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sp2 Carbon-Hydrogen Bond (C-H) Functionalization

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By

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Abstract

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Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Robert G. Bergman, Chair

Chapter 1. A review of the Bergman/Ellman group literature on rhodium-catalyzed direct sp^2 C-H bond functionalization reactions is presented. In addition, some well-known late transition-metal catalyzed sp^2 C-H bond functionalization reactions are described. These synthetic methods have valuable applications for organic chemistry and enable access to a number of interesting organic compounds and derivatives. These examples highlight the importance of this type of transformation and provide the background from which the results described in Chapters 2-5 may be viewed.

Chapter 2. Bridgehead bicyclic unsaturated enamines were prepared by a tandem rhodium-catalyzed C-H bond activation/alkenylation/electrocyclization of alkyne-tethered unsaturated imines. These strained bicyclic enamines exhibit unique reactivity: for example, they lead to N-alkylated products upon treatment with alkylating reagents and undergo double bond isomerization to alleviate ring strain upon reduction.

Chapter 3. An efficient method is reported for the preparation of multicyclic pyridines and quinolines by a rhodium-catalyzed intramolecular C-H bond functionalization process. The method shows good scope for branched and unbranched alkyl substituents on the pyridine ring and at the R position of the tethered alkene group. Starting materials capable of undergoing olefin isomerization to provide terminal 1,1-disubstituted alkenes also proved to be effective substrates.

Chapter 4. A method for the direct arylation of benzotriazepines is reported, employing an aryl iodide as the coupling partner, copper iodide as the catalyst, and lithium tert-butoxide as the base. A variety of electron-rich, electron-poor, and sterically hindered aryl iodides are compatible with the reaction conditions. The arylation reaction can also be performed outside a glovebox in air without a significant decrease in yield. Furthermore, convenient microwave conditions for carrying out this transformation are reported.

Chapter 5. The reaction of isopropyl Grignard reagent and 3-bromoquinoline leads to formation of interesting 3,4-disubstituted quinoline products in significant yields. This transformation was extensively studied for 3-bromoquinoline as the substrate, isopropyl magnesium chloride as the nucleophile, and a Brønsted acid or 3-bromopropene as electrophiles.

A brief survey of this transformation, identification of the reaction limitations, and a suggested mechanism are reported in this Chapter.

sp^2 Carbon-Hydrogen Bond (C-H) Functionalization

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Chapter I. Transition Metal-Catalyzed Direct sp^2 C-H Bond Functionalization

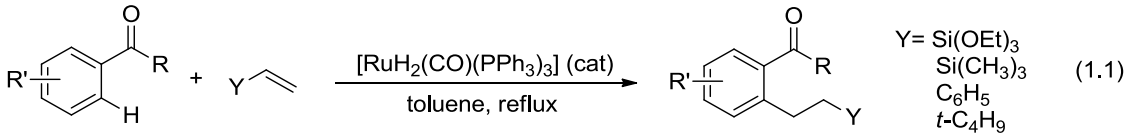
A review of the Bergman/Ellman group literature on rhodium-catalyzed direct sp^2 C-H bond functionalization reactions is presented. In addition, some well-known late transition-metal catalyzed sp^2 C-H bond functionalization reactions are described. These synthetic methods have valuable applications for organic chemistry and enable access to a number of interesting organic compounds and derivatives. These examples highlight the importance of this type of transformation and provide the background from which the results described in Chapters 2-5 may be viewed.

Introduction

One of the major challenges in synthetic organic chemistry is the ability to directly transform unfunctionalized precursors into complex molecules. In particular, the activation and subsequent functionalization of carbon-hydrogen (C-H) bonds promises to become increasingly important as a versatile method of forming carbon-carbon (C-C) bonds.[1] C-H bonds are ubiquitous in organic molecules, and the ability to selectively activate them would greatly increase the number of substrates available for synthetic use. The direct functionalization of C-H bonds is also atom-economical and has the potential to reduce toxic halogenated byproducts that result from many of the alternative methods for C-C bond formation.

Chelation Assisted C-H Bond Functionalization and Alkylation Reactions

The field of C-H bond activation chemistry emerged in the 1970s; however, the early works on catalytic C-H activation/functionalization were reported by Jordan et al. (1989) and Moore et al. (1992).[2a,b] The first synthetically useful catalytic C-H functionalization for carbon-carbon (C-C) bond formation was reported in 1993 by Murai and co-workers.[2c] This work involved a ruthenium-catalyzed coupling of an olefin to the *ortho* position of an aromatic ketone (eq 1.1).

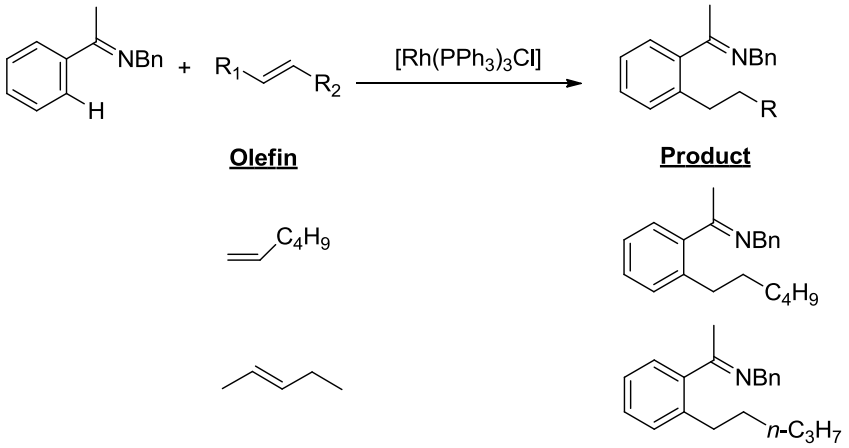


(1.1)

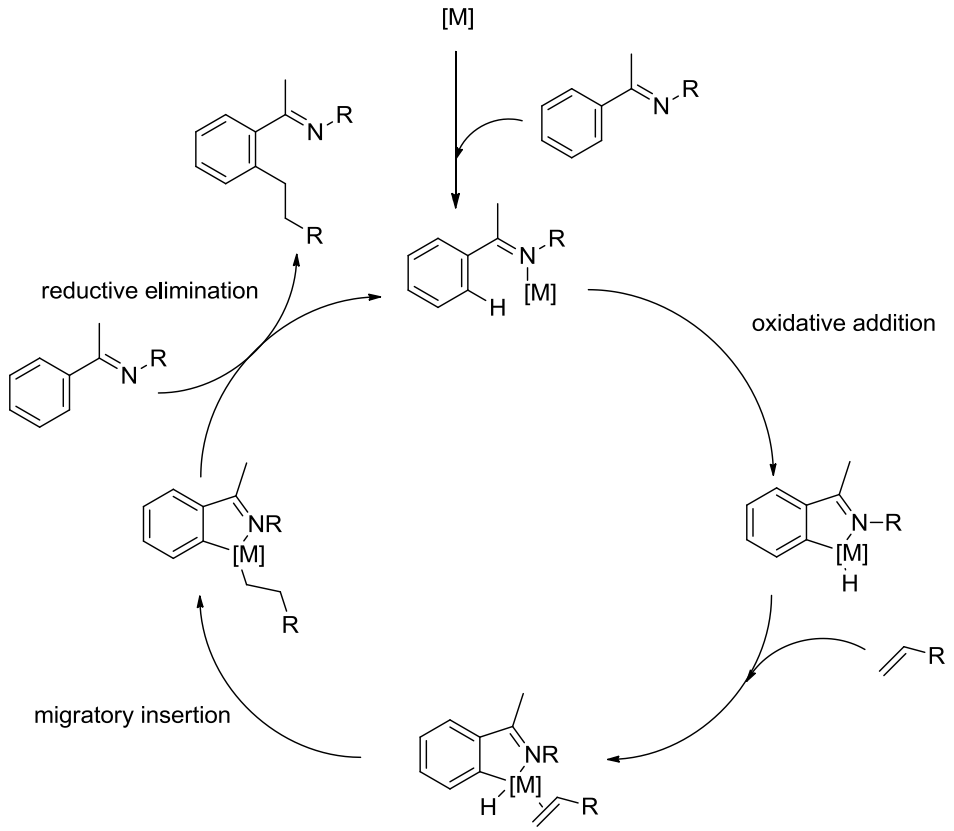
Despite high yields and good selectivity towards mono-alkylation at the *ortho* position, this chemistry was only applicable to terminal, non-isomerizable olefin substrates. Internal and isomerizable alkenes were not effective substrates for this reaction.

Later, Jun and co-workers expanded the olefin substrate scope of this transformation to include both terminal and internal olefins, though internal olefins underwent isomerization to terminal alkenes prior to alkylation to give linear products in all cases (Scheme 1.1).[3] By converting aromatic ketones to the corresponding ketimines, Rh catalyzed C-H activation at the *ortho* postion on the aromatic ring is assisted by chelation of the Lewis-basic imine nitrogen (Scheme 1.2).[4] Upon hydrolysis of the alkylated ketimine products, the corresponding ketones were isolated in high yields.

Scheme 1.1. The Imine Directed C-H Functionalization Reported by Jun.[3]



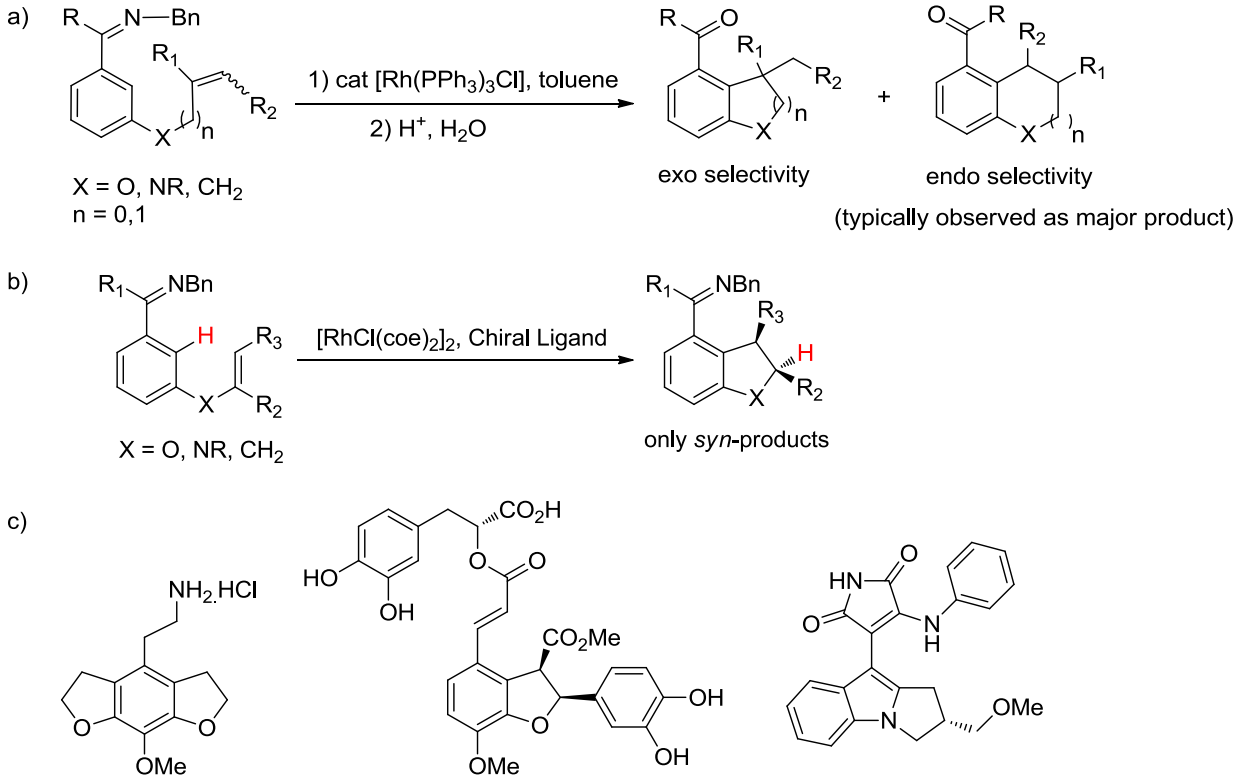
Scheme 1.2. Generally Accepted Mechanism of Chelation-Assisted Rh-catalyzed C-H Alkylation.



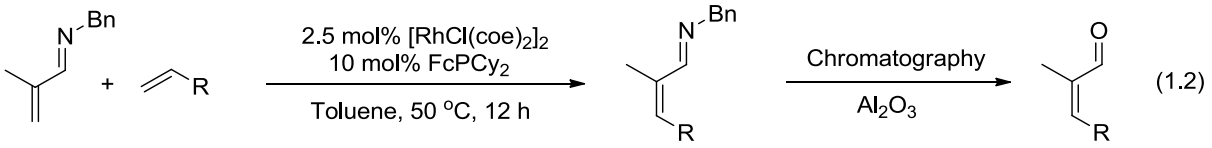
The Bergman/Ellman group has also been interested in the application of catalytic C-H functionalization chemistry. The groups have developed several important C-H functionalization methodologies.[5,6] One example is the cyclization of aromatic imines via Rh-catalyzed direct C-H activation (Figure 1.1a). This coupling proceeds selectively to the more hindered *ortho* site to

provide functionalized bicyclic ring systems that would be difficult to access by other methods. This intramolecular reaction can provide linear *or* branched coupling products depending on the alkene tether. The stereospecific nature of cyclization defines product stereochemistry based upon alkene geometry.[6a] Moreover, enantioselective catalytic intramolecular alkylation using chiral Rh catalysts have also been developed (Figure 1.1b).[7] The synthetic utility of these transformations has also been demonstrated by application to the syntheses of many complex molecules (Figure 1.1c).[8]

Figure 1.1. Examples of Synthetic Methodologies Developed in Bergman/Ellman Group.
a) Initial Report of Rh-catalyzed Intramolecular Cyclization.
b) Enantioselective Catalytic Cyclizations using Chiral Rh Catalysts.
c) Example of Complex Molecules Synthesized using Rh –catalyzed C-H Functionalization/Alkylation Chemistry.

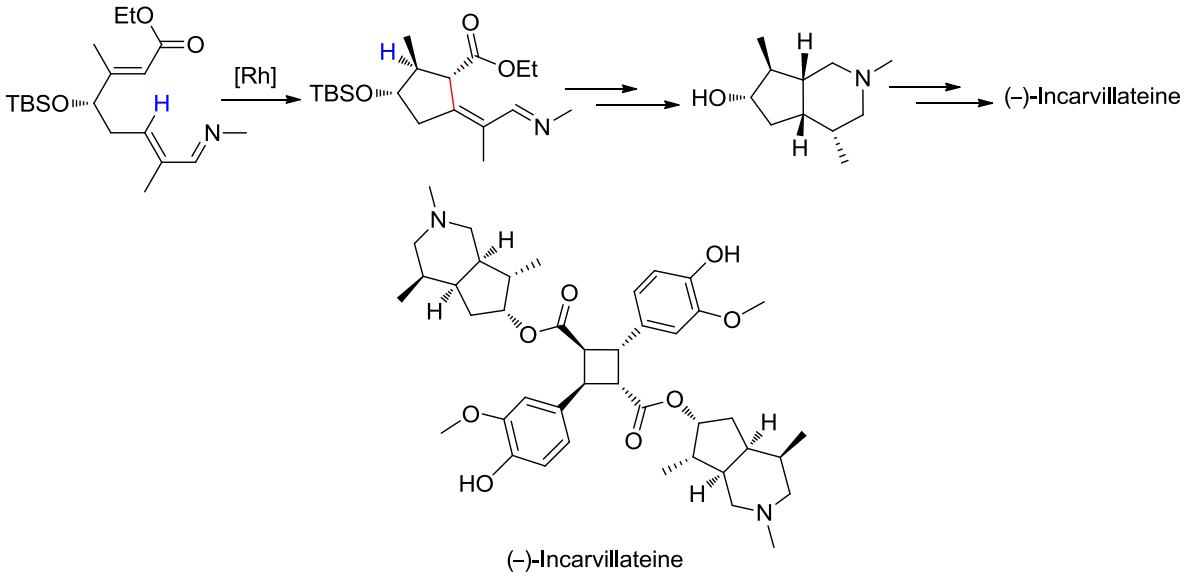


Based on reports of the C-H functionalization of aromatic systems by Jun and previous studies in the Bergman/Ellman group (Figure 1.1), the substrate scope of the imine-directed C-H activation/functionalization was expanded to include non-aromatic systems.[9,10] The alkylation of α,β-unsaturated imines with alkenes via the activation of a β C-H bond can be achieved in the presence of a Rh precatalyst (eq 1.2). After alumina column chromatography with concomitant imine hydrolysis, the β-alkylated α,β-unsaturated aldehyde is isolated primarily as the *Z* isomer.



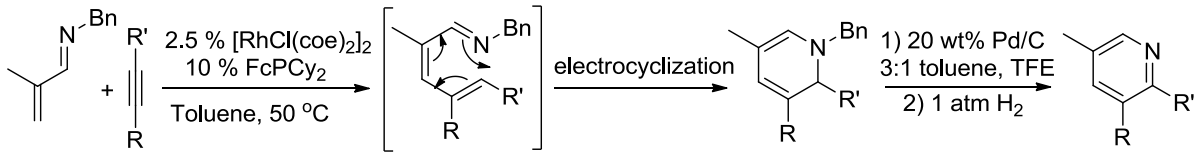
The synthetic utility of the olefinic C-H alkylation via Rh catalysis was demonstrated in the total synthesis of the natural product (−)-incarvillateine (Scheme 1.3).[11] A key step was a rhodium-catalyzed intramolecular alkylation of an olefinic C−H bond to set two stereocenters in a five-membered exocyclic, tetrasubstituted alkene.

Scheme 1.3. Rh-catalyzed C-H Functionalization was the Key Step for the Total Synthesis of (−)-Incarvillateine.



Additionally, α,β-unsaturated imines were found to react with internal alkynes to form conjugated aza-triene intermediates. These intermediates underwent facile electrocyclization *in situ* to afford dihydropyridine compounds, which could be further transformed into a variety of highly substituted pyridine derivatives under mild reaction conditions (Scheme 1.4).[12] The coupling between alkynes and imines via C-H functionalization had very good scope and gives highly substituted pyridine products in good yield.

Scheme 1.4. C-H Activation/Alkenylation of Olefinic C-H Bond.

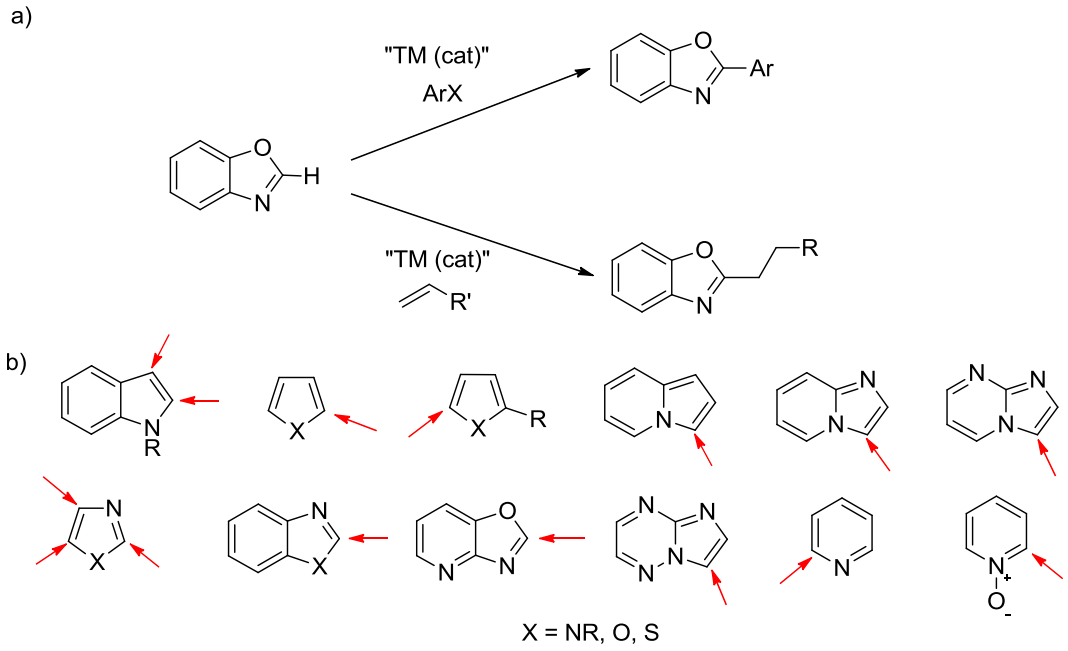


Direct C-H Functionalization of *N*-Heterocycles

N-heterocycles are present in a very large number of drugs and natural products.[13] For this reason, a significant interest among synthetic chemists is the development of methods to efficiently assemble the heterocycle as well as to further elaborate the heterocycle core once prepared. Among other strategies, C-H functionalization has shown increasing popularity in recent years.

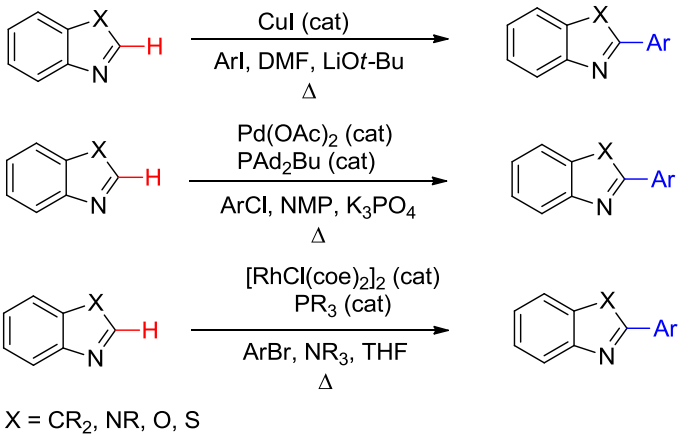
C-H bonds in heterocycles can be converted to C-R bonds via heterocycle alkylation and arylation using transition metal catalysts (ML_n) (Scheme 1.5a). Regioselectivity is usually controlled by electronic factors. However, alteration of solvents, additives, and the steric nature of the catalysts and/or substrates can change the regioselectivity. Mechanistically, the direct arylation of heterocycles is believed to occur primarily via four possible pathways: (1) an electrophilic aromatic substitution, (2) a Heck-type mechanism, (3) a carbanion cross-coupling mechanism, or (4) a carbene insertion mechanism. Again, the exact mechanism (and ultimately the observed regioselectivity) by which the direct arylation occurs is highly dependent upon the substrate, catalyst, reaction solvent, and additives present (Scheme 1.5b).[14]

Scheme 1.5. Examples of Direct C-H Functionalization of *N*-Heterocycles.
a) Direct C-H Functionalization (Arylation and Alkylation) of *N*-Heterocycles.
b) C-H Bond in Representative *N*-Heterocycles that can be Functionalized.



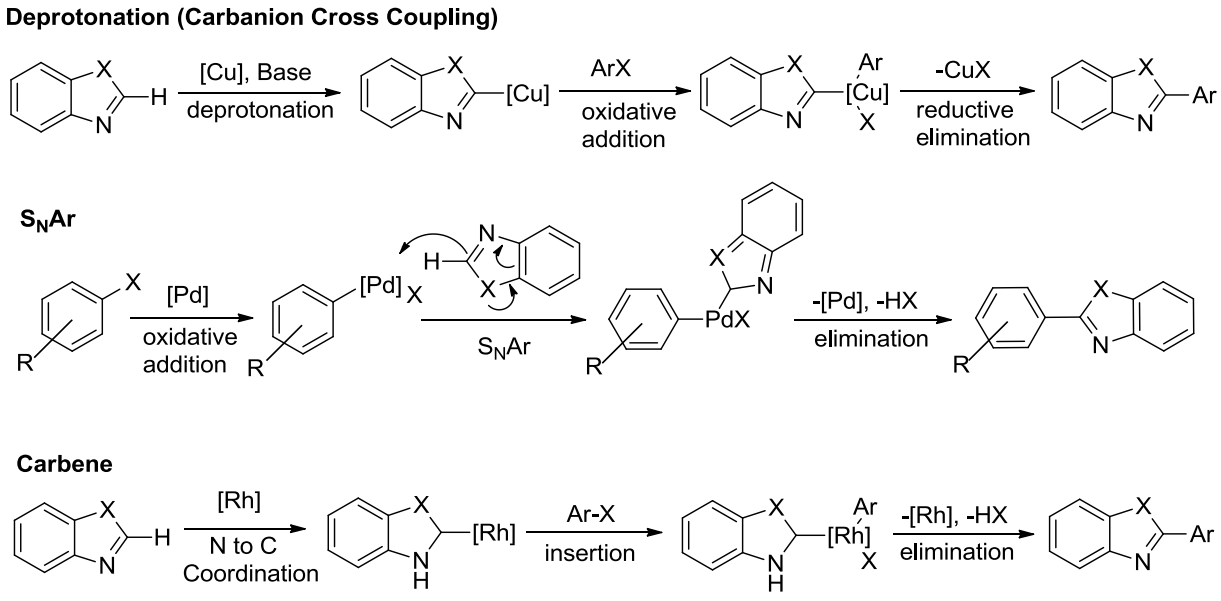
Some *N*-heterocycles can only be directly functionalized with a specific catalyst-ligand combination, while others can be directly functionalized with many catalysts using a number of reaction conditions. Examples of *N*-heterocycles that fall into the latter category are the azole class of compounds (Scheme 1.6).[10]

Scheme 1.6. Direct C-H Functionalization/Arylation of Azoles.



The mechanisms of azole arylation by Cu, Pd, and Rh are different (Scheme 1.7). For Cu catalysis, the transformation involves deprotonation to form a heteroaryl copper species followed by a coupling reaction. For Pd catalysis, the product was proposed to proceed via an S_NAr type mechanism. In contrast to the previous two transformations, azole arylation by a Rh catalyst was proposed to proceed by a carbene insertion mechanism. Each method has its own advantages and disadvantages.

Scheme 1.7. Generally Accepted Mechanisms for C-H Functionalization/Arylation of Azoles by Cu, Pd and Rh Catalysis.

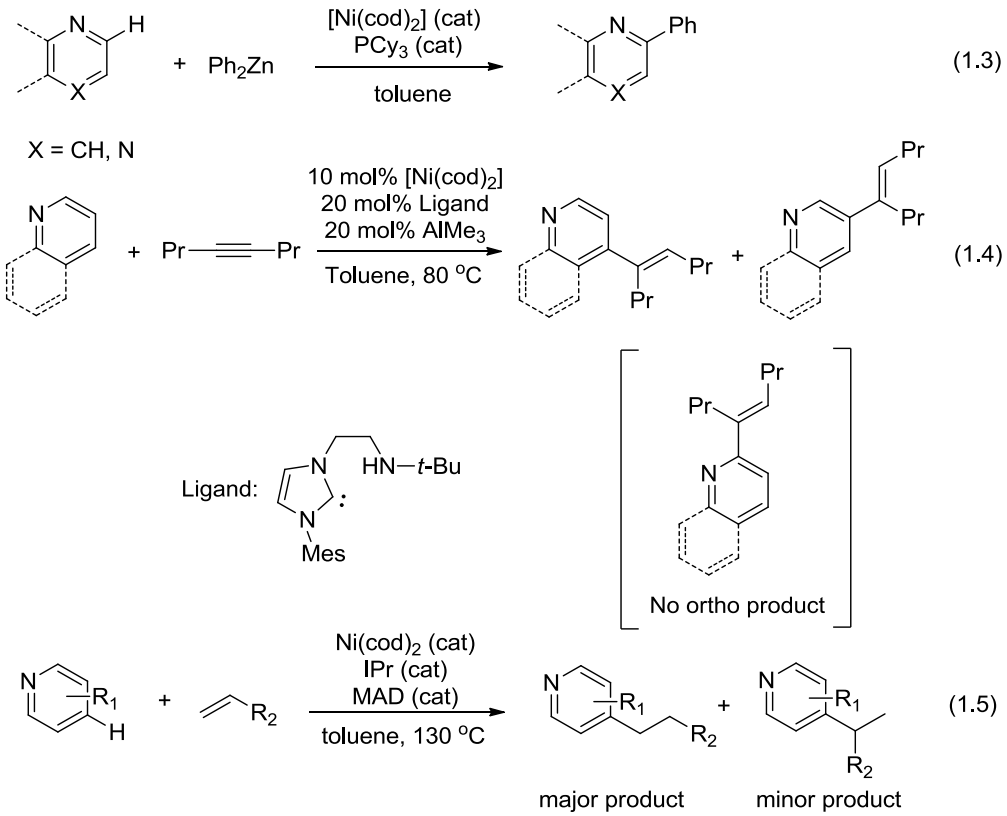


Direct C-H Functionalization in Pyridines

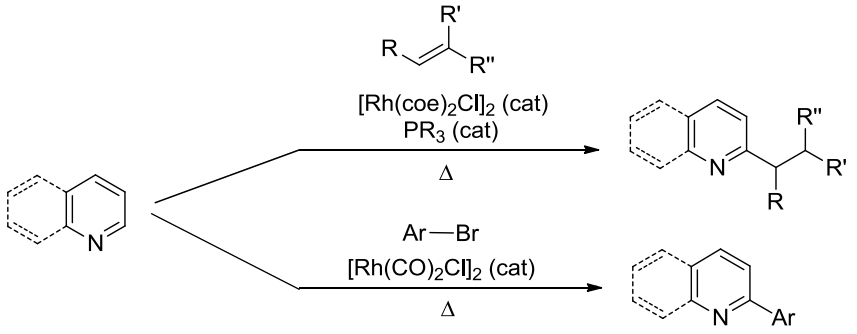
Of the *N*-heterocycles, pyridines are the most extensively used in pharmaceutical research. [13] Consequently, many efforts have been devoted to their synthesis using different chemistry. Traditional methods for pyridine synthesis involve the condensation of amines with carbonyl compounds as well as cycloaddition reactions; however, there are significant limitations to these methods due to both steric and electronic issues.[15]

C-H functionalization is an alternative method for pyridine synthesis or elaboration. Apart from the Bergman/Ellman synthesis of pyridine from imines and alkynes via C-H functionalization mentioned previously (Scheme 1.4),[12] reports by others have proven that C-H functionalization methods also allow the synthesis or elaboration of complex pyridines from simple and commercially available precursors. Examples are Cheng's pyridine synthesis from oximes and alkynes,[16a] Fagnou's pyridine synthesis from pyridine *N*-oxides and aryl bromides,[16b] Wu's pyridine/quinoline alkenylation from the *N*-oxides via Pd-catalyzed C-H functionalization,[16c] and Charette's pyridine synthesis from *N*-iminopyridinium ylides.[16d]

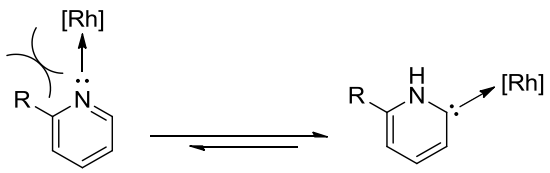
Nevertheless, there are only a few reports on the direct C-H functionalization of unactivated pyridines/quinolines. One example is by Chatani, who reported a method to convert pyridines and quinolines to *ortho* arylated products using nickel as a catalyst and a diarylzinc reagent as a coupling partner (eq 1.3).[17] Another example is by the Yap group which reported a Ni-catalyzed alkenylation method to convert pyridines and quinolines to *meta* and *para* alkenylated products (eq 1.4).[18] The most recent example is the selective C-4 alkylation of pyridine by nickel/Lewis acid catalysis by the Hiyama group (eq 1.5).[19] In addition, the Bergman/Ellman group discovered that pyridines/quinolines can be converted directly to more highly substituted derivatives via Rh-catalyzed C-H functionalization (Scheme 1.8). [20]



Scheme 1.8. Rh-catalyzed Direct C-H Functionalization of Pyridines/Quinolines.



