 1H), 3.89-3.87 (m, 2H), 3.76-3.68 (m, 1H), 3.50-3.42 (m, 1H), 1.04 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.1, 171.4, 150.5, 140.3, 131.4, 129.3, 129.2, 126.7, 126.5, 125.4, 125.0, 121.7, 121.0, 117.7, 65.7, 64.4, 61.7, 55.8, 53.6, 13.9. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for

$C_{24}H_{22}BrNNaO_3$ 474.0675; found 474.0681. **FTIR (cm^{-1})**3028, 2333, 1730, 1596, 1496, 1392, 1296.

Ethyl-9-(4-fluorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34e)

Following the general procedure, treatment of ethyl (*E*)-2-((4-fluorobenzylidene) amino)acetate **2e** (0.078 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-9-(4-fluorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34e** as a yellow oil (0.071 g, 73% yield).

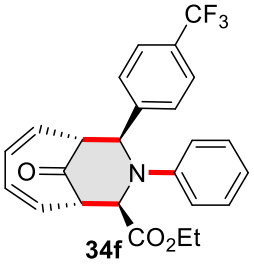


34e

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26-7.20 (m, 4H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.94-6.88 (m, 3H), 6.12-6.07 (m, 1H), 6.01-5.96 (m, 1H), 5.91-5.87 (m, 1H), 5.74-5.69 (m, 1H), 5.45 (s, 1H), 4.58 (m, 1H), 3.93-3.87 (m, 2H), 3.75-3.67 (m, 1H), 3.48-3.40 (m, 1H), 1.04 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.3, 171.3, 162.0 (d, *J* = 246.7 Hz), 150.5, 136.9 (d, *J* = 3.3 Hz), 129.2 (d, *J* = 8.2 Hz), 129.1, 126.6, 126.2, 125.3, 124.8, 120.7, 117.5, 115.0 (d, *J* = 21.3 Hz), 65.3, 64.1, 61.5, 55.8, 53.4, 13.8. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{24}H_{22}FNNaO_3$ 414.1476; found 414.1483. **FTIR (cm^{-1})**2958, 2364, 1730, 1598, 1503, 1389.

Ethyl-10-oxo-8-phenyl-9-(4-(trifluoromethyl)phenyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34f)

Following the general procedure, treatment of ethyl (*E*)-2-((4-(trifluoromethyl)benzylidene) amino)acetate **2f** (0.097 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification



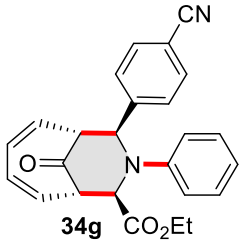
34f

via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-10-oxo-8-phenyl-9-(4-(trifluoromethyl)phenyl)-8- azabicyclo [4.3.1] deca-2,4-diene-7-carboxylate **34f** as a yellow oil (0.061 g, 55% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.49 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.26-7.20 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.93-6.90 (m, 1H), 6.16-6.11 (m, 1H), 6.04-6.00 (m, 1H), 5.94-5.90 (m, 1H), 5.76-5.71 (m, 1H), 5.49 (s, 1H), 4.59 (s, 1H), 3.93-3.87 (m, 2H), 3.72-3.64 (m, 1H), 3.44-3.36 (m, 1H), 1.01 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 202.9, 171.3, 150.4, 145.3 (unresolved quartet), 129.9 (q, *J* = 32.3 Hz), 129.3, 127.8, 126.8, 126.8 (q, *J* = 258.1 Hz), 126.6, 125.3, 125.3 (q, *J* = 3.9 Hz), 125.0, 121.1, 117.7, 66.0, 64.6, 61.7, 55.7, 53.6, 13.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{25}H_{23}F_3NO_3$ 442.1625; found 442.1631. **FTIR (cm^{-1})**2923, 2964, 1731, 1596, 1498, 1327.

Ethyl-9-(4-cyanophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34g)

Following the general procedure, treatment of ethyl (*E*)-2-((4-cyanobenzylidene) amino)acetate **2g** (0.081 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/50) of the crude reaction mixture afforded ethyl-9-(4-cyanophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34g** as yellow oil (0.025 g, 25% yield).

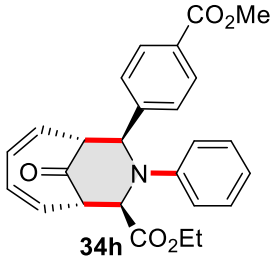


***R*f** (Pet. ether /EtOAc = 90/10): 0.21; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.23-7.19 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.18-6.14 (m, 1H), 6.07-6.03 (m, 1H), 5.93-5.89 (m, 1H), 5.77-5.73 (m, 1H), 5.42 (s, 1H), 4.60-4.59 (m, 1H), 3.85-3.83 (m, 2H), 3.80-3.72 (m, 1H), 3.58-3.50 (m, 1H), 1.06 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 202.21, 171.22, 150.09, 146.86, 132.23, 129.38, 128.14, 126.84, 125.44, 125.18, 121.49, 118.61, 117.98, 111.58, 66.39, 65.12, 61.72,

55.79, 53.75, 13.92. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3$ 399.1703; found 399.1706. **FTIR (cm^{-1})**2923, 2228, 1730, 1598, 1498, 1180, 754.

Ethyl-9-(4-(methoxycarbonyl)phenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34h)

Following the general procedure, treatment of methyl (*E*)-4-(((2-ethoxy-2-oxoethyl) imino)methyl)benzoate **2h** (0.093 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded ethyl-9-(4-(methoxycarbonyl)phenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34h** as a yellow oil (0.056 g, 52% yield).



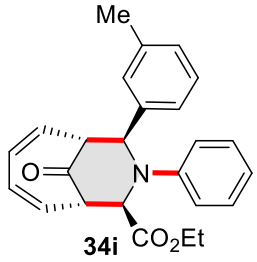
34h

***R*f** (Pet. ether /EtOAc = 90/10): 0.19; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.23-7.19 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.92-6.88 (m, 1H), 6.15-6.10 (m, 1H), 6.04-5.99 (m, 1H), 5.94-5.89 (m, 1H), 5.76-5.71 (m, 1H), 5.46 (s, 1H), 4.59-4.59 (m, 1H), 3.93-3.85 (m, 5H), 3.71-3.63 (m, 1H), 3.47-3.39 (m, 1H), 1.02 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 202.9, 171.2, 166.7, 150.5, 146.4, 129.7, 129.5, 129.3, 127.4, 126.7, 126.5, 125.6, 125.0, 121.1, 117.8, 66.1, 64.7, 61.6, 55.7, 53.7, 52.3, 13.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{26}H_{26}NO_5$ 432.1805; found 432.1808. **FTIR (cm^{-1})** 2957, 2364, 1725, 1599, 1499, 1282.

Ethyl-10-oxo-8-phenyl-9-(*m*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34i)

Following the general procedure, treatment of ethyl (*E*)-2-((3-methylbenzylidene)amino)acetate **2i** (0.077 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column

chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-10-oxo-8-phenyl-9-(*m*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34i** as a yellow oil (0.060 g, 62% yield).

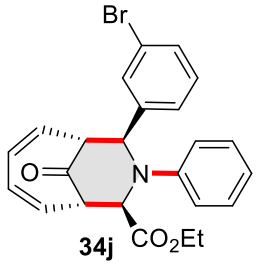


34i

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.23-7.19 (m, 2H), 7.15-7.09 (m, 3H), 7.04-6.99 (m, 3H), 6.90-6.87 (m, 1H), 6.09-6.05 (m, 1H), 5.99-5.95 (m, 1H), 5.91-5.87 (m, 1H), 5.74-5.70 (m, 1H), 5.46 (s, 1H), 4.59 (s, 1H), 3.97-3.89 (m, 2H), 3.68-3.60 (m, 1H), 3.39-3.31 (m, 1H), 2.27 (s, 3H), 0.99 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.8, 171.5, 151.0, 141.0, 137.9, 129.1, 128.4, 128.2, 128.1, 126.6, 126.1, 125.6, 124.8, 124.6, 120.4, 117.3, 65.8, 64.0, 61.5, 55.8, 53.4, 21.6, 13.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{25}H_{26}NO_3$ 388.1907; found 388.1916. **FTIR (cm^{-1})** 3029, 2365, 1730, 1599, 1497, 1176.

Ethyl-9-(3-bromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34j)

Following the general procedure, treatment of ethyl (*E*)-2-((3-bromobenzylidene) amino)acetate **2j** (0.101 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded ethyl-9-(3-bromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34j** as a yellow oil (0.074 g, 65% yield).

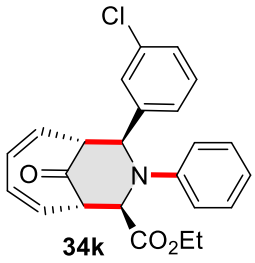


34j

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.40 (s, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.26-7.20 (m, 3H), 7.13-7.09 (m, 3H), 6.93-6.89 (m, 1H), 6.13-6.08 (m, 1H), 6.02-5.98 (m, 1H), 5.92-5.87 (m, 1H), 5.75-5.71 (m, 1H), 5.41 (s, 1H), 4.60-4.59 (m, 1H), 3.91-3.85 (m, 2H), 3.79-3.71 (m, 1H), 3.56-3.48 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 202.8, 171.3, 150.5, 143.6, 130.9, 130.5, 130.0, 129.3, 126.7, 126.5, 125.9, 125.4, 125.0, 122.5, 121.0, 117.6, 65.7, 64.6, 61.8, 55.7, 53.5, 13.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{23}BrNO_3$ 452.0856; found 452.0862. **FTIR (cm^{-1})** 2982, 1732, 1596, 1499, 1471, 1294.

Ethyl-9-(3-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34k)

Following the general procedure, treatment of ethyl (*E*)-2-((3-chlorobenzylidene) amino)acetate **2k** (0.85 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded ethyl-9-(3-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34k** as a yellow oil (0.064 g, 63% yield).

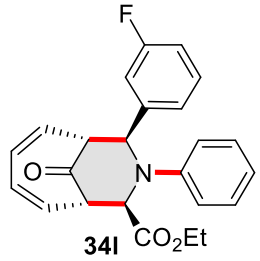


34k

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.26-7.16 (m, 6H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.92-6.89 (m, 1H), 6.13-6.08 (m, 1H), 5.02-5.98 (m, 1H), 5.92-5.87 (m, 1H), 5.76-5.71 (m, 1H), 5.41 (s, 1H), 4.60-4.60 (m, 1H), 3.91-3.85 (m, 2H), 3.79-3.71 (m, 1H), 3.56-3.48 (m, 1H), 1.07 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 202.8, 171.3, 150.5, 143.4, 134.3, 129.7, 129.3, 127.9, 127.6, 126.7, 126.5, 125.5, 125.4, 125.0, 121.0, 117.6, 65.8, 64.6, 61.7, 55.8, 53.5, 13.9. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{24}H_{22}ClNNaO_3$ 430.1180; found 430.1185. **FTIR (cm^{-1})**2983, 1731, 1596, 1499, 1389, 1243.

Ethyl-9-(3-fluorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34l)

Following the general procedure, treatment of ethyl (*E*)-2-((3-fluorobenzylidene) amino)acetate **2l** (0.078 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded ethyl-9-(3-fluorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34l** as a yellow oil (0.077 g, 79% yield).

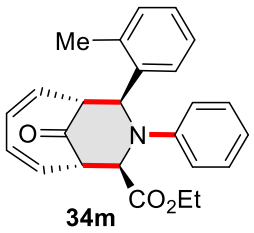


34l

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.23-7.18 (m, 3H), 7.11-6.99 (m, 4H), 6.92-6.88 (m, 2H), 6.13-5.88 (m, 3H), 5.76-5.71 (m, 1H), 5.43 (s, 1H), 4.60-4.60 (m, 1H), 3.91-3.85 (m, 2H), 3.78-3.70 (m, 1H), 3.56-3.48 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 202.9, 171.3, 162.7 (d, *J* = 247.2 Hz), 150.5, 143.9 (d, *J* = 6.5 Hz), 129.9 (d, *J* = 8.1 Hz), 129.3, 126.7, 126.5, 125.5, 125.0, 122.9 (d, *J* = 2.9 Hz), 120.9, 117.5, 114.7 (d, *J* = 21.2 Hz), 114.6 (d, *J* = 22.1 Hz), 65.8, 64.6, 61.6, 55.8, 53.5, 13.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{23}FNO_3$ 392.1656; found 392.1659. **FTIR (cm^{-1})** 2984, 1731, 1593, 1496, 1444, 1390.

Ethyl-10-oxo-8-phenyl-9-(*o*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34m)

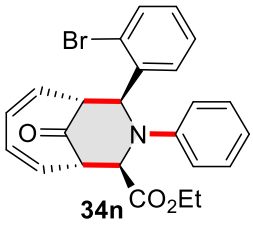
Following the general procedure, treatment of ethyl (*E*)-2-((2-methylbenzylidene) amino)acetate **2m** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-10-oxo-8-phenyl-9-(*o*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34m** as yellow oil (0.055g, 57% yield).



34m

***R*f** (Pet. ether /EtOAc = 92/08): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.24-7.20 (m, 2H), 7.15-7.09 (m, 3H), 7.04-6.99 (m, 3H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.09-6.05 (m, 1H), 5.99-5.87 (m, 2H), 5.74-5.69 (m, 1H), 5.47 (s, 1H), 4.59 (s, 1H), 3.98-3.90 (m, 2H), 3.67-3.59 (m, 1H), 3.37-3.29 (m, 1H), 2.27 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.8, 171.5, 151.0, 141.0, 138.0, 129.1, 128.4, 128.3, 128.1, 126.6, 126.1, 125.6, 124.8, 124.6, 120.4, 117.3, 65.8, 64.0, 61.5, 55.7, 53.4, 21.6, 13.8. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{25}H_{25}NNaO_3$ 410.1727; found 410.1733. **FTIR (cm^{-1})** 2924, 1730, 1599, 1497, 1391, 1176.

Ethyl-9-(2-bromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34n)

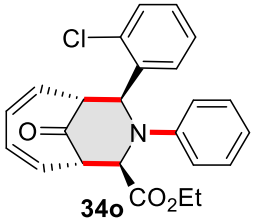


34n

Following the general procedure, treatment of ethyl (*E*)-2-((2-bromobenzylidene) amino)acetate **2n** (0.101 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded ethyl-9-(2-bromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34n** as a yellow oil (0.069 g, 61% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80-7.78 (m, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.29-7.26 (m, 1H), 7.16-7.06 (m, 3H), 6.88-6.78 (m, 3H), 6.26-6.16 (m, 2H), 6.05-6.00 (m, 1H), 5.94-5.90 (m, 1H), 5.50-5.50 (m, 1H), 4.63 (d, *J* = 5.4 Hz, 1H), 4.09-4.01 (m, 1H), 3.96-3.88 (m, 1H), 3.84-3.80 (m, 1H), 3.67-3.66 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 200.9, 172.4, 149.5, 141.0, 133.2, 129.6, 129.3, 128.9, 128.0, 127.5, 127.4, 126.8, 126.3, 122.8, 121.6, 118.5, 68.9, 66.6, 61.7, 58.3, 53.4, 14.0. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{23}BrNO_3$ 452.0856; found 452.0863. **FTIR (cm^{-1})** 2982, 1728, 1598, 1499, 1466, 1297.

Ethyl-9-(2-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34o)



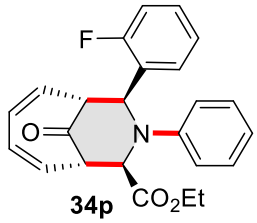
34o

Following the general procedure, treatment of ethyl (*E*)-2-((2-chlorobenzylidene) amino)acetate **2o** (0.85 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded ethyl-9-(2-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34o** as a white solid (0.066 g, 65% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.74-7.71 (m, 1H), 7.34-7.32 (m, 1H), 7.24-7.12 (m, 4H), 6.88-6.83 (m, 3H), 6.23-6.12 (m, 2H), 5.98-5.90 (m, 2H), 5.50 (d, *J* = 2.1 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 4.04-3.96 (m, 1H), 3.87-3.76 (m, 2H), 3.71-3.69 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 201.6, 172.3, 149.8, 139.4, 132.9, 129.8, 129.2, 129.0, 128.9, 127.3, 127.3, 127.0, 126.4, 126.4, 121.3, 118.1, 66.2, 65.9, 61.7, 57.8, 53.4, 14.0. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{23}ClNO_3$ 408.1361; found 408.1366. **FTIR (cm^{-1})** 2983, 1729, 1598, 1499, 1442, 1298.

Ethyl-9-(2-fluorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34p)

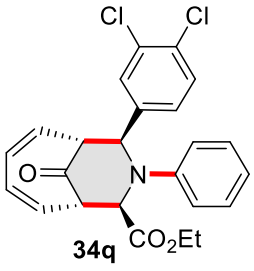
Following the general procedure, treatment of ethyl (*E*)-2-((2-fluorobenzylidene) amino)acetate **2p** (0.078 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-9-(2-fluorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34p** as a yellow oil (0.083 g, 85% yield).



34p

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.45-7.41 (m, 1H), 7.21-7.17 (m, 3H), 7.06-7.03 (m, 3H), 6.98-6.86 (m, 2H), 6.16-6.11 (m, 1H), 6.04-5.99 (m, 1H), 5.94-5.90 (m, 1H), 5.81-5.76 (m, 1H), 5.65 (s, 1H), 4.59-4.59 (m, 1H), 4.01-3.96 (m, 1H), 3.89-3.80 (m, 2H), 3.52-3.44 (m, 1H), 1.04 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.1, 171.8, 160.7 (d, *J* = 248.4 Hz), 150.2, 129.5 (d, *J* = 8.5 Hz), 128.8 (d, *J* = 4.8 Hz), 128.8, 128.6 (d, *J* = 14.6 Hz), 126.7, 126.3, 125.6, 125.4, 124.0 (d, *J* = 3.5 Hz), 120.8, 117.5, 115.2 (d, *J* = 22.2 Hz), 64.8, 61.6, 60.8, 56.5, 53.3, 13.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{23}FNO_3$ 392.1656; found 392.1659. **FTIR (cm^{-1})** 3030, 1730, 1597, 1497, 1453, 1218.

Ethyl-9-(3,4-dichlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34q)

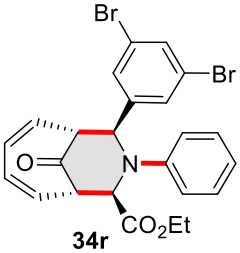


34q

Following the general procedure, treatment of ethyl (*E*)-2-((3,4-dichlorobenzylidene)amino)acetate **2q** (0.098 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded ethyl-9-(3,4-dichlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34q** as a yellow oil (0.054 g, 49% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.21; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37-7.36 (m, 1H), 7.32-7.30 (m, 1H), 7.23-7.19 (m, 2H), 7.16-7.12 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.93-6.90 (m, 1H), 6.16-6.11 (m, 1H), 6.05-6.01 (m, 1H), 5.92-5.87 (m, 1H), 5.77-5.73 (m, 1H), 5.34 (s, 1H), 4.59-4.59 (m, 1H), 3.85-3.37 (m, 3H), 3.66-3.58 (m, 1H), 1.09 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 202.3, 171.4, 150.2, 141.8, 132.5, 131.8, 130.4, 129.4, 129.3, 126.8, 126.7, 126.7, 125.5, 125.2, 121.3, 117.8, 65.8, 65.0, 61.8, 56.1, 53.6, 13.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{22}Cl_2NO_3$ 442.0971; found 442.0977. **FTIR (cm^{-1})** 3029, 1731, 1596, 1498, 1390, 1178.

Ethyl-9-(3,5-dibromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34r)



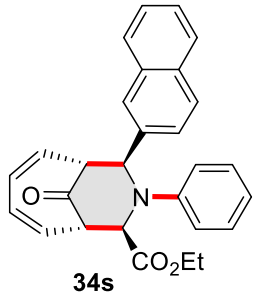
34r

Following the general procedure, treatment of ethyl (*E*)-2-((3,5-dibromobenzylidene) amino)acetate **2r** (0.131 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded ethyl-9-(3,5-dibromophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34r** as yellow oil (0.040 g, 30% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.31; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (s, 1H), 7.38-7.37 (m, 2H), 7.24-7.20 (m, 2H), 7.02 (m, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.17-6.12 (m, 1H), 6.07-6.02 (m, 1H), 5.91-5.87 (m, 1H), 5.79-5.74 (m, 1H), 5.28 (s, 1H), 4.61-4.60 (m, 1H), 3.92-3.68 (m, 4H), 1.13 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 201.72, 171.31, 150.04, 145.63, 133.41, 129.39, 129.03, 126.88, 126.85, 125.63, 125.38, 123.12, 121.46, 117.87, 66.09, 65.31, 62.01, 56.08, 53.63, 14.03. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{22}Br_2NO_3$ 529.9961; found 529.9965. **FTIR (cm^{-1})** 2926, 1732, 1598, 1498, 1242, 747.

Ethyl-9-(naphthalen-2-yl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34s)

Following the general procedure, treatment of ethyl (*E*)-2-((naphthalen-2-ylmethylene) amino)acetate **2s** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-9-(naphthalen-2-yl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34s** as yellow oil (0.079 g, 75% yield).

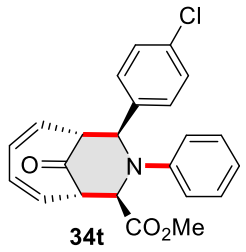


34s

***R*f** (Pet. ether /EtOAc = 92/08): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.80-7.73 (m, 2H), 7.68-7.66 (m, 2H), 7.47-7.43(m, 2H), 7.33-7.31 (m, 1H), 7.27-7.20 (m, 4H), 6.92 (t, *J* = 6.8 Hz, 1H), 6.15-6.10 (m, 1H), 6.02-5.93 (m, 2H), 5.75-5.70 (m, 1H), 5.66 (s, 1H), 4.61 (s, 1H), 4.13 (d, *J* = 8.1 Hz, 1H), 3.97 (d, *J* = 7.8 Hz, 1H), 3.36-3.28 (m, 1H), 3.03-2.95 (m, 1H), 0.83 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.8, 171.3, 150.9, 138.5, 132.9, 132.7, 129.2, 128.4, 127.9, 127.4, 126.6, 126.3, 126.3, 126.2, 125.7, 125.4, 124.8, 120.6, 117.4, 65.8, 64.1, 61.3, 55.6, 53.5, 13.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{25}NNaNO_3$ 446.1727; found 446.1734 . **FTIR (cm^{-1})** 3026, 1730, 1597, 1499, 1390, 1178.

Methyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34t)

Following the general procedure, treatment of methyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2t** (0.079 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded methyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34t** as yellow oil (0.068 g, 69% yield).

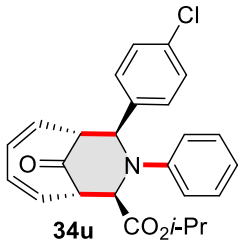


34t

***R*f** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26-7.12 (m, 8H), 6.93-6.89 (m, 1H), 6.11-6.06 (m, 1H), 5.99-5.87 (m, 2H), 5.72-5.67 (m, 1H), 5.49 (s, 1H), 4.60 (s, 1H), 3.95-3.88 (m, 2H), 3.17 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.5, 171.7, 150.6, 139.4, 133.6, 129.3, 129.0, 128.4, 126.6, 126.5, 125.0, 124.6, 120.8, 117.2, 64.9, 63.8, 55.4, 53.4, 52.1. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{20}ClNNaO_3$ 416.1024; found 416.1027. **FTIR (cm^{-1})** 3028, 2952, 1740, 1598, 1497, 1392.

Isopropyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34u)

Following the general procedure, treatment of isopropyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2u** (0.090 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 94/06) of the crude reaction mixture afforded isopropyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34u** as yellow solid (0.070 g, 66% yield).



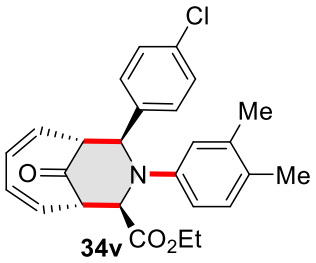
34u

***R*f** (Pet. ether /EtOAc = 90/10): 0.27; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26-7.16 (m, 6H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.90-6.87 (m, 1H), 6.17-6.12 (m, 1H), 6.09-6.04 (m, 1H), 5.92-5.87 (m,

1H), 5.81-5.77 (m, 1H), 5.29-5.29 (m, 1H), 4.57-4.48 (m, 2H), 3.82-3.77 (m, 2H), 1.08 (d, *J* = 6.2 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 202.4, 171.1, 150.2, 140.5, 133.5, 129.2, 128.7, 128.6, 126.9, 126.4, 126.3, 125.6, 121.2, 118.3, 69.9, 67.0, 65.7, 57.0, 53.8, 21.6, 21.51. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{25}H_{24}ClNNaO_3$ 444.1337; found 444.1340. **FTIR (cm^{-1})** 2981, 2364, 1728, 1598, 1496, 1242.

Ethyl-9-(4-chlorophenyl)-8-(3,4-dimethylphenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34v)

Following the general procedure, treatment of ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13b** (0.082 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 93/07) of the crude reaction mixture afforded ethyl-9-(4-chlorophenyl)-8-(3,4-dimethylphenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34v** as a yellow oil (0.058 g, 53% yield).

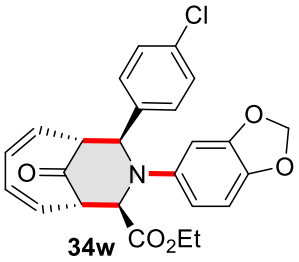


***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.18-7.18 (m, 4H), 6.96-6.81 (m, 3H), 6.15-6.09 (m, 1H), 6.03-5.98 (m, 1H), 5.91-5.87 (m, 1H), 5.75-5.70 (m, 1H), 5.34 (s, 1H), 4.53 (s, 1H), 3.86-3.84 (m, 2H), 3.77-3.69 (m, 1H), 3.53-3.45 (m, 1H), 2.19-2.17 (m, 6H), 1.04 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.4, 171.5, 148.6, 140.1, 137.3, 133.4, 130.3, 129.4, 128.9, 128.4, 126.7, 126.3, 125.6, 125.1, 119.7, 115.6, 66.0, 64.8, 61.5, 56.1, 53.8, 20.4, 19.0, 13.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{26}H_{27}ClNO_3$ 436.1674; found 436.1677. **FTIR (cm^{-1})** 3026, 2926, 1730, 1609, 1501, 1388.

Ethyl-8-(benzo[*d*][1,3]dioxol-5-yl)-9-(4-chlorophenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34w)

Following the general procedure, treatment of ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethane sulfonate **13c** (0.086 g, 0.25 mmol) and in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5

mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded ethyl-8-(benzo[*d*][1,3]dioxol-5-yl)-9-(4-chlorophenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34w** as a yellow oil (0.080 g, 71% yield).

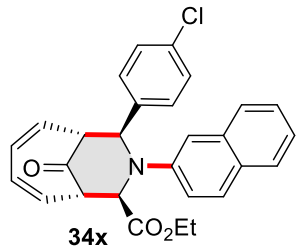


34w

***R*f** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.20-7.13 (m, 4H), 6.68-6.68 (m, 1H), 6.62-6.57 (m, 2H), 6.18-6.05 (m, 2H), 5.88-5.83 (m, 3H), 5.78-5.73 (m, 1H), 5.02 (s, 1H), 4.37 (d, *J* = 2.6 Hz, 1H), 3.84-3.73 (m, 3H), 3.64-3.56 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.1, 171.2, 148.0, 145.2, 143.3, 140.2, 133.5, 129.01, 128.5, 126.7, 126.2, 126.2, 125.6, 114.1, 108.2, 103.2, 101.2, 67.9, 66.3, 61.6, 57.0, 54.2, 13.9. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{25}H_{22}ClNNaO_5$ 474.1079; found 474.1081. **FTIR (cm^{-1})** 2899, 2364, 1730, 1487, 1215, 1037.

Ethyl-9-(4-chlorophenyl)-8-(naphthalen-2-yl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34x)

Following the general procedure, treatment of ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 3-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **13d** or 1-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **13e** (0.087 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-9-(4-chlorophenyl)-8-(naphthalen-2-yl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34x** as yellow oil (0.066 g, 58% yield from **13d** or 0.071, 62% from **13e**).



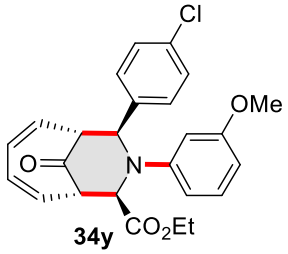
34x

***R*f** (Pet. ether /EtOAc = 90/10): 0.27; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.75-7.71 (m, 2H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.50-7.50 (m, 1H), 7.44-7.38 (m, 2H), 7.34-7.30 (m, 1H), 7.19 (s, 4H), 6.15-6.10 (m, 1H), 5.99-5.92 (m, 2H), 5.73-5.68 (m, 1H), 5.60 (s, 1H), 4.70 (s, 1H), 3.98-3.93 (m, 2H), 3.76-3.68 (m, 1H), 3.45-3.37 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 203.3, 171.3, 148.3, 139.4, 134.5, 133.7, 129.2, 129.0, 128.4, 127.6, 127.0, 126.7, 126.6, 126.5, 125.2, 124.8, 124.0, 119.0, 113.2, 65.3, 64.3, 61.7, 55.5, 53.7,

13.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{28}H_{25}ClNO_3$ 458.1517; found 458.1524. **FTIR (cm^{-1})** 3026, 2365, 1730, 1598, 1499, 1390.

Ethyl-9-(4-chlorophenyl)-8-(3-methoxyphenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34y)

Following the general procedure, treatment of ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13f** (0.082 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded ethyl-9-(4-chlorophenyl)-8-(3-methoxyphenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34y** as yellow oil (0.061 g, 56% yield).



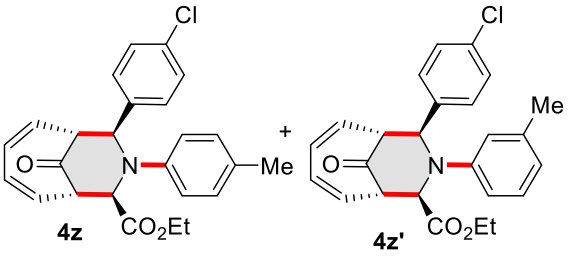
34y

***R*f** (Pet. ether /EtOAc = 90/10): 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.19 (s, 4H), 7.14-7.10 (m, 1H), 6.72-6.67 (m, 2H), 6.47-6.45 (m, 1H), 6.12-6.07 (m, 1H), 6.01-5.96 (m, 1H), 5.91-5.86 (m, 1H), 5.73-5.68 (m, 1H), 5.43 (s, 1H), 4.57 (s, 1H), 3.90-3.86 (m, 2H), 3.76 (m, 3H), 3.72-3.62 (m, 2H), 3.47-3.39 (m, 1H), 1.04 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 203.10, 171.29, 160.55, 152.10, 139.67, 133.60, 129.94, 128.92, 128.43, 126.69, 126.49, 125.33, 124.89, 110.08, 105.55, 104.20, 65.47, 64.32, 61.64, 55.65, 55.28, 55.32, 13.89. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{25}H_{25}ClNO_4$ 438.1467; found 438.1469. **FTIR (cm^{-1})** 2914, 1733, 1600, 1284, 1260, 1108.

Ethyl-9-(4-chlorophenyl)-10-oxo-8-(*p*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34z) and ethyl-9-(4-chlorophenyl)-10-oxo-8-(*m*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34z')

Following the general procedure, treatment of ethyl (*E*)-2-((4-chlorobenzylidene) amino)acetate **2a** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13g** (0.078 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in

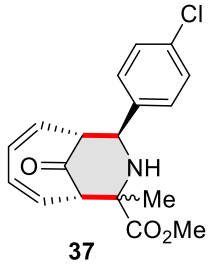
THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded Ethyl-9-(4-chlorophenyl)-10-oxo-8-(*p*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34z** and ethyl-9-(4-chlorophenyl)-10-oxo-8-(*m*-tolyl)-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34z'** as a mixture of regioisomers in 1.1:1 ratio as yellow oil (0.077 g, 73% yield).



***R*f** (Pet. ether /EtOAc = 90/10): 0.27; **^{1}H NMR (400 MHz, $CDCl_3$) of Major isomer** δ 7.19-7.18 (m, 4H), 7.11-7.07 (m, 1H), 7.00-7.00 (m, 2H), 6.91-6.90 (m, 1H), 6.13-6.08 (m, 1H), 6.03-5.97 (m, 1H), 5.91-5.86 (m, 1H), 5.75-5.70 (m, 1H), 5.42 (s, 1H), 4.57-4.51 (m, 1H), 3.89-3.85 (m, 2H), 3.77-3.68 (m, 1H), 3.53-3.43 (m, 1H), 2.26 (s, 3H), 1.06-1.02 (m, 3H). **Representative peaks of minor isomer ^{1}H NMR (400 MHz, $CDCl_3$)** 6.73-6.71 (m, 1H), 5.31 (s, 1H), 2.28 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) of Major isomer** δ 203.3, 171.5, 150.6, 140.0, 133.5, 129.0, 128.9, 128.4, 126.4, 125.4, 125.6, 125.1, 121.8, 118.4, 66.1, 64.9, 61.6, 56.1, 53.8, 21.9, 13.9. **Representative peaks of minor isomer ^{13}C NMR (100 MHz, $CDCl_3$)** 203.3, 171.4, 148.2, 139.8, 139.0, 130.7, 128.9, 118.3, 65.5, 64.4, 55.8, 53.6, 20.6. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{25}H_{25}ClNO_3$ 422.1517; found 422.1523. **FTIR (cm^{-1})** 2924, 2364, 1728, 1515, 1489, 1172.

Methyl-9-(4-chlorophenyl)-7-methyl-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (37)

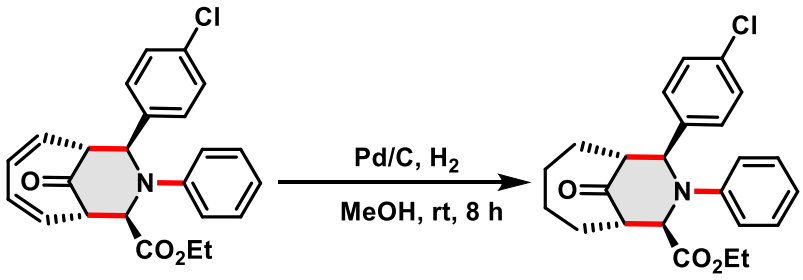
Following the general procedure, treatment of methyl (*E*)-3-((4-chlorobenzylidene)amino)-2-methylpropanoate **2v** (0.085 g, 0.375 mmol), cyclohepta-2,4,6-trien-1-one **33** (0.032 g, 0.3 mmol), and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **13a** (0.074 g, 0.25 mmol) in the presence of KF (0.029 g, 0.5 mmol) and 18-crown-6 (0.132 g, 0.5 mmol) in THF (2.5 mL) at 0 °C to rt for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture afforded methyl-9-(4-chlorophenyl)-7-methyl-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **37** as sticky liquid (0.049 g, 49% yield).



***R*f** (Pet. ether /EtOAc = 90/10): 0.16; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.13-6.08 (m, 1H), 5.99-5.95 (m, 1H), 5.62-5.57 (m, 1H), 4.94-4.89 (m, 1H), 4.26 (d, *J* = 3.8 Hz, 1H), 3.81-3.74 (m, 4H), 3.37-3.33 (m, 1H), 2.00 (bs, 1H), 1.43 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 205.28, 175.02, 137.48, 133.62, 128.64, 128.40, 127.73, 126.73, 123.16, 122.19, 67.89, 61.68, 58.46, 56.96, 52.87, 23.63. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{18}H_{19}ClNO_3$ 332.1048; found 332.1051. **FTIR (cm^{-1})** 2957, 2922, 2364, 1732, 1492, 1227.

3.6.9. Product Functionalization

a) Reduction of the Diene Moiety

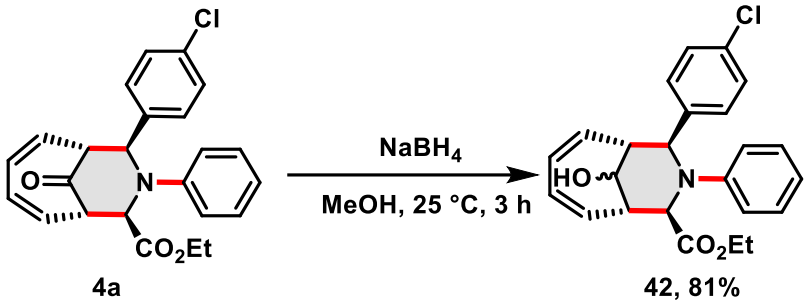


34a **41, 73%**

Following the literature procedure,[19] treatment of ethyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34a** (0.102 g, 0.25 mmol) with palladium-carbon catalyst (0.026 g, 0.025 mmol) in 5 mL MeOH for 8 h and followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/02) of the crude reaction mixture afforded ethyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]decane-7-carboxylate **41** as a colorless oil (0.075 g, 73% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25-7.22 (m, 1H), 7.19-7.04 (m, 5H), 6.74-6.71 (m, 1H), 6.65-6.61 (m, 2H), 4.13-3.97 (m, 2H), 3.31-3.17 (m, 2H), 2.95-2.87 (m, 1H), 2.53-2.48 (m, 1H), 1.83-1.77 (m, 2H), 1.71-1.58 (m, 4H), 1.52-1.42 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 214., 173.2, 147.7, 140.3, 129.3, 129.2, 128.5, 126.2, 118.5, 114.0, 61.3, 59.4, 54.0, 53.7, 36.6, 29.8, 28.2, 27.1, 26.0, 14.3. **FTIR (cm^{-1})** 2927, 2364, 1726, 1602, 1501, 1451.

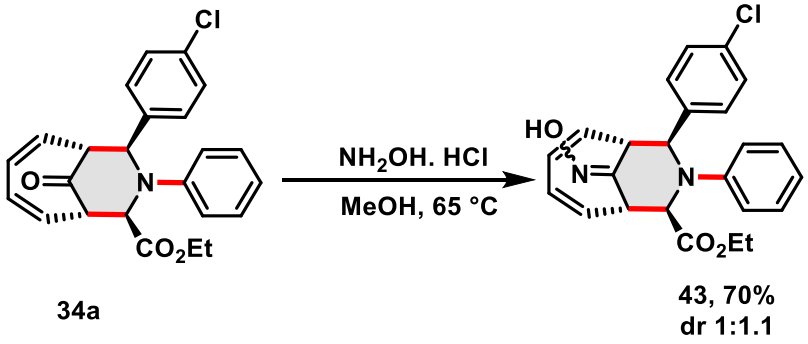
b) Reduction of ketone Moiety



Following the general procedure, treatment of ethyl-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **34a** (0.102 g, 0.25 mmol), $NaBH_4$ (0.038 g, 1.0 mmol) in MeOH (5 mL) at 25 °C for 3 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 82/18) of the crude reaction mixture afforded ethyl-9-(4-chlorophenyl)-10-hydroxy-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **42** as colorless oil (0.083 g, 81% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.19; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29-7.26 (m, 2H), 7.21-7.17 (m, 4H), 7.13-7.11 (m, 2H), 6.84-6.81 (m, 1H), 6.13-6.09 (m, 1H), 6.02-5.95 (m, 2H), 5.78-5.73 (m, 1H), 5.39 (s, 1H), 4.82-4.80 (m, 1H), 4.47 (m, 1H), 3.77-3.69 (m, 2H), 3.46-3.34 (m, 2H), 2.05-1.97 (m, 1H), 1.06 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.8, 151.9, 139.0, 133.0, 130.4, 129.9, 129.2, 128.9, 128.2, 127.7, 127.7, 119.5, 115.9, 61.1, 60.9, 60.8, 60.7, 43.4, 13.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{25}ClNO_3$ 410.1517; found 410.1521. **FTIR (cm^-)[1]** 3019, 2909, 2364, 1728, 1596, 1497, 1394.

c) Conversion of ketone to oxime



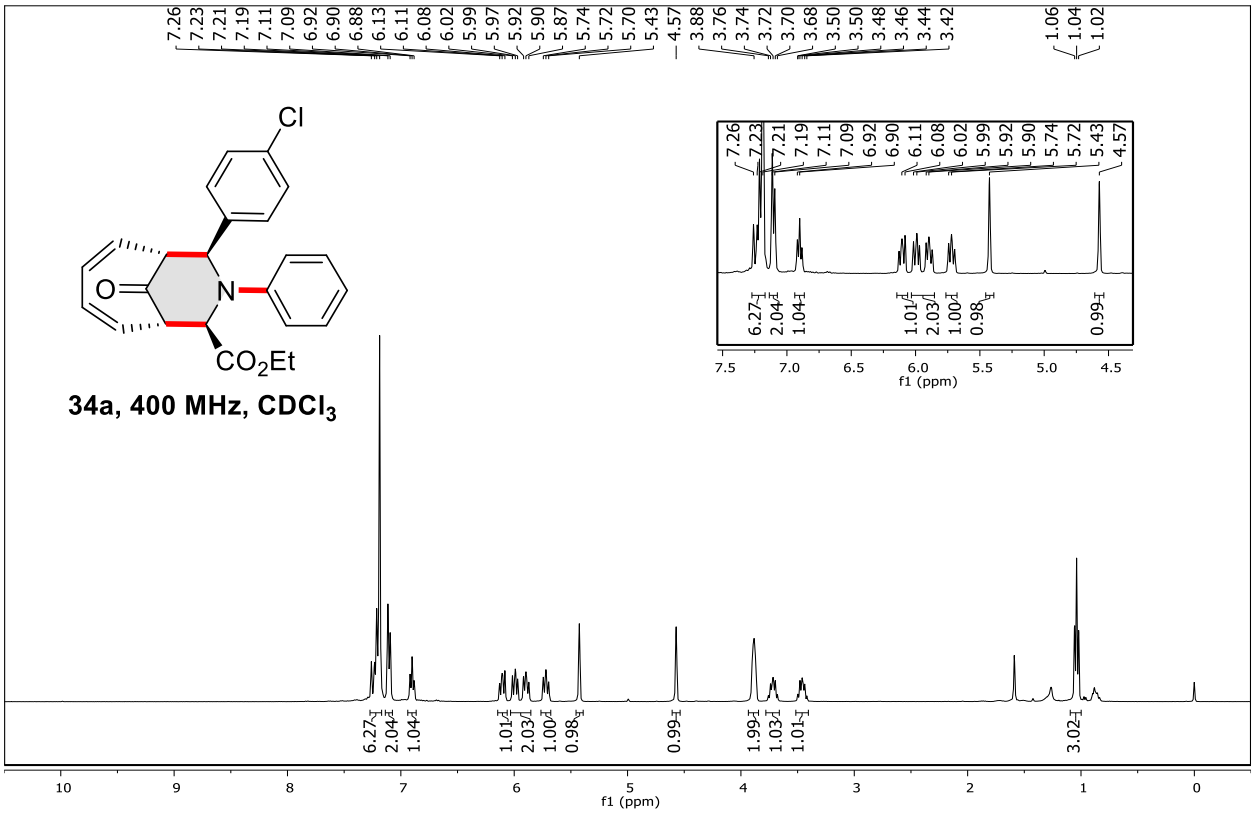
Compound **43** was synthesized following the modified literature procedure.[20] To a solution of **34a** (102 mg, 0.25 mmol, 1.0 equiv) in 2.5 mL MeOH was added $NaHCO_3$ (48

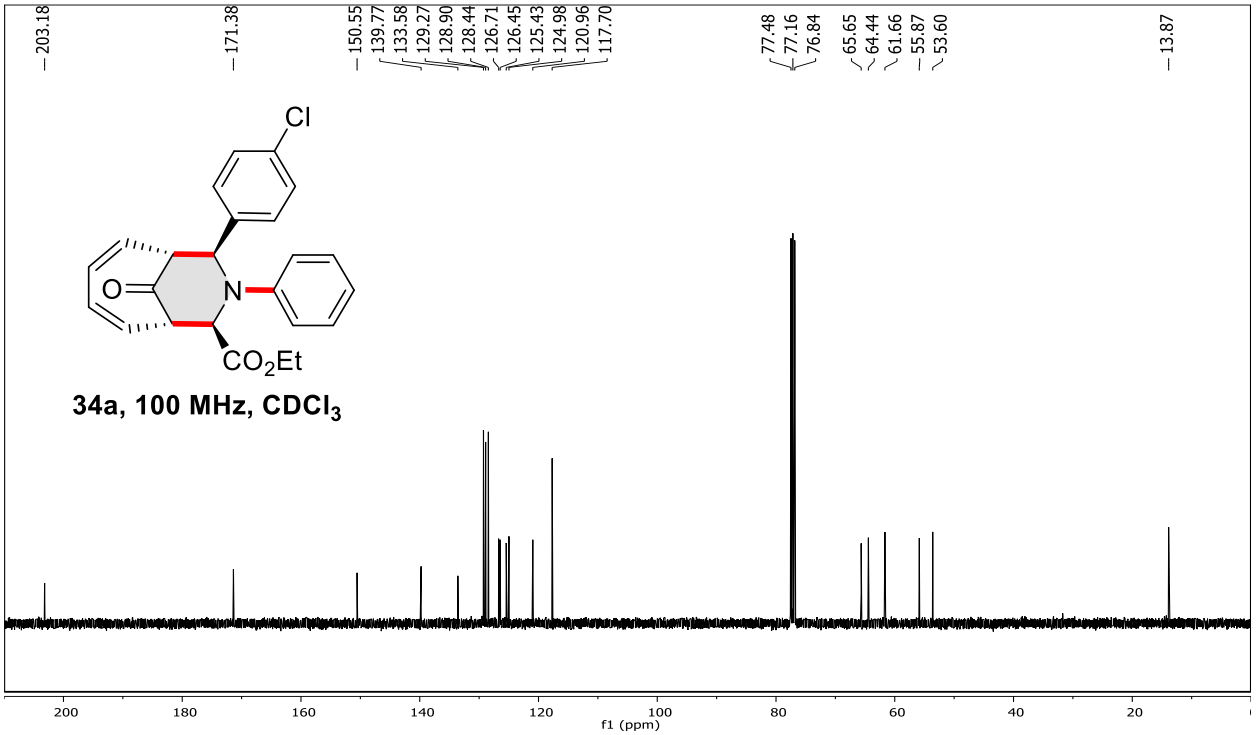
mg, 0.58 mmol, 2.3 equiv) and NH_2OH•HCl (40 mg, 0.58 mmol, 2.3 equiv), the mixture was stirred at 65 °C for 12 h. Then the reaction mixture was allowed to cool to room temperature, the solvent was evaporated and the residue was purified by column chromatography to give ethyl-9-(4-chlorophenyl)-10-(hydroxyimino)-8-phenyl-8 azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate **43** as a light yellow solid (74 mg, 70% yield; diastereomeric ratio determined by crude ^{1}H NMR is 1:1.1)

***R*f** (Pet. ether /EtOAc = 80/20): 0.32; **^{1}H NMR of major diastereomer (400 MHz, $CDCl_3$)** δ 8.56 (s, 1H), 7.33-7.12 (m, 8H), 6.91-6.87 (m, 1H), 6.12-6.02 (m, 2H), 5.97-5.82 (m, 2H), 5.44 (s, 1H), 4.95-4.94 (m, 1H), 4.37 (s, 1H), 4.06-4.05 (m, 1H), 3.78-3.67 (m, 1H), 3.29-3.23 (m, 1H), 1.06-1.01 (m, 3H). **^{13}C NMR of major diastereomer (100 MHz, $CDCl_3$)** δ 171.67, 153.37, 151.32, 139.69, 133.31, 129.19, 128.95, 128.20, 127.47, 127.01, 125.95 119.98, 116.89, 61.96, 61.61, 61.39, 43.14, 37.21, 13.87. **Representative peaks for minor diastereomer**: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08 (s, 1H), 5.29 (s, 1H), 4.41-4.40 (m, 1H), 4.00-3.99 (m, 1H), 3.39-3.31 (m, 1H). **^{13}C NMR of minor diastereomer (100 MHz, $CDCl_3$)** δ 171.79, 153.41, 151.05, 139.93, 133.24, 129.56, 129.30, 129.02, 127.63, 127.03, 125.85, 120.30, 117.16, 62.25, 61.55, 61.37, 44.66, 36.67, 13.81. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{24}H_{24}ClN_2O_3$ 423.1470; found 423.1476. **FTIR (cm^{-1})** 2926, 2364, 1728, 1585, 1496, 1150.

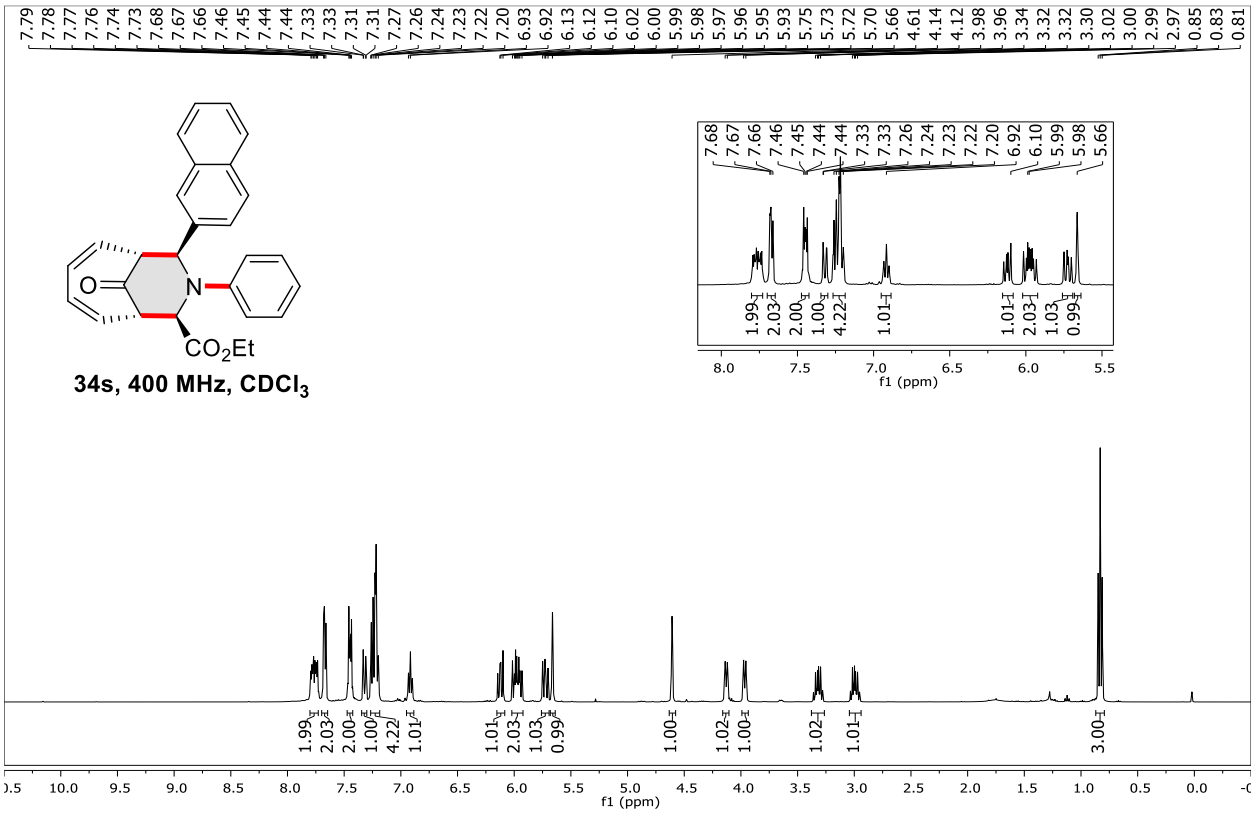
3.6.10. ^{1}H and ^{13}C NMR Spectra of Selected Compounds

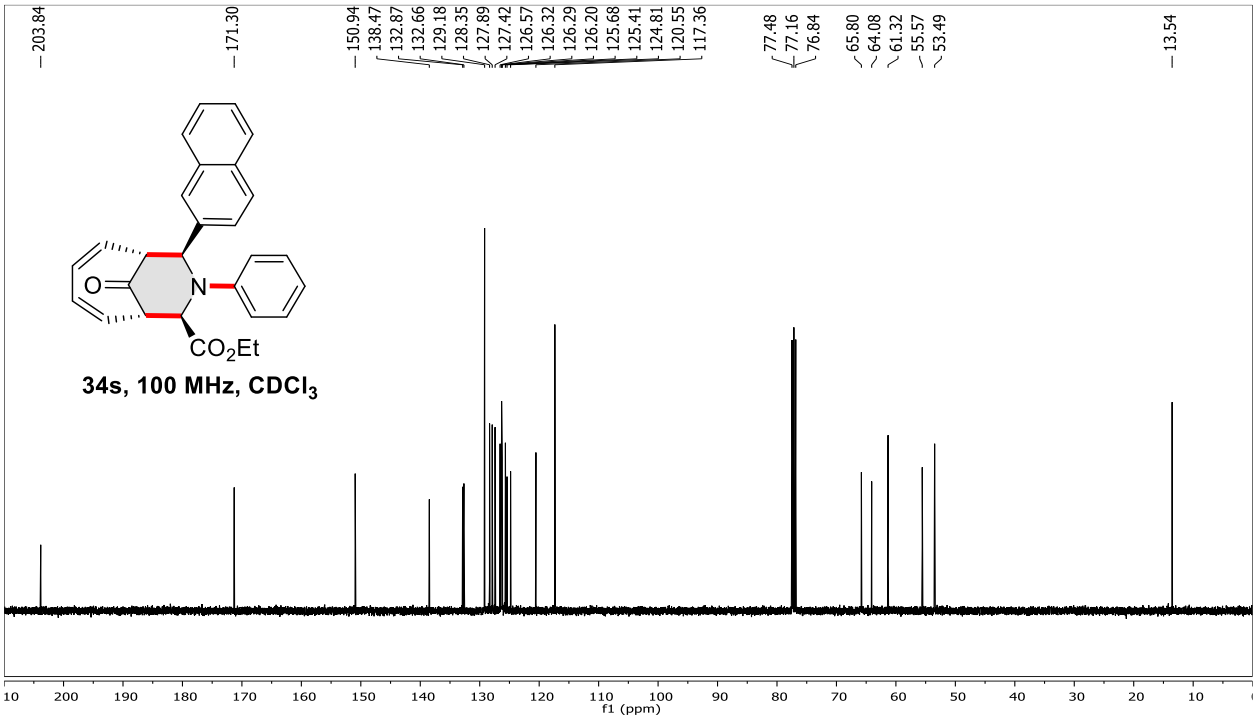
Ethyl-9-(4-chlorophenyl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34a)



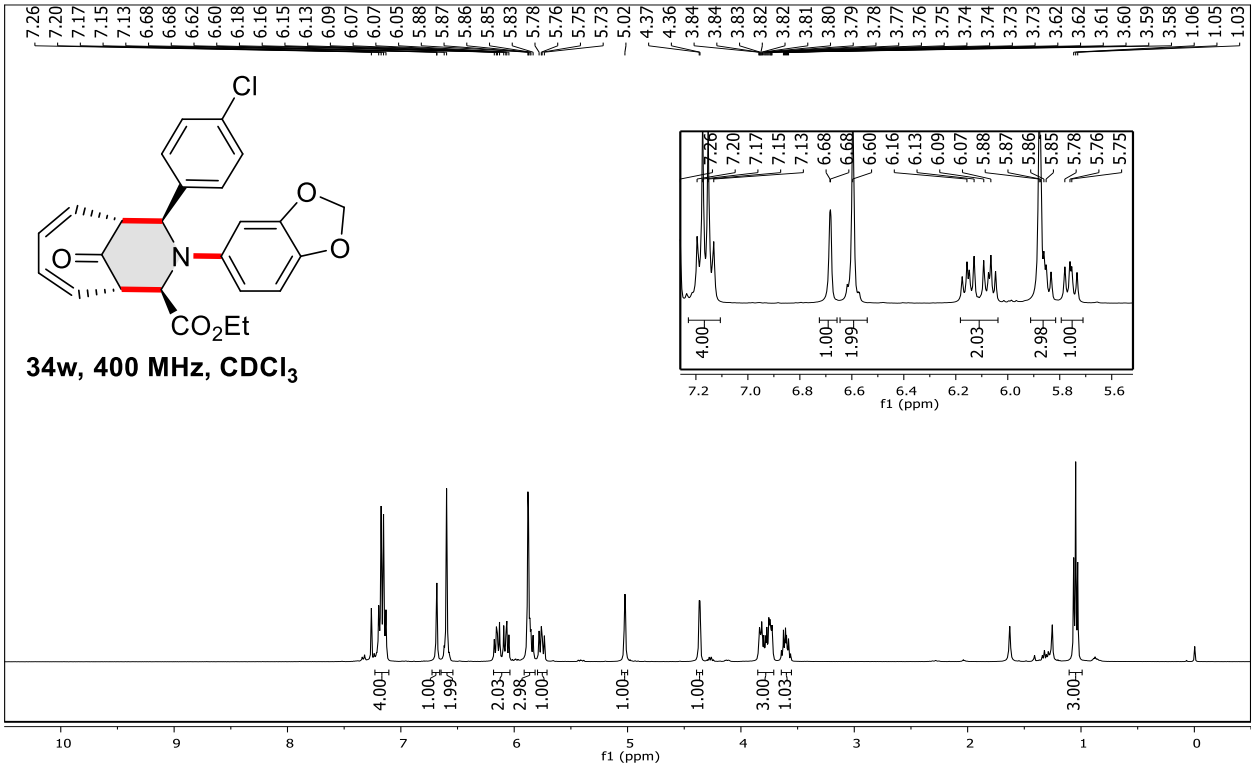


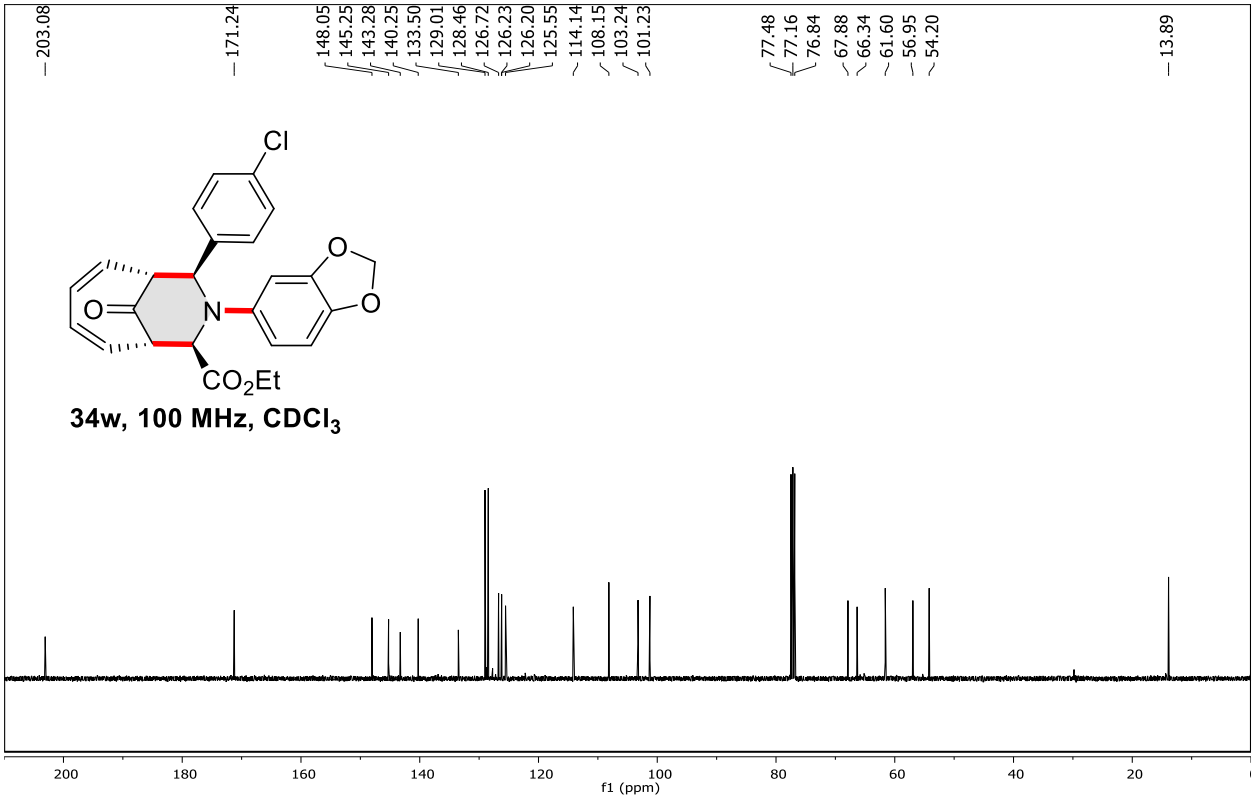
Ethyl-9-(naphthalen-2-yl)-10-oxo-8-phenyl-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34s)





Ethyl-8-(benzo[*d*][1,3]dioxol-5-yl)-9-(4-chlorophenyl)-10-oxo-8-azabicyclo[4.3.1]deca-2,4-diene-7-carboxylate (34w)





3.7. References

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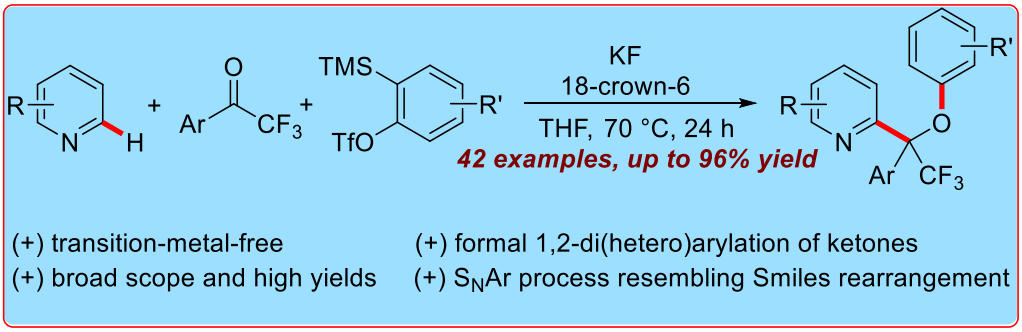
Chapter 4

Transition-Metal-Free C2-Functionalization of Pyridines via Aryne Three-Component Coupling

The direct C2-functionalization of pyridines via a transition-metal-free protocol using aryne multicomponent coupling is demonstrated in this Chapter. The reaction allowed a broad scope synthesis of C2 substituted pyridine derivatives bearing the -CF_3 group in good yields engaging α,α,α-trifluoroacetophenones as the third component. Activated keto esters could also be employed as the third component in this formal 1,2-di(hetero)arylation of ketones. The initially generated pyridylidene intermediate undergoes a nucleophilic attack on the carbonyl followed by an S_NAr process resembling the Smiles rearrangement to afford the desired products.

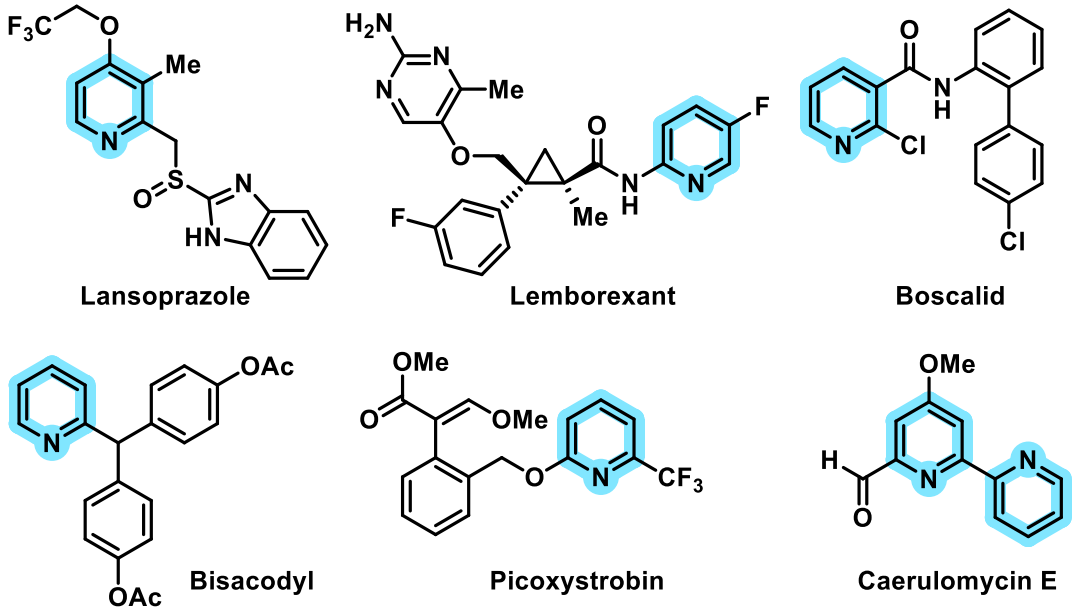


Chem. Eur. J. **2021,** *27*, 13864.

4.1. Introduction

In medicinal chemistry and materials science, pyridines are commonly found heterocyclic structural units, with many bioactive C2-functionalized pyridines having been already identified (Figure 4.1).[1] However, directly functionalizing pyridines is a major challenge in modern synthetic organic chemistry due to the low energy π-system, which results in poor selectivity and reactivity.[2] Despite significant progress in the past decade, direct functionalization of pyridines is still challenging because of limited accessible functional groups and poor regioselectivity. Generally, C2 selectivity is observed in these reactions, although some C4- and C3-functionalized products have been obtained. The use of strong acids, such as in the Minisci reaction, is necessary to enhance the reactivity of pyridines. However, this requirement for harsh activation conditions can restrict the use of this method for acid-sensitive functional groups. Thus, a unique protocol that eliminates the need for acid reagents would be extremely desirable.

Figure 4.1. Representative, Bioactive C2-Functionalized Pyridines

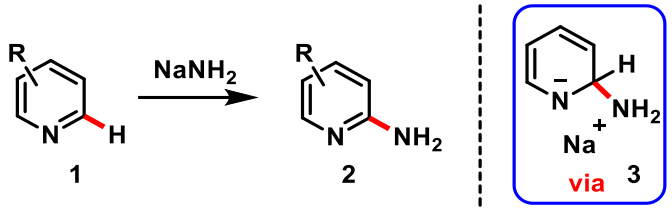


4.2. General Route for C2-Functionalized Pyridine Synthesis

The Chichibabin reaction is a long-established and effective method for selectively functionalizing the C2 position of pyridines **1**, utilizing their electrophilicity to obtain versatile 2-amino pyridines **2** (Scheme 4.1).[3] Chichibabin reaction operates through an addition-elimination pathway. Although this strategy does not require any acid, but the use

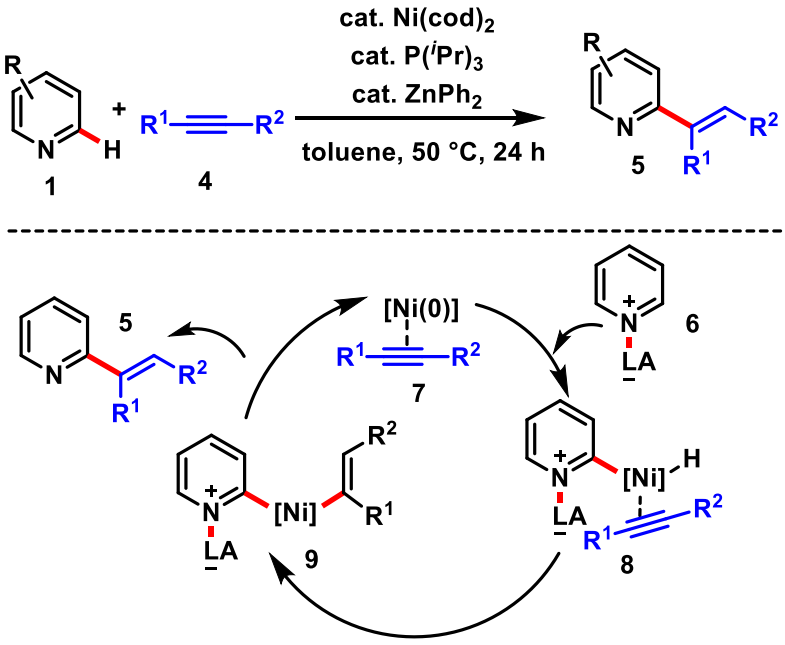
of highly basic sodium amide can be problematic for base-sensitive substrates. Furthermore, the century-old reaction is also plagued by dimerization, which presents additional issues.

Scheme 4.1. Chichibabin Reaction



Various methods have been employed to achieve the selective functionalization of the C2 position of pyridines, including S_NAr reactions,[4] reactions involving radical species,[5] deprotonation followed by metalations,[6] and metal-catalyzed C-H transformation reactions.[7] Undirected metal-catalyzed C-H transformation reactions are regarded as a potent approach among these methods. As for example, Hiyama and co-workers have demonstrated the efficacy of nickel-Lewis acid cooperative catalysis in achieving divergent direct C-2 alkenylation of pyridines, leading to the synthesis of a wide range of 2-alkenylated pyridines with high chemo-, regio-, and stereoselectivity under mild reaction conditions (Scheme 4.2).[8]

Scheme 4.2. Nickel/Lewis Acid-Cocatalyzed Reaction of Pyridine with Alkynes

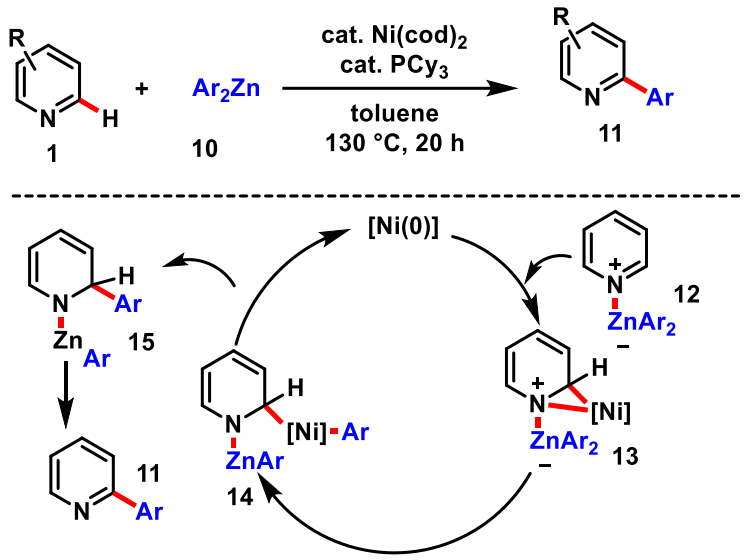


The addition of diphenylzinc as a Lewis acid results in the formation of alkenylpyridines. The reaction mechanism involves the activation of pyridine by the Lewis acid, followed by

oxidative addition to nickel(0). Hydronickelation then occurs with the alkyne **4**, producing the corresponding alkenylnickel species **8**, which finally undergoes reductive elimination to yield the desired product **5**.

Chatani and co-workers have reported a distinct method for arylating pyridines. By using diarylzinc reagents along with catalytic amounts of nickel and a phosphine ligand, pyridine can be converted into C2-arylated pyridines (Scheme 4.3).[9] During the reaction, the crucial intermediate 2-aryldihydropyridine **15** is formed, which eventually undergoes aromatization to produce the final product **11**.

Scheme 4.3. Nickel-Catalyzed C2-Arylation of Pyridine with Diarylzinc Reagent



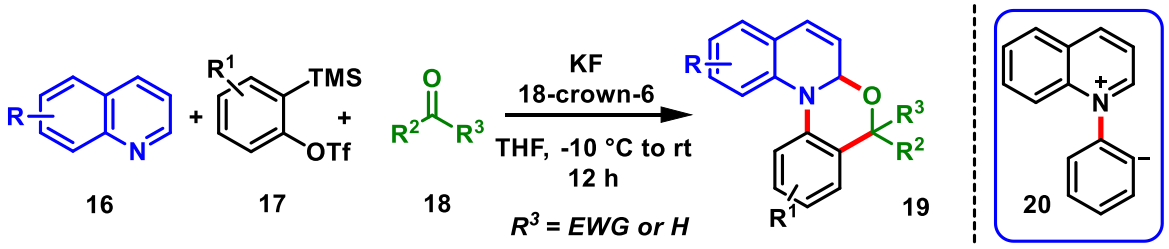
While several transition metal-catalyzed methods are effective in producing C2 functionalized pyridine derivatives, the expense and toxicity of the metal can restrict the potential application of the process. As a result, transition-metal-free approaches are often preferred over other methods. However, in many cases, before functionalizing at the C2 position, the pyridine core must be oxidized to the *N*-oxide.[10] Additionally, following the functionalization step, the *N*-oxide must be transformed back into pyridine. Although this approach is effective for C2 functionalization of pyridines, it suffers from a drawback in terms of step economy.

4.3. *N*-Heterocycle Triggered Aryne Multicomponent Coupling Reactions

In Chapter 1, it was discussed that several *N*-heterocycles, such as quinoline, isoquinoline, acridine, and 1,10-phenanthroline, can be used to initiate aryne multicomponent

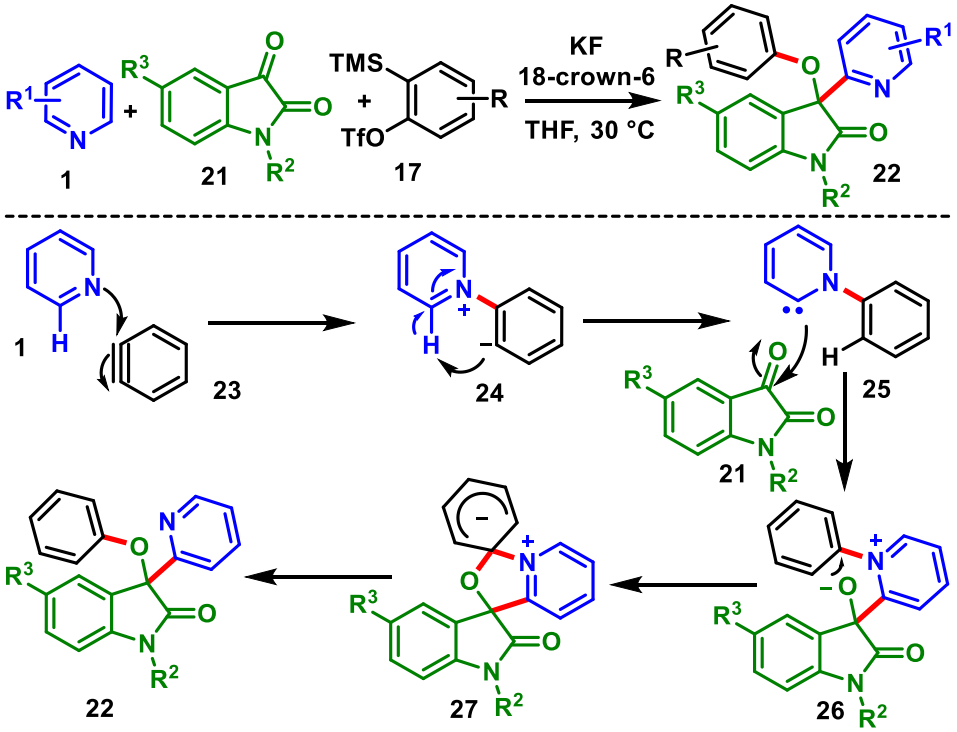
coupling reactions (MCR).[11] For example Biju and co-workers uncovered quinolines and isoquinolines as the nucleophilic triggers for aryne MCR.[12] As a result of heterocycle addition to aryne, it generates zwitterionic intermediate **20**, which was intercepted using activated carbonyl compounds or aldehydes **18**, leading to the diastereoselective synthesis of oxazino quinoline/isoquinoline derivatives **19** (Scheme 4.4).

Scheme 4.4. Quinoline Triggered Aryne Multicomponent Coupling Reaction



It is noteworthy that the reaction outcome changed significantly when the nucleophile was switched from isoquinoline to pyridine. Instead of forming the anticipated pyrido oxazino product, a novel rearrangement occurred, leading to the synthesis of 3,3-disubstituted oxindoles **22** (Scheme 4.5). The rearrangement mechanism involves a pyridylidene intermediate **25**, which is generated via an attack of pyridine **1** nitrogen on the

Scheme 4.5. Pyridine Triggered Aryne MCR with Isatin

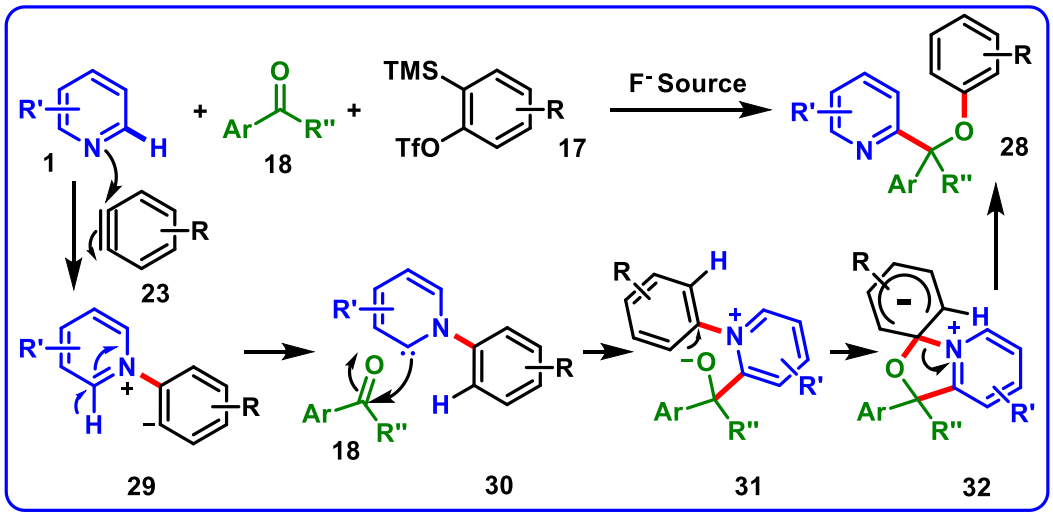


aryne **23** followed by intramolecular proton transfer. This intermediate is nucleophilic and reacts with *N*-substituted isatin to form intermediate **26**, which undergoes an S_NAr pathway similar to the Smiles rearrangement, ultimately leading to the formation of indolin-2-one **22**.

4.4. Statement of the Problem

The synthesis of C2 functionalized pyridine has proven to be a challenging task, as discussed in the preceding sections. To overcome these difficulties, synthetic organic chemists have employed various innovative protocols. As discussed, pyridine-triggered aryne MCR in previous section, which produces C2 substituted pyridine derivatives through a transition-metal-free pathway by in situ generating pyridylidene intermediate, is a unique method. However, this methodology has several limitations. Firstly, only selected 5-substituted isatins worked under the present reaction conditions. Secondly, only DMAP can be used as a nucleophilic trigger besides pyridine. Thirdly, only the 4,5-difluoro aryne precursor worked under the optimized reaction conditions. Moreover, when 4,5-dimethyl phenol or sesamol-derived aryne precursors were used, the expected products were not formed due to the in situ generated pyridylidene intermediate being quenched by the moisture present in the reaction medium. Despite these limitations, we aimed to explore the methodology further in greater detail and with more working examples. We hypothesized that activated carbonyls **18** (trifluoroacetophenones, α-ketoesters, aldehydes) could also serve as electrophilic triggers for efficient C2 functionalization of pyridines (Scheme 4.6).

Scheme 4.6. Pyridine Triggered Aryne MCR with Activated Carbonyls (Working Hypothesis)



Mechanistically, the reaction is initiated by the addition of pyridine **1** to in situ generated arynes **23**. Intramolecular proton transfer then generates the highly reactive pyridylidene intermediate **30**, which subsequently adds to activated carbonyls **18**. The generated intermediate then undergoes an S_NAr reaction similar to the Smiles rearrangement, ultimately producing C2 substituted pyridine derivatives **28**. Although reaction of pyridine with benzyne generated from the 2-(trimethylsilyl)aryl triflate (Kobayashi precursor) resulting in the formation of an alternating copolymer having 2-phenylene and the 2,3-dihydropyridine moieties are reported by Ihara and co-workers.[13] As a consequence of careful optimization herein we demonstrated transition-metal-free aryne triggered C2 functionalization of pyridines.

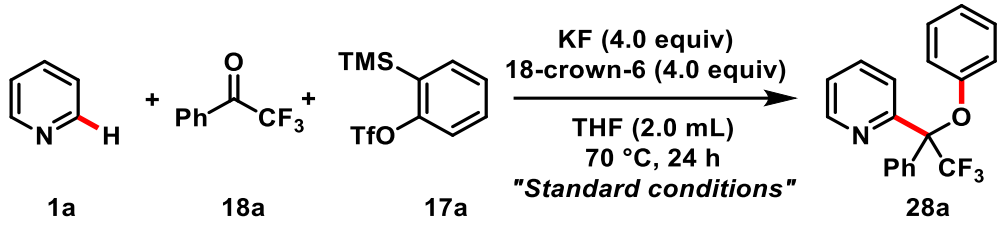
4.5. Results and Discussion

4.5.1. Optimization Studies

The present study commenced by the treatment of pyridine **1a** with α,α,α-trifluoroacetophenone **18a** and the benzyne formed in situ from 2-(trimethylsilyl)aryl triflate **17a** with the aid of KF and 18-crown-6 in THF (0.125 M) at 70 °C. A facile reaction occurred resulting in the formation of C2 substituted pyridine derivative bearing the $-CF_3$ group (**28a**) in 47% yield (based on ^{1}H NMR, Table 4.1, entry 1) under these conditions. With this initial result, detailed optimization studies were carried out. Increasing or decreasing the quantity of aryne precursor **17a** did not enhance the reactivity and hence the yield of **28a** (entries 2 and 3). In addition, switching the fluoride source from KF to CsF resulted in only 19% yield of **28a** (entry 4). When tetrabutyl ammonium fluoride (TBAF) was employed as a fluoride as the source, the reaction provided only traces of **28a** (entry 5). Decreasing the temperature of the reaction to 25 °C furnished only 32% yield of **28a** (entry 6) and performing the reaction in DME instead of THF provided **28a** in 41% yield (entry 7). Notably, when the reaction was done using 1.0 equiv of **1a** and 2.0 equiv of **17a**, the yield of **28a** was dropped to 17% (entry 8). Interestingly, performing the reaction under dilute conditions (0.05 M instead of 0.125 M) improved the yield of **28a** to 59% (entry 9). It is likely that the pyridine-aryne polymerization was inhibited under dilute conditions. Further dilutions (to 0.025 M) improved the yield of **28a** to 84% (entry 10), and finally, carrying out the reaction in 0.017 M concentration afforded the product **28a** in 93% isolated yield (entry 11). Hence entry 11

was found to be the optimized conditions for this reaction and this reaction conditions were used for further substrate scope analysis.

Table 4.1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions	yield of 28a (%)[b]
1	none	47
2	2.5 equiv of **17a** instead of 2.0 equiv	46
3	1.5 equiv of **17a** instead of 2.0 equiv	39
4[c]	CsF instead of KF/18-crown-6	19
5	TBAF instead of KF/18-crown-6	<5
6	25 °C instead of 70 °C	32
7	DME instead of THF	41
8	1.0 equiv of **1a** and 2.0 equiv of **18a**	17
9	0.05 M THF instead of 0.125 M	59
10	0.025 M THF instead of 0.125 M	84
11	*0.017 M THF instead of 0.125 M*	*94 (93)*

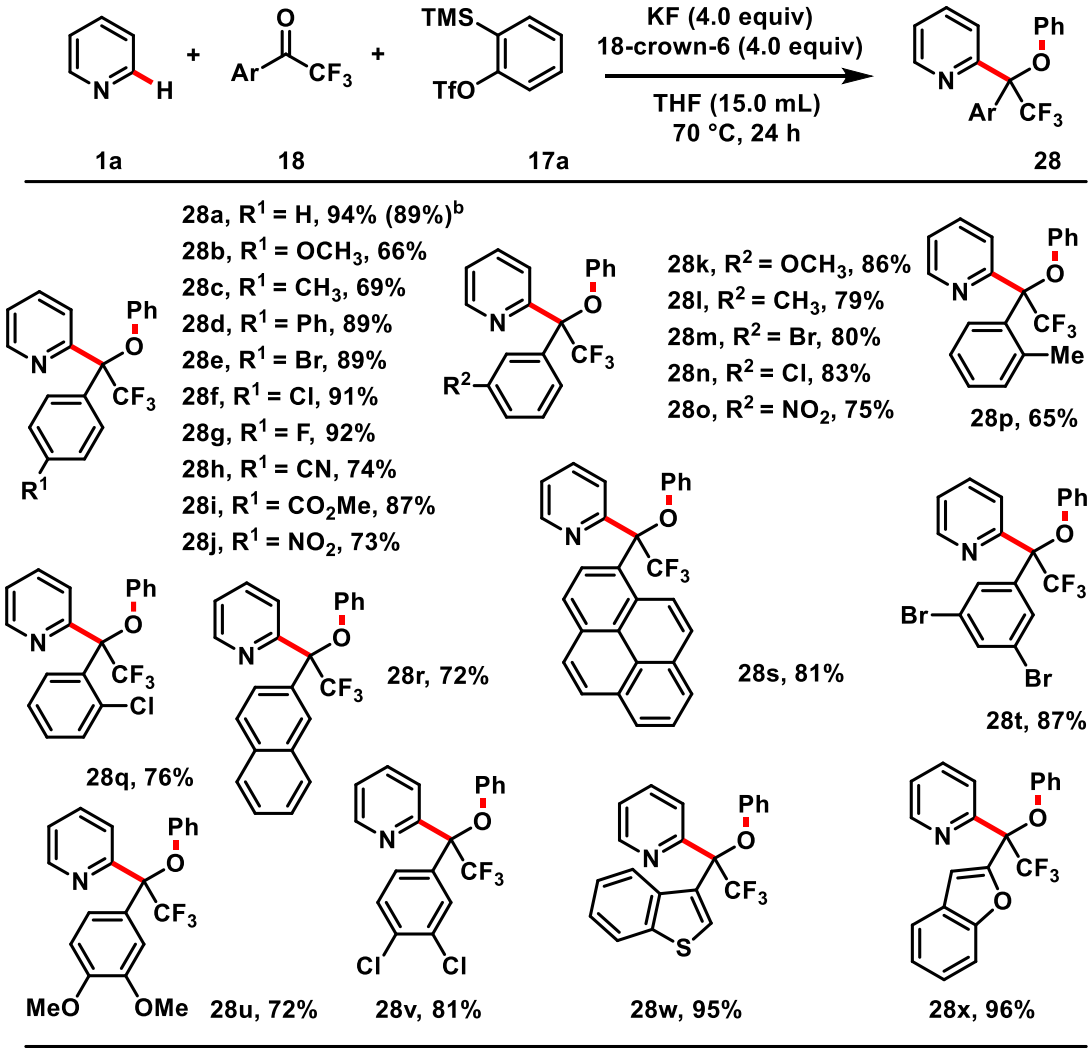
[a] Standard conditions: **1a** (0.375 mmol), **18a** (0.25 mmol), **17a** (0.5 mmol), KF (4 equiv), 18-crown-6 (4 equiv), THF (2.0 mL), 70 °C for 24 h. [b] Yields obtained from the ^{1}H NMR analysis of the crude reaction products employing CH_2Br_2 as the internal standard is provided. Isolated yield in parentheses. [c] CH_3CN was used as the solvent.

4.5.2. Substrate Scope of C2 Functionalization of Pyridines: Scope of α,α,α-Trifluoroacetophenones

After establishing the favourable reaction parameters, the scope and the limitations of this aryne MCC has been examined. First, the variation of α,α,α-trifluoroacetophenone **18** was tested (Scheme 4.7). Various 2,2,2-trifluoroacetophenone derivatives having electronically dissimilar groups at the 4-position of the aryl ring reacted smoothly under the optimized conditions and delivered the C2 substituted pyridine derivatives in good to excellent yields (**28a**-**28j**). Upon performing the reaction in a 1.0 mmol scale, **28a** was isolated in 89% yield highlighting the practical and scalable nature of the present aryne MCC. Moreover, aryl ketones bearing functional groups at the 3-position as well as 2-position of the benzene ring are well tolerated to afford the desired products in good yields (**28k**-**28q**).

Interestingly, the 2-naphthyl and pyrenyl substituted ketones provided the expected products **28r** and **28s** in 72% and 81% yield respectively. In addition, disubstituted and heteroaromatic ketones underwent the smooth rearrangement involving arynes to furnish the target products in high yields (**28t**-**28x**). Disappointingly, aliphatic CF_3-containing ketones cannot be used as the third components in the present pyridine-triggered rearrangement.

Scheme 4.7. Substrate Scope: Variation of α,α,α-Trifluoroacetophenones

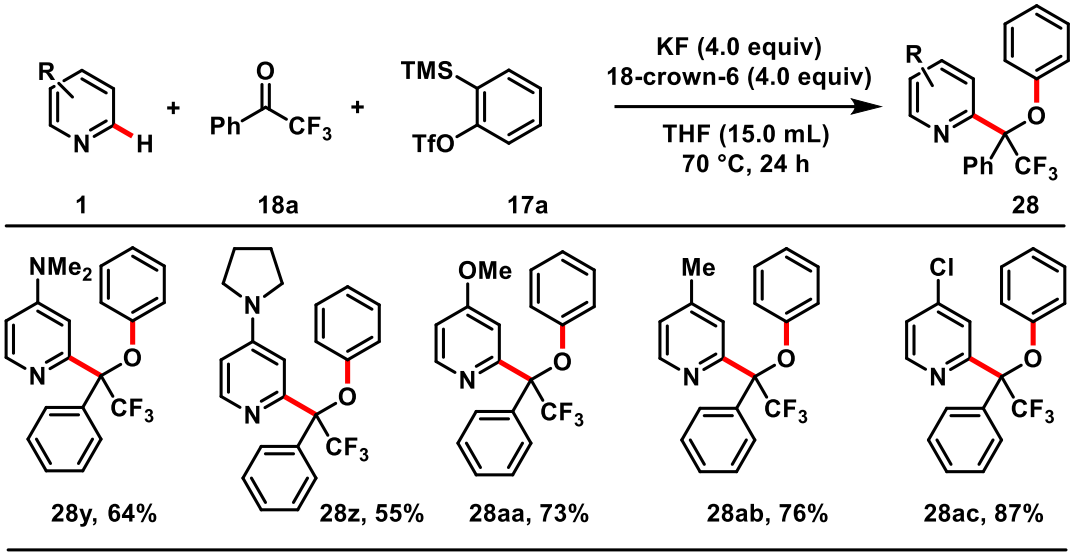


[a] General conditions: **1a** (0.375 mmol), **18** (0.25 mmol), **17a** (0.5 mmol), KF (4 equiv), 18-crown-6 (4 equiv), THF (15.0 mL; 0.017 M), 70 °C for 24 h. Yields of the isolated products are given. [b] Yield of the reaction performed on a 1.0 mmol scale.

4.5.3. Substrate Scope of C2 Functionalization of Pyridines: Scope of Pyridines

Next, we focused our attention on the variation of pyridine moiety. When dimethyl aminopyridine (DMAP) was used as the nucleophilic trigger, the desired product **28y** was formed in 64% yield. Moreover, different electron-rich and -neutral groups at the 4-position of pyridine ring were well tolerated under the optimized conditions to deliver the expected 2,4-disubstituted pyridine derivatives in moderate to good yields (**28z**-**28ac**). Unfortunately, electron-withdrawing groups at the 4-position of pyridine ring as well as substitution at the 2- and 3-position of the pyridine ring failed to afford the expected MCC product under the present reaction conditions.

Scheme 4.8. Substrate Scope: Variation of Pyridines



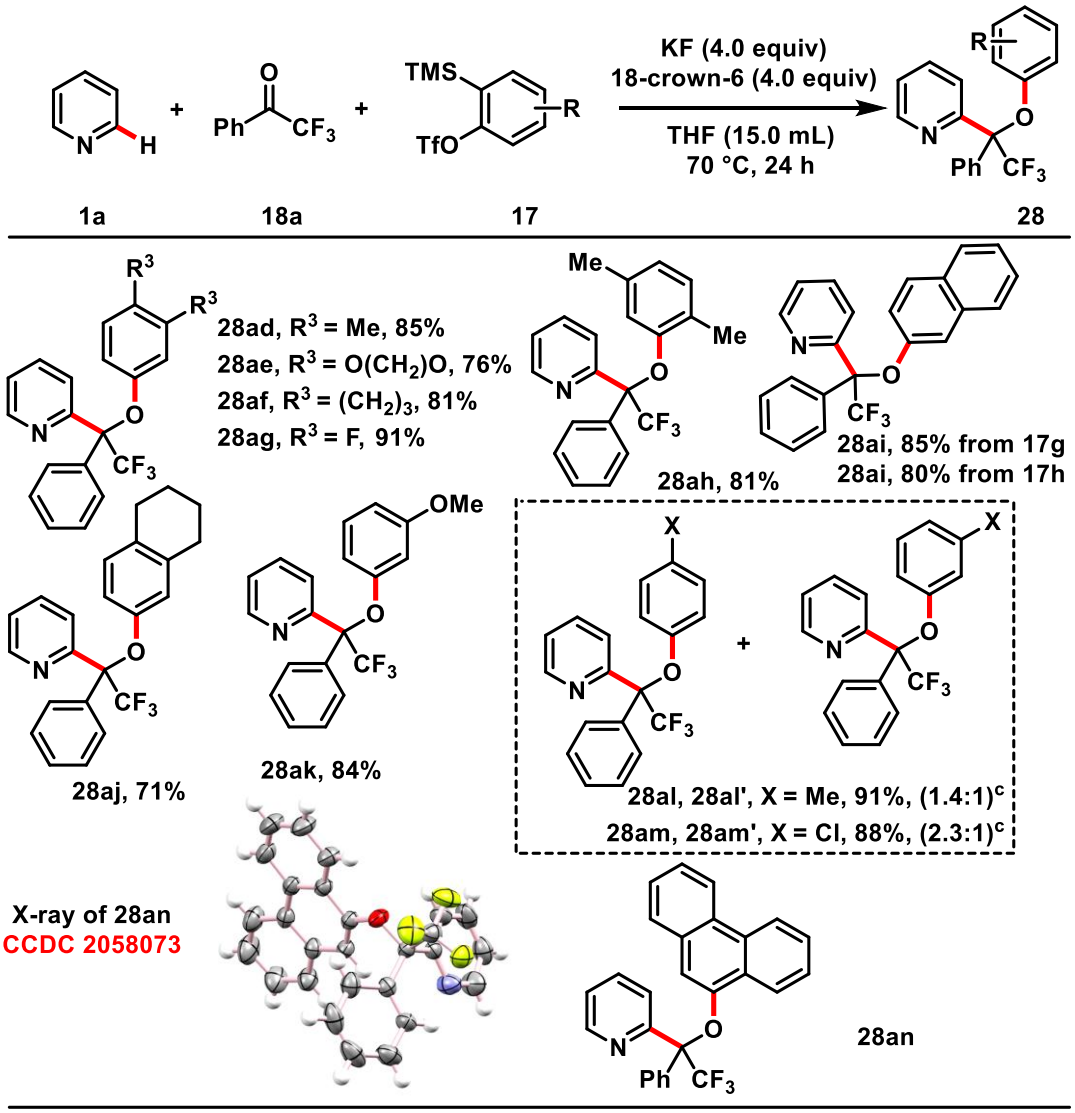
[a] General conditions: **1** (0.375 mmol), **18a** (0.25 mmol), **17a** (0.5 mmol), KF (4 equiv), 18-crown-6 (4 equiv), THF (15.0 mL; 0.017 M), 70 °C for 24 h. Yields of the isolated products are given.

