

**New Palladium- and Gold-Catalyzed Alkene and Alkyne Difunctionalization
Reactions for the Efficient, Stereoselective Synthesis of Azabicycles
and β -Alkoxy Ketones**

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in The University of Michigan
2012

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Dedication

To Steve

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List of Abbreviations

Boc.....	<i>tert</i> -butyloxycarbonyl
bt.....	benzotriazole
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
DavePhos	2-dicyclohexylphosphino-2'-(<i>N,N</i> -dimethylamino)-biphenyl
dba.....	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DPEphos.....	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dppf.....	1,1'-bis(diphenylphosphino)ferrocene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
JohnPhos.....	2-(dicyclohexylphosphino)biphenyl
MOMCl.....	methyl chloromethyl ether
NHC	<i>N</i> -heterocyclic carbene
Nixantphos.....	4,6-bis(diphenylphosphino)phenoxazine
PG.....	protecting group
PMP	<i>p</i> -methoxyphenyl
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
RCM.....	ring-closing metathesis
<i>t</i> BuXPhos.....	2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropylbiphenyl
Troc.....	2,2,2-trichloroethyloxycarbonyl
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Abstract

The research and development of new drug therapies is reliant upon synthetic methods that are able to deliver diverse drug-like molecules in a straightforward manner. Some of the most common structural motifs found in numerous pharmaceuticals and biologically active natural products are fused and bridging azabicyclic frameworks and 1,3-dioxygen units. However, methods for accessing these structures are limited in the types of scaffolds that can be prepared in an efficient manner from simple starting materials. To address this problem, the research described in this dissertation is focused on the development of novel palladium- and gold-catalyzed reactions for the direct synthesis of diverse azabicycles and 1,3-dioxygen units. Common to these new transformations is the metal-mediated difunctionalization of alkene and alkyne starting materials, allowing for the construction of azabicyclic and 1,3-dioxygen motifs with unique substitution patterns that cannot be easily accessed with existing methods.

Specifically, the first half of this dissertation details the work put forth on extending the scope of Pd-catalyzed alkene aminoarylation reactions towards the synthesis of biologically significant pyrrolizidine, indolizidine, and tropane scaffolds. The construction of pyrrolizidines and indolizidines was achieved by developing a novel Pd-catalyzed aminopalladation/carbopalladation cascade reaction of readily accessible *N*-allyl-2-allylaniline derivatives. This tandem reaction rapidly develops molecular complexity, as 3 bonds and 2 stereocenters are formed in a single step, providing diverse indolizidine or pyrrolizidine products in good yield and diastereoselectivity. Likewise, we devised an intramolecular Pd-catalyzed alkene aminoarylation methodology for arriving at pharmaceutically relevant benzo-fused tropanes. These transformations are highly efficient, generating 2 bonds, 1-2 stereocenters and the azabicyclic

scaffold in a single step, ultimately providing various tropane derivatives in excellent yield and diastereoselectivity.

The second half of this dissertation describes the multicomponent synthesis of β -alkoxy ketones through the development of novel Au-catalyzed carboalkoxylation reactions of alkynes with hemiacetals. The described Au-catalyzed transformation provides a non-traditional and atom-economical approach for β -alkoxy ketone synthesis via the intermolecular capture of gold(I) enol derivatives with *in situ* generated oxocarbenium ions. The intermolecular capture of gold(I) enol derivatives with carbon electrophiles is unprecedented and will likely facilitate the design of other useful Au-catalyzed transformations.

Chapter 1

Azabicycles: Significance and Preparation

1.1 Introduction

Fused and bridged bicyclic amines represent some of the most important and well-studied classes of *N*-heterocycles, as they are prominently displayed in countless pharmaceuticals and biologically relevant molecules.¹ Unique to both of these scaffolds is their structural rigidity, which has made them ideal targets for probing biological systems. As a result, the development of new methodologies that would garner azabicycles in a straightforward manner would greatly facilitate the exploration of these molecules as potential therapeutic agents. In recent years, Pd-catalyzed alkene difunctionalization reactions have emerged as powerful tools for the synthesis of pharmaceutically relevant nitrogen-containing heterocycles. In general, these transformations proceed through the cross-coupling of simple aminoalkene substrates with carbon-based electrophiles, generating the heterocyclic ring through the formation of a C–N and C–C bond with one or more stereocenters. Moreover, these methods are quite useful for generating analogs of a particular scaffold, as a wide variety of electrophilic coupling partners are readily available. As a result, this chapter aims to emphasize the importance of devising new synthetic methods for azabicycle construction and how Pd-catalysis can provide a straightforward and efficient means to these scaffolds.

1.2 Azabicycles in Natural Products and Biologically Active Targets

In general azabicycles contain either fused or bridging frameworks, with the nitrogen atom being located at or near the bridgehead. For example, azabicyclic frameworks that have the nitrogen atom removed from the bridgehead include

pharmaceuticals sedapain, an opioid analgesic, and sumatriptan (Imitrex®) a 5-HT_{1B/1D} agonist used for the treatment of migraines (Figure 1.1).² Conversely, the nitrogen atom positioned at the bridgehead is displayed in numerous natural products and biologically active molecules including natural product stemonine³ and marketed antiemetic granisetron (Kytril®).

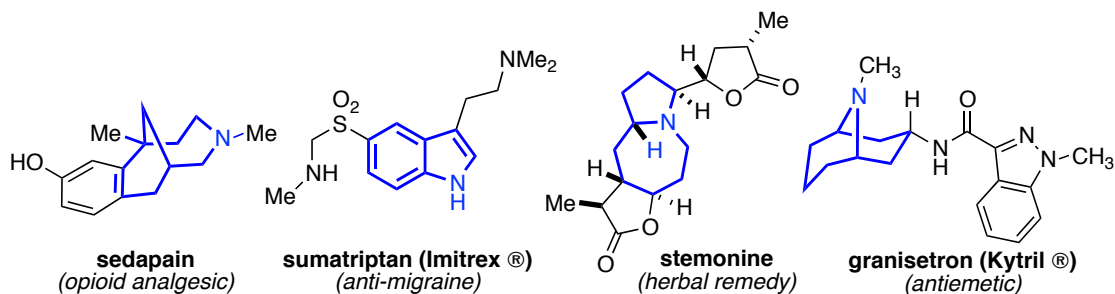


Figure 1.1 Presence of azabicycles in both pharmaceuticals and biologically active natural products

However, some of the most well studied fused and bridging azabicycles include the pyrrolizidine,⁴ indolizidine,⁵ and tropane alkaloids,⁶ due to their abundance in nature and desirable biological activities. Pyrrolizidine and indolizidine alkaloids are present in a myriad of natural sources including frogs and beetles, in addition to a wide variety of plant and fungi including red clover and orchids.⁷ Characteristic to pyrrolizidines is the presence of a fused 1-azabicyclo[3.3.0]octane ring system, which can be readily observed in mitomycin C⁸ and indicine *N*-oxide,⁹ both alkaloid natural products with potent antitumor activity (Figure 1.2). Likewise, biologically active indolizidine alkaloids (+)-antofine¹⁰ and (+)-gephyrotoxin¹¹ possess a slightly expanded 1-azabicyclo[4.3.0]nonane framework (Figure 1.2).

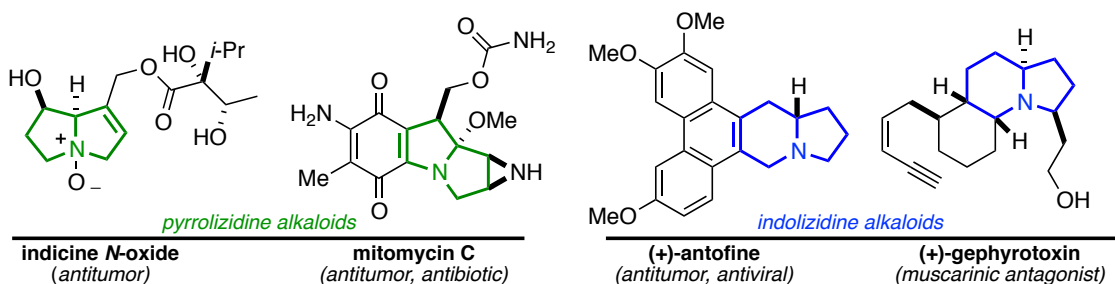


Figure 1.2 Biologically significant pyrrolizidine and indolizidine natural products

In turn, tropanes contain a bridging azabicyclo[4.3.1]octane scaffold, which can be found in numerous pharmaceuticals and biologically active natural products.⁶ In general, naturally occurring tropanes have been studied extensively as potential therapeutic targets due to their inhibition of acetylcholine or dopamine receptors. For instance, ipratropium bromide (Atrovent®)¹² is a marketed drug used to treat asthma and MK-801¹³ is a potential drug candidate with anticonvulsant properties (Figure 1.3). In addition, scopolamine is a natural product derived from nightshade that has been used for the treatment of nausea.¹⁴

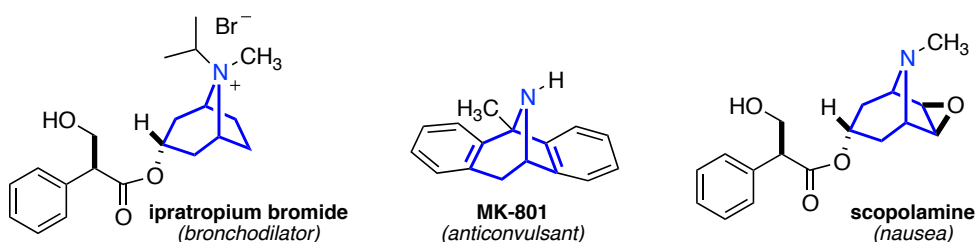


Figure 1.3 Tropane scaffold displayed in biologically active molecules

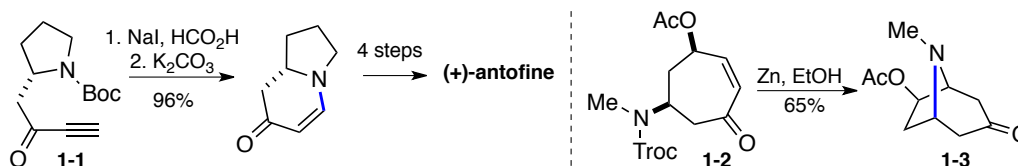
To aid in the exploration of the diverse biological activities that are exhibited by both fused and bridging azabicyclic molecules, there have been numerous synthetic methodologies developed to facilitate the construction of these units.¹⁵ In particular, there has been significant effort towards devising straightforward and efficient methods for the synthesis of pyrrolizidine, indolizidine, and tropane frameworks, as these frameworks are displayed in some of the most biologically active and naturally occurring molecules. To provide context for the research described in this dissertation the remainder of this chapter will focus on existing methods used for the preparation of pyrrolizidine, indolizidine, and tropane frameworks, with emphasis on methods that effect ring closure through both non-catalyzed or catalyst-mediated C-C and C-N bond forming reactions.

1.3 Non-Catalyzed Construction of Azabicyclic Framework

As previously mentioned, the array of biological activities that pyrrolizidine, indolizidine and tropane alkaloids possess have made them interesting targets to study and has resulted in the development of a myriad of transformations to

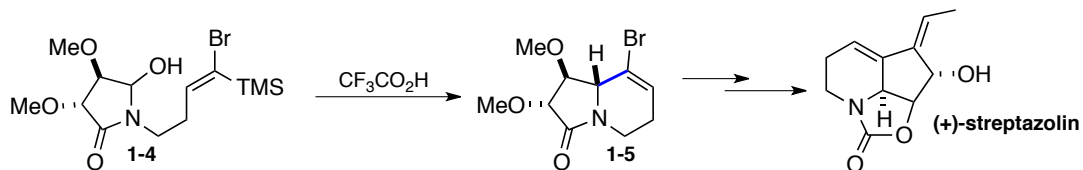
effect their synthesis.^{5a, 6, 16} Common to many of these methods is the formation of the azabicyclic scaffold, which typically occurs through either nucleophilic addition or alkylation reactions of pyrrolidines, *N*-acyliminium ion addition reactions or [3+2] cycloaddition reactions.

Intramolecular Michael addition reactions, with nitrogen nucleophiles, represent one of the most common and established means of arriving at fused and bridging azabicyclic scaffolds. For example, the synthesis of indolizidine antiviral (+)-antofine was accomplished through an intramolecular Michael addition of substrate **1-1** with sodium iodide and potassium carbonate (Scheme 1.1).¹⁷ Similarly, an intramolecular Michael addition of **1-2** was effective for the synthesis of dihydroxytropene **1-3** through the Zn-mediated deprotection and subsequent transannular addition of nitrogen to the enone.¹⁸



Scheme 1.1 Intramolecular Michael addition for azabicycle synthesis

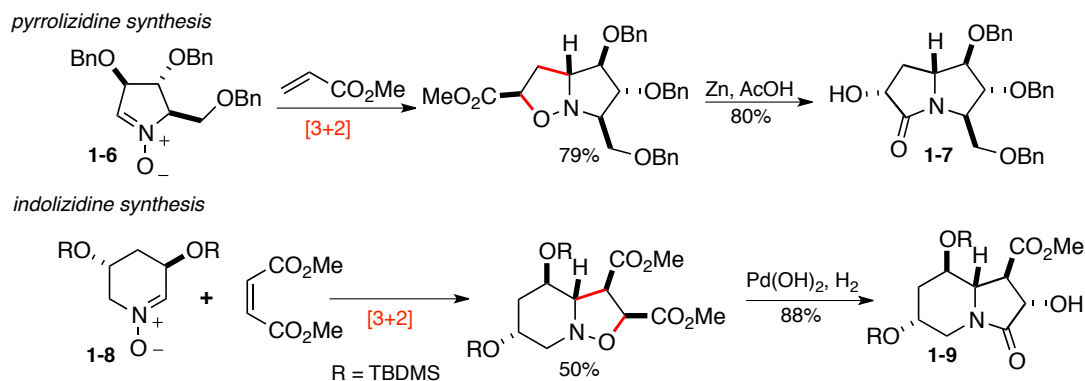
Another traditional route to pyrrolizidine and indolizidine scaffolds is through addition reactions to *N*-acyliminium ions.¹⁹ In general these reactions proceed through the acid-mediated *in situ* formation of an *N*-acyliminium ion that then undergoes nucleophilic addition with an electron rich alkene. For example, Overman and coworkers accomplished the total synthesis of natural antibiotic (+)-streptazolin via an intramolecular *N*-acyliminium ion addition reaction of **1-4** with a tethered vinyl silane to afford indolizidine intermediate **1-5** (Scheme 1.2).²⁰



Scheme 1.2 Intramolecular *N*-acyliminium ion addition for indolizidine synthesis

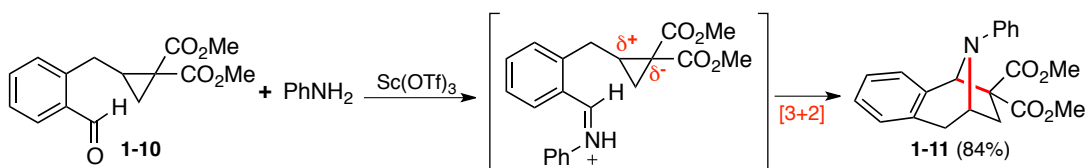
Cycloaddition reactions also represent an attractive approach for accessing azabicyclic frameworks, as several bonds and stereocenters can be generated in a single step during ring formation. For example, the synthesis of functionalized

pyrrolizidine **1-7** and indolizidine **1-9** was achieved through intermolecular [3+2] nitronc cycloaddition reactions of a dienophile with either nitronc substrates **1-6** or **1-8** (Scheme 1.3).²¹



Scheme 1.3 Examples of intermolecular [3+2] nitronc cycloaddition reactions for indolizidine and pyrrolizidine synthesis

In addition, it has been recently demonstrated that tropane scaffold **1-11** can be accessed through a Lewis acid-catalyzed intramolecular [3+2] cycloaddition reaction of cyclopropane substrate **1-10** with an *in situ* generated imine (Scheme 1.4).²² However, despite the synthetic utility of cycloaddition methods shown in Schemes 1.3 and 1.4, they employ complex starting materials and, in the case of nitronc cycloaddition reactions, require further synthetic transformation to attain the desired azabicyclic.



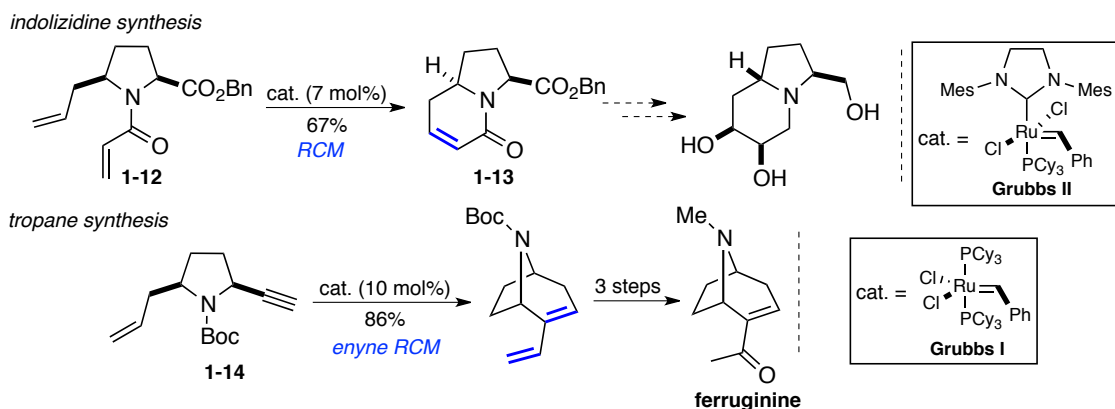
Scheme 1.4 Lewis acid-catalyzed [3+2] cycloaddition for tropane synthesis

1.4 Transition Metal-Catalyzed Synthesis of Azabicycles via Alkene/Alkyne Functionalization Reactions

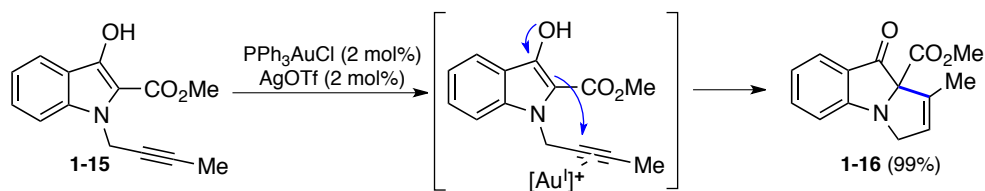
Transition metal catalysis has proven to be an attractive alternative to constructing azabicyclic frameworks by mediating non-traditional bond-forming events using normally unreactive alkene and alkynes as substrates. Common to these reactions is the chemoselective activation of alkenes/alkynes with the metal catalyst, which allows simple and readily accessible substrates to be

transformed into elaborate heterocycles. Although numerous transition metal catalyzed reactions have been developed for diverse pyrrolizidine, indolizidine, and tropane synthesis, the most commonly encountered methodologies employ ruthenium, gold, or nickel catalysts.

The development of ruthenium-catalyzed ring-closing metathesis (RCM) has dramatically altered how azabicyclic scaffolds are constructed, and has provided a unique and straightforward approach for synthesizing pyrrolizidine, indolizidine, and tropane frameworks.²³ Typical of these transformations is the use of a Grubbs'-type catalyst that allows diverse diene-containing substrates to undergo facile and selective intramolecular metathesis to afford cyclic products. For instance, the synthesis of indolizidine **1-13**, which is the core of several biologically active polyhydroxylated indolizidine alkaloids, was accomplished through the cyclization of diene **1-12** with Grubbs' second-generation catalyst (Scheme 1.5).²⁴ Moreover, RCM provided an efficient route to tropane-containing natural product ferruginine through the enyne ring-closing of *cis*-2,5-disubstituted pyrrolidine **1-14** with Grubbs' first-generation catalyst (Scheme 1.5).²⁵

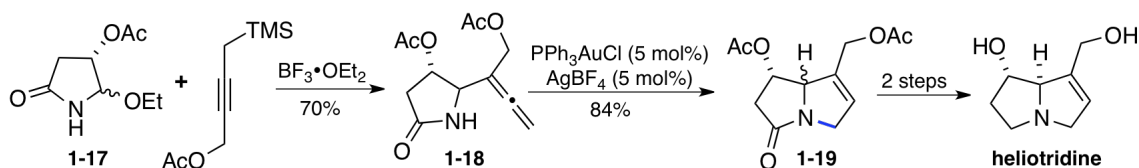


Recently, Au-catalysis has emerged as a viable approach for constructing azabicyclic frameworks through the selective activation of alkynes.²⁶ For example, Toste and coworkers were able to show that a Au(I)-phosphine catalyst facilitated the cyclization of alkyne substrate **1-15** to benzo-fused pyrrolizidine **1-16** (Scheme 1.6).²⁷



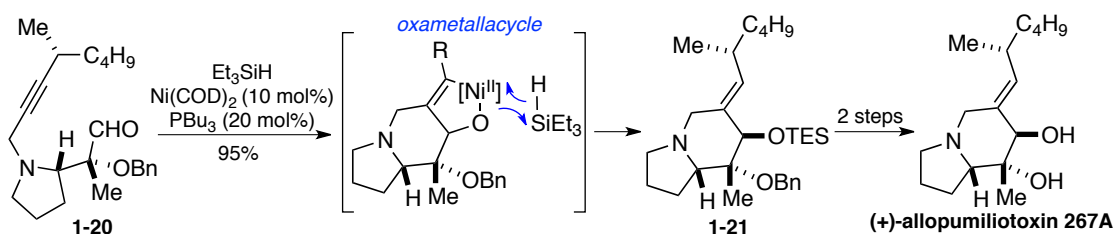
Scheme 1.6 Au(I)-catalyzed synthesis of benzo-fused pyrrolizidines

In addition, an approach that utilizes both *N*-acyliminium ion addition and Au-catalysis was employed for the synthesis of pyrrolizidine heliotridine (Scheme 1.7). This two-step transformation begins with **1-17** undergoing acid-mediated ionization and propargylsilane addition to yield allenyl lactam **1-18**. Allene intermediate **1-18** then serves as the substrate for Au-catalysis, undergoing selective allene activation and cyclization to heliotridine precursor **1-19**.²⁸



Scheme 1.7 Pyrrolizidine synthesis via Au(I)-catalyzed allene functionalization

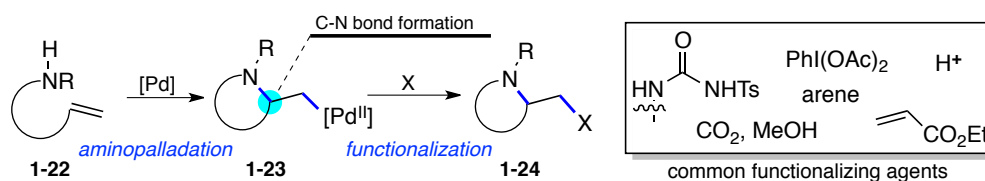
Another transition metal catalyzed transformation for fused azabicyclic synthesis are Ni-catalyzed reductive cyclization reactions of ynals.²⁹ These reactions proceed with high stereoselectivity due to the formation of highly organized oxametallacycles, which undergo facile reduction with triethylsilane to afford diverse pyrrolizidine and indolizidine products. The utility of this method was demonstrated in Montgomery's total synthesis of indolizidine alkaloid allopumiliotoxin 267A, which proceeded through the stereoselective reductive cyclization of **1-20** to **1-21** followed by two subsequent protecting group manipulations (Scheme 1.8).³⁰



Scheme 1.8 Synthesis of indolizidine alkaloid (+)-allopumiliotoxin 267A via Ni-catalysis

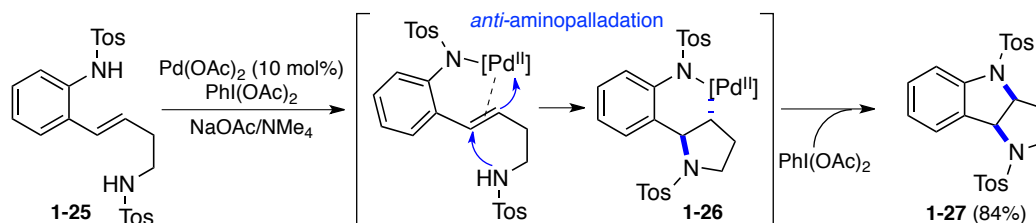
1.5 Palladium-Catalyzed Alkene Difunctionalization Reactions for *N*-Heterocycle Synthesis

Common to the aforementioned metal-catalyzed transformations is the construction of the azabicyclic framework through C-C bond formation, requiring the configuration of stereocenters adjacent to the nitrogen atom to be established prior to cyclization. In turn, Pd-catalyzed alkene difunctionalization reactions provide a complimentary approach to azabicyclic synthesis by effecting ring closure through the formation of both a C-N bond and a C-X bond.³¹ In general these reactions proceed through the aminopalladation of aminoalkene substrate **1-22** to Pd(II) intermediate **1-23**, generating a new C-N bond with concomitant ring closure (Scheme 1.9). Intermediate **1-23** can then be intercepted by a variety of reagents to afford functionalized heterocyclic product **1-24**.



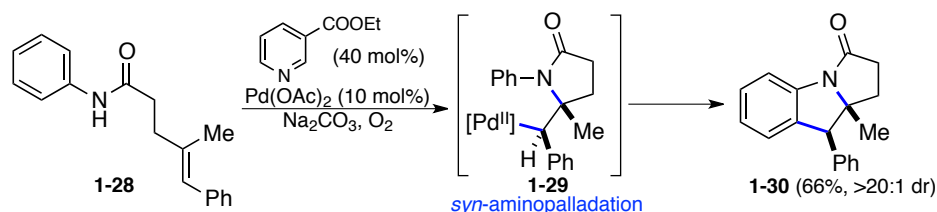
Scheme 1.9 General scheme for Pd-catalyzed alkene difunctionalization reactions

The stereochemical outcome of the aminopalladation step is dependent upon the reaction conditions employed and can occur through either *anti*- or *syn*-addition of the amine across the alkene.³² An example of an *anti*-aminopalladation process can be seen in the diastereoselective Pd-catalyzed diamination reaction of amine **1-25** to bisindoline **1-27** (Scheme 1.10).³³ Formation of **1-27** is the result of initial *anti*-aminopalladation of **1-25** to Pd(II) chelate **1-26**. Intermediate **1-26** is then oxidized to Pd(IV) via $\text{PhI}(\text{OAc})_2$ before undergoing reductive depalladation to bisindoline **1-27**.



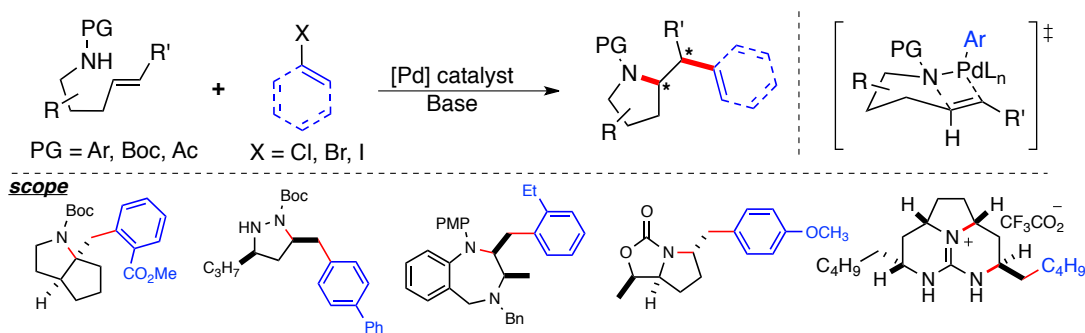
Scheme 1.10 Construction of bisindoline scaffold via an *anti*-aminopalladation process

In contrast, Yang and coworkers have recently devised a *syn*-aminopalladation methodology that allows for the stereocontrolled synthesis of pyrrolizidine scaffolds.³⁴ These intramolecular amidoarylation reactions proceed through initial *syn*-aminopalladation of substrate **1-28** to **1-29**, this intermediate then undergoes intramolecular C-H activation and reductive elimination to afford pyrrolizidine **1-30** (Scheme 1.11). Although this transformation allows both C-N and C-C bond formation, derivatization of the product must occur during substrate synthesis as the aryl coupling partner is tethered to the substrate.



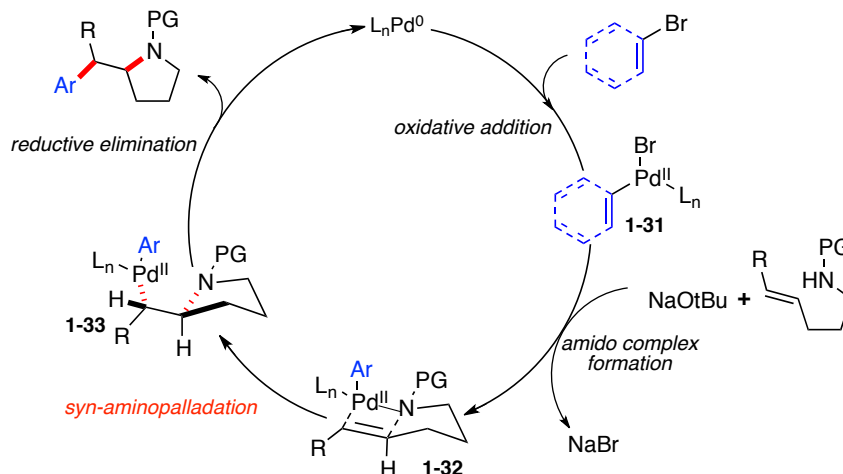
Scheme 1.11 Benzo-fused pyrrolizidines via Pd-catalyzed oxidative amidoarylation

In recent years, the Wolfe lab has developed a series of Pd-catalyzed alkene aminoarylation reactions for the synthesis of a variety of *N*-heterocycles including polycyclic guanidines,³⁵ pyrazolidines,³⁶ and benzodiazepines³⁷ (Scheme 1.12). Unique to these transformations is the cross-coupling of simple aminoalkene substrates with aryl or alkenyl halides, generating the heterocyclic ring through the formation of a C–N bond and C–C bond with good to excellent stereocontrol.³⁸ More importantly, these methods are quite useful for generating analogs of a particular scaffold, as a wide variety of aryl electrophiles are readily available.



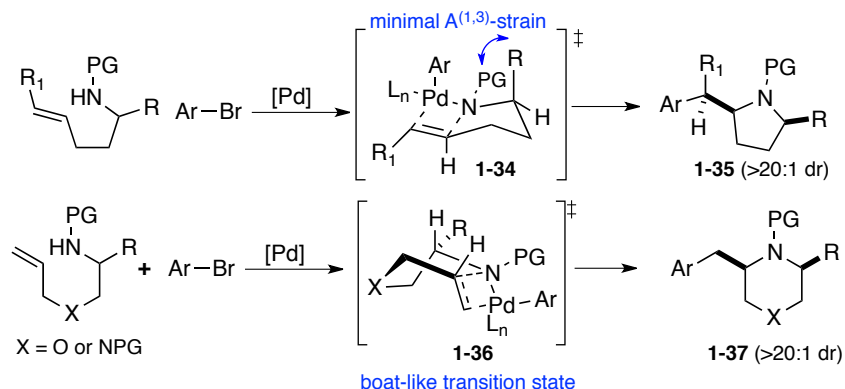
Scheme 1.12 General scheme of Pd-catalyzed alkene *syn*-aminoarylation methodology with representative *N*-heterocyclic products

The Pd-catalyzed alkene aminoarylation reactions have been shown to proceed via the catalytic cycle illustrated in Scheme 1.13. These transformations are initiated by oxidative addition of the aryl bromide to Pd(0) to afford **1-31**, which is converted to the key intermediate palladium(aryl)amido complex **1-32** via reaction with the amine substrate and base. Complex **1-32** undergoes intramolecular *syn*-migratory insertion of the alkene into the Pd–N bond (*syn*-aminopalladation) to yield **1-33**.³⁹ The pyrrolidine product is then generated by C–C bond-forming reductive elimination from **1-33**.



Scheme 1.13 Proposed catalytic cycle for Pd-catalyzed alkene aminoarylation reactions

The stereochemical outcome of these reactions is substrate controlled, and is determined during the alkene *syn*-aminopalladation event. As shown in Scheme 1.14, the selective synthesis of *cis*-2,5-disubstituted 5-membered heterocycles **1-35** proceed by way of transition state **1-34**, where axial orientation of the R-group minimizes A^(1,3)-strain with the nitrogen protecting group.^{38a} Likewise, the high diastereoselectivities (>20:1 dr) observed in the formation of *cis*-disubstituted morpholines and piperazines **1-37** are believed to be the result of *syn*-aminopalladation via boat-like transition state **1-36**.⁴⁰



Scheme 1.14 Stereochemical models for observed diastereoselectivity in the Pd-catalyzed construction of 5- and 6-membered *N*-heterocycles

1.6 Limitations in Palladium-Catalyzed Alkene Aminoarylation Reactions for *N*-Heterocycle Synthesis

Despite the demonstrated utility of Pd-catalyzed alkene aminoarylation reactions for diverse *N*-heterocycle synthesis, there have only been a handful of accounts that have employed this valuable reactivity for azabicyclo construction. Specifically, the application of this method towards the construction of fused *N*-heterocycles remains limited,^{38a, 41} and to the best of our knowledge has not been applied towards the synthesis of bridging azabicycles. As previously discussed, the development of new methodologies for fused and bridging azabicyclo construction are especially important since a variety of pharmaceuticals and biologically active natural products possess these scaffolds.

As a result, the work outlined in chapters 2 and 3 of this dissertation details our efforts towards expanding the scope of the Pd-catalyzed alkene aminoarylation reactions towards the synthesis of pyrrolizidine, indolizidine, and tropane scaffolds. In chapter 2 we discuss our approach towards fused *N*-heterocycle synthesis through the development of an aminopalladation/carbopalladation reaction cascade. This Pd-catalyzed cascade reaction forms 3 bonds and 2 stereocenters in a single step through the Pd-mediated construction of the bicyclic framework. In turn, chapter 3 details our approach towards the synthesis of bridging tropane scaffolds through the development of an intramolecular Pd-catalyzed alkene aminoarylation reaction.

In the end, the new transformations described in chapters 2 and 3 will likely find applications in the synthesis of new biologically active compounds in both academic and industrial labs. In addition, the developed reactions will provide novel strategy level disconnections that could furnish natural products and pharmaceutically relevant targets in a more straightforward manner. Lastly, these studies illustrate several new concepts in Pd-catalysis that may aid in the development of new useful organometallic reactions for heterocycle synthesis.

1.7 References

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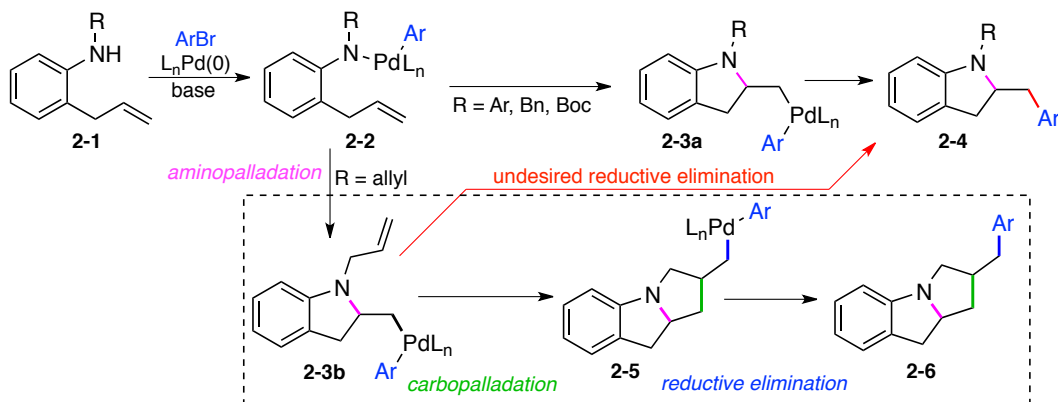
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Chapter 2

Synthesis of Polycyclic Nitrogen Heterocycles via Alkene Aminopalladation/Carbopalladation Cascade Reactions

2.1 Introduction

Over the past several years, our group has developed a method for the construction of nitrogen heterocycles via Pd-catalyzed carboamination reactions between aryl bromides and amines bearing pendant alkenes.¹ For example, treatment of an *N*-substituted 2-allylaniline derivative (e.g., **2-1**) with an aryl bromide in the presence of NaO^tBu and a palladium catalyst leads to the formation of 2-benzylindoline product **2-4**.² These reactions proceed via intramolecular alkene aminopalladation of palladium(aryl)(amido) complex **2-2** to yield **2-3a**, which undergoes reductive elimination to give **2-4** (Scheme 2.1).

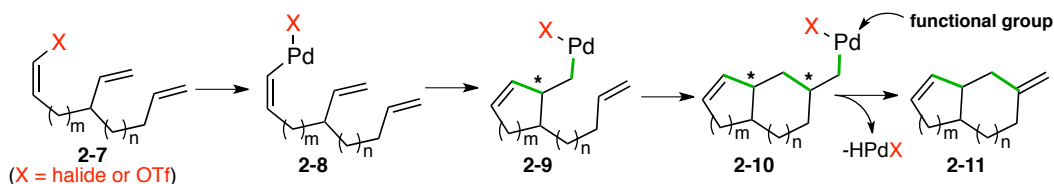


Scheme 2.1 Cascade aminopalladation/carbopalladation sequence

It seemed plausible that this method could be extended to cascade cyclization processes that yield tricyclic products if an intermediate related to **2-3a** could be intercepted with a pendant alkene. For example, if *N*,2-diallylaniline were employed as a substrate, alkene aminopalladation of **2-2** (R = allyl) would yield **2-**

3b, which could undergo intramolecular carbopalladation to give **2-5**. Reductive elimination would then yield **2-6**. Overall, this transformation would generate three bonds, two rings, and two stereocenters in a single step from a simple starting material. Importantly, this method would provide a new means to access benzo-fused 1-azabicyclo[3.3.0]octanes (**2-6**) and related 1-azabicyclo[4.3.0]nonanes. These scaffolds are a prominent feature of several natural products³ and have also served as key intermediates in the synthesis of analogous fully saturated ring systems.⁴

The approach outlined in Scheme 2.1 sharply contrasts with related Pd-catalyzed cascade Heck reactions between polyalkene substrates (**2-7**) bearing pendant alkenyl (or aryl) halides (Scheme 2.2).⁵ The Heck cascades occur through sequential intramolecular alkene carbopalladation reactions of R-Pd-X intermediates such as **2-8** or **2-9** (X = halide or pseudohalide) and are usually terminated by β -hydride elimination from the final R-Pd-X species (**2-10**) to generate an alkene (**2-11**). Thus, elements of molecular complexity present in **2-10** are removed in the terminal step, as the β -elimination leads to loss of a stereocenter and an organometallic functional group. In comparison, the final step of the aminopalladation/carbopalladation cascade shown in Scheme 2.1 (reductive elimination from **2-5** to yield **2-6**) would produce a C-Ar bond, and the stereocenters generated in each alkene insertion step would be retained in the product.⁶



Scheme 2.2 Comparison to cascade alkene carbopalladation

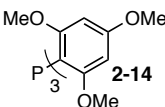
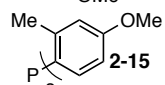
2.2 Optimization of Aminopalladation/Carbopalladation Sequence

Although the cascade aminopalladation/carbopalladation sequence could have considerable utility, to achieve our desired transformation, we would need to overcome a significant obstacle that is not present in the cascade Heck reactions. The key intermediates in the Heck cascades (**2-8** and **2-9**) contain only

a single C-Pd bond. Thus, premature termination of the cascade via competing reductive elimination from **2-8** or **2-9** cannot occur, as C-X bond forming reductive elimination from Pd(II) is thermodynamically unfavorable.⁷ In contrast, intermediate **2-3b** contains two Pd-C bonds that can potentially undergo competing irreversible C-C bond-forming reductive elimination to afford undesired monocyclized product **2-4**. In addition, the catalyst employed for the cascade cyclization must not only favor alkene insertion over reductive elimination from **2-3b** but also allow the requisite reductive elimination from **2-5** to proceed.

