**Formation of Derivatized Benzocyclobutenes and Bicyclic Ureas *via* Palladium-Catalyzed Alkene Difunctionalization**

by

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## Dedication

To my family and friends – thank you for all your support!

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## Table of Contents

Dedication ..... ii

Acknowledgements ..... iii

List of Tables ..... xv

List of Schemes ..... xvi

List of Abbreviations ..... xx

Abstract ..... xxv

Chapter 1 Syntheses and Utility of Benzocyclobutenes ..... 1

1.1 Notable Syntheses of Benzocyclobutenes ..... 1

1.2 Metal-Mediated Formation of Benzocyclobutenes ..... 6

1.3 Utility of Benzocyclobutenes ..... 19

1.4 Benzocyclobutenes and [4+2] Cycloadditions ..... 22

1.5 Works Cited ..... 29

Chapter 2 Formation of Benzocyclobutenes *via* Palladium-Catalyzed Alkene Difunctionalization ..... 33

2.1 Prior Palladium-Catalyzed Alkene Difunctionalizations ..... 33

2.2 Starting Material Syntheses ..... 34

2.3 Reaction Optimization ..... 35

2.4 Substrate Scope ..... 38

2.5 Proposed BCB Formation Mechanism ..... 40

2.6 Experimental Section ..... 42

2.7 Works Cited ..... 51

Chapter 3 Syntheses and Utility of Bicyclic Ureas.....53

3.1 Miscellaneous Syntheses of Cyclic Ureas.....53

3.2 Accessing Cyclic Ureas Through Palladium-Catalyzed Carboamination.....61

3.3 Utility and Significant Syntheses of Bicyclic Ureas.....69

3.4 Intramolecular Palladium-Catalyzed Carboamination: A Potential Route to Access Bicyclic Ureas.....79

3.5 Works Cited.....82

Chapter 4 Formation of Bicyclic Ureas *via* Intramolecular Palladium-Catalyzed Alkene Difunctionalization.....85

4.1 Synthesis of Phenyl Ureas.....85

4.2 Reaction Optimization for Indolinyl Bicyclic Ureas.....85

4.3 Synthesis of Benzyl Ureas.....90

4.4 Reaction Optimization for Tetrahydroisoquinolinyl Bicyclic Ureas.....90

4.5 Proposed Mechanisms for Bicyclic Urea Formations.....93

4.6 Future Directions: Purification and Substrate Scope.....96

4.7 Experimental Section.....99

4.8 Works Cited.....104

## List of Tables

Table 1 Optimization of BCB formation.....35

Table 2 Substrate Scope .....38

Table 3 Ligand screen for indolinyl bicyclic ureas.....87

Table 4 Assorted screens for indolinyl bicyclic ureas. .....89

Table 5 Ligand Screen for Tetrahydroisoquinolinyl Bicyclic Ureas .....92

Table 6 Base, Palladium Source, and Solvent Screen for Tetrahydroisoquinolinyl Bicyclic Ureas .....93

## List of Schemes

Scheme 1 First described formation of a BCB derivative.[2] ..... 1

Scheme 2 Notable examples of BCB formation *via* [2+2] cycloaddition.[3-7] ..... 3

Scheme 3Examples of [2+2] cycloadditions forming naphtho[*b*]cyclobutanes.[8-10] ..... 4

Scheme 4 Parham cyclizations forming BCB drivatives.[13-15] ..... 5

Scheme 5 Additional BCB formation reactions.[17-20] ..... 6

Scheme 6 Substrate scope of BCB formation via cobalt catalysis and the cobalt-mediated trimerization of hexa-1,5-diyne.[21] ..... 7

Scheme 7 Mechanism for BCB formation proposed by Bergman.[21] ..... 8

Scheme 8 Substrate scope for biphenyl BCBs.[23] ..... 10

Scheme 9 BCB formation mechanism as proposed by Dyker.[23] ..... 11

Scheme 10 Baudoin's optimized BCB formation conditions and substrate scope examples.[25] ..... 12

Scheme 11 BCBs formed by analogues of Baudoin's C–H activation mechanism.[26-28] ..... 13

Scheme 12 Substrates formed by Sorensen's reaction.[29] ..... 14

Scheme 13 Mechanism for Sorensen's BCB formation reaction.[29] ..... 15

Scheme 14 Example of BCB formation *via* Suzuki-Miyaura coupling.[30] ..... 16

Scheme 15 Formation of BCBs from [2+2] annulation of norbornene.[32, 33] ..... 17

Scheme 16 Formation of BCBs from alkenes and arylboronic acids.[34, 35] ..... 18

Scheme 17 Formation of BCB/coumaran spirocycles.[36, 37] ..... 19

Scheme 18 BCB-containing natural products and drugs.[38-41] ..... 20

Scheme 19 Formation of BCB-containing amino acids.[42-44] ..... 21

Scheme 20 BCB-containing monomers and generic BCB homopolymerization pathway.[45, 46] ..... 21

Scheme 21 Heat-induced ring opening of benzocyclobutene to form *ortho*-quinodimethane.....22

Scheme 22 Cava's proposed mechanism and [4+2] cycloaddition with the proposed intermediate.[51, 52].....23

Scheme 23 Polycyclic amides formed from [4+2] cycloadditions.[53].....24

Scheme 24 Various routes to estrone *via* BCB-facilitated [4+2] cycloadditions.[54-57].....25

Scheme 25 Additional steroid cores generated from BCBs.[58, 59].....26

Scheme 26 Formations of polycyclic fused-ring aromatic systems with BCBs.[60-63].....27

Scheme 27 Synthetic applications of BCB [4+2] cycloadditions.[15, 17, 64, 65].....28

Scheme 28 Top: prior studies. Bottom: current studies. .....34

Scheme 29 Syntheses of starting materials. .....34

Scheme 30 Nucleophile limitations. .....39

Scheme 31 Failed alkenes. .....40

Scheme 32 Proposed BCB formation mechanism. .....41

Scheme 33 Formation of cyclic ureas from diamines and phosgene.[2].....53

Scheme 34 Formation of cyclic ureas *via* palladium-catalyzed aminocarbonylation.[3] .....54

Scheme 35 Aminocarbonylation mechanism.[3] .....55

Scheme 36 *Gem*-dialkyl cyclic ureas formed *via* tungsten-mediated carbonylation.[4].....56

Scheme 37 Copper-catalyzed carbonylation to form ureas.[5].....56

Scheme 38 Cyclic ureas formed from TBAF-mediated 5-*exo*-dig cyclization.[6] .....57

Scheme 39 Proposed mechanism for TBAF-mediated 5-*exo*-dig cyclization.[6] .....57

Scheme 40 Cyclic ureas formed via cobalt-catalyzed HAT and radical-polar crossover.[7].....58

Scheme 41 Proposed mechanism for cobalt-catalyzed HAT and radical-polar crossover.[7] .....59

Scheme 42 Formation of a seven-membered cyclic urea *via* RCM.[8] .....60

Scheme 43 Cyclic ureas formed *via* copper catalysis.[9].....60

Scheme 44 Proposed mechanism for copper-catalyzed cyclic urea formation.[9].....61

Scheme 45 Imidazolidin-2-one formation reaction and selected substrates.[10].....62

Scheme 46 Proposed imidazolidin-2-one formation mechanism.[11] ..... 63

Scheme 47 Selected chiral imidazolidin-2-ones.[12] ..... 64

Scheme 48 Selected imidazolidin-2-ones with tethered amines.[13] ..... 65

Scheme 49 Mechanism for generating imidazolidin-2-ones through a Pd(II/IV) cycle.[14] ..... 66

Scheme 50 Palladium-catalyzed carboamination in the total synthesis of (+)-merobatzelladine.[15] ..... 67

Scheme 51 Selected substrates from the palladium-catalyzed formation of bicyclic ureas with alkenyl and aryl substituents.[16] ..... 67

Scheme 52 Selected substrates from additional hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones generated *via* palladium-catalyzed carboamination.[17] ..... 68

Scheme 53 Generic 1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-ones and 1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3(2*H*)-ones and applications of similar ring systems.[18, 25] .69

Scheme 54: Muñiz's formation of bicyclic ureas from palladium-catalyzed diamination.[26] ..... 70

Scheme 55 Proposed mechanism for palladium-catalyzed alkene diamination.[27] ..... 71

Scheme 56 Bicyclic ureas formed from bis(pyridine)iodonium tetrafluoroborate.[28] ..... 72

Scheme 57 Selected bicyclic ureas with ester substituents.[29] ..... 72

Scheme 58 Bicyclic ureas formed via gold(I/III) catalysis.[30] ..... 73

Scheme 59 Selected indolinyl ureas formed by gold(I) catalysis.[31] ..... 74

Scheme 60 Zhang's proposed mechanism for bicyclic urea formation.[31] ..... 75

Scheme 61 Indolinyl bicyclic ureas formed by copper(II) diamination.[32] ..... 76

Scheme 62 Chemler's proposed bicyclic urea formation mechanism.[32] ..... 77

Scheme 63 Bicyclic ureas formed *via* palladium catalysis and microwave irradiation.[33] ..... 78

Scheme 64 Indolinyl bicyclic ureas formed by iodonium-facilitated diamination.[34] ..... 78

Scheme 65 Selectivity study for the first palladium-catalyzed intramolecular carboamination.[35] 80

Scheme 66 Tropanes produced via intramolecular palladium-catalyzed carboamination.[36] ..... 80

Scheme 67 Tetrahydroindoloisoquinolines formed *via* intramolecular palladium-catalyzed carboamination.[37] ..... 81

Scheme 68 Synthesis of phenyl urea **4-5**.....85

Scheme 69 Generic proposed route to indolinyl bicyclic ureas with target bonds highlighted in red.....86

Scheme 70 Potential starting material decomposition pathway. .....88

Scheme 71 Synthesis of benzyl urea **4-16**.....90

Scheme 72 Generic proposed route to tetrahydroisoquinolinyl bicyclic ureas with target bonds highlighted in red. .....91

Scheme 73 Proposed mechanism for indolinyl bicyclic urea formation.....94

Scheme 74 Proposed mechanism for tetrahydroisoquinolinyl bicyclic urea formation. .....95

Scheme 75 Potential routes to functionalized bicyclic ureas. .....98

Scheme 76 Potential future substrates accessible through intramolecular palladium-catalyzed alkene difunctionalization. .....99

## List of Abbreviations

α.....alpha

acac.....acetylacetone

aq.....aqueous

Ar.....aryl (when bound to another atom)

Au……gold

β.....beta

Bn.....benzyl

Boc.....*tert*-butyloxycarbonyl

br.....broad

Bz.....benzo

$C_6D_6$……deuterated benzene

calcd.....calculated

$CDCl_3$……deuterated chloroform

CN.....cyano

Cp.....cyclopentadienyl

Cu……copper

Cy.....cyclohexyl

°C.....degrees Celsius

d.....doublet

dba .....dibenzylideneacetone

DCM.....dichloromethane/methylene chloride

DCE……dichloroethane

dd.....doublet of doublets

ddd .....doublet of doublet of doublets

ddt .....doublet of doublet of triplets

DMF.....dimethylformamide

DMSO.....dimethylsulfoxide

Dppb.....……..……...1,4-bis(diphenylphosphino)butane

DppBz…….…….…..1,2-bis(diphenylphosphino)benzene

dppf.....1,1'-bis(diphenylphosphino)ferrocene

dppm.....1,1-bis(diphenylphosphino)methane

dr.....diastereomeric ratio

EDG……..……..……...electron-donating group

ee……...enantiometric excess

equiv.....equivalents

eq.....equation

er.....enantiomeric ratio

ESI.....electrospray ionization

Et.....ethyl

Et2O……..……..……..diethyl ether

EtOH.....ethanol

EWG……..electron-withdrawing group

h/hr.....hour(s)

HRMS.....high resolution mass spectrometry

Hz……...hertz

IR.....infrared spectroscopy

LG……leaving group

LiHMDS/KHMDS.....lithium/potassium hexamethyldisilazide

J.....coupling constant

Ln/L.....general ligand

M.....molar (mol/L)

m.....multiplet

mCPBA.....*meta*-chloroperoxybenzoic acid

Me.....methyl

MeOH.....methanol

MHz……..……..megahertz

m.p.....melting point

MS.....molecular sieve

nBu……...butyl (straight chain)

NMR.....nuclear magnetic resonance

Nuc/Nuc-H.....nucleophile

OAc.....acetate

OMe.....methoxy

OtBu.....*tert*-butoxide

OTf.....triflate

p.....*para*

Pd.....palladium

pent.....pentet

PG/P.....protecting group

Ph.....phenyl

$PhCF_3$……trifluorotoluene

PMP……*para*-methoxyphenyl

prep TLC.....preparative thin-layer chromatography

q.....quartet

R.....general functional group

rr……..regiomeric ratio

rbf.....round-bottom flask

rt.....room temperature

s.....singlet

satd.....saturated

t.....triplet

TEA……..triethylamine

t-butyl/tBu.....*tert*-butyl

Tf.....triflyl

TFA.....trifluoroacetic acid

$Tf_2O$.....triflic anhydride

THF.....tetrahydrofuran

TLC.....thin-layer chromatography

TMS.....trimethylsilyl

Tol-$d^8$……..……..……deuterated toluene

Tolyl…….toluene (when bound to another atom)

Ts.....tosyl

T.S.....transition state

X.....general halide, counterion, or atom

Y.....general heteroatom/functional group

Z.....general atom or substitution

## Abstract

Palladium-catalyzed alkene difunctionalization offers an efficient and facile way to access a vast array of significant structural scaffolds. This thesis will focus on the development and optimization of palladium-mediated reactions to form benzocyclobutenes (BCBs) and bicyclic ureas. In both cases, these represent some of the mildest approaches to access these structures.

The first chapter of this thesis will provide a summary of the synthetic significance of BCBs, especially in terms of their utility in the context of Diels-Alder reactions. Synthetic strategies for the generation of BCBs will also be examined in detail. Additionally, this chapter will explore the challenges associated with forming this significantly strained fused-ring system. Chapter 2 will describe the process of developing a palladium-catalyzed alkene difunctionalization reactions to form BCBs from *ortho*-triflyl styrenes as well as the potential challenges associated with this transformation. Furthermore, the proposed mechanism of this reaction, the optimization process, and the scope of this reaction will be described in detail.

The third chapter will examine the medicinal uses and commonly encountered synthetic pathways for bicyclic ureas, specifically involving 1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-ones and 1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3(2*H*)-ones. Chapter 4 will then describe preliminary results pertaining to the formation of these ring systems by way of an intramolecular palladium-catalyzed carboamination reaction. This chapter will also explore the

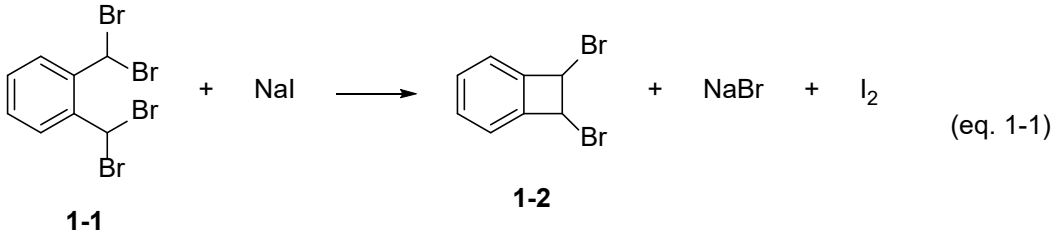
differing conditions required to form these ring systems and the mechanistic factors which possibly inform these differences.

## Chapter 1 Syntheses and Utility of Benzocyclobutenes

Benzocyclobutenes, or BCBs, are highly strained fused-ring system which have acted as a compelling synthetic target for many years. The longstanding interest in producing BCBs pertains to the challenges inherent to producing a ring system with such profound ring strain.[1] This chapter will provide a detailed examination of how BCBs have been previously synthesized and the ways in which BCBs have been utilized both in the context of organic synthesis and beyond.

### 1.1 Notable Syntheses of Benzocyclobutenes

The earliest example of the synthesis of a BCB derivative is a reaction described by Hans Finkelstein in 1910. He treated 1,2-bis(dibromomethyl)benzene (**1-1**) with two equivalents of sodium iodide in order to form dibromobenzocyclobutene (**1-2**) along with sodium bromide and elemental iodine as byproducts.[2] Since that time, more sophisticated and robust methods for the formation of derivatized BCBs have been developed, and prominent examples are described below.

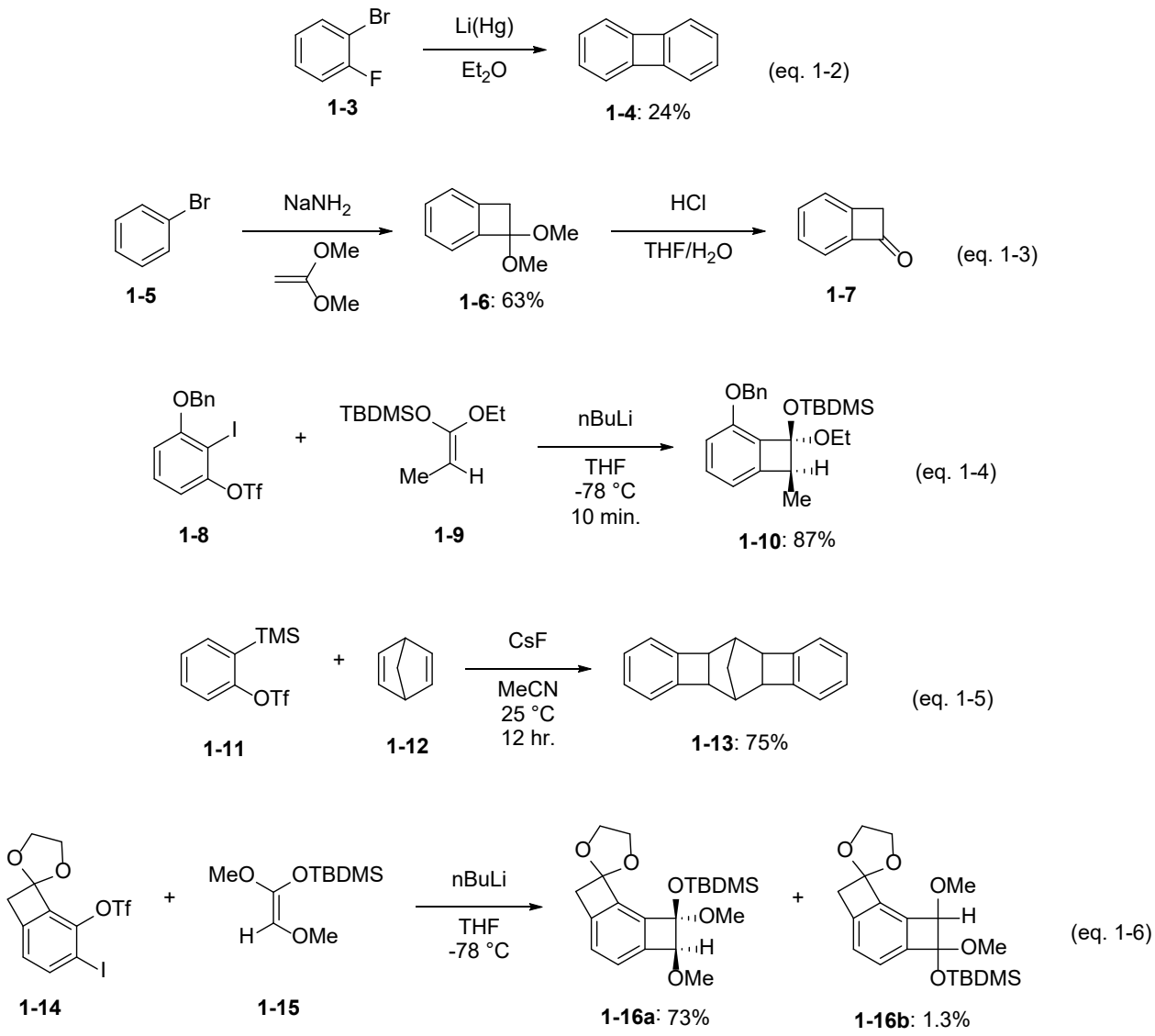



**1-1** **1-2**

Scheme 1 First described formation of a BCB derivative.[2]

One of the most frequently encountered reactions for forming BCBs is the [2+2] cycloaddition. An early example of [2+2] cycloadditions generating BCB derivatives was the

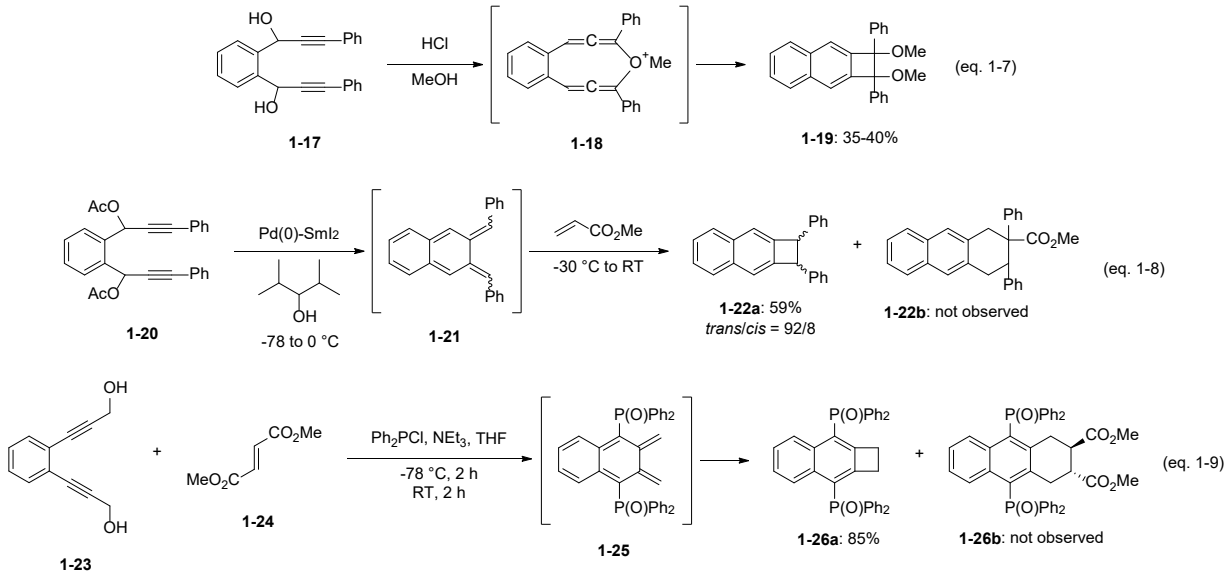
dimerization of benzyne to form biphenylene (**1-4**) as observed by Georg Wittig (eq. 1-2).[3] Since that time, numerous other reactions have found milder ways of generating the benzyne intermediate and more controlled ways of reacting it upon its formation, including regioselective and stereospecific reactions. One notable example includes reacting benzyne with a dimethoxyalkene in order to form a BCB ketal (**1-6**); this ketal is subjected to acidic conditions in order to form benzocyclobutenone **1-7**.[4] Similarly, benzynes with alkoxy groups (formed from trisubstituted benzenes like **1-8**) react with silyl alkenes like **1-9** to form highly substituted BCBs (**1-10**). The alkoxy group on the benzyne and the silyl group on the alkene work in tandem to drive regio- and stereoselectivity.[5] Benzynes have also undergone [2+2] cycloadditions with norbornenes to form norborenyl cores fused with two BCBs (eq. 1-5).[6] Further innovations have consisted of leveraging cyclobutenyl rings as a directing group for the formation of other fused cyclobutenyl rings on the same core aryl ring (eq. 1-6).[7]




Scheme 2 Notable examples of BCB formation *via* [2+2] cycloaddition.[3-7]

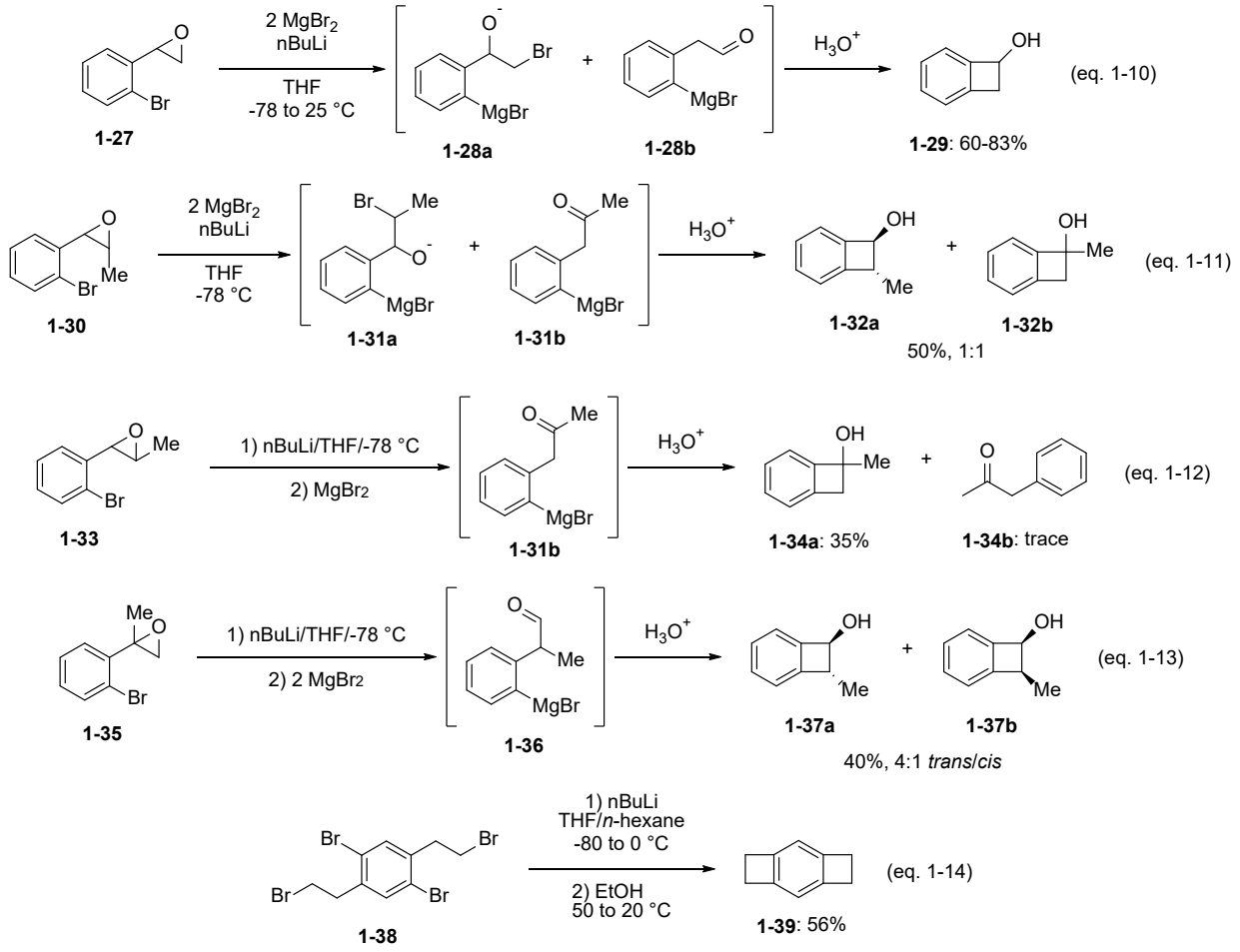
Furthermore, [2+2] cycloadditions have been leveraged in an intramolecular fashion to form other BCB-type moieties. One of the earliest recorded examples of generating BCBs in this way involved subjecting an *ortho*-dialkynylbenzene to acidic conditions in order to form a naphtho[*b*]cyclobutene in moderate yield (eq. 1-7).[8] Further developments on this reaction have included reducing *ortho*-dialkynylbenzenes with palladium(0)-samarium(II) iodide in order to produce *ortho*-naphthoquinodimethanes *in situ*. While these were prepared with the goal of acting as dienes in [4+2] cycloadditions, the diphenyl *ortho*-dialkynylbenzene spontaneously

formed the [2+2] cycloaddition product without reacting with a dienophile (eq. 1-8).[9] Similar effects have been observed with dialkylchlorophosphines; these can be used to form diphosphinyl *ortho*-naphthoquinodimethanes which undergo intramolecular [2+2] cycloadditions, even in the presence of a dienophile (eq. 1-9).[10]



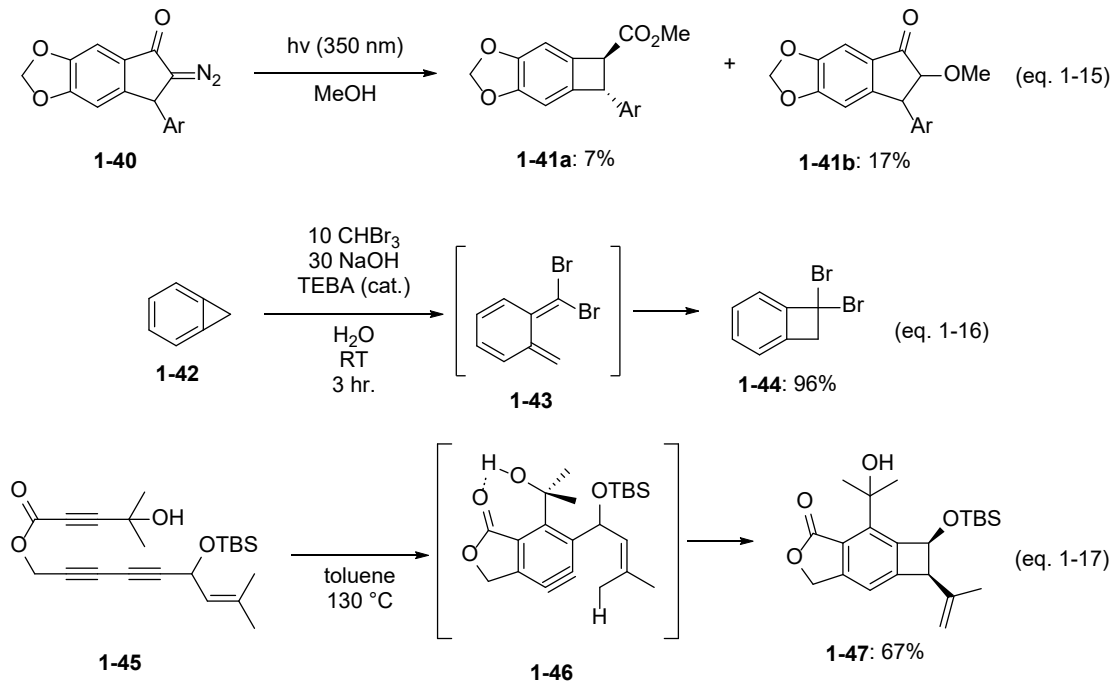

Scheme 3Examples of [2+2] cycloadditions forming naphtho[*b*]cyclobutanes.[8-10]

Another way to access BCBs is through a lithium-halogen exchange on a phenyl halide followed by an intramolecular nucleophilic attack at an electrophilic site *ortho* to the phenyllithium bond, often referred to as a Parham cyclization.[11, 12] This strategy was first leveraged by Tony Durst to form benzocyclobutenols in 1980 (eq. 1-10).[13] Soon thereafter, he did a comprehensive mechanistic study of this reaction and how different substituents drive regioselectivity. He found that regioselectivity in the case of epoxide electrophiles was dictated by whether they favored a direct ring opening mechanism or a rearrangement to an aldehyde or ketone prior to ring closing (eqs. 1-11, 1-12, 1-13).[14] This method has seen continued use in the context of total synthetic and process chemistry (eq. 1-14).[15, 16]




Scheme 4 Parham cyclizations forming BCB drivatives.[13-15]

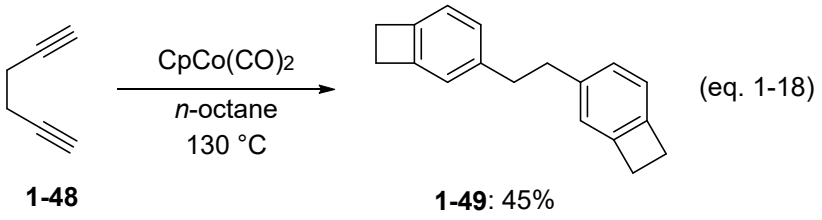
There are myriad other reactions which form BCBs that do not fit into the previously discussed reaction categories. For instance, Michael E. Jung reports forming a target BCB for a larger total synthesis by way of a Wolff rearrangement, albeit in modest yield (eq. 1-15).[17] Another notable strategy for accessing BCBs is reacting benzocyclopropenes with dihalocarbenes to generate dihalobenzocyclobutenes in high yield (eq. 1-16).[18, 19] Alder-ene type reactions of triynes have also been leveraged in order to generate highly substituted BCBs by leveraging steric strain as a driving force for accessing the strained cyclobutenyl ring (eq. 1-17).[20]

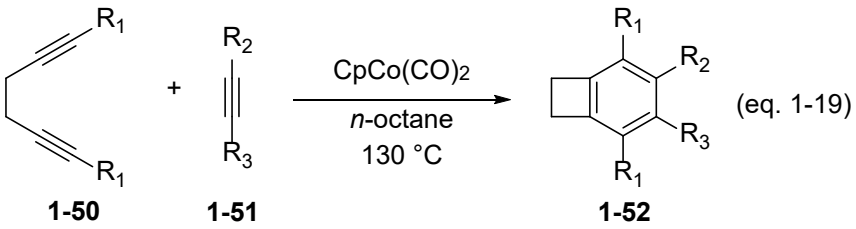



Scheme 5 Additional BCB formation reactions.[17-20]

## 1.2 Metal-Mediated Formation of Benzocyclobutenes

Another critical set of strategies for accessing BCBs involve transition metal catalysis. Among the earliest examples of this is using $\eta^5$-cyclopentadienylcobalt dicarbonyl to produce BCBs from trimerization of a diyne (eq. 1-18) or by combining a diyne with another alkyne (eq. 1-19). Generally, the yields for this transformation are relatively low. The reaction proves especially vulnerable to steric limitations; no product formed when oct-1-yne was reacted with hexa-1,5-diyne, and the only example of reacting a substituted diyne also failed to produce the expected product. Interestingly, two of the highest-yielding reactions were the cobalt-mediated trimerization of hexa-1,5-diyne to form two tethered BCBs and the reaction between hexa-1,5-diyne and diphenylacetylene.[21] In spite of the modest yields, this reaction has seen continued usage in the production of BCBs.[22]



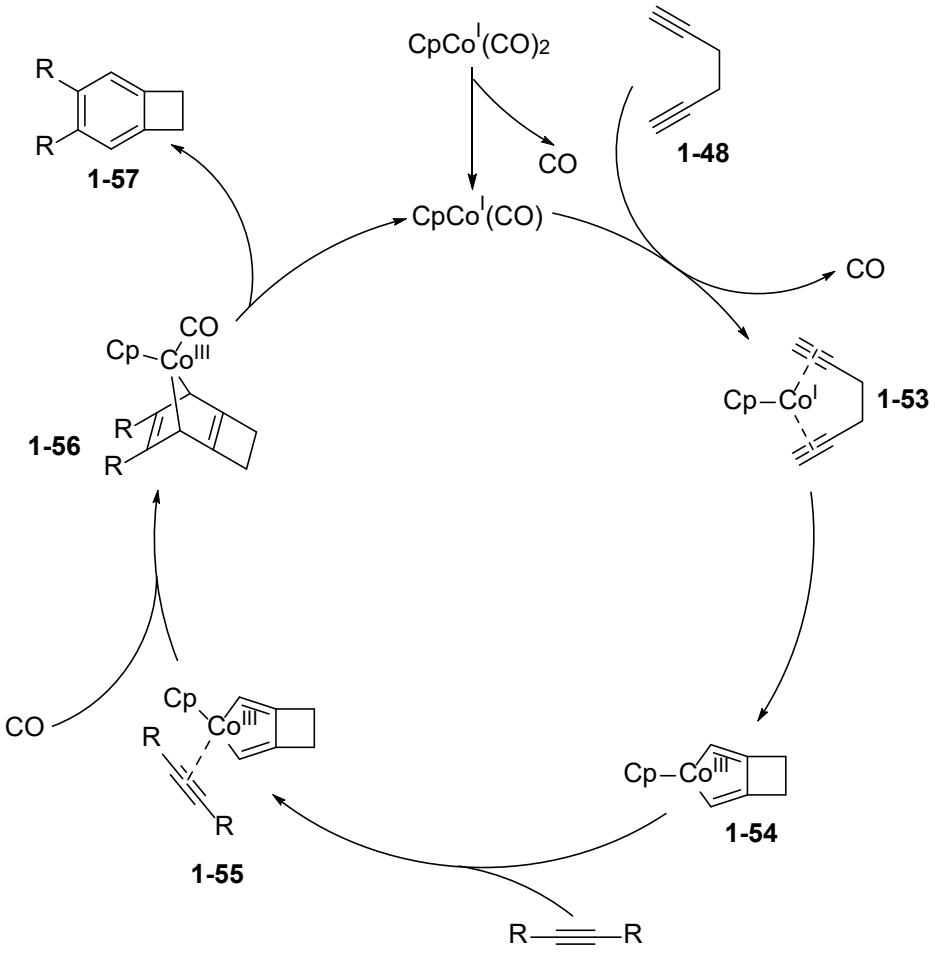




| entry | reactants | % yield |
|---|---|---|
| 1 | $R_1$=H, $R_2$=H, $R_3$=nHex | 0 |
| 2 | $R_1$=H, $R_2$=$R_3$=Ph | 48 |
| 3 | $R_1$=H, $R_2$=$R_3$=$CO_2Me$ | 14 |
| 4 | $R_1$=H, $R_2$=H, $R_3$=Ph | 17 |
| 5 | $R_1$=H, $R_2$=H, $R_3$=$CH_2OH$ | 14 |
| 6 | $R_1$=Me, $R_2$=$R_3$=$CO_2Me$ | 0 |

Scheme 6 Substrate scope of BCB formation via cobalt catalysis and the cobalt-mediated trimerization of hexa-1,5-diyne.[21]

The mechanism for this transformation begins with $\eta^5$-cyclopentadienylcobalt dicarbonyl losing one of its carbonyl ligands, generating the active catalyst for this reaction and opening a binding site for the diyne (**1-48**). The second carbonyl ligand is displaced by the diyne, resulting in the cobalt(I) atom being coordinated to both alkyne bonds in the diyne (**1-53**). Then, the cobalt undergoes oxidative addition to form a cobalt(III) metallocycle which contains the target four-membered ring (**1-54**). The alkyne subsequently bonds with an available bonding site on the cobalt atom, leading to a migratory insertion which forms the six-membered ring which will become the benzyl component of the BCB. This is also the point at which a carbon monoxide

molecule bonds with the cobalt(III) atom to fill in all of the available bonding sites (**1-56**). The final step is a reductive elimination which forms the desired BCB (**1-57**) and regenerates the cobalt catalyst (Scheme 7).[21]

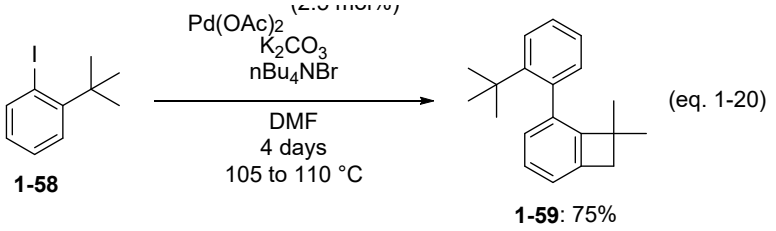


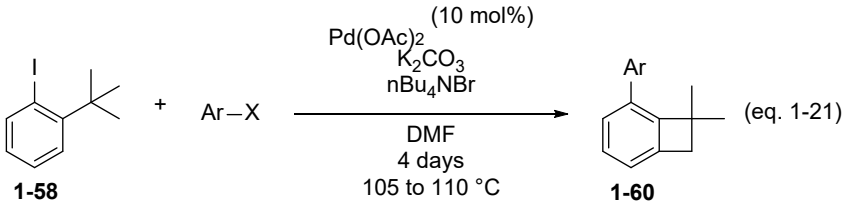

Scheme 7 Mechanism for BCB formation proposed by Bergman.[21]

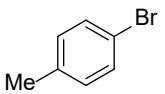
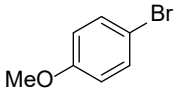
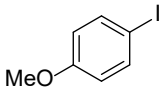
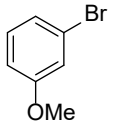
Compared to other transition metals, palladium has been among the most extensively utilized in the synthesis of BCBs. In a broad sense, this is generally accomplished by some form of C–H functionalization. Among the earliest examples of BCB formation *via* C–H functionalization was published in 1994 by Gerald Dyker. His work involves reacting *ortho*-iodo-*tert*-butylbenzene with assorted aryl halides to form biphenyl BCBs. Notably, this reaction

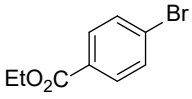
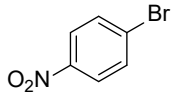
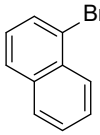
also represents one of the first examples of palladium performing C–H functionalization at an $sp^3$ hybridized carbon.