4.5.4. Substrate Scope of C2 Functionalization of Pyridines: Scope of Arynes

We also studied the scope of this multicomponent coupling with differently substituted arynes generated from the corresponding triflates (Scheme 4.9). Various 4,5-disubstituted symmetrical arynes bearing electronically divergent groups engendered from the corresponding precursors **17b**-**17e** also afforded the three-component coupling products in good yields (**28ad**-**28ag**). In addition, the 3,6-dimethyl benzyne formed from the respective precursor **17f** furnished **28ah** in 81% yield. Notably, both symmetrical, and

unsymmetrical naphthalyne generated from the precursors **17g** and **17h** produced **28ai** in 85% and 80% yield respectively. Additionally, the tetrahydronaphthyl unsymmetrical aryne generated from **17i** and 3-methoxy benzyne produced from **17j** provided the single regioisomer (**28aj** and **28ak**) in good yield. Furthermore, pyridine could add to the unsymmetrical benzynes initiated from the precursors **17k** and **17l** and intercept the

Scheme 4.9. Substrate Scope: Variation of Arynes



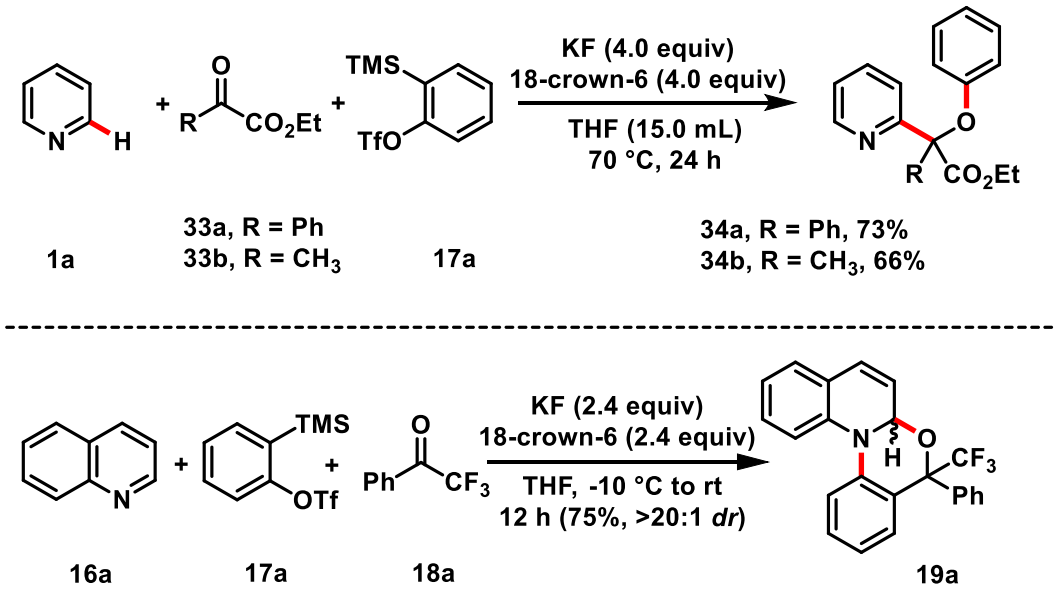
[a] General conditions: **1a** (0.375 mmol), **18a** (0.25 mmol), **17** (0.5 mmol), KF (4 equiv), 18-crown-6 (4 equiv), THF (15.0 mL; 0.017 M), 70 °C for 24 h. Yields of the isolated products are given. [c] Established by GC analysis.

intermediate with **18a** to furnish the inseparable mixture of regioisomers in good yields and moderate regioisomer ratio (1.4:1 for **28al** and **28al'**; 2.3:1 for **28am** and **28am'**). When this aryne triggered Smiles-type rearrangement was performed using the phenanthrene-derived aryne precursor **17m**, the corresponding product **28an** was formed in 94% yield. The structure of **28an** was confirmed by X-ray analysis.

4.5.5. Substrate Scope with Activated Ketones and Quinoline

The present aryne MCC is not limited to -CF_3 containing ketones as electrophilic third components but instead α-ketoesters can also be used to intercept the pyridylidene intermediates generated from pyridine and aryne. The reaction of **1a** and aryne generated from **17a** with activated ketone **33a** afforded the desired C2 functionalized pyridine derivative **34a** in 73% yield (Scheme 4.10). Similar reaction occurred with ethyl glyoxylate **33b** and the targeted product **34b** was formed in 66% yield. Moreover, the carbene generation in this aryne reaction via an intramolecular proton transfer is limited to pyridine derivatives as nucleophiles. The use of quinoline **16a** as the nucleophile furnished the benzooxazino quinoline derivative **19a** in 75% yield and >20:1 diastereomer ratio instead of the desired C2 substituted quinoline derivative. The product **19a** was formed by the generation of the 1,4-zwitterion from quinoline and aryne followed by its interception with **18a** in a (4+2) annulation reaction.

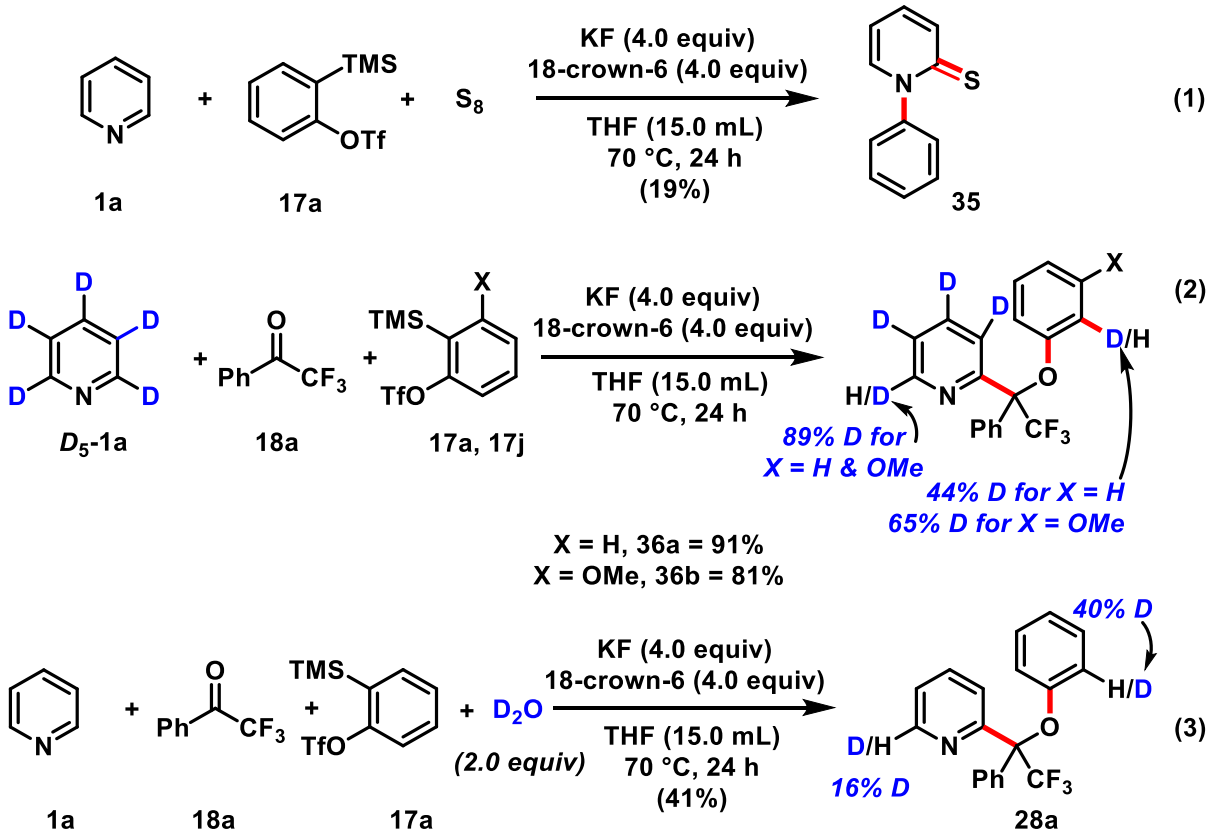
Scheme 4.10. Reaction Using Activated Ketones and Use of Quinoline as Nucleophile



4.5.6. Mechanistic Investigation

To get insight into the mechanism of the reaction and to shed light on the pyridylidene intermediates, we have performed mechanistic experiments. When the initially formed pyridine-aryne adduct was quenched with elemental sulfur under the optimized conditions, the 1-phenylpyridine-2(1H)-thione **35** was formed in 19% yield. This is an indication of the formation of the pyridylidene intermediate **30**, which was subsequently quenched by sulfur to form **36** (Scheme 4.11, eq 1). Moreover, performing the reaction using ***D*$_5$*-1a*** under the optimized conditions using benzyne generated from **17a**, the product **36a** was formed in 91% yield with 44% D incorporation at the 2-position of the benzene ring (eq 2). Similar reaction occurred with aryne generated from **17j** and the product **36b** was formed in 81% yield with 65% D incorporation at the 2-position. This result tends to indicate the generation of the pyridylidene intermediate **30** by the proton transfer from the initially formed zwitterion **29**. Even more puzzling was the incorporation of 11% H at the 6-position of

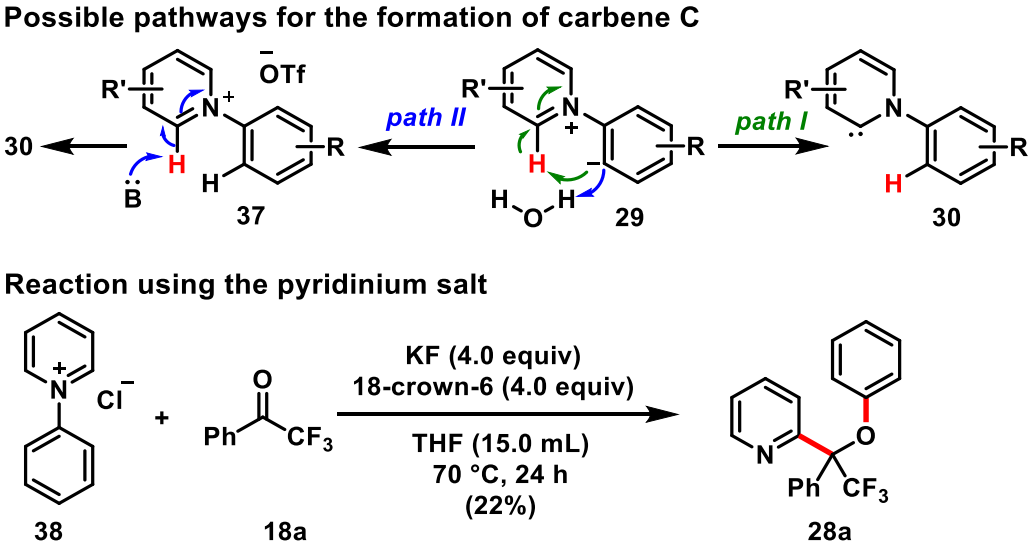
Scheme 4.11. Mechanistic Experiments



pyridine ring in **36**, which may be due to the presence of trace amounts of adventitious water in the reaction system (as the reaction was conducted in 15 mL of THF). To get further insights on this, we have performed a reaction in the presence of D_2O (2.0 equiv) under the optimized conditions (eq 3). The formation of product **28a** in 41% yield and 16% D incorporation at the C-6 position of pyridine appears to be an indication of the role of water in the proton exchange events.

From the above experiments, it is reasonable to assume that the nucleophilic pyridylidene intermediate **30** could be formed in two pathways. One is the intramolecular proton transfer of the 1,4-zwitterion **29**, which is mostly favoured (Scheme 4.12). Alternatively, the aryl anion **29** could be protonated by adventitious water to form the pyridinium triflate **37**, which in the presence of KF/18-crown-6 could undergo the deprotonation at the C-2 position of pyridine leading to the generation of **30**. In order to get information of the latter pathway, the pyridinium chloride **38** was treated with **18a** under optimized conditions. The formation of product **28a** in 22% yield is clearly an indication that the pyridinium **37** could also be an intermediate in the present reaction.

Scheme 4.12. Study Towards the Intermediacy of Pyridinium Salt

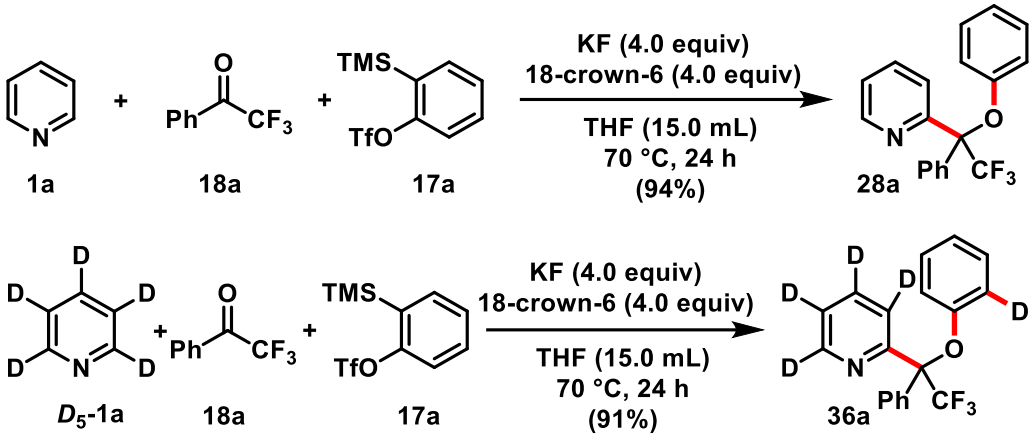


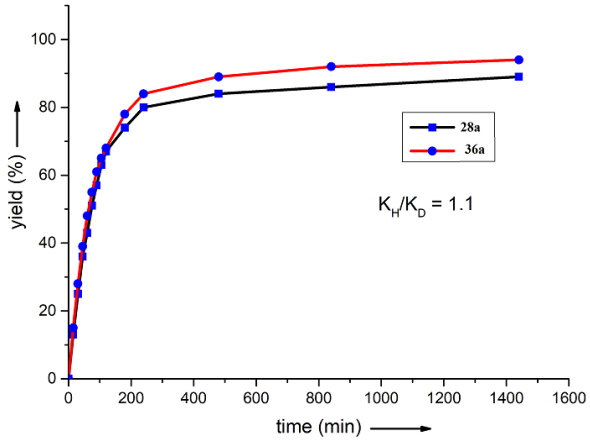
4.5.7. Kinetic Isotope Effect Studies

Finally, to get information on the involvement of the C-H bond-cleavage at the C-2 position of pyridine in the rate determining step of the reaction, we have performed kinetic studies using pyridine and deuterated pyridine. The observation of the K_H/K_D value of 1.10

is a clear indication that the conversion of intermediate **29** to **30** is not the slowest step in the present reaction (Scheme 4.13).

Scheme 4.13. Kinetic Isotope Effect Studies





4.6. Conclusion

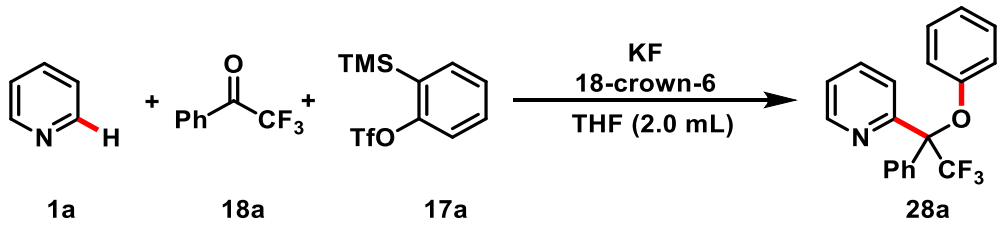
In conclusion, a transition-metal-free method for the functionalization of pyridine at the C2 position using aryne three-component coupling has been developed. Using α,α,α-trifluoroacetophenones as the third component, the reaction afforded C2-functionalized pyridine derivatives in good yields and broad scope with variation on all the three components. The reaction was also extended to α-keto esters as the electrophilic third component. The use of dilute reaction conditions inhibited the competing pyridine-aryne polymerization pathway in this formal 1,2-di(hetero)arylation of ketones. The nucleophilic pyridylidene intermediate generated from pyridine and aryne adds to the activated carbonyls in an S_NAr process (similar to the Smiles rearrangement) to afford the desired products. Detailed mechanistic studies were performed to get insight into the mechanism of the reaction.[14]

4.7. Experimental Details

4.7.1. General Information

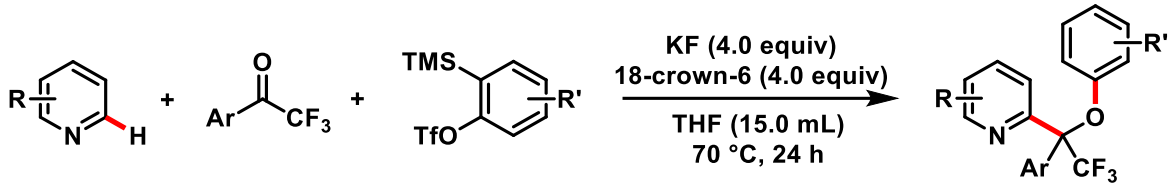
Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in oven-dried reaction vessels with Teflon screw caps. 25 °C Corresponds to the room temperature (rt) of the lab when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under nitrogen. 18-Crown-6 was recrystallized from dry CH_3CN and KF was dried by heating at 110 °C for 12 h and left to cool under nitrogen and stored in nitrogen filled glove-box. All the pyridines, 2,2,2-trifluoro-1-phenylethan-1-one, ethyl 2-oxopropanoate, ethyl 2-oxo-2-phenylacetate, quinoline were purchased from Alfa Aesar, TCI or Sigma-Aldrich and used as received. The trifluoroacetophenone derivatives **18b-18v** were synthesized from the following literature procedure.[15] The heteroaryl trifluoromethyl ketones **18w-18x** were synthesized from the following the literature procedure.[16] The 2(trimethylsilyl)phenyl trifluoromethane sulfonate and the other symmetric and unsymmetrical aryne precursors were synthesized following literature procedure.[17] Analytical thin layer chromatography was performed on TLC Silica gel 60 F254. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker Ultrashield spectrometer in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Infrared (FT-IR) spectra were recorded on a Bruker Alfa FT-IR, ν-max in cm^{-1}. HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument.

4.7.2. General Procedure for the Optimization of the Reaction Conditions



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF and 18-crown-6 in a nitrogen filled glove-box. Then THF was added outside the glove-box under nitrogen atmosphere. Then 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.25 mmol), pyridine **1a** and aryne precursor **17a** were added and reaction mixture was allowed to stir for given time. Yields were determined by the ^{1}H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard.

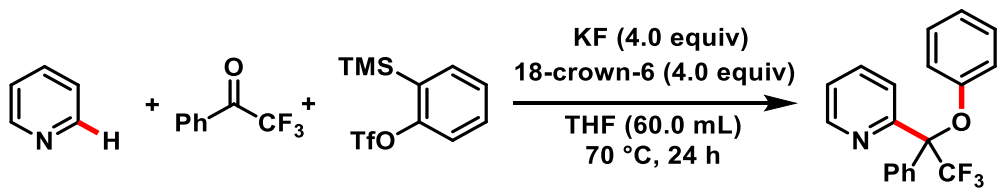
4.7.3. General Procedure for the Pyridine Triggered Aryne MCC with 2,2,2-Trifluoroacetophenones



1 **18** **17** **28**

To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in a glove-box. Then THF (15 mL) was added outside the glove-box under nitrogen atmosphere. Then α,α,α-trifluoroacetophenones **18** (0.25 mmol), pyridine **1** (0.375 mmol) and aryne precursor **17** (0.5 mmol) were added and reaction mixture was allowed to stir at 70 °C for 24 h. After completion of the reaction, solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford the corresponding C2 functionalized pyridine derivatives **28** in moderate to good yields.

Procedure for the 1.0 mmol Scale Reaction for the synthesis of 28a

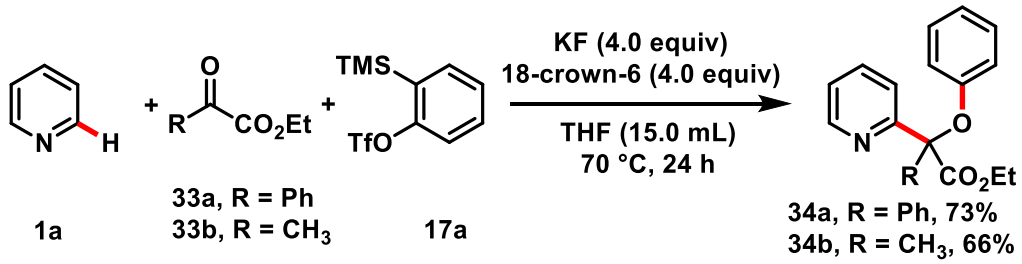


1a **18a** **17a** **28a**

To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.232 g, 4.0 mmol) and 18-crown-6 (1.056 g, 4.0 mmol) in a glove-box. Then THF (60 mL) was added outside the glove-box under nitrogen atmosphere. Then 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.173g, 1.0 mmol), pyridine **1a** (0.118 g, 1.5 mmol) and aryne precursor **17a** (0.597 g, 2.0 mmol) were added and the reaction mixture was allowed to stir

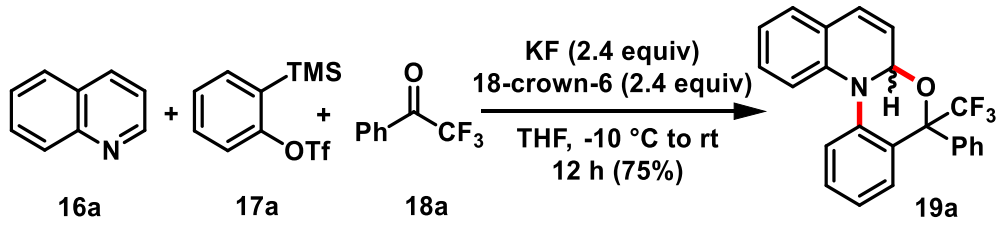
at 70 °C for 24 h. After completion of the reaction, solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford 2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine **28a** as a yellow oil (0.293 g, 89% yield).

4.7.4. Procedure for the Pyridine Triggered Aryne MCC with α-Keto Ester



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in a glove-box. Then THF (15 mL) was added outside the glove-box under nitrogen atmosphere. Then α-keto ester **33** (0.25 mmol), pyridine **1a** (0.030 g, 0.375 mmol) and aryne precursor **17a** (0.149 g, 0.5 mmol) were added and reaction mixture was allowed to stir at 70 °C for 24 h. After completion of the reaction, solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford the corresponding C-2 functionalized pyridine derivatives **34** in moderate to good yields.

4.7.5. Procedure for the Quinoline Triggered Aryne MCC with 2,2,2-Trifluoroacetophenone

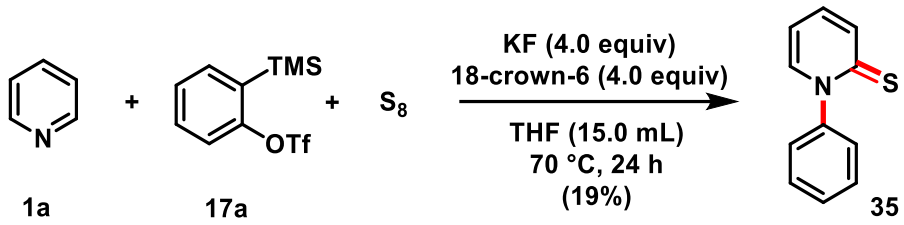


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added 18- crown-6 (0.158 g, 0.6 mmol), KF (0.035 g, 0.6 mmol) in a glove-box. Then THF (1 mL) was added outside the glove-box under nitrogen atmosphere. The resultant reaction mixture was cooled to -10 °C and kept stirring for 5 min. To the cooled stirring solution was then added 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.066g, 0.375 mmol), quinoline **16a** (0.032 g, 0.25 mmol) and the aryne precursor **17a** (0.089 g, 0.3 mmol). Then the reaction mixture

was gradually warmed to rt and kept for stirring at rt for 12 h. After 12 h, the reaction was stopped and the crude reaction mixture was purified by column chromatography on silica gel to afford the 5-phenyl-5-(trifluoromethyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-*a*]quinoline **19a** as > 20:1 diastereomeric ratio (0.071 g, 75%). The dr was determined by ^{1}H NMR analysis of crude reaction mixture.

4.7. 6. Mechanistic Studies

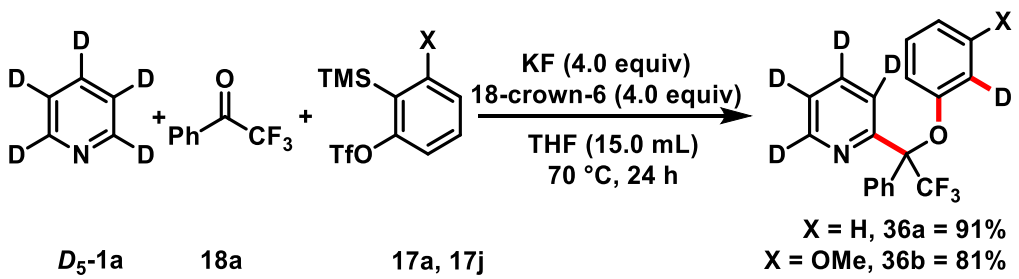
(a) Pyridylidene Intermediate Quenching with Sulfur



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in a glove-box. Then THF (15 mL) was added outside the glove-box under nitrogen atmosphere followed by the addition of pyridine **1a** (0.030 g, 0.375 mmol). Then the resultant reaction mixture was subjected for degassing (freeze-pump-thaw cycles). After that resultant reaction mixture was kept stirring at 30 °C for 5 min. Then to the solution was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 0.5 mmol) and sulfur (0.008 g, 0.25 mmol) and the reaction mixture was stirred at 70 °C for 24h. The crude reaction mixture was then purified by flash column chromatography (Pet. ether /EtOAc = 75/25) on silica gel to afford the 1-phenylpyridine-2(1H)-thione **35** as a yellow solid (0.009 g, 19 % yield).

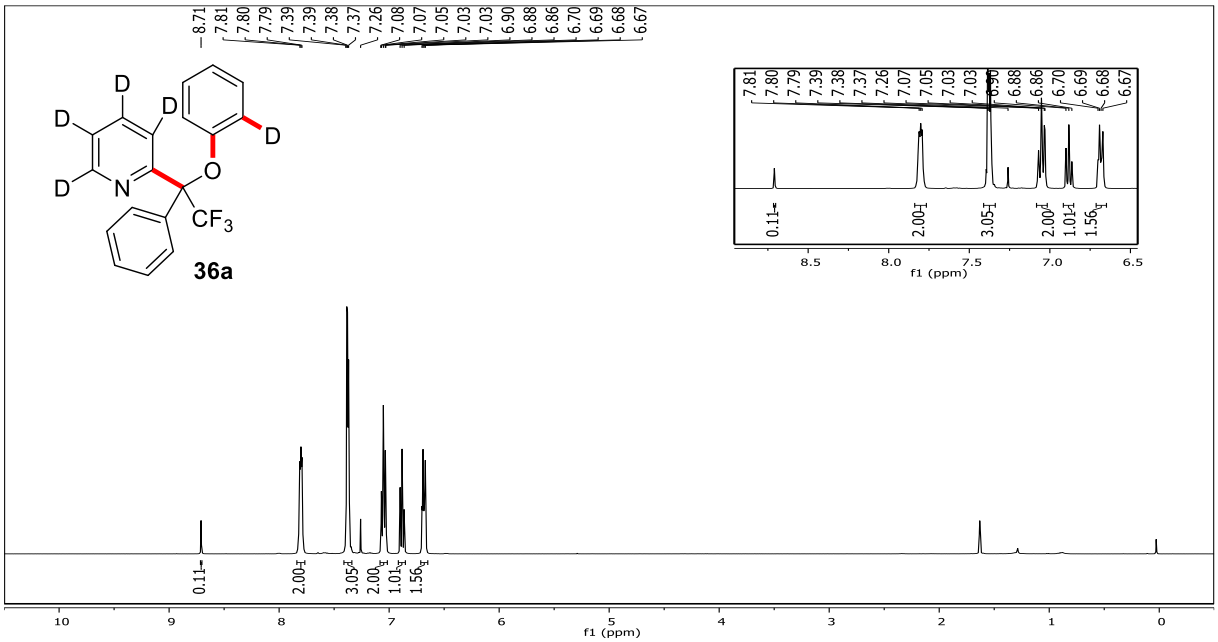
This study shed light on the generation of pyridylidene intermediate in the reaction.

(b) Deuterium Labeling Experiment

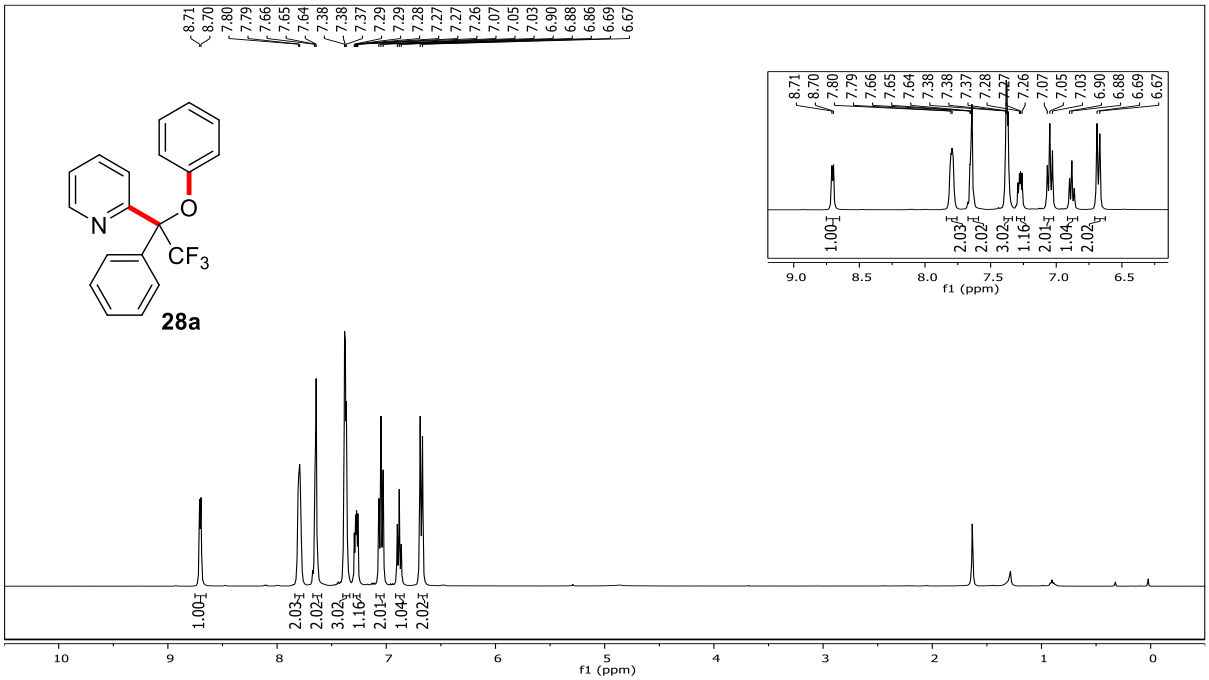


Following the general procedure, treatment of deuterated pyridine-d_5 ***D*$_5$-1a** (0.032 g, 0.375 mmol), aryne precursor **17** (0.5 mmol) and 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 0.25 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography of the crude reaction mixture afforded **36** as a yellow oil.

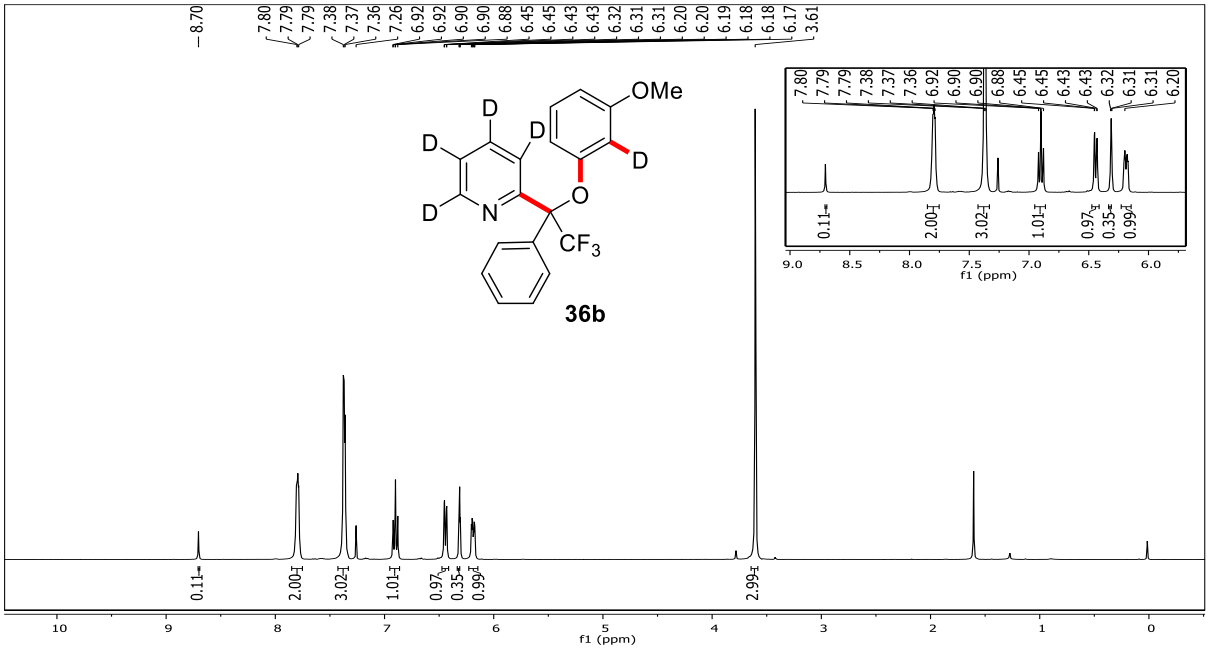
^{1}H NMR spectrum of 36a



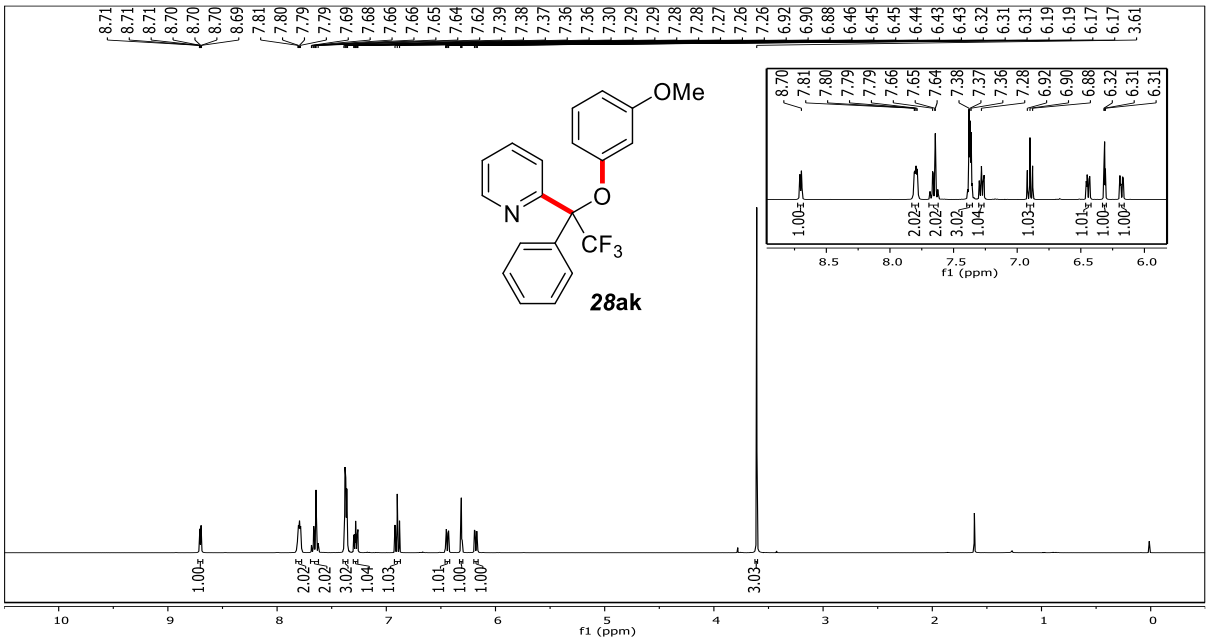
^{1}H NMR spectrum of 28a



^{1}H NMR spectrum of 36b

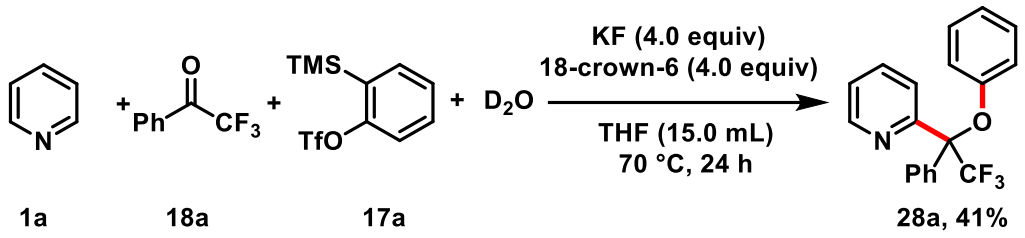


^{1}H NMR spectrum of 28ak



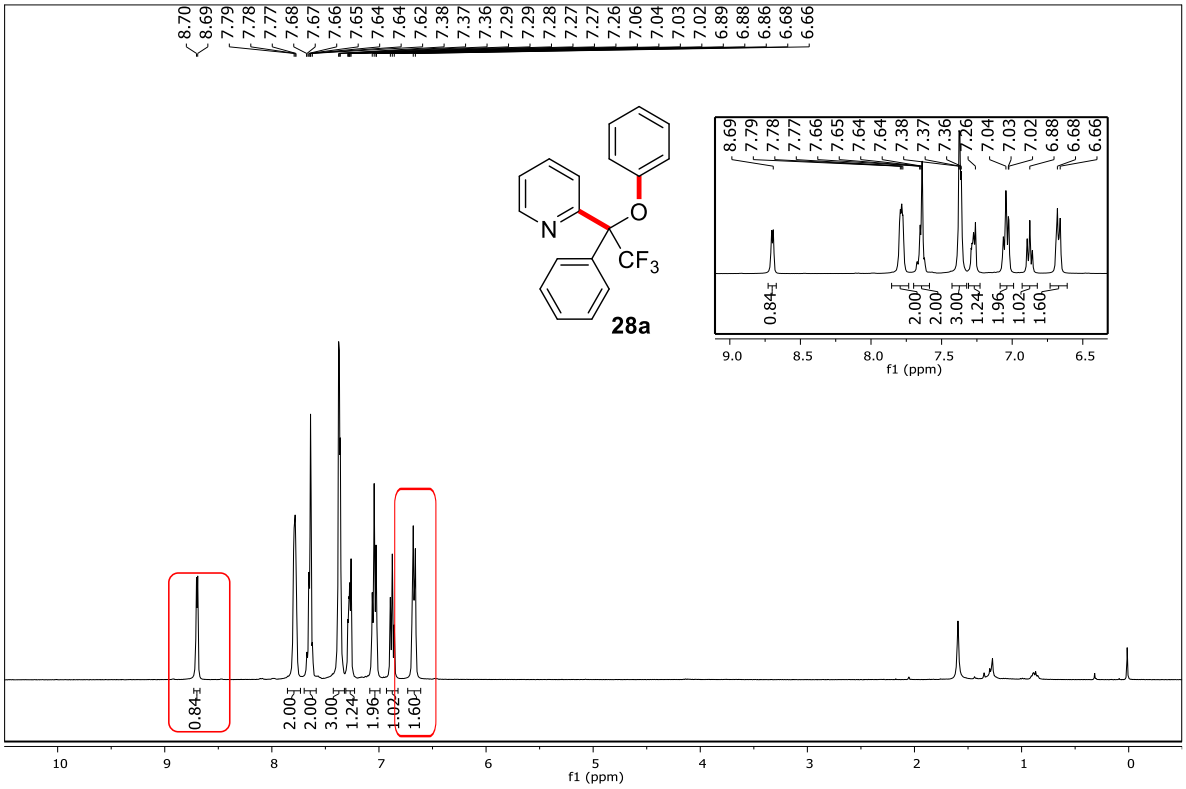
*These studies reveal that although when **D_5-1a** was used as nucleophilic trigger the products do not contain 100% deuterium. So, the aryl anion proton abstraction from pyridine is not fully intramolecular in nature. Also, around 11% hydrogen was present in product at the sixth position of the pyridine ring. To understand the mechanism in detail, more mechanistic studies were performed later.*

(c) Use of D_2O Under Optimized Reaction Conditions

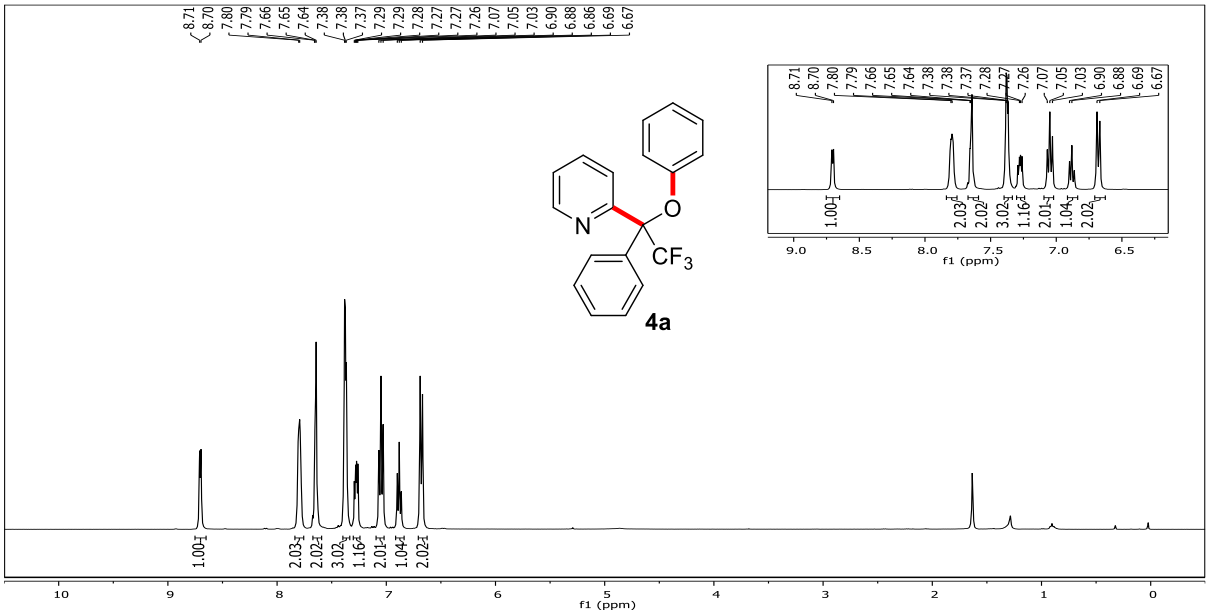


To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in a glove-box. Then THF (15 mL) was added outside the glove-box under nitrogen atmosphere. Then α,α,α-trifluoroacetophenone **18a** (0.043 g, 0.25 mmol), pyridine **1a** (0.030 g, 0.375 mmol) and aryne precursor **17a** (0.149 g, 0.5 mmol), deuterium oxide (0.01 g, 0.5 mmol) were added and reaction mixture was allowed to stir at 70 °C for 24 h. After completion of the reaction, solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford the corresponding C2 functionalized pyridine derivatives **28a** in 41% yields.

^{1}H NMR spectrum of 28a when D_2O was used in reaction

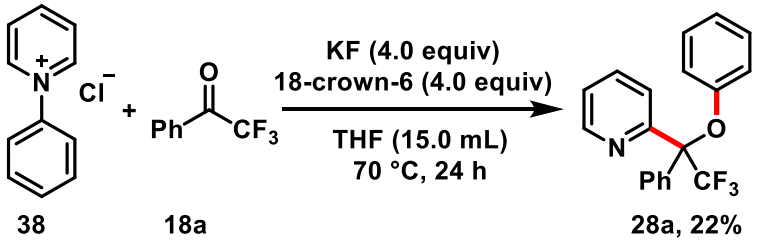


^{1}H NMR spectrum of 4a when no D_2O was used in reaction



*This study again shed light onto the protonation of intermediate **30** and after that deprotonation to generate the intermediate **30**.*

(d) Reaction of Pyridinium Ion 38 with α,α,α -Trifluoroacetophenone



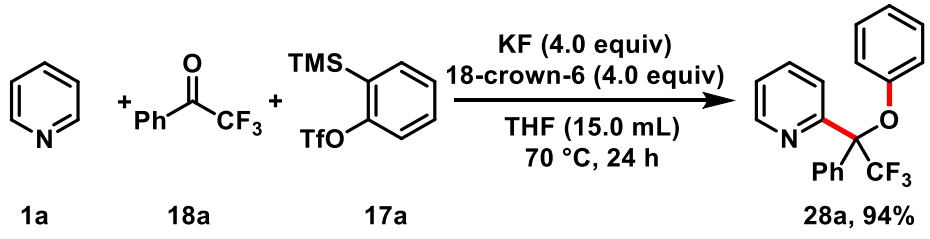
To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in a glove-box. After that 1-phenylpyridin-1-ium chloride **38** (0.375 mmol, 0.072 g) was added outside the glove-box under nitrogen atmosphere. Then THF (15 mL) was added to the reaction mixture followed by the addition of α,α,α -trifluoroacetophenone **18a** (0.043 g, 0.25 mmol) and then the reaction mixture was allowed to stir at 70 °C for 24 h. After completion of the reaction, solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford **28a** (0.018 g) in 22% yields.

*This study suggests that 1-phenylpyridin-1-ium could also be generated in the optimized reaction condition via protonation of intermediate **30**. Again, deprotonation can regenerate the intermediate **30** and the reaction can happen further to afford the expected C2 functionalized pyridine derivative. This study also shed light on the fact that when **D_5-1a** was used in the reaction we observed the formation of the expected product **36a** with 11% proton incorporation at the sixth position of pyridine ring.*

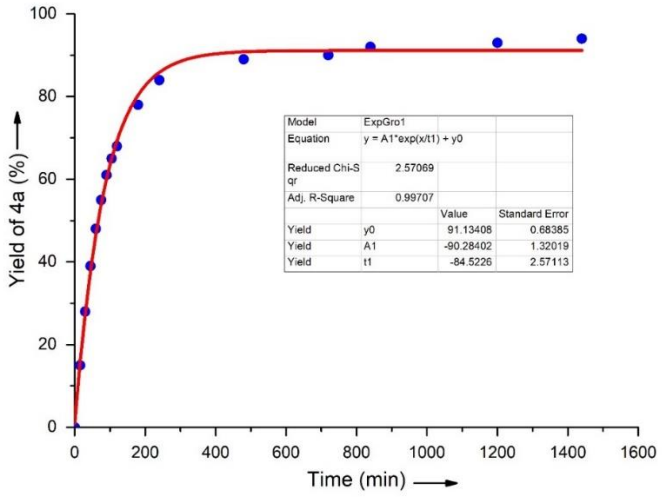
4.7.7. Kinetic Isotope Effect: Determination of k_H/k_D

Kinetic isotope effect study was done by monitoring the reaction of 2,2,2-trifluoro-1-phenylethan-1-one **18a**, aryne precursor **17a** with pyridine **1a** and deuterated pyridine ***D*$_5$-1a**. All the reactions were done by following the standard reaction protocol. After a defined time-interval, 200 µL of the reaction mixture was taken out from the mixture, filtered and concentrated to obtain crude residue, which was analysed using ^{1}H NMR using equivalent amount of 200 µL a standard solution of CH_2Br_2 as an external standard.

Set 1.



1a **18a** **17a** **28a, 94%**

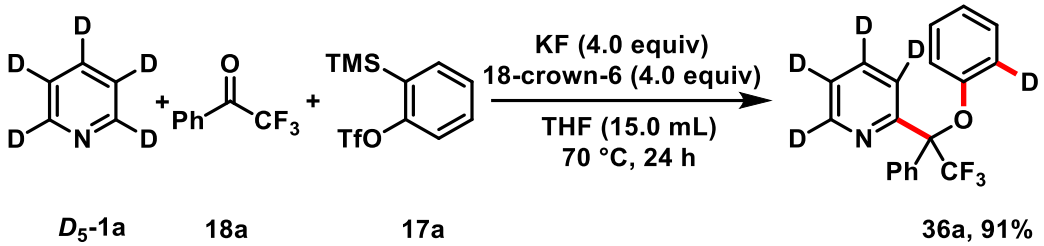


Rate = $R_H = K_H$ [**1a**]^x [**18a**]^y [**17a**]^z

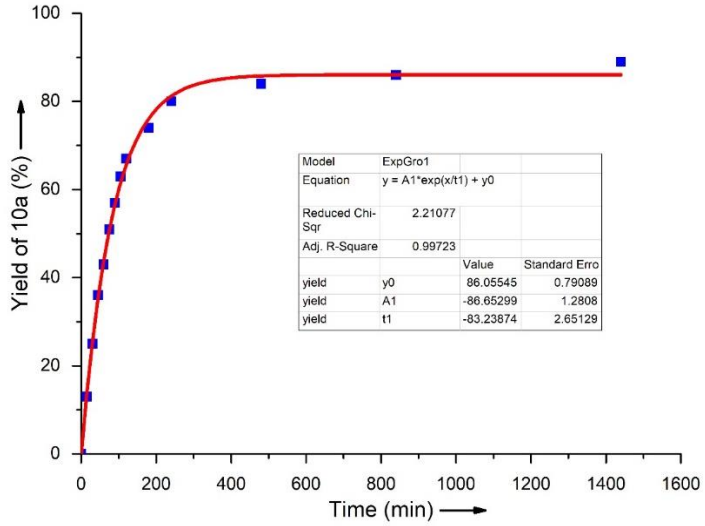
$R_H = K_H$ $[0.375]^x$ $[0.25]^y$ $[0.5]^z$

$0.8 = K_H$ $[0.375]^x$ $[0.25]^y$ $[0.5]^z$ …… equation (1)

Set 2.



***D*$_5$-1a** **18a** **17a** **36a, 91%**



Rate = $R_D = K_D$ [**D$_5$-1a**]^x [**18a**]^y [**17a**]^z

$R_H = K_D$ $[0.375]^x$ $[0.25]^y$ $[0.5]^z$

$0.72667 = K_D$ $[0.375]^x$ $[0.25]^y$ $[0.5]^z$ …… equation (2)

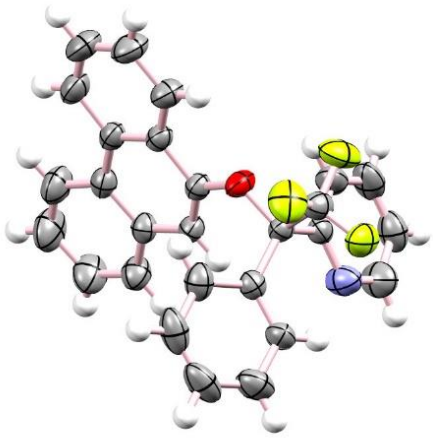
Hence from equation (1) and (2)

$K_H / K_D = 0.8 / 0.72667 = 1.1$

*These experiments indicate that the generation of intermediate **30** from intermediate **29** is not the rate determining step or slowest step in our reaction.*

4.7.8. ORTEP Diagram of 28an

Single crystal of **28an** (recrystallized from $CDCl_3$/n-hexane at 25 °C) was mounted and the diffraction data was collected at 296 K on a Bruker APEX-II CCD diffractometer using SMART/SAINT software. Intensity data were collected using MoKα radiation (λ=0.71073 A°).

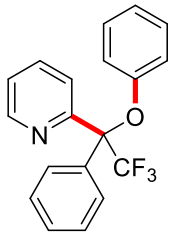


ORTEP Diagram of 28an

(CCDC 2058073, thermal ellipsoids are shown with 50% probability)

4.7.9. Synthesis and Characterization of Pyridine Derivatives

2-(2,2,2-Trifluoro-1-phenoxy-1-phenylethyl)pyridine (28a)



28a

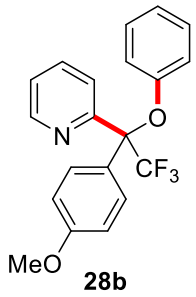
Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 µL, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine **28a** as a yellow oil (0.077 g, 93% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.27; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.70 (d, *J* = 4.8 Hz, 1H), 7.80-7.79 (m, 2H), 7.66-7.64 (m, 2H), 7.38-7.37 (m, 3H), 7.29-7.26 (m, 1H), 7.05 (t, *J* = 7.8 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.4, 154.7, 148.5, 136.5, 135.0, 129.7, 128.9, 128.8, 127.8, 125.1 (unresolved

quartet), 124.4 (q, *J* = 287.0 Hz), 123.6, 122.5, 120.2, 86.2 (q, *J* = 27.6 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{15}F_3NO$ 330.1100; found 330.1104. **FTIR (cm^{-1})** 3064, 1590, 1492, 1428, 1221, 1176.

2-(2,2,2-Trifluoro-1-(4-methoxyphenyl)-1-phenoxyethyl)pyridine (28b)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one **18b** (0.051 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(4-methoxyphenyl)-1-phenoxyethyl)pyridine **28b** as a yellow oil (0.059 g, 66% yield).

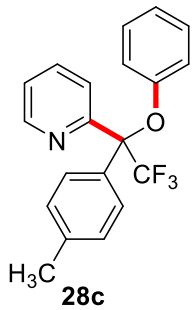


28b

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.21; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.71-8.69 (m, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.67-7.64 (m, 2H), 7.29-7.25 (m, 1H), 7.06-7.01 (m, 2H), 6.89-6.84 (m, 3H), 6.67-6.63 (m, 2H), 3.80 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 159.9, 155.6, 154.7, 148.6, 136.6, 131.2 (unresolved quartet), 128.9, 126.6, 125.1 (q, *J* = 1.8 Hz), 124.4 (q, *J* = 286.8 Hz), 123.7, 122.4, 120.2, 113.2, 85.9 (q, *J* = 27.8 Hz), 55.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{20}H_{16}F_3NNaO_2$ 382.1025; found 382.1035. **FTIR (cm^{-1})** 3064, 2935, 1611, 1583, 1515, 1463.

2-(2,2,2-Trifluoro-1-phenoxy-1-(p-tolyl)ethyl)pyridine (28c)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(p-tolyl)ethan-1-one **18c** (0.047 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-phenoxy-1-(p-tolyl)ethyl)pyridine **28c** as a yellow oil (0.059 g, 69% yield).

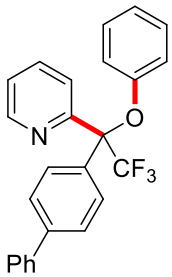


28c

***R*f** (Pet. ether /EtOAc = 95/05): 0.26; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.70 (d, *J* = 4.7 Hz, 1H), 7.67-7.63 (m, 4H), 7.29-7.24 (m, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.06-7.02 (m, 2H), 6.87 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 2H), 2.35 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.5, 154.8, 148.6, 138.9, 136.6, 131.9, 127.7 (unresolved quartet), 128.9, 128.7, 125.1 (q, *J* = 1.9 Hz), 124.4 (q, *J* = 287.0 Hz), 123.7, 122.5, 120.3, 86.2 (q, *J* = 27.5 Hz), 21.3. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO$ 344.1257; found 344.1263. **FTIR (cm^{-1})** 3065, 2923, 1590, 1490, 1431, 1222, 1175, 1057.

2-(1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28d)

Following the general procedure, treatment of 1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoroethan-1-one **18d** (0.062 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-(1-([1,1'-biphenyl]-4-yl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28d** as a yellow oil (0.100 g, 89% yield).



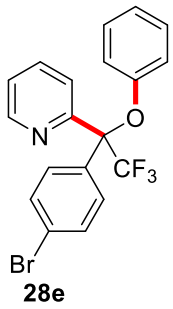
28d

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.75-8.73 (m, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.71-7.62 (m, 6H), 7.48-7.44 (m, 2H), 7.40-7.35 (m, 1H), 7.31-7.28 (m, 1H), 7.11-7.06 (m, 2H), 6.93-6.89 (m, 1H), 6.75-6.72 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.3, 154.7, 148.6, 141.6, 140.4, 136.6, 133.8, 130.3 (unresolved quartet), 128.9, 128.9, 127.7, 127.3, 126.5, 125.2 (q, *J* = 1.9 Hz), 124.3 (q, *J* = 287.6 Hz), 123.8, 122.5, 120.2, 86.1 (q, *J* = 27.6 Hz). **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{25}H_{18}F_3NNaO$ 428.1233; found 428.1237. **FTIR (cm^{-1})** 3062, 1590, 1490, 1431, 1222, 1177.

2-(1-(4-Bromophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28e)

Following the general procedure, treatment of 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one **18e** (0.063 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc =

99/01) of the crude reaction mixture afforded 2-(1-(4-bromophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28e** as a yellow oil (0.091 g, 89% yield).

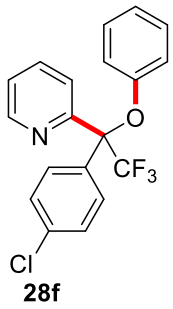


28e

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.65 (d, *J* = 4.7 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.62-7.59 (m, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.27-7.23 (m, 1H), 7.02 (m, 2H), 6.86 (t, J = 7.3 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 154.6, 154.4, 148.6, 136.7, 133.8, 131.7 (unresolved quartet), 131.0, 129.0, 125.2 (q, *J* = 2.1 Hz), 124.0 (q, *J* = 287.6 Hz), 123.9, 123.6, 122.6, 119.9, 85.6 (q, *J* = 27.8 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}BrF_3NO$ 408.0205; found 408.0211. **FTIR (cm^{-1})** 3065, 1591, 1491, 1431, 1251, 1176.

2-(1-(4-Chlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28f)

Following the general procedure, treatment of 1-(4-chlorophenyl)-2,2,2-trifluoroethan-1-one **18f** (0.052 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(1-(4-chlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28f** as a yellow oil (0.083 g, 91% yield).



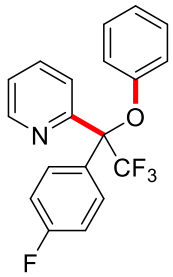
28f

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.68 (d, *J* = 4.4 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.67-7.61 (m, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.30-7.27 (m, 1H), 7.06-7.02 (m, 2H), 6.88 (m, 1H), 6.62 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 154.7, 154.4, 148.6, 136.8, 135.2, 133.2, 131.4 (q, *J* = 1.4 Hz), 129.0, 128.1, 125.2 (q, *J* = 2.1 Hz), 124.1 (q, *J* = 287.1 Hz), 123.9, 122.6, 119.9, 85.6 (q, *J* = 28.0 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}ClF_3NO$ 364.0711; found 364.0714. **FTIR (cm^{-1})** 3065, 1592, 1492, 1432, 1252, 1221.

2-(2,2,2-Trifluoro-1-(4-fluorophenyl)-1-phenoxyethyl)pyridine (28g)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-one **18g** (0.048 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g,

121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(4-fluorophenyl)-1-phenoxyethyl)pyridine **28g** as a yellow oil (0.080 g, 92% yield).

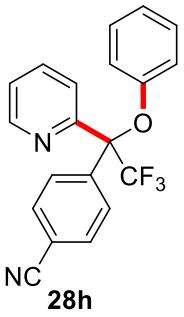


28g

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.70 (d, *J* = 4.7 Hz, 1H), 7.87-7.83 (m, 2H), 7.66-7.65 (m, 2H), 7.32-7.27 (m, 1H), 7.08-7.03 (m, 4H), 6.90-6.87 (m, 1H), 6.64 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 163.0 (d, *J* = 249.0 Hz), 154.9, 154.4, 148.6, 136.7, 132.1-132.0 (m), 130.4 (d, *J* = 3.3 Hz), 129.0, 125.2 (q, *J* = 1.9 Hz), 124.2 (q, *J* = 287.7 Hz), 123.9, 122.6, 120.0, 114.8 (d, *J* = 21.4 Hz), 85.6 (q, *J* = 27.8 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}F_4NO$ 348.1006; found 348.1015. **FTIR (cm^{-1})** 3065, 1584, 1511, 1490, 1433, 1221.

4-(2,2,2-Trifluoro-1-phenoxy-1-(pyridin-2-yl)ethyl)benzonitrile (28h)

Following the general procedure, treatment of 4-(2,2,2-trifluoroacetyl)benzonitrile **18h** (0.05 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 4-(2,2,2-trifluoro-1-phenoxy-1-(pyridin-2-yl)ethyl)benzonitrile **28h** as a yellow oil (0.066 g, 74% yield).

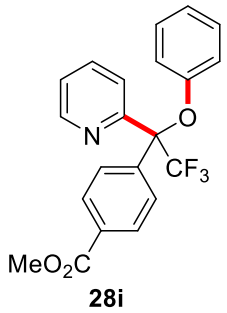


28h

***R*f** (Pet. ether /EtOAc = 95/05): 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.68-8.66 (m, 1H), 8.04 (d, *J* = 8.3 Hz, 2H), 7.68-7.61 (m, 4H), 7.32-7.29 (m, 1H), 7.07-7.02 (m, 2H), 6.91-6.87 (m, 1H), 5.59-6.57 (m, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 154.0, 153.8, 148.7, 139.7, 137.0, 131.5, 130.9 (unresolved quartet), 129.2, 125.3 (q, *J* = 2.1 Hz), 124.2, 123.8 (q, *J* = 287.0 Hz), 122.8, 119.7, 118.6, 113.0, 85.5 (q, *J* = 28.2 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{14}F_3N_2O$ 355.1053; found 355.1056. **FTIR (cm^{-1})** 3064, 2926, 2231, 1589, 1493, 1432, 1252, 1103, 1060.

Methyl-4-(2,2,2-trifluoro-1-phenoxy-1-(pyridin-2-yl)ethyl)benzoate (28i)

Following the general procedure, treatment of methyl 4-(2,2,2-trifluoroacetyl)benzoate **18i** (0.058 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 91/09) of the crude reaction mixture afforded methyl-4-(2,2,2-trifluoro-1-phenoxy-1-(pyridin-2-yl)ethyl)benzoate **28i** as a yellow oil (0.084 g, 87% yield).

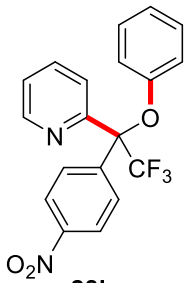


28i

***R*f** (Pet. ether /EtOAc = 95/05): 0.19; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.67 (d, *J* = 4.8 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.67-7.61 (m, 2H), 7.29-7.26 (m, 1H), 7.06-7.02 (m, 2H), 6.89-6.85 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 2H), 3.91 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.8, 154.7, 154.4, 148.7, 139.8, 136.8, 130.6, 130.0 (unresolved quartet), 129.0, 129.0, 125.2 (q, *J* = 1.9 Hz), 124.0 (q, *J* = 287.1 Hz), 123.9, 122.7, 120.0, 85.9 (q, *J* = 27.5 Hz), 52.3. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{21}H_{17}F_3NO_3$ 388.1155; found 388.1160. **FTIR (cm^{-1})** 2954, 1727, 1589, 1491, 1435, 1283.

2-(2,2,2-Trifluoro-1-(4-nitrophenyl)-1-phenoxyethyl)pyridine (28j)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(4-nitrophenyl)ethan-1-one **18j** (0.055 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(4-nitrophenyl)-1-phenoxyethyl)pyridine **28j** as a yellow oil (0.068 g, 73% yield).



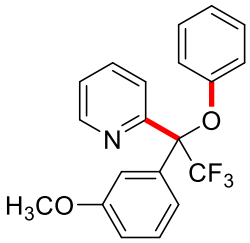
28j

***R*f** (Pet. ether /EtOAc = 95/05): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.67 (d, *J* = 4.7 Hz, 1H), 8.23 (d, *J* = 7.3 Hz, 2H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.70-7.62 (m, 2H), 7.33-7.30 (m, 1H), 7.07-7.03 (m, 2H), 6.89 (m, 1H), 6.59 (d, *J* = 8.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.0, 153.7, 148.7, 148.2, 141.5, 137.0, 131.3 (unresolved quartet), 129.2, 125.3 (q, *J* = 2.2

Hz), 124.3, 123.7 (q, *J* = 287.3 Hz), 122.9, 122.8, 119.7, 85.5 (q, *J* = 28.1 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}BF_3N_2O_3$ 375.0951; found 375.0958. **FTIR (cm^{-1})** 3064, 1588, 1525, 1490, 1351, 1219.

2-(2,2,2-Trifluoro-1-(3-methoxyphenyl)-1-phenoxyethyl)pyridine (28k)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(3-methoxyphenyl)ethan-1-one **18k** (0.051 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoro methanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(3-methoxyphenyl)-1-phenoxyethyl)pyridine **28k** as a colourless oil (0.077 g, 86% yield).

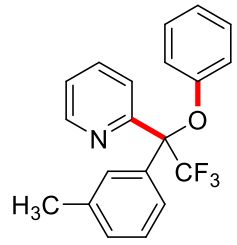


28k

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.70-8.69 (m, 1H), 7.66-7.60 (m, 2H), 7.43 (s, 1H), 7.31-7.25 (m, 3H), 7.07-7.03 (m, 2H), 6.93-6.86 (m, 2H), 6.70-6.68 (m, 2H), 3.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.1, 155.5, 154.7, 148.6, 136.7, 136.6, 128.9, 128.8, 125.1 (q, *J* = 1.8 Hz), 124.3 (q, *J* = 287.0 Hz), 123.7, 122.6, 122.1 (unresolved quartet), 120.4, 116.1 (unresolved quartet), 114.2, 86.2 (q, *J* = 27.7 Hz), 55.4. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO_2$ 360.1206; found 360.1213. **FTIR (cm^{-1})** 3063, 3007, 2938, 2837, 1589, 1491, 1430, 1255, 1221, 1046.

2-(2,2,2-Trifluoro-1-phenoxy-1-(*m*-tolyl)ethyl)pyridine (28l)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(m-tolyl)ethan-1-one **18l** (0.047 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-



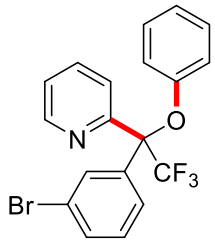
28l

(2,2,2-trifluoro-1-phenoxy-1-(*m*-tolyl)ethyl)pyridine **28l** as a colourless oil (0.068 g, 79% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.71 (d, *J* = 4.6 Hz, 1H), 7.68-7.60 (m, 3H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.29-7.18 (m, 3H), 7.05 (t, *J* = 7.8 Hz, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.8, 154.9, 148.6, 137.5, 136.5, 135.4, 130.2 (unresolved quartet), 129.8, 128.9, 127.8, 128.8 (unresolved quartet), 125.1 (q, *J* = 1.9 Hz), 124.4 (q, *J* = 287.0 Hz), 123.6, 122.7, 120.6, 86.5 (q, *J* = 27.4 Hz), 21.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO$ 344.1257; found 344.1261. **FTIR (cm^{-1})** 3065, 2923, 2859, 1590, 1490, 1221, 1057, 954.

2-(1-(3-Bromophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28m)

Following the general procedure, treatment of 1-(3-bromophenyl)-2,2,2-trifluoroethan-1-one **18m** (0.063 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(1-(3-bromophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28m** as a colourless oil (0.082 g, 80% yield).



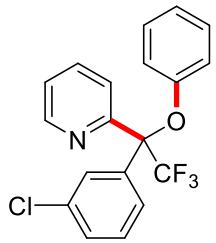
28m

***R*f** (Pet. ether /EtOAc = 95/05): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.70 (d, *J* = 4.0 Hz, 1H), 8.12 (s, 1H), 7.68-7.58 (m, 3H), 7.53-7.50 (m, 1H), 7.30-7.20 (m, 2H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.6, 154.3, 148.7, 137.3, 136.8, 132.9, 132.2, 129.4, 129.0, 128.5, 125.2 (q, *J* = 1.9 Hz), 124.0, 124.1 (q, *J* = 287.0 Hz), 122.8, 122.1, 120.1, 85.5 (q, *J* = 27.7 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}BrF_3NO$ 408.0205; found 408.0210. **FTIR (cm^{-1})** 3063, 2959, 1583, 1490, 1330, 1224, 1108, 949, 831.

2-(1-(3-Chlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28n)

Following the general procedure, treatment of 1-(3-chlorophenyl)-2,2,2-trifluoroethan-1-one **18n** (0.05 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g,

121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(1-(3-chlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28n** as a colourless oil (0.075 g, 83% yield).

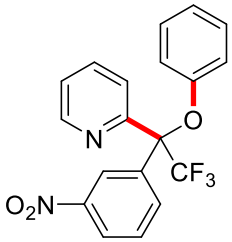


28n

***R*f** (Pet. ether /EtOAc = 95/05): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.70 (d, *J* = 4.1 Hz, 1H), 7.98 (s, 1H), 7.67-7.59 (m, 3H), 7.38-7.35 (m, 1H), 7.31-7.26 (m, 2H), 7.09-7.04 (m, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.7, 154.4, 148.7, 137.1, 136.7, 134.0, 130.1 (unresolved quartet), 129.2, 129.1, 129.0, 128.0 (unresolved quartet), 125.2 (q, *J* = 1.9 Hz), 124.0, 124.1 (q, *J* = 287.0 Hz), 122.8, 120.1, 85.6 (q, *J* = 27.9 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}ClF_3NO$ 364.0711; found 364.0713. **FTIR (cm^{-1})** 3067, 2925, 1590, 1490, 1430, 1251, 1220, 1178, 1057, 888.

2-(2,2,2-Trifluoro-1-(3-nitrophenyl)-1-phenoxyethyl)pyridine (28o)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(3-nitrophenyl)ethan-1-one **18o** (0.055 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(3-nitrophenyl)-1-phenoxyethyl)pyridine **28o** as a yellow oil (0.070 g, 75% yield).



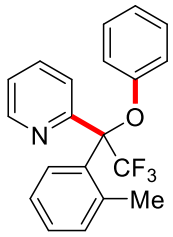
28o

***R*f** (Pet. ether /EtOAc = 95/05): 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.97 (s, 1H), 8.70 (d, *J* = 4.3 Hz, 1H), 8.26 (dd, J_1= 8.2 Hz, J_2= 1.2 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.70-7.63 (m, 2H), 7.54 (t, *J* = 8.1 Hz, 1H), 7.33-7.30 (m, 1H), 7.05 (t, *J* = 8.1 Hz, 2H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 153.9, 153.6, 148.8, 148.0, 137.0, 136.6, 136.1, 129.2, 128.7, 125.8 (unresolved quartet), 125.3 (q, *J* = 2.0 Hz), 124.3, 124.0, 123.8 (q, *J* = 287.0 Hz), 122.9, 119.7, 85.1 (q, *J* = 28.4 Hz). **HRMS (ESI)** m/z:

$[M+H]^+$ calcd for $C_{19}H_{14}F_3N_2O_3$ 375.0951; found 375.0953. **FTIR (cm^{-1})** 3067, 2955, 1548, 1485, 1330, 1226, 1057.

2-(2,2,2-Trifluoro-1-phenoxy-1-(o-tolyl)ethyl)pyridine (28p)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(*o*-tolyl)ethan-1-one **18p** (0.047 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-phenoxy-1-(*o*-tolyl)ethyl)pyridine **28p** as a yellow oil (0.056 g, 65% yield).

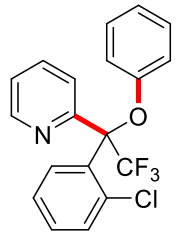


28p

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.57-8.56 (m, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.83-7.76 (m, 2H), 7.35-7.30 (m, 2H), 7.29-7.25 (m, 1H), 7.11-7.07 (m, 3H), 6.97-6.94 (m, 1H), 6.77 (d, *J* = 8.2 Hz, 2H), 1.77 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.7, 155.2, 148.8, 138.2, 136.3, 134.6, 132.8, 129.3, 129.1 (q, *J* = 3.2 Hz), 128.9, 125.9, 124.7 (q, *J* = 290.6 Hz), 124.0 (unresolved quartet), 123.4, 123.3, 120.8 (q, *J* = 1.4 Hz), 87.8 (q, *J* = 26.4 Hz), 21.2. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO$ 344.1257; found 344.1262. **FTIR (cm^{-1})** 3064, 2924, 1588, 1490, 1209, 1157.

2-(1-(2-Chlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28q)

Following the general procedure, treatment of 1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-one **18q** (0.052 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-(1-(2-chlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28q** as a yellow solid (0.069 g, 76% yield).



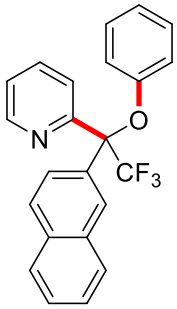
28q

***R*f** (Pet. ether /EtOAc = 95/05): 0.28; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.52-8.51 (m, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.01-7.98 (m, 1H), 7.80-7.76 (m, 1H), 7.44-7.24 (m, 4H), 7.12-7.08 (m,

2H), 6.99-6.96 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.8, 154.9, 148.5, 136.2, 134.7, 133.9, 132.1, 131.1 (q, *J* = 3.1 Hz), 130.6, 128.8, 126.8, 124.5 (q, *J* = 291.2 Hz), 124.2 (unresolved quartet), 123.7, 123.4, 121.6 (q, *J* = 1.5 Hz), 87.4 (q, *J* = 26.8 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}ClF_3NO$ 364.0711; found 364.0717. **FTIR (cm^{-1})** 3064, 1589, 1490, 1433, 1212, 1170.

2-(2,2,2-Trifluoro-1-(naphthalen-2-yl)-1-phenoxyethyl)pyridine (28r)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(naphthalen-2-yl)ethan-1-one **18r** (0.056 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(naphthalen-2-yl)-1-phenoxyethyl)pyridine **28r** as a brown oil (0.068 g, 72% yield).



28r

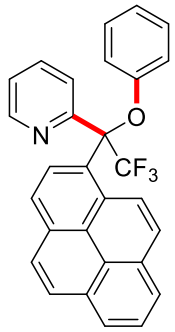
***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.73 (d, *J* = 4.6 Hz, 1H), 8.48 (s, 1H), 7.89-7.79 (m, 3H), 7.74-7.64 (m, 3H), 7.54-7.48 (m, 2H), 7.31-7.28 (m, 1H), 7.04 (t, *J* = 8.0 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.5, 154.8, 148.7, 136.6, 133.3, 132.7, 132.7, 129.6 (unresolved quartet), 129.0, 128.9, 127.6, 127.4, 127.1, 126.8 (unresolved quartet), 126.3, 125.3 (q, *J* = 1.9 Hz), 124.5 (q, *J* = 288.0 Hz), 123.8, 122.7, 120.4, 86.3 (q, *J* = 27.6 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{23}H_{17}F_3NO$ 380.1257; found 380.1263. **FTIR (cm^{-1})** 3065, 2926, 1590, 1485, 1251, 1058.

2-(2,2,2-Trifluoro-1-phenoxy-1-(pyren-1-yl)ethyl)pyridine (28s)

Following the general procedure, treatment of 2,2,2-trifluoro-1-(pyren-1-yl)ethan-1-one **18s** (0.074 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc =

95/05) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-phenoxy-1-(pyren-1-yl)ethyl)pyridine **28s** as a yellow solid (0.092 g, 81% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.61-8.58 (m, 1H), 8.44-8.42 (m, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 8.20-8.16 (m, 2H), 8.13-8.05 (m, 4H), 7.98-7.94 (m, 1H), 7.83-7.76 (m, 2H), 7.23-7.20 (m, 1H), 6.95-6.90 (m, 2H), 6.84-6.81 (m, 1H), 6.75 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 158.8, 155.4, 148.9, 136.5, 132.4, 131.3, 130.2, 129.9, 129.5, 128.8, 128.5, 127.8, 127.5, 127.0 (q, *J* = 3.4 Hz), 126.2, 125.8, 125.8, 125.6, 125.4, 125.0 (q, *J* = 288.0 Hz), 124.6, 124.5, 123.9 (unresolved quartet), 123.5, 123.5, 121.3 (unresolved quartet), 88.9 (q, *J* = 25.9 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{29}H_{18}F_3NNaO$ 476.1233; found 476.1240. **FTIR (cm^{-1})** 3048, 1589, 1489, 1432, 1211, 1166.

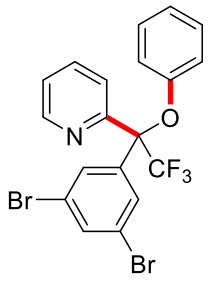


28s

2-(1-(3,5-Dibromophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28t)

Following the general procedure, treatment of 1-(3,5-dibromophenyl)-2,2,2-trifluoroethan-1-one **18t** (0.083 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(1-(3,5-dibromophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28t** as a yellow oil (0.106 g, 87% yield).

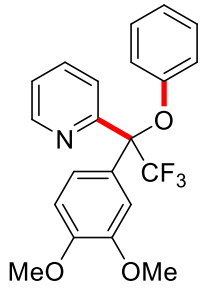
***R*f** (Pet. ether /EtOAc = 95/05): 0.25; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.69-8.68 (m, 1H), 7.98 (s, 2H), 7.71-7.63 (m, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.31-7.28 (m, 1H), 7.09-7.05 (m, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 154.0, 153.8, 148.8, 138.9, 136.9, 134.7, 131.7 (unresolved quartet), 129.5, 129.1, 125.3 (q, *J* = 2.1 Hz), 124.2, 123.8 (q, *J* = 287.7 Hz), 123.0, 122.4, 120.0, 117.9, 85.1 (q, *J* = 28.3 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{13}Br_2F_3NO$ 485.9311; found 485.9314. **FTIR (cm^{-1})** 3097, 1585, 1533, 1490, 1219, 1179.



28t

2-(1-(3,4-Dimethoxyphenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28u)

Following the general procedure, treatment of 1-(3,4-dimethoxyphenyl)-2,2,2-trifluoroethan-1-one **18u** (0.058 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(1-(3,4-dimethoxyphenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28u** as a yellow oil (0.070 g, 72% yield).

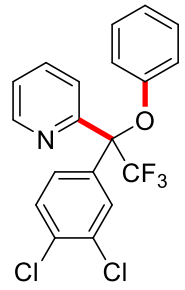


28u

***R*f** (Pet. ether /EtOAc = 95/05): 0.20; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.69 (dt, J_1= 4.7 Hz, J_2= 1.3 Hz, 1H), 7.65-7.64 (m, 2H), 7.35-7.24 (m, 3H), 7.05-7.00 (m, 2H), 6.87-6.80 (m, 2H), 6.65 (d, *J* = 7.9 Hz, 2H), 3.86 (s, 3H), 3.75 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.7, 154.7, 149.5, 148.6, 148.2, 136.5, 128.9, 127.0, 125.1 (unresolved quartet), 124.4 (q, *J* = 287.0 Hz), 123.6, 122.9 (unresolved quartet), 122.5, 120.3, 113.5, 110.3, 86.0 (q, *J* = 27.6 Hz), 56.0, 55.9. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{21}H_{18}F_3NNaO_3$ 412.1131; found 412.1132. **FTIR (cm^{-1})** 3064, 3007, 2936, 2837, 1592, 1517, 1220, 1028.

2-(1-(3,4-Dichlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28v)

Following the general procedure, treatment of 1-(3,4-dichlorophenyl)-2,2,2-trifluoroethan-1-one **18v** (0.061 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(1-(3,4-dichlorophenyl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28v** as a yellow oil (0.081 g, 81% yield).



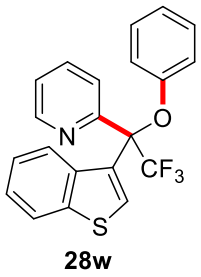
28v

***R*f** (Pet. ether /EtOAc = 95/05): 0.26; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.69 (d, *J* = 4.1 Hz, 1H), 8.16 (d, *J* = 1.4 Hz, 1H), 7.67-7.59 (m, 3H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.31-7.26 (m, 1H), 7.08-7.04 (m, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 154.0, 154.0, 148.7, 136.9, 134.8, 133.5, 132.2, 129.8, 129.4 (unresolved quartet),

129.1, 125.3 (q, *J* = 2.1 Hz), 124.1, 123.8 (q, *J* = 287.0 Hz), 122.8, 119.8, 117.9, 85.0 (q, *J* = 28.0 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{13}Cl_2F_3NO$ 398.0321; found 398.0322. **FTIR (cm^{-1})** 3058, 2962, 1589, 1255, 991, 954.

2-(1-(Benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28w)

Following the general procedure, treatment of 1-(benzo[*b*]thiophen-3-yl)-2,2,2-trifluoroethan-1-one **18w** (0.058 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 96/04) of the crude reaction mixture afforded 2-(1-(benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28w** as a yellow solid (0.092 g, 95% yield).

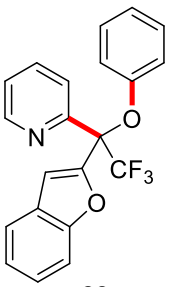


28w

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.61-8.60 (m, 1H), 8.28 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.81-7.79 (m, 1H), 7.77-7.73 (m, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.29-7.21 (m, 2H), 7.13-7.09 (m, 1H), 7.04-7.00 (m, 2H), 6.91-6.87 (m, 1H), 6.73 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.7, 154.8, 148.9, 139.9, 137.7, 136.7, 129.6 (unresolved quartet), 129.6, 128.9, 124.8 (unresolved quartet), 124.3 (q, *J* = 290.4 Hz), 124.3, 124.3, 124.2 (unresolved quartet), 123.9, 123.5, 122.7, 120.8 (unresolved quartet), 85.5 (q, *J* = 27.8 Hz). HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{21}H_{14}F_3NNaOS$ 408.0640; found 408.0646. **FTIR (cm^{-1})** 3062, 2924, 1588, 1490, 1430, 1173.

2-(1-(Benzofuran-2-yl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28x)

Following the general procedure, treatment of 1-(benzofuran-2-yl)-2,2,2-trifluoroethan-1-one **18x** (0.054 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc =



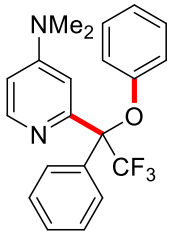
28x

91/09) of the crude reaction mixture afforded 2-(1-(benzofuran-2-yl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine **28x** as a yellow solid (0.089 g, 96% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.21; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.71-8.69 (m, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.78-7.73 (m, 1H), 7.56-7.54 (m, 1H), 7.41-7.31 (m, 3H), 7.26-7.17 (m, 2H), 7.04-7.00 (m, 2H), 6.89-6.85 (m, 1H), 6.80 (d, *J* = 8.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.8, 154.7, 153.8, 149.1, 148.7, 136.9, 129.0, 127.4, 125.4, 124.2, 123.9 (unresolved quartet), 123.5 (q, *J* = 287.7 Hz), 123.4, 123.2, 121.9, 120.2, 112.0 (unresolved quartet), 111.7, 83.5 (q, *J* = 29.0 Hz). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{15}F_3NO_2$ 370.1049; found 370.1056. **FTIR (cm^{-1})** 3065, 1590, 1491, 1429, 1253, 1220.

_N_,_N_-Dimethyl-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridin-4-amine (28y)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and *N*,*N*-dimethylpyridin-4-amine **1b** (0.046 g, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded *N*,*N*-dimethyl-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridin-4-amine **28y** as a yellow oil (0.060 g, 64% yield).



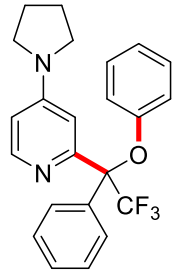
28y

***R*f** (Pet. ether /EtOAc = 95/05): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.30 (d, *J* = 6.0 Hz, 1H), 7.75-7.74 (m, 2H), 7.34-7.32 (m, 3H), 7.07-7.03 (m, 2H), 6.89-6.86 (m, 2H), 6.74 (d, *J* = 8.1 Hz, 2H), 6.48-6.46 (m, 1H), 2.89 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.5, 155.1, 154.7, 148.6, 135.6, 129.8 (unresolved quartet), 128.7, 127.7, 124.6 (q, *J* = 291.0 Hz), 122.4, 120.5, 107.9 (q, *J* = 1.9 Hz), 106.6, 86.6 (q, *J* = 26.9 Hz), 39.2. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{21}H_{20}F_3N_2O$ 373.1522; found 373.1524. **FTIR (cm^{-1})** 2934, 1601, 1545, 1490, 1448, 1223.

4-(Pyrrolidin-1-yl)-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine (28z)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149

g, 121 μL, 0.5 mmol) and 4-(pyrrolidin-1-yl)pyridine **1c** (0.056 g, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded 4-(pyrrolidin-1-yl)-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine **28z** as a yellow oil (0.055 g, 55% yield).

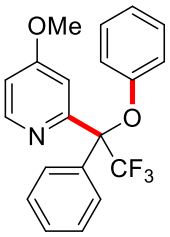


28z

***R*f** (Pet. ether /EtOAc = 95/05): 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.27 (d, *J* = 5.8 Hz, 1H), 7.74-7.73 (m, 2H), 7.33-7.31 (m, 3H), 7.08-7.04 (m, 2H), 6.89-6.85 (m, 1H), 6.76-6.74 (m, 3H), 6.36-6.34 (m, 1H), 3.25-3.15 (m, 4H), 1.99-1.93 (m, 4H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.3, 155.2, 152.1, 148.5, 135.6, 129.8 (unresolved quartet), 128.7, 128.7, 127.7, 124.6 (q, *J* = 286.6 Hz), 123.3, 120.5, 108.2 (q, *J* = 2.0 Hz), 106.9, 86.6 (q, *J* = 26.6 Hz), 47.1, 25.3. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{23}H_{22}F_3N_2O$ 399.1679; found 399.1683. **FTIR (cm^{-1})** 3067, 2975, 2850, 1601, 1543, 1492.

4-Methoxy-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine (28aa)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and 4-methoxypyridine **1d** (0.041 g, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 89/11) of the crude reaction mixture afforded 4-methoxy-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine **28aa** as a yellow oil (0.065 g, 73% yield).

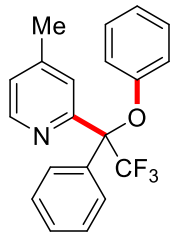


28aa

***R*f** (Pet. ether /EtOAc = 95/05): 0.24; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.51 (d, *J* = 5.7 Hz, 1H), 7.76-7.74 (m, 2H), 7.37-7.35 (m, 3H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.08-7.04 (m, 2H), 6.91-6.88 (m, 1H), 6.82-6.79 (m, 1H), 6.71 (d, *J* = 8.2 Hz, 2H), 3.74 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 166.2, 157.2, 154.8, 149.9, 135.0, 129.7 (unresolved quartet), 129.0, 128.9, 127.9, 124.4 (q, *J* = 286.2 Hz), 122.6, 120.4, 111.4 (q, *J* = 1.9 Hz), 109.9, 86.3 (q, *J* = 26.6 Hz), 55.3. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO_2$ 360.1206; found 360.1208. **FTIR (cm^{-1})** 3068, 2845, 1596, 1488, 1312, 1221.

4-Methyl-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine (28ab)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 µL, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and 4-methylpyridine **1e** (0.035 g, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 4-methyl-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine **28ab** as a yellow oil (0.065 g, 76% yield).

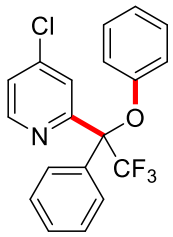


28ab

***R*f** (Pet. ether /EtOAc = 95/05): 0.26; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.54 (d, *J* = 4.8 Hz, 1H), 7.75-7.73 (m, 2H), 7.47-7.47 (m, 1H), 7.38-7.34 (m, 3H), 7.10-7.03 (m, 3H), 6.90-6.87 (m, 1H), 6.69 (d, *J* = 8.1 Hz, 2H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.4, 154.8, 148.4, 147.9, 135.3, 129.7 (q, *J* = 1.5 Hz), 128.9, 128.8, 127.9, 125.8 (q, *J* = 1.9 Hz), 124.7, 124.4 (q, *J* = 287.7 Hz), 122.6, 120.4, 86.4 (q, *J* = 27.5 Hz), 21.4. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO$ 344.1257; found 344.1264. **FTIR (cm^{-1})** 3064, 1598, 1491, 1449, 1255, 1221.

4-Chloro-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine (28ac)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 µL, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 µL, 0.5 mmol) and 4-chloropyridine **1f** (0.043 g, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 97/03) of the crude reaction mixture afforded 4-chloro-2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine **28ac** as a yellow oil (0.079 g, 87% yield).



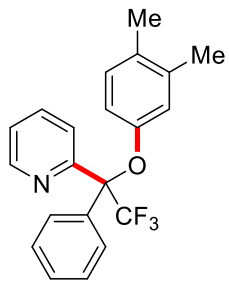
28ac

***R*f** (Pet. ether /EtOAc = 95/05): 0.28; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.58 (d, *J* = 5.3 Hz, 1H), 7.74-7.69 (m, 3H), 7.38-7.34 (m, 3H), 7.32-7.30 (m, 1H), 7.09-7.05 (m, 2H), 6.94-6.90 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 157.7, 154.5, 149.5, 145.0, 134.5, 129.7 (unresolved quartet), 129.2, 129.0, 128.1, 125.3 (unresolved quartet), 124.3 (q,

J = 288.5 Hz), 124.2, 123.0, 120.6, 86.2 (q, *J* = 27.5 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}ClF_3NO$ 364.0711; found 364.0714. **FTIR (cm^{-1})** 3065, 1596, 1491, 1221, 1158, 1108.

2-(1-(3,4-Dimethylphenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine (28ad)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 µL, 0.25 mmol), 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17b** (0.163 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(1-(3,4-dimethylphenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine **28ad** as a yellow oil (0.076 g, 85% yield).

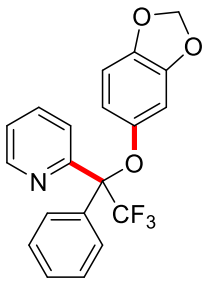


28ad

***R*f** (Pet. ether /EtOAc = 95/05): 0.26; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.70 (d, *J* = 4.9 Hz, 1H), 7.79-7.77 (m, 2H), 7.68-7.64 (m, 2H), 7.38-7.36 (m, 3H), 7.29-7.25 (m, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.24 (dd, *J1* = 8.3 Hz, *J2* = 2.6 Hz, 1H) 2.09 (s, 6H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.8, 152.7, 148.5, 137.4, 136.5, 135.4, 130.6, 129.7 (unresolved quartet), 129.5, 128.9, 127.8, 125.2 (q, *J* = 1.9 Hz), 124.4 (q, *J* = 287.7 Hz), 123.6, 121.5, 117.3, 86.0 (q, *J* = 27.5 Hz), 19.9, 18.9. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{21}H_{19}F_3NO$ 358.1413; found 358.1415. **FTIR (cm^{-1})** 3062, 2366, 1612, 1581, 1498, 1248.

2-(1-(Benzo[*d*][1,3]dioxol-5-yloxy)-2,2,2-trifluoro-1-phenylethyl)pyridine (28ae)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 µL, 0.25 mmol), 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl trifluoromethanesulfonate **17c** (0.171 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 96/04) of the crude reaction mixture afforded 2-(1-



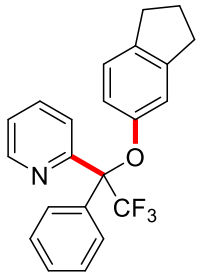
28ae

(benzo[*d*][1,3]dioxol-5-yloxy)-2,2,2-trifluoro-1-phenylethyl)pyridine **28ae** as a yellow oil (0.071 g, 76% yield).

***R*f** (Pet. ether /EtOAc = 95/05): 0.23; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.68-8.67 (m, 1H), 7.70-7.61 (m, 4H), 7.38-7.34 (m, 3H), 7.30-7.26 (m, 1H), 6.44 (d, *J* = 8.5 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 6.13 (dd, *J1* = 8.5 Hz, *J2* = 2.4 Hz, 1H) 5.83 (s, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.8, 149.5, 148.7, 147.5, 143.2, 136.5, 135.7, 129.6 (unresolved quartet), 129.0, 128.0, 125.1 (q, *J* = 1.8 Hz), 124.4 (q, *J* = 287.7 Hz), 123.7, 113.7, 107.4, 103.6, 101.4, 87.1 (q, *J* = 27.3 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{15}F_3NO_3$ 374.0999; found 374.1000. **FTIR (cm^{-1})** 3063, 2893, 1583, 1507, 1246, 1196.

2-(1-((2,3-Dihydro-1*H*-inden-5-yl)oxy)-2,2,2-trifluoro-1-phenylethyl)pyridine (28af)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 6-(trimethylsilyl)-2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate **17d** (0.169 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 96/04) of the crude reaction mixture afforded 2-(1-((2,3-dihydro-1*H*-inden-5-yl)oxy)-2,2,2-trifluoro-1-phenylethyl)pyridine **28af** as a yellow oil (0.074 g, 81% yield).

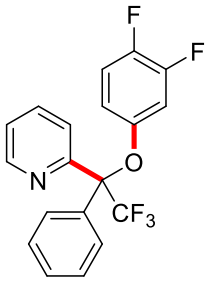


28af

***R*f** (Pet. ether /EtOAc = 95/05): 0.28; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.82-7.79 (m, 2H), 7.68-7.66 (m, 2H), 7.40-7.38 (m, 3H), 7.32-7.26 (m, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.61-6.61 (m, 1H), 6.40 (dd, *J1* = 8.2 Hz, *J2* = 1.7 Hz, 1H) 2.77-2.70 (m, 4H), 2.00 (quint, *J* = 7.4 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.8, 153.4, 148.5, 145.1, 138.1, 136.5, 135.4, 129.7 (unresolved quartet), 128.9, 127.8, 125.2 (q, *J* = 1.9 Hz) 124.4 (q, *J* = 287.8 Hz), 124.0, 123.6, 118, 116.4, 86.2 (q, *J* = 27.5 Hz), 33.0, 32.0, 25.7. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{22}H_{19}F_3NO$ 370.1413; found 370.1416. **FTIR (cm^{-1})** 3062, 2955, 1583, 1487, 1437, 1177.

2-(1-(3,4-Difluorophenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine (28ag)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 µL, 0.25 mmol), 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17e** (0.167 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 97/03) of the crude reaction mixture afforded 2-(1-(3,4-difluorophenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine **28ag** as a yellow oil (0.083 g, 91% yield).

