# Pd-Catalyzed Carboamination Reactions for the Synthesis of Imidazolidin-2-ones and Related Heterocycles

by

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**Acknowledgements**

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## List of Abbreviations

Ac ..... acetate
*t*-Am ..... *tert*-amyl
Ar ..... generic aryl group
BINAP ..... 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn ..... benzyl
Boc ..... *tert*-butoxycarbonyl
*t*-Bu ..... *tert*-butyl
CAN ..... ammonium cerium (IV) nitrate
Cbz ..... benzyloxycarbonyl
CDI ..... 1,1'-carbonyldiimidazole
$Cs_2CO_3$ ..... cesium carbonate
dba ..... trans, trans-dibenzylideneacetone
DPE Phos ..... bis(2-diphenylphosphinophenylether
dpp benzene ..... 1,2-bis(diphenylphosphino)benzene
dppb ..... 1,4-bis(diphenylphosphino)butane
DME ..... dimethoxyethane
DMAP ..... dimethylaminopyridine
DMF ..... dimethylformamide
DMSO ..... dimethylsulfoxide
dppe ..... 1,2-bis(diphenylphosphino)ethane
dppf ..... 1,1'-bis(diphenylphosphino)ferrocene
EDCI ..... 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et ..... ethyl
*i*-Pr ..... isopropyl
KO*t*-Bu ..... potassium *tert*-butoxide
KOH ..... potassium hydroxide
LiAlH4 ..... lithium aluminum hydride
Ln ..... generic ligand
Men ..... menthol
MsOH ..... methanesulfonic acid
NaO*t*-Bu ..... sodium *tert*-butoxide
Nixantphos ..... 4,6-bis(diphenylphosphino)phenoxazine
PEt3•HBF4 ..... triethylphosphonium tetrafluoroborate
Ph ..... phenyl
Pg ..... generic protecting group
Phanephos ..... 4,12-bis(diphenylphosphino)-[2.2]-paracyclophane
PMP ..... para-methoxyphenyl
SM ..... starting material
$P(2\text{-furyl})_3$ ..... tri-2-furylphosphine

P(*o*-tol)$_3$.....tri-*o*-tolylphosphine
THF.....tetrahydrofuran
Tf.....trifluoromethanesulfonyl
Xantphos.....9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene
X-Phos..... 2-(dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl

**Abstract**

Pd-Catalyzed Carboamination Reactions for the Synthesis of
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Chair: John P. Wolfe

Imidazolidin-2-ones and related heterocycles have many medicinal and synthetic uses. Progress toward expanding the scope of Pd-catalyzed carboamination to include the synthesis of these classes of heterocycles is demonstrated. 4,4- and 4,5-disubstituted imidazolidin-2-ones were generated in high yield from *N*-allylureas and aryl bromides. 4,5-disubstituted imidazolidin-2-ones and imidazolidin-2-ones derived from internal olefins were made in moderate to high diastereoselectivity. Vinyl halides were also shown to be effective coupling partners. Orthoganol deprotection of an *N*1-benzyl *N*3 *p*-methoxyphenyl protected imidazolidin-2-ones was achieved. An enantioselective synthesis of imidazolidin-2-ones using chiral ligands or chiral auxiliaries was pursued. Lastly, studies on the Pd-catalyzed carboamination of *N*-allylguanidines, *O*-allylcarbamate, homoallylsulfoximines, and *N*-allylsulfamides are described.

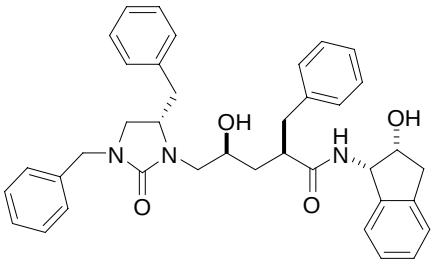
# Chapter I
# Introduction

## Importance of Imidazolidin-2-ones and Related Heterocycles

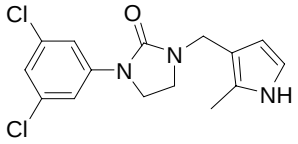
*Medicinal and Biological Relevance*

Heterocycles represent a privileged scaffold within the realm of medicinal and biological chemistry. For example, the imidazolidin-2-one **I-1** has shown potential as HIV protease inhibitor (Figure I-1).[1] The cyclic urea **I-2** has demonstrated potent activity as a 5-$HT_3$ antagonist.[2] The 5-$HT_3$ receptor has been implicated in anxiety, emesis, and drug abuse. 4,4-Disubstituted-2-imidazolidinones such as **I-3** have been investigated by Schering-Plough as potent Neurokinin antagonists,[3] which are useful for treating depression, anxiety, and nausea.

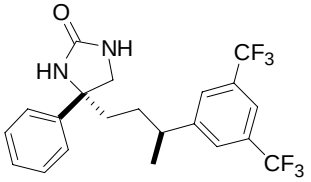
**Figure I-1.** Medicinally Important Imidazolidin-2-ones




**I-1**




**I-2**

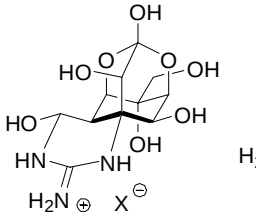



**I-3**

Replacement of the carbonyl oxygen of imidazolidin-2-ones with nitrogen gives cyclic guanidines. Cyclic guanidines are found in several natural products that exhibit potent biological activity (Figure I-2). For example, (-)-tetrodotoxin[4] **I-4** and (+)-saxitoxin[5] **I-7** are two powerful neurotoxins. Both of these compounds derive their toxicity from their ability to disrupt nerve impulses by blocking pores of voltage-gated $Na^+$ ion channels, thereby paralyzing their victims. Tetrodotoxin is found in the pufferfish, the blue-ringed octopus, and the rough-skinned newt.

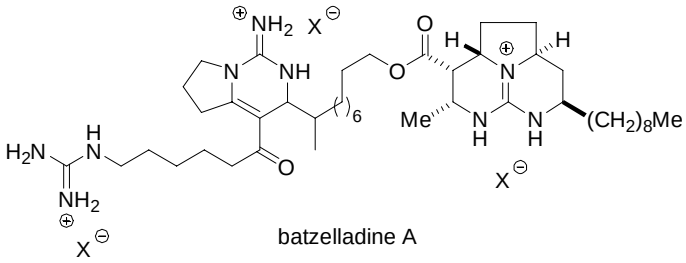
Several guanidine natural products have also been isolated from marine sponges. For example, Batzelladine A **I-5** is a member of polycyclic guanidine alkaloids that were isolated from Bahamian and Jamaican sponges in the mid-90's. [6] It inhibits the binding of the HIV glycoprotein gp-120 to the human CD4 receptor. Crambescidin 800 **I-6** is one of multiple crambescidin alkaloids found in the *Crambe crambe,* a bright red species of sponge found along the Mediterranean.[7] The crambescidins have been shown to inhibit Herpes simplex virus, type 1 (HSV-1) and are cytotoxic to L1210 murine leukemia cells and human cancer cell lines.

**Figure I-2.** Biologically Active Cyclic Guanidines



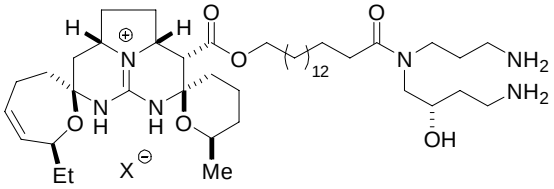
(-)-tetrodotoxin

**I-4**



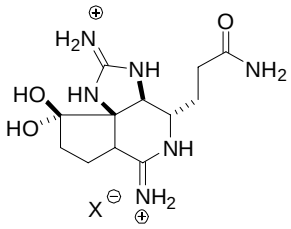
batzelladine A

**I-5**



crambescidin 800

**I-6**



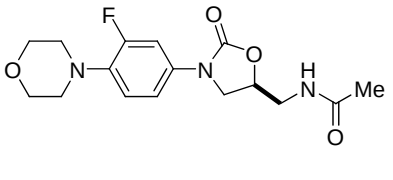
(+)-saxitoxin

**I-7**

Several other close cousins of imidazolidin-2-ones possess medicinal qualities, many of which are currently marketed for their therapeutic properties (Figure I-3). For instance, Linezolid **I-8**, an oxazolidinone containing antibiotic produced by Pfizer, is effective against vancomycin resistant gram-positive bacteria.[8] Interestingly, Bayer uses a similar scaffold for their anticoagulant Rivoraxaban[9]. AstraZeneca has marketed an oxazolidinone called Zolmitripan **I-9** for the treatment of migraines. Cyclic thioureas including carbimazole[10] **I-10** have been used for the treatment of hyperthyroidism. A subclass of cyclic thioureas, thiohydantoins, have been shown to possess many potentially therapeutic attributes such as modulation of high-density lipoprotein (HDL) levels[11] and inhibition of fatty acid amide hydrolase (FAAH). [12] RD-162 **I-11**, originally developed in the laboratory of Michael Jung at UCLA, has demonstrated efficacy against

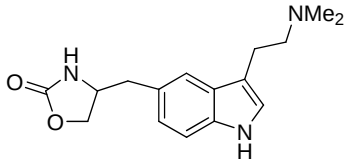
hormone-refractory prostate cancer.[13] The Groutas group has published several papers on the medicinal importance of cyclic sulfamides.[14] They are useful as serine protease inhibitors including human leukocyte elastase **I-12**, and can potentially be used for inflammatory diseases. Cyclic sulfamides have also been explored as potential treatments for sarcopenia[15] and Alzheimer's disease.[16]

**Figure I-3.** Other Medicinally Important Heterocycles



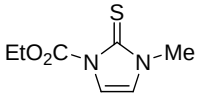
Linezolid (Zyvox)

**I-8**



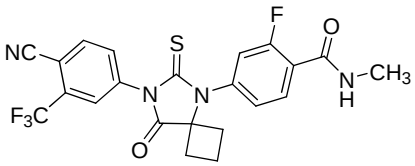
Zolmitripan (Zomig)

**I-9**



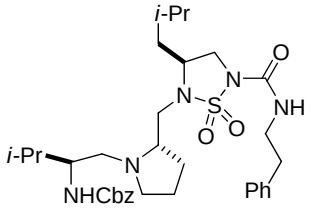
Carbimazole

**I-10**



RD162

**I-11**

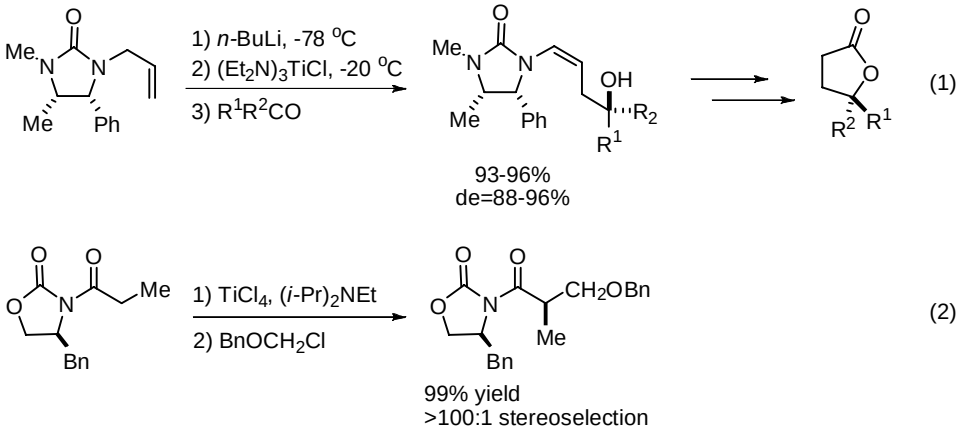


human leukocyte elastase inhibitor

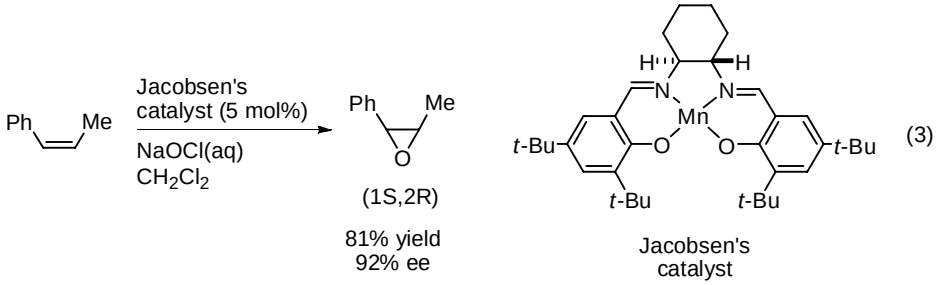
**I-12**

*Synthetic Relevance*

Imidazolidinones and oxazolidinones are synthetically important as chiral auxiliaries which can induce stereoselectivity in reactions. For example, Helmchen and coworkers demonstrated that imidazolidin-2-ones derived from ephedrine can be used in enantioselective homoaldol additions (eq 1).[17] Similarly, Evans has demonstrated the use of oxazolidinones for a variety of stereoselective transformations including the alkylation shown in eq 2.[18]

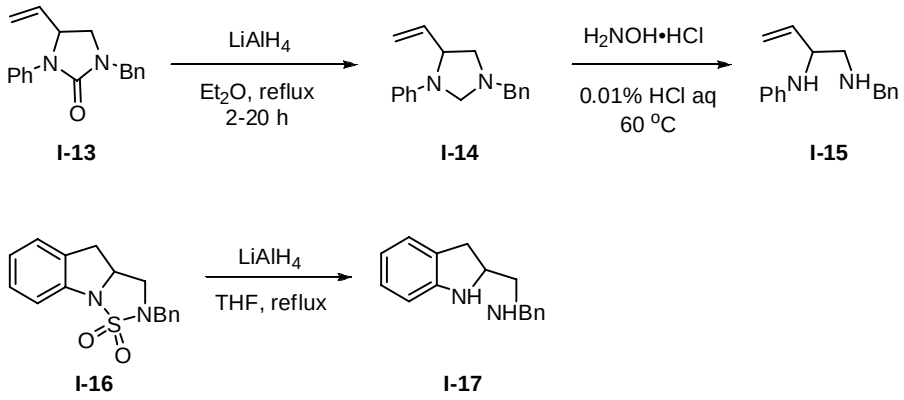



Imidazolidin-2-ones and cyclic sulfamides are also precursors to vicinal diamines which are valuable in and of themselves.[19] They are a feature of many *cis*-platin analogs, have been used in radiopharmaceuticals, and can act as opioid receptor agonists.[19] Vicinal diamines or their derivatives are also used as chiral ligands to allow for asymmetric transformations. For example, Jacobsen's catalyst, composed of a Mn metal center coordinated to a salen ligand derived from the vicinal diamine 1,2-aminocyclohexane, has been used in enantioselective epoxidations such as the one shown in eq. 3.[20]




Trost has shown that imidazolidin-2-ones can be transformed into vicinal diamines via a two step sequence involving LAH reduction of imidazolidinone **I-13** to imidazolidine **I-14** followed by hydrolysis with hydroxylamine to afford diamine **I-15** (Scheme I-1).[21] Likewise, Chemler demonstrated the direct conversion of cyclic sulfamide **I-16** to vicinal diamine **I-17** using an LAH reduction.[22]

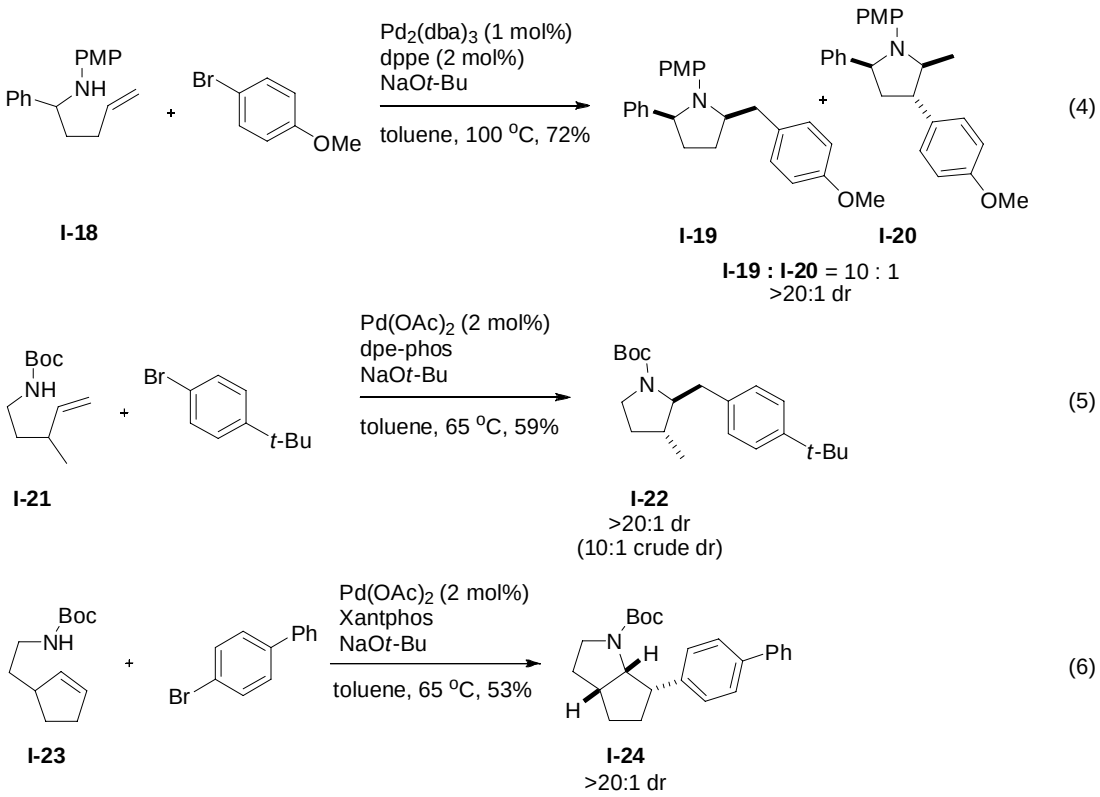
**Scheme I-1**. Diamines from Imidazolidin-2-ones and Cyclic Sulfamides




## Previous Examples of Pd-Catalyzed Alkene Carboamination Reactions

*Pd-Catalyzed Carboamination of γ-(N-arylamino) and γ-(N-Boc-amino) alkenes*

Previously in the Wolfe group, the Pd-catalyzed carboamination of γ-(*N*-arylamino) alkenes and γ-(*N*-Boc-amino) alkenes to afford substituted pyrrolidines has been demonstrated (eqs 4-6).[23] For example, reaction of a 1-substituted γ-(*N*-arylamino) alkene **I-18** with 4-bromoanisole gave *cis*-2,5-disubstituted pyrrolidine **I-19** and a regioisomer **I-20** in good yield and diastereoselectivity as a 10:1 mixture of regioisomers.[23a] Reaction of a 3-substituted γ-(*N*-Boc-amino) alkene **I-21** afforded the 2,4-*trans*-disubstituted pyrrolidine **I-22** in high diastereoselectivity as a single regioisomer.[23b,24] Additionally, the carboamination of an internal cyclic alkene **I-23** to afford to bicyclic pyrrolidine **I-24** proceeded with high diastereoselectivity.[23b]




Several notable features of these transformations may be summarized as follows:

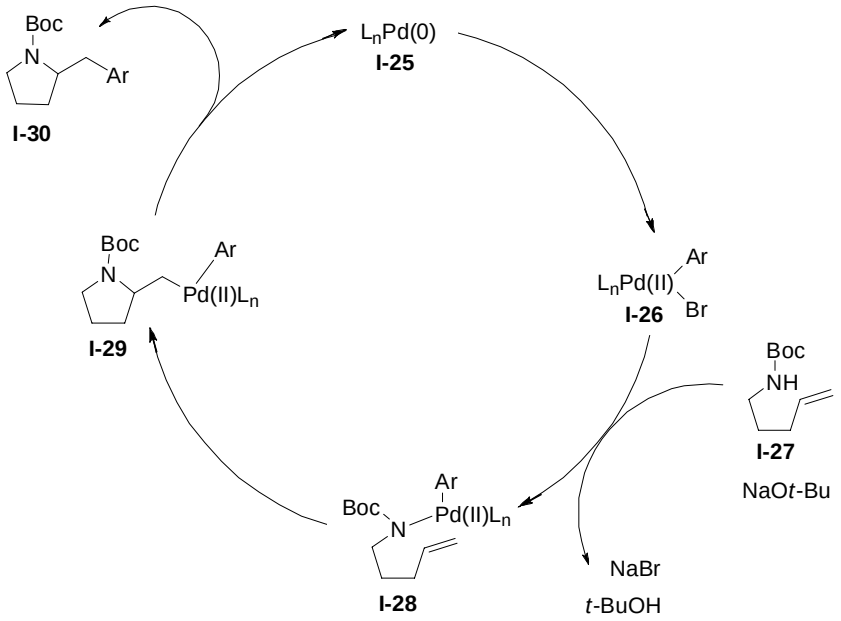
1) Two bonds (C-N and C-C) and up two stereocenters are generated in a single step.
2) 2,5-*cis* or 2,3-*trans*-disubstituted pyrrolidines are created in high diastereoselectivity (10:1 to >20:1). In contrast, 2,4-disubstituted pyrrolidines are formed in lower diastereoselectivity (2:1 to 3:1).
3) *Syn*-insertion of an olefin into a Pd-N bond is the stereochemical determining step in the reaction.[25]
4) The diastereoselectivity in eqs 4 and 5 is due to allylic strain interactions in the transition state whereas in eq 6 the diastereoselectivity arises from the *syn*-insertion of the olefin into the Pd-N bond.

*Mechanism*

The proposed mechanism shown in Scheme I-2 for this transformation commences with a Pd(0) catalyst **I-25**. This may be formed from a Pd(0) precatalyst such as $Pd_2(dba)_3$ or from a Pd(II) source such as $Pd(OAc)_2$, which is reduced to Pd(0) *in situ*.[26] Oxidative addition of an aryl halide generates Pd(II) intermediate **I-26**. Base

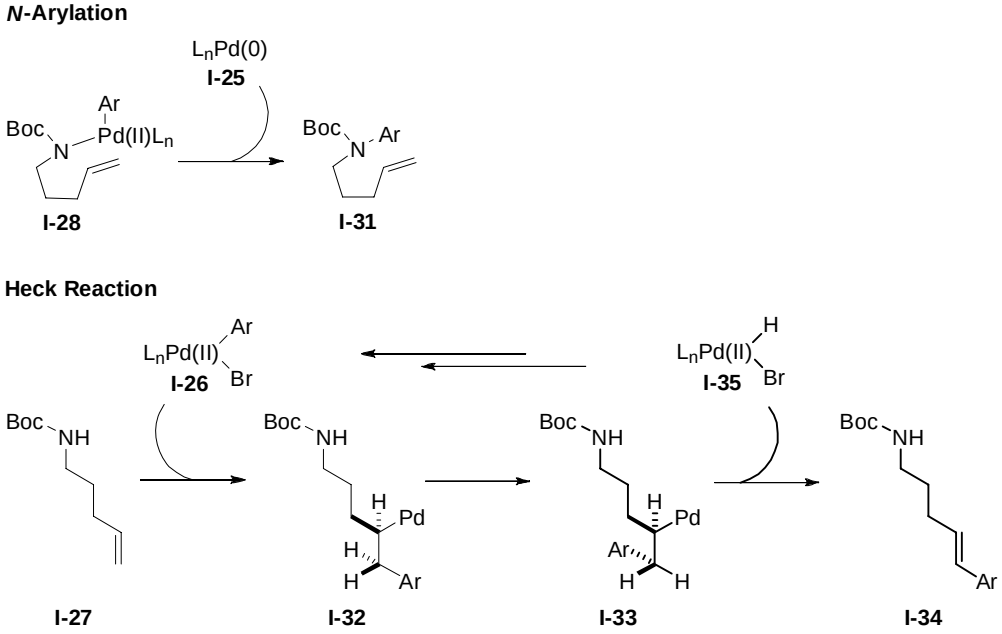
mediated Pd-N bond formation next gives Pd-amido complex **I-28**. A pendant olefin can then undergo *syn*-insertion into the Pd-N bond to afford Pd-alkyl complex **I-29**. Finally, C-C bond forming reductive elimination can occur to create the desired pyrrolidine **I-30** as well as regenerate the Pd catalyst. While several alternative mechanisms may be envisioned that would also lead to the pyrrolidine products, they were dismissed as they would either result in compounds with stereochemistry that differs from that observed, could not account for byproducts seen in the reaction, or would likely form byproducts which were not detected in the reaction.[27]

**Scheme I-2.** Proposed Mechanism of Pd-Catalyzed Carboamination




This mechanism bears attributes that resemble both the Buchwald-Hartwig amination[28] and the Heck reaction.[29] Reaction conditions used in Pd-catalyzed carboaminations of pentenyl amines are similar to those in *N*-arylations (Pd, phosphine ligand, strong base). Furthermore, byproducts resulting from both *N*-arylation and Heck pathways are seen in Pd-catalyzed carboamination (Scheme I-3). For instance, C-N bond forming reductive elimination from the Pd-amido complex **I-28** results in the arylation of the amine to afford **I-31**. Alternatively, *syn*-insertion of the olefin of **I-27** into Pd-oxidative addiction complex **I-26** leads to **I-32**. C-C bond rotation gives **I-33**. β-hydride elimination affords Heck product **I-34** and Pd-hydride **I-35**. Lastly, **I-35** is converted back to **I-26** to complete the catalytic cycle.

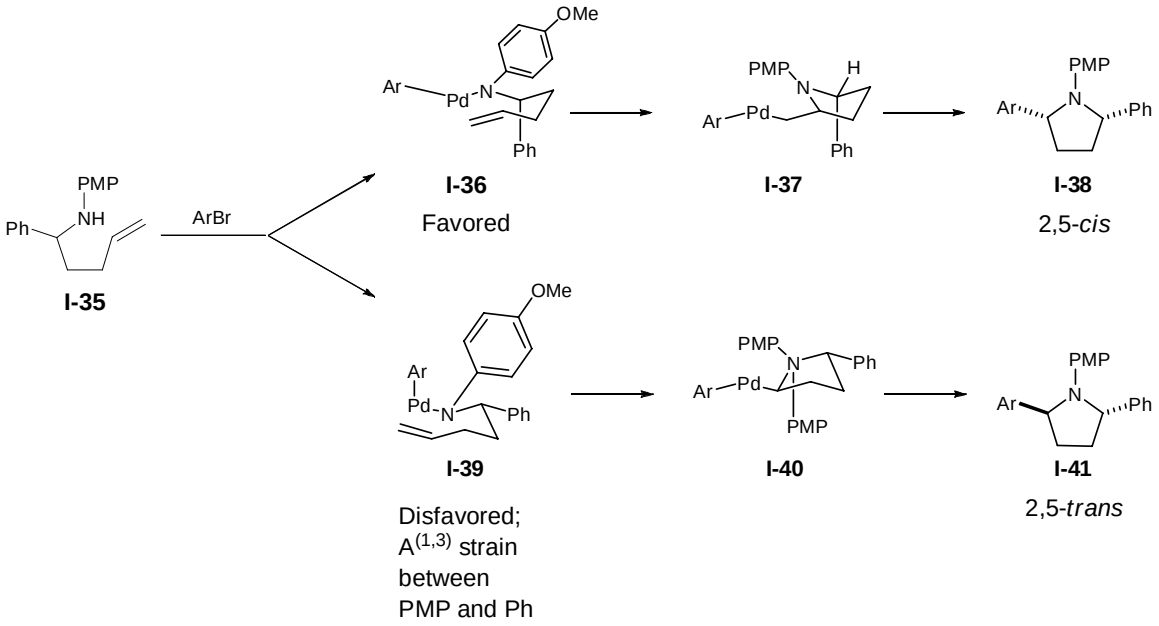
**Scheme I-3.** Alternative Reaction Pathways




*Stereochemical Considerations*

The stereochemistry of the pyrrolidine products is controlled by allylic ($A^{1,3}$) strain and 1,3-diaxial interactions present in the alkene aminopalladation transition state.[30] Depending on the position of the substituents on the substrate, each of these will control the stereoselectivity to a greater or lesser degree. For example, as shown in Scheme I-4, the 1-substituted γ-(*N*-arylamino) alkene **I-35** can lead to either the Pd-amido complex **I-36** or its flipped chair conformer **I-39**. **I-36** suffers from a 1,3-diaxial interaction between the phenyl substituent in the 1-position and an axial hydrogen in the 3-position. However, **I-39** possesses a strong allylic interaction between the protecting group on N and the equatorial phenyl substituent. The allylic strain in **I-39** appears to be more significant than the 1,3-diaxial interaction in **I-36** as the ratio of the *cis* and *trans* products **I-38** and **I-41** is >20:1.

**Scheme I-4.** Rational for Stereoselectivity



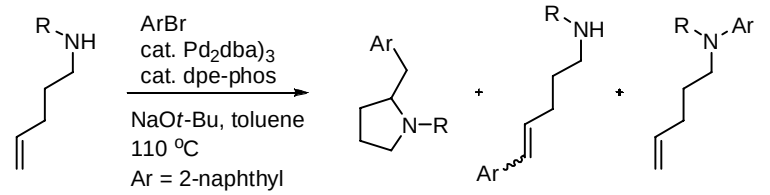

As alluded to earlier, the product stereochemistry in **I-24** from eq 6 is not derived from either allylic strain or diaxial interactions but rather from a completely diastereoselective insertion of the olefin into the Pd-N bond of the Pd-amido complex **I-28** in Scheme I-2. Importantly, prior to studies by the Wolfe group, reactions involving insertion of an alkene into a Pd-amido complex were rare.[25] As a consequence of this insertion, net *syn*-aminopalladation is seen across the double bond. Factors controlling the stereochemistry of oxypalladation and aminopalladation have been investigated in the Wolfe and Stahl groups[31] and remain an important area of research.

*Factors Affecting Product Distribution*

A prominent goal in goal in organic synthesis is control of product distribution by alteration of reaction parameters. Work in the Wolfe group has demonstrated that the relative rates of the competing reaction pathways to the desired carboamination can be influenced by both variance in the group on the cyclizing nitrogen as well as though judicious choice of phosphine ligand. For example, as shown in Table I-1, Beaudoin Bertrand and Wolfe found that the relative ratio of Heck, carboamination, and *N*-arylation products in the reactions of γ-aminoalkenes was dependent on the identity of the functional group on the nitrogen.[23b] Groups such as Ac, Boc, and 4-MeO-Bz resulted in preference for the desired cyclization **I-43** to either *N*-arylation or Heck. In contrast,

highly electron-poor groups such as Bz and 4-$F_3C$-Bz afforded a much higher percentage of the Heck product **I-44**. More electron-rich groups such as Bn and Ph allowed *N*-arylation of **I-45** to be competitive. [32]

**Table I-1**. Effect of Nitrogen Substituent on Product Ratio

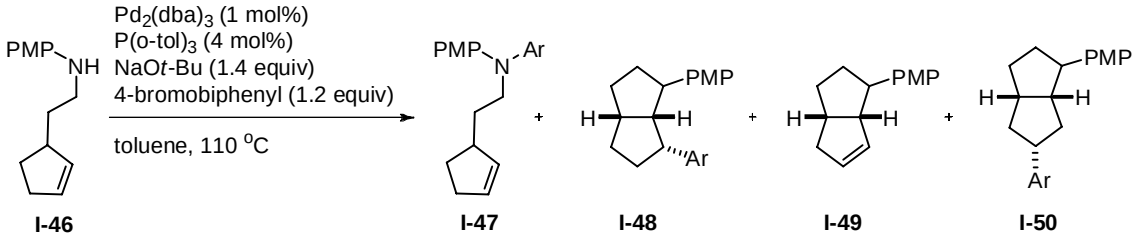



**I-42** **I-43** **I-44** **I-45**

| *N*-Substituent | GC ratio (isolated yield) | | |
|---|---|---|---|
| | **I-43** | **I-44** | **I-45** |
| R = Bn | — | 40 | 34 |
| R = Ph | 75 (63%) | — | 25 |
| R = Ac | 88 (72%) | 12 | — |
| R = Boc | 82 (77%) | 4 | — |
| R = 4-MeO-Bz | 77 (63%) | 23 | — |
| R = Bz | 58 (48%) | 42 | — |
| R = 4-$F_3C$-Bz | — | 89 | — |

In cyclizations to form octahydrocyclopenta[b]pyrroles[27] it was demonstrated that the identity of the phosphine ligand can have profound effect on the product distribution (Table I-2). Reaction of **I-46** under standard Pd-catalyzed reaction conditions afforded four products: **I-47** derived from *N*-arylation, **I-48** the desired carboamination product, **I-49** from formal oxidative amination and **I-50** a regioisomer of **I-48**. Ney and Wolfe found that *N*-arylation product **I-47** could be favored by the use of the bulky, monodentate, electron-rich ligands P(*t*-Bu)$_3$ and *t*-$Bu_2$P(*o*-biphenyl). The small, monodentate electron-rich ligands $PMe_3$, $PEt_3$ and $PhPMe_2$ selectively provided **I-49**. The best selectivity for the regioisomer **I-50** was obtained by using the medium-sized electron-rich ligands P(*t*-Bu)$_2$Me and $PCy_3$.

**Table I-2.** Effect of Phosphine Ligand on Product Ratio

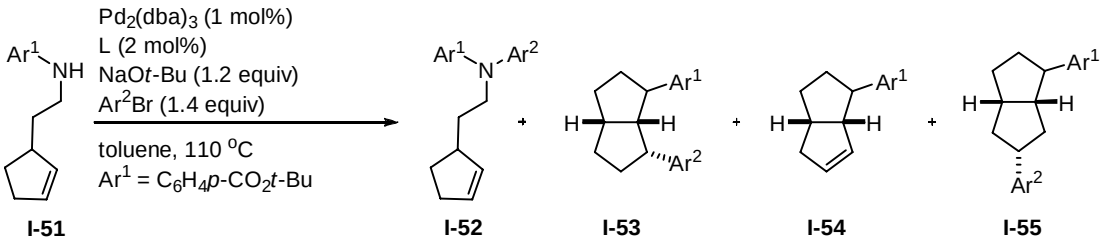



**I-46** **I-47** **I-48** **I-49** **I-50**

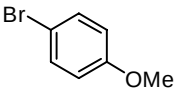
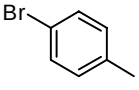
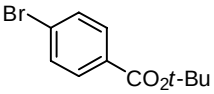
| Ligand | I-47 | I-48 | I-49 | I-50 |
|---|---|---|---|---|
| P(*t*-Bu)$_3$•HBF$_4$ | **98** | 2 | 0 | 0 |
| *t*-Bu$_2$P(*o*-biphenyl) | **94** | 6 | 0 | 0 |
| PMe$_3$•HBF$_4$ | 0 | 0 | **98** | 2 |
| PEt$_3$•HBF$_4$ | 0 | 0 | **92** | 8 |
| PhPMe$_2$ | 0 | 0 | **92** | 8 |
| P(*t*-Bu)$_2$Me•HBF$_4$ | 0 | 0 | 0 | **100** |
| PCy$_3$ | 2 | 2 | 6 | **90** |

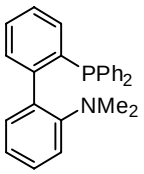
They also found that the electronics of the aryl halide could have an effect on the product distribution (Table I-3). When electron-rich 4-bromoanisole was used a 90:10 ratio of **I-53** to **I-54** was obtained. When electron-neutral 4-bromotoluene was used the desired carboamination product **I-53** was obtained exclusively. Lastly, when an electron-poor aryl halide was used *N*-arylation byproduct **I-52** was seen in addition to **I-53**.

**Table I-3.** Effect of Aryl Halide Electronics on Product Distribution




**I-51** **I-52** **I-53** **I-54** **I-55**

| $Ar^2$ | Crude Ratio **I-52:I-53:I-54:I-55** | Isolated Yield **I-53** |
|---|---|---|
|  | 0:90:10:0 | 58% |
|  | 0:100:0:0 | 75% |
|  | 30:60:10:0 | 49% |

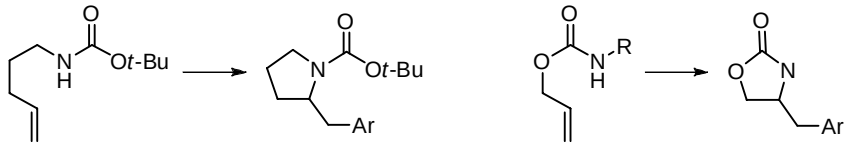



**L**

*From Pyrrolidines to Imidazolidin-2-ones and Other Heterocycles*

Given the successful cyclization of γ-(*N*-Boc-amino) alkenes we believed that the carboamination of *O*-allylcarbamates and *N*-allylureas might also be successful. *O*-allylcarbamates and *N*-allylureas would likely have similar nucleophilicities as γ-(*N*-Boc-amino) alkenes. Furthermore, as shown in Scheme I-5, the added rigidity of a urea or carbamate within the forming heterocycle (**I-58** → **I-59**) could make cyclization more entropically favorable compared to that of the pentenyl amines (**I-56** → **I-57**).

**Scheme I-5.** Two Modes of Cyclization




**I-56** **I-57** **I-58** **I-59**

*exo*-carbamate *endo*-carbamate

Our approach to the synthesis of these heterocycles would also have advantages over existing methods for their synthesis (described in Chapters 2-5). These substrates could be prepared in a concise manner from readily available starting materials. Thus, generation of a variety of different compounds should be straightforward. Our studies on the synthesis of these heterocycles via Pd-catalyzed carboamination are described in the chapters that follow.

## References


[1] a) De Lucca, G. V.; Lam, P. Y. S. *Drugs Future* **1998**, *23*, 987–994; b) Salituro, F. G.; Baker, C. T.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Porter, M. D.; Schairer,W. C.; Tung, R. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3637–3642; c) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159–1162; d) De Clerq, E. *Biochim. Biophys. Acta* **2002**, *1587*, 258–275; e) Kazmierski, W. M.; Furfine, E.; Gray-Nunez, Y.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5685–5687.

[2] Heidempergher, F.; Pillan, A.; Pinciroli, V.; Vaghi, F.; Arrigoni, C.; Bolis, G.; Caccia, C.; Dho, L.; McArthur, R.; Varasi, M. *J. Med. Chem.* **1997**, *40*, 3369–3380.

[3] a) Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinkski, J. J.; Shih, N.-Y. *Org. Lett.* **2003**, *5*, 4249–4251; b) Shue, H.-J.; Chen, X.; Shih, N.-Y.; Blythin, D. J.; Paliwal, S.; Lin, L.; Gu, D.; Schwerdt, J. H.; Shah, S.; Reichard, G. A.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Liu, F.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3896–3899; c) Shue, H.-J.; Chen, X.; Schwerdt, J. H.; Paliwal, S.; Blythin, D. J.; Lin, L.; Gu, D.; Wang, C.; Reichard, G. A.; Wang, H.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B.; Shih, N.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1065–1069.

[4] a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511; b) Mosher, H. S.; Fuhrman, F. A.; Buchwald, H. D.; Fischer, H. F. *Science* **1964**, *144*, 1100–1110.

[5] Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926–3927.

[6] Patil, A. D.; Kumar, N. V.; Kokke, W. C. Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.;Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182–1188.

[7] Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893–4903.

[8] Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Manninen, P. R. *J. Med. Chem.* **2008**, *51*, 1981–1990.

[9] Roehrig, S.; Straub, A.; Pohlmann, J.; Lampe, T.; Pernerstorfer, J.; Schlemmer, K-H.; Reinemr, P.; Perzborn, E. *J. Med. Chem.* **2005**, *48*, 5900–5908.

[10] a) Das, D.; Roy, G.; Mugesh, G. *J. Med. Chem*. **2008**, *51*, 7313–7317; b) Cooper, D. S. *N. Engl. J. Med.* **2005**, *352*, 905–917.

[11] Elokdah, H.; Sulkowski, T. S.; Abou-Gharbia, M.; Butera, J. A.; Chai, S-Y.; McFarlane, G. R.; McKean, M-L.; Babiak, J. L.; Adelman, S. J.; Quinet, E. M. *J. Med. Chem.* **2004**, *47*, 681–695.

[12] Muccioli, G. G.; Fazio, N.; Scriba, G. K. E.; Poppitz, W.; Cannata, F.; Poupaert, J. H.;Wouter, J.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 417–425.

[13] Borman, S. *C&E News* **2008**, *86*, *38*, 84–87.

[14] a) Zhong, J.; Gan, X.; Alliston, K. R.; Groutas, W. C. *Bioorg. Med. Chem.* **2004**, *12*, 589–593; b) Li, Y.; Yang, Q.; Dou, D.; Alliston, K. R.; Groutas, W. C. *Bioorg. Med. Chem.* **2008**, *16*, 692–698.

[15] Manfredi, M. C.; Bi, Y.; Nirschl, A. A.; Sutton, J. C.; Seethala, R.; Golla, R.; Beehler, B. C.; Sleph, P. G.; Grover, G. J.; Ostrowski, J.; Hamann, L. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4487–4490.

[16] Sparey, T.; Beher, D.; Best, J.; Biba, M.; Castro, J.; Clarke, E.; Hannam, J.; Harrison, T.; Lewis, H.; Madin, A.; Shearman, M.; Sohal, B.; Tsou, N.; Welch, C.; Wrigley, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4212–4216.

[17] Roder, H.; Helmchen, G.; Peters, E-M. Peters, K.; von Schnering, H-G. *Angew. Chem. Int., Ed. Engl.* **1984**, *23*, 898–899.

[18] Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990** *112*, 8215–8216.

[19] Lucet, D.; Le Gall, R.; Mioskowski, C. *Angew. Chem. Int., Ed.* **1998**, *37*, 2580–2627.

[20] Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.

[21] Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837.
[22] Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251.
[23] a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605–3608; b) Beaudoin Bertrand, M.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6647–6459.
[24] The higher regioselectivity seen with γ-(*N*-Boc-amino) alkenes may be due to a decrease in the rate of β-hydride that leads to regioisomer formation. See Ref. 24b for more discussion.
[25] a) Boncella, J. M.; Villanueva, L. A. *J. Organomet. Chem.* **1994**, *465*, 297–304; b) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963–2965; c) Helaja, J.; Göttlich, R. *J. Chem. Soc., Chem. Commun.* **2002**, 720–721; d) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45–46.
[26] For an example of reduction of $Pd(OAc)_2$ by a bidentate phosphine ligand see: Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241–3249.
[27] For an extensive discussion on and analysis of alternative mechanisms see: Ney, J.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651.
[28] For reviews on the Buchwald-Hartwig amination see: a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *291*, 131–209; b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417–1423.
[29] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
[30] For a discussion on allyic strain and 1,3-diaxial interactions see: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, University Science Books, Sausalito, CA, **2006**, pp. 100–105.
[31] a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901; b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335.
[32] a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245; b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048; c) Yamashita, M.; Cuevas Vicario, J. V.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 16347–16360.

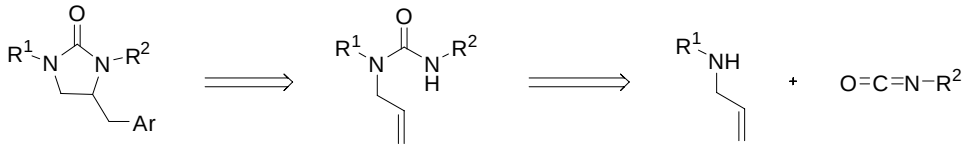
## Chapter II

## Racemic Synthesis of Imidazolidin-2-ones

### Synthetic Strategy and Substrate Synthesis

There are several methods of forming imidazolidin-2-ones including carbonylation of diamines,[1] ring opening of aziridines,[2] halocyclizations,[3] C-H amination,[4] intramolecular *N*-arylation,[5] Pd-catalyzed carboamination,[6] Pd-catalyzed allylic alkylation,[7] alkene diamination,[8] and ureidomercuration.[9] As a complementary approach, we envisioned that imidazolidin-2-ones **II-1** could be accessed from *N*-allylureas **II-2** via Pd-catalyzed carboamination methodology developed in the Wolfe lab (Scheme II-1). Analogous to the pyrrolidine synthesis delineated in Chapter I, this methodology would result in the simultaneous formation of a C-C and a C-N bond and up to two stereocenters.

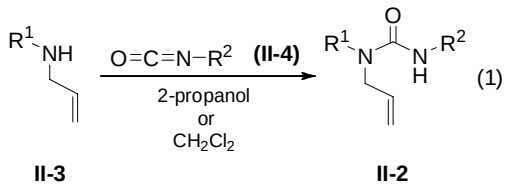
**Scheme II-1.** Synthetic Strategy




**II-1** **II-2** **II-3** **II-4**

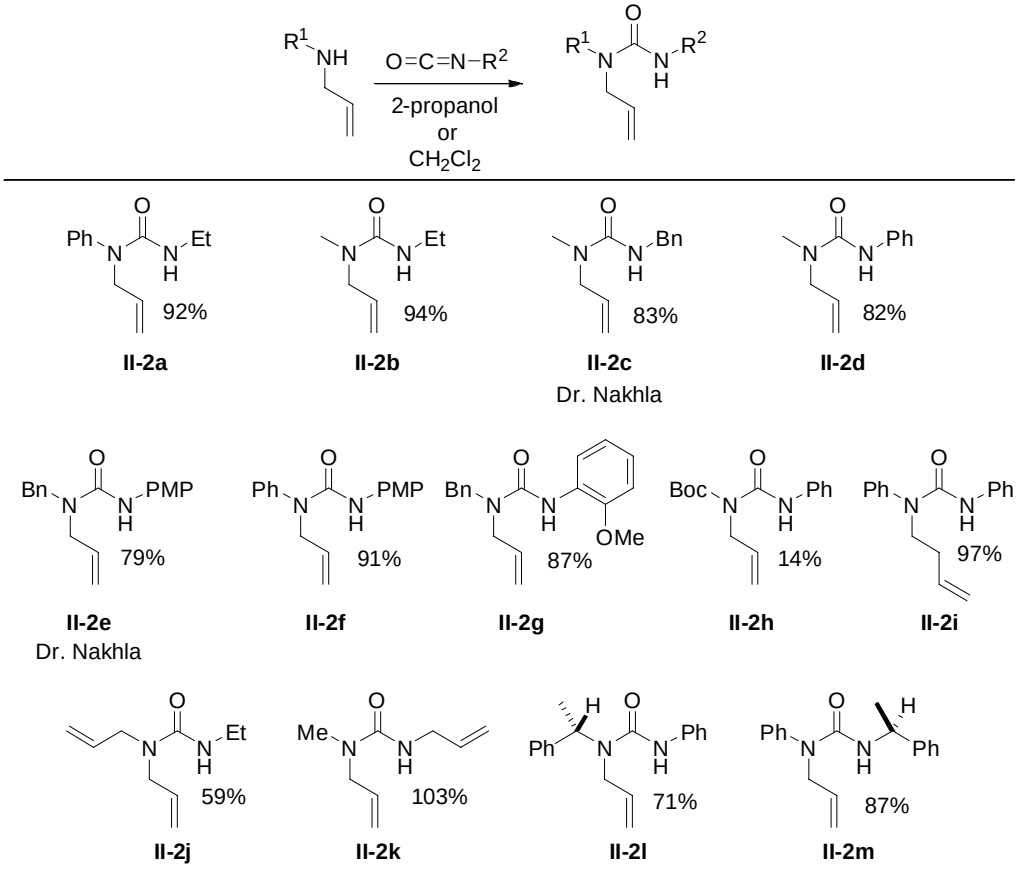
The requisite *N*-allylureas for the Pd-catalyzed carboamination were easily accessed via addition of allylic amines **II-3** to commercially available isocyanates **II-4** under the general conditions shown in eq 1. Formation of *N*-allylureas was generally complete within a couple of hours at room temperature.[10] For more reactive isocyanates, components were added initially at 0 $^{o}$C before warming to room temperature to prevent a large exotherm. While initially 2-propanol was chosen as the solvent based on literature precedent, it was found to react with some isocyanates to produce carbamates. Thus, the solvent of choice for subsequent reactions generally became $CH_2Cl_2$. The most challenging aspect of the synthesis of the *N*-allylureas was the synthesis of the allylic

amines which occasionally required several steps to achieve substitution in various locations on the pendant allyl group.[11]




Yields of the *N*-allylureas were generally 70 - 100% (Scheme II-2). The reaction of *N*-Boc-*N*-allylamine was a notable exception likely due to its lower nucleophilicity compared to other allylic amines. Use of NaH as base and a prolonged reaction time (3 days) was necessary to obtain a modest 14% yield of **II-2h**.