However, the scope of this reaction is relatively limited. The substrates with the highest yields were aryl bromides with activating groups *para* to the bromine atom. In contrast, aryl bromides with *meta* or *ortho* substituents or with *para* deactivating groups produced the respective biphenyl BCB in diminished yields. Additionally, the author explained that the 0% yields for substrates 3 and 5 are accounted for by a competing palladium-catalyzed Ullmann reaction.



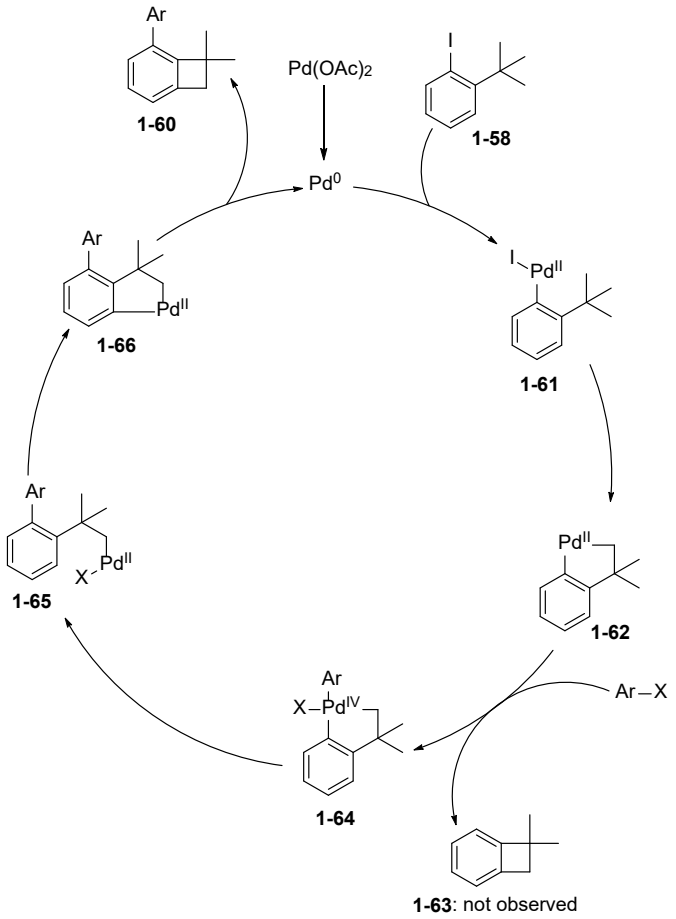

| entry | aryl halide | % yield |
|---|---|---|
| 1 |  | 56 |
| 2 |  | 59 |
| 3 |  | 0 |
| 4 |  | 37 |

| entry | aryl halide | % yield |
|---|---|---|
| 5 |  | 0 |
| 6 |  | 0 |
| 7 |  | 11 |

Scheme 8 Substrate scope for biphenyl BCBs.[23]

The mechanism for this transformation begins with palladium(0) performing an oxidative addition into the aryl iodine bond (**1-61**). This is followed by C–H activation at the *ortho tert*-butyl group (**1-62**). It is worth noting that a reductive elimination at this stage would form dimethylbenzocyclobutene (**1-63**), but this product is not observed; Dyker posits that this is because steric bulk is required to facilitate the strained reductive elimination. Instead of this pathway, the five-membered palladacycle undergoes a second oxidative addition with another aryl halide to form a palladium(IV) intermediate (**1-64**). A reductive elimination generates the

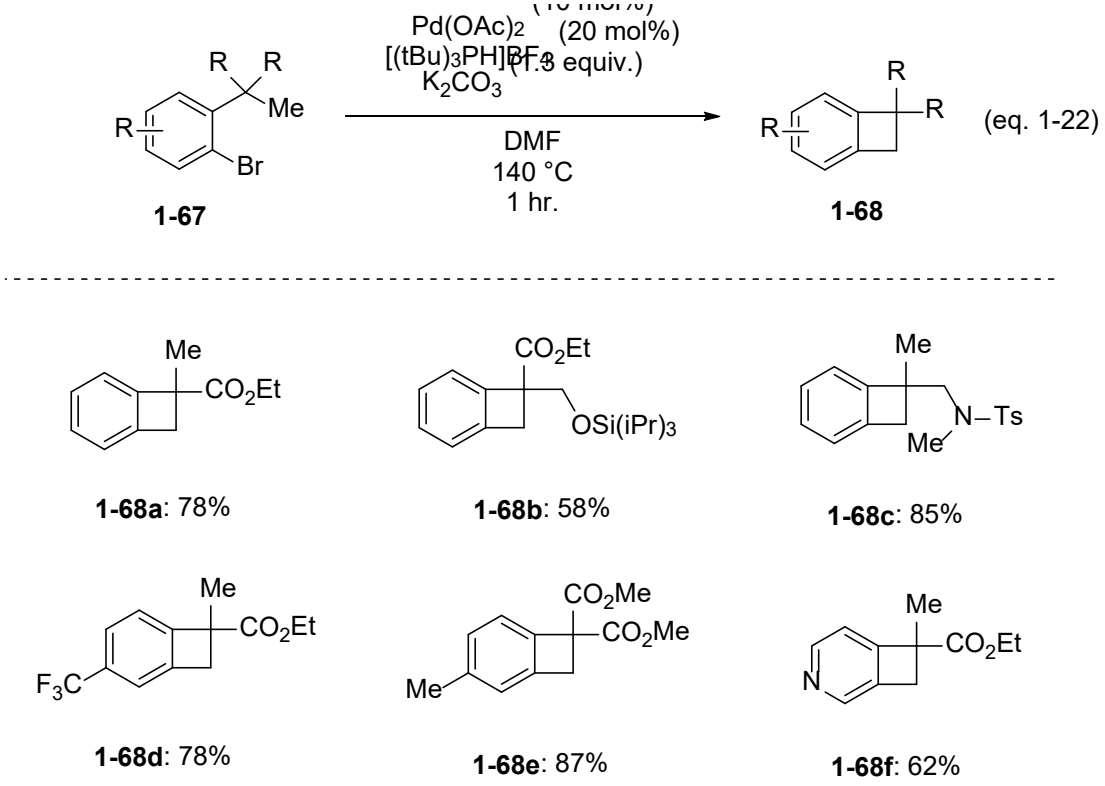
biphenyl bond (**1-65**), and this is followed by a second C–H activation *ortho* to the *tert*-butyl group to which the palladium is bonded (**1-66**). With the biphenyl group having been installed, this provides the steric bulk required to facilitate the strained reductive elimination to form the final BCB product (**1-60**).[23]




Scheme 9 BCB formation mechanism as proposed by Dyker.[23]

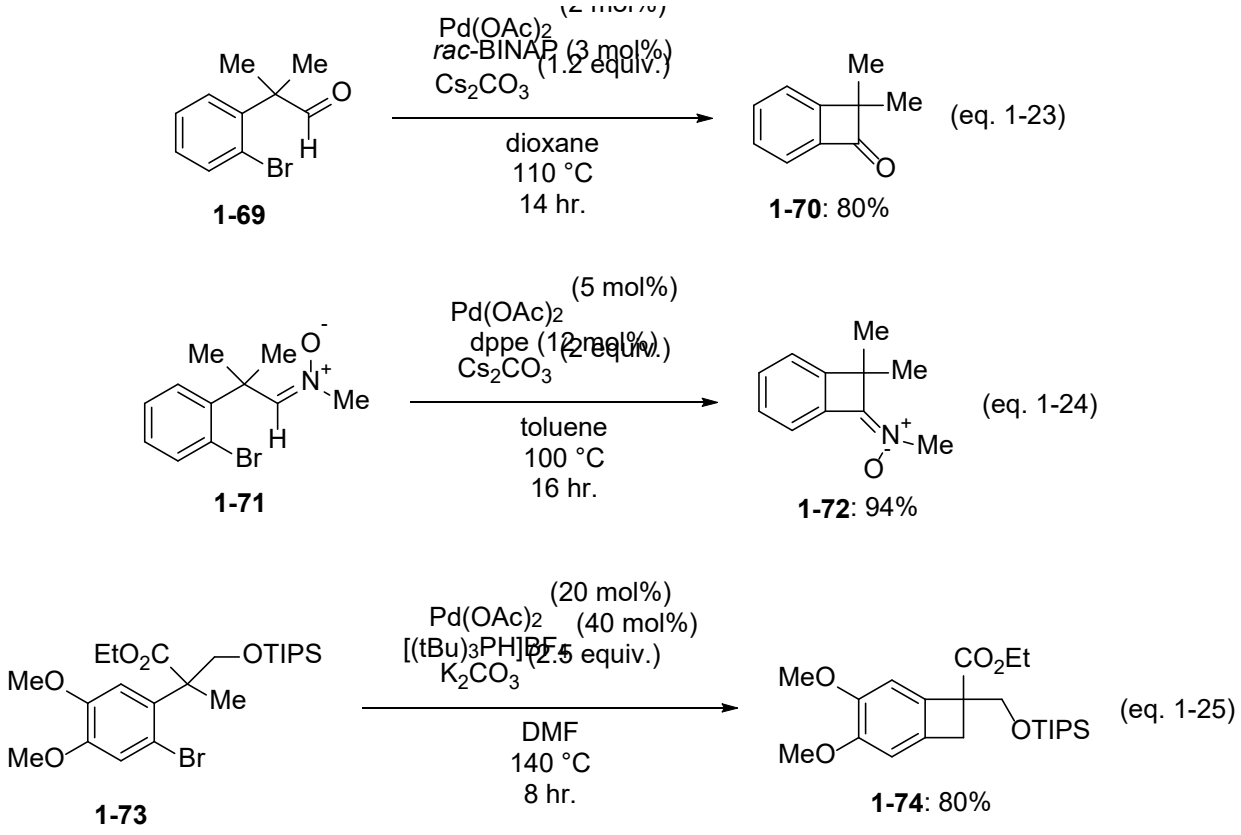
A major expansion in the scope of this method for BCB formation was reported by Olivier Baudoin, who was probing the reactivity of phenyl halides with a benzylic *gem*-diethyl group in the *ortho* position. More specifically, he optimized conditions for the formation of an external alkene on one of the benzylic ethyl groups by way of a C–H activation followed by a *β*-hydride elimination. When he applied these conditions to *gem*-dimethyl substrates which were incapable of this olefination, he found that this produced BCBs in good yields without needing to

leverage the steric bulk of a biphenyl group.[24] Subsequently, he discovered optimized conditions for the formation of BCBs, further expanding the scope of this reaction and improving the yields of the BCB products (eq. 1-22).[25]



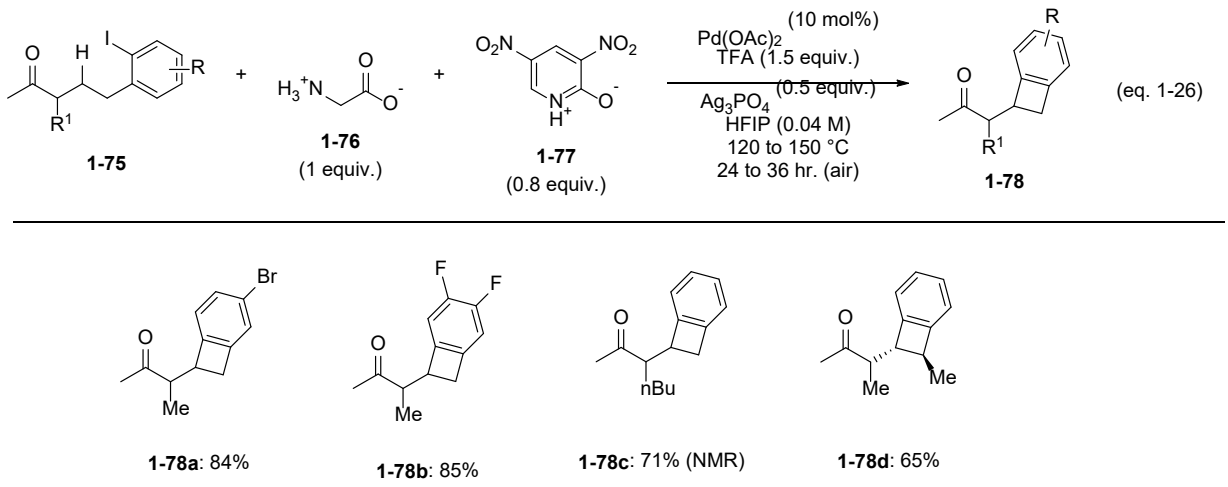

Scheme 10 Baudoin's optimized BCB formation conditions and substrate scope examples.[25]

This approach to generating BCB derivatives has since been leveraged to tolerate a wide array of different functionalities. One example of this is the conversion of aldehydes to benzocyclobutenones using racemic BINAP as a ligand (eq. 1-23). The authors of this study propose that this transformation takes place through C–H activation of the aldehyde hydrogen.[26] Another similar reaction consists of forming assorted benzocyclobutenyl ketonitrones with dppe as the optimal ligand (eq. 1-24).[27] This particular method for BCB synthesis has also been used in the synthesis of natural products containing BCB cores (eq. 1-25).[28]



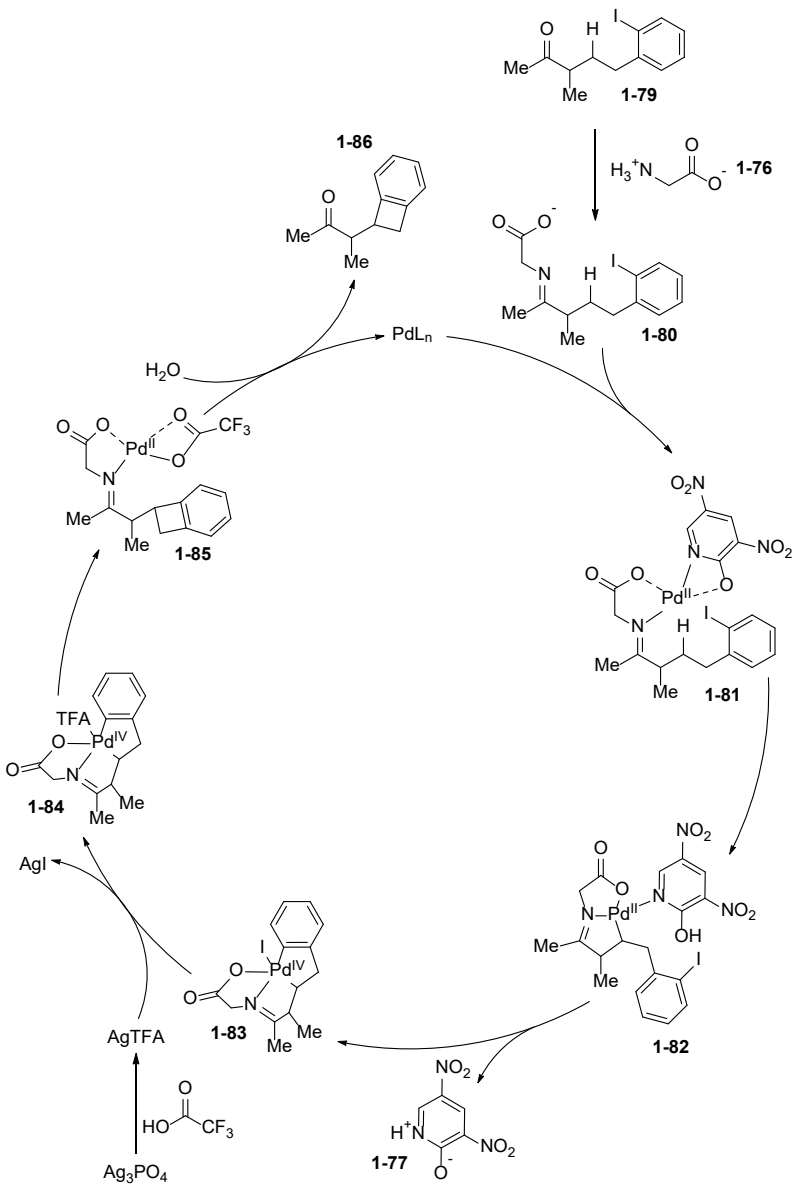

Scheme 11 BCBs formed by analogues of Baudoin's C–H activation mechanism.[26-28]

Despite the diverse collection of BCBs this method can produce, it comes with one major limitation. Namely, the benzylic carbon of any substrate must be a quaternary carbon. If this were not the case, the challenging and essential reductive elimination step to form the cyclobutenyl ring would be outcompeted by a facile *β*-hydride elimination to form a styrenyl alkene. However, a groundbreaking study by Erik J. Sorensen and his collaborators developed a reaction which forms BCBs in high yield without requiring a quaternary carbon in the benzylic position (eq. 1-26).




Scheme 12 Substrates formed by Sorensen's reaction.[29]

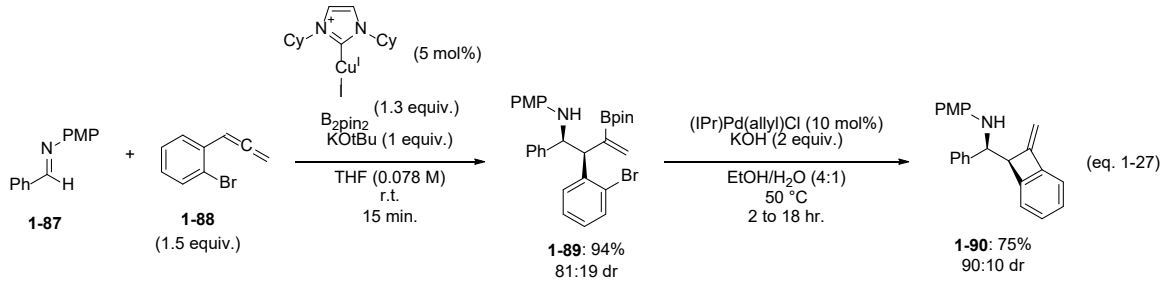
Two of the primary factors which allow this reaction to take place are the choice of ligand and the use of a transient directing group to ensure that the critical concerted metalation-deprotonation (CMD) step takes place at the correct hydrogen. This reaction begins with the installation of the transient directing group, and this is accomplished by reacting the starting ketone with glycine to form an imine (**1-80**). This imine then participates in a palladium(II) complex with the ligand (**1-81**). The imine and the ligand work together to place the palladium in the optimal position to undergo the target CMD step, forming a five-membered palladacycle (**1-82**). The palladium then oxidatively adds to the aryl-iodine bond and ejects the ligand, forming a palladium(IV) complex (**1-83**). Concurrently, silver phosphate is reacting with trifluoroacetic acid in the reaction mixture to form silver trifluoroacetate. The silver trifluoroacetate, in turn, performs a ligand exchange with the palladium atom to generate a new palladium-trifluoroacetate bond and silver iodide byproduct (**1-84**). The addition of the trifluoroacetate ligand is able to drive the formation of the cyclobutenyl ring *via* reductive elimination (**1-85**), and the transient directing group can be removed with an aqueous workup (**1-86**).[29]




Scheme 13 Mechanism for Sorensen's BCB formation reaction.[29]

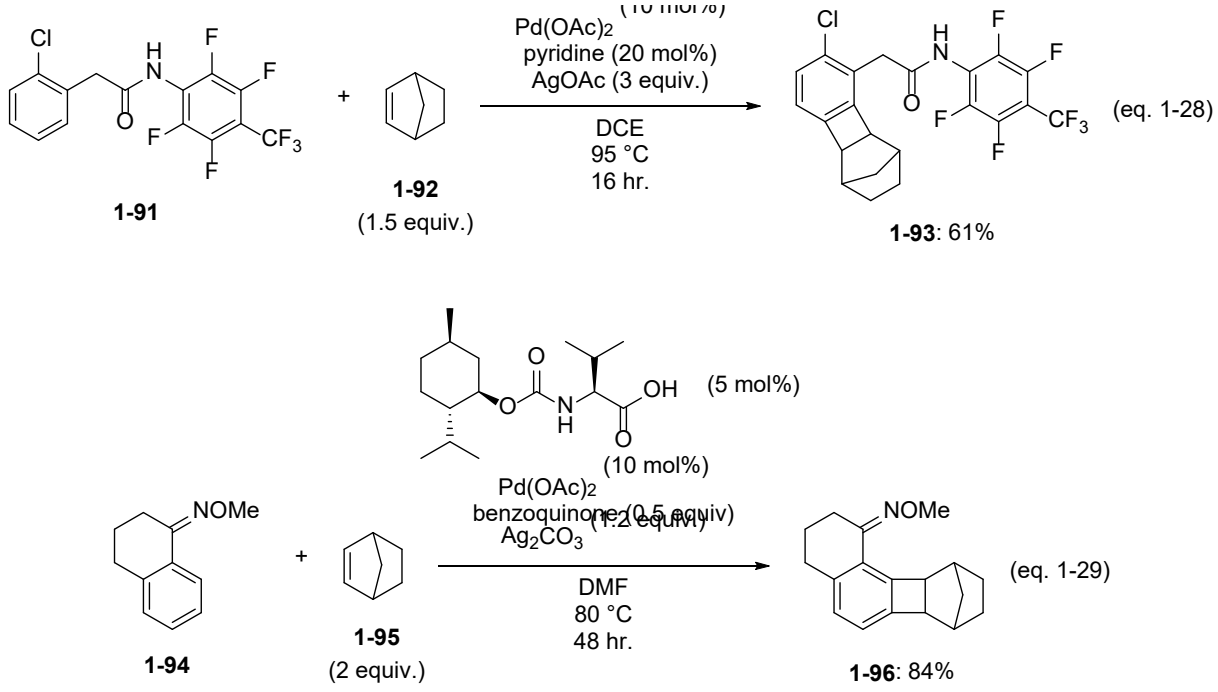
Another notable approach to generating BCBs is by way of a palladium-catalyzed Suzuki-Miyaura coupling. The starting material for this transformation is generated by a copper-mediated reaction between *N*-(4-methoxyphenyl)-1-phenylmethanimine (**1-87**), 1-(2-bromophenyl)allene (**1-88**), and bis(pinacolato)diboron to form the substrate primed for the subsequent Suzuki reaction (**1-89**). The optimal catalyst-ligand pairing for this reaction was a complex between allylpalladium(II) chloride and a diisopropyl imidazolium-derived carbene,

and potassium hydroxide was utilized as the base. This reaction is able to generate a wide range of derivatized BCBs in moderate to good yields and high diastereoselectivity (eq. 1-27).[30]



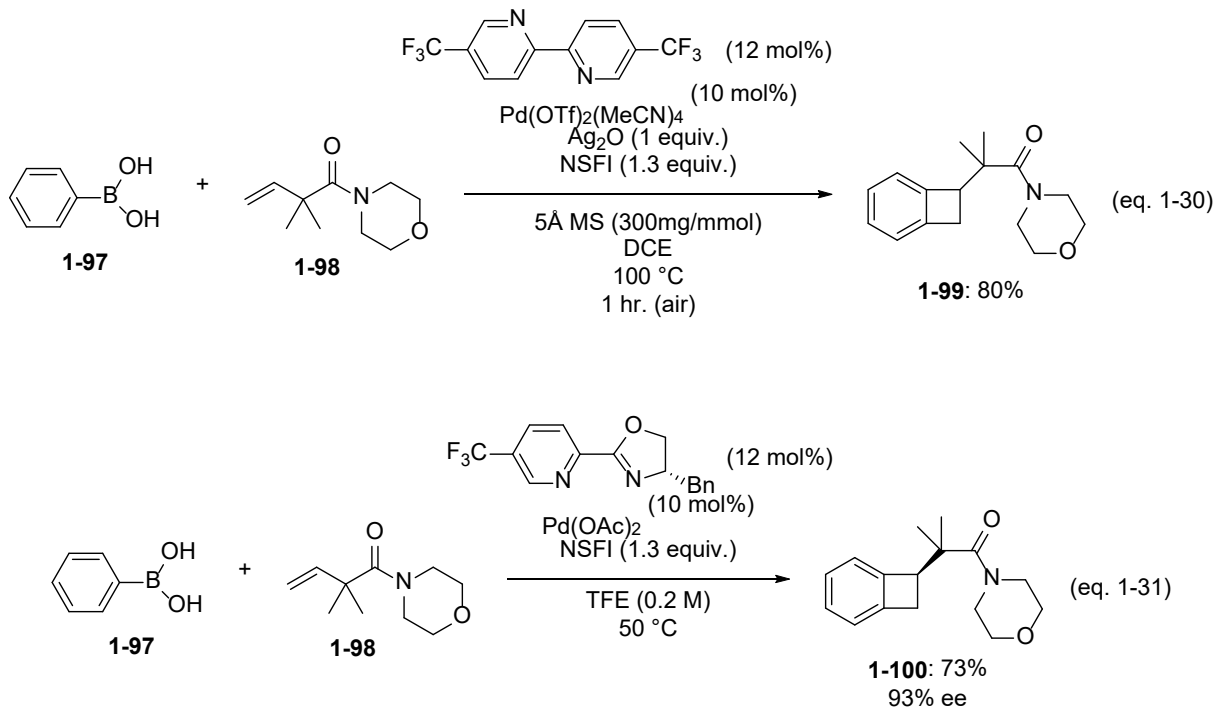

Scheme 14 Example of BCB formation *via* Suzuki-Miyaura coupling.[30]

One of the most prominent palladium-mediated pathways to access BCBs is through [2+2] annulations. This approach was initially developed as an extension of the reactivity observed in the Catellani reaction.[31] While Jin-Quan Yu and collaborators were developing a *meta*-directing analogue to the *ortho*-selective Catellani reaction, a ligand-free control experiment produced a BCB from the [2+2] annulation of an aryl species and norbornene in moderate yield (eq. 1-28).[32] Later, Yoshiji Takemoto and colleagues developed an optimized set of conditions for Yu's reaction. Their conditions utilized a palladium catalyst, an amino acid derived carbamate ligand, and a combination of benzoquinone and silver carbonate as oxidant. Additionally, an *O*-methyloxime was installed in the starting material to act as a directing group for the BCB ring (eq. 1-29).[33]



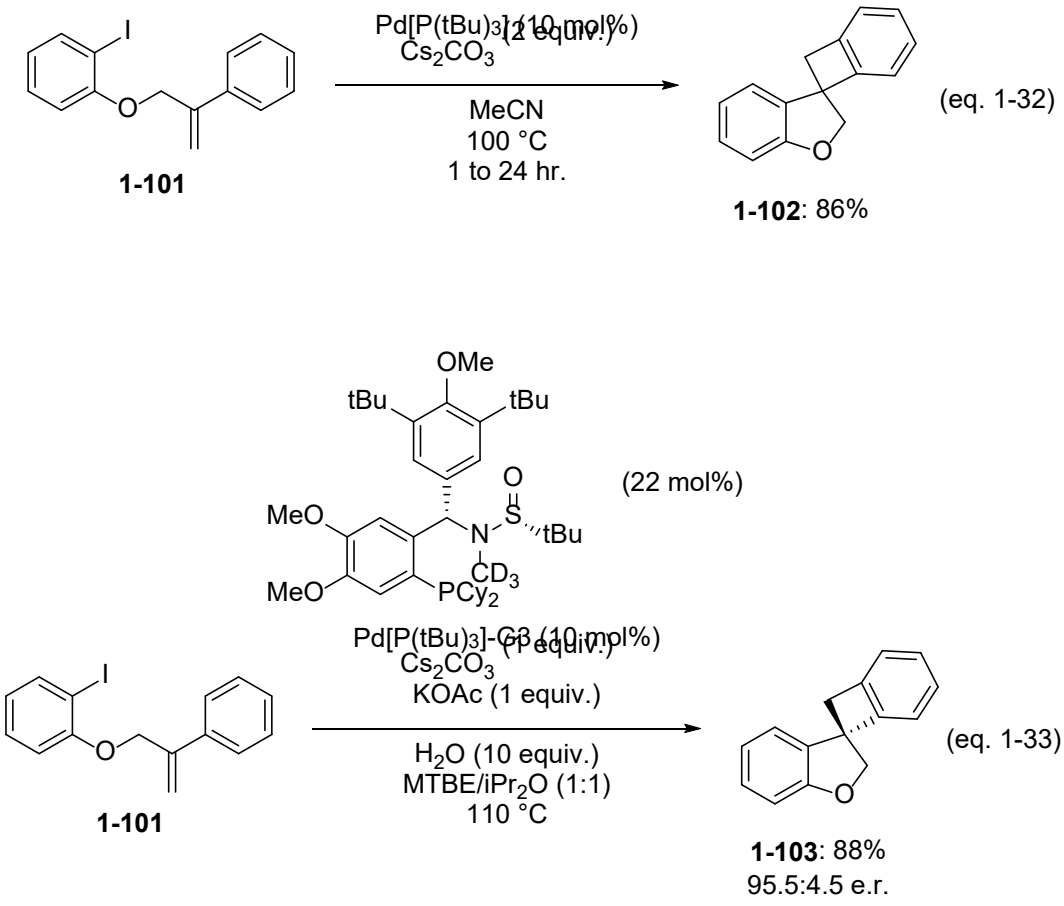

Scheme 15 Formation of BCBs from [2+2] annulation of norbornene.[32, 33]

[2+2] annulations to form BCBs are not restricted to the use of norbornene. For example, arylboronic acids have been coupled with alkenes to form BCBs containing amides. They use a bipyridenyl ligand for this reaction alongside silver oxide and *N*-fluorobenzenesulfonimide (NFSI) as oxidants (eq. 1-30).[34] A later study adapted this reaction to be stereoselective, with the only major alteration to the conditions being the use of a chiral ligand, namely a chiral pyridine-oxazoline (PyrOx) ligand. This produced a wide range of BCBs in moderate yield and enantiomeric excess (eq. 1-31).[35]




Scheme 16 Formation of BCBs from alkenes and arylboronic acids.[34, 35]