While the scope of the Rh-catalyzed *ortho* alkylation and arylation were reasonably general in terms of the alkene and aryl bromide inputs, substitution at the 2-position of the pyridine was necessary for the transformation to occur. This substitution was most likely to introduce a steric interaction that favors the formation of the *C*-bound Rh-complex, necessary for C-H functionalization against the formation of the *N*-bound form (eq 1.6), which was supported by the related studies of transition metal insertion into C-H bonds in pyridines carried out by Carmona and Onate.[21]



(1.6)

N-bound Rh Complex *C*-bound Rh Complex

Conclusions

This overview chapter has presented relevant examples in the area of C-H bond functionalization via Rh catalysis, as well as, highlighting some synthetically useful C-H functionalization chemistry by other metals. The use of direct C-H functionalization as a route toward the formation of new C-C bonds has been continuously fascinating to organic chemists who strive to achieve an ideal synthesis: an atom economical process starting from relatively simple precursors with minimal preactivation. The exploration of new catalyst systems for C-H functionalization has grown considerably over the last decade. More recent studies have focused on developing milder reaction conditions and fine-tuning catalyst systems to allow for the use of less expensive and more industrially attractive methods. In addition, as presented in this thesis, direct C-H functionalization chemistry also permitted access to more complex and underrepresented classes of nitrogen-containing heterocycles that were very difficult to obtain via other synthetic methods. The Rh-catalyzed intramolecular alkylation of imines and pyridines, which led to complex bridgehead enamines and bicyclic pyridines, respectively, will be reported in Chapters 2 and 3. In addition, the direct arylation of benzotriazepine heterocycles using Cu catalysis will be illustrated in Chapter 4. Lastly, a brief survey on the unusual disubstituted quinoline products generated from reactions of Grignard reagents and 3-bromoquinoline substrates will be revealed in Chapter 5.

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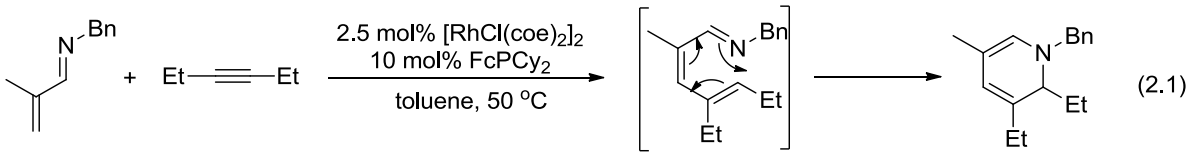
Chapter II. The Formation of Bridgehead Bicyclic Enamines via Tandem C-H Bond Activation/Alkenylation/Electrocyclization.

Bridgehead bicyclic unsaturated enamines were prepared by a tandem rhodium-catalyzed C-H bond activation/alkenylation/electrocyclization of alkyne-tethered unsaturated imines. These strained bicyclic enamines exhibit unique reactivity: for example, they lead to N-alkylated products upon treatment with alkylating reagents and undergo double bond isomerization to alleviate ring strain upon reduction. The majority of this work was published in a communication in The Journal of the American Chemical Society. (Yotphan, S.; Bergman, R. G.; Ellman, J. A. The Stereoselective Formation of Bicyclic Enamines with Bridgehead Unsaturation via Tandem C-H Bond Activation/Alkenylation/Electrocyclization. *J. Am. Chem. Soc.* **2008**, *130*, 2452-2453.)

Introduction

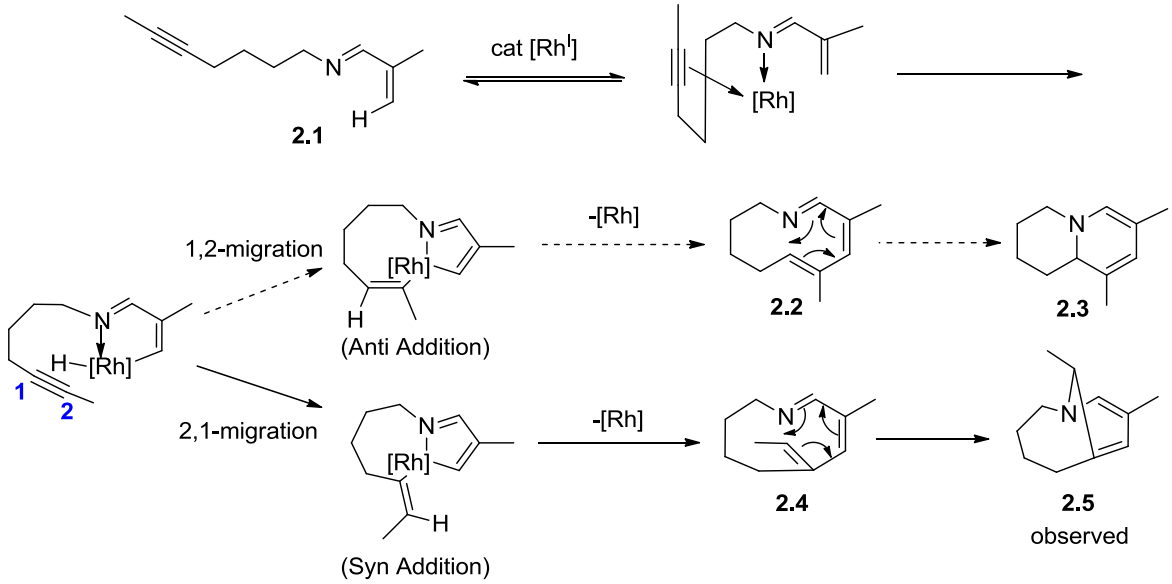
The first chapter briefly emphasized the advantages and challenges of directly forming carbon-carbon (C-C) bonds from carbon-hydrogen (C-H) bonds in organic synthesis and also described in particular the starting point of our work in the area of β−alkylation and alkenylation of α,β-unsaturated imines. As mentioned in the previous chapter, rhodium-catalyzed intermolecular C-H activation of α,β-unsaturated imines in the presence of alkynes leads to a tandem process in which coupling to the alkyne occurs at the *ortho*-C-H bond of the imine, followed by electrocyclization of the resulting azatriene intermediates to give dihydropyridines (eq 2.1).[1,2]



(2.1)

In this chapter, the substrate scope of the alkenylation reaction is expanded to include alkyne-tethered imine substrates. Consideration of the intramolecular version of this overall transformation (Scheme 2.1) raises interesting regiochemical issues. For example, in a compound such as **2.1**, where the nitrogen and alkyne are connected by a 4-carbon tether, the presumed first formed hydrido(vinyl)rhodium intermediate can add to the triple bond in a 1,2-fashion, producing complex **2.2** with a new endocyclic double bond. Alternatively, addition might occur in a 2,1-fashion, leading to product **2.4** with an exocyclic double bond. It turned out that this intramolecular cyclization occurred smoothly at 100 °C, and the exocyclic double bond route was exclusively followed. Remarkably, alkenylated product **2.4** does not resist further cyclization. Even though both the transition state for this process and the resulting product are presumably strained, the overall transformation leads to the unusual bridgehead doubly bonded[3] enamine **2.5** in good yields. The unique chemistry of conjugated enamine **2.5** is consistent with the increased strain of this structure as well as with the inhibited conjugation between the nitrogen lone pair and the adjacent double bond (vide infra).

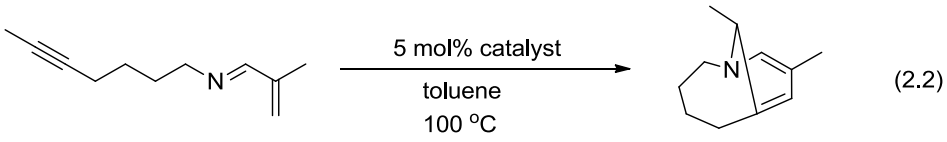
Scheme 2.1. Possible Sequences of Intramolecular C-H Functionalization.



Reaction Optimization

We began our investigation into the C-H activation/cyclization of alkyne-tethered imine **2.1** by extensively screening transition metal catalysts for this reaction. Rhodium-based catalysts were found to be the most efficient (Table 2.1), leading exclusively to the bridgehead dienamine; none of the catalysts that were employed in the screening process led to quinolizidine **2.3** or to the product of intramolecular Diels-Alder reaction. The optimized reaction conditions employed the electron-rich monophosphine ligand (*p*-NMe_2)$PhPEt_2$ in a 1:1 ratio relative to the metal (entry 6).[1b] Other phosphine ligands also provided product **2.5**, but lower yields were observed (entries 3, 5, and 8-10). Of particular note, the commercially available phosphine, PCy_3, gave yields that were nearly identical to those obtained using the optimized conditions (entry 4). By monitoring the progress of the reaction by NMR spectroscopy the nine-membered ring aza-triene intermediate **2.4** was observed to form initially, as proposed in Scheme 2.1. However, this intermediate underwent spontaneous electrocyclization to form **2.5**.[4] Presumably, in the Rh-H addition step, the geometry of the alkyne-tethered imine substrate requires exocyclic cyclization because syn addition of the C-H bond in the endocyclic cyclization transitions state would require a highly constrained Rh-chelated eight-membered ring transition state that incorporates a trans-double bond (Scheme 2.1).

Table 2.1. Optimization of the Reaction Conditions.[a]



(2.2)

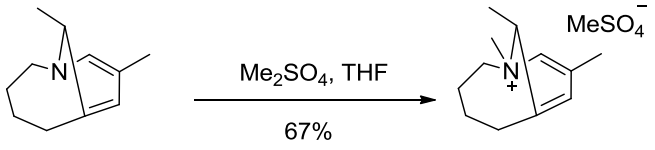
2.1 **2.5**

entry	catalyst	added ligand[a]	time (h)	% yield[b]
1	$Ru(H_2)CO(PPh_3)_3$	-	4	45
2	$Rh(PPh_3)_3Cl$	-	4	59
3	$[Rh(coe)_2Cl]_2$	PPh_3	2	41
4	$[Rh(coe)_2Cl]_2$	PCy_3	8	72
5	$[Rh(coe)_2Cl]_2$	$FcPCy_2$	4	52
6	**$[Rh(coe)_2Cl]_2$**	**(*p*-NMe_2)$PhPEt_2$**	**4**	**75 (54)[c]**
7	$[Rh(coe)_2Cl]_2$	(*p*-NMe_2)$PhPCy_2$	4	72
8	$[Rh(coe)_2Cl]_2$	(*p*-NMe_2)$_2PhPCy$	4	63
9	$[Rh(coe)_2Cl]_2$	(*p*-NMe_2)$PhPMe_2$	4	52
10	$[IrCl(cod)]_2$	PCy_3	4	15

[a] 5 mol % ligand (1:1 ligand:catalyst) was added. [b] All yields were determined by NMR integration relative to 2,6-dimethoxytoluene as an internal standard. [c] Isolated yield in parentheses.

Chemistry of Bridgehead Dienamine

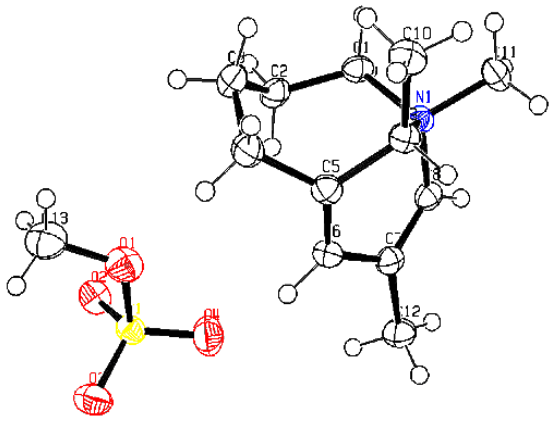
The chemistry of bridgehead dienamine **2.5** was investigated because of its novel structure. Upon treatment with Me_2SO_4, the bridgehead compound **2.5** was converted exclusively to *N*-methylated product **2.6** (eq 2.3), a regioselectivity that is opposite to that observed with acyclic and monocyclic enamines, which usually give *C*-alkylation.[5,6] Crystals of **2.6** suitable for X-ray analysis were obtained, and the resulting crystal structure (Figure 2.1) confirmed the structure for **2.5** proposed below (eq. 2.3). The bridgehead double bond of **2.6** is found to be significantly nonplanar (twist).[7] Deviation from the optimal planar geometry caused by the bicyclic structure in **2.5** presumably also results in poor delocalization of the nitrogen lone pair electrons into the adjacent diene orbitals, which would account for the observation of *N*-alkylation.[8]



(2.3)

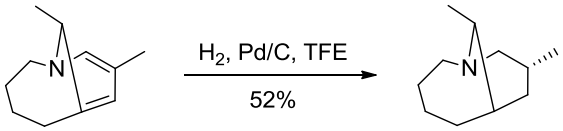
2.5 **2.6**

Figure 2.1. ORTEP Diagram with 50% Thermal Ellipsoids Illustrating the Results of the X-ray Crystal Structure Determination of **2.6**.



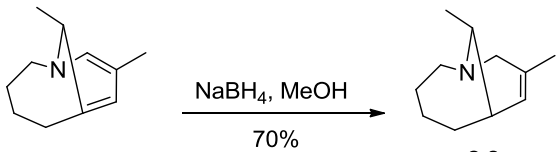
Hydrogenation of **2.5** under standard conditions gave the fully reduced tertiary amine product **2.7** as a single diastereomer (eq 2.4). Ring strain was also alleviated by reduction of **2.5** with $NaBH_4$ in methanol, which provided **2.8** as the only product (eq 2.5). This result contrasted with the reduction of 1,2-dihydropyridines under the same conditions, which is reported to provide a different double bond isomer.[9]

Scheme 2.2. Bridgehead Enamine **2.5** under Reduction Conditions.



(2.4)

2.5 **2.7**



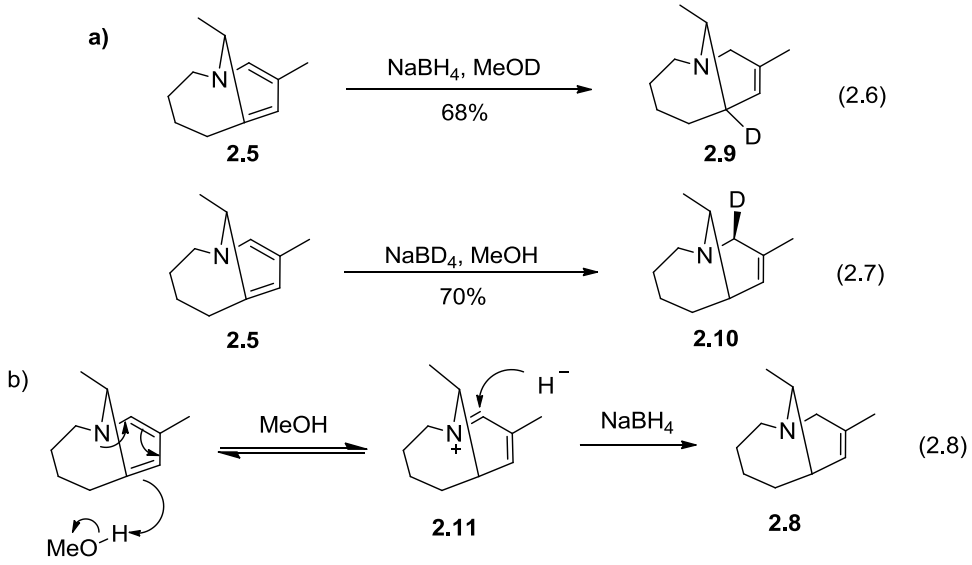
(2.5)

2.5 **2.8**

To investigate the mechanism of the borohydride reduction, two isotope labeling studies were conducted (Scheme 2.3). Reduction of **2.5** with $NaBH_4$ in MeOD-d_4 resulted in the placement of a deuterium at the bridgehead (eq 2.6), while treatment of **2.5** with $NaBD_4$ in MeOH results in a product that is deuterated on the carbon adjacent to nitrogen (eq 2.7). On the

basis of these observations, we propose that the overall reaction involves initial reversible protonation by MeOH to give the iminium intermediate **2.11**, followed by hydride attack on the strained iminium double bond (eq 2.8).

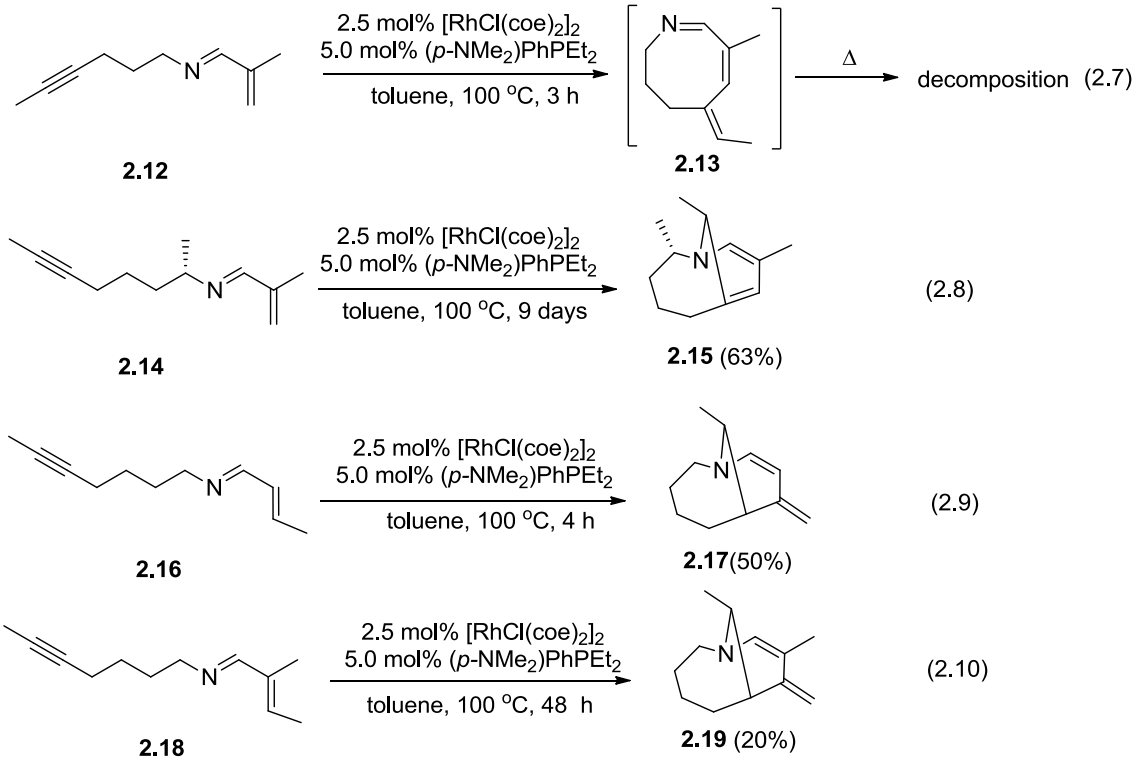
Scheme 2.3. a) Isotope Labeling Experiments of $NaBH_4$ Reduction.
b) The Proposed Mechanism of $NaBH_4$ Reduction.



C-H Functionalization of Other Imine Substrates

Other α,β-unsaturated aldimine substrates with tethered alkynyl groups were also examined (Scheme 2.4). Imine **2.12** with a tether shorter than **2.1** underwent C-H functionalization to form a smaller eight-membered ring aza-triene intermediate **2.13** (detectable by NMR spectroscopy). However, this unstable species decomposed over time and the bicyclic product analogous to **2.5** was not detected (eq 2.7). It is likely that the optimum geometry required for the cyclization to occur cannot be achieved for this eight-membered ring system. Imine **2.14** with a methyl group located α to the nitrogen provided bridgehead nine-membered ring **2.15** as a single diastereomer (eq 2.8). A prolonged reaction time was necessary because of a slow electrocyclization step. We also investigated the reaction of substrate **2.16**, but the expected bridgehead product was not obtained. Instead, bicyclic amine **2.17** with an exocyclic double bond was formed (eq 2.9). This product is likely formed by isomerization to relieve ring strain. However, a lower yield was obtained in the case of the more highly substituted imine **2.18** (eq 2.10).

Scheme 2.4. C-H Functionalization of Other Imine Substrates.[a]



[a] Yields were calculated by ^{1}H NMR integration relative toan internal standard.

Conclusions

In summary, we have demonstrated the Rh-catalyzed C-H activation of alkyne-tethered α,β-unsaturated imines, followed by reaction of the activated intermediate with alkynes. This leads to an intermediate that undergoes further spontaneous, presumably thermal, electrocyclization to form strained bicyclic enamines with a bridgehead unsaturation. These products show a unique behavior in alkylation and reduction as a consequence of the strain in the bicyclic system.

Experimental

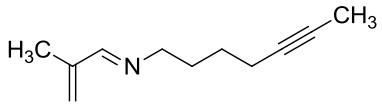
General Unless otherwise specified, all reagents were obtained from commercial suppliers and used without further purification. Molecular sieves (4 Å) were activated by heating at 300 °C under 0.5 mm Hg vacuum overnight to remove any traces of water and were stored in a nitrogen-filled dry box. Toluene was dried over alumina under a nitrogen atmosphere, degassed by purging with nitrogen for 5 minutes, and stored in a nitrogen-filled drybox. Tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were dried over alumina under a nitrogen atmosphere. Methacrolein and crotonaldehyde were distilled and used immediately. All reactions were performed under inert atmosphere using standard Schlenk-line techniques. Oven-dried glassware was used in all cases. Chromatography was performed on silica gel (SiO_2), Merck 60 230-240

mesh. ^{1}H and ^{13}C NMR spectra were measured with a Bruker AV-300, AV-400 or DRX-500 spectrometer in $CDCl_3$. NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 ppm for ^{1}H, and 77.23 ppm for ^{13}C). All multidimentional NMR spectra were measured in $CDCl_3$ with a Bruker AV-400 or AV-500 spectrometer. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. High resolution mass spectrometry (HRMS) was carried out by the University of California at Berkeley Mass Spectrometry Facility. For high-resolution EI mass spectrometry, a ProSpec spectrometer (magnetic sector instrument) equipped with an EI source (Micromass, Manchester, UK) was used. For high-resolution FAB mass spectrometry, a ZAB spectrometer (magnetic sector instrument) equipped with a FAB source (Micromass, Manchester, UK) was used. The X-Ray crystal structure was analyzed by Dr. Frederick J. Hollander and Geza Szigethy of the Berkeley CHEXray Facility.

Substrate Syntheses. $[RhCl(coe)_2]_2$[10], (*p*-NMe_2)$PhPEt_2$[1b], (*p*-NMe_2)$PhPCy_2$ [1b], $FcPCy_2$[1a], and other amine starting materials were prepared according to literature procedures.

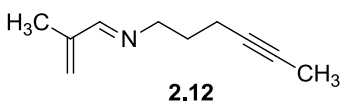
General Procedure for Imine Syntheses.

Alkyne-tethered amine (8.00 mmol) was dissolved in toluene (50.0 mL) in a 250 mL oven-dried round bottom flask. To this solution 4 Å molecular sieves (25.0 g) and the α,β-unsaturated aldehyde/ketone (8.00 mmol, 1.00 equiv) were added, and the reaction mixture was stirred at room temperature for 16 h. The resulting mixture was filtered over Celite, and the filter cake was washed with diethyl ether (50 mL). The filtrate was concentrated *in vacuo*. The crude product was purified by Kügelrohr distillation at 0.05 mm Hg to afford the desired imine product. The product was transferred to a vial and stored at -25 °C.



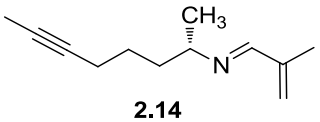
2.1

Imine 2.1. Imine **2.1** was prepared from hept-5-yn-1-amine[11] (890 mg, 8.00 mmol) and methacrolein (560 mg, 8.00 mmol) following the general procedure for imine syntheses described above to afford crude imine as a yellow oil. The crude oil was purified by Kügelrohr distillation (80-90 °C, 0.05 mm Hg) to give imine **2.1** as a colorless oil (678 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 5.57 (s, 1H), 5.36 (s, 1H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.18-2.13 (m, 2H), 1.93 (s, 3H), 1.78 (t, *J* = 2.5 Hz, 3H), 1.79-1.72 (m, 2H), 1.55-1.45 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 164.2, 143.9, 123.9, 79.0, 75.8, 61.1, 30.3, 27.0, 18.8, 17.4, 3.7. IR (film): 2919, 2859, 2841, 1641, 1619, 1452, 1362, 1333, 906 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{17}N$ $[M]^{+}$ 163.1361; Found 163.1324.



2.12

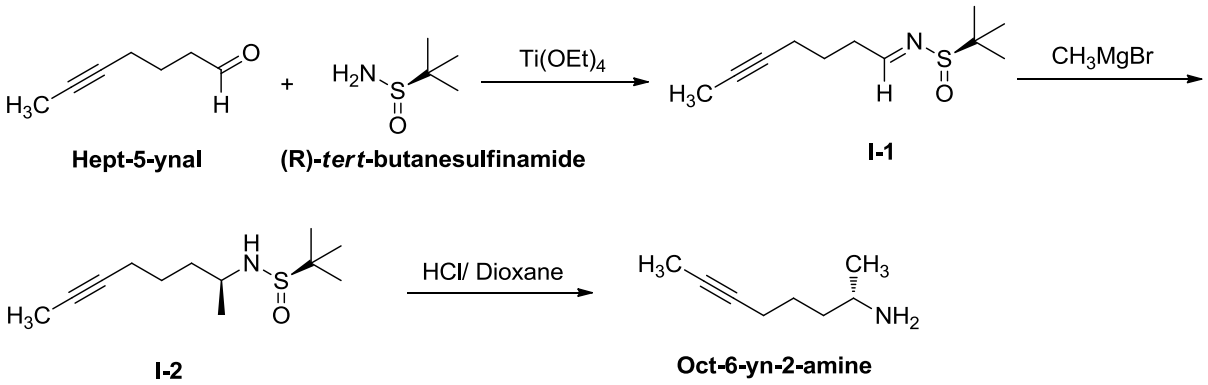
Imine 2.12. Imine **2.12** was prepared from hex-4-yn-1-amine[12](780 mg, 8.00 mmol) and methacrolein (560 mg, 8.00 mmol) following the general procedure for imine syntheses described above to afford crude imine as a yellow oil. The crude oil was purified by Kügelrohr distillation (80-85 °C, 0.05 mm Hg) to give imine **2.12** as a colorless oil (560 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 5.58 (s, 1H), 5.37 (s, 1H), 3.57 (t, *J* = 6.7 Hz, 2H), 2.18-2.13 (m, 2H), 1.92 (s, 3H), 1.78-1.83 (m, 5H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 164.7, 143.9, 124.1, 78.8, 76.1, 60.1, 30.1, 17.7, 16.6, 3.7. IR (film): 2946, 2920, 2842, 1738, 1724, 1668, 1641, 1620, 1446, 1435, 1366, 1229, 1217, 908 cm^{-1}. HRMS (EI+) Calcd for $C_{10}H_{15}N$ 149.1206 found 149.1209.



