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Cascade Intramolecular *N*-Arylation/Intermolecular Carboamination Reactions for the Construction of Tricyclic Heterocycles

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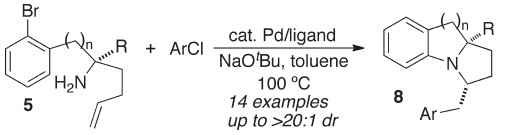
ABSTRACT



A new method for the stereoselective synthesis of tetrahydropyrroloindoles and hexahydropyrroloquinolines of general structure 8 is described. These products are formed through cascade Pd-catalyzed coupling reactions between aryl chlorides and unsaturated amine substrates 5. A single catalyst effects an intramolecular N-arylation reaction followed by an intermolecular alkene carboamination reaction to generate two rings, three bonds, and one stereocenter with good chemoselectivity, diastereoselectivity, and chemical yield.

Cascade reaction sequences that involve two fundamentally different metal-catalyzed transformations are powerful tools for organic synthesis.[1,2] These processes typically proceed via two or more different types of bond-forming events and lead to a rapid buildup of molecular complexity. Thus, the development of new sequential reaction cascades that provide stereocontrolled access to useful structural motifs remains of considerable merit.

We have previously described a cascade Pd-catalyzed intermolecular *N*-arylation/intermolecular carboamination reaction between γ-aminoalkenes and aryl bromides that affords 2-(arylmethyl)indolines or -pyrrolidines.[3,4] For example, treatment of **1** with 2 equiv of bromobenzene in the presence of NaO^{t}Bu and a catalyst composed of $Pd_2(dba)_3$ and Dpe-Phos (**4**) afforded *N*-phenyl-2-benzylindoline **2** in 92% yield (eq 1). Although this method provides an efficient approach to saturated nitrogen heterocycles, it suffers from two significant limitations. First of all, a rather cumbersome experimental protocol is necessary to achieve the chemoselective sequential coupling of two *different* aryl bromides to generate products such as **3** (eq 2).[3] The *N*-arylation reaction is conducted at 80 °C until the first aryl bromide is consumed. The reaction mixture is then cooled to rt, a second ligand is introduced to effect *in situ* ligand exchange, the second aryl bromide is then added, and heating is continued until the reaction proceeds to completion.[5] In addition to the complexity of the experimental procedure, this sequence of two intermolecular reactions is not amenable to the construction of

(1) For reviews, see: (a) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (b) Bruneau, C.; Derien, S.; Dixneuf, P. H. *Top. Organomet. Chem.* **2006**, *19*, 295.

(2) For selected recent examples, see: (a) Ohmura, T.; Kijima, A.; Suginome, M. *Org. Lett.* **2011**, *13*, 1238. (b) Gollner, A.; Koutentis, P. A. *Org. Lett.* **2010**, *12*, 1352. (c) Wang, X.; Liu, L.; Chang, W.; Li, J. *Eur. J. Org. Chem.* **2010**, 5391. (d) Pinto, A.; Neuville, L.; Zhu, J. *Tetrahedron Lett.* **2009**, *50*, 3602. (e) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255.

(3) (a) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (b) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575.

(4) For reviews on Pd-catalyzed carboamination reactions between aryl/alkenyl halides and amines bearing pendant alkenes, see: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (b) Wolfe, J. P. *Synlett* **2008**, 2913.

(5) This limitation is due to the fact that: (a) aryl bromides with similar steric and electronic properties (e.g., bromobenzene and 2-bromonaphthalene) undergo oxidative addition to Pd(0) with comparable rates; and (b) the rate of the carboamination step exceeds that of the *N*-arylation step with most catalyst systems. The sequential addition of the aryl halides avoids the first problem, and the *in situ* ligand exchange addresses the second. The ligand (*o*-biphenyl)P(^{t}Bu)$_2$ promotes rapid *N*-arylation and disfavors carboamination. When Dpe-Phos is added, a new catalyst is generated that facilitates the carboamination step. For further discussion, see ref 3a.

