Development of Lewis-Acid Catalyzed Carbocyclization Reactions; and the Total Synthesis of Herqulines B and C

by

Christopher Casey McAtee

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in the University of Michigan
2020

Doctoral Committee:

Professor Corinna S. Schindler, Chair
Professor Anna K. Mapp
Professor Corey R. J. Stephenson
Professor Paul Zimmerman

Christopher Casey McAtee

chriscmc@umich.edu

ORCID iD: 0000-0002-3211-6898

DEDICATION

To my family
- for your constant love and support -

ACKNOWLEDGEMENTS

During my graduate work at the University of Michigan, I have had the opportunity to meet, learn from, and mentor several people. All of whom, have contributed to my success and have helped me develop as a synthetic chemist.

First and foremost, I am grateful to my graduate mentor, Professor Corinna Schindler. As I was only in Corinna's third class of students, I knew it could have been a bit risky to join such a young group. However, this thought was soon tempered. In fact, the first time I met Corinna, she was in the lab running Biotage columns and purifying compounds. What I soon learned and became appreciative of over the years is Corinna's constant commitment to the "group" and her excitement for research. Certainly, this excitement has been passed on to all member of the lab. From day one in the Schindler group, I had the chance to take lead on "my own" projects and to run with it! No doubt this has contributed to my rapid development as a synthetic chemist and fostered a sense of responsibility in advancing my research forward. I am further appreciative of Corinna in letting me work on a broad range of research projects pertaining to carbonyl-olefin metathesis and complex molecule synthesis. No doubt that the synthetic skills that I have developed during our total synthesis of the herqulines will contribute to my success as a medicinal chemist. Thank you, Corinna, for also allowing me to travel to various national conferences to present my research. These have been invaluable experiences which have fostered my development in public speaking and allowed me to grow my professional scientific network.

The members of the entire Schindler group have been a constant source of support and motivation. While graduate school in organic chemistry can be challenging, working with a great group of colleagues everyday certainly makes it a bit easier. I am especially grateful to my colleagues who have directly collaborated with me on my research projects. Specifically, with Dr. Paul Riehl, we have been able to develop an efficient synthesis of polycyclic aromatic compounds. Paul has been a frequent source of creativity to me as well as the whole group. With Dr. Haley Albright, we worked together to develop a catalytic, aliphatic carbonyl olefin metathesis reaction. Thank you to my fellow cohort member, Daniel Nasrallah, for your collaboration on our project pertaining to cyclopentadienes in addition to your constant positive attitude. I am especially grateful to Dr. Xu Zhu and his mentorship. Together we have successfully been able to synthesize mycocyclosin and the herqulines. Undoubtably, you are the hardest worker I have met during my time at the University of Michigan and you have pushed me to be a better chemist. Go Team Herqulines (!) and good luck as you begin your independent career.

To the rest of the current Schindler lab and group alumni, thank you for being great friends and colleagues: Dr. Lara Cala Alvarez, Dr. Lizeth Gomez-Lopez, Dr. Emilia Groso, Dr. Ahlam Armaly, Dr. James Annand, Dr. Alexander Golonka, Dr. Jacob Ludwig, Marc Becker, Alistair Richardson, Hannah Vonesh, Ashlee Davis, Katie Rykaczewski, Mario Gaviria, Troy Zehnder, Lindsey Karp, Dr. Sukanta Bar, Dr. Joseph Gianino.

My dissertation committee has been exceptional. Thank you, Prof. Corey Stephenson, for granting me the opportunity to rotate in your research group. This was a valuable experience that allowed me to contribute to an ongoing photoredox catalysis project which has resulted in a co-authored publication. I certainly expect I will utilize photoredox chemistry during my career as an industrial chemist! I am grateful to have had the opportunity to work with Prof. Anna Mapp.

Teaching with you during my second year developed my leadership skills. Further, I am appreciative of your support during my job search! Thank you, Prof. Paul Zimmerman, for your thoughtful feedback during committee meetings and being a valuable theoretical collaborator on several of my research projects pertaining to carbonyl-olefin metathesis.

Prior to graduate school at Michigan, I have been influenced by many folks. First and foremost, I am grateful to Prof. Chriss E. McDonald (Lycoming College) for your friendship and mentorship. Without doubt, it was during my time in your research lab (aka Area 62) that established my trajectory toward graduate school. I became immediately excited by research and the challenge in answering difficult questions through organic synthesis. During my time at Michigan, it has been great to see how some of my early "discoveries" in your group have shaped your research. I want to also thank Prof. Richmond Sarpong who granted me the opportunity to work in his group as a Center for Selective C-H Functionalization Undergraduate Scholar. My experience at Berkeley cemented my desire to pursue graduate work in total synthesis and helped my transition from Lycoming College to the University of Michigan.

Undoubtably, meeting Taylor has been the best part of graduate school for me. I owe a great deal to you for being there every step of the way and making my time here that much easier. Every success I have had while at Michigan, has been in part, from your support. During these busy times, it has always been assuring to have you by my side. Coming home with you to Hendricks and Harper, has continually been one of my favorite parts of the day. I will always remember our times spent together in Michigan from our weekend trips to the Eastern Market in Detroit, up North to the Dunes, or taking our bikes to Michigan's state parks. Watching you develop as a chemist and into a scientist has constantly impressed me. Thank you for your constant

encouragement, love, and support! I cannot wait to see how we continue to grow together in life and in our careers!

There are few people that can say they have gone though graduate school with their sibling let alone their twin. Indeed, one of the best colleagues I have had during my graduate studies is my brother, Rory. I have always valued the opportunity to walk up to your hood and talk chemistry with you. You are the most driven person I know who always sets the standard. You have constantly taught me to be ambitious and to set my goals high. I am certain you will accomplish great things in your career. Rory, thanks for everything and here's to many more old-fashioned we will have together!

I owe a great deal of gratitude to my entire family. Your love and support has meant more to me than you will know! Each one of you I know have sacrificed for me to accomplish my dreams. Thank you! Dad, thanks for always asking how I am and for being the most authentic person I know You have shown me that family is most important in life. Mom, you are the happiest person around who has always encouraged me to go after my dreams! Brigid, Patrick and Ed, each of you make me a proud brother and I cannot wait to spend more time with you all when we move closer! Thank you to my Uncle Jimmy - you have always been a constant source of support, whether on the soccer field / cross-country course or in graduate school. Finally, to my grandmothers – you both have always been my biggest 'fan' and I will always strive to make you both proud!

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

ABSTRACT

Development of new catalytic methods to assemble carbon-carbon bonds is important in many areas of organic synthesis. These strategies enable the synthesis of biologically active compounds and functionalized materials. In this regard the olefin-olefin metathesis reaction has emerged as a vital carbon-carbon bond forming reaction as demonstrated by the transformation's broad application in natural product synthesis, pharmaceutical sciences, and organic materials. In comparison. the carbonyl-olefin metathesis (COM) reaction affords entry to similar olefin products. However, while the catalytic COM reaction is less developed in mechanistic understanding and substrate scope than the olefin-olefin metathesis derivative, several attractive qualities have prompted chemists to broaden the synthetic utility of COM.

Chapter 1 details the development of a new approach toward polycyclic aromatic compounds (PACs) based on the design principle of iron(III)-catalyzed COM reactions. This protocol is described by its operational simplicity, high functional group compatibility, while relying on $FeCl_3$ as an earth-abundant catalyst. Greater than 40 PACs are synthesized. Isolation and characterization of an aromatic oxetane provides evidence that this carbocyclization proceeds through an oxetane intermediate.

Chapter 2 describes an efficient synthesis of cyclopentadienes. Cyclopentadienes (CPs) are important scaffolds in organometallic chemistry and catalysis. This Lewis acid-catalyzed protocol garners 2,3,4-substituted cyclopentadienes incorporating electronically and sterically diverse functionalities, with complete regiocontrol. Our experimental and theoretical investigations

provides support for a mechanism that is related to catalytic COM reactions wherein Lewis acid-catalyzed cycloadditions between carbonyl and alkenes garners reactive oxetane intermediates. However in lieu of a [2+2]-cycloreversion, stepwise oxetane fragmentation results in the formation of cyclopentadienes via interrupted carbonyl-olefin metathesis. The scope of this method for cyclopentadiene synthesis is demonstrated in 24 examples and proceeds in up to 85% yield.

During our studies related to Lewis acid-catalyzed synthesis of functionalized cyclopentadienes from homoprenylated β-ketoesters (Chapter 2) we observed that sterically congested unsaturated ketones can undergo intramolecular α-tert-alkylation. Chapter 3 details our studies pertaining to the development of an intramolecular α-tert-alkylation reaction of unsaturated β-ketoesters. This approach gives rise to functionalized cyclopentanes and is characterized by its operational simplicity and the use of $Sc(OTf)_3$ as a Lewis acid catalyst. Of interest, cyclopentanes bearing heterocycles, sites for post reaction functionalization and spirocyclic architectures are all accessible.

Chapter 4 describes our scalable total synthesis of the secondary metabolite, mycocyclosin. This distorted cyclophane was initially isolated from *Mycobacterium tuberculosis* in 2009 by Belin and first synthesized by Hutton in 2012. Mycocylosin bears a highly strained 3,3'-dityrosine biaryl system which arises biosynthetically from an intramolecular oxidative dehydrogenative cross-coupling of cyclo(l-Tyr-l-Tyr) (cYY) catalyzed by the P450 enzyme CYP121. Scalable access to mycocyclosin and analogues via a palladium(0)-catalyzed macrocyclization is expected to enable the biological evaluation of these cyclodipeptides as tuberculosis antimicrobials.

The herquline alkaloids are characterized by their modest size, yet incredible molecular strain initially isolated by Ōmura in 1979. Comprising of a macrocyclic core, a bridging 1,4-dicarbonyl substructure, and an unsymmetrical, highly Lewis basic piperazine at the base, these

alkaloids have sparked the creativity of many synthetic chemists since their isolation nearly 40 years ago. Chapter 5 is a memorable narrative that recounts our synthetic journey in successfully assembling herquline B and C, which closely mirrors their biosynthetic origins. Fraught with unanticipated challenges that ultimately fueled reaction design and ingenuity, our synthetic campaign of the herqulines afforded countless lessons gained which we expect to be instructive to the synthetic community.

Chapter 1

Polycyclic Aromatic Compounds via $FeCl_3$-Catalyzed Carbonyl Olefin Metathesis

Portions of this chapter has been published in McAtee, C. C.; Riehl, P. S. Schindler, C. S. Polycyclic aromatic hydrocarbons via iron(III)-catalyzed carbonyl–olefin metathesis**.** *J. Am. Chem. Soc.* **2017**, *139*, 2960–2963.

1.1 Introduction

Polycyclic aromatic compounds (PACs),[1] including phenanthrenes, pyrenes, chrysenes and helicenes, are important structural motifs that exhibit desirable optical,[2] electronic,[3] and chelating[4] properties. Consequently, diverse fields of research such as materials science,[4] natural product synthesis,[6] asymmetric catalysis,[7] and molecular recognition[8] rely on efficient strategies to access condensed polyaromatic compounds. Established procedures toward these motifs include McMurry coupling reactions[9, 10] that are mediated by low-valent titanium reagents (Figure 1.1 B) or oxidative photocyclization strategies[11] of stilbene derivatives. These classical approaches[12] have been hampered by the need for stoichiometric reagents, harsh reaction conditions, or competing substrate dimerization. Complementary approaches have been developed to overcome these challenges that are based on Diels-Alder cycloaddition reactions,[13] radical cyclizations,[14] and metal-mediated cycloisomerizations.[15] Additionally, rhodium- and ruthenium-catalyzed

procedures have been reported that rely on bis(*N*-tosylhydrazone)[16] **2** as substrate (Figure 1.1 A) and olefin-metathesis reactions of bis(alkenes) [17] **4** (Figure 1.1 C).

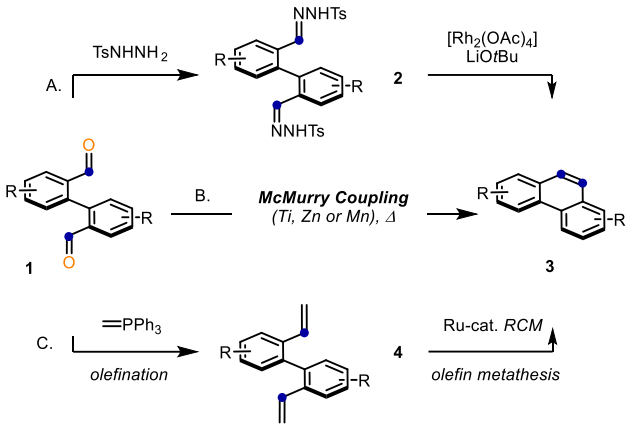


FIGURE 1.1. Existing strategies for the synthesis of polycyclic aromatic compounds.

We have recently reported the development of an efficient iron(III)-catalyzed carbonyl-olefin metathesis reaction[18] that proceeds under mild reaction conditions and ambient temperature. Our synthetic strategy for ring-closing metathesis enables the direct coupling of carbonyl and olefin functional groups upon activation by a Lewis acid catalyst to forge the desired alkene bonds. Based on this design principle, we report the development of a new strategy for the synthesis of polyaromatic hydrocarbons differing in their steric and electronic substitution patterns. This strategy is compatible with ketones as well as aldehydes and proceeds via intermediate oxetanes **6** to provide the corresponding carbonyl-olefin metathesis products in good to excellent yields (Figure 1.2).

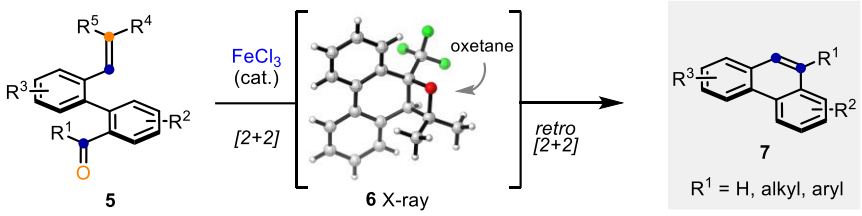
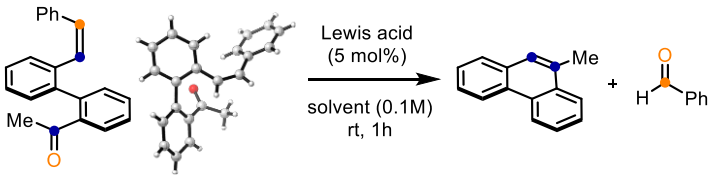


FIGURE 1.2. Our approach toward polycyclic aromatic compounds via $FeCl_3$ catalyzed carbonyl-olefin metathesis.

1.2 Results and Discussion

1.2.1 Optimization of reaction conditions

While several Lewis acids were previously found capable of promoting carbonyl-olefin metathesis reactions,[18] a fine-tuned combination of Lewis acidity[19] and oxophilicity[20] proved essential to give high yields of product. Indeed, when biaryl ketone **8** was reacted with a variety of Lewis acids (e.g. $TiCl_4$, $SnCl_4$, $FeCl_2$, $Cu(OTf)_2$) no formation or only trace amounts of the metathesis product **9** was observed (entries 1-4, Table 1.1). Catalytic amounts of $ZnCl_2$ under otherwise identical reaction conditions resulted in low yields of 9-methylphenanthrene (**9**, entry 5, Table 1.1). Stronger Lewis acids, $GaCl_3$ and $AlCl_3$,[18] were able to promote the desired transformation in 88% and 93% yield, respectively with complete conversion of starting material **8** (entries 7 and 8, Table 1.1). Notably, substoichiometric $BF_3 \cdot Et_2O$ led to the formation of **9** in only modest yield and conversion (entry 6, Table 1.1).[21] Ultimately, 5 mol% $FeCl_3$ in either dichloroethane or toluene was identified as an optimal set of reaction conditions, resulting in quantitative formation of the carbonyl-olefin metathesis product **9** in 97% and 99% yield, respectively (entries 9 and 11, Table 1.1). More dilute reaction conditions led to slightly lower yields of the desired product **9** (entry 10, Table 1.1). When the reaction was conducted in ethereal solvents (1,4-dioxane), or polar aprotic solvents (DMF), no formation of phenanthrene **9** was observed–presumably due to competing coordination of the solvent to the iron catalyst (entries 12 and 13, Table 1.1). Moreover, the Brønsted acids, anhydrous HCl[22] and *p*TsOH in dichloroethane, did not form phenanthrene **9** and resulted in quantitative reisolation of starting material (entries 16 and 17, Table 1.1).



8 **8** (*X-ray*) **9** **10**

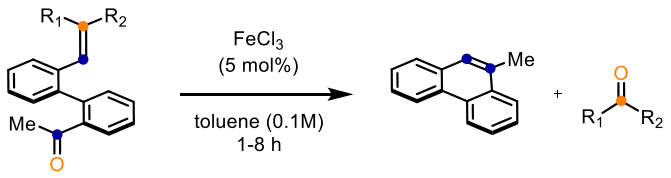
entry	Lewis acid	solvent	yield **9** (%)	conversion (%)
1	$TiCl_4$	DCE	3	7
2	$SnCl_4$	DCE	0	6
3	$FeCl_2$	DCE	0	2
4	$Cu(OTf)_2$	DCE	0	0
5	$ZnCl_2$	DCE	22	26
6	$BF_3{\cdot}Et_2O$	DCE	31	35
7	$AlCl_3$	DCE	93	100
8	$GaCl_3$	DCE	88	100
9	$FeCl_3$	DCE	97	100
10	$FeCl_3$	DCE (0.01M)	95	100
11	$FeCl_3$	toluene	99	100
12	$FeCl_3$	DMF	0	0
13	$FeCl_3$	1,4-dioxane (0.1M)	0	6
14	HCl	DCE	0	0
15	*p*TsOH	DCE	0	0

Conditions: biaryl **8** (0.13 mmol), Lewis or Brønsted acid (5 mol%) in solvent listed (0.1-0.01M), rt, 1h; yield determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as internal standard.

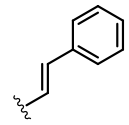
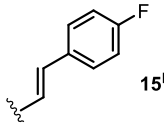
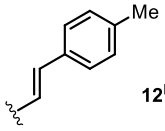
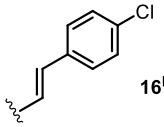
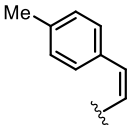
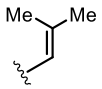
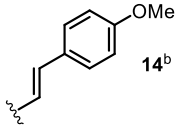
TABLE 1.1 Evaluation of reaction conditions for 9-methylphenanthrene (**9**) formation.

We next sought to investigate the ability of biaryl substrates with various olefin subunits (**11**-**19**) to undergo the desired iron(III)-catalyzed carbonyl-olefin metathesis reaction (Table 1.2). While both electron-rich and electron-poor styrenes (entries 1-6, Table 1.2) proved to be efficient substrates resulting in high yields of phenanthrene **9**, all but styrene **11** and prenylated **17** required elevated temperatures of 50 ˚C to proceed to full conversion. Notably, no difference in reactivity between *E*- and *Z*-isomers was observed; both *para*-methyl styrenes **12** and **13** formed metathesis product **9** in yields up to 89% which indicates an indiscriminate reaction pathway of the carbonyl-olefin metathesis reaction. Although the formation of the respective benzaldehydes was observed as the corresponding metathesis byproducts in the course of the reaction, they did not impede reaction progress. Moreover, substrates **11**-**16** bearing styrenyl moieties proved superior to their prenylated analog **17**, which resulted in the formation of phenanthrene **9** in only 79% yield (entries

1-7, Table 1.2). In comparison, no reaction was observed when terminal alkene **19** was subjected to the optimized reaction conditions (entry 9, Table 1.2). Conversion of biaryl **18** bearing a crotyl moiety under the reaction conditions resulted in low yields (18%) of the desired product.



11-19 **9**

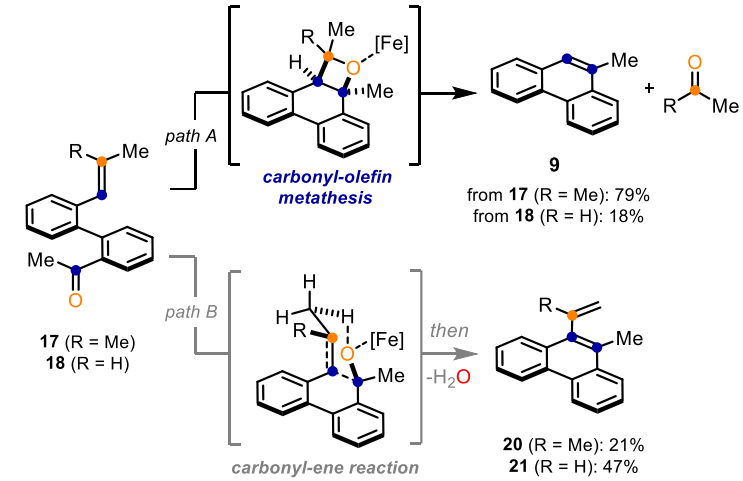
entry	alkene		yield (%)	entry	alkene		yield (%)
1		**11**[a]	90	5		**15**[b]	80
2		**12**[b]	82	6		**16**[b]	84
3		**13**[b]	89	7		**17**	79
4		**14**[b]	86	8		**18**[b]: R= Me	11
				9		**19**[b]: R= H	n.r.

Conditions: biaryl (0.13 mmol), $FeCl_3$ (5 mol%) in toluene (0.1 M); [a] mixture of *E/Z* (2:1) isomers; [b] reaction heated to 50°C.

TABLE 1.2. Alkenes evaluated as coupling partners in the $FeCl_3$ -catalyzed carbonyl olefin metathesis reaction.

The hampered yields of the non-styrenyl substrates **17** and **18** were found to be caused by a competing carbonyl-ene reaction pathway which led to the formation of **20** and **21** in 21% and 47% yield, respectively, when subjected to the optimized reaction conditions (Figure 1.3). These findings contrast distinctly with previous results obtained in our lab[18] in the iron(III)-catalyzed

carbonyl-olefin metathesis reaction of aliphatic aryl ketones, in which prenylated substrates proved superior to the analogous styrenes.



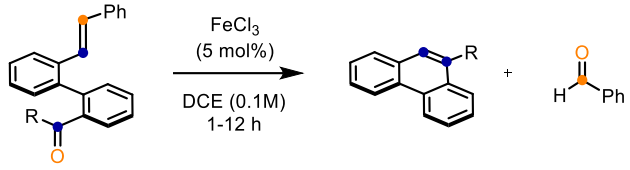
Conditions: biaryl (0.13 mmol), $FeCl_3$ (5 mol%) in dichloroethane (0.1M), rt, 1h; [a)] yield determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as internal standard.

FIGURE 1.3. Competing carbonyl-ene side reaction observed with prenyl alkenes.

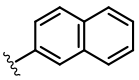
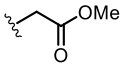
1.2.2. Scope of polycyclic aromatic compounds obtained

The conditions developed for the iron(III)-catalyzed carbonyl-olefin metathesis reaction proved efficient for a range of sterically and electronically differentiated ketones and aldehydes (entries 1-9, Table 1.3). Although aldehydes have previously been found unreactive in catalytic carbonyl-olefin ring-closing metathesis reactions,[18] **22b** was found to yield the desired metathesis product **23b** in 84% under the optimized conditions. In addition to methyl ketone **22a** and aldehyde **22b**, substrates bearing sterically demanding isopropyl (**22c**) and *tert*-butyl (**22d**) moieties formed the desired alkylated phenanthrenes in 79% and 55%, respectively, although the latter required elevated temperatures for efficient conversion (entries 3 and 4, Table 1.3). Phenyl and naphthyl substituted carbonyl substrates (**22e** and **22f)** were able to undergo metathesis in efficient yields (entries 5 and 6, Table 1.3). Importantly, biaryl enone **22g** led to the corresponding polycycle **23g**

incorporating an exocyclic alkene as a functional handle in 50% yield, albeit at elevated temperatures (entry 7, Table 1.3). Additionally, β-ketoester **22h** resulted in the formation of the desired metathesis product **23h** in satisfactory yield (72%), while electron-deficient trifluoromethyl ketone **22i** also proved viable as a substrate converting to 9-trifluoromethyl phenanthrene **23i** in 52% (entries 8 and 9, Table 1.3).



22 a-i **9, 23 b-i**

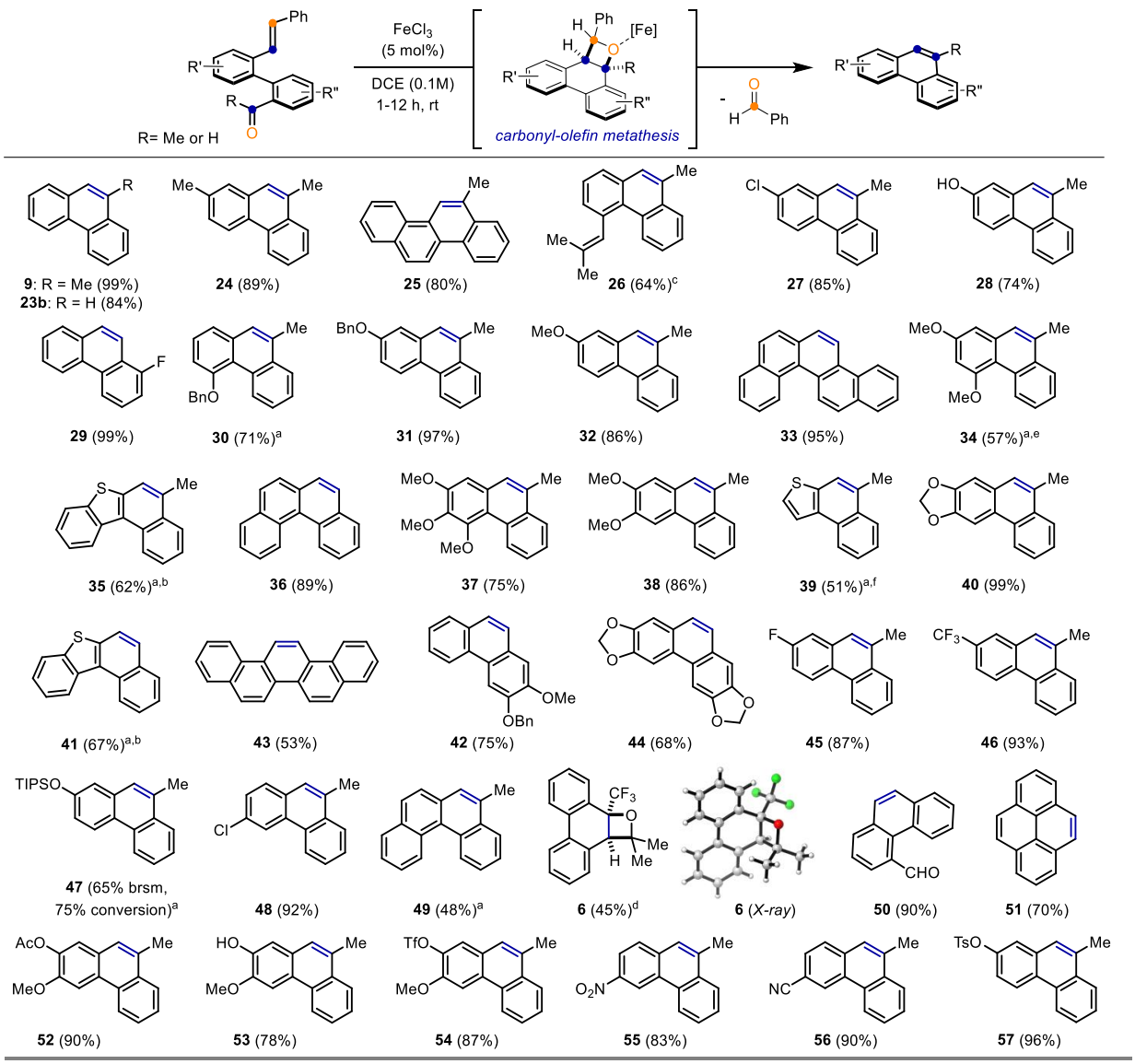
entry	substrate		yield (%)	entry	substrate		yield (%)
1		**22a**	99	6		**22f**	53
2		**22b**	75				
3		**22c**	79	7		**22g**[a]	50
4		**22d**	55[a]	8		**22h**	72
5		**22e**	67	9		**22i**[a]	52

Conditions: biaryl (0.13 mmol), $FeCl_3$ (5 mol%) in dichloroethane (0.1M), rt, 1-12h;
[a)] reaction heated to 50ºC.

TABLE 1.3. Carbonyls evaluated as coupling partners in the $FeCl_3$ -catalyzed carbonyl olefin metathesis reaction.

Various PAC frameworks were accessible utilizing the optimal reaction conditions for iron(III)-catalyzed carbonyl-olefin metathesis (Table 1.4). The respective substrates were prepared in a two-step sequence relying on initial olefination and subsequent cross-coupling reaction. Upon subjection to the optimized iron(III)-catalyzed carbonyl-olefin metathesis conditions, the desired products were obtained with benzaldehyde as the corresponding byproduct. Electron-deficient phenanthrenes bearing halogen, trifluoromethyl, nitro, or nitrile substitution were formed in yields greater than 85% (**27**, **29**, **45**, **46**, **55** and **56**, Table 1.4). Similarly, electron-rich substrates

incorporating methoxy or benzyl ether functionalities underwent the desired carbonyl-olefin metathesis reaction in excellent yields (**30**, **31**, **32**, **38**, **42**, Table 1.4). However, diminished yields of 75% and 57% were observed for substrates bearing *ortho*-methoxy substitution (**34** and **37**, Table 1.4). Dioxoles **40** and **44** were formed in 99% and 68% yield, respectively, under the optimized reaction conditions. Moreover, sulfur-containing heterocycles proved viable substrates for carbonyl-olefin metathesis and resulted in the formation of thiophene **39** and benzothiophenes **35** and **41** in good yields. Alternative strategies to these structural motifs are currently hampered by harsh reaction conditions and competing reaction pathways resulting in low overall yields.[23] Unprotected phenols as well as aldehydes are compatible with the optimized conditions for iron(III)-catalyzed carbonyl-olefin metathesis resulting in the formation of phenanthrene **28** or aldehyde **50** in 74% and 90% yield, respectively.



Conditions: biaryl (0.13 mmol), $FeCl_3$ (5 mol%), in DCE (0.1M), rt, 1-12 h; [a] reaction heated to 50°C; [b] reaction was run with 20 mol% catalyst loading; [c] starting material is bis-prenylated biaryl ketone (see Supporting Information for details); [d] substrate is the prenylated analog of **22i**; reaction was run in toluene as solvent; [e] starting material is reisolated; [f] substrate decomposition was observed at the elevated reaction temperatures; [g] low solubility in organic solvents.

TABLE 1.4. Polycyclic aromatic compounds obtained.

Moreover, extended polyaromatic hydrocarbons are accessible based on this metathesis strategy. Specifically, methylchrysene **25** is formed in 80% yield, while benzo(c)phenanthrene **36** is accessible in 89% yield from the respective biaryl aldehyde (Table 1.4). Notably, benza[a]anthracene **59** is afforded in excellent yield via a biscarbonyl-olefin metathesis event (Figure 1.4). Interestingly, when the prenylated analog of **22i** was converted under the optimized

reaction conditions, no formation of the desired carbonyl-olefin metathesis product **23i** was observed. The major product of this transformation was identified as oxetane **6** in 45% yield (Table 1.4). This result supports our hypothesis that iron(III)-catalyzed carbonyl-olefin metathesis reactions do proceed via oxetanes as reactive intermediates.[18]

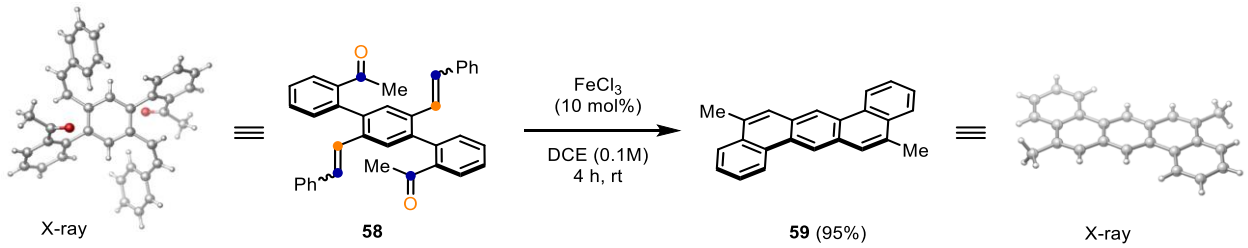


FIGURE 1.4. Iterative carbonyl-olefin metathesis reaction for the synthesis of extended polycyclic aromatic compounds.

1.3 Conclusion

The development of a new approach toward the synthesis of polyaromatic hydrocarbons is reported relying on the design principle of an iron(III)-catalyzed carbonyl-olefin metathesis reaction. This strategy is characterized by its operational simplicity, mild reaction conditions, as well as chemo- and regioselectivity. Analysis of the two reaction partners (olefin and carbonyl) revealed that the respective olefin moieties can readily couple to a variety of differentiated aryl-ketones or aryl aldehydes to garner the corresponding functionalized polyaromatic hydrocarbons as metathesis products. Isolation of aryl oxetane 6 supports the notion that this new strategy for the synthesis of polyaromatic hydrocarbons does indeed proceed via oxetanes as reactive intermediates.[18]

Chapter 2

Functionalized Cyclopentadienes via Catalytic Oxygen Atom Transfer

The work in the chapter is unpublished and has been carried out in collaboration with Daniel Nasrallah (University of Michigan) and Rory C. McAtee (University of Michigan).

2.1 Applications and synthesis of cyclopentadienes

Cyclopentadienes (Cps) have found widespread applications in various areas of research.[1] They are core structures of recently developed chiral Brønsted acid catalysts[2] and represent key building blocks to generate molecular complexity in [4+2]-cycloadditions.[3] In organometallic chemistry, cyclopentadienes are important ancillary ligands for transition metals[4] and *f*-block metals.[5]

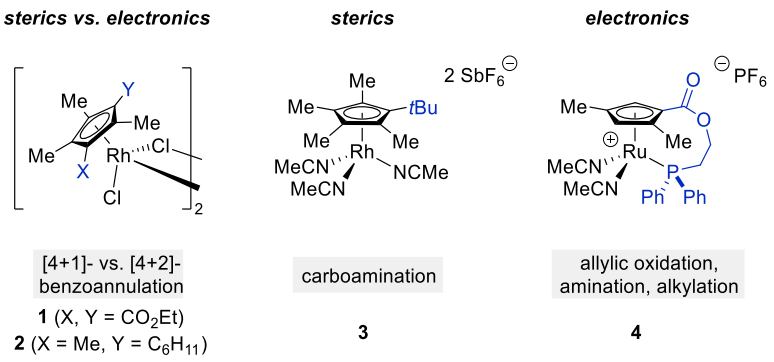


FIGURE 2.1 Applications of cyclopentadiene ligands.

Modifications of the Cp-ligand scaffold are known to induce changes in the physical properties and chemical reactivity of the coordinated metal.[6] In catalysis, this concept has been advanced as "ligand tuning" and relies heavily on the presence of sterically and electronically differentiated substituents incorporated in the cyclopentadiene framework to select for the desired reactivity.[6] For example, tuning the Lewis acidity of the coordinated Rhodium metal with either electron-withdrawing (**1**) or electron-donating (**2**) substituents promotes either [4+1]- or [4+2]-reaction pathways (Figure 2.1).[7] While ^{t}Bu Cp complex **3**[8] and bidentate Ruthenium species **4**[9] can facilitate carboamination or allylic substitutions, respectively.

The ability to modulate reactivity by tuning substituents on the ligand scaffold has made efficient methods for the synthesis of multi-functionalized Cps particularly desirable.[10] Recent elegant efforts have focused on the development of [3+2] –annulation approaches relying on phosphorene substrates[11] **5** and gold-catalyzed cycloisomerization[12] or [3+2]-cycloaddition reactions of allenes[13] **8** or **11** (Figure 2.2). Unfortunately, current strategies to access functionalized Cp-ligands often rely on multi-step reaction sequences, harsh reaction conditions, complex substrates and/or require precious metals.[14] Additionally, the selective introduction of electron-withdrawing groups, such as ester functionalities, frequently remains a challenge as these render the cyclopentadiene methylene more acidic which can lead to decomposition and/or facile 1,5-H atom migration.[15]

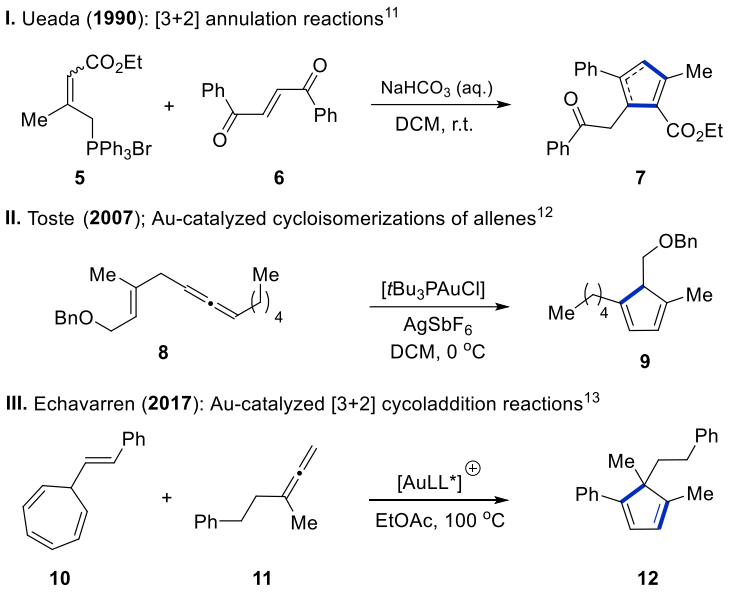


FIGURE 2.2 Selected strategies for cyclopentadiene synthesis.

Herein, we report a short, two-step sequence for the synthesis of cyclopentadienes bearing steric and electronically distinct functionalities (**15**), that proceed through reactive oxetane intermediates **14** (Figure 2.3). Our approach relies on $Sc(OTf)_3$ as a Lewis acid catalyst and readily accessible β-ketoesters (**13**) as substrates. Moreover, this transformation is characterized by its operational simplicity and regiocontrol of the cyclic diene formed.

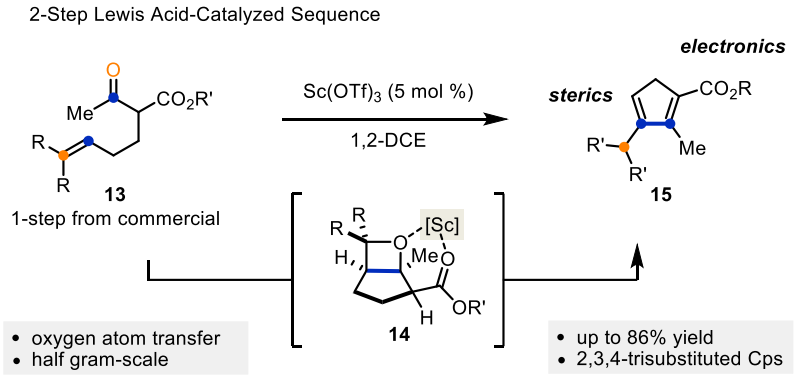


FIGURE 2.3 Two-step synthesis of cyclopentadienes.

2.2 Initial observation of cyclopentadiene formation from unsaturated β-ketoesters

During our studies aimed at iron-catalyzed carbonyl-olefin metathesis reactions,[16] we investigated β-ketoester **16** which had previously proven unreactive in the presence of $FeCl_3$ (Figure 2.4). Our hypothesis was that $Fe(OTf)_3$ could possibly function as a stronger Lewis acid and sufficiently activate **16** to provide the desired metathesis product **17**. However, the reaction did not result in the metathesis product **17** but instead formed a distinct compound that incorporated an *i*-Pr fragment based on ^{1}H- and ^{13}C-NMR analysis. Diversification of the compound under standard saponification conditions (LiOH, $THF/H_2O/MeOH$) proved crucial for its structural elucidation and led to the isolation of α,β-enone **19** which was confirmed by x-ray analysis. Polycycle **19** represents an oxidized pseudo-dimer of two Cp monomers and established **18** as the direct product obtained upon exposure of **16** to $Fe(OTf)_3$.

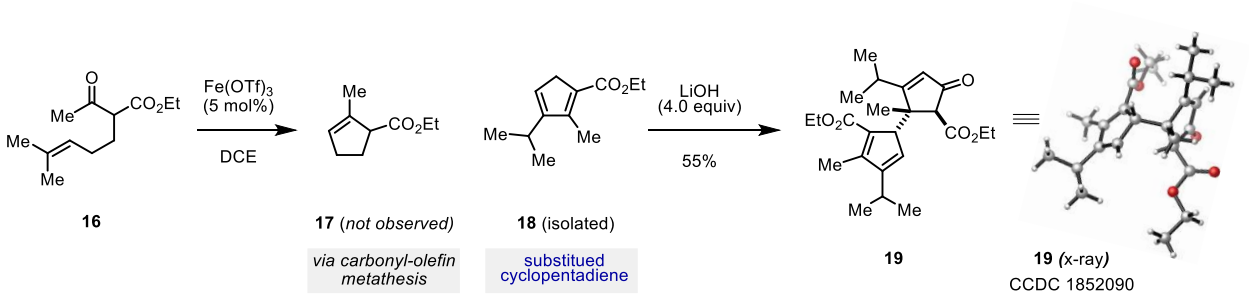


FIGURE 2.4 Initial observation and characterization of cyclopentadiene **19**.

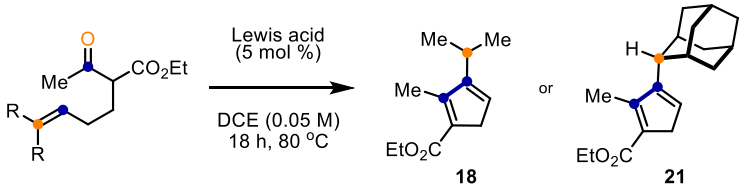
2.3 Results and discussion

2.3.1 Reaction optimization for cyclopentadiene formation

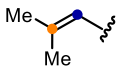
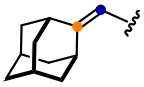
Based on the importance of multi-substituted Cps and the challenges associated with efficient synthetic access to those bearing electron-withdrawing groups, we hypothesized that our initial discovery could provide efficient synthetic access to steric and electronically distinct Cps.

Subsequent efforts focused on the evaluation of different Lewis acid catalysts upon reaction with β-ketoester **16** bearing a prenyl substituent (Table 2.1).

2.3.2. Optimization of reaction conditions



18 **21**

entry	substrate		Lewis acid	yield (%)	conversion (%)
1		**16**	$Fe(OTf)_3$	43	100
2		**16**	$Zn(OTf)_3$	0	20
3		**16**	$Mg(OTf)_2$	35	47
4		**16**	$GaCl_3$	36	100
5		**16**	$In(OTf)_3$	55	100
6		**16**	AgOTf + *t*BuCl	23	63
7		**16**	TfOH	18	100
8		**16**	$Sc(OTf)_3$	58	100
9[a]		**16**	$Sc(OTf)_3$	0	15
10[b]		**16**	$Sc(OTf)_3$	20	96
11[c]		**16**	$Sc(OTf)_3$	30	100
12[d]		**16**	$Sc(OTf)_3$	41	52
13[e]		**20**	$GaCl_3$	49	100
14[e]		**20**	$In(OTf)_3$	75	100
15[e]	**20**	**20**	$Sc(OTf)_3$	86	100

Conditions: all reactions were performed using 0.20 mmol β-ketoester, 5 mol% Lewis acid in solvent (0.05 M) at 80 °C for 18 hours. [a]40 °C. [b]20 mol% $Sc(OTf)_3$. [c]0.05 M DCM. [d]0.05 M in PhH.

TABLE 2.1 Optimization of reaction conditions for cyclopentadiene formation.

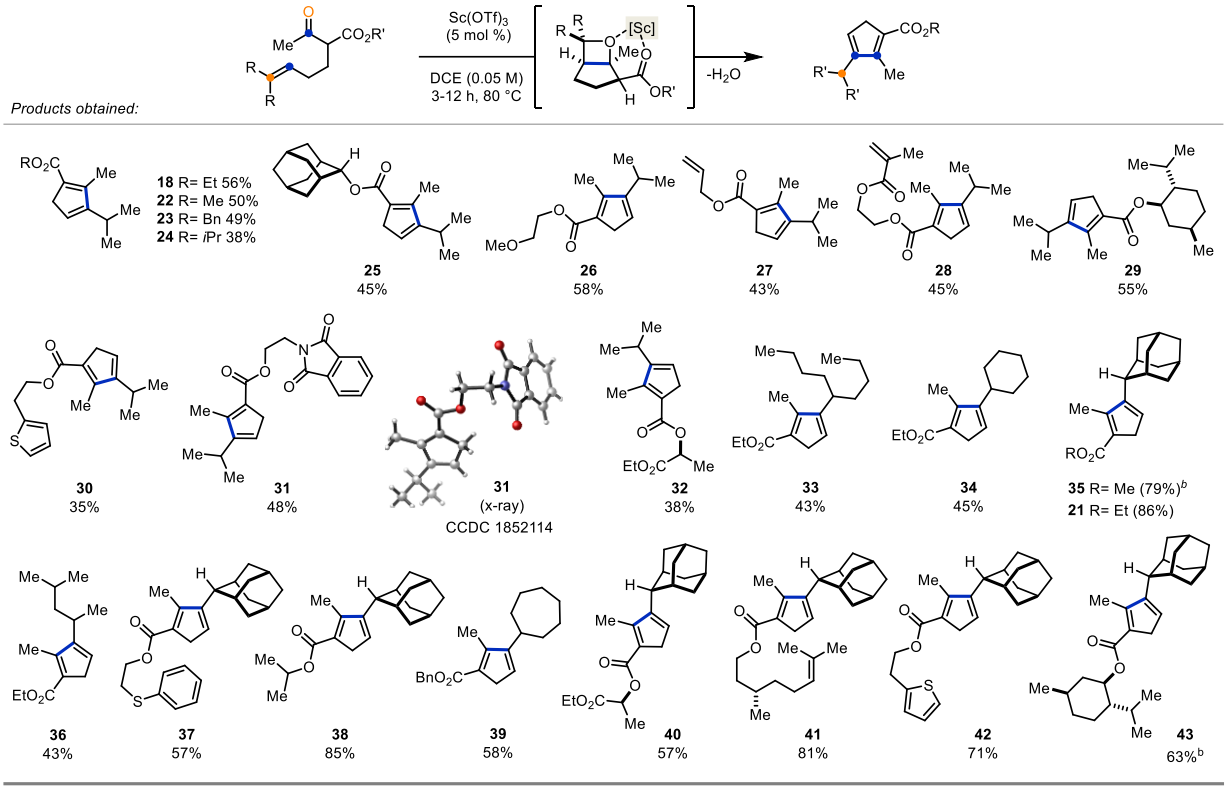
No formation of Cp **18** was observed using substoichiometric amounts of $Zn(OTf)_3$, while $Mg(OTf)_2$ was found more reactive and resulted in the formation of **18** in 35% yield (entries 2 and 3, Table 2.1). $GaCl_3$ led to a comparable yield of 36% while $In(OTf)_3$ proved more potent and formed **18** with increased yields of 55% (entries 4 and 5, Table 2.1). Based on the superior performance of triflate-based Lewis acids, we suspected triflic acid to be the active catalyst. However, when triflic acid was generated *in situ* (using AgOTf and *t*BuCl), Cp **18** was formed in diminished yields of 23% (entry 6, Table 2.1). Conversely, decreased yields of 18% were obtained

when triflic acid was used directly as catalyst (entry 7, Table 2.1). Subsequent efforts identified catalytic amounts (5 mol%) of $Sc(OTf)_3$ to be superior, affording Cp **18** in 58% yield at 80 ˚C (entry 8, Table 2.1). Notably, lower reaction temperatures of 40 ˚C, higher catalyst loadings and dichloromethane or benzene as reaction solvents resulted in decreased yields of the desired product (entries 9-12, Table 2.1). We next evaluated the sterically constrained adamantly-derived β-ketoester **20** upon its ability to form the desired cyclopentadiene **21**. Importantly, $Sc(OTf)_3$ also proved superior as Lewis acid catalyst for sterically demanding substrates such as **20** and provided **21** in 86% yield compared to $GaCl_3$ and $In(OTf)_3$ (entries 13-15, Table 2.1).

2.3.3 Substrate scope for cyclopentadiene formation

The conditions developed for the $Sc(OTf)_3$-catalyzed formation of cyclopentadienes proved efficient for a range of steric and electronically differentiated β-ketoesters (Table 2.2). Importantly, Cps incorporating methyl- (**22**), benzyl- (**23**), *iso*-propyl- (**24**), allyl- (**27**) and 2-adamantyl (**25**) esters were formed in good yields (Table 2.2). Acrylate derivative **28**, bearing a functional handle for further diversification, was suitable under the optimized reaction conditions and resulted in 45% yield. Diene **26** bearing an appended ether tether, which can function as a secondary coordination site in transition metal complexes,[17] was isolated in 58% yield. Notably, substrates incorporating pthalamides (**31**) and thiophenes (**30**) gave rise to the anticipated heterocyclic products in up to 71% yield. Furthermore, β-ketoesters containing chiral elements readily underwent $Sc(OTf)_3$-catalyzed carbocyclization which led to enantioenriched cyclopentadiene **29** and **32** derived from (-)-menthol and (-)-methyl-*L*-lactate, respectively. Moreover, when substrates comprising exocyclic olefins were subjected to the optimized reaction conditions, cyclohexane (**34**) and–heptane (**39**) were afforded in up to 58%. Additional elements of unsaturation present in the substrate were compatible with the optimized reaction conditions,

resulting in the formation of alkene **41** in 81% yield. Moreover, the title transformation could be readily scaled up to more than a half gram scale, without perturbing reactivity, to lead to **35** (79%) and **43** (63%).



Conditions: [a]0.1-0.2 mmol scale, $Sc(OTf)_3$ (5 mol%), DCE (0.05M), 80 °C, 3-12 h. [b]conducted on >0.5 g scale.

TABLE 2.2 Substrate scope and cyclopentadienes synthesized.

To highlight the versatility of the cyclopentadienes obtained herein we were able to demonstrate that sterically dense and electronically distict Cp **35** proved to be a competant Rh(III) ancillary ligand (Figure 2.5). Specifically, bench-stable Rh(III)-complex **44** was accessible in a two-step sequence from cyclopentadiene **35** in 61% overall yield (Figure 2.5). Related complexes have been shown to promote carbonyl hydrogenations.[19]

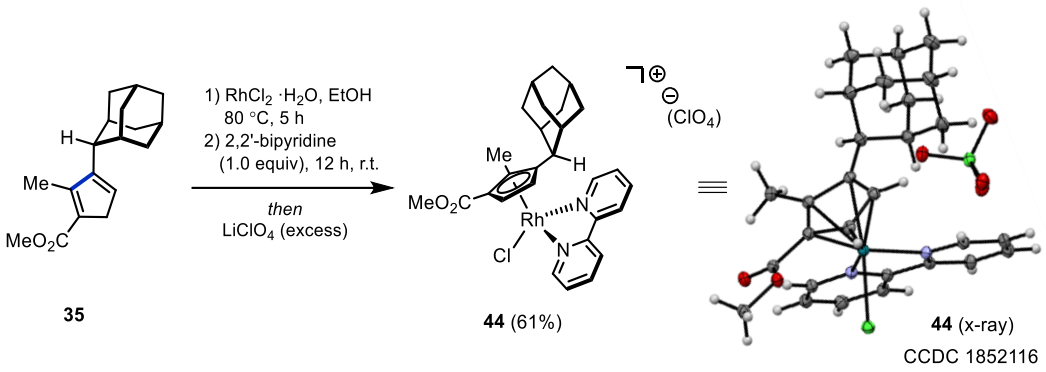


FIGURE 2.5 Synthesis of organometallic complex **44**.

2.3.4 Mechanistic hypothesis for cyclopentadiene formation

In order to gain insight into the controlling features of the $Sc(OTf)_3$-catalyzed formation of cyclopentadienes we conducted additional mechanistic investigations. We initially hypothesized that cyclopentadienes **18** and **21** are formed upon nucleophilic carbonyl addition of the pendant alkene followed by a 1,2-hydride shift. However, subsequent deuterium labeling studies did not provide experimental support for this initial mechanistic hypothesis (Figure 2.6). See supporting information for more details.

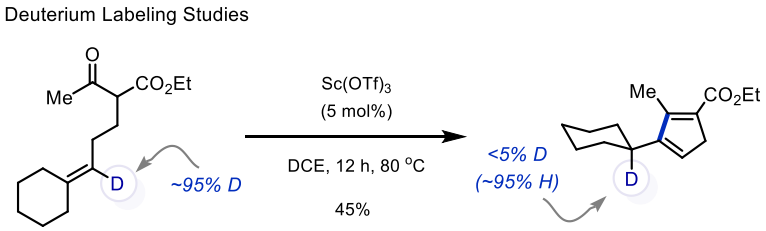


FIGURE 2.6 Deuterium labeling studies.

Based on these results, we considered alternate reaction pathways for the $Sc(OTf)_3$-catalyzed carbocyclization reaction, including a stepwise Prins-reaction or the formation of oxetanes as reactive intermediates. These mechanistic alternatives were then investigated

computationally (unrestricted B97-D density functional 6-31G* basis set) through quantum chemical simulations based on the Growing String Method[18] to determine the relative energies of the corresponding transition states and the respective minimal energy pathways (Figure 2.7). DFT studies favor a reaction pathway that relies on the formation of intermediate oxetane **46** and proceeds through transition state **45** in a single elementary step. Specifically, oxetane **46** is formed in an asynchronous, concerted [2+2]-cycloaddition to enable non-simultaneous bond forming events (see Supporting Information for complete computational details).

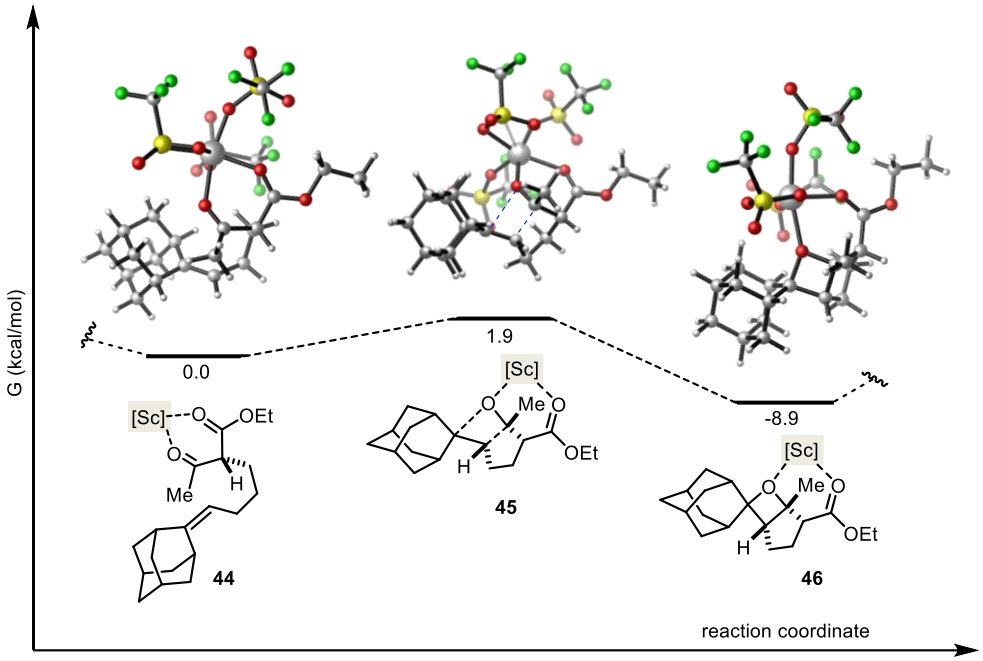


FIGURE 2.7 Abbreviated Gibbs free energy diagram for oxetane formation.

A mechanistic hypothesis (Figure 2.8) for the $Sc(OTf)_3$-catalyzed formation of cyclopentadienes relies on activation of β-ketoester **13** by the oxophilic $Sc(OTf)_3$ to results in Lewis acid-base complex **47**. Subsequent asynchronous, concerted [2+2]-cycloaddition of **47** leads to oxetane **48**. Concomitant fragmentation of oxetane **48** and deprotonation leads to α,β-unsaturated ester **49**–formally an oxygen-atom transfer (**47** → **49**). Finally, dehydration of **49**

yields diene **50** incorporating an exo-cyclic alkene, which isomerizes under the reaction conditions to thermodynamically stable cyclopentadiene **15**.

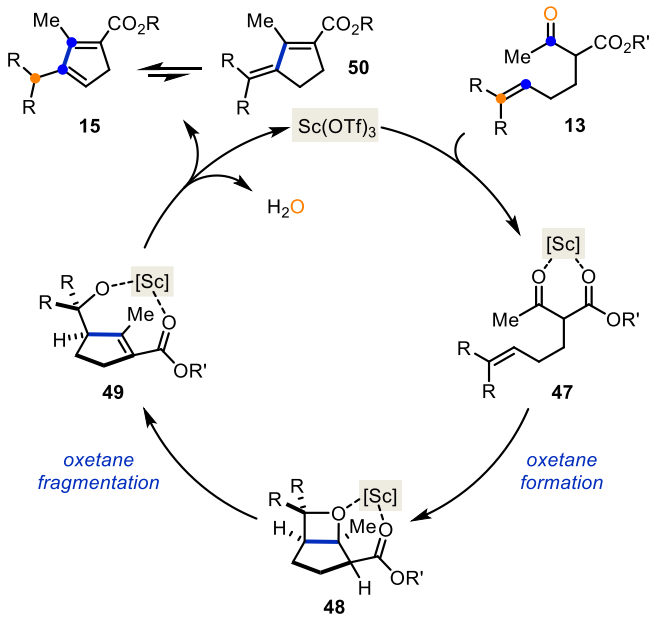


FIGURE 2.8 Mechanistic hypothesis for cyclopentadiene formation via oxygen atom transfer process

2.4 Conclusions

In summary, this report details a unique approach toward densely functionalized and electronically distinct cyclopentadi-enes which can serve as suitable ancillary ligands for transition metal complexes. The 2,3,4-cyclopentadienes afforded in this transformation are readily available in two synthetic transfor-mation from commercial materials. Characterized by its operational simplicity, robust substrate scope, and scalability this strategy complements the currently existing repertoire of syn-thetic strategies to access functionalized cyclopentadienes. Investigations based on DFT analysis provide theoretical support for a mechanistic hypothesis relying on catalytic oxygen atom transfer proceeding through an activated oxetane intermediate. We anticipate that the reaction described herein will impact areas of research that have benefited

from synthetic access to functionalied cyclopentadienes, in particular complex molecule synthesis, asymmetric catalysis, and organometallic chemistry.

Chapter 3

Functionalized Cyclopentanes via Sc(III)-Catalyzed Intramolecular Enolate Alkylation

Portions of this chapter have been published in McAtee, C. C.; Ellinwood, D. C.; McAtee, R. C.; Schindler, C. S. Functionalized cyclopentanes via Sc(III)-catalyzed intramolecular enolate alkylation. *Tetrahedron* **2018**, *74*, 3306–3313.

3.1 Introduction

The α-alkylation of carbonyl functionalities and related Schiff bases has proven valuable for the formation of carbon–carbon bonds in organic synthesis.[1] Traditionally, this is accomplished by employing basic conditions to deprotonate in the α-position to generate a reactive enolate which can engage a suitable electrophile in an addition reaction to afford the desired *C*-alkylated product.[2] These reactions have been developed into powerful synthetic strategies to access complex molecular structures;[2] however, limitations arising from competing over-alkylation[3] and difficulties in controlling the regioselectivity[1,2] still exist. Additionally, highly activated electrophiles such as primary halides bearing methyl, benzyl, or allyl substitution are superior substrates,[1] while their corresponding secondary analogs often undergo base-induced eliminations as competing reaction paths.[4]

In comparison, only few literature examples exist for the direct enolate anion coupling with tertiary alkyl halides to give rise to the corresponding α-*tert*-alkylation products due to the

preferred formation of E_1 elimination products.[5] To circumvent this challenge, Reetz and coworkers developed a unique strategy whereby silyl enol ether (**2**), derived from commercial ketone **1**, can engage tertiary carbocations generated *in situ* in the presence of tertiary halide and stoichiometric $TiCl_4$ (Figure 3.1 A).[5,6] Alternative strategies for α-*tert*-alkylation of carbonyl-containing compounds rely on intramolecular cyclization of enoltes and π-systems.[5,7,8] For example, homo-prenylated β-ketoester **4** was shown to undergo intramolecular cyclization to methyl ketone **5** upon reaction with stoichiometric amount of $SnCl_4$ (Figure 3.1 B).[9] This cyclization strategy is proposed to rely on initial enolate *O*-stannylation with concomitant formation of equimolar amounts of Brønsted acid. An intermediate carbocation is generated upon protonation of the alkene under acidic conditions which subsequently undergoes the final enolate alkylation to result in **5** as the α-*tert*-alkylation product.[9]

We have recently developed an iron-catalyzed carbonyl-olefin ring-closing metathesis reaction[10] of β-ketoesters such as **6a** to form the corresponding cyclopentene **7** as the exclusive products (Figure 3.1 C). In the course of these studies, we evaluated a series of additional Lewis acids in substoichiometric quantities and observed that *aliphatic* β-ketoesters such as **6b** formed the corresponding intramolecular α-*tert*-alkylation products **8** in low yields (Figure 3.1 C). Based on a paucity of general synthetic methodologies for catalytic intramolecular α-*tert*-alkylations of carbonyls, we sought to further investigate this reactivity. Herein, we report a mild and operationally simple approach toward α-*tert*-alkylation of aliphatic β-ketoesters relying on catalytic amount (5 mol%) of $Sc(OTf)_3$ as Lewis acid catalyst.

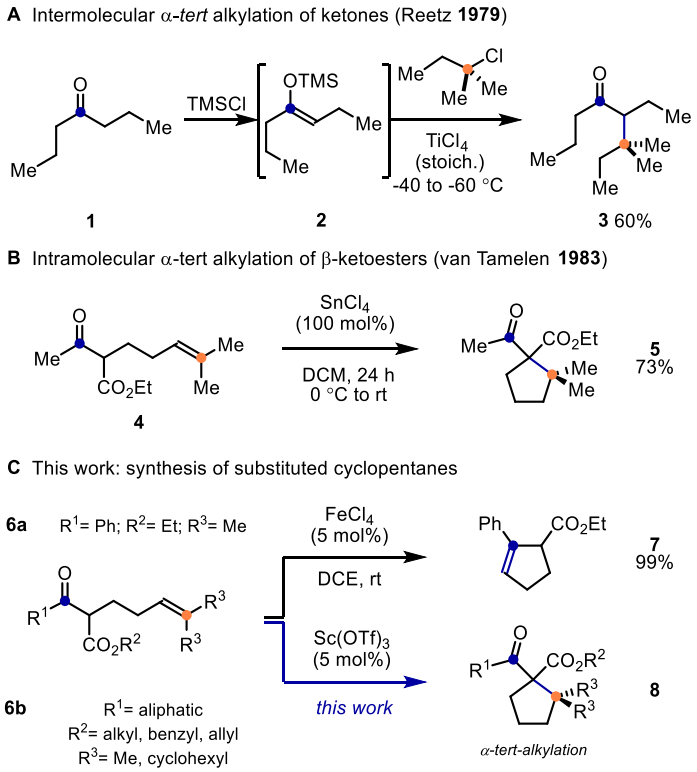


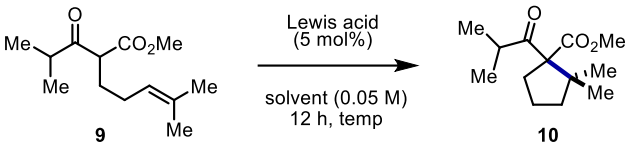
FIGURE 3.1 Previous strategies for α-tert-alkylaitons of carbonyls and this approach.

3.2 Results and discussion

3.2.1 Optimization of reaction conditions

In order to identify an optimal set of reaction conditions for the synthesis of 1,1,2,2-tetrasubstituted cyclopentanes via α-*tert*-alkylation of acyclic β-ketoesters, we initially focused on the evaluation of Lewis acids able to promote the desired transformation (Table 3.1). *Iso*-propyl ketone **9**, which is accessible in a single step from commercially available materials, was chosen as an initial scaffold to identify optimal reaction conditions. Surprisingly, catalytic amounts of strong Lewis acids such as $AlCl_3$ and $FeCl_3$ in 1,2-dichloroethane (DCE) at elevated temperatures led to no or poor formation of methyl ester **10**, and incomplete conversion of the starting material (entries 1 and 2, Table 3.1). However, relying on $SnCl_4$ or $GaCl_3$ as Lewis acid catalysts under otherwise identical reaction conditions led to the formation of **10** in 35% and 49% yield,

respectively, with complete conversion of β-ketoester **9** (entries 3 and 4, Table 3.1). Similar results were obtained when substrate **9** was converted in the presence of 5 mol% $In(OTf)_3$ or $Fe(OTf)_3$ (entries 5 and 6, Table 3.1). Subsequent efforts identified $Sc(OTf)_3$ as the optimal Lewis acid catalyst, resulting in the formation of **10** in 90% yield with complete conversion of β-ketoester **9** (entry 7, Table 3.1). Overall, yields and conversions were found to be lower when the reaction was conducted in nonpolar aromatic solvents including benzene (PhH) and toluene (PhMe) (entries 8 and 9, Table 3.1). Notably, increasing catalyst loading of $Sc(OTf)_3$ to 100 mol% led to the formation of the desired α-*tert*-alkylation product **10** in only 19% yield with complete conversion of substrate **9** (entry 10, Table 3.1). Furthermore, decreasing the reaction temperature to 40 °C with 5 mol% $Sc(OTf)_3$ in DCE or employing 5 mol % triflic acid (TfOH) in DCE at 80 °C proved to be ineffective toward promoting the desired reaction (entries 11 and 12, Table 3.1). Ultimately, conducting the transformation with 5 mol% $Sc(OTf)_3$ in DCE (0.05 M) at 80 °C was identified as optimal for the conversion of β-ketoester **9** to α-*tert*-alkylation product **10**.



entry	Lewis acid	temp	solvent	yield **10** (%)[a]	conversion (%)[a]
1	$AlCl_3$	80	DCE	0	3
2	$FeCl_3$	80	DCE	20	70
3	$SnCl_4$	80	DCE	35	100
4	$GaCl_3$	80	DCE	49	100
5	$In(OTf)_3$	80	DCE	58	100
6	$Fe(OTf)_3$	80	DCE	59	100
7	$Sc(OTf)_3$	80	DCE	90	100
8	$Sc(OTf)_3$	80	PhH	25	40
9	$Sc(OTf)_3$	80	PhMe	25	38
10[b]	$Sc(OTf)_3$	80	DCE	19	100
11	$Sc(OTf)_3$	40	DCE	0	11
12	TfOH	80	DCE	14	100

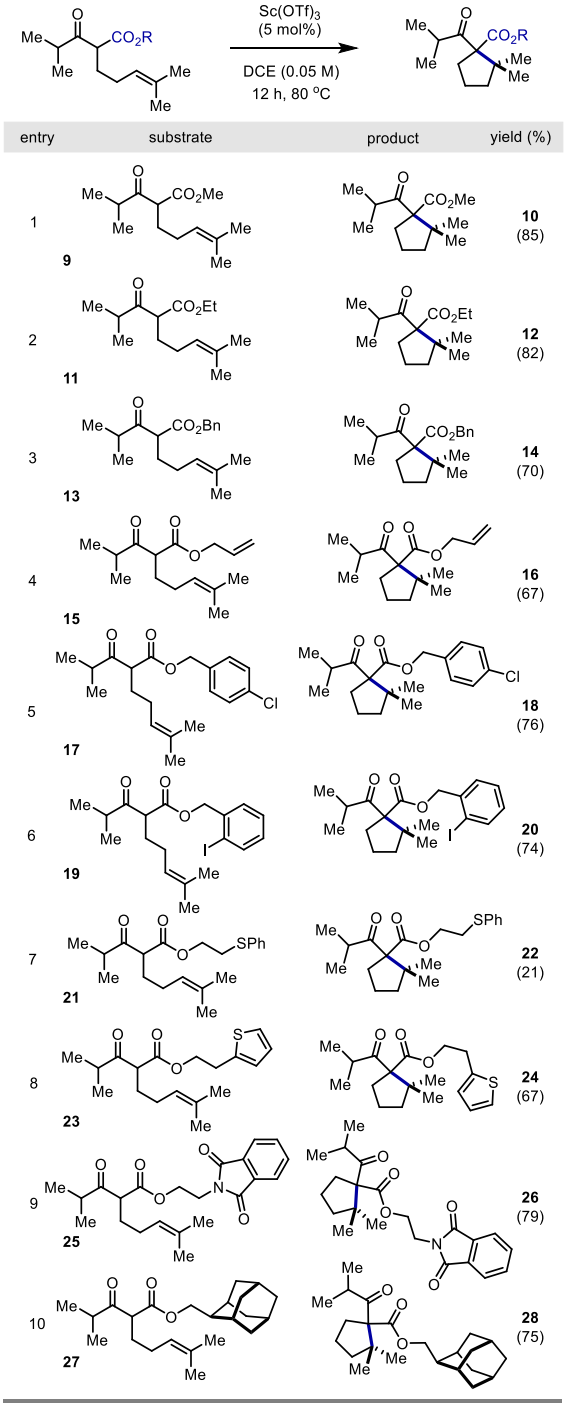
Conditions*:* reactions were performed using 0.20 mmol β-ketoester, 5 mol% Lewis acid in solvent (0.05 M) at 80 °C for 12 hours. [b]100 mol% $Sc(OTf)_3$.. [a]determined by crude NMR analysis with 1,3,5-trimethoxybenzene as internal standard.

TABLE 3.1 Lewis acid evaluation for intramolecular α-tert-alkylaitons of **9**.

3.2.2 Substrate scope for intramolecular α-tert-alkylaitons

We next turned our attention to evaluating the substrate scope amendable to the $Sc(OTf)_3$ catalyzed intramolecular α-*tert*-alkylation of acyclic β-ketoesters. The reaction conditions developed herein proved viable for a broad range of sterically and electronically distinct β-ketoesters as shown in Table 3.2. Substrates incorporating methyl- (**9**), ethyl- (**11**) and benzyl esters (**13**) were smoothly converted to the corresponding functionalized cyclopentanes (**10**, **12** and **14**) in up to 85% isolated yield (entries 1, 2 and 3, Table 3.2). Alkylation product **16** bearing an allyl ester as a functional group capable of undergoing secondary functionalization[11] was formed in 67% yield (entry 4, Table 3.2). Additionally, halo benzyl ester alkylation products **18** and **20** containing sites for functional manipulation were obtained in 78% and 74% yield, respectively (entries 5 and 6, Table 3.2). Substrates incorporating thiophenyl (**21**), thiophene (**23**) and pthalamide (**25**) gave rise to the anticipated polycyclic (**22**) and heterocyclic α-*tert*-alkylation

products **24** and **26** in up to 79% yield (entries 7, 8 and 9, Table 3.2). Furthermore, homo-prenylated β-ketoester **27** containing a sterically demanding adamantyl side chain was converted under the optimal reaction conditions to give rise to the desired product **28** in 75% yield (entry 10, Table 3.2).

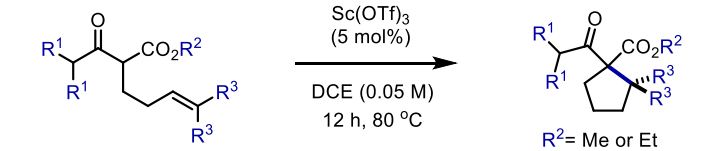


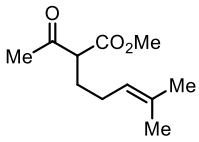
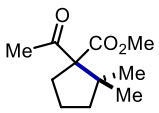
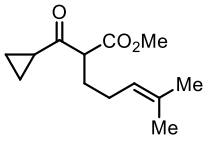
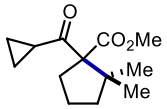
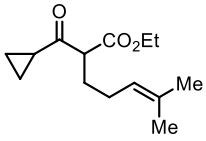
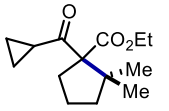
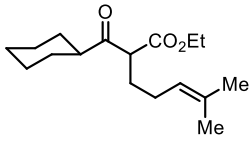
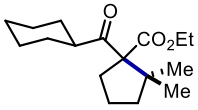
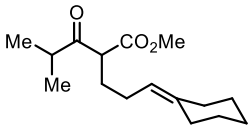
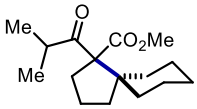
Conditions: Substrate (1.0 equiv), $Sc(OTf)_3$ (5 mol%) in dichloroethane (0.05 M) at 80 °C for 12 h.

TABLE 3.2 Diversification of the ester moiety for the intramolecular α-tert-alkylaitons of unsaturated ketones.

We next evaluated functional tolerance at the ketone subunit as well as the olefin moiety (Table 3.3). Importantly, *iso*-propyl ketones were tolerated well under the optimized reaction

conditions while sterically less congested methyl (**30**) and cyclopropyl (**32** and **34**) ketones underwent the desired alkylation in diminished yields of up to 40% (entries 1, 2 and 3, Table 3.3). Interestingly, sterically dense cyclohexyl ketone **35** restored favorable reactivity as polycycle **36** was isolated in 63% yield (entry 4, Table 3.3). Exocyclic olefin **37** underwent α-*tert*-alkylation affording a unique spirocyclic scaffold in good yield of 43% (entry 5, Table 3.3).



entry	substrate		product	yield (%)
1		**29**		**30** (38)
2		**31**		**32** (40)
3		**33**		**34** (35)
4		**35**		**36** (63)
5		**37**		**38** (43)

Conditions: Substrate (1.0 equiv), $Sc(OTf)_3$ (5 mol%) in dichloroethane (0.05 M) at 80 °C for 12 h.

TABLE 3.3 Carbonyl and alkene diversification for the intramolecular α-tert-alkylaitons of unsaturated ketones.

3.2.3 Mechanistic proposal

Our current mechanistic hypothesis for the $Sc(OTf)_3$-catalyzed carbocyclization of **9** to **10** is outlined in Figure 3.2. Scandium enolate **39** is generated upon coordination of the oxophilic

$Sc(OTf)_3$[12] to ketone **9**. The concomitant formation of equimolar amounts of Brønsted acid affords tertiary carbocation **40**, followed by incipient intramolecular enolate cyclization to liberate α-*tert*-alkylated product **10**.

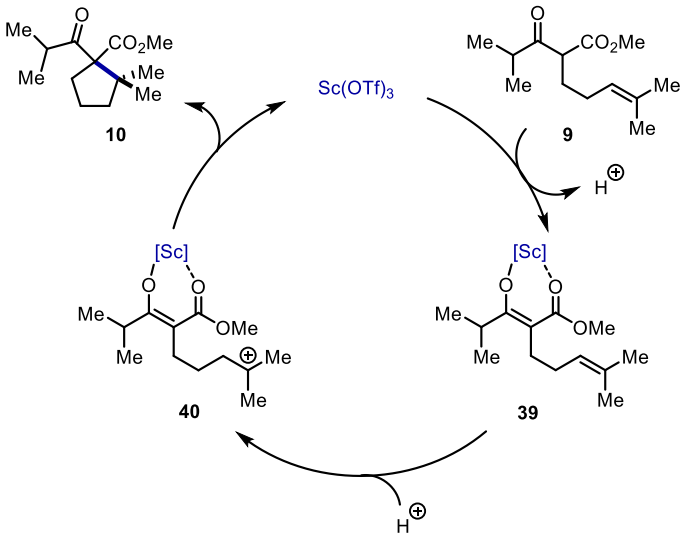


FIGURE 3.2 Mechanistic proposal for the intramolecular α-tert-alkylaiton of unsaturated ketones.

3.3 Conclusions

In conclusion, we have developed a mild and operationally robust protocol for the intramolecular α-*tert*-alkylation of readily available α-alkenyl β-ketoesters. This methodology gives access to electronically and sterically distinct 1,1,2,2-tetrasubstituted cyclopentanes via $Sc(OTf)_3$-catalyzed carbocyclization. Of interest, diversification at the ketone, ester and olefin were tolerated well under the developed reaction conditions and led to the desired products in good to excellent yields.

Chapter 4

Total Synthesis of Mycocyclosin via Pd-Catalyzed Macrocyclization

Portions of this chapter have been published in Zhu, X.; McAtee, C. C.; Schindler, C. S. Scalable synthesis of mycocyclosin. *Org. Lett.* **2018**, *20*, 2862–2866

4.1 Introduction

The human pathogen *Mycobacterium tuberculosis* is the organism responsible for the development of tuberculosis (TB), a chronic but curable infectious disease that is associated with up to 3 million deaths annually.[1] This incongruity between treatment and global health threat can be attributed to the rise of drug-resistant and multidrug-resistant strains for which the current front- and second-line antitubercular treatments have proven ineffective.[2] The genome of *M. tuberculosis* encodes a significant amount of cytochrome P450 enzymes, while only a select few are essential for *M. tuberculosis* virulence.[3] Furthermore, interest in these enzymes was enhanced by studies implicating them as targets for several azole-derived compounds that were previously identified as effective antimicrobial molecules.[4] Unfortunately, the use of azole-derived pharmacaphores often result in significant toxicity due to cross-reactivity with other cytochrome P450 enzymes within the host.

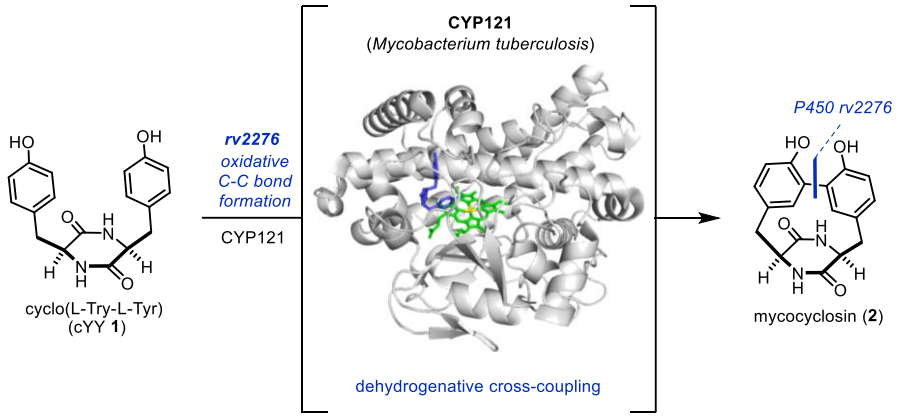


FIGURE 4.1 Biogenesis of mycocyclosin (**2**) from cYY (**1**).

The gene rv2276 encodes CYP121, a cytochrome P450 enzyme with a distinct metabolic role found exclusively in strains of *M. tuberculosis*, thereby making it one of the most logical candidates for evaluation as a potential drug target.[4a,5,6] Specifically, CYP121 converts cyclic dipeptide cYY (**1**) in a dehydrogenative cross-coupling reaction of the tyrosine subunits, accessing a highly strained 3,3'-dityrosine biaryl system, to form mycocyclosin (**2**) (Figure 4.1).[5] Moreover, cYY (**1**) is the only known substrate of CYP121 activity. As a result, the distinct scaffold of mycocyclosin can be used as a platform to design selective inhibitors of CYP121 that exhibit low toxicity to the host.[7]

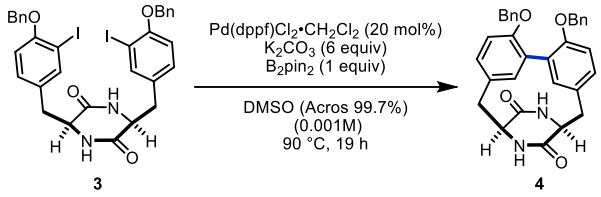
The first total synthesis of mycocyclosin (**2**) was reported by Hutton in 2012, in which the target molecule was assembled in eight synthetic transformations.[8] In the key step, a Suzuki-Miyaura cross-coupling effected the desired macrocyclization in 42% yield on a 50 mg scale.[8] With an interest in developing potent inhibitors of CYP121 based on structural analogy to mycocyclosin, we planned to take advantage of this previously reported route. In order to facilitate the biological evaluation of mycocyclosin and related derivatives as small molecule drug candidates for the inhibition of CYP121, we required a scalable and robust synthesis to access the constrained cyclophane. Unfortunately, when employing previously reported macrocyclization

conditions, we observed difficulties executing the Suzuki-Miyaura cross-coupling on scales larger than 50 mg. Herein, we report a synthesis of mycocyclosin and derivatives relying on a Pd(II)-catalyzed cross-coupling which can be carried out on up to gram scale.

4.2 Results and discussion

4.2.1 Optimization of cross-coupling conditions

Benzylated diketopip erazine (DKP) **3** is readily accessible from 3-iodo- L-tyrosine and was chosen as our initial substrate to evaluate reaction conditions for the scalable synthesis of strained cyclophane **4** *via* a Pd(II)-catalyzed macrocyclization (see Experimental procedures and operations for a complete summary of reaction conditions). When **3** was subjected to reaction parameters initially reported by Hutton ($Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (20 mol%), K_2CO_3 (6 equiv), B_2pin_2 (1 equiv) and DMSO at 90 °C), the anticipated biaryl product **4** was isolated in 39% yield on 50 mg scale in accordance with the literature (Table 4.1, Entry 1).[8] Interestingly, switching the DMSO source from Acros (anhydrous 99.7%) to DMSO dried over alumina *via* a solvent-dispensing system led to no isolable yield of the desired product in our hands (Table 4.1, Entry 2). Nevertheless, the yield of **4** could be further improved to 61% by increasing the amount of B_2pin_2 (Table 4.1, Entries 3-4). While increasing the B_2pin_2 ratio proved beneficial on smaller scale (50 mg), carrying out the biaryl-coupling on 100 and 500 mg scale, under otherwise identical reaction conditions, led to diminished yields of **4** in 44% and 25%, respectively (Table 4.1, Entries 5 and 6).



3 **4**

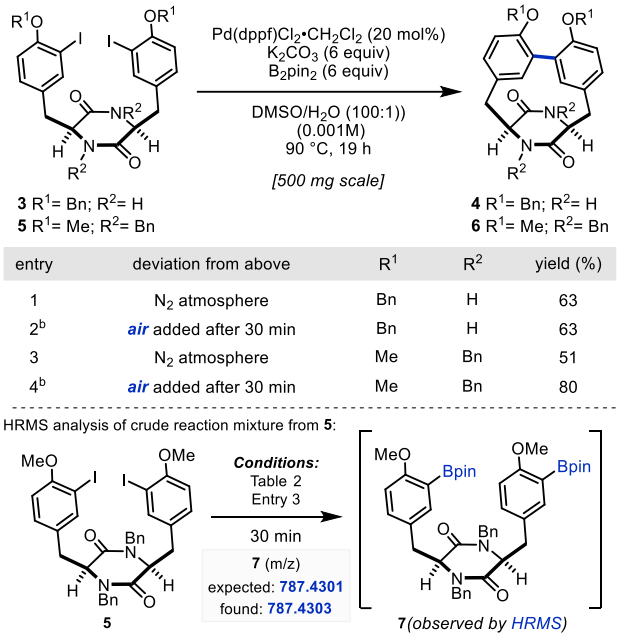
entry	deviation from above	yield **4** (%)
1	n/a	39
2[b]	DMSO (solvent dispensing system)	0
3	B_2pin_2 (2 equiv)	45
4	B_2pin_2 (4 equiv)	61
5	B_2pin_2 (4 equiv) [100 mg scale]	44
6	B_2pin_2 (4 equiv) [500 mg scale]	25
7[c]	B_2pin_2 (4 equiv), DMSO/H_2O (100:1) [50 mg scale]	63
8[c]	B_2pin_2 (6 equiv), DMSO/H_2O (100:1) [500 mg scale]	63

Karl Fischer Titration	***a.*** DMSO (Acros 99.7%) 464.8 ppm	***b.*** DMSO (solvent system) **197.2 ppm**

Conditions: [a]biaryl **3** (50 mg, 0.066 mmol to 500 mg, 0.66 mmol), $Pd(dppf)_2Cl_2•CH_2Cl_2$ (20 mol%) K_2CO_3 (6 equiv), B_2pin_2 (1.0 - 6.0 equiv as noted) and DMSO (N_2 sparged, ACROS Chemicals, 99.7%, 0.001M) at 90 ºC for 19 h. [b]DMSO from solvent dispensing system.[c]DMSO/H_2O = 100:1

TABLE 4.1 Optimization of macrocyclization conditions.

Inspired by Denmark's mechanistic insight into the Suzuki-Miyaura transmetallation step,9 we hypothesized that water may play a critical role in facilitating the biaryl coupling. Karl Fischer titration of our reaction solvent provided additional support for this proposal. Specifically, we observed a stark difference in water content of Acros DMSO (anhydrous 99.7%) and that from our solvent system (464.8 ppm and 197.2 ppm, respectively). Based on this analysis, we evaluated the mixed solvent system DMSO/H2O (100:1). Water proved to be beneficial and allowed for consistent formation of 4 in 63% isolated yield on 50 mg scale (Table 4.1, Entry 7). Moreover, an identical yield was obtained on half gram scale with 6 equiv of B_2pin_2 (Table 4.1, Entry 8).



entry	deviation from above	R^1	R^2	yield (%)
1	N_2 atmosphere	Bn	H	63
2[b]	***air*** added after 30 min	Bn	H	63
3	N_2 atmosphere	Me	Bn	51
4[b]	***air*** added after 30 min	Me	Bn	80

Conditions: [a]biaryl **3** or **5** (500 mg,1 equiv), $Pd(dppf)_2Cl_2$•CH_2Cl_2 (20 mol%) K_2CO_3 (6 equiv), B_2pin_2 (6.0 equiv) and DMSO/H_2O = 100:1 (N_2 sparged, ACROS Chemicals, 99.7%, 0.001M) at 90 ºC for 19 h. [b]5 mL air added after 30 min.

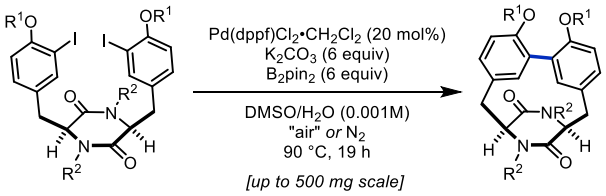
Table 4.2 Evaluating the addition of exogenous air on reaction yield.

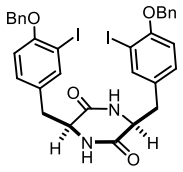
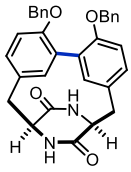
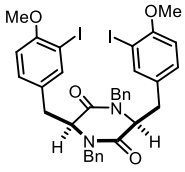
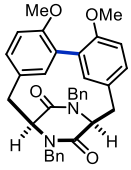
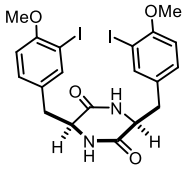
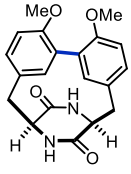
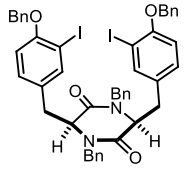
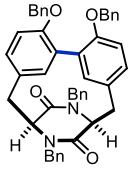
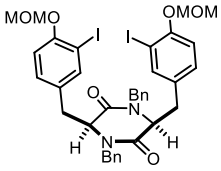
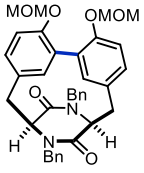
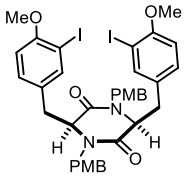
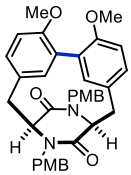
Observing that excess B_2pin_2 leads to increased reaction efficiency, we considered that an alternative reaction pathway to the Suzuki-Miyaura coupling may be plausible.[10] Recently, Jasti has elegantly demonstrated that pre-formed diboronic esters readily undergo Pd(II)-catalyzed intramolecular homocoupling in air to form strained macrocycles.[11] Similarly, we hypothesized that under our optimized reaction conditions for accessing **4**, the transformation may be proceeding *via* a diboronate in which trace contamination of air allows for productive catalysis. In an attempt to improve cross-coupling efficiency, we next evaluated the addition of air to the reaction. Notably, under aerobic conditions, catalysis was not inhibited as **3** converted to **4** in an identical yield of 63% as under an inert nitrogenous atmosphere on 500 mg scale (Table 4.2, Entry 2). In comparison, biaryl substrate **5** underwent the macrocyclization in a modest 51% yield under inert conditions (Table 4.2, Entry 3). Examination of the crude reaction mixture after 30 minutes by HRMS led us to observe the m/z ratio consistent with diboronate **7** (See Experimental procedures and operations

for details). Subsequently, subjecting **5** to the cross-coupling conditions with air as exogenous oxidant, under otherwise identical conditions, afforded **6** in an enhanced 80% isolated yield. Thus, depending on the biaryl substrate being evaluated under the cross-coupling conditions, the addition of air to the reaction can be advantageous.

4.2.2 Synthesis of mycocyclosin derivatives

With suitable reaction conditions in hand to access the desired cyclophane motif on half gram scale, we next sought to interrogate the functional group tolerance on the DKP and aryl subunits (Table 4.3). While the OBn-NH DKP scaffold (**3**) proved to be a viable cross-coupling substrate under either aerobic or anaerobic atmosphere, the corresponding OMe-NH DKP **8** proved to be sluggish under either set of reaction conditions (Table 4.3, Entries 3 and 4 versus 5 and 6).[12] Conversely, when substrates bearing acid sensitive MOM ethers (**12)** or oxidatively-labile PMB groups (**14**) were exposed to the Pd(II)-catalyzed cross-coupling reaction, the isolated yield of the anticipated [8.2.2] polycycle (**13** and **15**, respectively) were only modestly affected upon the incorporation of air (Table 4.3, Entries 9, 10, 11 and 12).



entry[a]	substrate	product	yield (%)
1			63% (N_2)
2			63% (air)[b]
	3	**4**	
3			51% (N_2)
4			80% (air)[b]
	5	**6**	
5			16% (N_2)
6			20% (air)[b]
	8	**9**	
7			29% (N_2)
8			64% (air)[b]
	10	**11**	
9			74% (N_2)
10			79% (air)[b]
	12	**13**	
11			62% (N_2)
12			61% (air)[b]
	14	**15**	

Conditions: [a]biaryl (1.0 equiv), $Pd(dppf)_2Cl_2•CH_2Cl_2$ (20 mol%) K_2CO_3 (6 equiv), B_2pin_2 (6.0 equiv) and DMSO/H_2O = 100:1 (N_2 sparged, ACROS Chemicals, 99.7%, 0.001M) at 90 ºC for 19 h.[b] 5 mL of air added via syringe after 30 mins.