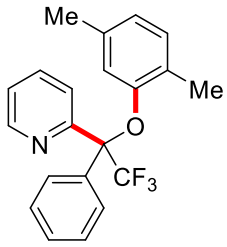


28ag

***R*f** (Pet. ether /EtOAc = 95/05): 0.27; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.68 (d, *J* = 4.7 Hz, 1H), 7.72-7.68 (m, 1H), 7.65-7.59 (m, 3H), 7.39-7.35 (m, 3H), 7.32-7.29 (m, 1H), 6.85-6.78 (m, 1H), 6.59-6.53 (m, 1H), 6.43-6.39 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.1, 150.7 (dd, *J1* = 8.6 Hz, *J2* = 2.9 Hz), 149.7 (dd, *J1* = 248.7 Hz, *J2* = 14.1 Hz), 148.9, 146.4 (dd, *J1* = 244.2 Hz, *J2* = 12.3 Hz), 136.8, 134.9, 129.5 (q, *J* = 1.5 Hz), 129.3, 128.1, 124.9 (q, *J* = 2.0 Hz), 124.2 (q, *J* = 286.9 Hz), 124.0, 116.7 (d, *J* = 1.6 Hz), 116.7 (q, *J* = 1.6 Hz), 110.6 (d, *J* = 20.5 Hz), 87.3 (q, *J* = 27.8 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{13}F_5NO$ 366.0912; found 366.0914. **FTIR (cm^{-1})** 3064, 1614, 1583, 1513, 1432, 1251.

2-(1-(2,5-Dimethylphenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine (28ah)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 µL, 0.25 mmol), 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17f** (0.163 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 µL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(1-(2,5-dimethylphenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine **28ah** as a yellow oil (0.073 g, 81% yield).



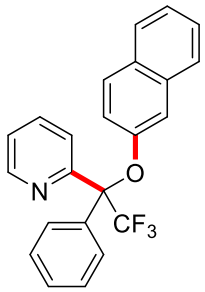
28ah

***R*f** (Pet. ether /EtOAc = 95/05): 0.26; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.73-8.71 (m, 1H), 7.83-7.82 (m, 2H), 7.66-7.62 (m, 1H), 7.55-7.53 (m, 1H), 7.39-7.37 (m, 3H), 7.29-7.26 (m, 1H),

7.01 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 5.84 (s, 1H), 2.43 (s, 3H), 1.87 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.3, 152.5, 148.4, 136.6, 135.4, 134.9, 130.6, 129.8 (unresolved quartet), 128.9, 127.8, 125.7, 125.1 (q, *J* = 1.9 Hz), 124.4 (q, *J* = 286.1 Hz), 123.7, 122.5, 119.3, 85.9 (q, *J* = 27.7 Hz), 21.1, 16.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{21}H_{19}F_3NO$ 358.1413; found 358.1414. **FTIR (cm^{-1})** 3062, 2924, 1583, 1506, 1250, 1178.

2-(2,2,2-Trifluoro-1-(naphthalen-2-yloxy)-1-phenylethyl)pyridine (28ai)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 3-(trimethylsilyl)naphthalen-2-yl trifluoro methanesulfonate **17g** (0.174 g, 0.5 mmol) or 1-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **17h** (0.174 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 98/02) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-phenoxy-1-phenylethyl)pyridine **28ai** as a yellow oil (0.081 g, 85% yield from **17g** or 0.076 g, 80% from **17h**).



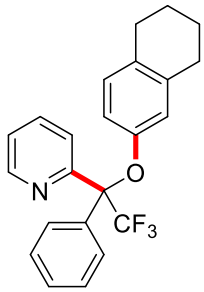
28ai

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.28; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.74 (d, *J* = 4.6 Hz, 1H), 7.89-7.88 (m, 2H), 7.70-7.68 (m, 2H), 7.63-7.59 (m, 2H), 7.45-7.38 (m, 4H), 7.36-7.29 (m, 2H), 7.28-7.24 (m, 1H), 7.09 (dd, *J1* = 9.0 Hz, *J2* = 2.4 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.2, 152.4, 148.7, 136.7, 134.8, 133.7, 129.8 (unresolved quartet), 129.6, 129.1, 129.0, 128.0, 127.5, 127.3, 126.3, 125.2 (q, *J* = 1.9 Hz), 124.6, 124.4 (q, *J* = 288.1 Hz), 123.8, 121.1, 116.0, 86.4 (q, *J* = 27.6 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{23}H_{17}F_3NO$ 380.1257; found 380.1260. **FTIR (cm^{-1})** 3060, 1630, 1594, 1468, 1251, 1178.

2-(2,2,2-Trifluoro-1-phenyl-1-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)ethyl)pyridine (28aj)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 1-(trimethylsilyl)-5,6,7,8-tetrahydro naphthalen-2-yl trifluoromethanesulfonate **17i** (0.176 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375

mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-phenyl-1-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)ethyl)pyridine **28aj** as a yellow oil (0.068 g, 71% yield).

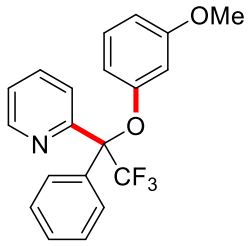


28aj

***R*f** (Pet. ether /EtOAc = 95/05): 0.26; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.70-8.68 (m, 1H), 7.78-7.76 (m, 2H), 7.67-7.62 (m, 2H), 7.37-7.35 (m, 3H), 7.28-7.24 (m, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.26 (dd, *J1* = 8.3 Hz, *J2* = 2.6 Hz, 1H), 2.57-2.53 (m, 4H), 1.71-1.64 (m, 4H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.8, 152.3, 148.5, 137.8, 136.6, 135.4, 131.2, 129.7 (unresolved quartet), 129.1, 128.9, 127.8, 125.2 (q, *J* = 1.9 Hz), 124.4 (q, *J* = 288.1 Hz), 123.6, 120.4, 117.4, 86.0 (q, *J* = 27.4 Hz), 29.5, 28.6, 23.3, 23.1. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{23}H_{21}F_3NO$ 384.1570; found 384.1577. **FTIR (cm^{-1})** 2930, 1581, 1497, 1423, 1249, 1177.

2-(2,2,2-Trifluoro-1-(3-methoxyphenoxy)-1-phenylethyl)pyridine (28ak)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17j** (0.164 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(3-methoxyphenoxy)-1-phenylethyl)pyridine **28ak** as a yellow oil (0.075 g, 84% yield).

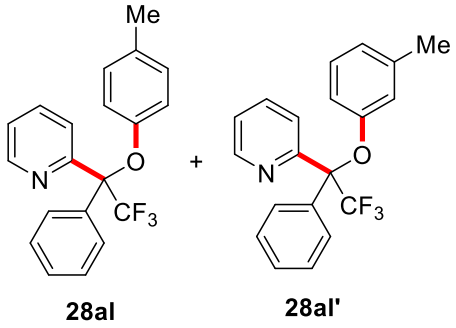


28ak

***R*f** (Pet. ether /EtOAc = 95/05): 0.26; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.71-8.69 (m, 1H), 7.81-7.79 (m, 2H), 7.69-7.62 (m, 2H), 7.39-7.36 (m, 3H), 7.30-7.26 (m, 1H), 6.92-6.88 (m, 1H), 6.46-6.43 (m, 1H), 6.31 (m, 1H), 6.18 (dd, *J1* = 8.2 Hz, *J2* = 2.2 Hz, 1H) 3.61 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 160.2, 155.8, 155.4, 148.6, 136.5, 135.0, 129.7 (unresolved quartet), 129.1, 129.0, 127.9, 125.1 (q, *J* = 1.9 Hz), 124.3 (q, *J* = 287.2 Hz), 123.7, 112.5,

108.6, 106.2, 86.2 (q, *J* = 27.7 Hz), 55.3. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO_2$ 360.1206; found 360.1213. **FTIR (cm^{-1})** 3063, 2923, 1611, 1582, 1509, 1252.

2-(2,2,2-Trifluoro-1-phenyl-1-(*m*-tolyloxy)ethyl)pyridine (28al) and 2-(2,2,2-Trifluoro-1-phenyl-1-(*p*-tolyloxy)ethyl)pyridine (28al')



28al 28al'

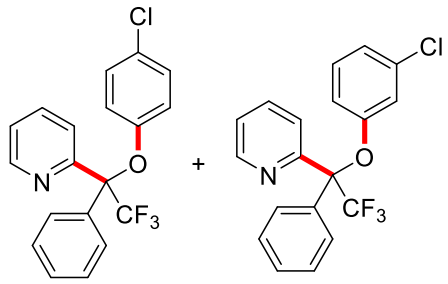
Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17k** (0.156 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-phenyl-1-(*m*-tolyloxy)ethyl)pyridine **28al** and 2-(2,2,2-trifluoro-1-phenyl-1-(*p*-tolyloxy)ethyl)pyridine **28al'** as a mixture of regioisomers in 1.4:1 ratio as a yellow oil (0.078 g, 91% yield).

***R*$_f$** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, CDCl$_3$) of Major isomer** δ 8.71-8.70 (m, 1H), 7.79-7.79 (m, 2H), 7.68-7.62 (m, 2H), 7.38-7.37 (m, 3H), 7.29-7.26 (m, 1H), 6.89-6.83 (m, 1H), 6.71-6.69 (m, 1H), 6.63 (s, 1H), 6.35-6.33 (m, 1H), 2.18 (s, 3H). **Representative peaks of minor isomer ^{1}H NMR (400 MHz, CDCl$_3$)** 6.57 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$) of Major isomer** δ 155.6, 154.7, 148.5, 136.6, 135.2, 129.7 (unresolved quartet), 129.4, 128.9, 127.9, 125.2 (q, *J* = 1.9 Hz), 124.4 (q, *J* = 287.6 Hz), 123.7, 121.0, 117.1, 86.2 (q, *J* = 27.6 Hz), 21.4. **Representative peaks of minor isomer ^{13}C NMR (100 MHz, CDCl$_3$)** 115.7, 152.5, 148.6, 139.1, 135.3, 20.6. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{20}H_{17}F_3NO$ 344.1257; found 344.1259. **FTIR (cm^{-1})** 3063, 2926, 1586, 1487, 1223, 1051.

2-(1-(3-Chlorophenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine (28am) and 2-(1-(4-Chlorophenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine (28am')

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 4-chloro-2-(trimethyl silyl)phenyl trifluoromethanesulfonate

17l (0.166 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 99/01) of the crude reaction mixture afforded 2-(1-(3-chlorophenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine **28am** and 2-(1-(4-chlorophenoxy)-2,2,2-trifluoro-1-phenylethyl)pyridine **28am'** as a mixture of regioisomers in 2.3:1 ratio as a yellow oil (0.103 g, 88% yield).

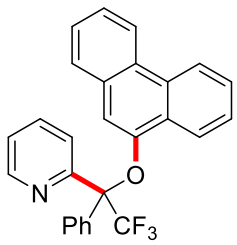


28am **28am'**

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, $CDCl_3$) of Major isomer** δ 8.70-8.69 (m, 1H), 7.74-7.66 (m, 3H), 7.62-7.60 (m, 1H), 7.38-7.38 (m, 3H), 7.31-7.26 (m, 1H), 7.01-6.99 (m, 2H), 6.62-6.60 (m, 2H). **Representative peaks of minor isomer ^{1}H NMR (400 MHz, $CDCl_3$)** 6.81 (s, 1H), 6.46 (d, *J* = 8.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$) of Major isomer** δ 155.4, 155.1, 148.8, 136.7, 134.7, 129.6 (unresolved quartet), 129.2, 128.9, 128.0, 125.1 (q, *J* = 2.0 Hz), 124.2 (q, *J* = 287.9 Hz), 123.9, 121.7, 121.0, 86.6 (q, *J* = 27.7 Hz). **Representative peaks of minor isomer ^{13}C NMR (100 MHz, $CDCl_3$)** 124.2 (q, *J* = 287.5 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{19}H_{14}ClF_3NO$ 364.0711; found 364.0715. **FTIR (cm^{-1})** 3064, 1586, 1488, 1429, 1223, 1184.

2-(2,2,2-Trifluoro-1-(phenanthren-9-yloxy)-1-phenylethyl)pyridine (28an)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.043 g, 35 μL, 0.25 mmol), 10-(trimethylsilyl)phenanthren-9-yl trifluoromethanesulfonate **17m** (0.199 g, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 95/05) of the crude reaction mixture afforded 2-(2,2,2-trifluoro-1-(phenanthren-9-yloxy)-1-phenylethyl)pyridine **28an** as a yellow solid (0.074 g, 94% yield).

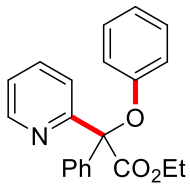


28an

***R*f** (Pet. ether /EtOAc = 95/05): 0.29; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.80-8.79 (m, 1H), 8.76-7.73 (m, 1H), 8.69-8.66 (m, 1H), 8.53 (d, *J* = 8.3 Hz, 1H), 8.10-8.08 (m, 2H), 7.80-7.73 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.56-7.52 (m, 1H), 7.46-7.33 (m, 5H), 7.28-7.21 (m, 2H), 6.23 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 154.2, 148.6, 147.4, 136.8, 133.2, 131.6, 131.6, 130.2 (unresolved quartet), 129.2, 127.9, 127.9, 127.4, 127.2, 127.1, 126.8, 126.8, 125.1, 125.1 (q, *J* = 2.2 Hz), 124.4 (q, *J* = 287.7 Hz), 124.0, 123.0, 122.8, 122.4, 112.2, 86.3 (q, *J* = 25.1 Hz). **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{27}H_{19}F_3NO$ 430.1413; found 430.1414. **FTIR (cm^{-1})** 3063, 1627, 1595, 1495, 1225, 1177.

Ethyl-2-phenoxy-2-phenyl-2-(pyridin-2-yl)acetate (34a)

Following the general procedure, treatment of ethyl 2-oxo-2-phenylacetate **33a** (0.044 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction mixture afforded ethyl-2-phenoxy-2-phenyl-2-(pyridin-2-yl)acetate **34a** as a yellow oil (0.061 g, 73% yield).



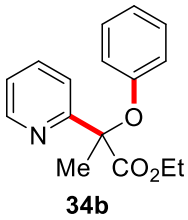
34a

***R*f** (Pet. ether /EtOAc = 95/05): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.53-8.52 (m, 1H), 7.81-7.78 (m, 3H), 7.68-7.64 (m, 1H), 7.32-7.22 (m, 3H), 7.17-7.12 (m, 3H), 6.93-6.89 (m, 3H), 4.25-4.08 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.9, 160.8, 156.1, 148.6, 138.7, 137.0, 129.1, 128.0, 127.8, 127.7, 122.7, 121.7, 121.3, 117.9, 87.5, 61.9, 13.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{21}H_{20}NO_3$ 334.1438; found 334.1444. **FTIR (cm^{-1})** 2985, 1741, 1591, 1492, 1256, 1220.

Ethyl-2-phenoxy-2-(pyridin-2-yl)propanoate (34b)

Following the general procedure, treatment of ethyl 2-oxopropanoate **33b** (0.029 g, 0.25 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **17a** (0.149 g, 121 μL, 0.5 mmol) and pyridine **1a** (0.030 g, 30 μL, 0.375 mmol) in the presence of KF (0.058 g, 1.0 mmol) and 18-crown-6 (0.264 g, 1.0 mmol) in THF (15.0 mL) at 70 °C for 24 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 92/08) of the crude reaction

mixture afforded ethyl-2-phenoxy-2-(pyridin-2-yl)propanoate **34b** as a yellow oil (0.045 g, 66% yield).

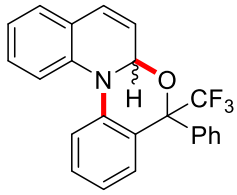


34b

***R*f** (Pet. ether /EtOAc = 95/05): 0.21; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.58-8.57 (m, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.78-7.74 (m, 1H), 7.27-7.22 (m, 3H), 7.03-6.99 (m, 1H), 6.95-6.93 (m, 2H), 4.26-4.20 (m, 2H), 1.91 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 172.0, 161.1, 155.2, 148.8, 137.1, 129.4, 122.9, 122.7, 120.4, 119.6, 84.6, 61.9, 22.54 14.0. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{16}H_{18}NO_3$ 272.1281; found 272.1288. **FTIR (cm^{-1})** 3062, 1747, 1591, 1492, 1249, 1191.

5-Phenyl-5-(trifluoromethyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-*a*]quinoline (19a)

Following the general procedure, treatment of 2,2,2-trifluoro-1-phenylethan-1-one **18a** (0.065 g, 0.375 mmol), 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **17a** (0.90 g, 73 μL, 0.3 mmol) and quinoline **16a** (0.032 g, 0.25 mmol) in the presence of KF (0.035 g, 0.6 mmol) and 18-crown-6 (0.159 g, 0.6 mmol) in THF (1.0 mL) at -10 °C to 25 °C for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 97/03) of the crude reaction mixture afforded 5-phenyl-5-(trifluoromethyl)-5*H*,6a*H*-benzo[4,5][1,3]oxazino[3,2-*a*]quinoline **19a** as a yellow oil (0.071 g, 75% yield).

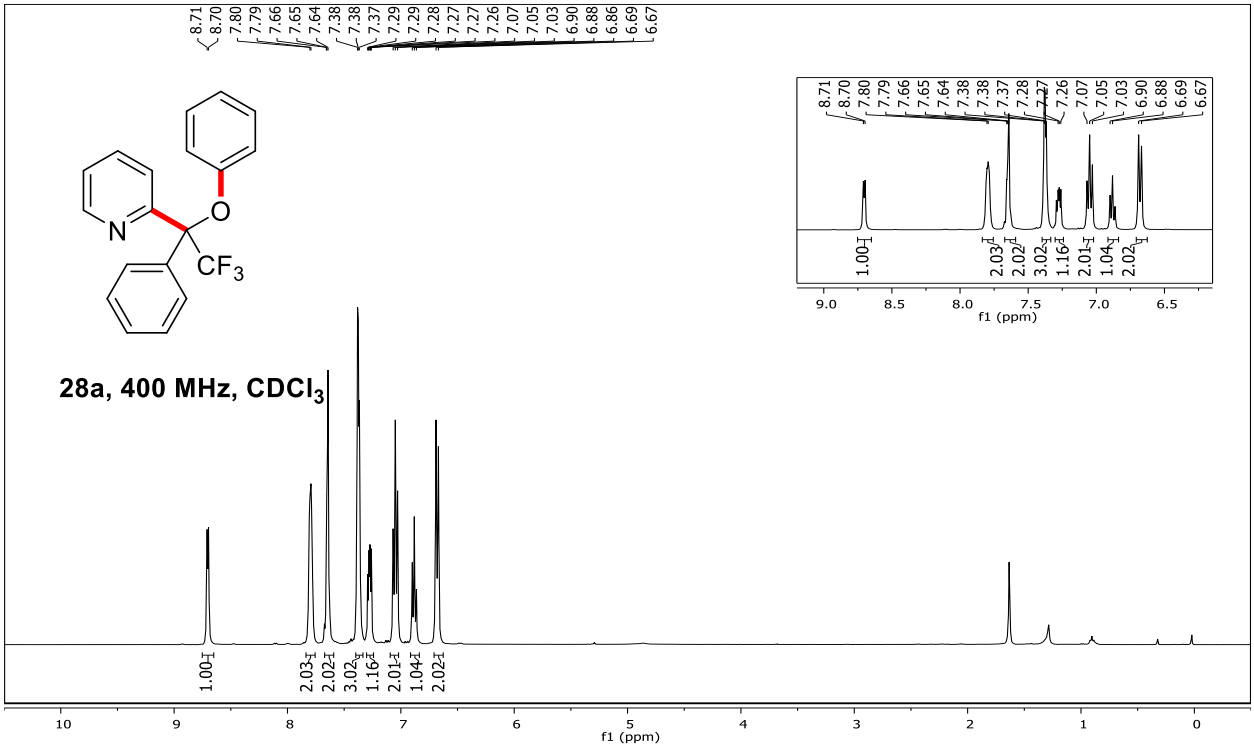


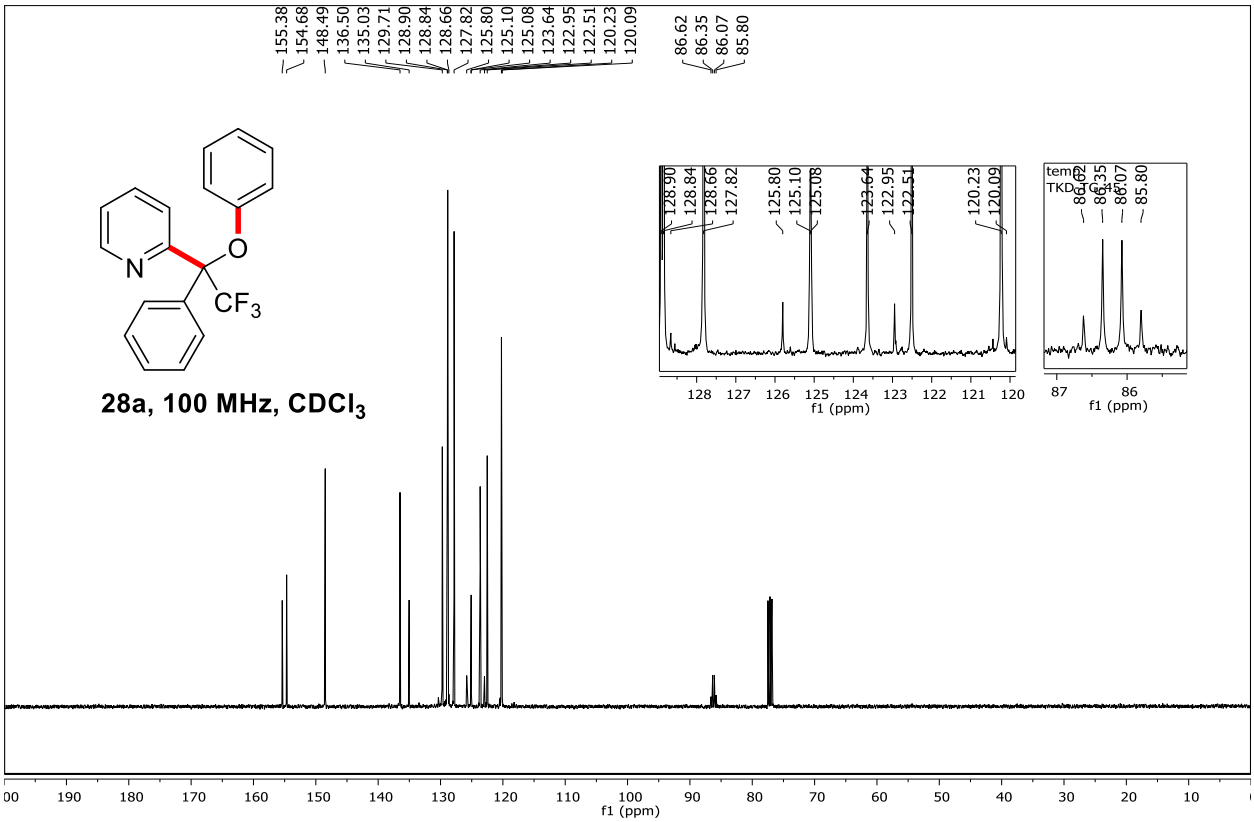
19a

***R*f** (Pet. ether /EtOAc = 95/05): 0.31; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.68-7.64 (m, 3H), 7.49-7.41 (m, 4H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.26-7.18 (m, 3H), 6.95-6.90 (m, 2H), 5.92-5.89 (m, 1H), 5.71 (d, *J* = 4.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 141.8, 139.0, 138.9, 130.8 (unresolved quartet), 130.2, 130.0, 129.0, 128.6, 128.6, 128.4, 128.0 (q, *J* = 2.1 Hz), 127.7 (unresolved quartet), 125.0, 124.5, 124.5 (q, *J* = 286.5 Hz), 120.6, 120.2, 116.7, 112.7, 82.4 (q, *J* = 28.7 Hz), 78.7. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{23}H_{17}F_3NO$ 380.1257; found 380.1260. **FTIR (cm^{-1})** 3037, 1598, 1492, 1452, 1307, 1164.

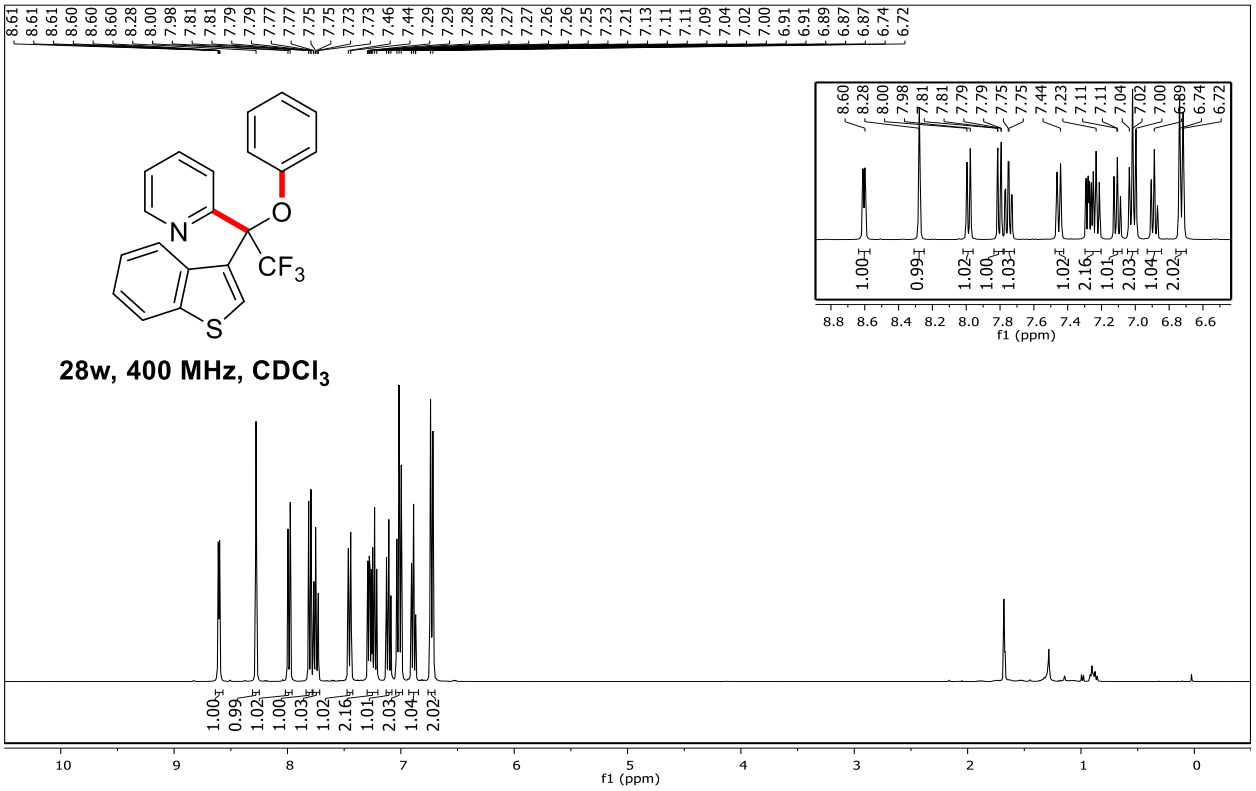
4.7.10. ^{1}H and ^{13}C NMR Spectra of Selected Compounds

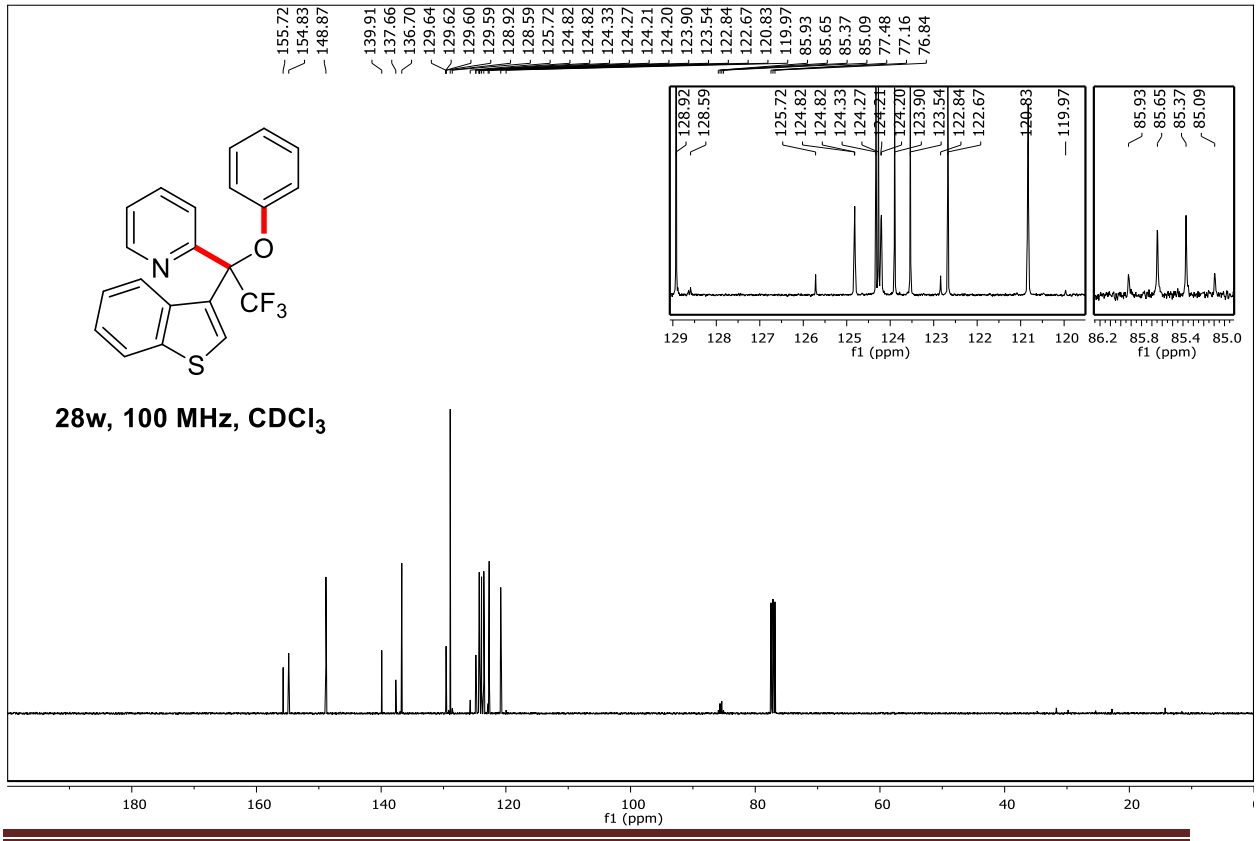
2-(2,2,2-Trifluoro-1-phenoxy-1-phenylethyl)pyridine (28a)



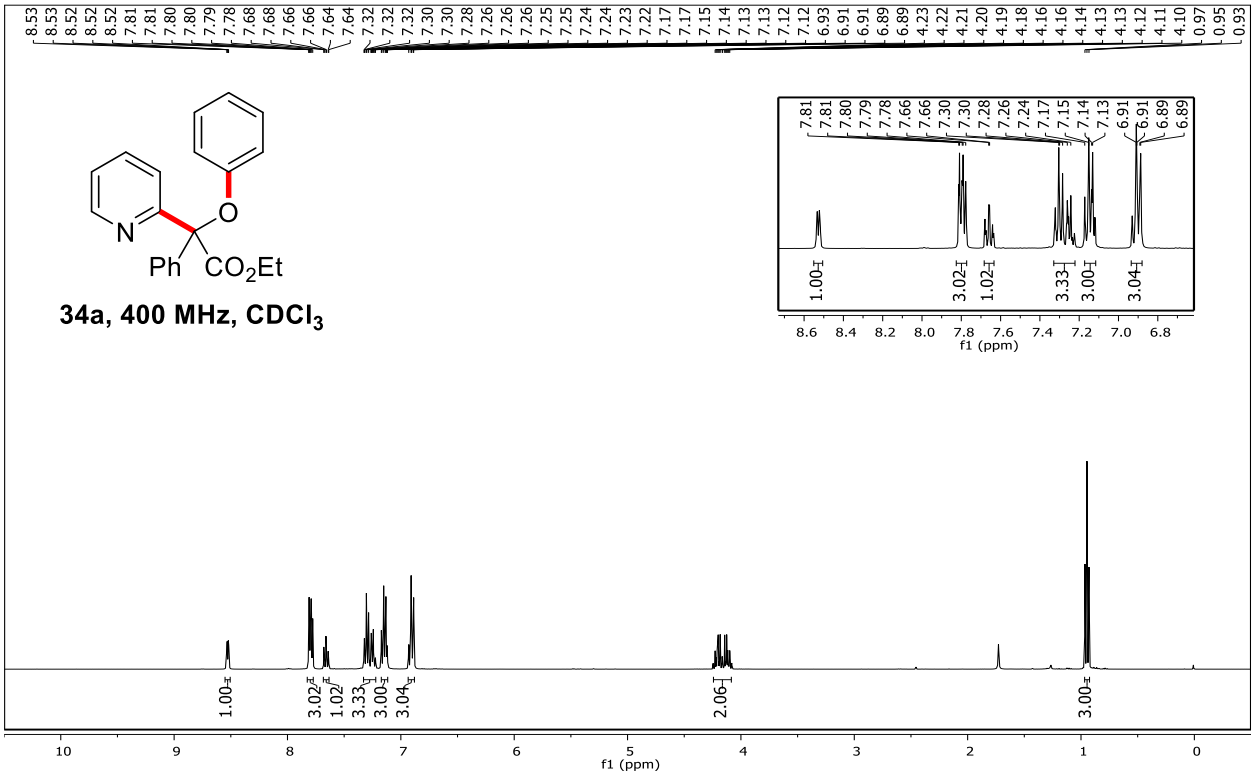


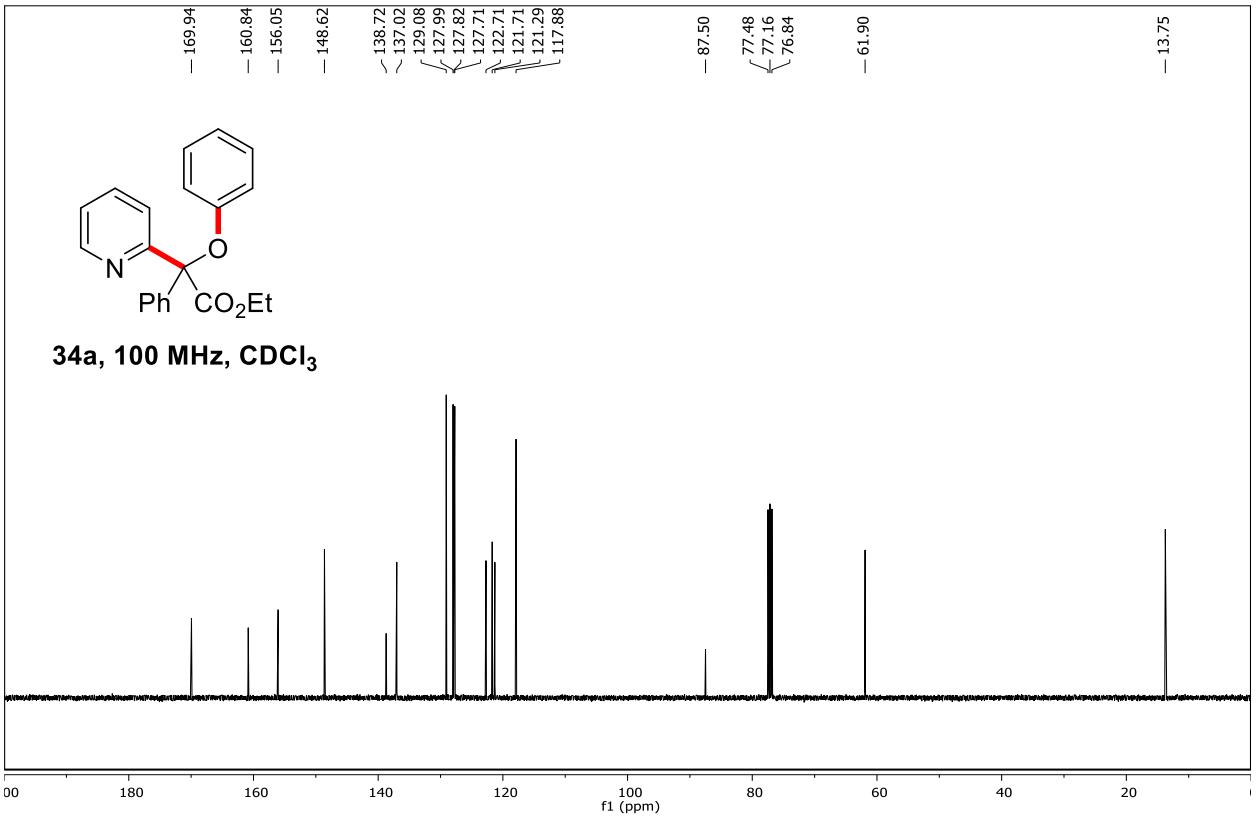
2-(1-(Benzo[*b*]thiophen-3-yl)-2,2,2-trifluoro-1-phenoxyethyl)pyridine (28w)





Ethyl-2-phenoxy-2-phenyl-2-(pyridin-2-yl)acetate (34a)





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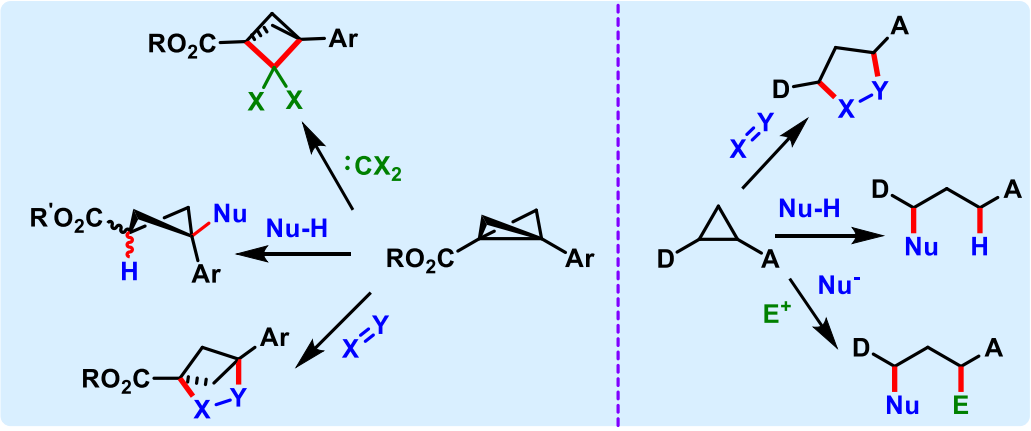
Chapter 5

Donor-Acceptor Cyclopropanes and Bicyclobutanes: An Overview

The advancement of novel reactive molecular entities plays a crucial role in enhancing the toolkit of synthetic organic chemists for constructing intricate architectures. Among these entities, donor-acceptor (D-A) cyclopropanes have emerged as particularly significant in this regard. This strained but kinetically stable intermediate can be further activated through various methods, including Lewis acid activation, organocatalysis, radical activation, and electrochemical activation. These activation processes enable a range of reactions, such as cycloaddition, ring-opening reactions, and 1,3-bisfunctionalization. This chapter offers an overview of the progress in this field, the distinctive characteristics of D-A cyclopropanes, their potential modes of reactivity, and other notable advancements. Additionally, this chapter also covers about highly strained bicyclobutane (BCB), which has gained popularity in recent years.



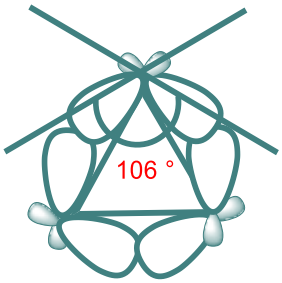
5.1. Introduction

Cyclopropanes exhibit huge potential for efficient and rapid transformations that can lead to increased complexity in the molecules in a limited number of steps.[1] Despite their high energy and a considerable ring strain of approximately 27 kcal mol^{-1}, the C-C bonds in cyclopropanes exhibit kinetic inertness, ensuring the structural integrity of the ring.[2] In contrast to saturated carbocycles, cyclopropanes can engage in electrophilic reactions under the influence of mineral acids and can undergo oxidative addition to transition metals.[3,4]

Various models can be employed to explain the bonding and distinct reactivity exhibited by cyclopropanes. Among these models, the strain model offers a straightforward rationale for how the highly strained cyclopropane system reduces its energy through a ring-opening reaction. Cyclopropane, with bond angle of 60° deviating significantly from the ideal sp^3 geometry and minimal electrostatic repulsion requirements, necessitates a co-planar arrangement of its three carbon atoms. Consequently, the C-H bonds in cyclopropane assume an eclipsed configuration, resulting not only in Baeyer strain but also torsional strain (referred to as Pitzer strain). Thus, several explanations for the enhanced reactivity of cyclopropanes, when compared to other cyclic alkanes, emphasize the alleviation of ring strain. However, relying solely on this model fails to fully account for the reactivity observed in cyclopropanes.

Förster initially proposed and later refined by Coulson and Moffitt, an alternative explanation for the unique bonding in cyclopropanes.[5-7] The σ-bonds in cyclopropanes exhibit a bent configuration (Figure 5.1). This results in approximately 20% less overlap between carbon atoms compared to ethane. The reduction in overlap contributes to the additional angular strain, consequently leading to the increased reactivity. The validity of this concept was supported by X-ray crystallographic data obtained from cyclopropane

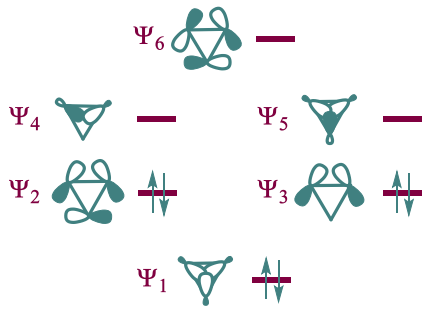
Figure 5.1. Orbitals by Förster, Coulson and Moffitt



derivatives, which confirmed the presence of maximum electron density outside the conventional bond axes.[8] However, this model encountered difficulties when attempting to account for the influence of electron-donating and electron-withdrawing substituents on the stability and reactivity of cyclopropanes.

The bonding in cyclopropanes is described in detail by the Walsh model.[9] According to this model, the bonding in cyclopropanes is better represented by a combination of sp^2 hybrid orbitals and p_z-orbitals. The three sp^2 orbitals combine in-phase to form a molecular orbital (MO) with a significant electron density at the center of the ring, known as the lowest energy orbital ψ_1. On the other hand, the three p_z orbitals extend outward towards the corners of an imaginary triangle and form a pair of degenerate highest occupied molecular orbitals (HOMOs) ψ_2 and ψ_3. These orbitals, referred to as the Walsh orbitals of cyclopropane (Figure 5.2), do not have their electron density aligned along the internuclear axis. They exhibit a resemblance to the bent bonds described in the Förster, Coulson, and Moffitt's model. These orbitals account for the π-character of the cyclopropane ring and energetically occupy relatively higher energy levels compared to those of a saturated hydrocarbon. The lowest unoccupied molecular orbitals (LUMOs) ψ_4 and ψ_5 follows a similar pattern to that of the ψ_1 orbital of sp^2 orbitals, but in a deconstructive manner. These LUMOs direct their electron density towards the center of the ring. Similarly, the highest energy unoccupied orbital ψ_6 is

Figure 5.2. Walsh Molecular Orbitals of Cyclopropane



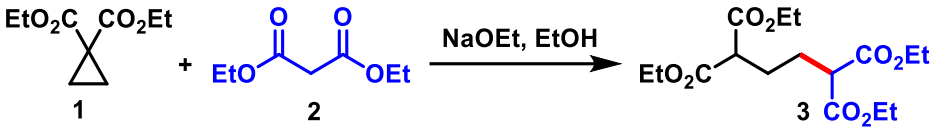
generated through the destructive overlap of *p*-orbitals. The Walsh orbitals exhibit strong π-donor characteristics and effectively interact with vacant orbitals that reside at lower energy levels.[10] The presence of electron density at the center of the ring, as explained by the ψ_1 orbital, introduces the concept of σ-aromaticity in cyclopropanes. The stabilization in cyclopropanes arises from the aromaticity resulting from the σ-bonds. The ring contains six electrons distributed across the three atoms, adhering to the (4n+2) rule of Hückel for

aromaticity. This stabilization may account for the reactivity of cyclopropanes towards electrophiles. The current understanding of the structure and reactivity of cyclopropanes encompasses the concepts of ring strain, distorted π-like bonds, and σ-aromaticity.

5.2. Substituted Cyclopropanes

Despite the significant ring strain in cyclopropanes, they tend to exhibit kinetic inertness. Consequently, the attachment of additional functional groups to the ring becomes necessary to enable mild and efficient synthetic transformations. Only a limited number of reactions involving cyclopropanes, such as specific ring-opening, ring-expansion, and pericyclic reactions, occur without the assistance of activating substituents; however, these reactions typically require harsh conditions. Examples of such reactivity include the vinylcyclopropane-cyclopentene or divinylcyclopropane-cycloheptadiene reactions.[11] Cyclopropanes that are substituted with electron-withdrawing groups are referred to as acceptor cyclopropanes. They behave in a manner analogous to γ-carbonyl cation equivalents or homologous Michael acceptors. On the other hand, cyclopropanes substituted with electron-donating groups are known as donor cyclopropanes, and they act as homologous enolate equivalents.[12] The first instance of a ring-opening reaction involving an activated cyclopropane was reported by Bone and Perkin in 1895.[13] The ring-opening of cyclopropane **1** using an enolate derived from diethyl malonate **2**, resulting in the formation of compound **3** with 50% yield (Scheme 5.1).

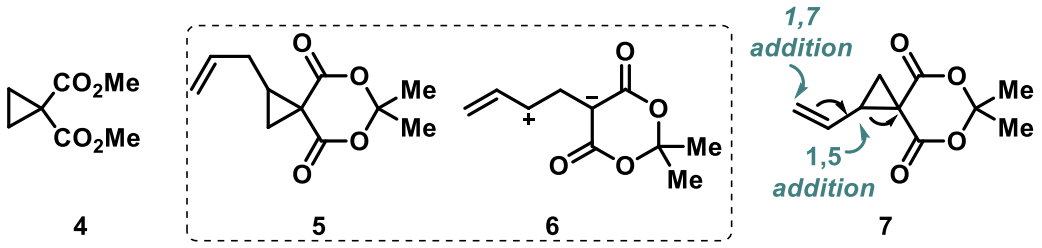
Scheme 5.1. Nucleophilic Ring-Opening of Acceptor Cyclopropanes



Subsequent studies delved into the exploration of Homologous Michael reactions involving activated cyclopropanes and a diverse array of nucleophiles, including amines, mercaptans, enamines, and cuprates.[14-16] However, the utilization of these intermolecular reactions has been hampered by the harsh reaction conditions and modest yields they often entail. To address this issue, Danishefsky and co-worker introduced a strategic modification by employing a spirocyclic moiety for diester activation instead of compound **4**, where the carbonyl groups are positioned orthogonal to the plane of the cyclopropane in compound **5**.[17] This configuration allows the emerging carbanion to distribute its charge over the

alkoxycarbonyl groups (Figure 5.3). The presence of a spirocyclic linkage facilitates enhanced charge separation in the transition state during ring-opening, leading to the stabilization of the presumed intermediate **6**. This phenomenon can be understood by comparing the relative acidity of Meldrum's acid to that of acyclic malonic esters. In-depth investigations into nucleophilic attacks on vinylcyclopropane conducted by Danishefsky and co-workers revealed that, when a spirocyclic motif is employed as the acceptor, an exclusive 1,5-attack is observed, whereas in the case of compound **7**, a competing 1,5- and 1,7-mode of nucleophilic addition occurs.[18] This mild reaction transformation highlights the significance of spiroactivated vinyl cyclopropanes in various synthetic strategies.

Figure 5.3. Spirocyclic Mode of Activation and Modes of Attack on a Vinyl Cyclopropane

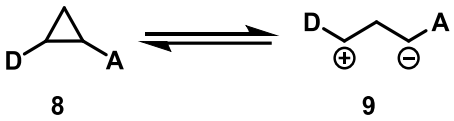


Spiroactivated cyclopropane's exceptional electrophilic properties were harnessed to synthesize trans-fused γ-lactones, surpassing the traditional method involving olefin epoxidation followed by nucleophilic attack with an acetic acid ester carbanion equivalent.[19] In Snider's 2001 report on the total synthesis of (±)-martinellic acid, the synthesis route involved the use of activated vinyl cyclopropane **5**.[20]

5.3. Donor-Acceptor Cyclopropanes

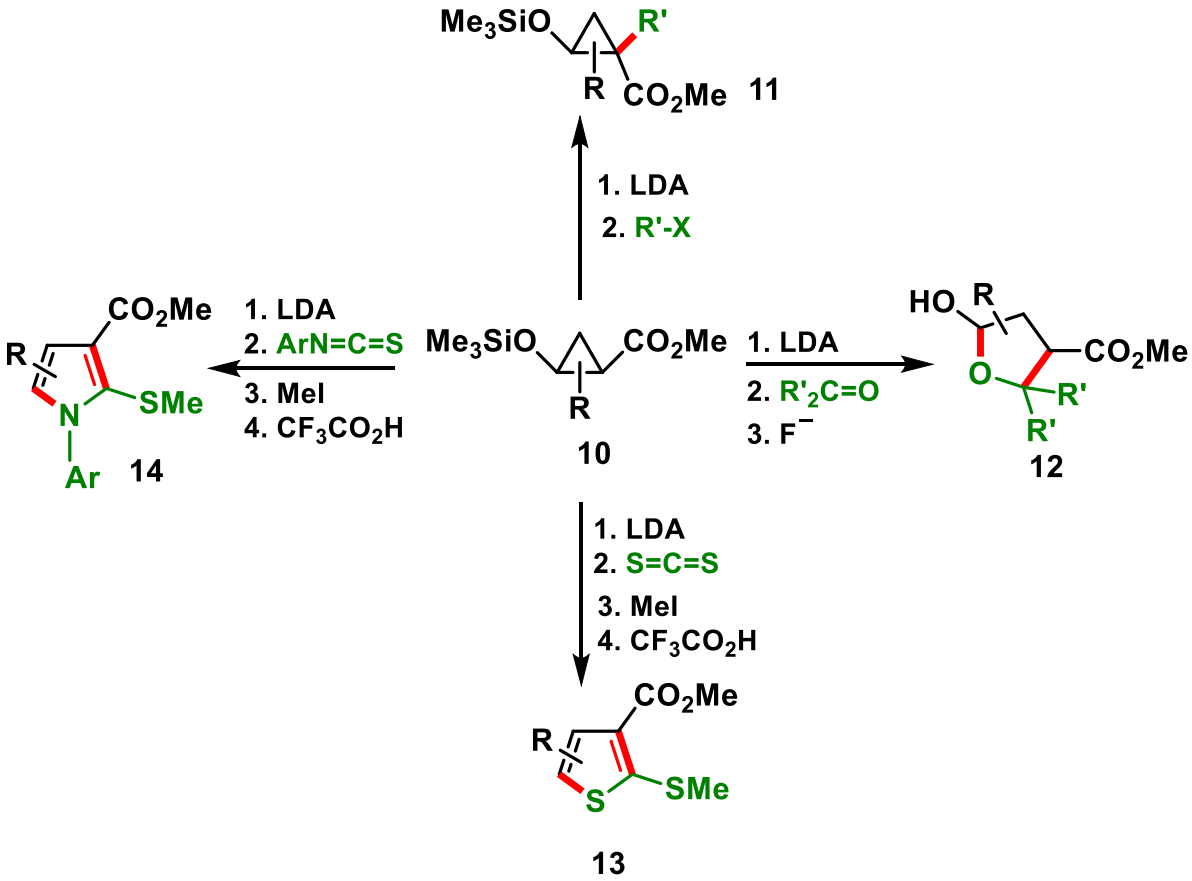
A significant breakthrough in the field of cyclopropane chemistry occurred when the three-membered ring was substituted with donor and acceptor moieties in a vicinal arrangement. The incorporation of these donor and acceptor substituents served as a push-pull mechanism, activating the ring and rendering the molecule susceptible to mild reaction conditions. Extensive research on the transformations of this molecule was conducted by Wenkert and Reissig in the 1980s.[21-26] All the observed reactions could be explained by considering a 1,3-zwitterionic relationship, in which the negative charge is stabilized by the electron-withdrawing group and the positive charge is stabilized by an electron-donating group (Figure 5.4).

Figure 5.4. Zwitterionic Relationship in Donor-Acceptor Cyclopropanes



As for example, methyl cyclopropanecarboxylates **10** displayed excellent reactivity when deprotonated using lithium diisopropylamide (LDA) and subsequently reacted with a wide range of electrophiles (Scheme 5.2). This efficient deprotonation reaction was not initially apparent, as enolates containing a cyclopropane ring were virtually unheard of in the 1980s. Surprisingly, the reaction with alkyl halides exhibited remarkable stereoselectivity,[27] resulting in the formation of C1 substituted cyclopropanes **11**. Upon ring-opening, these compounds led to highly substituted 1,4-dicarbonyl compounds. When the enolates were reacted with aldehydes or ketones, followed by treatment with fluoride, the resulting products were highly substituted tetrahydrofuran derivatives **12** (valuable γ-lactols for synthesis).[28]

Scheme 5.2. Initial Studies on Siloxy-substituted Cyclopropanecarboxylates

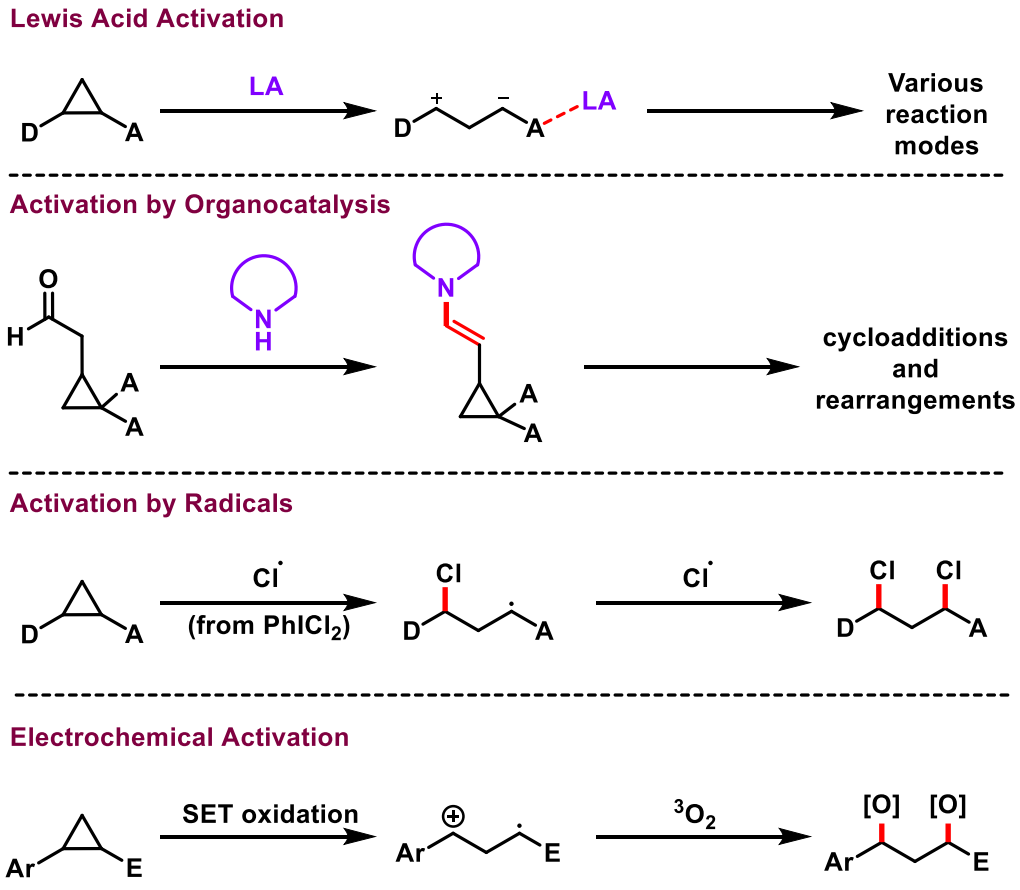


Alternatively, by reacting the enolates with carbon disulfide or aryl isothiocyanates, and subsequently adding methyl iodide, a convenient pathway to functionally diverse thiophene or pyrrole derivatives **13** or **14** was achieved.[29]

5.4. Different Activation Methods for Donor-Acceptor Cyclopropanes

Donor-acceptor cyclopropanes (DACs) can be activated through a variety of methods (Figure 5.5). The most extensively studied among these is Lewis acid catalysis.[30] However, alternative activation strategies, such as organocatalysis,[31] radical activation,[32] and electrochemical single electron transfer (SET) oxidation,[33] have also been investigated. By employing these diverse activation methods, one can access a wide range of intermediate species with unique reactivity profiles. This expands the potential for intriguing chemical processes involving D-A cyclopropanes and offers opportunities for their application in various synthetic pathways. The choice of activation method depends on the specific objectives of the desired transformation and the reactivity requirements of the D-A

Figure 5.5. Various Activation Modes for D-A Cyclopropanes

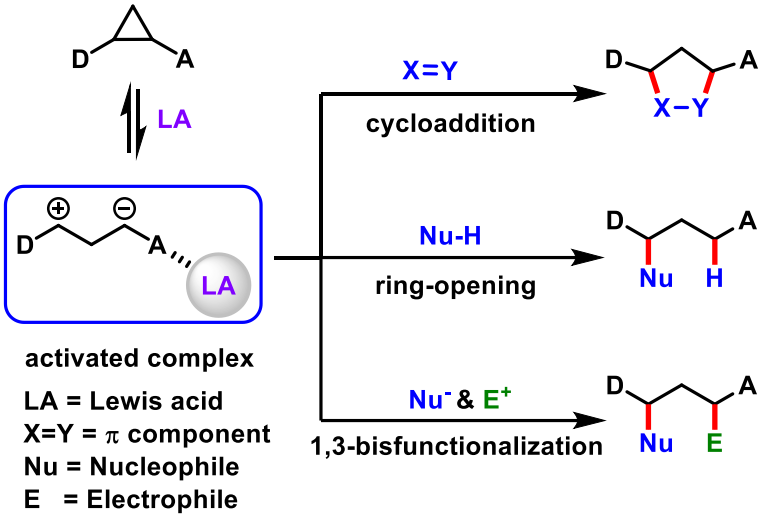


cyclopropanes substrate. Overall, these versatile activation strategies provide flexibility and pave the way for tailored approaches to explore and harness the potential of D-A cyclopropanes in diverse chemical contexts.

5.4.1. Reactions Based on Lewis Acid Activation Strategy

Under the influence of Lewis acids, activation of D-A cyclopropanes (DACs) occurs readily. Lewis acids interact with the acceptor motifs of D-A cyclopropanes, leading to increased electron-withdrawing properties. This polarization weakens the σ bond between the donor and acceptor carbon atoms, thus facilitating a wide range of reactions. The versatile reactivity of D-A cyclopropanes has been harnessed in various transformations, including cycloadditions,[34] ring-opening reactions,[35] and 1,3-bisfunctionalizations.[36] Figure 5.6 provides a visual representation of the general reactions of D-A cyclopropanes catalyzed by Lewis acids.

Figure 5.6. Different Reactivities of D-A Cyclopropanes by Lewis Acid Catalysis

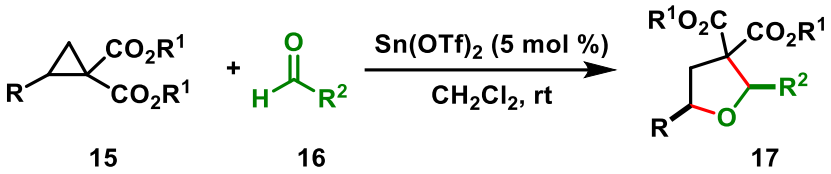


5.4.1.1. Cycloaddition Reactions of D-A Cyclopropanes Catalyzed by Lewis Acid

The cycloaddition reactions involving D-A cyclopropanes yield four-, five-, six-, or seven-membered rings, thereby introducing a variety of functional groups. These reactions, known as (3 + n) cycloadditions, result in the formation of saturated or partially unsaturated rings. Notably, these reactions exhibit a high degree of regioselectivity, wherein the carbon atom carrying the donor motif is selectively attacked by the negative portion of the incoming reactant. Some of the selected examples will be discussed in this section.

In 2008, Jhonson and co-workers reported a single-step, diastereoselective synthesis of cis-2,5-disubstituted tetrahydrofurans **17** through Lewis acid catalyzed [3+2] cycloadditions of D-A cyclopropanes **15** and aldehydes **16** (Scheme 5.3).[37] This methodology demonstrates excellent compatibility with various functional groups present on both reactants. The authors conducted a comprehensive investigation of the reaction mechanism, which involved stereochemical analysis and electronic profiling of the reactants. Experimental observations support an unconventional, stereospecific intimate ion pair mechanism, where the aldehyde acts as a nucleophile and the malonate serves as the nucleofuge. Notably, the reaction proceeds with inversion at the cyclopropane donor site, enabling the transfer of absolute stereochemical information to the products with remarkable fidelity. This mechanism enables the stereospecific synthesis of a diverse range of optically active tetrahydrofuran derivatives from enantioenriched D-A cyclopropanes.

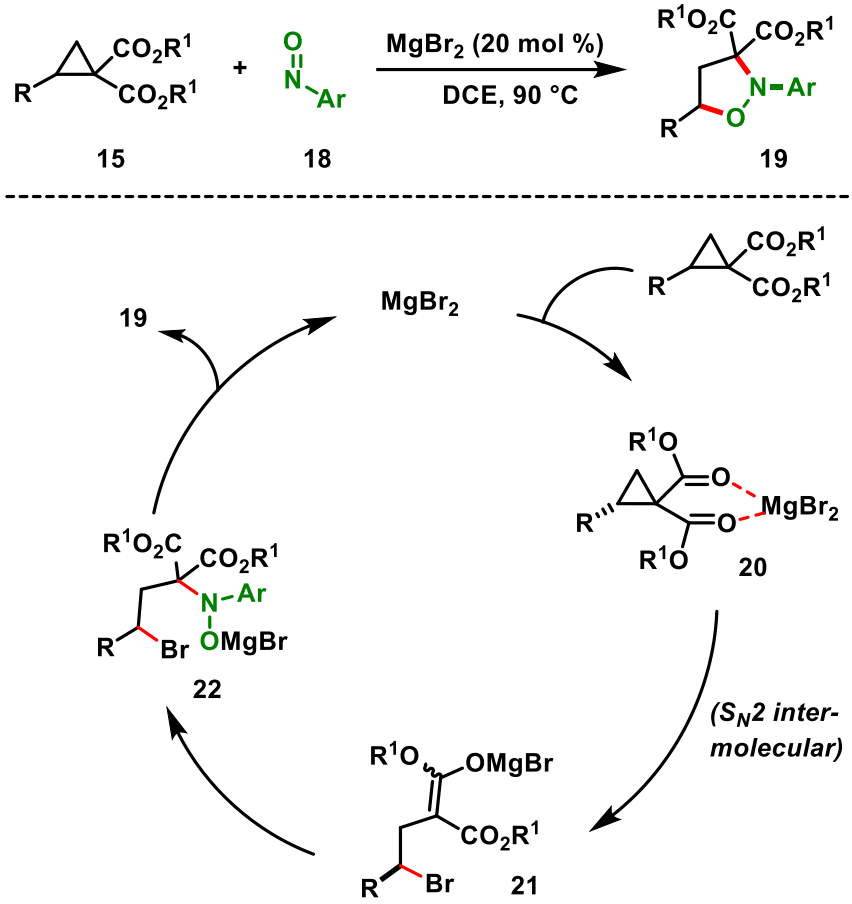
Scheme 5.3. [3+2] Cycloaddition of D-A Cyclopropanes with Aldehydes



15 **16** **17**

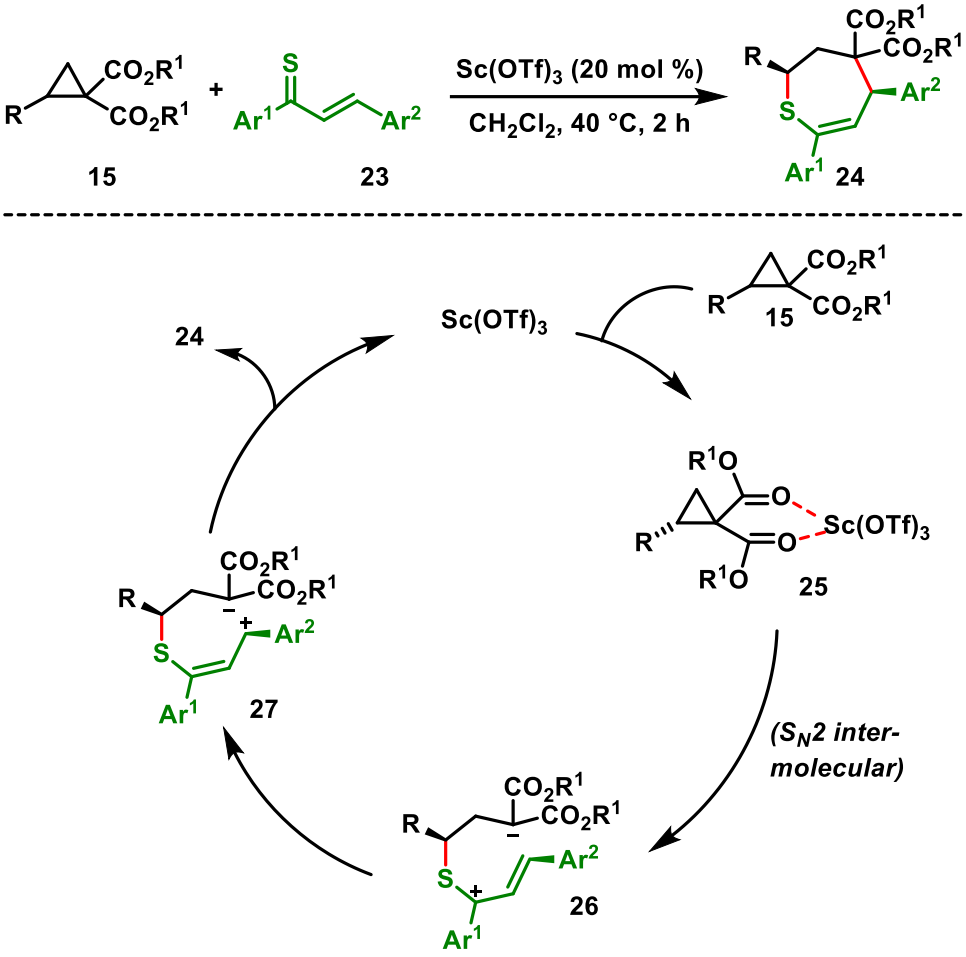
Studer and co-workers uncovered a novel $MgBr_2$-catalyzed formal [3+2] cycloaddition between donor-acceptor activated cyclopropanes and nitrosoarenes **18** (Scheme 5.4).[38] This methodology provides a valuable route to access a diverse range of structurally varied isoxazolidines **19**. Enantiopure D-A cyclopropanes undergo cycloaddition reaction with retention of stereochemistry at the stereogenic center. This is different from the [3+2] cycloaddition of D-A cyclopropanes with aldehydes, where the stereochemistry is reversed despite high stereospecificity. Mechanistically, the reaction initiates with the catalyst $MgBr_2$ interacting with the D-A cyclopropane, forming an activated $MgBr_2$-complexed cyclopropane **20**. The Br anion then opens the cyclopropane ring at the benzylic position through an S_N2 reaction, producing an enolate **21**. The enolate subsequently reacts with nitrosobenzene, leading to the formation of a magnesiated hydroxylamine **22**. Intermediate **22** ultimately undergoes an intramolecular S_N2 substitution, resulting in the closure of the catalytic cycle.

Scheme 5.4. [3+2] Cycloaddition of D-A Cyclopropanes with Nitrosoarenes



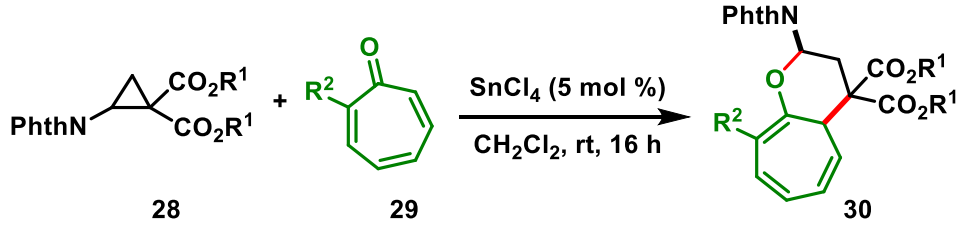
Werz and co-workers presented a highly effective method for synthesizing tetrahydrothiepines **24** through a [4+3]-cycloaddition reaction catalyzed by a Lewis acid. Thiochalcones **23** were utilized as sulfur containing four-atom building blocks. The transformation proceeds smoothly under mild conditions, demonstrate excellent tolerance towards various functional groups, and also exhibit stereospecificity. By employing optimized reaction conditions, the formation of undesired five-membered ring analogs was minimized, and a single diastereomer of the seven-membered ring system was obtained. The reaction mechanism involves the activation of D-A cyclopropanes by $Sc(OTf)_3$, facilitating an S_N2-like attack of thiochalcone. The resulting zwitterion **26** possesses a delocalized positive charge and does not undergo kinetically favored ring closure to form the undesired five-membered ring. Higher temperatures promote attack at the terminal, less-hindered carbon of the allyl system, leading to the thermodynamically favored seven-membered product **24** after releasing the Lewis acid (Scheme 5.5).[39]

Scheme 5.5. [4+3] Cycloaddition of D-A Cyclopropanes with Thiochalcone



Sierra and co-workers revealed a $SnCl_4$ catalyzed [8+3]-cycloaddition reaction, which involves tropone derivatives and donor-acceptor aminocyclopropanes as substrates (Scheme 5.6). This reaction yields amino-substituted tetrahydro cyclohepta[*b*]pyrans **30** with excellent reaction yields and exhibits complete regio- and diastereoselectivities. Through computational-DFT methods, it was determined that this transformation proceeds in a stepwise manner, involving a zwitterionic intermediate resembling the tropyl cation, which

Scheme 5.6. [8+3] Cycloaddition of D-A Aminocyclopropanes with Tropones



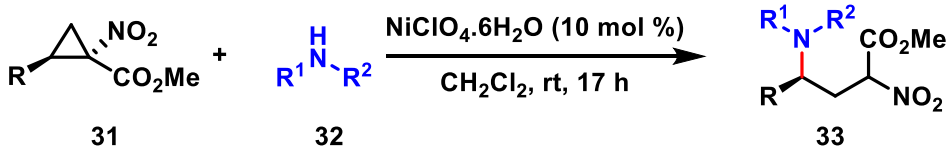
is partially stabilized by π-aromaticity. Subsequently, a ring closure step, controlling the regio- and diastereoselectivities, takes place from this intermediate, leading to the formation of the observed [8+3]-cycloadducts.[40]

5.4.1.2. Lewis Acid Catalyzed Ring-Opening Reactions of D-A Cyclopropanes

The construction of functionalized acyclic products through ring-opening reactions of D-A cyclopropanes represents a highly efficient and straightforward approach. The nucleophilic ring-opening reactions of activated cyclopropanes exhibit similarities to homologous Michael additions. However, in the case of D-A cyclopropanes, these ring-opening reactions can be described as bimolecular nucleophilic substitution reactions (S_N2), where the configuration at the reactive center undergoes inversion. Nucleophiles of various types, such as heteroatom nucleophiles (e.g., amines, phenols, thiols, azides) and carbon nucleophiles, can open the D-A cyclopropanes.[35] This section will delve into the discussion of selected reports that explore the utilization of Lewis acid catalysis in ring-opening reactions of D-A cyclopropanes.

In 2008, Charette and co-workers reported mild and efficient Lewis acid catalyzed ring-opening reactions of D-A cyclopropanes **31** employing amines **32** as the nucleophilic trigger (Scheme 5.7).[35a] Notably, the reaction proceeded at room temperature while retaining the enantiomeric excess at the electrophilic center of the cyclopropane. The protocol exhibited broad substrate compatibility, accommodating various amine nucleophiles and substituents in the 2-position of the cyclopropane ring. Later, Tong and co-workers demonstrated the amines triggered enantioselective ring-opening of D-A cyclopropanes.[41] The same group also developed the phenols addition to D-A cyclopropanes.[35c]

Scheme 5.7. Ring-Opening Reaction of D-A Cyclopropanes with Amine Nucleophiles

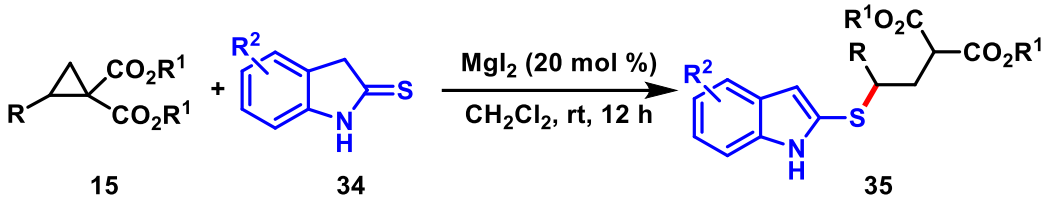


31 **32** **33**

Jiang and co-workers uncovered a MgI_2-catalyzed chemoselective ring-opening reaction of donor-acceptor cyclopropanes with indoline-2-thiones **34** as the sulfur nucleophiles in 2022 (Scheme 5.8).[42] This innovative method enabled the efficient synthesis of diverse γ-thioether functionalized butyric acid derivatives **35** containing 2-indole group,

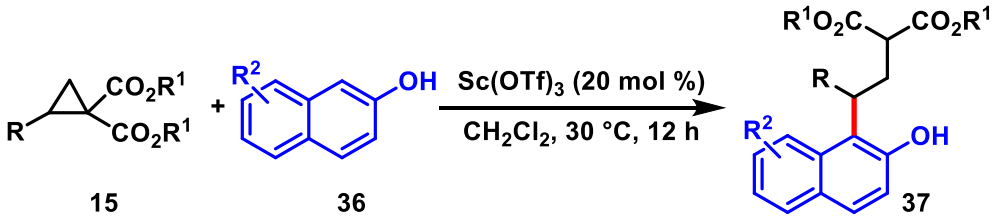
with good to high yields. Moreover, the resulting products could be easily transformed into sulfone and methionine analogues through straightforward conversion steps.

Scheme 5.8. Ring-Opening Reaction of D-A Cyclopropanes with Indoline-2-thiones



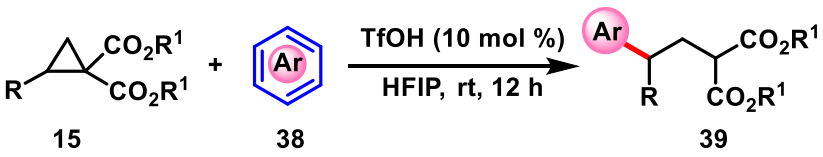
In 2016, Biju and co-workers reported Lewis acid catalyzed ring-opening reactions of D-A Cyclopropanes employing naphthols **36** as the nucleophilic trigger (Scheme 5.9).[35d] $Sc(OTf)_3$ was found to be the optimum catalyst for the desired transformation, and CH_2Cl_2 being the optimum solvent. The reaction works well with various substituted naphthols and D-A Cyclopropanes; in every case, the expected products were formed in good to excellent yields. Interestingly, when $Bi(OTf)_3$ was used as Lewis acid under slightly different reaction conditions, annulated products were formed instead of ring-opened ones.

Scheme 5.9. Ring-Opening of D-A Cyclopropanes with Naphthols



In a similar way to Lewis acid catalysis, Brønsted acid also possess the ability to activate D-A cyclopropanes, leading to ring-opening upon the addition of external nucleophiles. A significant work in this field was demonstrated by Moran and co-workers, who developed a unified Brønsted acid catalyzed nucleophilic ring-opening of D-A cyclopropanes (Scheme 5.10).[43] By combining TfOH (trifluoromethanesulfonic acid) and HFIP (hexafluoroisopropanol), a simple yet highly effective Brønsted acid system was

Scheme 5.10. Brønsted Acid Catalyzed Ring-opening of D-A Cyclopropanes



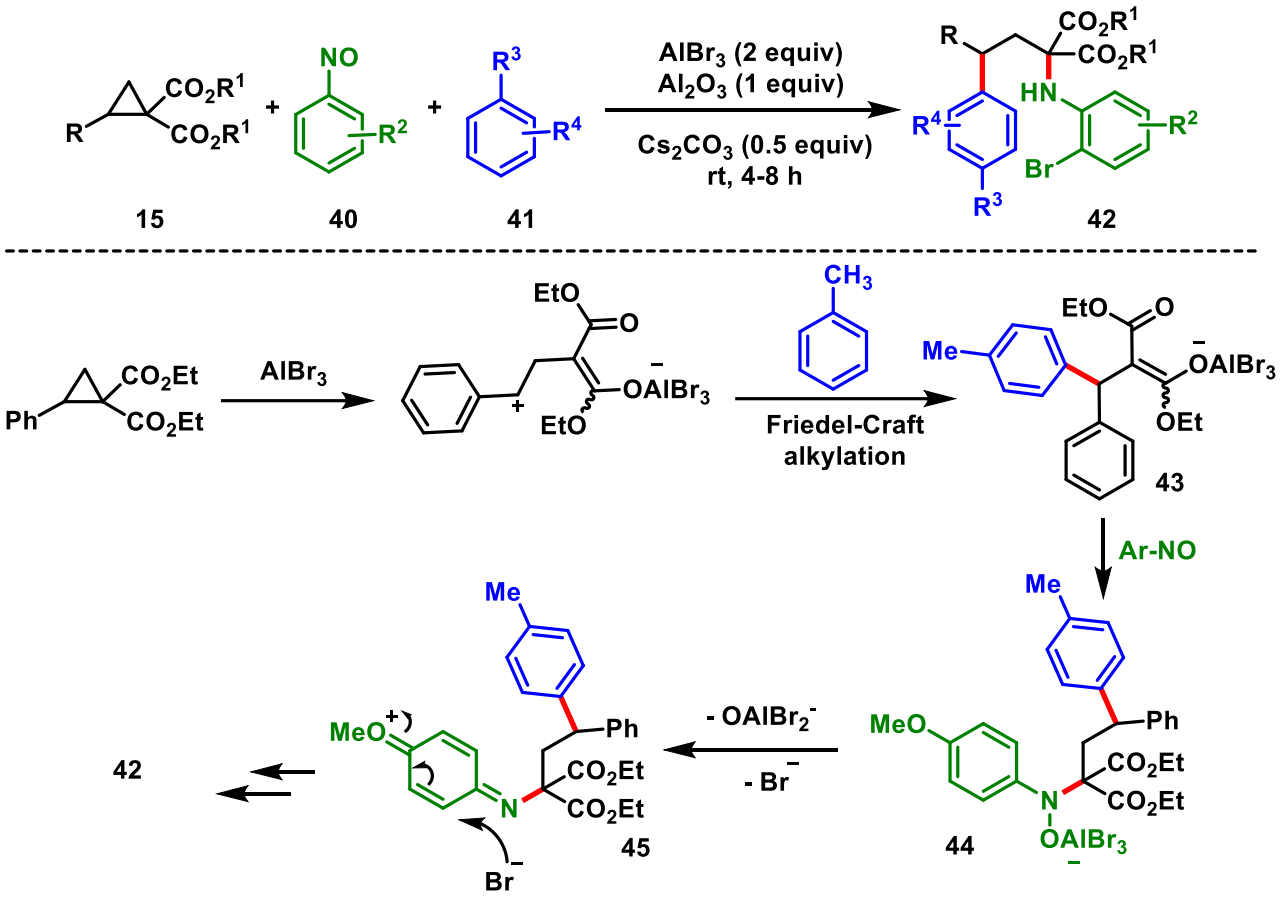
established, enabling previously unexplored classes of cyclopropanes to undergo nucleophilic ring-opening reactions for the first time. Preliminary investigations indicate that the ring-opening process occurs via a mechanistic pathway resembling S_N2 type of addition to D-A cyclopropanes.

5.4.1.3. Lewis Acid Catalyzed 1,3-Bisfunctionalization of D-A Cyclopropanes

In recent years, there has been growing interest among organic chemists in 1,3-bisfunctionalization reactions of D-A cyclopropanes, wherein a nucleophile triggers opened the ring while a suitable electrophile is trapped by the malonate anion. The significance of 1,3-bisfunctionalization in D-A cyclopropanes lies in its ability to introduce two functional groups simultaneously. However, this process poses significant challenges, particularly in finding the appropriate combination of nucleophile and electrophile for the reaction. Often, the compatibility of both components within the same reaction flask becomes a limiting factor. Consequently, there are only a limited number of reported reactions for the ring-opening 1,3-bisfunctionalization of D-A cyclopropanes to date. In the following sections, we will delve into the noteworthy reactions involving Lewis acid catalyzed ring-opening 1,3-bisfunctionalization of D-A cyclopropanes.

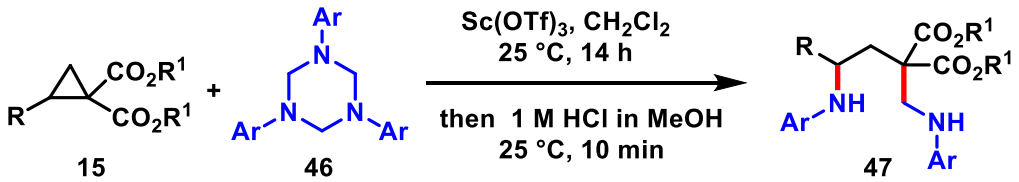
In 2016, Studer and co-workers discovered a novel method for the multicomponent 1,3-bisfunctionalization of D-A cyclopropanes (Scheme 5.11).[36c] This approach involved the use of arenes **41** and nitrosoarenes **40** as coupling partners to synthesize γ,γ-disubstituted *N*-arylated α-amino esters **42**. The Lewis acid $AlBr_3$ served as both a catalyst and a bromide anion donor, enabling regioselective bromination of the arenes. The reaction involved the formation of C-C, C-N, and C-Br bonds in a single flask. Mechanistically, the reaction proceeds through a Friedel-Crafts-type alkylation of the *para*-position of the toluene ring with D-A cyclopropanes, forming an intermediate enolate **43**. This enolate then reacts with *p*-methoxy nitrosobenzene, leading to the formation of intermediate **44**. The N-O bond in intermediate **44** was cleaved with assistance from the methoxy group, giving rise to a new intermediate **45**. The addition of a bromide ion from $AlBr_3$ to intermediate **45**, followed by tautomerization, led to the desired formation of γ,γ-disubstituted *N*-arylated α-amino esters **42**.

Scheme 5.11. 1,3-Bisfunctionalization of D-A Cyclopropanes with Arenes and Nitrosoarenes



In 2017, Werz and co-workers reported an interesting methodology involving the facial ring-opening reaction of D-A cyclopropanes, resulting in the formation of 1,4-diamines. The key step involved a (4+3) cycloaddition between D-A cyclopropanes **15** and triazinanes **46**, facilitated by the use of scandium triflate as a Lewis acid catalyst. This transformation enabled the synthesis of 1,3-diazepanes. Subsequent treatment with acid led to the efficient cleavage of the aminal moiety, yielding the desired 1,4-diamines **47**.

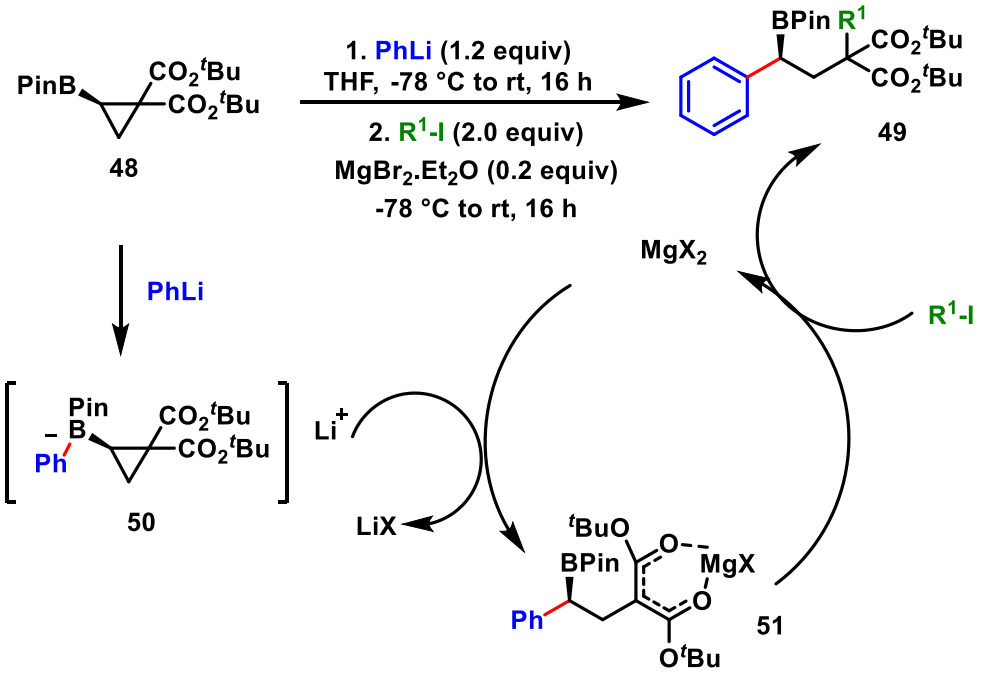
Scheme 5.12. 1-Amino-3-aminomethylation of D-A Cyclopropanes



Additionally, a one-pot reaction was performed, where both an amine and an aminomethyl group were introduced to the former cyclopropane (Scheme 5.12).[44]

In 2019, Aggarwal and co-workers reported an enantiospecific coupling reaction involving organolithium reagents and enantioenriched cyclopropyl boronic esters (Scheme 5.13).[36e] This transformation occurs through the formation of a boronate complex with an activated cyclopropane in the α position. The presence of two ester groups in the β position, as well as the strain in the cyclopropane, plays a crucial role in facilitating the 1,2-metalate rearrangement. When methyl iodide was employed as an electrophilic coupling partner, a three-component coupling product was obtained in a 77% yield. Additionally, the use of allyl iodide and Eschenmoser's salt as the third components proved successful, resulting in the formation of multicomponent products **49** with good yield and excellent enantioselectivity.

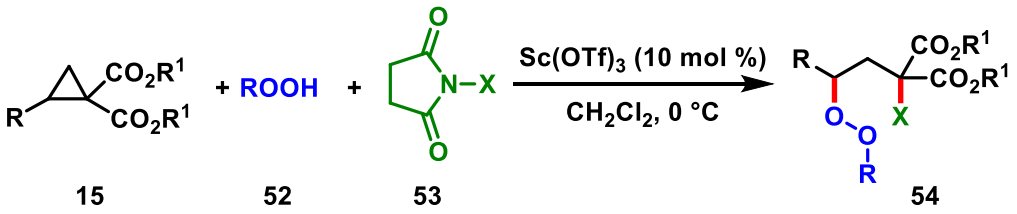
Scheme 5.13. 1,3-Bisfunctionalization of Boronic Ester Containing D-A Cyclopropanes



Saha and co-workers have introduced the use of hydroperoxides as nucleophilic triggers in multicomponent coupling reactions of D-A cyclopropanes. This innovative method allows for the construction of highly functionalized γ-peroxy carbonyls **54** through an ionic process, distinct from previously reported radical-based approaches. The ring-opening 1,3-halogenation-peroxidation reaction is straightforward to perform, requiring the presence of a hydroperoxide **52** and a suitable halogenating agent **53** (Scheme 5.14).[45] The

versatility of this methodology was demonstrated through various synthetic transformations of the 1,3-halogenation-peroxidation products, appealing to synthetic organic chemists.

Scheme 5.14. 1,3-Halogenation-peroxidation of D-A Cyclopropanes

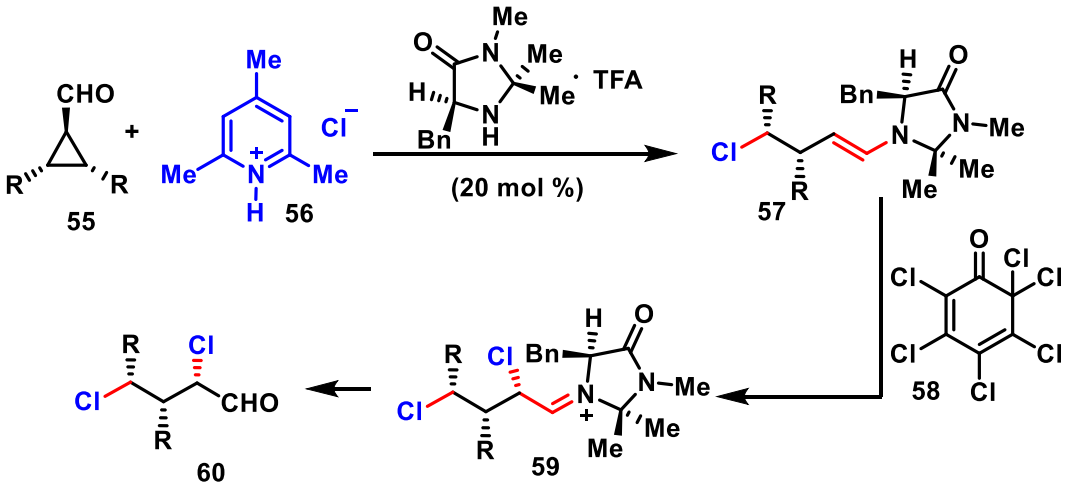


Reports regarding the related 1,3-bisfunctionalization of D-A cyclopropanes will be further discussed in Chapter 6 and 7.

5.4.2. Reactions Based on Organocatalytic Activation

In 2011, a smart design by Sparr and Gilmour enabled the development of an enantioselective 1,3-dichlorination method for cyclopropanes containing a formyl group (Scheme 5.15).[46] The process commenced with the generation of cyclopropyl iminium intermediate, which was then subjected to nucleophilic chloride ion **56**. This addition to the γ position of iminium intermediate generated an effective secondary enamine intermediate **57**. This method can be regarded as a formal umpolung strategy, utilizing a secondary amine to enable the use of nucleophilic chloride for γ-functionalization and the formation of intermediate **57**. The enamine intermediate subsequently underwent α-attack on electrophilic chlorine **58**, leading to the formation of intermediate **59**. Hydrolysis of intermediate **59** ultimately yielded the desired enantioselective 1,3-dichlorination product of cyclopropanes

Scheme 5.15. Enantioselective 1,3-Dichlorination of Cyclopropanes

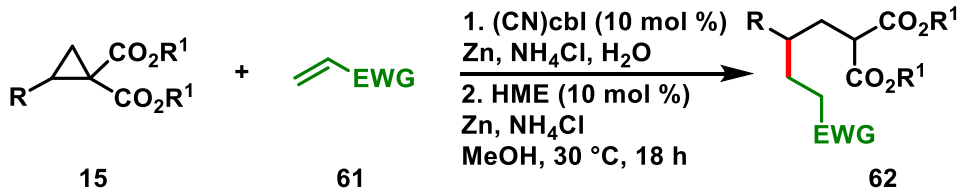


60. Due to the requirement for enamine formation, this reaction is restricted to reactive formyl groups as substituents. Later Werz and co-workers reported 1,3-chlorochalcogenation of cyclopropyl carbaldehydes using the similar strategy.[47]

5.4.3. Radical Reactions of D-A Cyclopropanes

Dichlorination of D-A cyclopropanes employing radical strategy will be discussed in detail in Chapter 6.[32] In 2022, Gryko and co-workers implemented a radical-based approach to invert the regioselectivity in reactions of donor-acceptor cyclopropanes and electrophilic olefins (Scheme 5.16).[48] Typically, olefins add to the acceptor end of the donor-acceptor cyclopropanes. However, in this unique methodology, the addition occurs from the donor side. The authors employed vitamin B_{12} catalysis to facilitate the conversion of an initially electrophilic center into a nucleophilic radical, which then reacts with SOMOphiles. This radical-based strategy effectively reverses the conventional regioselectivity, providing a valuable complement to classical approaches.