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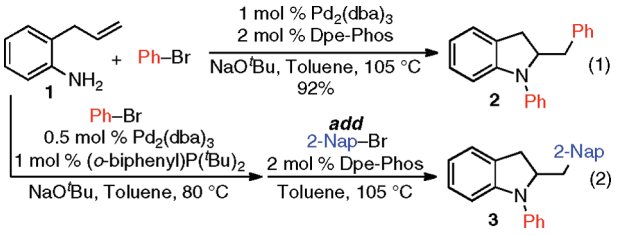
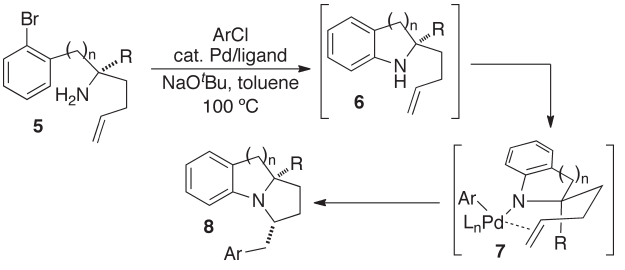
tricyclic heterocycles, which are an important class of compounds.



We reasoned that both of these limitations could be addressed through development of a related cascade reaction between aryl chlorides and γ-aminoalkenes **5** that contain pendant *o*-bromophenyl groups. As shown in Scheme 1, the chemoselective intramolecular *N*-arylation of a substrate such as **5** would yield **6**, which could then undergo a stereoselective intermolecular carboamination reaction with an exogenous aryl chloride via chairlike transition state **7** to afford **8**.[6] Given the differences in reactivity between aryl bromides and aryl chlorides toward Pd(0) complexes,[7] it seemed that chemoselectivity in the cascade could be achieved in a straightforward manner. *Intramolecular* amination of an aryl bromide should be considerably faster than *intermolecular* carboamination with an aryl chloride electrophile.[8] As such, it appeared that the desired sequential intramolecular *N*-arylation/intermolecular alkene carboamination reactions could potentially be effected using a single catalyst system, with both electrophiles present in the reaction mixture from the outset. In addition, the scaffolds generated via this strategy are displayed in a number of interesting biologically active compounds,[9] and similar fused tricyclic heterocycles have also been used as intermediates en route to bioactive molecules.[10,11]

Scheme 1. Cascade Intramolecular *N*-Arylation/Intermolecular Carboamination Strategy for Tricyclic Heterocycle Synthesis



Scheme 2. Synthesis of Enantiomerically Enriched Substrates

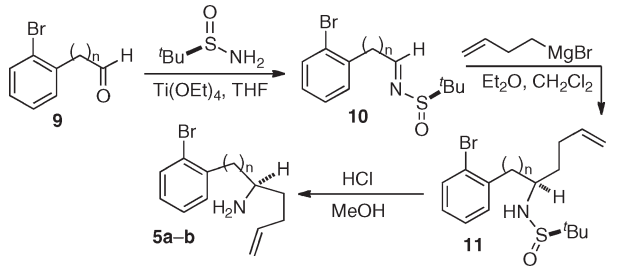
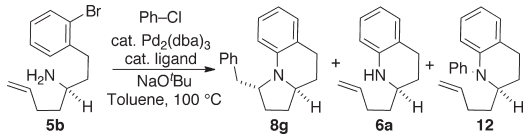
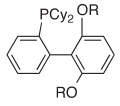
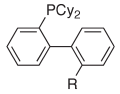
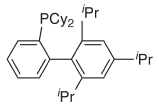
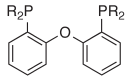


Table 1. Optimization of Reaction Conditions[a]



entry	ligand		product ratio **8g**:**6a**:**12**[b]
1		R = Me (**13**)	14:0:1
2		R = ^{i}Pr	4:0:1
3		R = NMe_2	3:0:1
4		R = Me	4:0:1
5		(**14**)	10:0:1
6		R = Ph (**4**)[c]	0:1:0
7		R = Cy (**15**)[c]	>20:0:1 (63% yield)[d]
8	PCy_3•HBF_4		>20:0:1

[a] Conditions: 1.0 equiv of **5b**, 1.2 equiv of PhCl, 2.4 equiv of NaO^{t}Bu, 1 mol % $Pd_2(dba)_3$, 4 mol % ligand, toluene (0.25 M), 100 °C, 5–24 h. [b] Product ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [c] The reaction was conducted using 2 mol % ligand. [d] The product was isolated with 25:1 dr, although analysis of the crude reaction mixture indicated the product had been formed with 8:1 dr.