Table 4.3 Functionalized mycocyclosin derivatives obtained.

As a means to provide a metric for molecular strain the arene displacement angles (α), which depict how distorted a benzene ring is from planarity, was determined for cyclophane **11** by acquiring a single crystal X-ray structure (Figure 4.2).[11b] Indeed, there proved to be significant variation between α_1, α_2 and α_3 which ranged from 5.7° to 9.7°.

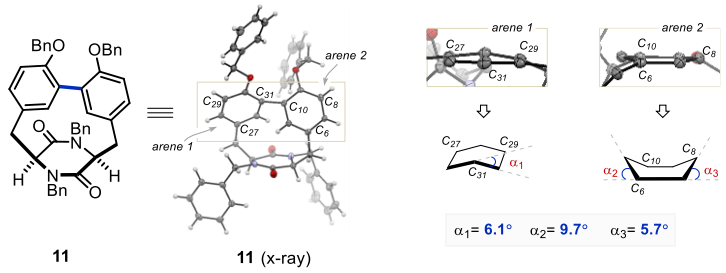


Figure 4.2 Arene displacement angles (α) of **11**.

4.2.3 Mechanistic proposal for Pd-catalyzed macrocyclization

Intrigued by our observation that H_2O and air are critical reaction additives in order to obtain reproducible yields for the Pd(II)-catalyzed macrocyclization on scale, we considered two complimentary mechanistic regimes generalized in Figure 4.3. Following initial Miyaura borylation of the bisiodide **16** leading to **17**, we hypothesize that $(Ar)Pd^{II}I$ can readily undergo anion metathesis with hydroxide to form $(Ar)Pd^{II}OH$, which allows for facile oxopalladium transmetallation with the aryl boronate (Figure 4.3, Path A).[13] Additionally, two consecutive borylations of **16** can provide **18**, which under *oxidative conditions*, can undergo Pd(II)-catalyzed homocoupling to form **19** (Figure 4.3, Path B).[11] If the rate of Suzuki-Miyaura coupling (**17**→**19**, k_1) is faster than the second borylation event (**17** →**18**, k_2), then the addition of oxidant to the reaction will not affect the overall reaction yield (see Table 4.3, Entries 11 and 12), Conversely, if k_2 is greater than k_1, exogenous oxidant should be advantageous (see Table 4.2, Entries 7 and 8).

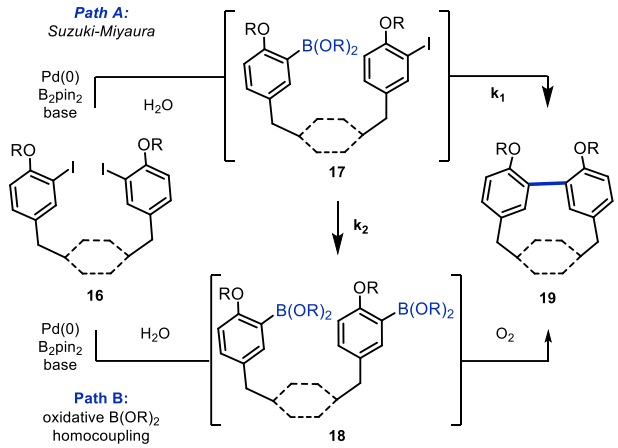


Figure 4.3 General formation of **19** from **16**.

With these considerations in mind, we propose that two catalytic cycles are operative, and complementary, for the formation of macrocycle **19** (Figure 4.4). Under an anaerobic atmosphere (Figure 4.4, Path A), monoboronate **17** can engage the Suzuki-Miyaura catalytic cycle by undergoing oxidative addition with $LPd^{(0)}$ (L= dppf) to **20**.[14] Conversion of **20** to palladium alkoxy **21** facilitates the incipient transmetallation event to **23** proceeding through a transient intermediate like **22**, initially identified by Denmark,[9] followed by reductive elimination to **19**. Additionally, based on the experimentally and computationally proposed mechanism by Adamo,[15] under oxidative conditions (Figure 4.4, Path B), $LPd^{(0)}$ may also be oxidized with O_2 to the corresponding palladium(II) peroxy intermediate **24**. Next, coordination of an aryl boronate ester (**18**) to **24**, affords **25**, which facilitates the first transmetallation event leading to boronic peroxo **26**. Attack of water on peroxide **26** generates palladium(II) hydroxy complex **21** which intercepts the Suzuki-Miyaura cycle (Figure 4.4, Path A).

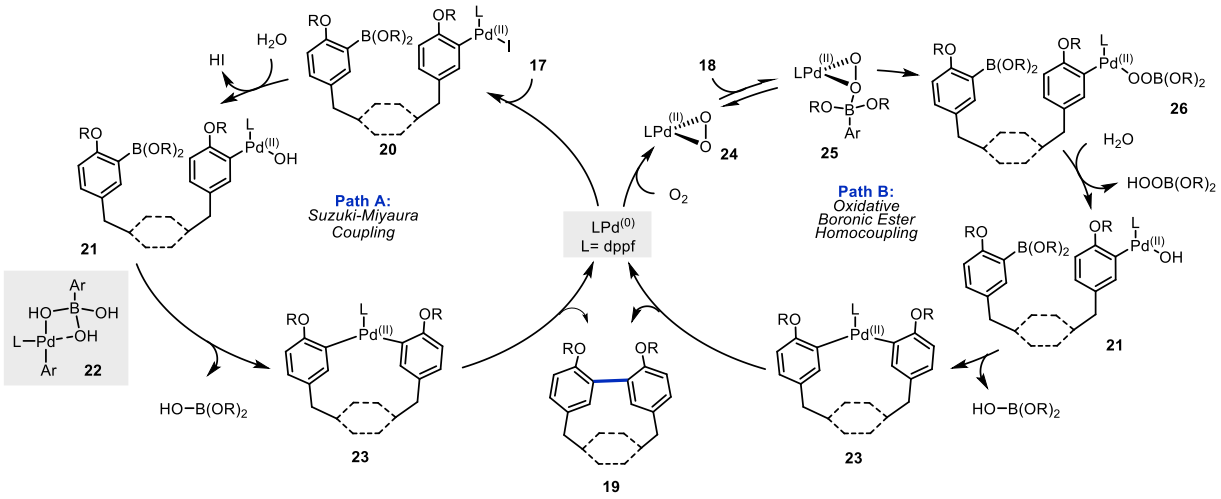


FIGURE 4.4 Proposed catalytic cycles for macrocyclization.

4.2.4 Total synthesis of mycocyclosin

Careful optimization of the palladium(II)-catalyzed macrocyclization allowed for a scalable synthesis of mycocyclsin (Figure 4.5). 3-Iodo-L-tyrosine **27** was smoothly converted to **28** in three steps with no column chromatography. At this stage, ester hydrolysis or Boc deprotection afforded **29** or **30**, respectively, in quantitative yields. Next, peptide coupling of **29** and **30** with HBTU, followed by acid promoted intramolecular cyclization provided DKP **3** in up to eight grams.[8] Diiodide **3** was readily transformed to cyclophane **4** by employing the optimized Pd(II)-catalyzed oxidative coupling conditions on both half gram and gram scale in yields up to 63%. Finally, benzyl ether removal to expose the free phenol afforded mycocyclosin **2** in excellent yield.[16] Overall, mycocyclosin could be accessible on gram scale in 22% yield from commercially available iodotyrosine starting material.

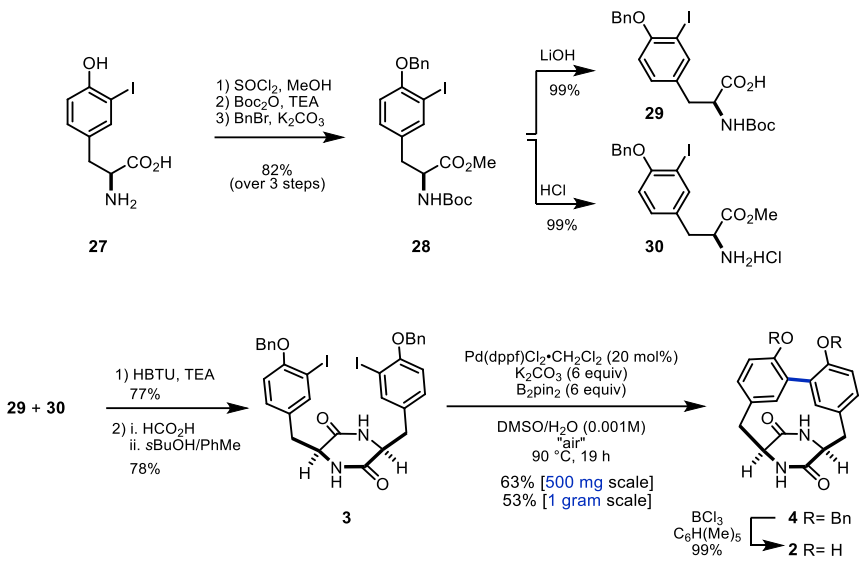


FIGURE 4.5 Total synthesis of mycocyclosin

4.3 Conclusion

In conclusion, we have developed a scalable approach to the strained macrocycle, mycocyclosin. Careful evaluation of the reaction conditions for the palladium(II) catalyzed cross-coupling reaction led us to observe that both water and air are critical reaction additives to promote efficient reactivity. Experimental support for the formation of a diboronate intermediate suggests that oxidative homocoupling to the strained biaryl architecture is plausible. We anticipate that this scalable entry to mycocyclosin will facilitate expedient access to potential *M. tuberculosis* antimicrobials.

Chapter 5

Evolution of the Total Syntheses of Herquline B and C

Portions of this chapter have been previously published in Zhu, X.;* McAtee, C. C.;* Schindler, C. S. Total syntheses of herqulines B and C. *J. Am. Chem. Soc.* **2019**, 141, 3409–3413. *contributed equally.

5.1 Introduction to the herquline alkaloids

In 1979, Ōmura and colleagues initially harvested the herquline alkaloids (Figure 5.1) from soil samples collected in the Saitama Prefecture of Japan, which were further identified to be secondary metabolites produced by the fungal strain *Penicillium herquei* Fg-372.[1] Initial investigations into the biological function of the herqulines showed no antimicrobial activity; however, these alkaloids did demonstrate antithrombotic properties.[2] Specifically, when platelet aggregation was induced by either platelet aggregation factor (PAF) or adenosine diphosphate (ADP) in platelet rich plasma from rabbit blood, herquline A **1** showed weak inhibition (IC_{50} =240 and 180 μM, respectively) while herquline B (**2**) (IC_{50} = 5.0 and 1.6 μM, respectively) was substantially more active.[2] Furthermore, in addition to possessing platelet aggregation properties, herquline A (**1**) was also shown to inhibit influenza virus replication.[3]

In a succeeding 1980 study, Ōmura had established the three-dimensional structure of herquline A (**1**) via single X-ray crystallographic analysis. This ultimately allowed for the unambiguous assignment of herquline A's illustrated relative configuration.[4] In comparison, the structure of herquline B (**2**) was determined solely by NMR analysis. Nevertheless, based on the

spectral data alone the configuration at C-3 and C-3' could not be assigned.[2] Importantly, the absolute configuration of herquline B (**2**) was delineated by Wood and coworkers in 2019 during its inaugural total synthesis.[5] In addition to herquline A (**1**) and herquline B (**2**), a third congener, herquline C (**3**), was unexpectedly isolated in 2016 by Tang and coworkers during investigations pertaining to uncovering the herquline alkaloids biosynthetic pathway.[6] Indeed, careful spectroscopic NMR studies conducted by Wood and colleagues during their total syntheses of herquline B (**2**) and C (**3**) determined that herquline C (**3**) was in fact a diastereomer of herquline B (**2**).[5]

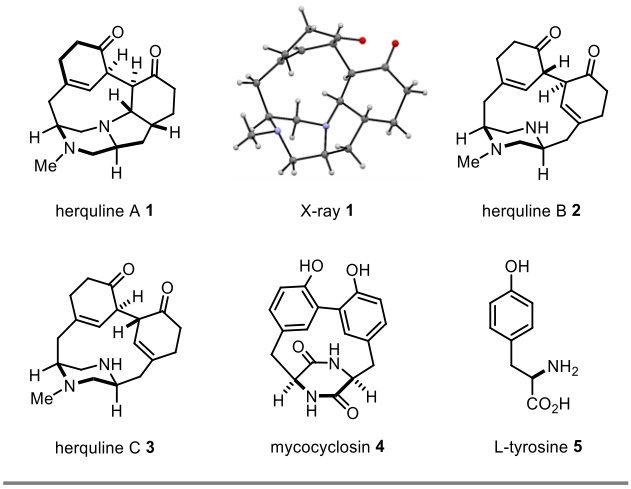


Figure 5.1 The herquline alkaloids, mycocyclosin and their common biosynthetic precursor L-tyrosine.

Since their initial isolation over 40 years ago, the herquline alkaloids have stimulated the interest of the synthetic community.[7] In spite of the modest stature of herquline A (**1**) (molecular weight 314 g/mol) the 6-9-6-5-6 pentacyclic reduced dipeptide bears considerable molecular strain due to the densely substituted embedded 9-membered macrocycle. Moreover, of the six tertiary stereocenters residing in herquline A (**1**), four of these are contiguous.[1] Additionally, a pyrrolidine

ring fused to a cyclohexanone subunit and a highly Lewis basic *N*-methylpiperazine constrains the molecule into a "bowl-shaped" conformation which is exemplified in the X-ray crystal structure of herquline A (**1**).[4] Further, the piperazine ring has been distorted into a high-energy boat configuration. The corresponding structural isomers, herquline B (**2**) and C (**3**), contain an unsymmetrical Lewis basic *N*-methylpiperazine at the base of the molecule. Moreover, a strained 12-membered macrocycle is enclosed within two bridging β,γ-unsaturated cyclohexenones.[2,6] Of particular interest to us and our synthetic efforts towards the herqulines, the bis-phenolic cyclodipeptide, mycocyclosin (**4**),[7] is a constitutional homolog of herquline B (**2**) and C (**3**). However, according to literature reports, these tyrosine (**5**)–based natural products, mycocyclosin (**4**) and the herqulines (**1**-**3**), are not biosynthetically related despite their structural similarities.

5.2 Biosynthesis of the herquline alkaloids

In late 2016, Tang, Houk, and colleagues reported a landmark study on the biosynthesis of the herquline alkaloids suggesting a reductive strategy of tyrosine subunits (Figure 5.2).[6] Specifically, six gene clusters were isolated and identified from *Penicillium herquei* comprising of a nonribosomal peptide synthase (*hqlA*), an *N*-methyl transferase (*hqlE*), a CYP450 oxidase (*hqlC*) and three short-chain dehydrogenases (*hqlB, hqlD, hqlF*).

Tang and Houk conducted several heterologous expression experiments in *Aspergillus nidulans* which culminated in a biosynthetic proposal for the herqulines (Figure 5.2). Particularly, the nonribosomal peptide synthase *hqlA* promotes the reductive transformation of tyrosine **4** via intermediate thioester **5** to aminoaldehyde **6**. A subsequent spontaneous condensation of two tyrosine-derived aminoalcohols **6** results in the formation of diimine **7**. Next, the dehydrogenase *hqlB* facilitates the reduction of diamine **7** to piperazine **8**. This intermediate then undergoes a dehydrogenative phenolic coupling in the presence of the CYP450 oxidase *hqlC* to give rise to

macrocycle **9**. Importantly, due to the significant instability of the doubly dearomatized tautomer the formation of the corresponding oxidized bisphenol (not shown) was observed. Nevertheless, a twofold reduction of piperazine **9** to bis-β,γ-unsaturated ketone **10** is facilitated by the dehydrogenase *hqlF* and NADPH. Finally, herquline C (**3**) is obtained upon *N*-methylation of intermediate **10** with the N-methyl transferase *hqlE*. Importantly, and of particular interest to our synthetic efforts, it was reported that under non-enzymatic conditions (i.e. pH 8 buffer), herquline C (**3**) appears to undergo a stereoselective cyclization to form herquline A **1** giving rise to a potential unifying strategy towards the herquline alkaloids. As such, motivated by this biosynthetic hypothesis, we anticipated that a successful synthesis of herquline B (**2**) or C (**3**) should thereby represent a viable approach to herquline A **1**.

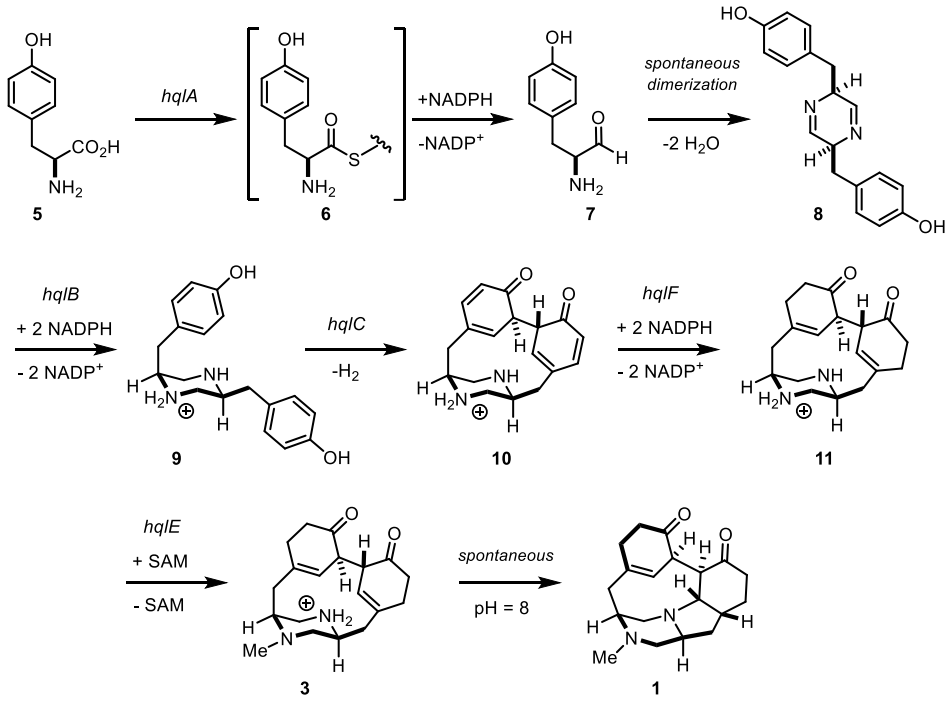


FIGURE 5.2. Tang's biosynthetic pathway of the herquline alkaloids.

5.3 Previous attempts toward the herqulines

Since their initial discovery, several research groups have worked towards synthetic strategies of the herquline alkaloids.[8] In the context of these studies, a number of creative synthetic approaches toward this family of natural products have been explored, unfortunately with limited success. A common challenge identified in these earlier studies is the assembly of the strained, macrocyclic core common to the herqulines. Additionally, the significant strain associated even with synthetic intermediates en route to the macrocycle has often led to unpredictable instability. While these early synthetic forays towards the herquline alkaloids did not result in completed syntheses, we would like to note that they did serve as valuable inspiration for us to develop a distinct synthetic plan (*vide infra*).

5.3.1 Studies by Kim and Kang

Kim and Kang initially disclosed a study toward herquline A in 1997.[8a] This strategy relied on an intramolecular oxidative spirocyclization / methanolysis of a tyrosine derivative to access the 5-6 fused indolizidine core of herquline A (Figure 5.3). Subjecting tyrosine analogue **12** to diacetoxy iodobenzne in methanol with base, led to spirocyclic dieneone intermediate **13**, which rearranged to enone **14** in modest overall yield. A four-step sequence comprising of acetal formation, palladium catalyzed hydrogenation, and Barton-McCombie deoxygenation afforded saturated azacyclic intermediate **15**. Methyl ester reduction of **15**, followed by TBS ether formation and *N*-Boc-deprotection garnered compound **16** in 66% yield over three steps. Unfortunately, all attempts to convert **16** to **17** via peptide coupling were not successful.

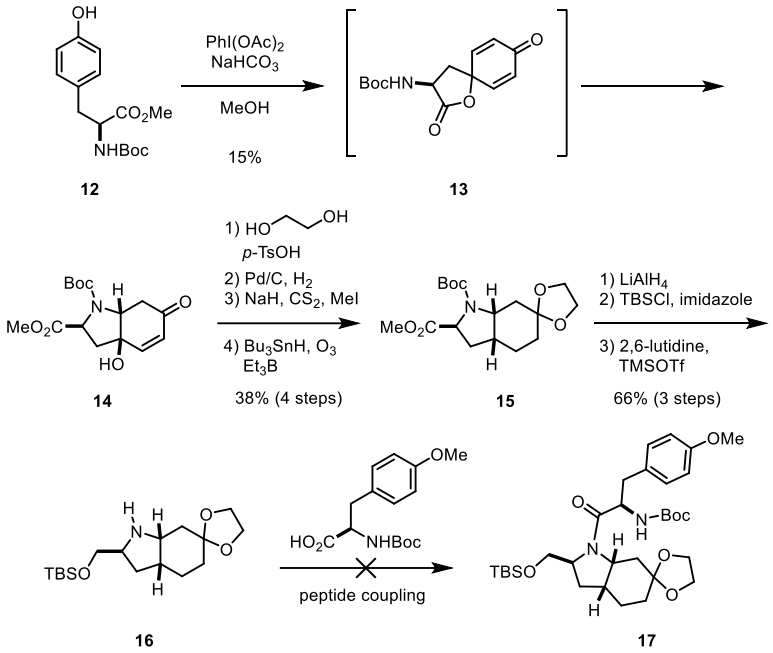


FIGURE 5.3 Kim and Kang's studies toward herquline A.

5.3.2 Studies by Atsumi and Noriyoshi

In 2003, Atsumi and Noriyoshi disclosed a synthetic study toward the herqulines (Figure 5.4).[8b] In this report, known diketopiperazine compound **18** could be functionalized to intermediate **19** wherein the phenols have been protected as the methylcarbonates and the diketopiperazine has been transformed to the corresponding bis(carboximidate). Interestingly, reacting **19** with $Ni(PPh_3)_2Cl_2$, zinc metal, PPh_3 and sodium hydride at reflux in toluene afforded macrocycle **20** in 82% isolated yield. Despite the overall efficiency of this macrocyclization, attempts to advance compound **20** forward via either deprotection or reduction have not been reported.

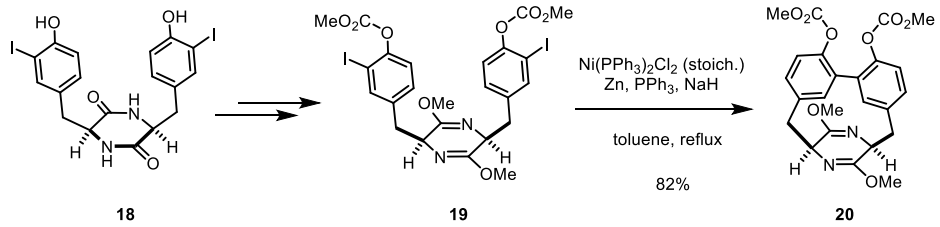


FIGURE 5.4 Atsumi and Noriyoshi's studies toward the herqulines.

5.3.3 Studies by Hart and Johnson

In 2004, Hart and Johnson reported a synthetic study toward the herqulines which comprised of two distinct approaches (Figure 5.5).[8c] Dimerization of aryl diiodide **21** with Bowman coupling conditions (pH 6 buffer, $Na_2S_2O_3$, NaOH) afforded biaryl dimer **22** in 53% yield. Next, phenol protection (MeI, K_2CO_3) to corresponding methyl ether **23** preceded in excellent yield. Intermediate **23** served as a key intermediate to evaluate Birch reduction conditions. The researchers found that treating **23** to Li(0) and liquid NH_3 at cryogenic temperatures led to skipped diene **24** which was detected by LCMS analysis. Reduction of the second aromatic ring was not observed. Due to overall poor material throughput, this route was not pursued.

An alternative approach investigated by Hart and Johnson relied on phenolic silylation of dipeptide **26** to macrocyclic compound **27**. It was hypothesized that intramolecular oxidative macrocyclization of silylcycle **27** would be accelerated by bringing the phenol subunits into proximity. Unfortunately, **27** was only observed in trace amounts presumably due to the high molecular strain.

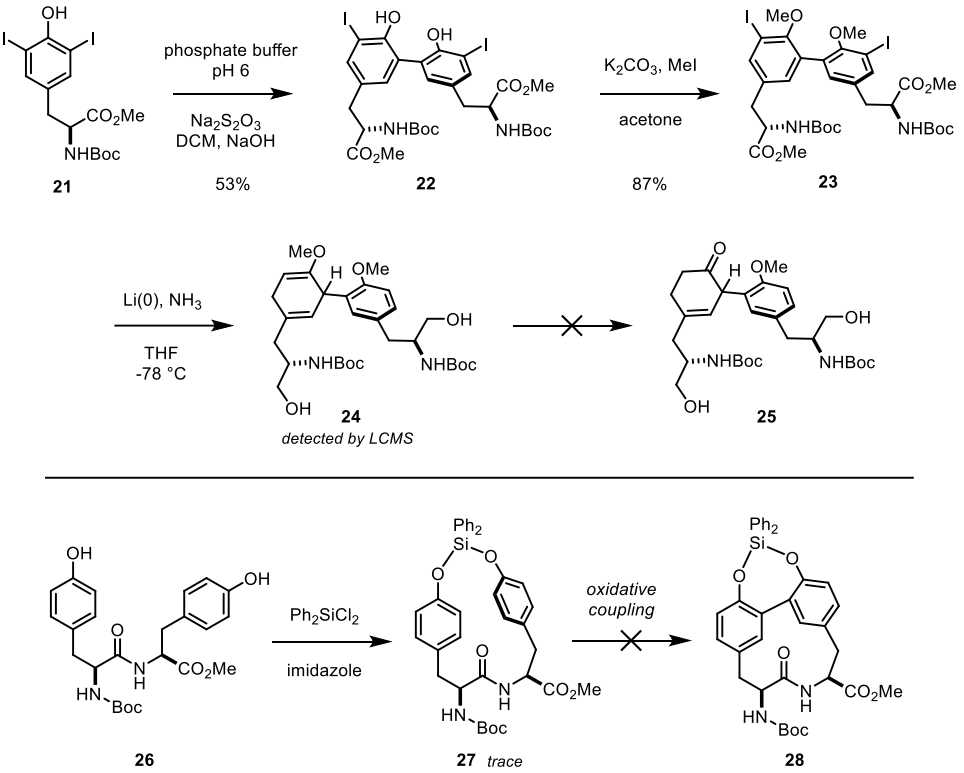


FIGURE 5.5 Hart and Johnson's studies toward the herqulines.

5.3.4 Studies by Stawaski and Trauner

In a unique approach, Stawski and Trauner attempted to access the herqulines from L-pyrroglutamate as starting material in 2012 (Figure 5.6).[8d] Thus, L-pyrroglutamate was advanced forward to previously reported symmetrical *N*-Boc piperazine **29** in five steps. A double Swern oxidation followed by base mediated intermolecular conjugate addition with methyl vinyl ketone led to functionalized piperazine intermediate **31**. Exposure of **31** to KOH and tetrabutylammonium hydroxide in aqueous ethanol led to intramolecular ring closure to bis(cyclohexanone) **32**. Next, base mediated iodination of **32** led to compound **33**. All attempts to effect iodoenone reductive coupling of **33** to herquline-type macrocycle **34** were not met with success.

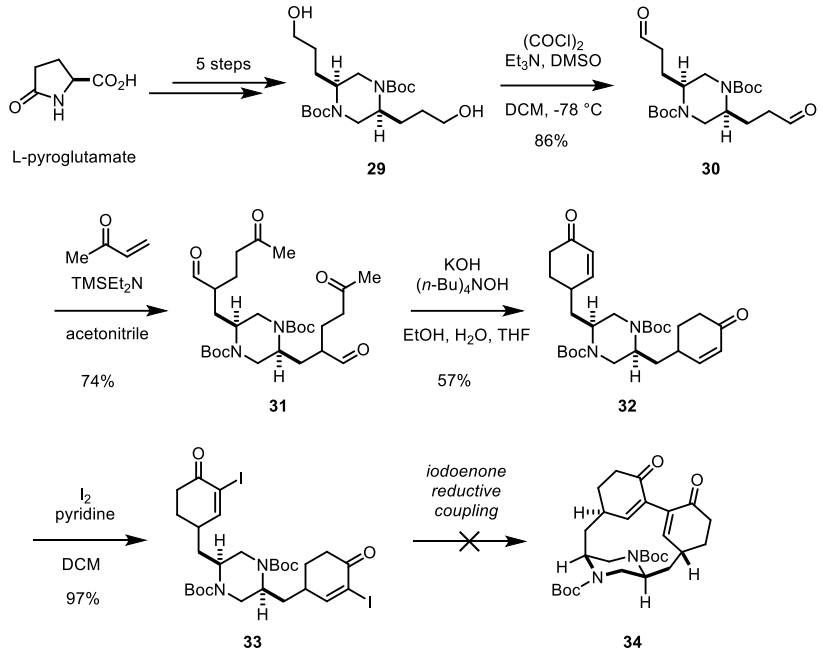


FIGURE 5.6 Stawaski and Trauner's studies toward the herqulines

5.3.5 Studies by Simpkins and Yang

Recently, Yang and Simpkins envisioned a route to access herquline A and B via coupling of two tyrosine derivatives (Figure 5.7).[8e] Known diketopiperazine **35** was subjected to lithium aluminum hydride followed by standard *N*-Boc protection conditions which led to C_2-symmetric piperazine **36** in 68% yield over two steps. A double arene iodination of **36** was successful utilizing iodine and silver triflate in methanol affording **37** in good yield and regioselectivity. With bis(aryliodide) **37** in hand, the authors attempted a variety of macrocyclization conditions to access macrocycle **38**. Compound **38** was isolated in 6% yield when **37** was treated with palladium-mediated cross-coupling conditions previously reported. Due to the poor overall yield of this transformation, no further investigations were carried out to reduce the biaryl moiety in order to obtain the unsaturation required for the herqulines.

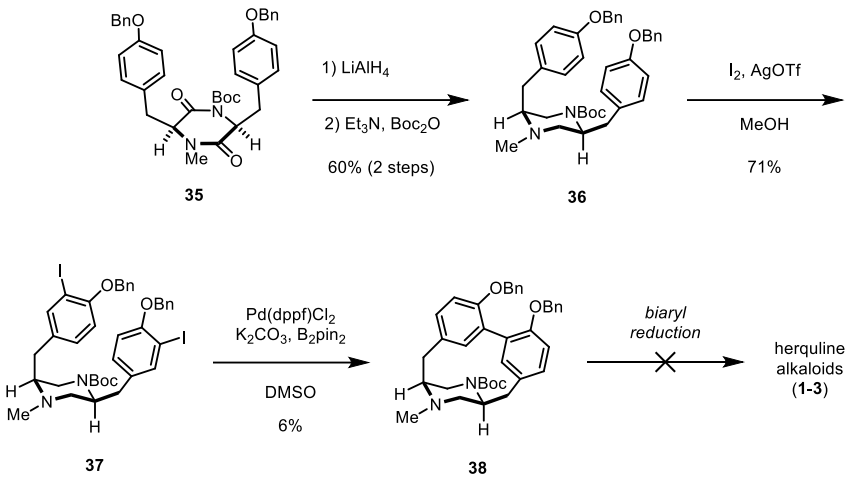


FIGURE 5.7 Simpkins and Yang's studies toward the herqulines

5.4 Total syntheses of herqulines B and C by Wood and Baran in 2019

Contemporaneous to our laboratory's own reported total synthesis of the herquline alkaloids in 2019, Wood[5] and Baran[9] disclosed elegant approaches to assemble herquline B (**2**) and C (**3**) from functionalized tyrosine building blocks, as shown in Figure 5.8. Wood and coworkers demonstrated that bis(aryldiiodide) **39**, could be elaborated to α-methoxy quinone **40** via a palladium-catalyzed macrocyclization and a subsequent phenol oxidative dearomatization with diacetoxy iodobenzene in methanol. The stepwise reduction of **40** with L-selectride followed by SmI_2 led to β,γ-unsaturated ketone **41**. At this point, Wood and colleagues identified that following methyl enolether formation ($CH(OMe)_3$, *p*-TsOH), the anisole subunit could be reduced to the corresponding skipped diene **42** with Birch reduction conditions (NH_3, Li(0), trifluoroethanol). After successfully reducing the biaryl moiety, they were positioned to assemble the piperazine ring system of the herqulines. As such, reacting amide **42** with DAST in DCM led to oxazoline **43**. Reductive ring-opening of **43** with lithium aluminum hydride (**43** → **44**), reductive amination, and a subsequent dehydroxychlorination garnered **45**. Base mediated

intramolecular ring closure and enol ether hydrolysis completed the total synthesis of herquline B (**2**) and C (**3**)

The approach by Baran and colleagues relied on cyclodipeptide **47** (from acyclic dipeptide **46**) as a precursor to a palladium-catalyzed oxidative coupling of the aryl iodide subunits.[9] Following macrocyclization of **47**, a regioselective Birch reduction utilizing trifluoroethanol (TFE) as an exogenous proton source led to compound **49**. Diketopiperazine reduction of biaryl **49** to **50** was accomplished with an iridium catalyst and a stoichiometric silane reductant, which proved crucial for the success of this approach. Ensuing enolether hydrolysis **50**, succeeded by acetal formation and a second Birch reduction reaction of the remaining anisole motif garnered **52** which delivered herquline B (**2**) and C (**3**) in short order.

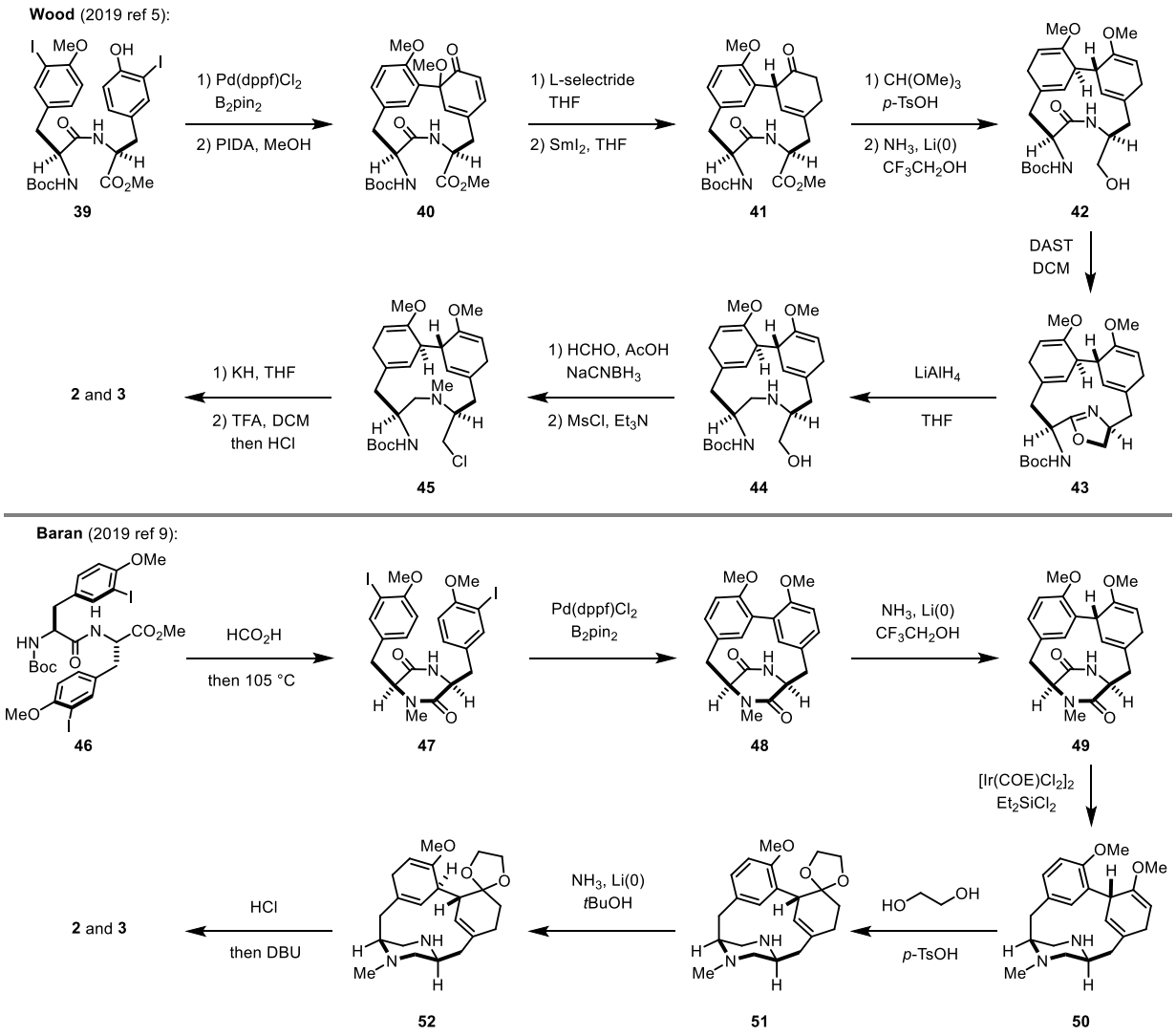


FIGURE 5.8. Abbreviated successful approaches reported by Wood and Baran to the herquline alkaloids.

Fascinated by the synthetic challenge posed by the highly strained architecture of the herqulines, as well as limited biological investigations, we set out in 2015 to devise a synthetic strategy toward this class of tyrosine-based natural products. Herein we report the evolution of our total synthesis of herquline B (**2**) and C (**3**). Particularly, we highlight several early strategies that led to both unforeseen obstacles and useful insight gained that ultimately guided our own successful entry to the herquline alkaloids.

5.5 Results and discussion

5.5.1 Initial strategy to herquline A

Our own studies towards the synthesis of the herqulines were guided by and builds on seminal work from Kim, Hart, Stawski and Yang.[8] Importantly, the challenge to construct the macrocyclic system late on in the synthetic sequence is well documented.[8] As such, this prompted us to develop a distinct approach toward the herqulines (**1**-**3**) which ultimately would rely on mycocyclosin (**4**),[7] or a functionalized analogue,[10] as a key synthetic intermediate. Thus, we expected the advantage of this strategy would be that the key macrocyclic ring formation would occur early in the synthesis. Strategically, we envisioned that through a series of well-coordinated, selective reductions of the mycocyclosin macrocyclic core, the herqulines could be directly accessible.

In an early synthetic proposal of herquline A (**1**) (Figure 5.9 A), it was envisioned that the β,γ-unsaturated ketone motif would be accessed in the final stages of the synthesis. We expected Birch reduction of **53** would give rise to the desired selectivity in **1** as a result of the bias imparted by the molecular strain inherent to the final natural product. Distorted piperazine **53** could be traced back to α,β-unsaturated ketone **54** which could readily undergo intramolecular aza-conjugate addition with the secondary amine. Cyclophane intermediate **54** would then be obtained from the olefin isomerization of **55**. Diketopiperazine reduction of **56** would garner key intermediate **55**. Further retrosynthetic analysis led us to propose that **56** may come from reductive dearomatization of reported mycocyclosin derivative **57**. The strained biaryl bond in **57** can be forged via palladium-catalyzed oxidative homocoupling of a corresponding bis(aryliodide) precursor.

In 1974, Birch had reported the transformation of biaryl anisole **58** to unsymmetrical bis(cyclohexadiene) **60** through a stepwise, arene reduction protocol (Figure 5.9 B).[11] Birch

reduction of the first aromatic ring proceeds without an exogenous proton source and provides diene **59** which arises from a highly stabilized, benzylic anion intermediate. Intermediate **59** can be further converted under reducing metal conditions in the presence of an exogenous alcohol, to **60**. The diene regiochemistry is predictable with the electron-donating groups residing in the product at the olefinic position. Based on this literature precedent, we expected the Birch reduction of biaryl **57** to proceed sequentially, analogous to the reduction of biaryl **58**, resulting in the formation of desired β,γ-unsaturated ketone **56**.

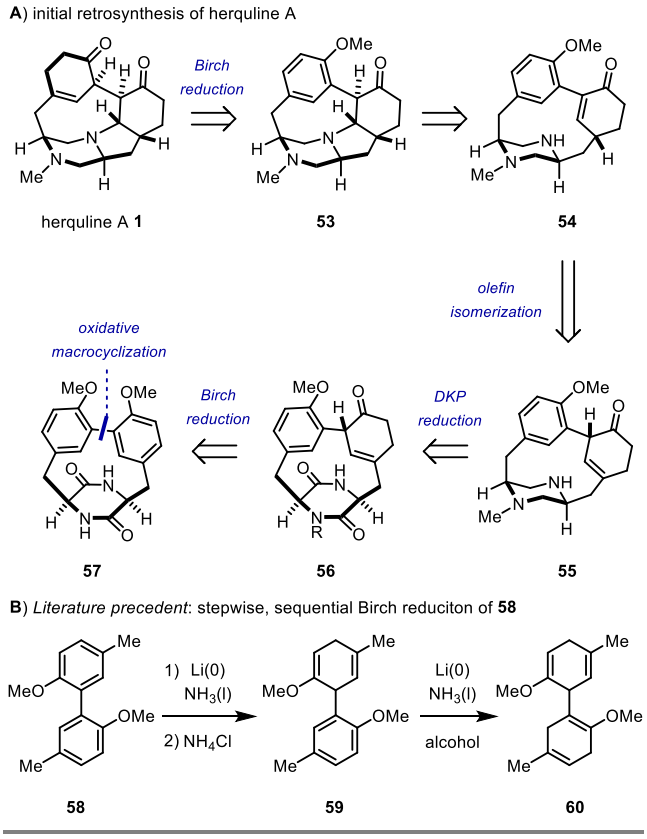


FIGURE 5.9 A) Initial retrosynthetic analysis of herquline A. B) Literature precedent for the stepwise reduction of anisole **58**.

5.5.2 Early Birch reduction studies of a mycocyclosin analogue

Hutton and coworkers first disclosed their synthesis of mycocyclosin (**4**) in 2012.[10] This expedient approach to access mycocyclosin relied on a palladium-catalyzed Suzuki-Miyaura cross-coupling to build up the biaryl core of the macrocyclic system. In accordance with the work of Hutton, we identified diiodide **64** as a suitable precursor to cyclophane **57**. Figure 5.10 summarizes the preparation of cyclodipeptide **64**. Iodinated L-tyrosine-derived peptide coupling partners **61** and **62** were each accessible in two steps. Amide coupling of **61** and **62** promoted by hexafluorophosphate benzotriazole tetramethyl uranium (HBTU) in the presence of base garnered peptide **63** in 87% yield. Exposure of **63** to formic acid effected *N*-Boc cleavage which set the stage for intramolecular thermal cyclization to **64** in good yield. Subsequently, subjecting dipeptide **64** to identical reaction conditions reported by Hutton in their synthesis of mycocyclosin ($Pd(dppf)Cl_2$•DCM, B_2pin_2, K_2CO_3 in DMSO at 90 °), symmetrical macrocycle **57** was isolated in 20% yield on half gram scale.[12]

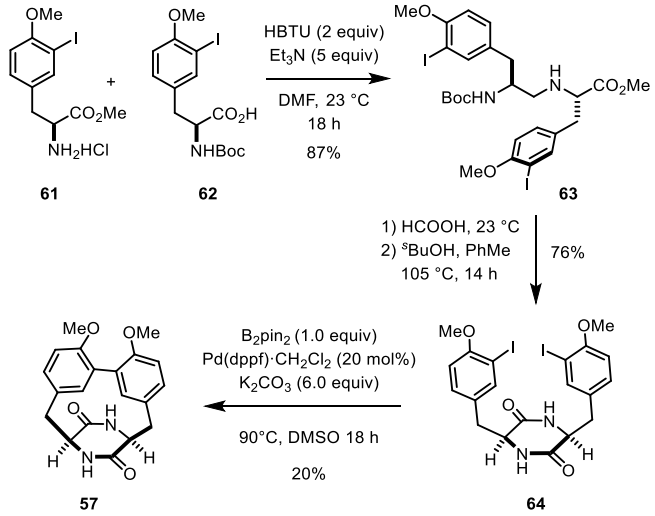


FIGURE 5.10 Synthesis of mycocyclosin derivative **19**.

With cyclodipeptide **57** in hand, we turned our attention to evaluating Birch reduction conditions of the strained biaryl system (Figure 5.11). Subjecting **57** to Na(0) in liquid ammonia in the presence of *tert*-butanol at -78 °C for one hour, afforded three chromatographically separable products in a combined yield of 77%. By 2D NMR analysis, we identified undesired 1,3-diene **65** as the major product from the reaction mixture, while **66** and **67** were both isolated as minor over-reduction products. Unfortunately, and contrary to our initial hypothesis, the desired 1,4-diene regioisomer **70** was not formed under these reaction parameters. While we were certainly surprised by the selective formation of 1,3-diene **65** over skipped diene **70**, we hypothesized that this compound arises via *in situ* isomerization of allylic *C*-centered radical **69** to the corresponding thermodynamically stable conjugated diene. Presumably, the immense molecular strain characteristic for these compounds promotes this isomerization event leading to undesired 1,3-diene **65**.

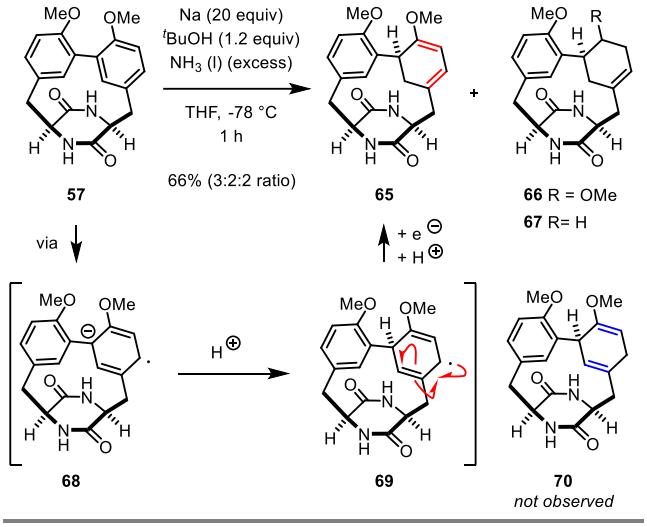


FIGURE 5.11 Birch reduction of diketopiperazine **57**.

In an effort to selectively access desired Birch product **70** from biaryl substrate **57**, several reaction conditions were explored to overcome the formation of undesired diene regioisomer **65**

and over-reduction side products **66** and **67**. Interestingly, Dryden, Webber, Burtner and Cella had noted in 1961 that impurities of ferric salts in commercially available ammonia tanks exhibit deleterious effects on Birch reductions by facilitating the reaction between lithium metal and *tert*-butanol.[13] Consequently, under Birch reduction conditions with $FeCl_3$ as a reaction additive, the authors reported abated formation of over-reduction products while unreacted starting material was isolated in increased amounts.

Following this seminal study by Dryden and coworkers, we carried out the Birch reduction of diketopiperazine **57** with added super-stoichiometric amounts of $FeCl_3$.[13] Although no over-reduction products were observed under this modified protocol, the undesired diene **65** remained the exclusive regioisomer formed (Figure 5.12). Moreover, we noted an analogous reaction profile when the Birch reduction was conducted without an exogenous proton source which is known to attenuate competing over-reductions (Figure 5.12).[14] Unfortunately, subsequent attempts to modify the Birch reduction conditions including proton source, co-solvent, metal (Li, Na, or K) quenching method, or order of reagent addition did not result in the formation of the desired 1,4-diene product **70**. Additionally, several structural alterations to either the phenol protecting groups or the diketopiperazine amide substituents of the Birch substrate did not afford the desired 1,4-diene product.

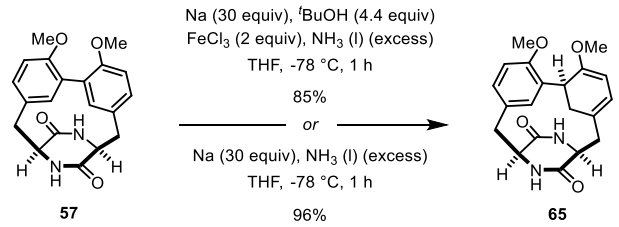


FIGURE 5.12 Abbreviated attempts to modify Birch reduction outcome of diketopiperazine **57**.

5.5.3 Modified dearomatization approach to 55

A thorough investigation of the Birch reduction conditions of mycocyclosin derivatives was unfortunately met with no success as the desired regiochemical diene disposition (i.e. in compound **70**) was never observed. As such, our subsequent efforts focused on identifying a modified strategy for arene dearomatization that could reliably provide the required regiochemistry of the bis(cyclohexenone) core within the herquline family of natural products.

Our subsequent revised synthetic design to access the herqulines was inspired by Yang and Simpkins.[8e] In their seminal investigations towards the total synthesis of herquline A, the researchers reported on the viability of tyrosine derivatives to undergo hypervalent iodine mediated dearomatizations to obtain the corresponding dienone products. We were further encouraged by Quideau and coworkers who demonstrated that $PhI(OAc)_2$ can promote the dearomatization of amide tethered *ortho*-methoxyphenols (**71**) to *ortho*-quinol acetate compound **72** (Figure 5.13 A).[15] Quideau further illustrated that exposure of **72** to tetrabutyl ammonium fluoride (TBAF) led to intramolecular amine cyclization to form azacycle **73**.[15] Considering these early studies, we postulated that subjecting an electron-rich, *ortho*-substituted phenol with an appropriate hypervalent iodine reagent could facilitate oxidative dearomatization of the phenolic subunit and thereby afford the desired alkene regiochemistry in the resultant dienone product. Thus, a revised retrosynthetic analysis toward key β,γ-unsaturated ketone intermediate **55** is shown in Figure 5.13 B.

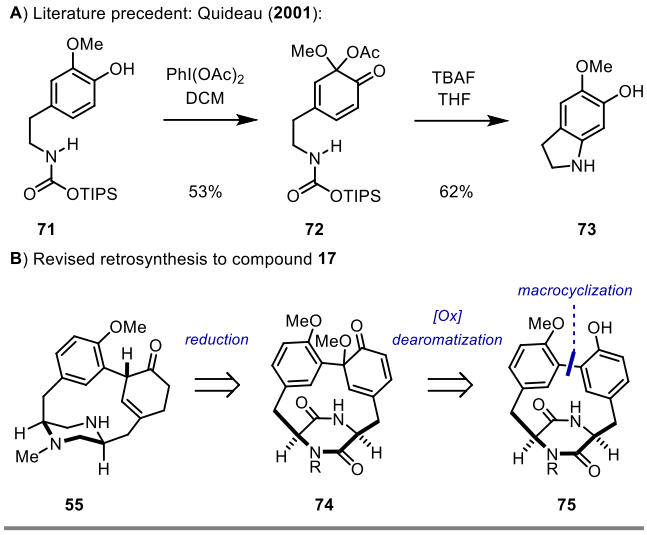


FIGURE 5.13 Revised strategy for dearomatization of mycocyclosin derivatives.

Following the design of a revised retrosynthetic approach toward the herqulines (**1**-**3**), we initiated the synthesis of key phenolic cyclophane intermediate **80**.[16] Building on prior insights obtained during our laboratory's earlier studies towards the herqulines, we considered it optimal to protect the phenols in **78** differentially as benzyl ether and anisole moieties. Thus, derivatized L-tyrosine analogs **76** and **77** were subjected to standard peptide coupling parameters (HBTU, Et_3N) at room temperature on greater than 80-gram scale, to yield the expected dipeptide (not shown). Exposure of the resultant linear dipeptide to acidic conditions (TFA, DCM) effected Boc-deprotection followed by intramolecular cyclization to the corresponding diketopiperazine. Finally, *N*-benzylation with benzyl bromide and sodium hydride in DMF garnered diiodo cyclic dipeptide **78** as the precursor for a palladium-catalyzed macrocyclization. Gratifyingly, treating diketopiperazine **78** to our previously optimized palladium-catalyzed cyclization conditions, afforded cyclophane **79** in 81% isolated yield. Additionally, we observed that this strain-inducing transformation was found to be readily amenable on up to 4-gram scale, while an increase in reaction concentration to 0.01M was also well tolerated without an observed drop in isolated yield.

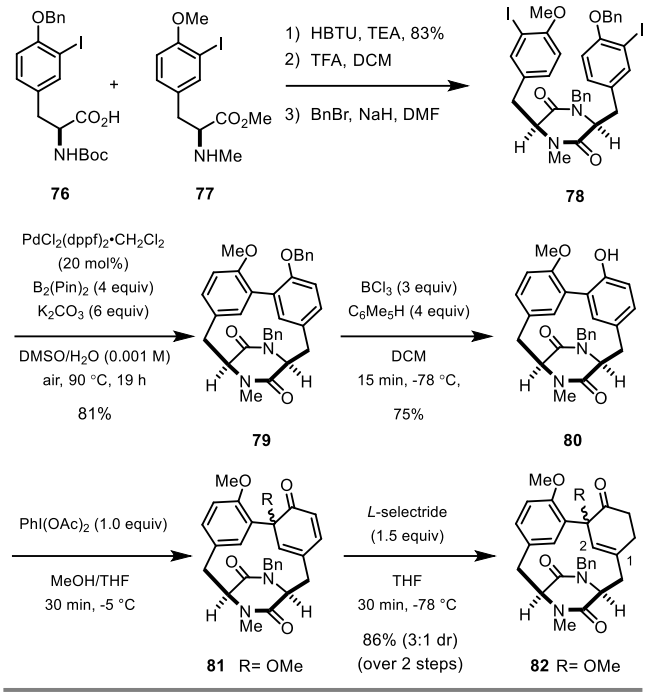


FIGURE 5.14. Synthesis of β,γ-unsaturated enone **82**.

With an efficient route to mycocyclosin derivative **79** in hand, we were poised to investigate an arene reduction strategy based on hypervalent iodine reagents (Figure 5.14).[17] Unfortunately, conversion of the benzyl ether in **79** to phenol **80** proved more problematic than previously anticipated. Initial attempts to hydrogenate benzyl ether **79** under a variety of traditional heterogenous catalytic conditions (Pd/C, PtO_2, $Pd(OH)_2$) led to unproductive reduction of the biaryl subunit prior to the desired deprotection. However, we did find that employing reaction conditions initially reported by Fukuyama, relying on BCl_3 and pentamethylbenzene at cryogenic temperatures, proved successful.[18] To our satisfaction, this Lewis acid-mediated debenzylation protocol resulted in the anticipated phenol **80** in 75% isolated yield. It is noteworthy that these reaction conditions were completely selective for benzyl ether removal as we never observed anisole demethylation.

Phenol dearomatization enabled by hypervalent iodine reagents is well known to proceed with concomitant nucleophile addition to the *ortho*- and *para*- positions of the aromatic moiety.[17] As anticipated, when phenol **80** was reacted with $PhI(OAc)_2$ in methanol at -6 °C, *ortho*-methoxyquinone **81** was isolated as a 3:1 mixture of diastereomers (Figure 5.14).[27] We attribute the excellent regioselectivity of this transformation to the highly stabilizing anisole moiety adjacent to an *in situ* generated benzylic cation intermediate. We opted to advance quinone **81** to the next step without column chromatography purification as it readily underwent nonspecific decomposition.

According to the work of Doty and coworkers, the combination of Lewis acidic bis[2,6-bis(1,1-dimethylethyl)-4-methylphenolato]methylaluminum (MAD) and L-selectride is particularly efficient in promoting conjugate reductions of cyclic α,β-unsaturated ketones.[19] The authors suggested that the sterically encumbered carbonyl bound Lewis acid in conjunction with a sterically demanding hydride source disfavors 1,2-reduction.[19] Importantly, when quinone **81** was subjected to L-selectride in THF at -78 °C, α-methoxyketone **82** was formed in 86% yield (over 2 steps) as a 3:1 mixture of diastereomers. Further, no indication of a competing 1,2-reduction pathway was observed (Figure 5.14). We postulate that ring strain release of *ortho*-methoxyquinone **81** upon 1,4-conjugate reduction is thermodynamically favored over the undesired 1,2-reduction pathway. Indeed, we were pleased to find that stepwise hypervalent iodine mediated dearomatization followed by 1,4-reduction of **81**, proved amendable to gram scale and provided the desired regioisomer incorporating unsaturation between the C1 and C2 position.

5.5.4 Reduction of diketopiperazine 82

Having secured access to intermediate **82**, our next task was to identify suitable reaction conditions for the reduction of the α-methoxyketone moiety to the corresponding cyclic ketone

(Figure 5.15). We found that methoxyketone **82** smoothly converted to unsaturated ketone **83** as a single diastereomer, when subjected to 2.2 equivalence of SmI_2 at 0 °C for 45 minutes. Single X-ray crystallographic analysis of **83** confirmed our original stereochemical assignment. Additionally, structural analysis of the intermediate bis-coordinated samarium-enolate **84** indicated that protonation from the back face (red arrow) is inhibited by the *N*-benzyl amide, which may contribute to the observed diastereoselectivity.

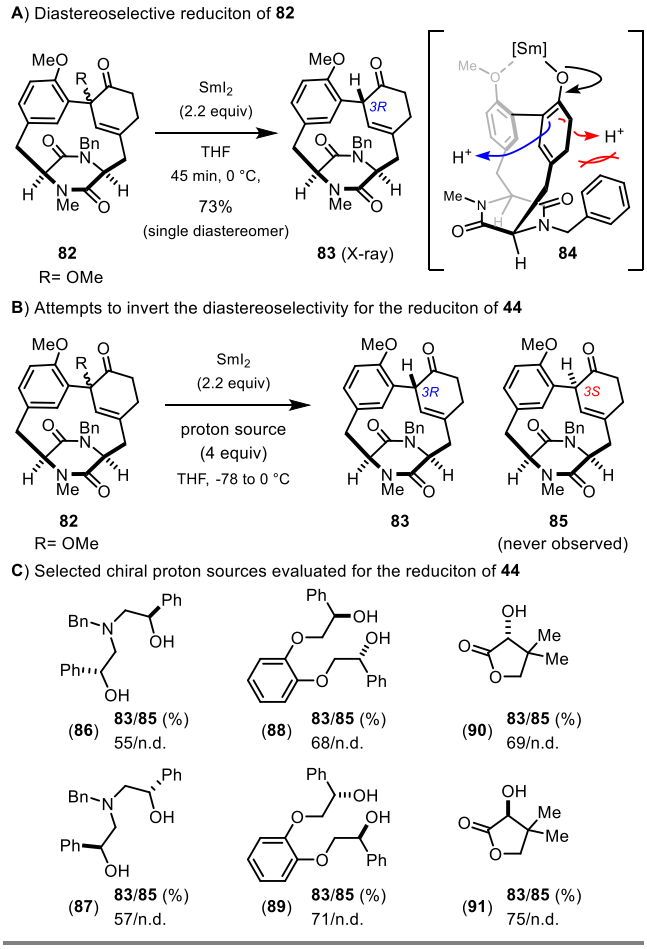
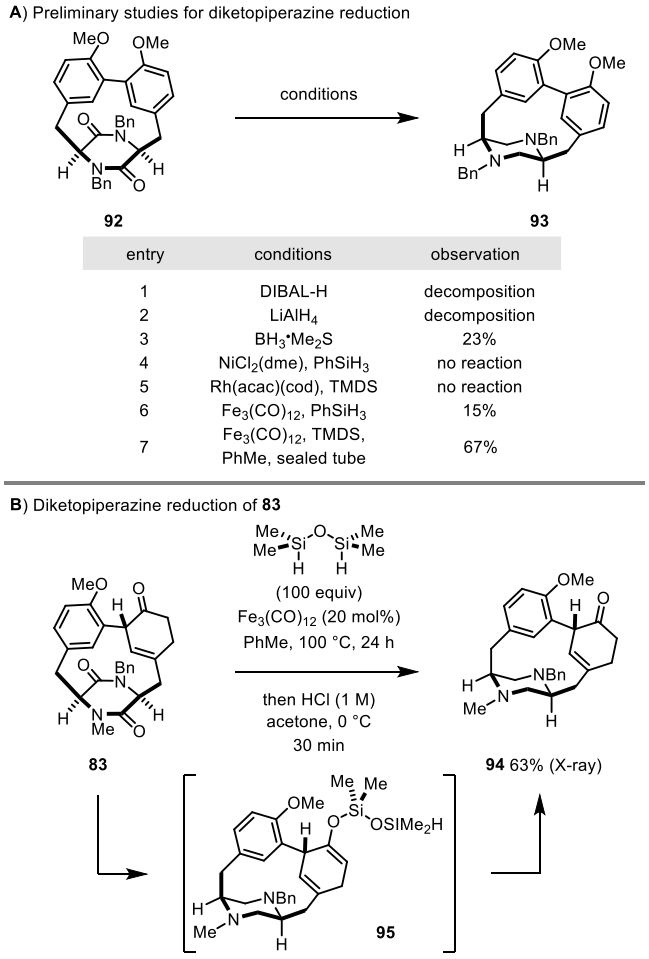


FIGURE 5.15 SmI_2-mediated reduction of α-methoxyketone **82**.

The excellent diastereoselectivity for the single-electron mediated reduction of **82** to **85** was a serendipitous observation. However, this prompted us to investigate strategies to invert the diastereoselctive outcome at C3 to obtain the stereochemical configuration required for herquline

A (**1**). We were inspired by the work of Takeuchi who had reported that samarium enolates generated by a SmI_2-mediated reaction between unsymmetrical dialkylketene and allyl halides, can undergo enantioselective protonation upon reaction with C2-symmetric chiral binols, as a proton source.[20] In subsequent reports, Mikami and coworkers had utilized chiral hydroxy ethers as proton sources for the SmI_2-mediated reduction of α-hetero substituted ketones bearing an α-phenyl substituent, in good enantioselectivities.[21] Furthermore, Procter has recently disclosed an enantioselective desymmetrizing ketyl-alkene radical cyclization of dienyl β-ketoesters facilitated by SmI_2 in conjunction with an aminodiol as an alcohol additive.[22] Encouraged by these previous studies, we examined the influence of exogenous proton sources (**86**-**91**) on the diastereoselective outcome for the reduction of intermediate **82**. Unfortunately, when benzylated aminodiols (**86**-**87**), catechol derived diols (**88**-**89**), or pantolactone additives (**90**-**91**) were evaluated as proton sources for the reduction of **82**, no change in the diastereoselctive outcome was observed, despite modest to good overall isolated yield of product. We expect that the Lewis basic anisole motif inhibits chelation of the bidentate alcohol additive to the samarium metal center. Thus, we reasoned that stereohemical inversion at C3 would need to occur later in the synthetic sequence to access herquline A (**1**).



entry	conditions	observation
1	DIBAL-H	decomposition
2	$LiAlH_4$	decomposition
3	BH_3•Me_2S	23%
4	$NiCl_2$(dme), $PhSiH_3$	no reaction
5	Rh(acac)(cod), TMDS	no reaction
6	$Fe_3(CO)_{12}$, $PhSiH_3$	15%
7	$Fe_3(CO)_{12}$, TMDS, PhMe, sealed tube	67%

FIGURE 5.16 A) Model system for diketopiperazine piperazine reduction. B) Diketopiperazine reduction of β,γ-unsaturated ketone **83**.

At this juncture we looked to advance our synthesis toward the herqulines by establishing robust reaction conditions for diketopiperazine reduction. Symmetrical biaryl diketopiperazine **92** was chosen as a model system in order to study this reactivity. Traditionally, diketopiperazine reductions have been achieved with strong reductants, including DIBAL-H or $LiAlH_4$.[23] However, exposing *N*-benzylated diketopiperazine to either of these reductants led to decomposition of cyclophane **92** (Figure 5.16 A, entry 1 and 2). Subjecting diketopiperazine substrate **92** to BH_3•SMe_2[24] led to 23% isolated yield of piperazine **93** in addition to inseparable mixtures of hemiaminal and mono-deoxygenated intermediates (Figure 5.16 A, entry 3). Further evaluation of

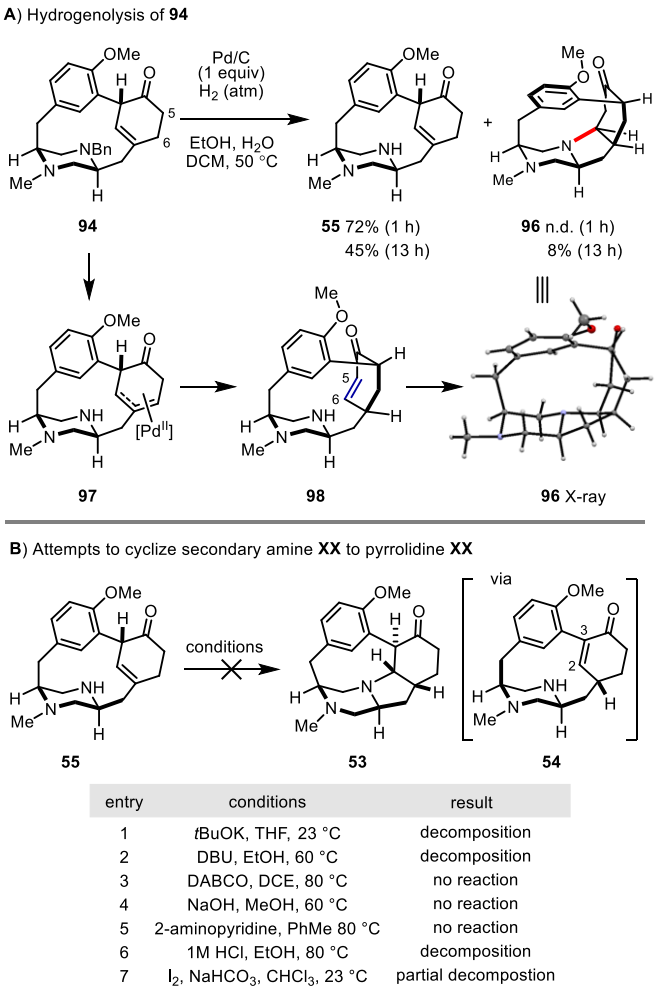
protocols which include nickel(II)[25] or rhodium(I)[26] catalysts in the presence of stoichiometric silane reductants afforded no reaction (Figure 5.16 A, entries 4 and 5). We found that reaction conditions initially described by Beller[27] for the reduction of amides relying on substoichiometric quantities of $Fe_3(CO)_{12}$ in the presence of $PhSiH_3$, furnished **93** in 15% isolated yield (Figure 5.16 A, entry 6). Altering the silane additive to 1,1,3,3-tetramethyldisiloxane (TMDS) in toluene at elevated temperatures afforded piperazine **93** in a markedly improved yield of 67% when the reaction was conducted in a sealed vessel (Figure 5.16 A, entry 7). We were pleased to find that these reaction conditions were general for a variety of diketopiperazine substrates and is expected to be a useful addition to the current armamentarium of diketopiperazine reductions.

Following optimization studies for the formation of piperazine **93**, we probed if these reaction conditions would be amendable for the chemoselective reduction of intermediate **83**. Indeed, after minimal reaction optimization, diketopiperazine **83** was efficiently converted to piperazine **94** when reacted with 20 mol% $Fe_3(CO)_{12}$ and super-stoichiometric TMDS at 100 °C for 24 hours in a sealed tube (Figure 5.16 B). Due to the low boiling-point of TMDS, high siloxane loadings were required at elevated temperatures to ensure full conversion of starting material. Moreover, the *in situ* silylation of the enone carbonyl under these reaction conditions to the corresponding silyl enolether **95** proved to be advantageous as it prevented undesired reduction. We found that exposing the crude reaction residue to aqueous HCl in acetone during workup gave rise to key piperazine intermediate **94** in 63% isolated yield.

5.5.5 Investigations toward pyrrolidine synthesis

At this point, following *N*-benzyl hydrogenolysis of compound **94**, we would be prepared to examine conditions for pyrrolidine formation (Figure 5.17). To this objective, treating *N*-benzyl piperazine **94** with palladium on carbon (1 equiv) under a hydrogenous atmosphere at elevated

temperatures for 1 hour led to the formation of secondary amine **55** in 72% yield. Curiously, carrying out this transformation for extended reaction times (13 h) under otherwise identical reaction conditions afforded piperazine **55** in a diminished yield of 45% in addition to strained pentacycle **96** in 8% isolated yield. The structure of **96** was confirmed by single X-ray crystallographic analysis. Mechanistically, we postulate that compound **96** arises through a palladium(II)-promoted allylic C–H electrophilic cleavage yielding η^3-allyl species **97**.[28] Palladium insertion followed by protodemtalation and alkene isomerization to C5 and C6 would lead to α,β-unsaturated enone **98**. Finally, intramolecular *aza*-conjugate addition of **98** would garner pyrrolidine **96**. Although this observation was encouraging that it may be possible to access the desired pyrrolidine core of herquline A (**1**) at this stage, we expected that it would be challenging to overcome the thermodynamic bias for the formation of α,β-unsaturated enone **98** (versus desired compound **54**).



entry	conditions	result
1	*t*BuOK, THF, 23 °C	decomposition
2	DBU, EtOH, 60 °C	decomposition
3	DABCO, DCE, 80 °C	no reaction
4	NaOH, MeOH, 60 °C	no reaction
5	2-aminopyridine, PhMe 80 °C	no reaction
6	1M HCl, EtOH, 80 °C	decomposition
7	I_2, $NaHCO_3$, $CHCl_3$, 23 °C	partial decompostion

Figure 5.17 A) hydrogenolysis of *N*-benzyl piperazine **94**. B) Attempted cyclization of **55** to **53**.

After achieving a viable approach to tetracycle **55**, we were hopeful that pyrrolidine **53** would be obtained *via* the in situ generated α,β-unsaturated ketone **54** (Figure 5.17 B). However, initial efforts relying on base mediated cyclization of **55** to **53** proved to be unsuccessful. Specifically, exposing **55** to KO^{t}Bu in THF or DBU in EtOH at 60 °C led to complete substrate decomposition (entries 1 and 2). Conversely, conditions including 1,4-diazabicyclo[2.2.2]octane (DABCO) in 1,2-dichlorethane, NaOH in methanol or 2-aminopyridine in toluene, led to complete recovery of starting material (entries 3-5). Attempts to promote alkene isomerization followed by intramolecular conjugate addition with aqueous Brønsted acids, also led to nonspecific decomposition (entry 6). Additionally, attempts to promote haloamination of **55** with I_2 and

$NaHCO_3$ did not provide the desired cyclized product **53**. We expect that compound **63** may be too unstable to access due to the molecular strain that would result from two bridging Csp^2 atoms.

Although having failed to cyclize piperazine **55** to pyrroldine **53** at this stage, we utilized this insight to develop a revised approach for the construction of the remaining C–N to access herquline A (**1**), as outlined in Figure 5.18. We reasoned that an alternative and distinct tactic toward herquline A (**1**) can proceed through hydroxy-piperazine **99**. Cyclophane **99** can arise from an intramolecular cyclization between an amine and epoxide or equivalent functionality. As such, intermediate **99** can be traced back to epoxy ketone **100** which in turn could be formed from previously described intermediates

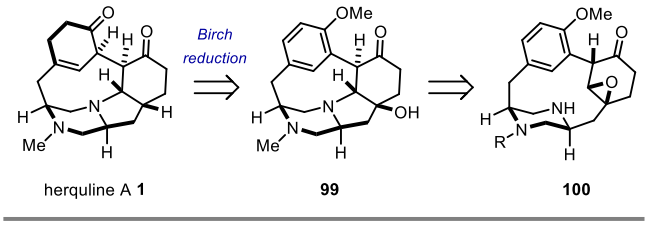


FIGURE 5.18 Alternative strategy for pyrrolidine formation.

To this end, diketopiperazine **83** was converted to acetal **101** which was readily epoxidized in the presence of *m*CPBA and $NaHCO_3$ leading to epoxyacetal **102** in 77% isolated yield over two steps (Figure 5.19). Epoxide **102** was isolated as a single diastereomer and its absolute configuration was corroborated by single crystal X-ray analysis. In an effort to effect a Meinwald rearrangement[29] of epoxyacetal **102** to the corresponding 1,3-ketoacetal (not shown), **102** was treated with $BF_3{\cdot}(OEt_2)$ in dichloromethane at -78 °C for 30 minutes. However, allylic alcohol **103** was the single product obtained, in excellent yield and regioselectivity. Other Lewis acids, including $InCl_3$ and $ZnBr_2$, led to an identical reaction profile. According to studies by Rajanbabu and Nugent,[30] subsequent attempts to reductively open epoxide **102** to the resultant secondary alcohol relying on $CpTi_2Cl$, Zn metal and 1,4-cyclohexadiene, also only resulted in allylic alcohol

103. Moving forward, oxidation of **103** with Dess-Martin perodinane led to smooth formation of functionalized cyclohexenone **104**, which was confirmed by X-ray crystallographic analysis. While intermediate **104** could be synthesized in good overall yield, all endeavors to advance toward diketopiperazine **106** either via 1,4-conjugate reduction (Stryker's reagent, L-selectride, SmI_2, titanocene) or heterogenous hydrogenation (Pd/C) only led to the formation of the corresponding allylic alcohol or recovery of starting material. Moreover, both advanced intermediate **103** and **104** could not be elaborated to piperazine **104** as they underwent complete decomposition under our previously optimized diketopiperazine reduction conditions.

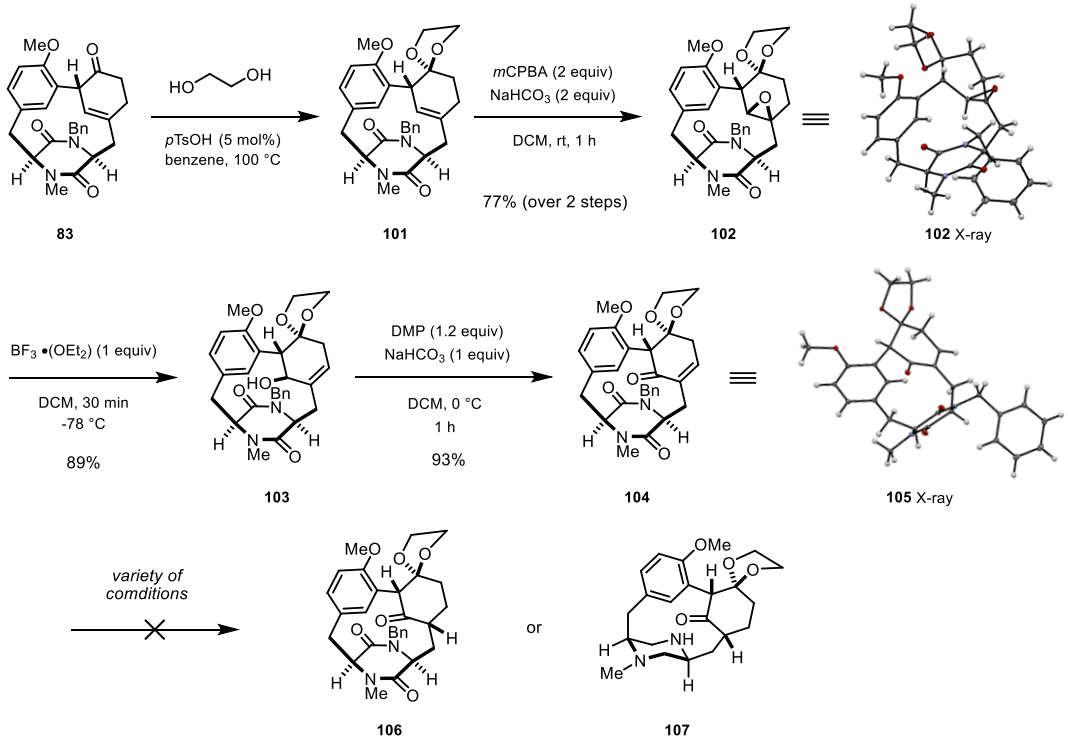


FIGURE 5.19 Synthesis of enone **104**.

Instead, having had initial success with epoxidation on the reduced mycocyclosin core yet facing down-stream challenges in progressing this material further, we decided to focus our efforts on derivatizing compound **94** forward in order to evaluate our epoxy-amine cyclization strategy (Figure 5.20). As such, β,γ-unsaturated ketone **94** was protected as the corresponding acetal under

standard conditions with ethylene glycol and *p*-TsOH at elevated temperatures. Subsequent epoxidation garnered epoxy *N*-oxide **108** as a single diastereomer. We found that crude *N*-oxide **108** could be chemooselectivity reduced with conditions previously disclosed by Lakshman and coworkers (B_2pin_2, ethylaminediamine).[31] Subsequent *N*-benzyl hydrogenolysis with palladium on carbon and H_2 led to key intermediate **109** in 65% yield over three steps, which provided single crystals suitable for X-ray analysis. With epoxy-amine **109** in hand, we surveyed a broad selection of bases (LiHMDS, NaOH, NaH) and Lewis acids ($FeCl_3$, BCl_3, $Zn(OTf)_2$) to determine their propensity to promote the cyclization of **109** to pyrrolidine **99**. Disappointingly, under all parameters investigated, only nonspecific decomposition or rearomatization of starting material **109** was detected.

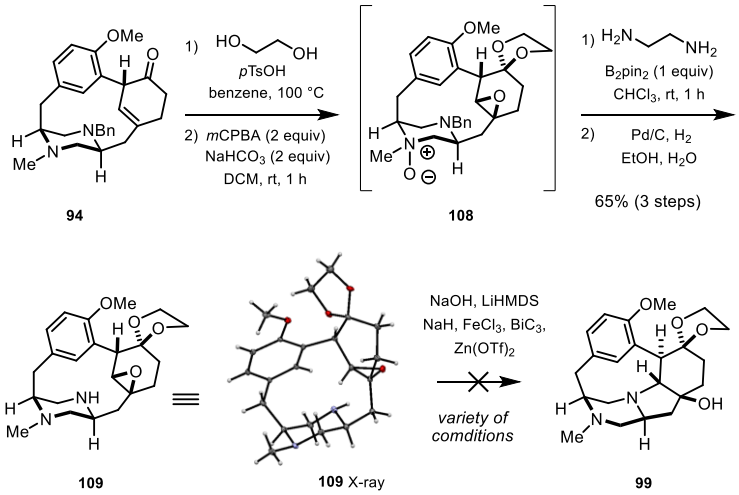


FIGURE 5.20 Attempted cyclization of **109** to **99**.

5.5.6 Inspiration from herquline biosynthesis by Tang

At this point in our studies we became aware of Tang's seminal work on the unique reductive biosynthesis of the herquline alkaloids.[6] They had identified a six-gene cluster from *Penicillium herquei* comprising of a nonribosomal peptide synthase (*hqlA*), an *N*-methyl

transferase (*hqlE*), a CYP450 oxidase (*hqlC*) and three short-chain dehydrogenases (*hqlB*, *hqlD*, *hqlF*). An abbreviated illustration of the biosynthetic formation of herquline A (**1**) is shown in Scheme 14. Particularly, bisphenol **9** undergoes dehydrogenative phenolic coupling in the presence of the CYP450 oxidase *hqlC* to give rise to the corresponding macrocycle. Next, a twofold reduction of the biaryl subunit to bis-β,γ-unsaturated ketone facilitated by the dehydrogenase *hqlF* and NADPH is then followed by *N*-methylation with N-methyl transferase *hqlE* to deliver compound **11**. Importantly, and of particular interest to our synthetic efforts toward the herqulines, it was reported that under non-enzymatic conditions (i.e. pH 8 buffer), herquline C (**3**) can undergo a stereoselective cyclization to form herquline A **1** giving rise to a potential unifying strategy towards the herquline alkaloids. Consequently, encouraged by this biosynthetic proposal, we expected that a successful synthesis of herquline B (**2**) or C (**3**) should thereby represent a viable approach to herquline A **1** (Figure 5.21). Thus, at this juncture we determined to redirect our synthetic efforts toward accessing herquline B (**2**) and C (**3**) from β,γ-unsaturated ketone **94**.

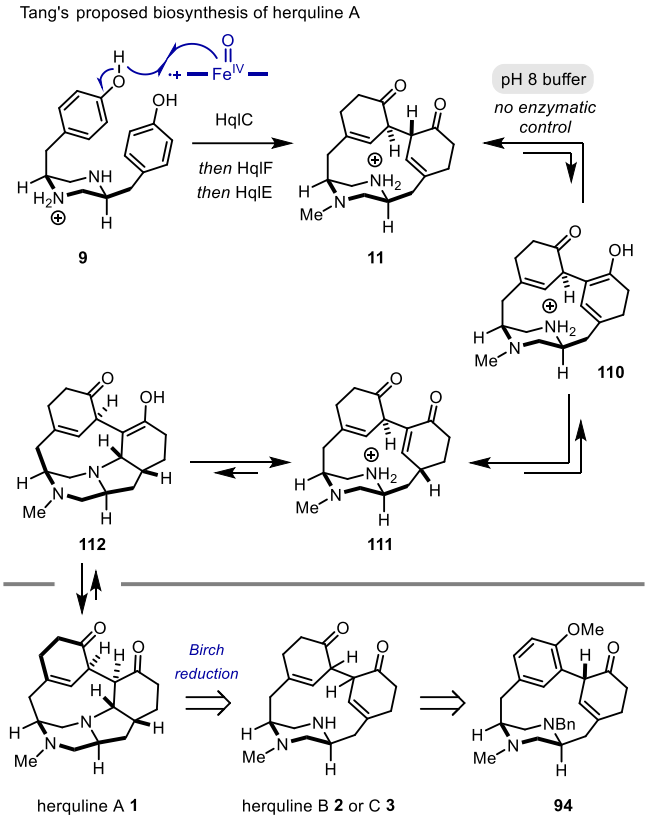


FIGURE 5.21 Abbreivated illustration of Tang's reported biosynthesis of the herquline alkaloids and revised synthetic approach toward the herqulines.

5.5.7 Late-stage Birch reduction studies

Completing the synthesis of herquline B (**2**) and C (**3**) from intermediate **94**, required a final dearomatization in addition to an *N*-benzyl deprotection. We set out to determine a set of reaction conditions for the selective reduction of anisole **94** (Figure 5.22). Interestingly, treating β,γ-unsaturated ketone **94** to Birch reduction conditions (Na(0), NH_3(l), ^{t}BuOH) at -78 °C for 1 hour gave rise to homoallylic alcohol **113** in 20% yield. Unfortunately, in addition to alcohol **113**, an intractable mixture of arene over reduction products was formed. We speculated that incorporating additional sp^3-hybridized centers in the form of acetal **114** would attenuate the overall reactivity of **94** by decreasing overall molecular strain. However, when acetal **114** was

subjected to reducing metal conditions, only unreacted starting material **114** was isolated with no indication of skipped diene **115** being generated. Upon surveying a range of Birch reduction protocols, including increased metal equivalences, extended reaction times, or additional proton source, we observed that acetal **114** proved to be completely inert under all parameters evaluated. These results stood in stark contrast to the established reactivity of ketone **94** under Birch reduction conditions. Based on the absence of reactivity of acetal **114**, we hypothesized that under Birch conditions, formation of alcohol **113** from ketone **94**, precedes *and* subsequently facilitates dearomatization of the anisole motif.

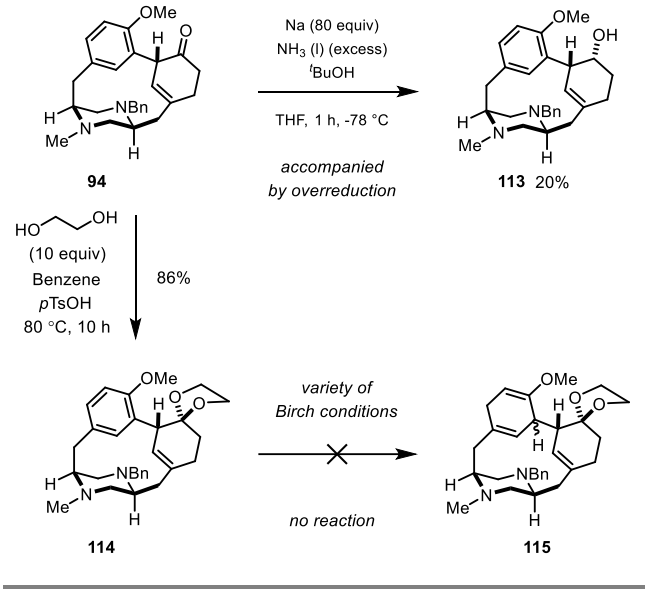


FIGURE 5.22 Birch reduction studies of ketone **94** and acetal **114**.

Hydroxyl promoted Birch reductions has only been reported in a few instances in the literatue.[32] In these limited examples, substrates for Birch reductions which contain appropriately positioned hydroxyl moieties can substantially influence reaction rates, alkene regioselectivity or proton stereoselectivity in the final product obtained (Figure 5.23). Fujita and colleagues in 1974 carried out a detailed mechanistic investigation of Birch reductions influenced by intramolecular hydroxyl groups, during their total synthesis of enmein (Figure 5.23 A).[33] The researchers found

that when terpene **116** was subjected to Birch reduction conditions for 40 minutes, three products were isolated and identified as conjugated enone **117** and cyclohexanones **118** and **119** in 9%, 64% and 22% yield, respectively. Fujita suggested the high reactivity of **116** was a direct result of participation from the neighboring hydroxyl groups which also influence the stereochemical configurational outcome of the resultant products.[33] Possible transition state structures that account for the product distribution observed (transition state A and B) are shown in Scheme 16. When X = H, stabilization of the carbanion and/or proton transfer from the hydroxyl group can occur. In comparison, when X = Li, anion stabilization likely results from a lithium bridge. Moreover, the authors noted that carbanion generation may be enhanced by electron transfer through the hydroxyl functionality.[33]

Paddon-Row and coworkers corroborate the significant role that distally connected, yet spatially adjacent hydroxyl groups to aromatic rings can have on Birch reduction outcomes.[34] For example, while hydroxy anthracene **120a** smoothly converted to *syn*-alcohol product **121** in quantitative yield, the corresponding methoxy analogue **120b** slowly (10 h) formed skipped diene **122** in poor overall yield, under otherwise identical reaction conditions (Figure 5.23 B).

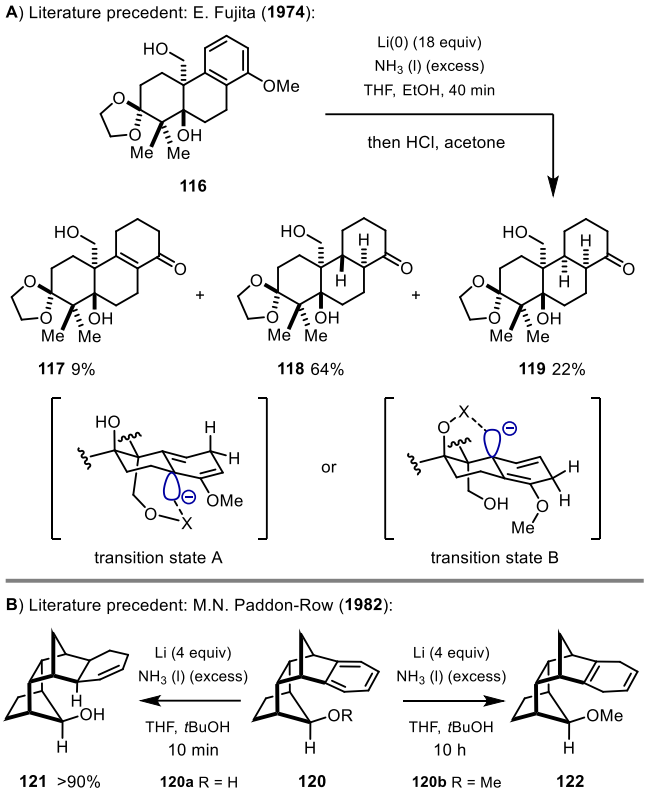


FIGURE 5.23 Literature precedent for hydroxyl-influenced selectivity in Birch reduction.

Despite the scant literature precedent for this unique reactivity in Birch reductions, we sought to determine if we could take advantage of this in our synthetic strategy towards herquline B (**2**) and C (**3**). To this end, diastereoselective reduction of β,γ-unsaturated ketone **94** with $NaBH_4$ in methanol led to smooth formation of hydroxy piperazine **113**, as a single diastereomer, which was subsequently confirmed by X-ray analysis (Figure 5.24).[16] To our satisfaction, when homoallylic alcohol **113** was subjected to super-stoichiometric Na(0) and liquid ammonia at -78 °C for 3 h, skipped diene **123** was isolated in 55% yield as a single diastereomer. The remaining mass balance of this transformation is unreacted starting material which can be recovered and recycled through. We expect that the C3' stereo-configuration in intermediate **123** can be rationalized via radical anion intermediate **125**. Finally, acidic hydrolysis of methyl enolether **123** with aqueous hydrochloric acid in acetone, provided hydroxy ketone **124** in excellent yield.

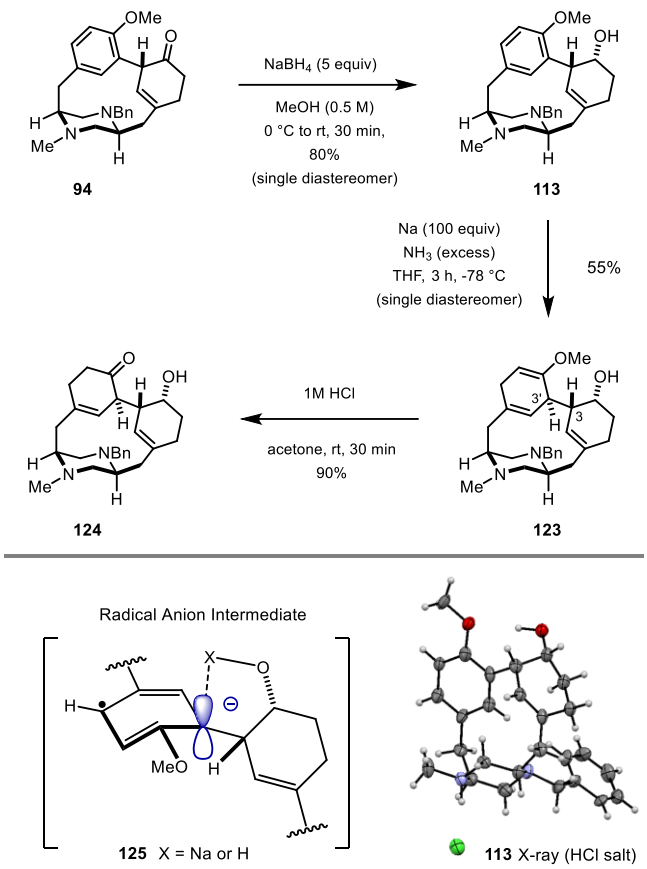
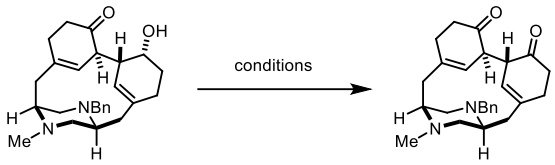


FIGURE 5.24 Intramolecular hydroxyl-directed Birch reduction of intermediate **113**.