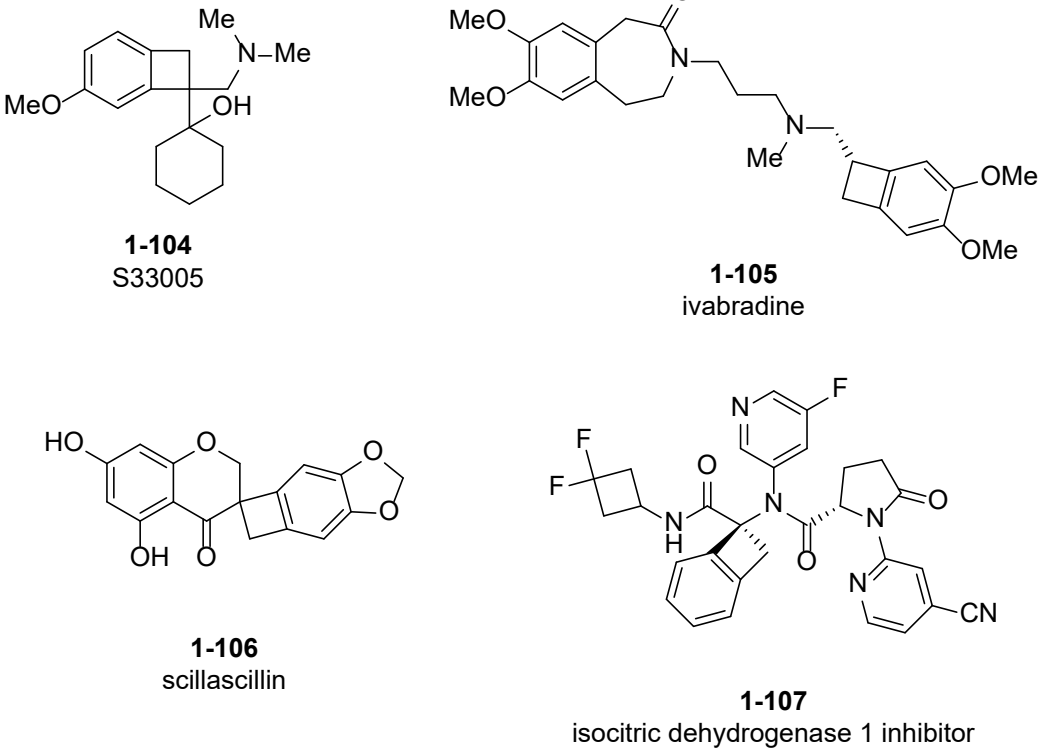
This reaction has an intramolecular counterpart which can form spirocyclic BCBs. This chemistry was first described by Franziska Schoenebeck and Mark Lautens for the synthesis of coumaran spirocycles. Interestingly, this reaction also tolerated the presence of a nitrogen atom and produced the respective spirocyclic indoline (eq. 1-32).[36] This reaction was later modified to be enantioselective; this was achieved by the implementation of a chiral XuPhos-type ligand (eq. 1-33).[37]




Scheme 17 Formation of BCB/coumaran spirocycles.[36, 37]

### 1.3 Utility of Benzocyclobutenes

BCBs have been observed as a component of an assortment of interesting and useful natural products and biologically active compounds. For instance, a small molecule containing a BCB ring system named S33005 displayed an affinity to human serotonin (5-HT) transporters (SERTs) and, to a lesser extent, norepinephrine transporters (NETs).[38] Another BCB-containing compound, ivabradine, is utilized as a drug to treat cardiovascular disease by way of suppressing the pacemaker ($I_f$) current.[39] Scillascillin, a BCB-containing homoisoflavone found in *Ledebouria hyderabadensis* bulbs, was observed to inhibit the MCF-7 and DU-145 human cancer cell lines.[40] BCB cores have also been observed in molecules which act as an isocitric dehydrogenase 1 inhibitor.[41]




**1-104**
S33005

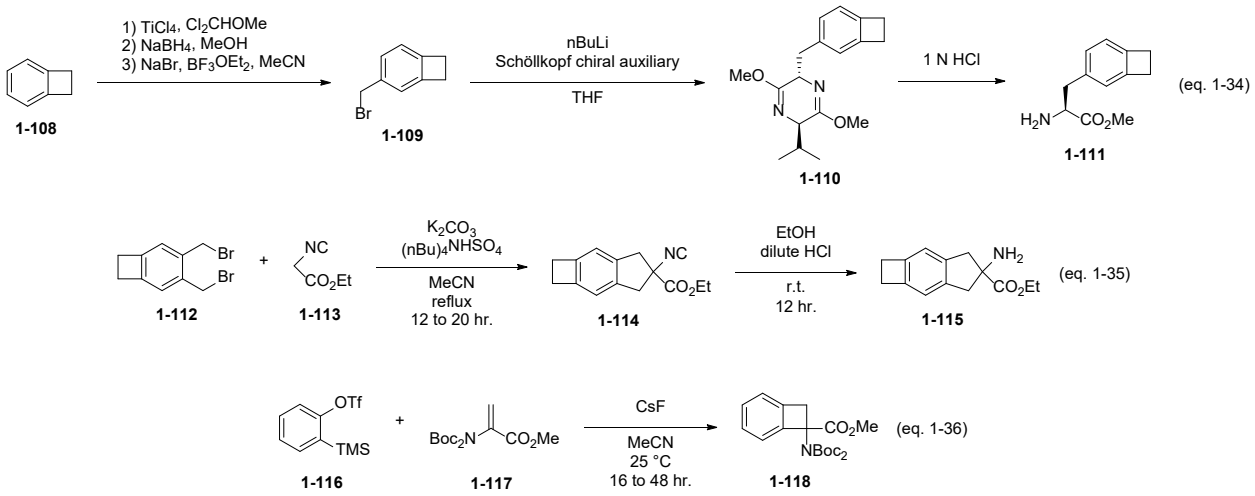
**1-105**
ivabradine

**1-106**
scillascillin

**1-107**
isocitric dehydrogenase 1 inhibitor

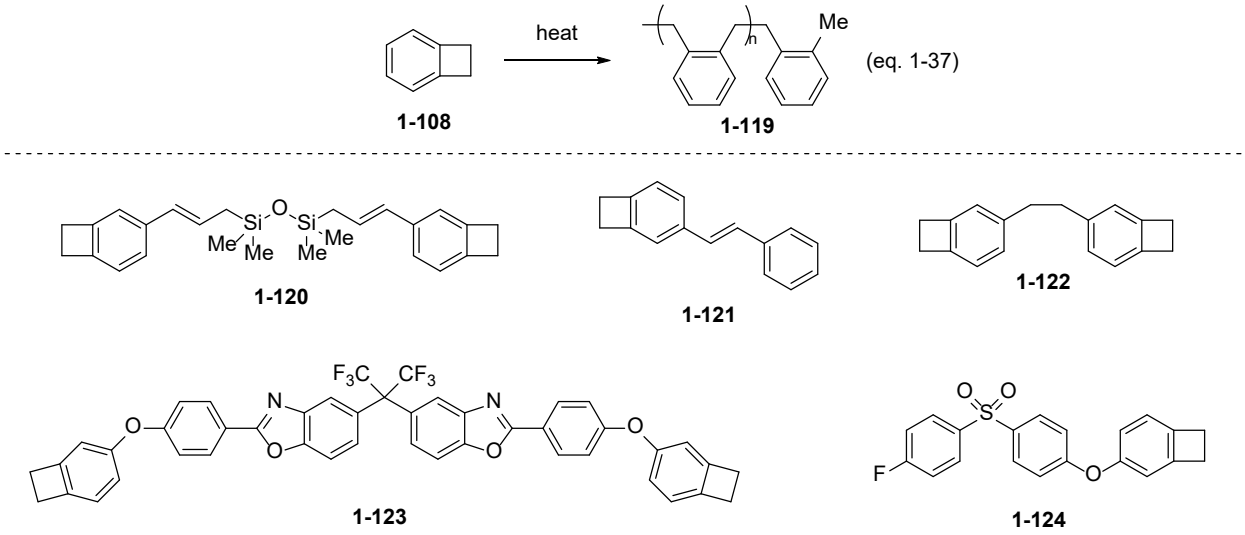
Scheme 18 BCB-containing natural products and drugs.[38-41]

A relatively recent application of BCBs is for the formation of artificial amino acids. This work has largely been pioneered by Sambasivarao Kotha who produced the first BCB-containing amino acids in 1999. These were produced by installing a bromomethyl group on benzocyclobutene, followed by using the Schöllkopf method to add a chiral auxiliary; the auxiliary is then removed by acid-mediated hydrolysis, forming the target amino acid in stereoselective fashion (eq. 1-34).[42] Later, Kotha developed a synthetic pathway to generate amino acids attached to the indane portion of a 2,4,5,6-tetrahydro-1*H*-cyclobuta[*f*]indene ring system. This was achieved by double alkylation of an *ortho*-di(bromomethyl)benzocyclobutene with ethyl 2-isocyanoacetate to form an indane ring with a strategically placed isonitrile group. This group is cleaved with acid, leaving a primary amine in its place (eq. 1-35).[43] More recent developments in this area have included the formation of BCB amino acids *via* [2+2] cycloaddition.[44]




Scheme 19 Formation of BCB-containing amino acids.[42-44]

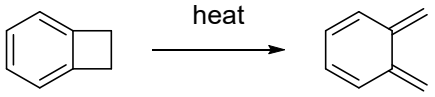
BCBs have also seen extensive use in polymer chemistry. This is a result of BCBs propensity to undergo ring opening at elevated temperatures which has been leveraged to form polymers from BCB-containing monomers. Early studies on the production of BCB polymers studied monomers containing silicate groups, alkenes, and alkyl groups.[45] Additional work has been done to produce BCB monomers with a greater degree of functionalization in order to continue generating unique polymers (Scheme 20).[46] Since this time, a wide scope of advances has been made in the development and usage of BCB-derived polymers.[47]




Scheme 20 BCB-containing monomers and generic BCB homopolymerization pathway.[45, 46]

## 1.4 Benzocyclobutenes and [4+2] Cycloadditions

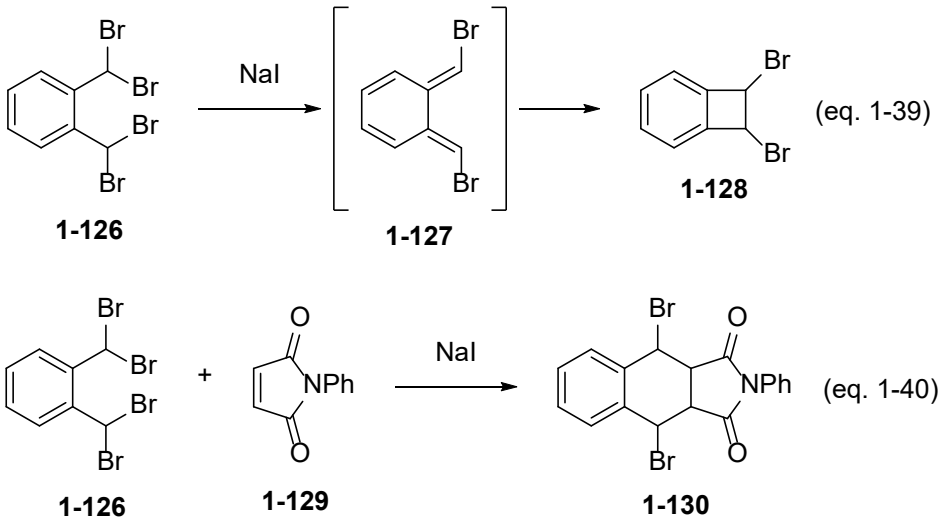
Within the field of organic chemistry, the most common application of BCBs is for [4+2] cycloadditions, also known as Diels-Alder reactions. While BCBs do not participate in Diels-Alder reactions directly, upon heating they undergo ring opening to form *ortho*-quinodimethanes *in situ* (eq. 1-38). As a result, BCBs can act as a controlled source of highly derivatized dienes and can enable the formation of various fused six-membered rings. This reaction has been employed in a wide variety of contexts over many decades; representative examples are described below.[48-50]




**1-108** **1-125** (eq. 1-38)

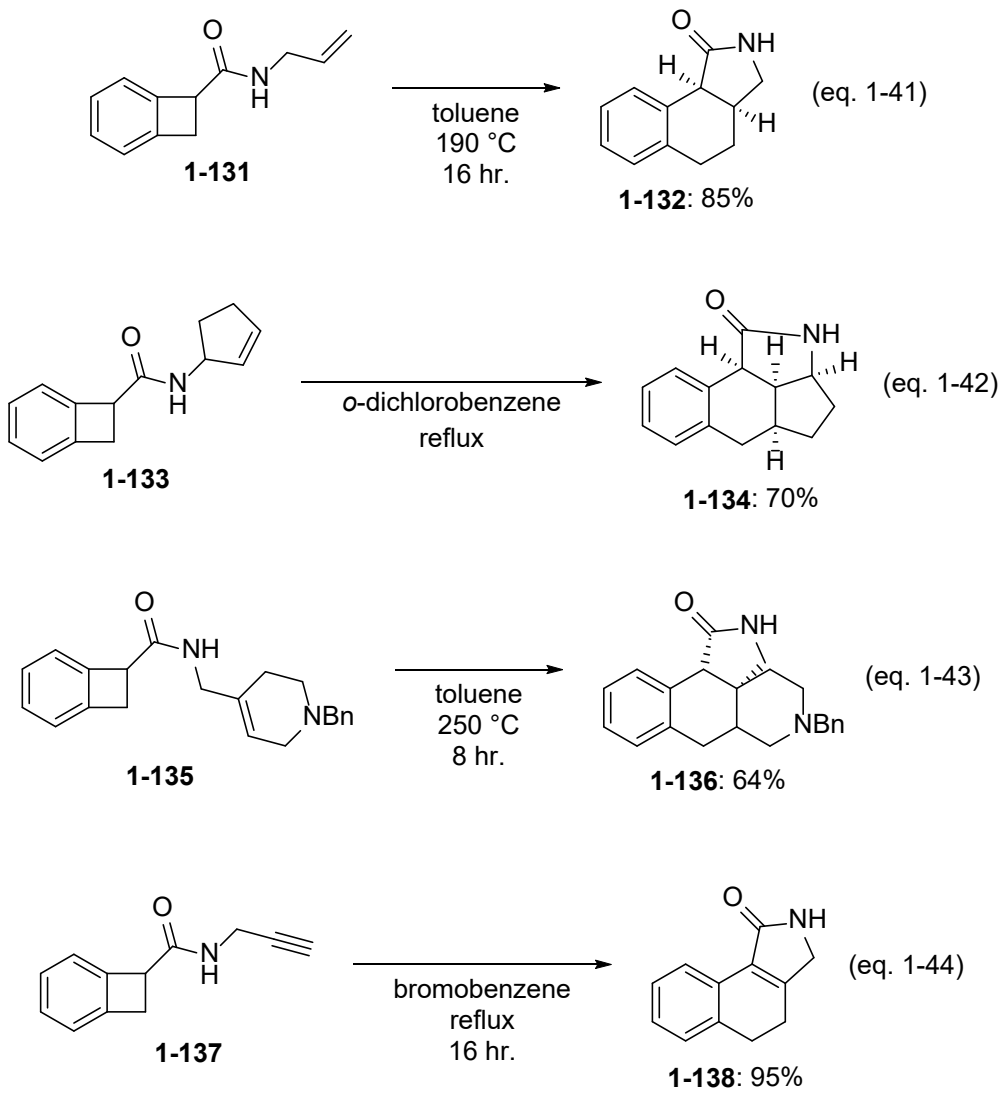
Scheme 21 Heat-induced ring opening of benzocyclobutene to form *ortho*-quinodimethane.

The history of using BCBs for [4+2] cycloadditions began at roughly the same time as the discovery of BCBs themselves. Much of the formative work in this area was conducted by Michael P. Cava in the late 1950s. He was the first researcher to generate BCBs since Finkelstein's original synthesis over forty years prior. At that time, he proposed that the formation of dihalobenzocyclobutenes from *ortho*-di(dihalomethyl)benzenes was achieved through the formation of a transient *ortho*-quinodimethane intermediate (eq. 1-39).[51] He later confirmed that this was the correct pathway when he was able to perform a [4+2] cycloaddition with the ortho-quinodimethane intermediate upon the addition of a dienophile to the reaction mixture (eq. 1-40).[52]



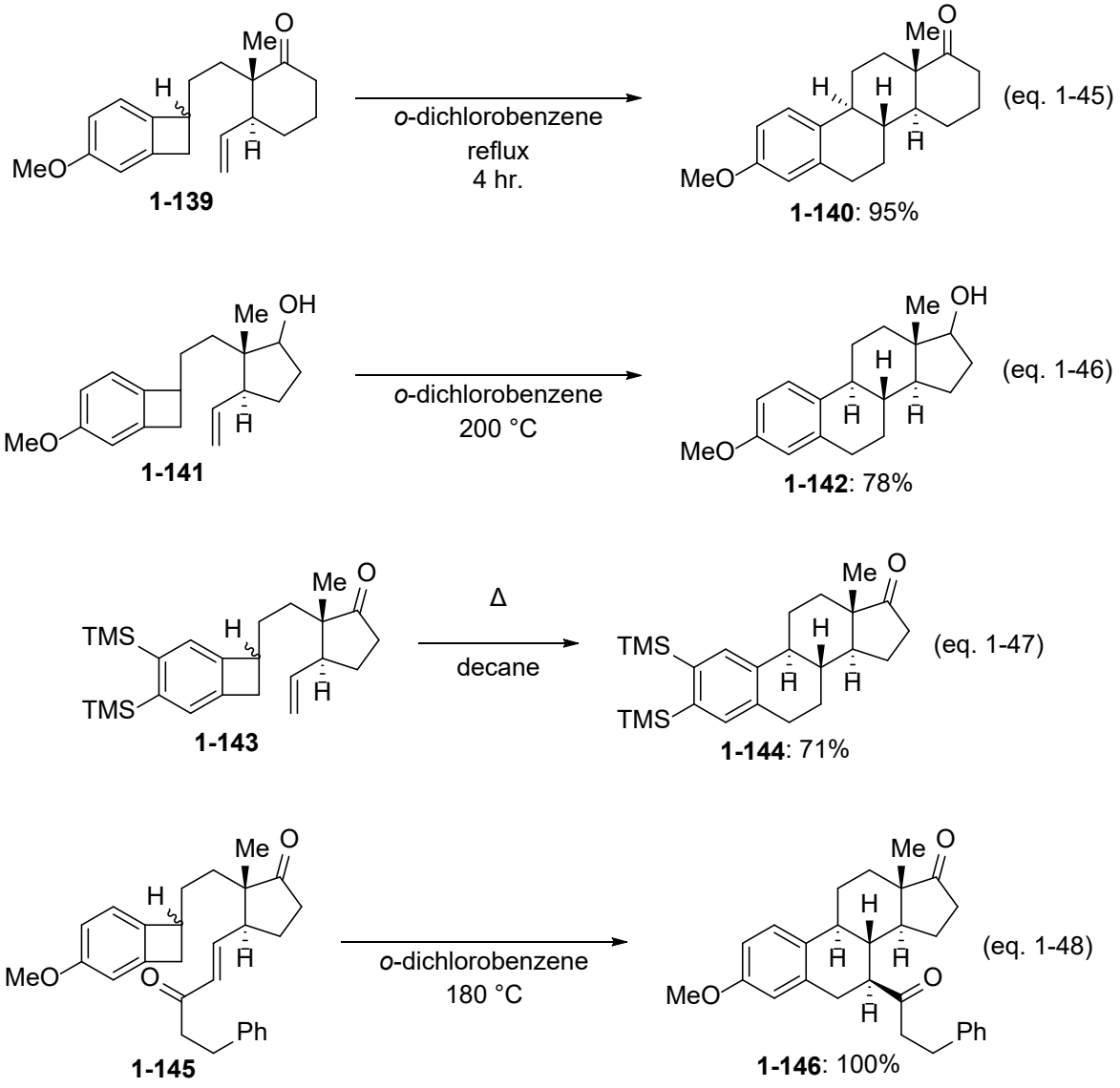

Scheme 22 Cava's proposed mechanism and [4+2] cycloaddition with the proposed intermediate.[51, 52]

Among the earliest examples of leveraging BCBs as a diene source was Wolfgang Oppolzer's study published in 1971. In this publication, BCB amides with tethered alkenes were subjected to high heat in order to induce a Diels-Alder reaction. Along with a comprehensive mechanistic study, he managed to produce various amide polycycles in high yield. This reaction also tolerated alkenes within rings and alkynes (Scheme 23).[53]



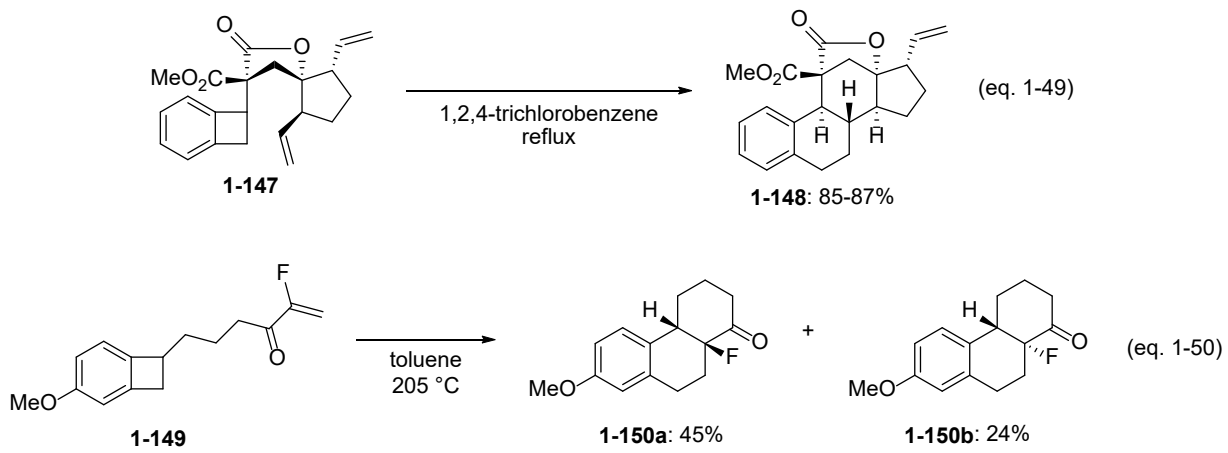

Scheme 23 Polycyclic amides formed from [4+2] cycloadditions.[53]

These intramolecular [4+2] cycloadditions have been utilized extensively in the formation of steroid cores. In particular, this reaction provides a one-step pathway to generating the B and C rings in stereoselective fashion and high yield. Many early attempts at leveraging this chemistry involved the total synthesis of estrone. In spite of their differences, each of these routes employ a strategically constructed BCB which is dissolved in *ortho*-dichlorobenzene or decane and subjected to high heat resulting in the formation of the desired steroid core (Scheme 24).[54-57]



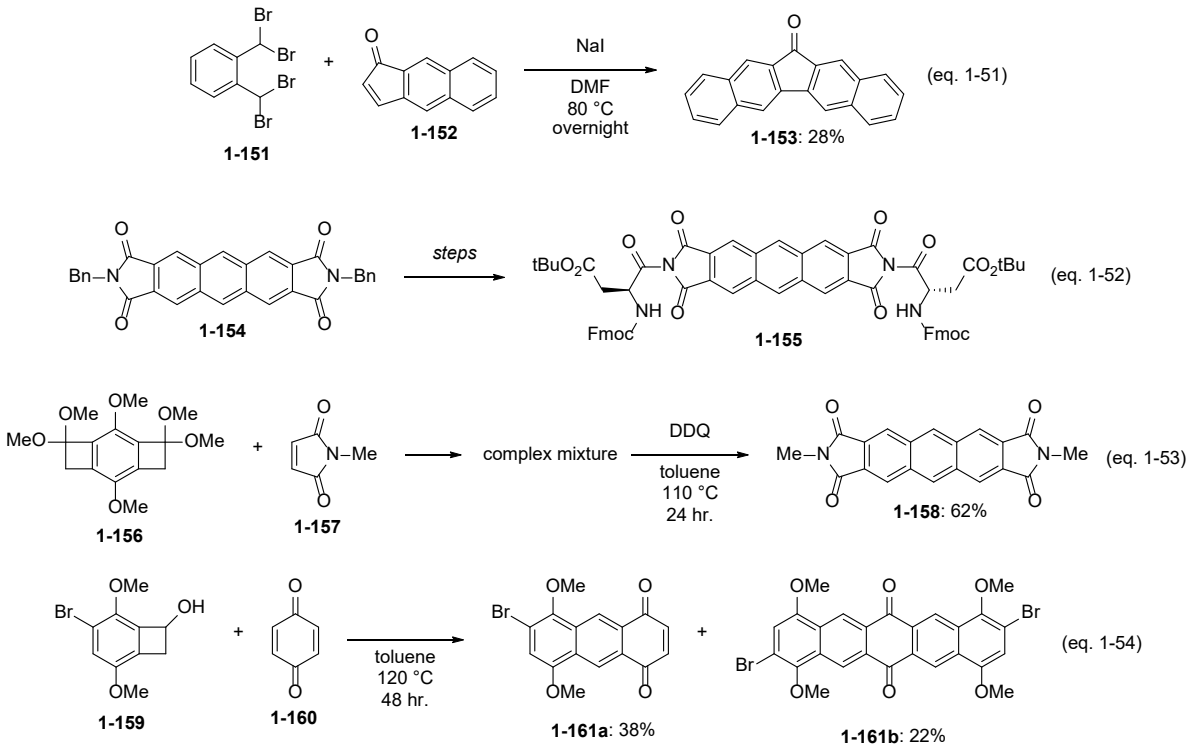

Scheme 24 Various routes to estrone *via* BCB-facilitated [4+2] cycloadditions.[54-57]

Additional strides have been made toward forming steroid cores with this technique in recent years. For example, a method was developed that generated the precursory BCB in three steps from buta-1,3-diene and iodobenzocyclobutene. The BCB was then refluxed in 1,2,4-trichlorobenzene to form the target steroid core (eq. 1-49).[58] Another notable discovery in this area pertains to the formation of fluorine-containing steroids. It has been found that a BCB tethered to a fluoroalkene can produce a steroid core in moderate yield (eq. 1-50).[59]



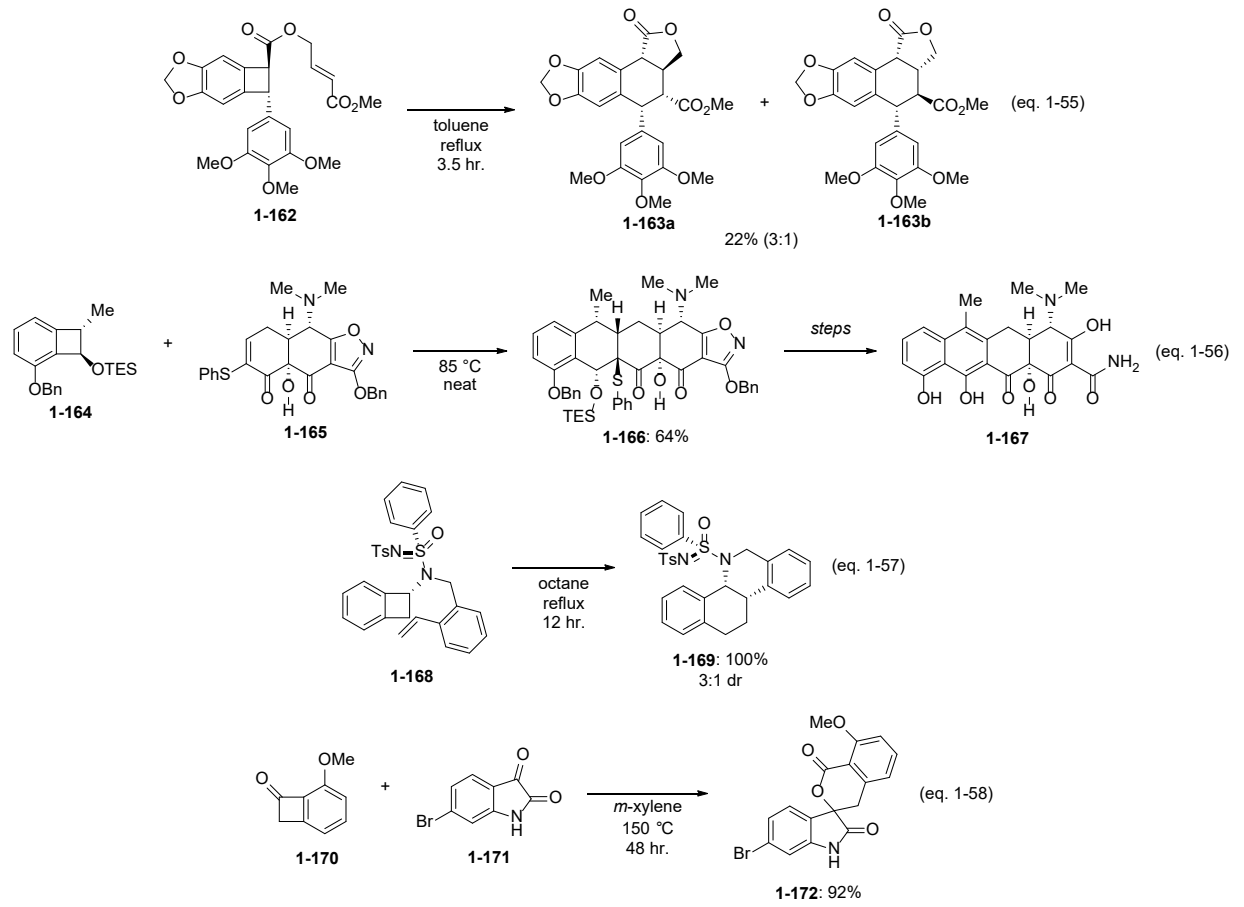

Scheme 25 Additional steroid cores generated from BCBs.[58, 59]

The Diels-Alder reaction of *ortho*-quinodimethanes has also been utilized in the formation of polycyclic fused-ring aromatic systems. In early attempts, this was achieved by way of Finkelstein and Cava's method of generating the *ortho*-quinodimethane *in situ* with an elimination facilitated by sodium iodide (eq. 1-51).[60] This technique was able to produce aromatic polycyclic imides which were capable of undergoing further functionalization (eq. 1-52).[61] Significantly, benzo[1,2:4,5]dicyclobutenes have been synthesized in order to generate large polycyclic aromatic systems in moderate yield from maleinimide or benzoquinone reacting with one or both cyclobutenyl rings (eqs. 1-53 and 1-54).[62, 63]




Scheme 26 Formations of polycyclic fused-ring aromatic systems with BCBs.[60-63]

The use of BCBs in [4+2] cycloadditions has also seen extensive implementation in the field of total synthesis. For instance, in 1984 this reaction was used as the final step in the formation of a podophyllotoxin analogue (eq. 1-55).[17] Additionally, this reaction has been employed to construct the aromatic portion of (-)-tetracycline (eq. 1-56).[15] In 2013, BCBs with chiral sulfur tethers performed an intramolecular Diels-Alder reaction in order to generate perhydroindole derivatives (eq. 1-57).[64] Furthermore, benzocyclobutenones have recently been found to participate in *hetero*-Diels-Alder reactions to produce 2-oxindole spirolactones through α-oxo-*ortho*-quinodimethane intermediates (eq. 1-58).[65]




Scheme 27 Synthetic applications of BCB [4+2] cycloadditions.[15, 17, 64, 65]

Given the myriad significant ways BCBs can be implemented in the scope of organic chemistry and beyond, it is not unreasonable that methods for synthesizing them have been in development for as long as they have existed as known compounds. While there are diverse options for synthesizing BCBs, these pathways have limitations in their utility on account of the fact that they require harsh conditions or expensive reagents, or they are limited in terms of their scope. Often, inert groups must be preinstalled on the starting material to prevent deleterious side reactions. In the following chapter, a new palladium-catalyzed method for producing malonate-substituted BCBs will be discussed in detail.

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(63) Mohamed Abdelmoniem, A.; Abdelshafy Abdelhamid, I.; Butenschön, H. Bidirectional Synthesis, Photophysical and Electrochemical Characterization of Polycyclic Quinones Using Benzocyclobutenes and Benzodicyclobutenes as Precursors. *Eur. J. Org. Chem.* **2021**, (46), 6319-6333.
(64) Mazurais, M.; Lescot, C.; Retailleau, P.; Dauban, P. A Short Asymmetric Synthesis of Octahydroindole Derivatives by Application of Catalytic C(sp3)–H Amination Reaction. *Eur. J. Org. Chem.* **2014**, (1), 66-79.
(65) Wurm, T.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. J. Thermal Hetero-Diels–Alder Reaction of Benzocyclobutenones with Isatins To Form 2-Oxindole Spirolactones. *J. Org. Chem* **2017**, (24), 13751-13755.

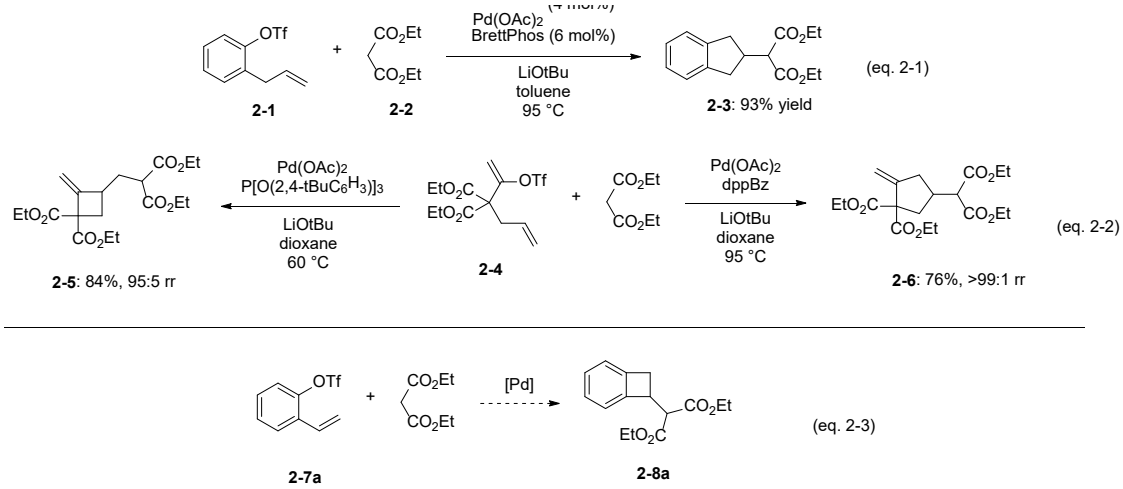
# Chapter 2 Formation of Benzocyclobutenes *via* Palladium-Catalyzed Alkene Difunctionalization[1]

## 2.1 Prior Palladium-Catalyzed Alkene Difunctionalizations

In recent years we have developed a series of cross-coupling reactions between 2-allylphenyl triflate derivatives or 1,5-diene-2-yl triflates and a range of nucleophiles that affect difunctionalization of the alkene to afford substituted indenes or exoalkylidene cyclopentanes.[1] For example, treatment of 2-allylphenyl triflate (**2-1**) with diethyl malonate (**2-2**) in the presence of lithium *tert*-butoxide and a catalyst composed of palladium(II) acetate and BrettPhos afforded indane **2-3** in 93% yield (Scheme 27, eq. 2-1).[2] Other nucleophiles such as amines,[3] indoles,[4] enolates,[5] alkyl nitriles,[6] and indenes[7] have also been successfully employed in these transformations. We have also shown that 1,5-diene-2-yl triflates (e.g., **2-4**) can be selectively transformed to either cyclopentane products (**2-6**) or cyclobutene products (**2-5**) under appropriate conditions (Scheme 27, eq. 2-2).[8]

Given our success with the cyclative alkene difunctionalization reactions of 2-allylphenyl triflates such as **2-1**, and with chemoselective formation of cyclobutanes such as **2-5**, we thought it may be possible to generate BCBs such as **2-8a** in a similar manner from 2-vinylphenyl triflate **2-7a** and related derivatives (Scheme 27, eq 2-3). This would provide a very concise route to substituted benzocyclobutenes, as substrates such as **2-7a** can be generated in two steps (olefination and triflation) from commercially available salicylaldehyde derivatives.

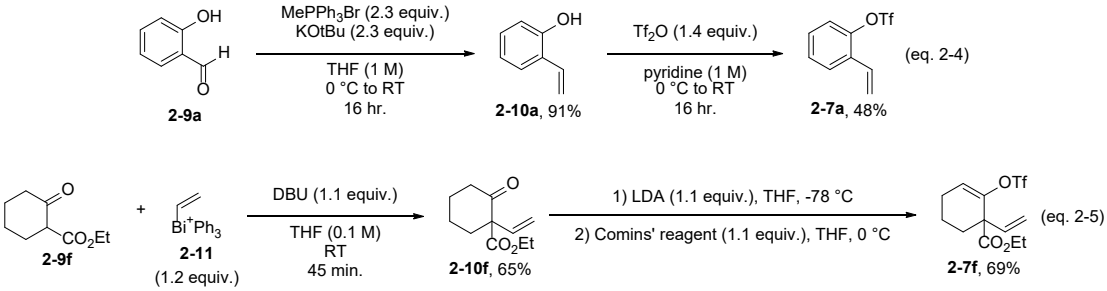
[1] I would like to acknowledge the efforts of Calliope Cutchins and Colin Priest toward starting material synthesis and substrate scope development for this project.