(6) For further discussion of transition states leading to fused bicyclic compounds in Pd-catalyzed alkene carboamination reactions, see: Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 2322.

(7) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

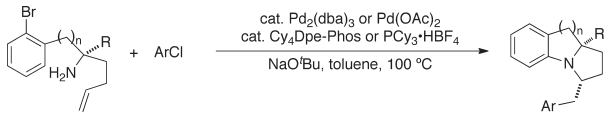
(8) For Pd-catalyzed carboamination reactions involving aryl chloride electrophiles, see: (a) Rosen, B. R.; Ney, J. E.; Wolfe, J. P. *J. Org. Chem.* **2010**, *75*, 2756. (b) Bagnoli, L.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Scarponi, C.; Tiecco, M. *J. Org. Chem.* **2010**, *75*, 2134. (c) Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7224.

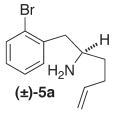
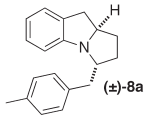
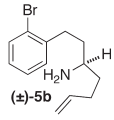
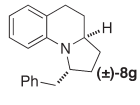
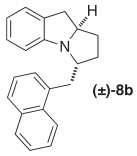
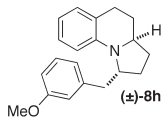
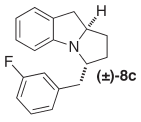
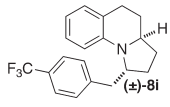
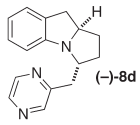
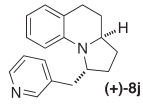
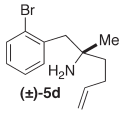
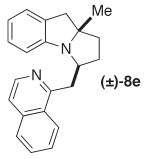
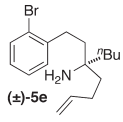
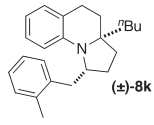
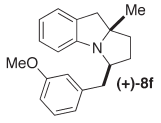
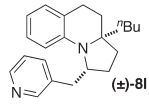
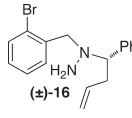
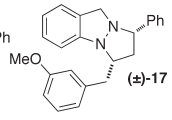
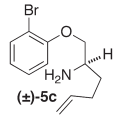
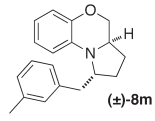
(9) (a) Hájícek, J.; Taimr, J.; Budesínsky, M. *Tetrahedron Lett.* **1998**, *39*, 505. (b) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127.

(10) (a) Jones, K.; Storey, J. M. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 769 and references cited therein. (b) Ito, Y.; Nakajo, E.; Nakatsuka, M.; Saegusa, T. *Tetrahedron Lett.* **1983**, *24*, 2881.

(11) For other recent complementary approaches to the synthesis of hexahydropyrroloquinolines and tetrahydropyrroloindoles structurally related to **8a**–**l**, see: (a) Kip, K.-T.; Yang, D. *Org. Lett.* **2011**, *13*, 2134. (b) Krogsgaard-Larsen, N.; Begtrup, M.; Herth, M. M.; Kehler, J. *Synthesis* **2010**, 4287. (c) Beemelmanns, C.; Blot, V.; Gross, S.; Lentz, D.; Reissig, H.–U. *Eur. J. Org. Chem.* **2010**, 2716. (d) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (e) Li, X.; Li, C.; Zhang, W.; Lu, X.; Han, S.; Hong, R. *Org. Lett.* **2010**, *12*, 1696. (f) Scarborough, C. C.; Bergant, A.; Sazama, G. T.; Guzei, I. A.; Spencer, L. C.; Stahl, S. S. *Tetrahedron* **2009**, *65*, 5084. (g) Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.* **2009**, *351*, 467.

