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Synthesis of Saturated 1,4-Benzodiazepines via Pd-Catalyzed Carboamination Reactions.

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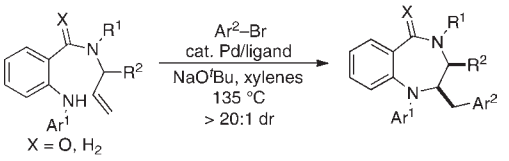
ABSTRACT



A new synthesis of 1,4-benzodiazepines and 1,4-benzodiazepin-5-ones is reported. The Pd-catalyzed coupling of *N*-allyl-2-aminobenzylamine derivatives with aryl bromides affords the heterocyclic products in good yield, and substrates bearing allylic methyl groups are transformed to *cis*-2,3-disubstituted products with >20:1 dr.

The benzodiazepine moiety is considered a privileged scaffold in medicinal chemistry, and many biologically active compounds bear this core.[1] Although much effort has been directed toward the construction of unsaturated 1,4-benzodiazepines,[2] fewer methods for the synthesis of saturated derivatives have been developed.[3] This remains an important goal, as saturated 1,4-benzodiazepines are displayed in both natural products and pharmaceutical leads (Figure 1). For example, anthramycin (**1**) is a naturally occurring antitumor antibiotic,[4] and analogs such as **2** display antileishmanial activity.[5] Benzodiazepine **3** is an inhibitor of mitochondrial F_1F_0 ATP hydrolase and has been examined as a potential candidate for treatment of cardiac ischemic conditions.[6] In addition, benzodiazepine **4** exhibits potent antitumor activity.[7]

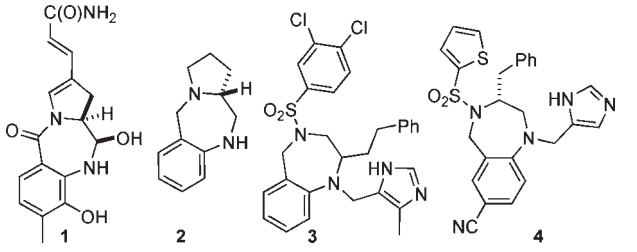


Figure 1. Biologically active saturated 1,4-benzodiazepines.

Our group has demonstrated that Pd-catalyzed carboamination reactions between aryl or alkenyl halides and amines bearing pendant alkenes are effective for the synthesis of a broad array of five-[8] and six-membered[9] nitrogen heterocycles.[10,11] However, our prior studies suggested that

(1) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65.
(2) Reviews: (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132.
(3) For recent examples, see: (a) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, *13*, 852. (b) Sakai, N.; Watanabe, A.; Ikeda, R.; Nakaike, Y.; Konakahara, T. *Tetrahedron* **2010**, *66*, 8837. (c) Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244. (d) Rujirawanich, J.; Gallagher, T. *Org. Lett.* **2009**, *11*, 5494. (e) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257. (f) Wang, J.-Y.; Guo, X.-F.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2008**, *73*, 1979.
(4) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791.
(5) Clark, R. L.; Carter, K. C.; Mullen, A. B.; Coxon, G. D.; Owusu-Dapaah, G.; McFarlane, E.; Thi, M. D. D.; Grant, M. H.; Tettey, J. N. A.; Mackay, S. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 624.
(6) Hamann, L. G.; Ding, C. Z.; Miller, A. V.; Madsen, C. S.; Wang, P.; Stein, P. D.; Pudzianowski, A. T.; Green, D. W.; Monshizadegan, H.; Atwal, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1031.
(7) (a) Hunt, J. T.; Ding, C. Z.; Batorsky, R.; Bednarz, M.; Bhide, R.; Cho, Y.; Chong, S.; Chao, S.; Gullo-Brown, J.; Guo, P.; Kim, S. H.; Lee, F. Y. F.; Leftheris, K.; Miller, A.; Mitt, T.; Patel, M.; Penhallow, B. A.; Ricca, C.; Rose, W. C.; Schmidt, R.; Slusarchyk, W. A.; Vite, G.; Manne, V. *J. Med. Chem.* **2000**, *43*, 3587. (b) Johnston, S. R. D. *IDrugs* **2003**, *6*, 72.