Scheme 28 Top: prior studies. Bottom: current studies.

## 2.2 Starting Material Syntheses

The styrenyl triflates required for this reaction can be accessed in two facile synthetic steps. First, a Wittig olefination converts commercially available salicylaldehydes to *ortho*-hydroxystyrenes using methyltriphenylphosphonium bromide as an ylide source and potassium *tert*-butoxide as base. Then, *ortho*-hydroxystyrenes are triflated with triflic anhydride in pyridine to form the desired *ortho*-triflyl styrene (eq. 2-4). In the case of the alkenyl triflate **2-7f**, ethyl 2-oxocyclohexanecarboxylate is combined with cationic vinylbismuth reagent **2-11** in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to produce the vinylated product **2-10f**. Then, this compound is triflated with Comins' reagent in a solution of lithium diisopropylamide (LDA) to form the final product (eq. 2-5).



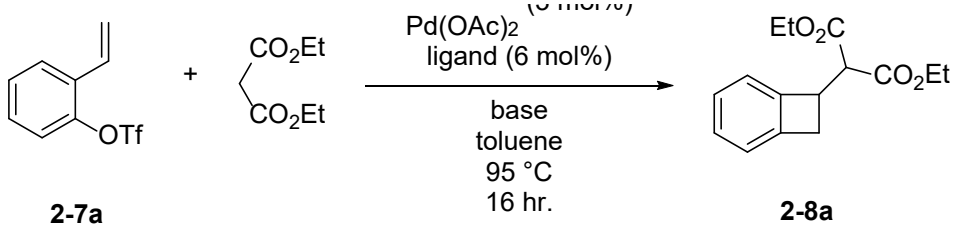

Scheme 29 Syntheses of starting materials.

## 2.3 Reaction Optimization

Given both the rich history of generating BCBs and their synthetic utility, we sought to determine whether palladium-catalyzed alkene difunctionalization could be leveraged to produce derivatized BCBs. Provided that this reaction has been able to produce a wide array of aryl fused-ring systems, especially indanes, we proposed that BCBs could be accessible by means of this pathway as well. However, we were cognizant of potential mechanistic pitfalls for this transformation. For one, the strain associated with forming the BCB four-membered ring would provide a potential barrier that the indane formation reactions do not have. Furthermore, the alkenyl portion of the *ortho*-triflyl styrenes would be electron deficient since it is in conjugation with the rest of the aryl ring. In spite of these potential hurdles, we decided to probe reaction conditions to determine if these issues are surmountable.

In order to probe the feasibility of this transformation, we selected 2-vinylphenyl triflate **2-7a** and diethyl malonate as the model electrophile and nucleophile, respectively. When these reactants were subjected to conditions that are effective for five-membered ring formation in intramolecular palladium catalyzed alkene difunctionalization, we were pleased to observe the generation of the desired BCB product **2-8a** in moderate yield (28%) as determined by $^{1}$H NMR analysis (Table 1, entry 1). We then began to try to optimize reaction conditions and catalyst composition to improve the yield of the desired product.

Table 1 Optimization of BCB formation




**2-7a** **2-8a**

| entry | ligand | base | Yield (%)[b] |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 1 | BrettPhos | LiO$^t$Bu | 38 |
| 2 | XPhos | LiOtBu | 2 |
| 3 | DavePhos | LiOtBu | 25 |
| 4 | DPE-Phos[c] | LiOtBu | 19 |
| 5 | CyJohnPhos | LiOtBu | 0 |
| 6 | dppf[c] | LiOtBu | 0 |
| 7 | $PCy_3$•$HBF_4$ | LiOtBu | 0 |
| 8 | JackiePhos | LiOtBu | 0 |
| 9 | P$^t$Bu$_3$•$HBF_4$ | LiOtBu | 0 |
| 10 | CPhos | LiOtBu | 40 |
| 11 | $^t$BuBrettPhos | LiOtBu | 0 |
| 12 | (±)-BINAP[c] | LiOtBu | 3 |
| 13 | XantPhos | LiOtBu | 6 |
| 14 | BrettPhos | LiOtBu | 38[d] |
| 15 | BrettPhos | LiHMDS | 34 |
| 16 | BrettPhos | $Cs_2CO_3$ | 0 |
| 17 | BrettPhos | NaOtBu | 0 |
| 18 | BrettPhos | $K_3PO_4$ | 0 |
| 19 | BrettPhos | $Li_2CO_3$ | 0 |
| 20 | BrettPhos | $Li_3PO_4$ | 0 |
| 21 | BrettPhos | KHMDS | 0 |

[a]Conditions: Reactions were conducted on a 0.2 mmol scale using 1.0 equiv **7a**, 3-5 equiv diethyl malonate, 1.4 equiv base, 3 mol % $Pd(OAc)_2$, 6 mol % ligand, toluene (0.1 M) for ca 16h at the indicated temperature. [b]NMR yield using phenanthrene as the internal standard. [c]The reaction was conducted using 3 mol % of the chelating bis-phosphine ligand. [d]The reaction was conducted using $Pd_2(dba)_3$ in place of $Pd(OAc)_2$.

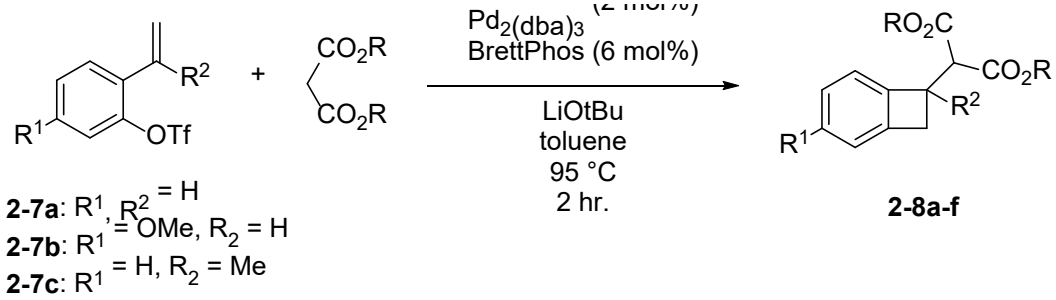
As shown in Table 1, factors that had the most significant bearing on the outcome of the reaction were the ligand and base; the reaction was less sensitive to other reaction parameters, such as solvent and precatalyst. The only ligands examined that produced significant amounts of **2-8a** were DPEPhos (19%) and electron-rich *ortho*-dicyclohexylbiphenylphosphine derivatives; BrettPhos provided the best results and generated the cleanest crude reaction mixtures of the ligands examined. Lithium *tert*-butoxide and lithium hexamethyldisilazide provided comparable results, but other bases failed to generate significant amounts of desired product. Initial

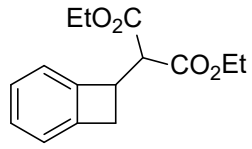
optimization studies were performed with a large excess of diethyl malonate and base (3−5 equiv). However, the diethyl malonate anion is sparingly soluble in toluene, and the excess malonate was difficult to separate from the benzocyclobutene product. When reactions were conducted with 1.4 equivalents of diethyl malonate, product yields were comparable to those obtained with a large excess of nucleophile. The precatalyst tris(dibenzylideneacetone)dipalladium(0) provided slightly higher yields and cleaner reactions than palladium(II) acetate (entry 14).

The reactions provided the best results, with complete consumption of starting material in two hours, when reactions were conducted at 95 °C with a 0.2 M substrate concentration. Higher temperatures did not provide improved results, whereas lower temperatures resulted in diminished yields. Reactions conducted at concentrations lower than 0.2 M required long run times to reach completion, and increasing the concentration beyond 0.2 M provided lower yields, presumably due to the poor solubility of the diethyl malonate anion.

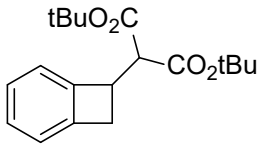
## 2.4 Substrate Scope

Table 2 Substrate Scope

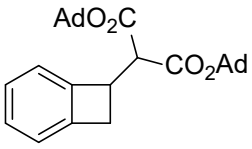


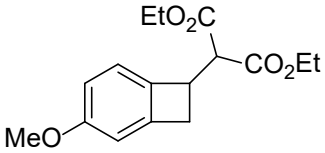

**2-8a**: 27%



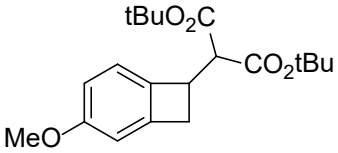

**2-8b**: 31%
48% (1 mmol)$_c$



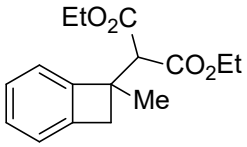

**2-8c**: 33%




**2-8d**: 17%




**2-8e**: 46%



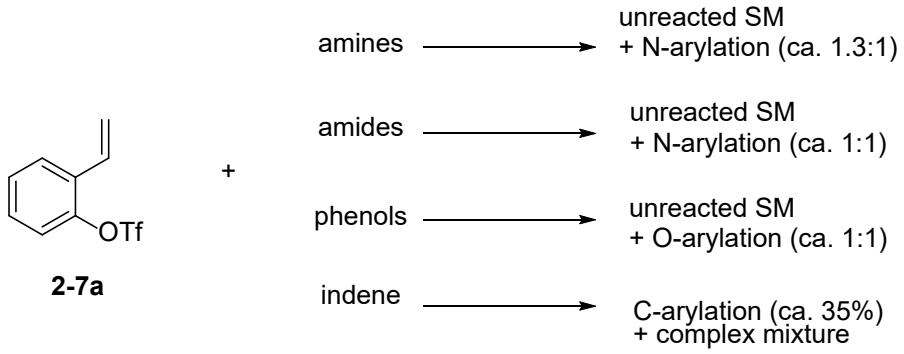

**2-8f**: 34%

[a]Conditions: Reactions were conducted on a 0.2 mmol scale using 1.0 equiv 11a−c, 1.4 equiv dialkyl malonate, 2 mol % $Pd_2(dba)_3$, 6 mol % BrettPhos, toluene (0.2 M), 95 °C, 2 h. [b]Isolated yield (average of two or more experiments). [c]The reaction was conducted on a 1.0 mmol scale.

Despite considerable optimization efforts, we were unable to generate desired products in yields that exceeded 50% (Table 2). The origin of the low yields is not entirely clear, as analysis of crude reaction mixtures that had been quenched with aqueous ammonium chloride showed only desired product along with other residual reaction components (excess malonate, phosphine ligand, dibenzylideneacetone, and toluene), and trace amounts of minor side products. However, it is possible that some material is lost due to competing $\beta$-hydride elimination of intermediate 15 in the catalytic cycle shown below (Scheme 3). This would lead to formation of an $\alpha,\beta$-

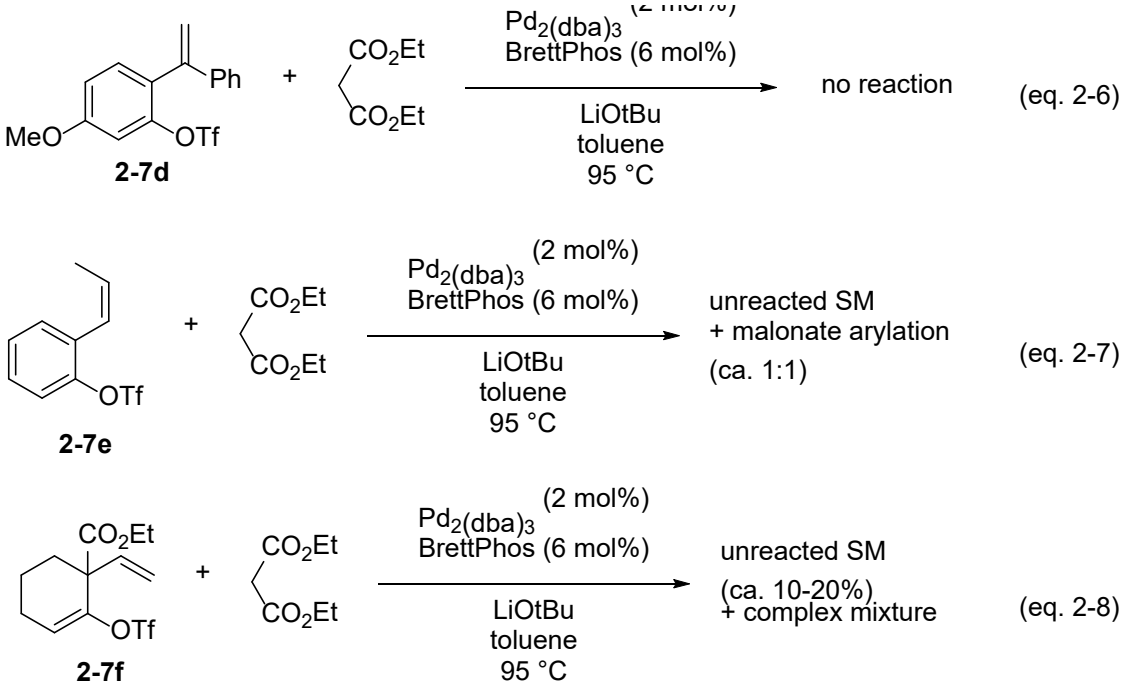
unsaturated malonate, which could polymerize under the reaction conditions. The improved yield of **2-8b** on a 1 mmol scale (48% as compared to 31% on a 0.2 mmol scale) also suggests that some material is lost during the small-scale chromatographic purification. The best yields were obtained using di-*tert*-butyl malonate, which may be due to increased solubility of the anion that is imparted by the *tert*-butyl groups.

The scope of this transformation appears to be limited to unsubstituted acyclic malonate nucleophiles. Reactions of other doubly activated carbon nucleophiles such as ethyl acetoacetate, ethyl cyanoacetate, 2,4-pentanedione, and 1,3-cyclohexanedione failed to generate the respective BCB products in greater than trace amounts. Additionally, these conditions were also not effective for the transformation of monosubstituted malonates, and a number of other nucleophiles such as amines, amides, phenols, and indene also did not lead to BCB formation (Scheme 28).




Scheme 30 Nucleophile limitations.

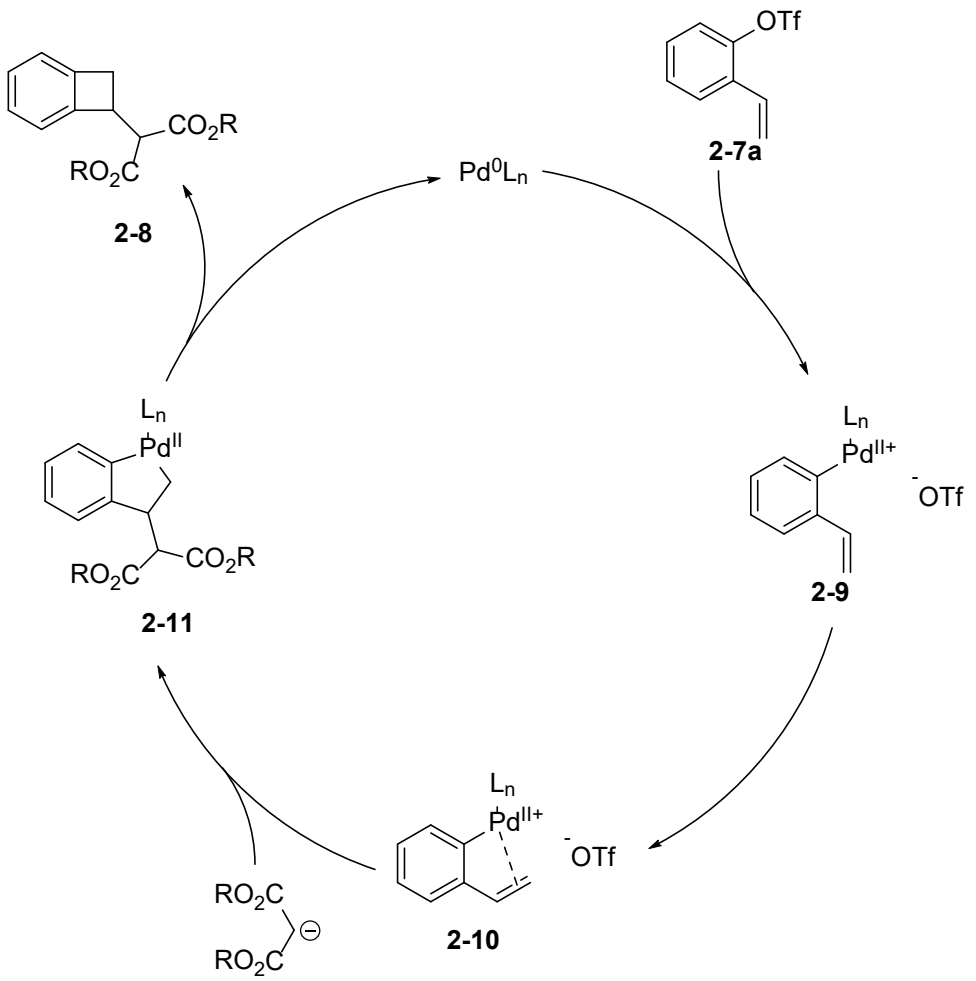
The reactions tolerate the presence of methoxy substitution on the aromatic ring, and substrate **2-7c**, which contains an internal methyl group on the alkene, was converted to **2-8f** in moderate yield. However, the reaction was sensitive to steric hindrance, as substrates **2-7d** and **2-7e** were not converted to BCB products (eqs 2-6–2-7). In addition, attempts to convert alkenyl triflate **2-7f** to a strained bicyclo[4.2.0]octene product were also unsuccessful (eq 2-8).




Scheme 31 Failed alkenes.

## 2.5 Proposed BCB Formation Mechanism

The mechanism of the BCB-forming reactions is likely similar to that of the analogous transformations that generate 5-membered ring products. As shown in Scheme 30, the reaction begins with oxidative addition of the aryl triflate (**2-7a**) to palladium(0), generating cationic palladium intermediate **2-9**. The alkene coordinates to the electron-deficient palladium center to provide **2-10**, which undergoes *anti*-nucleopalladation with the deprotonated malonate nucleophile to give **2-11**. Reductive elimination from **2-11** affords the substituted BCB product (**2-8**) and regenerates the palladium catalyst.




Scheme 32 Proposed BCB formation mechanism.

In conclusion, this reaction presents a facile means to access malonate ester substituted BCBs in moderate yield. We are pleased to observe that this reaction was able to tolerate various malonate ester nucleophiles and functionalization along the aryl ring. Despite its limitations, this reaction presents one of the fastest and mildest approaches to generating BCBs ever proposed. In addition, the presence of malonate esters offers a synthetic handle to further modify the tethered functional group on the BCB. This reaction could also be implemented to produce malonate ester bearing tetralins by way of heat-induced [4+2] cycloadditions.[9]

## 2.6 Experimental Section

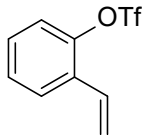
### General Considerations

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents, palladium precatalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. The starting materials 2-vinylphenol, 5-methoxy-2-vinylphenol,[10] (*Z*)-2- (prop-1-en-1-yl)phenol,[11] 2-(prop-1-en-2-yl)phenol,[12] ethyl 2-oxo-1-vinylcyclohexane-1-carboxylate,[13] 5-methoxy-2-(1-phenylvinyl)-phenol,[14] and diadamantyl malonate,[15] were synthesized according to previously established methods and their respective characterization data were consistent with those previously reported in the literature. Aryl and alkenyl triflate starting materials were stored in a freezer under nitrogen. Bulk quantities of lithium *tert*-butoxide were stored in a nitrogen-filled glovebox and small amounts were removed within a few days of use. HRMS measurements were obtained using a TOF mass-analyzer. Reactions that required heating were heated with a hot plate equipped with temperature control. Yields refer to isolated yields of compounds estimated to be ≥ 95% pure as determined by $^1$H NMR analysis unless otherwise noted. *The yields reported in the* Experimental Section *describe the result of a single experiment*, *whereas yields reported in* Table 2 *are average yields of two or more experiments. Thus*, *the yields reported in the* Experimental Section *may differ from those shown in* Table 2. In most instances all proton/carbon signals of diastereotopic atoms/groups were resolved; cases of accidental equivalence in carbon NMR spectra are noted in the tabulated NMR data below.

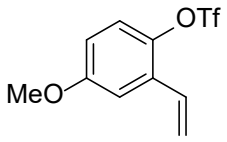
### General Procedure for the Synthesis of 2-Vinylphenyl Triflates (General Procedure A)

A flame-dried round-bottom flask equipped with a stir bar was cooled under a stream of nitrogen. Pyridine (1 M) and the starting 2-vinylphenols (1 equiv.) were added to the flask and

the solution was stirred briefly at room temperature. Then, the solution was cooled to 0 °C in an ice water bath and triflic anhydride (1.4 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir overnight. After the starting material had been completely consumed as judged by TLC analysis, the reaction was quenched with aqueous ammonium chloride, the mixture was transferred to a separatory funnel, and the aqueous layer was extracted with diethyl ether (3×). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica.

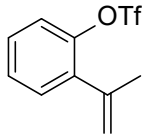



2-Vinylphenyl triflate (**2-7a**). The title compound was prepared from 2-vinylphenol (0.109 g, 0.91 mmol) using General Procedure A. The crude material was purified *via* column chromatography on silica gel using hexanes as eluent. This procedure afforded 0.110 g (48%) of the title compound as a pale-yellow oil. 1H NMR (600 MHz, $CDCl_3$) $\delta$ 7.65 (dd, $J$ = 7.2, 2.3 Hz, 1H), 7.39−7.31 (m, 2H), 7.30−7.24 (m, 1H), 6.94 (dd, $J$ = 17.5, 11.1 Hz, 1H), 5.86 (d, $J$ = 17.5 Hz, 1H), 5.49 (dd, $J$ = 11.0, 0.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) $\delta$ 146.9, 131.1, 129.3, 128.9, 128.4, 127.3, 121.7, 118.60, 118.59 (q, $J$ = 320.3 Hz). IR (film): 3071, 2918, 1632 $cm^{-1}$. HRMS (EI+) *m*/*z*: [M+] Calcd for $C_9H_7F_3O_3S$ 252.0068; found 252.0073.

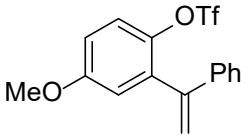



5-Methoxy-2-vinylphenyl Triflate (**2-7b**). The title compound was prepared from 5-methoxy-2-vinylphenol (0.97 g, 6.46 mmol) using General Procedure A. The crude material was purified *via* column chromatography on silica gel using 0.75% EtOAc/hexanes as eluent. This

procedure afforded 1.29 g (71%) of the title compound as a yellow oil. $^{1}$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.8 Hz, 1H), 6.91 (dd, $J$ = 8.8, 2.5 Hz, 1H), 6.79 (d, $J$ = 2.5 Hz, 1H), 5.72 (dd, $J$ = 17.4, 0.9 Hz, 1H), 5.36 (dd, $J$ = 11.1, 0.8 Hz, 1H), 3.83 (s, 3H). $^{13}$C{$^{1}$H} NMR (151 MHz, $CDCl_3$) $\delta$ 160.1, 147.2, 128.4, 127.6, 123.4, 118.5 (q, $J$ = 318.6 Hz), 116.2, 114.6, 107.1, 55.7. IR (film): 3096, 2842, 1617 cm$^{-1}$. HRMS (APCI+) *m*/*z*: [M+] Calcd for $C_{10}H_9F_3O_4S$ 282.0174; found 282.0151.

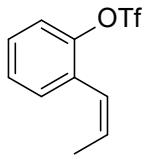



2-(Prop-1-en-2-yl)phenyl Triflate (**2-7c**). The title compound was prepared from 2-(prop-1-en-2-yl)phenol (0.802 g, 5.98 mmol) using General Procedure A. The crude material was purified *via* column chromatography on silica gel using hexanes as eluent. This procedure afforded 0.906 g (57%) of the title compound as a clear oil. $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.37−7.30 (m, 3H), 7.26 (m, 1H), 5.36 (p, $J$ = 1.6 Hz, 1H), 5.15 (t, $J$ = 1.2 Hz, 1H), 2.14−2.10 (m, 3H). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ 146.5, 139.8, 137.3, 130.2, 128.7, 128.3, 121.6, 118.61, 118.57 (q, $J$ = 320.0 Hz), 23.2. IR: 3090, 2979, 1641 cm$^{-1}$. HRMS (EI+) *m*/*z*: [M+] Calcd for $C_{10}H_9F_3O_3S$ 266.0224; found 266.0214.

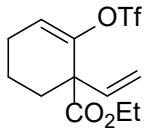



5-Methoxy-2-(1-phenylvinyl)phenyl Triflate (**2-7d**). The title compound was prepared from 5-methoxy-2-(1-phenylvinyl)phenol (0.534 g, 2.36 mmol) using General Procedure A. The crude material was purified *via* column chromatography on silica gel using 3% EtOAc/hexanes as eluent. This procedure afforded 0.437 g (52%) of the title compound as a pale-yellow oil. $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35−7.22 (m, 6H), 6.92 (dd, $J$ = 8.6, 2.4 Hz, 1H), 6.84 (d, $J$ = 2.5

Hz, 1H), 5.81 (s, 1H), 5.41 (s, 1H), 3.86 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 160.0, 147.6, 143.6, 140.1, 132.7, 128.3, 128.0, 127.7, 127.0, 118.6 (app d, $J$ = 320.0 Hz), 118.1, 113.8, 107.8, 55.8. IR: 3084, 2871, 1620 $cm^{-1}$. HRMS (EI+) *m*/*z*: [M+] Calcd for $C_{16}H_{13}F_3O_4S$ 358.0487; found 358.0471.




(*Z*)-2-(Prop-1-en-1-yl)phenyl triflate (**2-7e**). The title compound was prepared from (*Z*)-2-(prop-1-en-1-yl)phenol (0.903 g, 6.73 mmol) using General Procedure A. The crude material was purified *via* column chromatography on silica gel using hexanes as eluent. This procedure afforded 1.21 g (68%) of the title compound as a clear oil. $^{1}H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.42−7.24 (m, 4H), 6.46 (dq, $J$ = 11.5, 2.0 Hz, 1H), 6.02 (dq, $J$ = 11.4, 7.1 Hz, 1H), 1.78 (dd, $J$ = 7.1, 1.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ 147.4, 131.4, 131.3, 131.1, 128.4, 127.9, 122.8, 121.4, 118.6 (q, $J$ = 320.0 Hz), 14.6. IR: 3028, 2921, 1650 $cm^{-1}$. HRMS (EI+) *m*/*z*: [M+] Calcd for $C_{10}H_9F_3O_3S$ 266.0224; found 266.0225.



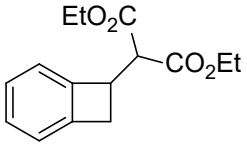

Ethyl 2-[(triflyl)oxy]-1-vinylcyclohex-2-ene-1-carboxylate (**2-7f**). A flame-dried round-bottom flask equipped with a stir bar was evacuated and backfilled with nitrogen three times. Tetrahydrofuran (4 mL) and diisopropylamine (0.95 mL, 6.78 mmol) were added to the flask, and the mixture was cooled to −78 °C in a dry ice/acetone bath for 10 min. A 2.5 molar solution of *n*-butyllithium in hexanes (2.64 mL, 6.6 mmol) was added to the solution dropwise. The solution was allowed to stir at −78 °C for 10 minutes. While the solution of LDA was stirring, a separate flame-dried round-bottom flask equipped with a stir bar was cooled to room temperature

under nitrogen and charged with ethyl 2-oxo-1-vinylcyclohexane-1-carboxylate (1.18 g, 6 mmol). The flask was evacuated and backfilled with nitrogen three times. Tetrahydrofuran (10 mL) was added to the flask containing the alkenyl substrate, and the resulting solution of ethyl 2-oxo-1-vinylcyclohexane-1-carboxylate was added dropwise to the cooled solution of LDA. The resulting mixture was stirred for 2 hours at −78 °C. Then an air-free solution of Comins' reagent (2-[N,N-bis-(trifluoromethylsulfonyl)amino]-5-chloropyridine; 2.59 g, 6.6 mmol) in anhydrous THF (10 mL) was added gradually to the cooled reaction mixture. The reaction mixture was briefly stirred at −78 °C, then was warmed to 0 °C in an ice/water bath where the flask was fully covered in ice. The reaction was then allowed to stir overnight and was then quenched with aqueous ammonium chloride and transferred to a separatory funnel. The mixture was extracted with diethyl ether (3×) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and condensed *in vacuo*. The crude material was purified *via* column chromatography on silica gel using 3% EtOAc/hexanes as eluent. This procedure afforded 1.36 g (69%) of the title compound as a pale-yellow oil. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.06 (dd, $J$ = 17.5, 10.7 Hz, 1H), 5.97 (t, $J$ = 4.1 Hz, 1H), 5.34 (d, $J$ = 10.7 Hz, 1H), 5.19 (d, $J$ = 17.5 Hz, 1H), 4.23 (qd, $J$ = 7.1, 1.0 Hz, 2H), 2.35 − 2.18 (m, 3H), 1.82 (ddd, $J$ = 13.2, 8.0, 3.2 Hz, 1H), 1.71−1.54 (m, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ 171.7, 146.4, 135.6, 119.9, 118.2 (app d, $J$ = 321.3 Hz), 61.9, 53.9, 34.1, 24.2, 17.3, 13.9. IR: 2945, 1736, 1681 cm$^{-1}$. HRMS (EI+) *m*/*z*: Calcd for $C_{12}H_{15}F_3O_5S$ 328.0952; found 328.0950.

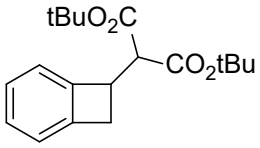
**General Procedure for Palladium-Catalyzed Alkene Difunctionalization Reactions (General Procedure B)**

A flame-dried 4 mL screw cap vial equipped with a stir bar was sealed with a septum cap, cooled under nitrogen, and charged with $Pd_2(dba)_3$ (3.66 mg, 0.004 mmol), BrettPhos (6.44 mg,

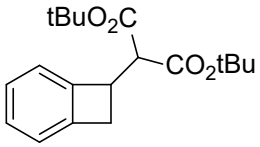
0.012 mmol), and lithium *tert*-butoxide (22.42 mg, 0.28 mmol). Toluene (1 mL, 0.2 M) was added *via* syringe, followed by the appropriate aryl or alkenyl triflate (0.2 mmol), and then the appropriate malonate nucleophile (0.28 mmol). The septum cap was then further sealed with electrical tape. The vial was heated to 95 °C with stirring for 2 hours (unless otherwise noted) until the starting material had been consumed as judged by TLC analysis. The mixture was then cooled to room temperature and quenched with saturated aqueous ammonium chloride (2 mL). The mixture was transferred to a separatory funnel, the aqueous layer was extracted with diethyl ether, and the ether extract was filtered through a sodium sulfate plug, and concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel to afford the desired product.



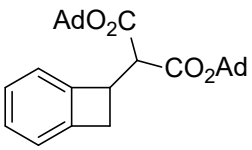

(±)-Diethyl 2-(benzocyclobutenyl)malonate (**2-8a**). The title compound was prepared from 2-vinylphenyl triflate (50 mg, 0.2 mmol) and diethyl malonate (43 $\mu$L, 0.28 mmol) using General Procedure B. The crude material was purified *via* column chromatography on silica gel using 5% EtOAc/hexanes as eluent. This procedure afforded 15 mg (29%) of the title compound as a bright yellow oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.23 (t, $J$ = 7.5 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.08 (t, $J$ = 7.8 Hz, 2H), 4.24 (dq, $J$ = 25.2, 7.3 Hz, 4H), 4.06 (ddd, $J$ = 10.9, 5.4, 2.5 Hz, 1H), 3.56 (d, $J$ = 10.8 Hz, 1H), 3.45 (dd, $J$ = 14.4, 5.3 Hz, 1H), 3.00 (dd, $J$ = 14.5, 2.6 Hz, 1H), 1.28 (dt, $J$ = 10.4, 7.2 Hz, 6H). $^{13}$C{$^1$H} NMR (176 MHz, $CDCl_3$) $\delta$ 168.7, 168.6, 145.9, 143.2, 128.1, 127.0, 123.0, 61.4, 55.8, 41.6, 35.1, 14.11, 14.09; one aromatic signal and one aliphatic signal are missing due to accidental equivalence. IR (film): 3068, 2981, 1729 cm$^{-1}$. HRMS (APCI+) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{18}O_4$ 263.1278; found 263.1277.



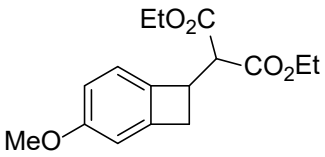

(±)-Di-*tert*-butyl 2-(benzocyclobutenyl)malonate (**2-8b**). The title compound was prepared from 2-vinylphenyl triflate (50 mg, 0.2 mmol) and di-*tert*-butyl malonate (63 $\mu$L, 0.28 mmol) using General Procedure B. The crude material was purified *via* column chromatography on silica gel using 2% EtOAc/hexanes as eluent. This procedure afforded 22 mg (35%) of the title compound as a bright yellow oil. $^{1}$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.21 (t, $J$ = 7.4 Hz, 1H), 7.18 (t, $J$ = 7.4 Hz, 1H), 7.11 (d, $J$ = 7.2 Hz, 1H), 7.06 (d, $J$ = 7.1 Hz, 1H), 3.98 (ddd, $J$ = 10.1, 5.3, 2.5 Hz, 1H), 3.45−3.37 (m, 2H), 3.01 (dd, $J$ = 14.4, 2.6 Hz, 1H), 1.46 (s, 18H). $^{13}$C{$^{1}$H} NMR (151 MHz, $CDCl_3$) $\delta$ 167.98, 167.97, 146.4, 143.4, 127.9, 126.8, 123.1, 122.8, 81.6, 81.5, 57.5, 41.6, 34.8, 27.91, 27.90. IR (film): 3006, 2977, 1723 cm$^{-1}$. HRMS (EI+) *m*/*z*: [M+] Calcd for $C_{19}H_{26}O_4$ 318.1831; found 318.1829.




(±)-Di-*tert*-butyl 2-(benzocyclobutenyl)malonate (**2-8b**). The title compound was prepared from 2-vinylphenyl triflate (0.252 g, 1 mmol) and di-*tert*-butyl malonate (0.31 mL, 1.4 mmol) using General Procedure B except on a 1 mmol scale. The crude material was purified *via* column chromatography on silica gel using 2% EtOAc/ hexanes as eluent. This procedure afforded 0.170 g (53%) of the title compound as a bright yellow oil. Characterization data were identical to those provided above.

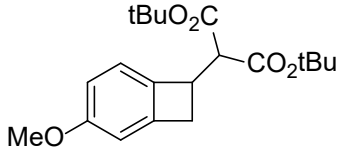


(±)-Diadamantyl 2-(benzocyclobutenyl)malonate (**2-8c**). The title compound was prepared from 2-vinylphenyl triflate (50 mg, 0.2 mmol) and diadamantyl malonate (0.104 g, 0.28 mmol) using General Procedure B. The crude material was purified *via* column chromatography on silica gel using 2% EtOAc/hexanes as eluent. This procedure afforded 34 mg (36%) of the title compound as a white solid, mp 56−60 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.26−7.14 (m, 2H), 7.11 (d, $J$ = 7.1 Hz, 1H), 7.05 (d, $J$ = 7.0 Hz, 1H), 3.96 (ddd, $J$ = 10.3, 5.4, 2.6 Hz, 1H), 3.45−3.35 (m, 2H), 3.00 (dd, $J$ = 14.4, 2.6 Hz, 1H), 2.18−2.16 (m, br, 6H), 2.12−2.10 (m, br, 12H), 1.70−1.63 (m, br, 12H). $^{13}$C{$^{1}$H} NMR (126 MHz, CDCl3) $\delta$ 167.8, 146.5, 143.5, 127.8, 126.8, 123.1, 122.8, 81.7, 81.6, 57.8, 41.7, 41.19, 41.17, 36.1, 35.0, 30.8; one carbonyl signal and two aliphatic signals are missing due to accidental equivalence. IR (film): 3070, 2909, 1723 cm$^{-1}$. HRMS (APCI+) $m/z$: [M + H]$^{+}$ Calcd for $C_{31}H_{38}O_4$ 475.2843; found 475.2862.