Table 2. Cascade Intramolecular *N*-Arylation/Intermolecular Carboamination Reactions[a]



entry	substrate	product	catalyst[b]	dr[c]	yield (%)[d]	entry	substrate	product	catalyst[b]	dr[c]	yield (%)[d]
1	 (±)-5a	 (±)-8a	A	>25:1 (20:1)	76	8	 (±)-5b	 (±)-8g	A	25:1 (12:1)	68
2	(±)-5a	 (±)-8b	A	8:1 (5:1)	78	9	(±)-5b	 (±)-8h	A	22:1 (8:1)	63
3	(±)-5a	 (±)-8c	B[e]	>25:1 (5:1)	42	10	(±)-5b	 (±)-8i	B[e]	7:1 (3:1)	56
4	(+)-5a 92% ee	 (–)-8d	B	8:1 (7:1) 86% ee	58	11	(+)-5b 88% ee	 (+)-8j	B	>25:1 (10:1) 92% ee	56
5	 (±)-5d	 (±)-8e	B	14:1 (5:1)	60	12	 (±)-5e	 (±)-8k	B	11:1 (12:1)	79
6	(–)-5d 87% ee	 (+)-8f	A	>25:1 (10:1) 91% ee	75	13	(±)-5e	 (±)-8l	B	10:1 (7:1)	47
7	 (±)-16	 (±)-17	C	15:1 (3:1)	45	14	 (±)-5c	 (±)-8m	A	15:1 (5:1)	35

[a] Conditions: Reactions were conducted on a 0.25 mmol scale using 1.0 equiv of substrate, 1.2 equiv of ArCl, 2.4 equiv of NaO^{t}Bu, catalyst (4 mol % [Pd]), toluene (0.25 M), 100 °C. [b] Catalyst A: $Pd(OAc)_2$ (4 mol %), Cy_4Dpe-Phos **15** (4 mol %). Catalyst B: $Pd_2(dba)_3$ (2 mol % complex), PCy_3•HBF_4 (4 mol %). Catalyst C: $Pd_2(dba)_3$ (2 mol % complex), X-Phos **14** (8 mol %). [c] Diastereomeric ratios are reported for the isolated products. Diastereomeric ratios in parentheses were observed in crude reaction mixtures. [d] Isolated yield (average of two experiments). [e] The reaction was conducted using 8 mol % PCy_3•HBF_4.

The starting materials required for the cascade reactions were accessible in either racemic or optically active form using concise (3–4 step) sequences. For example, the enantiomerically enriched substrates **5a**–**b** were prepared in 3 steps from aldehydes **9** via conversion to the corresponding sulfinyl imines **10** followed by addition of but-3-enylmagnesium bromide and cleavage of the *N*-Bus group from the resulting product **11** (Scheme 2).[12] A similar strategy was used for the generation of enantiomerically enriched ketimine-derived substrates **5d**–**e** (Table 2). Alternatively, substrates **5a**–**c** were synthesized as racemates via reductive amination of the corresponding ketones.[13,14]

In our preliminary studies we examined a number of different phosphine ligands for the Pd-catalyzed coupling of **5b** with chlorobenzene. Initial results obtained with S-Phos (**13**), which has been shown to provide optimal yields in many other carboamination reactions of aryl chlorides,[8a] were very promising (Table 1, entry 1). Substantial amounts of desired product **8g** were formed, along with a small amount of side product **12**, which results from competing *N*-arylation of intermediate **6a**. However, other

(12) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(13) Hydrazine substrate **16** was prepared in four steps from 2-bromobenzyl bromide, *tert*-butyl carbazate, benzaldehyde, and allylmagnesium bromide.

