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A Practical Synthesis of Indoles via a Pd-Catalyzed C–N Ring Formation

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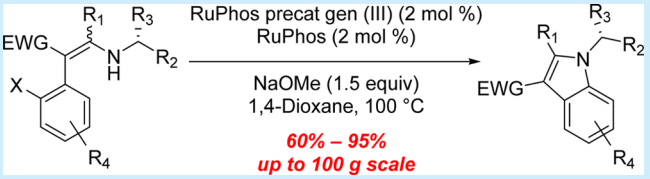
Supporting Information

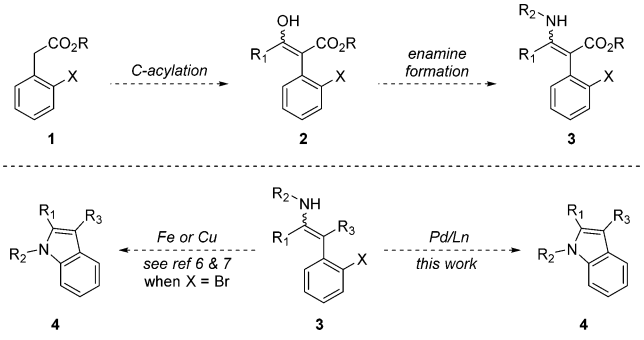
ABSTRACT: A method for the synthesis of *N*-functionalized C2-/C3-substituted indoles via Pd-catalyzed C–N bond coupling of halo-aryl enamines is described. The general strategy utilizes a variety of amines and *β*-keto esters which are elaborated into halo-aryl enamines as latent precursors to indoles. The preferred conditions comprising the RuPhos precatalyst and RuPhos in the presence of NaOMe in 1,4-dioxane tolerate a variety of substituents and are scalable for the construction of indoles in multigram quantities.



The indole nucleus is among the most ubiquitous structural motifs found in nature. Additionally, the indole architecture has consistently proven to be a valuable and privileged scaffold for drug discovery and development efforts in the pharmaceutical industry.[1] Consequently, methods devoted to the chemical synthesis of indoles have been an area of active research for over a century.[2]

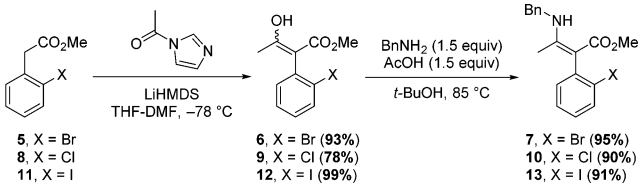
As part of our ongoing drug discovery and development programs, we were interested in the generation of C2-/C3-substituted indole scaffolds with systematic variations of the *N*-substituent.[3] While numerous classical methods for the construction of indoles have been well-established, the use of transition-metal-catalyzed reactions, in particular palladium catalysis, for the production of the indole nucleus has gained significant attention in recent years.[2a] In the context of palladium-catalyzed indole formation, the intramolecular C–N bond arylation of enamines onto pendant aryl halides was of particular interest.[4,5] We reasoned that appropriately functionalized halo-aryl enamines could serve as precursors for a Pd-mediated C–N bond arylation reaction in the production of substituted indole scaffolds (Scheme 1). Interestingly, similar C–N bond cyclizations utilizing either iron[6] or copper[7] catalysts have previously been disclosed.[8] We anticipated that the use of Pd catalysis, generally tolerant of a wide range of functionalities and applicable to complex molecules, coupled with a modular incorporation of substituted amines onto acyclic carbon frameworks, should allow for the production of C2-/C3-substituted indoles with varying *N*-substituents. Herein, we report an efficient, highly reactive, and scalable Pd-catalyzed intramolecular C–N bond formation protocol for the construction of indoles, under operationally simple conditions with fast reaction times (NaOMe, 1,4-dioxane, 100 °C).

