Development and Application of the Pd-Catalyzed Carboamination Reaction of Aminoalkenes with Aryl Halides

Brandon R. Rosen

University of Michigan

20 April 2011

This thesis has been read and approved by _____.

Date: ____/____/____

Acknowledgements

None of the work described in this thesis could have been carried out without the support of my research advisor, Professor John Wolfe. I thank him for providing a laboratory experience that, as far as I am concerned, could not have been matched anywhere else.

Over the last four years, I have worked with many extremely talented scientists. Matthew Leathen and Peter Mai were my closest mentors in the Wolfe group. I'd like to thank Amgen for a summer internship in 2008, where I worked with Sean Brown. Professor Richmond Sarpong and Jessica Wood, a graduate student in the Sarpong group, have supported me since the 2009 Amgen Scholars program at UC Berkeley. I also want to thank Antonio Navarro, Thomas Beauchamp, and Craig Ruble, as well as the rest of the DCSG group, for an enlightening and productive summer internship at Eli Lilly and Company in 2010. I want to thank the entire Wolfe group, everyone I worked with at Amgen, UC Berkeley and Eli Lilly for bearing with me over the last few years. Lastly, I want to thank Dr. Jim Harper and Professor Richard Miller for accepting me into their laboratory in the fall of 2007.

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Most importantly, I would like to thank my parents for their support (both emotional and financial) over the last 21 years or so. This thesis is dedicated to my girlfriend, Leah Simke, and her ability to tolerate the long hours of an organic chemist.

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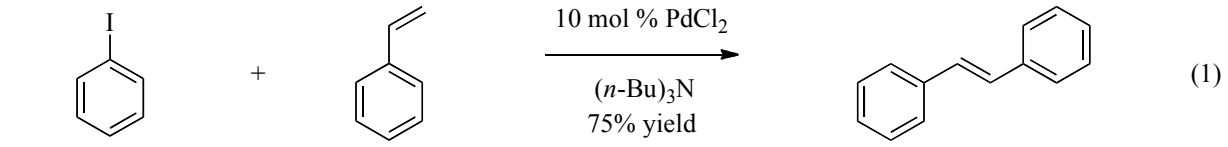
Chapter 1

Transition Metal-Catalyzed Coupling Reactions

1.1 Introduction

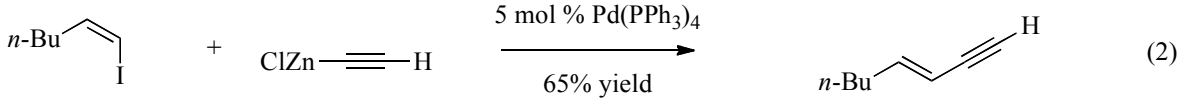
The past 40 years have seen major developments in the area of homogenous transition metal catalysis for the formation of C–C and carbon–heteroatom bonds. This growth has enabled coupling of aryl halides with numerous nucleophiles, including organotin compounds, alkynes, organozinc compounds, organosilicon compounds, boronic acids, olefins, and amines or alcohols. The significance of this type of chemistry was recognized in 2010, when the Nobel Prize in Chemistry was awarded jointly to Richard F. Heck,[1] Ei-ichi Negishi,[2] and Akira Suzuki[3] for their work on Pd-catalyzed cross-coupling reactions (eq. 1–3).

a) Heck Reaction



(1)

b) Negishi Reaction



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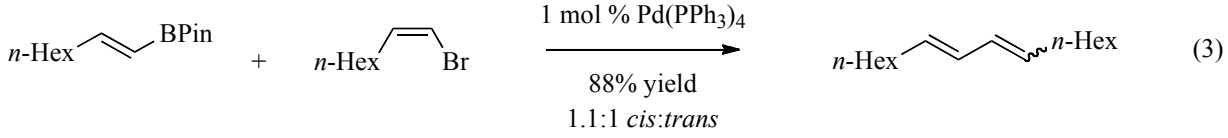
c) Suzuki Reaction

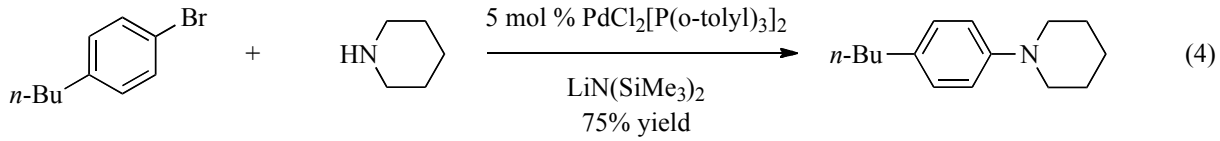


(3)

Each of the above reactions proceeds through a series of basic organometallic mechanistic steps: oxidative addition of an aryl or alkenyl halide to palladium (0), followed by either transmetallation or olefin insertion, and termination by either C–C bond-forming reductive

elimination or β-hydride elimination. A related transformation is the Buchwald-Hartwig amination, in which an amine is coupled with an aryl halide using a palladium catalyst (eq. 4).[4]

d) Buchwald-Hartwig Reaction



(4)

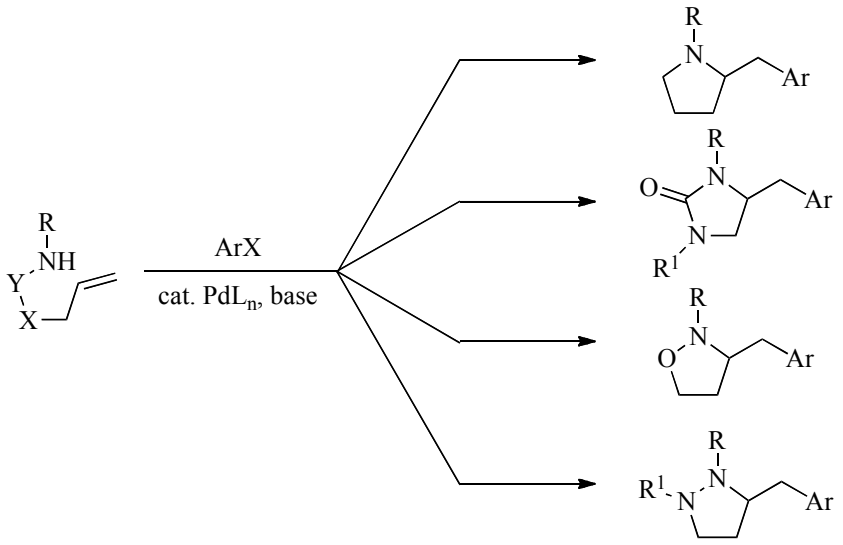
The conceptual simplicity of these reactions has resulted in many studies in which the coupling partner or composition of the metal catalyst can be optimized depending on the substrate. In particular, recent developments in this field have focused on the preparation of new ligands to enable general palladium-catalyzed cross-coupling conditions.[5] Additionally, the use of organometallic chemistry is a promising venue for the synthesis of medicinally relevant heterocycles in a highly stereoselective and convergent manner. As such, our group became interested in the potential of coupling γ-aminoalkenes with aryl or alkenyl halides.

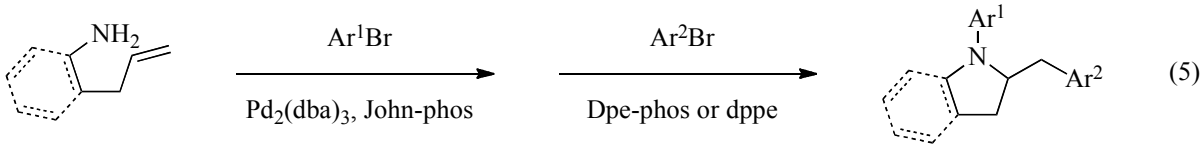
1.2 Pd-Catalyzed Alkene Difunctionalization Reactions

Over the past several years, our group has developed a methodology for the formation of five-membered *N*-heterocycles,[6] wherein the coupling of a γ-aminoalkene with an aryl or alkenyl halide is accomplished using a palladium catalyst system and a stoichiometric quantity of base. The heterocyclic products can be prepared in good yields with high levels of stereoselectivity; notably, these alkene difunctionalization reactions simultaneously form adjacent C–C and C–N bonds with high levels of stereoselectivity, as well as up to two stereocenters. We have successfully prepared *N*-protected pyrrolidines,[7a-c] imidazolidin-2-ones,[7d] isoxazolidines,[7e] and pyrazolidines[7f] using this chemistry (Scheme 1). Additionally, we have reported tandem *N*-arylation/carboamination reactions (eq. 5) through *in situ* modification of the palladium

catalyst.[7g] Of note, these reactions constitute rare examples of *syn*-insertion of an alkene into a Pd–N bond.

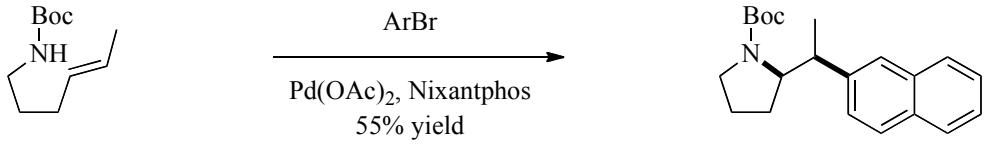
Scheme 1. Scope of Pd-Catalyzed Carboamination Reaction





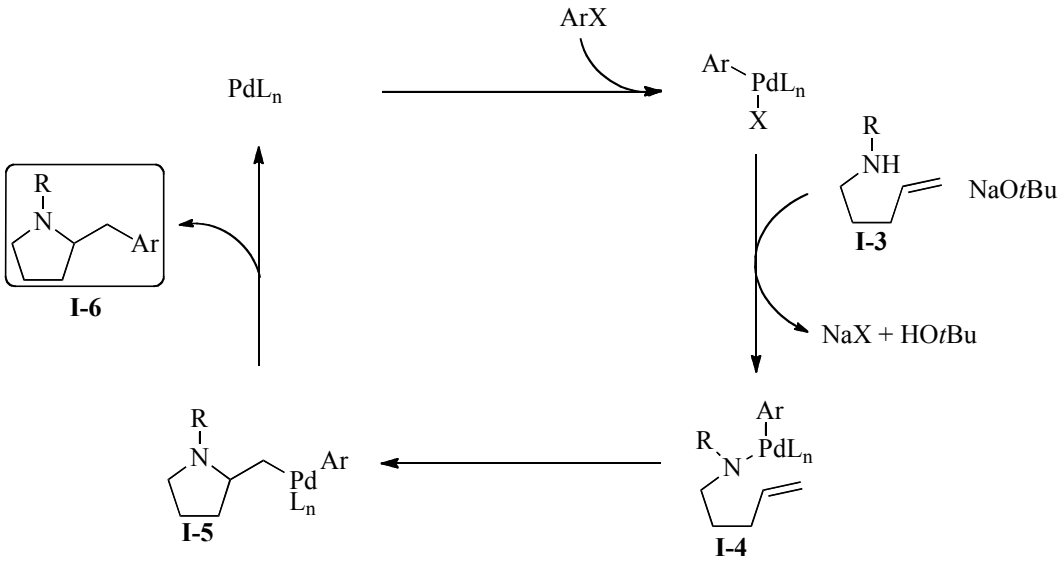
(5)

The general mechanism for this transformation is shown below (Scheme 2). The catalytic cycle is initiated by oxidative addition of the aryl bromide to Pd(0), followed by deprotonation and coordination with alkenylamine **I-3** to give palladium amido complex **I-4**. *Syn*-aminopalladiation providess intermediate **I-5**, which undergoes C–C bond-forming reductive elimination to give pyrrolidine **I-6**.[8] Evidence for *syn*-insertion of the alkene into the Pd–N bond is highlighted below in the conversion of internal alkene product **I-1** to pyrrolidine **I-2** (eq. 6).[7c]



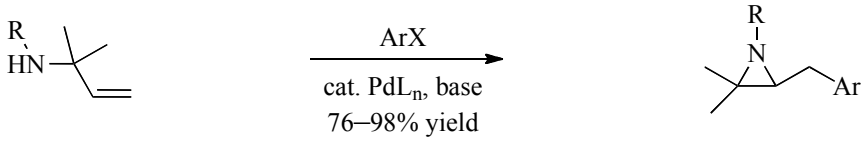
I-1 **I-2** (6)

Scheme 2. Mechanism of Pyrrolidine Formation *via* Pd-Catalyzed Carboamination

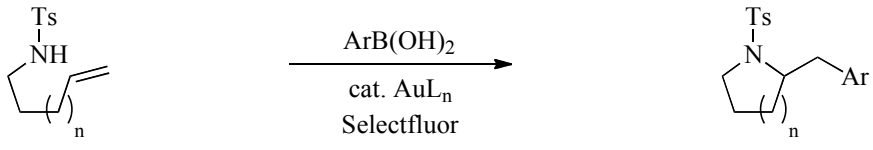


1.3 Related Alkene Difunctionalization Reactions

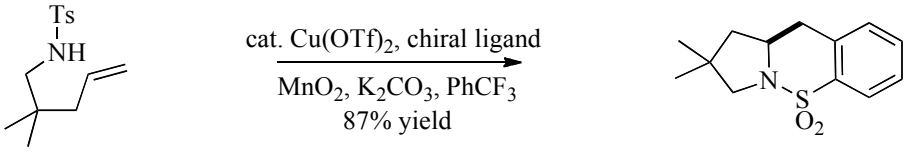
In addition to our work on Pd-catalyzed carboamination reactions, other groups have developed similar methodologies. In early 2010, Oshima and co-workers reported a synthetic route to substituted aziridines using a Pd-catalyzed carboamination reaction similar to our own (eq. 7).[9] Zhang and Toste reported gold-catalyzed carboamination reactions with aryl boronic acids using Selectfluor as an oxidant (eq. 8).[10] In contrast to the Pd-catalyzed carboamination reaction, the gold-catalyzed variant proceeds through *anti*-addition of the nucleophile and arene across the olefin. Additionally, Chemler has reported several examples of intramolecular Cu-catalyzed carboamination reactions to provide optically active sultams (eq. 9).[11]



(7)



(8)



(9)

1.4 Project Goals

The research described in this thesis aims to address several limitations of the Pd-catalyzed carboamination reaction. Chapter 2 will describe the synthesis of *cis*-3,5-disubstituted morpholines. Chapter 3 will focus on the development of conditions for the synthesis of substituted pyrrolidines and other heterocycles using inexpensive aryl chlorides as electrophiles. Chapter 4 will describe a catalytic asymmetric synthesis of the natural product (+)-aphanorphine with the key step being an enantioselective Pd-catalyzed carboamination reaction.

Chapter 2

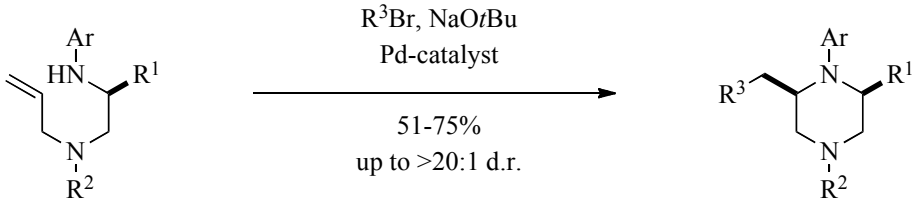
New Strategy for the Synthesis of Substituted Morpholines

2.1 Introduction

In recent years, drug discovery efforts have revealed several interesting biologically active compounds that contain C-substituted morpholine units.[12,13] Despite the medicinal importance of these molecules, the development of new approaches to their synthesis remains relatively unexplored.[12,14] For example, few methods allow the preparation of 3,5-disubstituted morpholines,[15] and only two approaches to the stereoselective synthesis of *cis*-3,5-disubstituted derivatives have been described.[13a,16] Both of these strategies are limited in scope, as one affords symmetrically disubstituted (meso) products,[16] and the other was used only for the generation of one single compound (*cis*-3-carbomethoxy-5-allylmorpholine).[13a]

2.2 Synthesis of *cis*-3,5-Disubstituted Morpholines

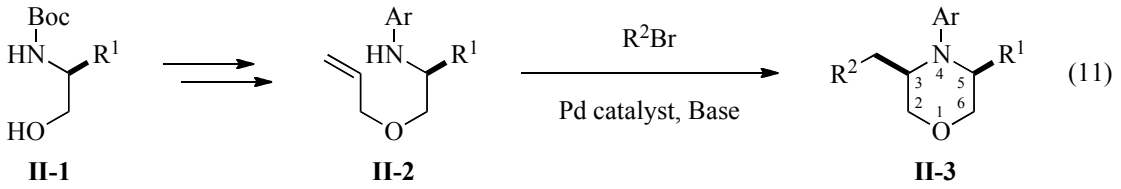
We recently reported a concise asymmetric synthesis of *cis*-2,6-disubstituted piperazines that involves Pd-catalyzed carboamination reactions of *N*-allyl ethylenediamine derivatives.[17] As highlighted in Equation 10, a number of *N*-allyl ethylenediamines can be converted to *cis*-2,6-disubstituted piperazines in moderate to good yields with excellent diastereoselectivity.