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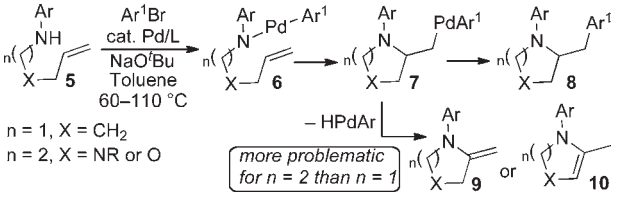
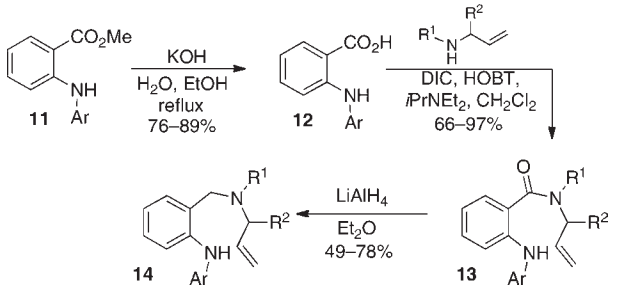
generation of seven-membered heterocycles via this strategy would be quite challenging, as both yields and reaction rates diminish with increasing ring size. This appears to be due to two main problems related to the mechanism of these transformations: as ring size increases, (a) *Syn*-aminopalladation of the alkene (Scheme 1), **6**→**7**, becomes more difficult due to entropic and stereoelectronic effects;[9,10] and (b) competing formation of enamine side products **9**−**10**, via β-hydride elimination from intermediate **7**, becomes more problematic.[9,10] The application of this methodology to the construction of seven-membered rings has not previously been demonstrated, and the formation of seven-membered nitrogen heterocycles via other metal-catalyzed alkene difunctionalization reactions is very rare.[12] For example, Michael has described a conceptually related Pd(II)-catalyzed C−H activation/carboamination of a *N*-allyl-2-(aminomethyl)aniline derivative that afforded a 3-substituted 1,4-benzodiazepine. However, only a single example was reported, and the yield was modest (53%).[12c]

Scheme 1. Mechanism and Competing Pathways



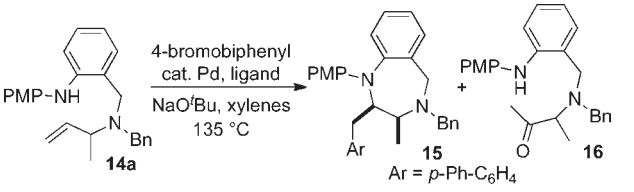
To determine the feasibility of forming seven-membered nitrogen heterocycles via Pd-catalyzed carboamination reactions, we elected to examine the synthesis of saturated 1,4-benzodiazepines. The substrates **14** for these studies were prepared in three steps from readily available diarylamines **11** (Scheme 2), which can be generated via Pd-catalyzed *N*-arylation of methyl-2-aminobenzoate.[13] Saponification of the ester followed by coupling of the resulting acid **12** with an allylic amine provided amides **13**. Reduction of the amides with $LiAlH_4$ then afforded **14** in moderate to good yield.

Scheme 2. Synthesis of Substrates



In our preliminary experiments we examined the Pd-catalyzed coupling of **14a** with 4-bromobiphenyl (Table 1). Our previous studies indicated that use of P(2-fur)$_3$ as a ligand gave satisfactory results in six-membered ring forming reactions.[9] However, use of this ligand in a reaction of **14a** provided desired product **15** in a modest 58% NMR yield, along with 13% of ketone **16**. This side product presumably results from hydrolysis of an enamine (**9**, n = 3), which is generated via a competing β-hydride elimination pathway (Scheme 1). In order to minimize this side reaction,

Table 1. Optimization of Reaction Conditions[a]



Pd-source	ligand	conversion (%)	yield **15** (%)[b]	yield **16** (%)[b]
$Pd_2(dba)_3$	P(2-fur)$_3$	91	58	13
$Pd_2(dba)_3$	S-Phos	100	0	0[c]
$Pd_2(dba)_3$	PCy_2Ph	100	46	8
$Pd_2(dba)_3$	PPh_2Cy	100	79	6
$PdCl_2(MeCN)_2$	**PPh_2Cy**	**100**	**79 (65)**[d]	**4**

[a] Conditions: 1.0 equiv of **14a**, 2.0 equiv of 4-bromobiphenyl, 2.0 equiv of NaO^{t}Bu, 2 mol % [Pd], 4 mol % ligand. Product **15** was formed with >20:1 dr. [b] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard. [c] The major product resulted from *N*-arylation of the starting material. [d] Isolated yield (average of two experiments).

several other monodentate ligands were examined. Use of S-Phos failed to afford the desired product.[14] Instead,

(8) Pyrrolidines: (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (b) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851. (c) Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 2322. Pyrazolidines: (d) Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907. Isoxazolidines: (e) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533. Imidazolidin-2-ones: (f) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838.