In our initial experiments, we sought to find a catalyst that would facilitate the desired cascade reaction. To this end, we examined the coupling of **2-1** (R = allyl) with bromobenzene using catalysts generated *in situ* from mixtures of palladium acetate and phosphine ligands (Table 2.1). As anticipated, these reactions afforded two major products: **2-12** and **2-13**. After some exploration, we discovered that bulky triaryl phosphines **2-14** and **2-15** provided **2-12** in acceptable chemical yields and diastereoselectivities.

Table 2.1 Optimization studies^a

entry	ligand	2-12:2-13	dr 2-12	yield of 2-12(%) ^b
1	DPEphos	2:1	1:1	24%
2	dppf	2:1	2:1	34%
3	nixantphos	0:100	--	--
4	P(<i>o</i> -tol) ₃	3:1	4:1	59%
5	PCy ₃ •HBF ₄	2:1	2:1	20%
6		6:1	3:1	68%
7		5:1	5:1	60% (50%) ^c

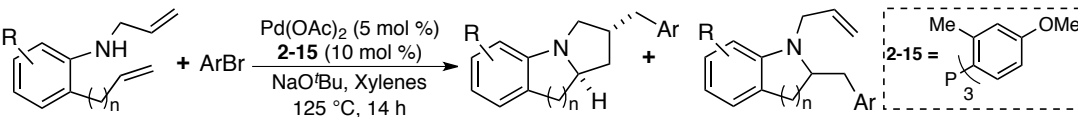
^a Conditions: Reactions were conducted using 1.0 equiv **2-12**, 1.5 equiv PhBr, 1.5 equiv NaO^tBu, xylenes (0.2 M), 125 °C, 14 h. ^b Yields were determined by ¹H NMR analysis of crude reaction mixtures that contained phenanthrene as an internal standard. The mass balance of these reaction mixtures was composed of products resulting from β-hydride elimination of intermediate **2-3b** or **2-5**. ^c Isolated yield

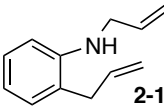
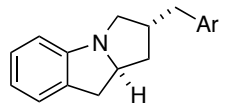
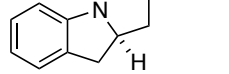
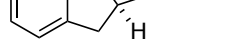
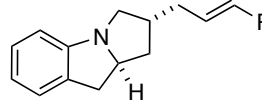
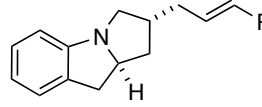
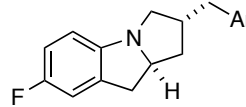
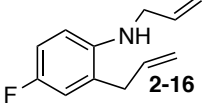
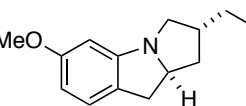
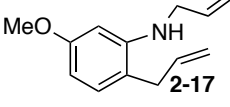
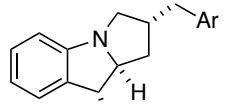
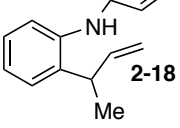
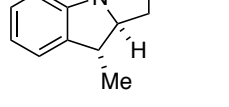
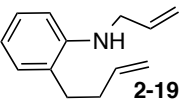
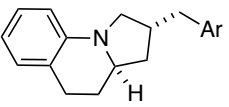
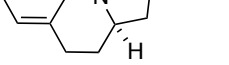
2.3 Exploration of Scope

Having discovered a viable catalyst system for the cascade cyclization reaction of **2-1**, we proceeded to examine analogous transformations of related substrates. As illustrated in Table 2.2, a number of *N*,2-diallylaniline derivatives

(**2-1**, **2-16** and **2-17**) were converted to benzo-fused-1-azabicyclo[3.3.0]octanes **2-20** to **2-25** in moderate yields and with moderate to good diastereoselectivities. Substitution at the benzylic position was tolerated, as illustrated by the conversion of **2-18** to **2-26** and **2-27**. The conversion of *N*-allyl-2-(but-3-enyl)aniline (**2-19**) to benzo-fused-1-azabicyclo[4.3.0]nonanes **2-28** and **2-29** was also achieved with moderate to good yields and selectivities. However, efforts to transform substrates bearing disubstituted alkenes have been unsuccessful. In addition, the coupling of 2-bromotoluene with **2-1** afforded monocyclic *N*-allyl-2-(2-methylbenzyl)indoline (**2-4**, Ar = 2-methylphenyl) as the major product, which was isolated in 72% yield. Only a small amount of the desired bicyclic compound was generated in this reaction.

Table 2.2 Scope of Pd-catalyzed cascade reactions^a

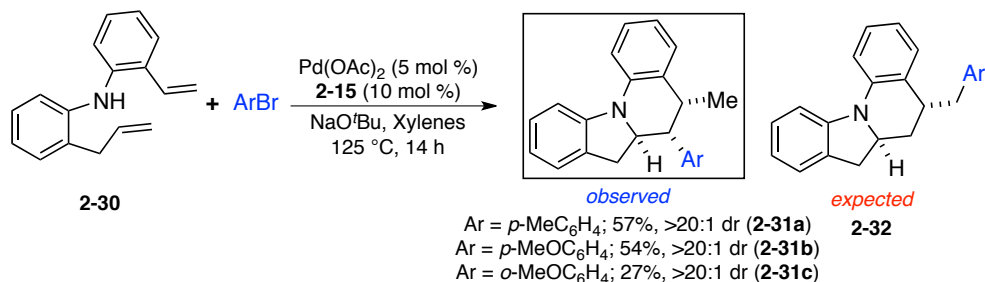


substrate	product	Ar	bicyclic: monocyclic ^b	dr ^c	yield ^d
		2-20 <i>p</i> -CF ₃ Ph	10:1	>20:1 (5:1)	46%
		2-21 <i>p</i> -MePh	3:1	10:1 (10:1)	66%
		2-22 <i>p</i> -MeOPh	5:1	13:1 (5:1)	53%
		2-23 <i>p</i> -MeOPh	2:1	3:1 (3:1)	42%
		2-24 <i>p</i> -(Me ₂ N)Ph	2:1	7:1 (3:1)	58%
		2-25 <i>p</i> -MePh	2:1	10:1 (5:1)	57%
		2-26 Ph	7:1	18:1 (7:1)	67%
		2-27 <i>p</i> -PhC(O)Ph	7:1	>20:1 (10:1)	68%
			2-28 Ph	5:1	3:1 (3:1)
		2-29 <i>p</i> -MeOPh	5:1	3:1 (3:1)	47%

^a Conditions: Reactions were conducted on a 0.3-0.5 mmol scale using 1.0 equiv substrate, 1.5 equiv ArBr, 1.5 equiv NaOtBu, xylenes (0.4 M), 125 °C, 14 h. ^b Ratio of bicyclic product:monocyclic product observed in crude reaction mixtures. ^c Diastereomeric ratios are for isolated material. Numbers in parentheses represent diastereomeric ratios observed in crude reaction mixtures. In some instances the minor diastereomer was partially or entirely removed during isolation. ^d Isolated yield (average of 2 or more exps).

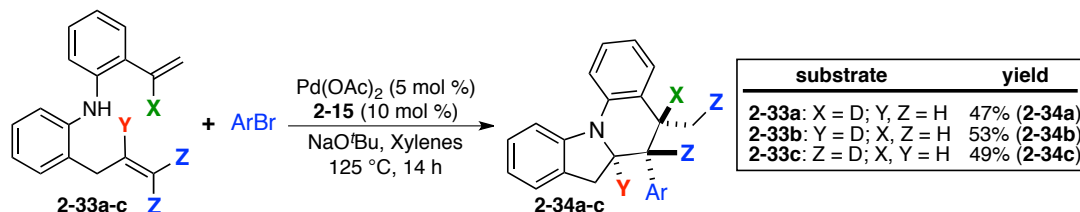
2.4 Observation of 1,3-Palladium Shift

Although most substrates examined afforded the anticipated products, reactions of **2-30** with aryl bromides provided surprising results (Scheme 2.3). The expected products **2-32a-c** were not obtained, but instead **2-31a-c** were generated in moderate yield and with excellent diastereoselectivity.



Scheme 2.3 Unexpected rearranged product from styrene-derived substrate **2-30**

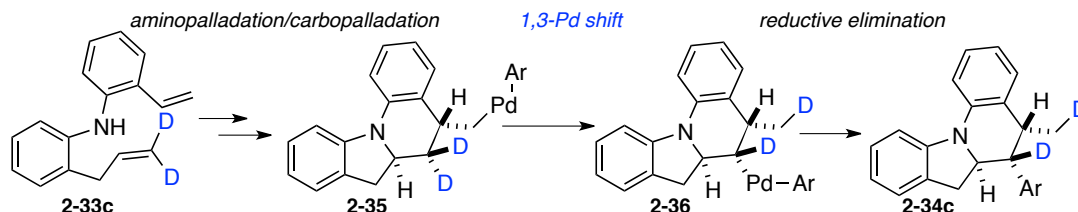
To probe the origin of this unexpected regioisomer, we conducted three experiments with deuterium-labeled substrates **2-33a-c**. As shown in Scheme 2.4, substrates **2-33a** and **2-33b** were converted to **2-34a** and **2-34b**, with no migration of the deuterium label observed in either case. In contrast, substrate **2-33c**, bearing deuterium atoms on the terminal carbon of the allyl group, was transformed to **2-34c** with migration of a deuterium atom to the C5-methyl group.



Scheme 2.4 Results of deuterium labeling studies with substrates **2-33a-c**

On the basis of this data, we suggest that formation of **2-34c** may proceed as illustrated in Scheme 2.5, with an initial aminopalladation/carbopalladation effecting the conversion of **2-33c** to key intermediate **2-35**. Next, a surprising and unprecedented 1,3-palladium/hydride shift would then yield **2-36**, which could undergo reductive elimination to afford **2-34c**. Although through-space palladium migrations have previously been observed,⁸ only a single report has described Pd-migration from one sp^3 -hybridized carbon to another.⁹ The conversion of **2-35**

to **2-36** is particularly surprising given the fact that **2-35** also contains hydrogen atoms that could potentially undergo β -elimination.



Scheme 2.5 Proposed mechanism for the formation of **2-34c**

2.5 Conclusions

In conclusion, we have developed a new cascade reaction for the synthesis of polycyclic nitrogen heterocycles that proceeds by way of sequential aminopalladation and carbopalladation. These transformations illustrate that catalyst tuning can allow alkene insertion processes to occur in preference to C-N or C-C bond-forming reductive elimination in $L_nPd(Ar)(NR_2)$ or $L_nPd(Ar)(R)$ complexes. In addition, we have observed the first occurrence of 1,3-palladium migration of an alkylpalladium intermediate. Studies on the scope of this method and the application of these concepts to the development of new catalytic reactions are underway.

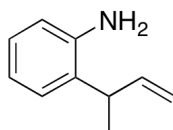
The work described in this chapter was published in *Organic Letters*.¹⁰

2.6 Experimental

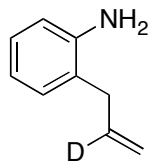
General: All reactions were carried out under an argon or nitrogen atmosphere in oven- or flame-dried glassware. All catalysts, reagents, and aryl bromides were obtained from commercial sources and were used without further purification. 2-Allylaniline and 4-methoxy-2-allylaniline were prepared according to published procedures.¹¹ Toluene, THF, ether, and dichloromethane were dried and purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY, HSQC, and NOESY experiments. Ratios of diastereomers were determined by 1H NMR and/or capillary GC analysis of crude reaction mixtures. Yields refer to isolated

yields of compounds estimated to be $\geq 95\%$ pure as determined by ^1H NMR, GC, and/or combustion analysis. The yields reported in the supporting information describe the result of a single experiment. Thus, the yields reported in the supporting information may differ from those shown in this Chapter.

Synthesis of Substrates

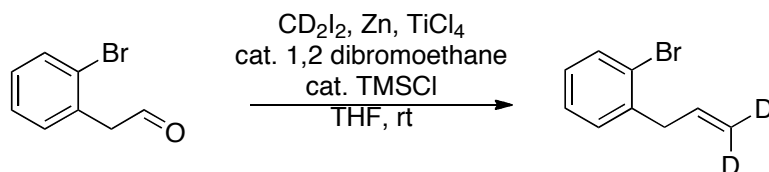


2-(But-3-en-2-yl)aniline (2-S1). A flame dried glass pressure tube equipped with a magnetic stirbar and a rubber septum was cooled under a stream of nitrogen and charged with a solution of *N*-(but-2-enyl)aniline¹² (1.37 g, 9.30 mmol) in xylenes (7.5 mL). The solution was cooled to 0 °C and $\text{BF}_3 \cdot \text{OEt}_2$ (1.62 mL, 13.9 mmol) was added slowly. The reaction mixture was warmed to rt and stirred for 15 min, then the tube was sealed with a Teflon screwcap stopper and placed in a 180 °C oil bath for 4 h. The mixture was then cooled to rt, the stopper was removed, and a solution of 1 M NaOH (10 mL) was added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (1 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography to afford 0.619 g (45%) of the title compound. ^1H NMR (300 MHz, CDCl_3) δ 7.08 (d, $J = 7.6$ Hz, 1 H), 7.03 (t, $J = 7.6$ Hz, 1 H), 6.76 (t, $J = 7.6$ Hz, 1 H), 6.65 (d, $J = 7.6$ Hz, 1 H), 5.96–5.88(m, 1 H), 5.08–5.03 (m, 2 H), 3.66 (s, br, 2 H), 3.45 (p, $J = 6.8$ Hz, 1 H), 1.37 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.3, 142.1, 128.8, 127.1, 127.0, 118.9, 116.2, 113.8, 38.2, 18.7; IR (film) 3448, 3366, 1621 cm^{-1} . MS (EI) 147.1050 (147.1048 calcd for $\text{C}_{10}\text{H}_{13}\text{N}$).



2-(2-Deuterioallyl)aniline (2-S2). The procedure described above for the aza-Claisen rearrangement of *N*-(but-2-enyl)aniline to **2-S1** was employed for the

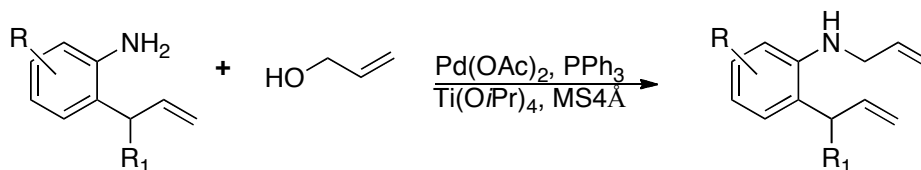
reaction of *N*-(2-deuterioallyl)aniline¹³ (541 mg, 4.0 mmol) with BF₃•OEt₂ (0.69 mL, 6.0 mmol) in 4 mL of xylenes. This procedure afforded 331 mg (62%) of the title compound as a yellow oil with 91% D incorporation. ¹H NMR (400 MHz, CDCl₃) δ 7.07–7.02 (m, 2 H), 6.73 (t, *J* = 11.2 Hz, 1 H), 6.66 (d, *J* = 7.6 Hz, 1 H), 5.11–5.08 (m, 2 H), 3.64 (s, br, 2 H), 3.29 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 144.7, 135.6 (t, *J* = 23.8 Hz), 130.1, 127.5, 123.9, 118.8, 115.9, 115.8, 36.3; IR (film) 3449, 3370, 1621 cm⁻¹. MS (EI) 134.0957 (134.0954 calcd for C₉H₁₀DN).



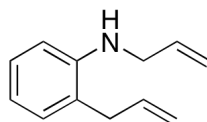
1-Bromo-2-(3,3-dideuterioallyl)benzene (2-S3). Zinc activation procedure:¹⁴ A flame dried round bottom flask equipped with a magnetic stirbar was charged with Zn¹⁵ (1.79 g, 27.5 mmol) and suspended in 30 ml of THF. Neat 1,2-dibromoethane (0.08 mL, 0.96 mmol) was added and the reaction mixture was heated to 60 °C for 2 min. The resulting mixture was cooled to room temperature, neat TMSCl (0.10 mL, 0.82 mmol) was added, and the stirring was continued for 15 min at rt.

Carbonyl methylenation procedure:¹⁶ Neat CD₂I₂ (4.1 g, 15.3 mmol) was added to the suspension of activated zinc, and the solution turned grey. The mixture was stirred at rt for 30 min, then TiCl₄ (0.42 mL, 3.82 mmol) was added to afford a brown reaction mixture. This mixture was stirred at rt for 30 min, then 2-(2-bromophenyl)acetaldehyde (761 mg, 3.82 mmol) was added. The mixture was stirred at rt for 20 min, at which time TLC analysis indicated the aldehyde had been completely consumed. Aqueous 3 M HCl (30 mL) was added and the mixture was transferred to a separatory funnel. The solution was extracted with ethyl acetate (3 x 30 mL), then the combined organic layers were washed with saturated aqueous NaHCO₃ (1 x 30 mL), and brine (1 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The crude product was purified by flash chromatography to afford 368 mg (48%) of the title compound as a yellow oil. ¹H NMR (400 MHz,

CDCl₃) δ 7.51 (d, *J* = 7.6 Hz, 1 H), 7.24–7.18 (m, 2 H), 7.06–7.02 (m, 1 H), 5.96–5.91 (m, 1 H), 3.48 (d, *J* = 6.8 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 139.4, 135.2, 132.7, 130.3, 127.7, 127.4, 124.5, 115.9 (p, *J* = 23.7 Hz), 40.0; IR (film) 3008, 1566, 1468, 1025 cm⁻¹. MS (EI) 198.0015 (198.0013 calcd for C₉H₇D₂Br).

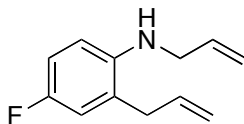


General Procedure 1: Pd-catalyzed synthesis of *N*-allylanilines.¹² A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with MS4Å (200 mg/mmol substrate), Pd(OAc)₂ (1 mol %), PPh₃ (4 mol %), Ti(O*i*Pr)₄ (25 mol %), the appropriate aniline derivative (1 equiv), allyl alcohol (1.2 equiv), and benzene (0.2 M). The resulting mixture was heated to 60 °C for 2–3.5 h until the starting material was consumed as judged by TLC analysis. The mixture was cooled to room temperature and quenched with 1 M NaOH (10–15 mL). The reaction mixture was transferred to a separatory funnel and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography.

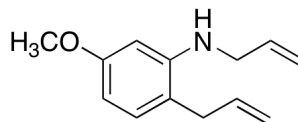


***N*,2-Diallylaniline (2-1).**¹⁷ General procedure 1 was employed for the alkylation of 2-allylaniline¹¹ (2.04 g, 15.3 mmol) with allyl alcohol (1.07 g, 18.4 mmol), Pd(OAc)₂ (34.3 mg, 0.15 mmol), PPh₃ (161 mg, 0.61 mmol), Ti(O*i*Pr)₄ (1.16 mL, 3.82 mmol), and MS4Å (3.06 g) in 76 mL of benzene. This procedure afforded 2.17 g (82%) of the title compound as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (t, *J* = 8.0 Hz, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 6.72 (t, *J* = 7.6 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 6.04–5.92 (m, 2 H), 5.28 (d, *J* = 10.8 Hz, 1 H), 5.20–5.10 (m, 3 H), 3.88 (s, br, 1 H), 3.81 (d, *J* = 7.2 Hz, 2 H), 3.32 (d, *J* = 6.0 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.1, 136.0, 135.4, 129.8, 127.6, 123.6,

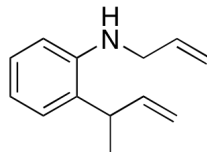
117.3, 116.3, 116.0, 110.8, 46.3, 36.5; IR (film) 3433, 1509 cm^{-1} . MS (ESI) 174.1285 (174.1283 calcd for $\text{C}_{12}\text{H}_{15}\text{N}$, $\text{M} + \text{H}^+$).



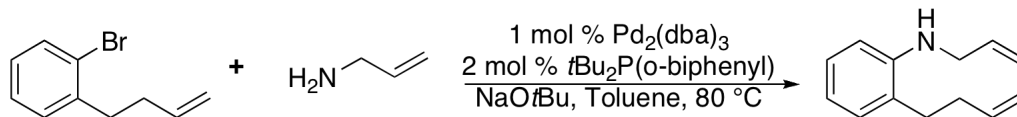
N,2-Diallyl-4-fluoroaniline (2-16). General procedure 1 was used for the alkylation of 2-allyl-4-fluoroaniline¹⁸ (960 mg, 6.3 mmol) with allyl alcohol (442 mg, 7.6 mmol), $\text{Pd}(\text{OAc})_2$ (14.1 mg, 0.063 mmol), PPh_3 (66.1 mg, 0.25 mmol), $\text{Ti}(\text{O}i\text{Pr})_4$ (0.48 mL, 1.58 mmol), and MS4\AA (1.26 g) in 30 mL of benzene. This procedure afforded 774 mg (64%) of the title compound as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 6.83–6.76 (m, 2 H), 6.51 (dd, $J = 4.4, 8.8$ Hz, 1 H), 5.97–5.84 (m, 2 H), 5.22 (d, $J = 15.6$ Hz, 1 H), 5.15–5.04 (m, 3 H), 3.72 (s, 2 H), 3.62 (s, br, 1 H), 3.23 (d, $J = 4.8$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.6 (d, $J = 234.8$ Hz), 142.2, 135.3, 135.1, 125.4 (d, $J = 6.9$ Hz), 116.8, 116.4 (d, $J = 22.2$ Hz), 116.1, 113.3 (d, $J = 21.8$ Hz), 111.5 (d, $J = 7.7$ Hz), 46.8, 36.2; IR (film) 3428, 3080, 1511 cm^{-1} . MS (EI) 191.1113 (191.1110 calcd for $\text{C}_{12}\text{H}_{14}\text{FN}$).



N,2-Diallyl-5-methoxyaniline (2-17). General procedure 1 was employed for the alkylation of 2-allyl-5-methoxyaniline¹¹ (700 mg, 4.3 mmol) with allyl alcohol (299 mg, 5.1 mmol), $\text{Pd}(\text{OAc})_2$ (9.6 mg, 0.043 mmol), PPh_3 (45.1 mg, 0.17 mmol), $\text{Ti}(\text{O}i\text{Pr})_4$ (0.33 mL, 1.07 mmol), and MS4\AA (860 mg) in 22 mL of benzene. This procedure afforded 705 mg (81%) of the title compound as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 6.95 (d, $J = 8.0$ Hz, 1 H), 6.25 (d, $J = 8.4$ Hz, 1 H), 6.22 (s, 1 H), 6.00–5.88 (m, 2 H), 5.27 (dd, $J = 2.4, 14.8$ Hz, 1 H), 5.17 (dd, $J = 1.6, 8.0$ Hz, 1 H), 5.12–5.07 (m, 2 H), 3.89 (s, br, 1 H), 3.78–3.75 (m, 5 H), 2.25 (d, $J = 6.4$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.7, 147.2, 136.5, 135.2, 130.3, 116.4, 116.1, 115.9, 101.1, 98.0, 55.1, 46.3, 35.9; IR (film) 3435, 3054, 1519 cm^{-1} . MS (EI) 203.1317 (203.1310 calcd for $\text{C}_{13}\text{H}_{17}\text{NO}$).

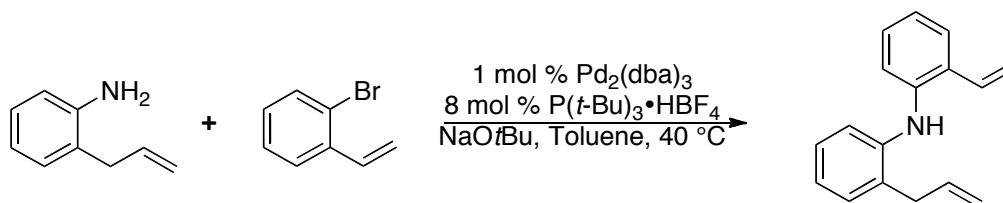


N-Allyl-2-(but-3-en-2-yl)aniline (2-18). General procedure 1 was used for the alkylation of **2-S1** (430 mg, 2.9 mmol) with allyl alcohol (203 mg, 3.5 mmol), Pd(OAc)₂ (6.5 mg, 0.029 mmol), PPh₃ (30.4 mg, 0.12 mmol), Ti(O*i*Pr)₄ (0.22 mL, 0.72 mmol), and MS4Å (580 mg) in 15 mL of benzene. This procedure afforded 469 mg (86%) of the title compound as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.14–7.09 (m, 2 H), 6.73 (t, *J* = 7.6 Hz, 1 H), 6.62 (d, *J* = 8.0 Hz, 1 H), 6.00–5.87 (m, 2 H), 5.25 (d, *J* = 17.2 Hz, 1 H), 5.16–5.04 (m, 3 H), 3.93 (s, br, 1 H), 3.76 (s, 2 H), 3.45 (p, *J* = 6.8 Hz, 1 H), 1.39 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 144.5, 142.3, 135.4, 128.4, 127.2, 126.7, 117.4, 116.0, 113.9, 111.2, 46.4, 37.9, 18.8; IR (film) 3430, 1508 cm⁻¹. MS (EI) 187.1370 (187.1361 calcd for C₁₃H₁₇N).

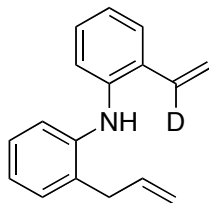


N-Allyl-2-(but-3-enyl)aniline (2-19).¹⁹ A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with Pd₂(dba)₃ (42.2 mg, 0.046 mmol), 2-(di-*tert*-butylphosphino)biphenyl (27.5 mg, 0.092 mmol), and sodium *tert*-butoxide (620 mg, 6.45 mmol). The tube was purged with nitrogen, then toluene (9 mL), 1-bromo-2-(but-3-enyl)benzene²⁰ (973 mg, 4.61 mmol), and allylamine (263 mg, 4.61 mmol) were added. The resulting mixture was heated to 80 °C for 14 h, at which time the starting material had been completely consumed as judged by TLC analysis. The mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (5 mL), and transferred to a separatory funnel. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 667 mg (84%) of the title compound as an orange oil. ¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, *J* =

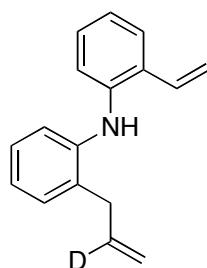
8.0 Hz, 1 H), 7.09 (d, $J = 7.6$ Hz, 1 H), 6.74 (t, $J = 7.6$ Hz, 1 H), 6.67 (d, $J = 8.4$ Hz, 1 H), 6.07–5.90 (m, 2 H), 5.33 (d, $J = 15.6$ Hz, 1 H), 5.22 (d, $J = 8.8$ Hz, 1 H), 5.13 (d, $J = 17.1$ Hz, 1 H), 5.05 (d, $J = 10.0$ Hz, 1 H), 3.84 (s, 2 H), 3.76 (s, 1 H), 2.62 (t, $J = 7.6$ Hz, 2 H), 2.45–2.40 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.4, 138.1, 135.5, 128.9, 127.1, 125.5, 117.2, 116.1, 115.0, 110.6, 46.5, 32.6, 30.6; IR (film) 3437, 3054, 1509 cm^{-1} . MS (EI) 187.1364 (187.1361 calcd for $\text{C}_{13}\text{H}_{17}\text{N}$).



2-Allyl-N-(2-vinylphenyl)aniline (2-30). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 2-allylaniline (1.50 g, 11.2 mmol), 2-bromostyrene (2.06 g, 11.2 mmol), sodium *tert*-butoxide (1.62 g, 16.9 mmol), $\text{Pd}_2(\text{dba})_3$ (103 mg, 0.11 mmol), $\text{P}(\text{tBu})_3\cdot\text{HBF}_4$ (261 mg, 0.90 mmol) and toluene (15 mL). The resulting mixture was heated to 40 °C for 14 h, at which time the starting material had been completely consumed as judged by TLC analysis. The mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (5 mL), and transferred to a separatory funnel. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 1.72 g (89%) of the title compound as light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 7.6$ Hz, 1 H), 7.22–7.15 (m, 3 H), 7.11–7.08 (m, 2 H), 7.01–6.93 (m, 2 H), 6.84 (dd, $J = 11.2, 17.2$ Hz, 1 H), 6.08–5.98 (m, 1 H), 5.71 (d, $J = 16.0$ Hz, 2 H), 5.32 (d, $J = 11.2$ Hz, 1 H), 5.21 (d, $J = 7.2$ Hz, 1 H), 5.15 (d, $J = 17.2$ Hz, 1 H), 3.43 (d, $J = 6.0$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.3, 140.8, 136.4, 132.8, 130.6, 129.0, 128.5, 128.3, 127.4, 127.2, 121.6, 121.3, 119.1, 118.2, 116.5, 116.2, 36.9; IR (film) 3422, 2961, 1459 cm^{-1} . MS (EI) 235.1352 (235.1361 calcd for $\text{C}_{17}\text{H}_{17}\text{N}$).

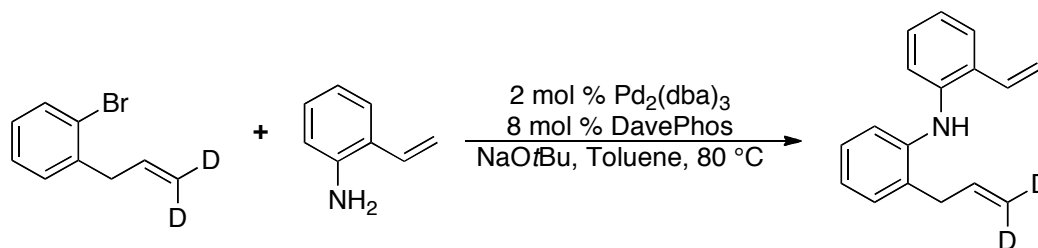


2-Allyl-N-[2-(1-deuteriovinyl)phenyl]aniline (2-33a). The procedure described above for the synthesis of **2-30** was employed for the coupling of α -D-*o*-bromostyrene²¹ (512 mg, 2.77 mmol) with 2-allylaniline (383 mg, 2.87 mmol), sodium *tert*-butoxide (413 mg, 4.31 mmol), Pd₂(dba)₃ (26.3 mg, 0.029 mmol), P(*t*Bu)₃·HBF₄ (66.6 mg, 0.23 mmol) and toluene (5 mL). The crude product was purified by flash chromatography to afford 494 mg (77%) of the title compound as a clear oil with 96% D incorporation. ¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, *J* = 7.6 Hz, 1 H), 7.19–7.12 (m, 3 H), 7.06 (t, *J* = 9.2 Hz, 2 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 6.92 (t, *J* = 7.2 Hz, 1 H), 5.99 (ddt, *J* = 5.9, 10.4, 16.4 Hz, 1 H), 5.66 (d, *J* = 3.4 Hz, 1 H), 5.64 (s, br, 1 H), 5.28 (s, 1 H), 5.18 (d, *J* = 9.9 Hz, 1 H), 5.12 (d, *J* = 17.2 Hz, 1 H), 3.40 (d, *J* = 5.9 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 142.3, 140.7, 136.4, 132.4 (t, *J* = 23.4 Hz), 130.6, 128.9, 128.6, 128.3, 127.4, 127.1, 121.7, 121.3, 119.1, 118.2, 116.5, 116.0, 36.9; IR (film) 3412, 3075, 1454 cm⁻¹. MS (EI) 236.1422 (236.1424 calcd for C₁₇H₁₆DN).



2-(2-Deuterioallyl)-N-(2-vinylphenyl)aniline (2-33b). The procedure described above for the synthesis of **2-30** was employed for the coupling of 2-bromostyrene (423 mg, 2.29 mmol) with **2-S2** (309 mg, 2.29 mmol), sodium *tert*-butoxide (330 mg, 3.43 mmol), Pd₂(dba)₃ (20.9 mg, 0.023 mmol), P(*t*Bu)₃·HBF₄ (53.1 mg, 0.18 mmol) and toluene (4 mL). The crude product was purified by flash chromatography to afford 400 mg (74%) of the title compound as a clear oil with 91% D incorporation. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 7.6 Hz, 1 H),

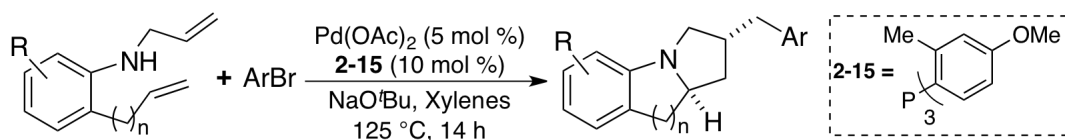
7.19–7.11 (m, 3 H), 7.06 (t, $J = 7.2$ Hz, 2 H), 6.97–6.89 (m, 2 H), 6.80 (dd, $J = 11.2, 17.6$ Hz, 1 H), 5.66 (dd, $J = 1.6, 17.2$ Hz, 1 H), 5.62 (s, 1 H), 5.28 (dd, $J = 1.2, 10.8$ Hz, 1 H), 5.16 (d, $J = 1.6$ Hz, 1 H), 5.10 (d, $J = 1.6$ Hz, 1 H), 3.39 (s, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.3, 140.7, 136.1 (t, $J = 23.7$ Hz), 132.8, 130.5, 129.0, 128.5, 128.3, 127.4, 127.2, 121.6, 121.3, 119.1, 118.3, 116.3, 116.2, 36.7; IR (film) 3411, 3073, 1455 cm^{-1} . MS (ESI) 237.1494 (237.1502 calcd for $\text{C}_{17}\text{H}_{16}\text{DN}$, $\text{M} + \text{H}^+$).



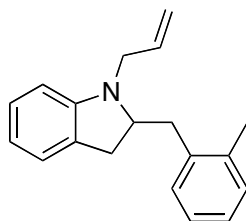
2-(3,3-Dideuterioallyl)-N-(2-vinylphenyl)aniline (2-33c). A flame-dried Schlenk tube equipped with a magnetic stirbar was cooled under a stream of nitrogen and charged with 2-vinylaniline (221 mg, 1.85 mmol), **2-S3** (368 mg, 1.85 mmol), sodium *tert*-butoxide (249 mg, 2.59 mmol), $\text{Pd}_2(\text{dba})_3$ (33.8 mg, 0.037 mmol), DavePhos (58.2 mg, 0.15 mmol) and 5 mL toluene (5 mL). The resulting mixture was heated to 80 °C for 1 h, at which time the starting material had been completely consumed as judged by TLC analysis. The mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (3 mL), and transferred to a separatory funnel. The mixture was extracted with EtOAc (3 x 10 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford 256 mg (58%) of the title compound (98% D incorporation) as a light yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.44 (d, $J = 7.5$ Hz, 1 H), 7.19–7.11 (m, 3 H), 7.06 (t, $J = 8.5$ Hz, 2 H), 6.95 (t, $J = 7.5$ Hz, 1 H), 6.91 (t, $J = 7.6$ Hz, 1 H), 6.79 (dd, $J = 10.5, 17.5$ Hz, 1 H), 5.97 (s, br, 1 H), 5.66 (dd, $J = 1.5, 17.5$ Hz, 1 H), 5.63 (s, br, 1 H), 5.27 (dd, $J = 1.5, 11.0$ Hz, 1 H), 3.39 (d, $J = 5.9$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.3, 140.7, 136.2, 132.7, 130.5, 129.0, 128.5, 128.3, 127.3, 127.1, 121.6, 121.3, 119.0, 118.2, 116.2, 36.8 (one carbon signal is absent due to

incidental equivalence); IR (film) 3412, 2924, 1456 cm^{-1} . MS (EI) 237.1488 (237.1487 calcd for $\text{C}_{17}\text{H}_{15}\text{D}_2\text{N}$).

Synthesis and Characterization of Heterocyclic Products

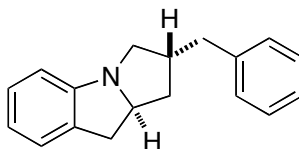


General Procedure 2: Synthesis of polycyclic nitrogen heterocycles via Pd-catalyzed cascade cyclization. A flame-dried Schlenk tube equipped with a magnetic stir bar was cooled under a stream of nitrogen and charged with $\text{Pd}(\text{OAc})_2$ (5 mol %), tri(*p*-methoxy-*o*-tolyl)phosphine (**2-15**)²² (10 mol %), and sodium *tert*-butoxide (1.5 equiv). The tube was purged with nitrogen, then a solution of amine substrate (1 equiv) and aryl halide (1.5 equiv) in xylenes (0.4 M substrate concentration) was added via syringe. The resulting mixture was heated to $125\text{ }^\circ\text{C}$ until the starting material had been consumed as judged by GC analysis (ca. 14 h). The mixture was cooled to room temperature, saturated aqueous ammonium chloride (3 mL) was added, and the resulting mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate (3 x 5 mL), the organic layers were combined, washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography.



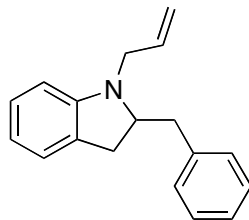
1-Allyl-2-(2-methylbenzyl)indoline (2-4, R = allyl). General procedure 2 was used for the reaction of **2-1** (40 mg, 0.23 mmol) with 2-bromotoluene (58 mg, 0.34 mmol), sodium *tert*-butoxide (33.2 mg, 0.34 mmol), $\text{Pd}(\text{OAc})_2$ (2.6 mg, 0.011 mmol), and ligand **2-15** (9.1 mg, 0.023 mmol) in xylenes (1 mL). The crude product was formed as a ca. 3:1 mixture of monocyclized to dicyclized products as judged by ^1H NMR analysis. Purification by flash chromatography afforded 44

mg (72%) of the monocyclized adduct as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.13–7.04 (m, 4 H), 6.96 (t, $J = 7.6$ Hz, 1 H), 6.91 (d, $J = 7.2$ Hz, 1 H), 6.55 (t, $J = 7.2$ Hz, 1 H), 6.39 (d, $J = 7.6$ Hz, 1 H), 5.85–5.78 (m, 1 H), 5.20 (dd, $J = 1.6$, 16.0 Hz, 1 H), 5.11 (dd, $J = 1.6$, 8.8 Hz, 1 H), 3.85 (dd, $J = 4.4$, 16.4 Hz, 1 H), 3.83–3.76 (m, 1 H), 3.60 (dd, $J = 7.2$, 16.4 Hz, 1 H), 3.14 (dd, $J = 4.4$, 13.2, 1 H), 2.84 (dd, $J = 8.4$, 15.6 Hz, 1 H), 2.66 (dd, $J = 8.8$, 16.0 Hz, 1 H), 2.61 (dd, $J = 9.2$, 13.2 Hz, 1 H), 2.25 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.9, 136.9, 136.2, 134.2, 130.3, 130.0, 128.6, 127.3, 126.4, 125.9, 124.2, 117.6, 117.1, 107.2, 64.0, 49.7, 37.5, 34.9, 19.7; IR (film) 3022, 2926, 1698, 1606, 1461, 1238, 1155, 919, 743 cm^{-1} . MS (ESI) 264.1756 (264.1752 calcd for $\text{C}_{19}\text{H}_{21}\text{N}$, $\text{M} + \text{H}^+$).

