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Cascade Pd-Catalyzed Intermolecular N-Arylation/Intramolecular Alkene Carboamination Reactions for the Synthesis of Dihydroindoloindoles

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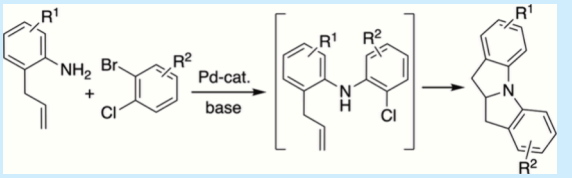
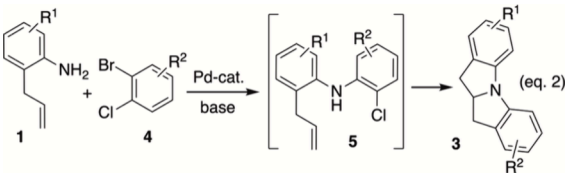
ABSTRACT: The palladium-catalyzed cross-coupling of 2-allylanilines with 1-bromo-2-chlorobenzene derivatives provides dihydroindoloindoles in moderate to good yield with up to 15:1 dr. The transformations involve initial Pd-catalyzed N-arylation to generate a substituted diphenylamine derivative, followed by intramolecular Pd-catalyzed carboamination of the alkene via an azapalladabenzocyclobutene intermediate to generate the tetracyclic products. The scope, mechanism, and stereocontrol of these reactions is described.

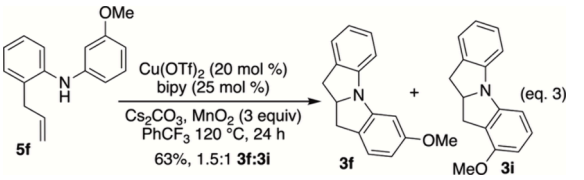


The synthesis of saturated polycyclic nitrogen heterocycles has been of longstanding interest due to the biological relevance of these compounds.[1] Cascade reactions are a potentially attractive means of generating these structures, as several different bonds and rings can be formed in a one-flask operation. For example, a cascade annulation reaction between 2-allylaniline, which contains both alkene and amine nucleophiles, and an arene bearing two adjacent electrophilic sites (**2**), could generate tetracyclic heterocycles (e.g., **3a**) with formation of three different bonds (eq 1). In practical terms,

we reasoned that a 1,2-bromochlorobenzene derivative (**4**) could be employed as the bis-electrophile,[2] and the transformation could be achieved through a Pd-catalyzed N-arylation reaction of **1**[3] followed by a subsequent Pd-catalyzed alkene carboamination reaction of intermediate **5** (eq 2).[4]



Chemler has reported a related synthesis of dihydroindoloindoles via intramolecular Cu-catalyzed alkene carboamination reactions of substrates such as **5f** (eq 3), but this approach is complementary to ours.[5] The Cu-catalyzed reactions lead to



C−H functionalization of the substrate's N-aryl group, so halogenated starting materials are not required. However, the C−H functionalization produces mixtures of regioisomers in reactions of substrates bearing *m*-substituted aryl groups (e.g., **3f** and **3i**), and requires a large excess of MnO_2.

In contrast, although halogenated substrates are required for our approach, this allows for control of product regiochemistry, and no oxidant other than the aryl halide is required. In addition to their potential synthetic utility, the Pd-catalyzed reactions would likely proceed via *syn*-migratory insertion of the alkene into a 4-membered palladium amido complex (Scheme 1, **18** to **19**), which has not previously been demonstrated.