(9) Piperazines: (a) Nakhla, J. S.; Schultz, D. M.; Wolfe, J. P. *Tetrahedron* **2009**, *65*, 6549. Morpholines: (b) Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107.

(10) Reviews: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (b) Wolfe, J. P. *Synlett* **2008**, 2913.

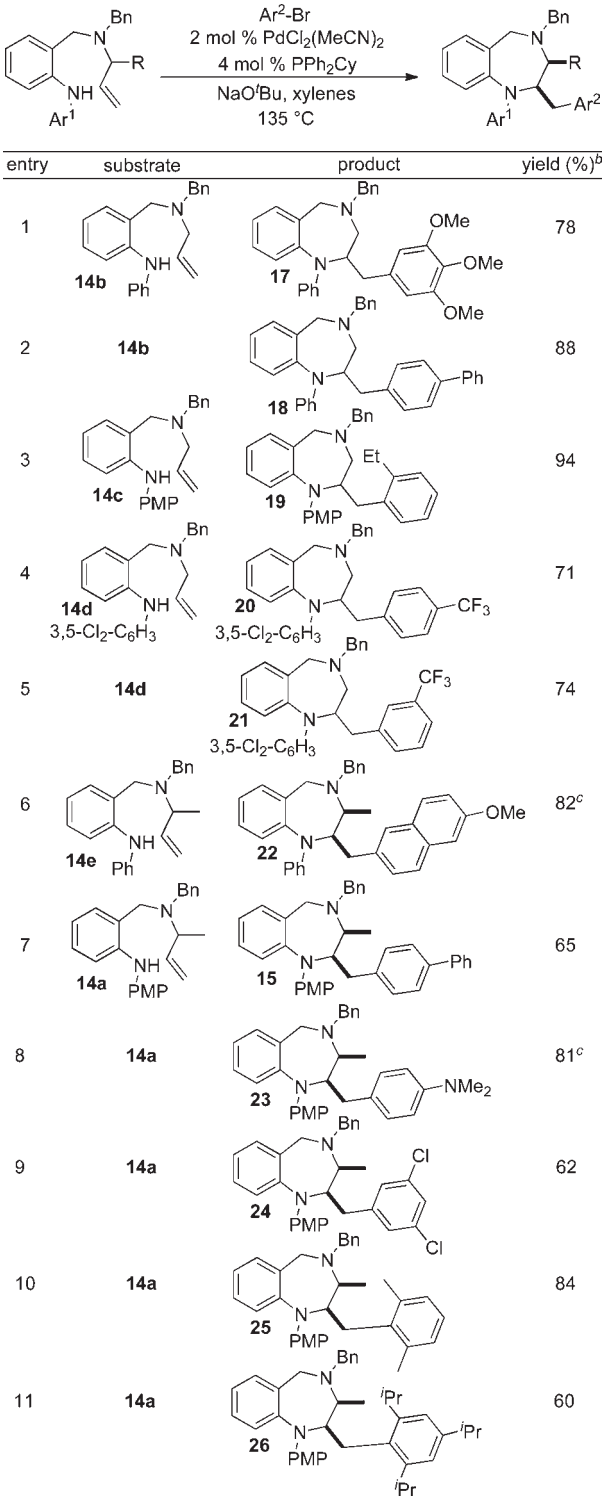
(11) For Cu- or Au-catalyzed carboamination reactions that afford 2-(arylmethyl)pyrrolidines and related heterocycles, see: (a) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009. (b) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. For alkene carboamination reactions involving solvent C−H bond functionalization, see: (c) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488.

(12) For hydroamination reactions, see: (a) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246. (b) Reznichenko, A. L.; Hultzsch, K. C. *Organometallics* **2010**, *29*, 24. (c) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275. For diamination reactions, see: (d) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. For Cope-type hydroamination reactions, see: (e) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

(13) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.

(14) S-Phos = 2-dicyclohexylphosphino-2′,6′-di-isopropoxy-1,1′-biphenyl.