(10)

We felt that a similar strategy would be applicable to the construction of 3,5-disubstituted morpholines. As shown in Equation 11, enantiopure *N*-Boc amino alcohols (**II-1**) could be converted to *O*-allyl ethanolamines **II-2** using standard methods. These compounds would then be transformed to the desired heterocycles **II-3** through Pd-catalyzed coupling with an aryl or

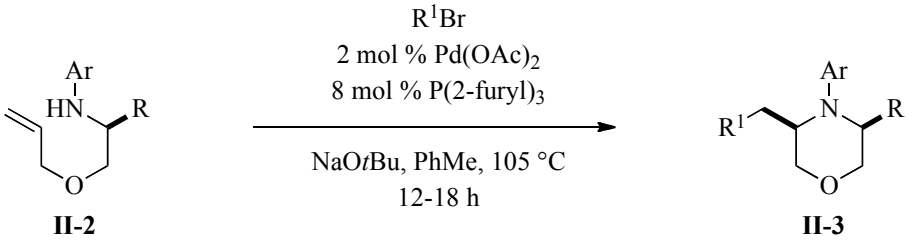
alkenyl halide. This modular synthetic strategy should provide access to a broad array of enantiopure *cis*-3,5-disubstituted morpholines that are difficult to generate using existing methods.

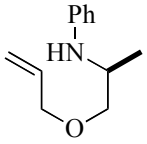
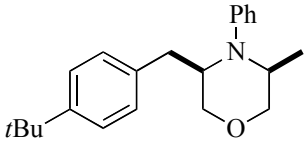
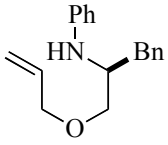
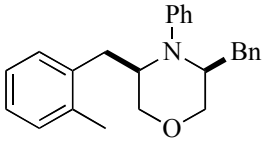
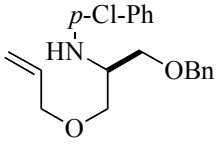
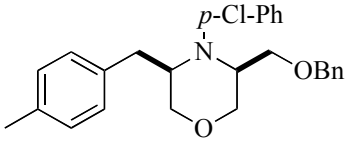
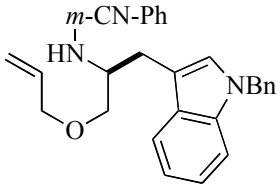
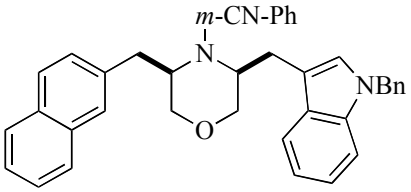


(11)

Treatment of Boc-protected amino alcohols **II-1** with NaH and allyl bromide afforded the corresponding allyl ethers. Cleavage of the Boc group with TFA followed by Pd–catalyzed *N*-arylation of the resulting amine trifluoroacetate salts provided substrates **II-2**. The use of a catalyst composed of $Pd(OAc)_2$ and $P(2\text{-furyl})_3$ afforded morpholines **II-3**. Representative examples of experiments conducted by Matthew Leathen, my graduate student mentor in the Wolfe group, are shown below in Table 1. Several *O*-allylethanolamines were effectively converted to the desired products, including heretoatom-containing substrates (Table 1, entries 3 and 4). Significantly, while the yields are modest, the diastereoselectivities are universally high (> 20:1 d.r.).

Table 1. Synthesis of *cis*-3,5-Disubstituted Morpholines[a].



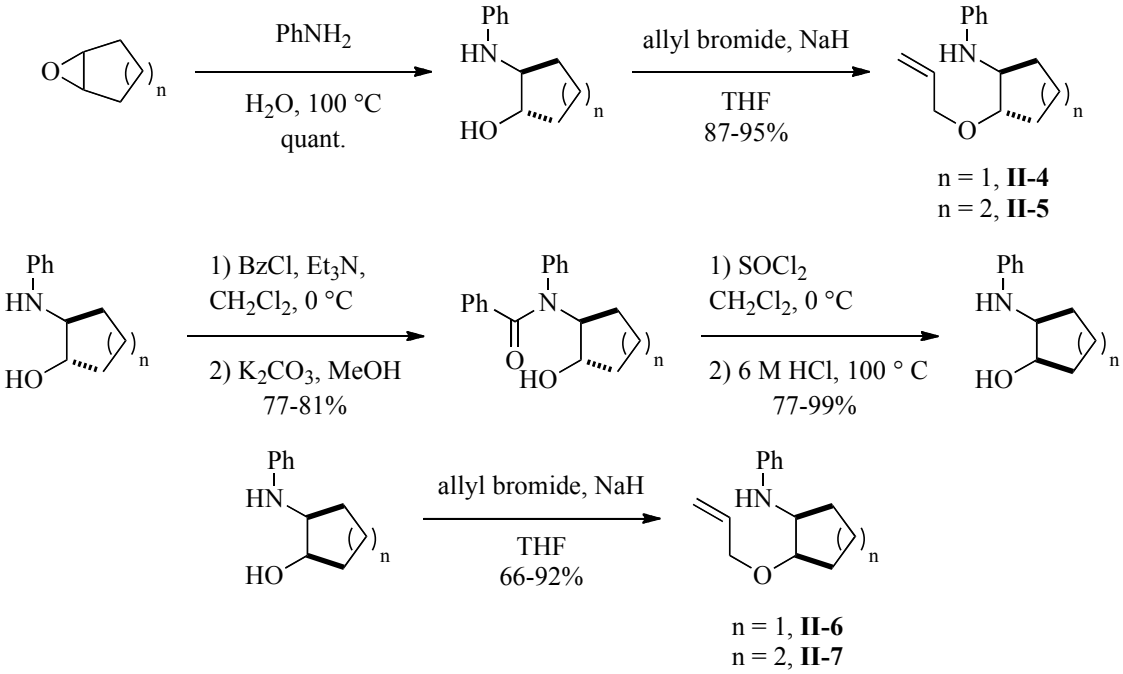
entry	substrate	product	yield[b]
1			53%
2			66%
3			49%
4			57%

[a] Conditions: 1.0 equiv substrate, 2.0 equiv R^1Br, 2.0 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.4 M), 105 °C. [b] Isolated Yield (average of two experiments).

2.3 Synthesis of Bicyclic Morpholines

To further explore the utility of this method for the synthesis of other substituted morpholines, I examined reactions of several *N*-aryl ethanolamine derivatives with different substitution patterns. As shown in Scheme 3, substrates **II-4** through **II-7** were prepared by *O*-allylation of 2-(*N*-phenylamino)cyclohexanol or -cyclopentanol.[18]

Scheme 3. Synthesis of Substrates.

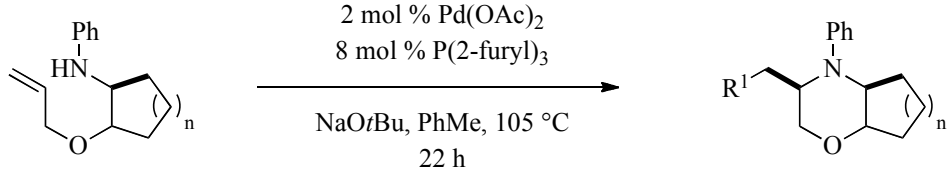


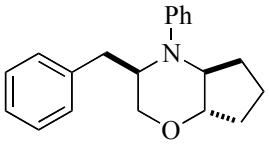
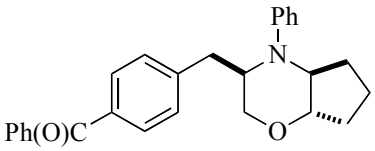
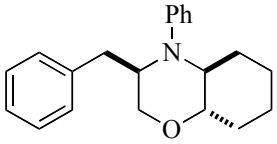
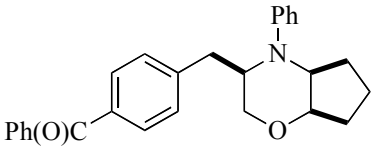
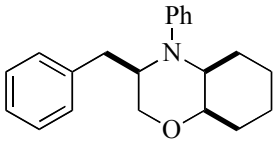
These substrates were coupled with aryl bromides using our optimized reaction conditions as shown in Table 2. These transformations afforded the desired bicyclic morpholines in moderate to good yields with excellent diastereoselectivities (> 20:1 d.r.). Of note, the carboamination reaction of electron-deficient aryl bromide 4-bromobenzophenone was successful with both substrates **II-4** and **II-6** (Table 2, entries 2 and 4).

The mechanism of the morpholine-forming carboamination reactions is likely similar to that of related transformations that generate piperazines, pyrrolidines, and other nitrogen-containing heterocycles. As shown in Scheme 4, the key intermediate in the conversion of **II-2** to **II-3** is palladium(aryl)(amido) complex **II-8**, which is produced by oxidative addition of the aryl bromide to Pd(0) followed by Pd–N bond formation. The relative stereochemistry of the substituted morpholine products is most consistent with a pathway involving *syn*-aminopalladation of **II-8** through a boat-like transition state (**II-9**) to afford **II-10** as shown in Scheme 4.[19] Reductive elimination from **II-10** would provide the *cis*-3,5-disubstituted

morpholine products **II-3**. ß-hydride elimination from **II-10** followed by Heck arylation would result in deleterious 3,4-dihydro-2*H*-1,4-oxazines observed in crude reaction mixtures.[20] This mechanism also accounts for the conversion and stereochemical outcome of the bicyclic morpholines shown in Table 2.

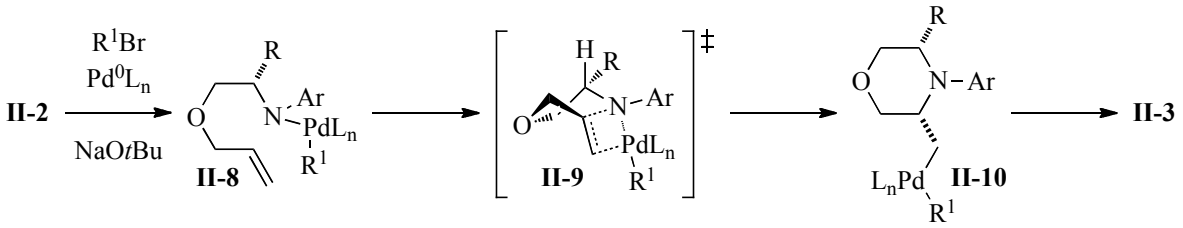
Table 2. Synthesis of Bicyclic Morpholines.



entry	substrate	product	yield[b]
1	**II-4**		73%
2	**II-4**		54%
3	**II-5**		56%
4	**II-6**		77%
5	**II-7**		65%

[a] Conditions: 1.0 equiv substrate, 2.0 equiv R^1Br, 2.0-2.7 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 8 mol % P(2-furyl)$_3$, toluene (0.4 M), 105 °C. [b] Isolated Yield (average of two experiments).

Scheme 4. Transition State Leading to 3,5-disubstituted Morpholines.



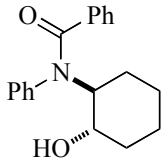
2.4 Conclusions

In conclusion, a concise asymmetric synthesis of *cis*-3,5-disubstituted morpholines from readily available enantiopure amino alcohol precursors has been described.[21] The modular nature of this approach permits variation of the morpholine substituents and also provides access to fused-ring morpholine derivatives. The strategies described above significantly expand the range of substituted morpholines that can be prepared in a concise, stereocontrolled manner.

2.5 Experimental Section

General: All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. Palladium (II) acetate and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. (±)-*trans*-2-(Phenylamino)cyclohexanol[22] and (±)-*trans*-(phenylamino)cyclopentanol[23] were synthesized *via* ring-opening cyclohexene oxide or cyclopentene oxide with aniline. Toluene and THF were purified using a GlassContour solvent purification system. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR and either capillary GC (known compounds) or ESI Mass Spectrometry (new compounds). The yields reported in this section describe the result of a single experiment, whereas the yields reported in Table 1 and Table 2 are average yields of two or more experiments. Thus, the yields reported in this section may differ from those shown in Table 1 and Table 2.

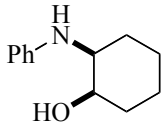
Synthesis of Substrates



II-S1

(±)-(1*S,2*S**)-*N*-(2-Hydroxycyclohexyl)-*N*-phenylbenzamide** (**II-S1**). A solution of (±)-*trans*-2-(phenylamino)cyclohexanol[22] (956 mg, 5.0 mmol) and triethylamine (2.1 mL, 15 mmol), in dichloromethane (10 mL), was cooled to 0 °C, and benzoyl chloride (0.6 mL, 4.9 mmol) was added dropwise. The reaction mixture was warmed to room temperature, stirred for 48 h, and transferred to a separatory funnel. The mixture was washed with 2 M HCl (2 x 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over

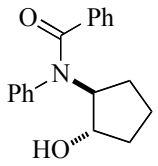
anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel using 2.5% MeOH/dichloromethane as the eluent to afford 1.13 g (77%) of the title compound as a white solid, m.p. 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.30–7.24 (m, 2 H), 7.24–7.06 (m, 8 H), 4.77–4.61 (m, 1 H), 3.53–3.37 (m, 1 H), 2.76 (s, br, 1 H), 2.12 (d, *J* = 12.0 Hz, 1 H), 2.01–1.89 (m, 1 H), 1.78–1.63 (m, 2 H), 1.52–1.29 (m, 2 H), 1.29–1.00 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 173.2, 139.5, 136.8, 130.8, 129.1, 128.7, 128.3, 127.63, 127.56, 71.7, 61.5, 35.7, 30.2, 25.2, 24.3; IR (film) 3319, 1622, cm^{-1}; MS (ESI) 318.1465 (318.1470 calcd for $C_{19}H_{21}NO_2$ M + Na^+).



II-S2

(±)-*cis*-2-(Phenylamino)cyclohexanol (**II-S2**). A solution of **II-S1** (3.0 g, 10.2 mmol) in dichloromethane (50 mL) under nitrogen was cooled to 0 °C and thionyl chloride (4.4 mL, 61 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated *in vacuo*, and 6 N HCl (50 mL) was added. The resulting mixture was heated to reflux with vigorous stirring for 6 h, then was cooled to rt, filtered, and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined ethyl acetate layers were discarded, and the aqueous layer was basified to pH > 9 using 5 M NaOH. The aqueous layer was then extracted with ether (3 x 50 mL), and the combined ether layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 15% EtOAc/hexanes as the eluent to afford 1.5 g (77%) of the title compound as a white solid, m.p. 75–77 °C (lit.[24] m.p. 72–74 °C). ^{1}H NMR (400 MHz, $CDCl_3$) d 7.24–7.17 (m, 2 H), 6.79–6.72 (m, 1 H), 6.68 (dd, *J* = 1.0, 7.8 Hz, 2 H), 4.09–4.02 (m, 1 H), 3.73 (s, br, 1 H), 3.44–3.37 (m, 1 H), 2.31 (s, br, 1 H), 1.90–1.80 (m, 1

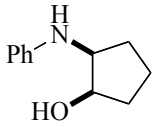
H), 1.76–1.56 (m, 5 H), 1.52–1.28 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 147.2, 129.2, 117.6, 113.7, 67.6, 54.8, 31.3, 27.0, 23.5, 20.0; IR (film) 3397, 1505 cm^{-1}; MS (ESI) 214.1211 (214.1208 calcd for $C_{12}H_{17}NO$, M + Na^+).



II-S3

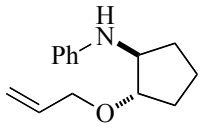
(±)-(1*S,2*S**)-*N*-(2-Hydroxycyclopentyl)-*N*-phenylbenzamide** (**II-S3**). A solution of (±)-*trans*-2-(phenylamino)cyclopentanol[23] (1.78 g, 10 mmol) and triethylamine (8.4 mL, 60 mmol) in dichloromethane (20 mL), was cooled to 0 °C with stirring and benzoyl chloride (3.5 mL, 30 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was transferred to a separatory funnel, washed with 2 M HCl (2 x 10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was dissolved in methanol (25 mL), and potassium carbonate (6.9 g, 50 mmol) was added slowly at room temperature. The reaction mixture was stirred at room temperature for 48 hours, and the reaction was quenched with saturated ammonium chloride (25 mL). The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a red-orange oil. The crude material was dissolved in a minimal amount of hot ethyl acetate and cooled in a –20 °C freezer until crystals formed. Filtration afforded 2.27 g (81%) of the title compound as a white solid, mp 109–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.30–7.03 (m, 10 H), 4.79–4.69 (m, 1 H), 4.28–4.18 (m, 1 H), 4.02 (s, br, 1 H), 1.97–1.86 (m, 2 H), 1.82–1.63 (m, 2 H), 1.61–1.50 (m, 1 H), 1.47–1.34 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 173.1, 140.1, 136.4, 130.3, 129.3, 128.8,

128.3, 127.64, 127.57, 76.8, 67.5, 32.5, 28.4, 21.0; IR (film) 3401, 1633 cm^{-1}; MS (ESI) 304.1312 (304.1313 calcd for $C_{18}H_{19}NO_2$, M + Na^+).