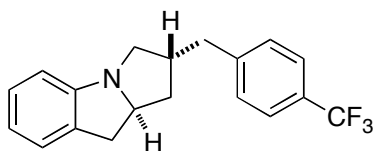


(2*R*,9*a*S)-2-Benzyl-2,3,9,9*a*-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (2-12).

General procedure 2 was used for the reaction of **2-1** (70 mg, 0.40 mmol) with bromobenzene (95 mg, 0.60 mmol), sodium *tert*-butoxide (57.6 mg, 0.60 mmol), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.020 mmol), and ligand **2-15** (15.8 mg, 0.040 mmol) in xylenes (1 mL). The crude product was formed as a 4:1 mixture of diastereomers with 5:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 51 mg (51%) of the title compound as a yellow oil with 14:1 dr. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.29–7.26 (m, 2 H), 7.20–7.15 (m, 3 H), 7.09–7.04 (m, 2 H), 6.73 (t, $J = 7.2$ Hz, 1 H), 6.57 (d, $J = 7.6$ Hz, 1 H), 4.17–4.10 (m, 1 H), 3.38 (dd, $J = 6.8$, 11.2 Hz, 1 H), 3.20 (dd, $J = 9.2$, 16.0 Hz, 1 H), 3.06 (dd, $J = 6.4$, 11.2 Hz, 1 H), 2.86 (dd, $J = 3.2$, 16.0 Hz, 1 H), 2.70 (d, $J = 7.6$ Hz, 2 H), 2.42–2.36 (m, 1 H), 1.74 (ddd, $J = 5.2$, 7.6, 12.8 Hz, 1 H), 1.55 (dt, $J = 7.9$, 16.0 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.2, 140.9, 130.3, 128.8, 128.4, 127.5, 125.9, 124.7, 119.5, 111.3, 63.5, 58.3, 40.2, 40.1, 37.7, 35.2; IR (film) 3023, 1602, 1479 cm^{-1} . MS (EI) 249.1513 (249.1518 calcd for $\text{C}_{18}\text{H}_{19}\text{N}$).



1-Allyl-2-benzylindoline (2-13). For purposes of characterization, monocyclized product **2-13** was isolated from the reaction of **2-1** (100 mg, 0.58 mmol) with bromobenzene (182 mg, 1.15 mmol), sodium *tert*-butoxide (83.6 mg, 0.87 mmol), Pd(OAc)₂ (6.5 mg, 0.029 mmol), in xylenes (2 mL) according to general procedure 2 except nixantphos (15.9 mg, 0.029 mmol) was used in place of ligand **2-15**. This procedure afforded the title compound (31 mg, 22 %) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.30 (t, *J* = 7.2 Hz, 2 H), 7.22–7.19 (m, 3 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 7.2 Hz, 1 H), 6.62 (t, *J* = 7.2 Hz, 1 H), 6.46 (d, *J* = 7.6 Hz, 1 H), 5.93–5.83 (m, 1 H), 5.29 (dd, *J* = 1.6, 17.2 Hz, 1 H), 5.20 (dd, *J* = 1.6, 10.4 Hz, 1 H), 3.94–3.82 (m, 2 H), 3.69 (dd, *J* = 7.6, 16.4 Hz, 1 H), 3.18 (dd, *J* = 4.0, 13.2 Hz, 1 H), 2.91 (dd, *J* = 8.4, 15.6 Hz, 1 H), 2.75–2.66 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 152.0, 138.7, 134.2, 129.2, 128.6, 128.4, 127.3, 126.2, 124.2, 117.5, 117.0, 107.1, 65.5, 49.7, 40.2, 34.8; IR (film) 3026, 2921, 1606, 1483, 1238 cm⁻¹. MS (ESI) 250.1599 (250.1596 calcd for C₁₈H₁₉N, M + H⁺).

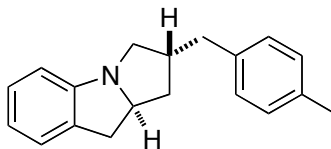


(2R,9aS)-2-[4-(Trifluoromethyl)benzyl]-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole (2-20). General procedure 2 was used for the reaction of **2-1** (50 mg, 0.29 mmol) with 4-bromobenzotrifluoride (97 mg, 0.43 mmol), sodium *tert*-butoxide (41.7 mg, 0.43 mmol), Pd(OAc)₂ (3.2 mg, 0.015 mmol), and ligand **2-15** (11.4 mg, 0.029 mmol) in xylenes (1 mL). The crude product was formed as a 5:1 mixture of diastereomers with 10:1 selectivity for dicyclization:monocyclization as judged by ¹H NMR analysis. Purification by flash chromatography afforded 45 mg

(46%) of the title compound as a red oil with >20:1 dr. In addition, a small amount of the minor (*cis*) diastereomer (4 mg, 4 %) was also isolated.

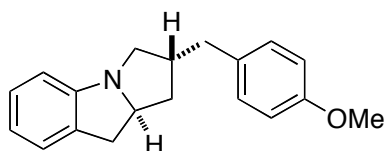
Major (*trans*) diastereomer: ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, $J = 8.0$ Hz, 2 H), 7.26 (d, $J = 8.0$ Hz, 2 H), 7.08 (t, $J = 7.6$ Hz, 1 H), 7.02 (d, $J = 7.2$ Hz, 1 H), 6.75 (t, $J = 7.6$ Hz, 1 H), 6.57 (d, $J = 7.6$ Hz, 1 H), 4.17–4.10 (m, 1 H), 3.39 (dd, $J = 6.8, 11.2$ Hz, 1 H), 3.21 (dd, $J = 9.6, 16.0$ Hz, 1 H), 3.05 (dd, $J = 6.4, 11.6$ Hz, 1 H), 2.87 (dd, $J = 3.2, 16.4$ Hz, 1 H), 2.76 (d, $J = 8.0$ Hz, 2 H), 2.45–2.40 (m, 1 H), 1.76–1.70 (m, 1 H), 1.61–1.54 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.0, 145.0, 130.2, 129.0, 127.6, 126.9 (q, $J = 268$ Hz), 125.3 (q, $J = 3.7$ Hz), 124.8, 119.7, 111.3, 63.5, 58.2, 39.9, 39.8, 37.6, 35.2 (one carbon signal is absent due to incidental equivalence); IR (film) 3054, 1421 cm^{-1} . MS (EI) 317.1378 (317.1391 calcd for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}$).

Minor (*cis*) diastereomer: ^1H NMR (400 MHz, C_6D_6) δ 7.32 (d, $J = 7.9$ Hz, 2 H), 7.15 (t, $J = 7.9$ Hz, 1 H), 7.04 (d, $J = 7.2$ Hz, 1 H), 6.83 (t, $J = 8.0$ Hz, 1 H), 6.65 (d, $J = 7.9$ Hz, 2 H), 6.55 (d, $J = 7.9$ Hz, 1 H), 3.71–3.64 (m, 1 H), 3.33 (dd, $J = 7.6, 9.9$ Hz, 1 H), 2.90 (dd, $J = 9.6, 15.9$ Hz, 1 H), 2.63 (dd, $J = 2.8, 15.9$ Hz, 1 H), 2.51 (dd, $J = 8.4, 9.9$ Hz, 1 H), 2.18–2.14 (m, 1 H), 2.10–1.98 (m, 2 H), 1.29 (dt, $J = 5.6, 11.2$ Hz, 1 H), 0.67 (m, 1 H). ^{13}C NMR (100 MHz, CDCl_3) δ 154.9, 144.9, 129.5, 129.1, 128.8, 127.7, 127.5 (q, $J = 168.6$ Hz), 125.3 (q, $J = 3.5$ Hz), 124.9, 119.4, 110.9, 65.4, 58.4, 42.5, 40.1, 38.3, 33.6; IR (film) 3059, 1482 cm^{-1} . MS (ESI) 318.1459 (318.1470 calcd for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}$, $\text{M} + \text{H}^+$).

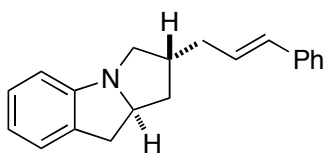


(2*R*,9*aS*)-2-(4-Methylbenzyl)-2,3,9,9*a*-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (2-21). General procedure 2 was used for the reaction of **2-1** (80 mg, 0.46 mmol) with 4-bromotoluene (118 mg, 0.69 mmol), sodium *tert*-butoxide (66.3 mg, 0.69 mmol), $\text{Pd}(\text{OAc})_2$ (5.2 mg, 0.023 mmol), and ligand **2-15** (18.2 mg, 0.046 mmol) in xylenes (1 mL). The crude product was formed as a 10:1 mixture of diastereomers with 3:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 80 mg (66%) of

the title compound as an orange oil with 10:1 dr. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.08–7.02 (m, 6 H), 6.72 (t, J = 6.8 Hz, 1 H), 6.55 (d, J = 8.0 Hz, 1 H), 4.15–4.08 (m, 1 H), 3.36 (dd, J = 7.2, 11.6 Hz, 1 H), 3.18 (dd, J = 9.6, 16 Hz, 1 H), 3.05 (dd, J = 6.4, 11.2 Hz, 1 H), 2.84 (dd, J = 2.8, 16 Hz, 1 H), 2.65 (d, J = 8.0 Hz, 2 H), 3.39–2.33 (m, 1 H), 2.30 (s, 3 H), 1.72 (ddd, J = 5.2, 7.2, 12.4 Hz, 1 H), 1.54 (dt, J = 8.4, 16.4 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.2, 137.8, 135.4, 130.3, 129.0, 128.6, 127.5, 124.7, 119.5, 111.3, 63.5, 58.3, 40.2, 39.7, 37.6, 35.1, 21.0; IR (film) 3053, 1479 cm^{-1} . MS (EI) 263.1674 (263.1674 calcd for $\text{C}_{19}\text{H}_{21}\text{N}$).

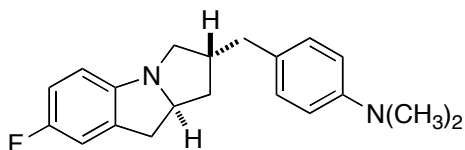


(2R,9aS)-2-(4-Methoxybenzyl)-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole (2-22). General procedure 2 was used for the reaction of **2-1** (50 mg, 0.29 mmol) with 4-bromoanisole (81 mg, 0.43 mmol), sodium *tert*-butoxide (41.6 mg, 0.43 mmol), $\text{Pd}(\text{OAc})_2$ (3.3 mg, 0.014 mmol), and ligand **2-15** (11.4 mg, 0.029 mmol) in xylenes (1 mL). The crude product was formed as a 5:1 mixture of diastereomers with 5:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 45 mg (56%) of the title compound as a red oil with 13:1 dr. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.07–7.03 (m, 4 H), 6.81 (d, J = 8.4 Hz, 2 H), 6.72 (t, J = 7.6 Hz, 1 H), 6.55 (d, J = 7.6 Hz, 1 H), 4.14–4.07 (m, 1 H), 3.77 (s, 3 H), 3.36 (dd, J = 7.2, 11.6 Hz, 1 H), 3.18 (dd, J = 9.2, 16.0 Hz, 1 H), 3.04 (dd, J = 6.0, 11.2 Hz, 1 H), 2.85 (dd, J = 2.4, 16.0 Hz, 1 H), 2.63 (d, J = 7.6 Hz, 2 H), 2.37–2.32 (m, 1 H), 1.72 (ddd, J = 5.2, 7.2, 12.4 Hz, 1 H), 1.54 (dt, J = 8.0, 12.8 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.9, 154.2, 132.9, 130.3, 129.7, 127.5, 124.7, 119.5, 113.8, 111.2, 63.5, 58.3, 55.2, 40.4, 39.2, 37.6, 35.1; IR (film) 3054, 1512 cm^{-1} . MS (EI) 279.1621 (279.1623 calcd for $\text{C}_{19}\text{H}_{21}\text{NO}$).



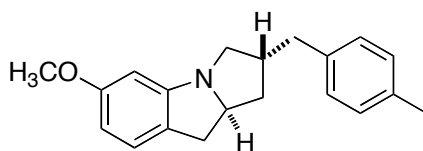
(2*R*,9*aS*)-2-Cinnamyl-2,3,9,9*a*-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole (2-23).

General procedure 2 was used for the reaction of **2-1** (80 mg, 0.46 mmol) with β -bromostyrene (169 mg, 0.92 mmol), sodium *tert*-butoxide (66.6 mg, 0.69 mmol), Pd(OAc)₂ (5.2 mg, 0.023 mmol), and ligand **2-15** (18.2 mg, 0.046 mmol) in xylenes (1 mL). The crude product was formed as a 3:1 mixture of diastereomers with 3:1 selectivity for dicyclization:monocyclization as judged by ¹H NMR analysis. Purification by flash chromatography afforded 56 mg (44%) of the title compound as a red oil with 3:1 dr. Data are for the mixture. ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.28 (m, 4 H), 7.23–7.19 (m, 1 H), 7.12–7.07 (m, 2 H), 6.76 (t, *J* = 7.2 Hz, 1 H), 6.61 (d, *J* = 7.6 Hz, 0.75 H), 6.57 (d, *J* = 7.6 Hz, 0.25 H), 6.43 (d, *J* = 15.6 Hz, 0.75 H), 6.36 (d, *J* = 15.6 Hz, 0.25 H), 6.21–6.13 (m, 1 H), 4.13–4.06 (m, 0.75 H), 4.06–4.00 (m, 0.25 H), 3.67 (dd, *J* = 8.0, 10.4 Hz, 0.25 H), 3.47 (dd, *J* = 6.8, 11.2 Hz, 0.75 H), 3.21 (dd, *J* = 9.2, 16.4 Hz, 0.75 H), 3.15 (d, *J* = 9.6 Hz, 0.25 H), 3.08 (dd, *J* = 5.6, 11.2 Hz, 0.75 H), 2.95 (dd, *J* = 2.8, 16.4 Hz, 0.25 H), 2.89 (dd, *J* = 2.8, 16 Hz, 0.75 H), 2.78 (t, *J* = 10.4 Hz, 0.25 H), 2.50–2.42 (m, 0.25 H), 2.34–2.21 (m, 2.75 H), 2.02 (dt, *J* = 5.6, 11.2 Hz, 0.25 H), 1.76 (ddd, *J* = 4.4, 7.2, 12.4 Hz, 0.75 H), 1.61 (dt, *J* = 8.0, 12.4 Hz, 0.75 H), 1.18–1.10 (m, 0.25 H); ¹³C NMR (100 MHz, CDCl₃) δ 155.1, 154.2, 137.5, 131.2, 130.9, 130.2, 129.6, 128.9, 128.8, 128.6, 128.5, 127.7, 127.6, 127.1, 126.0, 124.9, 124.8, 119.5, 119.2, 111.2, 110.9, 65.6, 63.6, 58.3, 58.2, 41.0, 38.4, 38.2, 37.6, 37.5, 35.0, 33.7; IR (film) 2925, 1602 cm⁻¹. MS (ESI) 276.1744 (276.1752 calcd for C₂₀H₂₁N, M + H⁺).



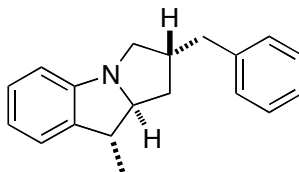
(2*R*,9*aS*)-4-(7-Fluoro-2,3,9,9*a*-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-2-yl)methyl-*N,N*-dimethylaniline (2-24). General procedure 2 was used for the reaction of **2-16** (80 mg, 0.42 mmol) with 4-bromo-*N,N*-dimethylaniline (125 mg, 0.63 mmol), sodium *tert*-butoxide (60.3 mg, 0.63 mmol), Pd(OAc)₂ (4.7 mg, 0.021 mmol), and ligand **2-15** (16.5 mg, 0.042 mmol) in xylenes (1 mL). The crude product was formed as a 3:1 mixture of diastereomers with 2:1 selectivity for

dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 85 mg (65%) of the title compound as a red oil with 7:1 dr. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.01 (d, $J = 8.4$ Hz, 2 H), 6.74 (d, $J = 8.8$ Hz, 2 H), 6.66 (d, $J = 6.4$ Hz, 2 H), 6.45–6.42 (m, 1 H), 4.16–4.09 (m, 1 H), 3.26 (dd, $J = 6.8, 11.2$ Hz, 1 H), 3.18 (dd, $J = 9.2, 16.4$ Hz, 1 H), 3.03 (dd, $J = 6.4, 11.6$ Hz, 1 H), 2.89 (s, 6 H), 2.82 (dd, $J = 3.2, 16.4$ Hz, 1 H), 2.58 (d, $J = 6.8$ Hz, 2 H), 2.36–2.29 (m, 1 H), 1.74 (ddd, $J = 5.2, 7.2, 12.4$ Hz, 1 H), 1.54 (dt, $J = 7.9, 12.8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.5 (d, $J = 236$ Hz), 150.4, 149.1, 131.9 (d, $J = 8.0$ Hz), 129.3, 128.8, 113.5 (d, $J = 23$ Hz), 112.8, 111.9 (d, $J = 24$ Hz), 111.5 (d, $J = 8.4$ Hz), 64.2, 58.9, 40.7, 40.5, 38.9, 37.7, 35.4; IR (film) 3401, 2926, 1521, 1483 cm^{-1} . MS (ESI) 311.1928 (311.1924 calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_2$, $\text{M} + \text{H}^+$).

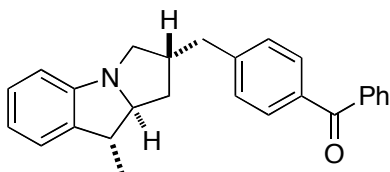


(2R,9aS)-6-Methoxy-2-(4-methylbenzyl)-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole (2-25). General procedure 2 was used for the reaction of **2-17** (70 mg, 0.34 mmol) with 4-bromotoluene (88 mg, 0.52 mmol), sodium *tert*-butoxide (49.6 mg, 0.52 mmol), $\text{Pd}(\text{OAc})_2$ (3.8 mg, 0.017 mmol), and ligand **2-15** (13.6 mg, 0.034 mmol) in xylenes (1 mL). The crude product was formed as a 5:1 mixture of diastereomers with 2:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 58 mg (57%) of the title compound as a yellow oil with 10:1 dr. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.09–7.03 (m, 4 H), 6.91 (d, $J = 7.6$ Hz, 1 H), 6.29–6.27 (m, 1 H), 6.14 (d, $J = 2.4$ Hz, 1 H), 4.16–4.09 (m, 1 H), 3.74 (s, 3 H), 3.35 (dd, $J = 6.8, 11.2$ Hz, 1 H), 3.13 (dd, $J = 8.8, 15.6$ Hz, 1 H), 3.03 (dd, $J = 6.0, 11.6$ Hz, 1 H), 2.78 (dd, $J = 2.4, 15.6$ Hz, 1 H), 2.65 (d, $J = 8.0$ Hz, 2 H), 2.41–2.35 (m, 1 H), 2.31 (s, 3 H), 1.72 (ddd, $J = 4.8, 7.2, 12.4$ Hz, 1 H), 1.53 (dt, $J = 8.4, 16.4$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.1, 155.6, 137.8, 135.4, 129.1, 128.7, 124.8, 122.5, 104.3, 98.0, 64.3, 58.0, 55.3, 40.3, 39.8, 37.6, 34.3,

20.9; IR (film) 2918, 1616, 1293, 1207 cm^{-1} . MS (EI) 293.1776 (293.1780 calcd for $\text{C}_{20}\text{H}_{23}\text{NO}$).

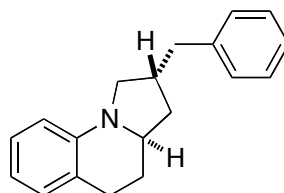


(2R,9R,9aS)-2-Benzyl-9-methyl-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole (2-26). General procedure 2 was used for the reaction of **2-18** (80 mg, 0.42 mmol) with bromobenzene (100 mg, 0.64 mmol), sodium *tert*-butoxide (61.6 mg, 0.64 mmol), $\text{Pd}(\text{OAc})_2$ (4.8 mg, 0.021 mmol), and ligand **2-15** (16.9 mg, 0.043 mmol) in xylenes (1 mL). The crude product was formed as a 7:1 mixture of diastereomers with 7:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 76 mg (68%) of the title compound as an orange oil with >20:1 dr. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.29 (m, 2 H), 7.26–7.19 (m, 3 H), 7.12 (t, J = 7.2 Hz, 1 H), 7.07 (d, J = 7.6 Hz, 1 H), 6.80 (t, J = 7.2 Hz, 1 H), 6.61 (d, J = 8.0 Hz, 1 H), 3.78–3.73 (m, 1 H), 3.38 (dd, J = 7.2, 11.2 Hz, 1 H), 3.21–3.15 (m, 1 H), 3.09 (dd, J = 6.4, 11.2 Hz, 1 H), 2.74 (d, J = 7.6 Hz, 2 H), 2.46–2.40 (m, 1 H), 1.82 (ddd, J = 6.0, 7.6, 12.8 Hz, 1 H), 1.62 (dt, J = 7.6, 12.8 Hz, 1 H), 1.35 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.6, 140.9, 136.3, 128.7, 128.3, 127.8, 126.0, 123.8, 119.7, 111.7, 72.2, 58.2, 42.8, 40.2, 40.0, 37.3, 21.5; IR (film) 3054, 1421 cm^{-1} . MS (EI) 263.1672 (263.1674 calcd for $\text{C}_{19}\text{H}_{21}\text{N}$).



(2R,9R,9aS)-4-((9-Methyl-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indol-2-ylmethyl)phenyl)phenylmethanone (2-27). General procedure 2 was used for the reaction of **2-18** (70 mg, 0.37 mmol) with 4-bromobenzophenone (146 mg, 0.56 mmol), sodium *tert*-butoxide (53.9 mg, 0.56 mmol), $\text{Pd}(\text{OAc})_2$ (4.2 mg, 0.019 mmol), and ligand **2-15** (14.7 mg, 0.037 mmol) in xylenes (1 mL). The crude product was formed as a 10:1 mixture of diastereomers with 7:1 selectivity for

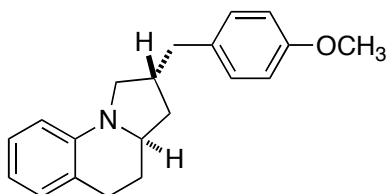
dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 94 mg (69%) of the title compound as a bright yellow oil with >20:1 dr. Data are for the major isomer. ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, $J = 6.8$ Hz, 2 H), 7.74 (d, $J = 4.8$ Hz, 2 H), 7.58 (t, $J = 7.6$ Hz, 1 H), 7.48 (t, $J = 7.6$ Hz, 2 H), 7.27 (d, $J = 8.0$ Hz, 2 H), 7.09 (t, $J = 7.6$ Hz, 1 H), 7.04 (d, $J = 7.6$ Hz, 1 H), 6.78 (t, $J = 7.2$ Hz, 1 H), 6.59 (d, $J = 7.6$ Hz, 1 H), 3.76–3.71 (m, 1 H), 3.38 (dd, $J = 7.2, 11.6$ Hz, 1 H), 3.19–3.13 (m, 1 H), 3.06 (dd, $J = 6.8, 11.6$ Hz, 1 H), 2.79 (d, $J = 8.0$ Hz, 2 H), 2.47–2.39 (m, 1 H), 1.80 (ddd, $J = 6.4, 7.6, 13.2$ Hz, 1 H), 1.62 (dt, $J = 7.6, 12.8$ Hz, 1 H), 1.32 (d, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.3, 153.4, 146.0, 137.8, 136.2, 135.5, 132.2, 130.4, 129.9, 128.7, 128.2, 127.8, 123.9, 119.9, 111.7, 72.2, 58.2, 42.8, 40.0, 39.9, 37.3, 21.5; IR (film) 3078, 1604, 1455 cm^{-1} . MS (ESI) 368.2004 (368.2014 calcd for $\text{C}_{26}\text{H}_{25}\text{NO}$, $\text{M} + \text{H}^+$)



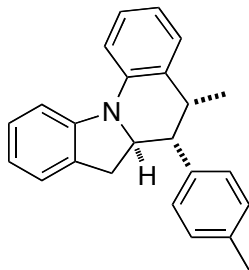
(2R,3aR)-2-Benzyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline (2-28).

General procedure 2 was used for the reaction of **2-19** (100 mg, 0.53 mmol) with bromobenzene (126 mg, 0.80 mmol), sodium *tert*-butoxide (76.9 mg, 0.80 mmol), $\text{Pd}(\text{OAc})_2$ (5.9 mg, 0.027 mmol), and ligand **2-15** (21.1 mg, 0.053 mmol) in xylenes (2 mL). The crude product was formed as a 3:1 mixture of diastereomers with 5:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 104 mg (73%) of the title compound as a clear oil with 3:1 dr. Data are for the mixture. ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.28 (m, 2 H), 7.24–7.16 (m, 3 H), 7.04 (t, $J = 8.0$ Hz, 1 H), 6.99–6.95 (m, 1 H), 6.57–6.53 (m, 1 H), 6.37 (d, $J = 7.6$ Hz, 0.75 H), 6.33 (d, $J = 8.0$ Hz, 0.25 H), 3.66–3.56 (m, 0.75 H), 3.52–3.45 (m, 0.25 H), 3.42–3.34 (m, 1 H), 3.09 (dd, $J = 2.8, 9.6$ Hz, 0.75 H), 2.94–2.88 (m, 0.75 H), 2.86–2.80 (m, 0.75 H), 2.78–2.77 (m, 0.75 H), 2.74–2.72 (m, 2 H), 2.71–2.60 (m, 1 H), 2.14 (dt, $J = 5.2, 11.2$ Hz, 0.25 H), 2.10–2.04 (m, 1 H), 1.95 (ddd, $J = 2.0, 6.0, 12.4$ Hz, 0.75 H),

1.65 (ddd, $J = 7.2, 9.6, 12.0$ Hz, 0.75 H), 1.47–1.36 (m, 1 H), 1.27 (q, $J = 11.6$ Hz, 0.25 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.8, 140.8, 140.7, 129.3, 128.9, 128.6, 128.5, 128.4, 127.2, 127.1, 126.1, 126.0, 121.4, 121.1, 115.0, 114.7, 110.4, 109.6, 59.1, 58.4, 56.0, 52.8, 52.7, 40.6, 40.4, 39.9, 39.6, 38.2, 37.9, 28.2, 28.1, 27.4; IR (film) 2929, 1602, 1504, 1326, 742 cm^{-1} . MS (ESI) 264.1756 (264.1752 calcd for $\text{C}_{19}\text{H}_{21}\text{N}$, $\text{M} + \text{H}^+$).

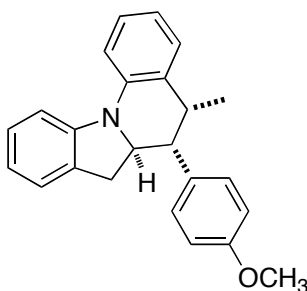


(2R,3aR)-2-(4-Methoxybenzyl)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline (2-29). General procedure 2 was used for the reaction of **2-19** (80 mg, 0.43 mmol) with 4-bromoanisole (119 mg, 0.64 mmol), sodium *tert*-butoxide (61.5 mg, 0.64 mmol), $\text{Pd}(\text{OAc})_2$ (4.8 mg, 0.021 mmol), and ligand **2-15** (16.8 mg, 0.043 mmol) in xylenes (1 mL). The crude product was formed as a 3:1 mixture of diastereomers with 5:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography afforded 60 mg (48%) of the title compound as a bright yellow oil with 3:1 dr. Data are for the mixture. ^1H NMR (400 MHz, CDCl_3) δ 7.14–7.09 (m, 2 H), 7.04 (t, $J = 7.6$ Hz, 1 H), 6.99–6.95 (m, 1 H), 6.85 (d, $J = 7.6$ Hz, 2 H), 6.57–6.51 (m, 1 H), 6.37 (d, $J = 8.0$ Hz, 0.75 H), 6.33 (d, $J = 8.0$ Hz, 0.25 H), 3.80 (s, 3 H), 3.65–3.57 (m, 0.75 H), 3.53–3.46 (m, 0.25 H), 3.41–3.33 (m, 1 H), 3.08 (dd, $J = 2.4, 9.6$ Hz, 0.75 H), 2.93–2.85 (m, 1.25 H), 2.79–2.72 (m, 1.5 H), 2.69–2.66 (m, 1.5 H), 2.64–2.54 (m, 1 H), 2.16–2.04 (m, 1.25 H), 1.93 (ddd, $J = 1.6, 6.0, 12.4$ Hz, 0.75 H), 1.64 (ddd, $J = 7.2, 9.9, 12.4$ Hz, 0.75 H), 1.46–1.36 (m, 1 H), 1.25 (q, $J = 11.6$ Hz, 0.25 H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.9, 144.8, 144.5, 132.9, 132.8, 129.9, 129.5, 128.5, 128.4, 127.2, 127.1, 121.4, 121.0, 115.0, 114.7, 113.8, 110.4, 109.6, 58.4, 55.9, 55.2, 52.7, 52.6, 39.9, 39.8, 39.7, 39.5, 38.3, 37.8, 28.2, 28.1, 27.4; IR (film) 2932, 2835, 1602, 1510, 1245 cm^{-1} . MS (ESI) 294.1860 (294.1858 calcd for $\text{C}_{20}\text{H}_{23}\text{NO}$, $\text{M} + \text{H}^+$).



(5R,6R,6aR)-5-Methyl-6-(p-tolyl)-5,6,6a,7-tetrahydroindolo[1,2-a]quinoline

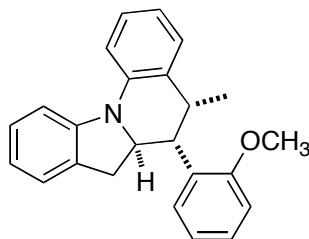
(2-31a). General procedure 2 was used for the reaction of **2-30** (75 mg, 0.32 mmol) with 4-bromotoluene (82 mg, 0.48 mmol), sodium *tert*-butoxide (45.9 mg, 0.49 mmol), Pd(OAc)₂ (3.6 mg, 0.016 mmol), and ligand **2-15** (12.3 mg, 0.032 mmol) in xylenes (1 mL). The crude product was formed as a 9:1 mixture of diastereomers with 20:1 selectivity for dicyclization:monocyclization as judged by ¹H NMR analysis. Purification by flash chromatography followed by recrystallization from ethyl acetate/hexanes afforded 60 mg (57%) of the title compound as a white solid, mp 169 °C, with >20:1 dr. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, *J* = 8.4 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.24–7.06 (m, 8 H), 6.90 (t, *J* = 7.2 Hz, 1 H), 6.78 (t, *J* = 7.2 Hz, 1 H), 4.64 (dt, *J* = 7.2, 11.6 Hz, 1 H), 3.23–3.17 (m, 2 H), 3.08–3.02 (p, *J* = 7.2 Hz, 1 H), 2.77 (dd, *J* = 6.8, 15.6 Hz, 1 H), 2.37 (s, 3 H), 1.11 (d, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.7, 139.6, 137.3, 136.1, 131.5, 130.2, 129.5, 129.1, 128.7, 127.0, 126.6, 125.0, 119.8, 119.5, 116.6, 109.6, 58.4, 46.3, 38.9, 33.9, 21.0, 18.8; IR (film) 3053, 1593 cm⁻¹. MS (EI) 325.1832 (325.1830 calcd for C₂₄H₂₃N).



(5R,6R,6aR)-6-(4-Methoxyphenyl)-5-methyl-5,6,6a,7-tetrahydroindolo[1,2-a]quinoline (2-31b).

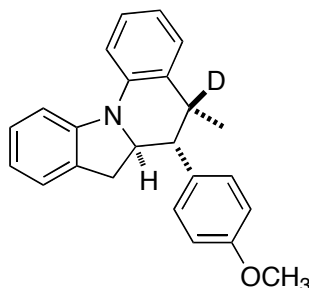
General procedure 2 was used for the reaction of **2-30** (100 mg, 0.43 mmol) with 4-bromoanisole (119 mg, 0.64 mmol), sodium *tert*-butoxide (61.3 mg, 0.64 mmol), Pd(OAc)₂ (4.8 mg, 0.021 mmol), and ligand **2-15** (16.8

mg, 0.042 mmol) in xylenes (1 mL). The crude product was formed as a 10:1 mixture of diastereomers with 20:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography followed by recrystallization from ethyl acetate/hexanes afforded 77 mg (54%) of the title compound as a white solid, mp 163 °C, with >20:1 dr. ^1H NMR (400 MHz, CDCl_3) δ 7.51 (d, $J = 7.6$ Hz, 1 H), 7.30 (d, $J = 7.6$ Hz, 1 H), 7.22 (t, $J = 7.6$ Hz, 1 H), 7.17 (d, $J = 7.6$ Hz, 1 H), 7.13–7.07 (m, 4 H), 6.93–6.88 (m, 3 H), 6.77 (t, $J = 7.2$ Hz, 1 H), 4.61 (dt, $J = 7.6, 11.2$ Hz, 1 H), 3.82 (s, 3 H), 3.22–3.16 (m, 2 H), 3.03 (p, $J = 6.8$ Hz, 1 H), 2.77 (dd, $J = 7.2, 15.6$ Hz, 1 H), 1.06 (d, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.2, 146.7, 139.6, 132.5, 131.5, 130.2, 129.7, 129.6, 127.0, 126.6, 125.0, 119.9, 119.5, 116.6, 113.9, 109.6, 58.6, 55.2, 45.9, 39.0, 33.9, 18.8; IR (film) 3054, 1513 cm^{-1} . MS (EI) 341.1785 (341.1780 calcd for $\text{C}_{24}\text{H}_{23}\text{NO}$).



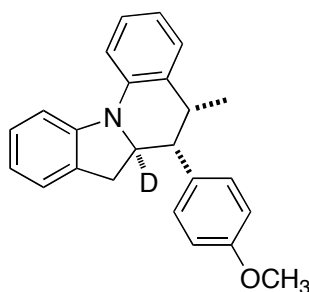
(5R,6R,6aR)-6-(2-Methoxyphenyl)-5-methyl-5,6,6a,7-tetrahydroindolo[1,2-a]quinoline (2-31c). General procedure 2 was used for the reaction of **2-30** (100 mg, 0.43 mmol) with 2-bromoanisole (119 mg, 0.64 mmol), sodium *tert*-butoxide (61.3 mg, 0.64 mmol), $\text{Pd}(\text{OAc})_2$ (4.8 mg, 0.021 mmol), and ligand **2-15** (16.8 mg, 0.042 mmol) in xylenes (1 mL). The crude product was formed as a 5:1 mixture of diastereomers with 6:1 selectivity for dicyclization:monocyclization as judged by ^1H NMR analysis. Purification by flash chromatography followed by recrystallization from ethyl acetate/hexanes afforded 39 mg (27%) of the title compound as a white solid, mp 174–175°C, with >20:1 dr. ^1H NMR (400 MHz, C_6D_6) δ 7.58 (d, $J = 7.9$ Hz, 1 H), 7.35 (d, $J = 7.9$ Hz, 1 H), 7.17–7.13 (m, 1 H), 7.11–7.03 (m, 3 H), 6.90–6.83 (m, 3 H), 6.78–6.73 (m, 2 H), 6.54 (d, $J = 8.4$ Hz, 1 H), 4.44 (s, br, 1 H), 3.79 (s, br, 1 H), 3.29 (s, br, 1 H), 3.11 (s, 3 H), 2.98 (dd, $J = 8.8, 15.6$ Hz, 1 H), 2.64 (dd, $J = 6.4, 15.9$ Hz, 1 H), 0.98 (d, $J = 7.2$ Hz, 3 H); ^{13}C

NMR (100 MHz, CDCl₃) δ 167.8, 146.8, 139.6, 132.2, 130.1, 129.8, 128.8, 128.5, 127.3, 126.9, 126.3, 124.9, 120.0, 119.9, 119.2, 117.3, 110.5, 108.9, 57.9, 55.2, 39.7, 35.7, 33.7, 19.5; IR (film) 3059, 1594 cm⁻¹. MS (EI) 341.1793 (341.1780 calcd for C₂₄H₂₃NO).

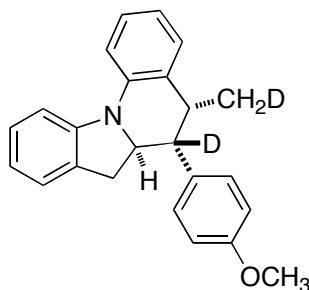


(5S,6R,6aR)-5-Deuterio-6-(4-methoxyphenyl)-5-methyl-5,6,6a,7-

tetrahydroindolo[1,2-a]quinoline (2-34a). General procedure 2 was used for the reaction of **2-33a** (80 mg, 0.33 mmol) with 4-bromoanisole (93 mg, 0.50 mmol), sodium *tert*-butoxide (48.8 mg, 0.51 mmol), Pd(OAc)₂ (3.8 mg, 0.017 mmol), and ligand **2-15** (13.5 mg, 0.033 mmol) in xylenes (1 mL). The crude product was formed as a 9:1 mixture of diastereomers with 13:1 selectivity for dicyclization:monocyclization as judged by ¹H NMR analysis. Purification by flash chromatography followed by recrystallization from ethyl acetate/hexanes afforded 55 mg (47%) of the title compound as a white solid, mp 168–169°C, with >20:1 dr. ¹H NMR (400 MHz, C₆D₆) δ 7.59 (d, *J* = 8.4 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 8.8 Hz, 1 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 6.96 (d, *J* = 7.2 Hz, 1 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 6.81 (t, *J* = 7.2 Hz, 1 H), 6.76 (d, *J* = 8.4 Hz, 2 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 4.32–4.25 (m, 1 H), 3.36 (s, 3 H), 2.91–2.85 (m, 2 H), 2.56 (dd, *J* = 7.2, 16.0 Hz, 1 H), 0.94 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 146.7, 139.6, 132.5, 131.5, 130.2, 129.7, 129.5, 127.0, 126.6, 125.0, 119.9, 119.5, 116.5, 113.9, 109.6, 58.6, 55.2, 45.9, 38.5 (t, *J* = 19.2 Hz), 33.9, 18.6; IR (film) 2960, 1590 cm⁻¹. MS (EI) 342.1842 (342.1842 calcd for C₂₄H₂₂DNO).