Scheme 1. General Strategy



We initially prepared *N*-benzyl enamine **7** as a model substrate in order to screen a variety of palladium sources and commercially available ligands for the intramolecular C–N bond formation (Scheme 2). To that end, the lithium enolate of *o*-bromophenylacetic ester was subjected to a Claisen condensation reaction with acetylimidazole to provide *β*-keto

Scheme 2. Generation of Halo-aryl Enamines



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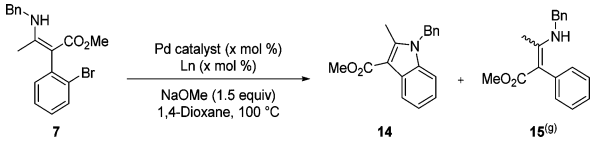
ester **6**.[9] The condensation of benzylamine with β-keto ester **6** in the presence of AcOH and *t*-BuOH (or EtOH) cleanly afforded enamine **7** as a single isomer.[10] Similarly, the aryl chloride and aryl iodide derived enamines, **10** and **13** respectively, were generated using the reaction sequences described within Scheme 2. Enamines **7**, **10**, and **13** were assigned as *Z*-isomers based on the observation of the downfield chemical shift of the N−H proton (8.50−11.50 ppm) within the respective ^{1}H NMR spectra. The large downfield chemical shift of the N−H proton can be attributed to the presence of a hydrogen bond between the N−H proton and the ester carbonyl.[11,12]

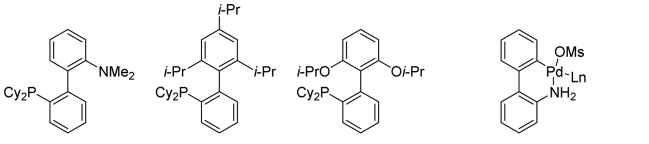
With enamine **7** in hand, we initiated our catalyst screen for the intramolecular C−N bond formation (Table 1). Buchwald's

Table 1. Catalyst Screen for Intramolecular C−N Bond Formation[a]



entry	Pd (2 mol %)	Ln (2 mol %)	(%) conversion[a]	ratio of **14:15:7**[b]
1	XPhos precat.	XPhos	72	5:1:1
2	$[t\text{-Bu}_3\text{PPdBr}]_2$[c]	–	27	5:0:14
3	$Pd_2(dba)_3$[d]	DavePhos	74	100:6:1
4	$Pd_2(dba)_3$[d]	XantPhos	16	10:1:8
5	$Pd(dppf)Cl_2$	–	62	5:1:5.5
6	$Pd_2(dba)_3$[d]	(±)-BINAP	2	33:1:3
7[e]	$Pd_2(dba)_3$[d]	$t\text{-Bu}_3\text{P}\cdot\text{HBF}_4$	100	44:1:0
8[e]	RuPhos precat.	–	100	100:1:0
9[e]	RuPhos precat.	RuPhos	100	70:1:0
10	$Pd_2(dba)_3$[d]	RuPhos	68[f]	11:1:0

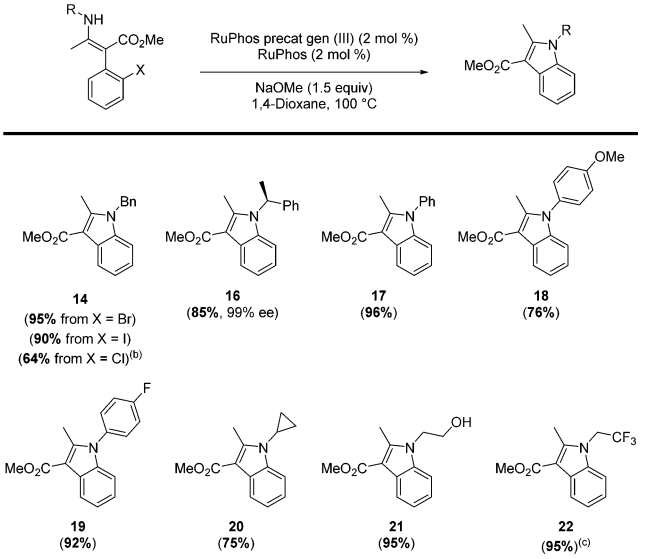
[a]Percent conversion was monitored by LCMS at 215 nm and reported as conversions (uncorrected) relative to starting enamine **7** after 1 h. [b]Relative ratios of **14**:**15**:**7** were measured by ^{1}H NMR integration of benzylic CH_2 protons after reaction was allowed to age over 24 h. [c]1 mol % of $[t\text{-Bu}_3\text{PPdBr}]_2$ was used. [d]1 mol % of $Pd_2(dba)_3$ was used. [e]Consumption of enamine **7** occurred at <2 h. [f]Percent conversion reported by LCMS at 215 nm as conversions (uncorrected) relative to starting enamine **7** after 2 h. [g]The stereochemistry of the resultant des-halo enamine **15** was not determined.