Scheme 5.16. Polarity Reversal Radical Addition to D-A Cyclopropanes



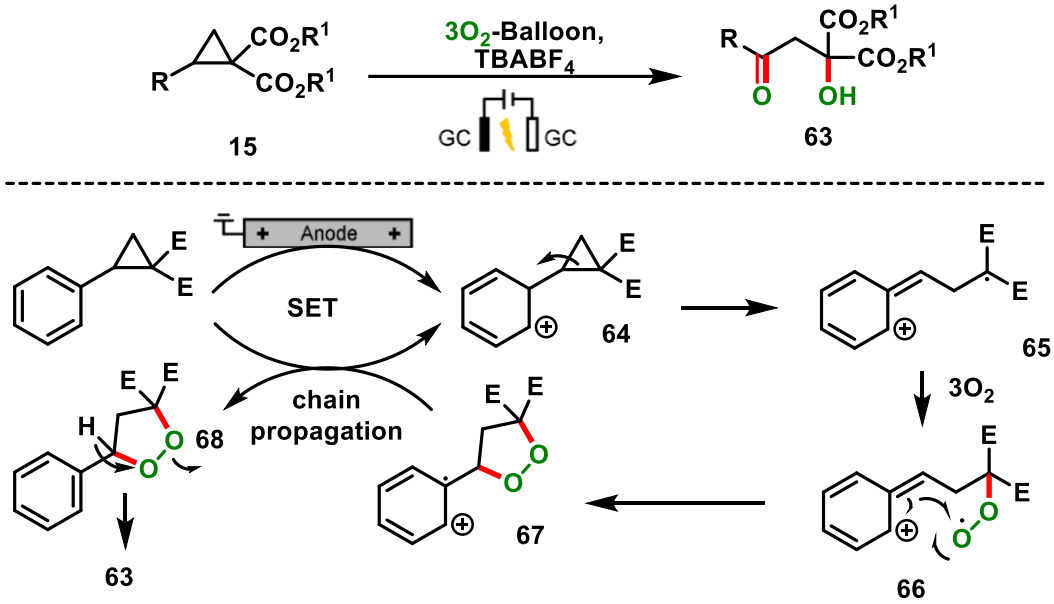
15 **61** **62**

5.4.3. Reactions Based on Electrochemical Activation

Werz and co-workers have showcased an electrochemical approach utilizing single electron transfer (SET) initiation to accomplish the ring-opening of D-A cyclopropanes.[33] Triplet oxygen was considered as the reaction partner due to its abundance, cost-effectiveness, and diradical nature. Intriguingly, under the optimized conditions, the desired β-hydroxy ketones **63** were obtained in moderate to high yields (Scheme 5.17). Notably, this methodology could also be extended to D-A cyclobutanes. The process involves the oxidation of the arene ring of the D-A cyclopropane at the anode, leading to the formation of radical cation **64** by breaking the C-C bond of the cyclopropane. The radical cation then undergoes a combination with triplet oxygen, followed by an intramolecular 5-exo-trig cyclization, resulting in the formation of another radical cation intermediate **66**. A chain propagation step leads to the formation of dioxolane **67**. Deprotonation of the dioxolane,

followed by O-O bond cleavage, ultimately yields the desired β-hydroxy ketones **63**. Interestingly, in 2021, Banerjee and co-workers independently demonstrated the same strategy for synthesizing β-hydroxy ketones.[49]

Scheme 5.17. Conversion of D-A Cyclopropanes to β-Hydroxy Ketones



5.5. Bicyclobutanes

Organic chemists have been fascinated by the distinctive chemistry exhibited by small, strained carbocyclic systems for a considerable time, both from a theoretical and fundamental perspective.[50] The renewed interest in these strained carbocyclic structures stems from their potential as bioisosteres, their high abundance of sp^3 carbons, and their limited presence in patent literature. Among various strained ring systems, the bicyclo[1.1.0]butane (BCB) stands out as the smallest bicyclic carbocycle and is considered one of the most highly strained carbocycles known. Despite being synthesized and studied for over 50 years, BCBs have predominantly been seen as peculiarities confined to laboratory settings. Nevertheless, recent advancements in the preparation, functionalization, and utilization of BCBs in "strain-release" transformations have elevated their status, positioning BCBs as potent tools for synthetic endeavors.[51]

The BCB framework possesses a distinctive "butterfly" shape characterized by a 123° angle between its two "wings". Consequently, the lengths of the exo (1.194 Å), endo (1.167 Å), and bridgehead (1.142 Å) C-H bonds vary.[52] It is intriguing that despite the considerable

strain present in BCB, the compound contains two nearly unaltered cyclopropane rings.[53] These rings exhibit almost identical bridgehead and side C-C bond lengths of approximately 1.50 Å. These C-C bond lengths have been determined through experimental techniques such as vibrational spectroscopy, microwave spectroscopy, and electron diffraction studies.[54] Supporting evidence for this distinctive structure can be obtained through NMR spectroscopy as well. The proton NMR spectrum demonstrates notable variations in chemical shifts for the endo, exo, and bridgehead protons, measuring 0.489, 1.500, and 1.358 ppm in $CDCl_3$, respectively. Furthermore, the increased *s*-character of the shorter bridgehead methine C-H bonds can be experimentally confirmed by observing the ^{13}C-^{1}H coupling constant, which measures 202 Hz.[55]

For quite some time, the assessment of strain energy within the BCB structure has been a subject of enduring theoretical curiosity. Recently, Meier introduced a group contribution method that yielded remarkable concordance between theoretical (217.5 kJ mol^{-1}) and experimental (217 kJ mol^{-1}) formation enthalpies. This approach predicts a strain energy of approximately 267 kJ mol^{-1} (~ 64 kcal mol^{-1}).[56] It is worth noting that while Baeyer strain is commonly acknowledged as the primary factor influencing the strain energy, the effects of bridgehead substituents also make a substantial contribution to the overall energy of the system. In addition, Inagaki has demonstrated that the presence of bridgehead substituents can significantly impact whether the bridgehead carbons exhibit an "inverted" tetrahedral configuration. This configuration arises when all four atoms bonded to carbon are situated on the same side of the plane containing the carbon. The extent of geminal delocalization between the bridgehead and side bonds plays a crucial role in determining this phenomenon. Based on an average angle value of 82° for the six "substituents" on both carbon atoms of the bridgehead bond, Chaquin has recently classified the bridgehead bond in BCB as an "inverted bond." In this bond, the smaller back lobes of the hybrid orbitals overlap to form the C-C σ-bond, while the larger lobes point outward.[57]

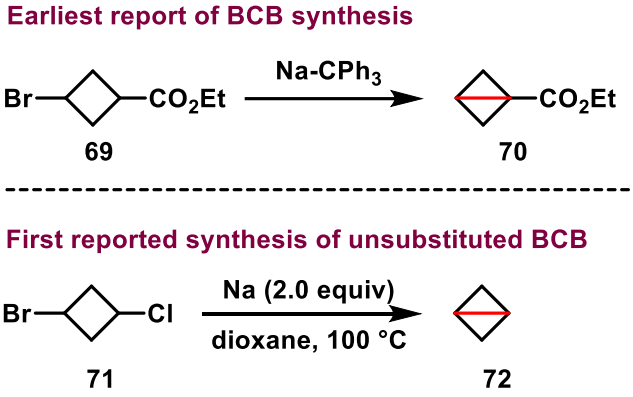
Accompanying the notable *s* character exhibited by the bridgehead carbons, the strained central C-C bond in BCB can be described as primarily composed of hybrid orbitals that possess a predominantly *p* character. This hybridization leads to a bent σ-bond with a considerable degree of π character, accounting for 26.1% of the bond character according to Newton's calculations.[58] Moreover, in a recent study examining the correlation between σ-

bond strength and bond angle across a range of hydrocarbons, Chaquin has indicated that the smaller bond angles observed in BCB correspond to a decrease in σ character but an increase in compensatory π contribution (accounting for 39.7% of the bond character), including the involvement of three-center, two-electron bonds with the methylenes.[58] As anticipated, the overall bond strength diminishes due to the presence of strain. The unique chemistry of BCB largely arises from the π character inherent in the bridgehead bond. This C-C bond is recognized for its reactivity towards a diverse array of electrophiles and nucleophiles. These reactions encompass solvolysis-type processes, addition reactions involving "hard" organometallic nucleophiles, as well as various thermal and photochemical cycloadditions.[50] Furthermore, the bridgehead bond has been observed to participate in tandem reactions with bridgehead aryl groups, forming part of a conjugated system.[59]

5.6. Reports on Synthesis of Bicyclobutanes

The initial synthesis of BCB compound was documented in 1959 by Wiberg and Ciula. They reported the reaction of ethyl 3-bromocyclobutane-1-carboxylate **69** with sodium triphenylmethylide, which resulted in the formation of ester-substituted BCB compound **70** (Scheme 5.18).[60] Subsequently, Wiberg and co-workers expanded this method to synthesize the parent, unsubstituted bicyclo[1.1.0]butane **72**, which was later included as a protocol in Organic Syntheses.[61] Shortly thereafter, in 1963, Srinivasan disclosed that the unsubstituted BCB hydrocarbon could be produced as a minor product (along with cyclobutene) during the photolysis of 1,3-butadiene.[62]

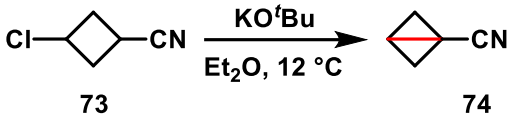
Scheme 5.18. BCB Synthesis by Wilberg



Although the initial methods for BCB synthesis were groundbreaking, they had limited capability in producing substituted derivatives. A significant advancement in this

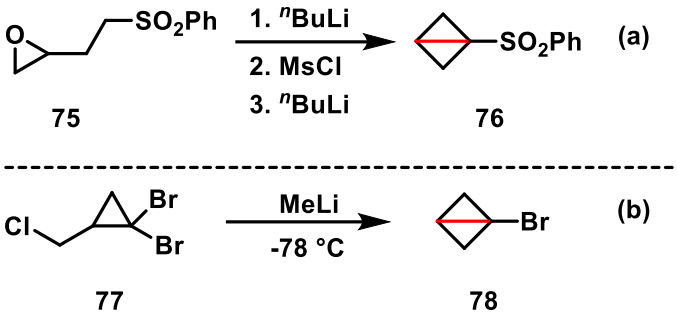
regard was reported by Sieja in 1971. Sieja utilized cyclobutanones, easily obtained through ketene/vinyl ether [2+2] cycloaddition, as a starting point to introduce bridgehead substituents in BCB scaffolds. By reacting these 3-alkoxy cyclobutanones with PhMgBr, the corresponding alcohols were obtained, which could be readily converted to tertiary chlorides. When these halides were treated with magnesium metal in refluxing THF, BCBs were formed.[63] A modified version of the abovementioned methods continues to be employed for the synthesis of BCB compounds. Sieja and Hall further demonstrated that this method could be employed to prepare BCBs **74** with nitrile substituents, which find application in polymerization studies and other ring-opening nucleophilic reactions (Scheme 5.19). Notably, the treatment of 3-chlorocyclo butanecarbonitrile **73** with potassium tert-butoxide offered convenient access to a cyanosubstituted BCB required for polymerization studies.[64]

Scheme 5.19. BCB by Anion Ring Closing Approach



Gaoni introduced an alternative method for synthesizing the strained BCB carbocycle in 1982 (Scheme 5.20, a).[65] Unlike the previous approaches that utilized 1,3-disubstituted cyclobutane derivatives as starting materials, this method involved a series of intramolecular cyclopropanation reactions to access BCB sulfones. The process began with readily available epoxy-sulfones **75**, which, upon treatment with ^{n}BuLi, underwent cyclopropane formation while simultaneously opening the epoxide ring. The resulting alcohol could then be converted into a sulfonate ester and subjected to a second lithiation/cyclopropanation sequence. Although this approach may seem somewhat indirect, it proved to be adaptable for various substituents and remained the state-of-the-art method for preparing substituted BCBs **76** for many years. In 1999, Brinker and co-workers introduced a highly versatile method for the synthesis of BCBs (Scheme 5.20, b).[57] This approach involves the utilization of 1,1-dibromocyclopropanes **77** as starting materials, which can be easily obtained through the dibromocarbene cyclopropanation of allyl chlorides. By treating this trihalide with two equivalents of an alkylithium reagent, a bicyclobutyllithium species is formed. This intermediate can then be reacted with a wide range of electrophiles, allowing for the incorporation of diverse substituents into the BCB framework.

Scheme 5.20. BCB via Net Cyclopropane Construction



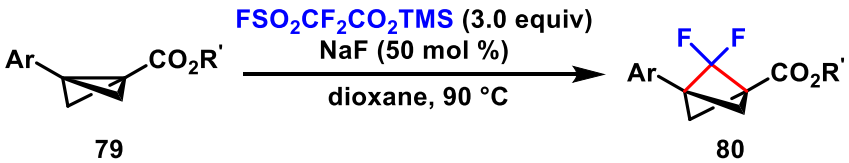
5.7. Different Types of Reactions of BCBs

BCBs exhibit a wide range of reactivity, including the possibility of undergoing carbene insertion reactions that leverage the strain present in the central C-C bond.[66] This type of reaction can result in the formation of ring expansion products. Another important area in this field involves annulation reactions, which have been employed to synthesize various bicyclic scaffolds.[67] Additionally, by adding nucleophiles or electrophiles, the central C-C bond can be cleaved, leading to the formation of decorated cyclobutane derivatives.[68] In this section, we will explore selected examples from each category to illustrate these reactions.

5.7.1. Carbene Insertion Reaction to BCBs

In 2019, Ma and co-workers successfully synthesized 2,2-difluorobicyclo [1.1.1]pentanes **80** through the difluorocarbene insertion into bicyclo[1.1.0]butanes **79** (Scheme 5.21).[69] This transformation proceeded under mild reaction conditions, utilizing readily available reagents. The authors proposed a diradical-carbene combination mechanism to explain the formation of the desired products. Remarkably, the desired products were obtained in high yields, which makes this method synthetically valuable. Furthermore, the authors demonstrated the stability of the obtained products under harsh reaction conditions, indicating their suitability for subsequent functionalization steps.

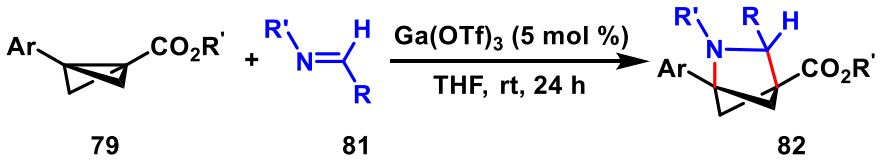
Scheme 5.21. Difluorocarbene Insertion into Bicyclo[1.1.0]Butanes



5.7.2. Annulation Reactions of BCBs

Leitch and co-workers introduced a Lewis acid-catalyzed method for the synthesis of azabicyclohexanes (BCHs) **82**, utilizing BCBs **79** and imines **81** (Scheme 5.22).[70] In this approach, the authors employed a formal [3+2] cycloaddition strategy using a BCB with a polarized central bond, leading to zwitterionic character and resembling the reactivity of donor-acceptor cyclopropanes. Lewis acids were utilized to promote enolate formation, thereby generating carbocations. Subsequently, enolate attack, potentially aided by Lewis acid activation of the imine, resulted in the formation of an intermediate, which underwent ring closure to yield the desired azabicyclohexane product.

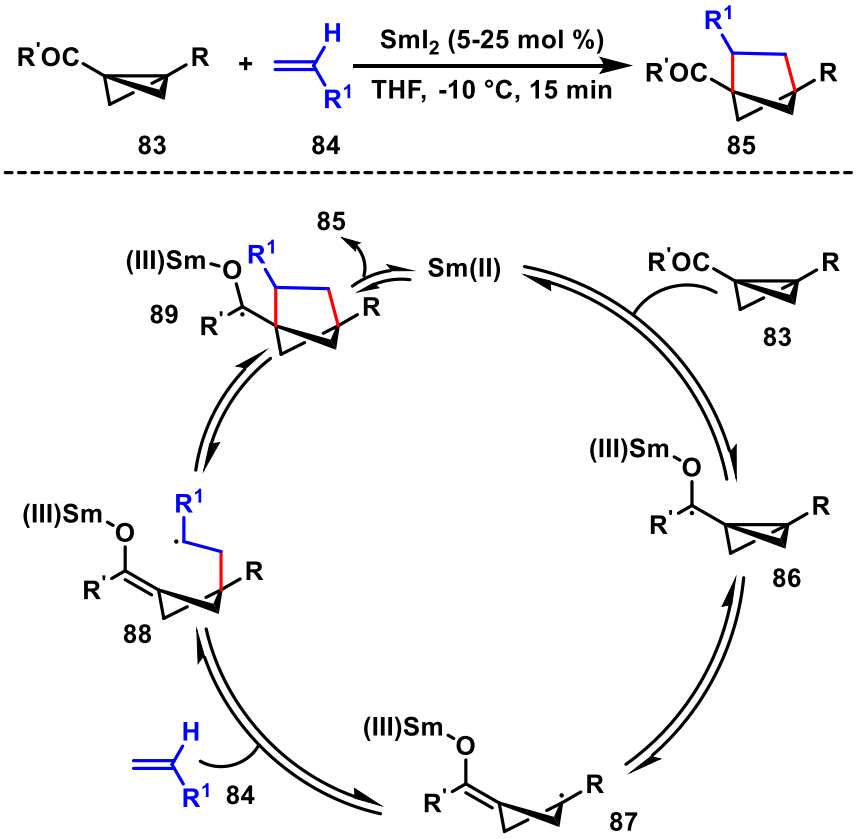
Scheme 5.22. Leitch's Approach to Aza-BCHs from BCBs



79 81 82

In 2023, Procter and co-workers accomplished the synthesis of BCHs **85** through a SmI_2-catalyzed radical relay process, utilizing BCBs **83** and olefins **84** (Scheme 5.23).[71] The key step in this process involves the single electron reduction of a BCB ketone, leading to the generation of a ketyl radical **86**, which undergoes rapid ring opening. The resulting cyclobutyl radical **87** then participates in a Giese-type addition with an olefin. The resulting Giese adduct radical **88** is strategically positioned for a 5-exo-trig cyclization, resulting in the regeneration of a ketyl radical **89**. The carbonyl group is subsequently restored through back-electron transfer, yielding a carbonyl-substituted BCH along with the Sm(II) catalyst. Notably, both the carbonyl group and the olefinic partner can be varied, and the process exhibits a high degree of tolerance towards structural complexity.

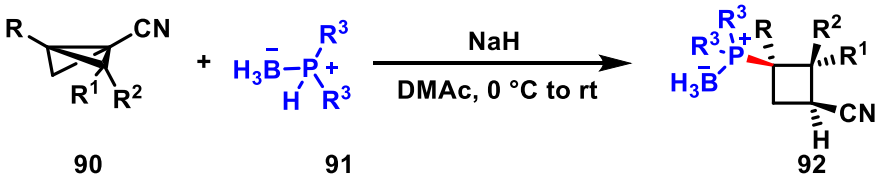
Scheme 5.23. Procter's Radical Relay Approach to BCH Construction



5.7.3. Functionalized Cyclobutanes Synthesis from BCBs

Wipf and co-workers showcased the hydrophosphination of bicyclo[1.1.0]butyl nitriles **90** using phosphine boranes **91** and phosphites (Scheme 5.24).[72] Typically, the reaction predominantly yields the syn diastereomer. Furthermore, the nitrile moiety can be reduced and transformed into various functional groups, allowing for the synthesis of bidentate ligands. These ligands introduce new conformational possibilities due to their attachment to the torsionally flexible yet sterically constrained cyclobutane scaffold. Related reactions will be further discussed in Chapter 8.

Scheme 5.24. Wipf 's Hydrophosphination



5.8. Focal Theme of This Part of the Thesis

As discussed in the previous part of the thesis, the central theme of this thesis is to utilize the strained intermediates in organic synthesis. The initial part examines aryne intermediates to disclose various unique transformations, while the latter section investigates the application of D-A cyclopropanes and bicyclobutanes in Lewis acid catalyzed ring-opening reactions, using diverse reaction partners. As an introduction to D-A cyclopropanes and bicyclobutanes chemistry this Chapter has illustrated the history, properties, and different modes of reactivity of these strained intermediates.

1,3-Bisfunctionalization of D-A cyclopropanes via insertion reaction received very scant attention mainly because of the compatibility of suitable reaction partners under Lewis acid conditions. In this context, $Yb(OTf)_3$ catalyzed mild and regioselective ring-opening 1,3-aminothiolation of D-A cyclopropanes using sulfenamides has been realized. The insertion of the C-C σ-bond of D-A cyclopropanes into the S-N σ-bond of sulfenamides allowed the synthesis of diverse γ-aminated α-thiolated malonic diesters in moderate to good yields with good functional group compatibility, which form the content of 6th Chapter.

Chapter 7 illustrates the successful application of alkyl halides and in situ generated dithiocarbamates (formed from amines and CS_2) in the 1,3-carbothiolation of donor-acceptor cyclopropanes. The present reaction is straightforward to perform and exhibits compatibility with various electrophilic partners and functional groups. The strategy enables the formation of three new bonds, namely C-N, C-S, and C-C, through a 1,3-bifunctionalization approach. Additionally, the reaction's stereospecific nature and its mechanism are thoroughly investigated and presented in this chapter.

Traditional radical-mediated ring-opening of bicyclo[1.1.0]butanes (BCBs) for cyclobutane synthesis suffers from poor diastereoselectivity. Although few reports on BCB ring-opening via polar mechanisms are available, the Lewis acid-catalyzed diastereoselective ring-opening of BCBs using carbon nucleophiles is still underdeveloped. A mild, diastereoselective $Bi(OTf)_3$-catalyzed ring-opening of BCBs employing naphthols has been presented in the 8th Chapter. The anticipated carbofunctionalized trisubstituted cyclobutanes were obtained via a bicoordinated bismuth complex and the products are formed in good to excellent yields with high regio- and diastereoselectivity. Detailed mechanistic experiments

and DFT studies, deep insight into the mode of addition and product functionalization has been discussed in this Chapter.

5.9. References

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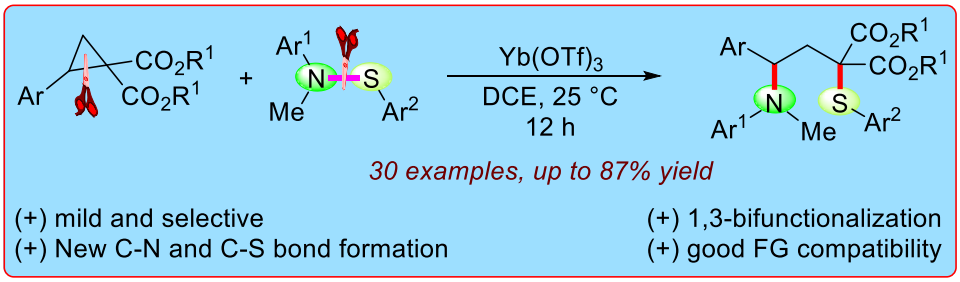
Chapter 6

Lewis Acid-Catalyzed Ring-Opening 1,3-Aminothiolation of Donor-Acceptor Cyclopropanes Using Sulfenamides

$Yb(OTf)_3$ Catalyzed mild and regioselective ring-opening 1,3-aminothiolation of donor-acceptor (D-A) cyclopropanes using sulfenamides has been demonstrated in this Chapter. The insertion of the C-C σ-bond of D-A cyclopropanes into the S-N σ-bond of sulfenamides allows the synthesis of diverse γ-aminated α-thiolated malonic diesters in moderate to good yields (up to 87%) with good functional group compatibility. Complete regioselectivity was observed in the ring opening of DACP with sulfonamides. The stereospecificity of the reaction was demonstrated using enantiopure D-A cyclopropane.

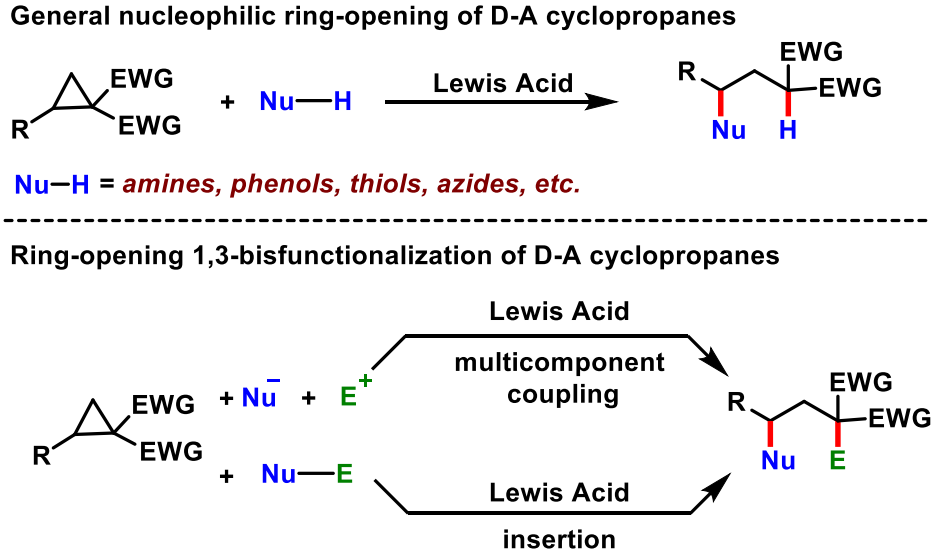


Org. Lett. **2020**, *22*, 2276.

6.1. Introduction

Donor-acceptor (D-A) cyclopropanes have become versatile polarized three-atom building block in organic synthesis in the last few years.[1, 2] Their adjacent arrangement of donor and acceptor moieties, makes it easy to cleave the ring under Lewis acid conditions.[3,4] Activated D-A cyclopropanes have the potential to undergo various types of reactions via the cleavage of the polarized C-C bond. For instance, (3 + n) annulation reactions (where n = 2,3,4) have been extensively studied for synthesizing carbocycles and heterocycles of various ring sizes.[5] Additionally, nucleophiles of various types, such as heteroatom nucleophiles (e.g., amines,[6] phenols,[7] thiols,[8] azides[9]) and carbon nucleophiles,[10] can open the D-A cyclopropanes. In these cases, the nucleophile adds to the carbon atom adjacent to the donor group, and the emerging negative charge near the acceptor group gets protonated, leading to the monofunctionalization of D-A cyclopropanes. If the resulting anion is intercepted with an electrophile instead of protonation it can lead to a valuable 1,3-bifunctionalization. This type of ring-opening 1,3-bifunctionalization of D-A cyclopropanes can be accomplished through three-component coupling or the insertion of D-A cyclopropanes into carbon-carbon or carbon-heteroatom bonds (Scheme 6.1). While the multicomponent coupling route for 1,3-bisfunctionalization has been broadly studied and several groups have made significant contributions in this field, the alternative pathway of 1,3-bifunctionalization via insertion has

Scheme 6.1. General Representation for Ring-opening Reactions of D-A cyclopropanes

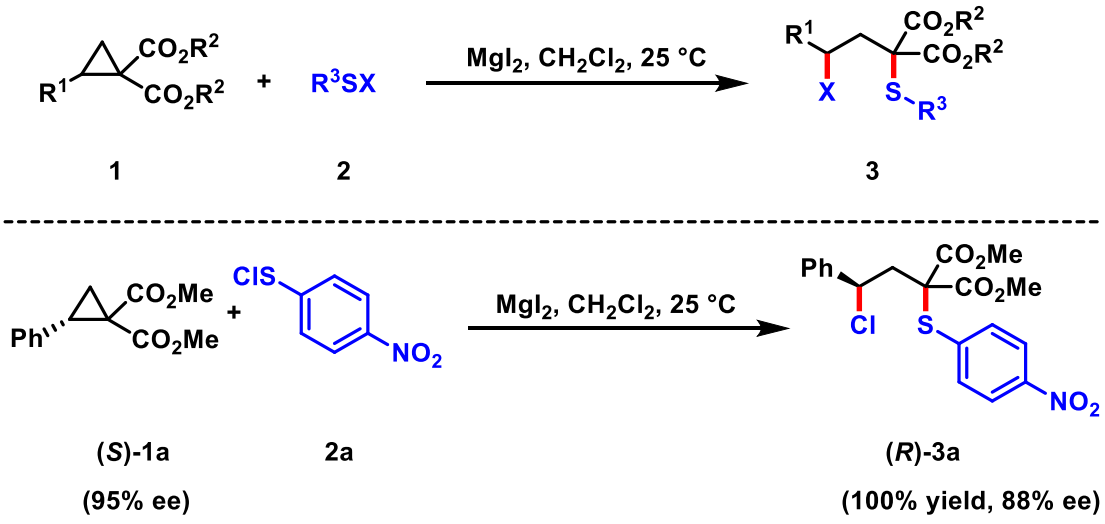


not received much attention.[11] Investigating the use of the insertion pathway for difunctionalizing D-A cyclopropanes could be an intriguing avenue to explore.

6.2. Insertion-Based 1,3-Difunctionalization of Donor-Acceptor Cyclopropanes

A generalized approach for the 1,3-halochalcogenation of D-A cyclopropanes has been developed by Werz and co-workers to synthesize γ-halogenated α-thiolated malonic diester derivatives **3**. The desired transformation was achieved using MgI_2 as the Lewis acid catalyst. D-A cyclopropanes having two geminal carboxylic esters were reacted with chalcogenyl chlorides or bromides to furnish the desired ring-opened products having the halogen atoms adjacent to the donor and the chalcogenyl residue next to the two acceptor groups. Several D-A cyclopropanes were reacted with readily available sulfenyl chlorides, selenyl chlorides, or sulfenyl bromides. The use of other donors such as oxygen, nitrogen, and even aromatic systems were also well tolerated. When enantiopure D-A cyclopropane was present, the 1,3-halochalcogenated product was obtained with inversion of configuration, indicating that the transformation was stereospecific and proceeded in an S_N2-like fashion. (Scheme 6.2).[12]

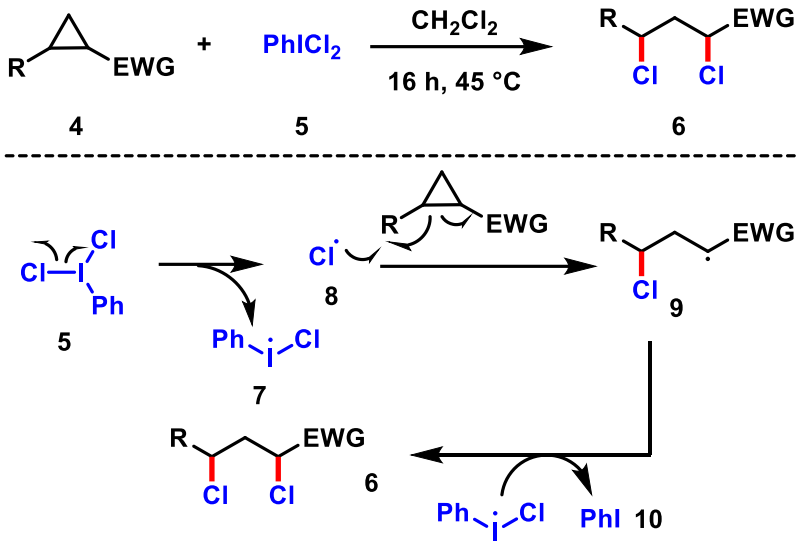
Scheme 6.2. 1,3-Halochalcogenation of D-A Cyclopropanes



The same group also developed 1,3-dichlorination of D-A cyclopropanes, using iodobenzene dichloride as the reagent of choice. This methodology did not proceed via direct insertion of heteroatom-heteroatom bonds. Readily available iodobenzene dichloride was

used to transform several cyclopropanes **4** into the corresponding ring-opened 1,3-dichlorinated compounds **6** with moderate to high yields. Dichloromethane was found to be the best solvent for this transformation. The reaction proceeds via homolytic cleavage of the I-Cl bond of iodobenzene dichloride, releasing a Cl radical **8**. This highly reactive radical species then adds to the weakest bond of the D-A cyclopropanes, generating another delocalized radical intermediate **9**. Intermediate **9** can either abstract Cl atom from $PhICl_2$ or merge with a Cl atom or with a PhICl radical **7**, releasing PhI **10** (Scheme 6.3).[13] In this context, the Gilmour and Werz research groups respectively reported the 1,3-dichlorination or 1,3-chlorochalcogenation of cyclopropylcarbaldehyde via iminium activation strategy.[14]

Scheme 6.3. Ring-Opening 1,3-Dichlorination of D-A Cyclopropanes

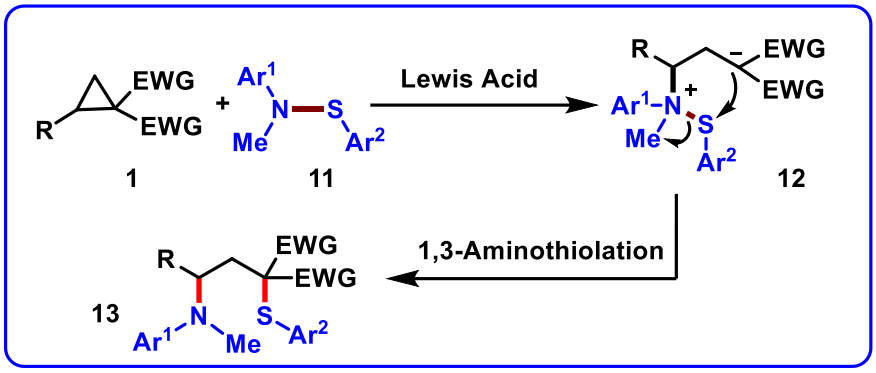


6.3. Statement of the Problem

As mentioned in the preceding section, the insertion route for 1,3-difunctionalization of D-A cyclopropanes are not well studied. In this context, we hypothesized that investigating the insertion of sulfenamides **11** into D-A cyclopropanes **1** could be a worthwhile endeavour. If successful, this approach could enable the synthesis of γ-aminated α-thiolated malonic diesters **13** via 1,3-aminothiolation of D-A cyclopropanes (Scheme 6.4). Our hypothesis was that the activation of D-A cyclopropanes **1** could be achieved through the use of Lewis acid, which would allow the nucleophilic nitrogen of sulfenamide **11** to add to the activated cyclopropanes and open the ring. The ring-opening of D-A cyclopropanes would generate a

carbanion at the acceptor terminus, which could then accept the *S*-aryl moiety from intermediate **12**, resulting in the production of γ-aminated α-thiolated malonic diesters **13**.

Scheme 6.4. 1,3-Aminothiolation of D-A Cyclopropanes Using Sulfenamides

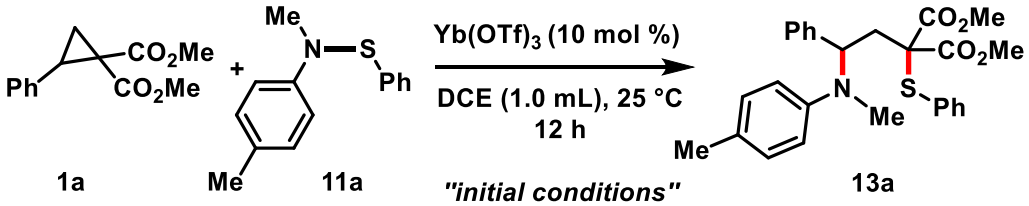


6.4. Results and Discussion

6.4.1. Optimization Studies

The study on sulfenamides insertion into D-A cyclopropane commenced with the treatment of cyclopropane **1a** with the sulfenamide **11a** in the presence of $Yb(OTf)_3$ (10 mol

Table 6.1. Optimization of the Reaction Conditions[a]



entry	variation of the initial conditions[a]	yield of 13a (%)[b]
1	*none*	*73*
2	no $Yb(OTf)_3$	<5
3	$Sc(OTf)_3$ instead of $Yb(OTf)_3$	15
4	$Sn(OTf)_2$ instead of $Yb(OTf)_3$	17
5	70 °C instead of 25 °C	43
6	0 °C instead of 25 °C	<5
7	CH_2Cl_2 instead of DCE	47
8	$CHCl_3$ instead of DCE	49
9	10 mol % TfOH instead of $Yb(OTf)_3$	<5
10	10 mol % PTSA instead of $Yb(OTf)_3$	<5
11	0.25 mmol **1a** & 0.3 mmol of **11a**	68
12	5 mol % $Yb(OTf)_3$	61

[a] Initial conditions: **1a** (0.30 mmol), **11a** (0.25 mmol), $Yb(OTf)_3$ (10 mol %), DCE (1.0 mL), 25 °C for 12 h. [b] Given are yield of chromatographically purified **13a**.

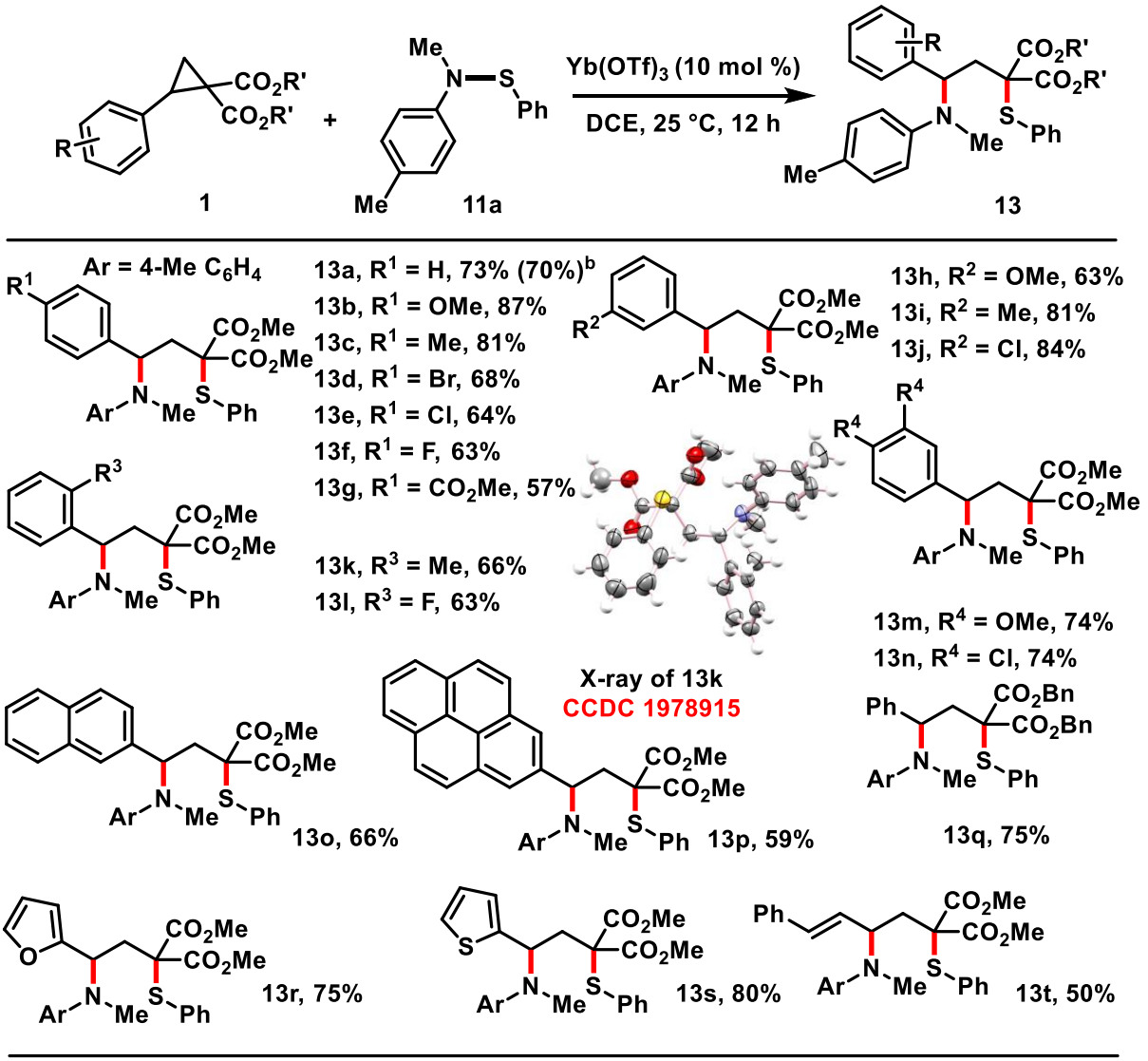
%) in dichloroethane (DCE) at 25 °C. Interestingly, under these conditions, a facile insertion reaction occurred leading to the formation of the γ-aminated α-thiolated malonic diester **13a** in 73% yield (Table 6.1, entry 1). Notably, product **13a** was not formed in the absence of the Lewis acid catalyst (entry 2). Other Lewis acids such as $Sc(OTf)_3$ and $Sn(OTf)_2$ returned reduced yield of **13a** under the present conditions (entries 3, 4). The performed reaction at 70 °C afforded reduced yield of **13a** and the reaction was sluggish at 0 °C (entries 5, 6). When the reaction was performed in other chlorinated solvents such as CH_2Cl_2 and $CHCl_3$, the desired product **13a** was formed in low yields (entries 7, 8). Only traces of **13a** was formed when the reaction was carried out in the presence of TfOH and PTSA indicating that Brønsted acid activation is not operating in this case (entries 9, 10). When the stoichiometry of **1a** and **11a** are reversed, **13a** was formed in a slightly reduced yield of 68% (entry 11). Moreover, 10 mol % $Yb(OTf)_3$ was required for good yield of **13a** as the reaction done with 5 mol % catalyst provided only 61% of **13a** (entry 12).

6.4.2. Substrate Scope of Sulfenamides Insertion into D-A Cyclopropanes: Scope of D-A Cyclopropanes

After having the optimized reaction conditions in hand (Table 6.1, entry 1), the substrate scope of this insertion reaction has been evaluated. First, we examined the scope of various D-A cyclopropanes in this insertion reaction (Scheme 6.5). A series of D-A cyclopropanes **1** bearing electron-releasing, -neutral, and -withdrawing, substituents at the 4-position of benzene ring on the donor terminus underwent smooth insertion to sulfenamide **11a** to give the corresponding 1,3-bifunctionalized derivatives in good yields (**13a**-**13g**). When this insertion reaction was performed on a 1.0 mmol scale, the expected product **13a** was formed in 70% yield demonstrating the scalable nature of this current insertion reaction. Moreover, D-A cyclopropanes having substitution at the 3-positon, 2-position and disubstitution on the aryl ring are well tolerated under the present conditions leading to the formation of the desired products in good yields (**13h**-**13n**). In the case of the methyl derivative **13k**, the structure was conformed using X-ray analysis. The naphthyl and pyrenyl groups worked well as donors (**13o**, **13p**), and the benzyl ester furnished the product **13q** in 75% yield. In addition, D-A cyclopropanes having heteroaryl groups such as furyl and thienyl

could be used as donors and the use of styrenyl moiety as donor was also tolerated under the present conditions (**13r-13t**).

Scheme 6.5. Substrate Scope: Variation of D-A Cyclopropanes

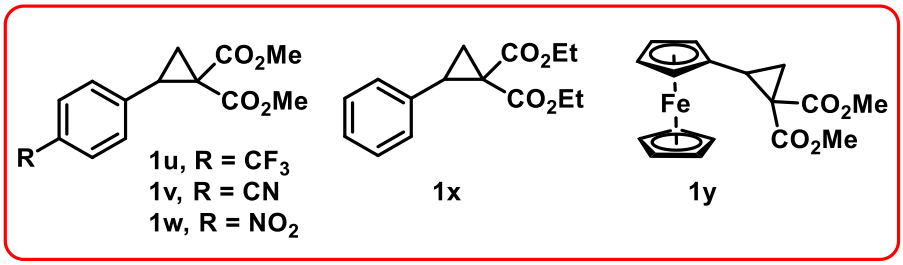


[a] General conditions: **1** (0.30 mmol), **11a** (0.25 mmol), $Yb(OTf)_3$ (10 mol %), DCE (1.0 mL), 25 °C for 12 h. Isolated yields are given. [b] Yield of the experiment conducted on a 1.0 mmol scale.

The present methodology did not work well with electron-withdrawing substituted D-A cyclopropanes (**1u-1w**) (Scheme 6.6). While the D-A cyclopropane derived from diethyl ester **1x** did produce the desired product under the current reaction conditions, but the product

could not be isolated in pure form. Unfortunately, the D-A cyclopropane **1y** derived from ferrocenecarboxaldehyde did not yield the desired product.

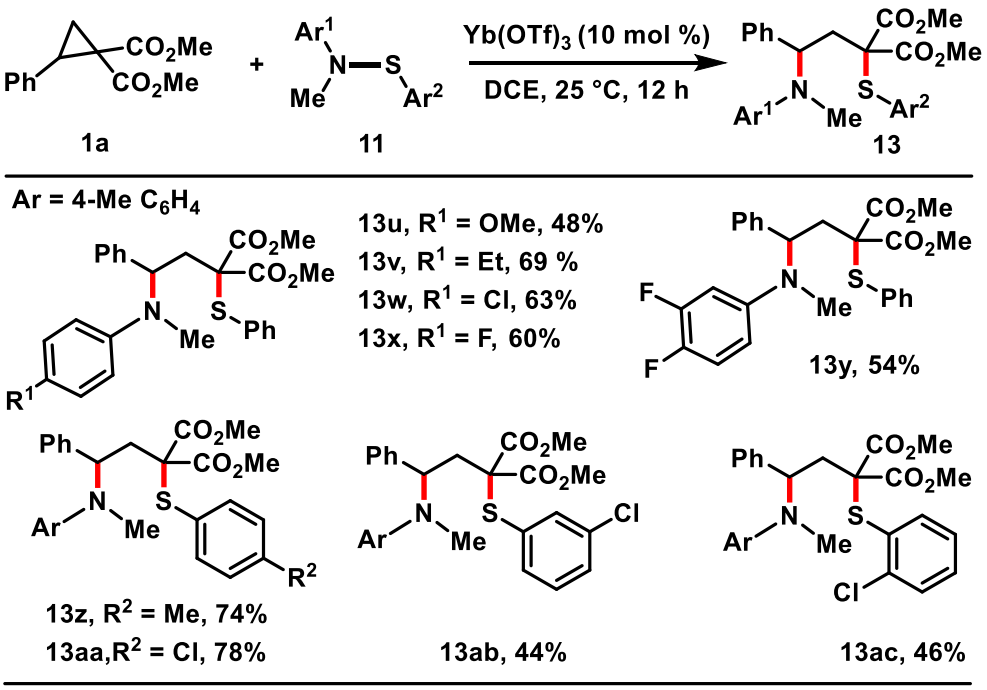
Scheme 6.6. Unsuccessful D-A Cyclopropanes



6.4.3. Substrate Scope of Sulfenamides Insertion into D-A Cyclopropanes: Scope of Sulfenamides

Next, we examined the scope of the reaction using various sulfenamides (Scheme 6.7). Sulfenamides resulting from *N*-methyl aniline derivatives bearing electron-releasing, and -neutral groups at the 4-position of the ring smoothly afforded the expected 1,3-aminothiolated products in moderate to good yields (**13u**-**13x**). Notably, the difluoro

Scheme 6.7. Substrate Scope: Variation of Sulfenamides



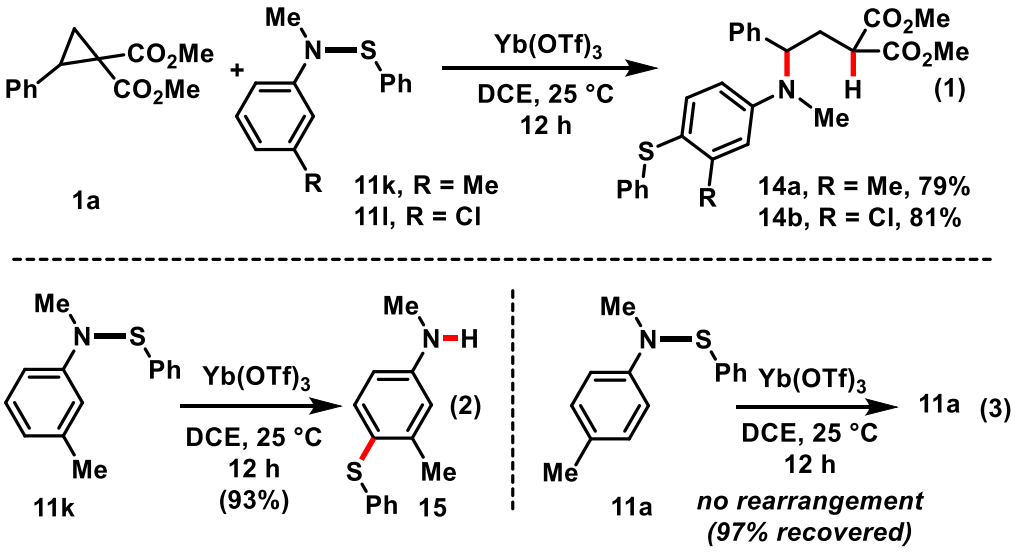
[a] General conditions: **1a** (0.6 mmol), **11** (0.5 mmol), $Yb(OTf)_3$ (10 mol %), DCE (2.0 mL), 25 °C for 12 h. Isolated yields are given.

substituted aniline derivative afforded the product **13y** in 54% yield. Moreover, sulfenamides derived from substituted benzenethiols bearing substituents at various position of the benzene ring was also well tolerated under optimized reaction conditions, and the desired products were formed in moderate to good yields (**13z**-**13ac**) thus demonstrating the versatile nature of the present insertion reaction. Unlikely, sulfeanimides derived from aliphatic amines and thiols failed to give the expected 1,3-aminothiolated products under present conditions.

6.4.4. Mechanistic Investigation

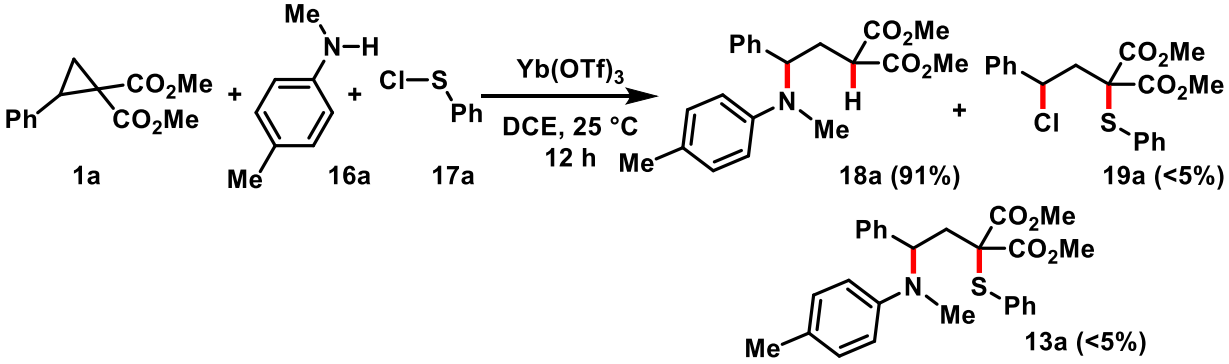
Interestingly, when the *N*,3-dimethylaniline-derived sulfenamide **11k** was subjected to the optimized reaction conditions, the desired 1,3-bifunctionalized product was not formed. Instead, the sulfenamide **11k** rearranges to *N*,3-dimethyl-4-(phenylthio) aniline **15** in the presence of $Yb(OTf)_3$ and then it adds to **1a** to give the *N*-H insertion product **14a** in 79% yield (Scheme 6.8, eq 1). Similar result was obtained with the 3-chloro derivative **11l** where the *N*-H insertion product **14b** was formed in 81% yield. To get insight into this rearrangement, the sulfenamide **11k** was subjected to $Yb(OTf)_3$ in DCE resulting in the formation of the rearranged aniline **15** in 93% yield (eq 2).[15] Moreover, this rearrangement was not observed when **11a** was subjected to $Yb(OTf)_3$ without **1a**. Thus, it was concluded that 4-substitution on the *N*-methyl aniline moiety of **11** was required for the insertion of sulfenamide to D-A cyclopropanes.

Scheme 6.8. Reaction Using *N*-Methyl 3-Substituted Aniline-Derived Sulfenamides



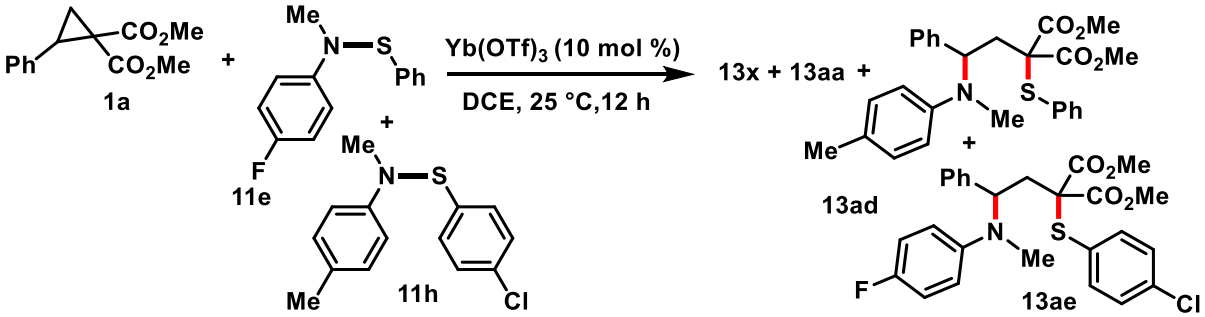
Given the fact that the sulfenamides **11** can be synthesized from the *N*-methyl aniline and sulfenyl chloride and considering the three-component 1,3-aminothiolation of D-A cyclopropanes demonstrated by Werz and co-workers, we tried the three-component reaction involving **1a**, **16a** and **17a** under the present conditions (Scheme 6.9).[16] To our surprise, the desired 1,3-aminothiolated product **13a** was not formed under the present conditions and instead the *N*-H insertion of **16a** to **1a** took place leading to the formation of **18a** in 91% yield. Moreover, the insertion product **19a** derived from **17a** was not observed under this condition. These studies indicate the role of preformed sulfenamides in this insertion reaction.

Scheme 6.9. Envisioned Three-Component Approach

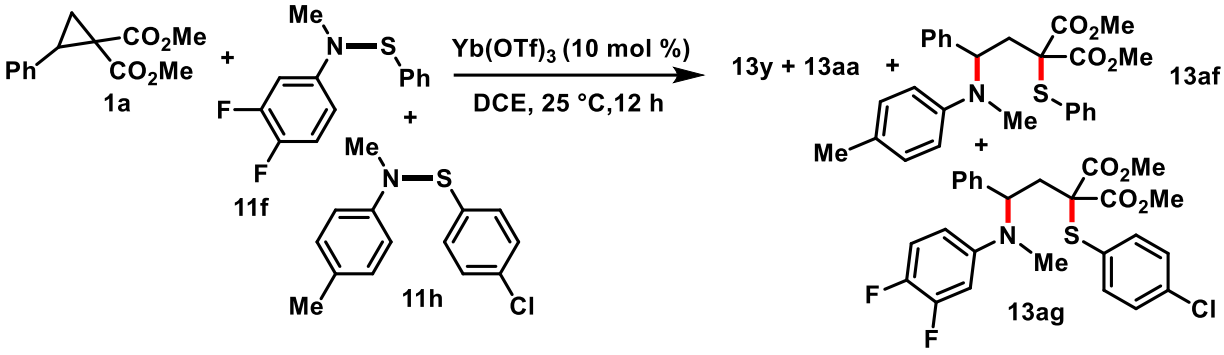


When two different sulfenamides (**11e** and **11h**) were subjected together under optimized reaction conditions, four γ-aminated α-thiolated malonic diester products were observed (Scheme 6.10). This confirmed the intermolecular nature of the reaction. To further confirm this, a different pair of sulfenamides (**11f** and **11h**) were subjected to the same reaction conditions, and once again, four products were detected (Scheme 6.11). These results provided insight into the stepwise mode of insertion and the intermolecular nature of the migration of the sulfur group.

Scheme 6.10. Crossover Experiments



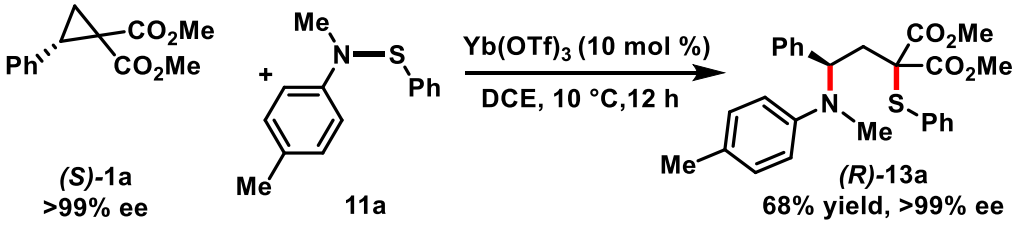
Scheme 6.11. Crossover Experiments with Other Sulfenamides



6.4.5. Stereospecific Reaction

To get insight into the mode of addition of sulfenamide to D-A cyclopropanes, we have performed the reaction using enantiomerically pure D-A cyclopropane. When the reaction of (*S*)-**1a** (>99% ee) was performed with **11a** under the optimized conditions, the product (*R*)-**13a** was formed in 72% yield and 52% ee. Moreover, treatment of (*S*)-**1a** under the Lewis acid conditions (without **11a**) resulted in the complete recovery of (*S*)-**1a** without loss of enantiopurity. This allowed us to perform the reaction at a low temperature. Gratifyingly, when the reaction of (*S*)-**1a** with **11a** was carried out at 10 °C, the desired product (*R*)-1**3a** was formed in 68% yield and >99% ee (Scheme 6.12). These results indicate that the nucleophilic attack of the sulfenamide proceeds in an S_N2 like fashion with complete stereospecificity.

Scheme 6.12. Stereospecific Reaction



6.5 Conclusion

In conclusion, the $Yb(OTf)_3$ catalyzed regioselective ring-opening 1,3-aminothiolation of D-A cyclopropanes using sulfenamides resulting in the synthesis of γ-aminated α-thiolated malonic diesters in moderate to good yields has been demonstrated. Mild conditions, selective product formation, and good functional group compatibility with

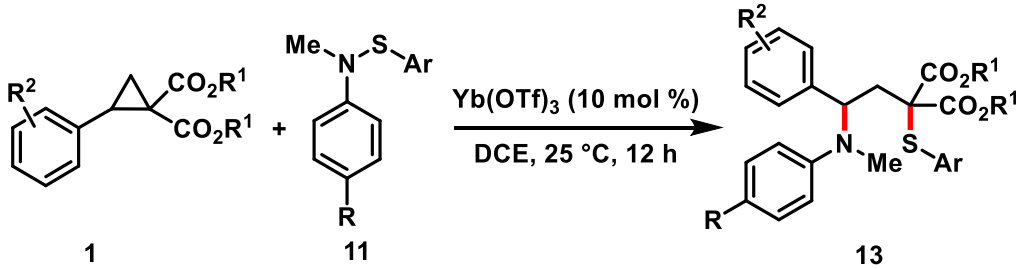
broad scope are the notable features of the present reaction. The reaction performed using enantiopure D-A cyclopropane indicated that the ring-opening is stereospecific and proceeds in an S_N2 like pathway.[17]

6.6. Experimental Details

6.6.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. 25 °C Corresponds to the room temperature of the lab when the experiments were carried out. Dry DCE was purchased from commercial sources and was stored under argon over 4Å molecular sieves. $Yb(OTf)_3$ was purchased from commercial sources and was stored in argon filled Glove-box. All D-A cyclopropane derivatives[18] and functionalized sulfenamides[19] were synthesized following literature procedures. Analytical thin layer chromatography was performed on TLC Silica gel 60 F254. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Unless and otherwise specified flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker Ultrashield spectrometer in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Infrared (FT-IR) spectra were recorded on a Bruker Alfa FT-IR, ν-max in cm^{-1}. HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument.

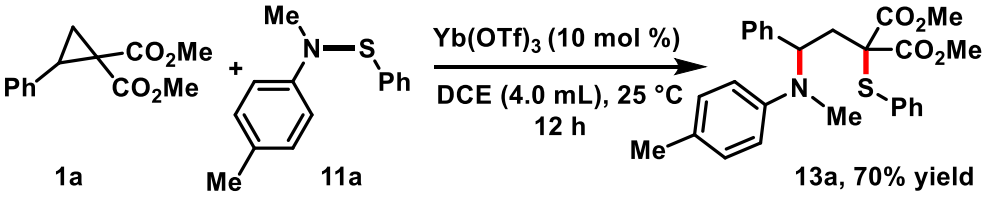
6.6.2. General Procedure for 1, 3-Aminothiolation of D-A Cyclopropanes



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (10 mol %) in a glove-box. The mixture was dissolved in DCE (4 mL per mmol) under argon atmosphere. The cyclopropane **1** (1.2 equiv) was added outside the glove-

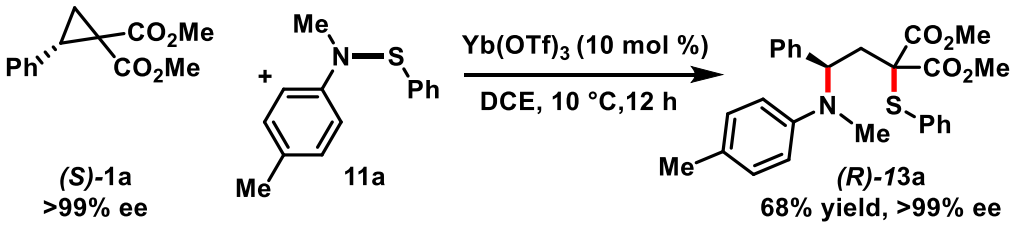
box under argon atmosphere. To the stirring solution, sulfenamide **11** (1.0 equiv) was added. Then, the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography on silica gel to afford the corresponding derivatives **13** in moderate to good yield.

Procedure for the 1.0 mmol Scale Reaction for the Synthesis of 13a



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (0.062g, 10 mol %) in a glove-box. The mixture was dissolved in 4 mL DCE under argon atmosphere. The cyclopropane **1a** (0.280 g, 1.2 mmol) was added outside the glove-box under argon atmosphere. To the stirring solution, sulfenamide **11a** (0.229 g, 1.0 mmol) was added. Then, the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 90/10) on silica gel to afford **13a** as a white solid (0.324 g, 70%).

6.6.3. General Procedure for 1,3-Aminothiolation of Enantiopure D-A Cyclopropane

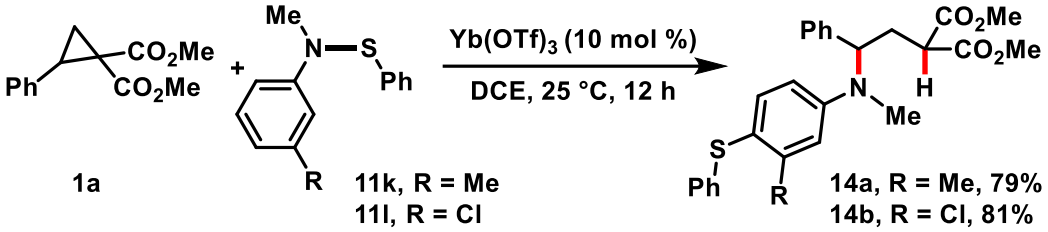


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (0.006 g, 0.01 mmol) in a glove-box. The mixture was dissolved in DCE (0.5 mL) under argon atmosphere at 10 °C. The enantiopure cyclopropane (*S*)-**1a** (0.028 g, 0.12 mmol) was added outside the glove-box under argon atmosphere. To the stirring solution, sulfenamide **11a** (0.023 g, 0.1 mmol) was added. Then, the reaction mixture was allowed to

react at 10 °C for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 90/10) on silica gel to afford (*R*)-**13a** in 68% yield and >99% ee. (*The absolute stereochemistry of the chiral centre was not unequivocally determined*)

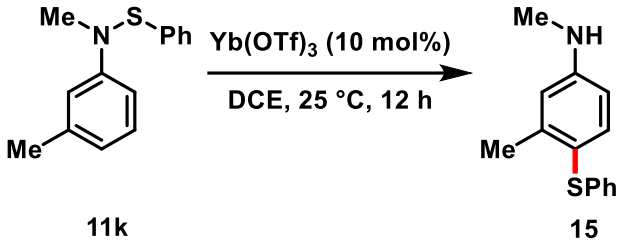
6.6.4. Mechanistic Experiments

(a) Reaction Using N,3-Dimethylaniline-Derived Sulfenamide



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in a glove-box. The mixture was dissolved in DCE (1.0 mL) under argon atmosphere. Cyclopropane **1a** (0.070 g, 0.3 mmol) was added outside the glove-box under argon atmosphere. To the stirring solution, sulfenamide **11k** or **11l** (0.25 mmol) was added. Then, the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column on silica gel to afford **14a / 14b** in 79% and 81% yields respectively.

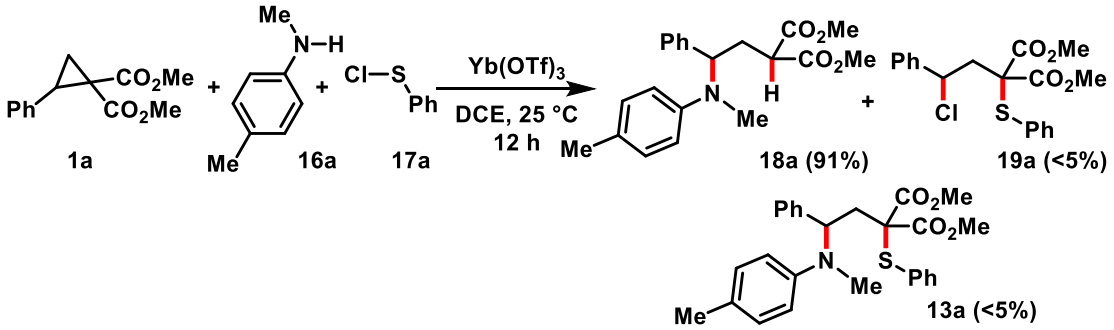
(b) Reaction of 11k Without D-A Cyclopropane 1a



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in a glove-box. The mixture was dissolved in DCE (1.0 mL) under argon atmosphere. To the stirring solution, sulfenamide **11k** (0.057 g, 0.25 mmol) was added. Then, the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica

gel and purified by flash column chromatography (Pet. ether /EtOAc = 93/07) on silica gel to afford **15** in 93% yield.

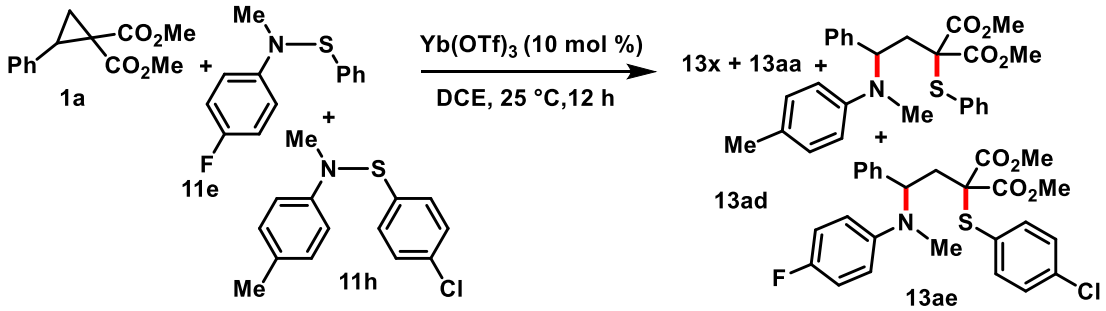
(c) Envisioned Three-Component Coupling



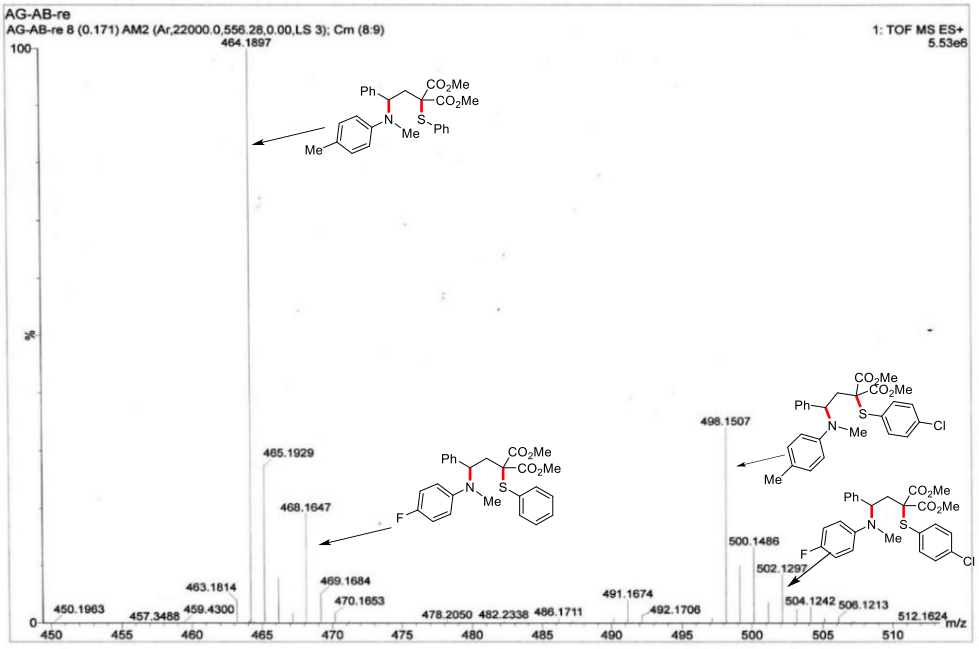
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in a glove-box. The mixture was dissolved in DCE (1.0 mL) under argon atmosphere. Cyclopropane **1a** (0.070 g, 0.3 mmol) was added outside the glove-box under argon atmosphere. To the stirring solution, *N*,4-dimethylaniline **16a** (0.030 g, 0.25 mmol) and phenyl hypochlorothioite **17a** (0.036 g, 0.25 mmol) were added. Then, the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 91/09) on silica gel to afford **18a** in 91% yield.

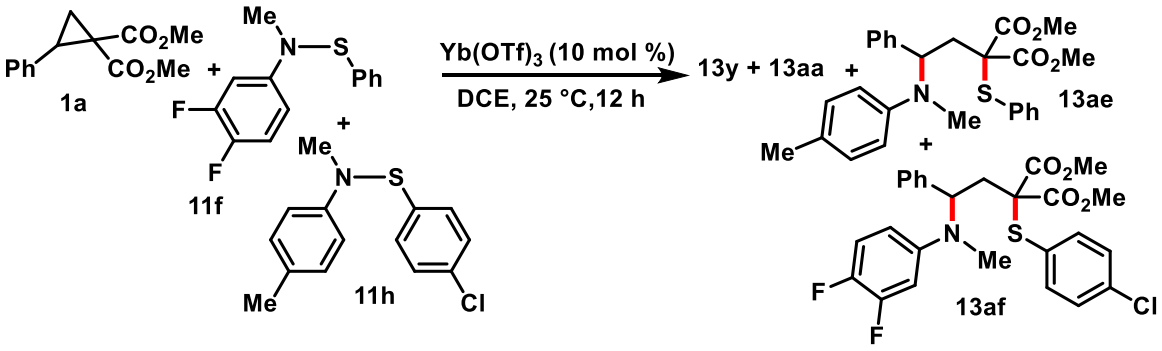
*The desired 1,3-aminothiolated product **13a** was not formed under this conditions and instead the N-H insertion of **16a** to **1a** took place leading to the formation of **18a** in 91% yield. Moreover, the insertion product **19a** derived from **17a** was not observed under this condition. These studies indicate the role of preformed sulfenamides in this insertion reaction.*

(d) Crossover Experiment Using Two Different Sulfenamides

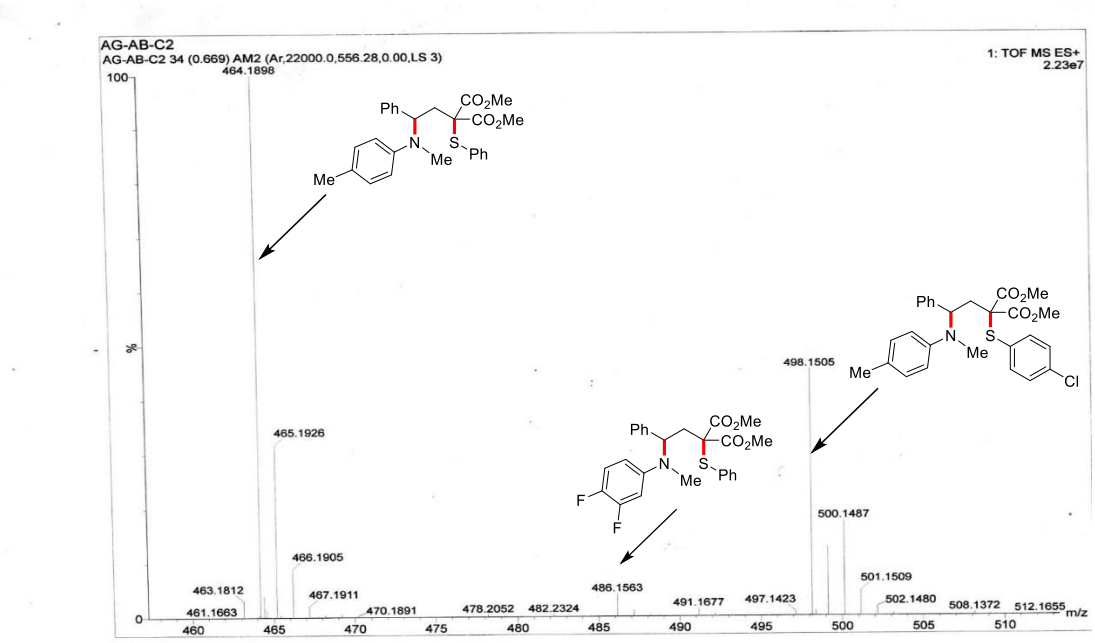


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (10 mol %) in a glove-box. The mixture was dissolved in 1 mL DCE under argon atmosphere. Cyclopropane **1a** (0.070 g, 0.3 mmol) was added outside the glove-box under argon atmosphere. To the stirring solution, sulfenamide **11e** (0.025 g, 0.125 mmol) and **11h** (0.029 g, 0.125 mmol) were added. Then, the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the crude mixture was passed through a small pad of silica and then the filtrate was evaporated and the crude products were analyzed using HRMS. In HRMS data, crossover products mass $[M+H]^+$ was detected along with normal products mass $[M+H]^+$.



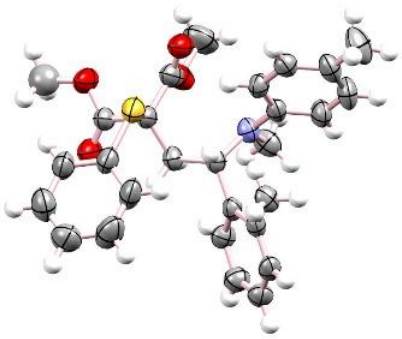


We also tested this crossover experiment employing other two different sulfenamides. To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added the $Yb(OTf)_3$ (10 mol %) in a glove-box. The mixture was dissolved in 1 mL DCE under argon atmosphere. The cyclopropane 1a (0.070 g, 0.3 mmol) was added outside the glove-box under argon atmosphere. To the stirring solution, sulfenamide **11f** (0.031 g, 0.125 mmol) and **11h** (0.029 g, 0.125 mmol) was added. Then, the reaction mixture was allowed to react at 25 °C for 12 h. After 12 h, the reaction was stopped, the crude mixture was passed through a small pad of silica and then the filtrate was evaporated to get the crude products, which was subsequently analysed using HRMS. In HRMS data, crossover product mass $[M+H]^+$ was detected along with normal products mass $[M+H]^+$.



6.6.5. ORTEP Diagram of 13k

Single crystal of **13k** (recrystallized from CH_2Cl_2/n-hexane at 25 °C) was mounted and the diffraction data was collected at 296 K on a Bruker APEX-II CCD diffractometer using SMART/SAINT software. Intensity data were collected using MoKα radiation (λ=0.71073 A°).



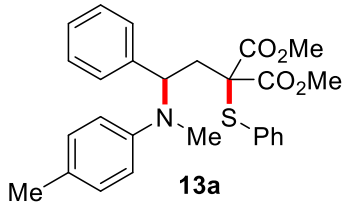
ORTEP Diagram of 13k

(CCDC 1978915, thermal ellipsoids are shown with 50% probability)

6.6.6. Synthesis and Characterization of γ-Aminated α-Thiolated Malonic Diesters

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)-2-(phenylthio)malonate (13a)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.070 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)-2-(phenylthio)malonate **13a** as a white solid (0.085 g, 73% yield).

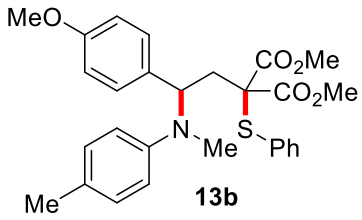


13a

***R*f** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41-7.39 (m, 2H), 7.37-7.34 (m, 1H), 7.27-7.22 (m, 5H), 7.10-7.07 (m, 4H), 6.98 (d, J = 8.6 Hz, 2 H), 5.69 (dd, J_1 = 10.8 Hz, J_2 = 2.5 Hz, 1H), 3.63 (s, 3H), 3.46 (s, 3H), 3.03 (dd, J_1 = 15.2 Hz, J_2 = 11.0 Hz, 1H), 2.43 (dd, J_1 = 15.2 Hz, J_2 = 2.8 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.11, 167.94, 148.51, 138.52, 137.11, 130.17, 129.59, 129.37, 129.18, 128.21, 127.81, 127.37, 116.54, 64.66, 60.19, 52.98, 34.73, 32.24, 20.54. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{30}NO_4S$: 464.1890, found: 464.1896. **FTIR (cm^{-1})** 2952, 1734, 1614, 1515, 1437, 1263.

Dimethyl-2-(2-(4-methoxyphenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13b)

Following the general procedure, treatment of dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate **1b** (0.079 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 85/15) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(4-methoxyphenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate **13b** as a white solid (0.108 g, 87% yield).

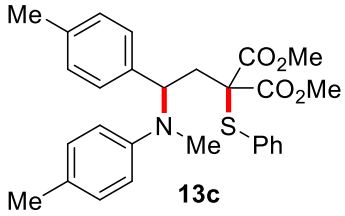


13b

***R*f** (Pet. ether / EtOAc = 90/10): 0.38; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40-7.33 (m, 3H), 7.26-7.25 (m, 2H), 7.08 (d, J = 8.5 Hz, 2 H), 6.98 (dd, J_1 = 8.6 Hz, J_2 = 6.6 Hz, 4H), 6.75 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.62 (s, 3H), 3.46 (s, 3H), 2.99 (dd, J_1 = 15.2 Hz, J_2 = 10.9 Hz, 1H), 2.37 (dd, J_1 = 15.2 Hz, J_2 = 2.8 Hz, 1H), 2.34 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.16, 167.97, 158.80, 148.66, 137.14, 130.81, 130.17, 129.59, 129.44, 129.19, 128.51, 127.83, 116.70, 113.50, 64.74, 59.80, 55.28, 53.01, 52.98, 34.91, 32.08, 20.56. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{32}NO_5S$: 494.1996, found: 494.2001. **FTIR (cm^{-1})** 2953, 1733, 1611, 1513, 1436, 1250.

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(*p*-tolyl)ethyl)-2-(phenylthio)malonate (13c)

Following the general procedure, treatment of dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate **1c** (0.074 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 93/07) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(*p*-tolyl)ethyl)-2-(phenylthio)malonate **13c** as a white solid (0.097 g, 81% yield).



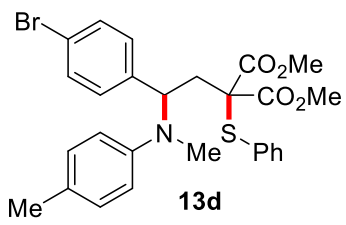
13c

***R*f** (Pet. ether / EtOAc = 90/10): 0.45; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42-7.39 (m, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.27-7.24 (m, 2H), 7.08 (d, J = 8.4 Hz, 2 H), 7.03 (d, J = 7.8 Hz, 2 H), 6.99-6.95 (m, 4H), 5.65 (dd, J_1 = 10.8 Hz, J_2 = 2.5 Hz, 1H), 3.63 (s, 3H), 3.46 (s, 3H),

3.02 (dd, J_1 = 15.1 Hz, J_2 = 10.8 Hz, 1H), 2.41 (dd, J_1 = 15.2 Hz, J_2 = 2.7 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.14, 167.95, 148.60, 137.11, 136.91, 135.53, 130.14, 129.56, 129.43, 129.17, 128.88, 127.69, 127.27, 116.52, 64.70, 59.91, 52.97, 52.96, 34.82, 32.21, 21.14, 20.54. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{32}NO_4S$: 478.2047, found: 478.2054. **FTIR (cm^{-1})** 2952, 1735, 1515, 1437, 1260, 1175.

Dimethyl-2-(2-(4-bromophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13d)

Following the general procedure, treatment of dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate **1d** (0.094 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 93/07) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(4-bromophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenyl thiol)malonate **13d** as a white solid (0.092 g, 68% yield).



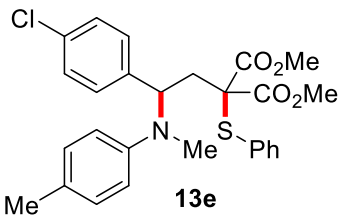
13d

***R*$_f$** (Pet. ether / EtOAc = 90/10): 0.46; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38-7.33 (m, 5H), 7.27-7.23 (m, 2H), 7.08 (d, J = 8.4 Hz, 2 H), 6.96-6.90 (m, 4H), 5.60 (dd, J_1 = 10.9 Hz, J_2 = 2.4 Hz, 1H), 3.64 (s, 3H), 3.46 (s, 3H), 2.99 (dd, J_1 = 15.0 Hz, J_2 = 10.9 Hz, 1H), 2.35-2.31 (m, 1H), 2.34 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.09, 167.86, 148.31, 137.40, 137.05, 131.36, 130.28, 129.71, 129.27, 129.07, 128.33, 121.40, 116.81, 64.51, 60.03, 53.08, 53.05, 34.56, 32.15, 20.56. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}BrNO_4S$: 542.0995, found: 542.1003. **FTIR (cm^{-1})** 2952, 1734, 1515, 1436, 1260, 1103.

Dimethyl-2-(2-(4-chlorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13e)

Following the general procedure, treatment of dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate **1e** (0.081 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc

= 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(4-chlorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate **13e** as a white solid (0.080 g, 64% yield).

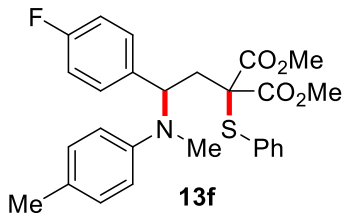


13e

***R*f** (Pet. ether / EtOAc = 90/10): 0.47; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38-7.34 (m, 3H), 7.27-7.23 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2 H), 7.08(d, *J* = 8.4 Hz, 2 H), 6.96 (t, *J* = 8.9 Hz, 4 H), 5.62 (dd, J_1 = 10.9 Hz, J_2 = 2.4 Hz, 1H), 3.64 (s, 3H), 3.46 (s, 3H), 2.98 (dd, J_1 = 15.3 Hz, J_2 = 10.7 Hz, 1H), 2.35 (dd, J_1 = 15.1 Hz, J_2 = 2.5 Hz, 1H), 2.34 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.09, 167.87, 148.34, 137.06, 136.92, 133.23, 130.27, 129.70, 129.30, 129.26, 128.72, 128.40, 128.31, 116.80, 64.53, 59.96, 53.07, 53.04, 34.64, 32.15, 20.56. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}ClNO_4S$: 498.15, found: 498.1506. **FTIR (cm^{-1})** 2952, 1731, 1615, 1516, 1436, 1266.

Dimethyl-2-(2-(4-fluorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13f)

Following the general procedure, treatment of dimethyl 2-(4-fluorophenyl)cyclopropane-1,1-dicarboxylate **1f** (0.076 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(4-fluorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate **13f** as a white solid (0.076 g, 63% yield).

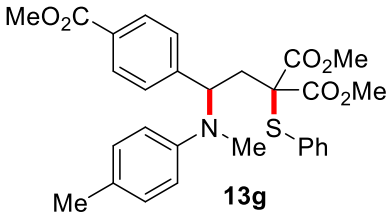


13f

***R*f** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39-7.34 (m, 3H), 7.27-7.23 (m, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.03-7.00 (m, 2H), 6.97-6.88 (m, 4H), 5.63 (dd, J_1 = 10.8 Hz, J_2 = 2.4 Hz, 1H), 3.64 (s, 3H), 3.47 (s, 3H), 2.99 (dd, J_1 = 15.2 Hz, J_2 = 10.8 Hz, 1H), 2.36-2.33 (m, 1H), 2.33 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.11, 167.90, 162.12 (*J* = 246.8 Hz), 148.42, 137.09, 134.27 (*J* = 3.3 Hz), 130.25, 129.68, 129.33, 129.23, 128.95 (*J* = 7.9 Hz), 128.23, 116.82, 115.03 (*J* = 21.3 Hz), 64.60, 59.89, 53.05, 34.85, 32.07, 20.56. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}FNO_4S$: 482.1796, found: 482.1803. **FTIR (cm^{-1})** 2954, 2364, 1734, 1513, 1436, 1225.

Dimethyl-2-(2-(4-(methoxycarbonyl)phenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio)malonate (13g)

Following the general procedure, treatment of dimethyl 2-(4-(methoxycarbonyl) phenyl)cyclopropane-1,1-dicarboxylate **1g** (0.088 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxyl amine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 86/14) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(4-(methoxycarbonyl)phenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2 (phenylthio)malonate **13g** as a white solid (0.074 g, 57% yield).

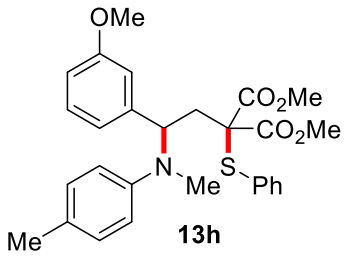


13g

***R*f** (Pet. ether / EtOAc = 90/10): 0.37; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.1 Hz, 2 H), 7.38-7.33 (m, 3H), 7.26-7.22 (m, 2H), 7.12-7.07 (m, 4H), 6.95 (d, *J* = 8.6 Hz, 2 H), 5.68 (dd, J_1 = 10.8 Hz, J_2 = 2.4 Hz, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 3.47 (s, 3H), 3.03 (dd, J_1 = 15.1 Hz, J_2 = 10.8 Hz, 1H), 2.40-2.35 (m, 1H), 2.35 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.07, 167.85, 166.98, 148.22, 143.49, 137.03, 130.27, 129.89, 129.70, 129.56, 129.31, 129.24, 128.37, 127.35, 116.77, 64.48, 60.32, 53.07, 53.05, 52.17, 34.49, 32.29, 20.54. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{29}H_{32}NO_6S$: 522.1945, found: 522.1948. **FTIR (cm^{-1})** 2954, 1748, 1612, 1516, 1437, 1284.

Dimethyl-2-(2-(3-methoxyphenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13h)

Following the general procedure, treatment of dimethyl 2-(3-methoxyphenyl)cyclopropane-1,1-dicarboxylate **1h** (0.079 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 87/13) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(3-methoxyphenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio)malonate **13h** as a white solid (0.078 g, 63% yield).

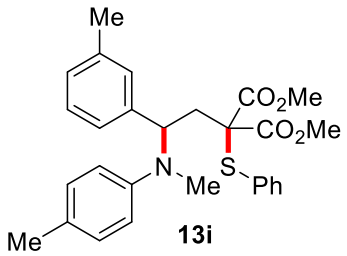


13h

***R*f** (Pet. ether / EtOAc = 90/10): 0.39; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41-7.33 (m, 3H), 7.27-7.23 (m, 2H), 7.14 (t, *J* = 7.9 Hz, 1H),7.07 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.75 (dd, J_1 = 15.1 Hz, J_2 = 10.8 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.59 (s, 1H), 5.64 (dd, J_1 = 10.8 Hz, J_2 = 2.4 Hz, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.46 (s, 3H), 3.00 (dd, J_1 = 15.1 Hz, J_2 = 10.9 Hz, 1H), 2.40 (dd, J_1 = 15.2 Hz, J_2 = 2.7 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.12, 167.96, 159.43, 148.58, 140.23, 137.13, 130.19, 129.59, 129.42, 129.21, 129.17, 127.89, 119.84, 116.64, 113.28, 112.54, 64.69, 60.27, 55.21, 53.00, 34.75, 32.32, 20.54. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{32}NO_5S$: 494.1996, found: 494.2000. **FTIR (cm^{-1})** 2952, 2363, 1734, 1608, 1516, 1262.

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(*m*-tolyl)ethyl)-2-(phenylthio)malonate (13i)

Following the general procedure, treatment of dimethyl 2-(*m*-tolyl)cyclopropane-1,1-dicarboxylate **1i** (0.075 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(*m*-tolyl)ethyl)-2-(phenylthio) malonate **13i** as a white solid (0.097 g, 81% yield).

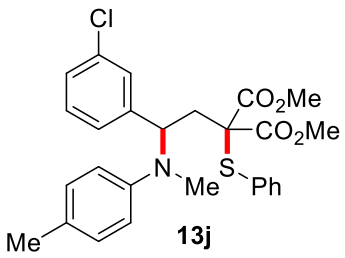


13i

***R*f** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42-7.34 (m, 3H), 7.28-7.24 (m, 2H), 7.13-7.07 (m, 3H), 7.03 (d, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 6.89-6.85 (m, 2H), 5.64 (dd, J_1 = 10.7 Hz, J_2 = 2.6 Hz, 1H), 3.62 (s, 3H), 3.46 (s, 3H), 3.02 (dd, J_1 = 15.2 Hz, J_2 = 10.8 Hz, 1H), 2.43 (dd, J_1 = 15.2 Hz, J_2 = 3.1 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.16, 168.51, 167.96, 148.53, 138.59, 137.70, 137.12, 130.14, 129.56, 129.48, 129.17, 128.09, 127.94, 127.65, 125.75, 124.66, 122.09, 64.69, 60.01, 52.97, 34.91, 32.34, 21.68, 20.54. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{32}NO_4S$: 478.2047, found: 478.2052. **FTIR (cm^{-1})** 2952, 1733, 1612, 1516, 1436, 1265.

Dimethyl-2-(2-(3-chlorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13j)

Following the general procedure, treatment of dimethyl 2-(3-chlorophenyl)cyclopropane-1,1-dicarboxylate **1j** (0.081 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 92/08) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(3-chlorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio)malonate **13j** as a white solid (0.105 g, 84% yield).

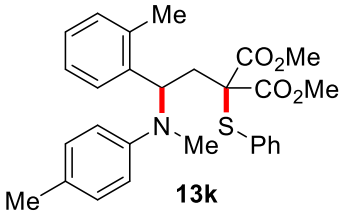


13j

***R*f** (Pet. ether / EtOAc = 90/10): 0.44; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42-7.36 (m, 3H), 7.30-7.26 (m, 2H), 7.22-7.14 (m, 2H), 7.12-7.08 (m, 3H), 6.98-6.93 (m, 3H), 5.65 (dd, J_1 = 10.7 Hz, J_2 = 2.6 Hz, 1H), 3.66 (s, 3H), 3.49 (s, 3H), 3.01 (dd, J_1 = 15.1 Hz, J_2 = 10.8 Hz, 1H), 2.40 (s, 3H), 2.40-2.36 (m, 1H), 2.31 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.02, 167.81, 148.16, 140.62, 137.02, 134.15, 130.26, 129.69, 129.55, 129.24, 128.25, 127.61, 127.22, 125.79, 116.62, 64.47, 60.01, 53.04, 53.02, 34.63, 32.26, 20.53. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}ClNO_4S$: 498.1500, found: 498.1504. **FTIR (cm^{-1})** 2951, 1734, 1612, 1570, 1435, 1262.

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(*o*-tolyl)ethyl)-2-(phenylthio)malonate (13k)

Following the general procedure, treatment of dimethyl 2-(*o*-tolyl)cyclopropane-1,1-dicarboxylate **1k** (0.074 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 92/8) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(*o*-tolyl)ethyl)-2-(phenylthio)malonate **13k** as a white solid (0.079 g, 66% yield).



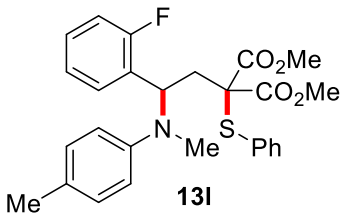
13k

***R*f** (Pet. ether / EtOAc = 90/10): 0.48; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34-7.26 (m, 4H), 7.23-7.19 (m, 2H), 7.17-7.04 (m, 7H), 5.68 (dd, J_1 = 8.5 Hz, J_2 = 4.8 Hz, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 2.99 (dd, J_1 = 15.2 Hz, J_2 = 8.6 Hz, 1H), 2.48-2.44 (m, 1H), 2.44 (s, 3H), 2.28

(s, 3H), 2.05 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.78, 168.13, 148.95, 137.64, 136.98, 136.39, 131.00, 130.07, 129.58, 129.43, 129.10, 128.76, 127.97, 127.17, 125.03, 118.31, 64.84, 57.48, 52.91, 52.85, 35.64, 32.14, 20.99, 20.61. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{32}NO_4S$: 478.2047, found: 478.2052. **FTIR (cm^{-1})** 2953, 1734, 1515, 1436, 1261, 1224.

Dimethyl-2-(2-(2-fluorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13l)

Following the general procedure, treatment of dimethyl 2-(2-fluorophenyl)cyclopropane-1,1-dicarboxylate **1l** (0.076 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(2-fluorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate **13l** as a white solid (0.076 g, 63% yield).



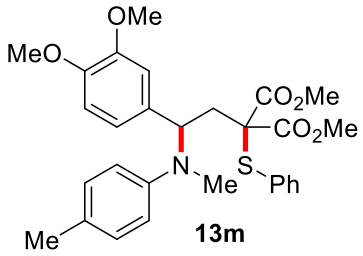
13l

***R*$_f$** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36 (d, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.23-7.14 (m, 4H), 7.08-6.95 (m, 6H), 5.88 (dd, J_1 = 10.3 Hz, J_2 = 3.3 Hz, 1H), 3.61 (s, 3H), 3.49 (s, 3H), 3.12 (dd, J_1 = 15.0 Hz, J_2 = 10.5 Hz, 1H), 2.46 (s, 3H), 2.28 (s, 3H), 2.27-2.23 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.02, 167.95, 160.81 (d, *J* = 246.5 Hz), 148.18, 137.10, 130.15, 129.66, (d, *J* = 5.2 Hz), 129.35, 129.25, 129.14, 129.00 (d, *J* = 8.2 Hz), 128.60, 125.00 (d, *J* = 16.1 Hz), 123.58 (d, *J* = 3.3 Hz), 117.50, 115.9 (d, *J* = 24.1 Hz), 64.71, 55.74, 53.01, 34.82, 32.08, 20.61. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}FNO_4S$: 482.1796, found: 482.1802. **FTIR (cm^{-1})** 2953, 1734, 1614, 1516, 1437, 1225.

Dimethyl-2-(2-(3,4-dimethoxyphenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13m)

Following the general procedure, treatment of dimethyl 2-(3,4-dimethoxyphenyl)cyclo propane-1,1-dicarboxylate **1m** (0.088 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in

DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 85/15) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(3,4-dimethoxyphenyl)-2-(methyl(*p*-tolyl) amino)ethyl)-2-(phenylthio)malonate **13m** as a white solid (0.097 g, 74% yield).

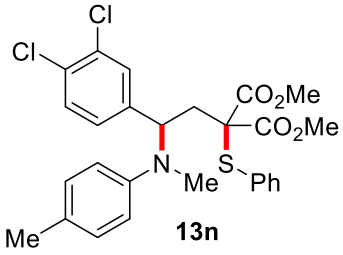


13m

***R*f** (Pet. ether / EtOAc = 90/10): 0.37; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.40-7.33 (m, 3H), 7.27-7.23 (m, 2H), 7.07 (d, *J* = 8.3 Hz, 2 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.62 (dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz, 1H), 6.47 (d, *J* = 1.6 Hz, 1H), 5.58 (dd, J_1 = 10.7 Hz, J_2 = 2.5 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H), 3.48 (s, 3H), 2.98 (dd, J_1 = 15.3 Hz, J_2 = 10.9 Hz, 1H), 2.38 (dd, J_1 = 15.3 Hz, J_2 = 2.7 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.16, 167.96, 148.86, 148.44, 148.25, 137.12, 131.17, 130.18, 129.55, 129.40, 129.18, 128.12, 119.35, 117.11, 110.89, 110.62, 64.70, 60.53, 55.87, 55.79, 52.99, 34.68, 32.09, 20.53. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{29}H_{34}NO_6S$: 524.2101, found: 524.2108. **FTIR (cm^{-1})** 2955, 1733, 1613, 1515, 1439, 1263.

Dimethyl-2-(2-(3,4-dichlorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio) malonate (13n)

Following the general procedure, treatment of dimethyl 2-(3,4-dichlorophenyl)cyclopropane -1,1-dicarboxylate **1n** (0.091 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with Yb(OTf)$_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 88/12) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(3,4-dichlorophenyl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio)malonate **13n** as a white solid (0.099 g, 74% yield).



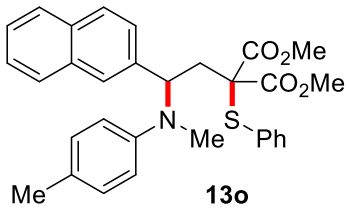
13n

***R*f** (Pet. ether / EtOAc = 90/10): 0.41; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.39-7.36 (m, 3H), 7.29-7.25 (m, 3H), 7.14-7.08 (m, 3H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.84 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1H), 5.59 (dd, J_1 = 10.8 Hz, J_2 = 2.3 Hz, 1H), 3.66 (s, 3H), 3.47 (s, 3H), 2.98 (dd, J_1 = 15.0 Hz, J_2 = 11.0 Hz, 1H), 2.36 (s, 3H), 2.32-2.28 (m, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.01, 167.74, 148.01, 138.71, 136.96, 132.34, 131.45, 130.34, 130.23,

129.77, 129.31, 129.13, 128.98, 128.63, 126.98, 116.80, 64.34, 59.81, 53.12, 53.07, 34.47, 32.18, 20.54. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{28}Cl_2NO_4S$: 532.1111, found: 532.1116. **FTIR (cm^{-1})** 2952, 2364, 1733, 1615, 1515, 1264.