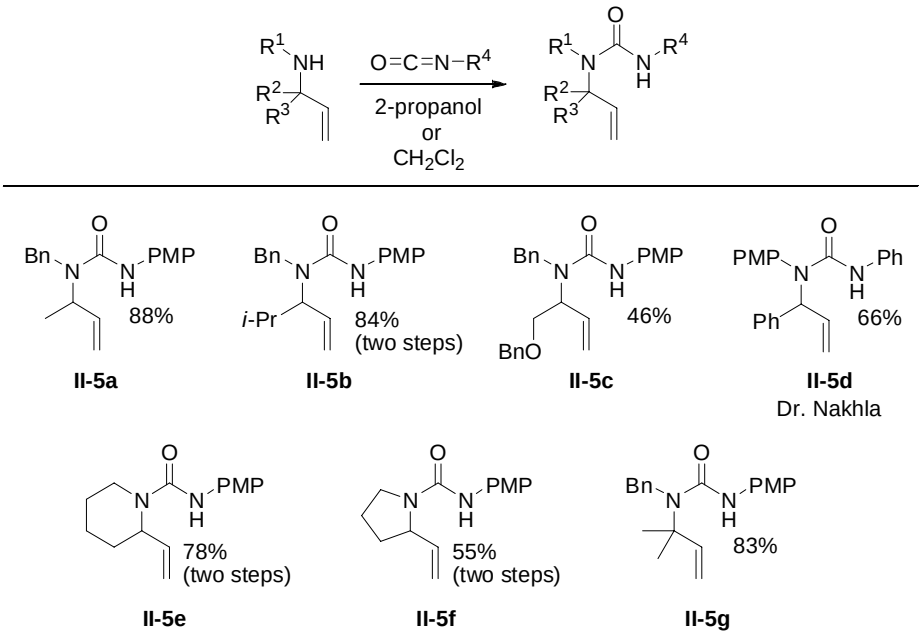
**Scheme II-2.** Synthesis of *N*-Allylureas




*N*-allylureas containing an allylic substituent or containing disubstituted alkenes could also be obtained in generally good yield (Schemes II-3 and II-4). **II-5c** required multiple methods of purification (column chromatography, acid-base extraction and recrystallization) to achieve an acceptable level of purity which resulted in a lower yield

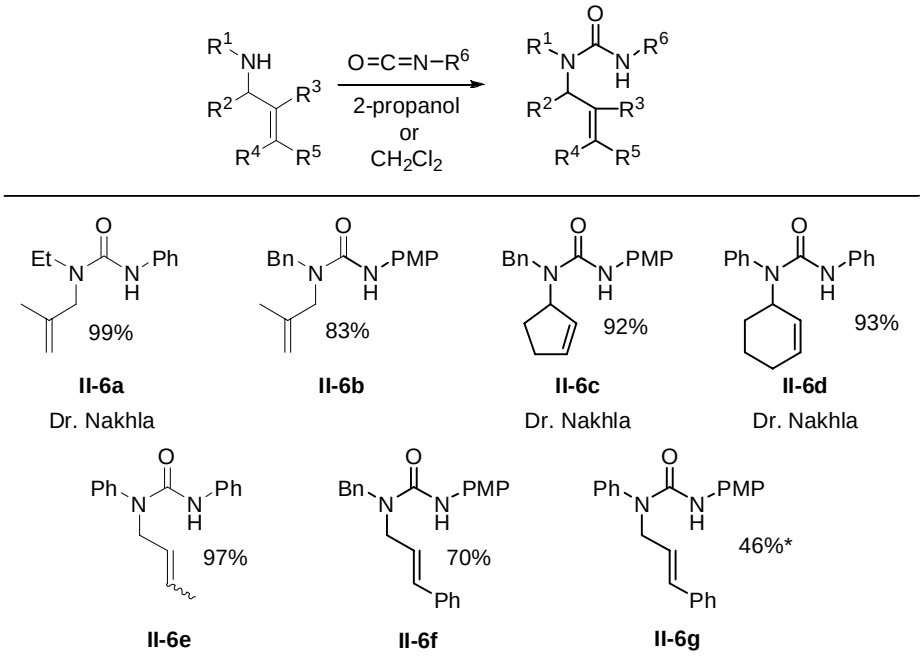
of the product. **II-6d** (Scheme II-4) also suffered a low yield likely because of purification issues. **II-5e** and **II-5f** (Scheme II-3) were generated in a two step sequence from the *N*-Boc-protected allylic amine via TFA deprotection and addition of the isocyanate to the crude allylic amine.

**Scheme II-3.** Synthesis of Allylically Substituted *N*-Allylureas




**II-5a** **II-5b** **II-5c** **II-5d** Dr. Nakhla **II-5e** **II-5f** **II-5g**

**Scheme II-4.** Synthesis of *N*-Allylureas Containing Disubstituted Alkenes



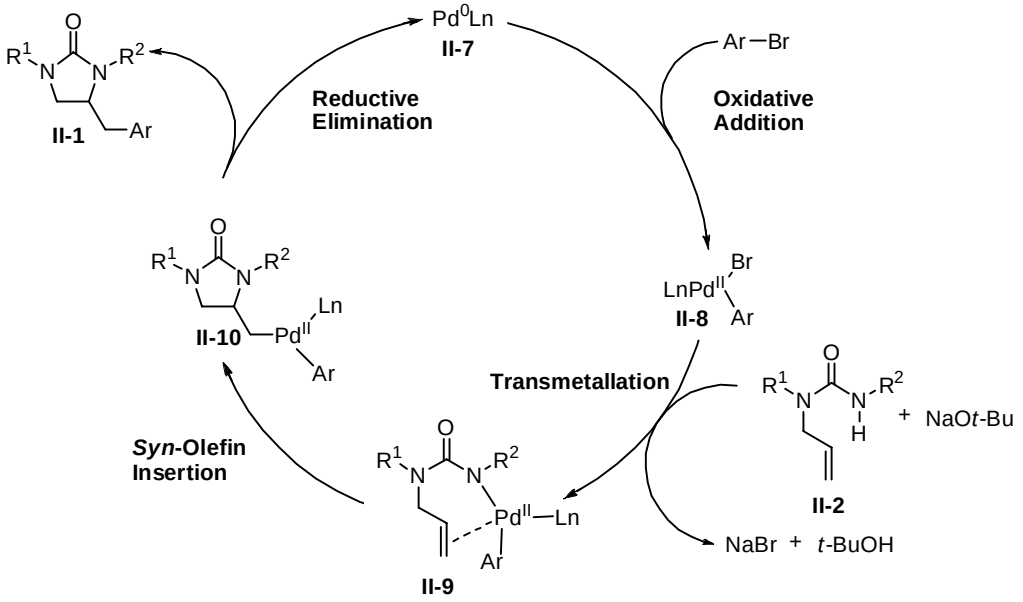

**II-6a** Dr. Nakhla **II-6b** **II-6c** Dr. Nakhla **II-6d** Dr. Nakhla **II-6e** **II-6f** **II-6g**

*Contains solvent and aromatic impurities

**Mechanism, Optimization, and Origin of Side Products**

The proposed catalytic cycle for the Pd-catalyzed carboamination (Scheme II-5) of *N*-allylureas is analogous to that of γ-(*N*-Boc-amino) alkenes for the formation of pyrrolidines. Oxidative addition of a Pd(0) catalyst **II-7** into an aryl halide generates a Pd(II) complex **II-8**. This reacts with the *N*-allylurea **II-2** and base to form **II-9**. *Syn*-insertion of the olefin into the Pd-N bond gives **II-10**. Finally, C-C bond forming reductive elimination gives the imidazolidin-2-one **II-1** and regenerates the catalyst.

**Scheme II-5.** Proposed Catalytic Cycle

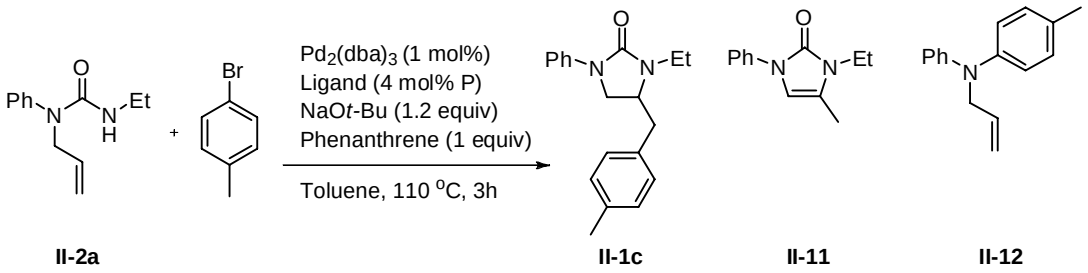



Initial studies were performed on 1,1-diallyl-3-ethylurea **II-2j** using conditions which had been previously shown in the Wolfe lab to be effective in Pd-catalyzed carboaminations to form heterocycles: Pd-catalyst, phosphine ligand, NaO*t*-Bu, and toluene. However, this substrate frequently gave complex mixtures of products including isomerization of the olefin.

Use of 1-allyl-3-ethyl-1-phenylurea **II-2a** greatly improved selectivity in these reactions. Previous experience in the Wolfe group suggested that the outcome of carboaminations is largely dependent on the nature of the phosphine ligand.[12] Thus, a series of phosphine ligands were screened to determine which one would give the highest selectivity and yield (Table II-1). Reaction of 1-allyl-3-ethyl-1-phenylurea **II-2a** with 4-bromotoluene, $Pd_2(dba)_3$, phosphine ligand, and NaO*t*-Bu, in toluene using phenanthrene as an internal NMR standard gave a mixture of three products including the desired

carboamination product **II-1a**, a formal oxidative amination product **II-11**,[13] and a diaryl allylamine **II-12**.

**Table II-1.** Optimization of Phosphine Ligand




**II-2a** **II-1c** **II-11** **II-12**

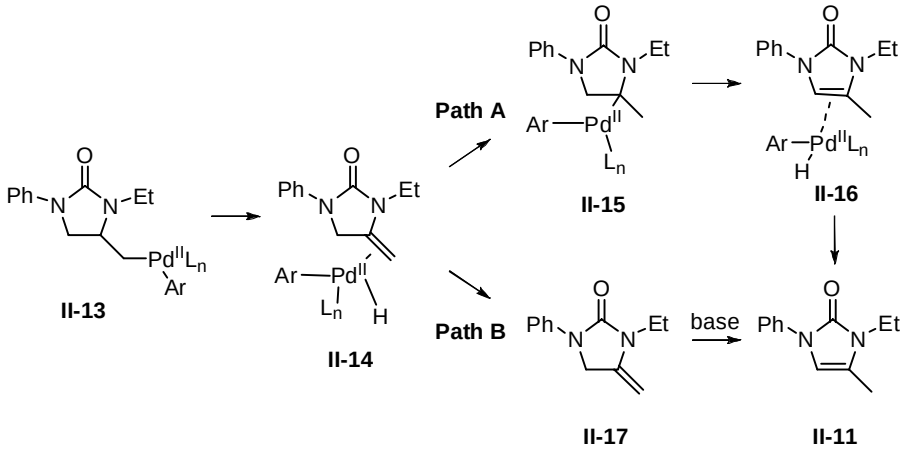
| | | % NMR Yield | | | |
|---|---|---|---|---|---|
| **Entry** | **Ligand** | **II-1c** | **II-11** | **II-12** | **Bite Angle ($\beta_n$)** |
| 1 | P(*o*-tol)$_3$ | 22 | 4 | 8 | — |
| 2 | dppb | 24 | 22 | 4 | 98 |
| 3 | dppe | 24 | 12 | 8 | 85 |
| 4 | dppf | 30 | 0 | 10 | 99 |
| 5 | DPEphos | 42 | 0 | 7 | 103 |
| 6 | Xantphos | 50 | 0 | 4 | 111 |

While all the ligands shown in Table II-1 gave **II-1c** as the major product, the more rigid phosphine ligands dppf, DPEphos and Xantphos gave the best selectivity for **II-1c** with respect to the other products. Of these three, Xantphos gave the highest yield of the desired product and was used for studies exploring the scope of Pd-catalyzed carboamination of *N*-allylureas. The yield of the desired carboamination product is roughly proportional to the natural bite angle of the phosphine ligand.[14] The use of chelating ligands is thought to slow the rate of β-hydride elimination because an open coordination site on the Pd is necessary for β-hydride elimination to occur.[15] Interestingly, Xantphos is also a choice ligand of *N*-arylations of ureas,[16] amides,[17] and oxazolidinones.[18]

The oxidative amination byproduct **II-11** can be formed from the following sequence shown in Scheme II-6. Beginning from the Pd-alkyl complex **II-13**, β-hydride elimination can give **II-14**. Reinsertion of the alkene into the Pd-H bond with opposite regiochemistry gives **II-15** (Path A). A second β-hydride elimination to afford **II-16** followed by displacement of the alkene from Pd would give **II-11**. Alternatively, alkene

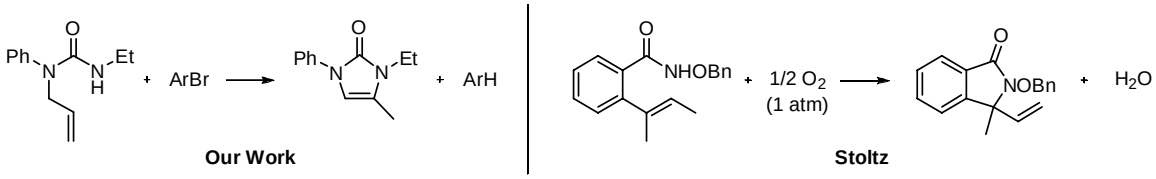
displacement can occur from the Pd in **II-14** leading to **II-17** (Path B). Base-mediated isomerization would then also form **II-11**. The catalytic cycle is then completed with C-H bond forming reductive elimination of the resulting arylpalladium hydride species to form an arene and regenerate the Pd(0) catalyst.

**Scheme II-6.** Formation of Oxidative Amination Byproduct **II-11**

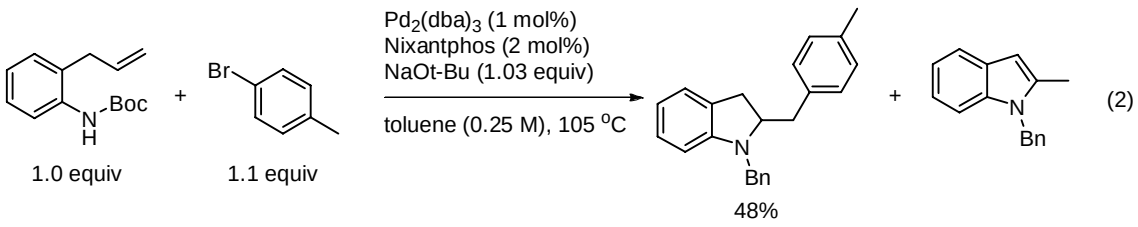



The overall transformation results in a net oxidation of the substrate and reduction of the aryl halide to an arene. This contrasts with aerobic oxidative aminations seen in the Stahl[13] and Stoltz[19] laboratories in that the oxidant, in our case, is an aryl halide instead of molecular oxygen (Scheme II-7).

**Scheme II-7.** Two Different Oxidation Methods

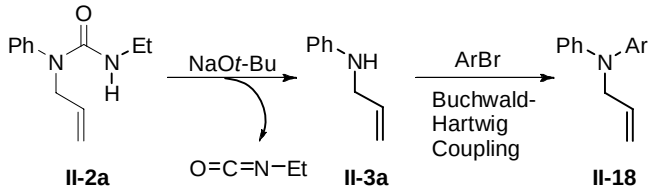



Precedent for competitive oxidative amination in a carboamination reaction was seen previously in the Wolfe group. For example, as shown in eq 2, in the reaction of *N*-benzyl-2-allylaniline with 4-bromotoluene to form an indoline, the oxidative amination product *N*-benzyl-2-methylindole was formed as a byproduct.[12a] Furthermore, as discussed in Chapter 1 oxidative amination products can even be preferentially formed over carboamination products with proper ligand choice.[12b]




Additionally, **II-2a** may also revert back to allylaniline **II-3a** and ethylisocyanate in the presence of sodium *tert*-butoxide as shown in Scheme II-8.[20] **II-3a** could then participate in a Buchwald-Hartwig coupling to generate **II-18** (**II-11** for Aryl = *p*-tolyl).

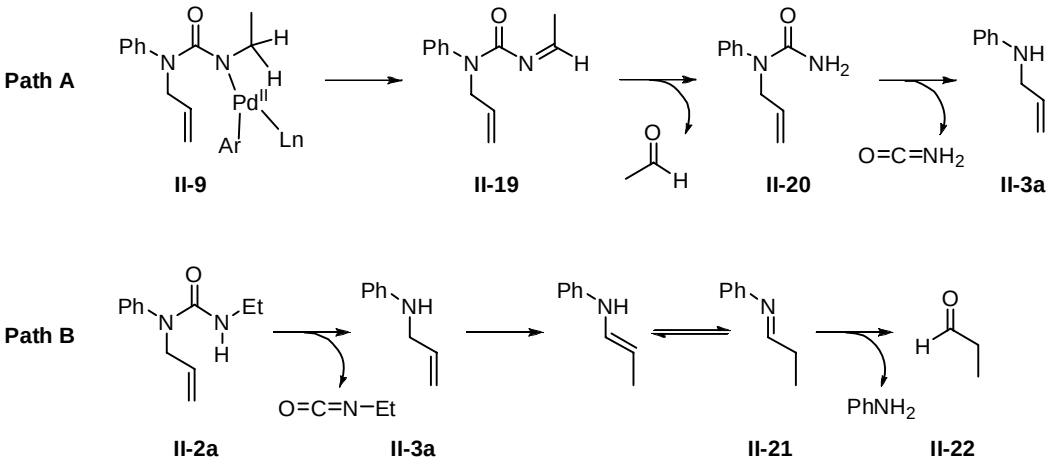
**Scheme II-8.** Formation of **II-18**



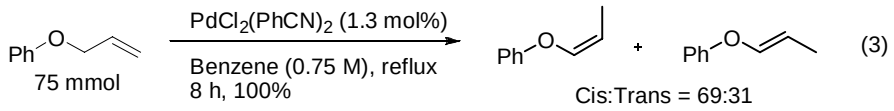

As is readily apparent from Table II-1, products **II-1c**, **II-11**, and **II-12** account for only 30-50% of the mass balance of the reaction. The remainder can be accounted for via decomposition pathways as shown in Scheme II-9. β-hydride elimination from Pd-amido complex **II-9** would generate aldimine **II-19** (Path A). Hydrolysis would then give acetaldehyde and 1-allyl-1-phenylurea **II-20**. Finally, base-mediated decomposition would yield isocyanate and *N*-allylaniline.

Alternatively, **II-2a** could first undergo base-mediated decomposition to form ethyl isocyanate and *N*-allylaniline (Path B). This could then isomerize to the imine **II-21** which upon hydrolysis could form propionaldehyde **II-22** and aniline.

**Scheme II-9.** Potential Decomposition Pathways



Pd-catalyzed isomerization of olefins has been documented in the literature. For example, Scheinmann has demonstrated that allyl phenyl ether can isomerize to *cis* and *trans* internal olefins under Pd catalysis (eq 3).[21,22,23] Isomerization of olefins by KO*t*-Bu has also been documented in the literature.[24]




(3)

The boiling points for some of the proposed decomposition products are as follows:

Acetaldehyde: 21 $^{o}$C

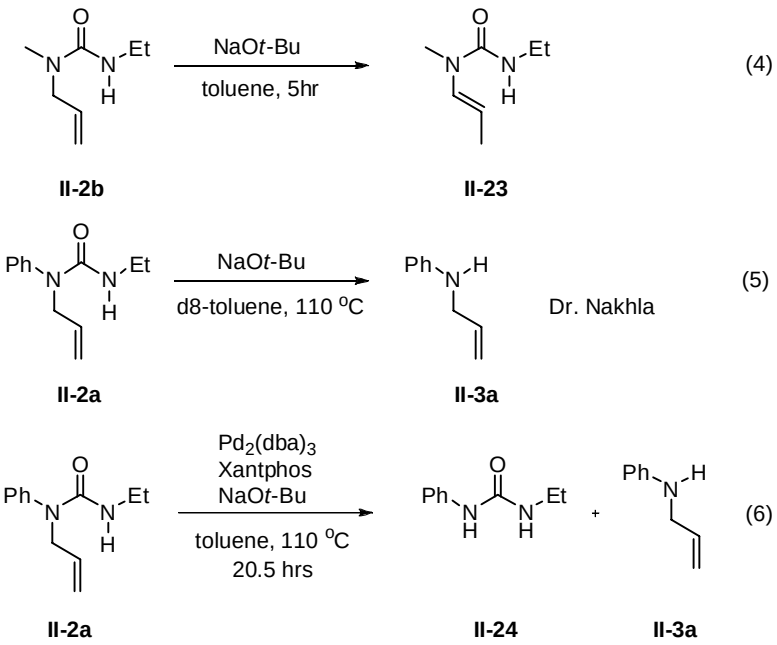
Propionaldehyde: 46-50 $^{o}$C

Aniline: 184 $^{o}$C

Ethyl Isocyanate: 60 $^{o}$C

It is likely that acetaldehyde, propionaldehyde and ethyl isocyanate will boil off under the reactions conditions. Aniline is likely present in the crude reaction mixture but might not be isolated under the column conditions used to isolated the carboamination product due to its high polarity relative to the carboamination product.

Control reactions were performed to confirm the decomposition of the substrates under the reaction conditions. Reaction of 1-allyl-3-ethyl-1-methylurea **II-2b** in the presence of NaO*t*-Bu and toluene (eq 4) resulted in the formation of the olefin isomerized product **II-23**. Similarly, when 1-allyl-3-ethyl-1-phenylurea **II-2a**, was treated with NaO*t*-Bu in an NMR tube at 110 $^{o}$C, the formation of *N*-allylaniline **II-3a** was observed (eq 5). **II-2a** was also reacted under standard Pd-catalysis conditions but in the absence of aryl halide. This reaction furnished 1-phenyl-1-ethyl urea **II-24** as well as *N*-allylaniline (eq 6). The reactions in eq 4 and eq 5 show that strong base mediates both isomerization of the double bond in *N*-allylureas as well as the decomposition of the *N*-allylureas to allylic amines. The reaction in eq 6 shows that deallylation can occur under the reaction conditions.

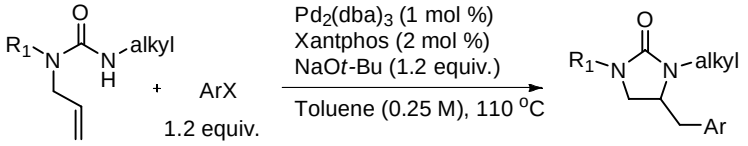


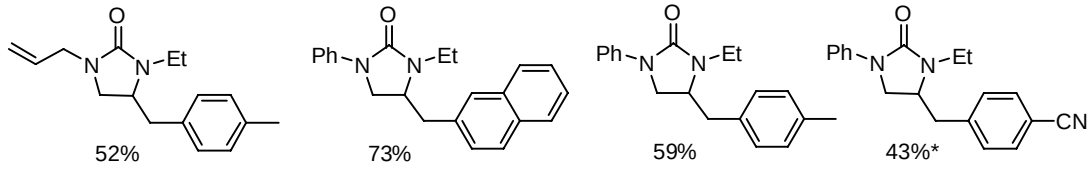

**Pd-Catalyzed Carboamination of *N*-Allylureas**

Having optimized the reaction conditions with respect to phosphine ligand we then went on to explore the scope of the Pd-catalyzed carboamination of *N*-allylureas (Scheme II-10). Gratifyingly, we found that 1-allyl-3-alkyl ureas successfully couple with a variety of aryl halides to provide access to imidazolidin-2-ones.

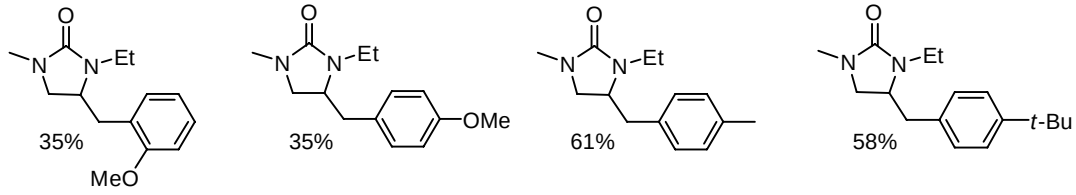
While good yields can be obtained for a variety of combinations of *N*-allylureas and aryl halides, reactions involving 2-bromoanisole and 4-bromoanisole were particularly challenging. The electron donating ability of the methoxy groups may slow down oxidative addition, C-C bond forming reductive elimination, or olefin insertion, and allow decomposition pathways to dominate.[25] Interestingly, the combination of 1-allyl-3-ethyl-1-phenyl urea **II-2a** and 4-bromobenzonitrile was expected to give a high yield for the cyclized product **II-1d** but instead gave only a modest 43% yield. A product derived from competing *N*-arylation was also isolated (~35%). This is in marked contrast to the reaction of 1-allyl-3-benzyl-1-methyl urea with the same aryl halide. The increased steric bulk of the benzyl group relative to an ethyl group may serve to slow the rate of *N*-arylation.

**Scheme II-10.** Synthesis of 3-Alkyl-4-Benzyl Imidazolidin-2-ones

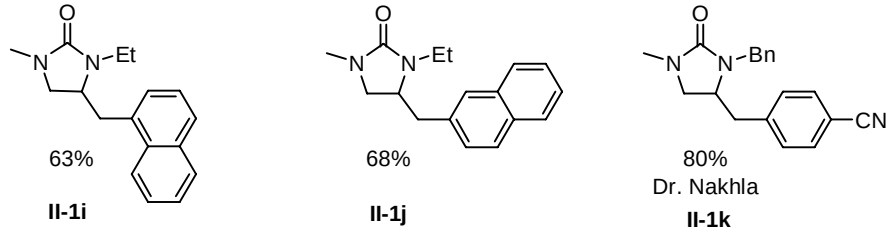



**II-1a** **II-1b** **II-1c** **II-1d**




**II-1e** **II-1f** **II-1g** **II-1h**

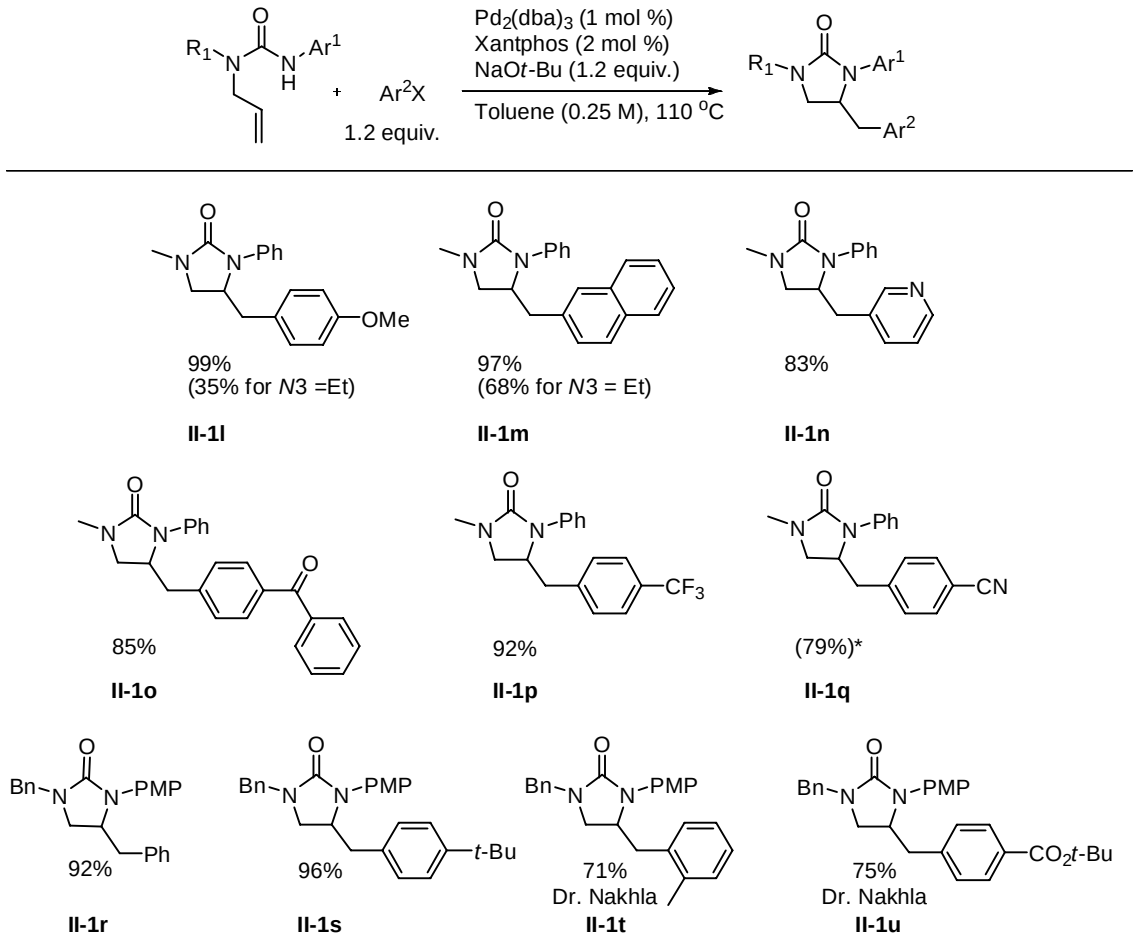



**II-1i** **II-1j** **II-1k**

*Contains 20% starting material and other impurities

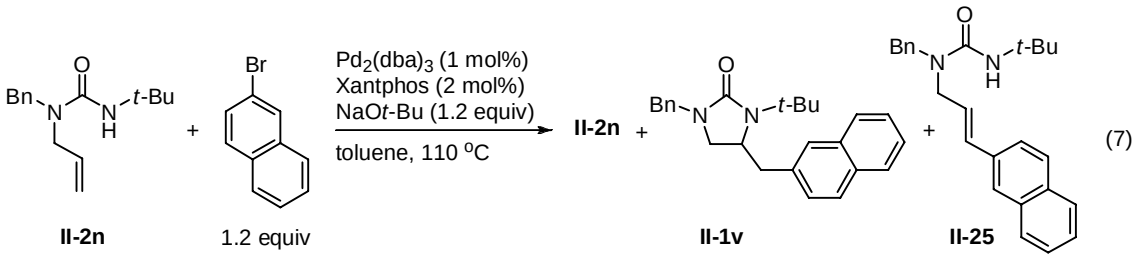
In contrast to substrates having alkyl groups on the cyclizing nitrogen, those with aryl groups on the cyclizing nitrogen uniformly give excellent yields irrespective of the aryl halide used (Scheme II-11). For example, replacement of Ph for Et on the cyclizing nitrogen as shown for **II-1l** gave a 64% increase in yield for 4-bromoanisole. Likewise, with 2-bromonaphthalene, a 29% increase in yield was seen **II-1m**. This increase in yield could be explained by the lack of a β-hydrogen for substrates having an aryl group on the cyclizing nitrogen. Thus the decomposition pathway in Scheme II-9 involving β-hydride elimination from the Pd-amido intermediate could not be accessed.

**Scheme II-11.** 3-Aryl-4-Benzyl Imidazolidin-2-ones



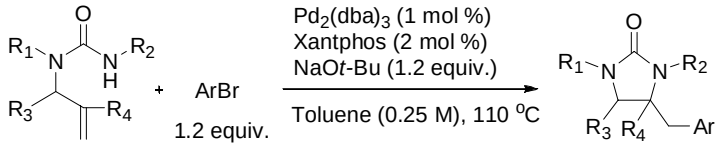

*Contains 20% aliphatic impurities

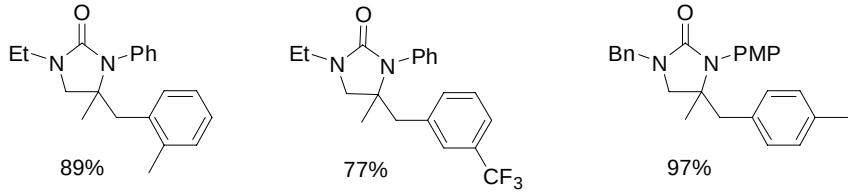
In an attempt to gain more insight into the origin of higher yields obtained with *N*3-phenyl ureas, the sterically bulky 1-allyl-1-benzyl-3-*tert*-butylurea **II-2n** was synthesized. This substrate would have a *t*-Bu group on the cyclizing nitrogen. Thus, if the yield of cyclization was high for this substrate it would lend credence to the hypothesis that β-hydride elimination is responsible for the lower yields seen for *N*3 alkyl ureas. Unfortunately, when this substrate was subjected to Pd catalysis the reaction proceeded to only 85% conversion after 20 h, and a byproduct **II-25** resulting from Heck arylation of the olefin was observed in addition to the desired carboamination product **II-1v** (eq 7). This seems to indicate that the steric hindrance of the *t*-Bu group on the cyclizing nitrogen slows the rate of carboamination considerably. As such, the increased yields observed with *N*3-phenyl substrates are presumably due to electronic effects.



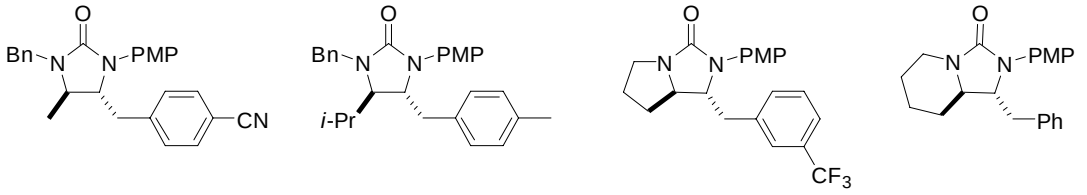

Having demonstrated the carboamination of simple *N*-allylureas we then sought to explore the effect of substitution on the allyl backbone (Scheme II-12). We were pleased to find that 1,1-disubstituted olefins cleanly gave the 4,4-disubstituted imididazolidin-2-ones, which have a quaternary carbon, in high yield. 4,5-disubstituted imidazolidin-2-ones were also generated in high yield from the corresponding allylically substituted *N*-allylureas. Notably, formation of these 4,5-disubstituted imidazolidin-2-ones was complete in an hour. Modest to excellent diastereoselectivity was achieved. As the group at the allylic position increased in size from Me to *i*-Pr the diastereoselectivity correspondingly increased (compare **II-26d** to **II-26e**).

**Scheme II-12.** 4,4- and 4,5-Disubstituted Imidazolidin-2-ones




**II-26a** **II-26b** **II-26c**




88%, 12:1(8:1) dr[a] **II-26d**

83%, >20:1 (>20:1) dr **II-26e**

87%, >20:1 (>20:1) dr **II-26f**

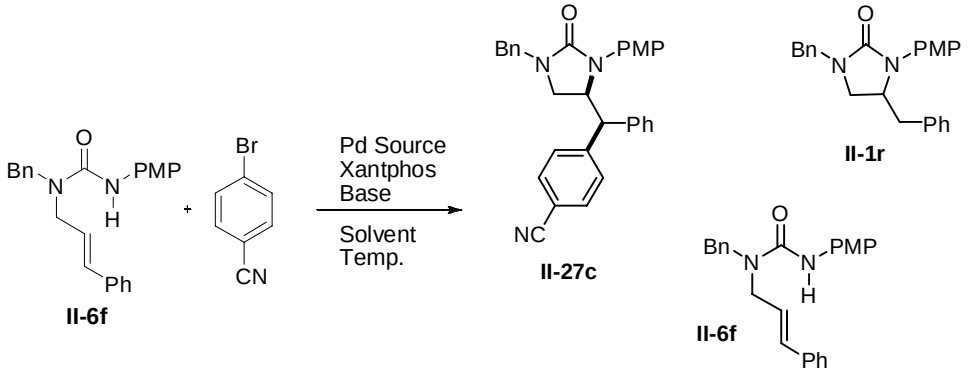
78%, 20:1 (11:1) dr **II-26g**

[a]Diastereomeric ratios are for isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures.

Reactions of substrates that had substitution at the terminal position of the olefin proved to be more challenging (Table II-2). The reaction of (*E*)-1-benzyl-1-cinnamyl-3-

(4-methoxyphenyl)urea **II-6f** with 4-bromobenzonitrile under the standard reaction conditions only afforded 11% of the desired cyclic urea **II-27c** due to competing hydroamination **II-1r**. However, previous work in the group led us believe that a weaker base, $Cs_2CO_3$, might also enable Pd-catalyzed carboamination.[26] Indeed, with the use of $Cs_2CO_3$, a competing base-mediated hydroamination pathway was completely shut down, and the desired carboamination product **II-27c** was formed in moderate yield. However, a 32% yield of **II-6f**, arising from a Heck reaction, was also generated. Further increases in yield of **II-27c** were realized by employing $Pd(OAc)_2$ and dioxane as the Pd source and solvent respectively.

**Table II-2.** Optimization of Reactions with Internal Olefins

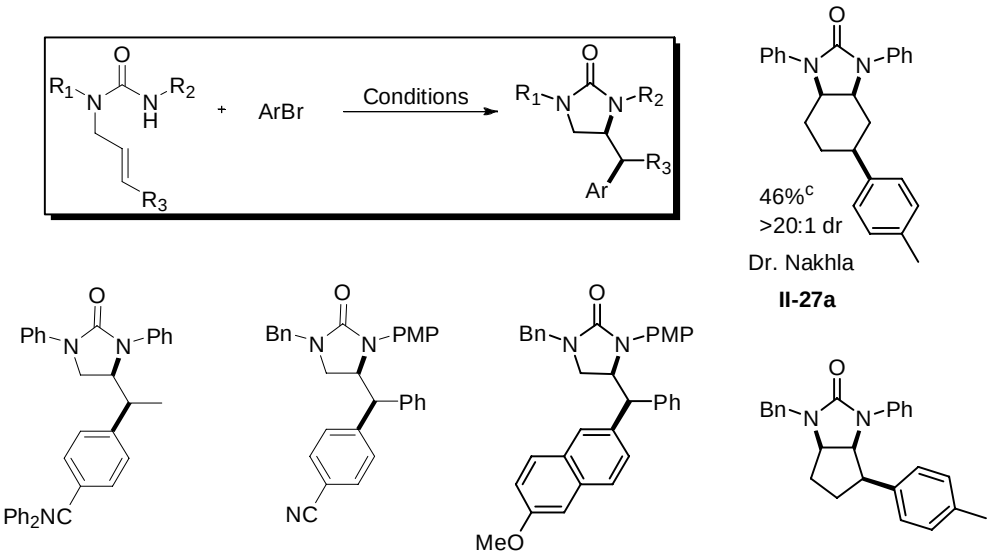



| | | | | Yield | | |
|---|---|---|---|---|---|---|
| **Pd Source** | **Base** | **Solvent** | **Temp.** | **II-27c** | **II-1r** | **II-6f** |
| $Pd_2(dba)_3$ | NaO*t*-Bu | Toluene | 110 °C | 11% | 70% | |
| $Pd_2(dba)_3$ | $Cs_2CO_3$ | Toluene | 110 °C | 59% | | 32% |
| $Pd_2(dba)_3$ | $Cs_2CO_3$ | Dioxane | 100 °C | 65% | | |
| $Pd(OAc)_2$ | $Cs_2CO_3$ | Dioxane | 100 °C | 76% | | |

Several imidazolidin-2-ones were prepared from internal olefin containing *N*-allylureas (Scheme II-13). Yields were moderate to good and in all cases the products were obtained as a single diastereomer. For the products in Scheme II-13, the diastereoselectivity stems from the *syn*-insertion of the olefin into the Pd-N bond. Both the electron-donating 2-bromo-6-methoxynaphthalene and the electron-withdrawing 4-bromobenzonitrile were tolerated as coupling partners. For some reactions, NaOt-Bu was an acceptable base for affording carboamination products. (**II-27a**, **II-27b**, **II-27e**) A

crystal structure of **II-27b** was obtained by Dr. Nakhla and Dr. Jeff Kampf. This confirmed the relative stereochemistry of the two stereocenters.

**Scheme II-13.** Imidazolidin-2-ones Derived from Internal Olefins



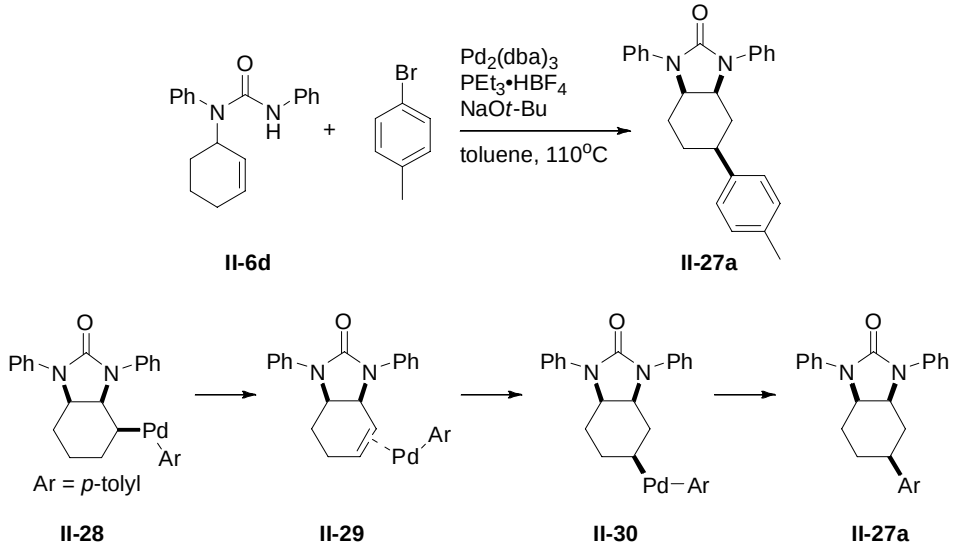

Conditions (a) $Pd_2(dba)_3$ (1 mol%), Xantphos (2 mol%), NaO*t*-Bu (1.2equiv), ArBr (1.2 equiv), Toluene (0.25 M), 110 $^oC$

Conditions (b) $Pd(OAc)_2$ (2 mol%), Xantphos (2 mol%), $Cs_2CO_3$ (1.2 equiv), Ar Br (1.2 equiv), Dioxane (0.25 M), 100 $^oC$

Conditions (c) Same as Conditions A but with $PEt_3$•$HBF_4$ (4 mol%) used instead of Xantphos

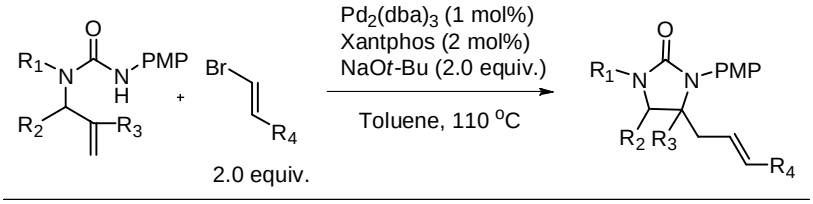
As shown in Scheme II-14, attempted carboamination of **II-6d** under the standard reaction conditions was unsuccessful. Fortunately, carboamination was achieved using $PEt_3$•$HBF_4$ as the phosphine ligand. However, the bicyclic product obtained **II-27a** was a regioisomer of the expected carboamination product. This regioisomer is thought to have arisen from intermediate **II-28**. β-hydride elimination of **II-28** would give **II-29** and subsequent reinsertion of the olefin into the Pd-H bond would afford Pd-alkyl **II-30**. Finally C-C bond forming reductive elimination would form the regioisomer **II-27a**.[12b]

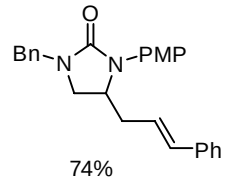
**Scheme II-14.** Formation of Regioisomer **II-27a**



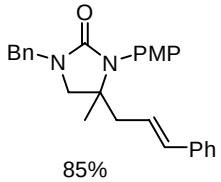

As shown in Scheme II-15, alkenyl halides can couple with a diverse set of *N*-allylureas to afford 4-monosubstituted, 4,4-disubstituted, and 4,5-disubstituted imidazolidin-2-ones in good to excellent yield similar to couplings with aryl bromides. Likewise, the stereoselectivity seen in the formation of **II-31c** is similar to that observed with an aryl bromide (7:1 vs. 8:1). In contrast, bicyclic imidazolildin-2-one **II-31d** was obtained as a 1.5:1 ratio of diastereomers compared to a 11:1 ratio of diastereomers seen when coupling with an aryl bromide.

**Scheme II-15.** Synthesis of 4-Allyl Imidazolidin-2-ones

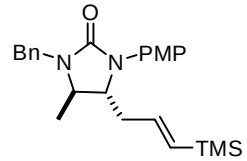


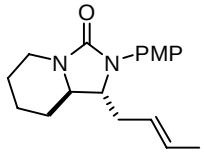
74%
[71-96% for ArBr]
**II-31a**



85%
[97% for ArBr]
**II-31b**



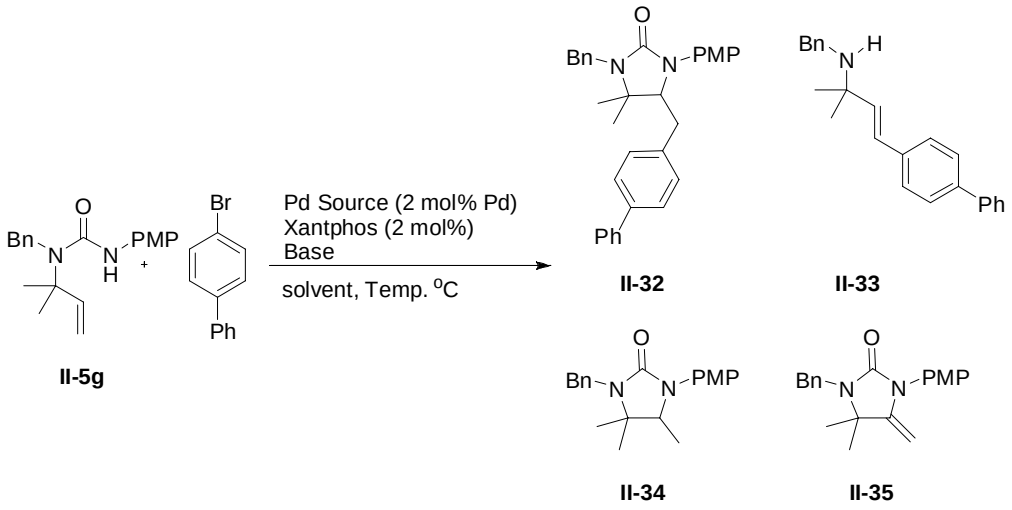
91%, 10:1 (7:1) dr
[88% (8:1) dr for ArBr]
**II-31c**



87%, 1.6:1 (1.5:1) dr
[78% (11:1) dr for ArBr]
**II-31d**

An illustrative example of attempted optimization of a challenging substrate is that of **II-5g** bearing two methyl groups in the allylic position (Table II-3). With the use of a strong base, NaO*t*-Bu, both the desired carboamination product **II-32** and hydroamination **II-34** were isolated. Upon switching to a weaker base, $Cs_2CO_3$, the hydroamination byproduct was no longer produced. However, Heck and oxidative amination byproducts (**II-33** and **II-35**) were then observed by crude NMR.

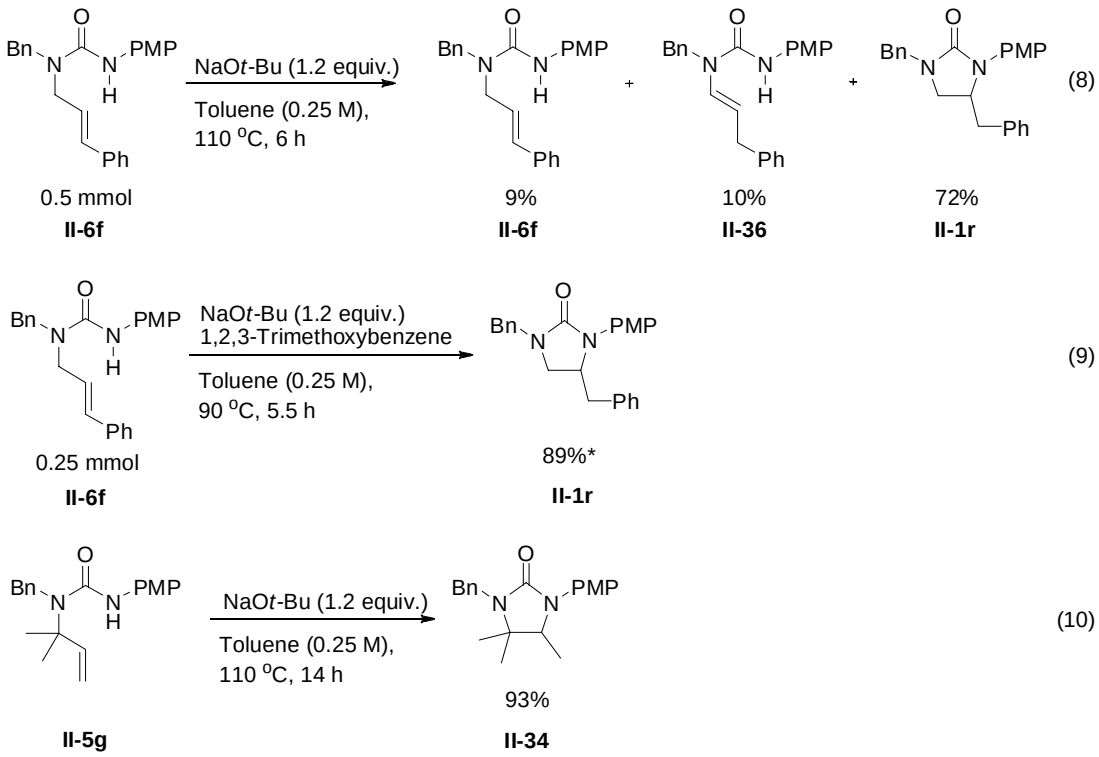
**Table II-3.** Synthesis of a 4,4,5-Trisubstituted Imidazolidin-2-one




| Scale (mmol) | Pd Source | Base | Base (equiv) | Solvent | Temp. | Time (h) | Ratios** II-32 | II-33 | II-34 | II-35 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.5 | $Pd_2(dba)_3$ | NaO*t*-Bu | 1.2 | toluene | 110 | 4.3 | 27* | N/A | 46* | N/A |
| 0.25 | $Pd(OAc)_2$ | $Cs_2CO_3$ | 1.2 | dioxane | 100 | 18.5 | 1.00 | 2.00 | 0 | 0.39 |
| 0.25 | $Pd(OAc)_2$ | $Cs_2CO_3$ | 2.4 | dioxane | 100 | 18.5 | 1.00 | 2.04 | 0 | 0.81 |

* = Isolated Yield ** = Relative Crude NMR ratios

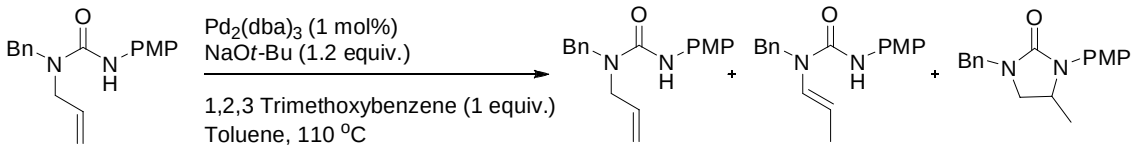
Several control reactions were performed which shed some light onto the origin of hydroamination byproducts (eqs 8-10). Taken together they provide convincing evidence that the formation of hydroamination products may be base-mediated. For instance, the reaction of **II-6f** with NaO*t*-Bu provided hydroamination product **II-1r** in 72% yield along with unreacted **II-6f** and alkene isomer **II-36** (eq 8). Curiously, the same reaction performed at 90 °C gave only hydroamination product **II-1r** in 89% yield. Lowering the temperature may have slowed the rate of olefin isomerization relative to hydroamination but it is unclear why unreacted **II-6f** is present in eq 8 but not in eq 9. Reaction of **II-5g** with NaO*t*-Bu efficiently afforded the hydroamination product **II-34** as well (eq 10). While the discrepancy in product distribution between eq 8 and eq 9 is perplexing it is apparent that base-mediated hydroamination can be a facile process for *N*-allylureas that have substitution along the allyl backbone.