II-S4

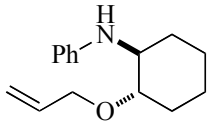
(±)-*cis*-2-(Phenylamino)cyclopentanol (**II-S4**). The conversion of **II-S3** (1.41 g, 5.0 mmol) to the title compound was accomplished using a procedure analogous to that described above for the synthesis of S2. This procedure afforded 880 mg (99%) of the title compound as a clear and colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.23–7.14 (m, 2 H), 6.81–6.61 (m, 3 H), 4.33–4.23 (m, 1 H), 3.69–3.53 (m, 1 H), 3.05 (s, br, 1 H), 2.17–2.01 (m, 1 H), 2.00–1.75 (m, 3 H), 1.69–1.49 (m, 2 H) (the OH signal was not observed due to broadening); ^{13}C NMR (100 MHz, $CDCl_3$) d 147.7, 129.3, 118.1, 113.5, 71.3, 59.4, 32.5, 30.1, 20.3; IR (film) 3398, 1504 cm^{-1}; MS (ESI) 178.1225 (178.1232 calcd for $C_{11}H_{15}NO$ M + H^+).



II-4

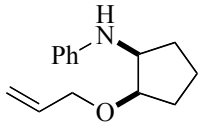
***trans*-2-(Allyloxy)cyclopentylaniline** (**II-4**). The conversion of *trans*-2-(phenylamino)cyclopentanol[23]. (500 mg, 2.82 mmol) to the title compound was accomplished using a procedure analogous to that described above for the synthesis of **II-7**. This procedure afforded 535 mg (87%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.19–7.10 (m, 2 H), 6.71–6.57 (m, 3 H), 5.98–5.83 (m, 1 H), 5.26 (dd, *J* = 1.6, 17.2 Hz, 1 H), 5.13 (d, *J* = 10.0 Hz, 1 H), 4.04–3.89 (m, 2 H), 3.74–3.65 (m, 2 H), 3.48 (s, br, 1 H), 2.25–2.10 (m, 1 H), 1.87–1.59 (m, 4 H), 1.43–1.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 147.6, 135.0,

129.0, 117.0, 116.4, 113.0, 84.9, 69.9, 59.8, 31.5, 30.0, 21.7; IR (film) 3404 cm^{-1}; MS (ESI) 218.1543 (218.1545 calcd for $C_{14}H_{19}NO$, M + H^+).



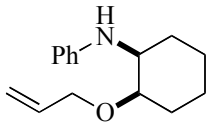
II-5

***trans*-2-(Allyloxy)cyclohexylaniline** (**II-5**). The conversion of *trans*-2-(phenylamino)cyclohexanol[10] (500 mg, 2.62 mmol) to the title compound was accomplished using a procedure analogous to that described above for the synthesis of **II-7**. This procedure afforded 578 mg (95%) of the title compound as an amber oil. Spectroscopic properties were consistent with those reported in the literature.



II-6

***cis*-2-(Allyloxy)cyclopentylaniline** (**II-6**). The conversion of **II-6** (532 mg, 3 mmol) was accomplished using a procedure analogous to that described above for the synthesis of **II-7**. This procedure afforded 601 mg (92%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.19–7.13 (m, 2 H), 6.70–6.59 (m, 3 H), 5.95–5.82 (m, 1 H), 5.26 (dq, *J* = 1.6, 15.3 Hz, 1 H), 5.15 (dq, *J* = 1.5, 9.0 Hz, 1 H), 4.34 (s, br, 1 H), 4.05–3.98 (m, 1 H), 3.96–3.89 (m, 2 H), 3.75–3.65 (m, 1 H), 2.07–1.94 (m, 1 H), 1.88–1.76 (m, 3 H), 1.71–1.51 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 148.0, 135.0, 129.2, 116.9, 116.7, 113.3, 79.9, 70.3, 56.1, 29.8, 29.4, 20.3; IR (film) 3401, 1602, 1505 cm^{-1}; MS (ESI) 240.1366 (240.1364 calcd for $C_{14}H_{19}NO$, M + Na^+).

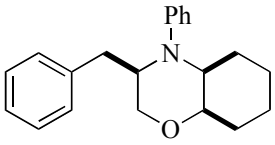


II-7

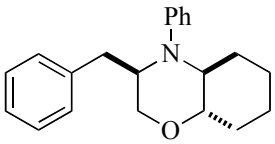
***cis*-2-(Allyloxy)cyclohexylaniline** (**II-7**). A solution of **II-S2** (764 mg, 4.0 mmol) in THF (16 mL) cooled to 0 °C under nitrogen with stirring. Solid NaH (216 mg, 5.6 mmol, 60% suspension in mineral oil) was added slowly, and the resulting mixture was stirred for 30 minutes at 0 °C. Allyl bromide (0.4 mL, 4.4 mmol) was added, and the mixture was warmed to room temperature. After the starting material had been completely consumed as judged by TLC analysis, the reaction was quenched with saturated aqueous NH_4Cl and transferred to a separatory funnel. The mixture was extracted with EtOAc (3 x 15 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 2% EtOAc/hexanes as the eluent to afford 610 mg (66%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.20–7.13 (m, 2 H), 6.70–6.60 (m, 3 H), 5.98–5.86 (m, 1 H), 5.31–5.24 (m, 1 H), 5.17–5.12 (m, 1 H), 4.16–4.03 (m, 2 H), 3.93–3.86 (m, 1 H), 3.71–3.66 (m, 1 H), 3.45–3.37 (m, 1 H), 2.05–1.97 (m, 1 H), 1.81–1.68 (m, 2 H), 1.67–1.50 (m, 2 H), 1.48–1.26 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 147.4, 135.4, 129.2, 117.0, 116.2, 113.6, 75.5, 69.6, 53.7, 28.3, 27.4, 24.2, 20.2; IR (film) 3402, 1505 cm^{-1}; MS (ESI) 232.1707 (232.1701 calcd for $C_{15}H_{21}NO$, M + H^+).

General Procedure 1: Synthesis of Morpholines *via* Pd-Catalyzed Carboamination. A Schlenk tube was evacuated, flame dried and backfilled with nitrogen. The tube was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), P(2-furyl)$_3$ (9.3 mg, 0.04 mmol), and NaO*t*Bu (96.1 mg, 1.0 mmol). The tube was evacuated and backfilled with nitrogen, then the aryl bromide (1.0 mmol) and a solution of the amine substrate (0.50 mmol) in toluene (1.25 mL) were added to the Schlenk tube (aryl bromides that were solids at room temperature were added as solids following the addition of NaO*t*Bu). The mixture was heated to 105 °C with stirring until the substrate was consumed as judged by GC analysis (*ca.* 22 h). The reaction mixture was cooled to room

temperature, saturated aqueous NH_4Cl (3 mL) was added, and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel.

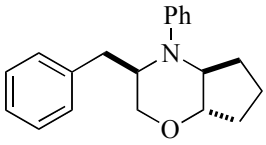


(±)-(3*R,4a*S**,8a*R**)-3-Benzyl-4-phenyloctahydro-2*H*-benzo[*b*][1,4]oxazine**. General Procedure 1 was employed for the coupling of bromobenzene with **II-7** (174 mg, 0.75 mmol). This procedure gave the title compound (150 mg, 65%) as white solid after purification by chromatography with 2% EtOAc/hexanes as the eluent. This material was judged to be of >20:1 d.r. by ^{1}H NMR analysis before and after purification. m.p. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.38–7.28 (m, 6 H), 7.26–7.20 (m, 1 H), 6.93–6.83 (m, 2 H), 6.79–6.71 (m, 1 H), 4.04 (d, J = 12.0 Hz, 1 H), 3.73–3.53 (m, 4 H), 3.05 (t, J = 12.0 Hz, 1 H), 2.80 (d, J = 13.0 Hz, 1 H), 2.08 (d, J = 14.0 Hz, 1 H), 1.95 (d, J = 12.0 Hz, 1 H), 1.86–1.49 (m, 5 H), 1.34–1.20 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 146.5, 139.9, 129.6, 129.3, 128.7, 126.3, 116.6, 111.8, 75.6, 67.8, 53.0, 37.2, 31.7, 25.4, 25.0, 20.9 (one aliphatic carbon signal is absent due to incidental equivalence); IR(film) 1598, 1503 cm^{-1}; MS (ESI) 308.2011 (308.2014 calcd for $C_{21}H_{25}NO$ + H^+).

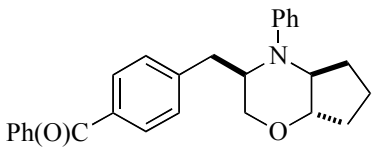


(±)-(3*R,4a*S**,8a*S**)-3-Benzyl-4-phenyloctahydro-2*H*-benzo[*b*][1,4]oxazine**. General Procedure 1 was employed for the coupling of bromobenzene with **II-5** (174 mg, 0.75 mmol). This procedure gave the title compound (126 mg, 55%) as a white crystalline solid, after purification by chromatography with 2% EtOAc/hexanes as the eluent. This material was judged

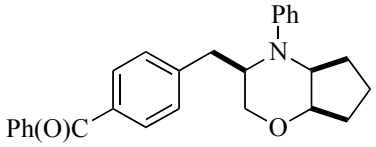
to be of >20:1 d.r. by ^{1}H NMR analysis before and after purification. m.p. 128–130 °C;^{1}H NMR (400 MHz, $CDCl_3$) d 7.40–7.08 (m, 8 H), 6.99–6.91 (m, 2 H), 3.78 (d, *J* = 11.3 Hz, 1 H), 3.48 (t, *J* = 10.3 Hz, 1 H), 3.37–3.24 (m, 2 H), 2.56 (d, *J* = 13.0 Hz, 2 H), 2.21–2.09 (t, *J* = 11.7 Hz, 1 H), 1.92 (d, *J* = 10.3 Hz, 1 H), 1.68 (d, *J* = 10.3 Hz, 1 H), 1.54 (d, *J* = 11.7 Hz, 1 H), 1.42–1.20 (m, 3 H), 1.16–0.94 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 148.7, 138.5, 129.1, 128.9, 128.2, 128.0, 126.3, 126.1, 80.8, 71.7, 66.6, 62.5, 37.5, 31.3, 29.7, 24.6, 24.5; IR (film) 1488, 1448 cm^{-1}; MS (ESI) 308.2018 (308.2014 calcd for $C_{21}H_{25}NO$, M + H$^+$).



(±)-(3*R,4a*S**,7a*S**)-3-Benzyl-4-phenyloctahydrocyclopenta[*b*][1,4]oxazine**. General Procedure 1 was employed for the coupling of bromobenzene with **II-4** (54 mg, 0.25 mmol). This procedure gave the title compound (52 mg, 71%) as yellow solid after purification by chromatography with 15% EtOAc/hexanes as the eluent. This material was judged to be of >20:1 d.r. by ^{1}H NMR analysis before and after purification. m.p. 84–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.39–7.33 (m, 2 H), 7.30–7.26 (m, 2 H), 7.24–7.28 (m, 3 H), 7.17–7.12 (m, 1 H), 7.04–7.00 (m, 2 H), 3.87 (dd, *J* = 3.1, 8.2 Hz, 1 H), 3.59–3.47 (m, 2 H), 3.30 (tt, *J* = 3.6, 10.1 Hz, 1 H), 2.75–2.63 (m, 2 H), 2.23 (dd, *J* = 3.8, 10.2 Hz, 1 H), 1.98–1.89 (m, 1 H), 1.69–1.52 (m, 3 H), 1.37–1.29 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 149.2, 138.6, 129.0, 128.9, 128.3, 126.5, 126.2, 126.0, 82.9, 72.8, 68.7, 61.8, 36.6, 26.7, 26.2, 17.4; IR (film) 1597, 1492, 1126 cm^{-1}; MS (ESI) 294.1844 (294.1858 calcd for $C_{20}H_{23}NO$, M + H$^+$).



(±)-(3*R,4a*S**,7a*S**)-Phenyl 4-(4-phenyloctahydrocyclopenta[*b*][1,4]oxazin-3-ylmethyl)phenyl ketone**. General Procedure 1 was employed for the coupling of 4-bromobenzophenone with **II-4** (163 mg, 0.75 mmol). This procedure gave the title compound (151 mg, 51%) as yellow solid after purification by chromatography with 15% EtOAc/hexanes as the eluent followed by heating under vacuum in a Kugelrohr apparatus (180 °C, 0.3 Torr) to remove hydrocarbon impurities. This material was judged to be of >20:1 d.r. by ^{1}H NMR analysis before and after purification. m.p. 84–86 °C;^{1}H NMR (400 MHz, $CDCl_3$) d 7.78–7.74 (m, 2 H), 7.69–7.65 (m, 2 H), 7.60–7.54 (m, 1 H), 7.49–7.44 (m, 2 H), 7.40–7.34 (m, 2 H), 7.30–7.25 (m, 2 H), 7.24–7.19 (m, 1 H), 7.15–7.10 (m, 2 H), 3.88 (dd, *J* = 3.3, 8.0 Hz, 1 H), 3.61–3.48 (m, 2 H), 3.40–3.31 (m, 1 H), 2.81–2.65 (m, 2 H), 2.37 (dd, *J* = 4.0, 10.0 Hz, 1 H), 2.00–1.89 (m, 1 H), 1.70–1.56 (m, 3 H), 1.38–1.29 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 196.3, 149.1, 143.8, 137.7, 135.6, 132.3, 130.3, 129.9, 129.1, 128.8, 128.2, 126.5, 126.1, 82.9, 72.7, 68.6, 61.6, 36.7, 26.6, 26.2, 17.4; IR (film) 1658, 1606 cm^{-1}; MS (ESI) 398.2119 (398.2120 calcd for $C_{27}H_{27}NO_2$, M + H$^+$).



(±)-(3*R,4a*S**,7a*R**)-Phenyl 4-(4-phenyloctahydrocyclopenta[*b*][1,4]oxazin-3-ylmethyl)phenyl ketone**. General Procedure 1 was employed for the coupling of 4-bromobenzophenone with **II-6** (109 mg, 0.5 mmol). This procedure gave the title compound (150 mg, 75%) as yellow oil after purification by chromatography with 10% EtOAc/hexanes as the eluent followed by heating under vacuum in a Kugelrohr apparatus (160 °C, 0.3 Torr) to remove hydrocarbon impurities. This material was judged to be of >20:1 d.r. by ^{1}H NMR analysis before and after purification. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.83–7.77 (m, 4 H), 7.63–

7.56 (m, 1 H), 7.52–7.45 (m, 2 H), 7.44–7.40 (m, 2 H), 7.37–7.30 (m, 2 H), 6.91 (d, *J* = 8.3 Hz, 2 H), 6.79 (t, *J* = 7.0 Hz, 1 H), 4.01–3.96 (m, 1 H), 3.89 (d, *J* = 11.6 Hz, 1 H), 3.83–3.68 (m, 2 H), 3.58–3.50 (m, 1 H), 3.11 (dd, *J* = 1.2, 13.0, 1 H), 2.95 (d, *J* = 13.0, 1 H), 2.38–2.25 (m, 1 H), 2.12–1.86 (m, 3 H), 1.74–1.50 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 196.3, 147.1, 144.7, 137.7, 135.8, 132.3, 130.6, 130.0, 129.6, 129.3, 128.3, 116.9, 111.9, 78.2, 66.0, 56.3, 52.7, 35.6, 31.3, 28.1, 21.6; IR (film) 1658, 1597 cm^{-1}; MS (ESI) 420.1925 (420.1939 calcd for $C_{27}H_{27}NO_2$, $M + Na^+$).

