Enantioselective Synthesis of Heterocycles via Palladium Catalyzed Alkene Difunctionalization Reactions

by

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Dedication

To my loving wife and daughter Vicki and Veralee. Thanks for all of your love, encouragement and support over the last five years.

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Ac……..……acetyl

Ar……aryl

Bn……..……..benzyl

Boc……..……*tert*-butyloxycarbonyl

Cbz……..carboxybenzyl

CDI……....carbonyl diimidazole

DCE…….dichloroethane

DCM…….dichloromethane

ee……..enantiomeric excess

er…….... enantiomeric ratio

Ln……....ligand

Me…….methyl

PMB……..*para*-methoxybenzyl

PMP……..*para*-methoxyphenyl

RT……..room temperature

TFA……trifluoroacetic acid

THF……tetrahydrofuran

Ts……4-toluenesulfonyl

Ph……..…phenyl

^{t}Bu……..*tert*-butyl

Abstract

Enantiopure nitrogen and oxygen containing heterocycles are prominently displayed in a variety of important pharmaceuticals and biologically active products. As such accessing these scaffolds in an enantioselective and efficient manner is an interesting challenge. We envisioned that novel asymmetric carboamination and carboetherification reactions would be powerful methods to synthesize these enantiopure heterocycles, as you can generate a library of enantiopure compounds in a facile manner with this approach. While these enantioselective carboamination and carboetherification reactions are robust methods of accessing enantiopure heterocycles, at the onset of the work detailed in this thesis all of the efforts in this area were related to the formation of 5-membered rings bearing a single nitrogen heteroatom.

As such, this thesis entails the development of new enantioselective carboamination and carboetherification reactions meant to address the above limitations. Chapter 2 details the development of an enantioselective carboamination reaction to access enantiopure imidazolidin-2-ones in up to 97:3 er. This work also shows how reaction conditions, namely the choice of aryl halide, use of water additive and substrate electronics, affect the final enantioselectivity observed in the products. Chapter 3 details the development of a general procedure to access tetrahydroquinolines, tetrahydroisoquinolines and tetrahydroquinoxalines all in > 95:5 er. Furthermore, these reactions in chapter 3 are rare transformations of this type that allow for the synthesis of quaternary centers in high enantioselectivity. Chapter 4 details the

development of a novel carboetherification reaction, and how using a modular TADDOL ligand scaffold allowed us to rationally design a ligand that afforded our desired products in >95:5 er. Lastly, Chapter 5 entails the initial results looking into the synthesis of enantiopure benzofused oxygen heterocycles.

Chapter 1

Enantioselective Transition Metal Catalyzed Alkene Di-Functionalization Reactions

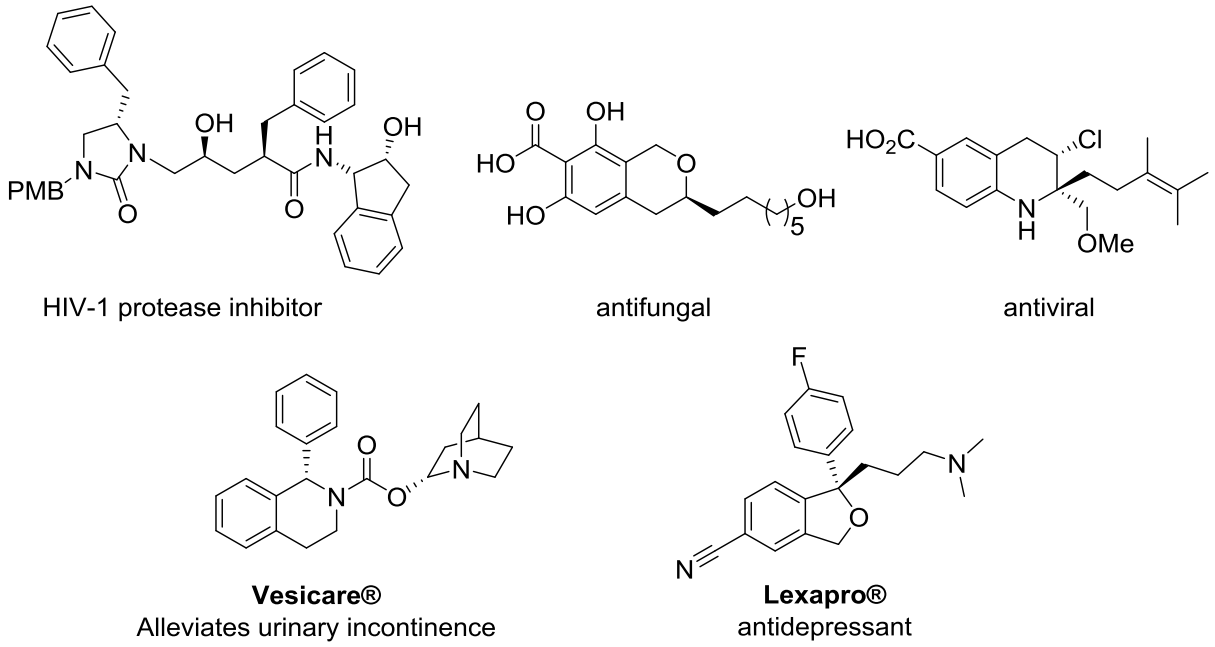
1.1 Introduction

Chemical transformations of alkenes by transition metal catalysis have proven to be highly effective reactions for a variety of processes. A few examples of these powerful reactions include hydrogenations and the Wacker oxidation.[1,2] These aforementioned transformations are utilized to form a range of useful chemical products and intermediates, not to mention a variety of consumer goods such as margarines and diesel fuel.[1,2]

Due to the synthetic utility of transition metal catalyzed reactions of alkenes,[1,2] using these transformations to afford new and interesting products is of importance to the chemical community. One specific area of significance is in the formation of new heterocyclic compounds. The importance of these heterocycles stems from the wide array of these motifs in biologically active compounds, natural products, and pharmaceuticals.[3] Also, many of these biologically active heterocycles are chiral, with the compounds possessing stereocenters adjacent to the heteroatom in the ring (Figure 1.1).[3] As such, the development of new reactions to access these chiral heterocycles from simple alkene precursors is of extreme importance to new methodological

advances in this area.

Figure 1.1 Biologically relevant enantiopure heterocycles

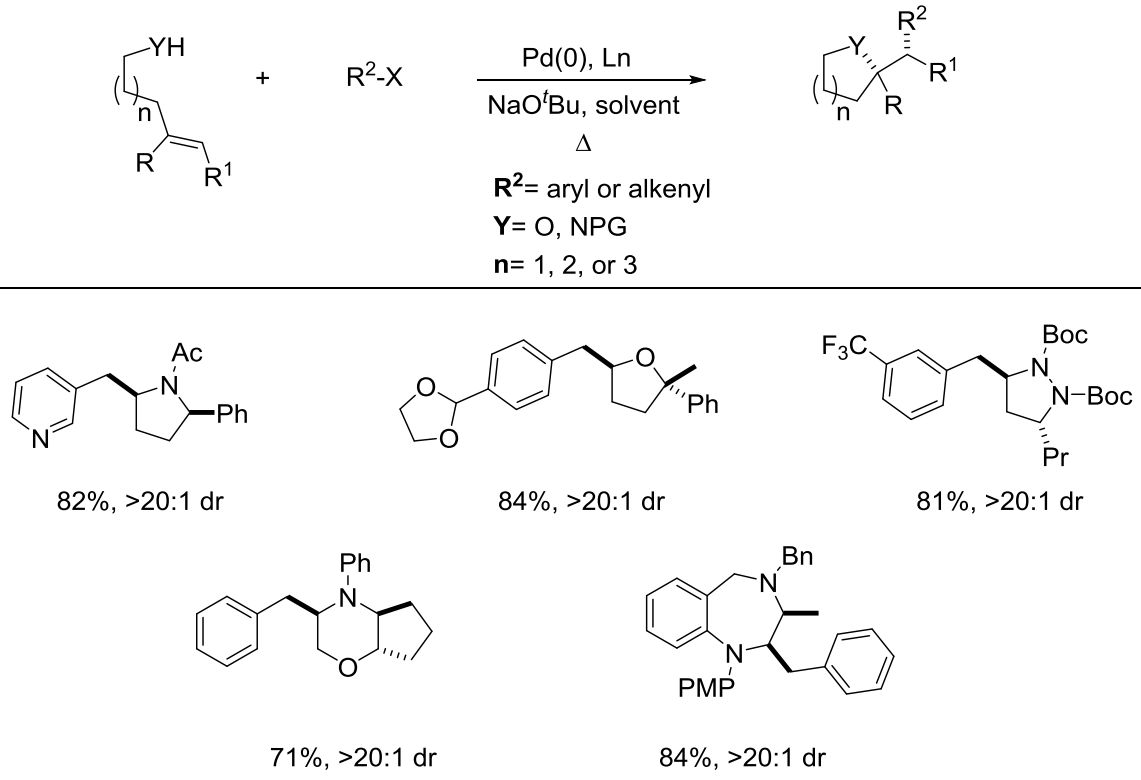


1.2 Stereoselective Synthesis of Heterocycles via Palladium Catalyzed Oxyarylation and Aminoarylation Reactions

Demonstrating the powerful nature of transition metal catalyzed reactions of alkenes, our group developed a new series of methods to form a variety of oxygen and nitrogen containing heterocycles via Pd-catalyzed di-functionalization reactions of alkenes (Scheme 1.1).[4] This chemistry was developed over the past decade or so, and these reactions have allowed us to access compounds that possess privileged motifs, which are noted in an array of biologically active compounds (Figure 1.1).[3] As shown in Scheme 1.1, we start with readily accessible substrates bearing a heteroatom tethered to an alkene. We subject these substrates to the reaction conditions noted in Scheme 1.1 to yield a product bearing a new heterocyclic ring, a new carbon-heteroatom bond, a

new carbon-carbon bond, and depending on alkene substitution up to 2 new stereocenters. This methodology has yielded a variety of interesting heterocycles including pyrrolidines, tetrahydrofurans, pyrazolidines, morpholines, and benzodiazapenes.[4] These products are afforded in high yields and excellent diastereoselectivities. Moreover, we can readily access libraries of compounds by simply changing the aryl or alkenyl electrophile in the reaction.

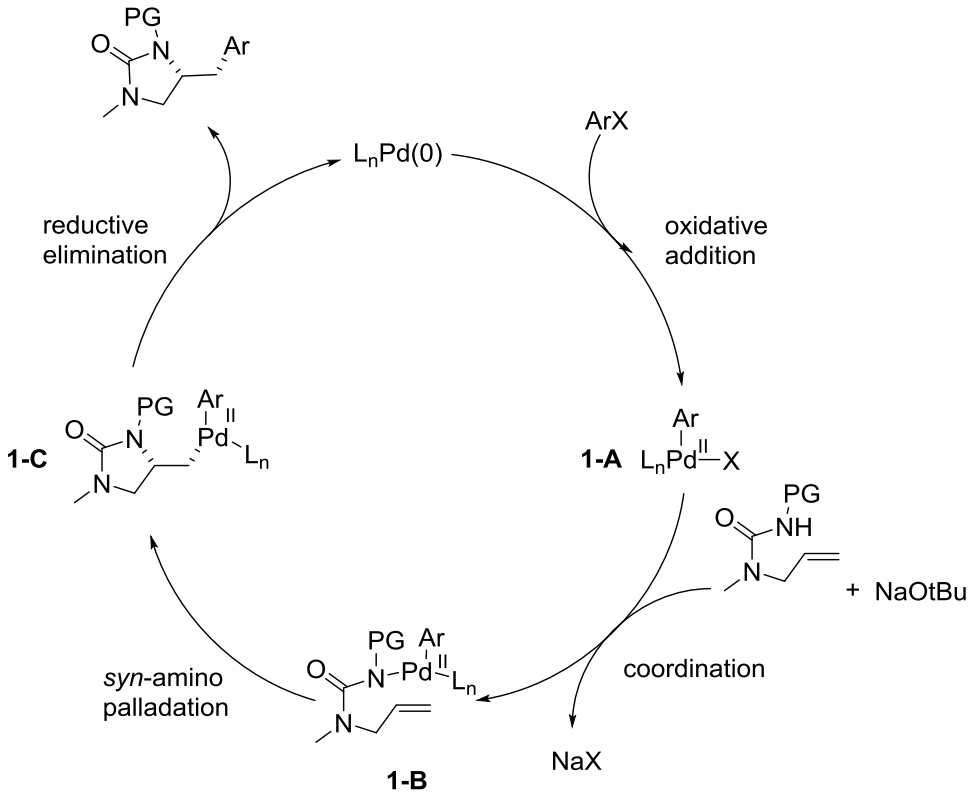
Scheme 1.1 Stereoselective synthesis of heterocycles by the Wolfe group



Through some well-designed experiments and deuterium labeling studies, our group was able to determine that these heterocycles are produced through a cis addition of the alkene into the Pd-heteroatom bond.[5,6] In terms of how the complete mechanism progresses, we envision that initially Pd(0) undergoes oxidative addition to

afford the Pd(II) intermediate **1-A**. After deprotonation of the substrate, subsequent coordination of the heteroatom to the palladium yields the intermediate **1-B**. **1-B** undergoes a syn-migratory insertion of the alkene into the Pd-N bond to afford intermediate **1-C**. Carbon-carbon bond forming reductive elimination from **1-C** affords the desired heterocyclic product and regenerates the Pd(0) catalyst.[6]

Figure 1.2 Catalytic cycle for Pd-catalyzed carboamination reaction



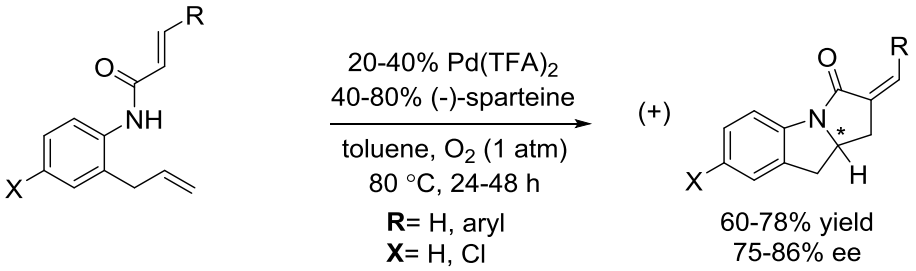
1.3 Enantioselective Carboamination Reactions of Alkenes Catalyzed by Transition Metals: A Recent Timeline of Relevant Events

A variety of research is directed towards the enantioselective addition of heteroatoms to alkenes via transition metals, and recent reviews highlight this field in depth.[7] However, our group is specifically interested in enantioselective di-

functionalization reactions of alkenes via Pd-catalyzed carboamination and carboetherification reactions. Although we reported our initial racemic carboamination and carboetherification reactions before 2005, an enantioselective variant of our chemistry was not published until 2010. During this time, related enantioselective transformations that form a C-N bond and a C-C bond across an alkene were published.

In 2006, a report from the Yang group detailed an enantioselective synthesis of indolines through an intramolecular Pd(II) catalyzed oxidative cyclization reaction.[8] This reaction proceeds through an amidopalladation followed by an intramolecular olefin insertion into a Pd(II) alkyl intermediate. Subsequent beta-hydride elimination affords the final product (Scheme 1.2). However, it is of note that this reaction is limited by the necessity of an intramolecular olefin addition for the C-C bond formation, which impedes the synthesis of a library of enantioenriched compounds.

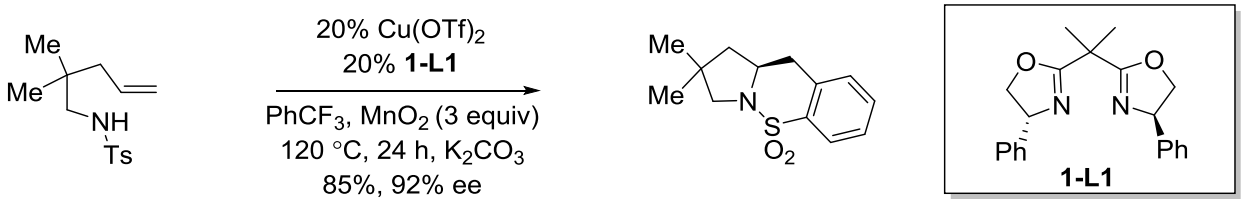
Scheme 1.2 Enantioselective oxidative cyclization reaction



Following the above reaction, in 2007 the Chemler group reported a Cu(II) catalyzed enantioselective carboamination reaction to afford enantioenriched sultams (Scheme 1.3).[9] Through some mechanistic work, they determined that their reaction proceeded via a syn aminocupration of the alkene.[9] That being said, their mechanism is quite different from ours displayed in Figure 1.2. Notably, after the syn aminocupration

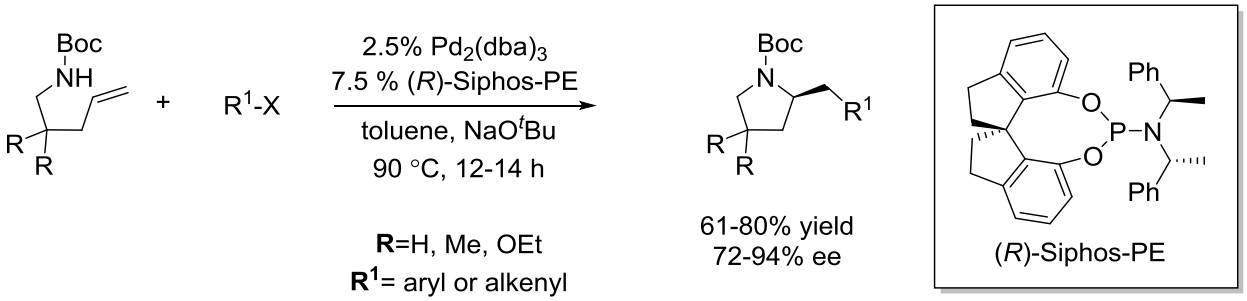
step in their mechanism, the Cu-C alkyl intermediate undergoes homolysis to afford an alkyl radical intermediate.[9] This alkyl radical is then trapped by an intramolecular addition into a nearby pi bond in the nitrogen protecting group. As shown in Scheme 1.3, this reaction works well to afford chiral sultams in good yields and enantioselectivities. However, like the aforementioned reaction in Scheme 1.2, this method relies on an intramolecular addition to form the C-C bond, which limits the facile synthesis of a library of compounds.

Scheme 1.3 Copper catalyzed enantioselective carboamination reaction



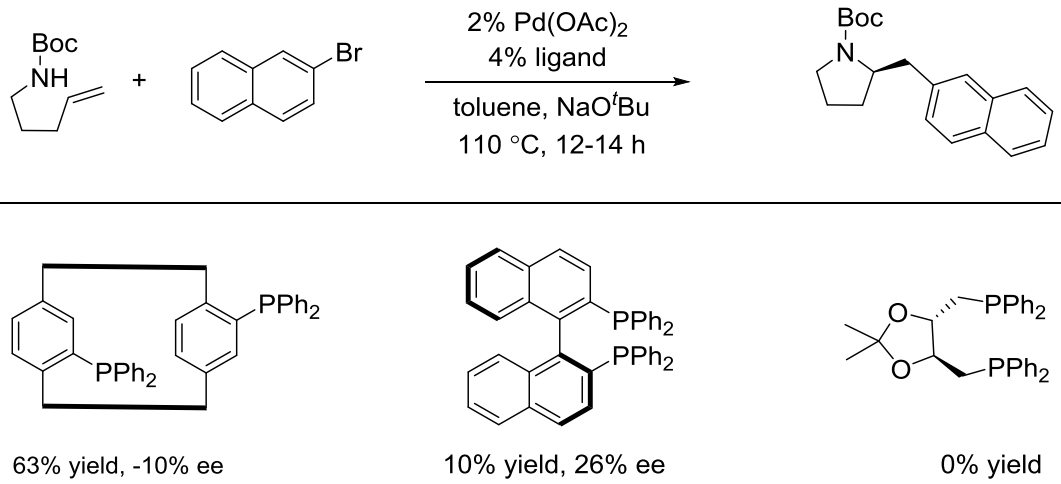
In 2010, Dr. Peter Mai from our group reported the Pd-catalyzed enantioselective synthesis of pyrrolidines via an asymmetric carboamination reaction (Scheme 1.4).[10] This reaction worked well to form a variety of different products in moderate to good yields and good enantioselectivities. Our carboamination reaction differs from the two reactions mentioned above in the fact that an external component (aryl or alkenyl halide) is used in the C-C bond forming step. This allows the user to quickly form a variety of new enantioenriched products by simply changing the aryl or alkenyl halide used in the reaction.

Scheme 1.4 Pd-catalyzed enantioselective synthesis of pyrrolidines



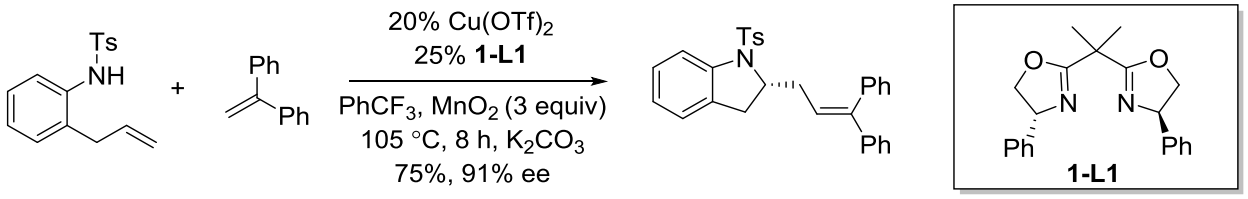
During our work in this area, we noted that chiral monodentate ligands were essential to achieving high enantioselectivities.[10] This is interesting as similar reactions, such as the reports by Yang and Chemler mentioned above, utilize bi-dentate ligands to afford the enantioenriched products.[8,9] True to this statement, a recent review stated that our reaction (Scheme 1.4) was the only successful application of a monodentate chiral ligand to an enantioselective alkene nucleopalladation reaction.[7b] We believe that these monodentate chiral ligands are vital to our reaction, as some recent mechanistic studies from our group illustrated that one arm of a bi-dentate ligand disassociates prior to the aminopalladation step.[6] Therefore, in our enantioselective carboamination reactions, a large portion of the bi-dentate chiral ligand would be placed away from the reaction site, potentially lowering the asymmetric induction in the products. Indeed this is what was observed by our group, and low levels of asymmetric induction were noted with chiral bi-dentate ligands in these reactions (Scheme 1.5).

Scheme 1.5 Poor enantioinduction with bi-dentate chiral ligands



After this report by our group, the Chemler group came out with another enantioselective Cu(II) catalyzed carboamination reaction in 2012 (Scheme 1.6).[9c] This work differed from their previous methodology, as it used an external agent, in this case a styrene, to trap the alkyl radical. Thus, this reaction now more closely resembles our carboamination methodology, with the potential to afford an array of products by switching out the styrene moiety that is used. However, changing the styrene from 1,1-diphenylethylene typically afforded products in lower enantioselectivities for this transformation.

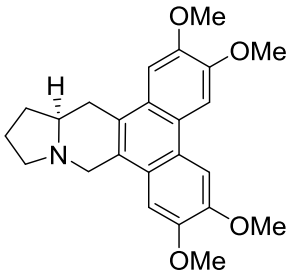
Scheme 1.6 Copper catalyzed enantioselective carboamination reaction



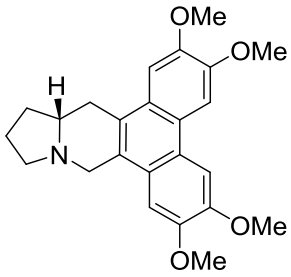
1.4 Application of Enantioselective Carboamination Reactions to Natural Product Synthesis

Although the above reactions were useful at synthesizing enantiopure heterocycles,[8,9,10] applying these new methodologies to access more complex targets was of interest as well. As such, our group and Chemler's group both utilized these carboamination reactions to access natural products and related derivatives. As noted in Figure 1.3, Chemler was able to afford (*S*)-tylophorine in 81% ee in 9 linear steps.[11a] The need for Chemler's group to attach the reacting arene to the substrate substantially added to their step count. A few years later, we were able to afford (*R*)-tylophorine in 88% ee in just 3 linear steps with our Pd-catalyzed carboamination reaction.[10] Our group was also able to show the utility of our methodology to afford (+)-aphanorphine in 81% ee.[10b]

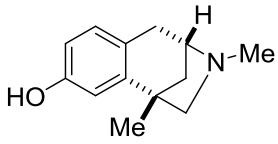
Figure 1.3 Natural products synthesized via enantioselective carboamination reactions



(*S*)-(+)-tylophorine
Chemler 2008
9 steps, 81% ee



(*R*)-(-)tylophorine
Wolfe 2010
3 steps, 88% ee

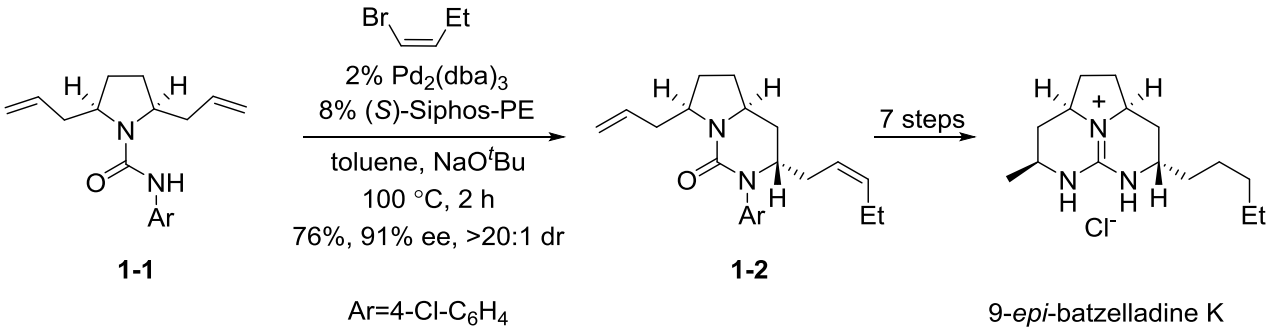


(+)-aphanorphine
Wolfe 2011
10 steps, 81% ee

Additionally, it would be interesting to utilize similar carboamination methodologies to help streamline other synthetic approaches to complex targets. Thus, in 2013 Dr. Nick Babij in our group elegantly displayed the utility of our enantioselective

carboamination reactions to do just that (Scheme 1.7).[12] He was able to develop an enantioselective desymmetrization reaction of substrate **1-1** to afford the complex bicyclic urea **1-2** with three new stereocenters in good yield and enantiomeric ratio. The work outlined in Scheme 1.7 below was a beautiful expansion of a similar reaction that will be discussed in chapter 2. This enantioselective desymmetrization reaction streamlined the synthesis of the bicyclic urea **1-2** and it was afforded in just 5 steps, compared to 10 steps needed to generate a similar intermediate in a previous synthesis of bicyclic ureas by our group.[13] Additionally, this reaction allowed access to enantiopure bicyclic ureas without the need of a stoichiometric chiral auxiliary. This method was also the first example of enantioselective six-membered ring forming reactions with our chemistry, and intermediate **1-2** was utilized to synthesize the tricyclic guanidine 9-*epi*-batzelladine K.

Scheme 1.7 Enantioselective Pd-catalyzed desymmetrization reactions

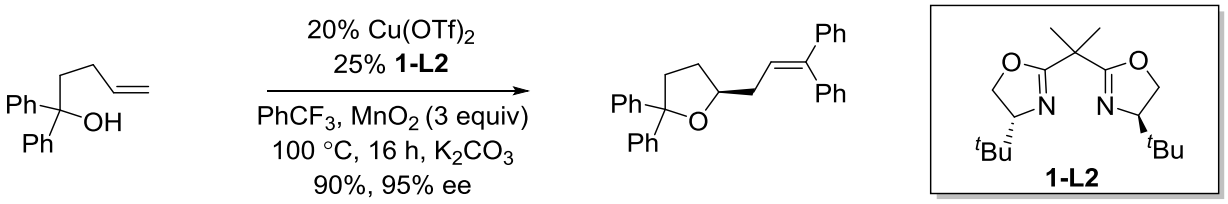


1.5 Enantioselective Copper Catalyzed Carboetherification Reactions

Recently in 2014, the Chemler group reported a Copper catalyzed enantioselective carboetherification reaction capable of generating products in up to 95 % ee.[14] The reactions were shown to work best when utilizing a system similar to that in

Scheme 1.6, where a styrene derivative can intercept the alkyl radical that is generated in the reaction (Scheme 1.8). This publication came out when we were in the middle of our own studies to afford tetrahydrofuran products enantioselectivly via a Pd-catalyzed carboetherification reaction. We will elaborate further in chapter 4 on our studies, but it is imagined that the two methods will be complimentary to each other as different products are formed during the course of the reactions.

Scheme 1.8 Copper catalyzed enantioselective carboetherification reactions



1.6 Application of Enantioselective Pd-Catalyzed Alkene Di-Functionalization Reactions to New Scaffolds

The initial enantioselective carboamination reaction by our group proved to be very successful for the synthesis of enantioenriched pyrrolidines.[10a] Similar enantioselective methodologies from other groups were successful as well,[8,9] and these reactions were even extended to the synthesis of a few natural products.[10b,11,12] That being said, there was still a lot of chemistry to explore in this area. We were uncertain if enantioselective carboamination reactions would have a broad application to an array of heterocycles. For instance, at the outset of my thesis there were no enantioselective carboamination methodologies that formed heterocycles bearing more than one nitrogen in the ring. Furthermore, carboamination reactions to form heterocyclic ring systems larger than five members in high enantioselectivity were unknown at this time

as well. Moreover, we desired to learn more about how reaction conditions and substrate structure affect the enantioselectivity of the products. As such, the following work outlined in chapters two through five will depict our recent efforts towards the expansion of carboamination and carboetherification reactions to form an array of enantioenriched heterocycles. Also, we will note how the substrate structure and reaction conditions affect the enantioselectivity of our carboamination products. Furthermore, we wanted to synthesize enantioenriched oxygen heterocycles, as at the outset this thesis research no groups had reported these reactions in high enantioselectivity.[14]

Chapter two details our studies into the synthesis of enantiomerically enriched cyclic ureas via an asymmetric Pd-catalyzed alkene carboamination reaction. In this chapter we note the importance of reactions conditions in achieving high enantioselectivities, and suggest that the enantiodetermining step in these reactions appears to be C-C bond forming reductive elimination. Chapter three explains our approach to the enantioselective synthesis of six membered benzo-fused heterocycles. We were able to form 3 distinct classes of benzo-fused products all in >95:5 er. Also, to the best of our knowledge, the reactions in chapter three are the first highly enantioselective transition metal catalyzed C-N bond forming reactions involving addition to a 1,1-disubstituted alkene.

To further expand the utility of our enantioselective reactions, our studies in chapter four entail the expansion into enantioselective carboetherification reactions. A key point in this chapter is the development of TADDOL ligands inspired by nature to help form the desired products in better enantioselectivities. Chapter 5 is an expansion

of the enantioselective carboetherification reactions to afford benzo-fused heterocycles. Promising yields and enantioselectivities are noted for these compounds, and further ligand and substrate development will be required to afford these products in better enantioselectivities and yields.

In all, it is believed that the reactions developed in chapters two through five will find a use in the synthesis of biologically relevant scaffolds.[3] Furthermore, it is envisioned that the data gathered on substrate electronics, enantiodetermining step, ligand structure, and reaction additives will help guide similar reaction development in the future.

1.7 References

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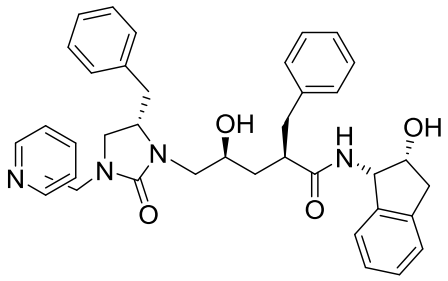
Chapter 2

Enantioselective Synthesis of Imidazolidin-2-ones via Pd-Catalyzed Carboamination Reactions

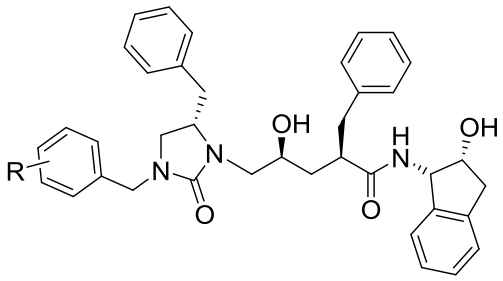
2.1 Introduction

The imidazolidin-2-one core is displayed in a variety of biologically active molecules,[1] and it is also used in other applications such as a precursor to 1,2-diamines[2] and as a monomer unit in biomaterials.[3] More specifically, chiral 4-substituted imidazolidin-2-ones have proven to be potent HIV-1 protease inhibitors (Figure 2.1),[1a] and other chiral imidazolidin-2-ones display an array of biological activities as well.[1d]

Figure 2.1 HIV-1 protease inhibitors



2-1: 3-py, K_i= 18.0 nM
2-2: 2-py, K_i= 41.0 nM
2-3: 4-py, K_i= 190.0 nM

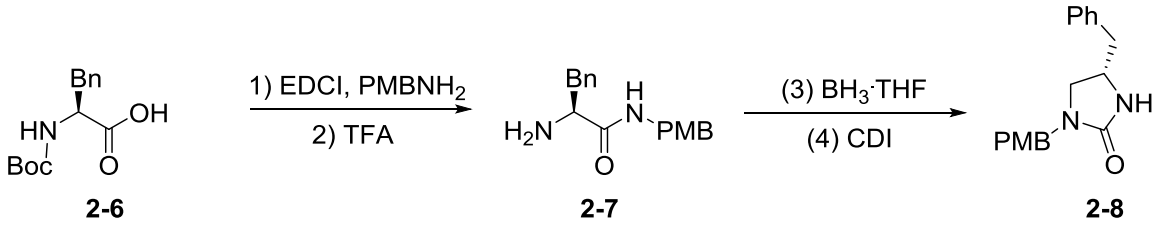


2-4: 4-OMe, K_i= 5.6 nM
2-5: 3-F, K_i= 3.2 nM

As is typical with many of the syntheses of chiral imidazaolidin-2-ones,[1a,3] the construction of the imidazolidin-2-one cores in Figure 2.1 commences with the chiral

precursor **2-6** (Scheme 2.1). Access to chiral imidazolidin-2-one **2-8** requires 4 synthetic steps from **2-6**. Furthermore, the synthesis of different imidazolidin-2-ones with varied aryl groups in the 4 position is limited to amino acid precursors that fit the necessary synthetic profile. As such, the ability to afford imidazolidin-2-ones from achiral precursors via transition metal catalysis would improve upon these aforementioned methods to access chiral imidazolidin-2-ones. Also, starting from achiral precursors allows for the synthesis of imidazolidin-2-ones from cheaper and more readily accessible achiral precursors.

Scheme 2.1 Synthesis of precursor 2-8 from boc-phenylalanine



2-6 **2-7** **2-8**

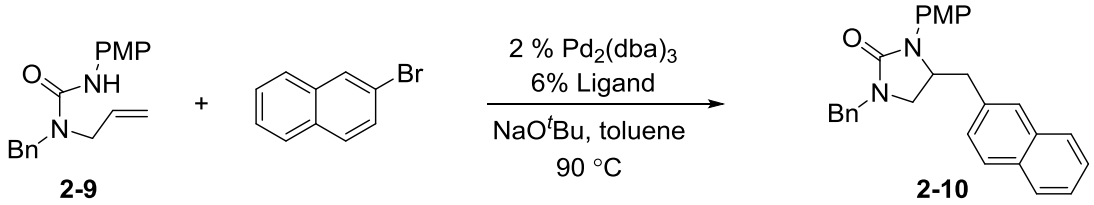
2.2 Previous Results

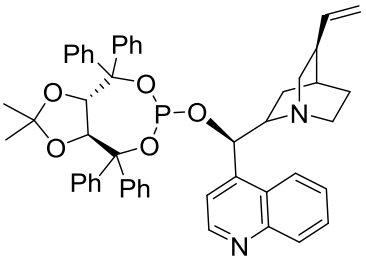
Due to the utility of the imidazolidin-2-one core,[1-3] the Wolfe group developed a method to access racemic imidazolidin-2-ones in good yields and diastereoselectivities.[4] Due to our interest in the development of novel enantioselective reactions,[5] the bioactivity of chiral imidazolidin-2-ones,[1-3] and the lack of methods available to afford enantioenriched imidazolidin-2-ones catalytically,[2,6] we decided it would be essential to develop an enantioselective variant of our carboamination reaction to access imidazolidin-2-ones.

Previous members of the Wolfe lab probed the enantioselective synthesis of imidazolidin-2-ones. Dr. Johnathon Fritz was able to afford enantioenriched imidazolidin-2-ones in up to 86% yield and 66:34 er with (S)-Phanephos, 2-bromotoluene, and substrate **2-9**.[7] However, it was not until after these initial reactions were completed that we understood the importance of monodentate ligands for achieving high enantioselectivities in our carboamination reactions.[5,8]

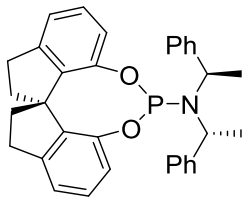
Dr. Peter Mai screened a broader variety of ligands with substrate **2-9**, and was able to show that ligand **2-L1** worked best, affording product **2-10** in 82:18 er and 52% yield. Furthermore, he also showed that ligand **2-L2** afforded the product in a similar enantiomeric ratio as well (Scheme 2.2).[9]

Scheme 2.2 Enantioselective carboamination reaction of substrate **2-9**





2-L1
52%, 82:18 er



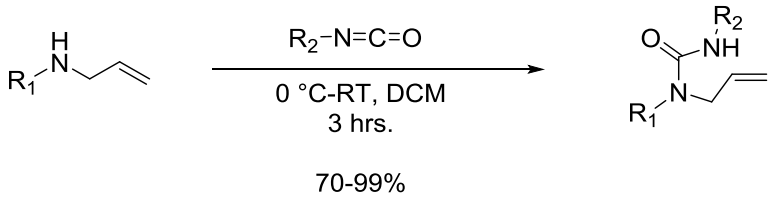
2-L2
(*S*)-Siphos-PE
77 %yield, 79:21 er

2.3 Initial Optimization of Reaction Conditions and Substrate

The anticipation at the outset of our studies into the enantioselective formation of imidazolidin-2-ones was that the ability to synthesize substrates in a straightforward

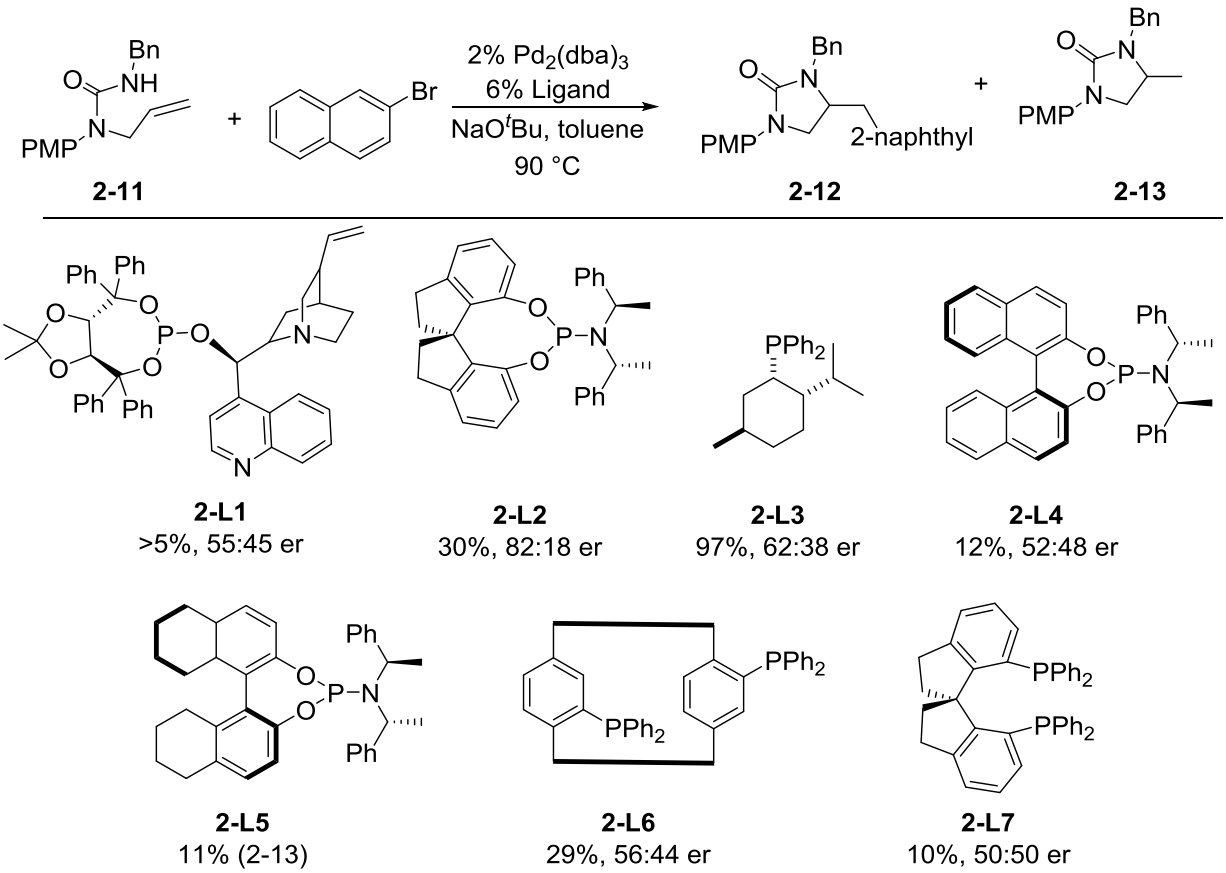
manner would be essential to the overall success of this project. Therefore, utilizing readily available allylamines and isocyanates to access the N-allyl urea substrates afforded us the opportunity to test a variety of different compounds for this methodology (Scheme 2.3). This was important to us as we wanted to amass more information on how substrate structure and reaction conditions affect enantioselectivity in carboamination reactions. More specifically we wanted to determine the role of the protecting group, reactants, and reaction additives in terms of how each piece affects enantioselectivity.

Scheme 2.3 Synthesis of N-allylurea substrates



We decided to undertake an initial ligand screen with substrate **2-11** to observe how the reaction progressed with a more electron rich benzyl protecting group. However, as noted in Table 2.1 the more electron rich protecting group led to the formation of the hydroamination side product **2-13**. The low yields shown below in Table 2.1 are indicative of the difficulty in separating the two products **2-12** and **2-13**.

Table 2.1 Initial ligand screen with substrate **2-11**[a]



2-L1
>5%, 55:45 er

2-L2
30%, 82:18 er

2-L3
97%, 62:38 er

2-L4
12%, 52:48 er

2-L5
11% (2-13)

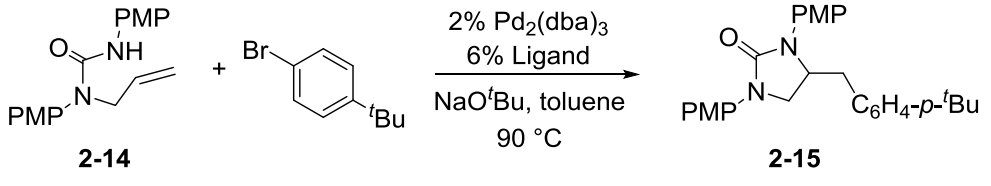
2-L6
29%, 56:44 er

2-L7
10%, 50:50 er

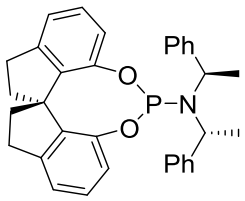
[a] Conditions: Reactions were conducted on a 0.15 mmol scale using 1.0 equiv substrate, 1.5 equiv Ar-Br, 1.5 equiv NaO^{t}Bu, toluene (0.2 M), 90 °C, 12-14 h. Yields and enantiomeric ratios refer to isolated compound **2-12** unless noted otherwise.

Changing to substrate **2-14** led to the sole formation of the carboamination product **2-15** (Table 2.2), with no competing hydroamination. Furthermore, use of 1-Bromo-4-*tert*-butylbenzene as the electrophile allowed for easier analysis of the products via HPLC. A few of the ligands tested for these reactions are shown in Table 2.2 below. The optimal ligand proved to be (*S*)-Siphos-PE (**2-L2**) affording the desired product in 99% yield and 81:19 er. Although **2-L10** afforded a promising result, a screen of similar ligand scaffolds did not lead to any improvement in enantioselectivity or yield.

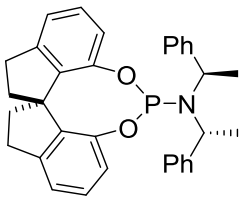
Table 2.2 Initial ligand screen with substrate **2-14**[a]



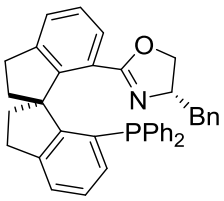
2-14 **2-15**



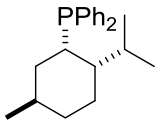
2-L2
(*S*)-Siphos-PE
99%, 81:19 er



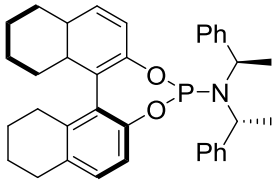
2-L8
(*R*)-Siphos-PE
67%, 56:44 er



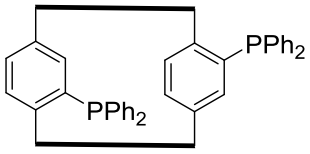
2-L9
55%, 52:48 er



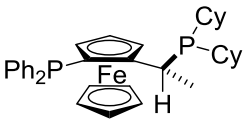
2-L3
90%, 66:34 er



2-L5
29%, 65:35 er



2-L6
60%, 64:36 er



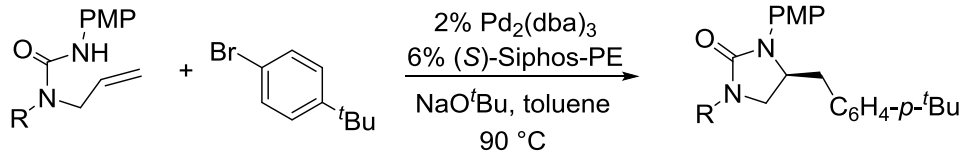
2-L10
9%, 85:15 er

[a] Conditions: Reactions were conducted on a 0.10 mmol scale using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.2 M), 90 °C, 12-14 h. Yields and enantiomeric ratios refer to isolated compound **2-15**.

With the optimal ligand (*S*)-Siphos-PE (**2-L2**) in hand further investigation of the protecting groups was initiated. We decided to alter the protecting group on the non-cyclizing nitrogen as noted in Table 2.3. Changing the protecting group to other phenyl based systems such as substrates **2-16** and **2-18**, afforded the products in lower yields and comparable enantioselectivities to substrate **2-14**. The optimal protecting group on the non-cyclizing nitrogen was found to be methyl, and when substrate **2-23** was subjected to the reaction conditions, product **2-24** was afforded in 93% yield and 89:11 er. Other alterations such as allyl (**2-21**) as the protecting group or using an unprotected nitrogen (**2-20**) afforded poorer results than **2-23** in the reaction. Since substrate **2-23**

bearing the N-methyl group afforded the best results in this system, we decided to use this structure for future investigations.

Table 2.3 Varying non-cyclizing nitrogen protecting group[a]

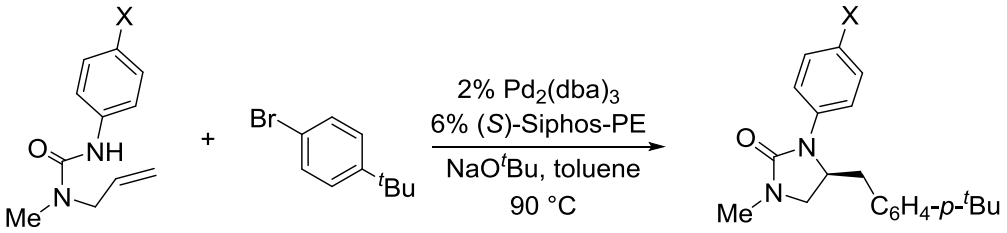


R	yield[b]	er
Ph (**2-16**)	27% (**2-17**)	78:22 er
p-^{t}Bu-C_6H_4 (**2-18**)	57% (**2-19**)	84:16 er
H (**2-20**)	0%	n/a
allyl (**2-21**)	93%[c] (**2-22**)	86:14 er
Me (**2-23**)	93% (**2-24**)	89:11 er

[a] Conditions: Reactions were conducted on a 0.10 mmol scale using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.2 M), 90 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds. [c] Used 4-bromobenzophenone.

To further improve the asymmetric induction of this reaction, we wanted to determine if the nucleophilicity of the nitrogen would affect the enantioselectivity of the products. As shown in Table 2.4, we synthesized a variety of substrates bearing electron poor and electron rich phenyl groups on the cyclizing nitrogen. The data in Table 2.4 shows that the enantioselectivity of the products increases when the nucleophilicity of the cyclizing nitrogen decreases. Unfortunately, under standard reaction conditions at 90 °C low chemical yields were noted for substrates **2-31** and **2-33**, with unreacted starting material still present in the crude reaction mixtures. However, simply heating the reaction up to 120 °C afforded the products in good yields, with little effect on the enantioselectivity. The best result was obtained with substrate **2-33,** affording the desired product **2-34** in 81% yield and 96:4 er.

Table 2.4 Electronic effects of cyclizing nitrogen[a]

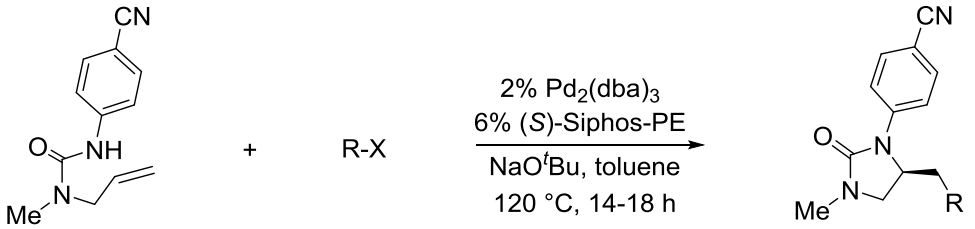


X	yield[b]	er
N(Bn)Me (**2-25**)	70% (**2-26**)	86:14 er
OMe (**2-23**)	93% (**2-24**)	89:11 er
H (**2-27**)	90% (**2-28**)	89:11 er
Br (**2-29**)	45% (**2-30**)	91:9 er
CN (**2-31**)[c]	87% (**2-32**)	93:7 er
NO_2 (**2-33**)[c]	81% (**2-34**)	96:4 er

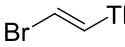
[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.2 M), 90 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds (average of two or more runs). [c] Reactions were conducted at 120 °C in xylenes.

Next, we wanted to explore scope of the reaction with different aryl halide electrophiles. Interestingly, when substrate **2-31** was subjected to the reaction conditions noted in Table 2.5 we observed that the enantioselectivity changed depending on the choice of aryl halide. The use of aryl iodides afforded products with lower enantioselectivities when compared to the use an aryl bromide (entries 1-6). However, this was only true when electron rich and electron neutral electrophiles were employed. When an electron poor aryl halide was subjected to the reaction conditions (entries 7-8), the use of the aryl iodide or the aryl bromide led to the same enantioselectivity for **2-38**. Employing aryl chlorides for these reactions led to no formation of the desired product, and the use of phenyl triflate led to the formation of a hydroamination product in 70% yield. Furthermore, extensive screening of other bases, solvents, palladium sources, and even halide abstraction agents such as silver salts failed to produce products in better enantioselectivities.

Table 2.5 Scope of asymmetric carboamination with **2-31**[a]



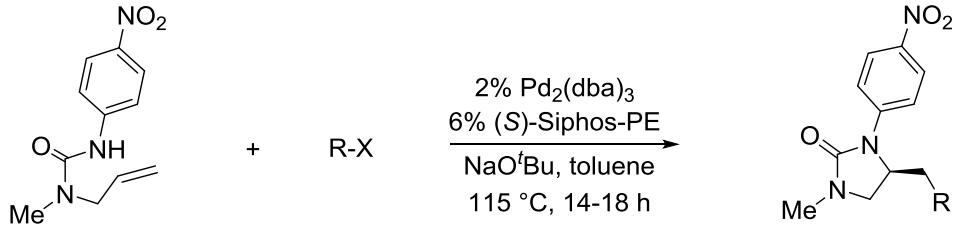
2-31 **2-35** to **2-40**

Entry	R-X	Product	yield[b]	er
1	*p*-^{t}Bu-C_6H_4-Br	**2-35**	89%	92:8
2	*p*-^{t}Bu-C_6H_4-I	**2-35**	90%	82:18
3	*p*-Me-C_6H_4-Br	**2-36**	86%	90:10
4	*p*-Me-C_6H_4-I	**2-36**	89%	85:15
5	Ph-Br	**2-37**	70%	90:10
6	Ph-I	**2-37**	80%	83:17
7	*p*-CF_3-C_6H_4-Br	**2-38**	62%	86:14
8	*p*-CF_3-C_6H_4-I	**2-38**	70%	86:14
9	*p*-OMe-C_6H_4-Br	**2-39**	73%	92:8
10		**2-40**	65%	93:7

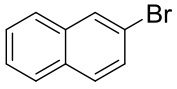
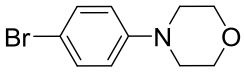
[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv Ar-X, 2.0 equiv NaO^{t}Bu, xylenes (0.2 M), 120 °C, 14-18 h. [b]Yields and enantiomeric ratios refer to isolated compounds (average of two or more runs).