*Contains 20% aliphatic impurities

Control reactions of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea **II-2e** were performed to determine the relative contribution of $Pd_2(dba)_3$ and NaO*t*-Bu toward decomposition and formation of byproducts (Table II-4). Reaction of **II-2e** with $Pd_2(dba)_3$ and NaO*t*-Bu resulted in complete consumption of **II-2e** and formation of approximately equal amounts of olefin isomerization product **II-37** and hydroamination product **II-38**. In contrast, the reaction of **II-2e** with just $Pd_2(dba)_3$ resulted in almost complete recovery of the **II-2e**. The reaction of **II-2e** with just NaO*t*-Bu gave **II-37** in 48% yield and **II-38** in 19% yield. These results suggest that, in the absence of ligand, base plays a larger role in the transformation of **II-2e** to olefin isomerization byproduct **II-37** and hydroamination byproduct **II-38** than $Pd_2(dba)_3$. It would be informative to perform the Pd reactions shown in Table II-4 with phosphine ligand present to ascertain whether ligands modulate the ability of the Pd center to catalyze the transformation of **II-2e** to **II-37** and **II-38** or to aid in substrate decomposition.

**Table II-4.** Control Reactions: Olefin Isomerization and Hydroamination

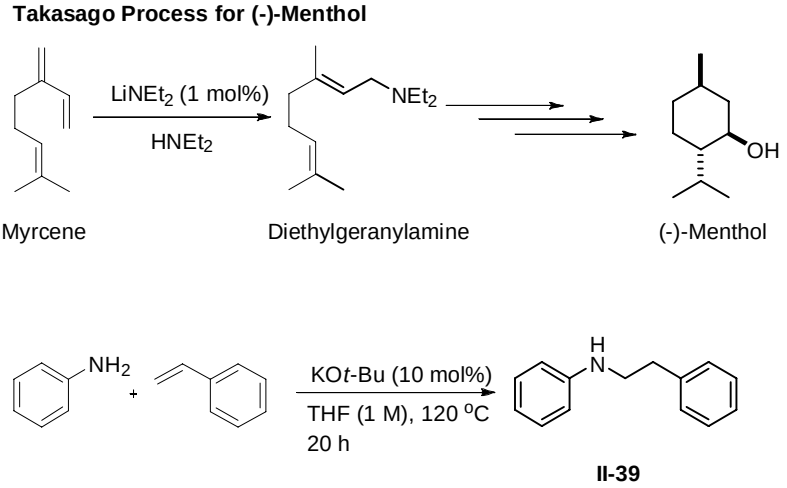



0.5 mmol **II-2e** | SM **II-2e** | Isomerized SM **II-37** | Hydroamination **II-38**

| $Pd_2(dba)_3$ (mol %) | NaO*t*-Bu (equiv.) | Time (h) | NMR Yield II-2e | II-37 | II-38 |
|---|---|---|---|---|---|
| 1 | 1.2 | 23 | 0 | 17 | 20 |
| 1 | 0 | 16 | 83 | 0 | 0 |
| 0 | 1.2 | 16 | 14 | 48 | 19 |

There are many examples of both metal[27] and base[28]-catalyzed hydroamination in the literature. Interestingly, though an undesired transformation in our reactions, hydroamination is a highly attractive means of making amine containing products as it offers theoretically 100% atom efficiency.[28] Base-catalyzed hydroamination initially involves the deprotonation of amines to from metal amides. Strong bases, alkali metals, alkali earth metals or lanthanides are typically employed to accomplish this transformation. These more nucleophilic amides can then add into olefins. Two examples of base-catalyzed hydroamination are shown in Scheme II-16. For instance, hydroamination of myrcene with diethylamine to form diethylgeranylamine is one step in the Takasago process which is used to make (-)-menthol on an industrial scale. *tert*-Butoxide bases can also be effective in catalyzing hydroamination. For example, Beller and coworkers demonstrated the hydroamination of styrene with aniline using KO*t*-Bu as the base to afford **II-39**.[29]

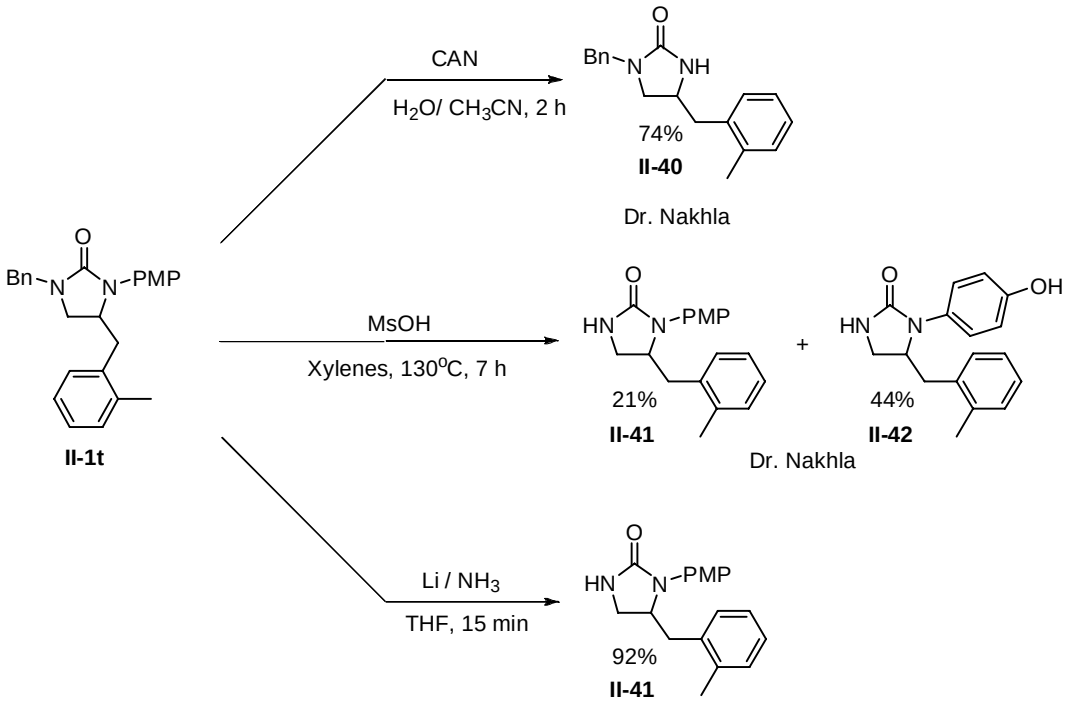
**Scheme II-16.** Examples of Base-catalyzed Hydroamination




## Orthogonal Deprotection

The utility of Pd-catalyzed carboamination of N-allylureas could be further extended if orthogonally deprotectable groups could be employed on *N*1 and *N*3 of the urea. Orthogonally deprotectable groups on *N*1 and *N*3 of the imidazolidin-2-one would allow the selective functionalization of either nitrogen. As shown in Scheme II-17, CAN (ammonium cerium(IV) nitrate) selectively cleaves the *p*-methoxyphenyl group of **II-1t** in the presence of the benzyl group to provide **II-40** in 74% yield.[30] Unfortunately, attempted selective deprotection of the benzyl group of **II-1t** using methanesulfonic acid[30] gave a poor yield (21%) of the desired product **II-41** and a byproduct **II-42** resulting from demethylation of **II-41**. However, $Li/NH_3$ reduction selectively and cleanly removed the benzyl group of **II-1t** to afford **II-41** in 92% yield. Birch reduction was prevented by quenching with diphenyl ether.[31]

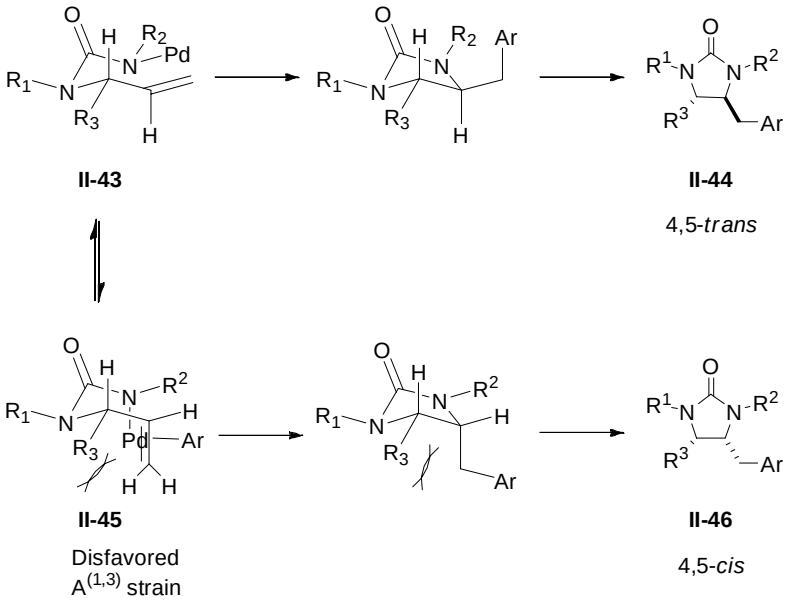
**Scheme II-17.** Orthogonal Deprotection of Imidazolidin-2-ones




**Stereochemical Considerations**

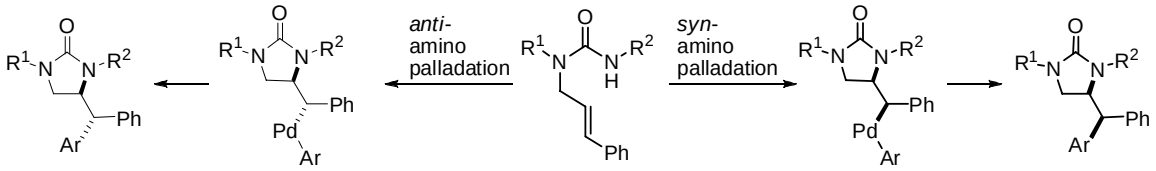
The diastereoselectivity seen in the formation of 4,5-disubstituted imidazolidinones[32,33] is a consequence of allylic strain present in the stereochemical determining step of the reaction. As shown in Scheme II-18, there are two possible conformations for the insertion of the olefin into the Pd-N bond **(II-43 and II-45)**.[34] $A^{(1,3)}$ strain between the allylic substituent and the terminal hydrogen will disfavor **II-45**, which would lead to the *cis* product **II-46**. A larger substituent in the allylic position results in greater $A^{(1,3)}$ strain and higher diastereoselectivity.[35] This explains why the substrate with the isopropyl group at the allylic position in Scheme II-12 gives >20:1 diastereoselectivity but the substrate with an allylic methyl group gives only 8:1 diastereoselectivity.

**Scheme II-18.** Rationale for Observed 4,5-Stereochemistry



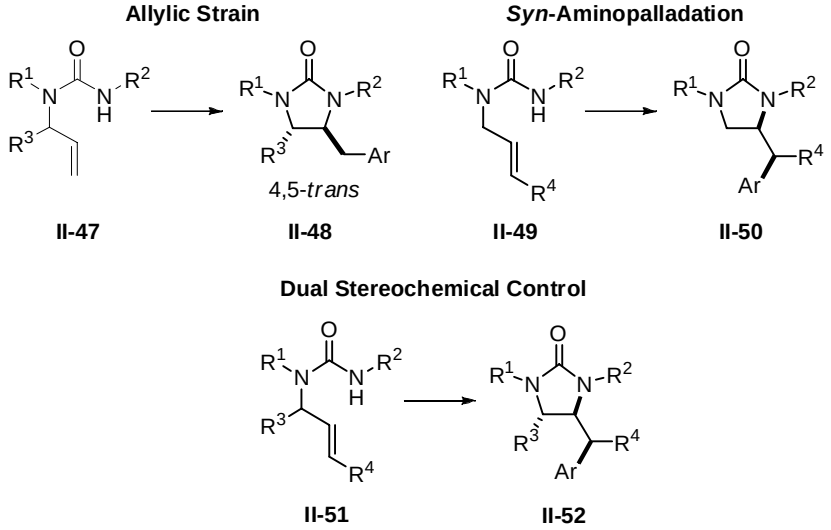

In contrast, the stereoselectivity observed in reaction of internal olefins was due to the stereoselective addition of Pd and N across the double bond. Addition of the Pd and N across an olefin (aminopalladation) can occur in either an *anti* or *syn* fashion (Scheme II-19). Under our reaction conditions only *syn*-aminopalladation is observed due to coordination of the Pd to the N prior to stereodetermining insertion of the olefin into the Pd-N bond.[36]

**Scheme II-19.** *Syn*- vs. *Anti*-aminopalladation of *N*-allylureas



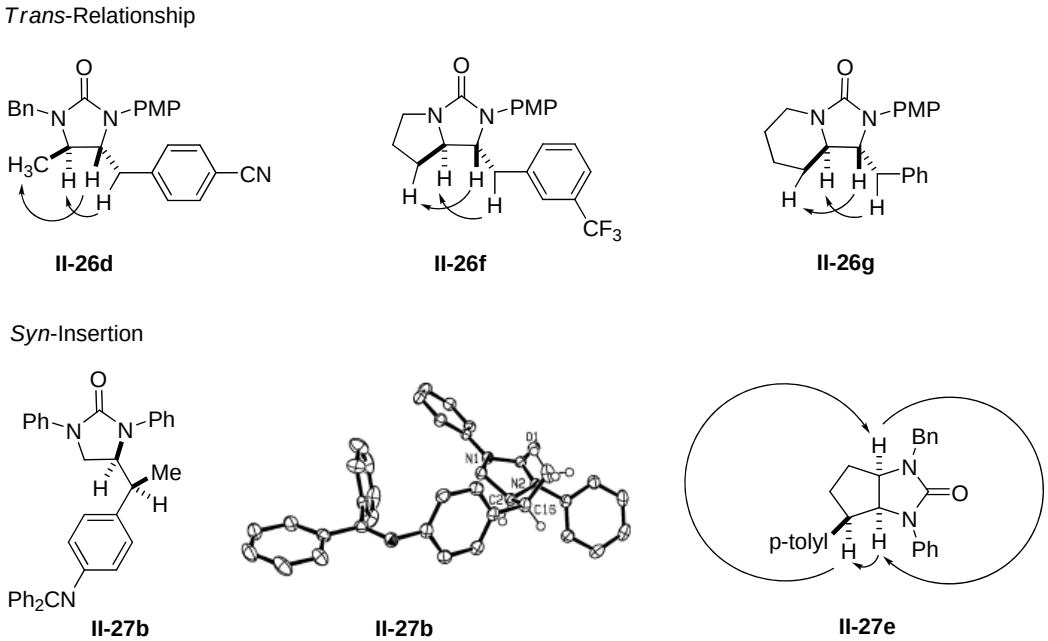

Thus, in our methodology two different modes of stereoselection are observed, as shown in Scheme II-20. The relative stereochemistry between C4 and C5 is determined by allylic strain (**II-47→II-48**) whereas the 4,1'-stereochemistry arises from *syn*-aminopalladation (**II-49→II-50**). As an interesting consequence, a substrate with both an allylic substituent and an internal olefin could potentially lead to a product in which three stereocenters are set simultaneously and stereospecifically (**II-51→II-52**).

**Scheme II-20.** Two Modes of Stereoselection




Stereochemical assignments were made based on nOe analysis and X-ray crystallography (Figure II-1). As shown in structures **II-26d**, **II-26f**, and **II-26g** nOes between hydrogens that were on the imidazolidin-2-one ring and hydrogens that were on carbons adjacent to the ring were used to confirm the *trans*-stereochemistry. *Syn*-aminopalladation onto the olefin was confirmed by X-ray crystallography of **II-27b** and nOe data **II-27e**.

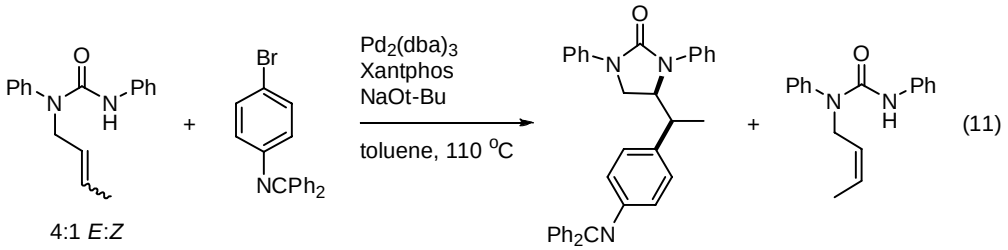
**Figure II-1.** Methods of Stereochemical Determination



**Conclusion and Future Directions**

In summary, *N*-allylureas make excellent substrates for Pd-catalyzed carboamination to form imidazolidin-2-ones. In addition to 4-substituted imidazolidin-2-ones, 4,4 and 4,5-disubstituted imidazolidin-2-ones, imidazolidin-2-ones from internal olefins and 4-allyl imidazolidin-2-ones can be generated. Diastereoselectivity is often high and results from allylic strain or stereoselective *syn*-insertion of the olefin into the Pd-N bond. Byproducts include oxidative amination, hydroamination, olefin isomerization and *N*-arylation: all well documented in the literature. Remaining mass balance is accounted for based on proposed decomposition pathways.

There are several experiments that would provide a deeper understanding of this transformation and would expand its scope. For instance, a comparison of the rate of carboamination of substrates which vary only in the configuration of the alkene double bond (*Z* vs. *E)* may give useful information about the transition state for the insertion of the olefin into the Pd-N bond. In a preliminary result, reaction of **II-6e** containing a 4:1 mixture of *E*:*Z* isomers gave a 50% yield of **II-27b** in greater >20:1 dr and unreacted (*Z*)-isomer was seen in the crude mixture (eq 11 and Scheme II-13). This implies that the rate of carboamination of (*E*)-alkenes is greater than that of the analogous (*Z*)-alkenes for *N*-allylureas.[26]




4:1 *E*:*Z*

**II-6e**

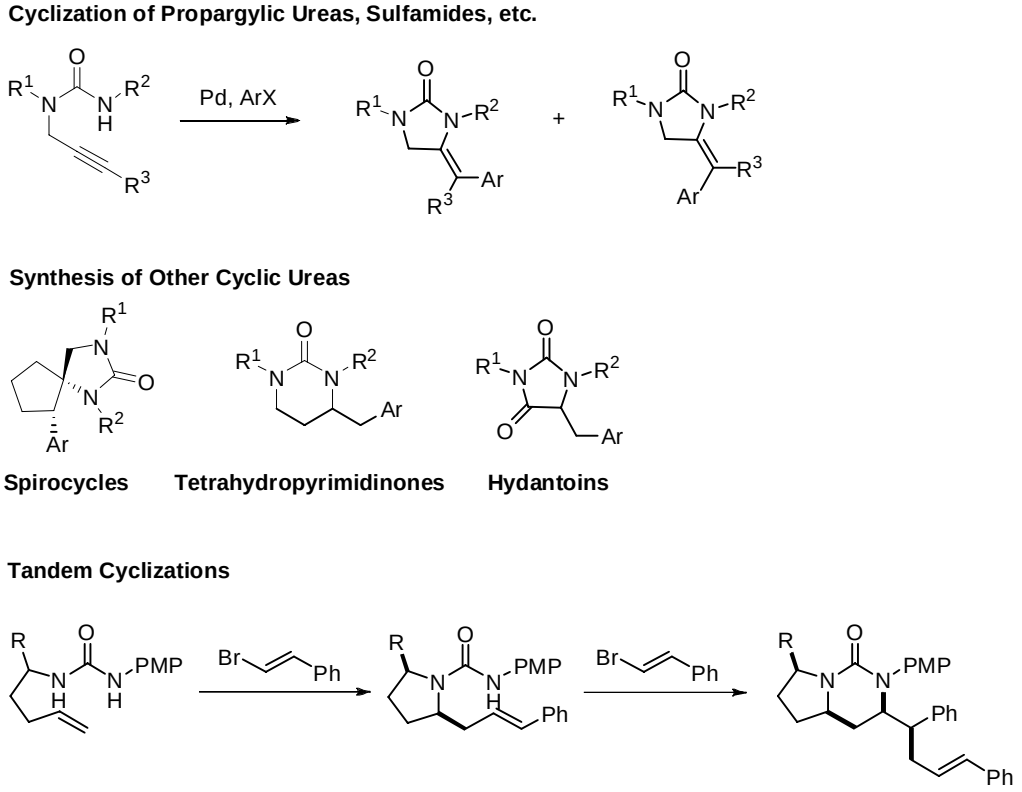
50%, >20:1 dr

**II-27b**

(11)

It would also be interesting to explore the carboamination of *N*-propargyl ureas: whether (*E*)- or (*Z*)-olefins can be preferentially formed by variation of phosphine ligand (Scheme II-21).[37] Other interesting products that could be formed from alkene-containing urea substrates include spirocycles, tetrahydropyrimidinones, and hydantoins. Lastly, it would be interesting to pursue a tandem reaction which would incorporate two vinyl halide coupling partners.

**Scheme II-21.** Future Directions




Having successfully demonstrated the racemic carboamination of *N*-allylureas we then sought to develop an enantioselective version of the same transformation using chiral ligands and auxiliaries. As the next chapter unfolds we shall see this remains a challenging endeavor.

## Experimental Section

### General

All reagents were purchased from commercial sources and were used as obtained unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (generally Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. *N*-Ethyl-2-methylallylamine was purchased from Aldrich Chemical Co. and used without purification. Toluene, THF, dichloromethane, and ether were purified using a Glass Contour solvent purification system. The chemical shift of $CDCl_3$ ranges from 7.27–7.22 for $^1H$ spectra and 77.23–77.00 for $^{13}C$ spectra. Product regiochemistry was assigned on the basis of $^1H$ NMR 2D-

COSY and HSQC experiments. Product stereochemistry was assigned on the basis of $^1$H NMR 2D-NOESY experiments. The stereochemistry of **II-27b** was assigned on the basis of X-Ray crystallographic analysis, and the stereochemistry of **II-27c** and **II-27d** was assigned based on analogy to **II-27b**. Reaction times described below have not been minimized.

**General Procedure for the Synthesis of *N*-Allylurea Substrates.** An oven- or flame-dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with the appropriate *N*-allylamine (1.0 equiv), the appropriate isocyanate (1.0–1.4 equiv), and isopropanol or $CH_2Cl_2$ (1.0 M). The reaction was stirred at room temperature until the starting amine had been completely consumed as judged by TLC or $^1$H NMR analysis. The reaction mixture was then concentrated *in vacuo* and the crude product was purified via flash chromatography on silica gel.

**1-Allyl-3-ethyl-1-phenylurea (II-2a).** Reaction of 1.57 g (11.8 mmol) of *N*-allylaniline with 1.17 g (16.5 mmol) of ethyl isocyanate following the general procedure afforded 2.22 g (92%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, $J$ = 7.0 Hz, 2 H), 7.28 (t, $J$ = 7.0 Hz, 1 H), 7.22–7.18 (m, 2 H), 5.92–5.83 (m, 1 H), 5.08–5.01 (m, 2 H), 4.28–4.24 (m, 2 H), 4.19 (s, 1 H), 3.23–3.15 (m, 2 H), 1.00 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.0, 142.1, 134.9, 130.0, 128.7, 127.7, 117.0, 52.4, 35.7, 15.7; IR (film) 3354, 1653 cm$^{-1}$. Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.66; H, 8.02; N, 13.69.

**1-Allyl-3-ethyl-1-methylurea (II-2b).** Reaction of 2.58 g (36.3 mmol) of *N*-methylallylamine with 3.60 g (50.6 mmol) of ethyl isocyanate following the general procedure afforded 4.79 g (94%) of the title compound as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.81–5.69 (m, 1 H), 5.18–5.14, (m, 1 H), 5.14–5.08 (m, 1 H), 4.33 (s, 1 H), 3.84 (d, $J$ = 5.6 Hz, 2 H), 3.23 (q, $J$ = 7.2 Hz, 2 H), 2.83 (s, 3 H), 1.09 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.1, 133.7, 116.1, 50.9, 35.5, 33.8, 15.5; IR (film) 3343, 1629, cm$^{-1}$. MS (ESI): 143.1178 (143.1184 calcd for $C_7H_{14}N_2O$, M + H$^+$).

**1-Allyl-3-benzyl-1-methylurea (II-2c).** Reaction of 1.36 g (19.1 mmol) of *N*-methylallylamine with 2.54 g (19.1 mmol) of benzyl isocyanate following the general procedure afforded 3.26 g (83%) of the title compound as a white solid, m.p. 60–64 °C.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.27–7.22 (m, 4 H), 7.20–7.17 (m, 1 H), 5.76–5.68 (m, 1 H), 5.12–5.10 (m, 1 H), 5.09–5.08 (m, 1 H), 4.97 (s, 1 H), 4.36 (d, *J* = 5.5 Hz, 2 H), 3.83–3.82 (m, 2 H), 2.81 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.2, 139.8, 133.8, 128.5, 127.5, 127.1, 116.4, 51.2, 44.9, 34.1; IR (film) 3336, 1634 $cm^{-1}$. Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.84; H, 7.96; N, 13.66.

**1-Allyl-1-methyl-3-phenylurea (II-2d).** Reaction of 0.829 g (11.7 mmol) of *N*-methylallylamine with 1.94 g (16.3 mmol) of phenyl isocyanate following the general procedure afforded 1.82 g (82%) of the title compound as a white solid, m.p. 73–76 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2 H), 7.29–7.23 (m, 2 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 6.38 (s, br, 1 H), 5.91–5.81 (m, 1 H), 5.30–5.21 (m, 2 H) 3.98–3.94 (m, 2 H), 3.00 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.7, 139.3, 133.6, 129.1, 123.1, 119.9, 117.2, 51.8, 34.9; IR (film) 3288, 1636 $cm^{-1}$. Anal. calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.80; H, 7.59; N, 14.77.

**1-Allyl-1-benzyl-3-(4-methoxyphenyl)urea (II-2e).** Reaction of 8.1 g (55.0 mmol) of *N*-allylbenzylamine with 8.2 g (55.0 mmol) of 4-methoxyphenylisocyanate following the general procedure afforded 12.82 g (79%) of the title compound as a white solid, m.p. 90–93 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5 H), 7.19–7.16 (m, 2 H), 6.81–6.78 (m, 2 H), 6.26 (s, 1 H), 5.87–5.80 (m, 1 H), 5.30–5.24 (m, 2 H), 4.56 (s, 2 H), 3.95 (d, *J* = 5.0 Hz, 2 H), 3.75 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 156.3, 155.9, 137.8, 134.0, 132.3, 128.9, 127.7, 127.6, 122.2, 117.4, 114.1, 55.6, 50.6, 49.9; IR (film) 3322, 1634 $cm^{-1}$. Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.68; H, 6.80; N, 9.45.

**1-Allyl-3-(4-methoxyphenyl)-1-phenylurea (II-2f).** Reaction of 0.93 g (7.0 mmol) of *N*-allylaniline with 1.04 g (7.0 mmol) of 4-methoxyphenylisocyanate in 14 mL of 2-propanol afforded 2.96 g (87 %) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, *J* = 8.0 Hz, 2 H), 7.37 (t, *J* = 6.5 Hz, 1 H), 7.32 (d, *J* = 7.5 Hz, 2 H), 7.19 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 4.5 Hz, 2 H), 6.05 (s, 1 H), 6.00–5.90 (m, 1 H), 5.13 (dd, *J* = 1.5, 6.0 Hz, 1 H), 5.11 (t, *J* = 1.5 Hz, 1 H), 4.34 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H). Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.51; H, 6.41; N, 9.91.

**1-Allyl-1-benzyl-3-(2-methoxyphenyl)urea (II-2g).** Reaction of 1.47 g (10 mmol) of *N*-allylbenzylamine with 2.09 g (14 mmol) of 2-methoxyphenylisocyanate

following the general procedure afforded 12.82 g (79%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.23–8.16 (m, 1 H), 7.40–7.25 (m, 5 H), 7.20 (s, 1 H), 6.98–6.88 (m, 2 H), 6.84–6.76 (m, 1 H), 5.91–5.79 (m, 1 H), 5.30 (dd, *J* = 1.6, 20.8 Hz, 1 H), 5.27 (dd, *J* = 1.6, 13.6 Hz, 1 H), 4.60 (s, 2 H), 4.00 (d, *J* = 5.2 Hz, 2 H), 3.72 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.16, 147.32, 137.42, 133.08, 128.77, 128.35, 127.20, 127.15, 121.54, 120.68, 118.50, 117.11, 109.50, 55.19, 50.25, 49.85; IR (film) 3395, 1668 cm$^{-1}$. Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.73; H, 6.86; N, 9.42.

**1-Allyl-1-tert-butoxycarbonyl-3-phenylurea (II-2h).** Reaction of 0.57 g (3.3 mmol) of *N*-tert-butoxycarbonylallylamine, and 0.094 g (3.9 mmol) of NaH (60% by weight) with 0.36 g (3.0 mmol) of phenylisocyanate in 3 mL of $CH_2Cl_2$ following the general procedure afforded 117 mg (14%) yield of the title compound. (Note: some of *N*-tert-butoxycarbonylallylamine was lost in transfer.) $^1$H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1 H), 7.52 (d, *J* = 7.6 Hz, 2 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 5.95–5.82 (m, 1 H), 5.19 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.15 (dd, 1.2, 10.0 Hz, 1 H) 4.40 (d, *J* = 5.2 Hz, 2 H), 1.54 (s, 9 H).

**1-(But-3-enyl)-1,3-diphenylurea (II-2i).** Reaction of 1.50 g (10.2 mmol) *N*-(but-3-enyl)aniline with 1.19 g (10 mmol) of phenylisocyanate in 10 mL of $CH_2Cl_2$ following the general procedure afforded 2.58 g (97%) of the title compound as an off-white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.5 Hz, 2 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 7.0 Hz, 2 H), 7.28–7.20 (m, 4 H), 6.98 (t, *J* = 7.5 Hz, 1 H), 6.10 (s, 1 H), 5.86–5.75 (m, 1 H), 5.08 (dd, *J* = 2.0, 17.0 Hz, 1 H), 5.03 (dd, *J* = 2.0, 10.5 Hz, 1 H), 3.83 (t, *J* = 7.5 Hz, 2 H), 2.34 (dd, *J* = 7.0, 14.5 Hz, 2 H); $^{13}$C (100 MHz, $CDCl_3$) 154.04, 141.16, 138.81, 135.35, 130.30, 128.78, 128.75, 128.21, 122.79, 119.14, 116.67, 48.67, 32.87; IR (film) 3321, 1675 cm$^{-1}$.

**1,1-Diallyl-3-ethylurea (II-2j).** Reaction of 0.49 g (5 mmol) of diallylamine with 0.50 g (7 mmol) of ethyl isocyanate in 7 mL of 2-propanol following the general procedure afforded 0.50 g (59%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.83–5.73 (m, 2 H), 5.20–5.13 (m, 4 H), 4.34 (s, 1 H), 3.85–3.81 (m, 4 H), 3.23 (dq, *J* = 5.6, 7.2 Hz, 2 H), 1.08 (t, *J* = 7.2 Hz, 3 H); $^{13}$C (100 MHz, $CDCl_3$)

158.20, 134.34, 116.60, 49.33, 35.68, 15.57; IR (film) 3350, 1627 $cm^{-1}$. Anal. calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.06; H, 9.72; N, 16.37.

**1,3-Diallyl-1-methylurea (II-2k).** Reaction of 1.14 g (16 mmol) of *N*-methylallylamine with 1.33 g (16 mmol) of allylisocyanate following the general procedure with $CH_2Cl_2$ as the solvent afforded 2.54 g (103%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.96–5.73 (m, 2 H), 5.27–5.04 (m, 4 H), 4.50 (s, 1 H), 3.96–3.82 (m, 4 H), 2.90 (s, 3 H).

**(*S*)-1-Allyl-1-(α-methylbenzyl)-3-phenylurea (II-2l).** Reaction of 1.81 g (11.2 mmol) of (*S*)-allyl-α-methylbenzylamine with 1.87 g (15.7 mmol) of phenylisocyanate following the general procedure afforded 2.22 g (71%) of the title compound as a white powder, m.p. 89–92°C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H), 7.38–7.31 (m, 4 H), 7.31–7.24 (m, 3 H), 7.01 (t, *J* = 7.0 Hz, 1 H), 6.59 (s, 1 H), 5.85 (q, *J* = 7.0 Hz, 1 H), 5.80–5.69 (m, 1 H), 5.35 (dd, *J* = 1.0, 17.5 Hz, 1 H), 5.28 (dd, *J* = 1.0, 10.0, 1 H), 3.75 (dd, *J* = 5.5, 17.5. 1 H), 3.68 (dd, *J* = 5.5, 18.0, 1 H), 1.57 (d, *J* = 7.0 Hz, 3 H).

**(*R*)-1-Allyl-1-phenyl-3-(1-phenylethyl)urea (II-2m)** Reaction of 1.33 g (10.0 mmol) of *N*-allylaniline with 1.47 g (10.0 mmol) of (*S*)(-)-1-phenylethyl isocyanate following the general procedure afforded 2.43 g (87%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.2 Hz, 2 H), 7.34–7.25 (m, 3 H), 7.25–7.17 (m, 5 H), 5.95–5.82 (m, 1 H), 5.11–4.97 (m, 3 H), 4.51 (d, *J* = 7.2 Hz, 1 H), 4.36–4.19 (m, 2 H), 1.35 (d, *J* = 7.2 Hz, 3 H).

**1-Benzyl-1-(but-3-en-2-yl)-3-(4-methoxyphenyl)urea (II-5a).** Reaction of 1.33 g (8.25 mmol) of *N*-benzylbut-3-en-2-ylamine[38,39] with 1.20 g (8.25 mmol) of 4-methoxyphenyl isocyanate according to the general procedure afforded 2.56 g (88%) of the title compound as a white solid, m.p. 95–97 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41–7.34 (m, 4 H), 7.34–7.29 (m, 1 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 6.77 (d, *J* = 9.0 Hz, 2 H), 6.18 (s, 1 H), 5.99 (ddd, *J* = 4.5, 11.0, 17.5 Hz, 1 H), 5.29–5.22 (m, 2 H), 5.05–4.98 (m, 1 H), 4.54 (d, *J* = 17.0 Hz, 1 H), 4.37 (d, *J* = 17.0 Hz, 1 H), 3.75 (s, 3 H), 1.34 (d, *J* = 7.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.6, 139.3, 138.1, 132.1, 129.0, 127.7, 126.7, 121.8, 116.1, 113.9, 55.5, 52.3, 47.3, 16.5; IR (film) 3338, 1638 $cm^{-1}$. Anal calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.75; H, 7.11; N, 9.13.

**1-Benzyl-3-(4-methoxyphenyl)-1-(4-methylpent-1-en-3-yl)urea (II-5b).** A flame dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with NaH (0.062 g, 1.55 mmol, 60% dispersion in mineral oil). The flask was purged with nitrogen and a solution of *(E)*-4-methylpent-2-en-1-ol[40] (1.55 g, 15.5 mmol) in ether (2 mL) was added dropwise. The reaction mixture was cooled to –5 °C and trichloroacetonitrile (2.24 g, 15.5 mmol) was added dropwise over 20 min. The reaction mixture was warmed to rt and stirred for 5 h, and then additional portions of NaH (0.062 g, 1.55 mmol, 60% dispersion in mineral oil), trichloroacetonitrile (0.5 mL, 5.0 mmol), and ether (5 mL) were added. The resulting mixture was stirred at rt for additional 6 h, and then concentrated *in vacuo*. The residue was diluted with pentane (15 mL) and methanol (0.04 mL). The resulting mixture was shaken vigorously for 1 min and then filtered through celite. The celite was rinsed with 15 mL of pentane and the solvent was removed *in vacuo*. The crude *(E)*-4-methylpent-2-enyl 2,2,2-trichloroacetimidate was transferred to a flame dried round bottom flask charged with a stirbar. Xylenes (100 mL) was added, and the resulting solution was heated to reflux with stirring for 8 h. The solution was then cooled to rt and filtered through a plug of silica gel. The plug was eluted with toluene and the resulting solution was concentrated *in vacuo*. The crude product was purified via flash chromatography to afford 3.05 g (80%) of 2,2,2-trichloro-*N*-(4-methylpent-1-en-3-yl)acetamide as an orange solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1 H), 5.86–5.74 (m, 1 H), 5.25 (d, *J* = 1.2 Hz, 1 H), 5.22 (d, *J* = 2.0 Hz, 1 H), 4.34–4.27 (m, 1 H), 2.00–1.87 (m, 1 H), 0.99–0.95 (m, 6 H). A round bottom flask was purged with nitrogen and charged with 2,2,2-trichloro-*N*-(4-methylpent-1-en-3-yl)acetamide (2.97 g, 12.1 mmol), aqueous NaOH (60 mL, 6 M, 360 mmol), and 60 mL EtOH. The reaction mixture was heated to reflux for 1 h, then cooled to rt and stirred for 1.5 h. The mixture was then transferred to a separatory funnel and extracted with ether. The combined organic extracts were dried over anhydrous $Na_2SO_4$ and decanted into a round bottom flask. The flask was purged with nitrogen, cooled to 0 °C, and triethylamine (6.7 mL, 48.4 mmol), benzoyl chloride (7.0 mL, 60.5 mmol), and 4-dimethylaminopyridine (0.15 g, 1.21 mmol) were added. The reaction mixture was stirred at rt for 27 h, then was quenched with aqueous $NaHCO_3$ and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with EtOAc (3 X

150 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 2.16 g (88%) of *N*-(4-methylpent-1-en-3-yl)benzamide as a tan solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2 H), 7.51 (t, *J* = 7.0 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 6.03 (d, *J* =7.5 Hz, 1 H), 5.90–5.81 (m, 1 H), 5.26–5.17 (m, 2 H), 4.62–4.54 (m, 1 H), 2.00–1.89 (m, 1 H), 0.99 (d, *J* = 3.5Hz, 3 H), 0.98 (d, *J* = 3.5 Hz, 3 H). A flame dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with *N*-(4-methylpent-1-en-3-yl)benzamide (1.68 g, 8.3 mmol) and cooled to 0 $^o$C. A solution of $LiAlH_4$ (34 mL, 34 mmol, 1.0 M in THF) was added and the solution was heated to reflux for 20 h. The reaction was placed in an ice bath and 1 mL water was slowly added followed by 1 mL 10M NaOH, 40 mL ether, and an additional 4 mL water. The solution was filtered through celite and the celite was rinsed with ether. The solvent was removed *in vacuo* to afford *N*-benzyl-4-methylpent-1-en-3-ylamine, which was then treated with 1.24 g (8.3 mmol) of 4-methoxyphenyl isocyanate for 2.5 h according to the general procedure to afford 2.36 g (84% over two steps) of the title compound as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41–7.35 (m, 4 H), 7.35–7.29 (m, 1 H), 7.00 (d, *J* = 9.0 Hz, 2 H), 6.74 (d, *J* = 9.0 Hz, 2 H), 6.06 (s, 1 H), 5.86 (ddd, *J* = 8.0, 10.5, 18.5 Hz, 1 H), 5.31 (d, *J* = 17.5 Hz, 1 H), 5.24 (d, *J* = 10.0 Hz, 1 H), 4.56 (d, *J* = 17.5 Hz, 1 H), 4.44 (d, *J* = 17.0 Hz, 1 H), 4.48–4.39 (m, 1 H), 3.73 (s, 3 H), 2.09–1.98 (m, 1 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 156.0, 155.5, 137.5, 136.3, 132.0, 128.8, 127.6, 126.8, 121.8, 118.5, 113.8, 65.1, 55.3, 48.1, 29.9, 20.2, 19.5; IR (film) 3337, 1640 cm$^{-1}$. Anal calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.28; H, 7.58; N, 8.16.

**1-Benzyl-1-(1-(benzyloxy)but-3-en-2-yl)-3-(4-methoxyphenyl)urea (II-5c).** (*Z*)-4-(benzyloxy)but-2-en-1-ol[41] was converted to the title compound using a procedure analogous to that employed for the synthesis of **27**. This procedure afforded 1.59 g (20% overall yield) of the title compound as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40–7.24 (m, 10 H), 7.20 (s, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 5.99–5.86 (m, 1 H), 5.32–5.20 (m, 2 H), 4.82–4.71 (m, 2 H), 4.54–4.40 (m, 3 H), 3.74 (s, 3 H), 3.77–3.71 (m, 1 H), 3.66 (dd, *J* = 7.2, 10.0 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.8, 155.3, 138.8, 137.4, 134.4, 132.6, 128.7, 128.5, 128.1, 128.0, 127.4, 127.2, 121.2,

118.2, 113.9, 73.6, 71.3, 58.3, 55.5, 48.7; IR (film) 3334, 1657 $cm^{-1}$. Anal. calcd for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.73. Found: C, 75.00; H, 6.80; N, 6.75.

***N*-(4-Methoxyphenyl)-2-vinylpiperidine-1-carboxamide (II-5e).** A flame-dried round-bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with *N*-(*tert*-butoxycarbonyl)-2-vinylpiperidine[42] (2.11 g, 10 mmol) and $CH_2Cl_2$ (100 mL). The solution was cooled to 0 °C and trifluoroacetic acid (15 mL, 202 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h, at which point the reaction was judged complete by TLC analysis. The reaction was quenched with 100 mL saturated aqueous $NaHCO_3$ and the resulting mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 150 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$ and decanted into a round-bottom flask equipped with a stirbar. The solution was cooled to 0 °C, 4-methoxyphenyl isocyanate (1.3 mL, 1.49 g, 10 mmol) was added, and the reaction was stirred at rt for 1.5 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel to afford 2.04 g (78%) of the title compound as a white solid, m.p. 101–103 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.2 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.43 (s, br, 1 H), 5.82 (ddd, *J* = 4.0, 10.8, 17.6 Hz, 1 H), 5.26 (d, *J* = 10.4 Hz, 1 H), 5.16 (d, *J* = 17.2 Hz, 1 H), 4.71 (s, br, 1 H), 3.97 (d, *J* = 13.6 Hz, 1 H), 3.76 (s, 3 H), 2.97 (dt, *J* = 3.2, 12.0 Hz, 1 H), 1.84–1.71 (m, 2 H), 1.70–1.59 (m, 2 H), 1.57–1.42 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.5, 136.5, 132.3, 122.1, 116.2, 113.9, 55.4, 53.1, 39.8, 29.2, 25.2, 19.2; IR (film) 3316, 1630 $cm^{-1}$. MS (ESI): 283.1418 (283.1422 calcd for $C_{15}H_{20}N_2O_2$, M + $Na^+$).

***N*-(4-Methoxyphenyl)-2-vinylpyrrolidine-1-carboxamide (II-5f).** A flame-dried round-bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with *N*-(tert-butoxycarbonyl)-2-vinylpyrrolidine[43] (0.647 g, 3.3 mmol) and $CH_2Cl_2$ (33 mL). The solution was cooled to 0 °C and trifluoroacetic acid (6 mL, 80.8 mmol) was added. The reaction mixture was warmed to rt and stirred for 4 h, at which point the reaction was judged complete by TLC analysis. The solvent was removed *in vacuo*, and the residue was redissolved in $CH_2Cl_2$ (20 mL). Solid $K_2CO_3$ (10 g) was added to the solution and the resulting suspension was stirred for 30 min then filtered through a fritted funnel. The solids were rinsed with $CH_2Cl_2$ (50 mL), and the resulting

solution of 2-vinylpyrrolidine was transferred to a round-bottom flask and cooled to 0 °C. The solution was treated with 4-methoxyphenyl isocyanate (0.49 g, 0.33 mmol) according to the general procedure to afford 445 mg (55%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.2 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.36 (s, 1 H), 5.90 (ddd, *J* = 6.8, 10.0, 16.8 Hz, 1 H), 5.34 (d, *J* = 16.8 Hz, 1 H), 5.27 (d, *J* = 10.4 Hz, 1 H), 4.32–4.23 (m, 1 H), 3.77 (s, 3 H), 3.69–3.58 (m, 1 H), 3.57–3.47 (m, 1 H), 2.24–2.12 (m, 1 H), 1.99–1.77 (m, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.1, 154.5, 139.2, 132.2, 121.2, 115.3, 113.6, 59.3, 55.2, 46.4, 32.6, 22.8; IR (film) 3318, 1648 cm$^{-1}$. MS (ESI): 247.1447 (247.1447 calcd for $C_{14}H_{18}N_2O_2$, M + $H^+$).

**1-Benzyl-3-(4-methoxyphenyl)-1-(2-methylbut-3-en-2-yl)urea (II-5g).** A flame-dried round bottom flask was cooled under a stream of nitrogen and charged with $[Ir(COD)Cl]_2$ (27 mg, 0.04 mmol), triphenyl phosphite (42 μL, 0.16 mmol), 2-methylbut-3-en-2-yl acetate[39] (256 mg, 2.0 mmol), benzylamine (643 mg, 6.0 mmol), and ethanol (4.4 mL). The resulting solution was heated to reflux under an atmosphere of nitrogen for 5 h. The solution was then cooled to rt, diluted with 25 mL of ether, transferred to a separatory funnel, and washed with 6M HCl (25 mL). The layers were separated, and the aqueous layer was taken to pH 10 through addition of 6M NaOH (10 mL). The aqueous layer was extracted with ether (2 x 25 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford 177 mg (51%) of *N*-benzyl-2-methylbut-3-en-2-ylamine as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 4 H), 7.27–7.19 (m, 1 H), 5.84 (dd, *J* = 10.8, 17.2 Hz, 1 H), 5.14–5.06 (m, 2 H), 3.64 (s, 1 H), 1.24 (s, 6 H), 1.04 (s, 1 H). Reaction of *N*-benzyl-2-methylbut-3-en-2-ylamine (375 mg, 2.14 mmol) with 4-methoxyphenyl isocyanate (278 μL, 2.14 mmol) according to the general procedure afforded 574 mg (83%) of the title compound as a white solid, m.p. 81–85$^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39–7.34 (m, 4 H), 7.30–7.24 (m, 1 H), 7.16 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 6.76 (s, 1 H), 6.24 (dd, *J* = 10.5, 18.0 Hz, 1 H), 5.27 (d, *J* = 17.5 Hz, 1 H), 5.18 (d, *J* = 11.0 Hz, 1 H), 4.71 (s, 2 H), 3.75 (s, 3 H), 1.54 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.0, 155.5, 147.1, 140.2, 132.3, 128.8, 127.0, 126.3, 121.5, 114.0, 112.3, 59.8, 55.5, 48.5, 26.5; IR (film) 3403, 1659 cm$^{-1}$. MS (ESI): 347.1741 (347.1735 calcd for $C_{20}H_{24}N_2O_2$, M + $Na^+$).

**1-Ethyl-1-(2-methylallyl)-3-phenylurea (II-6a).** Reaction of 0.99 g (10.0 mmol) of ethyl-(2-methylallyl)amine with 1.19 g (10.0 mmol) of phenyl isocyanate following the general procedure afforded 2.16 g (99%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2 H), 7.26–7.22 (m, 2 H), 7.00–6.96 (m, 1 H), 6.45 (s, 1 H), 5.012 (s, 1 H), 5.009 (s, 1 H), 3.82 (s, 2 H), 3.41 (q, *J* = 7.6 Hz, 2 H), 1.77 (s, 3 H), 1.18 (t, *J* = 6.8 Hz, 3 H); $^{13}$C (125 MHz, $CDCl_3$) δ 155.6, 142.1, 139.4, 128.9, 122.9, 119.7, 112.3, 53.2, 42.8, 20.0, 13.6; IR (film) 3331, 1626 cm$^{-1}$. MS (EI): 218.1411 (218.1419 calcd for $C_{13}H_{18}N_2O$).

**1-Benzyl-3-(4-methoxyphenyl)-1-(2-methylallyl)urea (II-6b).** Reaction of 1.61 g (10 mmol) of *N*-benzyl-2-methylprop-2-en-1-amine[44] with 1.49 g (10 mmol) of 4-methoxyphenyl isocyanate for 1 h according to the general procedure afforded 2.56 g (83%) of the title compound as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 9.0 Hz, 2 H), 6.37 (s, 1 H), 5.02 (s, 1 H), 5.01 (s, 1 H), 4.59 (s, 2 H), 3.86 (s, 2 H), 3.77 (s, 3 H), 1.75 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.3, 155.7, 141.5, 137.7, 132.2, 128.7, 127.6, 127.5, 121.8, 114.0, 112.3, 55.5, 53.0, 50.6, 19.8; IR (film) 3332, 1640 cm$^{-1}$. MS (ESI): 333.1573 (333.1579 calcd for $C_{19}H_{22}N_2O_2$, M + $Na^+$).

**1-Benzyl-1-(cyclopent-2-enyl)-3-phenyl-urea (II-6c).** *N*-Benzylcyclopent-2-enylamine was prepared from benzylamine (4.91 g, 45.8 mmol) and cyclopentadiene (6.04 g, 91.6 mmol) using Hartwig's procedure for hydroamination of cyclopentadiene.[45] This procedure generated 1.94 g (25%) of *N*-benzylcyclopent-2-enylamine as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 4 H), 7.24–7.20 (m, 1 H), 5.87–5.83 (m, 1 H), 5.82–5.80 (m, 1 H), 3.90–3.86 (m, 1 H), 3.83–3.77 (m, 2 H), 2.43–2.40 (m, 1 H), 2.28–2.16 (m, 2 H), 1.62–1.55 (m, 1 H), 1.28 (s, br, 1 H). Reaction of 1.94 g (11.2 mmol) of *N*-benzylcyclopent-2-enylamine with 1.33 g (11.2 mmol) of phenyl isocyanate following the general procedure afforded 3.0 g (92%) of the title compound as a white solid, m.p. 95–97 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 7.20 (m, 4 H), 6.98–6.94 (m, 1 H), 6.48 (s, 1 H), 6.03–6.00 (m, 1 H), 5.75–5.73 (m, 1 H), 5.38–5.36 (m, 1 H), 4.46 (q, *J* = 10.8, 16.8 Hz, 2 H), 2.49–2.39 (m, 1 H), 2.37–2.29 (m, 2 H), 1.75–1.68 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.9, 139.3, 138.4, 135.6, 131.6, 129.1, 128.9,

127.7, 126.9, 122.9, 119.7, 62.9, 48.1, 31.6, 28.6; IR (film) 3336, 1651 $cm^{-1}$. Anal. calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.25; H, 6.93; N, 9.50.

