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Synthetic Methods

Divergent Reactivity in Palladium-Catalyzed Annulation with Diarylamines and α,β-Unsaturated Acids: Direct Access to Substituted 2-Quinolinones and Indoles

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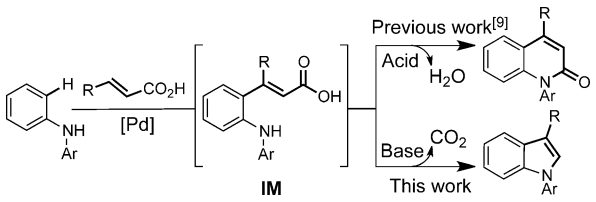
Abstract: A palladium-catalyzed C–H activation strategy has been successfully employed for exclusive synthesis of a variety of 3-substituted indoles. A [3+3] annulation for synthesizing substituted 2-quinolinones was recently developed by reaction of α,β-unsaturated carboxylic acids with diarylamines under acidic conditions. In the present work, an analogous [3+2] annulation is achieved from the same set of starting materials under basic conditions to generate 1,3-disubstituted indoles exclusively. Mechanistic studies revealed an *ortho*-palladation–π-coordination–β-migratory insertion–β-hydride elimination reaction sequence to be operative under the reaction conditions.

Indoles are a highly significant class of heterocycles with a wide range of biological activities[1] and, as such, numerous methods for their synthesis have been reported.[2] Recent developments for their access includes the use of transition metal-catalyzed heteroannulation of amines with different coupling partners using a directing group.[2i–t] Recently, 1,3-disubstitituted indoles have been of particular interest, owing to the limited reports of their synthesis and their unique biological activities.[3]

Methods for the synthesis of 3-arylated indoles involve metal-catalyzed C3 arylation using Pd catalysis.[4] To synthesize 1,3-diarylindoles, in 2015, Greaney and co-workers have reported a tandem arylation of indole with diaryliodonium salts.[5] Even so, methods for the regioselective synthesis of 3-substitituted indoles using readily accessible starting materials are still in great demand, due to their relevance in pharmaceuticals and in medicinal chemistry.[6]

Inspired by our recent successes in heteroannulation reactions via C–H activation[2i,7] and by progress in C–H activation of anilines,[8] we hypothesized an *ortho*-olefinated intermediate (**IM**; Scheme 1) as the common platform for generating indoles and 2-quinolinones. Our previous work showed that synthesis of 2-quinolinones would require a net dehydration ($-H_2O$) of **IM** (Scheme 1).[9] Subsequently, we envisioned that indole synthesis would be dependent on a decarboxylation ($-CO_2$) reaction. Successful implementation of this hypothesis for the regioselective synthesis of 1,3-diarylindole would require a C–C bond formation between α,β-unsaturated acid and diarylamine (Fujiwara–Moritani-type coupling[10]). Preliminary studies with palladium catalyst in acetic acid gave a mixture of 3-indole and 2-quinolinone in moderate yields. This particular observation further supported the presumption that a common intermediate could deliver these two heterocycles.



Scheme 1. Divergent reactivity in heterocycle synthesis.

By replacing acetic acid with a combination of trifluoroacetic acid (76 μL, 4 equiv) and methanol (2 mL) was previously found to suppress the decarboxylation and thereby allow the formation of 4-substituted-2-quinolinones exclusively.[9] In the present work, we set out to synthesize 3-substituted-*N*-arylindoles regioselectively from diarylamines and α,β-unsaturated acids. Exclusive formation of 3-substituted-*N*-arylindoles was particularly challenging because of the possibility of generating 4-substituted-2-quinolinone and 2-substituted-*N*-arylindoles. Formation of 4-substituted-2-quinolinone can be prevented by carrying out the reaction under basic conditions. However, a mixture of 2- and 3-substituted indoles was generated. Finally, use of $Pd(OAc)_2/K_2CO_3$ in methanol prevented the formation of 2-substituted indole completely.

The optimized reaction conditions with diphenylamine (**1a**, 1.0 mmol), cinnamic acid (**2a**, 0.25 mmol), palladium acetate ($Pd(OAc)_2$, 10 mol%), 1,10-phenanthroline (20 mol%), and K_2CO_3 (3 equiv) in 20:1 MeOH/H_2O (1 mL) and using $Cu(OAc)_2$ (1.0 equiv) as oxidant produced 1,3-diphenylindole **3a** exclusively in 84% yield (isolated in 80% yield).[11] Therefore, the CO_2H moiety of the α,β-unsaturated acid is acting as a traceless directing group during exclusive formation of the 1,3-diarylindole. The scope of the reaction was investigated by systematic variation of the substituents on the cinnamic acids (**3a–s**; Table 1). Substituents at *para* (**3b–i**), *meta* (**3j**, **k**), and *ortho* (**3l**, **m**) positions were incorporated successfully. Functional groups such as 4-CN, 4-CO_2Me, 4-NMe_2, 3-NO_2, and 3-CF_3 (**3g–k**) on