Chapter 3

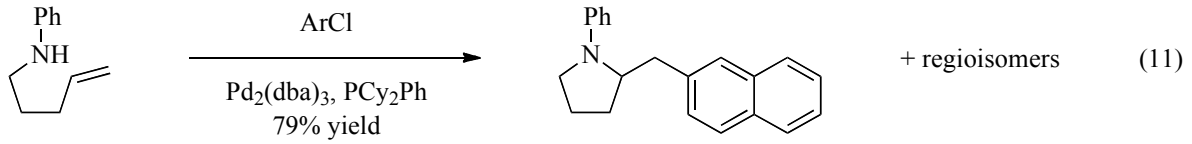
Use of Aryl Chlorides as Electrophiles in Pd-Catalyzed Alkene Difunctionalization Reactions

3.1 Introduction

Typically, aryl bromides have been employed as the electrophiles in Pd-catalyzed carboamination reactions. In order to expand the scope and utility of this chemistry, we felt it would be useful to investigate conditions under which similar products could be generated using analogous aryl chlorides as cross-coupling partners, in large part due to the significant economic benefits associated with aryl chlorides relative to aryl bromides. In our prior studies, we had found that chelating phosphine ligands with wide bite angles, such as DPEphos, Xantphos, or dppb, provided optimal results in many transformations of aryl bromides.[25] However, palladium catalysts supported by these ligands are not sufficiently active to facilitate transformations of aryl chlorides as electrophiles, which are considerably less reactive than the corresponding aryl bromides. Thus, to achieve our goal, we would need to discover catalysts that both activate aryl chlorides, and also promote the alkene carboamination process.[26]

3.2 Optimization Studies

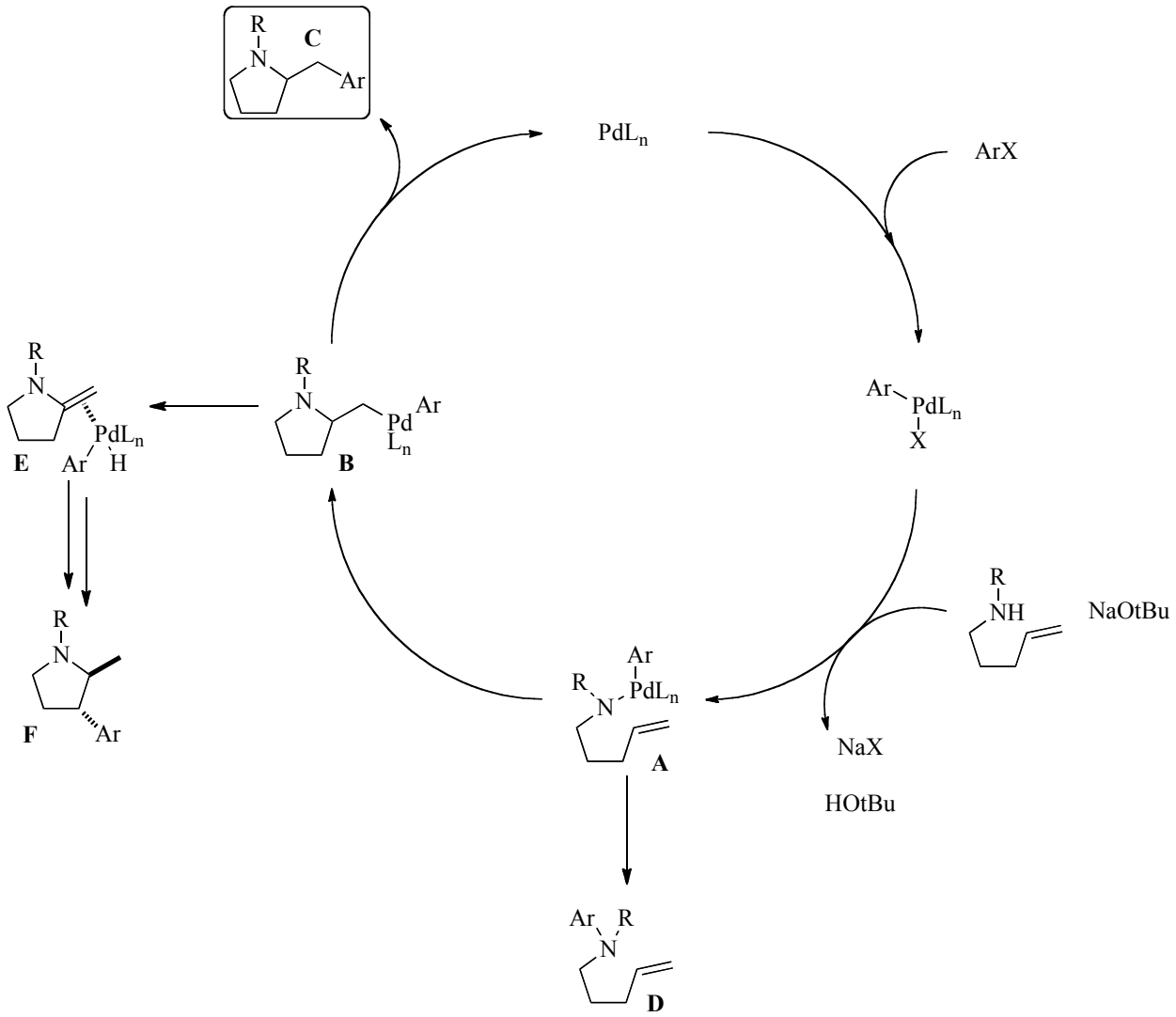
Earlier research in our group demonstrated that a catalyst composed of $Pd_2(dba)_3$ and PCy_2Ph was useful for the preparation of *N*-aryl pyrrolidines *via* carboamination reactions with aryl chlorides (eq. 11).[27] Use of this ligand, however, also led to the formation of small amounts of regioisomeric products that proved difficult to separate from the desired pyrrolidine.



(11)

The mechanism of the carboamination reaction involves *syn*-aminopalladation of intermediate **A**, followed by C–C bond-forming reductive elimination from intermediate **B** to give pyrrolidine product **C** (Scheme 5). Arylated product **D** results from competing C–N bond-forming reductive elimination of intermediate **A**.[28] Undesired regioisomers **F** can be generated through ß-hydrogen elimination of intermediate **B** followed by a series of hydridopalladation/ß-hydride elimination steps.

Scheme 5. Mechanism of Pyrrolidine and Side Product Formation

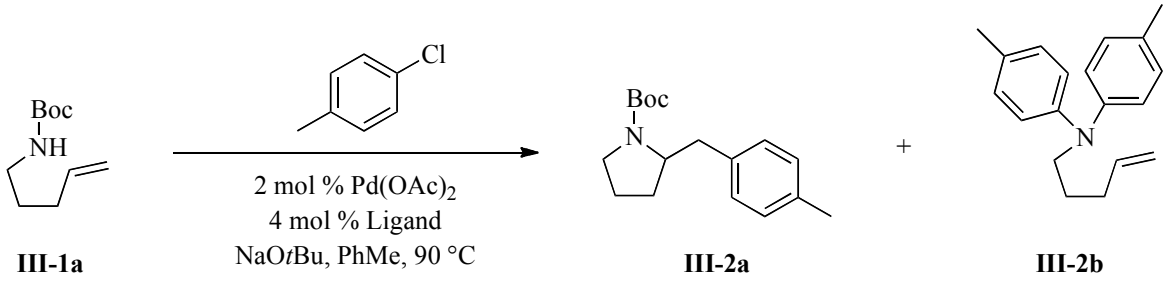


Our mechanistic analysis suggests that transformations of the analogous *N*-Boc protected substrates may be less problematic. The electron-withdrawing Boc group is known to slow the

rate of C–N bond-forming reductive elimination that leads to *N*-arylation.[29] We felt that bulky electron-rich ligands could be used to facilitate the C–C bond-forming step to avoid competing *N*-arylation. Additionally, the electron-withdrawing nature of the Boc group also disfavors ß-hydride elimination pathways that provide regioisomers, which should further aid in the selective formation of a single product.

With these mechanistic considerations in mind, we undertook a ligand screen with several ligands known to promote coupling reactions with aryl chlorides (Figure 1). The only side product observed in crude mixtures was **III-2b**, which resulted from base-mediated Boc cleavage followed by subsequent *N*-arylation reactions. We were pleased to find the ligand S-phos provided the desired pyrrolidine **III-2a** in 69% ^{1}H NMR yield with no formation of **III-2b**.[30]

Figure 1. Effects of Phosphine Ligands on Pyrrolidine Synthesis.



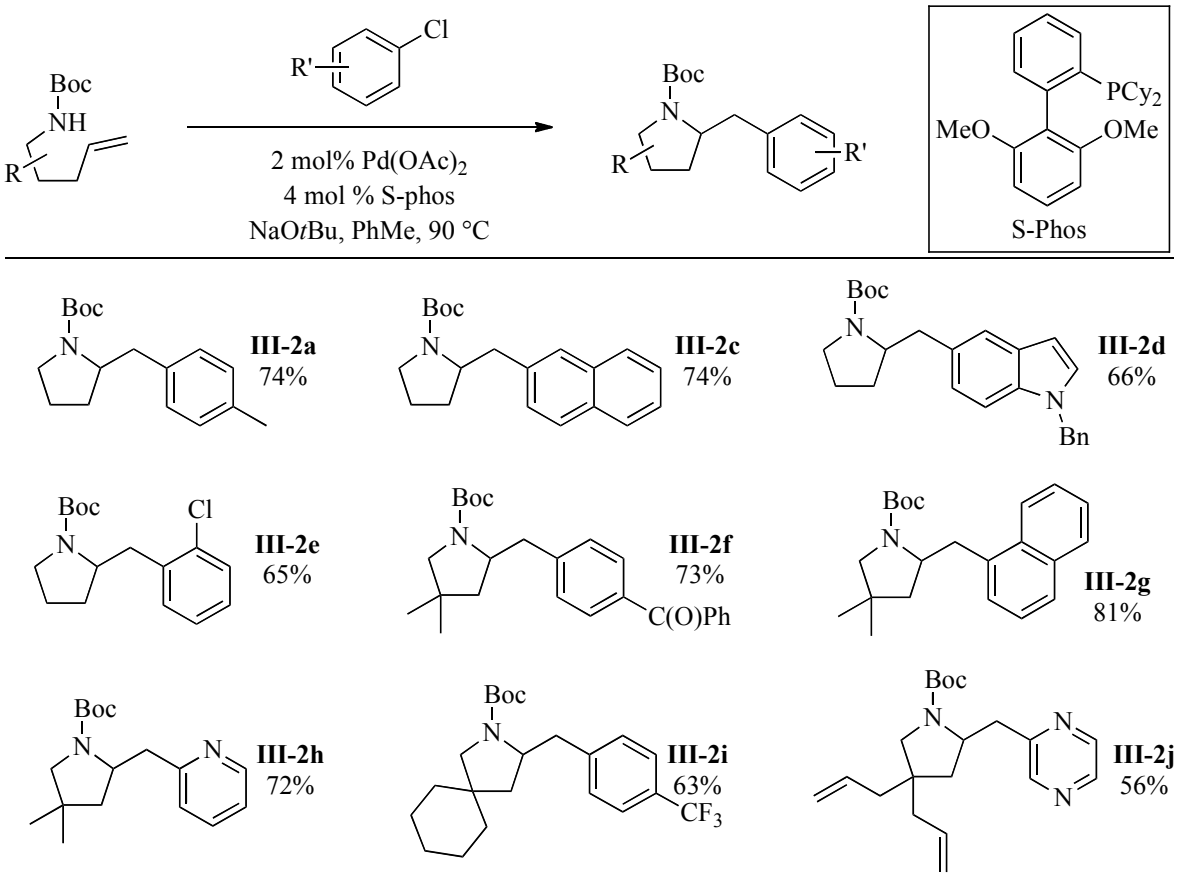
III-1a **III-2a** **III-2b**

Ligand	Yield III-2a	Yield III-2b
DPEphos	0%	0%
PCy_3•HBF_4	21%	27%
$P(t\text{-Bu})_2Me$•HBF_4	50%	7%
PCy_2Ph	21%	38%
S-phos	69%	0%
Brett-phos	52%	22%
Cy_4DPEphos	18%	22%

3.3 Scope and Limitations

In order to explore the scope of this method, we examined the coupling of a range of *N*-Boc-protected γ-aminoalkene derivatives.[31] As shown in Table 3, the transformations are effective with a variety of aryl chlorides, including electron-rich, electron-poor, and *ortho*-substituted compounds. Satisfactory results were also obtained with the heteroaromatic electrophiles *N*-benzyl-5-chloroindole, 2-chloropyridine, and 2-chloropyrazine (to give products **III-2d**, **III-2h**, and **III-2j**).[32] In all cases, no regioisomeric byproducts were observed in the crude reaction mixtures.

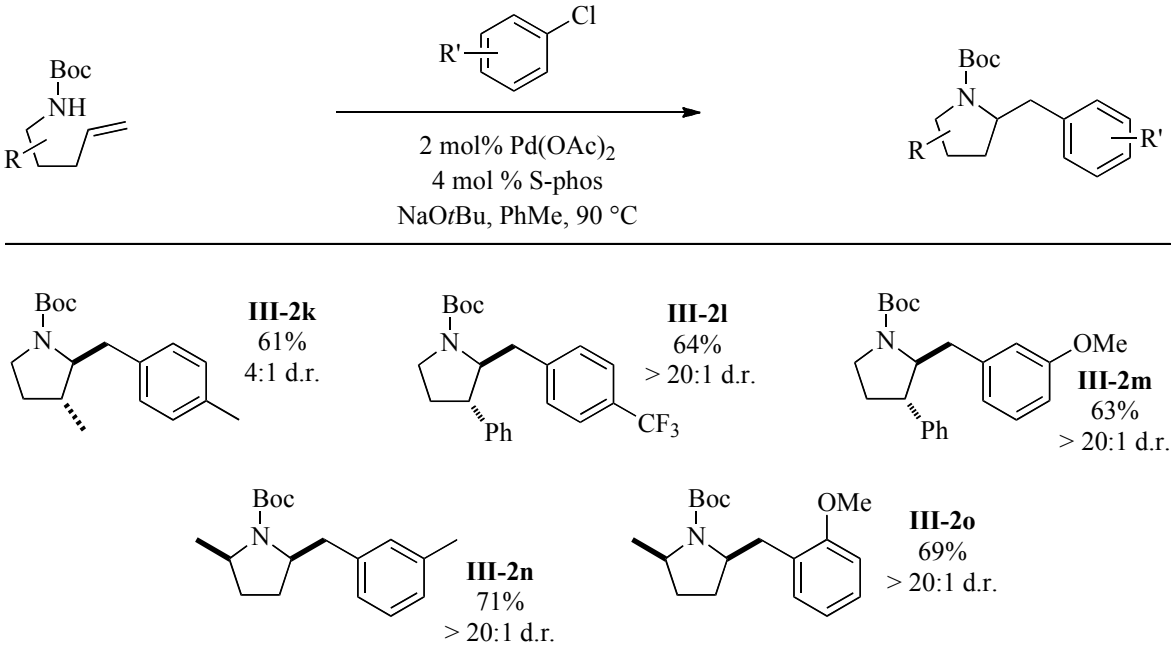
Table 3. Carboamination of (*N*-Boc)Aminoalkenes with Aryl Chlorides.[a]



[a] Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 1.2 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 4 mol % S-phos, toluene (0.25 M), 90 °C. [b] Isolated yield (average of two experiments).

The synthesis of *cis*-2,5-disubstituted products was achieved with excellent stereocontrol (**III-2n** and **III-2o**), and good to excellent selectivity was obtained in the synthesis of *trans*-2,3-disubstituted products (**III-2k**, **III-2l** and **III-2m**, Table 4). In all cases the products were generated with complete regioselectivity. Efforts to employ substrates bearing internal alkenes were unsuccessful due to competing base-mediated substrate decomposition.[33]

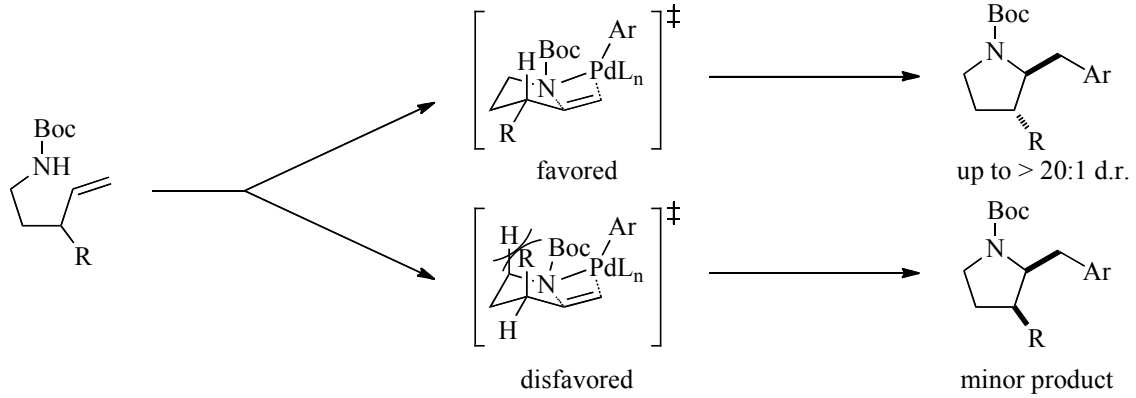
Table 4. Stereoselective Synthesis of Pyrrolidines.[a]



[a] Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 1.2 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 4 mol % S-phos, toluene (0.25 M), 90 °C. [b] Isolated yield (average of two experiments).

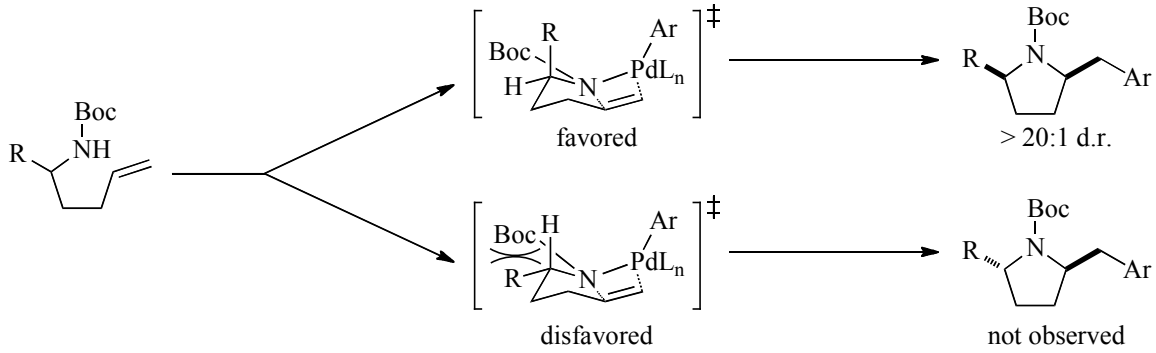
The stereochemistry of the pyrrolidine products generated in these reactions is likely determined in the *syn*-aminopalladation step of the catalytic cycle shown in Scheme 5. For example, substrates bearing allylic substituents are transformed into *trans*-2,3-disubstituted pyrrolidines **III-2k**, **III-2l**, and **III-2m** through the transition state shown in Figure 2. In these cases, the R group is oriented in a pseudoequatorial position in order to avoid disfavorable diaxial interactions. This transition state also accounts for the increased selectivity observed when R = Ph vs. R = Me.