**1-(Cyclohex-2-enyl)-1,3-diphenylurea (II-6d).** *N*-(Cyclohex-2-enyl)aniline was prepared from aniline (1.17 mL, 12.82 mmol) and 1,3-cyclohexadiene (4.11 g, 51.3 mmol) using Hartwig's procedure for hydroamination of 1,3-cyclohexadiene.[46] This procedure generated 2.0 g (90%) of *N*-(cyclohex-2-enyl)aniline as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.2 Hz, 2 H), 6.67 (t, *J* = 4.4 Hz, 1 H), 6.61 (d, *J* = 8.0 Hz, 2 H), 5.86–5.81 (m, 1 H), 5.75–5.72 (m, 1 H), 3.98 (s, br, 1 H), 3.67 (s, br, 1 H), 2.10–1.94 (m, 2 H), 1.93–1.84 (m, 1 H), 1.76–1.54 (m, 3 H). Reaction of 1.96 g (11.0 mmol) of *N*-(cyclohex-2-enyl)aniline with 1.31 g (11.0 mmol) of phenyl isocyanate following the general procedure afforded 3.0 g (93%) of the title compound as a white solid, m.p. 122–125 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.47–7.38 (m, 3 H), 7.28–7.17 (m, 6 H), 6.95 (t, *J* = 7.0 Hz, 1 H), 5.93 (s, 1 H), 5.75–5.68 (m, 2 H), 5.35–5.28 (m, 1 H), 1.99–1.75 (m, 3 H), 1.68–1.52 (m, 2 H), 1.46–1.37 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 154.5, 139.2, 138.6, 131.0, 130.2, 130.0, 129.6, 128.9, 128.8, 122.9, 119.4, 52.5, 28.4, 24.6, 21.6; IR (film) 3326, 1672 $cm^{-1}$. Anal. calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.73; H, 6.89; N, 9.46.

**(*E*)-1-(But-2-enyl)-1,3-diphenylurea (II-6e).** Reaction of 0.973 g (6.61 mmol) of (*E*)-*N*-(but-2-enyl)aniline[47] (4:1 mixture of *E*/*Z* isomers) with 0.867 g, (7.27 mmol) of phenyl isocyanate according to the general procedure afforded 1.70 g (97%) of the title compound as a white solid, m.p. 61–65 °C. This material was obtained as a 4:1 mixture of *E*/*Z* isomers as judged by $^1$H NMR analysis. Data are reported for the major isomer. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.2 Hz, 3 H), 7.36 (t, *J* = 7.2 Hz, 2 H), 7.32–7.17 (m, 4 H), 6.96 (t, *J* = 7.2 Hz, 1 H), 6.12 (s, 1 H), 5.63–5.48 (m, 2 H), 4.25 (d, *J* = 5.6 Hz, 2 H), 1.64 (d, *J* = 6.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 154.1, 141.6, 139.0, 130.3, 129.0, 128.9, 128.8, 128.2, 126.9, 122.9, 119.3, 51.7, 17.9; IR (film) 3323, 1675 $cm^{-1}$. Anal. calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.58; H, 6.94; N, 10.52.

**(*E*)-1-Benzyl-1-cinnamyl-3-(4-methoxyphenyl)urea (II-6f).** Reaction of 1.21 g (5.4 mmol) of (*E*)-*N*-benzylcinnamylamine[48] with 0.81 g (5.4 mmol) of 4-methoxyphenyl isocyanate for 36 h according to the general procedure afforded 1.41 g (70%) of the title

compound as a white solid, m.p. 127–130 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.44–7.23 (m, 10 H), 7.17 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 6.57 (d, *J* = 16.0 Hz, 1 H), 6.35 (s, 1 H), 6.21 (dt, *J* = 5.5, 15.5 Hz, 1 H), 4.62 (s, 2 H), 4.14 (d, *J* = 5.0 Hz, 2 H), 3.75 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.2, 155.8, 137.6, 136.1, 132.5, 132.0, 128.9, 128.7, 128.0, 127.7, 127.4, 126.4, 125.0, 122.0, 114.1, 55.5, 50.5, 49.5; IR (film) 3328, 1638 cm$^{-1}$. MS (ESI): 373.1927 (373.1916 calcd for $C_{24}H_{24}N_2O_2$, M + $Na^+$).

**1-Cinnamyl-3-(4-methoxyphenyl)-1-phenylurea (II-6g).** Reaction of 2.44 g (11.7 mmol) of *N*-cinnamylaniline with 1.74 g (11.7 mmol) of 4-methoxyphenylisocyanate in 12 mL of $CH_2Cl_2$ following the general procedure afforded 1.93 g (46%) of the title compound as a yellow powder, m.p. 119–122 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.5 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 4 H), 7.29 (t, 7.0 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 7.19 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 6.45–6.31 (m, 2 H), 6.04 (s, 1 H), 4.49 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H).

**General Procedure for Pd-Catalyzed Synthesis of Imidazolidin-2-ones.** An oven- or flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), Xantphos (2 mol %), NaO*t*Bu (1.2 equiv), the *N*-allylurea substrate (1.0 equiv), and the aryl bromide (1.2 equiv). The tube was purged with nitrogen, and undecane (0.125 equiv, internal standard) and toluene (4 mL/mmol urea substrate) were then added. If the acyclic urea and/or the aryl bromide were oils they were added at the same time as the toluene. The Schlenk tube was then heated to 110 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis of aliquots removed from the reaction mixture. The mixture was then cooled to rt, saturated aqueous $NH_4Cl$ (4–6 mL/mmol substrate) was added, and the mixture was extracted with methylene chloride or ethyl acetate (3 x 7 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

**3-Ethyl-4-methyl-1-phenyl-1,3-dihydroimidazol-2-one (II-11).** This material was isolated as a side product in the Pd-catalyzed coupling of 1-allyl-3-ethyl-1-phenylurea with 4-bromotoluene as described in Table 1 and was characterized by $^1$H NMR analysis. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.39 (t, *J* = 7.2

Hz, 2 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 6.31 (s, 1 H), 3.73 (q, *J* = 7.6 Hz, 14.8 Hz, 2 H), 2.12 (d, *J* = 1.6 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

**1-Allyl-3-ethyl-4-(4-methylbenzyl)imidazolidin-2-one (II-1a).** Reaction of 84.1 mg (0.5 mmol) of 1,1-diallyl-3-ethylurea with 102.6 mg (0.6 mmol) of 4-bromotoluene according to the general procedure afforded 67 mg (52%) of the title compound as a brown oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 2 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 5.74–5.60 (m, 1 H), 5.14–5.04 (m, 2 H), 3.83–3.72 (m, 2 H), 3.68 (dd, *J* = 5.2, 15.6 Hz, 1 H), 3.63–3.51 (m, 1 H), 3.17–3.02 (m, 3 H), 2.89 (dd, J = 6.8, 8.8 Hz, 1 H), 2.53 (dd, *J* = 9.6, 13.6 Hz, 1 H), 2.32 (s, 3 H), 1.13 (t, *J* = 7.2 Hz, 3 H).

**3-Ethyl-4-(naphthalen-2-ylmethyl)-1-phenylimidazolidin-2-one (II-1b).** Reaction of 102 mg (0.5 mmol) of 1-allyl-3-ethyl-1-phenylurea with 124 mg (0.6 mmol) of 2-bromonaphthalene for 2 h according to the general procedure afforded 121 mg (73%) of the title compound as a lime green solid, m.p. 132–135 °C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.86–7.77 (m, 3 H), 7.66 (s, 1 H), 7.52–7.43 (m, 4 H), 7.32 (dd, *J* = 2.0, 10.5 Hz, 1 H), 7.30–7.23 (m, 2 H), 6.97 (t, *J* = 7.6 Hz, 1 H), 4.12–4.03 (m, 1 H), 3.76–3.61 (m, 2 H), 3.49 (dd, *J* = 6.0, 9.2 Hz, 1 H), 3.38 (dd, *J* = 4.0, 13.6 Hz, 1 H), 3.28–3.18 (m, 1 H), 2.78 (dd, *J* = 9.6, 13.2 Hz, 1 H), 1.23 (t, *J* = 6.8 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 157.4, 140.6, 134.1, 133.7, 132.6, 128.9, 128.8, 128.0, 127.9, 127.7, 127.3, 126.6, 126.1, 122.3, 117.4, 53.0, 48.0, 39.4, 36.5, 13.2; IR (film) 1703 $cm^{-1}$. Anal. calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.00; H, 6.77; N, 8.32.

**3-Ethyl-4-(4-methylbenzyl)-1-phenylimidazolidin-2-one (II-1c).** Reaction of 102 mg (0.5 mmol) of 1-allyl-3-ethyl-1-phenylurea with 103 mg (0.6 mmol) of 4-bromotoluene for 1 h according to the general procedure afforded 91 mg (62%) of the title compound as a yellow solid, m.p. 93–95°C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 2 H), 7.27 (t, *J* = 7.2 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 6.98 (t, *J* = 7.2 Hz, 1 H), 3.98–3.88 (m, 1 H), 3.73–3.60 (m, 2 H), 3.43 (dd, *J* = 6.4, 9.2 Hz, 1 H), 3.25–3.11 (m, 2 H), 2.59 (dd, *J* = 9.6, 13.6 Hz, 1 H), 2.33 (s, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.4, 140.7, 136.7, 133.4, 129.7, 129.1, 128.8, 122.2, 117.3, 53.0, 47.9, 38.7, 36.4, 21.2, 13.1; IR (film) 1704 $cm^{-1}$. Anal. calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.81; H, 7.68; N, 9.50.

**4-((3-Ethyl-2-oxo-1-phenylimidazolidin-4-yl)methyl)benzonitrile (II-1d).** Reaction of 102.1 mg (0.5 mmol) of 1-allyl-3-ethyl-1-phenylurea with 109.2 mg (0.6 mmol) of 4-bromobenzonitrile following the general procedure without undecane afforded 65 mg (43%) of the title compound containing 15% starting material. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 7.5 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.28 (t, *J* = 7.0 Hz, 2 H), 7.00 (t, *J* = 7.5 Hz, 1 H), 4.04–3.98 (m, 1 H), 3.75–3.64 (m, 2 H), 3.38 (dd, *J* = 6.0, 9.5 Hz, 1 H), 3.25–3.10 (m, 2 H), 2.78 (dd, *J* = 9.0, 13.5 Hz, 1 H) 1.21 (t, *J* = 7.6 Hz, 3 H).

**3-Ethyl-4-(2-methoxybenzyl)-1-methylimidazolidin-2-one (II-1e).** Reaction of 71.1 mg (0.5 mmol) of 1-allyl-3-ethyl-1-methylurea with 112 mg (0.6 mmol) of 2-bromoanisole following the general procedure without undecane afforded 73 mg 59% of the title compound as a yellow oil. . $^1$H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.10 (dd, J = 1.6, 7.2 Hz, 1 H), 6.93–6.83 (m, 2 H), 3.89–3.79 (m, 1 H), 3.83 (s, 3 H), 3.64–3.52 (m, 1 H), 3.23 (dd, *J* = 4.0, 13.2 Hz, 1 H), 3.16–3.05 (m, 2 H), 2.93 (dd, *J* = 6.8, 8.4 Hz, 1 H), 2.73 (s, 3 H) 2.46 (dd, *J* = 9.6, 13.2 Hz, 1 H) 1.13 (s, *J* = 7.6 Hz, 3 H).

**3-Ethyl-4-(4-methoxybenzyl)-1-methylimidazolidin-2-one (II-1f).** Reaction of 71 mg (0.5 mmol) of 1-allyl-3-ethyl-1-methylurea with 112 mg (0.6 mmol) of 4-bromoanisole for 4 h according to the general procedure afforded 48 mg (39%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 3.87 (s, 3 H), 3.84–3.68 (m, 1 H), 3.60–3.43 (m, 1 H), 3.16–3.00 (m, 3 H), 2.89 (dd, *J* = 7.2, 8.8 Hz, 1 H), 2.70 (s, 3 H), 2.50 (dd, *J* = 9.6, 13.6 Hz, 1 H), 1.10 (t, *J* = 7.2 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.6, 155.9, 127.5, 126.2, 111.5, 52.7, 51.2, 48.1, 35.3, 33.8, 28.6, 10.3; IR (film) 1699 $cm^{-1}$. MS (ESI): 271.1408 (271.1422 calcd for $C_{14}H_{20}N_2O_2$, M + $Na^+$).

**3-Ethyl-1-methyl-4-(4-methylbenzyl)imidazolidin-2-one (II-1g).** Reaction of 71 mg (0.5 mmol) of 1-allyl-3-ethyl-1-methylurea with 131 mg of 4-iodotoluene following the general procedure where the substrate and undecane were added as a solution in toluene afforded 41 mg (35%) of the title compound as a brown oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 3.79–3.70 (m, 1 H), 3.58–3.49 (m, 1 H), 3.14–3.04 (m, 4 H), 2.90 (s, 3 H), 2.51 (dd, 10.0, 13.5 Hz, 1 H),

2.31 (s, 3 H), 1.11 (t, $J$ = 7.5 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.3, 136.5, 133.9, 129.5, 129.1, 53.9, 50.9, 38.5, 36.5, 31.4, 21.2, 13.0; IR (film) 1701 $cm^{-1}$. MS (ESI): 255.1476 (255.1473 calcd for $C_{14}H_{20}N_2O$, M + $Na^+$).

**4-(4-*tert*-Butylbenzyl)-3-ethyl-1-methylimidazolidin-2-one (II-1h).** Reaction of 71 mg (0.5 mmol) of 1-allyl-3-ethyl-1-methylurea with 128 mg (0.6 mmol) of 1-bromo-4-*tert*-butylbenzene for 3 h according to the general procedure afforded 94 mg (69%) of the title compound as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, $J$ = 8.0 Hz, 2 H), 7.08 (d, $J$ = 8.0 Hz, 2 H), 3.80–3.71 (m, 1 H), 3.60–3.49 (m, 1 H), 3.18–3.03 (m, 3 H), 2.91 (dd, $J$ = 7.2, 8.8 Hz, 1 H) 2.70 (s, 3 H), 2.52 (dd, $J$ = 10.0, 13.6 Hz, 1 H), 1.29 (s, 9 H), 1.11 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 161.3, 149.8, 133.9, 128.9, 125.7, 53.9, 51.0, 38.3, 36.5, 34.6, 31.5, 31.4, 13.0; IR (film) 1704 $cm^{-1}$. Anal. calcd for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55; N, 10.21. Found: C, 74.20; H, 9.61; N, 10.08.

**3-Ethyl-1-methyl-4-(naphthalen-1-ylmethyl)imidazolidin-2-one (II-1i).** Reaction of 71 mg (0.5 mmol) of 1-allyl-3-ethyl-1-methylurea with 124 mg (0.6 mmol) of 1-bromonaphthalene for 4 h according to the general procedure afforded 91 mg (68%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, $J$ = 8.5 Hz, 1 H), 7.89–7.85 (m, 1 H), 7.77 (d, $J$ = 8.0 Hz, 1 H), 7.57–7.48 (m, 2 H), 7.43–7.38 (m, 1 H), 7.32 (d, $J$ = 6.5 Hz, 1 H), 4.02–3.94 (m, 1 H), 3.72–3.59 (m, 2 H), 3.24–3.16 (m, 1 H), 3.03–2.96 (m, 2 H), 2.92 (dd, $J$ = 10.0, 14.0 Hz, 1 H), 2.72 (s, 3 H), 1.20 (t, $J$ = 13.5 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.3, 134.1, 133.1, 132.0, 129.2, 127.8, 127.4, 126.5, 125.9, 125.6, 123.2, 52.9, 51.0, 36.7, 35.9, 31.4, 13.4; IR (film) 1699 $cm^{-1}$. Anal. calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.97; H, 7.54; N, 10.37.

**3-Ethyl-1-methyl-4-(naphthalen-2-ylmethyl)imidazolidin-2-one (II-1j).** Reaction of 71 mg (0.5 mmol) of 1-allyl-3-ethyl-1-methylurea with 124 mg (0.6 mmol) of 2-bromonaphthalene for 4 h according to the general procedure afforded 91 mg (68%) of the title compound as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84–7.75 (m, 3 H), 7.62 (s, 1 H), 7.51–7.41 (m, 2 H), 7.28 (dd, $J$ = 1.6, 8.4 Hz, 1 H), 3.93–3.84 (m, 1 H), 3.64–3.53 (m, 1 H), 3.29 (dd, $J$ = 4.4, 13.2 Hz, 1 H), 3.19–3.08 (m, 2 H), 2.96 (dd, $J$ = 7.2, 8.8 Hz, 1 H), 2.72 (dd, $J$ = 9.6, 13.2 Hz, 1 H), 2.71 (s, 3 H), 1.15 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.3, 134.5, 133.6, 132.4, 128.5, 127.8, 127.7, 127.6,

127.3, 126.4, 125.9, 53.8, 50.9, 39.1, 36.5, 31.3, 13.0; IR (film) 1699 $cm^{-1}$. MS (ESI): 291.1474 (291.1473 calcd for $C_{17}H_{20}N_2O_2$, M + $Na^+$).

**4-(3-Benzyl-1-methyl-2-oxo-imidazolidin-4-ylmethyl)benzonitrile (II-1k).** Reaction of 110 mg (0.54 mmol) of 1-allyl-3-benzyl-1-methylurea with 118 mg (0.65 mmol) of 4-bromobenzonitrile for 8 h according to the general procedure afforded 131 mg (80%) of the title compound as a white solid, m.p. 114–118 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2 H), 7.34–7.23 (m, 5 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 4.83 (d, *J* = 15.2 Hz, 1 H), 4.07 (d, *J* = 15.2 Hz, 1 H), 3.61–3.54 (m, 1 H), 3.16–3.06 (m, 2 H), 2.90–2.86 (m, 1 H), 2.75 (s, 3 H), 2.65–2.60 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 161.2, 142.6, 137.2, 132.6, 130.1, 128.9, 128.3, 127.8, 118.8, 111.1, 53.4, 50.6, 46.4, 39.0, 31.4; IR (film) 2226, 1693 $cm^{-1}$. Anal. calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.69; H, 6.26; N, 13.70.

**4-(4-Methoxybenzyl)-1-methyl-3-phenylimidazolidin-2-one (II-1l).** Reaction of 95.1 mg (0.5 mmol) 1-allyl-1-methyl-3-phenylurea with 112.2 mg (0.6 mmol) of 4-bromoanisole following the general procedure but without undecane afforded 147 mg (99%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* =7.6 Hz, 2 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.45–4.36 (m, 1 H), 3.77 (s, 3 H), 3.33 (t, *J* = 8.4 Hz, 1 H), 3.16 (dd, *J* = 5.2, 9.2 Hz, 1 H), 3.03 (dd, *J* = 3.6, 14.0 Hz, 1 H), 2.78 (s, 3 H), 2.63 (dd, *J* = 9.2, 13.6 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.4, 158.1, 138.8, 130.1, 128.9, 128.3, 123.3, 120.6, 114.0, 55.1, 54.2, 49.0, 36.9, 30.9; IR (film) 1703 $cm^{-1}$. MS (ESI): 297.1612 (297.1603 calcd for $C_{18}H_{20}N_2O_2$, M + $H^+$).

**1-Methyl-4-(naphthalen-2-ylmethyl)-3-phenylimidazolidin-2-one (II-1m).** Reaction of 95 mg (0.5 mmol) of 1-allyl-1-methyl-3-phenylurea with 124 mg (0.6 mmol) of 2-bromonaphthalene for 1 h according to the general procedure afforded 153 mg (97%) of the title compound as an off-white solid, m.p. 122–126 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83–7.76 (m, 3 H), 7.61–7.56 (m, 3 H), 7.51–7.37 (m, 4 H), 7.27 (dd, *J* = 1.6, 8.4 Hz, 1 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 4.60–4.51 (m, 1 H), 3.37–3.26 (m, 2 H), 3.26–3.21 (m, 1 H), 2.83 (dd, *J* = 10.0, 14.0 Hz, 1 H), 2.79 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.5, 139.1, 134.3, 133.6, 132.5, 129.3, 128.6, 128.0, 127.9, 127.6, 127.4, 126.5, 126.0,

123.8, 121.1, 54.5, 49.4, 38.3, 31.3; IR (film) 1704 $cm^{-1}$. Anal. calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.36; H, 6.38; N, 8.60.

**1-Methyl-3-phenyl-4-(pyridin-3-ylmethyl)imidazolidin-2-one (II-1n).** Reaction of 95 mg (0.5 mmol) of 1-allyl-1-methyl-3-phenylurea with 95 mg (0.6 mmol) of 3-bromopyridine for 30 min according to the general procedure afforded 120 mg (90%) of the title compound as a pale green solid, m.p. 150–151 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.0 Hz, 1 H), 8.41 (s, 1 H), 7.53–7.48 (m, 2 H), 7.43–7.40 (m, 1 H), 7.39–7.34 (m, 2 H), 7.24–7.19 (m, 1 H), 7.12–7.07 (m, 1 H) 4.53–4.46 (m, 1 H), 3.41 (t, *J* = 9.0 Hz, 1 H), 3.14 (dd, *J* = 5.0, 9.0 Hz, 1 H), 3.02 (dd, *J* = 3.0, 14.0 Hz, 1 H), 2.80 (dd, *J* = 8.5, 14.0 Hz, 1 H), 2.75 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 158.2, 150.4, 148.5, 138.7, 137.1, 132.2, 129.3, 124.0, 123.8, 121.0, 53.8, 49.1, 35.3, 31.1; IR (film) 1684 $cm^{-1}$. Anal. calcd for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 71.97; H, 6.37; N, 15.36.

**4-(4-Benzoylbenzyl)-1-methyl-3-phenylimidazolidin-2-one (II-1o).** Reaction of 95 mg (0.5mmol) of 1-allyl-1-methyl-3-phenylurea with 157 mg (0.6 mmol) of 4-bromobenzophenone for 5 h according to the general procedure afforded 152 mg (82%) of the title compound as a white solid, m.p. 44–50 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78–7.72 (m, 4 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.55–7.50 (m, 2 H), 7.47 (t, *J* = 8.0 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.27–7.22 (m, 2 H), 7.10 (t, *J* = 7.0 Hz, 1 H), 4.56–4.49 (m, 1 H), 3.41 (t, *J* = 8.5 Hz, 1 H), 3.21–3.14 (m, 2 H), 2.82 (dd, *J* = 9.5, 14.0 Hz, 1 H), 2.80 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.3, 158.2, 141.5, 138.8, 137.6, 136.3, 132.6, 130.5, 130.0, 129.3, 129.1, 128.4, 123.7, 120.9, 54.0, 49.2, 38.1, 31.1; IR (film) 1704, 1656 $cm^{-1}$. Anal. calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.58; H, 6.11; N, 7.43.

**1-Methyl-3-phenyl-4-[4-(trifluoromethyl)benzyl]imidazolidin-2-one (II-1p).** Reaction of 95 mg (0.5 mmol) of 1-allyl-1-methyl-3-phenylurea with 135 mg (0.6 mmol) of 4-bromobenzotrifluoride for 1 h according to the general procedure afforded 158 mg (95%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52–7.49 (m, 4 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.24 (t, *J* = 4.0 Hz, 2 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 4.53–4.45 (m, 1 H), 3.38 (t, *J* = 8.8 Hz, 1 H), 3.18–3.09 (m, 2 H), 2.84–2.75 (m, 4 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.0, 140.5, 138.6, 129.5, 129.1 (q, *J* = 32.3 Hz), 129.0,

125.5 (q, $J$ = 3.7 Hz), 124.0 (q, $J$ = 270.3), 123.6, 120.8, 53.8, 48.9, 37.7, 30.9; IR (film) 1706 $cm^{-1}$. Anal. calcd for $C_{18}H_{17}F_3N_2O$: C, 64.66; H, 5.13; N, 8.38. Found: C, 64.79; H, 5.13; N, 8.29.

**4-((1-Methyl-2-oxo-3-phenylimidazolidin-4-yl)methyl)benzonitrile (II-1q).** Reaction of 95.1 mg (0.5 mmol) of 1-allyl-1-methyl-3-phenylurea with 109.2 mg of 4-bromobenzonitrile following the general procedure without undecane afforded 115 mg (79%) of the title compound as a white powder. This material contained 20% aliphatic impurities. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, $J$ = 8.0 Hz, 2 H), 7.48 (d, $J$ = 8.0 Hz, 2 H), 7.35 (t, $J$ = 8.0 Hz, 2 H), 7.21 (d, $J$ = 7.5 Hz, 2 H), 7.09 (t, $J$ = 7.0 Hz, 1 H), 4.56–4.42 (m, 1 H), 3.39 (t, $J$ = 9.0 Hz, 1 H), 3.20–2.99 (m, 2 H), 2.83 (dd, $J$ = 8.5, 14.0 Hz, 1 H), 2.27 (s, 3 H).

**1,4-Dibenzyl-3-(4-methoxyphenyl)imidazolidin-2-one (II-1r).** Reaction of 148.2 mg (0.5 mmol) of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea with 94.2 mg (0.6 mmol) of bromobenzene following the general procedure without undecane afforded 173 mg (93%) of the title compound as a white solid, m.p. 88–90 $^o$C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, $J$ =9.2 Hz, 2 H), 7.31–7.13 (m, 8 H), 7.00 (d, $J$ = 6.4 Hz, 2 H), 6.92 (d, $J$ = 8.8 Hz, 2 H), 4.41–4.27 (m, 3 H), 3.79 (s, 3 H), 3.20 (t, $J$ = 8.8 Hz, 1 H), 3.07–2.94 (m, 2 H), 2.62 (dd, $J$ = 9.2, 13.6 Hz, 1 H;  ); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.2, 156.2, 136.9, 136.2, 131.6, 129.1, 128.5, 128.4, 127.9, 127.2, 126.6, 123.4, 114.2, 55.3, 55.0, 47.8, 46.2, 37.9; IR (film) 1698 $cm^{-1}$. MS (ESI): 395.1738 (395.1735 calcd for $C_{28}H_{32}N_2O_2$, M + $Na^+$).

**1-Benzyl-4-(4-tert-butylbenzyl)-3-(4-methoxyphenyl)imidazolidin-2-one (II-1s).** Reaction of 148 mg (0.5 mmol) of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea with 128 mg (0.6 mmol) of 1-bromo-4-tert-butylbenzene for 30 min according to the general procedure afforded 206 mg (97%) of the title compound as an orange oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, $J$ = 9.2 Hz, 2 H), 7.35–7.20 (m, 7 H), 6.99–6.92 (m, 4 H), 4.48–4.29 (m, 3 H), 3.82 (s, 3 H), 3.26 (t, $J$ = 8.8 Hz, 1 H), 3.08 (dd, $J$ = 5.2, 8.8 Hz, 1 H), 3.00 (dd, $J$ = 3.2, 13.6 Hz, 1 H), 2.62 (dd, $J$ = 9.2, 13.6 Hz, 1 H), 1.29 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.1, 149.4, 136.9, 133.2, 131.6, 128.7, 128.4, 127.9, 127.2, 125.3, 123.3, 114.2, 55.3, 55.1, 47.8, 46.4, 37.5, 34.2, 31.2; IR (film) 1701 $cm^{-1}$. MS (ESI): 429.2523 (429.2542 calcd for $C_{28}H_{32}N_2O_2$, M + $H^+$).

**1-Benzyl-3-(4-methoxyphenyl)-4-(2-methylbenzyl)imidazolidin-2-one (II-1t).** Reaction of 148 mg (0.5 mmol) of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea with 103 mg (0.6 mmol) of 2-bromotoluene for 8 h according to the general procedure afforded 138 mg (71%) of the title compound as a white solid, m.p. 83–85 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42–7.40 (m, 2 H), 7.33–7.19 (m, 5 H), 7.09–7.03 (m, 3 H), 6.93–6.91 (m, 3 H), 4.41 (s, 2 H), 4.32–4.29 (m, 1 H), 3.80 (s, 3 H), 3.20 (t, *J* = 8.8 Hz, 1 H), 3.08–3.00 (m, 2 H), 2.56 (dd, *J* = 3.6, 14.0 Hz, 1 H), 2.14 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.6, 137.1, 136.4, 134.9, 131.7, 130.6, 129.7, 128.7, 128.3, 127.5, 126.9, 126.1, 124.1, 114.4, 55.5, 54.6, 48.1, 46.6, 35.5, 19.5; IR (film) 1699 $cm^{-1}$. Anal. calcd for $C_{25}H_{26}N_2O_2$: C, 77.69: H, 6.78; N, 7.25. Found: C, 77.80; H, 6.85; N, 7.33.

**4-[1-Benzyl-3-(4-methoxyphenyl)-2-oxoimidazolidin-1-ylmethyl]benzoic acid *tert*-butylester (II-1u).** Reaction of 148 mg (0.5 mmol) of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea with 154 mg (0.6 mmol) of 4-bromo-*tert*-butylbenzoate for 8 h according to the general procedure afforded 176 mg (75%) of the title compound as a yellow solid, m.p. 78–82 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 2 H), 7.43 (d, *J* = 9.0 Hz, 2 H), 7.29–7.24 (m, 3 H), 7.12 (d, *J* = 6.5 Hz, 2 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 8.5 Hz, 2 H), 4.39–4.28 (m, 3 H), 3.78 (s, 3 H), 3.21 (t, *J* = 9.0 Hz, 1 H), 3.01–2.97 (m, 2 H), 2.74 (dd, *J* = 5.0, 14.0 Hz, 1 H), 1.57 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 165.6, 158.3, 156.6, 141.2, 137.0, 131.7, 130.8, 129.8, 129.3, 128.7, 128.2, 127.6, 123.7, 114.6, 81.1, 55.6, 54.9, 48.1, 46.2, 38.1, 28.3; IR (film) 1700 $cm^{-1}$. Anal. calcd for $C_{29}H_{32}N_2O_4$: C, 73.70; H, 6.83; N, 5.93. Found: C, 73.40; H, 6.90; N, 5.81.

**1-Ethyl-4-methyl-4-(2-methylbenzyl)-3-phenylimidazolidin-2-one (II-26a).** Reaction of 109 mg (0.5 mmol) of 1-ethyl-1-(2-methylallyl)-3-phenylurea with 103 mg (0.6 mmol) of 2-bromotoluene for 5 h according to the general procedure afforded 135 mg (88%) of the title compound as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.0 Hz, 2 H), 7.34–7.28 (m, 3 H), 7.19–7.08 (m, 4 H), 3.44–3.34 (m, 2 H), 3.32–3.22 (m, 1 H), 3.05 (d, *J* = 13.5 Hz, 1 H), 2.92 (d, *J* = 8.5 Hz, 1 H), 2.79 (d, *J* = 14.0 Hz, 1 H), 2.25 (s, 3 H), 1.33 (s, 3 H), 1.13 (t, *J* = 7.5 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.2, 137.0, 136.8, 134.8, 130.6, 130.6, 129.3, 128.8, 126.8, 126.7, 125.7, 61.4, 53.1, 39.8,

38.5, 24.7, 20.0, 12.6; IR (film) 1698 $cm^{-1}$. Anal calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.54; H, 7.91; N, 9.01.

**1-Ethyl-4-methyl-3-phenyl-4-(3-trifluoromethylbenzyl)imidazolidin-2-one (II-26b).** Reaction of 109 mg (0.5 mmol) of 1-ethyl-1-(2-methylallyl)-3-phenylurea with 135 mg (0.6 mmol) of 3-bromobenzotrifluoride according to a slight modification of the general procedure in which the urea was added to the reaction mixture as a 0.25 M solution in toluene afforded 154 mg (81%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1 H), 7.42–7.38 (m, 3 H), 7.35–7.27 (m, 5 H), 3.41 (d, *J* = 9.0 Hz, 1 H), 3.37–3.31 (m, 1 H), 3.23–3.15 (m, 1 H), 3.09 (d, *J* = 16.0 Hz, 1 H), 2.92 (d, *J* = 9.0 Hz, 1 H), 2.76 (d, *J* = 13.5 Hz, 1 H), 1.29 (s, 3 H), 1.07 (t, *J* = 7.0 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.6, 136.9, 133.7, 130.8 (q, *J* = 32.2 Hz), 129.4, 129.2, 129.0, 127.2, 127.0 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 271 Hz), 123.9 (q, *J* = 3.7 Hz), 60.5, 53.0, 44.4, 38.4, 24.7, 12.8; IR (film) 1701 $cm^{-1}$. MS (ESI): 385.1501 (385.1504 calcd for $C_{20}H_{21}F_3N_2O$ M + $Na^+$).

**1-Benzyl-3-(4-methoxyphenyl)-4-methyl-4-(4-methylbenzyl)imidazolidin-2-one (II-26c).** Reaction of 155 mg (0.5 mmol) of 1-benzyl-3-(4-methoxyphenyl)-1-(2-methylallyl)urea with 103 mg (0.6 mmol) of 4-bromotoluene for 7.5 h according to the general procedure afforded 195 mg (97%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2 H), 7.32–7.28 (m, 3 H), 7.23 (d, *J* = 9.0 Hz, 2 H), 6.99 (d, *J* = 7.5 Hz, 2 H), 6.95 (d, *J* = 9.0 Hz, 2 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 4.54 (d, *J* = 15.0 Hz, 1 H), 4.34 (d, *J* = 15.0 Hz, 1 H), 3.84 (s, 3 H), 3.32 (d, *J* = 9.5 Hz, 1 H), 2.88 (d, *J* = 13.0 Hz, 1 H), 2.75 (d, *J* = 9.0 Hz, 1 H), 2.64 (d, *J* = 13.0 Hz, 1 H), 2.28 (s, 3 H), 1.19 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.4, 158.5, 137.3, 136.1, 133.1, 131.0, 130.0, 129.1, 128.8, 128.4, 128.2, 127.3, 114.1, 60.6, 55.3, 52.7, 47.9, 43.7, 24.0, 20.8; IR (film) 1699 $cm^{-1}$. MS (ESI): 423.2042 (423.2048 calcd for $C_{26}H_{28}N_2O_2$, M + $Na^+$).

**(±)-(4*R*,5*R*)-4-[1-Benzyl-3-(4-methoxyphenyl)-5-methyl-2-oxoimidazolidin-4-ylmethyl]benzonitrile (II-26d).** Reaction of 155 mg (0.5 mmol) of 1-benzyl-1-(but-3-en-2-yl)-3-(4-methoxyphenyl)urea with 109 mg (0.6 mmol) of 4-bromobenzonitrile for 1 h according to the general procedure afforded 181 mg (88%) of the title compound as a clear oil. This compound was isolated as a 12:1 mixture of diastereomers as judged by $^1$H NMR analysis. The crude reaction mixture contained an 8:1 mixture of diastereomers.

Data are for the major diastereomer. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 7.33–7.28 (m, 3 H), 7.24–7.10 (m, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.94 (d, *J* = 9.2 Hz, 2 H), 4.82 (d, *J* = 15.2 Hz, 1 H), 4.00–3.95 (m, 1 H), 3.95 (d, *J* = 15.2 Hz, 1 H), 3.83 (s, 3 H), 3.18 (dt, *J* = 6.4, 11.2 Hz, 1 H), 2.89 (dd, *J* = 4.0, 14.0 Hz, 1 H), 2.80 (dd, *J* = 7.2 Hz, 14.0 Hz, 1 H), 1.08 (d, *J* = 6.4 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.2, 141.6, 136.7, 132.0, 131.3, 130.1, 128.5, 127.9, 127.3, 123.2, 118.5, 114.3, 110.5, 61.8, 55.3, 51.0, 44.7, 37.2, 18.5; IR (film) 2227, 1697 cm$^{-1}$. MS (ESI): 412.2013 (412.2025 calcd for $C_{26}H_{25}N_3O_2$, M + $H^+$).

**(±)-(4*R*,5*R*)-1-Benzyl-5-isopropyl-3-(4-methoxyphenyl)-4-(4-methylbenzyl)imidazolidin-2-one (II-26e).** Reaction of 169 mg (0.5 mmol) of 1-benzyl-3-(4-methoxyphenyl)-1-(4-methylpent-1-en-3-yl)urea with 103 mg (0.6 mmol) of 4-bromotoluene for 1 h according to the general procedure afforded 171 mg (85%) of the title compound as a yellow oil. This compound was isolated as a >20:1 mixture of diastereomers as judged by $^1$H NMR analysis. The crude reaction mixture contained a >20:1 mixture of diastereomers. Data are for the major diastereomer. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 9.0 Hz, 2 H), 7.35–7.27 (m, 3 H), 7.17–7.12 (m, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 6.95 (d, *J* = 9.0 Hz, 2 H), 6.73 (d, *J* = 8.0 Hz, 2 H), 4.99 (d, *J* = 15.5 Hz, 1 H), 3.99 (dt, *J* = 3.0, 8.5, 1 H), 3.88 (d, *J* = 15.5 Hz, 1 H), 3.82 (s, 3 H), 3.09 (dd, *J* = 2.5, 3.5 Hz, 1 H), 2.80 (dd, *J* = 3.0, 13.5 Hz, 1 H), 2.51 (dd, *J* = 8.5, 13.5 Hz, 1 H), 2.29 (s, 3 H), 1.90–1.80 (m, 1 H), 0.76 (d, *J* = 7.0 Hz, 3 H), 0.46 (d, *J* = 6.5 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.0, 155.6, 137.2, 136.0, 132.8, 131.9, 129.5, 129.0, 128.5, 128.0, 127.2, 122.0, 114.3, 58.6, 55.9, 55.4, 44.9, 37.9, 27.7, 21.0, 17.1, 15.0; IR (film) 1695 cm$^{-1}$. MS (ESI): 451.2374 (451.2361 calcd for $C_{28}H_{32}N_2O_2$, M + $Na^+$).

**(±)-(1*R*,7a*R*)-2-(4-Methoxyphenyl)-1-(3-(trifluoromethyl)benzyl)tetrahydro-1H-pyrrolo[1,2-*c*]imidazol-3(2H)-one (II-26f)** Reaction of 62 mg (0.25 mmol) of *N*-(4-methoxyphenyl)-2-vinylpyrrolidine-1-carboxamide with 68 mg (0.3 mmol) of 3-bromobenzotrifluoride for 1 h according to the general procedure afforded 86 mg (88%) of the title compound as a yellow oil. This compound was isolated as a >20:1 mixture of diastereomers as judged by $^1$H NMR analysis. The crude reaction mixture contained a 20:1 mixture of diastereomers. Data are for the major diastereomer. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.39–7.31 (m, 4 H), 6.92 (d,

*J* = 9.2 Hz, 2 H), 4.29 (ddd, *J* = 2.4, 4.0, 9.6 Hz, 1 H), 3.81 (s, 3 H), 3.76–3.66 (m, 1 H), 3.50–3.41 (m, 1 H), 3.14 (dd, *J* = 3.6, 13.6 Hz, 1 H), 3.14–3.03 (m, 1 H), 2.85 (dd, *J* = 9.2, 14.0 Hz, 1 H), 2.02–1.88 (m, 1 H), 1.88–1.68 (m, 2 H), 1.46–1.29 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.3, 137.7, 132.6, 131.0, 130.8 (q, *J* = 32.2 Hz), 129.0, 125.8 (q, *J* = 3.6 Hz), 123.9 (q, *J* = 270.3 Hz), 123.6 (q, *J* = 3.7 Hz), 123.4, 114.4, 60.8, 60.8, 55.4, 45.1, 38.4, 30.8, 24.6; IR (film) 1702 cm$^{-1}$. MS (ESI): 391.1634 (391.1633 calcd for $C_{21}H_{21}F_3N_2O_2$, M + $H^+$).

**(±)-(1*R*,8a*R*)-1-Benzyl-2-(4-methoxyphenyl)hexahydroimidazo[1,5-*a*]pyridin-3(5H)-one (II-26g).** Reaction of 130 mg (0.5 mmol) of *N*-(4-methoxyphenyl)-2-vinylpiperidine-1-carboxamide with 94 mg (0.6 mmol) of bromobenzene for 1 h according to the general procedure afforded 137 mg (81%) of the title compound as a brown oil. This compound was isolated as a 20:1 mixture of diastereomers as judged by $^1$H NMR analysis. The crude reaction mixture contained an 11:1 mixture of diastereomers. Data are for the major diastereomer. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.0 Hz, 2 H), 7.32–7.27 (m, 2 H), 7.25–7.21 (m, 1 H), 7.13 (d, *J* = 7.0 Hz, 2 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 4.00–3.90 (m, 2 H), 3.81 (s, 3 H), 3.27–3.19 (m, 1 H), 3.07 (dd, *J* = 4.0, 14.0 Hz, 1 H), 2.74–2.61 (m, 2 H), 1.78–1.70 (m, 1 H), 1.62–1.54 (m, 1 H), 1.44–1.16 (m, 4 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.8, 156.2, 136.6, 131.7, 129.1, 128.5, 126.6, 123.7, 114.2, 62.2, 57.1, 55.3, 40.8, 37.7, 30.9, 24.6, 23.2; IR (film) 1702 cm$^{-1}$. MS (ESI): 359.1738 (359.1735 calcd for $C_{21}H_{24}N_2O_2$, M + $Na^+$).

**(±)-(4*R*,5*R*)-1-Benzyl-5-(benzyloxymethyl)-3-(4-methoxyphenyl)-4-(4-methylbenzyl)imidazolidin-2-one (II-26h).** Reaction of 208 mg (0.5 mmol) of 1-benzyl-1-(1-(benzyloxy)but-3-en-2-yl)-3-(4-methoxyphenyl)urea with 103 mg (0.6 mmol) of 4-bromotoluene for 5 h according to the general procedure afforded 78 mg (31%) of the title compound as a yellow oil. This compound was isolated as a 20:1 mixture of diastereomers as judged by $^1$H NMR analysis. The crude reaction mixture contained a 20:1 mixture of diastereomers. Data are for the major diastereomer. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 9.0 Hz, 2 H), 7.34–7.24 (m, 6 H), 7.17–7.09 (m, 4 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 6.77 (d, *J* = 7.5 Hz, 2 H), 4.78 (d, *J* = 15.0 Hz, 1 H), 4.27 (s, 2 H), 4.17 (m, 1 H), 4.05 (d, *J* = 15.5 Hz, 1 H), 3.81 (s, 3 H), 3.37 (dd, *J* = 5.0, 9.0 Hz, 1 H), 3.27 (dd, *J* = 5.0, 10.0 Hz, 1 H), 3.21 (dd, *J* = 5.0, 10.0 Hz, 1 H), 2.89

(dd, *J* = 3.0, 13.5 Hz, 1 H), 2.57 (dd, *J* = 8.5, 14.0 Hz, 1 H), 2.29 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 157.4, 156.0, 137.7, 137.4, 136.1, 132.7, 131.9, 129.3, 129.2, 128.4, 128.3, 128.0, 127.6, 127.5, 127.2, 123.1, 114.3, 72.9, 69.8, 58.1, 55.4, 55.0, 45.8, 37.3, 21.0; IR (film) 1698 $cm^{-1}$. MS (ESI): 529.2458 (529.2467 calcd for $C_{33}H_{34}N_2O_3$, M + $Na^+$).

**3-Benzyl-5-(biphenyl-4-ylmethyl)-1-(4-methoxyphenyl)-4,4-dimethylimidazolidin-2-one (II-32)** Reaction of 162 mg (0.5 mmol) of 1-benzyl-3-(4-methoxyphenyl)-1-(2-methylbut-3-en-2-yl)urea with 140 mg (0.6 mmol) of 4-bromobiphenyl for 4.5 h according to the general procedure afforded 79 mg (33%) of the title compound as a clear oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 6.8 Hz, 2 H), 7.46–7.37 (m, 4 H), 7.36–7.24 (m, 7 H), 7.24–7.17 (m, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 4.50 (d, *J* = 15.6 Hz, 1 H), 4.28 (d, *J* = 15.6 Hz, 1 H), 4.13 (dd, *J* = 4.4, 9.2 Hz, 1 H), 3.75 (s, 3 H), 3.03 (dd, *J* = 4.4, 14.8 Hz, 1 H), 2.80 (dd, *J* = 9.2, 14.8 Hz, 1 H), 1.20 (s, 3 H), 0.99 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.9, 140.6, 139.9, 139.1, 136.9, 131.8, 129.3, 128.7, 128.3, 127.6, 127.2, 127.0, 126.9, 126.8, 125.6, 114.1, 67.0, 59.8, 55.4, 43.1, 34.1, 26.7, 20.1; IR (film) 1698 $cm^{-1}$. MS (ESI): 477.2533 (477.2542 calcd for $C_{32}H_{32}N_2O_2$, M + $H^+$).

**(±)-(3a*S*,5*R*,7a*R*)-1,3-Diphenyl-5-(*p*-tolyl)octahydrobenzimidazol-2-one (II-27a).** Reaction of 50 mg (0.17 mmol) of 1-(cyclohex-2-enyl)-1,3-diphenylurea with 35 mg (0.21 mmol) of 4-bromotoluene for 8 h according to the general procedure using $PEt_3$•$HBF_4$ (4 mol %) in place of Xantphos afforded 33 mg (50%) of the title compound as a grey solid, m.p. 195–198 °C. Analysis of the crude reaction mixture by $^1$H NMR indicated that the desired product had formed with >20:1 dr. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 2 H), 7.44–7.40 (m, 2 H), 7.33–7.21 (m, 5 H), 7.08–7.00 (m, 5 H), 4.46–4.40 (m, 1 H), 4.32–4.29 (m, 1 H), 2.55–2.49 (m, 1 H), 2.36–2.29 (m, 1 H), 2.28–2.23 (m, 1 H), 2.26 (s, 3 H), 1.82–1.59 (m, 4 H); $^{13}$C (125 MHz, $CDCl_3$) δ 157.3, 142.6, 139.1, 138.1, 136.2, 129.4, 129.2, 126.7, 126.0, 125.3, 123.4, 119.9, 55.4, 53.6, 40.0, 35.6, 28.0, 25.4, 21.2 (one carbon signal is absent due to incidental equivalence); IR (film) 1702 $cm^{-1}$. MS (ESI): 405.1960 (405.1943 calcd for $C_{26}H_{26}N_2O$, M + $Na^+$).

**(±)-(1'*S*,4*R*)-4-1'-[(4-Benzhydrylideneamino)phenyl]ethyl-1,3-diphenylimidazolidin-2-one (II-27b).** Reaction of 133 mg (0.50 mmol) of (*E*)-1-(but-2-

enyl)-1,3-diphenyl urea (4:1 mixture of *E*:*Z* isomers) with 202 mg (0.6 mmol) of benzhydrilidene-(4-bromophenyl)amine[49] for 8 h according to the general procedure afforded 132 mg (51%) of the title compound as a yellow solid, m.p. 190–194 °C. Analysis of the crude reaction mixture by $^1$H NMR indicated that the desired product had formed with >20:1 dr. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74–7.72 (m, 2 H), 7.57–7.52 (m, 4 H), 7.48–7.38 (m, 5 H), 7.35 7.31 (m, 2 H), 7.29–7.22 (m, 3 H), 7.19–7.02 (m, 6 H), 6.71 (d, *J* = 8.4 Hz, 2 H), 4.63–4.59 (m, 1 H), 3.52–3.45 (m, 2 H), 3.36–3.33 (m, 1 H), 1.11 (d, *J* = 7.2 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.9, 155.5, 150.4, 140.2, 139.7, 138.0, 136.5, 135.7, 131.1, 129.8, 129.5, 129.3, 129.0, 128.8, 128.5, 128.1, 127.7, 124.7, 123.0, 122.5, 121.6, 118.0, 57.3, 42.8, 37.3, 10.5; IR (film) 1707, 1597 cm$^{-1}$. MS (ESI): 522.2546 (522.2545 calcd for $C_{36}H_{31}N_3O$, M + H$^+$).

**(±)-(1'*S*,4*R*)-4-{[1-Benzyl-3-(4-methoxyphenyl)-2-oxoimidazolidin-4-yl](phenyl)methyl}benzonitrile (II-27c).** Reaction of 186 mg (0.5 mmol) of 1-benzyl-1-cinnamyl-3-(4-methoxyphenyl)urea with 109 mg (0.6 mmol) of 4-bromobenzonitrile for 26 h according to a modified general procedure where $Pd(OAc)_2$ was used as the Pd source, $Cs_2CO_3$ was used as the base, dioxane was used as solvent and a reaction temperature of 100 °C afforded 179 mg (76%) of the title compound as a yellow oil. Analysis of the crude reaction mixture by $^1$H NMR indicated that the desired product had formed with >20:1 dr. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2 H), 7.30–7.22 (m, 6 H), 7.19 (d, *J* = 8.8 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.07–7.01 (m, 2 H), 7.00–6.94 (m, 2 H), 6.78 (d, *J* = 9.2 Hz, 2 H), 4.99 (p, *J* = 5.2 Hz, 1 H), 4.40 (d, *J* = 6.0 Hz, 1 H), 4.26 (s, 2 H), 3.78 (s, 3 H), 3.52 (t, *J* = 9.2 Hz, 1 H), 3.20 (dd, *J* = 4.4, 9.2 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.9, 156.3, 146.3, 138.3, 136.4, 132.0, 131.4, 129.1, 128.6, 128.4, 127.7, 127.3, 127.2, 124.3, 118.4, 114.0, 110.3, 56.2, 55.3, 52.9, 47.6, 45.2 (one carbon signal is absent due to incidental equivalence); IR (film) 2227, 1698 cm$^{-1}$. MS (ESI): 474.2181 (474.2182 calcd for $C_{31}H_{27}N_3O_2$, M + Na$^+$).

**(±)-(1'*S*,4*R*)-1-Benzyl-4-[6-methoxynaphthalen-2-yl(phenyl)methyl]-3-(4-methoxyphenyl)imidazolidin-2-one (II-27d).** Reaction of 93 mg (0.25 mmol) of 1-benzyl-1-cinnamyl-3-(4-methoxyphenyl)urea with 71 mg (0.3 mmol) of 2-bromo-6-methoxynaphthalene for 14 h according to a modified general procedure where $Pd(OAc)_2$ was used as the Pd source, $Cs_2CO_3$ was the base, dioxane was the solvent, and 100 °C

was the reaction temperature afforded 97 mg (73%) of the title compound as an off-white solid, m.p. 86–92 °C. Analysis of the crude reaction mixture by $^1$H NMR indicated that the desired product had formed with >20:1 dr. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.8, 16.4 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 3 H), 7.26–7.17, m, 6 H), 7.13 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.09–7.04 (m, 2 H), 7.01–6.95 (m, 2 H), 6.94–6.89 (m, 2 H), 6.83 (d, *J* = 9.2 Hz, 2 H), 5.14 (dt, *J* = 4.0, 9.6 Hz, 1 H), 4.62 (d, *J* = 3.6 Hz, 1 H), 4.20 (q, *J* = 15.2 Hz, 2 H), 3.88 (s, 3 H), 3.73 (s, 3 H), 3.63 (t, *J* = 9.2 Hz, 1 H), 3.38 (dd, *J* = 4.4, 8.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.6, 155.8, 139.2, 136.6, 135.8, 133.2, 131.7, 129.4, 129.1, 128.5, 128.4, 128.3, 127.8, 127.7, 127.2, 127.1, 126.9, 126.1, 123.1, 119.0, 114.2, 105.5, 55.8, 55.4, 55.3, 50.5, 47.7, 44.6; IR (film) 1698 cm$^{-1}$. MS (ESI): 529.2497 (529.2491 calcd for $C_{35}H_{32}N_2O_3$, M + H$^+$).