Strategic implementation of the secondary alcohol in **113** for an intramolecular hydroxyl-directed Birch reduction, established the final cyclohexanone substructure of the herquline alkaloids. A final oxidation to the corresponding 1,4-diketone subunit remained. (Table 5.1). Oxidation of **124** with pyridinium chlorochromate (PCC) or Dess-Martin periodinane (DMP) only afforded diketone **126** in 10% and 12% yield, respectively, even with extended reaction times. Ultimately, we were pleased to determine that standard Swern oxidation conditions (Et_3N, $(COCl)_2$, DMSO) resulted in diketone **126** in 82% yield after just 30 minutes of reaction time.



124 **126**

entry	conditions	**126** yield
1	PCC, DCM, 4 h	10%
2	DMP, $NaHCO_3$, 8 h	12%
3	$(COCl)_2$, Et_3N, DMSO, 30 min	82%

TABLE 5.1 Oxidation of hydroxy ketone **91** to diketone **93**.

5.5.8 Total synthesis of herquline B and C

Having secured a robust approach to 1,4-diketone **126**, a final *N*-benzyl hydrogenolysis would yield herquline C (**3**). Indeed, reacting *N*-benzyl piperazine **126** with one equivalence of palladium on carbon under an atmosphere of hydrogen at 45 °C for 30 minutes in aqueous ethanol, led to herquline C (**3**) in 95% yield (Figure 5.25).[16] Importantly, no over-reduction of the two, trisubstituted alkenes had occurred. We expect that the steric congestion of these olefin moieties embedded into the macrocyclic system, inhibited them from being reduced. Careful comparison of the ^{1}H and ^{13}C NMR spectra of synthetic herquline C (**3**) to NMR data reported by Tang and coworkers during their studies of the herquline biosynthetic pathway, were identical.

At this point, we anticipated that piperazine **126** could be readily advanced towards herquline B (**2**). Thus, exposure of diketone **126** to 2 equivalences of DBU in toluene at room temperatures, led to rapid epimerization of C3 and C3' stereocenters and gave rise to intermediate **127** in 97% yield (Figure 5.25). Compound **127** was successively transformed to herquline B (**2**) in 90% isolated yield when treated with identical heterogenous reduction conditions described above.

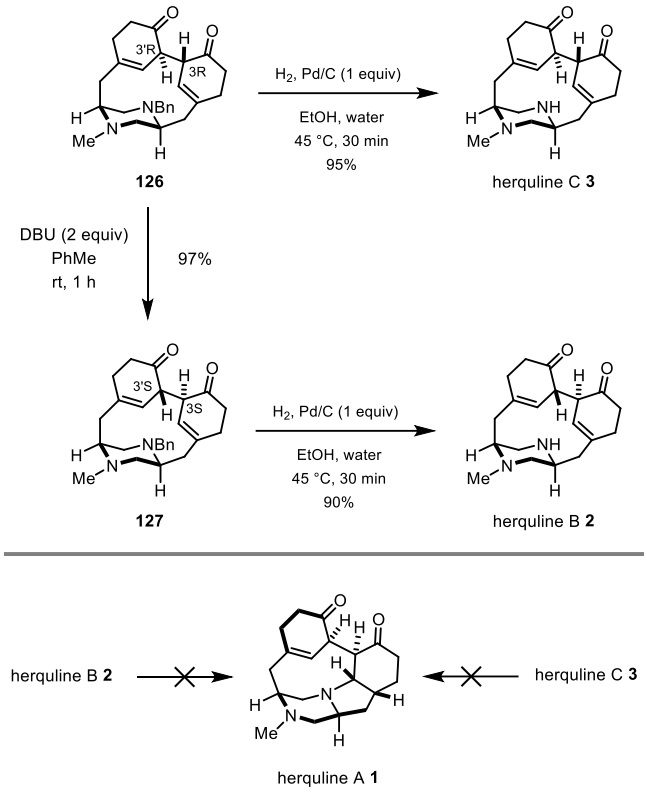


FIGURE 5.25 Completion of the total synthesis of herquline B and C.

In contrast to prior studies on the biosynthesis of the herquline alkaloids,[6] exhaustive experimentation in our own laboratory has revealed that neither herquline B (**2**) nor herquline C (**3**) undergo intramolecular stereoselective cyclization to herquline A (**1**)**.** These observations are further substantiated by the Wood[5] and Baran[9] laboratories during their respective syntheses of herquline B and herquline C.

5.6 Conclusion

Our total synthesis efforts towards herquline A (1), culminated in the successful synthesis of both herquline B (**2**) and herquline C (**3**). Crucial to the success of this work was the careful optimization of a palladium-catalyzed oxidative macrocyclization reaction for the construction of strained biaryls, an iron catalyzed diketopiperazine reduction, and an intramolecular hydroxyl

directed Birch reduction. Ongoing work is focused on leveraging the insights gained during the synthesis of **2** and **3** in order to synthesize herquline A.

APPENDIX A

A.1. Experimental procedures, operations, and references for Chapter 1

A.1.1. General laboratory information and procedures

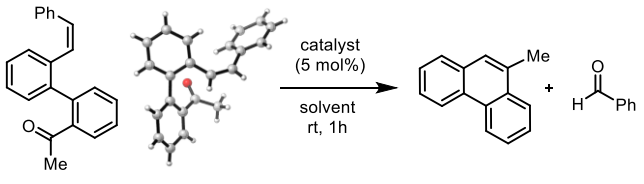
All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried round bottom flasks or glass vials fitted with rubber septa and/or septa equipped screw caps. Stainless steel syringes were used to transfer air or moisture-sensitive liquids. Flash chromatography was performed using silica gel Silia Flash® 40-63 micron (230-400 mesh) from Silicycle.

All chemicals were purchased from SigmaAldrich, Alfa Aesar, Acros Organics, Oakwood, TCI America, Frontier Scientific, Matrix Scientific, Ark Pharm, and Chem Impex International, and were used as received unless otherwise stated. Tetrahydrofuran was dried by being passed through columns of activated alumina. Proton Nuclear Magnetic Resonance NMR (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Unity Plus 400, Varian MR400, Varian vnmrs 500, Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for protons are reported in parts per million and are references to the NMR solvent peak ($CDCl_3$: δ 7.26; DMSO: δ2.62). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ77.23; DMSO: δ40.76). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, m = multiplet), and coupling constants in Hertz (Hz). Mass spectroscopic

(MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer. Infrared (IR) spectra were obtained using either an Avatar 360 FT-IR or Perkin Elmer Spectrum BX FT-IR spectrometer. IR data are represented as frequency of absorption (cm^{-1}).

A.1.2 Reaction optimization and Lewis acid / Brønsted acid evaluation

A flame-dried 1 – dram vial was charged with Lewis or Brønsted acid (5 mol%), solvent (0.1-0.01 M) and stirred at room temperature. To this solution was added starting biaryl **8a** (0.13 mmol), and the resultant mixture was stirred at room temperature. After 1 h the reaction mixture was passed through a short silica plug eluting with DCM (25 mL). The filtrate was concentrated under reduced pressure and yield determined by NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal standard.



8 **8** (x-ray) **9** **10**

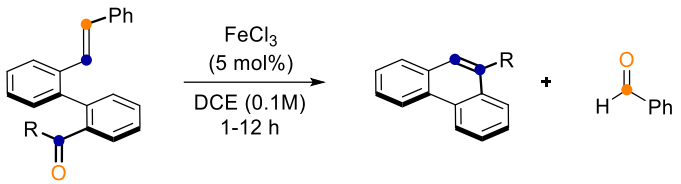
entry	Lewis Acid	solvent	yield **9** (%)[a]	conversion (%)
1	$TiCl_4$	DCE (0.1M)	3	7
2	$SnCl_4$	DCE (0.1M)	0	6
3	$FeCl_2$	DCE (0.1M)	0	2
4	$ZnCl_2$	DCE (0.1M)	22	26
5	$InCl_3$	DCE (0.1M)	16	38
6	$Yb(OTf)_3$	DCE (0.1M)	0	0
7	$Dy(OTf)_3$	DCE (0.1M)	0	4
8	$ScCl_3$	DCE (0.1M)	0	0
9	$AlCl_3$	DCE (0.1M)	93	100
10	$GaCl_3$	DCE (0.1M)	88	100
11	$FeSO_4 \bullet 7H_2O$	DCE (0.1M)	0	4
12	FeF_3	DCE (0.1M)	0	7
13	$Fe(acac)_3$	DCE (0.1M)	0	2
14	$MgBr_2$	DCE (0.1M)	0	0
15	CuCl	DCE (0.1M)	0	0
16	$BF_3 \bullet OEt_2$	DCE (0.1M)	31	35
17	$SbCl_3$	DCE (0.1M)	0	0
18	$FeBr_2$	DCE (0.1M)	0	0
19	$Mg(OTf)_2$	DCE (0.1M)	88	100
20	$Cu(OTf)_2$	DCE (0.1M)	0	0
21	$Cu(OAc)_2$	DCE (0.1M)	0	0
22	$Mn(acac)_3$	DCE (0.1M)	0	0
23	$Fe(OAc)_2$	DCE (0.1M)	0	15
24	$Fe(OTf)_3$	DCE (0.1M)	82	100
25	$FeCl_3$	DCE (0.1M)	97	100
26	$FeCl_3$	DCE (0.01M)	95	100
27	$FeCl_3$	DCE (0.05M)	91	100
28	$FeCl_3$	toluene (0.1M)	99	100
29	$FeCl_3$	DMF (0.1M)	0	0
30	$FeCl_3$	1,4-dioxane (0.1M)	0	6
31	HCl	DCE (0.1M)	0	0
32	*p*TsOH	DCE (0.1M)	0	0

TABLE A.1. Optimization table for the synthesis of **9**,

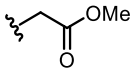
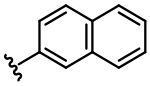
A.1.3 Evaluation of substituents on the carbonyl moiety

A flame-dried 1 – dram vial was charged with $FeCl_3$ (5 mol%), DCE (0.1 M) and stirred at room temperature. To this solution was added starting biaryl **22 a-l** (0.13 mmol), and the resultant mixture was stirred at room temperature unless noted otherwise. After completion of the reaction by TLC analysis, the mixture was passed through a short silica plug eluting with DCM (25 mL).

The filtrate was concentrated under reduced pressure and purified by flash column chromotography.



22 a-l **9, 23 b-l**

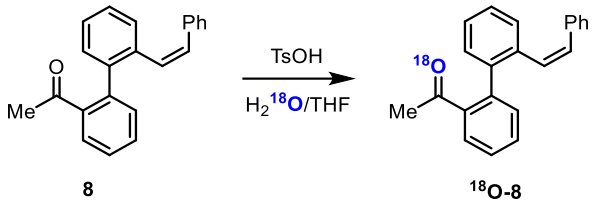
entry	substrate		yield (%)	entry	substrate		yield (%)
1		**22a**	99	7		**22g**[a]	50
2		**22b**	75				
3		**22c**	79	8		**22h**	72
4		**22d**	55[a]	9		**22i**[a]	52
5		**22e**	67	10		**22j**[b,c]	0
6		**22f**	53	11		**22k**[b,d]	0
				12		**22l**[b,d]	0

Conditions: biaryl (0.13 mmol), $FeCl_3$ (5 mol%) in dichloroethane (0.1M), rt, 1-12h; [a] reaction heated to 50ºC. [b] only starting material observed by crude NMR after 24 h at room temperature. [c] only starting material and decomposition observed by crude NMR after 24 h at 80 ºC. [d] only starting material observed by crude NMR after 24 h at 80 ºC.

TABLE A.2. Evaluation of carbonyl functionalities for the iron(III)-catalyzed carbonyl-olefin metathesis.

Both ketone substrates (**22a** and **22c-i**) and aldehyde **22b** underwent carbonyl-olefin metathesis. However, carboxylic acid derivatives (**22j-l**) failed to undergo the iron(III) chloride catalyzed carbonyl-olefin metathesis reaction, presumably as a result of their decreased electrophilicity as compared to ketones and aldehydes. Further, the enhanced Lewis basicity of **22j-l** can further inhibit catalysis.

A.1.4 ^{18}O Labeling studies for benzaldehyde formation



^{18}O-(*Z*)-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (^{18}O-8): *para*-Toluenesulfonic acid monohydrate (10 mg, 50 □mol) was placed in a screw-cap vial and 1 mL of benzene was added, then removed by rotary evaporator. This was repeated twice and the resulting solid was dried under high vacuum for 3 h. Nominal (*Z*)-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (**8**) (100 mg, 0.34 mmol) was added to the vial and a 1:1 mixture of $H_2{}^{18}O$ and THF (1.2 mL) was added. The reaction was heated to 70 °C overnight. The reaction mixture was cooled to room temperature and EtOAc was added and the vial was capped and shaken. The layers were separated and the aqueous layer was washed with two additional portions of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporator to afford spectroscopically pure **^{18}O-8**. **HRMS**: calculated for $C_{22}H_{19}{}^{18}O$ ([M+H$^+$]$^+$): 301.1473 Found: 301.1475.

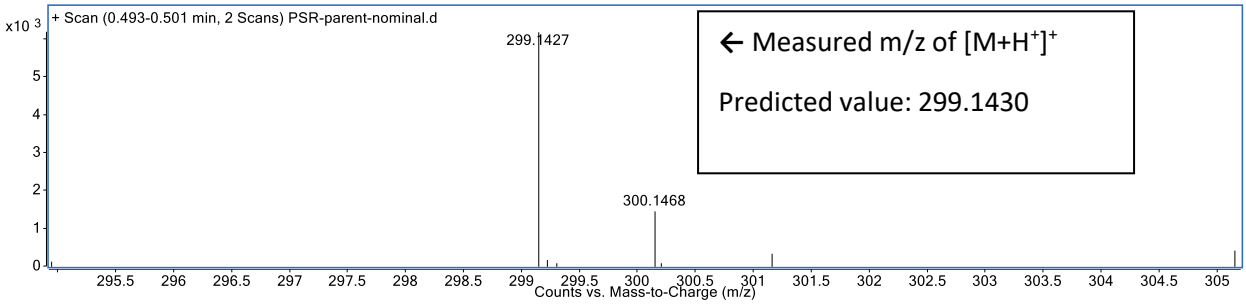


FIGURE A.1. HRMS for nominal **8**.

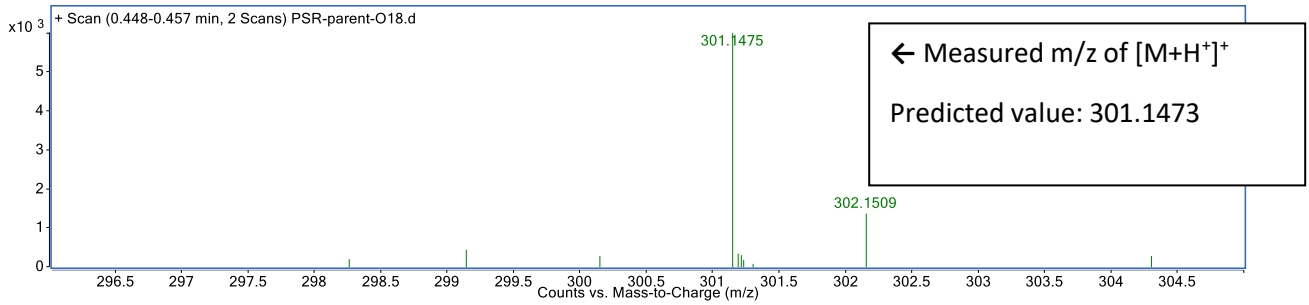
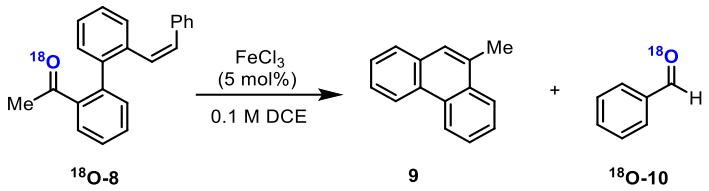


FIGURE A.2. HRMS for nominal **^{18}O-8**.



9-methylphenanthrene (9): The cyclization of **^{18}O-8** was performed on a 0.13 mmol scale with a total reaction time of 1 h according to the general procedure for carbonyl-olefin metathesis (Section 1.4.8). Purification by flash column chromatography eluting with hexanes/EtOAc provided 24 mg (96%) of **9** as a white solid. Before purification, an aliquot of the reaction mixture was removed and analyzed by HRMS and showed the formation of ^{18}O-benzaldehyde. **HRMS**: predicted for $C_7H_7{}^{18}O$ ([M+H+]+): 109.0534 Found: 109.0534.

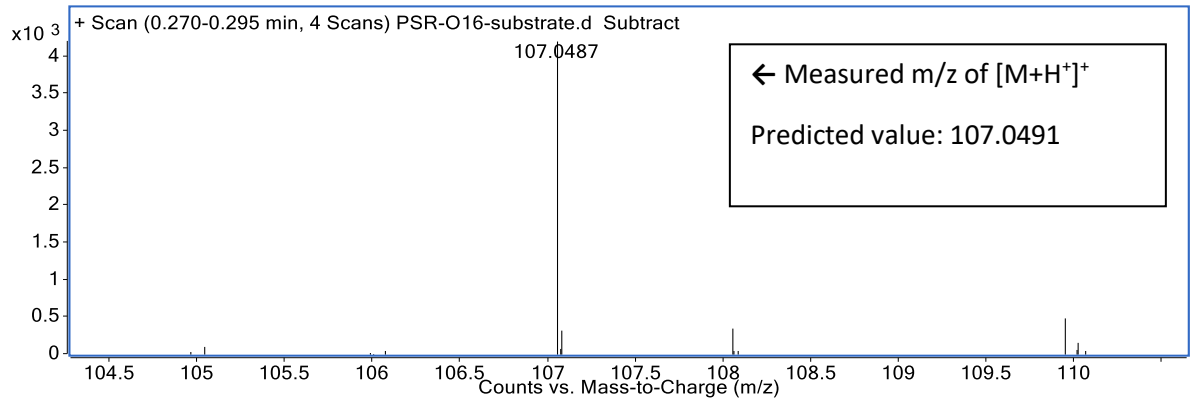


FIGURE A.3. HRMS for nominal **10** from carbonyl-olefin metathesis reaction of **8**:

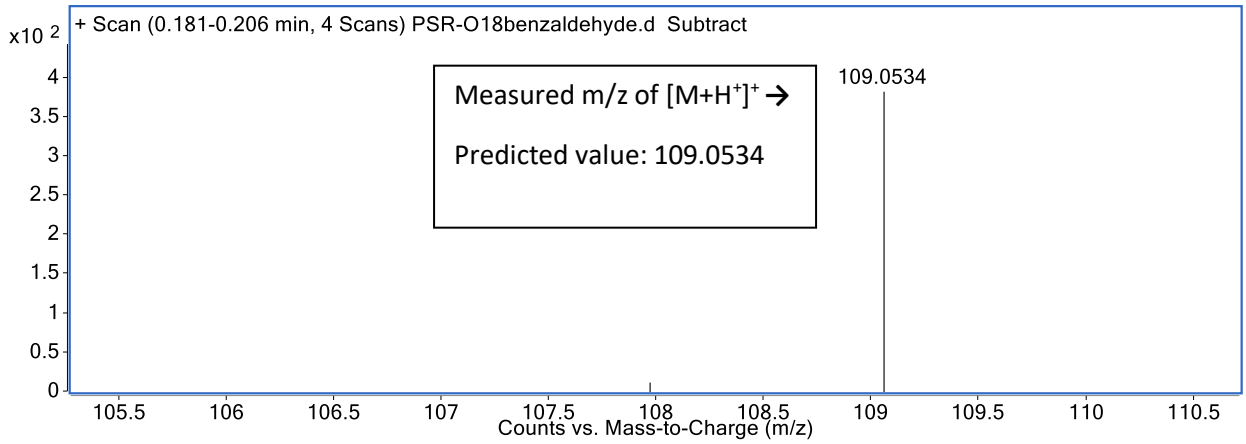
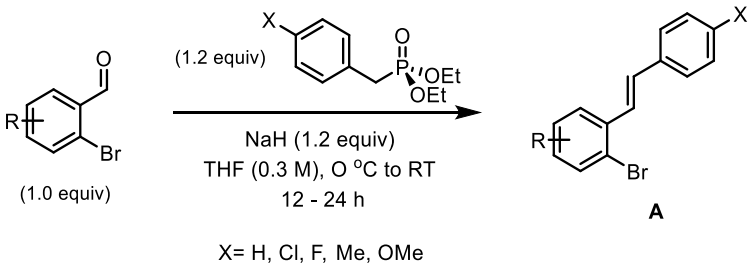


FIGURE A.4. HRMS for **^{18}O-10** from carbonyl-olefin metathesis reaction of **^{18}O-8**.

A.1.5 Synthesis of olefin starting materials

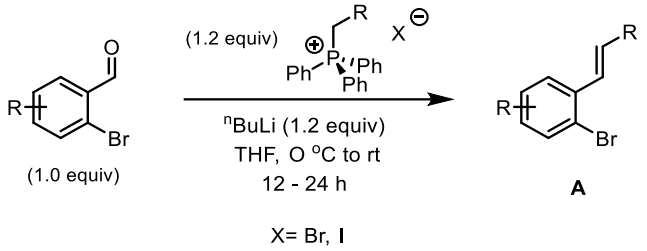
General olefination procedure A for substrate precursors (A):



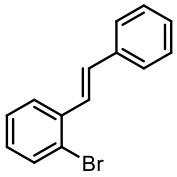
A 50 mL round bottom flask equipped with a magnetic stir bar was charged with diethyl benzylphosphonate (1.1 equiv) and dry THF (0.3 M). The solution was cooled to 0 °C with an ice bath followed by NaH addition (1.2 equiv). After stirring for 30 min at 0 °C the starting aryl aldehyde (1 equiv) was slowly added. The reaction was allowed to warm to room temperature and stirred until judged complete by TLC analysis (12-24 h). The reaction mixture was then cooled to 0 °C and quenched with aqueous ammonium chloride (n mL). The biphasic solution was extracted with ethyl acetate (3 × n mL). The combined organic phases were washed with brine (n mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* flash

column chromatography eluting with a mixture of hexanes and ethyl acetate to give the pure stilbene derivative (**A**).

General olefination procedure B for substrate precursors (A):

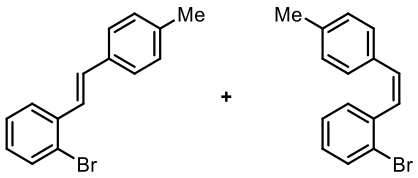


A 50 mL round bottom flask equipped with a magnetic stir bar was charged with Wittig salt (1.1 equiv) and dry THF (0.3 M). The solution was cooled to 0 °C with an ice bath followed by ^{n}BuLi addition (1.2 equiv). After stirring for 30 min at 0 °C the starting aryl aldehyde (1 equiv) was slowly added. The reaction was allowed to warm to room temperature and stirred until judged complete by TLC analysis (12-24 h). The reaction mixture was then cooled to 0 °C and quenched with aqueous ammonium chloride (n mL). The biphasic solution was extracted with ethyl acetate (3 × n mL). The combined organic phases were washed with brine (n mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography eluting with a mixture of hexanes and ethyl acetate to give the pure olefin (**A**).



(*E*)-1-bromo-2-styrylbenzene (A1): General olefination procedure **A** was followed employing 2-bromobenzaldehyde (54 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 12.71 g (91%) of **A1** as a clear oil. Spectroscopic data matched reported literature data.[25]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.63 – 7.51 (m, 3H), 7.47 (d, *J* = 16.2 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.27 (m,2H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 16.2 Hz, 1H).

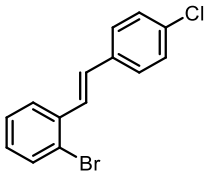


(*E*)-1-bromo-2-(4-methylstyryl)benzene + (*Z*)-1-bromo-2-(4-methylstyryl)benzene (*E*-A2 & *Z*-A2): General olefination procedure **A** was followed employing (2.72 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 218 mg (30%) of ***E*-A2** and 120 mg (16%) of ***Z*-A2** as a clear oil. Spectroscopic data matched reported literature data.[26] Spectral data for ***E*-A2.**

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 16.2 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.12 – 7.10 (m, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 2.38 (s, 3H).

Spectral data for ***Z*-A2**.

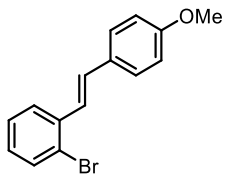
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.21 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.12 – 7.07 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.65 (d, *J* = 12.1 Hz, 1H), 6.56 (d, *J* = 12.1 Hz, 1H), 2.29 (s, 3H).



(*E*)-1-bromo-2-(4-chlorostyryl)benzene (A3): General olefination procedure **A** was followed (2.72 mmol scale). Purification by flash column chromatography eluting with hexanes/EtOAc

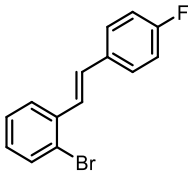
provided 425 mg (56%) of **A3** as a white powder. Spectroscopic data matched reported literature data.[27]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.42 (s, 1H), 7.33 (m, 3H), 7.15 – 7.11 (m, 1H), 6.98 (d, *J* = 16.2 Hz, 1H).



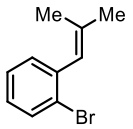
(*E*)-1-bromo-2-(4-methoxystyryl)benzene (A4): General olefination procedure **A** was followed (2.72 mmol scale). Purification by flash column chromatography eluting with hexanes/EtOAc provided 245 mg (31%) of **A4** as a white solid. Spectroscopic data matched reported literature data.[27]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.36 – 7.27 (m, 2H), 7.11 – 7.07 (m, 1H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 3H).



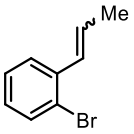
(*E*)-1-bromo-2-(4-fluorostyryl)benzene (A5): General olefination procedure **A** was followed (2.72 mmol scale). Purification by flash column chromatography eluting with hexanes/EtOAc provided 245 mg (53%) of **A5** as a clear oil. Spectroscopic data matched reported literature data.[27]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.39 (d, *J* = 16.2 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 16.2 Hz, 1H).



1-bromo-2-(2-methylprop-1-en-1-yl)benzene (A6): General olefination procedure **B** was followed employing 2-bromobenzaldehyde (12.4 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 2295 mg (89%) of **A6** as a clear oil. Spectroscopic data matched reported literature data.[28]

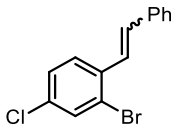
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.56 (m, 1H), 7.30 – 7.23 (m, 2H), 7.10 – 7.06 (m, 1H), 6.27 (s, 1H), 1.96 (s, 3H), 1.77 (s, 3H).



1-bromo-2-(prop-1-en-1-yl)benzene (A7): General olefination procedure **B** was followed employing ethyl triphenylphosphonium bromide (5.43 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 756 mg (71%) of **A7** as a *E/Z* (3:1) mixture, as a clear oil. Spectroscopic data matched reported literature data.[29]

1-bromo-2-vinylbenzene (A8): General olefination procedure **B** was followed employing 2-bromobenzaldehyde (7.07 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 890 mg (69%) of **A8** as a clear oil. Spectroscopic data matched reported literature data.[30]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.06 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.71 (d, *J* = 17.4 Hz, 1H), 5.37 (d, *J* = 10.9 Hz, 1H).



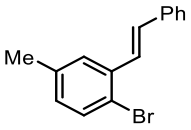
1-bromo-4-chloro-2-styrylbenzene (A9): General olefination procedure **A** was followed employing 2-bromo-5-chlorobenzaldehyde (2.62 mmol scale). Purification by flash column chromatography eluting with hexanes/EtOAc provided 395 mg (52%) of **A9** as an inseparable mixture of alkene isomers (3.88:1) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$;) δ 7.58 – 7.51 (m, 3H), 7.43 – 7.35 (m, 4H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 16.2 Hz, 1H), 6.88 – 6.84 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.66, 136.51, 134.04, 132.63, 128.88, 128.79, 128.60, 128.46, 128.32, 126.97, 126.49, 126.25.

IR (cm^{-1}): 2155.7, 1413.1, 1340.7, 1321.5, 1251.0, 1107.8, 1079.4, 1023.3, 954.9, 822.7, 803.5, 752.0, 684.7.

HRMS: Calculated for $C_{14}H_{10}BrCl^{+}$ ($[M]^{+}$): 291.9654 Found: 291.9659.



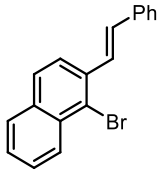
(*E*)-1-bromo-4-methyl-2-styrylbenzene (A10): General olefination procedure **A** was followed employing 2-bromo-5-methylbenzaldehyde (2.39 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 486 mg (74%) of **A10** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (t, *J* = 8.2 Hz, 1H), 7.48 – 7.34 (m, 1H), 7.32 – 7.24 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 2.34 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.34, 137.38, 1034.38, 133.65, 130.66, 128.92, 128.68, 128.08, 127.53, 126.94, 126.54, 124.15, 21.03.

IR (cm^{-1}): 3045.3, 1594.0, 1492.9, 1483.5, 1448.1, 1228.2, 1037.9, 965.2, 954.5, 811.6, 751.6, 705.3, 689.9.

HRMS: Calculated for $C_{15}H_{13}Br^{+}$ ($[M]^{+}$): 272.0201 Found: 272.0201.



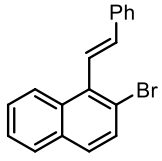
(*E*)-1-bromo-2-styrylnaphthalene (A11): General olefination procedure **A** was followed employing 1-bromo-2-naphthaldehyde (3.25 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 624 mg (62%) of **A11** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.5 Hz, 1H), 7.85 – 7.77 (m, 4H), 7.62 (d, *J* = 5.1 Hz, 2H), 7.60 – 7.58 (m, 1H), 7.53 – 7.49 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.36, 134.91, 134.11, 132.99, 132.35, 129.01, 128.80, 128.38, 128.29, 127.98, 127.97, 127.86, 127.12, 126.76, 124.41, 124.15.

IR (cm^{-1}): 3052.1, 1548.8, 1492.1, 1445.4, 1330.4, 1264.9, 1234.5, 958.3, 865.3, 804.5, 767.9, 738.5, 668.0, 657.0.

HRMS: Calculated for $C_{18}H_{13}Br^{+}$ ($[M]^{+}$): 308.0201 Found: 308.0196.



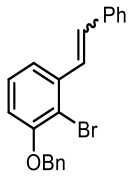
(*E*)-2-bromo-1-styrylnaphthalene (A12): General olefination procedure **A** was followed employing 2-bromo-1-naphthaldehyde[31] (2.98 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 818 mg (89%) of **A12** as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 7.86 – 7.81 (m, 1H), 7.69 – 7.59 (m, 4H), 7.54 – 7.47 (m, 2H), 7.43 (m, 2H), 7.35 (m, 2H), 6.89 (d, *J* = 16.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.10, 136.90, 135.67, 133.07, 133.02, 130.18, 129.00, 128.72, 128.57, 128.39, 127.08, 126.89, 126.39, 126.25, 126.17, 121.82.

IR (cm^{-1}): 3050.8, 2919.6, 1561.5, 1499.1, 1449.2, 1378.3, 1114.5, 967.9, 891.1, 820.5, 801.7, 744.6, 724.2, 687.9.

HRMS: Calculated for $C_{18}H_{13}Br^+$ ($[M]^+$): 308.0201 Found: 308.0196.



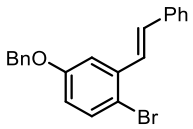
1-(benzyloxy)-2-bromo-3-styrylbenzene (A13): General olefination procedure **A** was followed employing 3-(benzyloxy)-2-bromobenzaldehyde[32] (1.0 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 156 mg (43%) of **A13** as an inseperable *E/Z* mixture (3.3:1), as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$; for major *E* isomer) δ 7.61 – 7.56 (m, 1H), 7.51 (dd, *J* = 17.6, 11.1 Hz, 2H), 7.46 – 7.28 (m, 4H), 7.27 – 7.22 (m, 1H), 7.21 – 7.12 (m, 3H), 7.10 – 6.98 (m, 1H), 6.90 – 6.77 (m, 2H), 6.75 – 6.61 (m, 1H), 5.19 (s, *J* = 8.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$; for the *E/Z* mixture) δ 155.30, 139.91, 138.93, 137.05, 136.59, 136.58, 136.38, 131.71, 131.20, 129.73, 129.05, 128.73, 128.58, 128.09, 128.06, 127.92, 127.85, 127.75, 127.53, 127.26, 127.03, 126.99, 126.87, 123.21, 119.23, 114.54, 113.96, 112.37, 112.05, 70.95, 70.88.

IR (cm^{-1}): 3024.3, 1588.2, 1561.4, 1494.5, 1446.0, 1425.9, 1378.1, 1289.7, 1267.4, 1054.9, 1026.8, 906.2, 772.9, 729.0, 691.5.

HRMS: Calculated for $C_{21}H_{18}BrO^+$ ($[M + H^-]^+$): 365.0536 Found: 365.0532.



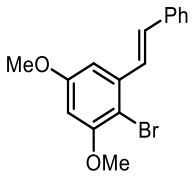
(*E*)-4-(benzyloxy)-1-bromo-2-styrylbenzene (A14): General olefination procedure **A** was followed employing 5-(benzyloxy)-2-bromobenzaldehyde[33] (2.84 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 1.04 g (67%) of **A14** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.25 (m, 11H), 6.99 (d, *J* = 16.2 Hz, 1H), 6.78 (dd, *J* = 8.8, 3.0 Hz, 1H), 5.10 (s, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 158.40, 138.13, 137.12, 136.77, 133.82, 131.80, 128.96, 128.89, 128.38, 128.36, 127.74, 127.66, 127.09, 116.00, 115.41, 113.22, 70.57.

IR (cm^{-1}): 1584.4, 1474.5, 1461.8, 1405.5, 1380.9, 12229.4, 1206.6, 1173.6, 1115.9, 1003.5, 955.8, 833.6, 823.0, 771.8, 739.7, 695.2, 657.9.

HRMS: Calculated for $C_{21}H_{18}BrO^{+}$ ($[M + H^{=}]^{+}$): 365.0536 Found: 365.0532.



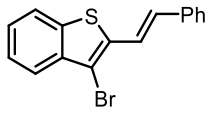
(*E*)-2-bromo-1,5-dimethoxy-3-styrylbenzene (A15): General olefination procedure **A** was followed employing 2-bromo-3,5-dimethoxybenzaldehyde[34] (3.60 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 1.15 g (64%) of **A15** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.51 (m, 3H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.27 (m,1H), 7.02 (d, *J* = 16.1 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 159.81, 157.09, 138.93, 137.15, 131.84, 128.94, 128.31, 128.19, 127.08, 105.34, 102.89, 99.29, 56.59, 55.81.

IR (cm^{-1}): 1580.5, 1446.0, 1414.7, 1349.9, 1282.6, 1204.5, 1165.4, 1070.5, 1019.7, 955.5, 822.8, 801.9, 750.1, 702.0, 688.7, 604.6.

HRMS: Calculated for $C_{16}H_{16}BrO_2^+$: 319.0328 Found: 319.0332.



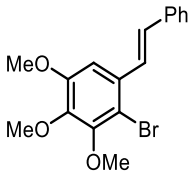
(*E*)-3-bromo-2-styrylbenzo[b]thiophene (A16): General olefination procedure **A** was followed employing 3-bromobenzo[b]thiophene-2-carbaldehyde (1.74 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 212 mg (67%) of **A16** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 16.1 Hz, 1H), 7.45 – 7.35 (m, 4H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 16.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.04, 137.45, 136.69, 136.58, 132.91, 129.05, 128.72, 127.08, 126.23, 125.46, 123.25, 122.50, 120.81, 108.77.

IR (cm^{-1}): 3023.3, 1488.7, 1430.0, 1318.0, 1295.4, 1253.9, 942.8, 921.8, 746.8, 721.8, 687.6.

HRMS: Calculated for $C_{21}H_{18}BrO^+$ ($[M]^+$): 313.9765 Found: 313.9760.



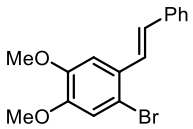
(*E*)-2-bromo-3,4,5-trimethoxy-1-styrylbenzene (A17): General olefination procedure **A** was followed employing 2-bromo-3,4,5-trimethoxybenzaldehyde[35] (3.64 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 1.27 g (51%) of **A17** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 16.1 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 6.94 (d, *J* = 16.1 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 153.03, 151.20, 143.13, 137.20, 133.06, 130.94, 128.96, 128.22, 127.91, 126.97, 111.38, 105.45, 61.44, 61.17, 56.44.

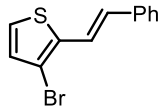
IR (cm^{-1}): 1479.0, 1447.6, 1422.3, 1388.8, 1345.6, 1238.2, 1207.8, 1166.3, 1104.4, 1050.5, 1005.8, 987.7, 957.8, 927.8, 862.4, 816.4, 752.4, 694.9.

HRMS: Calculated for $C_{17}H_{18}BrO_3^+$: 349.0434 Found: 349.0437.



(*E*)-1-bromo-4,5-dimethoxy-2-styrylbenzene (A18): General olefination procedure **A** was followed employing 2-bromo-4,5-dimethoxybenzaldehyde (2.09 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 601 mg (90%) of **A18** as a white solid. Spectroscopic data matched reported literature data.[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.5 Hz, 2H), 7.38 (m, 3H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.16 (s, 1H), 7.05 (s, 1H), 6.93 (d, *J* = 16.2 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H).



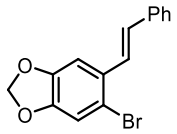
(*E*)-3-bromo-2-styrylthiophene (A19): General olefination procedure **A** was followed (3.85 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 652 mg (64%) of **A19** as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 6.0 Hz, 1H), 7.17 (d, *J* = 5.3 Hz, 1H), 6.99 (d, *J* = 4.3 Hz, 1H), 6.97 (d, *J* = 6.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.43, 136.84, 131.01, 130.51, 128.98, 128.30, 126.80, 124.13, 120.31, 111.13.

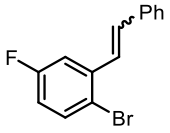
IR (cm^{-1}): 3103.2, 3023.1, 1504.2, 1487.7, 1429.8, 1146.7, 952.6, 882.9, 838.1, 751.3, 707.3, 688.2.

HRMS: Calculated for $C_{12}H_9BrS^+$ ($[M]^+$): 263.9603 Found: 263.9608.



(*E*)-5-bromo-6-styrylbenzo[d][1,3]dioxole (A20): General olefination procedure **A** was followed employing 6-bromobenzo[d][1,3]dioxole-5-carbaldehyde (2.95 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 728 mg (82%) of **A20** as a white solid. Spectroscopic data matched reported literature data .[37]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5 Hz, 2H), 7.38 (m, 2H), 7.31 – 7.24 (m, 2H), 7.15 (s, 1H), 7.04 (s, 1H), 6.89 (d, *J* = 16.1 Hz, 1H), 6.00 (s, 2H).



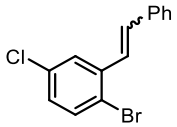
1-bromo-4-fluoro-2-styrylbenzene (A21): General olefination procedure **A** was followed employing 2-bromo-5-fluorobenzaldehyde (2.4 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 365 mg (55%) of **A21** as an inseparable mixture of alkene isomers (6.25:1) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$; for major *E* isomer) δ 77.61 (d, *J* = 2.4 Hz, 1H), 77.53 (d, *J* = 7.6 Hz, 2H), 77.48 (d, *J* = 8.5 Hz, 1H), 77.36 (dd, *J* = 15.3, 7.1 Hz, 3H), 77.29 (t, *J* = 7.3 Hz, 1H), 77.07 (dd, *J* = 8.6, 2.5 Hz, 1H), 77.01 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$ for major *E* isomer) δ 162.11 (d, *J*= 245.0), 138.7 (d, J= 8.7), 136.51, 134.17 (d, *J*= 8.7), 132.54, 128.79 128.43, 126.96, 126.57 (d, *J*= 2.5), 115.95 (d, *J*= 23.0), 113.24 (*J*= 23.5).

IR (cm^{-1}): 3024.0, 1599.1, 1571.3, 1457.9, 1410.0, 1255.6, 1159.6, 1027.7, 956.7, 746.6, 695.5, 596.0.

HRMS: Calculated for $C_{14}H_{10}BrF^+$ ($[M]^+$): 275.9950 Found: 275.9949.



2-bromo-4-chloro-1-styrylbenzene (A22): General olefination procedure **A** was followed employing 2-bromo-4-chlorobenzaldehyde (2.39 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 357 mg (52%) as an inseparable mixture of alkene isomers (3.86:1) of **A22** as clear crystals.

^{1}H NMR (500 MHz, $CDCl_3$; for the mixture of isomers) δ 7.64 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 2.05H), 7.53 – 7.48 (m, 1.11H), 7.38 (m, 3.08H), 7.32 (t, *J* = 7.3 Hz, 1.07H), 7.26 – 7.19 (m, 0.79H), 7.14 (m, 0.75H), 7.11 – 7.08 (m, 1.11H), 7.04 (d, *J* = 16.2 Hz, 1.28H), 6.72 (d, *J* = 12.1 Hz, 0.31H), 6.53 (d, *J* = 12.1 Hz, 0.31H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.93, 135.98, 133.78, 132.82, 132.17, 129.01, 128.53, 128.09, 127.50, 127.09, 126.51, 124.35.

IR (cm^{-1}): 3058.2, 1600.4, 1495.6, 1412.0, 1319.7, 1277.8, 1249.3, 1151.6, 1107.4, 1078.1, 1221.3, 954.4, 922.2, 822.2, 751.6, 709.9, 684.1.

HRMS: Calculated for $C_{14}H_{10}BrCl^+$ ($[M]^+$): 291.9654 found: 291.9659.

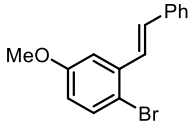
1-bromo-2-styryl-4-(trifluoromethyl)benzene (A23): General olefination procedure **A** was followed employing 2-bromo-5-(trifluoromethyl)benzaldehyde (2.39 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 249 mg (32%) of **A23** as an inseparable mixture of alkene isomers (6.25:1) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$; for major *E* isomer) δ 7.89 (s, 1H), 7.73 – 7.69 (m, 1H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 16.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.14 – 7.09 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$; for major *E* isomer) δ 138.01, 136.37, 133.65, 133.16, 130.15 (q, *J*= 33.7), 128.83, 128.60, 127.01, 126.11, 124.95 (q, *J*= 3.7), 123.38 (q, *J*= 3.7).

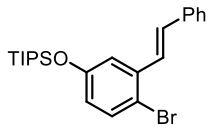
IR (cm^{-1}): 3058.2, 1631.2, 1600.4, 1495.6, 1412.0, 1319.7, 1277.8, 1249.3, 1151.6, 1107.4, 954.4, 751.6.

HRMS: Calculated for $C_{15}H_{10}BrF_3^+$ ($[M]^+$): 325.9918 found: 325.9925



(*E*)-1-bromo-4-methoxy-2-styrylbenzene (A24): General olefination procedure **A** was followed employing 2-bromo-5-methoxybenzaldehyde (2.39 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 549 mg (80%) of **A24** as a white solid. Spectroscopic data matched reported literature data.[38]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 2H), 7.49 – 7.36 (m, 4H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.85 (s, 3H



(*E*)-(4-bromo-3-styrylphenoxy)triisopropylsilane (A25): To a 50 mL round bottom flask equipped with a magnetic stir bar were added 2-bromo-5-hydroxy-benzaldehyde (500 mg, 2.49 mmol) and DMF (20 mL) at room temperature. To this reaction mixture was added imidazole (423 mg, 6.22 mmol) and triisopropylsilyl chloride (575 mg, 2.98 mmol). After 3 h, water was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude 2-bromo-5-((triisopropylsilyl)oxy)benzaldehyde (844 mg). The aldehyde was used without further purification.

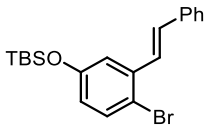
General olefination procedure **A** was followed employing 2-bromo-5-((triisopropylsilyl)oxy)benzaldehyde (1.69 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 325 mg (45%) of **A25** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.44 – 7.36 (m, 4H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 2.8 Hz, 1H), 6.97 (d, *J* = 16.2 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.8 Hz, 1H), 1.35 – 1.24 (m, 3H), 1.14 (d, *J* = 7.4 Hz, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.79, 138.05, 137.17, 133.71, 131.45, 128.93, 128.28, 127.80, 127.07, 120.96, 118.05, 115.44, 18.15, 12.88.

IR (cm^{-1}): 2942.9, 2865.3, 1586.6, 1461.3, 1403.9, 1291.0, 1173.6, 994.6, 958.6, 880.8, 826.4, 750.6, 720.2, 686.0, 434.1.

HRMS: Calculated for $C_{23}H_{31}BrOSi^+$ ($[M]^+$): 430.1328 found: 430.1326.



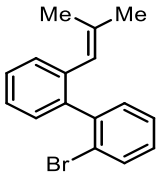
(*E*)-(4-bromo-3-styrylphenoxy)(tert-butyl)dimethylsilane (A26): General olefination procedure A was followed employing 2-bromo-5-((tert-butyldimethylsilyl)oxy)benzaldehyde[39] (1.90 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 385 mg (52%) of **A26** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.40 (m, 4H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.13 (s, *J* = 2.1 Hz, 1H), 6.97 (d, *J* = 16.2 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 1.01 (s, 9H), 0.23 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.40, 138.18, 137.17, 133.77, 131.57, 128.94, 128.30, 127.74, 127.08, 121.21, 118.34, 115.87, 25.91, 18.46, -4.15.

IR (cm^{-1}): 2927.6, 2856.0, 1586.6, 1560.2, 1461.7, 1289.8, 1253.2, 1172.3, 993.4, 958.5, 860.6, 836.0, 779.8, 750.1.

HRMS: Calculated for $C_{20}H_{25}BrOSi^{+}$ ($[M]^{+}$): 388.0858 found: 388.0864.



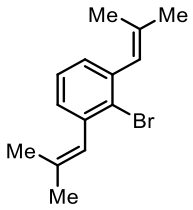
2-bromo-2'-(2-methylprop-1-en-1-yl)-1,1'-biphenyl (A27): General olefination procedure **A** was followed employing 2'-bromo-[1,1'-biphenyl]-2-carbaldehyde[40] (2.68 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 414 mg (54%) of **A27** as a clear oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.38 – 7.27 (m, 5H), 7.23 – 7.11 (m, 3H), 5.87 (s, 1H), 1.75 (s, *J* = 0.6 Hz, 3H), 1.71 (s, *J* = 1.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.42, 140.54, 137.34, 135.61, 132.46, 131.37, 129.63, 129.53, 128.46, 127.35, 126.81, 125.80, 123.82, 123.80, 26.20, 19.42.

IR (cm^{-1}): 2907.1, 1462.9, 1440.1, 1375.1, 1223.9, 1003.6, 827.6, 748.1, 699.7, 661.6, 617.1.

HRMS: Calculated for $C_{16}H_{15}Br^+$ ($[M]^+$): 286.0357 found: 286.0359



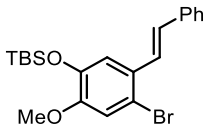
2-bromo-1,3-bis(2-methylprop-1-en-1-yl)benzene (A28): General olefination procedure **B** was followed employing 2-bromoisophthalaldehyde (0.8 mmol) and isopropyltriphenylphosphonium iodide (2.2 equiv) Purification by flash column chromatography eluting with hexanes/EtOAc provided 157 mg (74%) of **A28** as a clear oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 1H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.27 (s, 2H), 1.93 (s, *J* = 1.4 Hz, 6H), 1.74 (s, *J* = 1.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.01, 135.89, 128.76, 126.21, 125.86, 125.56, 26.07, 19.34.

IR (cm^{-1}): 2922.0, 1977.4, 1494.8, 1375.9, 1184.6, 1020.9, 905.1, 727.0.

HRMS: Calculated for $C_{14}H_{17}Br^+$ ($[M]^+$): 264.0514 found: 264.0512.



(*E*)-(4-bromo-2-methoxy-5-styrylphenoxy)(tert-butyl)dimethylsilane (A29): To a 100 mL round bottom flask equipped with a magnetic stir bar were added 2-bromo-5-hydroxy-4-methoxy-benzaldehyde (1500 mg, 6.49 mmol) and DCM (40 mL) at room temperature. To this reaction mixture was added imidazole (884 mg, 13.0 mmol) and TBSCl (1468 mg, 9.74 mmol). After 5 h,

water was added and the mixture was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude 2-bromo-5-[tert-butyl(dimethyl)silyl]oxy-4-methoxy-benzaldehyde. Purification by flash column chromatography eluting with hexanes/EtOAc provided 1592 mg (71%) of 2-bromo-5-[tert-butyl(dimethyl)silyl]oxy-4-methoxy-benzaldehyde as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.39 (s, 1H), 7.04 (s, 1H), 3.89 (s, 3H), 0.99 (s, 9H), 0.16 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 190.96, 156.94, 145.20, 126.98, 120.71, 120.62, 116.24, 56.16, 25.81, 18.62, -4.42.

IR (cm^{-1}): 2929.0, 2856.3, 1683.2, 1587.6, 1498.5, 1438.0, 1275.7, 1251.6, 1213.8, 1155.4, 1026.3, 855.0, 836.4, 780.8.

HRMS: Calculated for $C_{14}H_{21}O_3BrSi^+$ ($[M + H^+]^+$): 345.0516 found: 345.0516.

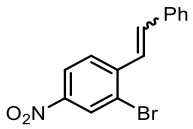
(*E*)-(4-bromo-2-methoxy-5-styrylphenoxy)(tert-butyl)dimethylsilane was prepared according to general olefination procedure **A** employing 2-bromo-5-[tert-butyl(dimethyl)silyl]oxy-4-methoxy-benzaldehyde (4.05 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 1100 mg (65%) of **A29** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 2H), 7.36 (m, 3H), 7.28 – 7.24 (m, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 6.86 (d, *J* = 16.1 Hz, 1H), 3.82 (s, 3H), 1.02 (s, 9H), 0.18 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.51, 144.87, 137.50, 129.77, 129.59, 128.88, 127.88, 127.34, 126.83, 118.49, 116.25, 115.77, 55.88, 25.94, 18.70, -4.37.

IR (cm^{-1}): 2955.1, 2925.7, 2853.4, 1592.7, 1499.9, 1436.4, 1389.1, 1272.9, 1249.7, 1167.8, 1032.4, 956.6, 862.4, 832.1, 783.1, 794.3.

HRMS: Calculated for $C_{21}H_{27}O_2BrSi^+$ ($[M]^+$): 418.0964 found: 418.0955.



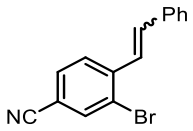
2-bromo-4-nitro-1-styrylbenzene (A30): General olefination procedure **B** was followed employing 2-bromo-4-nitrobenzaldehyde (2.17 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 485 mg (73%) as an inseparable mixture of alkene isomers (2.0:1.0) of **A30** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$; for *E*/*Z* mixture) δ 8.50 (m, 1.12H), 8.19 (dd, *J* = 8.7, 2.2 Hz, 0.33H), 7.94 (dd, *J* = 8.6, 2.2 Hz, 0.91H), 7.84 (d, *J* = 8.7 Hz, 0.36H), 7.61 (d, *J* = 7.3 Hz, 0.78H), 7.50 (d, *J* = 16.2 Hz, 0.50H), 7.44 (t, *J* = 7.4 Hz, 0.73H), 7.38 (t, *J* = 7.3 Hz, 0.39H), 7.33 (d, *J* = 8.6 Hz, 0.95H), 7.26 – 7.21 (m, 3.30H), 7.13 (m, 1.92H), 6.89 (d, *J* = 12.1 Hz, 1H), 6.63 (d, *J* = 12.1 Hz, 0.96H).

^{13}C NMR (125 MHz, $cdcl_3$; for *E*/*Z* mixture) δ 147.16, 146.96, 145.13, 143.77, 136.20, 135.81, 135.55, 134.54, 131.56, 129.45, 129.16, 128.73, 128.67, 128.36, 128.23, 127.90, 127.54, 126.83, 125.66, 124.36, 123.90, 122.76, 122.12.

IR (cm^{-1}): 3022.7, 2853.5, 1625.9, 1579.7, 1515.1, 1492.4, 1339.5, 1265.9, 1113.9, 1035.8, 892.4, 863.2, 771.0, 726.5, 695.4.

HRMS: Calculated for $C_{14}H_{10}BrNO_2^+$ ($[M]^+$): 302.9895 found: 302.9898.



3-bromo-4-styrylbenzonitrile (A31): General olefination procedure **A** was followed employing 3-bromo-4-formylbenzonitrile[41] (3.33 mmol). Purification by flash column chromatography afforded 200 mg (21% yield) of an *E/Z* mixture (1.5:1.0) of the title compound as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$, for *E/Z* mixture) δ 7.93 (d, *J* = 1.6 Hz, 1.5H), 7.72 (d, *J* = 8.3 Hz, 0.8H), 7.71 (d, *J* = 8.3 Hz, 1.5H), 7.57 (d, *J* = 7.5 Hz, 3.2H), 7.41 (t, *J* = 6.7 Hz, 25H), 7.39 – 7.32 (m, 4.7H), 7.24 – 7.20 (m, 2.6H), 7.11 – 7.06 (m,3.4H), 6.81 (d, *J* = 12.0 Hz, 1H), 6.54 (d, *J* = 12.1 Hz, 1H).

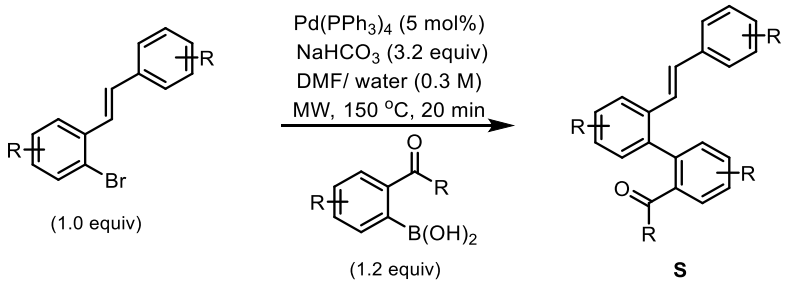
^{13}C NMR (176 MHz, $CDCl_3$, for *E/Z* mixture) δ 139.77, 138.93, 136.26, 135.37, 134.35, 134.30, 134.09, 134.00, 133.71, 131.55, 131.23, 130.23, 129.67, 129.14, 129.08, 129.06, 128.99, 128.73, 128.31, 127.45, 127.29, 125.50, 118.30, 118.11, 112.06, 111.39.

IR (cm^{-1}): 2229.4, 1467.2, 1222.9, 1156.4, 818.0, 754.5, 688.0, 607.3.

HRMS: calculated for $C_{15}H_{10}BrN^+$ ([M^+]): 282.9997 Found: 282.9986.

A.1.6 Synthesis of biaryl metathesis substrates

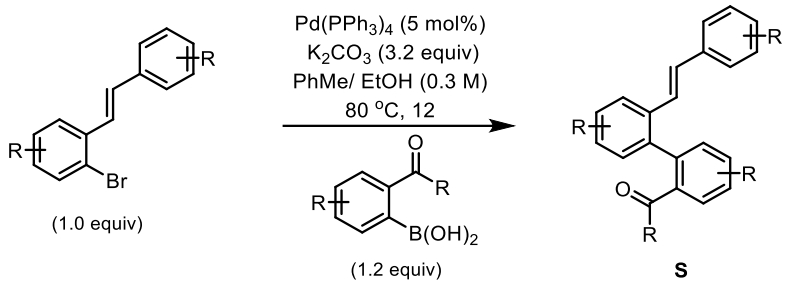
General cross-coupling procedure A for metathesis substrates (S):



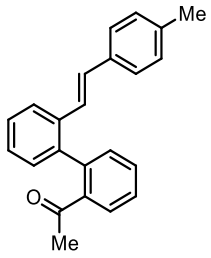
Procedure adopted from van der Eycken et al.[42] To a Chemglass microwave vial equipped with a magnetic stir bar were added 2-bromo-aryl styrene (1.0 equiv), $NaHCO_3$ (3.2 equiv), aryl

boronic acid (1.2 equiv), and $Pd(PPh_3)_4$ (5 mol%). A solution of DMF/ water (0.3 M; 1:1) was then added and the vial sealed. The vial was heated under microwave irradiation (150 ^oC, 20 min) at atmospheric pressure. After the reaction was allowed to cool to room temperature, it was diluted with ethyl acetate (n mL) and washed with water (3 × n mL) and brine (1 × n mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography eluting with a mixture of hexanes and ethyl acetate to give the pure coupled product (**S**).

General cross-coupling procedure B for metathesis substrates (S):



To a Chemglass reaction tube equipped with a magnetic stir bar were added aryl bromide (1.0 equiv), K_sCO_3 (3.2 equiv), aryl boronic acid (1.2 equiv), and $Pd(PPh_3)_4$ (5 mol%). A solution of toluene/ ethanol (0.3 M; 1:1) was then added and the vial sealed. The reaction was heated to 80 ^oC for 12 h. After the reaction was allowed to cool to room temperature, it was diluted with ethyl acetate (15 mL) and washed with water (3 × n mL) and brine (1 × n mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography eluting with a mixture of hexanes and ethyl acetate to give the pure cross coupled product (**S**).

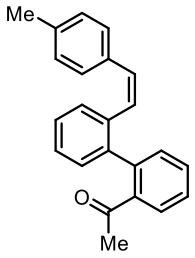


(*E*)-1-(2'-(4-methylstyryl)-[1,1'-biphenyl]-2-yl)ethan-1-one (12): Prepared according to general cross coupling procedure **A** between ***E*-A2** (0.55 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 109 mg (64% yield) of **12** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 6.9 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 8.7 Hz, 3H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.83 (d, *J* = 16.2 Hz, 1H), 2.32 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.93, 141.08, 140.03, 139.88, 137.88, 136.00, 134.73, 131.72, 131.03, 130.62, 130.52, 129.57, 128.48, 128.44, 127.82, 127.59, 126.72, 125.72, 125.65, 29.94, 21.47.

HRMS: calculated for $C_{23}H_{20}ONa^+$ ($[M + Na^+]^+$): 335.1406 Found 335.1404.



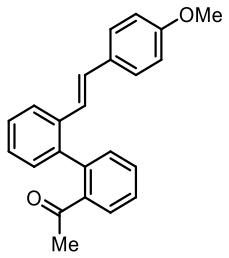
(*Z*)-1-(2'-(4-methylstyryl)-[1,1'-biphenyl]-2-yl)ethan-1-one (13): Prepared according to general cross coupling procedure **A** between ***Z*-A2** (0.40 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 61 mg (49% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.27 (s, *J* = 4.7 Hz, 2H), 7.23 – 7.15 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.41 (d, *J* = 12.3 Hz, 1H), 6.16 (d, *J* = 12.2 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.84, 140.64, 140.14, 137.31, 136.08, 133.99, 131.54, 130.95, 130.88, 130.21, 129.70, 129.55, 129.12, 128.98, 128.44, 128.12, 127.64, 127.60, 126.70, 29.66, 21.47.

IR (cm^{-1}): 3059.2, 3015.0, 2922.2, 1688.6, 1594.0, 1509.1, 1437.4, 1354.1, 1267.7, 1246.3, 908.5, 822.9, 761.0, 729.6.

HRMS: calculated for $C_{23}H_{20}ONa^+$ ($[M + Na^+]^+$): 335.1406 Found 335.1404.

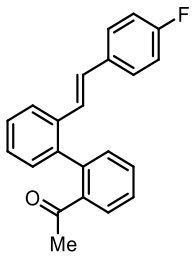


(*E*)-1-(2'-(4-methoxystyryl)-[1,1'-biphenyl]-2-yl)ethan-1-one (14): Prepared according to general cross coupling procedure **A** between **A4** (0.52 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 123 mg (72% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.27 – 7.23 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 16.2 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 16.2 Hz, 1H), 3.79 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.99, 159.58, 141.10, 139.92, 139.87, 136.11, 131.68, 131.03, 130.49, 130.33, 130.16, 128.47, 128.41, 128.02, 127.79, 127.40, 125.45, 124.55, 114.30, 55.51, 29.93.

HRMS: calculated for $C_{23}H_{24}O_2N^+$ ([M + NH_4^+]$^+$): 346.1802 Found 346.1801.



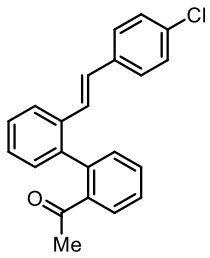
(*E*)-1-(2'-(4-fluorostyryl)-[1,1'-biphenyl]-2-yl)ethan-1-one (15): Prepared according to general cross coupling procedure **A** between **A5** (0.54 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 121 mg (71% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.29 – 7.24 (m, 3H), 7.21 (d, *J* = 7.5 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.77 (d, *J* = 16.2 Hz, 1H), 1.99 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.63, 162.33 (d, *J*= 247.4), 140.85, 139.91, 139.48, 135.47, 133.43 (d, *J*= 3.2), 131.39, 130.86, 130.24, 129.17, 128.28, 128.22, 128.08, 128.02, 127.63 (d, *J*= 11.0), 126.21 (d, *J*= 2.0), 125.36, 115.64, 115.47, 29.66.

IR (cm^{-1}): 3053.1, 1673.7, 1596.6, 1509.1, 1463.6, 1270.8, 1229.4, 1158.9, 973.8, 823.9, 759.7.

HRMS: calculated for $C_{22}H_{17}OFNa^+$ ([M + Na^+]$^+$): 339.1161 Found 339.1159.



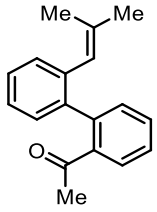
(*E*)-1-(2'-(4-chlorostyryl)-[1,1'-biphenyl]-2-yl)ethan-1-one (16): Prepared according to general cross coupling procedure **A** between **A3** (0.34 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 53 mg (47% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 6.9 Hz, 1H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.33 (m, 3H), 7.24 – 7.20 (m, 4H), 6.96 (d, *J* = 16.2 Hz, 1H), 6.82 (d, *J* = 16.2 Hz, 1H), 2.00 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.79, 141.07, 140.27, 139.64, 135.98, 135.54, 133.51, 131.64, 131.11, 130.49, 129.31, 129.01, 128.53, 128.47, 128.01, 127.96, 127.93, 127.30, 125.68, 29.89.

IR (cm^{-1}): 3054.0, 2249.2, 1683.6, 1491.5, 1354.4, 1245.4, 1088.2, 905.7, 812.3, 726.2, 430.0.

HRMS: calculated for $C_{22}H_{21}OClN^+$ ($[M + NH_4^+]^+$): 350.1306 Found 350.1305.



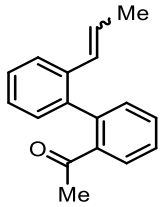
1-(2'-(2-methylprop-1-en-1-yl)-[1,1'-biphenyl]-2-yl)ethan-1-one (17): Prepared according to general cross coupling procedure **B** between **A6** (2.15 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 335 mg (62% yield) of the title compound as a clear oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.39 (td, *J* = 7.6, 1.1 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.31 – 7.26 (m, 2H), 7.26 – 7.21 (m, 2H), 5.79 (s, 1H), 1.97 (s, 3H), 1.75 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 202.47, 140.81, 140.60, 140.55, 137.19, 136.43, 131.33, 130.91, 130.12, 129.81, 128.13, 127.64, 127.44, 126.71, 124.44, 29.56, 26.46, 19.37.

IR (cm^{-1}): 2972.3, 2907.9, 1682.9, 1593.5, 1436.2, 1375.8, 1351.9, 1263.1, 1243.9, 1233.4, 952.9, 830.8, 750.2, 593.4.

HRMS: calculated for $C_{18}H_{18}ONa^+$ ($[M + Na^+]^+$): 250.1358 Found 250.1354.



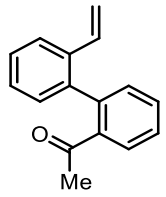
1-(2'-(prop-1-en-1-yl)-[1,1'-biphenyl]-2-yl)ethan-1-one (18): Prepared according to general cross coupling procedure **A** between **A7** (0.76 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 105 mg (58% yield) of the title compound as a clear oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 10.1, 5.0 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.2 Hz, 0.5H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.51 (td, *J* = 7.4, 1.2 Hz, 1H), 7.50 – 7.47 (m, 0.5H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41 (td, *J* = 7.6, 1.2 Hz, 0.5H), 7.39 – 7.36 (m, 1H), 7.34 (td, *J* = 7.7, 1.3 Hz, 1H), 7.32 – 7.29 (m, 0.5H), 7.28 – 7.22 (m, 3H), 7.14 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.18 – 6.10 (m, 2H), 6.05 (dd, *J* = 11.5, 1.8 Hz, 0.5H), 5.67 (dq, *J* = 11.6, 7.1 Hz, 0.5H), 1.98 (s, 1.5H), 1.95 (s, 3H), 1.80 (dd, *J* = 7.1, 1.8 Hz, 3H), 1.75 (d, *J* = 4.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.18, 202.85, 141.04, 140.79, 140.77, 140.43, 140.22, 139.20, 136.60, 136.00, 131.58, 131.39, 131.06, 131.01, 130.30, 130.04, 129.88, 129.09, 129.02, 128.45, 128.41, 128.34, 128.09, 127.95, 127.72, 127.71, 127.68, 127.21, 127.07, 125.76, 29.94, 29.78, 18.97, 14.58.

IR (cm^{-1}): 3018.0, 2362.3, 1681.9, 1593.2, 1468.3, 1435.6, 1352.5, 1263.7, 1232.9, 964.2, 749.8, 593.8.

HRMS: calculated for $C_{17}H_{17}O^+$ ($[M + H^+]^+$): 237.1274 Found 237.1278.



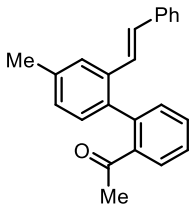
1-(2'-vinyl-[1,1'-biphenyl]-2-yl)ethan-1-one (19): Prepared according to general cross coupling procedure **A** between **A8** (0.82 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 42 mg (23% yield) of the title compound as a clear oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.51 (td, *J* = 7.5, 1.3 Hz, 1H), 7.44 (tt, *J* = 7.7, 3.9 Hz, 1H), 7.39 (dt, *J* = 7.5, 3.6 Hz, 1H), 7.31 (td, *J* = 7.5, 1.1 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.17 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.49 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.68 (dd, *J* = 17.4, 0.7 Hz, 1H), 5.17 (dd, *J* = 11.0, 0.8 Hz, 1H), 1.97 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 203.03, 140.89, 139.89, 139.78, 136.22, 134.93, 131.51, 131.00, 130.24, 128.43, 128.42, 127.93, 127.80, 125.60, 115.90, 29.90.

IR (cm^{-1}): 3067.3, 2251.0, 1683.6, 1417.3, 1355.0, 1268.8, 1245.3, 907.4, 762.7, 726.7, 647.7, 459.0.

HRMS: calculated for $C_{25}H_{28}ON^+$ ([M + H^+]$^+$): 223.1117 Found 223.1121.



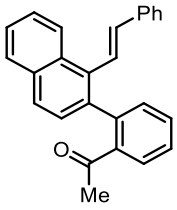
(*E*)-1-(4'-methyl-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S2): Prepared according to general cross coupling procedure **A** between **A10** (0.55 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 155 mg (90% yield) of the title compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.30 (m, 5H), 7.25 – 7.17 (m, 2H), 7.03 – 6.95 (m, 2H), 6.86 (d, *J* = 16.2 Hz, 1H), 2.38 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.83, 140.81, 139.85, 139.69, 137.45, 137.41, 132.77, 131.44, 130.89, 130.76, 129.45, 129.11, 128.57, 128.16, 127.53, 127.49, 126.44, 126.34, 125.37, 29.73, 21.13.

IR (cm^{-1}): 3021.1, 1680.3, 1594.6, 1353.5, 1266.4, 965.7, 812.8, 757.2, 730.6, 690.3, 595.0.

HRMS: calculated for $C_{23}H_{24}ON^+$ ([M + NH_4^+]$^+$): 330.1852 Found 300.1856.



(*E*)-1-(2-(1-styrylnaphthalen-2-yl)phenyl)ethan-1-one (S3): Prepared according to general cross coupling procedure **B** between **A12** (0.97 mmol) and 2-acetylphenylboronic acid.

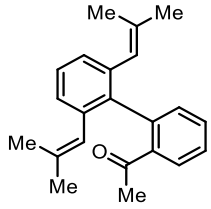
Purification by flash column chromatography eluting with hexanes/EtOAc afforded 154 mg (46% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 – 8.29 (m, 1H), 7.94 – 7.89 (m, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.40 (m, 3H), 7.34 – 7.29 (m, 4H), 7.28 – 7.22 (m, 1H), 7.17 (d, *J* = 16.6 Hz, 1H), 6.60 (d, *J* = 16.6 Hz, 1H), 2.06 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.30, 141.22, 140.55, 137.62, 137.51, 136.82, 133.57, 133.54, 131.97, 131.88, 131.12, 128.84, 128.67, 128.50, 128.07, 127.99, 127.67, 127.53, 126.75, 126.55, 126.22, 126.04, 125.42, 29.75.

IR (cm^{-1}): 3054.7, 1682.3, 1594.2, 1484.5, 1354.1, 1264.2, 1247.5, 969.2, 820.1, 732.6, 692.8, 597.0.

HRMS: calculated for $C_{26}H_{24}ON^{+}$ ($[M + NH_4^{+}]^{+}$): 366.1852 Found 366.1857.



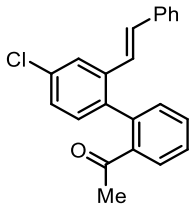
1-(2',6'-bis(2-methylprop-1-en-1-yl)-[1,1'-biphenyl]-2-yl)ethan-1-one (S4): Prepared according to general cross coupling procedure **B** between **A28** (0.97 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 154 mg (46% yield) of the title compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.67 (s, 2H), 1.93 (s, 3H), 1.75 (s, 6H), 1.66 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.37, 140.38, 139.87, 139.59, 137.34, 135.38, 131.61, 130.91, 128.32, 128.19, 127.23, 126.82, 124.97, 29.13, 26.40, 19.41.

IR (cm^{-1}): 2970.5, 2913.6, 2853.1, 1682.7, 1441.3, 1419.9, 1375.2, 1351.8, 1278.0, 1246.7, 847.0, 758.0, 730.9.

HRMS: calculated for $C_{22}H_{28}ON^+$ ($[M + NH_4^+]^+$): 322.2165 Found 322.2165



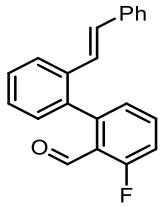
(*E*)-1-(4'-chloro-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S5): Prepared according to general cross coupling procedure **A** between **A22** (0.51 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 132 mg (78% yield) of the title compound as clear crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.28 (m, 6H), 7.23 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.77 (d, *J* = 16.2 Hz, 1H), 2.09 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.21, 140.74, 138.71, 138.65, 137.52, 136.99, 134.38, 131.80, 131.70, 131.58, 131.27, 128.90, 128.62, 128.30, 128.19, 127.65, 126.91, 125.58, 125.47, 29.87.

IR (cm^{-1}): 1687.6, 1595.8, 1468.8, 1354.6, 1264.0, 1094.4, 964.3, 909.7, 823.0, 731.0, 702.6, 595.2.

HRMS: calculated for $C_{22}H_{21}OClN^+$ ($[M + NH_4^+]^+$): 350.1306 Found 350.1311



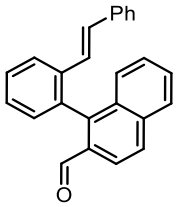
(*E*)-3-fluoro-2'-styryl-[1,1'-biphenyl]-2-carbaldehyde (S6): Prepared according to general cross coupling procedure **A** between 2-bromo-6-fluorobenzaldehyde (0.74 mmol) and (*E*)-(2-styrylphenyl)boronic acid.. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 153 mg (69% yield) of the title compound as a pale yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.63 – 7.59 (m, 1H), 7.47 (ddd, *J* = 8.0, 7.5, 0.8 Hz, 1H), 7.35 (td, *J* = 7.5, 1.1 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.25 – 7.20 (m, 3H), 7.17 – 7.14 (m, 1H), 7.04 (d, *J* = 16.2 Hz, 1H), 6.78 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 188.90, 162.45 (d, *J*= 263.5), 145.63, 137.01, 136.36 (d, J= 2.1), 136.20, 134.54 (d, *J*= 10.3), 131.09, 130.49, 128.78, 128.64, 127.90, 127.41 (d, *J*= 3.6), 127.35, 126.61, 125.94, 125.53, 123.17 (d, *J*= 6.8), 116.19 (d, *J*= 21.3).

IR (cm^{-1}): 3023.3, 2851.2, 1696.2, 1603.6, 1238.7, 1189.8, 962.0, 913.9, 798.5, 756.5, 735.3, 689.6.

HRMS: calculated for $C_{21}H_{15}OFNa^{+}$ ($[M + Na^{+}]^{+}$): 325.0999 Found 325.1003.



(*E*)-1-(2-styrylphenyl)-2-naphthaldehyde (S7): Prepared according to general cross coupling procedure **B** between 1-bromo-2-naphthaldehyde (1.28 mmol) and (*E*)-(2-styrylphenyl)boronic

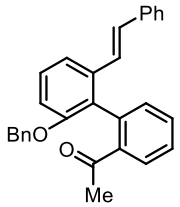
acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 322 mg (75% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.97 (m, 2H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.55 (m, 2H), 7.43 (dd, *J* = 18.1, 7.6 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 2H), 7.03 (d, *J* = 16.2 Hz, 1H), 6.51 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.53, 145.19, 137.52, 136.83, 136.12, 134.09, 132.46, 131.70, 131.57, 130.80, 128.95, 128.91, 128.63, 128.46, 128.28, 127.76, 127.66, 127.24, 127.12, 126.52, 125.83, 125.20, 122.09.

IR (cm^{-1}): 3057.1, 1688.0, 1594.3, 1493.6, 1429.1, 1379.3, 1330.2, 1264.0, 1239.8, 961.8, 821.6, 732.1, 691.0.

HRMS: calculated for $C_{25}H_{22}ON^{+}$ ($[M + NH_4^{+}]^{+}$): 357.1250 Found 357.1256.



(*E*)-1-(2'-(benzyloxy)-6'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S8): Prepared according to general cross coupling procedure **A** between **A13** (0..41 mmol) and 2-acetylphenylboronic acid.. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 62 mg (37% yield) of the title compound as a clear oil.

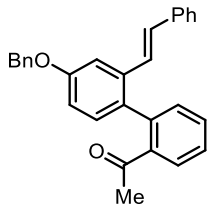
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.17 (m, 9H), 7.12 (d, *J* = 7.3

Hz, 2H), 7.00 (dd, *J* = 16.2, 1.8 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.76 (dd, *J* = 16.2, 2.3 Hz, 1H), 5.00 (s, 2H), 2.09 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.55, 155.74, 140.78, 137.50, 137.41, 137.27, 135.83, 132.53, 131.23, 130.54, 130.28, 128.93, 128.77, 128.53, 128.43, 127.81, 127.71, 127.68, 126.95, 126.76, 118.52, 111.87, 70.46, 29.19.

IR (cm^{-1}): 3024.3, 1683.0, 1596.4, 1569.1, 1451.0, 1263.4, 1057.4, 960.0, 786.9, 731.8, 692.0, 599.2.

HRMS: calculated for $C_{29}H_{28}O_2N^+$ ($[M + NH_4^+]^+$): 422.2115 Found 422.2119.



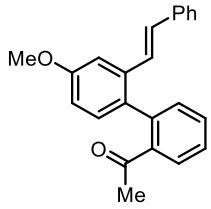
(*E*)-1-(4'-(benzyloxy)-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S9): Prepared according to general cross coupling procedure **A** between **A14** (2 x 211 mg, 0.58 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 63 mg (combined) (13% yield) of the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.19 (m, 14H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.04 – 6.91 (m, 2H), 6.86 (d, *J* = 16.2 Hz, 1H), 5.17 (s, 2H), 2.00 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.32, 159.01, 141.42, 139.40, 137.33, 137.04, 136.99, 133.10, 131.98, 131.71, 130.95, 130.87, 128.87, 128.85, 128.38, 128.34, 128.02, 127.86, 127.67, 126.83, 126.62, 114.39, 111.83, 70.43, 30.02.

IR (cm^{-1}): 1681.8, 1597.4, 1499.5, 1466.1, 1279.0, 1229.9, 1026.4, 996.6, 963.0, 756.3, 728.6.

HRMS: calculated for $C_{29}H_{28}O_2N^+$ ($[M + NH_4^+]^+$): 422.2115 Found: 422.2118.



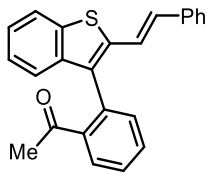
(*E*)-1-(4'-methoxy-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S10): Prepared according to general cross coupling procedure **A** between **A24** (150 mg, 0.52 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 128 mg (75% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.27 (m, 6H), 7.22 (t, *J* = 6.9 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 15.6, 9.4 Hz, 2H), 3.91 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.34, 159.79, 141.43, 139.45, 137.35, 136.97, 132.86, 132.01, 131.71, 130.94, 130.80, 128.86, 128.37, 128.01, 127.65, 126.84, 126.72, 113.70, 110.69, 55.62, 30.02.

IR (cm^{-1}): 2833.2, 1683.7, 1603.1, 1473.8, 1281.5, 1243.7, 1212.0, 1165.8, 1048.1, 971.0, 882.9, 809.2, 758.3, 728.1, 695.7, 596.6.

HRMS: calculated for $C_{23}H_{24}O_2N^+$ ($[M + NH_4^+]^+$): 346.1802 Found 346.1807..



(*E*)-1-(2-(2-styrylbenzo[b]thiophen-3-yl)phenyl)ethan-1-one (S11): Prepared according to general cross coupling procedure **A** between **A16** (100 mg, 0.32 mmol) and 2-acetylphenylboronic

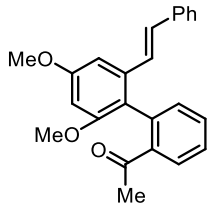
acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 98 mg (87% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.1 Hz, 3H), 7.31 (m, 4H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 16.0 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H), 1.97 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.64, 141.91, 140.73, 139.81, 138.00, 136.70, 134.49, 133.42, 132.37, 132.10, 131.68, 129.05, 128.92, 128.69, 128.41, 126.93, 125.70, 125.17, 122.93, 122.50, 120.61, 29.36.

IR (cm^{-1}**):** 1681.9, 1351.9, 1431.0, 1351.9, 1273.8, 1236.3, 948.9, 765.0, 752.0, 732.4, 689.5, 472.2.

HRMS: calculated for $C_{24}H_{22}ONS^+$ ($[M + NH_4^+]^+$): 372.1417 Found 372.1422.



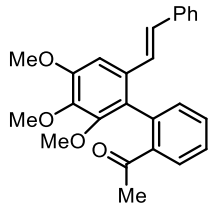
(*E*)-1-(2',4'-dimethoxy-6'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S12): Prepared according to General Cross Coupling Procedure A between **A15** (185 mg, 0.58 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 103 mg (50% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.27 (s, 1H), 7.23 – 7.14 (m, 2H), 6.99 (d, *J* = 16.2 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 16.2 Hz, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 3.93 (s, 3H), 3.69 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.20, 160.57, 157.84, 141.48, 137.76, 137.39, 135.32, 133.00, 131.06, 130.53, 128.81, 128.19, 127.91, 127.59, 127.18, 126.81, 122.48, 101.52, 98.34, 55.82, 55.64, 29.22.

IR (cm^{-1}): 1683.8, 1597.2, 1575.8, 1456.8, 1349.1, 1276.5, 1245.3, 1199.6, 1154.4, 1079.2, 1059.3, 960.3, 757.4, 736.8, 691.7.

HRMS: calculated for $C_{24}H_{23}O_3^+$ ($[M + H^+]^+$): 359.1642 Found: 359.1650.



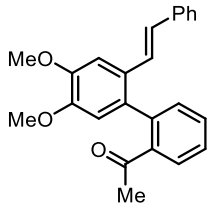
(*E*)-1-(2',3',4'-trimethoxy-6'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S13): Prepared according to General cross coupling procedure **A** between **A17** (150 mg, 0.43 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 70 mg (42% yield) of the title compound as a white solid.

^{1}H NMR (700 MHz, $CDCll_3$) δ 7.78 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.53 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (td, *J* = 7.6, 1.1 Hz, 1H), 7.30 – 7.23 (m, 5H), 7.20 (td, *J* = 5.8, 3.0 Hz, 1H), 7.05 (s, 1H), 6.89 (d, *J* = 16.1 Hz, 1H), 6.69 (d, *J* = 16.2 Hz, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.57 (s, 3H), 2.18 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.69, 153.45, 151.06, 142.23, 140.99, 137.45, 135.28, 132.74, 131.59, 131.03, 129.58, 128.82, 128.44, 127.78, 127.74, 126.94, 126.66, 104.29, 61.27, 60.74, 56.24, 29.22.

IR (cm^{-1}): 1687.8, 1591.3, 1475.8, 1400.5, 1345.5, 1235.2, 1094.3, 1003.1, 960.0, 753.0, 693.9.

HRMS: calculated for $C_{25}H_{22}O_4Na$ ($[M + Na^+]^+$): 411.1567 Found: 411.1572.



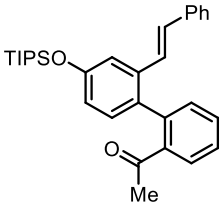
(*E*)-1-(4',5'-dimethoxy-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S14): Prepared according to general cross coupling procedure **A** between **A18** (150 mg, 0.47 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 121 mg (72% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.35 – 7.24 (m, 6H), 7.20 (t, *J* = 6.9 Hz, 1H), 6.93 (d, *J* = 16.2 Hz, 1H), 6.85 (d, *J* = 16.2 Hz, 1H), 6.69 (d, *J* = 2.7 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.49, 149.24, 148.95, 141.52, 139.36, 137.62, 132.94, 131.90, 130.92, 128.84, 128.65, 128.39, 128.32, 127.83, 127.67, 126.58, 126.47, 113.30, 108.02, 56.28, 56.23, 30.00.

IR (cm^{-1}): 3010.6, 1692.2, 1513.4, 1470.9, 1239.2, 1207.5, 1140.6, 1023.1, 947.6, 879.2, 831.6, 763.9, 751.9, 695.2.

HRMS: calculated for $C_{24}H_{26}O_3N^+$ ($[M + NH_4^+]^+$): 376.1807 Found 376.1899.



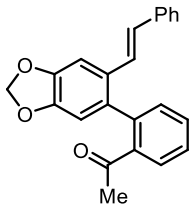
(*E*)-1-(2'-styryl-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-2-yl)ethan-1-one (S15): Prepared according to general cross coupling procedure **A** between **A25** (150 mg, 0.34 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 97 mg (59% yield) of the title compound as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.4, 1H), 7.42 (t, *J* = 7.5, 1H), 7.35 – 7.23 (m, 7H), 7.20 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.99 – 6.91 (m, 1H), 6.88 – 6.81 (m, 2H), 1.92 (s, 3H), 1.37 – 1.23 (m, 3H), 1.14 (d, *J* = 7.3 Hz, 18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.70, 156.47, 141.60, 139.47, 137.35, 136.96, 134.03, 133.84, 133.07, 131.89, 131.73, 130.86, 130.56, 128.90, 128.83, 128.72, 128.65, 128.35, 127.97, 127.62, 126.84, 126.66, 119.66, 116.79, 30.02, 18.18, 12.93.

IR (cm^{-1}): 2943.9, 2866.2, 1682.0, 1596.9, 1467.2, 1282.1, 1212.1, 994.9, 906.3, 881.8, 728.5, 689.4.

HRMS: calculated for $C_{31}H_{42}O_2NSi^+$ ($[M + NH_4^+]^+$): 488.2979 Found 488.2983.



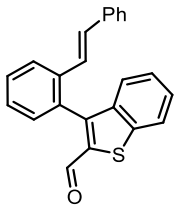
(*E*)-1-(2-(6-styrylbenzo[d][1,3]dioxol-5-yl)phenyl)ethan-1-one (S16): Prepared according to general cross coupling procedure **A** between **A20** (200 mg, 0.66 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 72 mg (32% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.29 (m, 6H), 7.25 – 7.16 (m, 1H), 6.90 (d, *J* = 16.1 Hz, 1H), 6.77 (d, *J* = 16.2 Hz, 1H), 6.70 (s, 1H), 6.06 (s, 2H), 2.10 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.84, 148.24, 147.49, 141.27, 139.46, 137.54, 134.34, 131.88, 131.09, 130.02, 128.84, 128.82, 128.40, 127.89, 127.69, 126.60, 126.38, 110.33, 105.16, 101.66, 29.95.

IR (cm^{-1}): 2889.6, 1681.7, 1474.4, 1234.7, 1206.7, 1037.8, 966.7, 935.8, 756.0, 725.0, 696.4, 590.7.

HRMS: calculated for $C_{23}H_{22}O_3N^+$ ($[M + NH_4^+]^+$): 360.1594 Found 360.1598



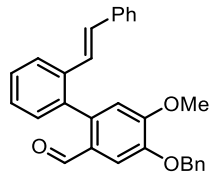
(E)-3-(2-styrylphenyl)benzo[b]thiophene-2-carbaldehyde (S17): Prepared according to general cross coupling procedure **B** between 3-bromobenzothiophene-2-carbaldehyde (1.24 mmol) and (*E*)-(2-styrylphenyl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 285 mg (67% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.50 (m, 3H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.38 (dd, *J* = 14.9, 7.6 Hz, 2H), 7.24 – 7.16 (m, 5H), 7.10 (d, *J* = 16.2 Hz, 1H), 6.78 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 185.95, 146.65, 141.94, 139.92, 139.72, 137.58, 137.02, 131.74, 131.36, 131.31, 129.67, 128.80, 128.68, 128.14, 127.70, 126.80, 126.00, 125.95, 125.93, 125.53, 123.49.

IR (cm^{-1}): 3025.1, 1661.9, 1520.2, 1346.8, 1264.3, 1208.4, 1168.7, 961.8, 905.7, 761.2, 726.7, 689.8, 664.2, 611.2.

HRMS: calculated for $C_{23}H_{16}OSNa^+$ ($[M + Na^+]^+$): 363.0814 Found 363.0819.



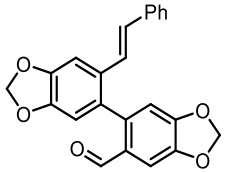
(*E*)-4-(benzyloxy)-5-methoxy-2'-styryl-[1,1'-biphenyl]-2-carbaldehyde (S18): Prepared according to general cross coupling procedure **B** between 5-(benzyloxy)-2-bromo-4-methoxybenzaldehyde[43] (300 mg, 0.93 mmol) and (*E*)-(2-styrylphenyl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 162 mg (41% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.63 (s, 1H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.28 (m, 4H), 7.24 – 7.19 (m, 1H), 7.04 (d, *J* = 16.2 Hz, 1H), 6.82 (m, 2H), 5.33 – 5.11 (m, 2H), 3.91 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 190.98, 154.12, 148.24, 140.21, 137.29, 137.07, 136.61, 136.53, 131.45, 130.92, 128.87, 128.79, 128.37, 128.06, 127.89, 127.84, 127.40, 126.80, 126.55, 125.56, 113.77, 110.51, 71.12, 56.52.

IR (cm^{-1}): 1671.5, 1588.0, 1506.0, 1346.7, 1277.6, 1236.2, 1134.6, 1013.9, 756.1, 746.0, 736.1, 691.6.

HRMS: calculated for $C_{29}H_{28}O_3N^+$ ($[M + NH_4^+]^+$): 438.2064 Found 438.2067.



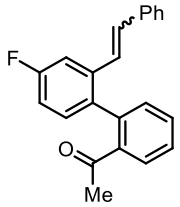
(*E*)-6'-styryl-[5,5'-bibenzo[d][1,3]dioxole]-6-carbaldehyde (S19): Prepared according to general cross coupling procedure **A** between **A20** (150 mg, 0.50 mmol) and (6-formylbenzo[d][1,3]dioxol-5-yl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 98 mg (53% yield) of the title compound as a white powder.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.47 – 7.46 (s, 1H), 7.31 – 7.17 (m, 6H), 6.90 (d, *J* = 16.1 Hz, 2H), 6.76 – 6.65 (m, 3H), 6.12 (d, *J* = 15.4 Hz, 2H), 6.05 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 190.53, 152.37, 148.54, 148.22, 147.32, 141.84, 137.35, 131.37, 130.54, 130.00, 129.35, 128.82, 127.86, 126.69, 126.10, 111.21, 110.98, 106.21, 105.00, 102.40, 101.78.

IR (cm^{-1}): 2848.0, 1681.7, 1609.3, 1497.5, 1473.2, 1421.6, 1346.5, 1243.8, 1208.0, 1036.4, 928.0, 874.1, 756.2, 691.9.

HRMS: calculated for $C_{23}H_{16}O_5Na^+$ ($[M + Na^+]^+$): 395.0890 Found 395.0894.



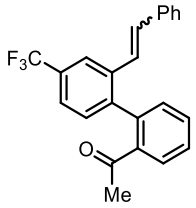
1-(4'-fluoro-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S20): Prepared according to general cross coupling procedure **A** between **A21** (150 mg, 0..54 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 81 mg (48% yield) as an *E/Z* mixture (3.33:1) of the title compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$; for major *E* isomer) δ 7.72 (d, *J* = 7.6 Hz, 1H), 7.54 (m,1H), 7.47 (m, 2H), 7.33 – 7.26 (m, 4H), 7.26 – 7.20 (m, 2H), 7.16 (m, 2H), 7.02 (m, 2H), 6.81 (d, *J* = 16.2 Hz, 1H), 2.06 (s, *J* = 4.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$; for major *E* isomer) δ 202.51, 162.93 (d, *J*= 245.0), 141.05, 138.82, 137.91 (d, *J*=7.5), 136.99, 132.02, 131.95, 131.88, 131.72, 131.19, 128.92, 128.56, 128.32, 128.09, 126.94, 125.75, 114.76 (d, *J*= 21.2), 112.06 (d, *J*= 22.5) 29.91.