RuPhos precatalyst (Gen III), either in the absence or presence of exogenous sources of the RuPhos ligand, provided clean and complete conversions of enamine **7** to the desired indole **14** within 1 h (entries 8 and 9, respectively).[13] Similarly, a catalyst system derived from $Pd_2(dba)_3$ and $t\text{-Bu}_3\text{P}\cdot\text{HBF}_4$ (1:1 Pd/Ln mol ratio) also afforded complementary conversion to **14** within 1 h (entry 7).[14] Under either set of conditions only trace quantities of proto-dehalogenation product **15** was observed. The cyclization reaction utilizing $Pd_2(dba)_3$ and the RuPhos ligand, while productive, afforded slower conversions to **14** (entry 10). After 2 h, 68% conversion to **14** was observed (by LCMS) and complete conversion to **14** was only achieved after aging the reaction mixture overnight at 100 °C. In contrast to the complex generated in situ from $Pd_2(dba)_3$ and $t\text{-Bu}_3\text{P}\cdot\text{HBF}_4$ (see entry 7), the cyclization of enamine **7** with the commercially available $[t\text{-Bu}_3\text{P}-\text{Pd}-\text{Br}]_2$ proved markedly inferior (entry 2). Buchwald's XPhos precatalyst (Gen III) system (entry 1), $Pd_2(dba)_3$ with the DavePhos ligand (entry 3), and $Pd(dppf)Cl_2\cdot CH_2Cl_2$ (entry 5) were also far less effective catalysts for this transformation, affording only 60%−70% conversion to **14** with increasing quantities of proto-dehalogenation byproduct **15**. Other commonly utilized ligands for C−N bond couplings, such as XantPhos and (±)-BINAP, provided the lowest levels of conversion within the 1 h time frame (entries 4 and 6, respectively).[15]

Although the RuPhos precatalyst (Gen III) and the $Pd_2(dba)_3$ and $t\text{-Bu}_3\text{P}\cdot\text{HBF}_4$ combination (1:1 Pd/Ln mol ratio) were equally effective catalyst systems for the cyclization, we chose to focus on the RuPhos precatalyst (Gen III) system and examined the incorporation of various amines to yield *N*-substituted indoles under our reaction conditions (Scheme 3).[16] The cyclization of enamine **7** onto the pendant aryl

Scheme 3. Examination of Amines on the Indole Ring Formation[a]



[a]Unless otherwise noted, cyclizations were performed on aryl bromides (i.e., X = Br). Yields were recorded for isolated products after an average of two experiments. [b] The cyclization of methyl 3-(benzylamino)-2-(2-chlorophenyl)but-2-enoate was heated to 100 °C for 2 h. [c] See Supporting Information for the synthesis of corresponding enamine from trifluoroethylammonium hydrochloride.

bromide afforded the desired indole **14** in 95% yield. Additionally, aryl iodides and aryl chlorides proved to be competent substrates for the C−N bond arylation, affording the indole **14** in 90% and 64% yields, respectively. In the C−N bond formation with aryl chloride typically 85% conversion to the desired indole was observed with ∼15% of starting material remaining unreacted (as judged by LCMS analysis). Increases in the catalyst loading or quantities of base failed to advance the conversion beyond 85% (as judged by LCMS analysis). Nonetheless, aryl chloride proved to be a viable substrate under the Pd-catalyzed intramolecular C−N bond formation, in