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(naphthalen-2-yl)ethyl)-2-(phenylthio) malonate (13o)

Following the general procedure, treatment of dimethyl 2-(naphthalen-2-yl)cyclopropane-1,1-dicarboxylate **1o** (0.085 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(naphthalen-2-yl)ethyl)-2-(phenylthio)malonate **13o** as a white solid (0.085 g, 66% yield).



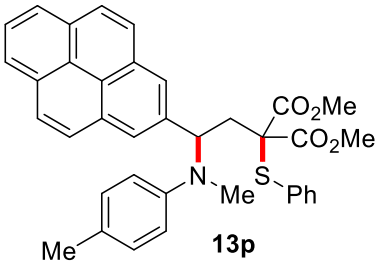
13o

***R*f** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79-7.76 (m, 2H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.57 (s, 1H), 7.48-7.41 (m, 4H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.26-7.21 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.56 (dd, J_1 = 10.5 Hz, J_2 = 1.8 Hz, 1H), 3.64 (s, 3H), 3.48 (s, 3H), 3.16 (dd, J_1 = 15.2 Hz, J_2 = 11.0 Hz, 1H), 2.58 (dd, J_1 = 15.2 Hz, J_2 =2.6 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 13C NMR (101 MHz, CDCl3) δ 169.20, 167.92, 137.11, 136.43, 133.17, 132.78, 130.22, 129.66, 129.33, 129.23, 128.22, 127.85, 127.60, 126.24, 126.10, 125.91, 125.43, 84, 64.65, 60.09, 53.07, 53.03, 34.63, 32.30, 20.57. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{31}H_{32}NO_4S$: 514.2047, found: 514.2053. **FTIR (cm^{-1})** 2953, 1732, 1612, 1515, 1435, 1224.

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(pyren-2-yl)ethyl)-2-(phenylthio)malonate (13p)

Following the general procedure, treatment of dimethyl 2-(pyren-1-yl)cyclopropane-1,1-dicarboxylate **1p** (0.108 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude

reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(pyren-2-yl)ethyl)-2-(phenylthio)malonate **13p** as a white solid (0.087 g, 59% yield).

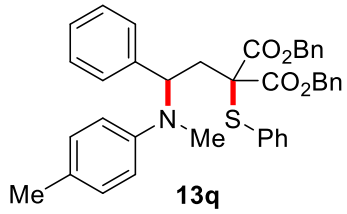


13p

***R*f** (Pet. ether / EtOAc = 90/10): 0.41; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.16-8.09 (m, 4H), 8.07-7.95 (m, 4H), 7.84 (d, *J* = 9.7 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.11-7.03 (m, 6H), 6.60 (dd, J_1 = 10.1 Hz, J_2 = 3.1 Hz, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 3.50 (dd, J_1 = 15.2 Hz, J_2 = 10.1 Hz, 1H), 2.54 (dd, J_1 = 15.1 Hz, J_2 = 3.3 Hz, 1H), 2.50 (s, 3H), 2.31 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.10, 168.12, 148.67, 137.04, 132.11, 131.44, 130.75, 130.53, 130.08, 129.56, 129.54, 129.27, 129.24, 129.12, 127.56, 127.32, 125.97, 125.69, 125.21, 125.17, 124.89, 124.14, 123.93, 118.91, 65.12, 57.18, 53.11, 53.02, 36.24, 32.63, 20.69. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{37}H_{34}NO_4S$: 588.2203, found: 588.2206. **FTIR (cm^{-1})** 2952, 1732, 1514, 1263, 1230, 1113.

Dibenzyl-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)-2-(phenylthio)malonate (13q)

Following the general procedure, treatment of dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate **1q** (0.116 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 93/07) of the crude reaction mixture using silica gel afforded dibenzyl-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)-2-(phenylthio)malonate **13q** as a white solid (0.115 g,75% yield).



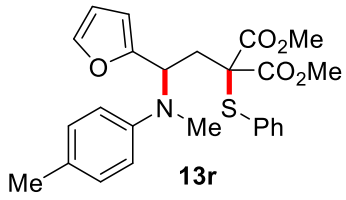
13q

***R*f** (Pet. ether / EtOAc = 90/10): 0.60; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36-7.35 (m, 3H), 7.33-7.23 (m, 11H), 7.17 (t, *J* = 7.7 Hz, 2H), 7.12-7.10 (m, 6H), 7.02 (d, *J* = 8.6 Hz, 2H), 5.75 (dd, J_1 = 10.9 Hz, J_2 = 2.4 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.92-4.88 (m, 2H), 4.82 (d, *J* = 12.3 Hz, 1H), 3.12 (dd, J_1 = 15.1 Hz, J_2 = 11.0 Hz, 1H), 2.49 (dd, J_1 = 15.1 Hz, J_2 = 2.6 Hz, 1H), 2.46 (s, 3H), 2.34 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.45, 167.33, 148.49, 138.64, 137.18, 135.19, 135.05, 130.02, 129.65, 129.29, 129.09, 128.59, 128.46, 128.42, 128.40, 128.22, 127.74, 127.34, 116.51, 67.90, 67.63, 64.59, 60.14, 34.75, 32.55,

20.55. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{39}H_{38}NO_4S$: 616.2516, found: 616.2519. **FTIR (cm^{-1})** 2953, 2364, 1731, 1514, 1262, 1217, 1106.

Dimethyl-2-(2-(furan-2-yl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio)malonate (13r)

Following the general procedure, treatment of dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate **1r** (0.067 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(furan-2-yl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio)malonate **13r** as a white solid (0.085 g, 75% yield).

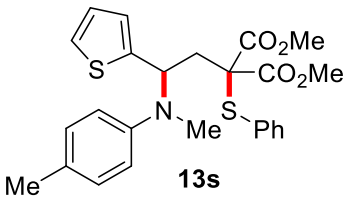


13r

***R*f** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43-7.37 (m, 3H), 7.31-7.27 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 2 H), 6.99 (d, *J* = 8.6 Hz, 2 H), 6.25-6.24 (m, 1H), 6.03 (d, *J* = 3.1 Hz, 1 H), 5.62 (dd, J_1 = 10.1 Hz, J_2 = 3.0 Hz, 1H), 3.65 (s, 3H), 3.48 (s, 3H), 2.89 (dd, J_1 = 15.3 Hz, J_2 = 10.1 Hz, 1H), 2.50 (s, 3H), 2.44 (dd, J_1 = 15.3 Hz, J_2 = 3.1 Hz, 1H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.87, 167.88, 153.84, 148.46, 141.89, 137.19, 130.23, 129.59, 129.19, 128.04, 116.15, 109.86, 107.01, 64.33, 55.04, 53.06, 53.04, 34.24, 32.93, 20.52. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{25}H_{28}NO_5S$: 454.1683, found: 454.1687. **FTIR (cm^{-1})** 2953, 1735, 1516, 1436, 1264, 1232.

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-(thiophen-2-yl)ethyl)-2-(phenylthio)malonate (13s)

Following the general procedure, treatment of dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate **1s** (0.072 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-



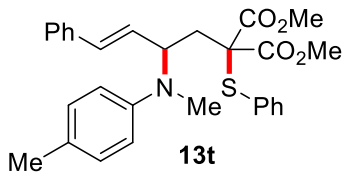
13s

(methyl(*p*-tolyl)amino)-2-(thiophen-2-yl)ethyl)-2-(phenylthio)malonate **13s** as a light yellow solid (0.094 g, 80% yield).

***R*f** (Pet. ether / EtOAc = 90/10): 0.39; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.44-7.37 (m, 3H), 7.31-7.27 (m, 2H), 7.12-7.10 (m, 3H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.91-6.86 (m, 1H), 6.75 (d, *J* = 3.5 Hz, 1H), 5.87 (dd, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H), 3.67 (s, 3H), 3.48 (s, 3H), 3.02 (dd, J_1 = 15.2 Hz, J_2 = 10.7 Hz, 1H), 2.49-2.44 (m, 4H), 2.30 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 168.93, 167.78, 147.96, 142.31, 137.18, 130.28, 129.69, 129.25, 129.17, 128.27, 126.45, 124.62, 123.99, 116.47, 64.50, 56.69, 53.06, 36.13, 32.25, 20.55. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{25}H_{28}NO_4S_2$: 470.1454, found: 470.1460. **FTIR (cm^{-1})** 3003, 2861, 1722, 1614, 1515, 1435, 1268, 1097, 924.

Dimethyl (*E*)-2-(2-(methyl(*p*-tolyl)amino)-4-phenylbut-3-en-1-yl)-2-(phenylthio) malonate (13t)

Following the general procedure, treatment of dimethyl (*E*)-2-styrylcyclopropane-1,1-dicarboxylate **1t** (0.078 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*p*-tolyl)thiohydroxylamine **11a** (0.057 g, 0.25 mmol) with Yb(OTf)$_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl (*E*)-2-(2-(methyl(*p*-tolyl)amino)-4-phenylbut-3-en-1-yl)-2-(phenylthio)malonate **13t** as a white solid (0.061 g, 50% yield).

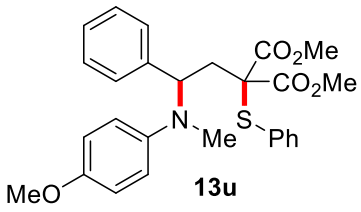


13t

***R*f** (Pet. ether / EtOAc = 90/10): 0.45; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.33-7.26 (m, 6H), 7.23-7.19 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2 H), 6.38 (d, *J* = 16.1 Hz, 1H), 6.15 (dd, J_1 = 16.3 Hz, J_2 = 6.0 Hz, 1H), 5.14-5.10 (m, 1H), 3.67 (s, 3H), 3.48 (s, 3H), 2.73 (dd, J_1 = 15.2 Hz, J_2 = 9.8 Hz, 1H), 2.63 (s, 3H), 2.29 (s, 3H), 2.24 (dd, J_1 = 15.2 Hz, J_2 = 3.3 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.16, 168.02, 148.24, 137.14, 136.89, 131.49, 130.24, 129.66, 129.45, 129.23, 128.65, 127.78, 127.69, 127.56, 126.50, 116.11, 64.33, 58.16, 53.15, 53.05, 35.45, 32.61, 20.51. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{29}H_{32}NO_4S$: 490.2047, found: 490.2053. **FTIR (cm^{-1})** 3026, 2953, 1731, 1614, 1516, 1437, 1264.

Dimethyl-2-(2-((4-methoxyphenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate (13u)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *N*-(4-methoxyphenyl)-*N*-methyl-*S*-phenylthiohydroxyl amine **11b** (0.123 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-((4-methoxyphenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate **13u** as a white solid (0.115 g, 48% yield).

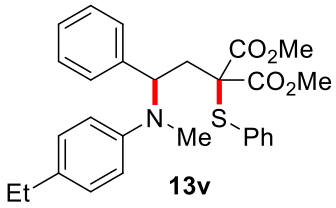


13u

***R*f** (Pet. ether / EtOAc = 90/10): 0.37; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39-7.37 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.26-7.20 (m, 5H), 7.02-6.99 (m, 4H), 6.86-6.84 (m, 2 H), 5.51 (dd, J_1 = 11.0 Hz, J_2 = 2.7 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.50 (s, 3H), 3.04 (dd, J_1 = 15.2 Hz, J_2 = 11.0 Hz, 1H), 2.43 (dd, J_1 = 15.3 Hz, J_2 = 2.9 Hz, 1H), 2.31 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.17, 168.04, 153.21, 145.25, 137.88, 137.12, 130.19, 129.38, 129.20, 128.12, 127.61, 127.44, 118.88, 114.40, 64.81, 61.88, 55.68, 53.02, 34.58, 32.37. **HRMS (ESI)** calculated $[M]^+$ for $C_{27}H_{29}NO_5S$: 479.1766, found: 479.1767. **FTIR (cm^{-1})** 2951, 1734, 1579, 1511, 1438, 1256.

Dimethyl-2-(2-((4-ethylphenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio)malonate (13v)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *N*-(4-ethylphenyl)-*N*-methyl-*S*-phenylthiohydroxylamine **11c** (0.122 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-((4-ethylphenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate **13v** as a white solid (0.165 g, 69% yield).



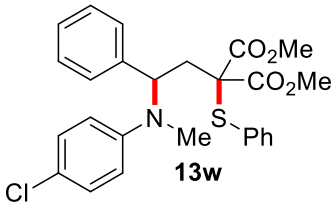
13v

***R*f** (Pet. ether / EtOAc = 90/10): 0.45; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (d, *J* = 7.1 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.27-7.22 (m, 5H), 7.12-7.07 (m, 4H), 6.99 (d, *J* = 8.6 Hz, 2

H), 5.69 (dd, J_1 = 10.6 Hz, J_2 = 2.8 Hz, 1H), 3.61 (s, 3H), 3.45 (s, 3H), 3.03 (dd, J_1 = 15.2 Hz, J_2 = 10.6 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 2.44 (dd, J_1 = 15.2 Hz, J_2 = 3.0 Hz, 1H), 2.39 (s, 3H), 1.23 (t, J = 7.6 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.11, 167.96, 148.64, 138.65, 137.12, 134.30, 130.16, 129.44, 129.18, 128.32, 128.23, 127.42, 127.37, 116.46, 64.68, 60.12, 52.97, 52.95, 34.86, 32.34, 27.98, 15.81. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{28}H_{32}NO_4S$: 478.2047, found: 478.2052. **FTIR (cm^{-1})** 2957, 1735, 1612, 1437, 1256, 1222.

Dimethyl-2-(2-((4-chlorophenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate (13w)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *N*-(4-chlorophenyl)-*N*-methyl-*S*-phenylthiohydroxylamine **11d** (0.125 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-((4-chlorophenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate **13w** as a white solid (0.152 g, 63% yield).



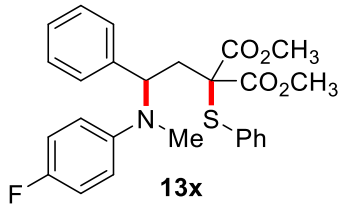
13w

***R*$_f$** (Pet. ether / EtOAc = 90/10): 0.45; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40-7.34 (m, 3H), 7.27-7.21 (m, 7H), 7.08-7.05 (m, 2H), 6.99 (d, J = 9.2 Hz, 2 H), 5.69 (dd, J_1 = 11.0 Hz, J_2 = 2.4 Hz, 1H), 3.64 (s, 3H), 3.45 (s, 3H), 3.02 (dd, J_1 = 15.3 Hz, J_2 = 11.0 Hz, 1H), 2.44 (dd, J_1 = 15.3 Hz, J_2 = 2.7 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.98, 167.95, 149.23, 138.31, 137.07, 130.31, 129.26, 129.14, 128.94, 128.43, 127.66, 127.16, 123.41, 117.31, 64.54, 60.02, 53.09, 53.05, 34.65, 32.41. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{26}H_{27}ClNO_4S$: 484.1344, found: 484.1349. **FTIR (cm^{-1})** 2952, 1734, 1594, 1497, 1437, 1263.

Dimethyl-2-(2-((4-fluorophenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate (13x)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *N*-(4-fluorophenyl)-*N*-methyl-*S*-phenylthiohydroxylamine **11e** (0.116 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in

DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-((4-fluorophenyl)(methyl)amino)-2-phenyl ethyl)-2-(phenylthio) malonate **13x** as a white solid (0.140 g, 60% yield).

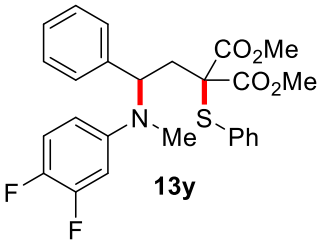


13x

***R*f** (Pet. ether / EtOAc = 90/10): 0.42; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.42-7.36 (m, 3H), 7.29-7.25 (m, 5H), 7.06-6.98 (m, 6H), 5.61 (dd, J_1 = 11.0 Hz, J_2 = 2.5 Hz, 1H), 3.67 (s, 3H), 3.52 (s, 3H), 3.08 (dd, J_1 = 15.2 Hz, J_2 = 11.1 Hz, 1H), 2.41 (dd, J_1 = 15.3 Hz, J_2 = 2.7 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.04, 167.99, 156.75 (d, J = 237.9 Hz), 147.33 (d, J = 2.0 Hz), 137.83, 137.06, 130.26, 129.24, 128.26, 127.60, 127.37, 118.19 (d, J = 7.4 Hz), 115.44 (d, J = 21.6 Hz), 64.66, 61.42, 53.06, 53.01, 34.51, 32.39. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{26}H_{27}FNO_4S$: 468.1639, found: 468.1646. **FTIR (cm^{-1})** 2952, 1733, 1509, 1436, 1224, 1103.

Dimethyl-2-(2-((3,4-difluorophenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate (13y)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *N*-(3,4-difluorophenyl) -*N*-methyl-*S*-phenylthiohydroxylamine **11f** (0.126 g, 0.5 mmol) with Yb(OTf)$_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-((3,4-difluorophenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate **13y** as a white solid (0.131 g, 54% yield).



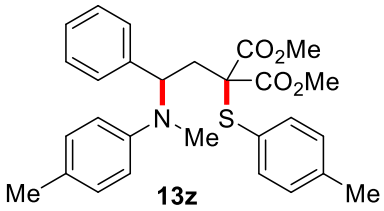
13y

***R*f** (Pet. ether / EtOAc = 90/10): 0.47; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.39-7.33 (m, 3H), 7.26-7.22 (m, 5H), 7.09-7.02 (m, 3H), 6.86-6.77 (m, 2 H), 5.58 (dd, J_1 = 11.0 Hz, J_2 = 2.5 Hz, 1H), 3.63 (s, 3H), 3.48 (s, 3H), 3.01 (dd, J_1 = 15.2 Hz, J_2 = 11.0 Hz, 1H), 2.40 (dd, J_1 = 15.2 Hz, J_2 = 2.7 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 168.92, 167.95, 150.53 (dd, J_1 = 245.0 Hz, J_2 = 13.0 Hz), 147.86 (dd, J_1 = 7.9 Hz, J_2 = 2.1 Hz), 143.81 (dd, J_1 = 238.8 Hz, J_2 = 12.8 Hz), 137.89, 137.03, 130.31, 129.26, 129.08, 128.45, 127.80, 127.18, 117.19 (dd, J_1 = 17.7 Hz, J_2 = 1.5 Hz), 111.85 (dd, J_1 = 5.2 Hz, J_2 = 2.9 Hz), 105.34 (d, J =

20.6 Hz), 64.53, 60.81, 53.07, 53.02, 34.60, 32.50. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{26}H_{26}F_2NO_4S$: 486.1545, found: 486.1551. **FTIR (cm^{-1})** 2953, 1730, 1598, 1517, 1437, 1246.

Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)-2-(*p*-tolylthio)malonate (13z)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *N*-methyl-*N*,*S*-di-*p*-tolylthiohydroxylamine **11g** (0.122 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)-2-(*p*-tolylthio)malonate **13z** as a white solid (0.177 g, 74% yield).

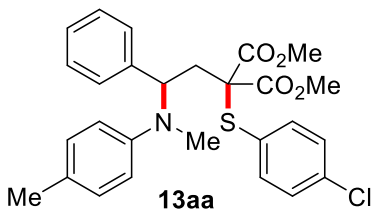


13z

***R*$_f$** (Pet. ether / EtOAc = 90/10): 0.47; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.26-7.23 (m, 3H), 7.11-7.05 (m, 6H), 7.00 (d, *J* = 8.5 Hz, 2 H), 5.72 (dd, J_1 = 10.7 Hz, J_2 = 2.5 Hz, 1H), 3.65 (s, 3H), 3.47 (s, 3H), 3.03 (dd, J_1 = 15.1 Hz, J_2 = 10.9 Hz, 1H), 2.43 (dd, J_1 = 15.2 Hz, J_2 = 2.7 Hz, 1H), 2.39 (s, 3H), 2.31 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.12, 167.95, 148.49, 140.47, 138.54, 137.01, 129.98, 129.54, 128.16, 127.71, 127.34, 127.32, 125.70, 116.50, 64.57, 60.13, 52.92, 52.89, 34.57, 32.18, 21.34, 20.50. **HRMS (ESI)** calculated $[M+H]^+$ for C28H32NO4S: 478.2047, found: 478.2049. **FTIR (cm^{-1})** 2952, 1734, 1613, 1516, 1435, 1263.

Dimethyl-2-((4-chlorophenyl)thio)-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl) malonate (13aa)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *S*-(4-chlorophenyl) -*N*-methyl-*N*-(*p*-tolyl)thiohydroxyl amine **11h** (0.132 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-



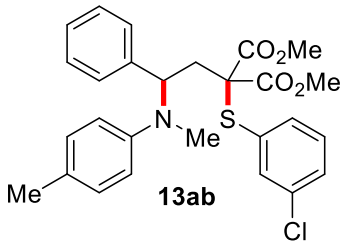
13aa

2-((4-chlorophenyl)thio)-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl) malonate **13aa** as a white solid (0.194 g, 78% yield).

***R*f** (Pet. ether / EtOAc = 90/10): 0.40; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33-7.31 (m, 2H), 7.26-7.21 (m, 5H), 7.09-7.07 (m, 4H), 6.95 (d, J = 8.6 Hz, 2 H), 5.61 (dd, J_1 = 10.6 Hz, J_2 = 2.7 Hz, 1H), 3.61 (s, 3H), 3.47 (s, 3H), 3.02 (dd, J_1 = 15.2 Hz, J_2 = 10.6 Hz, 1H), 2.43 (dd, J_1 = 15.2 Hz, J_2 = 3.0 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.91, 167.77, 148.46, 138.39, 138.33, 136.83, 129.63, 129.44, 128.30, 127.98, 127.51, 127.38, 116.62, 64.76, 60.26, 53.06, 53.05, 34.79, 32.24, 20.55. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}ClNO_4S$: 498.1500, found: 498.1506. **FTIR (cm^{-1})** 2952, 1730, 1613, 1516, 1437, 1265.

Dimethyl-2-((3-chlorophenyl)thio)-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl) malonate (13ab)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *S*-(3-chlorophenyl)-*N*-methyl-*N*-(*p*-tolyl)thio hydroxylamine **11i** (0.132 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-((3-chlorophenyl)thio)-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl) malonate **13ab** as a white solid (0.110 g, 44% yield).

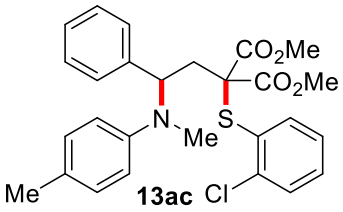


13ab

***R*f** (Pet. ether / EtOAc = 90/10): 0.40; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41-7.41 (m, 1H), 7.34-7.22 (m, 1H), 7.28-7.15 (m, 5H), 7.08-7.06 (m, 4H), 6.94 (d, J = 8.6 Hz, 2 H), 5.59 (dd, J_1 = 10.6 Hz, J_2 = 2.6 Hz, 1H), 3.62 (s, 3H), 3.47 (s, 3H), 3.04 (dd, J_1 = 15.3 Hz, J_2 = 10.7 Hz, 1H), 2.43 (dd, J_1 = 15.3 Hz, J_2 = 2.9 Hz, 1H), 2.38 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.91, 167.74, 148.44, 138.37, 136.82, 135.14, 134.64, 131.35, 130.41, 130.15, 129.65, 128.31, 127.98, 127.49, 127.40, 116.57, 64.91, 60.23, 53.12, 53.11, 34.94, 32.31, 20.56. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}ClNO_4S$: 498.1500, found: 498.1504. **FTIR (cm^{-1})** 2952, 1735, 1613, 1515, 1433, 1262.

Dimethyl-2-((2-chlorophenyl)thio)-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl) malonate (13ac)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.140 g, 0.6 mmol) and *S*-(2-chlorophenyl)-*N*-methyl-*N*-(*p*-tolyl)thiohydroxylamine **11j** (0.132 g, 0.5 mmol) with $Yb(OTf)_3$ (0.031 g, 0.05 mmol) in DCE (2.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-((2-chlorophenyl)thio)-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl) malonate **13ac** as a white solid (0.115 g, 46% yield).

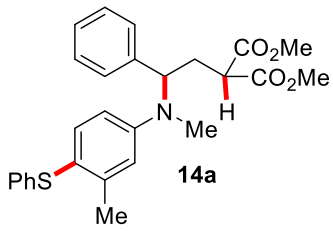


13ac

***R*f** (Pet. ether / EtOAc = 90/10): 0.40; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 7.40 (dd, J_1 = 8.0 Hz, J_2 = 1.4 Hz, 1H), 7.29-7.25 (m, 1H), 7.22-7.20 (m, 3H), 7.14-7.04 (m, 5H), 6.98 (d, J = 8.6 Hz, 2 H), 5.77 (dd, J_1 = 11.1 Hz, J_2 = 2.1 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 3H), 3.08 (dd, J_1 = 15.1 Hz, J_2 = 11.0 Hz, 1H), 2.43 (dd, J_1 = 15.3 Hz, J_2 = 2.5 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.99, 167.71, 148.52, 140.97, 139.24, 138.46, 131.47, 130.52, 129.58, 128.89, 128.15, 127.84, 127.37, 127.34, 127.25, 116.59, 64.82, 60.31, 53.18, 53.09, 34.77, 32.11, 20.55. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{29}ClNO_4S$: 498.1500, found: 498.1503. **FTIR (cm^{-1})** 2951, 1734, 1613, 1517, 1436, 1262.

Dimethyl-2-(2-(methyl(3-methyl-4-(phenylthio)phenyl)amino)-2-phenylethyl)malonate (14a)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.070 g, 0.3 mmol) and *N*-methyl-*S*-phenyl-*N*-(*m*-tolyl)thiohydroxylamine **11k** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g,0.025 mmol) in DCE (1.0 mL) at25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-(methyl(3-methyl-4-(phenylthio)phenyl)amino)-2-phenylethyl)malonate **14a** as a white solid (0.092 g, 79% yield).

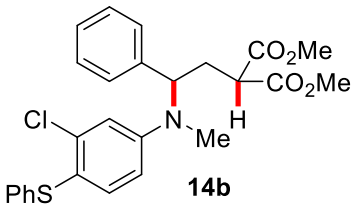


14a

***R*f** (Pet. ether / EtOAc = 90/10): 0.43;**^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.41 (d, *J* = 8.6 Hz, 1H), 7.37-7.33 (m, 2H), 7.30-7.26 (m, 3H), 7.24-7.20 (m, 2H), 7.10-7.04 (m, 3H), 6.78 (d, *J* = 2.7 Hz, 1H), 6.69 (dd, J_1 = 8.6 Hz, J_2 = 2.8 Hz, 1H), 5.22 (dd, J_1 = 10.7 Hz, J_2 = 4.7 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.54 (dd, J_1 = 8.9 Hz, J_2 = 5.5 Hz, 1H), 2.77 (ddd, J_1 = 13.9 Hz, J_2 = 8.9 Hz, J_2 = 4.8 Hz, 1H), 2.66-2.59 (m, 4H), 2.36 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.81, 169.67, 151.41, 143.72, 139.70, 139.60, 137.82, 128.85, 128.69, 127.62, 127.08, 126.30, 124.81, 117.72, 115.05, 111.54, 58.72, 52.74, 48.96, 31.65, 30.57, 21.51. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{27}H_{30}NO_4S$: 464.1890, found: 464.1895. **FTIR (cm^{-1})** 2952, 1754, 1731, 1591, 1488, 1438, 1264, 1152.

Dimethyl-2-(2-((3-chloro-4-(phenylthio)phenyl)(methyl)amino)-2-phenylethyl) malonate (14b)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.070 g, 0.3 mmol) and *N*-(3-chlorophenyl)-*N*-methyl-*S*-phenylthiohydroxylamine **11l** (0.062 g, 0.25 mmol) with Yb(OTf)$_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded dimethyl-2-(2-((3-chloro-4-(phenylthio)phenyl)(methyl)amino)-2-phenylethyl) malonate **14b** as a white solid (0.098 g, 81% yield).

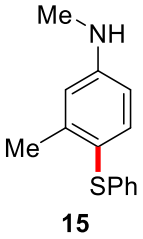


14b

***R*f** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.38-7.33 (m, 3H), 7.31-7.23 (m, 5H), 7.18-7.14 (m, 3H), 6.93 (d, *J* = 2.8 Hz, 1 H), 6.71 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 5.14 (dd, J_1 = 10.6 Hz, J_2 = 4.9 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.50-3.46 (m, 1H), 2.78-2.71 (m, 1H), 2.62 (s, 3H), 2.64-2.55(m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 169.65, 169.57, 151.69, 139.76, 139.02, 137.74, 137.19, 129.04, 128.84, 128.00, 127.88, 127.03, 125.87, 118.11, 114.15, 112.18, 58.90, 52.89, 52.86, 48.90, 31.81, 30.47. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{26}H_{27}ClNO_4S$: 484.1344, found: 484.1350. **FTIR (cm^{-1})** 2952, 1753, 1731, 1587, 1486, 1434.

_N_,3-Dimethyl-4-(phenylthio)aniline (15)

Following the general procedure, *N*-methyl-*S*-phenyl-*N*-(*m*-tolyl)thiohydroxyl amine **11k** (0.057 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 98/02) of the crude reaction mixture using silica gel afforded *N*,3-dimethyl-4-(phenylthio)aniline **15** as a colourless oil (0.053 g, 93% yield).

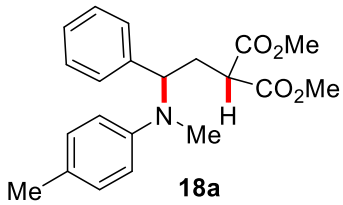


15

***R*f** (Pet. ether / EtOAc = 100/00): 0.31; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (d, *J* = 8.3 Hz, 1 H), 7.26-7.22 (m, 2H), 7.13-7.07 (m, 3H), 6.59 (d, *J* = 1.7 Hz, 1 H), 6.50 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1H), 3.87 (bs, 1H), 2.88 (s, 3H), 2.38 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.48, 143.95, 139.98, 138.11, 128.81, 126.00, 124.63, 117.22, 114.45, 110.80, 30.49, 21.11. **HRMS (ESI)** calculated $[M+]^+$ for $C_{14}H_{15}NS$: 229.0925, found: 229.0926. **FTIR (cm^{-1})** 3423, 2921, 1603, 1504, 1474, 1326.

Dimethyl 2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)malonate (18a)

Following the general procedure, treatment of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.085 g, 0.3 mmol), *N*,4-dimethylaniline **16a** (0.030 g, 0.25 mmol) and phenyl hypochlorothioite **17a** (0.036 g, 0.25 mmol) with $Yb(OTf)_3$ (0.015 g, 0.025 mmol) in DCE (1.0 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.ether/ EtOAc = 90/10) of the crude reaction mixture using silica gel afforded Dimethyl 2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)malonate **18a** as a white solid (0.080 g, 91% yield).

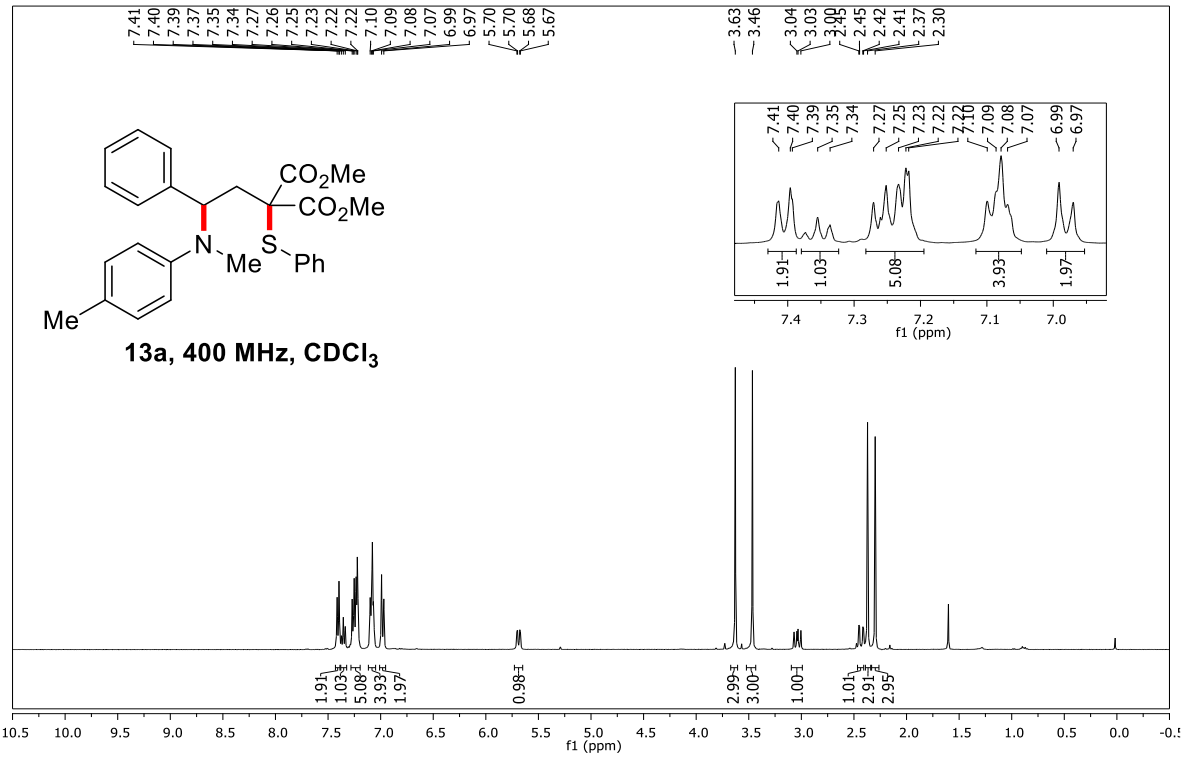


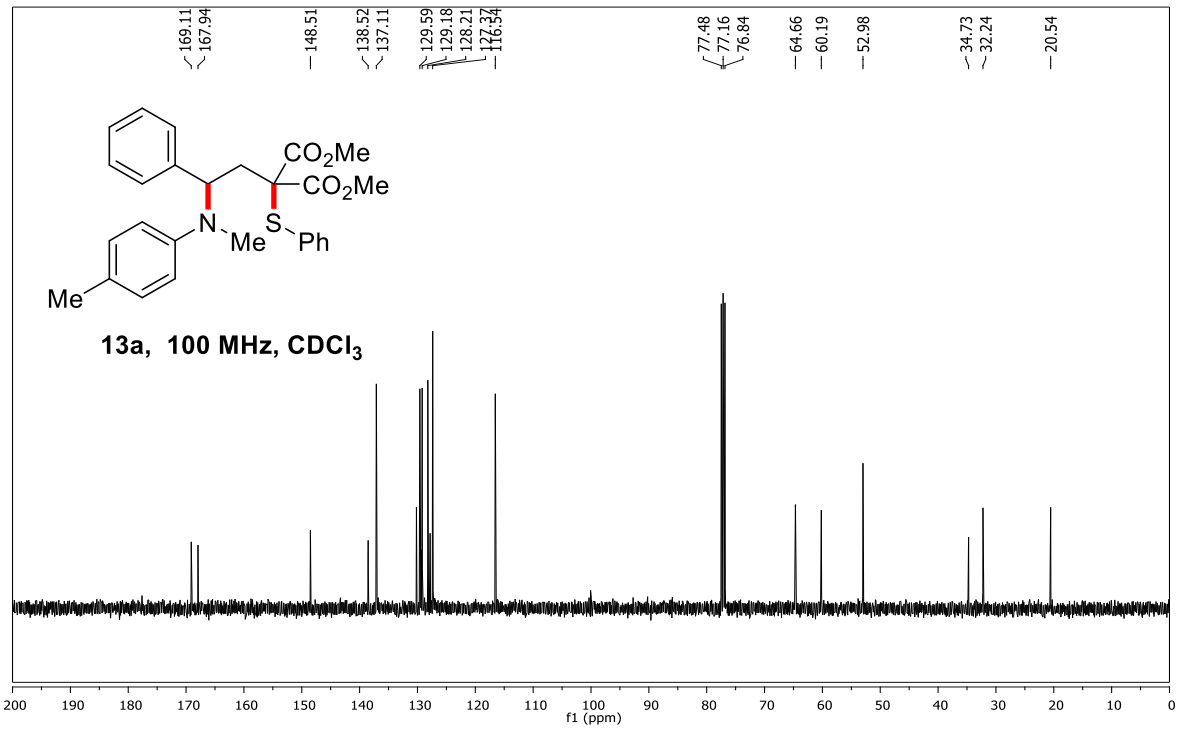
18a

***R*f** (Pet. ether / EtOAc = 90/10): 0.43; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32-7.24 (m, 3H), 7.21 (d, *J* = 6.9 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.07 (t, *J* = 8.4 Hz, 1H), 3.69 (s, 6H), 3.61 (t, *J* = 7.2 Hz, 1H), 2.69-2.65 (m, 2H), 2.57 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.95, 169.80, 148.55, 139.63, 129.75, 128.42, 127.34, 127.16, 126.88, 114.32, 60.20, 52.59, 49.17, 31.80, 30.62, 20.34. **HRMS (ESI)** calculated $[M+H]^+$ for $C_{21}H_{26}NO_4$: 356.1856, found: 356.1861. **FTIR (cm^{-1})** 2953, 1759, 1615, 1518, 1435, 1262.

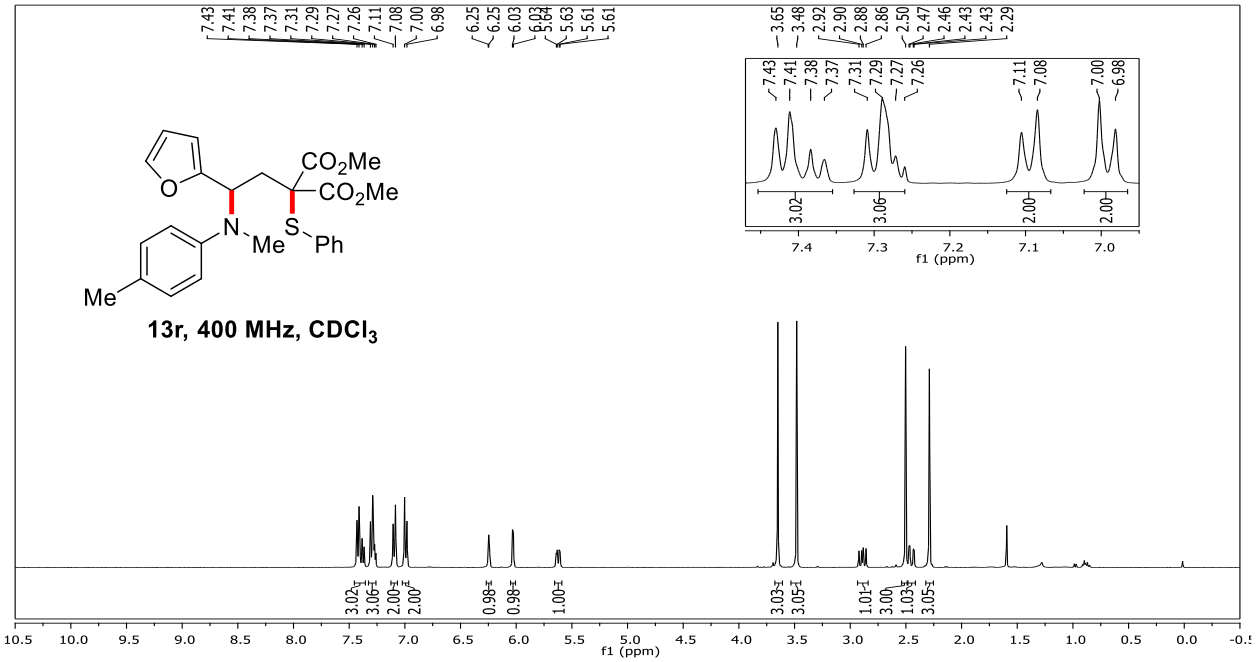
6.6.7. ^{1}H and ^{13}C NMR Spectra of Selected Compounds

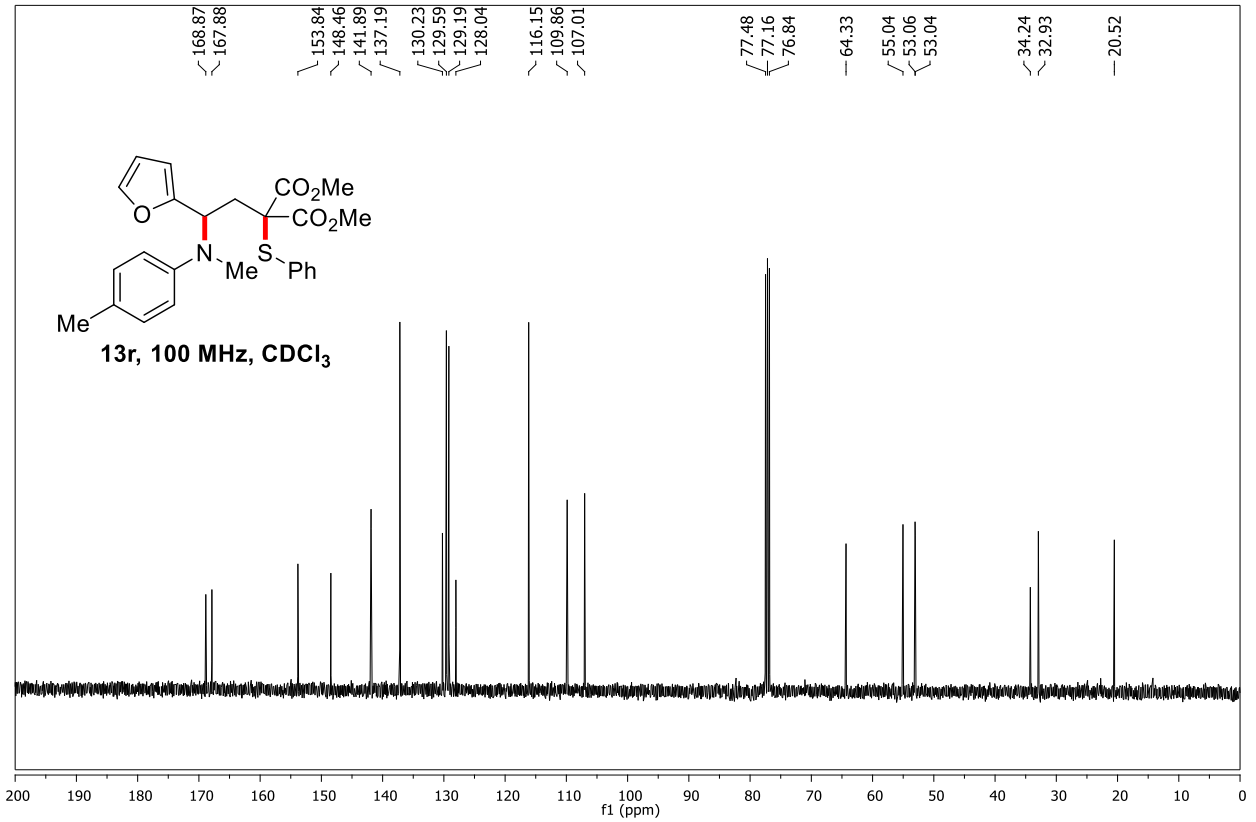
Dimethyl-2-(2-(methyl(*p*-tolyl)amino)-2-phenylethyl)-2-(phenylthio)malonate (13a)



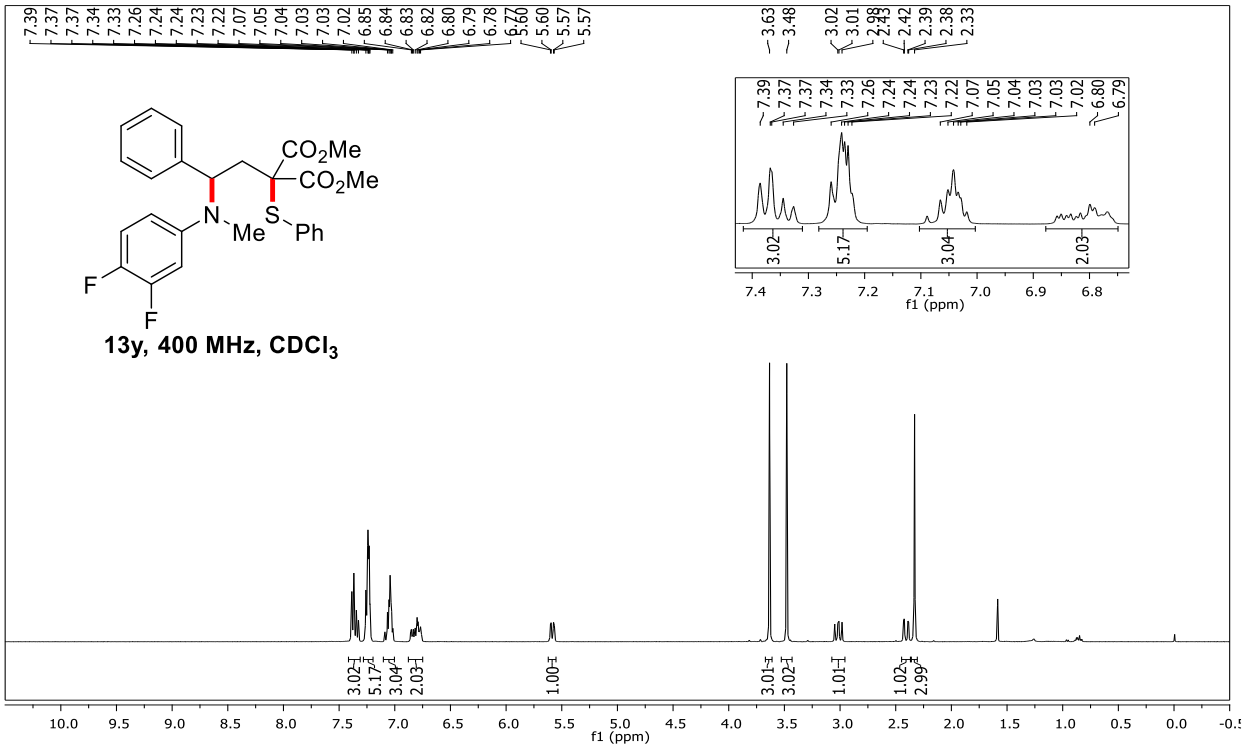


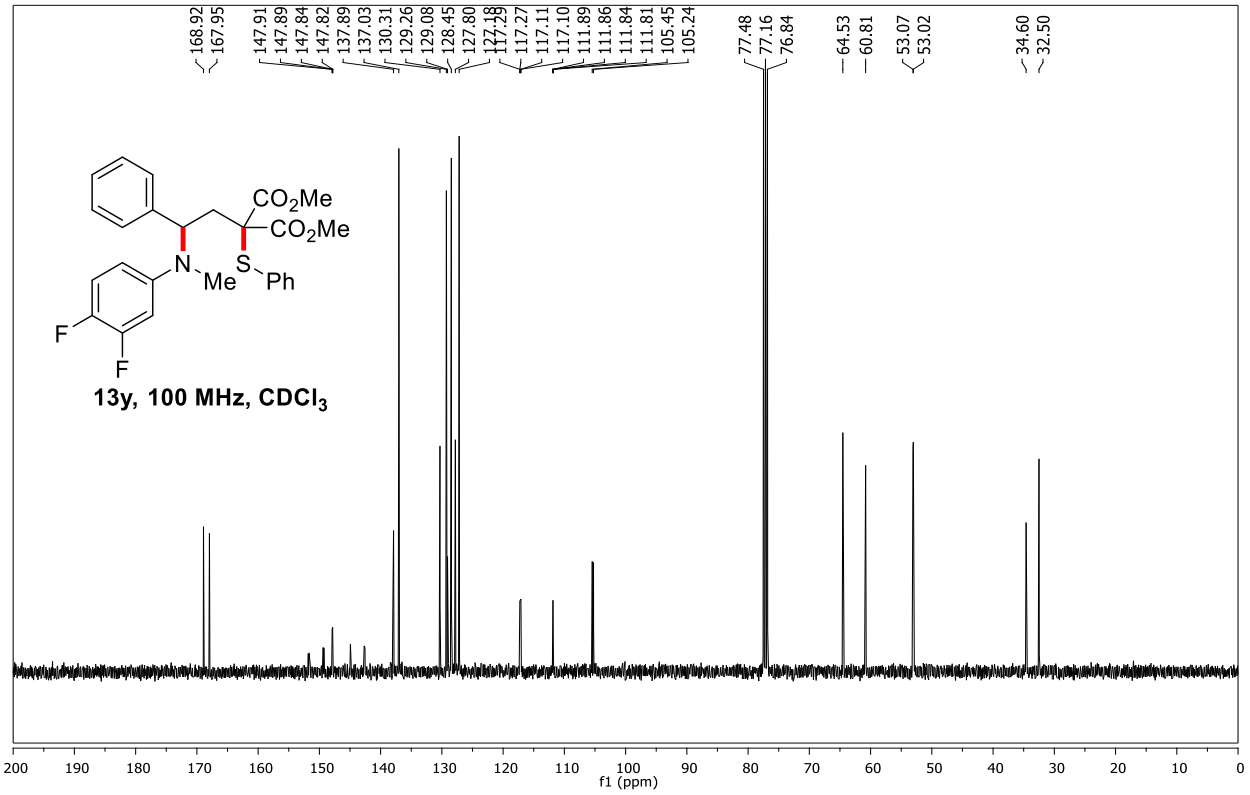
Dimethyl-2-(2-(furan-2-yl)-2-(methyl(*p*-tolyl)amino)ethyl)-2-(phenylthio)malonate (13r)





Dimethyl-2-(2-((3,4-difluorophenyl)(methyl)amino)-2-phenylethyl)-2-(phenylthio) malonate (13y)





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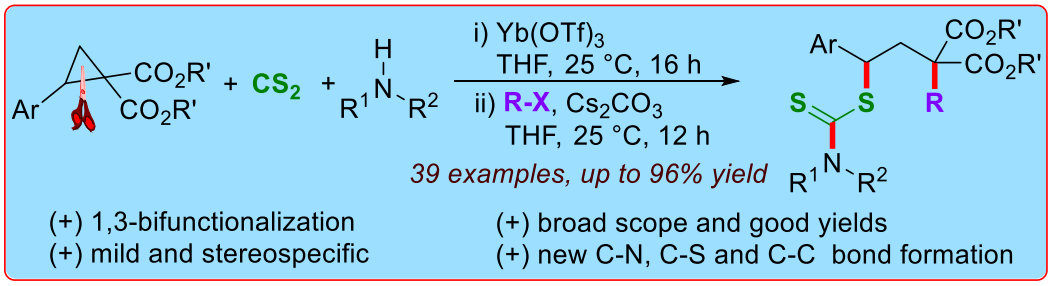
Chapter 7

Ring-Opening 1,3-Carbothiolation of Donor-Acceptor Cyclopropanes Using Alkyl Halides and in Situ Generated Dithiocarbamates

Ring-opening 1,3-carbothiolation of donor-acceptor (D-A) cyclopropanes employing alkyl halides and in situ generated dithiocarbamates (from amines and CS_2) has been demonstrated under mild conditions in this Chapter. The reaction is operationally simple and works with good functional group compatibility. Three new bonds including C-N, C-S and C-C are formed in this 1,3-bifunctionalization strategy. Electron-poor olefins can also be used as electrophiles instead of alkyl halides. The use of enantiomerically pure D-A cyclopropane afforded enantiopure 1,3-carbothiolated product thus demonstrating the stereospecificity of the reaction.



J. Org. Chem. **2022**, *87*, 6504.

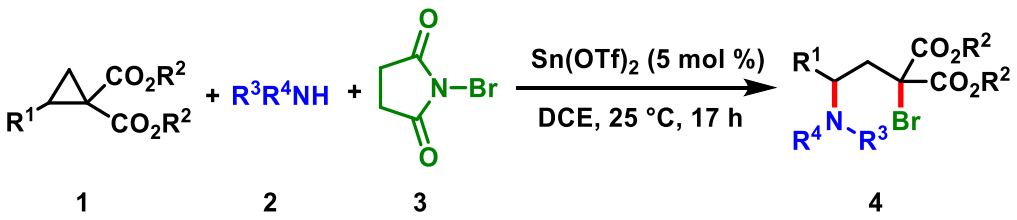
7.1. Introduction

Donor-acceptor (D-A) cyclopropanes have emerged as one of the popular, polarised three-carbon building blocks with potential applications in organic synthesis during the past several years.[1, 2] The cyclopropane ring is under strain due to the geometric constrains and can be ruptured in the presence of Lewis acids to generate 1,3-dipole.[3] The in situ generated 1,3-bipolar intermediate can be trapped in an annulation fashion with different carbon-carbon, carbon-heteroatom, and heteroatom-heteroatom bonds, leading to the synthesis of various carbocycles and heterocycles.[4] The Lewis acid catalyzed ring-opening reactions of D-A cyclopropanes is another area of interest in this field. Traditionally, in the absence of third electrophilic component, protic nucleophiles lead to the generation of monofunctionalized ring-opened products, and this chemistry is very well explored.[5] Although relatively less explored but another topic of recent interest in D-A cyclopropane chemistry is the 1,3-bifunctionalization.[6] This type of reactions can be accomplished either in multicomponent fashion or by the insertion of heteroatom-heteroatom bonds. The insertion reactions have been discussed in detail in the previous Chapter. Selected reports on multicomponent coupling reactions for 1,3-bifunctionalization of D-A cyclopropanes will be discussed in the upcoming section.

7.2. Multicomponent-Based 1,3-Bisfunctionalization of Donor-Acceptor Cyclopropanes

One of the seminal works in this area was uncovered by Studer and co-workers demonstrating the 1,3-aminobromination of D-A cyclopropanes **1** employing sulfonyl amides or electron-poor anilines **2** as the nucleophilic trigger and *N*-bromosuccinimide **3** as the source of bromine (Scheme 7.1).[7] The reaction proceeds under mild conditions with good functional group compatibility. $Sn(OTf)_2$ was found to be the optimized Lewis acid for this transformation and DCE being the optimum solvent. These γ-aminated α-brominated

Scheme 7.1. 1,3-Aminobromination of D-A Cyclopropanes

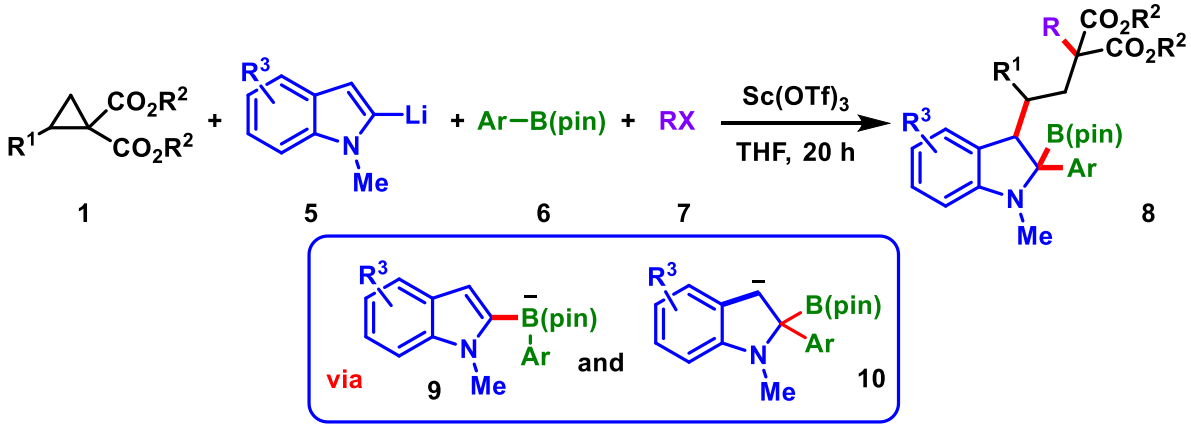


1 2 3 4

malonic diesters **4** also functioned as valuable substrates for the subsequent reactions to afford substituted γ-lactams and azetidines in good yields. Reaction with enantiopure D-A cyclopropanes proceeded with complete stereospecificity. Simple experimentation, ready access to starting materials, and good yields of products are the notable features for this transformation.

For the first time, the Studer group disclosed a four-component coupling reaction of D-A cyclopropanes involving indolyl boronate complexes **9** and alkyl halides **7**.[8] 2-Lithioindoles reacted with boronic esters to form the indolyl boronate complex which underwent dearomative coupling to form the desired product. Scandium triflate was found to be the optimum Lewis acid catalyst for this transformation. The reaction progressed with complete diastereoselectivity to afford indolines **8**. The formation of three C-C bonds and the construction of three contiguous stereocenters are the notable features for this transformation. The present transformation can tolerate several valuable functional groups, and, in most cases, the expected products were formed in moderate to good yields. The beneficial boron moiety is preserved in the product, thus offering useful options for further transformation.

Scheme 7.2. Four Component Coupling of D-A Cyclopropanes

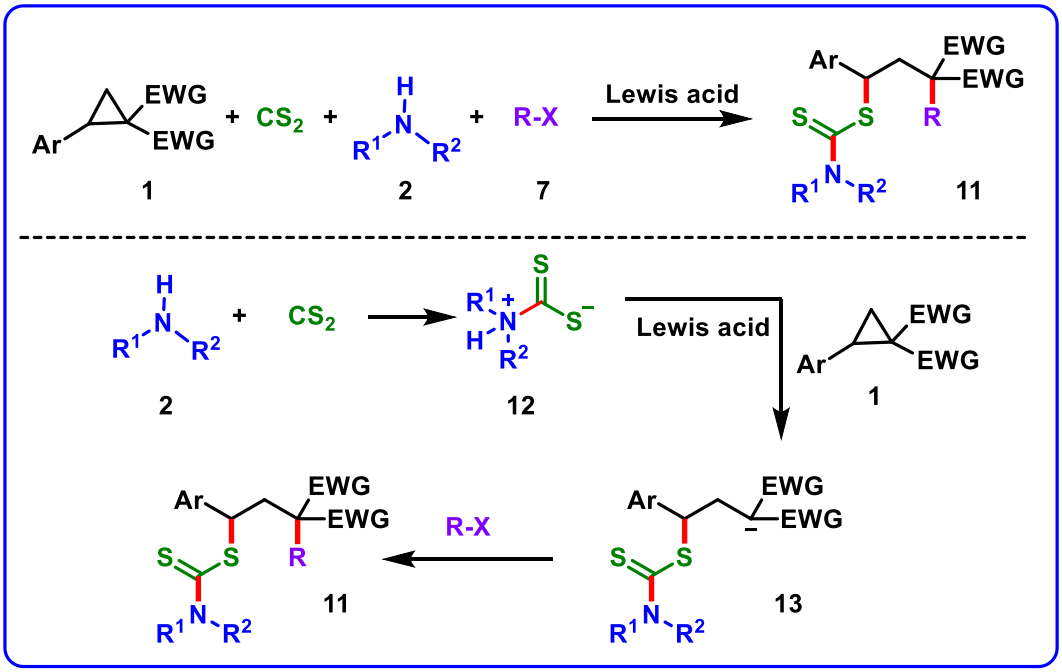


7.3. Statement of the Problem

Despite the limited number of multicomponent reactions documented in donor-acceptor cyclopropane chemistry, with the exception of the dearomative coupling reaction illustrated by the Studer group,[8] all other reactions are categorized as three-component coupling reactions. The pursuit of four-component coupling reactions poses significant challenges, but if successful, it has the potential to form three new chemical bonds.

Conversely, among numerous 1,3-bisfunctionalization reactions involving D-A cyclopropanes, the 1,3-carbothiolation reaction remains undiscovered. We hypothesized that dithiocarbamtaes **12** generated from the corresponding amines **2** and CS_2 can open D-A cyclopropanes in the presence of Lewis acid and the in situ generated carbanion **13** can be trapped with electrophilic fourth component i.e., alkyl halides **7** making 1,3-carbothiolation possible (Scheme 7.3). Notably, there are few challenges associated with this anticipated 1,3-carbothiolation reaction. The amines **2** can directly add to D-A cyclopropane **1** resulting in the synthesis of monofunctionalized ring-opened products before the dithiocarbamate formation.[9] Moreover, the in situ generated dithiocarbamate **12** can directly add to the alkyl halide **7**.[10] As a consequence of careful optimization studies, herein we demonstrate the 1,3-carbothiolation of D-A cyclopropanes. It may be noted in this context that functionalized dithiocarbamates are important because of the medicinal application of these compounds.[11]

Scheme 7.3. 1,3-Carbothiolation of D-A Cyclopropanes



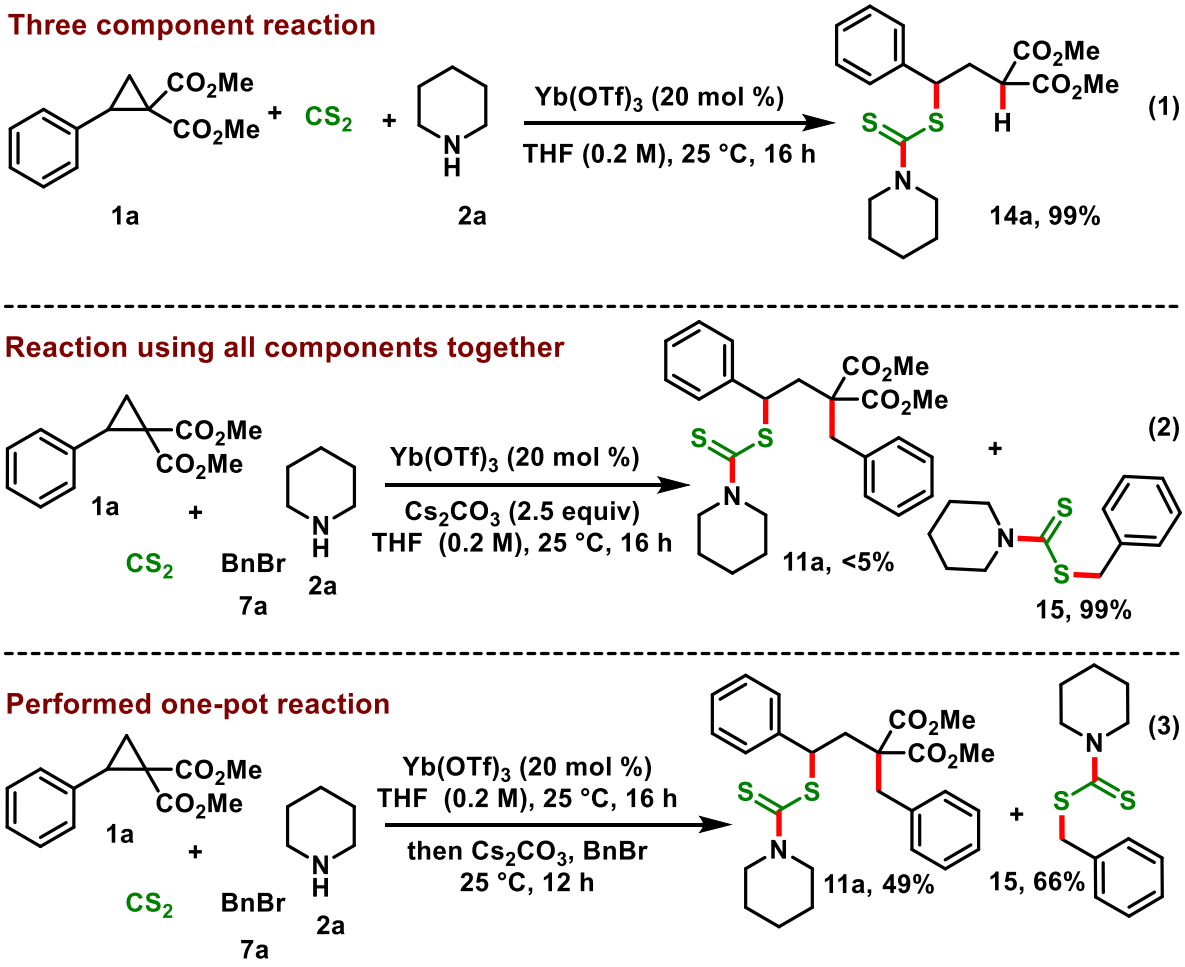
7.4. Results and Discussion

7.4.1. Initial Studies

To validate our hypothesis, we initially investigated the three-component coupling reaction to determine if the dithiocarbamate could effectively open the D-A cyclopropane ring. Encouragingly, when cyclopropane **1a** was treated with piperidine **2a** and CS_2 in the

presence of $Yb(OTf)_3$ in THF at 25 °C, the desired monofunctionalized ring-opened product **14a** was successfully formed in 99% yield (Scheme 7.4, eq 1). Impressed by this reactivity, we introduced benzyl bromide **7a** as the electrophilic fourth component in the presence of Cs_2CO_3 as a base. Unfortunately, the anticipated four-component coupling did not occur. Instead, the dithiocarbamate directly added to benzyl bromide **7a**, leading to the formation of benzyl piperidine-1-carbodithioate **15** (eq 2). Consequently, we conducted a one-pot reaction where benzyl bromide and Cs_2CO_3 were added after 12 hours. Under the current reaction conditions, the four-component product **11** was obtained with a yield of 49%. However, it is important to note that the benzyl piperidine-1-carbodithioate **15** was also produced with 66% yield (eq 3). Effort to improve the yield of four-component coupling was not successful and thus two step strategy was chosen for the current 1,3-carbothiolation reaction.

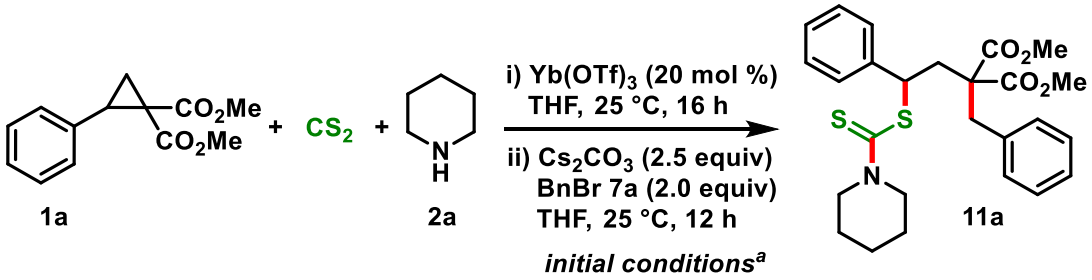
Scheme 7.4. Study towards the Four-Component Reaction



7.4.2. Optimization Studies

The present study was initiated by treating the cyclopropane **1a** with piperidine **2a** and CS_2 in the presence of $Yb(OTf)_3$ in THF at 25 °C. This was followed by the treatment of benzyl bromide **7a** and Cs_2CO_3. Interestingly, under these conditions, the desired 1,3-carbothiolated product **11a** was formed in 95% isolated yield (Table 7.1, entry 1). Decreasing the stoichiometry of CS_2 reduced the yield of **11a** to 63% (entry 2). Moreover, reducing the amount of **2a** and **7a** also resulted in lower yields of the product (entries 3, 4). The required $Yb(OTf)_3$ amount was 20 mol % and the reaction performed using 10 mol % of the Lewis acid also reduced the yield of **11a** (entry 5). Other Lewis acid such as $Sc(OTf)_3$ and $Sn(OTf)_2$ were found to be incompetent for this transformation (entries 6, 7). The reaction performed in other solvents such as dichloroethane and CH_2Cl_2 returned the product in 16% and 84%

Table 6.1. Optimization of the Reaction Conditions



entry	variation from the initial conditions	yield of 11a (%)[b]
1	*none*	*96 (95)*[c]
2	1.2 equiv of CS_2	63
3	1.2 equiv of **2a**	61
4	1.2 equiv of **7a**	57
5	10 mol% of $Yb(OTf)_3$	43
6	$Sc(OTf)_3$ instead of $Yb(OTf)_3$	24
7	$Sn(OTf)_2$ instead of $Yb(OTf)_3$	16
8	DCE instead of THF	16
9	CH_2Cl_2 instead of THF	84
10	1.2 equiv of Cs_2CO_3	51
11	K_2CO_3 instead of Cs_2CO_3	49
12	KO*t*-Bu instead of Cs_2CO_3	41

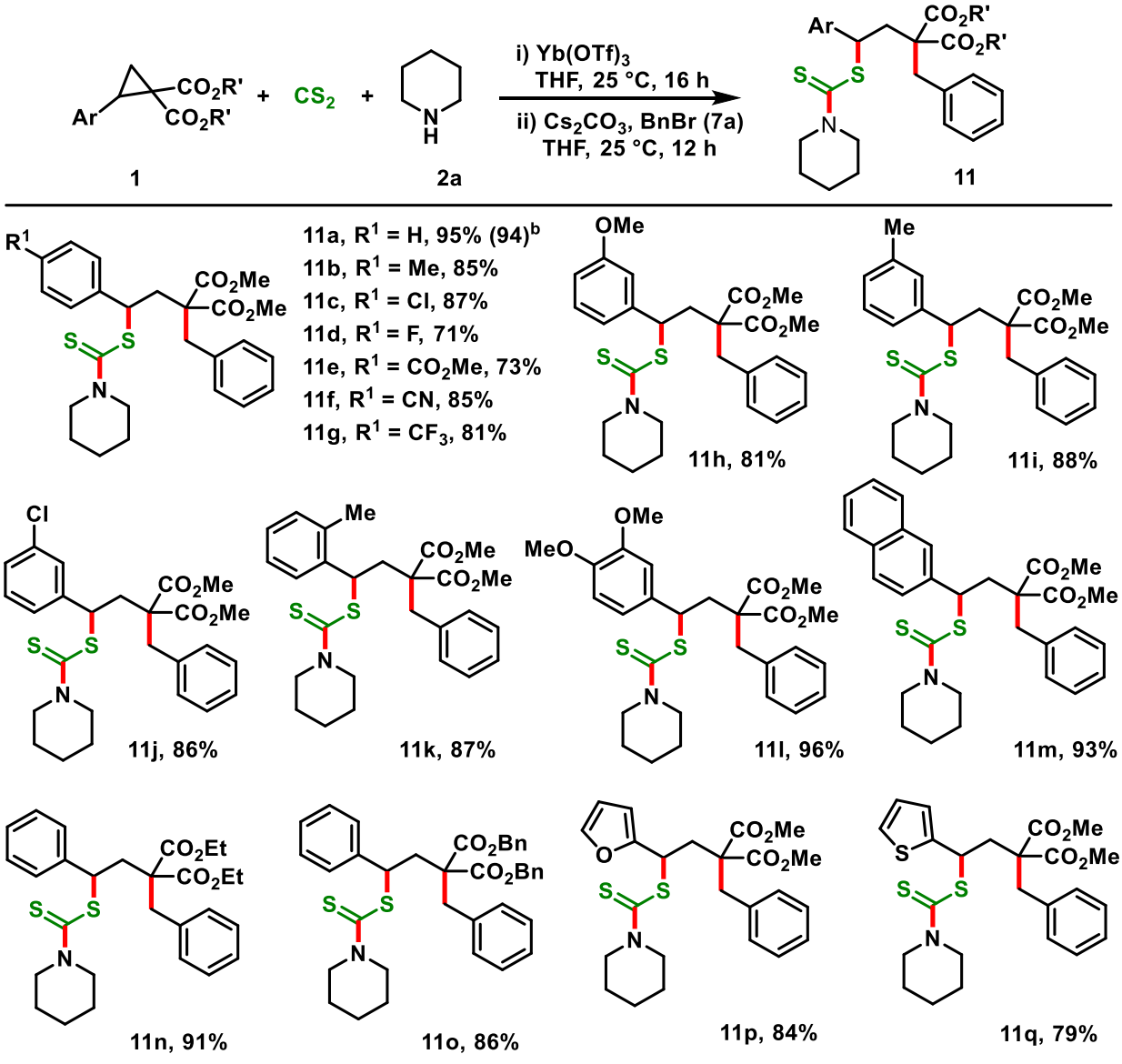
[a] Initial conditions: **1a** (0.2 mmol), CS_2 (0.3 mmol), **2a** (0.3 mmol), $Yb(OTf)_3$ (20 mol%), THF (1.0 mL), 25 °C for 16 h, filtration and evaporation of solvent, then BnBr **7a** (2.0 equiv), Cs_2CO_3 (2.5 equiv), THF (1.5 mL), 12 h. [b] Yields based on the ^1H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard. [c] Isolated yield.

yield respectively (entries 8, 9). Excess of Cs_2CO_3 was required (2.5 equiv) for the alkylation step as the reaction using 1.2 equiv afforded **11a** in only 51% yield (entry 10). In addition, use of other bases such as K_2CO_3 and KO^{t}Bu instead of Cs_2CO_3 provided reduced yield of **11a** (entries 11, 12). Thus entry 1 was taken forward for the substrate scope study.

7.4.3. Substrate Scope of 1,3-Carbothiolation of D-A Cyclopropanes: Scope of D-A Cyclopropanes

Having the optimized reaction conditions for this 1,3-carbothiolation reaction in

Scheme 7.5. Substrate Scope: Variation of D-A Cyclopropanes



[a] General conditions: **1** (0.2 mmol, 1.0 equiv), CS_2 (0.3 mmol), **2a** (0.3 mmol), $Yb(OTf)_3$ (20 mol %), THF (1 mL), 25 °C for 16 h, filtration and evaporation of solvent, then Cs_2CO_3 (2.5 equiv), BnBr **7a** (2 equiv), THF (1.5 mL), 12 h. Yields of the isolated products are given. [b] The yield of **11a** on a 1.0 mmol scale reaction.

hand, the substrate scope of the reaction has been examined. First, we investigated the scope of various D-A cyclopropanes in this 1,3-bifunctionalization reaction (Scheme 7.5). A wide variety of structurally and electronically different D-A cyclopropanes bearing electron-releasing, -neutral, and -withdrawing substituents at the 4-position of the benzene ring on the donor terminal underwent smooth reaction and the corresponding products were formed in good to excellent yields (**11a**-**11g**). In the case of **11a**, performing the reaction on 1.0 mmol scale, the desired product was formed in 94% yield signifying the scalable nature of this present multicomponent coupling reaction. Furthermore, D-A cyclopropanes bearing substitution at the 3- and 2- positions on the aryl moieties worked well under the present optimized conditions and the expected products were formed in good yields (**11h**-**11k**). Notably, a dimethoxy substituted cyclopropane also worked well under the optimized conditions to afford the product **11l** in 96% yield. The naphthyl moiety was tolerated nicely as a donor and ethyl and benzyl esters also provided the expected products in good yields (**11m**-**11o**). Finally, heteroaryl groups were also used as donors and these reactions furnished the target products in good yields (**11p**-**11q**).

7.4.4. Substrate Scope of 1,3-Carbothiolation of D-A Cyclopropanes: Scope of Amines

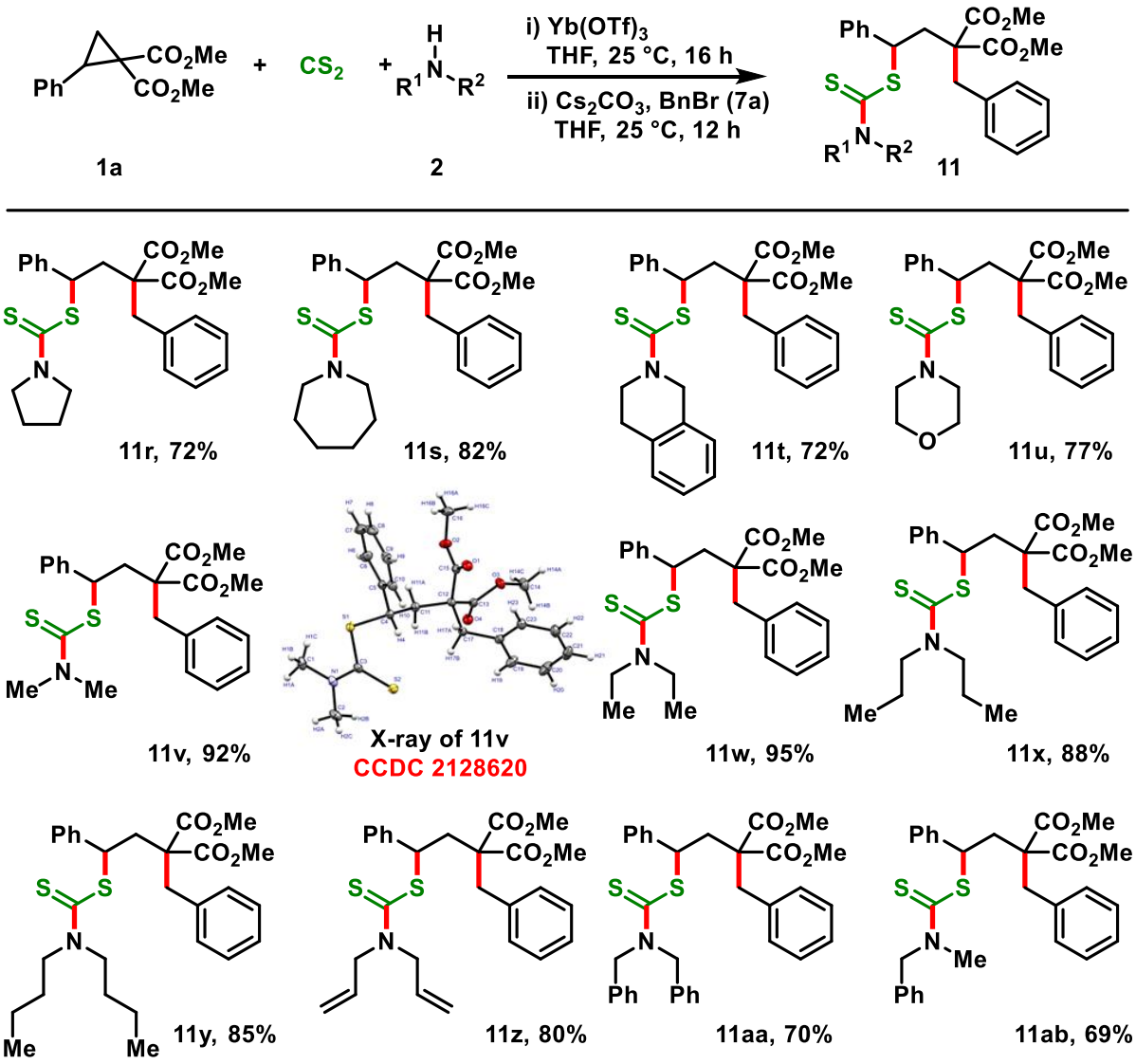
A wide variety of structurally diverse cyclic secondary aliphatic amines with varying ring size functioned well under the present reaction conditions and thus provided the corresponding 1,3-bifunctionalized products in good yields (**11r**-**11u**) (Scheme 7.6). Additionally, a series of symmetrical and unsymmetrical acyclic secondary aliphatic amines furnished the expected 1,3-carbothiolated products in good yields (**11v**-**11ab**). In the case of **11v**, the product structure was confirmed using X-ray analysis of the crystals.

7.4.5. Substrate Scope of 1,3-Carbothiolation of D-A Cyclopropanes: Scope of Alkyl Halides

To check the generality of this reaction, several electrophiles were tested under the optimized reaction conditions and delightfully in every case the desired products were

formed in good to excellent yields (Scheme 7.7). Alkyl halides such as methyl iodide, ethyl iodide, allyl bromide, and propargyl bromide furnished the expected products in good yields (**11ac-11af**). Moreover, benzyl bromide derivatives bearing substitution on the 4-position and 2-position of the benzene ring were well tolerated and the corresponding 1,3-bifunctionalized products were formed in good yields (**11ag-11aj**). Finally, cinnamyl

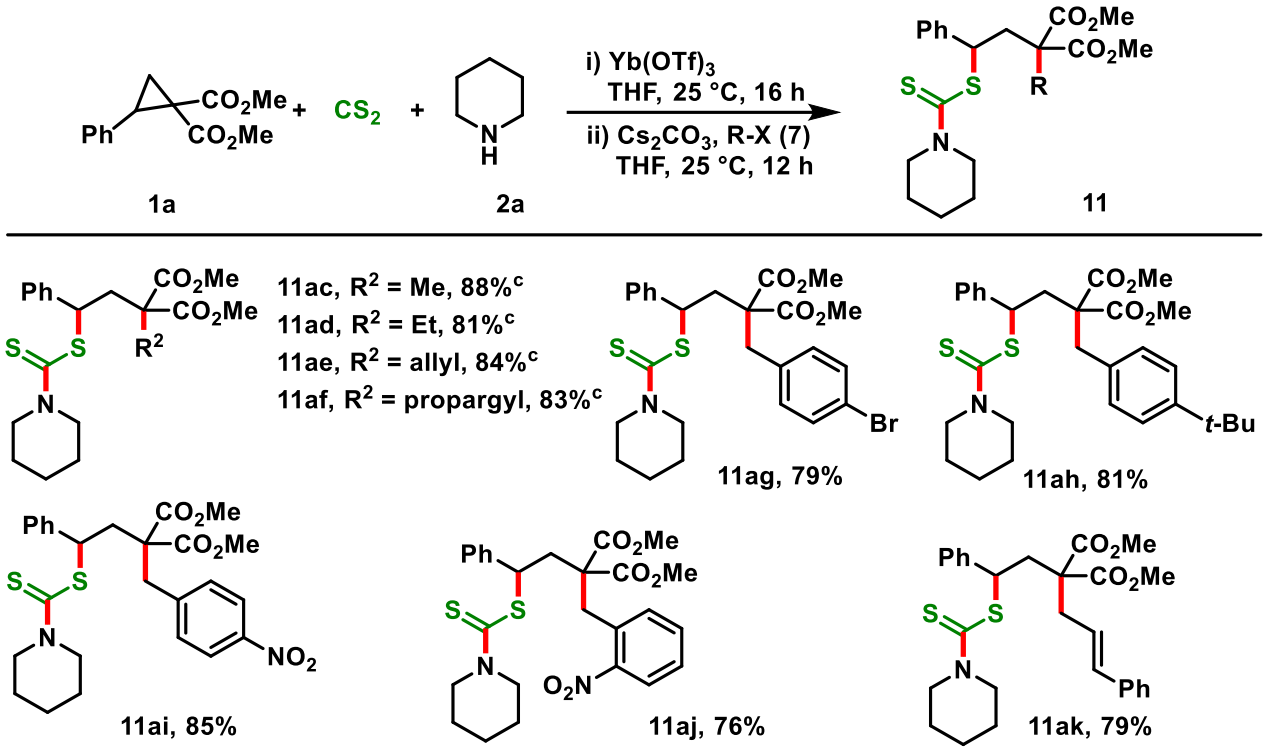
Scheme 7.6. Substrate Scope: Variation of Amines



[a] General conditions: **1a** (0.2 mmol, 1.0 equiv), CS_2 (0.3 mmol), **2** (0.3 mmol), $Yb(OTf)_3$ (20 mol %), THF (1 mL), 25 °C for 16 h, filtration and evaporation of solvent, then Cs_2CO_3 (2.5 equiv), BnBr **7a** (2 equiv), THF (1.5 mL), 12 h. Yields of the isolated products are given.

bromide could also act as the electrophilic fourth component, thus broadening the scope of the reaction further (**11ak**).

Scheme 7.7. Substrate Scope: Variation of Alkyl Halides

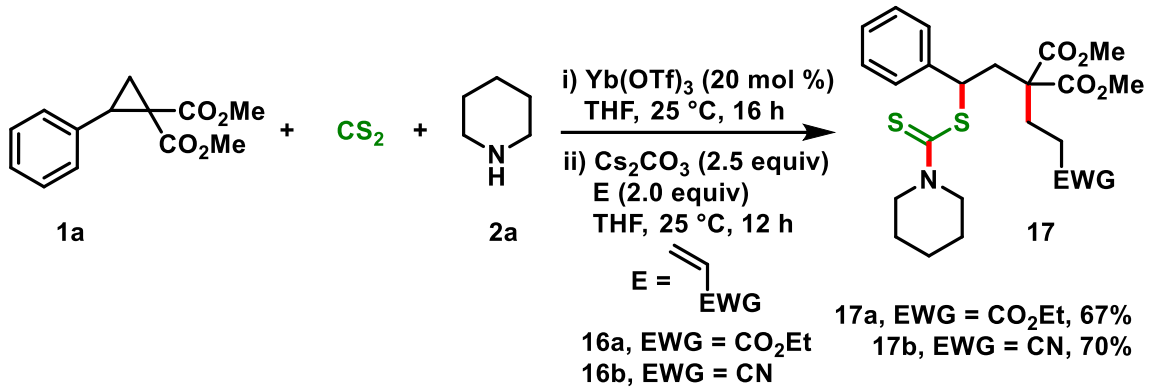


[a] General conditions: **1a** (0.2 mmol, 1.0 equiv), CS_2 (0.3 mmol), **2a** (0.3 mmol), $Yb(OTf)_3$ (20 mol %), THF (1 mL), 25 °C for 16 h, filtration and evaporation of solvent, then Cs_2CO_3 (2.5 equiv), R-X **7** (2 equiv), THF (1.5 mL), 12 h. Yields of the isolated products are given. [c] 3.0 equiv of R-X was used.

7.4.6. Substrate Scope of 1,3-Carbothiolation of D-A Cyclopropanes: Scope of Electron-Deficient Olefins

The present 1,3-carbothiolation reaction is not limited to alkyl halides as electrophilic component, but electron-poor olefins could also be used as the electrophilic component. When the reaction was conducted in the presence of ethyl acrylate **16a** as the electrophile, the 1,3-carbothiolated product **17a** was formed in 67% yield (Scheme 7.8). Similar results were obtained using acrylonitrile **16b** and the product **17b** was formed in 70% yield. The ring-opening of D-A cyclopropanes using dithiocarbamates was followed by a Michael addition in this case.

Scheme 7.8. Substrate Scope: Variation of Electron-Deficient Olefins

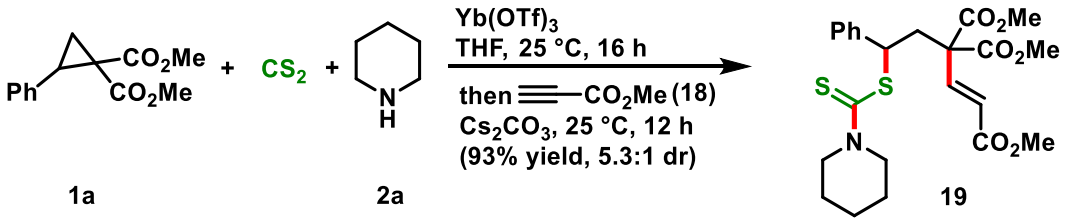


[a] General conditions: **1a** (0.2 mmol, 1.0 equiv), CS_2 (0.3 mmol), **2a** (0.3 mmol), $Yb(OTf)_3$ (20 mol %), THF (1 mL), 25 °C for 16 h, filtration and evaporation of solvent, then Cs_2CO_3 (2.5 equiv), E **16** (2 equiv), THF (1.5 mL), 12 h. Yields of the isolated products are given.

7.4.7. One-pot 1,3-Carbothiolation of D-A Cyclopropane

Interestingly, the reaction can be performed in a one-pot manner when methyl propiolate **18** was used as the electrophilic forth component. In slightly modified reaction conditions, the expected 1,3-carbothiolated product **19** was formed in 93% yield and 5.3:1 diastereomeric ratio (Scheme 7.9).

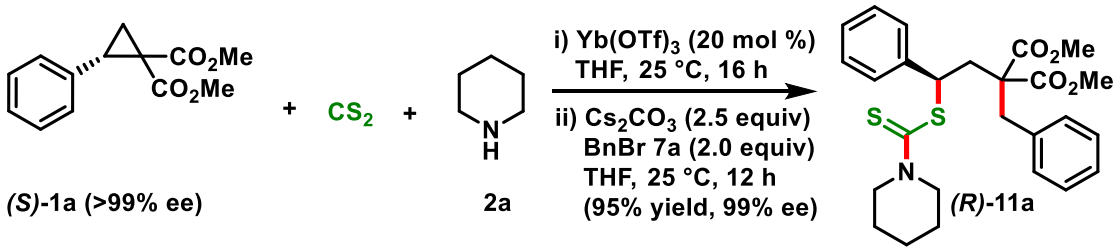
Scheme 7.9. One-pot 1,3-Carbothiolation of D-A Cyclopropanes



7.4.8. Stereospecific 1,3-Carbothiolation

To shed light on the mode of addition of dithiocarbamate to D-A cyclopropanes, an

Scheme 7.10. Stereospecific Reaction

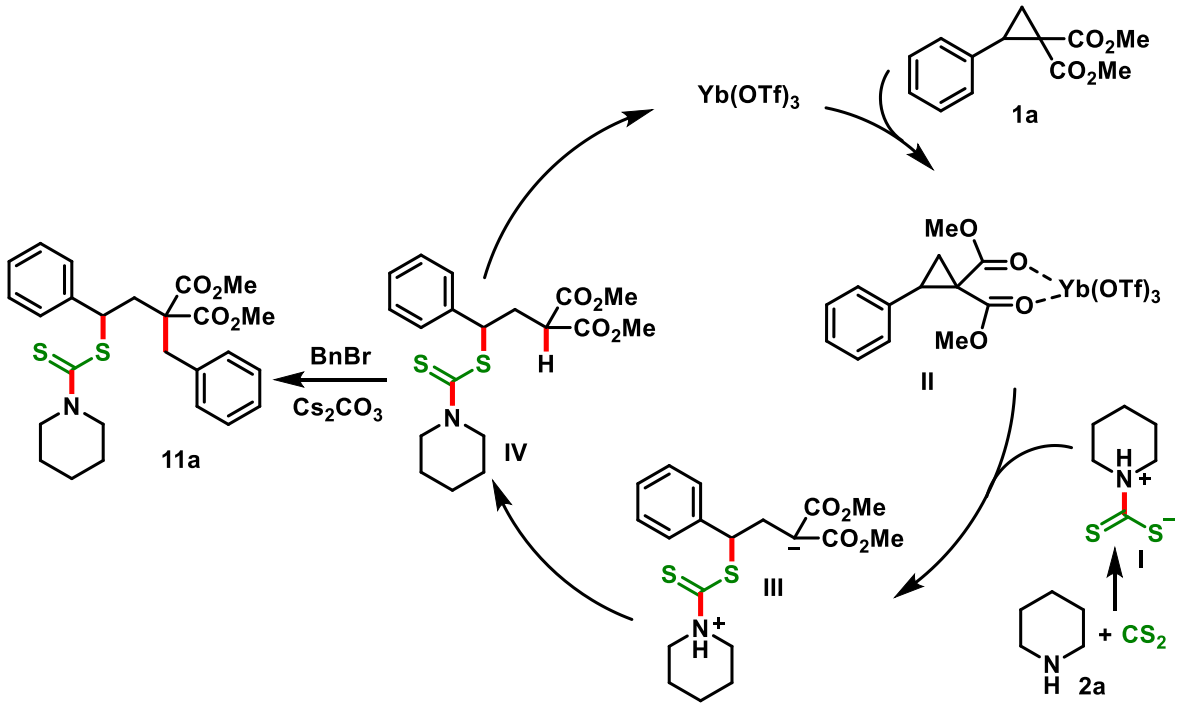


experiment was conducted using enantiomerically pure D-A cyclopropanes (Scheme 7.10). When the multicomponent reaction was carried in the presence of (*S*)-**1a**, the 1,3-carbothiolated product (*R*)-**11a** was isolated in 95% yield and 99% ee. This study sheds light on the S_N2-type addition of in situ generated dithiocarbamates on D-A cyclopropanes.

7.4.9. Proposed Catalytic Cycle

Mechanistically, the reaction proceeds via the nucleophilic addition of amine **2a** to CS_2 leading to the generation of the dithiocarbamate intermediate **I**. This dithiocarbamate **I** undergoes nucleophilic addition to Lewis acid activated D-A cyclopropane **II** to form the ring-opened intermediate **III**. The intermediate **III** undergoes a proton transfer step to produce the monofunctionalized intermediate **IV**, which undergoes deprotonation (using Cs_2CO_3) followed by the benzylation to furnish the desired carbothiolated product **11a**.

Scheme 7.11. Proposed Mechanism of the Reaction



7.5 Conclusion

In conclusion, ring-opening 1,3-carbothiolation of D-A cyclopropanes employing amines, CS_2, and alkyl halides has been demonstrated. [12] Not only alkyl halides but electron-deficient olefins could also be used as the electrophilic component in this reaction and in the presence of methyl propiolate the reaction can also be done in a one-pot manner. Mild

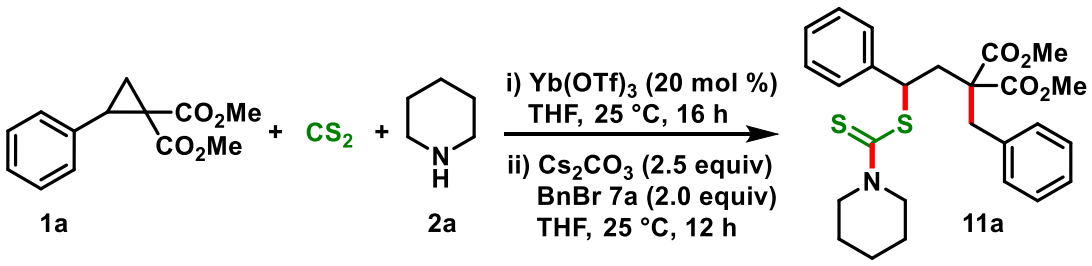
conditions, good functional group compatibility, selective product formation, three new bond formation and broad scope are the noteworthy features of this present 1,3-bifunctionalization reaction. The stereospecific nature of the reaction, proceeding via an S_N2-like ring-opening was confirmed by the reaction carried out using enantiopure cyclopropane.[13]

7.6. Experimental Details

7.6.1. General Information

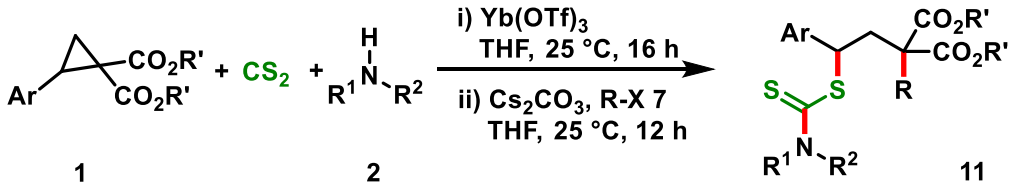
Unless otherwise specified, all reactions were carried out under an atmosphere of argon in flame-dried reaction vessels with Teflon screw caps. 25 °C corresponds to the room temperature of the lab when the experiments were carried out. THF was freshly purified by distillation over Na-benzophenone and was transferred under nitrogen. $Yb(OTf)_3$ and Cs_2CO_3 were purchased from commercial sources and was stored in argon filled Glove-box. All the amines, and CS_2 were purchased from Alfa Aesar, TCI, Sigma-Aldrich or Spectrochem and used directly as received. All D-A cyclopropane derivatives were synthesized following known literature procedures.[14] Analytical thin layer chromatography was performed on TLC Silica gel 60 F254. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Unless and otherwise specified flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker Ultrashield spectrometer in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Infrared (FT-IR) spectra were recorded on a Bruker Alfa FT-IR, ν-max in cm^{-1}. HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument.