2.14

Imine 2.14. Imine **2.14** was prepared from oct-6-yn-2-amine (see note below) (1.00 g, 8.00 mmol) and methacrolein (560 mg, 8.00 mmol) following the general procedure for imine syntheses to afford imine **2.14** The crude oil was purified by Kügelrohr distillation (80-95 °C, 0.05 mmHg) to give imine **2.14** as a yellow oil (705 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 5.55 (s, 1H), 5.34 (s, 1H), 3.18-3.13 (m, 1H), 2.13-2.09 (m, 2H), 1.93 (s, 3H), 1.78 (t, *J* = 2.4 Hz, 3H), 1.65-1.58 (m, 2H), 1.55-1.33 (m, 2H), 1.19 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.1, 144.0, 123.7, 79.0, 75.7, 66.4, 37.2, 26.5, 22.9, 18.9, 17.6, 3.7. IR (film): 3082, 2966, 2920, 2841, 1618, 1640, 1452, 1371, 1324, 1130, 1023, 963, 906 cm^{-1}. HRMS (EI+) Calcd for $C_{12}H_{19}N$ $[M]^+$ 177.1518 ; Found 177.1474.

<u>Note</u>: the Synthesis of Oct-6-yn-2-amine.

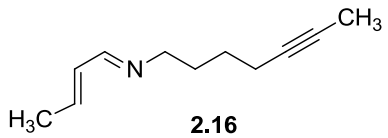


Compound I-1. A solution of $Ti(OEt)_4$ (18.1 g, 79.5 mmol, 2.50 equiv) and Hept-5-ynal[13] (3.50 g, 31.8 mmol, 1.00 equiv) in THF (180 mL) was prepared under a nitrogen atmosphere. To the solution was added (R)-*tert*-butanesulfinamide (5.78 g, 47.7 mmol, 1.50 equiv), and the resulting mixture was stirred at room temperature for 16 h. The mixture was then poured into an equal volume of brine while being stirred rapidly. The resulting suspension was filtered through a plug of Celite and the filter cake was washed with EtOAc (50 mL). The filtrate was transferred to a separatory funnel and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to

afford the crude sulfinyl imine **I-1**. The crude sulfinyl imine was purified by flash chromatography (SiO_2, hexanes/EtOAc= 9/1 to 3/1) affording **I-1** (4.25 g, 63%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (t, *J* = 4.4 Hz, 1H), 2.66-2.62 (m, 2H), 2.28-2.21 (m, 2H), 1.86-1.75 (m, 5H), 1.20 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.2, 78.1, 76.8, 56.7, 35.3, 24.8, 23.5, 18.4, 3.6. IR (film): 2920, 1622, 1474, 1455, 1363, 1184, 1079, 1014, 733, 676, 581 cm^{-1}. HRMS (FAB+) Calcd for $C_{11}H_{20}NSO$ $[MH]^+$ 214.1266; Found 214.1263.

Compound I-2. To a flame-dried flask was added **I-1** (4.00 g, 18.8 mmol, 1.00 equiv) in anhydrous diethyl ether (92.0 mL), and the solution was cooled to -40 ^oC (dry ice/CH_3CN). A solution of methyl magnesium bromide (MeMgBr) in diethyl ether (3.00 M, 12.5 mL, 2.00 equiv) was added dropwise over 10 min. The solution was allowed to slowly warm to room temperature for 1 h and then was stirred at room temperature for 16 h. The reaction solution was cooled to 0 ^oC and saturated NH_4Cl (100 mL) was added. The resulting suspension was diluted with brine (50 mL) and extracted with EtOAc (3 x 75 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated to afford the crude product. The crude product was purified by flash column chromatography (SiO_2, hexanes/EtOAc = 1:1) affording a single diastereomer of **I-2** (3.57 g, 83%) as a white solid. mp = 46.5-47.1 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40-3.34 (m, 1H), 2.88-2.86 (m, 1H), 2.14-2.13 (m, 2H), 1.78 (t, *J* = 2.4 Hz, 3H), 1.56-1.50 (m, 4H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 79.0, 76.1, 55.9, 52.5, 37.5, 25.4, 23.5, 22.8, 18.8, 3.7. IR (film): 3220, 2952, 2923, 1455, 1365, 1147, 1044, 1032, 972, 599, 506 cm^{-1}. HRMS (FAB+) Calcd for $C_{12}H_{24}NSO$ $[MH]^+$ 230.1579; Found 230.1579.

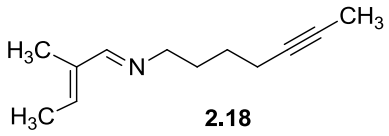
Oct-6-yn-2-amine. To a 0.2 M solution of **I-2** (3.50 g, 15.3 mmol) in dioxane (75.0 mL) was added 15.0 mL of MeOH (20 equiv) and 15.3 mL of 4.00 N HCl/dioxane (61.2 mmol, 4.0 equiv). The solution was stirred for 2 h at room temperature and was then concentrated *in vacuo*. The amine hydrochloride salt was obtained as a white solid after triturating with diethyl ether (2 x 20 mL). The amine hydrochloride salt was converted to its free base oct-6-yn-2-amine by treatment with 1 M NaOH (70 mL) followed by extraction with EtOAc (2 x 50 mL). NaCl (~ 20 g) was added to the aqueous phase and then was again extracted with EtOAc (50 mL). The combine organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated to afford oct-6-yn-2-amine (1.34 g, 70 %) as a yellow liquid, and it was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94-2.86 (m, 1H), 2.16-2.12 (m, 2H), 1.78 (t, *J* = 2.6 Hz, 3H), 1.58-1.37 (m, 4H), 1.26 (br s, 2H),1.07 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 79.3, 75.9, 46.9, 39.6, 26.2, 24.2, 19.0, 3.7. IR (film): 3367, 2956, 2922, 2863, 1730, 1591, 1456, 1372, 1242, 1127, 989, 710 cm^{-1}. HRMS (EI+) Calcd for $C_8H_{15}N$ $[M]^+$ 125.1204; Found 125.1238.



2.16

Imine 2.16. Imine **2.16** was prepared from hept-5-yn-1-amine (890 mg, 8.00 mmol) and crotonaldehyde (560 mg, 8.00 mmol) following the general procedure for imine syntheses to

afford imine **2.16**. The crude oil was further purified by Kügelrohr distillation (80-95 °C, 0.5 mmHg) to give imine **2.16** as a yellow oil (585 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.6 Hz, 1H), 6.22-6.17 (m, 2H), 3.43 (t, *J* = 7.0 Hz, 2H), 2.17-2.13 (m, 2H), 1.88 (d, *J* = 5.2 Hz, 3H), 1.78 (t, *J* = 2.6 Hz, 3H), 1.77-1.73 (m, 2H), 1.52-1.47 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 162.6, 140.2, 132.0, 79.0, 75.6, 60.7, 30.0, 26.7, 18.5, 18.3, 3.5. IR (film): 2919, 2831, 1657, 1626, 1438, 1375, 1333, 1185, 979, 927, 733 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{17}N$ $[M]^+$ 163.1361; Found 163.1376.



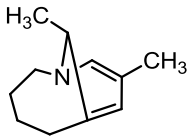
2.18

Imine 2.18. Imine **2.18** was prepared from hept-5-yn-1-amine (890 mg, 8.00 mmol) and (*E*)-2-methylbut-2-enal (675 mg, 8.00 mmol) following the general procedure for imine syntheses to afford imine **2.18**. The crude oil was further purified by Kügelrohr distillation (80-95 °C, 0.5 mmHg) to give imine **2.18** as a colorless oil (850 mg, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 5.94-5.89 (m, 1H), 3.45 (t, *J* = 7 Hz, 2H), 2.17-2.11 (m, 2H), 1.85-1.78 (m, 6H), 1.75-1.72 (m, 3H), 1.71-1.66 (m, 2H), 1.56-1.45 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.7, 136.9, 136.1, 79.3, 75.7, 61.0, 30.5, 27.0, 18.8, 14.3, 11.5, 3.7. IR (film): 3309, 2920, 2860, 2838, 2211, 1741, 1651, 1631, 1439, 1377, 1335, 1237, 1043, 912, 734 cm^{-1}. HRMS (EI+) Calcd for $C_{12}H_{19}N$ $[M]^+$ 177.1518 ; Found 177.1598.

General Procedure for C-H Activation NMR Experiments. In a nitrogen-filled inert atmosphere box, alkyne-tethered imine (0.10 M solution in 0.50 mL of toluene-d_8), 2,6-dimethoxytoluene (2-3 mg) as an internal standard and specified quantities of the catalyst and phosphine ligand were combined in a medium-walled NMR tube. The tube was fitted with a Cajon adapter and flame-sealed under vacuum. The NMR tube was placed in an oil bath at the specified temperature. The tube was periodically removed from the bath, cooled to room temperature, and analyzed by ^{1}H-NMR spectroscopy to monitor the progress of the reaction based on integration relative to 2,6-dimethoxytoluene.

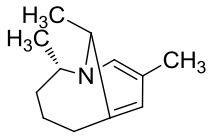
General Procedure for C-H Functionalization Reactions.

To a Schlenk tube in a nitrogen filled inert atmosphere box was added $[RhCl(coe)_2]_2$ (50.0 mg, 0.070 mmol, 2.50 mol%) dissolved in 5.0 mL of toluene, followed by the ligand (*p*-NMe_2)$PhPEt_2$ (30.0 mg, 0.140 mmol, 5.00 mol%) dissolved in 5.0 mL of toluene, followed by the desired imine (2.80 mmol, 1.00 equiv) dissolved in 18.0 mL toluene. The tube was sealed, removed from the inert atmosphere box, and heated in a 100 °C oil bath for 4 h. The tube was allowed to cool to room temperature, opened, and the solvent was removed *in vacuo*. The resulting crude brown oil was purified by Kügelrohr distillation to give the bicyclic enamine compound. The product was transferred to a vial and stored at -25 °C.



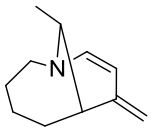
2.5

Bicyclic Enamine 2.5. Bicyclic enamine **2.5** was prepared from imine **2.1** (457 mg, 2.80 mmol) following the general procedure to afford a crude oil. The crude oil was further purified by Kügelrohr distillation (95-100 °C, 0.05 mm Hg) to give bicyclic enamine **2.5** as a yellow oil (245 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (s, 1H), 5.44 (s, 1H), 2.86 (q, *J* = 7.6 Hz, 1H), 2.73 (ddd, *J* = 14.4, 7.0, 4.0 Hz, 1H), 2.54 (dt, *J* = 12.2, 1.3 Hz, 1H), 2.53-2.42 (m, 1H), 2.25-2.14 (m, 1 H), 1.78-1.69 (m, 5H), 1.38 (d, *J* = 7.6 Hz, 3H), 1.13 (td, *J* = 14.4, 4.4 Hz, 1H), 0.74-0.62 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 135.1, 126.0, 125.1, 121.1, 57.1, 48.3, 30.3, 26.3, 24.9, 17.8, 13.6. IR (film): 2934, 2855, 1536, 1436, 1379, 1259, 1186, 1128, 1013, 838, 813, 794, 642, 520 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{17}N$ [M]$^{+}$ 163.1361; Found 163.1395.



2.15

Bicyclic Enamine 2.15. Bicyclic enamine **2.15** was prepared from imine **2.14** (500 mg, 2.80 mmol) following the general procedure. The crude oil was further purified by Kügelrohr distillation (95-100 °C, 0.05 mm Hg) to give bicyclic enamine **2.15** as a yellow oil (190 mg, 38 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 1H), 5.45 (s, 1H), 2.96 (q, *J* = 7.6 Hz, 1H), 2.90-2.84 (m, 1H), 2.57-2.52 (m, 1H), 2.34-2.20 (m, 1H), 1.86 (s, 3H), 1.78-1.68 (m, 2H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6 Hz, 3H), 1.08-1.05 (m, 1H), 0.60-0.48 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 135.5, 126.2, 125.3, 121.1, 57.1, 48.5, 30.6, 27.5, 25.9, 24.9, 18.3, 13.5. IR (film): 2945, 2850, 1542, 1451, 1328, 1264, 1173, 1022, 843, 797, 645 cm^{-1}. HRMS (EI+) Calcd for $C_{12}H_{19}N$ [M]$^{+}$ 177.1518; Found 177.1471.

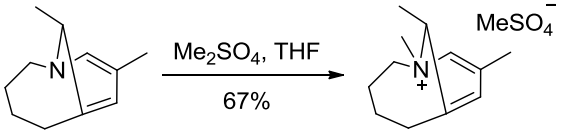


2.17

Bicyclic Enamine 2.17. Bicyclic enamine **2.17** was prepared from imine **2.16** (457 mg, 2.80 mmol) following the general procedure. The crude oil was purified by Kügelrohr distillation (95-100 °C, 0.05 mm Hg) to give bicyclic enamine **2.17** as a yellow oil (200 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (d, *J* = 6.8 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 4.53 (s, 1H), 4.33 (s, 1H), 3.53 (q, *J* = 7.2 Hz, 1H), 3.23-3.17 (m, 1H), 2.97-2.89 (m, 1H), 2.40 (s, 1H), 2.10-2.03 (m, 1H), 1.80-1.63 (m, 4H), 1.44-1.35 (m, 1H), 1.38 (d, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.4, 142.8, 108.1, 104.4, 55.3, 46.2, 45.7, 34.8, 23.0, 15.6, 1.23. IR (film): 3027,

2936, 2859, 1657, 1626, 1444, 1374, 1228, 1163, 980, 854 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{17}N$ $[M]^+$ 163.1361; Found 163.1401.

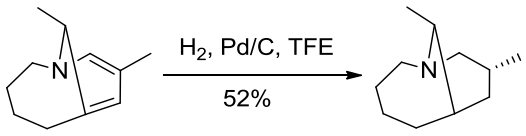
Functionalization of Bicyclic Enamine 2.5.



2.5 **2.6**

Salt 2.6. To a 20.0 mL scintillation vial containing a solution of compound **2.5** (100 mg, 0.61 mmol, 1.00 equiv) in THF (4.0 mL) dimethyl sulfate (Me_2SO_4) (92.0 mg, 0.73 mmol, 1.20 equiv) was added at room temperature. After 16 h, the resulting crystals were triturated in cold THF (0 °C). The solvent was removed under vacuum without heating to give salt **2.6** (73 mg, 67%) as a colorless crystalline solid. mp = 122.8-123.9 °C. ^{1}H NMR (400 MHz, DMSO- d_6): δ 6.46 (s, 1H), 6.31 (s, 1H), 4.40 (q, *J* = 7.2 Hz, 1H), 3.46-3.35 (m, 5H), 3.15 (s, 3H), 2.61 (t, *J*= 11 Hz,1H), 2.34 (q, *J* = 10.4 Hz, 1H), 2.04-1.94 (m, 1H), 1.85 (s, 3H), 1.80-1.60 (m, 3H), 1.50 (d, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 136.2, 133.4 (2C), 128.1, 65.0, 63.3, 52.8, 49.6, 29.8, 24.3, 23.7, 16.9, 9.7. IR (film): 3450, 3074, 2946, 1606, 1450, 1248, 1210, 1196, 1058, 1008, 888, 812, 733, 608, 576, 550 cm^{-1}. HRMS (FAB+) Calcd for $C_{12}H_{20}N$ $[M]^+$ 178.1596; Found 178.1591.

X-Ray Analysis of Salt 2.6. A fragment of a colorless needle-like crystal of $C_{13}H_{23}NSO_4$ having approximate dimensions of 0.50 x 0.31 x 0.20 mm was mounted on a Kapton loop using Paratone N hydrocarbon oil. All measurements were made on a Bruker APEX CCD area detector with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of -110 ± 1^{o}C. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans of 0.3^{o}counted for a total of 1.0 seconds per frame. For more detail of the X-Ray analysis, see Appendix 2.1.



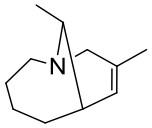
2.5 **2.7**

Compound 2.7. To a 25.0 mL round bottom flask containing a solution of compound **2.5** (200 mg, 1.23 mmol) in 2,2,2-trifluoroethanol (TFE) (6.00 mL) was added 10.0 % Pd/C (25.0 mg). The reaction mixture was stirred under an atmosphere of N_2 at room temperature for 5 min; then the flask was fitted with a hydrogen balloon. The flask was evacuated and back-filled with H_2 five times and the mixture was stirred at room temperature for 16 h under a H_2 atmosphere. The resulting mixture was filtered over Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by Kügelrohr distillation (90-100 °C, 0.05 mm Hg) to afford the desired product **2.7** (107 g, 52%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42-3.39 (m, 1H), 3.28-3.24 (m, 1H), 2.98-2.93 (m, 1H), 2.62-2.58 (m, 1H), 2.29 (t, *J* = 12 Hz, 1H), 2.00-1.90

(m, 3H) ,1.80-1.77 (m, 1H), 1.65-1.52 (m, 2H), 1.44-1.37 (m, 2H), 1.21-1.10 (m, 4H), 1.95-1.86 (m, 1H), 0.75 (d, J = 6.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 60.0, 51.1, 50.2, 37.6 (2C), 30.6, 28.9, 26.0, 24.1, 20.2, 15.9. IR (film): 3188, 2960, 2879, 1676, 1462, 1385, 1203, 1153, 1068, 897, 783 cm^{-1}. HRMS (FAB+) Calcd for $C_{11}H_{22}N$ $[MH]^+$ 168.1752; Found 168.1740.

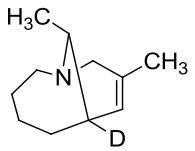
General Procedure for the $NaBH_4$ reduction of bicyclic compound 2.5.

To a 20.0 mL scintillation vial containing a solution of compound **2.5** (200 mg, 1.23 mmol, 1.00 equiv) in MeOH (5.00 mL) was added $NaBH_4$ (187 mg, 4.92 mmol, 4.00 equiv) at room temperature. The resulting mixture was stirred at room temperature for 16 h. Then H_2O (5.0 mL) and NaOH (1.50 g) were added to the biphasic mixture. The mixture was stirred for 5 min and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The resulting crude liquid was purified by Kügelrohr distillation (85-100^{o}C, 0.05 mm Hg) to give the reduced bicyclic product.



2.8

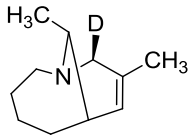
Compound 2.8. Compound **2.8** was prepared from **2.5** (200 mg, 1.23 mmol, 1.00 equiv) and $NaBH_4$ (187 mg, 4.92 mmol, 4.00 equiv) in MeOH (5.00 mL) following the general procedure. After Kügelrohr distillation (85-90 °C, 0.05 mm Hg), compound **2.8** (142 mg, 70%) was obtained as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47 (d, J = 5 Hz, 1H), 3.71-3.67 (m, 1H), 3.31-3.27 (m, 1H), 3.12-3.05 (m, 1H), 2.94-2.86 (m, 2H), 2.16 (br s, 1H), 1.92-1.76 (m, 3H), 1.68-1.61 (m, 2H), 1.59 (s, 3H), 1.36-1.28 (m, 1H), 1.25 (d, J = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 133.9, 128.1, 58.6, 54.5, 53.2, 38.7, 27.1, 26.6, 26.4, 20.6, 16.7. IR (film): 2914, 2858, 2819, 2726, 1465, 1441, 1389, 1180, 1135, 1107, 864 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{19}N$ $[M]^+$ 165.1518; Found 165.1516.



2.9

Compound 2.9. Compound **2.9** was prepared from **2.5** (200 mg, 1.23 mmol, 1.00 equiv) and $NaBH_4$ (187 mg, 4.92 mmol, 4.00 equiv) in MeOD-d_4 (5.00 mL) following the general procedure. After Kügelrohr distillation (85-90 °C, 0.05 mm Hg), compound **2.9** (138 mg, 68%) was obtained as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 1H), 3.70-3.65 (m, 1H), 3.30-3.25 (m , 1H), 3.13-3.03 (m, 1H), 2.93-2.86 (m, 2H), 1.94-1.76 (m, 3H), 1.68-1.56 (m, 2H), 1.58 (s, 3H), 1.35-1.30 (m, 1H), 1.26 (d, J = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 133.8, 128.1, 58.6, 54.5, 53.3, 38.0 (t, J= 22.0 Hz), 27.2, 26.6, 26.3, 20.6, 16.7. IR (film): 2915,

2858, 2819, 1464, 1441, 1386, 1169, 1126, 1076, 862 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{18}$ DN $[M]^+$ 166.1580; Found 166.1559.



2.10

Compound 2.10. Compound **2.10** was prepared from **2.5** (200 mg, 1.23 mmol, 1.00 equiv) and $NaBD_4$ (207 mg, 4.92 mmol, 4.00 equiv) in MeOH (5.00 mL) following the general procedure. After Kügelrohr distillation (85-90 °C, 0.05 mm Hg) compound **2.10** (142 mg, 70%) was obtained as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (d, *J* = 5.6 Hz, 1H), 3.32-3.25 (m , 1H), 3.11-3.02 (m, 1H), 2.92-2.82 (m, 2H), 2.15 (br s, 1H), 1.95-1.78 (m, 3H), 1.67-1.55 (m, 2H), 1.59 (s, 3H), 1.40-1.29 (m, 1H), 1.27 (d, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 133.8, 128.1, 58.1 (t, *J* = 20.5 Hz), 54.5, 53.2, 38.7, 27.1, 26.6, 26.4, 20.6, 16.6. IR (film): 3022, 2962, 2915, 2859, 2089, 1467, 1440, 1389, 1209, 1183, 1107, 862 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{18}DN$ $[M]^+$ 166.1580; Found 166.1571.

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(1) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**,130, 3645. (c) Colby, D.A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

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(4) Attempted isolation of the aza-triene intermediate resulted either in decomposition or spontaneous cyclization to give bridgehead product. Therefore, we are unable to determine whether electrocyclization is thermal rather than catalyzed by Rh, proton, or Lewis acid.

(5) Other methylating agents such as MeI also give *N*-methylation.

(6) Cook, A. G. In *Enamines: Synthesis, Structure and Reaction*; Marcel Dekker Inc.: New York-London, 1988; pp 181-204.

(7) Torsional angle = 146.2°.

(8) A similar *N*-methylation of a twisted bridgehead enamine has been reported in ref 3a.

(9) For the reduction of 1,2-dihydropyridines with $NaBH_4$ in MeOH, see: (a) Casini, A.; Di Rienzo, B.; Micheletti Moracci, F.; Tortorella, S.; Liberatore, F. *Tetrahedron Lett.* **1978**, *24*, 2139. (b) Jacobson, A. E.; May, E. L. *J. Med. Chem.* **1964**, *7*, 409. (c) Jacobson, A. E.; May, E. J. *J. Med. Chem.* **1965**, *8*, 563. (d) Hori, M.; Ban, M.; Imai, E.; Iwata, N.; Suzuki, Y.; Baba, Y.; Morita, T.; Fujiyama, H.; Nozaki, M.; Niwa, M. *J. Med. Chem.* **1985**, *28*, 1656.
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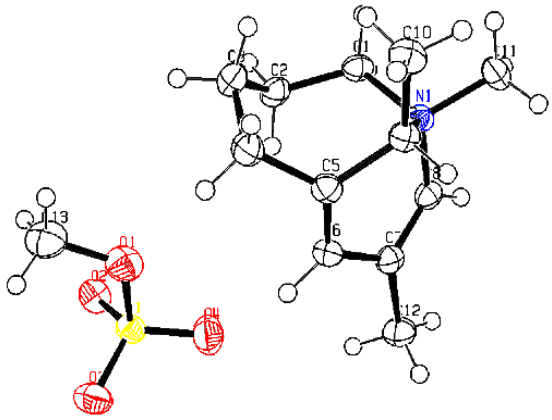
(12) Furstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.
(13) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc*. **1995**, *117*, 6787.

Appendix 2.1: X-ray Crystal Data for Complex 2.6

Figure A2.1-1.ORTEP Diagram of **2.6.**



The compound crystallizes in the centric space group $P2_1/n$ with one ion pair in the asymmetric unit. The closest inter-molecular contacts are to the oxygens of the methylsulfate anion and none of them is unusually short. Hydrogen atoms were included in calculated idealized positions and not refined. All intra-molecular bond distances and angles appear to be in normal ranges. The double bonds between C7 and C8 and C5 and C6 are localized. But the cyclization forces the environment of the C5=C6 double bond to be significantly non-planar (See Table of Torsion Angles).

EXPERIMENTAL DETAILS

Data Collection

A fragment of a colorless needlelike crystal of $SO_4C_{13}NH_{23}$ having approximate dimensions of 0.50 x 0.31 x 0.20 mm was mounted on a Kapton loop using Paratone N hydrocarbon oil. All measurements were made on a Bruker APEX[1] CCD area detector with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix, obtained from a least-squares refinement using the measured positions of 3702 reflections in the range $6.00 < 2\theta < 53.00°$ corresponded to a primitive monoclinic cell with dimensions:

a = 14.091(1) Å

b = 6.7690(6) Å β = 97.922(1)°

c = 15.090(1) Å

V = 1425.6(2) Å^3

For Z = 4 and F.W. = 289.39, the calculated density is 1.35 g/cm^3. The systematic absences of:

h0l: h+l ≠ 2n

0k0: k ≠ 2n

Uniquely determine the space group to be:

$P2_1/n$ (#14)

The data were collected at a temperature of -110 ± 1°C. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans of 0.3° counted for a total of 1.0 seconds per frame.

Data Reduction

Data were integrated by the program SAINT[2] to a maximum 2θ value of 52.8°.The data were corrected for Lorentz and polarization effects. Data were analyzed for agreement and possible absorptionusing XPREP[3]. An empirical absorption correction based on comparison of redundant and equivalent reflections was applied using SADABS[4]. (Tmax = 1.00, Tmin = 0.83).

Structure Solution and Refinement

The structure was solved by direct methods[5] and expanded using Fourier techniques[6]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[7] was based on 2387 observed reflections ($I > 3.00\sigma(I)$) and 172 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc|| / \Sigma|Fo| = 0.038$$

$$R_w = [(\Sigma w (|Fo| - |Fc|)^2 / \Sigma w\, Fo^2)]^{1/2} = 0.057$$

The standard deviation of an observation of unit weight[8] was 1.88. The weighting scheme was based on counting statistics and included a factor (p = 0.050) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta / \lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.27 and -0.17 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[9]. Anomalous dispersion effects were included in Fcalc[10]; the values for Δf' and Δf'' were those of Creagh and McAuley[11]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[12]. All calculations were performed using the teXsan[13] crystallographic software package of Molecular Structure Corporation.

Table A2.1-1. Crystal and Data Collection Parameters.