(5R,6R,6aS)-6a-Deuterio-6-(4-methoxyphenyl)-5-methyl-5,6,6a,7-tetrahydroindolo[1,2-a]quinoline (2-34b). General procedure 2 was used for the reaction of **2-33b** (80 mg, 0.33 mmol) with 4-bromoanisole (93 mg, 0.50 mmol), sodium *tert*-butoxide (48.8 mg, 0.51 mmol), Pd(OAc)₂ (3.8 mg, 0.017 mmol), and ligand **2-15** (13.5 mg, 0.033 mmol) in xylenes (1 mL). The crude product was formed as a 9:1 mixture of diastereomers with 18:1 selectivity for dicyclization:monocyclization as judged by ¹H NMR analysis. Purification by flash chromatography followed by recrystallization from ethyl acetate/hexanes afforded 62 mg (53%) of the title compound as a white solid, mp 168–169°C, with >13:1 dr. ¹H NMR (400 MHz, C₆D₆) δ 7.59 (d, *J* = 7.9 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 8.4 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 6.96 (d, *J* = 7.2 Hz, 1 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 6.76 (d, *J* = 8.4 Hz, 2 H), 6.67 (d, *J* = 8.4 Hz, 2 H), 3.35 (s, 3 H), 2.91–2.86 (m, 2 H), 2.83–2.78 (m, 1 H), 2.56 (d, *J* = 15.6 Hz, 1 H), 0.95 (d, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 146.7, 139.6, 132.5, 131.5, 130.2, 129.7, 129.5, 127.0, 126.6, 125.0, 119.9, 119.5, 116.6, 113.9, 109.6, 58.2 (t, *J* = 21.1 Hz), 55.2, 45.8, 38.9, 33.8, 18.7; IR (film) 2960, 1590 cm⁻¹. MS (EI) 342.1839 (342.1842 calcd for C₂₄H₂₂DNO).

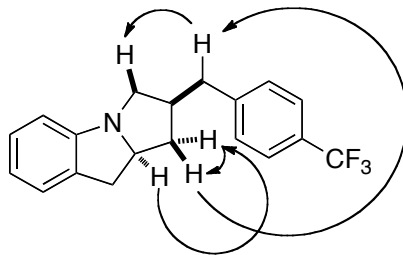


(5R,6S,6aR)-6-Deuterio-5-(deuteriomethyl)-6-(4-methoxyphenyl)-5,6,6a,7-tetrahydroindolo[1,2-a]quinoline (2-34c). General procedure 2 was used for

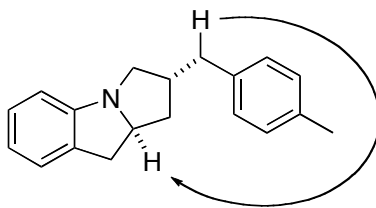
the reaction of **2-33c** (80 mg, 0.34 mmol) with 4-bromoanisole (93 mg, 0.50 mmol), sodium *tert*-butoxide (48.6 mg, 0.51 mmol), Pd(OAc)₂ (3.8 mg, 0.017 mmol), and ligand **2-15** (13.3 mg, 0.034 mmol) in xylenes (1 mL). The crude product was formed as a 8:1 mixture of diastereomers with 12:1 selectivity for dicyclization:monocyclization as judged by ¹H NMR analysis. Purification by flash chromatography followed by recrystallization from ethyl acetate/hexanes afforded 57 mg (49%) of the title compound as a white solid, mp 168–169°C, with >20:1 dr. ¹H NMR (400 MHz, C₆D₆) δ 7.58 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 7.9 Hz, 1 H), 7.16 (t, *J* = 6.8 Hz, 1 H), 7.06 (t, *J* = 7.9 Hz, 1 H), 7.03 (d, *J* = 7.9 Hz, 1 H), 6.95 (d, *J* = 7.2 Hz, 1 H), 6.90 (t, *J* = 8.4 Hz, 1 H), 6.80 (t, *J* = 7.2 Hz, 1 H), 6.76–6.73 (m, 2 H), 6.67–6.65 (m, 2 H), 4.27 (t, *J* = 6.8 Hz, 1 H), 3.34 (s, 3 H), 2.86 (dd, *J* = 8.8, 15.6 Hz, 1 H), 2.77 (t, *J* = 7.2 Hz, 1 H), 2.55 (dd, *J* = 6.8, 16 Hz, 1 H), 0.92 (d, *J* = 7.2 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 158.3, 146.7, 139.6, 132.4, 131.5, 130.2, 129.7, 129.6, 127.0, 126.6, 125.0, 119.9, 119.5, 116.6, 113.8, 109.6, 58.5, 55.2, 45.66 (t, *J* = 19.6 Hz), 38.8, 33.9, 18.5 (t, *J* = 19.6 Hz); IR (film) 2931, 1592, 1491 cm⁻¹. MS (ESI) 344.1974 (344.1983 calcd for C₂₄H₂₁D₂NO, M + H⁺).

Assignment of Stereochemistry

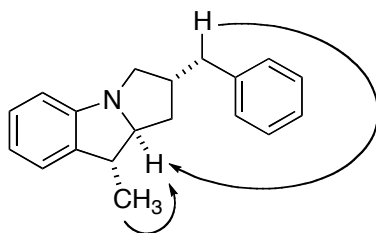
The relative stereochemistry of compound **2-20-minor diastereomer** was assigned on the basis of observed ¹H NMR nOe experiments. Significant nOe relationships are shown below.



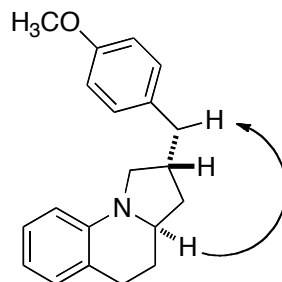
The relative stereochemistry of compound **2-21** was assigned on the basis of observed ¹H NMR nOe experiments. Significant nOe relationships are shown below.



The relative stereochemistry of compound **2-26** was assigned on the basis of observed ^1H NMR nOe experiments, with significant nOe relationships shown below.

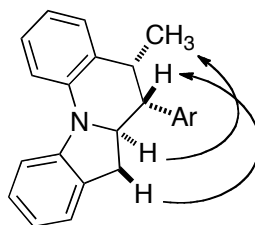


The relative stereochemistry of compound **2-29** was assigned on the basis of observed ^1H NMR nOe experiments, with significant nOe relationships shown below.



The relative stereochemistry of compound **2-31c** was assigned on the basis of observed ^1H NMR nOe experiments, with significant nOe relationships shown below. Further evidence of the relative stereochemistry was accomplished by single-crystal x-ray analysis of compound **2-31c**, which was recrystallized from EtOAc/hexanes.

nOe Relationships:



Ar = *o*-MeOPh

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Chapter 3

Intramolecular Alkene Carboamination Reactions for the Synthesis of Enantiomerically Enriched Tropane Derivatives

3.1 Introduction

The azabicyclic framework is widespread in both natural products and pharmaceutical targets that have a range of central nervous system (CNS) activities including anticholinergic, sedatory, and cognitive.¹ Benzo-fused tropanes are an interesting and important subclass of azabicycloalkanes. These ring systems are displayed in numerous drug leads and pharmaceuticals including **3-1**, which has been studied for the treatment of Type 2 diabetes,² and **3-2**, which is an antitumor drug candidate (Figure 3.1).³ MK-801 (dizocilpine), a related heterocycle bearing two fused aryl rings, has exhibited anticonvulsant activity⁴ and has also been used in animal models of schizophrenia.⁵

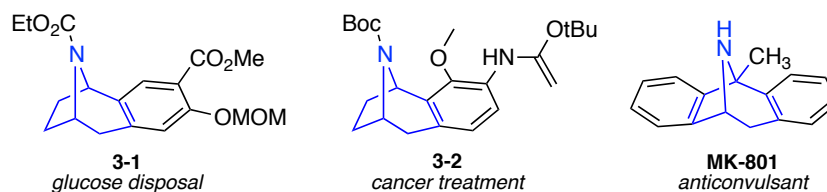
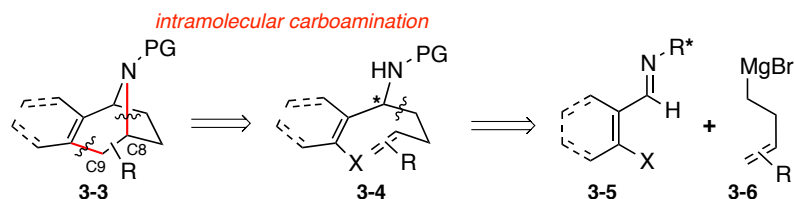


Figure 3.1 Biologically active benzo-fused tropanes

The medicinal relevance of azabicycloalkanes has stimulated considerable interest among synthetic chemists, and a great number of methods have been developed for the construction of saturated frameworks.⁶ In contrast, only a handful of routes have previously been developed for the synthesis of benzo-fused tropane scaffolds.⁷ We envisioned that an intramolecular Pd-catalyzed carboamination reaction⁸ of a γ -aminoalkene substrate such as **3-4**, which contains a 2-bromoaryl (or 2-bromoalkenyl) group adjacent to the amino moiety,

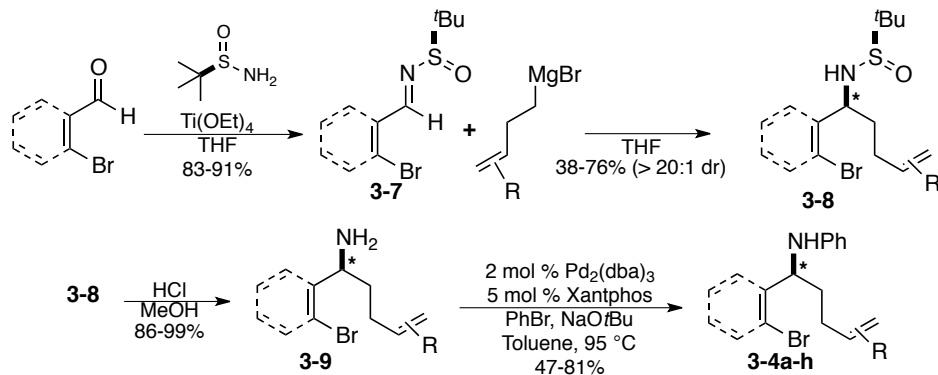
could provide a complementary approach to the benzo-tropane framework **3-3** (Scheme 3.1). This transformation would generate two bonds and 1–2 stereocenters (at C8 and C9) in a controlled fashion, and the requisite substrates could be prepared in enantiopure form via addition of unsaturated Grignard reagents **3-6** to readily available chiral imines **3-5**.



Scheme 3.1 Intramolecular carboamination strategy for benzo-fused tropane synthesis

3.2 Synthesis of Substrates

The enantioenriched substrates **3-4** required for the strategy outlined above were synthesized in four steps from readily accessible *o*-bromobenzaldehydes or β -bromo- α,β -unsaturated aldehydes (Scheme 3.2). Specifically, condensation of an appropriate bromoaldehyde with (*R_S*)-(+)-*tert*-butanesulfinamide⁹ afforded aldimine **3-7** as a single enantiomer. Subsequent 1,2-addition of a homoallylic Grignard reagent to **3-7** afforded *N*-*tert*-butanesulfinyl amines **3-8**. The Grignard addition reactions typically proceeded with 4–13:1 dr, but after flash chromatography the desired amine products were obtained with a high degree of stereochemical purity in moderate to good yields (51–76%).



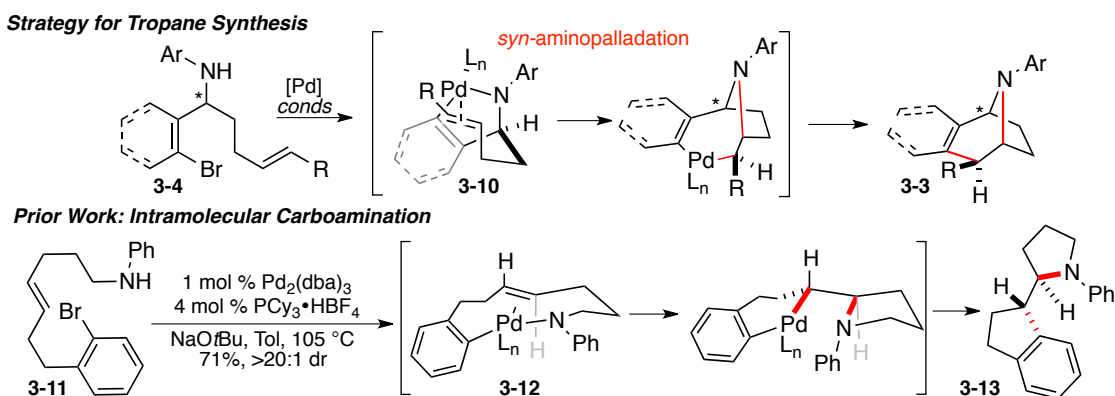
^a Overall yields of **3-4a-h** over four-step sequence: **3-4a**, 20%; **3-4b**, 36%; **3-4c**, 14%; **3-4d**, 41%; **3-4e**, 27%; **3-4f**, 31%; **3-4g**, 39%; **3-4h**, 41%.

Scheme 3.2 Synthetic route to tropane substrates **3-4a-h**^a

In some instances the diastereoselectivity of the Grignard addition was poor (2-3:1), resulting in lower yields (38-46%) of amine products after separation of the stereoisomers. Acid-mediated cleavage of the chiral auxiliary to give primary amines **3-9**, followed by a Pd/Xantphos-catalyzed *N*-arylation¹⁰ with bromobenzene, afforded desired *N*-phenyl- γ -aminoalkene substrates **3-4a-h** in good yield. Although these conditions usually provided good chemoselectivity for the desired *N*-arylation, in a few instances competing 2-benzyl pyrrolidine formation occurred, which led to modest yields. In addition, efforts to prepare substrates bearing quaternary stereocenters adjacent to the amino group were unsuccessful due to the low reactivity of *N*-sulfinyl ketimines towards organometallic nucleophiles.

3.3 Optimization of Intramolecular Carboamination Reaction

Our prior studies on Pd-catalyzed carboamination reactions that yield substituted pyrrolidines suggested the conversion of **3-4** to **3-3** was likely to occur via a key intramolecular aminopalladation of an intermediate Pd(aryl)(amido) complex such as **3-10** (Scheme 3.3).⁸ The general feasibility of this process was supported by prior studies in our lab, which illustrated that intramolecular carboaminations of substrates such as **3-11** effectively generated pyrrolidines bearing attached carbocyclic rings (e.g., **3-13**).¹¹



Scheme 3.3 Precedent for intramolecular carboamination mechanism

This latter transformation is believed to proceed via intramolecular (transannular) insertion of the alkene into macrocyclic Pd(aryl)(amido) complex **3-12**, which bears a single phosphine ligand. Recent mechanistic studies support

this hypothesis, as alkene aminopalladation occurred most rapidly from palladium complexes bearing one phosphine ligand.¹² As such, we elected to examine catalysts supported by monodentate phosphines in our initial experiments.

The optimization of conditions to effect the Pd-catalyzed synthesis of tropanes was explored using substrate **3-4a** (Table 3.1). Our optimization studies focused on the phosphine ligand structure, using otherwise standard conditions known to give satisfactory results in most carboamination reactions (NaO^tBu, toluene, 90–110 °C). Use of P(*o*-tol)₃ as the ligand led to incomplete conversion of the starting material and only afforded small quantities of desired tropane product **3-14** (entry 1). Improved results were obtained with the bulky electron-rich DavePhos ligand, but the reaction still failed to reach completion (entry 3). However, use of the slightly smaller electron-rich ligand PCy₃, employed as the tetrafluoroborate salt, led to complete consumption of the starting material and provided **3-14** in 77% isolated yield (entry 4). Finally, to probe the hypothesis that the key intermediate bears a single phosphine ligand, the efficacy of the bidentate ligand dppf was examined. As postulated, poor conversion of the starting material occurred and only a low yield of **3-14** was obtained (entry 5).

Table 3.1 Optimization of reactions conditions^a

Entry	Ligand	Conversion (%)	Yield of 3-14 (%) ^b
1	P(<i>o</i> -tol) ₃	59	21
2	P(<i>p</i> -F-C ₆ H ₄) ₃	100	69
3	DavePhos	76	40
4	PCy ₃ •HBF ₄	100	80 (77) ^c
5	dppf	35	11

^a Conditions: 1.0 equiv of **3-4a**, 2.0 equiv of NaO^tBu, 2 mol % Pd₂(dba)₃, 8 mol % ligand (4 mol % of dppf was used for the experiment shown in entry 5), toluene (0.1 M), 95 °C, 14 h. ^b Yields were determined by ¹H NMR analysis of crude reaction mixtures that contained phenanthrene as an internal standard. ^c Isolated yield(average of two exps).

3.4 Exploration of Reaction Scope

With optimized reaction conditions in hand, the scope and limitations of the intramolecular carboamination reactions were explored. Overall these transformations proved to be quite general and afforded various tropane derivatives in good yields and with no loss of enantiopurity (Table 3.2). Styrene-derived substrate **3-4b** smoothly underwent the intramolecular carboamination

reaction to yield dibenzotropane **3-15** in good yield, and the heteroaryl-fused tropane **3-16** was generated from pyridine derivative **3-4c** in good yield (entries 2 and 3). Cyclic alkenyl halides were also viable substrates, as **3-4d** was efficiently transformed to unsaturated tropane **3-17** (entry 4). Unfortunately, efforts to transform acyclic alkenyl halide substrates into tropane products were unsuccessful, as alkene isomerization and substrate decomposition occurred more rapidly than tropane formation.

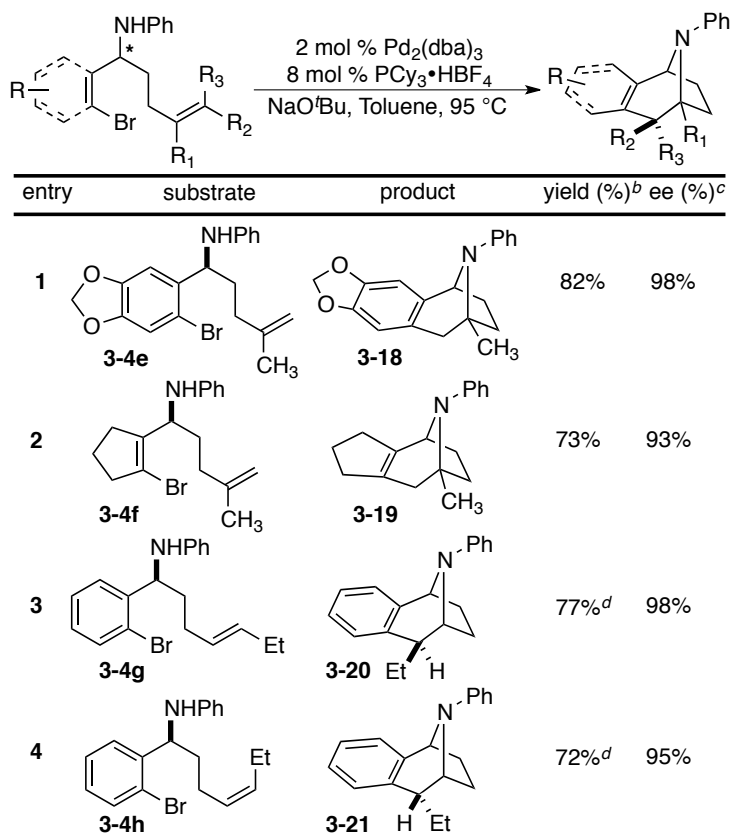
Table 3.2 Pd-catalyzed synthesis of unsubstituted tropanes^a

entry	substrate	product	yield (%) ^b	ee (%) ^c
1			77%	97%
2			80%	98%
3			81%	99%
4			73%	92%

^a Conditions: 1.0 equiv of amine, 1.5 equiv of NaO^tBu, 2 mol % Pd₂(dba)₃, 8 mol % PCy₃·HBF₄, toluene (0.1 M), 95 °C, 10 h.

^b Isolated yield(average of two experiments). ^c No racemization of the substrates occurred during the transformation; the enantiopurities of the starting materials were within 1% ee of the tropane products as determined by chiral HPLC analysis.

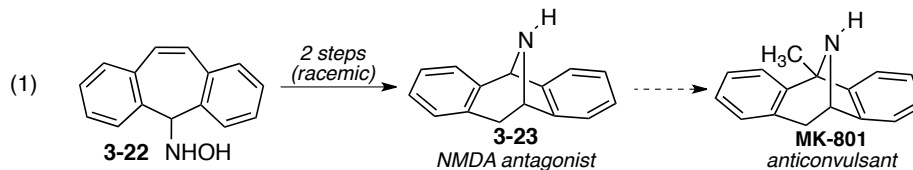
This method is also amenable to the generation of quaternary stereocenters, as seen in the conversion of 1,1-disubstituted alkene substrates **3-4e** and **3-4f** to **3-18** and **3-19**, respectively. The stereospecific conversion of *E*- and *Z*-alkene substrates **3-4g** and **3-4h** proceeded smoothly to provide disubstituted tropane products **3-20** and **3-21**. In these latter transformations, use of the slightly smaller ligand PPh₂Cy provided better results than our standard Pd/PCy₃ catalyst system.

Table 3.3 Pd-catalyzed synthesis of substituted tropanes^a

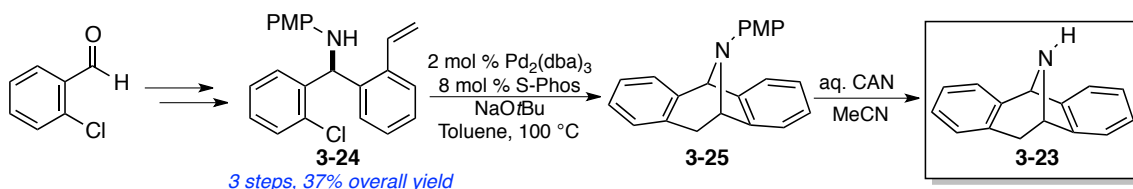
^a Conditions: 1.0 equiv of amine, 1.5 equiv of NaO^tBu, 2 mol % Pd₂(dba)₃, 8 mol % PCy₃·HBF₄, toluene (0.1 M), 95 °C, 10 h.
^b Isolated yield (average of two experiments). ^c No racemization of the substrates occurred during the transformation; the enantiopurities of the starting materials were within 1% ee of the tropane products as determined by chiral HPLC analysis.
^d The reaction was conducted at 125 °C using 8 mol % of PPh₂Cy as the ligand.

3.5 Pd-Catalyzed Synthesis of MK-801 Analog

To further demonstrate the utility of this method, we sought to prepare the MK-801 analog **3-23** (eq 1). This compound has served as a common intermediate en route to MK-801 and derivatives and also exhibits modest NMDA antagonist activity.^{4, 13} The synthesis of **3-23** has previously been accomplished via base-mediated transannular hydroamination of amino alkene **3-22**. This route afforded (±)-**3-23** in two steps from commercially available material.¹⁴ Although this is an effective approach to the racemate, an analogous route to enantioenriched samples of **3-23** has not been developed.⁴



In our synthesis of **3-23** we sought to effect the carboamination of a substrate related to diphenylmethanamine derivative **3-4b**, but with a cleavable group on the nitrogen atom in place of the *N*-phenyl substituent. Initial efforts to employ *N*-Boc-protected variants of **3-4b** were unsuccessful and led to either low conversion or decomposition of the starting material. As such, an *N*-PMP group was selected as the amine substituent, as this aryl protecting group can be cleaved under oxidizing conditions. Initial efforts to use 2-bromobenzaldehyde for the construction of the aryl bromide analog of **3-24** were unsuccessful, as *N*-arylation of the primary diarylmethanamine with 4-bromoanisole suffered from competing intramolecular Heck reaction of the bromoalkene. Thus, the requisite substrate **3-24** was prepared in three steps and with 37% overall yield from *o*-chlorobenzaldehyde using the route described above in Scheme 3.2. However, the Pd₂(dba)₃/PCy₃•HBF₄ catalyst system was not sufficiently reactive to promote complete conversion of **3-24** to **3-25**, and a significant amount of unreacted starting material was recovered. Thus, we were gratified to find that S-Phos, an electron-rich ligand recently shown to be effective in intermolecular carboamination reactions between aryl chlorides and *N*-substituted- γ -amino alkenes,¹⁵ led to complete substrate conversion (Scheme 3.5). These conditions provided desired tropane **3-25** in excellent yield and with no loss of enantiopurity. Treatment of **3-25** with CAN in aqueous acetonitrile at 0 °C led to clean removal of the PMP group and provided **3-23** in 74% yield.



Scheme 3.5. Pd-catalyzed synthesis of NMDA antagonist **3-23**

3.6 Conclusions

In conclusion, we have developed a new method for the synthesis of benzofused tropanes via an intramolecular Pd-catalyzed alkene carboamination reaction. This method allows for straightforward preparation of *N*-aryl benzotropanes bearing substituents at C8, C9, or on the fused arene ring. In

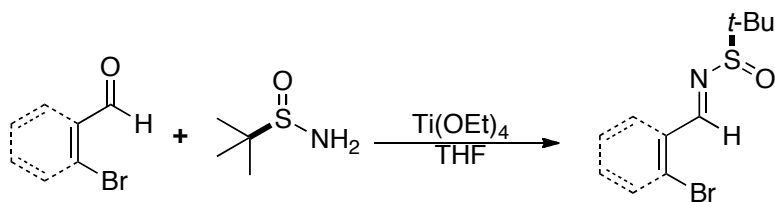
addition, *N*-H tropanes can be accessed through deprotection of *N*-PMP derivatives. Further studies on the application of this method to the construction of complex tropane alkaloids are currently underway.

The work described in this chapter was published in Organic Letters.¹⁶

3.7 Experimental

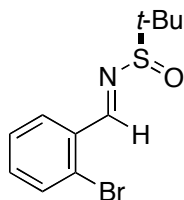
General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. All catalysts and reagents were obtained from commercial sources and were used without further purification. 2-Bromocyclohex-1-enecarboxaldehyde and 2-bromocyclopent-1-enecarboxaldehyde were prepared according to a published procedure.¹⁷ The synthesis of 4-bromo-2-methylbut-1-ene, (*E*)-1-bromohex-3-ene, and (*Z*)-1-bromohex-3-ene was accomplished via bromination of the corresponding homoallylic alcohols following the procedure reported by Berkowitz.¹⁸ Toluene, THF, and ether were dried and purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY, HSQC, and NOESY experiments. Ratios of diastereomers were determined by ¹H NMR. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ¹H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment. Thus, the yields reported in the supporting information may differ from those shown in this Chapter.

Synthesis of Substrates



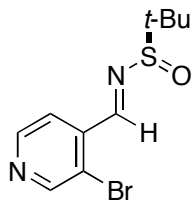
General Procedure 1: Synthesis of *N*-*tert*-Butanesulfinyl Imines via Condensation with (*R,S*)-(+)-*tert*-Butanesulfinamide with 2-Bromoaldehydes.¹⁹ A flame-dried flask was cooled under a stream of N_2 and

charged with the appropriate aldehyde (1.0-1.5 equiv) and sufficient THF to provide a 0.27 M solution. Neat $\text{Ti}(\text{OEt})_4$ (2 equiv) was added, the reaction mixture was stirred at rt for 5 min, then (R_S) -(+)-*tert*-butanesulfinamide (1 equiv) was added. The resulting mixture was stirred at rt until the *tert*-butanesulfinamide had been completely consumed as judged by TLC analysis. The reaction mixture was poured into an equal volume of brine and stirred for 10 min before the resulting suspension was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



***(R,E)*-N-(2-Bromobenzylidene)-2-methylpropane-2-sulfinamide (3-7a).**²⁰

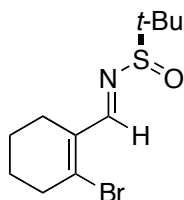
General procedure 1 was employed for the condensation of 2-bromobenzaldehyde (1.50 g, 6.55 mmol) with (R_S) -(+)-*tert*-butanesulfinamide (722 mg, 5.95 mmol) and $\text{Ti}(\text{OEt})_4$ (2.51 mL, 11.9 mmol) in 22 mL of THF. This procedure afforded 1.57 g (91%) of the title compound as a clear viscous oil with spectroscopic properties identical to those previously reported.²⁰



***(R,E)*-N-[(3-Bromopyridin-4-yl)methylene]-2-methylpropane-2-sulfinamide**

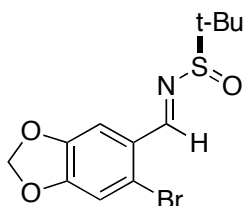
(3-7c). General procedure 1 was used for the condensation of 3-bromoisonicotinaldehyde²¹ (605 mg, 3.25 mmol) with (R_S) -(+)-*tert*-butanesulfinamide (392 mg, 3.23 mmol) and $\text{Ti}(\text{OEt})_4$ (1.37 mL, 6.51 mmol) in 12 mL of THF. This procedure afforded 820 mg (87%) of the title compound as a pale yellow solid: mp 92–93 °C. $[\alpha]_D^{23}$ –239.0 (*c* 2.5, CH_2Cl_2). ^1H NMR (400 MHz,

CDCl₃) δ 8.92 (s, 1 H), 8.87 (s, 1 H), 8.63 (d, *J* = 4.8 Hz, 1 H), 7.84 (d, *J* = 5.2 Hz, 1 H), 1.29 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 160.5, 153.5, 148.7, 139.0, 122.7, 122.4, 58.6, 22.7; IR (film) 1711 cm⁻¹. MS (ESI) 288.9999 (289.0005 calcd for C₁₀H₁₃BrN₂OS, M + H⁺).



(*R,E*)-*N*-[(2-Bromocyclohex-1-en-1-yl)methylene]-2-methylpropane-2-

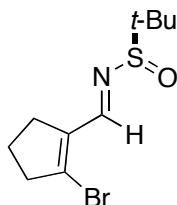
sulfinamide (3-7d). General procedure 1 was used for the condensation of 2-bromocyclohex-1-enecarboxaldehyde¹⁷ (1.39 g, 7.35 mmol) with (*R_S*)-(+)-*tert*-butanesulfinamide (891 mg, 7.35 mmol) and Ti(OEt)₄ (3.10 mL, 14.7 mmol) in 27 mL of THF. This procedure afforded 1.79 g (83%) of the title compound as a pale yellow solid: mp 84–85 °C. [α]_D²³ –422.6 (*c* 3.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 8.68 (s, 1 H), 2.74–2.71 (m, 2 H), 2.52–2.45 (m, 1 H), 2.39–2.31 (m, 1 H), 1.79–1.69 (m, 4 H), 1.19 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 163.6, 138.0, 132.6, 57.3, 38.4, 26.8, 24.4, 22.5, 21.4; IR (film) 1611 cm⁻¹. MS (ESI) 292.0365 (292.0365 calcd for C₁₁H₁₈BrNOS, M + H⁺).



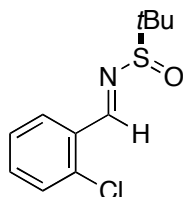
(*R,E*)-*N*-[(6-Bromobenzo[*d*][1,3]dioxol-5-yl)methylene]-2-methylpropane-2-

sulfinamide (3-7e). General procedure 1 was used for the condensation of 6-bromopiperonal (1.0 g, 4.4 mmol) with (*R_S*)-(+)-*tert*-butanesulfinamide (481 mg, 2.96 mmol) and Ti(OEt)₄ (2.11 mL, 7.92 mmol) in 15 mL of THF. This procedure afforded 1.13 g (86%) of the title compound as a white solid: mp 125–126 °C. [α]_D²³ –88.3 (*c* 1.6, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 8.86 (s, 1 H), 7.52 (s, 1 H), 7.07 (s, 1 H), 6.07–6.06 (d, *J* = 1.6 Hz, 2 H), 1.26 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 161.4, 151.7, 147.9, 126.8, 119.9, 113.1, 108.0, 102.5, 57.8, 22.6;

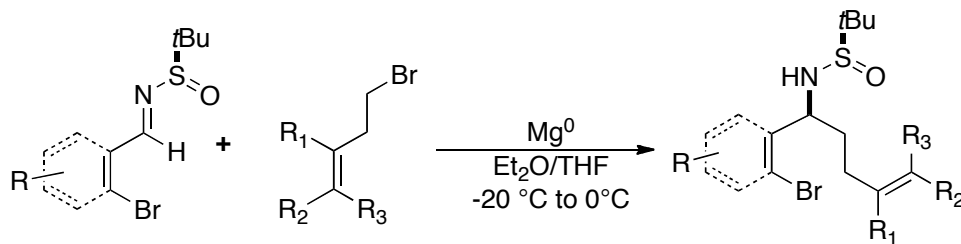
IR (film) 1605 cm^{-1} . MS (ESI) 331.9949 (331.9951 calcd for $\text{C}_{12}\text{H}_{14}\text{BrNO}_3\text{S}$, $\text{M} + \text{H}^+$).



(*R,E*)-*N*-[(2-Bromocyclopent-1-en-1-yl)methylene]-2-methylpropane-2-sulfonamide (3-7f). General procedure 1 was used for the condensation of 2-bromocyclopent-1-enecarboxaldehyde¹⁷ (1.54 g, 8.80 mmol) with (*R_S*)-(+)-*tert*-butanesulfonamide (1.05 g, 8.71 mmol) and $\text{Ti}(\text{OEt})_4$ (3.68 mL, 17.4 mmol) in 30 mL of THF. This procedure afforded 2.14 g (88%) of the title compound as a pale yellow solid: mp 73–74 °C. $[\alpha]_{\text{D}}^{23} -481.0$ (*c* 0.9, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1 H), 2.89 (t, *J* = 7.5 Hz, 2 H), 2.72–2.56 (m, 2 H), 2.05 (p, *J* = 7.6 Hz, 2 H), 1.21 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.1, 137.5, 135.4, 57.4, 42.1, 30.9, 22.5, 21.5; IR (film) 1611 cm^{-1} . MS (ESI) 278.0208 (278.0209 calcd for $\text{C}_{10}\text{H}_{16}\text{BrNOS}$, $\text{M} + \text{H}^+$).



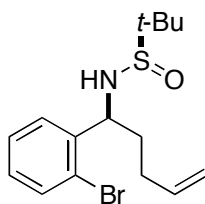
(*R,E*)-*N*-(2-Chlorobenzylidene)-2-methylpropane-2-sulfonamide (3-S1).²⁰ General procedure 1 was employed for the condensation of 2-chlorobenzaldehyde (1.00 g, 7.11 mmol) with (*R_S*)-(+)-*tert*-butanesulfonamide (862 mg, 7.11 mmol) and $\text{Ti}(\text{OEt})_4$ (3.0 mL, 14.2 mmol) in 25 mL of THF. This procedure afforded 1.47 g (85%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.²⁰



General Procedure 2: Synthesis of α -Branched Amines via Grignard Addition into Aldimines.

(a) Synthesis of Grignard Reagents: A flame-dried flask was cooled under a stream of N_2 and charged with freshly ground magnesium turnings (4–5 equiv). The magnesium was suspended in ether (1 M relative to the alkyl bromide), cooled to 0 °C in an ice/water bath, and the appropriate alkyl bromide (2.0–2.8 equiv) was added dropwise. After addition, the ice bath was removed, and the reaction mixture was stirred at rt for 1 h. Stirring was stopped, and the solution was filtered through glass wool prior to addition to the appropriate sulfinyl imine.

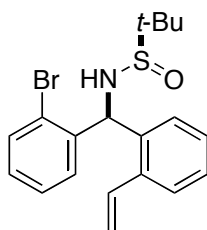
(b) 1,2-Grignard Addition of Grignard Reagents to Sulfinyl Imines: A flame-dried flask was cooled under a stream of N_2 and charged with a 0.2 M solution of the appropriate sulfinyl imine (1 equiv) in THF. The sulfinyl imine solution was cooled to –20 °C using an aqueous $CaCl_2$ /ice bath before the filtered Grignard reagent solution was added dropwise. After addition was complete the reaction mixture was warmed to 0 °C and stirred until TLC analysis indicated that the starting material had been completely consumed. Water was then added dropwise until the precipitation of magnesium salts occurred and the resulting solution could be easily decanted into a separate flask. The solution was concentrated *in vacuo* to afford the crude amine product, which was purified by flash chromatography on silica gel.



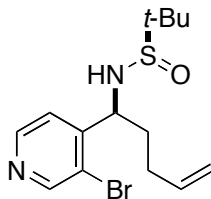
($R_S,1S$)-*N*-[1-(β -Bromophenyl)pent-4-en-1-yl]-2-methylpropane-2

sulfonamide (3-8a). General procedure 2a was followed for the generation of but-3-en-1-ylmagnesium bromide from 4-bromobut-1-ene (296 mg, 2.19 mmol) and magnesium turnings (107 mg, 4.39 mmol). The Grignard reagent was then added to a solution of **3-7a** (253 mg, 8.80 mmol) in THF (5 mL) according to general procedure 2b. The crude product was formed as a 4:1 mixture of diastereomers as judged by 1H NMR analysis. Purification by flash

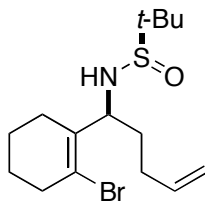
chromatography afforded 155 mg (51%) of the title compound as a clear oil with >20:1 dr. $[\alpha]_D^{23} -61.9$ (c 3.6, CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.8$ Hz, 1 H), 7.37 (d, $J = 7.6$ Hz, 1 H), 7.30 (t, $J = 7.6$ Hz, 1 H), 7.12 (t, $J = 8.0$ Hz, 1 H), 5.81 (ddt, $J = 6.4, 10.4, 16.8$ Hz, 1 H), 5.06 (dd, $J = 1.6, 16.8$ Hz, 1 H), 5.00 (dd, $J = 1.2, 10.4$ Hz, 1 H), 4.94–4.89 (m, 1 H), 3.53 (d, $J = 3.6$ Hz, 1 H), 2.20–2.11 (m, 1 H), 2.09–2.00 (m, 1 H), 1.99–1.88 (m, 2 H), 1.18 (s, 9 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 141.2, 137.3, 133.1, 128.8, 128.6, 127.5, 123.7, 115.6, 58.1, 55.7, 36.6, 30.0, 22.5; IR (film) 3309, 1065 cm^{-1} . MS (ESI) 344.0681 (344.0678 calcd for $\text{C}_{15}\text{H}_{22}\text{BrNOS}$, $\text{M} + \text{H}^+$).



($R_s,1S$)-*N*-[(2-Bromophenyl)(2-vinylphenyl)methyl]-2-methylpropane-2-sulfonamide (3-8b). General procedure 2a was followed for the generation of (2-vinylphenyl)magnesium bromide from 2-bromostyrene (2.00 g, 10.9 mmol) and magnesium turnings (505 mg, 20.8 mmol). The Grignard reagent was then added to a solution of **3-7a** (1.5 g, 5.2 mmol) in THF (25 mL) according to general procedure 2b. The crude product was formed as a 9:1 mixture of diastereomers as judged by $^1\text{H NMR}$ analysis. Purification by flash chromatography afforded 1.41 g (69%) of the title compound as a white solid with >20:1 dr: mp 152–154 $^\circ\text{C}$. $[\alpha]_D^{23} -5.4$ (c 1.5, CH_2Cl_2). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 7.6$ Hz, 1 H), 7.54 (t, $J = 7.9$ Hz, 2 H), 7.38–7.26 (m, 3 H), 7.20–7.15 (m, 2 H), 6.98 (d, $J = 7.6$ Hz, 1 H), 6.26 (s, 1 H), 5.69 (d, $J = 17.2$ Hz, 1 H), 5.45 (d, $J = 10.8$ Hz, 1 H), 3.58 (s, 1 H), 1.25 (s, 9 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 140.0, 137.3, 137.2, 133.8, 133.3, 130.1, 129.0, 128.3, 127.9, 127.7, 127.2, 126.7, 124.3, 117.8, 57.6, 56.1, 22.7; IR (film) 3421, 1068 cm^{-1} . MS (ESI) 392.0683 (392.0678 calcd for $\text{C}_{19}\text{H}_{22}\text{BrNOS}$, $\text{M} + \text{H}^+$).