7.6.2. General Procedure for the Optimization of the Reaction Conditions



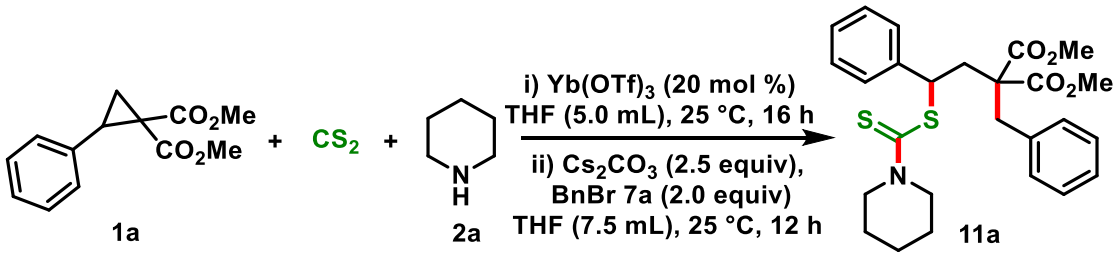
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added piperidine **2a** and CS_2 in 1 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) and $Yb(OTf)_3$ were added and then the reaction mixture was allowed to stir at 25 °C for 16 h. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated, and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 μL, 0.4 mmol) and then stirred for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated, and the crude mixture was passed through a pad of silica gel and eluted with EtOAc (3x10 mL). The reaction mixture was concentrated under reduced pressure and then the yield of **11a** was determined by the ^1H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard.

7.6.3. General Procedure for 1,3-Carbothiolation of D-A Cyclopropanes



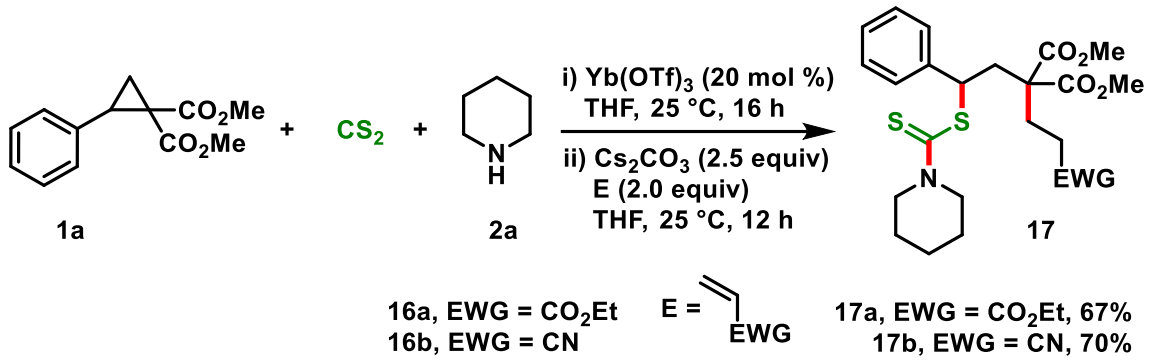
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added amine **2** (0.3 mmol) and CS_2 (0.023 g, 18 μL, 0.3 mmol) in 1 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution D-A cyclopropane **1** (0.2 mmol) and $Yb(OTf)_3$ (0.025 g, 0.04 mmol) were added and then the reaction mixture was allowed to stir at 25 °C for 16 h. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated, and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and alkyl halide **7** (2 or 3 equiv) and then stirring for 12 h. After 12 h, the solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet.ether-EtOAc as eluent) to afford the corresponding 1,3-carbothiolated product **11** in moderate to good yields.

Procedure for the 1.0 mmol Scale Reaction for the Synthesis of 11a



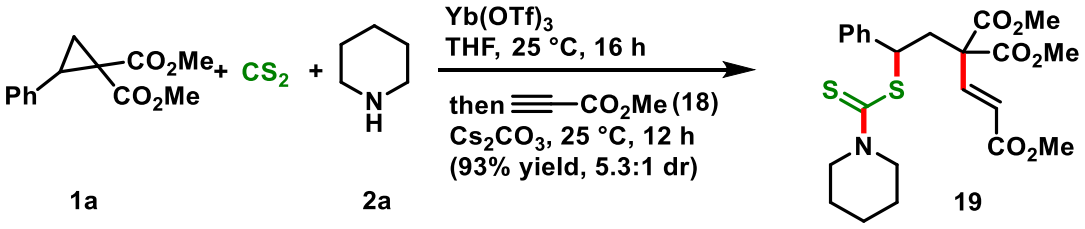
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added piperidine **2a** (0.128 g, 148 µL, 1.5 mmol), and CS_2 (0.114 g, 90 µL, 1.5 mmol) in 5 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.234 g, 1.0 mmol) and $Yb(OTf)_3$ (0.124 g, 0.2 mmol) were added and then the reaction mixture was allowed to stir at 25 °C for 16 h. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (10.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (50 mL). The solvent was evaporated, and the crude product was dissolved in THF (7.5 mL), followed by the addition of Cs_2CO_3 (0.814 g, 2.5 mmol) and (bromomethyl)benzene **7a** (0.342 g, 238 µL, 2.0 mmol) and then stirred for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 85/15) to afford dimethyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11a** as yellow oil (0.456 g, 94% yield).

7.6.4. General Procedure for 1,3-Carbothiolation of D-A Cyclopropanes Employing Electron Deficient Olefines



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), and CS_2 (0.023 g, 18 µL, 0.3 mmol) in 1 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) and $Yb(OTf)_3$ (0.025 g, 0.04 mmol) were added and then the reaction mixture was allowed to stir at 25 °C for 16 h. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated, and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and electron deficient olefins **16** (0.4 mmol, 2 equiv) and then stirring for 12 h. After 12 h, the solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet.ether-EtOAc as eluent) to afford the corresponding 1,3-carbothiolated product **17** in moderate to good yields.

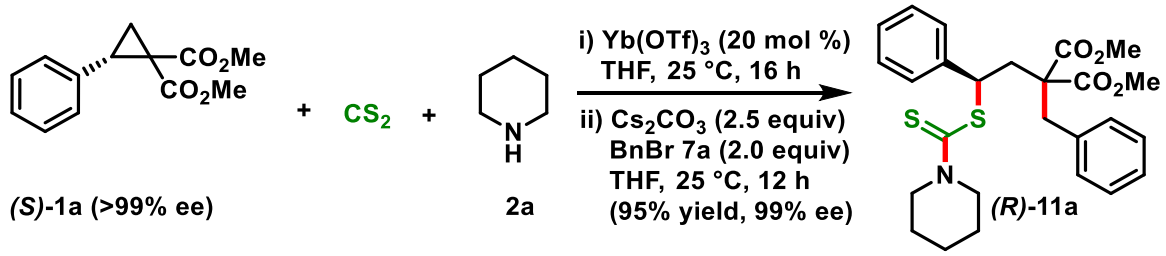
7.6.5. General Procedure for One-pot 1,3-Carbothiolation of D-A Cyclopropanes



To a flame-dried screw-capped test tube equipped with a magnetic stir bar were added amine **2a** (0.034 g, 39 µL, 0.4 mmol) and CS_2 (0.030 g, 24 µL, 0.4 mmol) in 1.5 mL of THF under a nitrogen atmosphere. The reaction mixture was stirred for 5 min, and then to the stirring solution were added D-A cyclopropane **1a** (0.047 g, 0.2 mmol) and $Yb(OTf)_3$ (0.025 g, 0.04 mmol). The reaction mixture was stirred at 25 °C for 16 h. After 16 h, Cs_2CO_3 (0.163 g, 0.5 mmol) and methyl propiolate **18** (0.034 g, 36 µL, 0.4 mmol) were added and stirred for 12 h. After 12 h, the solvent was evaporated, and the crude residue was pre adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 84/16) of the crude reaction mixture afforded trimethyl (*E*)-5-phenyl-5-((piperidine-1

carbonothioyl)thio)pent-1-ene-1,3,3-tricarboxylate **19** as yellow oil (0.089 g, 93% yield with 5.3:1 dr).

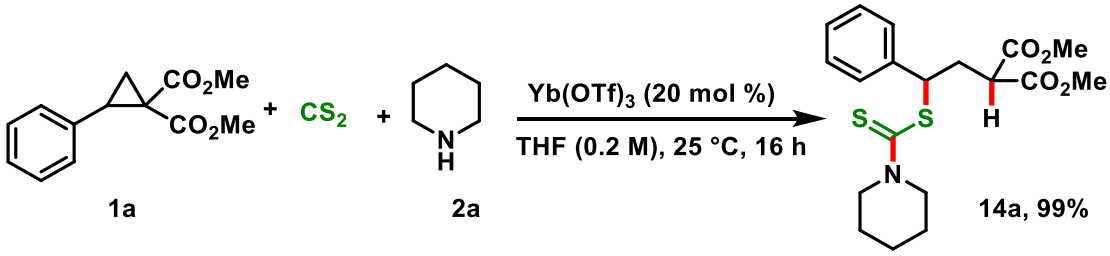
7.6.6. General Procedure for 1,3-Carbothiolation of Enantiopure D-A Cyclopropane



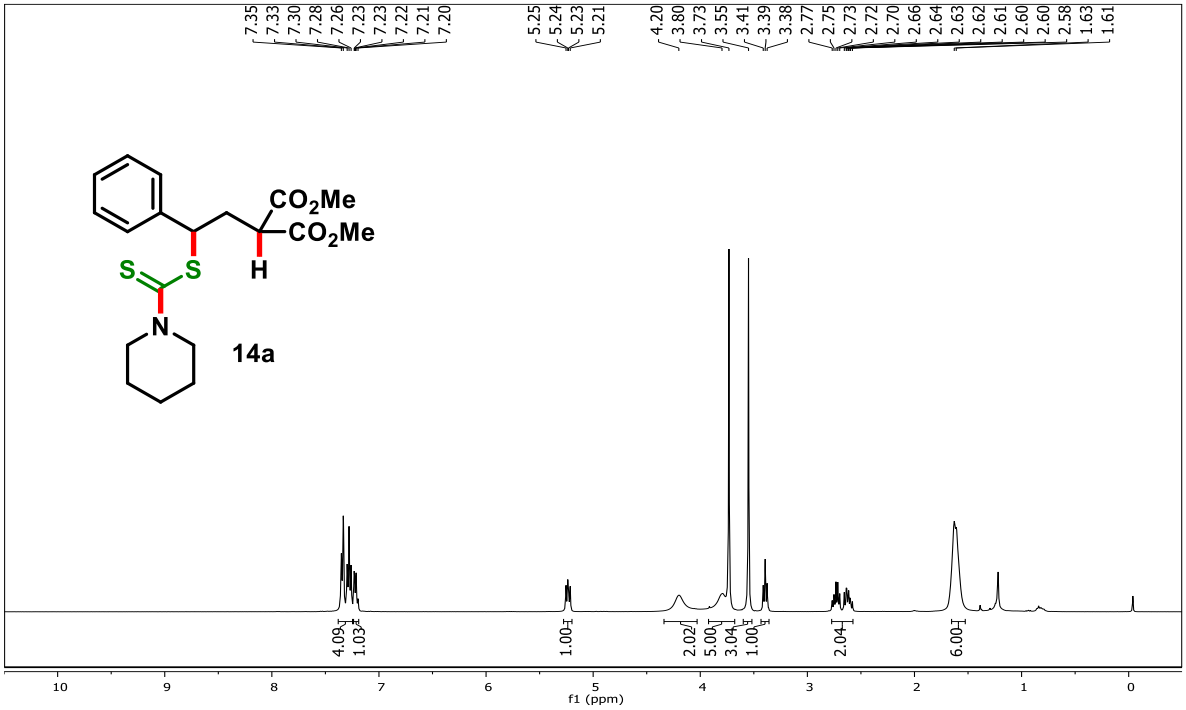
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), and CS_2 (0.023 g, 18 µL, 0.3 mmol) in 1 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution enantiopure cyclopropane (*S*)-**1a** (0.047 g, 0.2 mmol) and $Yb(OTf)_3$ (0.025 g, 0.04 mmol) were added and then the reaction mixture was allowed to stir at 25 °C for 16 h. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated, and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h. After 12 h, the solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 85/15) to afford (*R*)-**11a** in 95% yield and 99% ee. (*The absolute stereochemistry of the chiral centre was not unequivocally determined*)

7.6.7. Experiments for Envisioned Four-Component 1,3-Carbothiolation Reaction

(a) Three-Component Coupling Reaction

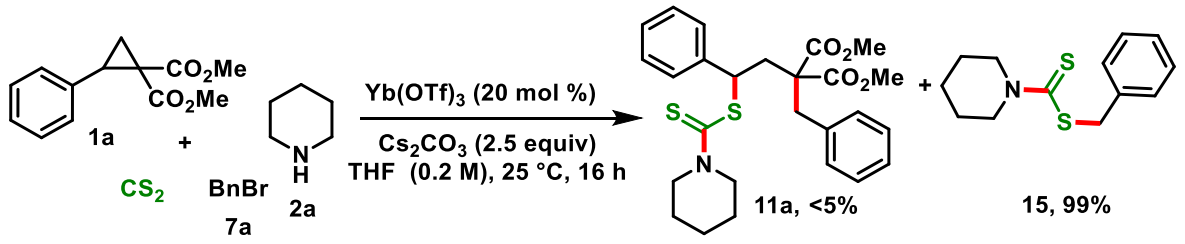


To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added piperidine **2a** (0.026 g, 30 µL, 0.3 mmol) and CS_2 (0.023 g, 18 µL, 0.3 mmol) in 1 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) and $Yb(OTf)_3$ (0.025 g, 0.04 mmol) were added and then the reaction mixture was allowed to stir at 25 °C for 16 h. . After 16 h, the solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 85/15) to afford dimethyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate **14a** as yellow oil (0.078 g, 99% yield).

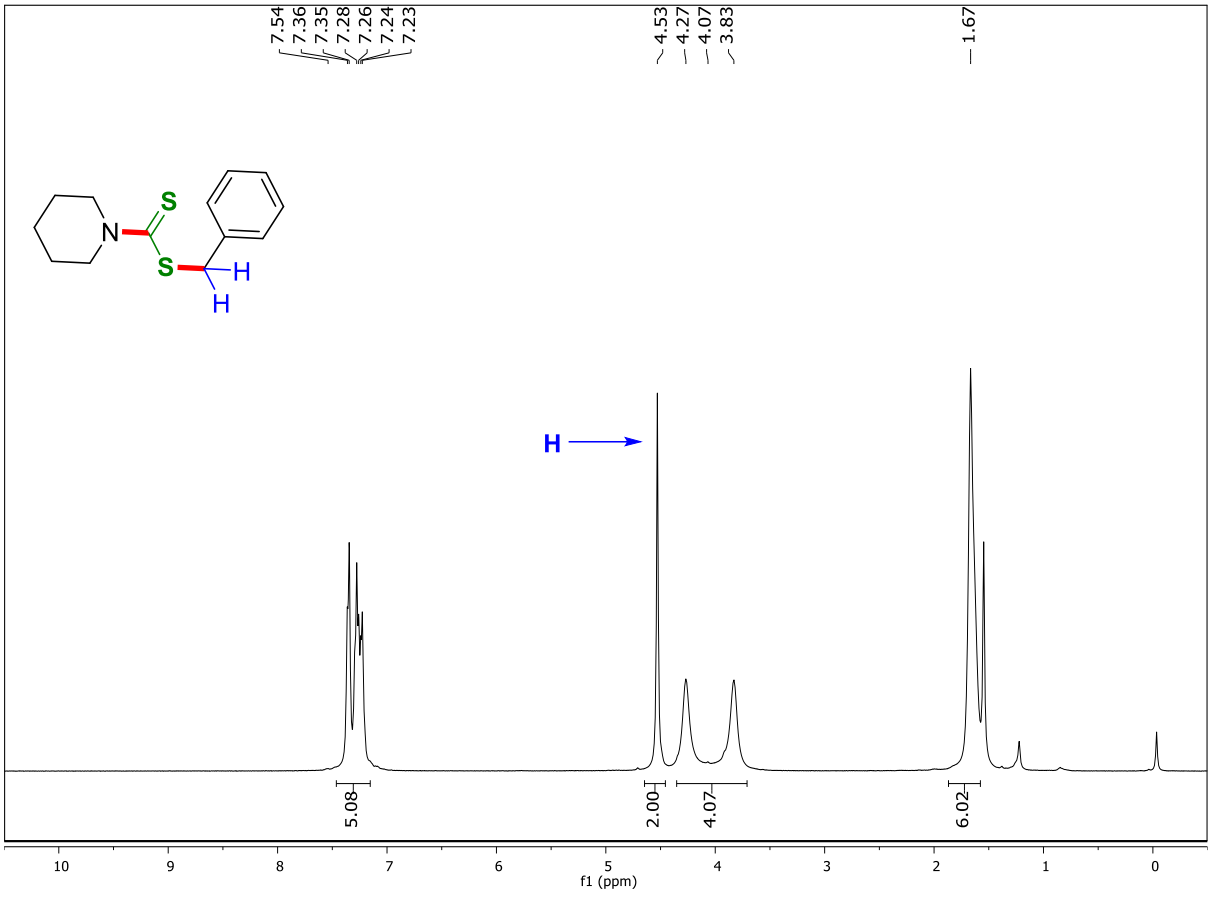


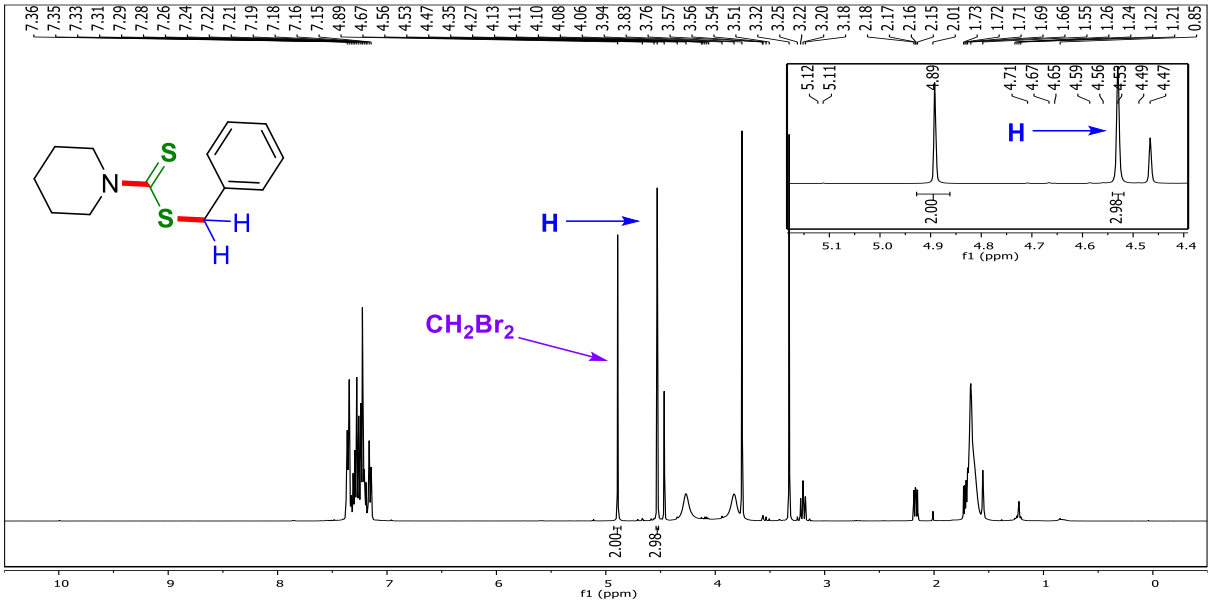
This study indicates that the nucleophilic ring-opening of D-A cyclopropanes using dithiocarbamates is feasible.

(b) Envisioned Four-Component Approach



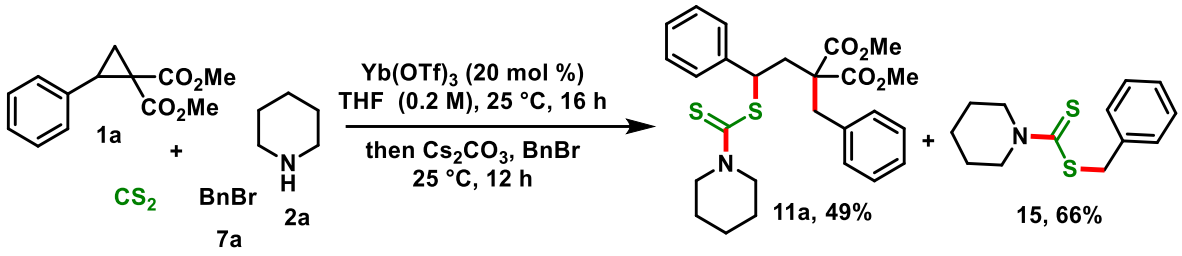
To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), and CS_2 (0.023 g, 18 µL, 0.3 mmol) in 1 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) and $Yb(OTf)_3$ (0.025 g, 0.04 mmol) were added followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 16 h. After 16 h, the reaction was stopped, the solvent was evaporated, and the crude mixture was passed through a pad of silica gel and eluted with EtOAc (3x10 mL). The reaction mixture was concentrated under reduced pressure and then the yield of **11a** and **15a** was determined by the ^1H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard.



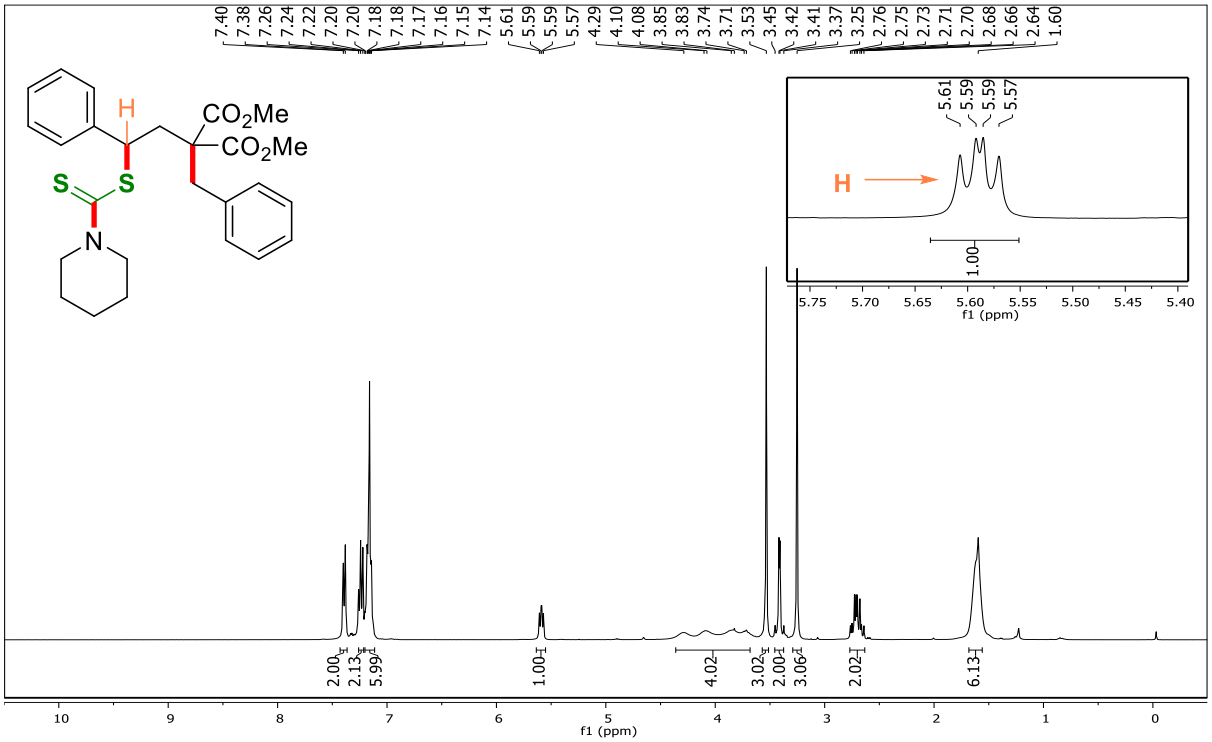


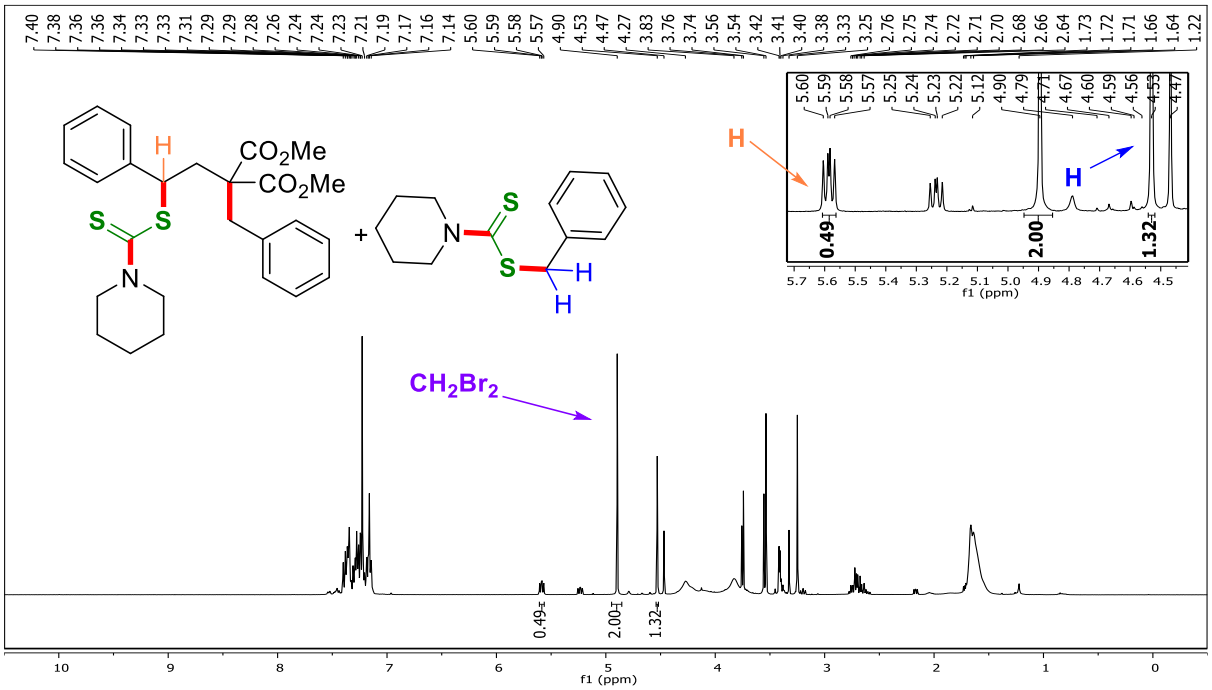
This study indicates that the nucleophilic ring-opening of D-A cyclopropanes using dithiocarbamates was less facile than the direct dithiocarbamate addition to benzyl bromide thus making the four-component coupling not feasible.

(c) Envisioned One-Pot Approach



To a flame-dried screw-capped test tube equipped with a magnetic stir bar was added piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), and CS_2 (0.023 g, 18 µL, 0.3 mmol) in 1 mL THF under argon atmosphere. The reaction mixture was stirred for 5 minutes and then to the stirring solution dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) and $Yb(OTf)_3$ (0.025 g, 0.04 mmol) were added and then the reaction mixture was allowed to stir at 25 °C for 16 h. After 16 h, Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) were added and stirred for 12 more hours. After that, the reaction was stopped, the solvent was evaporated, and the crude mixture was passed through a pad of silica gel and eluted with EtOAc (3x10 mL). The reaction mixture was concentrated under reduced pressure and then the yield of **11a** and **15** was determined by the ^1H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard.

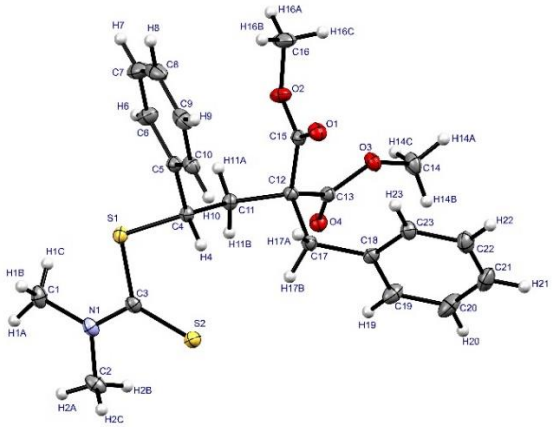




*This study indicates that the moderate yield of **11a** in this case is possibly the lack of compatibility of the Lewis acid with the base-mediated alkylation step.*

7.6.8. ORTEP Diagram of 11v

Single crystal of **11v** (recrystallized from $CDCl_3$/*n*-hexane at 25 °C) was mounted and the diffraction data was collected at 296 K on a Bruker APEX-II CCD diffractometer using SMART/SAINT software. Intensity data were collected using MoKα radiation (λ=0.71073 A°).



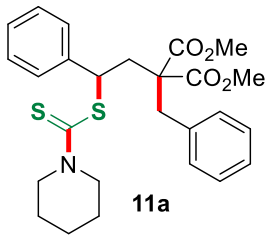
ORTEP Diagram of 11v

(CCDC 2128620, thermal ellipsoids are shown with 50% probability)

7.6.9. Synthesis and Characterization of 1,3-Carbothiolated Products

Dimethyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11a)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11a** as yellow oil (0.092 g, 95% yield).

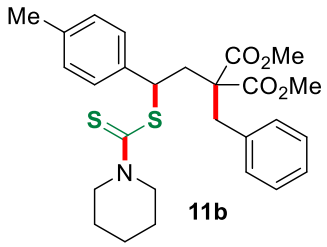


11a

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.26-7.22 (m, 2H), 7.20-7.14 (m, 6H), 5.61-5.57 (m, 1H), 4.29-3.71 (m, 4H), 3.53 (s, 3H), 3.45-3.37 (m, 2H), 3.25 (s, 3H), 2.76-2.64 (m, 2H), 1.60 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.1, 170.7, 141.6, 136.2, 130.2, 128.8, 128.3, 128.3, 127.5, 127.0, 58.7, 52.9, 52.3, 52.1, 52.0, 51.4, 38.9, 38.4, 26.0, 25.7, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{31}NNaO_4S_2$ 508.1587; found 508.1595. **FTIR (cm^{-1})** 2937, 2346, 1737, 1608, 1447, 1218.

Dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(*p*-tolyl)ethyl)malonate (11b)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-(*p*-tolyl) cyclopropane-1,1-dicarboxylate **1b** (0.050 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 μL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(*p*-tolyl)ethyl)malonate **11b** as yellow oil (0.085 g, 85% yield).

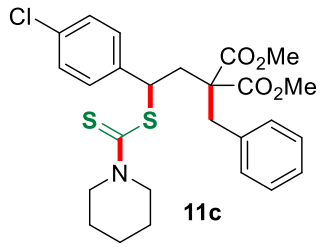


11b

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 (d, *J* = 7.9 Hz, 2H), 7.26-7.08 (m, 7H), 5.60-5.57 (m, 1H), 4.34-3.75 (m, 4H), 3.57 (s, 3H), 3.48-3.40 (m, 2H), 3.31 (s, 3H), 2.80-2.67 (m, 2H), 2.30 (s, 3H), 1.63 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.6, 171.1, 170.8, 138.5, 137.1, 136.4, 130.2, 129.0, 128.6, 128.2, 126.9, 58.8, 52.9, 52.3, 52.1, 51.8, 51.3, 39.0, 38.4, 25.8, 24.4, 21.2. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{33}NNaO_4S_2$ 522.1743; found 522.1748. **FTIR (cm^{-1})** 2938, 1736, 1446, 1217, 989, 745.

Dimethyl-2-benzyl-2-(2-(4-chlorophenyl)-2-((piperidine-1 carbonothioyl)thio)ethyl) malonate (11c)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(4-chlorophenyl) cyclopropane-1,1-dicarboxylate **1c** (0.054 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 84/16) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(4-chlorophenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11c** as yellow oil (0.090 g, 87% yield).

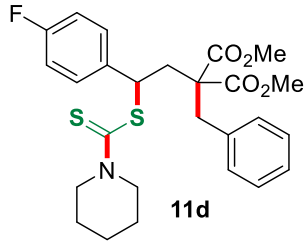


11c

***R*f** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.26-7.15 (m, 7H), 5.60-5.56 (m, 1H), 4.33-3.76 (m, 4H), 3.60 (s, 3H), 3.47-3.38 (m, 2H), 3.35 (s, 3H), 2.72-2.59 (m, 2H), 1.66 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 192.9, 171.0, 170.7, 140.6, 136.0, 133.2, 130.2, 130.1, 128.4, 128.4, 127.1, 58.6, 53.2, 52.4, 52.3, 51.6, 51.2, 38.5, 38.5, 26.1, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{30}ClNNaO_4S_2$ 542.1197; found 542.1204. **FTIR (cm^{-1})** 2935, 2346, 1736, 1614, 1445, 1220.

Dimethyl-2-benzyl-2-(2-(4-fluorophenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11d)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(4-fluorophenyl) cyclopropane-1,1-dicarboxylate **1d** (0.050 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the



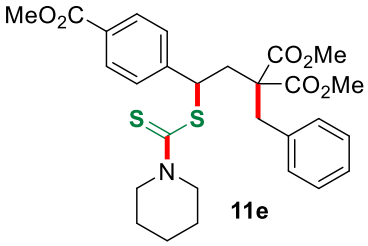
11d

crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 84/16) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(4-fluorophenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11d** as yellow oil (0.072 g, 71% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42-7.39 (m, 2H), 7.26-7.16 (m, 5H), 6.98-6.94 (m, 2H), 5.61-5.58 (m, 1H), 4.32-3.74 (m, 4H), 3.59 (s, 3H), 3.47-3.39 (m, 2H), 3.35 (s, 3H), 2.74-2.60 (m, 2H), 1.64 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.0, 171.0, 170.7, 162.0 (d, *J* = 247.0 Hz), 137.6 (d, *J* = 3.4 Hz), 136.0, 130.5 (d, *J* = 8.1 Hz), 130.1, 128.4, 127.1, 115.1 (d, *J* = 22.0 Hz), 58.6, 53.0, 52.4, 52.3, 51.4, 51.1, 38.8, 38.4, 26.1, 25.5, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{30}FNNaO_4S_2$ 526.1492; found 526.1497. **FTIR (cm^{-1})** 2938, 2345, 1736, 1617, 1445, 1218.

Dimethyl-2-benzyl-2-(2-(4-(methoxycarbonyl)phenyl)-2-((piperidine-1-carbonothioyl) thio)ethyl)malonate (11e)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(4-(methoxycarbonyl) phenyl) cyclopropane-1,1-dicarboxylate **1e** (0.058 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 81/19) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(4-(methoxycarbonyl)phenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate **11e** as yellow oil (0.079 g, 73% yield).



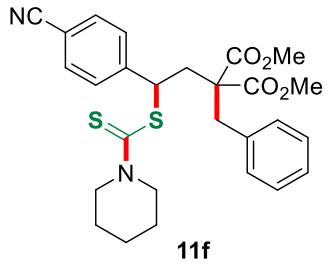
11e

***R*f** (Pet. ether /EtOAc = 90/10): 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.94 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.24-7.15 (m, 5H), 5.68-5.65 (m, 1H), 4.31-3.74 (m, 4H), 3.88 (s, 3H), 3.60 (s, 3H), 3.48-3.39 (m, 2H), 3.31 (s, 3H), 2.75-2.61 (m, 2H), 1.65 (bs, 6H). **^{13}C**

NMR (100 MHz, $CDCl_3$) δ 192.6, 170.9, 170.6, 166.9, 147.2, 135.9, 130.0, 129.6, 129.1, 128.8, 128.4, 127.1, 58.5, 53.1, 52.4, 52.2, 52.2, 51.4, 38.4, 38.2, 26.1, 25.5, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{33}NNaO_6S_2$ 566.1642; found 566.1648. **FTIR (cm^{-1})** 2939, 1730, 1601, 1448, 1268, 1212.

Dimethyl-2-benzyl-2-(2-(4-cyanophenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11f)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-(4-cyanophenyl) cyclopropane-1,1-dicarboxylate **1f** (0.052 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 μL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 82/18) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(4-cyanophenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11f** as yellow oil (0.087 g, 85% yield).



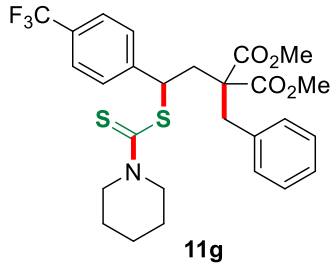
11f

***R*f** (Pet. ether /EtOAc = 90/10): 0.21; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56-7.52 (m, 4H), 7.26-7.13 (m, 5H), 5.66-5.62 (m, 1H), 4.33-3.73 (m, 4H), 3.63 (s, 3H), 3.46-3.39 (m, 2H), 3.39 (s, 3H), 2.69-2.53 (m, 2H), 1.64 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 192.2, 170.8, 170.6, 147.9, 135.6, 132.0, 130.0, 129.6, 128.5, 127.2, 118.8, 111.0, 58.3, 53.2, 52.5, 52.4, 51.6, 51.2, 38.5, 37.9, 26.1, 25.6, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{30}N_2NaO_4S_2$ 533.1539; found 533.1542. **FTIR (cm^{-1})** 2938, 2224, 1736, 1609, 1445, 1220.

Dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(4-(trifluoromethyl) phenyl)ethyl)malonate (11g)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-(4-(trifluoromethyl) phenyl) cyclopropane-1,1-dicarboxylate **1g** (0.060 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in

THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 86/14) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(4 (trifluoromethyl)phenyl) ethyl) malonate **11g** as yellow oil (0.090 g, 81% yield).

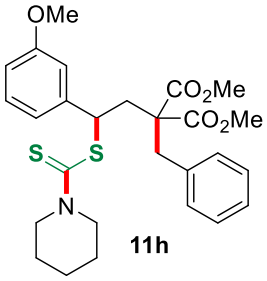


11g

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56-7.51 (m, 4H), 7.26-7.15 (m, 5H), 5.69-5.66 (m, 1H), 4.35-3.75 (m, 4H), 3.62 (s, 3H), 3.49-3.40 (m, 2H), 3.34 (s, 3H), 2.74-2.59 (m, 2H), 1.65 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 192.6, 171.0, 170.6, 146.3 (d, *J* = 1.2 Hz), 135.9, 130.1, 129.8 (q, *J* = 32.5 Hz), 129.2, 128.4, 127.2, 125.2 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.2 Hz), 58.4, 53.2, 52.4, 52.2, 51.5, 51.2, 38.5, 38.3, 26.2, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{30}F_3NNaO_4S_2$ 576.1461; found 576.1465. **FTIR (cm^{-1})** 2939, 2345, 1739, 1618, 1444, 1325.

Dimethyl-2-benzyl-2-(2-(3-methoxyphenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11h)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(3-methoxyphenyl) cyclopropane-1,1-dicarboxylate **1h** (0.053 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 80/20) of the



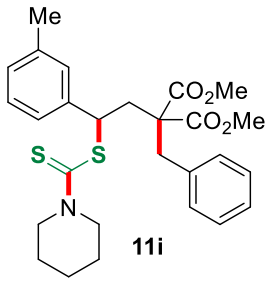
11h

crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(3-methoxyphenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11h** as white solid (0.084 g, 81% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.19; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.22-7.18 (m, 6H), 7.03-6.97 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.62-5.59 (m, 1H), 4.33-3.79 (m, 4H), 3.79 (s, 3H), 3.59 (s, 3H), 3.48-3.40 (m, 2H), 3.36 (s, 3H), 2.80-2.65 (m, 2H), 1.68 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.1, 170.8, 159.4, 143.1, 136.2, 130.2, 129.3, 128.3, 127.0, 121.0, 114.2, 113.2, 58.7, 55.3, 53.0, 52.3, 52.2, 52.0, 51.4, 38.8, 38.3, 26.1, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{33}NNaO_5S_2$ 538.1692; found 538.1697. **FTIR (cm^{-1})** 2935, 2346, 1735, 1597, 1447, 1231.

Dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(*m*-tolyl)ethyl)malonate (11i)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-(*m*-tolyl) cyclopropane-1,1-dicarboxylate **1i** (0.050 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 μL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(*m*-tolyl)ethyl)malonate **11i** as white solid (0.088 g, 88% yield).

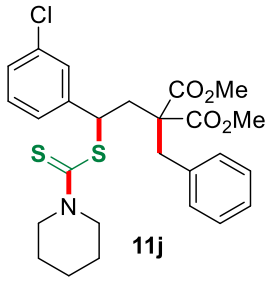


11i

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.24-7.15 (m, 8H), 7.02 (d, *J* = 7.2 Hz, 1H), 5.61-5.57 (m, 1H), 4.34-3.76 (m, 4H), 3.58 (s, 3H), 3.49-3.41 (m, 2H), 3.31 (s, 3H), 2.81-2.66 (m, 2H), 2.33 (m, 3H), 1.64 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.2, 170.8, 141.3, 137.9, 136.3, 130.2, 129.3, 128.3, 128.2, 128.2, 126.9, 125.8, 58.7, 53.0, 52.3, 52.1, 52.0, 51.4, 39.0, 38.3, 26.1, 25.5, 24.4, 21.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{33}NNaO_4S_2$ 522.1743; found 522.1746. **FTIR (cm^{-1})** 2936, 2344, 1737, 1612, 1445, 1217.

Dimethyl-2-benzyl-2-(2-(3-chlorophenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11j)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(3-chlorophenyl) cyclopropane-1,1-dicarboxylate **1j** (0.054 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 84/16) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(3-chlorophenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11j** as yellow oil (0.089 g, 86% yield).

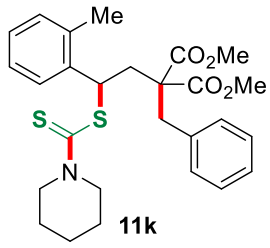


11j

***R*f** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39-7.32 (m, 2H), 7.26-7.16 (m, 7H), 5.62-5.58 (m, 1H), 4.34-3.78 (m, 4H), 3.60 (s, 3H), 3.47-3.39 (m, 2H), 3.39 (s, 3H), 2.74-2.59 (m, 2H), 1.65 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 192.8, 171.0, 170.7, 144.0, 136.0, 134.0, 130.1, 129.5, 128.7, 128.4, 127.6, 127.2, 127.1, 58.5, 53.2, 52.4, 52.3, 51.3, 38.5, 38.4, 26.2, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{30}ClNNaO_4S_2$ 542.1197; found 542.1204. **FTIR (cm^{-1})** 2937, 2345, 1736, 1590, 1446, 1217.

Dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(*o*-tolyl)ethyl)malonate (11k)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(*o*-tolyl) cyclopropane-1,1-dicarboxylate **1k** (0.050 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF



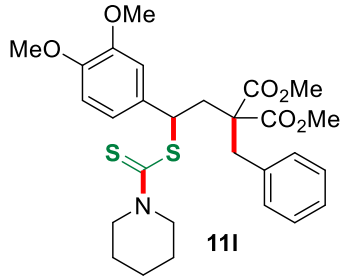
11k

(1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(*o*-tolyl)ethyl)malonate **11k** as yellow oil (0.087 g, 87% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37-7.35 (m, 1H), 7.26-7.13 (m, 8H), 5.73-5.69 (m, 1H), 4.26-3.84 (m, 4H), 3.52-3.46 (m, 2H), 3.46 (s, 3H), 3.17 (s, 3H), 2.98-2.86 (m, 2H), 2.51 (s, 3H), 1.68 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.8, 171.1, 170.8, 137.8, 136.9, 136.8, 130.9, 130.4, 128.7, 128.0, 127.5, 126.8, 125.7, 59.0, 52.9, 52.1, 51.9, 51.3, 49.2, 40.5, 39.2, 26.0, 25.6, 24.4, 20.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{33}NNaO_4S_2$ 522.1743; found 522.1748. **FTIR (cm^{-1})** 2940, 2344, 1735, 1449, 1221, 994.

Dimethyl-2-benzyl-2-(2-(3,4-dimethoxyphenyl)-2-((piperidine-1-carbonothioyl)thio) ethyl)malonate (11l)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(3,4-dimethoxyphenyl) cyclopropane-1,1-dicarboxylate **1l** (0.059 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(3,4-dimethoxyphenyl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate **11l** as yellow oil (0.105 g, 96% yield).



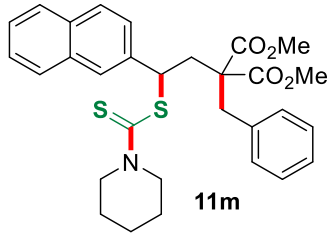
11l

***R*f** (Pet. ether /EtOAc = 90/10): 0.19; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.22-7.16 (m, 5H), 7.00-6.93 (m, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 5.58-5.54 (m, 1H), 4.32-3.13 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.87-3.76 (m, 2H), 3.58 (s, 3H), 3.47-3.38 (m, 2H), 3.34 (s, 3H), 2.78-2.65 (m,

2H), 1.65 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.1, 170.8, 148.5, 148.3, 136.2, 133.9, 130.1, 128.2, 126.9, 120.9, 111.8, 110.7, 58.6, 55.9, 55.9, 52.9, 52.3, 52.2, 51.9, 51.3, 38.9, 38.2, 26.0, 25.5, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{35}NNaO_6S_2$ 568.1798; found 568.1805. **FTIR (cm^{-1})** 2938, 1736, 1613, 1445, 1245, 1007.

Dimethyl-2-benzyl-2-(2-(naphthalen-2-yl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11m)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-(naphthalen-2-yl) cyclopropane-1,1-dicarboxylate **1m** (0.057 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 μL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 84/16) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(naphthalen-2-yl)-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11m** as yellow oil (0.100 g, 93% yield).



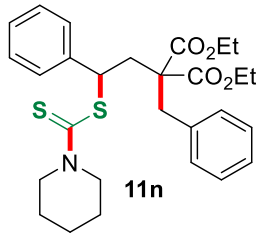
11m

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.91 (s, 1H), 7.84-7.77 (m, 3H), 7.56-7.54 (s, 1H), 7.47-7.41 (s, 2H), 7.26-7.16 (m, 5H), 5.85-5.81 (m, 1H), 4.32-3.77 (m, 4H), 3.58 (s, 3H), 3.56-3.47 (m, 2H), 3.13 (s, 3H), 2.85-2.83 (m, 2H), 1.65 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.1, 171.1, 170.7, 138.8, 136.2, 133.0, 132.7, 130.2, 128.3, 128.1, 128.1, 127.6, 127.0, 126.6, 126.2, 126.0, 58.6, 53.1, 52.3, 52.1, 52.1, 51.5, 38.6, 38.4, 26.1, 25.5, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{30}H_{33}NNaO_4S_2$ 558.1743; found 558.1747. **FTIR (cm^{-1})** 2925, 2344, 1736, 1624, 1439, 1224.

Diethyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11n)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and diethyl 2-phenylcyclopropane-1,1-dicarboxylate **1n** (0.052 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C

and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded diethyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11n** as yellow oil (0.093 g, 91% yield).

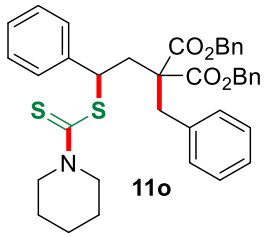


11n

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.29-7.17 (m, 8H), 5.64-5.60 (m, 1H), 4.35-3.40 (m, 10H), 2.78-2.67 (m, 2H), 1.66 (bs, 6H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 170.7, 170.3, 141.8, 136.4, 130.3, 128.8, 128.2, 127.4, 126.8, 61.3, 61.2, 58.6, 53.0, 52.0, 51.4, 38.7, 38.2, 26.0, 25.6, 24.4, 13.9, 13.8. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{35}NNaO_4S_2$ 536.1900; found 536.1905. **FTIR (cm^{-1})** 2946, 2344, 1732, 1450, 1212, 1005.

Dibenzyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11o)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate **1o** (0.077 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 86/14) of the crude reaction mixture afforded dibenzyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11o** as white solid (0.110 g, 86% yield).

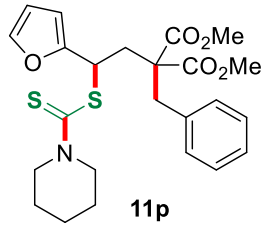


11o

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.29-7.10 (m, 18H), 5.72-5.69 (m, 1H), 4.98-3.91 (m, 2H), 4.83-4.80 (m, 1H), 4.45-3.73 (m, 5H), 3.56-3.48 (m, 2H), 2.88-2.75 (m, 2H), 1.66 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 170.4, 170.0, 141.8, 136.2, 135.3, 135.3, 130.3, 128.8, 128.5, 128.5, 128.3, 128.3, 128.3, 128.3, 128.2, 128.2, 127.5, 127.0, 67.2, 67.0, 58.9, 53.1, 52.0, 38.9, 38.3, 25.8, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{38}H_{39}NNaO_4S_2$ 660.2213; found 660.2217. **FTIR (cm^{-1})** 2934, 2342, 1735, 1601, 1452, 1207.

Dimethyl-2-benzyl-2-(2-(furan-2-yl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11p)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-(furan-2-yl) cyclopropane-1,1-dicarboxylate **1p** (0.045 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 μL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-(furan-2-yl)-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate **11p** as yellow oil (0.080 g, 84% yield).

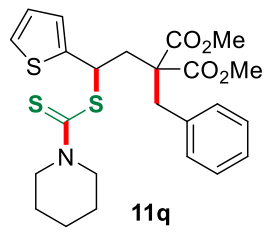


11p

***R*f** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 (s, 1H), 7.26-7.15 (m, 5H), 6.32-6.27 (m, 2H), 5.83-5.79 (m, 1H), 4.35-3.76 (m, 4H), 3.61 (s, 3H), 3.51 (s, 3H), 3.39-3.27 (m, 2H), 2.86-2.61 (m, 2H), 1.68 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.1, 170.9, 170.7, 153.1, 142.2, 136.1, 130.2, 128.3, 127.0, 110.5, 108.0, 58.6, 53.3, 52.5, 52.4, 51.4, 45.9, 38.4, 36.4, 26.0, 25.7, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{24}H_{29}NNaO_5S_2$ 498.1379; found 498.1385. **FTIR (cm^{-1})** 2936, 1735, 1603, 1444, 1222, 992.

Dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(thiophen-2-yl)ethyl) malonate (11q)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-(thiophen-2-yl) cyclopropane-1,1-dicarboxylate **1q** (0.048 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((piperidine-1-carbonothioyl)thio)-2-(thiophen-2-yl)ethyl)malonate **11q** as yellow oil (0.078 g, 79% yield).

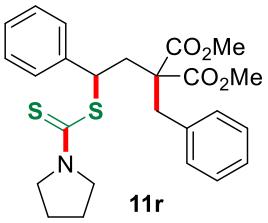


11q

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26-7.15 (m, 6H), 7.06 (d, *J* = 3.3 Hz, 1H), 6.89-6.86 (m, 1H), 6.03-5.99 (m, 1H), 4.37-3.75 (m, 4H), 3.61 (s, 3H), 3.46 (s, 3H), 3.46-3.41 (m, 2H), 2.84-2.69 (m, 2H), 1.68 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.0, 171.0, 170.8, 145.7, 136.1, 130.1, 128.4, 127.0, 126.4, 125.9, 124.8, 58.6, 53.5, 52.4, 51.6, 47.7, 39.4, 38.4, 26.1, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+K]^+$ calcd for $C_{24}H_{29}KNO_4S_3$ 530.0890; found 530.0892. **FTIR (cm^{-1})** 2938, 1736, 1448, 1220, 988, 861.

Dimethyl-2-benzyl-2-(2-phenyl-2-((pyrrolidine-1-carbonothioyl)thio)ethyl)malonate (11r)

Following the general procedure, a mixture of pyrrolidine **2b** (0.021 g, 25 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL,

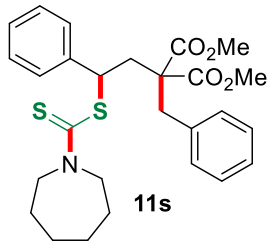


11r

0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-phenyl-2-((pyrrolidine-1-carbonothioyl)thio)ethyl)malonate **11r** as yellow solid (0.068 g, 72% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.30-7.20 (m, 8H), 5.66-5.62 (m, 1H), 3.96-3.82 (m, 2H), 3.58-3.54 (m, 5H), 3.49-3.40 (m, 2H), 3.31 (s, 3H), 2.79-2.67 (m, 2H), 2.08-1.87 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 190.5, 171.1, 170.7, 141.8, 136.2, 130.2, 128.7, 128.4, 128.3, 127.5, 127.0, 58.7, 55.1, 52.4, 52.2, 51.1, 50.5, 38.7, 38.3, 26.1, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{25}H_{29}NNaO_4S_2$ 494.1430; found 494.1436. **FTIR (cm^{-1})** 3600, 2933, 1736, 1612, 1430, 1185.

Dimethyl-2-(2-((azepane-1-carbonothioyl)thio)-2-phenylethyl)-2-benzylmalonate (11s)



11s

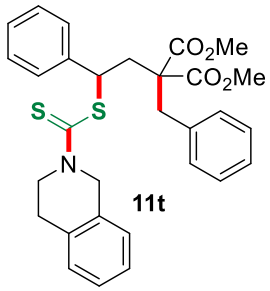
Following the general procedure, a mixture of azepane **2c** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-(2-((azepane-1-carbonothioyl)thio)-2-phenylethyl)-2-benzyl malonate **11s** as yellow oil (0.082 g, 82% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.30-7.20 (m, 8H), 5.62 (t, *J* = 7.1 Hz, 1H), 4.31-4.28 (m, 1H), 3.99-3.88 (m, 2H), 3.72-3.68 (m, 1H), 3.58 (s, 3H), 3.51-3.41 (m, 2H), 3.26 (s, 3H), 2.75-2.73 (m, 2H), 1.90-1.54 (m, 8H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 194.0, 171.1, 170.7, 141.6, 136.2, 130.2, 128.8, 128.3, 127.4, 127.0, 58.7, 55.8, 52.9, 52.3, 52.1, 51.7, 38.8, 38.3, 27.5, 26.7, 26.6, 26.2. **HRMS**

(ESI) m/z: $[M+Na]^+$ calcd for $C_{27}H_{33}NNaO_4S_2$ 522.1743; found 522.1749. **FTIR (cm^{-1})** 2947, 1735, 1489, 1439, 1417, 1269.

Dimethyl-2-benzyl-2-(2-phenyl-2-((1,2,3,4-tetrahydroisoquinoline-2-carbonothioyl) thio)ethyl)malonate (11t)

Following the general procedure, a mixture of 1,2,3,4-tetrahydroisoquinoline **2d** (0.040 g, 38 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-phenyl-2-((1,2,3,4-tetrahydroisoquinoline-2-carbonothioyl)thio)ethyl)malonate **11t** as pale yellow solid (0.077 g, 72% yield).



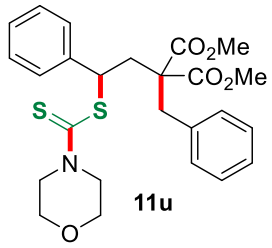
11t

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.21-7.08 (m, 12H), 5.61-5.57 (m, 1H), 5.28-4.82 (m, 2H), 4.33-4.28 (m, 1H), 3.90 (s, 1H), 3.47 (s, 3H), 3.39-3.31 (m, 2H), 3.19 (s, 3H), 2.84 (bs, 2H), 2.71-2.61 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 194.3, 171.1, 170.7, 141.6, 136.2, 130.2, 128.9, 128.4, 128.4, 127.6, 127.1, 58.8, 53.9, 52.4, 52.2, 51.7, 50.1, 48.1, 39.4, 38.9, 38.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{30}H_{31}NNaO_4S_2$ 556.1587; found 556.1590. **FTIR (cm^{-1})** 3602, 2931, 1735, 1598, 1427, 1199.

Dimethyl-2-benzyl-2-(2-((morpholine-4-carbonothioyl)thio)-2-phenylethyl)malonate (11u)

Following the general procedure, a mixture of morpholine **2e** (0.026 g, 26 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at

25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((morpholine-4-carbonothioyl)thio)-2-phenylethyl)malonate **11u** as yellow solid (0.075 g, 77% yield).

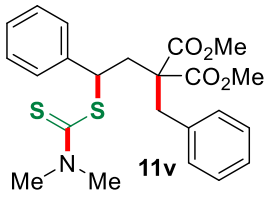


11u

***R*f** (Pet. ether /EtOAc = 90/10): 0.21; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.30-7.15 (m, 8H), 5.61 (t, *J* = 7.3 Hz, 1H), 4.12 (bs, 4H), 3.70 (bs, 4H), 3.56 (s, 3H), 3.46-3.39 (m, 2H), 3.28 (s, 3H), 2.78-2.68 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.3, 171.1, 170.6, 141.2, 136.1, 130.2, 128.8, 128.4, 128.4, 127.7, 127.1, 66.3, 58.6, 52.4, 52.2, 51.9, 38.8, 38.4, 29.8. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{25}H_{29}NNaO_5S_2$ 510.1379; found 510.1385. **FTIR (cm^{-1})** 3602, 2937, 1734, 1607, 1436, 1215.

Dimethyl-2-benzyl-2-(2-((dimethylcarbamothioyl)thio)-2-phenylethyl)malonate (11v)

Following the general procedure, a mixture of dimethylamine **2f** (150 µL(2 M solution in THF), 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 88/12) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((dimethylcarbamothioyl)thio)-2-phenylethyl)malonate **11v** as white solid (0.082 g, 92% yield).



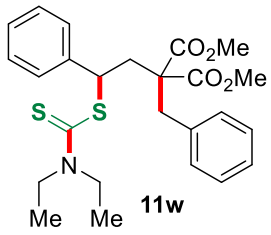
11v

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44-7.19 (m, 10H), 5.56-5.56 (m, 1H), 3.58-3.29 (m, 14H), 2.73-2.67 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ

194.8, 171.1, 170.7, 141.5, 136.1, 130.1, 128.8, 128.3, 127.6, 127.0, 58.6, 52.5, 52.4, 52.2, 45.4, 41.4, 38.6, 38.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{27}NNaO_4S_2$ 468.1274; found 468.1279. **FTIR (cm^{-1})** 2950, 1747, 1716, 1494, 1453, 1381.

Dimethyl-2-benzyl-2-(2-((diethylcarbamothioyl)thio)-2-phenylethyl)malonate (11w)

Following the general procedure, a mixture of diethylamine **2g** (0.022 g, 31 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 88/12) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((diethylcarbamothioyl)thio)-2-phenylethyl)malonate **11w** as yellow solid (0.090 g, 95% yield).



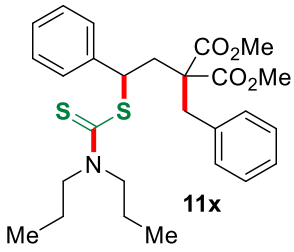
11w

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.30-7.26 (m, 2H), 7.23-7.16 (m, 6H), 5.59 (t, *J* = 7.4 Hz, 1H), 3.99-3.98 (m, 2H), 3.71-3.62 (m, 2H), 3.58 (s, 3H), 3.49-3.40 (m, 2H), 3.27 (s, 3H), 2.79-2.69 (m, 2H), 1.24 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.1, 170.7, 141.6, 136.3, 130.2, 128.8, 128.3, 128.3, 127.5, 127.0, 58.7, 52.3, 52.1, 52.0, 49.6, 46.7, 39.0, 38.4, 12.8, 11.7. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{25}H_{31}NNaO_4S_2$ 496.1587; found 496.1593. **FTIR (cm^{-1})** 3596, 2948, 1737, 1603, 1455, 1191.

Dimethyl-2-benzyl-2-(2-((dipropylcarbamothioyl)thio)-2-phenylethyl)malonate (11x)

Following the general procedure, a mixture of dipropylamine **2h** (0.030 g, 41 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at

25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with



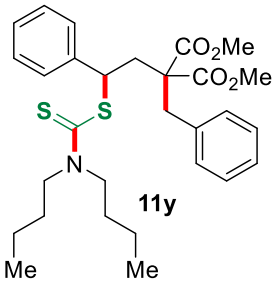
11x

CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 88/12) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((dipropylcarbamothioyl)thio)-2-phenylethyl)malonate **11x** as yellow solid (0.088 g, 88% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.30-7.26 (m, 2H), 7.21-7.19 (m, 6H), 5.60 (t, *J* = 7.3 Hz, 1H), 3.88-3.86 (m, 2H), 3.62-3.51 (m, 5H), 3.50-3.40 (m, 2H), 3.25 (s, 3H), 2.74 (d, *J* = 7.3 Hz, 2H), 1.73-1.64 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.9, 171.1, 170.7, 141.6, 136.3, 130.2, 128.9, 128.3, 128.3, 127.4, 127.0, 58.7, 57.0, 54.4, 52.3, 52.1, 52.0, 38.9, 38.4, 20.9, 19.8, 11.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{35}NNaO_4S_2$ 524.1900; found 524.1903. **FTIR (cm^{-1})** 3601, 2950, 1738, 1617, 1454, 1201.

Dimethyl-2-benzyl-2-(2-((dibutylcarbamothioyl)thio)-2-phenylethyl)malonate (11y)

Following the general procedure, a mixture of dibutylamine **2i** (0.039 g, 51 µL, 0.3 mmol),



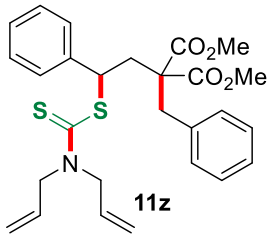
11y

CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenyl cyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 88/12) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((dibutylcarbamothioyl)thio)-2-phenylethyl)malonate **11y** as yellow oil (0.090 g, 85% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.30-7.20 (m, 8H), 5.60 (t, *J* = 7.0 Hz, 1H), 3.91 (t, *J* = 7.3 Hz, 2H), 3.58 (s, 3H), 3.58-3.54 (m, 2H), 3.50-3.40 (m, 2H), 3.25 (s, 3H), 2.74 (d, *J* = 7.0 Hz, 2H), 1.67-1.63 (m, 4H), 1.33-1.27 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 6H) . **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.7, 171.1, 170.7, 141.6, 136.3, 130.2, 128.9, 128.2, 127.4, 127.0, 58.7, 55.2, 52.5, 52.3, 52.1, 52.0, 38.9, 38.3, 29.6, 28.4, 20.2, 20.2, 13.9, 13.8. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{29}H_{39}NNaO_4S_2$ 552.2213; found 552.2216. **FTIR (cm^{-1})** 3604, 2945, 1736, 1598, 1455, 1197.

Dimethyl-2-benzyl-2-(2-((diallylcarbamothioyl)thio)-2-phenylethyl)malonate (11z)

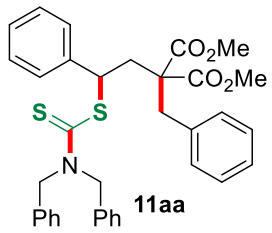
Following the general procedure, a mixture of diallylamine **2j** (0.029 g, 37 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-phenyl cyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 μL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 88/12) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((diallylcarbamothioyl)thio)-2-phenylethyl)malonate **11z** as yellow oil (0.079 g, 80% yield).



***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.30-7.26 (m, 2H), 7.22-7.18 (m, 6H), 5.85-5.74 (m, 2H), 5.57 (t, *J* = 7.2 Hz, 1H), 5.23-5.12 (m, 4H), 4.66-4.55 (m, 2H), 4.30-4.18 (m, 2H), 3.58 (s, 3H), 3.49-3.40 (m, 2H), 3.27 (s, 3H), 2.73-2.67 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.8, 171.1, 170.7, 141.4, 136.2, 131.1, 130.6, 130.2, 128.8, 128.3, 127.6, 127.0, 118.8, 118.5, 58.6, 56.5, 53.7, 52.5, 52.4, 52.2, 38.7, 38.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{27}H_{31}NNaO_4S_2$ 520.1587; found 520.1593. **FTIR (cm^{-1})** 3607, 2934, 1738, 1616, 1442, 1201.

Dimethyl-2-benzyl-2-(2-((dibenzylcarbamothioyl)thio)-2-phenylethyl)malonate (11aa)

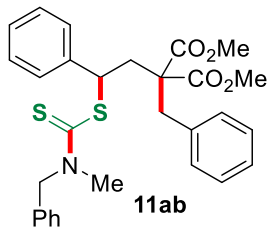
Following the general procedure, a mixture of dibenzylamine **2k** (0.060 g, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((dibenzylcarbamothioyl)thio)-2-phenylethyl)malonate **11aa** as yellow oil (0.083 g, 70% yield).



***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 7.3 Hz, 2H), 7.33-7.23 (m, 16H), 7.12 (bs, 2H), 5.69 (t, *J* = 7.3 Hz, 1H), 5.32-5.23 (m, 2H), 4.90-4.80 (m, 2H), 3.55-3.46 (m, 5H), 3.29 (s, 3H), 2.81-2.71 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.4, 171.1, 170.7, 141.5, 136.2, 130.2, 129.0, 128.9, 128.4, 128.3, 128.0, 127.8, 127.6, 127.3, 127.1, 58.6, 56.2, 54.1, 53.1, 52.4, 52.2, 38.5, 38.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{35}H_{35}NNaO_4S_2$ 620.1900; found 620.1903. **FTIR (cm^{-1})** 3593, 2929, 1736, 1611, 1445, 1198.

Dimethyl-2-benzyl-2-(2-((benzyl(methyl)carbamothioyl)thio)-2-phenylethyl)malonate (11ab)

Following the general procedure, a mixture of *N*-methyl-1-phenylmethanamine **2l** (0.036 g, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and

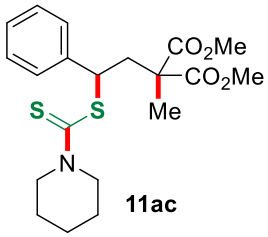


(bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-benzyl-2-(2-((benzyl(methyl)carbamothioyl) thio)-2-phenylethyl)malonate **11ab** as yellow oil (0.072 g, 69% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50-7.16 (m, 15H), 5.71-4.74 (m, 3H), 3.63-3.22 (m, 11H), 2.83-2.77 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.6, 195.4, 171.1, 170.7, 141.7, 141.4, 136.2, 135.6, 134.8, 130.2, 129.0, 128.9, 128.8, 128.3, 128.0, 127.8, 127.6, 127.1, 127.0, 59.6, 58.6, 57.7, 52.7, 52.4, 52.2, 43.3, 38.8, 38.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{29}H_{31}NNaO_4S_2$ 554.1586; found 554.1591. **FTIR (cm^{-1})** 3598, 2933, 1735, 1600, 1470, 1205.

Dimethyl-2-methyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11ac)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and iodomethane **7b** (0.085 g, 37 µL, 0.6 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-methyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11ac** as white solid (0.072 g, 88% yield).

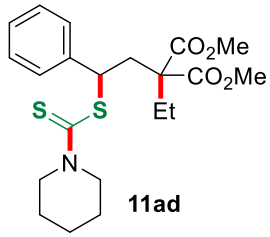


11ac

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 (d, *J* = 7.1 Hz, 2H), 7.26-7.16 (m, 3H), 5.26-5.22 (m, 1H), 4.18-3.76 (m, 4H), 3.63 (s, 3H), 3.16 (m, 3H), 2.80-2.78 (m, 2H), 1.61 (bs, 6H), 1.52 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.5, 172.5, 171.4, 139.2, 128.8, 128.4, 127.8, 53.2, 52.6, 52.5, 52.0, 51.2, 40.9, 26.0, 25.4, 24.2, 19.6. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{20}H_{27}NNaO_4S_2$ 432.1274; found 432.1282. **FTIR (cm^{-1})** 2942, 1737, 1450, 1241, 1113, 991.

Dimethyl-2-ethyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11ad)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and iodoethane **7c** (0.094 g, 48 µL, 0.6 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-ethyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11ad** as white solid (0.069 g, 81% yield).

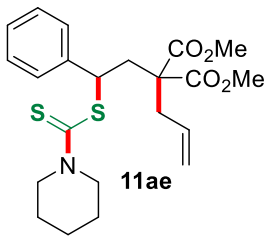


11ad

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 (d, *J* = 7.1 Hz, 2H), 7.29-7.26 (m, 2H), 7.22-7.19 (m, 1H), 5.31-5.28 (m, 1H), 4.21-3.80 (m, 4H), 3.66 (s, 3H), 3.25 (m, 3H), 2.86-2.75 (m, 2H), 2.17-2.08 (m, 1H), 2.04-1.95 (m, 1H), 1.65 (bs, 6H), 0.86 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.5, 171.8, 171.2, 140.2, 128.8, 128.4, 127.7, 57.8, 52.9, 52.5, 52.4, 52.0, 51.3, 37.9, 26.0, 25.6, 25.2, 24.4, 9.0. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{21}H_{29}NNaO_4S_2$ 446.1430; found 446.1435. **FTIR (cm^{-1})** 2945, 2347, 1734, 1445, 1225, 1114.

Dimethyl-2-allyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11ae)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF



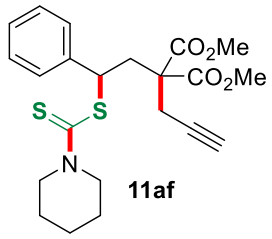
11ae

(1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and 3-bromoprop-1-ene **7d** (0.072 g, 52 µL, 0.6 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-allyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11ae** as yellow oil (0.073 g, 84% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 (d, *J* = 7.6 Hz, 2H), 7.30-7.26 (m, 2H), 7.23-7.19 (m, 1H), 5.83-5.72 (m, 1H), 5.40-5.36 (m, 1H), 5.15-5.05 (m, 2H), 4.21-3.80 (m, 4H), 3.65 (s, 3H), 3.29 (m, 3H), 2.87-2.69 (m, 4H), 1.65 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.2, 170.7, 140.5, 132.8, 128.8, 128.4, 127.7, 119.2, 57.5, 52.8, 52.4, 52.3, 52.1, 51.3, 38.4, 36.7, 26.0, 25.5, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{29}NNaO_4S_2$ 458.1430; found 458.1438. **FTIR (cm^{-1})** 2928, 2344, 1734, 1628, 1439, 1220.

Dimethyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)-2-(prop-2-yn-1-yl) malonate (11af)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and 3-bromoprop-1-yne **7e** (0.071 g, 0.6 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)-2-(prop-2-yn-1-yl)malonate **11af** as yellow oil (0.072 g, 83% yield).



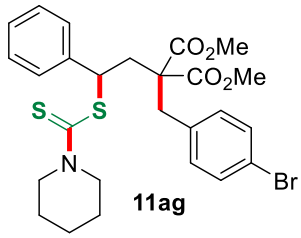
11af

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (d, *J* = 7.3 Hz, 2H), 7.30-7.20 (m, 3H), 5.33-5.29 (m, 1H), 4.21-3.79 (m, 4H), 3.74 (s, 3H), 3.43 (m, 3H), 2.99-2.89 (m, 3H), 2.75-2.70 (m, 1H), 2.01-1.99 (m, 1H), 1.65 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.2, 170.3, 169.9, 140.5, 128.6, 128.5, 127.8, 79.2, 71.8, 56.8, 52.9, 52.7,

52.4, 51.3, 37.7, 26.0, 25.5, 24.3, 23.1. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{27}NNaO_4S_2$ 456.1274; found 456.1278. **FTIR (cm^{-1})** 3602, 2927, 1741, 1614, 1436, 1221.

Dimethyl-2-(4-bromobenzyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11ag)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and 1-bromo-4-(bromomethyl)benzene **7f** (0.100 g, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 85/15) of the crude reaction mixture afforded dimethyl-2-(4-bromobenzyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11ag** as yellow oil (0.089 g, 79% yield).



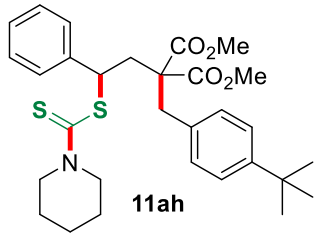
11ag

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 (d, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.30-7.26 (m, 2H), 7.23-7.19 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 5.60-5.56 (m, 1H), 4.31-4.16 (m, 2H), 3.85-3.76 (m, 2H), 3.56 (s, 3H), 3.44-3.37 (m, 2H), 3.24 (s, 3H), 2.79-2.69 (m, 2H), 1.66 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.2, 170.9, 170.5, 141.1, 135.3, 132.0, 131.3, 128.8, 128.4, 127.6, 121.0, 58.5, 53.1, 52.4, 52.2, 51.9, 51.4, 39.1, 37.8, 26.1, 25.6, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{30}BrNNaO_4S_2$ 586.0692; found 586.0695. **FTIR (cm^{-1})** 2934, 2345, 1735, 1447, 1218, 1001.

Dimethyl-2-(4-(*tert*-butyl)benzyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio) ethyl) malonate (11ah)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047

g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and 1-(bromomethyl)-4-(*tert*-butyl)benzenee **7g** (0.091 g, 74 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 86/14) of the crude reaction mixture afforded dimethyl-2-(4-(*tert*-butyl)benzyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11ah** as yellow oil (0.088 g, 81% yield).

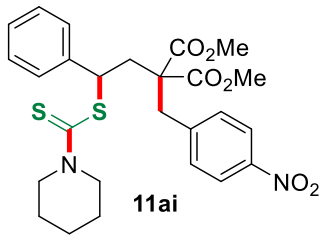


11ah

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.30-7.18 (m, 5H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.64-5.60 (m, 1H), 4.34-3.78 (m, 4H), 3.58 (s, 3H), 3.46-3.37 (m, 2H), 3.30 (s, 3H), 2.80-2.68 (m, 2H), 1.66 (bs, 6H), 1.28 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.2, 170.8, 149.7, 141.7, 133.0, 129.8, 128.8, 128.3, 127.4, 125.2, 58.6, 53.0, 52.3, 52.2, 52.0, 51.4, 38.8, 37.8, 34.5, 31.4, 26.1, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{30}H_{39}NNaO_4S_2$ 564.2213; found 564.2217. **FTIR (cm^{-1})** 2945, 2343, 1736, 1444, 1219, 999.

Dimethyl-2-(4-nitrobenzyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11ai)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and 1-(bromomethyl)-4-nitrobenzene **7h** (0.086 g, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 79/21) of the crude reaction mixture afforded dimethyl-2-(4-nitrobenzyl)-2-



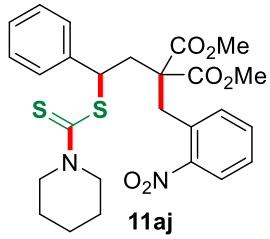
11ai

(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate **11ai** as yellow oil (0.090 g, 85% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.18; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.40-7.38 (m, 4H), 7.31-7.20 (m, 3H), 5.59-5.55 (m, 1H), 4.28-3.81 (m, 4H), 3.56 (s, 2H), 3.54 (s, 3H), 3.22 (s, 3H), 2.84-2.74 (m, 2H), 1.67 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.0, 170.5, 170.1, 147.0, 144.5, 140.4, 131.2, 128.8, 128.5, 127.8, 123.3, 58.6, 53.1, 52.5, 52.3, 52.0, 51.4, 39.6, 38.2, 26.1, 25.5, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{30}N_2NaO_6S_2$ 553.1437; found 553.1442. **FTIR (cm^{-1})** 2940, 1736, 1505, 1447, 1335, 1220.

Dimethyl-2-(2-nitrobenzyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (11aj)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 μL, 0.3 mmol), CS_2 (0.023 g, 18 μL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and 1-(bromomethyl)-2-nitrobenzene **7i** (0.086 g, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 79/21) of the crude reaction mixture afforded dimethyl-2-(2-nitrobenzyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl) thio)ethyl)malonate **11aj** as yellow oil (0.081 g, 76% yield).

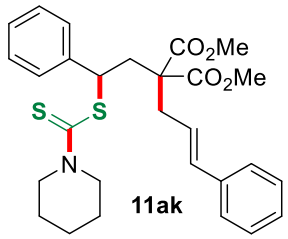


11aj

***R*f** (Pet. ether /EtOAc = 90/10): 0.18; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 1H),7.42-7.37 (m, 3H), 7.29-7.20 (m, 4H), 5.43-5.41 (m, 1H), 4.21 (bs, 2H), 3.89-3.70 (m, 4H), 3.44 (s, 3H), 3.15 (s, 3H), 2.97-2.84 (m, 2H), 1.65 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.2, 170.6, 170.2, 150.4, 139.7, 133.4, 132.2, 132.1, 128.9, 128.5, 127.9, 127.8, 124.7, 58.6, 52.9, 52.6, 52.4, 52.3, 51.3, 41.6, 34.5, 26.1, 25.5, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{30}N_2NaO_6S_2$ 553.1437; found 553.1445. **FTIR (cm^{-1})** 2937, 2344, 1735, 1532, 1442, 1229.

Dimethyl-2-cinnamyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11ak)

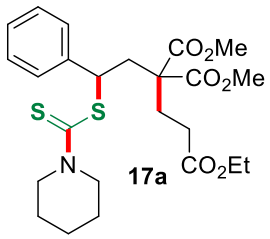
Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (*E*)-(3-bromoprop-1-en-1-yl)benzene **7j** (0.079 g, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 87/13) of the crude reaction mixture afforded dimethyl-2-cinnamyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate **11ak** as yellow oil (0.081 g, 79% yield).



***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (d, *J* = 7.7 Hz, 2H), 7.33-7.18 (m, 8H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.23-6.15 (m, 1H), 5.44-5.40 (m, 1H), 4.25-3.80 (m, 4H), 3.36 (s, 3H), 3.29 (s, 3H), 3.03-2.80 (m, 4H), 1.67 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 171.2, 170.8, 140.2, 137.4, 134.1, 128.9, 128.5, 128.5, 127.8, 127.4, 126.4, 124.4, 57.9, 52.9, 52.6, 52.4, 52.3, 51.3, 38.7, 36.1, 26.1, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{33}NNaO_4S_2$ 534.1743; found 534.1748. **FTIR (cm^{-1})** 2936, 2344, 1735, 1447, 1214, 984.

1-Ethyl 3,3-dimethyl-5-phenyl-5-((piperidine-1-carbonothioyl)thio)pentane-1,3,3-tricarboxylate (17a)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF

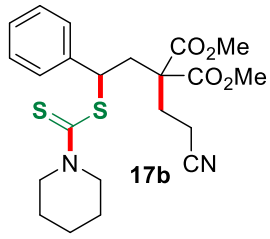


(1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and ethyl acrylate **16a** (0.040 g, 43 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded 1-ethyl 3,3-dimethyl-5-phenyl-5-((piperidine-1-carbonothioyl)thio)pentane-1,3,3-tricarboxylate **17a** as yellow oil (0.066 g, 67% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.17; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41-7.24 (m, 5H), 5.32-5.28 (m, 1H), 4.28-4.18 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.84 (bs, 2H), 3.69 (s, 3H), 3.27 (s, 3H), 2.92-2.81 (m, 2H), 2.67-2.59 (m, 1H), 2.49-2.15 (m, 3H), 1.70 (bs, 6H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.4, 172.7, 171.2, 170.6, 139.2, 128.9, 128.5, 127.9, 60.5, 56.4, 52.7, 52.5, 52.2, 51.3, 38.6, 29.8, 27.1, 26.0, 25.6, 24.3, 14.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{24}H_{33}NNaO_6S_2$ 518.1642; found 518.1646. **FTIR (cm^{-1})** 2943, 1719, 1476, 1454, 1428, 1283.

Dimethyl-2-(2-cyanoethyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate (17b)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and the mixture was stirred for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and filtered through a short pad of silica gel and eluted with EtOAc (10 mL). The solvent was evaporated and the crude product was dissolved in THF (1.5 mL), followed by the addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and acrylonitrile **16b** (0.021 g, 26 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 75/25) of the crude reaction mixture afforded dimethyl-2-(2-cyanoethyl)-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl) malonate **17b** as yellow oil (0.063 g, 70% yield).



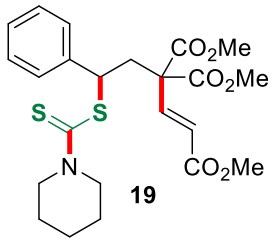
17b

***R*f** (Pet. ether /EtOAc = 90/10): 0.17; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32-7.23 (m, 5H), 5.21-5.17 (m, 1H), 4.28-3.80 (m, 4H), 3.71 (s, 3H), 3.18 (s, 3H), 2.90-2.65 (m, 3H), 2.52-2.32 (m, 3H), 1.67 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.3, 170.5, 169.8, 138.4, 128.9, 128.7, 128.2, 119.1, 56.1, 53.0, 52.4, 52.4, 51.4, 38.5, 28.1, 26.1, 25.5, 24.3, 13.3. **HRMS (ESI)**

m/z: $[M+Na]^+$ calcd for $C_{22}H_{28}N_2NaO_4S_2$ 471.1383; found 471.1384. **FTIR (cm^{-1})** 2915, 1723, 1485, 1426, 1206, 1172.

Trimethyl (*E*)-5-phenyl-5-((piperidine-1-carbonothioyl)thio)pent-1-ene-1,3,3-tricarboxylate (19)

Following the general procedure, a mixture of piperidine **2a** (0.034 g, 39 µL, 0.4 mmol), CS_2 (0.030 g, 24 µL, 0.4 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.5 mL) at 25 °C and the mixture was stirred for 16 h. Then, Cs_2CO_3 (0.163 g, 0.5 mmol) was added followed by the addition of methyl propiolate **18** (0.034 g, 36 µL, 0.4 mmol) and then stirring for 12 h followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 84/16) of the crude reaction mixture afforded trimethyl (*E*)-5-phenyl-5-((piperidine-1-carbonothioyl)thio)pent-1-ene-1,3,3-tricarboxylate **19** as yellow oil (0.089 g, 93% yield with 5.3:1 dr).

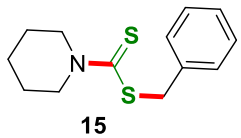


19

***R*f** (Pet. ether /EtOAc = 80/20): 0.33; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27-7.17 (m, 6H), 5.96 (d, *J* = 16.4 Hz, 1H), 5.15-5.11 (m, 1H), 4.21-4.14 (m, 2H), 3.75-3.70 (m, 2H), 3.70 (s, 3H), 3.68 (s, 3H), 3.32 (s, 3H), 3.11-3.07 (m, 1H), 2.93-2.86 (m, 1H), 1.63 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.2, 169.2, 169.0, 166.1, 142.8, 139.0, 129.0, 128.6, 127.9, 123.3, 59.0, 53.2, 52.7, 52.5, 51.7, 51.3, 42.5, 26.0, 25.5, 24.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{29}NNaO_6S_2$ 502.1329; found 502.1331. **FTIR (cm^{-1})** 2943, 1735, 1652, 1434, 1231, 1124.

Benzyl piperidine-1-carbodithioate (15)

Following the general procedure, a mixture of piperidine **2a** (0.026 g, 30 µL, 0.3 mmol), CS_2 (0.023 g, 18 µL, 0.3 mmol), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** (0.047 g, 0.2 mmol) were treated with $Yb(OTf)_3$ (0.025 g, 0.04 mmol) in THF (1.0 mL) at 25 °C and subsequent addition of Cs_2CO_3 (0.163 g, 0.5 mmol) and (bromomethyl)benzene **7a** (0.068 g, 48 µL, 0.4 mmol) and then stirring for 16 h followed by purification via silica gel flash column chromatography



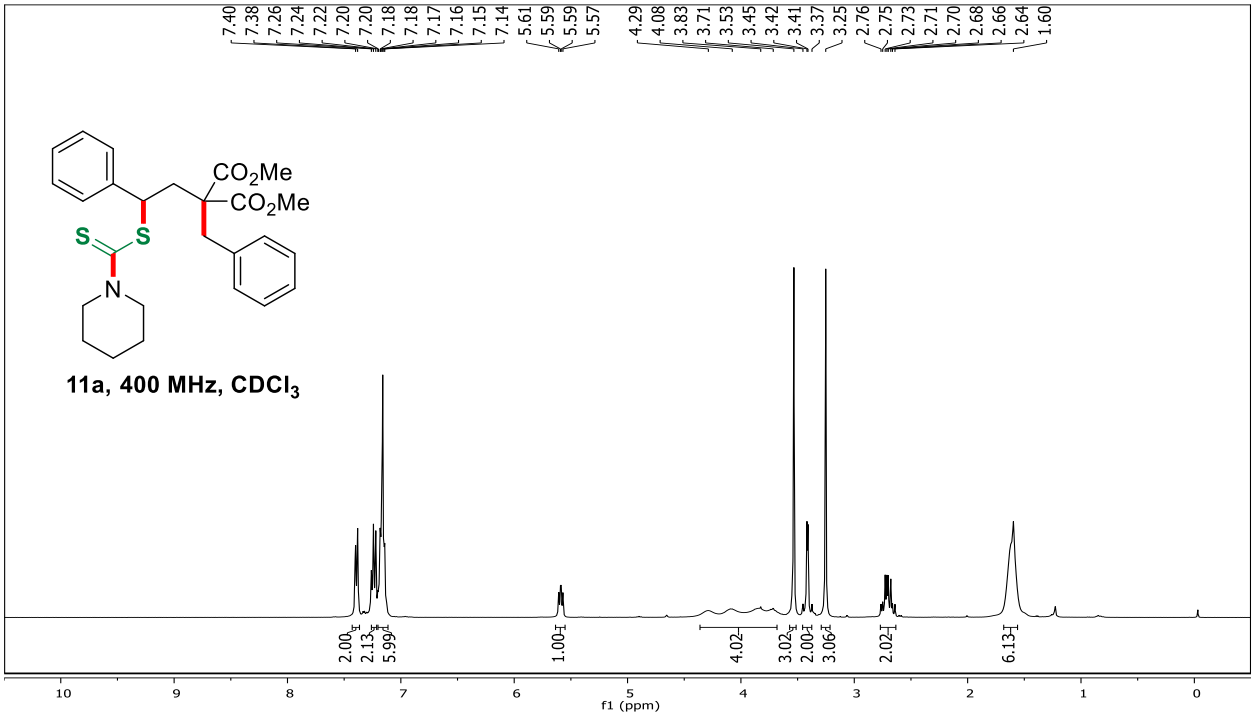
15

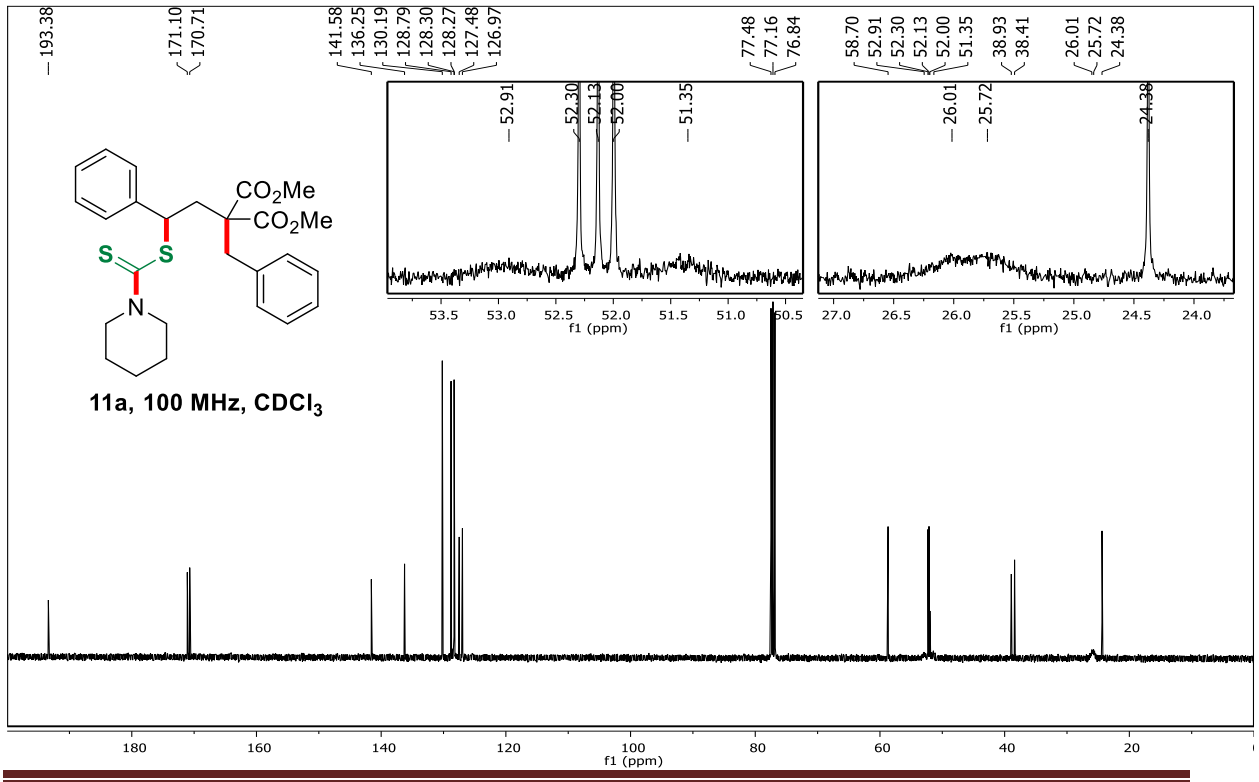
(Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded benzyl piperidine-1-carbodithioate **15** as yellow oil (0.075 g, 99% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.27; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54-7.23 (m, 5H), 4.53 (s, 2H), 4.27-3.83 (m, 4H), 1.67 (bs, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 195.4, 136.2, 129.5, 128.7, 127.6, 53.0, 51.5, 42.4, 26.1, 25.6, 24.4. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{13}H_{18}NS_2$ 252.0875; found 252.0878. **FTIR (cm^{-1})** 2916, 2346, 1643, 1426, 1225, 1105.