A. Crystal Data	
Empirical Formula	$SO_4C_{13}NH_{23}$
Formula Weight	289.39
Crystal Color, Habit	colorless, needlelike
Crystal Dimensions	0.50 X 0.31 X 0.20 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 14.091(1)Å
	b = 6.7690(6) Å
	c = 15.090(1) Å
	β = 97.922(1)°
	V = 1425.6(2) $Å^3$
Space Group	$P2_1/n$ (#14)
Z value	4
D_{calc}	1.348 g/cm^3
F_{000}	624.00
μ(MoKα)	2.37 cm^{-1}
B. Intensity Measurements	
Diffractometer	Bruker APEX CCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Detector Position	60.00 mm
Exposure Time	1.0 second per frame.
Scan Type	ω (0.3 degrees per frame)

$2\theta_{max}$	52.8°
No. of Reflections Measured	Total: 8212
	Unique: 2327 (R_{int} = 0.017)
Corrections	Lorentz-polarization
	Absorption (Tmax = 1.00 Tmin = 0.83)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\, w\, (|Fo| - |Fc|)^2$
Least Squares Weights	$w = 1/[\sigma^2(Fo)] = [\{4\sigma_c^2(Fo)+p^2(Fo^2)\}/4]^{-1}$
p-factor	0.0500
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2387
No. Variables	172
Reflection/Parameter Ratio	13.88
Residuals: R; Rw; Rall	0.038 ; 0.057; 0.046
Goodness of Fit Indicator	1.88
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.27 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.17 $e^-/Å^3$

Table A2.1-2. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
S1	0.78107(3)	-0.17018(7)	0.51164(3)	2.20(1)
O1	0.67124(9)	-0.2383(2)	0.4879(1)	3.06(3)
O2	0.83742(9)	-0.3391(2)	0.49150(9)	2.70(3)

O3	0.7955(1)	-0.1214(2)	0.60591(10)	3.18(3)
O4	0.7859(1)	-0.0067(2)	0.4522(1)	3.56(3)
N1	0.4956(1)	0.1581(2)	0.17242(10)	1.76(3)
C1	0.5151(1)	-0.0620(3)	0.1581(1)	2.06(4)
C2	0.5437(1)	-0.1931(3)	0.2395(1)	2.34(4)
C3	0.4667(1)	-0.2419(3)	0.2992(1)	2.63(4)
C4	0.4474(1)	-0.0766(3)	0.3661(1)	2.44(4)
C5	0.4803(1)	0.1131(3)	0.3294(1)	2.00(4)
C6	0.5690(1)	0.1816(3)	0.3536(1)	2.08(4)
C7	0.6178(1)	0.2908(2)	0.2889(1)	1.96(3)
C8	0.5859(1)	0.2680(2)	0.2024(1)	1.90(3)
C9	0.4280(1)	0.1923(3)	0.2420(1)	1.92(3)
C10	0.3272(1)	0.1180(3)	0.2127(1)	2.55(4)
C11	0.4531(1)	0.2441(3)	0.0833(1)	2.40(4)
C12	0.7086(1)	0.4023(3)	0.3182(1)	2.66(4)
C13	0.6456(1)	-0.4112(4)	0.5340(2)	3.54(5)
H1	0.4584	-0.1165	0.1262	2.4772
H2	0.5655	-0.0693	0.1223	2.4772
H3	0.5656	-0.3149	0.2185	2.8048
H4	0.5948	-0.1292	0.2761	2.8048
H5	0.4083	-0.2680	0.2614	3.1547
H6	0.4864	-0.3571	0.3327	3.1547
H7	0.3809	-0.0698	0.3707	2.9310
H8	0.4823	-0.1022	0.4234	2.9310
H9	0.6004	0.1598	0.4126	2.5002
H10	0.6213	0.3225	0.1590	2.2811
H11	0.4234	0.3313	0.2490	2.2997
H12	0.2886	0.1446	0.2582	3.0625
H13	0.3009	0.1833	0.1591	3.0625

H14	0.3287	-0.0203	0.2023	3.0625
H15	0.4407	0.3808	0.0903	2.8775
H16	0.4970	0.2278	0.0414	2.8775
H17	0.3949	0.1778	0.0623	2.8775
H18	0.6947	0.5159	0.3511	3.1964
H19	0.7522	0.3199	0.3550	3.1964
H20	0.7364	0.4419	0.2671	3.1964
H21	0.5799	-0.4408	0.5159	4.2450
H22	0.6838	-0.5194	0.5201	4.2450
H23	0.6560	-0.3880	0.5967	4.2450

Table A2.1-3. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S1	0.0229(3)	0.0337(3)	0.0261(3)	-0.0006(2)	0.0005(2)	0.0003(2)
O1	0.0221(7)	0.0474(9)	0.0447(9)	-0.0002(6)	-0.0023(6)	-0.0002(7)
O2	0.0279(7)	0.0402(8)	0.0347(8)	0.0055(5)	0.0056(6)	0.0012(6)
O3	0.0411(8)	0.0490(8)	0.0309(8)	-0.0094(7)	0.0052(6)	-0.0085(6)
O4	0.0468(9)	0.0423(9)	0.0447(9)	0.0020(7)	0.0009(7)	0.0121(7)
N1	0.0214(7)	0.0227(7)	0.0220(8)	0.0022(5)	0.0007(6)	-0.0016(6)
C1	0.0262(9)	0.0247(9)	0.0274(9)	0.0015(7)	0.0034(7)	-0.0085(7)
C2	0.0314(10)	0.0203(8)	0.036(1)	0.0025(7)	0.0015(8)	-0.0038(7)
C3	0.036(1)	0.0246(9)	0.038(1)	-0.0044(8)	0.0013(8)	0.0031(8)
C4	0.0296(10)	0.034(1)	0.029(1)	-0.0040(8)	0.0035(8)	0.0031(8)
C5	0.0278(9)	0.0263(9)	0.0225(9)	0.0016(7)	0.0048(7)	-0.0036(7)
C6	0.0285(9)	0.0273(9)	0.0223(9)	-0.0014(7)	-0.0002(7)	-0.0031(7)
C7	0.0209(8)	0.0210(8)	0.0315(10)	0.0025(6)	0.0008(7)	-0.0023(7)
C8	0.0221(8)	0.0213(8)	0.0290(10)	0.0003(7)	0.0042(7)	-0.0010(7)
C9	0.0229(9)	0.0247(9)	0.0253(9)	0.0031(6)	0.0038(7)	-0.0041(7)
C10	0.0226(9)	0.039(1)	0.035(1)	0.0020(7)	0.0033(8)	-0.0026(9)

C11	0.0313(10)	0.035(1)	0.0232(9)	0.0042(8)	-0.0013(7)	0.0028(8)
C12	0.0287(10)	0.033(1)	0.038(1)	-0.0063(8)	-0.0012(8)	-0.0022(8)
C13	0.030(1)	0.056(1)	0.049(1)	-0.0124(9)	0.0084(9)	-0.004(1)

Table A2.1-4. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
S1	O1	1.607(1)	S1	O2	1.448(1)
S1	O3	1.447(1)	S1	O4	1.431(2)
O1	C13	1.433(3)	N1	C1	1.536(2)
N1	C8	1.490(2)	N1	C9	1.528(2)
N1	C11	1.511(2)	C1	C2	1.524(3)
C2	C3	1.538(3)	C3	C4	1.555(3)
C4	C5	1.498(3)	C5	C6	1.336(3)
C5	C9	1.517(2)	C6	C7	1.469(3)
C7	C8	1.330(3)	C7	C12	1.498(2)
C9	C10	1.515(3)			

Table A2.1-5. Bond Lengths(Å)

atom	atom	distance	atom	atom	distance
C1	H1	0.95	C1	H2	0.95
C2	H3	0.95	C2	H4	0.95
C3	H5	0.95	C3	H6	0.95
C4	H7	0.95	C4	H8	0.95
C6	H9	0.95	C8	H10	0.95
C9	H11	0.95	C10	H12	0.95
C10	H13	0.95	C10	H14	0.95
C11	H15	0.95	C11	H16	0.95
C11	H17	0.95	C12	H18	0.95
C12	H19	0.95	C12	H20	0.95
C13	H21	0.95	C13	H22	0.95

C13	H23	0.95

Table A2.1-6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
O1	S1	O2	105.41(8)	O1	S1	O3	106.55(8)
O1	S1	O4	102.13(8)	O2	S1	O3	112.30(9)
O2	S1	O4	113.83(9)	O3	S1	O4	115.27(9)
S1	O1	C13	115.2(1)	C1	N1	C8	111.4(1)
C1	N1	C9	112.6(1)	C1	N1	C11	107.8(1)
C8	N1	C9	107.6(1)	C8	N1	C11	107.2(1)
C9	N1	C11	110.2(1)	N1	C1	C2	119.0(1)
C1	C2	C3	117.9(2)	C2	C3	C4	115.2(1)
C3	C4	C5	106.7(1)	C4	C5	C6	121.5(2)
C4	C5	C9	119.1(1)	C6	C5	C9	116.1(2)
C5	C6	C7	119.9(2)	C6	C7	C8	117.9(2)
C6	C7	C12	121.1(2)	C8	C7	C12	120.5(2)
N1	C8	C7	121.0(2)	N1	C9	C5	105.7(1)
N1	C9	C10	113.4(1)	C5	C9	C10	117.4(2)

Table A2.1-7. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
N1	C1	H1	107.0	N1	C1	H2	107.0
C2	C1	H1	107.0	C2	C1	H2	107.0
H1	C1	H2	109.5	C1	C2	H3	107.3
C1	C2	H4	107.3	C3	C2	H3	107.3
C3	C2	H4	107.3	H3	C2	H4	109.5
C2	C3	H5	108.0	C2	C3	H6	108.0
C4	C3	H5	108.0	C4	C3	H6	108.0
H5	C3	H6	109.5	C3	C4	H7	110.2
C3	C4	H8	110.2	C5	C4	H7	110.2

C5	C4	H8	110.2	H7	C4	H8	109.5
C5	C6	H9	120.0	C7	C6	H9	120.0
N1	C8	H10	119.5	C7	C8	H10	119.5
N1	C9	H11	106.6	C5	C9	H11	106.6
C10	C9	H11	106.6	C9	C10	H12	109.5
C9	C10	H13	109.5	C9	C10	H14	109.5
H12	C10	H13	109.5	H12	C10	H14	109.5
H13	C10	H14	109.5	N1	C11	H15	109.5
N1	C11	H16	109.5	N1	C11	H17	109.5
H15	C11	H16	109.5	H15	C11	H17	109.5
H16	C11	H17	109.5	C7	C12	H18	109.5
C7	C12	H19	109.5	C7	C12	H20	109.5
H18	C12	H19	109.5	H18	C12	H20	109.5
H19	C12	H20	109.5	O1	C13	H21	109.5
O1	C13	H22	109.5	O1	C13	H23	109.5
H21	C13	H22	109.5	H21	C13	H23	109.5
H22	C13	H23	109.5				

Table A2.1-8. Torsion Angles(^{o})

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O2	S1	O1	C13	57.1(2)	O3	S1	O1	C13	-62.4(2)
O4	S1	O1	C13	176.3(1)	N1	C1	C2	C3	70.7(2)
N1	C8	C7	C6	8.4(2)	N1	C8	C7	C12	-179.7(1)
N1	C9	C5	C4	-107.1(2)	N1	C9	C5	C6	52.6(2)
C1	N1	C8	C7	-91.4(2)	C1	N1	C9	C5	63.3(2)
C1	N1	C9	C10	-66.6(2)	C1	C2	C3	C4	-79.5(2)
C2	C1	N1	C8	72.2(2)	C2	C1	N1	C9	-48.8(2)
C2	C1	N1	C11	-170.6(1)	C2	C3	C4	C5	22.3(2)
C3	C4	C5	C6	-92.6(2)	C3	C4	C5	C9	65.9(2)

C4	C5	C6	C7	146.2(2)	C4	C5	C9	C10	20.5(2)
C5	C6	C7	C8	-20.0(2)	C5	C6	C7	C12	168.1(2)
C5	C9	N1	C8	-59.8(2)	C5	C9	N1	C11	-176.3(1)
C6	C5	C9	C10	-179.8(2)	C7	C6	C5	C9	-13.0(2)
C7	C8	N1	C9	32.4(2)	C7	C8	N1	C11	150.9(2)
C8	N1	C9	C10	170.3(1)	C10	C9	N1	C11	53.7(2)

Table A2.1-9. Non-bonded Contacts out to 3.75 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O1	C4	3.596(2)	1	O1	C12	3.623(3)	54501
O1	C4	3.634(3)	65603	O1	C6	3.668(2)	1
O2	C8	3.335(2)	64502	O2	C11	3.351(2)	64502
O2	C1	3.362(2)	54504	O2	C11	3.386(2)	54504
O2	C12	3.448(2)	54501	O2	C1	3.603(2)	64502
O2	N1	3.642(2)	64502	O3	C11	3.432(2)	4
O3	C10	3.433(2)	65603	O3	C3	3.639(3)	54504
O3	C10	3.728(3)	54504	O4	C11	3.367(2)	4
O4	C6	3.454(2)	1	O4	C8	3.491(2)	64502
O4	C12	3.513(2)	1	C2	C12	3.681(3)	54501
C2	C7	3.693(3)	54501	C5	C13	3.532(3)	65603
C10	C13	3.725(3)	44404	C12	C13	3.713(3)	56501

Reference A2.1.

(1) SMART: Area-Detector Software Package, Bruker Analytical X-ray Systems, Inc.: Madison, WI, **2001-03**.
(2) SAINT: SAX Area-Dectector Integration Program, V7.06; Bruker Analytical X-ray Systems Inc.: Madison, WI, **2005.**
(3) XPREP:(v 6.12) Part of the SHELXTL Crystal Structure Determination Package, Bruker Analytical X-ray Systems, Inc.: Madison, WI, **2001**.
(4) SADABS: Bruker-Nonius Area Detector Scaling and Absorption v. 2.10. Bruker Analytical X-ray Systems, Inc.: Madison, WI, **2005**.

(5) SIR97: Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. SIR97: A new tool for crystal structure determination and refinement. *J. App. Cryst.* **1998**.
(6) DIRDIF94: Beurskens, P.T.; Admiraal, G.; Beurskens, G.; Bosman, W.P.; de Gelder, R.; Israel, R.; Smits, J.M.M. The DIRDIF-94 program system: Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands. **1994**.
(7) Least-Squares: Function minimized $\Sigma w(|F_o|-|F_c|)^2$
(8) Standard deviation of an observation of unit weight:

$$[\Sigma w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$$

where N_o = number of observations
N_v = number of variables

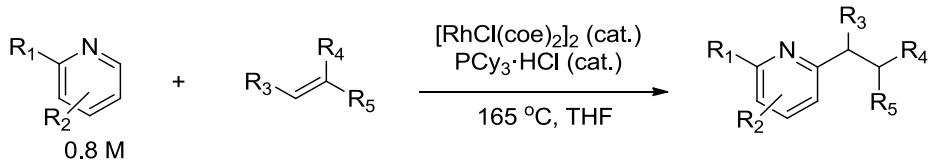
(9) Cromer, D. T.; Waber, J. T. International Tables for X-ray Crystallography, The Kynoch Press, Birmingham, England, **1974**; Vol. IV, Table 2.2 A.
(10) Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
(11) Creagh, D. C.; McAuley, W.J. International Tables for Crystallography. A.J.C. Wilson, ed., Kluwer Academic Publishers, Boston, **1992**; Vol C, Table 4.2.6.8, pp 219-222.
(12) Creagh, D. C.; Hubbell, J.H. International Tables for Crystallography. A.J.C. Wilson, ed., Kluwer Academic Publishers, Boston, **1992**; Vol C, Table 4.2.4.3, pp 200-206.
(13) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, **1985** and **1992**.

Chapter III. C-H Functionalization and Intramolecular Alkylation of Pyridines and Quinolines.

An efficient method is reported for the preparation of multicyclic pyridines and quinolines by a rhodium-catalyzed intramolecular C-H bond functionalization process. The method shows good scope for branched and unbranched alkyl substituents on the pyridine ring and at the R position of the tethered alkene group. Starting materials capable of undergoing olefin isomerization to provide terminal 1,1-disubstituted alkenes also proved to be effective substrates. The majority of this work was published in a communication. (Yotphan, S.; Bergman, R. G.; Ellman, J. A. Synthesis of Multicyclic Pyridine and Quninoline Derivatives via Intramolecular C-H Bond Functionalization. *Org. Lett.* **2010**, *12*, 2978-2981.)

Introduction

As briefly described in chapter 1, the synthesis of *N*-heterocycles is an important area of research due to their prevalence in natural products and drugs.[1] Of the *N*-heterocycles, pyridines are the most extensively used in pharmaceutical research,[2] and much effort has been devoted to their synthesis.[3,4] The functionalization of C-H bonds provides an atom-economical and direct approach to the preparation of substituted pyridines.[5,6] The Bergman/Ellman group has previously developed a method for the Rh(I)-catalyzed intermolecular alkylation of pyridines and quinolines to produce *ortho*-alkylated products (eq 3.1).[6]



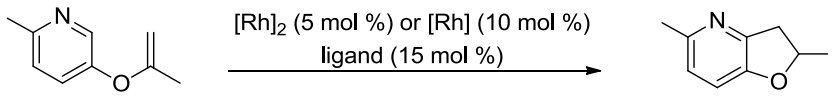
(3.1)

Significantly, pyridines lacking substitution at the 2-position (R_1= H) as well as 2,5-disubstituted pyridines did not undergo alkylation. Presumably, substituents at the 2- and 5-positions introduce steric interactions that either promote or attenuate, respectively, the propensity of forming the *C*-bound Rh complex necessary for C-H functionalization relative to the *N*-bound form.[7] Herein, an expansion of substrate scope for pyridine alkylation to include intramolecular cyclization of pyridines with alkenes tethered to the 5-position of the pyridine substrates is reported. This cyclization method provides a new reaction pathway for the efficient preparation of underrepresented classes of complex bicyclic pyridines and tricyclic quinolines that have considerable potential as useful scaffolds in drug discovery.[8]

Optimization of Reaction Conditions

Our investigation started with an examination of the enol ether tethered 2-methylpyridine substrate **3.1** using the optimized conditions for the intermolecular alkylation of pyridines: $[RhCl(coe)_2]_2$ as the precatalyst and PCy_3·HCl as an optimal ligand-additive combination (Table 3.1).[9] Under these conditions, cyclized product **3.2** was obtained in 70% yield (Table 3.1, entry 1). Thus, the tethered enol ether function located at the *meta* position of pyridine substrates does not block the intramolecular *ortho* C-H activation. No cyclization was observed in the absence of phosphine ligand or rhodium (entries 2 and 3). Notably, the HCl additive does not have a dramatic effect on the reaction (entry 4), which contrasts with the corresponding intermolecular reactions where alkylation only occurred in the presence of the acid catalyst.[6] According to a preliminary phosphine ligand screening (listed in Table 3.1, entries 5-10), PCy_3 and PAd_2Bu are optimal (entries 4 and 8-10). Although both $[RhCl(coe)_2]_2$ and $[RhCl(cod)]_2$ precatalysts gave good results (entries 2 and 8-10), we elected to use $[RhCl(cod)]_2$ for all subsequent studies due to its air and thermal stability, commercial availability, and higher reaction yield.

Table 3.1. Alkylation of Enol Tethered 2-Methyl Pyridine.[a]



(3.2)

0.8 M

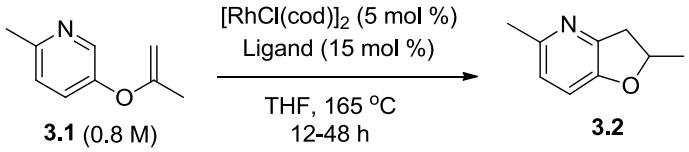
3.1 **3.2**

entry	catalyst	ligand[b]	yield (%)[c]
1	$[RhCl(coe)_2]_2$	$PCy_3 \cdot HCl$	70 (24 h)
2	$[RhCl(coe)_2]_2$	-	0
3	-	$PCy_3 \cdot HCl$	0
4	$[RhCl(coe)_2]_2$	PCy_3	70 (15 h)
5	$RhCl(PPh_3)_3$	-	0
6	$[RhCl(coe)_2]_2$	PPh_3	0
7	$[RhCl(coe)_2]_2$	P*t*-Bu_3	31 (24 h)
8	$[RhCl(coe)_2]_2$	PAd_2Bu	100 (24 h)
9	$[RhCl(cod)]_2$	PCy_3	99 (24 h)
10	$[RhCl(cod)]_2$	PAd_2Bu	99 (24 h)

[a] Partial screening data are listed. See Supporting Information for details of substrate synthesis. [b] coe =cis-cyclooctene, cod = cyclooctadiene. [c] reported yields are NMR yields, determined by ^1H NMR spectroscopy relative to an internal standard.

Upon extensive examination of the effects of other reaction parameters (effects of catalysts, ligands, additives, solvents, temperatures, and concentrations as listed in Scheme 3.1 and Table 3.2-3.3), we found that optimal reaction conditions are 5% $[RhCl(cod)]_2$ loading with 15% phosphine ligand and 0.8 M of substrate in THF at 165°C.

Scheme 3.1. Investigation of Phosphorus-based Ligands.[a]

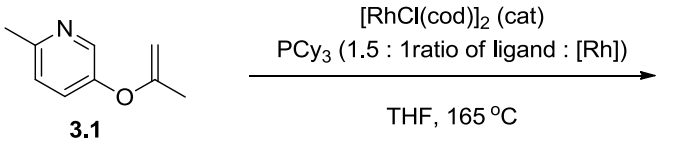


(3.3)

PPh_3	$P(OEt)_3$	$P(O\textit{i}\text{-}Pr)_3$	$P(\textit{i}\text{-}Pr)_3$	PBu_3	PCy_2Me	PAd_2Me
0%	0%	0%	0%	0%	0%	4%
$P(\textit{t}\text{-}Bu)_3$	PCy_3	$P(Cyp)_3$	PAd_2Bu	$PCy_3{\cdot}HCl$	$PAd_2Bu{\cdot}HCl$	$P(\textit{t}\text{-}Bu)_2(\textit{n}Bu){\cdot}HCl$
33%	99%	4%	100%	75%	69%	85%

[a] Reported yields listed under each ligand are NMR yields, determined by ^{1}H NMR spectroscopy relative to internal standard

Table 3.2. Effects of Concentration and Catalyst Loading.[a]

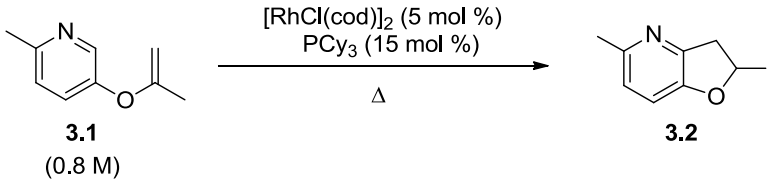


(3.4)

entry	catalyst loading	[substrate] (M.)	% yield[a]
1	5% $[Rh]_2$ (10% [Rh])	0.8	99-100 (24 h)
2	5% $[Rh]_2$ (10% [Rh])	0.4	80 (72 h)
3	5% $[Rh]_2$ (10% [Rh])	0.2	38 (120 h)
4	3.75% $[Rh]_2$ (7.5% [Rh])	0.8	91 (72 h)
5	2.5% $[Rh]_2$ (5% [Rh])	0.8	61 (72 h)
6	1% $[Rh]_2$ (2% [Rh])	0.8	58 (72 h)

[a] Reported yields are NMR yields, determined by ^{1}H NMR spectroscopy relative to internal standard

Table 3.3. Effects of Reaction Temperature and Solvent.



3.1 (0.8 M) **3.2**

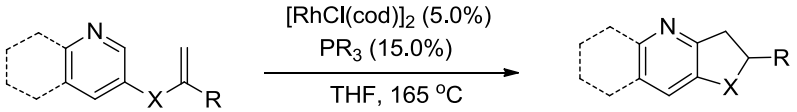
entry	solvent	temperature (°C)	% yield[a]
1	THF	rt	No Reaction
2	THF	100	No Reaction
3	THF	135	40% (72 h)
4	THF	165	100% (24 h)
5	Toluene	165	No Reaction
6	Dioxane	165	No Reaction
7	CPME	165	No Reaction

[a] Reported yields are NMR yields, determined by ^{1}H NMR spectroscopy relative to internal standard.

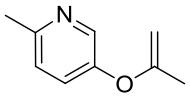
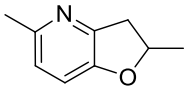
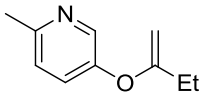
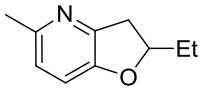
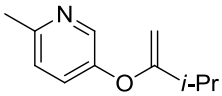
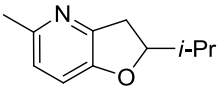
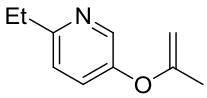
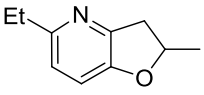
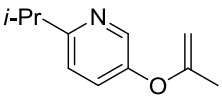
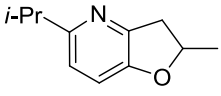
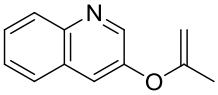
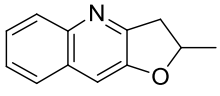
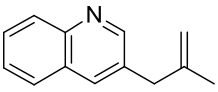
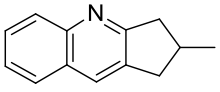
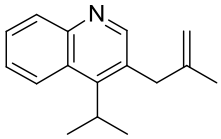
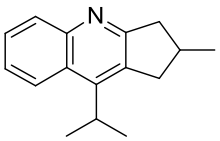
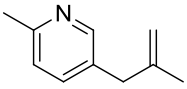
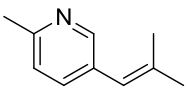
Investigation of Substrate Scope

Investigation of substrate scope (eq 3.6) revealed that PCy_3 in general gives similar or slightly better yields than PAd_2Bu for enol ether tethered substrates (Table 3.4, entries 1-7). Variation of the R substituent on the tethered enol ether group from methyl (**3.1**) to ethyl (**3.3**) or isopropyl (**3.5**) leads to the formation of cyclized products in 99% (**3.2** and **3.4**) and 58% (**3.6**) yields, respectively (entries 1-3). Variation of the *ortho*-pyridine substituent from methyl (**3.1**) to ethyl (**3.7**) or isopropyl (**3.9**) also results in good conversion to the fused products in 80% (**3.8**) and 58% (**3.10**) yields, respectively (entries 4 and 5). Enol ether tethered quinoline substrate **3.11** also undergoes cyclization in 80% yield (entry 6). On the other hand, for the allyl-tethered quinoline substrates (entries 7 and 8), the PAd_2Bu ligand was found to minimize the competitive double-bond isomerization pathway, resulting in higher cyclization yields. Unfortunately, for allyl-tethered pyridine substrate **3.17** only the conjugated pyridine product **3.18** that resulted from double-bond isomerization was observed (entry 9).

Table 3.4. Substrate Scope for Rh-catalyzed Intramolecular Alkylation.



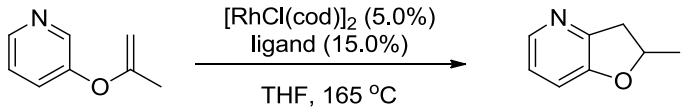
(3.6)

entry	substrate	product	ligand	yield (%)[a]
1	 **3.1**	 **3.2**	PCy_3	100 (96)
2	 **3.3**	 **3. 4**	PCy_3	99 (95)
3	 **3.5**	 **3.6**	PCy_3	58 (50)
4	 **3.7**	 **3.8**	PCy_3	80 (78)
5	 **3.9**	 **3.10**	PCy_3	58 (55)
6	 **3.11**	 **3.12**	PCy_3	80 (78)
7	 **3.13**	 **3.14**	PAd_2Bu	72 (71)
8	 **3.15**	 **3.16**	PAd_2Bu	70 (65)
9	 **3.17**	 **3.18**	PAd_2Bu	100 (95)

[a] NMR yields determined by ^1H NMR spectroscopy relative to an internal standard. Yields in parentheses correspond to isolated yields of pure product after column chromatography.

In contrast to intermolecular pyridine alkylation where *ortho* substitution is required for alkylation to proceed,[6] substrate **3.19**, which lacks alkyl substitution at the *ortho* position, undergoes cyclization under the reaction conditions (Scheme 3.2). In the case of substrate **3.19**, using PCy_3·HCl as a ligand results in a great improvement in yield (PCy_3·HCl gives 38% cyclized product while PCy_3 gives <10% product). It is likely that Rh coordination to the tethered alkene helps to promote C-H bond functionalization at the proximal site.

Scheme 3.2. Cyclization of Unsubstituted Pyridine.



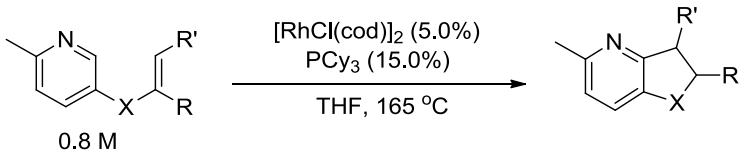
3.19 **3.20** (3.7)

ligand	yield (%)[a]
PCy_3·HCl	38 (35)
PCy_3	9

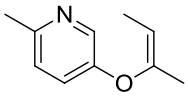
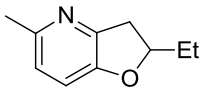
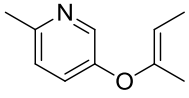
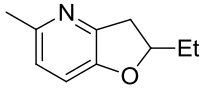
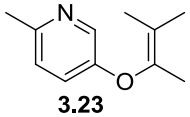
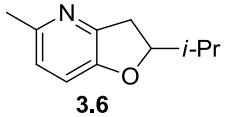
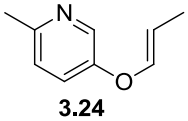
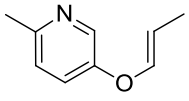
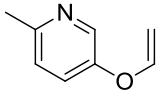
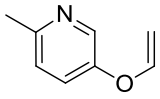
[a] NMR yields determined by ^{1}H NMR spectroscopy relative to an internal standard. Yield in parenthesis corresponds to isolated yields of pure product after column chromatography.

We also investigated the effects of different alkyl substituents on the tethered enol ether function (Table 3.5). Substrates **3.21-3.23** (entries 1-3) underwent intramolecular alkylation; however, the bicyclic pyridine products (**3.4** and **3.6**) were observed as a consequence of olefin isomerization to the less substituted 1,1-disubstituted regioisomer prior to cyclization (Scheme 3.3). Olefin isomerization is well-documented with Rh catalysts, including for intramolecular azole alkylation substrates.[10] The observation that 1,2-disubstituted alkenes (**3.24**) do not cyclize is also consistent with the presence of substituents on the vinyl ether group impeding the cyclization rate (entry 4). However, an α-substitution on the vinyl ether group also appears to be required for cyclization because the unsubstituted vinyl ether **3.25** was found to be unreactive (entry 5).

Table 3.5. Cyclization of Isomerizable Tethered Alkene Substrates.

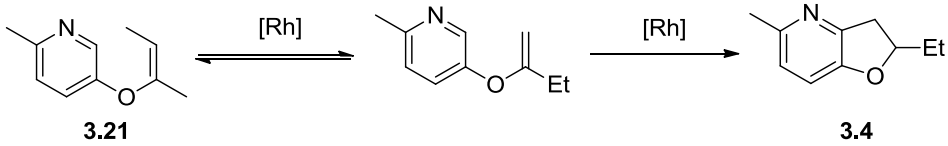


(3.8)

entry	substrate	product	yield (%)[a]
1	 **3.21**	 **3.4**	99
2	 **3.22**	 **3.4**	83
3	 **3.23**	 **3.6**	60
4	 **3.24**		No Reaction [b]
5	 **3.25**		No Reaction [c]

[a] reported yields are NMR yields, determined by ^{1}H NMR spectroscopy relative to an internal standard. [b] *E/Z* isomerization was observed. [c] hydrolysis of the enol group was observed.

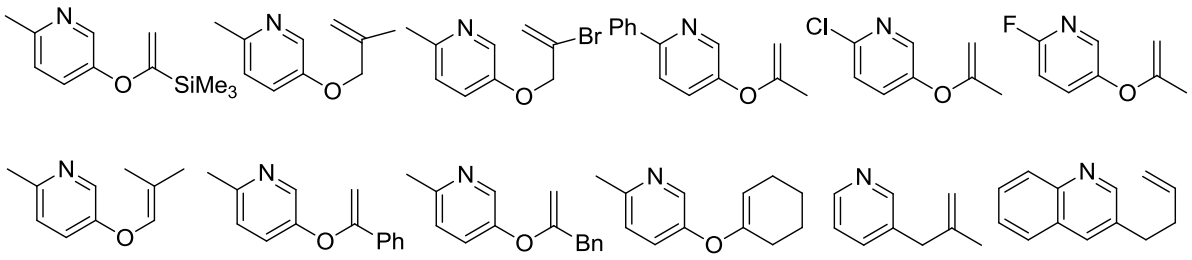
Scheme 3.3. Rhodium-Catalyzed Olefin Isomerization prior to Cyclization.