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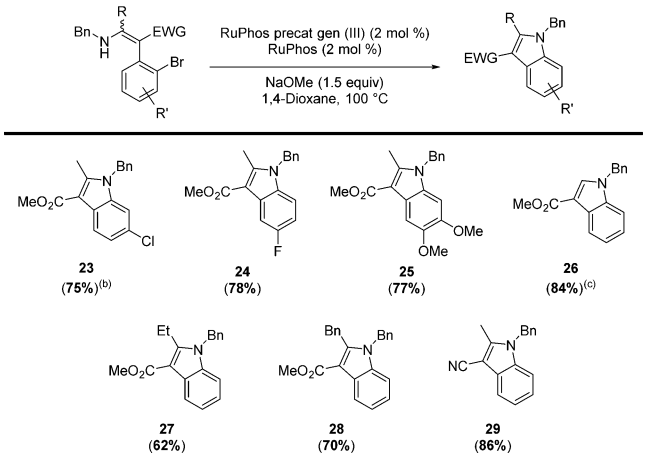
contrast to the previously reported Cu-catalyzed indole formation.

Generally, a variety of sterically encumbered or electronically deactivated amines were tolerated and incorporated into indoles (Scheme 3). Of particular interest was the use of chiral branched amines for the generation of chiral *N*-substituted indoles. Gratifyingly, (*S*)-(−)-α-methylbenzylamine was cleanly assimilated to afford indole **16** in 85% yield with no net loss of stereochemical integrity under these conditions (99% ee). *N*-Alkyl amines with attenuated reactivity were converted to *N*-alkyl indoles in generally acceptable synthetic yields (substrates 20−22).[17] Additionally, aromatic amines such as anilines were also examined for the C−N bond formation. Electron-neutral or -deficient anilines afforded indoles, **17** and **19** respectively, in >90% yields. The incorporation of electron-rich aniline, such as *p*-anisidine, provided indole **18** in lower but yet synthetically viable yields (76% yield).

The effect of varying the electronic or the steric environments for the Pd-catalyzed intramolecular C−N bond formation was subsequently investigated (Scheme 4). The

Scheme 4. Indole Formation with Various Aromatic Systems[a]



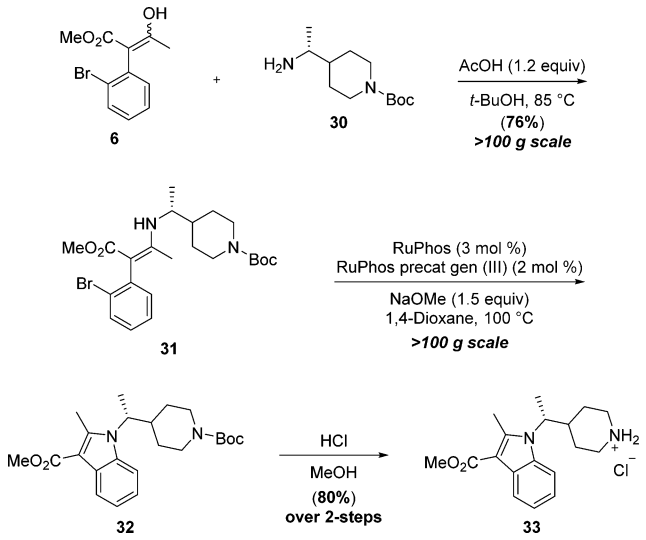
[a]Yields were recorded for isolated products after an average of two experiments. [b] Isolated as an average of 9:1 mixture of 6-chloroindole **23**: des-chloroindole **14**. [c] Reaction was only performed once on 500 mg scale, and yield was recorded after one reaction.