(14) See the Supporting Information for complete experimental details.

related biaryl(dialkyl)phosphine ligands failed to provide improved results (entries 2−5). As noted above, we have previously shown that Dpe-Phos (**4**) affords good results in sequential *N*-arylation/carboamination reactions that give 2-(arylmethylindoline) products.[3a] However, this ligand is not very reactive toward aryl chlorides, and use of this ligand in an attempted coupling of **5b** with chlorobenzene afforded only **6a**, which results from intramolecular *N*-arylation of the substrate. To address this problem, we examined the more electron-rich Cy_4Dpe-Phos ligand (**15**)[15] and were gratified to observe the product **8g** was generated in good yield using these conditions. In addition, the simple trialkyl phosphine PCy_3 (which was introduced to the reaction mixture as an air-stable tetrafluoroborate salt) also provided good selectivity for product **8g**. However, small amounts of several other unidentified side products were formed in the Pd/PCy_3 catalyzed reaction, so Cy_4Dpe-Phos was selected as the ligand of choice for our exploration of reaction scope.

As shown in Table 2, the cascade intramolecular *N*-arylation/intermolecular carboamination reactions are effective for the preparation of several different substituted tetrahydropyrroloindole and hexahydropyrroloquinoline derivatives. The products were formed with good to excellent levels of diastereoselectivity and in moderate to good chemical yield. Importantly, enantiomerically enriched starting materials are converted to the heterocyclic products with no erosion of optical purity.[16] The construction of fused tricycles bearing two heteroatoms (entries 7 and 14) was also achieved, although yields for these products were moderate.[17]

The $Pd(OAc)_2$/Cy_4Dpe-Phos catalyst proved to be effective for transformations of several different electron-rich or electron-neutral aryl chlorides. Attempts to employ this catalyst for reactions of electron-poor aryl chloride substrates led to the formation of large amounts of side products analogous to **12**, which result from sequential intramolecular and intermolecular *N*-arylation reactions. However, the use of a catalyst composed of $Pd_2(dba)_3$ and PCy_3•HBF_4 provided good results in the coupling of 4-chlorobenzotrifluoride with **5b** (entry 10). This latter catalyst system also provided optimal results in transformations involving chlorinated aromatic nitrogen heterocycles (entries 4, 5, 11, and 13). However, efforts to employ 2-chlorothiophene and 3-chlorothiophene as electrophiles in these transformations were unsuccessful.

In summary, cascade intramolecular *N*-arylation/intermolecular carboamination reactions provide a concise new approach to the generation of fused tricyclic nitrogen heterocycles. The reaction sequence leads to the formation of two rings, three bonds, and one stereocenter in a chemo- and stereoselective fashion. In addition, these experiments also illustrate the utility of the generally unexplored Cy_4Dpe-Phos ligand (**15**) for Pd-catalyzed cascade reactions involving both aryl bromide and aryl chloride electrophiles.[18]

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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.

(15) (a) Veits, Y. A.; Mutsenek, E. V.; Neganova, E. G.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2001**, *37*, 1583. (b) Veits, Y. A.; Mutsenek, E. V. *Russ. J. Gen. Chem.* **2005**, *75*, 207.

(16) Small differences in enantiopurity between substrates and products are attributed to experimental error resulting from a necessary use of Mosher amide NMR analysis to assay substrate enantiopurities. The enantiopurities of products were assayed by HPLC analysis.

(17) The cascade reaction of **16** with 3-bromoanisole was most effective when X-Phos (**14**) was employed as a ligand. A complex mixture of products was obtained when Cy_4Dpe-Phos or PCy_3•HBF_4 was used as a ligand for this transformation.

(18) To date, only a single report has appeared describing the utility of Cy_4Dpe-Phos in metal-catalyzed reactions (the Pd-catalyzed *N*-arylation of 4-bromoacetophenone with five different amines). See ref 15b. In general, the reactivity of electron-rich wide bite angle phosphine ligands in catalytic transformations has rarely been examined. For additional discussion, see: Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099.