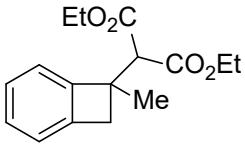



(±)-Diethyl 2-(3-methoxybenzocyclobutenyl)malonate (**2-8d**). The title compound was prepared from 5-methoxy-2-vinylphenyl triflate (56 mg, 0.2 mmol) and diethyl malonate (43 $\mu$L, 0.28 mmol) using General Procedure B. The crude material was purified *via* column chromatography on silica gel using 8% EtOAc/hexanes as eluent. This procedure afforded 14 mg (24%) of the title compound as a bright yellow oil. $^{1}$H NMR (600 MHz, $CDCl_3$) $\delta$ 6.99 (d, $J$ = 8.1 Hz, 1H), 6.73 (dd, $J$ = 8.1, 2.2 Hz, 1H), 6.67 (d, $J$ = 2.2 Hz, 1H), 4.30−4.18 (m, 4H), 3.97 (ddd, $J$ = 10.8, 5.3, 2.5 Hz, 1H), 3.76 (s, 3H), 3.51 (d, $J$ = 10.7 Hz, 1H), 3.39 (dd, $J$ = 14.4, 5.2 Hz, 1H), 2.93 (dd, $J$ = 14.4, 2.5 Hz, 1H), 1.27 (m, 6H). $^{13}$C{$^{1}$H} NMR (151 MHz, $CDCl_3$) $\delta$ 168.7, 168.6, 160.3, 143.9, 137.5, 124.0, 113.7, 108.7, 61.4, 56.1, 55.4, 40.7, 34.6, 14.12, 14.10;

one aliphatic signal is missing due to accidental equivalence. IR (film): 3005, 2955, 1728 $cm^{-1}$. HRMS (EI+) *m/z*: [M+] Calcd for $C_{16}H_{20}O_5$ 292.1311; found 292.1320.




(±)-Di-*tert*-butyl 2-(3-methoxybenzocyclobutenyl)malonate (**2-8e**). The title compound was prepared from 5-methoxy-2-vinylphenyl triflate (56.45 mg, 0.2 mmol) and di-*tert*-butyl malonate (62.69 $\mu$L, 0.28 mmol) using General Procedure B. The crude material was purified *via* column chromatography on silica gel using 4% EtOAc/hexanes as eluent. This procedure afforded 34.2 mg (49%) of the title compound as a bright yellow oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.1 Hz, 1H), 6.73 (d, $J$ = 8.1 Hz, 1H), 6.66 (s, 1H), 3.89 (ddd, $J$ = 10.4, 5.1, 2.4 Hz, 1H), 3.76 (d, $J$ = 1.6 Hz, 3H), 3.35 (m, 2H), 2.95 (dd, $J$ = 14.6, 2.6 Hz, 1H), 1.47−1.44 (m, 18H). $^{13}$C{$^1$H} NMR (176 MHz, CDCl3) $\delta$ 168.03, 168.02, 160.1, 144.1, 138.0, 124.2, 113.5, 108.6, 81.50, 81.45, 57.8, 55.4, 40.7, 34.3, 27.9; one aliphatic signal is missing due to accidental equivalence. IR (film): 3013, 2976, 1722 $cm^{-1}$. HRMS (EI+) *m/z*: [M+] Calcd for $C_{20}H_{28}O_5$ 348.1937; found 348.1939.




(±)-Diethyl 2-(7-methylbenzocyclobutenyl)malonate (**2-8f**). The title compound was prepared from 2-(prop-1-en-2-yl)phenyl triflate (53 mg, 0.2 mmol) and diethyl malonate (43 $\mu$L, 0.28 mmol) using General Procedure B, except the reaction was allowed to heat and stir overnight. The crude material was purified *via* column chromatography on silica gel using 4.5% EtOAc/hexanes as eluent. This procedure afforded 20 mg (37%) of the title compound as a bright

yellow oil. $^{1}$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.21 (t, $J$ = 7.4 Hz, 1H), 7.19−7.13 (m, 2H), 7.08 (d, $J$ = 7.2 Hz, 1H), 4.26−4.17 (m, 2H), 4.15 (q, $J$ = 7.2 Hz, 2H), 3.71 (s, 1H), 3.43 (d, $J$ = 14.3 Hz, 1H), 3.04 (d, $J$ = 14.3 Hz, 1H), 1.61 (s, 3H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.21 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{$^{1}$H} NMR (176 MHz, CDCl3) $\delta$ 168.4, 168.3, 150.8, 141.5, 128.1, 126.9, 123.6, 122.2, 61.12, 61.09, 58.7, 47.9, 43.6, 22.4, 14.1, 14.0. IR (film): 2985.46, 2930.89, 1727.63 cm$^{-1}$. HRMS (EI+) $m/z$: [M+] Calcd for $C_{16}H_{20}O_4$ 276.1362; found 276.1353.

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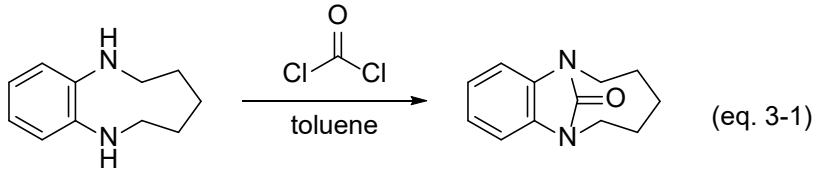
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## Chapter 3 Syntheses and Utility of Bicyclic Ureas

### 3.1 Miscellaneous Syntheses of Cyclic Ureas

Ureas are among the most significant functional groups in the context of organic chemistry on account of the fact that they are a critical component in a vast number of biologically active molecules. As such, there are an abundance of synthetic routes which can be implemented to construct urea derivatives. This section will primarily focus on selected routes that generate cyclic ureas, which have a wide range of uses in their own right.[1]

Among the earliest synthetic strategies for producing cyclic ureas is reacting diamines with phosgene (eq. 3-1).[2] This reaction was ubiquitous at one time because of the ease of access of both reactants; additionally, diverse diamines are readily accessible, lending this reaction to facile derivatization. While this is an effective method, it has fallen into disuse on account of the dangers associated with phosgene.

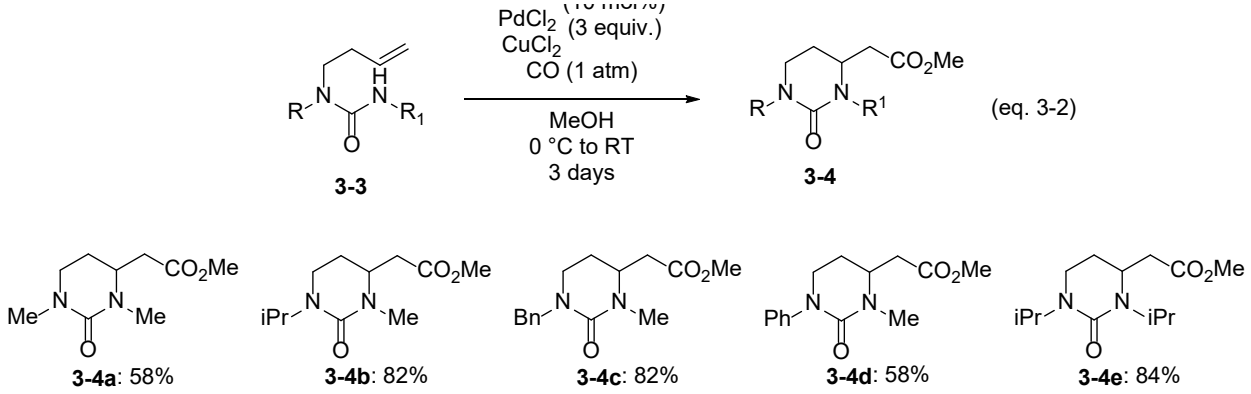



**3-1** **3-2**: 43% (eq. 3-1)

Scheme 33 Formation of cyclic ureas from diamines and phosgene.[2]

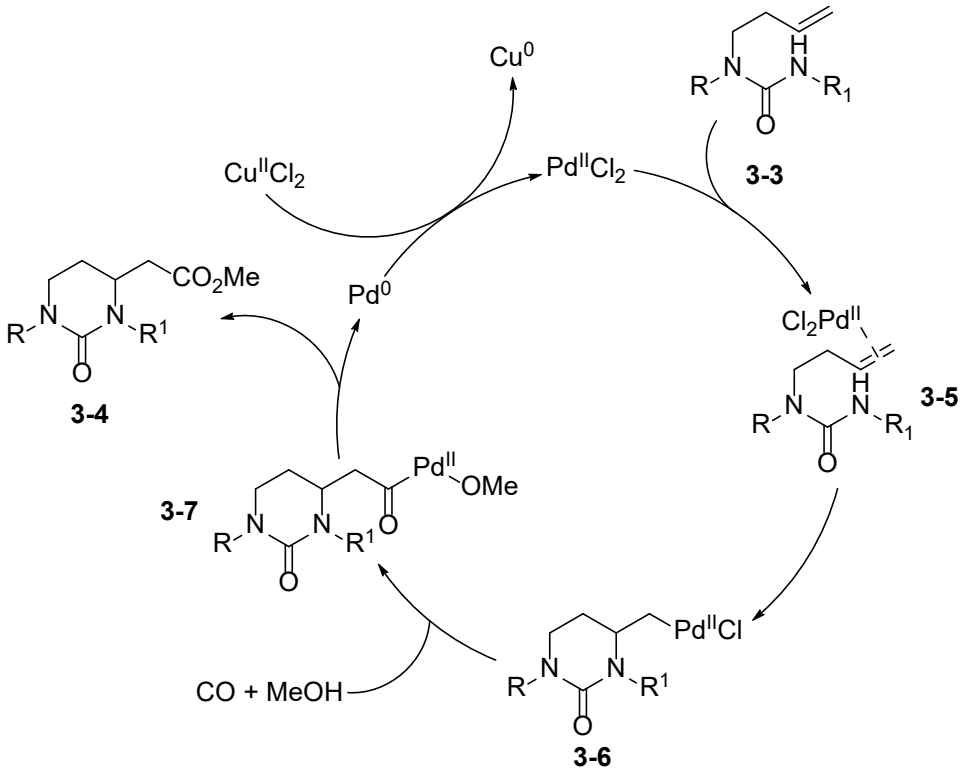
Another older method for producing cyclic ureas is performing a palladium-catalyzed aminocarbonylation on alkenyl ureas using Wacker-like conditions. More specifically, this reaction converts butenyl ureas to six-membered ureacycles with tethered ester groups in moderate to high yield (eq. 3-2). This transformation is facilitated by moderate steric bulk on the

nitrogen bearing the alkenyl group, as the substrates with the highest yield have isopropyl groups in this position (e.g., **3-4e**).



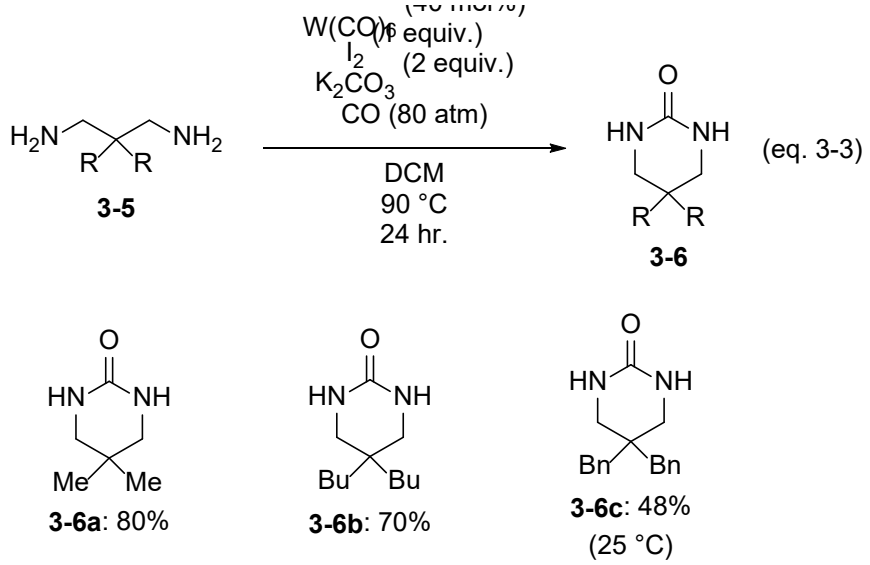

Scheme 34 Formation of cyclic ureas *via* palladium-catalyzed aminocarbonylation.[3]

This reaction begins with the palladium(II) catalyst coordinating to the alkene to form the complex **3-5**. Aminopalladation then generates the palladium-bearing cyclic urea **3-6**. The carbon monoxide atmosphere and methanol solvent then react with palladium to perform a carbonylation and ligand exchange, respectively (**3-7**). Subsequently, a reductive elimination forms the final product **3-4** and palladium(0) byproduct. The copper(II) chloride in the reaction mixture then oxidizes the palladium to regenerate the palladium(II) catalyst (Scheme 35).[3]



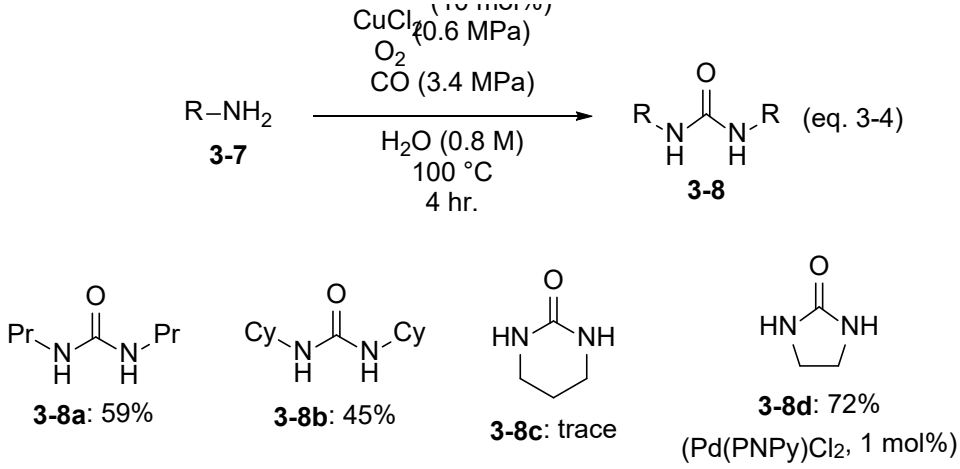

Scheme 35 Aminocarbonylation mechanism.[3]

Carbonylation reactions have proven to be a persistent pathway to accessing cyclic ureas. For instance, carbonylation of *gem*-dialkyl primary diamines to form *gem*-dialkyl cyclic ureas can be achieved with tungsten(0) hexacarbonyl and carbon monoxide. While this reaction tolerates several alkyl groups, it is able to produce ureas with smaller alkyl groups (i.e., methyl groups) in the highest yields (eq. 3-3).[4]



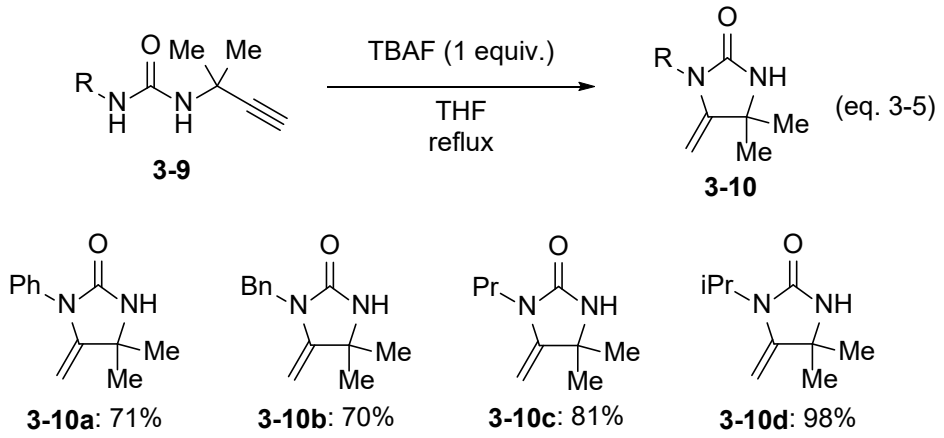

Scheme 36 *Gem*-dialkyl cyclic ureas formed *via* tungsten-mediated carbonylation.[4]

Another recent example of making ureas *via* carbonylation was a copper-facilitated reaction reported by Angelo Nacci and collaborators. This method is able to take two equivalents of a primary amine and form linear amines while under carbon monoxide atmosphere in moderate yields (eq. 3-4). While this method exhibits a low tolerance for intramolecular carbonylations with primary diamines (**3-8c**), exchanging the copper(II) catalyst for a palladium(II) catalyst vastly increases the yield for cyclic amines (**3-8d**).[5]



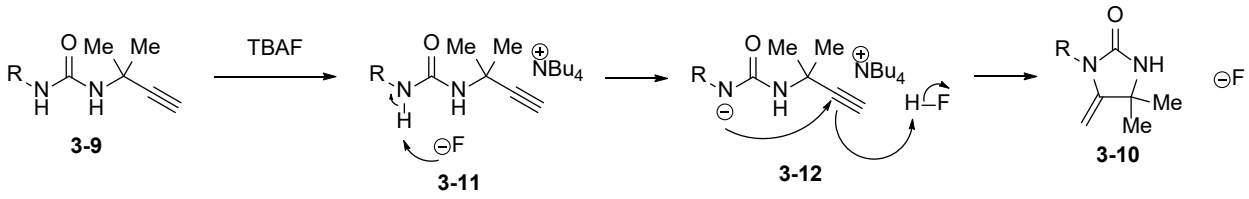

Scheme 37 Copper-catalyzed carbonylation to form ureas.[5]

Cyclic ureas have also been accessed through metal-free pathways. A notable example of this is the reaction of propargylic ureas (**3-9**) with tetra-*n*-butylammonium fluoride (TBAF) to form cyclic alkenyl ureas (**3-10**) in moderate to high yield. The non-aryl substrates produced the highest yields of product, with an isopropyl group attaining a nearly quantitative yield (**3-10d**).




Scheme 38 Cyclic ureas formed from TBAF-mediated 5-*exo*-dig cyclization.[6]

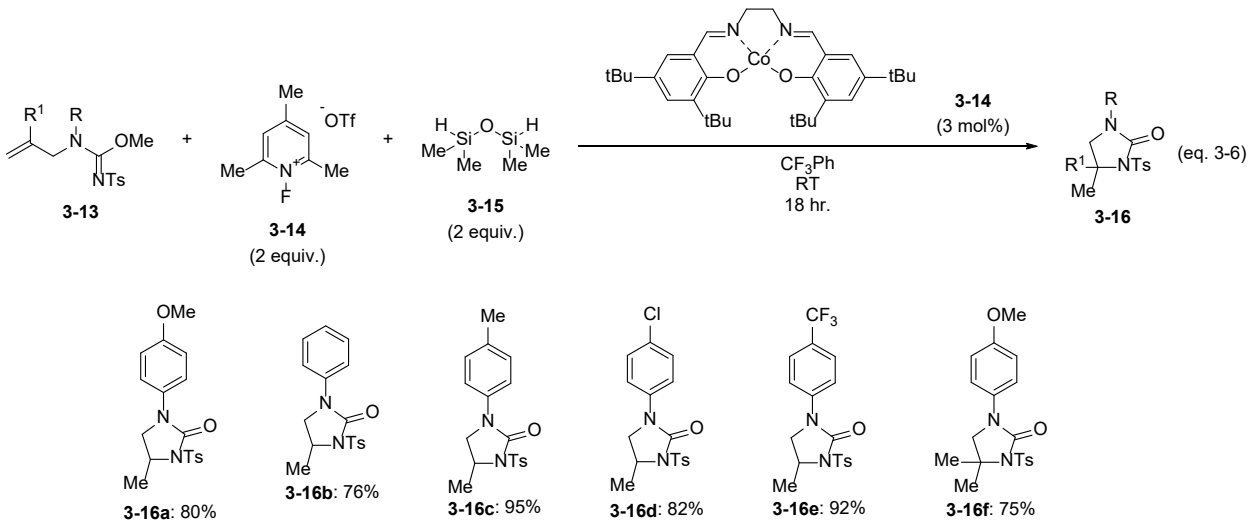
This reaction is able to take place because the tetra-*n*-butylammonium cation coordinates to the alkynyl $\pi$ electrons, and this primes the bond for a nucleophilic attack. The fluoride anion is also able to deprotonate the urea in catalytic fashion to form intermediate **3-11**. Then, the deprotonated urea performs a 5-*exo*-dig cyclization, and hydrogen fluoride protonates the alkene to form the neutral final product **3-10** (Scheme 38).[6]




Scheme 39 Proposed mechanism for TBAF-mediated 5-*exo*-dig cyclization.[6]

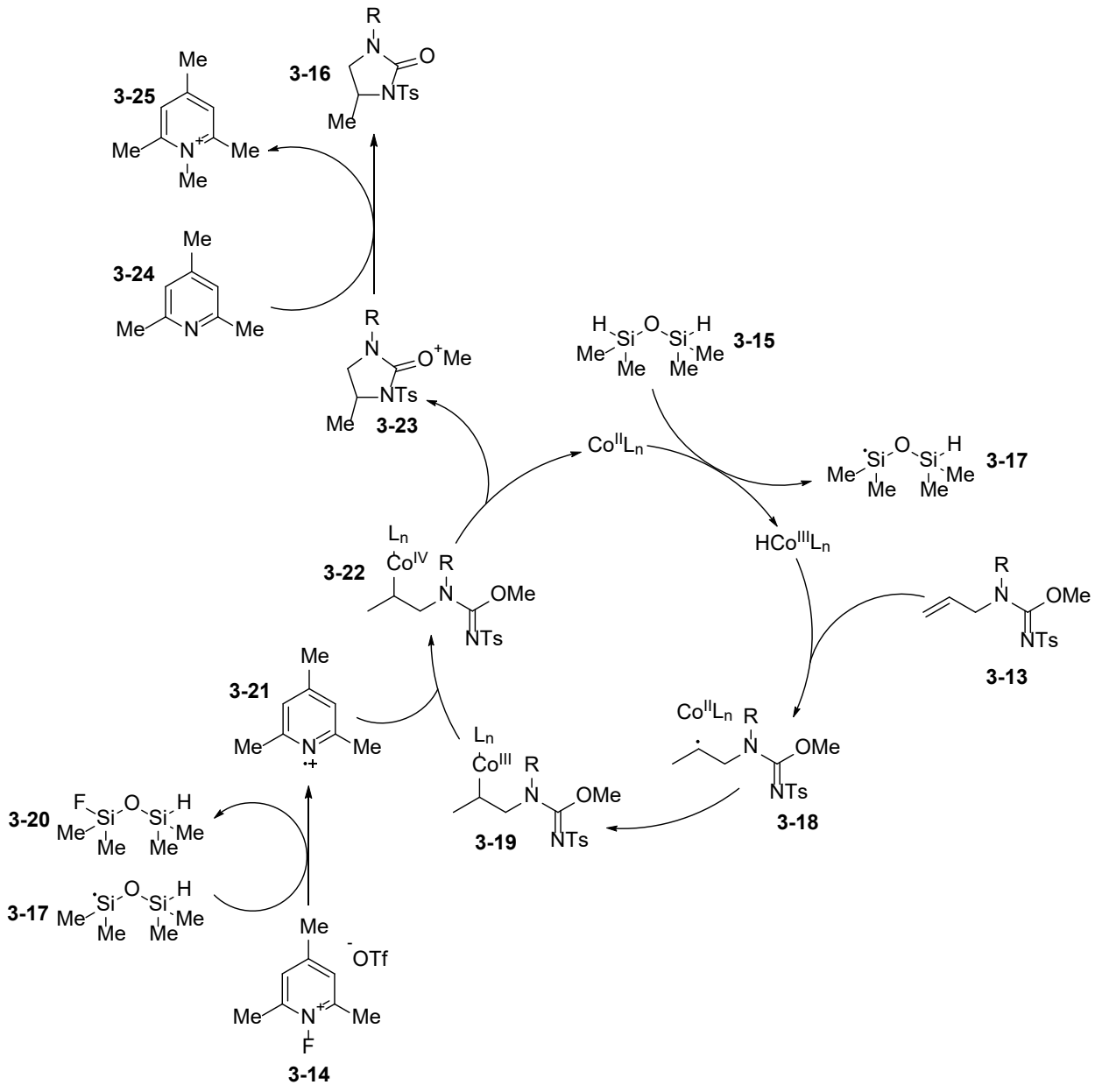
A particularly interesting route to access cyclic ureas involves cobalt-catalyzed hydrogen atom transfer (HAT) and radical-polar crossover involving alkenyl isoureas (**3-13**) to produce five-membered ureacycles (**3-16**) in moderate to high yield (eq. 3-6). This reaction is able to

produce ureas with a variety of aryl substitutions and is even able to tolerate substitution on the alkene in the case of product **3-16f**. The highest yields were observed with *para* methyl (**3-16c**) and trifluoromethyl (**3-16e**) substituents on the aryl ring.




Scheme 40 Cyclic ureas formed via cobalt-catalyzed HAT and radical-polar crossover.[7]

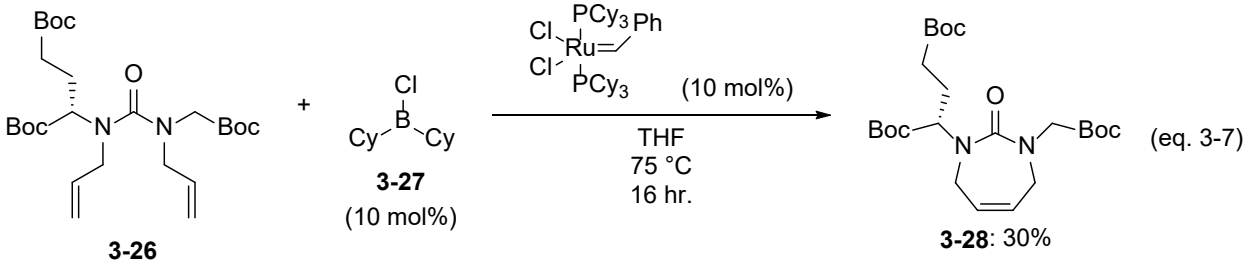
The mechanism for this transformation begins with the formation of a cobalt(III) hydride from the initial cobalt(II) catalyst and a silane hydrogen source (**3-15**). The cobalt(III) hydride then performs a transition-metal HAT on the alkene **3-13**. This generates a radical at the more substituted carbon (**3-18**), and this radical reacts with the regenerated cobalt(II) catalyst to form the cobalt(III) intermediate **3-19**. Concurrently, *N*-fluoro-2,4,6-collidinium triflate (**3-14**) reacts with silyl radical **3-17** to form the cationic 2,4,6-collidinium radical **3-21**. This radical then acts as an oxidant for **3-19**, bringing the oxidation state of the metal to cobalt(IV) (**3-22**). An $S_N2$-style nucleophilic attack from the isourea nitrogen generates the target ring (**3-23**) and regenerates the cobalt(II) catalyst. The ring is dealkylated by neutral 2,4,6-collidine (**3-24**) to form the final product (**3-16**) (Scheme 41).[7]




Scheme 41 Proposed mechanism for cobalt-catalyzed HAT and radical-polar crossover.[7]

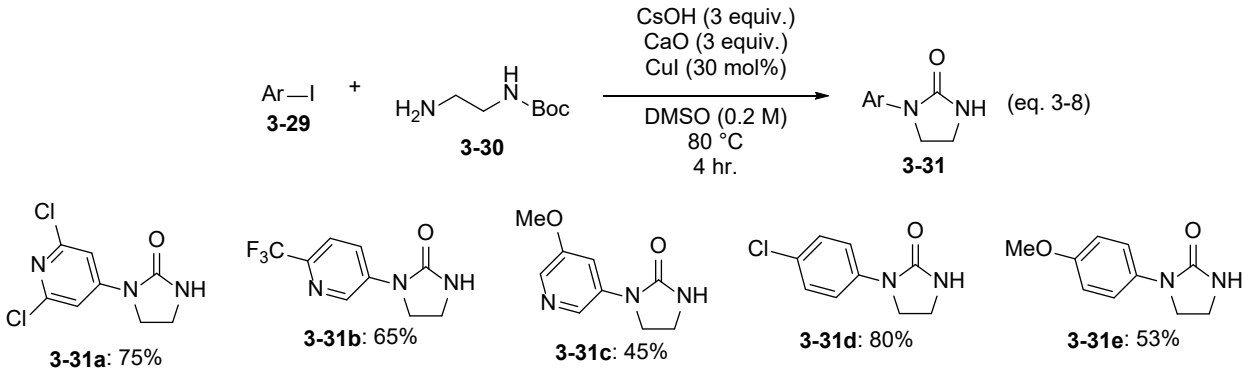
Another strategy that has been implemented to access ureacycles is ring-closing metathesis (RCM). This particular method was used to produce a seven-membered alkenyl cyclic urea which is a scaffold to access prostate-specific membrane antigen (PSMA) inhibitors. In addition to the Grubbs first generation catalyst, a common RCM reagent,

chlorodicyclohexylborane (CBU) is added to act as a Lewis acid. This prevents the Grubbs catalyst from chelating to the alkene and preventing the desired RCM (eq. 3-7).[8]




Scheme 42 Formation of a seven-membered cyclic urea *via* RCM.[8]

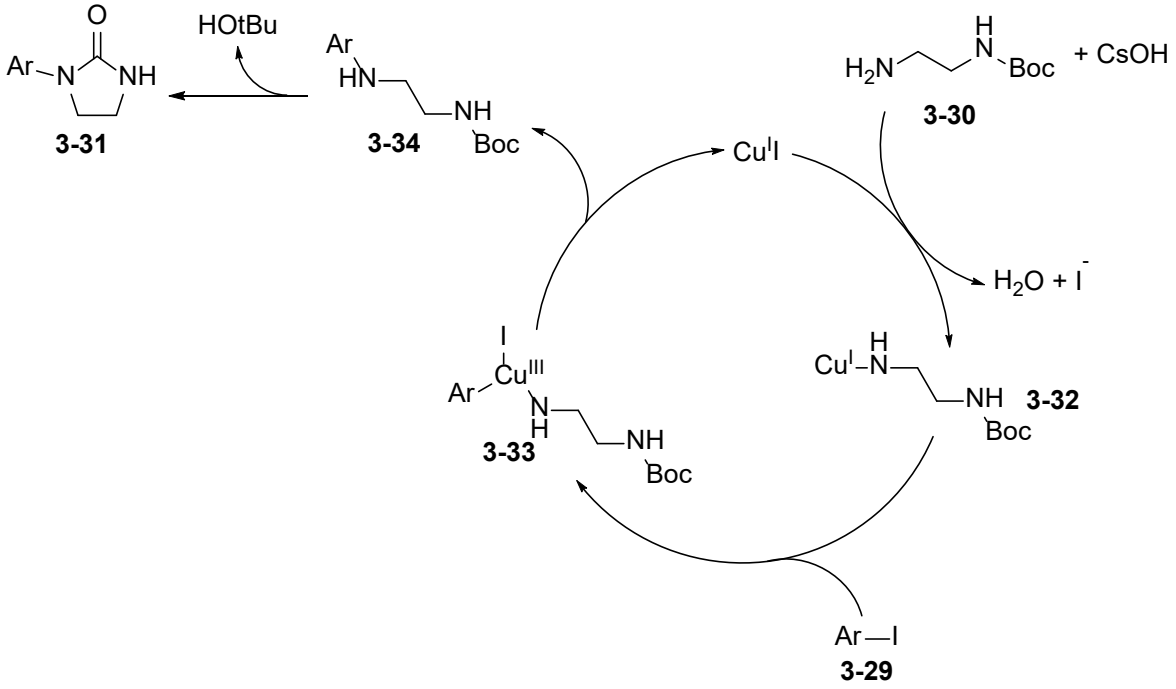
Copper(I) iodide has also been employed to generate five-membered cyclic ureas with aryl substituents from the coupling of aryl iodides and diaminecarbamates (eq. 3-8). While the reaction is able to form product with a multitude of pyridinyl and phenyl groups, the highest yields are observed with aryl groups that are electron withdrawing. For example, the highest-yielding pyridine has two chlorines (**3-31a**), while the highest-yielding benzene has a chlorine *para* to the cyclic urea (**3-31d**).