C−N bond cyclization of enamine substrates with orthogonally reactive aryl halides to yield halo-indoles was also examined. For example, the cyclization of an enamine substrate that contained a 2-bromo-4-chlorophenyl motif afforded the 6-chloroindole **23** in 75% yield, as an average of a 9:1 mixture of **23** to des-chloroindole **14**. The intramolecular C−N bond formation onto both electron-deficient and -rich aryl bromides provided the corresponding substituted indoles, **24** and **25** in 78% and 77% yields, respectively. These results suggest that electronic factors inherent within the aromatic ring contribute minimally during the cyclization event.

Notably, the current synthetic scheme allows for the controlled incorporation of varying substituents at the C2-position of indoles. Using the general protocol, the des-methyl 1*H*-indole 3-carboxylate ester **26** could be produced in 84% yield, comparable to previously established Cu-catalyzed protocols (see ref 7b). Further diversification of the C2-position with other alkyl groups was also achieved in synthetically useful yields (see indoles **27** and **28**). Interestingly, the inclusion of the C3-nitrile functionality was also successful. The cyclization of 3-(benzylamino)-2-(2-bromophenyl)but-2-enenitrile afforded 1-benzyl-2-methyl-1*H*-indole-3-carbonitrile (**29**) in 86% yield.

From the outset of this methodology, our goal was to develop a practical and scalable protocol for the construction of *N*-substituted indoles. Using the optimal procedure(s) outlined above, we set out to examine the feasibility of the current method for the large scale production of *N*-substituted 2-methyl-1*H*-indole-3-carboxylate; of particular interest to us was the construction of methyl (*R*)-1-(1-(1-(*tert*-butoxycarbonyl)-piperidin-4-yl)ethyl)-2-methyl-1*H*-indole-3-carboxylate (Scheme 5). To implement this vision, β-keto ester **6** was

Scheme 5. Large Scale Pd-Catalyzed C−N Bond Cyclization



condensed with chiral amine[18] **30** to yield enamine **31**. Enamine **31** was subsequently subjected to the Pd-catalyzed intramolecular C−N bond formation to cleanly afford indole **32** on greater than 100 g scales. The *N*-Boc piperidine **33** was deprotected with HCl to furnish the chiral indole piperidine hydrochloride salt **33** in 80% yield over two steps. The operationally simple approach allowed for the production of requisite indole **33** on a large scale.

In summary, we have developed a practical, robust, and scalable Pd-catalyzed intramolecular C−N bond forming strategy for the construction of *N*-functionalized C2-/C3-substituted indole scaffolds. We demonstrated that enamines derived from a broad variety of amines (alkyl, branched/chiral, or aromatic) can be assimilated into indole rings with ease. Additionally, indoles with diverse substitutions (around the aromatic ring and C2-positions) and electronic properties may also be synthesized. Notably, we have also established that the existing protocol can be used effectively in the large scale production of indoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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(3) Our initial attempts to functionalize the relatively non-nucleophilic indole N−H group via direct alkylation, thereby varying the *N*-substituent, proved to be problematic (not shown). As such, we were prompted to seek alternative synthetic strategies to achieve this goal.

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(8) While the Cu catalyzed reactions offer the advantage of inexpensive reaction conditions, the transformation is limited by the use of anhydrous bases (see ref 7c) and aryl bromides (see ref 7a−c).

(9) Other activated acids (such as anhydrides or esters) have also been utilized for the Claisen Condensation reaction. See Supporting Information for details.

(10) The use of other lower boiling solvents, such as MeOH, generally led to lower yields and conversion of the enamine. *t*-BuOH and EtOH afforded the cleanest and best yield for the enamine formation.

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(16) In our hands, addition of exogenous amounts of RuPhos ligand afforded more reproducible results for the indole formation.

(17) Our attempts to condense *tert*-butylamine or 1-adamantlyamine with *β*-keto ester **6** failed to deliver the corresponding *tert*-butyl or adamantyl enamine for Pd-catalyzed cyclization. This failure in enamine formation was attributed to considerably attenuated nucleophilicity of these amines and an increase in the steric hindrance in the substrates.

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