In order to further optimize the reaction, we wanted to test the electrophile scope with **2-33**, which gave higher enantioselectivity than substrate **2-31** in preliminary screens. Initially, electron poor aryl bromides afforded irreproducible results under our reaction conditions. We assumed that this variability must be due to one of the reaction components. The most inconsistent component of our reaction mixture is NaO^{t}Bu, as this base is very hygroscopic. As such, we believed the quality of the base (i.e. amount of water retained) may be affecting the enantioselectivity of product **2-41**. We tested this theory by adding water to the reaction. As noted in Table 2.6, reactions utilizing electron poor aryl halides always benefited from the addition of 2.0 equivalents

Table 2.6 Scope of asymmetric carboamination with **2-33**[a]



2-33 **2-41** to **2-52**

Entry	R-X	Additive[b]	Product	yield[c]	er
1	*p*-CF_3-C_6H_4-Br	—	**2-41**	58%	89:11
2	*p*-CF_3-C_6H_4-Br	H_2O	**2-41**	72%	97:3
3	*p*-CF_3-C_6H_4-Br	NaOH	**2-41**	58%	96:4
4	*m*-CF_3-C_6H_4-Br	—	**2-42**	64%	89:11
5	*m*-CF_3-C_6H_4-Br	H_2O	**2-42**	68%	94:6
6	*o*-CF_3-C_6H_4-Br	H_2O	**2-43**	56%	91:9
7	*p*-PhC(O)-C_6H_4-Br	—	**2-44**	65%	90:10
8	*p*-PhC(O)-C_6H_4-Br	H_2O	**2-44**	82%	93:7
9	*p*-F-C_6H_4-Br	—	**2-45**	40%	90:10
10	*p*-F-C_6H_4-Br	H_2O	**2-45**	65%	97:3
11	*p*-Cl-C_6H_4-Br	—	**2-46**	75%	92:8
12	*p*-Cl-C_6H_4-Br	H_2O	**2-46**	74%	96:4
13	*p*-^{t}Bu-C_6H_4-Br	_	**2-47**	81%	95:5
14	*p*-^{t}Bu-C_6H_4-I	_	**2-47**	60%[d]	74:26
15	PhBr	_	**2-48**	83%	94:6
16	*p*-MeO-C_6H_4-Br	TFA	**2-49**	80%	95:5
17	*m*-MeO-C_6H_4-Br	_	**2-50**	75%	92:8
18		_	**2-51**	71%	94:6
19		H_2O	**2-52**	80%	93:7

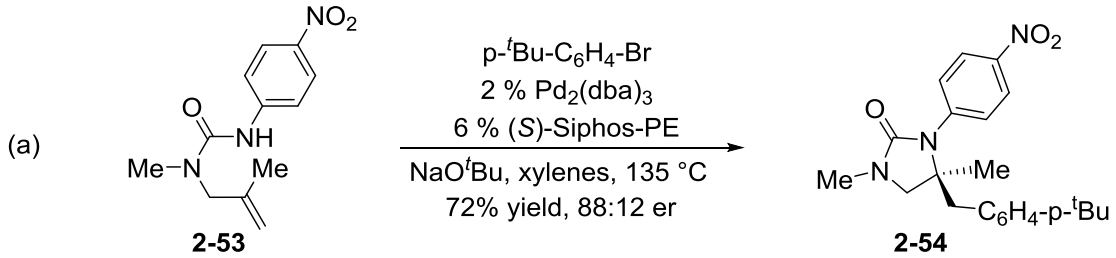
[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv Ar-X, 2.0 equiv NaO^{t}Bu, xylenes (0.2 M), 115 °C, 14-18 h. [b] Additive is either 2.0 equiv of H_2O or 40% TFA. [c] Yields and enantiomeric ratios refer to isolated compounds (average of two or more runs).

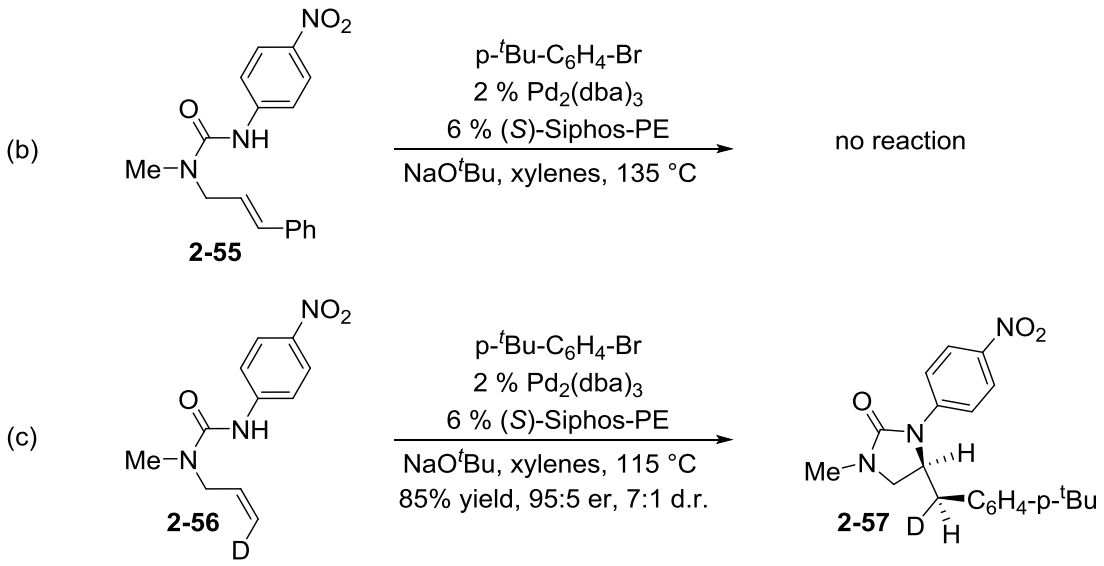
of water to the reaction (entries 1-12). Other amounts of water were tested under the reaction conditions, and although 0.50 equivalents of water was able to afford higher enantioselectivities, the use of 2.0 equivalents of water led to better reproducibility. Also, we realized that any water added to the reaction mixture would result in the formation of

a hydroxide ion. Thus, we tested the reaction with NaOH as the base (entry 3) and **2-41** was afforded in high enantioselectivity, albeit with a slightly lower yield. Furthermore, the carboamination reaction with **2-33** also showed the same halide ion effect that was previously mentioned in Table 2.5, and lower enantioselectivities were noted when an aryl iodide was used in place of an aryl bromide (Table 2.6 entries 13-14). The reaction also performs well with electron neutral and electron rich aryl bromides (entries 13-19).

We also explored the use of disubstituted alkenes under our reaction conditions. The reaction with the 1,1-disubstituted alkene **2-53** worked well to afford **2-54** in 72% yield and 88:12 er (Scheme 2.4 a). However, conversion of **2-53** to form the quaternary carbon in **2-54** required heating the reaction up to 135 °C. The use of the 1,2-disubstituted alkene **2-55** afforded no product, even under higher temperatures. To determine the stereochemistry of the addition to the alkene, we synthesized the Z-deuterioalkene **2-56** and subjected it to our reaction conditions. This reaction proceeded via a net syn-addition to the alkene to afford the **2-57** in 85% yield, 95:5 er, and 7:1 dr (Scheme 2.4 c).[10]

Scheme 2.4 Reactivity of disubstituted alkenes

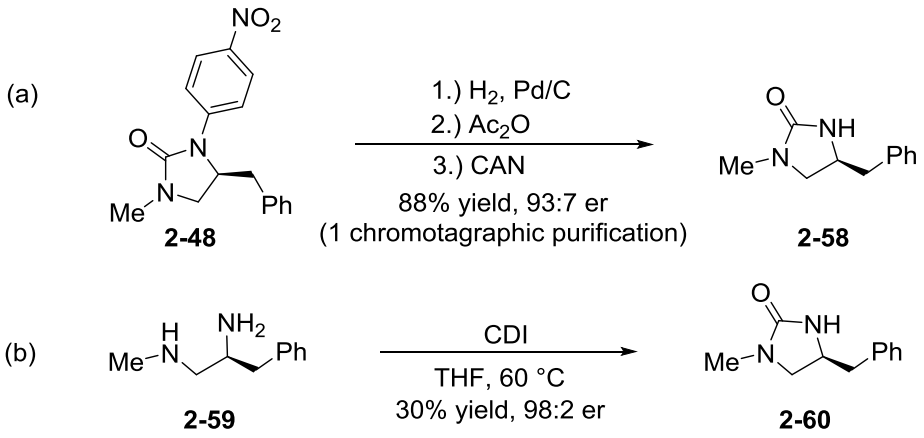




2.4 **Determination of Absolute Stereochemistry**

In order to determine the absolute stereochemistry of the imidazolidin-2-one products from our asymmetric carboamination reactions (Tables 2.5 and 2.6), and to show the feasibility of deprotecting the *p*-nitrophenyl group, **2-48** was subjected to the reaction conditions noted in Scheme 2.5 a. A simple and efficient procedure involving the reduction of the nitro group, acylation, and then oxidative cleavage with CAN afforded **2-58** in 88% yield and 93:7 er. This 3 step procedure required only a single chromatographic step. In order to determine the absolute stereochemistry of **2-58**, we needed to synthesize an authentic sample from a compound with a known absolute configuration. Thus, **2-59** was synthesized from the readily available amino acid L-phenylalanine.[11] Heating **2-59** with CDI afforded **2-60**, and chiral HPLC and optical rotation data confirmed that **2-60** and **2-58** are the same enantiomer.

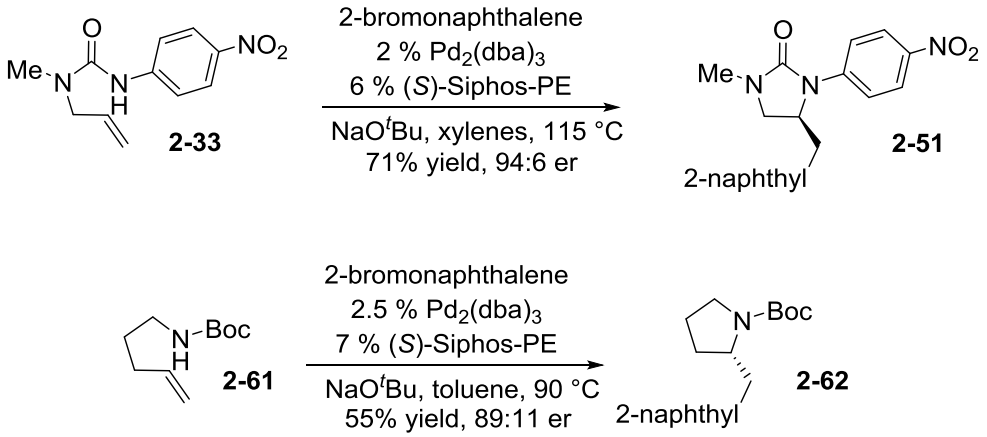
Scheme 2.5 Deprotection and determination of absolute configuration of **2-48**



2.5 Explanation of Electronic, Additive, and Halide Ion Effects on Enantioselectivity

In Tables 2.4, 2.5, and 2.6, a number of interesting effects on product enantioselectivity were observed based on slight changes to the substrate and reaction conditions. Interestingly, previous asymmetric carboamination reactions that afforded pyrrolidine products did not note any of these effects under very similar reaction conditions.[5] Additionally, the imidazoldin-2-one product **2-51** and pyrrolidine product **2-62** proceed with opposite absolute asymmetric induction under identical reaction conditions (Scheme 2.6). Furthermore, formation of pyrrolidine products is inhibited by the addition of water, and no product was formed with water added to the system. Also, the pyrrolidine products show no difference in asymmetric induction when changing from aryl bromides to aryl iodides.[5]

Scheme 2.6 Stereochemistry of imidazolidin-2-one versus pyrrolidine products

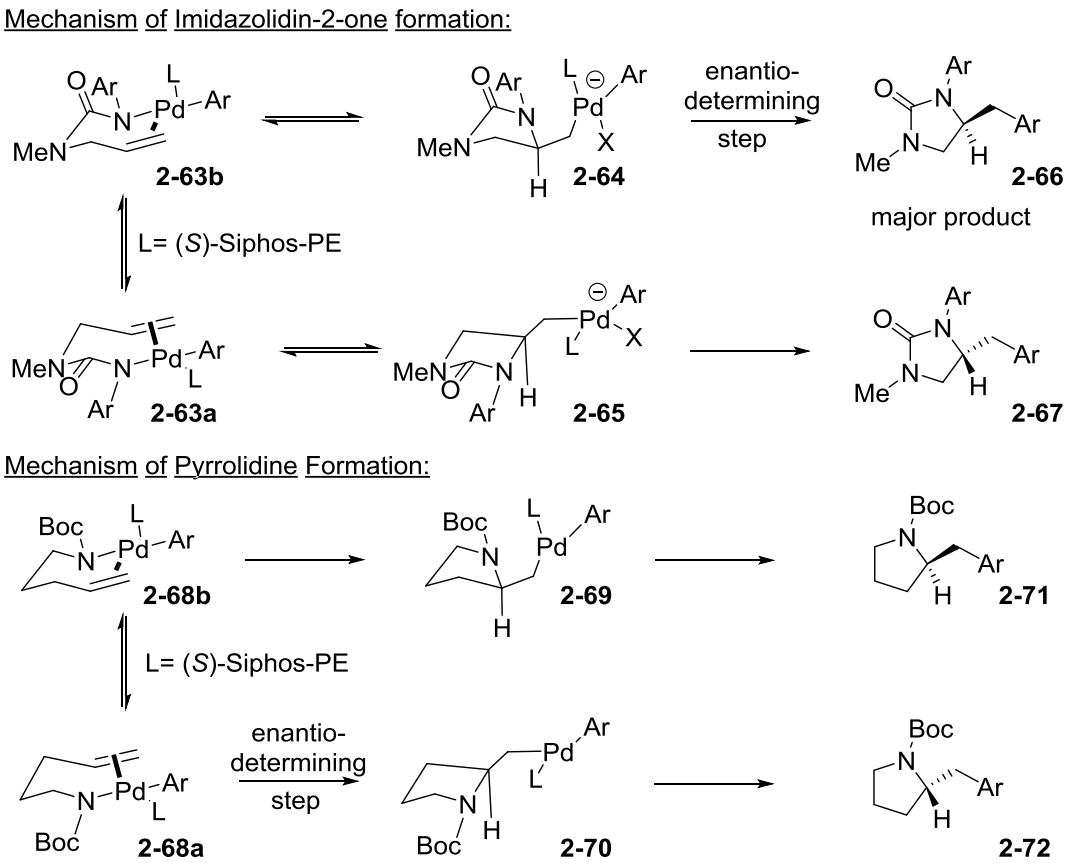


Although there are differences in the absolute product stereochemistry in the carboamination reactions of **2-33** compared to **2-61**, these reactions also have similarities. Both reactions from Scheme 2.6 have been shown to proceed through a syn-addition to the alkene based on deuterium labeling studies. Also, the asymmetric induction in the above reactions is not effected in either case by the Pd to ligand ratio. Furthermore, both reactions undergo the same mechanism, initiating with oxidative addition of the aryl halide to Pd(0) followed by substrate deprotonation to afford complexes **2-63a,b** and **2-68a,b** (Scheme 2.7). These complexes undergo syn-insertion into the Pd-N bond to yield **2-64** and **2-70** respectively, which undergo reductive elimination to afford the major enantiomers **2-66** and **2-72**.

We believe that a change in the enantiodetermining step is the cause of difference in the absolute stereochemistry of the imidazolidin-2-one (**2-51**) versus the pyrrolidine (**2-62**). The stereocenter of both products is generated in the migratory insertion step, but there are two steps that could be enantiodetermining: 1.) migratory insertion (i.e., **2-68a** to **2-70**) or 2.) reductive elimination (i.e., **2-64** to **2-66**), but only if

the insertion step is reversible. In the case of the formation of the pyrrolidine products, the relatively electron rich *N*-boc pentenylamine **2-61** likely undergoes an irreversible migratory insertion,[5] and then a relatively fast reductive elimination from **2-70**[12] to afford the major pyrrolidine enantiomer **2-72**.

Scheme 2.7 Mechanism of imidazolidin-2-one versus pyrrolidine formation



However, we believe that the electronic effect in the N-allyl urea substrates (Table 2.4) and the effect of anionic ligands (see Tables 2.5 and 2.6) are consistent with a mechanism that proceeds through a reversible migratory insertion followed by an enantiodetermining reductive elimination. One of the main reasons for the change in the enantiodetermining step for the formation of the imidazolidin-2-one products has to do

with the relative electron richness of the cyclizing nitrogen in substrate **2-33**. The pka of **2-33** is approximately 17.0 compared to 23.0 for substrate **2-61**,[13] and thus **2-33** is a lot less nucleophilic than **2-61**. The use of a more electron poor cyclizing nitrogen in complexes related to **2-64,65** and **2-69,70** has been shown to decrease the rate of reductive elimination[8] and promote beta-amidate elimination[14] (retroaminopalladation) from these complexes. Therefore, the more electron poor N-allylurea substrates **2-31** and **2-33** likely have a more facile equilibration from **2-65**→**2-63a**→**2-63b**→**2-64**. Reductive elimination then occurs faster from **2-64** than from **2-65** based on the chirality of the ligand to yield the major product **2-66**. The equilibration of **2-65**→**2-63a** occurs less readily for the more electron rich *N*-allyl urea substrates **2-23,25,27** leading to more formation of the minor enantiomer **2-67**, and therefore a lower enantioselectivity in the corresponding products in Table 2.4.

We also believe that the effect of anionic ligands (i.e. the hydroxide from added water and the iodide from aryl iodides) is due to their ability to alter the rate of the reductive elimination step, and thus affect the equilibration of **2-65**→**2-63a**. The combination of the small hydroxide ligand and electron-poor aryl halides leads to improved enantioselectivities in the formation of imidazolidin-2-ones. This result is consistent with the electron rich hydroxide ligand slowing down the reductive elimination (and thereby facilitating equilibration of **2-65**→**2-63a**) of electron-poor aryl halides, which typically undergo a relatively quick C-C bond forming reductive elimination.[15] Likewise, the addition of water to related reactions with electron-rich and electron-neutral aryl bromides led to no change in the enantioselectivity of the products (in most cases), as these groups already undergo relatively slow reductive eliminations.

Furthermore, we believe that the relatively large iodide ligand may help to increase the rate of reductive elimination through a steric effect,[16] and thus afford more of the minor enantiomer which erodes the enantioselectivity (Table 2.5). We believe that these anionic ligand effects arise through binding to the metal center after the aminopalladation step, as related aminopalladation reactions have been shown to proceed through 4-coordinate Pd complexes such as **2-63a,b** and **2-68a,b**.[8,17]

2.6 Conclusions

We have shown the utility of our asymmetric carboamination reactions to afford enantioenriched imidazolidin-2-ones from readily accessible N-allyl urea derivatives. Products are generated in good yields and good enantiomeric ratios up to 97:3. More importantly, we noted that the enantiodetermining step is likely influenced by the substrate structure, and we have shown that substrate electronics and additives greatly affect the levels of enantioselectivity in the products. This information will likely be very useful in the development of future enantioselective carboamination reactions.

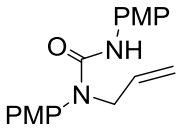
The work in this chapter was published in Angewandte Chemie International Edition. [18]

2.7 Experimental

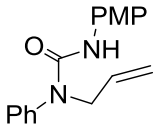
General: Reactions were carried out under nitrogen in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium and (*S*)-Siphos-PE were purchased from Strem Chemical Co. and used without further purification. All other reagents including all aryl and alkenyl bromides were purchased from commercial sources and used as received unless otherwise noted. Xylenes were purified by distillation over CaH_2 prior to use in

reactions. Methylene chloride and toluene were purified using a GlassContour solvent system. All yields refer to isolated compounds that are estimated to be ≥95% pure as judged by ^{1}H NMR analysis. The yields reported here refer to a single experiment and may differ from those reported in chapter 2 which are an average of 2 or more runs.

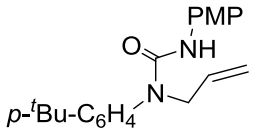
General procedure for the synthesis of *N*-allylurea substrates. A flame-dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen. The flask was charged with the appropriate isocyanate (1.0 equiv) and methylene chloride (0.60 M). The resulting solution was cooled to 0 °C and stirred for 5 min, then the allylic amine (1.1 equiv) was added dropwise. The solution was warmed to rt and stirred for five h. The mixture was then concentrated in vacuo and purified by flash chromatography on silica gel.



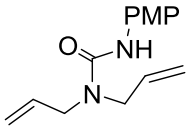
1-allyl-1,3-bis(4-methoxyphenyl)urea (2-14): The reaction of 0.60 g (3.68 mmol) of N-allyl-4-methoxyaniline with 0..48 mL (3.35 mmol) of 4-methoxyphenyl isocyanate according to the general procedure afforded 750 mg (71%) of the title compound as a white solid, mp 52-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.14 (m, 4H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J*= 9.00 Hz, 2H), 6.02 (s, br, 1H), 5.96–5.86 (m, 1H), 5.10 (s, 1H), 5.06 (d, *J* = 5.5 Hz, 1H), 4.27 (d, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 3.72 (s, 3H).



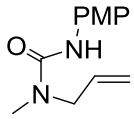
1-allyl-3-(4-methoxyphenyl)-1-phenylurea (2-16): The reaction of 0.50 mL (3.68 mmol) of N-allylaniline with 0.48 mL (3.35 mmol) of 4-methoxyphenyl isocyanate according to the general procedure afforded 662 mg (70%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, *J*= 7.6 Hz, 2H), 7.38 (t, *J*= 6.8 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J*= 9.1 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 6.06 (s, br, 1H), 6.01-5.92 (m, 1H), 5.16-5.10 (m, 2H), 4.35 (d, *J* = 6.2 Hz, 2H), 3.77 (s, 3H).



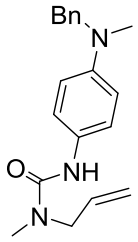
1-allyl-1-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)urea (2-18): The reaction of 607 mg (3.21 mmol) of N-allyl-4-*tert*-butylaniline with 0.40 mL (2.92 mmol) of 4-methoxyphenyl isocyanate according to the general procedure afforded 900 mg (90%) of the title compound as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 2H), 7.23-7.15 (m, 4H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.08 (s, br, 1H), 5.99-5.88 (m, 1H), 5.16-5.07 (m, 2H), 4.29 (d, *J* = 6.2 Hz, 2H), 3.73 (s, 3H), 1.33 (s, 9H).



1,1-diallyl-3-(4-methoxyphenyl)urea (2-21): The reaction of 0.40 mL (3.30 mmol) of Diallylamine with 0.539mL (3.00 mmol) of 4-methoxyphenyl isocyanate according to the general procedure afforded 695 mg (93%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.2 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.35 (s, br, 1H), 5.94–5.86 (m, 2H), 5.33-5.26 (m, 4H), 3.98 (d, *J* = 5.6 Hz, 4H), 3.79 (s, 3H).

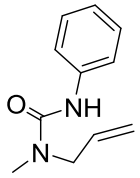


1-Allyl-3-(4-methoxyphenyl)-1-methylurea (2-23): The reaction of 0.47 mL (4.92 mmol) of N-allylmethylamine with 0.58 mL (4.47 mmol) of 4-methoxyphenyl isocyanate according to the general procedure afforded 841 mg (85%) of the title compound as a white solid, mp 52-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.61 (s, br, 1H), 5.90–5.78 (m, 1H), 5.25 (d, *J* = 5.5 Hz, 1H), 5.22 (s, 1H), 3.94 (d, *J* = 5.3 Hz, 2H), 3.76 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.7, 133.5, 132.2, 122.1, 116.8, 114.0, 55.5, 51.5, 34.5; IR (film) 1638 cm^{-1}. MS (CI) 221.1280 (221.1285 calcd for $C_{12}H_{16}N_2O_2$, M + H^+).

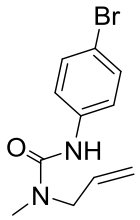


1-Allyl-3-{4-[benzyl(methyl)amino]phenyl}-1-methylurea (2-25): A flame dried schlenk flask equipped with a stirbar was cooled under a stream of nitrogen and charged with 1-allyl-3-(4-bromophenyl)-1-methylurea (1.00 g, 3.72 mmol), lithium bis(trimethylsilyl)amide (1.37 g, 4.46 mmol), $Pd_2(dba)_3$ (34.1 mg, 0.0372 mmol), and DavePhos (35.1 mg, 0.0893 mmol). The flask was purged with N_2 pressure for 30 s then THF (8.2 mL) and N-methyl benzylamine (0.58 mL, 4.46 mmol) were added. The resulting mixture was heated to 65 °C with stirring for 15 h, then was cooled to rt. A solution of of 1M HCl (8 mL) was added and the resulting mixture was stirred at rt for five min. A solution of saturated aqueous $NaHCO_3$ (8 mL) was slowly added and the mixture was transferred to a separatory funnel after bubbling ceased. The mixture was

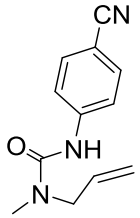
extracted with ethyl acetate (3 x 20 mL) then the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 450 mg (40%) of the title compound as a light brown solid, mp 93-97 °C. 1H NMR (400 MHz, CDCl3) δ 7.31–7.14 (m, 7H), 6.68 (d, *J* = 9.0 Hz, 2H), 6.18 (s, br, 1H), 5.83 (ddt, *J* = 5.5, 5.2, 12.0 Hz, 1H), 5.26–5.19 (m, 2H), 4.46 (s, 2H), 3.93 (d, *J* = 5.5 Hz, 2H), 2.96 (s, 3H), 2.94 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 156.2, 146.5, 138.9, 133.6, 128.8, 128.4, 126.8, 126.7, 122.5, 116.7, 113.0, 57.0, 51.4, 38.7, 34.4; IR (film) 1637 cm-1. MS (CI) 310.1916 (310.1914 calcd for $C_{19}H_{23}N_3O$, M + H+).



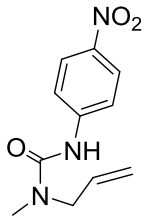
1-Allyl-1-methyl-3-phenylurea (2-27): The reaction of 0.37 mL (3.85 mmol) of *N*-allylmethylamine with 0.42 mL (3.50 mmol) of phenyl isocyanate according to the general procedure afforded 644 mg (88%) of the title compound as a white solid, mp 71-74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.48 (s, br, 1H), 5.88–5.78 (m, 1H), 5.26–5.19 (m, 2H), 3.93 (d, *J* = 5.5 Hz, 2H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 139.2, 133.4, 128.8, 122.9, 119.8, 116.9, 51.5, 38.7, 34.5; IR (film) 1639 cm^{-1}. MS (CI) 191.1180 (191.1179 calcd for $C_{11}H_{14}N_2O$, M + H$^+$).



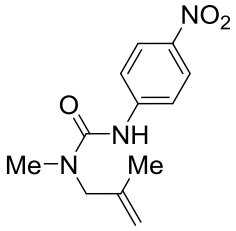
1-Allyl-3-(4-bromophenyl)-1-methylurea (2-29): The reaction of 0.80 mL (8.44 mmol) of N-allylmethylamine with 1.51 g (7.67 mmol) of 4-bromophenyl isocyanate according to the general procedure afforded 1.88 g (91%) of the title compound as a white solid, mp 123-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.47 (s, br, 1H), 5.81 (ddt, *J* = 5.5, 5.6, 9.9 Hz, 1H), 5.27–5.19 (m, 2H), 3.92 (d, *J* = 5.3 Hz, 2H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.3, 133.2, 131.7, 121.4, 117.0, 115.2, 51.5, 34.6; IR (film) 1634 cm^{-1}. MS (CI) 269.0282 (269.0284 calcd for $C_{11}H_{13}BrN_2O$, M + H^+).



1-Allyl-3-(4-cyanophenyl)-1-methylurea (2-31): The reaction of 0.73 mL (7.65 mmol) of *N*-allylmethylamine with 1.00 g (6.96 mmol) of 4-cyanophenyl isocyanate according to the general procedure afforded 1.17 g (78%) of the title compound as a white solid, mp 119-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 6.69 (s, br, 1H), 5.86 (ddt, *J* = 5.1, 5.4, 11.9 Hz, 1H), 5.32–5.25 (m, 2H), 3.80 (d, *J* = 5.4 Hz, 2H), 3.03 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 143.5, 133.1, 132.9, 119.2, 119.0, 117.4, 105.3, 51.6, 34.8; IR (film) 1664 cm^{-1}. MS (CI) 216.1135 (216.1131 calcd for $C_{12}H_{13}N_3O_3$, M + H^+).

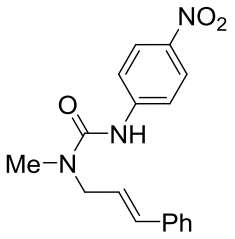


1-Allyl-1-methyl-3-(4-nitrophenyl)urea (2-33): The reaction of 0.77 mL (8.09 mmol) of *N*-allylmethylamine with 1.21 g (7.35 mmol) of 4-nitrophenyl isocyanate according to the general procedure afforded 1.61 g (93%) of the title compound as a yellow solid, mp 78-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.2 Hz, 2H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.00 (s, br, 1H), 5.84 (ddt, *J* = 5.3, 5.6, 11.4 Hz, 1H), 5.32–5.22 (m, 2H), 3.98 (d, *J* = 5.3 Hz, 2H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 145.6, 142.2, 132.8, 125.0, 118.4, 117.4, 51.6, 34.8; IR (film) 1660 cm^{-1}. MS (CI) 236.1037 (236.1030 calcd for $C_{11}H_{13}N_3O_3$, M + H^+).



1-Methyl-1-(2-methylallyl)-3-(4-nitrophenyl)urea (2-53): A flame dried flask equipped with a stirbar was cooled under a stream of nitrogen and charged with 3-bromo-2-methylpropene (4.60 mL, 45 mmol). The flask was cooled to 0 °C and stirred for five min, then methylamine (27.2 mL, 225 mmol, 33% solution in EtOH) was added and the resulting mixture was warmed to rt and stirred for 15 h. A solution of 1M NaOH (20 mL) was added and the resulting mixture was transferred to a separatory funnel. The mixture was extracted with ether (3 x 20 mL) then the combined organic layers were washed with 1M NaOH (1x12 mL), dried over anhydrous Na_2SO_4, filtered, and partially

concentrated *in vacuo* (to remove excess methylamine) to afford *N*,2-dimethylprop-2-en-1-ylamine as a solution in ethanol. The solution was transferred to a flask equipped with a stirbar and cooled to –10 °C. Neat 4-nitrophenyl isocyanate (1.64 g, 10 mmol) was added and the resulting solution and the reaction was slowly warmed to rt over the course of five h. The reaction mixture was then concentrated in vacuo and the crude product was purified by flash column chromatography to yield 350 mg (14 %) of the title compound as a yellow solid, mp 79-82 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.3 Hz, 2H), 7.52 (d, *J* = 9.1 Hz, 2H), 6.92 (s, br, 1H), 5.03 (s, 1H) 4.96 (s, 1H), 3.90 (s, 2H), 3.05 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 145.5, 142.3, 141.0, 125.0, 118.3, 112.5, 55.2, 35.3, 19.7; IR (film) 1658 cm^{-1}. MS (CI) 250.1191 (250.1186 calcd for $C_{12}H_{15}N_3O_3$, M + H^+).

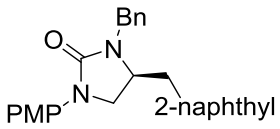


1-cinnamyl-1-methyl-3-(4-nitrophenyl)urea (2-55): A flame dried flask equipped with a stirbar was cooled under a stream of nitrogen and charged with cinnamyl bromide (4.33 g, 22 mmol). The flask was cooled to 0 °C and stirred for five min, then methylamine (27.2 mL, 225 mmol, 33% solution in EtOH) was added and the resulting mixture was warmed to rt and stirred for 15 h. A solution of 1M NaOH (20 mL) was added and the resulting mixture was transferred to a separatory funnel. The mixture was extracted with ether (3 x 20 mL) then the combined organic layers were washed with 1M NaOH (1x12 mL), dried over anhydrous Na_2SO_4, filtered, and partially concentrated *in vacuo* (to remove excess methylamine) to afford *(E)-N-methyl-3-*

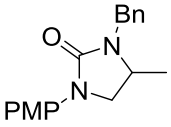
phenylprop-2-en-1-amine as a solution in ethanol. The solution was transferred to a flask equipped with a stirbar and cooled to –10 °C. Neat 4-nitrophenyl isocyanate (1.44g, 8.8 mmol) was added and the resulting solution and the reaction was slowly warmed to rt over the course of five h. The reaction mixture was then concentrated in vacuo and the crude product was purified by flash column chromatography to yield 430 mg (16 %) of the title compound as a white solid, mp 120-124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.1 Hz, 2H), 7.55 (d, *J* = 9.3 Hz, 2H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.1 Hz, 1H), 6.92 (s, br, 1H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.23 (dt, *J* = 5.9, 15.9 Hz, 1H), 4.17 (d, *J*= 5.9 Hz, 2H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 145.4, 142.4, 135.9, 132.8, 128.7, 128.2, 126.5, 125.1, 123.9, 118.4, 51.2, 34.8; IR (film) 1659 cm^{-1}. MS (CI) 312.1353 (312.1343 calcd for $C_{17}H_{17}N_3O_3$, M + H^+).

General procedure for asymmetric Pd-catalyzed carboamination reactions of *N*-allylurea derivatives. A flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and then charged with $Pd_2(dba)_3$ (2 mol %), (*S*)-Siphos-PE (6 mol %), the urea substrate (1.0 equiv), and NaO^{t}Bu (2.0 equiv). The flask was purged with N_2, then the aryl or alkenyl halide (2.0 equiv), the additive (H_2O 2.0 equiv or TFA 40 mol % if needed) and xylenes (0.20 M, for reactions at 120 °C) or toluene (0.20 M, for reactions at 90 °C) were added. The resulting mixture was heated to 90 °C or 120 °C with stirring until the starting material had been consumed as judged by TLC analysis. The reaction mixture was then cooled to rt, saturated aqueous ammonium chloride (6mL/mmol substrate) was added, and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate (3 x 5 mL) then the combined

organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

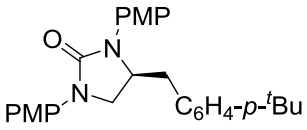


(S)-3-benzyl-1-(4-methoxyphenyl)-4-(naphthalen-2-ylmethyl)imidazolidin-2-one (2-12). The general procedure was employed for the coupling of 1-allyl-3-benzyl-1-(4-methoxyphenyl)urea (0.15 mmol, 45 mg) and 2-bromonaphthalene (0.30 mmol, 60 mg), using a catalyst composed of $Pd_2(dba)_3$ (0.003 mmol, 2.8 mg) and (*S*)-Siphos-PE (0.009 mmol, 4.5 mg), a reaction temperature of 90 °C, and a reaction time of 12 h. This procedure afforded the title compound (18.8 mg**,** 30%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.79-7.75 (m, 2H), 7.57 (s, 1H), 7.50-7.46 (m, 2H),7.43- 7.33 (m, 7H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 9.3 Hz, 2H), 5.00 (d, *J* = 15.1 Hz, H), 4.24 (d, *J* = 15.1 Hz, 1H), 3.91-3.84 (m, 1H), 3.79 (s, 3H), 3.62 (app. t, *J* = 9.0 Hz, 1H), 3.49 (dd, *J* = 6.3, 9.0 Hz, 1H), 3.37 (dd, *J* = 4.3, 13.5 Hz, 1H), 2.79 (dd, *J* = 9.6, 13.5 Hz, 1H). The enantiopurity was determined to be 82:18 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 20% IPA/Hexanes, 2.0 mL/min, λ 254 nm, RT= 9.4 and 11.3 min).

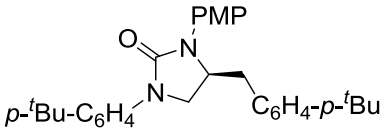


3-benzyl-1-(4-methoxyphenyl)-4-methylimidazolidin-2-one (2-13). The general procedure was employed for the coupling of 1-allyl-3-benzyl-1-(4-methoxyphenyl)urea (0.15 mmol, 45 mg) and 2-bromonaphthalene (0.30 mmol, 60 mg), using a catalyst

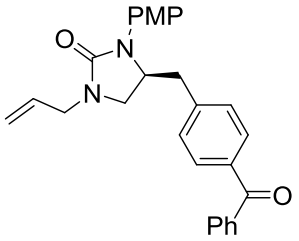
composed of $Pd_2(dba)_3$ (0.003 mmol, 2.8 mg) and 2-L5 (0.009 mmol, 4.5 mg), a reaction temperature of 90 °C, and a reaction time of 12 h. This procedure afforded the title compound in 7.0 mg (11%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 2H) 4.85 (d, *J* = 15.4 Hz, 1H), 4.16 (d, *J* = 15.1 Hz, 1H), 3.87 (app. t, *J* = 8.7 Hz, 1H), 3.81 (s, 3H), 3.65-3.58 (m, 1H), 3.34 (dd, *J* = 7.3, 8.5 Hz, 1H), 1.27 (d, *J* = 6.1 Hz, 3H).



(S)-4-(4-(tert-butyl)benzyl)-1,3-bis(4-methoxyphenyl)imidazolidin-2-one (2-15). The general procedure was employed for the coupling of 1-allyl-1,3-bis(4-methoxyphenyl)urea (0.10 mmol, 31.2 mg) and 1-bromo-4-*tert*-butylbenzene (0.15 mmol, 32.0 mg), using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 90 °C, and a reaction time of 12 h. This procedure afforded the title compound (42.1 mg**,** 99%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.39 (m, 4H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.52–4.42 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.61 (dd, *J* = 5.8, 8.9 Hz, 1H), 3.11 (dd, *J* = 2.9, 13.7 Hz, 1H), 2.72 (dd, *J* = 9.5, 13.6 Hz, 1H), 1.34 (s, 9H).The enantiopurity was determined to be 81:19 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 10% IPA/Hexanes, 1.50 mL/min, λ 254 nm, RT= 21.1 and 23.3 min).

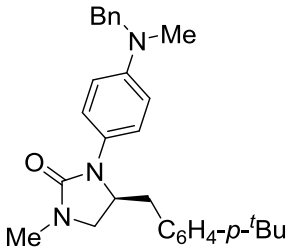


(S)-4-(4-(tert-butyl)benzyl)-1-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)imidazolidin-2-one (2-19). The general procedure was employed for the coupling of 1-allyl-1-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)urea (0.10 mmol, 33.8 mg) and 1-bromo-4-*tert*-butylbenzene (0.20 mmol, 42.6 mg), using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 90 °C, and a reaction time of 12 h. This procedure afforded the title compound (27.4 mg**,** 58%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (m, 4H), 7.36–7.31 (m, 4H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.53–4.46 (m, 1H), 3.87 (app. t, *J* = 9.4 Hz, 1H), 3.85 (s, 3H), 3.66 (dd, *J* = 5.3, 9.1 Hz, 1H), 3.11 (dd, *J* = 5.3, 9.1 Hz, 1H), 2.72 (dd, *J* = 9.5, 14.4 Hz, 1H), 1.32 (s, 9H), 1.30 (s, 9H). The enantiopurity was determined to be 84:16 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 10% IPA/Hexanes, 1.50 mL/min, λ 254 nm, RT= 6.6 and 7.9 min).



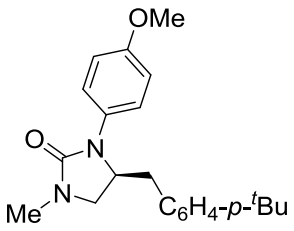
(S)-1-allyl-4-(4-(tert-butyl)benzyl)-3-(4-methoxyphenyl)imidazolidin-2-one (2-22). The general procedure was employed for the coupling of 1,1-diallyl-3-(4-methoxyphenyl)urea (0.10 mmol, 24.6 mg) and 4-bromobenzophenone (0.20 mmol, 52.2 mg), using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 90 °C, and a reaction time

of 12 h. This procedure afforded the title compound (40 mg**,** 93%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.69 (m, 4H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 9.2 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.74–5.63 (m, 1H), 5.18–5.11 (m, 2H), 4.46–4.38 (m, 1H), 3.79 (s, 3H), 3.36 (app. t, *J* = 8.9 Hz, 1H), 3.16-3.11 (m, 2H), 2.80 (dd, *J* = 8.9, 13.6 Hz, 1H).The enantiopurity was determined to be 86:14 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 20% IPA/Hexanes, 2.00mL/min, λ 254 nm, RT**=** 17.0 and 36.0 min).

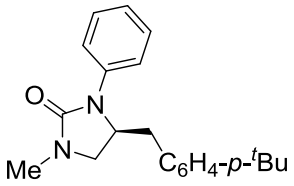


(–)-(4*S*)-3-{4-[Benzyl(methyl)amino]phenyl}-4-[4-(*tert*-butyl)benzyl]-1-methylimidazolidin-2-one (2-26). The general procedure was employed for the coupling of 1-allyl-3-{4-[benzyl(methyl)amino]phenyl}-1-methylurea (0.10 mmol, 30.9 mg) and 4-bromo-*tert*-butylbenze (0.20 mmol, 42.6 mg), using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 90 °C, and a reaction time of 12 h. This procedure afforded the title compound (28.7 mg**,** 65%) as an orange oil: $[\alpha]^{23}_{D}$ –23.2 (*c* 0.68, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 9H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 4.52 (s, 2H), 4.28–4.20 (m, 1H), 3.30 (app. t, *J* = 8.6 Hz, 1H), 3.12 (dd, *J* = 6.1, 8.8 Hz, 1H), 3.06 (dd, *J* = 3.3, 13.7 Hz, 1H), 3.00 (s, 3H), 2.79 (s, 3H) 2.58 (dd, *J* = 10.0, 13.5 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$); 159.5, 149.6, 147.3, 139.0, 133.8, 128.8, 128.6, 128.2, 126.9, 126.8, 125.5, 124.5, 112.9, 57.0, 55.9, 50.1, 38.7, 38.0, 34.4, 31.4, 31.3; IR (film) 1704 cm^{-1}; MS (CI) 442.2866 (442.2859 calcd for $C_{29}H_{35}N_3O$,

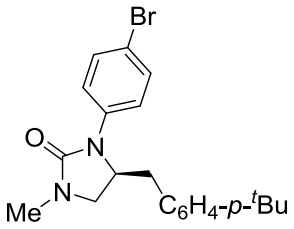
M + H^+). The enantiopurity was determined to be 86:14 er by chiral HPLC analysis (Chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.50 mL/min, λ 198 nm, RT= 6.1 and 9.2 min).



(–)-(4*S*)-4-[4-(*tert*-Butyl)benzyl]-3-(4-methoxyphenyl)-1-methylimidazolidin-2-one (2-24). The general procedure was employed for the coupling of 1-allyl-3-(4-methoxyphenyl)-1-methylurea (0.10 mmol, 22.1 mg) and 4-bromo-*tert*-butylbenze (0.20 mmol, 42.6 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 90 °C, and a reaction time of 12 h. This procedure afforded the title compound (33.0 mg, 93%) as an orange oil: $[\alpha]^{23}_D$ –10.1 (*c* 0.76, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.37–4.29 (m, 1H), 3.82 (s, 3H), 3.36 (app. t, *J* = 8.7 Hz, 1H), 3.17 (dd, *J* = 5.9, 9.2 Hz, 1H), 3.05 (dd, *J* = 3.7, 13.7 Hz, 1H), 2.81 (s, 3H), 2.62 (dd, *J* = 9.8, 13.7 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.0, 156.4, 149.6, 133.5, 131.8, 128.8, 125.5, 123.8, 114.3, 55.5, 55.4, 49.8, 37.8, 34.4, 31.3, 31.2; IR (film) 1700 cm^{-1}; MS (CI) 353.2232 (353.2224 calcd for $C_{22}H_{28}N_2O_2$, M + H^+). The enantiopurity was determined to be 89:11 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.50 mL/min, λ 198 nm, RT= 5.3 and 8.1 min).

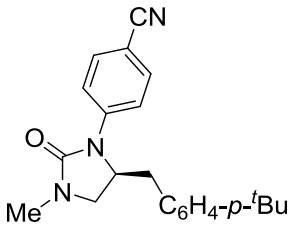


(–)-(4*S*)-4-[4-(*tert*-Butyl)benzyl]-1-methyl-3-phenylimidazolidin-2-one (2-28). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-phenylurea (0.10 mmol, 17.6 mg) and 4-bromo-*tert*-butylbenze (0.20 mmol, 42.6 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (29.0 mg**,** 90%) as white solid, mp 67–70 °C: $[\alpha]^{23}_{D}$ –19.4 (*c* 0.55, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.12–7.06 (m, 3H), 4.48–4.40 (m, 1H), 3.37 (app. t, *J* = 8.6 Hz, 1H), 3.20 (dd, *J* = 4.9, 8.4 Hz, 1H), 3.11 (dd, *J* = 3.3, 13.8 Hz, 1H), 2.81 (s, 3H), 2.64 (dd, *J* = 9.8, 13.8 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.3, 149.7, 138.9, 133.5, 129.0, 128.8, 125.6, 123.4, 120.7, 54.4, 49.4, 37.5, 34.4, 31.3, 31.0; IR (film) 1707 cm^{-1}; MS (CI) 323.2125 (323.2118 calcd for $C_{21}H_{26}N_2O$, M + H^+). The enantiopurity was determined to be 89:11 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 8% IPA/Hexanes, 1.0 mL/min, λ 198 nm, RT= 9.5 and 10.1 min).



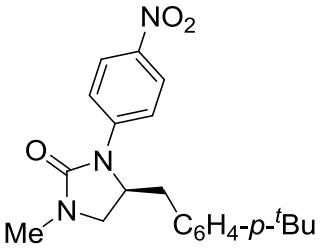
(–)-(4*S*)-3-(4-Bromophenyl)-4-[4-(*tert*-butyl)benzyl]-1-methylimidazolidin-2-one (2-30). The general procedure was employed for the coupling of 1-allyl-3-(4-bromophenyl)-1-methylurea (0.10 mmol, 26.9 mg) and 4-bromo-*tert*-butylbenze (0.20

mmol, 42.6 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (18.0 mg**,** 45%) as an orange oil: $[\alpha]^{23}_{D}$ –41.6 (*c* 0.42, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.43 (m, 4H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.44–4.38 (m, 1H), 3.39 (app. t, *J* = 8.8 Hz, 1H), 3.22 (dd, *J* = 4.6, 9.0 Hz, 1H), 3.07 (dd, *J* = 3.7, 13.8 Hz, 1H), 2.82 (s, 3H), 2.66 (dd, *J* = 9.5, 13.8 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.9, 150.0, 138.1, 133.3, 131.9, 128.8, 125.6, 121.9, 116.0, 54.2, 49.2, 37.4, 34.3, 31.3, 31.9; IR (film) 1708 cm^{-1}; MS (CI) 401.1230 (401.1223 calcd for $C_{21}H_{25}BrN_2O$, M + H^+). The enantiopurity was determined to be 91:9 ee by chiral HPLC analysis (chrialcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.50 mL/min, λ 198 nm, RT= 4.3 and 6.0 min).



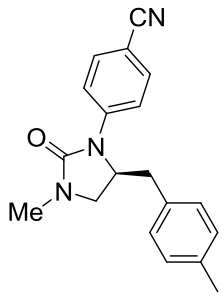
(–)-(5*S*)-4-{5-[4-(*tert*-Butyl)benzyl]-3-methyl-2-oxoimidazolidin-1-yl}benzonitrile (2-32): The general procedure was employed for the coupling of 1-allyl-3-(4-cyanophenyl)-1-methylurea (0.10 mmol, 21.5 mg) and 4-bromo-*tert*-butylbenze (0.20 mmol, 42.6 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 120 °C and a reaction time of 14 h. This procedure afforded the title compound (30.2 mg, 87%) as a light orange solid, mp 108–113 °C: $[\alpha]^{23}_{D}$ –73.6 (*c* 0.91, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 4.50 (m, 1H), 3.46 (app. t, *J* = 8.8 Hz, 1H), 3.28 (dd, *J* = 3.5, 9.2 Hz, 1H), 3.10 (dd, *J* = 3.5, 14.1

Hz, 1H), 2.83 (s, 3H) 2.73 (dd, *J* = 9.2, 14.0 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 150.2, 143.2, 133.1, 132.6, 128.8, 125.7, 119.2, 118.5, 105.0, 53.6, 48.7, 37.3, 34.5, 31.3, 30.8; IR (film) 1712 cm^{-1}; MS (CI) 348.2082 (348.2070 calcd for $C_{22}H_{25}N_3O$, M + H$^+$). The enantiopurity was determined to be 93:7 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 5.4 and 8.6 min).

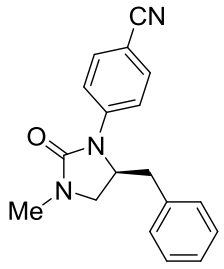


(–)-(4*S*)-4-[4-(*tert*-Butyl)benzyl]-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-34). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 4-bromo-tert-butylbenzene (0.40 mmol, 85.2 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (59.6 mg, 81%) as a bright yellow solid, mp 115–118 °C: $[\alpha]^{23}_D$ –102.3 (*c* 1.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.2 Hz, 2H), 7.78 (d, *J* = 9.4 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.9 (d, *J* = 8.2 Hz, 2H), 4.56–4.49 (m, 1H), 3.48 (app. t, *J* = 9.0 Hz, 1H), 3.29 (dd, *J* = 3.0, 9.3 Hz, 1H), 3.11 (dd, *J* = 3.5, 13.8 Hz, 1H), 2.83 (s, 3H), 2.75 (dd, *J* = 9.0, 13.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 150.3, 145.2, 141.9, 132.5, 128.8, 125.8, 125.0, 117.7, 53.7, 48.6, 37.3, 34.5, 31.3, 30.8; IR (film) 1717 cm^{-1}. MS (CI) 368.1968 (368.1969 calcd for $C_{21}H_{25}N_3O_3$, M + H$^+$). The enantiopurity was determined to be 96:4 er by chiral HPLC analysis (chiralcel

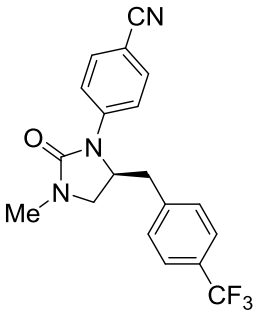
ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.50 mL/min, λ 198 nm, RT= 6.1 and 9.4 min).



(–)-(5*S*)-4-[3-Methyl-5-(4-methylbenzyl)-2-oxoimidazolidin-1-yl]benzonitrile (2-36). The general procedure was employed for the coupling of 1-allyl-3-(4-cyanophenyl)-1-methylurea (0.10 mmol, 21.5 mg) and 4-bromotoluene (0.20 mmol, 34.2 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 120 °C and a reaction time of 14 h. This procedure afforded the title compound (26.3 mg, 86%) as a light orange solid, mp 123–126 °C: $[\alpha]^{23}_{D}$ –55.7 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.51–4.45 (m, 1H), 3.44 (app. t, *J* = 9.0 Hz, 1H), 3.26 (dd, *J* = 3.7, 9.2 Hz, 1H), 3.09 (dd, *J* = 3.4, 13.9 Hz, 1H), 2.82 (s, 3H) 2.72 (dd, *J* = 9.3, 13.9 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 143.2, 136.9, 133.1, 132.5, 129.5, 129.0, 119.2, 118.5, 105.0, 53.5, 48.5, 37.2, 30.8, 21.0; IR (film) 1712 cm^{-1}; MS (CI) 306.1608 (306.1601 calcd for $C_{19}H_{19}N_3O$, M + H^+). The enantiopurity was determined to be 90:10 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 5.4 and 8.6 min).

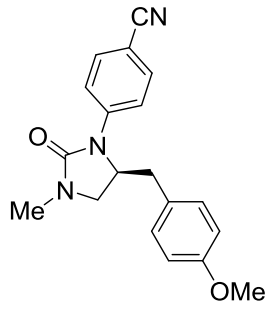


(*S*)-4-(5-benzyl-3-methyl-2-oxoimidazolidin-1-yl)benzonitrile (2-37). The general procedure was employed for the coupling of 1-allyl-3-(4-cyanophenyl)-1-methylurea (0.10 mmol, 21.5 mg) and bromobenzene (0.20 mmol, 31.4 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 120 °C and a reaction time of 14 h. This procedure afforded the title compound (21.8 mg, 70%) as a light orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H), 7.39-7.25 (m, 3H), 7.14 (d, *J* = 6.8 Hz, 2H), 4.52–4.45 (m, 1H), 3.42 (app. t, *J* = 9.0 Hz, 1H), 3.24 (dd, *J* = 3.5, 9.1 Hz, 1H), 3.10 (dd, *J* = 3.3, 13.8 Hz, 1H), 2.79 (s, 3H) 2.74 (dd, *J* = 9.1, 13.9 Hz, 1H). The enantiopurity was determined to be 90:10 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 254 nm, RT= 10.4 and 17.5 min).



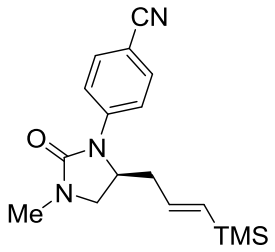
(–)-(5*S*)-4-{3-Methyl-2-oxo-5-[4-(trifluoromethyl)benzyl]imidazolidin-1-yl}benzonitrile (2-38). The general procedure was employed for the coupling of 1-allyl-3-(4-cyanophenyl)-1-methylurea (0.10 mmol, 21.5 mg) and 4-bromobenzotrifluoride (0.20 mmol, 45.0 mg), using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg)

and (*S*)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 120 °C and a reaction time of 14 h. This procedure afforded the title compound (20.7 mg**,** 62%) as a light orange solid, mp 120–124 °C: $[\alpha]^{23}_{D}$ –29.5 (*c* 1.12, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.72 (d, *J*= 8.9 Hz, 2H), 7.64 (d, *J*= 8.9 Hz, 2H), 7.57 (d, *J*= 8.0 Hz, 2H), 7.27 (d, *J*= 8.2 Hz, 2H), 4.56-4.52 (m, 1H), 3.46 (app. t, *J*= 9.0 Hz, 1H), 3.20 (dd, *J*= 3.4, 9.0 Hz, 1H), 3.13 (dd, *J*= 3.3, 14.1 Hz, 1H), 2.97 (dd, *J*= 8.7, 14.0 Hz, 1H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 142.9, 139.7, 133.2, 129.7 (q, 32.4 Hz), 129.6, 125.8(q, 3.8 Hz), 124.0 (q, 272.0 Hz), 119.1, 118.7, 105.5, 53.0, 48.4, 37.5, 30.7 ; IR (film) 1717 cm^{-1}; MS (CI) 360.1322 (360.1318 calcd for $C_{19}H_{16}F_3N_3O$, M + H^+). The enantiopurity was determined to be 86:14 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 200nm, RT= 8.9 and 16.6 min).