Table 2. Synthesis of Saturated 1,4-Benzodiazepines[a]



[a] Conditions: Reactions were conducted on a 0.15 mmol scale using 1.0 equiv of substrate, 2.0 equiv of ArBr, 2.0 equiv of NaO^{t}Bu, 2 mol % $PdCl_2(MeCN)_2$, 4 mol % PPh_2Cy, xylenes (0.2 M), 135 °C, 18–24 h reaction time. [b] Isolated yield (average of two experiments). In all cases, 2,3-disubstituted products were obtained with >20:1 dr. [c] This product contained ca. 8% of ketone side product **16**.

competing *N*-arylation of the starting material was observed. However, after additional experimentation we discovered that a catalyst composed of $PdCl_2(MeCN)_2$ and PPh_2Cy provided acceptable results (79% NMR yield), and upon isolation the desired product **15** was obtained in 65% yield.

As shown in Table 2, the transformations were effective for a number of different substrate combinations. Aryl bromides bearing electron-donating or electron-withdrawing groups were coupled in good yields. However, *N*-arylation of the substrate was observed with highly electron-poor aryl bromides such as 4-bromo-2-fluorobenzonitrile. In most cases reactions were also effective for aryl bromides bearing *o*-alkyl substituents (entries 3, 10–11) including the very hindered 2,4,6-triisopropylbromobenzene (entry 11). However, no reaction was observed in the attempted coupling of 1-bromo-2-chlorobenzene with **14a**, and no desired product was obtained in a reaction between 1-bromopentamethylbenzene and **14d**; competing Heck arylation of the starting material was observed. Efforts to employ alkenyl bromides have thus far been unsuccessful.

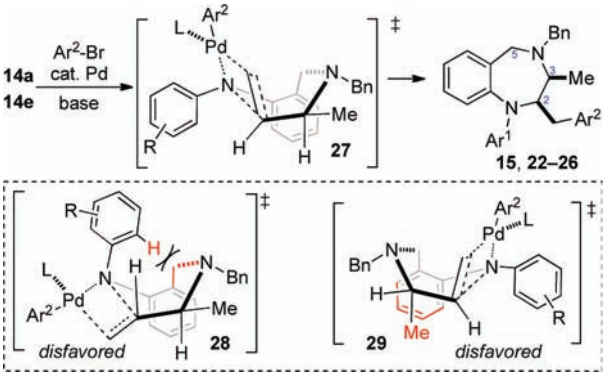
Although sterically bulky aryl bromides were reasonably well-tolerated, transformations of hindered diamine substrates proved to be more challenging. For example, substrates that contained an allylic-methyl group were stereoselectively transformed to *cis*-2,3-disubstituted products with >20:1 dr (entries 6–11). However, substrates bearing either larger substituents at the allylic position, or 1,1-disubstituted alkenes, failed to react. The electronic properties of the *N*-aryl group on the cyclizing nitrogen atom did not have a large influence on chemical yield, as substrates bearing *N*-phenyl, *N*-PMP, and *N*-(3,5-dichlorophenyl) groups were all effectively converted to products in moderate to good yield. However, attempts to employ substrates with a benzyl group on the cyclizing nitrogen atom were unsuccessful.

The stereochemical outcome of transformations involving substrates **14a** and **14e** is likely determined during C–N bond-forming alkene aminopalladation of an intermediate palladium(aryl)(amido) complex.[8–10,15] Our prior studies have indicated that alkene aminopalladations proceed via organized transition states in which the alkene is eclipsed with the Pd–N bond. This suggests reactions of substrates **14a** and **14e**, which afford *cis*-2,3-disubstituted products, most likely occur via boat-like transition state **27** (Scheme 3).[16] Pathways leading to the *trans*-disubstituted products appear to be high in energy. Chair-like transition state **28** suffers from unfavorable steric interactions between the *N*-aryl group and the C5 methylene unit, and boat-like transition state **29** is presumably disfavored due to the axial orientation of the C3 methyl group.

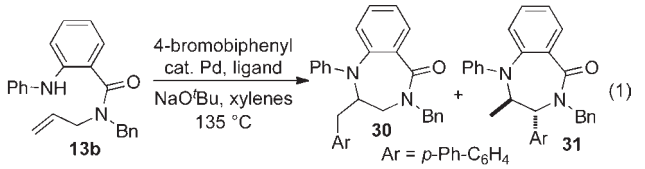
(15) (a) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276. (b) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *Organometallics* **2011**, *30*, 1269. (c) Hanley, P. S.; Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 6302.