3.21 **3.4** (3.9)

In addition to the substrates mentioned above, we also investigated the intramolecular alkylation reactions of the substrates illustrated in Figure 3.1; however, they do not undergo cyclization under the reaction conditions/optimized for the successful systems.

Figure 3.1. Substrates that did not undergo Cyclization.[a]



[a] Reaction conditions : 5% $[RhCl(cod)]_2$ loading with 15% phosphine ligand and 0.8 M of substrate in THF at 165°C.

Conclusions

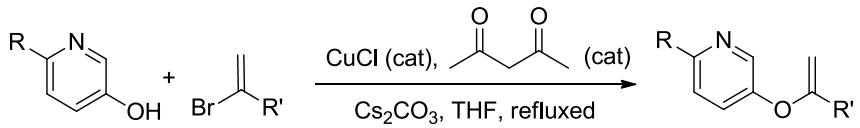
In conclusion, cyclization of tethered pyridines and quinolines produces multicyclic derivatives via C-H activation. The cyclization reactions show good scope for branched and unbranched alkyl substituents on the pyridine ring and at the α-position of the vinyl ether group. Moreover, isomerization of the double bond on the alkene tether enables cyclization to be accomplished via isomerization of trisubstituted enol ether substrates.

Experimental

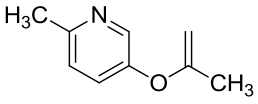
General Experimental. Unless otherwise specified, all reagents were obtained from commercial suppliers and used without further purification. Diethyl ether (Et_2O), dioxane, methylene chloride (CH_2Cl_2), tetrahydrofuran (THF) and toluene were dried over alumina under a nitrogen atmosphere. All reactions were performed under an inert atmosphere using standard Schlenk techniques unless specified otherwise. Oven-dried glassware was used in all cases. Chromatography was performed on silica gel (SiO_2), (60Å silica gel, MP Silitech 32-63D). ^1H and ^{13}C NMR spectra were measured with a Bruker AV-400 or DRX-500 spectrometer in $CDCl_3$. NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 ppm for ^1H and 77.23 ppm for ^{13}C). IR spectra were recorded on Thermo Scientific Nicolet FTIR iS10 spectrometer equipped with an attenuated total reflectance accessory, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. High resolution mass spectra were carried out by the University of California, Berkeley QB3/CChem Mass Spectrometry Facility. For high-resolution EI mass spectrometry, a ProSpec spectrometer (magnetic sector instrument) equipped with an EI source (Micromass, Manchester, UK) was used. For high-resolution ESI spectrometry, either a Q-TOP Premier spectrometer from Waters or a LTQ Orbitrap spectrometer from Thermo was used.

Procedure for the Synthesis of Substrates

General Procedure for the Synthesis of Enol-Tethered Pyridine/Quinoline Substrates[11]

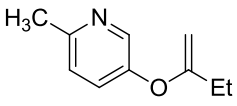


To a 100 mL round bottom flask, a mixture of Cs_2CO_3 (4.90 g, 15.0 mmol, 1.50 equiv), CuCl (0.25 g, 2.50 mmol, 0.25 equiv), and acetylacetone (0.50 g, 5.0 mmol, 0.50 equiv) in tetrahydrofuran (THF) (30 mL) was stirred at room temperature. After 5 min, 3-hydroxypyridine (10.0 mmol, 1.00 equiv) and vinyl bromide (20.0 mmol, 2.00 equiv) were added, and the mixture was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel (SiO_2) column chromatography to afford the pure enol-tethered pyridine.



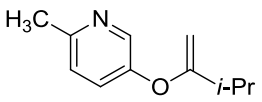
3.1

Pyridine 3.1. Compound **3.1** was prepared from 3-hydroxy-6-methylpyridine (1.09 g, 10.0 mmol, 1.00 equiv) and 2-bromopropene (1.70 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.1** as a yellow liquid (1.12 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 2.0 Hz, 1H), 7.29-7.26 (m, 1H), 7.14-7.12 (m, 1H), 4.17 (s, 1H), 3.89 (s, 1H), 2.54 (s, 3H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.1, 154.1, 149.8, 142.6, 128.9, 123.7, 89.6, 23.9, 20.2. IR (film): 2993, 2958, 2925, 1664, 1483, 1373, 1254, 1231, 1026, 965, 819 cm^{-1}. HRMS (EI+) Calcd for $C_9H_{11}NO$ $[M]^+$ 149.0841; Found 149.0841.



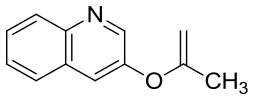
3.3

Pyridine 3.3. Compound **3.3** was prepared from 3-hydroxy-6-methylpyridine (1.09 g, 10.0 mmol, 1.00 equiv) and 2-bromobutene (2.05 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.3** as a yellow liquid (1.17 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 3.6 Hz, 1H), 7.26-7.23 (m, 1H), 7.12-7.09 (m, 1H), 4.15 (d, *J* = 3.0 Hz, 1H), 3.85 (d, *J* = 3.0 Hz, 1H), 2.52 (s, 3H), 2.28 (q, *J* = 10 Hz, 2H), 1.15 (t, *J* = 10 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.3, 153.7, 149.7, 142.4, 128.7, 123.5, 87.6, 27.0, 23.7, 11.6. IR (film): 2973, 2925, 1637, 1482, 1274, 1245, 1230, 1062, 950, 822, 733 cm^{-1}. HRMS (EI+) Calcd for $C_{10}H_{13}NO$ $[M]^+$ 163.0997; Found 163.0997.



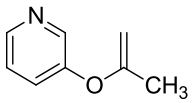
3.5

Pyridine 3.5. Compound **3.5** was prepared from 3-hydroxy-6-methylpyridine (1.09 g, 10.0 mmol, 1.00 equiv) and 2-bromo-3-methylbut-1-ene (2.20 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford compound **3.5** as a yellow liquid (1.04 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.32-7.28 (m, 1H), 7.19-7.12 (m, 1H), 4.15 (s, 1H), 3.90 (s, 1H), 2.28 (*sep*, 1H), 2.01 (s, 3H), 1.17 (d, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.0, 151.3, 149.5, 132.0, 126.4, 123.7, 90.5, 34.1, 24.8, 15.8. IR (film): 2970, 2899, 1617, 1450, 1247, 1239, 1227, 1172, 998, 846, 725 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{15}NO$ $[M]^+$ 177.1154; Found 177.1150.



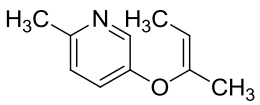
3.11

Quinoline 3.11. Compound **3.11** was prepared from 3-hydroxyquinoline[12] (1.45 g, 10.0 mmol, 1.00 equiv) and 2-bromopropene (1.70 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford quinoline **3.11** as a yellow oil (1.33 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 3.5 Hz, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.77-7.72 (m, 2H), 7.68-7.62 (m, 1H), 7.56-7.51 (m, 1H), 4.32 (d, *J* = 2.4 Hz, 1H), 4.05 (d, *J* = 2.4 Hz, 1H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.4, 148.7, 146.5, 145.1, 129.2, 128.6, 128.1, 127.1, 127.0, 123.4, 91.3, 19.8. IR (film): 2924, 2847, 1941, 1642, 1601, 1495, 1336, 1246, 1201, 1162, 986, 848, 783, 750, 735 cm^{-1}. HRMS (ESI+) Calcd for $C_{12}H_{12}NO$ $[MH]^+$ 186.0913; Found 186.0912.



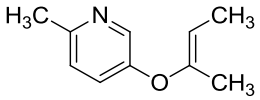
3.19

Pyridine 3.19. Compound **3.19** was prepared from 3-hydroxypyridine (0.95 g, 10.0 mmol, 1.00 equiv) and 2-bromopropene (1.70 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 5:1) to afford pyridine **3.19** as a yellow liquid (0.81 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.38-7.36 (m, 1H), 7.31-7.24 (m, 1H), 4.24 (d, *J* = 2.0 Hz, 1H), 3.97 (d, *J* = 2.0 Hz, 1H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.6, 145.3, 145.2, 143.5, 128.0, 127.9, 91.0, 20.1. IR (film): 2966, 2924, 1645, 1577, 1474, 1421, 1258, 1230, 1100, 1022, 962, 819, 711 cm^{-1}. HRMS (EI+) Calcd for C_8H_9NO $[M]^+$ 135.0684; Found 135.0682.



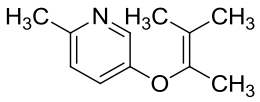
3.21

Pyridine 3.21. Compound **3.21** was prepared from 3-hydroxy-6-methyl pyridine (1.09 g, 10.0 mmol, 1.00 equiv) and (*Z*)-2-bromobut-2-ene (2.03 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.21** as a yellow liquid (1.08 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.16-7.03 (m, 2H), 5.08-5.03 (m, 1H), 2.48 (s, 3H), 1.78 (s, 3H), 1.60-1.52 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.2, 150.5, 147.3, 138.0, 123.4, 123.3, 111.0, 23.4, 18.2, 10.5. IR (film): 2978, 2921, 1694, 1571, 1479, 1384, 1307, 1220, 1213, 1184, 1093, 961, 827, 734 cm^{-1}. HRMS (EI+) Calcd for $C_{10}H_{13}NO$ $[M]^+$ 163.0997; Found 163.0999.



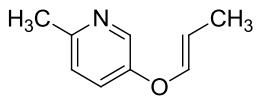
3.22

Pyridine 3.22. Compound **3.22** was prepared from 3-hydroxy-6-methyl pyridine (1.09 g, 10.0 mmol, 1.00 equiv) and (*E*)-2-bromobut-2-ene (2.04 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.22** as a yellow liquid (1.10 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 3.6 Hz, 1H), 7.17-7.13 (m, 1H), 7.07-7.04 (m, 1H), 4.89-4.82 (m, 1H), 2.49 (s, 3H), 1.85 (d, *J* = 1.2 Hz, 3H), 1.59 (d, *J* = 9.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.4, 150.8, 140.7, 140.6, 126.4, 123.6, 105.7, 23.8, 14.6, 12.0. IR (film): 2923, 1682, 1672, 1481, 1386, 1230, 1176, 1098, 1025, 829, 719 cm^{-1}. HRMS (EI+) Calcd for $C_{10}H_{13}NO$ $[M]^+$ 163.0997; Found 163.0994.



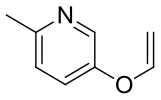
3.23

Pyridine 3.23. Compound **3.23** was prepared from 3-hydroxy-6-methyl pyridine (1.09 g, 10.0 mmol, 1.00 equiv) and 2-bromo-3-methylbut-2-ene (2.30 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.23** as a yellow liquid (0.87 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.35-7.30 (m, 2H), 2.47 (s, 3H), 1.78 (s, 3H), 1.71 (s, 3H), 1.58 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.2, 150.9, 140.6, 137.9, 123.5, 123.0, 119.0, 23.5, 18.9, 17.3, 14.7. IR (film): 2913, 2850, 1612, 1599, 1487, 1306, 1246, 1109, 1005, 998, 831, 721 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{15}NO$ $[M]^+$ 177.1154; Found 177.1149.



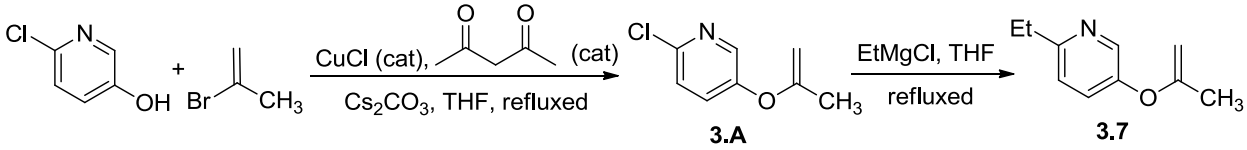
3.24

Pyridine 3.24. Compound **3.24** was prepared from 3-hydroxy-6-methyl pyridine (1.09 g, 10.0 mmol, 1.00 equiv) and 1-bromopropene (1.70 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.24** as a yellow liquid (1.12 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.19-7.16 (m, 1H), 7.08-7.06 (m, 1H), 6.37 (dq, *J* = 12, 1.6 Hz, 1H), 5.42-5.34 (m, 1H), 2.49 (s, 3H), 1.66 (dd, *J* = 6.8, 1.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.4, 151.9, 141.9, 138.5, 124.2, 123.6, 109.2, 22.7, 12.4. IR (film): 3021, 2923, 1676, 1574, 1481, 1234, 1217, 1090, 924, 825, 72 cm^{-1}. HRMS (ESI+) Calcd for $C_9H_{10}NO$ $[MH]^+$ 150.0913; Found 150.0920.



3.25

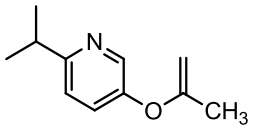
Pyridine 3.25. Compound **3.25** was prepared from 3-hydroxy-6-methyl pyridine (1.09 g, 10.0 mmol, 1.00 equiv) and iodoethene (3.02 g, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.25** as a yellow liquid (0.67 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 3.8 Hz, 1H), 7.23-7.19 (m, 1H), 7.10-7.07 (m, 1H), 6.59 (dd, *J* = 18.4, 8 Hz, 1H), 4.74 (dd, *J* = 18.4, 2.4 Hz, 1H), 4.45 (dd, J = 8, 2.4 Hz, 1H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.5, 151.2, 148.4, 139.4, 125.3, 123.8, 95.9, 23.9. IR (film): 3062, 1642, 1601, 1423, 1343, 1271, 1209, 1176, 1133, 997, 948, 853, 749 cm^{-1}. HRMS (EI+) Calcd for C_8H_9NO $[M]^+$ 135.0684; Found 135.0683.



3.A **3.7**

Pyridine 3.7. Compound **3.7** was prepared from 2-chloro-5-hydroxy pyridine (1.29 g, 10.0 mmol, 1.00 equiv) and 2-bromopropene (1.70 mL, 20.0 mmol, 2.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 10:1) to afford a chloro-pyridine enol substrate (**3.A**) as a clear liquid (1.03 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 2.8 Hz, 1H), 7.38-7.35 (m, 1H), 7.31-7.28 (m, 1H), 4.20 (s, 1H), 4.08 (s, 1H), 2.00 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.2, 151.0, 145.7, 142.5, 131.0, 124.7, 91.2, 19.7. IR (film): 2925, 1648, 1450, 1367, 1231, 1106, 1020, 955, 830, 681 cm^{-1} . HRMS (EI+) Calcd for C_8H_8NOCl $[M]^+$ 169.0294; Found 169.0294. Then, an oven dried and N_2 flushed 100 mL round bottom flask equipped with a magnetic stir bar and septum was charged with the substrate **3.A** (0.85 g, 5.00 mmol, 1.00 equiv) and dry THF (10.0 mL, 0.50 M concentration of substrate). The mixture was stirred at 0 °C for 15 min. Then, EtMgCl (2.00 M, 3.75 mL, 7.50 mmol, 1.50 equiv) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was then heated to reflux for 6 h. Upon completion, the reaction mixture was cooled to room temperature, saturated NH_4Cl solution (20 mL) was added, and the mixture was extracted with EtOAc (3x20 mL). The organic extract was concentrated *in vacuo*, and the crude

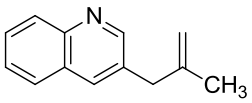
product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford pyridine **3.7** as a clear liquid (1.14 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.30-7.27 (m, 1H), 7.14-7.12 (m, 1H), 4.16 (s, 1H), 3.90 (s, 1H), 2.80 (q, *J* = 7.6 Hz, 2H), 1.99 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.8, 159.0, 149.6, 142.4, 128.7, 122.3, 89.5, 30.6, 20.0, 13.9. IR (film): 2969, 2935, 1665, 1637, 1440, 1246, 1167, 1118, 958, 818 cm^{-1}. HRMS (EI+) Calcd for $C_{10}H_{13}NO$ [M]$^+$ 163.0997; Found 163.0994.



3.9

Pyridine 3.9. An oven dried and N_2 flushed 100 mL round bottom flask equipped with a magnetic stir bar and septum was charged with substrate **3.A** (0.85 g, 5.00 mmol, 1.00 equiv) and dry THF (10.0 mL, 0.50 M concentration of substrate). The mixture was stirred at 0 °C for 15 min. Then, *i*-PrMgCl (2.00 M, 3.75 mL, 7.50 mmol, 1.50 equiv) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was then heated to reflux for 8 h. Upon completion, the reaction mixture was cooled to room temperature and saturated NH_4Cl solution (20 mL) was added. The mixture was then extracted with EtOAc (3x20 mL). The organic extract was concentrated *in vacuo*, and the crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 9:1) to afford compound **3.9** as a yellow liquid (0.32 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 2.4 Hz, 1H), 7.35-7.27 (m, 1H), 7.20-7.10 (m, 1H), 4.17 (s, 1H), 3.91 (s, 1H), 3.70 (sep, *J* = 7.4 Hz, 1H), 1.99 (s, 3H), 1.28 (d, *J* = 7.4 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.8, 156.0, 150.6, 130.9, 125.2, 122.9, 89.0, 35.5, 23.4, 20.8. IR (film): 2978, 2919, 1685, 1607, 1480, 1296, 1147, 1110, 961, 805 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{15}NO$ [M]$^+$ 177.1154; Found 177.1150.

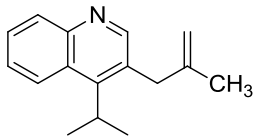
Procedures for the Synthesis of Allyl-Tethered Pyridine/Quinoline Substrates.



3.13

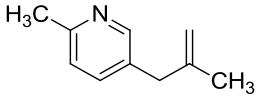
Quinoline 3.13. An oven dried and N_2 flushed 100 mL round bottom flask equipped with a magnetic stir bar and septum was charged with 3-bromoquinoline (2.04 g, 10.0 mmol, 1.00 equiv), dry THF (10.0 mL, 1.00 M concentration of substrate) and CuCl (1.00 g, 10.0 mmol, 1.00 equiv). The mixture was stirred at 0 °C for 15 min. Then, *i*-PrMgCl (2.00 M, 10.0 mL, 20.0 mmol, 2.00 equiv) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at this temperature for 3 h, and 3-bromo-2-methylprop-1-ene (4.00 mL, 40.0 mmol, 4.00 equiv) was added to the mixture. The reaction mixture was stirred for 15 h at room temperature. Upon reaction completion, saturated NH_4Cl solution (20 mL) was added, and the mixture was extracted with EtOAc (3x30 mL). The organic extract was concentrated *in vacuo*, and the crude product was purified by column chromatography (SiO_2, Hex: EtOAc = 3:2) to afford quinoline **3.13** as a yellow solid (1.42 g, 78%). mp = 42.0-43.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.70-7.64 (m, 1H), 7.55-

7.51 (m, 1H), 4.91 (s, 1H), 4.79 (s, 1H), 3.51 (s, 2H), 1.74 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 152.2, 147.0, 143.9, 134.9, 132.3, 129.2, 128.7, 128.1, 127.4, 126.6, 113.0, 41.8, 22.2. IR (film): 3060, 2970, 2901, 1651, 1495, 1442, 1376, 890, 787, 720 cm^{-1}. HRMS (ESI+) Calcd for $C_{13}H_{14}N$ $[MH]^+$ 184.1121; Found 184.1127.



3.15

Quinoline 3.15. An oven-dried and N_2 flushed round bottom flask equipped with a magnetic stir bar and a septum was charged with 3-bromoquinoline (2.04 g, 10.00 mmol, 1.00 equiv.) dissolved in dry THF (10.0 mL, 1.00 M concentration of substrate), and *i*-PrMgCl (10.0 mL, 2.00 M, 20.0 mmol, 2.00 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and 3-bromo-2-methylprop-1-ene (4.00 mL, 40.0 mmol, 4.00 equiv) was added. The reaction mixture was slowly warmed to room temperature and stirred for an additional 15 h. After the reaction was complete, saturated NH_4Cl solution (20 mL) was added, and the mixture was extracted with EtOAc (3x30 mL). The solution was concentrated *in vacuo*, and the crude product was purified by SiO_2 column chromatography (Hex: EtOAc = 3:2) to afford quinoline **3.15** as a yellow oil (1.31 g, 59%) [The scope, limitations and mechanism of this very interesting transformation are discussed in Chapter 5]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.64-7.60 (m, 1H), 7.51-7.47 (m, 1H), 4.87 (s, 1H), 4.42 (s, 1H), 3.66-3.61 (m, *br*, 1H), 3.53 (s, 2H), 1.82 (s, 3H), 1.53 (d, *J* = 7.2 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.4, 151.1, 148.3, 144.3, 130.6, 129.1, 127.8, 126.8, 125.4, 125.3, 112.3, 39.8, 29.4, 23.1, 22.0. IR (film): 3085, 2963, 1568, 1503, 1448, 1258, 1091, 1012, 892, 788, 760 cm^{-1}. HRMS (ESI+) Calcd for $C_{16}H_{20}N$ $[MH]^+$ 226.1590; Found 226.1594.



3.17

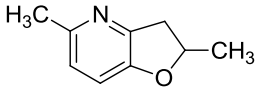
Pyridine 3.17. An oven-dried and N_2 flushed round bottom flask equipped with a magnetic stir bar and a septum was charged with 5-bromo-2-methylpyridine (1.71 g, 10.00 mmol, 1.00 equiv.) dissolved in dry THF (10.0 mL, 1.00 M concentration of substrate), and *i*-PrMgCl (10.0 mL, 2.00 M, 20.0 mmol, 2.00 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and 3-bromo-2-methylprop-1-ene (4.00 mL, 40.0 mmol, 4.0 equiv) was added. The reaction mixture was slowly warmed to room temperature and stirred for an additional 15 h. After the reaction was complete, saturated NH_4Cl solution (20 mL) was added, and the mixture was extracted with EtOAc (3x30 mL). The crude product was concentrated *in vacuo* and purified by SiO_2 column chromatography (Hex: EtOAc = 1:1) to afford pyridine **3.17** as a yellow liquid (1.05 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.36 (d, *J* = 10.4 Hz, 1H), 7.07 (d, *J* = 10.4 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.25 (s, 2H), 2.51 (s, 3H), 1.66 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 156.1, 149.5, 144.2, 136.7,

131.8, 122.8, 112.4, 41.1, 24.0, 22.0. IR (film): 3081, 2971, 2919, 1650, 1575, 1477, 1422, 1375, 1028, 892, 781, 715 cm^{-1}. HRMS (ESI+) Calcd for $C_{10}H_{14}N$ $[MH]^+$ 148.1126; Found 148.1123.

General Procedure for Catalytic Alkylation Reactions (NMR Experiments). [6]

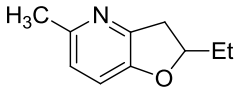
In a nitrogen-filled Vacuum Atmospheres inert atmosphere box, $[RhCl(cod)]_2$ (0.008 g, 0.016 mmol, 0.050 equiv), ligand (0.048 mmol, 0.150 equiv), alkene tethered pyridine substrate (0.32 mmol, 1.00 equiv), 2,6-dimethyltoluene (0.015 g, 0.100 mmol, 0.100 equiv) as an internal standard, and THF solvent (reaction diluted to a total concentration of 0.80 M) were combined in a small vial. The reaction mixture was then transferred to a medium-walled NMR tube. The tube was fitted with a Cajon adapter and flame-sealed under vacuum. The NMR tube was placed in an oil bath at 165°C. The tube was periodically removed from the bath, cooled to room temperature, and analyzed by ^{1}H-NMR spectroscopy to monitor the progress of the reaction based on integration relative to the internal standard.

To work up the reaction, the NMR tube was cooled to room temperature. The reaction mixture was transferred to a small scintillation vial using 1.0 mL of CH_2Cl_2 to rinse NMR tube. The mixture was then concentrated *in vacuo* to afford crude product. The crude product was further purified by SiO_2 column chromatography.



3.2

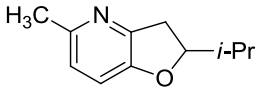
Bicyclic pyridine 3.2. Compound **3.2** was prepared from pyridine **3.1** (0.048 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PCy_3 ligand (0.014 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 24 h). Upon completion of reaction as determined by NMR analysis (NMR yield = 100%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure bicyclic pyridine **3.2** (0.045 g, 96%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89-6.83 (m, 2H), 4.99-4.94 (m, 1H), 3.42-3.36 (m, 1H), 2.92-2.86 (m, 1H), 2.46 (s, 3H), 1.49 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.3, 150.0, 149.7, 121.6, 115.9, 79.1, 38.6, 23.5, 22.1. IR (film): 2974, 2926, 1603, 1446, 1225, 1029, 924, 902, 829, 818 cm^{-1}. HRMS (EI+) Calcd for $C_9H_{11}NO$ $[M]^+$ 149.0841; Found 149.0839.



3.4

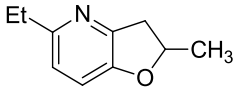
Bicyclic pyridine 3.4. Compound **3.4** was prepared from pyridine **3.3** (0.052 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PCy_3 ligand (0.014 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 48 h). Upon completion of reaction (NMR yield = 99%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure bicyclic pyridine **3.4** (0.490 g, 95%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89- 6.84 (m, 2H), 4.81-4.71

(m, 1H), 3.37-3.28 (m, 1H), 2.97-2.84 (m, 1H), 2.44 (s, 3H), 1.88-1.67 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 151.4, 149.8, 149.4, 121.5, 115.8, 84.0, 36.3, 29.0, 23.2, 9.3. IR (film): 2924, 2844, 1578, 1235, 1302, 1235, 1129, 929, 823, 734 cm^{-1}. HRMS (EI+) Calcd for $C_{10}H_{13}NO$ $[M]^+$ 163.0997; Found 163.0994.



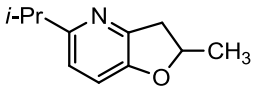
3.6

Bicyclic pyridine 3.6. Compound **3.6** was prepared from pyridine **3.5** (0.057 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PCy_3 ligand (0.014 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 ^{o}C, for 72 h). Upon completion of reaction (NMR yield = 58%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 3:2) to afford pure bicyclic pyridine **3.6** (0.028 g, 50%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92-6.79 (m, 2H), 5.14-4.98 (m, 1H), 3.64-3.49 (m, 1H), 3.15-3.00 (m, 1H), 2.42 (s, 3H), 2.25-2.10 (m, 1H), 1.16 (d, *J* = 9.0 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): 151.3, 149.5, 149.0, 122.7, 119.8, 84.9, 36.9, 33.8, 24.7, 17.2. IR (film): 2920, 2849, 1529, 1248, 1315, 1246, 1100, 929, 819, 767 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{15}NO$ $[M]^+$ 177.1154; Found 177.1150.



3.8

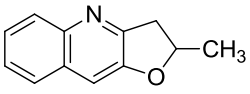
Bicyclic pyridine 3.8. Compound **3.8** was prepared from pyridine **3.7** (0.052 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PCy_3 ligand (0.014 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 48 h). Upon completion of reaction (NMR yield = 80%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure bicyclic pyridine **3.8** (0.040 g, 78%) as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91-6.84 (m, 2H), 4.97-4.96 (m, 1H), 3.43-3.36 (m, 1H), 2.93-2.87 (m, 1H), 2.73-2.70 (m, 2H), 1.50-1.48 (m, 3H), 1.26-1.23 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 151.3, 149.9, 120.2, 115.8, 79.0, 38.5, 30.5, 21.9, 14.6. IR (film): 2969, 2930, 1602, 1449, 1429, 1232, 1029, 914, 833, 731 cm^{-1}. HRMS (EI+) Calcd for $C_{10}H_{13}NO$ $[M]^+$ 163.0997; Found 163.0993.



3.10

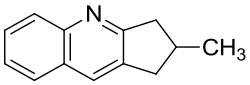
Bicyclic pyridine 3.10. Compound **3.10** was prepared from pyridine **3.9** (0.057 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PCy_3 ligand (0.014 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 48 h). Upon completion of reaction (NMR yield = 58%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 3:2) to afford pure bicyclic pyridine **3.10**

(0.031 g, 55%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99-6.86 (m, 2H), 5.00-4.84 (m, 1H), 3.94-3.81 (m, 1H), 3.44-3.31 (m, 1H), 2.96-2.80 (m, 1H), 1.43 (d, *J* = 9.0 Hz, 3H), 1.24 (d, *J* = 9.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.0, 151.5, 149.0, 121.2, 119.8, 80.7, 42.1, 39.5, 24.8, 21.4. IR (film): 2989, 2899, 1592, 1401, 1300, 1257, 1114, 926, 844 cm^{-1}. HRMS (EI+) Calcd for $C_{11}H_{15}NO$ $[M]^+$ 177.1154; Found 177.1157.



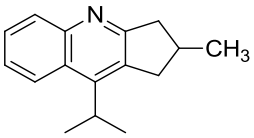
3.12

Bicyclic quinoline 3.12. Compound **3.12** was prepared from quinoline **3.11** (0.060 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PCy_3 ligand (0.014 g, 0.048 mmol, 0.150 equiv) following the general procedure (heating at 165 °C, for 48 h). Upon completion of reaction (NMR yield = 80%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure bicyclic quinoline **3.12** (0.046 g, 78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.0 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.50-7.40 (m, 2H), 7.20 (s, 1H), 5.05-4.98 (m, 1H), 3.56-3.47 (m, 1H), 3.07-2.98 (m, 1H), 1.51 (d, *J* = 8.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 156.3, 151.3, 144.1, 128.5, 126.8, 126.3, 126.2, 124.8, 109.7, 79.1, 38.5, 21.9. IR (film): 3036, 2971, 2929, 1603, 1420, 1309, 1136, 1080, 1018, 776, 751 cm^{-1}. HRMS (EI+) Calcd for $C_{12}H_{11}NO$ $[M]^+$ 185.0841; Found 185.0844.