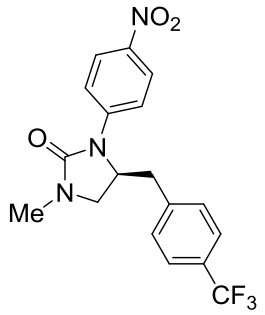


(–)-(5*S*)-4-[5-(4-Methoxybenzyl)-3-methyl-2-oxoimidazolidin-1-yl]benzonitrile (2-39). The general procedure was employed for the coupling of 1-allyl-3-(4-cyanophenyl)-1-methylurea (0.10 mmol, 21.5 mg) and 4-bromoanisole (0.20 mmol, 37.4 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (S)-Siphos-PE (0.006 mmol, 3.0 mg), a reaction temperature of 120 °C and a reaction time of 14 h. This procedure afforded the title compound in (23.5 mg, 73%) as a light orange solid, mp 87–91 °C: $[\alpha]^{23}_{D}$ –52.9 (*c* 0.37, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.46 (m, 1H), 3.79

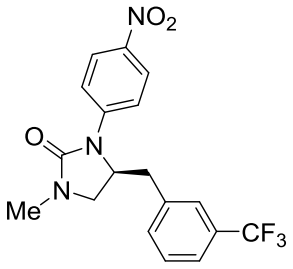
(s, 3H), 3.43 (app. t, *J* = 9.0 Hz, 1H), 3.24 (dd, *J* = 3.3, 9.2 Hz, 1H), 3.04 (dd, *J* = 3.3, 14.0 Hz, 1H), 2.80 (s, 3H) 2.71 (dd, *J* = 9.0, 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.9, 143.2, 133.1, 130.2, 127.5, 118.5, 114.2, 105.0, 55.3, 53.5, 48.5, 36.7, 30.8; IR (film) 1711 cm^{-1}; MS (CI) 322.1548 (322.1550 calcd for $C_{19}H_{19}N_3O_2$, M + H^+). The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 12.3 and 23.3 min.)



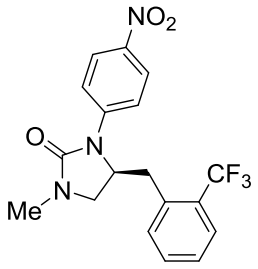
(+)-(*E*,5*S*)-4-(3-Methyl-2-oxo-5-(3-(trimethylsilyl)allyl)imidazolidin-1-yl)benzonitrile (2-40). The general procedure was employed for the coupling of 1-allyl-3-(4-cyanophenyl)-1-methylurea (0.10 mmol, 21.5 mg) and 2-bromovinyltrimethylsilane (0.20 mmol, 35.8 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0mg), a reaction temperature of 120 °C and a reaction time of 14 h. This procedure afforded the title compound (20.0 mg, 64%) as a light orange solid, mp 130–133 °C: $[\alpha]^{23}_D$ +6.4 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 5.87 (dt, *J* = 6.2, 18.5 Hz, 1H), 5.76 (d, *J* = 18.7 Hz, 1H), 4.35 (m, 1H), 3.56 (app. t, *J* = 9.0 Hz, 1H), 3.23 (dd, *J* = 3.4, 9.1 Hz, 1H), 2.88 (s, 3H) 2.53 (m, 1H), 2.38 (m, 1H) 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 143.1, 138.8, 136.5, 133.0, 127.5, 119.1, 118.6, 105.0, 51.6, 48.8, 38.9, 30.8, –1.4; IR (film) 1702 cm^{-1}; MS (CI) 314.1685 (314.1683 calcd for $C_{17}H_{23}N_3OSi$, M + H^+). The enantiopurity was determined to be 93:7er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 200 nm, RT= 3.9 and 5.1 min).



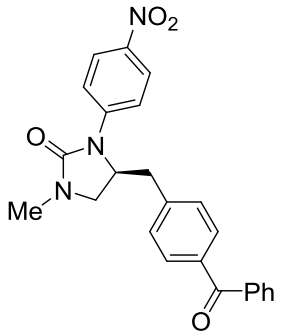
(–)-(4*S*)-1-Methyl-3-(4-nitrophenyl)-4-[4-(trifluoromethyl)benzyl]imidazolidin-2-one (2-41). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 4-bromobenzotrifluoride (0.40 mmol, 90.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), H_2O (0.40 mmol, 7 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (54.6 mg**,** 72%) as a bright yellow solid, mp 161–164 °C: $[\alpha]^{23}_D$ –75.1 (*c* 11.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.2 Hz, 2H), 7.78 (d, *J* = 9.3 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.64–4.58 (m, 1H), 3.51 (app. t, *J* = 9.0 Hz, 1H), 3.24 (dd, *J* = 3.1, 9.3 Hz, 1H), 3.17 (dd, *J* = 3.1, 9.3 Hz, 1H), 3.01 (dd, *J* = 8.6, 14.0 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 144.8, 142.1, 139.6, 129.6 (q, 65.2 Hz), 129.5, 125.8 (q, 3.81), 125.1, 123.9 (q, 272.0 Hz), 117.8, 53.2, 48.3, 37.5, 30.7; IR (film) 1708 cm^{-1}. MS (CI) 380.1211 (380.1217 calcd for $C_{18}H_{16}F_3N_3O_3$, M + H^+). The enantiopurity was determined to be 97:3 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 9.3 and 16.8 min).



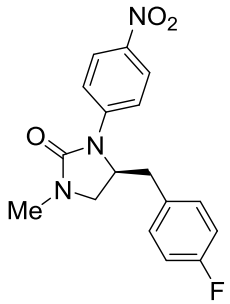
(–)-(4*S*)-1-Methyl-3-(4-nitrophenyl)-4-[3-(trifluoromethyl)benzyl]imidazolidin-2-one (2-42). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 3-bromobenzotrifluoride (0.40 mmol, 90.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), H_2O (0.40 mmol, 7 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (53.1 mg, 70%) as a bright yellow solid, mp 145–148 °C: $[\alpha]^{23}_D$ –64.1 (*c* 1.16, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.0 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.38 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 4.65–4.58 (m, 1H), 3.53 (app. t, *J* = 9.0 Hz, 1H), 3.24 (dd, *J* = 2.7, 9.2 Hz, 1H), 3.15 (dd, *J* = 3.5, 14.1 Hz, 1H), 2.93 (dd, *J* = 8.4, 14.0 Hz, 1H), 2.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 144.9, 142.1, 136.1, 132.7, 131.2 (q, *J* = 32.4 Hz), 129.4, 125.8 (q, *J* = 3.8 Hz), 125.1, 124.2 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 271.8 Hz), 117.8, 53.1, 48.4, 37.6, 30.7; IR (film) 1714 cm^{-1}. MS (CI) 380.1224 (380.1217 calcd for $C_{18}H_{16}F_3N_3O_3$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 7.7 and 13.0 min).



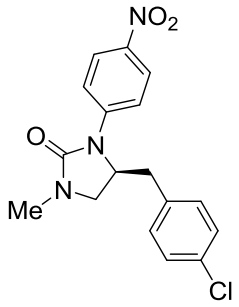
(–)-(4*S*)-1-Methyl-3-(4-nitrophenyl)-4-[2-(trifluoromethyl)benzyl]imidazolidin-2-one (2-43). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 2-bromobenzotrifluoride (0.40 mmol, 90.0 mg), using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), H_2O (0.40 mmol, 7 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (42.5 mg, 56%) as a bright yellow solid, mp 70–73 °C: $[\alpha]^{23}_D$ –98.7 (*c* 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.0 Hz, 2H), 7.72–7.64 (m, 3H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 4.72–4.64 (m, 1H), 3.43 (app. t, *J* = 9.0 Hz, 1H), 3.36 (dd, *J* = 5.1, 14.4 Hz, 1H), 3.20 (dd, *J* = 2.0, 9.3 Hz, 1H), 2.96 (dd, *J* = 9.0, 14.3 Hz, 1H), 2.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 145.1, 142.0, 134.4, 132.1, 129.2 (q, *J* = 30.0 Hz), 127.5, 126.6 (q, *J* = 5.7 Hz), 124.8, 124.4 (q, *J* = 272.3 Hz), 118.0, 53.1, 48.3, 35.0, 30.9 (one peak is missing due to incidental equivalence); IR (film) 1722 cm^{-1}. MS (CI) 380.1226 (380.1217 calcd for $C_{18}H_{16}F_3N_3O_3$, M + H^+). The enantiopurity was determined to be 91:9 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 7.9 and 12.5 min).



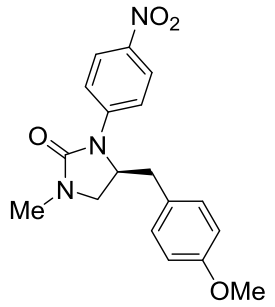
(–)-(4*S*)-4-(4-Benzoylbenzyl)-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-44). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 4-bromobenzophenone (0.40 mmol, 104.4 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), H_2O (0.40 mmol, 7 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (68.1 mg**,** 82%) as a bright yellow solid, mp 115–118 °C: $[\alpha]^{23}_D$ –53.7 (*c* 0.97, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.3 Hz, 2H), 7.80–7.72 (m, 6H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 4.65–4.58 (m, 1H), 3.50 (app. t, *J* = 9.0 Hz, 1H), 3.26 (dd, *J* = 3.1, 9.2 Hz, 1H), 3.18 (dd, *J* = 3.5, 14.0 Hz, 1H), 2.91 (dd, *J* = 8.8, 13.9 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 156.6, 145.0, 142.1, 140.3, 137.3, 136.6, 132.6, 130.6, 130.0, 129.2, 128.4, 125.1, 117.8, 53.2, 48.4, 37.8, 34.4, 30.8; IR (film) 1715, 1657 cm^{-1}. MS (CI) 416.1620 (416.1605 calcd for $C_{24}H_{21}N_3O_4$, M + H^+). The enantiopurity was determined to be 93:7 er by chiral HPLC analysis (ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 39.0 and 54.9 min.)



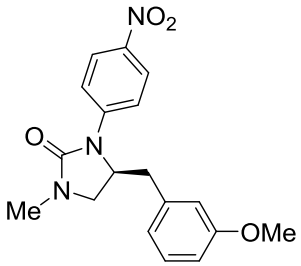
(–)-(4*S*)-4-(4-Fluorobenzyl)-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-45). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 4-bromofluorobenzene (0.40 mmol, 70.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), H_2O (0.40 mmol, 7 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (43.0 mg**,** 65%) as a bright yellow solid, mp 153–157 °C: $[\alpha]^{23}_D$ –75.4 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.3 Hz, 2H), 7.88 (d, *J* = 9.3 Hz, 2H), 7.14–7.08 (m, 2H), 7.01 (app. t, *J* = 8.6 Hz, 2H), 4.58–4.51 (m, 1H), 3.49 (app. t, *J* = 9.0 Hz, 1H), 3.24 (dd, *J* = 3.1, 9.2 Hz, 1H), 3.06 (dd, *J* = 3.3, 14.0 Hz, 1H), 2.86–2.75 (m, 1H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (d, *J* = 245.0 Hz), 156.6 145.0, 142.0, 131.1 (d, *J*= 3.5 Hz), 130.7 (d, *J* = 8.0 Hz), 125.1, 117.7, 115.8 (d, *J* = 21.3 Hz), 53.4, 48.2, 36.8, 30.7; IR (film) 1717 cm^{-1}. MS (CI) 330.1258 (330.1248 calcd for $C_{17}H_{16}FN_3O_3$, M + H^+). The enantiopurity was determined to be 97:3 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 12.0 and 22.7 min).



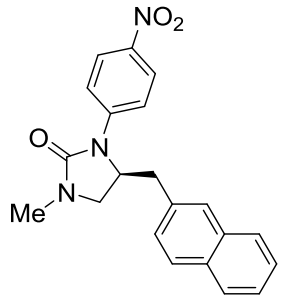
(–)-(4*S*)-4-(4-Chlorobenzyl)-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-46). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 4-bromochlorobenzene (0.40 mmol, 76.6 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), H_2O (0.40 mmol, 7 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (51.2 mg**,** 74%) as a bright yellow solid, mp 144–147 °C: $[\alpha]^{23}_D$ –72.9 (*c* 0.81, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.3 Hz, 2H), 7.78 (d, *J* = 9.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.57–4.50 (m, 1H), 3.48 (app. t, *J* = 9.0 Hz, 1H), 3.23 (dd, *J* = 3.1, 9.1 Hz, 1H), 3.08 (dd, *J* = 3.3, 14.0 Hz, 1H), 2.85–2.78 (m, 1H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 144.9, 142.1, 133.8, 133.3, 130.5, 129.0, 125.1, 117.7, 53.3, 48.2, 37.0, 34.4; IR (film) 1716 cm^{-1}. MS (CI) 346.0956 (346.0953 calcd for $C_{17}H_{16}ClN_3O_3$, M + H^+). The enantiopurity was determined to be 96:4 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 12.5 and 22.7 min).



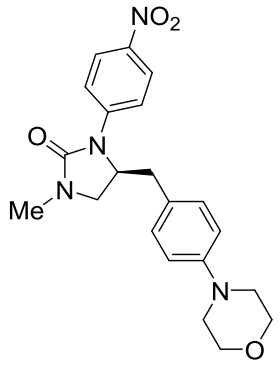
(–)-(4*S*)-4-(4-Methoxybenzyl)-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-49). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 4-bromoanisole (0.40 mmol, 74.8 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), TFA (0.08 mmol, 6 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (55.3 mg, 81%) as a bright yellow solid, mp 110–113 °C: $[\alpha]^{23}_{D}$ –71.3 (*c* 0.98, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.2 Hz, 2H), 7.79 (d, *J* = 9.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.52–4.48 (m, 1H), 3.77 (s, 3H), 3.46 (app. t, *J* = 8.9 Hz, 1H), 3.26 (dd, *J* = 3.2, 9.0 Hz, 1H), 3.04 (dd, *J* = 3.4, 14.1 Hz, 1H), 2.79 (s, 3H), 2.74 (dd, *J* = 8.9, 14.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 156.7, 145.2, 141.9, 130.2, 127.3, 125.0, 117.7, 114.3, 55.3, 53.7, 48.3, 36.8, 30.8; IR (film) 1717 cm^{-1}. MS (CI) 342.1457 (342.1448 calcd for $C_{18}H_{19}N_3O_4$, M + H^+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (chrialcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 14.1 and 25.9 min.)



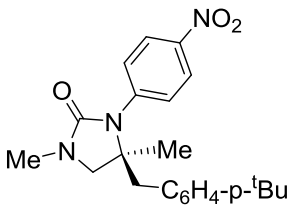
(–)-(4*S*)-4-(3-Methoxybenzyl)-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-50). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 3-bromoanisole (0.40 mmol, 74.8 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (51.2 mg, 75%) as a bright yellow solid, mp 110–114 °C: $[\alpha]^{23}_{D}$ –94.2 (*c* 0.73, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.1 Hz, 2H), 7.77 (d, *J* = 9.3 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.65 (s, 1H), 4.56–4.48 (m, 1H), 3.76 (s, 1H), 3.44 (app. t, *J* = 9.0 Hz, 1H), 3.26 (dd, *J* = 2.9, 9.2 Hz, 1H), 3.08 (dd, *J* = 3.3, 13.9 Hz, 1H), 2.79 (s, 3H), 2.73 (dd, *J* = 9.0, 13.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 156.7, 145.1, 141.9, 137.1, 129.9, 125.0, 121.4, 117.6, 115.4, 112.0, 55.2, 53.5, 48.4, 37.7, 30.8; IR (film) 1716 cm^{-1}. MS (CI) 342.1461 (342.1448 calcd for $C_{18}H_{19}N_3O_4$, M + H^+). The enantiopurity was determined to be 92:8 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 12.6 and 19.6 min).



(–)-(4*S*)-1-Methyl-4-(naphthalen-2-ylmethyl)-3-(4-nitrophenyl)imidazolidin-2-one (2-51). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 2-bromonaphthalene (0.40 mmol, 82.8 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (51.3 mg, 71%) as a bright yellow solid, mp 152–155 °C: $[\alpha]^{23}_{D}$ –116.7 (*c* 0.74, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.1 Hz, 2H), 7.86–7.78 (m, 5H), 7.62 (s, 1H), 7.54–7.46 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 1H), 4.68–4.61 (m, 1H), 3.46 (app. t, *J* = 9.2 Hz, 1H), 3.36–3.28 (m, 2H), 2.93 (dd, *J* = 9.3, 13.9 Hz, 1H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 145.1, 142.0, 133.4, 133.0, 132.4, 128.7, 128.0, 127.7, 127.4, 126.9, 126.5, 126.0, 125.0, 117.8, 53.6, 48.5, 37.9, 30.8; IR (film) 1715 cm^{-1}. MS (CI) 362.1507 (362.1499 calcd for $C_{21}H_{19}N_3O_3$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 9.4 and 17.4 min).

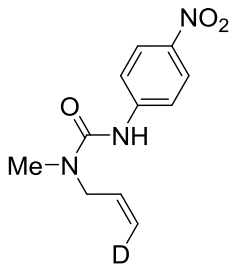


(–)-(4*S*)-1-Methyl-4-(4-morpholinobenzyl)-3-(4-nitrophenyl)imidazolidin-2-one (2-52). The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (0.20 mmol, 47.0 mg) and 4-(4-bromophenyl)morpholine (0.40 mmol, 96.8 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and (*S*)-Siphos-PE (0.012 mmol 6.1 mg), H_2O (0.40 mmol, 7 µL) as an additive, a reaction temperature of 115 °C and a reaction time of 18 h. This procedure afforded the title compound (63.4 mg, 80%) as a bright yellow solid, mp 125–129 °C: $[\alpha]^{23}_D$ –91.0 (*c* 0.97, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.2 Hz, 2H), 7.78 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.53–4.45 (m, 1H), 3.90–3.81 (m, 4H), 3.46 (app. t, *J* = 8.9 Hz, 1H), 3.27 (dd, *J* = 2.9, 9.2 Hz, 1H), 3.18–3.08 (m, 4H), 3.04 (dd, *J* = 3.2, 14.1 Hz, 1H), 2.81 (s, 3H), 2.72 (dd, *J* = 8.8, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 150.4, 145.2, 141.9, 130.0, 126.6, 125.0, 117.7, 115.9, 67.1, 53.8, 49.3, 48.4, 36.8, 30.8; IR (film) 1717 cm^{-1}. MS (CI) 397.1872 (397.1870 calcd for $C_{21}H_{24}N_4O_4$ $M+H^+$). The enantiopurity was determined to be 93:7 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 195 nm, RT= 25.7 and 33.0 min).



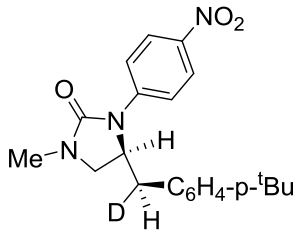
(+)-(4*S*)-4-[4-(*tert*-Butyl)benzyl]-1,4-dimethyl-3-(4-nitrophenyl)imidazolidin-2-one (2-54): The general procedure was employed for the coupling of 1-methyl-1-(2-methylallyl)-3-(4-nitrophenyl)urea (0.10 mmol, 24.9 mg) and 4-bromo-*tert*-butylbenzene (0.20 mmol, 42.6 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol, 3.0mg), a reaction temperature of 135 °C and a reaction time of 18 h. This procedure afforded the title compound (27.5 mg, 72%) as a yellow oil: $[\alpha]^{23}_{D}$ +70.2 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.1 Hz, 2H), 7.54 (d, *J* = 9.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 3.49 (d, *J* = 9.1 Hz, 1H), 3.11 (d, *J* = 13.5 Hz, 1H), 3.23 (d, *J* = 8.8 Hz, 1H), 2.81 (d, *J* = 14.4 Hz, 1H), 2.74 (s, 3H), 1.47, (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 150.2, 144.5, 144.3, 132.3, 129.7, 125.6, 125.4, 124.4, 61.5, 56.3, 44.2, 34.5, 313, 30.6, 25.1; IR (film) 1716 cm^{-1}; MS (CI) 382.2133 (382.2125 calcd for $C_{22}H_{27}N_3O_3$, M + H^+). The enantiopurity was determined to be 88:12 er by chiral HPLC analysis (ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 7.5 and 7.9 min.)

Deuterium Labeling Studies:



(*Z*)-1-(3-*d*-Allyl)-1-methyl-3-(4-nitrophenyl)urea (2-56):[19] A flame dried round bottom flask equipped with a stir bar was cooled to rt under a stream of N_2 and charged with *N*-methylallylamine (5.0 mmol, 0.47 mL) and Et_2O (10 mL). The resulting solution was cooled to –42 °C using a CO_2/CH_3CN bath and stirred for 5 min. A solution of *n*-BuLi in hexanes (3.12 mL, 1.6 M, 5 mmol) was added slowly and the resulting mixture was stirred at –42 °C for 20 min. A solution of *t*-BuLi in pentane (3.50 mL, 1.4 M, 5 mmol) was added slowly and the resulting solution was stirred at –42 °C for 30 min. The CO_2/CH_3CN bath was replaced with a brine/ice bath and the reaction mixture was allowed to slowly warm to room temperature as the ice melted. The bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was then cooled to –78 °C and D_2O (1.8 mL, 100 mmol) from freshly cracked ampules was slowly added. The resulting mixture was warmed to rt and stirred overnight. The reaction mixture was cooled to 0 °C, quenched with H_2O (2 mL) and transferred to a separatory funnel. The mixture was extracted with Et_2O (2 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and filtered to afford a solution of (*Z*)-*N*-methyl-3-deuterioallylamine. The solution was transferred to a round bottom flask and cooled to 0 °C. A solution of 4-nitrophenylisocyanate (3.63 mmol, 596 mg) in CH_2Cl_2 (4 mL) was slowly added and the resulting mixture was warmed to rt and stirred for 5 h. The

reaction mixture was then concentrated in vacuo and the crude product was purified by flash chromatography on silica gel to afford the title compound as (315 mg, 37% yield, >95% deuterium incorporation) a yellow solid, mp 80–83 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.2 Hz, 2H), 7.51 (d, *J* = 9.2 Hz, 2H), 6.88 (s, br, 1H), 5.87–5.82 (m, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 3.98 (d, *J* = 5.3 Hz, 2H), 3.03 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.5, 145.5, 142.3, 132.7, 125.0, 118.4, 117.2 (t, *J* = 23.8 Hz), 51.6, 34.8; IR (film) 1652 cm^{-1}. MS (CI) 237.1099 (237.1092 calcd for $C_{11}H_{12}DN_3O_3$, M + H^+).

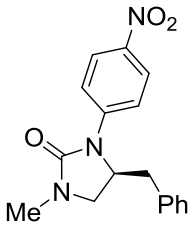


(–)-(1'*R*,4*S*)-1'-Deuterio-4-[4-(*tert*-butyl)benzyl]-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-57). The general procedure was employed for the coupling of (*Z*)-1-(3-*d*-allyl)-1-methyl-3-(4-nitrophenyl)urea (0.10 mmol, 23.6 mg) and 4-bromo-tert-butylbenzene (0.20 mmol, 42.6 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and (*S*)-Siphos-PE (0.006 mmol 3.0 mg), a reaction temperature of 115 °C, and a reaction time of 18 h. This procedure afforded the title compound (32.1 mg, 85%) as a bright yellow solid, mp 110–113 °C, $[\alpha]^{23}_{D}$ –104 (*c* 1.00, CH_2Cl_2). This material was judged to be a 7:1 mixture of diastereomers by ^{1}H NMR analysis. Data are for the major isomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 4.54–4.50 (m, 1H), 3.48 (app. t, *J* = 8.7 Hz, 1H), 3.29 (dd, *J* = 2.6, 9.0 Hz, 1H), 3.09 (d, *J* = 3.2 Hz, 0.12 H), 2.74 (d, *J* = 9.0 Hz, 0.88 H), 2.83 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.7, 150.3, 145.2, 141.9, 132.4, 128.8, 125.8, 125.0, 117.7, 53.7, 48.6, 37.0 (t, *J* = 17.7 Hz),

34.5, 31.3, 30.8; IR (film) 1717 cm^{-1}. MS (CI) 369.2034 (369.2031 calcd for $C_{21}H_{24}DN_3O_3$, M + H^+). The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 6.3 and 9.5 min). The 1'*R*,4*S* relative stereochemistry was assigned on the basis of comparison of NMR data to those obtained for a sample of the title compound prepared using a catalyst composed of $Pd_2(dba)_3$ and DPE-Phos, which has previously been shown to effect the *syn*-carboamination of *N*-allylurea derivatives.[4]

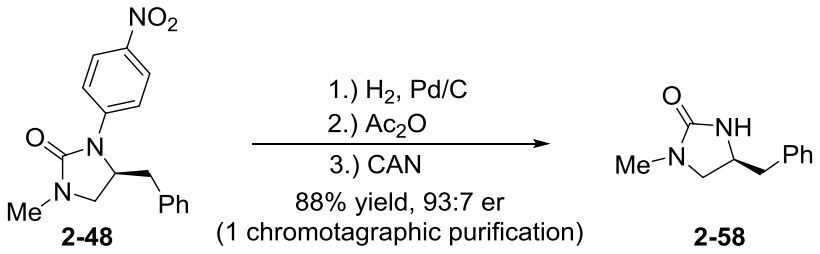
Deprotection of 2m and Assignment of Absolute Sterochemistry:

The absolute stereochemistry of the urea products was assigned by deprotection of **2-48** (prepared via Pd-catalyzed carboamination of **2-33**) to urea **2-58**. The optical rotation of **2-58** was of the same sign (–) as that of a separate sample of **2-58** prepared from L-phenylalanine as described below.



(–)-(4*S*)-4-Benzyl-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (2-48): The general procedure was employed for the coupling of 1-allyl-1-methyl-3-(4-nitrophenyl)urea (1.0 mmol, 235.2 mg) and bromobenzene (1.2 mmol, 188.4 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.02 mmol, 18.0 mg) and (*S*)-Siphos-PE (0.06 mmol, 30.0 mg), a reaction temperature of 115 °C, and a reaction time of 18 h. This procedure afforded the title compound (256.9 mg, 83%) as a bright yellow solid, mp 125–128 °C: $[\alpha]^{23}_D$ –108.9 (*c* 1.22, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.3 Hz, 2H), 7.80 (d, *J* = 9.3 Hz, 2H), 7.33 (t, *J* = 6.9 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 2H), 4.58–4.52

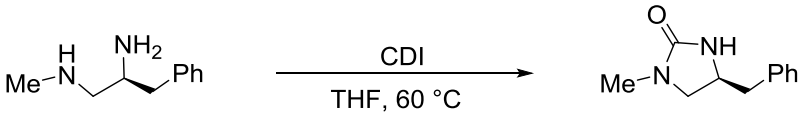
(m, 1H), 3.47 (app. t, *J* = 8.8 Hz, 1H), 3.28 (dd, *J* = 2.9, 9.2 Hz, 1H), 3.14 (dd, *J* = 3.2, 13.9 Hz, 1H), 2.83–2.77 (m, 1H), 2.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 145.1, 142.0, 135.5, 129.2, 128.9, 127.3, 125.0, 117.7, 53.7, 48.4, 37.7, 30.8; IR (film) 1717 cm^{-1}; MS (CI) 312.1347 (312.1343 calcd for $C_{17}H_{17}N_3O_3$, M + H^+). The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 15% IPA/Hexanes, 1.5 mL/min, λ 198 nm, RT= 10.5 and 17.1 min).



2-48 **2-58**

(–)-(4*S*)-4-Benzyl-1-methylimidazolidin-2-one (2-58). A glass microwave tube equipped with a stirbar was charged with 4-Benzyl-1-methyl-3-(4-nitrophenyl)imidazolidin-2-one (77.8 mg, 0.25 mmol,), 10% Pd/C (38.9 mg, 5% w/w Pd), ethyl acetate (2 mL) and methanol (1 mL). The tube was placed into a stainless steel bomb that was pressurized with H_2 to 50 psi and the reaction mixture was then stirred at rt for 12 h. The reaction vessel was then depressurized and the mixture was filtered through a pad of celite. The celite was washed with methanol (25 mL) and the combined organic solutions were concentrated in vacuo. The crude product from this reaction was dissolved in CH_2Cl_2 (0.7 mL) and transferred to a flame dried Schlenk tube equipped with a stir bar that had been cooled under a stream of nitrogen. Acetic anhydride (28 µL, 0.30 mmol) was added to the flask and the resulting solution was stirred at rt for 5 h. A solution of saturated aqueous Na_2CO_3 (5 mL) was added to the reaction vessel and the resulting mixture was transferred to a separatory funnel. The mixture was extracted with

CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product from this reaction was placed into a round bottom flask equipped with a stir bar and dissolved in CH_3CN (3.5 mL) and H_2O (0.70 mL). The mixture was cooled to 0 °C, stirred for 5 min, then ceric ammonium nitrate (1.13 mmol, 618.0 mg) was added in one portion. The resulting mixture was stirred at 0 °C for 25 min then saturated aqueous sodium sulfite (6 mL) was added. The mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL) then dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound (41.6 mg, 88% overall yield) as a brown oil, $[\alpha]^{23}_D$ –27.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.1 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.1 Hz, 2H), 4.82–4.52 (s, br, 1H), 3.85 (m, 1H), 3.47 (app. t, *J* = 8.6 Hz, 1H), 3.13 (dd, *J* = 6.1, 8.8 Hz, 1H), 2.81 (app. d, *J* = 7.1 Hz, 2H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 137.1, 129.0, 128.8, 126.9, 52.7, 51.1, 42.0, 30.5; IR (film) 1699 cm^{-1}; MS (CI) 191.1181 (191.1179 calcd for $C_{11}H_{14}N_2O$, M + H^+). The enantiopurity was determined to be 93:7 er by chiral HPLC analysis (Lux Amylose-2, 25 cm x 4.6 mm, 10% IPA/Hexanes, 1.0 mL/min, λ 210 nm, RT= 21.3 and 22.7 min).



(–)-(4*S*)-4-Benzyl-1-methylimidazolidin-2-one (2-60) A flame-dried round bottomed flask equipped with a stirbar was cooled under a stream of nitrogen and charged with (*S*)-*N*^{1}-methyl-3-phenylpropane-1,2-diamine[11] (100.0 mg, 0.60 mmol) and THF (1 mL).

Solid CDI (90.0 mg, 0.56 mmol) was added and the resulting mixture was heated to 60 °C with stirring for 12 h. The reaction mixture was then cooled to rt and the solvent was removed in vacuo. The product was purified by flash chromatography on silica gel to afford the title compound (32.0 mg, 30% yield); $[\alpha]^{23}_{D}$ –37.2 (*c* 0.90, CH_2Cl_2). The spectroscopic properties of this compound were identical to that of compound **6.** The enantiopurity was determined to be 98:2 er by chiral HPLC analysis (Lux Amylose-2, 25 cm x 4.6 mm, 10% IPA/Hexanes, 1.0 mL/min, λ 210 nm, RT= 21.3 and 22.7 min).

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(10) The minor diastereomer most likely arises from reversible b-hydride elimination/re-insertion pathways. See: Hay, M.B.; Wolfe, J.P. *J. Am. Chem. Soc*. **2005**, *127*, 16468-16476.

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(12) The observation that deuterated urea substrate **2-56** is converted to a 7:1 mixture of diastereomers whereas the analogous deuterated carbamate is transformed with >20:1d.r.[5] is consistent with relatively fast reductive elimination in the carbamate system as compared to the urea. See: (a) Ref. 11 (b) Bertrand, M.B.; Neukom, J.D.; Wolfe, J.P. *J. Org. Chem.* **2008**, *73*, 8851 – 8860.

(13) Our estimation of the relative electron-richness of the N-Bocpentenylamine versus the p-nitrophenyl urea are based on a comparison of pKa values for N^1,N^1-dimethyl-N2-(p-nitrophenyl) urea (pKa=15.9, DMSO) versus N-Boc-benzylamine (pKa=22.9, DMSO); the stronger acid possesses a less electron rich nitrogen atom. See: (a) Cheng, J.P.; Xian, M.; Wang, K.; Zhu, X.; Yin, Z.; Wang, P.G. *J. Am. Chem. Soc.* **1998**, *120*, 10266 – 10267; (b) Mita, T.; Chen, J.; Sugawara, M.; Sato, Y. *Angew. Chem. Int. Ed*. **2011**, *50*, 1393 –1396.

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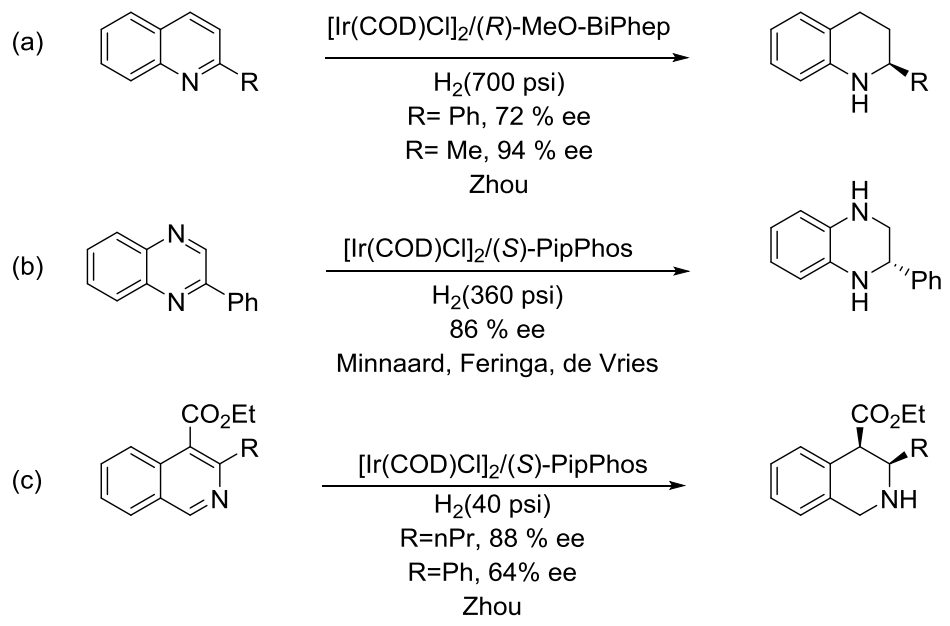
Chapter 3

Enantioselective Synthesis of Tetrahydroquinolines, Tetrahydroquinoxalines, and Tetrahydroisoquinolines via Pd-Catalyzed Alkene Carboamination Reactions

3.1 Introduction

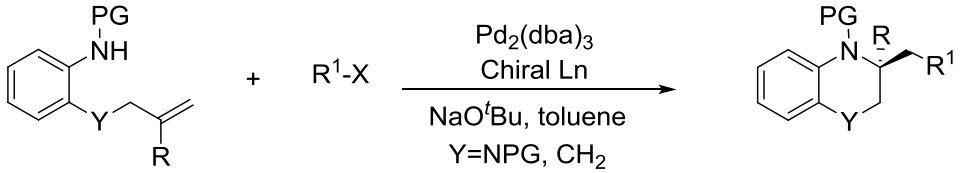
Benzo-fused heterocycles are prominent in a variety of natural products and biologically active compounds.[1] As such, many groups have attempted to construct molecules of this nature in an enantioselective fashion. Typically, enantioenriched benzo-fused heterocycles are synthesized via the asymmetric hydrogenation of an aromatic heterocycle (Figure 3.1).[2,3] However, a major drawback to this methodology is that no new carbon-heteroatom or carbon-carbon bonds are formed in the reaction, which inhibits the facile access to a library of compounds. Also, these hydrogenations require high pressure,[4] which is not suitable for simple reaction set up in a typical laboratory environment. Other methods to access these benzo-fused heterocycles include asymmetric hydroamination reactions,[4] asymmetric imine addition reactions,[5] C–H functionalizations,[6] asymmetric alkylations,[7] asymmetric N-allylations,[8] and asymmetric N-arylations.[9] However, these transformations in most cases are limited to the formation of tertiary carbon stereocenters. The use of asymmetric catalysis to generate heterocycles bearing quaternary stereocenters is very rare.[5b,

Figure 3.1 Typical synthesis of benzo-fused heterocycles



We envisioned forming a variety of benzo-fused heterocycles through our recently developed asymmetric Pd-catalyzed carboamination reactions. [10] Moreover, we wanted to demonstrate the utility of this methodology to form quaternary stereocenters through the use of substrates bearing 1,1-disubstituted alkenes (Scheme 3.1).[11] This chapter describes the enantioselective synthesis of tetrahydroquinolines, tetrahydroquinoxalines, and tetrahydroisoquinolines with a single catalyst system. The reactions reported herein are the first examples of highly enantioselective (>95:5 e.r.) transition metal catalyzed C-N bond formation involving addition to 1,1-disubstituted alkenes.[12]

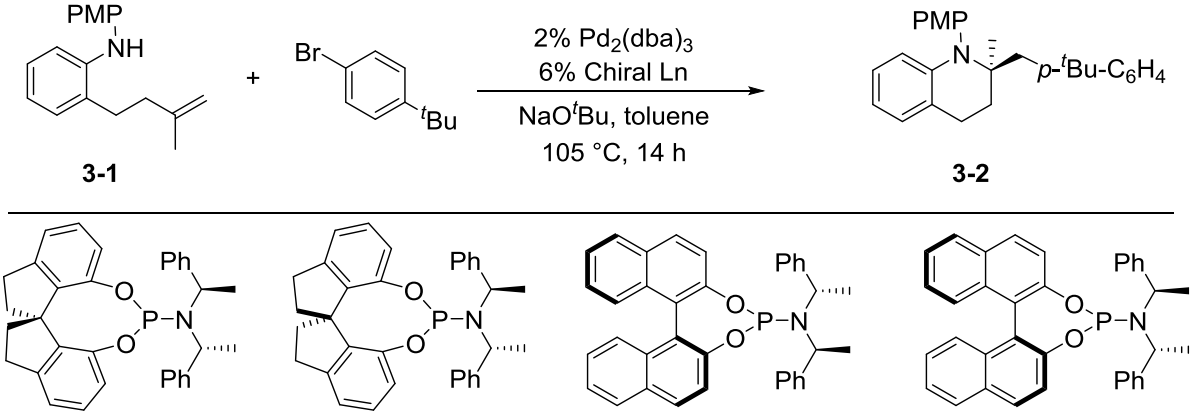
Scheme 3.1 Envisioned route to access enantioenriched benzo-fused heterocycles



3.2 Initial Optimization of Reaction Conditions and Substrates

To initiate our studies we examined the feasibility of the reaction of substrate **3-1** and a catalyst composed of $Pd_2(dba)_3$ and (*S*)-Siphos-PE (**3-L1**). Previous attempts by our group to cyclize onto 1,1-disubstituted alkenes led to diminished enantioselectivity.[10b] Gratifyingly, the reaction of **3-1** under these conditions led to the formation of product **3-2** in 86% yield and 92:8 er (Table 3.1). The use of a variety of other ligands, palladium sources, bases, or solvents did not improve the outcome of the reaction.

Table 3.1 Initial ligand screen with substrate **3-1**[a]



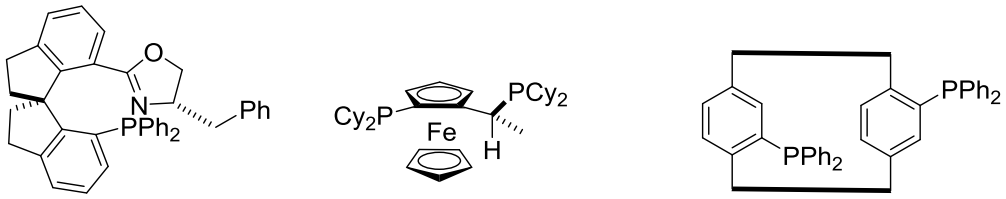
3-1 **3-2**

3-L1
86 % yield, 92:8 er

3-L3
84% yield, 68:32 er

3-L4
78 % yield, 59:41 er

3-L5
84% yield, 54:46 er



3-L6
65% yield, 83:17er

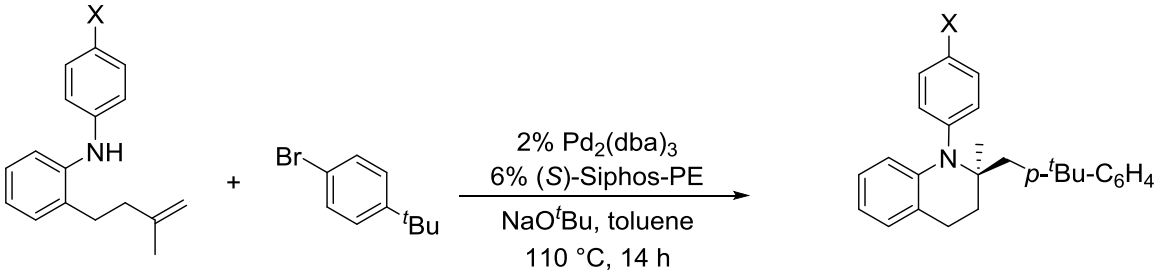
3-L7
25% yield, 62:38 er

3-L8
86% yield, 64:38 er

[a] Conditions: Reactions were conducted on a 0.10 mmol scale using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.2 M),105 °C, 12-14 h. Yields and enantiomeric ratios refer to isolated compound **3-2.**

In our aforementioned carboamination methodology to afford imidazolidin-2-ones,[10b] we noted that the use of a more electron poor N-allyl urea substrate afforded products in better enantioselectivities than the analogous electron rich N-allyl urea substrates. Thus, in order to determine the correlation between nitrogen nucleophilicity and asymmetric induction in this system, substrates **3-1** to **3-7** were synthesized and subjected to the reaction conditions. Interestingly, enhancing the nitrogen nucleophilicity was beneficial to the enantioselectivity of the tetrahydroquinoline products. As such it was shown that the highest enantioinduction was observed from the reaction of **3-7** bearing a *p*-NMe_2 group. Heating the reaction of substrate **3-7** up to 125 °C afforded the product in 95% yield and with no change in enantioselectivity (entry 5).

Table 3.2 Electronic effects[a]



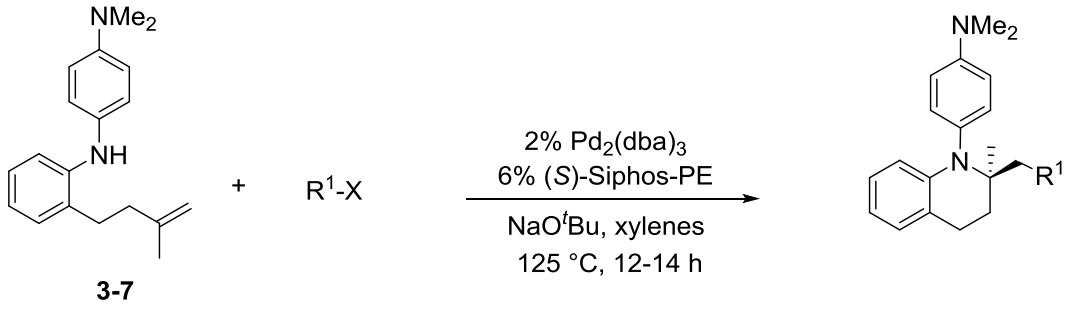
Entry	X	Product	yield[b]	er
1	CN (**3-3**)	**3-4**	51%	62:38
2	^{t}Bu (**3-5**)	**3-6**	93%	87:13
3	OMe (**3-1**)	**3-2**	86%	92:8
4	NMe_2 (**3-7**)	**3-8**	60%	95:5
5[c]	NMe_2 (**3-7**)	**3-8**	95%	95:5

[a] Conditions: Reactions were conducted on a 0.10 mmol scale using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.2 M),110 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds. [C] Reaction was heated to 125 °C.

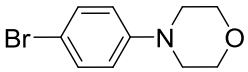
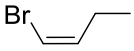
3.3 Electrophile and Substrate Scope for the Synthesis of Tetrahydroquinolines, Tetrahydroquinoxalines, and Tetrahydroisoquinolines

In order to test the versatility of this transformation, a series of aryl and alkenyl halides were subjected to the reaction conditions with substrate **3-7** (Table 3.3). Electron rich aryl halides (entries 1-3), electron poor aryl halides (entries 4-6), and a variety of alkenyl bromides (entries 7-9) all afforded products in good yield and er.

Table 3.3 Enantioselective synthesis of tetrahydroquinolines with **3-7**[a]



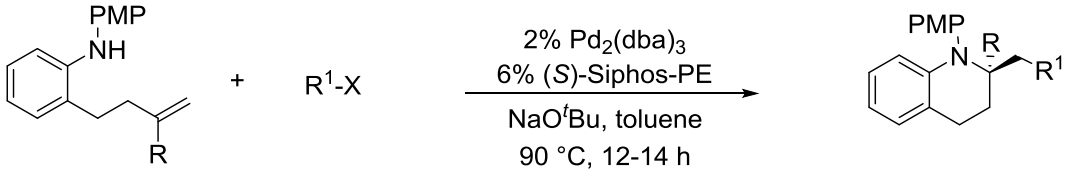
3-7

Entry	R-X	Product	yield[b]	er
1	*p*-^{t}Bu-C_6H_4-Br	**3-8**	95%	95:5
2		**3-12**	87%	95:5
3	*p*-MeO-C_6H_4-Br	**3-13**	88%	95:5
4	*p*-CF_3-C_6H_4-Br	**3-14**	89%	94:6
5	*m*-CF_3-C_6H_4-Br	**3-15**	94%	92:8
6	*p*-PhC(O)-C_6H_4-Br	**3-16**	82%	96:4
7		**3-17**	82%	93:7
8		**3-18**	65%	97:3
9		**3-19**	74%	96:4

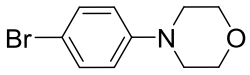
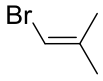
[a] Conditions: Reactions were conducted on a 0.20 mmol scale using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, xylenes (0.2 M),125 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds.

We also subjected substrate **3-1** to a variety of aryl and alkenyl halides as well. This reaction worked well for electron poor and electron rich aryl halides, as well as for alkenyl bromides (entries 1-8). Conducting the reaction on a larger scale using half of the standard catalyst loading afforded product **3-22** in a comparable yield and er to the small scale reaction (entry 6). The presence of substituents larger than a methyl group on the alkene had an adverse effect on the reaction outcome (entries 9-10).

Table 3.4 Enantioselective synthesis of tetrahydroquinolines[a]



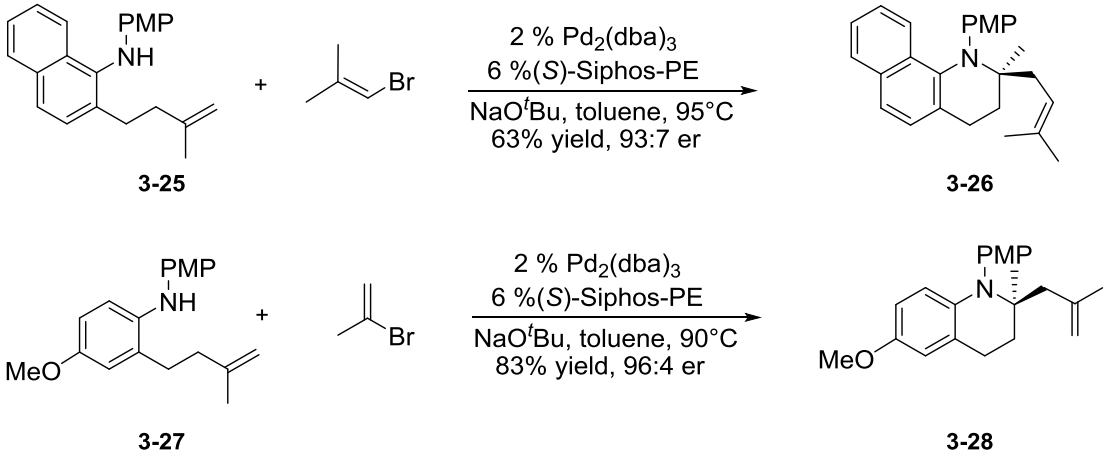
3-1: Ar=PMP, R=Me; **3-9:** Ar=PMP, R=Et
3-10: Ar=PMP, R=Ph; **3-11:** Ar=PMP, R=^{i}Pr

Entry	R-X	Substrate	Product	yield[b]	er
1	*p*-^{t}Bu-C_6H_4-Br	**3-1**	**3-2**	86%	92:8
2	*p*-^{t}Bu-C_6H_4-I	**3-1**	**3-2**	85%	92:8
3		**3-1**	**3-20**	88%	94:6
4	*p*-Cl-C_6H_4-Br	**3-1**	**3-21**	81%	89:11
5	*p*-PhC(O)-C_6H_4-Br	**3-1**	**3-22**	82%	95:5
6[c]	*p*-PhC(O)-C_6H_4-Br	**3-1**	**3-22**	77%	94:6
7		**3-1**	**3-23**	96%	95:5
8		**3-1**	**3-24**	83%	96:4
9	Ph-Br	**3-9**	**3-25**	86%	75:25
10	Ph-Br	**3-10**	-	NR	N/A
11	Ph-Br	**3-11**	-	NR	N/A

[a] Conditions: Reactions were conducted on a 0.20 mmol scale using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.2 M), 90 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds. [C] Reaction was ran on 1.0 mmol scale with half of the catalyst loading.

To further demonstrate the robust nature of these reactions, we wanted to form these carboamination products from compounds bearing differently substituted backbones. As such, the naphthyl ring fused substrate **3-25** and the methoxy substituted substrate **3-27** were subjected to the reaction conditions noted in Scheme 3.2. These reactions afforded their respective products in 63% yield and 93:7 er (**3-26**) and 83% yield and 96:4 er (**3-28**).

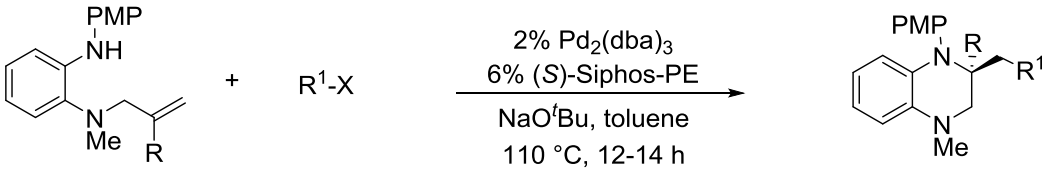
Scheme 3.2 Different substrate backbones



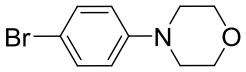
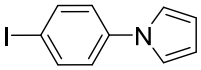
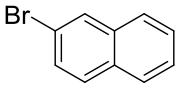
To further investigate the utility of this reaction, we wanted to synthesize a product containing multiple heteroatoms. As such we synthesized substrate **3-29** (Table 3.5) and subjected it to the same catalyst system and conditions that were used for the tetrahydroquinoline products. This reaction worked well with a variety of aryl halides (entries 1-5) affording an array of tetrahydroquinoxaline products in good yields and enantioselectivities. The reaction also worked well with an alkenyl bromide (entry 6) affording **3-37** in 74% and 98:2 er. Substrate **3-30**, bearing an $–CH_2OBn$ substituted alkene, afforded product **3-38** in similar yield and enantioselectivity as compared to **3-29.** However, the phenyl substitutued alkene substrate **3-31** proved to be unreactive. A

variety of protecting groups were tested on the non-cyclizing nitrogen including Boc, Bn, Et, and PMP, all of which led to lower yields and enantioselectivities in the observed reaction products.

Table 3.5 Enantioselective synthesis of tetrahydroquinoxalines[a]



3-29: R=Me
3-30: R=CH_2OBn
3-31: R=Ph

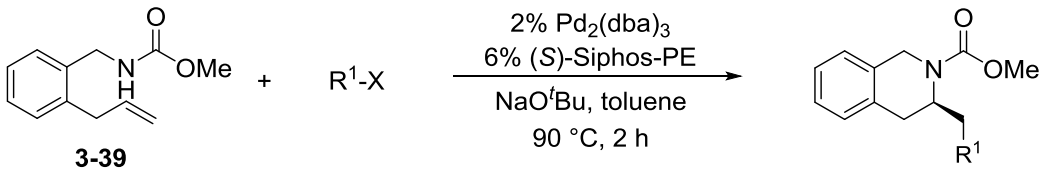
Entry	R-X	Substrate	Product	yield[b]	er
1	Ph-Br	**3-29**	**3-32**	79%	97:3
2	*p*-PhC(O)-C_6H_4-Br	**3-29**	**3-33**	78%	96:4
3		**3-29**	**3-34**	82%	96:4
4[c]		**3-29**	**3-35**	70%	93:7
5		**3-29**	**3-36**	84%	93:7
6		**3-29**	**3-37**	74%	98:2
7	Ph-Br	**3-30**	**3-38**	79%	96:4
8	Ph-Br	**3-31**	-	NR	N/A

[a] Conditions: Reactions were conducted on a 0.20 mmol scale using 1.0 equiv substrate, 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.2 M), 110 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds. [C] Reaction was conducted at 120 °C in xylenes.

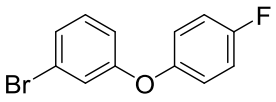
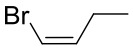
We wanted to further demonstrate the utility of these reactions by forming tetrahydroisoquinoline products. However, initial attempts to access these products by cyclizing onto 1,1-disubstituted alkenes proved unfruitful. However, with the use of a methyl carbamate protecting group[13] we were able to afford tetrahydroisoquinoline products with tertiary stereocenters in moderate yields and good enantioselectivities

(Table 3.6). The use of other groups on the cyclizing nitrogen such as PMP, Ac, Boc, Cbz, and a variety of other carbamates afforded either no product or lower yields and enantioselectivities for the corresponding products.

Table 3.6 Enantioselective synthesis of tetrahydroisoquinolines[a]



3-39

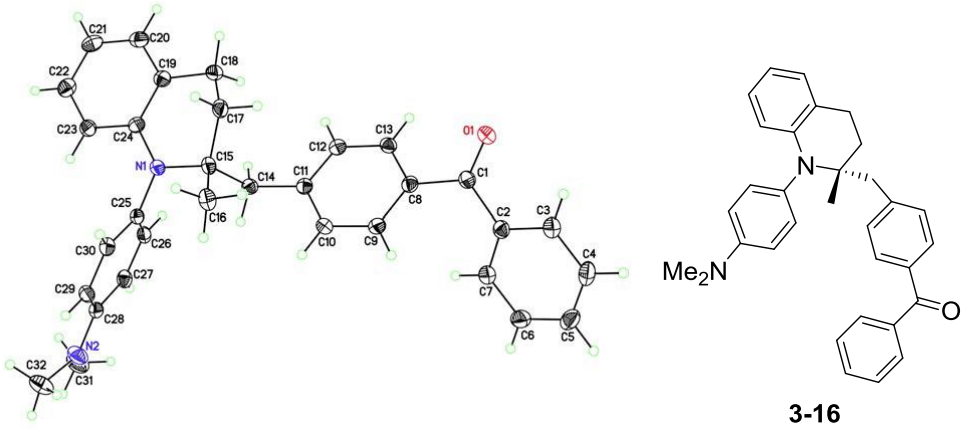
Entry	R-X	Product	yield[b]	er
1	*p*-MeO-C_6H_4-Br	**3-40**	51%	93:7
2	*p*-MeO-C_6H_4-I	**3-40**	52%	93:7
3	*o*-MeO-C_6H_4-I	**3-41**	42%	80:20
4	*p*-CF_3-C_6H_4-Br	**3-42**	72%	93:7
5		**3-43**	61%	93:7
6		**3-44**	56%	93:7
7[c]		**3-44**	55%	94:6
8	Ph-Br	**3-45**	69%	94:6
9[c]	Ph-Br	**3-45**	64%	95:5

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 1.2 equiv Ar-Br, 1.2 equiv NaO*t*Bu, toluene (0.125 M), 90 °C, 2 h. [b]Yields and enantiomeric ratios refer to isolated compounds. [C] Reactions was conducted at 70 °C for 12 h.