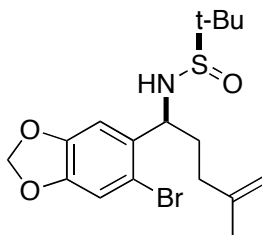


(*R_S*,1*S*)-*N*-[1-(3-Bromopyridin-4-yl)pent-4-en-1-yl]-2-methylpropane-2-sulfinamide (4-8c). General procedure 2a was followed for the generation of but-3-en-1-ylmagnesium bromide from 4-bromobut-1-ene (957 mg, 7.09 mmol) and magnesium turnings (276 mg, 11.4 mmol). The Grignard reagent was then added to a solution of **3-7c** (820 mg, 2.84 mmol) in THF (15 mL) according to general procedure 2b. The crude product was formed as a 2:1 mixture of diastereomers as judged by ¹H NMR analysis. Purification by flash chromatography afforded 373 mg (38%) of the title compound as an orange oil with >20:1 dr. [α]_D²³ -68.9 (*c* 1.5, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 8.69 (s, 1 H), 8.50 (d, *J* = 4.8 Hz, 1 H), 7.33 (d, *J* = 4.8 Hz, 1 H), 5.81 (ddt, *J* = 6.4, 9.9, 16.8 Hz, 1 H), 5.09 (d, *J* = 13.9 Hz, 1 H), 5.04 (d, *J* = 8.8 Hz, 1 H), 4.87–4.83 (m, 1 H), 3.64 (d, *J* = 4.0 Hz, 1 H), 2.24–2.09 (m, 2 H), 2.04–1.86 (m, 2 H), 1.21 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 152.3, 150.3, 148.4, 136.7, 123.2, 121.7, 116.2, 57.4, 55.9, 35.7, 29.8, 22.4; IR (film) 3292, 1067 cm⁻¹. MS (ESI) 345.0626 (345.0631 calcd for C₁₄H₂₁BrN₂OS, M + H⁺).

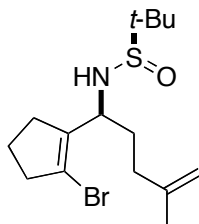


(*R_S*,1*S*)-*N*-[1-(2-Bromocyclohex-1-en-1-yl)pent-4-en-1-yl]-2-methylpropane-2-sulfinamide (4-8d). General procedure 2a was followed for the generation of but-3-en-1-ylmagnesium bromide from 4-bromobut-1-ene (1.58 g, 11.7 mmol) and magnesium turnings (429 mg, 17.6 mmol). The Grignard reagent was then added to a solution of **4-7d** (984 mg, 3.36 mmol) in THF (20 mL) according to general procedure 2b. The crude product was formed as a 12:1 mixture of diastereomers as judged by ¹H NMR analysis. Purification by flash chromatography afforded 774 mg (66%) of the title compound as a white solid

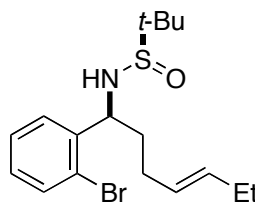
with >20:1 dr: mp 56-57 °C. $[\alpha]_D^{23} -45.2$ (c 1.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 5.81 (ddt, *J* = 6.4, 9.9, 16.8 Hz, 1 H), 5.05 (dd, *J* = 1.2, 17.2 Hz, 1 H), 4.98 (dd, *J* = 0.8, 9.9 Hz, 1 H), 4.62 (td, *J* = 3.6, 7.6 Hz, 1 H), 3.07 (d, *J* = 3.2 Hz, 1 H), 2.56–2.52 (m, 2 H), 2.17–1.91 (m, 4 H), 1.71–1.57 (m, 6 H), 1.18 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.5, 134.3, 123.0, 115.3, 58.8, 55.4, 37.0, 33.2, 30.0, 25.5, 24.8, 22.5, 22.2; IR (film) 3430 cm⁻¹. MS (ESI) 348.0995 (348.0991 calcd for C₁₅H₂₆BrNOS, M + H⁺).



(*R*_S,1*S*)-*N*-[1-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-4-methylpent-4-en-1-yl]-2-methylpropane-2-sulfonamide (3-8e). General procedure 2a was followed for the generation of (3-methylbut-3-en-1-yl)magnesium bromide from 4-bromo-2-methylbut-1-ene (1.07 g, 7.22 mmol) and magnesium turnings (350 mg, 14.4 mmol). The Grignard reagent was then added to a solution of **3-7e** (1.2 g, 3.6 mmol) in THF (20 mL) according to general procedure 2b. The crude product was formed as a 3:1 mixture of diastereomers as judged by ¹H NMR analysis. Purification by flash chromatography afforded 665 mg (46%) of the title compound as a colorless oil with >20:1 dr. $[\alpha]_D^{23} -86.5$ (c 2.4, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 6.99 (s, 1 H), 6.84 (s, 1 H), 5.98 (d, *J* = 2.4 Hz, 2 H), 4.84 (s, br, 1 H), 4.75 (s, 1 H), 4.71 (s, 1 H), 3.48 (s, br, 1 H), 2.12–2.04 (m, 1 H), 2.00–1.89 (m, 3 H), 1.72 (s, 3 H), 1.19 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.6, 147.5, 144.6, 134.4, 114.3, 112.6, 110.7, 108.0, 101.8, 57.8, 55.7, 35.5, 33.8, 22.55, 22.52; IR (film) 3301, 1064 cm⁻¹. MS (ESI) 402.0738 (402.0733 calcd for C₁₇H₂₄BrNO₃S, M + H⁺).

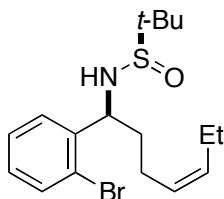


(*R*_s,1*S*)-*N*-[1-(2-Bromocyclopent-1-en-1-yl)-4-methylpent-4-en-1-yl]-2-methylpropane-2-sulfinamide (3-8f). General procedure 2a was followed for the generation of (3-methylbut-3-en-1-yl)magnesium bromide from 4-bromo-2-methylbut-1-ene (928 mg, 6.23 mmol) and magnesium turnings (213 mg, 8.76 mmol). The Grignard reagent was then added to a solution of **3-7f** (611 mg, 2.20 mmol) in THF (15 mL) according to general procedure 2b. The crude product was formed as a 9:1 mixture of diastereomers as judged by ¹H NMR analysis. Purification by flash chromatography afforded 544 mg (71%) of the title compound as a colorless oil with 20:1 dr. $[\alpha]_D^{23} -59.6$ (c 1.7, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 4.74 (s, 1 H), 4.72 (s, 1 H), 4.35 (td, *J* = 3.2, 6.4 Hz, 1 H), 3.17 (d, *J* = 3.2 Hz, 1 H), 2.69–2.64 (m, 2 H), 2.38–2.64 (m, 1 H), 2.28–2.23 (m, 1 H), 2.07–1.98 (m, 1 H), 1.95–1.91 (m, 3 H), 1.81–1.71 (m, 5 H), 1.19 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 144.6, 139.5, 120.2, 110.6, 55.4, 54.0, 40.1, 33.9, 32.4, 29.7, 22.5, 22.4, 21.8; IR (film) 3301, 1062 cm⁻¹. MS (ESI) 348.0992 (348.0991 calcd for C₁₅H₂₆BrNOS, M + H⁺).

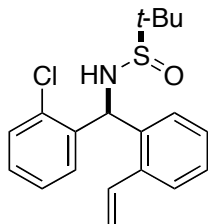


(*R*_s,1*S*,4*E*)-*N*-[1-(2-Bromophenyl)hept-4-en-1-yl]-2-methylpropane-2-sulfinamide (3-8g). General procedure 2a was followed for the generation of (*E*)-hex-3-en-1-ylmagnesium bromide from (*E*)-1-bromohex-3-ene (1.52 g, 9.37 mmol) and magnesium turnings (365 mg, 15.0 mmol). The Grignard reagent was then added to a solution of **3-7a** (1.08 g, 3.75 mmol) in THF (20 mL) according to general procedure 2b. The crude product was formed as a 4:1 mixture of diastereomers as judged by ¹H NMR analysis. Purification by flash chromatography afforded 782 mg (56%) of the title compound as a white solid with >20:1 dr: mp 60-61 °C. $[\alpha]_D^{23} -63.5$ (c 2.6, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 5.53–5.47 (m, 1 H), 5.41–5.34 (m, 1 H), 4.93–4.89 (m, 1 H), 3.51 (d, *J* = 3.2 Hz, 1 H), 2.12–1.86 (m, 6 H), 1.18 (s, 9 H), 0.96 (t, *J* =

7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.4, 133.5, 133.1, 128.7, 127.5, 123.8, 58.0, 55.7, 37.3, 28.9, 25.5, 22.5, 13.7 (two aromatic carbon signals are absent due to accidental equivalence); IR (film) 3301, 1066 cm^{-1} . MS (ESI) 372.0991 (372.0991 calcd for $\text{C}_{17}\text{H}_{26}\text{BrNOS}$, $\text{M} + \text{H}^+$).

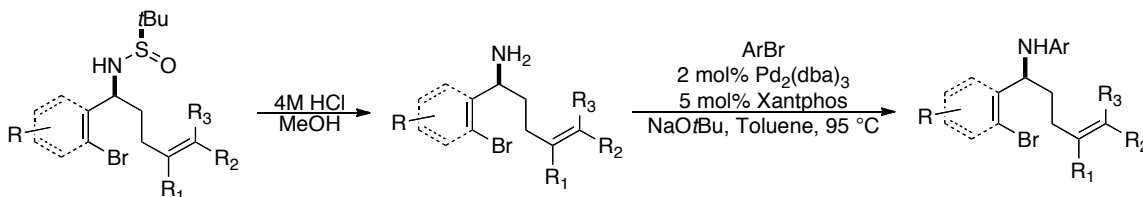


($R_S,1S,4Z$)-*N*-[1-(2-Bromophenyl)hept-4-en-1-yl]-2-methylpropane-2-sulfonamide (3-8h). General procedure 2a was followed for the generation of (*Z*)-hex-3-en-1-ylmagnesium bromide from (*Z*)-1-bromohex-3-ene (1.09 g, 6.69 mmol) and magnesium turnings (337 mg, 13.9 mmol). The Grignard reagent was then added to a solution of **3-7a** (1.0 g, 3.5 mmol) in THF (20 mL) according to general procedure 2b. The crude product was formed as a 4:1 mixture of diastereomers as judged by ^1H NMR analysis. Purification by flash chromatography afforded 769 mg (59%) of the title compound as a clear oil with >20:1 dr. $[\alpha]_D^{23} -77.5$ (c 1.2, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.54 (d, $J = 7.6$ Hz, 1 H), 7.38 (d, $J = 7.9$ Hz, 1 H), 7.30 (t, $J = 7.9$ Hz, 1 H), 7.12 (t, $J = 7.6$ Hz, 1 H), 5.43–5.29 (m, 2 H), 4.93–4.89 (m, 1 H), 3.57 (d, $J = 3.2$ Hz, 1 H), 2.18–2.11 (m, 1 H), 2.06–1.87 (m, 5 H), 1.18 (s, 9 H), 0.93 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.2, 133.0, 132.9, 128.7, 128.6, 127.4, 123.8, 58.1, 55.7, 37.4, 23.7, 22.4, 20.4, 14.1 (one aromatic carbon signal is absent due to accidental equivalence); IR (film) 3301, 1067 cm^{-1} . MS (ESI) 372.0995 (372.0997 calcd for $\text{C}_{17}\text{H}_{26}\text{BrNOS}$, $\text{M} + \text{H}^+$).



($R_S,1S$)-*N*-[(2-Chlorophenyl)(2-vinylphenyl)methyl]-2-methylpropane-2-sulfonamide (3-S2). General procedure 2a was followed for the generation of (2-

vinylphenyl)magnesium bromide from 2-bromostyrene (1.68 g, 9.03 mmol) and magnesium turnings (398 mg, 16.4 mmol). The Grignard reagent was then added to a solution of **3-S1** (1.0 g, 4.1 mmol) in THF (25 mL) according to general procedure 2b. The crude product was formed as a 13:1 mixture of diastereomers as judged by ^1H NMR analysis. Purification by flash chromatography afforded 1.04 g (73%) of the title compound as a white solid with >20:1 dr: mp 149–150 °C. $[\alpha]_D^{23} -12.1$ (c 6.3, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 7.6$ Hz, 1 H), 7.50 (d, $J = 7.6$ Hz, 1 H), 7.34–7.15 (m, 6 H), 7.02 (d, $J = 7.9$ Hz, 1 H), 6.31 (d, $J = 2.4$ Hz, 1 H), 5.66 (dd, $J = 1.2, 17.2$ Hz, 1 H), 5.42 (dd, $J = 1.6, 10.8$ Hz, 1 H), 3.58 (d, $J = 2.4$ Hz, 1 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.4, 137.2, 137.1, 133.8, 133.7, 129.8, 129.6, 128.7, 128.2, 127.8, 127.6, 126.7, 126.6, 117.7, 56.0, 55.1, 22.6; IR (film) 3306, 1069 cm^{-1} . MS (ESI) 348.1183 (347.1111 calcd for $\text{C}_{19}\text{H}_{22}\text{ClNOS}$, $\text{M} + \text{H}^+$).

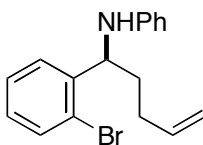


General Procedure 3: Conversion of *N*-*tert*-Butanesulfinamides to *N*-aryl amines.

(a) Sulfinamide Deprotection: A flame-dried flask was cooled under a stream of N_2 and charged with a 0.2 M solution of the appropriate sulfinamide (1 equiv) in methanol. A 4 M solution of HCl in dioxane (2 equiv) was then added and the resulting solution was stirred at rt until the starting material had been consumed as judged by TLC analysis (ca. 1-2 h). The reaction mixture was basified to $\text{pH} > 11$ with 10 M NaOH and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a primary amine product that was carried forward without further purification.

(b) *N*-Arylation of Primary Amines: A flame-dried Schlenk tube was cooled under a stream of N_2 and charged with sodium *tert*-butoxide (1.5 equiv), $\text{Pd}_2(\text{dba})_3$ (2 mol% complex, 4 mol% Pd), and Xantphos (5 mol%). The tube was purged with

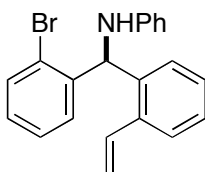
N₂ and the aryl bromide (1.2-1.3 equiv) and a 0.1 M solution of the appropriate primary amine (1 equiv) in toluene was added. The resulting mixture was heated to 90 °C with stirring until the starting material had been completely consumed as judged by TLC analysis (ca. 2–4 h). The reaction mixture was cooled to rt, quenched with saturated aqueous ammonium chloride (5 mL), and transferred to a separatory funnel. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



(S)-N-[1-(2-Bromophenyl)pent-4-en-1-yl]aniline (3-4a). General procedure 3a was used for the deprotection of **3-8a** (385 mg, 1.12 mmol) with 4 M HCl (0.6 mL, 2.23 mmol). This procedure afforded 242 mg (90%) of (S)-1-(2-bromophenyl)pent-4-en-1-amine (**3-9a**) as a clear oil. $[\alpha]_D^{23} -38.2$ (c 8.6, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 9.2 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 5.84 (ddt, *J* = 6.8, 10.4, 17.2 Hz, 1 H), 5.03 (dd, *J* = 1.2, 17.2 Hz, 1 H), 4.97 (dd, *J* = 2.0, 10.0 Hz, 1 H), 4.36 (t, *J* = 6.0 Hz, 1 H), 2.23–2.15 (m, 1 H), 2.14–2.06 (m, 1 H), 1.89–1.80 (m, 1 H), 1.74–1.65 (m, 1 H), 1.46 (s, br, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.1, 138.1, 132.9, 128.2, 127.7, 127.2, 123.4, 114.8, 53.9, 37.1, 30.7; IR (film) 3388, 3321 cm⁻¹. MS (ESI) 240.0379 (240.0388 calcd for C₁₁H₁₄BrN, M + H⁺).

General procedure 3b was used for the *N*-arylation of **3-9a** (100 mg, 0.42 mmol) with bromobenzene (98 mg, 0.62 mmol) using 5 mol% of (±)-BINAP in place of Xantphos as the ligand. This procedure afforded 63 mg (48%) of the title compound as a yellow oil. $[\alpha]_D^{23} +96.9$ (c 1.3, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.11–7.05 (m, 3 H), 6.64 (t, *J* = 8.4 Hz, 1 H), 6.46 (d, *J* = 8.4 Hz, 2 H), 5.87 (ddt, *J* = 6.4, 10.0, 16.8 Hz, 1 H), 5.05 (dd, *J* = 3.2, 18.8 Hz, 1 H), 5.00 (dd, *J* = 1.6 Hz, 10.4 Hz, 1 H), 4.77–4.75 (m, 1 H), 4.17 (s, br, 1 H), 2.34–2.19 (m, 2 H),

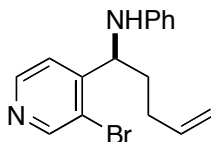
1.99–1.91 (m, 1 H), 1.78–1.69 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.8, 142.5, 137.6, 132.9, 129.1, 128.4, 127.8, 127.5, 123.1, 117.4, 115.4, 113.1, 56.6, 36.4, 30.6; IR (film) 3424, 1603, 1504 cm^{-1} . MS (ESI) 316.0692 (316.0701 calcd for $\text{C}_{17}\text{H}_{18}\text{BrN}$, $\text{M} + \text{H}^+$). The enantiopurity was determined to be 97% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 5% *i*PrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 5.00 and 5.43 min).



(S)-N-[(2-Bromophenyl)(2-vinylphenyl)methyl]aniline (3-4b). General procedure 3a was used for the deprotection of **3-8b** (825 mg, 2.10 mmol) with 4 M HCl (1.05 mL, 4.2 mmol). This procedure afforded 460 mg (76%) of (S)-(2-bromophenyl)(2-vinylphenyl)methanamine (**3-9b**) as a green oil. $[\alpha]_D^{23} +16.2$ (*c* 0.9, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, J = 16.8 Hz, 1 H), 7.49–7.47 (m, 1 H), 7.36–7.34 (m, 1 H), 7.30–7.24 (m, 4 H), 7.13–7.09 (m, 1 H), 6.95 (dd, J = 10.8, 17.2 Hz, 1 H), 5.75 (s, 1 H), 5.59 (dd, J = 1.6, 17.6 Hz, 1 H), 5.27 (dd, J = 1.6, 10.8 Hz, 1 H), 1.73 (s, br, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.9, 140.7, 136.7, 134.3, 132.9, 128.9, 128.5, 127.9, 127.7, 127.3, 126.3, 123.9, 116.6, 55.0; IR (film) 3375, 3317, 1421, 1265 cm^{-1} . MS (ESI) 271.0112 (271.0122 calcd for $\text{C}_{15}\text{H}_{12}\text{Br}$, $\text{M} - \text{NH}_2$).

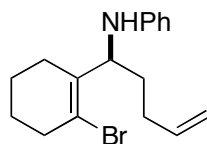
General procedure 3b was used for the *N*-arylation of **3-9b** (412 mg, 1.43 mmol) with bromobenzene (269 mg, 1.72 mmol) using 5 mol% of (\pm)-BINAP in place of Xantphos as the ligand. This procedure afforded 395 mg (76%) of the title compound as a green oil. $[\alpha]_D^{23} +102.3$ (*c* 18.7, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.55 (t, J = 6.8 Hz, 2 H), 7.43 (d, J = 7.6 Hz, 1 H), 7.27–7.21 (m, 2 H), 7.15–7.06 (m, 4 H), 7.02–6.94 (m, 2 H), 6.67 (t, J = 7.6 Hz, 1 H), 6.43 (d, J = 8.0 Hz, 2 H), 6.01 (d, J = 4.4 Hz, 1 H), 5.65 (dd, J = 1.2, 17.2 Hz, 1 H), 5.26 (dd, J = 1.2, 10.8 Hz, 1 H), 4.06 (d, J = 4.4 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.7, 140.4, 137.9, 137.5, 133.9, 133.2, 129.6, 129.1, 128.9, 127.9, 127.8, 127.5, 127.4, 126.4, 124.1, 117.8, 117.0, 113.0, 58.4; IR (film) 3428, 1601 cm^{-1} . MS

(ESI) 364.0686 (364.0695 calcd for C₂₁H₁₈BrN, M + H⁺). The enantiopurity was determined to be 99% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 100% hexanes, 1.5 mL/min, λ = 231 nm, RT = 12.24 and 15.38 min).



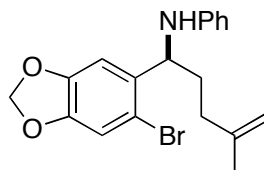
(S)-N-[1-(3-Bromopyridin-4-yl)pent-4-en-1-yl]aniline (3-4c). General procedure 3a was used for the deprotection of **3-8c** (373 mg, 1.08 mmol) with 4 M HCl (0.5 mL, 2.2 mmol). This procedure afforded 250 mg (90%) of (S)-1-(3-bromopyridin-4-yl)pent-4-en-1-ylamine (**3-9c**) as an orange oil. $[\alpha]_D^{23} -41.2$ (c 6.4, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 8.63 (s, 1 H), 8.47 (d, J = 5.0 Hz, 1 H), 7.45 (d, J = 5.0 Hz, 1 H), 5.83 (ddt, J = 7.0, 10.5, 17.5 Hz, 1 H), 5.05 (dd, J = 1.5, 17.0 Hz, 1 H), 4.99 (dd, J = 1.0 Hz, 10.0 Hz, 1 H), 4.30 (dd, J = 5.0, 8.0 Hz, 1 H), 2.23–2.17 (m, 1 H), 2.17–2.09 (m, 1 H), 1.94–1.79 (m, 1 H), 1.67–1.55 (m, 1 H), 1.51 (s, br, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 153.9, 151.8, 148.6, 137.4, 122.2, 121.5, 115.3, 53.3, 36.3, 30.3; IR (film) 3389, 3323, 1582 cm⁻¹. MS (ESI) 241.0332 (241.0335 calcd for C₁₀H₁₃BrN₂, M + H⁺).

General procedure 3b was used for the N-arylation of **3-9c** (163 mg, 0.68 mmol) with bromobenzene (129 mg, 1.35 mmol). This procedure afforded 99 mg (46%) of the title compound as an orange semi-solid. $[\alpha]_D^{23} +74.3$ (c 4.6, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 8.68 (s, 1 H), 8.38 (d, J = 5.2 Hz, 1 H), 7.31 (d, J = 4.8 Hz, 1 H), 7.09 (t, J = 8.0 Hz, 2 H), 6.67 (t, J = 7.2 Hz, 1 H), 6.41 (d, J = 8.4 Hz, 2 H), 5.85 (ddt, J = 6.8, 10.4, 16.8 Hz, 1 H), 5.08–5.01 (m, 2 H), 4.69 (d, J = 5.6 Hz, 1 H), 4.25 (s, br, 1 H), 2.35–2.19 (m, 2 H), 2.04–1.90 (m, 1 H), 1.76–1.66 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 152.1, 151.9, 148.7, 146.2, 136.9, 129.2, 122.3, 121.4, 117.9, 115.9, 113.0, 56.1, 35.4, 30.4; IR (film) 3432, 1603, 1505 cm⁻¹. MS (ESI) 317.0645 (317.0648 calcd for C₁₆H₁₇BrN₂, M + H⁺). The enantiopurity was determined to be 99% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 20% *i*PrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 3.26 and 3.84 min).



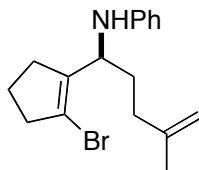
(S)-N-[1-(2-Bromocyclohex-1-en-1-yl)pent-4-en-1-yl]aniline (3-4d). General procedure 3a was used for the deprotection of **3-8d** (753 mg, 2.16 mmol) with 4 M HCl (1.08 mL, 4.32 mmol). This procedure afforded 483 mg (92%) of (S)-1-(2-bromocyclohex-1-en-1-yl)pent-4-en-1-ylamine (**3-9d**) as an orange oil. $[\alpha]_D^{23} +3.1$ (c 2.5, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 5.83 (ddt, *J* = 6.8, 9.9, 16.8 Hz, 1 H), 5.03 (dd, *J* = 1.6, 15.2 Hz, 1 H), 4.95 (dd, *J* = 1.2 Hz, 9.9 Hz, 1 H), 4.04 (t, *J* = 7.6 Hz, 1 H), 2.51–2.49 (m, 2 H), 2.25–2.17 (m, 1 H), 2.15–2.09 (m, 1 H), 2.05–1.96 (m, 2 H), 1.72–1.61 (m, 4 H), 1.56–1.47 (m, 2 H), 1.27 (s, br, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 138.3, 138.1, 120.1, 114.6, 55.3, 37.0, 34.1, 30.6, 24.9, 24.8, 22.4; IR (film) 3375, 3292 cm⁻¹. MS (ESI) 244.0693 (244.0695 calcd for C₁₁H₁₈BrN, M + H⁺).

General procedure 3b was used for the *N*-arylation of **3-9d** (415 mg, 1.70 mmol) with bromobenzene (320 mg, 2.04 mmol). This procedure afforded 442 mg (81%) of the title compound as a green oil. $[\alpha]_D^{23} +96.6$ (c 1.4, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.15 (t, *J* = 7.6 Hz, 2 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.55 (d, *J* = 8.4 Hz, 2 H), 5.87 (ddt, *J* = 6.4, 10.0, 16.8 Hz, 1 H), 5.05 (d, *J* = 17.2 Hz, 1 H), 4.99 (d, *J* = 10.0 Hz, 1 H), 4.47 (q, *J* = 7.2 Hz, 1 H), 3.67 (d, *J* = 6.4 Hz, 1 H), 2.53 (s, br, 2 H), 2.30–2.23 (m, 1 H), 2.21–2.11 (m, 1 H), 2.01–1.91 (m, 2 H), 1.70–1.51 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.3, 137.9, 136.6, 129.2, 121.1, 117.2, 115.0, 112.9, 57.2, 36.9, 33.3, 30.3, 25.5, 24.7, 22.2; IR (film) 3428, 1602 cm⁻¹. MS (ESI) 320.1002 (320.1008 calcd for C₁₇H₂₂BrN, M + H⁺). The enantiopurity was determined to be 93% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 1% *i*PrOH/hexanes, 0.5 mL/min, λ = 231 nm, RT = 6.03 and 7.05 min).



(S)-N-[1-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-4-methylpent-4-en-1-yl]aniline (3-4e). General procedure 3a was used for the deprotection of **3-8e** (620 mg, 1.54 mmol) with 4 M HCl (0.8 mL, 3.1 mmol). This procedure afforded 395 mg (86%) of (S)-1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-4-methylpent-4-en-1-ylamine (**3-9e**) as a colorless oil. $[\alpha]_D^{23} -23.6$ (c 0.6, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.00–6.96 (m, 2 H), 5.96 (d, *J* = 3.6 Hz, 2 H), 4.72 (s, 1 H), 4.69 (s, 1 H), 4.31–4.27 (m, 1 H), 2.16–2.09 (m, 1 H), 2.04–1.96 (m, 1 H), 1.84–1.75 (m, 1 H), 1.73 (s, br, 3 H), 1.70–1.64 (m, 1 H), 1.43 (s, br, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.7, 146.9, 145.3, 138.5, 113.3, 112.5, 110.0, 107.0, 101.6, 53.9, 36.1, 34.5, 22.5; IR (film) 3381, 3317 cm⁻¹. MS (ESI) 298.0434 (298.0437 calcd for C₁₃H₁₆BrNO₂, M + H⁺).

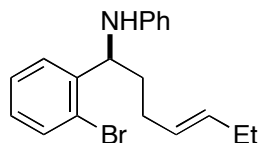
General procedure 3b was used for the *N*-arylation of **3-9e** (327 mg, 1.10 mmol) with bromobenzene (224 mg, 1.43 mmol). This procedure afforded 331 mg (80%) of the title compound as a yellow oil. $[\alpha]_D^{23} +33.2$ (c 1.4, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.10 (t, *J* = 6.4 Hz, 2 H), 6.99 (s, 1 H), 6.89 (s, 1 H), 6.53 (t, *J* = 7.2 Hz, 1 H), 6.46 (d, *J* = 7.9 Hz, 2 H), 5.92 (d, *J* = 1.2 Hz, 1 H), 5.89 (d, *J* = 1.6 Hz, 1 H), 4.75 (s, 1 H), 4.70 (s, 1 H), 4.65 (s, br, 1 H), 4.12 (s, br, 1 H), 2.27–2.19 (m, 1 H), 2.17–2.09 (m, 1 H), 1.97–1.89 (m, 1 H), 1.78–1.68 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.9, 147.2, 146.8, 144.9, 136.2, 129.1, 117.5, 113.1, 113.0, 112.7, 110.4, 107.1, 101.6, 56.8, 35.4, 34.4, 22.7; IR (film) 3429, 1602 cm⁻¹. MS (ESI) 374.0740 (374.0756 calcd for C₁₉H₂₀BrNO₂, M + H⁺). The enantiopurity was determined to be 98% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 1% *i*PrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 8.35 and 11.97 min).



(S)-N-[1-(2-Bromocyclopent-1-en-1-yl)-4-methylpent-4-en-1-yl]aniline (3-4f). General procedure 3a was used for the deprotection of **3-8f** (554 mg, 1.55 mmol) with 4 M HCl (0.78 mL, 3.1 mmol). This procedure afforded 354 mg (94%) of (S)-

1-(2-bromocyclopent-1-en-1-yl)-4-methylpent-4-en-1-ylamine (**3-9f**) as a colorless oil. $[\alpha]_D^{23} -11.1$ (c 9.7, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 4.72 (s, 1 H), 4.69 (s, 1 H), 3.83–3.77 (m, 1 H), 2.65–2.62 (m, 2 H), 2.47–2.39 (m, 1 H), 2.31–2.22 (m, 1 H), 2.10–2.03 (m, 1 H), 1.98–1.89 (m, 3 H), 1.73 (s, 3 H), 1.67–1.52 (m, 2 H), 1.17 (s, br, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.1, 143.3, 116.1, 109.7, 50.2, 39.8, 34.2, 33.5, 28.8, 22.3, 21.4; IR (film) 3376, 3314 cm⁻¹. MS (ESI) 244.0696 (244.0695 calcd for C₁₁H₁₈BrN, M + H⁺).

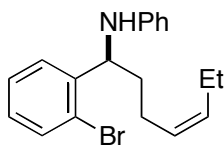
General procedure 3b was used for the *N*-arylation of **3-9f** (254 mg, 1.04 mmol) with bromobenzene (245 mg, 1.56 mmol). This procedure afforded 174 mg (52%) of the title compound as an orange oil. $[\alpha]_D^{23} +101.6$ (c 1.0, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.15–7.11 (m, 2 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 2 H), 4.75 (s, 1 H), 4.71 (s, 1 H), 4.26 (t, *J* = 7.2 Hz, 1 H), 3.62 (s, br, 1 H), 2.66–2.61 (m, 2 H), 2.23–2.13 (m, 3 H), 2.09–2.04 (m, 1 H), 1.89–1.66 (m, 7 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.2, 144.9, 141.6, 129.1, 117.8, 117.3, 113.1, 110.2, 52.4, 40.1, 33.9, 32.0, 29.6, 22.6, 21.4; IR (film) 3424, 1601, 1505 cm⁻¹. MS (ESI) 320.1005 (320.1008 calcd for C₁₇H₂₂BrN, M + H⁺). The enantiopurity was determined to be 94% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 0.3% *i*PrOH/hexanes, 0.5 mL/min, λ = 231 nm, RT = 5.11 and 5.62 min).



(1S,4E)-N-[1-(2-Bromophenyl)hept-4-en-1-yl]aniline (3-4g). General procedure 3a was used for the deprotection of **3-8g** (751 mg, 2.02 mmol) with 4 M HCl (1.01 mL, 4.04 mmol). This procedure afforded 535 mg (99%) of (1S,4E)-1-(2-bromophenyl)hept-4-en-1-ylamine (**3-9g**) as a yellow oil. $[\alpha]_D^{23} -26.5$ (c 2.0, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.51 (d, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.30 (t, *J* = 7.2 Hz, 1 H), 7.08 (t, *J* = 7.2 Hz, 1 H), 5.52–5.39 (m, 2 H), 4.35 (t, *J* = 7.2 Hz, 1 H), 2.15–2.06 (m, 1 H), 2.04–1.96 (m, 3 H), 1.85–1.76 (m, 1 H), 1.69–1.62 (m, 1 H), 1.45 (s, br, 2 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 145.3, 132.8, 132.6, 128.2, 128.1, 127.7, 127.3, 123.4, 53.9, 37.8,

29.5, 25.5, 13.9; IR (film) 3380, 3314 cm^{-1} . MS (ESI) 268.0694 (268.0695 calcd for $\text{C}_{13}\text{H}_{18}\text{BrN}$, $\text{M} + \text{H}^+$).

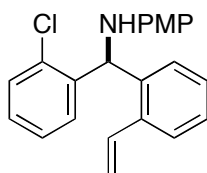
General procedure 3b was used for the *N*-arylation of **3-9g** (513 mg, 1.91 mmol) with bromobenzene (390 mg, 2.49 mmol). This procedure afforded 513 mg (78%) of the title compound as a yellow solid, mp 53–54 °C. $[\alpha]_{\text{D}}^{23} +101.6$ (c 3.6, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, $J = 7.6$ Hz, 1 H), 7.38 (d, $J = 8.0$ Hz, 1 H), 7.20 (t, $J = 7.6$ Hz, 1 H), 7.18–7.03 (m, 3 H), 6.63 (t, $J = 7.6$ Hz, 1 H), 6.44 (d, $J = 8.0$ Hz, 2 H), 5.53–5.41 (m, 2 H), 4.76–4.72 (m, 1 H), 4.17 (d, $J = 4.8$ Hz, 1 H), 2.25–2.12 (m, 2 H), 2.00–1.91 (m, 2 H), 1.90–1.86 (m, 1 H), 1.73–1.64 (m, 1 H), 0.95 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.9, 142.7, 133.2, 132.9, 129.1, 128.3, 127.8, 127.7, 127.5, 123.0, 117.3, 113.1, 56.6, 37.1, 29.4, 25.6, 13.8; IR (film) 3424, 1602, 1505 cm^{-1} . MS (ESI) 344.1009 (344.1014 calcd for $\text{C}_{19}\text{H}_{22}\text{BrN}$, $\text{M} + \text{H}^+$). The enantiopurity was determined to be 99% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 1% *i*PrOH/hexanes, 0.5 mL/min, $\lambda = 231$ nm, RT = 7.18 and 8.22 min).



(1S,4Z)-N-[1-(2-Bromophenyl)hept-4-en-1-yl]aniline (3-4h). General procedure 3a was used for the deprotection of **3-8h** (693 mg, 1.86 mmol) with 4 M HCl (0.9 mL, 3.7 mmol). This procedure afforded 469 mg (94%) of (1S,4Z)-1-(2-bromophenyl)hept-4-en-1-ylamine (**3-9h**) as a yellow oil. $[\alpha]_{\text{D}}^{23} -29.1$ (c 2.8, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 7.6$ Hz, 1 H), 7.46 (d, $J = 8.0$ Hz, 1 H), 7.31 (t, $J = 6.8$ Hz, 1 H), 7.08 (t, $J = 7.6$ Hz, 1 H), 5.42–5.33 (m, 2 H), 4.35 (t, $J = 5.6$ Hz, 1 H), 2.19–2.06 (m, 2 H), 2.05–1.98 (m, 2 H), 1.84–1.75 (m, 1 H), 1.69–1.60 (m, 1 H), 1.54 (s, br, 2 H), 0.95 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.2, 132.8, 132.3, 128.2, 128.1, 127.7, 127.2, 123.5, 54.1, 37.9, 24.2, 20.5, 14.3; IR (film) 3381, 3317, 1589 cm^{-1} . MS (ESI) 268.0700 (268.0701 calcd for $\text{C}_{13}\text{H}_{18}\text{BrN}$, $\text{M} + \text{H}^+$).

General procedure 3b was used for the *N*-arylation of **3-9h** (531 mg, 1.98 mmol) with bromobenzene (404 mg, 2.57 mmol). This procedure afforded 550 mg (81%)

of the title compound as a yellow oil. $[\alpha]_D^{23} +107.6$ (*c* 1.8, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.10–7.04 (m, 3 H), 6.63 (t, *J* = 8.0 Hz, 1 H), 6.44 (d, *J* = 8.4 Hz, 2 H), 5.44–5.37 (m, 2 H), 4.76–4.72 (m, 1 H), 4.17 (d, *J* = 5.2 Hz, 1 H), 2.27–2.22 (m, 2 H), 2.02 (p, *J* = 7.6 Hz, 2 H), 1.96–1.86 (m, 1 H), 1.71–1.64 (m, 1 H), 0.91 (t, *J* = 8.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.9, 142.7, 133.0, 132.9, 129.1, 128.4, 127.8, 127.6, 127.4, 123.0, 117.3, 113.1, 56.8, 37.2, 24.2, 20.5, 14.2; IR (film) 3429, 1602, 1505 cm⁻¹. MS (ESI) 344.1009 (344.1014 calcd for C₁₉H₂₂BrN, M + H⁺). The enantiopurity was determined to be 95% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 1% *i*PrOH/hexanes, 0.5 mL/min, λ = 254 nm, RT = 7.08 and 8.33 min).



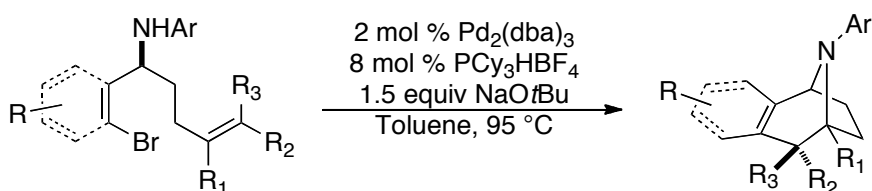
(S)-N-[(2-Chlorophenyl)(2-vinylphenyl)methyl]-4-methoxyaniline (3-24).