IR (cm^{-1}): 3056.2, 1685.7, 1602.9, 1578.3, 1498.3, 1468.4, 1354.0, 1264.4, 1196.4, 1158.5, 961.6, 757.3, 731.2.

HRMS: calculated for $C_{22}H_{21}OFN^+$ ([M + NH_4^+]$^+$): 334.1632 Found 334.1604.



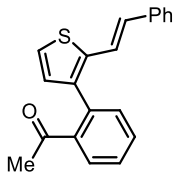
1-(2'-styryl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)ethan-1-one (S21): Prepared according to general cross coupling procedure **A** between **A23** (200 mg, 0.66 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 72 mg (32% yield) as an *E/Z* mixture (3.33:1.0) of the title compound as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$; for *E/Z* mixture) δ 7.99 (s, 1H), 7.78 (dt, *J* = 10.1, 0.96H), 7.76 – 7.72 (m, 0.28H), 7.61 – 7.56 (m, 1.89H), 7.55 – 7.51 (m, 1.45H), 7.51 – 7.44 (m, 0.60H), 7.32 (m, 5.89H), 7.27 – 7.16 (m, 2.62H), 7.07 (d, *J* = 16.2 Hz, 1H), 6.82 (d, *J* = 16.2 Hz, 0.30H), 6.51 (d, *J* = 12.2 Hz, 0.28H), 6.15 (d, *J* = 12.2 Hz, 1H), 2.32 (s, 0.79H), 2.17 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$, for *E* isomer) δ 201.21, 143.60, 139.97, 138.54, 136.69, 136.36, 131.99, 131.32, 131.29, 130.41, 128.70, 128.57, 128.24, 128.16, 126.70, 125.26, 124.15 (q, *J*= 271.2 Hz), 123.83 (q, *J*= 8.6 Hz), 122.29 (q, *J*= 3.7 Hz), 29.36.

IR (cm^{-1}): 3057.9, 2360.1, 1687.7, 1324.3, 1244.8, 1160.8, 1112.2, 1081.7, 968.0, 771.7, 757.1, 735.8, 692.2.

HRMS: calculated for $C_{23}H_{21}OF_3N^+$ ([M + NH_4^+]$^+$): 384.1570 Found 384.1575



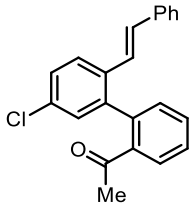
(*E*)-1-(2-(2-styrylthiophen-3-yl)phenyl)ethan-1-one (S22): Prepared according to General cross coupling procedure **A** between **A19** (150 mg, 0.57 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 98 mg (57% yield) of the title compound as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 3H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 6.2 Hz, 2H), 6.97 – 6.92 (m, 3H), 2.08 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.72, 141.55, 139.20, 139.11, 136.99, 134.72, 131.45, 131.17, 130.42, 130.03, 128.89, 128.47, 128.14, 128.01, 126.66, 123.87, 120.30, 29.79.

IR (cm^{-1}): 3102.9, 3026.1, 1670.0, 1593.1, 1443.2, 1350.7, 1279.8, 1268.2, 1233.7, 951.8, 768.2, 733.9, 713.3, 683.9, 665.9.

HRMS: calculated for $C_{20}H_{17}OS^{+}$ ($[M + H^{+}]^{+}$): 305.0995 Found 305.0992.



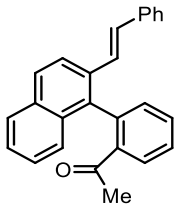
(*E*)-1-(5'-chloro-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S23): Prepared according to general cross coupling procedure **A** between **A9** (150 mg, 0.51 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 103 mg (63% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.39 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.33 – 7.26 (m, 5H), 7.26 – 7.19 (m, 2H), 6.99 (d, *J* = 16.2 Hz, 1H), 6.76 (d, *J* = 16.2 Hz, 1H), 2.13 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 201.75, 141.83, 140.45, 138.58, 137.18, 134.48, 133.28, 131.58, 131.40, 131.09, 129.99, 128.87, 128.68, 128.47, 128.33, 128.11, 126.88, 126.79, 125.57, 29.74.

IR (cm^{-1}): 3058.2, 1687.1, 1494.8, 1464.8, 1354.1, 1264.1, 1097.0, 963.4, 813.4, 758.6, 731.8, 690.4.

HRMS: calculated for $C_{22}H_{21}OClN^+$ ($[M + NH_4^+]^+$): 350.1306 Found 350.1308.



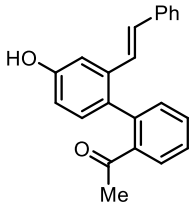
(*E*)-1-(2-(2-styrylnaphthalen-1-yl)phenyl)ethan-1-one (S24): Prepared according to general cross coupling procedure **A** between **A11** (200 mg, 0.65 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 89 mg (40% yield) of the title compound as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (q, *J* = 8.8 Hz, 3H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.27 (m, 6H), 7.23 – 7.19 (m, 1H), 7.15 (d, *J* = 16.3 Hz, 1H), 6.87 (d, *J* = 16.3 Hz, 1H), 1.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.67, 141.26, 137.70, 137.51, 137.15, 133.16, 133.06, 132.99, 132.53, 131.69, 130.61, 129.00, 128.84, 128.62, 128.31, 128.23, 127.95, 126.99, 126.95, 126.80, 126.48, 126.17, 122.97, 29.56.

IR (cm^{-1}): 3056.9, 1680.9, 1594.1, 1353.5, 1273.7, 1244.7, 958.3, 811.2, 760.7, 739.7, 791.1, 596.1.

HRMS: calculated for $C_{26}H_{24}ON^+$ ($[M + NH_4^+]^+$): 366.1852 Found 366.1857.



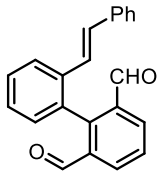
(*E*)-1-(4'-hydroxy-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S25): Prepared according to general cross coupling procedure **A** between **A26** (150 mg, 0.35mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 71 mg (66% yield) of the title compound as a pale white solid. The *tert*-butyldimethylsilyl ether was cleaved under the reaction conditions.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.30 (m, 5H), 7.22 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 16.2 Hz, 1H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.16 (s, 1H), 2.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.70, 155.85, 141.39, 139.39, 137.28, 137.24, 132.91, 132.03, 131.90, 131.02, 130.94, 128.87, 128.37, 128.06, 127.69, 126.85, 126.38, 115.20, 112.09, 30.03.

IR (cm^{-1}): 3207.0, 1679.1, 1572.4, 1475.5, 1305.9, 1213.9, 963.3, 833.6, 773.6, 759.9, 728.2, 696.0.

HRMS: calculated for $C_{22}H_{22}O_2N^+$ ($[M + NH_4^+]^+$): 332.1645 Found 332.1648.



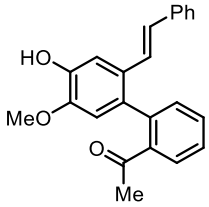
(*E*)-2'-styryl-[1,1'-biphenyl]-2,6-dicarbaldehyde (S26): Prepared according to general cross coupling procedure **B** between 2-bromoisophthalaldehyde (300 mg, 1.41 mmol) and (*E*)-(2-styrylphenyl)boronic acid 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 89 mg (40% yield) of the title compound as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.74 (s, *J* = 0.6 Hz, 1H), 8.30 (d, *J* = 7.7 Hz, 2H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.55 (td, *J* = 7.8, 0.7 Hz, 1H), 7.41 (td, *J* = 7.5, 1.1 Hz, 1H), 7.30 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 2H), 7.23 – 7.19 (m, 3H), 7.04 (d, *J* = 16.1 Hz, 1H), 6.61 (d, *J* = 16.1 Hz, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 190.92, 147.16, 137.77, 136.75, 135.15, 132.94, 132.48, 131.69, 131.40, 129.86, 129.00, 128.85, 128.42, 127.65, 126.87, 125.91, 125.34.

IR (cm^{-1}): 3061.7, 2868.2, 1678.0, 1449.2, 1386.1, 1232.3, 963.8, 921.3, 794.4, 763.0, 746.5, 691.4.

HRMS: calculated for. $C_{22}H_{20}O_2N^+$ ($[M + NH_4^+]^+$): 330.1489 Found 330.1493.



(*E*)-1-(4'-hydroxy-5'-methoxy-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S27): Prepared according to general cross coupling procedure **A** between **A29** (150 mg, 0.35 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with

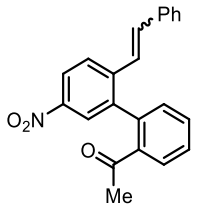
hexanes/EtOAc afforded 107 mg (87% yield) of the title compound as a pale white solid. The *tert*-butyldimethylsilyl ether was cleaved under the reaction conditions.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.36 (s, 1H), 7.32 – 7.26 (m, 5H), 7.19 (t, *J* = 6.9 Hz, 1H), 6.93 (d, *J* = 16.1 Hz, 1H), 6.82 (d, *J* = 16.1 Hz, 1H), 6.65 (s, 1H), 5.66 (s, 1H), 3.87 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 203.75, 146.46, 145.88, 141.59, 139.37, 137.62, 132.30, 131.95, 130.85, 129.18, 129.07, 128.80, 128.25, 127.77, 127.63, 126.62, 126.03, 112.71, 111.31, 56.31, 30.05.

IR (cm^{-1}): 3535.8, 1677.3, 1594.1, 1509.6, 1278.0, 1238.4, 1141.7, 905.2, 724.1, 647.3.

HRMS: calculated for $C_{23}H_{20}O_3Na$ ($[M + Na^+]^+$): 367.1305, found: 367.1302.



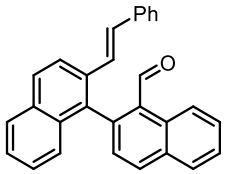
1-(5'-nitro-2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (S28): Prepared according to general cross coupling procedure **A** between **A30** (100 mg, 0.33 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 71 mg (63% yield) of the title compound as a pale yellow foam and an *E/Z* mixture (1.62:1.0).

^{1}H NMR (700 MHz, $CDCl_3$, for *E/Z* mixture) δ 8.23 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.09 (dd, *J* = 12.3, 2.3 Hz, 1.41H), 7.97 (dd, *J* = 8.6, 2.3 Hz, 0.63H), 7.84 (t, *J* = 12.4, 2H), 7.81 – 7.78 (m, 0.61H), 7.61 (tt, *J* = 7.0, 3.5 Hz, 1H), 7.59 – 7.48 (m, 2.36H), 7.40 (d, *J* = 8.6 Hz, 0.72H), 7.34 – 7.17 (m, 9.95H), 7.13 (d, *J* = 16.2 Hz, 1.15H), 6.76 (d, *J* = 16.3 Hz, 1.11H), 6.56 (d, *J* = 12.3 Hz, 0.72H), 6.10 (d, *J* = 12.3 Hz, 0.68H), 2.43 (s, 1.86H), 2.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, for *E/Z* mixture) δ 200.38, 200.34, 146.87, 146.66, 142.95, 142.87, 142.39, 141.78, 139.37, 139.01, 138.46, 138.13, 136.52, 135.92, 134.36, 133.69, 131.97, 131.90, 131.76, 131.46, 130.19, 129.18, 128.99, 128.95, 128.90, 128.82, 128.70, 128.59, 128.23, 127.35, 127.15, 126.04, 124.93, 124.89, 124.66, 123.00, 122.05, 29.26, 28.74.

IR (cm^{-1}): 2954.2, 1733.9, 1688.2, 1516.9, 1343.4, 1283.6, 1246.5, 1232.9, 1044.2, 943.8, 759.0, 707.5.

HRMS: Calculated for $C_{22}H_{17}O_3N^+$ ($[M]^+$): 343.1208 found: 343.1205.



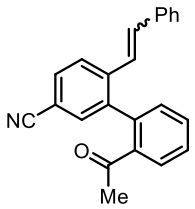
(*E*)-2-styryl-[1,2'-binaphthalene]-1'-carbaldehyde (S29): Prepared according to general cross coupling procedure **A** between 2-bromo-1-naphthaldehyde (150 mg, 0.64 mmol) and (*E*)-(2-styrylnaphthalen-1-yl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 103 mg (42% yield) of **S29** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 9.40 (d, *J* = 8.6 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.97 (q, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.45 (m, 2H), 7.35 – 7.31 (m, 1H), 7.29 (d, *J* = 6.9 Hz, 1H), 7.23 – 7.15 (m, 7H), 6.83 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.59, 146.04, 137.20, 135.00, 134.41, 134.00, 133.81, 133.68, 132.85, 131.32, 130.85, 130.17, 129.75, 129.65, 129.07, 128.87, 128.81, 128.72, 128.30, 128.11, 127.34, 127.29, 126.88, 126.80, 126.59, 126.44, 126.38, 122.87.

IR (cm^{-1}): 2858.1, 2361.9, 1678.2, 1590.9, 1558.1, 1505.4, 1429.6, 1180.0, 1147.6, 1059.2, 966.5, 817.6, 745.7.

HRMS: calculated for $C_{29}H_{24}ON^+$ ([M + NH_4^+]$^+$): 402.1852 Found 402.1853.



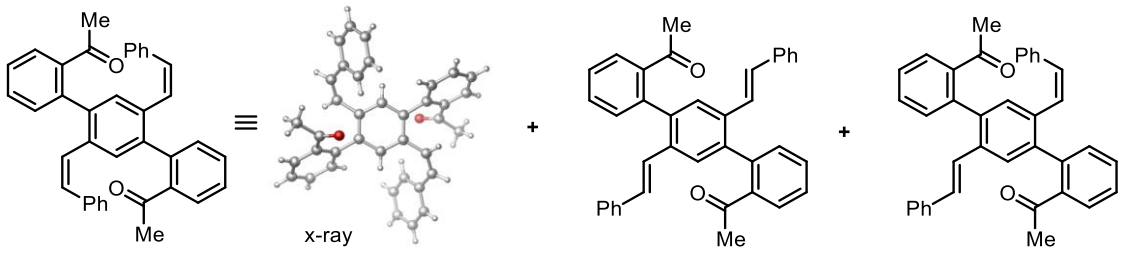
2'-acetyl-6-styryl-[1,1'-biphenyl]-3-carbonitrile (S30): Prepared according to general cross coupling procedure **A** between 3-bromo-4-styrylbenzonitrile (**A31**) (130 mg, 0.46 mmol) and 2-acetylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 79 mg (53% yield) of an *E/Z* mixture (3.0:1.0) of the title compound as a yellow-white solid.

^{1}H NMR (500 MHz, $CDCl_3$, for *E/Z* mixture) δ 7.99 (s, 1H), 7.81 – 7.73 (m, 1.3H), 7.63 – 7.45 (m, 4.2H), 7.35 – 7.20 (m, 9.3H), 7.17 (t, *J* = 6.7 Hz, 1H), 7.02 (d, *J* = 16.2 Hz, 1.1H), 6.71 (d, *J* = 16.2 Hz, 1.1H), 6.50 (d, *J* = 12.2 Hz, 0.4H), 6.04 (d, *J* = 12.2 Hz, 0.4H).

^{13}C NMR (126 MHz, $CDCl_3$, for *E/Z* mixture) δ 200.79, 200.64, 145.15, 139.60, 138.51, 137.16, 136.64, 133.05, 132.84, 131.75, 131.70, 131.36, 131.08, 130.82, 130.78, 130.54, 130.50, 129.38, 129.02, 128.97, 128.83, 128.76, 128.73, 128.60, 128.50, 128.25, 126.97, 126.93, 124.72, 119.01, 112.15, 29.32, 28.80.

IR (cm^{-1}): 2223.6, 1682.8, 1245.6, 973.0, 894.6, 827.8, 777.6, 756.4, 732.4, 695.7, 606.7.

HRMS: calculated for $C_{23}H_{18}NO$ ([M+H^+]$^+$): 324.1383 Found: 324.1381.



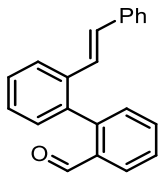
1,1'-(2',5'-distyryl-[1,1':4',1''-terphenyl]-2,2''-diyl)bis(ethan-1-one) (58): Prepared according to general cross coupling procedure **A** between ((2,5-dibromo-1,4-phenylene)bis(ethene-2,1-diyl))dibenzene[44] (100 mg, 0.23 mmol), 2-acetylphenylboronic acid (93 mg, 0.57 mmol), $Pd(PPh_3)_4$ (26 mg, 10 mol%), $NaHCO_3$ (115 mg, 1.36 mmol) and DMF/H_2O (1:1; 0.1 M). Purification by flash column chromatography eluting with hexanes/EtOAc afforded 39 mg (33% yield) of an inseperable *Z/Z', E/E'* and *E/Z'* mixture as a yellow-white solid**.** This isomeric mixture was used in the title reaction without further resolution.

^{1}H NMR (700 MHz, $CDCl_3$, for *Z/Z', E/E' and E/Z' mixture*) δ 7.79 (d, *J* = 11.2 Hz, 0.49H), 7.73 (m, 1.42H), 7.69 (d, *J* = 7.3 Hz, 0.76H), 7.67 – 7.58 (m, 2.66H), 7.58 – 7.51 (m, 1.03H), 7.50 – 7.33 (m, 7.62H), 7.33 – 7.15 (m, 16.90H), 7.02 (m, 2.76H), 6.94 – 6.87 (m, 0.64H), 6.75 (m, *J* = 19.2 Hz, 0.66H), 6.43 (d, *J* = 12.1 Hz, 1.75H), 6.26 (d, *J* = 12.2 Hz, 0.57H), 6.18 (d, *J* = 12.2 Hz, 1.72H), 2.31 (s, 6H), 2.18 (s, 0.84H), 2.14 (s, 1.24H).

^{13}C NMR (175 MHz, $CDCl_3$, *Z/Z', E/E'* and *E/Z'* mixture) δ 202.66, 201.67 (broad), 141.22, 140.88, 140.30, 140.15, 139.73 (broad), 139.24, 137.32, 136.96 (broad), 136.83, 135.38, 135.34, 135.30, 135.27 (overlap), 135.23, 135.14, 135.06, 134.91, 132.36, 132.30, 132.01, 131.58 (overlap), 131.51 (overlap), 131.30, 131.22, 131.08, 130.86, 130.72 (overlap), 130.69, 130.47, 129.85, 129.07 (broad), 128.86, 128.81, 128.68, 128.54 (overlap), 128.43 (overlap), 128.30 (overlap), 128.27, 128.24, 128.21, 128.18, 128.15, 128.09, 127.95 (overlap), 127.46 (overlap), 127.28 (overlap), 126.85, 126.80, 125.84, 125.63, 30.13 (broad), 30.01 (overlap), 29.93 (overlap), 29.77.

IR (cm^{-1}): 3052.7, 1688.1, 1595.2, 1354.2, 1264.0, 963.6, 923.6, 762.3, 732.1, 697.0.

HRMS: calculated for $C_{38}H_{34}NO_2^+$ ($[M+NH_4^+]^+$): 536.2584 Found: 536.2575.



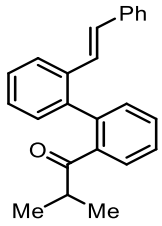
(*E*)-2'-styryl-[1,1'-biphenyl]-2-carbaldehyde (22b): Prepared according to general cross coupling procedure **A** between **A1** (6 x 150 mg) and 2-formylphenylboronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 500 mg (51% yield) of the title compound as a clear oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.08 – 8.06 (m, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.40 – 7.34 (m, 3H), 7.30 – 7.25 (m, 7H), 7.21 (ddd, *J* = 8.6, 5.7, 3.3 Hz, 1H), 7.03 (d, *J* = 16.2 Hz, 1H), 6.78 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 192.26, 144.81, 137.27, 136.84, 134.55, 133.81, 131.67, 131.27, 131.16, 128.85, 128.83, 128.35, 128.05, 127.53, 127.48, 126.80, 126.47, 125.68.

IR (cm^{-1}): 1686.9, 1596.6, 1498.7, 1466.8, 1279.2, 1264.8, 1230.4, 1204.8, 1171.3, 999.9, 962.8, 756.4, 729.4, 690.9.

HRMS: calculated for $C_{21}H_{17}O^+$ ($[M + H^+]^+$): 307.1090 Found: 307.1099.



(*E*)-2-methyl-1-(2'-styryl-[1,1'-biphenyl]-2-yl)propan-1-one (22c): Prepared according to general cross coupling procedure **A** between 1-(2-bromophenyl)-2-methylpropan-1-one.[45] (131

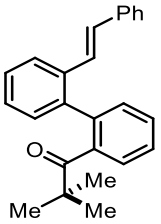
mg) and (*E*)-(2-styrylphenyl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 90 mg (48% yield) of the title compound as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 14.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.36 – 7.27 (m, 6H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 16.2 Hz, 1H), 6.94 (d, *J* = 16.2 Hz, 1H), 2.62 – 2.49 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (17 MHz, $CDCl_3$) δ 210.94, 141.27, 139.81, 138.87, 137.59, 135.70, 131.74, 130.79, 130.33, 130.16, 128.83, 128.40, 128.32, 127.87, 127.79, 127.60, 126.90, 126.82, 125.70, 39.72, 19.37, 18.31.

IR (cm^{-1}): 1735.0, 1685.8, 1594.4, 1495.4, 1465.0, 1379.9, 1212.2, 977.7, 760.3, 734.9, 690.1.

HRMS: calculated for $C_{24}H_{26}ON^{+}$ ($[M + NH_4^{+}]^{+}$):: 344.2009 Found: 344.2015.



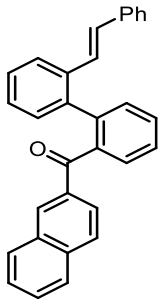
(*E*)-2,2-dimethyl-1-(2'-styryl-[1,1'-biphenyl]-2-yl)propan-1-one (22d): Prepared according to general cross coupling procedure **A** between 1-(2-bromophenyl)-2,2-dimethylpropan-1-one.[46] (150 mg) and (*E*)-(2-styrylphenyl)boronic acid.. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 92 mg (43% yield) of the title compound as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.17 (m, 14H), 7.03 (d, *J* = 8.3 Hz, 2H), 0.93 (s, 9H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 215.51, 142.18, 139.33, 137.73, 136.64, 135.96, 131.95, 131.85, 129.86, 128.84, 128.31, 128.19, 127.78, 127.48, 127.27, 127.11, 126.80, 125.87, 125.62, 44.93, 27.61.

IR (cm^{-1}): 1683.9, 1235.5, 963.6, 759.1, 690.5.

HRMS: calculated for $C_{25}H_{28}ON^+$ ($[M + NH_4^+]^+$): 358.2165 Found: 358.2169.



(*E*)-naphthalen-2-yl(2'-styryl-[1,1'-biphenyl]-2-yl)methanone (22f): To a 50 mL round bottom flask equipped with a magnetic stir bar was added a solution of 2-bromonaphthalene (1455 mg, 7.03 mmol) and 20 mL of THF. To this solution was added magnesium shavings (158 mg, 6.49 mmol) and a crystal of I_2. The mixture was allowed to stir at rt for 1 h. Next, the mixture was cooled to 0 ^oC with an ice-bath and at which time 2-bromobenzaldehyde (1000 mg, 5.40 mmol) in a solution of THF (5 mL) was added. The reaction mixture was allowed to sir at 0 ^oC and slowly warmed to rt. When judged complete by TLC analysis, the reaction was quenched with NH_4Cl (aq.) (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over $MgSO_4$, and concentrated in *vacuo* to yield the crude alcohol (1002 mg). This was used in the next step without further purification.

To a 50 mL round bottom flask was added the crude alcohol (1000 mg) and 15 mL of DMSO. Next, IBX (1341 mg, 4.79 mmol) was added to the reaction solution at rt and allowed to stir for 3 h. The reaction was quenched with water (20 mL) and stirred for an addition 1 h. Next the reaction

was filtered and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in *vacuo*. The crude ketone was purified by flash column chromotagraphy with hexanes/EtOAc to afford 756 mg (44% over two steps) of (2-bromophenyl)(naphthalen-2-yl)methanone as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.02 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.94 (s, 1H), 7.90 (m, 3H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.50 – 7.34 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.08, 141.08, 136.13, 133.75, 133.48, 133.32, 132.64, 131.39, 129.99, 129.30, 129.15, 128.88, 128.08, 127.46, 127.07, 125.00, 119.89.

IR (cm^{-1}): 3057.8, 1660.1, 1430.1, 1290.7, 1232.9, 1200.2, 1112.4, 919.3, 850.3, 926.8, 778.5, 754.0, 735.5, 689.1.

HRMS: calculated for $C_{17}H_{11}OBrNa^+$ ($[M + Na^+]^+$): 332.9885 Found 332.9884.

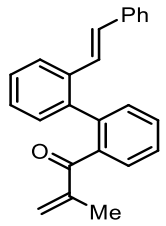
(*E*)-naphthalen-2-yl(2'-styryl-[1,1'-biphenyl]-2-yl)methanone was prepared according to general cross coupling procedure **A** between (2-bromophenyl)(naphthalen-2-yl)methanone (150 mg, 0.48 mmol) and (*E*)-(2-styrylphenyl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 93 mg (47% yield) of **22f** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.77 – 7.71 (m, 2H), 7.68 – 7.60 (m, 3H), 7.58 – 7.43 (m, 5H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.25 (m, 4H), 7.22 – 7.16 (m, 2H), 7.16 – 7.09 (m, 2H), 7.05 (d, *J* = 16.2 Hz, 1H), 6.78 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.83, 140.54, 140.08, 139.44, 137.70, 135.70, 135.43, 134.90, 132.48, 132.14, 131.74, 130.82, 130.55, 130.34, 129.71, 129.36, 128.74, 128.38, 128.11, 127.99, 127.77, 127.38, 127.35, 127.32, 126.73, 126.52, 125.58, 125.08.

IR (cm^{-1}): 3051.7, 1660.8, 1623.2, 1291.7, 1117.7, 964.3, 919.4, 781.2, 759.6, 748.8, 732.0, 695.3.

HRMS: calculated for $C_{31}H_{23}O^+$ ([M + H^+]$^+$): 411.1743 Found 411.1751.



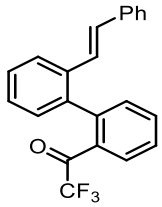
(*E*)-2-methyl-1-(2'-styryl-[1,1'-biphenyl]-2-yl)prop-2-en-1-one (22g): Prepared according to general cross coupling procedure **A** between 1-(2-bromophenyl)-2-methylprop-2-en-1-one (150 mg, 0.66 mmol) and (*E*)-(2-styrylphenyl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 127 mg (59% yield) of the title compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.37 – 7.28 (m, 6H), 7.24 (q, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.93 (d, *J* = 16.2 Hz, 1H), 5.55 (s, 1H), 5.39 (s, 1H), 1.68 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.34, 145.28, 140.32, 139.64, 139.62, 137.67, 135.58, 131.53, 130.94, 130.03, 129.70, 128.78, 128.57, 128.08, 127.91, 127.77, 127.35, 127.32, 127.29, 126.73, 125.56, 17.41.

IR (cm^{-1}): 3055.8, 1657.2, 1494.5, 1435.7, 1327.9, 1264.3, 1196.0, 1015.2, 963.2, 906.2, 760.5, 732.5, 690.4.

HRMS: calculated for $C_{24}H_{24}ON^+$ ([M + NH_4^+]$^+$): 342.1852 Found 342.1860.



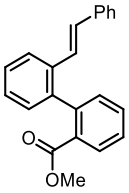
(*E*)-2,2,2-trifluoro-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (22i): Prepared according to general cross coupling procedure **A** between 1-(2-bromophenyl)-2,2,2-trifluoroethan-1-onemethanone (200 mg, 0.79 mmol) and (*E*)-(2-styrylphenyl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 115 mg (41% yield) of the title compound as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.54 (td, *J* = 7.7, 1.2 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.32 (td, *J* = 7.5, 1.1 Hz, 1H), 7.29 – 7.23 (m, 4H), 7.23 – 7.18 (m, 1H), 7.15 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.96 (d, *J* = 16.2 Hz, 1H), 6.73 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 183.12 (q, *J*= 35),142.72, 138.62, 137.17, 135.59, 133.18, 132.44, 131.77, 130.94, 129.61, 128.99, 128.97, 128.50, 128.29, 127.66, 127.58, 127.51, 126.53, 126.19, 125.73, 115.94 (q, *J*= 292).

IR (cm^{-1}): 3024.4, 1725.4, 1594.7, 1494.9, 1199.5, 1182.5, 1140.8, 962.1, 933.9, 757.8, 736.0, 689.8, 661.0.

HRMS: calculated for $C_{22}H_{16}OF_3^+$ ($[M + H^+]^+$): 353.1148 Found 353.1149.



Methyl (*E*)-2'-styryl-[1,1'-biphenyl]-2-carboxylate (22j): Prepared according to general cross coupling procedure **A** between methyl 2-bromobenzoate (6 x 258 mg) and (*E*)-(2-

styrylphenyl)boronic acid. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 652 mg (29% yield) of the title compound as a thick clear oil.

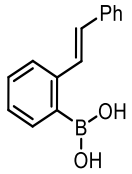
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.26 (m, 6H), 7.19 (m, 2H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.81 (d, *J* = 16.2 Hz, 1H), 3.54 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$):δ 168.09, 141.91, 140.83, 137.69, 135.55, 131.89, 131.67, 131.51, 130.12, 129.86, 129.62, 128.75, 127.84, 127.68, 127.63, 127.33, 127.15, 126.72, 125.07, 52.16.

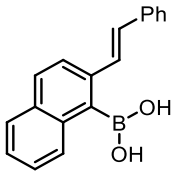
IR (cm^{-1}): 1727.4, 1596.8, 1430.3, 1250.6, 1124.6, 1082.1, 961.0, 749.1, 7124, 690.1

HRMS: calculated for $C_{22}H_{19}O_2^+([M + H^+]^+)$: 315.1380 Found: 315.1380.

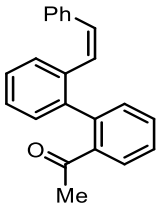
A.1.7 Miscellaneous procedures



(*E*)-(2-styrylphenyl)boronic acid: Prepared according to the reported literature procedure:[47] (*E*)-1-bromo-2-styrylbenzene **(A1)** (3.0 g, 11.6 mmol) was dissolved in THF (60 mL) and cooled to -78 °C. Next,. *n*BuLi (2.5 M in hexane, 7.0 mL, 17.4 mmol) was added dropwise and the reaction mixture was stirred for 30 minutes before triisopropoxyborate (4.0 mL, 17.4 mmol) was added slowly. The reaction mixture was allowed to warm to rt with stirring overnight. The reaction mixture was quenched with 1M HCl and allowed to stir for 1 hour before being concentrated by rotary evaporator and extracted with two portions of DCM (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporator. The solid product was dried under high vacuum and used without further purification.



(*E*)-(2-styrylnaphthalen-1-yl)boronic acid: (*E*)-1-bromo-2-styrylnaphthalene **(A11)** (300 mg, 0.97 mmol) was dissolved in THF (9 mL) and cooled to -78 ^{o}C. Next, *n*-BuLi (2.5 M in hexane, 0.47 mL, 1.07 mmol) was added dropwise and the reaction mixture was stirred for 30 minutes before triisopropoxyborate (0.34 mL, 1.46 mmol) was added slowly. The reaction mixture was allowed to warm to rt with stirring overnight. The reaction mixture was quenched with 1M HCl and allowed to stir for 1 hour before being concentrated by rotary evaporator and extracted with two portions of DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporator. The orange semi-solid product was dried under high vacuum and used without further purification.



(*Z*)-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (8): General olefination procedure **B** was followed employing 2'acetyl-[1,1'-biphenyl]-2-carbaldehyde[49] (9.37 mmol). Purification by flash column chromatography eluting with hexanes/EtOAc provided 1485 mg (53%) of **8** and its alkene isomer (E:Z; 2.2:1) as a clear oil. Recrystallization from hexanes afforded exclusively the *Z* alkene (**8**). Spectroscopic data for *E/Z* mixture prior to recrystallization:

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 0.5H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.39 (m, 1.5H), 7.30 (m, 9.5H),

7.23 – 7.15 (m, 4H), 7.02 (d, *J* = 16.2 Hz, 1H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.45 (d, *J* = 12.2 Hz, 0.5H), 6.22 (d, *J* = 12.2 Hz, 0.5H), 2.14 (d, *J* = 0.5 Hz, 1.5H), 2.00 (d, *J* = 0.4 Hz, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 202.88, 202.75, 141.04, 140.61, 140.17, 140.10, 139.79, 137.47, 136.94, 135.87, 135.80, 131.69, 131.53, 131.04, 130.91, 130.64, 130.52, 130.22, 129.71, 129.24, 129.21, 129.05, 128.84, 128.75, 128.49, 128.46, 128.41, 128.15, 127.92, 127.87, 127.77, 127.70, 127.65, 127.45, 126.79, 126.68, 125.71, 29.93, 29.66.

IR (cm^{-1}): 1684.6, 1593.5, 1494.4, 1467.9, 1453.8, 1352.4, 1244.0, 1073.6, 1003.7, 962.2, 757.2, 732.5, 690.4.

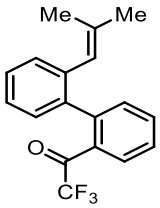
Spectroscopic data for **8**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.7 Hz, 1H), 7.43 (pd, *J* = 7.4, 1.6 Hz, 2H), 7.32 (dd, *J* = 10.3, 4.3 Hz, 1H), 7.29 – 7.14 (m, 9H), 6.45 (d, *J* = 12.3 Hz, 1H), 6.22 (d, *J* = 12.3 Hz, 1H), 2.14 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 202.77, 140.72, 140.60, 140.10, 136.94, 135.87, 131.54, 131.03, 130.91, 130.22, 129.71, 129.21, 129.05, 128.41, 128.15, 127.70, 127.66, 127.45, 29.67.

IR (cm^{-1}): 3014.2, 1688.4, 1591.9, 1473.5, 1444.4, 1350.8, 1245.4, 965.9, 776.0, 762.5, 703.8, 692.9, 596.0.

HRMS: calculated for $C_{22}H_{18}O^+$ ($[M]^+$): 298.1358 Found 298.1365.



2,2,2-trifluoro-1-(2'-(2-methylprop-1-en-1-yl)-[1,1'-biphenyl]-2-yl)ethan-1-one (S31): A 25 mL round bottom flask containing a stirred solution of 2-bromo-2'-(2-methylprop-1-en-1-yl)-1,1'-biphenyl **(A27**, 350 mg, 1.22 mmol) in THF (10 mL)**,** was cooled to -78 °C. At which time, ^{n}BuLi

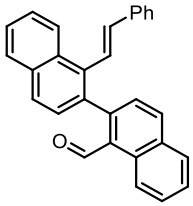
(2.5 M in hexanes, 0.54 mL, 1.34 mmol) was slowly added. This solution was allowed to stir for 30 min. Next, ethyl trifluoroacetate (0.26 mL, 2.19 mmol) was added. The resultant mixture was allowed to slowly warm to room temperature over 3 h. The reaction mixture was quenched with NH_4Cl^+ (aq) (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was accomplished employing flash column chromatography with hexanes/EtOAc to afford 156 mg (42%) of **S31** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.66 (td, *J* = 7.6, 1.2 Hz, 1H), 7.48 (td, *J* = 7.8, 1.1 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.27 – 7.20 (m, 2H), 5.68 (s, 1H), 1.71 (s, 3H), 1.67 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 181.89 (q, *J*= 34.6), 143.35, 139.05, 137.45, 136.13, 133.29, 132.00, 131.44, 129.98, 129.09, 128.39, 128.38, 127.38, 127.07, 126.79, 123.75, 116.10 (q, *J*= 292.9).

IR (cm^{-1}): 3072.0, 1454.2, 1435.9, 1229.8, 1162.6, 1138.1, 1115.3, 1056.5, 1016.2, 927.8, 736.3, 694.6, 647.8.

HRMS: calculated for $C_{18}H_{19}OF_3N^+$ ($[M + NH_4^+]^+$): 322.1413 Found 322.1414.



(*E*)-1'-styryl-[2,2'-binaphthalene]-1-carbaldehyde (S32): Sodium hydride (60% dispersion in mineral oil, 31mg, 0.77 mmol) was suspended in THF (6 mL) and cooled on an ice bath. Diethyl benzylphosphonate (0.134 mL, 0.64 mmol) was added via syringe and stirred for 30 minutes. [2,2'-binaphthalene]-1,1'-dicarbaldehyde[48] was added as a solid and the reaction mixture was allowed

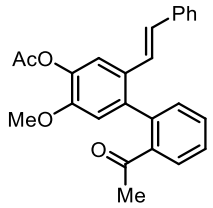
to warm to rt over 1 h. The reaction mixture was then heated to 50 °C for 6 hours. The mixture was allowed to cool to room temperature and quenched with water, then neutralized with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4. The resulting crude product was purified by silica gel column chromatography eluting with hexanes/EtOAc to afford 136 mg (27%) of the title compound as a foamy yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.22 (s, 1H), 9.30 (d, *J* = 8.6 Hz, 1H), 8.35 (dd, *J* = 6.1, 3.5 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.96 (dd, *J* = 6.1, 3.4 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.62 – 7.56 (m, 3H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.25 – 7.16 (m, 6H), 6.65 (d, *J* = 16.5 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 194.59, 149.05, 137.57, 137.20, 135.13, 134.97, 134.16, 133.78, 133.28, 131.89, 130.71, 129.48, 129.29, 128.88, 128.78, 128.72, 128.53, 128.12, 127.34, 127.20, 127.01, 126.71, 126.62, 126.17, 126.06, 125.29.

IR (cm^{-1}): 3048.5, 1680.9,1590.0, 1503.3, 1429.8, 1264.0, 1175.8, 1057.3, 964.5, 819.8, 733.7.

HRMS: calculated for $C_{29}H_{20}O^+$ ($[M]^+$):: 384.1514 Found: 384.1518. .



(*E*)-2'-acetyl-5-methoxy-2-styryl-[1,1'-biphenyl]-4-yl acetate (S34): To a 10 mL flame-dried round bottom flask was added **S27** (100 mg, 0.29 mmol) along with DCM (2 mL) under an atmosphere of nitrogen. After cooling the resultant mixture to 0 ºC, DMAP (0.35 mg, 2.9 μmol), Ac_2O (41.2 μL, 0.47 mmol) and TEA (60.5 μL, 0.44 mmol) were successively added. The reaction mixture was slowly allowed to warm to room temperature. After 8 h, the reaction was quenched

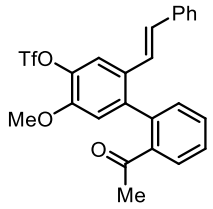
with NH_4Cl^+ (aq) (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was accomplished employing flash column chromatography with hexanes/EtOAc to afford 109 mg (97%) of **S34** as a clear foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.56 (td, *J* = 7.5, 1.3 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.27 (m, 4H), 7.21 (dq, *J* = 8.6, 4.3 Hz, 1H), 6.92 (d, *J* = 16.2 Hz, 1H), 6.79 (m, 2H), 3.83 (s, 3H), 2.39 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.98, 169.07, 150.57, 141.19, 139.99, 138.85, 138.51, 137.40, 131.58, 131.02, 129.48, 128.82, 128.78, 128.34, 128.11, 127.73, 126.59, 125.38, 119.94, 114.25, 56.25, 29.98, 20.88.

IR (cm^{-1}): 3053.8, 2056.0, 1759.6, 1685.6, 1506.0, 1438.2, 1205.0, 1133.4, 1022.1, 961.9, 732.2.

HRMS: calculated for $C_{25}H_{26}O_4N$ ($[M + NH_4^+]^+$): 404.1856, found: 404.1856.



(*E*)-2'-acetyl-5-methoxy-2-styryl-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (S35): To a 10 mL flame-dried round bottom flask was added **S27** (100 mg, 0.29 mmol) along with DCM (4 mL) under an atmosphere of nitrogen. After cooling the resultant mixture to 0 ^oC, Tf_2O (58. μL, 0.35 mmol) and TEA (88 μL, 0.58 mmol) were successively added. The reaction mixture was slowly allowed to warm to room temperature. After 4 h, the reaction was quenched with NH_4Cl (aq) (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over

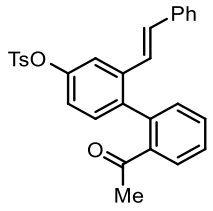
$MgSO_4$ and concentrated under reduced pressure. Purification was accomplished employing flash column chromatography with hexanes/EtOAc to afford 97 mg (70%) of **S35** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.52 (m, 1H), 7.34 – 7.30 (m, 1H), 7.29 (d, *J* = 4.3 Hz, 4H), 7.25 – 7.20 (m, 1H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.85 (s, 1H), 6.70 (d, *J* = 16.2 Hz, 1H), 3.90 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.91, 150.42, 141.12, 140.59, 138.75, 138.23, 136.99, 131.47, 131.38, 130.62, 129.35, 128.89, 128.64, 128.57, 128.15, 126.75, 124.74, 119.55, 114.84, 119.01 (q, *J* = 318.8), 56.62, 29.69.

IR (cm^{-1}**):** 3032.2, 1688.9, 1609.7, 1503.3, 1419.3, 1320.0, 1240.0, 1204.5, 1136.6, 1101.0, 856.2, 756.2, 734.5.

HRMS: calculated for $C_{24}H_{23}O_5NF_3S$ ($[M + NH_4^+]^+$): 494.1244, found: 494.1244.



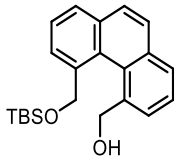
(*E*)-2'-acetyl-2-styryl-[1,1'-biphenyl]-4-yl 4-methylbenzenesulfonate (S36): To a 10 mL flame-dried round bottom flask was added **S25** (120 mg, 0.38 mmol) along with DCM (4 mL) under an atmosphere of nitrogen. After cooling the resultant mixture to 0 ^oC, TsCl (87 mg, 0.38 mmol) and TEA (0.16 mL, 1.15 mmol) were successively added. The reaction mixture was slowly allowed to warm to room temperature. After 12 h, the reaction was quenched with NH_4Cl^+ (aq) (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was accomplished employing flash column chromatography with hexanes/EtOAc to afford 85 mg (48%) of **S36** as a pale yellow foam.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.9 Hz, 2H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.36 (m, 3H), 7.31 – 7.21 (m, 6H), 7.09 (d, *J* = 8.3, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 16.2 Hz, 1H), 6.71 (d, *J* = 16.2 Hz, 1H), 2.46 (s, 3H), 1.98 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 202.08, 149.78, 145.74, 140.84, 138.99, 138.49, 137.62, 136.86, 132.55, 132.06, 131.59, 131.53, 131.25, 130.02, 128.92, 128.63, 128.38, 128.27, 126.89, 125.36, 121.34, 119.42, 29.80, 21.98.

IR (cm^{-1}): 2959.5, 1687.5, 1448.5, 1428.9, 1284.2, 1232.5, 1178.1, 1092.1, 943.9, 880.6, 707.6.

HRMS: calculated for $C_{29}H_{28}O_4NS^+$ ($[M + NH_4^+]^+$): 486.1734, found: 486.1730.



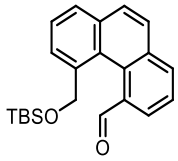
(5-(((tert-butyldimethylsilyl)oxy)methyl)phenanthren-4-yl)methanol (S37i-a): Phenanthrene-4,5-diyldimethanol[49] (893 mg, 3.75 mmol) was dissolved in DMF (4 mL). TBSCl (678 mg, 4.5 mmol) and imidazole (765 mg, 11.2 mmol) were added and the reaction mixture was stirred overnight. The reaction was diluted with water and diethyl ether. The layers were separated and the aqueous layer was washed with two portions of ether. The combined organic layers were washed with brine and dried over $MgSO_4$, then concentrated by rotary evaporator. The product was purified by silica gel column chromatography eluting with hexanes/ethyl acetate to afford 281 mg (21% yield) of the title product as a clear oil. This reaction was carried out twice and the combined product was used in the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.73 (m, 4H), 7.69 – 7.54 (m, 4H), 5.06 (d, *J* = 12.1 Hz, 1H), 4.99 (d, *J* = 12.1 Hz, 1H), 4.86 (d, *J* = 12.2 Hz, 1H), 4.75 (d, *J* = 12.1 Hz, 1H), 0.76 (s, 9H), -0.22 (s, 3H), -0.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.62, 139.33, 133.54, 127.89, 127.71, 127.65, 127.15, 127.04, 126.96, 126.88, 126.86, 126.72, 126.56, 63.82, 63.54, 25.96, 18.34, -5.29, -5.37.

IR (cm^{-1}): 2926.2, 2884.4, 2854.1, 1469.7, 1251.3, 1164.4, 1101.7, 1066.3, 1004.1, 955.6, 889.6, 824.3, 772.6, 723.7, 673.8.

HRMS: calculated for $C_{22}H_{28}O_2SiNa^+$ ($[M+Na^+]^+$): 375.1751 Found: 375.1753.



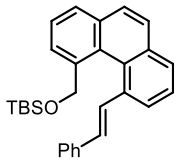
5-(((tert-butyldimethylsilyl)oxy)methyl)phenanthrene-4-carbaldehyde (S37i-b): (5-(((tert-butyldimethylsilyl)oxy)methyl)phenanthren-4-yl)methanol (**S37i-a**) (514 mg, 1.50 mmol), tetrapropylammonium perruthenate (26 mg, 0.07 mmol) and *N*-methylmorpholine *N*-oxide (256 mg, 2.1 mmol) were combined and dissolved in DCM (15 mL). The reaction mixture was stirred at room temperature until judged complete by TLC. The reaction mixture was filtered through a plug of silica eluting with DCM and the solvent was removed by rotary evaporator. The crude product was purified by silica gel column chromatography eluting with hexanes/ethyl acetate, affording 416 mg (81% yield) of product as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.93 (s, 1H), 8.22 (d, *J* = 7.3 Hz, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.79 – 7.65 (m, 4H), 5.03 (br d, *J* = 79.4 Hz, 2H), 0.75 (s, 9H), -0.12 – -0.37 (br m, 6H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 191.83, 140.94, 135.38, 134.14, 133.84, 133.09, 129.91, 128.38, 128.29, 128.10, 127.20, 126.79, 126.55, 126.48, 126.00, 63.50, 25.95, 18.35, -5.33.

IR (cm^{-1}): 1685.4, 1469.9, 1249.6, 1219.7, 1074.3, 832.0, 774.1, 723.9.

HRMS: calculated for $C_{22}H_{26}O_2SiNa^+$ ($[M+Na^+]^+$): 373.1594 Found: 373.1596.



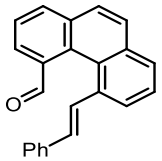
(*E*)-tert-butyldimethyl((5-styrylphenanthren-4-yl)methoxy)silane (S37i-c): NaH (1.33 g, 5.85 mmol) was added to a solution of diethyl benzylphosphonate (1.33 g, 5.85 mmol) in DMF (5 mL) at 0 °C and allowed to stir for 30 min, at which time a solution of 5-(((tert-butyldimethylsilyl)oxy)methyl)phenanthrene-4-carbaldehyde (**S37i-b**) (410 mg, 1.17 mmol) in DMF (3 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, before cooling to 0 °C and quenching with water. The aqueous layer was washed with three portions of ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography eluting with hexanes/ethyl acetate to afford 374 mg (75% yield) of the title compound as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.79 (dd, *J* = 12.7, 7.7 Hz, 2H), 7.71 – 7.55 (m, 4H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.33 (dd, *J* = 19.3, 11.8 Hz, 3H), 7.25 (m, *J* = 13.4 Hz, 2H), 7.05 (d, *J* = 16.4 Hz, 1H), 5.05 (d, *J* = 12.9 Hz, 1H), 4.75 (d, *J* = 13.0 Hz, 1H), 0.66 (s, 9H), -0.33 (s, 3H), -0.45 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 140.29, 137.72, 137.01, 134.48, 133.32, 130.41, 129.11, 128.98, 128.80, 128.30, 127.85, 127.34, 127.32, 126.99, 126.81, 126.62, 126.57, 126.40, 124.25, 64.70, 25.98, 18.39, -5.43, -5.47.

IR (cm^{-1}): 1470.0, 1251.4, 1070.4, 973.1, 834.0, 775.1, 755.4, 721.6, 960.0, 667.7.

HRMS: Calculated for $C_{25}H_{23}OSi^+$ ($[M-C_4H_9]^+$): 367.1518 Found: 367.1518



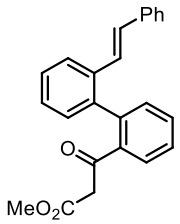
(*E*)-5-styrylphenanthrene-4-carbaldehyde (S37): (*E*)-tert-butyldimethyl((5-styrylphenanthren-4-yl)methoxy)silane (**S37i-d**) (360 mg, 0.85 mmol) was dissolved in THF (8.5 mL) and cooled to 0 °C before a solution of TBAF (1M in THF, 2.2 mL, 2.20 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 3 h, at which time the reaction mixture was diluted with water and diethyl ether. The layers were separated and the organic layer was washed with saturated aqueous ammonium chloride and brine and dried over $MgSO_4$. The solvent was removed by rotary evaporator and the crude material was dissolved in DMSO (3 mL) and IBX (285 mg, 1.01 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water and diethyl ether and filtered through a pad of celite. The layers were separated and the aqueous layer was extracted with two more portions of ether. The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated by rotary evaporator. The crude product was purified by silica gel column chromatography to afford 106 mg (41% yield) of the title compound as a yellow-white foam.

^{1}H NMR (401 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.21 (d, *J* = 7.4 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.90 (dd, *J* = 15.6, 7.5 Hz, 2H), 7.84 – 7.63 (m, 5H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.29 (d, *J* = 7.4 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 189.13, 138.51, 137.43, 135.70, 134.71, 133.95, 132.82, 132.67, 129.97, 128.94, 128.70, 128.32, 128.06, 127.99, 127.57, 127.37, 127.03, 126.89, 126.82, 126.81, 126.27.

IR (cm^{-1}): 1725.7, 1684.3, 1447.6, 1275.5, 1213.9, 1133.5, 1018.3, 969.2, 907.5, 831.5, 761.3, 719.3, 690.1, 646.2.

HRMS: calculated for $C_{23}H_{17}O^+$ ($[M+H^+]^+$): 309.1274 Found: 309.1270.



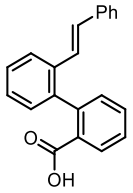
Methyl (*E*)-3-oxo-3-(2'-styryl-[1,1'-biphenyl]-2-yl)propanoate (22h): Sodium hydride (60% dispersion in mineral oil, 181 mg, 4.5 mmol) was suspended in dimethyl carbonate (10 mL) and a solution of **11** (450 mg, 1.5 mmol) in dimethyl carbonate (5 mL) was added dropwise at room temperature. The reaction mixture was then heated to reflux and monitored until complete by TLC analysis. Purification by flash column chromatography eluting with hexanes/EtOAc afforded 174 mg (33% yield) as a mixture of keto/enol tautomers. NMR spectra in $CDCl_3$ appeared as a mixture of keto/enol tautomers.

^{1}H NMR (500 MHz, DMSO) δ 7.83 (t, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.38 – 7.26 (m, 5H), 7.16 (dd, *J* = 29.9, 22.6 Hz, 3H), 6.73 (d, *J* = 16.3 Hz, 1H), 3.70 (d, *J* = 16.6 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.48 (s, 2H).

^{13}C NMR (126 MHz, DMSO) δ 196.16, 167.31, 139.41, 139.38, 138.30, 136.91, 134.96, 131.67, 131.61, 129.95, 129.84, 128.74, 128.70, 128.09, 127.91, 127.74, 127.48, 126.26, 126.20, 125.93, 125.37, 51.74, 47.48.

IR (cm^{-1}): 1741.0, 1692.7, 1616.5, 1593.4, 1470.7, 1436.2, 1388.6, 1319.3, 1273.1, 1241.4, 1092.8, 1073.1, 983.4, 962.8, 823.9.

HRMS: calculated for $C_{24}H_{24}O_3N^+$: 374.1751 Found: 374.1755.



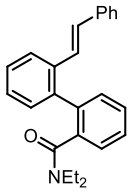
(*E*)-2'-styryl-[1,1'-biphenyl]-2-carboxylic acid (22k): Potassium trimethylsilanoate (1.16g, 9.1 mmol) was dissolved in THF (10 mL) and transferred to a solution of ester **22j** (570 mg, 1.83 mmol) in THF (8 mL) and the mixture was stirred overnight at rt. The solvent was then stripped by rotary evaporator and the crude mixture was taken up in diethyl ether and extracted with two portions of aqueous sodium hydroxide (1M). The combined aqueous layers were then acidified to pH 1 with concentrated HCl and extracted with four portions of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated by rotary evaporator to afford 545 mg (83% yield) of the title compound as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (td, *J* = 7.8, 1.1 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.23 (m, 6H), 7.19 (ddd, *J* = 8.5, 5.8, 2.8 Hz, 1H), 7.16 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.95 (d, *J* = 16.2 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 171.54, 142.60, 140.50, 137.69, 135.58, 132.41, 132.20, 131.02, 130.12, 129.95, 129.60, 128.73, 127.91, 127.68, 127.67, 127.30, 127.05, 126.74, 125.26.

IR (cm^{-1}): 2534.3, 1691.0, 1570.9, 1470.9, 1405.9, 1293.6, 1276.9, 1145.9, 965.9, 805.0, 767.8, 754.8, 691.8, 659.6

HRMS: calculated for $C_{21}H_{16}O_2Na^+$ ($[M+Na^+]^+$): 323.1043 Found: 323.1043.



(E)-N,N-diethyl-2'-styryl-[1,1'-biphenyl]-2-carboxamide (22l): (*E*)-2'-styryl-[1,1'-biphenyl]-2-carboxylic acid (**22k**) (250 mg, 0.83 mmol) was treated with thionyl chloride (0.60 mL, 8.3 mmol) and heated to reflux for 3 h, at which time the reaction mixture was allowed to cool and volatiles were removed by rotary evaporator. The resulting crude material was dissolved in DCM (10 mL) and diethylamine (0.17 mL, 1.66 mmol) was added. The reaction mixture was stirred until judged complete by TLC. The solvent was removed by rotary evaporator and the crude material was purified directly by silica gel column chromatography eluting with hexanes/EtOAc to afford 296 mg (61% yield) of the title compound as a thick yellow oil.

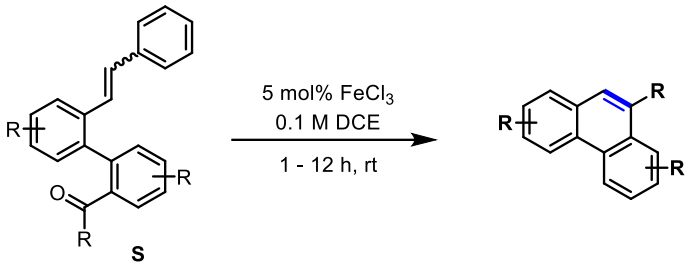
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 3H), 7.38 – 7.13 (m, 9H), 7.05 (m, 2H), 3.73 (s, 1H), 2.94 (m, 2H), 2.63 (br s, 1H), 0.96 (br s, 1H), 0.86 – 0.65 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.15, 137.70, 131.55, 129.79, 128.84, 128.19, 127.88, 126.72, 125.35, 42.71, 38.16, 13.90, 12.08.

IR (cm^{-1}): 1623.3, 1494.1, 1424.4, 1379.3, 1362.2, 1312.3, 1287.7, 1220.0, 1085.8, 962.3, 910.7, 760.0, 729.4, 690.8.

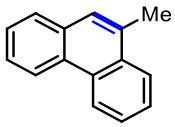
HRMS: calculated for $C_{25}H^{26}NO$ ($[M+H^+]^+$): 356.2009 Found: 356.2012.

A.1.8 Synthesis of metathesis products



General procedure for Carbonyl-Olefin Metathesis:

A flame-dried 1–dram vial was charged with $FeCl_3$ (1 mg, 0.13 mmol) and DCE (1.3 mL) PhMe was used as solvent when indicated. The solution was stirred at room temperature. To this mixture was added starting ketone **S** (0.13 mmol), and the resultant mixture was stirred for the indicated time at room temperature, unless otherwise specified. Upon completion (as determined by TLC analysis), the reaction mixture was passed through a short silica plug eluting with DCM (25 mL). The filtrate was concentrated under reduced pressure, and the crude material was purified using column chromatography, with the indicated eluent to give the pure metathesis adducts.



9-methylphenanthrene (9): The cyclization of **8** was performed on 0.13 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 25 mg (99%) of **9** as a white solid. Spectroscopic data matched reported literature data.[16]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 7.8 Hz, 1H), 8.66 (d, *J* = 7.9 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.62 – 7.53 (m, 3H), 2.75 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 132.46, 132.06, 132.00, 130.36, 129.65, 127.80, 126.71, 126.55, 126.49, 126.19, 125.78, 124.64, 122.98, 122.43, 20.02.

9-methylphenanthrene (9): The cyclization of **11** was performed on 0.13 mmol scale in PhMe as solvent, with a total reaction time of 24 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 22.5 mg (90%) of **9** as a white solid.

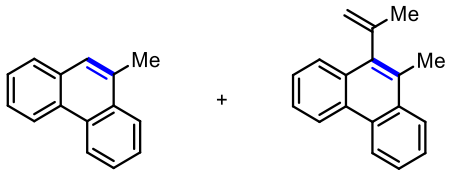
9-methylphenanthrene (9): The cyclization of **12** was performed on 0.13 mmol scale in PhMe as solvent, with a total reaction time of 8 h at 50 ^{o}C. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 20.5 mg (82%) of **9** as a white solid.

9-methylphenanthrene (9): The cyclization of **13** was performed on 0.13 mmol scale in PhMe as solvent, with a total reaction time of 8 h at 50 ^{o}C. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 22.2 mg (89%) of **9** as a white solid.

9-methylphenanthrene (9): The cyclization of **14** was performed on 0.13 mmol scale in PhMe as solvent, with a total reaction time of 6 h at 50 ^{o}C. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 21.4 mg (86%) of **9** as a white solid.

9-methylphenanthrene (9): The cyclization of **15** was performed on 0.13 mmol scale in PhMe as solvent, with a total reaction time of 6 h 50 ^{o}C. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 20.0 mg (80%) of **9** as a white solid.

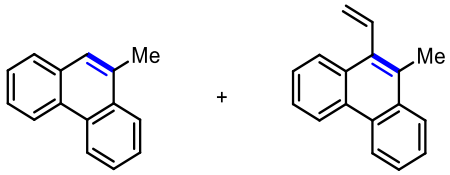
9-methylphenanthrene (9): The cyclization of **16** was performed on 0.13 mmol scale in PhMe as solvent, with a total reaction time of 6 h 50 ^{o}C. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 21.0 mg (84%) of **9** as a white solid.



9-methylphenanthrene + 9-methyl-10-(prop-1-en-2-yl)phenanthrene[50] **(9 + 20):** The cyclization of **17** was performed on 0.13 mmol scale in PhMe as solvent, with a total reaction time of 1 h at rt . Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 26 mg of **9** (19.8 mg, 79%) and **9b** (6.2 mg, 21%) as an inseparable mixture (1.0:0.26; ratio by NMR analysis), as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$; as a mixture of **9** and **9b**) δ 8.73 (d, *J* = 11.4 Hz, 1.10H), 8.70 (d, *J* = 8.9 Hz, 0.34H), 8.66 (d, *J* = 8.0 Hz, 0.94H), 8.15 – 8.10 (m, 0.25H), 8.10 – 8.04 (m, 0.92H), 8.01 (d, *J* = 7.8 Hz, 0.25H), 7.81 (d, *J* = 7.4 Hz, 0.98H), 7.66 (m, 2.24H), 7.62 – 7.52 (m, 3.04H), 5.57 (s, 0.26H), 5.00 (s, 0.28H), 2.74 (s, 3H), 2.69 (s, 0.69H), 2.14 (s, 0.57H).

^{13}C NMR (125 MHz, $CDCl_3$; as a mixture of **9** and **9b**) δ 144.46, 138.48, 132.48, 132.09, 132.02, 131.98, 130.46, 130.38, 129.68, 129.61, 129.53, 128.86, 128.68, 128.56, 128.30, 127.82, 127.58, 126.73, 126.63, 126.57, 126.51, 126.21, 125.90, 125.80, 125.60, 124.89, 124.66, 123.00, 122.77, 122.53, 122.45, 116.71, 24.86, 20.04, 16.49.

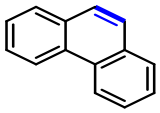


9-methylphenanthrene + 9-methyl-10-vinylphenanthrene (9 + 21): The cyclization of **18** was performed on 0.12 mmol scale in PhMe as solvent, with a total reaction time of 6 h at 50 ºC . Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 19 mg

of **9** (4.5 mg, 18%) and **9c** (13.3 mg, 47%) as an inseparable mixture (0.4:1.0; ratio by NMR analysis), as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$; as a mixture of **9** and **9c**) δ 8.72 (m, 2.19H), 8.67 (d, *J* = 7.9 Hz, 0.36H), 8.14 (m, 1.74H), 8.08 (d, *J* = 7.6 Hz, 0.36H), 7.82 (d, *J* = 7.5 Hz, 0.45H), 7.72 – 7.63 (m, 2.38H), 7.63 – 7.53 (m, 2.39H), 7.13 (dt, *J* = 25.0, 12.5 Hz, 1.05H), 5.85 (d, *J* = 11.4 Hz, 1H), 5.42 (d, *J* = 17.9 Hz, 0.97H), 2.76 (s, 3.82H).

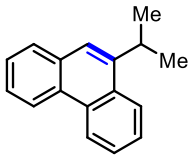
^{13}C NMR (125 MHz, $CDCl_3$; as a mixture of **9** and **9c**) δ 135.75, 133.93, 132.69, 132.30, 132.23, 131.35, 130.59, 129.93, 129.89, 129.55, 129.36, 129.29, 129.22, 128.04, 126.94, 126.88, 126.79, 126.73, 126.62, 126.46, 126.42, 126.26, 126.01, 125.90, 125.32, 124.87, 123.21, 122.98, 122.77, 122.66, 121.79, 20.25, 17.17.



Phenanthrene (23b): The cyclization of **22b** was performed on 0.13 mmol scale (37 mg) with a total reaction time of 4 h. Purification by flash column chromatography eluting with hexanes/EtOAc provided 18 mg (75%) of **23b** as a white solid. Spectroscopic data matched that reported.[51]

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.70 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 7.8 Hz, 2H), 7.75 (s, 2H), 7.67 (t, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 2H).

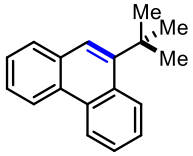
^{13}C NMR (176 MHz, $CDCl_3$) δ 132.26, 130.52, 128.78, 127.13, 126.77, 122.87.



9-Isopropylphenanthrene (23c): The cyclization of **22c** was performed on 0.13 mmol scale with a total reaction time of 4 h. Purification by flash column chromatography eluting with hexanes/EtOAc provided 23 mg (79%) of **23c** as a colorless oil.[52]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 – 8.71 (m, 1H), 8.69 – 8.62 (m, 1H), 8.21 (m, 1H), 7.91 – 7.80 (m, 1H), 7.74 – 7.46 (m, 5H), 3.82 – 3.69 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H).

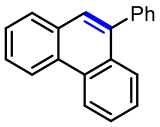
^{13}C NMR (175 MHz, $CDCl_3$) δ 142.80, 132.19, 131.12, 130.96, 129.59, 128.51, 126.75, 126.66, 126.16, 126.12, 124.17, 123.52, 122.59, 122.42, 28.83, 23.55.



9-(*tert*-butyl)phenanthrene (23d): The cyclization of **22d** was performed on 0.13 mmol scale with a total reaction time of 12 h at 50 °C. Purification by flash column chromatography eluting with hexanes/EtOAc provided 16.4 mg (55%) of **23d** as a white solid. Spectroscopic data matched that reported.[53]

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.82 – 8.77 (m, 1H), 8.64 (d, *J* = 8.1 Hz, 1H), 8.54 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.76 (s, 1H), 7.61 (m, 4H), 1.70 (s, 9H).

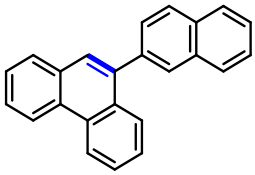
^{13}C NMR (175 MHz, $CDCl_3$) δ 144.19, 132.01, 131.87, 131.06, 129.86, 128.89, 127.88, 126.78, 126.44, 125.58, 125.52, 124.31, 123.87, 122.40, 36.15, 32.06.



9-Phenylphenanthrene (23e): The cyclization of **22e** was performed on 0.13 mmol scale (47 mg) with a total reaction time of 24 h. Purification by flash column chromatography eluting with hexanes/EtOAc provided 22 mg (67%) of **23e** as a white solid. Spectroscopic data matched that reported.[54]

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.79 (d, *J* = 8.3 Hz, 1H), 8.74 (d, *J* = 8.2 Hz, 1H), 7.92 (t, *J* = 8.7 Hz, 2H), 7.79 – 7.38 (m, 10H).

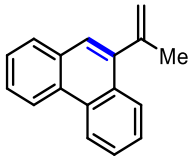
^{13}C NMR (176 MHz, $CDCl_3$) δ 141.02, 139.00, 131.78, 131.36, 130.84, 130.28, 130.17, 128.88, 128.52, 127.72, 127.58, 127.15, 127.06, 126.80, 126.71, 126.66, 123.11, 122.75.



9-(naphthalen-2-yl)phenanthrene (23f): The cyclization of **22f** was performed on 0.13 mmol scale with a total reaction time of 24 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 21 mg (53%) of **23f** as a white solid. Spectroscopic data matched reported literature data.[55]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 8.3 Hz, 1H), 8.76 (d, *J* = 8.2 Hz, 1H), 8.03 (s, 1H), 8.00 – 7.89 (m, 5H), 7.79 (s, 1H), 7.69 (m, 3H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.60 – 7.50 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.92, 138.60, 133.70, 132.89, 131.82, 131.46, 130.89, 130.26, 128.92, 128.91, 128.65, 128.29, 128.08, 128.00, 127.88, 127.24, 127.11, 126.87, 126.78, 126.73, 126.56, 126.31, 123.16, 122.79.



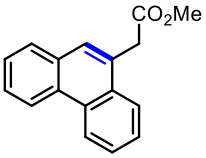
9-(prop-1-en-2-yl)phenanthrene (23g): The cyclization of **22g** was performed on 0.13 mmol scale with a total reaction time of 12 h at 50 °C. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 14 mg (50%) of **23g** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 8.2 Hz, 1H), 8.68 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.69 – 7.55 (m, 5H), 5.44 (s, 1H), 5.15 (s, 1H), 2.25 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.25, 141.05, 131.89, 130.49, 130.02, 128.65, 126.90, 126.67, 126.66, 126.54, 126.52, 125.14, 123.14, 122.69, 116.33, 25.25.

IR (cm^{-1}): 3072.8, 2923.1, 1492.8, 1449.3, 1372.0, 1258.0, 1040.0, 905.3, 767.6.

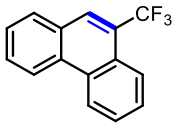
HRMS: calculated for $C_{17}H_{14}$ $[M]^+$: 218.1096, found: 218.1096.



Methyl 2-(phenanthren-9-yl)acetate (23h): The cyclization of **22h** was performed on 0.13 mmol scale (49 mg) with a total reaction time of 24 h. Purification by flash column chromatography eluting with hexanes/EtOAc provided 24 mg (72%) of **23h** as a pale yellow solid. Spectroscopic data matched that reported.[56]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.72 (m, 1H), 8.67 (d, *J* = 8.2 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.88 – 7.83 (m, 1H), 7.72 – 7.54 (m, 55H), 4.13 (s, 2H), 3.70 (s, 3H).

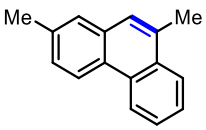
^{13}C NMR (175 MHz, $CDCl_3$) δ 172.26, 131.76, 131.29, 130.95, 130.45, 129.19, 129.12, 128.60, 127.13, 126.98, 126.91, 126.73, 124.62, 123.44, 122.73, 52.44, 39.86.



9-(trifluoromethyl)phenanthrene (23i): The cyclization of **22i** was performed on 0.13 mmol scale (47 mg) with a total reaction time of 1 h at 50 °C. Purification by flash column chromatography eluting with hexanes/EtOAc provided 16.5 mg (52%) of **23i** as a white solid. Spectroscopic data matched that reported.[57]

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.2 Hz, 1H), 8.71 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.19 (s, 1H), 7.97 (t, *J* = 9.5 Hz, 1H), 7.78 (t, *J* = 7.1 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.0 Hz, 1H).

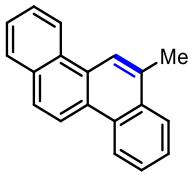
^{13}C NMR (175 MHz, $CDCl_3$) δ 132.02, 131.20, 130.14, 129.68, 129.21, 127.69, 127.58, 127.55, 127.27 (q, J= 6.3 Hz), 127.04, 125.41 (q, J= 2.7 Hz) , 124.89 (q, J= 29.8), 123.40, 122.91.



2,9-dimethylphenanthrene (24): The cyclization of **S2** was performed on 0.13 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 24 mg (89%) of **24** as a white solid. Spectroscopic data matched reported literature data.[58]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 – 8.67 (m, 1H), 8.46 (s, 1H), 8.11 – 8.01 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.56 (s, 1H), 7.39 (dd, *J* = 24.8, 8.0 Hz, 1H), 2.73, 3H), 2.63 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.60, 132.43, 131.60, 130.36, 130.16, 129.92, 128.50, 127.89, 126.77, 126.57, 126.19, 124.84, 123.18, 122.44, 22.31, 20.19.



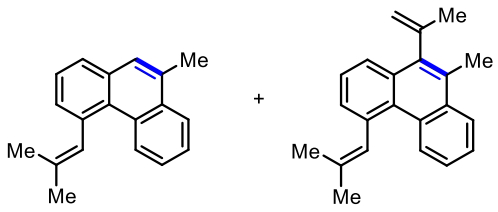
6-methylchrysene (25): The cyclization of **S3** was performed on 0.15 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 29 mg (80%) of **25** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 14.7, 8.3 Hz, 2H), 8.71 (d, *J* = 9.1 Hz, 1H), 8.58 (s, 1H), 8.21 – 8.12 (m, 1H), 8.03 – 7.90 (m, 2H), 7.71 (qdd, *J* = 6.8, 6.2, 1.4 Hz, 3H), 7.66 – 7.56 (m, 1H), 2.91 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.38, 132.49, 132.17, 130.87, 130.42, 128.74, 127.53, 126.73, 126.68, 126.56, 126.51, 126.46, 124.93, 123.79, 123.32, 121.75, 121.36, 20.85.

IR (cm^{-1}): 2923.8, 1596.5, 1513.9, 1483.1, 1438.3, 1399.6, 1244.5, 1156.1, 1035.6, 873.9, 823.3, 755.2.

HRMS: calculated for $C_{19}H_{14}$ $[M]^+$: 242.1096 found: 242.1095.



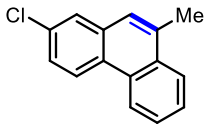
9-methyl-4-(2-methylprop-1-en-1-yl)phenanthrene + 9-methyl-4-(2-methylprop-1-en-1-yl)-10-(prop-1-en-2-yl)phenanthrene (26 + 26b): The cyclization of **S4** was performed on 0.12 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 28 mg of **26** (18 mg, 64%) and **26b** (10 mg, 30%) as an inseparable mixture (1:0.69; ratio by NMR analysis), as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$; as a mixture of **26** and **26b**) δ 9.28 (d, *J* = 8.4 Hz, 1H), 9.24 (d, *J* = 8.5 Hz, 0.57H), 8.13 (d, *J* = 8.2 Hz, 0.66H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 0.64H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.66 – 7.55 (m, 3.62H), 7.52 (m, 1.76H), 7.37 (t, *J* = 8.3 Hz, 1.66H), 6.83 (s, 1H), 6.81 (s, 0.55H), 5.57 (s, 0.63H), 5.01 (s, 0.62H), 2.73 (s, 3H), 2.69 (s, 1.52H), 2.15 (s, 1.64H), 2.10 (s, *J* = 3.6 Hz, 4.43H), 1.88 (s, 1.60H), 1.83 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$; as a mixture of **26** and **26b**) δ 145.22, 139.09, 136.66, 136.55, 133.45, 133.28, 133.14, 132.80, 132.37, 132.35, 132.00, 131.80, 131.10, 130.45, 130.20, 130.02, 129.92, 128.81, 128.75, 128.31, 127.94, 127.67, 127.14, 126.26, 126.11, 125.89, 125.71, 125.49, 125.30, 124.81, 124.53, 124.41, 116.94, 26.14, 26.09, 25.17, 20.22, 19.88, 19.80, 16.85.

HRMS (26): calculated for $C_{19}H_{18}$ ([M]$^{+}$): 246.1409, found: 246.1405.

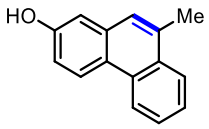
HRMS (26b): calculated for $C_{19}H_{18}$ ([M]$^{+}$): 286.1722, found: 286.1721.



2-chloro-9-methylphenanthrene (27): The cyclization of **S5** was performed on 0.13 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 25 mg (85%) of **27** as a white solid. Spectroscopic data matched reported literature data.[58]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 9.7, 7.0 Hz, 1H), 8.55 (dd, *J* = 8.8, 2.3 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.72 – 7.62 (m, 2H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 15.8 Hz, 1H), 2.74 (d, *J* = 7.7 Hz, 3H).

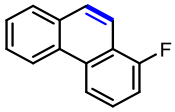
^{13}C NMR (125 MHz, $CDCl_3$) δ 134.24, 133.26, 132.52, 132.15, 130.15, 128.21, 127.01, 126.93, 126.84, 126.42, 125.85, 125.00, 124.35, 123.13.



9-methylphenanthren-2-ol (28): The cyclization of **S25** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 24 mg (75%) of **28** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.2 Hz, 1H), 8.54 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (s, 1H), 7.17 – 7.13 (m, 2H), 4.95 (b, 1H), 2.72 (s, 3H).

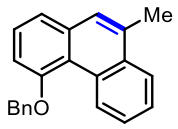
^{13}C NMR (175 MHz, $CDCl_3$) δ 154.13, 133.51, 133.42, 131.03, 130.48, 126.36, 125.89, 125.59, 124.68, 124.43, 124.14, 122.42, 115.76, 111.06, 20.06.



1-fluorophenanthrene (29): The cyclization of **S6** was performed on 0.13 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 26 mg (99%) of **29** as a pale yellow solid. Spectroscopic data matched reported literature data.[59]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.2 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 9.1 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.71 – 7.54 (m, 3H), 7.29 (m, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 159.28 (d, *J* = 250.1 Hz), 132.15 (d, *J* = 4.4 Hz), 132.08, 129.64 (d, *J* = 2.6 Hz), 128.78, 127.37 (d, *J* = 1.8 Hz), 127.10, 127.0, 126.47 (d, *J* = 8.7 Hz), 123.01, 121.56 (d, *J* = 15.4 Hz), 118.51 (d, *J* = 7.0 Hz), 118.39 (d, *J* = 3.9 Hz), 111.01 (d, *J* = 20.4 Hz).



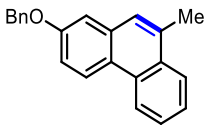
4-(benzyloxy)-9-methylphenanthrene (30): The cyclization of **S8** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 24 mg (71%) of **30** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (t, *J* = 12.2 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.52 (m, 5H), 7.50 – 7.42 (m, 4H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.17 (dd, *J* = 5.9, 3.1 Hz, 1H), 5.40 (s, *J* = 11.4 Hz, 2H), 2.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.57, 137.00, 134.59, 133.07, 132.59, 130.47, 129.03, 128.65, 128.00, 127.66, 127.23, 126.45, 125.98, 125.80, 123.97, 121.25, 120.30, 109.39, 71.24, 20.15.

IR (cm^{-1}): 2921.0, 1567.5, 1441.5, 1301.0, 1241.4, 1229.9, 1055.6, 880.7, 744.7, 757.7, 715.8, 691.5.

HRMS: calculated for $C_{22}H_{19}O$ ($[M + H^+]^+$): 299.1436, found: 299.1430.



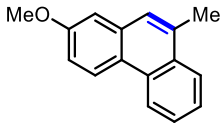
2-(benzyloxy)-9-methylphenanthrene (31): The cyclization of **S9** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 38 mg (97%) of **31** as a yellow-white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.2 Hz, 1H), 8.56 (d, *J* = 8.9 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.60 – 7.54 (m, 1H), 7.51 (m, *J* = 8.2 Hz, 3H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.30 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.27 (d, *J* = 2.6 Hz, 1H), 5.23 (s, 2H), 2.73 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 157.73, 137.19, 133.57, 133.41, 131.29, 130.71, 128.84, 128.23, 127.79, 126.58, 126.53, 125.78, 124.88, 124.39, 124.38, 122.74, 116.88, 109.52, 70.34, 20.28.

IR (cm^{-1}): 1600.2, 1492.1, 1447.3, 1382.6, 1363.1, 1305.8, 1228.0, 1181.0, 1020.4, 995.7, 887.6, 827.8, 777.5, 7449, 720.7, 694.1.

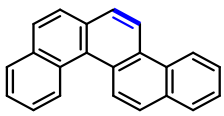
HRMS: Calculated for $C_{22}H_{19}O^+$ ($[M + H^+]^+$): 299.1430 Found: 299.1433.



2-methoxy-9-methylphenanthrene (32): The cyclization of **S10** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 25 mg (86%) of **32** as a white solid. Spectroscopic data matched reported literature data.[58]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 8.2, 0.5 Hz, 1H), 8.55 (d, *J* = 9.0 Hz, 1H), 8.02 (dt, *J* = 10.1, 5.0 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.61 – 7.55 (m, 1H), 7.52 (s, 1H), 7.23 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 3.96 (s, 1H), 2.73 (d, *J* = 0.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.55, 133.62, 133.40, 131.26, 130.75, 126.59, 126.52, 125.73, 124.88, 124.33, 124.23, 122.72, 116.41, 108.21, 55.60, 20.28.

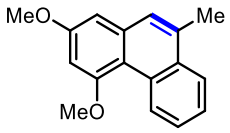


benzo[c]chrysene (33): The cyclization of **S29** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc

(9:1) provided 35 mg (96%) of **33** as a white solid. Spectroscopic data matched reported literature data.[11b]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (t, *J* = 8.3 Hz, 2H), 8.89 – 8.80 (m, 2H), 8.09 – 8.00 (m, 3H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.77 – 7.62 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.85, 131.83, 131.24, 130.77, 130.43, 130.27, 128.74, 128.71, 128.39, 128.27, 127.75, 127.26, 126.87, 126.85, 126.80, 126.64, 126.44, 126.31, 126.16, 123.57, 122.08.



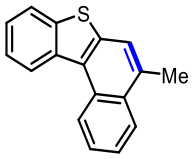
2,4-dimethoxy-9-methylphenanthrene (34): The cyclization of **S12** was performed on 0.13 mmol scale with a total reaction time of 12 h at 50 °C. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 19 mg (57%) of **34** as a white solid. Starting material was not fully consumed in the reaction.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.61 (d, *J* = 8.6 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.50 (s, 1H), 6.85 (s, 1H), 6.74 (s, 1H), 4.10 (d, *J* = 1.5 Hz, 3H), 3.96 (d, *J* = 1.6 Hz, 3H), 2.71 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 160.03, 158.39, 135.61, 133.85, 131.77, 130.92, 128.11, 127.29, 126.31, 125.07, 124.25, 115.16, 101.04, 98.95, 55.94, 55.58, 20.39.

IR (cm^{-1}): 1613.2, 1572.0, 1449.7, 1345.8, 1325.2, 1208.3, 1158.8, 1104.8, 1062.2, 1004.8, 890.9, 802.5, 753.4, 717.9, 626.2.

HRMS: Calculated for $C_{17}H_{17}O_2^+$ ($[M + H^+]^+$) : 253.1223 Found: 253.1224.



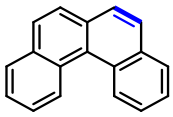
5-methylbenzo[b]naphtho[1,2-d]thiophene (35): The cyclization of **S11** was performed on 0.13 mmol scale with a total reaction time of 4 h at 50 °C and 20 mol% $FeCl_3$. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 20 mg (62%) of **35** as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (d, *J* = 8.5 Hz, 1H), 8.83 (d, *J* = 8.3 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 2.82 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.56, 138.74, 137.08, 134.26, 131.51, 131.03, 128.01, 126.99, 125.67, 125.07, 125.01, 124.99, 124.63, 123.89, 123.42, 121.78, 20.44.

IR (cm^{-1}): 2920.2, 1594.0, 1510.6, 1461.3, 1373.9, 1235.6, 1211.7, 1163.8, 886.0, 745.4.

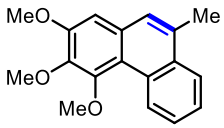
HRMS: calculated for $C_{17}H_{12}S$ $[M]^+$: 248.0660 found: 248.0662.



benzo[c]phenanthrene (36): The cyclization of **S7** was performed on 0.14 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (19:1) provided 29 mg (89%) of **36** as a white solid. Spectroscopic data matched reported literature data.[60]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 7.9 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.72 – 7.68 (m, 2H), 7.64 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.49, 130.97, 130.30, 128.52, 127.89, 127.45, 127.33, 126.83, 126.10, 125.83.



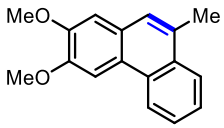
2,3,4-Trimethoxy-9-methylphenanthrene (37): The cyclization of **S13** was performed on 0.13 mmol scale (51 mg) with heating to 50°C for a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc provided 32 mg (87%) of **37** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 – 9.53 (m, 1H), 8.08 – 7.99 (m, 1H), 7.68 – 7.55 (m, 2H), 7.47 (s, 1H), 7.03 (s, 1H), 4.03 (s, 3H), 4.01 (s, 6H), 2.70 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 152.70, 152.61, 142.49, 132.52, 131.89, 130.35, 130.28, 127.21, 126.87, 126.56, 125.69, 124.43, 118.31, 104.79, 61.52, 60.47, 56.06, 20.30.

IR (cm^{-1}): 1598.3, 1493.4, 1449.7, 1399.5, 1356.0, 1248.0, 1140.7, 1089.1, 1000.6, 890.2, 760.1, 750.5, 701.4.

HRMS: Calculated for $C_{18}H_{19}O_3^+$: 283.1329 Found: 283.1329.



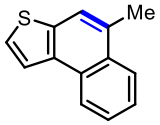
2,3-dimethoxy-9-methylphenanthrene (38): The cyclization of **S14** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 28 mg (86%) of **38** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.9 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.99 (s, 1H), 7.67 – 7.61 (m, 1H), 7.61 – 7.56 (m, 1H), 7.50 (s, 1H), 7.18 (s, 1H), 4.11 (s, 3H), 4.04 (s, 3H), 2.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.57, 148.98, 131.48, 130.94, 130.10, 127.33, 126.14, 126.06, 125.70, 125.00, 124.25, 122.72, 107.96, 103.53, 56.22, 56.11, 20.11.

IR (cm^{-1}): 2935.6, 1604.6, 1504.5, 1463.5, 1437.4, 1391.4, 1251.0, 1216.2, 1193.9, 1154.7, 1021.6, 752.1.

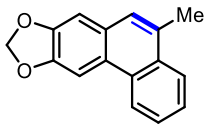
HRMS: calculated for $C_{17}H_{17}O_2$ ($[M + H^+]^+$): 253.1223, found: 253.1224.



5-methylnaphtho[2,1-b]thiophene (39): The cyclization of **S22** was performed on 0.13 mmol scale with a total reaction time of 12 h 50 °C. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 13 mg (51%) of **39** as a white solid. Starting material decomposition was observed at elevated reaction temperatures Spectroscopic data matched reported literature data.[61]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.33 (m, 1H), 8.10 – 8.05 (m, 1H), 7.98 – 7.93 (m, 1H), 7.75 (s, 1H), 7.65 – 7.60 (m, 1H), 7.60 – 7.55 (m, 1H), 7.50 (d, *J* = 5.4 Hz, 1H), 2.77 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.48, 135.01, 131.42, 130.71, 129.58, 126.34, 125.36, 125.08, 124.71, 124.29, 122.19, 121.02, 20.25.



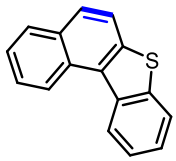
5-methylphenanthro[2,3-d][1,3]dioxole (40): The cyclization of **S16** was performed on 0.13 mmol scale with a total reaction time of 1 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 31 mg (99%) of **40** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 – 8.47 (m, 1H), 8.05 – 8.01 (m, 1H), 8.00 (s, 1H), 7.66 – 7.55 (m, 2H), 7.47 (s, 1H), 7.15 (s, 1H), 6.09 (s, 2H), 2.71 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.71, 147.68, 131.49, 131.01, 130.40, 128.58, 126.63, 126.13, 125.85, 125.79, 124.92, 122.98, 105.36, 101.39, 101.04, 20.04.

IR (cm^{-1}): 2902.5, 1482.0, 1451.9, 1395.9, 1225.8, 1180.6, 1036.5, 938.4, 881.8, 847.4, 758.2, 701.0.

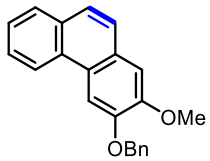
HRMS: calculated for $C_{16}H_{13}O_2$ ($[M + H^+]^+$): 237.0910, found: 237.0910.



benzo[b]naphtho[1,2-d]thiophene (41): The cyclization of **S17** was performed on 0.13 mmol scale with a total reaction time of 6 h at 50 ºC and 20 mol% $FeCl_3$. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 21 mg (67%) of **41** as a pale yellow solid. Spectroscopic data matched reported literature data.[62]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (d, *J* = 8.5 Hz, 1H), 8.87 (d, *J* = 8.3 Hz, 1H), 8.03 (dd, *J* = 11.6, 8.3 Hz, 2H), 7.91 (q, *J* = 8.7 Hz, 2H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.72, 138.60, 136.70, 131.92, 130.64, 129.44, 129.03, 127.84, 127.13, 125.21, 124.89, 124.80, 124.71, 123.20, 123.18, 121.07.



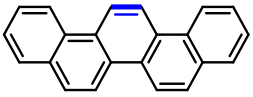
3-(benzyloxy)-2-methoxyphenanthrene (42): The cyclization of **S18** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 31 mg (75%) of **42** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.3 Hz, 1H), 8.04 (s, *J* = 5.3 Hz, 1H), 7.86 (t, *J* = 8.3 Hz, 1H), 7.62 (m, 2H), 7.56 – 7.50 (m, 1H), 7.43 – 7.37 (m, 1H), 7.33 (dd, *J* = 13.5, 6.1 Hz, 1H), 7.29 (s, 1H), 5.32 (s, 1H), 4.12 (d, *J* = 3.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.05, 148.71, 137.05, 131.60, 129.91, 128.87, 128.85, 128.17, 127.57, 127.26, 126.38, 126.20, 125.80, 125.35, 122.38, 110.86, 103.95, 71.08, 56.34.

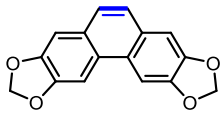
IR (cm^{-1}): 2930.4, 1602.1, 1506.5, 1467.2, 1379.8, 1265.1, 1216.8, 1156.0, 1012.3, 855.1, 739.8, 695.6.

HRMS: calculated for $C_{22}H_{19}O_2$ ($[M + NH_4^+]^+$): 332.1645, found: 332.1644.



Picene (43): The cyclization of **S32** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by preparative thin layer chromatography eluting with hexanes/EtOAc (4:1) provided 19 mg (53%) of **43** as a pale brown solid. Picene **43** is very insoluble in organic solvents. Spectroscopic data matched reported literature data.[63]

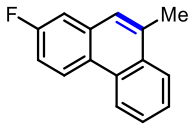
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 2H), 8.87 (d, *J* = 8.4 Hz, 2H), 8.80 (d, *J* = 9.2 Hz, 2H), 8.03 (t, *J* = 9.0 Hz, 3H), 7.75 (t, *J* = 7.1 Hz, 2H), 7.67 (t, *J* = 7.3 Hz, 3H).



phenanthro[2,3-d:6,7-d']bis([1,3]dioxole) (44): The cyclization of **S19** was performed on 0.11 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 20 mg (68%) of **44** as a white solid. Spectroscopic data matched reported literature data.[64]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.50 (s, 1H), 7.18 (s, 1H), 6.08 (s, 2H).

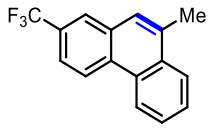
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.17, 147.20, 127.96, 126.56, 124.99, 105.70, 101.43, 100.66.



2-fluoro-9-methylphenanthrene (45): The cyclization of **S20** was performed on 0.14 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 26 mg (87%) of **45** as a white solid. Spectroscopic data matched reported literature data.[58]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 14.5, 6.7 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.66 (qd, *J* = 13.6, 6.9 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.49 – 7.39 (m, 1H), 7.32 (tt, *J* = 16.1, 8.1 Hz, 1H), 2.74 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.63 (d, *J* = 245.8 Hz), 134.25, 133.62 (d, *J* = 8.7 Hz), 131.75, 130.38, 126.55, 126.48, 126.20 (d, *J* = 3.6 Hz), 125.02, 125.0 (d, *J*= 8.7), 123.02, 114.87 (d, *J* = 23.7 Hz), 112.03 (d, *J* = 20.3 Hz), 20.27.

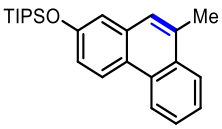


9-methyl-2-(trifluoromethyl)phenanthrene (46): The cyclization of **S21** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (12:1) provided 31 mg (93%) of **46** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (m, 3H), 8.13 – 8.06 (m, 2H), 7.78 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.63 (s, 1H), 2.76 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 134.22, 132.74, 131.67, 131.29, 129.62, 128.32 (q, *J* = 32.2 Hz), 127.61, 126.76, 126.43, 125.07 (q, *J* = 4.2 Hz), 124.85, 124.45 (q, *J*= 271.3), 123.40, 123.31, 121.60 (q, *J* = 3.2 Hz).