3.4 Assignment of Absolute Configuration

The absolute stereochemistry of product **3-16** was established by single crystal x-ray analysis as shown below. The stereochemistry of all other products was assigned based on analogy to **3-16**.

Figure 3.2 X-ray crystal structure of **3-16**



3.5 Conclusions

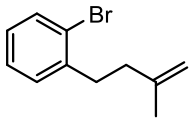
In conclusion, we developed an enantioselective synthesis of three separate classes of molecules: tetrahydroquinolines, tetrahydroquinoxalines, and tetrahydroisoquinolines. This methodology was carried out using a single catalyst system composed of $Pd_2(dba)_3$/(*S*)-Siphos-PE, which afforded good enantioselectivities for all three of the benzo-fused heterocycles that were synthesized. The work in this chapter not only shows the utility of enantioselective carboamination reactions, but it also offers a good alternative to the synthesis of benzo-fused heterocycles compared to more conventional means such as hydrogenation. Lastly, the reactions displayed here in chapter 3 are rare examples of highly enantioselective addition reactions between 1,1-disubstituted alkenes and amine nucleophiles.

The work in this chapter was published in Chemical Science.[14]

3.6 Experimental

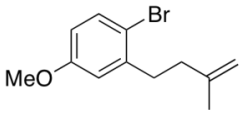
General: Reactions were carried out under nitrogen in flame-dried glassware.

Tris(dibenzylideneacetone)dipalladium and (*S*)-Siphos-PE were purchased from Strem Chemical Co. and used without further purification. 2-Allylbenzonitrile was prepared according to a slight modification of a literature procedure (BuMgCl was used in place of BuMgBr).[15] (*Z*)-1-bromobut-1-ene was synthesized according to a published procedure.[16] All other reagents including all aryl and alkenyl bromides were purchased from commercial sources and used as received unless otherwise noted. Xylenes were purified by distillation over CaH_2 prior to use in reactions. Methylene chloride and toluene were purified using a GlassContour solvent system. All yields refer to isolated compounds that are estimated to be $\geq$95% pure as judged by ^{1}H NMR or GC analysis. The yields reported herein describe the result of a single experiment, whereas yields reported chapter 3 describe the average of two or more runs, and the two may differ.

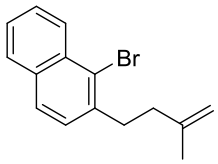


1-Bromo-2-(3-methylbut-3-en-1-yl)benzene (3-S1a): A flame-dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen. 2-bromobenzyl bromide (1.25 g, 5.0 mmol), and THF (5 mL) were added to the flask and the resulting solution was cooled to 0 °C. 2-methylallylmagnesium chloride (20 mL, 10 mmol, 0.5 M solution in THF) was slowly added and the resulting mixture was moved into an oil bath and heated to 40 °C for 1.5 h. The mixture was then cooled to rt and quenched with 4 mL of 2M H_2SO_4. Water (5 mL) and ether (15 mL) were added and the mixture was transferred to a separatory funnel. The layers were separated, the aqueous layer was extracted with diethyl ether (3x15 mL), and the organic layers were then combined, dried over anhydrous sodium sulfate, and concentrated in vacuo. The product was

purified via flash chromatography on silica gel using hexanes as the eluent to afford 1.06 g (95%) of the title compound as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1 H), 7.25–7.21 (m, 1 H), 7.08–7.02 (m, 1 H), 4.79 (s, 1 H), 4.76 (s, 1 H), 2.91–2.86 (m, 2 H), 2.32 (t, *J* = 8.6 Hz, 2 H), 2.81 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 145.1; 141.5; 132.9; 130.36; 127.7; 127.5; 124.6; 110.7; 38.1; 34.9; 22.7; IR (film) 2933, 1648, 1439 cm^{-1}**.**

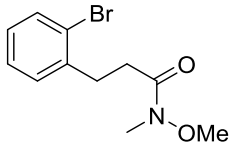


1-Bromo-4-methoxy-2-(3-methylbut-3-en-1-yl)benzene (3-S1b): The conversion of 2-bromo-5-methoxybenzyl bromide (1.40 g, 5.0 mmol) was accomplished using a procedure analogous to that described above for the preparation of **S1b** except using 2.5 equiv of 2-methylallylmagnesium chloride. This procedure afforded 1.15 g (90%) of the title compound as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 3.1 Hz, 1 H), 6.62 (dd, *J* = 3.1, 8.7 Hz, 1 H), 4.77 (s, 1 H), 4.75 (s, 1 H), 3.78 (s, 3 H), 2.83–2.78 (m, 2 H), 2.29 (t, *J* = 8.5 Hz, 2 H), 1.79 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.1, 145.3, 142.6, 133.4, 116.1, 115.0, 113.2, 110.6, 55.6, 38.0, 35.1, 22.7; IR (film) 2933, 1571, 1471 cm^{-1}.



1-Bromo-2-(3-methylbut-3-en-1-yl)naphthalene (3-S1c): The conversion of 1-bromo-2-(bromomethyl)naphthalene (0.60 g, 2.0 mmol) was accomplished using a procedure

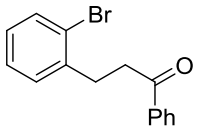
analogous to that described above for the preparation of **S1a** except using 2.5 equiv of 2-methylallylmagnesium chloride and a reaction temperature of 45 °C instead of 40 °C for the heated segment of the reaction. This procedure afforded 1.15 g (80%) of the title compound as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.5 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.3 Hz, 1 H), 7.58 (t, *J* = 7.0 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.3 Hz, 1 H), 4.78 (d, *J* = 5.1 Hz, 2 H), 3.12 (t, *J* = 8.8 Hz, 2 H), 2.39 (t, *J* = 8.9 Hz, 2 H), 1.85 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 145.4, 139.8, 133.4, 132.8, 128.19, 128.18, 127.7, 127.5, 127.4, 126.0, 123.8, 110.7, 38.3, 36.2, 22.8; IR (film) 2916, 1603, 1494 cm^{-1}.



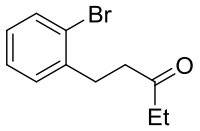
3-(2-bromophenyl)-N-methoxy-N-methylpropanamide: According to a literature prodecure,[17] a round bottom flask was equipped with a stirbar and charged with 3-(2-bromophenyl)propionic acid (4.00 g, 17.5 mmol), N,O-dimethylhydroxylamine hydrochloride (2.90 g, 29.7 mmol), THF (35 mL, 0.5 M), water (35 mL, 0.5 M), and aqueous 1 M NaOH (3 mL).). A solution of EDCI (8.39 g, 43.8 mmol) and 1 M NaOH (7 mL) in water (117 mL) was then added dropwise over 20 min. After the addition was complete, 1 M NaOH (5.5 mL) was added to raise the pH of the solution to 4.5 and the mixture was then stirred at rt for 8 h. The reaction mixture was then saturated with solid sodium chloride, transferred to a separatory funnel, and extracted with ethyl acetate (5 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash

chromatography on silica gel to afford the title compound as a clear oil (4.49 g, 94%).[1]H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 1 H), 7.29 (d, *J* = 7.3 Hz, 1 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.07 (t, *J* = 7.3 Hz, 1 H), 3.63 (s, 3 H), 3.18 (s, 3 H), 3.07 (t, *J* = 7.6 Hz, 2 H), 2.76 (t, *J* = 7.3 Hz, 2 H); [13]C NMR (125 MHz, $CDCl_3$) δ173.4, 140.6, 132.9, 130.9, 128.0, 127.6, 124.4, 61.3, 32.1, 32.0, 31.3; This compounds properties were identical to that as stated in the literature.[17]

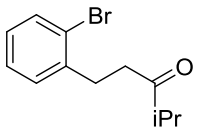
General procedure A: addition of grignard to 3-(2-bromophenyl)-N-methoxy-N-methylpropanamide. A flame dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with 3-(2-bromophenyl)-N-methoxy-N-methylpropanamide (1.0 equiv.). Then diethyl ether (0.40 M) was added to the flask and it was cooled to 0 °C. The grignard reagent (1.50 equiv.) was added dropwise and the reaction was allowed to slowly warm to room temperature and stir for 5 hours. The reaction mixture was then cooled back to 0 °C and it was quenched with saturated ammonium chloride (1mL/mmol substrate) and then water (5mL/mmol substrate) was added. This mixture was transferred to a separatory funnel and extracted with EtOAc. The combined organic layers were dried with sodium sulfate and concentrated in vacuo. The crude products were purified by flash chromatography on silica gel.



3-(2-bromophenyl)-1-phenylpropan-1-one (3-S2a): General procedure A was used for the reaction of 3-(2-bromophenyl)-N-methoxy-N-methylpropanamide (2.72 g, 10 mmol), and phenylmagnesium bromide (1 M THF, 15 mL). This procedure afforded 1.92 grams (66%) of the title product as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2 H), 7.57-7.52 (m, 2H), 7.45 (t, *J* = 7.8 Hz, 2 H), 7.31 (d, *J* = 6.9 Hz, 1 H), 7.24 (t, *J* = 8.1 Hz, 1 H), 7.07 (t, *J* = 7.3 Hz, 1 H), 2.82 (t, *J* = 7.3 Hz, 2 H), 2.45 (t, *J* = 7.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 140.6, 136.8, 133.2, 132.9, 130.9, 128.7, 128.1, 128.0, 127.7, 124.4, 38.7, 30.1. This compounds properties were identical to that as stated in the literature.[18]

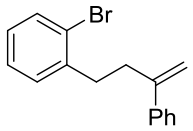


1-(2-bromophenyl)pentan-3-one (3-S2b): General procedure A was used for the reaction of 3-(2-bromophenyl)-N-methoxy-N-methylpropanamide (1.10 g, 4.04mmol), and ethylmagnesium bromide (3 M THF, 2.02 mL). This procedure afforded 775 mgs (80%) of the title product as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1 H), 7.21-7.16 (m, 2 H), 7.01 (t, *J* = 8.0 Hz, 1 H), 2.97 (t, *J* = 7.7 Hz, 2 H), 2.70 (t, *J* = 7.8 Hz, 2 H), 2.48 (q, *J* = 7.3 Hz, 2 H), 1.01 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ210.0, 140.3, 132.7, 130.5, 127.8, 127.5, 124.1, 41.9, 35.9, 30.3, 7.7; IR (film) 2973, 2936, 1711 cm^{-1}.

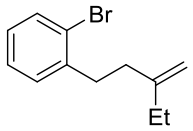


1-(2-bromophenyl)-4-methylpentan-3-one (3-S2c): General procedure A was used for the reaction of 3-(2-bromophenyl)-N-methoxy-N-methylpropanamide (2.72 g, 10mmol), and isopropylmagnesium chloride (2 M THF, 7.50 mL). This procedure afforded 625 mgs (25%) of the title product as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1 H), 7.24-7.19 (m, 2 H), 7.05 (t, *J* = 8.2 Hz, 1 H), 3.00 (t, *J* = 7.5 Hz, 2 H), 2.77 (t, *J* = 7.7 Hz, 2 H), 2.57 (sep., *J* = 7.0 Hz, 1 H), 1.06 (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ213.4, 140.6, 132.8, 130.7, 127.9, 127.5, 124.2, 41.0, 40.0, 30.5, 18.1; IR (film) 2967, 2932, 1708 cm^{-1}.

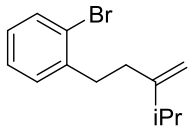
General procedure B: wittig reaction of ketones. A flame dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with methyltriphenylphosphonium bromide (1.4 equiv.). Then THF (0.15 M) was added to the flask and it was cooled to 0 °C. Potassium tert-butoxide (1.4 equiv.) was then added all at once and the mixture was allowed to stir at 0 °C for 45 minutes. To this mixture was added the appropriate ketone from above (1.0 equiv.) slowly in a solution of THF (0.65 M). The reaction mixture was then allowed to slowly warm to room temperature and stir for 16 hours. After 16 hours the reaction was concentrated in vacuo and then filtered through celite with hexanes. The filtrate was then concentrated in vacuo and the crude product was purified by flash chromatography on silica gel.



1-bromo-2-(3-phenylbut-3-en-1-yl)benzene (3-S1d): General procedure A was used for the reaction of methyltriphenylphosphonium bromide (3.31 g, 9.28mmol), KO^{t}Bu (1.04 g, 9.28mmol), and 3-(2-bromophenyl)-1-phenylpropan-1-one (1.92 g, 6.63mmol). This procedure afforded 1.06 grams (56%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 2 H), 7.34 (t, *J* = 6.3 Hz, 2 H), 7.30–7.13 (m, 3H), 7.04 (t, *J* = 8.0 Hz, 1 H), 5.31 (s, 1 H), 5.08 (s, 1 H), 2.91-2.83 (m, 2 H), 2.82-2.76 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ147.6, 141.2, 140.9, 132.8, 130.6, 128.4, 127.7, 127.5, 127.4, 126.2, 124.4, 112.9, 35.5, 35.4. This compounds properties were identical to that as stated in the literature.[18]



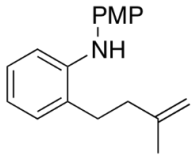
1-bromo-2-(3-methylenepentyl)benzene (3-S1e): General procedure A was used for the reaction of methyltriphenylphosphonium bromide (620 mgs, 1.73mmol), KO^{t}Bu (194 mgs, 1.73mmol), and 1-(2-bromophenyl)pentan-3-one (300 mgs, 1.24mmol). This procedure afforded 163 mgs (55%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1 H), 7.23 (d, *J* = 4.7 Hz, 2 H), 7.08-7.04 (m, 1 H), 4.80 (s, 2 H), 2.89 (t, *J* = 8.2 Hz, 2 H), 2.35 (t, *J* = 8.6 Hz, 2 H), 2.13 (q, *J* = 7.4 Hz, 2 H), 1.08 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ150.7, 141.6, 132.8, 130.3, 127.6, 127.4, 124.4, 108.3, 36.4, 35.1, 29.0, 12.4; IR (film) 3024, 2920, 1494 cm^{-1}.



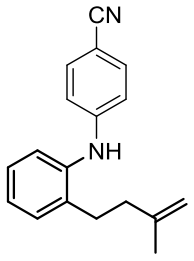
1-bromo-2-(4-methyl-3-methylenepentyl)benzene (3-S1e): General procedure A was used for the reaction of methyltriphenylphosphonium bromide (1.19 g, 3.34mmol), KO^{t}Bu (774 mgs, 3.34mmol), and 1-(2-bromophenyl)-4-methylpentan-3-one (610 mgs, 2.40mmol). This procedure afforded 230 mgs (38%) of the title compound as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1 H), 7.25 (d, *J* = 4.4 Hz, 2 H), 7.09-7.05 (m, 1 H), 4.86 (s, 1 H), 4.81 (s, 1 H), 2.89 (t, *J* = 8.2 Hz, 2 H), 2.37-2.31 (m, 3 H), 1.10 (d, *J* = 7.0 Hz, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.2, 141.7, 132.8, 130.3, 127.6, 127.4, 124.4, 107.0, 35.4, 34.5, 34.0, 21.9; IR (film) 2959, 2927, 1470 cm^{-1}.

General procedure C: synthesis of 2-(3-methylbut-3-en-1-yl)aniline substrates. A flame dried Schlenk flask equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (0.75 mol %), XPhos (2.25 mol %), 1-bromo-2-(3-methylbut-3-en-1-yl)benzene (1.0 equiv), the appropriate aniline derivative (1.2 equiv), and NaO^{t}Bu (1.5 equiv). The flask was then purged with nitrogen, and toluene (0.5 M) was added. The resulting mixture was heated to 105 °C with stirring until the starting material had been consumed as judged by TLC, GC, or ^{1}H NMR analysis of an aliquot removed from the reaction mixture (ca. 12 h). The reaction mixture was then cooled to rt, saturated aqueous ammonium chloride (6 mL/mmol substrate) was added, and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate (3 x 20 mL) then the organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified

by flash chromatography on silica gel using a hexanes/Et_2O mixture as the eluent.

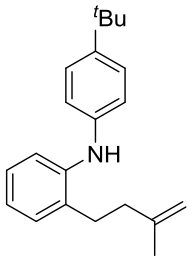


***N*-(4-Methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (3-1).** General Procedure C was employed for the coupling of 1-bromo-2-(3-methylbut-3-en-1-yl)benzene (1.125 g, 5.0 mmol) and *p*-anisidine (738 mg, 6.0 mmol). This procedure afforded 1.09 g (82%) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.7 Hz, 1 H), 7.18 (t, *J* = 8.7 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 6.98–6.92 (m, 3H), 5.40 (s, br, 1 H), 4.88 (s, 1 H), 4.86 (s, 1 H), 3.86 (s, 3 H), 2.82 (t, *J* = 8.4 Hz, 2 H), 2.45 (t, *J* = 8.4 Hz, 2 H), 1.88 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.0, 145.6, 142.8, 137.0, 130.2, 129.7, 127.0, 121.5, 120.7, 117.0, 114.8, 110.5, 55.6, 37.4, 29.9, 22.8; IR (film) 3398, 2933, 1507 cm^{-1}; MS (ESI+) 268.1704 (268.1696 calcd for $C_{18}H_{21}NO$, M + H^+).

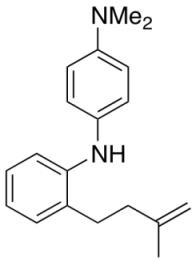


4-{[2-(3-Methylbut-3-en-1-yl)phenyl]amino}benzonitrile (3-3). General Procedure C was employed for the coupling of 1-bromo-2-(3-methylbut-3-en-1-yl)benzene (225 mg, 1.0 mmol) and *p*-cyanoaniline (142 mg, 1.20 mmol) except using a catalyst loading of 1 mol % $Pd_2(dba)_3$. This procedure afforded 223 mg (28%) of the title compound as a

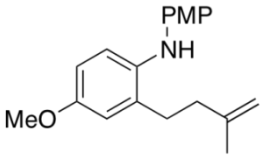
yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 11.9 Hz, 2 H), 7.30 (d, *J* = 11.2 Hz, 1 H), 7.28–7.16 (m, 3 H), 6.75 (d, *J* = 12.6 Hz, 2 H), 5.89 (s, br, 1 H), 4.74 (s, 1 H), 4.65 (s, 1 H), 2.73 (t, *J* = 10.5 Hz, 2 H), 2.26 (t, *J* = 11.9 Hz, 2 H), 1.72 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 149.9, 145.2, 137.8, 137.4, 133.8, 130.5, 127.3, 126.1, 125.3, 120.3, 114.2, 110.9, 100.5, 38.4, 30.1, 22.7; IR (film) 3338, 2927, 2213, 1513 cm^{-1}; MS (ESI+) 263.1546 (263.1543 calcd for $C_{18}H_{18}N_2$, M + H$^+$).



***N*-[4-(*tert*-Butyl)phenyl]-2-(3-methylbut-3-en-1-yl)aniline (3-5).** General Procedure C was employed for the coupling of 1-bromo-2-(3-methylbut-3-en-1-yl)benzene (225 mg, 1.0 mmol) and *p-tert*-butylaniline (0.19 mL, 1.2 mmol). This procedure afforded 210 mg (72%) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (d, *J* = 9.1 Hz, 2 H), 7.37 (d, *J* = 7.7 Hz, 1 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.25 (t, *J* = 7.7 Hz, 1 H), 7.09–7.03 (m, 3 H), 5.52 (s, br, 1 H), 4.91 (s, 1 H), 4.88 (s, 1 H), 2.87 (t, *J* = 8.4 Hz, 2 H), 2.46 (t, *J* = 9.1 Hz, 2 H), 1.90 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 145.6, 143.5, 141.7, 141.5, 132.1, 129.9, 127.0, 126.2, 121.9, 119.2, 117.6, 110.7, 37.8, 34.2, 31.7, 30.1, 22.8; IR (film) 3398, 2961, 1514 cm^{-1}; MS (ESI+) 294.2228 (294.2216 calcd for $C_{21}H_{27}N$, M + H$^+$).

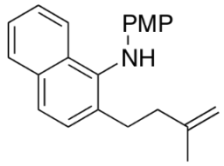


***N*^{1},*N*^{1}-Dimethyl-*N*^{4}-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (3-7).** General Procedure C was employed for the coupling of 1-bromo-2-(3-methylbut-3-en-1-yl)benzene (1.10 g, 4.88 mmol) and 4-(dimethylamino)aniline (798 mg, 5.86 mmol). This procedure afforded 1.16 g (85%) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, C_6D_6) δ 7.15–7.13 (m, 1 H), 7.10 (d, *J* = 9.7 Hz, 1 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 6.86 (t, *J* = 7.3 Hz, 1 H), 6.61 (d, *J* = 8.9 Hz, 2 H), 5.06 (s, 1 H), 4.78 (s, 2 H), 2.61 (t, *J* = 7.8 Hz, 2 H), 2.56 (s, 6 H), 2.29 (t, *J* = 8.5 Hz, 2 H), 1.62 (s, 3 H); ^{13}C NMR (175 MHz, C_6D_6) δ 147.5, 145.6, 144.5, 134.0, 129.8, 129.4, 127.3, 123.4, 120.2, 116.4, 114.5, 110.8, 41.0, 37.5, 30.2, 22.7; IR (film) 3410, 2934, 1516 cm^{-1}; MS (ESI+) 281.2018 (281.2012 calcd for $C_{19}H_{24}N_2$, M + H$^+$).

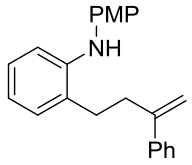


4-Methoxy-N-(4-methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (3-27). General Procedure C was employed for the coupling of 1-bromo-4-methoxy-2-(3-methylbut-3-en-1-yl)benzene (420 mg, 1.65 mmol) and *p*-anisidine (243 mg, 1.98 mmol) and a reaction time of 3 h. This procedure afforded 421 mg (86%) of the title compound as an orange oil. ^{1}H NMR (700 MHz, C_6D_6) δ 7.05 (d, *J* = 8.7 Hz, 1 H), 6.88 (d, *J* = 2.7 Hz, 1 H), 6.77 (d, *J* = 8.9 Hz, 2 H), 6.68–6.62 (m, 3 H), 4.77–4.74 (m, 2 H), 4.66 (s, br, 1 H), 3.40 (s, 3

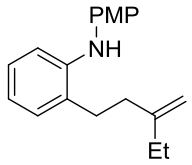
H), 3.36 (s, 3 H), 2.64 (t, *J* = 8.9 Hz, 2 H), 2.24 (t, *J* = 8.3 Hz, 2 H), 1.59 (s, 3 H); ^{13}C NMR (175 MHz, C_6D_6) δ 156.3, 153.7, 145.1, 140.3, 137.0, 135.0, 124.4, 117.3, 115.6, 114.8, 111.9, 110.4, 54.8, 54.7, 38.0, 30.2, 22.2; IR (film) 3379, 2933, 1509 cm^{-1}; MS (ESI+) 297.1726 (297.1723 calcd for $C_{19}H_{23}NO_2$, M + H$^+$).



***N*-(4-Methoxyphenyl)-2-(3-methylbut-3-en-1-yl)naphthalen-1-amine (3-25).** General Procedure C was employed for the coupling of 1-bromo-2-(3-methylbut-3-en-1-yl)naphthalene (380 mg, 1.38 mmol) and *p*-anisidine (204 mg, 1.65 mmol) except using a catalyst composed of $Pd_2(dba)_3$ (25 mg, 0.0276 mmol, 2.0 mol %) and JohnPhos (16.5 mg, 0.0552 mmol, 4.0 mol %). This procedure afforded 308 mg (70%) of the title compound as a yellow solid, mp 80–84 °C. ^{1}H NMR (700 MHz, C_6D_6) δ 8.06 (d, *J* = 8.2 Hz, 1 H), 7.71 (d, *J* = 7.2 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 1 H), 7.28–7.23 (m, 3 H), 6.66 (d, *J* = 8.9 Hz, 2 H), 6.36 (d, *J* = 8.9 Hz, 2 H), 4.93 (s, 1H), 4.73 (d, *J* = 15.2 Hz, 2 H), 3.30 (s, 3 H), 2.80 (t, *J* = 8.8 Hz, 2 H), 2.24 (t, *J* = 8.2 Hz, 2 H), 1.60 (s, 3 H); ^{13}C NMR (175 MHz, C_6D_6) δ 153.4, 145.2, 142.1, 136.7, 135.9, 134.2, 132.5, 128.6, 128.5, 128.4, 126.4, 125.7, 124.6, 115.4, 115.2, 111.0, 55.2, 39.1, 31.1, 22.5; IR (film) 3382, 2959, 1505 cm^{-1}; MS (ESI+) 317.1771 (317.1771 calcd for $C_{22}H_{23}NO$, M + H$^+$).

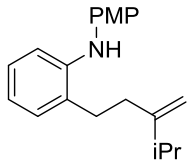


N-(4-methoxyphenyl)-2-(3-phenylbut-3-en-1-yl)aniline (3-10). General Procedure C was employed for the coupling of 1-bromo-2-(3-phenylbut-3-en-1-yl)benzene (1.06 g, 3.70 mmol) and *p*-anisidine (547 mg, 4.44 mmol) using a catalyst composed of $Pd_2(dba)_3$ (25 mg, 0.0277 mmol, 0.75 mol %) and XPhos (40 mg, 0.083 mmol, 2.25 mol %). This procedure afforded 1.18 (95%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 2 H), 7.42-7.32 (m, 3 H), 7.24-7.08 (m, 3 H), 6.98-6.85 (m, 5 H), 5.38 (s, 1 H), 5.20 (br s, 1 H), 5.14 (s, 1H), 3.83 (s, 3 H), 2.92 (t, *J* = 8.8 Hz, 2 H), 2.80 (t, *J* = 9.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ154.8, 147.7, 147.6, 142.6, 140.7, 136.9, 130.1, 129.8, 128.5, 127.6, 127.0, 126.1, 121.1, 120.7, 117.2, 114.7, 113.0, 55.6, 35.3, 30.5; IR (film) 3406, 2938, 1508 cm^{-1}; MS (ESI+) 330.1852 (330.1852 calcd for $C_{23}H_{23}NO$, M + H^+).

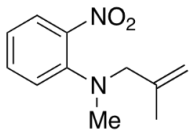


N-(4-methoxyphenyl)-2-(3-methylenepentyl)aniline (3-9). General Procedure C was employed for the coupling of 1-bromo-2-(3-methylenepentyl)benzene (160 mg, 0.67 mmol) and *p*-anisidine (99 mg, 0.80 mmol) except using a catalyst composed of $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol, 1.5 mol %) and XPhos (12.7 mg, 0.0268 mmol, 4.0 mol %). This procedure afforded 170 mg (90%) of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.3 Hz, 1 H), 7.09 (t, *J* = 7.8 Hz, 1 H), 7.04 (d, *J* =

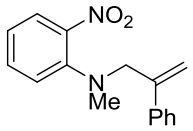
7.8 Hz, 1 H), 6.98 (d, *J* = 9.2 Hz, 2 H), 6.90-6.83 (m, 3H), 5.30 (br s, 1 H), 4.8 (s, 2 H), 3.80 (s, 3 H), 2.73 (t, *J* = 7.8 Hz, 2 H), 2.39 (t, *J* = 8.3 Hz, 2 H), 2.10 (q, *J* = 7.3 Hz, 2 H), 1.06 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ155.0, 151.2, 142.8, 136.9, 130.2, 129.6, 126.9, 121.3, 120.6, 116.7, 114.8, 108.2, 55.7, 35.9, 30.2, 29.1, 12.4; IR (film) 3392, 2960, 1508 cm^{-1}; MS (ESI+) 282.1849 (282.1852 calcd for $C_{19}H_{23}NO$, M + H^+).



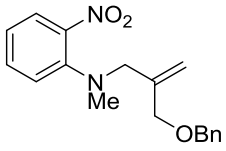
N-(4-methoxyphenyl)-2-(4-methyl-3-methylenepentyl)aniline (3-11). General Procedure C was employed for the coupling of 1-bromo-2-(4-methyl-3-methylenepentyl)benzene (150 mg, 0.59 mmol) and *p*-anisidine (88 mg, 0.71 mmol) except using a catalyst composed of $Pd_2(dba)_3$ (11 mg, 0.0118 mmol, 2.0 mol %) and XPhos (11 mg, 0.0236 mmol, 4.0 mol %). This procedure afforded 170 mg (97%) of the title compound as a pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.3 Hz, 1 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 6.87-6.83 (m, 3H), 5.29 (br s, 1 H), 4.82 (s, 1 H), 4.77 (s, 1 H), 3.79 (s, 3 H), 2.72 (t, *J* = 8.0 Hz, 2 H), 2.36 (t, *J* = 8.5 Hz, 2 H), 2.28 (sep. *J* = 7.0 Hz, 1 H), 1.04 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ155.7, 155.0, 142.8, 136.8, 130.2, 129.7, 126.9, 121.7, 120.5, 116.6, 114.7, 106.9, 55.7, 34.1, 33.9, 30.4, 21.9 ; IR (film) 3389, 2958, 1508 cm^{-1}; MS (ESI+) 296.2007 (296.2009 calcd for $C_{20}H_{25}NO$, M + H^+).



***N*-Methyl-*N*-(2-methylallyl)-2-nitroaniline (3-S3a).** A flame dried flask equipped with a stir bar was cooled under nitrogen and charged with 1-Fluoro-2-nitrobenzene (2.10 mL, 20 mmol) and anhydrous DMF (20 mL). Methylamine (20 mL, 40 mmol, 2.0 M in THF) was added and the resulting mixture was heated to 50 °C for 12 hours. The reaction mixture was then cooled to rt, and excess methylamine and THF were evaporated in vacuo to afford crude *N*-methyl-2-nitroaniline, which was dissolved in DMF (15 mL) and added slowly to a flame dried flask containing a suspension of NaH (880 mg, 22 mmol, 60% in mineral oil) in DMF (10 mL) that had been cooled to 0 °C. The resulting mixture was stirred for 30 minutes at 0 °C then 3-bromo-2-methylpropene (3.05 mL, 30 mmol), was added slowly. The ice bath was removed, the reaction flask was placed in an oil bath (rt) and then was heated to 100 °C for 6 h. The mixture was then allowed to cool to room temperature and saturated aqueous NH_4Cl (40 mL) and EtOAc (80 mL) were added. The mixture was transferred to a separatory funnel, the layers were separated, and the organic layer was separated and washed with brine (2 x 10 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using hexanes/Et_2O as the eluant to afford 2.25 g (51%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 4.91 (s, 1 H), 4.84 (s, 1 H), 3.71 (s, 2 H), 2.76 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 140.6, 140.1, 133.1, 126.6, 119.8, 118.5, 113.1, 60.6, 40.2, 20.2; IR (film) 2914, 1604, 1512 cm^{-1}.

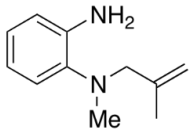


N-methyl-2-nitro-N-(2-phenylallyl)aniline (3-S3b): Following the above procedure, 1-Fluoro-2-nitrobenzene (0.97 mL, 9.25 mmol) and methylamine (9.25 mL, 18.5 mmol, 2.0 M in THF) were reacted to form the crude *N*-methyl-2-nitroaniline. This crude product was added dropwise to a flame dried round bottom flask containing a suspension of NaH (60% in mineral oil 406 mg, 10.15 mmol) in DMF at 0 °C. Again, following the above procedure, (3-bromoprop-1-en-2-yl)benzene[5] (2.73 g, 13.85 mmol) was added to this mixture. The above procedure afforded the title compound in 1.64 g (66%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 1 H), 7.38-7.26 (m, 6 H), 6.95 (d, *J* = 8.6 Hz, 1 H), 6.82 (t, *J* = 7.4 Hz, 1 H), 5.51 (s, 1 H), 5.22 (s, 1 H), 4.22 (s, 2 H), 2.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 142.5, 139.6, 138.9, 132.9, 128.3, 127.9, 126.3, 126.0, 119.5, 118.2, 114.3, 58.0, 39.9; IR (film) 2931, 1604, 1511 cm^{-1}.



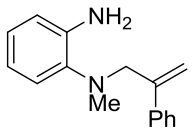
N-(2-((benzyloxy)methyl)allyl)-N-methyl-2-nitroaniline (3-S3c): Following the above procedure, 1-Fluoro-2-nitrobenzene (0.84 mL, 8.00 mmol) and methylamine (8 mL, 16 mmol, 2.0 M in THF) were reacted to form the crude *N*-methyl-2-nitroaniline. This crude product was added dropwise to a flame dried round bottom flask containing a suspension of NaH (60% in mineral oil, 352 mg, 8.80 mmol) in DMF at 0 °C. Again, following the above procedure, (((2-(chloromethyl)allyl)oxy)methyl)benzene[6] (2.35 g,

12.00 mmol) was added to this mixture. The above procedure afforded the title compound in 810 mg (33%) as a yellow oil containing a slight unknown impurity which was carried on to the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 1 H), 7.40-7.23 (m, 6 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.82 (t, *J* = 7.2 Hz, 1 H), 5.24 (s, 1 H), 5.12 (s, 1 H), 4.46 (s, 2 H), 3.98 (s, 2 H), 3.89 (s, 2 H), 2,76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.6, 145.6, 141.1, 138.1, 133.0, 128.4, 127.7, 127.6, 126.4, 119.8, 118.5, 115.1, 72.4, 71.3, 56.7, 40.4; IR (film) 2916, 2848, 1511 cm^{-1}.

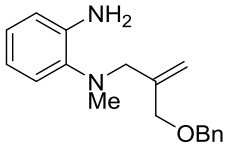


***N*^{1}-Methyl-*N*^{1}-(2-methylallyl)benzene-1,2-diamine (3-S3d).** A flame dried flask equipped with a stir bar was cooled under nitrogen and charged with Zinc dust (8.56 g, 130.9 mmol) and anhydrous ethanol (75 mL). The resulting suspension was vigorously stirred, glacial acetic acid (7.50 mL, 131 mmol) was added, and the mixture was cooled to 0 °C. A solution of *N*-methyl-*N*-(2-methylallyl)-2-nitroaniline (1.80 g, 8.7 mmol) in anhydrous ethanol (15 mL) was added, the ice bath was removed, and the mixture was stirred vigorously at room temperature for 2 h. The mixture was then filtered through celite and the filtrate was evaporated in vacuo. The resulting material was dissolved in EtOAc (50 mL), transferred to a separatory funnel, and washed with saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was washed with EtOAc (2 x 50 mL). The combined organic layers were then washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using hexanes/Et_2O as the eluant to

afford 1.12 g (73%) of the title compound as a red oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.8 Hz, 1 H), 6.91 (t, *J* = 7.8 Hz, 1 H), 6.76–6.71 (m, 2 H), 5.03 (s, 1 H), 4.90 (s, 1 H), 4.00 (s, br, 2 H), 3.35 (s, 2 H), 2.58 (s, 3 H), 1.78 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.2, 141.8, 140.4, 124.4, 120.5, 118.6, 115.3, 112.5, 62.6, 40.5, 20.6; IR (film) 3441, 2970, 1607, 1499 cm^{-1}.

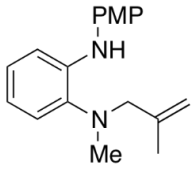


N1-methyl-N1-(2-phenylallyl)benzene-1,2-diamine (3-S3e): Following the above procedure, Zinc dust (5.99 g, 91.7 mmol), Acetic Acid (5.30 mL, 91.7 mmol), and N-methyl-2-nitro-N-(2-phenylallyl)aniline (1.64 g, 6.11 mmol) were reacted to afford the title compound in 802 mg (55%) as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2 H), 7.35–7.25 (m, 3 H), 7.08 (d, *J* = 7.83 Hz, 1 H), 6.93 (t, *J* = 7.6 Hz, 1 H), 6.75 (t, *J* = 7.8 Hz, 1 H), 6.70 (d, *J* = 7.8 Hz, 1 H), 5.46 (s, 1 H), 5.39 (s, 1 H), 3.88 (s, 2 H), 3.78 (s, br, 2 H), 2.60 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 142.1, 140.1, 139.9, 128.2, 127.6, 126.5, 124.6, 120.9, 118.3, 115.1, 114.6, 60.4, 40.6; IR (film) 3439, 3347, 1606, 1499 cm^{-1}.

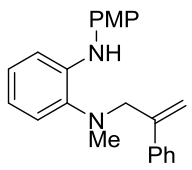


N1-(2-((benzyloxy)methyl)allyl)-N1-methylbenzene-1,2-diamine (3-S3f): Following the above procedure, Zinc dust (2.55 g, 39 mmol), Acetic Acid (2.25 mL, 39 mmol), and N-(2-((benzyloxy)methyl)allyl)-N-methyl-2-nitroaniline (810 mg, 2.60 mmol) were

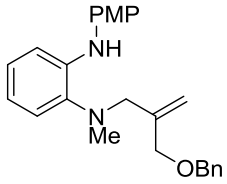
reacted to afford the title compound in 372 mg (50%) as a red oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4 H), 7.30-7.27 (m, 1 H), 7.01 (d, *J* = 7.7 Hz, 1 H), 6.89 (t, *J* = 7.5 Hz, 1 H), 6.70 (t, *J* = 7.7 Hz, 1 H), 6.67 (d, *J* = 7.8 Hz, 1 H), 5.26 (s, 1 H), 5.22 (s, 1 H), 4.50 (s, 2 H), 4.09 (s, 2 H), 4.03 (br s, 2 H), 3.49 (s, 2 H), 2.59 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ143.4, 141.8, 139.6, 138.2, 128.4, 127.8, 127.7, 124.4, 120.3, 118.1, 115.2, 115.1, 72.0, 71.5, 58.8, 40.4; IR (film) 2920,1604, 1494 cm^{-1}.



***N*^{1}-(4-Methoxyphenyl)-*N*^{2}-methyl-*N*^{2}-(2-methylallyl)benzene-1,2-diamine (3-29).** General Procedure C was employed for the coupling of 4-bromoanisole (0.80 mL, 6.35 mmol) and *N*^{1}-methyl-*N*^{1}-(2-methylallyl)benzene-1,2-diamine (1.12 g, 6.35 mmol), except using a catalyst composed of $Pd_2(dba)_3$ (116 mg, 0.127 mmol, 2.0 mol %) and JohnPhos (75 mg, 0.250 mmol, 4.0 mol %) and a reaction temperature of 85 °C. This procedure afforded 1.49 g (79%) of the title compound as a red oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.16–7.10 (m, 4 H), 6.98 (t, *J* = 7.3 Hz, 1 H), 6.89 (d, *J* = 7.5 Hz, 2 H), 6.81 (t, *J* = 7.3 Hz, 1 H), 6.57 (s, br, 1 H), 5.07 (s, 1 H), 4.95 (s, 1 H), 3.83 (s, 3 H), 3.39 (s, 2 H), 2.65 (s, 3 H), 1.81 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 155.1, 143.1, 141.2, 140.2, 136.2, 124.5, 122.0, 120.7, 118.9, 114.8, 113.0, 112.7, 63.2, 55.7, 40.8, 20.7; IR (film) 3355, 2933, 1510 cm^{-1}; MS (ESI+) 283.1807 (283.1805 calcd for $C_{18}H_{22}N_2O$, M + H$^+$)

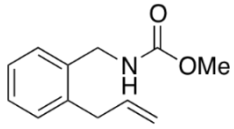


N1-(4-methoxyphenyl)-N2-methyl-N2-(2-phenylallyl)benzene-1,2-diamine (3-31): General Procedure C was employed for the coupling of 4-bromoanisole (0.41 mL, 3.3 mmol) and N1-methyl-N1-(2-phenylallyl)benzene-1,2-diamine (790 mg, 3.3 mmol), except using a catalyst composed of $Pd_2(dba)_3$ (60 mg, 0.066 mmol, 2.0 mol %) and JohnPhos (40 mg, 0.132 mmol, 4.0 mol %) and a reaction temperature of 85 °C. This procedure afforded 750 mg (66%) of the title compound as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ .757-7.52 (m, 2 H), 7.46-7.40 (m, 3H), 7.30 (d, *J* = 7.8 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 7.12 (t, *J* = 7.4 Hz, 1 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 6.98-6.89 (m, 3 H), 6.41 (s, br, 1 H) 5.56 (s, 1 H), 5.48 (s, 1 H), 4.03 (s, 2 H), 3.89 (s, 3 H), 2.73 (s, 3 H); ^{13}C NMR (100 MHz $CDCl_3$) δ 154.8, 145.8, 140.5, 140.4, 139.9, 135.6, 128.3, 127.5, 126.5, 124.8, 121.8, 121.3, 118.4, 115.2, 114.4, 112.2, 61.0, 55.4, 41.0; IR (film) 3347, 2947, 1510 cm^{-1}; MS (ESI+) 239.1537 (239.1543 calcd for $C_{23}H_{24}N_2O$, M + H^+)



N1-(2-((benzyloxy)methyl)allyl)-N2-(4-methoxyphenyl)-N1-methylbenzene-1,2-diamine (3-30): General Procedure C was employed for the coupling of 4-bromoanisole (0.165 mL, 1.32 mmol) and N1-(2-((benzyloxy)methyl)allyl)-N1-methylbenzene-1,2-diamine (372 mg, 1.32 mmol), except using a catalyst composed of $Pd_2(dba)_3$ (26 mg, 0..0264 mmol, 2.0 mol %) and JohnPhos (16 mg, 0.528 mmol, 4.0 mol %) and a reaction temperature of 85 °C. This procedure afforded 380 mg (75%) of the title compound as a red oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32–7.26 (m, 4 H), 7.13 (d, *J* = 7.7 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 8.7 Hz, 2 H), 6.96 (t, *J* = 7.8 Hz, 1 H),

6.84 (d, *J* = 8.9 Hz, 2 H), 6.78 (t, *J* = 7.7 Hz, 1 H), 6.73 (s, br, 1 H), 5.29 (s, 1 H), 4.44 (s, 2 H), 4.09 (s, 2 H), 3.80 (s, 3 H), 3.53 (s, 2 H), 2.65 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 155.0, 143.2, 140.4, 140.2, 138.1, 135.9, 129.4, 127.8, 127.6, 124.4, 122.5, 120.5, 118.4, 115.5, 114.5, 112.7, 71.7, 71.4, 59.4, 55.6, 40.7; IR (film) 3338, 2946, 1509 cm^{-1}; MS (ESI+) 389.2226 (389.2224 calcd for $C_{25}H_{28}N_2O_2$, M + H$^+$)

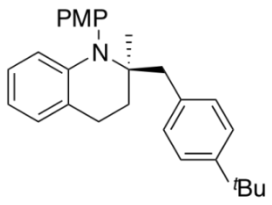


Methyl (2-allylbenzyl)carbamate (3-39). A flame dried round bottom flask equipped with a stir bar was cooled under a stream of nitrogen and charged with ether (20 mL) and $LiAlH_4$ (39 mL, 39 mmol, 1.0 M in ether). The mixture was cooled to 0 °C, stirred for five min, then a solution of 2-allylbenzonitrile[15] (2.80 g, 19.5 mmol) in ether (15 mL) was added slowly dropwise. The reaction mixture was stirred for 1.5 h at 0 °C and then was slowly quenched with 1.5 mL H_2O, 1.5 mL 15% NaOH and 3.0 mL H_2O. The resulting mixture was stirred at rt for 20 min, then the salts were filtered off through a fritted funnel. The filtrate was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford 2-allylbenzylamine, which was used without further purification.

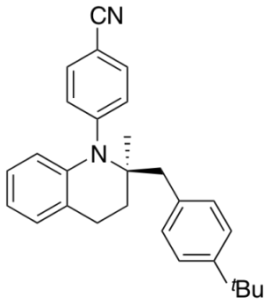
The crude 2-allylbenzylamine product from above was dissolved in dichloromethane (60 mL) and added to a flame dried round bottom flask equipped with a stir bar. Solid K_2CO_3 (2.95 g, 21.3 mmol) was added to the flask and the resulting mixture was cooled to 0 °C. Methyl chloroformate (1.0 equiv., 1.5 mL) was then slowly added, and the resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The crude product was purified by

flash chromatography on silica gel using hexanes/Et_2O as the eluent to afford 3.18 g (79%) as a clear oil. ^{1}H NMR (500 MHz, d8-toluene, 90 °C) δ 7.07 (d, *J* = 6.6 Hz, 1 H), 7.02–6.93 (m, 3 H), 5.82–7.72 (m, 1 H), 4.91 (d, *J* = 10.0 Hz, 1 H); 4.85 (d, *J* = 16.9 Hz, 1 H), 4.58 (s, br, 1 H), 4.16 (d, *J* = 5.9 Hz, 2 H), 3.42 (s, 3 H), 3.18 (d, *J* = 6.1 Hz, 2 H); ^{13}C NMR (125 MHz, d8-toluene, 90 °C) δ 157.7, 139.2, 138.5, 138.2, 131.2, 130.0, 128.8, 127.9, 116.7, 52.6, 44.1, 38.0; IR (film) 3326, 2949, 1702, 1527 cm^{-1}; MS (CI+) 206.1175 (206.1176 calcd for $C_{12}H_{15}NO_2$, M + H^+)

General Procedure D: Asymmetric Pd-catalyzed carboamination reactions. A flame dried Schlenk flask equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol %), (S)-Siphos-PE (6 mol %), the aryl or alkenyl halide (1.0–2.0 equiv.), NaO^tBu (1.3–2.0 equiv.), and the amino alkene substrate. The flask was purged with nitrogen, and toluene (0.1 M) was added (xylenes was used as solvent in cases where reactions were heated over 110 °C). The resulting mixture was heated to 80–125 °C with stirring for 2–15 hrs. The reaction mixture was then cooled to rt, saturated aqueous ammonium chloride (6 mL/mmol) was added, and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel using hexanes/Et_2O as the eluant.

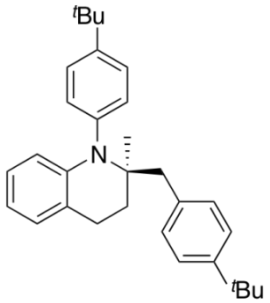


(*R*)-(+)-2-[4-(*tert*-Butyl)benzyl]-1-(4-methoxyphenyl)-2-methyl-1,2,3,4 tetrahydroquinoline (3-2). General Procedure D was employed for the coupling of *N*-(4-methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (27 mg, 0.10 mmol) and 1-bromo-4-*tert*-butylbenzene (43 mg, 0.20 mmol) using NaO^{t}Bu (19 mg, 0.20 mmol) as the base and a reaction temperature of 110 °C for 14 h. This procedure afforded 35 mg (86%) of the title compound as a white solid, mp 47–50 °C. This material was judged to be 92:8 er by chiral HPLC analysis (Chiracel ADH, 25 cm x 4.6 mm, 0.5% IPA/Hexanes, 1 mL/min, λ 254 nm, RT= 6.1 and 7.3 min). $[\alpha]^{23}_{D}$ +50.6 (*c* 3.33, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8 Hz, 2 H), 7.13–7.05 (m, 4 H), 7.04–6.91 (m, 3 H), 6.87 (t, *J* = 7.6 Hz, 1 H), 6.62 (t, *J* = 7.1 Hz, 1 H), 6.04 (d, *J* = 8.3 Hz, 1 H), 3.87 (s, 3 H), 3.11 (ddd, *J* = 5.6, 9.6, 15.9 Hz, 1 H), 2.95–2.82 (m, 3 H), 1.96 (dt, *J* = 5.9, 12.3 Hz, 1 H), 1.82–1.76 (m, 1 H), 1.33 (s, 9 H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 149.0, 146.4, 136.2, 135.2, 133.4, 130.5, 129.1, 126.5, 124.8, 120.9, 116.0, 115.1, 114.8, 114.4, 57.4, 55.4, 44.6, 34.4, 32.3, 31.4, 25.9, 24.5 (an extra peak at 114.4 is present due to apparent slow bond rotation); IR (film) 2961, 1603, 1507 cm^{-1}; MS (ESI+) 400.2632 (400.2635 calcd for $C_{28}H_{33}NO$, M + H$^+$).



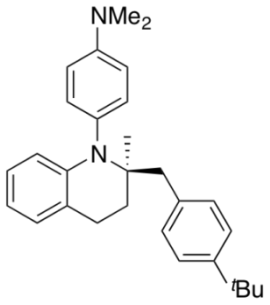
(*R*)-(+)-4-{2-[4-(*tert*-Butyl)benzyl]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl}benzonitrile (3-4). General Procedure D was employed for the coupling of 4-{[2-(3-

methylbut-3-en-1-yl)phenyl]amino}benzonitrile (26 mg, 0.10 mmol,) and 1-bromo-4-*tert*-butylbenzene (43 mg, 0.20 mmol) using NaO^{t}Bu (19 mg, 0.20 mmol) as the base and a reaction temperature 110 °C for 14 h. This procedure afforded 20 mg (51%) of the title compound as an orange oil. This material was judged to be 62:38 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 1% IPA/Hexanes, 1 mL/min, λ 254 nm, RT= 5.6 and 8.0 min). $[\alpha]^{23}_{D}$ +50.3 (*c* 0.68, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 7.02 (d, *J* = 8.2 Hz, 2 H), 6.91 (t, *J* = 8.0 Hz, 1 H), 6.88–6.78 (m, 2 H), 6.73 (t, *J* = 7.3 Hz, 1 H), 6.15 (d, *J* = 8.2 Hz, 1 H), 3.09 (ddd, *J* = 6.3, 11.2, 17.3 Hz, 1 H), 2.93–2.86 (m, 2 H), 2.66 (d, *J* = 13.1 Hz, 1 H), 1.95 (ddd, *J* = 4.2, 6.3, 13.3 Hz, 1 H), 1.84 (ddd, *J* = 6.0, 11.2, 13.2 Hz, 1 H), 1.31 (s, 9 H), 1.05 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 150.0, 149.7, 145.0, 134.8, 133.1, 132.3, 130.7, 129.7, 126.8, 125.1,123.1, 119.1, 118.6, 118.5, 109.0, 58.2, 43.4, 34.6, 33.7, 31.6, 26.7, 24.2; IR (film) 2962, 1596, 1500 cm^{-1}; MS (ESI+) 395.2472 (395.2482 calcd for $C_{28}H_{30}N_2$, M + H$^+$).



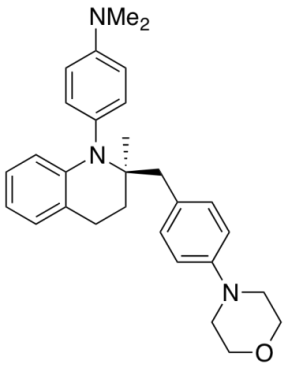
(*R*)-(+)-2-[4-(*tert*-Butyl)benzyl]-1-[4-(tert-butyl)phenyl]-2-methyl-1,2,3,4-tetrahydroquinoline (3-6). General Procedure D was employed for the coupling of *N*-[4-(*tert*-butyl)phenyl]-2-(3-methylbut-3-en-1-yl)aniline (29 mg, 0.10 mmol) and 1-bromo-4-*tert*-butylbenzene (43 mg, 0.20 mmol) using NaO^{t}Bu (19 mg, 0.20 mmol) as the base

and a reaction temperature of 110 °C for 14 h. This procedure afforded 40 mg (93%) of the title compound as a pale yellow solid, mp 59–63 °C. This material was judged to be 87:13 er by chiral HPLC analysis (LuxAmylose, 25 cm x 4.6 mm, 1% IPA/Hexanes, 0.3 mL/min, λ 254nm, RT= 12.0 and 12.5 min). $[\alpha]^{23}_{D}$ +40.3 (*c* 2.30, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.12–6.98 (m, 5 H), 6.87 (t, *J* = 7.3 Hz, 1 H), 6.62 (t, *J* = 7.1 Hz, 1 H), 6.04 (d, *J* = 8.3 Hz, 1 H), 3.12 (ddt, *J* = 5.6, 11.1, 15.5 Hz, 1 H), 2.94–2.81 (m, 3 H), 1.99–1.92 (m, 1 H), 1.80 (ddd, *J* = 5.7, 9.6, 13.2 Hz, 1 H), 1.39 (s, 9 H), 1.33 (s, 9 H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 149.1, 146.4, 140.9, 135.4, 132.0, 130.7, 129.3, 126.6, 126.4, 124.9, 121.0, 116.2, 115.5, 57.5, 44.8, 34.8, 34.6, 32.5, 31.7, 31.6, 26.1, 24.7; IR (film) 2962, 1600, and 1507 cm^{-1}; MS (ESI+) 426.3174 (426.3155 calcd for $C_{31}H_{39}N$, M + H^+).



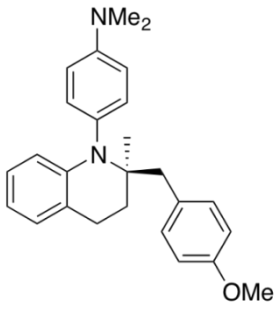
(*R*)-(+)-4-{2-[4-(*tert*-Butyl)benzyl]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl)-*N*,*N*-dimethylaniline (3-8). General Procedure D was employed for the coupling of N^1,N^1-dimethyl-N^4-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 1-bromo-4-*tert*-butylbenzene (85 mg, 0.40 mmol), using NaO^{t}Bu (38 mg, 0.40 mmol,) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 80 mg (95%) of the title compound as a white solid, mp 144–147 °C. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ADH, 25 cm x

4.6 mm, 1.2% IPA/Hexanes, 2 mL/min, λ 254 nm, RT = 3.6 and 5.0 min). $[\alpha]^{23}_{D}$ +31.8 (*c* 1.75, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.1 Hz, 2 H), 7.15–7.01 (m, 5 H), 6.90 (t, *J* = 7.1 Hz, 1 H), 6.85–6.78 (m, 2 H), 6.63 (t, *J* = 7.1 Hz, 1 H), 6.12 (d, *J* = 8.3 Hz, 1 H), 3.20–3.09 (m, 1 H), 3.08–2.94 (m, 7 H), 2.92–2.83 (m, 2 H), 1.98 (m, 1 H), 1.82 (ddd, *J* = 5.3, 9.6, 13.0 Hz, 1 H), 1.36 (s, 9 H), 1.15 (s, 3 H); ^{13}C NMR (125 MHz $CDCl_3$) δ 149.3, 149.0, 147.0, 135.5, 133.2, 132.3, 130.6, 129.1, 126.6, 124.9, 120.8, 115.7, 115.0, 113.4, 113.1, 57.6, 44.9, 40.8, 34.5, 32.4, 31.6, 26.0, 24.7 (an extra peak at 113.1 is present due to apparent slow bond rotation); IR (film) 2961, 1609, 1516 cm^{-1}; MS (ESI+) 413.2955 (413.2951 calcd for $C_{29}H_{36}N_2$, M + H^+).