Figure 2. Stereochemical Rationale for 2,3-disubstituted Pyrrolidines.



Cis-2,5-disubstituted pyrrolidines **III-2n** and **III-2o** could also be prepared with high selectivity through the transition state shown in Figure 3. In this case, the C1-R group is oriented in a pseudoaxial position, which avoids $A^{(1,3)}$-strain between the R group and the nitrogen protecting group.

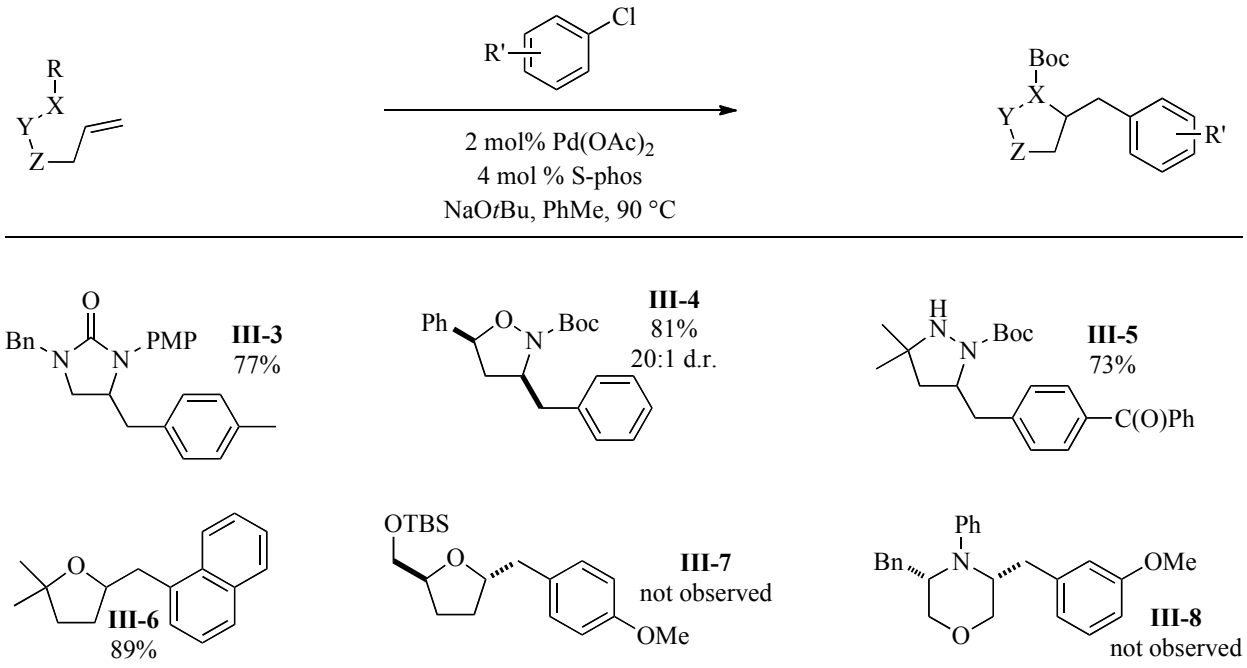
Figure 3. Stereochemical Rationale for 2,5-disubstituted Pyrrolidines.



Following our success with *N*-Boc-aminopropylalkenes, we proceeded to examine the utility of the $Pd(OAc)_2$/S-phos catalyst in carboamination and carboetherification reactions of aryl chlorides to generate other heterocycles. As shown in Table 5, imidazolidin-2-one **III-3**, isoxazolidine **III-4**, and pyrazolidine **III-5** could be prepared from the corresponding alkenylamines. The heterocyclic products were obtained in good chemical yield, and **III-4** was formed in good diastereoselectivity (20:1 d.r.). Tetrahydrofuran **III-6** was prepared in 89% yield,

although a 13:1 mixture of regioisomers was generated. Unfortunately, attempts to effect a similar transformation for the preparation of **III-7** were unsuccessful; instead, oxidation of the alcohol starting material was observed, which suggests that alkene oxypalladation from an intermediate analogous to **A** is relatively slow with S-phos as a ligand. As a result, ß-hydride elimination from this intermediate is the predominant reaction pathway with the secondary alcohol substrate. Morpholine product **III-8** and its *N*-Boc analogue could not be prepared due to competing *N*-arylation of the substrate.[34]

Table 5. Synthesis of Other Heterocycles Using Aryl Chlorides as Electrophiles.[a]



[a] Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 1.2 equiv NaO*t*Bu, 2 mol % $Pd(OAc)_2$, 4 mol % S-phos, toluene (0.25 M), 90 °C. [b] Isolated yield (average of two experiments).

3.4 Conclusions

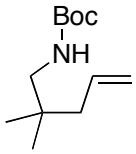
In conclusion, we have developed conditions that allow use of inexpensive and readily available aryl chloride electrophiles in many Pd-catalyzed carboamination and carboetherification reactions. These studies significantly expand the scope and utility of this

method for heterocycle synthesis and also illustrate several remaining challenges for catalyst development in the field.

3.5 Experimental Section

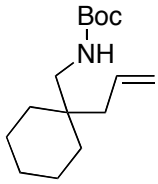
General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Palladium (II) acetate and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All reagents and aryl chlorides except 1-benzyl-5-chloro-1*H*-indole[35] were obtained from commercial sources and were used as obtained. *N*-(pent-4-en-1-yl)aniline, [36] *N*-(hex-5-en-2-yl)-4-methoxyaniline,[36] 4-methoxy-*N*-(3-phenylpent-4-en-1-yl)aniline,[36] *N*-[2-(cyclopent-2-en-1-yl)ethyl]aniline,[37] *tert*-butyl pent-4-en-1-ylcarbamate,[38] (±)-*tert*-butyl (3-methylpent-4-en-1-yl)carbamate,[38] 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea,[39] (±)-*tert*-butyl (1-phenylbut-3-en-1-yl)oxycarbamate, [40] *tert*-butyl 2-(2-methylpent-4-en-2-yl)hydrazinecarboxylate[41] and 2-methylhex-5-en-2-ol[42] were prepared according to published procedures. The relative stereochemistry of products with two or more stereocenters was assigned by comparison of ^{1}H and 13C-NMR spectra to related compounds prepared by Pd-catalyzed alkene carboamination that have been previously reported in the literature.[36–42] Toluene and diethyl ether were purified using a GlassContour solvent purification system. The yields reported in this section describe the result of a single experiment, whereas the yields reported in Tables 3–5 are average yields of two or more experiments. Thus, the yields reported in this section may differ from those shown in Table 3–5.

Synthesis of Substrates

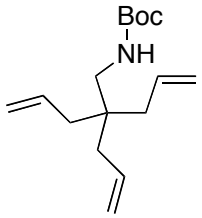


***tert*-Butyl (2,2-dimethylpent-4-en-1-yl)carbamate**.[43] To a stirred solution of 2,2-dimethylpent-4-en-1-ylamine (920 mg, 8.4 mmol) in diethyl ether (17 mL) was added di-*tert*-butyl dicarbonate

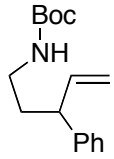
(2.02 g, 9.3 mmol). The resulting mixture was stirred until the starting material had been consumed as judged by TLC analysis. A solution of 1 M NaOH (ca. 40 mL) was added to the system, and the mixture was stirred vigorously overnight. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*, and the crude product was purified by flash chromatography on silica gel to afford 1.60 g (89%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.74 (m, 1 H), 5.10–4.98 (m, 2 H), 4.56 (s, br, 1 H), 2.95 (d, J = 6.4 Hz, 2 H), 1.96 (d, J = 7.4 Hz, 2 H), 1.44 (s, 9 H), 0.67 (s, 6 H).



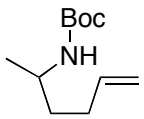
***tert*-Butyl [(1-allylcyclohexyl)methyl]carbamate**. The conversion of (1-allylcyclohexyl)methanamine[44] (2.17 g, 14.2 mmol) to the title compound was accomplished using a procedure analogous to that described above for the synthesis of *tert*-butyl (2,2-dimethylpent-4-en-1-yl)carbamate. This procedure afforded 3.52 g (83%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88–5.73 (m, 1 H), 5.08–5.00 (m, 2 H), 4.52 (s, br, 1 H), 3.01 (d, J = 6.3 Hz, 2 H), 2.01 (d, J = 8.4 Hz, 2 H), 1.49–1.33 (m, 15 H), 1.30–1.20 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 134.7, 117.3, 78.9, 46.9, 40.5, 36.9, 33.2, 28.4, 26.1, 21.4; IR (film) 3359, 1699 cm^{-1}; MS (ESI): 276.1948 (276.1939 calcd for $C_{15}H_{27}NO_2$, M + Na^+).



***tert*-Butyl (2,2-diallylpent-4-en-1-yl)carbamate**. The conversion of 2,2-diallylpent-4-en-1-ylamine[45] (1.2 g, 7.3 mmol) was accomplished using a procedure analogous to that described above for the synthesis of *tert*-butyl (2,2-dimethylpent-4-en-1-yl)carbamate. This procedure afforded 1.5 g (77%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.71 (m, 3 H), 5.10–4.99 (m, 6 H), 4.63–4.50 (s, br, 1 H), 3.00 (d, J = 6.1 Hz, 2 H), 1.97 (d, J = 7.6 Hz, 6 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 134.0, 117.9, 78.9, 45.9, 40.1, 39.5, 28.3; IR (film) 3356, 1698, 1638 cm^{-1}; MS (ESI): 288.1934 (288.1939 calcd for $C_{16}H_{27}NO_2$, M + Na^+).



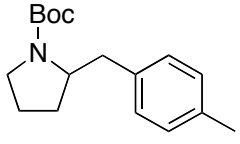
(±)-*tert*-Butyl (3-phenylpent-4-en-1-yl)carbamate. The conversion of (±)-3-phenylpent-4-en-1-ylamine[46] (670 mg, 4.2 mmol) was accomplished using a procedure analogous to that described above for the synthesis of *tert*-butyl (2,2-dimethylpent-4-en-1-yl)carbamate. This procedure afforded 629 mg (58%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2 H), 7.23–7.17 (m, 3 H), 6.01–5.90 (m, 1 H), 5.11–5.02 (m, 2 H), 4.56 (s, br, 1 H), 3.31 (dd, J = 7.5, 14.9 Hz, 1 H), 3.17–2.99 (m, 2 H), 1.99–1.82 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 143.4, 141.4, 128.5, 127.4, 126.4, 114.5, 79.0, 47.4, 38.9, 35.3, 28.3; IR (film) 3351, 1699 cm^{-1}; MS (ESI): 284.1625 (284.1626 calcd for $C_{16}H_{23}NO_2$, M + Na^+).



(±)-*tert*-Butyl hex-5-en-2-ylcarbamate. The conversion of (±)-hex-5-en-2-ylamine[47] (519 mg, 5.2 mmol) was accomplished using a procedure analogous to that described above for the

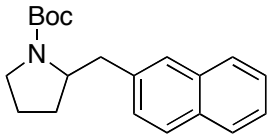
synthesis of *tert*-butyl (2,2-dimethylpent-4-en-1-yl)carbamate. This procedure afforded 776 mg (75%) of the title compound as a clear and colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83–5.67 (m, 1 H), 5.02–4.85 (m, 2 H), 4.40 (s, br, 1 H), 3.70–3.48 (m, 1 H), 2.03 (dd, *J* = 7.4, 14.7 Hz, 2 H), 1.55–1.29 (m, 11 H), 1.05 (dd, *J* = 2.4, 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.0, 114.6, 78.7, 46.0, 36.4, 30.2, 28.3, 21.1; IR (film) 3338, 1683 cm^{-1}; MS (ESI): 222.1469 (222.1470 calcd for $C_{11}H_{21}NO_2$, M + Na^+).

General Procedure 1: Pd-catalyzed carboamination of γ-*N*-(Boc)aminoalkenes and related nucleophiles. A Schlenk tube was evacuated, flame-dried and backfilled with nitrogen. The tube was charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-Phos, 8.2 mg, 0.02 mmol) and NaO*t*Bu (57.7 mg, 0.60 mmol). The tube was evacuated and backfilled with nitrogen three times. A solution of the amine substrate (0.50 mmol) and the aryl chloride (0.60 mmol) in toluene (4 mL/mmol amine substrate) was added to the Schlenk tube *via* syringe (aryl chlorides that were solids are room temperature were added neat in one portion following the addition of NaO*t*Bu). The mixture was heated in a 90 °C oil bath with stirring until the starting material had been consumed as judged by GC analysis (6–12 h). The reaction mixture was cooled to room temperature, and saturated aqueous NH_4Cl (2 mL) and EtOAc (2 mL) were added to the system. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were concentrated *in vacuo*, and the crude product was purified by flash chromatography on silica gel.

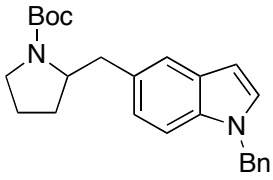


(±)-*tert*-Butyl 2-(4-methylbenzyl)pyrrolidine-1-carboxylate (**III-2a**). General procedure 1 was employed for the coupling of 4-chlorotoluene (71 μL, 0.60 mmol) with *tert*-butyl pent-4-en-1-

ylcarbamate (93 mg, 0.50 mmol) to afford 95 mg (69%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.03–6.89 (m, 4 H), 4.03–3.91 (m, 1 H), 3.33–3.23 (m, 1 H), 3.20–3.01 (m, 2 H), 2.51 (dd, *J* = 8.9, 13.0 Hz, 1 H), 2.13 (s, 3 H), 1.55–1.28 (m, 13 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 154.6, 137.1, 135.9, 130.0, 129.6, 78.9, 59.5, 59.4, 47.2, 30.3, 29.1, 23.7, 21.2; IR (film) 1693, 1394, 1172 cm^{-1}; MS (ESI): 298.1779 (298.1783 calcd for $C_{17}H_{25}NO_2$, M + Na^+).

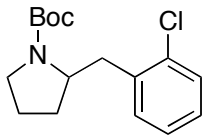


(±)-*tert*-Butyl 2-(naphthalen-2-ylmethyl)pyrrolidine-1-carboxylate (**III-2c**). General procedure 1 was employed for the coupling of 2-chloronapthalene (98 mg, 0.60 mmol) with *tert*-butyl pent-4-en-1-ylcarbamate (93 mg, 0.50 mmol) to afford 126 mg (81%) of the title compound as a pale yellow oil. Spectroscopic properties were consistent with those reported in the literature.[38]

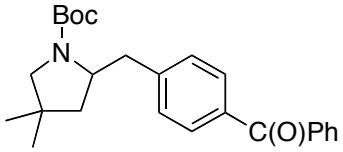


(±)-*tert*-Butyl 2-[(1-benzyl-1*H*-indol-5-yl)methyl]pyrrolidine-1-carboxylate (**III-2d**). General procedure 1 was employed for the coupling of 1-benzyl-5-chloro-1*H*-indole (145 mg, 0.60 mmol) with *tert*-butyl pent-4-en-1-ylcarbamate (93 mg, 0.50 mmol) to afford 125 mg (64%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.46 (s, 1 H), 7.04–7.01 (m, 2 H), 6.97–6.95 (m, 3 H), 6.84 (d, *J* = 7.0 Hz, 2 H), 6.73 (d, *J* = 2.9 Hz, 1 H), 6.42 (d, *J* = 2.9 Hz, 1 H), 4.79 (s, 2 H), 4.13–4.04 (m, 1 H), 3.36–3.24 (m, 2 H), 3.24–3.16 (m, 1 H), 2.65 (dd, *J* = 9.2, 13 Hz, 1 H), 1.67–1.55 (m, 1 H), 1.55–1.40 (m, 11 H), 1.40–1.28 (m, 1 H); ^{13}C

NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 154.3, 138.2, 136.1, 130.9, 130.0, 128.2, 127.6, 127.1, 124.0, 122.0, 121.8, 109.7, 102.1, 78.4, 59.6, 40.2, 46.9, 40.8, 30.0, 28.7, 23.4; IR (film) 1689, 1395, 1171 cm^{-1}; MS (ESI): 413.2191 (413.2205 calcd for $C_{25}H_{30}N_2O_2$, M + Na^+).