The feasibility of the coupling of **1** with **4** was supported by our prior syntheses of tetrahydroindoloisoquinolines (e.g., **7**, eq 4) through fully intramolecular Pd/PCy_3-catalyzed alkene carboamination reactions of substrates such as **6**.[6,7] As such, in initial experiments we examined the Pd-catalyzed cross-coupling of 2-allylaniline (**1a**) with *o*-bromochlorobenzene (**4a**) using PCy_3 as the ligand for palladium. However, these

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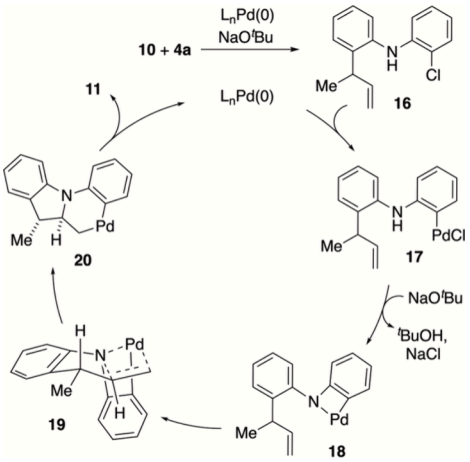
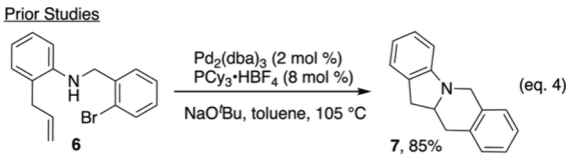
Scheme 1. Catalytic Cycle



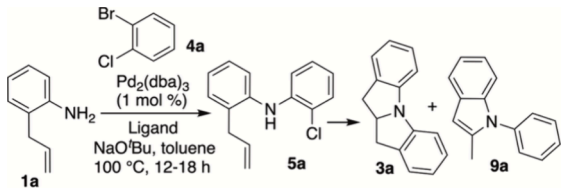


conditions produced only *N*-phenyl-2-methylindole **9b** (Table 1, entry 1), which results from β-hydride elimination prior to the reductive elimination step in the catalytic cycle (Scheme 1).[8]

We then began to explore the reactivity of dialkylbiaryl phosphine derivatives as ligands for this transformation, as they are sufficiently electron-rich to promote oxidative addition of the aryl chloride, and they also have demonstrated efficacy in alkene carboamination reactions.[3a] As shown in Table 1, the cascade reaction initially generates phenylenediamine intermediate **5a**, which can undergo the intramolecular alkene carboamination reaction to afford product **3a**. The main side product formed in these reactions is *N*-phenyl-2-methylindole **9a**.[7] Less electron-rich ligands such as Xantphos and DPE-Phos were effective for the N-arylation step, but not the subsequent alkene carboamination.[9] After some exploration we found that RuPhos provided results superior to those obtained with other ligands, and slightly improved results were obtained with a 0.1 M reaction concentration. Efforts to use 1,2-dibromobenzene or 1,2-dichlorobenzene in place of **4a** failed to produce **3a** and instead provided mixtures of **5a** and unreacted **1a**.

With optimized conditions in hand, we explored the scope of this transformation. As shown in Table 2, the reactions are

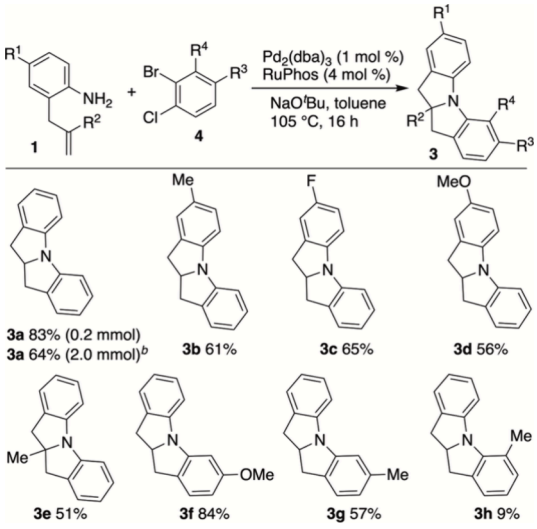
Table 1. Initial Studies[a]