(16) The major stereoisomers could also arise from chairlike transition states in which the methyl groups are oriented in axial positions. However, these transition states appear to be higher in energy than **27** due to 1,3-diaxial interactions and unfavorable steric interactions between the *N*-aryl group and the C5 methylene similar to those illustrated in **28**.

Scheme 3. Origin of Observed Diastereoselectivity



In order to further explore the scope of benzodiazepine-forming reactions, we examined the use of amides **13** as substrates for the carboamination reactions. As shown in eq 1, the conditions that were optimized for transformations of diamine substrates provided good yields of **30** in the coupling of **13b** with 4-bromobiphenyl, although small amounts of regioisomer **31** were also obtained.[17] After some additional optimization we found that use of P(4-F-C_6H_4)$_3$ as a ligand provided slightly improved selectivities. The regioisomer was separable by chromatography, and **30** was obtained in 76% isolated yield. These modified conditions proved to be useful for the coupling of amides **13b**, **13d**, and **13f** with a number of different aryl bromides (Table 3). However, efforts to employ an amide substrate bearing an allylic methyl group were unsuccessful; complex mixtures of regioisomers were obtained.



ligand = PPh_2Cy: 90% NMR yield, 10:1 regioselectivity

ligand = P(4-F-C_6H_4)$_3$: 87% NMR Yield, 13:1 regioselectivity

76% Isolated Yield 30

In conclusion we have developed an efficient entry into saturated 1,4-benzodiazepines and 1,4-benzodiazepin-5-ones via Pd-catalyzed alkene carboamination reactions. The method is effective for a variety of different aryl bromide coupling partners, and *cis*-2,3-disubstituted 1,4-benzodiazepines are formed with >20:1 dr. These transformations are rare examples of seven-membered ring-forming alkene difunctionalization reactions. Further studies toward enantioselective synthesis of 1,4-benzodiazepines and application of this strategy to biologically active targets are currently in progress.

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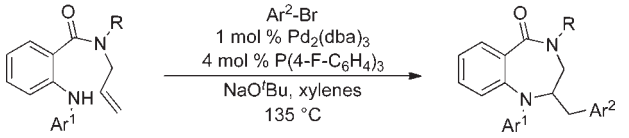
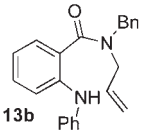
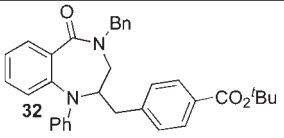
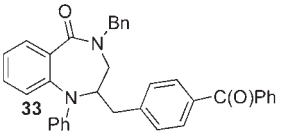
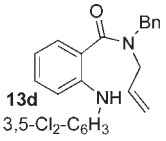
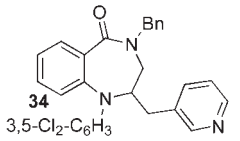
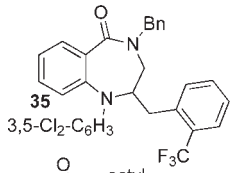
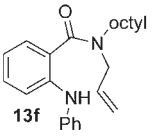
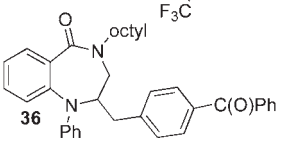
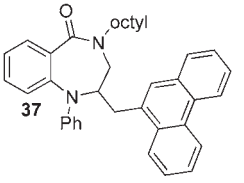
(17) This regioisomer likely originates from competing β-hydride elimination processes similar to those illustrated in Scheme 1. For further discussion, see: Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644.

Table 3. Synthesis of 1,4-Benzodiazepin-5-one Products[a]



entry	substrate	product	yield (%)[b]
1	 **13b**	 **32**	67
2	**13b**	 **33**	62
3	 **13d** 3,5-Cl_2-C_6H_3	 **34** 3,5-Cl_2-C_6H_3	74
4	**13d**	 **35** 3,5-Cl_2-C_6H_3	48
5	 **13f**	 **36**	70
6	**13f**	 **37**	77

[a] Conditions: Reactions were conducted on a 0.15 mmol scale using 1.0 equiv of substrate, 2.0 equiv of ArBr, 2.0 equiv of NaO^{t}Bu, 1 mol % $Pd_2(dba)_3$, 4 mol % P(4-F-C_6H_4)$_3$, xylenes (0.2 M), 135 °C, 18−24 h reaction time. [b] Isolated yield (average of two experiments).

Supporting Information Available. Experimental procedures, characterization data for all new compounds, descriptions of stereochemical assignments, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.