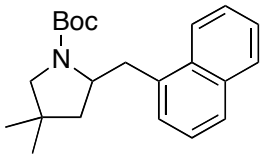


(±)-*tert*-Butyl 2-(2-chlorobenzyl)pyrrolidine-1-carboxylate (**III-2e**). General procedure 1 was employed for the coupling of 1,2-dichlorobenzene (80 μL mg, 0.60 mmol) with *tert*-butyl pent-4-en-1-ylcarbamate (93 mg, 0.50 mmol) to afford 107 mg (73%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.14 (d, *J* = 8.0 Hz, 1 H), 7.09 (d, *J* = 7.4 Hz, 1 H), 6.88 (t, *J* = 7.4 Hz, 1 H), 6.79 (t, *J* = 7.6, 1 H), 4.16–4.08 (m, 1 H), 3.34–3.24 (m, 1 H), 3.23–3.12 (m, 2 H), 2.77 (dd, *J* = 8.6, 13.1 Hz, 1 H), 1.55–1.36 (m, 13 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 154.2, 137.9, 135.0, 132.0, 129.8, 126.8, 78.6, 58.2, 58.1, 46.6, 37.4, 29.9, 28.7, 23.4; IR (film) 1692, 1393, 1172 cm^{-1}; MS (ESI): 318.1224 (318.1237 calcd for $C_{16}H_{22}ClNO_2$ M + Na^+).

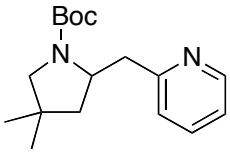


(±)-*tert*-Butyl 2-(4-benzoylbenzyl)-4,4-dimethylpyrrolidine-1-carboxylate (**III-2f**). General procedure 1 was employed for the coupling of 4-chlorobenzophenone (130 mg, 0.60 mmol) with *tert*-butyl (2,2-dimethylpent-4-en-1-yl)carbamate (107 mg, 0.50 mmol) to afford 137 mg (70%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.85–7.75 (m, 4 H), 7.35–7.17 (m, 5 H), 4.26–4.13 (m, 1 H), 3.58–3.43 (m, 2 H), 2.90 (d, *J* = 10.7 Hz, 1 H), 2.78 (dd, *J* = 4.2, 8.7 Hz, 1 H), 1.66–1.54 (m, 10 H), 1.46–1.36 (m, 1 H), 0.94 (s, 3 H), 0.90 (s, 3

H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 195.2, 155.2, 144.5, 139.4, 137.0, 132.1, 131.9, 79.3, 60.5, 59.2, 46.1, 41.8, 37.5, 29.1, 26.8, 26.6, 26.4 (two signals are missing due to incidental equivalence); IR (film) 1694, 1661, 1397, 1164 cm^{-1}; MS (ESI): 416.2192 (416.2202 calcd for $C_{25}H_{31}NO_3$ M + Na^+).

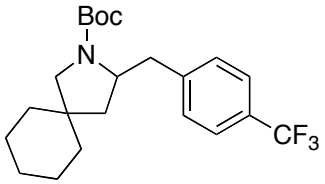


(±)-*tert*-Butyl 4,4-dimethyl-2-(naphthalen-1-ylmethyl)pyrrolidine-1-carboxylate (III-2g). General procedure 1 was employed for the coupling of 1-chloronaphthalene (82 μL, 0.60 mmol) with *tert*-butyl (2,2-dimethylpent-4-en-1-yl)carbamate (107 mg, 0.50 mmol) to afford 141 mg (83%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 8.55 (s, br, 1 H), 7.66–7.52 (m, 2 H), 7.41–7.31 (m, 1 H), 7.28–7.14 (m, 3 H), 4.36–4.26 (m, 1 H), 4.21–4.09 (m, 1 H), 2.91 (d, J = 10.7 Hz, 1 H), 2.72 (dd, J = 9.9, 12.8 Hz, 1 H), 1.51 (s, 9 H), 1.40–1.22 (m, 2 H), 0.82 (s, 3 H), 0.68 (s, 3 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 155.2, 136.0, 134.8, 133.4, 128.9, 127.3, 126.1, 125.1, 124.8, 79.0, 60.2, 58.2, 46.2, 39.3, 37.2, 28.8, 26.4 (3 signals are missing due to incidental equivalence); IR (film) 1684, 1396, 1164 cm^{-1}; MS (ESI): 362.2082 (362.2096 calcd for $C_{22}H_{29}NO_2$, M + Na^+).

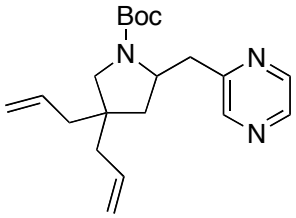


(±)-*tert*-Butyl 4,4-dimethyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxylate (III-2h). General procedure 1 was employed for the coupling of 2-chloropyridine (57 μL, 0.60 mmol) with *tert*-butyl (2,2-dimethylpent-4-en-1-yl)carbamate (107 mg, 0.50 mmol) to afford 107 mg (73%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 8.38

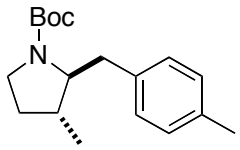
(d, J = 4.5 Hz, 1 H), 7.12 (t, J = 7.6 Hz, 1 H), 6.98–6.94 (m, 1 H), 6.69–6.65 (m, 1 H), 4.28 (dq, J = 3.5, 8.2 Hz, 1 H), 3.53 (dd, J = 3.0, 13.0 Hz, 1 H), 3.36 (d, J = 10.4 Hz, 1 H), 2.91 (dd, J = 8.9, 12.8 Hz, 1 H), 2.76 (d, J = 10.8 Hz, 1 H), 1.71–1.51 (m, 2 H), 1.46 (s, 9 H), 0.83 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 160.3, 154.8, 149.4, 135.5, 123.7, 120.8, 78.6, 60.1, 58.0, 45.8, 43.4, 37.1, 28.7, 26.7, 26.1; IR (film) 1694, 1398, 1165 cm^{-1}; MS (ESI): 313.1890 (313.1892 calcd for $C_{19}H_{26}N_2O_2$, M + Na^+).



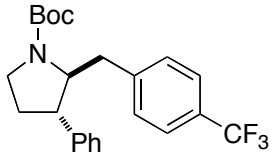
(±)-*tert*-Butyl 3-[4-(trifluoromethyl)benzyl]-2-azaspiro[4.5]decane-2-carboxylate (III-2i). General procedure 1 was employed for the coupling of 4-chlorobenzotrifluoride (80 μL, 0.60 mmol) with *tert*-butyl [(1-allylcyclohexyl)methyl]carbamate (127 mg, 0.50 mmol) to afford 132 mg (67%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.36 (d, J = 7.8 Hz, 2 H), 7.07 (d, J = 7.6 Hz, 2 H), 3.97 (dq, J = 3.7, 8.0 Hz, 1 H), 3.55 (d, J = 11.5 Hz, 1 H), 3.22 (dd, J = 2.7, 12.9 Hz, 1 H), 2.69 (d, J = 11.0 Hz, 1 H), 2.59 (dd, J = 8.7, 13.0 Hz, 1 H), 1.58–1.50 (m, 1 H), 1.46 (s, 9 H), 1.23–1.10 (m, 11 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 158.8, 144.1, 130.2, 125.4, 79.3, 58.3, 42.4, 41.7, 37.0, 35.2, 29.0, 26.8, 24.4, 23.5, 21.4 (2 signals are missing due to incidental equivalence, and the CF_3 quartet is obscured by the nmr solvent); IR (film) 1694, 1398, 1325 cm^{-1}; MS (ESI): 420.2118 (420.2126 calcd for $C_{22}H_{30}F_3NO_2$, M + Na^+).



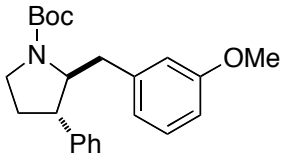
(±)-*tert*-Butyl 4,4-diallyl-2-(pyrazin-2-ylmethyl)pyrrolidine-1-carboxylate (III-2j). General procedure 1 was employed for the coupling of chloropyrazine (54 μL, 0.60 mmol) with *tert*-butyl (2,2-diallylpent-4-en-1-yl)carbamate (133 mg, 0.50 mmol) to afford 93 mg (54%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 8.35 (s, 1 H), 8.11–8.03 (m, 2 H), 5.66–5.47 (m, 2 H), 4.96–4.83 (m, 4 H), 4.23–4.15 (m, 1 H), 3.51 (d, *J* = 11.0 Hz, 1 H), 3.29 (dd, *J* = 3.5, 13.3 Hz, 1 H), 2.87 (dd, *J* = 8.2, 12.9 Hz, 1 H), 2.71 (d, *J* = 11.4 Hz, 1 H), 1.88 (t, *J* = 6.3 Hz, 4 H), 1.71–1.63 (m, 1 H), 1.60–1.52 (m, 1 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 155.4, 154.5, 145.9, 143.3, 142.5, 134.6, 118.0, 117.8, 117.5, 117.2, 79.0, 57.0, 55.9, 44.0, 41.8, 41.4, 40.6, 28.6; IR (film) 1694, 1398, 1160 cm^{-1}; MS (ESI): 366.2151 (366.2157 calcd for $C_{20}H_{29}N_3O_2$).



(±)-(2*S,3*R**)-*tert*-Butyl 3-methyl-2-(4-methylbenzyl)pyrrolidine-1-carboxylate (III-2k)**. General procedure 1 was employed for the coupling of 4-chlorotoluene (36 μL, 0.30 mmol) with (±)-*tert*-butyl (3-methylpent-4-en-1-yl)carbamate (50 mg, 0.25 mmol). Analysis of the crude reaction mixture indicated the product was formed with 4:1 d.r. as judged by ^{1}H NMR analysis. Upon purification, 41 mg (57%) of the title compound was obtained as a yellow oil with 4:1 d.r. Data are for the major diastereomer. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.05–7.00 (m, 2 H), 6.95–6.91 (m, 2 H), 3.65–3.58 (m, 1 H), 3.49–3.40 (m, 1 H), 3.11–2.98 (m, 2 H), 2.72–2.61 (m, 1 H), 2.12 (s, 3 H), 1.92–1.83 (m, 1 H), 1.52–1.46 (m, 10 H), 1.12–1.02 (m, 1 H), 0.67 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 154.4, 136.6, 135.5, 129.7, 129.0, 78.5, 66.4, 45.6, 37.2, 31.4, 28.7, 20.8, 19.3, 19.2; IR (film) 1694, 1394, 1177 cm^{-1}; MS (ESI): 312.1934 (312.1939 calcd for $C_{18}H_{27}NO_2$, M + Na^+).

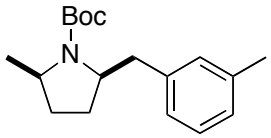


(±)-(2*S,3*S**)-*tert*-Butyl 3-phenyl-2-[4-(trifluoromethyl)benzyl]pyrrolidine-1-carboxylate** (**III-2l**). General procedure 1 was employed for the coupling of 4-chlorobenzotrifluoride (40 μL, 0.30 mmol) with (±)-*tert*-butyl (3-phenylpent-4-en-1-yl)carbamate (65 mg, 0.25 mmol). Analysis of the crude reaction mixture indicated the product was formed with >20:1 d.r. as judged by ^{1}H NMR analysis. Upon purification, 68 mg (67%) of the title compound was obtained as a pale yellow oil with >20:1 d.r. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.30 (d, J = 8.0 Hz, 2 H), 7.05–7.00 (m, 3 H), 6.98–6.91 (m, 2 H), 6.84 (d, J = 7.4 Hz, 2 H), 4.19–4.12 (m, 1 H), 3.63–3.54 (m, 1 H), 3.08–2.92 (m, 2 H), 2.89–2.79 (m, 2 H), 1.78–1.68 (m, 1 H), 1.61–1.51 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 154.2, 143.5, 143.2, 130.3, 127.1, 126.7, 126.4, 79.2, 65.1, 49.1, 42.3, 39.6, 32.5, 28.6 (two signals are missing due to incidental equivalence, and the CF_3 quartet is obscured by the nmr solvent); IR (film) 1692, 1394, 1325 cm^{-1}; MS (ESI): 428.1804 (428.1813 calcd for $C_{23}H_{26}F_3NO_2$, M + Na^+).

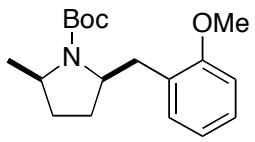


(±)-(2*S,3*S**)-*tert*-Butyl 2-(3-methoxybenzyl)-3-phenylpyrrolidine-1-carboxylate** (**III-2m**). General procedure 1 was employed for the coupling of 3-chloroanisole (37 μL, 0.30 mmol) with (±)-*tert*-butyl (3-phenylpent-4-en-1-yl)carbamate (65 mg, 0.25 mmol). Analysis of the crude reaction mixture indicated the product was formed with >20:1 d.r. as judged by ^{1}H NMR analysis. Upon purification, 57 mg (62%) of the title compound was obtained as a pale yellow oil with >20:1 d.r. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.04–6.92 (m, 6 H), 6.81–6.73 (m, 2 H),

6.63 (dd, J = 2.2, 8.2 Hz, 1 H), 4.25–4.20 (m, 1 H), 3.65–3.56 (m, 1 H), 3.44 (s, 3 H), 3.17–3.08 (m, 1 H), 3.06–2.86 (m, 3 H), 1.85–1.74 (m, 1 H), 1.63–1.53 (m, 1 H), 1.47 (s, 9 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 160.6, 154.2, 144.3, 140.6, 129.3, 129.0, 127.2, 126.5, 122.6, 116.2, 112.6, 78.9, 65.5, 54.9, 48.5, 46.4, 39.9, 32.2, 28.7; IR (film) 1690, 1394 cm^{-1}; MS (ESI): 390.2044 (390.2045 calcd for $C_{23}H_{29}NO_3$, M + Na^+).

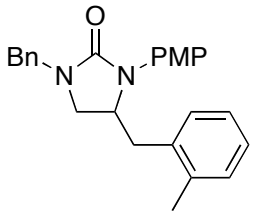


(±)-(2*R,5*R**)-*tert*-Butyl 2-methyl-5-(3-methylbenzyl)pyrrolidine-1-carboxylate (III-2n)**. General procedure 1 was employed for the coupling of 3-chlorotoluene (71 μL, 0.60 mmol) with (±)-*tert*-butyl hex-5-en-2-ylcarbamate (100 mg, 0.50 mmol). Analysis of the crude reaction mixture indicated the product was formed with >20:1 d.r. as judged by ^{1}H NMR analysis. Upon purification, 105 mg (72%) of the title compound was obtained as a pale yellow oil with >20:1 d.r. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.07–7.00 (m, 1 H), 6.99–6.95 (m, 1 H), 6.93 (d, J = 7.6 Hz, 1 H), 6.85 (d, J = 7.4 Hz, 1 H), 4.03–3.95 (m, 1 H), 3.80 (qt, J = 6.2, 6.4 Hz, 1 H), 3.14 (dd, J = 3.8, 13.1 Hz, 1 H), 2.54 (dd, J = 9.0, 13.2 Hz, 1 H), 2.16 (s, 3 H), 1.64–1.43 (m, 12 H), 1.31–1.20 (m, 1 H), 1.10 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 154.6, 139.8, 137.7, 130.7, 129.0, 127.7 127.1, 78.5, 60.7, 54.7, 42.2, 32.0, 28.8, 28.7, 21.9, 21.2; IR (film) 1692, 1390, 1177 cm^{-1}; MS (ESI): 312.1945 (312.1939 calcd for $C_{18}H_{27}NO_2$, M + Na^+).

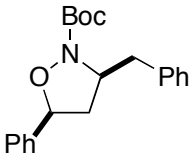


(±)-(2*R,5*R**)-*tert*-Butyl 2-(2-methoxybenzyl)-5-methylpyrrolidine-1-carboxylate (III-2o)**. General procedure 1 was employed for the coupling of 2-chloroanisole (76 μL, 0.60 mmol) with (±)-*tert*-butyl hex-5-en-2-ylcarbamate (100 mg, 0.50 mmol). Analysis of the crude reaction

mixture indicated the product was formed with >20:1 d.r. as judged by ^{1}H NMR analysis. Upon purification, 108 mg (71%) of the title compound was obtained as a pale yellow oil with >20:1 d.r. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100 °C) δ 7.12 (d, *J* = 7.3 Hz, 1 H), 7.03–6.98 (m, 1 H), 6.77 (t, *J* = 7.3 Hz, 1 H), 6.60 (d, *J* = 8.1 Hz, 1 H), 4.19–4.12 (m, 1 H), 3.87–3.79 (m, 1 H), 3.46 (s, 3 H), 3.18 (dd, *J* = 4.8, 13.1 Hz, 1 H), 2.78 (dd, *J* = 8.8, 13.0 Hz, 1 H), 1.71–1.56 (m, 2 H), 1.53–1.31 (m, 11 H), 1.19 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$, 100 °C) δ 158.6, 154.6, 131.8, 131.7, 127.4, 120.8, 111.1, 78.3, 59.8, 55.0, 54.7, 35.9, 32.2, 29.0, 28.7, 22.1; IR (film) 1693, 1390, 1364 cm^{-1}; MS (ESI): 328.1886 (328.1889 calcd for $C_{18}H_{27}NO_3$, M + Na^+).