**(±)-(3a*S*,4*R*,6a*R*)-1-Benzyl-3-phenyl-4-(*p*-tolyl)hexahydrocyclopentaimidazol-2-one (II-27e).** Reaction of 150 mg (0.51 mmol) of 1-benzyl-1-cyclopent-2-enyl-3-phenylurea with 105 mg (0.62 mmol) of 4-bromotoluene for 8 h according to the general procedure afforded 172 mg (88%) of the title compound as a white solid, m.p. 170–174 °C. Analysis of the crude reaction mixture by $^1$H NMR indicated that the desired product had formed with >20:1 dr. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, 4 H), 7.30–7.24 (m, 1 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 6.94–6.91 (m, 5 H), 6.75–6.70 (m, 3 H), 4.90 (d, *J* = 15.5 Hz, 1 H), 4.78 (t, *J* = 7.5 Hz, 1 H), 4.15 (d, *J* = 15.0 Hz, 1 H), 4.10–4.07 (m, 1 H), 3.21–3.16 (m, 1 H), 2.15–2.06 (m, 5 H), 1.94–1.89 (m, 1 H), 1.67–1.59 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.7, 140.0, 137.3, 136.2, 135.2, 129.2, 128.8, 128.63, 128.60, 127.9, 127.7, 122.1, 120.2, 61.1, 58.5, 51.4, 45.9. 29.9, 29.3, 21.0; IR (film) 1699 cm$^{-1}$. MS (ESI): 405.1957 (405.1943 calculated for $C_{26}H_{26}N_2O$, M + Na$^+$).

**(*E*)-1-Benzyl-4-cinnamyl-3-(4-methoxyphenyl)imidazolidin-2-one (II-31a).** Reaction of 148 mg (0.5 mmol) of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea with 183mg (1.0 mmol) of β-bromostyrene for 3 h according to the general procedure afforded 147 mg (74%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.2, 2 H), 7.34–7.19 (m, 10 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.33 (d, *J* = 15.6 Hz, 1 H), 6.01 (dt, *J* = 7.2, 15.6 Hz, 1 H), 4.47 (d, *J* = 14.8 Hz, 1 H), 4.41 (d, *J* = 14.8 Hz, 1 H), 4.33–4.24 (m, 1 H), 3.81 (s, 3 H), 3.42 (t, *J* = 9.2 Hz, 1 H), 3.13, (dd, *J* = 5.6, 9.2, 1 H), 2.55–2.38 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.4, 136.9, 136.7, 133.7,

131.4, 128.5, 128.4, 128.0, 127.4, 127.3, 126.0, 123.9, 123.3, 114.2, 55.4, 53.6, 48.0, 46.4, 35.7; IR (film) 1698 $cm^{-1}$. MS (ESI): 399.2075 (399.2073 calcd for $C_{26}H_{26}N_2O_2$, M + $H^+$).

**(*E*-)-1-Benzyl-4-cinnamyl-3-(4-methoxyphenyl)-4-methylimidazolidin-2-one (II-31b).** Reaction of 155 mg (0.5 mmol) of 1-benzyl-3-(4-methoxyphenyl)-1-(2-methylallyl)urea with 183 mg (1.0 mmol) of β-bromostyrene for 1.5 h according to the general procedure afforded 177 mg (86%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34–7.18 (m, 12 H), 6.93 (d, *J* = 9.2 Hz, 2 H), 6.32 (d, *J* = 16 Hz, 1 H), 6.16–6.05 (m, 1 H), 4.55 (d, *J* = 15.2 Hz, 1 H), 4.34 (d, *J* = 15.2 Hz, 1 H), 3.83 (s, 3 H), 3.31 (d, *J* = 8.8 Hz, 1 H), 2.99 (d, *J* = 8.8 Hz, 1 H), 2.51 (ddd, *J* = 1.2, 6.8, 14.4 Hz, 1 H), 2.25 (ddd, *J* = 0.8, 7.6, 14.0 Hz, 1 H), 1.29 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.4, 158.5, 137.1, 136.8, 134.0, 130.8, 128.9, 128.4, 128.4, 128.0, 127.4, 127.2, 126.0, 123.9, 114.1, 59.7, 55.3, 53.2, 47.9, 42.3, 25.6; IR (film) 1698 $cm^{-1}$. MS (ESI): 435.2047 (435.2048 calcd for $C_{27}H_{28}N_2O_2$, M + $Na^+$).

**(±)-(*E*)-(4*R*,5*R*)-1-Benzyl-3-(4-methoxyphenyl)-5-methyl-4-[3-(trimethylsilyl)allyl]imidazolidin-2-one (II-31c).** Reaction of 155 mg (0.5 mmol) of 1-benzyl-1-(but-3-en-2-yl)-3-(4-methoxyphenyl)urea with 179 mg (1.0 mmol) of 2-bromovinyltrimethylsilane for 1 h according to the general procedure using Nixantphos in place of Xantphos afforded 187 mg (92%) of the title compound as a clear oil. This compound was isolated as a 10:1 mixture of diastereomers as judged by $^1$H NMR analysis The crude reaction mixture contained a 7:1 mixture of diastereomers. Data are for the major diastereomer. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 7 H). 6.90 (d, *J* = 9.0 Hz, 2 H), 5.77 (dt, *J* = 6.5, 18.5 Hz, 1 H), 5.54 (d, *J* = 18.5 Hz, 1 H), 4.83 (d, *J* = 15.5 Hz, 1 H), 4.13 (d, *J* = 15.0 Hz, 1 H), 3.80 (s, 3 H), 3.76–3.70 (m, 1 H), 3.33–3.25 (m, 1 H), 2.44–2.37 (m, 1 H), 2.32–2.23 (m, 1 H), 1.19 (d, *J* = 6.5, 3 H), -0.03 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 157.9, 156.4, 139.9, 137.3, 135.3, 131.6, 128.5, 128.0, 127.2, 124.2, 114.1, 61.3, 55.3, 52.4, 45.2, 38.8, 18.6, -1.5; IR (film) 1699 $cm^{-1}$. Anal calcd for $C_{24}H_{32}N_2O_2Si$: C, 70.55; H, 7.89; N, 6.86. Found: C, 70.66; H, 7.95; N, 6.81.

**(±)-(*E*)-(1*R*,8a*R*)-1-(But-2-enyl)-2-(4-methoxyphenyl)hexahydroimidazo[1,5-a]pyridin-3-(5H)-one (II-31d).** Reaction of 130 mg (0.5 mmol) of *N*-(4-methoxyphenyl)-2-vinylpiperidine-1-carboxamide with 121 mg (1.0 mmol) of 1-bromo-

1-propene for 40 min according to the general procedure afforded 130 mg (87%) of the title compound as a brown oil. The crude reaction mixture contained a 1.5:1 mixture of diastereomers as judged by $^1$H NMR analysis. Upon purification the compound was obtained as a 1.6:1 mixture of diastereomers. Data are for the mixture. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2 H), 6.88 (d, *J* = 9.2 Hz, 2 H), 5.64–5.42 (m, 1 H), 5.36–5.24 (m, 1 H), 3.99 (d, *J* = 12.0 Hz, 1 H), 3.79 (s, 3 H), 3.76–3.65 (m, 1 H), 3.28–3.16 (m, 1 H), 2.74 (dt, *J* = 3.2, 13.2 Hz, 1 H), 2.41–2.14 (m, 2 H), 1.94–1.86 (m, 1 H), 1.82–1.74 (m, 1 H), 1.67–1.52 (m, 4 H), 1.50–1.31 (m, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.1, 131.8, 129.0, 125.0, 123.8, 114.1, 60.7, 56.9, 55.4, 40.8, 34.5, 31.0, 24.7, 23.4, 18.0; IR (film) 1699 cm$^{-1}$. MS (ESI): 323.1729 (323.1735 calcd for $C_{18}H_{24}N_2O_2$, M + $Na^+$).

**Selective Deprotection of II-1t**

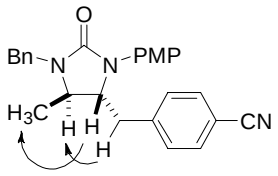
**1-Benzyl-4-(2-methylbenzyl)imidazolidin-2-one (II-40).** A round bottom flask was charged with 1-benzyl-3-(4-methoxyphenyl)-4-(2-methylbenzyl)imidazolidin-2-one (**II-1t**) (77 mg, 0.2 mmol) and $CH_3CN$ (2 mL). The resulting solution was cooled to 0 °C, and a solution of ceric ammonium nitrate (329 mg, 0.6 mmol) in water (3 mL) was slowly added over 3 min. The reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was then transferred to a separatory funnel and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with saturated aqueous $Na_2SO_3$ (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (15 mL). The organic layer was then dried over anhydrous $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to afford 41 mg (73%) of the title compound as a yellow solid, m.p. 91–96 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 2 H), 7.31–7.24 (m, 3 H), 7.17–7.09 (m, 3 H), 7.08–7.02 (m, 1 H), 4.62 (s, 1 H), 4.38 (s, 2 H), 3.92–3.80 (m, 1 H), 3.38 (t, *J* = 8.4 Hz, 1 H), 3.03 (dd, *J* = 6.0, 8.8 Hz, 1 H), 2.79 (d, *J* = 7.2 Hz, 2 H), 2.27 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 137.0, 136.2, 135.2, 130.6, 129.6, 128.6, 128.0, 127.4, 126.9, 126.2, 49.9, 49.7, 47.4, 39.0, 19.5; IR (film) 3242, 1697 cm$^{-1}$. MS (ESI): 303.1461 (303.1473 calcd for $C_{18}H_{20}N_2O$, M + $Na^+$).

**1-(4-Methoxyphenyl)-5-(2-methylbenzyl)imidazolidin-2-one (II-41).** A flame-dried three-necked round bottom flask was cooled under a stream of argon and equipped with a dry ice/ acetone cold finger. The flask was cooled to –78 °C and charged with liquid ammonia (30 mL). Li wire (20 mg, 3 mmol) was added and the solution turned blue. The solution was stirred at –78 °C for 5 min and then a solution of 1-benzyl-3-(4-methoxyphenyl)-4-(2-methylbenzyl)imidazolidin-2-one (**22**) (116 mg, 0.3mmol) in THF (10 mL) was added. The resulting mixture was stirred at –78 °C for 40 min, then a solution of diphenyl ether (320 μL, 6 mmol) in THF (20 mL) was added and the mixture immediately turned clear. The solution was warmed to rt and 1mL of water was added. The resulting mixture was concentrated *in vacuo*, and the crude product was purified by flash chromatography on silica gel to afford 82 mg (92%) of the title compound as a white solid, m.p. 126–131 $^{o}$C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $J$ = 9.2 Hz, 2 H), 7.19–7.10 (m, 3 H), 7.10–7.04 (m, 1H), 6.94 (d, $J$ = 8.8 Hz, 2 H), 4.99 (s, 1 H), 4.50–4.37 (m, 1 H), 3.82 (s, 3 H), 3.44 (t, $J$ = 8.4 Hz, 1 H), 3.27 (dd, $J$ = 5.6, 8.0 Hz, 1 H), 3.09 (dd, $J$ = 3.6, 14.0 Hz, 1 H), 2.70 (dd, $J$ = 10.4, 14.0 Hz, 1 H), 2.24 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.0, 136.3, 134.9, 130.9, 130.5, 129.6, 126.8, 126.0, 125.1, 114.4, 57.6, 55.4, 43.0, 35.6, 19.4; IR (film) 3247, 1704, cm$^{-1}$. MS (ESI): 319.1412 (319.1422 calcd for $C_{18}H_{20}N_2O_2$, M + $Na^+$).

**Assignment of Product Stereochemistry**

**Stereochemistry of II-26d, II-26e** and **II-31c**

The stereochemistry of **II-26d** was assigned by $^{1}$H NMR nOe experiments as shown below.

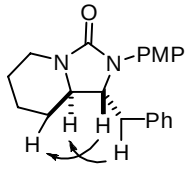



**II-26d**

The stereochemistry of **II-26e**, and **II-31c** was assigned based on analogy to **II-26d**.

**Stereochemistry of II-26g** and **II-31d**

The stereochemistry of **II-26g** was assigned by $^{1}$H NMR nOe experiments as shown below.

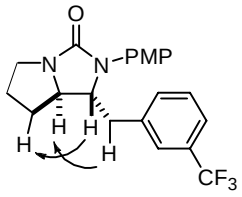



**II-26g**

The stereochemistry of **II-31d** was assigned based on analogy to **II-26g**.

**Stereochemistry of II-26f**

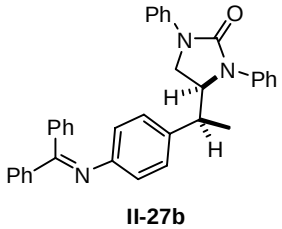
The stereochemistry of **II-26f** was assigned by $^{1}$H NMR nOe experiments as shown below.



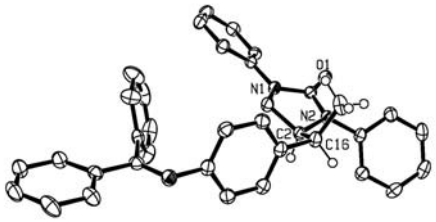

**II-26f**

**Stereochemistry of II-27b–II-27d**

The stereochemistry of **II-27b** was assigned by single crystal x-ray analysis as shown below.



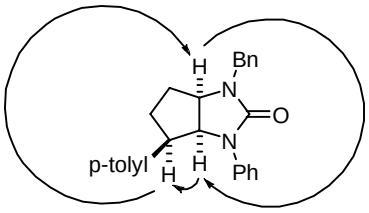

**II-27b**




The stereochemistry of **II-27c** and **II-27d** was assigned based on analogy to **II-27b**.

**Stereochemistry of II-27e**

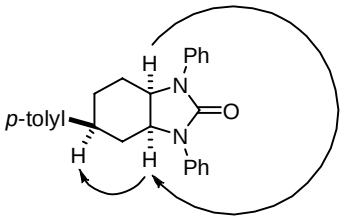
The stereochemistry of **II-27e** was assigned by $^{1}$H NMR nOe experiments as shown below.




**II-27e**

**Stereochemistry of II-27a**

The stereochemistry of **II-27a** was assigned by $^{1}$H NMR nOe experiments as shown below.




**II-27a**

## References


[1] a) Qian, F.; McCusker, J. E.; Zhang, Y.; Main, A. D.; Chlebowski, M.; Kokka, M.; McElwee-White, L. *J. Org. Chem.* **2002**, *67*, 4086–4092; b) Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741–4750.

[2] a) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837; b) Kim, M. S.; Kim, Y.-W.; Hahm, H. S.; Jang, J. W.; Lee, W. K.; Ha, H.-J. *Chem. Commun.* **2005**, 3062–3064.

[3] a) Hunt, P. A.; May, C.; Moody, C. J. *Tetrahedron Lett.* **1988**, *29*, 3001–3002; b) Balko, T. W.; Brinkmeyer, R. S.; Terando, N. H. *Tetrahedron Lett.* **1989**, *30*, 2045–2048; c) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330–7335.

[4] Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076.

[5] a) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311–3314; b) Benedí, C.; Bravo, F.; Uriz, P.; Fernandez, E.; Claver, C.; Castillon, S. *Tetrahedron Lett.* **2003**, *44*, 6073–6077.

[6] a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002; b) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113–2122; c) Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2699–2702.

[7] Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12–13.

[8] For leading references see: a) Muniz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763–773; b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689; c) Bar, G. L.J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309.

[9] Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Tetrahedron Lett.* **1983**, *24*, 11–14.

[10] Reactions times for the synthesis of *N*-allylureas were not optimized.

[11] For a more detailed account of the synthesis of the allylic amines see: Fritz, J. A.; Wolfe, J. P. *Tetrahedron*, **2008**, *64*, 6838–6852.

[12] a) Beaudoin Bertrand, M.; Wolfe, J. P. *Tetrahedron*, **2005**, *61*, 6447–6459. b) Ney, J.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651.

[13] For a review of Pd-catalyzed aerobic oxidative aminations see: Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910–1923.

[14] van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741-2769.

[15] a) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810–3813. b) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179–4181.

[16] a) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron*, **2001**, *42*, 4381–4384. b) Abad, A.; Agulló, C.; Cunat, A. C.; Vilanova, C. *Synthesis*, **2005**, *6*, 0915–0924. Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett.* **2006**, *8*, 5089–5091.

[17] a)Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104. b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048. c) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433–2435.

[18] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539–2541.

[19] Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895.

[20] For an example of base-mediated decomposition of carbamates see: Tom, N. J.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905–906.

[21] Golborn, P.; Scheinmann, F. *J. Chem. Soc. Perkin Trans.1* **1973**, 2870–2875.

[22] For an example of Ru and Rh-catalyzed transformations of an allylic amine to an imine followed by hydrolysis see: Jun, C-H.; Lee, H.; Park, J-B.; and Lee, D-Y. *Org. Lett.* **1999**, *1*, 2161–2164.

[23] For other examples of metal-catalyzed double bond isomerization see: a) Mirza-Aghayan, M.; Boukherroub, R.; Bolourtchian, M.; Hoseini, M.; Tabar-Hydar, K. *J. Organometallic Chem.* **2003**, *678*, 1–4. b) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106,* 5208–5217.

[24] a) Schriescheim, A.; Rowe, Jr. C. A. *J. Am. Chem. Soc.* **1962**, *84*, 3160–3164. b) Bank, S.; Rowe, Jr. C. A.; Schriesheim, A. *J. Am. Chem. Soc.* **1963**, *85*, 2115–2118. c) Price, C. C.; Snyder, W. H. *Tetrahedron Lett.* **1962**, *2*, 69–73.

[25] For a study on the effect of aryl halide electronics on C-C bond forming reductive elimination see: Culkin, D.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398–3416.
[26] For a previous example of use of $Cs_2CO_3$ in carboamination reactions and a comparison of the reactivity of (*E*) and (*Z*)-alkene substrates see: Beaudoin Bertrand, M.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851–8860.
[27] Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892.
[28] Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795–813.
[29] Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H.
*Angew. Chem. Int. Ed.* **1998**, *37*, 3389–3391.
[30] Suh, M-J.; Kim, S. W.; Beak, S. I.; Ha, H-J.; Lee, W. K. *Synlett*, **2004**, 489–492.
[31] Kim, M. Y.; Starrett Jr., J. E.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383–5389.
[32] a) For other syntheses of *trans*-4,5-disubstituted imidazolidin-2-ones see Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc*. **2007**, *129*, 762–763. b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496–7497.
[33] For a synthesis of *cis*-4,5-disubstituted imidazolidin-2-ones see: Muniz, K.; Streuff, J.; Chávez, P.; Hövelmann, C. H. *Chem. Asian J.* **2008**, *3*, 1248–1255.
[34] Insertion reactions occur with the olefin parrallel to the Pd-N bond. See: a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. b) Thorn, D. L.; Hoffman, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079–2090.
[35] For a review on the effect of $A^{(1,3)}$ strain on stereoselectivity see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
[36] For an example of *anti*-aminopalladation of *N*-allylureas see refs 6a and 6b.
[37] For a previous example of substrate and ligand control of the ratio of *syn*- and *anti*-carboamination see: Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901.
[38] Trost, B. M.; Sacchi, K. L.; Schroeder, G. M.; Asakawa, N. *Org. Lett.* **2002**, *4*, 3427–3430.
[39] Takeuchi, R.; Ue, N; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525–9534.
[40] Green, M. P. Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett*. **2002**, *43*, 6609–6611.
[41] Schmidt, B; Pohler, M; Costisella, B. *Tetrahedron* **2002**, *58*, 7951–7958.
[42] Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6040–6043.
[43] Molander, G. A.; Romero, J. A. C. *Tetrahedron*, **2005**, *61*, 2631–2643.
[44] Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464–470.
[45] Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669–3679.
[46] Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828–1839.
[47] Barluenga, J.; Fananas, F. J.; Villamana, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1*. **1984**, 2685–2692.
[48] Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett,* **2007**, *9*, 3371–3374.
[49] Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 4960–4976.

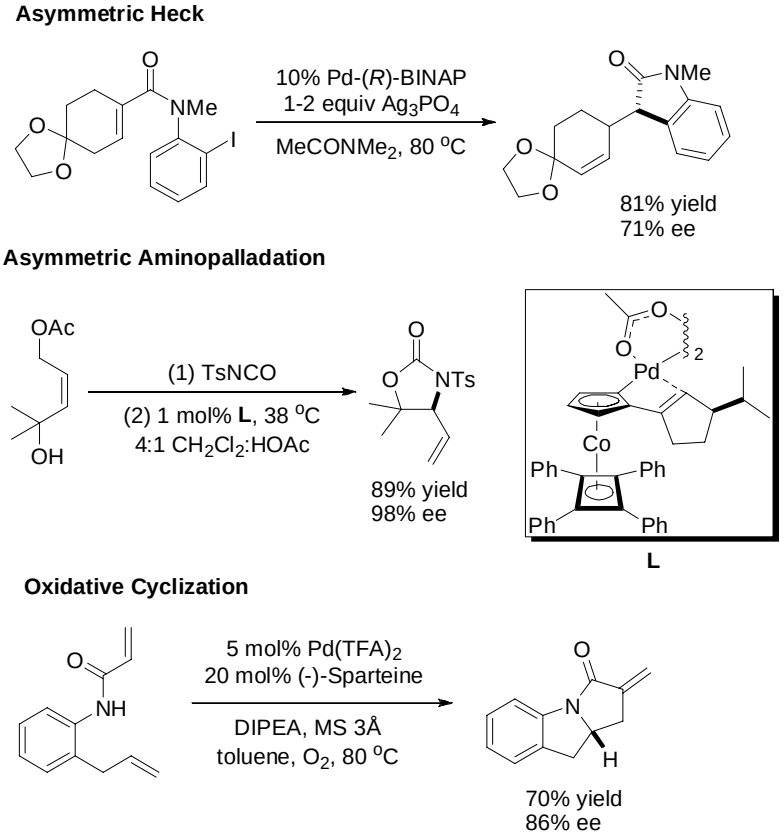
# Chapter III

## Asymmetric Synthesis of Imidazolidin-2-ones

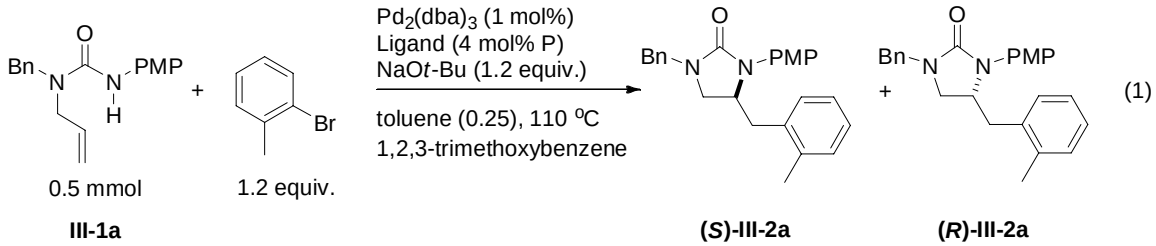
### Asymmetric Synthesis Through Chiral Phosphine Ligands

The ability to generate imidazolidin-2-ones enantioselectively would further enhance the utility of Pd-catalyzed carboamination of *N*-allylureas. One method of achieving enantioselectivity in reactions is through the use of chiral ligands on the metal. Many examples in the literature of asymmetric Pd-catalyzed insertion reactions using chiral ligands are Heck reactions.[1] As shown in Scheme III-1, one example of this is Overman's enantioselective synthesis of oxindoles. Instances of enantioselective aminopalladation reactions are less common. Again the Overman group has demonstrated an enantioselective cyclization of an *O*-allylcarbamate to an oxazolidinone using an exotic bimetallic catalyst.[2] Yang and coworkers provide examples of asymmetric aza-Wacker-type cyclizations using (-)-sparteine.[3]

**Scheme III-1.** Asymmetric Pd-Catalyzed Reactions of Olefins

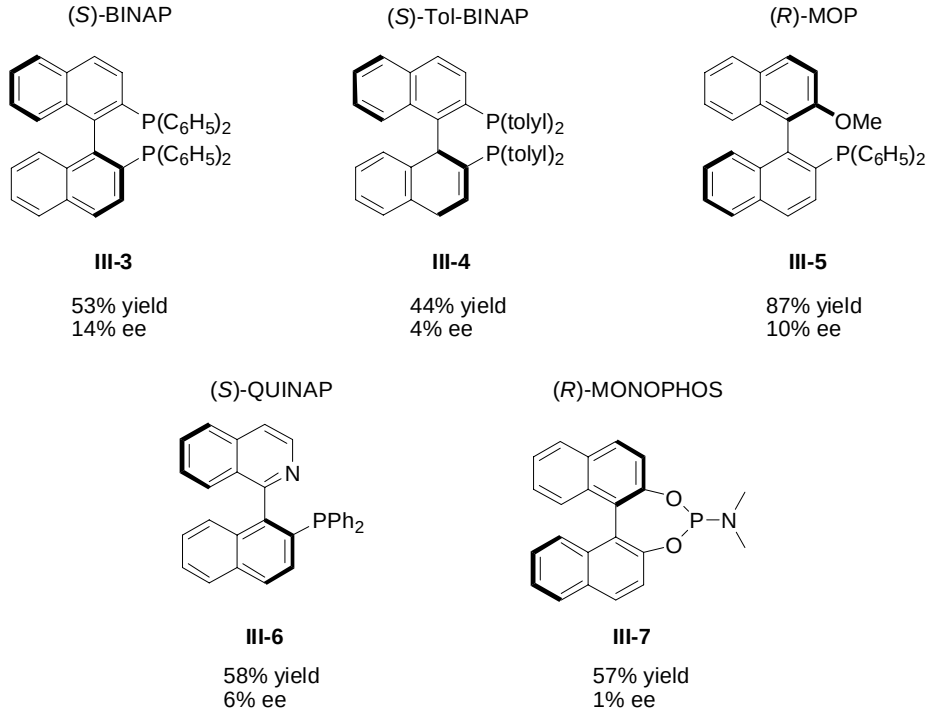



In attempts to employ this strategy toward an asymmetric synthesis of imidazolidin-2-ones, we initially explored the use of chiral phosphine ligands. Shown in eq 1, reaction of **III-1a** with 2-bromotoluene was our model system for determining the enantioselectivity associated with each phosphine ligand surveyed. With an achiral ligand, two products are expected to be obtained in this reaction: **(*S*)-III-2a** and (***R*)-III-2a**. It was our hope that with the appropriate chiral ligand and reaction conditions either one of the products could be formed in preference to the other.




BINAP analogs gave moderate to excellent yields of the desired product (44–87%) but with poor enantiomeric excess (1–14%) as shown in Figure III-1.

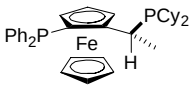
**Figure III-1.** Results with BINAP Analogs




Ferrocene containing ligands (Figure III-2) provided poor to good yields of the carboamination product with, on average, higher enantiomeric excess than seen with BINAP analogs. While it is difficult to draw a trend that accounts for the yields and enantiomeric excess seen with all the ligands in Figure III-2, a comparison of the results of **III-11**, **III-12**, and **III-13** shows that the substituent on the phosphorus has a significant impact on the chemical yield and a more subtle but noticeable impact on the enantiomeric excess of the product. For example, **III-13**, which bears two inductively withdrawing 3,5-$CF_3$-phenyl groups on the leftmost phosphorus, gives a 20% yield of the carboamination product. **III-11**, bearing electron-neutral phenyl substituents, gives a 50% yield of the desired product. Lastly, **III-12**, which has resonance donating 2-furyl groups on the same phosphorus, affords an 70% yield of the same product. Note that **III-10**, **III-11**, **III-12**, and **III-13** are analogs of (*R*)-(*S*)-JOSIPHOS **III-8**.

**Figure III-2.** Results with Ferrocene Containing Ligands

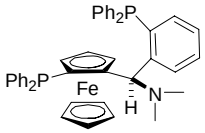
(*R*)-(*S*)-JOSIPHOS



**III-8**

31%* yield
53% ee

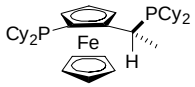
TANIAPHOS



**III-9**

61% yield
11% ee

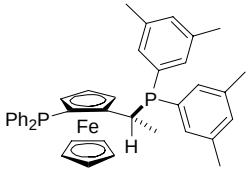
(*R*)-(-)-1-[(*S*)-2-(Dicyclohexylphosphino) ferrocenyl]ethyldicyclohexylphosphine



**III-10**

20%* yield
20% ee

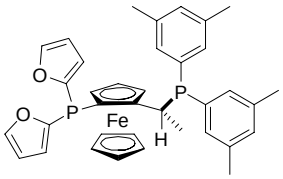
(*R*)-(-)-1-[(*S*)-2-(Diphenylphosphino) ferrocenyl]ethyldi(3,5-dimethylphenyl) phosphine



**III-11**

50% yield
37% ee

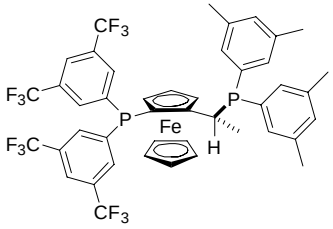
(*S*)-(+)-1-[(*R*)-2-(Di-2-furylphosphino) ferrocenyl]ethyldi-3,5-xylylphosphine



**III-12**

70% yield
31% ee

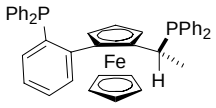
(*R*)-(-)-1-[(*S*)-2-(Di(3,5-bis-trifluoromethylphenyl) phosphino)ferrocenyl]ethyldi(3,5-dimethyl phenylphosphine



**III-13**

20% yield
17% ee

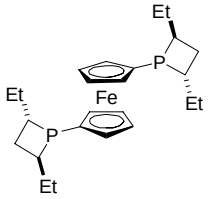
(*R*)-(+)-1-[(*R*)-2-(2'-Diphenylphosphinophenyl) ferrocenyl]ethyldiphenylphosphine



**III-14**

78% yield
17% ee

(*S*,*S*)-Et-FerroTANE



**III-15**

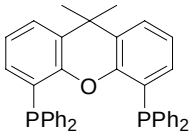
64% yield
10% ee

* denotes NMR yields

Several other phosphine ligands were screened with the results shown in Figure III-3 and Figure III-4. Several ligands had notable results. (*R*,*R*)-DIOP **III-17**, (*S*,*S*)-BDPP **III-20**, and (*S*)-NMDPP **III-26** afforded the desired carboamination product in high yield but low ee. (*S*,*S*)-CHIRAPHOS **III-23** provided the desired product in comparatively high ee but low yield. CTH-(*S*)-3,5-xylyl-PHANEPHOS **III-18** and (*S*)-PHANEPHOS **III-19** afforded the best combination of yield and enantiomeric excess.

**Figure III-3.** Results with Bidentate Phosphine Ligands

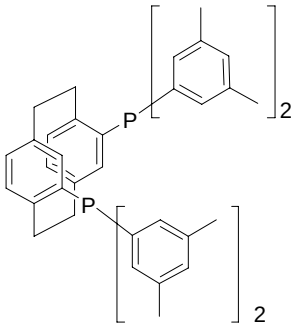
Xantphos



**III-16**

75% yield
1% ee

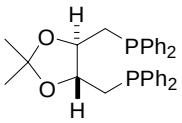
CTH-(*S*)-3,5-xylyl-PHANEPHOS



**III-18**

84% Yield
35% ee

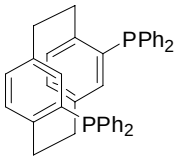
(*R*,*R*)-DIOP



**III-17**

90% yield
16% ee

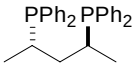
(*S*)-PHANEPHOS



**III-19**

86% Yield
32% ee

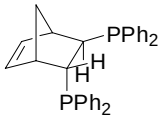
(*S*,*S*)-BDPP



**III-20**

87% yield
1% ee

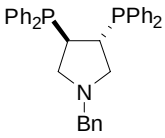
(*R*,*R*)-NORPHOS



**III-21**

68% yield
19% ee

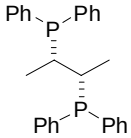
catASium® D(*R*)



**III-22**

66% yield
22% ee

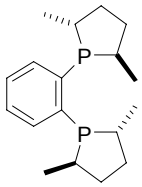
(*S*,*S*)-CHIRAPHOS



**III-23**

38% Yield
47%ee

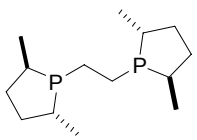
(*S*,*S*)-Me-DUPHOS



**III-24**

17%* yield
N/A ee

(*R*,*R*)-Me-BPE



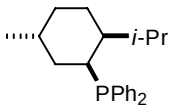
**III-25**

27%* yield
13% ee

* denotes NMR yield
% ee was not obtained on (*S*,*S*-Me-DUPHOS)
due to low chemical yield

**Figure III-4.** Results with Other Miscellaneous Ligands

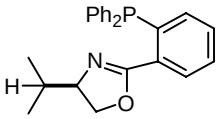
(*S*)-NMDPP




**III-26**

93% yield
14% ee

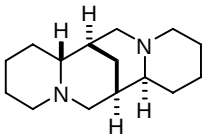
(*R*)-(+)-2-[2-(diphenylphosphino) phenyl]-4-(1-methylethyl)-4,5 -dihydrooxazole




**III-27**

69% yield
1% ee

(-)-Sparteine




**III-28**

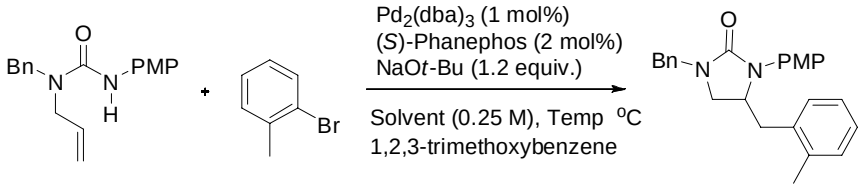
16% yield
6% ee

A survey of the results shown in Figures 1-4 illustrates the following important points:

1) The best combination of yield and enantiomeric excess came from the PHANEPHOS or JOSIPHOS type ligands.
2) This substrate and reaction condition currently provides an enantiomeric excess no higher than 53%.
3) This ligand screen reveals several ligands in addition to Xantphos which can achieve yields greater than 80% including PHANEPHOS, CTH-(*S*)-xylylPHANEPHOS, (*R*,*R*)-DIOP, (*S*,*S*)-BDPP, (*S*)-NMDPP, (*R*)-MOP. While each of these represents fairly diverse structures, each of them has at least two phenyl groups attached to the phosphorus atom. This knowledge may be useful in the future for designing ligands for particularly challenging substrates.

As shown in Tables III-1–III-2 and Schemes III-2, several other conditions were screened to determine if they would have any effect on enantioselectivity. Solvent choice has little effect on ee although a moderate increase was seen with *t*-BuOH and water (Table III-1).

**Table III-1.** Effect of Solvent on Enantioselectivity



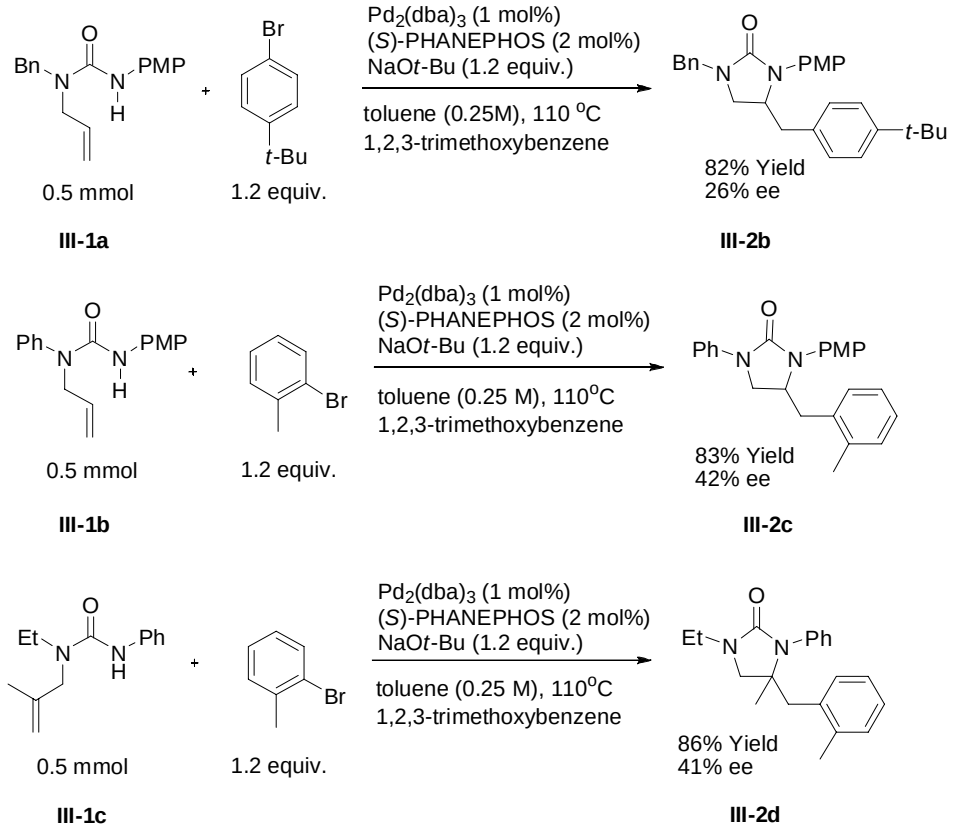

0.5 mmol 1.2 equiv.

| Solvent | Temp. °C | Yield | %ee |
|---|---|---|---|
| Toluene | 110 | 86 | 32 |
| THF | 65 | 20* | N/A |
| DME | 85 | 17* | N/A |
| Dioxane | 100 | 47 | 34 |
| *t*-Amyl Alcohol | 100 | 57 | 37 |
| *t*-Butanol | 82 | 62 | 41 |
| DMF | 150 | <6* | N/A |
| Water (KOH as base) | 100 | 13 | 45 |

* denotes NMR yield. An isolated yield and %ee were not obtained for reactions with low NMR yields

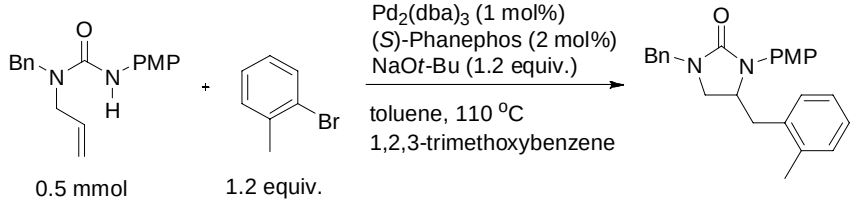
We also explored substrate and aryl halide effects on enantioselectivity (Scheme III-2). Use of 1-bromo-4-*tert*-butylbezene instead of 2-bromotoluene as a coupling partner with **III-1a** resulted in a decrease in ee from 32% to 26%. Substitution of phenyl for benzyl on the non-cyclizing nitrogen appears to impart a slight increase in enantioselectivity (10%) (**III-1b → III-2c**). Lastly, it was thought that increased substitution on the olefin could have a beneficial effect on ee **(III-1c → III-2d)**. This also gave a small increase in enantioselectivity (9%).

**Scheme III-2.** Effect of Substrate on Enantioselectivity




Other miscellaneous conditions were examined to determine their effect on enantioselectivity as shown in Scheme III-4. For instance, doubling the amount of ligand had little effect on enantioselectivity. Lowering the temperature of the reaction from 110 $^{o}$C to 65 $^{o}$C increased the enantioselectivity by 16%. Further decrease in temperature to 25 $^{o}$C accompanied by use of iodotoluene as the aryl halide resulted in low conversion to the desired product. Use of KO-*t*Bu as base resulted in a dramatic decrease in yield and a small decrease in enantioselectivity. Use of $Cs_2CO_3$ as base or of $Pd(OAc)_2$ as the Pd source resulted in minimal gain in enantioselectivity.

**Table III-2.** Effect of Other Parameters on Enantioselectivity




0.5 mmol 1.2 equiv.

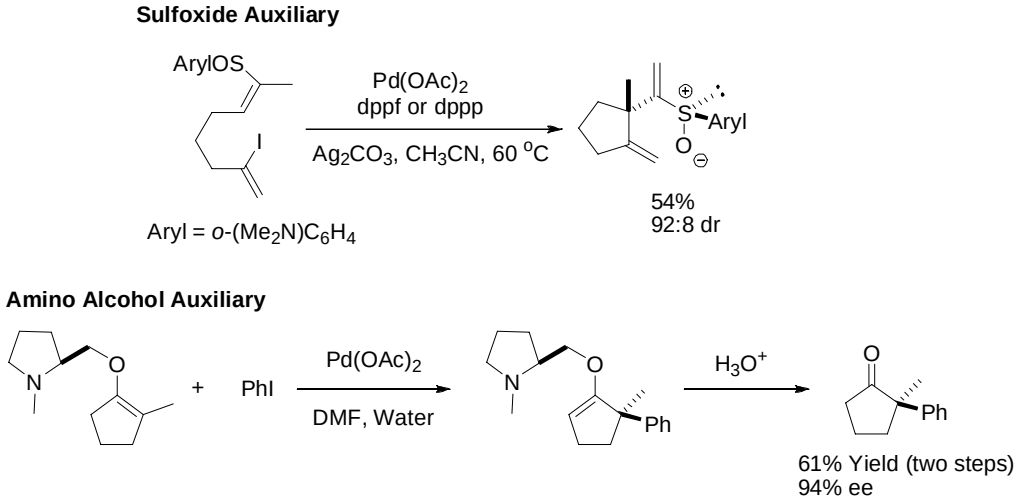
| Condition | Yield | %ee |
|---|---|---|
| As shown above | 86 | 32 |
| Twice as much ligand | 93 | 36 |
| 2-iodotoluene, 25 °C | 18%* | N/A |
| 65 °C | (98)** | 48 |
| KO*t*-Bu as base | 30 | 19 |
| $Cs_2CO_3$ as base | 82 | 35 |
| $Pd(OAc)_2$ | 89 | 36 |

* denotes NMR yield
** contains 11% of starting material

## Asymmetric Synthesis Through Chiral Auxiliaries

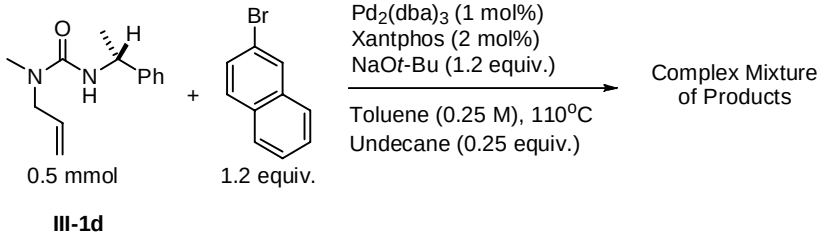
A second approach that was pursued toward achieving an asymmetric transformation was the use of a chiral auxiliary.[4] To our knowledge there are no examples of Pd-catalyzed aminopalladation reaction using chiral auxiliaries. However, there are a few examples of Heck reactions which employ chiral auxiliaries. The majority of these are from the Carretero and Hallberg groups. For instance, as shown in Scheme III-3, Carretero has demonstrated that sulfoxides are an effective chiral auxiliary for intramolecular Heck reactions.[5] Removal of the auxiliary was not trivial as it required oxidation to the sulfone followed by a two-step desulfonylation procedure. The Hallberg group used an inexpensive amino alcohol to effect an enantioselective intermolecular Heck reaction.[6] Acid-mediated hydrolysis cleaved the auxiliary to give the α-arylated cyclopentanone in 94% ee.

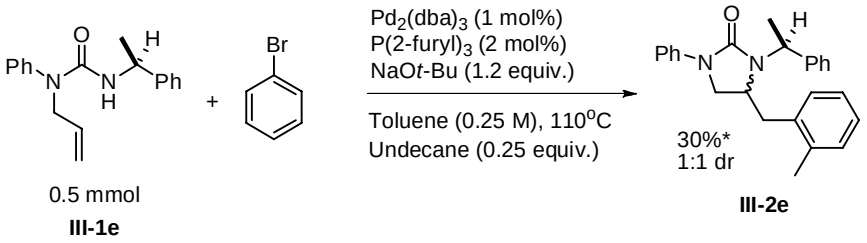
**Scheme III-3.** Asymmetric Heck Reactions Through Use of Chiral Auxiliaries

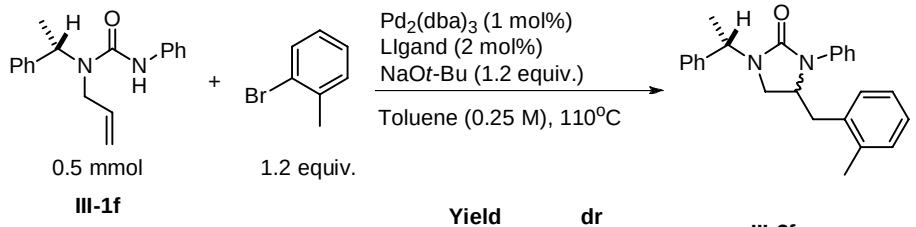



To explore the feasibility of using chiral auxiliaries to achieve high enantioselectivity in the Pd-catalyzed carboamination of *N*-allylureas substrates **III-1d** – **III-1f** were synthesized (Scheme III-4). Reaction of **III-1d** resulted in a complex mixture of products. Replacement of the Me group with a Ph group on the non-cyclizing nitrogen gave an approximately 30% yield of the carboamination product, but as a 1:1 mixture of diastereomers. Use of α-methylbenzyl on *N*1 was also explored. Reaction of **III-1f** resulted in a high yield of **III-2f** but the diastereoselectivity was insignificant. Reaction using (*S*)-PHANEPHOS resulted in a decrease in diastereoselectivity. This is likely due to a mismatch between (*S*)-PHANEPHOS and the chiral auxiliary.

**Scheme III-4.** Results with α-Methylbenzyl as a Chiral Auxiliary



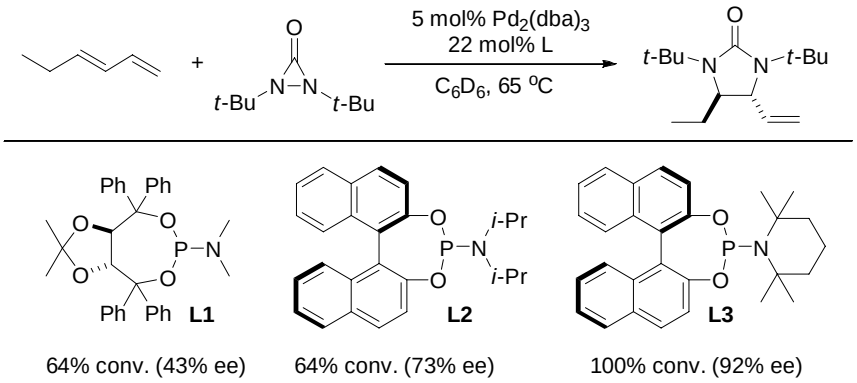

| Ligand | Yield (III-2f) | dr (III-2f) |
|---|---|---|
| Xantphos | 90** | 2:1 |
| (S)-PHANEPHOS | 87 | 1:1.3 |

*Contains 25% impurities
**Contains 15% solvent

## Conclusion and Future Directions

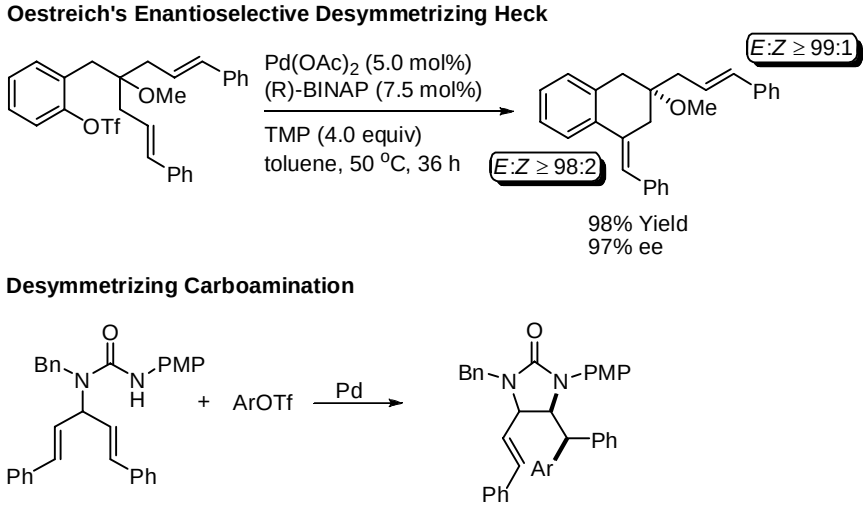
In summary, thus far, neither the use of chiral ligands nor chiral auxiliaries were particularly successful in achieving an asymmetric carboamination of *N*-allylureas. The best enantiomeric excess was 53% obtained through the use of (*R*)-(*S*)-Josiphos. With use of chiral auxiliaries the best diastereoselectivity observed was 2:1. However, recent work in the Wolfe lab has suggested that other phosphoramidites besides (*R*)-MONOPHOS may be more successful for asymmetric cyclization.[7] Also, recent work by Shi demonstrated that large variations in enantioselectivity can be observed Pd-catalyzed diamination reactions with different phosphoramidite ligands as shown in Scheme III-5.[8]

**Scheme III-5.** Dependence of ee on Structure of Phosphoramidite




Another strategy we could use for achieving high enantioselectivity is through a desymmetrizing carbopalladation analogous to the desymmetrizing intramolecular Heck reaction (Scheme III-6).[9]

**Scheme III-6.** Enantioselectivity Through Desymmetrization



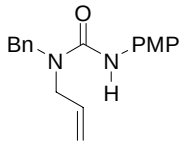

## Experimental Section

### General

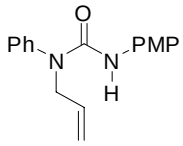
All reagents were purchased from commercial sources and were used as obtained unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (generally Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. *N*-Ethyl-2-methylallylamine was purchased from Aldrich Chemical Co. and used without purification. Toluene, THF,

dichloromethane, and ether were purified using a Glass Contour solvent purification system. Product regiochemistry was assigned on the basis of $^1$H NMR 2D-COSY and HSQC experiments. Product stereochemistry was assigned on the basis of $^1$H NMR 2D-NOESY experiments. Reaction times described below have not been minimized.