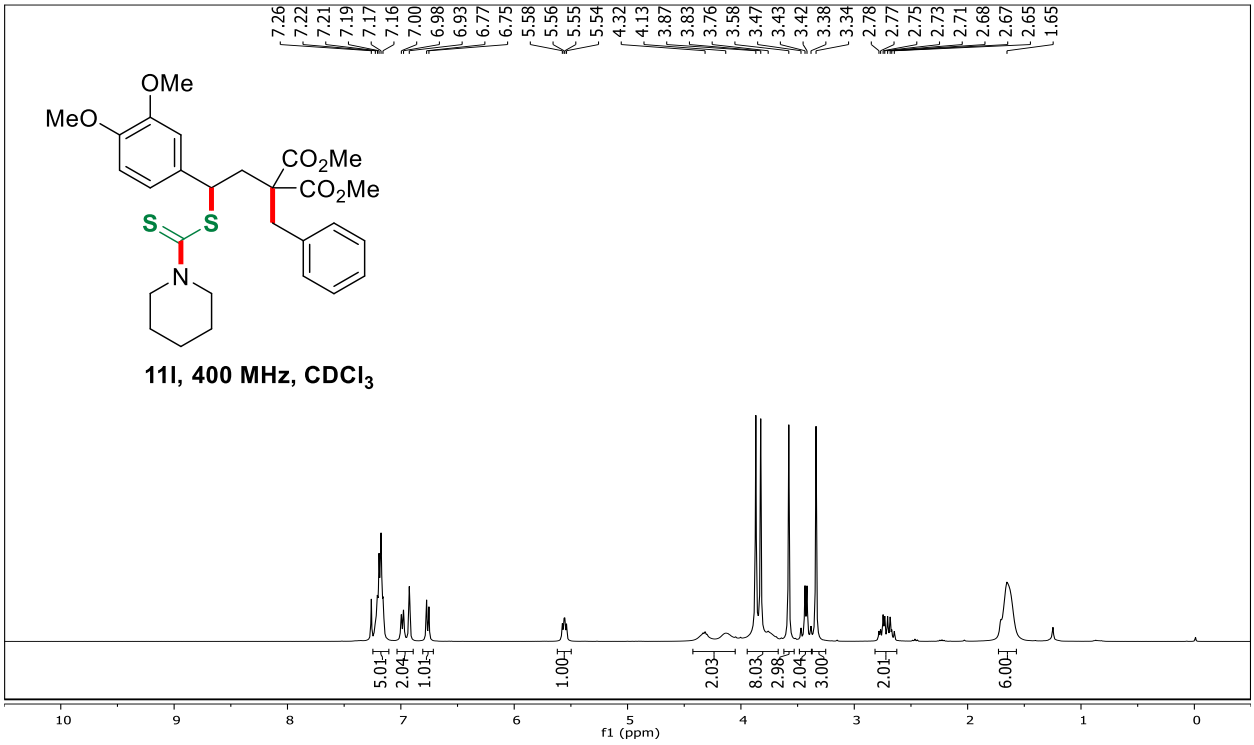
7.6.10. ^{1}H and ^{13}C NMR Spectra of Selected Compounds

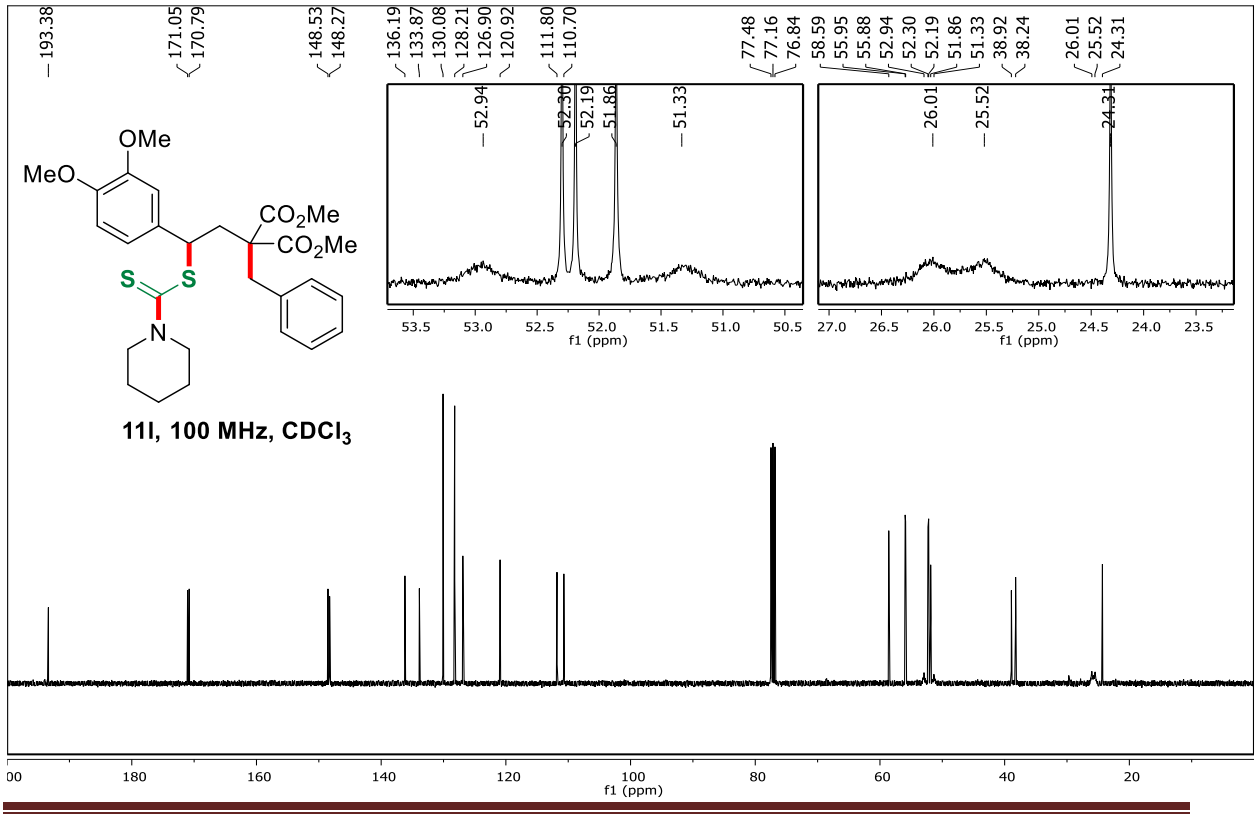
Dimethyl-2-benzyl-2-(2-phenyl-2-((piperidine-1-carbonothioyl)thio)ethyl)malonate (11a)



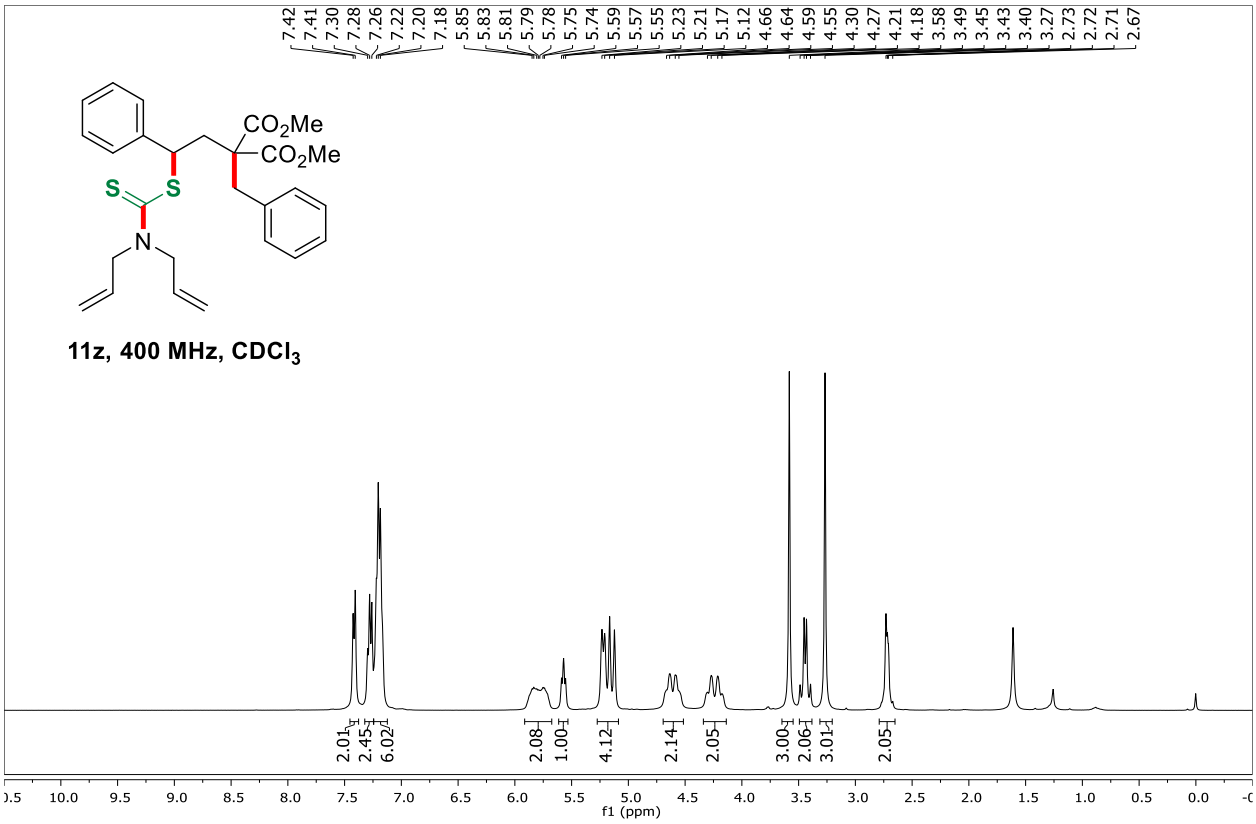


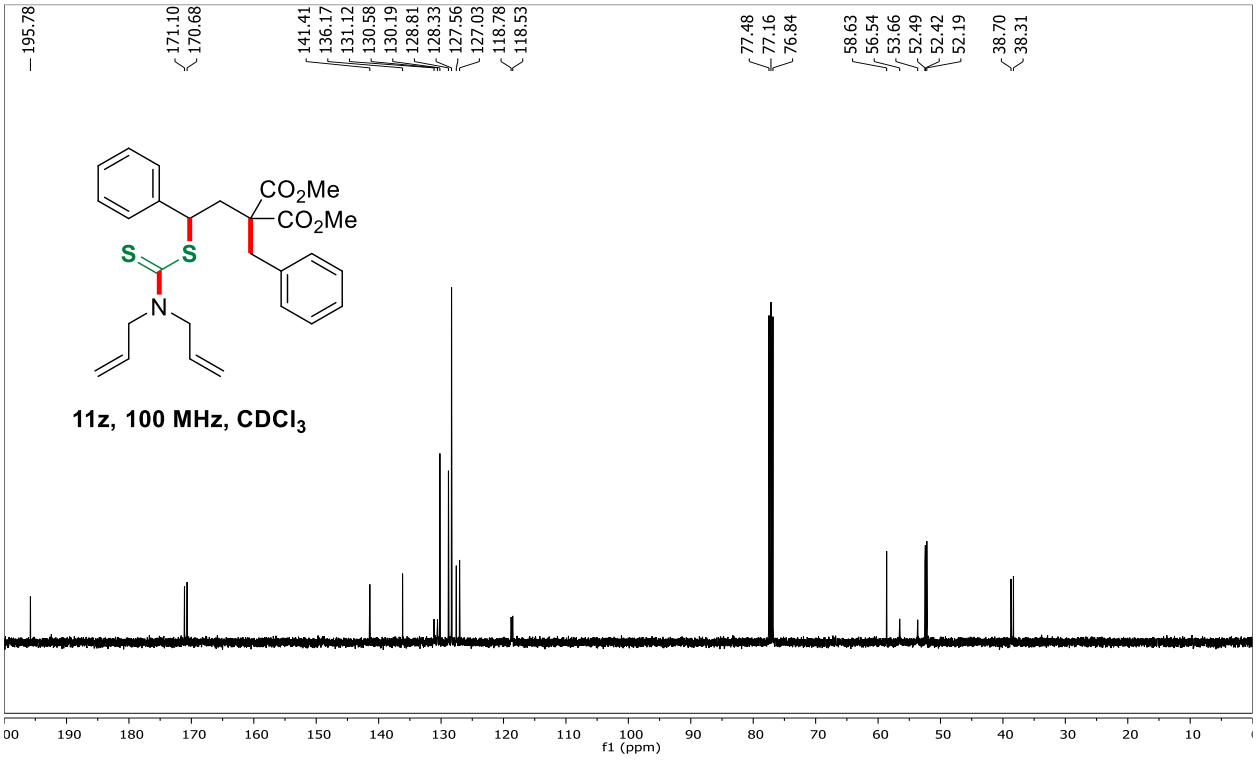
Dimethyl-2-benzyl-2-(2-(3,4-dimethoxyphenyl)-2-((piperidine-1-carbonothioyl)thio) ethyl)malonate (11l)



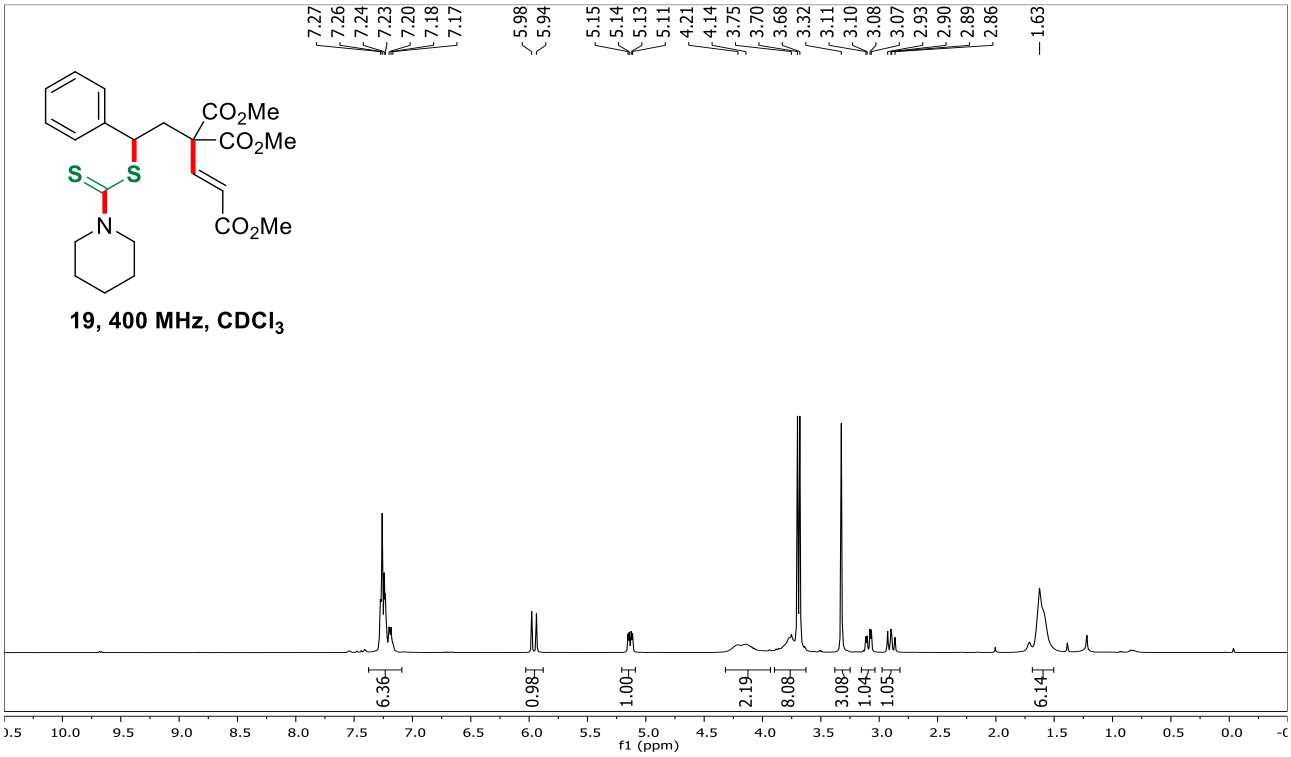


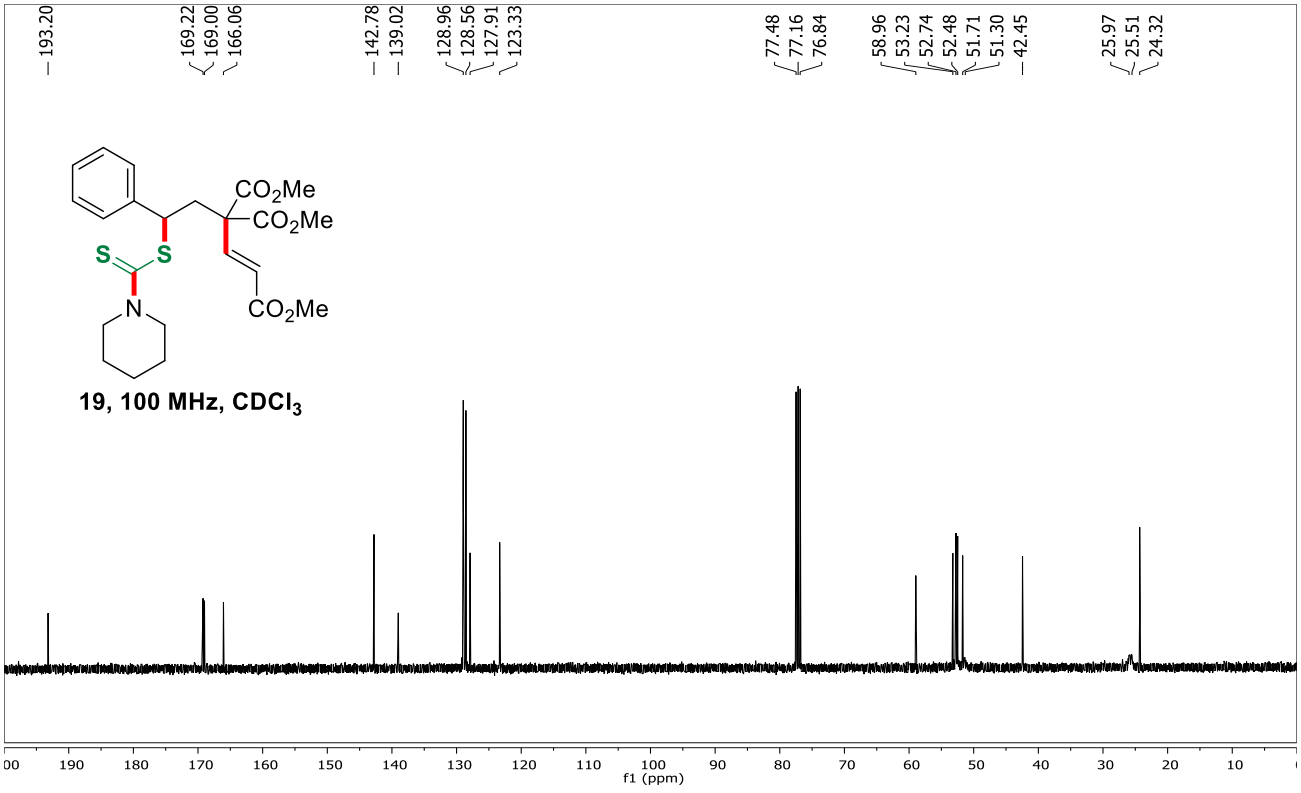
Dimethyl-2-benzyl-2-(2-((diallylcarbamothioyl)thio)-2-phenylethyl)malonate (11z)





Trimethyl (*E*)-5-phenyl-5-((piperidine-1-carbonothioyl)thio)pent-1-ene-1,3,3-tricarboxylate (19)





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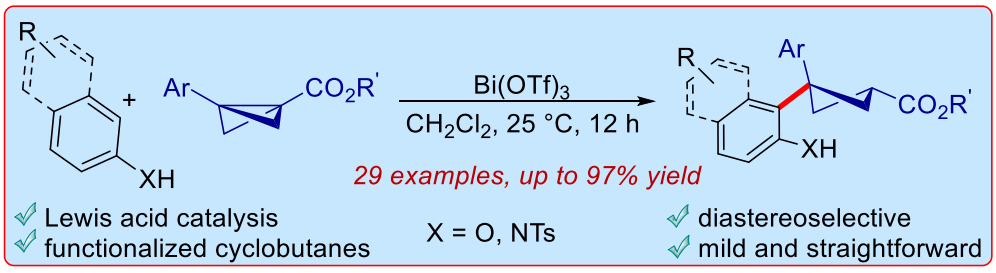
Chapter 8

Lewis Acid-Catalyzed Diastereoselective Carbofunctionalization of Bicyclobutanes Employing Naphthols

Traditional radical-mediated ring-opening of bicyclo[1.1.0]butanes (BCBs) for cyclobutane synthesis suffers from poor diastereoselectivity. Although few reports on BCB ring-opening via polar mechanisms are known, the Lewis acid-catalyzed diastereoselective ring-opening of BCBs using carbon nucleophiles is still underdeveloped. The focal theme of this Chapter is the mild and diastereoselective $Bi(OTf)_3$-catalyzed ring-opening of BCBs employing 2-naphthols has been reported. The anticipated carbofunctionalized trisubstituted cyclobutanes were obtained via the bicoordinated bismuth complex and the products are formed in good to excellent yields with high regio- and diastereoselectivity. The scope of the reaction was further extended using electron-rich phenols and naphthylamine. The functionalization of the synthesized trisubstituted cyclobutanes shows the synthetic utility of the present method.



Chem. Sci. **2023,** *14*, 6585.

8.1. Introduction

For decades, chemists have been fascinated by the concept of molecular strain. Extensive research on the properties and reactivity of strained carbocyclic systems has led to the development of numerous useful synthetic transformations.[1] In fact, the field of contemporary synthetic chemistry now includes the term "strain-release" reactions.[2] Among the highly strained cyclic compounds, bicyclo[1.1.0]butanes (BCBs) stand out due to their small size and substantial strain energy. Consequently, BCBs have garnered considerable attention from both theoretical and practical perspectives.[3] They serve as building blocks for creating diverse complex bicyclic structures, primarily through annulation reactions.[4] Additionally, these intricate BCB frameworks can also be functionalized without breaking the central C-C bond.[5] The development of heterolytic and homolytic ring-opening processes of BCBs has improved significantly in recent years, enabling access to structurally complex cyclobutane derivatives.

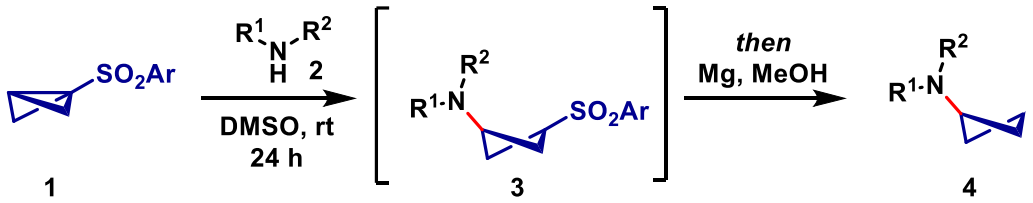
In the field of medicinal chemistry, there has been a growing interest in utilizing cyclobutanes as fundamental building blocks. These compounds offer unique structural designs and possess favorable electronic, steric, and conformational properties.[6] However, the synthesis of these four-membered rings poses significant challenges, resulting in limited methods for preparing cyclobutanes with diverse synthetically relevant and pharmaceutically valuable functional groups.[7] As a result, chemists have recently turned their attention to highly strained bicycles like BCBs in search of innovative protocols for synthesizing these important motifs. The upcoming section will discuss selected reports for cyclobutane synthesis from bicyclobutanes.

8.2. Functionalized Cyclobutane Synthesis from Bicyclobutanes

In 2016, Baran and co-workers uncovered the ring-opening reactions of BCBs with amine or amide nucleophiles, which marked a crucial turning point in revitalizing interest in BCBs. This innovative technique, known as ‘strain-release amination’, proved to be valuable for incorporating the cyclobutylamino motif into diverse medically relevant compounds (Scheme 8.1).[8] Aryl sulfones were utilized as the activating groups for BCBs, but these groups could be selectively removed as well through reduction. Importantly, the strain-release approach demonstrated broad applicability, as both azabicyclobutanes and [1.1.1]

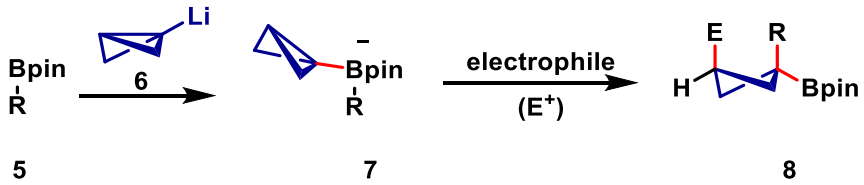
propellane exhibited similar reactivity towards various amine or amide nucleophiles. Notably, this ring-opening reaction was applicable only for heteroatom nucleophiles. Additionally, Wipf and co-workers also showed that the phosphine-borane anions can also be utilized as nucleophilic triggers to attack nitrile-BCBs.[9]

Scheme 8.1. Strain-Release Amination Strategy



In addition, Aggarwal and co-workers explored the nucleophilic reactivity of BCBs through the in situ formation of highly strained BCB boronates **7** using lithiated BCBs **6** and boronic esters **5**. These complexes, characterized by high strain, possess the ability to undergo reactions with diverse nucleophiles, enabling the construction of highly functionalized cyclobutanes **8** with high diastereoselectivity (Scheme 8.2).[10] This boronate transfer process was utilized for a series of conceptually similar reactions designed for diverse cyclobutanes synthesis. It is important to highlight that the generation of the highly nucleophilic lithiated BCBs necessitated the use of 1,1-dibromo-2-(chloromethyl) cyclopropane and *tert*-butyl lithium, which presents challenges in terms of handling and synthetic manipulation.

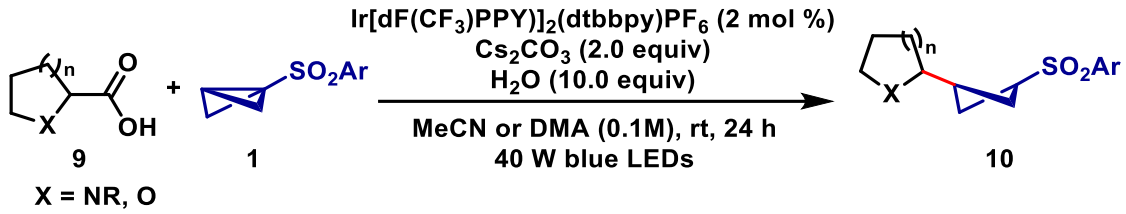
Scheme 8.2. Boronate Transfer Process for Cyclobutane Synthesis



Moreover, BCBs can undergo ring-opening reactions through the addition of radicals. For instance, Ernouf and co-workers demonstrated a photoredox-catalyzed decarboxylative radical addition method for synthesizing functionalized cyclobutanes via the ring-opening of BCBs **1** (Scheme 8.3).[11] This reaction involves formal Giese-type addition of C(sp^3)-centered radicals to highly strained bicyclo[1.1.0]butanes. The use of mild photoredox conditions, employing a readily available and stable phenyl sulfonyl bicyclo[1.1.0]butane, proved to be suitable for a wide range of α-amino and α-oxy carboxylic acids, thereby providing a concise

pathway to substituted cyclobutanes **10**. However, it should be noted that the developed method lacks diastereoselectivity, with diastereomeric ratios ranging from 1:1 to 3.5:1 in most cases.

Scheme 8.3. Photochemical Strain-Release-Driven Cyclobutylation

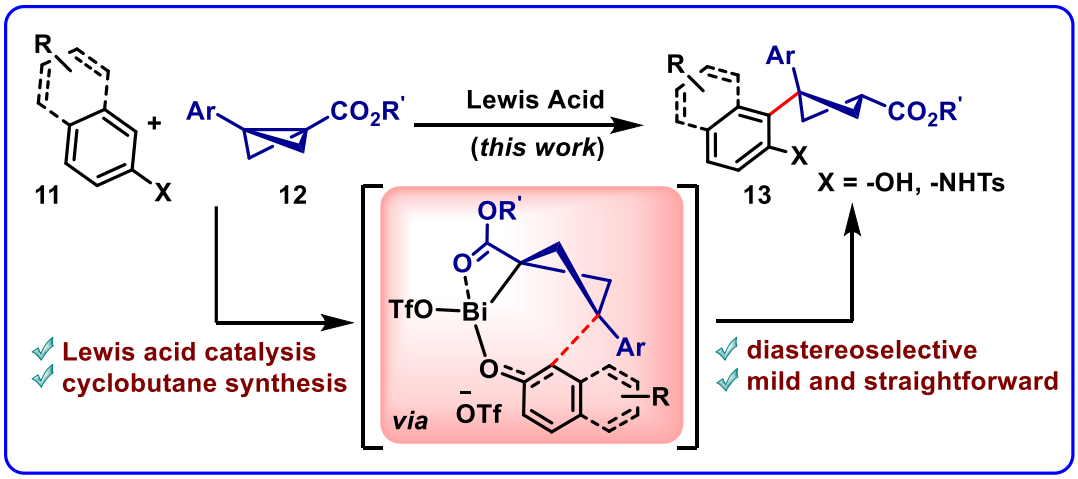


Similarly, Jui,[12] Gryko,[13] and Studer[14] also demonstrated radical-mediated ring-opening reactions of BCBs; but these reactions also suffered from poor diastereoselectivity. In another approach, Fox and co-workers presented the homoconjugate addition of organocuprates to BCBs, followed by the trapping of the resulting enolate with an electrophile.[15] While this chemistry showcased a novel application of BCBs, the cyclobutane products often exhibited low levels of diastereoselectivity.

8.3. Statement of the Problem

As discussed in the previous section, the synthesis of cyclobutanes from bicyclobutanes has encountered challenges in terms of low diastereoselectivity or complicated reaction procedures. Drawing inspiration from Aggarwal's boronate transfer process,[10] we hypothesized that Lewis acids could potentially function similarly to boronates. We speculated that a similar ordered transition state involving the nucleophile and BCBs can

Scheme 8.4. Lewis Acid-Catalyzed Carbofunctionalization of BCBs Employing Naphthols



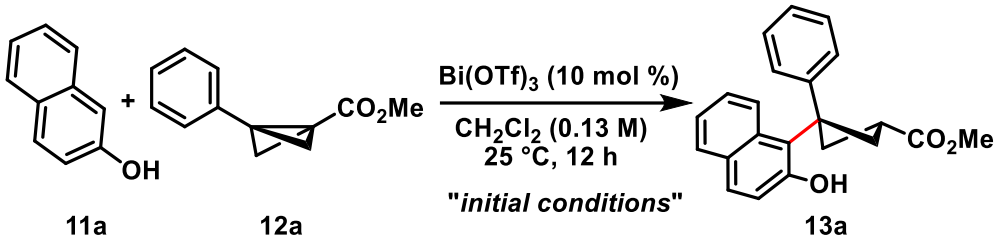
be attained by a strategic choice of substituents having distinct propensity to coordinate to a Lewis acid, leading to high diastereoselectivity. Recently, Leitch and co-workers developed the Lewis acid-catalyzed method for the divergent synthesis of azabicyclohexanes and cyclobutenyl amines from bicyclobutanes.[16] However, the application of such strategy for the Lewis acid catalyzed ring-opening carbofunctionalization of bicyclobutanes has not been reported yet. The ability of Lewis acids to coordinate with naphthols motivated us to select it as the nucleophilic trigger.[17] We envisioned that the Lewis acid could coordinate with both BCBs and naphthols, bringing them into proximity and enabling the carbofunctionalization of bicyclobutanes possible, ultimately leading to the formation of trisubstituted cyclobutanes (Scheme 8.4). In this context, it is worth noting that functionalized trisubstituted cyclobutanes serve as important building blocks in medicinal chemistry.[18]

8.4. Results and Discussion

8.4.1. Optimization Studies

With the envisioned idea in mind, the present studies were initiated by the treatment of 2-naphthol **11a** with the BCB **12a** in the presence of $Bi(OTf)_3$ (10 mol %) in CH_2Cl_2 at 25 °C. Using these conditions, the anticipated carbofunctionalized product **13a** was formed in 91% yield as a single diastereomer (Table 8.1, entry 1). Interestingly, the possible side products originating from the direct addition of hydroxyl group of 2-naphthol to bicyclobutane was not observed under these conditions. Other Lewis acids such as $Sc(OTf)_3$ and $Yb(OTf)_3$ provided a reduced yield of **13a** under the present conditions (entries 2, 3). When triflic acid was used as a Brønsted acid catalyst, no desired product was obtained (entry 4). Other solvents were found to be ineffective for this desired transformation (entries 5, 6). It is worth mentioning that, using MeCN as the solvent, the expected product was formed in 86% yield and 3:1 diastereomeric ratio (entry 7). Carrying out the reaction at 0 °C didn't improve the yield of **13a** (entry 8). Moreover, increasing the amount of **12a** to 1.5 equiv did not improve the yield of **13a** considerably (entry 9). Lowering the amount of Lewis acid or performing the reaction at dilute conditions resulted in lower yield of the carbofunctionalized product (entries 10, 11). Hence, entry 1 was chosen as the optimal condition for this diastereoselective carbofunctionalized cyclobutane synthesis.

Table 8.1. Optimization of the Reaction Conditions[a]



11a 12a 13a

entry	variation of the initial conditions	yield of 13a (%)[b]
1	*none*	*91*
2	Sc $(OTf)_3$ instead of $Yb(OTf)_3$	28
3	$Yb(OTf)_3$ instead of $Yb(OTf)_3$	15
4	TfOH instead of $Yb(OTf)_3$	17
5	DCE instead of CH_2Cl_2	78
6	THF instead of CH_2Cl_2	39
7[c]	MeCN instead of CH_2Cl_2	86
8	0 °C instead of 25 °C	84
9	1.5 equiv of **12a**	92
10	5 mol % $Bi(OTf)_3$	83
11	0.06 M CH_2Cl_2	81

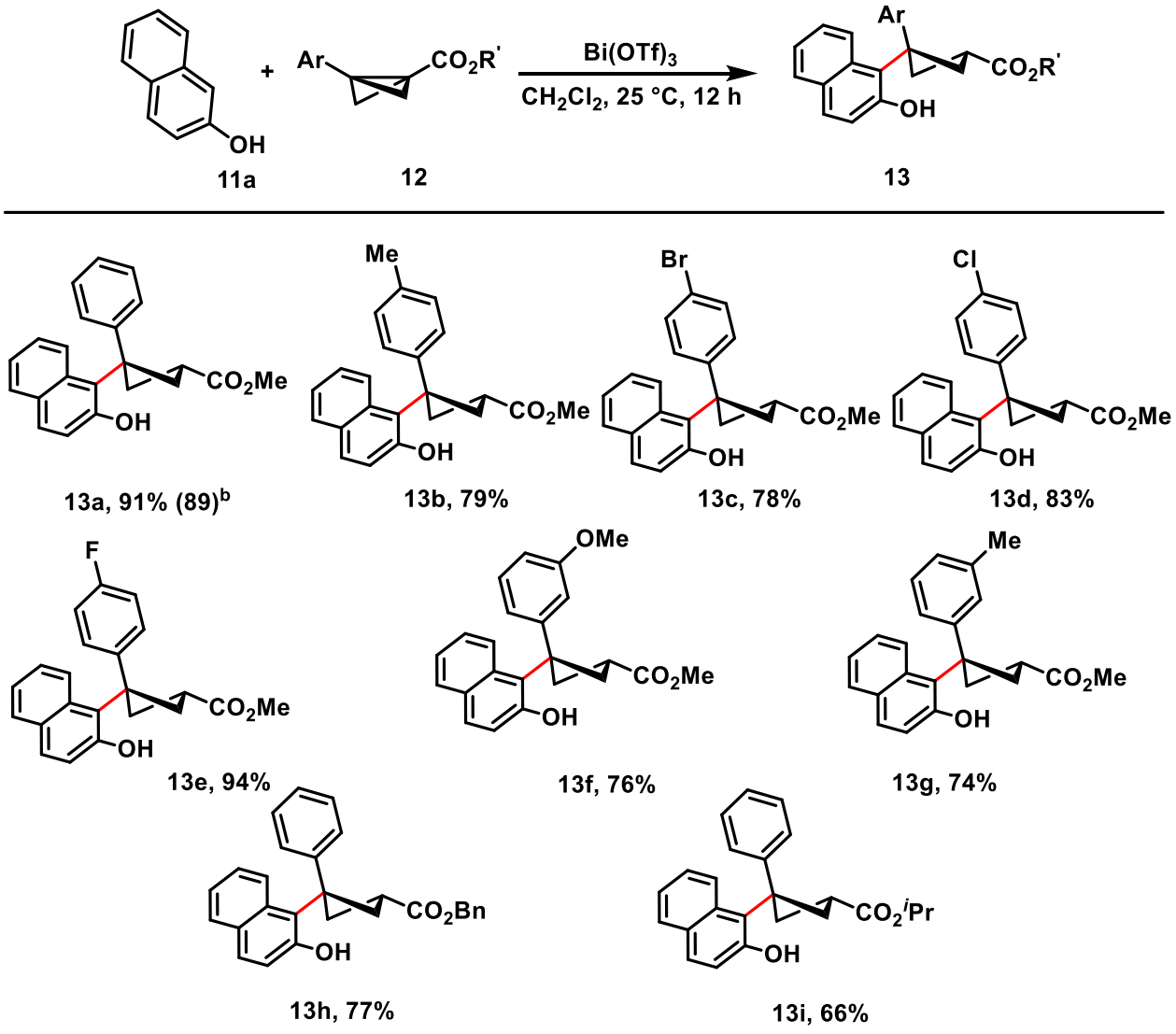
[a] Initial conditions: **11a** (0.20 mmol), **12a** (0.24 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1.5 mL), 25 °C for 12 h. [b] Given are the yield of chromatographically purified **13a**. [c] 3.0:1 diastereomeric ratio was obtained in this case and the dr value was determined from ^1H NMR of the crude reaction mixture.

8.4.2. Substrate Scope of Carbofunctionalization of Bicyclobutanes: Scope of Bicyclobutanes

With the identified reaction conditions in hand, we evaluated the scope and drawbacks of this diastereoselective carbofunctionalization of BCBs (Scheme 8.5). The variation on the BCBs was examined first. A variety of bicyclo[1.1.0]butanes having electron-releasing, -neutral, or -withdrawing groups at the 4-position of the benzene ring underwent smooth ring-opening reaction leading to the diastereoselective formation of the desired carbofunctionalized products in good yields (**13a-13e**). The developed carbofunctionalization reaction was scalable, as evidenced by the isolation of **13a** in 89% yield when the reaction was carried out on a 2.0 mmol scale. Furthermore, BCBs with substituents at the 3-position of the aryl ring tolerated well under the current conditions, resulting in the formation of the expected cyclobutane products in high yields (**13f-13g**). Disappointingly, 2-substituted aryl BCBs failed to give the desired product under the present

reaction conditions, most likely for steric reasons. Moreover, this regio- and diastereoselective ring-opening reaction was not limited to methyl ester derived BCBs but benzyl and isopropyl substituted BCBs afforded the target products in good yields (**13h**-**13i**). It may be noted that the reaction performed using 3-unsubstituted BCB with ester at 1-position failed to afford the desired ring-opened product under the optimized conditions.

Scheme 8.5. Substrate Scope: Variation of Bicyclobutanes[a]

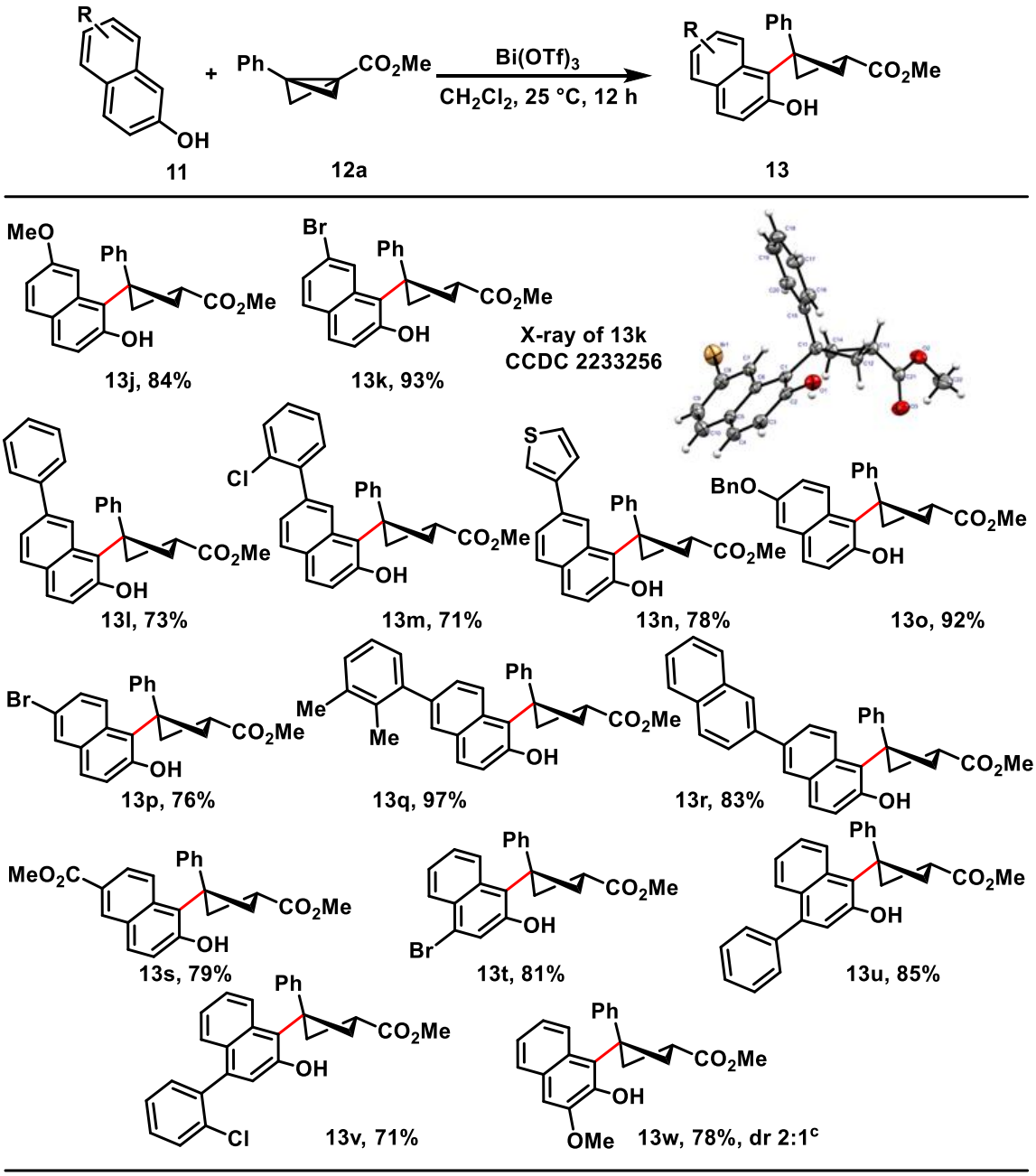


[a] General conditions: **: 11a** (0.20 mmol), **12** (0.24 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1.5 mL), 25 °C for 12 h. Provided are isolated yields of products. [b] Yield of the experiment conducted on a 2.0 mmol scale.

8.4.3. Substrate Scope of Carbofunctionalization of Bicyclobutanes: Scope of Naphthols

The scope of the reaction was then evaluated using variously substituted naphthols.

Scheme 8.6. Substrate Scope: Variation of Naphthols[a]



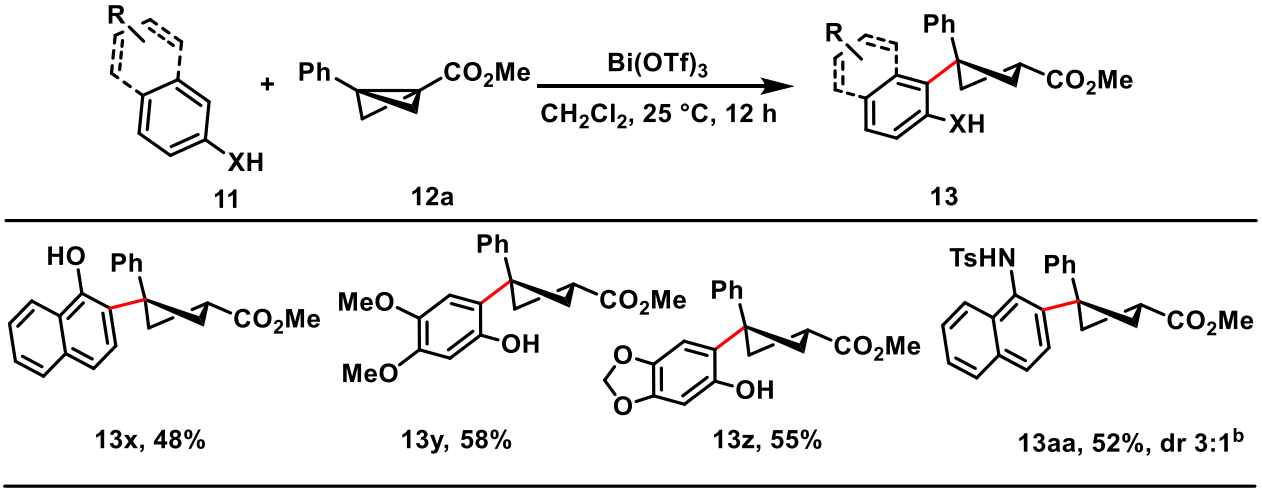
[a] General conditions: **11** (0.20 mmol), **12a** (0.24 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1.5 mL), 25 °C for 12 h. Provided are isolated yields of products. [c] The dr value was determined from ^1H NMR of the crude reaction mixture.

The reaction conducted using 7-methoxynaphthalen-2-ol **11b** as the nucleophilic trigger furnished the desired product **13j** in 84% yield (Scheme 8.6). 7-bromo substituted 2-naphthol **11c** also worked well and the anticipated product **13k** was formed in 93% yield. In this case, the product structure was confirmed using X-analysis of the crystal. Moreover, 2-naphthols with various aryl and heteroaryl substitutions at the 7-position of the naphthol ring afforded good yields of carbofunctionalized cyclobutanes (**13l-13n**). A wide range of 2-naphthols with electron-releasing, -withdrawing, or -neutral groups at the 6-position of the naphthol ring yielded the desired products in a single diastereomer (**13o-13s**). Various 4-substituted 2-naphthols could also be used as substrates to obtain the corresponding carbofunctionalized cyclobutanes (**13t-13v**) under the optimized reaction conditions. The reaction using 3-methoxy 2-naphthol afforded the target product **13w** in 78% yield and 2:1 dr.

8.4.4. Substrate Scope of Carbofunctionalization of Bicyclobutanes: Scope of Nucleophiles

Interestingly, this carbofunctionalization reaction of BCB is not only limited to 2-naphthol as the nucleophilic trigger, but 1-naphthol also worked under the present reaction conditions and the target product **13x** was formed in 48% yield (Scheme 8.7). This ring-opening reaction can also be extended further towards electron-rich phenols as the nucleophile and in that case the products (**13y**, **13z**) were obtained in moderate yields.

Scheme 8.7. Substrate Scope: Variation of Nucleophiles[a]



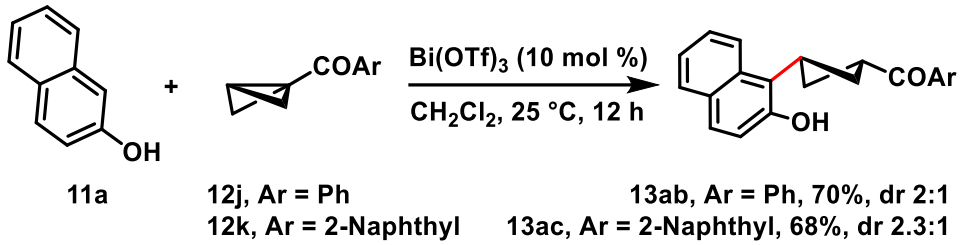
[a] General conditions: **11** (0.20 mmol), **12a** (0.24 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1.5 mL), 25 °C for 12 h. Provided are isolated yields of products. [b] The dr value was determined from ^1H NMR of the crude reaction mixture.

Finally, naphthylamine could also be used as the nucleophile to open BCB and the reaction furnished the functionalized cyclobutane **13aa** in 52% yield with 3:1 dr.

8.4.5. Substrate Scope of Carbofunctionalization of Bicyclobutanes: Scope of Unsubstituted Ketone BCBs

The reaction of monosubstituted ketone derived BCB **12j** with **11a** under the optimized conditions afforded the cyclobutyl ketone **13ab** in 70% yield and inseparable mixture of diastereomers in 2:1 ratio (Scheme 8.8). Similar results are obtained with the 2-naphthyl-derived BCB **12k**, and the product **13ac** was formed in 68% yield and 2.3:1 dr. These experiments tend to indicate that the aryl group of BCB has a major role in this diastereoselective ring-opening reaction.

Scheme 8.8. Substrate Scope: Variation of Unsubstituted Ketone BCBs[a]



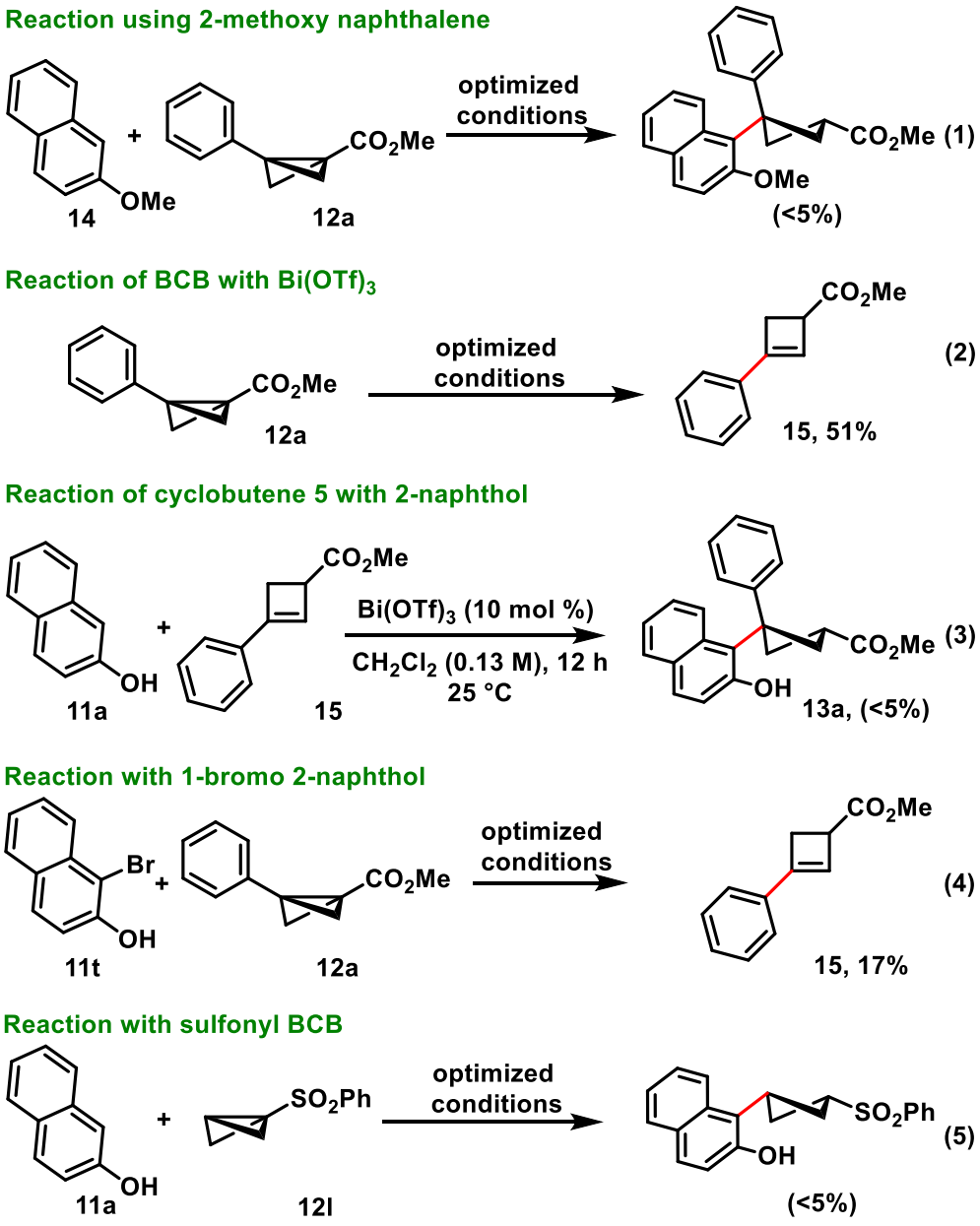
[a] General conditions: **11** (0.20 mmol), **12j-12k** (0.24 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1.5 mL), 25 °C for 12 h. Provided are isolated yields of products. The dr value was determined from ^1H NMR of the crude reaction mixture.

8.4.6. Mechanistic Experiments

A few mechanistic experiments were carried out to get insight into the mechanism of the present reaction. When the reaction was performed in the absence of $Bi(OTf)_3$, no product formation was observed, indicating that the Lewis acid is crucial for this reaction. Moreover, reaction conducted using methyl protected 2-naphthol **14** did not afford the desired product shedding light on the role of the free -OH in this carbofunctionalization reaction. In the absence of the free -OH group, it is likely that the carbofunctionalization process was deemed unfavourable due to the lack of proper coordination between 2-naphthol and $Bi(OTf)_3$ (Scheme 8.9, eq 1). The reaction of BCB **12a** with $Bi(OTf)_3$ in the absence of 2-naphthol **11a** furnished the cyclobutene **15** in 51% yield under the optimized reaction conditions (eq 2). This study indicates that in the absence of 2-naphthol, BCB can directly coordinate with

Lewis acid, which results in the formation of **15**. Most probably, 2-naphthol reduces the Lewis acidity of $Bi(OTf)_3$ and therefore no cyclobutene product was obtained under our optimized reaction conditions. To rule out the possibility of the carbofunctionalized product formation via the intermediacy of the cyclobutene **15**, 2-naphthol **11a** and **15** were subjected to the present reaction conditions. However, the desired product **13a** was not formed, thereby confirming that the reaction was not proceeding via the cyclobutene intermediate **15** (eq 3).

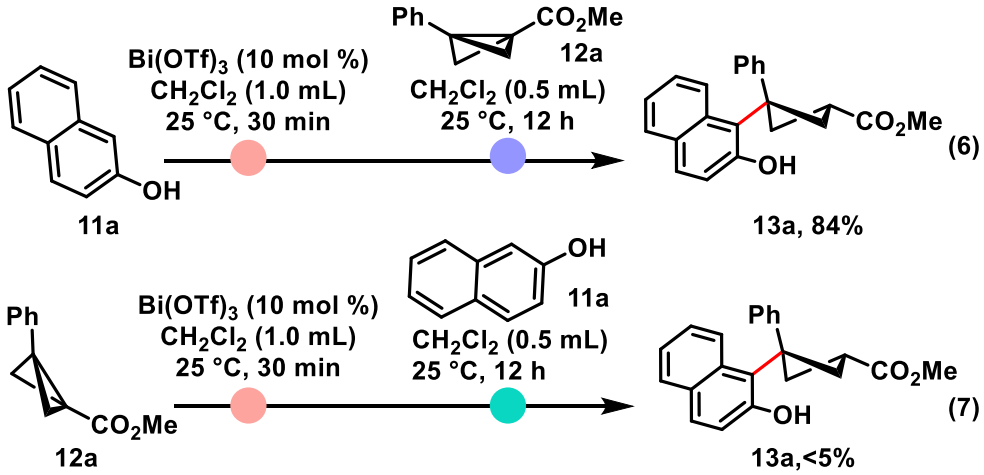
Scheme 8.9. Mechanistic Experiments



When the reaction was performed using 1-bromo 2-naphthol **11s** under the optimized conditions, the desired ring-opening product of BCB was not formed, and the cyclobutene **15** was formed in 17% yield (eq 4).[19] This indicates that the present reaction does not work with 2-naphthols with a substituent at the 1-position. Performing the reaction using sulfonyl group-containing BCB did not afford the desired ring-opening product shedding light on the importance of carbonyl moiety of BCB for effective Lewis acid binding in this diastereoselective ring-opening reaction (eq 5).

We also examined how the mode of reagent addition affects the reaction outcome. When 2-naphthol and $Bi(OTf)_3$ were stirred for 30 min and subsequently BCB **12a** was added, the expected product **13a** was formed in 84% yield (Scheme 8.10, eq 6). It is noteworthy that reversing the order of reagent addition did not result in the product formation (eq 7). These two reactions support the hypothesis about the intermediacy of a bicoordinated Bi-complex for the fruitful transformation. The pre-complexation of the Lewis acid with 2-naphthol (presumably) lowers the acidity of the Lewis acid thereby effectively halting the BCB decomposition; the soft coordination with BCB ester with the precomplexed $Bi(OTf)_3$ (with 2-naphthol) forms the bicoordinated Bi-complex which enables the diastereoselective ring-opening of activated BCB. Reversing the mode of addition leads to decomposition of the BCB, as the acidity of Lewis acid could not be reduced by 2-naphthol coordination.

Scheme 8.10. Dependence of the Reaction on the Mode of Addition

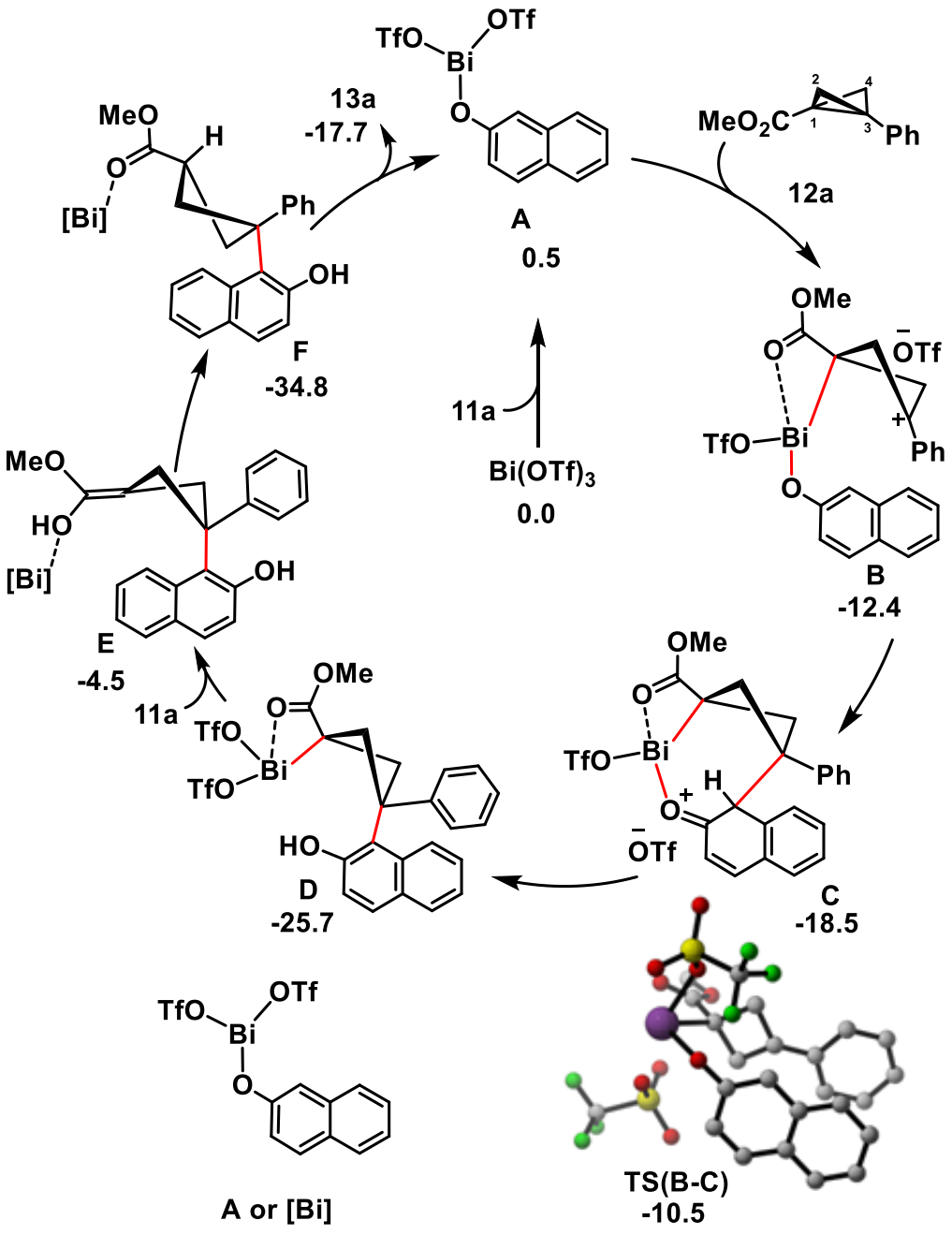


8.4.7. Proposed Mechanism

Based on the mechanistic studies and DFT calculations, a catalytic cycle for this diastereoselective ring-opening reaction is presented in Scheme 8.11. Initially, the

coordination between $Bi(OTf)_3$ and 2-naphthol **11a** forms the intermediate **A**. This intermediate **A** serves to be the catalytically active species in this transformation. Following this, BCB **12a** also coordinates with intermediate **A** displacing one of the triflate ions, and forms the cationic intermediate **B**. Interestingly, the BCB coordinates via C1, thereby

Scheme 8.11. Proposed Catalytic Cycle



Relative free energy values are given in kcal mol^{-1}.

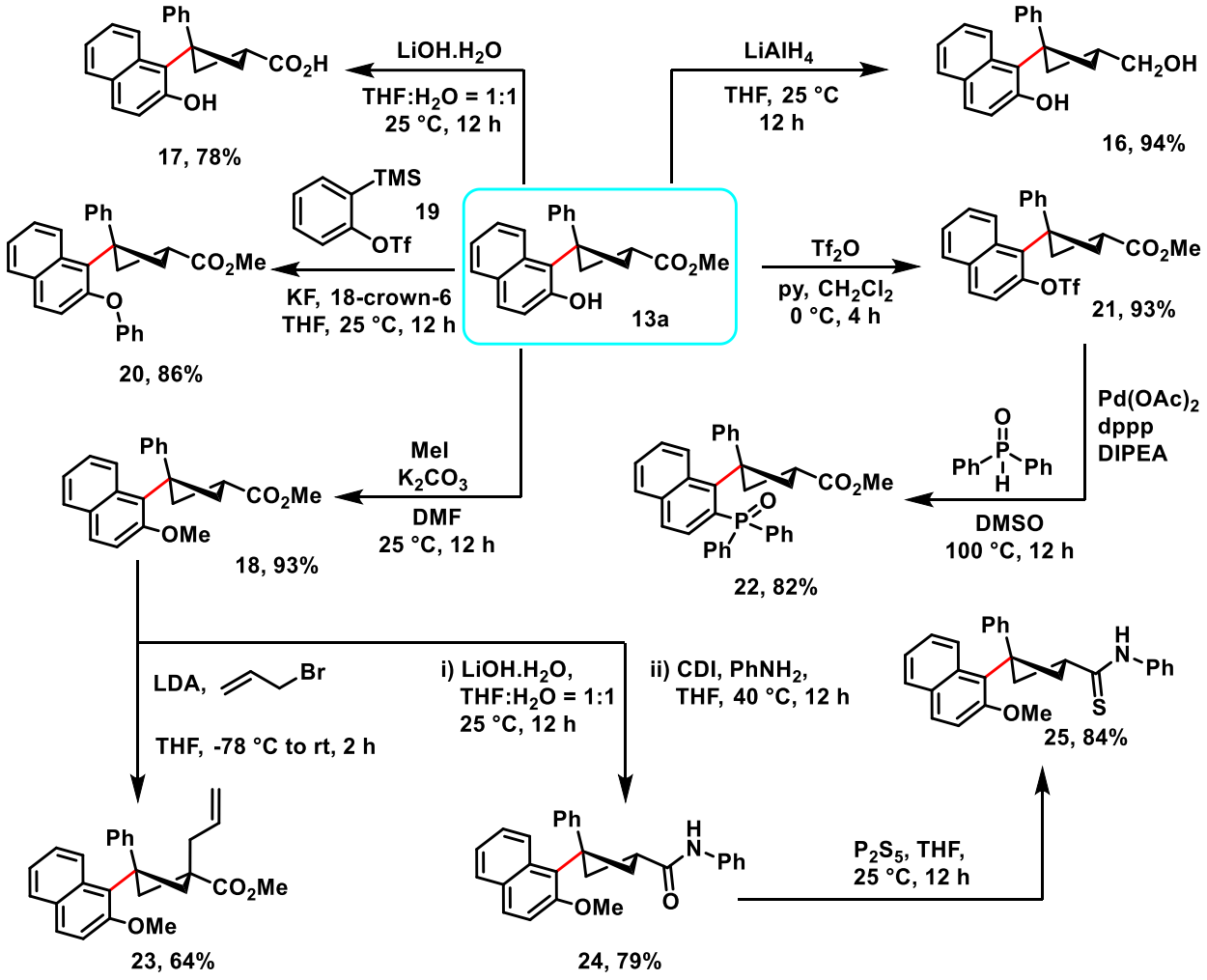
generating a positive charge on C3 and further activating it towards the nucleophilic attack. Subsequently, nucleophilic attack of 2-naphthol moiety on BCB occurs through **TS(B-C)**, leading to the formation of the intermediate **C**. This nucleophilic attack presents an activation free energy barrier of only 1.9 kcal/mol making it a highly facile process. This is followed by a 1,3-proton transfer that restores the aromaticity of 2-naphthol and generates the intermediate **D**. Further proton transfer result in the final product **F** via a proposed intermediate **E**, where the proton is envisioned to transfer from a second molecule of **11a**. Notably, the proton transfer from intermediate **E** can happen from either face of the substrate resulting in the formation of two diastereomeric products. Thus, this step is most likely to be the diastereo-determining step of this transformation. The DFT studies indicated that the TSs for the direct proton transfer was of very high energy, thus, suggesting that assisted proton transfer via triflate, 2-naphthol, etc., could take place. It was found that the observed diastereomer **13a** is 1.7 kcal/mol more stable than the other diastereomer. Therefore, it is reasonable to assume that the diastereoselectivity determining step has the thermodynamic influence.

8.4.8. Synthetic Utility of Trisubstituted Cyclobutanes

The trisubstituted cyclobutane **13a** synthesized using the present method can be employed as a synthetically useful precursor for the synthesis of functionalized cyclobutanes (Scheme 8.12). Reduction of the ester group in **13a** using $LiAlH_4$ provided the primary alcohol **16** in 94% yield. Moreover, the methyl ester in **13a** was hydrolysed to form the free carboxylic acid **17** in 78% yield. Methyl protection of the free -OH group was carried out and the expected product **18** was formed in 93% yield. In addition, the cyclobutane derivative **13a** can be easily *O*-arylated under transition-metal-free conditions using arynes as the aryl source. Thus, when **13a** was treated with benzyne produced from the triflate precursor **19** using KF (with 18-crown-6 as an additive), the desired product **20** was obtained in 86% yield. Furthermore, treatment of the cyclobutane **13a** with triflic anhydride in the presence of pyridine furnished the desired product **21** in 93% yield. Subsequent treatment of **21** with diphenylphosphine oxide in the presence of catalytic amount of $Pd(OAc)_2$ furnished the phosphine oxide **22** in 82% yield. Additionally, the α-allylation of the methyl protected methyl ester **18** using allyl bromide under basic conditions provided the desired allylation product **23** with two all-carbon quaternary stereocenter in 64% yield. The ester functionality

in **8** could easily be converted to an amide moiety in two steps and the target amide **24** was formed in 79% yield. Subsequently, the amide was converted into the thioamide derivative **25** in 84% yield by the treatment with P_2S_5.

Scheme 8.11. Synthetic Utility of Trisubstituted Cyclobutanes



8.5 Conclusion

In conclusion, a Lewis acid-catalyzed diastereoselective carbofunctionalization of BCBs utilizing 2-naphthols as the nucleophilic trigger leading to the formation of tricyclic cyclobutanes has been realized. The desired transformation relies on the bicoordinated bismuth complex as the crucial intermediate. The present reaction is operationally simple, advances smoothly under mild conditions and can tolerate various functional groups. This reaction is not restricted to 2-naphthols as the nucleophilic trigger; electron-rich phenols and

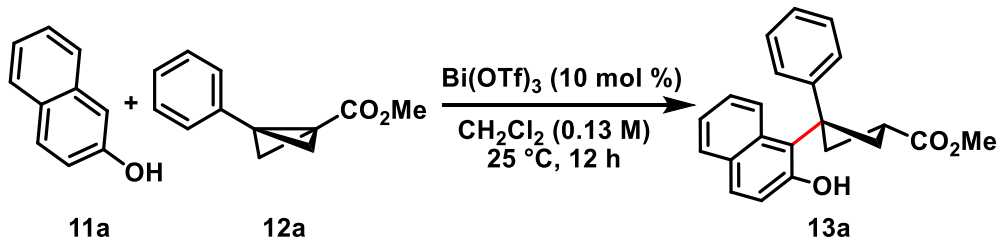
naphthylamine can also act as the nucleophile. Mechanistic experiments and DFT studies were carried out to get insight into the possible course of the reaction. To reveal synthetic handles for additional synthetic transformations, functional group interconversions were also performed.[20]

8.6. Experimental Details

8.6.1. General Information

Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in oven-dried reaction vessels with Teflon screw caps. 25 °C Corresponds to the room temperature (rt) of the lab when the experiments were carried out. CH_2Cl_2 was freshly purified by distillation over CaH_2 under nitrogen atmosphere. Naphthols were purchased from either Alfa Aesar, TCI, BLD pharm or Sigma-Aldrich and were used as received. All BCBs were synthesized following the literature procedure.[21] Aryl/ heteroaryl 2-naphthols were synthesized following known literature procedure via Suzuki coupling.[22] Analytical thin layer chromatography was performed on TLC Silica gel 60 F254. Visualization was accomplished with short wave UV light or $KMnO_4$ staining solutions followed by heating. Unless and otherwise specified flash chromatography was performed on silica gel (230-400 mesh) by standard techniques eluting with Pet. Ether-EtOAc solvent system. All compounds were fully characterized. ^1H and ^{13}C NMR spectra were recorded on Bruker Ultrashield spectrometer in $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Infrared (FT-IR) spectra were recorded on a Bruker Alfa FT-IR, ν-max in cm^{-1}. HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument.

8.6.2. General Procedure for the Optimization of the Reaction Conditions

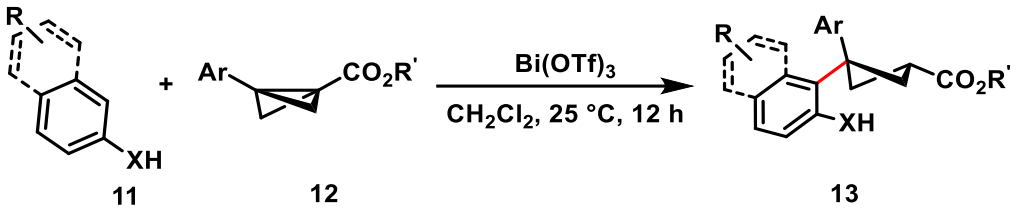


11a 12a 13a

To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, 2-naphthol **11a** (0.029 g,

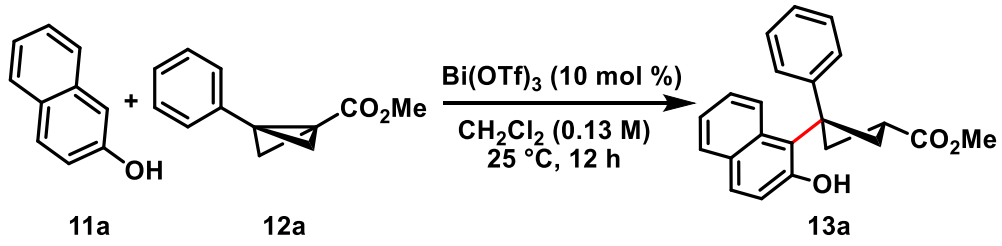
0.2 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, methyl 3-phenylbicyclo [1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the solvent was evaporated and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 80/20) on silica gel to afford **13a** as a yellow solid.

8.6.3. General Procedure for the Lewis Acid Catalyzed Diastereoselective Carbofunctionalization of Bicyclobutanes



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, nucleophile **11** (0.2 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, BCBs **12** (0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Later the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet.ether-EtOAc as eluent) to afford **13** in good to excellent yields.

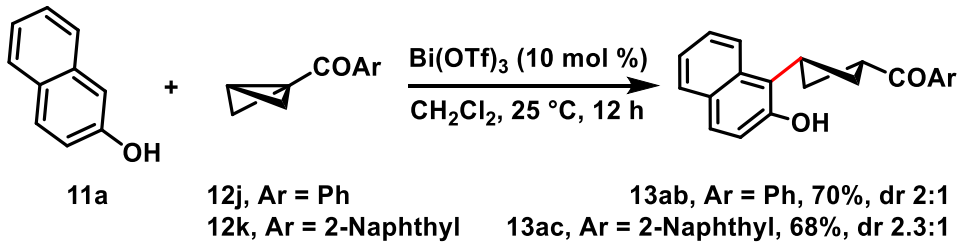
Procedure for the 2.0 mmol Scale Reaction for the Synthesis of 13a



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.131 g, 0.2 mmol) inside the glove box. After that, 2-naphthol **11a** (0.288 g, 2.0 mmol) and 10 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere.

Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.452 g, 2.4 mmol) and 5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 80/20) on silica gel to afford **13a** as a yellow solid (0.592 g, 89% yield).

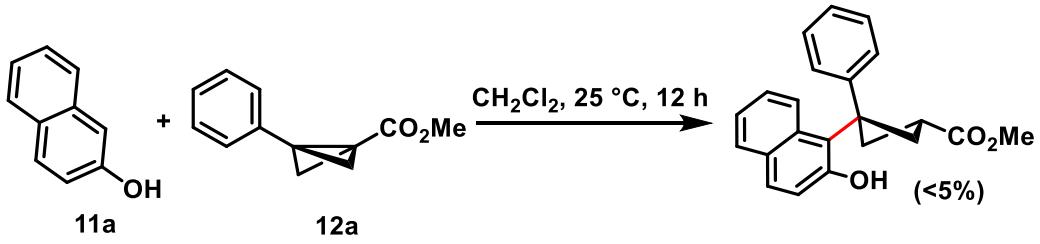
8.6.4. General Procedure for the Reaction of Unsubstituted Ketone BCBs



To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, 2-naphthol **11a** (0.029 g, 2.0 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 5 minutes. After 5 minutes, keto BCBs **12j** or **12k** (0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Later the reaction mixture was stirred for 12 h. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet.ether-EtOAc as eluent) to afford **13ab** or **13ac** in moderate to good yields.

8.6.5. Mechanistic Experiments

(a) Reaction in the Absence of $Bi(OTf)_3$

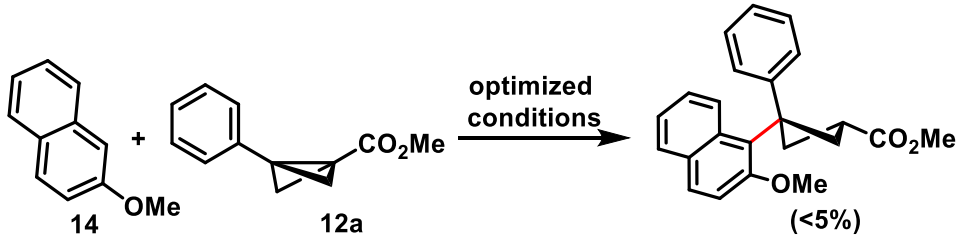


To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added 2-naphthol **11a** (0.029 g, 2.0 mmol) and 1.0 mL CH_2Cl_2 under nitrogen atmosphere. Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, methyl 3-phenylbicyclo

[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Later the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction mixture was passed through a pad of silica gel and then eluted with EtOAc (3x10 mL), and the solvent was evaporated to get the crude products, which was analyzed using ^{1}H NMR spectroscopy.

This study indicates that the 2-naphthol triggered diastereoselective BCB ring-opening is a Lewis acid catalyzed process.

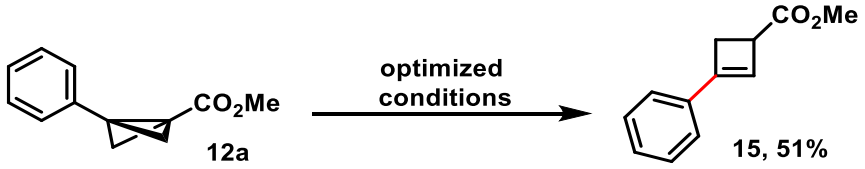
(b) Reaction Using 2-Methoxy Napthalene



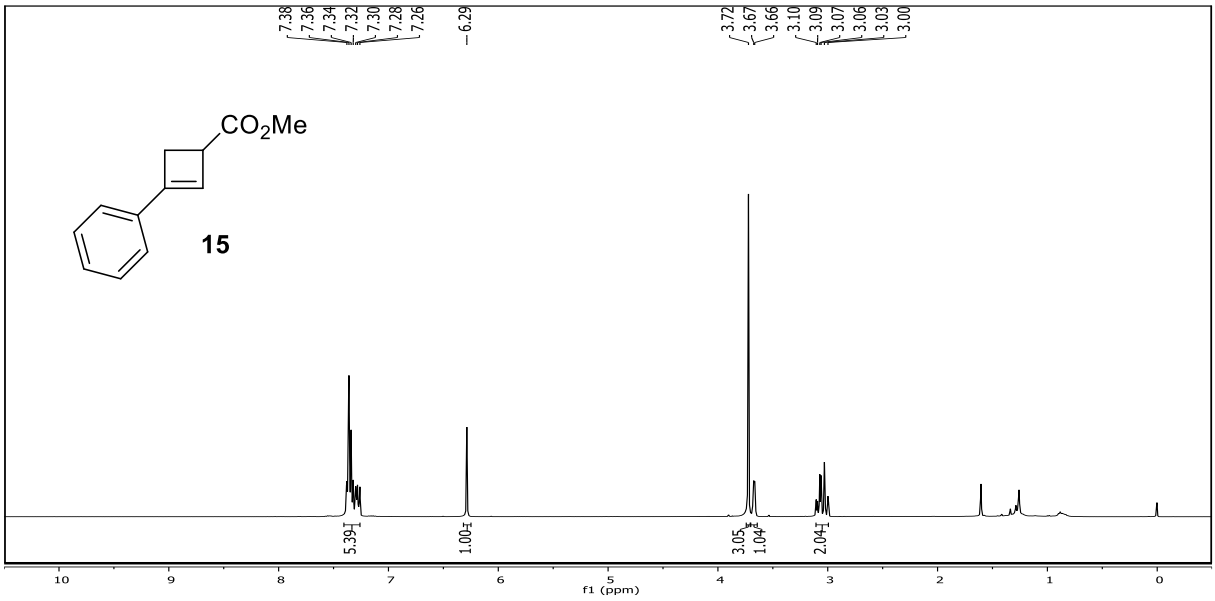
To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, 2-methoxynaphthalene **14** (0.032 g, 0.2 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction mixture was passed through a pad of silica gel and then eluted with EtOAc (3x10 mL), and the solvent was evaporated to get the crude products, which was analyzed using ^{1}H NMR spectroscopy.

This study indicates the crucial role of free -OH group in the 2-naphthol triggered, Lewis acid catalyzed diastereoselective ring-opening of BCB.

(c) Reaction of BCB with $Bi(OTf)_3$

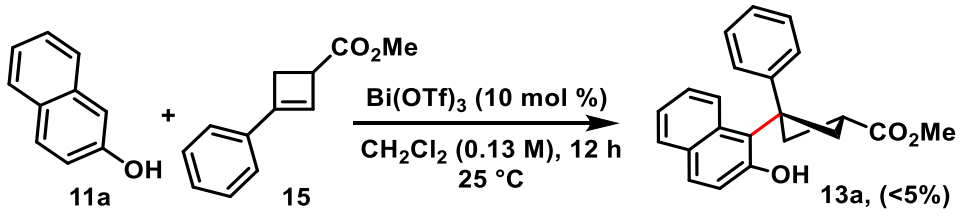


To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.038 g, 0.2 mmol) and 1.5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction was stopped, the solvent was evaporated and the crude residue pre-adsorbed on silica gel and purified by flash column chromatography (Pet. ether /EtOAc = 97/03) on silica gel to afford **15** as a colorless oil (0.019 g, 51% yield).

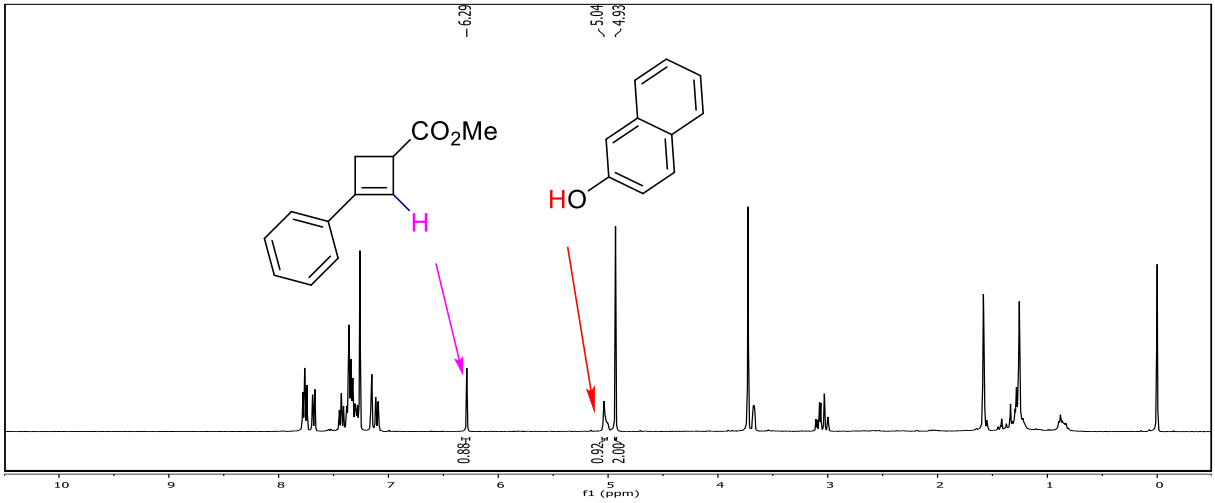


This study indicates that in the absence of 2-naphthol, BCB can directly coordinate with Lewis acid, which facilitate the decomposition of BCB. Most probably, 2-naphthol reduces the Lewis acidity of $Bi(OTf)_3$ and therefore no cyclobutene product was obtained in our optimized reaction conditions. But the question arises whether the carbofunctionalized product formation is possible via the intermediacy of cyclobutene.

(e) Reaction of Cyclobutene 15 with 2-Naphthol

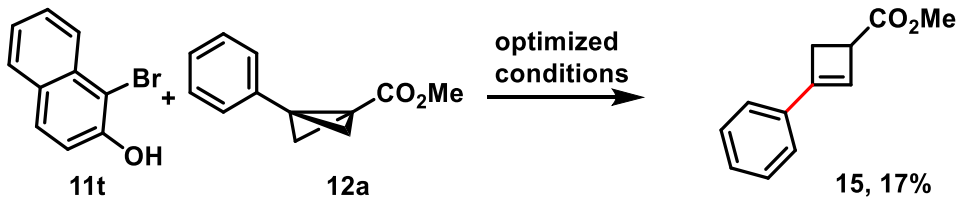


To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, 2-naphthol **11a** (0.029 g, 2.0 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, methyl 3-phenylcyclobut-2-ene-1-carboxylate **15** (0.038 g, 0.2 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Later the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction mixture was passed through a pad of silica gel and then eluted with EtOAc (3x10 mL), and the solvent was evaporated to get the crude products, which was analyzed using ^1H NMR spectroscopy.



The findings of this study have ruled out the possibility of cyclobutene formation occurring during the present carbofunctionalization reaction.

(f) Reaction With 1-Bromonaphthalen-2-ol

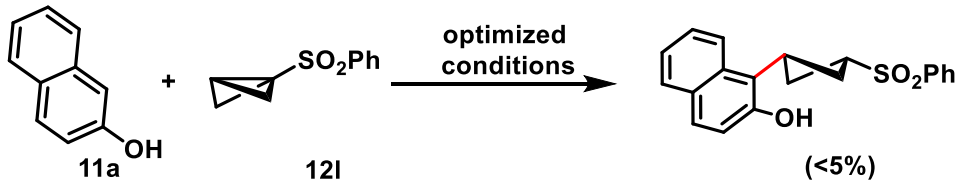


To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, 1-bromonaphthalen-2-ol **11t** (0.045 g, 0.2 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, methyl 3-

phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction mixture was passed through a pad of silica gel and then eluted with EtOAc (3x10 mL), and the solvent was evaporated to get the crude products, which was analyzed using ^{1}H NMR spectroscopy. In this case, the cyclobutene **15** was formed in 17% (crude ^{1}H NMR analysis).

This indicates that the present reaction does not work with 2-naphthols with a substituent at the 1-position.

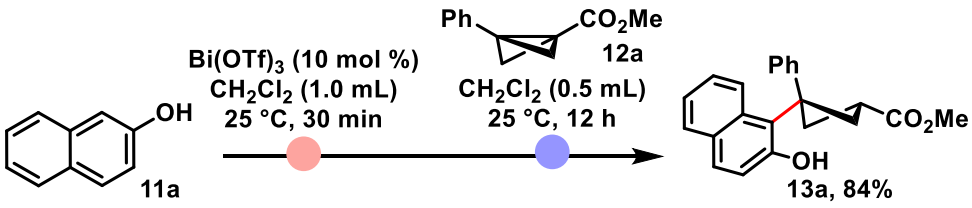
(g) Reaction with Sulfonyl BCB



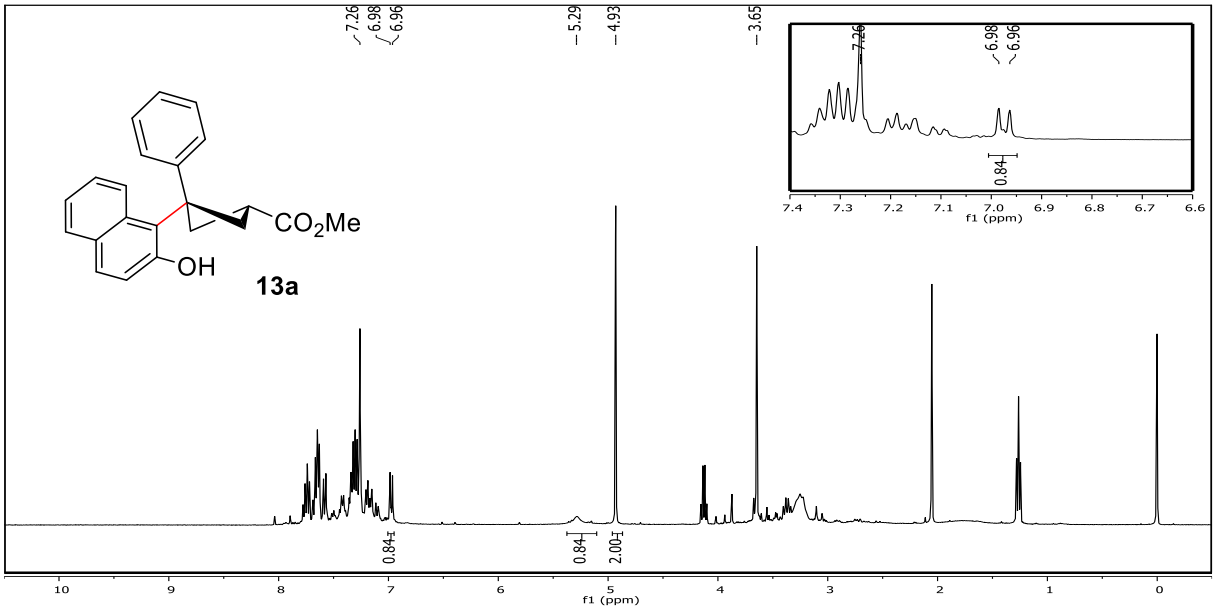
To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, 2-naphthol **11a** (0.029 g, 0.2 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 5 minutes at 25 °C. After 5 minutes, 1-(phenylsulfonyl)bicyclo [1.1.0]butane **12l** (0.047 g, 0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction mixture was passed through a pad of silica gel and then eluted with EtOAc (3x10 mL), and the solvent was evaporated to get the crude products, which was analyzed using ^{1}H NMR spectroscopy. In this case, no desired product formation was observed.

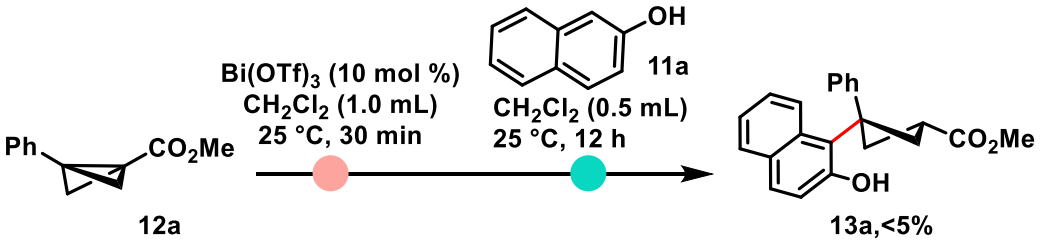
This study sheds light on the importance of ester moiety of BCB for effective Lewis acid binding in this diastereoselective ring-opening reaction.

(h) Dependence of the Reaction on the Mode of Addition



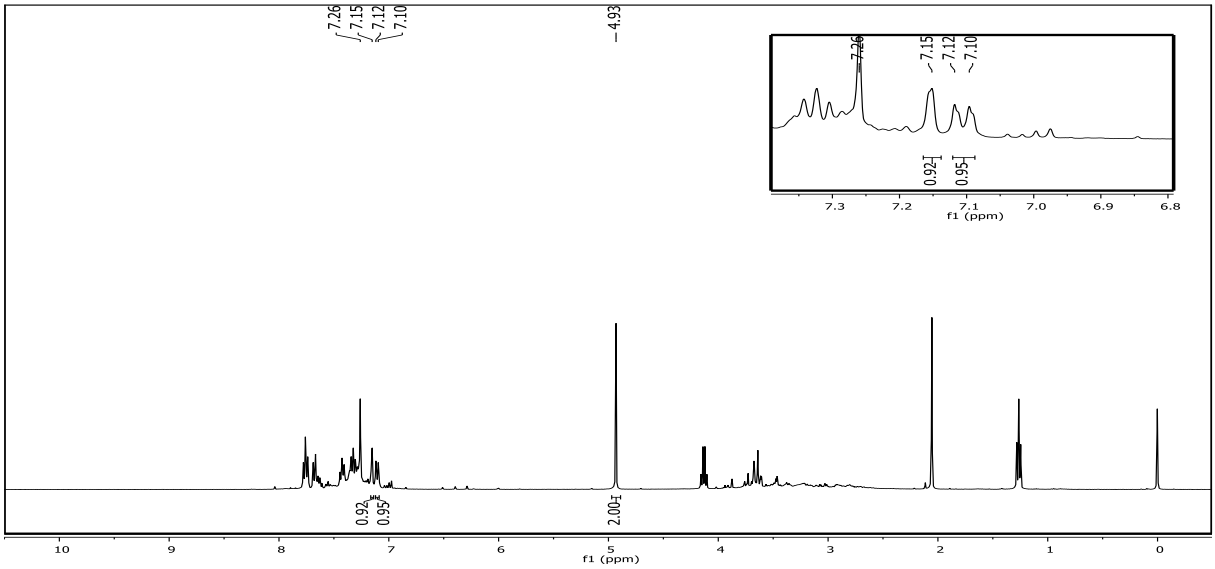
To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, 2-naphthol **11a** (0.029 g, 0.2 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred for 30 minutes at 25 °C. After 30 minutes, methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction was stopped, the solvent was evaporated, and the crude mixture was passed through a pad of silica gel and eluted with EtOAc (3x10 mL). The reaction mixture was concentrated under reduced pressure and then the yield of **13a** was determined by the ^1H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard.





To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added the $Bi(OTf)_3$ (0.013 g, 0.02 mmol) inside the glove box. After that, methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) and 1.0 mL CH_2Cl_2 were added outside the glove box under nitrogen atmosphere. Then the mixture was stirred

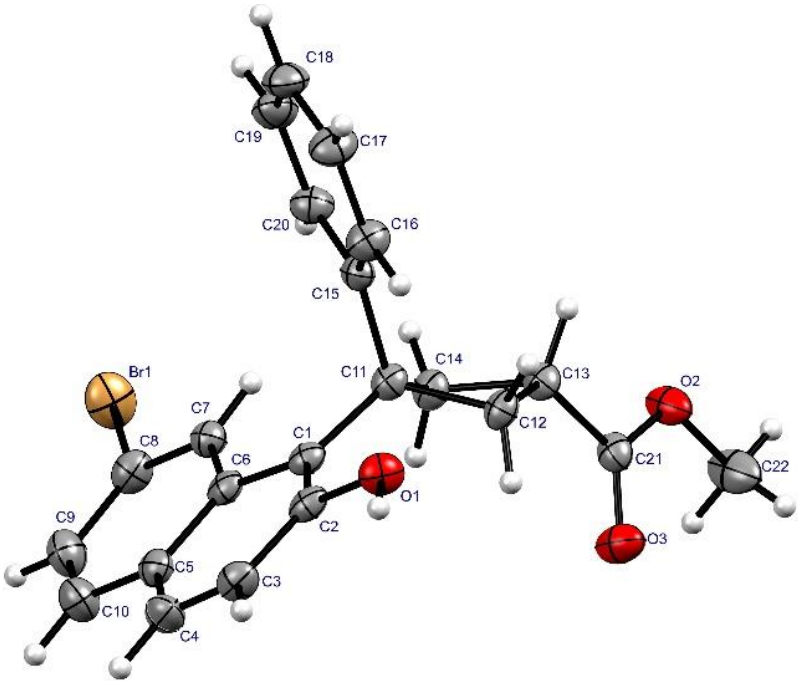
for 30 minutes at 25 °C. After 30 minutes, 2-naphthol **11a** (0.029 g, 0.2 mmol) and 0.5 mL CH_2Cl_2 were added subsequently. Then, the reaction mixture was stirred for 12 h at 25 °C. After 12 h, the reaction was stopped, the solvent was evaporated, and the crude mixture was passed through a pad of silica gel and eluted with EtOAc (3x10 mL). The reaction mixture was concentrated under reduced pressure and then the yield of **13a** was determined by the ^{1}H NMR analysis of the crude reaction products using CH_2Br_2 as the internal standard (^{1}H NMR revealed that naphthol was unreacted under this conditions).



These two reactions support our hypothesis about the intermediacy of bicoordinated Bi-complex for the present transformation. The pre-complexation of the Lewis acid with 2-naphthol (presumably) lowers the acidity of the Lewis acid thereby effectively halting the BCB decomposition; the soft coordination with BCB ester with the precomplexed Bi(OTf)$_3$ (with 2-naphthol) forms the bicoordinated Bi-complex, which enables the diastereoselective ring- opening of activated BCB. Reversing the mode of addition leads to decomposition of the BCB, as the acidity of Lewis acid could not be reduced by the 2-naphthol coordination.

8.6.6. ORTEP Diagram of 13k

Single crystal of **13k** (recrystallized from EtOAc/n-hexane at 25 °C) was mounted and the diffraction data was collected at 173 K on a Bruker APEX-II CCD diffractometer using SMART/SAINT software. Intensity data were collected using MoKα radiation (λ=0.71073 A°).



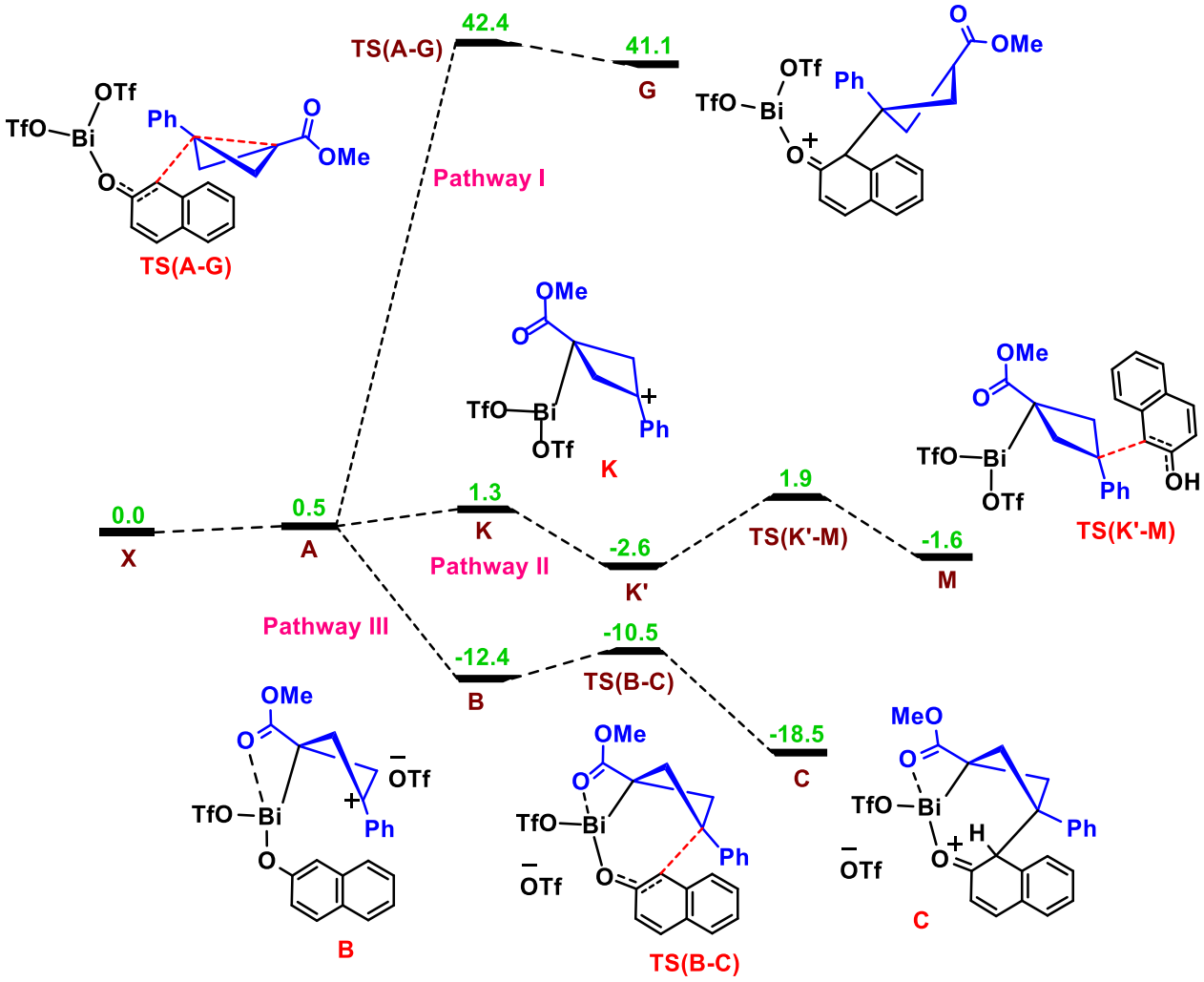
ORTEP Diagram of 13k

(CCDC 2233256, thermal ellipsoids are shown with 50% probability)

8.6.7. DFT Studies

To understand the mechanism of the reaction, preliminary DFT studies were performed. The desired product **13a** is obtained by reacting 2-naphthol **11a** with BCB (bicyclobutane) **12a** in the presence of $Bi(OTf)_3$. Initially, naphthol coordinates to bismuth triflate (**X**) to produce intermediate **A**, where one of the triflate ligands abstracts a proton and departs as triflic acid. From intermediate **A**, there are three different pathways through which the reaction can proceed. In pathway I, the Bi bound naphthol acts as a nucleophile at reacts via its C1 position with the incoming BCB through **TS(A-G)** to give intermediate **G**. In Pathway II, BCB coordinates to Bi displacing the initially bound naphthol ion leading to the positively charged intermediate **K**. In Pathway III, BCB coordinates to **A** displacing a triflate ion instead of the naphthol ion to yield intermediate **B**. The positive charge formed at the carbon center C2 of the cyclobutane can be stabilized by the phenyl group attached to the same carbon. In the first two cases the barrier is high as compared to the third case where we are getting the intermediate **B** (Figure 8.1). So, for further studies we continued this pathway. Now nucleophilic attack of naphthol to the C2 of BCB happens via **TS(B-C)** to give the intermediate **C**.