Scheme 43 Cyclic ureas formed *via* copper catalysis.[9]

This transformation begins with the copper(I) iodide catalyst undergoing a ligand exchange with the diaminecarbamate to form intermediate **3-32**. This copper(I) intermediate is then able to perform an oxidative addition to an aryl iodide to generate the copper(III) species **3-33**. A reductive elimination installs the aryl group on the diaminecarbamate (**3-34**) and

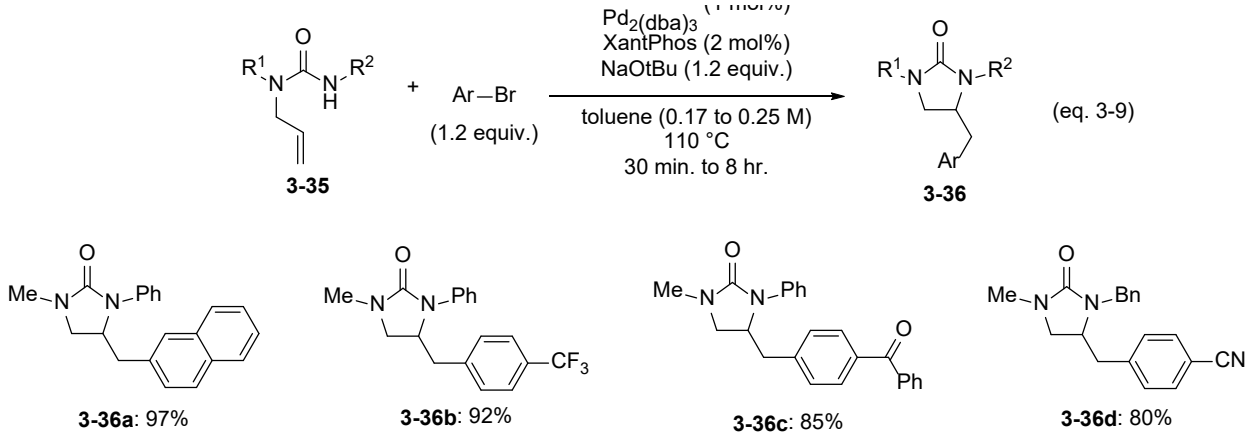
regenerates the copper(I) catalyst. An intramolecular nucleophilic attack produces the final ureacycle **3-31** (Scheme 44).[9]




Scheme 44 Proposed mechanism for copper-catalyzed cyclic urea formation.[9]

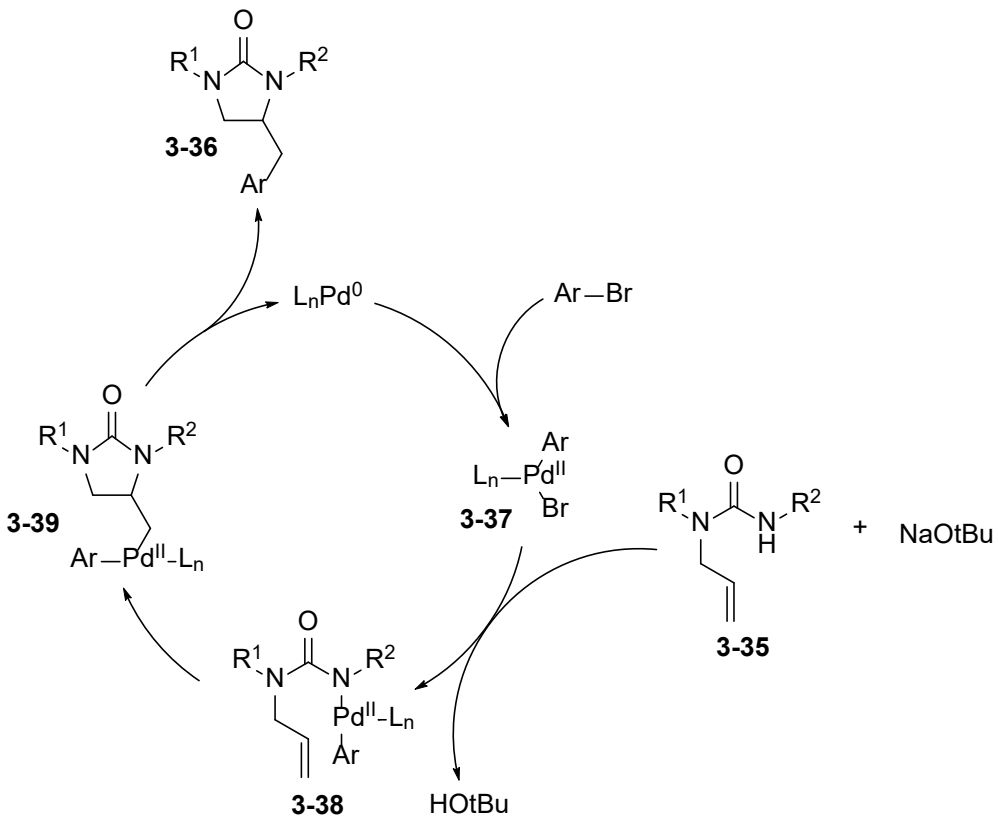
### 3.2 Accessing Cyclic Ureas Through Palladium-Catalyzed Carboamination

Among the most significant synthetic strategies for producing cyclic ureas is palladium-catalyzed carboamination. This method was initially developed by Wolfe and coworkers in 2006 to form derivatized imidazolidin-2-ones, or five-membered cyclic ureas. These products are formed by a palladium(0) and XantPhos mediated reaction between *N*-allylureas and aryl bromides. This was able to produce several aryl imidazolidin-2-ones in moderate to high yield (eq. 3-9).[10]



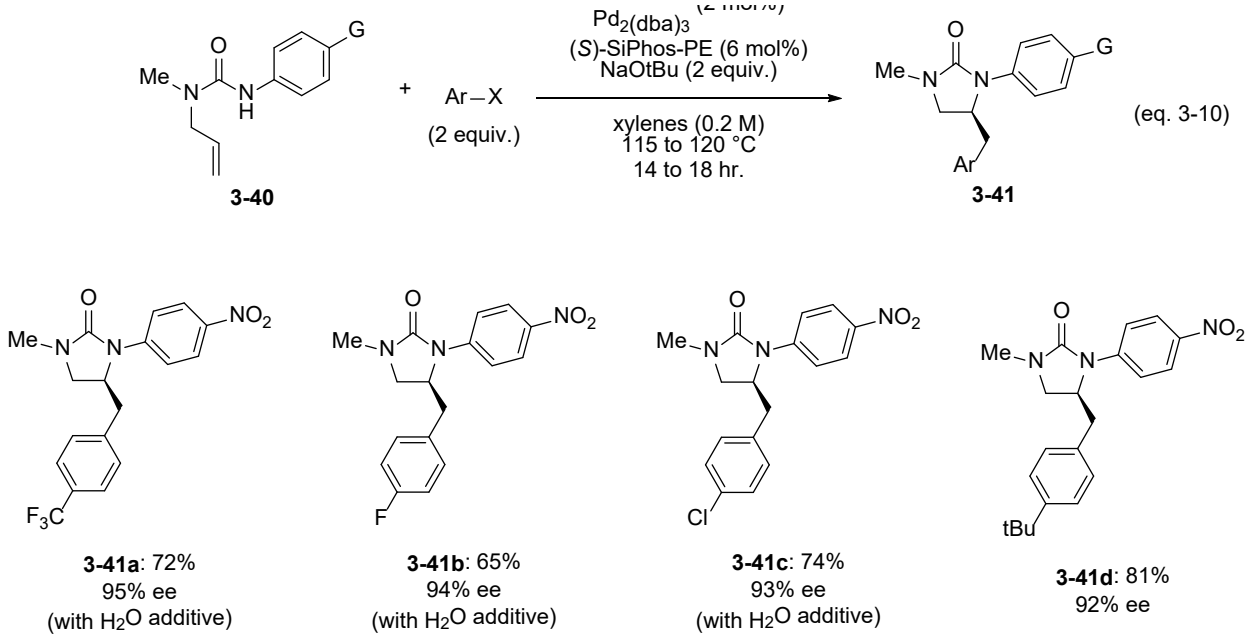

Scheme 45 Imidazolidin-2-one formation reaction and selected substrates.[10]

The mechanism for this reaction begins with palladium(0) performing an oxidative addition into the aryl bromide bond (**3-37**). Then, the deprotonated *N*-allylurea displaces the bromide on the palladium to form a palladium-amido complex (**3-38**). A migratory insertion step results in the creation of the imidazolidin-2-one ring (**3-39**). The catalytic cycle concludes with a reductive elimination to form the final product (**3-36**) and to regenerate the palladium(0) catalyst (Scheme 46).[11]



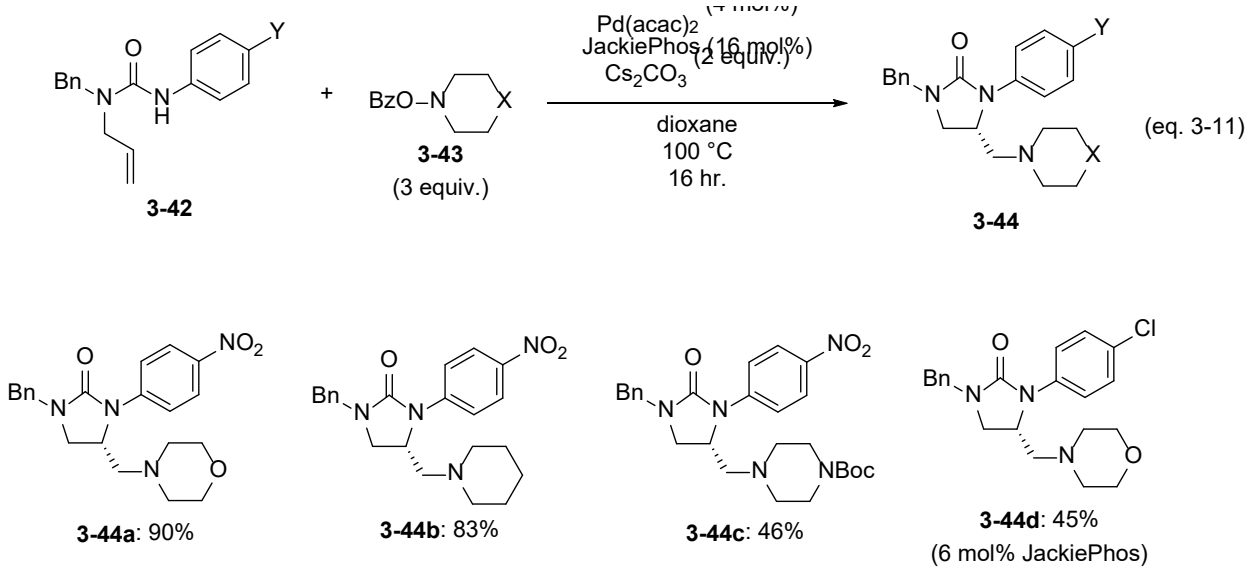

Scheme 46 Proposed imidazolidin-2-one formation mechanism.[11]

Notably, this reaction also has an asymmetric analogue. The primary distinction between this reaction and the original conditions is the choice of ligand. The optimal ligand for this asymmetric reaction was found to be (*S*)-SiPhos-PE, a chiral phosphine which has been used in the context of other asymmetric carboaminations. When implemented for the formation of chiral imidazolidin-2-ones, these conditions were observed to produce a wide range of substrates in both high yields and enantiomeric excess (eq. 3-10).[12]



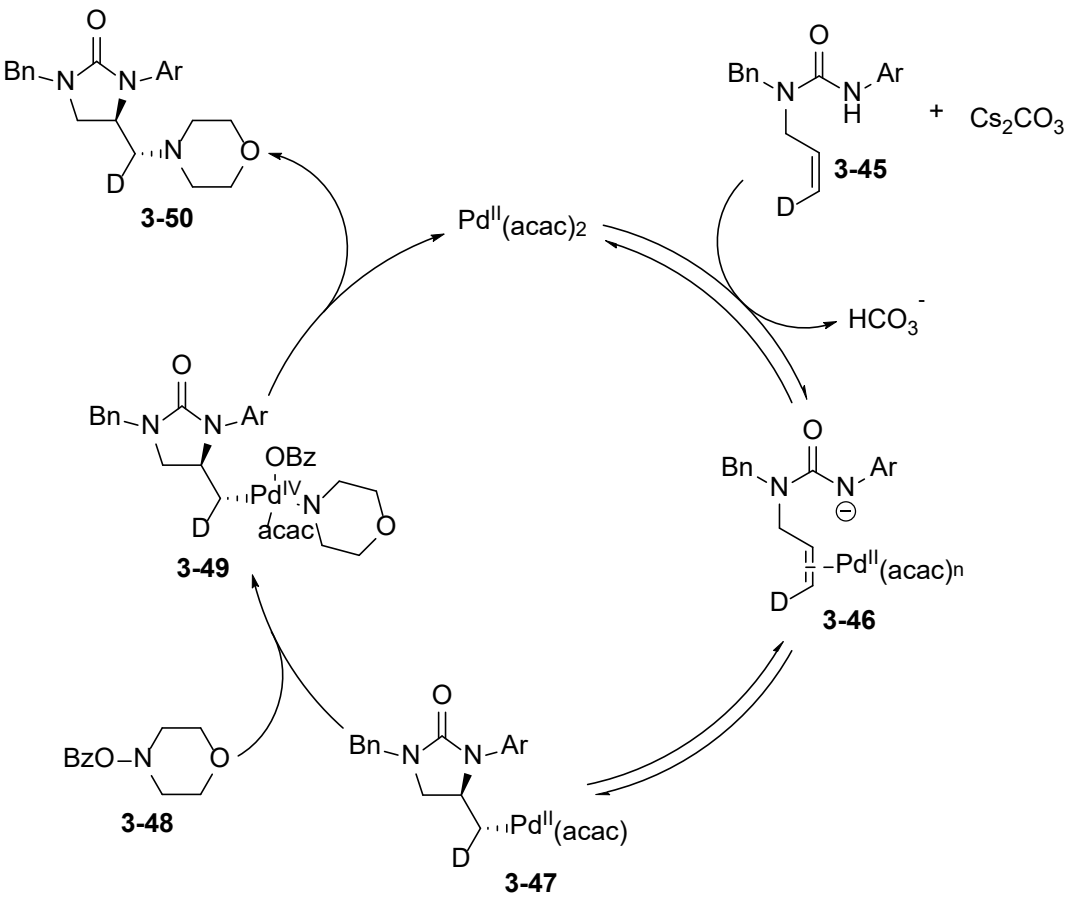

Scheme 47 Selected chiral imidazolidin-2-ones.[12]

An umpolung version of reaction has also been developed by Wolfe and collaborators to facilitate the formation of imidazolidin-2-ones with non-aryl substituents, including morpholine, piperidine, and piperazine. Among the most notable changes to the reaction are the ligand and palladium source. Instead of XantPhos, this reaction uses JackiePhos, an electron-deficient biaryl dialkylphosphine. Additionally, the palladium source is palladium(II) bis(acetylacetonate) as opposed to a palladium(0) source. These reagents are able to form derivatized imidazolidin-2-ones in moderate to high yields, with the highest yields belonging to substrates with tethered morpholine groups (eq. 3-11).[13]



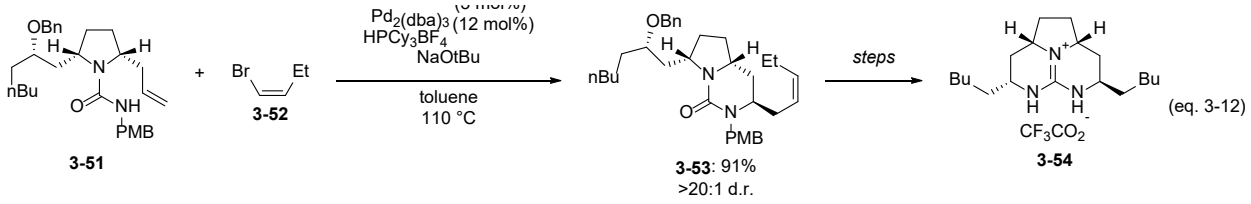

Scheme 48 Selected imidazolidin-2-ones with tethered amines.[13]

Mechanistic investigations have revealed that the formation of these derivatives is achieved through a distinct pathway to their aryl counterparts. The initial step involves the palladium(II) catalyst coordinating to the alkene tethered to the deprotonated acyclic urea (**3-46**). Then, the palladium performs a reversible aminopalladation of the alkene to form the core imidazolidin-2-one ring (**3-47**). This is followed by the palladium undergoing an irreversible oxidative addition into the nitrogen-benzoyl ester bond to form a palladium(IV) complex (**3-49**). This leads to a reductive elimination which forms the desired product (**3-50**) and regenerates the palladium(II) catalyst (Scheme 49).[14]



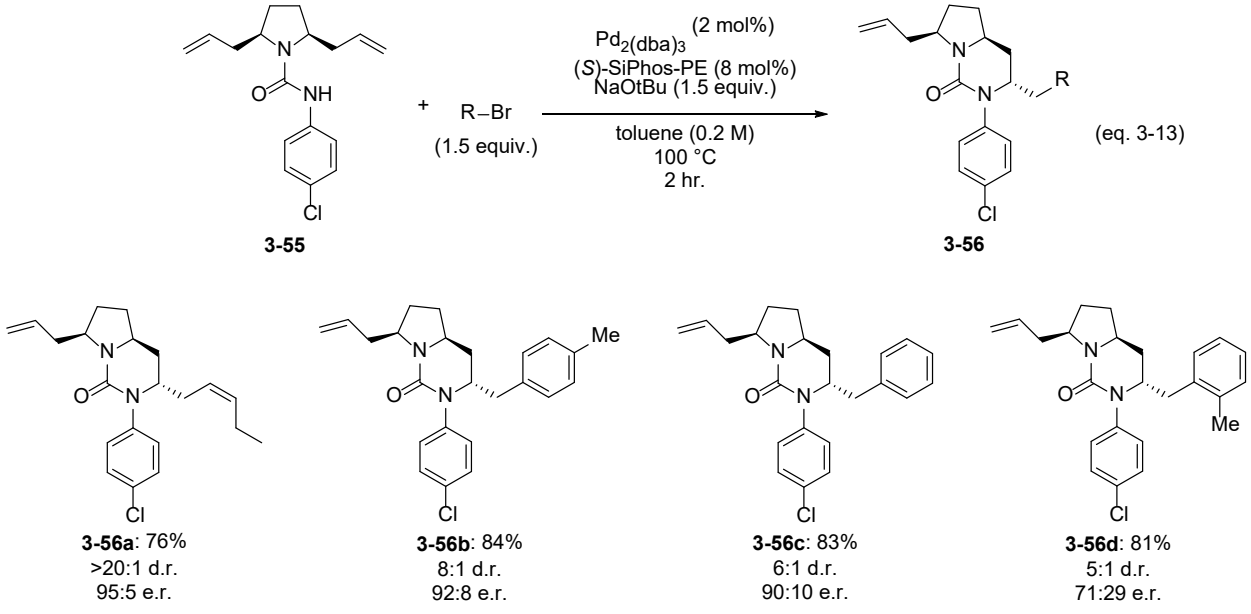

Scheme 49 Mechanism for generating imidazolidin-2-ones through a Pd(II/IV) cycle.[14]

The Wolfe group has also leveraged palladium-catalyzed carboamination to produce hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones, a type of bicyclic urea. This was initially developed as a key step in the total synthesis of (+)-merobatzelladine B, a natural product with antimicrobial activity. More specifically, a cyclic urea with a tethered alkene (**3-51**) and 1-bromobut-1-ene (**3-52**) are combined with tris(dibenzylideneacetone)dipalladium(0) and tricyclohexylphosphine tetrafluoroborate to form bicyclic urea **3-53**. This compound, in turn, can be carried forward to the target natural product (**3-54**) with additional synthetic steps.[15]



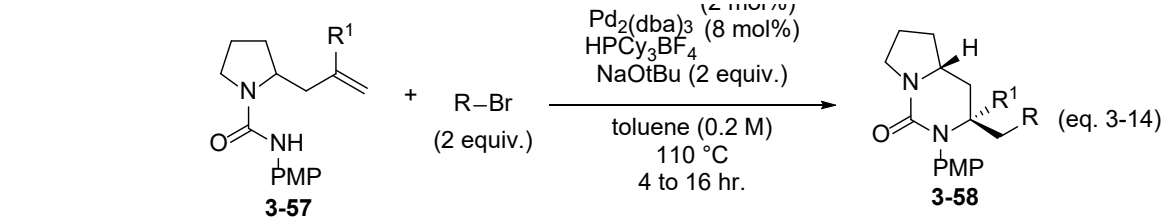

Scheme 50 Palladium-catalyzed carboamination in the total synthesis of (+)-merobatzelladine.[15]

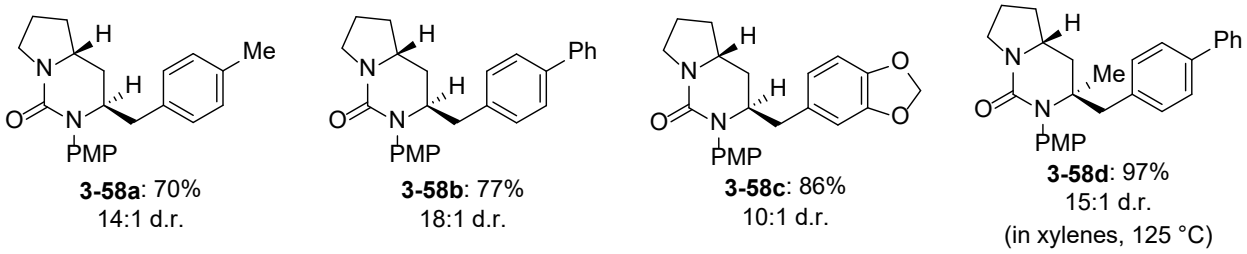
After this reaction was applied in the context of total synthesis, it was redeveloped to generate various hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones with aryl and alkenyl substituents. The optimal conditions for this transformation are nearly identical to those implemented in the asymmetric formation of imidazolidin-2-ones; namely, a palladium(0) catalyst and (*S*)-SiPhos-PE work in conjunction to produce bicyclic ureas in high yield and with high diastereoselectivity and enantioselectivity. While this reaction is able to form target products from aryl bromide reactants, the greatest degree of stereoselectivity is observed with linear alkenyl bromides (eq. 3-13).[16]




Scheme 51 Selected substrates from the palladium-catalyzed formation of bicyclic ureas with alkenyl and aryl substituents.[16]

This reaction was later revisited to further optimize the yields and selectivity associated with aryl substituents. This was achieved by implementing tricyclohexylphosphine (introduced to the reaction as the air-stable tetrafluoroborate salt) as the ligand for this process. This change resulted in high yields and diastereoselectivities for reactions with toluyl and biphenyl bromides. Additionally, this reaction tolerated substitution on the internal carbon of the substrate alkene, and a yield as high as 97 percent was observed when this urea ($R^1$ = Me) was reacted with biphenyl bromide (eq. 3-14).[17]



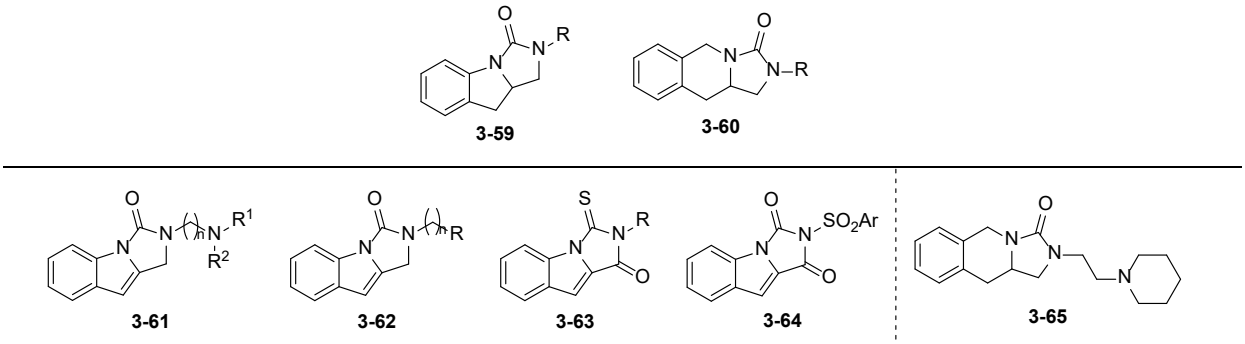




Scheme 52 Selected substrates from additional hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones generated *via* palladium-catalyzed carboamination.[17]

Collectively, these reactions demonstrate the robustness and versatility of leveraging palladium-catalyzed carboamination for the synthesis of cyclic ureas. This reaction's ability to access an array of substituted imidazolidin-2-ones and hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones clearly demonstrate its capacity to form interesting molecules, and this chemistry is not strictly limited to these particular structures. In the following section, two cyclic ureas which have yet to be generated with this specific palladium-catalyzed carboamination mechanism will be described alongside established synthetic pathways which produce them.

### 3.3 Utility and Significant Syntheses of Bicyclic Ureas

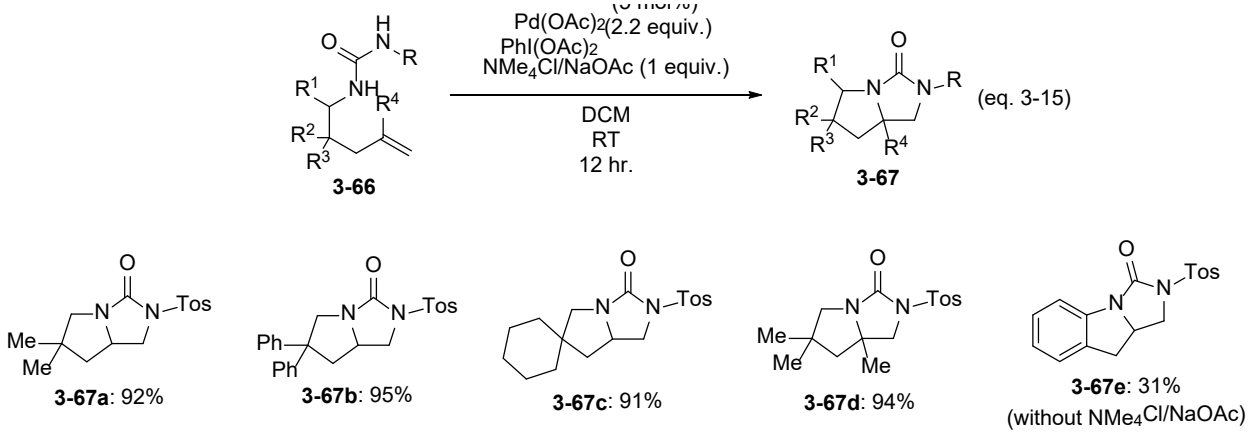
Two bicyclic urea systems which are of potential significance are 1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-ones (**3-59**), which contain an indoline core, and 1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3(2*H*)-ones (**3-60**), which have a tetrahydroisoquinoline core. While the saturated version of the former ring system is rarely encountered, its unsaturated indole counterpart and closely related ring systems have seen extensive utilization in the context of medicinal chemistry.[18] In particular, these bicyclic ureas have been used as central nervous system (CNS) depressants (**3-61**),[19] 5-$HT_3$ receptor antagonists (**3-62**),[20] tumor necrosis factor-α (TNF-α) antagonists (**3-63**),[21] human chymase inhibitors (**3-64**),[22] hepatitis C virus polymerase (HCVP) inhibitors,[23] and vascular endothelial growth factor (VEGF) inhibitors.[24] The latter tetrahydroisoquinoline-based urea, on the other hand, has been synthesized on only one occasion as a potential $\sigma_1$ ligand (**3-65**).[25]




Scheme 53 Generic 1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-ones and 1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3(2*H*)-ones and applications of similar ring systems.[18, 25]

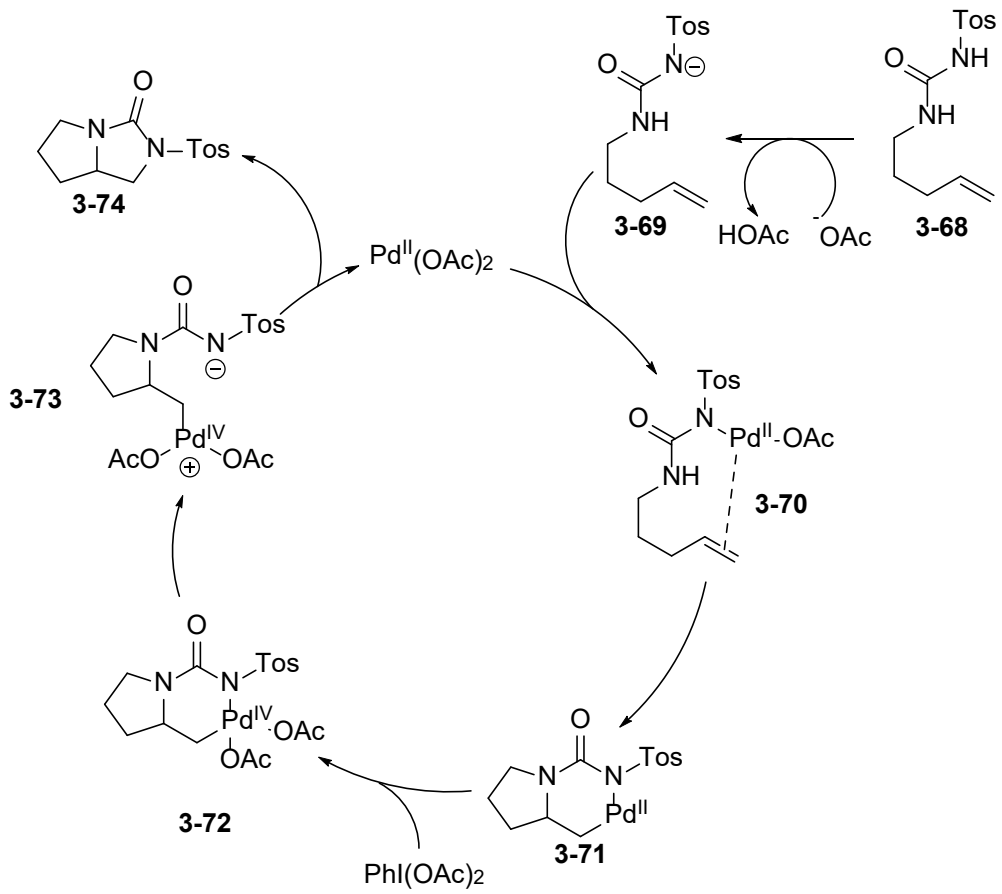
The most common and effective way to access indolinyl bicyclic ureas and other polycyclic ureas is through metal-mediated alkene diamination, and this method was fundamentally shaped by the work of Kilian Muñiz. In 2005, he described a palladium-catalyzed diamination reaction which was able to generate various bicyclic ureas from acyclic alkenyl ureas in yields over 90 percent. Additionally, this reaction was also able to form an indolinyl

bicyclic urea (**3-67e**) in moderate yield (eq. 3-15). This work differs from the previously discussed carboaminations from the Wolfe group since the transformation is achieved by combining a palladium(II) catalyst with a hypervalent iodine oxidant.[26]



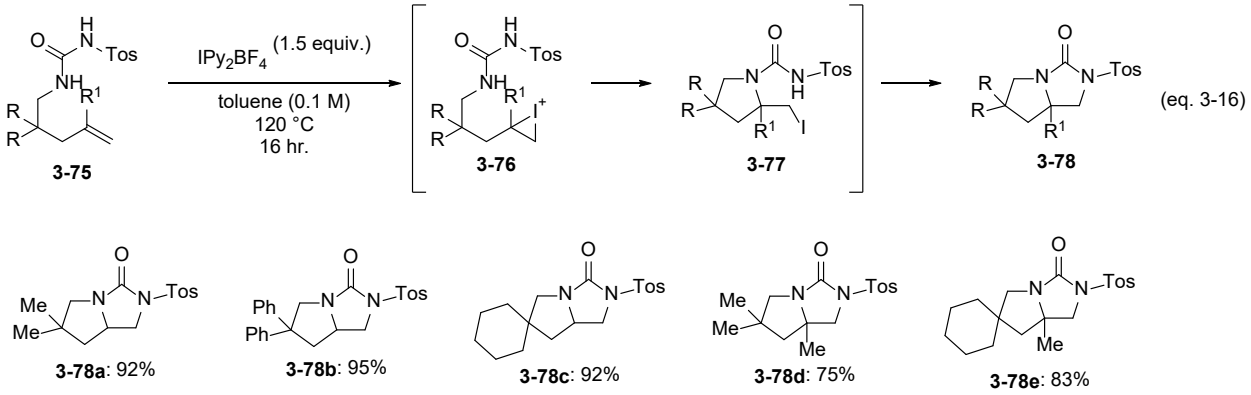

Scheme 54: Muñiz's formation of bicyclic ureas from palladium-catalyzed diamination.[26]

A later mechanistic study reveals how this reaction is able to take place. First, the deprotonated acyclic urea **3-69** binds to the palladium(II) catalyst to form intermediate **3-70**, where the palladium is both bonded to the nitrogen and coordinated to the urea's attached alkene. A *syn*-aminopalladation leads to the six-membered palladacycle intermediate **3-71**. Then, phenyliodine(III) diacetate oxidizes the palladium(II) atom to palladium(IV) (**3-72**). The palladium(IV) atom subsequently dissociates from the urea nitrogen to form the cationic palladium species **3-73**. The second ring of the bicyclic urea **3-74** is formed by a bimolecular nucleophilic substitution ($S_N2$)-style *anti*-amination-depalladation (Scheme 55).[27]



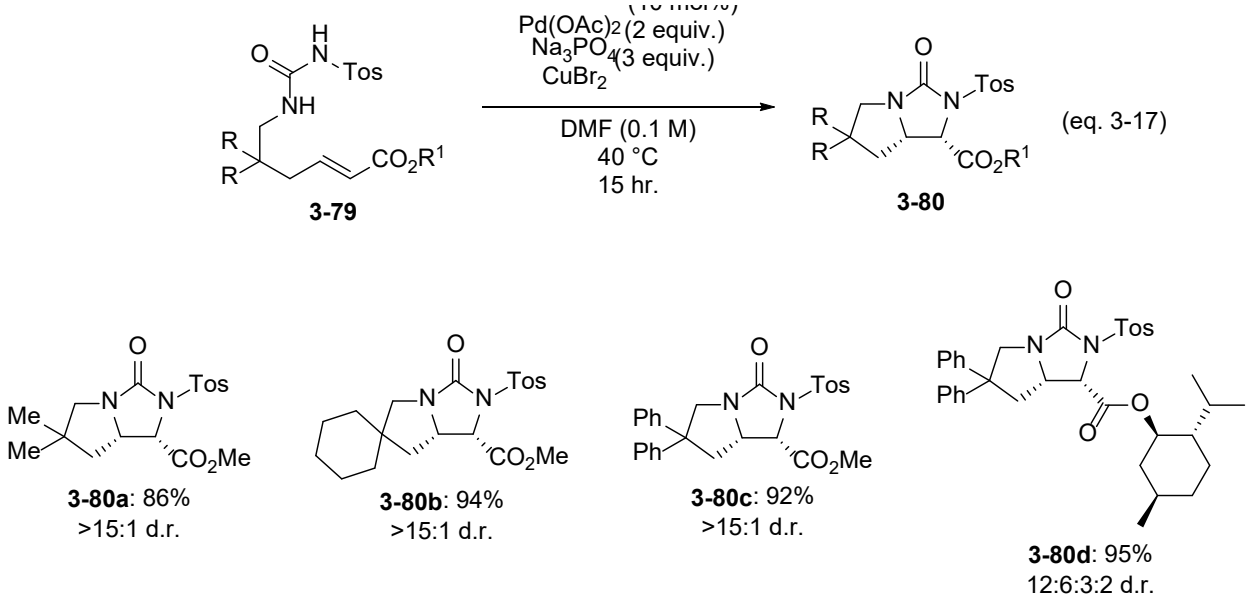

Scheme 55 Proposed mechanism for palladium-catalyzed alkene diamination.[27]

Muñiz's work in forming bicyclic ureas is not limited to metal-catalyzed methods. In 2008, he devised a reaction where bicyclic ureas are generated from alkenyl ureas and bis(pyridine)iodonium tetrafluoroborate, an electrophilic iodine source. This is achieved by the urea alkene attacking the electrophilic iodine, and this forms an iodonium intermediate (**3-76**). A 5-*exo-trig* cyclization forms the first of the two rings, and a second intramolecular nucleophilic attack forms the second ring (**3-78**). This reaction was able to form the desired ureas in yields comparable to those observed with metal-mediated strategies. This fact was underscored by Muñiz and collaborators running parallel palladium-catalyzed reactions in tandem with the bis(pyridine)iodonium tetrafluoroborate mediated reactions to demonstrate their comparable yields (eq. 3-16).[28]



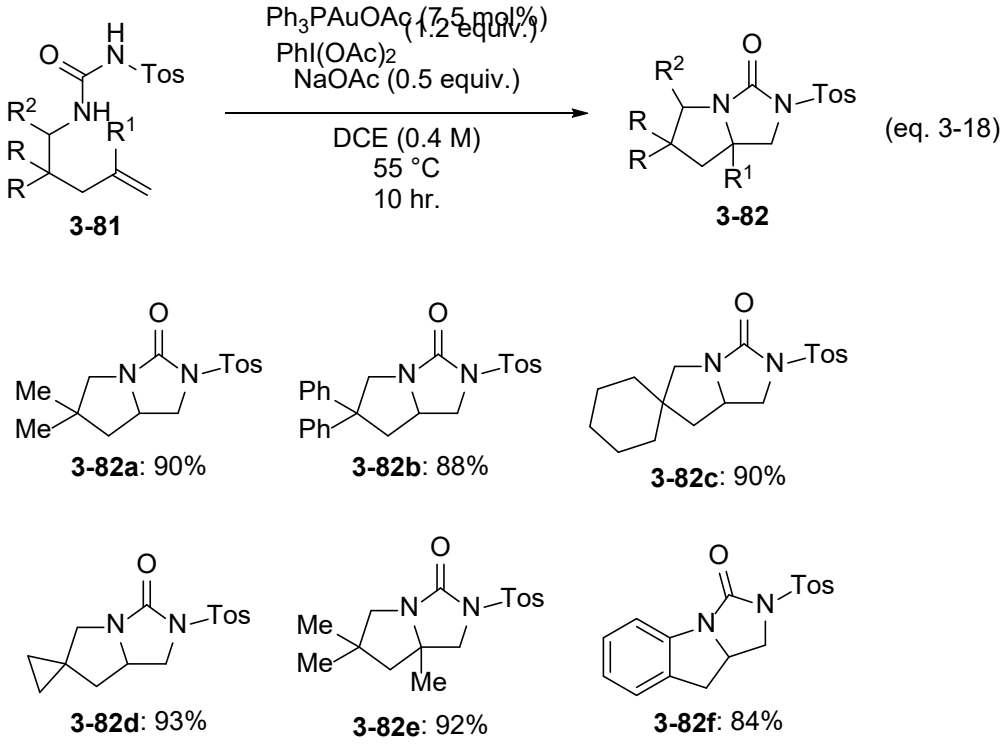

Scheme 56 Bicyclic ureas formed from bis(pyridine)iodonium tetrafluoroborate.[28]