entry	ligand	solvent	1a:5a:3a:9a[b]
1	$PCy_3 \cdot HBF_4$	toluene	0:0:0:0[c]
2	Brettphos	toluene	0:100:0:0
3	CyJohnphos	toluene	0:50:18:32
4	SPhos	toluene	17:52:0:31
5	XPhos	toluene	0:0:28:72
6	CPhos	toluene	0:21:58:21
7	DavePhos	toluene	0:0:72:28
8	RuPhos	toluene	0:0:77:23
9	RuPhos	toluene[d]	0:0:70:30
10	RuPhos	toluene[e]	0:0:83:17
11	RuPhos	$PhCF_3$[e]	0:0:59:41
12	RuPhos	dioxane[e]	0:0:56:44

[a]Conditions: reactions were conducted on a 0.2 mmol scale using 1.0 equiv **1a**, 1.2 equiv **4a**, 2.4 equiv NaO^tBu, 1 mol % $Pd_2(dba)_3$, 4 mol % ligand, toluene (0.2 M), 95 °C, 16 h. [b]Ratios were determined by ^1H NMR analysis of crude reaction mixtures. The number provided for **5a** includes N-arylation products that had undergone isomerization of the alkene. [c]The reaction generated 2-methylindole as the sole product. [d]The reaction was conducted with a 0.5 M concentration. [e]The reaction was conducted with a 0.1 M concentration.

Table 2. Substrate Scope[a]



[a]Conditions: reactions were conducted on a 0.2 mmol scale using 1.0 equiv **1**, 1.2 equiv **4**, 2.4 equiv NaO^tBu, 1 mol % $Pd_2(dba)_3$, 4 mol % RuPhos, toluene (0.1 M), 105 °C, 16 h. All yields are isolated yields (average of two or more experiments). [b]The reaction was conducted on a 2.0 mmol scale.

effective with several *p*-substituted N-allylanilines, producing **3a–d** in moderate to good yield. The presence of a methyl group on the internal alkene carbon was also tolerated, as **3e** was isolated in 51% yield. Importantly, the regioselective synthesis of products **3f,g**, which contain *m*-substituents, was accomplished in moderate to good yield using the appropriate commercially available bromochlorobenzene derivative. In contrast, the coupling of 2-allylaniline with 2-bromo-1-chloro-3-methylbenzene provided **3h** in only 9% isolated yield.

In order to probe stereocontrol in these transformations, substrate **10**, which contains an allylic methyl group, was synthesized and converted to **11** in 67% yield and 15:1 dr (eq 5).[10] Internal alkene substrate **12**, which was initially prepared via a literature route as a 1:1 mixture of alkene stereoisomers,[11] was converted to **13** in 43% yield and 5:1 dr (eq 6). This indicates the *Z* alkene stereoisomer is transformed to product much faster than the *E* alkene, which is converted to side products rather than a dihydroindoloindole.[12] When *Z*-**12** (>20:1 *Z*:*E*) was used in this transformation **13** was produced

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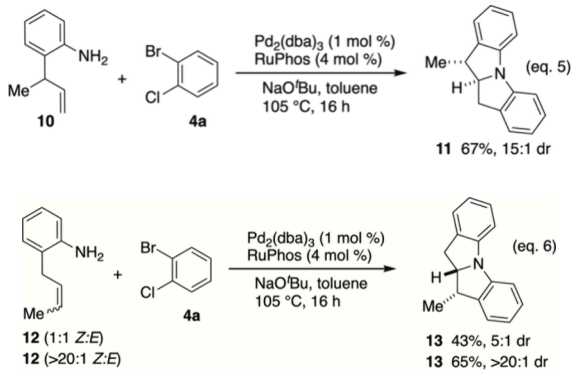
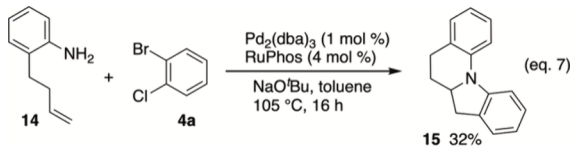
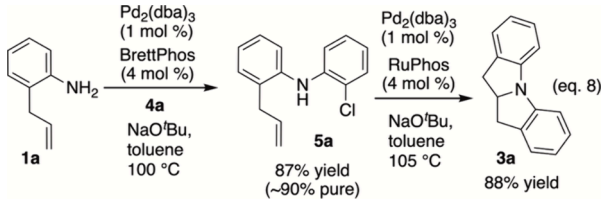