IR (cm^{-1}): 2923.3, 1361.7, 1331.8, 1279.8, 1200.6, 1165.7, 1114.1, 1075.8, 906.2, 825.4, 754.8, 723.6, 706.0.

HRMS: Calculated for $C_{16}H_{11}F_3^+$ ($[M]^+$): 260.0813 found: 260.0813.



triisopropyl((9-methylphenanthren-2-yl)oxy)silane (47): The cyclization of **S15** was performed on 0.13 mmol scale with a total reaction time of 6 h at 50 °C. Purification by flash column

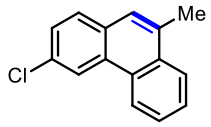
chromatography eluting with hexanes/EtOAc (19:1) provided 15 mg (65% brsm) of **47** as a white solid and 10 mg of recovered **S15** (75% conv).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.2 Hz, 1H), 8.51 (d, *J* = 8.9 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.71 (s, 3H), 1.33 (h, *J* = 7.4 Hz, 3H), 1.15 (d, *J* = 7.5 Hz, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.01, 133.68, 133.10, 131.34, 130.75, 126.48, 125.75, 124.86, 124.49, 124.15, 122.75, 120.49, 116.19, 20.26, 18.21, 12.98.

IR (cm^{-1}): 2943.0, 2866.7, 1611.6, 1491.8, 1462.6, 1450.2, 1308.0, 1251.9, 1175.7, 967.9, 884.1, 858.6, 737.8.

HRMS: Calculated for $C_{24}H_{32}OSi^+$ ($[M]^+$): 364.2222 found: 364.2230.



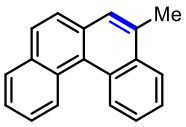
3-chloro-9-methylphenanthrene (48): The cyclization of **S23** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 24 mg (92%) of **48** as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.65 – 8.62 (m, 1H), 8.61 (d, *J* = 1.5 Hz, 1H), 8.08 – 8.04 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.55 (s, 1H), 7.51 (dd, *J* = 8.4, 2.0 Hz, 1H), 2.73 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 133.16, 132.50, 131.93, 130.97, 130.48, 129.62, 129.41, 127.37, 127.28, 126.73, 126.24, 124.96, 123.27, 122.41, 20.24.

IR (cm^{-1}): 1750.7, 1594.9, 1491.1, 1445.6, 1429.2, 1410.0, 1371.0, 1214.3, 1160.8, 1093.6, 1065.2, 1019.4, 944.8, 870.6, 803.9, 743.7, 715.7, 684.1.

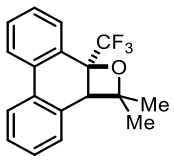
HRMS: calculated for $C_{15}H_{11}Cl$ $[M]^+$: 226.0549 found: 226.0546.

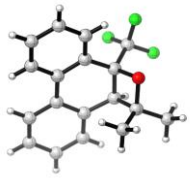


5-methylbenzo[c]phenanthrene (49): The cyclization of **S24** was performed on 0.12 mmol scale with a total reaction time of 12 h at 50 °C. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 14 mg (48%) of **49** as a yellow solid. Spectroscopic data matched reported literature data.[58]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (d, *J* = 8.3 Hz, 1H), 9.08 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.73 – 7.64 (m, 4H), 7.60 (t, *J* = 7.4 Hz, 1H), 2.82 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.45, 133.28, 130.99, 130.67, 130.43, 128.74, 128.60, 128.07, 127.70, 127.33, 126.66, 126.56, 126.29, 126.01, 125.86, 125.65, 124.64, 19.98.





x-ray

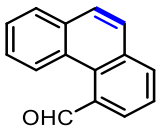
(2aR,10bS)-2,2-dimethyl-10b-(trifluoromethyl)-2a,10b-dihydro-2H-phenanthro[9,10-b]oxete (6): The cyclization of **S31** was performed on 0.13 mmol scale in PhMe with a total reaction time of 4 h. Purification by preparative thin layer chromatography eluting with hexanes/EtOAc (9:1) provided 17.8 mg (45%) of **6** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 2.3 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 4.34 (s, 1H), 1.66 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 132.78, 131.92, 130.34, 130.24, 129.72, 129.09, 128.93, 128.89, 128.68, 128.67, 123.71, 123.51, 88.47, 46.43, 30.76, 24.98.

IR (cm^{-1}): 2924.2, 2851.2, 1449.9, 1303.9, 1259.8, 1227.9, 1154.4, 1019.4, 974.2, 940.1, 844.2, 774.4, 757.7, 738.5, 731.0. Unable to observe the trifluoromethyl quartet after 3000 scans.

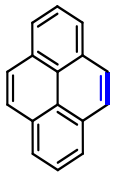
HRMS: calculated for $C_{17}H_{14}$ $[M]^+$: 304.1075 found: 304.1080.



phenanthrene-4-carbaldehyde (50): The cyclization of **S26** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 27 mg (90%) of **50** as a pale yellow solid. Spectroscopic data matched reported literature data.[62]

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.14 – 8.07 (m, 3H), 8.00 (d, *J* = 7.1 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.75 – 7.68 (m, 3H).

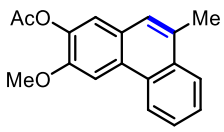
^{13}C NMR (125 MHz, $CDCl_3$) δ 193.33, 135.53, 133.73, 133.46, 133.39, 130.68, 129.33, 128.87, 128.47, 128.20, 127.83, 127.03, 126.81, 126.33.



pyrene (51): The cyclization of **S37** was performed on 0.13 mmol scale with a total reaction time of 30 minutes. Purification by flash column chromatography eluting with hexanes/EtOAc provided 18 mg (70%) of **51** as an off-white solid. Spectroscopic data matched reported literature data.[66]

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.19 (d, *J* = 7.5 Hz, 2H), 8.09 (s, 2H), 8.02 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 131.34, 127.61, 126.08, 125.16, 124.87.



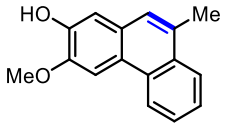
3-methoxy-9-methylphenanthren-2-yl acetate (52): The cyclization of **S34** was performed on 0.13 mmol scale with a total reaction time of 4 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 33 mg (90%) of **52** as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 – 8.57 (m, 1H), 8.08 (s, 1H), 8.07 – 8.03 (m, 1H), 7.67 – 7.62 (m, 2H), 7.47 (s, 2H), 4.06 (s, 3H), 2.71 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.42, 150.19, 140.31, 132.33, 131.22, 129.87, 128.82, 126.80, 126.68, 126.22, 126.05, 125.06, 123.16, 121.00, 104.54, 56.26, 20.99, 20.10.

IR (cm^{-1}): 2938.3, 1761.7, 1620.9, 1607.1, 1503.6, 1463.4, 1440.0, 1366.9, 1254.9, 1211.1, 1195.4, 1135.2, 1027.7, 908.7, 754.2, 734.2, 624.9.

HRMS: calculated for $C_{18}H_{17}O_3$ ($[M + H^+]^+$): 281.1172, found: 281.1172.



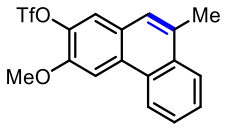
3-methoxy-9-methylphenanthren-2-ol (53): The cyclization of **S27** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 24 mg (78%) of **53** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.98 (s, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (s, 1H), 7.28 (s, 1H), 5.90 (s, 1H), 4.12 (s, 3H), 2.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.81, 145.95, 131.42, 131.04, 130.24, 127.87, 126.14, 126.03, 125.62, 125.04, 124.04, 122.58, 111.05, 102.79, 56.25, 20.12.

IR (cm^{-1}): 3396.0, 2932.2, 1529.5, 1503.2, 1438.0, 1246.4, 1216.6, 1157.6, 1029.4, 840.1, 750.0.

HRMS: calculated for $C_{16}H_{15}O_2$ ($[M + H^+]^+$): 239.1067, found: 239.1064.



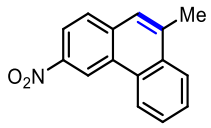
3-methoxy-9-methylphenanthren-2-yl trifluoromethanesulfonate (54): The cyclization of **S35** was performed on 0.13 mmol scale with a total reaction time of 2 h. Purification by flash column chromatography eluting with hexanes/EtOAc (10:1) provided 42 mg (87%) of **54** as a pale yellow solid.

^{1}H NMR (500 MHz, $cdcl_3$) δ 8.60 – 8.56 (m, 1H), 8.11 (s, 1H), 8.08 – 8.02 (m, 1H), 7.71 – 7.66 (m, 2H), 7.64 (m, 1H), 7.48 (s, 1H), 4.12 (s, 3H), 2.71 (s, 3H).

^{13}C NMR (125 MHz, $cdcl_3$) δ 149.40, 138.68, 132.45, 132.10, 129.92, 129.11, 127.26, 126.39, 126.13, 125.48, 124.95, 123.10, 120.66, 118.82 (q, *J*= 318.8), 105.13, 56.29, 19.84.

IR (cm^{-1}): 2930.0, 1622.4, 1506.0, 1418.7, 1246.1, 1201.3, 1139.0, 1101.3, 1026.3, 968.0, 862.4, 755.5.

HRMS: Calculated for $C_{17}H_{13}O_4F_3S^+$ ($[M]^+$): 370.0487 found: 370.0486.



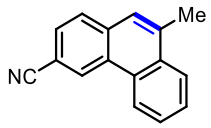
9-methyl-3-nitrophenanthrene (55): The cyclization of **S28** was performed on 0.13 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 26 mg (93%) of **55** as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.76 (d, *J* = 7.5 Hz, 1H), 8.34 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.76 (pd, *J* = 7.0, 1.5 Hz, 2H), 7.64 (s, 1H), 2.79 (s, *J* = 0.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.64, 137.86, 135.93, 132.55, 130.53, 129.40, 129.05, 128.17, 127.75, 125.99, 125.29, 123.49, 120.72, 119.26, 20.57.

IR (cm^{-1}): 3085.7, 1609.8, 1503.9, 1333.3, 1302.0, 1100.1, 889.2, 872.3, 750.0, 741.9, 710.4.

HRMS: Calculated for $C_{15}H_{11}NO_2^+$ ($[M]^+$): 237.0790 found: 237.0786.



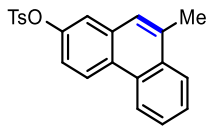
9-methylphenanthrene-2-carbonitrile (56): The cyclization of **S30** was performed on a 0.13 mmol scale with a total reaction time of 25 h. Purification by flash column chromatography eluting with hexanes/EtOAc provided 25 mg (90%) of **56** as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.0 Hz, 2H), 8.16 (s, 1H), 8.11 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.80 – 7.70 (m, 3H), 7.59 (s, 1H), 2.77 (s, 3H). ^{13}C NMR (176 MHz, $CDCsl_3$) δ 135.17, 133.26, 133.05, 132.41, 131.66, 129.58, 128.44, 127.46, 127.28, 125.90, 125.19, 123.80, 123.79, 119.55, 110.03, 20.32.

^{13}C NMR (176 MHz, $CDCl_3$) δ 135.17, 133.26, 133.05, 132.41, 131.66, 129.58, 128.44, 127.46, 127.28, 125.90, 125.19, 123.80, 123.79, 119.55, 110.03, 20.32.

IR (cm^{-1}): 2225.4, 1487.6, 1438.5, 1407.9, 1245.7, 1212.6, 1155.9, 892.0, 860.3, 825.1, 775.7, 751.3, 717.9, 622.7, 606.9.

HRMS: calculated for $C_{16}H_{11}N$ ($[M+H^+]^+$): 218.0964 Found: 218.0960.



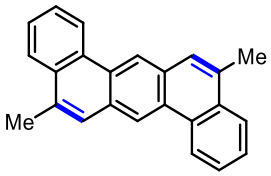
9-methylphenanthren-2-yl 4-methylbenzenesulfonate (57): The cyclization of **S36** was performed on 0.13 mmol scale with a total reaction time of 4 h. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 45 mg (96%) of **57** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 – 8.57 (m, 1H), 8.53 (d, *J* = 9.0 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.69 – 7.62 (m, 2H), 7.45 (d, *J* = 2.2 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.18 (dd, *J* = 9.0, 2.3 Hz, 1H), 2.71 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.20, 145.53, 134.28, 132.91, 132.63, 132.21, 130.00, 129.96, 128.78, 128.49, 127.13, 126.89, 126.28, 125.00, 124.46, 123.24, 120.41, 120.33, 21.92, 20.23.

IR (cm^{-1}): 3065.9, 2925.3, 1611.2, 1597.2, 1491.1, 1448.8, 1368.6, 1189.6, 1177.0, 1091.5, 947.4, 829.6, 737.2.

HRMS: calculated for $C_{22}H_{22}O_3NS^+$ ($[M + NH_4^+]^+$): 380.1315 found: 380.1312.



5,12-dimethylbenzo[k]tetraphene (59): The cyclization of **58** was performed on 0.075 mmol scale with a total reaction time of 4 h and 10 mol% $FeCl_3$. Purification by flash column chromatography eluting with hexanes/EtOAc (9:1) provided 21 mg (90%) of **59** as a pale yellow solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.03 (s, 2H), 8.89 (d, *J* = 7.9 Hz, 2H), 8.08 (d, *J* = 7.9 Hz, 2H), 7.79 (s, 2H), 7.73 (t, *J* = 7.4 Hz, 2H), 7.69 (t, *J* = 6.6 Hz, 2H), 2.78 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 132.55, 132.49, 130.59, 130.56, 129.04, 127.40, 127.10, 126.62, 124.97, 123.39, 121.31, 20.46.

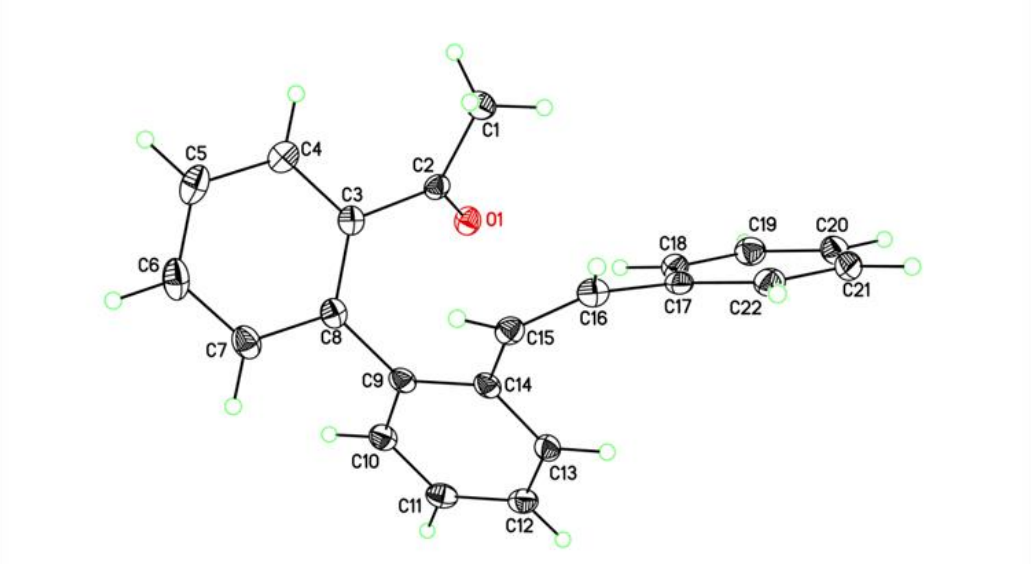
IR (cm^{-1}): 2920.0, 1628.1, 1438.4, 1273.5, 1028.7, 897.9, 859.4, 755.5, 700.5.

HRMS: Calculated for $C_{24}H_{18}^+$ ($[M]^+$): 306.1409 found: 306.1401.

A.1.9 X-ray crystallographic data

*Structure Determination of (Z)-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one (**9**)*

(CCDC 1505968)



Colorless block-like crystals of **(Z)-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one** were grown from a hexane/ethyl acetate solution of the compound at 22 deg. C. A crystal of dimensions 0.16 x 0.16 x 0.14 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 5 sec. for high angle. The integration of the data yielded a total of 12297 reflections to a maximum 2θ value of 136.43° of which 2831 were independent and 2729 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the xyz centroids 5758 reflections above $10\sigma(I)$. Analysis of the data showed negligible decay during data collection; the data were processed with CrystalClear 2.0 and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2014/6) software

package, using the space group P1bar with Z = 2 for the formula $C_{22}H_{18}O$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0446 and wR2 = 0.1039 [based on I > 2sigma(I)], R1 = 0.0454 and wR2 = 0.1045 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

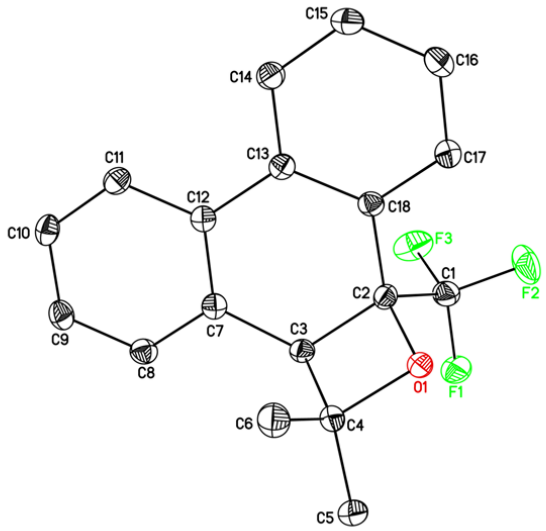
Sheldrick, G.M. SHELXTL, v. 2014/6; Bruker Analytical X-ray, Madison, WI, 2014.

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

Crystal data and structure refinement for **(*Z*)-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one**

Identification code	**(*Z*)-1-(2'-styryl-[1,1'-biphenyl]-2-yl)ethan-1-one**
Empirical formula	C22 H18 O
Formula weight	298.36
Temperature	85(2) K
Wavelength	1.54178 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 7.85230(10) A alpha = 77.261(5) deg. b = 9.3906(2) A beta = 84.541(6) deg. c = 11.5779(8) A gamma = 71.939(5) deg.
Volume	791.35(6) A^3
Z, Calculated density	2, 1.252 Mg/m^3
Absorption coefficient	0.580 mm^-1
F(000)	316
Crystal size	0.160 x 0.160 x 0.140 mm
Theta range for data collection	3.916 to 68.215 deg.
Limiting indices	-9<=h<=9, -11<=k<=11, -13<=l<=13
Reflections collected / unique	12297 / 2831 [R(int) = 0.0465]
Completeness to theta = 67.679	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.925 and 0.843
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2831 / 0 / 210
Goodness-of-fit on F^2	1.122
Final R indices [I>2sigma(I)]	R1 = 0.0446, wR2 = 0.1039
R indices (all data)	R1 = 0.0454, wR2 = 0.1045
Extinction coefficient	0.077(3)
Largest diff. peak and hole	0.239 and -0.296 e.A^-3

*Structure Determination of 2,2-dimethyl-10b-(trifluoromethyl)-2a,10b-dihydro-2H-phenanthro[9,10-b]oxete (**6**)*



(CCDC 1505967)

Colorless plates of **2,2-dimethyl-10b-(trifluoromethyl)-2a,10b-dihydro-2H-phenanthro[9,10-b]oxete** were grown from a dichloromethane solution of the compound at 22 deg. C. A crystal of dimensions 0.17 x 0.12 x 0.04 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 4 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 21527 reflections to a maximum 2θ value of 138.38° of which 2617 were independent and 2584 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids 17451 reflections above 10σ(I). Analysis of the data showed negligible decay

during data collection; the data were processed with CrystalClear 2.0 and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2014/6) software package, using the space group P2(1)/n with Z = 4 for the formula $C_{18}H_{15}OF_3$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0478 and wR2 = 0.1172 [based on I > 2sigma(I)], R1 = 0.0480 and wR2 = 0.1175 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Sheldrick, G.M. SHELXTL, v. 2014/6; Bruker Analytical X-ray, Madison, WI, 2014.

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

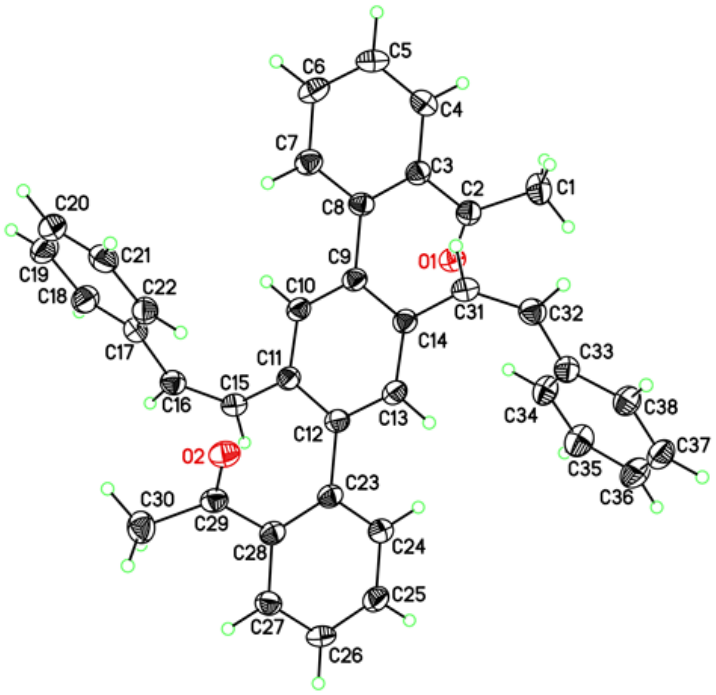
CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Crystal data and structure refinement for **2,2-dimethyl-10b-(trifluoromethyl)-2a,10b-dihydro-2H-phenanthro[9,10-b]oxete**

Identification code	**2,2-dimethyl-10b-(trifluoromethyl)-2a,10b-dihydro-2H-phenanthro[9,10-b]oxete**
Empirical formula	C18 H15 F3 O
Formula weight	304.30
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 7.88370(10) A alpha = 90 deg. b = 12.60220(10) A beta = 95.2380(10) deg. c = 14.49740(10) A gamma = 90 deg.
Volume	1434.33(2) A^3
Z, Calculated density	4, 1.409 Mg/m^3
Absorption coefficient	0.955 mm^-1
F(000)	632
Crystal size	0.170 x 0.120 x 0.040 mm
Theta range for data collection	4.658 to 69.189 deg.
Limiting indices	-9<=h<=9, -15<=k<=15, -17<=l<=17
Reflections collected / unique	21527 / 2617 [R(int) = 0.0536]
Completeness to theta = 67.684	98.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.91522
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	2617 / 0 / 202
Goodness-of-fit on F^2	1.136
Final R indices [I>2sigma(I)]	R1 = 0.0478, wR2 = 0.1172
R indices (all data)	R1 = 0.0480, wR2 = 0.1175
Extinction coefficient	0.0278(14)
Largest diff. peak and hole	0.326 and -0.401 e.A^-3

Structure Determination for 1,1'-(2',5'-di((Z)-styryl)-[1,1':4',1''-terphenyl]-2,2''-diyl)bis(ethan-1-one)



(CCDC 1530039)

Colorless block-like crystals of **1,1'-(2',5'-di((*Z*)-styryl)-[1,1':4',1''-terphenyl]-2,2''-diyl)bis(ethan-1-one)** were grown from a dichloromethane/hexane solution of the compound at 22 deg. C. A crystal of dimensions 0.21 x 0.11 x 0.10 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation

width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 5 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 41858 reflections to a maximum 2θ value of 138.66° of which 5089 were independent and 4803 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids 21176 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2014/6) software package, using the space group P2(1)/n with Z = 4 for the formula $C_{38}H_{30}O_2$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0597 and wR2 = 0.1647 [based on I > 2sigma(I)], R1 = 0.0615 and wR2 = 0.1673 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Sheldrick, G.M. SHELXTL, v. 2014/6; Bruker Analytical X-ray, Madison, WI, 2014.

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

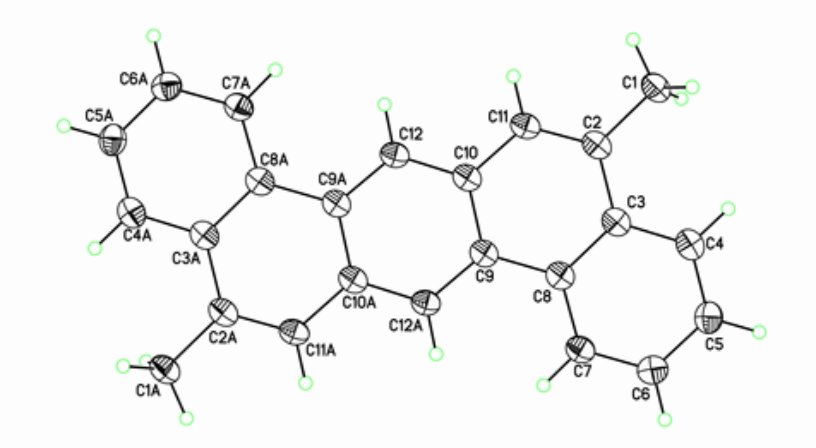
CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Crystal data and structure refinement for **1,1'-(2',5'-di((*Z*)-styryl)-[1,1':4',1''-terphenyl]-2,2''-diyl)bis(ethan-1-one)**

Identification code	**1,1'-(2',5'-di((*Z*)-styryl)-[1,1':4',1''-terphenyl]-2,2''-diyl)bis(ethan-1-one)**
Empirical formula	C38 H30 O2
Formula weight	518.62
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 10.62617(10) A alpha = 90 deg. b = 19.11003(16) A beta = 90.5435(8) deg. c = 13.49063(11) A gamma = 90 deg.

Volume	2739.37(4) A^3
Z, Calculated density	4, 1.257 Mg/m^3
Absorption coefficient	0.590 mm^-1
F(000)	1096
Crystal size	0.210 x 0.110 x 0.100 mm
Theta range for data collection	4.011 to 69.330 deg.
Limiting indices	-12<=h<=12, -23<=k<=22, -16<=l<=16
Reflections collected / unique	41858 / 5089 [R(int) = 0.0539]
Completeness to theta = 67.684	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.84698
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5089 / 0 / 364
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0597, wR2 = 0.1647
R indices (all data)	R1 = 0.0615, wR2 = 0.1673
Extinction coefficient	0.0013(3)
Largest diff. peak and hole	0.581 and -0.346 e.A^-3

Structure Determination for 5,12-dimethylbenzo[k]tetraphene



(CCDC 1530358)

Yellow plates of **5,12-dimethylbenzo[k]tetraphene** were grown from a dichloromethane/hexane solution of the compound at 22 deg. C. A crystal of dimensions 0.17 x 0.11 x 0.11 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A)

operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 4 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 22025 reflections to a maximum 2θ value of 138.26° of which 1452 were independent and 1420 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids 14219 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2014/6) software package, using the space group Pbca with Z = 4 for the formula $C_{24}H_{18}$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. The molecule lies on an inversion center of the crystal lattice. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0399 and wR2 = 0.0975 [based on I > 2sigma(I)], R1 = 0.0404 and wR2 = 0.0979 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Sheldrick, G.M. SHELXTL, v. 2014/6; Bruker Analytical X-ray, Madison, WI, 2014.

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Crystal data and structure refinement for **5,12-dimethylbenzo[k]tetraphene**

Identification code	ccm530
Empirical formula	C24 H18
Formula weight	306.38

Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 13.92565(12) A alpha = 90 deg.
	b = 6.76441(5) A beta = 90 deg.
	c = 16.55751(12) A gamma = 90 deg.
Volume	1559.70(2) A^3
Z, Calculated density	4, 1.305 Mg/m^3
Absorption coefficient	0.556 mm^-1
F(000)	648
Crystal size	0.170 x 0.110 x 0.110 mm
Theta range for data collection	5.343 to 69.132 deg.
Limiting indices	-16<=h<=16, -8<=k<=8, -20<=l<=20
Reflections collected / unique	22025 / 1452 [R(int) = 0.0537]
Completeness to theta = 67.684	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.88200
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1452 / 0 / 111
Goodness-of-fit on F^2	1.122
Final R indices [I>2sigma(I)]	R1 = 0.0399, wR2 = 0.0975
R indices (all data)	R1 = 0.0404, wR2 = 0.0979
Extinction coefficient	0.0197(14)
Largest diff. peak and hole	0.226 and -0.285 e.A^-3

A.1.10 References

1) a) Harvey, R.G. Polycyclic Aromatic Hydrocarbons, Wiley-VCH, New York, 1997; b) Gingras, M.; *Chem. Soc. Rev.* **2013**, *42*, 968; c) Gingras, M.; Felix, G.; Peresutti, R. *Chem. Soc. Rev.* **2013**, *42*, 1007; d) Gingras, M. *Chem. Soc. Rev.* **2013**, *42*, 1051; e) Floyd, A.J.; Dyke, S.F.; Ward, S.E. *Chem. Rev.* **1976**, *76*, 509. For additional examples, see: e) Uchida, K.; Ito, S.; Nakano, M.; Abe, M.; Kubo, T. *J. Am. Chem. Soc.* **2016**, *138*, 2399; f) Ji, F.; Li, X.; Wu, W.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 11246.

2) Wigglesworth, T.J.; Sud, D.; Norsten, T.B.; Lekhi, V.S.; Branda, N.R. *J. Am. Chem. Soc.* **2005**, *127*, 7272.

3) Furche, F.; Ahlrichs, R.; Wachsmann, C.; Weber, E.; Sobanski, A.; Vögtle, F.; Grimme, S. *J. Am. Chem. Soc.* **2000**, *122*, 1717.

4) Xu, Y.; Zhang, Y.X.; Sugiyama, H.; Umano, T.; Osuga, H.; Tanaka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6566.

5) a) Lovinger, A.J.; Nuckolls, C.; Katz, T.J. *J. Am. Chem. Soc.* **1998**, *120*, 264; b) Zöphel, L.; Enkelmann, V.; Müllen, K. *Org. Lett.* **2013**, *15*, 804.

6) Kovacs, A.; Vasas, A.; Hohmann, J. *Phytochemistry* **2008**, *69*, 1084.

7) For representative examples, see: a) Knowles, R.R.; Lin, S.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2010**, *132*, 5030; b) Narcis, M.J.; Takenaka, N. Eur. *J. Org. Chem.* **2014**, *1*, 21.

8) Dreher, S.D.; Katz, T.J.; Lam, K.-C.; Rheingold, A.L. *J. Org. Chem.* **2000**, *65*, 815.

9) McMurry, J.E.; Lectka, T.; Rico, J.G. *J. Org. Chem.* **1989**, *54*, 3748.

10) Dubois, F.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 5039.

11) a) Flammang-Barbieux, M.; Nasielski, J.; Martin, R.H. *Tetrahedron Lett.* **1967**, *8*, 743; b) Liu, L.; Yang, B.; Katz, T.J.; Poindexter, M.K. *J. Org. Chem.* **1991**, *56*, 3769; c) Martin, R.H. *Angew. Chem. Int. Ed.* **1974**, *13*, 649.

12) For homolytic aromatic substitution strategy, see Harrowven, D.C.; Guy, I.L.; Nanson, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 2242.

13) a) Carreño, M.C.; González-López, M.; Urbano, A. *Chem. Comm.* **2005**, *5*, 611; b) Liu, L.; Katz, T.J. *Tetrahedron Lett.* **1990**, *31*, 3983; c) Katz, T.J.; Liu, L.; Willmore, N.D.; Fox, J.M.; Rheingold, A.L.; Shi, S.; Nuckolls, C.; Rickman, B.H. *J. Am. Chem. Soc.* **1997**, *119*, 10054; d) Fox, J.M.; Goldberg, N.R.; Katz, T.J. *J. Org. Chem.* **1998**, *63*, 7456; e) Dreher, S.D.; Weix, D.J.; Katz, T.J. *J. Org. Chem.* **1999**, *64*, 3671..

14) a) Harrowven, D.C.; Guy, I.L.; Nanson, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 2242; b) Harrowven, D.C.; Nunn, M.I.T.; Fenwick, D.R. *Tetrahedron Lett.* **2002**, *43*, 7345.

15) For examples, see: a) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264; b) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.* **2004**, *10*, 4556; c) Komeyama, K.; Igawa, R.; Takaki, K. *Chem. Comm.* **2010**, *46*, 1748; d) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636; e) Chernyak, N.; Gevorgyan, V. *Adv. Synth. Catal.* **2009**, *351*, 1101.

16) Xia, Y.; Liu, Z.; Xiao, Q.; Qu, P.; Ge, R.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 5714.

17) a) Iuliano, A.; Piccioli, P.; Fabbri, D. *Org. Lett.* **2004**, *6*, 3711; b) Donohoe, T.J.; Orr, A.J.; Bingham, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2664.

18) a) This work was first reported as Ludwig, J.R.; Gianino, J.B.; Schindler, C.; Abstracts of Papers, 250th ACS National Meeting & Exposition, Boston, MA, United States, August 16th-20^{th,} 2015, ORGN-388; b) Ludwig, J.R.; Zimmerman, P.M.; Gianino, J.B.; Schindler, C.S. *Nature* **2016**, *533*, 374.

19) For metal-mediated carbonyl-olefin metathesis reactions, see: a) Schopov, I.; Jossifov, C. *Makromol. Chem., Rapid Commun.* **1983**, *4*, 659; b) Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc.* **1993**, *115*, 3800. For carbonyl-olefin metathesis reactions proceeding via oxetan photoadducts, see: c) Jones, G., II; Schwartz, S.B.; Marton, M.T. *J. Chem. Soc., Chem. Comm.* **1973**, *11*, 374; d) Jones, G., II; Acquadro, M.A.; Carmody, M.A. *J. Chem. Soc., Chem. Comm.* **1975**, *6*, 206; e) Carless, H.A.J.; Trivedi, H.S. *J. Chem. Soc., Chem. Commun.* **1979**, *8*, 382; f) D'Auria, M.; Racioppi, R.; Viggiani, L. *Photochem. Photobiol. Sci.* **2010**, *9*, 1134; g) Pérez-Ruiz, R.; Gil, S.; Miranda, M.A. *J. Org. Chem.* **2005**, *70*, 1376; h) Pérez-Ruiz, R.; Miranda, M.A.; Alle, R.; Meerholz, K.; Griesbeck, A.G. *Photochem. Photobiol. Sci.* **2006**, *5*, 51; i) Valiulin, R.A.;

Arisco, T.M.; Kutateladze, A.G. *J. Org. Chem.* **2011**, *76*, 1319; j) Valiulin, R.A.; Arisco, T.M.; Kutateladze, A.G. *J. Org. Chem.* **2013**, *78*, 2012. For Brønsted and Lewis acid mediated carbonyl-olefin metathesis reactions, see: k) Soicke, A.; Slavov, N.; Neudörfl, J.-M.; Schmalz, H.-G. *Synlett* **2011**, *17*, 2487; l) van Schaik, H.-P.; Vijn, R.-J.; Bickelhaupt, F. *Angew. Chem. Int. Ed.* **1994**, *33*, 1611; m) Bah, J.; Franzén, J.; Naidu, V.R. *Eur. J. Org. Chem.* **2015**, *8*, 1834; n) Jossifov, C.; Kalinova, R.; Demonceau, A. *Chim. Oggi* **2008**, *26*, 85; for catalytic carbonyl-olefin metathesis reactions proceeding via (3+2)/retro-(3+2)-cycloaddition, see: o) Griffith, A.K.; Vanos, C.M.; Lambert, T.H. *J. Am. Chem. Soc.* **2012**, *134*, 18581; p) Hong, X.; Liang, Y.; Griffith, A.K.; Lambert, T.H.; Houk, K.N. *Chem. Sci.* **2014**, *5*, 471.

20) a)Satchell, D.P.N.; Satchell, R.S. *Chem. Rev.* **1969**, *69*, 251; b) Jensen, W.B. *Chem. Rev.* **1978**, *78*, 1.

21) Kepp, K.P. *Inorg. Chem.* **2016**, *55*, 9461.

22) In the carbonyl-olefin metathesis reaction leading to cyclopentenes and cyclohexenes, catalytic amounts of $BF_3 \cdot Et_2O$ formed the metathesis products in 71% (86% conversion).

23) Arnáiz, F.J. *J. Chem. Educ.* **1995**, *72*, 1139.

24) a) Sanz, R.; Fernández, Y.; Castroviejo, M.P.; Pérez, A.; Fañanás, F.J. *J. Org. Chem.* **2006**, *71*, 6291; b) Che, R.; Wu, Z.; Li, Z.; Xiang, H.; Zhou, X. *Chem. Eur. J.* **2014**, *20*, 7258; c) Qiao, Z.; Ge, N.; Jiang, X. *Chem. Comm.* **2015**, *51*, 10295.

25) Sharma, U.; Kancherla, R.; Naveen, T.; Agasti, S.; Maiti, D. *Angew. Chem. Int. Ed*. **2014**, *53*, 11895.

26) de Meijere, A.; Zhong Song, Z.; Lansky, A.; Hyuda, S.; Rauch, K.; Noltemeyer, M.; König, B.; Knieriem, B. *Eur. J. Org. Chem.* **1998**, 2289.

27) Xue, F.; Li, X.; Wan. D. *J. Org. Chem.*, **2011**, *76*, 7256.

28) Lin, M-Y.; Das, A.; Liu, R-S. *J. Am. CHem. Soc.* **2006**, *126*, 9340.

29) Barbasiewicz, M.; Michalak, M.; Grela, K. *Chem. Eur. J*., **2012**, *18*, 14237.

30) Byrne, P.A.; Gilheany, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 9225.

31) Paul, S.; Samanta, S.; Ray, J. K. *Tetrahedron. Lett.* **2010**, *51*, 5604.

32) Van Otterlo, W. A. L.; Michael, J. P.; Fety'tr'rnandes, M. A.; de Koning , C. B. *Tetrahedron Lett.* **2004**, *45*, 5091.

33) Lin, J.; Zhang, W.; Jiang, N.; Niu, Z.; Bao, K.; Zhang, L.; Liu, D.; Pan, C.; Yao, X. J. *Nat. Prod.* **2008**, *71*, 1938.

34) Pal, P.; Jana, N.; Nanda, S. *Org. Biomol. Chem*. **2014**, *12*, 8257.

35) Edwards, D. J.; Hadfield, J. A.; Wallace, T. W.; Ducki, S. *Org. Biomol. Chem.* **2011**, *9*, 219.

36) Qi, W.-Y.; Zhu, T.-S.; Xu, M.-H. *Org. Lett.* **2011**, *13*, 3410.

37) Jung, M. E.; Lam, P. S. Y.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087.

38) Wang, Y.; McGonigal, P. R.; Herle, B.; Besora,´ M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801.

39) Laue, S.; Greiner, L.; Wöltinger, J.; Liese, A. *Adv. Synth. Catal.* **2001**, *343*, 711.

40) Wang, H.; Zhao, W.; Zhou, Y.; Duan, Z.; Mathey, F. *Eur. J. Inorg. Chem.* **2011**, 4585.

41) Dubost, E.; Fossey, C.; Cially, T.; Rault, S.; Fabis, F. *J. Org. Chem.* **2011**, *76*, 6414.

42) Appukkuttan, P.; Dehaen, W.; van der Eycken, E. *Chem. Eur. J.* **2007**, *13*, 6452.

43) Chen, H.; Long, H.; Cui, X.; Zhou, J.; Xu, M.; Yuan, G. *J. Am. Chem. Soc.* **2014**, *136*, 2583.

44) Yang, X.; Liu, D.; Miao, Q. Angew. Chem., Int. Ed. **2014**, *53*, 6786.

45) Krishna, J.; Reddy, A. G. K.; Satyanarayana, G. *Tetrahedron Lett.* **2014**, *55*, 861.

46) Hewitt, J. F. M.; Williams, L.; Aggarwal, P.; Smith, C. D.; France, D. J. *Chem. Sci*. **2013**, *4*, 3538.

47) Sasaki, K.; Hayashi, T. *Tetrahedron: Asymmetry*. **2012**, *23*, 373.

48) Sumimoto, M.; Arisawa, M.; Matsuda, M.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 7432.

49) Rubin, Y.; Dick, K.; Diederich, F.; Georgiadis, T. M. *J. Org. Chem*. **1986**, *51*, 3270.

50) Ni, S.; Shu, W.; Ma, S. *Synlett* **2013**, *24*, 2310.

51) Sakai, N.; Nakjima, T.; Yoneda, S.; Konakahara, T.; Ogiwara, Y. *J. Org. Chem.* **2014**, *79*, 10619.

52) Sakai, N.; Nakjima, T.; Yoneda, S.; Konakahara, T.; Ogiwara, Y. *J. Org. Chem.* **2014**, *79*, 10619.

53) Jayath, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc*. **2006**, *128*, 2232

54) Nagata, T.; Hirano, K.; Tetsuya, S.; Miura, Masahiro. *J. Org. Chem.* **2014**, *79*, 8960.

55) Serrano, J. L.; Pérez, J.; García, L.; Sánchez, G.; García, J.; Lozano, P.; Zende, V.; Kapdi, A. *Organometallics*, **2015**, *34*, 522.

56) Kwon, Y.; Cho, H.; Kim, S. *Org. Lett*. **2013**, *15*, 920.

57) Chen, M.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2013**, *52*, 11628.

58) Shu, C.; Li, L.; Chen, C.-B.; Shen, H.-C.; Ye, L.-W. *Chem. Asian J*., **2014**, *9*, 1525.

59) Li, Z.; Twieg, R. J. *Chem. - Eur. J.* **2015**, *21*, 15534.

60) Murai, M.; Hosokawa, N.; Roy, D.; Takai, K. *Org. Lett.*, **2014**, *16*, 4134.

61) Tominaga, Y.; Tedjamulia, M. L.; Castle, R. N.; Lee, M. L. . *J. Heterocycl. Chem.* **1983**, *20*, 487.

62) Rafiq, S.; Sivasakthikumaran, R.; Mohanakrishnan, A. *Org. Lett.* **2014**, *16*, 2720.

63) Chang, N. H.; Chen, X. C.; Nonobe, H.; Okuda, Y.; Mori, H.; Nakajima, K.; Nishihara, Y. *Org. Lett.* **2013**, *15*, 3558.

64) Barrett, T. N.; Braddock, D. C.; Monta, A.; Webb, M. R.; White, A. J. P. *J. Nat. Prod.*, **2011**, *74*, 1980.

65) Bair, K. W.; Andrews, C. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1991**, *34*, 1983.

66) Akanksha; Maiti, D. *Green Chem.* **2012**, *14*, 2314.

APPENDIX B

B.1. Experimental procedures, operations, and references for Chapter 2

B.1.1 General laboratory information and procedures

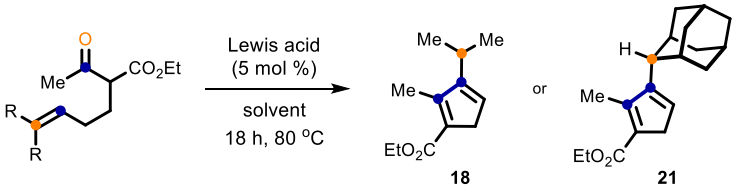
All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried round bottom flasks or glass vials fitted with rubber septa and/or septa equipped screw caps. Stainless steel syringes were used to transfer air or moisture-sensitive liquids. Flash chromatography was performed using silica gel Silia Flash® 40-63 micron (230-400 mesh) from Silicycle.

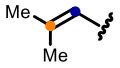
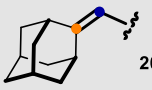
All chemicals were purchased from SigmaAldrich, Alfa Aesar, Acros Organics, Oakwood, TCI America, Frontier Scientific, Matrix Scientific, Ark Pharm, and Chem Impex International, and were used as received unless otherwise stated. Tetrahydrofuran was dried by being passed through columns of activated alumina. Proton Nuclear Magnetic Resonance NMR (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Unity Plus 400, Varian MR400, Varian vnmrs 500, Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for protons are reported in parts per million and are references to the NMR solvent peak ($CDCl_3$: δ 7.26; DMSO: δ 2.62). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.23; DMSO: δ 40.76). Data are represented as follows: chemical shift,

integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, m = multiplet), and coupling constants in Hertz (Hz). Mass spectroscopic (MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer. Infrared (IR) spectra were obtained using either an Avatar 360 FT-IR or Perkin Elmer Spectrum BX FT-IR spectrometer. IR data are represented as frequency of absorption (cm^{-1}).

B.1.2 Reaction optimization for the synthesis of functionalized cyclopentadienes

A flame-dried 4–dram vial was charged with Lewis acid (5 mol %), solvent (0.1–0.01 M) and stirred at room temperature. To this solution was added starting ketone **16** or **20** (0.2 mmol), and the resultant mixture was stirred at the indicated temperature. After 3 or 18 h (see table below) the reaction mixture was passed through a short silica plug eluting with DCM (25 mL). The filtrate was concentrated under reduced pressure and yield determined by NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal standard.



entry	substrate	Lewis acid	solvent	yield (%)	conv. (%)
1	 **16**	$Fe(OTf)_3$	DCE (0.05 M)	43	100
2		$Zn(OTf)_3$	DCE (0.05 M)	0	20
3		$Dy(OTf)_3$	DCE (0.05 M)	0	18
4		$Yb(OTf)_3$	DCE (0.05 M)	0	9
5		$Mg(OTf)_2$	DCE (0.05 M)	35	47
6		$GaCl_3$	DCE (0.05 M)	36	100
7		$In(OTf)_3$	DCE (0.05 M)	55	100
8		$InCl_3$	DCE (0.05 M)	40	84
9		$FeCl_3$	DCE (0.05 M)	29	100
10		AgOTf + *t*BuCl	DCE (0.05 M)	23	63
11		TfOH	DCE (0.05 M)	18	100
12		$Sc(OTf)_3$	DCE (0.05 M)	58	100
13[a]		$Sc(OTf)_3$	DCE (0.05 M)	0	15
14[b]		$Sc(OTf)_3$	DCE (0.05 M)	20	96
15		$Sc(OTf)_3$	DCM (0.05 M)	30	100
16		$Sc(OTf)_3$	$PhCF_3$ (0.05 M)	34	71
17		$Sc(OTf)_3$	PhCl (0.05 M)	32	82
18		$Sc(OTf)_3$	PhH (0.05 M)	41	52
19		$Sc(OTf)_3$	DCE (0.1 M)	35	100
20		$Sc(OTf)_3$	DCE (0.01 M)	37	93
21[c]	 **20**	$GaCl_3$	DCE (0.05 M)	49	100
22[c]		$In(OTf)_3$	DCE (0.05 M)	75	100
23[c]		$Sc(OTf)_3$	DCE (0.05 M)	86	100

Conditions*:* all reactions were performed using 0.15 mmol β-ketoester, 5 mol% Lewis acid in solvent (0.05 M) at 80 °C for 18 hours. [a]40 °C. [b]20 mol% $Sc(OTf)_3$. [c]Reaction time of 3 h.

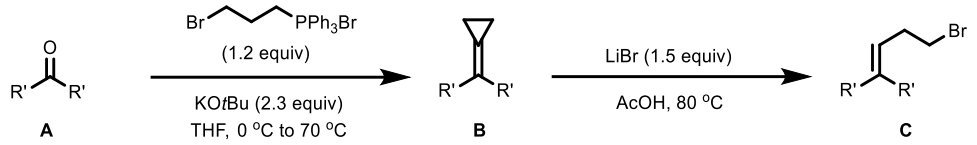
TABLE B.1 Reaction optimization for cyclopentadiene formation.

B.1.3 Synthesis of cyclopentadiene precursors

Synthesis of alkyl bromides

5-Iodo-2-methylpent-2-ene was synthesized using a reported literature protocol.[20] The synthesis of C1, C2, C3, C4 and C5 were accomplished using a two-step approach: ***1)*** Wittig olefination (A → B)[2] and ***2)*** nucleophilic cyclopropyl ring opening[3] (B → C). Xu and Xie have previously synthesized cyclopropane intermediates cyclopropylidenecycloheptane (**B2**), 2-

cyclopropylideneadamantane (**B3**), and nonan-5-ylidenecyclopropane (**B4**) from the corresponding ketones employing this Wittig olefination strategy.[21]



(A1) cyclohexanone
(A2) cycloheptanone
(A3) 2-adamantanone
(A4) 5-nonanone
(A5) 4-methyl-2-pentanone

(B1) cyclopropylidenecyclohexane
(B2) cyclopropylidenecycloheptane
(B3) 2-cyclopropylideneadamantane
(B4) nonan-5-ylidenecyclopropane
(B5) (4-methylpentan-2-ylidene)cyclopropane

(C1) (3-bromopropylidene)cyclohexane
(C2) (3-bromopropylidene)cycloheptane
(C3) 2-(3-bromopropylidene)adamantane
(C4) 5-(3-bromopropylidene)nonane
(C5) (*E*)-1-bromo-4,6-dimethylhept-3-ene

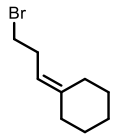
Representative Wittig Olefination Procedure for the Synthesis of ***B***[21]

3-Bromopropyltriphenylphosphonium bromide was prepared using a literature procedure. Under an inert atmosphere, 3-bromopropyltriphenylphosphonium bromide (37.1 g, 80 mmol) and dry THF (120 mL) were added to a flame-dried, 250 mL round-bottom flask equipped with a stir bar. Then, *t*-BuOK (17.2 g, 153 mmol) was added at room temperature in three portions over 30 min. After addition, the reaction mixture was stirred at room temperature for an additional 30 min, then heated to reflux for 2 h. Next, adamantan-2-one (10.0 g, 66.6 mmol, 1 equiv) was then added slowly and the mixture was stirred at 60 °C overnight. The reaction mixture was then cooled to room temperature and quenched by the addition of water water (120 mL). The aqueous solution was extracted with hexanes (3 × 50 mL). The combined organic layers were washed with brine (4 × 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (hexanes) to afford **B3** in 53% yield as a white crystalline solid.

Representative Cyclopropyl Ring-Opening Procedure for the Synthesis of ***C***[22]

To a flame-dried 50 mL round bottom flask equipped with a magnetic stir bar was added **B3** (1.0 g, 5.74 mmol) and AcOH (7.0 mL). Then, LiBr (747 mg, 8.61mmol) was added in one portion.

The flask was equipped with a condenser and the reaction solution was heated to 80 °C. After 30 min at this temperature there was complete conversion of the starting material by TLC analysis. The reaction was cooled down to room temp and then water was added. The mixture was poured into a seperatory funnel along with diethyl ether (50 mL). Then, an aqueous solution of K_2CO_3 was added ***SLOWLY*** to the seperatory funnel until hydrogen gas evolution ceased. The organics were separated, dried and concentrated under reduced pressure. The crude oil was purified via flash column chromatography over silica with hexanes to 10% EtOAc in Hex to afford 2-(3-bromopropylidene)adamantane **C3** (73%, 1.46 g, 4.2 mmol) as a clear oil.

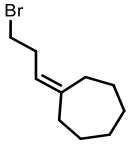


(3-Bromopropylidene)cyclohexane (C1):

Partial characterization data.

^{1}H NMR (700 MHz, cdcl$_3$) δ 5.07 (t, *J* = 7.3 Hz, 1H), 3.32 (t, *J* = 7.4 Hz, 2H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.15 – 2.11 (m, 2H), 2.08 (t, *J* = 5.5 Hz, 2H), 1.57 – 1.49 (m, 6H).

^{13}C NMR (176 MHz, cdcl$_3$) δ 143.58, 117.80, 37.44, 33.49, 31.27, 29.23, 28.90, 28.16, 27.14.

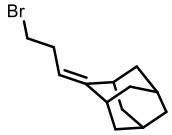


(3-Bromopropylidene)cycloheptane (C2):

Partial characterization data.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.13 (t, *J* = 7.1 Hz, 1H), 3.35 (t, *J* = 7.3 Hz, 2H), 2.56 (q, *J* = 7.2 Hz, 2H), 2.26 – 2.18 (m, 4H), 1.62 – 1.56 (m, 4H), 1.53 – 1.45 (m, 4H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 145.00, 121.52, 38.09, 33.30, 31.76, 30.46, 30.17, 29.51, 29.42, 27.41.

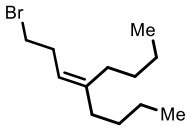


(3-bromopropylidene)adamantine (C3):

Partial characterization data.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.03 (t, *J* = 7.3 Hz, 1H), 3.32 (t, *J* = 7.4 Hz, 2H), 2.78 (s, 1H), 2.55 (q, *J* = 7.4 Hz, 2H), 2.35 (s, 1H), 1.95 (s, 2H), 1.90 – 1.84 (m, 4H), 1.82 (s, 2H), 1.76 (d, *J* = 11.7 Hz, 2H), 1.71 (d, *J* = 11.9 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 151.63, 112.78, 40.85, 40.09, 39.31, 37.51, 33.72, 32.62, 30.82, 28.86.

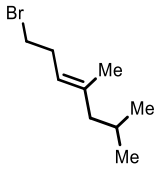


5-(3-bromopropylidene)nonane (C4):

Partial characterization data.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.09 (t, *J* = 7.1 Hz, 1H), 3.33 (t, *J* = 7.4 Hz, 2H), 2.57 (q, *J* = 7.3 Hz, 2H), 2.04 – 1.95 (m, 4H), 1.39 – 1.22 (m, 8H), 0.88 (m, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 143.29, 120.53, 36.51, 33.09, 31.48, 30.68, 30.28, 29.97, 22.85, 22.46, 14.04, 14.01.



1-bromo-4,6-dimethylhept-3-ene (C5):

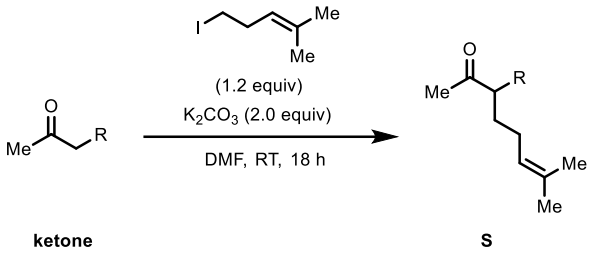
Partial characterization data. E/Z ratio of 1:0.4.

^{1}H NMR (mixture of E/Z isomers, 700 MHz, $CDCl_3$) δ 5.20 – 5.06 (m, 1H), 3.33 (m, 2H), 2.57 (m, 2H), 1.88 (m, 2H), 1.81 – 1.70 (m, 1H), 1.68 (s, 1H), 1.59 (s, 2H), 0.86 (m, 6H).

^{13}C NMR (mixture of E/Z isomer, 176 MHz, $CDCl_3$) δ 137.99, 137.84, 122.32, 121.99, 49.43, 41.19, 32.92, 32.87, 31.69, 31.65, 26.48, 25.90, 23.68, 22.46, 22.34, 16.09.

B.1.4 Synthesis of cyclopentadiene substrates (S)

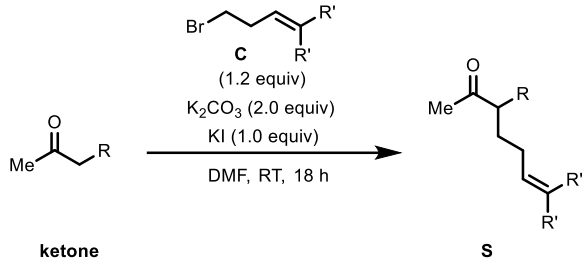
General alkylation procedure A



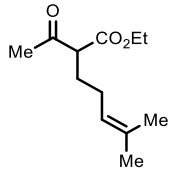
To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was successively added ketone (1.0 equiv), DMF (0.3 M) and K_2CO_3 (2.0 equiv). The flask was topped with a rubber septum and a nitrogen inlet. 5-iodo-2-methylpent-2-ene (1.3 equiv) was then added dropwise to the reaction suspension *via* syringe and the resultant solution was allowed to stir at room temp. When there was complete consumption of starting material (determined by TLC), EtOAc (30 mL) was added to the reaction mixture and then poured into an extraction funnel along with water (40 mL) and then separated. The organic phase was further extracted with water (3 × 30 mL), washed

with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified with flash column chromatography over silica with EtOAc in hexanes to afford the cyclopentadiene precursor.

General alkylation procedure B.



To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was successively added ketone (1.0 equiv), DMF (0.3 M), K_2CO_3 (2.0 equiv) and KI (1.0 equiv). The flask was topped with a rubber septum and a nitrogen inlet. Alkyl bromide (**C**, 1.2 equiv) was then added dropwise to the reaction suspension *via* syringe and the resultant solution was allowed to stir at room temp. When there was complete consumption of starting material (determined by TLC), EtOAc (30 mL) was added to the reaction mixture and then poured into an extraction funnel along with water (40 mL) and then separated. The organic phase was further extracted with water (3 × 30 mL), washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified with flash column chromatography over silica with EtOAc in hexanes to afford the cyclopentadiene precursor.



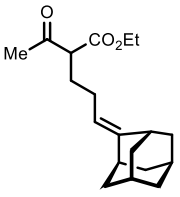
Ethyl 2-acetyl-6-methylhept-5-enoate (16). General alkylation procedure **A** was followed employing ethyl 3-oxobutanoate (15.4 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 28% (868 mg, 4.09 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (t, *J* = 7.2 Hz, 1H), 4.19 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 1H), 2.21 (s, 3H), 2.02 – 1.95 (m, 2H), 1.95 – 1.81 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 170.2, 133.6, 123.1, 61.6, 59.6, 29.1, 28.6, 26.1, 26.1, 18.0, 14.5.

IR (cm^{-1}): 2906.2, 2855.2, 1735.0, 1711.5, 1451.0, 1242.8, 1041.7, 982.6.

HRMS (ESI+) *m/z* calcd for $C_{12}H_{20}NaO_3^+$ $[M+Na]^+$: 235.1305, found 235.1304.



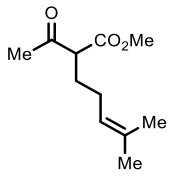
Ethyl 2-acetyl-5-(2-adamantylidene)pentanoate (20). General alkylation procedure **B** was followed employing ethyl 3-oxobutanoate (7.68 mmol) and alkyl bromide **C3**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 32% (755 mg, 2.48 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (t, *J* = 7.2 Hz, 1H), 4.25 – 4.14 (m, 2H), 3.44 (t, *J* = 7.1 Hz, 1H), 2.72 (s, 1H), 2.32 (s, 1H), 2.22 (s, 3H), 2.03 – 1.63 (m, 16H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.80, 170.28, 149.85, 114.64, 61.61, 59.50, 40.92, 40.20, 40.17, 39.34, 39.32, 37.57, 32.45, 29.14, 29.04, 28.94, 24.62, 14.46.

IR (cm^{-1}): 2902.0, 2847.8, 1737.6, 1713.4, 1447.9, 1357.3, 1241.3, 1097.2, 1022.5, 851.5, 714.8.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{28}NaO_3^+$ $[M+Na]^+$: 327.1931, found 327.1928.



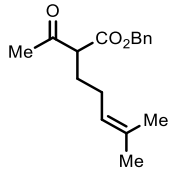
Methyl 2-acetyl-6-methylhept-5-enoate (S1). General alkylation procedure **A** was followed employing methyl 3-oxobutanoate (6.46 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 28% (356 mg, 1.80 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.73 (s, 3H), 3.44 (t, *J* = 7.2 Hz, 1H), 2.21 (s, 3H), 2.02 – 1.94 (m, 2H), 1.89 (m 2H), 1.68 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 170.7, 133.7, 123.1, 59.3, 52.7, 29.2, 28.6, 26.1, 26.1, 18.0.

IR (cm^{-1}): 2952.7, 1742.1, 1714.3, 1435.4, 1357.8, 1199.3, 1144.4, 1108.5, 1052.3, 985.9, 833.6.

HRMS (ESI+) *m/z* calcd for $C_{11}H_{18}NaO_5^+$ $[M+Na]^+$: 221.1148, found 221.1147.



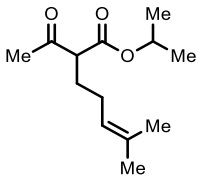
Benzyl 2-acetyl-6-methylhept-5-enoate (S2). General alkylation procedure **A** was followed employing benzyl 3-oxobutanoate (3.90 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 26% (282 mg, 1.03 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.20 – 5.12 (m, 2H), 5.04 (t, J = 6.5 Hz, 1H), 3.47 (t, J = 7.0 Hz, 1H), 2.17 (s, 3H), 2.02 – 1.82 (m, 4H), 1.66 (s, 3H), 1.54 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 170.1, 135.7, 133.7, 128.9, 128.8, 128.7, 123.0, 67.4, 59.5, 29.2, 28.6, 26.0, 18.0.

IR (cm^{-1}): 2927.9, 1739.7, 1712.5, 1454.6, 1376.6, 1357.2, 1213.7, 1138.6, 961.9, 749.7, 696.8.

HRMS (ESI+) *m/z* calcd for $C_{17}H_{22}NaO_3^+$ $[M+Na]^+$: 297.1461, found 297.1462.



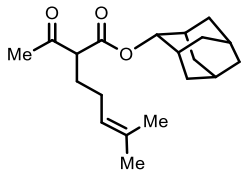
Isopropyl 2-acetyl-6-methylhept-5-enoate (S3). General alkylation procedure **A** was followed employing isopropyl 3-oxobutanoate (5.20 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 35% (417 mg, 1.84 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 – 5.01 (m, 2H), 3.37 (t, *J* = 7.2 Hz, 1H), 2.20 (s, 3H), 2.05 – 1.94 (m, 2H), 1.94 – 1.78 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H), 1.25 (dd, *J* = 6.2, 2.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.71, 169.75, 133.52, 123.21, 69.16, 59.81, 29.05, 28.50, 26.05, 22.06, 21.95, 18.02.

IR (cm^{-1}): 2980.2, 2932.7, 1735.3, 1712.0, 1451.9, 1374.6, 1244.6, 1145.5, 1103.8, 826.0.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{22}NaO_5^+$ $[M+Na]^+$: 249.1461, found 249.1465.



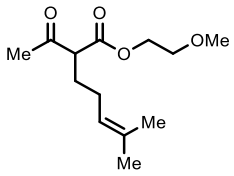
2-adamantyl 2-acetyl-6-methyl-hept-5-enoate (S4). General alkylation procedure **A** was followed employing 2-adamantyl 3-oxobutanoate (3.17 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 16% (161 mg, 0.51 mmol) as a clear, colorless liquid.

^{1}H NMR (700 MHz, $cdcl_3$) δ 5.18 – 5.14 (m, 1H), 5.08 (s, 1H), 3.54 (t, *J* = 7.2 Hz, 1H), 2.33 (s, 3H), 2.13 – 1.89 (m, 13H), 1.86 (d, *J* = 11.6 Hz, 2H), 1.82 (s, 2H), 1.78 (s, 3H), 1.69 – 1.63 (m, 5H).

^{13}C NMR (176 MHz, $cdcl_3$) δ 203.8, 169.6, 133.5, 123.3, 78.4, 59.9, 37.6, 36.7, 36.6, 36.6, 32.3, 32.2, 32.1, 29.3, 28.6, 27.5, 27.3, 26.1, 26.1, 18.0.

IR (cm^{-1}): 2906.2, 2855.2, 1735.1, 1711.5, 1451.0, 1355.9, 1242.9, 1144.1, 1100.2, 1041.7, 982.7, 914.7.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{30}NaO_3^+$ [M+Na]$^+$: 341.2087, found 341.2086.



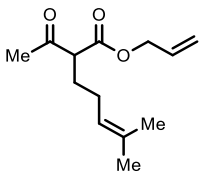
2-Methoxyethyl 2-acetyl-6-methylhept-5-enoate (S5). General alkylation procedure **A** was followed employing 2-methoxyethyl 3-oxobutanoate (4.68 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 30% (343 mg, 1.42 mmol) as a clear, colorless liquid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.06 (t, *J* = 7.2 Hz, 1H), 4.33 – 4.24 (m, 2H), 3.59 (t, *J* = 4.7 Hz, 2H), 3.49 – 3.45 (m, 1H), 3.37 (s, 3H), 2.23 (s, 3H), 2.03 – 1.96 (m, 2H), 1.95 – 1.82 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.6, 170.3, 133.7, 123.1, 70.6, 64.4, 59.3, 59.3, 29.2, 28.6, 26.1, 26.1, 18.0.

IR (cm^{-1}): 2926.8, 1740.4, 1713.2, 1449.7, 1358.4, 1241.7, 1198.2, 1127.5, 1029.5, 838.8.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{23}O_4^+$ [M+H]$^+$: 243.1591, found 243.1589.



Allyl 2-acetyl-6-methylhept-5-enoate (S6). General alkylation procedure **A** was followed employing allyl 3-oxobutanoate (5.28 mmol). Purification by flash column chromatography (over

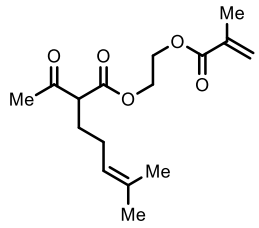
silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 29% (344 mg, 1.53 mmol) as a clear, colorless liquid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 16.3, 10.5, 5.9 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.06 (ddd, *J* = 7.2, 6.0, 1.2 Hz, 1H), 4.65 – 4.59 (m, 2H), 3.47 – 3.45 (m, 1H), 2.22 (s, 3H), 2.03 – 1.96 (m, 2H), 1.96 – 1.83 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.5, 169.9, 133.7, 131.9, 123.1, 119.3, 66.2, 59.4, 29.3, 28.6, 26.1, 18.0.

IR (cm^{-1}): 2929.3, 1740.6, 1713.8, 1440.3, 1358.1, 1238.8, 1140.6, 984.5, 932.1, 833.6.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{20}NaO_4^+$ $[M+Na]^+$: 263.1254, found 263.1255.



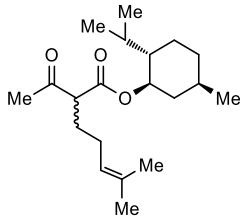
2-(Methacryloyloxy)ethyl 2-acetyl-6-methylhept-5-enoate (S7). General alkylation procedure **A** was followed employing 2-(methacryloyloxy)ethyl 3-oxobutanoate (3.50 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 19% (201 mg, 0.68 mmol) as a clear, colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.60 (s, *J* = 2.6 Hz, 1H), 5.05 (t, *J* = 7.1 Hz, 1H), 4.42 – 4.33 (m, 4H), 3.46 (t, *J* = 7.1 Hz, 1H), 2.21 (s, 3H), 2.06 – 1.78 (m, 7H), 1.68 (s, 3H), 1.56 (s, *J* = 4.8 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.2, 169.9, 167.33, 136.1, 133.7, 126.6, 122.9, 63.2, 62.5, 59.2, 29.2, 28.5, 26.1, 26.0, 18.6, 18.0.

IR (cm^{-1}): 2963.2, 1715.06, 1637.9, 1451.0, 1358.3, 1319.3, 1140.9, 1047.4, 944.3, 814.1.

HRMS (ESI+) *m/z* calcd for $C_{16}H_{24}NaO_5^+$ $[M+Na]^+$: 319.1516, found 319.1516.



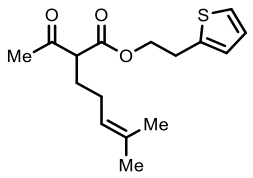
(*1R,2S,5R*)-2-isopropyl-5-methylcyclohexyl 2-acetyl-6-methylhept-5-enoate (S8). General alkylation procedure **A** was followed employing [(*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl] 3-oxobutanoate (3.12 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (5% to 25%), afforded the title compound in 26% (263 mg, 0.82 mmol) as a clear, colorless liquid and a mixture of inconsequential diastereomers.

^{1}H NMR (500 MHz, cdcl$_3$) δ 5.09 – 5.02 (m, 1H), 4.78 – 4.68 (m, 1H), 3.39 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.20 (d, *J* = 1.7 Hz, 3H), 2.05 – 1.94 (m, 3H), 1.94 – 1.78 (m, 3H), 1.75 – 1.66 (m, 5H), 1.58 (d, *J* = 5.8 Hz, 3H), 1.48 (ddd, *J* = 24.7, 13.8, 11.0 Hz, 1H), 1.43 – 1.34 (m, 1H), 1.10 – 0.94 (m, 2H), 0.94 – 0.82 (m, 7H), 0.80 – 0.68 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.55, 169.89, 169.76, 133.52, 133.49, 123.19, 75.76, 75.68, 60.02, 60.01, 47.19, 47.16, 41.01, 40.86, 34.51, 31.72, 29.02, 28.64, 28.44, 26.52, 26.36, 26.06, 26.04, 23.57, 23.43, 22.32, 21.13, 21.09, 18.05, 18.01, 16.42, 16.21.

IR (cm^{-1}): 2955.7, 2926.1, 2869.8, 1735.9, 1711.9, 1454.3, 1356.5, 1241.2, 1142.4, 1096.9, 982.2, 912.3, 844.2.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{35}O_3^+$ $[M+NH_4]^+$: 323.2581, found 323.2583.



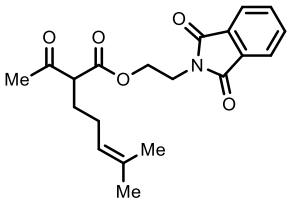
2-(Thiophen-2-yl)ethyl 2-acetyl-6-methylhept-5-enoate (S9). General alkylation procedure **A** was followed employing 2-(thiophen-2-yl)ethyl 3-oxobutanoate (3.53 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 48% (494 mg, 1.66 mmol) as a clear, colorless liquid.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 5.1, 1.0 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 5.04 (dd, *J* = 9.9, 4.1 Hz, 1H), 4.41 – 4.27 (m, 2H), 3.43 (t, *J* = 7.1 Hz, 1H), 3.17 (t, *J* = 6.6 Hz, 2H), 2.15 (s, 3H), 2.01 – 1.78 (m, 4H), 1.68 (s, 3H), 1.56 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 170.0, 139.8, 133.6, 127.2, 126.0, 124.4, 123.1, 65.7, 59.4, 29.5, 29.2, 28.5, 26.0, 18.0.

IR (cm^{-1}): 2963.1, 2917.3, 1739.7, 1712.6, 1438.4, 1357.2, 1139.7, 985.3, 828.3, 695.3.

HRMS (ESI+) *m/z* calcd for $C_{16}H_{22}NaSO_3^+$ $[M+Na]^+$: 317.1182, found 317.1185.



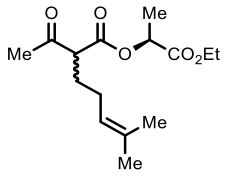
2-(1,3-Dioxoisoindolin-2-yl)ethyl 2-acetyl-6-methylhept-5-enoate (S10). General alkylation procedure **A** was followed employing 2-(1,3-dioxoisoindolin-2-yl)ethyl 3-oxobutanoate (1.82 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (5% to 25%), afforded the title compound in 45% (293 mg, 0.82 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.01 (t, *J* = 7.1 Hz, 1H), 4.38 (t, *J* = 5.3 Hz, 2H), 3.98 (td, *J* = 5.1, 1.9 Hz, 2H), 3.41 (t, *J* = 7.1 Hz, 1H), 2.19 (s, 3H), 1.96 – 1.80 (m, 4H), 1.65 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 169.9, 168.2, 134.4, 133.4, 132.1, 123.6, 122.9, 62.5, 58.9, 37.1, 29.3, 28.5, 25.9, 25.9, 17.9.

IR (cm^{-1}): 2932.3, 1769.3, 1706.6, 1458.0, 1321.2, 1187.4, 1045.5, 1009.2, 845.9, 718.6.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{23}NNaO_5^+$ $[M+Na]^+$: 380.1468, found 380.1469.



(*S*)-1-Ethoxy-1-oxopropan-2-yl 2-acetyl-6-methylhept-5-enoate (S11). General alkylation procedure **A** was followed employing (*S*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (3.71 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex

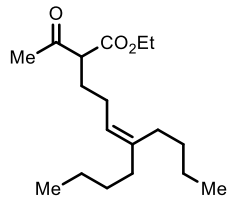
(5% to 25%), afforded the title compound in 8% (89 mg, 0.31 mmol) as a clear, colorless liquid and a mixture of inconsequential diasteromers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 – 5.02 (m, 2H), 4.20 (qd, *J* = 7.1, 2.6 Hz, 2H), 3.49 (dt, *J* = 14.0, 7.2 Hz, 1H), 2.28 (d, *J* = 6.8 Hz, 3H), 2.07 – 1.97 (m, 2H), 1.97 – 1.83 (m, 2H), 1.69 (s, 3H), 1.58 (d, *J* = 4.8 Hz, 2H), 1.50 (t, *J* = 7.0 Hz, 3H), 1.27 (td, *J* = 7.1, 2.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.2, 202.9, 170.6, 169.7, 133.7, 133.6, 123.1, 69.7, 61.9, 61.9, 59.3, 59.1, 29.4, 29.0, 28.6, 28.5, 26.1, 25.9, 25.9, 18.0, 17.2, 17.1, 14.4, 14.4.

IR (cm^{-1}): 2981.6, 1742.2, 1715.6, 1448.4, 1357.8, 1270.1, 1203.3, 1132.5, 1095.4, 1047.3, 1018.5, 901.3.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{28}NO_5^+$ $[M+NH_4]^+$: 302.1962, found 302.1969.



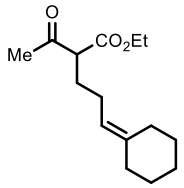
Ethyl 2-acetyl-6-butyldec-5-enoate (S12). General alkylation procedure **B** was followed employing ethyl 3-oxobutanoate (**2.31** mmol) and alkyl bromide **C4**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 40% (275 mg, 0.93 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (t, *J* = 7.1 Hz, 1H), 4.19 (qt, *J* = 5.0, 2.6 Hz, 2H), 3.42 (t, *J* = 7.2 Hz, 1H), 2.22 (s, 3H), 2.04 – 1.79 (m, 8H), 1.38 – 1.23 (m, 11H), 0.89 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 170.2, 141.9, 122.8, 61.6, 59.6, 36.9, 31.0, 30.7, 30.1, 29.1, 28.8, 25.7, 23.2, 22.8, 14.43, 14.4, 14.3.

IR (cm^{-1}): 2956.0, 2928.9, 2859.1, 1740.7, 1715.3, 1465.7, 1357.4, 1241.5, 1178.4, 1141.5, 1095.8, 1024.1, 857.4.

HRMS (ESI+) *m/z* calcd for $C_{18}H_{32}NaO_3^+$ $[M+Na]^+$: 319.2244, found 319.2244.



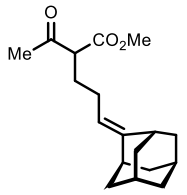
Ethyl 2-acetyl-5-cyclohexylidenepentanoate (S13). General alkylation procedure **B** was followed employing ethyl 3-oxobutanoate (2.31 mmol) and alkyl bromide **C1**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 24% (136 mg, 0.54 mmol) as a clear, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (t, *J* = 7.3 Hz, 1H), 4.22 – 4.16 (m, 2H), 3.44 – 3.40 (m, 1H), 2.22 (s, 3H), 2.06 (m, 4H), 2.00 (m, 2H), 1.95 – 1.79 (m, 2H), 1.56 – 1.44 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 170.2, 141.8, 119.7, 61.6, 59.4, 37.5, 29.1, 28.9, 28.9, 28.8, 28.1, 27.2, 25.1, 14.4.

IR (cm^{-1}): 2925.6, 2853.0, 1739.1, 1713.4, 1446.3, 1357.6, 1240.4, 1147.7, 1112.2, 1094.4, 1022.4, 853.3.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{28}NO_3^+$ $[M+NH_4]^+$: 270.2064, found 270.2064.



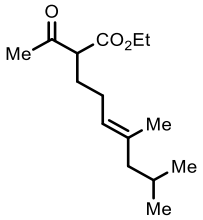
Methyl 2-acetyl-5-(2-adamantylidene)pentanoate (S14). General alkylation procedure **B** was followed employing methyl 3-oxobutanoate (3.44 mmol) and alkyl bromide **C3**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 34% (340 mg, 1.17 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 1H), 2.71 (s, 1H), 2.32 (s, 1H), 2.22 (s, 3H), 2.02 – 1.88 (m, 5H), 1.85 (m, 7H), 1.73 (m, 2H), 1.67 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 170.7, 149.9, 114.5, 59.3, 52.7, 40.9, 40.2, 40.2, 39.3, 39.3, 37.6, 32.5, 29.2, 29.1, 28.9, 24.6.

IR (cm^{-1}): 2901.6, 2847.1, 1743.1, 1714.7, 1447.7, 1356.9, 1242.9, 1147.1, 1098.0, 714.7.

HRMS (ESI+) *m/z* calcd for $C_{18}H_{30}NO_3^+$ $[M+NH_4]^+$: 308.2220, found 308.2223.



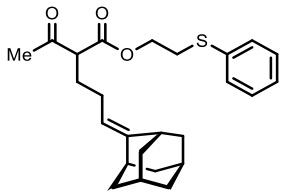
Ethyl (*E*)-2-acetyl-6,8-dimethylnon-5-enoate (S15). General alkylation procedure **B** was followed employing ethyl 3-oxobutanoate (2.31 mmol) and alkyl bromide **C5**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 47% (277 mg, 1.09 mmol), as an *E/Z* (1:0.32) mixture, as a clear colorless oil.

^{1}H NMR (500 MHz, as an *E/Z* mixture, $CDCl_3$) δ 5.15 – 5.09 (m, 0.32H), 5.05 (t, *J* = 7.10 Hz, 1H), 4.19 (m, 2.84H), 3.42 (m, 1.31H), 2.22 (s, 4.15H), 2.00 (m, 2.95H), 1.95 – 1.79 (m, 6.13H), 1.78 – 1.68 (m, 1.34H), 1.66 (s, 1.12H), 1.54 (s, 4.25H), 1.30 – 1.24 (m, 4.283H), 0.84 (t, *J* = 7.0 Hz, 8.78H).

^{13}C NMR (126 MHz, as an *E/Z* mixture, $CDCl_3$) δ 203.69, 203.64, 170.23, 170.21, 136.63, 136.52, 124.62, 124.17, 61.62, 59.65, 59.52, 49.87, 41.37, 29.17, 29.12, 28.74, 28.59, 26.86, 26.26, 25.98, 25.93, 24.06, 22.83, 22.81, 22.75, 22.70, 16.20, 14.46.

IR (cm^{-1}): 2955.6, 2870.0, 1714.1, 1464.8, 1367.4, 1150.0, 1019.3, 859.9, 611.8.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{27}O_3^+$ $[M+H]^+$: 255.1955, found 255.1951.



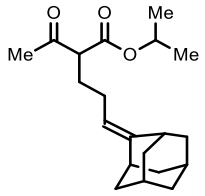
2-(Phenylthio)ethyl 2-acetyl-5-adamantan-2-ylidene)pentanoate (S16). General alkylation procedure **B** was followed employing 2-(phenylthio)ethyl 3-oxobutanoate (3.15 mmol) and alkyl bromide **C3**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 34% (439 mg, 1.06 mmol) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 4.97 (t, *J* = 7.3 Hz, 1H), 4.33 – 4.24 (m, 2H), 3.44 (dd, *J* = 7.8, 6.5 Hz, 1H), 3.14 (dd, *J* = 10.6, 3.8 Hz, 2H), 2.71 (s, 1H), 2.32 (s, *J* = 13.2 Hz, 1H), 2.23 (s, 3H), 2.02 – 1.96 (m, 2H), 1.96 – 1.91 (m, 2H), 1.92 – 1.79 (m, 8H), 1.73 (d, *J* = 11.8 Hz, 2H), 1.67 (d, *J* = 12.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.45, 170.01, 149.91, 135.14, 130.38, 129.44, 127.08, 114.51, 63.78, 59.25, 40.88, 40.17, 40.13, 39.31, 39.29, 37.53, 32.66, 32.44, 29.27, 29.00, 28.94, 28.89, 24.60.

IR (cm^{-1}): 2900.7, 2846.2, 1741.2, 1712.6, 1447.6, 1356.5, 1143.2, 1091.2, 714.8, 690.1.

HRMS (ESI+) *m/z* calcd for $C_{25}H_{36}NSO_3^+$ $[M+NH_4]^+$: 430.2410, found 430.2411.



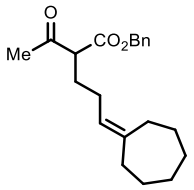
Isopropyl 2-acetyl-5-(2-adamantylidene)pentanoate (S17). General alkylation procedure **B** was followed employing isopropyl 3-oxobutanoate (3.47 mmol) and alkyl bromide **C3**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 13% (145 mg, 0.46 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (h, *J* = 6.2 Hz, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 3.42 – 3.36 (m, 1H), 2.73 (s, 1H), 2.32 (s, 1H), 2.21 (s, 3H), 2.03 – 1.91 (m, 4H), 1.91 – 1.78 (m, 7H), 1.74 (m, 2H), 1.68 (m, 2H), 1.25 (dd, *J* = 6.2, 3.2 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.8, 169.8, 149.8, 114.7, 69.2, 59.8, 40.9, 40.2, 40.2, 39.4, 39.3, 37.6, 32.4, 29.1, 29.00, 28.9, 24.6, 22.1, 22.0.

IR (cm^{-1}): 2902.3, 2847.5, 1735.7, 1712.0, 1448.3, 1358.4, 1146.2, 1103.3, 948.9, 714.7.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{30}NaO_3^+$ $[M+Na]^+$: 341.2087, found 341.2089.



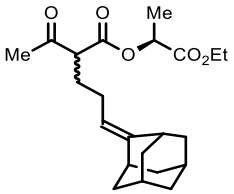
Ethyl 2-acetyl-6-butyldec-5-enoate (S18). General alkylation procedure **B** was followed employing benzyl 3-oxobutanoate (3.90 mmol) and alkyl bromide **C2**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 14% (175 mg, 0.53 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 5.16 (d, *J* = 13.3 Hz, 2H), 5.05 (t, *J* = 6.2 Hz, 1H), 3.48 (t, *J* = 6.8 Hz, 1H), 2.21 – 2.11 (m, 6H), 2.04 – 1.81 (m, 5H), 1.51 (m, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 170.1, 143.4, 135.7, 129.0, 128.8, 128.7, 123.3, 67.4, 59.6, 38.1, 30.3, 30.2, 29.7, 29.5, 29.20, 28.6, 27.4, 25.6.

IR (cm^{-1}): 2920.3, 2849.8, 1740.1, 1713.1, 1454.1, 1356.9, 1236.2, 1211.7, 1137.3, 1027.9, 957.1, 749.4, 696.5.

HRMS (ESI+) *m/z* calcd for $C_{21}H_{28}NaO_3^+$ $[M+Na]^+$: 351.1931, found 351.1937.



[(1*S*)-2-Ethoxy-1-methyl-2-oxo-ethyl] 2-acetyl-5-(2-adamantylidene)pentanoate (S19). General alkylation procedure **B** was followed employing (*S*)-1-ethoxy-1-oxopropan-2-yl 3-oxobutanoate (2.46 mmol) and alkyl bromide **C3**. Purification by flash column chromatography

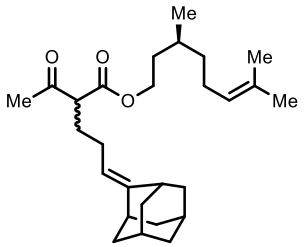
(over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 22% (201 mg, 0.53 mmol) as a clear, colorless liquid and a mixture of inconsequential diastereomers.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.15 – 5.08 (m, 1H), 5.00 (m, 1H), 4.22 (m, 2H), 3.55 – 3.49 (m, 1H), 2.76 (m, 1H), 2.31 (m, 4H), 2.07 – 1.99 (m, 2H), 1.99 – 1.91 (m, 3H), 1.87 (m, 7H), 1.75 (d, *J* = 11.5 Hz, 2H), 1.70 (d, *J* = 11.4 Hz, 2H), 1.54 – 1.48 (m, 3H), 1.29 (td, *J* = 7.1, 2.8 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.2, 203.0, 170.7, 169.7, 169.7, 149.9, 114.6, 114.6, 69.7, 69.7, 61.9, 61.9, 59.2, 59.1, 40.9, 40.2, 40.2, 39.3, 37.6, 37.6, 32.4, 32.4, 29.4, 29.1, 29.0, 28.9, 28.9, 24.6, 24.4, 17.2, 17.1, 14.4, 14.4.

IR (cm^{-1}): 2902.8, 2847.6, 1742.8, 1715.8, 1448.0, 1357.6, 1202.5, 1132.1, 1095.1, 1047.2, 854.4.

HRMS (ESI+) *m/z* calcd for $C_{22}H_{36}NO_5^+$ $[M+NH_4]^+$: 394.2588, found 394.2597.



[(3*S*)-3,7-Dimethyloct-6-enyl] 2-acetyl-5-(2-adamantylidene)pentanoate (S20). General alkylation procedure **B** was followed employing (*S*)-3,7-dimethyloct-6-en-1-yl 3-oxobutanoate (2.08 mmol) and alkyl bromide **C3**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 19% (163 mg, 0.39 mmol) as a clear, colorless liquid and a mixture of inconsequential diastereomers.

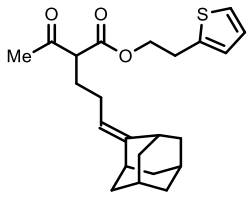
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (t, *J* = 6.7 Hz, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 4.23 – 4.09 (m, 2H), 3.44 (t, *J* = 7.1 Hz, 1H), 2.72 (s, 1H), 2.32 (s, 1H), 2.22 (s, 3H), 2.04 – 1.90 (m, 7H), 1.90 –

1.78 (m, 7H), 1.78 – 1.62 (m, 8H), 1.60 (s, 3H), 1.58 – 1.50 (m, 1H), 1.50 – 1.39 (m, 1H), 1.34 (ddd, J = 21.3, 9.7, 6.0 Hz, 1H), 1.18 (dt, J = 13.9, 8.4 Hz, 1H), 0.91 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 170.4, 149.8, 131.8, 124.8, 114.6, 64.2, 59.5, 40.9, 40.2, 40.2, 39.3, 39.3, 37.6, 37.3, 37.3, 35.7, 32.5, 29.8, 29.2, 29.1, 28.9, 26.1, 25.7, 24.6, 19.7, 18.0.

IR (cm^{-1}): 2904.8, 2847.7, 1740.3, 1714.7, 1448.1, 1355.9, 1240.8, 1146.1, 1098.1, 1060.8, 714.7.

HRMS (ESI+) *m/z* calcd for $C_{27}H_{46}NO_3^+$ $[M+NH_4]^+$: 432.3472, found 432.3479.



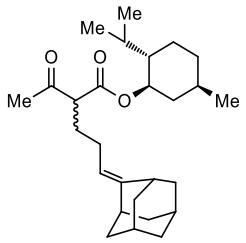
2-(2-Thienyl)ethyl 2-acetyl-5-(2-adamantylidene)pentanoate (S21). General alkylation procedure **B** was followed employing 2-(thiophen-2-yl)ethyl 3-oxobutanoate (2.36 mmol) and alkyl bromide **C3**. Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (1% to 15%), afforded the title compound in 22% (199 mg, 0.52 mmol) as a clear, colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, J = 5.1 Hz, 1H), 6.95 – 6.92 (t, J= 5.1 Hz, 1H), 6.85 (d, J = 3.2 Hz, 1H), 4.96 (t, J = 7.2 Hz, 1H), 4.42 – 4.30 (m, 2H), 3.46 (t, J = 7.1 Hz, 1H), 3.17 (t, J = 6.7 Hz, 2H), 2.70 (s, 1H), 2.31 (s, 1H), 2.16 (s, 3H), 2.03 – 1.89 (m, 5H), 1.89 – 1.78 (m, 7H), 1.73 (d, J = 11.7 Hz, 2H), 1.67 (d, J = 11.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 170.1, 149.9, 139.8, 127.3, 126.0, 124.5, 114.6, 65.7, 59.4, 40.9, 40.2, 40.2, 39.3, 39.3, 37.6, 32.5, 29.5, 29.2, 29.0, 28.9, 24.6.

IR (cm^{-1}): 2900.4, 2846.4, 1740.4, 1713.0, 1447.7, 1356.6, 1238.7, 1143.4, 1097.7, 1038.0, 849.5, 692.7.

HRMS (ESI+) *m/z* calcd for $C_{23}H_{34}NSO_3^+$ $[M+NH_4]^+$: 404.2254, found 404.2258.



[(*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl] 2-acetyl-5-(2-adamantylidene)pentanoate (S22). General alkylation procedure **A** was followed employing [(*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl] 3-oxobutanoate (4.16 mmol). Purification by flash column chromatography (over silica), eluting with EtOAc in Hex (5% to 25%), afforded the title compound in 32% (550 mg, 1.33 mmol) as a clear, colorless semi-solid and a mixture of inconsequential diastereomers.

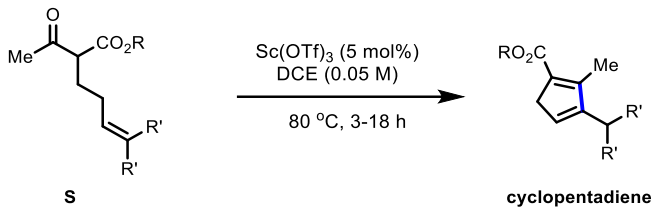
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (q, *J* = 7.2 Hz, 1H), 4.77 – 4.68 (m, 1H), 3.73 (s, 1H), 3.41 (dd, *J* = 11.6, 7.0 Hz, 1H), 2.73 (s, 1H), 2.32 (s, 1H), 2.23 – 2.15 (m, 3H), 2.06 – 1.77 (m, 13H), 1.77 – 1.60 (m, 6H), 1.53 (dd, *J* = 36.8, 12.8 Hz, 2H), 1.44 – 1.33 (m, 1H), 1.13 – 0.94 (m, 2H), 0.94 – 0.80 (m, 6H), 0.78 – 0.69 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.65, 203.59, 169.97, 169.86, 149.79, 149.71, 114.70, 75.75, 75.68, 60.08, 59.98, 47.18, 43.78, 41.01, 40.89, 40.86, 40.20, 40.17, 39.41, 39.36, 39.32, 37.59, 34.52, 32.45, 31.73, 29.14, 29.03, 28.94, 26.52, 26.39, 24.67, 24.61, 23.55, 23.45, 22.34, 21.14, 21.12, 16.38, 16.22.

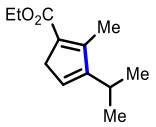
IR (cm^{-1}): 2903.3, 2847.9, 1710.9, 1448.3, 1356.7, 1240.9, 1145.2, 982.2, 844.9, 714.0.

HRMS (ESI+) *m/z* calcd for $C_{27}H_{43}O_3^+$ $[M+H]^+$: 415.3207, found 415.3211.