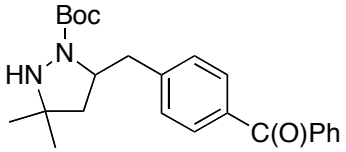


(±)-1-Benzyl-3-(4-methoxyphenyl)-4-(2-methylbenzyl)imidazolidin-2-one (III-3).[39] General procedure 1 was employed for the coupling of 2-chlorotoluene (70 μL, 0.60 mmol) with 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea (148 mg, 0.50 mmol) to afford 145 mg (75%) of the title compound as a yellow oil. Spectroscopic properties were consistent with those reported in the literature.[39]

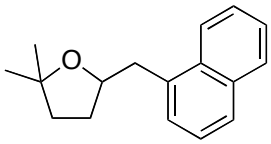


(±)-(3*S,5*S**)-*tert*-Butyl 3-benzyl-5-phenylisoxazolidine-2-carboxylate (III-4)**.[40] General procedure 1 was employed for the coupling of chlorobenzene (61 μL, 0.60 mmol) with (±)-*tert*-butyl (1-phenylbut-3-en-1-yl)oxycarbamate (132 mg, 0.50 mmol). Analysis of the crude reaction mixture indicated the product was formed with 20:1 d.r. as judged by ^{1}H NMR analysis. Upon

purification 133 mg (78%) of the title compound was obtained as a pale yellow oil with 20:1 d.r. Spectroscopic properties were consistent with those reported in the literature.[40]



(±)-*tert*-Butyl 5-(4-benzoylbenzyl)-3,3-dimethylpyrazolidine-1-carboxylate (III-5). General procedure 1 was employed for the coupling of 4-chlorobenzophenone (130 mg, 0.60 mmol) with *tert*-butyl 2-(2-methylpent-4-en-2-yl)hydrazinecarboxylate (107 mg, 0.50 mmol) to afford 144 mg (73%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.72 (m, 4 H), 7.61–7.55 (m, 1 H), 7.51–7.44 (m, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 4.35 (s, br, 1 H), 3.60 (s, br, 1 H), 3.18 (dd, *J* = 4.1, 12.9 Hz, 1 H), 2.80 (dd, *J* = 8.4, 12.9 Hz, 1 H), 1.99 (dd, *J* = 7.6, 12.3 Hz, 1 H), 1.57–1.41 (m, 10 H), 1.17 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 143.4, 137.7, 135.8, 132.2, 130.3, 129.9, 129.4, 128.3, 80.2, 60.9, 60.0, 47.1, 41.0, 28.5, 25.1, 24.7 (one signals is missing due to incidental equivalence); IR (film) 3251, 1713, 1659 cm^{-1}; MS (ESI): 417.2144 (417.2154 calcd for $C_{24}H_{30}N_2O_3$, M + Na^+).



(±)-2,2-Dimethyl-5-(naphthalen-1-ylmethyl)tetrahydrofuran (III-6).[42] General procedure 1 was employed for the coupling of 1-chloronapthalene (82 μL, 0.60 mmol) with 2-methylhex-5-en-2-ol (57 mg, 0.50 mmol) to afford 107 mg (89%) of the title compound as a 13:1 mixture of regioisomers. Spectroscopic properties were consistent with those reported in the literature.[42]

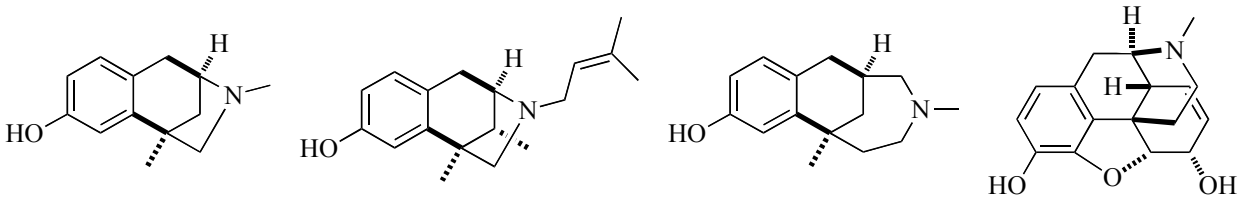
Chapter 4

Enantioconvergent Total Synthesis of (+)-Aphanorphine

4.1 Introduction

The natural product (-)-aphanorphine (**IV-1**) was isolated in 1988 from the blue-green alga *Aphanizomenon flos-aquae* by Shimizu and Clardy.[48] Although the biological activity of **IV-1** has not been fully established, **IV-1** shares common structural features with other benzomorphane analogues (Figure 4), several of which possess analgesic activity. Because of this unique structure, aphanorphine has been the subject of several total synthesis projects over the past several years.[49,50]

Figure 4. Select Benzomorphane Alkaloids.



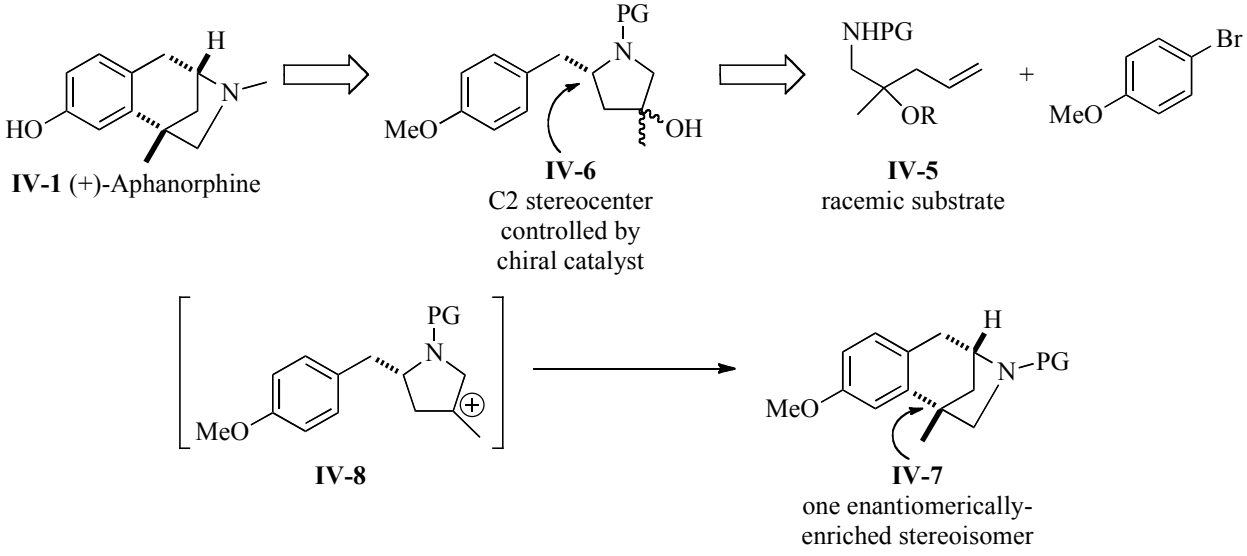
IV-1 (-)-Aphanorphine **IV-2** (-)-Pentazocine **IV-3** (-)-Eptazocine **IV-4** (-)-Morphine

While both the natural and unnatural enantiomers of **IV-1** have been prepared, many approaches have relied on chiral pool strategies. As such, the choice of target enantiomer must be determined early on in the synthesis. We felt we could develop an alternative route to **IV-1** whereby a simple *racemic* starting material could be converted to an enantiomerically-enriched precursor *via* an enantioselective Pd-catalyzed carboamination reaction developed in our laboratory.[51] This synthetic route would represent a unique approach to natural products, as few natural product syntheses have been reported that employ a C–C bond-forming enantioconvergent step.[52] Additionally, most enantioconvergent strategies rely on kinetic resolution methods to facilitate separation of the two enantiomers, whereas our strategy would convert *both enantiomers* of the starting material into the enantioenriched natural product.

4.2 Retrosynthetic Analysis

All of the work described in this chapter was carried out in close collaboration with Peter Mai, a graduate student in our group. Our approach to **IV-1** would rely on two key transformations: an intramolecular Friedel-Crafts alkylation similar to that used in a few previous aphanorphine syntheses, and an enantioselective carboamination reaction of racemic starting material. As shown in Scheme 6, a catalyst-controlled asymmetric carboamination reaction of racemic substrate **IV-5** could be used to set the C2 stereocenter of pyrrolidine **IV-6**, thereby providing a mixture of enantiomerically-enriched diastereomers. This mixture of diastereomers could be converted to a single enantiomerically-enriched stereoisomer **IV-7** *via* a Friedel-Crafts alkylation, which would proceed through a carbocation intermediate **IV-8**.

Scheme 6. Enantioconvergent Approach to (+)-Aphanorphine.



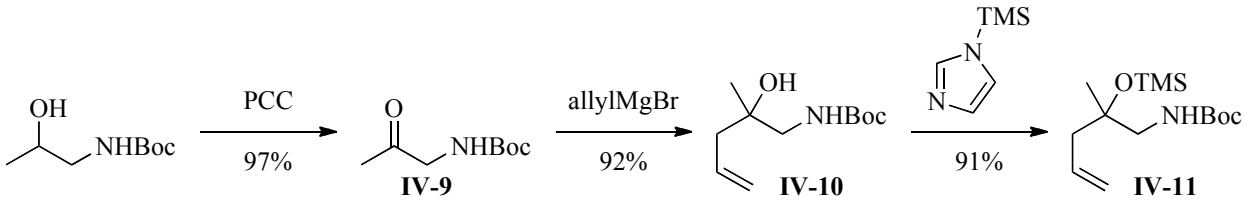
This approach overcomes several limitations of previous syntheses of **IV-1**. For example, either enantiomer of **IV-1** could be accessed, because the absolute stereochemistry of the carboamination reaction would be dictated by the selection of an appropriate ligand.[53] Additionally, racemic substrate **IV-5** could be easily prepared from readily available materials,

and selection of a modified aryl halide in the carboamination step would afford a pyrrolidine that would be potentially useful for generating analogues of **IV-1**.

4.3 Total Synthesis of (+)-Aphanorphine

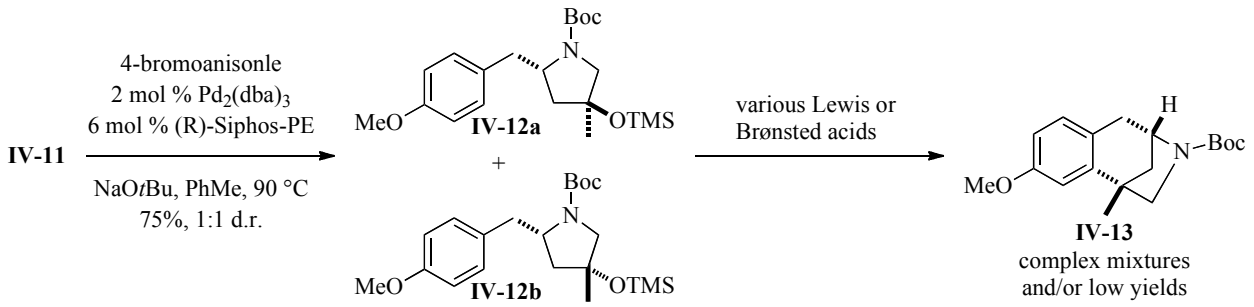
The precursor for the key asymmetric carboamination reaction was prepared in four steps as shown in Scheme 7. Oxidation of *N*-Boc-1-amino-2-propanol to ketone **IV-9** was accomplished in 97% yield using PCC. Grignard addition of allylmagnesium bromide afforded tertiary alcohol **IV-10** in 92% yield, and protection in neat TMS-imidazole gave the carboamination substrate **IV-11** in 91% yield. Of note, all of these steps can be performed on multi-gram scale without chromatography.

Scheme 7. Synthesis of Carboamination Substrate.



Previous studies on the Pd-catalyzed carboamination reaction have illustrated that diastereoselectives are generally low with substrates bearing a single homoallylic substituent, and the similarity in size of the homoallylic groups in **IV-11** (CH_3 vs. OTMS) suggested that there would be little substrate bias toward either diastereomer. We were pleased to see that exposure of **IV-11** to previously reported conditions for enantioselective alkene carboamination reactions using (*R*)-Siphos-PE as a ligand proceeded in 75% yield to afford a 1:1 mixture of diastereomers **IV-12a** and **IV-12b** (Scheme 8).[54]

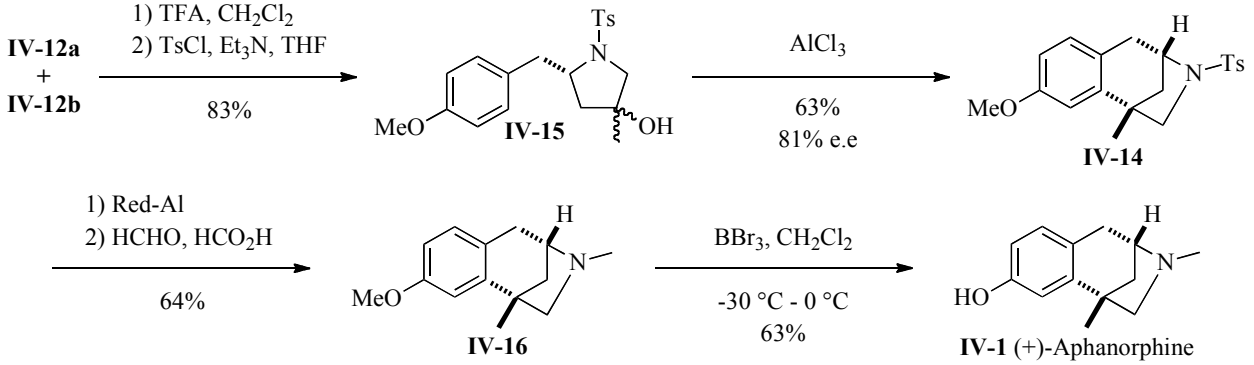
Scheme 8. Pd-Catalyzed Carboamination of IV-11 and Attempted Preparation of IV-13.



Unfortunately, extensive attempts to effect the transformation of these diastereomers to tricycle **IV-13** were unsuccessful. Additionally, cleavage of the *O*-TMS group using TBAF and subjecting the resulting alcohol to various conditions predominantly resulted in substrate decomposition. Competing cleavage of the Boc group was frequently observed, along with the formation of numerous side products and minimal product formation. Although we were unable to access intermediate **IV-13**, **IV-14** has previously served as an intermediate in total syntheses of aphanorphine. Treatment of **IV-12a** and **IV-12b** with excess TFA in CH_2Cl_2 cleanly deprotected both the *N*-Boc and *O*-TMS groups, and tosylation of the resulting pyrrolidine derivative provided **IV-15** as a 1:1 mixture of diastereomers (Scheme 9).

Intramolecular Friedel-Crafts alkylation of substrate **IV-15** using $AlCl_3$ provided tricycle **IV-14** in 63% yield. **IV-14** was found to be 81% e.e. by HPLC analysis. Subsequent removal of the *N*-tosyl group with Red-Al followed by *N*-methylation using Eschweiler-Clarke conditions provided **IV-16**. Although BBr_3-mediated demethylation of **IV-16** has been previously reported, this step proved to be quite challenging.[55] Careful temperature control of the reaction mixture was required to obtain satisfactory results, and gradual warming from -30 °C to 0 °C in 10 °C increments over the course of 2 hours enabled the transformation of **IV-16** to (+)-aphanorphine in 63% yield (Scheme 9).

Scheme 9. Completion of the Total Synthesis of (+)-Aphanorphine.

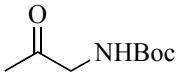


4.4 Conclusions

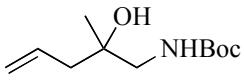
In conclusion, we have demonstrated an enantioconvergent total synthesis of (+)-aphanorphine with the key step being an asymmetric Pd-catalyzed carboamination reaction. This synthesis relies on the conversion of a racemic starting material to an enantioenriched mixture of diastereomers, followed by the enantioconvergent formation of an all-carbon quaternary center through a Friedel-Crafts alkylation. Future studies will focus on the application of this approach to the synthesis of other benzomorphane analogues as well as the preparation of structural analogues of **IV-1**.

4.5 Experimental Section

General: All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. Tris(dibenzylideneacetone)dipalladium and (*R)*-Siphos-PE were purchased from Strem Chemical Co. and used without further purification. All reagents were obtained from commercial sources and were used as obtained. Toluene, THF, methylene chloride and diethyl ether were purified using a GlassContour solvent purification system. The yields reported in this section describe the result of a single experiment, whereas the yields reported in Schemes 7–9 are average yields of two or more experiments. Thus, the yields reported in this section may differ from those shown in Schemes 7–9.