**General Procedure for the Synthesis of *N*-Allylurea Substrates.** An oven- or flame-dried round bottom flask equipped with a stirbar was cooled under a stream of nitrogen and charged with the appropriate *N*-allylamine (1.0 equiv), the appropriate isocyanate (1.0–1.4 equiv), and isopropanol or $CH_2Cl_2$ (1.0 M). The reaction was stirred at room temperature until the starting amine had been completely consumed as judged by TLC or $^1$H NMR analysis. The reaction mixture was then concentrated *in vacuo* and the crude product was purified via flash chromatography on silica gel.

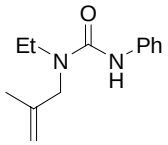



**1-Allyl-1-benzyl-3-(4-methoxyphenyl)urea (III-1a).** Reaction of 8.1 g (55.0 mmol) of *N*-allylbenzylamine with 8.2 g (55.0 mmol) of 4-methoxyphenylisocyanate following the general procedure afforded 12.82 g (79%) of the title compound as a white solid, m.p. 90–93 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5 H), 7.19–7.16 (m, 2 H), 6.81–6.78 (m, 2 H), 6.26 (s, 1 H), 5.87–5.80 (m, 1 H), 5.30–5.24 (m, 2 H), 4.56 (s, 2 H), 3.95 (d, *J* = 5.0 Hz, 2 H), 3.75 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 156.3, 155.9, 137.8, 134.0, 132.3, 128.9, 127.7, 127.6, 122.2, 117.4, 114.1, 55.6, 50.6, 49.9; IR (film) 3322, 1634 cm$^{-1}$. Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.68; H, 6.80; N, 9.45.

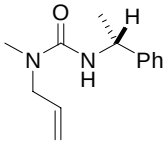



**1-Allyl-3-(4-methoxyphenyl)-1-phenylurea (III-1b).** Reaction of 0.93 g (7.0 mmol) of *N*-allylaniline with 1.04 g (7.0 mmol) of 4-methoxyphenylisocyanate following the general procedure afforded 1.80 g (91 %) of the title compound as a white solid, m.p. 70–73 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, *J* = 8.0 Hz, 2 H), 7.37 (t, *J* = 6.5 Hz, 1

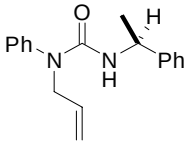
H), 7.32 (d, *J* = 7.5 Hz, 2 H), 7.19 (d, *J* = 9.0 Hz, 2 H), 6.79 (d, *J* = 4.5 Hz, 2 H), 6.05 (s, 1 H), 6.00–5.90 (m, 1 H), 5.13 (dd, *J* = 1.5, 6.0 Hz, 1 H), 5.11 (t, *J* = 1.5 Hz, 1 H), 4.34 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H). Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.51; H, 6.41; N, 9.91.




**1-Ethyl-1-(2-methylallyl)-3-phenylurea (III-1c).** Reaction of 0.99 g (10.0 mmol) of ethyl-(2-methylallyl)amine with 1.19 g (10.0 mmol) of phenyl isocyanate following the general procedure afforded 2.16 g (99%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2 H), 7.26–7.22 (m, 2 H), 7.00–6.96 (m, 1 H), 6.45 (s, 1 H), 5.012 (s, 1 H), 5.009 (s, 1 H), 3.82 (s, 2 H), 3.41 (q, *J* = 7.6 Hz, 2 H), 1.77 (s, 3 H), 1.18 (t, *J* = 6.8 Hz, 3 H); $^{13}$C (125 MHz, $CDCl_3$) δ 155.6, 142.1, 139.4, 128.9, 122.9, 119.7, 112.3, 53.2, 42.8, 20.0, 13.6; IR (film) 3331, 1626 cm$^{-1}$. MS (EI): 218.1411 (218.1419 calcd for $C_{13}H_{18}N_2O$).

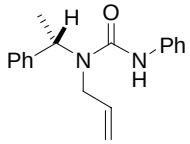



**(*R*)-1-Allyl-1-methyl-3-(1-phenylethyl)urea (III-1d)** Reaction of 0.34 g (4.78 mmol) of *N*-methylallylamine with 0.984 g (6.69 mmol) of (*R*)-(+)-α-methylbenzylisocyanate following the general procedure afforded 1.066 g (100%) of the title compound as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 3 H), 7.23–7.12 (m, 2 H), 5.78–5.68 (m, 1 H), 5.15–5.06 (m, 2 H), 5.00–4.91 (m, 1 H), 4.61 (d, *J* = 7.0 Hz, 1 H), 3.87–3.75 (m, 2 H), 2.81 (s, 3 H), 1.41 (d, *J* = 6.5 Hz, 3 H).



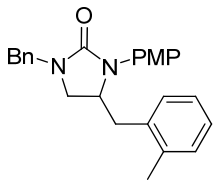

**(*S*)-1-Allyl-1-phenyl-3-(1-phenylethyl)urea (III-1e)** Reaction of 1.33 g (10.0 mmol) of *N*-allylaniline with 1.47 g (10.0 mmol) of (*S*)(-)-1-phenylethyl isocyanate following the general procedure afforded 2.43 g (87%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.2 Hz, 2 H), 7.34–7.25 (m, 3 H), 7.25–

7.17 (m, 5 H), 5.95–5.82 (m, 1 H), 5.11–4.97 (m, 3 H), 4.51 (d, *J* = 7.2 Hz, 1 H), 4.36–4.19 (m, 2 H), 1.35 (d, *J* = 7.2 Hz, 3 H).

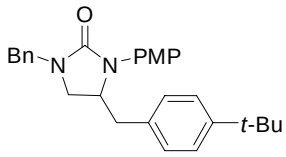


**(*S*)-1-Allyl-3-phenyl-(1-phenylethyl)urea (III-1f)** Reaction of 1.81 g (11.2 mmol) of (*S*)-allyl-α-methylbenzylamine with 1.87 g (15.7 mmol) of phenylisocyanate following the general procedure afforded 2.22 g (71%) of the title compound as a white powder, m.p. 89–92°C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2 H), 7.38–7.31 (m, 4 H), 7.31–7.24 (m, 3 H), 7.01 (t, *J* = 7.0 Hz, 1 H), 6.59 (s, 1 H), 5.85 (q, *J* = 7.0 Hz, 1 H), 5.80–5.69 (m, 1 H), 5.35 (dd, *J* = 1.0, 17.5 Hz, 1 H), 5.28 (dd, *J* = 1.0, 10.0, 1 H), 3.75 (dd, *J* = 5.5, 17.5. 1 H), 3.68 (dd, *J* = 5.5, 18.0, 1 H), 1.57 (d, *J* = 7.0 Hz, 3 H).

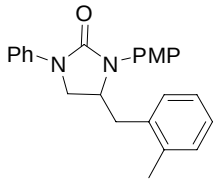
**General Procedure for Pd-Catalyzed Synthesis of Imidazolidin-2-ones.** An oven- or flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), Ligand (4 mol % P), NaO*t*Bu (1.2 equiv), the *N*-allylurea substrate (1.0 equiv), and the aryl bromide (1.2 equiv). The tube was purged with nitrogen and toluene (4 mL/mmol urea substrate) was then added. If the acyclic urea and/or the aryl bromide were oils they were added at the same time as the toluene. The Schlenk tube was then heated to 110 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis of aliquots removed from the reaction mixture. The mixture was then cooled to rt, saturated aqueous $NH_4Cl$ (4–6 mL/mmol substrate) was added, and the mixture was extracted with methylene chloride or ethyl acetate (3 x 7 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel. Enantioselectivities were measured by HPLC analysis using a Shimadzu LC-10AT liquid chromatograph and a Chiracel OD column (eluent: 20:80 isopropanol:hexanes; flow rate: 1 mL/min; observation frequency: 231nm. Optimization of column conditions was conducted using a racemic mixture of **III-2a** generated from reaction of **III-1a** and 2-bromotoluene with Xantphos as the ligand.




**1-Benzyl-3-(4-methoxyphenyl)-4-(2-methylbenzyl)imidazolidin-2-one (III-2a).** Reaction of 148 mg (0.5 mmol) of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea with 103 mg (0.6 mmol) of 2-bromotoluene for 8 h according to the general procedure afforded 138 mg (71%) of the title compound as a white solid, m.p. 83–85 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42–7.40 (m, 2 H), 7.33–7.19 (m, 5 H), 7.09–7.03 (m, 3 H), 6.93–6.91 (m, 3 H), 4.41 (s, 2 H), 4.32–4.29 (m, 1 H), 3.80 (s, 3 H), 3.20 (t, $J$ = 8.8 Hz, 1 H), 3.08–3.00 (m, 2 H), 2.56 (dd, $J$ = 3.6, 14.0 Hz, 1 H), 2.14 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.6, 137.1, 136.4, 134.9, 131.7, 130.6, 129.7, 128.7, 128.3, 127.5, 126.9, 126.1, 124.1, 114.4, 55.5, 54.6, 48.1, 46.6, 35.5, 19.5; IR (film) 1699 cm$^{-1}$. Anal. calcd for $C_{25}H_{26}N_2O_2$: C, 77.69: H, 6.78; N, 7.25. Found: C, 77.80; H, 6.85; N, 7.33.

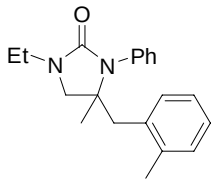



**1-Benzyl-4-(4-tert-butylbenzyl)-3-(4-methoxyphenyl)imidazolidin-2-one (III-2b).** Reaction of 148 mg (0.5 mmol) of 1-allyl-1-benzyl-3-(4-methoxyphenyl)urea with 128 mg (0.6 mmol) of 1-bromo-4-tert-butylbenzene for 30 min according to the general procedure afforded 206 mg (97%) of the title compound as an orange oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, $J$ = 9.2 Hz, 2 H), 7.35–7.20 (m, 7 H), 6.99–6.92 (m, 4 H), 4.48–4.29 (m, 3 H), 3.82 (s, 3 H), 3.26 (t, $J$ = 8.8 Hz, 1 H), 3.08 (dd, $J$ = 5.2, 8.8 Hz, 1 H), 3.00 (dd, $J$ = 3.2, 13.6 Hz, 1 H), 2.62 (dd, $J$ = 9.2, 13.6 Hz, 1 H), 1.29 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.1, 149.4, 136.9, 133.2, 131.6, 128.7, 128.4, 127.9, 127.2, 125.3, 123.3, 114.2, 55.3, 55.1, 47.8, 46.4, 37.5, 34.2, 31.2; IR (film) 1701 cm$^{-1}$. MS (ESI): 429.2523 (429.2542 calcd for $C_{28}H_{32}N_2O_2$, M + H$^+$).

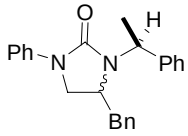



**3-(4-Methoxyphenyl)-4-(2-methylbenzyl)-1-phenylimidazolidin-2-one (III-**

**2c).** Reaction of 141 mg (0.5 mmol) of 1-allyl-3-(4-methoxyphenyl)-1-phenyl urea with 103 mg (0.6 mmol) of 2-bromotoluene for 13 h according to the general procedure afforded 74 mg (40%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 9.0 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.21-7.08 (m, 4 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 6.95 (d, *J* = 9.0 Hz, 2 H), 4.52–4.43 (m, 1 H), 3.82 (s, 3 H), 3.87–3.76 (m, 1 H), 3.63 (dd, *J* =5.5, 9.0 Hz, 1 H), 3.18 (dd, *J* = 3.5, 14.0 Hz, 1 H), 2.67 (dd, *J* = 10.5, 13.5 Hz, 1 H), 2.25 (s, 3 H).

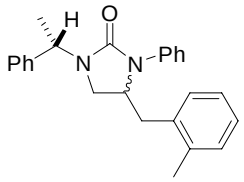



**1-Ethyl-4-methyl-4-(2-methylbenzyl)-3-phenylimidazolidin-2-one (III-2d).** Reaction of 109 mg (0.5 mmol) of 1-ethyl-1-(2-methylallyl)-3-phenylurea with 103 mg (0.6 mmol) of 2-bromotoluene for 5 h according to the general procedure afforded 135 mg (88%) of the title compound as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.0 Hz, 2 H), 7.34–7.28 (m, 3 H), 7.19–7.08 (m, 4 H), 3.44–3.34 (m, 2 H), 3.32–3.22 (m, 1 H), 3.05 (d, *J* = 13.5 Hz, 1 H), 2.92 (d, *J* = 8.5 Hz, 1 H), 2.79 (d, *J* = 14.0 Hz, 1 H), 2.25 (s, 3 H), 1.33 (s, 3 H), 1.13 (t, *J* = 7.5 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 159.2, 137.0, 136.8, 134.8, 130.6, 130.6, 129.3, 128.8, 126.8, 126.7, 125.7, 61.4, 53.1, 39.8, 38.5, 24.7, 20.0, 12.6; IR (film) 1698 $cm^{-1}$. Anal calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.54; H, 7.91; N, 9.01.




**(*S*)-4-(2-Methylbenzyl)-1-phenyl-3-(1-phenylethyl)imidazolidin-2-one (III-2e).** Reaction of 140 mg (0.5 mmol) of (*R*)-1-allyl-1-phenyl-3-(1-phenylethyl)urea with 4.6 mg (0.02 mmol) of tri-2-furylphosphine and 94 mg (0.6 mmol) of bromobenzene for 5.5 h according to the general procedure afforded 53 mg (30%) of the title compound as a clear oil. Analysis of the crude reaction mixture by $^1$H NMR indicated that the desired product had formed with 1.1:1.0 dr. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54–6.88 (m, 15 H), 5.45 (q, *J* = 7.5 Hz, 1 H), 4.03–3.95 (m, 1 H), 3.57 (t, *J* = 9.0 Hz, 1 H), 3.40 (dd, *J* = 6.0,

9.5 Hz, 1 H), 2.66 (dd, *J* = 3.5, 13.5 Hz, 1 H), 2.19 (dd, *J* = 10.5, 13.5 Hz, 1 H), 1.78 (d, *J* = 7.0 Hz, 3 H).




**(*S*)-4-(2-Methylbenzyl)-3-phenyl-(1-phenylethyl)imidazolidin-2-one (III-2f).** Reaction of 140 mg (0.5 mmol) of (*S*)-1-allyl-3-phenyl-1-(1-phenylethyl)urea with 5.8 mg (0.01 mmol) of (*S*)-PHANEPHOS and 103 mg (0.6 mmol) of 2-bromotoluene for 22 h according to the general procedure afforded 161 mg (87%) of the title compound as a yellow oil. Analysis of the crude reaction mixture by $^1$H NMR indicated that the desired product had formed with >2:1 dr. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 1.5, 9.0 Hz, 2 H), 7.42–7.04 (m, 12 H), 5.45–5.36 (m, 1 H), 4.47–4.35 (m, 1 H), 3.13–3.08 (m, 2 H), 2.96 (t, *J* = 9.0 Hz, 1 H), 2.68 (dd, *J* = 10.0, 14.0 Hz, 1 H), 2.29 (s, 3H), 1.55 (d, *J* = 7.5 Hz, 3 H).

[1] For reviews on enantioselective Heck reactions see: Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516. Dounay, A. B.; Overman, L. E.; *Chem. Rev.* **2003**, *103*, 2945–2963. Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284–3308.
[2] Kirsch, S. F.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 2859–2861.
[3] Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689.
[4] For a review on chiral auxiliaries see: Gnas, Y.; Glorius, F. *Synthesis*, **2006**, *12*, 1899–1930.
[5] Buezo, N. D.; Mancheño, O. G.; Carretero, J. C. *Org. Lett.* **2000**, *2*, 1451–1454.
[6] Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430–3431.
[7] Peter Mai, unpublished results
[8] Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689.
[9] For a leading reference see: Machott, A. B.; Straub, B. F.; Oestreich, M. *J. Am. Chem. Soc.* **2007**, *129*, 13455–13463.

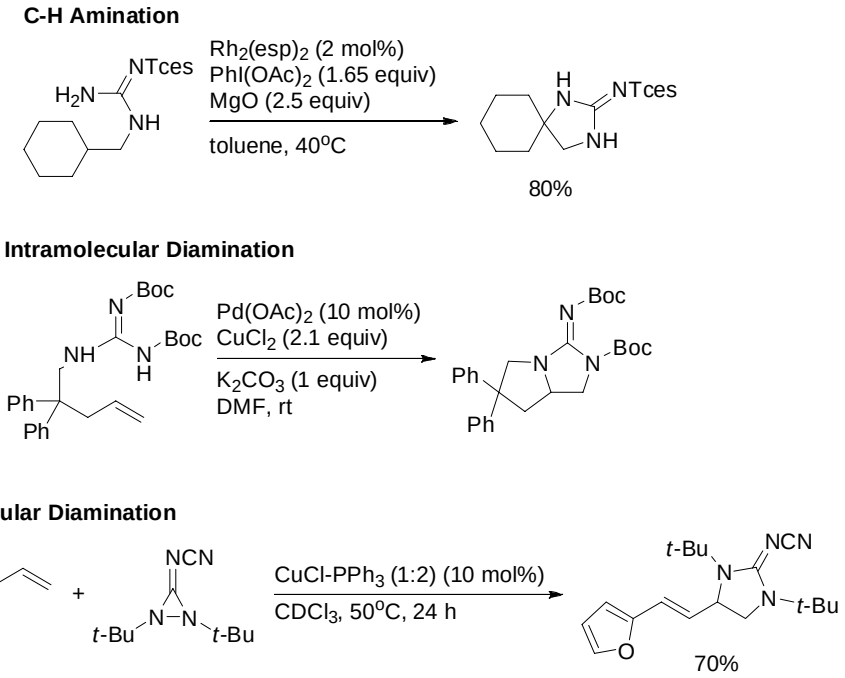
# Chapter IV

## Synthesis of Cyclic Guanidines

### Introduction

As described in Chapter 1, several cyclic guanidines exhibit potent biological activity and represent important medicinal targets. Cyclic guanidines can be synthesized using many of the same techniques that are used for the synthesis of imidazolidin-2-ones For example, as shown in Scheme IV-1, Du Bois and coworkers demonstrated the rhodium-catalyzed C-H amination of an acyclic guanidine to form a cyclic guanidine.[1] Intramolecular and intermolecular diaminations to generate cyclic guanidines have also been shown by Muñiz[2] and Shi.[3]

**Scheme IV-1.** Methods for the Synthesis of Cyclic Guanidines

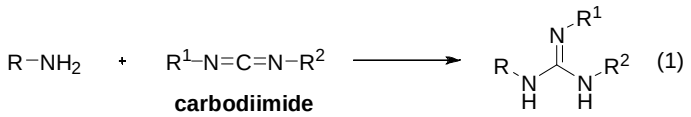



Pd-catalyzed carboamination of *N*-allylguanidines would represent a complimentary approach to the synthesis of cyclic guanidines. Given the successful

cyclization of N-allylureas we felt that the structurally similar *N*-allylguanidines represented a promising candidate for Pd-catalyzed carboamination.

**Synthesis of *N*-Allylguanidines**

Generally, guanidines are made via nucleophilic attack of an amine onto a carbodiimide (the nitrogen analog of an isocyanate) equivalent, as shown in eq 1.

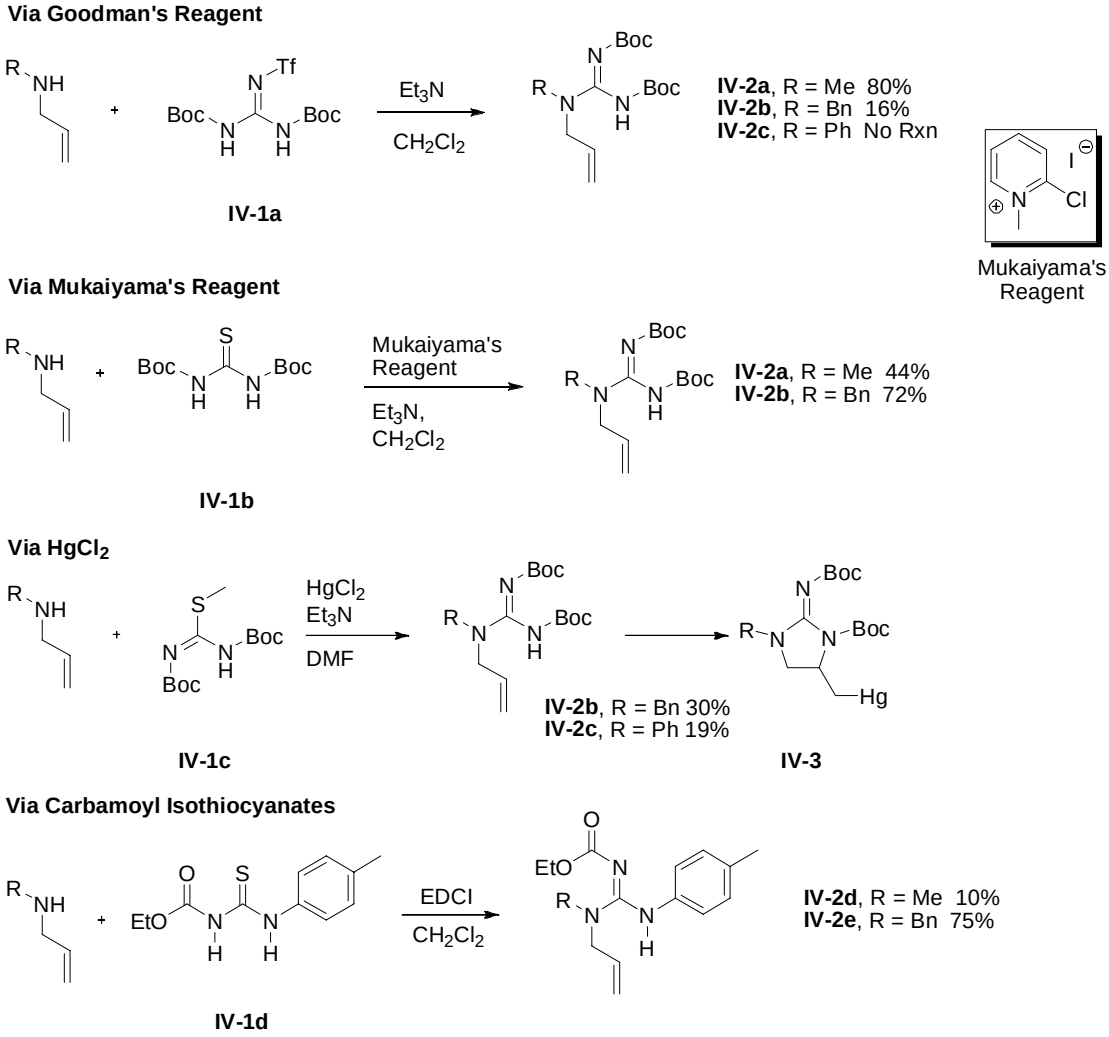


(1)

Two important carbodiimide precursors used in the synthesis of guanidines are *N,N′*-di-Boc-*N″*-triflylguanidine **IV-1a** developed by Goodman and coworkers[4] and carbamate protected thioureas. Thioureas are activated by various reagents such as Mukaiyama's reagent[5] and EDCI[6] to aid in the formation of the carbodiimide.

As shown in Scheme IV-2, *N,N′*-di-Boc-*N″*-triflylguanidine was reacted with three different allylic amines with varying degrees of success. While it was effectively coupled with *N*-methylallylamine to afford the desired *N*-allylguanidine in 80% yield, reactions with *N*-benzylallylamine and allylaniline were less successful. Reaction of Mukaiyama's reagent and *N,N*'-bis-Boc-thiourea **IV-1b** with *N*-methylallylamine proceeded in moderate yield (44%) to afford **IV-2a**. *N*-benzylallylamine reacted to form **IV-2b** in good yield (72%). Attempts at synthesizing *N*-allylguanidines via a combination of *N,N′*-bis-Boc-isothiourea **IV-1c** and $HgCl_2$ were low yielding. This may be because of the ability of $HgCl_2$ to activate olefins to nucleophilic attack potentially forming alkyl mercury compound **IV-3**.[7,8] Finally, reaction of *N*-methylallylamine with carbamoyl isocyanate **IV-1d** using EDCI as a coupling reagent afforded **IV-2d** in poor yield (10%). However, the reaction was effective with *N*-benzylallylamine.

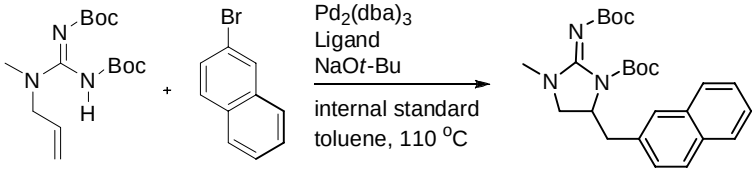
**Scheme IV-2.** Synthesis of *N*-Allylguanidines




## Pd-Catalyzed Carboamination Reactions of *N*-Allylguanidines

A screening of various phosphine ligands was performed to find the optimum ligand for the Pd-catalyzed carboamination of **IV-2a** to form **IV-4a**. As shown in Table IV-1, Nixantphos and Xantphos afforded good yields of the desired carboamination product. X-Phos gave a modest yield of the desired product. However, all other ligands gave low yields of the cyclization product. The remainder of the mass balance may be accounted for via decomposition pathways. This possibility was explored with control reactions which will be discussed later.

**Table IV-1.** Optimization of Phosphine Ligand




**IV-2a** **IV-4a**

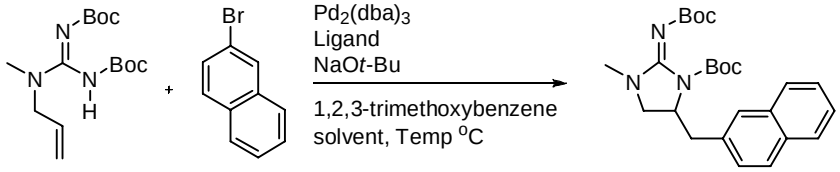
| Ligand | Time (h)** | NMR Yield | Isolated Yield |
|---|---|---|---|
| Xantphos | 18 | N/A | 57 |
| Nixantphos | 12 | 63 | 66 |
| DPPE | 14 | N/A | 14* |
| DPPB | 2 | 0 | N/A |
| DPE Phos | 17 | 0 | N/A |
| DPPF | 16.5 | 17 | N/A |
| DPPM | 22.5 | 0 | N/A |
| BINAP | 3 | 0 | N/A |

| Ligand | Time (h) | NMR Yield | Isolated Yield |
|---|---|---|---|
| X-Phos | 21 | 31 | N/A |
| $P(2\text{-furyl})_3$ | 24 | 0 | N/A |
| $P(o\text{-tol})_3$ | 3 | 0 | N/A |
| $PPh_3$ | 4 | 0 | N/A |
| $P(Cy)_3 \cdot HBF_4$ | 20.5 | 0 | N/A |
| $P[Ph(2,4,6\text{-Me})]_3$ | 16 | 0 | N/A |
| $P[Ph(2,4,6\text{-OMe})]_3$ | 16 | 14 | N/A |
| $P(C_6F_5)_3$ | 25 | 0 | N/A |
| $P(t\text{-Bu})_3 \cdot HBF_4$ | 25 | 7 | N/A |

* Contains 30% starting material and other impurities
** Reaction times are unoptimized.

Solvents and temperatures were also screened in order to improve the yield (Table IV-2). When the transformation was carried out in THF or *t*-BuOH at 65 °C no reaction occurred (Entries 1 and 2). Likewise, it was found that a temperature greater than 90 °C was required for the desired reaction to occur with dioxane as the solvent (Entries 3–5). However, with Xantphos as the ligand and toluene as the solvent some cyclization occurred at 80 °C (Entry 7). The yield was slightly increased by running the reaction at 110 °C (Entry 8). Note that with Nixantphos as the ligand, dioxane and toluene seem to give comparable yields (Entries 5 and 6). It may be useful to explore other solvent and temperature combinations including DME/ 80 °C, *t*-BuOH/ 80 °C. and Xylenes 135 °C to see their effect on yield.

**Table IV-2.** Optimization of Solvent and Temperature



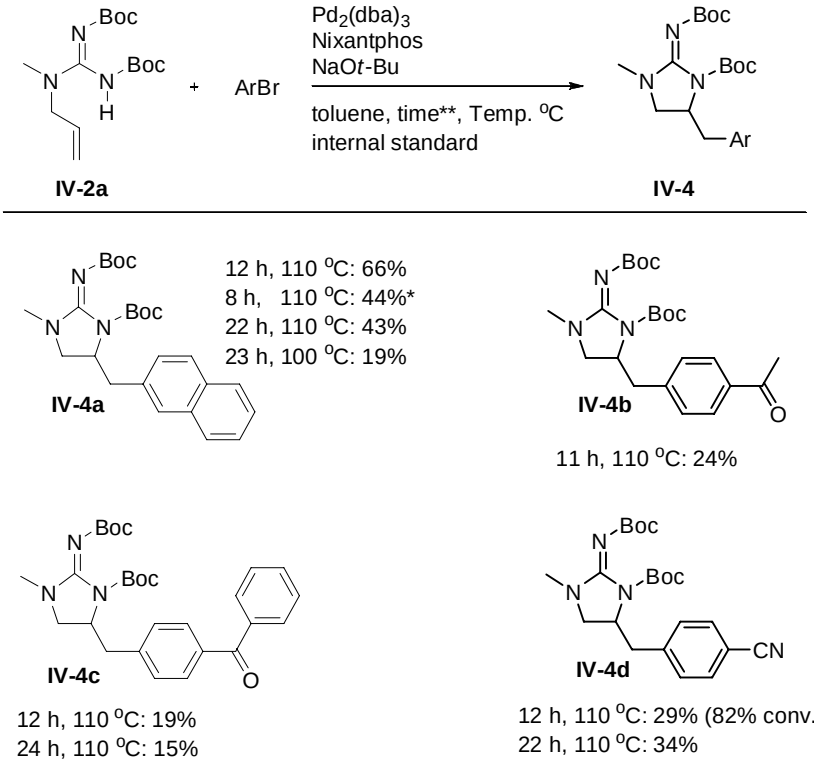

| Entry | Ligand | Time (h)** | Solvent | Temp. | NMR Yield | Isolated Yield | Result |
|---|---|---|---|---|---|---|---|
| 1 | Nixantphos | 21 | THF | 65 | | | Unreacted SM |
| 2 | Nixantphos | 21 | t-BuOH | 65 | | | Unreacted SM |
| 3 | Nixantphos | 19 | dioxane | 80 | | | Unreacted SM |
| 4 | Nixantphos | 6 | dioxane | 90 | | | Unreacted SM |
| 5 | Nixantphos | 7 | dioxane | 100 | N/A | 71* | |
| 6 | Nixantphos | 12 | toluene | 110 | 63 | 66 | |
| 7 | Xantphos | 40 | toluene | 80 | 57 | 45 | |
| 8 | Xantphos | 18 | toluene | 110 | N/A | 57 | |

* Contains 15% solvent and other impurities
** Reaction times are unoptimized.

## Reaction Scope

A variety of electron-neutral and electron-poor aryl halides were coupled to *N*-allylguanidine **IV-2a** to form **IV-4** under Pd-catalyzed carboamination conditions with the results shown in (Scheme IV-3). A good yield (66%) of **IV-4a** was obtained using 2-bromonapthalene as the aryl halide. However, results for multiple trials were very inconsistent ranging from 19%–66%. This inconsistency may be due to variations in substrate purity for different batches. Reactions of 4-bromoacetophenone, 4-benzophenone, and 4-bromobenzonitrile with **IV-2a** to give **IV-4b**, **IV-4c**, and **IV-4d** respectively all occurred in low yields ranging from 15–34%.

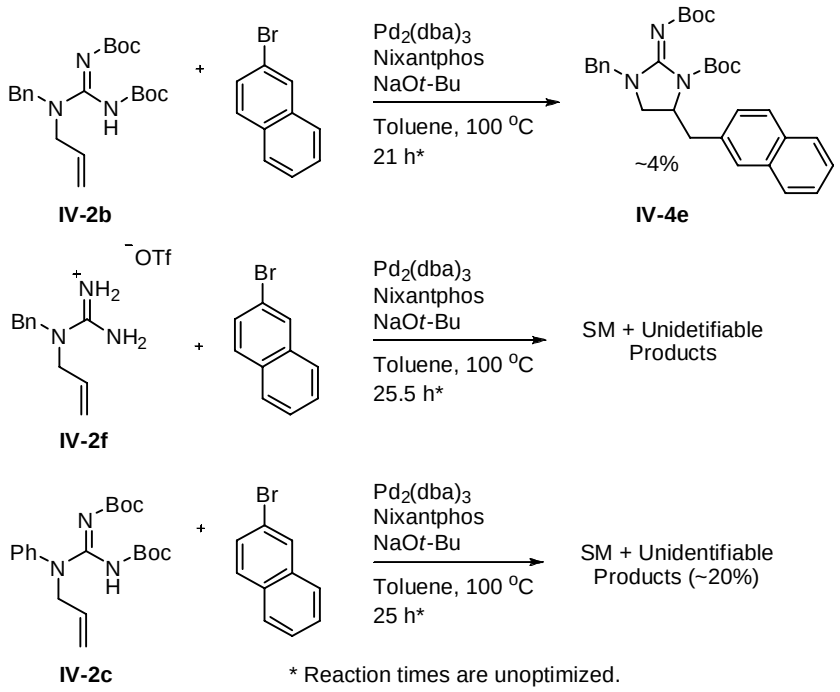
**Scheme IV-3.** Reaction Scope with Various Aryl Halides




* Contains 10% benzene
** Reaction times are unoptimized.

The scope of the reaction with respect to variation in the *N*-allylguanidine component of the reaction was also briefly examined (Scheme IV-4). In addition to substrate **IV-2a** which has an *N*3 methyl group, substrates were prepared with benzyl and phenyl on the non-cyclizing nitrogen (*N*3). These afforded lower yields than their methylated counterpart. For example, reaction of **IV-2b** with 2-bromonaphthalene proceeded to only give an approximately 4% yield of carboamination product **IV-4e**. Reaction of **IV-2f** resulted in unreacted starting material and unidentified products. Finally, reaction of **IV-2c**, with phenyl on the non-cyclizing nitrogen, gave the same outcome.

**Scheme IV-4.** Reaction Scope with Various *N*-Allylguanidines



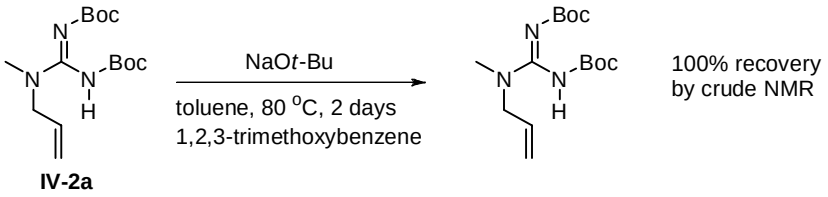

* Reaction times are unoptimized.

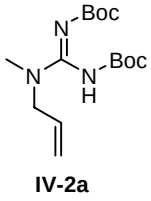
## Control Experiments

Control experiments were conducted to study whether **IV-2a** decomposed under the reaction conditions (Scheme IV-5). For example, reaction of **IV-2a** with NaO*t*-Bu at 80 °C resulted in no loss of **IV-2a** after 2 days according analysis of the crude NMR. Reaction of **IV-2a** with Pd and Xantphos in addition to the base resulted in 31% decomposition of the substrate according the NMR analysis.

A separate experiment indicated instability of **IV-2a** at higher temperatures without base or Pd present. In this experiment **IV-2a** was stirred only with an NMR standard (phenanthrene) in toluene and the integration of the Boc peak relative to the internal standard was monitored to check for decomposition. Initially, the mixture was placed in a room temperature oil bath and an aliquot was taken at 30 min. The oil bath was then heated to 50 °C and an hour later another aliquot was taken. The oil bath was then heated to 80 °C and yet another hour later another aliquot was withdrawn. Lastly, the oil bath was heated to 110 °C and an hour later the final aliquot was taken. Some slight decomposition (loss of starting material) was observed at 80 °C, and at 110 °C the NMR spectrum showed significant decomposition to various products.

**Scheme IV-5.** Studies of Substrate Decomposition

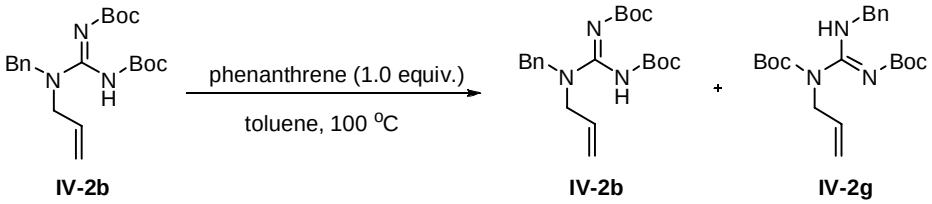



| Temp. | Time | % NMR Yield of IV-2a |
|---|---|---|
| rt | 30 min | 118 |
| 50 | 1 h | 105 |
| 80 | 1 h | 82 |
| 110 | 1 h | 7 |

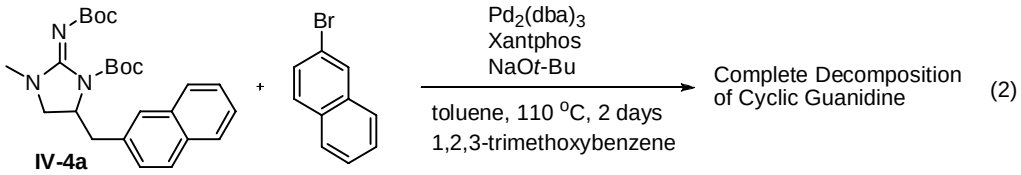
A control experiment was also conducted on **IV-2b** shown in Scheme IV-6. When **IV-2b** was stirred with phenanthrene in toluene at 100 °C, a roughly 40:60 mixture of **IV-2b** and **IV-2g** was observed at 20 minutes by NMR. This same ratio of products was observed after an hour. However, after 4 hours, complete decomposition of **IV-2b** and **IV-2g** occurred. **IV-2g** could have resulted from a [3,3] sigmatropic rearrangement of **IV-2b**.[9]

**Scheme IV-6.** 1-Allyl-1-Benzylguanidine Isomerization




| | % NMR Yield | | |
|---|---|---|---|
| Time | IV-2b | IV-2g | (IV-2b + IV-2g) |
| 20 min. | 44 | 60 | 104 |
| 60 min. | 39 | 60 | 99 |
| 4 h (crude) | Decomposition | | |

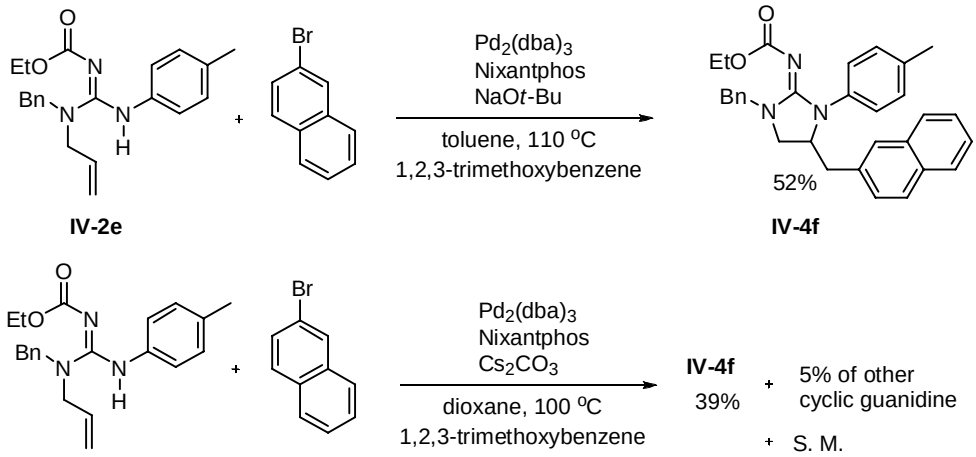
Resubjection of the product **IV-4a** to the reaction conditions, as shown in eq 2, indicates that it is not stable under the reaction conditions. This means it is important to stop the reaction as soon as it is complete to obtain the maximum yield.




## Reactions of Carbamoyl Guanidines

In Chapters 1 and 2 it was demonstrated that the identity of the group on the cyclizing nitrogen could have a significant impact on the chemical yield of the desired product in Pd-catalyzed carboamination reactions. A similar trend could be expected to observed in the Pd-catalyzed carboamination of *N*-allylguanidines to form cyclic guanidines. Substrate **IV-2e**, having a tolyl group instead of Boc group on the cyclizing nitrogen would test this hypothesis (Scheme IV-7). Reaction of **IV-2e** with 2-bromonaphthalene afforded a 52% yield of **IV-4f**. Reaction of **IV-2e** with $Cs_2CO_3$ as the base afforded in a slightly diminished yield of **IV-4f** as well as unreacted **IV-2e** and a small amount of an unidentified cyclic guanidine.

**Scheme IV-7.** Reactions of *N*-Allylcarbamoyl Guanidines



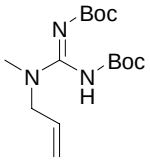

## Conclusions and Future Directions

Studies toward carboamination of *N*-allylguanidines were more challenging than those of *N*-allylureas both in terms of substrate synthesis and in terms of the Pd-catalyzed carboamination reaction. For example, reactions of allylic amines with guanylating reagents were often low yielding. Control studies in Scheme IV-4, Scheme IV-5 and eq 2 above also indicate substrate and/or product decomposition is a significant challenge. The scope of this transformation is currently narrow both in terms of the *N*-allylguanidine and the aryl halide used.

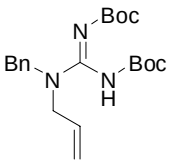
## Experimental Section

### General

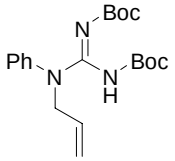
All reagents were purchased from commercial sources and were used as obtained unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides were obtained from commercial sources (generally Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. *N*-Ethoxycarbonyl-*N*'-(4-methylphenyl)-thiourea was synthesized according to a literature procedure.[6] Toluene, THF, dichloromethane, and ether were purified using a Glass Contour solvent purification system. Product regiochemistry was assigned on the basis of $^1$H NMR 2D-COSY and HSQC experiments. Reaction times described below have not been minimized.



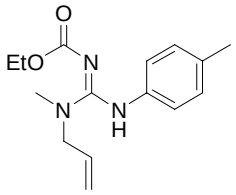

**$N^1$-Allyl-$N^2$,$N^3$-bis(*tert*-butoxycarbonyl)-$N^1$-methylguanidine (IV-2a).** To a flame-dried round-bottom flask charged with a stirbar was added *N*,*N*'-di-Boc-*N*''-triflylguanidine (3.26 g, 8.33 mmol), $CH_2Cl_2$ (42 mL), *N*-methylallylamine (0.65 g, 9.16 mmol), and triethyl amine (0.93 g, 9.16 mmol). After 17.5 h the reaction mixture was washed with 2M $NaHSO_4$ (30 mL) and saturated aqueous $NaHCO_3$ (30 mL) Each washing was extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organics were then washed with aqueous NaCl (30 mL) and dried with $Na_2SO_4$. The reaction mixture was then concentrated in vacuo and the crude product was purified via flash chromatography on silica gel, triturated with pentane, and filtered to afford 1.44 g (55%) of the title compound as a white solid, m.p. 71–74 $^o$C. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1 H), 5.91–5.77 (m, 1 H), 5.31–5.17 (m, 2 H), 4.08 (d, *J* = 5.6 Hz, 2 H), 2.97 (s, 3 H), 1.49 (s, 18 H).



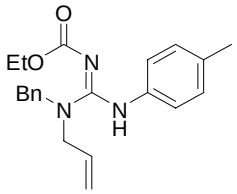
***N*$^1$-Allyl-*N*$^1$-benzyl-*N*$^2$,*N*$^3$-bis(*tert*-butoxycarbonyl)guanidine (IV-2b).** To a flame-dried round-bottom flask charged with a stirbar was added *N*,*N*'-bis-Boc-thiourea (0.99 g, 3.6 mmol), $CH_2Cl_2$ (36 mL), *N*-benzylallylamine (0.47 mL, 0.44 g, 3.0 mmol), triethylamine (0.91 mL, 0.67 g, 6.6 mmol) and Mukaiyama's reagent (0.92 g, 3.6 mmol). After 6.5 h the solvent was evaporated *in vacuo*. The residue was redissolved in ether (55 mL) and washed with water (55 mL). The reaction mixture was then concentrated *in vacuo*, dried with $Na_2SO_4$, and purified via flash chromatography on silica gel, to afford 995 mg (85%) of the title compound as a clear yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1 H), 7.36–7.21 (m, 5 H), 5.85–5.72 (m, 1 H), 5.19 (d, *J* = 9.2 Hz, 1 H), 5.13 (d, *J* = 17.2 Hz, 1 H), 4.66 (s, 2 H), 3.97 (s, 2 H), 1.51 (s, 9 H), 1.49 (s, 9 H).




***N*$^1$-Allyl-*N*$^2$,N$^3$-bis(tert-butoxycarbonyl)-*N*$^1$-phenylguanidine (IV-2c).** Known compound. For characterization data see: Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300–2309.

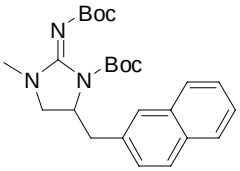



***N*$^1$-Allyl-*N*$^2$-(ethoxycarbonyl)-*N*$^3$-(4-methylphenyl)-*N*$^1$-methylguanidine (IV-2d).** To a flame-dried round-bottom flask charged with *N*-Ethoxycarbonyl-*N*'-(4-methylphenyl)-thiourea (0.71 g, 3.0 mmol), methylallylamine (0.29 mL, 3.0 mmol), and anhydrous dichloromethane (30 mL) and cooled in an ice bath was added EDCI (1.15g, 6.0 mmol). The solution was stirred under nitrogen for 1.5 hours at which point it was washed with 1% HCl (30 mL), water (30 mL), and brine (30 mL). The reaction mixture was then concentrated in vacuo and the crude product was purified via flash chromatography on silica gel to afford 84 mg (10%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 5.82–5.69 (m, 1 H), 5.24–5.10 (m, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.97 (d, *J* = 6.4 Hz, 2 H), 2.72 (s, 3 H), 2.31 (s, 3 H), 1.31 (t, *J* = 6.8 Hz, 3 H).

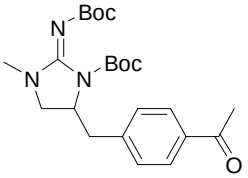


**$N^1$-Allyl-$N^1$-benzyl-$N^2$-(ethoxycarbonyl)-$N^3$-(4-methylphenyl)guanidine (IV-2e).** To a flame-dried round-bottom flask charged with *N*-Ethoxycarbonyl-*N*'-(4-methylphenyl)-thiourea (1.43 g, 6.0 mmol), benzylallylamine (0.88 g, 6.0 mmol), and anhydrous dichloromethane (60 mL) and cooled in an ice bath was added EDCI (2.30 g, 12.0 mmol). The solution was stirred under nitrogen for one hour at which point it was washed with 1% HCl (60 mL), water (60 mL), and brine (60 mL). The reaction mixture was then concentrated *in vacuo* and the crude product was purified via flash chromatography on silica gel to afford 1.67 g (79%) of the title compound as a white powder. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1 H), 7.33–7.23 (m, 4 H), 7.18 (d, *J* = 6.5 Hz, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 5.74–5.63 (m, 1 H), 5.16 (dd, *J* = 1.0, 10.0 Hz, 1 H), 5.04 (dd, *J* = 1.5, 16.0 Hz, 1 H), 4.48 (s, 1 H) 4.15 (q, *J* = 7.0 Hz, 2 H), 3.81 (d, *J* = 6.0 Hz, 2 H), 2.30 (s, 3 H), 1.32 (t, *J* = 7.5 Hz, 3 H).

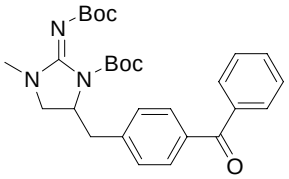
**General Procedure for Pd-Catalyzed Synthesis of Cyclic Guanidines.** An oven- or flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and charged with the $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), Nixantphos (2 mol %), NaO*t*-Bu (1.2 equiv), *N*-allylguanidine substrate (1.0 equiv), the aryl bromide (1.2 equiv) and 1,2,3-trimethoxybenzene (1.0 equiv). The tube was purged with nitrogen, and toluene (4 mL/mmol guanidine substrate) was then added. If the acyclic urea and/or the aryl bromide were oils they were added at the same time as the toluene. The Schlenk tube was then heated to 110 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis of aliquots removed from the reaction mixture. The mixture was then cooled to rt, saturated aqueous $NH_4Cl$ (4–6 mL/mmol substrate) was added, and the mixture was extracted with methylene chloride or ethyl acetate (3 x 7 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.



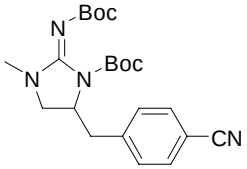

***N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-methyl-4-(naphthalen-1-ylmethyl)-imidazolidin-2-oneimine (IV-4a).** Reaction of 157 mg (0.5 mmol) of *N*¹-Allyl-*N*²,*N*³-bis(*tert*-butoxycarbonyl)-*N*¹-methylguanidine with 4.6 mg (0.005 mmol) of $Pd_2(dba)_3$, 5.5 mg (0.01 mmol) of Nixantphos, 58 mg (0.6 mmol) of NaO*t*-Bu, 124 mg (0.6 mmol) of 2-bromonaphthalene and 84 mg (0.5 mmol) of 1,2,3-trimethoxybenzene in toluene (2 mL) at 110 °C for 12 h according to the general procedure afforded 146 mg (66%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.85–7.78 (m, 3 H), 7.71 (s, 1 H), 7.52–7.42 (m, 2 H), 7.38 (dd, *J* = 1.6, 8.4 Hz, 1 H), 4.51–4.42 (m, 1 H), 3.44 (dd, *J* = 8.0, 9.6 Hz, 1 H), 3.37 (dd, *J* = 4.8, 13.6 Hz, 1 H), 3.08 (dd, *J* = 1.6, 10.0 Hz, 1 H), 2.94 (dd, *J* = 9.2, 13.6 Hz, 1 H), 2.84 (s, 3 H), 1.56 (s, 9 H), 1.47 (s, 9 H).