B.1.5 Synthesis of cyclopentadienes



General procedure for Sc(OTf)$_3$-catalyzed cyclopentadiene formation: A flame-dried 4 – dram vial was charged with Sc(OTf)$_3$ (5 mol %) and DCE (0.05 M), and stirred at room temperature. To this solution was added starting ketone **S** (1 equiv) in DCE (1 mL), and the resultant mixture was stirred for the indicated time at 80 °C, unless otherwise specified. Upon completion (as determined by TLC analysis), the reaction mixture was passed through a short silica plug eluting with DCM (25 mL). The filtrate was concentrated under reduced pressure, and the crude material was purified over silica *via* flash column chromatography, with the indicated eluent to give the pure cyclopentadiene adducts.



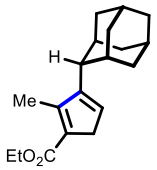
Ethyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (18). The cyclization of **16** was performed on 0.19 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 20.4 mg (56%, 0.11 mmol) of **18** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.18 (s, 2H), 2.69 – 2.56 (m, 1H), 2.35 (t, *J* = 2.2 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.7, 155.9, 155.9, 130.7, 129.3, 59.8, 40.8, 27.0, 22.8, 14.8, 13.6.

IR (cm^{-1}): 2961.8, 1696.6, 1550.4, 1457.3, 1372.9, 1328.0, 1273.6, 1218.8, 1095.3, 1039.7, 976.4, 748.2.

HRMS (ESI+) *m/z* calcd for $C_{12}H_{18}NaO_2^+$ $[M+Na]^+$: 217.1199, found 217.1193.



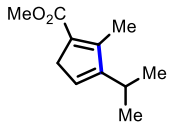
Ethyl 3-(2-adamantyl)-2-methyl-cyclopenta-1,3-diene-1-carboxylate (21): The cyclization of **20** was performed on 0.20 mmol scale with a total reaction time of 3 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 49.5 mg (86%, 0.17 mmol) of **21** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 4.30 – 4.17 (m, 2H), 3.24 (s, 2H), 2.72 (s, 1H), 2.35 – 2.26 (m, 3H), 2.02 (d, *J* = 22.1 Hz, 4H), 1.98 – 1.82 (m, 6H), 1.76 (s, 2H), 1.59 – 1.48 (m, 2H), 1.37 – 1.27 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.77, 157.08, 151.98, 131.88, 130.26, 59.75, 44.08, 41.13, 39.97, 38.34, 32.62, 31.67, 28.39, 28.03, 14.85, 14.14.

IR (cm^{-1}): 2901.4, 2848.8, 1695.9, 1546.5, 1448.7, 1217.1, 1063.6, 736.3, 703.3.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{27}O_2^+$ $[M+H]^+$: 287.2006, found 287.2006.



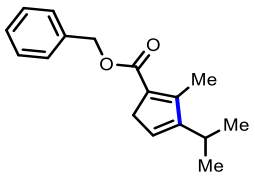
Methyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (22). The cyclization of **S1** was performed on 0.19 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 18.0 mg (50%, 0.10 mmol) of **22** as a pale-yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.22 (s, 1H), 3.75 (s, 3H), 3.17 (s, 2H), 2.63 (m, 1H), 2.35 (s, 3H), 1.14 (d, *J*=6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.7, 156.0, 155.5, 129.9, 129.1, 50.8, 40.4, 26.6, 22.4, 13.2.

IR (cm^{-1}): 2962.1, 1704.7, 1550.9, 1434.6, 1353.8, 1274.8, 1222.7, 1096.7, 1039.9, 749.1.

HRMS (ESI+) *m/z* calcd for $C_{11}H_{17}O_2^+$ $[M+H]^+$: 181.1223, found 181.1222.



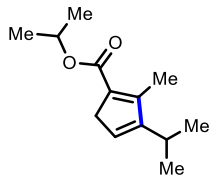
Benzyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (23). The cyclization of **S2** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 25.0 mg (49%, 0.098 mmol) of **23** as a clear oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 6.24 (s, 1H), 5.24 (s, 2H), 3.23 (s, 2H), 2.64 (m, 1H), 2.37 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.0, 156.5, 155.6, 136.8, 129.9, 129.3, 128.5, 127.9, 127.9, 65.2, 40.5, 26.6, 22.4, 13.3.

IR (cm^{-1}): 2960.7, 1697.6, 1548.9, 1454.9, 1380.3, 1328.2, 1215.9, 1093.4, 1063.4, 1027.3, 746.5, 695.9.

HRMS (ESI+) *m/z* calcd for $C_{17}H_{20}O_2Na^+$ $[M+H]^+$: 279.1356, found 279.1369.



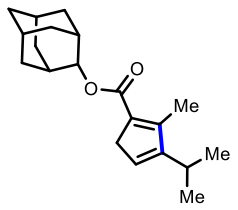
Isopropyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (24). The cyclization of **S3** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 16.0 mg (38%, 0.077 mmol) of **24** as a pale-yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.21 (s, 1H), 5.11 (h, *J* = 6.2 Hz, 1H), 3.17 (d, *J* = 1.6 Hz, 2H), 2.63 (h, *J* = 6.7 Hz, 1H), 2.34 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 7H), 1.14 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.0, 155.6, 155.1, 130.8, 128.7, 66.5, 40.5, 26.6, 22.4, 22.1, 13.2.

IR (cm^{-1}): 2965.1, 2933.6, 1696.1, 1590.9, 1466.7, 1373.1, 1272.6, 1223.5, 1107.4, 1033.6, 750.2.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{21}O_2^+$ $[M+H]^+$: 209.1536, found 209.1534.



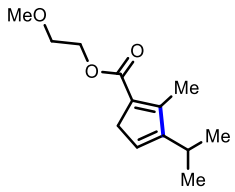
2-Adamantyl 3-isopropyl-2-methyl-cyclopenta-1,3-diene-1-carboxylate (25). The cyclization of **S4** was performed on 0.16 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 25.0 mg (45%, 0.069 mmol) of **25** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.06 (s, 1H), 3.23 (s, 2H), 2.64 (h, *J* = 6.7 Hz, 1H), 2.38 (s, 3H), 2.12 – 2.01 (m, 4H), 1.91 – 1.78 (m, 6H), 1.75 (s, 2H), 1.59 (d, *J* = 11.9 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 155.6, 155.0, 131.1, 128.8, 40.5, 37.5, 36.4, 32.1, 27.4, 27.1, 26.6, 22.4, 13.3.

IR (cm^{-1}): 2905.8, 2854.3, 1692.6, 1550.9, 1358.5, 1273.0, 1224.9, 1211.6, 1098.3, 1064.3, 1035.0, 746.6.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{29}O_2^+$ $[M+H]^+$: 301.2162, found 301.2162.



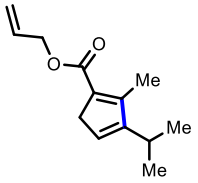
2-Methoxyethyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (26). The cyclization of **S5** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 26.0 mg (58%, 0.12 mmol) of **26** as a pale-yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.23 (s, 1H), 4.34 – 4.29 (t, *J* = 7.0 Hz, 2H), 3.67 – 3.64 (t, *J* = 7.6 Hz, 2H), 3.40 (s, 3H), 3.25 – 3.16 (s, 2H), 2.63 (h, *J*= 6.8 Hz, 1H), 2.35 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.1, 156.3, 155.6, 129.9, 129.2, 70.8, 62.6, 59.0, 40.4, 26.6, 22.4, 13.3.

IR (cm^{-1}): 2963.9, 1710.6, 1452.4, 1378.7, 1199.9, 1126.6, 1026.9, 864.9, 733.3, 702.0.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{21}O_3^+$ $[M+H]^+$: 225.1485, found 225.1482.



Allyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (27). The cyclization of **S6** was performed on 0.19 mmol scale with a total reaction time of 12 h. Purification by flash column

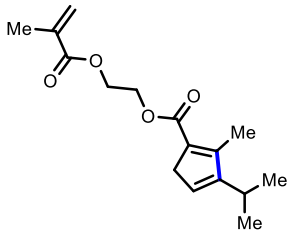
chromatography over silica eluting with 5% EtOAc in hexanes provided 17.0 mg (43%, 0.082 mmol) of **27** as a pale-yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.24 (s, *J* = 10.7 Hz, 1H), 5.99 (m, 1H), 5.35 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.23 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.68 (d, *J* = 5.5 Hz, 2H), 3.21 (s, 2H), 2.64 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.36 (t, *J* = 2.3 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 164.9, 156.3, 155.6, 132.9, 129.9, 129.2, 117.3, 64.1, 40.4, 26.6, 22.4, 13.3.

IR (cm^{-1}): 2961.5, 1699.1, 1549.3, 1455.9, 1375.6, 1327.8, 1272.7, 1215.2, 1093.8, 1035.7, 980.0, 900.5, 746.9.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{19}O_2^+$ $[M+H]^+$: 207.1380, found 207.1381.



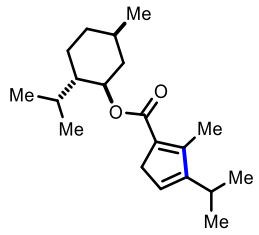
2-(Methacryloyloxy)ethyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (28). The cyclization of **S7** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 25.0 mg (45%, 0.090 mmol) of **28** as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.13 (s, 1H), 5.58 (s, 1H), 4.42 (s, 4H), 3.18 (s, 2H), 2.64 (h, *J* = 6.6 Hz, 1H), 2.34 (s, 3H), 1.95 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 164.8, 156.5, 155.6, 136.0, 129.7, 129.5, 125.9, 62.7, 61.2, 40.4, 26.6, 22.4, 18.3, 13.3.

IR (cm^{-1}): 2960.4, 1719.7, 1699.6, 1549.3, 1451.8, 1375.7, 1318.5, 1273.6, 1161.2, 1039.4, 941.3, 746.2.

HRMS (ESI+) *m/z* calcd for $C_{16}H_{23}O_4^+$ $[M+H]^+$: 279.1591, found 279.1593.



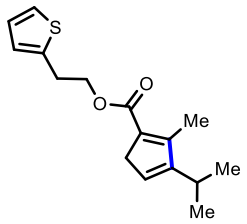
(*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (29): The cyclization of **S8** was performed on 0.18 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 31.4 mg (55%, 0.103 mmol) of **29** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 1H), 4.78 (td, *J* = 10.8, 4.3 Hz, 1H), 3.17 (s, 2H), 2.64 (dt, *J* = 12.7, 6.3 Hz, 1H), 2.35 (s, 3H), 2.08 (d, *J* = 11.8 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.69 (dd, *J* = 9.4, 6.8 Hz, 2H), 1.49 – 1.40 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.01 (dd, *J* = 23.2, 11.9 Hz, 2H), 0.90 (dd, *J* = 6.7, 3.2 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.30, 156.04, 155.66, 131.11, 129.12, 73.41, 47.65, 41.69, 40.86, 34.77, 31.80, 26.96, 26.78, 23.98, 22.81, 22.44, 21.21, 16.88, 13.58.

IR (cm^{-1}): 2955.5, 2925.6, 2869.1, 1692.8, 1550.2, 1455.2, 1369.2, 1219.2, 1063.7, 899.4, 746.5.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{33}O_2^+$ $[M+H]^+$: 305.2475, found 305.2478.



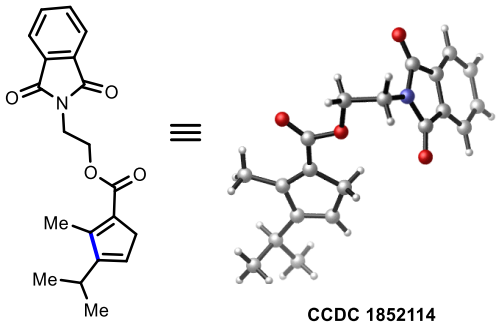
2-(Thiophen-2-yl)ethyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (30). The cyclization of **S9** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 19.2 mg (35%, 0.695 mmol) of **30** as a colorless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.15 (d, *J* = 5.1 Hz, 1H), 6.97 – 6.92 (m, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.24 (s, 1H), 4.39 (t, *J* = 6.6 Hz, 2H), 3.27 – 3.17 (m, 4H), 2.64 (h, *J* =.9 Hz, 1H), 2.33 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.4, 156.7, 156.0, 140.9, 130.3, 129.6, 127.1, 125.8, 124.2, 64.2, 40.8, 29.9, 26.9, 22.8, 13.6.

IR (cm^{-1}): 2959.1, 1696.6, 1549.3, 1439.0, 1273.0, 1216.9, 1133.4, 1094.9, 1067.8, 1037.3, 900.3, 736.8, 693.2.

HRMS (ESI+) *m/z* calcd for $C_{16}H_{21}O_2S^+$ $[M+H]^+$: 277.1257, found 277.1256.



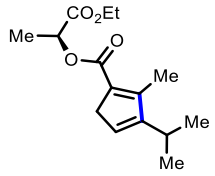
2-(1,3-Dioxoisoindolin-2-yl)ethyl 3-isopropyl-2-methylcyclopenta-1,3-diene-1-carboxylate (31). The cyclization of **S10** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% to 20% EtOAc in hexanes provided 32.3 mg (48%, 0.095 mmol) of **31** as colorless crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 6.20 (s, 1H), 4.41 (t, *J* = 5.4 Hz, 2H), 4.03 (t, *J* = 5.4 Hz, 2H), 3.10 (s, 2H), 2.64 – 2.55 (m, 1H), 2.27 (t, *J* = 2.2 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 165.0, 157.1, 155.8, 134.3, 132.4, 129.9, 129.8, 123.6, 60.9, 40.7, 37.6, 26.9, 22.7, 13.5.

IR (cm^{-1}): 2961.2, 17772.9, 1715.6, 1690.0, 1546.9, 1462.8, 1376.7, 1276.8, 1139.5, 985.2, 880.6, 748.9.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{21}O_4NNa^+$ $[M+Na]^+$: 362.1363, found 362.1364.



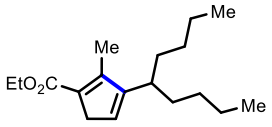
[(1*S*)-2-Ethoxy-1-methyl-2-oxo-ethyl] 3-isopropyl-2-methyl-cyclopenta-1,3-diene-1-carboxylate (32). The cyclization of **S11** was performed on 0.18 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 18.1 mg (47%, 0.068 mmol) of **32** as a colorless oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.27 (s, 1H), 5.16 (q, *J* = 7.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.31 – 3.15 (m, 2H), 2.64 (h, *J* = 6.6 Hz, 1H), 2.36 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.14 (dd, *J* = 6.8, 1.2 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.8, 164.7, 157.6, 156.0, 130.1, 129.6, 68.2, 61.5, 40.8, 26.9, 22.8, 22.7, 17.5, 14.5, 13.7.

IR (cm^{-1}): 2964.2, 1752.5, 1698.6, 1548.4, 1448.2, 1369.3, 1273.5, 1201.1, 1097.5, 1025.9, 907.1, 730.1.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{23}O_4^+$ $[M+H]^+$: 267.1591, found 267.1589.



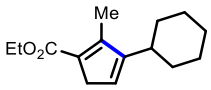
Ethyl 2-methyl-3-(nonan-5-yl)cyclopenta-1,3-diene-1-carboxylate (33). The cyclization of **S12** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 35.6 mg (43%, 0.128 mmol) of **33** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.22 (s, 2H), 2.48 – 2.36 (m, 1H), 2.32 (t, *J* = 2.3 Hz, 3H), 1.51 – 1.43 (m, 4H), 1.36 – 1.12 (m, 11H), 0.88 – 0.82 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 156.7, 153.6, 131.0, 130.3, 59.7, 41.0, 37.5, 35.4, 30.1, 23.3, 14.9, 14.4, 13.8.

IR (cm^{-1}): 2924.9, 2856.1, 1700.5, 1547.7, 1457.7, 1374.4, 1219.2, 1105.1, 1055.5, 899.7, 746.7.

HRMS (ESI+) *m/z* calcd for $C_{18}H_{31}O_2^+$ $[M+H]^+$: 279.2319, found 279.2322.



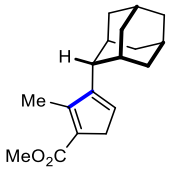
Ethyl 3-cyclohexyl-2-methylcyclopenta-1,3-diene-1-carboxylate (34). The cyclization of **S13** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 20.9 mg (45%, 0.089 mmol) of **34** as a pale-yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.18 (d, *J* = 1.0 Hz, 2H), 2.33 (t, *J* = 2.3 Hz, 3H), 2.24 (t, *J* = 11.5 Hz, 1H), 1.76 (m, 4H), 1.44 – 1.12 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 156.0, 155.0, 130.5, 129.8, 59.7, 41.0, 37.1, 33.5, 33.4, 27.1, 27.0, 26.6, 14.9, 13.6.

IR (cm^{-1}): 29.25.3, 2852.4, 1705.7, 1447.7, 1365.6, 1222.2, 1058.4, 890.3, 735.1, 702.8.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{23}O_2^+$ $[M+H]^+$: 235.1693, found 235.1694.



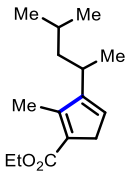
Methyl 3-(2-adamantyl)-2-methyl-cyclopenta-1,3-diene-1-carboxylate (35): The cyclization of **S14** was performed on 2.24 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 480 mg (79%, 1.76 mmol) of **35** as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.46 (s, 1H), 3.75 (s, 3H), 3.22 (dd, *J* = 4.0, 2.0 Hz, 2H), 2.71 (s, 1H), 2.31 (t, *J* = 2.3 Hz, 3H), 2.03 (s, 2H), 1.98 (d, *J* = 14.2 Hz, 2H), 1.94 (m, 1H), 1.91 – 1.87 (m, 4H), 1.82 (m, 1H), 1.75 (s, 2H), 1.58 (d, *J* = 12.3 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 166.14, 157.55, 152.00, 132.07, 129.86, 51.16, 44.10, 41.13, 39.99, 38.36, 32.64, 31.69, 28.41, 28.05, 14.17.

IR (cm^{-1}): 2900.8, 2848.1, 1698.2, 1548.9, 1433.7, 1332.8, 1065.5, 960.8, 899.8, 737.7.

HRMS (ESI+) *m/z* calcd for $C_{18}H_{25}O_2^+$ $[M+H]^+$: 273.1849, found 273.1857.



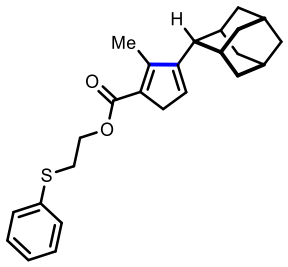
Ethyl 2-methyl-3-(4-methylpentan-2-yl)cyclopenta-1,3-diene-1-carboxylate (36): The cyclization of **S15** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 20.2 mg (43%, 0.086 mmol) of **36** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.19 (s, 2H), 2.61 – 2.52 (m, 1H), 2.34 (t, *J* = 2.3 Hz, 3H), 1.67 – 1.59 (m, 1H), 1.45 – 1.39 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.24 (ddd, *J* = 12.3, 9.3, 5.3 Hz, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.72, 156.08, 155.22, 130.60, 129.94, 59.74, 46.54, 40.91, 29.67, 25.91, 23.56, 22.63, 21.01, 14.84, 13.60.

IR (cm^{-1}): 2956.8, 2869.9, 1710.9, 1466.4, 1367.0, 1264.5, 1053.5, 1025.4, 735.4, 703.4.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{25}O_2^+$ $[M+H]^+$: 237.1849, found 237.1845



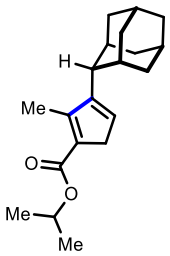
2-(Phenylthio)ethyl 3-(adamantan-2-yl)-2-methylcyclopenta-1,3-diene-1-carboxylate (37): The cyclization of **S16** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 45.1 mg (57%, 0.114 mmol) of **37** as a colorless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.30 – 7.24 (m, 2H), 7.20 – 7.14 (m, 1H), 6.45 (s, 1H), 4.33 (t, *J* = 6.9 Hz, 2H), 3.23 – 3.14 (m, 3H), 2.69 (s, 1H), 2.29 (t, *J* = 2.3 Hz, 2H), 2.06 – 1.79 (m, 9H), 1.74 (s, 2H), 1.61 – 1.50 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.87, 157.70, 151.65, 135.45, 132.00, 129.66, 129.27, 128.98, 126.35, 62.07, 43.70, 40.72, 39.59, 37.96, 32.60, 32.24, 31.30, 28.01, 27.65, 13.88.

IR (cm^{-1}): 2900.3, 2847.7, 1697.2, 1546.9, 1439.1, 1214.8, 1066.3, 1025.5, 737.9, 690.6.

HRMS (ESI+) *m/z* calcd for $C_{25}H_{30}NaO_2^+$ $[M+Na]^+$: 417.1859, found 417.1854.

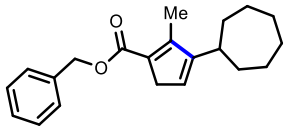


Isopropyl 3-(2-adamantyl)-2-methyl-cyclopenta-1,3-diene-1-carboxylate (38): The cyclization of **S17** was performed on 0.20 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 51.0 mg (85%, 0.17 mmol) of **38** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 0.9 Hz, 1H), 5.11 (hept, *J* = 6.2 Hz, 1H), 3.22 (dd, *J* = 4.0, 2.0 Hz, 2H), 2.71 (s, 1H), 2.30 (t, *J* = 2.3 Hz, 3H), 2.06 – 1.80 (m, 10H), 1.76 (s, 2H), 1.58 (d, *J* = 11.8 Hz, 2H), 1.29 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.35, 156.62, 151.99, 131.71, 130.76, 67.45, 66.84, 44.10, 41.17, 39.99, 38.36, 32.63, 31.69, 28.41, 28.04, 22.48, 14.12. **IR** (cm^{-1}): 2900.8, 2848.3, 1692.6, 1549.5, 1449.1, 1370.7, 1238.5, 1221.2, 1106.9, 741.1.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{29}O_2^+$ $[M+H]^+$: 301.2162, found 301.2163.



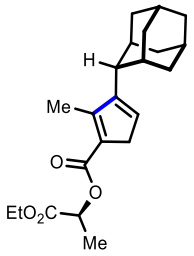
Benzyl 3-cycloheptyl-2-methylcyclopenta-1,3-diene-1-carboxylate (39). The cyclization of **S18** was performed on 0.17 mmol scale with a total reaction time of 12 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 30.0 mg (58%, 0.096 mmol) of **39** as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 6.21 (s, 1H), 5.21 (s, 2H), 3.26 – 3.18 (s, 1H), 2.44 (m, 1H), 2.36 – 2.29 (m, 3H), 1.88 – 1.79 (m, 2H), 1.79 – 1.71 (m, 2H), 1.70 – 1.60 (m, 3H), 1.48 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 156.9, 156.2, 137.2, 130.0, 129.70, 128.8, 128.2, 128.2, 65.5, 40.9, 38.6, 35.0, 28.4, 27.3, 13.8.

IR (cm^{-1}): 2919.8, 2851.9, 1694.9, 1547.5, 1453.7, 1377.1, 1321.5, 1215.4, 1048.3, 900.2, 732.7, 695.3.

HRMS (ESI+) *m/z* calcd for $C_{21}H_{27}O_2^+$ $[M+H]^+$: 311.2006, found 311.2006.



[(*1S*)-2-Ethoxy-1-methyl-2-oxo-ethyl] 3-(2-adamantyl)-2-methyl-cyclopenta-1,3-diene-1-carboxylate (40): The cyclization of **S19** was performed on 0.13 mmol scale with a total reaction

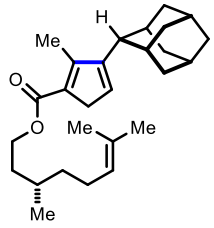
time of 4 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 27.1 mg (57%, 0.076 mmol) of **40** as a viscous, colorless oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.16 (q, *J* = 7.0 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.29 (qd, *J* = 25.0, 2.0 Hz, 2H), 2.72 (s, 1H), 2.32 (t, *J* = 2.3 Hz, 3H), 2.04 (s, 2H), 2.00 (t, *J* = 10.8 Hz, 2H), 1.95 (d, *J* = 2.7 Hz, 1H), 1.93 – 1.87 (m, 4H), 1.84 (s, 1H), 1.76 (s, *J* = 10.7 Hz, 2H), 1.59 (d, *J* = 12.9 Hz, 2H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 171.82, 164.72, 158.80, 152.08, 132.68, 129.18, 68.22, 61.52, 44.05, 41.11, 39.96, 39.93, 38.32, 32.61, 32.57, 31.64, 28.36, 28.00, 17.51, 14.49, 14.28.

IR (cm^{-1}): 2901.7, 2848.9, 1753.9, 1700.3, 1547.3, 1448.6, 1368.8, 1238.3, 1196.9, 1125.5, 1094.4, 740.6.

HRMS (ESI+) *m/z* calcd for $C_{22}H_{31}O_4^+$ $[M+H]^+$: 359.2217, found 359.2220.



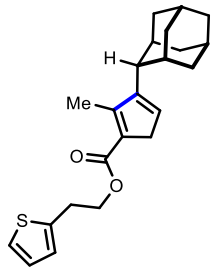
[(3*S*)-3,7-Dimethyloct-6-enyl] 3-(2-adamantyl)-2-methyl-cyclopenta-1,3-diene-1-carboxylate (41): The cyclization of **S20**was performed on 0.84 mmol scale with a total reaction time of 5 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 27.0 mg (81%, 0.068 mmol) of **41** as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 5.09 (ddd, *J* = 7.1, 5.8, 1.4 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.22 (dd, *J* = 3.9, 2.0 Hz, 2H), 2.72 (s, 1H), 2.31 (t, *J* = 2.3 Hz, 3H), 2.08 – 1.65 (m, 18H),

1.60 (s, 4H), 1.49 (dt, J = 20.9, 7.1 Hz, 1H), 1.42 – 1.31 (m, 1H), 1.30 – 1.14 (m, 3H), 0.94 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.83, 157.02, 152.01, 131.88, 131.65, 130.30, 125.00, 62.33, 44.09, 41.14, 39.97, 38.34, 37.37, 36.03, 32.62, 31.66, 29.94, 28.38, 28.02, 26.07, 25.77, 19.84, 18.02, 14.15.

HRMS (ESI+) *m/z* calcd for $C_{27}H_{41}O_2^+$ $[M+H]^+$: 397.3101, found 397.3104.



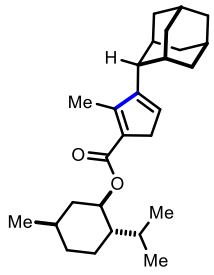
2-(2-Thienyl)ethyl 3-(2-adamantyl)-2-methyl-cyclopenta-1,3-diene-1-carboxylate (42): The cyclization of **S21** was performed on 0.13 mmol scale with a total reaction time of 5 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 34.0 mg (71%, 0.092 mmol) of **42** as a pale yellow oil.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.16 (d, J = 5.0 Hz, 1H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 6.89 (d, J = 3.0 Hz, 1H), 6.48 (s, 1H), 4.39 (t, J = 6.6 Hz, 2H), 3.26 (d, J = 1.8 Hz, 2H), 3.22 (t, J = 6.6 Hz, 2H), 2.72 (s, 1H), 2.29 (t, J = 2.1 Hz, 3H), 2.04 (s, J = 11.5 Hz, 2H), 2.00 (d, J = 12.7 Hz, 2H), 1.96 (m, 2H), 1.90 (m, 4H), 1.84 (s, 1H), 1.76 (s, 2H), 1.59 (d, J = 12.4 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.41, 157.88, 152.03, 140.87, 132.25, 129.81, 127.13, 125.78, 124.23, 64.18, 44.06, 41.17, 39.95, 38.32, 32.61, 31.65, 29.93, 28.37, 28.01, 14.19.

IR (cm^{-1}): 2902.3, 2848.6, 1695.3, 1547.4, 1449.3, 1216.5, 1066.9, 962.9, 734.3, 695.5.

HRMS (ESI+) *m/z* calcd for $C_{23}H_{28}O_2S^+$ [M+]$^+$: 368.1810, found 368.1801.



[(*1R,2S,5R*)-2-isopropyl-5-methyl-cyclohexyl] 3-(2-adamantyl)-2-methyl-cyclopenta-1,3-diene-1-carboxylate (43): The cyclization of **S22** was performed on 1.21 mmol scale with a total reaction time of 3 h. Purification by flash column chromatography over silica eluting with 5% EtOAc in hexanes provided 303 mg (58%, 0.76 mmol) of **43** as a colorless solid.

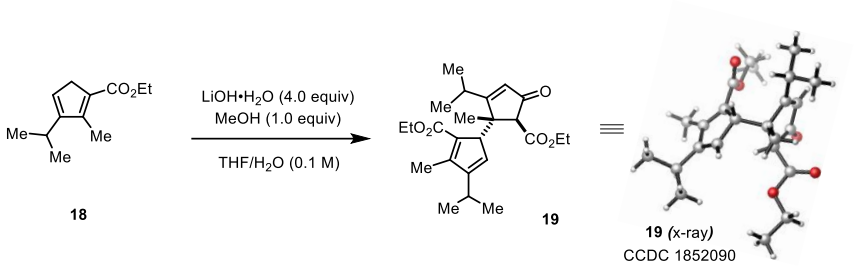
^{1}H NMR (700 MHz, $CDCl_3$) δ 6.45 (s, 1H), 4.78 (td, *J* = 10.8, 4.4 Hz, 1H), 3.24 – 3.20 (s, 2H), 2.72 (s, 1H), 2.31 (t, *J* = 2.3 Hz, 3H), 2.12 – 2.05 (m, 1H), 2.05 – 1.99 (m, 4H), 1.98 – 1.82 (m, 7H), 1.76 (s, 2H), 1.73 – 1.67 (m, 2H), 1.59 (d, *J* = 12.1 Hz, 2H), 1.54 – 1.49 (m, 1H), 1.47 – 1.42 (m, 1H), 1.13 – 1.06 (m, 1H), 1.01 (q, *J* = 12.0 Hz, 1H), 0.90 (dd, *J* = 6.8, 3.9 Hz, 7H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 165.32, 156.82, 152.09, 131.71, 130.65, 73.40, 47.63, 44.12, 41.69, 41.20, 40.00, 38.36, 34.77, 32.65, 31.80, 31.70, 28.41, 28.05, 26.77, 23.97, 22.44, 21.22, 16.88, 14.13.

IR (cm^{-1}): 2903.2, 2849.4, 1687.7, 1548.4, 1449.7, 1239.0, 1221.3, 1062.8, 961.7, 899.3, 736.6.

HRMS (ESI+) *m/z* calcd for $C_{27}H_{41}O_2^+$ [M+H]$^+$: 397.3101, found 397.3099.

B.1.6 Synthesis of enone 19



To a 50-mL round bottom flask equipped with a magnetic stir bar, was added cyclopentadiene **18**, MeOH (23 µL,1.03 mmol) and a solvent mixture of THF/water (7:3; 0.1 M). The solution was cooled in an ice bath and then LiOH•H_2O (173 mg, 4.12 mmol) was added in one portion. The reaction was slowly warmed to rt. When TLC analysis indicated complete consumption of starting material, the reaction was quenched with the addition of NH_4Cl (aq.). The mixture was poured into a separatory funnel and extracted with EtOAc (3 × 8 mL). The combined organics were washed with brine, dried over anhydrous Na_2CO_3 and concentrated under reduced pressure to afford a white solid. The crude material was recrystallized from EtOH in hexanes to afford **19** (55%, 113 mg, 0.281 mmol) as a clear colorless solid.

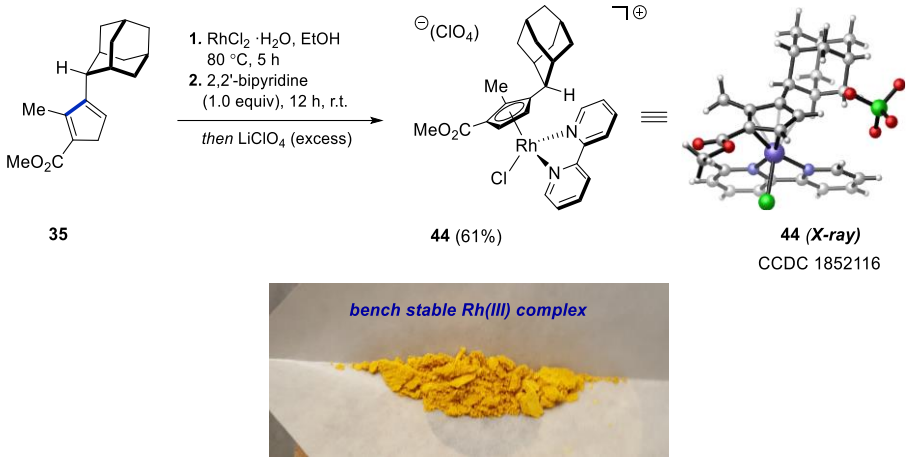
^{1}H NMR (700 MHz, $CDCl_3$) δ 6.17 (s, 1H), 5.86 (s, 1H), 4.16 (m, 4H), 3.70 (s, 1H), 2.79 (s, 1H), 2.69 (ddd, *J* = 26.3, 16.6, 9.7 Hz, 1H), 2.56 (dt, *J* = 13.6, 6.9 Hz, 1H), 2.10 (s, *J* = 1.7 Hz, 3H), 1.46 (s, *J* = 16.5 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 6.6 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 202.38, 194.47, 169.89, 166.57, 155.35, 153.36, 134.03, 131.07, 127.19, 61.26, 60.60, 59.44, 58.72, 53.05, 29.40, 27.01, 25.35, 22.78, 22.44, 22.31, 14.72, 14.55, 14.47, 13.31.

IR (cm^{-1}): 2967.7, 1701.94, 1606.4, 1465.3, 1369.5, 1224.3, 1150.2, 1023.9, 733.6, 701.6.

HRMS (ESI+) *m/z* calcd for $C_{24}H_{35}O_5^+$ $[M+H]^+$: 430.2479, found 403.2480.

B.1.7 Synthesis of Rh(III)Cp complex 44



To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was added $RhCl_3$•$3H_2O$ (128 mg, 0.486 mmol), cyclopentadiene 35 (132 mg, 0.486 mmol) and EtOH (7 mL). This solution was refluxed under a nitrogenous atmosphere for 6 h to give a dark red precipitate. The suspension was subsequently cooled to room temp followed by addition of 2,2'-bipyridine (75.9 mg, 0.486 mmol). This afforded a clear pale-yellow solution which was left to stir for 3 h. After this time, the reaction mixture was filtered to remove insoluble materials. To the eluent was added $LiClO_4$ (103 mg, 0.972 mmol) which led to the formation of a bright orange solid. The solid was filtered and washed with cold EtOH to garner Rh(III)Cp complex **44** (61%, 178 mg, 0.298 mmol).

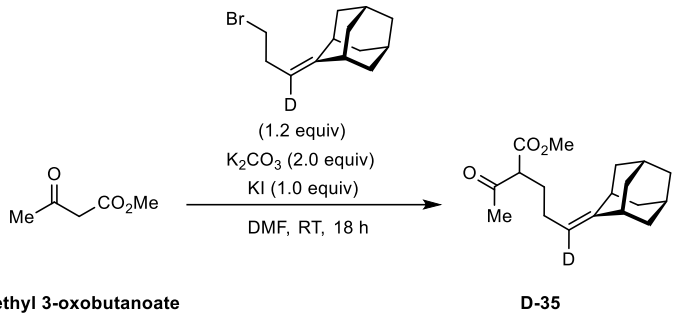
^{1}H NMR (700 MHz, $CDCl_3$) δ 9.12 (d, *J* = 5.3 Hz, 1H), 8.91 (d, *J* = 5.3 Hz, 1H), 8.35 (dd, *J* = 7.9, 2.3 Hz, 2H), 8.15 (dd, *J* = 17.9, 7.8 Hz, 2H), 7.71 – 7.65 (m, 2H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.31 (d, *J* = 2.7 Hz, 1H), 3.90 (s, 3H), 2.74 (s, 1H), 2.18 (s, 3H), 2.15 (s, 1H), 2.11 (d, *J* = 13.6 Hz, 1H), 2.02 – 1.91 (m, 4H), 1.97 – 1.94 (m, 3H), 1.91 – 1.80 (m, 3H), 1.76 (t, *J* = 15.6 Hz, 3H), 1.65 (d, *J* = 13.0 Hz, 1H), 1.58 (d, *J* = 13.1 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 164.46, 155.20, 154.98, 153.86, 152.77, 140.69, 140.56, 127.88, 127.67, 124.54, 124.39, 53.51, 41.08, 39.03, 38.93, 37.10, 32.96, 31.97, 31.94, 29.84, 27.31, 26.78, 11.40.

IR (cm^{-1}): 3117.8, 2902.9, 2847.9, 1728.2, 1447.4, 1224.9, 1066.3, 771.5, 647.3.

HRMS (ESI-) *m/z* calcd for $C_{28}H_{31}O_2ClN_2Rh^-$ $[M]^-$: 565.1135, found 565.1123.

B.1.8 Deuterium labeling studies to exclude a 1,2-*H* shift mechanism



methyl 3-oxobutanoate **D-35**

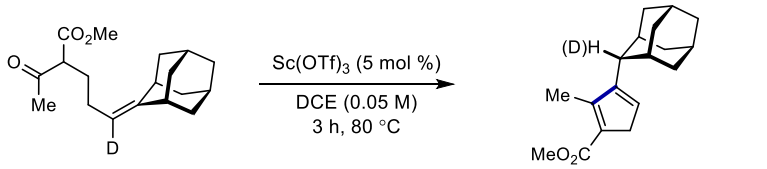
Methyl 2-acetyl-5-(2-adamantylidene)-5-deuterio-pentanoate To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was successively added methyl 3-oxobutanoate (400 mg, 3.44 mmol, 1.0 equiv), DMF (0.3 M), K_2CO_3 (2.0 equiv) and KI (1.0 equiv). The flask was topped with a rubber septum and a nitrogen inlet. 2-(3-Bromo-1-deuterio-propylidene)adamantane (1.2 equiv) was then added dropwise to the reaction suspension *via* syringe and the resultant solution was allowed to stir at room temp. When there was complete consumption of starting material (determined by TLC), EtOAc (30 mL) was added to the reaction mixture and then poured into an extraction funnel along with water (40 mL) and then separated. The organic phase was further extracted with water (3 × 30 mL), washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified with flash column chromatography over silica with EtOAc in hexanes to afford the deuterated cyclopentadiene precursor as a clear liquid in 40% (404 mg, 1.39 mmol).

^{1}H NMR (700 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.49 – 3.45 (m, 1H), 2.71 (s, 1H), 2.31 (s, 1H), 2.22 (s, 3H), 1.97 (m, 2H), 1.93 (m, 2H), 1.88 – 1.79 (m, 8H), 1.73 (d, J = 11.8 Hz, 2H), 1.66 (m, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 203.74, 170.74, 149.85, 114.17, 59.25, 52.67, 40.83, 40.19, 40.16, 39.32, 39.24, 37.55, 32.41, 29.21, 29.05, 28.91, 24.50.

IR (cm^{-1}): 2901.6, 2847.4, 1741.6, 1714.6, 1447.2, 1356.6, 1242.5, 1148.5, 948.9, 671.5.

HRMS (ESI+) *m/z* calcd for $C_{18}H_{29}O_3DN^+$ $[M+NH_4]^+$: 309.2283, found 309.2274.



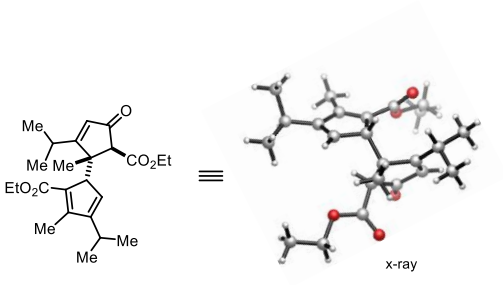
D-35

85%

[Deutero incorporation not detected by HRMS analysis]

A flame-dried 4 – dram vial was charged with $Sc(OTf)_3$ (5 mol %) and DCE (0.05 M), and stirred at room temperature. To this solution was added deuterated substrate (40 mg, 0.137 mmol, 1 equiv) in DCE (1 mL), and the resultant mixture was stirred for 3 h at 80 °C. Upon completion (as determined by TLC analysis), the reaction mixture was passed through a short silica plug eluting with DCM (25 mL). The filtrate was concentrated under reduced pressure, and the crude material was purified over silica *via* flash column chromatography, with EtOAc in hexanes (1% to 10%) to give the pure cyclopentadiene in 85% (32 mg, 0.117 mmol). Analysis of the cyclopentadiene by HRMS analysis did not indicate incorporation of deuterium. Only compound **35** was detected.

B.1.9 X-ray crystallographic data



Structure Determination. CCDC 1852090

Colorless plates of **ccm042** were grown from a diethylether/hexane solution of the compound at 22 deg. C. A crystal of dimensions 0.18 x 0.17 x 0.04 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (l = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in w. The exposure times were 1 sec. for the low angle images, 8 sec. for high angle. The integration of the data yielded a total of 17286 reflections to a maximum 2q value of 136.48° of which 3977 were independent and 3496 were greater than 2s(I). The final cell constants (Table S1) were based on the xyz centroids 14973 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with CrystalClear 2.0 and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2014/6) software package, using the space group P1bar with Z = 2 for the formula C24H34O5. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F2 converged at R1 = 0.0569 and wR2 = 0.1579 [based on I > 2sigma(I)], R1 = 0.0611 and wR2 = 0.1624 for all data. Additional details

are presented in Table S1 and are given as Supporting Information in a CIF file.

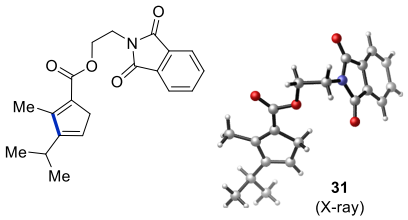
Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Sheldrick, G.M. SHELXTL, v. 2014/6; Bruker Analytical X-ray, Madison, WI, 2014.

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

Crystal data and structure refinement for ccm042.

Identification code	ccm042
Empirical formula	C24 H34 O5
Formula weight	402.51
Temperature	85(2) K
Wavelength	1.54187 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 10.77750(10) A alpha = 65.135(4) deg.
	b = 10.8431(9) A beta = 66.770(5) deg.
	c = 12.2002(9) A gamma = 62.986(6) deg.
Volume	1115.34(14) A^3
Z, Calculated density	2, 1.199 Mg/m^3
Absorption coefficient	0.663 mm^-1
F(000)	436
Crystal size	0.18 x 0.17 x 0.04 mm
Theta range for data collection	4.127 to 68.239 deg.
Limiting indices	-12<=h<=12, -13<=k<=12, -14<=l<=14
Reflections collected / unique	17286 / 3977 [R(int) = 0.0666]
Completeness to theta = 67.687	98.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.973 and 0.640
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3977 / 0 / 271
Goodness-of-fit on F^2	1.090
Final R indices [I>2sigma(I)]	R1 = 0.0569, wR2 = 0.1579
R indices (all data)	R1 = 0.0611, wR2 = 0.1624
Extinction coefficient	0.0094(13)
Largest diff. peak and hole	0.378 and -0.323 e.A^-3



Structure Determination. CCDC 1852114

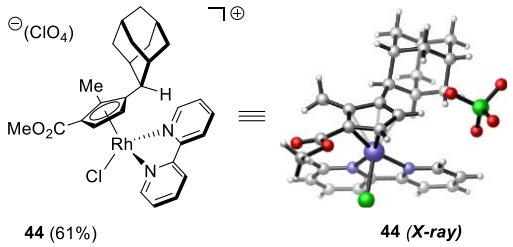
Colorless needles of **ccmpth2** were grown from a dichloromethane/hexanes solution of the compound at 22 deg. C. A crystal of dimensions 0.24 x 0.02 x 0.02 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 2 sec. for the low angle images, 12 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 25307 reflections to a maximum 2θ value of 140.41° of which 3193 were independent and 2714 were greater than 2σ(I). The final cell constants (Table S7) were based on the xyz centroids of 8045 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group Pna2(1) with Z = 4 for the formula $C_{20}H_{21}NO_4$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0803 and wR2 = 0.2145 [based on I > 2sigma(I)], R1 = 0.0963 and wR2 = 0.2690 for all data. Additional details are presented in Table S7 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).
CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Crystal data and structure refinement for ccmpth2.

Identification code	ccmpth2
Empirical formula	C20 H21 N O4
Formula weight	339.38
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Orthorhombic, Pna2(1)
Unit cell dimensions	a = 20.5326(10) A alpha = 90 deg. b = 18.6873(10) A beta = 90 deg. c = 4.4753(2) A gamma = 90 deg.
Volume	1717.17(15) A^3
Z, Calculated density	4, 1.313 Mg/m^3
Absorption coefficient	0.746 mm^-1
F(000)	720
Crystal size	0.240 x 0.020 x 0.020 mm
Theta range for data collection	3.198 to 70.207 deg.
Limiting indices	-23<=h<=24, -22<=k<=22, -5<=l<=5
Reflections collected / unique	25307 / 3193 [R(int) = 0.1097]
Completeness to theta = 67.684	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.52314
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3193 / 1 / 229
Goodness-of-fit on F^2	1.120
Final R indices [I>2sigma(I)]	R1 = 0.0803, wR2 = 0.2145
R indices (all data)	R1 = 0.0963, wR2 = 0.2690
Absolute structure parameter	0.1(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.481 and -0.419 e.A^-3



44 (61%) **44** ***(X-ray)***

Structure Determination. CCDC 1852116

Orange blocks of **ccmrh3** were grown from a chloroform-D solution of the compound at 22 deg. C. A crystal of dimensions 0.10 x 0.10 x 0.05 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 3 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 23964 reflections to a maximum 2θ value of 138.64° of which 5828 were independent and 5729 were greater than 2σ(I). The final cell constants (Table S13) were based on the xyz centroids of 13850 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P1bar with Z = 2 for the formula $C_{29}H_{31}DN_2O_6Cl_5Rh$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0526 and wR2 = 0.1388 [based on I > 2sigma(I)], R1 = 0.0532 and wR2 = 0.1409 for all data. Additional details are presented in Table S13 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Table S13. Crystal data and structure refinement for ccmrh3.

Identification code	ccmrh3
Empirical formula	C29 H31 Cl5 D N2 O6 Rh
Formula weight	785.73
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 11.4969(4) A alpha = 93.121(2) deg. b = 12.0883(3) A beta = 101.191(3) deg. c = 12.6690(3) A gamma = 109.410(3) deg.
Volume	1615.55(9) A^3
Z, Calculated density	2, 1.615 Mg/m^3
Absorption coefficient	8.455 mm^-1
F(000)	796
Crystal size	0.100 x 0.100 x 0.050 mm
Theta range for data collection	3.586 to 69.320 deg.
Limiting indices	-13<=h<=13, -14<=k<=14, -14<=l<=15
Reflections collected / unique	23964 / 5828 [R(int) = 0.0413]
Completeness to theta = 67.684	97.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.58278
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5828 / 0 / 390
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1388
R indices (all data)	R1 = 0.0532, wR2 = 0.1409
Extinction coefficient	n/a
Largest diff. peak and hole	2.683 and -0.943 e.A^-3

B.1.10 References

1) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis.*; University Science Books: Sausalito, **2009**.

2) (a) Gheewala, C. D.; Collins, B. E.; Lambert, T. H. *Science* **2016**, *351*, 961. (b) Gheewala, C. D.; Radtke, M. A.; Hui, J.; Hon, A. B.; Lambert, T. H. *Org. Lett.* **2017**, *19*, 4227.

3) For representative examples, see: (a) Winterfefeldt, E. *Chem. Rev.* **1993**, *93*, 827. (b) Yoon, H.; Chae, W. *Tetrahedron Lett.* **1997**, *38*, 5169. (c) Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction: Selected Practical Methods;* Wiley, New York, **2002**. (d) Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett*. **2004**, *6*, 1589. (e) Zhang, W. H.; Luo, S. J.; Fang, F.; Chen, Q. H.; Hu, H. W.; Jia, X. H.; Zhai, H. B. *J. Am. Chem. Soc*. **2005**, *127*, 18. (f) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8885. (g) Mukherjee, S.; Corey, E. J. *Org. Lett*. **2010**, *12*, 1024. (h) García-Mera, X.; Rodríguez-Borges, J. E.; Vale, M. L. C.; Alves, M. J. *Tetrahedron* **2011**, *67*, 7162. (i) Calandra, N. A.; King, S. M.; Herzon, S. B. *J. Org. Chem.* **2013**, *78*, 10031.

4) (a) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965. (b) Togni, A.; Halterman, R. L. *Metallocenes*; Wiley-VCH: Weinheim, Germany, **1996**, Vol. 1; and Vol. 2, **1998**. (c) McKnight, A. L.; Waymouth, R. M. *Chem. Rev*. **1998**, *98*, 2587. (d) Resconi, L.; Cavallo, L.; Fait, A.; Piemontesi, F. *Chem. Rev*. **2000**, *100*, 1253.

5) (a) Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729. (b) Schumann, H.; Meese-Marktscheffel, J. A.; Esser, L. *Chem. Rev*. **1995**, *95*, 865. (c) Evans, W. J.; Davis, B. L. *Chem. Rev*. **2002**, *102*, 2119.

6) For reviews and select recent examples of functionalized cyclopentadienyl ligands, see: (a) Macomber, D. W.; Hart, W. P.; Rausch, M. D. *Adv. Organomet. Chem.* **1982**, *21*, 1. (b) Muller,

C.; Vos, D.; Jutzi, P. *J. Organomet. Chem*. **2000**, *600*, 127. (c) Jia, Z.-J.; Merten, C.; Gontla, R.; Daniliuc, C. G.; Antonchick, A. P.; Waldmann, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 2429. (d) Trifonova, E. A.; Ankudinov, N. M.; Mikhaylov, A. A.; Chusov, D. A. Nelyubina, Y. V.; Perekalin, D. S. *Angew. Chem., Int. Ed.* **2018**, *57*, 7714.

7) Hong, S. Y.; Jeong, J.; Chang, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 2408.

8) Piou, T.; Rovis, T. *Nature* **2015**, *527*, 86.

9) (a) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-a.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405. (b) Onitsuka, K.; Okuda, H.; Sasai, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1454. (c) Kanbayashi, N.; Onitsuka, K. *Angew. Chem., Int. Ed*. **2011**, *50*, 5197.

10)For syntheses of cyclopentadienes, see: (a) Xi, Z.; Song, Q.; Chen, J.; Guan, H.; Li, P. *Angew. Chem. Int. Ed.* **2001**, *40*, 1913. (b) Lv, Y.; Yan, X.; Yan, L.; Wang, Z.; Chen, J.; Deng, H.; Shao, M.; Zhang, H.; Cao, W. *Tetrahedron* **2013**, *69*, 4205. (c) Cheng, X.; Zhu, L.; Lin, M.; Chen, J.; Huang, X. *Chem. Commun.* **2017**, *53*, 3745. (d) Bankar, S. K.; Singh, B.; Tung, P.; Ramasastry, S. S. V. *Angew. Chem., Int. Ed.* **2018**, *57*, 1678.

11)(a) Hatanaka, M.; Himeda, Y.; Ueda, I. *J. Chem. Soc., Chem. Commun.* **1990**, 526. (b) Hatanaka, M.; Himeda, Y.; Ueda, I. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2269.

12)Lee, J. H.; Toste, F. D. *Angew. Chem. Int. Ed*. **2007**, *46*, 912.

13)Yin, X.; Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 14591.

14)(a) Day, V. W.; Stults, B. R.; Reimer, K. J.; Shaver, A. *J. Am. Chem. Soc.* **1974**, *96*, 4008. (b) Reimer, K. J.; Shaver, A. *J. Organomet. Chem.* **1975**, *93*, 239. (c) Laganis, E. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1980**, 102, 6633. (d) Paprott, G.; Seppelt, K. *J. Am. Chem. Soc.* **1984**, *106*, 4060. (e) Jones, S. S.; Rausch, M. D.; Bitterwolf, T. E. *J. Organomet. Chem*. **1990**, *396*, 279.

(f) Zheng, Y.; Mao, J.; Weng, Y.; Zhang, X.; Xu, X. *Org. Lett.* **2015**, *17*, 5638. (g) Funami, H.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed*. **2007**, *46*, 909.

15)(a) Wilson, P. J.; Wells, J. H. *Chem. Rev.* **1944**, *34*, 1. (b) Fang, H.; Zhao, C.; Li, G.; Xi, Z. *Tetrahedron* **2003**, *59*, 3779. (c) Datta, S.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc*. **2005**, *127*, 11606. (d) Zhou, S.; Yan, B.; Liu, Y. *J. Org. Chem.* **2005**, *70*, 4006. (e)Schmidt, E. Y.; Bidusenko, I. A.; Ushakov, I. A.; Vashchenko, A. V.; Trofimov, B. A. *Org. Lett*. **2017**, *19*, 3127.

16)(a) Ludwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S. *Nature* **2016**, *533*, 374. (b) McAtee, C. C.; Riehl, P. S.; Schindler, C. S. *J. Am. Chem. Soc.* **2017**, *139*, 2960. (c) Ludwig J. R.; Phan S.; McAtee C. C.; Zimmerman P. M.; Devery J. J., III; Schindler C. S. *J Am. Chem. Soc.* **2017**, *139*, 10832. (d) Groso, E.J.; Golonka, A.N.; Harding, R.A.; Alexander, B.W.; Sodano, T.M.; Schindler, C.S. *ACS Catalysis* **2018**, *8*, 2006.

17)For example, see: (a) Miyazawa, A.; Kase, T.; Hashimoto, K.; Choi, J-c.; Sakakura, T.; Ji-z, J. *Macromolecules* **2004**, *37*, 8840. (b) Hou, X.-F.; Cheng, Y.-Q.; Wang, X.; Jin, G.-X. *J. Organomet. Chem.* **2005**, *690*, 1855.

18)Zimmerman, P.M. *J. Comput. Chem*. 2015, 36, 601.

19)Wang, W.H.; Suna, Y.; Himeda, Y.; Muckerman, J. T. Fujita, E. *Dalton Trans*. **2013**, *42*, 9628.

20)Guo, X.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 12377.

21)Xie, H.; Xu, B. *Eur. J. Org. Chem.* **2016**, 2594.

22) Huang, J.-W.; Shi, M. *Tetrahedron* **2004**, *60*, 2057.

APPENDIX C

C.1. Experimental procedures, operations, and references for Chapter 3

General procedure for the synthesis of β-ketoester substrate precursors via transesterification of methyl 4-methyl-3-oxopentanoate

The starting β-ketoester substrate precursors (benzyl 4-methyl-3-oxopentanoate, allyl 4-methyl-3-oxopentanoate, 4-chlorobenzyl 4-methyl-3-oxopentanoate, 2-iodobenzyl 4-methyl-3-oxopentanoate, 2-(phenylthio)ethyl 4-methyl-3-oxopentanoate, 2-(thiophen-2-yl)ethyl 4-methyl-3-oxopentanoate, 2-(1,3-dioxoisoindolin-2-yl)ethyl 4-methyl-3-oxopentanoate and (adamantan-2-yl)methyl 4-methyl-3-oxopentanoate) were synthesized according to the following protocol: To a stirred solution of methyl 4-methyl-3-oxopentanoate (7.0 mmol, 1 equiv) and toluene (25 mL, 0.3 M) was added DMAP (20 mol%) and the respective alcohol (21.0 mmol, 3.0 equiv). The resultant suspension was then heated to reflux. After 24 h, the mixture was cooled to rt and concentrated under reduced pressure to afford a crude oil. The residue was purified via flash column chromotagraphy over silica with ethyl acetate in hexanes (5% to 30%) to afford the desired transesterified β-ketoester.

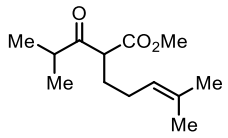
The following β-ketoester substrate precursors are commercially available: methyl 4-methyl-3-oxopentanoate, ethyl 4-methyl-3-oxopentanoate, methyl 3-oxobutanoate, methyl 3-

cyclopropyl-3-oxopropanoate, ethyl 3-cyclopropyl-3-oxopropanoate and ethyl 3-cyclohexyl-3-oxopropanoate.

C.1.1 Synthesis of substrates

General procedure for the synthesis of carbocyclization substrates **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25**, **27**, **29**, **31**, **33**, and **35**

To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was successively added β-ketoester (3.5 mmol, 1.0 equiv), DMF (0.3 M) and K_2CO_3 (2.0 equiv). The flask was topped with a rubber septum and a nitrogen inlet. 5-iodo-2-methylpent-2-ene[13] (1.3 equiv) was then added dropwise to the reaction suspension *via* syringe and the resultant solution was allowed to stir at rt. When there was complete consumption of starting material (determined by TLC), EtOAc (30 mL) was added to the reaction mixture and then poured into an extraction funnel along with water (40 mL) and then separated. The organic phase was further extracted with water (3 × 30 mL), washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified via flash column chromatography over silica with EtOAc in hexanes (5% to 20%) to afford the carbocyclization substrate.

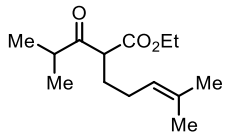


Methyl 2-isobutyryl-6-methylhept-5-enoate **(9):** Isolated as a clear oil (40%).

^{1}H NMR (401 MHz, $CDCl_3$) δ 5.04 (tt, *J* = 7.1, 1.4 Hz, 1H), 3.69 (s, 3H), 3.61 (t, *J* = 7.0 Hz, 1H), 2.75 (hept, *J* = 6.9 Hz, 1H), 2.02 – 1.91 (m, 2H), 1.91 – 1.77 (m, 2H), 1.67 (s, 3H), 1.55 (s, 3H), 1.08 (t, *J* = 7.8, 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4, 17, 0.7, 133.6, 123.2, 56.6, 52.6, 40.8, 28.7, 26.2, 26.1, 18.7, 18.5, 18.0.

IR (cm^{-1}): 2964.6, 1720.4, 1445.5, 1202.5, 1157., 8, 1103.0, 1007.6, 834.8. **HRMS** (ESI+) *m/z* calcd for $C_{13}H_{22}O_3Na^+$ [M+Na^+]: 246.1461, found 249.1465.



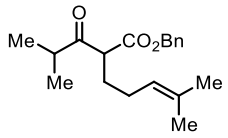
Ethyl 2-isobutyryl-6-methylhept-5-enoate **(11):** Isolated as a clear oil (57%).

^{1}H NMR (401 MHz, $CDCl_3$) δ 5.05 (ddd, *J* = 7.2, 5.6, 1.4 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.59 (t, *J* = 7.0 Hz, 1H), 2.76 (hept, *J* = 6.9 Hz, 1H), 1.96 (q, *J* = 7.4 Hz, 2H), 1.85 (m, 8.6, 6.4 Hz, 2H), 1.67 (s, *J* = 1.4 Hz, 3H), 1.56 (s, *J* = 1.3 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 8.0, 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4, 170.1, 133.3, 123.2, 61.4, 56.7, 40.7, 28.6, 26.1, 25.9, 18.6, 18.4, 17.9, 14.4.

IR (cm^{-1}): 2970.7, 1720.2, 1453.3, 1369.8, 1159.4, 1100.5, 1019.6, 846.7.

HRMS (ESI+) *m/z* calcd for $C_{14}H_{25}O_3^+$ [M+H]$^+$: 241.1798, found 241.1798.



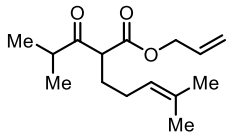
Benzyl 2-isobutyryl-6-methylhept-5-enoate **(13):** Isolated as a clear oil (24%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H), 5.15 (s, 2H), 5.05 (t, *J* = 7.0 Hz, 1H), 3.66 (t, *J* = 7.0 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.01 – 1.82 (m, 4H), 1.67 (s, 3H), 1.54 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.24, 170.03, 135.80, 133.55, 128.91, 128.72, 128.63, 123.21, 67.30, 56.75, 40.87, 28.72, 26.20, 26.04, 18.68, 18.39, 18.04.

IR (cm^{-1}): 2965.8, 1717.5, 1452.3, 1370.0, 1149.8, 1001.8, 832.5, 741.2, 696.4.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{27}O_3^+$ $[M+H]^+$: 303.1955, found 303.1958.



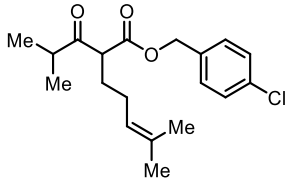
Allyl 2-isobutyryl-6-methylhept-5-enoate **(15)**: Isolated as a clear oil (32%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.31 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.60 (d, *J* = 5.8 Hz, 2H), 3.65 (t, *J* = 7.1 Hz, 1H), 2.78 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.98 (m, 2H), 1.94 – 1.83 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H), 1.12 – 1.09 (m, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.4, 169.9, 133.6, 132.0, 123.2, 119.1, 66.1, 56.7, 40.9, 28.7, 26.2, 26.1, 18.7, 18.5, 18.1.

IR (cm^{-1}): 2968.5, 1718.4, 1451.1, 1368.9, 1155.1, 986.9, 934.0.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{25}O_3^+$ $[M+H]^+$: 253.1798, found 253.1797.



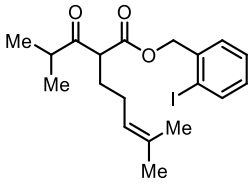
4-Chlorobenzyl 2-isobutyryl-6-methylhept-5-enoate (**17):** Isolated as clear oil (42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.32 (s, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 5.10 (s, 2H), 5.04 (tt, *J* = 7.2, 1.5 Hz, 1H), 3.65 (t, *J* = 7.0 Hz, 1H), 2.73 (hept, *J* = 6.9 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.91 – 1.81 (m, 2H), 1.67 (s, 3H), 1.53 (s, 3H), 1.06 (d, 6H).

^{13}C NMR (126 MHz $CDCl_3$) δ 209.2, 169.9, 134.6, 134.3, 133.6, 130.0, 129.1, 129.1, 123.1, 66.4, 56.6, 40.9, 28.7, 26.1, 26.0, 18.5, 18.3, 17.9.

IR (cm^{-1}): 2966.9, 1717.6, 1452.8, 1369.3, 1150.0, 1092.2, 1006.9, 810.1.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{26}ClO_3^+$ $[M+H]^+$: 337.1565 , found 337.1565.



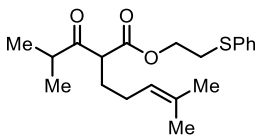
2-Iodobenzyl 2-isobutyryl-6-methylhept-5-enoate **(19):** Isolated as a clear oil (31%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.34 (m, 2H), 7.04 – 7.00 (m, 1H), 5.17 (s, 2H), 5.06 (t, *J* = 7.0 Hz, 1H), 3.71 (t, *J* = 7.0 Hz, 1H), 2.83 – 2.76 (m, 1H), 2.01 – 1.83 (m, 4H), 1.68 (s, *J* = 15.7 Hz, 3H), 1.55 (s, 3H), 1.08 (dd, *J* = 6.8, 1.0 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.13, 169.77, 139.89, 138.24, 133.61, 130.38, 130.08, 128.75, 123.20, 98.85, 71.07, 56.59, 41.01, 28.80, 26.27, 26.06, 18.69, 18.46, 18.10.

IR (cm^{-1}): 2965.8, 1716.8, 1449.1, 1370.4, 1147.5, 1007.0, 833.4, 748.5, 642.9.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{26}O_3I^+$ $[M+H]^+$: 429.0921, found 429.0923.



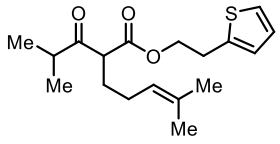
2-(Phenylthio)ethyl 2-isobutyryl-6-methylhept-5-enoate **(21)**: Isolated as a clear oil (33%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (d, *J* = 7.1 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 5.15 – 4.95 (m, 1H), 4.27 (t, *J* = 7.0 Hz, 2H), 3.62 (t, *J* = 7.1 Hz, 1H), 3.14 (td, *J* = 6.9, 3.2 Hz, 2H), 2.79 (hept, *J* = 6.9 Hz, 1H), 1.99 (q, *J* = 7.4 Hz, 2H), 1.94 – 1.79 (m, 2H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.11 (dd, *J* = 12.0, 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0, 169.8, 135.0, 133.3, 130.1, 129.2, 126.8, 123.0, 63.5, 56.3, 40.7, 32.4, 28.5, 26.0, 25.8, 18.4, 18.3, 17.9.

IR (cm^{-1}): 2965.7, 1718.4, 1583.3, 1449.2, 1151.6, 1002.9, 832.3, 736.9, 689.4.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{29}O_3S^+$ $[M+H]^+$: 349.1832, found 349.1836.



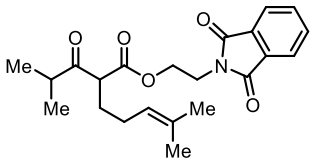
2-(Thiophen-2-yl)ethyl 2-isobutyryl-6-methylhept-5-enoate **(23):** Isolated as a clear oil (31%).

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.16 (d, *J* = 4.0 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 5.05 (t, *J* = 7.0 Hz, 1H), 4.34 (td, *J* = 6.7, 2.5 Hz, 2H), 3.63 (t, *J* = 6.9 Hz, 1H), 3.15 (t, *J* = 6.7 Hz, 2H), 2.72 (hept, *J* = 6.9 Hz, 1H), 1.96 (q, *J* = 7.4 Hz, 2H), 1.92 – 1.76 (m, 2H), 1.68 (s, 3H), 1.56 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.2, 170.0, 139.8, 133.5, 127.2, 125.9, 124.4, 123.2, 65.6, 56.5, 40.9, 29.5, 28.7, 26.2, 26.0, 18.6, 18.4, 18.0.

IR (cm^{-1}): 2965.8, 1718.8, 1583.7, 1448.7, 1152.0, 1003.7, 832.5, 739.4, 689.2.

HRMS (ESI+) *m/z* calcd for $C_{18}H_{27}O_3S^+$ $[M+H]^+$: 323.1675, found 323.1680.



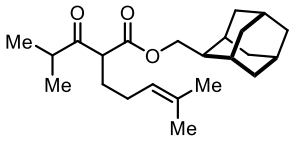
2-(1,3-Dioxoisoindolin-2-yl)ethyl 2-isobutyryl-6-methylhept-5-enoate **(25):** Isolated as a clear oil (32%).

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.01 (tt, *J* = 7.1, 1.4 Hz, 1H), 4.45 – 4.27 (m, 2H), 4.06 – 3.83 (m, 2H), 3.61 (t, *J* = 7.0 Hz, 1H), 2.72 (hept, *J* = 6.9 Hz, 1H), 1.92 (q, *J* = 7.5 Hz, 2H), 1.87 – 1.73 (m, 2H), 1.65 (s, 3H), 1.52 (s, 3H), 1.02 (dd, *J* = 6.9, 2.7 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.06, 170.0, 168.3, 134.4, 133.4, 132.3, 123.7, 123.2, 62.4, 56.1, 41.0, 37.2, 28.7, 26.2, 26.0, 18.5, 18.3, 18.0.

IR (cm^{-1}): 2960.1, 1709.3, 1386.2, 1153.7, 999.5, 880.4, 790.5, 714.7.

HRMS (ESI+) *m/z* calcd for $C_{22}H_{28}NO_5^+$ $[M+H]^+$: 386.1962, found 386.1961.



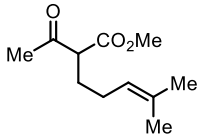
Adamantan-2-yl)methyl 2-isobutyryl-6-methylhept-5-enoate **(27)***:* Isolated as a clear oil (28%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (td, *J* = 6.9, 6.2, 3.4 Hz, 1H), 3.82 – 3.51 (m, 3H), 2.80 (hept, *J* = 6.9 Hz, 1H), 2.01 – 1.94 (m, 6H), 1.94 – 1.79 (m, 2H), 1.72 (d, *J* = 12.0 Hz, 3H), 1.68 (s, 2H), 1.66 – 1.60 (m, 4H), 1.57 (s, 2H), 1.50 (d, *J* = 2.9 Hz, 6H), 1.11 (dd, *J* = 9.8, 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4, 170.3, 133.4, 123.3, 75.1, 56.6, 41.0, 39.5, 37.2, 33.5, 28.7, 28.3, 26.2, 26.0, 18.7, 18.4, 18.1.

IR (cm^{-1}): 2904.6, 1718.0, 1450.9, 1343.9, 1156.8, 991.8, 828.5.

HRMS (ESI+) *m/z* calcd for $C_{23}H_{37}O_3^+$ $[M+H]^+$: 361.2737, found 361.2741.



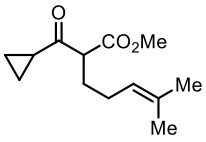
Methyl 2-acetyl-6-methylhept-5-enoate **(29):** Isolated as a clear oil (28%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.73 (s, 3H), 3.44 (t, *J* = 7.2 Hz, 1H), 2.21 (s, 3H), 2.02 – 1.94 (m, 2H), 1.89 (m 2H), 1.68 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 170.7, 133.7, 123.1, 59.3, 52.7, 29.2, 28.6, 26.1, 26.1, 18.0.

IR (cm^{-1}): 2952.7, 1742.1, 1714.3, 1435.4, 1357.8, 1199.3, 1144.4, 1108.5, 1052.3, 985.9, 833.6.

HRMS (ESI+) *m/z* calcd for $C_{11}H_{18}O_3Na^+$ $[M+Na^+]$: 221.1148, found 221.1147.



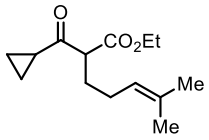
Methyl 2-(cyclopropanecarbonyl)-6-methylhept-5-enoate **(31):** Isolated as a clear oil (59%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.10 – 5.06 (m, 1H), 3.73 (s, 3H), 3.58 (t, *J* = 7.2 Hz, 1H), 2.08 – 1.88 (m, 5H), 1.69 (s, 3H), 1.58 (s, 3H), 1.10 – 1.04 (m, 2H), 0.95 – 0.89 (m, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 205.81, 170.84, 133.60, 123.18, 59.47, 52.63, 28.72, 26.16, 26.07, 20.00, 18.02, 12.13, 11.96.

IR (cm^{-1}): 2951.1, 1736.6, 1699.2, 1440.4, 1379.6, 1160.1, 1011.6, 900.4, 836.7.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{21}O_3^+$ $[M+H]^+$: 225.1485, found 225.1478.



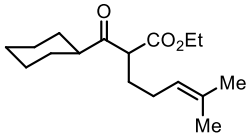
Ethyl 2-(cyclopropanecarbonyl)-6-methylhept-5-enoate **(33)**: Isolated as a clear oil (70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (ddd, *J* = 8.7, 5.1, 1.5 Hz, 1H), 4.21 (dq, *J* = 7.1, 3.0 Hz, 2H), 3.57 (t, *J* = 7.1 Hz, 1H), 2.07 (ddd, *J* = 7.8, 4.5, 3.3 Hz, 1H), 2.02 (q, *J* = 8.1, 7.0 Hz, 2H), 1.94 (ddq, *J* = 13.3, 8.8, 6.7, 6.3 Hz, 2H), 1.70 (s, 3H), 1.59 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.11 – 1.04 (m, 2H), 0.93 (tt, *J* = 5.5, 1.8 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 205.9, 170.4, 133.5, 123.3, 61.5, 59.7, 28.6, 26.2, 26.1, 19.9, 18.0, 14.5, 12.1, 11.9.

IR (cm^{-1}): 2974.0, 1731.7, 1700.5, 1445.7, 1378.7, 1182.2, 1024.1, 857.2.

HRMS (ESI+) *m/z* calcd for $C_{14}H_{22}O_3Na^+$ $[M+Na]^+$: 261.1461, found 261.1458.



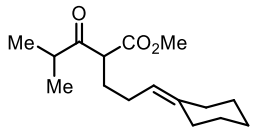
Ethyl 2-(cyclohexanecarbonyl)-6-methylhept-5-enoate **(35)***:* Isolated as a clear oil (51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (tt, *J* = 7.2, 1.4 Hz, 1H), 4.16 (dq, *J* = 7.1, 2.1 Hz, 2H), 3.58 (t, *J* = 7.1 Hz, 1H), 2.50 (ddd, *J* = 11.2, 6.7, 3.3 Hz, 1H), 1.96 (q, *J* = 7.5 Hz, 2H), 1.91 – 1.75 (m, 6H), 1.68 (s, 3H), 1.57 (s, 3H), 1.39 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 6H)..

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.7, 170.2, 133.3, 123.3, 61.4, 56.9, 50.8, 28.9, 28.6, 26.2, 26.0, 26.0, 26.0, 25.8, 18.0, 14.4.

IR (cm^{-1}): 2927.3, 2858.9, 1714.7, 1447.6, 1370.7, 1151.9, 1027.9, 848.9, 731.7.

HRMS (ESI+) *m/z* calcd for $C_{12}H_{29}O_3^+$ $[M+H]^+$: 281.2111, found 281.2117.



Methyl 2-(3-cyclohexylidenepropyl)-4-methyl-3-oxopentanoate **(37):** To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was successively added β-ketoesters (3.5 mmol, 1.0 equiv), DMF (0.3 M) KI (1.0 equiv) and K_2CO_3 (2.0 equiv). The flask was topped with a rubber septum and a nitrogen inlet. (3-Bromopropylidene)cyclohexane (1.3 equiv) was then added dropwise to the reaction suspension *via* syringe and the resultant solution was allowed to stir at rt. When there was complete consumption of starting material (determined by TLC), EtOAc (30 mL) was added to the reaction mixture and then poured into an extraction funnel along with water (40 mL) and then separated. The organic phase was further extracted with water (3 × 30 mL), washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified via flash column chromatography over silica with EtOAc in hexanes (5% to 20%) to afford the carbocyclization substrate **37**. Isolated as a clear oil (39%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.01 (t, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 3.67 – 3.61 (m, 1H), 2.81 – 2.73 (hept, *J* = 6.6 Hz, 1H), 2.11 – 2.02 (m, 4H), 1.98 (q, *J* = 7.3 Hz, 2H), 1.90 (td, *J* = 14.3, 7.4 Hz, 1H), 1.83 (td, *J* = 14.0, 7.3 Hz, 1H), 1.58 – 1.41 (m, 6H), 1.10 (dd, *J* = 13.1, 6.9 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 209.49, 170.70, 141.82, 119.79, 56.49, 52.59, 40.84, 37.50, 29.07, 29.03, 28.99, 28.14, 27.21, 25.29, 18.69, 18.53.

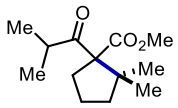
IR (cm^{-1}): 2926.3, 2853.8, 1718.1, 1444.6, 1207.1, 1158.3, 1007.7, 843.3, 652.2.

HRMS (ESI+) *m/z* calcd for $C_{16}H_{27}O_3^+$ $[M+H]^+$: 267.1955, found 267.1956.

C.1.2 Synthesis of α-tert-alkylation products

General procedure for the $Sc(OTf)_3$ catalyzed intramolecular enolate alkylation to access cyclopentanes **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, **30**, **32**, **34**, **36** and **38**

A flame-dried 4–dram vial was charged with $Sc(OTf)_3$ (4.9 mg, 0.01 mmol) and DCE (3 mL), and stirred at room temperature. To this solution was added starting β-ketoester (0.2 mmol) in DCE (1 mL), and the resultant mixture was stirred for 12 h at 80 °C. Upon completion (as determined by TLC analysis), the reaction mixture was passed through a short silica plug eluting with DCM (25 mL). The filtrate was concentrated under reduced pressure, and the crude material was purified over silica *via* flash column chromatography with ethyl acetate in hexanes (0% to 15%) to afford the pure cyclized products.



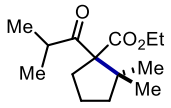
Methyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(10):** Isolated as a clear oil (38.7 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.79 (hept, *J* = 6.7 Hz, 0H), 2.41 (ddd, *J* = 14.0, 10.1, 6.4 Hz, 0H), 2.06 (ddd, *J* = 14.3, 10.0, 4.4 Hz, 0H), 1.86 – 1.73 (m, 1H), 1.73 – 1.63 (m, 0H), 1.62 – 1.54 (m, 1H), 1.14 (s, 1H), 1.04 (t, *J* = 6.8 Hz, 2H), 0.98 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1, 173.4, 72.5, 52.0, 46.6, 40.4, 39.2, 31.7, 26.6, 24.4, 21.0, 20.3, 19.9.

IR (cm^{-1}): 2960.3, 1709.5, 1457.8, 1374.1, 1211.9, 1100.3, 732.7.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{23}O_3^+$ $[M+H]^+$: 227.1642, found 227.1643.



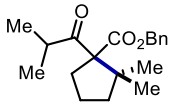
Ethyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(12):** Isolated as a clear oil (39.2 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 – 4.14 (m, 2H), 2.80 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.42 (ddd, *J* = 14.2, 10.3, 6.5 Hz, 1H), 2.05 (ddd, *J* = 14.0, 9.9, 4.4 Hz, 1H), 1.86 – 1.73 (m, 2H), 1.72 – 1.63 (m, 1H), 1.60 – 1.55 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 3H), 1.05 (t, *J* = 6.5 Hz, 6H), 0.98 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.2, 172.9, 72.5, 61.2, 46.5, 40.4, 39.1, 31.6, 26.6, 24.5, 21.2, 20.29, 20.00, 14.43.

IR (cm^{-1}): 2963.9, 1708.9, 1460.4, 1373.8, 1207.0, 1097.6, 1041.6, 853.3, 736.9.

HRMS (ESI+) *m/z* calcd for $C_{14}H_{25}O_3^+$ $[M+H]^+$: 241.1798, found 241.1799.



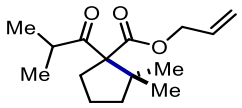
Benzyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(14):** Isolated as a clear oil (42.1 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 5.17 (s, 2H), 2.78 (hept, *J* = 6.7 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.07 (ddd, *J* = 14.1, 9.9, 4.4 Hz, 1H), 1.87 – 1.72 (m, 2H), 1.72 – 1.63 (m, 1H), 1.60 – 1.53 (m, 1H), 1.14 (s, 3H), 1.00 – 0.92 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.02, 172.70, 135.54, 128.96, 128.90, 128.75, 72.51, 67.18, 46.75, 40.41, 39.14, 31.69, 26.60, 24.48, 21.07, 20.31, 19.81.

IR (cm^{-1}): 2962.1, 1708.5, 1458.8, 1372.8, 1201.6, 1096.1, 736.1, 698.4.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{27}O_3^+$ $[M+H]^+$: 303.1955, found 303.1958.



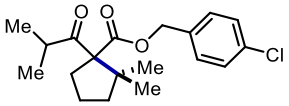
Allyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(16):** Isolated as a clear oil (34.0 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 16.5, 10.4, 6.0 Hz, 1H), 5.36 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.27 (dd, *J* = 10.4, 0.9 Hz, 1H), 4.67 – 4.58 (m, 2H), 2.81 (hept, *J* = 6.6 Hz, 1H), 2.43 (ddd, *J* = 14.1, 10.3, 6.5 Hz, 1H), 2.07 (ddd, *J* = 14.1, 9.9, 4.4 Hz, 1H), 1.86 – 1.54 (m, 4H), 1.16 (s, 3H), 1.04 (dd, *J* = 6.6, 4.2 Hz, 6H), 0.99 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 212.02, 172.58, 131.86, 119.59, 72.49, 66.05, 46.63, 40.39, 39.16, 31.65, 26.64, 24.47, 21.16, 20.31, 19.96.

IR (cm^{-1}): 2962.8, 1708.5, 1460.6, 1371.9, 1256.5, 1202.9, 1098.5, 995.4, 934.7, 733.0.

HRMS (ESI+) *m/z* calcd for $C_{15}H_{25}O_3^+$ $[M+H]^+$: 253.1798, found 253.1802.



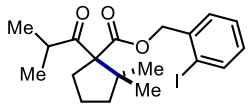
4-Chlorobenzyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(18):** Isolated as a clear oil (34.3 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (q, *J* = 8.6 Hz, 4H), 5.12 (d, *J* = 1.9 Hz, 2H), 2.76 (hept, *J* = 6.6 Hz, 1H), 2.42 (ddd, *J* = 14.1, 10.2, 6.5 Hz, 1H), 2.08 (ddd, *J* = 14.2, 9.9, 4.4 Hz, 1H), 1.86 – 1.72 (m, 2H), 1.72 – 1.63 (m, 1H), 1.60 – 1.53 (m, 1H), 1.13 (s, 3H), 0.97 (dd, *J* = 15.1, 6.7 Hz, 6H), 0.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 211.9, 172.6, 134.7, 134.1, 130.4, 129.2, 72.5, 66.3, 46.8, 40.4, 39.2, 31.7, 26.6, 24.5, 21.0, 20.3, 19.9.

IR (cm^{-1}): 2964.4, 1708.3, 1464.6, 1373.3, 1257.8, 1200.7, 1092.2, 1012.9, 811.9, 731.8.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{26}IO_3^+$ $[M+H]^+$: 337.1565, found 337.1567.



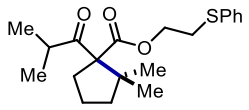
2-Iodobenzyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(20):** Isolated as a clear oil (63.0 mg, 86%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.41 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.35 (td, *J* = 7.5, 0.8 Hz, 1H), 7.02 (td, *J* = 7.7, 1.4 Hz, 1H), 5.24 – 5.17 (m, 2H), 2.88 – 2.77 (m, 1H), 2.51 – 2.42 (m, 1H), 2.11 (ddd, *J* = 14.1, 10.0, 4.4 Hz, 1H), 1.84 – 1.74 (m, 2H), 1.74 – 1.66 (m, 1H), 1.64 – 1.54 (m, 1H), 1.15 (s, 3H), 0.99 (s, 3H), 0.98 (dd, *J* = 8.8, 6.7 Hz, 6H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 212.06, 172.51, 139.91, 138.11, 130.45, 130.44, 128.78, 99.28, 72.57, 70.97, 46.96, 40.43, 39.18, 31.80, 26.64, 24.63, 21.00, 20.37, 19.79.

IR (cm^{-1}): 2961.2, 1706.8, 1458.2, 1372.2, 1198.6, 1097.0, 1011.0, 740.7, 645.3.

HRMS (ESI+) *m/z* calcd for $C_{19}H_{26}O_3I^+$ $[M+H]^+$: 429.0921, found 429.0920.



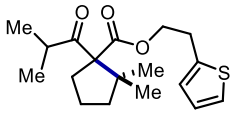
2-(Phenylthio)ethyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(22):** Isolated as a clear oil (14.5 mg, 21%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.32 (dd, *J* = 8.6, 6.9 Hz, 2H), 7.26 – 7.21 (m, 1H), 4.30 (qt, *J* = 11.3, 7.0 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 2.85 (p, *J* = 6.7 Hz, 1H), 2.42 (ddd, *J* = 14.2, 10.3, 6.5 Hz, 1H), 2.08 (ddd, *J* = 14.1, 9.9, 4.5 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.82 – 1.74 (m, 1H), 1.74 – 1.65 (m, 1H), 1.61 – 1.55 (m, 3H), 1.17 (s, 3H), 1.06 (dd, *J* = 11.1, 6.6 Hz, 6H), 1.01 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.96, 171.77, 134.15, 129.32, 128.50, 126.10, 71.52, 62.49, 45.81, 39.42, 38.18, 31.61, 30.70, 29.06, 25.69, 23.53, 20.09, 19.35, 18.94.

IR (cm^{-1}): 2933.7, 1706.8, 1582.9, 1462.2, 1374.3, 1201.4, 1093.8, 739.4, 691.6.

HRMS (ESI+) *m/z* calcd for $C_{20}H_{29}O_3S^+$ $[M+H]^+$: 371.1651, found 371.1650.



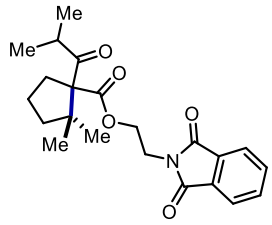
2-(Thiophen-2-yl)ethyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(24):** Isolated as a clear oil (43.0 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.86 (dd, *J* = 3.4, 1.1 Hz, 1H), 4.36 (qt, *J* = 10.9, 6.8 Hz, 2H), 3.19 (t, *J* = 6.8 Hz, 2H), 2.77 (p, *J* = 6.6 Hz, 1H), 2.40 (ddd, *J* = 14.1, 10.3, 6.5 Hz, 1H), 2.06 (ddd, *J* = 14.2, 9.9, 4.5 Hz, 1H), 1.85 – 1.77 (m, 1H), 1.72 – 1.63 (m, 1H), 1.59 – 1.50 (m, 2H), 1.11 (s, 3H), 0.98 (dd, *J* = 6.6, 3.7 Hz, 6H), 0.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1, 172.9, 139.9, 127.3, 126.1, 124.4, 72.5, 65.6, 46.8, 40.4, 39.1, 31.7, 29.5, 26.6, 24.5, 21.0, 20.3, 19.7.

IR (cm^{-1}): 2964.7, 1709.1, 1459.4, 1261.4, 1207.6, 1099.5, 728.6.

HRMS (ESI+) *m/z* cald for $C_{18}H_{27}O_3S^+$ $[M+Z]^+$: 323.1680, found 323.1676.



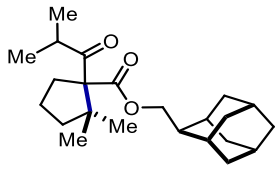
2-(1,3-Dioxoisoindolin-2-yl)ethyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(26):** Isolated as a waxy solid (35.6 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.48 – 4.35 (m, 2H), 4.05 – 3.99 (m, 2H), 2.79 (hept, *J* = 6.7 Hz, 1H), 2.35 (ddd, *J* = 14.1, 9.9, 6.2 Hz, 1H), 2.06 (ddd, *J* = 15.2, 9.8, 4.4 Hz, 1H), 1.79 – 1.63 (m, 3H), 1.55 – 1.50 (m, 1H), 1.07 (s, 3H), 0.94 (s, 3H), 0.93 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 211.9, 172.7, 168.2, 134.5, 132.2, 123.7, 72.4, 62.0, 46.9, 40.3, 39.0, 37.1, 31.6, 26.4, 24.5, 20.8, 20.3, 19.6.

IR (cm^{-1}): 2958.3, 1708.5, 1386.2, 1196.1, 1012.6, 716.0.

HRMS (ESI+) *m/z* calcd for $C_{22}H_{28}NO_5^+$ $[M+H]^+$: 386.1962, found 386.1962.



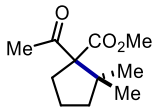
Adamantan-2-yl)methyl 1-isobutyryl-2,2-dimethylcyclopentane-1-carboxylate **(28):** Isolated as a clear oil (50.2 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (d, *J* = 10.9 Hz, 1H), 3.63 (d, *J* = 10.9 Hz, 1H), 2.87 (p, *J* = 6.7 Hz, 1H), 2.43 (ddd, *J* = 14.0, 10.2, 6.4 Hz, 1H), 2.09 (ddd, *J* = 14.3, 9.9, 4.4 Hz, 1H), 1.99 (s, 3H), 1.85 – 1.62 (m, 8H), 1.55 (d, *J* = 2.5 Hz, 8H), 1.18 (s, 3H), 1.03 (dd, *J* = 12.7, 6.7 Hz, 6H), 1.00 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3, 175.2, 77.5, 74.7, 48.7, 42.5, 41.8, 40.9, 39.2, 35.3, 33.8, 30.3, 28.8, 26.7, 22.9, 22.4, 21.6.

IR (cm^{-1}): 2905.7, 1708.1, 1457.2, 1371.9, 1206.6, 1098.8, 999.6, 734.6.

HRMS (ESI+) *m/z* calcd for $C_{23}H_{37}O_3^+$ $[M+H]^+$: 361.2737, found 361.2737.



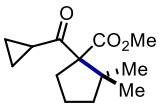
Methyl 1-acetyl-2,2-dimethylcyclopentane-1-carboxylate **(30):** Isolated as a clear oil (11.0 mg, 28%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.32 – 2.25 (m, 1H), 2.17 – 2.09 (m, 4H), 1.81 – 1.73 (m, 2H), 1.73 – 1.64 (m, 2H), 1.10 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 205.25, 173.48, 72.23, 52.26, 46.07, 40.73, 31.92, 29.38, 26.32, 24.53, 20.28.

IR (cm^{-1}): 2960.1, 1705.9, 1433.6, 1249.4, 1115.3, 1088.6, 908.7, 728.4, 648.2.

HRMS (ESI+) *m/z* calcd for $C_{11}H_{19}O_3^+$ $[M+H]^+$: 199.1329, found 199.1323.



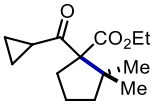
Methyl 1-(cyclopropanecarbonyl)-2,2-dimethylcyclopentane-1-carboxylate **(32):** Isolated as a clear oil (18.0 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.39 – 2.30 (m, 1H), 2.29 – 2.20 (m, 1H), 1.98 – 1.86 (m, 1H), 1.79 – 1.64 (m, 4H), 1.11 (d, *J* = 6.1 Hz, 6H), 1.02 (t, *J* = 4.6 Hz, 2H), 0.89 – 0.81 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.15, 173.64, 72.43, 52.19, 45.88, 40.84, 31.83, 26.19, 25.01, 20.27, 20.10, 12.26, 11.86.

IR (cm^{-1}): 2954.5, 1696.9, 1446.2, 1375.7, 1210.9, 1107.8, 1052.7, 943.9, 823.0.

HRMS (ESI+) *m/z* calcd for $C_{13}H_{21}O_3^+$ $[M+H]^+$: 225.1485, found 225.1483.



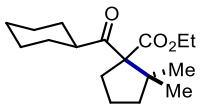
Ethyl 1-(cyclopropanecarbonyl)-2,2-dimethylcyclopentane-1-carboxylate **(34):** Isolated as a clear oil (16.1mg, 34%).

^{1}H NMR (401 MHz, $CDCl_3$) δ 4.20 (qq, *J* = 7.2, 3.7 Hz, 2H), 2.40 – 2.19 (m, 2H), 1.94 (tt, *J* = 8.8, 4.5 Hz, 1H), 1.81 – 1.64 (m, 4H), 1.27 (t, *J* = 7.1, 1.0 Hz, 3H), 1.12 (d, *J* = 9.5 Hz, 6H), 1.03 (t, 2H), 0.85 (dd, *J* = 7.8, 3.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.17, 173.07, 72.38, 61.07, 45.74, 40.93, 31.84, 26.16, 25.07, 20.24, 20.16, 14.49, 12.21, 11.96.