Figure 8.1. Free energy profile (kcal/mol) for different possible pathways. Relative free energies (ΔG) (kcal/mol) are given at the $SMD_{(DCM)}$/B3LYP-D3(BJ)/6-311++G(d,p),LANL2DZ(Bi)// B3LYP-D3/6-31G(d,p),LANL2DZ(Bi) level of theory.



The low barrier for this TS (transition state) can be explained by the high electrophilicity of BCB due to the positive charge. After this 1,3-proton transfer, rearomatization of naphthol via **TS(C-D)** takes place to give intermediate **D**. Another naphthol molecule comes and binds to Bi, resulting in the formation of enol intermediate **E**. From this intermediate hydrogen can be transferred from above face or below face of substrate giving rise to two different diastereomers (Figure 8.2). Most likely, this proton transfer (tautomerization) is the diastereodetermining step of the reaction. Now the tautomerization via **TS(E-F)** gives the intermediate **F** where the product is weakly coordinated to Bi. Ultimately, metal dissociation results in the formation of the final product,

3a. The presence of a highly strained four-membered ring formation during proton transfer contributes to the high energy barriers in both TSs, **TS(C-D)** and **TS(E-F)** (Figure 8.3). This indicates the possibility of a distinct mechanism for the proton transfer step, potentially assisted by the naphthol or triflate ion present in the reaction mixture. Additional investigations are needed to further examine the proton transfer process. We also calculated the energy of both the products (diastereomers) and found that P_{major} is 1.7 kcal/mol more stable than P_{minor} which corresponds to around 17:1 diastereomeric ratio which is in good agreement with experimental value of 20:1.

Figure 8.2. Free energy profile (kcal/mol) for the formation of the major product from intermediate **C**. Relative free energies (ΔG) (kcal/mol) are given at the $SMD_{(DCM)}$/B3LYP-D3BJ/6-311++G(d,p),LANL2DZ(Bi)// B3LYP-D3/6-31G(d,p),LANL2DZ(Bi) level of theory.

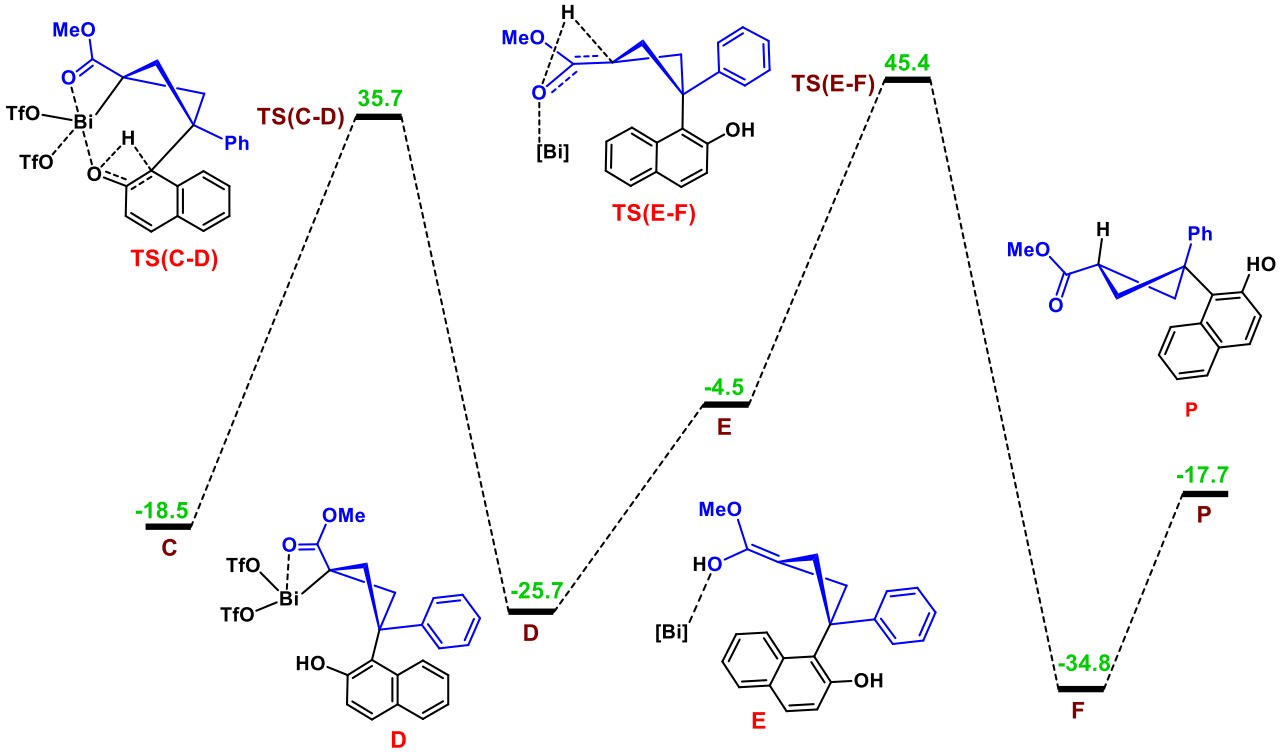
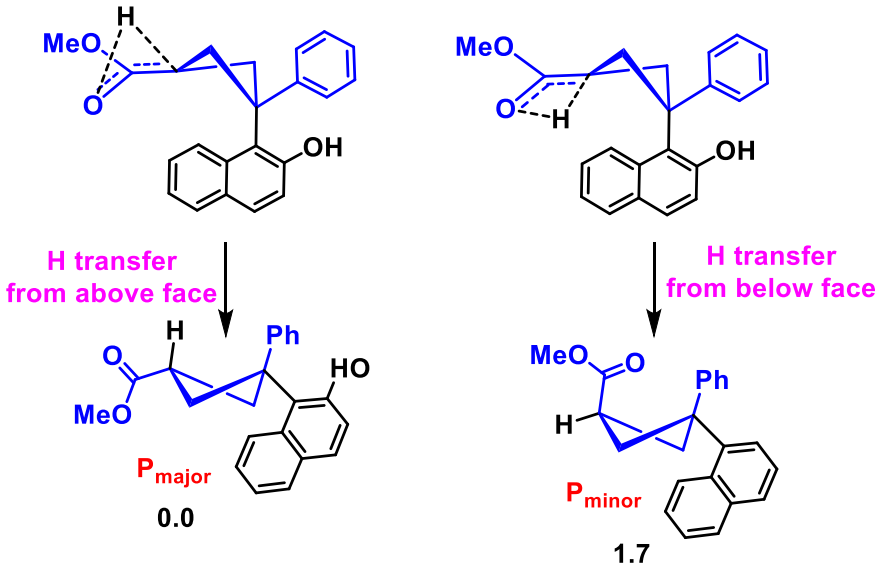


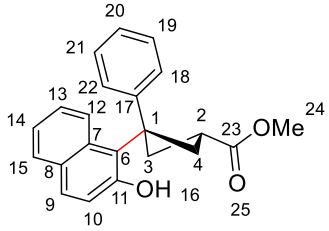
Figure 8.3. Formation of the diastereomers via 1,3-proton transfer. Relative energies are given in kcal/mol.



8.6.8. Synthesis and Characterization of Carbofunctionalized Cyclobutanes

Methyl-3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13a)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13a** as yellow solid (0.060 g, 91% yield).

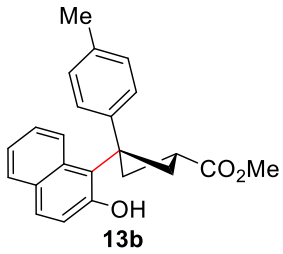


13a

***R*f** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71-7.65 (m, 4H, *12-15*), 7.44 (d, *J* = 8.9 Hz, 1H, *9*), 7.36-7.18 (m, 5H, *18-22*), 6.94 (d, *J* = 8.8 Hz, 1H, *10*), 6.20 (s, 1H, *16*), 3.68 (s, 3H, *24*), 3.43-3.29 (m, 5H, *2-4*). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.8 (*23*), 150.8 (*11*), 146.6 (*17*), 132.3 (*7*), 129.8 (*8*), 128.9 (*13*), 128.8 (*14*), 128.6 (*19,21*), 126.6 (*6*), 126.4 (*9*), 126.3 (*15*), 125.9 (*18,22*), 124.5 (*20*), 122.7 (*12*), 118.8 (*10*), 52.1 (*24*), 46.1 (*1*), 40.6 (*3,4*), 34.5 (*2*). **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}NaO_3$ 355.1305; found 355.1308. **FTIR (cm^{-1})** 3351, 2947, 1691, 1615, 1432, 1259.

Methyl-3-(2-hydroxynaphthalen-1-yl)-3-(*p*-tolyl)cyclobutane-1-carboxylate (13b)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and



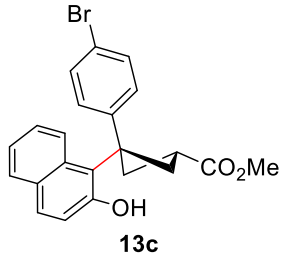
13b

methyl 3-(*p*-tolyl)bicyclo[1.1.0]butane-1-carboxylate **12b** (0.048 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxynaphthalen-1-yl)-3-(*p*-tolyl) cyclo butane-1-carboxylate 1**3b** as yellow solid (0.055 g, 79% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72-7.64 (m, 2H), 7.54-7.49 (m, 3H), 7.36-7.24 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 5.75 (s, 1H), 3.66 (s, 3H), 3.44-3.25 (m, 5H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.3, 150.6, 143.6, 136.0, 132.3, 129.9, 129.4, 128.9, 128.8, 126.9, 126.3, 125.9, 124.7, 122.8, 118.9, 52.0, 45.8, 40.8, 34.5, 21.0. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}NaO_3$ 369.1461; found 369.1463. **FTIR (cm^{-1})** 3370, 2935, 1699,1511, 1437, 1194.

Methyl-3-(4-bromophenyl)-3-(2-hydroxynaphthalen-1-yl)cyclobutane-1-carboxylate (13c)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and



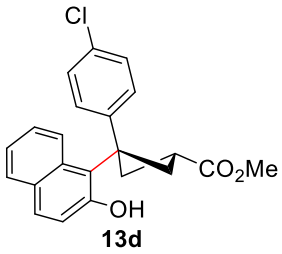
13c

methyl 3-(4-bromophenyl)bicyclo [1.1.0]butane-1-carboxylate **12c** (0.064 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(4-bromophenyl)-3-(2-hydroxynaphthalen-1-yl)cyclobutane-1-carboxylate **13c** as light yellow solid (0.076 g, 78% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.68-7.50 (m, 4H), 7.42-7.22 (m, 5H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.15 (s, 1H), 3.66 (s, 3H), 3.40-3.24 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.5, 150.6, 145.8, 132.1, 131.6, 129.8, 129.0, 128.7, 128.4, 126.4, 126.0, 124.2, 122.93, 120.2, 118.8, 52.1, 45.9, 40.6, 34.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}BrNaO_3$ 433.0415; found 433.0410. **FTIR (cm^{-1})** 3368, 2946, 1700, 1494, 1435, 1259.

Methyl-3-(4-chlorophenyl)-3-(2-hydroxynaphthalen-1-yl)cyclobutane-1-carboxylate (13d)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and methyl 3-(4-chlorophenyl)bicyclo [1.1.0]butane-1-carboxylate **12d** (0.053 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(4-chlorophenyl)-3-(2-hydroxynaphthalen-1-yl)cyclobutane-1-carboxylate **13d** as yellow solid (0.061 g, 83% yield).

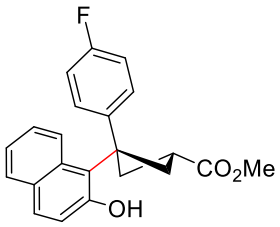


13d

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.68 (d, *J* = 8.1 Hz, 1H), 7.60-7.58 (m, 3H), 7.40-7.22 (m, 5H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.55-6.45 (m, 1H), 3.69 (s, 3H), 3.55-3.07 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.8, 150.8, 145.3, 132.1, 132.0, 129.8, 129.0, 129.0, 128.7, 128.0, 126.0, 124.2, 122.8, 118.8, 52.2, 45.9, 40.6, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}ClNaO_3$ 389.0915; found 389.0918. **FTIR (cm^{-1})** 3355, 2948, 1698, 1498, 1344, 1211.

Methyl-3-(4-fluorophenyl)-3-(2-hydroxynaphthalen-1-yl)cyclobutane-1-carboxylate (13e)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and methyl 3-(4-fluorophenyl)bicyclo [1.1.0]butane-1-carboxylate **12e** (0.049 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(4-fluorophenyl)-3-(2-hydroxynaphthalen-1-yl)cyclobutane-1-carboxylate **13e** as yellow solid (0.066 g, 94% yield).



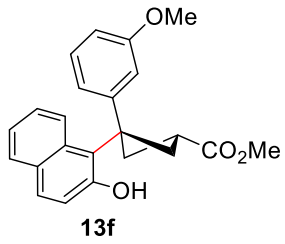
13e

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71-7.58 (m, 5H), 7.49-7.25 (m, 4H), 6.99-6.94 (m, 2H), 6.60 (s, 1H), 3.70 (s, 3H), 3.38-3.21 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.7, 161.4 (d, *J* = 244.4 Hz), 150.8, 142.4 (d, *J* = 3.3 Hz), 132.8, 132.1, 129.2, 129.0, 128.9, 128.0 (d, *J* = 7.9 Hz), 125.9, 124.2, 122.8, 118.8, 115.2 (d, *J* =

21.1 Hz), 52.1, 45.8, 40.8, 34.4. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}FNaO_3$ 373.1216; found 373.1217. **FTIR (cm^{-1})** 3345, 2952, 1704, 1503, 1431, 1215.

Methyl-3-(2-hydroxynaphthalen-1-yl)-3-(3-methoxyphenyl)cyclobutane-1-carboxylate (13f)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and

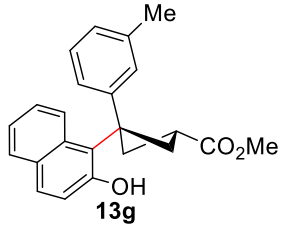


13f

methyl 3-(3-methoxyphenyl)bicyclo [1.1.0]butane-1-carboxylate **12f** (0.052 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxynaphthalen-1-yl)-3-(3-methoxyphenyl)cyclobutane-1-carboxylate **13f** as yellow solid (0.055 g, 76% yield). ***R*f** (Pet. ether /EtOAc = 90/10): 0.21; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70-7.64 (m, 2H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.36-7.22 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.74 (dd, *J1* = 7.7 Hz, *J2* = 1.6 Hz, 1H), 6.14 (s, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.48-3.25 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.4, 159.9, 150.8, 148.5, 132.3, 129.9, 129.6, 128.9, 128.8, 126.6, 125.9, 124.6, 122.8, 118.8, 113.6, 110.8, 55.3, 52.0, 46.2, 40.6, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}NaO_4$ 385.1410; found 385.1415. **FTIR (cm^{-1})** 3366, 2947, 1704, 1591, 1434, 1213.

Methyl-3-(2-hydroxynaphthalen-1-yl)-3-(*m*-tolyl)cyclobutane-1-carboxylate (13g)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and



13g

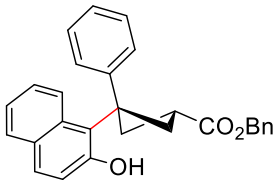
methyl 3-(*m*-tolyl)bicyclo[1.1.0]butane-1-carboxylate **12g** (0.048 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxynaphthalen-1-yl)-3-(*m*-tolyl) cyclo-butane-1-carboxylate **13g** as yellow solid (0.062 g, 74% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73-7.66 (m, 2H), 7.50-7.44 (m, 3H), 7.37-7.34 (m, 1H), 7.30-7.26 (m, 1H), 7.22-7.18 (m, 1H), 7.03-6.95 (m, 2H), 5.86 (s, 1H), 3.69 (s, 3H), 3.44-3.27 (m, 5H), 2.33 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ

176.5, 150.7, 146.5, 138.2, 132.3, 129.8, 128.8, 128.8, 128.6, 127.2, 127.0, 126.8, 125.8, 124.6, 123.4, 122.8, 118.8, 52.0, 46.0, 40.6, 34.5, 21.9. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}NaO_3$ 369.1467; found 369.1469. **FTIR (cm^{-1})** 3362, 2947, 1702, 1505, 1434, 1209.

Benzyl 3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13h)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and benzyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12h** (0.063 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded benzyl 3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclo butane-1-carboxylate **13h** as sticky solid (0.063 g, 77% yield).

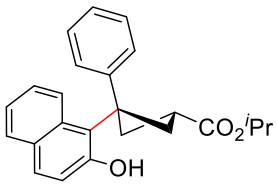


13h

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75-7.70 (m, 4H), 7.46-7.29 (m, 10H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.34 (s, 1H), 5.18 (s, 2H), 3.54-3.36 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.2, 150.8, 146.6, 135.8, 132.3, 129.7, 128.9, 128.7, 128.7, 128.6, 128.4, 128.3, 126.4, 126.3, 125.9, 124.5, 122.7, 118.8, 66.8, 46.2, 40.6, 34.7. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{24}NaO_5$ 431.1618; found 431.1623. **FTIR (cm^{-1})** 3052, 2358, 1704, 1505, 1261, 1025.

Isopropyl 3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13i)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and isopropyl 3-phenylbicyclo[1.1.0] butane-1-carboxylate **12i** (0.051 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded isopropyl 3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclo butane-1-carboxylate **13i** as sticky solid (0.048 g, 66% yield).



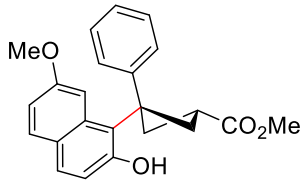
13i

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72-7.66 (m, 4H), 7.43-7.26 (m, 5H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.53 (s, 1H), 5.10-5.01 (m, 1H), 3.52-3.28 (m, 5H), 1.26 (s, 3H), 1.25 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.0, 150.9, 146.7, 132.3, 129.8,

128.9, 128.7, 128.6, 126.6, 126.5, 125.8, 124.6, 122.7, 118.9, 68.3, 46.1, 40.6, 34.9, 21.9. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{24}H_{24}NaO_3$ 383.1618; found 383.1625. **FTIR (cm^{-1})** 3315, 2926, 2356, 1703, 1502, 1215.

Methyl-3-(2-hydroxy-7-methoxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13j)

Following the general procedure, treatment of 7-methoxynaphthalen-2-ol **11b** (0.035 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxy-7-methoxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13j** as yellow solid (0.061 g, 84% yield).



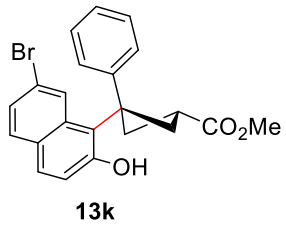
13j

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.21; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69-7.67 (m, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.33-7.29 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.96-6.92 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.77 (s, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.41-3.27 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.3, 157.6, 151.2, 146.5, 133.5, 130.2, 128.7, 128.5, 126.4, 126.4, 125.7, 125.2, 116.4, 114.9, 104.1, 55.2, 52.0, 46.2, 36.9, 34.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}NaO_4$ 385.1410; found 385.1413. **FTIR (cm^{-1})** 3358, 2937, 1701, 1620, 1444, 1216.

Methyl-3-(7-bromo-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13k)

Following the general procedure, treatment of 7-bromonaphthalen-2-ol **11c** (0.045 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using

silica gel afforded methyl-3-(7-bromo-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13k** as yellow solid (0.076 g, 93% yield).

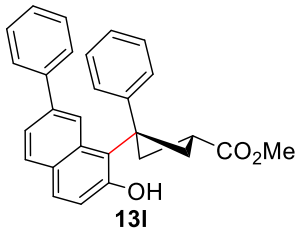


13k

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 1.2 Hz, 1H), 7.67-7.65 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.34-7.30 (m, 3H), 7.28-7.19 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.74 (s, 1H), 3.72 (s, 3H), 3.51-3.08 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 177.2, 151.7, 146.1, 133.4, 130.4, 128.8, 128.6, 128.0, 126.7, 126.5, 126.3, 125.9, 125.8, 120.3, 119.1, 52.3, 46.0, 40.6, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}BrNaO_3$ 433.0410; found 433.0411. **FTIR (cm^{-1})** 3352, 2950, 1704, 1613, 1495, 1204.

Methyl-3-(2-hydroxy-7-phenylnaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13l)

Following the general procedure, treatment of 7-phenylnaphthalen-2-ol **11d** (0.044 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0] butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxy-7-phenylnaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13l** as orange solid (0.060 g, 73% yield).

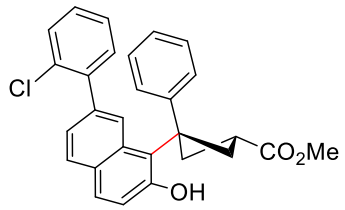


13l

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 (s, 1H), 7.79-7.73 (m, 3H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.65-7.46 (m, 4H), 7.40-7.31 (m, 3H), 7.22-7.18 (m, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.27 (s, 1H), 3.70 (s, 3H), 3.52-3.35 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.8, 151.1, 146.6, 141.8, 138.4, 132.5, 129.4, 129.0, 129.0, 128.7, 128.4, 127.5, 127.3, 126.8, 126.4, 126.4, 122.8, 122.4, 118.9, 52.1, 46.2, 40.6, 34.6. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{24}NaO_3$ 431.1623; found 431.1622. **FTIR (cm^{-1})** 3368, 2949, 1708, 1489, 1437, 1210.

Methyl-3-(7-(2-chlorophenyl)-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13m)

Following the general procedure, treatment of 7-(2-chlorophenyl)naphthalen-2-ol **11e** (0.051 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(7-(2-chlorophenyl)-2-hydroxynaphthalen-1-yl)-3-phenyl cyclobutane-1-carboxylate **13m** as yellow solid (0.063 g, 71% yield).

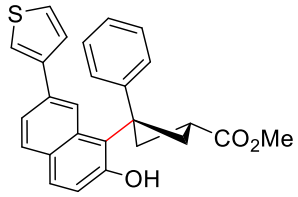


13m

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78-7.68 (m, 4H), 7.51-7.45 (m, 2H), 7.40-7.26 (m, 6H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.19 (s, 1H), 3.69 (s, 3H), 3.37-3.35 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.7, 151.1, 146.5, 141.1, 136.7, 132.7, 132.0, 131.8, 130.2, 129.0, 128.7, 128.6, 128.6, 127.0, 127.0, 126.5, 126.4, 125.4, 124.5, 119.3, 52.1, 46.2, 40.9, 34.6. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{23}ClNaO_3$ 465.1228; found 465.1233. **FTIR (cm^{-1})** 3241, 2948, 1690, 1434, 1334, 1221.

Methyl-3-(2-hydroxy-7-(thiophen-3-yl)naphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13n)

Following the general procedure, treatment of 7-(thiophen-3-yl)naphthalen-2-ol **11f** (0.045 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxy-7-(thiophen-3-yl)naphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13n** as yellow solid (0.065 g, 78% yield).



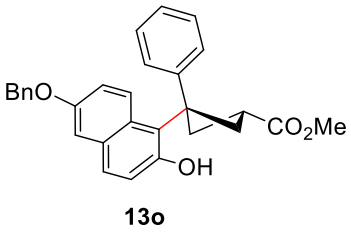
13n

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.91 (s, 1H), 7.78-7.71 (m, 3H), 7.54-7.39 (m, 7H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.39 (s, 1H), 3.70 (s, 3H), 3.57-3.12 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.8, 151.2, 146.6, 143.0, 133.0, 132.5, 132.3, 129.4, 128.9, 128.8, 128.5, 126.7, 126.5, 126.5, 126.4, 121.9, 121.8,

120.5, 118.7, 52.2, 46.3, 40.6, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{22}NaO_3S$ 437.1182; found 437.1184. **FTIR (cm^{-1})** 3343, 2950, 1699, 1618, 1443, 1213.

Methyl-3-(6-(benzyloxy)-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13o)

Following the general procedure, treatment of 6-(benzyloxy)naphthalen-2-ol **11g** (0.050 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(6-(benzyloxy)-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13o** as yellow solid (0.081 g, 92% yield).

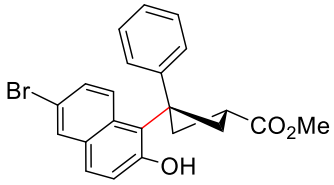


13o

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.65-7.58 (m, 3H), 7.48-7.28 (m, 8H), 7.21-7.10 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 1H), 5.67 (s, 1H), 5.13 (s, 2H), 3.68 (s, 3H), 3.43-3.07 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.3, 154.6, 149.2, 146.6, 137.2, 132.3, 130.9, 129.2, 128.7, 128.7, 128.1, 127.6, 127.6, 127.2, 126.4, 126.1, 119.4, 118.6, 108.8, 70.2, 52.0, 46.2, 40.7, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{29}H_{26}NaO_4$ 461.1723; found 461.1727. **FTIR (cm^{-1})** 3401, 2946, 1709, 1607, 1367, 1228.

Methyl 3-(6-bromo-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13p)

Following the general procedure, treatment of methyl 6-bromonaphthalen-2-ol **11h** (0.045 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl 3-(6-bromo-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13p** as yellow solid (0.062 g, 76% yield).



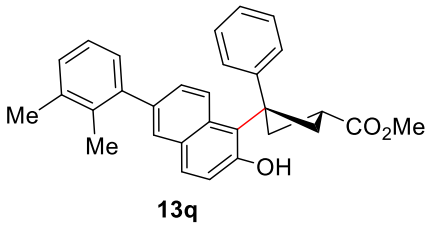
13p

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 1.6 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.53-7.50 (m, 1H), 7.41-7.38 (m, 1H), 7.32-7.17 (m, 4H), 6.92

(d, *J* = 8.7 Hz, 1H), 6.79 (s, 1H), 3.72 (s, 3H), 3.43-3.28 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 177.1, 151.2, 146.3, 131.0, 130.8, 130.7, 129.0, 128.7, 127.7, 126.8, 126.5, 126.3, 126.2, 119.9, 116.4, 52.2, 46.1, 40.6, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for **$C_{22}H_{19}BrNaO_3$** 433.0410; found 433.0412. **FTIR (cm^{-1})** 3320, 2939, 2356, 1702, 1589, 1209.

Methyl-3-(6-(2,3-dimethylphenyl)-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13q)

Following the general procedure, treatment of 6-(2,3-dimethylphenyl)naphthalen-2-ol **11i** (0.050 g, 0.2 mmol) and methyl 3-phenyl bicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(6-(2,3-dimethylphenyl)-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13q** as yellow solid (0.087 g, 97% yield).



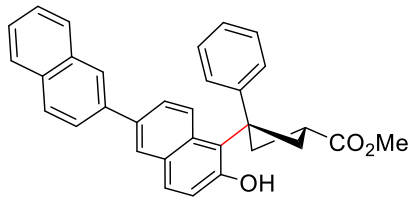
13q

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71-7.53 (m, 5H), 7.35-7.32 (m, 3H), 7.23-7.12 (m, 4H), 7.00 (d, *J* = 8.7 Hz, 1H), 5.63 (s, 1H), 3.69 (s, 3H), 3.43-3.31 (m, 5H), 2.36 (s, 3H), 2.18 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.2, 150.6, 146.5, 142.1, 137.3, 137.2, 134.4, 131.0, 129.8, 129.0, 128.9, 128.9, 128.8, 128.1, 128.0, 126.8, 126.5, 125.4, 124.2, 119.1, 52.0, 46.2, 40.6, 34.5, 20.8, 17.3. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{30}H_{28}NaO_3$ 459.1931; found 459.1937. **FTIR (cm^{-1})** 3349, 2946, 1689, 1486, 1440, 1208.

Methyl-3-(6-hydroxy-[2,2'-binaphthalen]-5-yl)-3-phenylcyclobutane-1-carboxylate (13r)

Following the general procedure, treatment of [2,2'-binaphthalen]-6-ol **11j** (0.054 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash

column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(6-hydroxy-[2,2'-binaphthalen]-5-yl)-3-phenylcyclobutane-1-carboxylate **13r** as yellow solid (0.076 g, 83% yield).

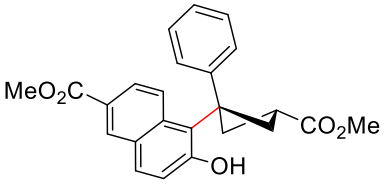


13r

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.11 (s, 1H), 7.98 (s, 1H), 7.89-7.87 (m, 3H), 7.82-7.73 (m, 5H), 7.51-7.49 (m, 2H), 7.42 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.46 (s, 1H), 3.73 (s, 3H), 3.58-3.37 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 177.0, 151.0, 146.6, 138.3, 135.0, 133.9, 132.6, 131.5, 130.1, 129.1, 128.7, 128.6, 128.3, 127.8, 127.0, 126.5, 126.4, 126.4, 126.4, 125.9, 125.6, 125.6, 125.5, 125.1, 119.3, 52.2, 46.2, 40.6, 34.6. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{32}H_{26}NaO_3$ 481.1774; found 481.1780. **FTIR (cm^{-1})** 3359, 2947, 1700, 1602, 1436, 1200.

Methyl 6-hydroxy-5-(3-(methoxycarbonyl)-1-phenylcyclobutyl)-2-naphthoate (13s)

Following the general procedure, treatment of methyl 6-hydroxy-2-naphthoate **11k** (0.04 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl 6-hydroxy-5-(3-(methoxycarbonyl)-1-phenylcyclobutyl)-2-naphthoate **13s** as yellow solid (0.062 g, 79% yield).

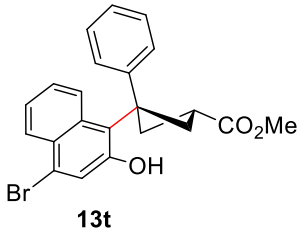


13s

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.69-7.64 (m, 3H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.32-7.26 (m, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.0 (d, *J* = 8.8 Hz, 1H), 6.72 (s, 1H), 3.96 (s, 3H), 3.70 (s, 3H), 3.40-3.25 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.9, 167.6, 153.0, 146.2, 134.8, 132.0, 130.3, 128.7, 126.8, 126.5, 126.4, 125.3, 124.6, 124.2, 119.6, 52.3, 52.2, 46.0, 40.5, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{24}H_{22}NaO_5$ 413.1359; found 413.1365. **FTIR (cm^{-1})** 3384, 2951, 2356, 1722, 1434, 1300.

Methyl-3-(4-bromo-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13t)

Following the general procedure, treatment of 4-bromonaphthalen-2-ol **11l** (0.045 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0] butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(4-bromo-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13t** as yellow solid (0.067 g, 81% yield).

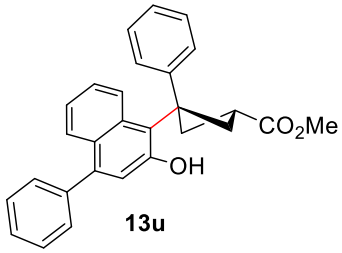


13t

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08-8.06 (m, 1H), 7.67-7.61 (m, 3H), 7.38-7.29 (m, 5H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 3.75 (s, 3H), 3.49-3.29 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 177.4, 150.7, 146.2, 133.1, 128.7, 128.0, 127.9, 126.8, 126.6, 126.5, 126.3, 124.8, 124.1, 122.6, 122.2, 52.4, 46.0, 40.7, 34.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{19}BrNaO_3$ 433.0410; found 433.0412. **FTIR (cm^{-1})** 3220, 2942, 1693, 1500, 1429, 1224.

Methyl-3-(2-hydroxy-4-phenylnaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13u)

Following the general procedure, treatment of 4-phenylnaphthalen-2-ol **11m** (0.044 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxy-4-phenylnaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13u** as yellow solid (0.069 g, 85% yield).



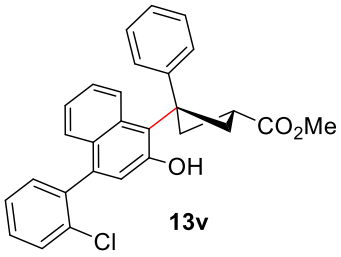
13u

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73-7.68 (m, 4H), 7.40-7.31 (m, 6H), 7.26-7.17 (m, 4H), 6.92 (s, 1H), 6.15 (s, 1H), 3.68 (s, 3H), 3.49-3.32 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.7, 150.1, 146.7, 141.0, 140.2, 132.7, 130.0, 128.7, 128.3, 128.2, 127.3, 127.0, 126.5, 126.4, 126.1, 125.8, 124.8, 122.9, 119.8, 52.1, 46.1, 40.6, 34.5.

HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{28}H_{24}NaO_3$ 431.1618; found 431.1620. **FTIR (cm^{-1})** 3365, 2945, 1697, 1602, 1434, 1214.

Methyl-3-(4-(2-chlorophenyl)-2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13v)

Following the general procedure, treatment of 4-(2-chlorophenyl)naphthalen-2-ol **11n** (0.051 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(4-(2-chlorophenyl)-2-hydroxynaphthalen-1-yl)-3-phenyl cyclobutane-1-carboxylate **13v** as yellow solid (0.063 g, 71% yield).

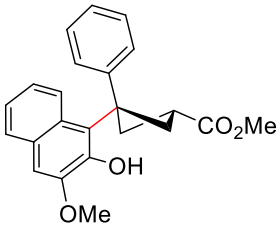


13v

***R*f** (Pet. ether /EtOAc = 90/10): 0.23; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.76-7.73 (m, 3H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.38-7.17 (m, 9H), 6.92 (s, 1H), 6.43 (bs, 1H), 3.68 (s, 3H), 3.56-3.14 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.7, 150.0, 146.6, 138.9, 138.0, 134.1, 132.5, 132.1, 129.6, 129.0, 128.7, 128.5, 128.1, 126.8, 126.7, 126.6, 126.4, 125.8, 124.8, 123.0, 120.2, 52.1, 46.2, 40.7, 34.6. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{23}ClNaO_3$ 465.1228; found 465.1235. **FTIR (cm^{-1})** 3350, 2948, 1702, 1434, 1369, 1208.

Methyl-3-(2-hydroxy-3-methoxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13w)

Following the general procedure, treatment of 3-methoxynaphthalen-2-ol **11o** (0.035 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxy-3-methoxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13w** as sticky solid (0.056 g, 78% yield, 2:1 dr).



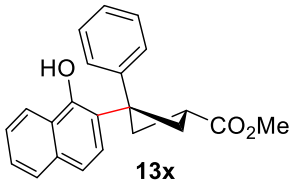
13w

***R*f** (Pet. ether /EtOAc = 90/10): 0.21; **^{1}H NMR (400 MHz, $CDCl_3$) of Major isomer** δ 7.73-7.64 (m, 4H), 7.34-7.12 (m, 5H), 7.02 (s, 1H), 6.34 (s, 1H), 3.98 (s, 3H), 3.65 (s, 3H), 3.57-

3.04 (m, 5H). **Representative peaks of minor isomer ^{1}H NMR (400 MHz, $CDCl_3$)** 7.57 (d, *J* = 8.3 Hz, 1H), 7.06 (s, 1H), 6.45 (s, 1H), 4.02 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) of Major isomer** δ 175.7, 147.1, 146.6, 142.9, 129.4, 128.5, 127.62, 127.60, 126.6, 126.4, 125.2, 124.4, 123.8, 123.4, 104.8, 56.0, 51.7, 46.3, 39.7, 34.4. **Representative peaks of minor isomer ^{13}C NMR (100 MHz, $CDCl_3$)** 176.3, 147.6, 143.4, 129.5, 125.2, 105.0, 56.1, 51.8, 48.1, 33.9. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}NaO_4$ 385.1410; found 385.1415. **FTIR (cm^{-1})** 3412, 2944, 1717, 1428, 1246, 1187.

Methyl-3-(1-hydroxynaphthalen-2-yl)-3-phenylcyclobutane-1-carboxylate (13x)

Following the general procedure, treatment of naphthalen-1-ol **11p** (0.029 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(1-hydroxynaphthalen-2-yl)-3-phenylcyclo butane-1-carboxylate **13x** as white solid (0.032 g, 48% yield).

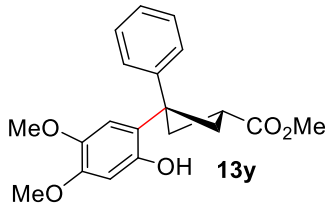


13x

***R*$_f$** (Pet. ether /EtOAc = 90/10): 0.22; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10-8.08 (m, 1H), 7.84-7.82 (m, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.49-7.42 (m, 2H), 7.37-7.32 (m, 4H), 7.24-7.20 (m, 1H), 4.95 (s, 1H), 3.70 (s, 3H), 3.15-3.03 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.4, 149.5, 146.2, 134.0, 129.2, 127.6, 127.1, 126.2, 126.1, 125.7, 125.6, 125.4, 124.3, 121.5, 120.3, 52.0, 45.5, 37.2, 33.0. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}NaO_3$ 355.1305; found 355.1310. **FTIR (cm^{-1})** 3359, 2949, 1701, 1434, 1344, 1213.

Methyl-3-(2-hydroxy-4,5-dimethoxyphenyl)-3-phenylcyclobutane-1-carboxylate (13y)

Following the general procedure, treatment of 3,4-dimethoxyphenol **11q** (0.031 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(2-hydroxy-4,5-dimethoxyphenyl)-3-phenylcyclobutane-1-carboxylate **13y** as yellow oil (0.040 g, 58% yield).

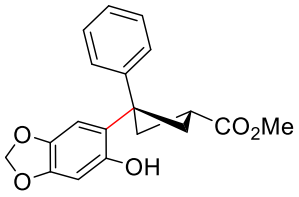


13y

***R*f** (Pet. ether /EtOAc = 90/10): 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32-7.28 (m, 4H), 7.20-7.16 (m, 1H), 7.06 (s, 1H), 6.41 (s, 1H), 4.35 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 3.12-3.06 (m, 1H), 2.99-2.91 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.6, 149.2, 148.4, 146.8, 142.9, 128.9, 126.7, 126.0, 122.8, 111.4, 102.8, 57.3, 56.1, 52.0, 45.1, 37.1, 33.0. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{20}H_{22}NaO_5$ 365.1359; found 365.1360. **FTIR (cm^{-1})** 3311, 2940, 1692, 1517, 1352, 1197.

Methyl-3-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)-3-phenylcyclobutane-1-carboxylate (13z)

Following the general procedure, treatment of benzo[*d*][1,3]dioxol-5-ol **11r** (0.028 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0] butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)-3-phenylcyclobutane-1-carboxylate **13z** as yellow oil (0.036 g, 55% yield).

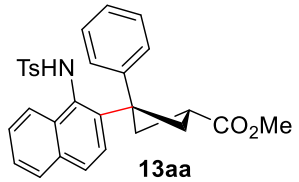


13z

***R*f** (Pet. ether /EtOAc = 90/10): 0.20; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28-7.23 (m, 4H), 7.17-7.13 (m, 1H), 7.01 (s, 1H), 6.33 (s, 1H), 5.90 (s, 2H), 4.44 (s, 1H), 3.64 (s, 3H), 3.10-3.01 (m, 1H), 2.90-2.88 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.6, 148.9, 147.0, 146.8, 141.6, 128.8, 126.6, 126.0, 124.1, 106.5, 101.3, 100.1, 52.0, 45.4, 37.1, 33.1. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{19}H_{18}NaO_5$ 349.1046; found 349.1054. **FTIR (cm^{-1})** 3389, 2918, 1706, 1495, 1432, 1167.

Methyl-3-(1-((4-methylphenyl)sulfonamido)naphthalen-2-yl)-3-phenylcyclobutane-1-carboxylate (13aa)

Following the general procedure, treatment of 4-methyl-*N*-(naphthalen-1-yl)benzenesulfonamide **11s** (0.059 g, 0.2 mmol) and methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate **12a** (0.045 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet.



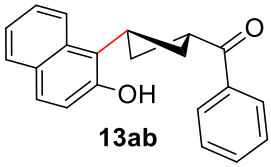
13aa

ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded methyl-3-(1-((4-methylphenyl)sulfonamido)naphthalen-2-yl)-3-phenylcyclobutane-1-carboxylate **13aa** as white solid (0.051 g, 52% yield, 3:1 dr).

***R*f** (Pet. ether /EtOAc = 90/10): 0.20; **^{1}H NMR (400 MHz, $CDCl_3$) of Major isomer** δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.45-7.36 (m, 3H), 7.31-7.13 (m, 8H), 7.05 (s, 1H), 3.66 (s, 3H), 3.12-3.05 (m, 5H), 2.36 (s, 3H). **Representative peaks of minor isomer ^{1}H NMR (400 MHz, $CDCl_3$)** 7.92 (d, *J* = 8.3 Hz, 1H), 3.70 (s, 3H), 2.37 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$) of Major isomer** δ 175.2, 146.3, 144.2, 143.9, 136.7, 131.2, 130.6, 130.0, 129.7, 128.7, 128.5, 127.5, 126.3, 126.1, 126.0, 125.9, 124.1, 122.6, 122.2, 52.0, 47.4, 38.9, 33.2, 21.6. **Representative peaks of minor isomer ^{13}C NMR (100 MHz, $CDCl_3$)** 175.5, 47.8, 38.7, 33.1. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{29}H_{27}NNaO_4S$ 508.1553; found 508.1561. **FTIR (cm^{-1})** 3354, 2791, 1710, 1595, 1210, 1149.

3-(2-Hydroxynaphthalen-1-yl)cyclobutyl)(phenyl)methanone (13ab)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and



13ab

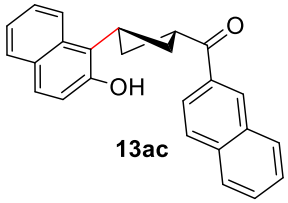
bicyclo[1.1.0]butan-1-yl(phenyl)methanone **12j** (0.038 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 84/16) of the crude reaction mixture using silica gel afforded 3-(2-hydroxynaphthalen-1-yl)cyclobutyl)(phenyl)methanone **13ab** as colorless oil (0.042 g, 70% yield, 2.2:1 dr).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$) of Major isomer** δ 8.02-7.96 (m, 3H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.63-7.56 (m, 2H), 7.50-7.41 (m, 3H), 7.32-7.28 (m, 1H), 7.08 (d, *J* = 8.9 Hz, 1H), 6.53 (s, 1H), 4.46-4.37 (m, 1H), 4.22-4.09 (m, 1H), 3.21-3.11 (m, 2H), 2.99-2.88 (m, 2H). **Representative peaks of minor isomer ^{1}H NMR (400 MHz, $CDCl_3$)** 7.05 (d, *J* = 9.0 Hz, 1H), 5.62 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) of Major isomer** δ 202.8, 152.5, 135.8, 133.4, 133.3, 133.1, 129.4, 128.8, 128.7, 128.5, 126.2, 123.2, 123.0, 120.6, 119.5, 39.0, 32.3, 29.8. **Representative peaks of minor isomer ^{13}C NMR (100 MHz, $CDCl_3$)** 202.1, 151.9, 135.6, 129.5, 126.3, 121.8, 39.1, 29.8. **HRMS (ESI)** m/z:

$[M+Na]^+$ calcd for $C_{21}H_{18}NaO_2$ 325.1199; found 325.1204. **FTIR (cm^{-1})** 3354, 2926, 1663, 1325, 1221, 1079.

3-(2-Hydroxynaphthalen-1-yl)cyclobutyl)(naphthalen-2-yl)methanone (13ac)

Following the general procedure, treatment of naphthalen-2-ol **11a** (0.029 g, 0.2 mmol) and



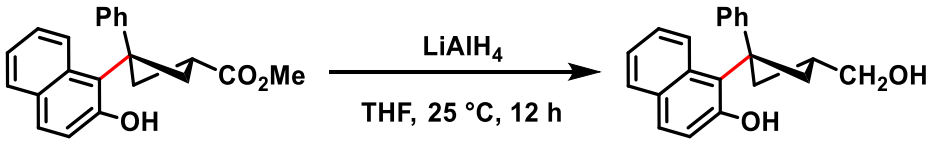
13ac

bicyclo[1.1.0]butan-1-yl(naphthalen-2-yl)methanone **12k** (0.050 g, 0.24 mmol) with $Bi(OTf)_3$ (0.013 g, 0.02 mmol) in CH_2Cl_2 (1.5 mL) at 25 °C for 12 h followed by flash column chromatography (Pet. ether/ EtOAc = 80/20) of the crude reaction mixture using silica gel afforded 3-(2-hydroxynaphthalen-1-yl)cyclobutyl)(naphthalen-2-yl)methanone **13ac** as yellow solid (0.048 g, 68% yield, 2.3:1 dr).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$) of Major isomer** δ 8.52 (s, 1H), 8.11-7.87 (m, 5H), 7.76-7.74 (m, 1H), 7.63-7.53 (m, 3H), 7.48-7.41 (m, 1H), 7.33-7.29 (m, 1H), 7.11-7.06 (m, 1H), 6.57 (s, 1H), 4.54-4.25 (m, 2H), 3.28-3.17 (m, 2H), 3.06-2.91 (m, 2H). **Representative peaks of minor isomer ^{1}H NMR (400 MHz, $CDCl_3$)** 5.64 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) of Major isomer** δ 202.7, 152.6, 135.9, 133.3, 132.7, 130.5, 130.2, 129.8, 129.5, 128.8, 128.7, 128.5, 128.0, 126.9, 126.3, 124.3, 123.3, 123.0, 120.7, 119.5, 118.9, 39.0, 32.4, 31.2 **Representative peaks of minor isomer ^{13}C NMR (100 MHz, $CDCl_3$)** 202.0, 151.9, 39.2, 31.2. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{25}H_{21}O_2$ 353.1536; found 353.1542. **FTIR (cm^{-1})** 3330, 2921, 1662, 1509, 1358, 1219.

8.6.9. Procedure for Product Functionalization

a) Reduction of the ester to alcohol



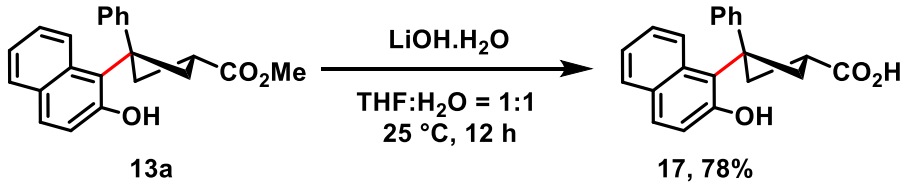
13a **16, 94%**

Compound **16** was prepared using the literature procedure.[23] To a 25 mL two neck round bottom flask equipped with stir bar, LiAlH4 (0.015 g, 0.4 mmol) was dissolved in dry THF (1.0 mL). The reaction mixture was cooled to 0 °C with ice bath. Then, the solution of methyl-3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13a** (0.066 g, 0.2 mmol) in dry THF (1.0 mL) was added slowly and reaction mixture was allowed to stir for

12h at room temperature. After this time, the reaction was cooled to 0 °C and quenched with 10% KOH solution (2.0 mL). The resulting suspension was filtered through celite, washed with ethyl acetate. The combined filtrate was dried, concentrated and purified by flash column chromatography (Pet. ether /EtOAc = 80/20) of the crude reaction mixture afforded 1-(3-(hydroxymethyl)-1-phenylcyclobutyl)naphthalen-2-ol **16** as a white solid (0.057 g, 94% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.17; **^{1}H NMR (400 MHz, $(CD_3)_2CO$)** δ 8.64 (s, 1H), 7.82-7.72 (m, 4H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.32-7.18 (m, 5H), 7.11 (t, *J* = 7.3 Hz, 1H), 3.56-3.52 (m, 3H), 3.11 (bs, 3H), 2.62-2.60 (m, 2H). **^{13}C NMR (100 MHz, $(CD_3)_2CO$)** δ 152.7, 149.5, 133.6, 130.4, 129.4, 128.9, 128.8, 128.6, 127.4, 126.3, 126.0, 125.6, 123.0, 120.0, 67.1, 47.1, 41.5, 34.2, **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{21}H_{20}NaO_2$ 327.1356; found 327.1361. **FTIR (cm^{-1})** 3458, 2926, 2359, 1436, 1338, 1230.

b) Conversion of ester to acid



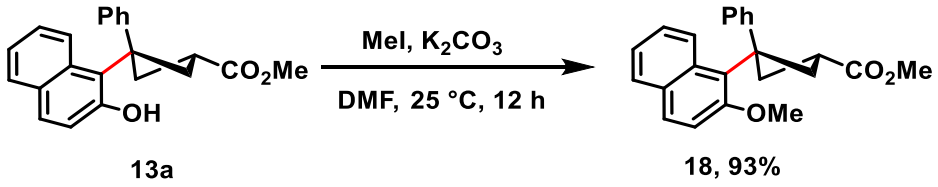
13a **17, 78%**

Following the general procedure,[16] methyl-3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13a** (0.066 g, 0.2 mmol) and lithium hydroxide monohydrate (0.017 g, 0.4 mmol) were dissolved in THF:H_2O (1+1 mL) at 25 °C and stirred for 12 h. The mixture was then concentrated under reduced pressure. The resulting residue was dissolved in water (5 mL) and acidified with 1 M HCl to adjust the pH to 4-6. Once the solution reached the desired pH range, the aqueous phase was extracted with DCM (5 mL). The organic layer was dried using anhydrous Na_2SO_4 and concentrated under reduced pressure, followed by purification via silica gel flash column chromatography (Pet. ether /EtOAc = 70/30) of the crude reaction mixture afforded 3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylic acid **17** as white solid (0.050 g, 78% yield).

***R*f** (Pet. ether /EtOAc = 70/30): 0.28; **^{1}H NMR (400 MHz, DMSO-d_6)** δ 12.02 (s, 1H), 9.73 (s, 1H), 7.76-7.65 (m, 4H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.32-7.13 (m, 6H), 3.37-2.87 (m, 5H). **^{13}C NMR (100 MHz, DMSO-d_6)** δ 176.0, 151.9, 147.3, 131.8, 128.7, 128.6, 128.2, 128.1,

126.2, 126.1, 125.8, 125.5, 123.9, 122.0, 119.2, 45.6, 33.8. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{21}H_{18}NaO_3$ 341.1148; found 341.1153. **FTIR (cm^-)[1]** 3375, 2354, 1650, 1220, 991.

c) Conversion of alcohol to methyl ether

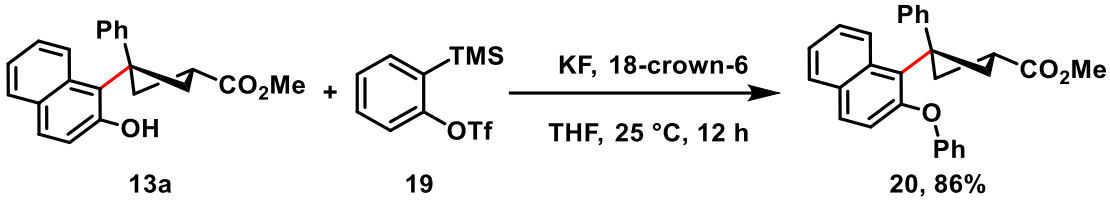


13a **18, 93%**

Compound **18** was synthesized following the modified literature procedure.[24] To a solution of **13a** (0.066 g, 0.2 mmol) in 2.0 mL DMF was added K_2CO_3 (0.041 g, 0.3 mmol) and methyl iodide (0.042 g, 0.3 mmol) then the mixture was stirred at 25 °C for 12 h. Then the solvent was evaporated, and the residue was purified by column chromatography to give methyl-3-(2-methoxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **18** as a white solid (0.064 g, 93% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.25; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79-7.65 (m, 5H), 7.39-7.18 (m, 6H), 3.98 (s, 3H), 3.65 (s, 3H), 3.38-3.13 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.7, 154.3, 146.8, 132.0, 130.1, 129.8, 128.9, 128.8, 128.5, 126.5, 126.2, 125.9, 124.8, 123.1, 114.2, 56.2, 51.7, 46.5, 41.0, 34.6. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{22}NaO_3$ 369.1461; found 369.1464. **FTIR (cm^-)[1]** 2954, 1727, 1598, 1439, 1251, 1153.

d) Arylation of 13a



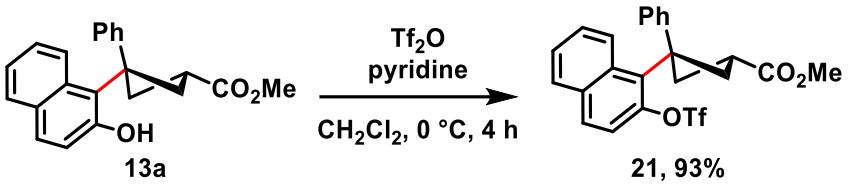
13a **19** **20, 86%**

To an oven-dried screw-capped test tube equipped with a magnetic stir bar was added KF (0.035 g, 0.6 mmol) and 18-crown-6 (0.158 g, 0.6 mmol) in a nitrogen filled glove box. After that **13a** (0.066 g, 0.2 mmol) was added outside the glove-box in nitrogen atmosphere. Then THF (1.0 mL) was added followed by the addition of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **19** (0.090 g, 0.3 mmol). The mixture was stirred at 25 °C for 12 h. Then the solvent was evaporated, and the residue was purified by column chromatography

to give methyl-3-(2-phenoxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **20** as a colorless oil (0.082 g, 86% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.5 Hz, 1H), 7.81-7.74 (m, 3H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.46-7.31 (m, 6H), 7.22-7.18 (m, 1H), 7.14-7.07 (m, 4H), 3.62 (s, 3H), 3.46-3.19 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.4, 157.3, 151.2, 146.2, 133.6, 132.2, 131.3, 129.9, 129.0, 128.9, 128.6, 126.6, 126.3, 126.1, 125.3, 124.4, 123.0, 120.2, 118.6, 51.7, 46.6, 40.9, 34.6. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{24}NaO_3$ 431.1618; found 431.1622. **FTIR (cm^-)^1** 2948, 1727, 1587, 1487, 1367, 1218.

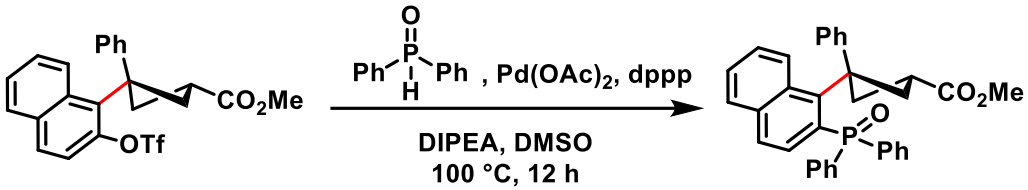
e) Triflyl protection of 13a



Compound **21** was synthesized following the literature procedure.[25] To a solution of methyl-3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **13a** (0.066 g, 0.2 mmol) and pyridine (0.043g, 0.54 mmol) in CH_2Cl_2 (2 mL) was added Tf_2O (0.073 g, 0.26 mmol) dropwise at 0 °C under argon. The mixture was stirred at 0 °C for 3 h, then the reaction was quenched by the addition of water (1 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (10:1) to afford **21** as a colorless oil (0.086 g, 93% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.24; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93-7.87 (m, 2H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.55-7.46 (m, 5H), 7.38-7.34 (m, 2H), 7.30-7.26 (m, 1H), 3.69 (s, 3H), 3.61-3.54 (m, 1H), 3.36-3.24 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.2, 145.6, 145.3, 136.5, 133.1, 132.2, 130.0, 129.1, 128.9, 127.02, 126.99, 126.7, 126.5, 126.3, 129.4 (unresolved quartet), 118.4 (*q*, *J* = 320 Hz), 52.0, 46.0, 40.0 (unresolved quartet), 34.2. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{23}H_{19}F_3NaO_5S$ 487.0798; found 487.0802. **FTIR (cm^-)^1** 3055, 1729, 1585, 1489, 1369, 1217.

f) Conversion of -OTf to diphenylphosphine oxide

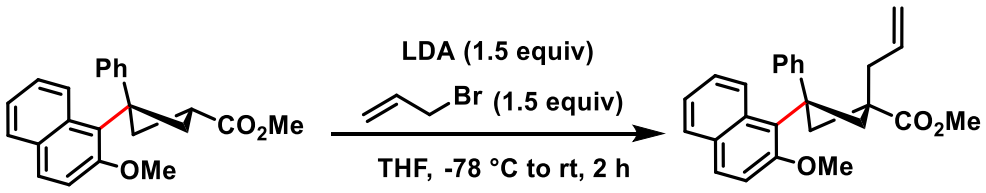


21 **22, 82%**

Compound **22** was synthesized following the literature procedure.[26] A solution of $Pd(OAc)_2$ (2 mg, 10 mol%), dppp (4 mg, 10 mol%) in DMSO (0.5 mL) was vigorously stirred at room temperature for 30 min under Ar atmosphere. Then **21** (0.050 g, 0.1 mmol), DIPEA (0.052 g, 4.0 equiv) and diphenylphosphine oxide (0.045 g, 0.22 mmol) were added sequentially before heating at 100 °C in an oil bath for 12 h. The reaction was removed to room temperature and quenched by water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo and the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (1:1) to afford **22** as a colorless oil (0.042 g, 82% yield).

***R*f** (Pet. ether /EtOAc = 70/30): 0.12; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.94-7.89 (m, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.65-7.54 (m, 7H), 7.48-7.22 (m, 11H), 3.44-3.20 (m, 4H), 3.38 (s, 3H), 2.90-2.87 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 175.6, 155.6 (d, *J* = 5.3 Hz), 148.2, 137.3 (d, *J* = 107.0 Hz), 135.4 (d, *J* = 2.5 Hz), 133.6 (d, *J* = 99.4 Hz), 132.2 (d, *J* = 9.8 Hz), 132.1 (d, *J* = 11.8 Hz), 131.86 (d, *J* = 9.2 Hz), 131.84 (d, *J* = 3.8 Hz), 131.3 (d, *J* = 2.8 Hz), 130.2 (d, *J* = 14.2 Hz), 128.8 (d, *J* = 11.9 Hz), 128.6, 128.4 (d, *J* = 11.9 Hz), 127.6 (d, *J* = 41.0 Hz), 126.7, 126.1 (d, *J* = 16.1 Hz), 125.7 (d, *J* = 13.3 Hz), 51.6, 49.1 (d, *J* = 3.6 Hz), 44.0 (d, *J* = 45.9 Hz), 33.5. **^{31}P NMR** (**162 MHz, $CDCl_3$**) δ 32.8. **HRMS (ESI)** m/z: $[M+H]^+$ calcd for $C_{34}H_{30}O_3P$ 517.1927; found 517.1930. **FTIR (cm^-)[1]** 3055, 2223, 1726, 1436, 1193, 1031.

g) Allylation of 18

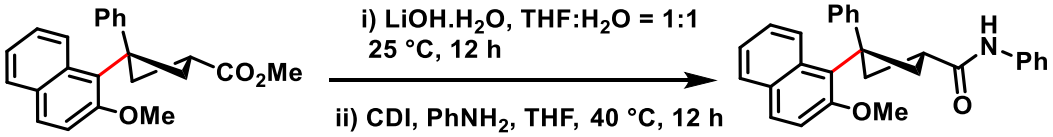


18 **23, 64%**

Compound **23** was synthesized following the literature procedure.[27] To a -78 °C solution of **18** (0.052 g, 0.15 mmol) in THF (1.0 mL), was slowly added LDA (0.11 mL, 1.5 equiv (2M in THF)). The reaction mixture was stirred for 30 min. Allyl bromide (0.027 g, 1.5 equiv) was then added dropwise into the reaction mixture. The reaction mixture was then warmed naturally to room temperature and stirred for 1.5 h. The reaction mixture was quenched by the addition of saturated aq. NH_4Cl and extracted with Et_2O three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo and the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (9:1) to afford **23** as a colorless oil (0.037 g, 64% yield).

***R*f** (Pet. ether /EtOAc = 90/10): 0.27; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.83 (d, *J* = 8.9 Hz, 1H), 7.78-7.73 (m, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 8.4 Hz, 1H), 7.31-7.22 (m, 4H), 7.11 (t, *J* = 7.3 Hz, 1H), 5.69-5.58 (m, 1H), 4.97-4.93 (m, 2H), 3.99 (s, 3H), 3.70 (bs, 2H), 3.52 (s, 3H), 2.99 (bs, 2H), 2.37 (d, *J* = 7.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 177.4, 154.2, 147.1, 133.5, 131.9, 130.4, 129.9, 128.9, 128.8, 128.1, 126.9, 125.9, 125.8, 125.2, 123.1, 117.5, 114.4, 56.2, 51.8, 45.6, 45.2, 44.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{26}H_{26}NaO_3$ 409.1774; found 409.1783. **FTIR (cm^-)^1** 2190, 2129, 1696, 1212, 1083.

h) Amidation of 18



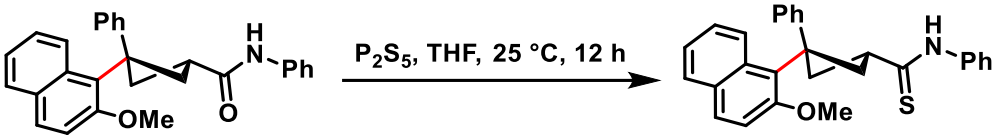
18 **24, 79%**

Methyl-3-(2-methoxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate **18** (0.069 g, 0.15 mmol) and lithium hydroxide monohydrate (0.017 g, 0.4 mmol) were dissolved in THF:H_2O (1+1 mL) at 25 °C and stirred for 12 h. The mixture was then concentrated under reduced pressure. The resulting residue was dissolved in water (5 mL) and acidified with 1 M HCl to adjust the pH to 4-6. Once the solution reached the desired pH range, the aqueous phase was extracted with DCM (5 mL). The organic layer was dried using anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the acid derivative. The acid derivative was used directly for the next step without purification.

Compound **24** was synthesized following the literature procedure.[28] Carbonyldiimidazole (0.036 g, 0.22 mmol) was added to the solution of the acid derivative (0.2 mmol) in THF (1.0 mL), and the solution was stirred at 40 °C for 2 h. The reaction mixture was cooled to rt, aniline (0.020 g, 0.22 mmol) was added, and the reaction mixture was stirred at 40 °C for 10 h. The obtained mixture was concentrated under vacuum, the residue was dissolved in CH_2Cl_2, washed with 5% aq HCl, $NaHCO_3$, and brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo and the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (5:1) to afford **24** as a white solid (0.064 g, 79% yield) (over two steps).

***R*f** (Pet. ether /EtOAc = 90/10): 0.27; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.77-7.67 (m, 5H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.37-7.26 (m, 7H), 7.21-7.19 (m, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 3.96 (s, 3H), 3.31-3.21 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.8, 154.3, 146.9, 138.1, 132.0, 129.9, 129.8, 129.1, 128.9, 128.8, 128.5, 126.6, 126.2, 125.9, 124.7, 124.2, 123.1, 119.7, 114.2, 56.2, 46.2, 40.7, 37.5. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{25}NNaO_2$ 430.1778; found 430.1783. **FTIR (cm^{-1})** 3246, 2124, 1976, 1651, 1499, 1253.

i) Thioamide formation of 24



24 **25, 84%**

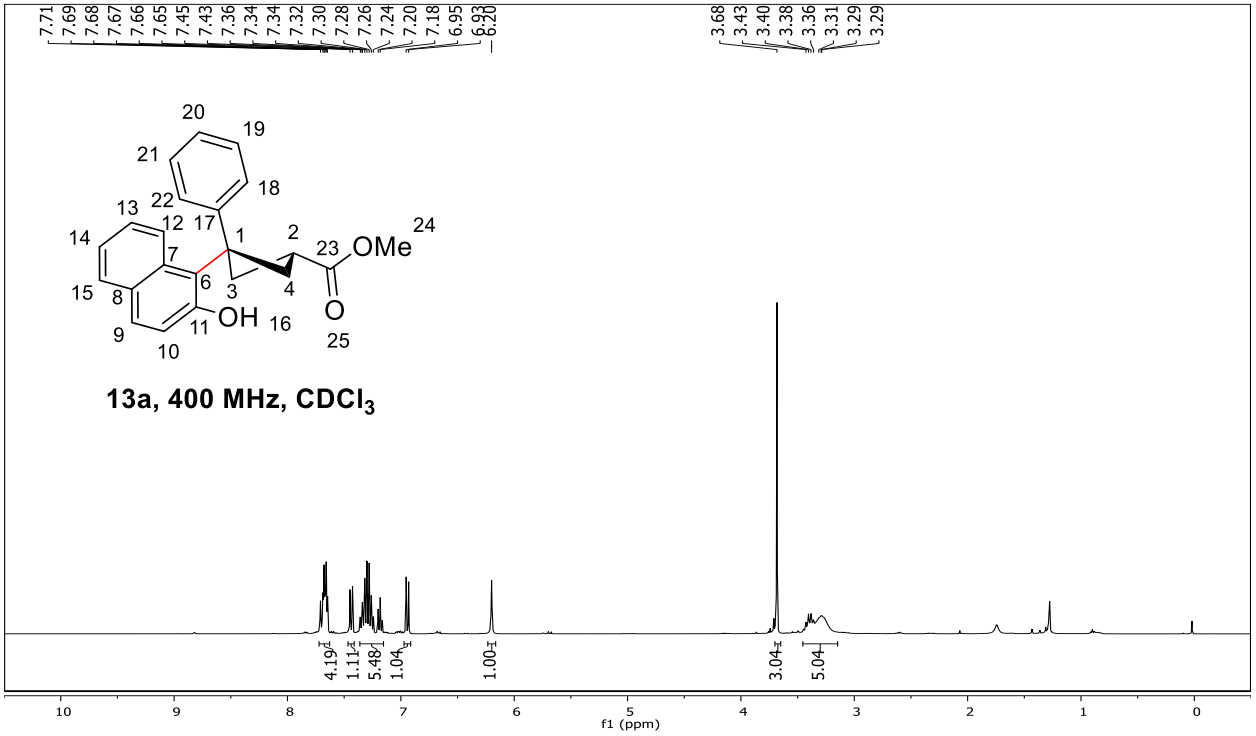
Compound **25** was synthesized following the literature procedure.[29] Compound **24** (0.043 g, 0.1 mmol) and P_2S_5 (0.111 g, 0.25 mmol) were dissolved in THF (2.0 mL) under argon atmosphere and stirred for 12 h at 25 °C. After 12 h, the solvent was evaporated, and the crude residue was pre-adsorbed on silica gel and purified by flash column chromatography on silica gel (Pet. ether /EtOAc = 90/10) to afford **25** as a sticky solid (0.036 g, 84% yield).

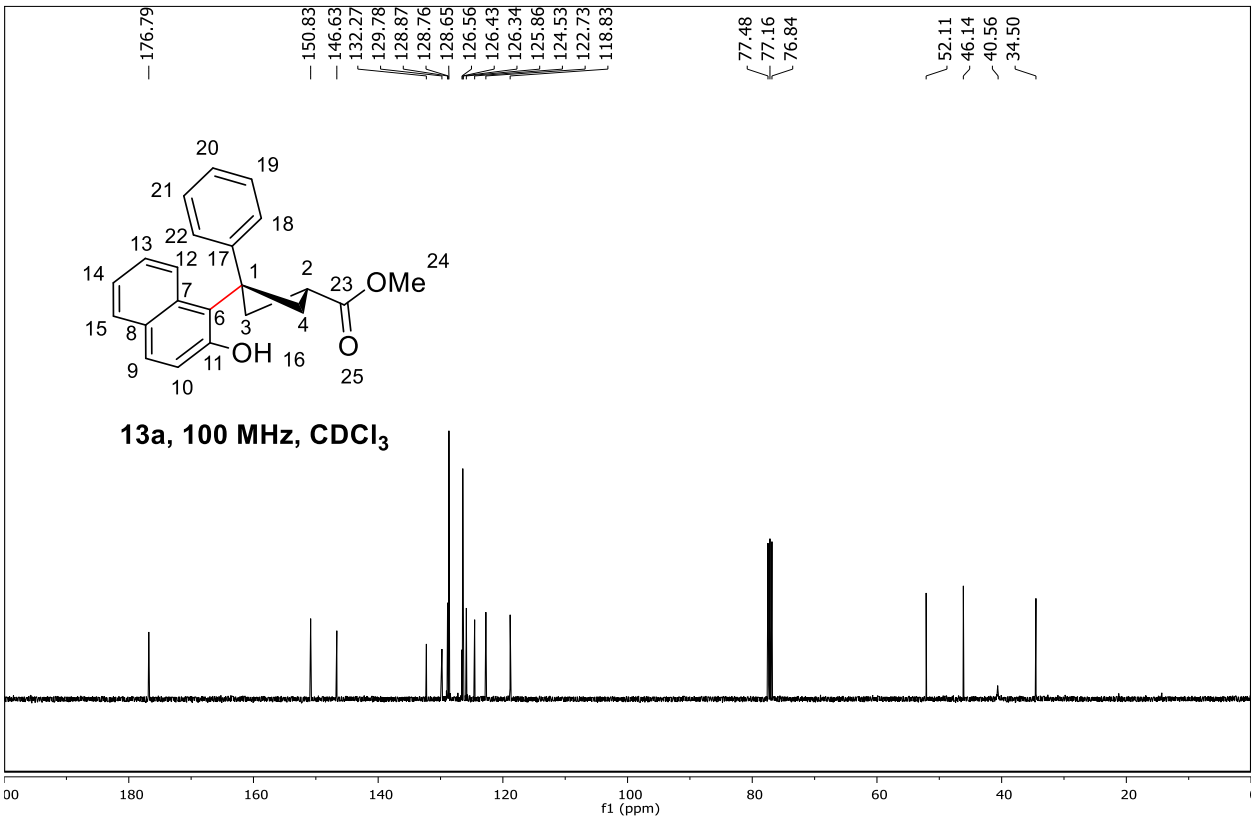
***R*f** (Pet. ether /EtOAc = 90/10): 0.29; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.56 (s, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.78-7.74 (m, 4H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.46-7.29 (m, 7H), 7.26-7.17 (m, 2H), 4.00 (s, 3H), 3.66-3.23 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 207.0, 154.2, 146.7, 138.5, 132.0, 129.9, 129.8, 129.0, 128.9, 128.9, 128.5, 126.9, 126.7, 126.3, 126.0, 124.7,

123.8, 123.2, 114.2, 56.3, 46.0, 45.2. **HRMS (ESI)** m/z: $[M+Na]^+$ calcd for $C_{28}H_{25}NNaOS$ 446.1549; found 446.1556. **FTIR (cm^{-})[1]** 3243, 2130, 1979, 1932, 1788, 1334.

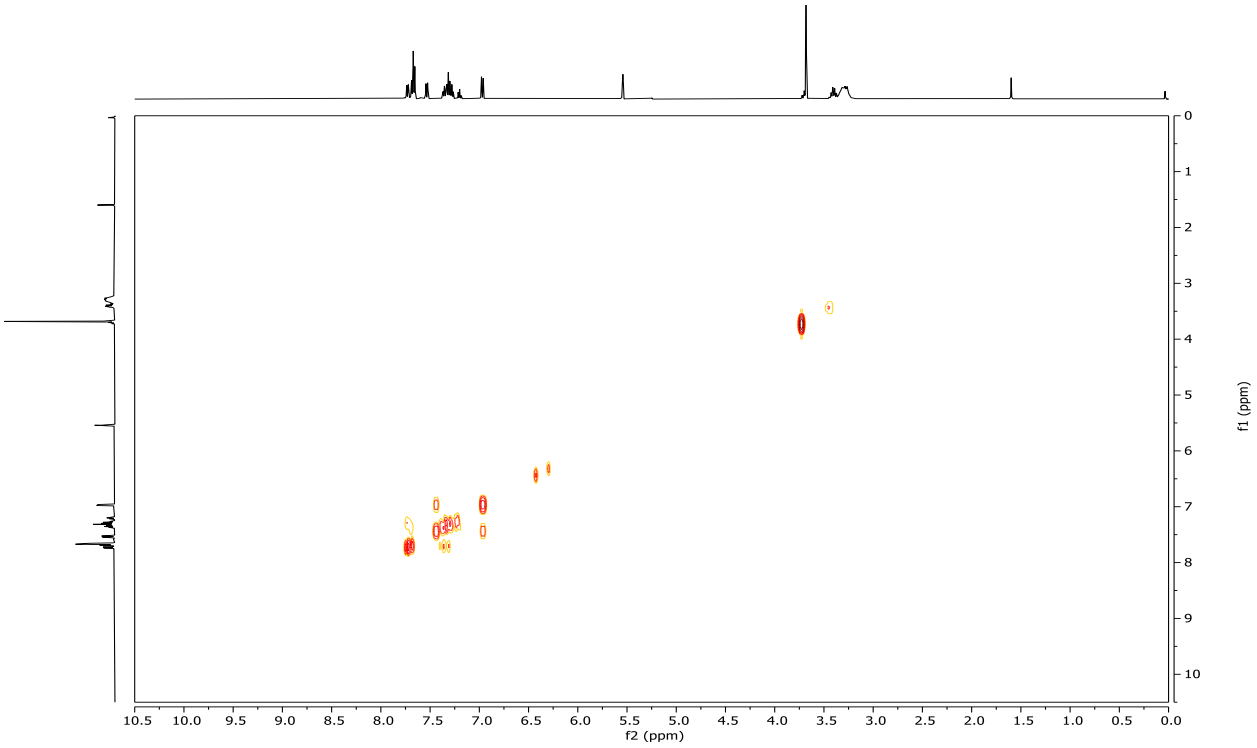
8.6.10. ^{1}H and ^{13}C NMR Spectra of Selected Compounds

Methyl-3-(2-hydroxynaphthalen-1-yl)-3-phenylcyclobutane-1-carboxylate (13a)

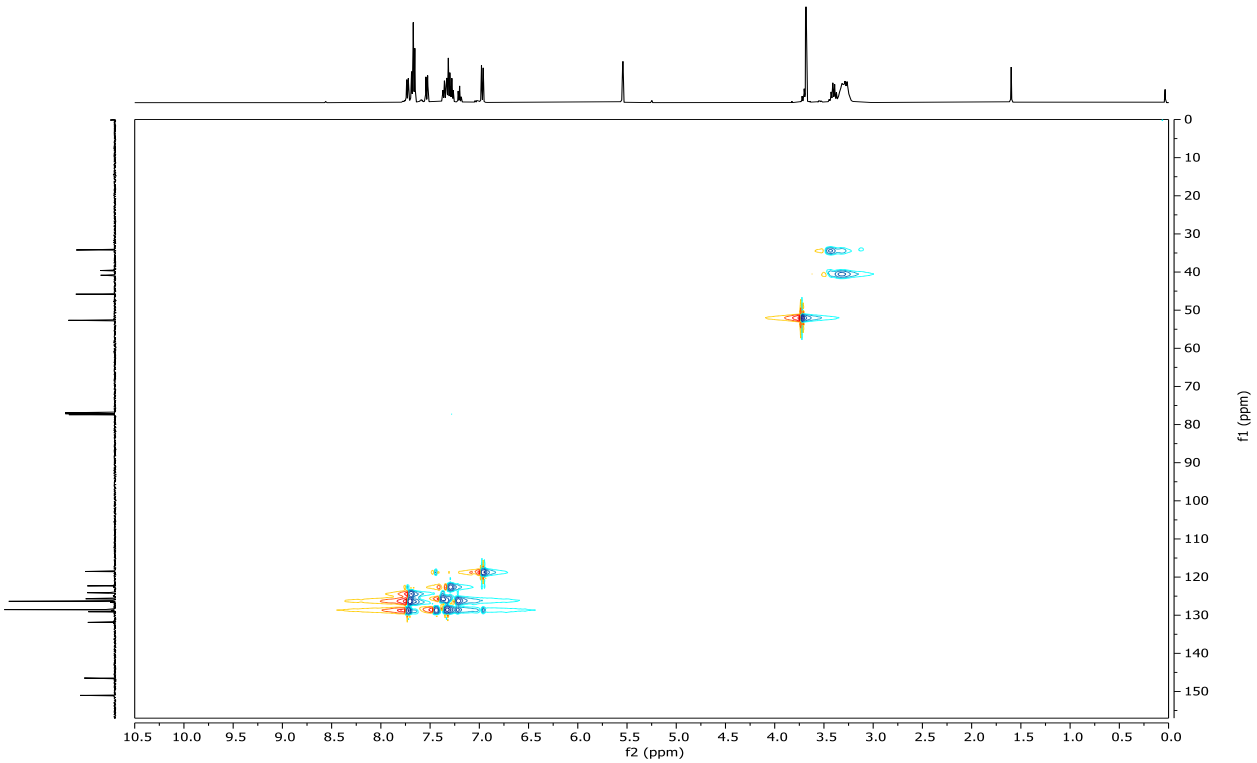




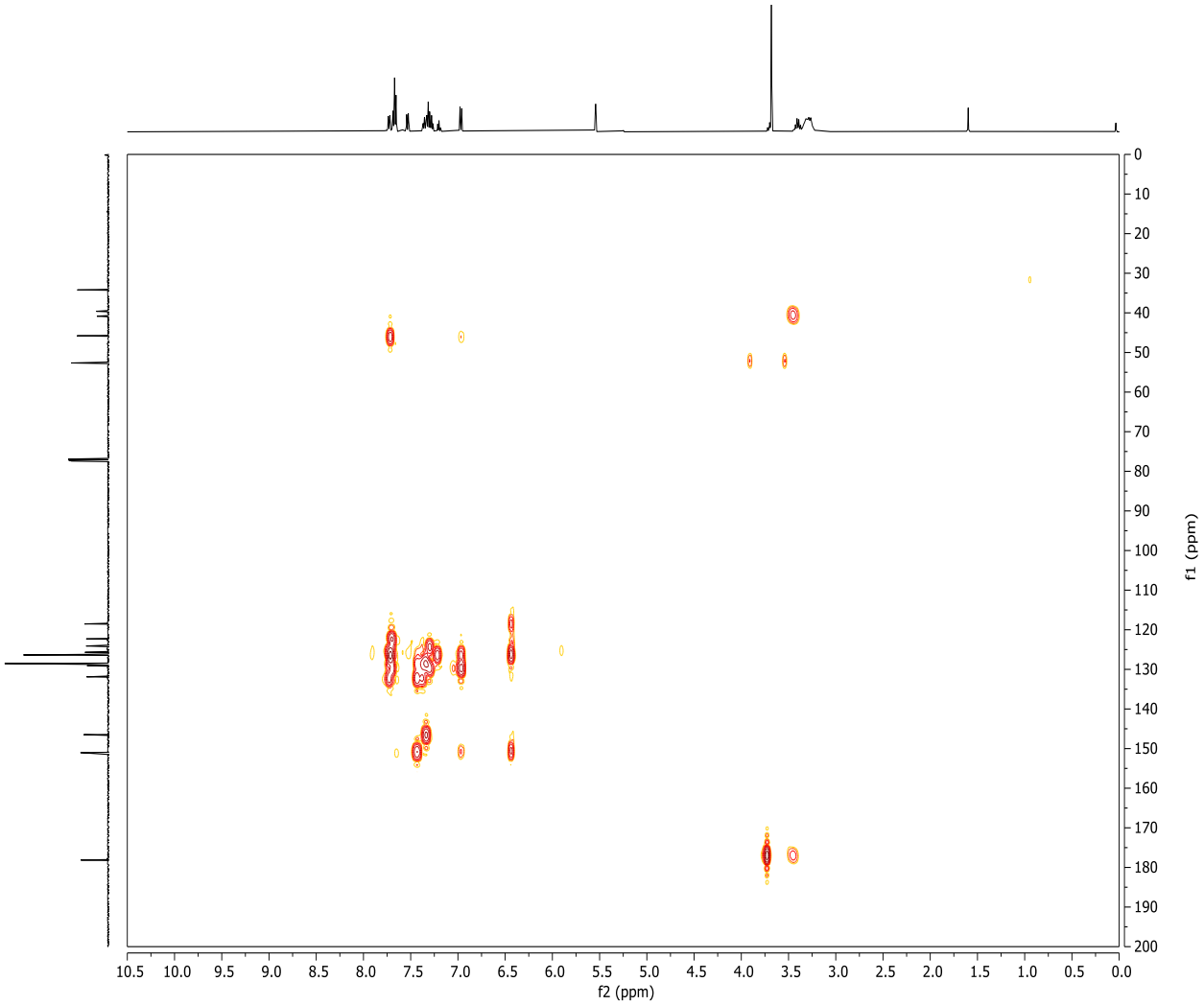
^{1}H COSY (400 MHz, $CDCl_3$)



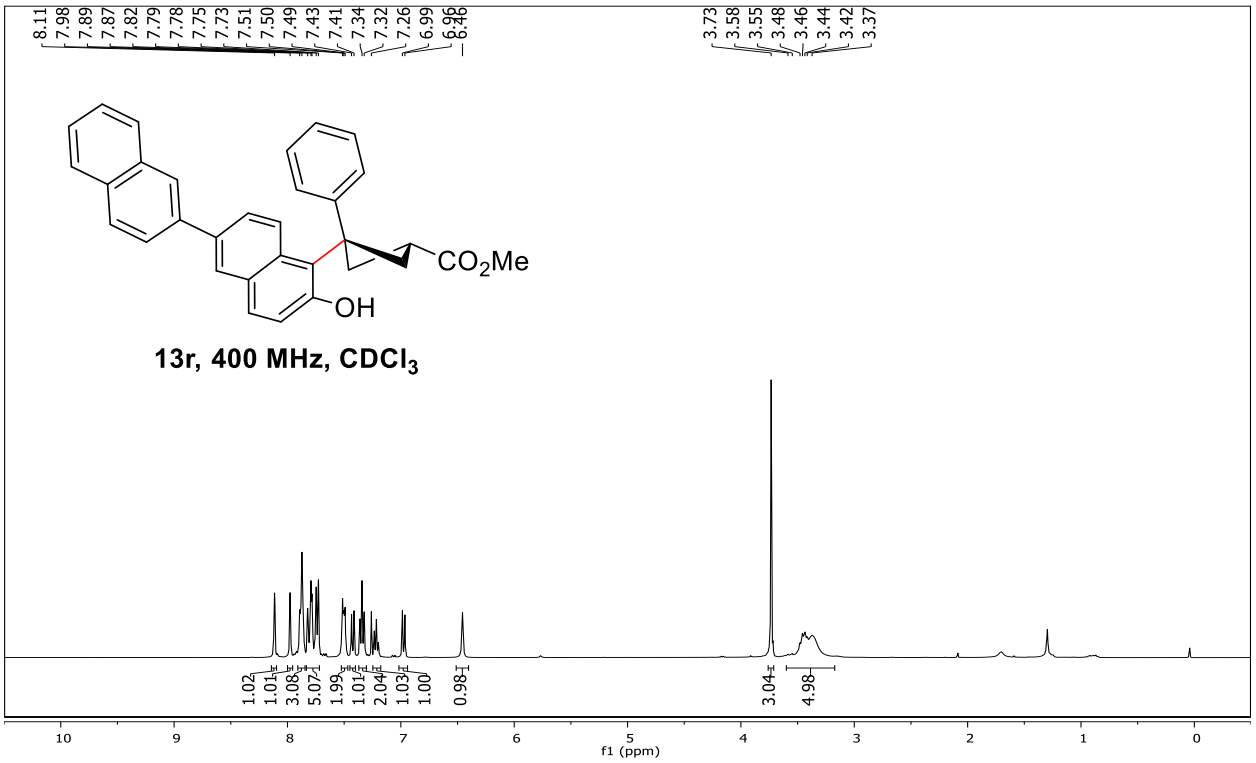
^{1}H/^{13}C HSQC (400/100 MHz, $CDCl_3$)

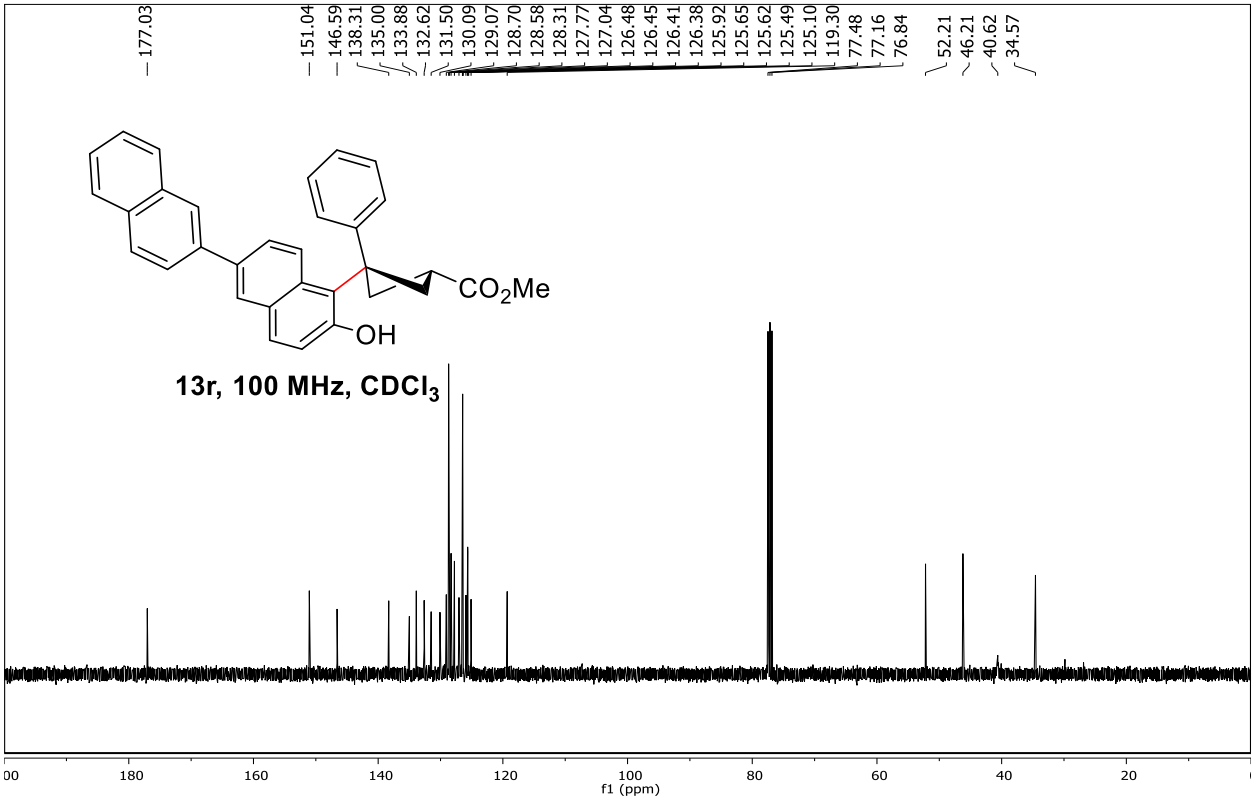


$^{1}H/^{13}C$ HMBC (400/100 MHz, $CDCl_3$)

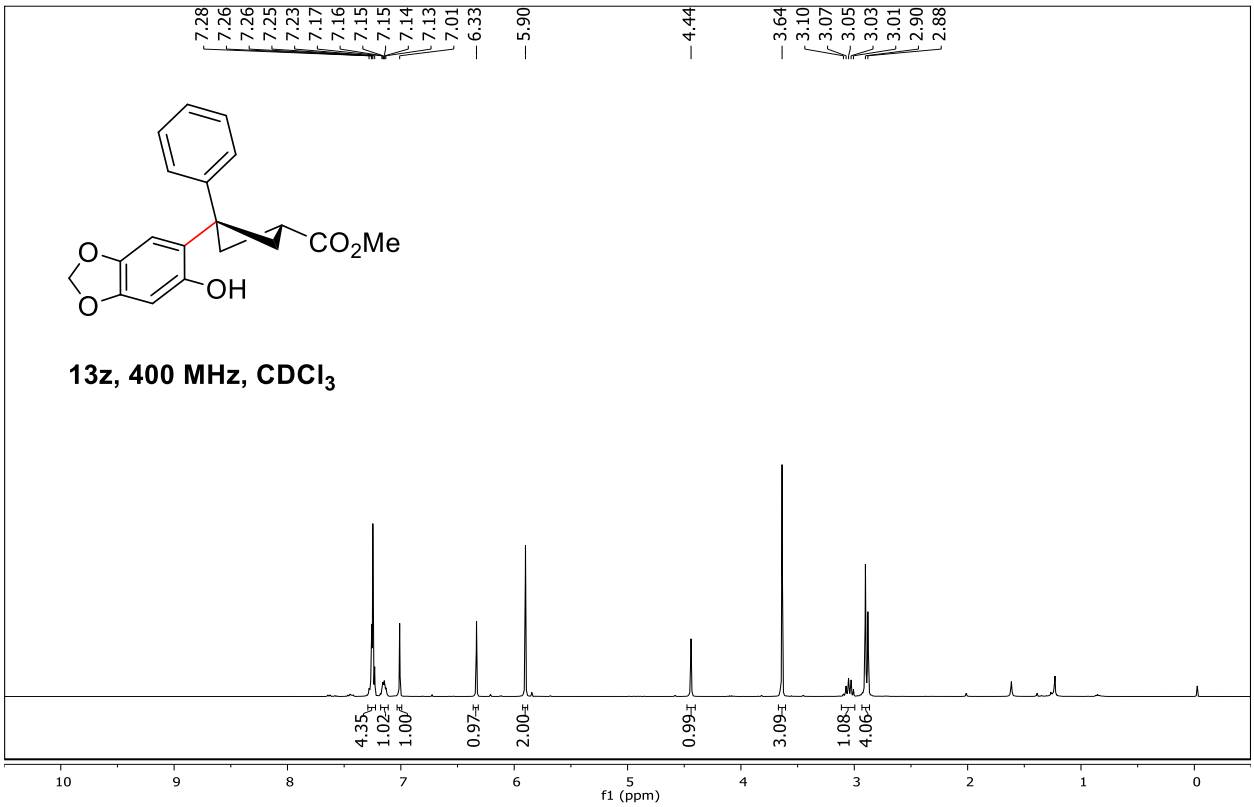


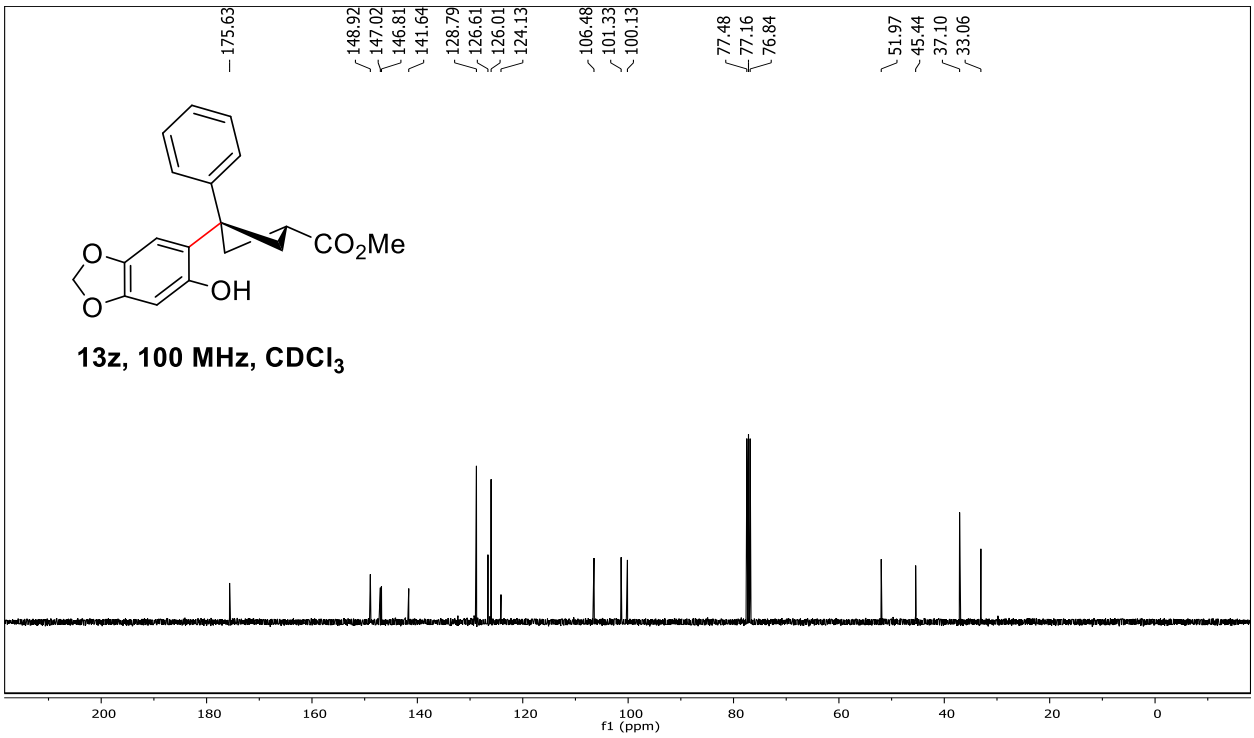
Methyl-3-(6-hydroxy-[2,2'-binaphthalen]-5-yl)-3-phenylcyclobutane-1-carboxylate (13r)





Methyl-3-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)-3-phenylcyclobutane-1-carboxylate (13z)





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List of Abbreviations

Ar	Aryl
bs	Broad singlet
BCB	Bicyclo[1.1.0]butane
$Bi(OTf)_3$	Bismuth trifluoromethanesulfonate
Bn	Benzyl
^{t}Bu	Tertiary Butyl
^{n}BuLi	*n*-Butyl lithium
Cs_2CO_3	Cesium carbonate
CsF	Cesium fluoride
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublet
DFT	Density functional theory
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E^+	Electrophile
ESI	Electron spray ionization
Et	Ethyl
eV	Electron volt
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HDDA	Hexadehydro-Diels-Alder
HMDS	Bis(trimethylsilyl)amine
HPLC	High Performance Liquid Chromatography
LUMO	Lowest Occupied Molecular Orbital
HOMO	Highest Occupied Molecular Orbital
HRMS	High-resolution mass spectrometry

Hz	Hertz
IR	Infra red
J	Coupling constant in NMR
KF	Potassium fluoride
K_2CO_3	Potassium carbonate
KO^tBu	Potassium *tert*-butoxide
LA	Lewis acid
LDA	Lithium diisopropyl amide
LHMDS	Lithium bis(trimethylsilyl)amide
m	Multiplet
MCC	Multicomponent Coupling
MCR	Multicomponent Coupling Reaction
Me	Methyl
MeCN	Acetonitrile
min	Minute(s)
mL	Millilitres
mmol	Millimole
MP	Melting point
MW	Microwave
NBS	N-Bromo Succinimide
NIS	N-Iodo Succinimide
NMR	Nuclear Magnetic Resonance
Nu^-	Nucleophile
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Ph	Phenyl
^{i}Pr	Isopropyl
PTSA	*p*-Toluenesulfonic acid
p-Tol	*para*-Tolyl
q	Quartet
rt	Room Temperature
s	Singlet

$Sc(OTf)_3$	Scandium trifluoromethanesulfonate
$Sn(OTf)_2$	Tin trifluoromethanesulfonate
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBAT	Tetrabutylammoniumdifluorotriphenylsilicate
Tf	Trifluromethanesulfonyl
Tf_2O	Trifluoromethanesulfonic anhydride
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
UV	Ultra violet
W	Watt
$Yb(OTf)_3$	Ytterbium trifluoromethanesulfonate

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