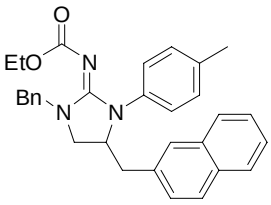

***N*²,*N*³-Bis(*tert*-butoxycarbonyl)-*N*¹-methyl-4-(4-Acetylbenzyl)-imidazolidin-2-oneimine (IV-4b).** Reaction of 157 mg (0.5 mmol) of *N*¹-Allyl-*N*²,*N*³-bis(*tert*-butoxycarbonyl)-*N*¹-methylguanidine with 4.6 mg (0.005 mmol) of $Pd_2(dba)_3$, 5.5 mg (0.01 mmol) of Nixantphos, 58 mg (0.6 mmol) of NaO*t*-Bu, 119 mg (0.6 mmol) of 4'-bromoacetophenone and 84 mg (0.5 mmol) of 1,2,3-trimethoxybenzene in toluene (2 mL) at 110 °C for 11 h according to the general procedure afforded 51 mg (24%) of the title compound as a white powder. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 4.40 (dd, *J* = 6.4, 13.6 Hz, 1 H), 3.48 (dd, *J* = 8.4, 10.0 Hz, 1 H), 3.20 (dd, *J* = 5.6, 13.6, 1 H), 2.99 (dd, *J* = 1.6, 10.0 Hz, 1 H), 2.89 (dd, *J* = 8.4, 14.0 Hz, 1 H), 2.83 (s, 3 H), 2.60 (s, 3 H), 1.54 (s, 9 H) 1.45 (s, 9 H).



**$N^2$,$N^3$-Bis(*tert*-butoxycarbonyl)-$N^1$-methyl-4-(4-Benzoylbenzyl)-imidazolidin-2-oneimine (IV-4c).** Reaction of 78 mg (0.25 mmol) of $N^1$-Allyl-$N^2$,$N^3$-bis(*tert*-butoxycarbonyl)-$N^1$-methylguanidine with 2.3 mg (0.005 mmol) of $Pd_2(dba)_3$, 2.8 mg (0.005 mmol) of Nixantphos, 28.8 mg (0.3 mmol) of NaO*t*-Bu, 78 mg (0.3 mmol) of 4-bromobenzophenone and 42 mg (0.25 mmol) of 1,2,3-trimethoxybenzene in toluene (1 mL) at 110 $^oC$ for 12 h according to the general procedure afforded 24 mg (19%) of the title compound as an off-white powder after lyophilization with benzene to remove solvent. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.79 (d, $J$ = 6.5 Hz, 4 H), 7.60 (t, $J$ = 7.0 Hz, 1 H), 7.49 (t, $J$ = 8.0 Hz, 2 H), 7.43–7.34 (m, 2 H), 4.43 (dd, $J$ = 8.0, 13.0 Hz, 1 H), 3.50 (t, $J$ = 9.5 Hz, 1 H), 3.24 (dd, $J$ = 5.0, 13.5 Hz, 1 H), 3.03 (d, $J$ = 9.5, 1 H), 2.92 (dd, $J$ = 8.5, 13.5 Hz, 1 H), 2.85 (s, 3 H), 1.53 (s, 9 H), 1.48 (s, 9 H).




**$N^2$,$N^3$-Bis(*tert*-butoxycarbonyl)-$N^1$-methyl-4-(4-nitrilebenzyl)imidazolidin-2-oneimine (IV-4d).** Reaction of 157 mg (0.5 mmol) of $N^1$-Allyl-$N^2$,$N^3$-bis(*tert*-butoxycarbonyl)-$N^1$-methylguanidine with 4.6 mg (0.005 mmol) of $Pd_2(dba)_3$, 5.5 mg (0.01 mmol) of Nixantphos, 58 mg (0.6 mmol) of NaO*t*-Bu, 109 mg (0.6 mmol) of 4-bromobenzonitrile and 84 mg (0.5 mmol) of 1,2,3-trimethoxybenzene in toluene (2 mL) at 110 $^oC$ for 26 h according to the general procedure afforded 71 mg (34%) of the title compound as a white powder after being lyophilized with benzene and azeotroped with pentane and  to remove ethyl acetate.. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.62 (d, $J$ = 8.5 Hz, 2 H), 7.45 (d, $J$ = 8.0 Hz, 2 H), 4.40 (dd, $J$ = 6.0, 13.0 Hz, 1 H), 3.54 (dd, $J$ = 8.0, 9.5 Hz, 1 H), 3.13 (dd, $J$ = 6.5, 13.5 Hz, 1 H), 2.96 (dd, $J$ = 1.5, 10.0 Hz, 1 H), 2.91 (dd, $J$ = 7.0, 13.5 Hz, 1 H), 2.81 (s, 3 H), 1.53 (s, 9 H), 1.40 (s, 9 H).




**$N^1$-Benzyl-$N^2$-ethoxycarbonyl-$N^3$-(4-methylphenyl)-4-(naphthalen-1-ylmethyl) imidazolidin-2-oneimine (IV-4f).** Reaction of 176 mg (0.5 mmol) of $N^1$-Allyl-

$N^1$-benzyl-$N^2$-(ethoxycarbonyl)-$N^3$-(4-methylphenyl)guanidine with 4.6 mg (0.005 mmol) of $Pd_2(dba)_3$, 5.5 mg (0.01 mmol) of Nixantphos, 58 mg (0.6 mmol) of NaOt-Bu, 124 mg (0.6 mmol) of 2-bromonaphthalene and 84.1 mg (0.5 mmol) of 1,2,3-trimethoxybenzene in toluene at 110 $^oC$ for 11 h according to the general procedure afforded 125 mg (52%) of the title compound as a yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.79–7.73 (m, 1 H), 7.68 (t, *J* = 8.5 Hz, 2 H), 7.47–7.19 (m, 12 H), 7.10 (dd, *J* = 1.5, 8.5 Hz, 1 H), 4.56 (d, *J* = 15.0 Hz, 1 H), 4.43 (d, *J* = 15.0 Hz, 1 H), 4.35–4.26 (m, 1 H), 3.79–3.66 (m, 2 H), 3.28 (t, J = 9.0 Hz, 1 H), 3.20–3.10 (m, 2 H), 2.82 (dd, *J* = 10.0, 13.5 Hz, 1 H), 2.36 (s, 3 H), 1.03 (t, *J* = 7.0 Hz, 3 H).

## References

[1] Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076.
[2] Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun.* **2008**, 2334–2336.
[3] Zhao, B.; Du, H.; Shi, Y. *Org. Lett.* **2008**, *10*, 1087–1090.
[4] Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804–3805.
[5] Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540–1542.
[6] Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566–1568..
[7] For examples of aminomercuration of *N*-allylguanidines see: Esser, F. *Synthesis*, **1987**, *5*, 460–466.
[8] For other examples of aminomercuration of olefins see: a) Danishefsky, S.; Taniyama, E.; Webb II, R. R. *Tetrahedron Lett.* **1983**, *24*, 11–14. b) Kranjule, N. S.; Markad, S. D.; Shinde, V. S.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 4667–4670. c) Roy, A.; Roberts, F. G.; Wilderman, P. R.; Zhou, K.; Peters, R. J.; Coates, R. M.
[9] For an example of a 1,3-Diaza-Claisen rearrangement used to form a guanidine see: Bowser, A. M.; Madalengoitia, J. S. *Org. Lett.* **2004**, *6*, 3409–3412.

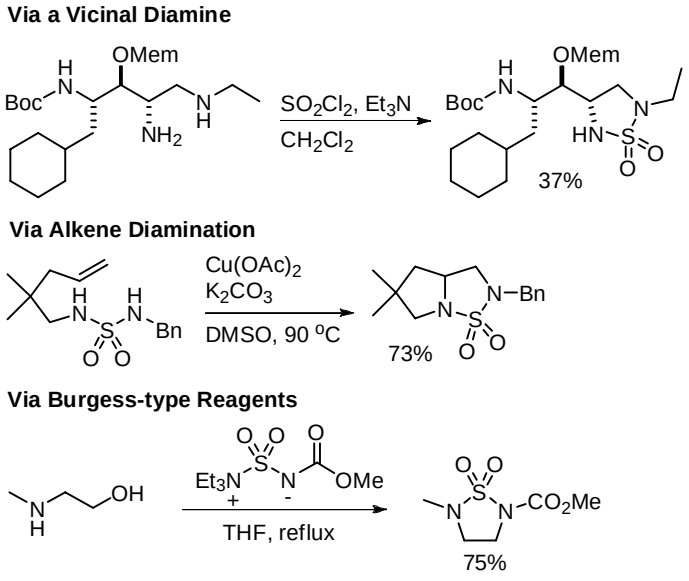
# Chapter V

## Synthesis of Cyclic Sulfamides

### Introduction

While presenting to a Merck chemist my research on Pd-catalyzed carboamination reactions of *N*-allylureas he asked me if we had been able to apply it to the construction of cyclic sulfamides. Since this class of heterocycles was deemed important to a pharmaceutical company we explored the possibility of generating cyclic sulfamides via Pd-catalyzed carboamination of *N*-allylsulfamides. As briefly mentioned in Chapter 1, cyclic sulfamides have received attention as a potential treatment for Alzheimer's disease[1] and sarcopenia,[2] as elastase inhibitors,[3] and as precursors for vicinal diamines.[4] Notably, the conversion of cyclic sulfamides to vicinal diamines is more operationally simple than that of imidazolidin-2-ones in that it only requires one step. There are several methods available for making cyclic sulfamides including cyclization of a vicinal diamine,[5] alkene diamination,[6] and reaction of Burgess-type reagents with aminoalcohols,[7] as shown in Scheme V-1.

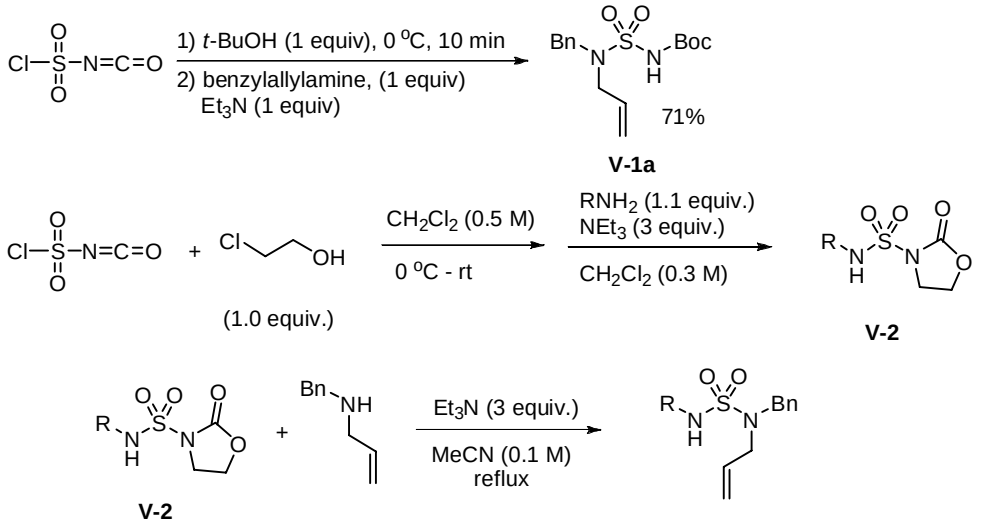
**Scheme V-1.** Representative Routes to Cyclic Sulfamides



While each of these methods displays unique approaches to the synthesis of cyclic sulfamides none of them results in the concomitant formation of a C-C and a C-N bond simultaneously. It was our hope that using our Pd-catalyzed carboamination technology that such a synthesis of cyclic sulfamides could be achieved.

The necessary *N*-allylsulfamides were synthesized by reaction of an alcohol and an amine with the bis-electrophile chlorosulfonyl isocyanate, as shown in Scheme V-2. For example, reaction of chlorosulfonyl isocyanate with *t*-BuOH followed by reaction of the intermediate carbamate with benzylallylamine generated **V-1a** in 71% yield.[8] Similarly, Montero has shown that reaction of chlorosulfonyl isocyanate with 2-chloroethanol followed by an amine generates oxizolidin-2-one **V-2**. **V-2** acts as a sulfonyl transfer reagent and reacted with benzylallylamine to give the desired *N*-allylsulfamides **(V-1b–V-1d)**.[9]

**Scheme V-2.** Synthesis of *N*-Allylsulfamides

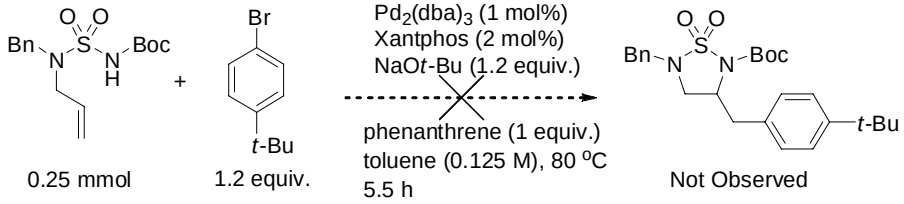



| Entry | R | Overall Yield |
|---|---|---|
| **V-1b** | Bn | 53% |
| **V-1c** | Ph | 57% |
| **V-1d** | PMP | 58% |

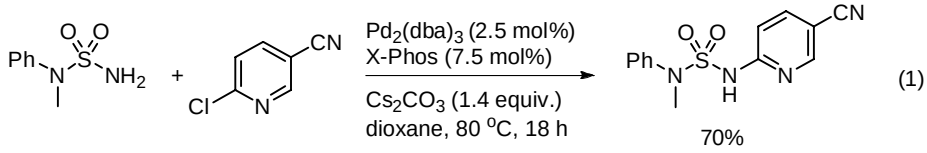
Due to ease of preparation, the first *N*-allylsulfamide examined contained benzyl and Boc protecting groups on the nitrogens (Scheme V-3). However when subjected to Pd-catalyzed carboamination conditions the substrate appeared to undergo decomposition. Our hypothesis is that with a Boc group on the cyclizing nitrogen the

carboamination is too slow to compete with various decomposition pathways due to inadequate nucleophilicity of the nitrogen.

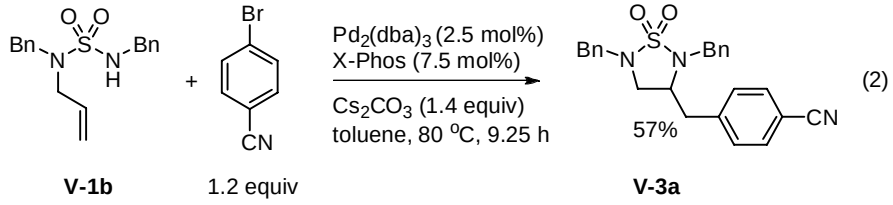
**Scheme V-3.** Attempted Cyclization of a Boc Protected Sulfamide




At this point we came upon a report by Alcaraz and coworkers that showed that sulfamides can be *N*-arylated with the appropriate choice of ligand (eq 1).

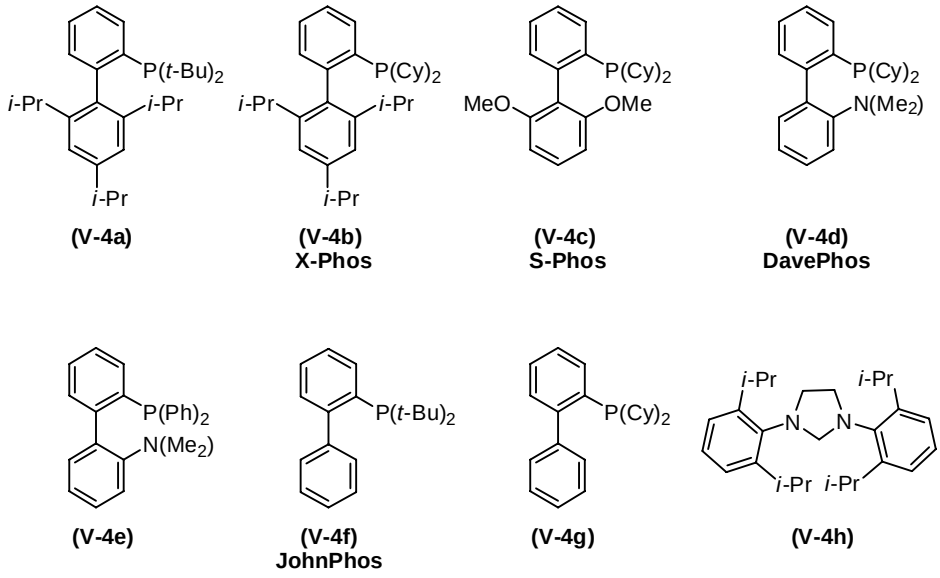



This inspired us to try their conditions on a substrate with a benzyl group on the cyclizing nitrogen **V-1b** (eq 2). To our delight, Xantphos, X-Phos and 2-dicyclohexyl-2-*N*,*N*-dimethylaminobiphenyl could all be successfully used to afford the desired cyclic sulfamide. The cleanest looking reaction was observed with X-Phos as the ligand. This reaction was quenched and purified to give the cyclic sulfamide **V-3a** in 57% isolated yield.




With this positive results in hand, a ligand screen, shown in Table V-1, using the above conditions was conducted to find the optimum ligand for the reaction. Several biphenyl based ligands **(V-4a – V-4g)** and a *N*-heterocyclic carbene ligand **(V-4h)** were used in this ligand screen (Figure V-1).

**Figure V-1.** Some ligands Used in Optimization



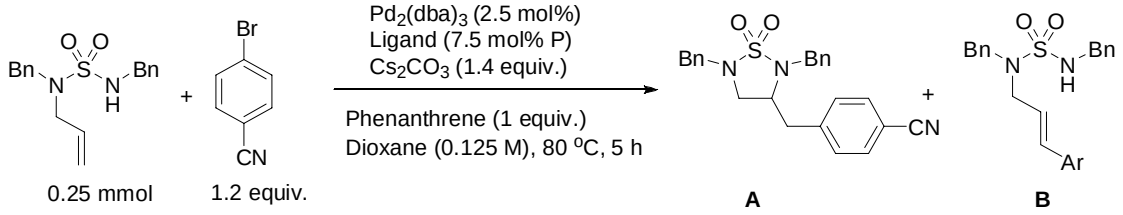

**(V-4a)** **(V-4b) X-Phos** **(V-4c) S-Phos** **(V-4d) DavePhos**

**(V-4e)** **(V-4f) JohnPhos** **(V-4g)** **(V-4h)**

As shown in Table V-1, this ligand screen demonstrated several interesting trends. For example, bidentate phosphine ligands containing an ether linkage and large bite angle (Xantphos, Nixantphos, and DPE Phos) showed moderate selectivity for the desired cyclic product over the Heck byproduct. All other bidentate ligands (dppb etc.) gave a high percentage of Heck product. Among monodentate ligands, some of the biaryl ligands **(V-4a–V-4g)** were particularly effective at carboaminating *N*-allylsulfamides. Three ligands bearing $P(Cy)_2$ groups, **(V-4b, V-4c,** and **V-4d)** gave the best yields. Interestingly, the $P(Ph)_2$ analog of **V-4d** reversed the ratio of carboamination to Heck. (Compare **V-4d** and **V-4e**). Also important is that replacement of $P(t\text{-Bu})_2$ for the $P(Cy)_2$ group on **V-4b** results in a dramatic drop in % conversion. (Compare **V-4a** and **V-4b**). Thus while it seems important to have a relatively electron-rich group on the phosphorus (Cy vs. Ph), it is also important that the group has not too much steric bulk (Cy vs. *t*-Bu).

Also notable is that ligands with groups in the ortho position of the bottom ring gave significantly better selectivity for the desired carboamination. (Compare **V-4b**, **V-4c**, and **V-4d** to **V-4g**).

**Table V-1.** Variation in Ligands (Representative Results)

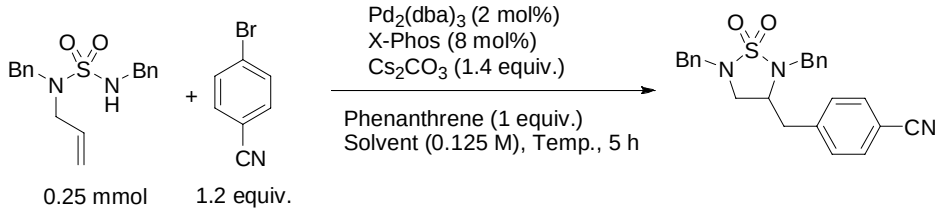



| Ligand | % Conv.* | Ratio A:B |
|---|---|---|
| Xantphos | 100 | 1.5:1 |
| Nixantphos | 91 | 1.6:1 |
| **(V-4a)** | 6 | 0:1 |
| **(V-4b)** | 82 | 8:1 |
| **(V-4c)** | 52 | 6:1 |
| **(V-4d)** | 78 | 5:1 |
| **(V-4e)** | 100 | 1:4 |
| **(V-4f)** | 73 | 1:7 |
| **(V-4g)** | 83 | 1:2 |
| dppb | 100 | 0:1 |
| $P(2\text{-furyl})_3$ | 100 | 0:1 |
| **(V-4h)** | 100 | 0:1 |

* NMR yields calculated by reference to phenanthrene

A solvent screen showed that toluene was the optimum solvent for the reaction in terms of reaction rate (Table V-2). However, dioxane, *t*-BuOH, and DME also gave good selectivity for the cyclic product relative to the Heck product.

**Table V-2.** Solvent Screen



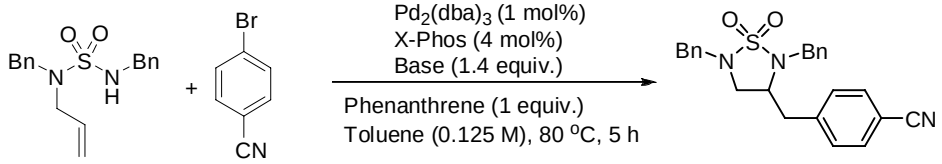

0.25 mmol 1.2 equiv.

| Solvent | Temp. $^{o}$C | % Conv.* | Ratio A:B |
|---|---|---|---|
| Dioxane | 80 | 73 | 8:1 |
| Toluene | 80 | 100 | 17:1 |
| *t*-BuOH | 80 | 66 | 9:1 |
| DME | 80 | 50 | 10:1 |
| THF | 65 | 29 | 5:1 |

* NMR yields calculated by reference to phenanthrene.

A screening of common bases used in Pd-catalyzed carboamination reactions showed that NaO*t*-Bu and $Cs_2CO_3$ are effective bases for cyclization of *N*-allylsulfamides (Table V-3). Weaker bases gave lower conversions of the substrate to product.

**Table V-3.** Base Screen




0.25 mmol 1.2 equiv.

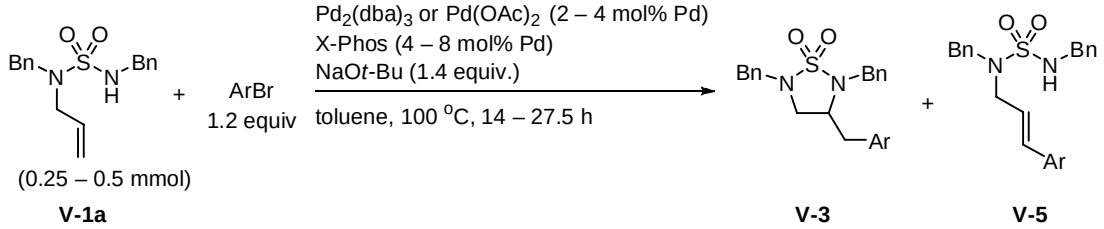
| Base | % Conv.* | Ratio A:B |
|---|---|---|
| NaO*t*-Bu | 56 | 9:1 |
| $Cs_2CO_3$ | 48 | 17:1 |
| $K_2CO_3$ | 7 | 1:0 |
| $K_3PO_4$ | 26 | 1:0 |
| $NaHCO_3$ | 0 | N/A |

* NMR yields calculated by reference to phenanthrene.

Having explored the optimum ligand, base, and solvent we then sought to explore the scope of the carboamination of *N*-allylsulfamides (Table V-4). While the reaction is quite clean and selective for electron poor aryl halides for electron neutral halides the selectivity for carboamination over Heck degrades substantially.[10] In fact, the ratio of carboamination to Heck is proportional to $\sigma_p$ determined from the Hammett equation. Some reactions also appeared to be stalling around 90% conversion. To alleviate this

problem, the catalyst loading was doubled and the temperature was increased from 80 °C to 100 °C.

**Table V-4.** Comparison of Various Aryl Bromides in the Pd-Catalyzed Carboamination of *N*-Allylsulfamides




| Ar | Isolated Yield A | Ratio of V-3 to V-5 | $\sigma_p^*$ |
|---|---|---|---|
| *p*-CN-Ph | 79 | >20 : 1 | 0.71 |
| *p*-$CF_3$-Ph | 84 | 25 : 1 | 0.53 |
| *p*-PhC(O)Ph | 75 | 25 : 1 | 0.47 |
| *p*-F-Ph | 39 | 2.9 : 1 | 0.15 |
| 2-naphthyl | N/A | 1.4 : 1 | 0.00 |
| *p*-(*t*-Bu)-Ph | N/A | 1.6 : 1 | -0.15 |

* $\sigma_p$ values taken from Isaacs, N. S. *Physical Organic Chemistry 2nd Ed*; Pearson: England, 1995, p 152. Values for benzophenone and naphthalene taken from acetophenone and benzene respectively.

## Conclusions and Future Directions

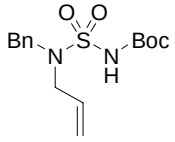
In conclusion, *N*-allylsulfamides are promising substrates for Pd-catalyzed carboamination to afford cyclic sulfamides. Initial studies showed that an electron-rich group on the cyclizing nitrogen is necessary for cyclization to occur. The principle challenge in further development of this methodology is a competitive Heck arylation pathway. The choice of ligand was demonstrated to be crucial for optimizing the ratio of products derived from the desired carboamination versus those derived from the Heck

reaction. Select biaryl phosphine ligands gave a particularly favorable ratio of carboamination to Heck. The electronics of the aryl halide were also important in determining the relative rates of these two transformations. Use of electron-poor aryl halides afforded Pd-catalyzed carboamination products in excellent yields. However, the Heck reaction becomes a competitive pathway when electron-neutral aryl halides are used as coupling partners. Solvent and base were shown to be important parameters for the rate of carboamination but do not affect the ratio of carboamination and Heck products. Future studies that could potentially expand the scope of the carboamination reaction to electron-neutral and electron-rich aryl halides include exploring other ligands, varying the electronics of the cyclizing nitrogen, and varying the number of equivalent of base used. Greater insight into factors that affect the rates of Pd-catalyzed carboamination and Heck reactions is expected to be helpful in directing these studies.

## Experimental Section

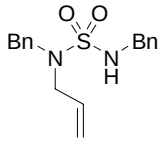
### General

All reagents were purchased from commercial sources and were used as obtained unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides and aryl iodides were obtained from commercial sources (generally Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. Toluene, THF, dichloromethane, and ether were purified using a Glass Contour solvent purification system. Product regiochemistry was assigned on the basis of $^1$H NMR 2D-COSY and HSQC experiments. Reaction times described below have not been minimized.

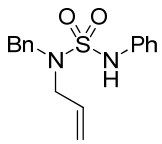



**1-Allyl-1-benzyl-3-*tert*-butoxycarbonylsulfamide (V-1a).** To a solution of chlorosulfonyl isocyanate (0.44 mL, 5.0 mmol) in $CH_2Cl_2$ (10 mL) at 0 $^oC$ was added *t*-BuOH (0.48 mL, 5.0 mmol). After stirring for 10 min at 0 $^oC$, $Et_3N$ (0.69 mL, 5.0 mmol) and benzylallylamine (0.78 mL, 5.0 mmol) were added and the solution was stirred an additional 20 h. $CH_2Cl_2$ (10 mL) was added and the solution was washed with 1 M HCl

(3 X 10 mL) and water (2 x 10 mL) and dried with $Na_2SO_4$. Solvent was removed *in vacuo*, and resulting residue was purified by flash chromatography to give 1.158 g (71%) of the title compound as a white solid, m.p. 71–75 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42–7.25 (m, 5 H), 7.08 (s, 1 H), 5.86–5.73 (m, 1 H), 5.22 (d, *J* = 10.0 Hz, 1 H), 5.18 (d, *J* = 18.0 Hz, 1 H), 4.56 (s, 2 H), 3.88 (d, *J* = 6.8 Hz, 2 H), 1.50 (s, 9 H).

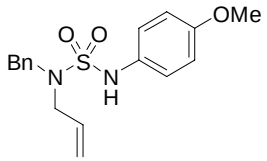



**1-Allyl-1,3-bis-benyzlsulfamide (V-1b).** To a solution of chlorosulfonyl isocyanate (0.44 mL, 5.0 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C was added a solution of 2-chloroethanol (0.34 mL, 5.0 mmol) in $CH_2Cl_2$ (5 mL). After 1.5 h a solution of benzylamine (0.49 mL, 5.5 mmol) and $Et_3N$ (2.09 mL, 15.0 mmol) in $CH_2Cl_2$ (5 mL) was added at 0 °C. The resulting mixture was stirred overnight and after 22 h was diluted with $CH_2Cl_2$ (20 mL), washed with 1 M HCl (2 x 20 mL), and dried with $Na_2SO_4$. Solvent was removed *in vacuo*, and to the resulting crude oxizolidinone was added acetonitrile (50 mL), benzylallylamine (0.86 mL, 5.5 mmol), and $Et_3N$ (2.1 mL, 15.0 mmol). After refluxing the solution for 20 h, the solvent was removed via rotary evaporator. The remaining residue was partitioned between $CH_2Cl_2$ (50 mL) and 1 M HCl (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 50 mL) and the combined organics were dried with $Na_2SO_4$. Solvent was removed *in vacuo*, and resulting residue was purified by flash chromatography to give 0.836 g (53%) of the title compound as a white solid, m.p. 54–57 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 10 H), 5.88–5.78 (m, 1 H), 5.24 (dd, *J* = 1.0, 10.0 Hz, 1 H), 5.19 (dd, *J* = 1.5, 17.0 Hz, 1 H), 4.40 (s, 2 H), 4.29 (t, *J* = 6.5 Hz, 1 H), 4.18 (d, *J* = 6.0 Hz, 2 H), 3.77 (d, *J* = 6.5 Hz, 2 H).



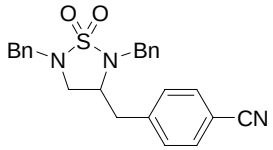

**1-Allyl-1-benzyl-3-phenylsulfamide (V-1c).** To a solution of chlorosulfonyl isocyanate (1.31 mL, 15.0 mmol) in $CH_2Cl_2$ (15 mL) at 0 °C was added a solution of 2-chloroethanol (1.01 mL, 15.0 mmol) in $CH_2Cl_2$ (15 mL). After 30 min a solution of aniline (1.5 mL, 16.5 mmol) and $Et_3N$ (6.5 mL, 46.6 mmol) in $CH_2Cl_2$ (15 mL) was added at 0 °C. The resulting mixture was stirred at rt and after 46 h was diluted with

$CH_2Cl_2$ (50 mL), washed with 1 M HCl (2 x 50 mL), and dried with $Na_2SO_4$. Solvent was removed *in vacuo*, and to the resulting crude oxizolidinone was added acetonitrile (150 mL), benzylallylamine (2.57 mL, 16.5 mmol), and $Et_3N$ (6.27 mL, 45.0 mmol). After refluxing the solution for 21 h, the solvent was removed via rotary evaporator. The remaining residue was partitioned between $CH_2Cl_2$ (50 mL) and 1 M HCl (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 50 mL) and the combined organics were dried with $Na_2SO_4$. Solvent was removed *in vacuo*, and resulting residue was purified by flash chromatography to give 2.601 g (57%) of the title compound as an white solid, m.p. 57–59 $^oC$. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5 H), 7.20–7.12 (m, 3 H), 7.09 (d, *J* = 7.2 Hz, 2 H), 6.31 (s, 1 H), 5.66–5.52 (m, 1 H), 5.17 (dd, *J* = 1.2, 10.0 Hz, 1 H), 5.10 (dd, *J* = 1.2, 17.2 Hz, 1 H), 4.37 (s, 2 H), 3.72 (d, *J* = 6.4 Hz, 2 H).

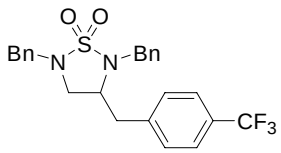



**1-Allyl-1-benzyl-3-(4-methoxyphenyl)sulfamide (V-1d).** To a solution of chlorosulfonyl isocyanate (1.31 mL, 15.0 mmol) in $CH_2Cl_2$ (15 mL) at 0 $^oC$ was added a solution of 2-chloroethanol (1.01 mL, 15.0 mmol) in $CH_2Cl_2$ (15 mL). After 4 h a solution of *p*-anisidine (2.03 g, 16.5 mmol) and $Et_3N$ (6.5 mL, 46.6 mmol) in $CH_2Cl_2$ (15 mL) was added at 0 $^oC$. The resulting mixture was stirred at rt and after 48 h was diluted with $CH_2Cl_2$ (50 mL), washed with 1 M HCl (2 x 50 mL), and dried with $Na_2SO_4$. Solvent was removed *in vacuo*, and to the resulting crude oxizolidinone was added acetonitrile (150 mL), benzylallylamine (2.57 mL, 16.5 mmol), and $Et_3N$ (6.27 mL, 45.0 mmol). After refluxing the solution for 21 h, the solvent was removed via rotary evaporator. The remaining residue was partitioned between $CH_2Cl_2$ (50 mL) and 1 M HCl (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 50 mL) and the combined organics were dried with $Na_2SO_4$. Solvent was removed *in vacuo*, and resulting residue was purified by flash chromatography to give 2.871 g (58%) of the title compound as an off-white solid, m.p. 77–79 $^oC$. $^1H$ NMR (500 MHz, $CDCl_3$) 7.32–7.26 (m, 3 H), 7.21–7.16 (m, 2 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 6.10 (s, 1 H), 5.66–5.54 (m, 1 H), 5.17 (dd, *J* = 1.5, 10.5 Hz, 1 H), 5.10 (dd, *J* = 1.5, 17.5 Hz, 1 H), 4.33 (s, 2 H), 3.81 (s, 3 H), 3.69 (d, *J* = 6.5, 2 H).

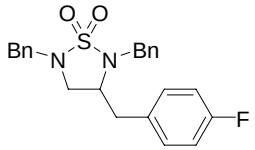
**General Procedure for Pd-Catalyzed Synthesis of Cyclic Sulfamides.** An oven- or flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and charged with the $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd), X-Phos (4 mol %), NaO*t*-Bu (1.4 equiv), 1-allyl-1,3-bis-benyzlsulfamide (1.0 equiv), and the aryl bromide (1.2 equiv). The tube was purged with nitrogen, and toluene (4-8 mL/mmol substrate) was then added. If the aryl bromide was an oil it was added at the same time as the toluene. The Schlenk tube was then heated to 100 °C with stirring until the starting material had been consumed as judged by GC or $^1$H NMR analysis of aliquots removed from the reaction mixture. The mixture was then cooled to rt, saturated aqueous $NH_4Cl$ (2 mL) was added, and the mixture was extracted with methylene chloride or ethyl acetate (3 x 7 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.




**4-((2,5-Dibenzyl-1,2,5-thiadiazolidine-1,1-dioxide-3-yl)methyl)benzonitrile (V-3a).** Reaction of 79.1 mg (0.25 mmol) of 1-allyl-1,3-bis-benyzlsulfamide with 2.3 mg (0.0025 mmol) of $Pd_2(dba)_3$, 4.8 mg (0.01 mmol) of X-Phos, 33.6 mg (0.35 mmol) of NaO*t*-Bu, and 54.6 mg (0.3 mmol) of 4-bromobenzonitrile in toluene (2 mL) at 100 $^o$C for 17.5 h according to the general procedure afforded 82 mg (79%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5, 2 H), 7.39–7.27 (m, 10 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 4.41 (d, *J* = 14.5 Hz, 1 H), 4.26 (d, *J* = 13.5 Hz, 1 H), 4.21 (d, *J* = 15.0 Hz, 1 H), 4.05 (d, *J* = 13.5 Hz, 1 H), 3.53–3.45 (m, 1 H), 3.11 (dd, *J* = 7.5, 9.5 Hz, 1 H), 2.89 (dd, *J* = 5.5, 13.5 Hz, 1 H), 2.73 (dd, *J* = 6.0, 9.5 Hz, 1 H), 2.68 (dd, *J* = 8.5, 13.5 Hz, 1 H) $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.6, 134.9, 134.6, 132.3, 129.9, 128.9, 128.8, 128.7, 128.6, 128.2, 118.5, 110.9, 56.8, 51.7, 50.4, 49.2, 39.6 (This spectrum contains one coincidental carbon.); IR (film) 2228, 1305, 1165 cm$^{-1}$. MS (ESI): 433.1359 (433.1362 calcd for $C_{24}H_{23}N_3O_2S$, M + $Na^+$).



**2,5-Dibenzyl-3-(4-(trifluoromethyl)benzyl)-1,2,5-thiadiazolidine-1,1-dioxide (V-3b).** Reaction of 158.2 mg (0.5 mmol) of 1-allyl-1,3-bis-benyzlsulfamide with 4.5 mg (0.02 mmol) of $Pd(OAc)_2$, 19.1 mg (0.04 mmol) of X-Phos, 67.3 mg (0.7 mmol) of NaO*t*-Bu, and 135.0 mg (0.6 mmol) of 4-bromobenzotrifluoride in toluene (2 mL) at 100 °C for 14 h according to the general procedure afforded 194 mg (84%) of the title compound as an off-white solid, m.p. 103–104. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2 H), 7.38–7.29 (m, 10 H), 6.97 (d, *J* = 7.5 Hz, 2 H), 4.43 (d, *J* = 14.5 Hz, 1 H), 4.26 (t, *J* = 14.5 Hz, 2 H), 4.06 (d, *J* = 14.0 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.09 (dd, *J* = 7.0, 9.5 Hz, 1 H), 2.90 (dd, *J* = 5.5, 13.5 Hz, 1 H), 2.76 (dd, *J* = 5.5, 9.5 Hz, 1 H), 2.68 (dd, *J* = 9.0, 13.5 Hz, 1 H) IR (film) 1326 $cm^{-1}$. MS (ESI): 483.1327 (483.1330 calcd for $C_{24}H_{23}F_3N_2O_2S$, M + $Na^+$).



**2,5-Dibenzyl-3-(4-fluorobenzyl)-1,2,5-thiadiazolidine-1,1-dioxide (V-3c).** Reaction of 79.1 mg (0.25 mmol) of 1-allyl-1,3-bis-benyzlsulfamide with 2.3 mg (0.0025 mmol) of $Pd_2(dba)_3$, 4.8 mg (0.01 mmol) of X-Phos, 33.6 mg (0.35 mmol) of NaO*t*-Bu, and 52.5 mg (0.3 mmol) of 4-bromofluorobenzene in toluene (2 mL) at 100 °C for 23 h according to the general procedure afforded 40 mg (39%) of the title compound as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34–7.20 (m, 10 H), 6.82–6.72 (m, 4 H), 4.32 (d, *J* = 15.0 Hz, 1 H), 4.21 (d, *J* = 3.0 Hz, 1 H), 4.19 (d, *J* = 3.5 Hz, 1 H), 3.96 (d, *J* = 13.5 Hz, 1 H), 3.40–3.32 (m, 1 H), 2.97 (dd, *J* = 6.5, 9.0 Hz, 1 H), 2.75 (dd, *J* = 5.0, 13.5 Hz, 1 H), 2.68 (dd, *J* = 6.0, 9.5 Hz, 1 H), 2.51 (dd, *J* = 9.0, 13.5 Hz, 1 H); IR (film) 1510 $cm^{-1}$. MS (ESI): 433.1359 (433.1362 calcd for $C_{23}H_{23}FN_2O_2S$, M + $Na^+$).

## References

[1] Sparey, T.; Beher, D.; Best, J. Biba, M; Castro, J. L.; Clarke, E.; Hannam, J.; Harrison, T.; Lewis, H.; Madin, A.; Shearman, M.; Sohal, B.; Tsou, N.; Welch, C.; Wrigley, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4212–4216.
[2] Manfredi, M. C.; Bi, Y.; Nirschl, A. A.; Sutton, J. C.; Seethala, R.; Golla, R.; Beehler, B. C.; Sleph, P. G.; Grover, G. J.; Ostrowski, J.; Hamann, L. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4487–4490.
[3] a) Zhong, J.; Gan, X.; Alliston, K. R.; Groutas, W. C. *Bioorg. Med. Chem.* **2004**, *12*, 589–593. b) Li, Y. Yang, Q.; Dou, D.; Alliston, K. R.; Groutas, W. C. *Bioorg. Med. Chem.* **2008**, *16*, 692–698.
[4] Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251.
[5] Rosenberg, S. H.; Dellaria, J. F.; Kempf, D. J.; Hutchins, C. W.; Woods, K. W.; Maki, R. G.; De Lara, E.; Spina, K. P.; Stein, H. H.; Cohen, J.; Baker, W. R.; Plattner, J. J.; Kleinert, H. D.; Perun, T. J. *J. Med. Chem*. **1990**, *33*, 1582–1590.
[6] a) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251. b) Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224–8227. c) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125–7127.
[7] Nicolaou, K. C.; Snyder, S. A.; Longbottom, D. A.; Nalbandian, A. Z.; Huang, X. *Chem. Eur. J.* **2004**, *10*, 5581–5606.
[8] Salim, S. S.; Bellingham, R. K.; Brown, R. C. D. *Eur. J. Org. Chem.* **2004**, 800–806.
[9] a) Dewynter, G.; Abdaoui, M.; Regainia, Z.; Montero, J-L. Tetrahedron **1996**, *52*, 14217–14224. b) Borghese, A.; Antoine, L.; Van Hoeck, J. P.; Mockel A.; Merschaert, A. *Org. Proc. Res. Dev.* **2006**, *10*, 770–775.
[10] In most cases the Heck product was inseperable from the desired carboamination product.

# Chapter VI

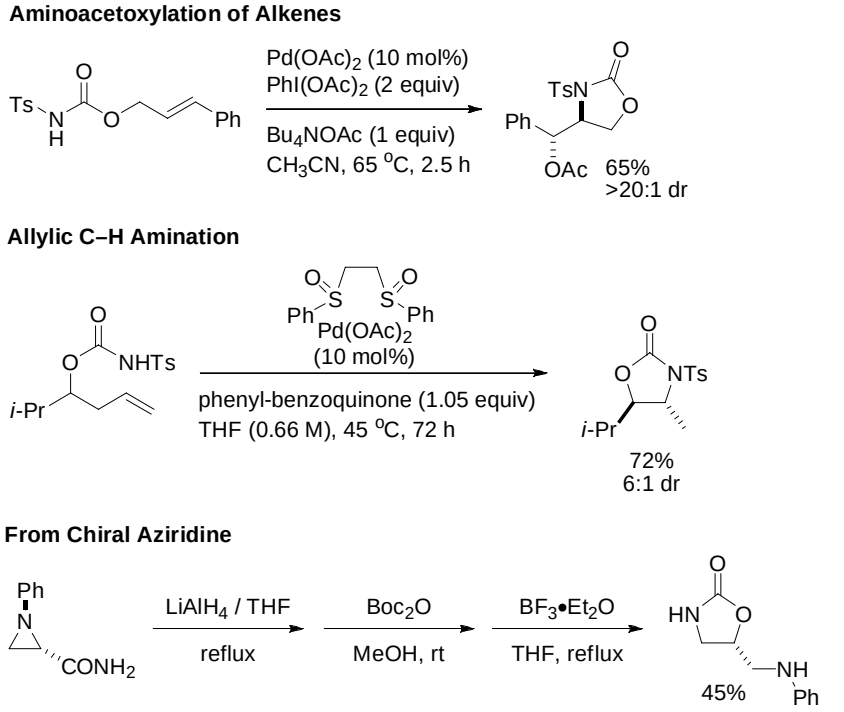
## Studies Toward the Synthesis of Oxazolidin-2-ones, Imidazolidin-2-thiones, and Cyclic Sulfoximines

### Pd-Catalyzed Carboamination of *O*-Allylcarbamates[1]

There are several other classes of heterocycles that could potentially be generated from Pd-catalyzed carboamination reactions. In this chapter, studies toward the synthesis of oxizolidin-2-ones, imidazolidin-2-thiones, and isothiazoline-*S*-oxides, will be discussed.

As shown in Chapter 1, there are several medicinal and synthetic uses for oxazolidin-2-ones. They represent an extremely important new class of antibiotics[2] and Evan's auxiliary (an oxizolidin-2-one) is one of the most important chiral auxiliaries for controlling stereochemistry. There are several known methods for their synthesis. For instance, as shown in Scheme VI-1 they have been recently made though amino acetoxylation of alkenes,[3] allylic C-H amination,[4] and from chiral precursors such as aziridines.[5] However, given the ever present threat of antibiotic resistance[6] it is crucial to develop new methods of developing oxiziolidin-2-ones, especially ones which allow for rapid formation of multiple analogs. We felt that Pd-catalyzed carboaminations would be particularly well suited for meeting this need as simple variation of the aryl or vinyl halide coupling partner allows for a library of compounds to be quickly generated.

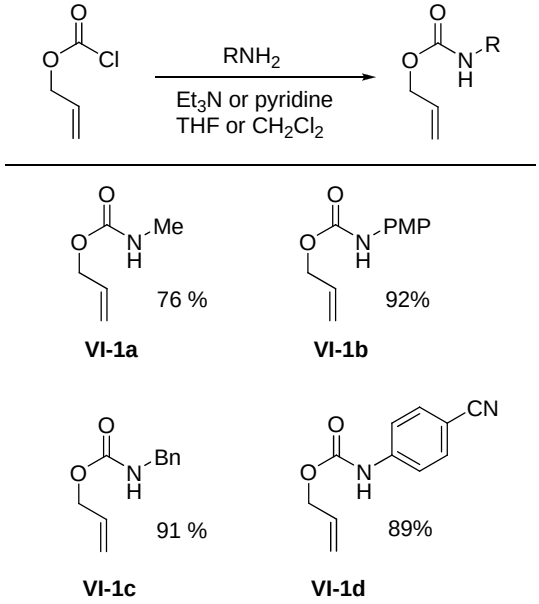
**Scheme VI-1.** Recent Routes to Oxazolidin-2-ones




## Synthesis of O-Allylcarbamates

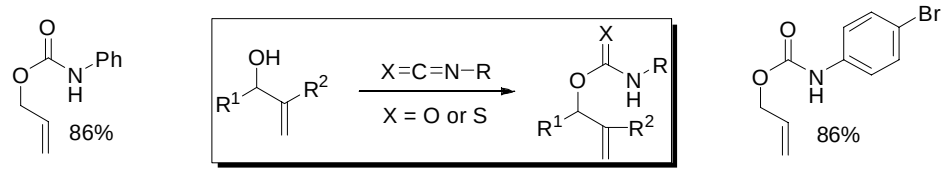
As shown in Scheme VI-2, *O*-allylcarbamates can easily be synthesized from reaction of an amine with allylchloroformate. Alternatively, as shown in Scheme VI-3, when substitution on the allylic backbone is desired, reaction of the appropriate allylic alcohol with an isocyanate gives an *O*-allylcarbamate. In both cases yields of the desired *O*-allylcarbamates are generally greater than 75%.

**Scheme VI-2.** Synthesis of *O*-Allylcarbamates from Allyl chloroformate




**VI-1a** **VI-1b** **VI-1c** **VI-1d**

**Scheme VI-3.** Synthesis of *O*-Allylcarbamates from Isocyanates[1]



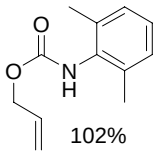




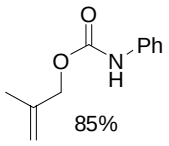
**Fritz/ Zhu***
**VI-1e**



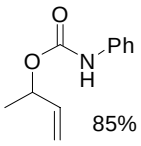

**Fritz**
**VI-1f**



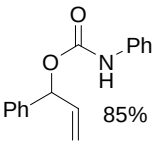

**Fritz**
**VI-1g**



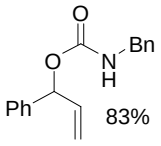

**Zhu**
**VI-1h**



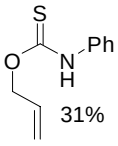

**Fritz/ Zhu**
**VI-1i**




**Fritz**
**VI-1j**




**Zhu**
**VI-1k**




**Zhu**
**VI-1l**

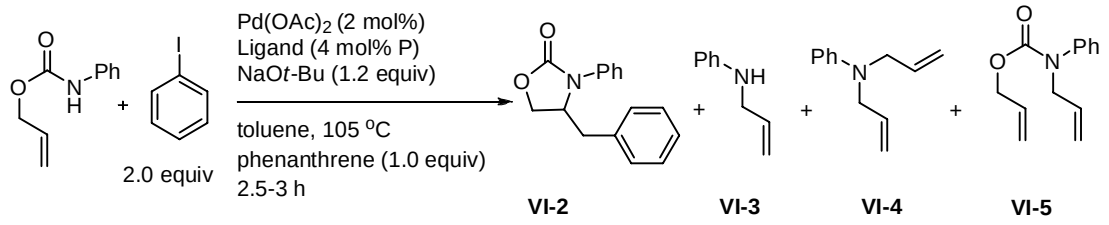
*Names below structures indicate the student(s) who synthesized these substrates.

## Synthesis of Oxazolidin-2-ones from *O*-Allylcarbamates

In order to determine the optimal ligand to effect Pd-catalyzed carboamination of *O*-allylcarbamates, allyl phenylcarbamate was reacted with iodobenzene in the presence

of the ligands shown in Table VI-1. Four products were isolated **VI-2**–**VI-5**. The best yields of the carboamination product, **VI-2**, were obtained with DPE Phos and P(2-furyl) phosphine. As is evident from the results, about 50% of the mass balance remains unaccounted for. Control reactions (Tables VI-3–VI-5) demonstrate that the substrate is susceptible to Pd and base catalyzed decomposition.