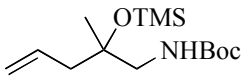


***tert*-Butyl (2-oxopropyl)carbamate** (**IV-9**).[56] A flame-dried flask was cooled under a stream of nitrogen and charged with pyridinium chlorochromate (12.3 g, 57 mmol) and CH_2Cl_2 (50 mL). The flask was cooled in an ice-water bath and (±)-*tert*-butyl (2-hydroxypropyl)carbamate (5.0 g in 10 mL CH_2Cl_2, 28.5 mmol) was added to the solution. The resulting mixture was stirred overnight at rt, and Et_2O (100 mL) was added to the system. The resulting black tar was filtered through a plug of silica gel and concentrated. The crude product was purified by flash chromatography on silica gel to afford 4.7 g (96%) of the title compound as a yellow oil. Spectroscopic properties were consistent with those reported in the literature.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, br, 1 H), 4.03 (d, J = 4.5 Hz, 2 H), 2.18 (s, 3 H), 1.44 (s, 9 H).



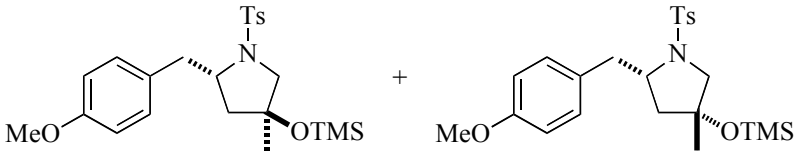
(±)-*tert*-Butyl (2-hydroxy-2-methylpent-4-en-1-yl)carbamate (**IV-10**). A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of allylmagnesium bromide

(92 mL, 1 M in Et_2O) and additional Et_2O (25 mL). The resulting solution was cooled in an ice-water bath, and a solution of *tert*-butyl (2-oxopropyl)carbamate (8.0 g, 46 mmol) in Et_2O (25 mL) was added slowly *via* syringe. The resulting mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (*ca*. 1.5 h). The mixture was cooled in an ice-water bath, and the reaction was quenched by the slow addition of water (100 mL). The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to afford 9.3 g (94%) of the title compound as a brown oil that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95–5.81 (m, 1 H), 5.21–5.07 (m, 2 H), 4.90 (s, br, 1 H), 3.13 (d, J = 6.2 Hz, 2 H), 2.40 (s, 1 H), 2.23 (d, J = 7.4 Hz, 2 H), 1.45 (s, 9 H), 1.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 133.4, 118.3, 79.1, 72.2, 49.6, 44.2, 28.1, 24.1; IR (film) 3369, 1694 cm^{-1}; MS (ESI): 238.1417 (238.1419 calc for $C_{11}H_{21}NO_3$, M + Na^+).



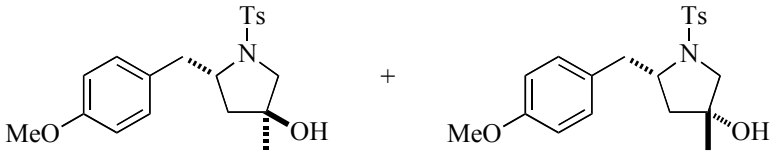
(±)-*tert*-Butyl {2-methyl-2-[(trimethylsilyl)oxy]pent-4-en-1-yl}carbamate (**IV-11**). A flame-dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with (±)-*tert*-butyl (2-hydroxy-2-methylpent-4-en-1-yl)carbamate (5.0 g, 23 mmol). Neat 1-(trimethylsilyl)-1*H*-imidazole (6.8 mL, 46 mmol) was added, and the resulting mixture was stirred at rt until the starting material had been consumed as judged by TLC analysis (*ca*. 4 h). Water (10 mL) was added to the system and the resulting mixture was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to afford 6.0 g (90%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.73 (m,

1 H), 5.09–5.01 (m, 2 H), 4.74 (s, br, 1 H), 3.16–2.99 (m, 2 H), 2.23 (d, J = 7.2 Hz, 2 H), 1.45 (s, 9 H), 1.19 (s, 3 H), 0.13 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 133.9, 117.9, 79.0, 75.7, 50.0, 45.2, 28.3, 24.9, 2.5; IR (film) 3368, 1720 cm^{-1}; MS (ESI): 310.1815 (311.1833 calcd for $C_{14}H_{29}NO_3Si$, M + Na^+).



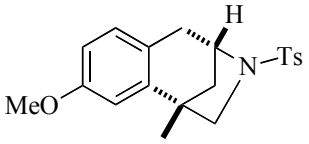
(+)-(2*S*,4*RS*)-*tert*-Butyl 2-(4-methoxybenzyl)-4-methyl-4-[(trimethylsilyl)oxy]pyrrolidine-1-carboxylate (**IV-12a-b**). A flame-dried Schlenk tube was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (191 mg, 0.2 mmol), (*R*)-Siphos-PE (303 mg, 0.06 mmol) and NaO^{t}Bu (960 mg, 0.5 mmol). The tube was evacuated and backfilled with nitrogen three times, then a solution of (±)-tert-butyl {2-methyl-2-[(trimethylsilyl)oxy]pent-4-en-1-yl}carbamate (3.0 g, 10 mmol) and 4-bromoanisole (3.74 g, 20 mmol) in toluene (30 mL) was added via syringe. The resulting mixture was stirred at rt for 1 min then was immersed in 90 °C oil bath and stirred overnight (ca 14 h). The mixture was then cooled to room temperature and saturated aqueous ammonium chloride (10 mL) was added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford 3.1 g (75%) of the title compound as a pale yellow oil. The product was judged to be a 1:1 mixture of rotamers and a 1:1 mixture of diastereomers by ^{1}H NMR analysis. Data are for the mixture. $[a]^{23}_D$ +18.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.03 (m, 2 H), 6.86–6.78 (m, 2 H), 4.19–3.82 (m, 1 H), 3.79 (s, 3 H), 3.76–3.10 (m, 2 H), 2.93–2.54 (m, 2 H), 1.94–1.79 (m, 1 H), 1.77–1.66 (m, 1 H), 1.55–1.47 (m, 9 H), 1.33–1.26 (m, 3 H), 0.14 (s, 4.5 H), 0.07 (s, 4.5 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 157.8, 157.7, 154.9, 154.7, 154.3, 130.8, 130.5, 130.3, 130.2, 130.0, 126.5, 113.6, 113.5, 113.4, 113.3, 79.0, 78.9, 78.8, 78.6, 78.0, 77.8, 77.6, 59.9, 59.7, 59.1, 59.0, 58.8, 58.2, 57.9, 54.7, 46.6, 45.5, 44.5, 43.4, 39.6, 39.4, 38.3, 38.2, 28.3, 28.1, 28.0, 26.6, 26.5, 24.8, 24.7, 2.2, 1.9, 1.8, 1.7; IR (film) 2972, 1699, 1684 cm^{-1}; MS (ESI): 416.2228 (416.2233 calcd for $C_{21}H_{35}NO_4Si$, $M + Na^+$).



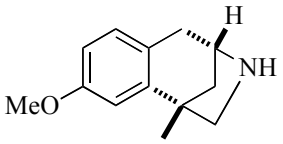
(+)-(5*S*,3*RS*)-5-(4-Methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (**IV-15**). [57] A round-bottom flask equipped with a stirbar was charged with (+)-(2*S*,4*RS*)-*tert*-butyl 2-(4-methoxybenzyl)-4-methyl-4-[(trimethylsilyl)oxy]pyrrolidine-1-carboxylate and CH_2Cl_2 (7.6 mL). The resulting solution was cooled to 0 °C, trifluoroacetic acid (5.7 mL, 76.2 mmol) was added to the system, and the solution was warmed to rt and stirred until the starting material had been consumed as judged by TLC analysis (*ca*. 10 min). The reaction mixture was diluted with water, basified with aqueous NH_4OH and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was dissolved in THF (5 mL) and the resulting solution was added to a stirring solution of triethylamine (3.2 mL, 22.9 mmol), tosyl chloride (2.18 mg, 11.4 mmol) and THF (10 mL). The reaction mixture was stirred overnight at rt, and saturated aqueous $NaHCO_3$ (10 mL) was added to the system. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to afford 2.3 g (80%) of the title compound as a colorless oil.[57] The product was judged to be a 1:1 mixture of diastereomers

by ^{1}H NMR analysis. Data are for the mixture. [a]$^{23}_D$ +65.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.73 (m, 2 H), 7.36–7.30 (m, 2 H), 7.20 (d, *J* = 8.0 Hz, 1.2 H), 7.14 (d, *J* = 8.4 Hz, 0.8 H), 6.88–6.80 (m, 2 H), 4.02–3.94 (m, 0.5 H), 3.83–3.75 (m, 3.5 H), 3.42–3.37 (m, 1 H), 3.30–3.21 (m, 1 H), 3.18–3.07 (m, 1 H), 3.03 (d, *J* = 10.4 Hz, 0.6 H), 2.83 (dd, *J* = 9.2, 13.6 Hz, 0.4 H), 2.44–2.41 (m, 3 H), 1.84–1.74 (m, 1 H), 1.64–1.54 (m, 2 H), 1.19 (m, 1 H), 1.09 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 143.7, 143.6, 133.9, 130.9, 130.6, 130.0, 129.8, 129.7, 129.6, 127.8, 127.7, 113.9, 113.7, 76.1, 76.0, 61.7, 61.6, 61.5, 61.0, 55.2, 45.5, 43.2, 41.1, 41.0, 25.4, 24.1, 21.5 (5 peaks are incidentally equivalent).

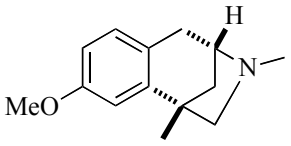


(+)-(*1S,4S*)-8-Methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[*d*]azepine (IV-14).[58] A flame-dried round-bottom flask was charged with aluminum trichloride (8.0 g, 60 mmol) and CH_2Cl_2 (100 mL). The flask was cooled to 0 °C, and a solution of (+)-(5*S,*3*RS*)-5-(4-methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (2.15 g, 5.7 mmol) in CH_2Cl_2 (20 mL) was added *via* syringe. The resulting mixture was allowed to slowly warm to rt and was stirred overnight. The reaction mixture was poured into a solution of saturated aqueous $NaHCO_3$ (50 mL). The mixture was transferred to a separatory funnel, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to afford 1.2 g (60%) of the title compound as a pale yellow solid. The enantiomeric excess was determined to be 81% e.e. by chiral HPLC analysis (Chiralpak AD-H 0.46 cm x 25 cm, 1 % *i*PrOH/hexanes, 1 mL/min, λ = 254 nm, major RT = 8.0, minor RT = 9.8 min). Spectroscopic properties were consistent with those previously reported in the literature.

[a]$^{23}_{D}$ +16.0 (*c* 1.0, CH_2Cl_2) [for *ent*-13 lit.[58] [α]$^{27}_{D}$ –16.9 (*c* 0.89, $CHCl_3$)]; mp: 137–140 °C (lit.[58] mp 136–138 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 2.5 Hz, 1 H), 6.72 (dd, *J* = 2.6, 8.3 Hz, 1 H), 4.41–4.35 (m, 1 H), 3.78 (s, 3 H), 3.40 (dd, *J* = 1.2, 8.7 Hz, 1 H), 3.11 (d, *J* = 16.6 Hz, 1 H), 3.02 (d, *J* = 8.6 Hz, 1 H), 2.93 (dd, *J* = 2.8, 16.5 Hz, 1 H), 2.42 (s, 3 H), 1.79 (d, *J* = 11.5 Hz, 1 H), 1.50–1.38 (m, 4 H).

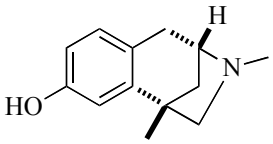


(+)- *(*1*S*,4*S*)-8-Methoxy-1-methyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo[*d*]azepine (IV-S1). A flame-dried round-bottom flask was charged with (+)-(1*S*,4*S*)-8-methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[*d*]azepine (1.1 g, 3.1 mmol) and xylene (15 mL). A solution of Red-Al was added (3.5 M in toluene, 3.3 mL, 11.4 mmol), and the mixture was heated at reflux for 1 h. The solution was cooled to 0 °C, diluted with ether and a few drops of water were added to the system. The solution was filtered through a pad of celite and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford 450 mg (71%) of the title compound as a yellow oil. [a]$^{23}_{D}$ +38.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.71 (dd, *J* = 3.0, 8.5 Hz, 1 H), 3.85–3.79 (m, 4 H), 3.11–3.02 (m, 2 H), 2.92 (d, *J* = 10 Hz, 1 H), 2.78 (m, 2 H), 1.96–1.92 (m, 1 H), 1.86 (d, *J* = 11 Hz, 1 H), 1.49 (s, 3 H).



(–)-8-*O*-Methylaphanorphine (IV-16). A flame-dried round-bottom flask was charged with (+)-(1*S*,4*S*)-8-methoxy-1-methyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo[*d*]azepine (300 mg, 1.5

mmol), a solution of 37% aqueous formalin (1.8 mL) and formic acid (2.8 mL). The reaction mixture was heated at 100 °C for 1.5 h, cooled to rt, diluted with water (10 mL) and basified with 10% aqueous NaOH. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 20 mL). 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 294 mg (90%) of the title compound as a pale yellow oil. Spectroscopic properties were consistent with those previously reported in the literature. $[a]^{23}_D$ –5.8 (*c* 1.0, $CHCl_3$), [lit.[59] $[\alpha]^{27}_D$ –7.4 (*c* 0.35, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 2.8 Hz, 1 H), 6.68 (dd, *J* = 2.8, 8.4 Hz, 1 H), 3.78 (s, 3 H), 3.42 (m, 1 H), 3.02 (d, *J* = 16.4 Hz, 1 H), 2.88–2.84 (m, 1 H), 2.82 (d, *J* = 1.2 Hz, 1 H), 2.76 (d, *J* = 9.2 Hz, 1 H), 2.48 (s, 3 H), 2.02 (ddd, *J* = 1.2, 5.6, 10.8 Hz, 1 H), 1.48 (s, 3 H).



(+)-Aphanorphine (**IV-1**). Demethylation of (–)-8-*O*-methylaphanorphine was carried out according to the reported procedure.[60] A flame-dried round-bottom flask was charged with 15 (40 mg, 0.18 mmol) and CH_2Cl_2 (1 mL) and cooled to –30 ˚C. BBr_3 (1.0 M in CH_2Cl_2, 0.36 mL) was added slowly dropwise. The reaction mixture was stirred for 30 min at –30 ˚C, 30 min at –20 ˚C, 30 min at –10 ˚C and 30 min at 0 ˚C. The reaction was quenched at 0 °C with aqueous $NaHCO_3$, and the mixture extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was taken up in 2 mL of 3 M NaOH and heated at 100 °C for 5 min. The solution was acidified with 1 M HCl and basified with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude solid

was triturated with acetone to afford 23 mg (63%) of the title compound as a white solid. Spectroscopic properties were consistent with those present in the literature. $[a]^{23}_{D}$ +28.0 (*c* 0.1, MeOH) [lit.[59] $[\alpha]^{27}_{D}$ +37.5 (*c* 0.16, MeOH)]; mp 202–208 °C (lit.[59] mp 215–222). ^{1}H NMR (400 MHz, CD_3OD) δ 6.89 (d, *J* = 8 Hz, 1 H), δ 6.67 (d, *J* = 2.4 Hz, 1 H), δ 6.56 (dd, *J* = 2.4, 8.4 Hz, 1 H), 3.38 (m, 1 H), 2.97 (d, *J* = 16.8 Hz, 1 H), 2.85 (m, 2 H), 2.63 (d, *J* = 9.6 Hz, 1 H), 2.40 (s, 3 H), 2.01 (q, *J* = 5.6 Hz, 1 H), 1.83 (d, *J* = 11.2 Hz, 1 H), 1.44 (s, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.6, 148.6, 131.2, 125.2, 114.5, 110.9, 72.7, 63.4, 44.3, 42.8, 42.1, 36.7, 21.7.

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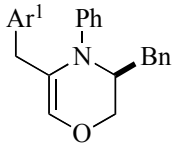
[20] A side product analogous to **II-S7** was observed in *ca*. 5–15% yield in crude reaction mixtures.



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[30] S-phos = 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl.

[31] Substrates for the Pd-catalyzed carboamination reaction can be prepared *via* alkylation of the corresponding nitrile followed by LAH reduction and Boc protection. Substrates can be also prepared from a Mitsunobu reaction of the corresponding alcohol with phthalimide followed by cleavage of the phthalimide and Boc protection. For more information, see reference 32.

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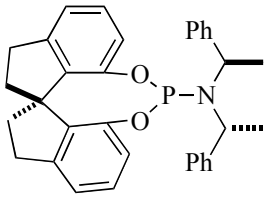
[53] Our selection of the unnatural antipode of **IV-1** was due in part to the commercial availability of a ligand which gave us synthetically useful yields and enantioselectivities.

[54] (*R*)-Siphos-PE = (11a*R*)-(+)-10,11,12,13-Tetrahydrodiindeno[7,1-de:1',7'-fg][1,3,2]dioxaphosphocin-5-bis[(*R*)-1-phenylethyl]amine



(*R*)-Siphos-PE

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