The scope of bicyclic ureas accessible by alkene diamination reactions was further expanded when a procedure was developed to incorporate ester substituents onto these rings. The optimal conditions for this transformation are nearly identical to those employed in the original palladium-catalyzed alkene diamination reaction, but the hypervalent iodine oxidant is exchanged for copper(II) bromide. These conditions are able to produce ester-substituted bicyclic ureas in both high yield and diastereoselectivity. This reaction also tolerates a variety of ester alkyl groups, including a menthyl group (eq. 3-17).[29]



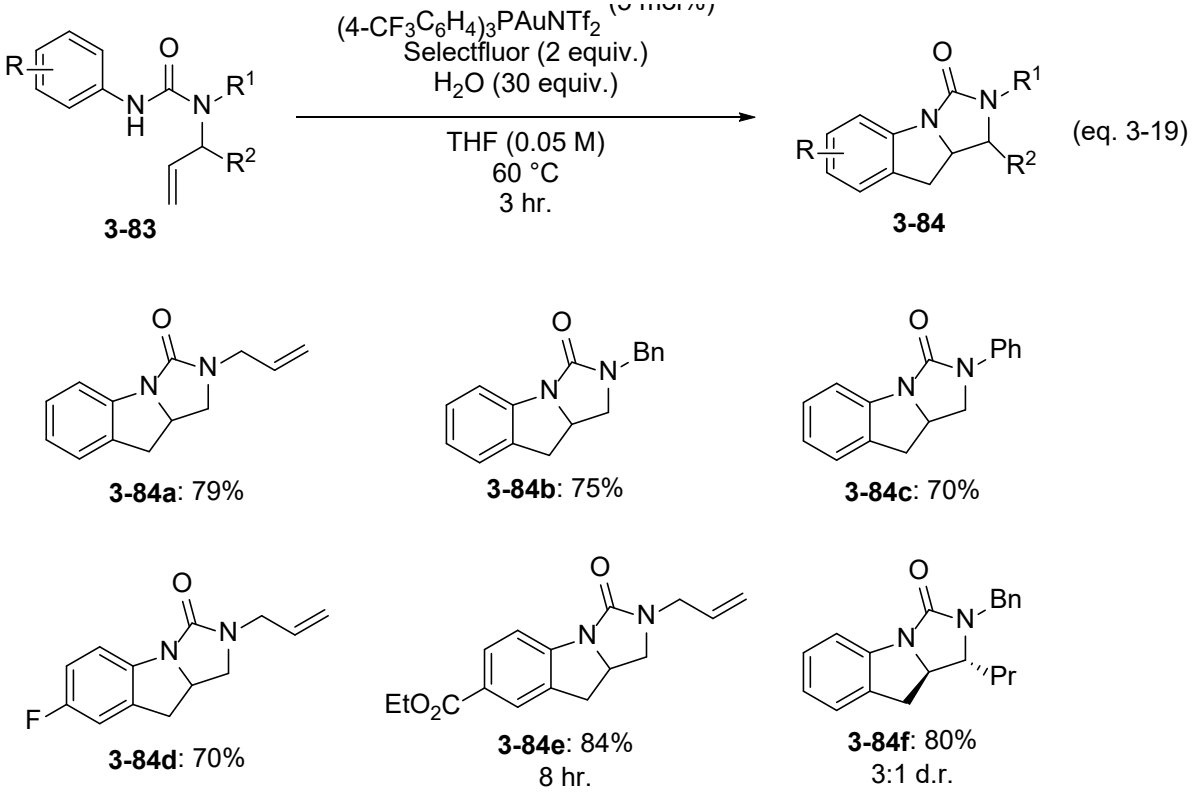

Scheme 57 Selected bicyclic ureas with ester substituents.[29]

The Muñiz group has also accessed cyclic ureas by way of gold(I/III) catalysis. When acyclic alkenyl ureas were reacted with a gold(I) catalyst and phenyliodine(III) diacetate, bicyclic ureas were produced in yields comparable to those observed in their earlier palladium(II/IV) catalysis study. Notably, this gold-mediated reaction is able to produce an indolinyl urea (**3-82f**) in much higher yield than the previously described palladium-catalyzed reaction (eq. 3-18). From a mechanistic standpoint, this transformation proceeds through a pathway almost identical to its palladium counterpart described in Scheme 55. The gold(I) catalyst coordinates to the urea alkene, a 5-*exo*-trig cyclization forms the first ring, the gold atom is oxidized to gold(III), and the urea nitrogen performs an $S_N2$-style attack to form the second ring of the bicyclic urea and to regenerate the gold(I) catalyst. The only substantive difference between these pathways is that the gold atom never directly binds to the urea nitrogen.[30]




Scheme 58 Bicyclic ureas formed via gold(I/III) catalysis.[30]

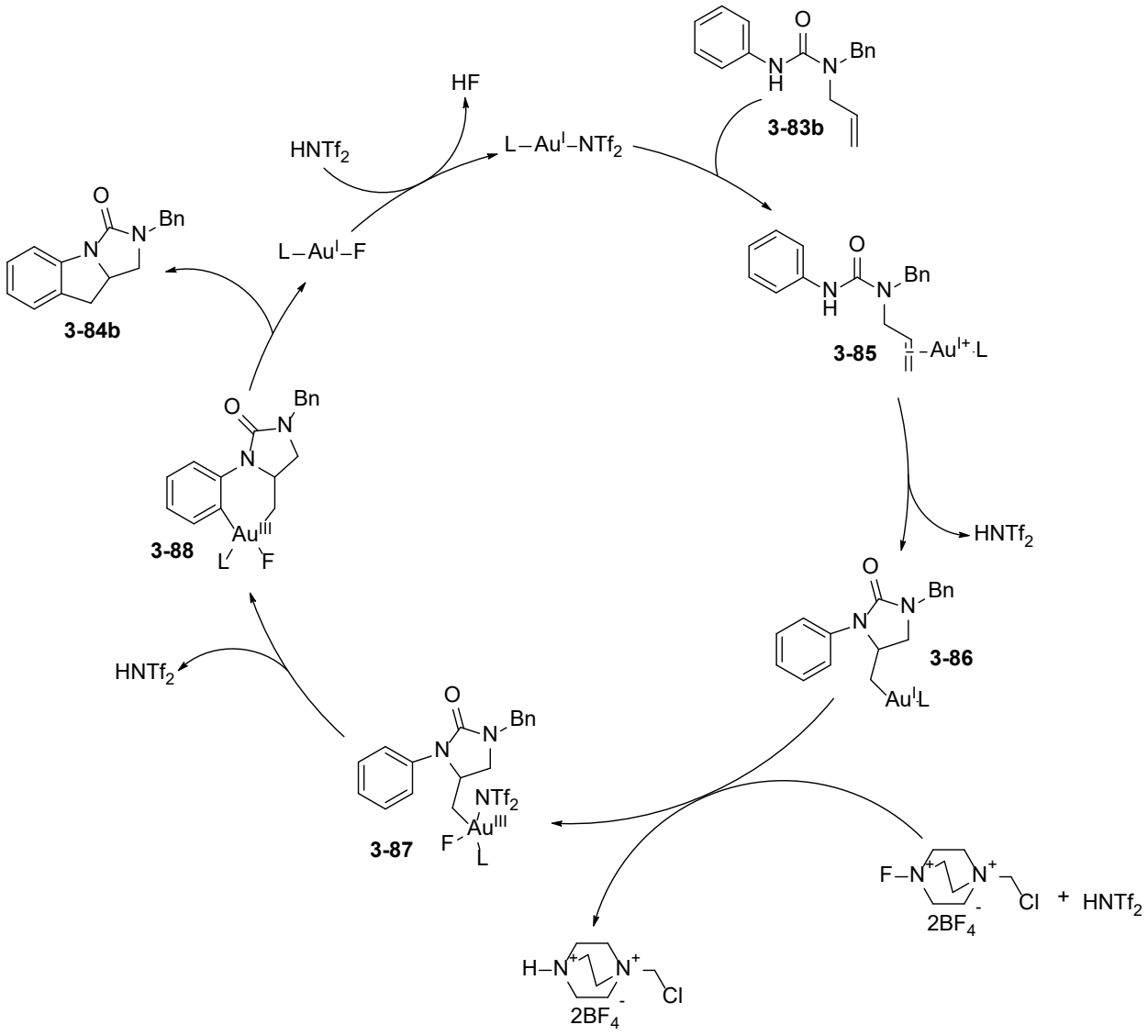
One of the first examples of a reaction specifically designed to synthesize indolinyl bicyclic ureas was described by Liming Zhang and collaborators in 2011. Much like the previously described work from Muñiz, it is a gold(I)-facilitated cyclization of acyclic alkenyl ureas (**3-83**). It is able to form indolinyl ureas (**3-84**) with various protecting groups on the urea nitrogen and substitution along the aromatic ring in high yield (eq. 3-19). When there is a substitution on the allyl group, the reaction exhibits mild diastereoselectivity (**3-84f**).




Scheme 59 Selected indolinyl ureas formed by gold(I) catalysis.[31]

Despite the superficial similarities between Muñiz and Zhang's gold-catalyzed reactions, they proceed through substantially different mechanisms. Zhang's reaction begins with the gold(I) catalyst coordinating to the urea alkene (**3-83b**), forming a cationic gold intermediate (**3-85**). An intramolecular nucleophilic attack at the internal position of the alkene forms the first of the two rings of the target bicycle (**3-86**). Then, Selectfluor acts as oxidant which converts the

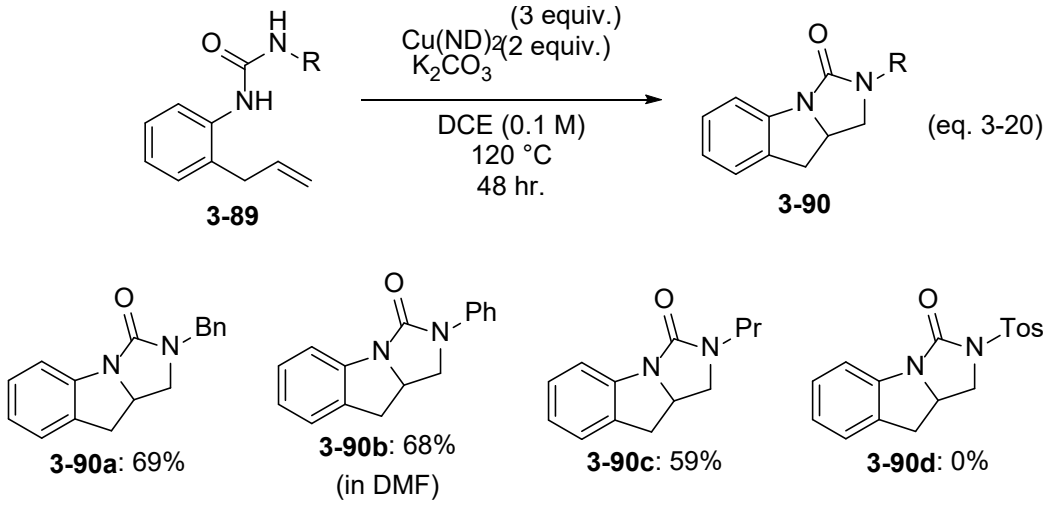
gold(I) complex **3-86** to gold(III) intermediate **3-87**. A C–H functionalization step results in the generation of a six-membered auracycle (**3-88**). Finally, a reductive elimination forms the indolinyl bicyclic urea (**3-84b**) and regenerates the gold(I) catalyst (Scheme 60).[31]




Scheme 60 Zhang's proposed mechanism for bicyclic urea formation.[31]

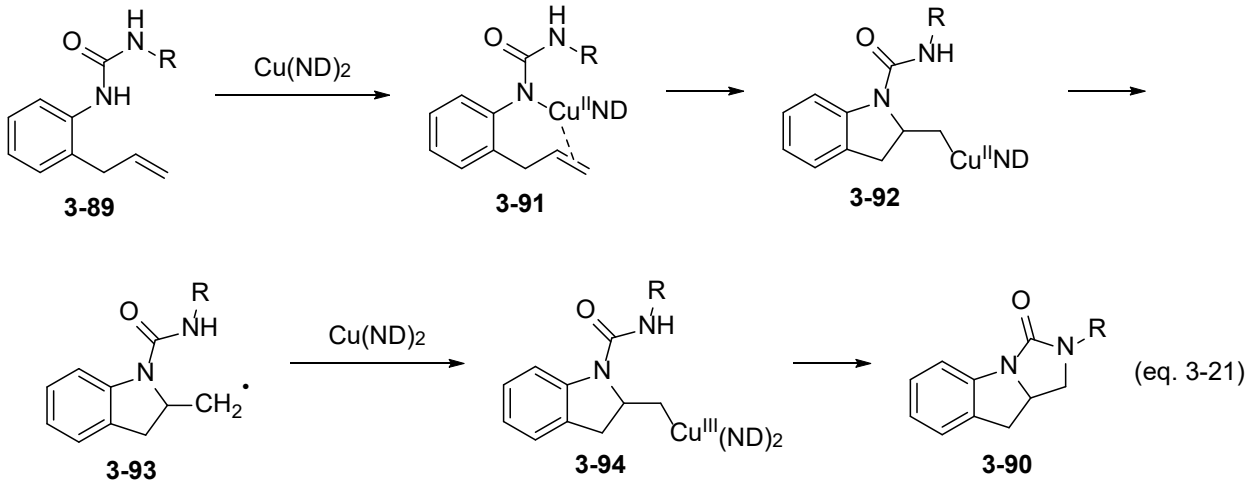
Another significant reaction which forms this particular ring structure is a copper(II)-mediated alkene diamination proposed by Sherry R. Chemler. This transformation combines *ortho*-allyl phenyl ureas (**3-89**), stoichiometric copper(II) neodecanoate, and a base to synthesize indolinyl ureas (**3-90**) in moderate yields (eq. 3-20). Additionally, this reaction is limited to a few

protecting groups on the nitrogen since the tosylated starting material failed to generate any product (**3-90d**). No other substitutions were investigated in this study.



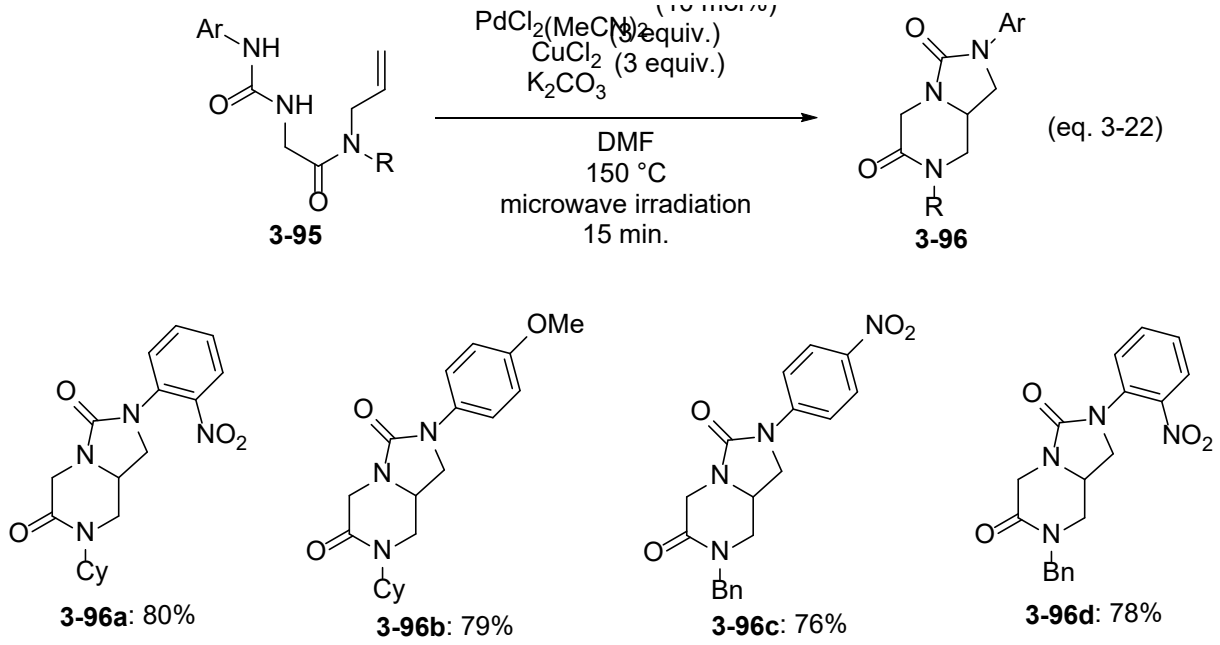

Scheme 61 Indolinyl bicyclic ureas formed by copper(II) diamination.[32]

The mechanism for this process begins with copper(II) neodecanoate coordinating to the allyl alkene (**3-91**). This facilitates an intramolecular nucleophilic attack from the urea nitrogen at the internal carbon of the alkene, forming intermediate **3-92**. The copper-carbon bond subsequently undergoes a homolytic cleavage, forming a primary radical (**3-93**). This radical reacts with another molecule of copper(II) neodecanoate to produce a copper(III) species (**3-94**). Then, the copper(III) atom either performs a ligand exchange followed by a reductive elimination to generate the final bicyclic urea, or the copper(III) is displaced by an $S_N2$ attack from the free urea nitrogen to form the second ring (eq. 3-21).[32]



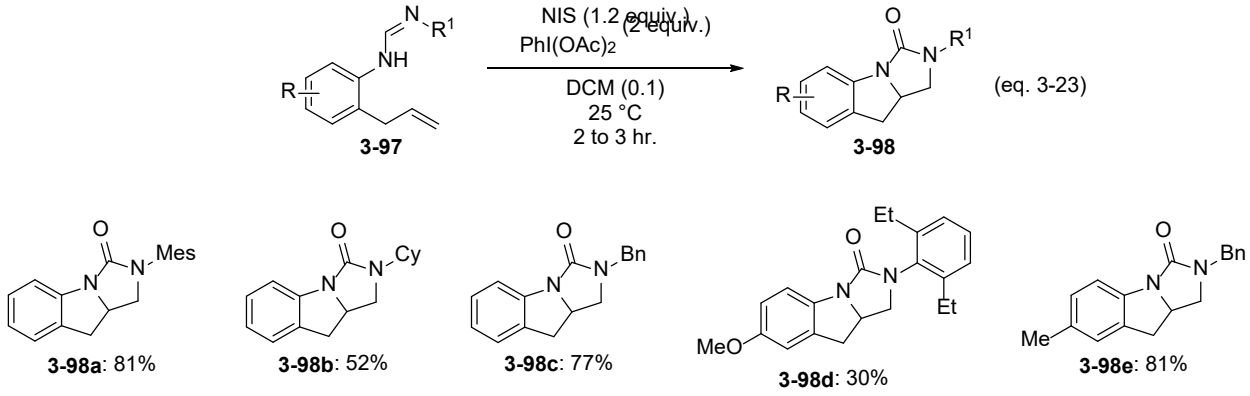

Scheme 62 Chemler's proposed bicyclic urea formation mechanism.[32]

Another recently developed method for making bicyclic ureas combines palladium catalysis and microwave irradiation to produce the target molecules. In principle, this reaction is a derivation of Muñiz's earlier work as it is an intramolecular alkene diamination reaction brought about by a palladium(II) source and copper(II) chloride as an oxidant; the only major difference is that microwave irradiation allows the reaction to rapidly reach the elevated temperatures required to go to completion. This technique is able to produce substrates with different aryl protecting groups on the urea and different alkyl protecting groups on the connected amide in high yield (eq. 3-22).[33]




Scheme 63 Bicyclic ureas formed *via* palladium catalysis and microwave irradiation.[33]

Indolinyl bicyclic ureas have also been accessed in through a pathway similar to Muñiz's metal-free alkene diamination described in eq. 3-16. In this case, *ortho*-allyl *N*-aryl formamidines are reacted with *N*-iodosuccinimide (NIS) and phenyliodonium(III) diacetate to form bicyclic ureas (eq. 3-23). This reaction tolerates several protecting groups on the urea and certain substituents on the aryl portion of the molecule. A notable exception to this is an aryl methoxy group, which the authors claim destabilizes the intermediate or the product (**3-98d**).[34]

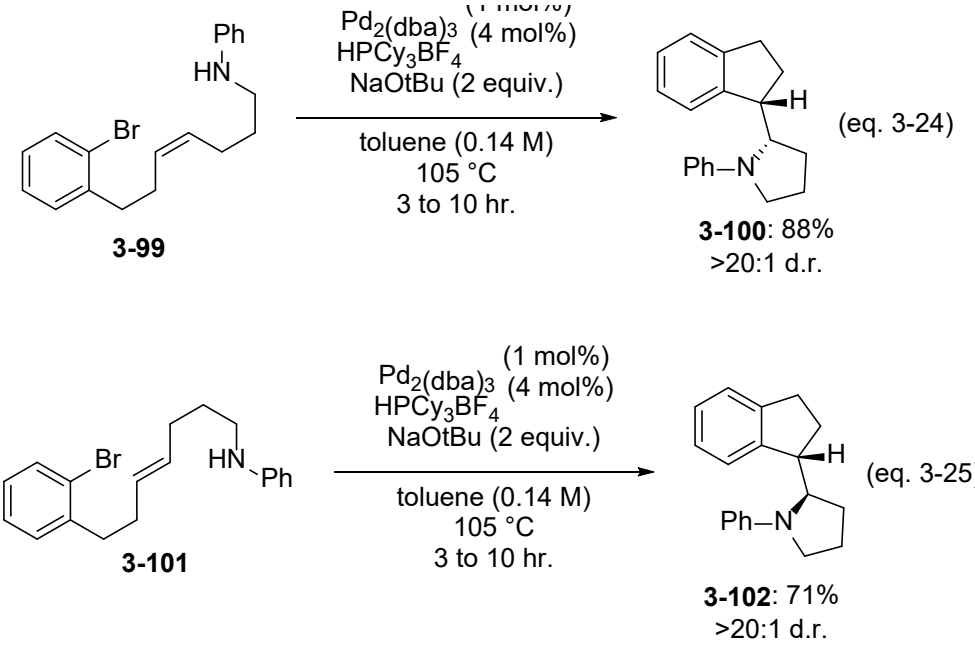



Scheme 64 Indolinyl bicyclic ureas formed by iodonium-facilitated diamination.[34]

While each of these reactions provide useful pathways for accessing a variety of bicyclic ureas, they are not without limitations. The primary factor which seems to be absent in the majority of these transformations is their capacity for derivatization, as few of these reactions report products generated from starting materials which are functionalized on their respective alkenyl chain. The next section will examine a reaction which could be implemented to resolve this issue while maintaining high yields for the target products.

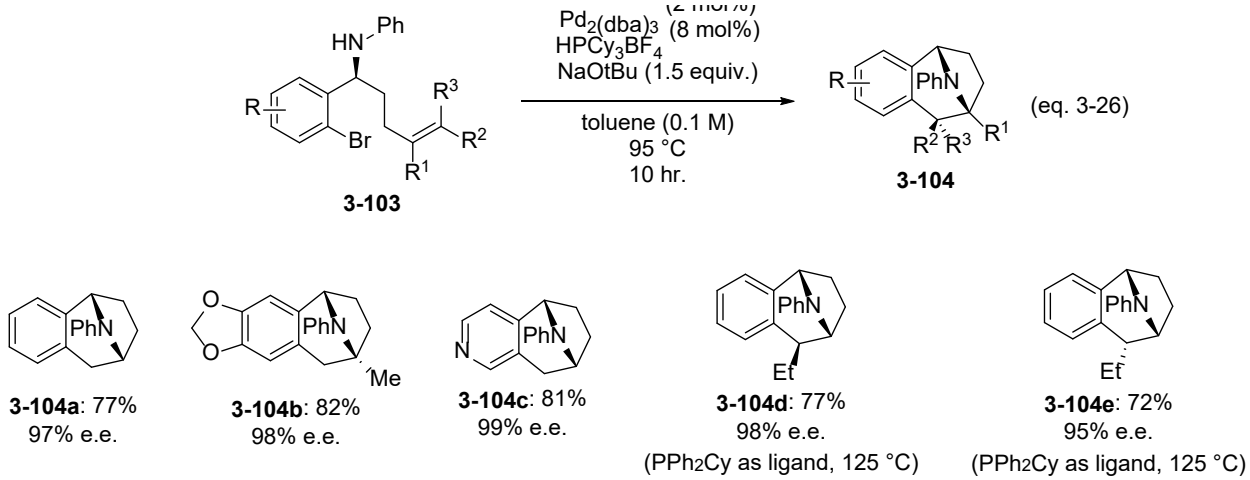
### 3.4 Intramolecular Palladium-Catalyzed Carboamination: A Potential Route to Access Bicyclic Ureas

The study of intramolecular palladium-catalyzed carboaminations began with a study published by the Wolfe group in 2006. These reactions took alkenyl amines with aryl bromide tethers to form indanes bonded to protected pyrrolidines in high yield. In order to probe the stereoselectivity of this transformation, both a *Z* and an *E* alkene (**3-99** and **3-101**, respectively) were subjected to the optimized reaction conditions in order to observe the stereochemical outcomes. Both **3-100** and **3-102** were formed with high diastereoselectivity from their respective starting materials, indicating that this process vastly favors *syn* addition over *anti* addition.[35]



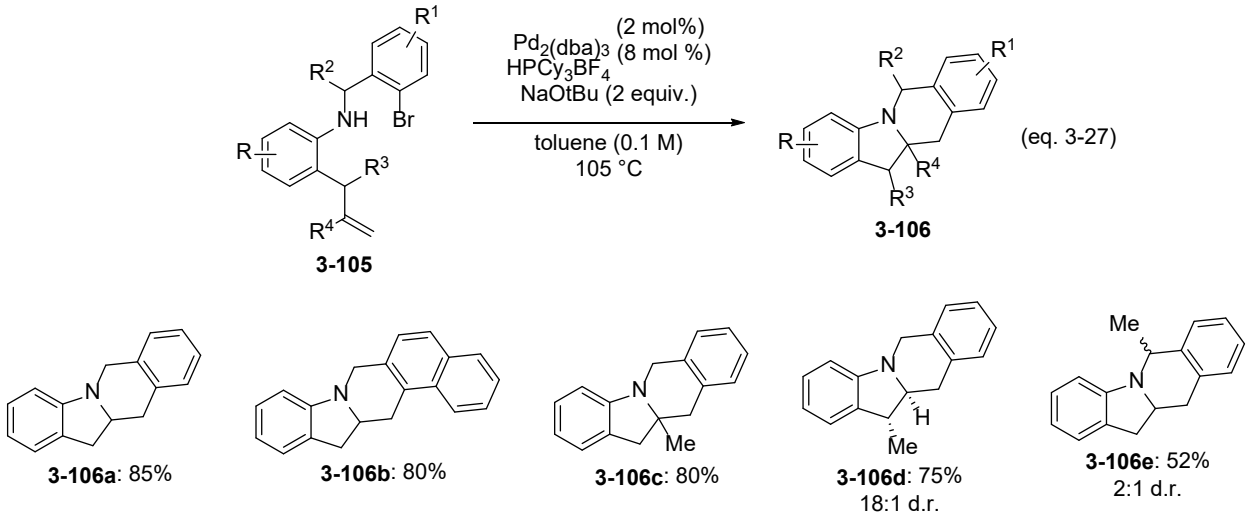

Scheme 65 Selectivity study for the first palladium-catalyzed intramolecular carboamination.[35]

This reaction was later implemented to form tropanes, a highly sought after ring structure, from *ortho*-bromoaryl alkenyl amines. Using conditions similar to those from the prior study, Wolfe and collaborators were able to produce derivatized tropanes in high yield. Significantly, this reaction was able to tolerate substitutions on every position of the alkene to form molecules **3-104b**, **3-104d**, and **3-104e**. Furthermore, each reaction was able to generate product in exceedingly high enantioselectivity (eq. 3-26).[36]




Scheme 66 Tropanes produced via intramolecular palladium-catalyzed carboamination.[36]

Another synthetically interesting set of molecules generated from intramolecular palladium-catalyzed carboamination are tetrahydroindoloisoquinolines, a type of amine tetracycle. The same conditions which were able to facilitate the formation of tropanes managed to produce a variety of tetrahydroindoloisoquinolines in high yields (eq. 3-27). Like its predecessor, this reaction also demonstrates a fairly high tolerance for functionalization along the alkene and on other portions of the molecule. The only exception is a substitution in the benzylic position next to the nitrogen, where a methyl substituent diminishes the yield and has moderate diastereoselectivity (**3-106e**).[37]




Scheme 67 Tetrahydroindoloisoquinolines formed *via* intramolecular palladium-catalyzed carboamination.[37]

Despite the synthetic utility demonstrated by this methodology, intramolecular palladium-catalyzed carboaminations have not been utilized to form any kind of polycyclic urea to date. In the following chapter, the optimization process for developing a such pathway to bicyclic ureas will be discussed in detail. In addition, the differing optimized conditions for different bicyclic urea systems will be explained in terms of their respective proposed mechanisms.

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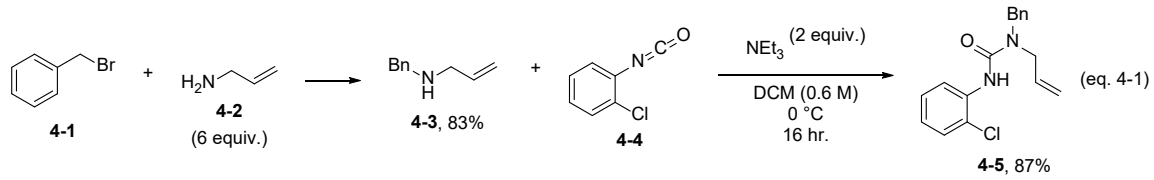
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# Chapter 4 Formation of Bicyclic Ureas *via* Intramolecular Palladium-Catalyzed Alkene Difunctionalization[2]

## 4.1 Synthesis of Phenyl Ureas

The acyclic ureas that can be used to form indolinyl ureas can be produced in two synthetic steps. To begin, benzyl bromide and allylamine undergo an $S_N2$ reaction to form *N*-allylbenzylamine (**4-3**). Then, this secondary amine reacts with 2-chlorophenyl isocyanate and triethylamine base to generate the target urea **4-5**.




Scheme 68 Synthesis of phenyl urea **4-5**.

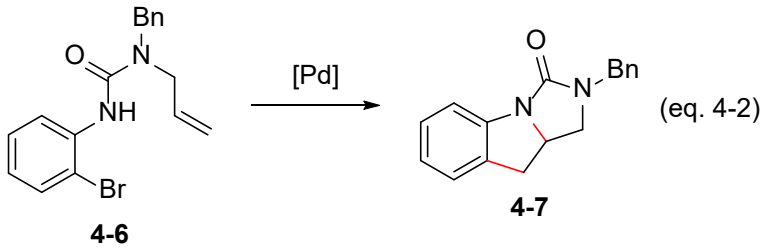
## 4.2 Reaction Optimization for Indolinyl Bicyclic Ureas

Since intramolecular palladium-catalyzed carboamination has been successfully implemented in the formation of a variety of notable and useful heterocycles, we hypothesized that we could make similarly interesting and significant urea-containing bicycles employing the same method. From a mechanistic standpoint, we predicted that exchanging the typical amine groups for ureas would not have deleterious effects on the outcome of this transformation.

[2] I would like to acknowledge Calliope Cutchins, Nathan Martinez, and Avery Reimink for their contributions to starting material synthesis and reaction optimization for this project. I would also like to acknowledge Dr. Andrew Cruz for his early reaction optimization work for this study.

Additionally, the relative ease of access of the starting materials would allow the desired reaction to act as a highly efficient pathway to access an assortment of fused-ring ureas.

In light of the previous success of palladium-catalyzed intramolecular carboaminations, we sought to investigate whether this method could be applied to the formation of 1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-ones, or bicyclic ureas with indoline cores (**4-6**). The starting material required for this transformation would be an *ortho*-bromophenyl urea with a tethered allyl group (**4-6**).

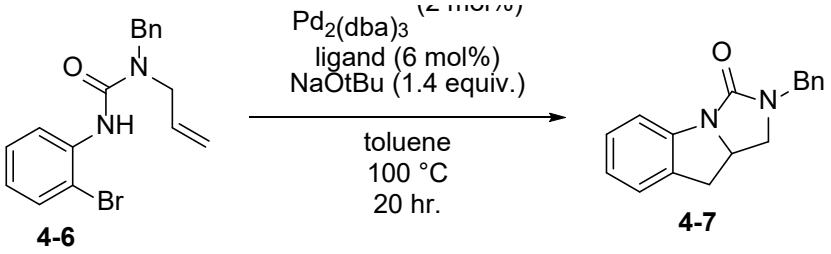



**4-6** **4-7**

Scheme 69 Generic proposed route to indolinyl bicyclic ureas with target bonds highlighted in red.

In order to assess if this transformation were possible, we began with a ligand screen where we monitored how much starting material was consumed. Across all the ligands we tried, the two ligands which showed the highest conversions were BrettPhos and CPhos, electron-rich dialkyl biaryl phosphine ligands. Bidentate ligands, on the other hand, facilitated very little conversion of the alkenyl starting material (Table 3). These reactions did not generate any side products that were detected by $^{1}$H NMR analysis of crude reaction mixtures; reactions that provided <100% conversion returned unreacted starting material.

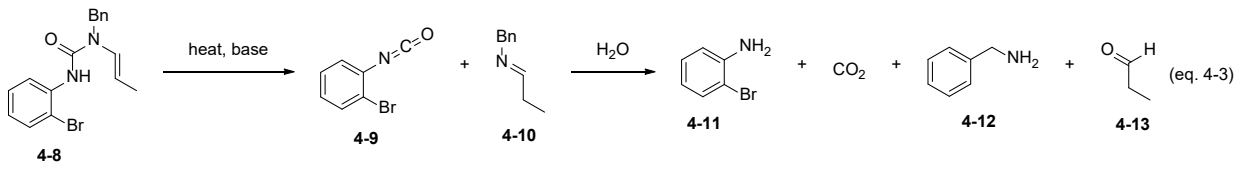
Table 3 Ligand screen for indolinyl bicyclic ureas.




| reaction number | ligand | conversion (%) |
|---|---|---|
| **1** | XantPhos | 0 |
| **2** | NiXantPhos | 0 |
| **3** | CPhos | 100 |
| **4** | DPEPhos | 30 |
| **5** | BrettPhos | 100 |

[a]Conditions: Reactions were conducted on a 0.1 mmol scale using 1.0 equiv **4-6**, 1.4 equiv NaO$^t$Bu, 2 mol % $Pd_2(dba)_3$, 6 mol % ligand, toluene (0.1 M) for ca 16h at the indicated temperature.

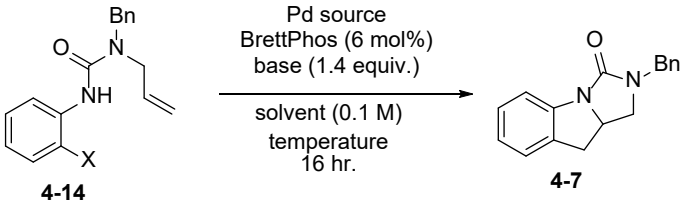
However, despite the fact that reactions appeared to cleanly convert starting material to desired product, when we attempted to isolate the desired product from the BrettPhos reaction, we only obtained a yield of 41 percent. With this in mind, we sought to determine what other factors we could change in order to increase the reaction output. This pursuit was complicated by the fact that there was no major byproduct that was accounting for the moderate yield. We hypothesized that the starting material might be decomposing to low molecular-weight components that were lost during workup. For example, if the *N*-allyl group isomerized to the corresponding enamine and the urea decomposed to 2-bromophenyl isocyanate upon heating with base, the products generated upon aqueous workup would be carbon dioxide, 2-bromoaniline, benzylamine, and propionaldehyde (eq. 4-3).




Scheme 70 Potential starting material decomposition pathway.