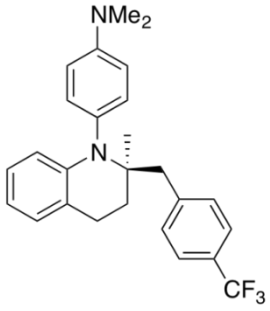
(*R*)-(+)-*N,N*-Dimethyl-4-[2-methyl-2-(4-morpholinobenzyl)-3,4-dihydroquinolin-1(2*H*)-yl]aniline (3-12). General Procedure D was employed for the coupling of *N*^{1},*N*^{1}-dimethyl-*N*^{4}-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 4-(4-bromophenyl)morpholine (97 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 77 mg (87%) of the title compound as a yellow solid, mp 158–161 °C. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ADH, 25 cm x 4.6 mm, 1% IPA/Hexanes, 2 mL/min, λ 254 nm, RT = 14.6 and 20.1 min). $[\alpha]^{23}_{D}$

+24.7 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.03 (m, 5 H), 6.92–6.77 (m, 5 H), 6.61 (t, *J* = 7.2 Hz, 1 H), 6.10 (d, *J* = 8.3 Hz, 1 H), 3.92–3.86 (m, 4 H), 3.20–3.14 (m, 4 H), 3.10–3.04 (m, 1 H), 3.02 (s, 6 H), 2.92–2.79 (m, 3 H), 1.95 (m, 1 H), 1.78 (ddd, *J* = 5.5, 9.5, 13.2 Hz, 1 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 149.1, 147.0, 133.2, 133.1, 132.2, 131.6, 130.1, 129.1, 126.6, 120.8, 115.7, 115.3, 115.0, 113.3, 113.0, 67.1, 57.6, 49.6, 44.5, 40.8, 32.3, 25.9, 24.7 (extra peaks at 133.1 and 113.0 are present due to apparent slow bond rotation); IR (film) 2963, 1609, 1514 cm^{-1}; MS (ESI+) 442.285 (442.28 calcd for $C_{29}H_{35}N_3O$, M + H$^+$).



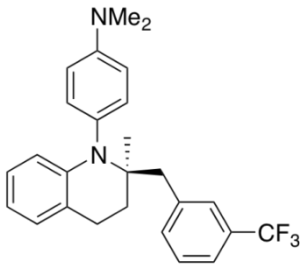
(*R*)-(+)-4-[2-(4-Methoxybenzyl)-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]-*N,N*-dimethylaniline (3-13). General Procedure D was employed for the coupling of *N*^{1},*N*^{1}-dimethyl-*N*^{4}-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 4-bromoanisole (75 mg, 0.40 mmol), using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 68 mg (88%) of the title compound as a yellow solid, mp 101–105 °C. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ADH, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1 mL/min, λ 254 nm, RT= 10.2 and 15.1 min). $[\alpha]^{23}_D$ +30.6 (*c* 2.10, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.01 (m, 5 H), 6.90 (t, *J* = 7.3 Hz, 1 H), 6.85–6.77 (m, 4 H), 6.62 (t, *J* = 7.4 Hz, 1 H), 6.10 (d, *J* = 8.1 Hz, 1 H), 3.82 (s, 3 H),

3.14–3.05 (m, 1 H), 3.02 (s, 6 H), 2.92–2.80 (m, 3 H), 1.94 (dt, *J* = 6.0, 12.5 Hz, 1 H), 1.79 (ddd, *J* = 5.5, 9.4, 13.3 Hz, 1 H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz $CDCl_3$) δ 158.1, 149.2, 146.9, 133.2, 133.0, 132.3, 131.8, 130.7, 129.1, 126.6, 120.8, 115.8, 115.1, 113.4, 113.3, 113.0, 57.5, 55.3, 44.5, 40.8, 32.3, 25.8, 24.6 (extra peaks at 133.0 and 113.0 are present due to apparent slow bond rotation); IR (film) 2962, 1609, 1512 cm^{-1}; MS (ESI+) 387.2432 (387.2431 calcd for $C_{26}H_{30}N_2O$, M + H^+).



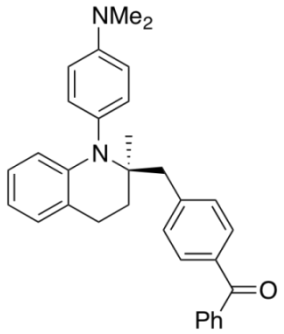
(*R*)-(+)-*N,N*-Dimethyl-4-{2-methyl-2-[4-(trifluoromethyl)benzyl]-3,4-dihydroquinolin-1(2*H*)-yl}aniline (3-14). General Procedure D was employed for the coupling of *N*^{1},*N*^{1}-dimethyl-*N*^{4}-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 4-bromobenzotrifluoride (90.0 mg, 0.40 mmol), using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 75.6 mg (89%) of the title compound as a white solid, mp 127-130 °C. This material was judged to be 94:6 er by chiral HPLC analysis (Chiracel ADH, 25 cm x 4.6 mm, 1% IPA/Hexanes, 1 mL/min, λ 254 nm, RT= 6.1 and 8.9 min). $[\alpha]^{23}_D$ +31.5 (*c* 1.43, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.14–6.97 (m, 3 H), 6.91 (t, *J* = 7.7 Hz, 1 H), 6.86–6.76 (m, 2 H), 6.65 (t, *J* = 7.1 Hz, 1 H), 6.14 (d, *J* = 8.2 Hz, 1 H), 3.15–2.85 (m, 10 H), 1.95 (dt, *J* = 6.0, 12.4 Hz, 1 H), 1.79 (ddd, *J* = 5.6, 9.5, 13.1, Hz, 1 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz $CDCl_3$) δ 149.4,

146.8, 143.0, 133.0, 132.2, 131.2, 129.2, 128.6 (q, *J* = 32 Hz), 126.8, 124.6 (q, *J* = 270 Hz), 124.9 (q, *J* = 3 Hz), 120.8, 116.2, 115.6, 113.4, 113.0, 57.3, 45.2, 40.6, 32.4, 25.7, 24.4 (an extra peak at 113.0 is present due to apparent slow bond rotation); IR (film) 2971, 1610, 1517 cm^{-1}; MS (ESI+) 425.2202 (425.2199 calcd for $C_{26}H_{27}F_3N_2$, M + H^+).



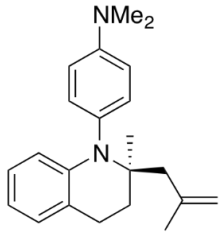
(*R*)-(+)-*N,N*-Dimethyl-4-{2-methyl-2-[3-(trifluoromethyl)benzyl]-3,4-dihydroquinolin-1(2*H*)-yl}aniline (3-15). General Procedure D was employed for the coupling of *N*^{1},*N*^{1}-dimethyl-*N*^{4}-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 3-bromobenzotrifluoride (90 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 80 mg (94%) of the title compound as a brown solid, mp 91–94 °C. This material was judged to be 92:8 er by chiral HPLC analysis (Chiracel ADH, 25 cm x 4.6 mm, 1 % IPA/Hexanes, 1 mL/min, λ 254 nm, RT= 4.2 and 5.4 min). $[\alpha]^{23}_D$ +22.5 (*c* 1.35, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.3 Hz, 1 H), 7.46–7.35 (m, 3 H), 7.12–6.93 (m, 3 H), 6.91 (t, *J* = 7.5 Hz, 1 H), 6.85–6.75 (m, 2 H), 6.65 (t, *J* = 7.3 Hz, 1 H), 6.15 (d, *J* = 8.3 Hz, 1 H), 3.15–3.02 (m, 7 H), 3.00–2.97 (m, 2 H), 3.93–3.85 (m, 1 H), 1.95 (dt, *J* = 5.9, 13.9 Hz, 1 H), 1.82 (ddd, *J* = 5.50, 9.40, 13.30 Hz, 1 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 146.8, 139.7, 134.3, 133.0, 132.9, 132.3, 130.4

(q, *J* = 31 Hz), 129.2, 128.5, 127.5 (q, *J* = 4 Hz), 126.8, 124.4 (q, *J* = 270 Hz), 123.2 (q, *J*= 4 Hz), 120.8, 116.3, 115.7, 113.4, 112.9, 57.3, 45.3, 40.8, 32.6, 25.8, 24.6 (extra peaks at 132.9 and 112.9 are present due to apparent slow bond rotation); IR (film) 2971, 1609, 1518 cm^{-1}; MS (ESI+) 425.22 (425.2199 calcd for $C_{26}H_{27}F_3N_2$, M + H^+).



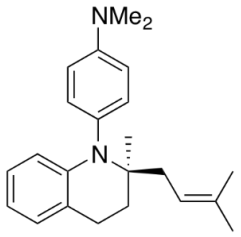
(*R*)-(+)-[4-({1-[4-(Dimethylamino)phenyl]-2-methyl-1,2,3,4-tetrahydroquinolin-2-yl}methyl)phenyl](phenyl)methanone (3-16). General Procedure D was employed for the coupling of *N*^{1},*N*^{1}-dimethyl-*N*^{4}-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 4-bromobenzophenone (104 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 76 mg (82%, 93% pure) of the title compound as a yellow solid, mp 156–159 °C. This material was judged to be 96:4 er by chiral HPLC analysis (Chiracel ADH, 25 cm x 4.6 mm, 5 % IPA/Hexanes, 1 mL/min, λ 254 nm, RT= 11.6 and 25.8 min). $[\alpha]^{23}_D$ +32.7 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.10–6.98 (m, 3 H), 6.91 (t, *J* = 7.7 Hz, 1 H), 6.79 (dd, *J* = 8.5, 19.0 Hz, 2 H), 6.63 (t, *J* = 7.1 Hz, 1 H), 6.13 (d, *J* = 8.3 Hz, 1 H), 3.15–3.08 (m, 1 H), 3.06–3.00 (m, 7 H), 2.99 (d, *J* = 12.8 Hz, 1 H), 2.89 (dt, *J* = 5.9, 16.6 Hz, 1 H), 1.98 (dt, *J* = 5.9, 12.4 Hz, 1 H), 1.83 (ddd, *J* = 5.5, 9.6, 13.2 Hz, 1 H), 1.15 (s, 3 H); ^{13}C NMR

(175 MHz, $CDCl_3$) δ 196.4, 149.2, 146.6, 143.8, 137.8, 135.4, 132.8, 132.2, 132.0, 130.7, 130.0, 129.8, 129.0, 128.2, 126.6, 120.6, 116.0, 115.3, 113.2, 112.8, 57.4, 45.3, 40.6, 32.5, 25.9, 24.4 (2 extra peaks in the arene region are present due to apparent slow bond rotation); IR (film) 2927, 1656, 1517 cm^{-1}; MS (ESI+) 461.2583 (461.2587 calcd for $C_{32}H_{32}N_2O$, M + H^+).

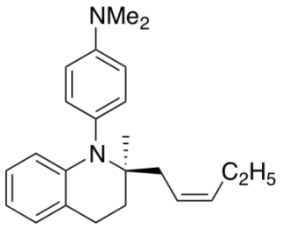


(*R*)-(+)-*N*,*N*-dimethyl-4-[2-methyl-2-(2-methylallyl)-3,4-dihydroquinolin-1(2*H*)-yl]aniline (3-17). General Procedure D was employed for the coupling of *N*^{1},*N*^{1}-dimethyl-*N*^{4}-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 2-bromopropene (48 mg 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 55 mg (86%) of the title compound as an off-white solid, mp 76–79 °C. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ODH, 25 cm x 4.6 mm, 1% IPA/Hexanes, 0.2 mL/min, λ 254nm, RT = 13.4 and 15.2 min). $[\alpha]^{23}_D$ +37.7 (*c* 1.81, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12–7.00 (m, 3 H), 6.85 (t, *J* = 7.1 Hz, 1 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 6.58 (t, *J* = 7.3 Hz, 1 H), 6.04 (d, *J* = 8.3 Hz, 1 H), 4.92 (s, 1 H), 4.78 (s, 1 H), 3.06–2.98 (m, 7H), 2.85 (dt, *J* = 5.9, 16.5 Hz, 1 H), 2.50 (d, *J* = 13.1 Hz, 1 H), 2.29 (d, *J* = 13.0 Hz, 1 H), 2.07 (dt, *J* = 5.9, 13.1 Hz, 1 H), 1.93 (ddd, *J*= 5.5, 9.6, 13.2 Hz, 1 H), 1.80 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 146.8, 142.7, 133.1, 132.3, 129.1, 126.6, 120.8, 115.7, 115.5, 114.9, 113.3, 113.0, 57.2, 46.9,

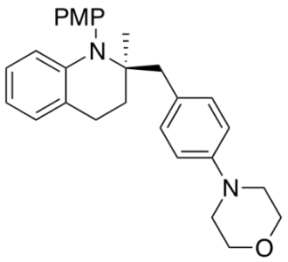
40.8, 33.0, 27.1, 25.5, 24.7 (an extra peak at 113.0 is present due to apparent slow bond rotation); IR (film) 2969, 1609, 1517 cm^{-1}; MS (ESI+) 321.2329 (321.2325 calcd for $C_{22}H_{28}N_2$, M + H^+).



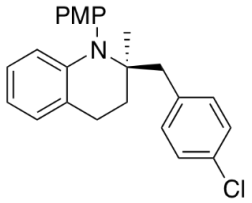
(*R*)-(+)-*N*,*N*-Dimethyl-4-[2-methyl-2-(3-methylbut-2-en-1-yl)-3,4-dihydroquinolin-1(2*H*)-yl]aniline (3-18). General Procedure D was employed for the coupling of N^1,N^1-dimethyl-N^4-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and 1-bromo-2-methyl-1-propene (54 mg 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 66 mg (98%) of the title compound as an orange oil. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 0.9% IPA/Hexanes, 0.1 mL/min, λ 254 nm, RT = 26.1 and 28.2 min). $[\alpha]^{23}_D$ +53.4 (*c* 2.35 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12–6.96 (m, 3 H), 6.83 (t, *J* = 7.1 Hz, 1 H), 6.77 (d, *J* = 8.3Hz, 2 H), 6.55 (t, *J* = 7.1 Hz, 1 H), 6.02 (d, *J* = 8.3 Hz, 1 H), 5.19 (t, *J* = 7.3 Hz, 1 H), 3.01 (s, 3 H), 2.88–2.82 (m, 1 H), 2.32 (dd, *J*= 7.2, 14.4 Hz, 1 H), 2.20 (dd, *J* = 7.5, 14.4 Hz, 1 H), 2.00 (dt, *J* = 6.2, 12.9 Hz, 1 H), 1.79 (ddd, *J*= 5.9, 8.1, 13.5 Hz, 1 H), 1.72 (s, 3 H), 1.56 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 147.2, 133.6, 133.0, 132.3, 129.1, 126.6, 121.0, 120.3, 115.5, 114.8, 113.3, 57.6, 40.8, 37.9, 32.8, 26.3, 25.9, 24.7, 18.3; IR (film) 2967, 1608, 1516 cm^{-1}; MS (ESI+) 335.2136 (335.2482 calcd for $C_{23}H_{30}N_2$, M + H^+).



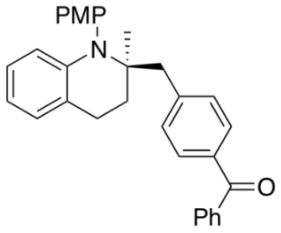
(*Z,R*)-(+)-*N,N*-Dimethyl-4-[2-methyl-2-(pent-2-en-1-yl)-3,4-dihydroquinolin-1(2*H*)-yl]aniline (3-19). General Procedure D was employed for the coupling of N^1,N^1-dimethyl-N^4-[2-(3-methylbut-3-en-1-yl)phenyl]benzene-1,4-diamine (56 mg, 0.20 mmol) and (Z)-1-bromo-1-butene (54 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 125 °C (xylenes) for 14 h. This procedure afforded 61 mg (91%) of the title compound as an off-white solid, mp 122–125 °C. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 0.8% IPA/Hexanes, 0.1 mL/min, λ 254 nm, RT = 30.0 and 33.3 min). $[\alpha]^{23}_{D}$ +59.3 (*c* 1.50, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16–6.93 (m, 3 H), 6.88 (t, *J* = 7.3 Hz, 1 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.59 (t, *J* = 7.1 Hz, 1 H), 6.09 (d, *J* = 8.3 Hz, 1 H), 5.55–5.38 (m, 2 H), 3.04 (s, 6 H), 2.95–2.85 (m, 2 H), 2.45 (dd, *J* = 7.3, 14.4 Hz, 1 H), 2.30 (dd, *J* = 7.2, 14.4 Hz, 1 H), 2.12–1.92 (m, 3 H), 1.86 (ddd, *J* = 5.7, 8.4, 13.6 Hz, 1 H), 1.18 (s, 3 H), 0.98 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 147.1, 134.0, 133.0, 132.2, 129.1, 126.6, 124.5, 120.9, 115.6, 114.8, 113.2, 57.2, 40.8, 36.9, 32.8, 26.0, 24.6, 21.0, 14.3; IR (film) 2964, 1609, 1517 cm^{-1}; MS (ESI+) 335.2495 (335.2482 calcd for $C_{23}H_{30}N_2$, M + H$^+$).



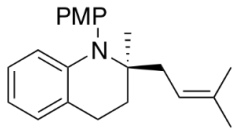
(*R*)-(+)-4-(4-{[1-(4-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroquinolin-2-yl]methyl}phenyl)morpholine (3-20). General Procedure D was employed for the coupling of *N*-(4-methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (54 mg, 0.20 mmol) and 4-(4-bromophenyl)morpholine (97 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 90 °C for 14 h. This procedure afforded 70 mg (82%) of the title compound as a white solid, mp 62–65 °C. This material was judged to be 94:6 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 5% IPA/Hexanes, 1 mL/min, λ 254 nm, RT = 8.8 and 11.1 min). $[\alpha]^{23}_{D}$ +56.1 (*c* 1.11, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.14–7.05 (m, 5 H), 7.02–6.95 (m, 2 H), 6.88 (t, *J* = 7.2 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 6.63 (t, *J* = 7.2 Hz, 1 H), 6.05 (d, *J* = 8.4 Hz, 1 H), 3.92–3.84 (m, 7 H), 3.18–3.12 (m, 4H), 3.09 (ddd, *J* = 5.7, 9.6, 15.9 Hz, 1 H), 2.89–2.81 (m, 2 H), 2.78 (d, *J* = 13.2 Hz, 1 H), 1.94 (dt, *J* = 6.0, 12.5 Hz, 1 H), 1.78 (ddd, *J* = 5.5, 9.6, 13.2 Hz, 1 H), 1.09 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.2, 149.7, 146.6, 136.2, 133.6, 133.5, 131.6, 129.8, 129.2, 126.6, 121.0, 116.1, 115.3, 115.2, 114.9, 114.5, 67.1, 57.5, 55.5, 49.5, 44.4, 32.3, 25.8, 24.6 (extra peaks at 133.5 and 114.5 are present due to apparent slow bond rotation); IR (film) 2928, 1606, 1505 cm^{-1}; MS (ESI+) 429.2521 (429.2537 calcd for $C_{28}H_{32}N_2O_2$, M + H$^+$).



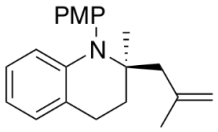
(*R*)-(+)-2-(4-Chlorobenzyl)-1-(4-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroquinoline (3-21). General Procedure D was employed for the coupling of *N*-(4-methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (54 mg, 0.20 mmol) and 4-bromochlorobenzene (77 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 90 °C for 14 h. This procedure afforded 62 mg (82%) of the title compound as a viscous oil. This material was judged to be 89:11 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 0.4% IPA/Hexanes, 1.1 mL/min, λ 254 nm, RT = 8.9 and 10.5 min). $[\alpha]^{23}_{D}$ +56.2 (*c* 0.97, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 7.15–6.91 (m, 7 H), 6.89 (t, *J* = 7.3 Hz, 1 H), 6.65 (t, *J* = 7.3 Hz, 1 H), 6.08 (d, *J* = 8.3 Hz, 1 H), 3.87 (s, 3 H), 3.04 (ddd, *J* = 5.8, 9.6, 15.9 Hz, 1 H), 2.87–2.79 (m, 3 H), 1.90 (dt, *J* = 5.9, 13.4 Hz, 1 H), 1.77 (ddd, *J* = 5.6, 9.6, 13.3 Hz, 1 H), 1.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 146.4, 136.9, 136.3, 133.4, 132.3, 132.2, 129.3, 128.2, 126.7, 121.0, 116.5, 115.7, 115.1, 114.5, 57.3, 55.6, 44.6, 32.5, 25.8, 24.5 (an extra peak at 114.5 is present due to apparent slow bond rotation); IR (film) 2928, 1604, 1505 cm^{-1}; MS (ESI+) 378.1620 (378.1619 calcd for $C_{24}H_{24}ClNO$, M + H$^+$).



(*R*)-(+)-(4-{[1-(4-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroquinolin-2-yl]methyl}phenyl)(phenyl)methanone (3-22). General Procedure D was employed for the coupling of *N*-(4-methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (54 mg, 0.20 mmol) and 4-bromobenzophenone (104 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 90 °C for 14 h. This procedure afforded 74 mg (83%) of the title compound as a white solid, mp 58–61 °C. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 8% IPA/Hexanes, 1 mL/min, λ 254 nm, RT = 10.4 and 16.5 min). $[\alpha]^{23}_{D}$ +44.7 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.1 Hz, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 7.15–6.91 (m, 5 H), 6.89 (t, *J* = 7.1 Hz, 1 H), 6.65 (t, *J* = 6.4 Hz, 1 H), 6.08 (d, *J* = 8.1 Hz, 1 H), 3.87 (s, 3 H), 3.10 (ddd, *J*= 5.8, 9.7, 16.1 Hz, 1 H), 3.02–2.93 (m, 2 H), 2.87 (dt, *J* = 5.8, 16.7 Hz, 1 H), 1.95 (dt, *J* = 5.9, 13.2 Hz, 1 H), 1.82 (ddd, *J* = 5.6, 9.7, 13.2 Hz, 1 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 158.3, 146.4, 143.7, 137.9, 136.3, 135.7, 133.4, 132.4, 130.8, 130.1, 130.0, 129.3, 128.4, 126.8, 121.0, 116.6, 115.8, 115.1, 114.5, 57.5, 55.5, 45.3, 32.6, 26.1, 24.5 (an extra peak at 114.5 is present due to apparent slow bond rotation); IR (film) 2928, 1656, 1603, 1505 cm^{-1}; MS (ESI+) 448.2269 (448.2271 calcd for $C_{31}H_{29}NO_2$, M + H$^+$).

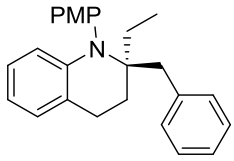


(*R*)-(+)-1-(4-Methoxyphenyl)-2-methyl-2-(3-methylbut-2-en-1-yl)-1,2,3,4-tetrahydroquinoline (3-23). General Procedure D was employed for the coupling of *N*-(4-methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (54 mg, 0.20 mmol) and 1-Bromo-2-methyl-1-propene (41 µL, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 90 °C for 14 h. This procedure afforded 63 mg (98%) of the title compound as an orange oil. This material was judged to be 95:5 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 0.8% IPA/Hexanes, 0.2 mL/min, λ 254 nm, RT = 22.3 and 24.4 min). $[\alpha]^{23}_{D}$ +58.0 (*c* 1.11, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.08 (m, 2 H), 7.07 (d, *J* = 7.3 Hz, 1 H), 6.99 (d, *J* = 9.1 Hz, 2 H), 6.87 (t, *J* = 7.3 Hz, 1 H), 6.61 (t, *J* = 7.4 Hz, 1 H), 6.02 (d, *J* = 8.3 Hz, 1 H), 5.23 (app. t, *J* = 7.1 Hz, 1 H), 3.88 (s, 3 H), 2.95–2.85 (m, 2 H), 2.34 (dd, *J* = 7.2, 14.3 Hz, 1 H), 2.22 (dd, *J* = 7.5, 14.3 Hz, 1 H), 2.05 (dt, *J* = 6.4, 13.0 Hz, 1 H), 1.89–1.81 (m, 1 H), 1.77 (s, 3 H), 1.60 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 146.8, 136.2, 133.8, 133.4, 129.2, 126.6, 121.1, 120.0, 115.9, 114.9, 114.7, 57.5, 55.5, 37.9, 32.8, 26.3, 25.9, 24.6, 18.3; IR (film) 2926, 1599, 1507 cm^{-1}; MS (ESI+) 322.2170 (322.2165 calcd for $C_{22}H_{27}NO$, M+H$^+$).



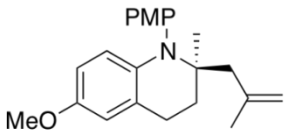
(*R*)-(+)-1-(4-Methoxyphenyl)-2-methyl-2-(2-methylallyl)-1,2,3,4-tetrahydroquinoline (3-24). General Procedure D was employed for the coupling of *N*-(4-methoxyphenyl)-2-

(3-methylbut-3-en-1-yl)aniline (54 mg, 0.20 mmol) and 2-Bromopropene (35 µL, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 90 °C for 14 h. This procedure afforded 52 mg (85%) of the title compound as an orange oil. This material was judged to be 96:4 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 0.8% IPA/Hexanes, 0.2 mL/min, λ 254 nm, RT = 22.9 and 23.9 min). $[\alpha]^{23}_{D}$ +49.8 (*c* 1.04, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.00 (m, 3 H), 6.98 (d, *J* = 8.2 Hz, 2 H), 6.85 (t, *J* = 7.4 Hz, 1 H), 6.61 (t, *J* = 7.0 Hz, 1 H), 6.00 (d, *J* = 8.2 Hz, 1 H), 4.95 (s, 1 H), 4.77 (s, 1 H), 3.87 (s, 3 H), 3.02 (ddd, *J* = 5.5, 9.2, 15.7 Hz, 1 H), 2.85 (dt, *J* = 6.0, 16.8 Hz, 1 H), 2.48 (d, *J* = 13.1 Hz, 1 H), 2.27 (d, *J* = 13.2 Hz, 1 H), 2.07 (dt, *J* = 5.8, 12.3, Hz, 1 H), 1.93 (ddd, *J*= 5.7, 9.6, 14.0 Hz, 1 H), 1.81 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 146.4, 142.4, 136.2, 133.5, 129.2, 126.6, 121.0, 116.1, 115.7, 115.1, 114.8, 57.1, 55.5, 46.8, 32.9, 27.0, 25.4, 24.6; IR (film) 2928, 1599, and 1506 cm^{-1}; MS (ESI+) 308.2008 (308.2009 calcd for $C_{21}H_{25}NO$, M + H$^+$).



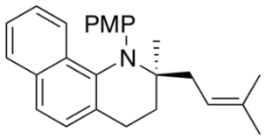
(R)-2-benzyl-2-ethyl-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3-25): General Procedure D was employed for the coupling of N-(4-methoxyphenyl)-2-(3-methylenepentyl)aniline (28 mg, 0.10 mmol) and Bromobenzene (21 µL, 0.20 mmol) using NaO^{t}Bu (19 mg, 0.20 mmol) as the base and a reaction temperature of 110 °C for 12 h. This procedure afforded 31 mg (86%) of the title compound as an viscous white oil. This material was judged to be 75:25 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 1.00% IPA/Hexanes, 0.75 mL/min, λ 254 nm, RT = 6.1 and 7.5 min).

$[\alpha]^{23}_{D}$ +13.03 (*c* 1.35, CH_2Cl_2); ^{1}H NMR (700 MHz, C_6D_6) δ 7.26 (t, *J*= 7.2 Hz, 2 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.18-7.09 (m, 3 H), 7.06 (d, *J* = 7.3 Hz, 1 H), 6.93-6.71 (m, 4 H), 6.62 (t, *J* = 7.3 Hz, 1 H), 6.11 (d, *J* = 8.3 Hz, 1 H), 3.82 (s, 3 H), 3.16 (ddd, *J* = 17.0, 11.5, 5.9 Hz, 1 H), 2.95 (d, *J* = 13.5 Hz, 1 H), 2.90–2.81 (m, 2 H), 1.95–1.83 (m, 2H), 1.54-1.47 (m, 1 H), 1.37 dq, *J*= 14.5, 7.2 Hz, 1H) 0.88 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.8, 147.3, 138.5, 136.9, 133.1, 130.9, 128.9, 127.9, 126.4, 126.1, 122.1, 117.0, 116.4, 114.4, 60.7, 55.4, 42.2, 29.2, 27.8, 24.2, 8.5; IR (film) 2927, 1599, and 1507 cm^{-1}; MS (ESI+) 358.2163 (358.2165 calcd for $C_{25}H_{27}NO$, M + H^+).



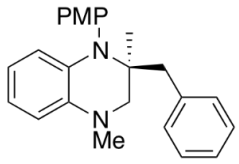
(*R*)-(+)-6-Methoxy-1-(4-methoxyphenyl)-2-methyl-2-(2-methylallyl)-1,2,3,4-tetrahydroquinoline (3-28). General Procedure D was employed for the coupling of 4-methoxy-*N*-(4-methoxyphenyl)-2-(3-methylbut-3-en-1-yl)aniline (60 mg, 0.20 mmol) and 2-bromopropene (35 µL, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 90 °C for 14 h. This procedure afforded 55 mg (82%) of the title compound as an orange oil. This material was judged to be 96:4 er by chiral HPLC analysis (lux-amylose, 15 cm x 4.6 mm, 2.5% IPA/Hexanes, 0.2 mL/min, λ 254 nm, RT = 29.7 and 32.9). $[\alpha]^{23}_{D}$ +68.3 (*c* 1.13, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.16–7.03 (m, 2 H), 6.93 (d, *J* = 7.7 Hz, 2 H), 6.65 (d, *J* = 2.9 Hz, 1 H), 6.47 (dd, *J* = 3.0, 8.9 Hz, 1 H), 5.98 (d, *J* = 9.1 Hz, 1 H), 4.92 (s, 1 H), 4.76 (s, 1 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 2.98 (ddd, *J* = 5.8, 9.6, 16.0 Hz, 1 H), 2.83 (dt, *J* = 5.9,16.8 Hz, 1 H), 2.40 (d, *J* = 13.1 Hz, 1 H), 2.25 (d, *J* = 13.1 Hz, 1 H), 2.01 (dt, *J* = 6.0, 13.2 Hz, 1 H), 1.90 (ddd, *J* = 5.6, 9.6,

13.1 Hz, 1 H), 1.80 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 157.9, 150.9, 142.5, 140.8, 137.2, 133.3, 122.2, 116.7, 115.3, 114.4, 114.2, 112.5, 56.7, 55.7, 55.4, 46.4, 32.9, 26.6, 25.3, 24.7; IR (film) 2933, 1493 cm^{-1}; MS (ESI+) 337.2032 (337.2036 calcd for $C_{22}H_{27}NO_2$, M^+).

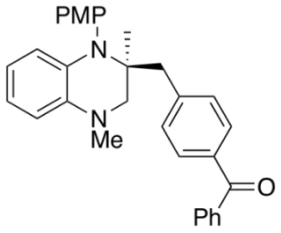


(*R*)-(+)-1-(4-Methoxyphenyl)-2-methyl-2-(3-methylbut-2-en-1-yl)-1,2,3,4-tetrahydrobenzo[h]quinoline (3-26). General Procedure D was employed for the coupling of *N*-(4-Methoxyphenyl)-2-(3-methylbut-3-en-1-yl)naphthalen-1-amine (63 mg, 0.20 mmol) and 1-Bromo-2-methyl-1-propene (41 µL, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 95 °C for 18 h. This procedure afforded 47 mg (63%) of the title compound as a clear oil. This material was judged to be 93:7 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 0.8% IPA/Hexanes, 0.150 mL/min, λ 254 nm, RT = 38.1 and 40.9 min). $[\alpha]^{23}_D$ +281.2 (*c* 1.67, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 8.34 (d, *J* = 8.5 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 7.18-7.00 (m, 3 H), 6.95 (d, *J* = 8.2 Hz, 2 H), 6.51 (d, *J* = 8.3 Hz, 2 H), 5.48-5.43 (m, 1 H), 3.14 (s, 3 H), 2.85-2.76 (m, 2H), 2.44 (dd, *J* = 7.0, 14.6 Hz, 1 H), 2.12 (dd, *J* = 7.6, 14.6 Hz, 1 H), 1.78 (dt, *J* = 9.0, 13.5 Hz, 1 H), 1.66 (s, 3 H), 1.52-1.44 (m, 1H), 1.35 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ□157.2, 143.2, 142.4, 134.9, 133.3, 131.6, 131.3, 128.0, 126.4, 125.8, 125.7, 125.4, 123.8, 121.9, 114.1, 58.9, 55.0, 37.7, 28.7, 27.4, 26.6, 25.9, 18.4 (one peak missing from arene region due to apparent overlap); IR (film) 2926, 1502, and 1390 cm^{-1}; MS (ESI+) 372.2326 (372.2322

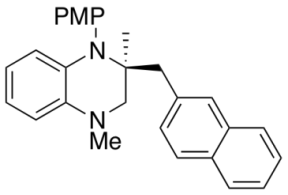
calcd for $C_{26}H_{29}NO$, M + H^+).



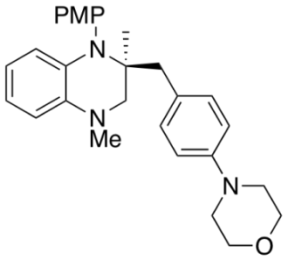
(*S*)-(–)-2-Benzyl-1-(4-methoxyphenyl)-2,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (3-32). General Procedure D was employed for the coupling of *N*^{1}-(4-methoxyphenyl)-*N*^{2}-methyl-*N*^{2}-(2-methylallyl)benzene-1,2-diamine (59 mg, 0.20 mmol) and bromobenzene (42 µL, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 110 °C for 14 h. This procedure afforded 57 mg (79%) of the title compound as an orange oil. This material was judged to be 97:3 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 1% IPA/Hexanes, 1mL/min, λ 254 nm, RT = 5.1 and 7.9 min). $[\alpha]^{23}_D$ –28.9 (*c* 1.19, CH_2Cl_2); ^{1}H NMR (700 MHz, C_6D_6) δ 7.15 (d, *J* = 7.5 Hz, 2 H), 7.11 (d, *J* = 6.6 Hz, 1 H), 7.08 (d, *J* = 7.5 Hz, 2 H), 6.96 (d, *J* = 8.5 Hz, 2 H), 6.86 (t, *J* = 7.5 Hz, 1 H), 6.81–6.75 (m, 2 H), 6.74 (t, *J* = 7.8 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 3.32 (s, 3 H), 3.22 (d, *J* = 12.6 Hz, 1 H), 2.83 (d, *J* = 12.6 Hz, 1 H), 2.70 (d, *J* = 10.9 Hz, 1 H), 2.65 (d, *J* = 10.9 Hz, 1 H), 2.62 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.7, 139.1, 137.0, 136.5, 136.5, 133.5, 131.2, 128.4, 128.3, 126.5, 119.2, 118.4, 115.5, 115.0, 111.9, 58.0, 57.5, 54.9, 44.1, 38.9, 23.8 (an extra peak at 136.5 is present due to apparent slow bond rotation); IR (film) 2928, 1503 cm^{-1}; MS (ESI+) 359.2118 (359.2118 calcd for $C_{24}H_{26}N_2O$, M + H^+).



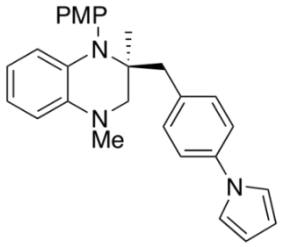
(*S*)-(+)-(4-{[1-(4-Methoxyphenyl)-2,4-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-yl]methyl}phenyl)(phenyl)methanone (3-33). General Procedure D was employed for the coupling of N^1-(4-methoxyphenyl)-N^2-methyl-N^2-(2-methylallyl)benzene-1,2-diamine (59 mg, 0.2 mmol) and 4-bromobenzophenone (104 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 110 °C for 14 h. This procedure afforded 72 mg (78%) of the title compound as a light yellow solid, mp 63–66 °C. This material was judged to be 96:4 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 3% IPA/Hexanes, 1 mL/min, λ 254 nm, RT = 18.2 and 25.9 min), $[\alpha]^{23}_{D}$ +18.7 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.0 Hz, 2 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.5 Hz, 1 H), 7.08 (t, *J* = 7.6 Hz, 2 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 6.87(t, *J* = 7.5 Hz, 1 H), 6.80 (d, *J* = 8.2 Hz, 2 H), 6.75 (t, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 3.34 (s, 3 H), 3.22 (d, *J* = 12.4 Hz, 1 H), 2.81 (d, *J* = 12.3 Hz, 1 H), 2.65 (d, *J* = 11.1 Hz, 1 H), 2.61–2.56 (m, 4 H), 0.85 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 195.5, 158.8, 138.6, 136.8, 136.4, 136.3, 136.2, 133.4, 132.0, 131.0, 130.2, 130.2, 128.4, 119.3, 118.6, 115.6, 115.0, 112.0, 57.9, 57.6, 55.0, 43.9, 38.9, 23.8 (one aromatic carbon signal is missing due to incidental equivalence); IR (film) 2972, 1656 1504 cm^{-1}; MS (ESI+) 463.2371 (463.2380 calcd for $C_{31}H_{30}N_2O_2$, M + H$^+$).



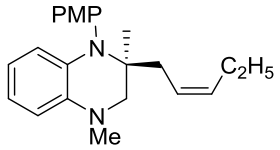
(*S*)-(+)-1-(4-Methoxyphenyl)-2,4-dimethyl-2-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroquinoxaline (3-36). General Procedure D was employed for the coupling of *N*^{1}-(4-methoxyphenyl)-*N*^{2}-methyl-*N*^{2}-(2-methylallyl)benzene-1,2-diamine (59 mg, 0.2 mmol) and 2-bromonaphthalene (83 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 110 °C for 14 h. This procedure afforded 67 mg (82%) of the title compound as a light yellow solid, mp 62–65 °C. This material was judged to be 93:7 er by chiral HPLC analysis (lux-amylose, 15 cm x 4.6 mm, 3% IPA/Hexanes, 0.25 mL/min, λ 254 nm, RT = 27.9 and 30.2 min), $[\alpha]^{23}_{D}$ +8.56 (*c* 1.39, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.70–7.64 (m, 2 H), 7.59 (t, *J* = 8.2 Hz, 1 H), 7.52 (s, 1 H), 7.33–7.26 (m, 2 H), 7.22 (t, *J* = 8.4 Hz, 1 H), 7.08–6.98 (m, 2 H), 6.90 (t, *J* = 7.7 Hz, 1 H), 6.84–6.74 (m, 4 H), 6.44 (d, *J* = 8.0 Hz, 1 H), 3.40 (d, *J* = 12.8 Hz, 1 H), 3.35 (s, 3 H), 2.96 (d, *J* = 12.8 Hz, 1 H), 2.71–2.62 (m, 5 H), 0.93 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.7, 137.0, 136.6, 136.5, 136.4, 134.1, 133.7, 133.5, 132.8, 129.8, 129.7, 128.0, 127.7, 126.2, 125.7, 119.3, 118.4, 115.4, 115.0, 112.0, 57.9, 57.8, 55.0, 44.1, 38.9, 23.9; IR (film) 2969, 1504 cm^{-1}; MS (ESI+) 409.2268 (409.2274 calcd for $C_{28}H_{28}N_2O$, M + H$^+$).



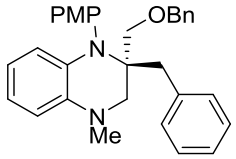
(*S*)-(+)-4-(4-{[1-(4-Methoxyphenyl)-2,4-dimethyl-1,2,3,4-tetrahydroquinoxalin-2-yl]methyl}phenyl)morpholine (3-34). General Procedure D was employed for the coupling of N^1-(4-methoxyphenyl)-N^2-methyl-N^2-(2-methylallyl)benzene-1,2-diamine (59 mg, 0.2 mmol) and 4-(4-bromophenyl)morpholine (97 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 110 °C for 14 h. This procedure afforded 73 mg (82%) of the title compound as a white solid, mp 72–75 °C. This material was judged to be 96:4 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 2% IPA/Hexanes, 1 mL/min, λ 254 nm, RT = 16.3 and 17.8 min), $[\alpha]^{23}_{D}$ +21.6 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 7.8 Hz, 2 H), 6.88 (t, *J* =7.2 Hz, 1 H), 6.83–6.72 (m, 4 H), 6.67 (d, *J* = 8.3 Hz, 2 H), 6.43 (d, *J* = 7.0 Hz, 1 H), 3.58 (t, *J* = 4.6 Hz, 4 H), 3.33 (s, 3 H), 3.25 (d, *J* = 12.9 Hz, 1 H), 2.87 (d, *J* = 12.9 Hz, 1 H), 2.83 (d, *J* = 10.8 Hz, 1 H), 2.79 (d, *J* = 4.7 Hz, 4 H), 2.72 (d, *J* = 10.9 Hz, 1 H), 2.70 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.7, 150.3, 137.1, 136.6, 136.5, 133.5, 131.8, 130.0, 128.2, 119.2, 118.3, 115.7, 115.4, 114.9, 111.9, 67.0, 58.1, 57.7, 54.9, 49.6, 43.3, 39.0, 23.8 (an extra peak appears at 136.5 is present due to apparent slow bond rotation); IR (film) 2957, 1504 cm^{-1}; MS (ESI+) 444.2645 (444.2646 calcd for $C_{28}H_{33}N_3O_2$, M + H$^+$).



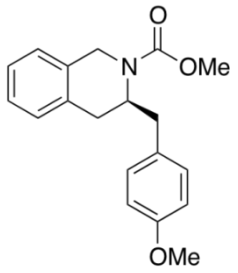
(*S*)-(+)-2-[4-(1*H*-pyrrol-1-yl)benzyl]-1-(4-methoxyphenyl)-2,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (3-35). General Procedure D was employed for the coupling of *N*^{1}-(4-methoxyphenyl)-*N*^{2}-methyl-*N*^{2}-(2-methylallyl)benzene-1,2-diamine (59 mg, 0.2 mmol) and 1-(4-iodophenyl)pyrrole (108 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 120 °C in xylenes for 14 h. This procedure afforded 60 mg (70%) of the title compound as an white solid, mp 65–68 °C. This material was judged to be 93:7 er by chiral HPLC analysis (Chiracel ADH, 15 cm x 4.6 mm, 1% IPA/Hexanes, 1 mL/min, λ 254 nm, RT = 16.2 and 22.5 min), $[\alpha]^{23}_{D}$ +22.7 (*c* 0.88, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.03–6.94 (m, 8 H), 6.89 (t, *J* = 7.3 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 6.76 (d, *J* = 7.7 Hz, 1 H), 6.74 (d, *J* = 7.8 Hz, 1 H), 6.45 (t, *J* = 1.9 Hz, 2 H), 6.42 (d, *J* = 7.8 Hz, 1 H), 3.34 (s, 3 H), 3.18 (d, *J* = 12.8 Hz, 1 H), 2.79 (d, *J* = 12.8 Hz, 1 H), 2.69–2.63 (m, 5 H), 0.89 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.7, 139.5, 136.9, 136.5, 136.1, 136.0, 135.6, 133.0, 131.6, 119.6, 118.94, 118.93, 118.1, 115.2, 114.6, 111.6, 110.7, 57.9, 57.5, 55.0, 43.3, 39.0, 23.8 (an extra peak at 136.0 is present due to apparent slow bond rotation); IR (film) 2970, 2360, 2339.4, 1519, 1504 cm^{-1}; MS (ESI+) 424.2380 (424.2383 calcd for $C_{28}H_{29}N_3O$, M + H^{+}).



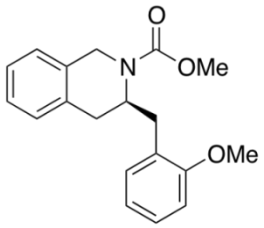
(S,Z)-1-(4-methoxyphenyl)-2,4-dimethyl-2-(pent-2-en-1-yl)-1,2,3,4-tetrahydroquinoxaline (3-37). General Procedure D was employed for the coupling of N^1-(4-methoxyphenyl)-N^2-methyl-N^2-(2-methylallyl)benzene-1,2-diamine (59 mg, 0.2 mmol) and *Z*-1-bromobutene (54 mg, 0.40 mmol) using NaO^{t}Bu (38 mg, 0.40 mmol) as the base and a reaction temperature of 110 °C for 14 h. This procedure afforded 50 mg (75%) of the title compound as a clear oil. This material was judged to be 98:2 er by chiral HPLC analysis (Chriacel ADH, 15 cm x 4.6 mm, 0.50% IPA/Hexanes, 1 mL/min, λ 254 nm, RT = 6.6 and 9.3 min), $[\alpha]^{23}_{D}$ +21.7 (*c* 2.4, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.04 (d, *J*= 7.3 Hz, 2 H), 6.84 (t, *J* = 7.3 Hz, 1 H), 6.78 (d, *J* = 8.6 Hz, 2 H), 6.72 (t, *J* = 7.7 Hz, 1 H), 6.65 (d, *J* = 7.8 Hz, 1 H), 6.35 (d, *J* = 8.0 Hz, 2 H), 5.50–5.41 (m, 1 H), 5.40–5.32 (m, 1 H), 3.32 (s, 3 H), 2.95 (d, *J* = 10.8 Hz, 1 H), 2.79 (d, *J* = 10.8 Hz, 1 H), 2.70–2.61 (m, 4 H), 2.48 (dd, *J*= 13.7, 7.1 Hz, 1H), 2.05–1.90 (m, 2H), 1.04 (s, 3 H), 0.89 (t, *J*= 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 137.4, 136.4, 136.3, 134.5, 133.6, 124.8, 119.2, 118.2, 115.0, 114.9 111.8, 59.2, 57.0, 54.9, 39.4, 36.0, 23.9, 21.0, 14.5; IR (film) 2957, 1671, 1504 cm^{-1}; MS (ESI+) 337.2276 (337.2274 calcd for $C_{22}H_{28}N_2O$, M + H$^+$).



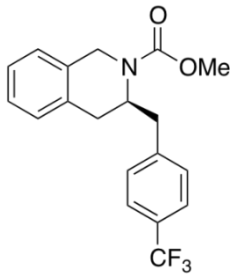
(S)-2-benzyl-2-((benzyloxy)methyl)-1-(4-methoxyphenyl)-4-methyl-1,2,3,4-tetrahydroquinoxaline (3-38): General Procedure D was employed for the coupling of N1-(2-((benzyloxy)methyl)allyl)-N2-(4-methoxyphenyl)-N1-methylbenzene-1,2-diamine (39 mg, 0.1 mmol) and Bromobenzene (21 µL, 0.20 mmol) using NaO^tBu (19 mg, 0.20 mmol) as the base and a reaction temperature of 125 °C for 12 h. This procedure afforded 37 mg (79%) of the title compound as a viscous white oil. This material was judged to be 96:4 er by chiral HPLC analysis (Chriacel ADH, 15 cm x 4.6 mm, 1.00% IPA/Hexanes, 1 mL/min, λ 254 nm, RT = 7.0 and 10.6 min), $[\alpha]^{23}_D$ -19.51 (*c* 1.23, CH_2Cl_2); ^{1}H NMR (700 MHz, C_6D_6) δ 7.31 (t, *J*= 7.5 Hz, 2 H), 7.28-7.18 (m, 7 H), 7.16 (d, *J* = 7.3 Hz, 2 H), 6.98-6.90 (m, 1 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 6.69-6.64 (m, 2H), 6.51 (t, *J*= 7.2 Hz, 1 H), 6.08 (d, *J*= 8.0 Hz, 1 H), 4.29 (d, *J* = 11.8 Hz, 1 H), 4.24 (d, *J* = 11.8 Hz, 1 H), 3.82 (s, 3 H), 3.39 (d, *J* = 9.9 Hz, 1 H), 3.23 (d, *J* = 11.1 Hz, 1 H), 3.21 (d, *J* = 9.7 Hz, 1 H) 3.09 (d, *J* = 13.3 Hz, 1 H), 3.04 (d, *J* = 10.9 Hz, 1 H), 3.00 (d, *J* = 13.1 Hz, 1 H), 2.92 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.1, 138.2, 138.1, 136.4, 136.0, 135.8, 133.4, 132.8, 130.9, 128.3, 128.1, 127.5, 127.4, 126.3, 118.2, 117.6, 115.0, 114.6, 114.2, 111.1, 72.9, 72.1, 60.6, 55.4, 54.1, 40.3, 39.2 (extra peaks at 132.8 and 114.2 are present due to apparent slow bond rotation); IR (film) 2923, 2859, 1504 cm^{-1}; MS (ESI+) 465.2536 (465.2537 calcd for $C_{31}H_{32}N_2O_2$, M + H^+).



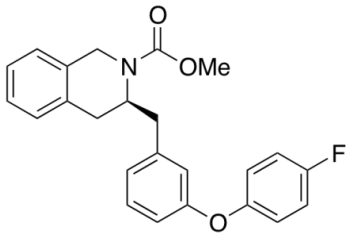
(*S*)-(+)-Methyl 3-(4-methoxybenzyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3-40). General Procedure D was employed for the coupling of (2-allylbenzyl)carbamate (51 mg, 0.25 mmol) and 4-bromoanisole (60 mg, 0.32 mmol) using NaO^{t}Bu (31 mg, 0.32 mmol) as the base and a reaction temperature of 90 °C for 2 h. This procedure afforded 40 mg (51%) of the title compound as a colorless oil. This material was judged to be 93:7 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 5% IPA/Hexanes, 1 mL/min, λ 215 nm, RT = 5.8 and 12.1 min), $[\alpha]^{23}_D$ +48.8 (*c* 0.86, CH_2Cl_2); ^{1}H NMR (700 MHz, d8-toluene, 95 °C) δ 7.01–6.95 (m, 2 H), 6.92 (d, *J* = 8.2 Hz, 2 H), 6.88–6.83 (m, 2 H), 6.69 (d, *J* = 8.5 Hz, 1 H), 4.82 (d, *J* = 16.6 Hz, 1 H), 4.73 (s, br, 1 H), 4.34 (d, *J* = 16.7 Hz, 1 H), 3.60 (s, 3 H), 3.49 (s, 3 H), 2.74–2.67 (m, 2 H), 2.67 (d, *J* = 13.6 Hz, 1 H), 2.35 (dd, *J* = 9.0, 13.5, Hz 1 H); ^{13}C NMR (175 MHz, d8-toluene, 95 °C) δ 159.6, 156.4, 134.2, 134.9, 131.6, 130.8, 129.8, 127.3, 126.9, 126.8, 114.9, 55.3, 52.7, 52.4, 44.3, 38.4, 32.5; IR (film) 2952, 1695 cm^{-1}; MS (ESI+) 312.1589 (312.1594 calcd for $C_{19}H_{21}NO_3$, M + H$^+$).



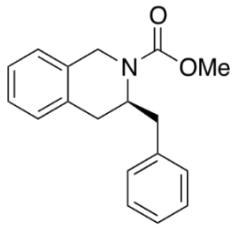
(*S*)-(+)-Methyl 3-(2-methoxybenzyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3-41). General Procedure D was employed for the coupling of (2-allylbenzyl)carbamate (51 mg, 0.25 mmol) and 2-iodoanisole (85 mg, 0.32 mmol) using NaO^{t}Bu (31 mg, 0.32 mmol) as the base and a reaction temperature of 90 °C for 2 h. This procedure afforded 33 mg (42%) of the title compound as a white solid, mp 74-77 °C. This material was judged to be 80:20 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 5% IPA/Hexanes, 1 mL/min, λ 215 nm, RT = 5.7 and 8.2 min), $[\alpha]^{23}_{D}$ +77.0 (*c* 0.67, CH_2Cl_2); ^{1}H NMR (700 MHz, d8-toluene, 95 °C) δ 7.02–6.92 (m, 5 H), 6.88–6.82 (m, 2 H), 6.73 (t, *J* = 7.5 Hz, 1 H), 6.56 (d, *J* = 8.1 Hz, 1 H), 4.88 (s, br, 1 H), 4.80 (d, *J* = 16.8 Hz, 1 H), 4.32 (d, *J* = 16.8 Hz, 1 H), 3.44 (s, 3H), 3.41 (s, 3 H), 2.80–2.72 (m, 2 H), 2.64 (dd, *J* = 8.1, 13.2 Hz, 1 H), 2.46 (d, *J* = 15.9 Hz, 1 H); ^{13}C NMR (175 MHz, d8-toluene, 95 °C) δ 159.1, 156.7, 134.3, 134.2, 131.9, 130.0, 127.2, 126.9, 126.8, 121.3, 111.5, 55.6, 52.4, 51.3, 44.3, 33.7, 33.4 (two aromatic carbon signals are missing due to incidental equivalence); IR (film) 2951, 1698 cm^{-1}; MS (ESI+) 312.1593 (312.1594 calcd for $C_{19}H_{21}NO_3$, M + H$^+$).



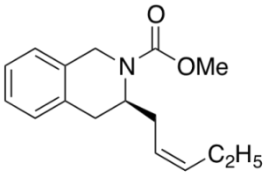
(*S*)-(+)-Methyl 3-[4-(trifluoromethyl)benzyl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3-42). General Procedure D was employed for the coupling of (2-allylbenzyl)carbamate (51 mg, 0.25 mmol) and 4-bromobenzotrifluoride (72 mg, 0.32 mmol) using NaO^{t}Bu (31 mg, 0.32 mmol) as the base and a reaction temperature of 90 °C for 2 h. This procedure afforded 63 mg (72%) of the title compound as a colorless oil. This material was judged to be 93:7 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 5% IPA/Hexanes, 1 mL/min, λ 215 nm, RT = 4.4 and 9.3 min), $[\alpha]^{23}_{D}$ +39.5 (*c* 1.24, CH_2Cl_2); ^{1}H NMR (700 MHz, d8-toluene, 95 °C) δ 7.32 (d, *J*= 7.8 Hz, 2 H), 7.03–6.94 (m, 2 H), 6.92 (d, *J* = 7.8 Hz, 2 H), 6.87–6.79 (m, 2 H), 4.67 (d, *J* = 16.6 Hz, 1 H), 4.58 (s, br, 1 H), 4.19 (d, *J* = 16.7 Hz, 1 H), 3.47 (s, 3 H), 2.68–2.62 (m, 2 H), 2.34–2.26 (m, 2 H); ^{13}C NMR (175 MHz, d8-toluene, 95 °C) δ 156.3, 143.8, 133.9, 133.5, 130.3, 129.7, 127.5, 127.2, 126.8, 125.8, 152.5, 152.3, 44.3, 39.1, 32.6 (two aromatic carbon signals are missing due to incidental equivalence); IR (film) 2954, 1695 cm^{-1}. MS (ESI+) 350.1365 (350.1362 calcd for $C_{19}H_{18}F_3NO_2$, M + H$^+$).