General procedure 3a was used for the deprotection of **3-S2** (974 mg, 2.80 mmol) with 4 M HCl (1.4 mL, 5.6 mmol). This procedure afforded 620 mg (91%) of (S)-(2-chlorophenyl)(2-vinylphenyl)methanamine (**3-S3**) as a yellow oil. $[\alpha]_D^{23} +32.1$ (*c* 4.9, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.46 (m, 1 H), 7.36–7.17 (m, 7 H), 6.97 (dd, *J* = 10.8, 17.2 Hz, 1 H), 5.81 (s, 1 H), 5.61 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.27 (dd, *J* = 1.2, 11.2 Hz, 1 H), 1.72 (s, br, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 142.4, 140.7, 136.6, 134.1, 133.2, 129.5, 128.5, 128.2, 127.8, 127.3, 127.0, 126.3, 116.6, 52.4 (one aromatic carbon signal is absent due to accidental equivalence); IR (film) 3375, 3314, 1421, 1266 cm⁻¹. MS (EI) 243.0811 (243.0815 calcd for C₁₅H₁₄ClN).

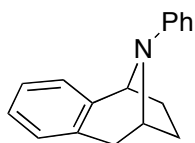
General procedure 3b was used for the *N*-arylation of **3-S3** (542 mg, 2.22 mmol) with 4-bromoanisole (500 mg, 2.67 mmol) using 8 mol% of (2-Biphenyl)di-*tert*-butylphosphine (JohnPhos) in place of Xantphos as the ligand. This procedure afforded 438 mg (56%) of the title compound as a white solid: mp 126–127 °C. $[\alpha]_D^{23} +151.8$ (*c* 0.6, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 7.6 Hz, 1

H), 7.47–7.45 (m, 1 H), 7.37–7.35 (m, 1 H), 7.25 (t, $J = 7.2$ Hz, 1 H), 7.23–7.19 (m, 2 H), 7.14 (t, $J = 7.2$ Hz, 1 H), 7.03–6.96 (m, 2 H), 6.67 (d, $J = 9.2$ Hz, 2 H), 6.40 (d, $J = 8.8$ Hz, 2 H), 5.99 (d, $J = 3.6$ Hz, 1 H), 5.65 (dd, $J = 1.6, 17.2$ Hz, 1 H), 5.27 (dd, $J = 1.2, 10.8$ Hz, 1 H), 3.84 (d, $J = 2.8$ Hz, 1 H), 3.66 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.1, 141.1, 139.2, 138.2, 137.2, 133.9, 133.7, 129.8, 129.4, 128.6, 127.8, 127.7, 127.4, 126.9, 126.4, 116.9, 114.7, 114.0, 56.6, 55.6; IR (film) 3424, 1511 cm^{-1} . MS (ESI) 350.1306 (349.1233 calcd for $\text{C}_{22}\text{H}_{20}\text{ClNO}$, $\text{M} + \text{H}^+$). The enantiopurity was determined to be 99% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 1% *i*PrOH/hexanes, 0.1 mL/min, $\lambda = 231$ nm, RT = 36.73 and 38.67 min).

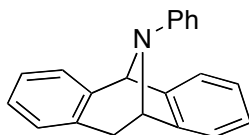
Synthesis and Characterization of Tropane Products



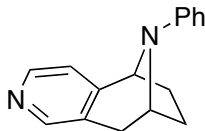
General Procedure 4: Pd-Catalyzed Synthesis of Tropane Derivatives: A flame-dried Schlenk tube was cooled under a stream of N_2 and charged with $\text{Pd}_2(\text{dba})_3$ (2 mol % complex, 4 mol % Pd), $\text{PCy}_3 \cdot \text{HBF}_4$ (8 mol %), and sodium *tert*-butoxide (1.5 equiv). The tube was purged with N_2 and a 0.1 M solution of amine substrate (1 equiv) in toluene was added via syringe. The resulting mixture was heated to 95 °C until the starting material had been consumed as judged by TLC analysis (ca. 14 h). The reaction mixture was cooled to rt and saturated aqueous ammonium chloride (3 mL) was added. The resulting mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



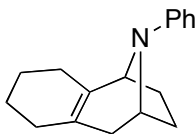
(5*S*,8*R*)-10-Phenyl-6,7,8,9-tetrahydro-5*H*-5,8-epiminobenzo[7]annulene (3-14). General procedure 4 was used for the cyclization of substrate **3-4a** (62 mg, 0.19 mmol) to tropane derivative **3-14**. This procedure afforded 36 mg (78%) of the title compound as a light yellow oil with >20:1 dr. $[\alpha]_D^{23} +19.0$ (c 3.4, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.14–7.08 (m, 4 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 6.90 (d, *J* = 7.2 Hz, 1 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 4.73 (d, *J* = 5.6 Hz, 1 H), 4.53 (t, *J* = 5.9 Hz, 1 H), 3.30 (dd, *J* = 4.4, 16.8 Hz, 1 H), 2.42 (d, *J* = 16.8 Hz, 1 H), 2.38–2.28 (m, 2 H), 1.98–1.93 (m, 1 H), 1.83–1.78 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.1, 141.1, 132.5, 129.7, 129.0, 126.4, 126.1, 125.8, 117.9, 116.2, 58.2, 54.5, 35.6, 32.9, 29.2; IR (film) 3055, 1601, 1266, 740 cm⁻¹. MS (ESI) 236.1434 (236.1439 calcd for C₁₇H₁₇N, M + H⁺). The enantiopurity was determined to be 97% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 5% *i*PrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 4.30 and 4.77 min).



(5*R*,10*S*)-12-Phenyl-10,11-dihydro-5*H*-5,10-epiminodibenzo[*a,d*][7]annulene (3-15). General procedure 4 was used for the cyclization of substrate **3-4b** (86 mg, 0.24 mmol) to tropane derivative **3-15**. This procedure afforded 56 mg (83%) of the title compound as a yellow foam with >20:1 dr. $[\alpha]_D^{23} -198.0$ (c 1.8, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, *J* = 6.8 Hz, 1 H), 7.24 (t, *J* = 8.4 Hz, 2 H), 7.21–7.11 (m, 4 H), 7.03 (t, *J* = 7.2 Hz, 1 H), 6.96 (t, *J* = 7.2 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 6.75–6.70 (m, 2 H), 5.50 (s, 1 H), 5.37 (d, *J* = 5.2 Hz, 1 H), 3.44 (dd, *J* = 5.2, 17.2 Hz, 1 H), 2.55 (d, *J* = 17.2 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.4, 146.1, 141.7, 139.7, 131.6, 130.4, 129.1, 127.2, 127.1, 126.9, 125.9, 125.2, 121.7, 119.9, 118.5, 115.9, 63.3, 60.0, 28.5; IR (film) 3055, 1602, 1265, 739 cm⁻¹. MS (ESI) 284.1443 (284.1434 calcd for C₂₁H₁₇N, M + H⁺). The enantiopurity was determined to be 98% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 4% *i*PrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 9.37 and 14.62 min).

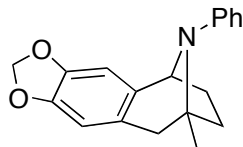


(5S,8R)-10-Phenyl-6,7,8,9-tetrahydro-5H-5,8-epiminocyclohepta[c]pyridine (3-16). General procedure 4 was used for the cyclization of substrate **3-4c** (32 mg, 0.10 mmol) to tropane derivative **3-16**. This procedure afforded 19 mg (80%) of the title compound as a yellow oil with >20:1 dr. $[\alpha]_D^{23} -16.5$ (c 3.8, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 8.33 (d, *J* = 4.8 Hz, 1 H), 8.17 (s, 1 H), 7.14 (t, *J* = 7.2 Hz, 2 H), 7.08 (d, *J* = 5.2 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 6.72 (t, *J* = 7.2 Hz, 1 H), 4.71 (d, *J* = 6.0 Hz, 1 H), 4.59 (t, *J* = 6.4 Hz, 1 H), 3.26 (dd, *J* = 4.4, 16.8 Hz, 1 H), 2.44 (d, *J* = 16.8 Hz, 1 H), 2.41–2.32 (m, 2 H), 1.97–1.92 (m, 1 H), 1.83–1.78 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 150.8, 149.8, 147.2, 146.6, 129.2, 128.4, 120.9, 118.6, 116.2, 57.5, 54.3, 35.2, 29.9, 29.1; IR (film) 3054, 1598, 1264, 742 cm⁻¹. MS (ESI) 237.1387 (237.1386 calcd for C₁₆H₁₆N₂, M + H⁺). The enantiopurity was determined to be 99% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 20% *i*PrOH/hexanes, 1 mL/min, λ = 231 nm, RT = 6.91 and 9.11 min).

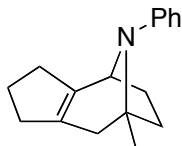


(5S,8R)-10-Phenyl-2,3,4,5,6,7,8,9-octahydro-1H-5,8-epiminobenzo[7]annulene (3-17). General procedure 4 was used for the cyclization of substrate **3-4d** (86 mg, 0.25 mmol) to tropane derivative **3-17**. This procedure afforded 47 mg (73%) of the title compound as a pale yellow solid with >20:1 dr: mp = 84–85 °C. $[\alpha]_D^{23} +60.1$ (c 1.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.18 (t, *J* = 7.9 Hz, 2 H), 6.78 (d, *J* = 7.9 Hz, 2 H), 6.72 (t, *J* = 7.2 Hz, 1 H), 4.29 (dd, *J* = 4.8, 7.6 Hz, 1 H), 3.78 (d, *J* = 6.0 Hz, 1 H), 2.47 (d, *J* = 16.8 Hz, 1 H), 2.28–2.21 (m, 1 H), 2.09–1.95 (m, 3 H), 1.89 (td, *J* = 2.8, 11.6 Hz, 1 H), 1.73–1.35 (m, 8 H); ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 132.9, 128.8, 124.4, 117.6, 116.3, 57.8, 54.7, 35.6, 33.4, 30.0, 28.9, 28.1, 22.9, 22.7; IR (film) 3054, 1599, 1265, 739 cm⁻¹. MS (ESI) 240.1748 (240.1747 calcd for C₁₇H₂₁N, M + H⁺). The enantiopurity was

determined to be 92% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 1% *i*PrOH/hexanes, 1 mL/min, $\lambda = 231$ nm, RT = 2.74 and 3.74 min).

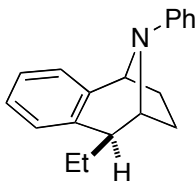


(5*S*,8*R*)-8-Methyl-11-phenyl-6,7,8,9-tetrahydro-5*H*-5,8-epiminocyclohepta [4,5]-benzo [1,2-*d*][1,3]dioxole (3-18). General procedure 4 was used for the cyclization of substrate **3-4e** (73 mg, 0.19 mmol) to tropane derivative **3-18**. This procedure afforded 47 mg (82%) of the title compound as a light pink oil with >20:1 dr. $[\alpha]_D^{23} -13.9$ (c 4.7, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.10 (t, $J = 7.6$ Hz, 2 H), 6.95 (d, $J = 6.8$ Hz, 2 H), 6.84 (t, $J = 7.6$ Hz, 1 H), 6.63 (s, 1 H), 6.40 (s, 1 H), 5.88 (d, $J = 7.2$ Hz, 2 H), 4.45 (d, $J = 6.4$ Hz, 1 H), 2.71 (d, $J = 16.4$ Hz, 1 H), 2.35 (d, $J = 16.4$ Hz, 1 H), 2.29–2.20 (m, 1 H), 2.01–1.89 (m, 2 H), 1.76–1.70 (m, 1 H), 1.62 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.7, 145.9, 145.8, 134.1, 128.3, 126.4, 121.3, 121.0, 108.9, 105.5, 100.6, 63.6, 61.7, 40.3, 38.1, 33.6, 29.1; IR (film) 3054, 1597, 1265, 1041, 738 cm⁻¹. MS (ESI) 294.1488 (294.1494 calcd for C₁₉H₁₉NO₂, M + H⁺). The enantiopurity was determined to be 98% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 2% *i*PrOH/hexanes, 0.5 mL/min, $\lambda = 231$ nm, RT = 11.35 and 11.92 min).

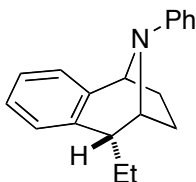


(4*S*,8*R*)-7-Methyl-9-phenyl-1,2,3,4,5,6,7,8-octahydro-4,7-epiminoazulene (3-19). General procedure 4 was used for the cyclization of substrate **3-4f** (75 mg, 0.22 mmol) to tropane derivative **3-19**. This procedure afforded 41 mg (73%) of the title compound as a yellow oil with >20:1 dr. $[\alpha]_D^{23} -60.0$ (c 4.7, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.19–7.15 (m, 2 H), 6.97–6.94 (d, $J = 6.8$ Hz, 2 H), 6.87 (t, $J = 7.2$ Hz, 1 H), 3.95 (d, $J = 5.6$ Hz, 1 H), 2.44–2.39 (m, 2 H), 2.10–2.01 (m, 4 H), 1.97–1.83 (m, 4 H), 1.73–1.67 (m, 2 H), 1.59 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 147.3, 138.1, 132.1, 128.2, 121.0, 120.4, 61.6, 59.9, 39.8, 39.2, 34.7, 32.9, 30.7, 29.2, 22.3; IR (film) 3054, 1599, 1266, 735 cm⁻¹. MS (ESI)

240.1749 (240.1747 calcd for C₁₇H₂₁N, M + H⁺). The enantiopurity was determined to be 93% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 0.1% *i*PrOH/hexanes, 0.3 mL/min, λ = 231 nm, RT = 12.26 and 13.17 min).

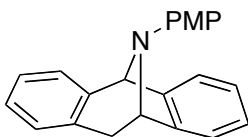


(5S,8R,9S)-9-Ethyl-10-phenyl-6,7,8,9-tetrahydro-5H-5,8-epiminobenzo[7]annulene (3-20). General procedure 4 was used for the cyclization of substrate **3-4g** (70 mg, 0.20 mmol) to tropane derivative **3-20**. This procedure afforded 43 mg (80%) of the title compound as a light yellow oil with >20:1 dr. [α]²³_D -3.6 (c 5.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.22–7.07 (m, 6 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.75 (t, *J* = 6.4 Hz, 1 H), 4.83 (d, *J* = 5.6 Hz, 1 H), 4.44 (d, *J* = 7.6 Hz, 1 H), 2.47 (dd, *J* = 4.4, 10.4 Hz, 1 H), 2.22–2.04 (m, 2 H), 1.81–1.73 (m, 2 H), 1.72–1.62 (m, 1 H), 1.59–1.53 (m, 1 H), 1.14 (t, *J* = 7.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 149.5, 140.9, 138.1, 129.7, 129.1, 126.6, 125.9, 124.9, 118.4, 115.2, 60.4, 58.7, 50.3, 33.9, 29.7, 28.6, 12.8; IR (film) 3054, 1598, 1265, 727 cm⁻¹. MS (ESI) 264.1746 (264.1747 calcd for C₁₉H₂₁N, M + H⁺). The enantiopurity was determined to be 98% ee by chiral HPLC analysis (Chiralcel OD-H, 0.46 cm x 15 cm, 1% *i*PrOH/hexanes, 0.5 mL/min, λ = 231 nm, RT = 5.37 and 6.55 min).

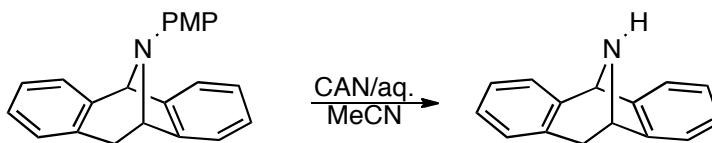


(5S,8R,9R)-9-Ethyl-10-phenyl-6,7,8,9-tetrahydro-5H-5,8-epiminobenzo[7]annulene (3-21). General procedure 4 was used for the cyclization of substrate **3-4h** (74 mg, 0.22 mmol) to tropane derivative **3-21**. This procedure afforded 37 mg (73%) of the title compound as a light yellow oil with >20:1 dr. [α]²³_D -35.1 (c 3.7, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.14–7.07 (m, 6 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.66 (t, *J* = 7.6 Hz, 1 H), 4.69 (d, *J* = 5.9 Hz, 1 H), 4.51 (t, *J* = 6.4 Hz, 1

H), 3.18 (dt, $J = 4.4, 10.4$ Hz, 1 H), 2.33–2.42 (m, 1 H), 2.18–1.96 (m, 3 H), 1.86 (td, $J = 2.8, 9.2$ Hz, 1 H), 1.53–1.45 (m, 1 H), 1.09 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.9, 140.2, 137.4, 129.1, 127.2, 126.7, 125.9, 125.7, 117.7, 115.9, 58.8, 56.8, 39.1, 34.8, 23.4, 21.9, 11.9; IR (film) 3054, 1599, 1265, 737 cm^{-1} . MS (ESI) 264.1745 (264.1747 calcd for $\text{C}_{19}\text{H}_{21}\text{N}$, $\text{M} + \text{H}^+$). The enantiopurity was determined to be 95% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 2% *i*PrOH/hexanes, 1 mL/min, $\lambda = 254$ nm, RT = 4.04 and 5.08 min).



(5R,10S)-12-(4-Methoxyphenyl)-10,11-dihydro-5H-5,10-epiminodibenzo[a,d][7]annulene (3-25). General procedure 4 was used for the cyclization of substrate **3-24** (224 mg, 0.64 mmol) to tropane derivative **3-25** using 8 mol% of 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-Phos) in place of $\text{PCy}_3 \cdot \text{HBF}_4$ as the ligand. This procedure afforded 142 mg (71%) of the title compound as a pale pink foam with >20:1 dr. $[\alpha]_{\text{D}}^{23} -225.7$ (c 2.2, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.37 (d, $J = 6.8$ Hz, 1 H), 7.26–7.21 (m, 2 H), 7.18–7.09 (m, 2 H), 7.05 (t, $J = 7.2$ Hz, 1 H), 6.99 (t, $J = 7.2$ Hz, 1 H), 6.88–6.84 (m, 2 H), 6.77–6.73 (m, 3 H), 5.42 (s, 1 H), 5.28 (d, $J = 5.2$ Hz, 1 H), 3.68 (s, 3 H), 3.41 (dd, $J = 5.2, 16.8$ Hz, 1 H), 2.55 (d, $J = 17.2$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.6, 147.6, 141.8, 140.5, 139.6, 131.7, 130.3, 127.1, 127.0, 126.8, 125.9, 125.1, 121.8, 119.9, 117.3, 114.5, 64.0, 60.8, 55.4, 28.5; IR (film) 3054, 1605, 1038, 743 cm^{-1} . MS (ESI) 313.1474 (313.1467 calcd for $\text{C}_{22}\text{H}_{19}\text{NO}$, $\text{M} + \text{H}^+$). The enantiopurity was determined to be 99% ee by chiral HPLC analysis (Chiralpak AD-H, 0.46 cm x 25 cm, 6% *i*PrOH/hexanes, 1 mL/min, $\lambda = 231$ nm, RT = 18.77 and 32.06 min).

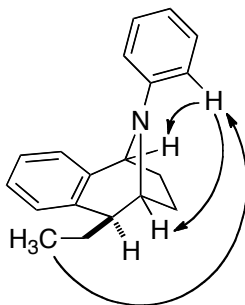


(5*R*,10*S*)-10,11-dihydro-5*H*-5,10-epiminodibenzo[*a,d*][7]annulene (3-23).¹⁴ A flame-dried Schlenk tube was cooled under a stream of N₂ before being charged with a 0.1 M solution of **3-25** (41 mg, 0.13 mmol) in acetonitrile. The tropane solution was cooled to 0 °C before a 0.3 M aqueous solution of CAN (215 mg, 0.39 mmol) was added dropwise. After the addition was complete the reaction continued for 1 h at 0 °C before solvent was removed *in vacuo*. The remaining solids in the flask were dissolved in water (5 mL) and washed with ether (2 x 5 mL). The aqueous layer was basified to pH = 9 with 1 M NaOH and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 20 mg (74%) of primary amine product as an orange oil. $[\alpha]_D^{23} -131.0$ (*c* 2.0, CH₂Cl₂) (Optical rotation data for this compound has not been reported and as a result we cannot provide a comparison of values). ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, *J* = 6.8 Hz, 1 H), 7.17 (d, *J* = 7.2 Hz, 1 H), 7.14–7.05 (m, 5 H), 6.94 (d, *J* = 6.8 Hz, 1 H), 4.96 (s, 1 H), 4.71 (d, *J* = 5.6 Hz), 3.38 (dd, *J* = 5.6, 16.8 Hz, 1 H), 2.69 (d, *J* = 16.8 Hz, 1 H), 2.59 (s, br, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 149.4, 143.8, 141.5, 131.9, 130.4, 127.2, 126.8, 126.7, 125.6, 123.9, 121.6, 119.9, 63.0, 59.0, 33.2.

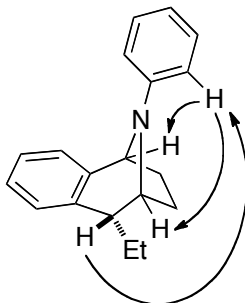
Assignment of Stereochemistry

The absolute stereochemistry of the substrates **3-4a-h** and **3-24** was assigned based on stereochemical models developed by Ellman.²²

The relative stereochemistry of compound **3-20** was assigned on the basis of observed ¹H NMR nOe experiments. Significant nOe relationships are shown below.



The relative stereochemistry of compound **3-21** was assigned on the basis of observed ^1H NMR nOe experiments. Significant nOe relationships are shown below.



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Chapter 4

β -Alkoxy Ketones: Significance and Preparation

4.1 Introduction

β -Alkoxy ketones are one of the most prevalent structural elements in both biologically active pharmaceutical targets and natural products.¹ In addition, β -alkoxy ketones serve as key synthetic intermediates for accessing other important 1,3-dioxygen units, such as 1,3-diols and 1,3-dicarbonyls, which are essential synthetic building blocks for both small molecule and polymer synthesis. As a result, numerous methods have been developed that garner β -alkoxy ketones in a straightforward manner; however, only a handful of these routes are catalytic. Catalytic methods for β -alkoxy ketone synthesis are particularly advantageous as there would be minimal byproduct formation and potential for greater functional group compatibility. More importantly, catalysis has the capability to furnish β -alkoxy ketones with diverse substitution patterns due to non-traditional bond forming events. One avenue for arriving at β -alkoxy ketones is through Au-catalysis, which has recently emerged as an efficient means for small molecule synthesis due to gold's ability to mediate unique C-C and C-O bond formation through selective alkyne activation. In contrast to other catalytic methods for β -alkoxy ketone synthesis, Au-catalysis would proceed under mild conditions and without pre-functionalized starting materials, ultimately yielding products that would otherwise be challenging to access. Thus, the focus of this chapter is to highlight the importance of developing new synthetic methods for β -alkoxy ketone synthesis and how Au-catalysis would be an attractive and efficient route for their synthesis.

4.2 Prevalence of β -Alkoxy Ketones in Pharmaceuticals and Biologically Active Natural Products

The β -alkoxy ketone motif is prominently displayed in flavanone,² dihydrochalcone,³ and polyether⁴ containing natural products with a wide range of interesting biological activities. For instance, the health benefits of fruits and vegetables can be attributed to the presence of flavanone-containing natural products, such as naringenin, the principal flavanone of grapefruit that has antioxidant and anti-inflammatory activity (Figure 4.1).⁵ While taxifolin, a flavanone common in conifers and acai palm, has antioxidant and anti-ovarian cancer activity.⁶ Another flavanone that is receiving interest is silibinin, the chief flavanone of milk thistle, which exhibits anti-cancer activity against a wide variety of carcinoma cells including prostate,⁷ colon,⁸ and lung.⁹

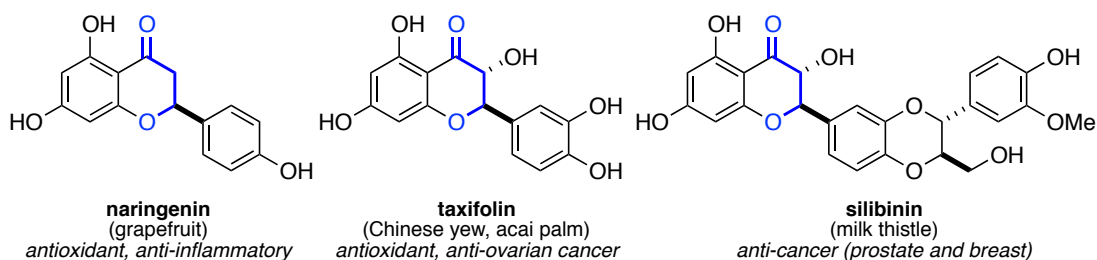


Figure 4.1 Flavonoid natural products with β -alkoxy ketone motif

Another class of natural products that bear β -alkoxy ketones are the dihydrochalcones, such as **4-1**, a compound isolated from the bark of *Millettia leucantha* which has anti-HSV activity (Figure 4.2).¹⁰ Lastly, the ionophore antibiotics, such as *Streptomyces* derived lasalocid A, have the β -alkoxy ketone motif embedded within their key polyether frameworks.¹¹

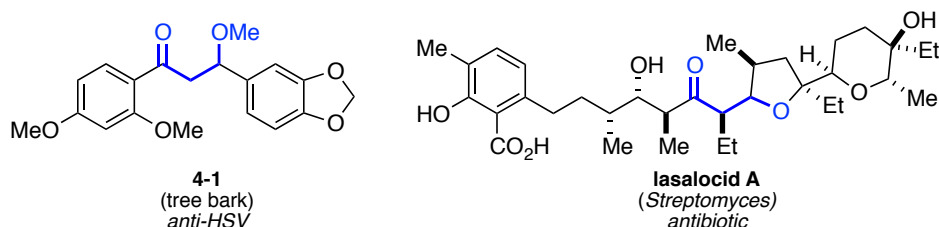
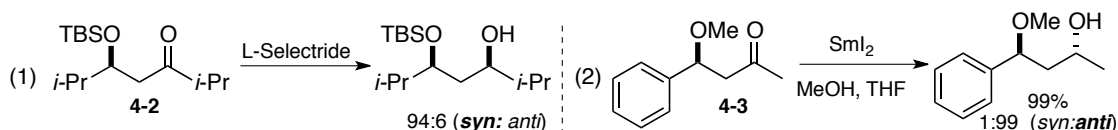


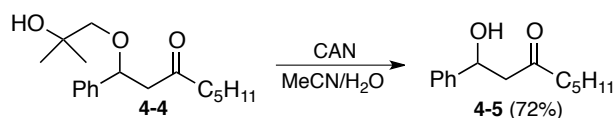
Figure 4.2. Biologically active natural products with β -alkoxy ketone motif

4.3 β -Alkoxy Ketones as Important Synthetic Intermediates

The 1,3-dioxygen core of β -alkoxy ketones can also serve as a platform for entry into other important classes of molecules such as *syn*- and *anti*-1,3-diol monoethers and β -hydroxy ketones. The synthesis of 1,3-diol monoethers is of particular interest since these scaffolds serve as masked 1,3-diol precursors that would allow the oxygen atoms to be differentiated for reactivity. For instance, the hydride reduction of β -alkoxy ketone **4-2** with L-Selectride gave exclusively the *syn*-1,3-diol monoether due to a chelation control mechanism (eq 1).¹² In contrast, reducing ketone **4-3** with samarium diiodide, a one-electron reducing agent, affords the *anti*-1,3-diol monoether due to the alkoxy substituent serving as a directing group for reduction (eq 2).¹³



In turn, β -alkoxy ketones can also undergo selective C-O bond cleavage to afford β -hydroxy ketones. For example, the cleavage of the hydroxyethyl unit on ketone **4-4** was selectively achieved with CAN to afford β -hydroxy ketone **4-5** in good yield (Scheme 4.1).¹⁴

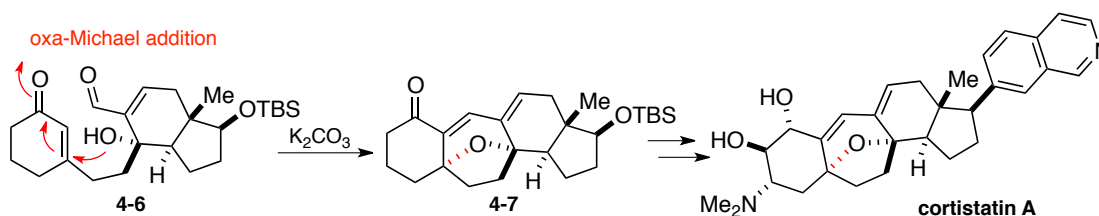


Scheme 4.1 CAN-mediated synthesis of β -hydroxy ketones from β -alkoxy ketones

4.4 Non-Catalytic Approaches for β -Alkoxy Ketone Synthesis

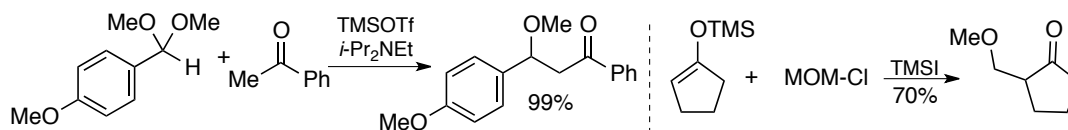
Given the prevalence of β -alkoxy ketones in biologically active compounds and their utility as chemical building blocks, there has been considerable interest in devising synthetic methods that would deliver this class of compounds in a straightforward manner. The most common non-catalyzed methods for accessing β -alkoxy ketones are through either oxa-Michael reactions or addition reactions of silyl enol ethers. The synthesis of β -alkoxy ketones via oxa-Michael reactions occurs through the base-mediated addition of alkoxides to enones; however, due to the low nucleophilicity of alkoxides, these reactions are typically limited to

intramolecular systems.¹⁵ For instance, key β -alkoxy ketone intermediate **4-7** in Nicolaou's synthesis of cortistatin A was realized through an intramolecular oxa-Michael addition/aldol/dehydration cascade reaction with substrate **4-6** (Scheme 4.2).¹⁶ Despite oxa-Michael reactions being a straightforward route for accessing cyclic β -alkoxy ketones, these reactions still suffer from the reversible addition of the alkoxide to the conjugated system, further limiting the scope and utility of the method.



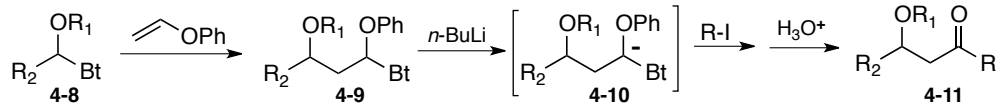
Scheme 4.2 Intramolecular oxa-Michael addition for the synthesis of cortistatin A via β -alkoxy ketone **4-7**

In turn, the intermolecular synthesis of β -alkoxy ketones can be readily achieved through Mukaiyama Aldol-type addition reactions of either *in situ* or preformed silyl enol ethers with acetals¹⁷ or α -chloroethers¹⁸ (Scheme 4.3). Although these addition reactions are effective at forming a diverse array of β -alkoxy ketones, both require the preformation of either the acetal or silyl enol ether, which can limit the types of products that are accessible.



Scheme 4.3 Silyl enol ether addition reactions for β -alkoxy ketone synthesis

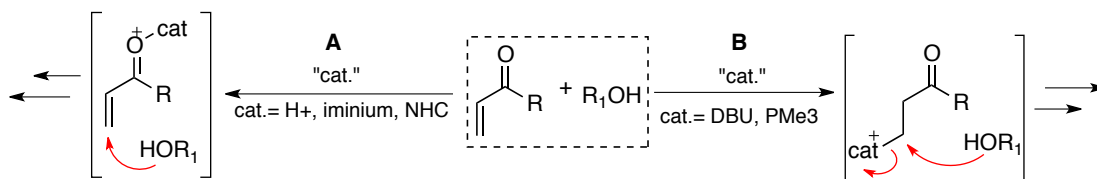
Katritzky and coworkers have also designed a non-traditional approach for β -alkoxy ketone synthesis that utilizes 1-(α -alkoxyalkyl)benzotriazoles (Scheme 4.4).¹⁹ In these reactions the benzotriazole catalyst facilitates the formation of acyl anion synthon **4-8** that undergoes addition to phenyl vinyl ether to yield intermediate **4-9**. The β -alkoxy ketone product **4-11** is then liberated through the lithiation and subsequent electrophilic trapping of intermediate **4-10** with a various alkyl iodides.



Scheme 4.4 Benzotriazole-mediated synthesis of β -alkoxy ketones

4.5 Catalytic Approaches for β -Alkoxy Ketone Synthesis

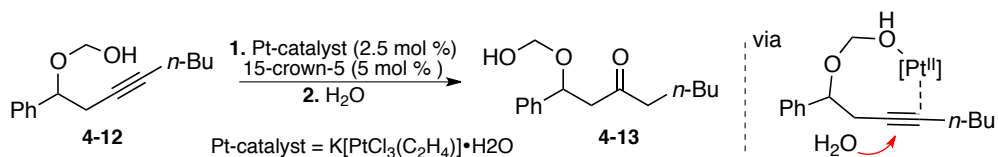
Recently there has been more interest in developing catalytic methods for β -alkoxy ketone synthesis, as this has potential in providing a more efficient approach to this class of compounds. Oxa-Michael reactions have proven to be the most amenable for developing new catalytic methods and have been shown to proceed with a wide variety of catalysts including Brønsted acids,²⁰ iminium ions,²¹ PMe_3 ,²² DBU,²³ and *N*-heterocyclic carbenes (NHC).²⁴ Common to all these methods is the activation of the β -carbon of the enone starting material prior to addition of the oxygen nucleophile. In the case of Brønsted acid, iminium ion and NHC-catalyzed methods, conjugate addition of the alcohol is facilitated by the enone becoming polarized due to the carbonyl oxygen binding to the catalyst (Scheme 4.5 **A**). Conversely, PMe_3 or DBU catalyzed reactions begin with conjugate addition of the catalyst to the enone with subsequent $\text{S}_{\text{N}}2$ displacement with an alcohol (Scheme 4.5 **B**).



Scheme 4.5 β -Alkoxy ketone synthesis via catalyzed oxa-Michael reactions

In contrast to the catalyzed oxa-Michael additions that rely upon the use of standard enone and alcohol coupling partners, other catalyzed methods that afford β -alkoxy ketones through non-traditional bond formations have also been developed. For example, a Pt(II)-catalyzed methodology has recently been described that utilizes homopropargylic alcohol **4-12** for arriving at β -alkoxy ketone **4-13** (Scheme 4.6).²⁵ In these reactions the homopropargylic alcohol **4-12** serves as a directing group, guiding the Pt-catalyzed hydration of the alkyne to occur regioselectively. Key to these transformations is platinum's ability to

activate pi-systems for nucleophilic addition, overall allowing normally unreactive alkynes to undergo chemoselective reactivity.²⁶ More importantly, the use of alkynes as ketone surrogates provides a new strategy level disconnection for this class of compounds, allowing for the construction of β -alkoxy ketones that may be challenging to access with more traditional methods.



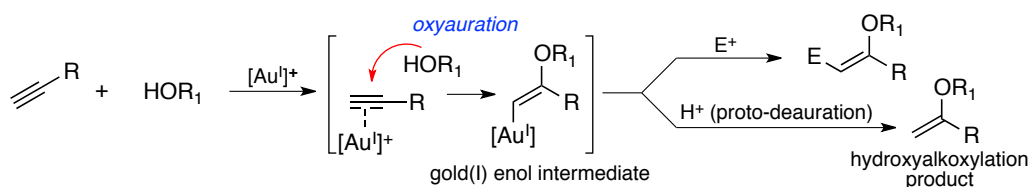
Scheme 4.6 Pt-catalyzed regioselective synthesis of β -alkoxy ketones

In spite of this unique reactivity, the activation of alkynes with Pt(II)-catalysts is typically achieved without the presence of phosphine ligands on the metal,²⁷ which prevents catalyst tuning through ligand modifications. As a result, the scope and utility of Pt(II)-catalysis for β -alkoxy ketone synthesis is limited to only substrates that can successfully be transformed with a given Pt(II)-catalyst. Conversely, Au(I)-catalysts have a similar reactivity profile as Pt(II)-catalysts and have been shown to effectively activate alkynes in the presence of phosphine ligands.²⁸ The ability to tune the reactivity of Au(I)-catalysts through ligand modifications has led to the development of countless Au(I)-phosphine catalyst systems that efficiently transform a variety of alkynes into useful small molecules.²⁹ In addition, Au(I)-catalysts display exceptionally high catalytic activity and are proven to be a more stable, versatile, and selective substitute for many reactions traditionally catalyzed by Pt(II).³⁰ Accordingly, Au(I)-catalyzed hydroalkoxylations of alkynes has shown to be a viable route for C-C and C-O bond formation,³¹ yet there remain no methodologies that utilize this reactivity for β -alkoxy ketone synthesis. As a result, the development of new Au(I)-catalyzed reactions that employ alkynes for β -alkoxy ketone synthesis has the potential to furnish this class of compounds in a novel and efficient manner.

4.6 C-C and C-O Bond Formation via Au(I)-Catalyzed Alkyne Activation

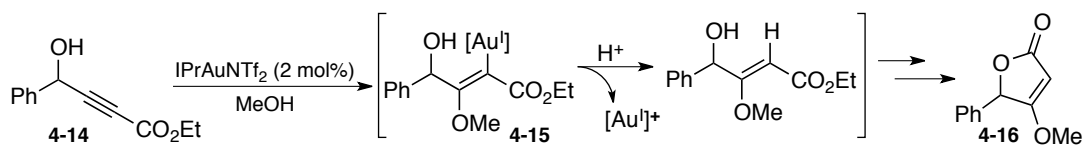
The feasibility of implementing Au(I)-catalysis for β -alkoxy ketone synthesis has been demonstrated through the development of several Au(I)-catalyzed

transformations that proceed through initial oxyauration of alkynes (Scheme 4.7).³¹⁻³² Characteristic to these transformations is the formation of gold(I) enol intermediates that participate in bond forming reactions similar to enols, generating products that bear resemblance to β -alkoxy ketones.³³ In general, these transformations begin with the oxyauration of alkynes with an oxygen nucleophile to afford gold(I) enol intermediates (Scheme 4.7). These gold(I) enol intermediates can then undergo either proto-deauration or electrophilic trapping to yield enol ether derivatives.



Scheme 4.7 General scheme of Au(I)-catalyzed oxyauration reactions

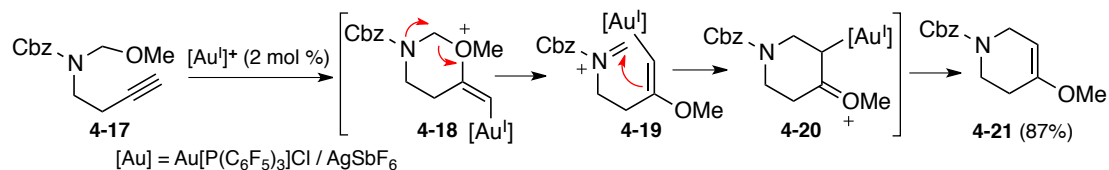
Due to the polarization of the gold-carbon bond of vinyl gold(I) species, the most common reaction outcome of Au(I)-catalyzed oxyauration reactions is proto-deauration.²⁷ For example, Nolan and coworkers have recently described an IPrAuNTf₂ catalyzed hydroalkoxylation reaction between acetylenic ester **4-14** and methanol for the synthesis of 4-alkoxy-2-furanone **4-16** (Scheme 4.8).³⁴ This reaction proceeds through the Au(I)-catalyzed addition of methanol to **4-14**, affording gold(I) enol intermediate **4-15** which then undergoes proto-deauration and subsequent lactonization to afford furanone product **4-16**. Although protonolysis is an efficient means for transforming alkynes into enol ethers, the deauration step eliminates the possibility of further utilizing the reactivity of gold(I) enol intermediates for other bond forming events.