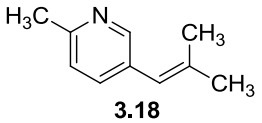
3.14

Bicyclic quinoline 3.14. Compound **3.14** was prepared from quinoline **3.13** (0.059 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PAd_2Bu ligand (0.017 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 48 h). Upon completion of reaction (NMR yield = 72%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure bicyclic quinoline **3.14** (0.041 g, 71%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.67-7.59 (m, 1H), 7.49-7.43 (m, 1H), 3.32-3.20 (m, 2H), 2.82-2.76 (m, 1H), 2.71-2.61 (m, 2H), 1.21 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.5, 147.5, 135.5, 130.4, 128.5, 128.3, 127.5, 127.4, 125.4, 42.8, 38.8, 32.8, 20.7. IR (film): 3050, 2953, 2868, 1629, 1569, 1497, 1403, 1317, 1214, 920, 833, 750, 730 cm^{-1}. HRMS (ESI+) Calcd for $C_{13}H_{14}N$ $[MH]^+$ 184.1126; Found 184.1129.



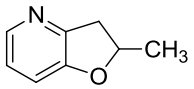
3.16

Bicyclic quinoline 3.16. Compound **3.16** was prepared from quinoline **3.15** (0.072 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PAd_2Bu ligand (0.017 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 48 h). Upon completion of reaction (NMR yield = 70%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure bicyclic quinoline **3.16** (0.047 g, 65%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 11.0 Hz, 1H), 7.99 (d, *J* = 11.0 Hz, 1H), 7.53 (t, *J* = 10.0 Hz, 1H), 7.38 (t, *J* = 10.0 Hz, 1H), 3.78-3.68 (m, 1H), 3.31-3.16 (m, 2H), 2.75-2.69 (m, 2H), 2.53 (septet, *J* = 9.4 Hz, 1H), 1.39 (d, *J* = 9.4 Hz, 6H), 1.16 (d, *J* = 8.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 167.4, 148.0, 147.7, 132.2, 129.5, 127.7, 125.9, 125.0, 123.5, 42.7, 39.3, 32.3, 21.3, 21.2, 20.8. IR (film): 2956, 2870, 1571, 1504, 1459, 1330, 1205, 975, 751, 732 cm^{-1}. HRMS (ESI+) Calcd for $C_{16}H_{10}N$ $[MH]^+$ 226.1590; Found 226.1588.



3.18

Pyridine 3.18. Compound **3.18** was prepared from pyridine **3.17** (0.047 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and PCy_3 ligand (0.014 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 48 h). Upon completion of reaction (NMR yield = 100%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure pyridine **3.18** (0.044 g, 95%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 3.0 Hz, 1H), 7.40 (dd, *J* = 10.6, 3.0 Hz, 1H), 7.07 (d, *J* = 10.6 Hz, 1H), 6.16 (s, 1H), 2.51 (s, 3H), 1.90 (s, 3H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.3, 149.2, 137.3, 136.0, 131.2, 122.5, 121.4, 26.8, 24.0, 19.3. IR (film): 2964, 2930, 1561, 1498, 1446, 1368, 1175, 930, 890, 826, 756 cm^{-1}. HRMS (ESI+) Calcd for $C_{10}H_{14}N$ $[MH]^+$ 148.1126; Found 148.1124.



3.20

Bicyclic pyridine 3.20. Compound **3.20** was prepared from pyridine **3.19** (0.044 g, 0.320 mmol, 1.00 equiv), $[RhCl(cod)]_2$ catalyst (0.008 g, 0.016 mmol, 0.050 equiv) and $PCy_3{\cdot}HCl$ ligand (0.016 g, 0.048 mmol, 0.150 equiv), following the general procedure (heating at 165 °C, for 72 h). Upon completion of reaction (NMR yield = 38%), the crude product was further purified by flash column chromatography (SiO_2, Hex: EtOAc = 1:1) to afford pure pyridine bicyclic pyridine **3.20** (0.015 g, 35%) as a clear solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s *br*, 1H), 6.93-6.90 (m, 2H), 4.97-4.88 (m, 1H), 3.40-3.33 (m, 1H), 2.90-2.78 (m, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.0, 150.8, 141.1, 122.4, 115.4, 79.1, 38.2, 21.9. IR (film): 3056, 2975, 2925, 1602, 1577, 1426, 1268, 1192, 1104, 1027, 905, 791, 722 cm^{-1}. HRMS (EI+) Calcd for C_8H_9NO $[M]^+$ 135.0684; Found 135.0683.

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Chapter IV. Application of Copper-Catalyzed Direct Arylation to the Synthesis of 5-Aryl Benzotriazepines.

A method for the direct arylation of benzotriazepines is reported, employing an aryl iodide as the coupling partner, copper iodide as the catalyst, and lithium tert-butoxide as the base. A variety of electron-rich, electron-poor, and sterically hindered aryl iodides are compatible with the reaction conditions. The arylation reaction can also be performed outside a glovebox in air without a significant decrease in yield. Furthermore, convenient microwave conditions for carrying out this transformation are reported. The majority of this work was published in a communication. (Yotphan, S.; Bergman, R. G.; Ellman, J. A. Application of Daugulis Copper-Catalyzed Direct Arylation to the Synthesis of 5-Aryl Benzotriazepines. *Org. Lett.* **2009**, *11*, 1511-1514.)

Introduction

Benzodiazepines and benzotriazepines are classes of nonaromatic heterocycles that have emerged as privileged pharmacophore structures due to their wide-ranging biological activities.[1] Examples of well-known benzodiazepines include Valium (diazepam), Librium (chlordizepoxide), Xanax (alprazolam), and Ativan (lorazepam).[2] In addition, a number of benzotriazepines are currently being evaluated in clinical trials.[3] As a consequence, strategies for the rapid synthesis and functionalization of these classes of compounds are of considerable interest to both academic and industrial researchers.[4]

The Bergman/Ellman group has previously reported on the Rh-catalyzed direct functionalization of a range of nitrogen heterocycles,[5] with many of these transformations documented to proceed via Rh-bound *N*-heterocyclic carbene (NHC) intermediates (Scheme 4.1, Figure 4.1).

Scheme 4.1. Rh- catalyzed C-H Functionalization of Azoles.

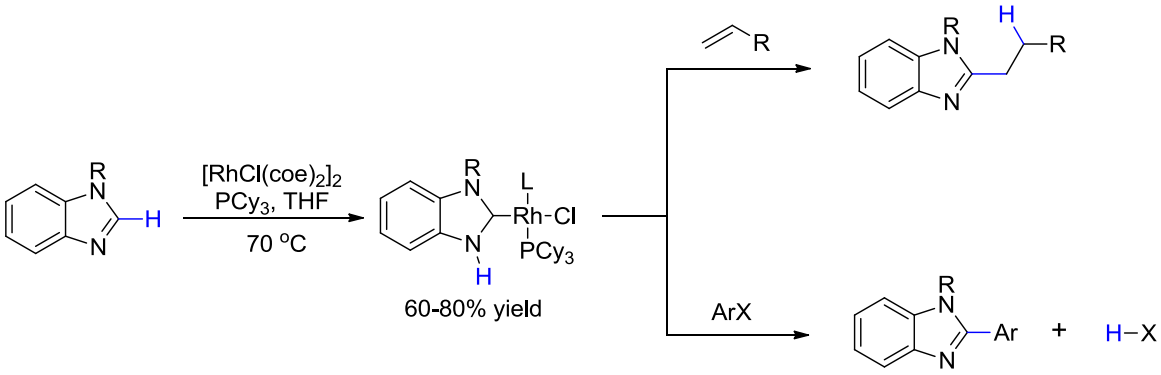
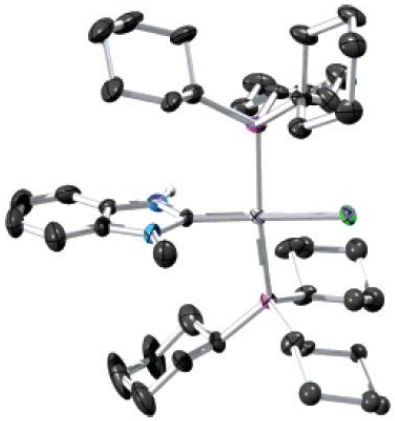


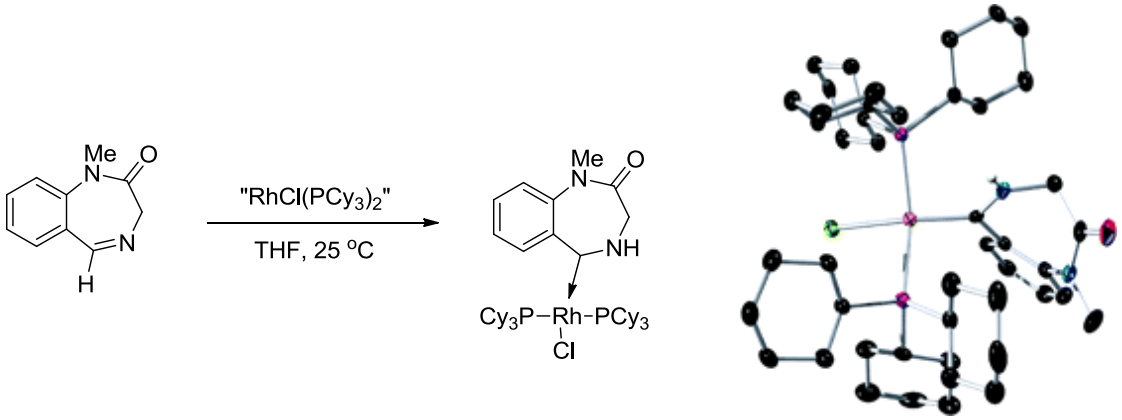
Figure 4.1. ORTEP Diagram of the Isolated NHC-Rh Complex.



We speculated that benzodiazepines and triazepines should be capable of forming NHC-metal complexes and were able to isolate and characterize a 1,4-benzodiazepine NHC-Rh complex (Scheme 4.2).[6] However, we were not able to achieve the Rh-catalyzed direct arylation of either 1,4-benzodiazepines or triazepines under a wide range of reaction conditions and

therefore focused on alternative transition metal catalysts for the direct arylation of these classes of heterocycles. Herein we report that benzotriazepines can be efficiently arylated via copper catalysis.[7]

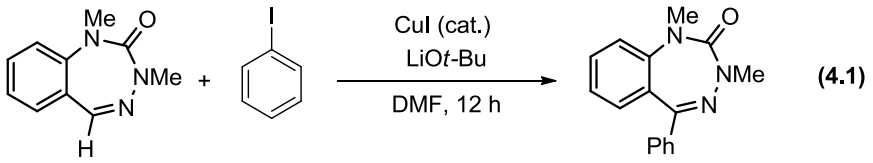
Scheme 4.2. Benzodiazepine NHC-Rhodium Complex.



Reaction Optimization and Proposed Catalytic Cycle of Direct Arylation

The direct arylation of benzotriazepine **4.1** was initially explored using copper catalysts according to the conditions reported by Daugulis and co-workers for the direct arylation of aromatic C-H bonds: CuI (10 mol %), LiO*t*-Bu (2 equiv), and PhI (3 equiv) in DMF at 140 °C.[8,9] Under these conditions arylated product **4.2** was obtained in a promising 40% isolated yield (Table 4.1), although the reaction time necessary for complete conversion (12 h) (entry 1) was longer than that reported by Daugulis for the arylation of azoles (10-30 min) (entry 2). To increase product yield, we first examined catalyst loading and temperature (Table 4.1). The use of stoichiometric CuI resulted in quantitative conversion of the benzotriazepine **4.1** to the arylated product **4.2** (entries 4 and 5). Decreasing the amount of CuI negatively affected the yield of the arylated product, as did lowering the reaction temperature (entries 6-8). With the aim of developing a catalytic direct arylation, we chose 20 mol % of the copper catalyst and 140 °C for further evaluation of reaction parameters.

Table 4.1. Effect of Catalyst Loading and Temperature.



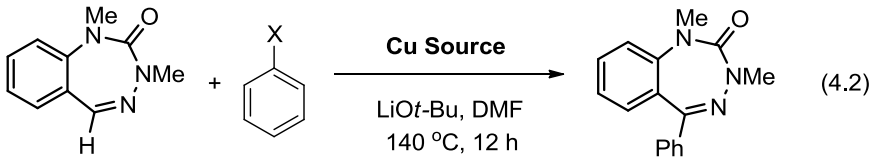
4.1 **4.2**

entry	catalyst loading	temperature (°C)	% yield
1	10%	140	36(40[b])
2	10%	140	5[c]
3	100%	140	19[c]
4	100%	140	99 (98[b])
5	200%	140	100
6	20%	140	79 (75[b])
7	20%	100	16
8	20%	rt	5

[a] Conditions: benzotriazepine substrate (1 equiv), PhI (3 equiv), LiO*t*-Bu (2 equiv). Yields were determined by GC integration relative to hexamethylbenzene as an internal standard. [b] Isolated yield. [c] Reaction time = 30 min.

In this survey, we first examined the effect of the copper source and the electrophilic coupling partner (Table 4.2). Without copper, no reaction was observed (entry 1). Interestingly, both Cu(I) and Cu(II) catalysts could be employed in this transformation. However, Cu(I) complexes tended to result in higher yields. Consistent with Daugulis's observations for the arylation of aromatic heterocycles, only aryl iodides are effective coupling partners, with aryl bromides and chlorides giving little or no product (entries 9 and 10). This result suggested that this method should be useful for the chemoselective arylation at iodide-substituted centers in the presence of other halogen substituents (*vide infra*).

Table 4.2. Effect of Copper Source and Phenyl Halide Coupling Partner. [a]



(4.2)

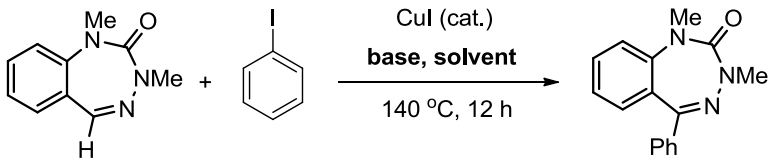
4.1 **4.2**

entry	Cu catalyst	PhX	% yield
1	None	PhI	0
2	$CuCl_2$	PhI	55
3	$CuBr_2$	PhI	57
4	$Cu(OAc)_2$	PhI	42
5	CuCl	PhI	65
6	CuBr	PhI	66
7	CuOAc	PhI	58
8	**CuI**	**PhI**	**79**
9	CuI	PhBr	5[b]
10	CuI	PhCl	0

[a] Conditions: benzotriazepine substrate (1 equiv), PhX (3 equiv), Cu catalyst (20 mol %), LiO*t*-Bu (2 equiv). Yields were determined by GC integration relative to hexamethylbenzene as an internal standard. [b] Reaction time = 24 h.

Upon examining different bases and solvents (Table 4.3), LiO*t*-Bu and DMF were found to be optimal. Stronger bases resulted in significantly lower yields as well as starting material decomposition (entries 2-4). Either no reaction or low conversion was observed when weaker bases were employed (entries 5-7). The mechanism of this direct arylation reaction (Scheme 4.3) is likely to be similar to that previously reported by Daugulis and co-workers for the Cu-catalyzed arylation of aromatic C-H bonds, wherein the base is necessary for deprotonation/metalation.[8] Weaker bases such as K_3PO_4, which is effective for the direct arylation of azoles and polyfluoroarenes, did not work well for benzotriazepine substrates presumably because of the much higher pK_a value of the benzotriazepine sp^2 C-H bond. For this heterocycle class, the stronger base, LiO*t*-Bu, as well as prolonged reaction times, were apparently necessary for deprotonation/metalation. A variety of solvents was evaluated with LiO*t*Bu as the base and in all cases resulted in much poorer conversion relative to DMF (entries 8-11).

Table 4.3. Effect of Base and Solvent. [a]



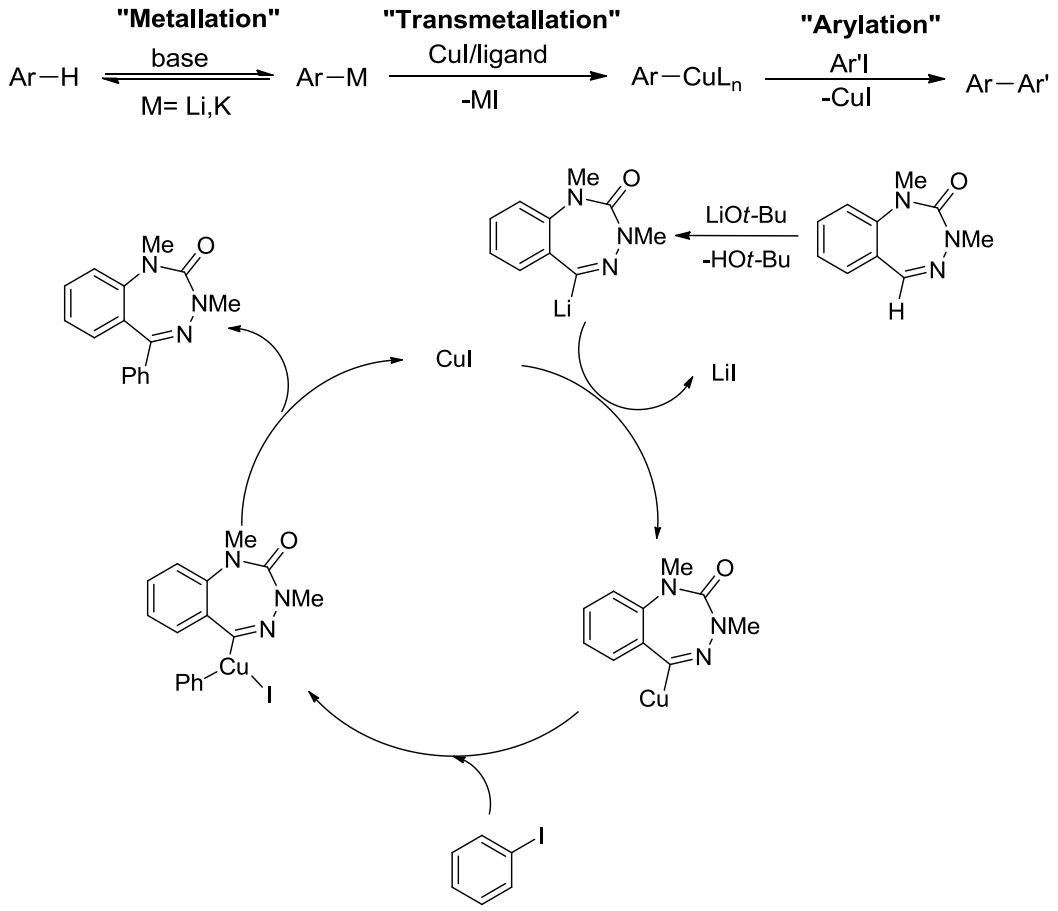
(4.3)

4.1 **4.2**

entry	base	solvent	% yield
1	**LiO*t*-Bu**	**DMF**	**79**
2	NaO*t*-Bu	DMF	15
3	KO*t*-Bu	DMF	10
4	LDA	DMF	7
5	Na_2CO_3	DMF	0[b]
6	Cs_2CO_3	DMF	0[b]
7	K_3PO_4	DMF	15[b]
8	LiO*t*-Bu	DMA	52
9	LiO*t*-Bu	THF	60
10	LiO*t*-Bu	dioxane	36[b]
11	LiO*t*-Bu	toluene	8

[a] Conditions: benzotriazepine substrate (1 equiv), PhI (3 equiv), CuI (20 mol %), base (2 equiv). Solvent (1.0 M. of benzotriazepine substrate). Yields were determined by GC integration relative to hexamethylbenzene as an internal standard. [b] Reaction time = 24 h.

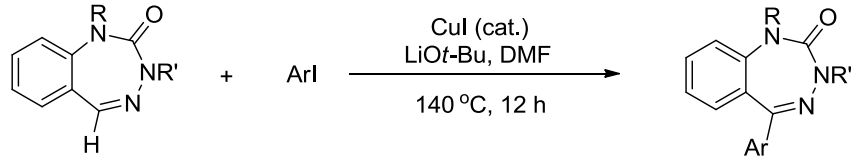
Scheme 4.3. Proposed Catalytic Cycle for Direct Arylation of Benzotriazepines.



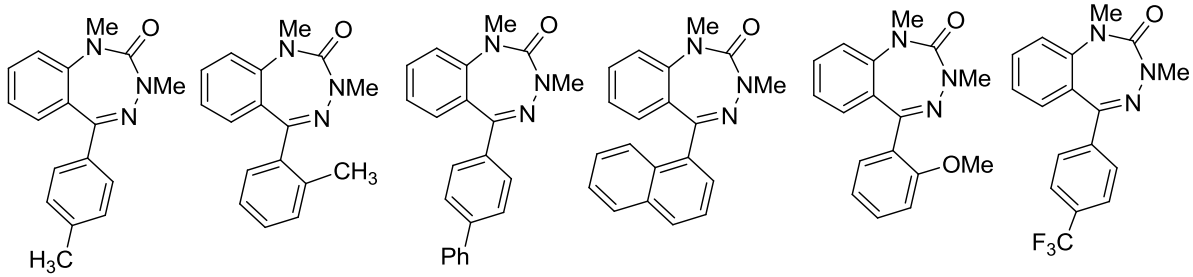
Substrate Scope of Benzotriazepine Direct Arylation

Using the optimal reaction conditions, the scope of the catalytic direct arylation reaction was then examined (Scheme 4.4). Benzotriazepine **4.1** could be successfully coupled to both electron-poor and electron-rich aryl iodides to give benzotriazepines **4.9, 4.10,** and **4.12** and benzotriazepines **4.4**, **4.5**, **4.8**, and **4.11**, respectively. *Ortho*-substituted aryl iodides could also be coupled in high yields (benzotriazepines **4.5** and **4.8**). Good functional group compatibility was observed with alkoxy (**4.8**), chloro (**4.10**), nitro (**4.12**), and pyridyl (**4.14**) groups all being compatible with the reaction conditions. Although 2-iodopyridine coupled in only modest yields with 20 mol % CuI, the yield of **4.14** could be significantly improved by employing stoichiometric quantities of CuI. A vinyl iodide was coupled (**4.13**) with stoichiometric CuI resulting in a doubling of the yield relative to that obtained when 20 mol % CuI was used. The *N*-Bn-protected benzotriazepine substrate was also an effective reaction partner in this transformation (**4.15**). In contrast, benzotriazepines with free N-H groups, e.g., **4.3** (R = H), are not effective substrates as a result of competitive *N*-arylation.

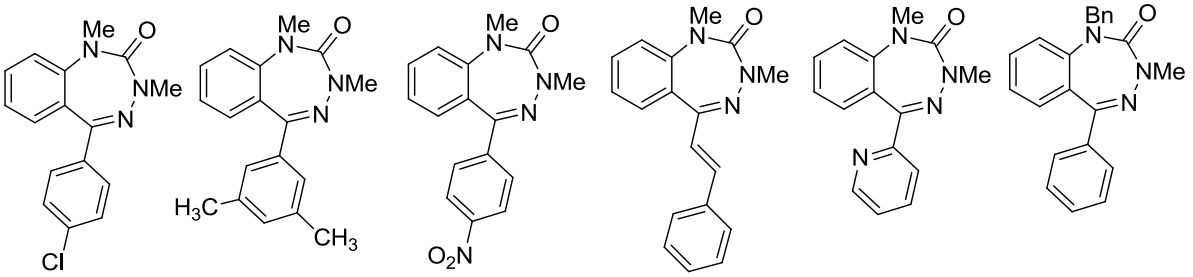
Scheme 4.4. Benzotriazepine Direct Arylation Substrate Scope. [a]



4.1 R= Me, R'= Me
4.3 R= Bn , R' =Me



4.4 80%
4.5 80%
4.6 78%
4.7 85%
4.8 66%
4.9 68%



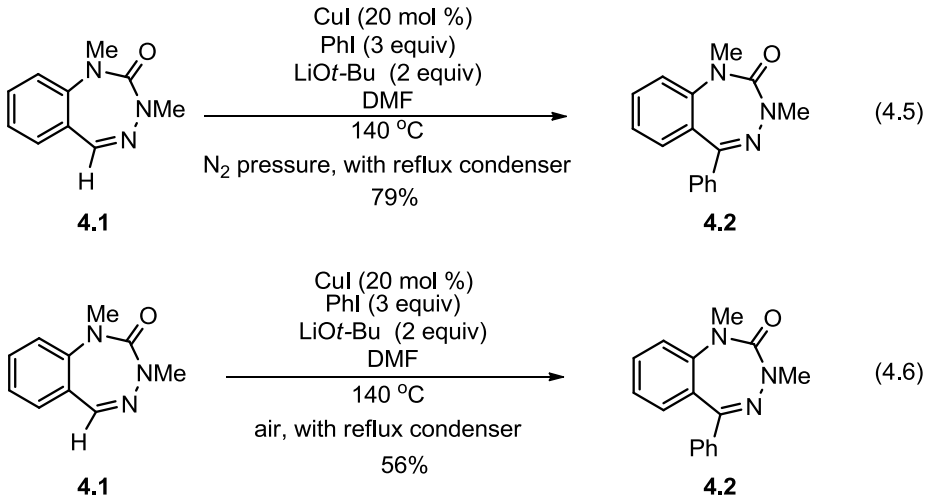
4.10 55%
4.11 55%
4.12 48%
4.13 15% (29%)
4.14 25% (40%)
4.15 88%

[a] Conditions: benzotriazepine substrate (1 equiv), aryl iodide (3 equiv), CuI (20 mol %), LiO*t*-Bu (2 equiv). Reported yields were isolated yields. Yields in parentheses were isolated yield when employing 1 equiv of CuI.

More Convenient Reaction Conditions.

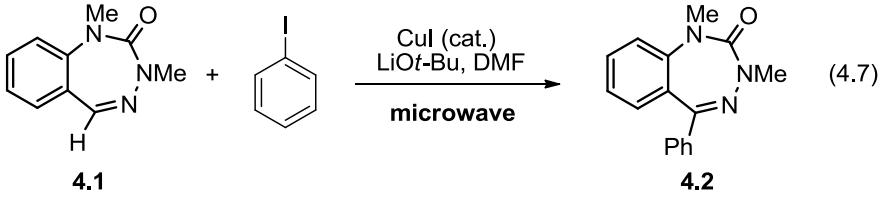
We also found that this reaction can be conducted outside of the glovebox in air without significantly decreasing the yield of product (Scheme 4.5).

Scheme 4.5. Arylation Reaction Outside of Glovebox.



Moreover, microwave irradiation could be used to shorten reaction times (Table 4.4). With this method of heating, 1 equiv of CuI was optimal, and at this stoichiometry, complete conversion was observed within 1 h at 140 °C (entry 5).

Table 4.4. Microwave Assisted Benzotriazepine Arylation.[a]



entry	catalyst loading	conditions	% yield[a]
1	20%	140 °C, 12 h	62
2	20%	150 °C, 6 h	57
3	20%	160 °C, 1 h	51
4	20%	200 °C, 30 min	33
5	**1 equiv**	**140** °C**, 1 h**	**98 (99[b])**

[a] Conditions: benzotriazepine substrate (1 equiv), PhI (3 equiv), LiO*t*-Bu (2 equiv). Yields were GC yields determined by integration relative to hexamethylbenzene as an internal standard. [b] Isolated yield.

Conclusions

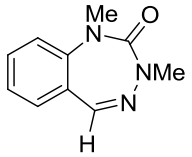
In conclusion, we have developed an efficient Cu-catalyzed protocol for the direct arylation of benzotriazepines, a class of heterocycles that are actively being investigated as drug candidates. This is the first example of the copper-mediated coupling of nonaromatic heterocycles. The transformation can be conducted either under inert atmosphere or in air, and can be conveniently performed using microwave irradiation. Further studies to expand the substrate scope to benzodiazepines and other benzazepine derivatives are currently underway.

Experimental

General Experimental. Unless otherwise specified, all reagents were obtained from commercial suppliers and used without further purification. Diethyl ether (Et_2O), benzene, toluene, dioxane, tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were dried over alumina under a nitrogen atmosphere. Dimethylformamide (DMF) and dimethylacetamide (DMA) were distilled over anhydrous magnesium sulfate ($MgSO_4$) under a nitrogen atmosphere and stored in a glovebox. All reactions were performed under an inert atmosphere using standard Schlenk techniques unless specified otherwise. Oven-dried glassware was used in all cases. Chromatography was performed on silica gel (SiO_2), (60Å silica gel, MP Silitech 32-63D). ^1H and ^{13}C NMR spectra were measured with a Bruker AV-400 or DRX-500 spectrometer in $CDCl_3$. NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 ppm for ^1H and 77.23 ppm for ^{13}C). IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. Elemental analyses were carried out by the University of California at Berkeley Micro-Mass Facility.