in 65% yield and >20:1 dr. This method is also modestly effective for six-membered ring formation, as the coupling of butenylaniline **14** with *o*-bromochlorobenzene provided tetrahydroindoloquinoline **15**, albeit in a modest 32% yield (eq 7).



The mechanism of these transformations appears to be similar to that of previously reported Pd-catalyzed alkene carboamination reactions. As shown in Scheme 1, an initial Pd-catalyzed *N*-arylation reaction between **10** and **4a** produces **16**. Oxidative addition of the aryl chloride **16** to Pd(0) provides **17**, which is converted to 4-membered amido complex **18** upon reaction with NaO^{t}Bu. Coordination of the alkene to Pd followed by *syn*-migratory insertion of the alkene into the Pd–N bond via transition state **19** provides **20**. Reductive elimination from **20** then affords the desired product **11** and regenerates the active Pd(0) catalyst.

In order to provide further support for this mechanism, we carried out the Pd-catalyzed *N*-arylation of 2-allylaniline **1a** with **4a** to afford **5a** in 87% yield, which contained ∼10% of the corresponding styrene resulting from partial isomerization of the alkene (eq 8). When **5a** was subjected to our standard reaction conditions, **3a** was produced in 88% isolated yield (eq 8).



In conclusion, we have described a new method for the synthesis of dihydroindoloindoles via cascade Pd-catalyzed intramolecular N-arylation/alkene carboamination reactions. These transformations affect the regioselective cross-coupling of 2-allylanilines with 1,2-bromochlorobenzenes to afford the products in moderate to good yield with synthetically useful levels of diastereoselectivity. These are the first examples of Pd-catalyzed alkene carboamination reactions that appear to proceed via 4-membered palladium amido complexes. Future work will be directed toward the preparation, characterization, and study of these and other related 4-membered amido complexes.[13]

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01747.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Author Contributions

M.R.C. and S.D. made equal contributions to this work.

Notes

The authors declare no competing financial interest.

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(9) See the Supporting Information for additional information about optimization studies.

(10) We briefly examined the use of other ligands in the transformation of **10** to determine if there would be a change in diastereoselectivity. However, use of Davephos as ligand also produced **11** in 15:1 dr as judged by ^{1}H NMR analysis, and CPhos failed to produce desired product. This is consistent with our results in other alkene difunctionalization reactions, where stereochemical outcome is controlled by substrate structure rather than ligand structure. See: Nakhla, J. S.; Wolfe, J. P. "A concise asymmetric synthesis of *cis*-2,6-disubstituted *N*-aryl piperazines via Pd-catalyzed carboamination reactions.". *Org. Lett.* **2007**, *9*, 3279.

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(12) A trace of unreacted alkene starting material was also observed in the crude reaction mixture, but assignment of the E/Z ratio of the unreacted material was not possible due to the complexity of the spectrum.

(13) The directed *ortho* C-H functionalization of N-phenyl aldimines using palladium catalysis has been described, and these transformations may involve 4-membered amino-palladcycles. However, in these cases the interaction between the neutral imine and the metal appears to be weak since the N-ligand is neutral and the four-membered ring is strained. See: Tan, X.; Jing, Y.; Wu, J.; Li, J.; Yang, Z.; Wu, W.; Ke, Z.; Jiang, H. Palladium catalyzed ortho-C(sp2)−H activation/cyclization of aryl amines assisted by imine and vinylacetic acid. *Nature Commun.* **2024**, *15*, 9877.

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