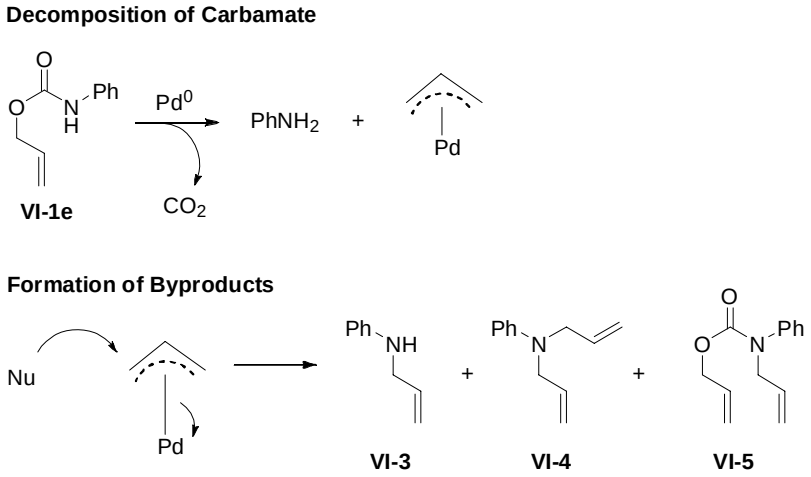
**Table VI-1.** Ligand Screen




| | | | % NMR Yield | | | |
|---|---|---|---|---|---|---|
| **Entry** | **Ligand** | **NMR % Conversion** | **VI-2** | **VI-3** | **VI-4** | **VI-5** |
| (1) | DPE Phos | 87 | 31 | 5 | 0 | 13 |
| (2) | Nixantphos | 100 | 5 | trace | 0 | trace |
| (3) | $P(2\text{-furyl})_3$ | 88 | 32 | 0 | 0 | 15-30 |
| (4) | Xantphos | 100 | 7 | trace | trace | 6 |
| (5) | Dppb | 100 | trace | 18 | trace | 26 |
| (6) | $P(o\text{-tol})_3$ | 82 | 4 | 1 | 0 | 6 |

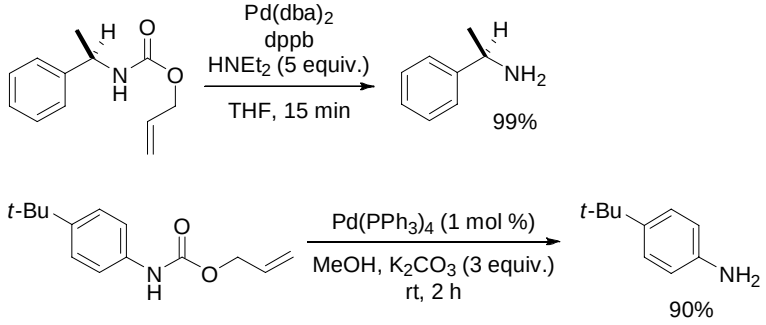
To explain the formation of the byproducts **VI-3**, **VI-4**, and **VI-5** that were isolated we propose the $Pd^0$ initially attacks the *O*-allylcarbamate **VI-1e** to give aniline, $CO_2$, and a Pd π-allyl species (Scheme VI-4). The Pd π-allyl species can then be attacked by aniline, allylaniline, or the substrate to give byproducts **VI-3**, **VI-4**, and **VI-5**.

**Scheme VI-4.** Decomposition of *O*-Allylcarbamates




There are several examples of deprotections of *O*-allylcarbamates to give amines by a $Pd^0$ species in the literature, two of which are shown in Scheme VI-5.[7]

**Scheme VI-5.** Alloc Deprotections in the Literature




Numerous other reaction conditions were varied to increase the rate of the desired Pd-catalyzed carboamination reaction relative to decomposition pathways. For instance, one set of parameters frequently varied to optimize for a desired reaction pathway are those having to do with the Pd catalyst (catalyst loading, Pd:L, and Pd source) We found that an increases in catalyst loading resulted in a small increase in yield of the carboamination product (10%). The Pd:L ratio had no significant effect on the reaction outcome and while early studies indicated that $Pd(OAc)_2$ led to higher conversions than $Pd_2(dba)_3$, later studies indicated that these two Pd sources gave identical ratios of substrate to desired product.

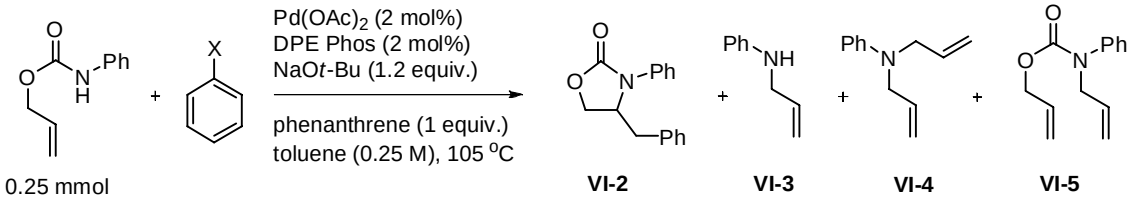
Another set of variables typically explored are solvent, base and reaction temperature. Dioxane, *t*-BuOH, and xylenes were found to perform better than toluene as solvents for the carboamination reaction.[8] KO*t*-Bu and LiO*t*-Bu gave higher yields of the

carboamination product than NaO*t*-Bu when *t*-BuOH and P(2-furyl)$_3$ were used as the solvent and ligand. NaO*t*-Bu was the best base in toluene. 1.2 equivalents of base was the optimum amount. Use of higher equivalents of base (2.0 and 3.0) did not produce any of the desired product. It is likely that the rates of substrate decomposition are proportional to the concentration of base in the reaction. Higher yields of the desired product were seen at 105 $^{o}$C rather than at lower temperatures.

Lastly, variations in substrate structure can have significant impact on the yield of the desired reaction. More specifically, it was thought that by modulating the nucleophilicity of the cyclizing nitrogen that the product distribution could be changed. Unfortunately, variation of the R group on the cyclizing nitrogen (Ph, PMP, Bn) provided no significant increase in the yield of the desired carboamination product. Another strategy often employed in increasing the rate of the cyclization reaction is to place substituents on the backbone of substrate. This lowers the degrees of freedom of the substrate in the transition state for cyclization making the transformation more entropically favorable (Thorpe effect). We attempted take advantage of this effect by placing methyl or phenyl in the allylic position of the *O*-allylcarbamate backbone. However, this also resulted in no significant increase in the yield of the desired carboamination product.

One parameter that was significant was the identity of the halide in the aryl halide coupling partner. As shown in Table VI-2, in the attempted coupling of the *O*-allylcarbamate with aryl bromides and aryl chlorides Pd π-allyl chemistry completely out competes the desired carboamination process. This can be explained by the rates of oxidative addition of Pd into aryl bromides and aryl chlorides relative to aryl iodides, as once oxidative addition occurs the Pd cannot carry out π-allyl chemistry.

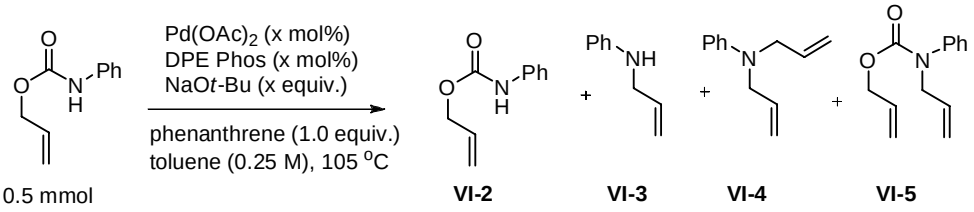
**Table VI-2.** Variation in Aryl Halide and Aryl Halide Equivalents




| X | ArX (equiv.) | NMR % Conv. | NMR % VI-2 | NMR % VI-3 | NMR % VI-4 | NMR % VI-5 | Total |
|---|---|---|---|---|---|---|---|
| Cl | 2.0 | 100 | 0 | 27 | 61 | 0 | 88 |
| Br | 2.0 | 100 | 0 | 30 | 15 | 0 | 45 |
| I | 2.0 | 88 | 47 | 0 | 0 | 6 | 65 |
| I | 2.0 | ~100 | 58 | 0 | 0 | 5 | 63 |

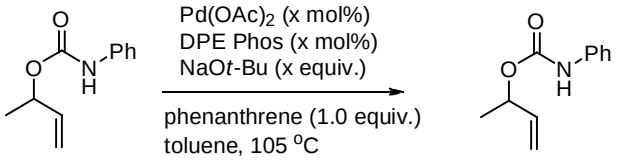
As shown in Tables VI-3–Table VI-5, several control reactions were performed to ascertain if and/or how the substrate decomposes under the reaction conditions. Several observations can be made. For example, the entries 2 and 3 in Table VI-3 demonstrate that *N*-Allylcarbamates are susceptible to both Pd and NaO*t*-Bu mediated decomposition. Entry 2 shows that treated with base only 28% of the starting material is remaining after 20 min and that the rest of the mass balance is unaccounted for. Entry 3 shows that when subjected to Pd none of the substrate is remaining after 20 min, byproducts **VI-3** and **VI-4** are formed (each in 33% yield), and that 34% of the mass balance is unaccounted for. However, the substrate is stable without Pd or NaO*t*-Bu present (Table VI-6, entry 3).

**Table VI-3.** Control Reactions 1: Decomposition by Pd and NaO*t*-Bu




| Entry | $Pd(OAc)_2$ (mol %) | DPE Phos (mol %) | NaO*t*-Bu (equiv) | Time | NMR % VI-2 | NMR % VI-3 | NMR % VI-4 | NMR % VI-5 | Total |
|---|---|---|---|---|---|---|---|---|---|
| (1) | 2 | 2 | 1.2 | 20 min | 0 | 22 | 25 | 0 | 47 |
| (2) | 0 | 0 | 1.2 | 20 min | 28 | 0 | 0 | 0 | 28 |
| (3) | 2 | 2 | 0 | 20 min | 0 | 33 | 33 | 0 | 66 |

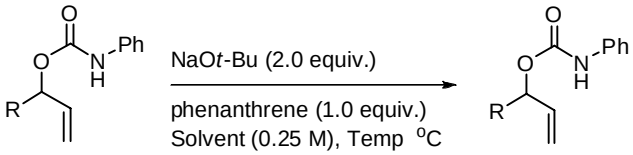
**Table VI-4.** Control Reactions 2: Decomposition by Pd and NaO*t*-Bu




| Entry | Scale | $Pd(OAc)_2$ (mol %) | DPE Phos (mol %) | NaO*t*-Bu (equiv) | Time (h) | % NMR Yield of SM |
|---|---|---|---|---|---|---|
| (1) | 0.5 | 4 | 4 | 1.2 | 0.5 | 12 |
| (2) | 0.25 | 0 | 0 | 1.2 | 9.0 | 37 |
| (3) | 0.25 | 0 | 0 | 0 | 0.5 | ~100 |

Rong Zhu, a visiting undergraduate from Peking University, also examined the relative rates of decomposition of substrates with various groups (R) at the allylic position (Table V-5). A comparison of the %NMR yield of the substrate at 2–2.5 hours shows that there does not appear to be a correlation between the size of R and the rate of decomposition. Furthermore, a comparison of the results with NaO*t*-Bu vs. $Cs_2CO_3$ seems to indicate that decomposition of the substrate is faster with NaO*t*-Bu than with $Cs_2CO_3$.

**Table VI-5.** Control Reactions 3: Decomposition by NaO*t*-Bu




0.5 mmol

| R | Base | Solvent | Temp. °C | Time (h) | % NMR Yield of SM |
|---|---|---|---|---|---|
| H | NaO*t*-Bu | Toluene | 105 | 2 | 9 |
| Me | NaO*t*-Bu | Toluene | 105 | 2 | 37 |
| Ph | NaO*t*-Bu | Toluene | 105 | 2 | 0 |
| H | $Cs_2CO_3$ | Dioxane | 100 | 2.5 | 80 |
| Me | $Cs_2CO_3$ | Dioxane | 100 | 2.5 | 79 |
| Ph | $Cs_2CO_3$ | Dioxane | 100 | 2.5 | 87 |

**Rong Zhu**

In summary, initial studies toward the Pd-catalyzed carboamination of *O*-allylcarbamates have been conducted. These results indicate that while Pd-catalyzed

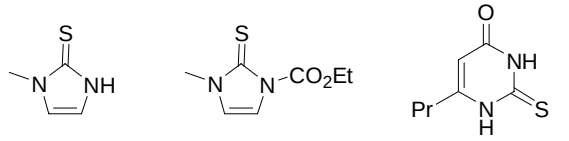
carboamination is feasible with these substrates, decomposition pathways still pose a significant challenge. Thus *O*-allylcarbamates provide an excellent opportunity for testing the development of ligands which will further increase the rate of Pd-carboamination reactions relative to other transformations. In the case of *O*-allylcarbamates, base-mediated decomposition and Pd-π-allyl chemistry are the specific challenges to overcome. As shown in table V-13, ligands which allow the use of milder bases while maintaining high rates of Pd-catalyzed carboamination will solve the problem of base-mediated decomposition. Likewise ligands which favor oxidative addition of Pd into aryl halides over oxidative addition into the C-O bond of the *O*-allylcarbamate should eliminate Pd-π-allyl chemistry as a competing pathway. Lautens and Jiao have demonstrated Heck reactions in which oxidative addition into an aryl iodide occurs in preference to the Pd-π-allyl chemistry. [9]

**Pd-Catalyzed Carboamination of *N*-Allylthioureas**

Although the Pd-catalyzed carboamination reactions of *O*-allylcarbamates gave low yields, we felt that related reactions of *N*-allylthioureas would be less likely to undergo decomposition via Pd-π-allyl pathways and would thus lead to higher yields of the desired cyclized products. Furthermore, a comparison of the cyclization of *N*-allylureas and *N*-allylthioureas would provide an opportunity to study how the electronics of the substrate influence the reaction pathway and rate.

As described in Chapter 1 cyclic thioureas are well known for antithyroid properties. For example, methimazole, carbimazole, and propylthiouracil are standard medicines used in the treatment of hyperthyroidism (Scheme VI-6).[10]

**Scheme VI-6.** Cyclic Thiourea Antithyroid Drugs

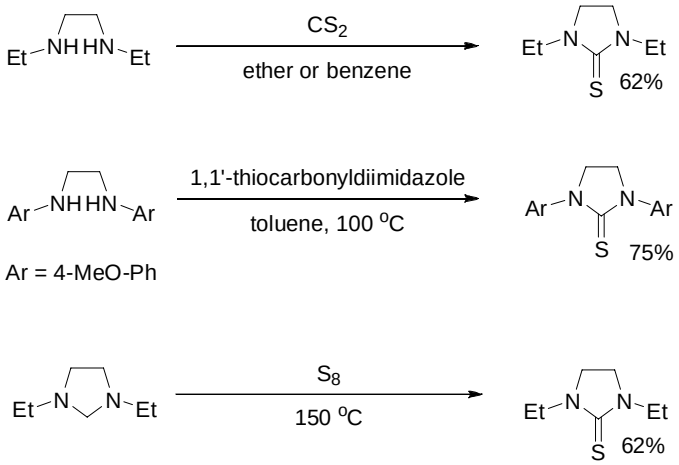



**Methimazole** **Carbimazole** **Propylthiouracil**

A subclass of cyclic thioureas, imidazolidin-2-thiones are generally formed via the reaction of diamines with $CS_2$, as shown in Scheme VI-7.[11] Alternatively, they may be formed via the reaction of diamines with thiocarbonyldiimidazole[12] or by reaction of imidazolidines with sulfur.[13] In contrast to imidazolidin-2-ones, and imidazolidin-2-one

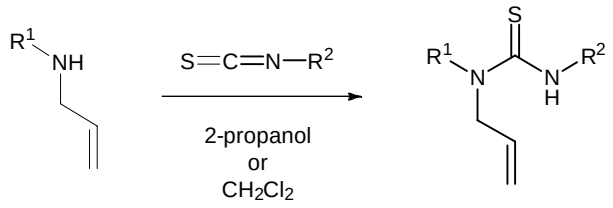
imines, their are few methods for the synthesis of imidazolidin-2-thiones that do not rely on vicinal diamines or imidazolidines as precursors. Thus a general diastereoselective synthesis of imidazolidin-2-thiones remains unrealized and would be of great benefit to the synthetic community. We felt that the Pd-catalyzed carboamination of *N*-allylthioureas would represent a significant addition to the synthetic methodologies available for making this class of heterocycles.

**Scheme VI-7.** Methods of Synthesizing Imidazolidin-2-thiones




*N*-allylthioureas can be synthesized in a similar manner to *N*-allylureas via reaction of allylic amines with isothiocyanates, as shown in Table VI-6. Yields of the *N*-allylthioureas ranged from 72% to 102%.

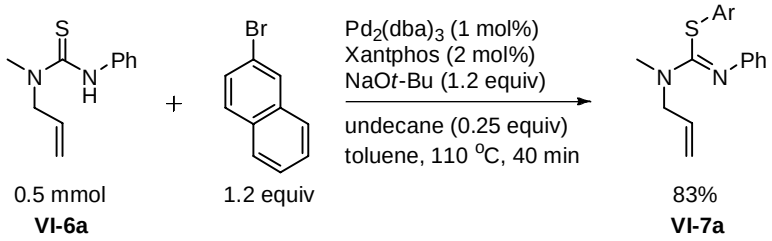
**Table VI-6.** Synthesis of *N*-Allylthioureas

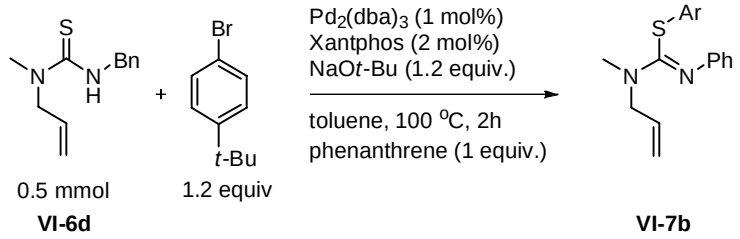



| # | $R^1$ | $R^2$ | Isothiocyanate (equiv) | Time (h) | Yield |
|---|---|---|---|---|---|
| **VI-6a** | Me | Ph | 1.4 | 3 | 85% |
| **VI-6b** | Bn | *i*-Pr | 1.2 | 7.5 | 102% |
| **VI-6c** | Bn | $CO_2Et$ | 0.8 | 1 | 72% |
| **VI-6d** | Me | Bn | 0.8 | 2 | 97% |

Interestingly, when **VI-6a** was subjected to the standard conditions of Pd-catalysis, arylation product **VI-7a** was isolated instead of the desired cyclization product (Scheme VI-8).[14,15] At 110 °C this arylation is rapid and provided an 83% yield of product in only 40 minutes. Reaction of **VI-6d**, which contained a benzyl group is on the cyclizing nitrogen produced similar results, forming **VI-7b** in 83% NMR yield when treated with 1-bromo-4-*tert*-butyl benzene under standard carboamination conditions.

**Scheme VI-8.** *S*-Arylation of *N*-Allylthioureas



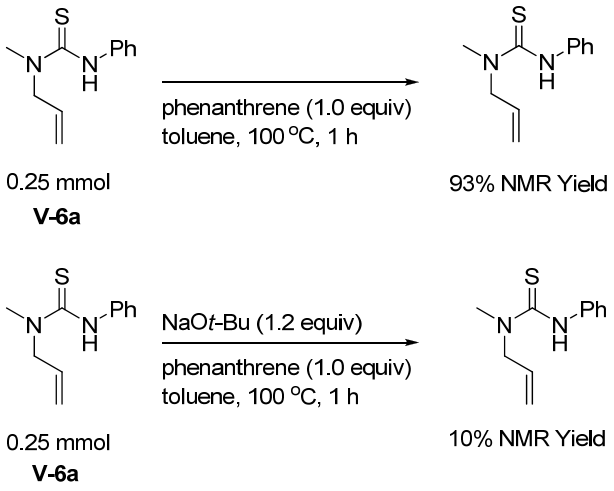

| Sample Method | NMR Yield |
|---|---|
| Celite Fitlration | 83 |
| $NH_4Cl$ Quench | 84 |

Several ligands were screened for the transformation shown above with the hope that one would preferentially give carboamination instead of the arylation product. Unfortunately, most ligands led to low reactivity or decomposition of the substrate. Use of Nixantphos, DPE Phos or P(2-fuyl)$_3$ as ligands led to small amounts of an unidentified product.

Control reactions explain the origin of the decomposition observed in the ligand screen. As shown in Scheme VI-9, *N*-allylthioureas appears to be thermally stable. Reaction of **VI-6a** with only the internal standard in toluene returned a 93% NMR yield of the substrate after one hour. However, *N*-allylthioureas are susceptible to base mediated decomposition. When **VI-6a** was reacted with NaO*t*-Bu, 90% of it was consumed in an hour. Thus, unless the desired Pd-catalyzed carboamination reaction is

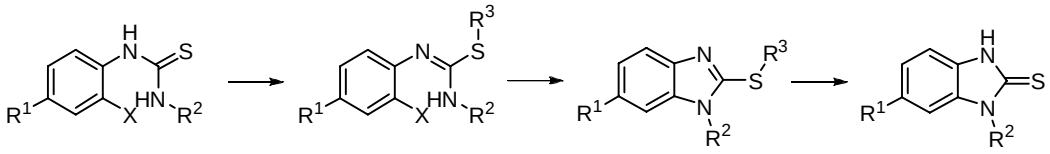
fast very little cyclized product will be seen due to base-mediated decomposition.

**Scheme VI-9.** Control Reactions




In summary, *N*-allylthioureas demonstrate markedly different reactivity than *N*-allylureas, giving S-arylation under the same conditions in which the analogous ureas afford the desired cyclized products. They are also susceptible to base-mediated decomposition. In future studies, modulation of the electronics of the group on *N*3 of the substrate may allow cyclization to be competitive with *S*-arylation. Should cyclization occur, it is likely that *S*-cyclization will predominate. A recently successful strategy employed by Patel for affording *N*-cyclization in preference to *S*-cyclization involves alkylation of the sulfur, followed by cyclization, and deprotection (Scheme VI-10).[15a] Alternatively, modulating the hardness of the aryl halide electrophile may also influence ratio of *S* and *N*-cyclization.[16]

**Scheme VI-10.** Patel's Strategy for *N*-Cyclization

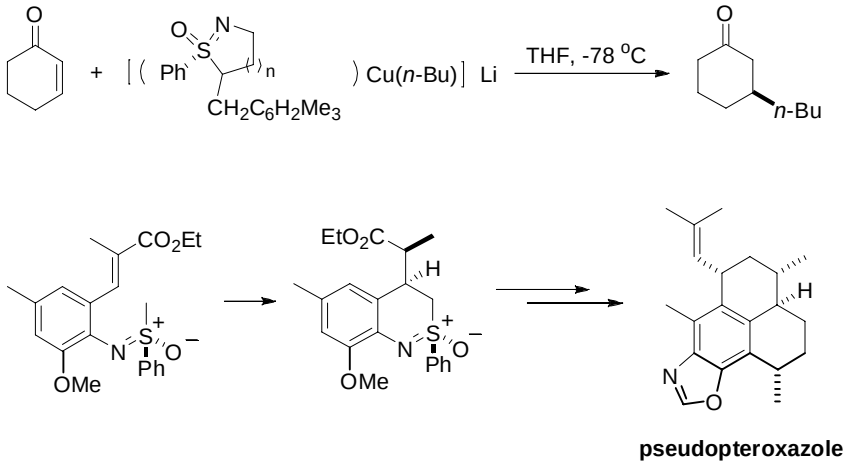


**Pd-Catalyzed Carboamination of Allylsulfoximines**

Another interesting target for Pd-catalyzed carboamination is cyclic sulfoximines. The stereogenic sulfur atom in sulfoximines can be used to control stereochemical outcomes of reactions. For instance, as shown in Scheme VI-11, they have been used by Boβhammer and Gais to impart stereocontrol in copper-catalyzed enantioselective conjugate additions.[17] Harmata and coworkers have demonstrated the use of sulfoximines

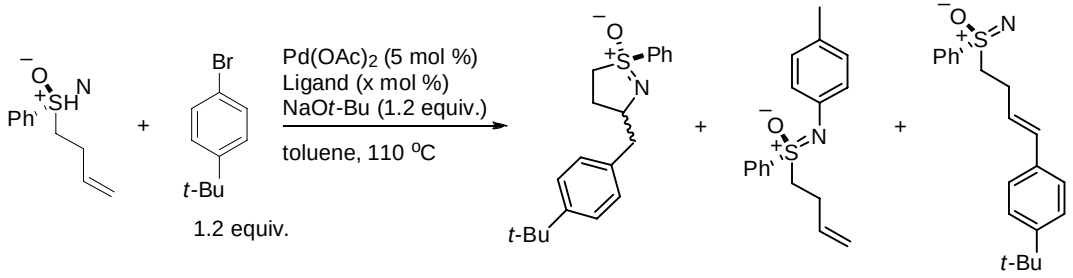
to generate stereocenters at benzylic positions. This is achieved through addition of a sulfoximine carbanion into an α,β-unsaturated ester. Further transformations eventually cleave this chiral auxiliary. This strategy has been highlighted in the synthesis of pseudoteroxazole[18] as well as (+)-curcuphenol,[19] (+)-curcumene[19] and (+)-erogorgiaene.[20] The Pd-catalyzed carboamination of sulfoximines could also potentially provide interesting and unusual heterocycles that could be of medicinal interest.

**Scheme VI-11.** Applications of Cyclic Sulfoximines




Professor Harmata kindly provided us with two homoallylic sulfoximine substrates, **V-8a** and **V-8b**, which allowed us to conduct preliminary feasibility studies on sulfoximine carboamination reactions. First, as shown in Table VI-7, we examined the reaction of **V-8a** with 1-bromo-4-*tert*-butylbenzene using a few different ligands. Three products derived from Pd-catalyzed carboamination, *N*-arylation, and Heck arylation were observed in the reaction mixtures. Of the ligands screened, Xantphos and DPE Phos afforded the carboamination product.

**Table VI-7.** Cyclization of Sulfoximines



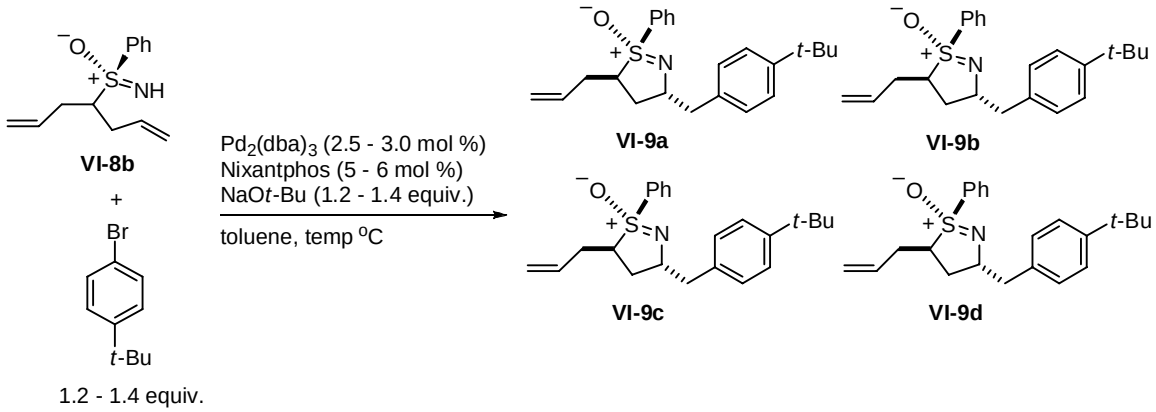

**VI-8a** **Carboamination*** ***N*-Arylation** **Heck**

| Ligand | Time (h) | Ligand (mol %) | Result |
|---|---|---|---|
| DPE phos | 9 | 5 | *N*-Arylation/ Carboamination/ Heck |
| dppe | 23 | 5 | *N*-Arylation/ Heck |
| Xantphos | 6.5 | 5 | *N*-Arylation/ Carboamination/ Heck/ Complex Mixture |
| ($t$-Bu)$_3$P•HBF$_4$ | 6 | 10 | Heck/ Complex Mixture |
| Xantphos | 4 | 10 | *N*-Arylation/ Carboamination (trace) |

*The diastereoselectivity of the carboamination product could not be determined from the crude reaction mixture.

While this first substrate did cleanly afford the desired product, a substrate bearing an additional allylic group led to good yields of the carboamination product. This reaction could potentially form the four diastereomers shown in Table VI-8, three of which were observed in our reaction. NOESY analysis indicated that the stereochemistry between C3 and C5 is *cis*. Thus, the major isomer is **VI-8c** or **VI-8d**.

**Table VI-8.** Cyclization of Diallylsulfoximines



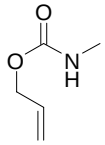

| Time | Temp | Conv. | Yield | dr |
|---|---|---|---|---|
| 4.5 h | 110 °C | 100% | 60% | 1.00 : 0.20 : 0.09 |
| 4 h | 80 °C | 100% | 65% | 1.00 : 0.14 : 0.05 |
| 20 h | 50 °C | 24% | N/A | N/A |

In conclusion, homoallylsulfoximines are promising substrates for Pd-catalyzed carboamination to afford cyclic sulfoximines. The reactions appeared to be cleaner when a substituent was along the backbone of the substrate (Thorpe effect) and Nixantphos was used as the ligand. Isolated reactions gave good yields (60-65%) and diastereoselectivities that were 20:2:1 between the three stereocenters.

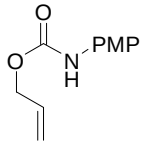
## Experimental Section

### General

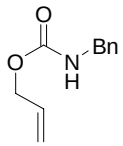
All reagents were purchased from commercial sources and were used as obtained unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) and all phosphine ligands were purchased from Strem Chemical Co. and used without further purification. All aryl bromides and aryl iodides were obtained from commercial sources (generally Aldrich Chemical Co. or Acros Chemical Co.) and were used as obtained. Toluene, THF, dichloromethane, and ether were purified using a Glass Contour solvent purification system. Product regiochemistry was assigned on the basis of $^1$H NMR 2D-COSY and HSQC experiments. Product stereochemistry was assigned on the basis of $^1$H NMR 2D-NOESY experiments. Reaction times described below have not been minimized.



**Allyl methylcarbamate (VI-1a).** To a flame dried flask was added methyl amine 40% by weight (4 mL) and toluene (12 mL). To the solution was slowly added allyl chloroformate (1.76 mL). The solution was stirred 3.5 h, the organic and aqueous layers were separated, and the organic layer was dried with $Na_2SO_4$. The organics were dried with $Na_2SO_4$ and the solvent was removed *in vacuo*. The residue was purified via flash chromatography to afford 1.49 g (76%) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.02–5.82 (m, 1 H), 5.30 (d, *J* = 17.1 Hz, 1 H), 5.20 (d, *J* = 10.2 Hz, 1 H), 4.57 (d, *J* = 5.4 Hz, 3 H), 2.81 (d, *J* = 5.1 Hz, 3 H).

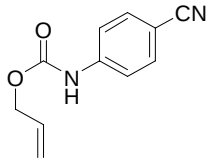


**Allyl 4-methoxyphenylcarbamate (VI-1b).** To a flame dried flask was added *p*-anisidine (1.23 g, 10 mmol), pyridine (1.62 mL, 20 mmol), and $CH_2Cl_2$ (10 mL). The solution was placed in an ice bath and allyl chloroformate (1..28 mL, 12 mmol) was added. After stirring for 6 h, the solution was washed with 1 M HCl (20 mL), water (20 mL), and brine (20 mL). The organics were dried with $Na_2SO_4$ and the solvent was removed *in vacuo*. The residue was purified via flash chromatography to afford 1.897 g (92%) of the title compound as a brown solid mp 40–43 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2 H), 6.85 (d, *J* = 9.2 Hz, 2 H), 6.50 (s, 1 H), 6.04–5.90 (m, 1 H), 5.36 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.26 (dd, *J* =1.2, 10.4 Hz, 1 H), 4.66 (d, *J* = 6.0 Hz, 2 H), 3.79 (s, 3 H).

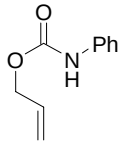


**Allyl benzylcarbamate (VI-1c).** To a flame dried flask was added benzyl amine (1.09 mL, 10 mmol), pyridine (1.62 mL, 20 mmol), and $CH_2Cl_2$ (10 mL). The solution was placed in an ice bath and allylchloroformate (1.28 mL, 12 mmol) was added. After stirring for 6 h, the solution was washed with 1 M HCl (20 mL), water (20 mL), and brine

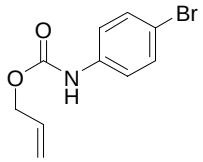
(20 mL). The organics were dried with $Na_2SO_4$ and the solvent was removed in vacuo. The residue was purified via flash chromatography to afford 1.747 g (91%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5 H), 6.00–5.87 (m, 1 H), 5.31 (d, *J* = 17.2 Hz, 1 H), 5.22 (d, *J* = 10.4 Hz, 1 H), 5.02 (s, 1 H), 4.61 (d, *J* = 5.6 Hz, 2 H), 4.39 (d, *J* = 6.4 Hz, 2 H).



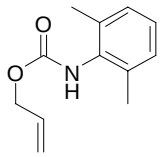

**Allyl 4-cyanophenylcarbamate (VI-1d).** To a flame dried flask was added 4-aminobenzonitrile (1.18 g, 10 mmol), pyridine (1.62 mL, 20 mmol), and $CH_2Cl_2$ (10 mL). The solution was placed in an ice bath and allylchloroformate (1.28 mL, 12 mmol) was added. After stirring for 6 h, the solution was washed with 1 M HCl (20 mL), water (20 mL), and brine (20 mL). The organics were dried with $Na_2SO_4$ and the solvent was removed in vacuo. The residue was purified via flash chromatography to afford 1.8g (89%) of the title compound as a yellow solid mp 123–125 $^o$C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 6.85 (s, 1 H), 6.06–5.90 (m, 1 H), 5.38 (dd, *J* = 1.6, 17.6 Hz, 1 H), 5.30 (dd, *J* = 1.2, 10.4 Hz, 1 H), 4.69 (d, *J* = 5.6 Hz, 2 H).



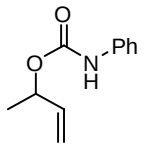

**Allyl phenylcarbamate (VI-1e).** A flame dried flask was charged with phenylisocyanate (1.1 mL, 10 mmol) in $CH_2Cl_2$ (10 mL). The solution was placed in an ice bath and allyl alcohol (1.2 mL, 18 mmol) was added. The solution was stirred 24 h at rt and the solvent was removed *in vacuo*. The residue was purified via flash chromatography to afford 1.52 g (86%) of the title compound as a white solid, mp 68–70 $^o$C. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2 H), 7.31 (t, *J* = 7.2 Hz, 2 H), 7.06 (t, *J* = 7.2 Hz, 1 H), 6.66 (s, 1 H), 6.06–5.88 (m, 1 H), 5.36 (dd, *J* = 1.5, 17.1 Hz, 1 H), 5.26 (dd, *J* = 1.2, 10.2 Hz, 1 H), 4.67 (dt, *J* = 1.5, 4.2 Hz, 2 H).



**Allyl 4-bromophenylcarbamate (VI-1f).** A flame dried flask was charged with 4-bromophenylisocyanate (1.98 g, 10 mmol), allylalcohol (1.4 mL, 20 mmol) and THF (10 mL) which were refluxed for 14.5 h. The solvent was removed *in vacuo* and the residue was purified via flash chromatography to afford 2.2 g (86%) of the title compound as a white solid, mp 62–65 $^{o}$C. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, $J$ = 8.8 Hz, 2 H), 7.28 (d, $J$ = 8.4 Hz, 2 H), 6.61 (s, 1 H), 6.03–5.90 (m, 1 H), 5.36 (dd, $J$ = 1.6, 17.2 Hz, 1 H), 5.27 (dd, $J$ = 1.2, 10.4 Hz, 1 H), 4.67 (dt, $J$ = 1.2, 6.0 Hz, 2 H).

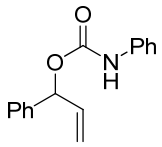


**Allyl 2,6-dimethylphenylcarbamate (VI-1g).** A flame dried flask was charged with 2,6-dimethylphenylisocyanate (1.39 mL, 10 mmol), allylalcohol (1.02 mL, 15 mmol), $Et_3N$ (2.08 mL, 15 mmol), DMAP (0.611 g, 5 mmol) and THF (20 mL). The flask was purged with nitrogen and stirred at 65 $^{o}$C for 5.25 h. The solvent was removed *in vacuo* and the residue was purified via flash chromatography to afford 2.099 g (100%) of the title compound as a white solid, mp 60–63 $^{o}$C. $^{1}$H NMR (400 MHz, toluene, 100 $^{o}$C) δ 6.44–6.35 (m, 3 H), 5.38–5.24 (m, 1 H), 4.85 (s, 1 H), 4.65 (d, $J$ = 16.8 Hz, 1 H), 4.51 (d, $J$ = 10.8 Hz, 1 H), 4.02 (d, $J$ = 6.0 Hz, 2 H), 1.66–1.61 (m, 6 H).

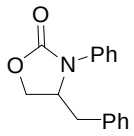


**But-3-en-2-yl phenylcarbamate (VI-1i).** A round-bottom flask was charged with phenylisocyanate (1.1 mL, 10 mmol), 3-buten-2-ol (1.3 mL, 15 mmol) and THF (10 mL) The solution was stirred at rt for 24.5 h, a second portion of 3-buten-2-ol (1.3 mL, 15 mmol) was added, and the solution was refluxed 1.5 days. The solvent was removed *in vacuo* and the residue was purified via flash chromatography to afford 1.204 g (63%) of the title compound as a white solid, mp 56–58 $^{o}$C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $J$ = 8.0 Hz, 2 H), 7.30 (t, $J$ = 7.5 Hz, 2 H), 7.06 (t, $J$ = 6.5 Hz, 1 H), 6.57 (s, 1 H), 5.95–

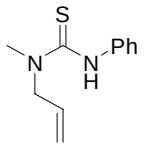
5.85 (m, 1 H), 5.40–5.34 (m, 1 H), 5.30 (d, $J$ = 17.5 Hz, 1 H), 5.17 (d, $J$ = 10.5 Hz, 1 H), 1.38 (d, $J$ = 7.0 Hz, 3 H).



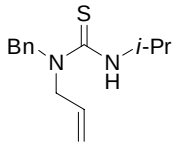
**1-Phenylallyl phenylcarbamate (VI-1j).** To a flask charged with 1-phenylprop-2-en-1-ol (1.058 g, 7.88 mmol) was added DMAP (0.402 g, 3.29 mmol), $Et_3N$ (1.37 mL, 9.86 mmol), phenyl isocyanate (0.71 mL, 6.57 mmol), and $CH_2Cl_2$ (7 mL). The solution was stirred 15 h and a second portion of $Et_3N$ (1.37 mL, 9.86 mmol) was added. The solvent was removed *in vacuo* and the residue was purified via flash chromatography to afford 1.417 g (85%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.43–7.26 (m, 9 H), 7.06 (t, $J$ = 7.5 Hz, 1 H), 6.67 (s, 1 H), 6.28 (d, $J$ = 6.0 Hz, 1 H), 6.13–6.03 (m, 1 H), 5.36 (d, $J$ = 17.0 Hz, 1 H), 5.29 (d, $J$ = 10.5 Hz, 1 H).



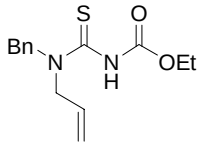
**4-Benzyl-3-phenyloxazolidin-2-one (VI-II).** An oven- or flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), DPE-phos (2.7 mg, 0.005 mmol), NaO*t*-Bu (28.8 mg, 0.3 mmol), allyl phenylcarbamate (44.3 mg, 0.25 mmol), iodobenzene (102.0 mg, 0.5 mmol), and phenanthrene (44.6 mg, 0.25 mmol). The tube was purged with nitrogen, and toluene 1 mL was then added. The Schlenk tube was then placed in a 105 $^o$C oil bath for 1 h. The mixture was then cooled to rt, saturated aqueous $NH_4Cl$ (2 mL) was added, and the mixture was extracted with methylene chloride or ethyl acetate (3 x 7 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford 13 mg (21%) of the title compound as an orange oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, $J$ = 7.6 Hz, 2 H), 7.44 (t, $J$ = 7.6 Hz, 2 H), 7.37–7.19 (m, 4 H), 7.12 (d, $J$ = 6.8 Hz, 2 H), 4.72–4.60 (m, 1 H), 4.35 (t, $J$ = 8.8 Hz, 1 H), 4.21 (dd, $J$ = 4.8, 8.8 Hz, 1 H), 3.14 (dd, $J$ = 3.2, 13.6 Hz, 1 H) 2.77 (dd, $J$ = 9.6, 13.6 Hz, 1 H).



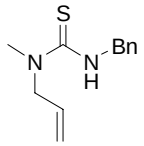
**1-Allyl-1-methyl-3-phenylthiourea (VI-6a).** Charged an oven-dried flask charged with methylallylamine (0.947 g, 13.32 mmol), phenyl isothiocyanate (2.60 g, 19.23 mmol), and 2-propanol (19 mL). The solution was stirred 3 h, the solvent was removed *in vacuo*, and the residue was purified via flash chromatography to afford 2.87 g (90%) of the title compound as a white powder, mp 70–73. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 4 H), 7.20 (t, *J* = 7.2 Hz, 1 H), 7.11 (s, 1 H), 5.99–5.87 (m, 1 H), 5.38–5.26 (m, 2 H), 4.42 (d, *J* = 5.2 Hz, 2 H), 3.31 (s, 3 H) $^{13}$C NMR (100 MHz, $CDCl_3$) δ 182.1, 139.6, 131.7, 128.5, 125.6, 125.3, 117.7, 55.9, 38.9.



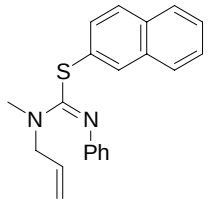
**1-Allyl-1-benzyl-3-isopropylthiourea (VI-6b).** Charged an flame-dried flask charged with benzylallylamine (0.736 g, 5.0 mmol), isopropyl isothiocyanate (0.607 g, 6.0 mmol), and $CH_2Cl_2$ (5 mL). The solution was stirred 7.5 h, the solvent was removed *in vacuo*, and the residue was purified via flash chromatography to afford 1.265 g (100%) of the title compound as a clear oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.42–7.25 (m, 5 H), 5.87–5.75 (m, 1 H), 5.33 (d, *J* = 6.8 Hz, 1 H), 5.28–5.18 (m, 2 H), 4.97 (s, 2 H), 4.67–4.54 (m, 1 H), 4.23 (d, *J* = 5.2 Hz, 2 H), 1.15 (d, *J* = 6.8 Hz, 6 H).



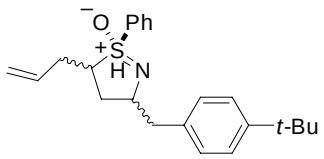
**1-Allyl-1-benzyl-3-ethoxycarbonylthiourea (VI-6c).** Charged an flame-dried flask charged with benzylallylamine (0.88 g, 6.0 mmol), ethoxycarbonyl isothiocyanate (0.66 g, 5.0 mmol), and $CH_2Cl_2$ (6 mL). The solution was stirred 1 h, the solvent was removed *in vacuo*, and the residue was purified via flash chromatography to afford 1.0 g (72%) of the title compound as a red oil. $^{1}$H NMR (400 MHz, toluene 100 $^{o}$C) δ 7.17–6.94 (m, 5 H), 6.91 (s, 1 H), 5.70–5.57 (m, 1 H), 5.01–4.78 (m, 4 H), 4.12 (d, *J* = 5.6 Hz, 2 H), 3.83 (q, *J* = 6.8 Hz, 2 H), 0.99–0.87 (m, 3 H).



**1-Allyl-3-benzyl-1-methylthiourea (VI-6d).** Charged an flame-dried flask charged with methylallylamine (0.6 g, 8.4 mmol), benzyl isothiocyanate (1.04 g, 7.0 mmol), and $CH_2Cl_2$ (5 mL). The solution was stirred 2 h, the solvent was removed *in vacuo*, and the residue was purified via flash chromatography to afford 1.50 g (97%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5 H), 5.89–5.79 (m, 1 H), 5.60 (s, 1 H), 5.24 (dd, *J* = 1.0, 10.5 Hz, 1 H), 5.19 (dd, *J* = 1.5, 17.5 Hz, 1 H), 4.86 (d, *J* = 5.0 Hz, 2 H), 4.39 (d, *J* = 5.0 Hz, 2 H), 3.19 (s, 3 H).



**(*E*)-Naphthalen-2-yl N-allyl-N-methyl-N'-phenylcarbamimidothioate (VI-7a).** A flame-dried Schlenk tube equipped with a stirbar was cooled under a stream of nitrogen and charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), Xantphos (5.8 mg, 0.01 mmol), NaO*t*-Bu (57.6 mg, 0.6 mmol), 1-allyl-1-methyl-3-phenylthiourea (103.2 mg, 0.5 mmol), 2-bromonaphthalene (124.2 mg, 0.6 mmol), and undecane (19.5 mg, 0.125 mmol). The tube was purged with nitrogen, and toluene **(**2 mL) was then added. The Schlenk tube was then placed in a 110 $^o$C oil bath for 35 min. The mixture was then cooled to rt, saturated aqueous $NH_4Cl$ (2 mL) was added, and the mixture was extracted with methylene chloride or ethyl acetate (3 x 7 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford 138 mg (83%) of the title compound as an yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80–7.72 (m, 1 H), 7.70–7.62 (m, 2 H), 7.60 (d, *J* = 1.6 Hz, 1 H), 7.49–7.41 (m, 2 H), 7.24 (d, *J* = 6.8 Hz, 1 H), 7.07 (t, *J* = 8.0 Hz, 2 H), 6.86 (t, *J* = 7.2 Hz, 1 H), 6.73 (d, *J* = 6.8 Hz, 2 H), 5.79–5.66 (m, 1 H), 5.23–5.10 (m, 2 H), 4.19 (d, *J* = 6.0 Hz, 2 H), 3.06 (s, 3 H).




**5-Allyl-3-(4-*tert*-butylbenzyl)-1-phenylisothiazoline-*S*-oxide (VI-9).** A Schlenk tube equipped with a stirbar was flame-dried under vacuum, backfilled with nitrogen, and charged with $Pd_2(dba)_3$ (5.8 mg, 0.0063 mmol), Nixantphos (6.9 mg, 0.0125 mmol), and NaO*t*-Bu (28.8 mg, 0.3 mmol). The tube was purged with nitrogen and *S*-(hepta-1,6-dien-4-yl)-*S*-phenylsulfoximine (58.8 mg, 0.25 mmol), 1-bromo-4-*tert*-butyl benzene (63.9 mg, 0.3 mmol), and toluene (2 mL) was then added. The Schlenk tube was then placed in a 80 $^{o}$C oil bath for 4 h. The mixture was then removed from the oil bath, saturated aqueous $NH_4Cl$ (2 mL) was added, and the mixture was extracted with methylene chloride (3 x 7 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel to afford 60 mg (65 %) of the title compound as an yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.2 Hz, 2 H), 7.60 (t, *J* = 7.2 Hz, 1 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 5.66–5.52 (m, 1 H), 5.07 (dd, *J* = 1.6, 17.2 Hz, 1 H), 4.96 (dd, *J* = 1.2, 10.0 Hz, 1 H), 4.18–4.06 (m, 1 H), 3.40 (dd, *J* = 5.2, 13.2 Hz, 1 H), 3.30–3.14 (m, 1 H), 2.76 (dd, *J* = 8.8, 13.6 Hz, 1 H), 2.72–2.56 (m, 1 H), 2.56–2.30 (m, 2 H), 1.80–1.64 (m, 1 H), 1.31 (s, 9 H).

[1] These studies were conducted in collaboration with Rong Zhu, a summer REU student from Peking University.
[2] Brickner, S. J.; Barbachyn, M. R.; Hutchinson, D. K.; Manninen, P. R. *J. Med. Chem.* **2008**, *51*, 1981–1990.
[3] Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691.
[4] Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274–7276.
[5] Morán-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.* **2008**, *10*, 1935–1938.
[6] Walsh, C. T.; Wright, G. *Chem. Rev.* **2005**, *105*, 391–393.
[7] a) Genêt, J. P.; Blart, E.; Savignac, M.; Lemeune, S.; Leamaire-Audoire, S.; Bernard, J. M. *Synlett* **1993**, 680–682. b) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M-H.; Thayumanavan, S. *J. Org. Chem.* **2003**, *68*, 1146–1149.
[8] Toluene gave a better yield of the desired carboamination product when a Pd:P ration of 1:2 was used rather than the 1:3 Pd:P ratio used in the solvent screening.
[9] a) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745–4747. b) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729–4732.
[10] a) Das, D.; Roy, G.; Mugesh, G. *J. Med. Chem.* **2008**, *51*, 7313–7317. b) Cooper, D. S. *N. Engl. J. Med.* **2005**, *352*, 905–917.
[11] Hussain, M. H.; Lien, E. J. *J. Med. Chem.* **1971**, *14*, 138–144. b) Donia, R. A.; Shotton, J. A.; Bentz, L. O.; Smith, Jr. G. E. P. *J. Org. Chem.* **1949**, *14*, 946–951.
[12] Yang, D.; Chen, Y-C.; Zhu, N-Y. *Org. Lett.* **2004**, *6*, 1577–1580.
[13] Denk, M. K.; Gupta, S.; Brownie, J.; Tajammul, S.; Lough, A. J. *Chem. Eur. J.* **2001**, *7*, 4477–4486.
[14] C–S bond forming reductive elimination is thought to be faster than C–N forming reductive elimination. See Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947.
[15] Intramolecular arylation reaction of 2-haloaniline derived thioureas gives exclusively *S*-arylation products in preference to *N*-arylation products. See a) Murru, S.; Patel, J. L.; Bras, J. L.; Muzart, J. *J. Org. Chem.* **2009**, *74*, 2217–2220. b) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446–447.
[16] The site of alkylation of an ambident nucleophile is partially a function of the hardness of the electrophile. For a discussion see Isaacs, N. S. *Physical Organic Chemistry 2nd Ed*; Pearson: England, 1995; pp 274–280.
[17] Boβhammer, S.; Gais, H-J. *Synthesis* 919–927.
[18] Harmata, M.; Hong, X. *Org. Lett.* **2005**, *7*, 3581–3583.
[19] Harmata, M.; Hong, X.; Barnes, C. *Tetrahedron Lett.* **2003**, *44*, 7261–7264.
[20] Harmata, M.; Hong, X.; Schreiner, P. R. *J. Org. Chem.* **2008**, *73*, 1290–1296.