(*S*)-(+)-Methyl 3-[3-(4-fluorophenoxy)benzyl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3-43). General Procedure D was employed for the coupling of (2-allylbenzyl)carbamate (51 mg, 0.25 mmol) and 3-bromo-4'-fluorodiphenyl ether (85 mg, 0.32 mmol) using NaO^{t}Bu (31 mg, 0.32 mmol) as the base and a reaction temperature of 90 °C for 2 h. This procedure afforded 60 mg (61%) of the title compound as colorless oil. This material was judged to be 93:7 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 5% IPA/Hexanes, 1 mL/min, λ 215 nm, RT = 7.7 and 13.3 min), $[\alpha]^{23}_{D}$ +48.3 (*c* 1.18, CH_2Cl_2); ^{1}H NMR (700 MHz, d8-toluene, 95 °C) δ 7.02–6.93 (m, 3 H), 6.83–6.68 (m, 9 H), 4.68 (d, *J* = 16.8 Hz, 1 H), 4.62 (s, br, 1 H), 4.20 (d, *J* = 16.6 Hz, 1 H), 3.46 (s, 3 H), 2.71–2.62 (m, 2 H), 2.39 (d, *J* = 15.9 Hz, 1 H), 2.31 (dd, *J* = 8.5, 13.5 Hz, 1 H); ^{13}C NMR (175 MHz, d8-toluene, 95 °C) δ 159.8 (d, *J* = 241 Hz), 158.8, 156.3, 154.2, 141.8, 134.0, 133.6, 130.2, 129.7, 127.4, 127.0, 126.8, 124.9, 121.1 (d, *J* = 7 Hz), 120.3, 117.2, 116.8 (d, *J* = 23 Hz), 52.5, 44.3, 39.2, 32.8 (one aliphatic carbon signal is missing due to incidental equivalence); IR (film) 2952, 1695, 1500 cm^{-1}; MS (ESI+) 392.1658 (392.1656 calcd for $C_{24}H_{22}FNO_2$, M + H$^+$).



(*S*)-(+)-Methyl 3-benzyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3-45). General Procedure D was employed for the coupling of (2-allylbenzyl)carbamate (51 mg, 0.25 mmol) and bromobenzene (51 mg, 0.32 mmol) using NaO^{t}Bu (31 mg, 0.32 mmol) as the base and a reaction temperature of 90 °C for 2 h. This procedure afforded 48 mg (68%) of the title compound as a colorless oil. This material was judged to be 94:6 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 5% IPA/Hexanes, 0.5 mL/min, λ 215nm, RT = 9.9 and 18.5 min), $[\alpha]^{23}_{D}$ +63.2 (*c* 1.28, CH_2Cl_2); ^{1}H NMR (700 MHz, d8-toluene, 90 °C) δ 7.10–7.03 (m, 2 H), 7.03–6.95 (m, 5 H), 6.87–6.81 (m, 2 H), 4.72 (d, *J* = 16.7 Hz, 1 H), 4.66 (s, br, 1 H), 4.24 (d, *J* = 16.7 Hz, 1 H), 3.49 (s, 3 H), 2.72 (dd, *J* = 5.8, 13.3 Hz, 1 H), 2.67 (dd, *J* = 5.6, 15.7 Hz, 1 H), 2.41 (d, *J* = 15.7 Hz, 1 H), 2.37 (dd, *J* = 8.9, 13.5 Hz, 1 H); ^{13}C NMR (125 MHz, d8-toluene, 90 °C) δ 156.3, 139.7, 134.1, 133.8, 130.0, 129.7, 129.0, 127.3, 126.9, 126.9, 126.8, 52.6, 52.4, 44.3, 39.3, 32.5; IR (film) 2953 1697 cm^{-1}; MS (ESI+) 282.1491 (282.1489 calcd for $C_{18}H_{19}NO_2$, M + H$^+$).

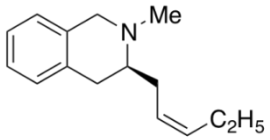


(*Z,S*)-(+)-Methyl-3-[4-(trifluoromethyl)benzyl]-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (3-44). General Procedure D was employed for the coupling of (2-allylbenzyl)carbamate (51 mg, 0.25 mmol) and (*Z*)-1-bromo-1-butene (43 mg, 0.32

mmol) using NaO^{t}Bu (31 mg, 0.32 mmol) as the base and a reaction temperature of 90 °C for 2 h. This procedure afforded 36 mg (57%) of the title compound as a colorless oil. This material was judged to be 93:7 er by chiral HPLC analysis (ODH, 15 cm x 4.6 mm, 1% IPA/Hexanes, 1 mL/min, λ 215 nm, RT = 6.7 and 22.1 min), $[\alpha]^{23}_{D}$ +46.7 (*c* 1.12, CH_2Cl_2); (The mixture was found to exist as a 2.5:1 mixture of rotomers in the nmr, with most of the minor rotomer peaks appearing partially in the major rotomer peaks, however coupling constants given are all for the major rotomer) ^{1}H NMR (700 MHz, d8-toluene, 95 °C) δ 6.98–6.93 (m, 2 H), 6.88–6.84 (m, 2 H), 6.83–6.79 (m, 2 H), 5.38–5.33 (m, 1 H), 5.30–5.25 (m, 1 H), 4.78 (d, *J* = 16.7 Hz, 1 H), 4.48 (s, br, 1 H), 4.19 (d, *J* = 16.7 Hz, 1 H), 3.55 (s, 3 H), 2.78 (dd, *J* = 6.1, 15.6 Hz, 1 H), 2.46 (d, *J* = 15.7 Hz, 1 H), 2.20–2.15 (m, 1 H), 2.00–1.95 (m, 1 H), 1.90-1.84 (m, 0.63 H), 1.80 (quin, *J* = 7.30 Hz, 1.45 H), 0.87 (t, *J* = 7.5 Hz, 0.76 H), 0.80 (t, *J* = 7.5 Hz, 2.22 H); ^{13}C NMR (125 MHz, d8-toluene, 95 °C) δ 156.4, 134.5, 134.1, 133.9, 129.7, 127.2, 126.9, 126.6, 125.7, 52.6, 51.1, 44.1, 33.1, 30.7, 21.2, 14.5; IR (film) 2958, 1699 cm^{-1}; MS (ESI+) 260.1644 (260.1645 calcd for $C_{16}H_{21}NO_2$, M + H$^+$).

Confirmation of product 3-44 structure.

The NMR spectrum of **3-44** was complicated due to apparent rotomers. In order to rule out the presence of *E*:*Z* alkene stereoisomers the product was reduced with $LiAlH_4$ to form the analogous *N*-methyl isoquinoline derivative **3-S4**.



(*Z*,*S*)-(–)-2-methyl-3-(pent-2-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (3-S4). A flame-

dried round-bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with **3-44** (35 mg, 0.136 mmol) and THF (4 mL). The resulting solution was cooled to 0°C and after five minutes of stirring $LiAlH_4$ (0.27 mL, 0.27 mmol, 1.0M in THF) was added dropwise. The resulting solution was heated to reflux for 1.5 h then cooled to rt and quenched with 0.1 mL H_2O followed by 0.1 mL of a 15% aqueous NaOH solution. The mixture was filtered and the solid was washed with ether (2 x 5) mL. The combined organic solutions were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford 20 mg (69%) of the product as a clear oil; $[\alpha]^{23}_D$ –24.7 (*c* 1.86, CH_2Cl_2). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.13–7.09 (m, 2 H), 7.08–7.05 (m, 1 H), 7.04–7.00 (m, 1 H), 5.53–5.48 (m, 1 H), 5.44–5.39 (m, 1 H), 3.82 (d, *J* = 15.5 Hz, 1 H), 3.68 (d, *J* = 15.6 Hz, 1 H), 2.79–2.72 (m, 1 H), 2.69–2.58 (m, 2 H), 2.36 (s, 3 H), 2.32–2.27 (m, 1 H), 2.10–2.04 (m, 1H), 2.03 (quint, *J* = 7.5 Hz, 2 H), 0.97 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 134.3, 134.0, 133.7, 128.8, 126.2, 126.1, 125.6, 125.4, 59.1, 56.4, 41.0, 32.3, 28.3, 20.7, 14.2; IR (film) 2960, 1456 cm^{-1}; MS (ESI+) 216.1747 (216.1747 calcd for $C_{15}H_{21}N$, M + H^+).

3.7 References

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Chapter 4

Development of Enantioselective Carboetherification Reactions for the Synthesis of Oxygen Heterocycles: Use of a Modular Chiral Alcohol Moiety to Access Rationally Designed Taddol Phosphite Ligands

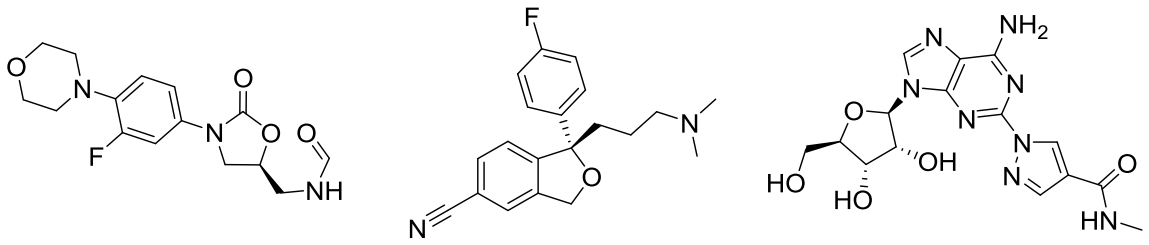
4.1 Introduction

Oxygen heterocycles are prominent moieties displayed in an array of natural products and biologically active compounds .[1,2] Families of compounds, such as the as the annonaceous acetogenins, contain chiral 2,5-substitutued THF's which are powerful inhibitors of the mitochondrial complex.[1] Also, chiral 2-substituted oxygen heterocycles are noted in a variety of pharmaceuticals displaying an array of biological activities (Figure 4.1).[2] As such, synthesizing THF's in an enantioselective fashion is an interesting challenge in organic synthesis.

Although many groups have shown the utility of adding amines enantioselectively onto alkenes with transistion metal catalyisis to access chiral amine heterocyles,[3,4] relatively few methods exist for the analogous enantioselective synthesis of oxygen heterocycles.[4b,5] Recently, we showed the importance of N-protecting groups in developing enantioselective carboamination reactions.[3a,c] Consequently, the lack of an interchangeable protecting group on the oxygen heteroatom may be a reason for the dearth of related enantioselective carboetherification reactions, as the lack of

this protecting group could make it hard to achieve high enantioselectivities.

Figure 4.1 Biologically active chiral oxygen heterocycles



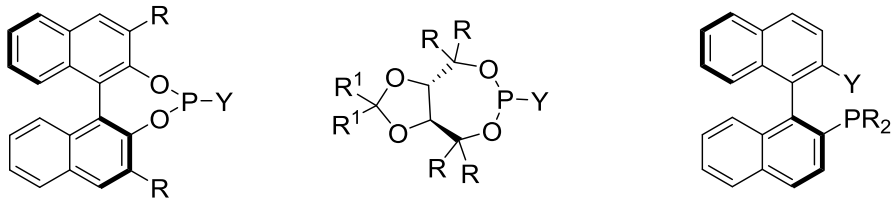
Zyvox® (Linezolid)
antibiotic

Lexapro® (Escitalopram)
antidepressant

Lexiscan® (Regadenoson)
coronary vasodilator

The ability to easily alter a portion of the substrate or catalyst system in enantioselective reactions is essential to the development of new methodology.[6] Since the oxygen heteroatom in our substrates lacks an extra protecting group, we decided to alter the ligand in our reaction. As such, our strategy was to utilize modular ligand scaffolds which are easy to synthesize and manipulate, as we assumed these two criteria would be essential to our reaction development (Scheme 4.1).

Scheme 4.1 Modular ligand scaffolds



BINOL
R=Ar, alkyl
Y=-OR, -NR_2

TADDOL
R=Ar, alkyl
R^1= Ar, alkyl
Y=-OR, -NR_2

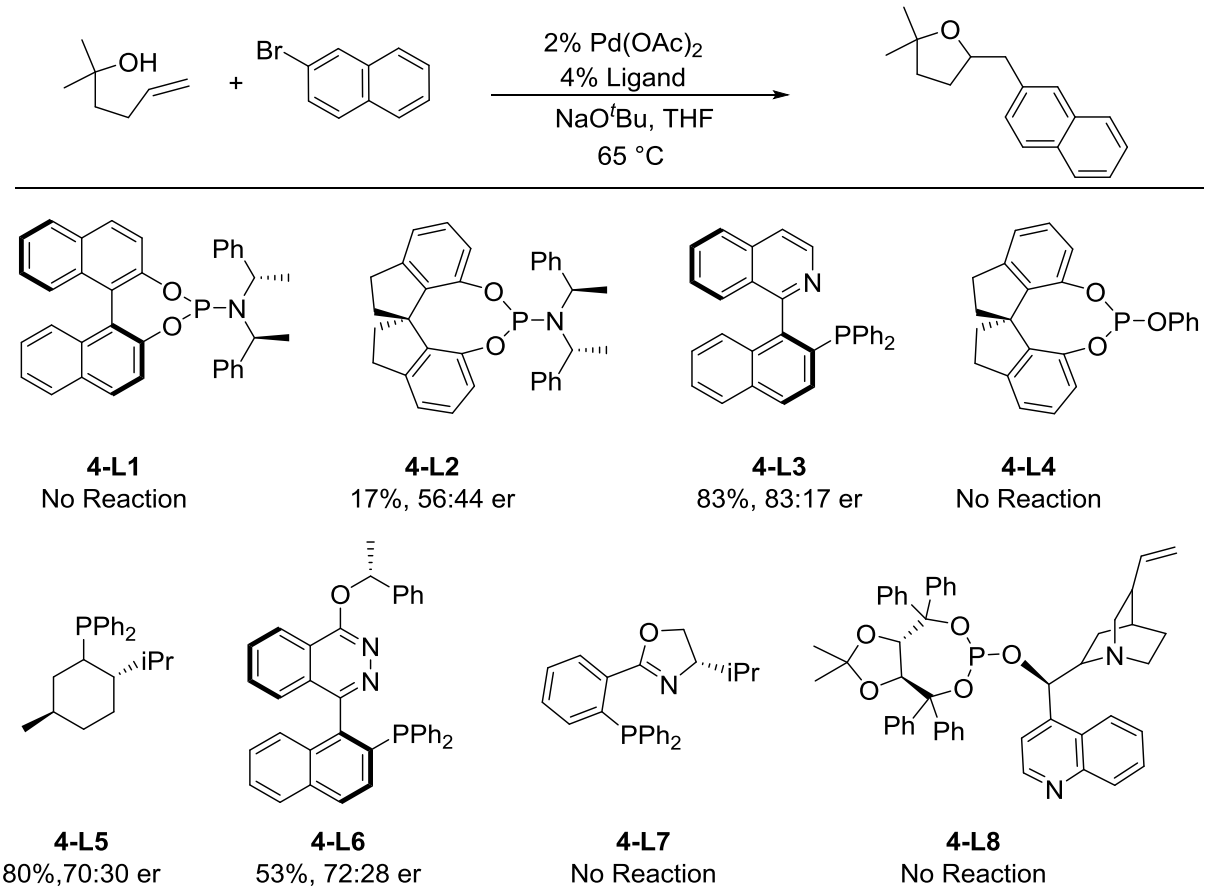
Binaphthyl
R=Ar, alkyl
Y=-OR, -NR_2

4.2 Previous Results

Previously in our group, Dr. Qifei Yang and Dr. Duy Mai both looked into the enantioselective synthesis of tetrahydrofurans.[7] As shown in Table 4.1, a screen with a variety of different ligands failed to reveal a candidate that was promising. Furthermore,

irreproducible results were obtained when attempting similar reactions with ligand scaffold **4-L3**. Although, even if this result had been reproducible, making analogues of this scaffold is time consuming and expensive.[8] Thus, we decided to synthesize analogues of easily accessible modular ligand scaffolds (Figure 4.2).

Table 4.1 Previous ligand screens

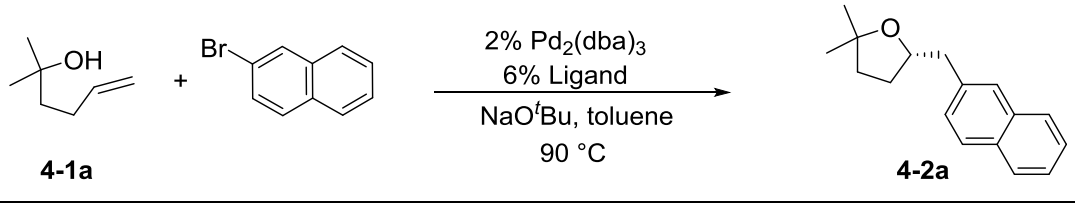


4.3 Initial Screen of Synthesized Ligands

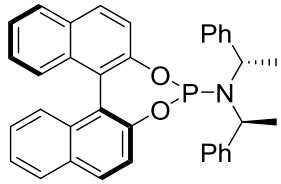
It was peculiar that ligand **4-L1** was unreactive in the system shown above (Table 4.1), as previously this scaffold afforded product in related carboamination reactions. Furthermore, similar ligands such as **4-L2** above provided the desired product, albeit in low yields. As such, we decided to run the reaction of **4-1a** with ligand **4-L1** under slightly different conditions with elevated temperatures. Gratifyingly, these

reaction conditions afforded the desired product **4-2a**, albeit in low yield and er (Table 4.2). Unfortunately, a variety of other BINOL ligands did not lead to desired levels of enantioselectivity.

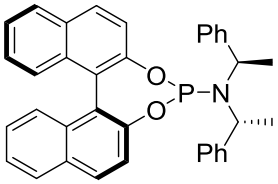
Table 4.2 Use of binol ligands with substrate **4-1a**[a]



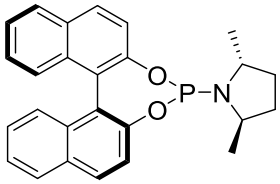
4-1a **4-2a**



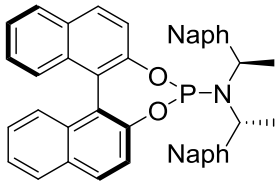
4-L1
28%, 74:26 er



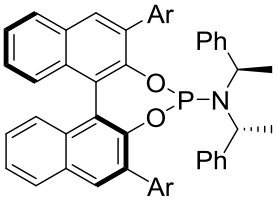
4-L9
46 %, 71:29 er



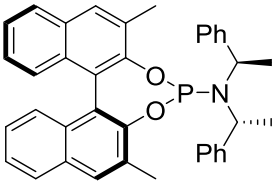
4-L10
35%, 51:49 er



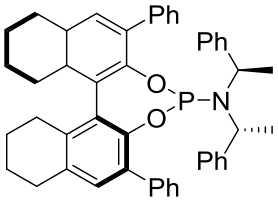
4-L11
50%, 63:37 er



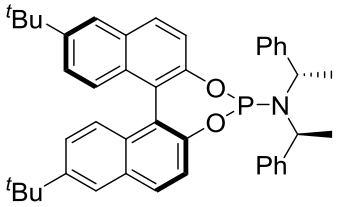
4-L12
5%, 67:33 er
Ar=2,4,6-triisopropylbenzene



4-L13
39%, 60:40 er



4-L14
30%, 70:30 er



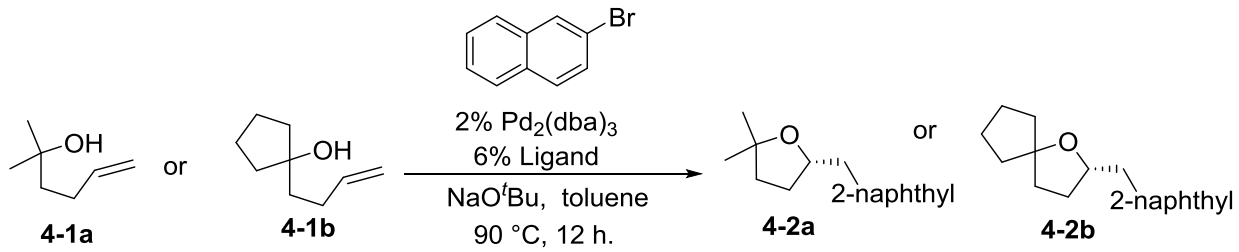
4-L15
50%, 80:20 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds.

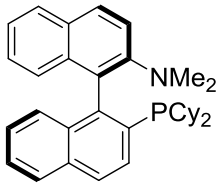
Since BINOL phosphoramidite ligands (Table 4.2) afforded poor enantioselectivities and yields, we decided to look at chiral ligands bearing scaffolds similar to racemic ligands that worked well for this reaction.[9] As such, we tested electron rich chiral binaphthyl based ligands (Table 4.3). Unfortunately, poor results were obtained with **4-L16** and **4-L17** in our reaction. We also tested the electron rich PHOX ligand **4-L18**, and it afforded poor results as well. However, PHOX ligand **4-L20** gave

better enantioselectivity, but slight modifications of this scaffold yielded inferior results for our reaction (**4-L21**). Since product **4-2b** was better for HPLC analysis, it was utilized for further ligand screens.

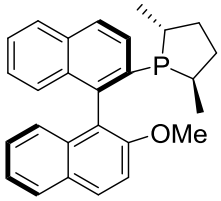
Table 4.3 Screen with binaphthyl and phox ligands[a]



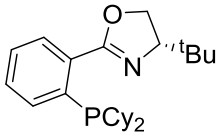
4-1a **4-1b** **4-2a** **4-2b**



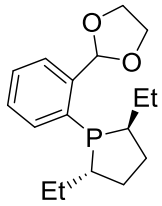
4-L16
4-2a: 51%, -66:44 er



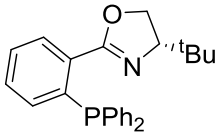
4-L17
4-2a: 85%, -59:41 er



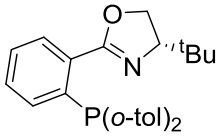
4-L18
4-2a: 53%, 51:49 er
4-2b: 20%, 52:48 er



4-L19
4-2b: 68%, -54:46 er



4-L20
4-2b: 25%, 77:23 er



4-L21
4-2b: 55%, 66:34 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds. A (-) in front of the er refers to the opposite enantiomer being formed.

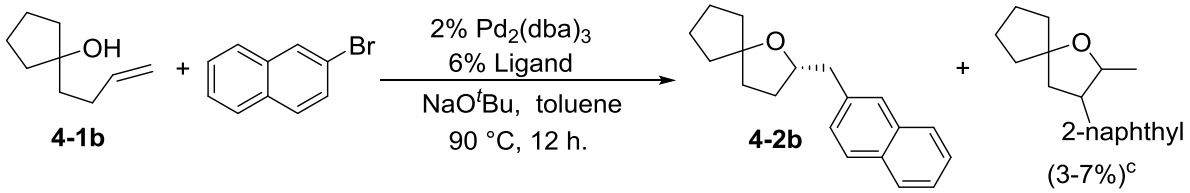
4.4 Ligand Design for Enantioselective Carboetherification Reactions

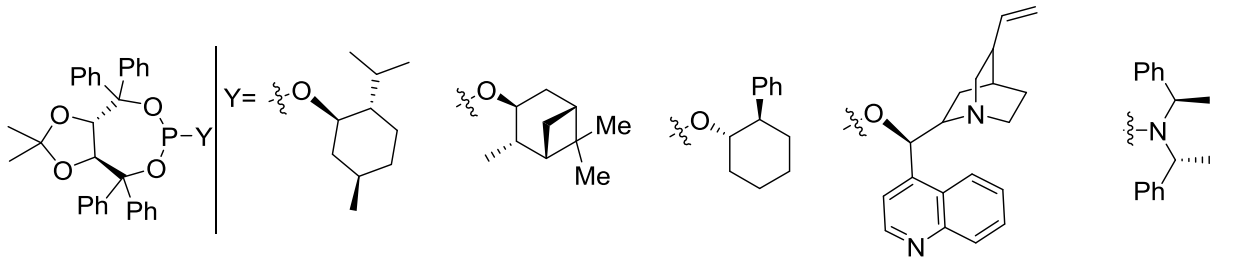
Due to the disappointing results that were obtained with the ligands above (Table 4.3 and 4.2), we decided to take a different approach with our ligand synthesis. Two criteria were important for the new ligand design: 1.) The backbone needed to be easily accessible and amenable to alteration and 2.) The chiral alcohol or amine portion needed to be cheap and readily accessible. As such, we decided to test TADDOL

based ligands with our reaction, as these moieties are highly amenable to variation. TADDOL is also derived from tartaric acid, which makes it cheap and easy to synthesize. Additionally, chiral alcohols would be used in our ligand as well, since there are a variety of cheap and naturally occurring chiral alcohols to select from. We envisioned that we could exploit nature's chemical diversity to identify a chiral alcohol framework that would be suitable for ligands used in our enantioselective carboetherification reactions.

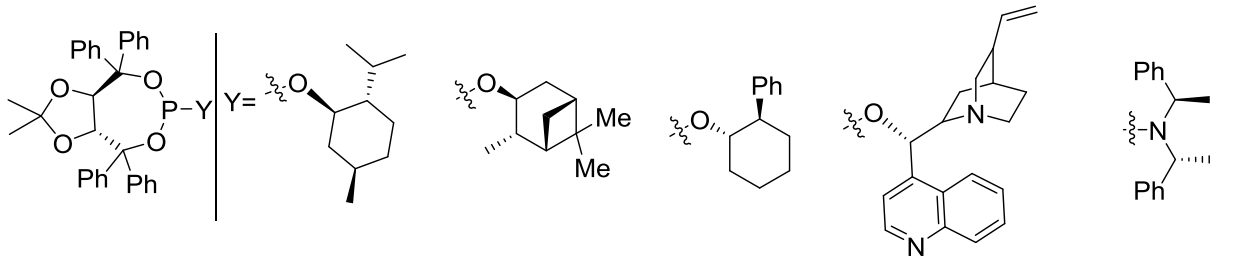
As such, we synthesized the ligands in Table 4.4 from commercially available chiral alcohols. **4-L22** and **4-L23**, ligands bearing menthol as the chiral alcohol portion, afforded good yields and decent er's for our reaction. Similar ligands, such as **4-L24** and **4-L25** which possessed isopinocampheol as the chiral alcohol portion, yielded inferior results for this reaction. As an attempt to improve the enantioselectivity, ligands **4-L26** and **4-L27** were synthesized to mimic the framework of the menthol ligand. These ligands afforded good yields and moderate enantioselectivities (better than **4-L22** and **4-L23**) for our reactions. In terms of enantioselectivity, the best ligand was **4-L8** with cinchonidine as the chiral alcohol, which afforded product **4-2b** in 25% yield and 95:5 er. Lastly, TADDOL ligands bearing the chiral bisphenethylamine moiety gave poor results, and also a small amount of regioisomer (3-7%) was detected in most of the crude NMR mixtures.

Table 4.4 TADDOL ligand screen[a]





4-L22	4-L24	4-L26	4-L8	4-L29
72%, 81:19 er	45%, 75:25 er	63%, 85:15	25%, 95:5 er	20%, 59:41 er



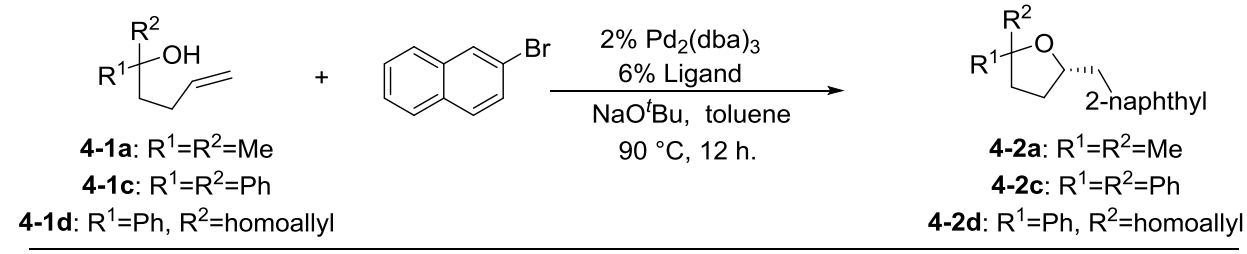
4-L23	4-L25	4-L27	4-L28	4-L30
75%, -79:21 er	40%, -73:27 er	80%, -84:16	10%, -90:10 er	No Product

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds.[c] A slight amount of regioisomer was noted in the NMR.

To test the substrate scope with the cinchona derived ligands **4-L8** and **4-L28**, as they afforded the highest enantioselectivities (Table 4.4), reactions with these ligands were carried out with substrates **4-1a**, **4-1c**, and **4-1d** (Table 4.5). As noted below, ligands **4-L8** and **4-L28** worked for substrate **4-1a**, affording product **4-2a** in low to moderate yields and decent enantioselectivities. However, these cinchona based ligands failed to afford any product under the reaction conditions with substrates **4-1c** and **4-1d**. Moreover, altering the cinchona alkaloid (**4-L31** and **4-L32**) or the TADDOL

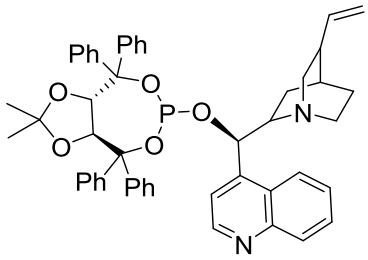
back bone (**4-L33**, **4-L34**, **4-L35**, and **4-L36**) failed to increase the yield or enantioselectivity of **4-2a**. Synthesis of similar ligand scaffolds which resembled the cinchona alkaloid afforded poor results as well.[10]

Table 4.5 Substrate scope with cinchona taddol ligands[a]

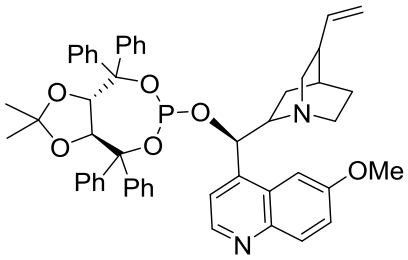


4-1a: R^1=R^2=Me
4-1c: R^1=R^2=Ph
4-1d: R^1=Ph, R^2=homoallyl

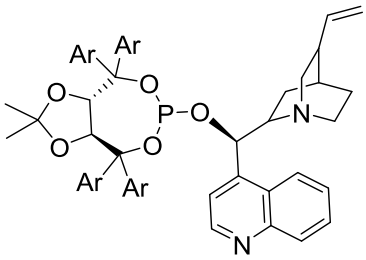
4-2a: R^1=R^2=Me
4-2c: R^1=R^2=Ph
4-2d: R^1=Ph, R^2=homoallyl



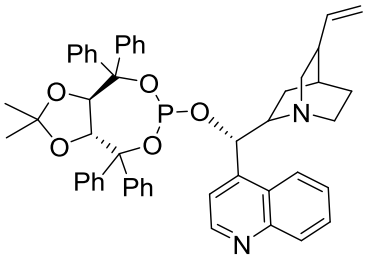
4-L8
4-2a: 60%, 85:15 er
4-2c: No product
4-2d: No product



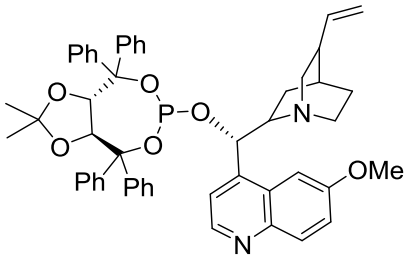
4-L31
4-2a: 27%, 83:17 er



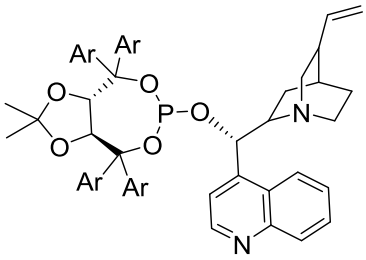
4-L33: Ar=*p*-Me-C_6H_4
4-2a: 25%, 84:16 er
4-L34: Ar=*p*-CF_3-C_6H_4
4-2a: 15%, 60:40 er



4-L28
4-2a: 52%, -89:11 er
4-2c: No product
4-2d: No product



4-L32
4-2a: 45%, -89:11 er



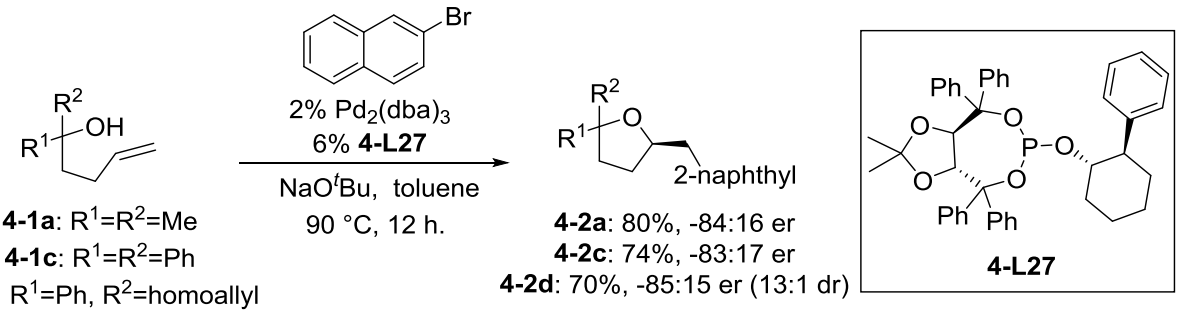
4-L35: Ar=2-naphthyl
4-2a: 20%, -59:41 er
4-L36: Ar=*p*-CF_3-C_6H_4
4-2a: 50%, -56:44 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds. A small amount (~5%) of regioisomer was detected by NMR in these reactions.

Since ligand **4-L27** afforded product **4-2b** in 80% yield and -84:16 er, we wanted to test the substrate scope with this ligand. Additionally, we knew that the chiral 2-

phenylcyclohexanol could be easily synthesized via an enzymatic resolution, which we imagined would lend itself to the facile synthesis of analogues bearing this scaffold as well.[11] Gratifyingly, the carboetherification reactions of substrates **4-1a**, **4-1c**, and **4-1d** all afforded their respective products in good yields and decent enantioselectivities (Table 4.6).

Table 4.6 Substrate scope with **4-L27**[a]



4-1a: R^1=R^2=Me
4-1c: R^1=R^2=Ph
4-1d: R^1=Ph, R^2=homoallyl

4-2a: 80%, -84:16 er
4-2c: 74%, -83:17 er
4-2d: 70%, -85:15 er (13:1 dr)

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds. [c]A small amount of regioisomer was detected by NMR for product 4-2a.

4.5 Synthesis and Enzymatic Resolution of 2-substitutued Cyclohexanols

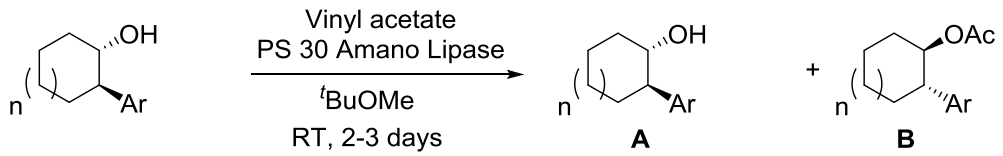
As part of our rational design of ligands, the chiral 2-phenylcyclohexanol scaffold was selected due to its similarity to menthol which worked well in ligands for our reactions (Table 4.4), and also due to the ease of synthesis for this compound.[11] Use of chiral 2-phenylcyclohexanol/TADDOL-based phosphite ligands, afforded good yields and moderate enantioselectivities for a range of products (Table 4.6 and 4.4). To further explore this ligand scaffold, we imagined systematically accessing a variety of TADDOL ligands by modifying the aryl group of this chiral alcohol.

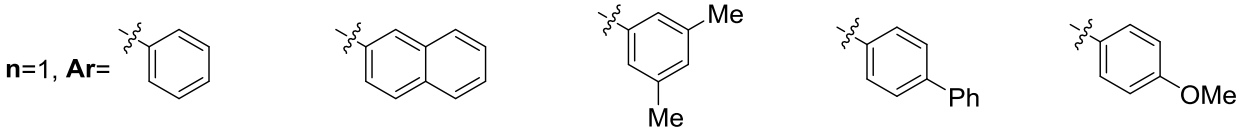
To access these desired chiral alcohols, we needed to find a synthetic route that would afford these alcohols in good enantioselectivities. To this extent, we became interested in a resolution procedure, which had previously been used to afford 2-

phenylcyclohexanol in perfect enantioselectivity.[11] To our knowledge the scope of this specific resolution procedure to afford other 2-arylcyclohexanols has yet to be established. Thus, in Table 4.7 below, we display the complete scope of this enzymatic resolution procedure to afford an array of chiral 2-arylcyclohexanols. In most cases we only determined the er of the free alcohol (**A** Table 4.7), and as long as it was >99:1 er we did not test the corresponding er of the acetylated product (**B** Table 4.7). This methodology worked well to access variety of 2-arylcyclohexanols in excellent enantioselectivities. Additionally, the resolution of 2-phenylcyclopentanol yielded 4-**A10** in 39% yield and >97:3 er. The main limitation of this resolution is the use of sterically hindered groups as noted in **4-A8**, **4-A9** and **4-A11**. No resolution was observed in these cases even under increased catalyst loading and longer reaction times.

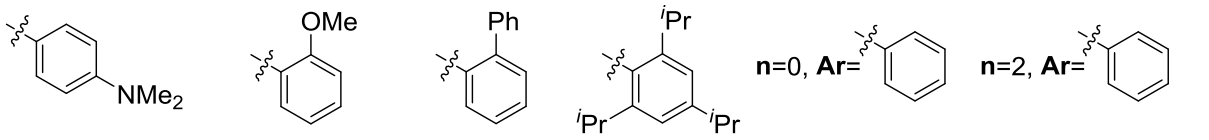
To further determine the effects of the chiral cyclohexanol portion of our TADDOL ligands on the outcome of our carboetherification reactions, we decided to synthesize chiral cyclohexanols with different groups in the 2 position. As shown in Table 4.8, a handful of chiral cyclohexanols were synthesized bearing heteroatoms in the 2 position. The larger chiral alcohols, including **4-A13** and **4-A14**, required increased reaction times, temperature, and catalyst loading. Even still, these reactions did not go to completion. Thus, we isolated the acylated products of these larger alcohols (**B** Table 4.8) and deacylated them in the presence of K_2CO_3 and methanol to determine the enantioselectivity by HPLC analysis. These deacylated products were afforded in perfect enantioselectivity. Thus, with variety of new chiral alcohols in hand (Tables 4.7 and 4.8), we synthesized a selection of new phosphite ligands to test in our enantioselective carboetherification reactions.

Table 4.7 Enzymatic resolution of 2-arylcyclohexanols[a]





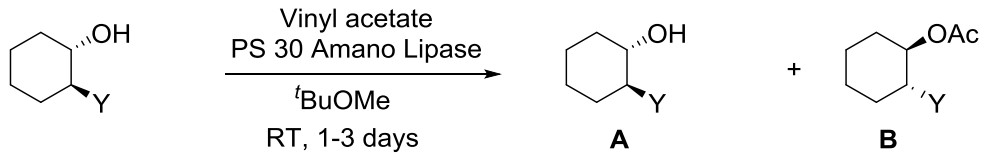
4-A1	4-A2	4-A3	4-A4	4-A5
A: 47%,>99:1 er	**A**: 45%,>99:1 er	**A**: 47%,>99:1 er	**A**: 46%,>99:1 er	**A**: 48%,>99:1 er
B: 45%, ND[c]	**B**: 44%, ND[c]	**B**: 47%, ND[c]	**B**: 44%, ND[c]	**B**: 47%, ND[c]

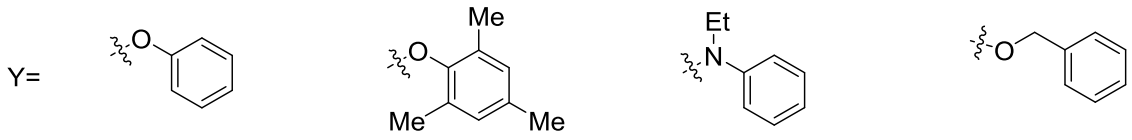


4-A6	4-A7	4-A8	4-A9	4-A10	4-A11
A: 49%,>99:1 er	**A**: 48%, 99:1 er	NR[d]	NR[d]	**A**: 39%,>97:3 er	NR[d]
B: 47%, ND[c]	**B**: 48%, ND[c]			**B**: 46%, ND[c]	

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 10 equiv vinyl acetate, 100 mg enzyme per 1 mmol substrate, ^{t}BuOMe (0.30 M), RT, 2-3 days until complete by HPLC analysis. [b]Yields and enantiomeric ratios refer to isolated compounds. [c]ND means er not determined. [d]NR means no resolution observed by HPLC under standard reaction conditions.

Table 4.8 Enzymatic resolution other cyclohexanols[a]





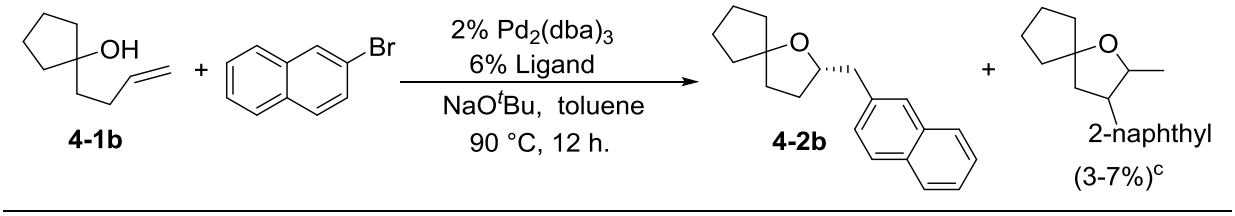
4-A12	4-A13[d]	4-A14[d]	4-A15
A: 49%,>99:1 er	**A**: ND[c],>67:33 er	**A**: ND[c],>68:32 er	**A**: 41%,>99:1 er
B: 50%, >99:1 er	**B**: 20%, >99:1 er	**B**: 19%, >99:1 er	**B**: 50%, 96:4 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate, 10 equiv vinyl acetate, 100 mg enzyme per 1 mmol substrate, ^{t}BuOMe (0.30 M), RT, 2-3 days until complete by HPLC analysis. [b]Yields and enantiomeric ratios refer to isolated compounds. [c]ND means yield not determined, and the er was determined by taking an aliquot from the reaction. [d]Reaction was ran for 1 day at RT and 4 days at 37 °C, and on the 3rd day an extra 50 mg of enzyme per 1mmol of substrate was added.

4.6 Evaluation of 2-substituted Cyclohexanol TADDOL Phosphite Ligands

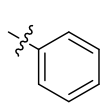
As displayed in Table 4.9 below, we synthesized a diverse set of ligands with differing groups on the chiral cyclohexanol. Unfortunately, no clear trends were noticed in terms of substituents, and all ligands tested afforded similar results. The best result was determined when using the biphenyl substituted ligand **4-L41**, which gave the product in 60% yield and 88:12 er.

Table 4.9 Effect of 2-substituted cyclohexanol on enantioselectivity[a]

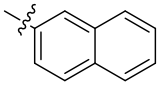


4-1b **4-2b**

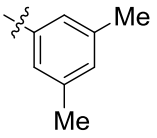
R=



DI: **4-L26**
4-2b: 63%, 85:15 er
DII: **4-L27**
4-2b: 80%, -84:16 er

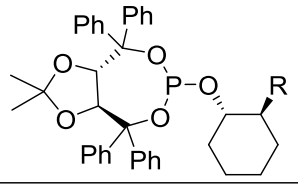


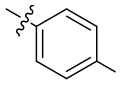
DI: **4-L37**
4-2b: 58%, 86:14 er
DII: **4-L38**
4-2b: 70%, -83:17 er



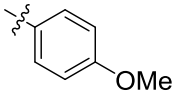
DI: **4-L39**
4-2b: 70%, 86:14 er
DII: **4-L40**
4-2b: 73%, -86:14 er

Diastereomer I (DI)

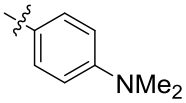




DI: **4-L41**
4-2b: 60%, 88:12 er
DII: **4-L42**
4-2b: 61%, -87:13 er

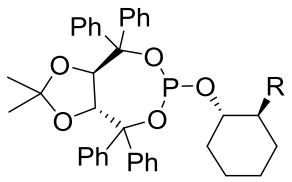


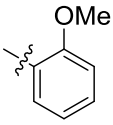
DI: **4-L43**
4-2b: 62%, 86:14
DII: **4-L44**
4-2b: 70%, -85:15 er



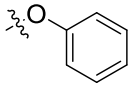
DI: **4-L45**
4-2b: 64%, 86:14 er
DII: **4-L46**
4-2b: 70%, -85:15 er

Diastereomer II (DII)





DI: **4-L47**
4-2b: 50%, 86:14 er
DII: **4-L48**
4-2b: 55%, -86:14 er

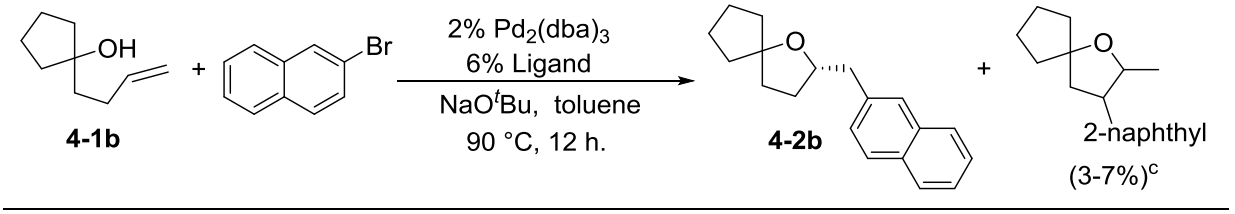


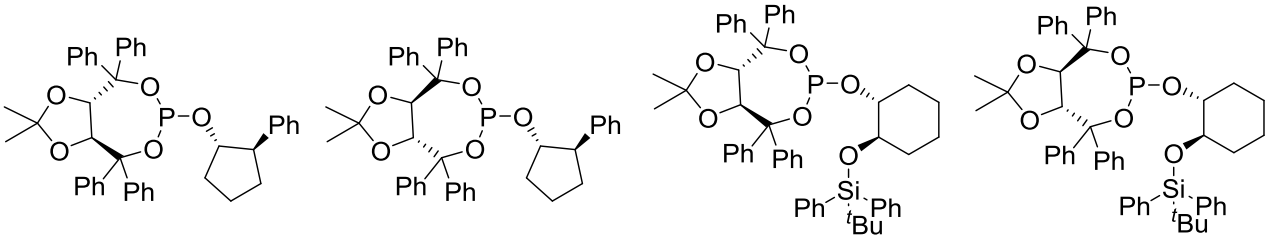
DI: **4-L49**
4-2b: 52%, 79:21 er
DII: **4-L50**
4-2b: 46%, -59:41 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds.

We also evaluated other ligands based on chiral cyclohexanols that we had synthesized, and also ligands from chiral cyclohexanols obtained by other means (Table 4.10). Again, no clear trends were noted, but based on the result from **4-L54** compared to **4-L50** (Table 4.9), it seemed increasing the sterics of the ligand might increase the enantioselectivity (Table 4.10). As such we synthesized the ligands **4-L56-57** and **4-L61-62**. Ligands **4-L56-57** possessed an extra chiral center, but failed to increase the enantioselectivity of our products. Ligands **4-L61-62** possessed an even larger moiety in the 2-position of the chiral alcohol, but these ligands also failed to improve the reaction outcomes. Also, utilizing a cis isomer instead of the trans isomer failed to improve the results as well (**4-L60**).

Table 4.10 Other chiral cyclohexanol based ligands[a]



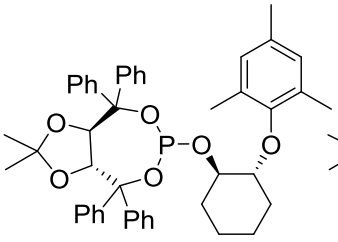


4-L50
50%, 73:27 er

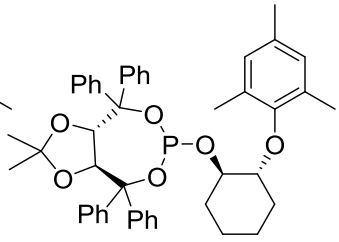
4-L51
43%, -68:32 er

4-L52
55%, 65:35 er

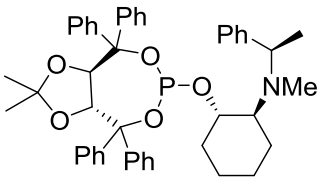
4-L53
50%, -67:33 er



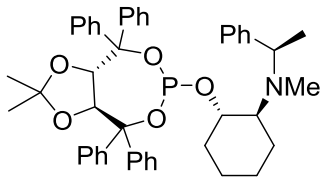
4-L54
55%, -89:11 er



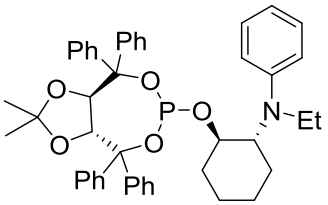
4-L55
53%, 66:34 er



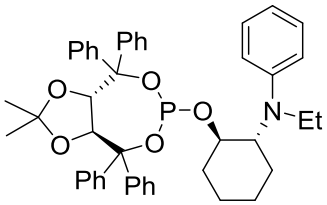
4-L56
75%, -83:17 er



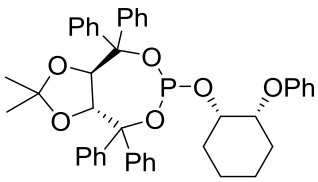
4-L57
58%, 82:18 er



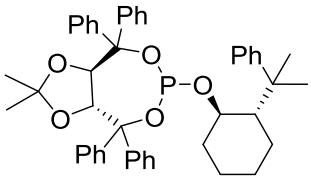
4-L58
55%, -86:14 er



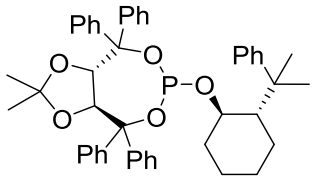
4-L59
75%, 85:15 er



4-L60
25%, -73:27 er



4-L61
48%, -82:18 er



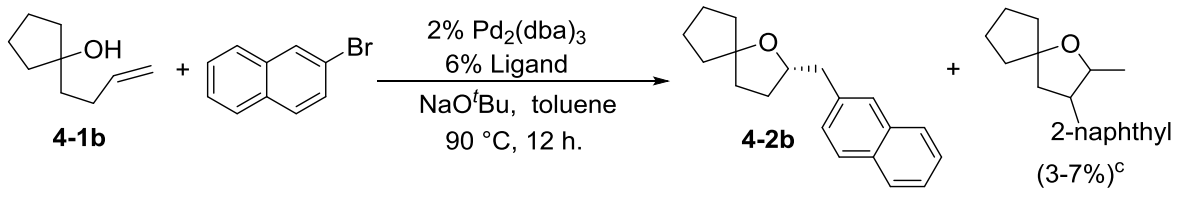
4-L62
58%, 82:18 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds.

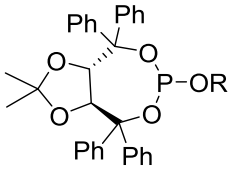
Interestingly, for most ligand scaffolds screened in all of the tables above (with only a few exceptions) both diastereomers of the ligands yielded similar results. Thus, we wanted to test racemic variants of the 2-arylcyclohexanols in these TADDOL phosphite ligands. As shown in Table 4.11 below, we discovered that some racemic ligands gave similar er's and yields when compared to their chiral counterparts. Consequently, we thought we might be able to increase the enantioselectivity of **4-2b** without the need of chiral alcohol derivatives, as the use of racemic alcohols allows us to test other larger ligands that were inaccessible through the enzymatic resolution procedure. Unfortunately, we were unable to increase the enantioselectivity of product **4-2b** with these racemic ligands, and just like in Table 4.10 increasing the size of the 2-substituent on the cyclohexanol decreased the yield and er. However, potentially 1 of the 2 diastereomers of these bulky racemic ligands was reacting more rapidly than the other one, and the diastereomer that was affording the product was yielding lower enantioselectivities. As such, we separated the two diastereomers of racemic **4-L66** to

give us **4-L70** and **4-L71** in 5:1 and 10:1 dr respectively. We subjected both diastereomers to the reaction conditions, and disappointingly neither diastereomer afforded **4-2b** in excellent enantioselectivity (Table 4.9). Thus, simply enhancing the steric bulk of these ligands seems to help the enantioselectivity to a slight extent (Table 4.9), but too much steric bulk seems to lower the observed enantioselectivity for product **4-2b** as well (Tables 4.10 and 4.11). Other racemic ligands were also ineffective at improving the reaction outcomes (**4-L72-75**).

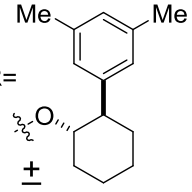
Table 4.11 Effect of racemic cyclohexanols on enantioselectivity[a]



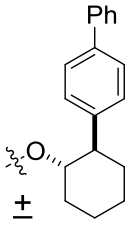
4-1b **4-2b**



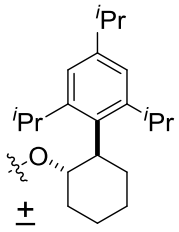
-OR=



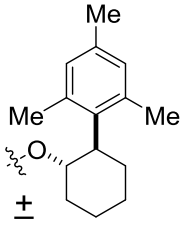
4-L63
72%, 85:15 er



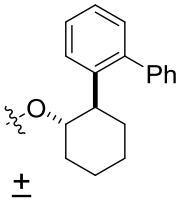
4-L64
60%, 86:14 er



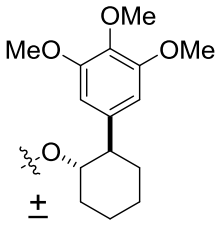
4-L65
8%, 70:30 er



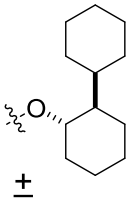
4-L66
30%, 83:17 er



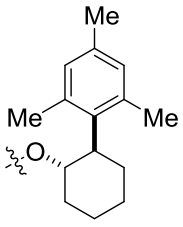
4-L67
50%, 82:18 er



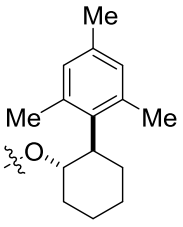
4-L68
72%, 82:18 er



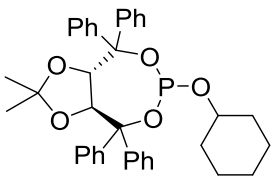
4-L69
55%, 80:20 er



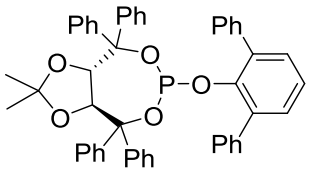
4-L70 (5:1 dr)
35%, 78:22 er



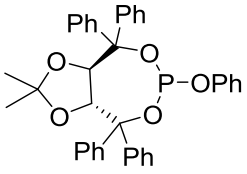
4-L71 (10:1 dr)
29%, 85:15 er



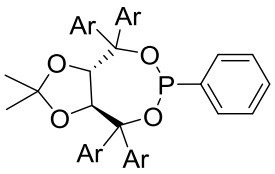
4-L72
52%, 59:41 er



4-L73
20%, 66:33 er



4-L74
25%, -73:27 er

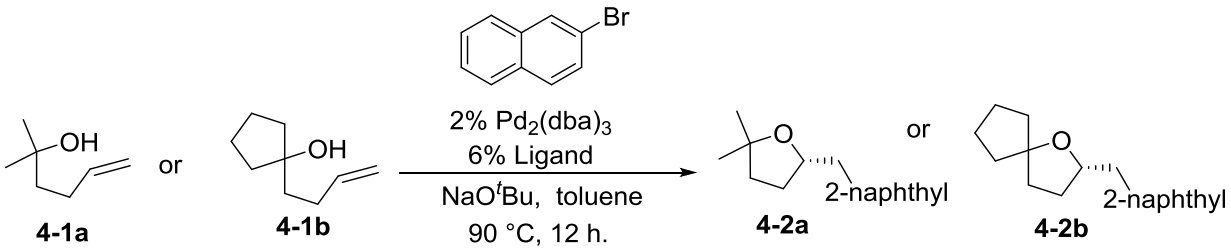


4-L75
Ar= 3,5-diethylbenzene
20%, 59:41 er

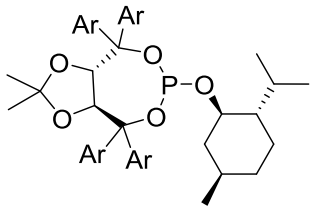
[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.0 equiv ArBr, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds. [C] Absolute configuration of **4-L70** and **4-L71** was not determined.