Scheme 4.8 Au(I)-catalyzed tandem hydroalkoxylation/lactonization of **4-14**

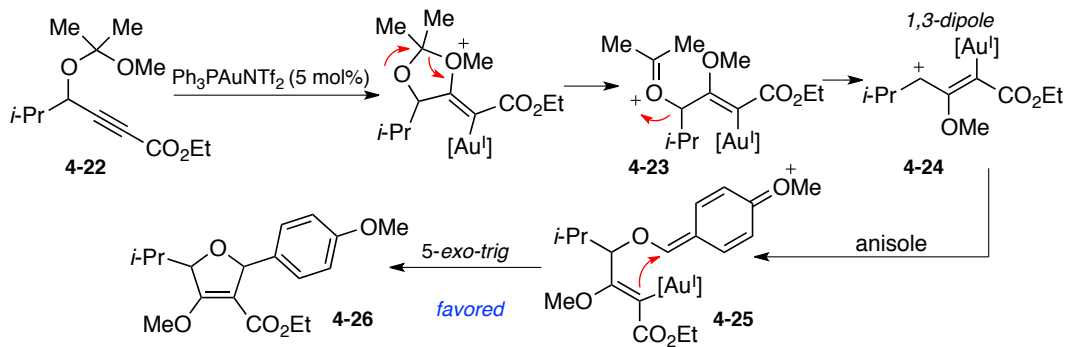
Thus, in order to expand the scope and utility of oxyauration reactions, there have been efforts to develop methodologies that allow for the electrophilic capture of gold(I) enol intermediates for C-C bond formation. However, due to

how readily gold(I) enol intermediates undergo proto-deauration, there have been only a handful of methods that have successfully intercepted these species with carbon-based electrophiles. For example, the synthesis of piperidines was realized through the Au(I)-catalyzed cycloisomerization of *N,O*-acetal substrate **4-17** (Scheme 4.9).³⁵ These transformations proceed via initial intramolecular oxyauration of *N,O*-acetal **4-17** to gold(I) enol intermediate **4-18**, with subsequent fragmentation to iminium ion **4-19**. Since the electrophilic iminium ion is tethered to the gold(I) enol intermediate, preferential electrophilic capture occurs over proto-deauration, yielding intermediate **4-20** which then undergoes demetallation to piperidine product **4-21**.



Scheme 4.9 Intramolecular capture of iminium ions with gold(I) enol intermediates

Zhang and coworkers have also shown ketals to participate in oxyauration reactions through the development of Au(I)-catalyzed [3+2] cycloadditions reactions.³⁶ Similar to the oxyauration of *N,O*-acetals, ketal **4-22** undergoes an initial migration and fragmentation to afford gold(I) enol intermediate **4-23** with a tethered oxocarbenium ion (Scheme 4.10). However, since intramolecular electrophilic capture of the oxocarbenium ion would proceed through a disfavored 5-*endo-trig* cyclization, fragmentation of the oxocarbenium ion to 1,3-dipole **4-24** occurs. Intermediate **4-24** is then trapped by anisole to yield **4-25** that then readily undergoes favorable 5-*exo-trig* cyclization to dihydrofuran **4-26**.



Scheme 4.10 Oxyauration of alkynes with ketals for furan synthesis

In the end, the Au(I)-catalyzed oxyauration of *N,O*-acetals and ketals demonstrates the feasibility of synthesizing β -alkoxy ketone through the capture of carbon electrophiles with gold(I) enol intermediates. However, these Au(I)-catalyzed transformations have several limitations that narrow the scope and utility of these methods for difunctionalizing alkynes. For instance, both reactions require the pre-formation of the *N,O*-acetal/ketal prior to Au-catalysis, which adds another step to the transformation and confines the scope to only *N,O*-acetals/ketals that can be easily prepared. More importantly, these Au(I)-catalyzed methodologies can only access cyclic products due to the *intramolecular* capture of the gold(I) enol intermediates, which does not provide a means for accessing acyclic products. As a result, we sought to address these limitations by developing a Au(I)-catalyzed methodology for β -alkoxy ketone synthesis. Specifically, the following chapter will discuss our efforts towards the development of an *intermolecular* Au(I)-catalyzed methodology that utilizes *in situ* generated hemiacetals for the preparation of β -alkoxy ketones.

4.7 References

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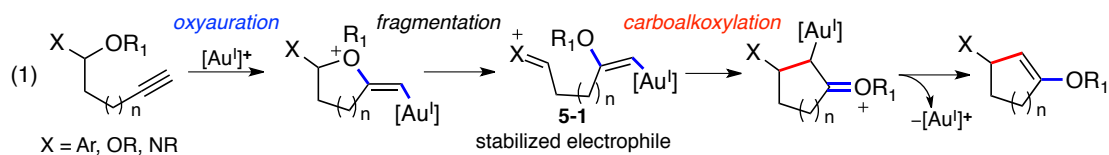
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Chapter 5

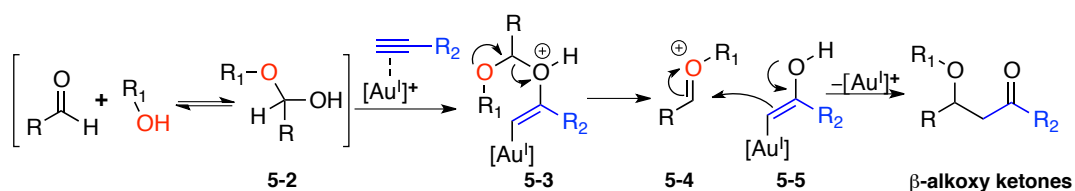
β -Alkoxy Ketone Synthesis via Au(I)-Catalyzed Carboalkoxylation Reactions of Alkynes

5.1 Introduction

In recent years, Au-catalysis has proven to be a practical and convenient approach to small molecule synthesis, with a variety of unique Au-catalyzed transformations occurring under mild conditions.¹ Many of these reactions are facilitated by gold's ability to selectively activate alkynes for nucleophilic attack, thereby allowing normally unreactive alkynes to serve as organometallic functional groups that can participate in a wide range of reactions.² One of the most useful of these transformations is the generation of gold(I) enol intermediates through the oxyauration of alkynes with oxygen nucleophiles.³ Due to the strong tendency of gold(I) enol intermediates to undergo proto-deauration, the products are typically the result of net hydroalkoxylation of the alkyne.⁴ However, gold(I) enol intermediates have considerable untapped potential for use as nucleophiles in C-C bond-forming carboalkoxylation reactions,⁵ but due to the efficiency of proto-deauration there have only been a handful of instances whereby gold(I) enols have been successfully captured with carbon electrophiles. Essential to all of these prior reports was the formation of stabilized carbon electrophile **5-1** tethered to a gold(I) enol intermediate (eq 1), which was achieved through the *intramolecular* attack of an ether,⁶ ketal,⁷ or hemiaminal⁸ onto a pendant alkyne followed by fragmentation of the resulting intermediate.

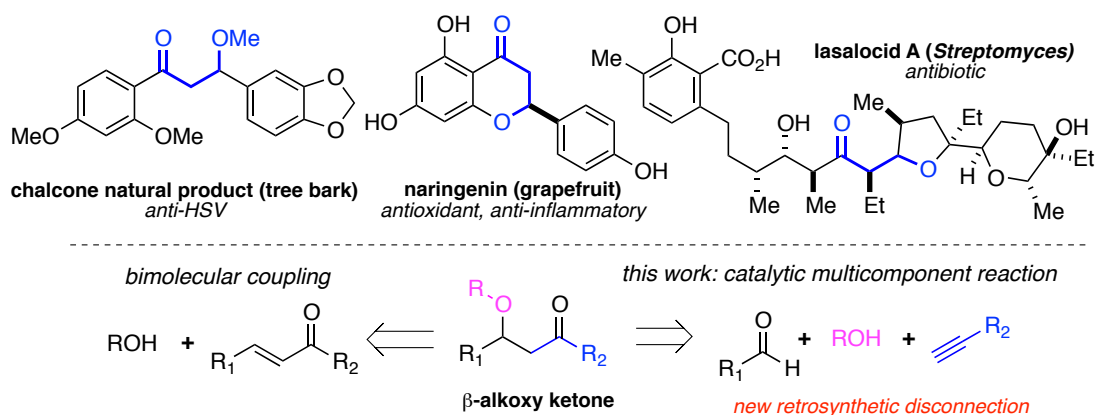


Given these prior studies, we envisioned that an *intermolecular* addition of gold(I) enol intermediates to carbon electrophiles could be achieved through the formation of stabilized oxocarbenium ions from hemiacetals. Specifically, the requisite hemiacetals **5-2** could be generated *in situ* from aldehydes and alcohols (Scheme 5.1). Intermolecular oxyauration of the alkyne with hemiacetal **5-2** would provide **5-3**, which could undergo fragmentation to gold(I) enol **5-5** and oxocarbenium ion **5-4**. The oxocarbenium ion and the gold(I) enol intermediate could then undergo intermolecular addition to furnish β -alkoxy ketone products.



Scheme 5.1 Proposed mechanism for Au(I)-catalyzed synthesis of β -alkoxy ketones from hemiacetals

β -Alkoxy ketones are important chemical building blocks that are prevalent in numerous biologically active molecules including flavanone⁹ and polyether natural products.¹⁰ Traditional routes for accessing this important class of molecules typically rely upon the bimolecular coupling of enones and alcohols (Scheme 5.2).¹¹ As a result, the intermolecular addition of gold(I) enol intermediates to oxocarbenium ions would provide a new retrosynthetic disconnection for accessing β -alkoxy ketone products.

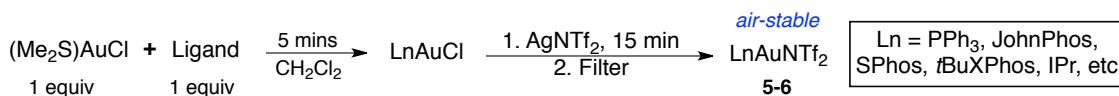


Scheme 5.2 Importance of designing new methods for β -alkoxy ketone synthesis

5.2 Methodology Design and Reaction Optimization

The intermolecular capture of carbon electrophiles by gold(I) enol intermediates is unprecedented, and in order to allow successful reactivity several challenges had to be addressed. First, hemiacetals have not been shown to undergo oxyuration with alkynes, thus judicious choice of aldehyde, alcohol, and alkyne to allow requisite hemiacetal formation and subsequent oxyuration is required. Moreover, to have successful intermolecular addition, the resulting oxocarbenium ion will have to be sufficiently stable to undergo selective capture by the gold(I) enol intermediate as opposed to undergoing capture with excess alcohol present in the reaction mixture. As a result, we decided to initially explore the Au(I)-catalyzed oxyuration of hemiacetals with phenylacetylene given its propensity for undergoing oxyuration.¹² Also, it was decided that a relatively stabilized oxocarbenium ion intermediate could be generated from the hemiacetal derived from an aromatic aldehyde, such as 4-bromobenzaldehyde, and methanol.

With a model system in place, reaction optimization began through the exploration of air-stable phosphine and NHC Au(I) bis-(trifluoromethanesulfonyl)imidate ($\text{ Tf}_2\text{ N}^-$) catalysts that have been shown to facilitate numerous oxyuration transformations.¹³ As a result, following the methods developed by Gagosz, a variety of L Au NTf_2 catalysts (**5-6**) were easily prepared through the metathesis of either commercially available or synthesized ligated-AuCl species with Ag NTf_2 (Scheme 5.3).¹⁴

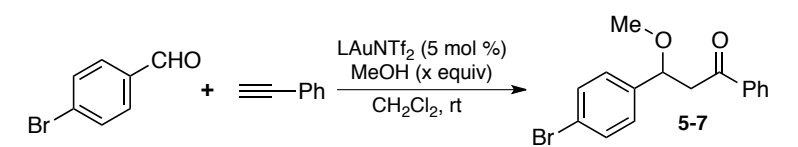


Scheme 5.3 Synthesis of Au(I)-catalysts **5-6**

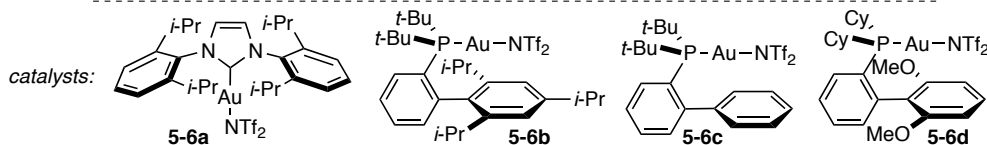
Initial experiments with NHC catalyst IPr Au NTf_2 **5-6a** (Table 5.1, entry 1) showed absolutely no reactivity; however, switching to phosphine derived catalysts, $\text{ PPh}_3\text{ Au NTf}_2$ (entry 2) and $\text{ P}(p\text{-CF}_3\text{-C}_6\text{H}_4)_3\text{ Au NTf}_2$ (entry 3) began to show modest formation of β -alkoxy ketone product **5-7**. Given these results, biaryl-phosphine Au(I)-catalysts were also explored due to their demonstrated

success mediating a variety of other Au(I)-catalyzed transformations.¹³ Interestingly, while *t*-BuXPhosAuNTf₂ **5-6b** (entry 4) provided no product formation, switching the biaryl portion of the ligand to JohnPhosAuNTf₂ **5-6c** (entry 5) began to show desired product formation. Given the observed dramatic changes in reactivity we next tried SPhosAuNTf₂ **5-6d** since this ligand has been shown to stabilize organo gold intermediates and facilitate a variety of different Au-catalyzed transformations. Gratifyingly, SPhosAuNTf₂ proved to be optimal and afforded desired β -alkoxy ketone **5-7** in the highest yield (entry 6).

Table 5.1 Optimization of reaction conditions^a



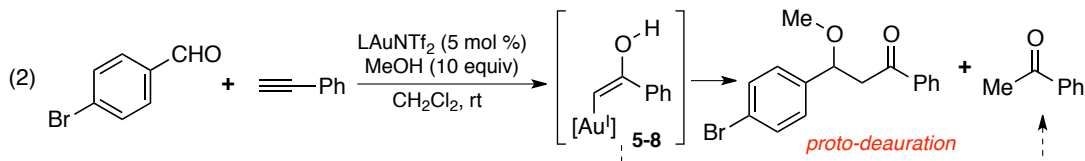
entry	catalyst	equiv MeOH	conv. (%)	yield 5-7 (%) ^b
1	IPrAuNTf ₂ (5-6a)	10	0	0
2	PPh ₃ AuNTf ₂	10	15	6
3	P(<i>p</i> -CF ₃ -C ₆ H ₄) ₃ AuNTf ₂	10	47	48
4	<i>t</i> -BuXPhosAuNTf ₂ (5-6b)	10	0	0
5	JohnPhosAuNTf ₂ (5-6c)	10	60	60
6	SPhosAuNTf ₂ (5-6d)	10	89	77
7	5-6d	2	76	65
8	5-6d	3	93	73
9	AgNTf ₂	3	0	0
10	HNTf ₂	3	0	0



^a Conditions: 1.0 equiv of 4-bromobenzaldehyde, 1.5 equiv phenylacetylene, *x* equiv MeOH, 5 mol % Au(I)-catalyst, CH₂Cl₂ (0.1 M), rt, 10 h. ^b Yields were determined by ¹H NMR analysis of crude reaction mixtures that contained phenanthrene as an internal standard.

However, one of the main issues while optimizing these transformations was the observed unreacted aldehyde/hemiacetal with concurrent acetophenone formation (eq 2). We speculated that the formation of acetophenone was likely the result of premature proto-deauration from the gold(I) enol intermediate **5-8** due to either competing proto-deauration in the presence of excess methanol, or due to the relatively low concentration of the requisite oxocarbenium ion intermediate. Thus, to potentially diminish the premature proto-deauration from

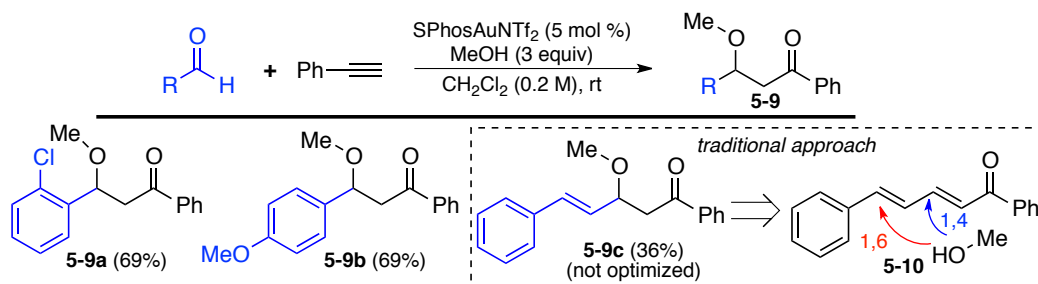
intermediate **5-8** and allow greater starting material consumption, we decided to vary the amount of alcohol present in the reaction mixture.



To our delight, the use of ten equivalents of methanol was not required and the same level of reactivity could be achieved with only three equivalents (entry 8). Lastly, control experiments were run with AgNTf₂ and HNTf₂ (entries 9 and 10) and confirmed that the observed reactivity was the result of Au(I)-catalysis.

5.3 Scope of Aldehyde Reaction Partner

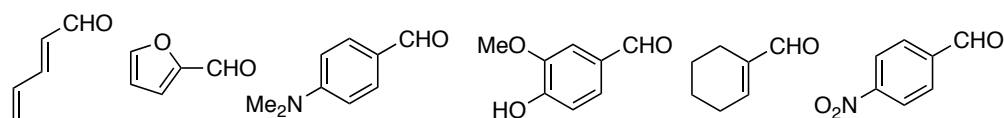
With optimized conditions in hand, we decided to explore the scope of the reaction by varying the aldehyde partner, using phenylacetylene and methanol as the other components. Since reaction optimization was performed on a benzaldehyde derivative, we decided to examine other aryl aldehydes as potential reaction partners for β -alkoxy ketone synthesis. Both electron withdrawing and donating substituents on the aryl aldehyde were well tolerated, forming β -alkoxy ketones **5-9a** and **5-9b** in good yield (Scheme 5.4). Next, we decided to employ *trans*-cinnamaldehyde, speculating that alkene conjugation should also stabilize the requisite oxocarbenium ions similar to an aryl group. Gratifyingly this reaction also proceeded efficiently to yield desired product **5-9c**, which further shows the complementarity of this strategy to other methods. For example, attempts to generate similar products through the conjugate addition methanol to enone **5-10** would likely suffer from competing 1,4- and 1,6-addition.



Scheme 5.4 Aryl aldehyde scope with phenylacetylene and methanol

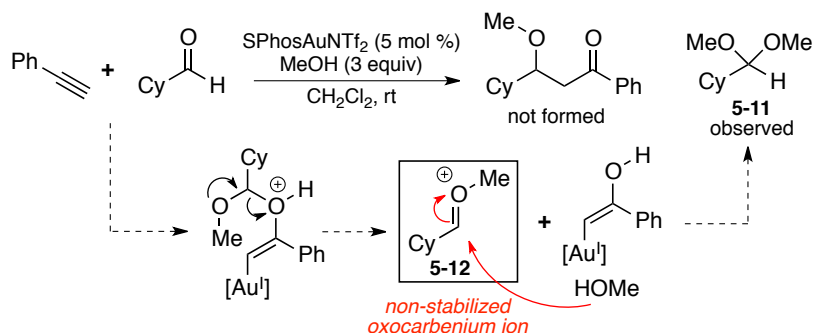
However, attempts to employ other conjugated aldehydes, such as those shown in Scheme 5.5, resulted in a complex mixture of products, likely due to the aldehydes participating in multiple side reactions under the Au-catalyzed conditions. In addition, benzaldehyde derivatives bearing dimethylamino, nitro, or hydroxyl groups were also unreactive under the Au(I)-catalyzed conditions.

unsuccessful aldehydes



Scheme 5.5 Unsuccessful conjugated aldehyde reaction partners

In turn, when aliphatic aldehyde cyclohexane carboxaldehyde was employed, only dimethyl acetal **5-11** was formed, which may result from the formation of oxocarbenium **5-12** followed by immediate methanol trapping (Scheme 5.6). Overall, this result lends support for the importance of having an electron-stabilizing group on the aldehyde to allow preferential trapping of the oxocarbenium ion by gold(I) enol intermediates.

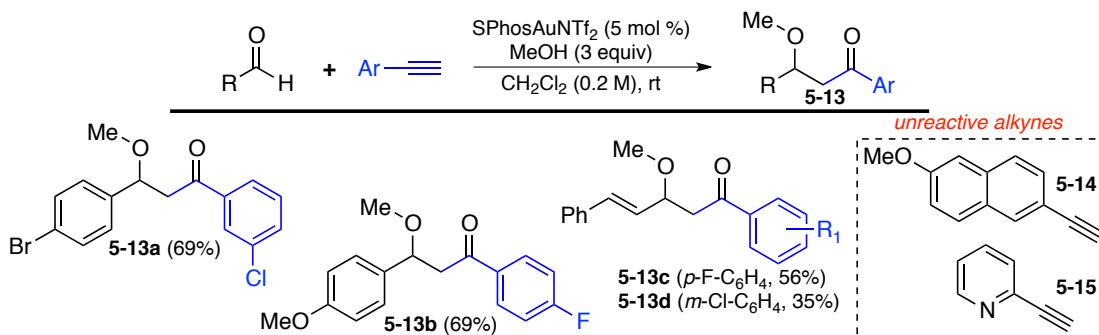


Scheme 5.6 Suggested mechanism for the formation of dimethyl acetal **5-11**

5.4 Investigation of Alkyne Reaction Partner

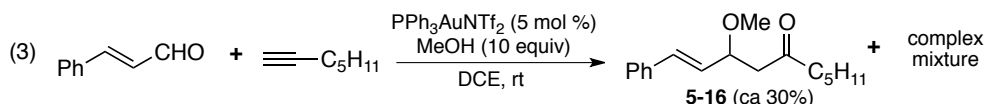
Given the observed limitations of the aldehyde reaction partner, we turned our attention towards investigating both aryl and aliphatic alkynes as another way of introducing diversity into the β -alkoxy ketone products. Accordingly, we began to explore the scope of the Au(I)-transformation by subjecting several aryl alkynes to the optimized conditions. Notable aryl alkynes that were successful reaction partners were 3-chlorophenylacetylene and 1-ethynyl-4-fluorobenzene, which allowed for the formation of diverse aryl-substituted β -alkoxy ketone products **5-**

13a-d (Scheme 5.7). However, attempts to employ other aromatic alkynes, such as 2-ethynyl-naphthalene derivative **5-14** or 2-ethynylpyridine **5-15**, were unsuccessful. No reaction was observed in these cases using either the optimized conditions or with other Au(I)-catalysts.



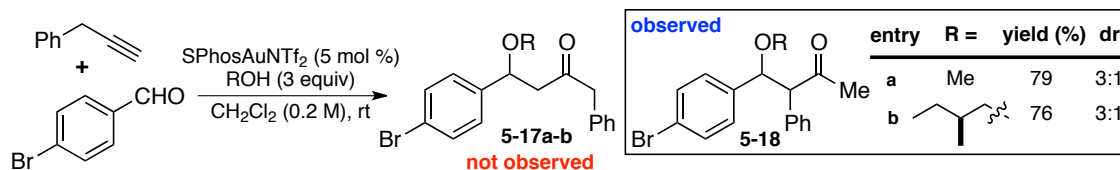
Scheme 5.7 Scope of aryl alkyne reaction partner

Next we decided to examine the reactivity of terminal aliphatic alkynes, as this would allow for the synthesis of β -alkoxy ketones with two different sets of enolizable hydrogens, which would be challenging to access through traditional methods. For instance, enolate addition reactions that employ unsymmetrical dialkylketones (such as 3-hexanone) often suffer from low regioselectivity during enolate formation, which leads to the formation of regioisomeric products. In contrast, our approach would likely garner products as a single isomer due to the regioselective oxyauration of alkynes. Initial exploration of utilizing terminal alkynes began with 1-heptyne, which after undergoing Au(I)-catalyzed carboalkoxylation with *trans*-cinnamaldehyde led to the formation of **5-16** in ca 30% yield in addition to a complex mixture of products (eq 3). Although the transformation with 1-heptyne is unoptimized it demonstrated the feasibility of aliphatic alkynes undergoing regioselective activation, and led us to investigate other aliphatic alkynes.



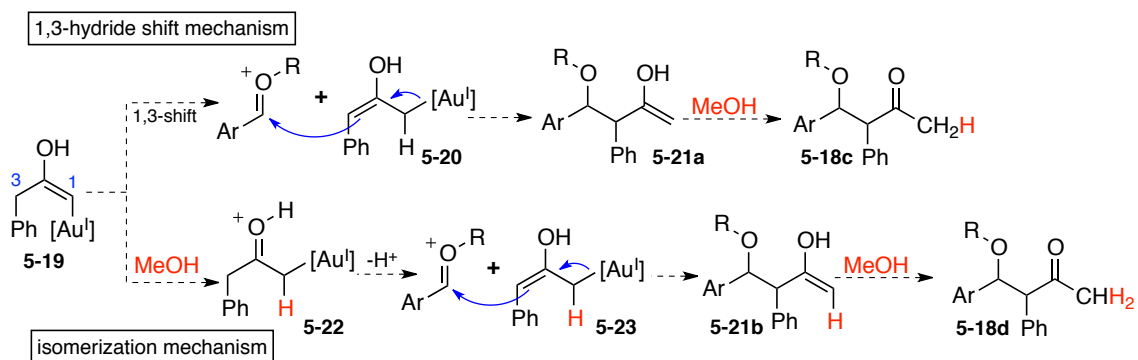
Given that 1-heptyne led to a complex mixture of products, we wondered whether an electron-stabilizing group on the alkyne was required to selectively mediate the Au(I)-catalyzed transformation. As a result, we decided to employ 3-

phenyl-1-propyne, as the benzyl substituent may facilitate the initial oxyauration and lead to more selective reactivity. However, the reaction of 3-phenyl-1-propyne and 4-bromobenzaldehyde, with either methanol or butanol, resulted in the formation of α -phenyl- β -alkoxy ketones **5-18a** and **5-18b**, respectively, and not the expected regioisomers **5-17a-b** (Scheme 5.8).



Scheme 5.8 Unexpected formation of β -alkoxy ketone regioisomer **5-18**

The regiochemical outcome of these reactions is quite interesting, and suggests that these Au(I)-catalyzed transformations may proceed through a different mechanism compared to the other reactions described above (Scheme 5.1). Presently, we hypothesize that the reaction 3-phenyl-1-propyne begins with the formation of expected gold(I) enol intermediate **5-19**, which could then undergo either a 1,3-hydride shift or a series of isomerization¹⁵ events to eventually lead to **5-18** (Scheme 5.9). The two mechanisms illustrated in Scheme 5.9 differ in the manner in which the terminal carbon of the alkyne is eventually reduced to a methyl group.

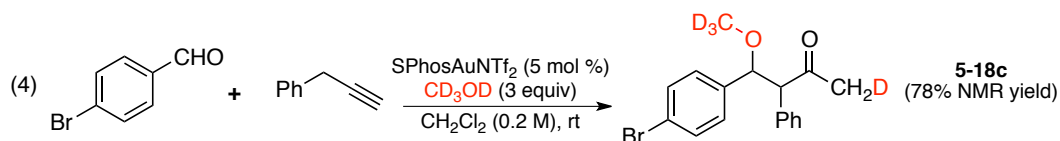


Scheme 5.9 Possible mechanisms for the formation of isomerized β -alkoxy ketone **5-18**

In the case of a 1,3-hydride shift, a hydrogen from C-3 would migrate to C-1, generating Au(I)-intermediate **5-20**, which could then undergo deauration and nucleophilic addition to the oxocarbenium ion to afford enol **5-21a**.¹⁶ The resulting enol could then undergo tautomerization, with the assistance of methanol, to

afford β -alkoxy ketone **5-18c**. In turn, the isomerization pathway could proceed with initial protonation with methanol to afford oxocarbenium ion **5-22**, which could then be deprotonated to form enol **5-23**, an intermediate similar to **5-20**. Au(I)-intermediate **5-23** could then undergo a similar nucleophilic attack as **5-20** to afford enol **5-21b**. The conversion of **5-21b** to β -alkoxy ketone **5-18d** could then proceed through the acquisition of a *second* proton from the methanol.

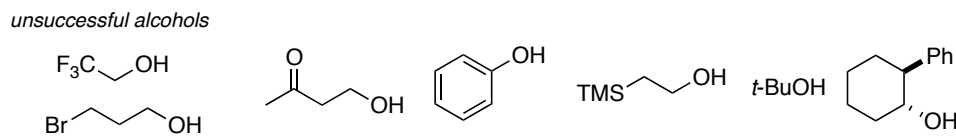
Unique to these two mechanisms is the number of methanol protons that are incorporated into the final product, with **5-18c** acquiring one and **5-18d** acquiring two. As a result, we decided to probe the mechanism of product formation by performing the same experiment using methanol- d_4 . Gratifyingly, clean mono-deuterium incorporation occurred at the terminal carbon of the alkyne, affording **5-18c** and lending support for the 1,3-hydride shift mechanism (eq 4). To the best of our knowledge, 1,3-hydride shifts from vinyl gold intermediates are rare;¹⁷ however, 1,3-Au shifts of gold acetylides have been well documented.¹⁸



Given the unique reactivity observed with external alkynes, we are currently exploring internal alkynes, in addition to enynes and propargylic alcohols, for their application in the Au-catalyzed synthesis of β -alkoxy ketones.

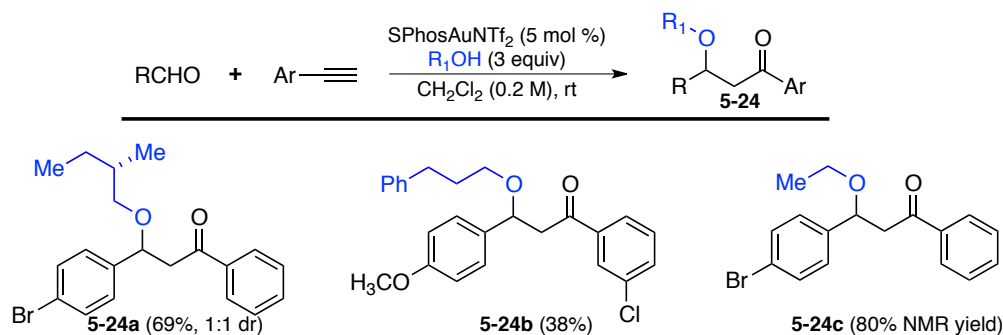
5.5 Scope of Alcohol Reaction Partner

While initially exploring the scope of the alcohol reaction partner, it was observed that use of either electron-poor or sterically encumbered alcohols led to no conversion of the starting materials (Scheme 5.10). We believe this observed lack of reactivity might result from the formation of the requisite hemiacetal in only very low concentrations due to the relatively low nucleophilicity of these alcohols.



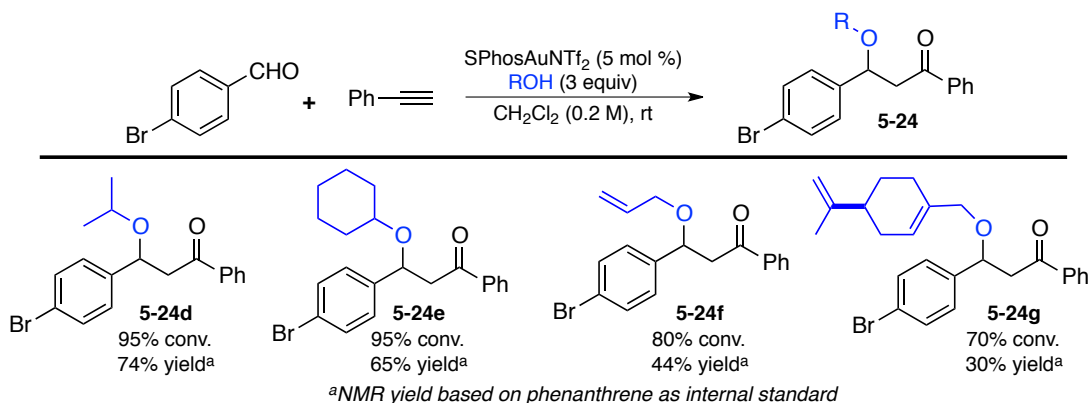
Scheme 5.10 Unsuccessful alcohol reaction partners

As a result, we turned our attention towards exploring electronically neutral or electron-rich alcohols that were not as sterically encumbered as those employed previously. For instance, (*S*)-2-methylbutan-1-ol, which is less sterically congested than 2-phenyl cyclohexanol, underwent clean conversion to β -alkoxy ketone **5-24a** with 1:1 dr (Scheme 5.11). In addition, the aliphatic alcohols 3-phenylpropanol and ethanol were also suitable reaction partners, forming β -alkoxy ketones **5-24b** and **5-24c**, respectively.



Scheme 5.11 Initial scope of Au(I)-catalyzed transformation with aliphatic alcohols

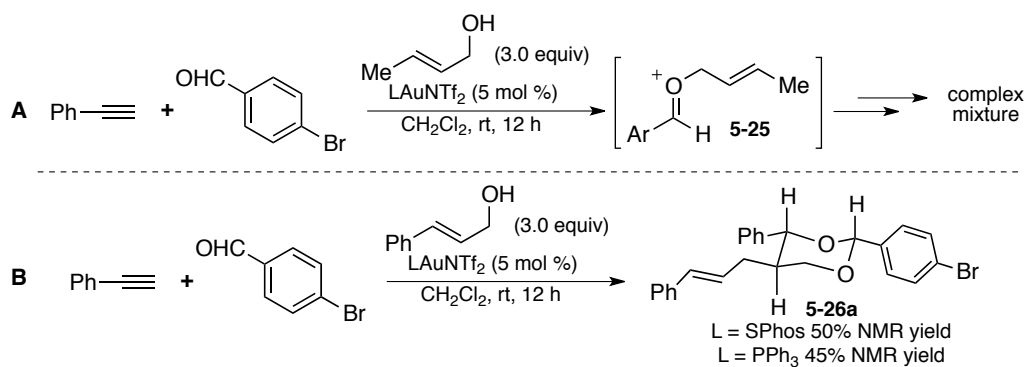
In addition, initial screening of other aliphatic alcohols showed promise for diverse β -alkoxy ketone synthesis through the successful incorporation of both secondary and allylic alcohols. For instance, secondary alcohols isopropanol and cyclohexanol both were successful reaction partners, affording β -alkoxy ketones **5-24d** and **5-24e** in good yield (Scheme 5.12). In addition, allyl alcohol and naturally derived (+)-perillyl alcohol could also be incorporated into β -alkoxy ketone products, yielding **5-24f** and **5-24g** in moderate yield.



Scheme 5.12 Preliminary data on employing cyclic and allyl alcohols

Although these transformations still need to be optimized they showcase the potential of this methodology for diverse β -alkoxy ketone synthesis. Specifically, the use of allyl alcohols would allow for the incorporation of an alkenyl functional group handle, which could then be used to further transform the β -alkoxy ketone products. Moreover, the incorporation of cyclohexanol and (+)-perillyl alcohol suggests there may be potential to append structurally related alcohols such as sugars, or other alcohol-containing natural products, to β -alkoxy ketones.

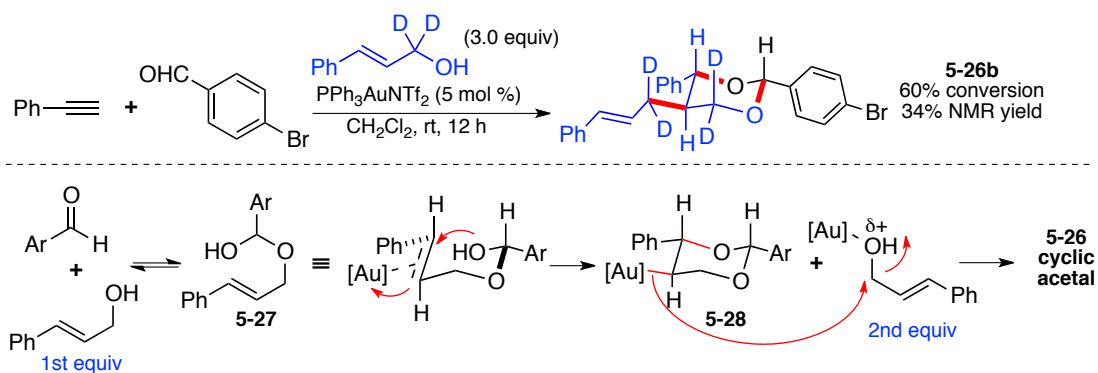
Since allyl alcohol was able to participate in the Au-catalyzed transformation, other allyl alcohol derivatives, such as crotyl and cinnamyl alcohol, were also explored. Unfortunately, the use of crotyl alcohol led to a complex mixture of products after screening a variety of catalysts, potentially due to the increased reactivity of oxocarbenium **5-25** (Scheme 5.13, **A**). However, when cinnamyl alcohol was employed the main product observed was cyclic acetal **5-26a**, which was formed as a single diastereomer in ca 50% yield with both SPhosAuNTf₂ and PPh₃AuNTf₂ (Scheme 5.13, **B**). Since our prior studies showed that these Au(I)-catalyzed reactions usually proceeded with low diastereoselectivity, we sought to explore the origin of product formation by using cinnamyl alcohol-d₂.



Scheme 5.13 Outcome of using substituted allyl alcohol derivatives

The deuterium-labeling experiment revealed the formation of cyclic acetal **5-26b**, which is the result of the product being formed through the assembly of two equivalents of alcohol and one equivalent of aldehyde (Scheme 5.14). Interestingly, while phenylacetylene was not incorporated into the product, its presence was essential for product formation. No reaction was observed in the absence of phenylacetylene, although similar reactivity was observed when only

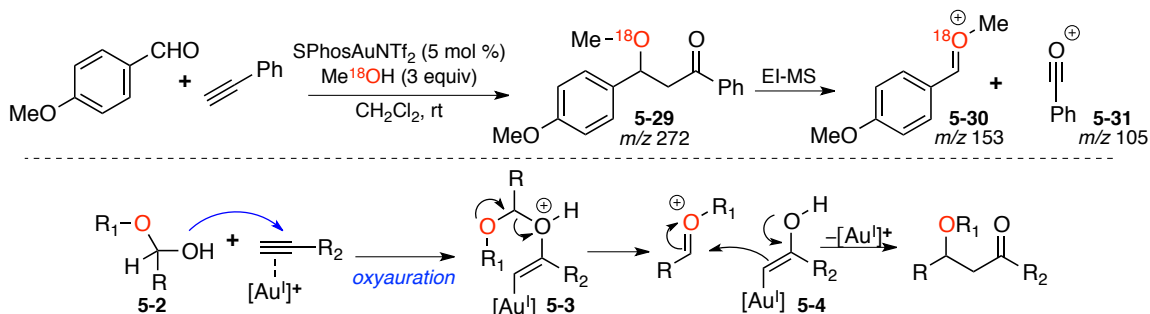
10 mol% was employed. As a result, we believe that the alkyne is serving as an ancillary ligand for the Au(I)-catalyst. Given these observed results we are currently in favor of a mechanism that begins with the formation of hemiacetal **5-27** from cinnamyl alcohol and aldehyde (Scheme 5.14). However, in contrast to the hemiacetal attacking an activated alkyne, preferential activation and *intramolecular* stereoselective attack of the cinnamyl alkene occurs, yielding alkyl gold intermediate **5-28** as a single diastereomer. The second equivalent of cinnamyl alcohol would then undergo Au-activation followed by nucleophilic attack by intermediate **5-28** to afford cyclic acetal **5-26**. To the best of our knowledge this type of reactivity is unprecedented and studies are currently underway to optimize this reaction and further explore this novel transformation.