IR (cm^{-1}): 2960.2, 1696.9, 1456.6, 1375.4, 1207.5, 1097.7, 1045.8, 948.5, 863.6.

HRMS (ESI+) *m/z* calcd for $C_{14}H_{23}O_3^+$ $[M+H]^+$: 239.1642, found 239.1647.



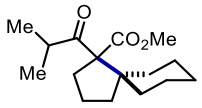
Ethyl 1-(cyclohexanecarbonyl)-2,2-dimethylcyclopentane-1-carboxylate **(36)***:* Isolated as a clear oil (25.3mg, 45%).

^{1}H NMR (401 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 7.1, 2.8 Hz, 2H), 2.65 – 2.50 (m, 2H), 2.10 (m, 2H), 1.89 (d, *J* = 12.4 Hz, 1H), 1.63 (m, 9H), 1.36 (s, 3H), 1.09 (s, 6H), 0.95 (t, *J* = 7.1 Hz, 3H)..

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 172.5, 72.3, 60.8, 49.9, 46.3, 40.4, 31.6, 31.3, 29.8, 26.6, 26.0, 26.0, 25.9, 24.3, 20.3, 14.1.

IR (cm^{-1}): 2930.2, 1705.8, 1454.1, 1369.8, 1207.1, 1091.1, 850.5, 737.5.

HRMS (ESI+) *m/z* calcd for $C_{17}H_{29}O_3^+$ $[M+H]^+$: 281.1111, found 281.2114



Methyl 1-isobutyrylspiro[4.5]decane-1-carboxylate **(38):** Isolated as a clear oil (23.1mg, 43%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 2.80 (p, *J* = 6.7 Hz, 1H), 2.36 (ddd, *J* = 14.0, 10.1, 7.2 Hz, 1H), 2.00 (ddd, *J* = 13.9, 9.7, 4.1 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.78 – 1.65 (m, 2H), 1.64 – 1.52 (m, 4H), 1.41 – 1.32 (m, 2H), 1.31 – 1.23 (m, 2H), 1.17 – 1.06 (m, 2H), 1.02 (dd, *J* = 10.8, 6.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2, 172.3, 73.1, 51.0, 50.1, 38.4, 31.7, 31.0, 30.7, 30.0, 25.3, 22.8, 22.1, 20.1, 19.2, 18.8.

IR (cm^{-1}): 2929.6, 1709.4, 1450.8, 1227.8, 1090.1, 938.9, 833.9.

HRMS (ESI+) *m/z* calcd for $C_{16}H_{27}O_3^+$ $[M+H]^+$: 267.1955, found 267.1954.

C.1.3. References

1) Stork G. *Pure Appl Chem.* **1975**.43:553.

2) Cainein D, Augustine RL, *Carbon-Carbon Bond Formation,* Vol. 1, New York: Marcel Dekker. 1979.

3) a) Posner GH, Lentz CM, *J Am Chem Soc.* **1979**.101:934. b) Megishi E, Idacavage MJ, DiPasguale F, Silveira A. *Tetrahedron Lett.* **1979**.20:845.

4) Zook HD, Kelly WL, Posey IY. *J Org Chem*. **1968**.33:3477.

5) Reetz MT. *Angew Chem Int Ed*. **1982**.21:96. and references cited therein.

6) a) Reetz MT, Maier WF. *Angew Chem Int Ed*. **1978**.17:48. b) Reetz MT, Hűttenhain S, Waltz P, Lòwe U. *Tetrahedron Lett.* **1979**.51:4971.

7) For example, see: a) Corey EJ, Girotra NN, Mathew CT. *J Am Chem Soc*. **1969**.91:1557. b) Stork G, Grieco A. *J Am Chem Soc*. 1969.91:2407. c) Ohloff G, Näf F, Decorzant R, Thommen W, Sundt E. Helv Chim Acta. **1973**.56:1414. d) Reetz MT, Chatziiosifidis I, Schwellnus K. *Angew Chem Int Ed.* **1981**.20:687. e) Sum FW, Weiler L. *J Am Chem Soc.* **1979**.101:4401. f) Patil NT, Kavthe RD, Shinde VS. *Tetrahedron* **2012**.68:8079.

8) For discussion and select examples of metal catalyzed Conia-ene reacions, see: a) Hack D, Blűmel M, Chauhan P, Phillipps AR, Enders D. *Chem Soc Rev*. **2015**; 44:6059.

APPENDIX D

D.1 Experimental procedure, operations, and references for Chapter 4

D.1.1 General information

All moisture-sensitive reactions were performed under a nitrogen atmosphere in flame-dried glassware fitted with rubber septa. Stainless steel syringes were used to transfer air or moisture-sensitive liquids. Flash chromatography was performed using silica gel SiliaFlash®40-63 micron (230-400 mesh) from Silicycle.

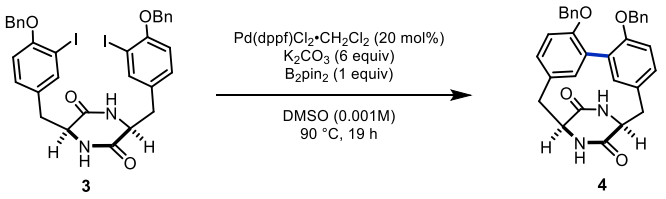
All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Frontier Scientific, Matrix Scientific, Ark Pharm, and Chem Impex International, and were used as received unless otherwise stated. $B_2(pin)_2$ and DMSO (99.7%) purchased from Acros Organics showed better reactivity for the biaryl coupling reaction. Proton Nuclear Magnetic Resonance NMR (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for protons are reported in parts per million and are references to the NMR solvent peak ($_{CDCl3}$: δ = 7.26; DMSO-d_6: δ = 2.54). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ = 77.23; DMSO-d_6: δ = 40.76). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, m = multiplet), and coupling constants in Hertz (Hz). Mass spectroscopic (MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an

Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer. Infrared (IR) spectra were obtained using either an Avatar 360 FT-IR or Perkin Elmer Spectrum BX FT-IR spectrometer. IR data are represented as frequency of absorption (cm^{-1}).

D.1.2 Optimization of macrocyclization conditions

General procedure for macrocyclization:

To a flame-dried 250 mL round-bottom flask was charged with the diketopiperazine substrate **3** (50.0 mg, 0.0659 mmol), a stir bar, and then was brought into a glove box. Palladium catalyst, base, and di-boron reagent were weighted into the same flask, which was sealed with a rubber septum and taken out of the glove box. Nitrogen sparged Solvent (66.0 mL, 0.001M) in a second flask was cannulated into the reaction mixture under nitrogen protection and stirred at 90 ^{o}C for 19 h. Reaction was cooled down to room temperature and poured into a separation funnel containing 15 mL 1N HCl and 50 mL water. The mixture was extracted with $CHCl_3$-isopropanol (3:1) three times (3 × 20 mL) and the combined organic layers were washed with water twice and then brine. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. Yields of product **4** were determined by NMR analysis of the crude reaction mixture with 1-bromo-2,4-dimethoxylbenzene as internal standard except for entries 20 and 21. For entry 11, 33 mL of DMSO was used. For entry 19, DMSO was degassed by freeze-pump-thaw method. For entry 20, 5 mL of air was added to the reaction flask *via* syringe after 30 min.



entry	deviation from above	yield (%)
1	n/a	39
2	DMSO from solvent system	0
3	KOAc instead of K_2CO_3	17
4	$Pd(dppf)Cl_2•CH_2Cl_2$ (20 mol%)	14
5	$Pd(OAc)_2$ (20 mol%), dppb (25 mol%) instead of $Pd(dppf)Cl_2•CH_2Cl_2$	trace
6	$Pd(OAc)_2$ (20 mol%), (*o*-Tol)$_3$P (25 mol%) instead of $Pd(dppf)Cl_2•CH_2Cl_2$	16
7	1,4-dioxane instead of DMSO	NR
8	PhMe instead of DMSO	NR
9	Bis(catecholato)diboron instead of B_2pin_2	trace
10	Bis(neopentyl glycolato)diboron instead of B_2pin_2	36
11	B_2pin_2 (2 equiv), DMSO (0.002M)	36
12	B_2pin_2 (2 equiv)	45
13	B_2pin_2 (3 equiv)	57
14	**B_2pin_2 (4 equiv)**	**61**
15	$PdCl_2(PPh_3)_2$ (20 mol%), B_2pin_2 (4 equiv)	58
16	B_2pin_2 (4 equiv) [100 mg scale]	44
17	B_2pin_2 (4 equiv) [500 mg scale]	25
18	B_2pin_2 (4 equiv), DMSO/H_2O (100:1) [50 mg scale]	63
19	B_2pin_2 (4 equiv), DMSO/H_2O (100:1) [50 mg scale]	26 fpt[a]
20	**B_2pin_2 (6 equiv), DMSO/H_2O (100:1) [500 mg scale]**	**63/63[b]**
21	**B_2pin_2 (6 equiv), DMSO/H_2O (100:1) [1.0 g scale]**	**53**

Conditions: Reactions are conducted using 50 mg of substrate (0.0659 mmol) unless otherwise noted. [a]fpt = freeze-pump-thaw solvent. [b]5 mL of air was added to the reaction after 30 min via syringe.

TABLE D.1. Survey of reaction conditions for macrocycle formation.

D.1.3 Karl Fisher titration and determination of bisboronate intermediate by HRMS

Coulometric Karl Fisher titration was conducted on Coulometric KF Titrator C20S instrument from Mettler Toledo™ with 0.01% water standard and Karl-Fisher reagent (CombiCoulomat fritless) from Sigma-Aldrich

Karl Fischer Titration

	solvent	water content
1)	DMSO (Acros 99.7%)	464.8 ppm
2)	DMSO (solvent system)	197.2 ppm

Observation of bisboronate intermediate by HRMS

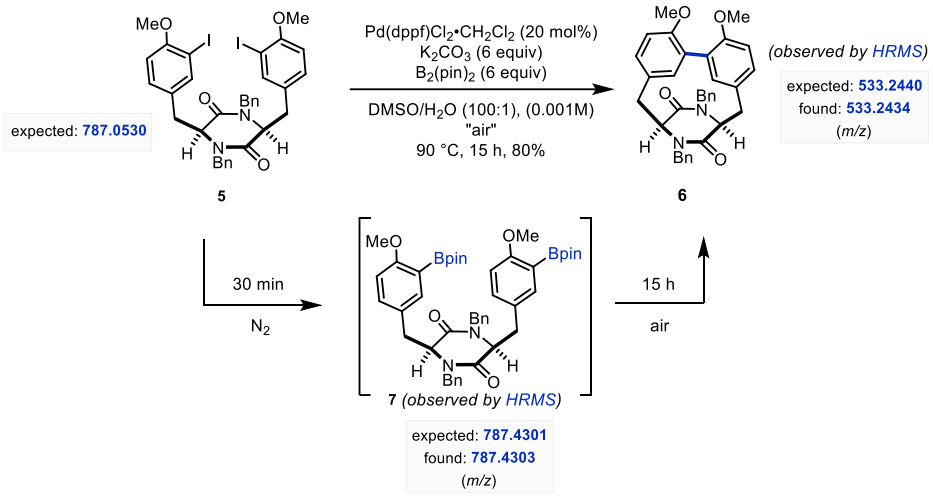


FIGURE D.1. Observing bisboronate intermediate by HRMS

Under nitrogen atmosphere, substrate **5** was subjected to the optimized reaction conditions (Figure 4.6). After 30 min at 90 ^{o}C, an aliquot was taken out of the reaction *via* syringe and transferred immediately into a 2 mL HPLC vial containing MeCN protected with nitrogen inlet. High Resolution Mass spectroscopic (HRMS) data of the prepared sample was taken immediately. The expected peaks of intermediate **7** and product **6** (Figure 4.7) are observed. No peak of the starting material was detected, nor of a monoiodide-monoboronate intermediate. Then, 5 mL of air was added to the reaction and it was kept stirring for 15 hours. HRMS spectra showed full conversion of intermediate **7** to the final product **6** (Figure 4.8).

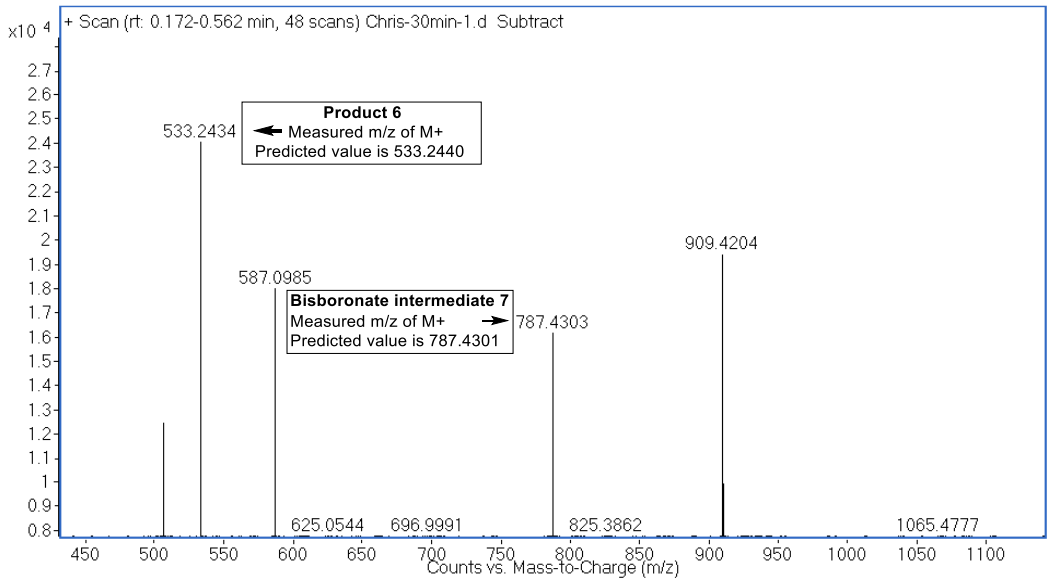


FIGURE D.2 HRMS of intermediate **7** after 30 minutes

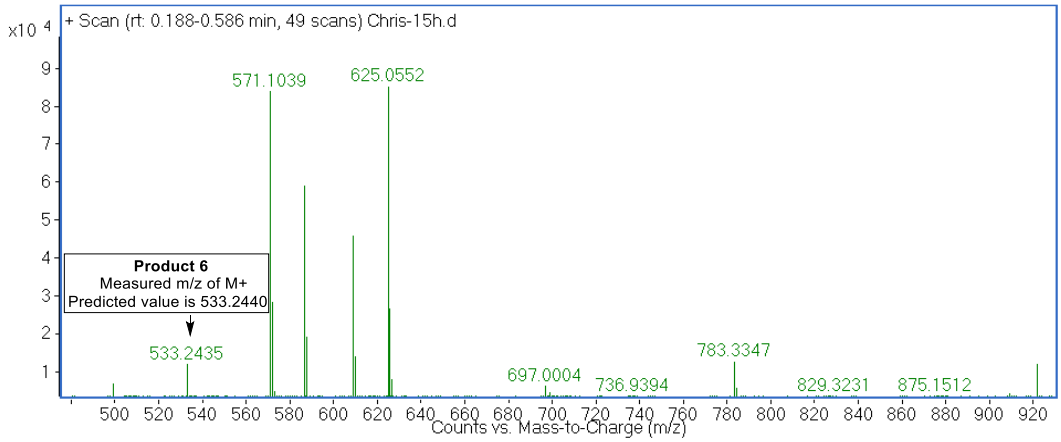
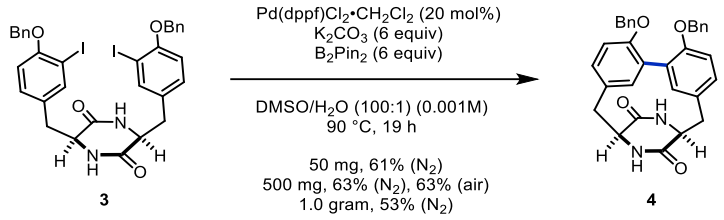


FIGURE D.3. HRMS of macrocycle product **6.**

D.1.4 Synthesis of mycocyclosin derivatives via macrocyclization

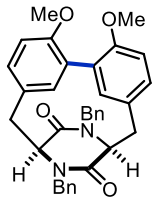
*Typical procedure for synthesis of **4** in aerobic atmosphere (500 mg scale):*



(4^2S,4^5S)-1^6,2^6-bis(benzyloxy)-4(2,5)-piperazina-1,2(1,3)-dibenzenacyclopentaphane-4^3,4^6-dione (**4**): To a flame-dried 1 L round bottom flask equipped with a stir bar was added the DKP substrate **3** (500 mg, 1.32 mmol). The flask was brought into glove box. $Pd(dppf)_2Cl_2•CH_2Cl_2$ (108 mg, 0.132 mmol, 20 mol%), K_2CO_3 (547 mg, 0.396 mmol, 6 equiv), and B_2pin_2 (1.00 g, 0.396 mmol, 6 equiv) were weighted into the flask and then sealed with a septa. The flask was removed from the glovebox and DMSO (656 mL, 0.001M, sparged with nitrogen gas for 4 h) was cannulated into the flask under N_2 protection. The mixture was heated at 90 ºC with vigorous stirring for 30 min followed by addition of 5 mL of air *via* syringe. The reaction mixture was allowed to stir for 19 h. The reaction mixture was cooled down to room temperature and poured into a separation funnel containing 100 mL 1*N* HCl and 500 mL water. The mixture was extracted with $CHCl_3$-isopropanol (3:1) three times (200 mL × 3) and the combined organic layers were washed with water twice and then brine. The organic layer was separated and dried over Na_2SO_4, concentrated under reduced pressure to give the crude material which was purified by column chromatography eluting with 2% MeOH in DCM to remove relatively nonpolar impurities and 4% MeOH in DCM to get the product **4** as white solid in 63% yield (211 mg, 0.418 mmol). Spectroscopic data matched reported literature data.[8]

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (2H, s), 7.37-7.35 (4H, m), 7.28-7.23 (6H, m), 6.99 (2H, d, *J* = 8.2 Hz), 6.89 (2H, d, *J* = 8.2 Hz), 6.57 (2H, s), 5.18 (2H, d, *J* = 12.2 Hz), 5.12 (2H, d, *J* = 12.2 Hz), 4.33 (2H, d, *J* = 5.7 Hz), 3.54 (2H, d, *J* = 15.5 Hz), 2.66 (2H, dd, *J* = 5.7, 15.5 Hz).

^{13}C NMR (125 MHz, DMSO-d_6): δ 169.4, 155.2, 142.7, 138.6, 131.6, 130.9, 129.4, 128.8, 128.6, 128.5, 113.9, 70.9, 56.7, 34.6.



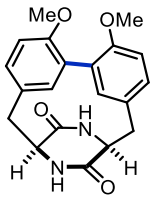
(4^2S,4^5S)-4^1,4^4-dibenzyl-1^6,2^6-dimethoxy-4(2,5)-piperazina-1,2(1,3)-dibenzenacyclopenta-phane-4^3,4^6-dione (**6**): White solid, 500 mg scale, in either inert (51% yield) or aerobic atmosphere (80% yield) for 15 h.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (6H, m), 7.23 (4H, d, *J* = 6.9 Hz), 7.08 (2H, dd, *J* = 2.1, 8.2 Hz), 6.78 (2H, d, *J* = 8.3 Hz), 6.65 (2H, d, *J* = 1.9 Hz,), 5.41 (2H, d, *J* = 15.0 Hz), 4.27 (2H, d, *J* = 5.9 Hz), 4.07 (2H, d, *J* = 15.9 Hz), 3.93 (6H, s), 3.51 (2H, d, *J* = 15.0 Hz), 2.96 (2H, dd, *J* = 6.1, 16.0 Hz,).

^{13}C NMR (176 MHz, $CDCl_3$) δ 167.51, 155.6, 142.2, 135.2, 129.3, 129.3, 128.9, 128.3, 128.0, 125.4, 111.9, 58.9, 56.0, 46.2, 33.0.

IR (cm^{-1}): 2932, 1642, 1509, 1417, 1318, 1262, 1244, 1145, 1023, 808, 670.

HRMS: Calculated for $C_{34}H_{33}N_2O_4^+$ $([M+H^+])^+$: 533.2440 Found: 533.2436.



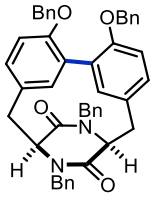
(4^2S,4^5S)-1^6,2^6-dimethoxy-4(2,5)-piperazina-1,2(1,3)-dibenzenacyclopentaphane-4^3,4^6-dione (**9**): White solid, 500 mg scale, in either inert (16% yield) or aerobic atmosphere (20% yield) for 19 h.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (2H, s), 7.05 (2H, d, *J* = 8.0 Hz), 8.87 (2H, d, *J* = 8.0 Hz), 6.53 (2H, s), 4.37 (2H, d, *J* = 5.5 Hz), 3.84 (6H, s), 3.58 (2H, d, *J* = 15.5 Hz), 2.69 (2H, dd, *J* = 5.5, 15.5 Hz).

^{13}C NMR (175 MHz, DMSO-d_6) δ 169.4, 156.1, 142.6, 131.8, 130.5, 128.2, 112.6, 56.8, 56.7, 34.7.

IR (cm^{-1}): 2927, 2678, 1659, 1443, 1264, 1250, 1049, 1021, 730, 700.

HRMS: Calculated for $C_{20}H_{21}N_2O_4^+$ $([M+H^+])^+$: 353.1501 Found: 353.1499



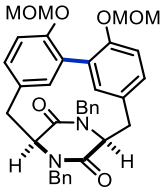
(4^2S,4^5S)-4^1,4^4-dibenzyl-1^6,2^6-bis(benzyloxy)-4(2,5)-piperazina-1,2(1,3)-dibenzenacyclopentaphane-4^3,4^6-dione (**11**). CCDC 1837911. White solid, 50 mg scale, in either inert (29% yield) or aerobic atmosphere (64% yield) for 15 h.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.22 (20H, m), 7.05 (2H, dd, *J* = 2.5, 8.0 Hz), 6.81 (2H, d, *J* = 8.0 Hz), 6.72 (2H, d, *J* = 2.5 Hz), 5.41 (2H, d, *J* = 15.0 Hz), 5.24 (2H, d, *J* = 12.0 Hz), 5.21 (2H, d, *J* = 12.0 Hz), 4.29 (2H, d, *J* = 6.0 Hz), 4.08 (2H, d, *J* = 16.0 Hz), 3.50 (2H, d, *J* = 15.0 Hz), 2.97 (2H, dd, *J* = 6.0, 16.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 155.0, 142.5, 137.5, 135.4, 130.3, 129.4, 129.2, 128.6, 128.5, 128.2, 127.9, 127.6, 126.1, 114.1, 59.2, 46.4, 33.3.

IR (cm^{-1}): 2934, 1643, 1507, 1416, 1244, 1146, 996, 731.

HRMS: Calculated for $C_{46}H_{41}N_2O_4^+$ $([M+H^+])^+$: 685.3066 Found: 685.3057



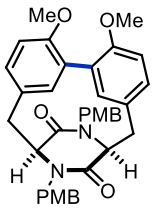
(4^2S,4^5S)-4^1,4^4-dibenzyl-1^6,2^6-bis(methoxymethoxy)-4(2,5)-piperazina-1,2(1,3)-dibenzenacyclop-entaphane-4^3,4^6-dione (**13**): White solid, 150 mg scale, in either inert (74% yield) or aerobic atmosphere (79% yield) for 15 h.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (6H, m), 7.22 (4H, d, *J* = 7.3 Hz), 7.05 (2H, dd, *J* = 7.3, 8.2 Hz), 6.98 (2H, d, *J* = 8.2 Hz), 6.70 (2H, s), 5.39 (2H, d, *J* = 15.0 Hz), 5.28 (2H, dd, *J* = 6.2, 19.3 Hz,), 4.29 (2H, d, *J* = 5.3 Hz), 4.07 (2H, d, *J* = 16.1 Hz), 3.51 (6H, s), 2.98 (2H, dd, *J* = 5.3, 15.5, Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 153.3, 142.2, 135.3, 130.8, 129.5, 129.2, 128.5, 128.2, 115.9, 95.4, 59.2, 56.4, 46.5, 33.3, 25.1.

IR (cm^{-1}): 2975, 1645, 1507, 1418, 1245, 1152, 1076, 992, 699.

HRMS: Calculated for $C_{36}H_{37}N_2O_6^+$ $([M+H^+])^+$: 593.2652 Found: 593.2643



(4^2S,4^5S)-4^1-benzyl-1^6,2^6-dimethoxy-44-(4-methoxybenzyl)-4(2,5)-piperazina-1,2(1,3)-dibenze-nacyclopentaphane-4^3,4^6-dione (**15**) : White solid, 150 mg scale, in either inert (62% yield) or aerobic atmosphere (61% yield) for 15 h.

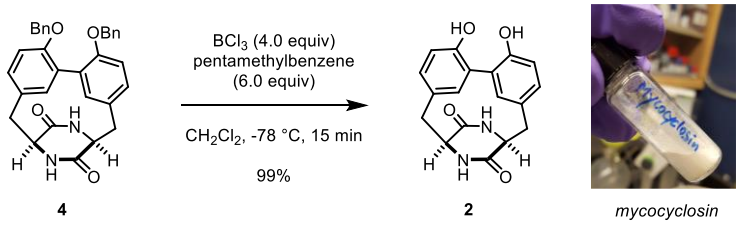
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (4H, d, *J* = 8.5 Hz), 7.07 (2H, dd, *J* = 2.5, 8.0 Hz), 6.85 (4H, d, *J* = 8.0 Hz), 6.77 (2H, d, *J* = 8.5 Hz), 6.64 (2H, d, *J* = 2.5 Hz), 5.32 (2H, d, *J* = 15.0 Hz), 4.22 (2H, d, *J* = 6.0 Hz), 4.07 (2H, d, *J* = 15.0 Hz), 3.93 (6H, s), 3.80 (6H, s), 3.43 (2H, d, *J* = 15.0 Hz), 2.97 (2H, dd, *J* = 6.0, 16.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 159.6, 155.8, 142.5, 129.9, 129.5, 127.4, 125.7, 114.5, 112.1, 59.0, 56.3, 55.5, 45.7, 33.3, 25.1.

IR (cm^{-1}): 2933, 1642, 1510, 1413, 1241, 1175, 1025, 809, 678.

HRMS: Calculated for $C_{36}H_{37}N_2O_6^+$ $([M+H^+])^+$: 593.265 Found: 593.2643.

D.1.5 Synthesis of mycocyclosin via BCl_3-mediated debenzylation



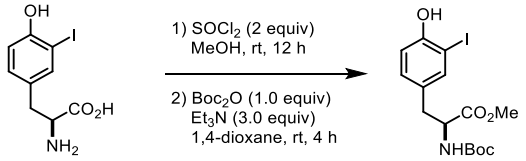
(4^2S,4^5S)-1^6,2^6-dihydroxy-4(2,5)-piperazina-1,2(1,3)-dibenzenacyclopentaphane-4^3,4^6-dione (**2**): To a 50 mL flame-dried round bottom schlenk flask was added stir bar, OBn-mycocyclosin derivative **4** (161 mg, 0.319 mmol), and pentamethylbenzene (284 mg, 1.92 mmol, 6.0 equiv) followed by CH_2Cl_2 (30 mL, 0.01M) *via* syringe under nitrogen atmosphere. The clean solution

was cooled down to -78 ºC in acetone-dry ice bath. BCl_3 (1.0 M in hexane) (1.28 mL, 1.28 mmol, 4.0 equiv) was added slowly via syringe over 20 min to give a yellow heterogenous reaction mixture, which was kept stirring at the same temperature for 15 min. TLC analysis showed full conversion and the BCl_3 was quenched with $CHCl_3$-MeOH (10:1) before being warmed up to room temperature. The crude mixture was transferred to another round bottom flask and concentrated to remove any low boiling point impurities. Diethyl ether (20 mL) was added to the flask and the suspension was sonicated for 1 min before being kept in fridge (4 ºC) for 12 h. The solid was then filtrated and washed with diethyl ether (3 × 5 mL). The cake was collected, dried under high vacuum to give the pure product as a white solid in 99% yield (104 mg, 0.319 mmol). Spectroscopic data matched reported literature data.[8]

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (2H, s), 7.99 (2H, s), 6.82 (2H, dd, *J* = 2.5, 8.0 Hz), 6.60 (2H, d, *J* = 8.0 Hz), 6.55 (2H, d, *J* = 2.5 Hz), 4.31 (2H, d, *J* = 5.5 Hz), 3.43 (2H, d, *J* = 15.5 Hz), 2.62 (2H, dd, *J* = 5.5, 15.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 154.2, 142.7, 131.1, 129.2, 126.5, 116.0, 56.9, 34.6

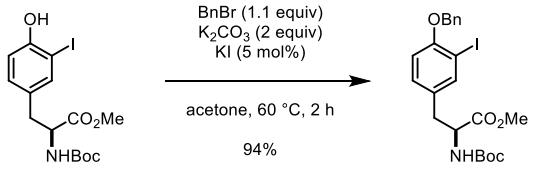
D.1.6 Synthesis of starting material



Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-3-iodophenyl)propanoate (**27a)**. To a flame dried 100 mL round bottom flask equipped with stir bar was added commercially available 3-iodo-**L**-Tyrosine (8.40 g, 27.4 mmol) and anhydrous methanol (54 mL, 0.5 M) at 0 ºC. To the suspension was added $SOCl_2$ (4.0 mL, 54.7 mmol, 2 equiv) dropwise and the reaction was stirred for overnight at room temperature. NMR analysis indicated full conversion of starting material.

The reaction mixture was concentrated to give a white solid, which was re-dissolved in dioxane-H_2O (4:1) (54 mL, 0.5 M). TEA (11.4 mL, 82.1 mmol, 3.0 equiv) and Boc_2O (6.3 mL, 27.4 mmol, 1.0 equiv) were added at room temperature and the mixture was stirred for 4 h. The reaction mixture was concentrated to remove dioxane and transferred to a separation funnel containing water and 15 mL 1N HCl. The mixture was extracted with EtOAc (100 mL × 3) and combined organic layers were washed with brine, dried over Na_2SO_4, concentrated to give the product **27a** in 87% yield (10.0 g, 23.7 mmol). NMR analysis indicated no further purification needed and the material was used directly for the next step. Spectroscopic data matched reported literature data.[17]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (1H, s), 7.01 (1H, dd, *J* = 2.0, 8.0 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 5.01 (1H, d, *J* = 8.0 Hz), 4.52 (1H, dd, *J* = 6.5, 14.0 Hz), 3.72 (3H, s), 3.04 (1H, dd, *J* = 6.0, 14.0 Hz), 2.94 (1H, dd, *J* = 6.0, 14.0 Hz), 1.43 (9H, s).

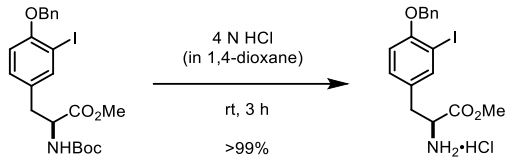


27a **28**

Methyl (*S*)-3-(4-(benzyloxy)-3-iodophenyl)-2-((*tert*-butoxycarbonyl)-amino)propanoate (**28**). To a 250 mL flame dried round bottom flask, at room temperature, **27a** (9.2 g, 21.8 mmol), acetone (44 mL, 0.5 M), and K_2CO_3 (6.04 g, 43.7 mmol, 2.0 equiv) were added to give a heterogenous reaction mixture, which was stirred for 15 min before BnBr (2.7 mL, 22.9 mmol, 1.1 equiv) was added. The reaction was heated at 60 ºC for 2 h. TLC analysis indicated full conversion. Evaporation to remove acetone and the crude product was diluted with water and extracted with EtOAc (100 mL × 3). The organic layer was washed with brine and dried over Na_2SO_4, concentrated to give the product **28** as a white solid in 94% yield (10.5 g, 25.6 mmol). NMR

analysis indicated no further purification needed and the material was used directly for the next step. Spectroscopic data matched reported literature data.[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (1H, s), 7.48 (2H, d, *J* = 7.5 Hz), 7.39 (2H, dd, *J* = 7.5, 7.5 Hz), 7.32 (1H, dd, *J* = 7.5, 7.5 Hz), 7.03 (1H, dd, *J* = 2.0, 8.5 Hz), 6.77 (1H, d, *J* = 8.5 Hz), 5.12 (2H, s), 4.98 (1H, d, *J* = 8.5 Hz), 4.52 (1H, dd, *J* = 7.0, 14.0 Hz), 3.72 (3H, s), 3.03 (1H, dd, *J* = 5.5, 14.0 Hz), 2.94 (1H, dd, *J* = 5.5, 14.0 Hz), 1.43 (9H, s).



28 **30**

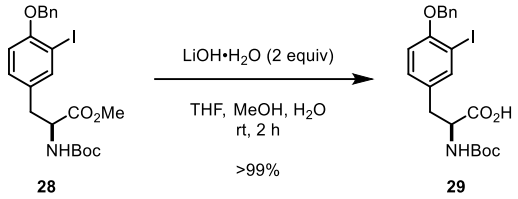
Methyl (*S*)-2-amino-3-(4-(benzyloxy)-3-iodophenyl)propanoate, HCl salt (**30**): To a 100 mL flame dried round bottom flask equipped with stir bar was added **28** (5.0 g, 9.78 mmol) under N_2 atmosphere at room temperature. Dioxane (10 mL, 1.0 M) was added followed by HCl (4 N in dioxane) (24.4 mL, 97.8 mmol , 10 equiv) to give a clean solution, which was stirred for 4 h to form a heterogenous mixture. TLC analysis indicated full conversion. The mixture was evaporated to give the desired salt **30** (4.38 g, 9.78 mmol, quant. yield) without further purification.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.49 (3H, s), 7.72 (1H, d, *J* = 2.0 Hz), 7.53 (2H, d, *J* = 7.0 Hz), 7.46 (2H, dd, *J* = 7.0, 7.5 Hz), 7.37 (1H, dd, *J* = 7.5, 7.5 Hz), 7.24 (1H, dd, *J* = 2.0, 8.0 Hz), 7.09 (1H, d, *J* = 8.0 Hz), 5.23 (2H, s), 4.33 (1H, dd, *J* = 6.5, 7.0 Hz), 3.74 (3H, s), 3.07 (2H, d, *J* = 6.5 Hz).

^{13}C NMR (125 MHz, DMSO-d_6): δ 170.7, 157.3, 141.0, 137.9, 132.0, 130.3, 129.7, 129.0, 128.4, 114.2, 88.3, 71.3, 54.4, 53.8, 35.6.

IR (cm^{-1}): 2820, 2626, 1738, 1599, 1492, 1446, 1312, 1248, 1078, 814, 737.

HRMS: Calculated for (free amine) $C_{17}H_{19}INO_3^+$ ($[M+H^+]$)$^+$: 412.0410 Found: 412.0403.



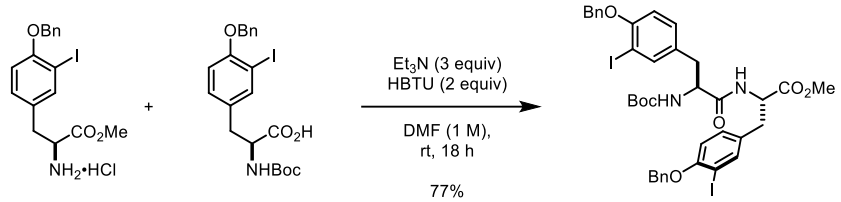
(*S*)-3-(4-(benzyloxy)-3-iodophenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid (**29**): To a 100 mL flame dried round bottom flask equipped with a stir bar was added **28** (5.5 g, 10.8 mmol) under an N_2 atmosphere at room temperature. Mixed reaction solvent (MeOH-THF-H_2O=1:1:1, 30 mL, 0.3 M) was added to the flask followed by LiOH monohydrate (9.03 g, 21.5 mmol, 2.0 equiv). The mixture was stirred for 2 h at room temperature. TLC analysis indicated full consumption of starting material. The reaction mixture was placed under reduced pressure to remove volatiles and the crude product was suspended in water and EtOAc. The organic layer was removed, and the aqueous layer was acidified to pH 2 with 1*N* HCl. The precipitated white solid was re-dissolved in EtOAc (200 mL), washed with brine and dried over Na_2SO_4, and concentrated to give product **29** (5.35 g, 10.8 mmol, quantitative yield) as a mixture of rotamers. The material was used directly in the next step without further purification.

Major isomer: **^{1}H NMR** (700 MHz, $CDCl_3$): δ 7.64 (1H, s), 7.48 (2H, d, *J* = 7.7 Hz), 7.38 (2H, dd, *J* = 7.0, 7.7 Hz), 7.31 (1H, dd, *J* = 7.0, 7.7 Hz), 7.10 (1H, d, *J* = 7.7 Hz), 6.78 (1H, d, *J* = 7.7 Hz), 5.10 (2H, s), 4.99 (1H, d, *J* = 8.4 Hz), 4.55 (1H, dd, *J* = 7.0, 14.0 Hz), 3.11 (1H, dd, *J* = 7.0, 14.0 Hz), 2.97 (1H, dd, *J* = 7.0, 14.0 Hz), 1.43 (9H, s).

Major isomer: **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.0, 156.4, 155.3, 140.3, 136.4, 130.4, 130.3, 128.5, 127.9, 127.0, 112.6, 86.8, 80.5, 70.9, 54.3, 36.4, 28.3.

IR (cm^{-1}): 2978, 1711, 1598, 1487, 1368, 1250, 1157, 1045, 732.

HRMS: Calculated for $C_{21}H_{24}INO_5^+$ ($[M^+]$)$^+$: 497.0699 Found: 497.0699.



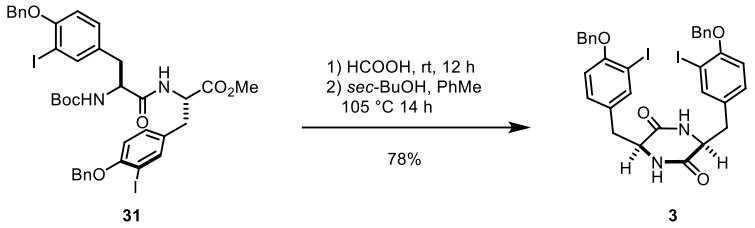
Synthesis of methyl (*S*)-3-(4-(benzyloxy)-3-iodophenyl)-2-((*S*)-3-(4-(benzyloxy)-3-iodophenyl)-2-((tert-butoxycarbonyl)amino)propanamido)propanoate (**31**): To a 100 mL flame dried round bottom flask equipped with stir bar was added **29** (4.38 g, 9.78 mmol) and **30** (5.35 g, 10.8 mmol, 1.1 equiv) obtained above. DMF (22 mL, 0.5 M) was added followed by HBTU (5.57 g, 14.7 mmol, 1.5 equiv) and TEA (8.2 mL, 58.7 mmol, 6.0 equiv). The mixture was stirred at room temperature for 18 h under N_2 atmosphere before transferred to a separation funnel containing water (500 mL) and 1N HCl (75 mL). The mixture was extracted with EtOAc (100 mL × 3). The organic layer was washed with water for 5 times and then brine, dried over Na_2SO_4, concentrated. The crude material was purification by flash chromatography (EtOAc:Hexane = 30:70) to give the product **31** in 79% yield (6.69 g, 7.51 mmol) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (1H, d, *J* = 2.5 Hz), 7.47-7.43 (4H, m), 7.39-7.35 (4H, m), 7.32-7.28 (2H, m), 7.12 (1H, d, *J* = 8.5 Hz), 6.89 (1H, d, *J* = 2.5, 8.5 Hz), 6.77 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 8.0 Hz), 6.36 (1H, d, *J* = 8.0 Hz), 5.10 (4H, d, *J* = 6.5 Hz), 4.94 (1H, br), 4.73 (1H, dd, H = 6.5, 12.5 Hz), 4.27 (1H, br), 3.69 (3H, s), 3.00-2.83 (4H, m), 1.41 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 170.7, 156.60, 156.57, 155.5, 140.41, 140.36, 136.62, 136.59, 131.1, 130.6, 130.4, 130.3, 128.7 (overlapped), 128.08, 128.07, 127.18, 127.15, 112.9, 112.7, 87.2, 86.9, 71.13, 71.07, 55.9, 53.5, 52.7, 37.0, 36.8, 29.9, 28.5.

IR (cm^{-1}): 3317, 2926, 1740, 1650, 1487, 1380, 1249, 1163, 1044, 1019, 732, 694.

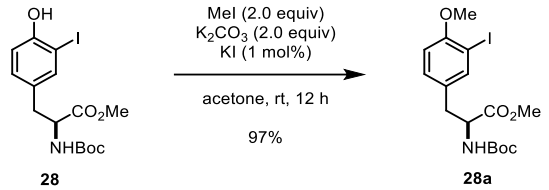
HRMS: Calculated for $C_{33}H_{33}I_2N_2O_5^+$ ([M-Boc+H$^+$])$^+$: 791.0479 Found: 791.0466



(3*S*,6*S*)-3,6-bis(4-(benzyloxy)-3-iodobenzyl)piperazine-2,5-dione (**3**): A flame dried 100 mL round bottom flask was equipped with stir bar and dipeptide (5.7 g, 6.4 mmol). Formic acid (60 mL) was added to the flask and the reaction mixture was stirred at room temperature for 12 h. TLC indicated fully consumption of the starting material to give the corresponding free amine. The solvent was then removed under reduced pressure. The residue formic acid was removed by azeotropic distillation with toluene. The obtained yellow solid was suspended in *sec*-butanol-toluene (4:1, 50 mL, 0.13M). The suspension was heated to 105 ºC to give a pale-yellow clean solution. After 14 h, a white solid precipitated and was collected by filtration. The cake was washed with EtOAc (2 × 10 mL) and dried under high vacuum to give the substrate **3** as a white solid in 78% yield (3.80 g, 5.21 mmol).

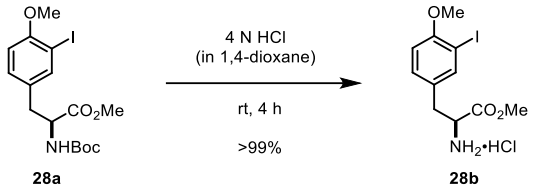
^{1}H NMR (500 MHz, DMSO-d_6): δ 8.08 (2H, d, J = 2.5 Hz), 7.51 (2H, d, J = 2.0 Hz), 7.47 (4H, d, J = 7.0 Hz), 7.37 (4H, dd, J = 7.0, 7.5 Hz), 7.32 (2H, dd, J = 7.0, 7.5 Hz), 7.04 (2H, dd, J = 2.0, 8.5 Hz), 7.01 (2H, d, J = 8.5 Hz), 5.19 (4H, s), 4.00 (2H, dd, J = 4.5, 7.0 Hz), 2.52 (2H, dd, J = 4.5, 14.0 Hz), 2.31 (2H, dd, J = 7.0, 14.0 Hz).

^{13}C NMR (125 MHz, DMSO-d_6): δ 167.4, 156.8, 141.3, 137.9, 132.3, 132.2, 129.6, 128.9, 128.3, 113.9, 87.9, 71.3, 56.6, 39.1



Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-iodo-4-methoxy-phenyl)propanoate (**28a**): To a 250 mL flame dried round bottom flask, was added **28** (10 g, 23.7 mmol), acetone (50 mL, 0.5 M), KI (39.4 mg, 1 mol%), and K_2CO_3 (6.56 g, 47.5 mmol, 2.0 equiv) which was allowed to stir at room temperature . This heterogenous reaction mixture was stirred for 15 min before MeI (3.0 mL, 47.5 mmol, 2.0 equiv) was added. The reaction was stirred at room temperature overnight. TLC analysis indicated full consumption of starting material. The reaction mixture was placed under vacuum to remove volatiles and the crude product was diluted with water and extracted with EtOAc (100 mL × 3). The organic layer was washed with brine and dried over Na_2SO_4, concentrated to give a crude residue which was purified by flash chromatography (EtOAc:Hexane = 30:70) to give product **28a** as white solid in 97% yield (10.0 g, 23.0 mmol). Spectroscopic data matched reported literature data.[19]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (1H, s), 7.07 (1H, dd, *J* = 2.5, 8.5 Hz), 6.74 (1H, d, *J* = 8.5 Hz), 4.98 (1H, d, *J* = 8.0 Hz), 4.52 (1H, ddd, *J* = 6.0, 8.0, 14.0 Hz), 3.85 (3H, s), 3.73 (3H, s), 3.05 (1H, dd, *J* = 6.0, 14.0 Hz), 2.94 (1H, dd, *J* = 6.0, 14.0 Hz), 1.43 (9H, s).



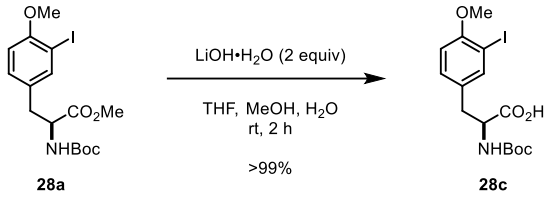
Methyl (*S*)-2-amino-3-(3-iodo-4-methoxyphenyl)propanoate, HCl salt (**28b**): To a 100 mL flame dried round bottom flask equipped with a stir bar was added **28a** (5.0 g, 11.5 mmol) under N_2 atmosphere at room temperature. Dioxane (10 mL) was added followed by HCl (4 M in dioxane) (11.5mL, 46 mmol, 10 equiv) to give a clear solution, which was stirred for 4 h to form a cloudy, heterogenous mixture. TLC analysis indicated full consumption of starting material. The mixture was evaporated under reduced pressure to give the desired salt **28b** (4.38 g, 9.78 mmol, quant. yield) without further purification.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.56 (3H, br), 7.69 (1H, d, J = 2.0 Hz), 7.26 (1H, dd, J = 2.0, 8.5 Hz), 7.01 (1H, d, J = 8.5 Hz), 4.31 (dd, J = 6.5, 6.5 Hz), 3.85 (3H, s), 3.74 (3H, s), 3.08 (2H, dd, J = 6.5, 15.0 Hz).

^{13}C NMR (125 MHz, DMSO-d_6): δ 170.5, 158.3, 141.0, 132.1, 130.0, 112.7, 87.5, 57.6, 54.4, 53.8, 35.5.

IR (cm^{-1}): 2819, 2631, 1744, 1598, 1493, 1237, 1063, 824.

HRMS: Calculated for (free amine) $C_{11}H_{15}INO_3^+$ ($[M+H^+]$)$^+$: 336.0097 Found: 336.0095.



28a 28c

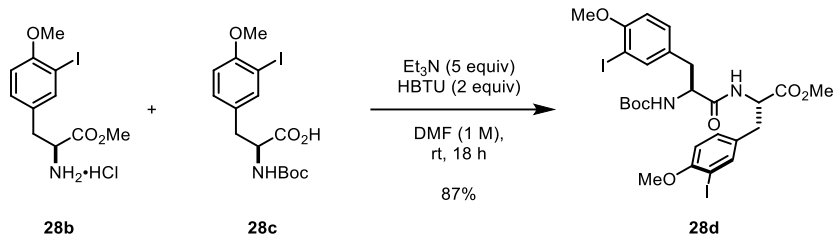
(*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-iodo-4-methoxyphenyl)-propanoic acid (**28c**): To a 100 mL flame dried round bottom flask equipped with stir bar was added **28a** (5.0 g, 11.5 mmol) under N_2 atmosphere at room temperature. Mixed solvent system (MeOH-THF-H_2O=1:1:1, 115 mL, 0.1 M) was added to the flask followed by LiOH monohydrate (964 mg, 23 mmol, 2.0 equiv). The mixture was stirred for 2 h at room temperature. TLC analysis indicated full conversion. Evaporation to remove solvents and the crude product was diluted with water and EtOAc. The organic layer was discarded, and the aqueous layer was acidified to pH 2 with 1N HCl. The precipitated white solid was re-dissolved in EtOAc (200 mL), washed with brine and dried over Na_2SO_4, concentrated to give product **28c** (4.8 g, 11.4 mmol, quantitative yield) as a mixture of rotamers (3:2 ratio). The material was used directly for the next step without further purification.

Major isomer: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.5 (1H, br), 7.57 (1H, s), 7.12 (1H, d, *J* = 8.5 Hz), 8.72 (1H, d, *J* = 8.5 Hz), 5.06 (1H, d, *J* = 8.0 Hz), 4.55 (1H, dd, *J* = 6.5, 14.0 Hz), 3.82 (3H, s), 3.14-3.07 (1H, m), 2.96 (1H, dd, *J* = 6.5, 14.0 Hz), 1.42 (9H, s).

Major isomer: **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.1, 157.4, 155.5, 140.5, 130.9, 130.6, 111.1, 86.1, 80.5, 56.5, 54.5, 36.6, 28.5.

IR (cm^{-1}): 2976, 2538, 1711, 1599, 1490, 1394, 1367, 1253, 1157, 1048, 811.

HRMS: Calculated for $C_{15}H_2INO_5^+$ $([M^+])^+$: 421.0386 Found: 421.0386



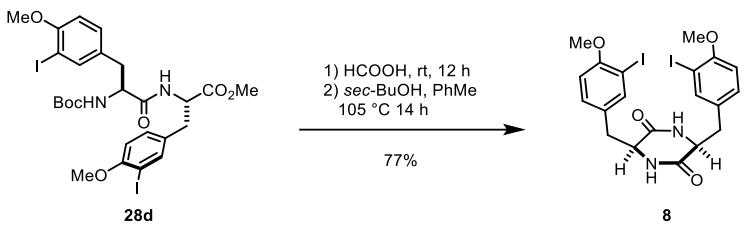
Methyl (*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-iodo-4-meth-oxyphenyl)propanamido)-3-(3-iodo-4-methoxyphenyl)propanoate (**28d**): To a 100 mL flame dried round bottom flask equipped with stir bar was added **28b** (4.05 g, 10.9 mmol) and **28c** (4.59 g, 10.9 mmol, 1.0 equiv) along with DMF (13 mL, 0.8 M) was added followed by HBTU (8.27 g, 21.8 mmol, 2.0 equiv) and TEA (7.6 mL, 54.5 mmol, 5.0 equiv). The mixture was stirred at room temperature for 18 h under N_2 atmosphere before transferring to a separation funnel containing water (500 mL) and 1*N* HCl (75 mL). The mixture was extracted with EtOAc (100 mL × 3). The organic layer was washed with water then brine, dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography (EtOAc:Hexane = 30:70) to give product **28d** in 87% yield (7.0 g, 9.48 mmol) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (1H, d, *J* = 2.0 Hz), 7.39 (1H, d, *J* = 2.0 Hz), 7.14 (1H, dd, *J* = 2.0 , 8.0 Hz), 6.91 (1H, d, *J* = 2.0, 8.0 Hz), 6.72 (1H, d, *J* = 8.5 Hz), 6.68 (1H, d, *J* = 8.5 Hz), 6.33 (1H, d, *J* = 7.5 Hz), 4.94 (1H, s), 4.73 (1H, dd, *J* = 6.5, 13.0 Hz), 4.28 (1H, s), 3.84 (6H, s), 3.70 (3H, s), 3.03-2.91 (4H, m), 1.41 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 170.8, 157.48, 157.45, 155.5, 140.4, 140.3, 130.8, 130.6, 130.5, 130.0, 111.2, 111.0, 86.4, 86.1, 80.7, 56.6, 56.5, 56.0, 53.5, 52.7, 37.1, 36.8, 28.5.

IR (cm^{-1}):3294, 2937, 1740, 1652, 1599, 1489, 1251, 1048, 1018, 810.

HRMS: Calculated for $C_{21}H_{25}I_2N_2O_5^+$ ($[M\text{-}Boc+H^+]$)$^+$: 638.9853 Found: 638.9834



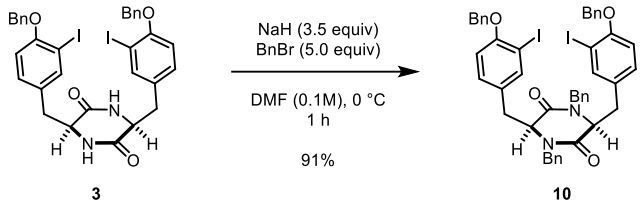
(3*S*,6*S*)-3,6-bis(3-iodo-4-methoxybenzyl)piperazine-2,5-dione (**8**): A flame dried 100 mL round bottom flask was equipped with stir bar and dipeptide (7.0 g, 9.48 mmol). Formic acid (30 mL) was added to the flask and the reaction mixture was stirred at room temperature for 12 h. TLC indicated fully consumption of the starting material to give the corresponding free amine. The solvent was then removed under reduced pressure. The residue formic acid was removed by azeotropic distillation with toluene. The obtained yellow solid was suspended in *sec*-butanol-toluene (4:1, 15 mL, 0.6 M). The suspension was heated to 105 ºC to give a pale-yellow clean solution. After 14 h, a white solid precipitated and was collected by filtration. The cake was washed with EtOAc (2 × 10 mL) and dried under high vacuum to give substrate **8** as a white solid in 77% yield (4.4 g, 7.26 mmol).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.09 (2H, d, J = 2.5 Hz), 7.47 (2H, d, J = 2.5 Hz), 7.04 (2H, dd, J = 2.0, 8.5 Hz), 6.90 (2H, d, J = 8.5 Hz), 4.01 (2H, dd, J = 5.5, 7.0 Hz), 3.82 (6H, s), 2.56 (2H, dd, J = 7.0, 14.0 Hz), 2.36 (2H, dd, J = 5.5, 14.0 Hz).

^{13}C NMR (125 MHz, DMSO-d_6): δ 167.4, 157.7, 141.2, 132.3, 131.9, 112.3, 87.0, 57.5, 56.5, 38.8.

IR (cm^{-1}): 3459, 2933, 1642, 1509, 1417, 1318, 1262, 1244, 1145, 1023, 808, 700.

HRMS: Calculated for $C_{20}H_{21}I_2N_2O_4^+$ ([M+H$^+$])$^+$: 606.9591 Found: 606.9572



3 10

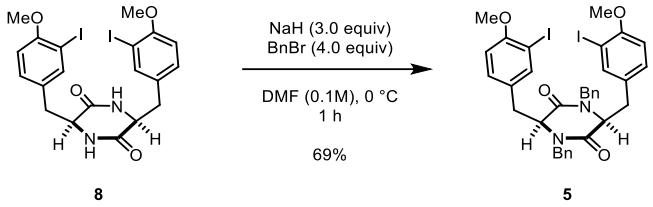
(3*S*,6*S*)-1,4-dibenzyl-3,6-bis(4-(benzyloxy)-3-iodobenzyl)piperazine-2,5-dione (**10**): To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added diketopiperazine **3** (1.0 g, 1.32 mmol) along with DMF (13 mL) and a nitrogen inlet. The solution was cooled to 0 ºC with an ice-bath and then NaH (60% dispersion in mineral oil, 185 mg, 4.62 mmol, 3.5 equiv) was added portion wise. After stirring at 0 ºC for 15 minutes, benzyl bromide (0.78 mL, 6.59 mmol, 5.0 equiv) was added to the reaction mixture slowly *via* syringe. The reaction was stirred at 0 C for 1 hour, TLC analysis indicated complete consumption of starting material. Then, the rest of NaH was quenched with deionized water. After pouring into a separatory funnel, the mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water twice and brine, dried over Na_2SO_4 and concentrated in *vacuo* to give the crude material, which was purified by flash column chromatography over silica with EtOAc in Hexanes (10% to 25%). The title compound **10** was obtained in 91% (1.12 g, 1.20 mmol) as a white solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 2.1 Hz), 7.43 (4H, d, *J* = 7.7 Hz), 7.32-7.7.27 (12H, m), 6.97 (4H, 3.5, 14.7 Hz), 6.95 (2H, dd, J = 2.1, 8.4 Hz), 6.81 (2H, d, *J* = 8.4 Hz), 5.31 (2H, d, *J* = 14.7 Hz), 5.17 (2H, d, *J* = 12.6 Hz), 5.13 (2H, d, *J* = 12.6 Hz), 4.07 (2H, dd, *J* = 4.9, 6.3 Hz), 3.56 (2H, d, *J* = 14.7 Hz), 2.72 (2H, dd, *J* = 4.9, 14.0 Hz), 2.31 (2H, dd, *J* = 6.3, 14.0 Hz).

^{13}C NMR (175 MHz, $CDCl_3$) δ 166.0, 156.8, 140.6, 136.4, 135.4, 131.5, 130.9, 129.2, 128.8, 128.4, 128.3, 128.2, 127.2, 113.1, 87.5, 71.1, 60.7, 47.7, 37.7.

IR (cm^{-1}): 3030, 2934, 1643, 1604, 1507, 1416, 1244, 1060, 996, 731, 696.

HRMS: Calculated for $C_{46}H_{41}I_2N_2O_4^+$ ($[M+H^+]$)$^+$: 939.1156 Found: 939.1142



8 **5**

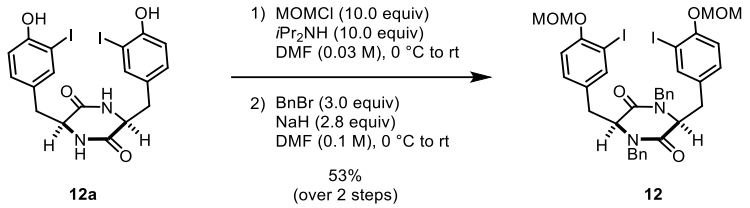
(3*S*,6*S*)-1,4-dibenzyl-3,6-bis(3-iodo-4-methoxybenzyl)piperazine-2,5-dione (**5**): To a flame dried 250 mL round bottom flask equipped with a magnetic stir bar was added diketopiperazine **8** (4.5 g, 7.42 mmol) along with DMF (60 mL) and a nitrogen inlet. The solution was cooled to 0 ºC with an ice-bath and then NaH (60% dispersion in mineral oil, 853 mg, 22.3 mmol) was added in one portion. Following stirring at 0 ºC for 30 minutes, benzyl bromide (3.53 mL, 29.7 mmol) was added to the reaction mixture over two minutes *via* syringe. After slowly warming to room temperature over 1 hour, TLC analysis indicated complete consumption of starting material. Then, the solution was re-cooled with an ice-bath and deionized water (30 mL) was added subsequently . After pouring into a separatory funnel, the mixture was extracted with EtOAc (3 × 40 mL). The combined organics were washed with water (40 mL), brine (40 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified *via* flash column chromatography over silica with EtOAc in Hexanes (10% to 25%) affording the title compound **5** in 69% (4.0 g, 5.09 mmol) as a free-flowing white powder.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (2H, s), 7.33–7.22 (6H m,), 7.02–7.00 (6H, m), 6.79 (2H, d, *J* = 8.5 Hz), 5.30 (2H, d, *J* = 14.5 Hz), 4.09 (2H, dd, *J* = 6.3, 6.5 Hz), 3.81 (6H, s), 3.59 (2H, d, *J* = 14.5 Hz), 2.76 (2H, dd, *J* = 6.3, 14.5 Hz), 2.37 (2H, dd, *J* = 6.5, 14.5 Hz).

^{13}C NMR (175 MHz, $CDCl_3$) δ 166.0, 157.8, 140.5, 135.4, 131.1, 131.0, 129.1, 128.4, 128.3, 111.2, 86.6, 60.7, 56.7, 47.7, 37.7.

IR (cm^{-1}): 2936, 2836, 1651, 1597, 1489, 1449, 1251, 1047, 807, 724.

HRMS: Calculated for $C_{34}H_{33}I_2N_2O_3^+$ ($[M+H^+]$)$^+$: 787.0530 Found: 787.0525.



(3*S*,6*S*)-1,4-dibenzyl-3,6-bis(3-iodo-4-(methoxymethoxy)benzyl)piperazine-2,5-dione (12): To a flame-dried 100 mL round bottom flask equipped with a magnetic stir bar was added diketopiperazine **12a**[i] (500 mg, 0.87 mmol) and DMF (30 mL). The pale yellow solution was subsequently cooled to 0 ºC with an ice bath. At this time, *i*Pr$_2$NH (1.22 mL, 8.65 mmol, 10.0 equiv) was added *via* syringe to the reaction solution, followed by dropwise addition of MOMCl (0.66 mL, 8.65 mmol, 10.0 equiv). This resulted in a dark orange/red color which persisted through the duration of the reaction. The resultant mixture was left to warm slowly to room temperature overnight followed by the addition of deionized water (20 mL) at 0 ºC. After pouring the reaction mixture into a saperatory funnel, the solution was extracted with EtOAc (3 × 20 mL). The combined organics were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude MOM protected diketopiperazine was used in the next step without further purification.

To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added the crude MOM protected diketopiperazine along with DMF (30 mL) and a nitrogen inlet. The solution was cooled to 0 ºC with an ice-bath and then NaH (60% dispersion in mineral oil, 92 mg, 2.42 mmol, 2.8 equiv) was added in one portion. Following stirring at 0 ºC for 30 minutes, benzyl bromide (0.32 mL, 2.59 mmol, 3.0 equiv) was added to the reaction mixture over two minutes *via* syringe. After slowly warming to room temperature over 1 hour, TLC analysis indicated complete consumption of starting material. Then, the solution was re-cooled with an ice-bath and the rest of

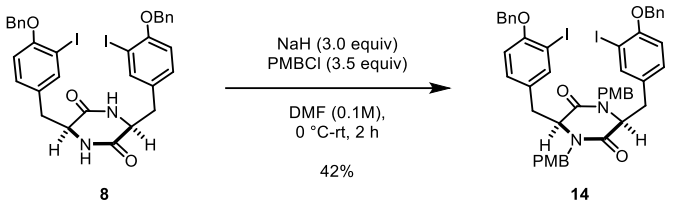
NaH was subsequently quenched by the addition of deionized water (30 mL). After pouring into a separatory funnel, the mixture was extracted with EtOAc (3 × 40 mL). The combined organics were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified *via* flash column chromatography over silica with EtOAc in Hexanes (10% to 30%) affording the title compound **12** in 53% (over two steps, 390 mg, 0.46 mmol) as a free flowing white powder.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (2H d, *J* = 2.0 Hz), 7.35–7.29 (6H, m), 7.06-7.02 (6H, m), 6.99 (2H, dd, J = 2.0, 8.5 Hz), 5.35 (2H, d, *J* = 14.5 Hz), 5.23 (4H, s), 4.11 (2H, dd, J = 4.5, 6.0 Hz), 3.68 (2H, d, *J* = 14.0 Hz), 3.44 (6H, s), 2.74 (2H, dd, *J* = 4.5, 14.5 Hz), 2.37 (2H, dd, *J* = 6.0, 14.5 Hz,).

^{13}C NMR (175 MHz, $CDCl_3$) δ 166.1, 155.8, 140.6, 135.6, 132.5, 131.1, 129.3, 128.6, 128.5, 115.3, 95.3, 87.9, 60.8, 56.8, 47.8, 37.8.

IR (cm^{-1}): 2929, 1652, 1597, 1486, 1450, 1239, 1151, 1080, 980, 725, 696.

HRMS: Calculated for $C_{36}H_{37}I_2N_2O_6^+$ $([M+H^+])^+$: 847.0741 Found: 847.0725



(3*S*,6*S*)-3,6-bis(3-iodo-4-methoxybenzyl)-1,4-bis(4-methoxybenzyl)-piperazine-2,5-dione (**14**): To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added diketopiperazine **8** (1.0 g, 1.65 mmol) along with DMF (15 mL) and a nitrogen inlet. The solution was cooled to 0 ºC with an ice-bath and then NaH (60% dispersion in mineral oil, 190 mg, 4.95 mmol, 3.0 equiv) was added in one portion. Following stirring at 0 ºC for 30 minutes, PMBCl (0.78 mL, 5.77 mmol, 3.5 equiv) was added to the reaction mixture over two minutes *via* syringe. After slowly warming to room temperature over 2 hours, TLC analysis indicated complete consumption of starting material. Then, the solution was re-cooled with an ice-bath and subsequently the rest of NaH was quenched by the addition of deionized water (15 mL). After pouring into a separatory funnel, the mixture was extracted with EtOAc (3 × 20 mL). The combined organics were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified *via* flash column chromatography over silica with EtOAc in Hexanes (20% to 50%) affording the title compound **14** in 42% (590 mg, 0.70 mmol) as a free-flowing white powder.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 2.0 Hz), 7.00 (2H, dd, *J* = 2.1, 8.4 Hz), 6.95 (4H, d, *J* = 8.4 Hz), 6.83 (4H, d, *J* = 8.4 Hz), 6.79 (2H, d, *J* = 8.4 Hz), 5.22 (2H, d, *J* = 14.7 Hz), 4.06 (2H, dd, *J* = 4.8, 6.0 Hz), 3.86 (6H, s), 3.80 (6H, s), 3.58 (2H, d, *J* = 14.7 Hz), 2.72 (2H, dd, *J* = 4.8, 14.3 Hz), 2.36 (2H, dd, *J* = 6.0, 14.3 Hz).

^{13}C NMR (175 MHz, $CDCl_3$) δ 165.9, 159.6, 157.7, 140.5, 131.2, 131.0, 129.9, 127.5, 114.5, 111.2, 86.6, 60.5, 56.7, 55.5, 47.2, 37.7.

IR (cm^{-1}): 2933, 2834, 1651, 1610, 1511, 1490, 1438, 1245, 1175, 1047, 1018, 804.

HRMS: Calculated for $C_{36}H_{37}I_2N_2O_6^+$ $([M+H^+])^+$: 847.0741 Found: 847.0733

D.1.7 References

(1) Martens, G.; Wilkinson, R. J. *Lancet* **2007**, *370*, 2030.

(2) Zhang, Y. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 529.

(3) a) Cole, S. T.; Brosch, R.; Parkhill, J.; Garnier, T.; Churcher, C.; Harris, D.; Gordon, S. V.; Eiglmeier, K.; Gas, S.; Barry, C. E. III; Tekaia, F.; Badcock, K.; Basham, D.; Brown, D.; Chillingworth, T.; Connor, R.; Davies, R.; Devlin, K.; Feltwell, T.; Gentles, S.; Hamlin, N.; Holroyd, S.; Hornsby, T.; Jagels, K.; Krogh, A.; McLean, J.; Moule, S.; Murphy, L.; Oliver, K.; Osborne, J.; Quail, M.A.; Rajandream, M.-A.; Rogers, J.; Rutter, S.; Seeger, K.; Skelton, J.; Squares, R.; Squares, S.; Sulston, J. E.; Taylor, K.; Whitehead, S.; Barrell, B. G. *Nature*, **1998**, *393*, 537. b) McLean, K. J.; Clift, D.; Lewis, D. G.; Sabri, M.; Balding, P. R.; Sutcliffe, M. J.; Leys, D.; Munro, A. W. *Trends. Microbiol.* **2006**, *14*, 220. c) McLean, K. J.; Belcher, J.; Driscoll, M. D.; Fernandez, C. C.; Le Van, D.; Bui, S.; Golovanova, M.; Munro, A. W. *Future Med. Chem.* **2010**, *2*, 1339.

(4) a) McLean, K. J.; Carroll, P.; Lewis, D. G.; Dunford, A. J.; Seward, H. E.; Neeli, R.; Cheesman, M. R.; Marsollier, L.; Douglas, P.; Smith, W. E.; Rosenkrands, I.; Cole, S. T.; Leys, D.; Parish, T.; Munro, A. W. *J. Biol. Chem.* **2008**, *283*, 33406. b) Ahmad, Z.; Sharma, S.; Khuller, G. K. *FEMS Microbiol. Lett.* **2006**, *261*, 181. c) Ahmad, Z.; Sharma, S.; Khuller, G. K. *FEMS Microbiol. Lett.* **2006**, *258*, 200. d) Burguiere, A.; Hitchen, P. G.; Dover, L. G.; Dell, A.; Besra, G. S. *Microbiology*, **2005**, *151*, 2087. e) McLean, K. J.; Marshall, K. R.; Richmond, A.; Hunter, I. S.; Fowler, K.; Kieser, T.; Gurcha, S. S.; Besra, G. S.; Munro, A. W. *Microbiology*, **2002**, *148*, 2937.

(5) a) Dumas, V. G.; Defelipe, L. A.; Petruk, A. A.; Turjanski, A. G.; Marti, M. A. *Proteins* **2014**, *82*, 1004. b) Belin, P.; Le Du, M. H.; Fielding, A.; Lequin, O.; Jacquet, M.; Charbonnier, J.-B.; Lecoq, A.; Thai, R.; Courc-on, M.; Masson, C.; Dugave, C.; Genet, R.; Pernodet, J.-L.; Gondry, M. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 7426.

(6) Fonvielle, M.; Le Du M. H.; Lequin, O.; Lecoq, A.; Jacquet, M.; Thai, R.; Dubois, S.; Grach, G.; Gondry, M.; Belin, P. *J. Biol. Chem.* **2013**, *288*, 17347.

(7) Schuuster, I.; Bernhardt, R. *Drug. Met. Rev.* **2007**, *39*, 481.

(8) Cochrane, J. R.; White, J. M.; Willie, U.; Hutton, C. A. *Org. Lett.* **2012**, *14*, 2402.

(9) a) Thomas, A. A.; Denmark, S. E. *Science* **2016**, *352*, 329. b) Thomas, A. A.; Wang, H.; Zahrt, A. F.; Denmark, S. E. *J. Amer. Chem. Soc.* **2017**, *139*, 3805.

(10) Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477.

(11) a) Evans, P. J.; Darzi, E. R.; Jasti, R. *Nat. Chem*. **2014**, *6*, 404. b) Darzi, E. R.; White, B. M.; Loventhal, L. K.; Zakharov, L. N.; Jasti, R. *J. Amer. Chem. Soc*. **2017**, *139*, 3106. For further discussion on oxidative homocoupling of aryl boronic acids and esters, see: c) Dhital R. N.; Sakurai, H. *Asian J. Org. Chem.* **2014**, *3*, 668. d) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett*. **2003**, *44*, 1541. e) Parnish, J. P.; Jung, Y. C.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett*. **2002**, *43*, 7899.

(12) Under both sets of reaction conditions, there was complete conversion of starting material with no isolable side-products.

(13) a) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362. b) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. - Eur. J.* **2012**, *18*, 6616. c) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. d) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. - Eur. J.* **2011**, *17*, 2492. e) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

(14) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(15) a) Liu, Q.; Li, G.; He, J.; Liu, J.; Li, P.; Lei, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 3371. b) Lakmini, H.; Ciofini, I.; Jutand, A.; Amatore, C.; Adamo, C. *J. Phys. Chem. A* **2008**, 112, 12896. c) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829. d) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.

(16) Okano, K.; Okuyama, K.-i.; Fukuyama, T.; Tokuyama, H. *Synlett*, **2008**, 1977.

(17) Walker, W. H. IV; Rokita, S. E. *J. Org. Chem.* **2003**, *68*, 1563.

(18) Liu, J.; Luo, C.; Smith, P. A.; Chin, J. K.; Page, M. G. P.; Paetzel, M.; Romesberg, F. E. *J. Am. Chem. Soc*. **2011**, *133*, 17869.

(19) Dufour, J.; Neuville, L.; Zhu, J. *Chem. Eur. J.* **2010**, *16*, 10523

APPENDIX E

E.1. Experimental procedures, operations, and references for Chapter 5

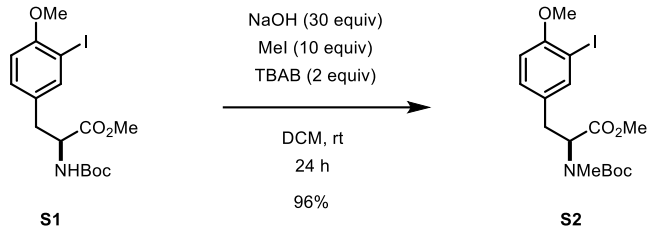
E.1.1 General information

All moisture-sensitive reactions were performed under a nitrogen atmosphere in flame-dried glassware fitted with rubber septa. Stainless steel syringes were used to transfer air or moisture-sensitive liquids. Flash chromatography was performed using silica gel SiliaFlash®40-63 micron (230-400 mesh) from Silicycle.

All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Frontier Scientific, Matrix Scientific, Ark Pharm, and Chem Impex International, and were used as received unless otherwise stated. $B_2(pin)_2$ and DMSO (99.7%) purchased from Acros Organics showed better reactivity for the biaryl coupling reaction. Proton Nuclear Magnetic Resonance NMR (1H NMR) spectra and carbon nuclear magnetic resonance (13C NMR) spectra were recorded on a Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for protons are reported in parts per million and are references to the NMR solvent peak ($CDCl_3$: δ = 7.26; DMSO-*d*6: δ = 2.54). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ = 77.23; DMSO-*d*6: δ = 40.76). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, m = multiplet), and coupling

constants in Hertz (Hz). Mass spectroscopic (MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer. Infrared (IR) spectra were obtained using either an Avatar 360 FT-IR or Perkin Elmer Spectrum BX FT-IR spectrometer. IR data are represented as frequency of absorption (cm^{-1}). Optical rotation data were obtained using a JASCO P-2000 Polarimeter and are reported as (c = grams/100mL), where D indicates the sodium D line (589 nm) and T indicates temperature (all optical rotation values were obtained at ambient operating temperature, ca. 22-28 °C).

E.1.2 Synthetic procedures



Compound S2

To a stirred solution of **S1**[1] (20.3 g, 46.6 mmol) and DCM (325 mL) in a 500 mL round-bottom flask was added NaOH (56.0 g, 1.40 mol), TBAB (30.1 g, 93.3 mmol), and MeI (29.0 mL, 46.6 mmol). This suspension was left to stir for 24 h at room temperature. At this time, the resulting mixture was poured into an extraction funnel along with saturated $NH_4Cl_{(aq)}$. The organic layer was separated and the aqueous layer was further extracted with DCM (2 × 200 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a thick oil **S2**, which was purified via flash column chromatography (over silica) with an eluent system of 5% to 25% EtOAc in hexanes to afford the title compound as a colorless, clear viscous oil (20.1 g, 44.7 mmol, 96%).

R_f = 0.50 (30% EtOAc in hexanes; UV)

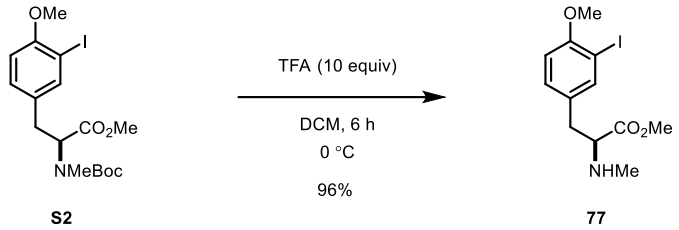
^{1}H NMR (major rotamer, 500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.05 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H,), 4.51 (m, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.18 (m, 1H), 2.93 (m, 1H), 2.72 (s, 3H), 1.40 (s, 9H);

^{13}C NMR (major rotamer,125 MHz, $CDCl_3$) δ 172.3, 171.8, 157.3, 140.5, 140.0, 130.5, 130.2, 111.1, 61.6, 56.6, 52.5, 52.4, 37.2, 33.9, 28.5;

IR (cm^{-1}): 2974, 1742, 1692, 1492, 1438, 1147, 1050, 810;

HRMS: calculated for $C_{12}H_{17}IN_2O_3$ $[M\text{-}Boc+H]^+$ 350.0253; found 350.0246.

$[\alpha]_D^{24.5\ °C}$ = – 37.2° (c= 2.6, CH_2Cl_2)



S2 **77**

Compound 77

A flame-dried, 500 mL round-bottom flask was charged with **S2** (12.5 g, 27.8 mmol) and a stir bar. Then, DCM (75 mL) was added. The resulting solution was cooled to 0 °C with an ice bath followed by the slow addition of TFA (20.7 mL, 278 mmol) to the reaction flask. After stirring for 6 h, there was complete consumption of starting material by TLC. The reaction solution was poured into an extraction funnel along with saturated $NaHCO_{3(aq)}$. The organic layer was removed, washed with brine and concentrated under reduced pressure to afford **77**. The material was pure by NMR analysis and used in the next step without further purification.

$\mathbf{R_f}$ = 0.2 (10% MeOH in DCM; UV);

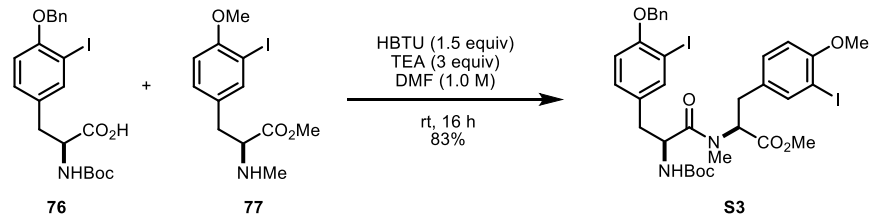
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.8 Hz, 1H), 7.11 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.38 (dd, *J* = 7.0, 7.0 Hz, 1H), 2.85 (m, 2H), 2.36 (s, 3H);

^{13}C NMR (175 MHz, $CDCl_3$) δ 174.8, 157.2, 140.1, 131.5, 130.4, 110.9, 86.1, 64.8, 56.5, 51.9, 38.2, 34.9;

IR (cm^{-1}): 2946, 2797, 1730, 1490, 1437, 1349, 1252, 1113, 1016, 732;

HRMS: calculated for $C_{12}H_{17}IN_2O_3$ $[M+H]^+$ 350.0253; found 350.0244.

$[\alpha]_D^{24.3\,^\circ C}$= +22..0° (c= 3.0, CH_2Cl_2)



Compound S3

To an oven-dried, 500 mL round-bottom flask equipped with a magnetic stir bar was added **76** (94.4 mmol, 1.3 equiv), **77** (72.6 mmol, 1.0 equiv), HBTU (109 mmol, 1.5 equiv) and DMF (75 mL) under an atmosphere of nitrogen. This solution was cooled to 0 °C with an ice bath. Next, TEA (218 mmol, 30 mL, 3 equiv) was slowly added to the reaction mixture *via* syringe down the neck of the flask. The reaction mixture immediately turned deep-red and became homogeneous. This mixture was left to warm to room temperature over the course of 16 h. After this time, the reaction was poured into an extraction funnel and partitioned between 1 M HCl (~150 mL) and EtOAc (~200 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 × 200 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a thick oil. Peptide **S3** was purified via flash column chromotagraphy (over silica) with an eluent system of 50% to 60% EtOAc in hexanes to afford the title compound as a colorless foam (mixture of rotamers, 49.7 g, 60.0 mmol, 83%).

$\mathbf{R_f}$ = 0.70 (70% EtOAc in hexanes; UV);

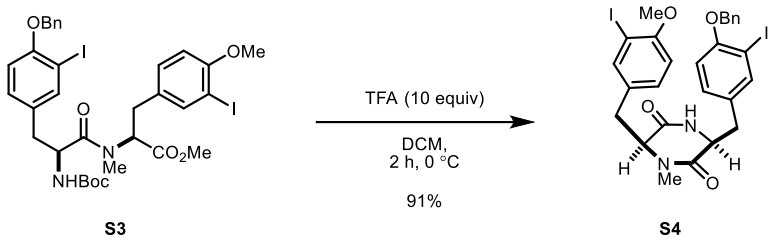
^{1}H NMR (major rotamer, 700 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.58 (s, 1H), 7.47 (m, 2H), 7.37 (m, 2H), 7.31 (dd, *J* = 7.7, 9.1 Hz, 1H), 7.10 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.75 (m, 1H), 6.67 (m, 1H), 5.11 (m, 2H), 5.1 (m, 1H), 4.70 (m, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.23 (ddd, *J* = 5.6, 14.7, 18.2 Hz, 1H), 2.95 (m, 1H), 2.87 (m, 1H), 2.80 (s, 3H), 2.76 (m, 1H), 1.39 (s, 9H);

^{13}C NMR (major rotamer, 175 MHz, $CDCl_3$) δ171.7, 170.6, 157.0, 156.1, 154.9, 140.4, 140.3, 139.7, 136.5, 130.9, 130.8, 130.6, 130.3, 130.0, 129.9, 128.5, 127.9, 127.0, 126.9, 112.4, 110.7, 86.6, 85.8, 79.8, 70.9, 59.1, 56.3, 52.5, 51.5, 37.5, 33.2, 28.3;

IR (cm^{-1}): 3312, 2974, 1740, 1705, 1644, 1489, 1366, 1279, 1252, 1165, 1047;

HRMS: calculated for $C_{28}H_{31}I_2N_2O_5$ $[M\text{-}Boc+H]^+$ 729.0322; found 729.0310.

$[\alpha]_D^{23.8\,^\circ C}$ = – 17.2° (c= 1.2, CH_2Cl_2)



S3 **S4**

Compound S4

To a flame-dried, 100 mL round-bottom flask equipped with a magnetic stir bar was added peptide **16** (2.0 g, 2.41 mmol) followed by DCM (5 mL). The flask was equipped with a septum, nitrogen inlet and subsequently cooled to 0 °C with an ice-bath. Next, TFA (24.1 mmol, 10 equiv, 1.79 mL) was slowly added to the reaction mixture. The reaction temperature was maintained at 0 °C over the course of 2 h with vigorous stirring. At this time, TLC analysis indicated full consumption of starting material. The residual TFA in the reaction was quenched with the careful addition of saturated $NaHCO_{3\ (aq.)}$ which was added to the reaction mixture until the formation of bubbles ceased. The solution was then left to stir for 15 minutes. Alter this period of time, the mixture was poured into an extraction funnel along with DCM (25 mL) and H_2O (15 mL). The organic layer was separated and the aqueous layer was further extracted with DCM (2 × 20 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a white solid. The crude mixture was purified via flash column chromatography (over silica) with an eluent system of 50% to 100% EtOAc in hexanes to afford the title compound as an off-white solid (1.53 g, 2.2 mmol, 91%).

$\mathbf{R_f}$ = 0.5 (65% EtOAc in hexanes; CAM stain and UV);

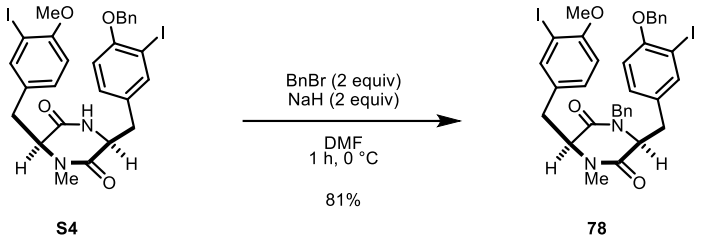
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.43 (m, 3H), 7.35 (m, 2H), 7.30 (m, 1H), 7.05 (m, 1H), 6.90 – 6.79 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.07 (s, 1H), 5.28 (s, 1H), 5.05 (s, 2H), 4.10 (s, 1H), 3.84 (m, 4H), 3.02 (br, 5H), 2.88 (d, *J* = 13.3 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.3, 158.0, 156.7, 141.1, 140.2, 136.5, 131.6, 130.8, 130.6, 129.4, 128.8, 128.2, 127.2, 113.1, 111.3, 87.7, 86.8, 71.2, 63.3, 56.9, 56.8, 40.0, 35.7, 33.5;

IR (cm^{-1}): 3052, 1681, 1653, 1488, 1454, 1278, 1253, 1046, 1017, 730, 700;

HRMS: calculated for $C_{27}H_{27}I_2N_2O_4$ $[M+H]^+$ 697.0060; found 697.0053.

$[\alpha]_D^{23.9°C}$ = – 69.2° (c= 1.0, CH_2Cl_2)



S4 **78**

Compound 78

Cyclodipeptide **S4** (1.8 g, 2.59 mmol) was added to a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar. After the addition of DMF (20 mL), the flask was capped with a rubber septum and a nitrogen inlet. Upon cooling the reaction flask down to 0 °C with an ice bath, NaH (198 mg, 5.17 mmol) was added in one portion. After the resultant mixture was left to stir for 10 minutes, benzyl bromide (0.62 mL, 5.17 mmol) was added to the reaction via syringe. TLC analysis of the reaction indicated full consumption of starting material after 1 h of stirring at 0 °C. At this time, the reaction was quenched with the slow addition of water (~10 mL) and poured into an extraction funnel which contained EtOAc (25 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 × 25 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a colorless oil. The crude mixture was purified via flash column chromatography (over silica) with an eluent system of 30% to 80% EtOAc in hexanes to afford the title compound as a free-flowing, white solid (1.7 g, 2.10 mmol, 81%).

R_f = 0.14 (70% EtOAc in hexanes; CAM stain and UV);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.1 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 6.8 Hz, 2H), 7.29 (m, 6H), 7.08 – 7.03 (m, 3H), 6.94 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.79 (dd, *J* = 9.9, 8.5 Hz, 2H), 5.38 (d, *J* = 14.7 Hz, 1H), 5.18 – 5.10 (m, 2H), 4.07 (dd, *J* = 6.1, 4.7 Hz, 1H), 4.03 –

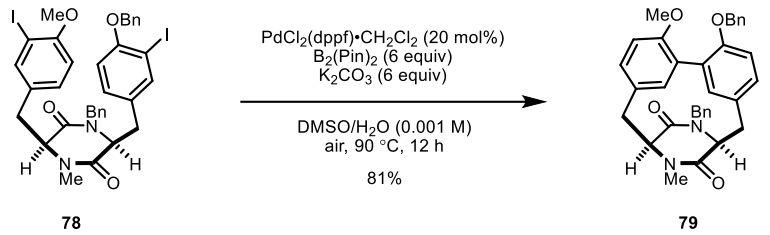
4.00 (m, 1H), 3.85 (s, 3H), 3.64 (d, *J* = 14.7 Hz, 1H), 2.80 – 2.74 (m, 4H), 2.65 (dd, *J* = 14.3, 4.5 Hz, 1H), 2.34 (dd, *J* = 14.4, 5.8 Hz, 1H), 2.19 (dd, *J* = 14.3, 6.3 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.6, 157.9, 156.9, 140.8, 140.6, 136.5, 135.5, 131.5, 131.4, 131.1, 131.0, 129.3, 128.9, 128.9, 128.5, 128.3, 127.3, 113.2, 111.4, 87.6, 86.7, 71.3, 64.7, 60.4, 56.8, 47.6, 38.2, 37.6, 34.0.

IR (cm^{-1}): 3029, 2939, 1653, 1489, 1333, 1253, 1047, 1017, 809, 733, 698;

HRMS: calculated for $C_{34}H_{33}I_2N_2O_4$ $[M+H]^+$ 787.0530; found 787.0520.

$[\alpha]_D^{23.9°C}$ = – 7.6° (c= 0.4, CH_2Cl_2)



78 79

Compound 79

A 4-dram, flame-dried vial was brought into a glovebox. To the vial was added $PdCl_2(dppf)•CH_2Cl_2$ (104 mg, 0.127 mmol), B_2pin_2 (969 mg, 3.81 mmol) and K_2CO_3 (527 mg, 3.81 mmol). The vial was capped and removed from the glovebox. Next, **79** (500 mg, 0.64 mmol) was added to a 1 L, round-bottom flask containing a magnetic stir bar and degassed DMSO/H_2O (600 mL, 100:1). Following the addition of **79**, the contents of the vial were poured into the flask in one portion and the flask was capped with a rubber septum. Next, the reaction flask was lowered into a preheated (90 °C) aluminum heating mantle, wrapped in aluminum foil, and a syringe of air (5 mL) was added after 30 minutes of stirring. After stirring at 90 °C for 12 h, the reaction mixture was cooled to room temperature and poured into an extraction funnel containing water (~350 mL) and 1 M HCl (~100 mL). The aqueous mixture was extracted with DCM (3 × 200 mL). The combined organics were then washed with water, brine and concentrated under reduced pressure to garner a thick oil. The crude residue was purified via flash column chromatography (over silica) with an eluent system of 20% to 70% EtOAc in hexanes to afford the title compound as a free-flowing, white solid (275 mg, 0.52 mmol, 81%).

$\mathbf{R_f}$ = 0.29 (70% EtOAc in hexanes; CAM stain and UV);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.28 (m, 7H), 7.24 (m, 1H), 7.03 (d, *J* = 10.7 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.61 (s, 1H), 6.53 (s, 1H), 5.47 (d, *J* = 15.0 Hz, 1H), 5.26 (s, 2H), 4.41 (d, *J* = 5.7 Hz, 1H), 4.21 – 4.15 (m, 2H), 3.98 (d, *J* =

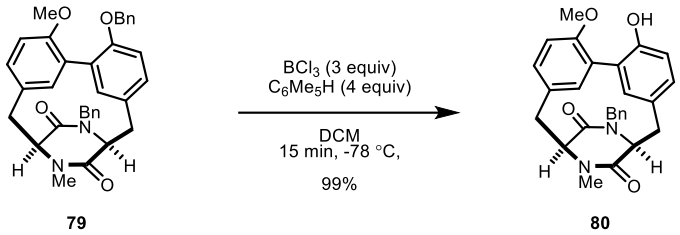
16.1 Hz, 1H), 3.92 (s, 3H), 3.44 (d, *J* = 15.0 Hz, 1H), 2.99 – 2.94 (m, 1H), 2.92 – 2.86 (m, 1H), 2.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 167.3, 155.9, 154.9, 142.5, 142.3, 137.8, 135.5, 129.8, 129.7, 129.5, 129.3, 128.9, 128.9, 128.7, 128.6, 128.4, 128.0, 127.6, 126.2, 125.8, 114.8, 112.4, 71.1, 62.6, 59.1, 56.4, 46.3, 34.2, 33.3, 31.8.

IR (cm^{-1}): 3054, 1648, 1509, 1399, 1264, 1024, 730, 700;

HRMS: calculated for $C_{34}H_{33}N_2O_4$ $[M+H]^+$ 533.2440; found 533.2442.

$[\alpha]_D^{24.1°C}$= +6.1° (c= 0.8, CH_2Cl_2)



79 **80**

Compound 80

Mycocyclosin derivative **80** (1.3 g, 2.44 mmol) and pentamethylbenzene (1.45 g, 9.76 mmol) were weighed out into a flame-dried 500 mL round bottom flask equipped with a magnetic stir bar. The flask was capped with rubber septum and evacuated and refilled with $N_{2(g)}$ three times. DCM (150 mL) was then added to the flask. The reaction was cooled to -78 °C with a dry ice/acetone bath followed by addition of BCl_3 (7.32 mL, 1 M in DCM, 7.32 mmol) via syringe over 15 minutes. After complete addition of BCl_3, there was full conversion of the starting material by TLC analysis. Next, a solution of $CHCl_3$/MeOH (50 mL, 10:1) was added to the reaction and was left to warm to room temperature. The reaction mixture was concentrated under reduced pressure. The crude residue was purified via flash column chromatography (over silica) with an eluent system of 40% to 100% EtOAc in hexanes to afford the title compound as an off-white solid (1.1 g, 2.42 mmol, 99%).