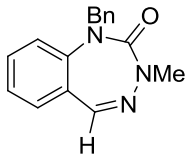
General Procedure for the Synthesis of Benzotriazepine Substrates.[3]

To a 250 mL round bottom flask, bis-(trichloromethyl)carbonate (2.00 g, 6.70 mmol, 0.34 equiv) and DCM (30 mL) were added. To the stirred solution at -40 °C, a solution of 2-aminobenzaldehyde (20.0 mmol, 1.00 equiv) and triethylamine (NEt_3) (8.40 mL, 60.0 mmol, 3.0 equiv) in DCM (20 mL) was added dropwise under N_2. The mixture was maintained at -40 °C for 1 h, and a solution of hydrazine (0.93 g, 20.0 mmol, 1.0 equiv) in DCM (20 mL) was added slowly to the reaction mixture. The reaction mixture was allowed to warm to rt and was stirred for 24 h. The solution was washed with H_2O (2 x 50 mL) and dried over anhydrous Na_2SO_4. The solution of crude product was filtered and the filtrate was concentrated *in vacuo*. The resultant residue was purified by SiO_2 column chromatography to afford the pure product.



4.1

Benzotriazepine 4.1. Compound **4.1** was prepared from 2-(methylamino)benzaldehyde (literature procedures[6,10]) (2.70 g, 20.0 mmol, 1.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, DCM: EtOAc = 19:1) to afford benzotriazepine **1a** as a yellow-brown solid (1.90 g, 50%). mp = 70.8-72.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.48-7.44 (m, 1H), 7.24-7.14 (m, 2H), 7.084 (d, *J* = 8.0 Hz, 1H), 3.24 (s, 3H), 3.17 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1, 153.8, 145.7, 132.0, 128.1, 127.3, 124.1, 119.8, 39.9, 36.2. IR (film): 2922, 1655, 1589, 1502, 1423, 1320, 751, 739, 564, 546 cm^{-1}. Anal calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21; Found: C, 63.41; H, 5.74; N, 21.98.



4.3

Benzotriazepine 4.3. Compound **4.3** was prepared from 2-(benzylamino)benzaldehyde[11] (4.22 g, 20.0 mmol, 1.00 equiv) following the general procedure. The crude product was purified by column chromatography (SiO_2, DCM) to afford benzotriazepine **4.3** as a yellow-brown solid (1.04 mg, 20%). mp = 96.5-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.06 (s, 1H), 7.35-7.30 (m, 2H), 7.25-7.12 (m, 5H), 7.10-7.03 (m, 2H), 4.98 (s, 2H), 3.20 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.9, 149.7, 146.3, 139.1, 134.8, 132.4, 128.5, 123.6, 121.9, 120.4, 114.1, 112.4, 48.0, 31.7. IR (film): 2978, 2911, 1652, 1594, 1477, 1420, 1155, 1068, 749, 662, 539 cm^{-1}. Anal calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84; Found: C, 72.79; H, 5.91; N, 15.50.

General Procedure for Screening of Benzotriazepine Arylation.

Outside a glovebox a Schlenk flask (10 mL) equipped with a stir bar was charged with benzotriazepine substrate **4.1** (94.6 mg, 0.500 mmol, 1.0 equiv) and hexamethylbenzene (16.2 mg, 0.100 mmol, 0.1 equiv). The flask was flushed with N_2 and brought into the glovebox. The copper catalyst (0.100 mmol, 0.2 equiv), base (1.00 mmol, 2.0 equiv), aryl halide (1.50 mmol, 3.0 equiv), and solvent (0.5 mL) were combined and added to the Schlenk flask. The Schlenk flask was capped and removed from the glovebox. The reaction mixture was stirred for 10 min at rt before placing the reaction flask in a preheated oil bath at 140 °C. The reaction progress was monitored by GC on an Agilent 6890N chromatograph equipped with an Agilent column (DB-1, polysiolxane, 15 m, 0.25 mm ID). The yield was determined by integration of the product peaks relative to hexamethylbenzene as an internal standard. The GC conditions are as follows: initial temp: 150 °C (1 min), ramp at 40 °C/min to 325 °C, hold at 325 °C (5 min). Retention times: hexamethylbenzene internal standard (3.8 min), benzotriazepine substrate **4.1** (4.6 min), arylated benzotriazepine product **4.2** (7.1 min). Aliquots from the reaction were concentrated by rotary evaporation (50 °C, 15 mmHg) and diluted with 0.5 mL of CH_2Cl_2 for GC analyses.

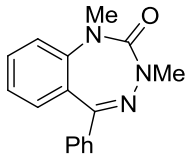
Reaction outside of the glovebox: a 5 mL round bottom flask equipped with stir bar was charged with benzotriazepine substrate (94.6 mg, 0.5 mmol, 1.0 equiv) and hexamethylbenzene (16.2 mg, 0.1 mmol, 0.1 equiv). The flask was flushed with N_2 and anhydrous copper catalyst

(0.1 mmol, 0.2 equiv), anhydrous base (1.0 mmol, 2.0 equiv), anhydrous aryl halide (1.5 mmol, 3.0 equiv), and anhydrous solvent (0.5 mL) were added. The flask was equipped with a reflux condenser and the reaction mixture was stirred for 10 min at rt before placing the reaction flask in a preheated oil bath at 140 °C. The reaction progress was monitored as described previously.

Microwave irradiation method: a microwave vial (0.5-2 mL) equipped with a stir bar was charged with benzotriazepine substrate (94.6 mg, 0.500 mmol, 1.0 equiv) and hexamethylbenzene (16.2 mg, 0.100 mmol, 0.1 equiv). The vial was flushed with N_2 and anhydrous copper catalyst (0.100 mmol, 0.2 equiv), anhydrous base (1.00 mmol, 2.0 equiv), anhydrous aryl halide (1.50 mmol, 3.0 equiv), and anhydrous solvent (0.5 mL) were added. The vial was capped. The reaction mixture was stirred for 10 min at rt before heating the reaction flask with a microwave reactor at 140 °C. The reaction progress was monitored as described previously.

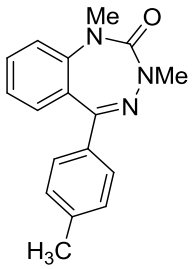
General Procedure for Direct Arylation of Benzotriazepines.

Outside the glovebox a 10 mL Schlenk flask equipped with a stir bar was charged with the benzotriazepine (1.00 mmol, 1.0 equiv). The flask was flushed with N_2 and transferred into the glovebox. Copper iodide (38.1 mg, 0.200 mmol, 0.2 equiv), Li*O*t*Bu (160 mg, 2.00 mmol, 2.0 equiv), aryl halide (3.00 mmol, 3.0 equiv), and DMF (1.0 mL) were added to the Schlenk flask. The Schlenk flask was capped and removed from the glovebox. The reaction mixture was stirred for 10 min at rt before placing the reaction flask in a preheated oil bath at 140 °C. After completion of the reaction as judged by GC, the reaction mixture was cooled to rt and diluted with 3:1 DCM: EtOAc (50 mL). The resulting solution was washed and extracted with H_2O (2 x 40 mL). The organic extract was dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford crude product. The crude product was further purified by SiO_2 column chromatography.



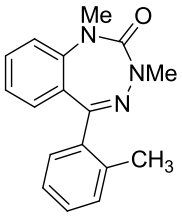
4.2

Arylated benzotriazepine 4.2. Compound **4.2** was prepared from benzotriazepine **4.1** (189.2 mg, 1.000 mmol, 1.0 equiv) and phenyl iodide (612 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.2** (198 mg, 75%) as a yellow solid. mp = 82.3-83.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.40 (m, 1H), 7.37-7.30 (m, 3H), 7.12(d, *J* = 8.4 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.82-6.77 (m, 3H), 3.56 (s, 3H), 3.52 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.7, 150.0, 149.9, 140.2, 132.5, 129.9, 129.4, 122.5, 121.6, 119.5 (2C), 114.1, 31.6, 31.1. IR (film): 2922, 1678, 1627, 1592, 1475, 1268, 1071, 1003, 768, 746, 701, 663, 538, 524 cm^{-1}. Anal calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84; Found: C, 72.25; H, 5.55; N, 15.59.



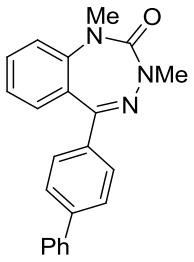
4.4

Arylated benzotriazepine 4.4. Compound **4.4** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 4-iodotoluene (654 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.4** (223 mg, 80%) as a yellow solid. mp = 99.0-100.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.36 (m, 2H), 7.10-7.07 (m, 3H), 6.79-6.75 (m, 1H), 6.67 (d, *J* =8.4 Hz, 2H), 3.51 (s, 3H), 3.48 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.8, 147.3, 145.3, 140.1, 132.4 (2C), 131.8, 130.4, 129.4, 121.6, 119.3, 114.0, 31.1 (2C), 21.1. IR (film): 3032, 2938, 1670, 1625, 1599, 1473, 1422, 1288, 1166, 820, 746, 660, 547, 529 cm^{-1}. Anal calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04; Found: C, 72.88; H, 6.01; N, 14.85.



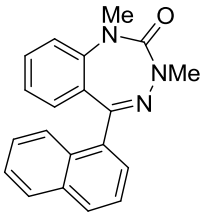
4.5

Arylated benzotriazepine 4.5. Compound **4.5** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 2-iodotoluene (654 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.5** (222 mg, 80%) as a yellow solid. mp = 112.2-113.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.38 (m, 1H), 7.28-7.25 (m, 1H), 7.20-7.18 (m, 1H), 7.13-7.08 (m, 2H), 6.97-6.92 (m, 1H), 6.78-6.76 (m, 1H), 6.64-6.62 (m, 1H), 3.53 (s, 6H), 2.09 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.7, 148.5, 144.6, 139.8, 132.6, 131.0, 128.4, 127.4, 127.0 (2C), 122.5, 122.0, 118.5, 114.0, 31.5, 31.1, 18.3. IR (film): 3348, 3092, 2905, 2816, 1657, 1638, 1585, 1477, 1425, 1173, 768, 750, 665, 629 cm^{-1}. Anal calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04; Found: C, 72.84; H, 6.01; N, 14.81.



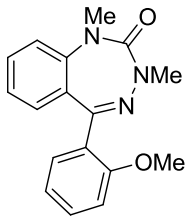
4.6

Arylated benzotriazepine 4.6. Compound **4.6** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-iodo-4-phenylbenzene (840 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 20:1) to afford pure compound **4.6** (266 mg, 78%) as a yellow solid. mp = 139.0-141.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.57 (m, 2H), 7.36-7.31 (m, *J*= 8.4 Hz, 2H), 7.46-7.41 (m, 4H), 7.36-7.30 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.90-6.87 (m, 2H), 6.83-6.75 (m, 1H), 3.56 (s, 3H), 3.54 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.5, 149.4, 141.0, 140.2, 135.1, 132.6, 129.4, 129.0, 128.9, 128.5, 127.0, 126.8, 126.7, 121.8, 120.0, 114.1, 31.7, 31.2. IR (film): 3027, 2948, 1634, 1595, 1477, 1373, 1073, 846, 767, 732, 697, 665, 559 cm^{-1}. Anal calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31; Found: C, 77.09; H, 5.59; N, 12.11.



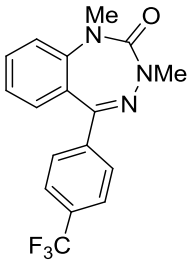
4.7

Arylated benzotriazepine 4.7. Compound **4.7** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-iodonaphthalene (762 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 20:1) to afford pure compound **4.7** (268 mg, 85%) as a yellow solid. mp = 69.5-72.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.49-7.44 (m, 1H), 7.41-7.32 (m, 3H), 7.21-7.15 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.67-6.59 (m, 1H), 3.63 (s, 3H), 3.55 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.6, 146.4, 145.8, 140.0, 134.8, 132.6, 129.0, 128.2, 126.7, 126.5, 126.2, 125.5, 123.8, 122.3, 121.9, 114.0, 113.8, 112.9, 31.7, 31.1. IR (film): 3354, 3052, 1681, 1605, 1571, 1479, 1426, 1270, 1070, 1002, 773, 747, 662, 627 cm^{-1}. Anal calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32; Found: C, 76.42; H, 5.21; N, 13.11.



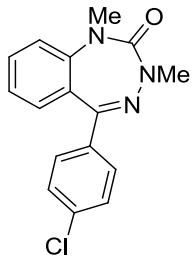
4.8

Arylated benzotriazepine 4.8. Compound **4.8** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-iodo-2-methoxybenzene (702 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.8** (194 mg, 66%) as a brown solid. mp = 119.1-122.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.38 (m, 2H), 7.09-7.07 (m, 1H), 7.01-6.98 (m, 1H), 6.93-6.87 (m, 2H), 7.81-6.73 (m, 2H), 3.66 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.7, 149.1 (2C), 146.2, 139.5, 139.1, 132.5, 128.2, 123.2, 121.8 (2C), 120.6, 113.9, 112.1, 55.9, 31.7, 31.1. IR (film): 2943, 2835, 1676, 1625, 1477, 1234, 1110, 1023, 745, 663 cm^{-1}. Anal calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23; Found: C, 68.98; H, 5.79; N, 14.04.



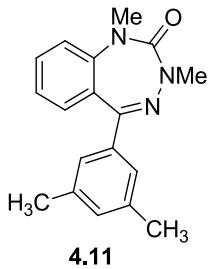
4.9

Arylated benzotriazepine 4.9. Compound **4.9** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-trifluoromethyl-4-iodobenzene (816 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.9** (226 mg, 68%) as an off-white solid. mp = 127.9-129.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.49-7.45 (m, 1H), 7.30-7.28 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.89-6.82 (m, 3H), 3.57 (s, 3H), 3.47 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.2, 151.4, 145.7, 140.3, 133.0, 129.2, 127.2, 127.1 (q, *J* = 3.1 Hz), 124.8 (q, *J* = 271 Hz), 124.2 (q, *J* = 32 Hz), 121.9, 119.6, 114.3, 31.7, 31.2 . ^{19}F NMR (375 MHz, $CDCl_3$) = δ -60.3 . IR (film): 1679, 1687, 1635, 1601, 1479, 1322, 1091, 1064, 845, 745, 588 cm^{-1}. Anal calcd for $C_{17}H_{14}F_3N_3O$: C, 61.26; H, 4.23; N, 12.61; Found: C, 61.38; H, 4.41; N, 12.35.



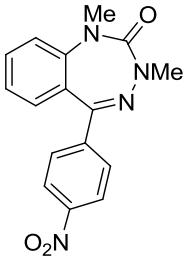
4.10

Arylated benzotriazepine 4.10. Compound **4.10** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-chloro-4-iodobenzene (712 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.10** (164 mg, 55%) as a slightly yellow solid. mp = 131.0-132.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.43 (m, 1H), 7.36-7.31 (br m, 1H), 7.28-7.26 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 8.4 Hz, 2H), 3.55 (s, 3H), 3.50 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.5, 148.6(2C), 145.9, 140.2, 132.8, 129.9, 129.3, 127.4, 121.8, 120.9, 114.2, 31.6, 31.2. IR (film): 2945, 1672, 1625, 1602, 1473, 1405, 2389, 1073, 833, 745, 609, 540 cm^{-1}. Anal calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02; Found: C, 63.72; H, 4.39; N, 13.70.



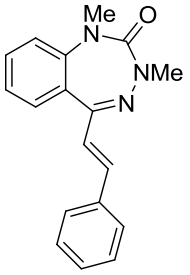
4.11

Arylated benzotriazepine 4.11. Compound **4.11** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-iodo-3,5-dimethylbenzene (694 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.11** (161 mg, 55%) as a yellow solid. mp = 145.2-148.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.38 (m, 2H), 7.10-7.07 (m, 1H), 6.81-6.77 (m, 1H), 6.66 (s, 1H), 6.42 (s, 2H), 3.52 (s, 3H), 4.47 (s, 3H), 2.25 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.8, 149.8 (2C), 144.8, 140.1, 139.5, 132.4, 129.5, 124.2, 121.7, 117.0, 114.0, 31.1(2C), 21.6. IR (film): 2913, 1672, 1622, 1590, 1481, 1290, 840, 744, 683 cm^{-1}. Anal calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32; Found: C, 73.34; H, 6.54; N, 14.03.



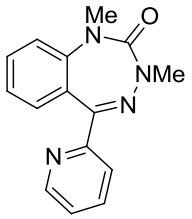
4.12

Arylated benzotriazepine 4.12. Compound **4.12** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-iodo-4-nitrobenzene (747 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 19:1) to afford pure compound **4.12** (148 mg, 48%) as a dark yellow solid. mp = 150.0-153.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.51-7.47 (m, 1H), 7.26-7.19 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.56 (s, 3H), 3.51 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 156.5, 151.2, 145.9, 142.6, 140.4, 133.6, 129.2, 126.2, 122.2, 119.7, 114.6, 112.7, 31.8, 31.3. IR (film): 3107, 2949, 1626, 1578, 1475, 1328, 1291, 1267, 1108, 1071, 1001, 850, 749, 603 cm^{-1}. Anal calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06; Found: C, 61.51; H, 4.41; N, 18.11.



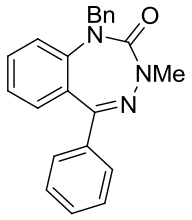
4.13

Arylated benzotriazepine 4.13. Compound **4.13** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-((*E*)-2-iodovinyl)benzene[12] (690 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 20:1) to afford pure compound **4.13** (84 mg, 29%) as a yellow solid. mp = 113.5-115.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-8.02 (m, 1H), 7.70 (d, *J* = 13.8 Hz, 1H), 7.55-7.51 (m,1H), 7.42-7.37 (m, 2H), 7.32-7.28 (m, 2H), 7.19-7.10 (m, 3H), 6.51 (d, *J* = 13.8 Hz, 1H), 3.52 (s, 3H), 3.51(s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.6, 149.0, 140.0, 137.8, 137.7 (2C), 132.8, 129.7, 128.9, 126.5, 125.9, 122.1 (2C), 114.0, 31.1 (2C). IR (film): 3061, 3020, 2925, 2854, 1672, 1588, 1558, 1475, 1409, 1290, 1072, 945, 760, 748, 688, 506 cm^{-1}. Anal calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42; Found: C, 74.46; H, 5.70;N, 14.11.



4.14

Arylated benzotriazepine 4.14. Compound **4.14** was prepared from benzotriazepine **4.1** (189 mg, 1.00 mmol, 1.0 equiv) and 1-iodopyridine (615 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM/ EtOAc = 1:2) to afford pure compound **4.14** (105 mg, 40%) as a brown solid. mp = 96.0-99.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 4.4 Hz, 1H), 7.61-7.57 (m, 1H), 7.42-7.34 (m, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.93-6.90 (m, 1H), 6.79-6.73 (m, 2H), 3.49 (s, 3H), 3.48 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.8, 151.2, 149.4, 147.6, 140.2, 138.5, 133.1, 129.1, 121.9, 118.0, 115.3, 114.2, 113.3, 31.7, 31.1. IR (film): 2941, 1678, 1582, 1606, 1554, 1419, 1294, 1269, 1074, 773, 742, 665, 503 cm^{-1}. Anal calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04; Found: C, 67.74; H, 5.07; N, 20.65.



4.15

Arylated benzotriazepine 4.15. Compound **4.15** was prepared from benzotriazepine **4.3** (265 mg, 1.00 mmol, 1.0 equiv) and phenyl iodide (612 mg, 3.00 mmol, 3.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, DCM) to afford pure compound **4.15** (300 mg, 88%) as a yellow solid. mp = 118.0-120.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.25 (m, 9H), 7.07-7.01 (m, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 6.76-6.72 (m, 1H), 5.35 (s, 2H), 3.60 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.0, 149.9, 145.1, 139.5, 136.5, 132.5, 129.9, 129.5 (2C), 129.1, 127.6, 126.6, 122.5, 121.8, 119.4, 115.1, 47.8, 31.8. IR (film): 3029, 2943, 1680, 1596, 2472, 1416, 1269, 1156, 1049, 773, 695, 657, 525 cm^{-1}. Anal calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31; Found: C, 77.24; H, 5.43; N, 12.15.

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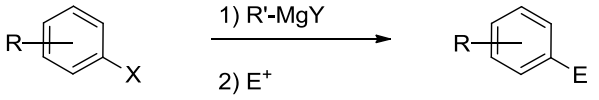
Chapter V. The Unusual Formation of 3,4-Disubstituted Quinolines from Grignard Reactions.

The reaction of isopropyl Grignard reagent and 3-bromoquinoline leads to formation of interesting 3,4-disubstituted quinoline products in significant yields. This transformation was extensively studied for 3-bromoquinoline as the substrate, isopropyl magnesium chloride as the nucleophile, and a Brønsted acid or 3-bromopropene as electrophiles. A brief survey of this transformation, identification of the reaction limitations, and a suggested mechanism are reported in this Chapter. Some of the synthetic details of this work were published in a communication. (Yotphan, S.; Bergman, R. G.; Ellman, J. A. Synthesis of Multicyclic Pyridine and Quninoline Derivatives via Intramolecular C-H Bond Functionalization. *Org. Lett.* **2010**, *12*, 2978-2981.)

Introduction

Grignard reagents can act as strong bases and good nucleophiles.[1] They also undergo transmetallation (halogen/metal exchange).[2] These capabilities make them versatile reagents particularly for carbon-carbon bond formation reactions, which are fundamental to organic synthesis (eq 5.1).[3] The ionic character of the Grignard carbon-metal bond is between that of organo-lithium and organo-zinc compounds.[4] This reactivity along with their stability, ease of handling, and commercial availability have made Grignard reagents among the most popular of all organometallic reagents.[5]



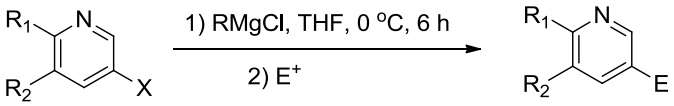
(5.1)

X = Br, I, OTf
E = Alkyl-Cl, Alkyl-Br, Alkyl-I
Y = Cl, Br

As mentioned in Chapters 1 and 3, pyridines are the most extensively used nitrogen-containing heterocycles in pharmaceutical research.[6] Much effort is devoted to finding efficient methods for their synthesis.[7] One practical synthetic method for the preparation of alkyl pyridines is the direct conversion of commercially available halogenated pyridine precursors via transmetallation to the corresponding pyridyl salt using Grignard or organolithium reagents, followed by reaction with electrophiles.

During the preparation of alkyl tethered pyridine and quinoline substrates described in Chapter 3, we observed that Grignard reagent-based transmetallation and alkylation took place cleanly, for example, the alkylation of 3-bromopyridine with 3-bromo-2-methylprop-1-ene yielded 3-(2-methylallyl)pyridine (Scheme 5.1). In contrast, the reaction of *i*-PrMgCl and 3-bromoquinoline (**5.1**) in the presence of 3-bromo-2-methylprop-1-ene as an electrophile did not result in the expected monoalkylation product **5.2** (Scheme 5.2). Instead, the 3,4-disubstituted product **5.3** was obtained as a major product of the reaction. The presence of a CuX (X = Cl, Br,I) salt is necessary to obtain the monoalkylated product **5.2** from the reaction (eq.5.2).

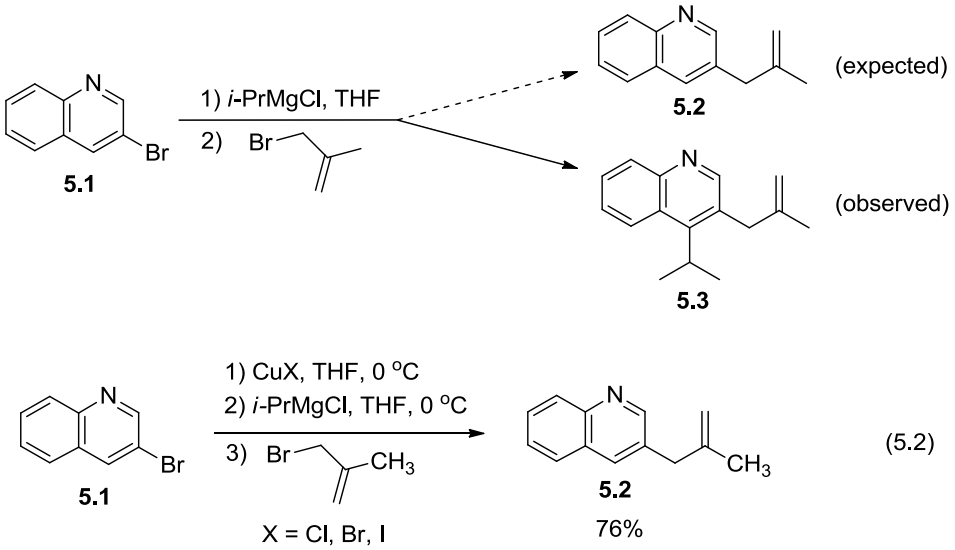
Scheme 5.1. Transmetallation and Alkylation of 3-Halopyridines.



1.0 M

R = Me, Et, *i*-Pr, Ph
R_1 = H, Me
R_2 = H, Me, Ph
E = H^+, 3-bromoprop-1-ene, alkylbromide
X = Br, I

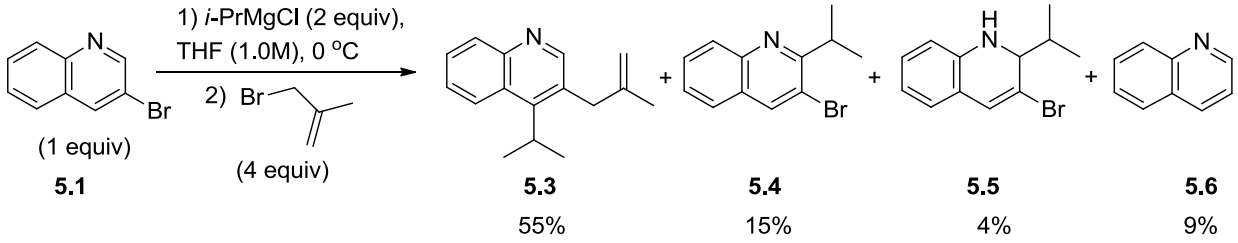
Scheme 5.2. Observation of Disubstituted Quinolines from Grignard Reaction.



Reaction Optimization and Scope

Obtaining a disubstituted quinoline product from the reaction described in Scheme 5.2 was unexpected; however, the chemistry is interesting, and could lead to a useful transformation for a preparation of quinoline derivatives. Therefore, dialkylation reaction was studied and the structures of by-products were identified.[8] The yield of the dialkylated quinoline product **5.3** was improved, and the amount of by-products (compounds **5.4, 5.5** and **5.6**) were minimized by optimizing reaction conditions (Scheme 5.3). Using 1, 2 or more equivalents of *i*-PrMgCl gave comparable results with respect to product distribution, but the overall yield was highest when using 2 equivalents of *i*-PrMgCl.

Scheme 5.3. Optimized reaction conditions for the preparation of 5.3 from reaction of i-PrMgCl and 3-bromoquinoline.



Note: 55% yield of the dialkylated product **5.3** was obtained with 2 equivalents of *i*-PrMgCl while the use of 1 equivalent gave 29% yield and 3 equivalents resulted in 34% yield of **5.3**.

Product **5.7** was obtained as the major product when replacing 3-bromo-2-methylprop-1-ene with acetic acid as the electrophile (Scheme 5.4). The regioselectivity of this reaction is consistent with that observed in the previous reaction and the same by-products were formed as well. According to these observations, the formation of major products could be a consequence

of the Grignard reagent adding to 3-bromoquinoline substrate **5.1** at the C-4 position, followed by reaction of the resulting intermediate with electrophiles (H^+ and 3-bromo-2-methylprop-1-ene) that takes place at the C-3 position on the quinoline ring (Figure 5.1).

Scheme 5.4. Reaction of *i*-PrMgCl and 3-bromoquinoline using CH_3COOH as an electrophile (Queching Experiment).

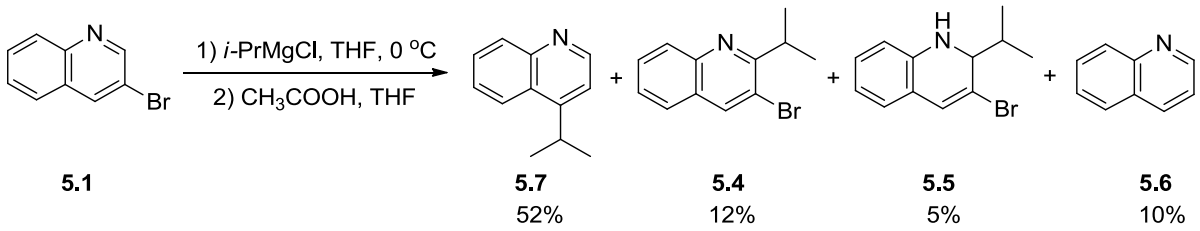
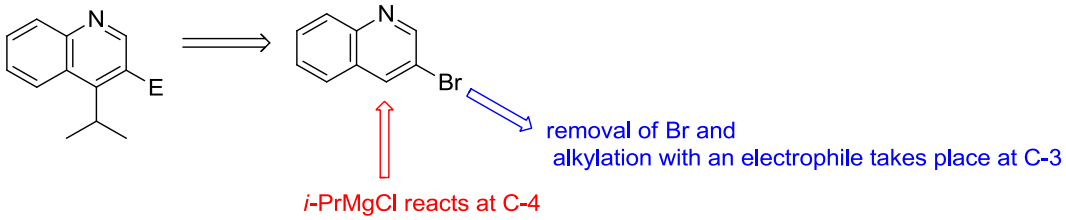


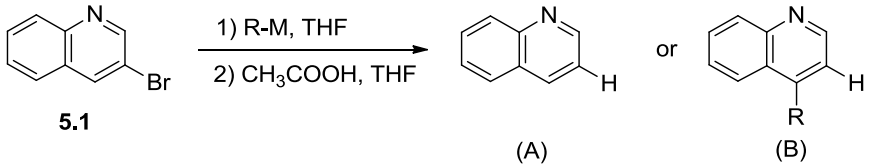
Figure 5.1. Prediction of a major product structure.