Scheme 5.14 Proposed mechanism for Au(I)-catalyzed formation of cyclic acetal **5-26**

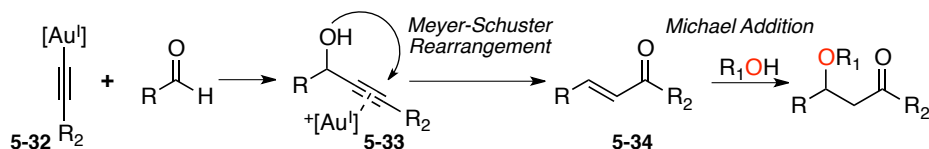
5.6 Exploration of Mechanism

As noted above (Scheme 5.1), our proposed mechanism involves oxygen transfer from the aldehyde to the alkyne, with the alcohol being incorporated into the product through the formation of an oxocarbenium ion. In order to probe this mechanistic hypothesis isotopically enriched β -alkoxy ketone **5-29** was synthesized by using methanol- ^{18}O as the alcohol (Scheme 5.15). Analysis of **5-29** by EI-MS indicated the generation of fragments **5-30** and **5-31**, which illustrates oxygen transfer from the aldehyde onto the alkyne and incorporation of methanol- ^{18}O at the benzylic position of the product. This experiment lends further support for the oxyauration of a hemiacetal **5-2** onto an activated alkyne followed by intermolecular rearrangement to product.



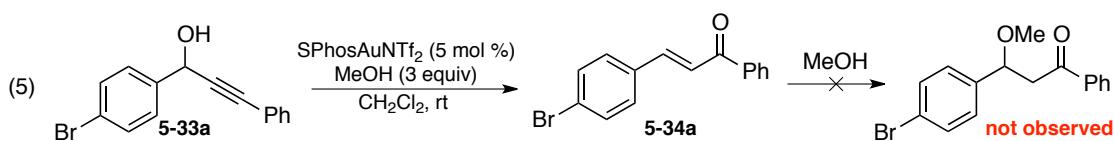
Scheme 5.15 Support for hemiacetal oxyauration/fragmentation pathway

However, a second possible mechanism for product formation involves the initial formation of propargylic alcohol **5-33** through the 1,2-addition of Au(I)-acetylide **5-32** to an aldehyde (Scheme 5.16).¹⁹ In the presence of gold catalysts, propargylic alcohols can isomerize to enones **5-34** via a Meyer-Schuster rearrangement, which would cause the observed oxygen transfer.²⁰ Lastly, formation of the observed product would then occur through the oxa-Michael addition of an alcohol to enone **5-34**.



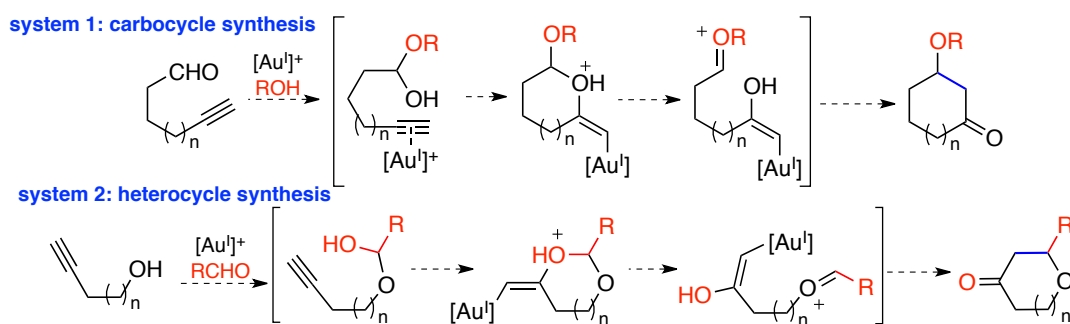
Scheme 5.16 Alternative mechanism for β -alkoxy ketone synthesis

In order to determine if the mechanism in Scheme 5.16 was operating, propargylic alcohol **5-33a** was synthesized and subjected to the optimized reaction conditions (eq 5). While **5-33a** readily underwent a Au(I)-catalyzed Meyer-Schuster rearrangement to enone **5-34a**, the resulting enone product was not transformed to a β -alkoxy ketone under the reaction conditions. Given this outcome and the general reactivity observed while exploring these transformations, we currently favor the mechanism shown in Scheme 5.15 that involves hemiacetal attack onto an activated alkyne followed by ionization and trapping.



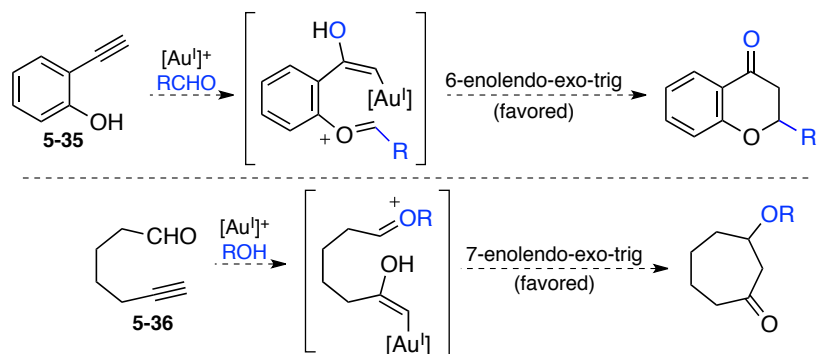
5.7 Future Directions

With the recently gained mechanistic insight in hand and the overall novelty of the Au(I)-catalyzed transformation, there remain several avenues that warrant further exploration. For instance, the synthesis of cyclic products could be achieved by investigating intramolecular systems, where two of the reactive functionalities would be tethered. The observation that oxygen transfer occurs from the aldehyde to the alkyne will be useful in the rational design of intramolecular substrates. Two types of intramolecular systems of interest are ones in which the alkyne is tethered to the alcohol or the aldehyde, giving rise to either heterocyclic or carbocyclic frameworks, respectively (Scheme 5.17).



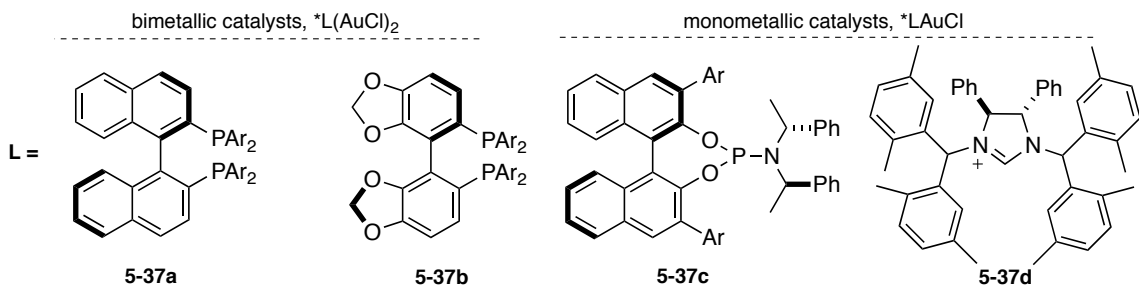
Scheme 5.17 Intramolecular systems for carbocycle and heterocycle construction

In order for these transformations to be successful it will be necessary to employ substrates with long enough tethers to ensure Baldwin's rules are obeyed for favorable endocyclic ring closure. Thus, interesting substrates that would proceed through favorable cyclization would include **5-35**, which would allow entry into the flavonoid natural products, or **5-36** that would allow heptacyclic ring synthesis via 7-enolendo-exo-trig cyclization (Scheme 5.18).²¹



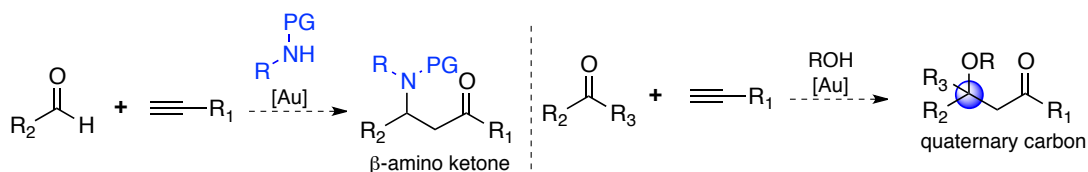
Scheme 5.18 Interesting substrates that would undergo favorable cyclization

Another area worth investigating is the use of chiral Au(I)-catalysts for the asymmetric synthesis of β -alkoxy ketones. The linear geometry of Au(I)-catalysts has made enantioselective Au(I)-catalysis challenging, as the asymmetric environment induced by the ligand is far removed from the enantiodetermining site.²² However, several chiral Au(I)-catalysts, such as monometallic and bimetallic catalysts **5-37a-d**, have recently been designed and successfully implemented in several asymmetric Au(I)-catalyzed transformations (Scheme 5.19).²³ As a result, we intend on initially investigating catalysts **5-37a-d**, the result of which will guide the development of other chiral Au(I)-catalysts for the enantioselective synthesis of β -alkoxy ketones.



Scheme 5.19 Examples of chiral Au(I)-catalysts

Lastly, a broader goal of the project is to expand the methodology to include other nucleophiles and electrophiles besides alcohols and aldehydes. For instance the employment of amines would allow entry into β -amino ketones, which may prove to be a synthetically useful route for arriving at structurally related β -amino acids (Scheme 5.20).



Scheme 5.20 Expansion of scope to include other nucleophiles and electrophiles

Given that amines are more nucleophilic than alcohols, one potential challenge will be controlling the chemoselectivity of the transformation, as competing hydroamination may occur.²⁴ As a result, tuning amine nucleophilicity through the use of protecting groups will likely be critical in achieving successful

reactivity. In addition, advancing the scope of the electrophile beyond aldehydes would allow this methodology to be more general. For example, the use of ketones would garner β -alkoxy ketone products with a quaternary carbon (Scheme 5.20). More importantly, the use of a chiral Au(I)-catalyst would provide a new means of establishing chirality at quaternary centers, which are traditionally hard to access.

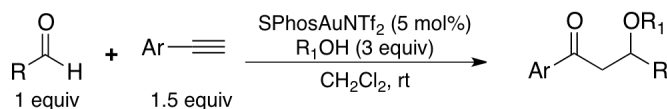
5.8 Conclusions

The work outlined in this chapter details several novel Au(I)-catalyzed transformations that proceed through the generation and capture of gold(I) enol intermediates for β -alkoxy ketone synthesis. These Au-catalyzed transformations provide a significantly different approach to β -alkoxy ketone synthesis, allowing for diverse product formation through the multicomponent assembly of the reaction partners. More importantly, the intermolecular capture of gold(I) enol species is unprecedented and the findings in this chapter will likely lead to the development of other useful Au(I)-catalyzed reactions that utilize the intermolecular capture of gold(I) enol intermediates with electrophiles.

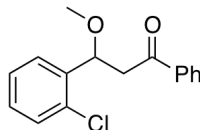
5.9 Experimental

General: All reactions were carried out at room temperature in sealed tubes under a nitrogen atmosphere. All (NHC)AuNTf₂ and (phosphine)AuNTf₂ catalysts were prepared according to procedures reported by Gagosz.¹⁴ All aldehydes, alcohols and alkynes were purchased from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and used without further purification. The ¹⁸O experiment in Scheme 5.15 was conducted with methanol-¹⁸O (95 atom% ¹⁸O) purchased from Icon Isotopes. The synthesis of cinnamyl alcohol-d₂ was accomplished using a procedure reported by Price.²⁵ Dichloromethane was purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY, HSQC, and NOESY experiments. Ratios of diastereomers were determined by ¹H NMR. Yields refer to isolated yields of compounds estimated to be $\geq 95\%$ pure as determined by ¹H NMR analysis unless otherwise noted.

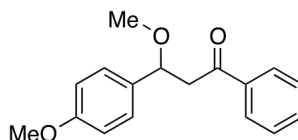
Synthesis and Characterization of β -Alkoxy Ketone Products



General procedure 1: Au-catalyzed synthesis of β -alkoxy ketones. An oven-dried tube was equipped with a magnetic stir bar and cooled under a stream of N₂ before being charged with SPhosAuNTf₂ (5 mol%). The tube was then charged with a 0.1 M CH₂Cl₂ solution of aldehyde (1 equiv), alkyne (1.5 equiv) and alcohol (3 equiv) before being sealed with a septum. The resulting mixture was stirred at room temperature and monitored for completion by TLC analysis. Upon starting material consumption, the mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate.

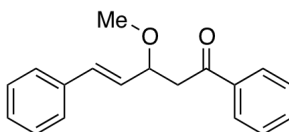


3-(2-chlorophenyl)-3-methoxy-1-phenylpropan-1-one (5-9a). The reaction of 2-chlorobenzaldehyde (40 mg, 0.28 mmol) with phenylacetylene (44 μ l, 0.43 mmol) and methanol (34 μ l, 0.84 mmol) was conducted according to the general procedure 1 using 5 mol% of JohnPhosAuNTf₂ in place of SPhosAuNTf₂. This procedure afforded 54 mg (69%) of the title compound as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 8.0 Hz, 2 H), 7.58-7.54 (m, 2 H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 7.24 (t, *J* = 7.5 Hz, 1 H), 5.34 (dd, *J* = 3.0, 9.5 Hz, 1 H), 3.39 (dd, *J* = 9.5, 16.5 Hz, 1 H), 3.28 (s, 3 H), 3.15 (dd, *J* = 3.0, 16.5 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 197.1, 138.9, 136.9, 133.1, 132.6, 129.6, 128.7, 128.5, 128.2, 127.3, 127.2, 76.1, 57.4, 45.5. MS (ESI) 297.0655 (297.0653 calcd for C₁₆H₁₅ClO₂, M + Na⁺).

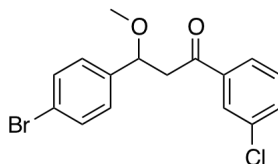


3-methoxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (5-9b). The reaction of *p*-anisaldehyde (40 mg, 0.29 mmol) with phenylacetylene (49 μ l, 0.44 mmol)

and methanol (35 μ l, 0.87 mmol) was conducted according to the general procedure 1. This procedure afforded 54 mg (69%) of the title compound as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.94 (d, J = 8.5 Hz, 2 H), 7.54 (t, J = 7.5 Hz, 1 H), 7.44 (t, J = 8.0 Hz, 2 H), 7.33 (d, J = 7.0 Hz, 2 H), 6.91 (d, J = 6.5 Hz, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 197.8, 159.3, 137.2, 133.4, 133.0, 128.5, 128.2, 127.9, 113.9, 79.1, 56.6, 55.2, 47.1. MS (ESI) 293.1154 (293.1148 calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3$, $\text{M} + \text{Na}^+$).

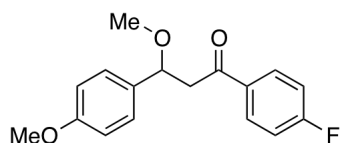


(E)-3-methoxy-1,5-diphenylpent-4-en-1-one (5-9c). The reaction of *trans*-cinnamaldehyde (30 mg, 0.23 mmol) with phenylacetylene (38 μ l, 0.34 mmol) and methanol (28 μ l, 0.69 mmol) was conducted according to the general procedure 1. This procedure afforded 22 mg (36%) of the title compound as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.88 (d, J = 7.5 Hz, 2 H), 7.49 (t, J = 6.5 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 2 H), 7.32 (d, J = 7.0 Hz, 2 H), 7.25 (t, J = 8.0 Hz, 2 H), 7.17 (t, J = 7.0 Hz, 1 H), 6.67 (d, J = 16.0 Hz, 1 H), 6.17 (dd, J = 7.5, 16.0 Hz, 1 H), 4.47 (ddd, 5.0, 7.5, 7.5 Hz, 1 H), 3.46 (dd, J = 7.5, 16.0 Hz, 1 H), 3.35 (s, 3 H), 3.07 (dd, J = 5.5, 16.5 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 197.6, 137.2, 136.3, 133.1, 132.6, 128.8, 128.6, 128.2, 127.8, 126.5, 78.3, 56.7, 44.8 (one aromatic signal absent due to accidental equivalence). MS (ES+) 289.0 (289.1 calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2$, $\text{M} + \text{Na}^+$).



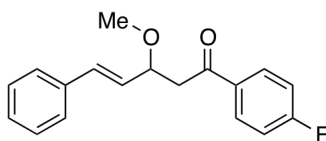
3-(4-bromophenyl)-1-(3-chlorophenyl)-3-methoxypropan-1-one (5-13a). The reaction of 4-bromobenzaldehyde (30 mg, 0.16 mmol) with 3-chloro-1-ethynylbenzene (30 μ l, 0.24 mmol) and methanol (20 μ l, 0.48 mmol) was conducted according to the general procedure 1 using 5 mol% of JohnPhosAuNTf₂ in place of SPhosAuNTf₂. This procedure afforded 40 mg

(69%) of the title compound as an off white solid: mp = 68-70°C. ^1H NMR (500 MHz, CDCl_3) δ 7.89 (s, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 9.0 Hz, 2 H), 7.39 (t, J = 8.0 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 2 H), 4.82 (dd, J = 4.5, 8.0 Hz, 1 H), 3.52 (dd, J = 8.5, 16.5 Hz, 1 H), 3.21 (s, 3 H), 3.01 (dd, J = 4.5, 16.5 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.0, 140.2, 138.5, 134.9, 133.1, 131.7, 129.9, 128.4, 128.3, 126.3, 121.8, 78.8, 56.9, 47.0. MS (ESI) 374.9754 (374.9758 calcd for $\text{C}_{16}\text{H}_{14}\text{BrClO}_2$, $\text{M} + \text{Na}^+$).



1-(4-fluorophenyl)-3-methoxy-3-(4-methoxyphenyl)propan-1-one (5-13b).

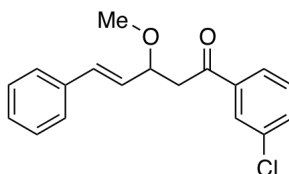
The reaction of *p*-anisaldehyde (40 mg, 0.29 mmol) with 1-ethynyl-4-fluorobenzene (50 μl , 0.44 mmol) and methanol (36 μl , 0.87 mmol) was conducted according to the general procedure 1. This procedure afforded 52 mg (62%) of the title compound as an orange oil. ^1H NMR (400 MHz, CDCl_3) δ 7.97-7.93 (m, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 7.10-7.06 (m, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 4.78 (dd, J = 4.8, 8.4 Hz, 1 H), 3.79 (s, 3 H), 3.53 (dd, J = 8.4, 16.4 Hz, 1 H), 3.18 (s, 3 H), 3.01 (dd, J = 4.8, 16.4 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.2, 165.6 (d, J = 254.6 Hz), 159.2, 133.6 (d, J = 3.1 Hz), 133.1, 130.8 (d, J = 9.3 Hz), 127.8, 115.5 (d, J = 21.8 Hz), 113.9, 79.1, 56.5, 55.2, 46.9. MS (ESI) 311.1059 (311.1054 calcd for $\text{C}_{17}\text{H}_{17}\text{FO}_3$, $\text{M} + \text{Na}^+$).



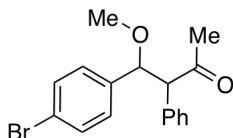
(E)-1-(4-fluorophenyl)-3-methoxy-5-phenylpent-4-en-1-one (5-13c).

The reaction of *trans*-cinnamaldehyde (40 mg, 0.30 mmol) with 1-ethynyl-4-fluorobenzene (52 μl , 0.45 mmol) and methanol (36 μl , 0.90 mmol) was conducted according to the general procedure 1. This procedure afforded 48 mg (56%) of the title compound as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.99 (t, J = 7.5 Hz, 2 H), 7.39 (d, J = 8.5 Hz, 2 H), 6.66 (d, J = 16.0 Hz, 1 H), 6.15 (dd, J = 7.5, 16.0 Hz, 1 H), 4.44 (ddd, J = 4.5, 8.0, 8.0 Hz, 1 H), 3.43 (dd, J = 8.0, 16.5

Hz, 1 H), 3.33 (s, 3 H), 3.01 (dd, $J = 4.5, 16.0$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.1, 165.7 (d, $J = 254.2$ Hz), 136.2, 133.6 (d, $J = 2.9$ Hz), 132.6, 130.9 (d, $J = 8.8$ Hz), 128.6, 128.5, 127.9, 126.5, 115.6 (d, $J = 21.6$ Hz), 78.3, 56.6, 44.7. MS (ESI) 307.1111 (307.1105 calcd for $\text{C}_{18}\text{H}_{17}\text{FO}_2$, $\text{M} + \text{Na}^+$).



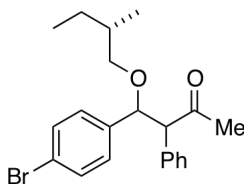
(E)-1-(3-chlorophenyl)-3-methoxy-5-phenylpent-4-en-1-one (5-13d). The reaction of *trans*-cinnamaldehyde (40 mg, 0.30 mmol) with 3-chloro-1-ethynylbenzene (56 μl , 0.45 mmol) and methanol (37 μl , 0.90 mmol) was conducted according to the general procedure 1 using 5 mol% of JohnPhosAuNTf₂ in place of SPhosAuNTf₂. This procedure afforded 32 mg (35%) of the title compound as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.94 (s, 1 H), 7.84 (d, $J = 7.5$ Hz, 1 H), 7.53 (d, $J = 8.0$ Hz, 1 H), 7.42-7.39 (m, 3 H), 7.33 (t, $J = 8.0$ Hz, 2 H), 7.26 (t, $J = 7.0$ Hz, 1 H), 6.67 (d, $J = 16.0$ Hz, 1 H), 6.15 (dd, $J = 8.0, 16.0$ Hz, 1 H), 4.44 (ddd, $J = 4.5, 8.0, 8.0$ Hz, 1 H), 3.43 (dd, $J = 8.0, 16.0$ Hz, 1 H), 3.34 (s, 3 H), 3.03 (dd, $J = 4.5, 8.0$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.5, 138.8, 136.2, 134.9, 133.0, 132.8, 129.9, 128.6, 128.5, 128.4, 127.9, 126.6, 126.4, 78.3, 56.7, 44.9. MS (ESI) 323.0810 (323.0809 calcd for $\text{C}_{18}\text{H}_{17}\text{ClO}_2$, $\text{M} + \text{Na}^+$).



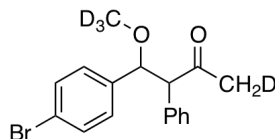
4-(4-bromophenyl)-4-methoxy-3-phenylbutan-2-one (5-18a). The reaction of 4-bromobenzaldehyde (40 mg, 0.22 mmol) with 3-phenyl-1-propyne (40 μl , 0.32 mmol) and methanol (27 μl , 0.66 mmol) was conducted according to the general procedure 1. The crude product was formed as a 3:1 mixture of diastereomers as judged by ^1H NMR analysis. Purification by flash chromatography afforded 45 mg (62%) of the title compound as a white solid with >20:1 dr. In addition, a small amount of the minor diastereomer (8 mg, 11%) was also isolated.

Major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ 7.25 (d, $J = 8.5$ Hz, 2 H), 7.14-7.13 (m, 3 H), 6.99-6.98 (m, 2 H), 6.89 (d, $J = 8.5$ Hz, 2 H), 4.74 (d, $J = 10.0$ Hz, 1 H), 3.92 (d, $J = 10.5$ Hz, 1 H), 3.19 (s, 3 H), 2.21 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.7, 138.0, 133.9, 131.0, 129.0, 128.9, 128.6, 127.6, 121.4, 84.4, 65.8, 56.9, 30.9. MS (ESI) 355.0310 (355.0304 calcd for $\text{C}_{17}\text{H}_{17}\text{BrO}_2$, $\text{M} + \text{Na}^+$).

Minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ 7.45 (d, $J = 8.5$ Hz, 2 H), 7.35 (m, 5 H), 7.22 (d, $J = 8.5$ Hz, 2 H), 4.75 (d, $J = 8.5$ Hz, 1 H), 3.96 (d, $J = 9.0$ Hz, 1 H), 3.03 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.3, 139.4, 135.5, 131.4, 129.4, 129.0, 128.7, 127.6, 121.8, 82.8, 66.6, 56.9, 30.5. MS (ESI) 355.0311 (355.0304 calcd for $\text{C}_{17}\text{H}_{17}\text{BrO}_2$, $\text{M} + \text{Na}^+$).



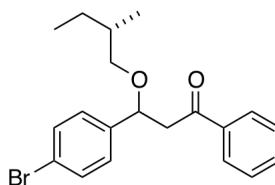
4-(4-bromophenyl)-4-((S)-2-methylbutoxy)-3-phenylbutan-2-one (5-18b). The reaction of 4-bromobenzaldehyde (40 mg, 0.22 mmol) with 3-phenyl-1-propyne (40 μl , 0.32 mmol) and (S)-2-methylbutan-1-ol (71 μl , 0.66 mmol) was conducted according to the general procedure 1. This procedure afforded 65 mg (76%) of the title compound as a 3:1 mixture of diastereomers that were inseparable by flash chromatography. Data are for the mixture. ^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, $J = 8.5$ Hz, 0.7 H), 7.32-7.31 (m, 1.32 H), 7.24 (d, $J = 8.5$ Hz, 1.7 H), 7.20 (d, $J = 8.0$ Hz, 0.7 H), 7.14-7.13 (m, 2 H), 7.03-7.01 (m, 1.4 H), 6.89 (d, $J = 8.5$ Hz, 1.4 H), 4.79 (d, $J = 10.0$ Hz, 1 H), 3.94 (d, $J = 10.5$ Hz, 1 H), 3.16-3.02 (m, 1.7 H), 2.88-2.80 (m, 0.3 H), 2.23 (s, 2 H), 1.89 (s, 1H), 1.57-1.54 (m, 0.7 H), 1.40-1.34 (m, 1 H), 1.16-1.06 (m, 1 H), 0.88-0.82 (m, 6.4 H), 0.67-0.64 (m, 1 H), 0.59-0.57 (m, 1 H). ^{13}C NMR (125 MHz) 206.1, 206.4, 140.1, 138.8, 134.1, 131.5, 131.3, 130.9, 129.5, 129.3, 129.2, 128.9, 128.8, 128.5, 128.3, 127.4, 127.3, 121.5, 121.3, 83.3, 83.2, 81.4, 81.3, 74.4, 74.3, 74.1, 74.0, 66.8, 66.7, 65.8, 35.0, 34.9, 34.8, 34.6, 31.2, 30.6, 26.1, 26.0, 25.8, 25.7, 16.6, 16.5, 16.4, 16.2, 11.2, 11.1, 10.9. MS (ESI) 411.0939 (411.0930 calcd for $\text{C}_{21}\text{H}_{25}\text{BrO}_2$, $\text{M} + \text{Na}^+$).



4-(4-bromophenyl)-4-methoxy-3-phenylbutan-2-one-d₄ (5-18c). The reaction of 4-bromobenzaldehyde (40 mg, 0.22 mmol) with 3-phenyl-1-propyne (40 μ l, 0.32 mmol) and methanol-d₄ (26 μ l, 0.65 mmol) was conducted according to the general procedure 1, with one equivalent of phenanthrene (39.2 mg, 0.22 mmol) as an internal standard. The crude product was formed in 78% as a 1.5:1 mixture of diastereomers as judged by ¹H NMR analysis.

Major diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, J = 8.0 Hz, 2 H), 7.12-7.11 (m, 3 H), 6.98-6.96 (m, 2 H), 6.87 (d, J = 8.4 Hz, 2 H), 4.72 (d, J = 9.9 Hz, 1 H), 3.91 (d, J = 9.9 Hz, 1 H), 2.19-2.17 (m, 2 H); ¹³C NMR (176 MHz, CDCl₃) δ 206.8, 138.1, 131.1, 129.0, 128.9, 128.8, 128.6, 127.6, 121.5, 84.3, 65.7, 30.6 (t, J = 19.0 Hz) (the signal corresponding to -OCD₃ could not be detected). MS (ESI) 359.0556 (359.0555 calcd for C₁₇H₁₃D₄BrO₂, M + Na⁺).

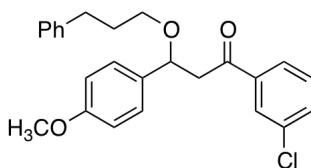
Minor diastereomer: ¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, J = 8.4 Hz, 2 H), 7.35-7.31 (m, 5 H), 7.22 (d, J = 8.4 Hz, 2 H), 4.75 (d, J = 8.8 Hz, 1 H), 3.96 (d, J = 8.8 Hz, 1 H), 1.86-1.85 (m, 2 H); ¹³C NMR (176 MHz, CDCl₃) δ 206.3, 139.4, 135.4, 131.5, 129.4, 129.0, 128.7, 127.6, 121.8, 82.7, 66.6, 30.3 (t, J = 19.7 Hz) (the signal corresponding to -OCD₃ could not be detected). MS (ESI) 359.0555 (359.0555 calcd for C₁₇H₁₃D₄BrO₂, M + Na⁺).



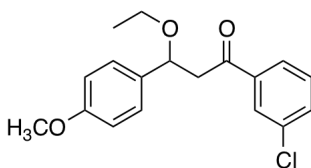
3-(4-bromophenyl)-3-((S)-2-methylbutoxy)-1-phenylpropan-1-one (5-24a).

The reaction of 4-bromobenzaldehyde (40 mg, 0.22 mmol) with phenylacetylene (36 μ l, 0.32 mmol) and (S)-2-methylbutan-1-ol (71 μ l, 0.66 mmol) was conducted according to the general procedure 1. This procedure afforded 57 mg (69%) of the title compound as a 1:1 mixture of diastereomers that were inseparable by flash chromatography. Data are for the mixture. ¹H NMR (400 MHz, CDCl₃) δ

7.91 (d, $J = 7.2$ Hz, 2 H), 7.53 (t, $J = 5.6$ Hz, 1 H), 7.48-7.41 (m, 4 H), 7.27 (d, $J = 8.4$ Hz, 2 H), 4.87 (dd, $J = 5.2, 8.8$ Hz, 1 H), 3.55 (dd, $J = 8.4, 16.0$ Hz, 1 H), 3.15-3.11 (m, 1 H), 3.08-3.03 (m, 1 H), 2.99 (ddd, $J = 2.4, 4.8, 16.4$ Hz, 1 H), 1.54-1.48 (m, 1 H), 1.36-1.26 (m, 1 H), 1.05-0.95 (m, 1 H), 0.78-0.76 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.7, 141.3, 137.3, 133.1, 131.6, 128.5, 128.4, 128.3, 128.2, 121.4, 77.8, 77.7, 74.5, 74.4, 47.2, 35.0, 34.9, 26.1, 26.0, 16.6, 16.4, 11.3, 11.2. MS (ESI) 397.0775 (397.0774 calcd for $\text{C}_{20}\text{H}_{23}\text{BrO}_2$, $\text{M} + \text{Na}^+$).

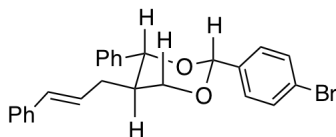


1-(3-chlorophenyl)-3-(4-methoxyphenyl)-3-(3-phenylpropoxy)propan-1-one (5-24b). The reaction of *p*-anisaldehyde (40 mg, 0.29 mmol) with 3-chloro-1-ethynylbenzene (54 μl , 0.44 mmol) and 3-phenyl-1-propanol (117 μl , 0.87 mmol) was conducted according to the general procedure 1. This procedure afforded 45 mg (38%) of the title compound as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.95 (s, 1 H), 7.84 (d, $J = 8.0$ Hz, 1 H), 7.50 (d, $J = 7.5$ Hz, 1 H), 7.38 (t, $J = 7.5$ Hz, 1 H), 7.31 (d, $J = 8.5$ Hz, 2 H), 7.23 (t, $J = 7.0$ Hz, 2 H), 7.14 (t, $J = 7.5$ Hz, 1 H), 7.08 (d, $J = 8.5$ Hz, 2 H), 6.90 (d, $J = 8.5$ Hz, 2 H), 4.87 (dd, $J = 4.5, 8.5$ Hz, 1 H), 3.80 (s, 3 H), 3.57 (dd, $J = 8.5, 16.0$ Hz, 1 H), 3.55-3.31 (m, 1 H), 3.29-3.24 (m, 1 H), 3.00 (dd, $J = 4.5, 16.0$ Hz, 1 H), 2.61-2.49 (m, 2 H), 1.80-1.74 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.9, 159.3, 142.1, 139.0, 134.8, 133.7, 132.9, 129.8, 128.5, 128.4, 128.2, 127.8, 126.4, 125.7, 113.9, 77.8, 67.9, 55.3, 47.4, 32.3, 31.4. MS (ESI) 431.1383 (431.1384 calcd for $\text{C}_{25}\text{H}_{25}\text{ClO}_3$, $\text{M} + \text{Na}^+$).



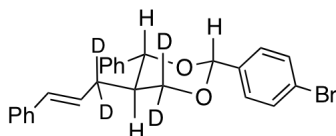
1-(3-chlorophenyl)-3-ethoxy-3-(4-methoxyphenyl)propan-1-one (5-24c). ^1H NMR (500 MHz, CDCl_3) δ 7.91 (s, 1 H), 7.80 (d, $J = 7.5$ Hz, 1 H), 7.50 (d, $J = 8.0$ Hz, 1 H), 7.37 (t, $J = 8.0$ Hz, 1 H), 7.31 (d, $J = 8.5$ Hz, 2 H), 6.89 (d, $J = 8.5$ Hz, 2 H), 4.90 (dd, $J = 4.5, 8.0$ Hz, 1 H), 3.80 (s, 3 H), 3.54 (dd, $J = 8.0, 16.0$ Hz, 1 H),

3.39-3.33 (m, 2 H), 3.04 (dd, $J = 5.0, 16.5$ Hz, 1 H), 1.10 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.7, 159.2, 138.8, 134.8, 133.8, 132.8, 129.8, 128.3, 127.7, 126.3, 113.9, 77.1, 64.1, 55.2, 47.5, 15.1. MS (ESI) 341.0919 (341.0915 calcd for $\text{C}_{18}\text{H}_{19}\text{ClO}_3$, $\text{M} + \text{Na}^+$).



***rac*-(2*R*,4*R*,5*R*)-2-(4-bromophenyl)-5-cinnamyl-4-phenyl-1,3-dioxane (3-26a).**

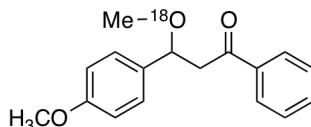
The reaction of 4-bromobenzaldehyde (10 mg, 0.05 mmol) with *trans*-cinnamyl alcohol- d_2 (22 mg, 0.16 mmol) and phenylacetylene (8 μl , 0.08 mmol) was conducted according to the general procedure 1, with one equivalent of phenanthrene (9.6 mg, 0.05 mmol) as an internal standard. The crude product was formed as a single diastereomer in ca 50% as judged by ^1H NMR analysis. ^1H NMR (500 MHz, CDCl_3) δ 7.48-7.44 (m, 4 H), 7.42-7.37 (m, 4 H), 7.36-7.33 (m, 1 H), 7.29-7.24 (m, 4 H), 7.22-7.18 (m, 1 H), 6.29 (d, $J = 16.5$ Hz, 1 H), 5.94 (ddd, $J = 6.0, 8.5, 14.5$ Hz, 1 H), 5.63 (s, 1 H), 4.53 (d, $J = 10.0$ Hz, 1 H), 4.39 (dd, $J = 4.5, 11.5$ Hz, 1 H), 3.77 (t, $J = 11.5$ Hz, 1 H), 2.29-2.24 (m, 1 H), 2.12-2.07 (m, 1 H), 1.89 (dt, $J = 8.5, 14.5$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 191.0, 139.2, 137.1, 132.4, 132.2, 131.3, 130.9, 128.5, 128.0, 127.7, 127.2, 126.1, 125.9, 100.9, 85.0, 71.8, 40.5, 31.4. MS (ESI) 434.0875 (434.0881 calcd for $\text{C}_{25}\text{H}_{23}\text{BrO}_2 \text{M}^+$)



***rac*-(2*R*,4*R*,5*R*)-2-(4-bromophenyl)-5-cinnamyl-4-phenyl-1,3-dioxane- d_4 (3-26b).**

The reaction of 4-bromobenzaldehyde (30 mg, 0.16 mmol) with *trans*-cinnamyl alcohol- d_2 (65 mg, 0.48 mmol) and phenylacetylene (26 μl , 0.24 mmol) was conducted according to the general procedure 1, with one equivalent of phenanthrene (28.8 mg, 0.16 mmol) as an internal standard. The crude product was formed as a single diastereomer in ca 34% (60% conversion) as judged by ^1H NMR analysis. ^1H NMR (400 MHz, CDCl_3) δ 7.48-7.19 (m, 14 H), 6.28 (d, $J =$

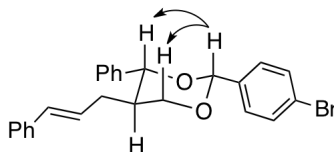
15.9 Hz, 1 H), 5.93 (d, $J = 15.5$ Hz, 1 H), 5.62 (s, 1 H), 4.53 (d, $J = 10.4$ Hz, 1 H), 2.24 (d, $J = 9.9$ Hz, 1 H). MS (ESI) 438.1127 (438.1132 calcd for $C_{17}H_{18}D_4BrO_2$, M^+).



3-methoxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one-18O (5-29). The reaction of *p*-anisaldehyde (30 mg, 0.22 mmol) with phenylacetylene (36 μ l, 0.33 mmol) and methanol-18O (27 μ l, 0.66 mmol) was conducted according to the general procedure 1. This procedure afforded 32 mg (53%) of the title compound as a yellow oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J = 8.4$ Hz, 2 H), 7.52 (t, $J = 8.4$ Hz, 1 H), 7.42 (t, $J = 7.2$ Hz, 2 H), 7.31 (d, $J = 8.4$ Hz, 2 H), 6.89 (d, $J = 8.8$ Hz, 2 H), 4.80 (dd, $J = 4.8, 8.0$ Hz, 1 H), 3.79 (s, 3 H), 3.56 (dd, $J = 8.0, 16.4$ Hz, 1 H), 3.19 (s, 3 H), 3.06 (dd, $J = 4.8, 16.8$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 159.2, 137.2, 133.3, 133.0, 128.5, 128.2, 127.9, 113.9, 79.1, 56.6, 55.2, 47.1. MS (ESI) 295.1193 (295.1191 calcd for $C_{17}H_{18}O_2^{18}O$, $M + Na^+$).

Assignment of Stereochemistry

The relative stereochemistry of compound **3-26a** was assigned on the basis of observed 1H NMR nOe experiments. Significant nOe relationships are shown below.



5.7 References

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