As such, we ran a screen of reduced temperatures to determine whether this would resolve the issue. Unfortunately, this did not substantially increase the yield (Table, 4, entries 2-4). Another screen sought to ascertain whether solvent effects would help reduce the postulated substrate decomposition we were observing. While most solvents we screened significantly reduced the yield, trifluorotoluene increased the NMR yield to approximately 70 percent (Table 4, entries 5-8). Altering the base produced similar results; no combination of base strength and counterion effects was able to bring the yield above 60 percent (Table 4, entries 9-12). Yet another variable we tested was the halogen on the starting material. Upon exchanging the bromine for a chlorine and subjecting this new starting material to the original conditions, we were pleased to find that the target product was generated in quantitative yield as determined by $^{1}$H NMR analysis with an NMR standard.

Table 4 Assorted screens for indolinyl bicyclic ureas.



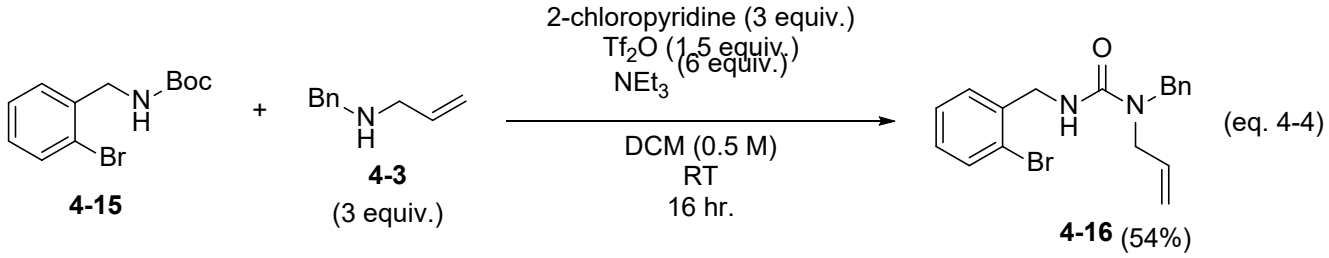

**4-14** **4-7**

| reaction number | halogen | Pd source | base | solvent | temperature (°C) | NMR yield (%)[b] |
|---|---|---|---|---|---|---|
| **1** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | toluene | 100 | 41 (isolated) |
| **2** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | toluene | 60 | 31 |
| **3** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | toluene | 70 | 45 |
| **4** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | toluene | 80 | 53 |
| **5** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | dioxane | 100 | 45 |
| **6** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | trifluorotoluene | 100 | 70 |
| **7** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | DME | 80 | 25 |
| **8** | Br | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | DMF | 100 | 0 |
| **9** | Br | $Pd_2(dba)_3$ (2 mol%) | LiOtBu | toluene | 100 | 60 |
| **10** | Br | $Pd_2(dba)_3$ (2 mol%) | LiHMDS | toluene | 100 | 35 |
| **11** | Br | $Pd_2(dba)_3$ (2 mol%) | KOtBu | toluene | 100 | 0 |
| **12** | Br | $Pd_2(dba)_3$ (2 mol%) | $Cs_2CO_3$ | toluene | 100 | 30 |
| **13** | Br | $Pd(OAc)_2$ (4 mol%) | $Cs_2CO_3$ | trifluorotoluene | 100 | 40 |
| **14** | Cl | $Pd_2(dba)_3$ (2 mol%) | NaOtBu | toluene | 100 | quant. |

[a]Conditions: Reactions were conducted on a 0.1 mmol scale using 1.0 equiv **4-13**, 1.4 equiv base, 2 mol % $Pd_2(dba)_3$ or 4 mol % $Pd(OAc)_2$, 6 mol % BrettPhos, solvent (0.1 M) for ca 16h at the indicated temperature. [b]NMR yield using phenanthrene as the internal standard.

### 4.3 Synthesis of Benzyl Ureas

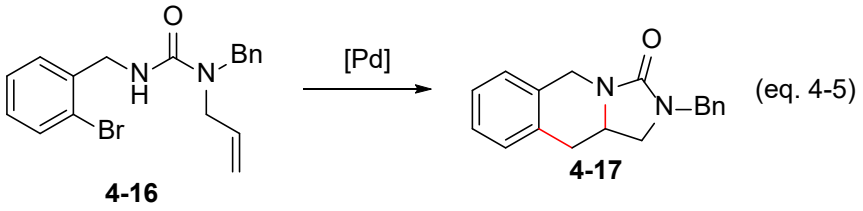
The benzyl acyclic ureas can be used to generate tetrahydroisoquinolinyl bicyclic ureas are synthesized in a similar manner to their phenyl analogues. Like before, *N*-allylbenzylamine is produced from an $S_N2$ reaction between benzyl bromide and allylamine (eq. 4-1). Then, this amine is combined with a *tert*-butoxycarbonyl (Boc)-protected 2-bromobenzylamine (**4-15**), 2-chloropyridine, triethylamine, and triflic anhydride to generate the final benzylic urea **4-16**. This set of reagents work together to form 2-bromobenzyl isocyanate *in situ* which can then react with *N*-allylbenzylamine to produce the desired product (eq. 4-4).




Scheme 71 Synthesis of benzyl urea **4-16**.

### 4.4 Reaction Optimization for Tetrahydroisoquinolinyl Bicyclic Ureas

Given the success we obtained in the formation of indolinyl bicyclic ureas, we sought to determine whether this methodology could be expanded to form tetrahydroisoquinolinyl bicyclic ureas akin to 4-16. From the standpoint of the starting material, this would require moving the allyl urea to the benzylic position of the *ortho*-bromoaryl ring (4-15). Pursuing this potential route was also of particular interest since it would act as the first method ever designed to generate this urea ring system.

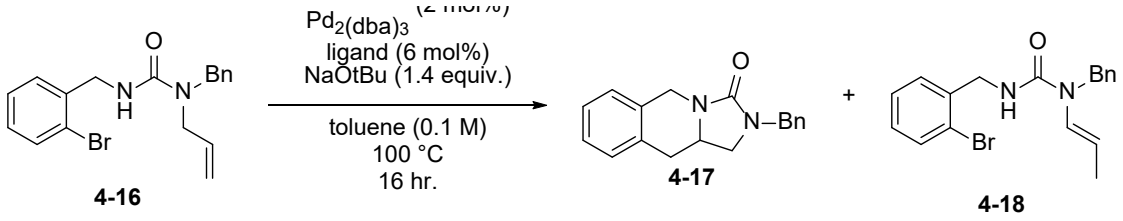



**4-16** **4-17**

Scheme 72 Generic proposed route to tetrahydroisoquinolinyl bicyclic ureas with target bonds highlighted in red.

In order to probe the feasibility of this transformation, we began with a ligand screen holding all other factors constant. Discouragingly, every reaction produced 15 percent yield or lower of the desired product regardless of the denticity or electronic properties of the ligands selected for the screen. Upon close examination of the crude reaction mixtures, we learned that each of the reactions were succumbing to the same issue; namely, most of the yield was accounted for by the isomerization of the alkene in the starting material to the internal position (**4-18**). This side product was produced in yields ranging from 24 to 60 percent, and it provided critical insight into why the desired bicyclic product **4-17** was not being formed. The observed alkene isomerization is facilitated by strong base, and this reaction can occur much faster than any potential palladium-catalyzed process. As such, we hypothesized that sodium *tert*-butoxide was the reagent inhibiting the target transformation.

Table 5 Ligand Screen for Tetrahydroisoquinolinyl Bicyclic Ureas

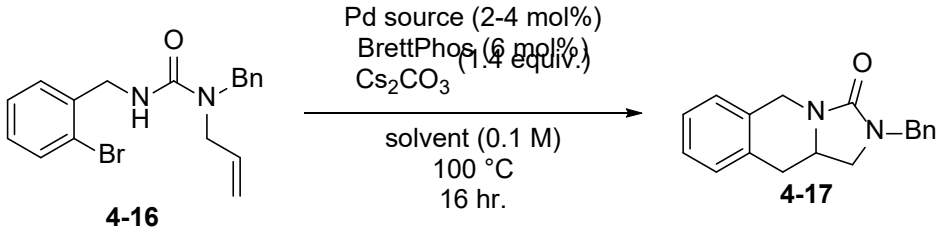



| reaction number | ligand (6 mol%) | Yield of 4-17[b] | Yield of 4-18[b] |
|---|---|---|---|
| **1** | BrettPhos | 15 | 50 |
| **2** | CPhos | 15 | 45 |
| **3** | JohnPhos | 15 | 45 |
| **4** | $HPCy_3BF_4$ | 5 | 60 |
| **5** | $PPh_3$ | 5 | 40 |
| **6** | DPEPhos | 5 | 24 |
| **7** | XantPhos | 15 | 50 |

[a]Conditions: Reactions were conducted on a 0.1 mmol scale using 1.0 equiv **4-16**, 1.4 equiv NaO$^t$Bu, 2 mol % $Pd_2(dba)_3$, 6 mol % ligand, toluene (0.1 M) for ca 16h at the indicated temperature. [b]NMR yield using phenanthrene as the internal standard.

In an attempt to resolve this issue, we exchanged sodium *tert*-butoxide for cesium carbonate, a much weaker base. While screening the reactivity of this base, we selected BrettPhos as the ligand since it was determined to be optimal for the indolinyl urea formation reaction. We also changed the palladium source and solvent to see which combination of reagents would form the most target product alongside the new base. Utilizing cesium carbonate had a profound effect on the reaction's outcome, bringing the yield of the tetrahydroisoquinolinyl urea up to 85 percent in certain instances. When this base was combined with palladium(II) acetate as catalyst and toluene as solvent, the yield of the desired product was observed to be quantitative *via* NMR (Table 6).

Table 6 Base, Palladium Source, and Solvent Screen for Tetrahydroisoquinolinyl Bicyclic Ureas




**4-16** **4-17**

| Reaction Number | Pd Source | Solvent | Yield (%)[b] |
|---|---|---|---|
| **1** | $Pd_2(dba)_3$ (2 mol%) | toluene | 85 |
| **2** | $Pd(OAc)_2$ (4 mol%) | trifluorotoluene | 85 |
| **3** | $Pd(OAc)_2$ (4 mol%) | toluene | quant. |

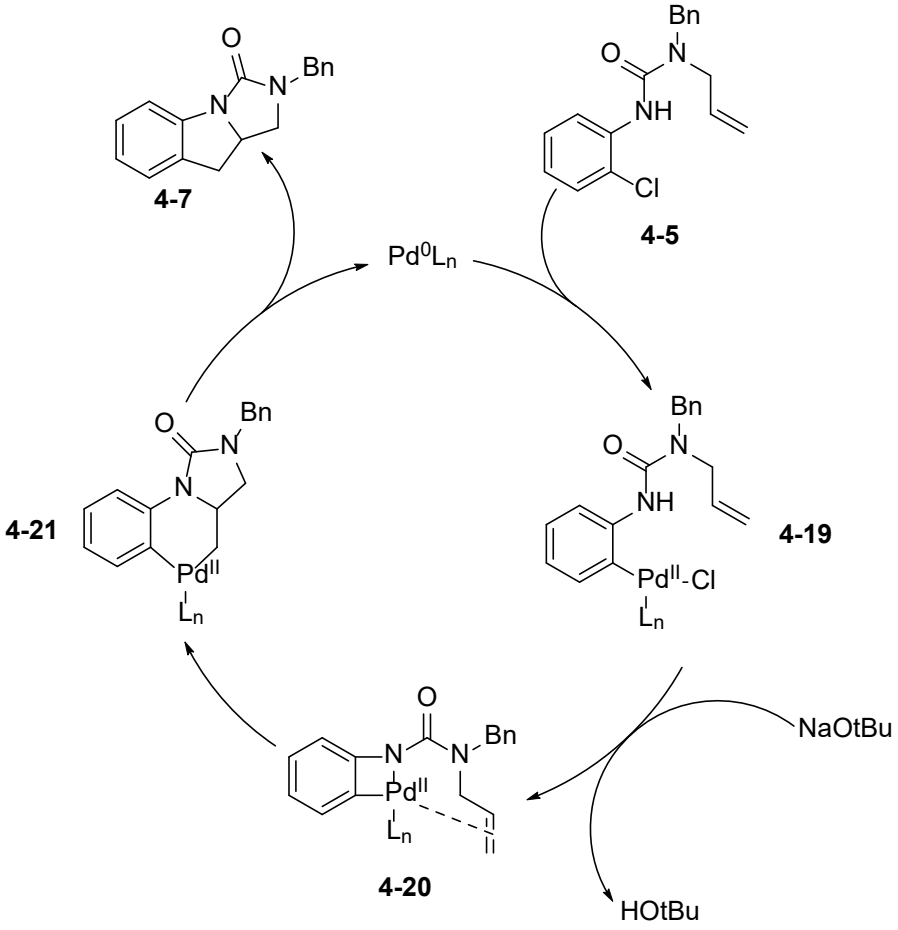
[a]Conditions: Reactions were conducted on a 0.1 mmol scale using 1.0 equiv **4-16**, 1.4 equiv $Cs_2CO_3$, 2 mol % $Pd_2(dba)_3$ or 4 mol % $Pd(OAc)_2$, 6 mol % BrettPhos, toluene or trifluorotoluene (0.1 M) for ca 16h at the indicated temperature. [b]NMR yield using phenanthrene as the internal standard.

The optimized conditions for this reaction represent the first example of a method specifically tailored for the generation of tetrahydroisoquinolinyl bicyclic ureas. Provided that the final product can be accessed in three facile synthetic steps from commercial starting materials, this could prove to be a useful method to access various molecules of potential synthetic and pharmaceutical interest. Furthermore, these two successful palladium-catalyzed intramolecular carboaminations could inform the development of pathways to access additional heterocyclic ring systems.

## 4.5 Proposed Mechanisms for Bicyclic Urea Formations

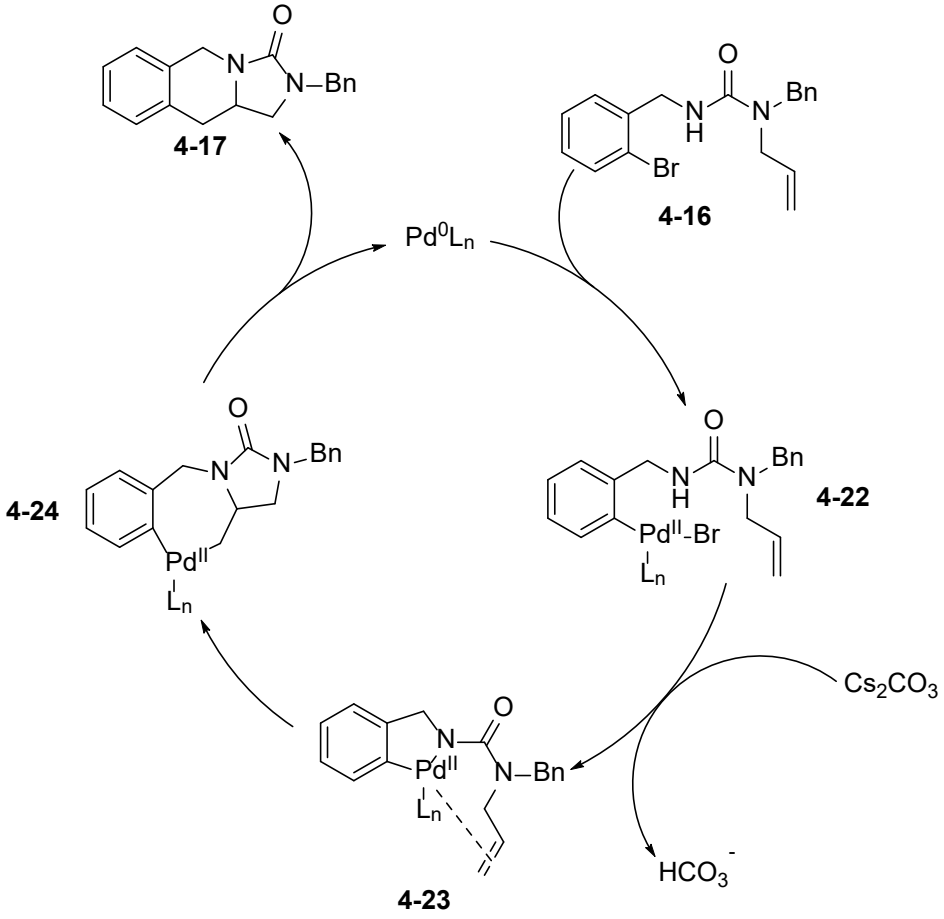
The mechanisms we propose for the two methods we have developed are quite similar, but their commonalities and differences are worth examining in detail. This comparison can provide helpful insights into the distinct conditions required to produce each ring system. In the case of the indolinyl bicyclic ureas, the mechanism begins with an oxidative addition to form

intermediate **4-19**. Deprotonation of the urea leads to the formation of four-membered palladacycle **4-20**. A migratory insertion step generates the five-membered urea ring fused to a six-membered palladacycle (**4-21**). Finally, reductive elimination produces the desired bicyclic urea (**4-7**) and regenerates the palladium catalyst. The relative instability of palladacyclic intermediate **4-20** is likely what resulted in the decomposition products observed during the optimization process, as the palladacycle formation is likely reversible, and may be thermodynamically unstable, which would slow the rate of alkene migratory insertion (Scheme 73).




Scheme 73 Proposed mechanism for indolinyl bicyclic urea formation.

The tetrahydroisoquinolinyl counterpart to this reaction proceeds in a similar manner. The palladium catalyst undergoes an oxidative addition (**4-22**), then it forms a palladacycle with the urea once it has been deprotonated by cesium carbonate (**4-23**). Notably, this palladacycle is five-membered, so it is not as strained as the intermediate in the indolinyl urea reaction. As such, decomposition to low molecular weight components did not prove to be as significant an issue when this reaction was being optimized. Subsequently, migratory insertion results in the production of the fused ring scaffold **4-24**, and reductive elimination produces the final product **4-17**.




Scheme 74 Proposed mechanism for tetrahydroisoquinolinyl bicyclic urea formation.

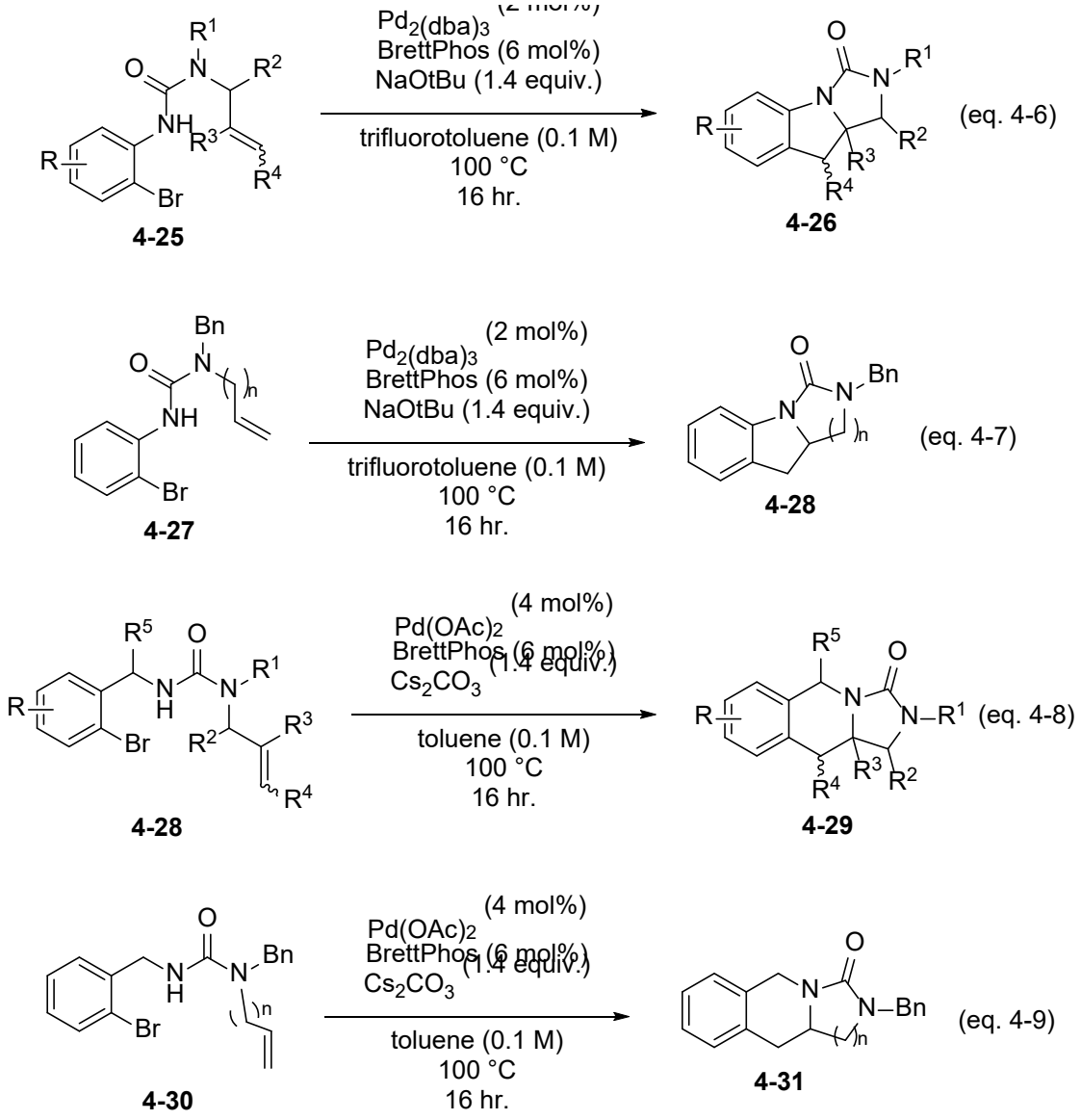
We are glad to report that we have successfully developed conditions that form indolinyl and tetrahydroisoquinolinyl ureas in high yield by NMR as ascertained by an NMR standard.

Interestingly, accessing these different ring systems require different conditions; this distinction could provide insights into the mechanistic differences between the formation of these ureacycles with further investigation. Another notable aspect of this work is that, in the case of the tetrahydroisoquinolinyl ureas, we have developed the first methodological route to accessing these ring systems. This could present the opportunity to ascertain their potential synthetic and medicinal utility.

### 4.6 Future Directions: Purification and Substrate Scope

The future directions for this project fall into two main categories, the first of which is the determination of an effective procedure for purifying the bicyclic urea products. A persistent issue we have encountered over the course of the optimization process is an inability to obtain isolated yields that are congruent with the yields determined by NMR. Despite NMR and crude mass data indicating that the yields of our desired products are nearly quantitative, our attempts at isolating the products have only been able to reach yields of 65 to 70 percent via column chromatography. In our ongoing work to resolve this issue, we have determined that this is likely related to the bicyclic ureas' profoundly low solubility in hexanes, which we have been using as the nonpolar component of our column chromatography mobile phase. Strategies we are actively pursuing to resolve this problem include modifications to our approach to column chromatography. For instance, we are investigating whether running columns with a solvent gradient or with the addition of a polyhalogenated solvent like chloroform will help mitigate the moderate solubility of our target products. Additionally, since the products are known to be solids, we are developing crystallization techniques as another potential avenue to purification. We are also running experiments to see if the reaction is amenable to reduced catalyst and ligand loading since this could eliminate the need for purification altogether.

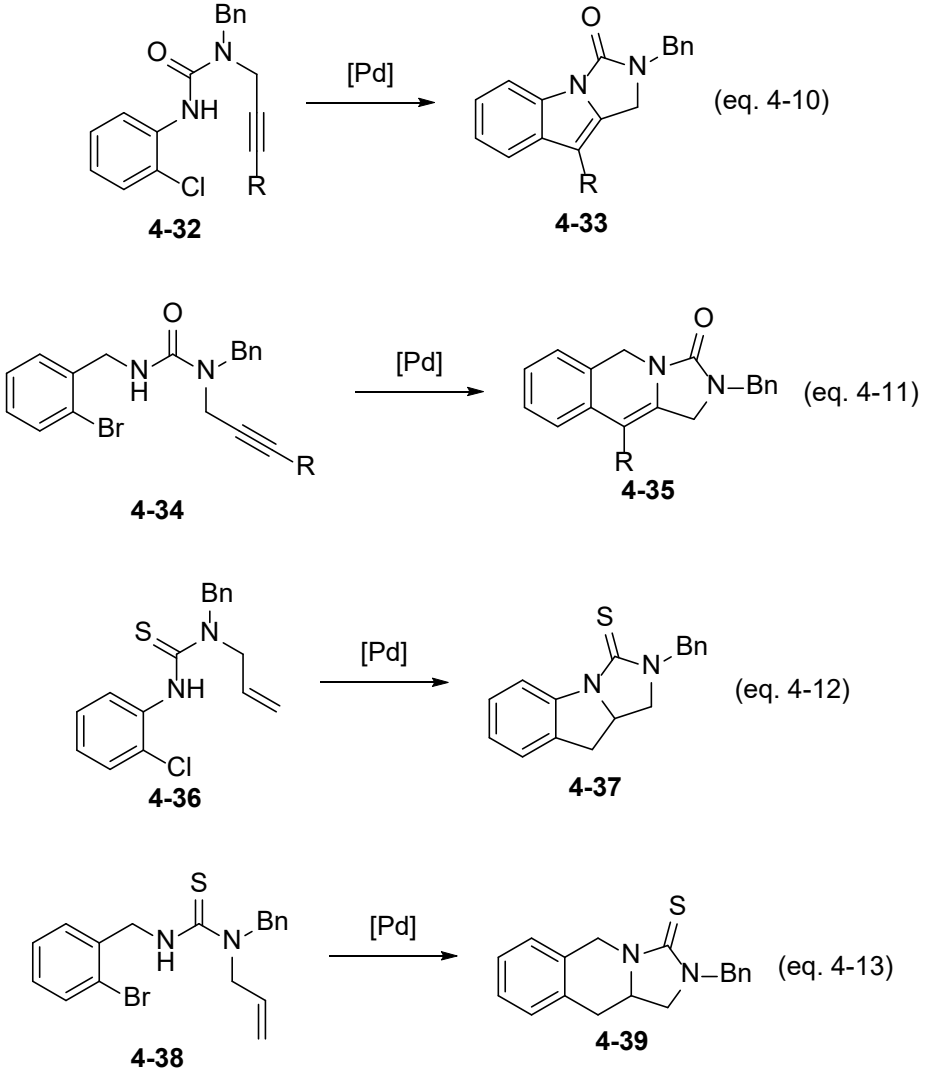
The other major direction for this project we are actively pursuing is the investigation of substrate scope. Each of the two ring structures this project is focused on lend themselves to a high degree of derivatization, and we are currently producing starting materials which will be used to assess the degree to which our optimized conditions will tolerate functionalization along the alkenyl, aryl, alkyl, portions of the molecule (eqs. 4-6 and 4-8). Furthermore, we will modify the length of the urea alkenyl chain to determine whether more complex urea ring systems can be formed (eqs. 4-7 and 4-9).




Scheme 75 Potential routes to functionalized bicyclic ureas.

Furthermore, even more diverse ring systems could be accessed by changing the saturation of the alkenyl chain. By replacing it with an alkynyl group, this could provide a scaffold to form alkenyl bicylic ureas like **4-33** and **4-35**. If the carbonyl group were exchanged for a thiocarbonyl group, this could provide a route to access various thioureas like **4-37** and **4-39**. Although, since these substrates would have significantly different chemical properties

compared to what we are currently investigating, generating these products would likely require reoptimization of the reaction conditions to accommodate these differences.




Scheme 76 Potential future substrates accessible through intramolecular palladium-catalyzed alkene difunctionalization.

## 4.7 Experimental Section

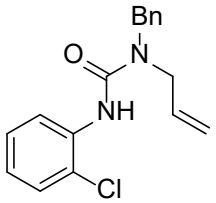
**General Considerations:** All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents, palladium precatalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. The starting material *N*-allylbenzylamine[1] were synthesized according to previously established methods and

its characterization data were consistent with those previously reported in the literature. Alkenyl urea starting materials were stored in a freezer under nitrogen. Bulk quantities of sodium *tert*-butoxide were stored in nitrogen-filled glove box and small amounts were removed within a few days of use. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by $^1$H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Table 2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Table 2.

**Preparation and Characterization of Starting Materials**

**General Procedure for Synthesizing Phenyl Ureas (General Procedure A)**

A flame-dried round-bottom flask equipped with a stir bar was cooled under a stream of nitrogen. 2-Chlorophenylisocyanate (1 equiv.) and triethylamine (2 equiv.) were added to DCM (0.6 M) at 0 °C. Then, *N*-allylbenzylamine (1.1 equiv.) was added to the reaction and the mixture was warmed to room temperature and stirred overnight. After the starting material had been completely consumed as judged by TLC analysis, the crude mixture was extracted with DCM and water, and the organic layer was washed with 1 M HCl, $NaHCO_3$ (aq.), and brine. The organic layer was subsequently dried over $Na_2SO_4$ and filtered. The filtrate was then concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica.

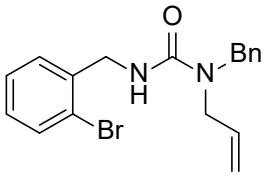



**1-Allyl-1-benzyl-3-(2-chlorophenyl)urea (4-5).** The title compound was prepared from 2-chlorophenylisocyanate (0.6 mL, 5 mmol) and *N*-allylbenzylamine (0.81 g, 5.5 mmol) using

General Procedure A. The crude material was purified *via* column chromatography on silica gel using 6% EtOAc/hexanes as eluent. This procedure afforded 0.52 g (87%) of the title compound as a viscous clear liquid. $^1$H NMR (700 MHz MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.40 – 7.33 (m, 4H), 7.32 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 7.03 (s, 1H), 6.93 (td, *J* = 7.7, 1.5 Hz, 1H), 5.86 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.33 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.30 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.62 (s, 2H), 4.02 (d, *J* = 5.4 Hz, 2H).

**General Procedure for Synthesizing Benzyl Ureas (General Procedure B)**

A flame-dried round-bottom flask equipped with a stir bar was cooled under a stream of nitrogen. *N*-Boc-2-bromobenzylamine (1 equiv.) was added to DCM (0.5 M). Then, 2-chloropyridine (3 equiv.) and triflic anhydride (1.5 equiv.) were added to the reaction and the new mixture was allowed to stir for 50 minutes. Then, triethylamine (6 equiv.) and *N*-allylbenzylamine (3 equiv.) were added to the reaction, and this was left to stir overnight. After the starting material had been completely consumed as judged by TLC analysis, the crude mixture was concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica.[2]



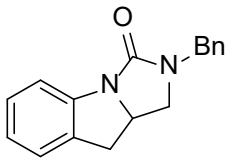

**1-Allyl-1-benzyl-3-(2-bromobenzyl)urea (4-16).** The title compound was prepared from *N*-Boc-2-bromobenzylamine (0.72 g, 2.5 mmol) and *N*-allylbenzylamine using General Procedure B. The crude material was purified *via* column chromatography on silica gel using 24 % EtOAc/hexanes as eluent. This procedure afforded 0.49 g (54%) of the title compound as a white solid. $^1$H NMR (700 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.32 (dd,

*J* = 8.6, 6.9 Hz, 2H), 7.26 (dt, *J* = 9.1, 4.9 Hz, 4H), 7.11 (t, *J* = 7.7 Hz, 1H), 5.82 – 5.71 (m, 1H), 5.19 (d, *J* = 7.9 Hz, 1H), 5.17 – 5.16 (m, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 4.50 (s, 2H), 4.47 (dd, *J* = 6.0, 1.9 Hz, 2H), 3.88 (d, *J* = 5.4 Hz, 2H).

**Preparation and Characterization of Products**

**General Procedure for Palladium-Catalyzed Alkene Difunctionalization Reactions (General Procedure C)**

A flame-dried 4 mL screw cap vial equipped with a stir bar was sealed with a septum cap, cooled under nitrogen, and charged with $Pd_2(dba)_3$ (1.83 mg, 0.002 mmol), BrettPhos (3.22 mg, 0.006 mmol), and sodium *tert*-butoxide (13.45 mg, 0.14 mmol). Toluene (1 mL, 0.1 M) was added *via* syringe, followed by the appropriate urea (0.1 mmol). The septum cap was then further sealed with electrical tape. The vial was heated to 100 °C with stirring overnight until the starting material had been consumed as judged by TLC analysis. The mixture was then cooled to room temperature and quenched with saturated aqueous ammonium chloride (2 mL). The mixture was transferred to a separatory funnel, the aqueous layer was extracted with diethyl ether, and the ether extract was filtered through a sodium sulfate plug, and concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel to afford the desired product.

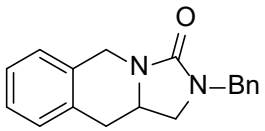



**(±)-2-Benzyl-1,2,9,9a-tetrahydro-3*H*-imidazo[1,5-*a*]indol-3-one (4-7).** The title compound was prepared from 1-allyl-1-benzyl-3-(2-chlorophenyl)urea (30.1 mg, 0.1 mmol) using General Procedure C. The crude material was purified *via* column chromatography on silica gel using as eluent. This procedure afforded 21.1 mg (80%) of the title compound as a white solid. $^1$H NMR

(700 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.29 (q, *J* = 4.0 Hz, 3H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.59 (td, *J* = 9.2, 6.7 Hz, 1H), 4.56 (d, *J* = 15.1 Hz, 1H), 4.31 (d, *J* = 15.0 Hz, 1H), 3.67 (t, *J* = 9.1 Hz, 1H), 3.28 – 3.16 (m, 2H), 2.95 (dd, *J* = 15.7, 9.4 Hz, 1H).

**General Procedure for Palladium-Catalyzed Alkene Difunctionalization Reactions (General Procedure D)**

A flame-dried 4 mL screw cap vial equipped with a stir bar was sealed with a septum cap, cooled under nitrogen, and charged with $Pd(OAc)_2$ (0.898 mg, 0.004 mmol), BrettPhos (3.22 mg, 0.006 mmol), and cesium carbonate (45.61 mg, 0.14 mmol). Toluene (1 mL, 0.1 M) was added *via* syringe, followed by the appropriate urea (0.1 mmol). The septum cap was then further sealed with electrical tape. The vial was heated to 100 °C with stirring overnight until the starting material had been consumed as judged by TLC analysis. The mixture was then cooled to room temperature and quenched with saturated aqueous ammonium chloride (2 mL). The mixture was transferred to a separatory funnel, the aqueous layer was extracted with diethyl ether, and the ether extract was filtered through a sodium sulfate plug, and concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel to afford the desired product.




**(±)-2-Benzyl-1,5,10,10a-tetrahydroimidazo[1,5-*b*]isoquinolin-3(2*H*)-one (4-17).** The title compound was prepared from 1-allyl-1-benzyl-3-(2-bromobenzyl)urea (35.9 mg, 0.1 mmol) using General Procedure D. The crude material was purified *via* column chromatography on silica gel using 38% EtOAc/hexanes as eluent. This procedure afforded 20.1 mg (72%) of the

title compound as a white solid. $^{1}$H NMR (700 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.1, 6.8 Hz, 2H), 7.31 – 7.27 (m, 3H), 7.21 (dd, *J* = 8.1, 6.4 Hz, 1H), 7.16 (td, *J* = 5.9, 2.8 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 4.93 (d, *J* = 16.9 Hz, 1H), 4.47 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 4.29 (d, *J* = 16.9 Hz, 1H), 3.72 (ddt, *J* = 10.4, 8.1, 4.6 Hz, 1H), 3.47 (t, *J* = 8.4 Hz, 1H), 3.01 (dd, *J* = 8.7, 4.7 Hz, 1H), 2.82 – 2.77 (m, 2H).

## 4.8 Works Cited

(1) Cadwallader, D.; Tiburcio, T. R.; Cieszynski, G. A.; Le, C. M. Synthesis of Carbamoyl Fluorides Using a Difluorophosgene Surrogate Derived from Difluorocarbene and Pyridine N-Oxides. *J. Org. Chem* **2022**, (17), 11457-11468.
(2) Spyropoulos, C.; Kokotos, C. G. One-Pot Synthesis of Ureas from Boc-Protected Amines. *J. Org. Chem* **2014**, (10), 4477-4483.