Since the by-products **5.4**-**5.6** were generated in both reactions (Schemes 5.3 and 5.4), the results suggest that more than one reaction pathway could occur competitively. Small amounts of quinoline **5.6** isolated from the reaction could suggest that the transmetallation pathway also took place. The presence of by-products **5.4** and **5.5** in eq 5.2 and eq 5.3 could imply competitive Grignard addition between the C-2 (minor pathway) and C-4 (major pathway) sites of the precursor **5.1** (*vide infra*).

The effect of organometallic reagents was explored by performing quenching experiments using CH_3COOH in THF (Table 5.1). Except when the secondary *i*-PrMgCl was used as the nucleophile (entry 3), quinoline products were formed in low to modest yields. Methyl (entry 4), primary alkyl (entry 5), aryl (entry 6), and tertiary alkyl (entry 7) Grignard reagents all provided low yields of products. Nevertheless, the major products of the transformation were 4-alkyl substituted quinolines (Table 5.1, entries 3 to 5, 7, and 8). These results suggest that transmetallation is not the most favorable pathway for the reaction of 3-bromoquinoline substrate with Grignard reagents.

Table 5.1. Effects of Organometallic Reagents.[a,b]



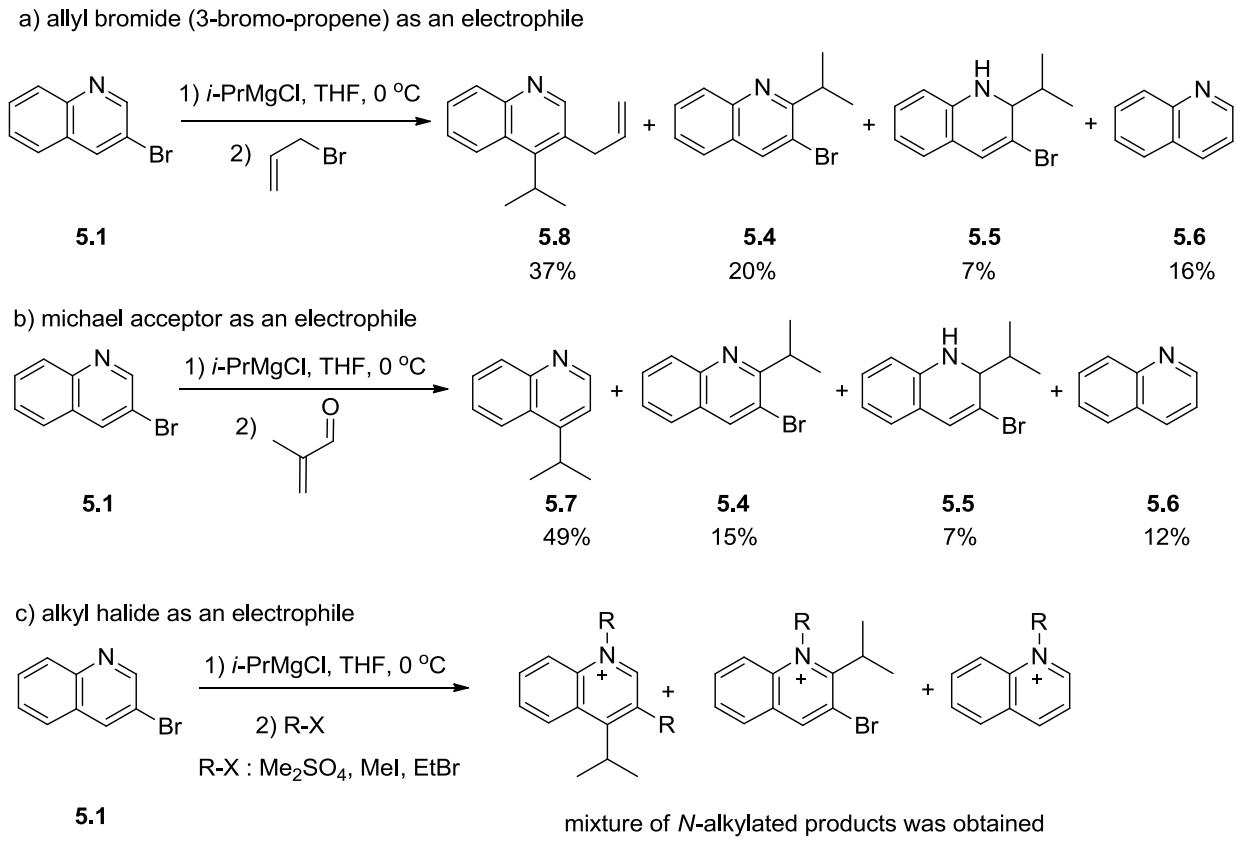
5.1 (A) (B)

entry	R-M	% yield of product	
		(A)	(B)
1	*n*-BuLi	4	0
2	LDA	3	9
3	*i*-PrMgCl	9	49
4	EtMgCl	2	6
5	MeMgCl	3	14
6	PhMgCl	4	0
7	*t*-BuMgCl	2	11
8	*i*-PrMgBr	7	29

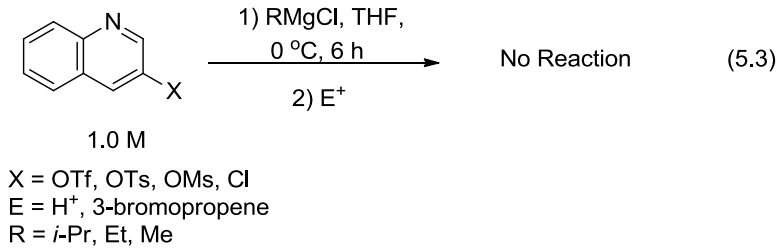
[a] Reaction Conditions: 3-bromoquinoline (1 equiv), R-M (2 equiv), THF (1 M), CH_3COOH (4 equiv).
[b] Either decomposition or oxidation of substrate to yield *ortho*-alkylated/arylated 3-bromo quinoline was accounted for the rest of the mass balance.

Apart from 3-bromo-2-methylprop-1-ene and H^+ as electrophiles, we found that the use of 3-bromoprop-1-ene also resulted in disubstitution to provide quinoline **5.8** in 37% yield (Scheme 5.5a). However, the use of Michael acceptors did not give successful conversion to the corresponding disubstituted product (Scheme 5.5b). Furthermore, *C*-alkylation was not observed when using other good electrophiles such as MeI, Me_2SO_4, or EtBr as a consequence of the competitive formation of *N*-alkylated products, which were obtained as major products (Scheme 5.5c).

Scheme 5.5. Effect of electrophiles.



Altering the substrate from 3-bromoquinoline to other 3-haloquinoline substrates and subjecting them to the same reaction conditions did not result in either mono or dialkylation products. In most cases, the starting materials were recovered (eq 5.3).

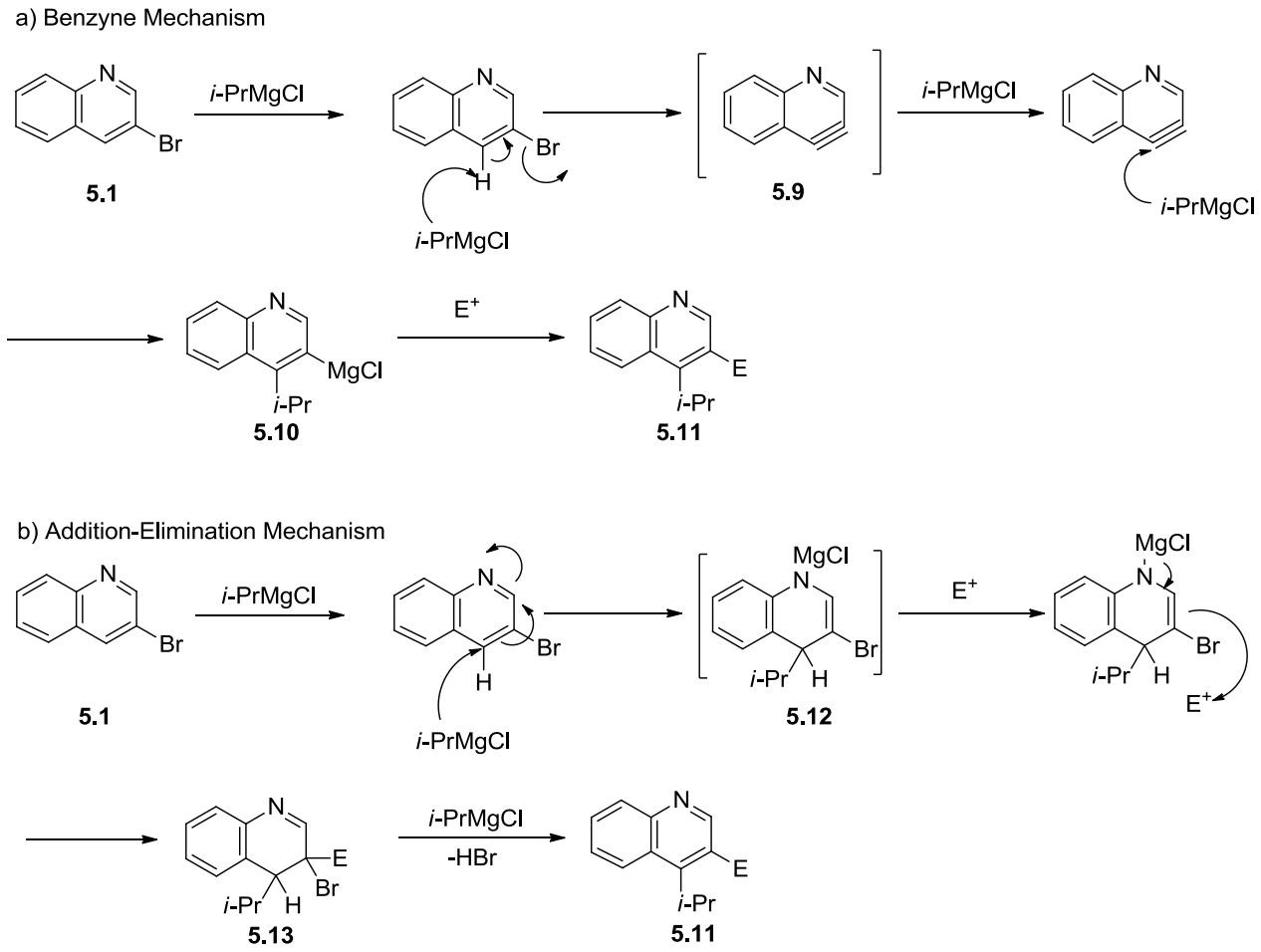


Proposed Mechanism

It is interesting that unusual disubstituted products were formed in the reaction between *i*-PrMgCl and 3-bromoquinoline followed by addition of an electrophile. This appealing reactivity of 3-bromoquinoline and an organometallic reagent has not been previously reported in the literature. However, the scope of this transformation is very limited. Good yields were only obtained when the secondary *i*-PrMgCl was added to 3-bromoquinoline.

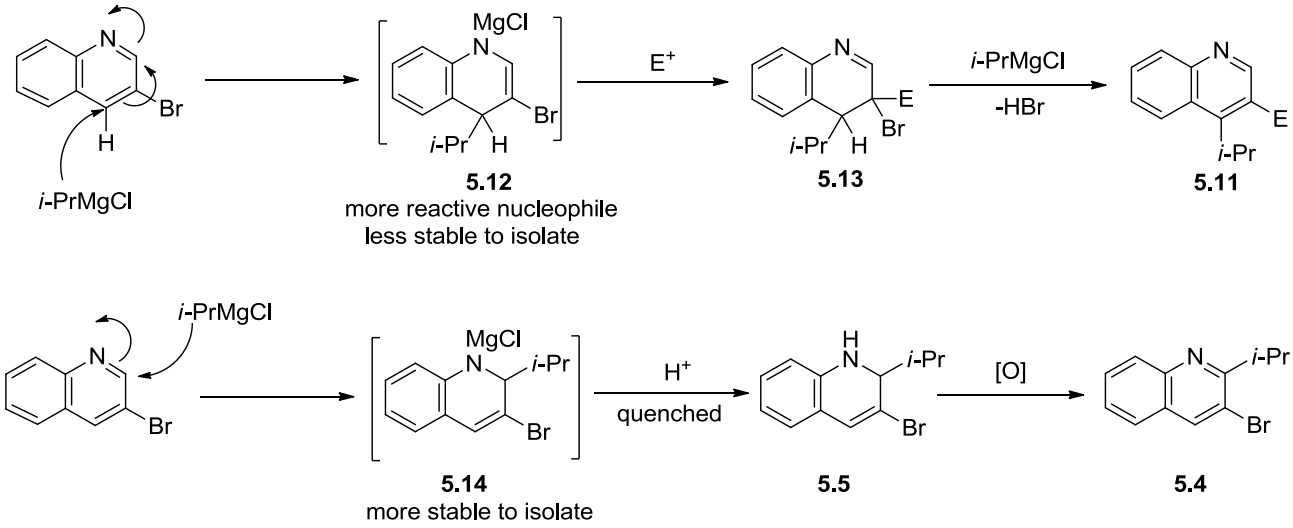
One possible reaction mechanism could be a benzyne-type reaction,[9] where *i*-PrMgCl acts as base in the first step to deprotonate 3-bromoquinoline substrate **5.1** at the 4-position (Scheme 5.6a). After deprotonation and subsequent elimination, the benzyne intermediate (**5.9**) would be formed. Then, another molecule of *i*-PrMgCl would attack the intermediate **5.9** at the C-4 position promoting alkylation at the C-3 position (**5.10**) to give the disubstituted product **5.11**. However, the use of an organometallic reagent to both generate and add into a benzyne intermediate has not previously been reported.[10] An alternative mechanism could also be operative in which the addition of the Grignard reagent to the substrate would occur prior to elimination of bromide ion (Scheme 5.6b). In this mechanism, *i*-PrMgCl would act as nucleophile in the first step, adding onto substrate **5.1** to generate the intermediate **5.12**. In the presence of a proper electrophile, C-3 alkylation would take place (**5.13**). Then, elimination of HBr would form the aromatic quinoline compound (**5.11**). Elimination could occur either with *i*-PrMgCl serving as the base or during the reaction work up.

Scheme 5.6. Proposed Mechanisms of the Product Formation.
a) via Benzyne Intermediate b) via Addition-Elimination



The addition-elimination mechanism is likely to be more reasonable because additions of organometallic reagents to pyridines/quinolines have been reported in the literature.[11] Furthermore, the presence of by-products **5.4** and **5.5** seems to support this proposed mechanism as depicted in Scheme **5.7**. As mentioned previously, the competitive Grignard additions at C-4 and C-2 would be possible. Thus, intermediate **5.12** and intermediate **5.14** would be generated after reaction of *i*-PrMgCl with substrate. The intermediate **5.12** could further react with proper electrophiles to generate compound **5.13**, which can eliminate HBr to form the stable disubstituted quinoline **5.11**. On the other hand, intermediate **5.14** would not be as reactive as **5.13**; thus it could be isolated after quenching at the end of reaction to give **5.5**. Additionally, compound **5.5** could undergo oxidization to form by-product **5.4**.

Scheme 5.7. Comparison of *i*-PrMgCl Addition at C-2 and C-4 according to Addition-Elimination Mechanism.



Conclusions

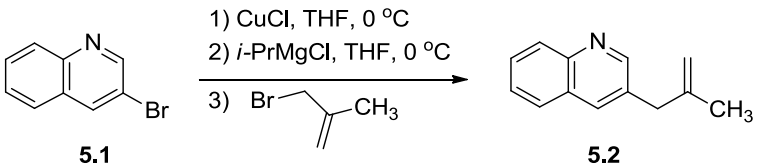
In summary, this Chapter describes an unusual reaction in which a disubstituted product is obtained in significant yield from the addition reaction of *i*-PrMgCl to 3-bromoquinoline followed by addition of an electrophile. Good yields of these products were obtained when a Brønsted acid or methallyl bromide were used as the electrophiles.

Experimental

General Experimental. Unless otherwise specified, all reagents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was dried over alumina under a nitrogen atmosphere. All reactions were performed under an inert atmosphere using standard Schlenk techniques unless specified otherwise. Oven-dried glassware was used in all cases. Chromatography was performed on silica gel (SiO_2), (60 Å silica gel, MP

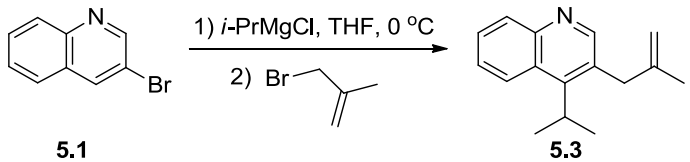
Silitech 32-63D). ^{1}H and ^{13}C NMR spectra were measured with a Bruker AV-400 spectrometer in $CDCl_3$. NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C). IR spectra were recorded on a Thermo Scientific Nicolet FTIR *iS10* spectrometer equipped with an attenuated total reflectance accessory, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. High resolution mass spectra were carried out by the University of California, Berkeley QB3/CChem Mass Spectrometry Facility. For high-resolution EI mass spectrometry, a ProSpec spectrometer (magnetic sector instrument) equipped with an EI source (Micromass, Manchester, UK) was used. For high-resolution ESI spectrometry, either a Q-TOP Premier spectrometer from Waters or a LTQ Orbitrap spectrometer from Thermo was used.

Reaction of Grignard Reagents and 3-Bromoquinoline.



5.1 **5.2** 76%

Quinoline 5.2. An oven dried and N_2-flushed 100 mL round bottom flask equipped with a magnetic stir bar and septum was charged with 3-bromoquinoline **5.1** (0.400 g, 2.00 mmol, 1.00 equiv), dry THF (2.00 mL, 1.00 M concentration of substrate) and CuCl (0.20 g, 2.00 mmol, 1.00 equiv). The mixture was stirred at 0 °C for 15 min. Then *i*-PrMgCl (2.00 M, 2.0 mL, 4.00 mmol, 2.00 equiv) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at this temperature for 3 h, and then 3-bromo-2-methylprop-1-ene (0.80 mL, 8.00 mmol, 4.00 equiv) was added to the mixture. The reaction mixture was stirred for 15 h at room temperature. Upon reaction completion, saturated NH_4Cl solution (5 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The organic extract was concentrated *in vacuo*, and the crude product was purified by column chromatography (SiO_2, Hex:EtOAc = 3:2) to afford quinoline **5.2** as a yellow solid (0.27 g, 76%). mp = 42.0-43.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.70-7.64 (m, 1H), 7.55-7.51 (m, 1H), 4.91 (s, 1H), 4.79 (s, 1H), 3.51 (s, 2H), 1.74 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 152.2, 147.0, 143.9, 134.9, 132.3, 129.2, 128.7, 128.1, 127.4, 126.6, 113.0, 41.8, 22.2. IR (film): 3060, 2970, 2901, 1651, 1495, 1442, 1376, 890, 787, 720 cm^{-1}. HRMS (ESI+) Calcd for $C_{13}H_{14}N$ $[MH]^+$ 184.1121; Found 184.1127.

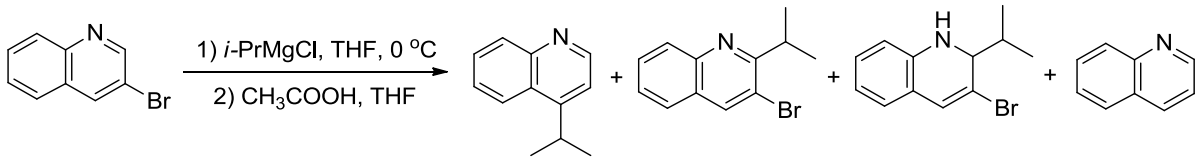


5.1 **5.3** 55%

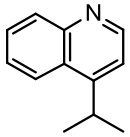
Quinoline 5.3. An oven-dried and N_2-flushed round bottom flask equipped with a magnetic stir bar and a septum was charged with 3-bromoquinoline **5.1** (0.400 g, 2.00 mmol, 1.00 equiv) dissolved in dry THF (2.00 mL, 1.00 M concentration of substrate), and *i*-PrMgCl

(2.00 mL, 2.00 M, 4.00 mmol, 2.00 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and then 3-bromo-2-methylprop-1-ene (0.80 mL, 8.00 mmol, 4.00 equiv) was added. The reaction mixture was slowly warmed to room temperature and stirred for an additional 15 h. After the reaction was complete, saturated NH_4Cl solution (5 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The solution was concentrated *in vacuo*, and the crude product was purified by SiO_2 column chromatography (Hex:EtOAc = 3:2) to afford quinoline **5.3** as a yellow oil (0.24 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.64-7.60 (m, 1H), 7.51-7.47 (m, 1H), 4.87 (s, 1H), 4.42 (s, 1H), 3.66-3.61 (m, *br*, 1H), 3.53 (s, 2H), 1.82 (s, 3H), 1.53 (d, *J* = 7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.4, 151.1, 148.3, 144.3, 130.6, 129.1, 127.8, 126.8, 125.4, 125.3, 112.3, 39.8, 29.4, 23.1, 22.0. IR (film): 3085, 2963, 1568, 1503, 1448, 1258, 1091, 1012, 892, 788, 760 cm^{-1}. HRMS (ESI+) Calcd for $C_{16}H_{20}N$ $[MH]^+$ 226.1590; Found 226.1594.

Quenching Experiments.

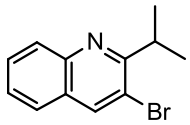


An oven-dried and N_2-flushed round bottom flask equipped with a magnetic stir bar and a septum was charged with 3-bromoquinoline **5.1** (0.40 g, 2.00 mmol, 1.00 equiv) dissolved in dry THF (2.00 mL, 1.00 M concentration of substrate), and *i*-PrMgCl (2.00 mL, 2.00 M, 4.00 mmol, 2.00 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 6 h, and then a solution of 1 M CH_3COOH in THF (8.00 mL) was added. The reaction mixture was slowly warmed to room temperature and stirred for an additional 2 h. Then, saturated $NaHCO_3$ solution was added to the mixture in order to neutralize the pH. The organic residue was isolated from the mixture by extraction with EtOAc (3 x 5 mL). The combined organic extract was dried over anhydrous Na_2SO_4, and the resulting organic solution was concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography (Hex:EtOAc = 4:1) to afford four different products: quinoline **5.7** as a yellow oil (0.17 g, 52%), quinoline **5.4** as a yellow oil (0.06 g, 12%), quinoline **5.5** as a yellow oil (0.02 g, 5%), and quinoline **5.6** as a slightly yellow liquid (0.09 g, 10%).

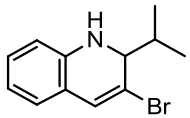


Quinoline 5.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, *J* = 4.8 Hz, 1H), 8.14-8.10 (m, 2H), 7.72 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.57 (dt, *J* = 1.2, 8.4 Hz, 1H), 7.31 (d, *J* = 4.8 Hz, 1H), 3.76 (sept, *J* = 6.8 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.4, 150.4, 148.3, 130.3, 128.8, 126.9, 126.2, 123.1, 116.9, 28.3, 22.9. IR (film): 3064, 2929, 2872,

2160, 2030, 1589, 1569, 1461, 1417, 1386, 1242,894,845, 764, 699 cm^{-1}. HRMS (ESI+) Calcd for $C_{12}H_{14}N$ $[MH]^+$ 172.1121; Found 172.1123.

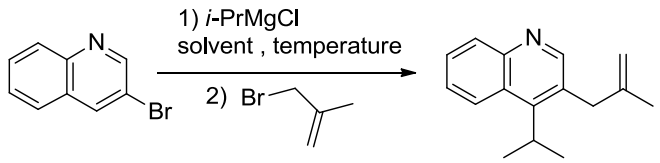


Quinoline 5.4. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.70-7.66 (m, 2H), 7.51-7.47 (m, 1H), 3.72 (sept, *J* = 6.8 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 146.8, 139.0, 129.6, 129.4, 128.1, 126.7, 126.6, 118.9, 34.5, 21.7. IR (film): 3058, 2964, 2926, 2869, 2160, 2029, 1590, 1487, 1456, 1400, 1297, 1136, 1089, 971, 902, 784, 756 cm^{-1}. HRMS (ESI+) Calcd for $C_{12}H_{13}BrN$ $[MH]^+$ 250.0226; Found 250.0226.



Quinoline 5.5. ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (t, *J* = 10.0 Hz, 1H), 6.78-6.74 (m, 2H), 6.53 (t, *J* = 10.0 Hz, 1H), 6.40 (d, *J* = 10.8 Hz, 1H), 4.28 (s, 1H), 3.91 (s *br*, 1H), 2.22-2.17 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.0, 139.0, 129.3, 126.5, 119.8, 118.7, 117.3, 112.0, 64.5, 33.2, 18.9, 15.8. IR (film): 3058, 2965, 2926, 2869, 2160, 2028, 1577, 1486, 1400, 1297, 1136, 1089, 971, 902, 858, 784, 739, 722 cm^{-1}. HRMS (ESI+) Calcd for $C_{12}H_{15}BrN$ $[MH]^+$ 252.0382; Found 252.0380.

Reaction Optimization (screening of stoichiometric ratio and concentrations). An oven dried and N_2-flushed 25 mL round bottom flask equipped with a magnetic stir bar and septum was charged with 3-bromoquinoline **5.1** (0.100 g, 0.50 mmol, 1.00 equiv), and various anhydrous solvents. Then *i*-PrMgCl (2.00 M, various amounts) was added dropwise to the reaction mixture at various temperatures. The reaction mixture was stirred at the constant temperature for various amounts of time, and then 3-bromo-2-methylprop-1-ene (various amount) was added to the mixture. The reaction mixture was stirred for 15 h at room temperature. Upon reaction completion, saturated NH_4Cl solution (1 mL) was added. The mixture was extracted with EtOAc (3 x 1 mL). The organic extract was concentrated *in vacuo*, and the crude product was purified by column chromatography (SiO_2, Hex:EtOAc = 3:2) to afford quinoline **5.3** as a yellow solid.



5.1 **5.3**

Table 5.2. Effect of Stoichiometric Ratio.

entry	ratio of 3-bromoquinoline : *i*-PrMgCl : CH_3COOH in THF	yield of **5.3** (%)
1	1 : 1 : 1	27
2	1 : 2 : 2	46
3	1 : 2 : 4	55
4	1 : 1 : 2	29
5	1 : 3 : 6	33
6	1 : 4 : 8	36

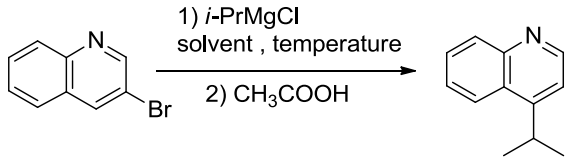
Note: bromoquinoline (**5.1**) (1.0 M in THF), 0°C, 6 h reaction time prior to addition of 3-bromo-2-methylprop-1-ene .

Table 5.3. Effect of Substrate Concentrations.

entry	concentration of 3-bromoquinoline (M.)	yield of **5.3**(%)
1	1	55
2	2	21
3	0.5	40
4	0.2	19

Note: bromoquinoline (**5.1**, 100 mg, 1 equiv), THF (various amount), *i*-PrMgCl (2 equiv), 0°C, 6 h reaction time prior to addition of 3-bromo-2-methylprop-1-ene (4 equiv).

Reaction Optimization (screening of solvents, times, temperatures). An oven dried and N_2-flushed 25 mL round bottom flask equipped with a magnetic stir bar and septum was charged with 3-bromoquinoline **5.1** (0.100 g, 0.50 mmol, 1.00 equiv), and various anhydrous solvents. Then *i*-PrMgCl (2.00 M, various amounts) was added dropwise to the reaction mixture at various temperatures. The reaction mixture was stirred at the constant temperature for various amounts of time, and then 3-bromo-2-methylprop-1-ene (various amount) was added to the mixture. The reaction mixture was stirred for 15 h at room temperature, and then a solution of 1 M CH_3COOH in THF (various amount) was added. The reaction mixture was slowly warmed to room temperature and stirred for an additional 2 h. Then, saturated $NaHCO_3$ solution was added to the mixture in order to neutralize the pH. The mixture was extracted with EtOAc (3 x 1 mL). The organic extract was concentrated *in vacuo*, and the crude product was purified by column chromatography (SiO_2, Hex:EtOAc = 3:2) to afford quinoline **5.7** as a yellow liquid.



5.1 **5.7**

Table 5.4. Effect of Solvents.

entry	solvent	yield of **5.7**(%)
1	THF	51
2	diethyl ether	11
3	toluene	13
4	dioxane	19

Note: bromoquinoline (**5.1**, 100 mg, 1 equiv), Solvent (1M conc of starting material), *i*-PrMgCl (2 equiv), 0^{o}C, 6 h reaction time prior to quenching with CH_3COOH/THF.

Table 5.5. Effect of Temperature and Time.

entry	temperature (^{o}C)	time (h)	yield of **5.7**(%)
1	0	1	22
2	0	2	31
3	0	4	42
4	0	6	55
5	0	8	52
6	0	12	51
7	-78	6	5
8	-40	6	7
9	-20	6	44
10	rt	6	25

Note: bromoquinoline (**5.1**, 100 mg, 1 equiv), Solvent (1M conc of starting material), *i*-PrMgCl (2 equiv), various temperatures and reaction time prior to quenching with CH_3COOH/THF.

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