R_f = 0.17 (70% EtOAc in hexanes; CAM stain and UV);

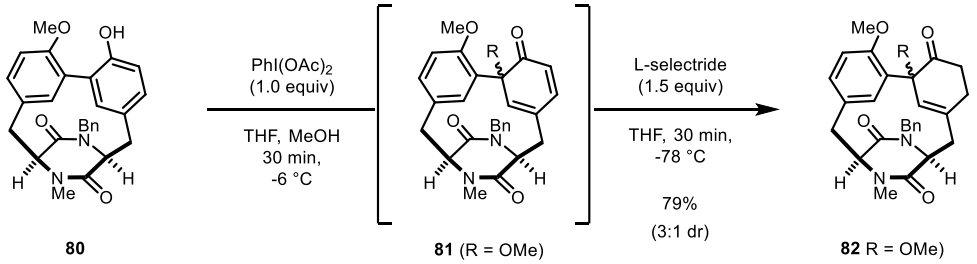
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 3H), 7.27 – 7.22 (m, 2H), 7.11 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.02 (m, 2H), 6.81 (s, 1H), 6.77 (t, *J* = 8.1 Hz, 2H), 6.00 (s, 1H), 5.47 (d, *J* = 15.1 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.26 (d, *J* = 5.8 Hz, 1H), 4.19 (d, *J* = 16.3 Hz, 1H), 3.99 (d, *J* = 16.5 Hz, 1H), 3.94 (s, 3H), 3.55 (d, *J* = 15.1 Hz, 1H), 3.07 (dd, *J* = 16.5, 6.0 Hz, 1H), 2.98 (dd, *J* = 16.5, 6.0 Hz, 1H), 2.81 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 167.7, 155.5, 152.6, 142.5, 141.7, 135.6, 129.8, 129.5, 129.3, 128.5, 128.3, 128.1, 127.1, 126.9, 125.9, 115.5, 110.5, 62.6, 59.5, 56.3, 46.7, 33.9, 33.2, 31.6;

IR (cm^{-1}): 3306, 2931, 1688, 1652, 1498, 1452, 1333, 1252, 1027, 733;

HRMS: calculated for $C_{27}H_{27}N_2O_4$ $[M+H]^+$ 443.1971; found 443.1970.

$[\alpha]_D^{24.2\,^\circ C}$ = +27.9° (c= 1.1, CH_2Cl_2)



Compound 82

To a flame-dried, 500 mL round-bottom flask equipped with a magnetic stir bar was added phenol **80** (2.0 g, 4.52 mmol) and a solvent mixture of MeOH/THF (200 mL, 5:1). The flask was topped with a rubber septum and the solution was cooled to -6 °C with an ice/brine bath. $PhI(OAc)_2$ (1.46 g, 4.52 mmol) and $NaHCO_3$ (835 mg, 9.94 mmol) were then successively added to the reaction mixture. The solution immediately turned bright yellow and was homogeneous. After 30 minutes of stirring at -6 °C, TLC indicated complete consumption of starting material. At this time, the reaction solution was concentrated under reduced pressure to afford a crude yellow residue which was passed through a short plug of neutral aluminum oxide with 50% EtOAc in hexanes (~150 mL) and EtOAc (~150 mL). The eluent was combined and concentrated to afford **81** as a yellow solid which was used directly without further purification. **81** was added to a flame-dried 250 mL, round-bottom flask equipped with a magnetic stir bar followed by the addition of THF (100 mL). The resultant yellow suspension was cooled to -78 °C. Next, *L*-selectride (4.97 mL. 1 M in THF, 4.97 mmol) was added slowly over 5 min. After letting the reaction mixture stir for an additional 30 min at -78 °C, the temperature was raised to 0 °C and saturated $NH_4Cl_{(aq.)}$ (5 mL) was added dropwise to quench residual *L*-selectride. The reaction solution was poured into an extraction funnel containing H_2O (75 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3 × 75 mL). The combined organics were then

washed with water, brine and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (over silica) with an eluent system of 50% to 80% EtOAc in hexanes to afford the title compound as a white solid (1.69 g, 3.56 mmol, 79% from **80**, 3:1 dr).

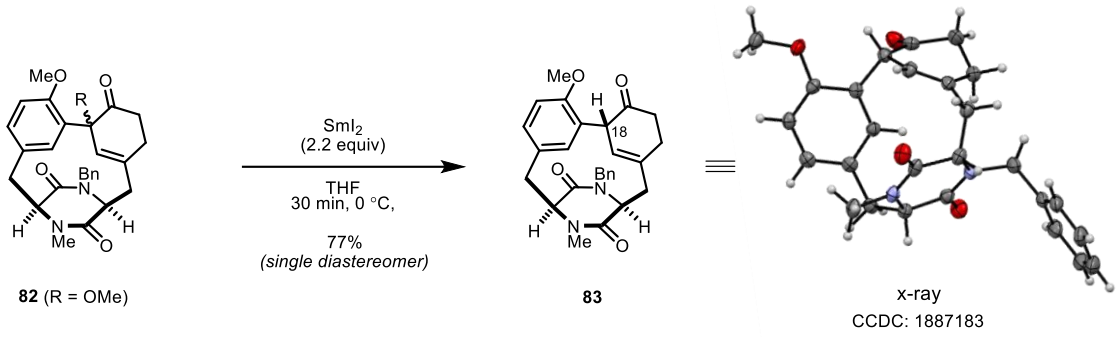
$\mathbf{R_f}$ = 0.25 (70% EtOAc in hexanes; CAM stain and UV);

^{1}H NMR (peaks of major diastereomer, 500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.9 Hz, 1H), 7.32 (m, 2H), 7.22 – 7.19 (m, 2H), 7.13 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 3.2 Hz, 1H), 5.52 (d, *J* = 14.6 Hz, 1H), 4.46 (s, 1H), 4.13 – 4.07 (m, 1H), 3.74 (s, 3H), 3.61 (d, *J* = 14.6 Hz, 1H), 3.44 (s, 3H), 3.41 – 3.21 (m, 4H), 3.18 (s, 3H), 2.64 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.28 (dd, *J* = 8.4, 4.6 Hz, 2H), 2.02 (m, 1H);

^{13}C NMR (mixture of diastereomers, 126 MHz, $CDCl_3$) δ 206.2, 165.0, 164.5, 157.9, 140.2, 136.8, 136.6, 135.2, 132.1, 131.9, 131.5, 131.3, 129.2, 128.9, 128.7, 127.6, 110.7, 84.0, 62.7, 59.6, 59.5, 55.7, 55.6, 53.8, 53.7, 47.1, 46.9, 36.9, 33.7, 32.8, 31.9, 30.1;

IR (cm^{-1}): 2935, 1724, 1648, 1502, 1440, 1255, 1029, 729, 700;

HRMS: calculated for $C_{28}H_{31}N_2O_5$ $[M+H]^+$ 475.2233; found 475.2228.



82 (R = OMe) **83**

Compound 83

α-Methoxy ketone **82** (770 mg, 1.62 mmol) was weighed out into a flame-dried 100 mL, round-bottom flask equipped with a magnetic stir bar. The flask was topped with a septum and nitrogen inlet. Next, the flask was evacuated and refilled with $N_{2(g)}$ three times which was followed by the addition of THF (25 mL) via syringe. With an ice bath, the reaction flask was cooled to 0 °C. Freshly prepared SmI_2 in THF (35.7 mL, 0.1 M, 3.57 mmol) was then added to the reaction mixture via syringe over a period of 30 min. After, the SmI_2 addition period, TLC indicated complete consumption of starting material. Then, a mixture of MeOH/H_2O (10 mL, 2:1) was added to the flask to quench the reaction. The reaction suspension was poured into an extraction funnel containing water (20 mL), 1 M HCl (5 mL) and EtOAc (20 mL). After separating the organic layer, the aqueous layer was further extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a yellow residue. The crude mixture was purified via flash column chromatography (over silica) with an eluent system of 20% to 75% EtOAc in hexanes to afford the title compound as a free-flowing, white solid (555 mg, 1.25 mmol, 77%) and as a single diastereomer. The configuration at C18 was determined to be R by single crystal x-ray analysis.

R_f = 0.37 (70% EtOAc in hexanes; CAM stain and UV);

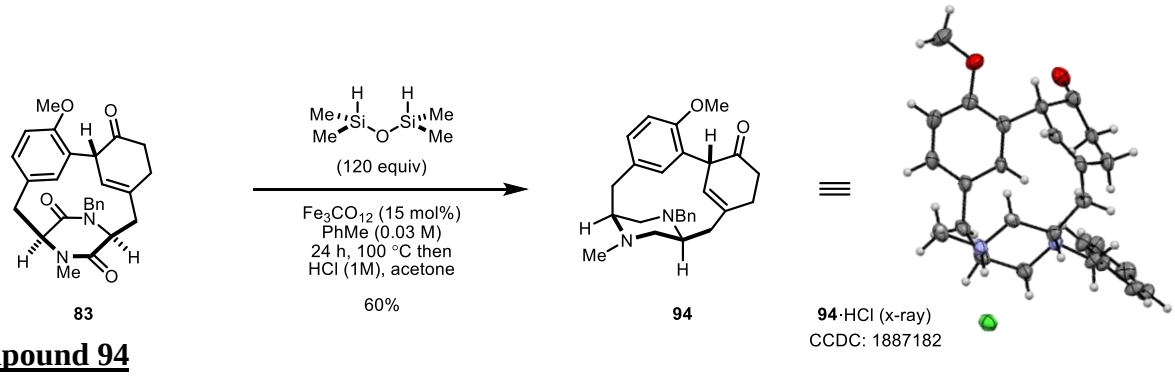
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.94 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 5.90 (d, *J* = 14.6 Hz, 1H), 5.80 (s, 1H), 4.52 (d, *J* = 4.2 Hz, 1H), 4.41 (d, *J* = 7.6 Hz, 1H), 4.19 (d, *J* = 5.1 Hz, 1H), 3.98 (dd, *J* = 15.6, 8.1 Hz, 2H), 3.82 (s, 3H), 3.49 (d, *J* = 14.3 Hz, 1H), 3.01 (dd, *J* = 16.6, 7.7 Hz, 1H), 2.80 – 2.51 (m, 5H), 2.50 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 166.7, 164.7, 156.6, 135.4, 135.0, 133.2, 130.7, 129.4, 128.8, 128.8, 128.7, 126.5, 126.3, 112.1, 60.5, 60.0, 56.4, 47.6, 47.3, 38.6, 36.1, 33.8, 31.5, 30.8;

IR (cm^{-1}): 2933, 1711, 1646, 1505, 1443, 1327, 1255, 1028, 732, 702;

HRMS: calculated for $C_{27}H_{29}N_2O_4$ $[M+H]^+$ 445.2127; found 445.2120.

$[\alpha]_D^{23.7°C}$ = +5.3° (c= 0.3, CH_2Cl_2)



Compound 94

To an oven-dried, 15 mL Chemglass pressure tube, equipped with a magnetic stir bar was added enone **83** (80 mg, 0.18 mmol). The pressure tube was then brought into a glovebox, Fe_3CO_{12} (13.9 mg, 0.027 mmol) was added and the tube closed with the screw-cap. After removing the pressure tube from the glovebox, 1,1,3,3-tetramethyldisiloxane (3.8 mL, 21.6 mmol) was then added followed by toluene (6 mL) under a constant stream of $N_{2(g)}$. The screw-cap was placed back on the reaction tube and then it was submerged into a 100 °C, preheated, oil-bath. After 24 h of stirring at the indicated temperature, the reaction was cooled to room temperature. The reaction suspension was poured into a round-bottom flask and concentrated under reduced pressure. To the resultant black crude residue was added a stir bar, acetone (1 mL) and 1 M HCl (1 mL). This was left to stir for 15 min at room temperature. The solution was diluted with EtOAc (15 mL) and poured into an extraction funnel containing water (15 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_{3\ (aq)}$ and brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a yellow residue. The crude mixture was purified via flash column chromatography (over silica) with an eluent system of 2% to 7% MeOH in DCM to afford the piperazine **94** as an off-white solid (45.1 mg, 0.108 mmol, 60%).

$\mathbf{R_f}$ = 0.40 (7% MeOH in DCM; CAM stain and UV);

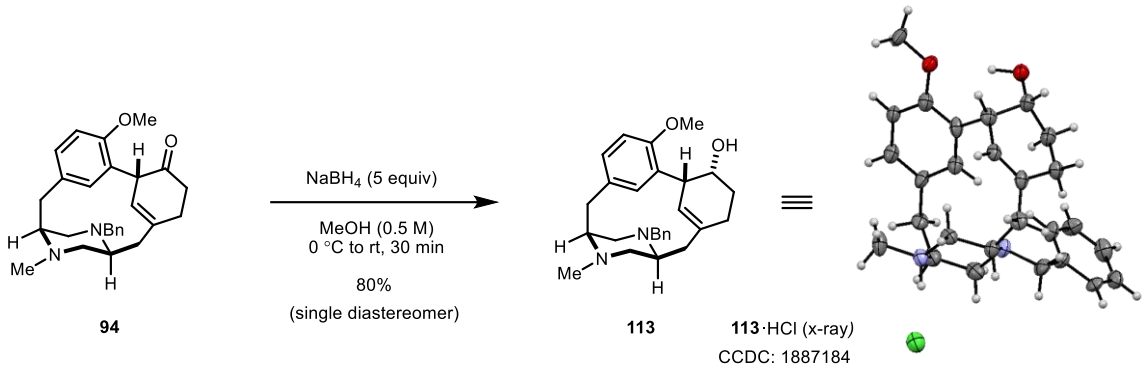
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.34 – 7.30 (m, 4H), 7.25 (m, 1H), 6.99 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.56 (s, 1H), 4.69 (s, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 3.86 (s, 3H), 3.34 (m, 2H), 3.13 (m, 1H), 3.09 – 3.01 (m, 4H), 2.98 – 2.89 (m, 1H), 2.86 (dd, *J* = 14.5, 5.4 Hz, 1H), 2.66 (ddd, *J* = 14.1, 12.1, 6.8 Hz, 1H), 2.59 (m, 1H), 2.49 – 2.44 (m, 2H), 2.36 (s, 4H), 2.19 (d, *J* = 14.5 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 156.8, 137.7, 137.5, 135.5, 132.6, 130.7, 129.4, 128.6, 128.0, 127.6, 111.6, 60.5, 59.7, 58.2, 56.4, 51.6, 47.9, 40.8, 40.2, 37.8, 36.8, 31.8;

IR (cm^{-1}): 2925, 1712, 1501, 1451, 1256, 1027, 810.1, 730, 698;

HRMS: calculated for $C_{27}H_{33}N_2O_2$ $[M+H]^+$ 417.2542; found 417.2537.

$[\alpha]_D^{23.8°C}$ = +15.6° (c= 0.3, CH_2Cl_2)



Compound 113

Piperazine **94** (180 mg, 0.432 mmol) was added to a flame-dried 50 mL, round-bottom flask equipped with a magnetic stir followed by the addition of MeOH (10 mL). The resultant suspension was cooled to 0 °C with an ice-bath and then $NaBH_4$ (81.7 mg, 2.16 mmol) was added slowly. The reaction was left to warm to room temperature over the course of 30 minutes. After TLC, indicated complete consumption of starting material. saturated $NH_4Cl_{(aq.)}$ was added dropwise to the reaction mixture until bubble evolution ceased. After pouring the solution into an extraction funnel containing H_2O (10 mL) and EtOAc (10 mL), the layers were separated. The aqueous layer was further extracted with EtOAc (2 × 15 mL). The combined organics were then washed with brine and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (over silica) with an eluent system of 5% MeOH in DCM to afford the title compound as a white solid (144 mg, 0.344 mmol, 80%).

$\mathbf{R_f}$ = 0.33 (7% MeOH in DCM; CAM stain and UV);

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.37 (s, 1H), 4.68 (d, *J* = 14.8 Hz, 1H), 4.35 – 4.31 (m, 1H), 4.23 (t, *J* = 5.2 Hz, 1H), 3.85 (s, 3H), 3.51 (t, *J* = 10.8 Hz,

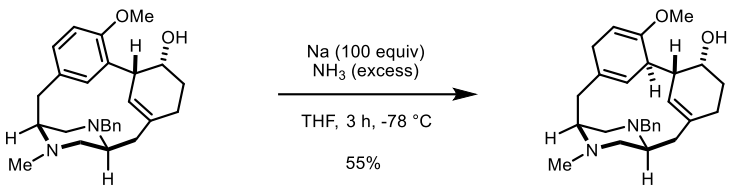
1H), 3.26 (s, 1H), 3.10 – 2.99 (m, 4H), 2.87 (s, 1H), 2.76 (dd, *J* = 14.3, 5.2 Hz, 1H), 2.44 (dd, *J* = 17.6, 5.2 Hz, 3H), 2.21 (s, 4H), 2.06 – 1.99 (m, 2H), 1.86 – 1.77 (m, 1H);

^{13}C NMR (176 MHz, $CDCl_3$) δ 157.0, 141.2, 138.8, 134.6, 129.5, 129.0, 129.0, 127.9, 127.2, 126.0, 109.8, 68.7, 61.1, 60.5, 59.2, 56.7, 55.9, 52.6, 41.6, 41.3, 38.7, 36.3, 30.0, 27.2;

IR (cm^{-1}): 3230, 2924, 2778, 1653, 1498, 1453, 1248, 1063, 1027;

HRMS: calculated for $C_{26}H_{33}N_2O_2$ $[M+H]^+$ 419.2699; found 419.2693.

$[\alpha]_D^{24.8\,^\circ C}$ = +7.8° (c= 0.1, CH_2Cl_2)



113 **123**

Compound 123

An oven-dried, 3-neck 100 mL, round-bottom flask equipped with a magnetic stir bar was cooled to -78 °C under an atmosphere of argon. $NH_{3(l)}$ (~70 mL) was condensed into the flask. $Na_{(s)}$ (165 mg, 7.17 mmol, rinsed with n-hexanes prior to use) was carefully added to the flask. The resulting dark blue solution was left to stir for 10 min. Then, a solution of **113** (30 mg, 0.072 mmol) in THF (3 mL) was carefully added via syringe to the flask. The reaction mixture was left to vigorously stir for 3 h and the dark blue color persisted. The reaction was quenched by the addition of $NH_4Cl_{(s)}$. The cold bath was removed and the $NH_{3(l)}$ was left to evaporate under a stream of nitrogen for 1.5 h. To the flask was added water (20 mL) and EtOAc (20 mL) which was poured into an extraction funnel. After removing the organics, the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a clear residue. The crude material was purified via flash column chromatography (over silica) with an eluent system of 2% to 5% MeOH in DCM to afford diene **123** as a colorless oil (16.5 mg, 0.039 mmol, 55%).

$\mathbf{R_f}$ = 0.55 (7% MeOH in DCM; CAM stain);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 5.39 (s. 2H), 4.73 (dd, *J* = 4.6, 2.1 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.91 (d, *J* = 13.9 Hz, 1H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.65 (dd, *J* = 13.5, 10.9 Hz, 1H), 3.55 (s, 3H), 3.36 – 3.20 (m, 2H),

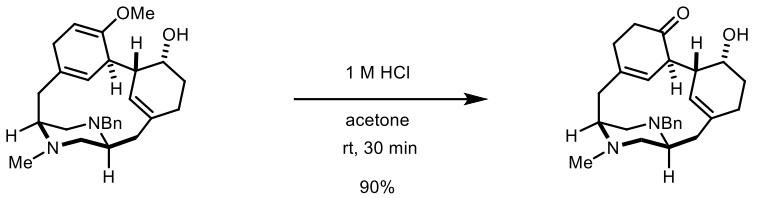
2.91 – 2.83 (m, 1H), 2.68 (s, 1H), 2.63 – 2.36 (m, 5H), 2.32 – 2.22 (m, 4H), 2.15 (m, 2H), 2.00 (dd, *J* = 17.1, 7.3 Hz, 1H), 1.80 (dd, *J* = 13.3, 7.3 Hz, 2H), 1.74 (d, *J* = 13.1 Hz, 1H), 1.62 (s, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 140.9, 136.9, 134.5, 128.5, 127.09, 127.05, 126.2, 92.7, 70.1, 59.4, 55.9, 55.8, 55.1, 54.6, 49.6, 46.3, 45.2, 41.3, 40.5, 37.4, 3.5, 30.5, 29.3;

IR (cm^{-1}): 3366, 2932, 2833, 2421, 1650, 1499, 1452, 1247, 1027, 733;

HRMS: calculated for $C_{26}H_{33}N_2O_2$ $[M+H]^+$ 421.2855; found 421.2850.

$[\alpha]_D^{24.4°C}$= +27.1 ° (c= 0.5, CH_2Cl_2)



123 **124**

Compound 124

A flame-dried, 10 mL round bottom flask was charged with diene **31** (16.5 mg, 0.039 mmol) and acetone (1 mL). Then, 1 M HCl (100 μL) was added. The resulting solution was left to stir at room temperature for 30 minutes. At this time, acetone was evaporated and the residue was taken up in EtOAc (5 mL). The organic solution was poured into an extraction funnel and washed with water (3 mL) and saturated $NaHCO_{3(aq)}$ (3 mL). The organic layer was dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a clear residue. The crude material was purified via flash column chromatography (over silica) with an eluent system of 2% to 5% MeOH in DCM to afford hydroxyl ketone **32** as a colorless oil (14.4 mg, 0.035 mmol, 90%).

R_f = 0.66 (9% MeOH in DCM; CAM stain and UV);

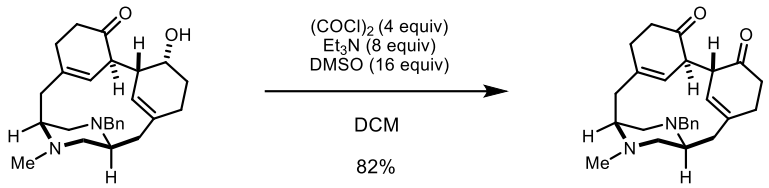
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.23 (m, 1H), 5.50 (s, 1H), 5.29 (s, 1H), 4.17 – 4.10 (m, 1H), 3.92 – 3.76 (m, 2H), 3.60 – 3.54 (m, 1H), 3.40 (s, 1H), 3.24 (s, 1H), 2.85 (m, 2H), 2.80 – 2.68 (m, 1H), 2.58 – 2.43 (m, 4H), 2.38 (m, 1H), 2.33 – 2.09 (m, 7H), 2.02 (m, 1H), 1.91 – 1.80 (m, 2H), 1.80 – 1.66 (m, 2H), 1.60 (s, 1H), 1.26 (m, 1H);

^{13}C NMR (176 MHz, $CDCl_3$) δ 215.8, 140.7, 137.6, 128.6, 128.5, 127.6, 127.2, 125.7, 69.4, 59.3, 57.0, 56.5, 55.6, 50.0, 49.2, 45.5, 45.4, 41.1, 40.5, 39.0, 31.8, 30.0, 29.8;

IR (cm^{-1}): 3407, 2924, 2853, 1708, 1665, 1461, 1074;

HRMS: calculated for $C_{26}H_{35}N_2O_2$ $[M+H]^+$ 407.2699; found 407.2693.

$[\alpha]_D^{23.7\,^\circ C}$ = +15.1° (c= 0.15, CH_2Cl_2)



124 **126**

Compound 126

An oven dried Schlenk tube with a magnetic stir bar, was cooled to -78 °C, and charged with a solution of $(COCl)_2$ (9.7 μL, 0.11 mmol) in DCM (0.5 mL) under a nitrogenous atmosphere. Then, a solution of DMSO (16.1 μL, 0.23 mmol) in DCM (0.5 mL) was added dropwise via syringe. This solution was left to stir at this temperature for 5 min. At this time a solution of **124** (11.5 mg, 0.028 mmol) in DCM (2 mL) was added to the reaction vessel via syringe. The resulting solution was left to stir at -78 °C. After stirring for 15 min, a solution of TEA (47.3 μL, 0.34 mmol) in DCM (1 mL) was added to the reaction flask via syringe. The resulting suspension was left to stir at -78 °C for 1 h. Then, the temperature was raised to -40 °C (CH_3CN /dry ice bath) for 45 min. At this time, TLC indicated full consumption of the starting material. The reaction was quenched by the dropwise addition of H_2O (~1 mL). The reaction mixture was poured into an extraction funnel along with EtOAc (5 mL) and the layers separated. The aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organics were then washed with brine and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (over silica) with an eluent system of 50% EtOAc in hexanes to afford the title compound as a clear oil (9.4 mg, 0.023 mmol, 82%).

$\mathbf{R_f}$ = 0.40 (50% EtOAc in hexanes; CAM stain and UV);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 5.19 (s, 1H), 5.10 (s, 1H), 3.94 (s, 1H), 3.90 – 3.81 (m, 2H), 3.74 (d, *J* = 13.7 Hz, 1H), 3.38 (dd, *J* = 13.6, 11.1 Hz, 1H), 3.04 –

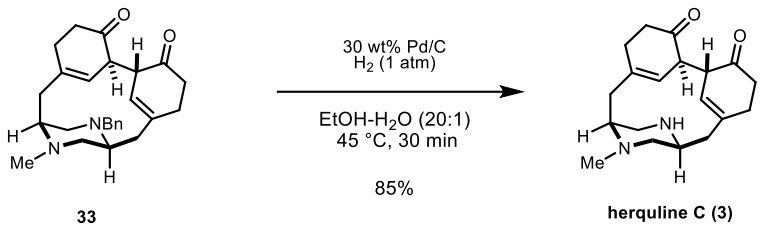
2.94 (m, 1H), 2.87 (s, 1H), 2.77 (t, *J* = 15.4 Hz, 1H), 2.69 (dd, *J* = 13.0, 7.7 Hz, 1H), 2.58 (ddd, *J* = 19.5, 13.2, 6.4 Hz, 2H), 2.53 – 2.30 (m, 8H), 2.24 (m, 4H), 2.16 – 2.07 (m, 1H), 1.82 (d, *J* = 13.7 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 213.2, 211.6, 140.5, 139.9, 138.9, 128.6, 128.5, 127.3, 126.2, 124.9, 59.4, 55.9, 55.4, 55.1, 51.4, 49.5, 45.4, 42.5, 40.5, 40.0, 38.7, 34.0, 32.9, 30.1;

IR (cm^{-1}): 2923, 2853, 1710, 1451, 1338, 1248, 1115;

HRMS: calculated for $C_{26}H_{33}N_2O_2$ $[M+H]^+$ 405.2542; found 405.2540.

$[\alpha]_D^{23.8\,^\circ C}$= +27.4° (c= 0.4, CH_2Cl_2)



Herquline C (3)

A 25 mL round bottom flask with a magnetic stir bar and the substrate (11 mg, 0.027 mmol), was added 30 wt% Pd/C (11 mg) under N_2 atmosphere. The flask was sealed with septa and solvent (EtOH-H_2O=20:1, 2.7 mL) was added by syringe. The heterogenous reaction mixture was sparged with H_2 for 10 min and then heated to 45 ºC under H_2 atmosphere (1 atm, balloon) for 30 min. At this time, TLC indicated full consumption of the starting material. The reaction mixture was filtered through a plug of celite and washed with EtOAc. The filtrate was concentrated and purified via flash column chromatography (over amino phase silica) with an eluent system of 2% MeOH in DCM to afford the herquline C as a sticky oil (7.3 mg, 0.023 mmol, 85%)

R_f = 0.10 (10% MeOH in DCM; CAM stain);

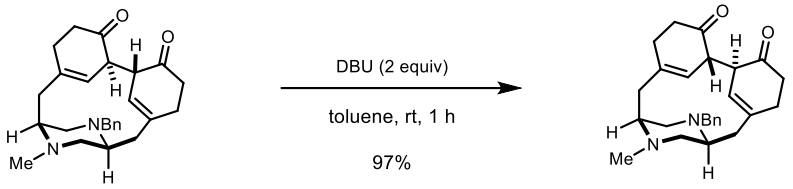
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (m, 1H), 5.14 (m, 1H), 3.98 (br s, 1H), 3.18 (dd, *J* = 13.5, 7.0 Hz, 1H), 3.12 (m, 1H), 2.79 (m, 3H), 2.64 (m, 3H), 2.48 (m, 5H), 2.35 (m, 2H), 2.34 (s, 3H), 2.22 (d, *J* = 13.5 Hz, 1H), 2.15 (dd, *J* = 12.0, 6.3 Hz, 1H), 2.10 (d, *J* = 12.0 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.0, 210.8, 139.6, 138.5, 125.4, 125.2, 76.7, 58.5, 58.1, 50.7, 50.4, 48.9, 46.6, 44.5, 40.4, 40.0, 39.3, 38.9, 34.0, 33.1;

IR (cm^{-1}): 2926, 2855, 2805, 1710, 1443, 1183

HRMS: calculated for $C_{19}H_{27}N_2O_2$ $[M+H]^+$ 315.2073 found 315.2062.

$[\alpha]_D^{24.9\,^\circ C}$ = +66.4 (c=0.2, CH_2Cl_2)



126 127

Compound 127

To the solution of substrate **126** (6.0 mg, 0.015 mmol) in toluene (1.3 mL) was added DBU (4.5 mg, 0.030 mmol, in 0.2 mL toluene) via syringe at room temperature under Ar atmosphere. The reaction was stirred for one hour and then the solvent was evaporated under reduced pressure. The crude product was filtered through a plug (over amino phase silica) quickly with 20% EtOAc in hexanes to remove DBU. The epimerized product **127** was obtained as a clean colorless oil (5.8 mg, 0.014 mmol, 97%) and no further purification is required.

$\mathbf{R_f}$ = 0.40 (50% EtOAc in hexanes; CAM stain and UV);

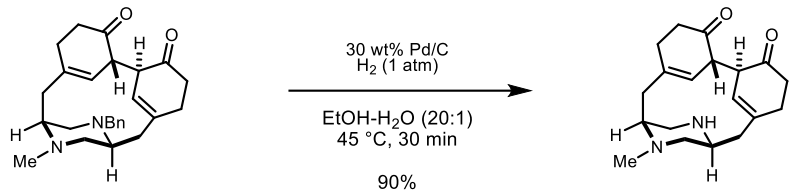
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 (m, 4H), 7.23 (m, 1H), 5.31 (s, 1H), 5.19 (s, 1H), 3.95 (br s, 1H), 3.75 (br s, 1H), 3.69 (d, *J* = 13.3 Hz, 1H), 3.58 (d, *J* = 13.3 Hz, 1H), 2.92 (d, *J* = 14.7 Hz, 1H), 2.82 (br s, 1H), 2.75 (m, 3H), 2.60 (m, 3H), 2.44 (m, 2H), 2.35 (d, *J* = 11.9 Hz, 1H), 2.22 (m, 5H), 2.20 (s, 3H), 1.84 (dd, *J* = 14.7, 7.0 Hz, 1H), 1.59 (br s, 1H), 1.45 (d, *J* = 14.7 Hz, 1H);

^{13}C NMR (175 MHz, $CDCl_3$) δ 213.1, 211.7, 142.2, 138.8, 135.1, 129.2, 128.5, 127.2, 124.5, 123.8, 62.1, 59.3, 57.4, 56.1, 50.5, 49.8, 48.8, 43.3, 40.3, 39.6, 36.4, 34.9, 34.0, 31.7;

IR (cm^{-1}): 2919, 2851, 1711, 1454, 1346, 1185;

HRMS: calculated for $C_{26}H_{33}N_2O_2$ $[M+H]^+$ 405.2542 found 405.2534.

$[\alpha]_D^{24.2\,^\circ C}$ = – 71.6° (c= 0.2, CH_2Cl_2)



127 **herquline B (2)**

Herquline B (2)

To a 5 mL round bottom flask containing substrate **127** (2.0 mg, 0.049 mmol) was added 30 wt% Pd/C (2 mg) under N_2 atmosphere. The mixed solvent of EtOH and water (20:1, 2.1 mL) was added and then the heterogenous reaction mixture was sparged with hydrogen balloon for 10 min before heated to 45 ºC. TLC indicated full conversion of starting material after 30 min. The hydrogen balloon was removed and the reaction mixture was filtrated through a plug of celite and washed with EtOAc. The filtrate was concentrated to give the desired product herquline B (1.4 mg, 0.045 mmol, 90%). No further purification was required.

R_f = 0.10 (10% MeOH in DCM; CAM stain);

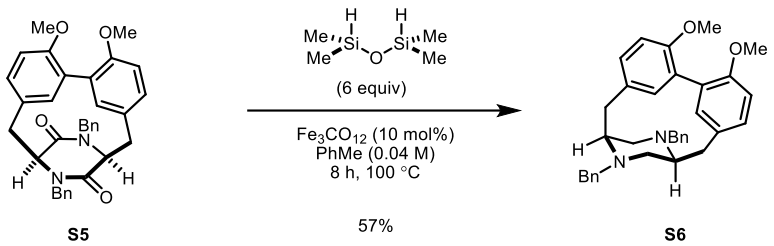
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (br s, 1H), 5.25 (br s, 1H), 3.95 (br s, 1H), 3.82 (br s, 1H), 3.12 (m, 1H), 2.94 (d, *J* = 10.0 Hz, 1H), 2.87 (dd, *J* = 10.5, 4.0 Hz, 1H), 2.70 (m, 3H), 2.67 (m, 1H), 2.62 (m, 1H), 2.54 (m, 1H), 2.50 (m, 5H), 2.35 (m, 2H), 2.25 (s, 3H), 2.23 (m, 1H), 1.78 (dd, *J* = 10.5, 4.0 Hz, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.0, 209.9, 138.2, 136.2, 126.7, 124.0, 59.4, 53.2, 51.9, 50.8, 48.8, 45.6, 42.9, 42.2, 39.6, 39.3, 37.4, 32.8, 30.7;

IR (cm^{-1}): 3409, 2923, 2852, 1710, 1439, 1343, 1185;

HRMS: calculated for $C_{19}H_{27}N_2O_2$ $[M+H]^+$ 315.2073 found 315.2058;

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23.8\,^{\circ}C}}$ = –51.1° (c=0.1, CH_2Cl_2)



Compound S6

To an oven-dried, 15 mL Chemglass pressure tube, equipped with a magnetic stir bar was added cyclophane **S5** (50 mg, 0.091 mmol). The pressure tube was then brought into a glovebox, Fe_3CO_{12} (4.69 mg, 9.1 μmol) was added and the tube closed with the screw-cap. After removing the pressure tube from the glovebox, 1,1,3,3-tetramethyldisiloxane (97 μL, 0.55 mmol) was then added followed by toluene (2.5 mL) under a constant stream of $N_{2(g)}$. The screw-cap was placed back on the reaction tube and then it was submerged into a 100 °C, preheated, oil-bath. After 8 h of stirring at the indicated temperature, the reaction was cooled to room temperature. To resultant black crude residue was diluted with EtOAc (15 mL) and poured into an extraction funnel containing water (15 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a yellow residue. The crude mixture was purified via flash column chromatography (over silica) with an eluent system of 5% to 20% EtOAc in hexanes to afford the piperazine **93** as an off-white solid (27.0 mg, 0.052 mmol, 57%).

$\mathbf{R_f}$ = 0.63 (40% EtOAc in hexanes; CAM stain and UV)

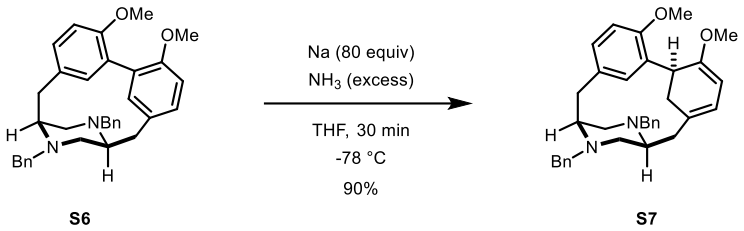
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.14 (s, 2H), 7.08 – 6.99 (m, 6H), 6.96 (dd, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 6.33 (d, *J* = 7.2 Hz, 4H), 4.03 (s, 6H), 3.61 (d, *J* = 12.5 Hz, 2H), 3.05 (dd, *J* = 15.9, 7.0 Hz, 2H), 2.86 (t, *J* = 7.8 Hz, 2H), 2.78 (d, *J* = 15.9 Hz, 2H), 2.68 (d, *J* = 12.7 Hz, 2H), 2.60 (dd, *J* = 12.6, 8.9 Hz, 2H), 2.53 (d, *J* = 12.5 Hz, 2H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 155.9, 148.3, 138.2, 129.9, 129.0, 128.8, 128.8, 128.1, 127.2, 110.1, 60.9, 59.4, 56.8, 55.9, 41.7.

IR (cm^{-1}): 2929, 2796, 1511, 1452, 1260, 1169, 1045, 1028.

HRMS: calculated for $C_{34}H_{37}N_2O_2$ $[M+H]^+$ 505.2855; found 505.2851.

$[\alpha]_D^{24.5\,^\circ C}$ = – 52.5° (c= 0.6, CH_2Cl_2)



Compound S7

An oven-dried, 3-neck 50 mL, round-bottom flask equipped with a magnetic stir bar was cooled to -78 °C under an atmosphere of argon. $NH_{3(l)}$ (~30 mL) was condensed into the flask. $Na_{(s)}$ (72.9 mg, 3.17 mmol, rinsed with *n*-hexanes prior to use) was carefully added to the flask. The resulting dark blue solution was left to stir for 10 min. Then, a solution of **S6** (20 mg, 0.039 mmol) in THF (3 mL) was carefully added *via* syringe to the flask. The reaction mixture was left to vigorously stir for 30 min and the dark blue color persisted. The reaction was quenched by the addition of $NH_4Cl_{(s)}$. The cold bath was removed and the $NH_{3(l)}$ was left to evaporate under a stream of nitrogen for 1.5 h. To the flask was added water (10 mL) and EtOAc (10 mL) which was poured into an extraction funnel. After removing the organics, the aqueous layer was further extracted with EtOAc (2 × 8 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a clear residue. The crude material was purified via flash column chromatography (over silica) with an eluent system of 20% to 60% EtOAc in hexanes to afford diene **S7** as a colorless oil (18.1 mg, 0.036 mmol, 90%).

$\mathbf{R_f}$ = 0.16 (75% EtOAc in hexanes; CAM stain and UV);

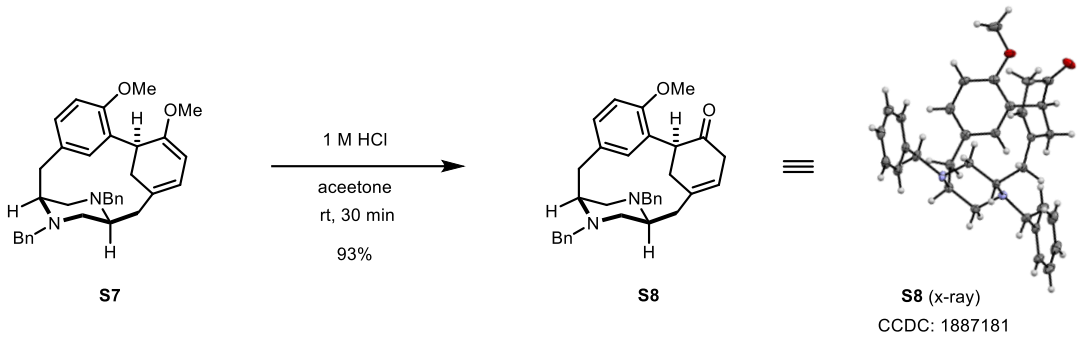
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.1 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.33 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.28 (dd, *J* = 7.7, 7.7 Hz), 7.10 (d, *J* = 7.0 Hz, 1H, 7.06 (dd, *J* = 7.7, 7.0 Hz, 2H), 6.78 (dd, *J* = 2.1, 7.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.33 (d, *J* = 7.0 Hz, 2H), 5.26 (dd, *J* = 13.3, 2.8 Hz, 1H), 4.11 (d, *J* = 14.0 Hz, 1H), 3.97 (d, *J* = 14.0 Hz, 1H), 3.91 (s, 3H), 3.87 (d, *J* =

9.1 Hz, 1H), 3.64 (s, 3H), 3.30 (d, *J* = 12.6 Hz, 1H), 3.28 (d, *J* = 10.5 Hz), 3.08 (dd, *J* = 12.0, 4.9 Hz, 1H), 2.93 (dd, *J* = 7.0, 6.3 Hz), 2.83 (m, 1H), 2.67 (d, *J* = 14.0 Hz, 1H), 2.56 (m, 3H), 2.39 (d, *J* = 11.9 Hz, 1H), 2.33 (d, *J* = 16.1 Hz, 1H), 2.34 (dd, *J* = 15.4, 6.3 Hz, 1H), 2.10 (dd, *J* = 11.9, 6.3 Hz, 1H), 1.89 (d, *J* = 14.0 Hz, 1H);

^{13}C NMR (176 MHz, $CDCl_3$) δ 162.1, 153.3, 139.3, 138.5, 134.4, 131.8, 130.9, 129.8, 129.2, 128.6, 128.3, 128.1, 127.1, 126.6, 126.4, 122.4, 109.7, 93.8, 62.2, 61.2, 60.1, 58.4, 56.6, 55.2, 52.9, 51.7, 38.0, 37.8, 34.4, 33.9;

IR (cm^{-1}): 2929, 2834, 1599, 1498, 1453, 1243, 1160, 1029, 731, 699;

HRMS: calculated for $C_{34}H_{39}N_2O_2$ $[M+H]^+$ 507.3012; found 507.2999.



S7 **S8** **S8** (x-ray)
CCDC: 1887181

Compound S8

A flame-dried, 10 mL round bottoom flask was charged with diene **S7** (5.0 mg, 9.9 μmol) and acetone (2 mL). Then, 1 M HCl (10 drops) was added. The resulting solution was left to stir at room temperature for 30 minutes. At this time, acetone was evaporated and the residue was taken up in EtOAc (2 mL). The organic solution was poured into an extraction funnel and washed with water (2 mL) and saturated $NaHCO_{3(aq)}$ (1 mL). The organic layer was dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a clear residue. The crude material was purified via flash column chromatography (over silica) with an eluent system of 20% to 60% EtOAc in hexanes to afford enone **S8** as a white foam (4.5 mg, 9.1 μmol, 93%).

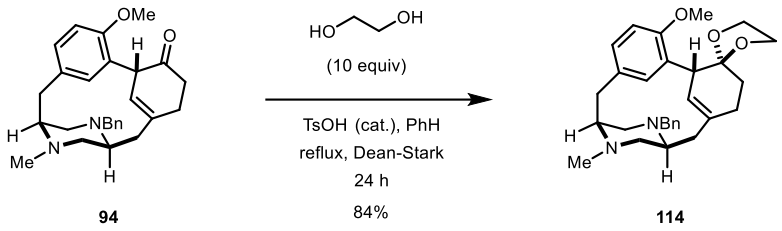
$\mathbf{R_f}$ = 0.67 (75% EtOAc in hexanes; CAM stain and UV);

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.28 (m, 6H), 7.23 (m, 4H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.99 (br s, 1H), 4.64 (d, *J* = 13.3 Hz, 1H), 3.9 br s, 1H), 3.78 (s, 3H), 3.66 (m, 2H), 3.52 (d, *J* = 16.8 Hz, 1H), 3.09 m, 2H), 3.02 (d, *J* = 13.3 Hz, 1H), 2.90 (m, 5H), 2.75 (d, *J* = 16.1 Hz, 2H), 2.64 (m, 2H), 2.40 (dd, *J* = 4.9, 11.9 Hz, 1H), 2.28 (dd, *J* = 4.9, 11.9 Hz, 1H), 1.94 (d, *J* = 14.7 Hz, 1H);

^{13}C NMR (176 MHz, $CDCl_3$) δ 211.7, 156.2, 139.3, 138.6, 136.0, 134.7, 132.0, 129.6, 128.9, 128.82, 128.78, 128.4, 127.14, 127.10, 125.8, 124.2, 110.2, 60.5, 60.3, 58.6, 58.0, 55.8, 55.5, 51.1, 50.3, 39.6, 38.5, 36.6, 35.8;

IR (cm^{-1}): 2918, 2849, 1503, 1452, 1245, 1027, 732, 698.

HRMS: calculated for $C_{33}H_{37}N_2O_2$ $[M+H]^+$ 493.2855; found 493.2849.



Compound 114

A flame-dried, 10 mL round-bottom flask was charged with ketone **94** (30.0 mg, 0.072 mmol) and a stir bar. Benzene (4 mL), ethylene glycol (40.6 μL, 0.72 mmol) and TsOH (2 crystals) were then successively added. The flask was equipped with a Dean-Stark apparatus and heated in an aluminum block for 24 h at 100 °C. After this time, the reaction was cooled to room temperature, benzene evaporated and EtOAc (5 mL) was added. The solution was poured into a sep funnel along with water (5 mL). The organics were separated and the aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a clear residue. The crude mixture was purified via flash column chromatography (over silica) with an eluent system of 3% to 7% MeOH in DCM to afford the acetal **114** as an white solid (28.0 mg, 0.061 mmol, 84%).

$\mathbf{R_f}$ = 0.55 (7% MeOH in DCM; CAM stain and UV);

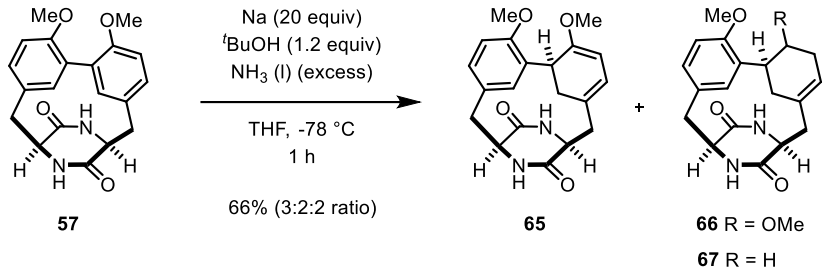
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.25 (m, 1H), 6.96 (d, *J* = 6.8 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.37 (d, *J* = 3.1 Hz, 1H), 4.75 (d, *J* = 14.7 Hz, 1H), 4.21 – 4.16 (m, 2H), 4.13 (m, 1H), 4.01 (m, 2H), 3.90 – 3.85 (br s, 3H), 3.65 (s, 2H), 3.17 (m, 2H), 3.11 (d, *J* = 14.7 Hz, 2H), 3.06 (d, *J* = 12.9 Hz, 1H), 2.84 (dd, *J* = 14.4, 4.8 Hz, 2H), 2.54 (m, 1H), 2.46 – 2.30 (m, 5H), 2.07 – 2.00 (m, 2H), 1.72 (m, 1H);

^{13}C NMR (176 MHz, $CDCl_3$) δ 157.3, 139.6, 137.9, 132.8, 131.5, 129.6, 129.2, 129.0, 127.8, 127.6, 111.1, 108.9, 65.3, 65.1, 60.2, 59.8, 56.4, 56.1, 53.8, 51.5, 43.0, 40.6, 37.7, 35.4, 30.1, 29.6, 29.2;

IR (cm^{-1}): 2927, 1500, 1451, 1264, 1116, 1051, 730, 699.

HRMS: calculated for $C_{29}H_{37}N_2O_3$ $[M+H]^+$ 461.2799; found 461.2799.

$[\alpha]_D^{24.9\,^\circ C}$ = +67.5° (c= 1.2, CH_2Cl_2)



Compound 65

An oven-dried, 3-neck 25 mL, round-bottom flask equipped with a magnetic stir bar was cooled to -78 °C under an atmosphere of argon. NH_3(l) (~20 mL) was condensed into the flask. Na(s) (26 mg, 1.14 mmol, rinsed with n-hexanes prior to use) was carefully added to the flask. The resulting dark blue solution was left to stir for 10 min. Then, a solution of **57** (20 mg, 0.057 mmol) in THF (6 mL) and *t*BuOH (5 mg, 0.068 mmol) was carefully added via syringe to the flask. The reaction mixture was left to vigorously stir for 1 hour and the dark blue color persisted. The reaction was quenched by the addition of NH_4Cl(s). The cold bath was removed and the NH_3(l) was left to evaporate under a stream of nitrogen for 1.5 h. To the flask was added water (5 mL) and EtOAc (5 mL) which was poured into an extraction funnel. After removing the organics, the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organics were washed with brine, dried over solid Na_2SO_4, and concentrated under reduced pressure to afford a clear residue. The crude material was purified via flash column chromatography (over silica) with an eluent system of 5% MeOH in DCM hexanes to afford diene **65** as a colorless oil (6 mg, 0.017 mmol, 30%), **67** as a colorless oil (3.4 mg, 0.010 mmol, 18%) and **66** as a colorless oil (3.6 mg, 0.010 mmol, 18%).

*Characterization data for compound **65***

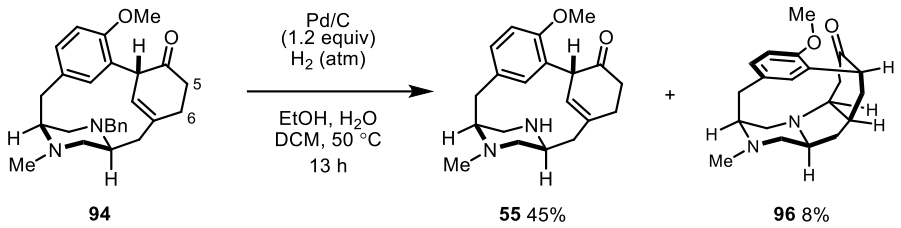
^{1}H NMR (500 MHz, DMSO) δ 8.29 (s, 1H), 7.58 (s, 1H), 7.34 (s, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.92 (s, *J* = 2.6 Hz, 1H), 5.04 (d, *J* = 6.3 Hz, 1H), 4.27 (d, *J* = 7.4 Hz, 1H), 4.12 (s, 1H), 3.76 – 3.61 (m, 4H), 3.49 – 3.38 (m, 4H), 2.93 – 2.80 (m, 1H), 2.74 (dd, *J* =

15.6, 7.7 Hz, 1H), 2.64 (d, *J* = 13.3 Hz, 1H), 2.37 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.08 (d, *J* = 17.4 Hz, 1H).

^{13}C NMR (176 MHz, DMSO) δ 167.0, 165.6, 160.8, 152.4, 133.1, 129.6, 128.3, 127.1, 124.2, 122.1, 110.8, 92.5, 55.7, 54.4, 53.5, 53.1, 36.7, 36.0, 34.7, 32.5.

IR: 2924, 2853, 1670, 1505, 1454, 1378, 1253, 1215, 1034, 804.

HRMS $C_{20}H_{23}N_2O_4$ [M+H$^+$] predicted 355.1653; found 355.1653



Compound 96

To a 25 mL flame-dried round bottom flask equipped with a magnetic stir bar was weighed *N*-benzyl amine **94** (56.8 mg, 0.136 mmol). Next, Pd/C (57.8 mg, 0.164 mmol, 30 wt%) was added to the reaction flask. The flask was topped with a rubber septum, and placed under vacuum and backfilled with an atmosphere of nitrogen. Then, a mixture of ethanol and water (20:1, 6 mL) was added via syringe down the neck of the flask. The resultant suspension was purged with a balloon of hydrogen for 15 minutes. After purging the reaction mixture, the reaction was heated to 50 °C for 13 h. At this time, the reaction was cooled to room temperature, and faltered through a pad of celite. The eluent was concentrated and the crude residue was purified via flash column chromatography over silica (5% MeOH in DCM) to afford **55** (20 mg, 0.061, 45%) as a clear oil and **96** (3.4 mg, 0.010 mmol, 8%) as an off white solid.

The NMR data for compound **55** was constant with previous literature reports.[9]

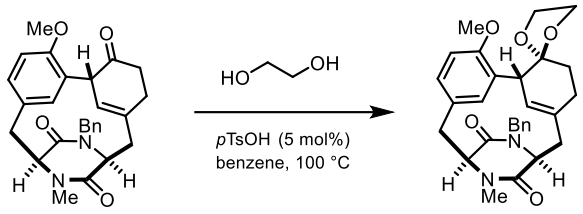
*Characterization data for compound **96***

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.97 – 6.88 (m, 2H), 6.51 (d, *J* = 8.0 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.81 (s, 3H), 3.24 (m, 2H), 3.00 – 2.93 (m, 2H), 2.68 (d, *J* = 14.0 Hz, 1H), 2.64 – 2.58 (m, 1H), 2.57 – 2.46 (m, 5H), 2.39 – 2.33 (m, 1H), 2.27 (m, 2H), 2.19 – 2.12 (m, 1H), 1.92 – 1.86 (m, 1H), 1.56 (t, *J* = 10.6 Hz, 1H), 1.38 (s, 1H), 0.35 (ddd, *J* = 12.1, 9.9, 5.8 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 214.8, 156.7, 138.7, 129.0, 127.9, 126.5, 124.6, 107.3, 59.6, 56.2, 55.5, 54.7, 48.6, 42.2, 38.4, 38.2, 34.5, 32.0, 31.5, 30.1.

HRMS $C_{20}H_{27}N_2O_2$ [M+H$^+$] predicted 327.2073; found 327.2068

IR: 2921, 1713, 1501, 1449, 1251, 1168, 1029, 799, 731, 699



83 101

Compound 101

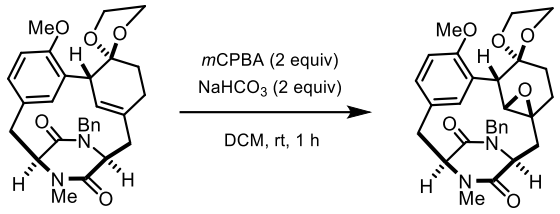
To a flame-dried 10 mL round bottom flask equipped with a stir bar was added cyclic ketone (100 mg, 0.225 mmol). Then to the flask was added benzene (5 mL), anhydrous ethylene glycol (0.381 mL, 6.75 mmol), and *p*-TsOH (8.56 mg, 0.045 mmol). The flask was subsequently equipped with oven-dried Dean-Stark, a condenser and a nitrogen inlet. The reaction was heated to 100 °C in an oil bath for 24 h. After this time, the reaction was cooled to room temperature, dried over Na_2SO_4(s), filtered through cotton, and concentrated to a crude residue Next, the residue was taken up in ethyl acetate, and poured into an extraction funnel which contained water and ethyl acetate. The organics were removed, and the aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over Na_2SO_4(s), filtered through cotton, and concentrated to a crude residue. The crude product was purified via flash column chromatography over silica (70% ethyl acetate in hexanes) to yield the acetal protected product as a white solid in 77% yield (85.0 mg, 0.174 mmol).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 7.05 (s, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.89 (d, *J* = 14.6 Hz, 1H), 5.61 (s, *J* = 2.7 Hz, 1H), 4.41 (d, *J* = 7.5 Hz, 1H), 4.22 – 4.15 (m, 3H), 4.08 – 3.95 (m, 5H), 3.81 (s, 3H), 3.31 (d, *J* = 14.3 Hz, 1H), 3.02 (dd, *J* = 16.6, 7.9 Hz, 1H), 2.66 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.53 (dt, *J* = 15.3, 6.9 Hz, 1H), 2.45 (s, 3H), 2.31 (dd, *J* = 17.9, 7.5 Hz, 1H), 2.08 (ddd, *J* = 13.7, 11.1, 7.7 Hz, 1H), 1.67 – 1.61 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 166.8, 164.8, 156.7, 135.5, 133.1, 132.2, 131.9, 129.2, 128.7, 128.5, 127.6, 127.2, 125.4, 111.1, 109.0, 65.0, 65.0, 60.2, 60.0, 55.8, 47.6, 41.3, 34.2, 33.5, 31.2, 29.1, 27.3.

HRMS $C_{29}H_{33}N_2O_5$ [M+H^+] predicted 489.2389; found 489.2381

IR: 3054, 1647, 1506, 1446, 1327, 1264, 1108, 1053, 909, 729, 701



101 102

Compound 102

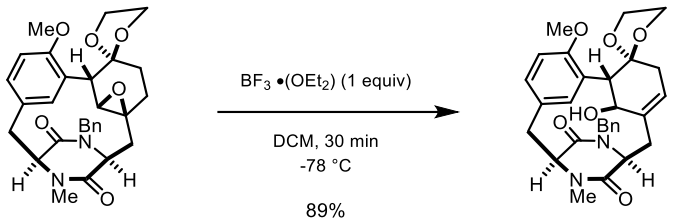
To a flame-dried 50 mL round bottom flask equipped with a stir bar was added acetal (370 mg, 0.757 mmol) substrate. Then to the flask was added dichloromethane (25 mL), $NaHCO_3$ (127 mg, 1.51 mmol), followed by *m*CPBA (348 mg, 1.51 mmol). The flask was topped with a rubber septum and a nitrogen inlet. The reaction stirred at room temperature for 30 minutes. By TLC analysis there was complete consumption of starting material. The reaction was quenched by the addition of water and aqueous $NaHCO_3$. Next, the reaction mixture was poured into an extraction funnel with dichloromethane. The organic layer was removed, and the aqueous layer was further extracted with dichloromethane (3 × 15 mL). The combined organics were dried over Na_2SO_4(s), filtered through cotton, and concentrated to a crude residue. Purification of the epoxy acetal product was accomplished with flash column chromatography over silica (75% ethyl acetate in hexanes) to afford the title compound as a white solid in 82% yield (312 mg, 0.618 mmol).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.95 (s, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 5.94 (d, *J* = 14.6 Hz, 1H), 4.46 (d, *J* = 7.9 Hz, 1H), 4.15 (d, *J* = 5.2 Hz, 1H), 4.08 (dd, *J* = 13.0, 6.6 Hz, 1H), 4.00 (m, 3H), 3.90 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.82 (s, 3H), 3.75 (dd, *J* = 12.6, 6.5 Hz, 1H), 3.70 (q, *J* = 6.9 Hz, 1H), 3.12 (m, 2H), 2.80 (dd, *J* = 15.3, 5.7 Hz, 1H), 2.51 (s, 3H), 2.47 (dd, *J* = 15.2, 1.8 Hz, 1H), 2.35 (dt, *J* = 15.5, 7.9 Hz, 1H), 2.23 – 2.17 (m, 1H), 1.82 – 1.76 (m, 1H), 1.73 – 1.67 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 166.9, 164.5, 156.3, 135.0, 129.3, 128.9, 128.7, 128.7, 128.6, 126.3, 126.2, 111.5, 108.5, 65.1, 64.4, 62.6, 60.0, 56.4, 55.8, 55.4, 47.6, 39.9, 36.0, 34.2, 31.7, 27.0, 26.7.

HRMS $C_{29}H_{32}N_2O_6Na$ [M+Na^+] predicted 527.2153; found 527.2154

IR: 2930, 1653, 1508, 1425, 1395, 1332, 1254, 1128, 1090, 950, 823, 720.



102 103

Compound 103

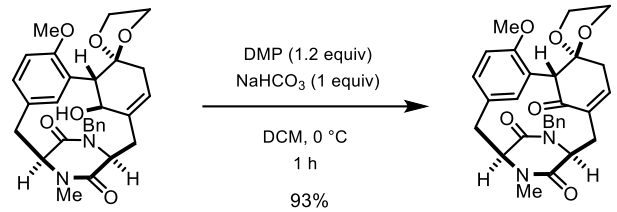
To a flame-dried 25 mL round bottom flask equipped with a stir bar was added epoxide (50 mg, 0.1 mmol) substrate. Then to the flask was added dichloromethane (6 ml). The flask was topped with a rubber septum and a nitrogen inlet and cooled to 0 °C with an ice-bath. Next, $BF_3 \cdot (OEt)_2$ (14.7 µL, 0.1 mmol) was added via syringe. The reaction was left to stirred 0 °C for 30 minutes. By TLC analysis there was complete consumption of starting material. The reaction was quenched by the addition of water (1 mL). Next, the reaction mixture was poured into an extraction funnel with dichloromethane. The organic layer was removed, and the aqueous layer was further extracted with dichloromethane (3 × 5 mL). The combined organics were dried over Na_2SO_4(s), filtered through cotton, and concentrated to a crude residue. Purification of the allylic alcohol product was accomplished with flash column chromatography over silica (70% to 90% ethyl acetate in hexanes) to afford the title compound as a white solid in 89% yield (45 mg, 0.089 mmol).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 5H), 7.21 (s, 1H), 6.98 (d, *J* = 6.7 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 5.86 (d, *J* = 14.6 Hz, 1H), 5.74 (dd, *J* = 4.9, 2.0 Hz, 1H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.28 – 4.17 (m, 3H), 4.06 (M, 2H), 3.97 (dd, *J* = 20.4, 12.3 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 2H), 3.57 (br, 1H), 3.37 (d, *J* = 13.4 Hz, 1H), 3.04 (dd, *J* = 16.8, 8.0 Hz, 1H), 2.93 (dd, *J* = 14.5, 5.4 Hz, 1H), 2.48 (s, 3H), 2.44 (d, *J* = 18.1 Hz, 1H), 2.25 (dd, *J* = 18.5, 5.0 Hz, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 166.9, 164.9, 156.2, 136.8, 135.2, 129.2, 128.7, 128.5, 128.2, 126.8, 126.6, 125.7, 111.3, 108.9, 74.7, 64.8, 64.6, 59.8, 57.9, 55.8, 47.2, 43.2, 33.8, 33.6, 32.0, 31.3.

HRMS $C_{29}H_{32}N_2O_6Na$ [M+Na^+] predicted 527.2153; found 527.2154

IR: 3054, 1650, 1507, 1321, 1264, 1122, 1032, 731, 702.



103 **104**

Compound 104

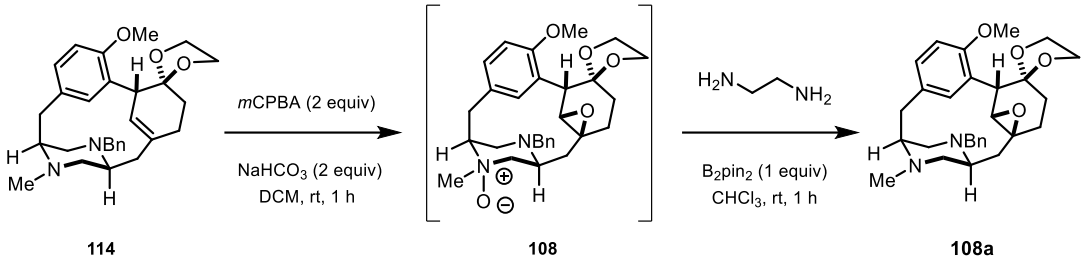
To a flame-dried 10 mL round bottom flask equipped with a stir bar was added allylic alcohol (10 mg, 0.0.2 mmol) substrate. Then to the flask was added dichloromethane (1 mL). The resultant mixture was cooled to 0 °C with an ice-bath. Next, $NaHCO_3$ (3.3 mg), followed by DMP (10.1 mg, 0.024 mmol) was added. The flask was topped with a rubber septum and a nitrogen inlet. The reaction stirred at 0 °C and warmed to room temperature over 1 hour. By TLC analysis there was complete consumption of starting material. The reaction was quenched by the addition of water. Next, the reaction mixture was poured into an extraction funnel with dichloromethane. The organic layer was removed, and the aqueous layer was further extracted with dichloromethane (3 × 2 mL). The combined organics were dried over Na_2SO_4(s), filtered through cotton, and concentrated to a crude residue. Purification of the epoxy acetal product was accomplished with flash column chromatography over silica (60% to 90% ethyl acetate in hexanes) to afford the title compound as a white solid in 93% yield (9.4 mg, 0.019 mmol).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 3.2 Hz, 1H), 5.86 (d, *J* = 14.5 Hz, 1H), 4.42 (s, 1H), 4.35 (d, *J* = 7.8 Hz, 1H), 4.24 – 4.15 (m, 3H), 4.06 (m, 2H), 3.97 (m, 3H), 3.81 (s, 3H), 3.01 (dd, *J* = 16.7, 7.9 Hz, 1H), 2.83 (d, *J* = 19.2 Hz, 1H), 2.69 (dd, *J* = 14.4, 5.9 Hz, 1H), 2.57 (dd, *J* = 19.2, 5.4 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 195.7, 167.1, 163.9, 156.7, 144.6, 136.4, 135.1, 129.3, 129.1, 128.6, 128.6, 126.5, 125.6, 122.5, 111.9, 109.5, 65.2, 64.8, 59.8, 58.0, 55.9, 53.7, 47.6, 35.3, 33.6, 31.2, 26.9.

HRMS $C_{29}H_{31}N_2O_6$ [M+H^+] predicted 503.2177; found 503.2182

IR: 3056, 2935, 1687, 1653, 1507, 1438, 1323, 1260, 1120, 1027, 723, 697.



114 108 108a

Compound 108a

To a flame-dried 25 mL round bottom flask equipped with a magnetic stir bar was added acetal (200 mg, 0.434 mmol) and dichloromethane (9 mL). The flask was topped with a septum. The solution was cooled to 0 °C with an ice bath. $NaHCO_3$ (73 mg, 0.868 mmol) was then added followed by a dichloromethane solution of *m*CPBA (214 mg, 0.868 mmol). This mixture was left to stir for 30 minutes and allowed to warm to room temperature. After this reaction time, the reaction was quenched by the addition of $Na_2S_3O_3$ (aq.). This solution was poured into an extraction funnel which contained water and dichloromethane. The organic layer was removed then the aqueous layer was further extracted with dichloromethane (3 × 10 mL). The combined organics were dried over Na_2SO_4(s), filtered through cotton, and concentrated to a crude residue. The crude *N*-oxide was added to a flame-dried 25 mL round bottom flask along with chloroform (9 mL) and a stir bar. After adding a rubber septum, the solution was cooled to 0 °C with an ice bath. Next, B_2pin_2 (110 mg, 0.434 mmol) was added to the reaction flask. The resulting mixture was stirred for 15 minutes and warmed to room temperature. Ethylamine diamine (0.29 mL, 4.34 mmol) was subsequently added to the reaction flask. After stirring for 1 hour, TLC analysis indicated complete consumption of starting material. The reaction mixture was concentrated and taken up in ethyl acetate. This solution was poured into an extraction funnel which contained water and ethyl acetate. The organic layer was removed then the aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over Na_2SO_4(s), filtered through

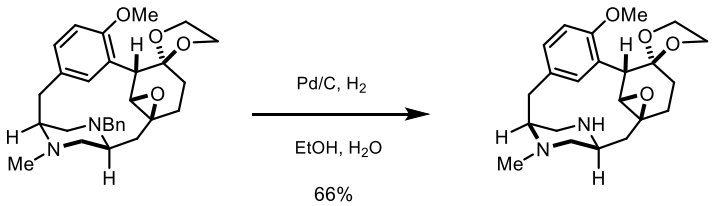
cotton, and concentrated to a crude residue. Purification of the epoxy acetal product was accomplished with flash column chromatography over silica (7% methanol in dichloromethane) to afford the title compound as a white solid in 93% yield (200 mg, 0.41 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.23 (m, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 4.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 4.67 (d, *J* = 14.6 Hz, 1H), 4.13 (s, 1H), 4.05 (dd, *J* = 13.2, 6.8 Hz, 1H), 3.92 – 3.75 (m, 5H), 3.70 (dd, *J* = 13.8, 6.8 Hz, 1H), 3.38 (t, *J* = 11.8 Hz, 1H), 3.19 (s, 1H), 3.08 (s, 2H), 3.03 (s, 1H), 2.95 (d, *J* = 14.7 Hz, 1H), 2.88 (dd, *J* = 15.1, 5.6 Hz, 1H), 2.72 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.66 (dd, *J* = 14.5, 6.8 Hz, 1H), 2.33 – 2.18 (m, 5H), 2.14 – 2.03 (m, 2H), 1.87 – 1.81 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 138.5, 137.5, 130.3, 128.8, 128.1, 126.9, 125.5, 110.5, 108.3, 64.9, 64.6, 64.4, 60.9, 60.8, 60.2, 56.0, 56.0, 56.0, 53.2, 41.9, 40.9, 39.4, 38.0, 30.1, 28.2, 28.0.

HRMS $C_{29}H_{37}N_2O_4$ [M+H^+] predicted 477.2753; found 477.2760

IR: 2926, 2880, 1672, 1504, 1451, 1349, 1255, 1168, 1130, 1069, 734.



108a **109**

Compound 109

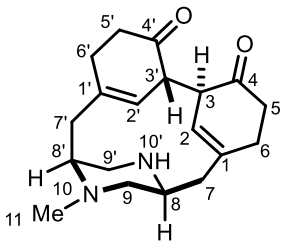
A 10 mL round bottom flask with a magnetic stir bar and substrate (15 mg, 0.032 mmol), was added 5 wt% Pd/C (16 mg) under N_2 atmosphere. The flask was sealed with septa and solvent (EtOH-H_2O=20:1, 2 mL) was added by syringe. The heterogenous reaction mixture was sparged with H_2 for 10 min and then heated to 60 ºC under H_2 atmosphere (1 atm, balloon) for 18 hours/ At this time, TLC indicated full consumption of the starting material. The reaction mixture was filtered through a plug of celite and washed with EtOAc. The filtrate was concentrated and purified via flash column chromatography (over amino phase silica) with an eluent system of 2% MeOH in DCM to afford the title compound (8 mg, 0.021 mmol, 66%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 4.11 (dd, *J* = 13.4, 6.6 Hz, 1H), 4.06 (s, 1H), 3.94 (dd, *J* = 13.8, 7.0 Hz, 1H), 3.85 – 3.78 (m, 5H), 3.32 – 3.15 (m, 5H), 3.12 – 3.02 (m, 2H), 2.94 (s, 1H), 2.49 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.38 (m, 1H), 2.34 – 2.28 (m, 4H), 2.20 – 2.14 (m, 1H), 1.94 (dd, *J* = 11.1, 4.3 Hz, 1H), 1.71 – 1.66 (m, 3H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 155.7, 138.0, 130.8, 130.0, 125.2, 110.3, 108.9, 65.0, 64.8, 64.4, 56.9, 55.8, 55.5, 53.3, 53.3, 52.8, 42.4, 40.9, 40.3, 39.8, 30.7, 27.3.

HRMS $C_{22}H_{31}N_2O_4$ [M+H$^+$] predicted 387.2284; found 387.2262

E.1.3 Tabulated NMR data for herquline B and C

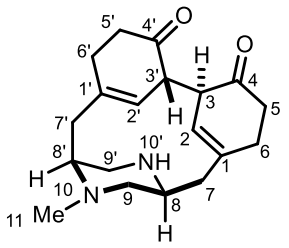


herquline B (**2**)

^{1}H NMR (500 MHz, $CDCl_3$)

reported by Omura[3]

	natural herquline B	*synthetic herquline B*	*Δppm*
H2	5.31 m	5.30 br, s	0.01
H2'	5.25 m	5.25 br, s	-
H3'	3.95 m	3.95 br, s	-
H3	3.80 m	3.82 br, s	0.02
H8	3.25 m	3.12 m	0.12
H9'	3.01 dd	2.94 d	0.07
	2.92 dd	2.87 dd	0.05
H7'	2.73, br d	2.70 d	0.02
	1.78 dd	1.78 dd	-
H5'	2.68 m	2.70 m	0.02
	2.48 m	2.48 m	-
H5	2.68 m	2.67 m	0.01
	2.48 m	2.48 m	-
H6'	2.67 m	2.70 m	0.03
	2.48 m	2.50 m	0.02
H6	2.61 m	2.62 m	0.01
	2.32 m	2.35 m	0.02
H9	2.57 m	2.54 m	0.03
H7	2.56 m	2.52 m	0.04
	2.28 m	2.30 m	0.02
H8'	2.41 m	2.35 m	0.06
11-Me	2.26 s	2.25 s	0.01

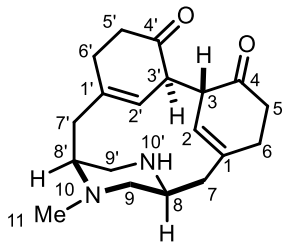


herquline B (**2**)

^{13}C NMR (126 MHz, $CDCl_3$)

reported by Omura[3]

	natural herquline B	*synthetic herquline B*	*Δppm*
C4	211.9	211.9	-
C4'	209.8	209.8	-
C1	138.4	138.1	0.3
C1'	135.7	136.1	0.4
C2'	127.2	126.6	0.6
C2	124.8	123.9	0.9
C8'	59.1	59.3	0.2
C9	53.2	53.1	0.1
C8	51.6	51.8	0.2
C3'	50.9	50.7	0.2
C3	48.9	48.7	0.2
C9'	44.8	45.5	0.7
11-Me	42.9	42.8	0.1
C7	41.7	42.1	0.4
C5	39.7	39.5	0.2
C5'	39.4	39.2	0.2
C7'	37.0	37.3	0.3
C6'	33.2	32.7	0.5
C6	30.8	30.6	0.2

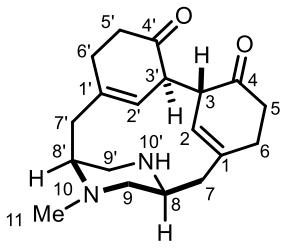


herquline C (**3**)

^{12}C NMR (126 MHz, $CDCl_3$)

reported by Tang[2]

	natural herquline C	*synthetic herquline C*	*Δppm*
C4'	212.2	212.2	-
C4	211.0	211.0	-
C1'	139.8	139.8	-
C1	138.7	138.7	-
C2	125.5	125.6	0.1
C2'	125.4	125.4	-
C8'	58.6	58.7	0.1
C9	58.1	58.3	0.2
C3	50.8	50.9	0.1
C8	50.5	50.5	-
C3'	49.0	49.1	0.1
C9'	46.9	46.8	0.1
11-Me	44.6	44.6	-
C7	40.6	40.6	-
C5'	40.2	40.2	-
C5	39.4	39.4	-
C7'	39.1	39.1	-
C6	34.2	34.2	-
C6'	33.3	33.3	-



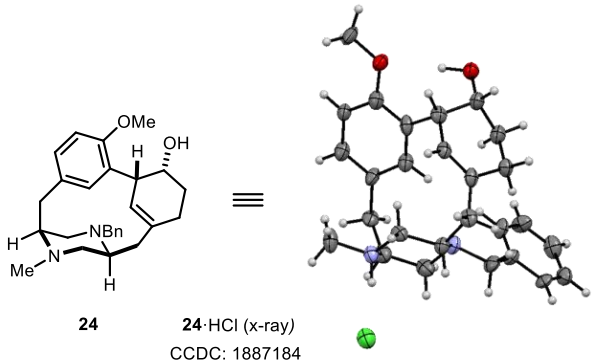
herquline C (**3**)

^{1}H NMR (500 MHz, $CDCl_3$)

reported by Tang[2]

	natural herquline C	*synthetic herquline C*	*Δppm*
H2'	5.26, m	5.25, m	0.01
H2	5.14, m	5.14, m	-
H3	3.99, br, s	3.98, br, s	0.01
H3'	3.83, br, s	3.83, br, s	-
H9'	3.17, dd	3.17, dd	-
	2.65, overlaps	2.65, overlaps	-
H8	3.13, m	3.12, m	0.01
H6'	2.83, m	2.82, m	0.01
	2.40, m	2.40, m	-
H9	2.81, m	2.81, m	-
	2.15, m	2.15, m	-
H6	2.76, m,	2.77, m,	0.01
	2.46, m	2.46, m	-
H5	2.68, m	2.68, m	-
	2.48 overlaps	2.48 overlaps	-
H5'	2.62, m	2.62, m	-
	2.51, m	2.51, m	-
H7'	2.48, overlaps	2.48, overlaps	-
	2.11, m br, d	2.10, m br, d	0.01
H7	2.38, m overlaps	2.37, m overlaps	0.01
	2.22, m br, d	2.22, m br, d	-
11-Me	2.35, s	2.34, s	0.01
H8'	2.32, m	2.32, m	-

E.1.4 X-ray crystallographic data



Structure Determination.

Colorless plates of **zxpzoh_sq** were grown from a dichloromethane/hexane solution of the compound at 25 deg. C. A crystal of dimensions 0.14 x 0.10 x 0.02 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 4 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 21326 reflections to a maximum 2θ value of 139.12° of which 4842 were independent and 4524 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the xyz centroids of 10201 reflections above $10\sigma(I)$. Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2018/3) software package, using the space group P2(1) with Z = 2 for the formula $C_{27}H_{35}N_2O_2Cl$ + [solvent]. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of idealized and refined positions. Full matrix least-

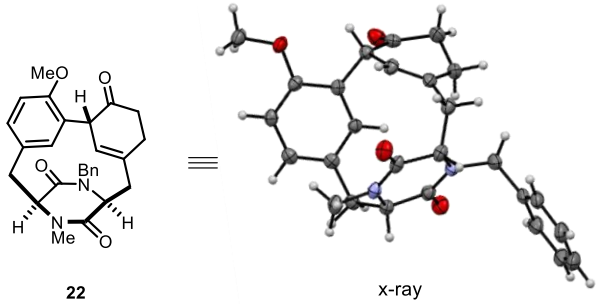
squares refinement based on F^2 converged at R1 = 0.0892 and wR2 = 0.2434 [based on I > 2sigma(I)], R1 = 0.0929 and wR2 = 0.2514 for all data. The SQUEEZE subroutine of the PLATON program suite was used to address the disordered solvent present in a solvent accessible void present in the structure. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).
CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.
CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Crystal data and structure refinement for zxpzoh_sq.

Identification code	zxpzoh_sq
Empirical formula	C27 H35 Cl N2 O2
Formula weight	455.02
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 10.8605(2) A alpha = 90 deg. b = 8.50510(10) A beta = 106.459(2) deg. c = 15.6375(4) A gamma = 90 deg.
Volume	1385.24(5) A^3
Z, Calculated density	2, 1.091 Mg/m^3
Absorption coefficient	1.392 mm^-1
F(000)	488
Crystal size	0.140 x 0.100 x 0.020 mm
Theta range for data collection	2.947 to 69.560 deg.
Limiting indices	-13<=h<=13, -10<=k<=10, -18<=l<=18
Reflections collected / unique	21326 / 4842 [R(int) = 0.0674]
Completeness to theta = 67.684	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.80293

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4842 / 1 / 296
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0892, wR2 = 0.2434
R indices (all data)	R1 = 0.0929, wR2 = 0.2514
Absolute structure parameter	0.15(4)
Extinction coefficient	0.017(3)
Largest diff. peak and hole	1.415 and -0.579 e.A^-3



22 ≡ x-ray

CCDC: 1887183

Structure Determination.

Colorless prisms of **zx749** were grown from a dichloromethane/pentane solution of the compound at 25 deg. C. A crystal of dimensions 0.20 x 0.18 x 0.11 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 2 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 35893 reflections to a maximum 2θ value of 138.42° of which 4292 were independent and 4183 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the xyz centroids of 20649 reflections above $10\sigma(I)$. Analysis of the data showed

negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P2(1)2(1)2(1) with Z = 4 for the formula $C_{27}H_{28}N_2O_4(H_2O)_{0.5}$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. The low occupance water solvate is disordered over two sites. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0337 and wR2 = 0.0899 [based on I > 2sigma(I)], R1 = 0.0351 and wR2 = 0.0927 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation. G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

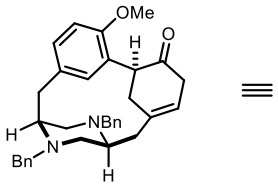
CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

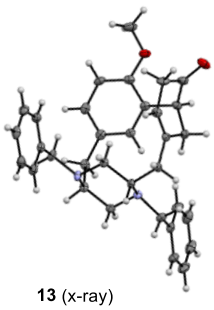
Crystal data and structure refinement for zx749.

Identification code	zx749
Empirical formula	C27 H29 N2 O4.50
Formula weight	453.52
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 12.11400(10) A alpha = 90 deg. b = 12.97770(10) A beta = 90 deg. c = 14.75780(10) A gamma = 90 deg.
Volume	2320.10(3) A^3
Z, Calculated density	4, 1.298 Mg/m^3
Absorption coefficient	0.717 mm^-1
F(000)	964
Crystal size	0.200 x 0.180 x 0.110 mm
Theta range for data collection	4.537 to 69.218 deg.
Limiting indices	-14<=h<=14, -15<=k<=15, -17<=l<=17
Reflections collected / unique	35893 / 4292 [R(int) = 0.0451]

Completeness to theta = 67.684 100.0 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.00000 and 0.79765
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 4292 / 0 / 319
Goodness-of-fit on F^2 1.077
Final R indices [I>2sigma(I)] R1 = 0.0337, wR2 = 0.0899
R indices (all data) R1 = 0.0351, wR2 = 0.0927
Absolute structure parameter -0.13(8)
Extinction coefficient 0.0012(3)
Largest diff. peak and hole 0.437 and -0.169 e.A^-3



13

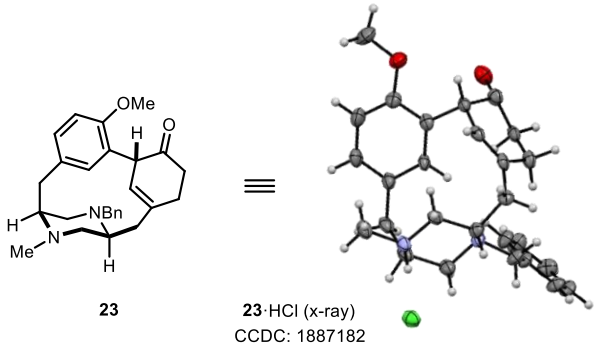


13 (x-ray)
CCDC: 1887181

Crystal data and structure refinement for ccm925a.

Identification code ccm925a
Empirical formula C33 H36 N2 O2
Formula weight 492.64
Temperature 85(2) K
Wavelength 1.54184 A
Crystal system, space group Monoclinic, P2(1)
Unit cell dimensions a = 7.21026(9) A alpha = 90 deg.
b = 12.31353(12) A beta = 96.9925(10) deg.
c = 15.41477(14) A gamma = 90 deg.
Volume 1358.40(2) A^3
Z, Calculated density 2, 1.204 Mg/m^3
Absorption coefficient 0.581 mm^-1
F(000) 528
Crystal size 0.220 x 0.180 x 0.170 mm
Theta range for data collection 2.888 to 69.339 deg.
Limiting indices -8<=h<=7, -14<=k<=14, -18<=l<=18
Reflections collected / unique 20605 / 4866 [R(int) = 0.0482]
Completeness to theta = 67.684 100.0 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.00000 and 0.86261

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4866 / 1 / 337
Goodness-of-fit on F^2	1.087
Final R indices [I>2sigma(I)]	R1 = 0.0322, wR2 = 0.0820
R indices (all data)	R1 = 0.0326, wR2 = 0.0825
Absolute structure parameter	0.1(2)
Extinction coefficient	0.0218(11)
Largest diff. peak and hole	0.311 and -0.191 e.A^-3



23 **23**·HCl (x-ray)
CCDC: 1887182

Structure Determination.

Colorless plates of **ccm979** were grown from a dichloromethane/hexane solution of the compound at 23 deg. C. A crystal of dimensions 0.14 x 0.10 x 0.04 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 5 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 21092 reflections to a maximum 2θ value of 138.53° of which 4378 were independent and 4252 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the xyz centroids of 15401 reflections above $10\sigma(I)$. Analysis of the data showed negligible decay during data collection. The structure was solved and refined

with the Bruker SHELXTL (version 2016/6) software package, using the space group P2(1) with Z = 2 for the formula $C_{27}H_{33}N_2O_2Cl(H_2O)_{0.5}$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of idealized and refined positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0640 and wR2 = 0.1693 [based on I > 2sigma(I)], R1 = 0.0655 and wR2 = 0.1718 for all data. The SQUEEZE subroutine of the PLATON program suite was used to address the disordered solvent present in the structure. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Crystal data and structure refinement for ccm979_sq.

Identification code	ccm979_sq
Empirical formula	C27 H34 Cl N2 O2.50
Formula weight	462.01
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 10.8485(3) A alpha = 90 deg.
	b = 8.5152(3) A beta = 106.083(3) deg.
	c = 15.5978(6) A gamma = 90 deg.
Volume	1384.49(8) A^3
Z, Calculated density	2, 1.108 Mg/m^3
Absorption coefficient	1.415 mm^-1
F(000)	494
Crystal size	0.140 x 0.100 x 0.040 mm

Theta range for data collection 2.948 to 69.263 deg.
Limiting indices -13<=h<=13, -9<=k<=9, -18<=l<=18
Reflections collected / unique 21092 / 4378 [R(int) = 0.0660]
Completeness to theta = 67.684 99.2 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.00000 and 0.68390
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 4378 / 55 / 317
Goodness-of-fit on F^2 1.037
Final R indices [I>2sigma(I)] R1 = 0.0640, wR2 = 0.1693
R indices (all data) R1 = 0.0655, wR2 = 0.1718
Absolute structure parameter 0.05(2)
Extinction coefficient 0.0068(12)
Largest diff. peak and hole 0.999 and -0.312 e.A^-3

E.1.5 References

1) Ōmura, S.; Hirano, A.; Iwai, Y.; Masuma, R. *J. Antibiot.* **1979**, *32*, 786.
2) Enomoto, Y.; Shiomi, K.; Hayashi, M.; Masuma, R.; Kawakubo, T.; Tomosawa, K.; Iwai, Y.; Ōmura, S. *J. Antibiot.* **1996**, *49*, 50.
3) Chiba, T.; Asami, Y.; Suga, T.; Watanabe, Y.; Nagai, T.; Momose, F.; Nonaka, K.; Iwatsuki, M.; Yamada, H.; Ōmura, S.; Shiomi, K. *Biosci., Biotechnol., Biochem.* **2017**, *81*, 59.
4) Furusaki, A.; Matsumoto, T.; Ogura, H.; Takayanagi, H.; Hirano, A.; Ōmura, S. *J. Chem. Soc., Chem. Commun.* **1980**, 698.
5) Cox, J. B.; Kimishima, A.; Wood, J. L. *J. Am. Chem. Soc.* **2019**, *141*, 25.
6) Yu, X.; Liu, F.; Zou, Y.; Tang, M.-C.; Hang, L.; Houk, K. N.; Tang, Y. *J. Am. Chem. Soc.* **2016**, *138*, 13529.
7) (a) Belin, P.; Le Du, M. H.; Fielding, A.; Lequin, O.; Jacquet, M.; Charbonnier, J.-B.; Lecoq, A.; Thai, R.; Courcon, M.; Masson, C.; ¸Dugave, C.; Genet, R.; Pernodet, J.-L.;

Gondry, M. *Proc. Natl. Acad. Sci.* U. S. A. **2009**, *106*, 7426. (b) Fonvielle, M.; Le Du, M. H.; Lequin, O.; Lecoq, A.; Jacquet, M.; Thai, R.; Dubois, S.; Grach, G.; Gondry, M.; Belin, P. *J. Biol. Chem.* **2013**, *288*, 17347. (c) Dornevil, K.; Davis, I.; Fielding, A. J.; Terrell, J. R.; Ma, L.; Liu, A. *J. Biol. Chem.* **2017**, *292*, 13645.

8) For studies toward the herquline alkaloids see: (a) Kim, G. T. Ph.D. Thesis, Korea Advanced Institute of Science and Technology, November 1997. (b) Kawai, N.; Atsumi, T.; Arai, N.; Kuwajima, I. *Nippon Kagakkai, Koen Yokushu* **2003**, *83*,777. (c) Hart, J. M. Ph.D. Thesis, University of Leeds, June 2004. (d) Stawski, P. S. Ph.D. Thesis, Ludwigs-Maximilians-Universität München, December 2012. (e) Yang, H. Ph.D. Thesis, University of Birmingham, August 2015.

9) He, C.; Stratton, T. P.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 29.

10) Cochrane, J. R.; White, J. M.; Wille, U.; Hutton, C. A. *Org. Lett.* **2012**, *14*, 2402.

11) (a) Birch, A.J., Nadamuni, G. *J. Chem. Soc. Perkin Trans. 1*, **1974**, 545; (b) Lindow, D.F., Cortez, C.N., Harvey, R.G. *J. Am. Chem. Soc.* **1972**, *94*, 5406.

12) Zhu, X.; McAtee, C. C.; Schindler, C. S. *Org. Lett.* **2018**, *20*, 2862.

13) Dryden, H. I., JR; Webber, G. M.; Burtner, R. R.; Cella, J. A. *J. Org. Chem.* **1961**, *26*, 3237.

14) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1.

15) Quideau, S.; Pouysegu, L.; Avellan, A.-V.; Whelligan, D. K.; Looney, M. A. *Tetrahedron Lett.* **2001**, *42*, 7393.

16) Zhu, X.; McAtee, C. C.; Schindler, C. S. *J. Am. Chem. Soc.* **2019**, *141*, 3409.

17) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235.

18) Okano, K.; Okuyama, K.-i.; Fukuyama, T.; Tokuyama, H. *Synlett* **2008**, *2008*, 1977.

19) Doty, B. J.; Morrow, G. W. *Tetrahedron Lett.* **1990**, *31*, 6125.

20) (a) Takeuchi, S.; Miyoshi, N.; Ohgo, Y. *Chem. Lett.* **1992**, 551. (b) Takeuchi, S.; Ohira, A.; Miyoshi, N.; Mashio, H.; Ohgo, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1763.

21) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron* **1999**, *55*, 4595.

22) Kern, N.; Plesniak, M. P.; McDouall, J. J. W.; Procter, D. *J. Nat. Chem.* **2017**, *9*, 1198.

23) Volkov, A.; Tinnis, F.; Slagbrand, T.; Trillo, P.; Adolfsson, H. *Chem. Soc. Rev.* **2016**, *45*, 6685.

24) Bannister, R. M.; Brookes, M. H.; Evans, G. R.; Katz R. B.; Tyrrell, N. D. *Org. Process Res. Dev*, **2000**, *4*, 467.

25) Simmons, B. J.; Hoffmann, M.; Hwang, J.; Jackl, M. K.; Garg, N. K. *Org. Lett.* **2017**, *19*, 1910.

26) Das, S.; Li, Y.; Lu, L.-Q.; Junge, K.; Beller, M. *Chem. – Eur. J.* **2016**, *22*, 7050.

27) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9507.

28) Sen, A.; Lai, T. W. *Inorg. Chem.* **1984**, *23*, 3257.

29) (a) Rickborn, B. Acid-catalyzed Rearrangements of Epoxides. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; pp 733−775. (b) Wang, Z. Meinwald Rearrangement. *Comprehensive Organic Name Reactions and Reagents*; Wiley: Hoboken, NJ, 2010; pp 1880−1882.

30) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

31) Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011** , *76*, 7842.

32) Pellissier, H.; Santelli, M. *Org. Prep. Proced. Intern.* **2002**, *34*, 609, 611.

33) Fujita, E.; Shibuya, M.; Nakamura, S.; Okada, Y.; Fujita, T. *J. Chem. Soc. Perkin 1* **1974**, 165.

34) Cotsaris, E.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1982**, 1206.