Ligands that possessed differing backbones were tested in these reactions too. Again, no changes we made to the ligands seemed to increase the enantioselectivity of our reactions (Table 4.12). The one exception was ligand **4-L77**, but synthesis of this ligand was challenging and we decided against using it for our reactions. As such, the best ligand from our screens for enantioselective carboetherification reactions was ligand **4-L41** (Table 4.9).

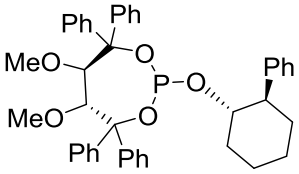
Table 4.12 Changes to the taddol backbone[a]



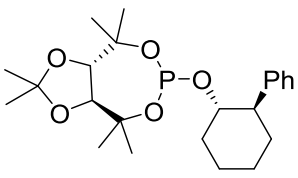
4-1a or **4-1b** → **4-2a** or **4-2b**



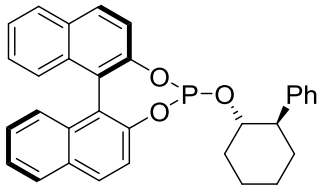
4-L76
Ar= *p*-CF_3-C_6H_4
4-2a: 76%, 64:36 er



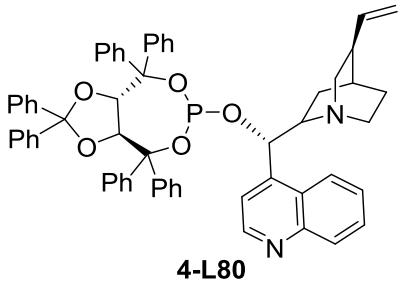
4-L77
4-2b: 52%, -88:12 er



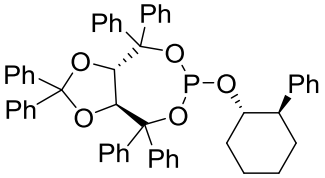
4-L78
4-2a: trace by NMR



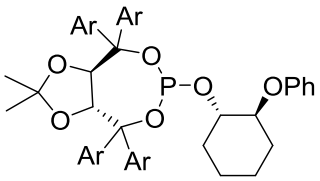
4-L79
4-2a: No product



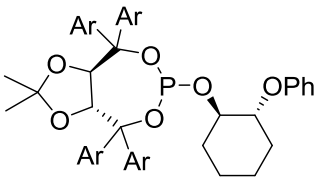
4-L80
4-2a: 35%, 87:13 er



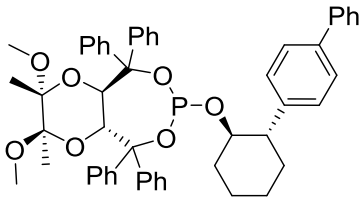
4-L81
4-2a: 66%, 76:24 er



4-L82
Ar= 3,5-dimethylbenzene
4-2b: 28%, -56:44 er



4-L83
Ar= 3,5-dimethylbenzene
4-2b: 38%, -69:31 er



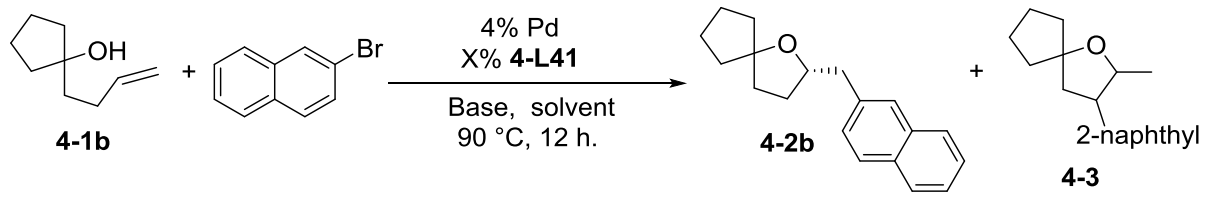
4-L84
4-2b: 48%, -76:24 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.0 equiv Ar-Br, 2.0 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 hrs. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds.

4.7 Evaluation of Substrate and Electrophile Scope

Before we began testing the scope of this reaction, we wanted to make sure we had the optimal reaction conditions in hand. Thus, we tested a variety of different solvents, Pd sources, Pd:Ln ratios, and concentrations for our reaction. From Table 4.13, the best set of conditions was entry 8 using $Pd(COD)Cl_2$ and dioxane in the reactions. However, in subsequent reactions $Pd(COD)Cl_2$ yielded isolated products that were not as clean when compared to the use of $Pd_2(dba)_3$ for substrate **4-2c**. Thus it was not used in further screens. It was also shown that no reaction is observed in the absence of ligand. Moreover, the Pd:Ln ratio does not affect the enantioselectivity observed for the reaction products, meaning that a mono-ligated complex is likely for the enantiodetermining step.

Table 4.13 Optimization of reaction conditions[a]



4-1b 4-2b 4-3

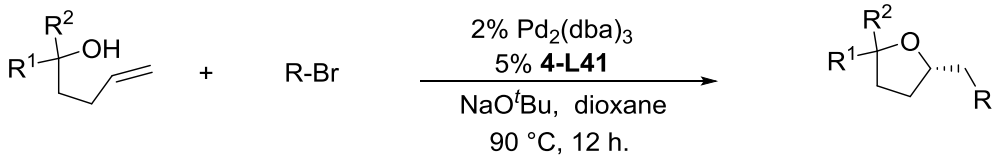
Entry	% 4-L41	Pd Source	Solvent	Conc. [M]	4-2b	dr(4-2b:4-3)
1	6%	$Pd_2(dba)_3$	toluene	0.10	60%, 88:12 er	6:1
2	0%	$Pd_2(dba)_3$	toluene	0.10	trace	N/A
3	6%	$Pd_2(dba)_3$	CF_3Ph	0.10	50%, 86:14 er	10:1
4	6%	$Pd_2(dba)_3$	dioxane	0.10	61%, 89:11 er	6:1
5	6%	$Pd_2(dba)_3$	^tBuOH	0.10	trace (30% 4-1b)	N/A
6	6%	$Pd_2(dba)_3$	monoglyme	0.10	10%, ND[c]	ND[c]
7	6%	$Pd(OAc)_2$	dioxane	0.10	30%, ND	ND
8	6%	$Pd(COD)Cl_2$	dioxane	0.10	67%, 90:10 er	11:1
9	6%	Pd(norbornadiene)Cl_2	dioxane	0.10	45%, ND	ND
10	6%	$Pd(CH_3CN)Cl_2$	dioxane	0.10	50%, ND	ND
11	6%	$PdBr_2$	dioxane	0.10	56%, ND	ND
12	6%	$Pd(COD)Cl_2$	dioxane	0.05	60%, 89:11 er	12:1
13	6%	$Pd(COD)Cl_2$	dioxane	0.20	53%, 88:12 er	10:1
14	3%	$Pd(COD)Cl_2$	dioxane	0.10	57%, 90:10 er	8:1
15	12%	$Pd(COD)Cl_2$	dioxane	0.10	53%, 90:10 er	13:1

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.0 equiv ArBr, 2.0 equiv NaO^tBu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields and enantiomeric ratios refer to isolated compounds. ND means not determined.

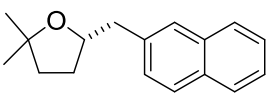
In order to determine the robustness of the enantioselective carboetherification reactions with **4-L41**, we decided to examine the scope of the reaction with different substrates (Table 4.14). Products **4-2a** and **4-2b** were afforded in moderate enantioselectivities, and a small amount of regioisomer was isolated with product **4-2b**. The gem-diphenyl substrate **4-1c** worked very well under our conditions, and the desired product **4-2c** was afforded in moderate yield and good enantioselectivity (67% and 95:5 er). The gem-diphenyl substrate also gave >95:5 er for product **4-2h**. In a few cases, interesting effects of the solvent were noted (Table 4.14). Morever, the

enantioselectivity appears to vary based on the nucleophilicity of the starting substrate as well (**4-2e** and **4-2f**). Likewise, the position of the nitrogen in heteroaryl electrophile may be affecting the enantioselectivity as well (**4-2i** and **4-2j**.) Studies are currently ongoing to determine the nature of all these effects.

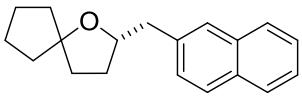
Table 4.14 Substrate scope[a]



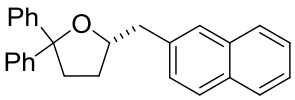
4-1a-g **4-2a-g**



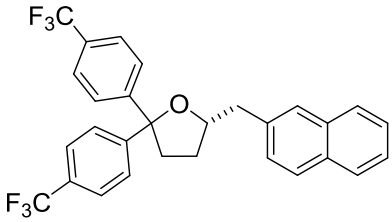
4-2a
44%, 75:25 er
52%, 88:12 er (in toluene)



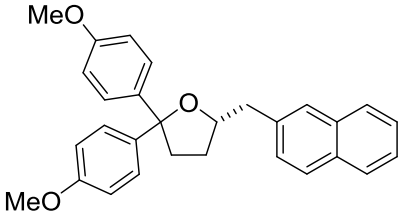
4-2b[d]
58% (10:1 dr), 89:11 er
62% (6:1 dr),[e] 88:12 er (in toluene)



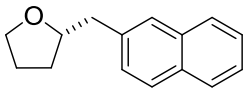
4-2c[c]
67%, 95:5 er
4-L26: 70%, 92:8 er
72%, 91:9 er (in toluene)



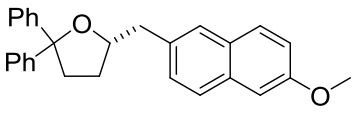
4-2e
58%, 90:10 er



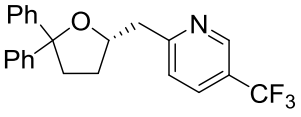
4-2f
50%, 94:6 er



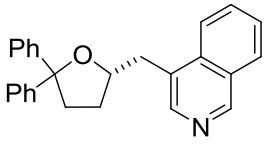
4-2g[c]
23%, 60:40 er



4-2h
66%, 95:5 er



4-2i
92%, 51:49 er



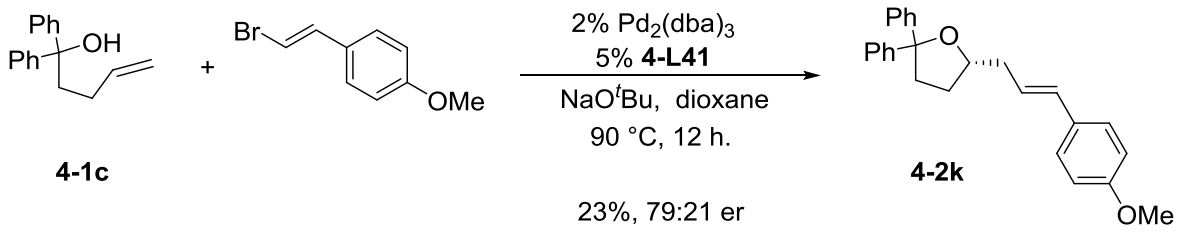
4-2j
19%, 63:37 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.20 mmol), 1.8 equiv ArBr, 2.0 equiv NaO^{t}Bu, dioxane (0.10 M), 90 °C, 12-14 h. [b]Yields and enantiomeric ratios refer to isolated compounds. [C] 1.4 equiv ArBr was used.[d]Small amount of regioisomer detected (from beta-hydride elimination after insertion).[e] Yield and product:isomer ratio are from NMR.

4.8 Determination of Absolute Configuration

To determine the absolute configuration of our molecules, we synthesized product **4-2k** to compare it to the known compound form the literature.[5] Product **4-2k** was afforded in 23% yield by NMR, and we were able to isolate pure material with the product matching spectral data in the literature perfectly. Under our conditions **4-2k** was obtained in 79:21 er. The optical rotation of **4-2k** was +4.54° (literature value was +8.30°). Thus, we determined that the configuration of our molecule matched that in the literature, and we were forming compounds with an (S) configuration.

Scheme 4.2 Determination of absolute configuration



4-1c **4-2k**

4.9 Conclusions

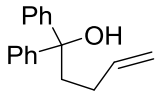
We showed that a modular TADDOL ligand scaffold was key to designing a useful ligand for Pd-catalyzed enantioselective carboetherification reactions. We discovered that altering the TADDOL backbone was not beneficial, but changing the chiral alcohol in the ligand scaffold did have an impact on the reaction outcome. Using naturally occurring chiral alcohols as an inital guide in our ligand synthesis, we were able to synthesize a ligand framework (**4-L41**) that afforded our products in good yield and enantioselectivity (up to 95:5 er). Furthermore, ligand **4-L41** works for a variety of substrates as well, showing the robust nature of this scaffold. Work is currently ongoing

to unravel the full electrophile scope, and also the scope of alkene substitution that will be tolerated in these reactions.

4.10 Experimental

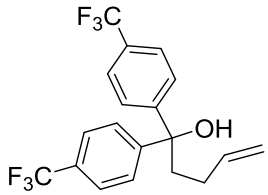
General: Reactions were carried out under nitrogen in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium was purchased from Strem Chemical Co. and used without further purification. Xylenes were purified by distillation over CaH_2 prior to use in reactions. Methylene chloride and toluene were purified using a GlassContour solvent system. All other solvents and aryl halides were purchased from commercial sources and used as is. 1-(but-3-en-1-yl)cyclopentan-1-ol (**4-1b**)[12] and 2-methylhex-5-en-2-ol (**4-1a**)[12] were synthesized by following literature procedures. Ligands in Table 4.4 were all synthesized according to a literature procedure.[6b] All yields refer to isolated compounds that are estimated to be $\geq$95% pure as judged by ^{1}H NMR or GC analysis. The yields reported in the supporting information describe the result of a single experiment.

Synthesis of Substrates:



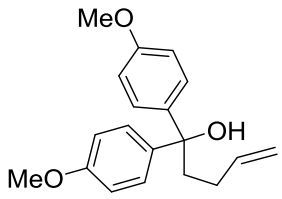
1,1-diphenylpent-4-en-1-ol (4-1c): A flame dried round bottom flask under nitrogen was equipped with a stir bar and charged with 4-pentenoyl chloride (5 mmol, 0.551 mL, 1.0 equiv.) followed by the addition of 50 mL of dry diethyl ether. The mixture was cooled to 0 °C in an ice bath for five minutes, and then PhMgBr (1M in THF, 20 mL, 4 equiv.) was added drop wise to the flask. After stirring for 12 hours, the flask was cooled to 0 °C in an ice bath and slowly quenched with 10 mL saturated ammonium chloride. The mixture was extracted 3x25 mL ethyl acetate and the combined organic layers were

dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel using hexanes/EtOAc as the eluant. This procedure afforded 864 mgs (72%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43(d, *J* = 7.4 Hz, 4 H), 7.33 (t, *J* = 8.1 Hz, 4 H), 7.24 (t, *J* = 6.6 Hz, 2 H), 6.85–6.78 (m, 2 H), 5.06–4.96 (m, 2 H), 2.44–2.38 (m, 2 H), 2.18 (s, 1 H), 2.12–2.04 (m, 2 H). Spectroscopic data was consistent with that previously stated in the literature.[13]



1,1-bis(4-(trifluoromethyl)phenyl)pent-4-en-1-ol (4-1e): A flame dried round bottom flask under nitrogen was equipped with a stir bar and charged with freshly ground Mg turnings (25 mmol, 0.607 g, 2.50 equiv.) followed by the addition of 15 mL of dry THF. To this was added 4-bromobenzotrifluoride (25 mmol, 3.50 mL, 2.5 equiv.) all at once. An ice bath was used to control the exothermic reaction, and it was allowed to stir until almost all of the Mg was gone. At the same time, a flame dried round bottom flask under nitrogen was equipped with a stir bar and charged with 4-pentenoic acid (10 mmol, 1.02 mL, 1.0 equiv.) followed by the addition of 20 mL of dry benzene. The mixture was cooled to 0 °C in an ice bath for five minutes and then oxallyl chloride (20 mmol, 1.75 mL, 2.0 equiv.) was slowly added to the flask. It was allowed to warm to room temperature and stir for one hour. After this time, the solvent was removed in vacuo, and the round bottom flask was placed under nitrogen and equipped with a stir bar. 15 mL of dry THF was added to this crude 4-pentenoyl chloride and it was cooled

to 0 °C in an ice bath. The freshly prepared grignard reagent from above was added drop wise to the flask containing the crude 4-pentenoyl chloride. It was allowed to warm to room temperature and after stirring for 12 hours the flask was cooled to 0 °C in an ice bath and slowly quenched with 10 mL saturated ammonium chloride. The mixture was extracted 3x25 mL ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel using hexanes/EtOAc as the eluant. This procedure afforded 1.25 g (34%) of the title compound as a light yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 4 H), 7.56 (d, *J* = 8.3 Hz, 4 H), 5.94–5.83 (m, 1 H), 5.10–4.99 (m, 2 H), 2.51–2.42 (m, 2 H), 2.35 (br., s, 1 H), 2.15–2.06 (m, 2 H); ^{13}C NMR (125 MHz $CDCl_3$) δ 158.9, 158.7, 158.5, 141.8, 139.6, 139.0, 137.5, 135.9, 132.5, 131.0, 128.6, 127.4, 124.8, 115.0, 114.8, 113.7, 113.6, 113.5, 77.9, 55.4, 41.4, 34.3, 28.6 (C-F couplings for this compound were not taken into account and peaks were listed as displayed in the spectra) ; IR (film) 3473.3, 2357.5, and 1617.2 cm^{-1}; MS (EI+) 374.1107 (374.1105 calcd for $C_{19}H_{16}F_6O$, M^+).



1,1-bis(4-methoxyphenyl)pent-4-en-1-ol (4-1f): A flame dried round bottom flask under nitrogen was equipped with a stir bar and charged with freshly ground Mg turnings (8.68 mmol, 0.211 g, 3.10 equiv.) followed by the addition of 8 mL of dry THF. To this was added 4-bromoanisole (8.42 mmol, 1.05 mL, 3.0 equiv.) all at once. One drop of dibromoethane was added to the reaction, and it was allowed to stir until almost

all of the Mg was gone. The grignard was cooled to 0 °C in an ice bath for five minutes, and then 4-pentenoyl chloride (2.80 mmol, 0.310 mL, 1.0 equiv.) in 5 mL of dry THF was added drop wise to this flask. It was allowed to warm to room temperature and after stirring for 12 hours, the flask was cooled to 0 °C in an ice bath and slowly quenched with 5 mL saturated ammonium chloride. The mixture was extracted 3x15 mL ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel using hexanes/EtOAc as the eluant. This procedure afforded 200 mgs (25%) of the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 4 H), 6.84 (d, *J* = 9.0 Hz, 4 H), 5.90–5.80 (m, 1 H), 5.03–4.92 (m, 2 H), 3.74 (s, 6 H) 2.35–2.30 (m, 2 H), 2.09–2.02 (m, 3 H); ^{13}C NMR (125 MHz $CDCl_3$) δ 158.3, 139.4, 138.8, 127.2, 114.6, 113.4, 55.2, 41.2, 28.5.

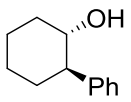
General Procedure A: Synthesis of Racemic 2-Arylcyclohexanols

Freshly ground magnesium turnings (1.45 equiv.) were added to a flame dried 2-neck round bottom flask under nitrogen, and it was equipped with a reflux condenser. Dry THF (1 M) was added to the flask. The appropriate aryl bromide (1.50 equiv.) was added in THF (3 M). If the reaction commenced to auto-reflux, it was controlled with an ice bath. If the reactions failed to initiate, the reactions were heated under conditions that allowed for a controlled reflux until the magnesium turnings were gone. Once the magnesium turnings had disappeared, the reaction was cooled to -20 °C for 10 minutes. After this time, 8 mol% CuCl was added to the reaction, immediately followed by the addition of cyclohexene oxide (1.0 equiv.) in THF (2 mL THF: 1mL oxide). The mixture

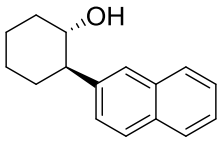
was allowed to slowly warm to room temperature and then stirred at that temperature for 4 hours. The reaction was then cooled to 0 °C and quenched with saturated ammonium chloride (1mL/mmol). The mixture was filtered through a pad of celite, and added to a separatory funnel. It was extracted 3x with ethyl acetate (1mL/mmol) and then dried over sodium sulfate. The solvent was then evaporated in vacuo and the crude residue was purified by flash chromatography on silica gel to afford the desired product.

General Procedure B: Synthesis of Enantiomerically Pure 2-Arylcyclohexanols

To a flame dried round bottom flask under nitrogen was added PS 30 Amano Lipase (100 mgs / 1 mmol alcohol). To this was added the appropriate (+/-) trans-2-arylcyclohexanol (1.0 equiv.) followed by *tert*-Butyl methyl ether (3 mL / 1 mmol). To this mixture was added vinyl acetate (10 equiv.) and the reactions were allowed to stir 1-3 days until completed based on chiral HPLC analysis. When complete, the mixture was filtered on a fritted funnel and the enzyme was washed with diethyl ether and then recycled for future use if desired. The solvent was then evaporated in vacuo and the crude residue was purified by flash chromatography on silica gel to afford the desired products. Typically although the acetylated product was isolated the enantioselectivity of this product was not determined by HPLC except when noted.

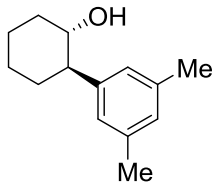


(1S,2R)-2-phenylcyclohexan-1-ol (4-A1): The title compound was synthesized as previously noted in the literature, and all spectroscopic data matched as well.[11] This material was judged to be >99:1 er by chiral HPLC analysis (Chiracel OJH, 25 cm x 4.6 mm, 4.00% IPA/Hexanes, 0.75 mL/min, λ 215 nm, RT= 12.4 and 13.3 min).



(1S,2R)-2-(naphthalen-2-yl)cyclohexan-1-ol (4-A2): According to general procedure A the grignard reagent was formed with Mg (43.5 mmol, 1.05 g) and 2-Bromonaphthalene (45 mmol, 9.31 g). Then CuCl (2.4 mmol, 0.238 g) was added followed by cyclohexene oxide (30 mmol, 3.04 mL). This procedure afforded 3.30 g (48 %) of racemic 4-A2 as a white solid.

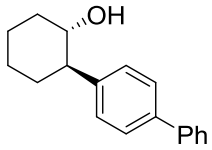
PS 30 Amano Lipase (662 mgs), racemic 4-A1 (6.62 mmol, 1.50 g), ^{t}BuOMe (18 mL), and vinyl acetate (6.1 mL, 66.2 mmol) were reacted according to general procedure B for 3 days. This procedure afforded 678 mgs (45%) of the title compound as a white solid. Spectroscopic data matched the reported data in the literature.[16] This material was judged to be >99:1 er by chiral HPLC analysis (Chiracel OJH, 25 cm x 4.6 mm, 4.00% IPA/Hexanes, 0.75 mL/min, λ 225 nm, RT= 35.0 and 43.0 min).



(1S,2R)-2-(3,5-dimethylphenyl)cyclohexan-1-ol (4-A3): According to general procedure A the grignard reagent was formed with Mg (29 mmol, 0.704 g) and 5-Bromo-*m*-xylene (30 mmol, 4.08 mL). Then CuCl (1.6 mmol, 0.158 g) was added followed by cyclohexene oxide (20 mmol, 2.02 mL). This procedure afforded 3.00 g (73 %) of racemic 4-A3 as a white solid.

PS 30 Amano Lipase (662 mgs), racemic 4-A3 (6.62 mmol, 1.35 g), ^{t}BuOMe (18 mL), and vinyl acetate (6.1 mL, 66.2 mmol) were reacted according to general procedure B

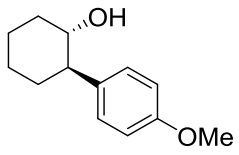
for 3 days. This procedure afforded 634 mgs (47%) of the title compound as a white solid, mp 57–60 °C. This material was judged to be >99:1 er by chiral HPLC analysis (Chiracel OJH, 25 cm x 4.6 mm, 4.00% IPA/Hexanes, 0.50 mL/min, λ 225 nm, RT= 8.4 and 9.1 min). $[\alpha]^{23}_{D}$ -39.0 (*c* 2.50, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.91–6.88 (m, 3 H), 3.66 (td, *J* = 10.2, 4.2 Hz, 1 H), 2.37 (td, *J* = 11.2, 3.6 Hz, 1 H), 2.33 (s, 6H), 2.15–2.10 (m, 1 H), 1.89–1.83 (m, 2 H), 1.76 (app. d, *J* = 13.6 Hz, 1 H), 1.62 (s, 1H), 1.56–1.30 (m, 4 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 143.3, 138.4, 128.7, 125.9, 74.5, 53.3, 34.6, 33.5, 26.3, 25.3, 21.5; IR (film) 3445.7, 2925.4, and 1603.4 cm^{-1}; MS (ESI+) 227.1410 (227.1406 calcd for $C_{14}H_{20}O$, M + Na^{+}).



(1S,2R)-2-([1,1'-biphenyl]-4-yl)cyclohexan-1-ol (4-A4): According to general procedure A the grignard reagent was formed with Mg (48.2mmol, 1.17 g) and 4-Bromobiphenyl (50 mmol,11.65 g). Then CuCl (2.66 mmol, 0.257 g) was added followed by cyclohexene oxide (33.3 mmol, 3.36 mL). This procedure afforded 4.00 g (48 %) of racemic 4-A4 as a white solid.

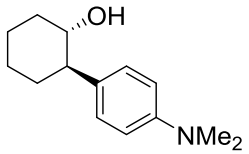
PS 30 Amano Lipase (1.50 g), racemic 4-A4 (14.8 mmol, 3.74 g), ^{t}BuOMe (40 mL), and vinyl acetate (13.6 mL, 148 mmol) were reacted according to general procedure B for 3 days. This procedure afforded 1.72 (46%) of the title compound as a white solid, mp 122–125 °C. This material was judged to be >99:1 er by chiral HPLC analysis (Chiracel OJH, 25 cm x 4.6 mm, 4.00% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 21.8 and 25.0 min). $[\alpha]^{23}_{D}$ -13.99 (*c* 3.38, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62–7.57 (m, 4 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 7.37–7.34 (m, 3 H), 3.72 (td, *J* = 10.0, 4.2 Hz, 1 H), 2.51 (td, *J*

= 11.1, 3.6 Hz, 1 H), 2.1–2.15 (m, 1 H), 1.95–1.88 (m, 2 H), 1.81 (app. d, *J* = 13.2 Hz, 1 H), 1.64–1.35 (m, 5 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 142.6, 141.1, 140.0, 128.9, 128.5, 127.7, 127.3, 127.2, 74.6, 53.1, 34.5, 33.5, 26.2, 25.3; IR (film) 3548.0, 2918.6, and 1490.0 cm^{-1}; MS (ESI+) 270.1850 (270.1852 calcd for $C_{18}H_{20}O$, M + NH_4^+).



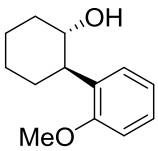
(1S,2R)-2-(4-methoxyphenyl)cyclohexan-1-ol (4-A5): According to general procedure A the grignard reagent was formed with Mg (8.03 mmol, 195 mg) and 4-Bromoanisole (8.31 mmol,1.04 mL). Then CuCl (0.44 mmol, 0.045 g) was added followed by cyclohexene oxide (5.54 mmol, 0.560 mL). This procedure afforded 0.800 g (70 %) of racemic 4-A5 as a white solid.

PS 30 Amano Lipase (0.335 g), racemic 4-A5 (3.35 mmol, 0.692 g), ^{t}BuOMe (9 mL), and vinyl acetate (3.08 mL, 33.5 mmol) were reacted according to general procedure B for 2 days. This procedure afforded 330 mgs (48%) of the title compound as a white solid, mp 73–76 °C. This material was judged to be >99:1 er by chiral HPLC analysis (Chiracel OJH, 25 cm x 4.6 mm, 5.00% IPA/Hexanes, 1.00 mL/min, λ 225 nm, RT= 15.7 and 17.3 min). $[\alpha]^{23}_D$ -107.0 (*c* 1.17, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.62–7.57 (m, 4 H), 7.45 (t, *J* = 7.7 Hz, 2 H), 7.37–7.34 (m, 3 H), 3.72 (td, *J* = 10.0, 4.2 Hz, 1 H), 2.51 (td, *J* = 11.1, 3.6 Hz, 1 H), 2.18–2.15 (m, 1 H), 1.95–1.88 (m, 2 H), 1.81 (app. d, *J* = 13.2 Hz, 1 H), 1.64–1.35 (m, 5 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 142.6, 141.1, 140.0, 128.9, 128.5, 127.7, 127.3, 127.2, 74.6, 53.1, 34.5, 33.5, 26.2, 25.3; IR (film) 3411.9, 2926.7, and 1611.5 cm^{-1}; MS (ESI+) 229.1196 (229.1199 calcd for $C_{13}H_{18}O_2$, M + Na^+).



(1S,2R)-2-(4-(dimethylamino)phenyl)cyclohexan-1-ol (4-A6): According to general procedure A the grignard reagent was formed with Mg (14.5 mmol, 352 mg) and4-Bromo-N,N-dimethylaniline (15.0 mmol,3.01 g). Then CuCl (0.80 mmol, 0.079 g) was added followed by cyclohexene oxide (10.0 mmol, 1.01 mL). This procedure afforded 1.50 g (68 %) of racemic 4-A6 as a white solid.

PS 30 Amano Lipase (0.455 g), racemic 4-A6 (4.45 mmol, 1.00 g), ^{t}BuOMe (14 mL), and vinyl acetate (4.19 mL, 45.5 mmol) were reacted according to general procedure B for 2 days. This procedure afforded 493mgs (49%) of the title compound as a white solid, mp 63–66 °C. This material was judged to be >99:1 er by chiral HPLC analysis (Chiracel ODH, 15 cm x 4.6 mm, 2.50% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 8.5 and 9.4 min). $[\alpha]^{23}_{D}$ -31.8 (*c* 2.55, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.5 Hz, 2 H), 3.60 (td, *J* = 10.2, 4.5 Hz, 1 H), 2.95 (s, 6H), 2.34 (td, *J* = 11.3, 3.8 Hz, 1 H), 2.15–2.10 (m, 1 H), 1.88–1.82 (m, 2 H), 1.76 (app. d, *J* = 13.1 Hz, 1 H), 1.65 (s, br, 1 H), 1.54–1.30 (m, 4 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 149.9, 131.0, 128.7, 113.3, 74.8, 52.4, 40.9, 34.4, 33.5, 26.4, 25.3; IR (film) 3403.9, 2922.7, and 1613.1 cm^{-1}; MS (ESI+) 220.1694 (220.1696 calcd for $C_{14}H_{21}NO$, M + H^{+}).



(1S,2R)-2-(2-methoxyphenyl)cyclohexan-1-ol (4-A7): According to general procedure A the grignard reagent was formed with Mg (24.2 mmol, 585 mg) and 2-Bromoanisole

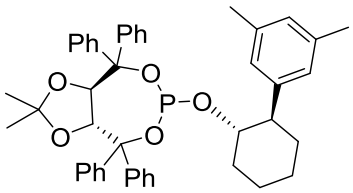
(25.0 mmol, 3.11 mL). Then CuCl (1.32 mmol, 0.132 g) was added followed by cyclohexene oxide (16.66 mmol, 1.65 mL). This procedure afforded 1.39 g (41 %) of racemic 4-A7 as a clear oil.

PS 30 Amano Lipase (0.491 g), racemic 4-A7 (4.91 mmol, 1.00 g), ^{t}BuOMe (12 mL), and vinyl acetate (4.52 mL, 49.2 mmol) were reacted according to general procedure B for 3 days. This procedure afforded 490 mgs (48%) of the title compound as a clear oil. This material was judged to be 99:1 er by chiral HPLC analysis (Chiracel ADH, 25 cm x 4.6 mm, 4.0% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 12.4 and 13.3 min). $[\alpha]^{23}_{D}$ -62.4 (*c* 1.65, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.2 Hz, 1 H), 7.20 (t, *J* = 8.2 Hz, 1 H), 6.96 (t, *J* = 7.5 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 3.82 (s, 3H), 3.73 (td, *J* = 10.0, 4.9 Hz, 1 H), 3.04–2.96 (m, 1 H), 2.16–2.02 (m, 1 H), 1.88–1.70 (m, 4 H), 1.53–1.31 (m, 4 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 157.9, 131.7, 127.6, 127.5, 121.2, 111.0, 74.2, 55.7, 45.3, 35.4, 32.5, 26.4, 25.3; IR (film) 3420.3, 2928.4, and 1599.4 cm^{-1}; MS (ESI+) 229.1154 (229.1199 calcd for $C_{13}H_{18}O_2$, M + H^+).

General Procedure C: Synthesis of Chiral Phosphite 2-Arylcyclohexanol Ligands

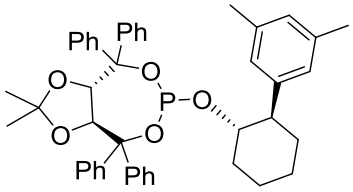
The following ligands were synthesized according to a slightly modified literature procedure.[6b] A flame dried round bottom flask was charged with the appropriate chiral 2-arylcyclohexanol (1.05 equiv.) and dry DCM (0.50 M). To this flask containing the stirring chiral 2-arylcyclohexanol was added PCl_3 (1.05 equiv.) and this mixture was allowed to stir for 1 hour at room temperature. After this time, dry NEt_3 (4.0 equiv.) was added drop wise and the mixture stirred for thirty minutes. Next, the appropriate Taddol precursor (1.00 equiv.) was added to the mixture in dry DCM (0.50 M). The reaction was

allowed to stir 12 to 14 hours and then diethyl ether was added 5 mL/ mmol and the mixture was filtered through celite. The solvent was evaporated in vacuo and the crude residue was purified by flash chromatography on silica gel to afford the desired products.

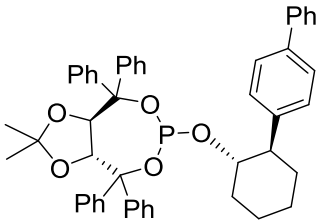


(3aR,8aR)-6-(((1S,2R)-2-(3,5-dimethylphenyl)cyclohexyl)oxy)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4-L40): According to general procedure C (1S,2R)-2-(3,5-dimethylphenyl)cyclohexan-1-ol (0.337 mmol, 69 mgs) was stirred with PCl_3 (0.337 mmol, 30 µL) for 1 hour. Next, NEt_3 (1.48 mmol, 180 µL) was added. After 30 minutes, (R,R)-Taddol (0.321 mmol, 150 mgs) was added and the reaction stirred for 12-14 hours. This procedure afforded 120 mgs (53%) of the title compound as a white foamy solid, mp 73–76 °C. $[\alpha]^{23}_{D}$ -243.5 (*c* 1.20, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 2 H), 7.36 (t, *J* = 7.7 Hz, 4 H), 7.29–7.25 (m, 4 H), 7.24–7.11 (m, 8 H), 7.00 (d, *J* = 6.9 Hz, 2 H), 6.84 (s, 2H), 6.73 (s, 1H), 4.87 (s, 2H), 4.65 (app. qd, *J* = 10.1, 4.2 Hz, 1 H), 2.59–2.54 (m, 1 H), 2.33–2.28 (m, 1 H), 1.98 (s, 6H), 1.90–1.85 (m, 1 H), 1.79–1.72 (m, 2 H), 1.67–1.60 (m, 1 H), 1.56–1.49 (m, 1 H), 1.42–1.27 (m, 2 H), 1.22 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 146.6, 146.1, 143.7, 141.7, 141.3, 137.5, 129.2, 129.0, 128.9, 128.1, 127.9, 127.8, 127.53, 127.48, 127.4, 127.3, 127.27, 127.22, 127.20, 126.4, 111.9, 83.0, 82.8, 82.7, 82.29, 82.27, 81.8, 81.7, 77.8, 35.8, 33.9, 27.6, 26.1, 25.4, 25.3, 21.2 (Due to the complexity of the spectra all the peaks are listed without taking into consideration C-P couplings); ^{31}P NMR (283 MHz $CDCl_3$) δ 139.0; IR (film) 2935.2, 1601.9, and 1447.3 cm^{-}

^{1}; MS (ESI+) 699.3226 (699.3234 calcd for $C_{45}H_{47}O_5P$, M + H^+).

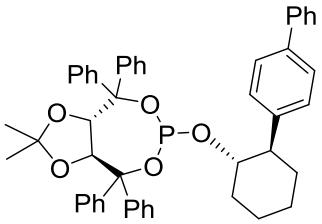


(3aS,8aS)-6-(((1S,2R)-2-(3,5-dimethylphenyl)cyclohexyl)oxy)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4-L39): According to general procedure C (1S,2R)-2-(3,5-dimethylphenyl)cyclohexan-1-ol (0.337 mmol, 69 mgs) was stirred with PCl_3 (0.337 mmol, 30 µL) for 1 hour. Next, NEt_3 (1.48 mmol, 180 µL) was added. After 30 minutes, (S,S)-Taddol (0.321 mmol, 150 mgs) was added and the reaction stirred for 12-14 hours. This procedure afforded 110 mgs (50%) of the title compound as a white foamy solid, mp 70–73 °C. $[\alpha]^{23}_{D}$ -56.7 (*c* 0.95, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2 H), 7.35–7.29 (m, 8 H), 7.27–7.15 (m, 10 H), 6.79 (s, 2H), 6.76–6.74 (m, 1 H), 5.02 (d, *J* = 8.3 Hz, 1 H), 4.90 (d, *J* = 8.3 Hz, 1 H), 4.65 (app. qd, *J* = 9.8, 4.3 Hz, 1 H), 2.54–2.59 (m, 1 H), 2.23–2.19 (m, 1 H), 2.02 (s, 6H), 1.90–1.86 (m, 1 H), 1.84–1.79 (m, 1 H), 1.77–1.72 (m, 1 H), 1.63–1.56 (m, 1 H), 1.46–1.40 (m, 2 H), 1.34–1.26 (m, 1 H), 1.10 (s, 3 H), 0.28 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 146.5, 146.2, 143.5, 142.1, 141.4, 137.4, 129.0, 128.8, 128.2, 127.9, 127.8, 127.6, 127.5, 127.4, 127.34, 127.27, 127.2, 127.1, 126.4, 83.1, 82.5, 82.44, 82.38, 82.02, 81.99, 77.82, 77.77, 51.65, 51.63, 35.5, 33.4, 27.5, 26.0, 25.6, 25.4, 21.3 (Due to the complexity of the spectra all the peaks are listed without taking into consideration C-P couplings); ^{31}P NMR (283 MHz $CDCl_3$) δ 137.8; IR (film) 2925.2, 1602.3, and 1446.8 cm^{-1}; MS (ESI+) 699.3226 (699.3234 calcd for $C_{45}H_{47}O_5P$, M + H^+).



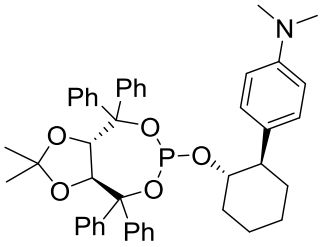
(3aR,8aR)-6-(((1S,2R)-2-([1,1'-biphenyl]-4-yl)cyclohexyl)oxy)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4-L40):

According to general procedure C (1S,2R)-2-([1,1'-biphenyl]-4-yl)cyclohexan-1-ol (0.337 mmol, 85 mgs) was stirred with PCl_3 (0.337 mmol, 30 µL) for 1 hour. Next, NEt_3 (1.48 mmol, 180 µL) was added. After 30 minutes, (R.R)-Taddol (0.321 mmol, 150 mgs) was added and the reaction stirred for 12-14 hours. This procedure afforded 85 mgs (35%) of the title compound as a white foamy solid, mp 180–183 °C. $[\alpha]^{23}_{D}$ -130.6 (*c* 3.81, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2 H), 7.42–7.06 (m, 27 H), 4.98–4.95 (m, 1 H), 4.92 (d, *J* = Hz, 8.5 Hz, 1 H), 4.63–4.57 (m, 1 H), 2.75–2.70 (m, 1 H), 2.32 (app. d, *J* = 13.4 Hz, 1 H), 1.98 (app. d, *J* = 13.6 Hz, 1 H), 1.89–1.76 (m, 2 H), 1.72–1.56 (m, 2 H), 1.45–1.34 (m, 2 H), 1.22 (s, 3 H), 0.33 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 146.6, 146.1, 143.0, 141.8, 141.3, 141.2, 139.4, 129.4, 129.0, 128.91, 128.88, 128.6, 128.0, 127.8, 127.53, 127.47, 127.44, 127.37, 127.33, 127.29, 127.2, 127.14, 127.11, 127.1, 126.88, 112.0, 82.9, 82.7, 82.6, 82.12, 82.10, 81.91, 81.87, 78.10, 78.08, 51.39, 51.37, 35.7, 33.8, 27.6, 26.0, 25.5, 25.3 (Due to the complexity of the spectra all the peaks are listed without taking into consideration C-P couplings); ^{31}P NMR (283 MHz $CDCl_3$) δ 140.7; IR (film) 2932.0, and 1446.9 cm^{-1}; MS (ESI+) 747.3232 (747.3234 calcd for $C_{49}H_{47}O_5P$, M + H^+).



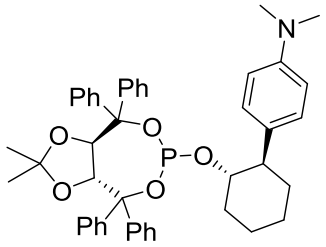
(3aS,8aS)-6-(((1S,2R)-2-([1,1'-biphenyl]-4-yl)cyclohexyl)oxy)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (4-L41):

According to general procedure C (1S,2R)-2-([1,1'-biphenyl]-4-yl)cyclohexan-1-ol (1.01 mmol, 255 mgs) was stirred with PCl_3 (1.01 mmol, 86 µL) for 1 hour. Next, NEt_3 (4.04 mmol, 534 µL) was added. After 30 minutes, (S,S)-Taddol (0.963 mmol, 450 mgs) was added and the reaction stirred for 12-14 hours. This procedure afforded 520 mgs (72%) of the title compound as a white foamy solid, mp 115–118 °C. $[\alpha]^{23}_{D}$ -226.2 (*c* 1.11, CH_2Cl_2); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2 H), 7.38–7.02 (m, 27 H), 4.94–4.90 (m, 1 H), 4.88 (d, *J* = Hz, 8.4 Hz, 1 H), 4.56 (app. qd, *J* = 9.9, 3.7 Hz, 1 H), 2.71–2.66 (m, 1 H), 2.28 (app. d, *J* = 13.8 Hz, 1 H), 1.95 (app. d, *J* = 13.2 Hz, 1 H), 1.81–1.73 (m, 2 H), 1.69–1.50 (m, 2 H), 1.41–1.31 (m, 2 H), 1.19 (s, 3 H), 0.30 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 146.6, 146.1, 143.0, 141.8, 141.25, 141.23, 139.4, 129.4, 129.0, 128.92, 128.89, 128.6, 128.0, 127.8, 127.54, 127.48, 127.45, 127.38, 127.34, 127.30, 127.18, 127.15, 127.12, 127.06, 126.9, 112.0, 82.9, 82.7, 82.6, 82.12, 82.10, 81.92, 81.88, 78.10, 78.09, 51.39, 51.37, 35.7, 33.8, 27.6, 26.0, 25.5, 25.3 (Due to the complexity of the spectra all the peaks are listed without taking into consideration C-P couplings); ^{31}P NMR (202 MHz $CDCl_3$) δ 140.6; IR (film) 2931.7, 1486.2, and 1446.7 cm^{-1}; MS (ESI+) 747.3224 (747.3234 calcd for $C_{49}H_{47}O_5P$, M + H^+).



4-((1R,2S)-2-(((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)cyclohexyl)-N,N-dimethylaniline (4-L45):

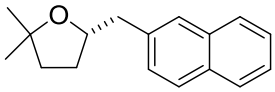
According to general procedure C (1S,2R)-2-(4-(dimethylamino)phenyl)cyclohexan-1-ol (0.675 mmol, 148 mgs) was stirred with PCl_3 (0.675 mmol, 59 µL) for 1 hour. Next, NEt_3 (2.57 mmol, 356 µL) was added. After 30 minutes, (S,S)-Taddol (0.642 mmol, 300 mgs) was added and the reaction stirred for 12-14 hours. This procedure afforded 166 (35%) of the title compound as a white foamy solid, mp 91–94 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.50–7.44 (m, 7 H), 7.42 (t, *J* = Hz, 7.6 Hz, 2 H), 7.38–7.25 (m, 11 H), 7.16 (d, *J* = Hz, 8.7 Hz, 2 H), 6.56 (d, *J* = Hz, 8.7 Hz, 2 H), 5.14–5.12 (m, 1 H), 5.08 (d, *J* = Hz, 8.3 Hz, 1 H), 4.55–4.49 (m, 1 H), 2.81 (s, 6 H), 2.63–2.58 (m, 1 H), 2.30–2.25 (m, 1 H), 2.02–1.96 (m, 1 H), 1.92–1.80 (m, 2 H), 1.73–1.66 (m, 1 H), 1.58–1.47 (m, 2 H), 1.43–1.35 (m, 1 H),1.21 (s, 3 H), 0.42 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 149.3, 146.5, 146.0, 142.02, 142.01, 141.4, 131.7, 129.1, 129.0, 128.93, 128.91, 128.1, 127.7, 127.6, 127.5, 127.31, 127.30, 127.26, 127.2, 127.10, 127.06, 112.8, 112.2, 83.02, 83.00, 82.5, 82.4, 82.33, 82.31, 81.92, 81.90, 78.33, 78.30, 50.45, 50.43, 40.9, 35.40, 33.3, 27.5, 26.0, 25.6, 25.4 (Due to the complexity of the spectra all the peaks are listed without taking into consideration C-P couplings); ^{31}P NMR (283 MHz $CDCl_3$) δ 138.4; IR (film) 2931.9, 1613.3, and 1520.8 cm^{-1}.



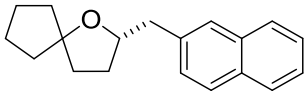
4-((1R,2S)-2-(((3aR,8aR)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro [1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)cyclohexyl)-N,Ndimethylaniline (4-L46): According to general procedure C (1S,2R)-2-(4-(dimethylamino)phenyl)cyclohexan-1-ol (0.675 mmol, 148 mgs) was stirred with PCl_3 (0.675 mmol, 59 µL) for 1 hour. Next, NEt_3 (2.57 mmol, 356 µL) was added. After 30 minutes, (R,R)-Taddol (0.642 mmol, 300 mgs) was added and the reaction stirred for 12-14 hours. This procedure afforded 235 (51%) of the title compound as a white foamy solid, mp 94–97 °C. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (d, *J* = Hz 7.2 Hz, 2 H), 7.47 (d, *J* = Hz, 7.3 Hz, 2 H), 7.43 (d, *J* = Hz, 7.3 Hz, 2 H), 7.34–7.28 (m, 4 H), 7.27–7.17 (m, 12 H), 6.53 (d, *J* = Hz, 8.7 Hz, 2 H), 5.02–4.98 (m, 1 H), 4.95 (d, *J* = Hz, 8.3 Hz, 1 H), 4.57–4.51 (m, 1 H), 2.68 (s, 6H), 2.64–2.59 (m, 1 H), 2.33–2.29 (m, 1 H), 1.95 (app. d, *J* = 13.1 Hz, 1 H), 1.83–1.74 (m, 2 H), 1.69–1.57 (m, 2 H), 1.44–1.32 (m, 2 H), 1.27 (s, 3 H), 0.36 (s, 3 H); ^{13}C NMR (175 MHz $CDCl_3$) δ 149.3, 146.7, 146.0, 141.8, 141.1, 131.9, 129.1, 129.0, 128.90, 128.88, 128.08, 127.63, 127.61, 127.5, 127.29, 127.27, 127.23, 127.2, 127.1, 127.0, 112.7, 112.2, 82.99, 82.97, 82.4, 82.33, 82.30, 82.28, 81.89, 81.87, 78.31, 78.27, 50.43, 50.40, 40.8, 35.4, 33.3, 27.5, 26.0, 25.6, 25.3(Due to the complexity of the spectra all the peaks are listed without taking into consideration C-P couplings); ^{31}P NMR (283 MHz $CDCl_3$) δ 140.7; IR (film) 2931.7, 1614.1, and 1520.9 cm^{-1}.

General procedure for asymmetric Pd-catalyzed carboetherification reactions of

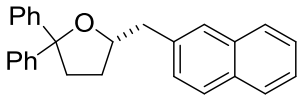
alcohol derivatives. A flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and then charged with $Pd_2(dba)_3$ (2 mol %), 4-L41 (5 mol %), the alcohol substrate (1.0 equiv), and NaO^tBu (1.50-2.0 equiv). The flask was purged with N_2, then the aryl or alkenyl halide (1.40-2.0 equiv), and dioxane or toluene (0.10 M) was added. The resulting mixture was heated to 90 °C with stirring until the starting material had been consumed as judged by TLC analysis (ca. 12 h). The reaction mixture was then cooled to rt, saturated aqueous ammonium chloride (6mL/mmol substrate) was added, and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate (3 x 5 mL) then the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.



(S)-2,2-dimethyl-5-(naphthalen-2-ylmethyl)tetrahydrofuran (4-2a): The general procedure was employed for the coupling of 2-methylhex-5-en-2-ol (0.20 mmol, 22.8 mg) and 2-bromonaphthalene (0.1.80 mmol, 75.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and 4-L41 (0.010 mmol 7.5 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (21.1 mg, 44%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.76 (m, 3 H), 7.67 (s, 1H), 7.50–7.37 (m, 3 H), 4.35–4.27 (m, 1 H), 3.17 (dd, *J* = 5.3, 13.3Hz, 1 H), 2.88 (dd, *J* = 7.7, 13.3 Hz, 1 H), 1.97–1.91 (m, 1 H), 1.78–1.68 (m, 3 H), 1.29 (s, 3 H), 1.27 (s, 3H). Other spectral data matched that of the literature.[12] The enantiopurity was determined to be 75:25 er by chiral HPLC analysis (chiralcel OJH, 25 cm x 4.6 mm, 1.00% IPA/Hexanes, 1.50 mL/min, λ 254 nm, RT= 7.0 and 7.5 min).

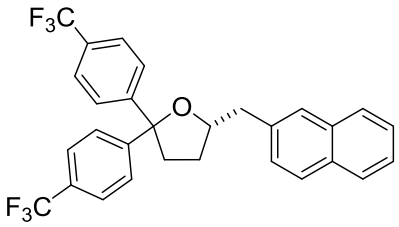


(S)-2-(naphthalen-2-ylmethyl)-1-oxaspiro[4.4]nonane (4-2b): The general procedure was employed for the coupling of 1-(but-3-en-1-yl)cyclopentan-1-ol (0.20 mmol, 28.0 mg) and 2-bromonaphthalene (0.38 mmol, 75.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and 4-L41 (0.010 mmol 7.5 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (31.1 mg, 58%, 10:1 dr) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.79 (m, 3 H), 7.67 (s, 1 H), 7.49–7.35 (m, 3 H), 4.29–4.22 (m, 1 H), 3.15 (dd, *J* = 5.0, 13.6 Hz, 1 H), 2.87 (dd, *J* = 7.7, 13.3 Hz, 1 H), 1.95–1.87(m, 1 H), 1.86–1.49 (m, 11 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ136.6, 133.7, 132.3, 128.4, 127.84, 127.79, 127.75, 127.7, 91.6, 79.2, 43.0, 39.4, 38.6, 36.6, 24.2; IR (film) 2953.3, 2360.5, 2338.1, 1508.1 cm^{-1}. The enantiopurity was determined to be 89:11 er by chiral HPLC analysis (chiralcel OJH, 25 cm x 4.6 mm, 1.00% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 10.5 and 12.8 min).



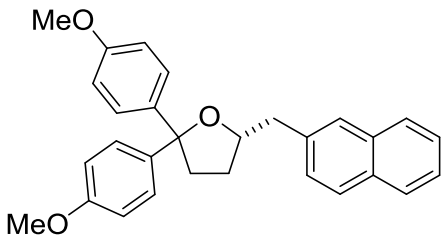
(S)-5-(naphthalen-2-ylmethyl)-2,2-diphenyltetrahydrofuran (4-2c): The general procedure was employed for the coupling of 1,1-diphenylpent-4-en-1-ol (0.20 mmol, 47.7 mg) and 2-bromonaphthalene (0.28 mmol, 58.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and 4-L41 (0.010 mmol 7.5 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (48.7mg, 67%) as a white solid, mp 83–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.2 Hz, 1 H), 7.81 (d, *J* = 8.6 Hz, 2 H), 7.74 (s, 1 H), 7.55–7.44 (m, 7 H), 7.37–7.31 (m, 4 H), 7.28–7.21 (m, 2 H), 4.53 (app. quin, *J* = 6.7 Hz, 1 H), 3.34 (dd, *J* = 6.0, 13.6 Hz, 1

H), 3.02 (dd, *J* = 7.0, 13.6 Hz, 1 H), 2.71–2.64 (m, 1 H), 2.58–2.51 (m, 1 H), 2.03–1.95 (m, 1 H), 1.89–1.81 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 146.9, 136.6, 133.7, 132.3, 128.31, 128.25, 128.2, 127.88, 127.87, 127.8, 127.6, 126.76, 126.74, 126.1, 126.0, 125.4, 88.5, 79.9, 42.8, 38.8, 31.0; IR (film) 2933.8, 1600.9, 1446.4 cm^{-1}. The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 2.00% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 5.2 and 6.3 min).

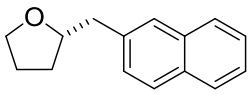


(S)-5-(naphthalen-2-ylmethyl)-2,2-bis(4-(trifluoromethyl)phenyl)tetrahydrofuran (4-2e): The general procedure was employed for the coupling of 1,1-bis(4-(trifluoromethyl)phenyl)pent-4-en-1-ol (0.20 mmol, 74.8 mg) and 2-bromonaphthalene (0.38 mmol, 75.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and 4-L41 (0.010 mmol 7.5 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (58.0 mg, 58%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.74 (m, 3 H), 7.69 (s, 1 H), 7.61–7.53 (m, 8 H), 7.51–7.44 (m, 2 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 4.51 (app. quin, *J* = 6.6 Hz, 1 H), 3.26 (dd, *J* = 6.0, 13.6 Hz, 1 H), 3.02 (dd, *J* = 6.6, 13.7 Hz, 1 H), 2.68–2.59 (m, 1 H), 2.55–2.46 (m, 1 H), 2.03–1.94 (m, 1 H), 1.90–1.80 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 150.2, 136.0, 133.7, 132.4, 129.55, 129.48, 129.29, 129.22, 128.1, 128.03, 127.97, 127.8, 127.7, 126.3, 126.2, 125.6, 125.5 (q, *J*= 3.8 Hz), 125.4 (q, *J*= 3.8 Hz), 87.8, 80.4, 42.6, 38.7, 30.8 (Other than the 2 reported quartets, C-F couplings for this compound were not taken into account and peaks were listed as displayed in the spectra); IR (film) 2953.3,

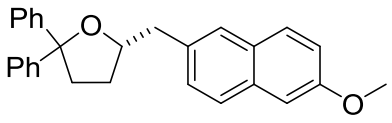
2360.5, 2338.1, and 1508.1cm^{-1}. The enantiopurity was determined to be 90:10 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 2.50% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 5.0 and 5.5 min).



(S)-2,2-bis(4-methoxyphenyl)-5-(naphthalen-2-ylmethyl)tetrahydrofuran (4-2f): The general procedure was employed for the coupling of 1,1-bis(4-methoxyphenyl)pent-4-en-1-ol (0.20 mmol, 59.7 mg) and 2-bromonaphthalene (0.38 mmol, 75.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and 4-L41 (0.010 mmol 7.5 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (42.0 mg, 50%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 1 H), 7.80 (d, *J* = 8.1 Hz, 2 H), 7.71 (s, 1 H), 7.50–7.41 (m, 3 H), 7.40–7.33 (m, 4 H), 6.88–6.81 (m, 4 H), 4.48 (app. quin, *J* = 6.7 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3H), 3.31 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.99 (dd, *J* = 7.1, 13.4 Hz, 1 H), 2.62–2.54 (m, 1 H), 2.49–2.41 (m, 1 H), 2.00–1.92 (m, 1 H), 1.87–1.79 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 139.9, 139.1, 136.6, 133.7, 132.3, 128.3, 127.9, 127.74, 127.67, 127.3, 127.2, 126.0, 125.4, 113.6, 113.4, 88.0, 79.8, 55.4, 42.8, 39.0, 31.1; IR (film) 2935.9, 1608.1, and 1507.7 cm^{-1}. The enantiopurity was determined to be 94:6 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 5.00% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 10.7 and 19.5 min).

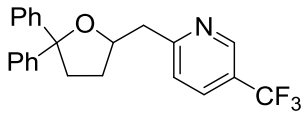


(S)-2-(naphthalen-2-ylmethyl)tetrahydrofurantetrahydrofuran (4-2g): The general procedure was employed for the coupling of pent-4-en-1-ol (0.20 mmol, 17.2 mg) and 2-bromonaphthalene (0.28 mmol, 58.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and 4-L41 (0.010 mmol 7.5 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (9.9 mg, 23%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.75 (m, 3 H), 7.68 (s, 1 H), 7.48–7.36 (m, 3 H), 4.18 (app. quin, *J* = 6.5 Hz, 1 H), 3.95–3.89 (m, 1 H), 3.79–3.73 (m, 1 H), 3.08 (dd, *J* = 6.4, 13.5 Hz, 1 H), 2.92 (dd, *J* = 6.4, 13.7 Hz, 1 H), 1.98–1.82 (m, 3 H), 1.66–1.57 (m, 1 H). Other spectral data matched that of the literature.[12] The enantiopurity was determined to be 60:40 er by chiral HPLC analysis (chiralcel OJH, 25 cm x 4.6 mm, 1.00% IPA/Hexanes, 1.50 mL/min, λ 254 nm, RT= 19.8 and 26.1 min).

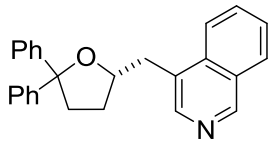


(S)-5-(naphthalen-2-ylmethyl)-2,2-diphenyltetrahydrofuran (4-2h): The general procedure was employed for the coupling of 1,1-diphenylpent-4-en-1-ol (0.20 mmol, 47.7 mg) and 2-bromonaphthalene (0.38 mmol, 75.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.004 mmol, 3.7 mg) and 4-L41 (0.010 mmol 7.5 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (52.0 mg, 66%) as a white solid, mp 93–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (app. dd, *J* = 3.2, 8.6 Hz, 2 H), 7.65 (s, 1 H), 7.53–7.46 (m, 4 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.36–7.28 (m, 4 H), 7.27–7.13 (m, 4 H), 4.50 (app. quin, *J* = 6.7 Hz, 1 H), 3.94 (s, 3H), 3.29 (dd, *J* = 5.9, 13.7 Hz, 1 H), 2.97 (dd, *J* = 7.1, 13.7 Hz, 1 H), 2.69–2.61 (m, 1 H), 2.55–2.48 (m, 1 H), 2.00–1.93 (m, 1 H), 1.87–1.79 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

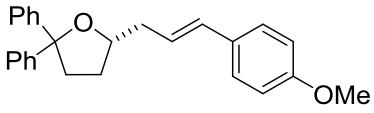
157.4, 147.4, 146.9, 134.2, 133.3, 129.2, 128.6, 128.3, 128.2, 127.7, 126.74, 126.72, 126.1, 126.0, 118.8, 105.8, 88.5, 80.0, 55.4, 42.6, 38.8, 30.9; IR (film) 2936.5, 1604.9, and 1447.5 cm^{-1}. The enantiopurity was determined to be 95:5 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 2.00% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 7.5 and 8.9 min).



(S)-5-(naphthalen-2-ylmethyl)-2,2-diphenyltetrahydrofuran (4-2i): The general procedure was employed for the coupling of 1,1-diphenylpent-4-en-1-ol (0.20 mmol, 47.7 mg) and 2-bromo-5-trifluoromethylpyridine (0.40 mmol, 90.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.009 mmol, 3.7 mg) and 4-L41 (0.020 mmol 15.0 mg), a reaction temperature of 90 °C and a reaction time of 12 h in 2 mL of toluene. This procedure afforded the title compound (71.0 mg, 92%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 7.81 (dd, *J* = 2.1, 8.2 Hz, 1 H), 7.43–7.38 (m, 5 H), 7.31–7.25 (m, 4 H), 7.22–7.16 (m, 2 H), 4.61 (app. quin, *J* = 6.5 Hz, 1 H), 3.26 (dd, *J* = 7.1, 13.7 Hz, 1 H), 3.13 (dd, *J* = 5.6, 13.7 Hz, 1 H), 2.68–2.61 (m, 1 H), 2.55–2.48 (m, 1 H), 2.10–2.02 (m, 1 H), 1.90–1.82 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 147.1, 146.6, 146.2 (q, *J*= 3.8 Hz), 133.3 (q, *J*= 2.8), 128.3, 128.2, 126.9, 126.8, 126.0, 125.9, 124.0, 88.6, 78.4, 45.0, 38.7, 31.1; IR (film) 2948.3, 1607.9, and 1326.8 cm^{-1}. The enantiopurity was determined to be 51:49 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 1.00% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 8.0 and 9.2 min).



(S)-5-(naphthalen-2-ylmethyl)-2,2-diphenyltetrahydrofuran (4-2i): The general procedure was employed for the coupling of 1,1-diphenylpent-4-en-1-ol (0.10 mmol, 23.8 mg) and 4-bromoisoquinoline (0.14 mmol, 29.0 mg) using a catalyst composed of $Pd_2(dba)_3$ (0.002 mmol, 1.8 mg) and 4-L41 (0.005 mmol 3.7 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (19%, 7.0 mg) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1 H), 8.47 (s, 1 H), 8.12 (d, *J* = 8.5 Hz, 1 H), 8.02 (d, *J* = 8.3 Hz, 1 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.64 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 7.4 Hz, 2 H), 7.41 (d, *J* = 7.4 Hz, 2 H), 7.32–7.15 (m, 6 H), 4.57 (app. quin, *J* = 6.6 Hz, 1 H), 3.55 (dd, *J* = 6.0, 14.3 Hz, 1 H), 3.22 (dd, *J* = 6.8, 13.9 Hz, 1 H), 2.70–2.58 (m, 2 H), 2.02–1.83 (m, 2 H). The enantiopurity was determined to be 63:37 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 1.50% IPA/Hexanes, 1.25 mL/min, λ 254 nm, RT= 39.1 and 42.1 min).



(S,E)-5-(3-(4-methoxyphenyl)allyl)-2,2-diphenyltetrahydrofuran (4-2k): The general procedure was employed for the coupling of 1,1-diphenylpent-4-en-1-ol (0.20 mmol, 47.7 mg) and (E)-1-(2-bromovinyl)-4-methoxybenzene[15] (0.40 mmol, 85.0 mg) using a catalyst composed of $Pd(COD)Cl_2$ (0.008 mmol, 2.3 mg) and 4-L41 (0.012 mmol 8.9 mg), a reaction temperature of 90 °C and a reaction time of 12 h. This procedure afforded the title compound (18%, 14.0 mg) as a clear oil. $[\alpha]^{23}_D$ 4.54 (*c* 0.22, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 4 H), 7.33–7.23 (m, 6 H), 7.22–7.15 (m, 2

H), 6.83 (d, *J* = 8.8 Hz, 2 H), 6.40 (d, *J* = 16.0 Hz, 1 H), 6.83 (dt, *J* = 7.0, 15.7 Hz, 1 H), 4.31–4.21 (m, 1 H), 3.80 (s, 3H), 2.70–2.58 (m, 2 H), 2.57–2.40 (m, 2 H), 2.06–1.86 (m, 1 H), 1.81–1.70 (m, 1 H). Other spectral data matched that of the literature.[5] The enantiopurity was determined to be 79:21 er by chiral HPLC analysis (chiralcel ADH, 25 cm x 4.6 mm, 0.50% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 17.5 and 18.8 min).

4.11 References

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(10) If you break the cinchona alkaloids up into two separate chiral portions you have a chiral benzylic alcohol (the quinoline portion) and the chiral 1,2-aminoalcohol. The use of ligands synthesized with chiral alcohols meant to mimic just one portion of the cinchona

alkaloids i.e. (R)-*sec*-phenethyl alcohol (to mimic the chiral benzylic alcohol) or *N*-Me-L-prolinol (to mimic the chiral 1,2-aminoalcohol) afforded products in low yields and er. Thus, just having one of the chiral portions of the cinchona ligands does not seem to increase the yield, and it just lowers the enantioselectivity. Also, the use of chiral alcohols similar to the cinchona alkaloids, such as (1*R*,2*S*)-(−)-*N*-Methylephedrine, affords poor results for our reactions as well.

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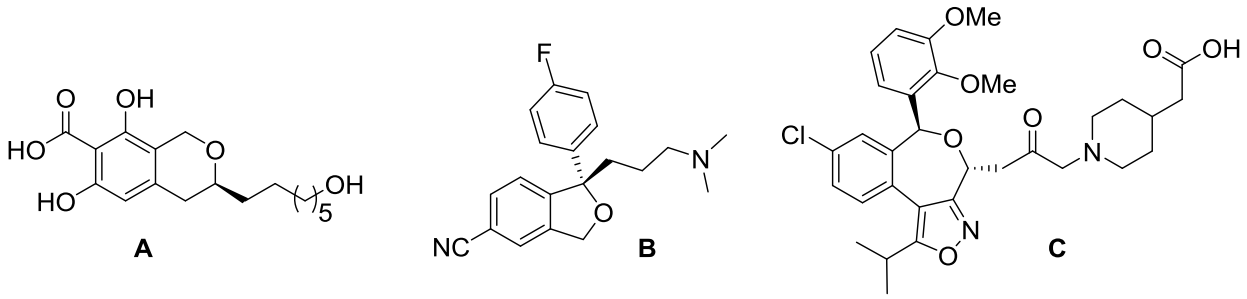
Chapter 5

Synthesis of Benzo-fused Oxygen Heterocycles

5.1 Introduction and Importance of Benzo-fused Oxygen Heterocycles

Enantiopure benzo-fused oxygen heterocycles are displayed in a variety of natural products, biologically active compounds, and pharmaceuticals.[1] These biologically active oxygen heterocycles include compounds of different ring sizes (Figure 5.1) including isochromans (**A**),[1a] isobenzofurans (**B**),[1b] and oxepines (**C**).[1c] These compounds display interesting and diverse biological activities serving as antidepressants, antifungal agents, and also squalene synthase inhibitors. [1]

Figure 5.1 Biologically active benzo-fused oxygen heterocycles



antifungal

Lexapro® (Escitalopram) antidepressant

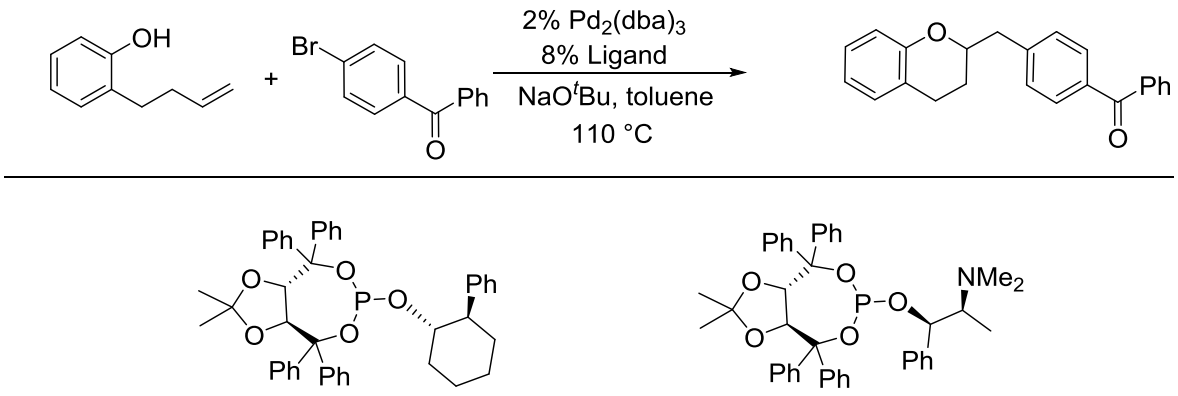
Novel squalene synthase inhibitor

Due to the array of interesting biological activities possessed by these chiral benzo-fused oxygen heterocycles, accessing these compounds from simple precursors is of interest to the synthetic community. One such method of obtaining chiral benzo-fused oxygen heterocycles would be the addition of a heteroatom across an alkene via

transition metal catalysis. As mentioned in chapter 4, similar enantioselective methodologies exist for the synthesis of amine heterocycles, but only a few of these methods exist for the related synthesis of oxygen heterocycles.[2,3]

We envisioned that benzo-fused oxygen heterocycles could be accessed through an enantioselective carboetherification reaction. Previously in our group, Dr. Amanda Ward demonstrated the utility of synthesizing chromans in a racemic manner to afford an array of benzofused oxygen heterocycles.[5] Also, unpublished work by Dr. Ward showed that a screen of chiral ligands failed to afford these chroman products in high enantioselectivities (Scheme 5.1). After initial attempts at improving the chroman system with different ligands and reactions conditions, we decided to synthesize a slightly different class of benzo-fused oxygen heterocycles.

Scheme 5.1 Previous reactions to afford enantiopure chromans

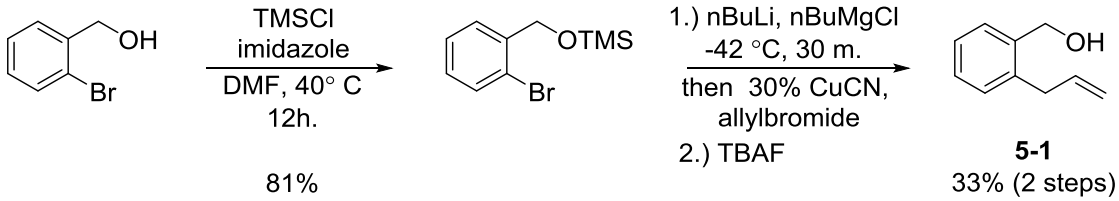


5.2 Initial Substrate Synthesis and Ligand Screen

Previous work in our group demonstrated that enantioselectivity was influenced by the electronics of the cyclizing heteroatom.[5] Thus, we decided to alter the electronics of the chroman system mentioned above (Scheme 5.1) by moving the oxygen

heteroatom one carbon unit away from the ring. Based on literature pKa values,[6] this change should have a substantial effect on the electronics of our cyclizing oxygen, making it considerably more electron rich. Furthermore, substrates of this nature would allow us to access isochromans, which are attractive synthetic targets as well (Figure 5.1).[1a] To test our hypothesis that altering the electronics might increase enantioselectivity, we synthesized substrate **5-1** in a straightforward manner from readily available 2-bromobenzylalcohol (Scheme 5.2).

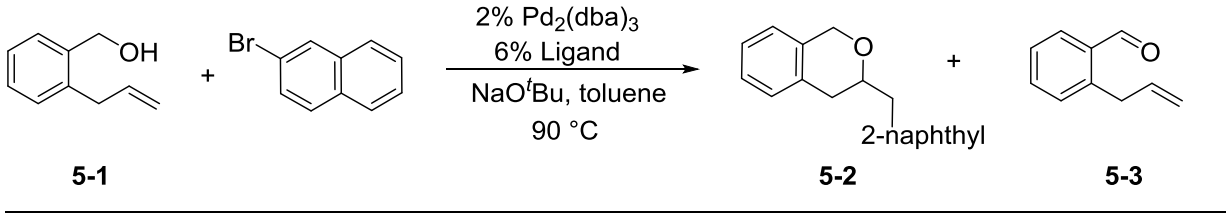
Scheme 5.2 Synthesis of substrate **5-1**



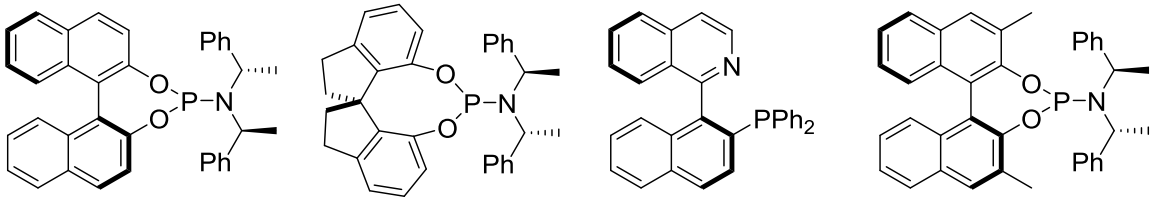
With substrate **5-1** in hand, we undertook a ligand screen with conditions similar to those noted in the previous chapters. Parallel to our approach in chapter 4, we were interested in initially testing ligand scaffolds that were modular, and as such we screened various TADDOL and BINOL based ligands (Table 5.1). All of the non-TADDOL based ligand systems in Table 5.1 afforded isochroman product **5-2** in poor yields and enantioselectivities. However, we were excited to see product **5-2** was afforded in good enantioselectivity (94:6 er), albeit poor yield (15%), when **5-L7** was used as the ligand. Part of the reason for the poor yield arises from a side reaction forming the oxidized product **5-3**. Although starting material was noted in the crude NMR (10%), heating the reaction to a higher temperature only afforded **5-2** in 20% yield, and side product **5-3** was still observed in the crude reaction mixture in 25% yield. Due

to the poor yield of product **5-2**, we decided to examine different reaction conditions for this transformation.

Table 5.1 Initial ligand screen of substrate **5-1**[a]



5-1 **5-2** **5-3**

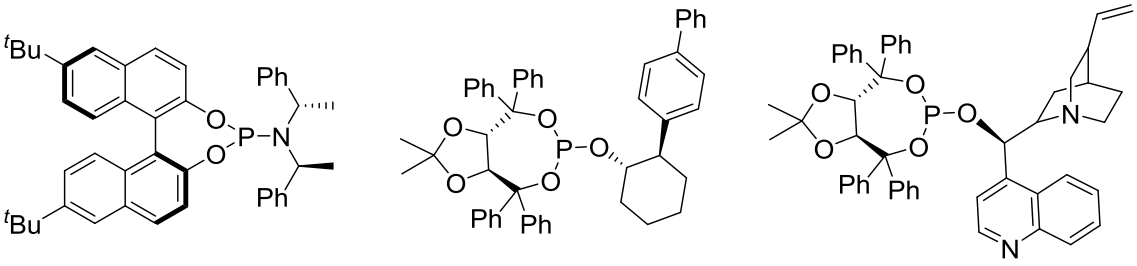


5-L1
25%, 74:26 er

5-L2
20 % yield, 66:34 er

5-L3
<5%, 60:40 er

5-L4
15%, 57:43 er



5-L5
25 %, 65:35 er

5-L6
15%, 82:18 er

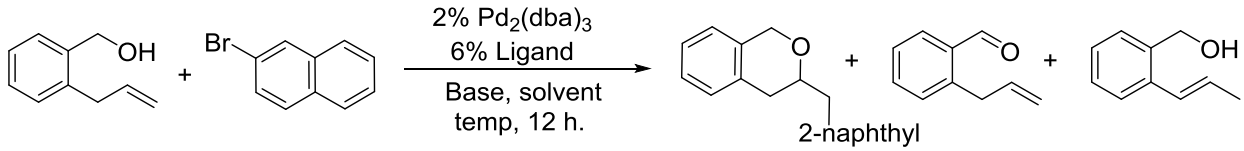
5-L7
15%, 94:6 er
10% **5-1**, 20% **5-3**

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 1.50 equiv Ar-Br, 1.50 equiv NaO^{t}Bu, toluene (0.10 M), 90 °C, 12-14 h. [b]Yields refer to NMR yields, and enantiomeric ratios refer to isolated compounds.

Initially, we tested different bases in this reaction to observe how the nature of the base affects the yield of oxidation product. As shown in Table 5.2, the base is important for the formation of the oxidation product **5-3**, but the choice of base can also affect the isomerization of **5-1** to the conjugated alkene **5-4**. A clear trend on how different bases affect the reaction outcome was not observed, and slight differences in the nature of the base led to varied results. For instance, the use of K_2CO_3 (entry 2) led

to no formation of desired product **5-2**, and the only noted product was the isomerized alkene **5-4** in 45% yield. On the other hand, the use of Cs_2CO_3 (entry 3) led to formation of desired product **5-2** in 10% yield, and also the formation of the oxidized product **5-3** in 35% yield. Furthermore, lowering the reaction temperature (entry 5) with ligand **5-L7** led to no formation of any of the products. Changing the ligand to **5-L6** and using a lower temperature did afford **5-2** in 15% yield (entry 6), but the enantioselectivity was almost unchanged compared to the normal reaction conditions in Table 5.1.

Table 5.2 Effects of changing reaction conditions on yield[a]



5-1 **5-2** **5-3** **5-4**

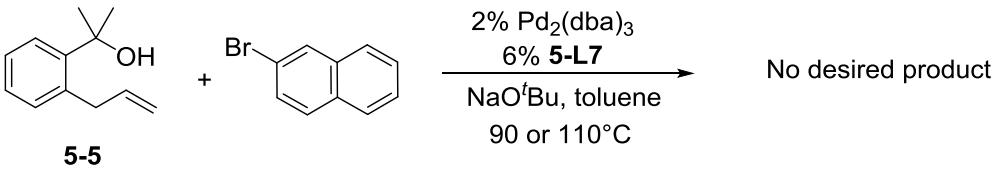
Entry	Base	Solvent	Temp	Ligand	5-1	5-2	5-3	5-4	er
1	NaHMDS	toluene	90 °C	**5-L7**	26%	5%	25%	0%	ND[d]
2	K_2CO_3	toluene	90 °C	**5-L7**	0%	0%	0%	45%[c]	NA
3	Cs_2CO_3	toluene	90 °C	**5-L7**	0%	10%	35%	trace	ND[d]
4	2,6-^{t}Bu-pyridine	toluene	90 °C	**5-L7**	0%	0%	0%	42%	NA
5	NaO^{t}Bu	THF	65 °C	**5-L7**	70%	0%	0%	0%	NA
6	NaO^{t}Bu	THF	65 °C	**5-L6**	0%	15%	0%	10%	83:17
7	NaO^{t}Bu	THF	45 °C	**5-L6**	50%	13%	0%	trace	ND[d]
8	NaHMDS	DCE	75 °C	**5-L7**	36%	trace	7%	7%	ND[d]
9	Cs_2CO_3	DCE	75 °C	**5-L7**	34%	0%	3%	7%	NA
10	NaHMDS	DCE	75 °C	**5-L6**	10%	5%	7%	5%	ND[d]
11	Cs_2CO_3	DCE	75 °C	**5-L6**	10%	0%	2%	50%	NA
12	Cs_2CO_3	dioxane	90 °C	**5-L6**	0%	30%[c]	30%	0%	ND[d]
13	Cs_2CO_3	CF_3Ph	90 °C	**5-L6**	30%	0%[c]	trace	6%	ND[d]

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 1.50 equiv Ar-Br, 1.50 equiv base, solvent (0.10 M), 45-90°C, 12 h. [b]Yields refer to NMR yields, and enantiomeric ratios refer to isolated compounds. [c]A product arising from a suspected heck reaction was noticed in the crude nmr. [d]ND means not determined for the reaction, as we were more concerned with improving yields.

The combination of a specific base in different solvents also has drastic effects on the reaction selectivity. For instance (entries 11, 12, 13) Cs_2CO_3 in DCE yields the isomerized product **5-4** in 50% yield. Cs_2CO_3 in dioxane affords the desired product **5-2** and the oxidized product **5-3** both in 30% yield. Cs_2CO_3 in CF_3Ph does not favor any of the products being formed and starting material **5-1** still remains in 30%. In some reactions Heck products appeared in quantities of up to 15%. While some of the mass balance is still unaccounted for, it is possible other side products and decomposition products were washed away during the standard workup for these reactions.

To try and eliminate one of the side reactions during the formation of product **5-2** above, substrate **5-5** (Scheme 5.3) was synthesized as it would not be able to undergo the oxidation to an aldehyde. Unexpectedly, this reaction was unproductive and no desired product was noted in the crude reaction mixtures and/or the isolated material. Although some apparent Heck product was isolated from this reaction, the rest of the mass balance is unknown at this time.

Scheme 5.3 Reaction of **5-5** under the standard conditions



5-5

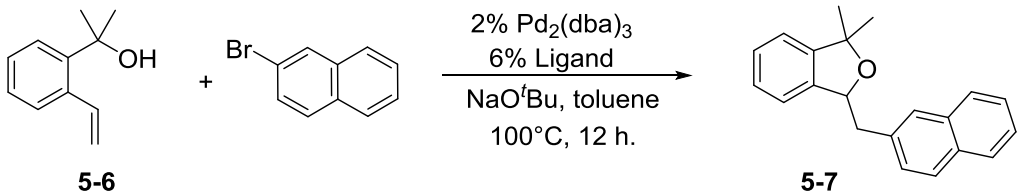
Although we were unable to afford isochroman **5-2** in high yields, we were still interested in the synthesis of other benzo-fused oxygen heterocycles. Additionally, we can use what we learned from the synthesis of isochroman **5-2** and apply that knowledge to access new substrates that will not undergo facile isomerization or oxidation reactions. To this extent, we synthesized substrate **5-6**, which would allow us

to access chiral isobenzofurans. Notably, this heterocyclic motif is utilized in the Lexapro (Figure 5.1), which was the 12th bestselling pharmaceutical in the USA in 2010.[1b]

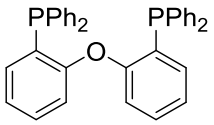
To access isobenzofurans enantioselectivly, we were interested in screening ligands that afforded good enantioselectivities for the isochroman system. However, as noted in Table 5.3, **5-L6** and **5-L7** were poor ligands for this transformation. Fortunately, the chiral PHOX ligand **5-L9** afforded the product in excellent yield, albeit in fairly low enantioselectivity. Changing the isopropyl group in **5-L9** to the *tert*-butyl group in **5-L12** did increase the enantioselectivity. Unfortunately, other changes to the system, such as altering the phosphine, had a deleterious effect on the enantioselectivity. Furthermore, other ligand systems, such as the chiral binaphthyl ligands **5-L16** and **5-L17**, failed to afford the product in higher enantioselectivities as well.

To improve the substrate scope of these reactions, we wanted to attempt the synthesis of isobenzofuran products that contained a quaternary center in the molecule, as these compounds would resemble the antidepressant Lexapro (Figure 5.1). Additionally, our group has a general interest in forming products bearing quaternary centers, as these motifs are typically difficult to access by heteroatom additions to 1,1-disubstituted alkenes with transition metals.[5c] As such, we synthesized substrate **5-8** and subjected it to our carboetherification reaction conditions. Product **5-9** was afforded in good yield albeit in poor enantioselectivity (Table 5.4).

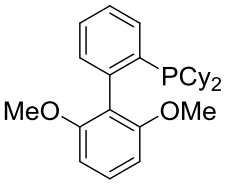
Table 5.3 Ligand screen with substrate **5-6**[a]



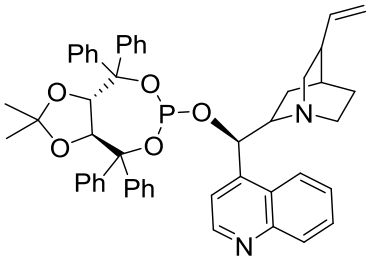
5-6 **5-7**



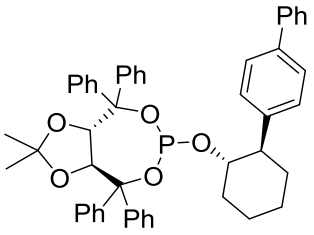
DPEPhos
90%



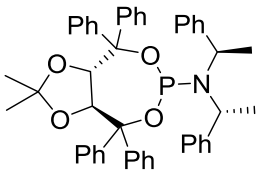
SPhos
60%



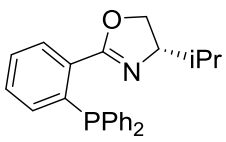
5-L7[c]
No product



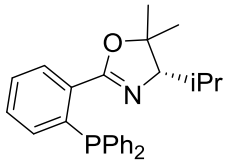
5-L6
5%, 75:25 er



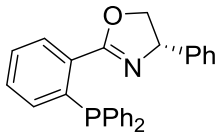
5-L8
0%



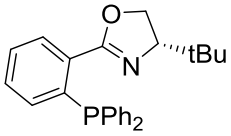
5-L9
91%, 74:26 er



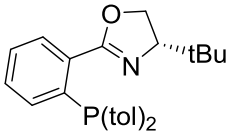
5-L10
84%, 73:27 er



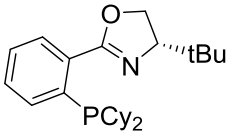
5-L11
65%, 58:42 er



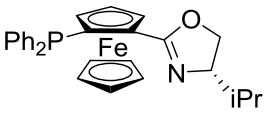
5-L12
62%, 81:19 er



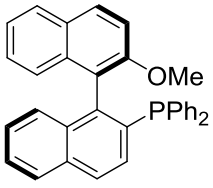
5-L13
91%, 66:34 er



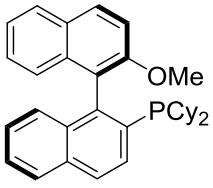
5-L14
35%, 65:35 er



5-L15
66%, 60:40 er



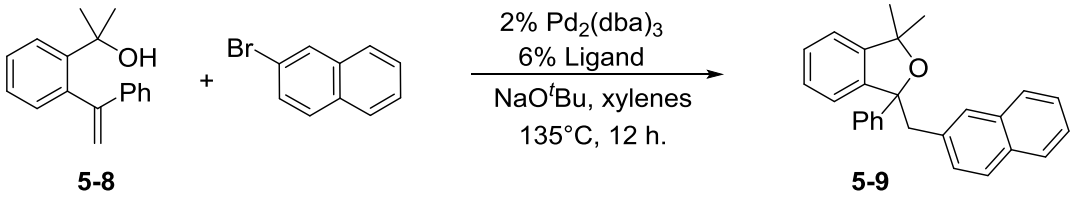
5-L16
93%, 70:30 er



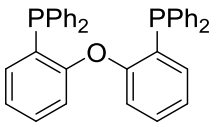
5-L17
55%, 57:43 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.00 equiv Ar-Br, 2.00 equiv NaO^{t}Bu, toluene (0.10 M), 100 °C, 12 h. [b]Yields refer to NMR yields, and enantiomeric ratios refer to isolated compounds. [c]A product arising from a suspected heck reaction was noticed in the crude nmr.

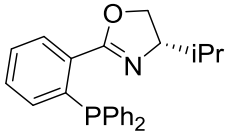
Table 5.4 Formation of an enantioenriched quaternary center[a]



5-8 **5-9**



DPEPhos
70%



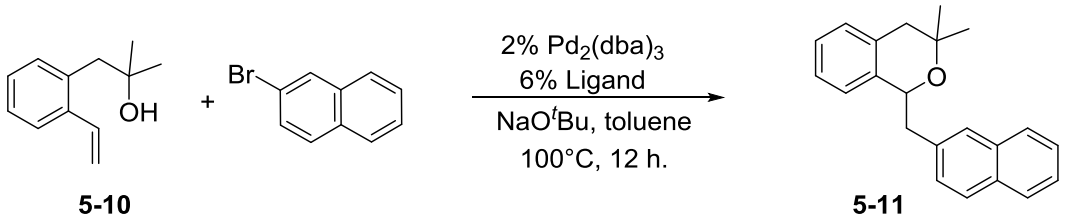
5-L19
73%, 67:33 er

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.00 equiv Ar-Br, 2.00 equiv NaO^{t}Bu, xylenes (0.10 M), 135 °C, 12 h. [b]Yields refer to NMR yields, and enantiomeric ratios refer to isolated compounds

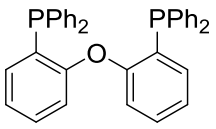
We also wanted to look back into the synthesis of isochromans, as we realized the potential to generate the other isomer of isochroman with our carboetherification reactions. The substrate **5-10** to access this new isomer bears a styrenyl group (Table 5.5). Thus, we decided to use a PHOX ligand for this reaction, as these ligands performed well with the styrenyl substrates in Tables 5.3 and 5.4. Unfortunately, subjecting substrate **5-10** to our reaction conditions failed to afford isochroman **5-11** in good yield or enantioselectivity.

We were also interested in the synthesis of seven membered ring oxepines, which are noted in interesting biologically active motifs (Figure 5.1). Unfortunately, the reaction of substrate **5-12** under the conditions in Table 5.6 failed to yield any desired product with the chiral ligands tested. However, product was noted in the case of the racemic ligand DPEPhos (by crude NMR analysis), and different reaction conditions and chiral ligands need to be tested for this substrate in the future.

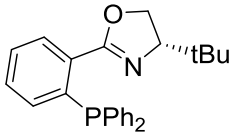
Table 5.5 Synthesis of isochroman **5-11**[a]



5-10 **5-11**



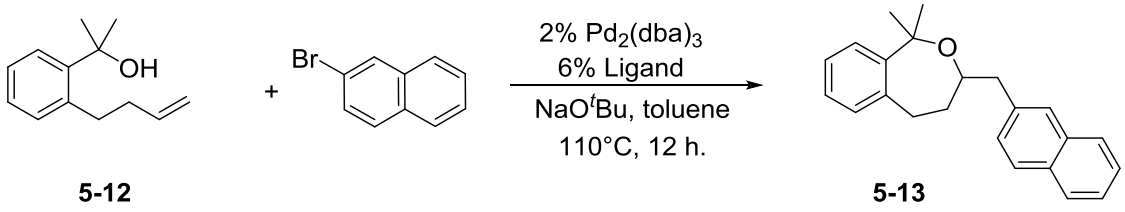
DPEPhos
40%



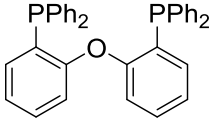
5-L12
3%, ND
25%, 57:43 er (130 °C)

[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.00 equiv Ar-Br, 2.00 equiv NaO^{t}Bu, toluene (0.10 M), 100 °C, 12 h. [b]Yields refer to NMR yields, and enantiomeric ratios refer to isolated compounds.

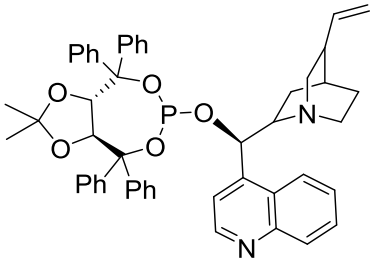
Table 5.6 Synthesis of 7-membered rings[a]



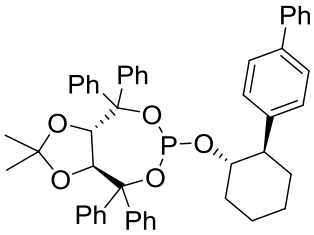
5-12 **5-13**



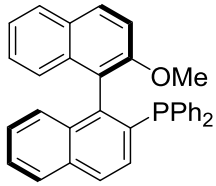
DPEPhos
30%



5-L7[c]
No product



5-L6[c]
No product



5-L16[c]
No product

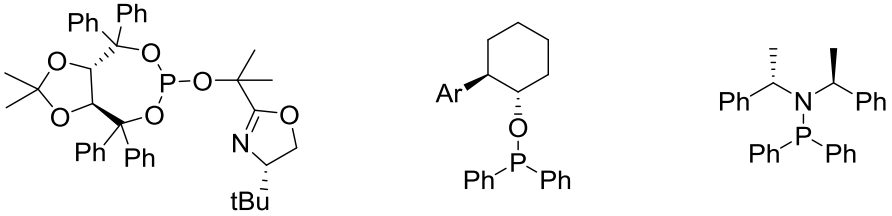
[a] Conditions: Reactions were conducted using 1.0 equiv substrate (0.10 mmol), 2.00 equiv Ar-Br, 2.00 equiv NaO^{t}Bu, toluene (0.10 M), 110 °C, 12 h. [b]Yields refer to NMR yields. [C]**5-12** was no longer present in the crude nmr.

5.3 Conclusions

The work described above demonstrates the potential of these enantioselective carboetherification reactions to afford a variety of different compounds. The formation of the isochroman **5-2** is especially promising as it already affords products in up to 94:6 er. However, optimization of this reaction needs to be re-examined. PHOX ligands should be investigated further, as they might be able to hinder the oxidation side product. Furthermore, the formation of isobenzofurans (**5-7** and **5-9**) is interesting as it is the first Pd-catalyzed carboamination or carboetherification reaction to take place with a styrene in high yields. Moreover, altering the electronics of these systems could lead to better enantioselectivity, and it would be useful to determine how the nucleophilicity of the oxygen atom affects the enantioselectivity of the products mentioned in chapter 5 (Figure 5.2). Lastly, some ideas for new ligands for these transformations are shown below in Figure 5.2, as these ligands resemble scaffolds that were effective for the reactions in chapter 5.

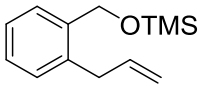
Figure 5.2 New substrates and ligand scaffolds

R^1= CF_3, OMe, CH_3, CN, or F



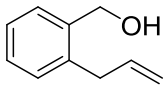
5.4 Experimental

General: Reactions were carried out under nitrogen in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium was purchased from Strem Chemical Co. and used without further purification. All other reagents including all aryl and alkenyl bromides were purchased from commercial sources and used as received unless otherwise noted. 2-(2-vinylphenyl)propan-2-ol[7] and 1-bromo-2-(1-phenylvinyl)benzene[8] were prepared according to literature procedures. Xylenes were purified by distillation over CaH_2 prior to use in reactions. Toluene was purified using a GlassContour solvent system. All yields refer to isolated compounds that are estimated to be $\geq$90% pure as judged by ^{1}H NMR or GC analysis unless otherwise noted. The yields reported herein chapter 5 describe the result of a single experiment, and in some cases only NMR yields are noted as some products were difficult to separate and accurate isolated yields could not be determined. Absolute configurations of the molecules in this chapter have yet to be determined.

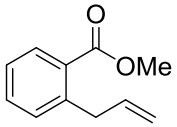


((2-allylbenzyl)oxy)trimethylsilane (5-S1): Butylmagnesium chloride (2.0 M THF, 4.00 mmol, 2.0 mL) was added to a flame dried round bottom flask that was equipped with a stir bar. 8 mL of dry THF was added to this and the solution was stiffed at 0 °C for 5 minutes. To this, was added nBuLi (2.5 M Hexanes, 8.1 mmol, 3.24 mL) and it was stirred at 0 °C for 10 minutes. After this time, the mixture was cooled to -42 °C in a dry ice/acetonitrile bath. To this mixture was then added ((2-bromobenzyl)oxy)trimethylsilane in 30 mL dry THF and it was stirred for 30 minutes. After this time a mixture of CuCN (30%, 2.43 mmol, 217 mgs) and LiCl (60%, 4.86

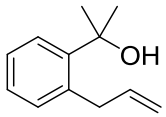
mmol, 206 mgs) was added in 5 mL dry THF immediately followed by the addition of allyl bromide (32.4 mmol, 2.80 mL). This mixture was allowed to stir for 30 minutes and it was then quenched by adding 80 mL of EtOAc and 10 mL of saturated ammonium chloride. This mixture then stirred for 30 minutes and it was added to a separatory funnel and the organics were collected and washed 1x 20 mL brine. The organics were dried with sodium sulfate and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound in 775 mgs (43%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.40 (m, 1 H), 7.26–7.22 (m, 2 H), 7.20–7.16 (m, 1 H), 6.03–5.93 (m, 1 H), 5.08 (d, *J* = 10.3 Hz, 1 H), 5.01 (d, *J* = 17.1 Hz, 1 H), 4.72 (s, 2H), 3.43 (d, *J* = 6.03 Hz, 2 H), 0.17 (s, 9H).



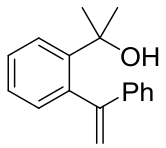
(2-allylphenyl)methanol (5-1): To a solution of ((2-allylbenzyl)oxy)trimethylsilane (775 mgs, 3.52 mmol) in 8 mL dry THF was added TBAF (1M THF, 7.04 mL). This mixture was allowed to stir for 2 hours at room temperature and then the THF was removed in vacuo. The crude residue was dissolved in 40 mL diethyl ether and washed 1 x 10 mL brine. The organics were dried with sodium sulfate and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound in 395 mgs (76%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38 (m, 1 H), 7.31–7.24 (m, 2 H), 7.24–7.20 (m, 1 H), 6.07–5.98 (m, 1 H), 5.12–5.07 (m, 1 H), 5.05–4.99 (m, 1 H), 4.73 (d, *J* = 5.9 Hz, 2 H), 4.73 (d, *J* = 5.9 Hz, 2 H), 3.50 (d, *J* = 6.1 Hz, 2 H), 1.65-1.62 (m, 1H).



Methyl 2-allylbenzoate (5-S2): Starting with Methyl 2-bromobenzoate (5mmol, 0.72 mL) and following the procedure for 5-S1 above, the title compound was afforded in 440 mgs (50%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.4 Hz, H), 7.45 (t, *J* = 7.7 Hz, H), 7.33–7.28 (m, 2 H), 6.07–5.98 (m, 1 H), 5.09–5.00 (m, 2 H), 3.90 (s, 3 H), 4.73 (d, *J* = 6.3 Hz, 2 H).

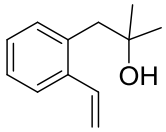


2-(2-allylphenyl)propan-2-ol (5-5): Methyl 2-allylbenzoate (480 mgs, 2.72 mmol) was added to a flame dried flask with 30 mL diethyl ether. The flask was cooled to 0 °C while the mixture stirred. MeMgBr (3 M Et_2O, 3.60 mL) was added dropwise to this solution. After 5 hours it was quenched with 5 mL of a satured ammonium chloride solution. The aqueous layer was extracted 3 x 20 mL diethyl ether and the organic layers were combined, dried with sodium sulfate, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound in 265 mgs (55%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 1 H), 7.27–7.16 (m, 3 H), 6.12–6.03 (m, 1 H), 5.10–4.96 (m, 2 H), 3.85–3.80 (m, 2 H), 1.67 (s, 6H).

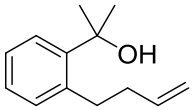


2-(2-(1-phenylvinyl)phenyl)propan-2-ol (5-8): 1-bromo-2-(1-phenylvinyl)benzene[8] (2.31 mmol, 600 mgs) was added to a flame dried flask under nitrogen with 5 mL dry diethyl ether. This solution was cooled to 0 °C and then nBuLi (2.5M hexanes, 0.92 mL)

was added slowly. This mixture was stirred at 0 °C for one hour and then acetone (4.62 mmol, 0.34 mL) was added slowly in 2 mL dry diethyl ether. This was allowed to stir for 30 minutes at 0 °C and then 30 minutes at room temperature before it was quenched by the addition of 5 mL of a saturated ammonium chloride solution. It was extracted 3 x 10 mL diethyl ether, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound in 320mgs (58%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.53 (m, 1 H), 7.39–7.23 (m, 7 H), 7.16–7.14 (m, 1 H), 5.90 (s, 1H), 5.13 (s, 1H), 1.49 (s, 6H).



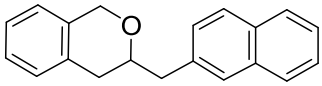
2-methyl-1-(2-vinylphenyl)propan-2-ol (5-10): 2-bromostyrene (16 mmol, 2mL) was added to a flame dried flask with 45 mL dry THF. It was cooled to -78 °C. nBuLi (2.5 M hexanes, 7.0 mL) was added drop wise over 15 minutes with a syringe pump. After stirring for 1.5 hours at this temperature, isobutylene oxide (17 mmol, 1.50 mL) was added over 5 minutes. The solution was allowed to stir at this temperature for 30 minutes and then it was allowed to stir at room temperature for 1 hour. The reaction was quenched by the addition of 20 mL of a saturate ammonium chloride solution. It was extracted 3 x 25 mL diethyl ether, dried over sodium sulfate, and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound in 813 mgs (29%) as a white solid.



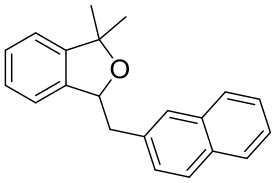
2-(2-(but-3-en-1-yl)phenyl)propan-2-ol (5-12): 1-bromo-2-(but-3-en-1-yl)benzene (4.73 mmol, 1.00 g) was added in 0.50 mL diethyl ether to a flame dried flask containing freshly ground magnesium turnings (6.15 mmol, 150 mgs). Once the Grignard reagent starts forming 5 mL of diethyl ether is slowly added. Stir for 1 hour. Cool to 0 °C and add acetone (14.2 mmol, 1.04 mL) in 1 mL dry diethyl ether. Stir for 4 hours and then quench with 3 mL of a saturated ammonium chloride solution. Extract 3 x 15 mL diethyl ether, dry sodium sulfate, and evaporate in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound in 550 mgs (61%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.88 Hz, 1H), 7.27–7.14 (m, 3 H), 6.01–5.91 (m, 1 H), 5.15–4.99 (m, 2 H), 3.14–3.05 (m, 2 H), 2.46–2.38 (m, 2 H), 1.78–1.65 (m, 7 H).

General Procedure A: Asymmetric Pd-catalyzed carboamination reactions. A flame dried Schlenk flask equipped with a stir bar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (2 mol %), Ligand (6 mol %), the aryl or alkenyl halide (1.0–2.0 equiv.), NaO^tBu (1.3–2.0 equiv.), and the oxy alkene substrate. The flask was purged with nitrogen, and toluene (0.1 M) was added (xylenes was used as solvent in cases where reactions were heated over 110 °C). The resulting mixture was heated to 80–125 °C with stirring for 12–15 hrs. The reaction mixture was then cooled to rt, saturated aqueous ammonium chloride (6 mL/mmol) was added, and the mixture was transferred to a separatory funnel. The mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and

concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel using hexanes/Et_2O as the eluant.

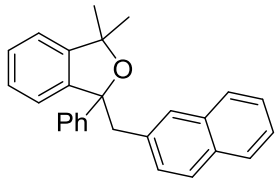


3-(naphthalen-2-ylmethyl)isochromane (5-2): According to general procedure A (2-allylphenyl)methanol (0.10 mmol, 14.8 mgs), $Pd_2(dba)_3$ (2%, 0.002 mmol, 1.8 mgs), 5-L7 (6%, 0.006 mmol, 4.7 mgs), NaO^tBu (0.15 mmol, 14.4 mgs), and 2-bromonaphthalene (0.15 mmol, 31.0 mgs) were all reacted to afford the title compound in 15 % yield (according to NMR) as a clear oil. Isolated material was determined to be 94:6 er by chiral HPLC analysis (chiralcel ODH, 15 cm x 4.6 mm, 1.00% IPA/Hexanes, 1.00 mL/min, λ 225 nm, RT= 8.9 and 11.1 min). ^1H NMR (500 MHz, $CDCl_3$) δ 7.86–7.80 (m, 3 H), 7.75 (s, 1H), 7.51–7.42 (m, 3 H), 7.17–7.13 (m, 2 H), 7.07–6.98 (m, 2 H), 4.90 (d, *J* = 15.2 Hz, 1H), 4.83 (d, *J* = 15.2 Hz, 1H), 4.09–4.02 (m, 1 H), 3.26 (dd, *J* = 6.8, 13.7 Hz, 1H), 3.04 (dd, *J* = 6.3, 13.9 Hz, 1H), 2.84 (dd, *J* = 11.0, 16.1 Hz, 1H), 2.71 (dd, *J* = 2.7, 16.4Hz, 1H).

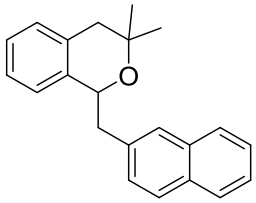


1,1-dimethyl-3-(naphthalen-2-ylmethyl)-1,3-dihydroisobenzofuran (5-7): According to general procedure A 2-(2-vinylphenyl)propan-2-ol[7] (0.10 mmol, 16.2 mgs), $Pd_2(dba)_3$ (2%, 0.002 mmol, 1.8 mgs), (*S*)-^{t}BuPHOX (6%, 0.006 mmol, 2.3 mgs), NaO^tBu (0.20 mmol, 19.2 mgs), and 2-bromonaphthalene (0.20 mmol, 41.0 mgs) were all reacted to afford the title compound in 19.0 mgs (65 %) as a clear oil. The product was determined

to be 81:19 er by chiral HPLC analysis (chiralcel ODH, 15 cm x 4.6 mm, 1.00% IPA/Hexanes, 1.00 mL/min, λ 254 nm, RT= 4.1 and 5.0 min). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.78 (m, 3 H), 7.72 (s, 1H), 7.50–7.42 (m, 3 H), 7.31–7.26 (m, 1 H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.60 (app. t, *J* = 6.2 Hz, 1H), 3.34 (dd, *J* = 6.4, 13.7 Hz, 1H), 3.24 (dd, *J* = 6.2, 13.9 Hz, 1H), 1.50 (s, 3H), 1.49 (s, 3H).



1,1-dimethyl-3-(naphthalen-2-ylmethyl)-3-phenyl-1,3-dihydroisobenzofuran (5-9): According to general procedure A 2-(2-(1-phenylvinyl)phenyl)propan-2-ol (0.15 mmol, 36.0 mgs), $Pd_2(dba)_3$ (2%, 0.002 mmol, 1.8 mgs), (*S*)-^{i}PrPHOX (6%, 0.006 mmol, 2.3 mgs), NaO^{t}Bu (0.20 mmol, 19.2 mgs), and 2-bromonaphthalene (0.20 mmol, 41.0 mgs) were all reacted to afford the title compound in 40.0 mgs (73 %) as a clear oil. The product was determined to be 67:33 er by chiral HPLC analysis (chiralcel ODH, 15 cm x 4.6 mm, 1.00% IPA/Hexanes, 0.500 mL/min, λ 254 nm, RT= 6.8 and 7.5 min). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.65 (m, 4 H), 7.61–7.57 (m, 2 H), 7.50 (s, 1H), 7.42–7.32 (m, 5 H), 7.29–7.23 (m, 2 H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 3.60 (app. s, 2H), 1.40 (s, 3H), 1.17 (s, 3H).



3,3-dimethyl-1-(naphthalen-2-ylmethyl)isochromane (5-11): According to general procedure A 2-methyl-1-(2-vinylphenyl)propan-2-ol (0.15 mmol, 17.6mgs), $Pd_2(dba)_3$ (2%, 0.002 mmol, 1.8 mgs), (*S*)-^{t}BuPHOX (6%, 0.006 mmol, 2.3 mgs), NaO^{t}Bu (0.20 mmol, 19.2 mgs), and 2-bromonaphthalene (0.15 mmol, 31.0 mgs) were all reacted to afford the title compound as a clear oil (25 % yield by NMR, product co-eluted with ArBr and an accurate isolated yield was not obtained). A small amount of isolated product was determined to be 57:43 er by chiral HPLC analysis (chiralcel OJH, 25 cm x 4.6 mm, 0.00% IPA/Hexanes, 1.00 mL/min, λ 225 nm, RT= 36.0 and 48.8 min). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.73 (m, 2 H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.64 (s, 1H), 7.45–7.36 (m, 3 H), 7.21–7.12 (m, 3 H), 6.99 (d, *J* = 7.3 Hz, 1H), 5.15 (app. t, *J* = 5.4 Hz, 1H), 3.40 (dd, *J* = 4.3, 14.0 Hz, 1H), 3.22 (dd, *J* = 6.6, 14.3 Hz, 1H), 2.62 (d, *J* = 15.4 Hz, 1H), 2.42 (d, *J* = 15.6 Hz, 1H), 1.34 (s, 3H), 1.11 (s, 3H).

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