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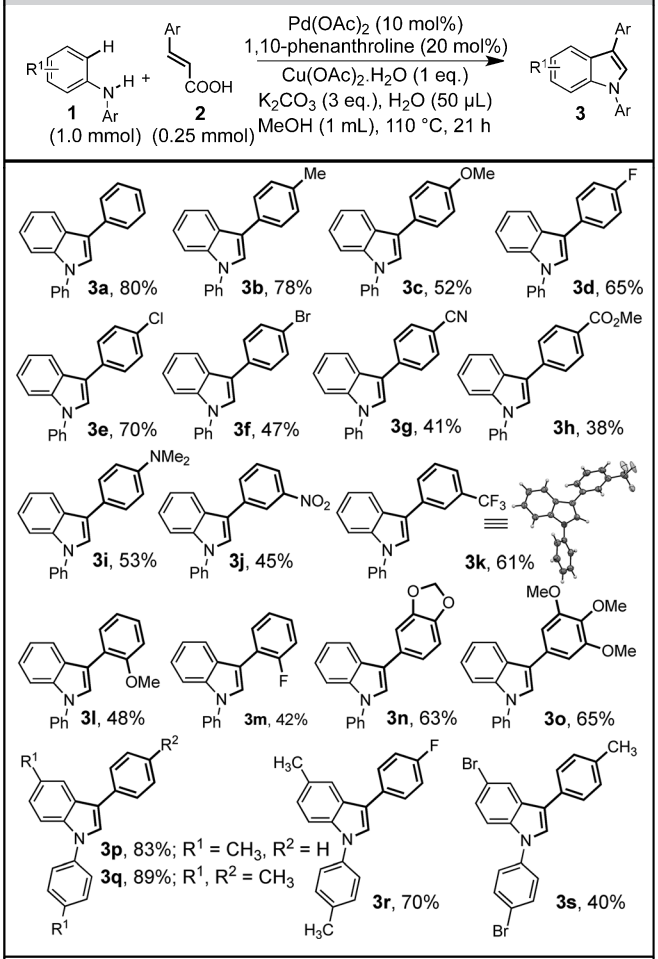
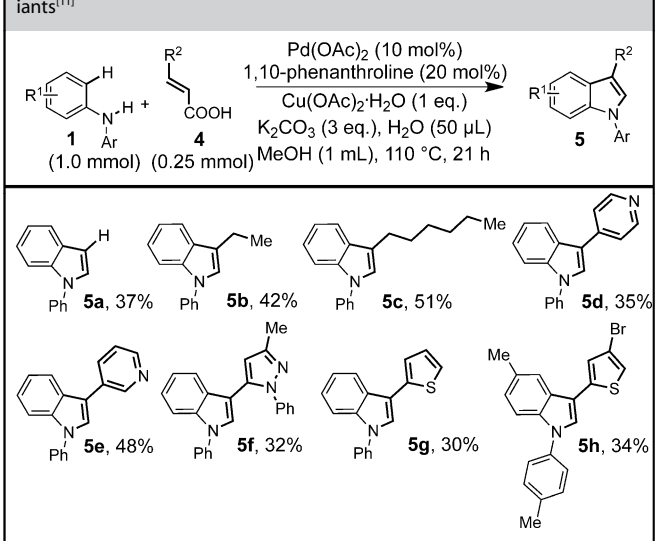
Table 1. *N*-aryl-3-substituted indoles:[a] aromatic variants.[11]



[a] Yields refer to isolated product.

Table 2. *N*-aryl-3-substituted indoles:[a] Aliphatic and heterocyclic variants[11]



[a] Yields refer to isolated product.

the arene ring were retained. Although reactions with all of the substrates were successful, electron-rich cinnamic acids gave better yields, which revealed electronic and steric dependence (e.g., **3b** vs. **3d** and **3m**). The halides F, Cl, and Br at the *ortho* or *para* position were well tolerated (**3d**–**f** and **3m**). As expected, substituted diarylamines gave 1,3-disubstituted indoles in excellent yields (**3p**–**r**).

Olefin reaction partners are often problematic in Pd-catalyzed coupling reactions, giving rise to undesired side products due to their tendency to undergo β-hydride elimination.[12] Interestingly, aliphatic acrylic acids also gave the 3-substituted indole with complete selectivity (**5a**–**c**; Table 2). Reactivity of the acrylic acids was found to increase with chain length (**5a**–**c**).

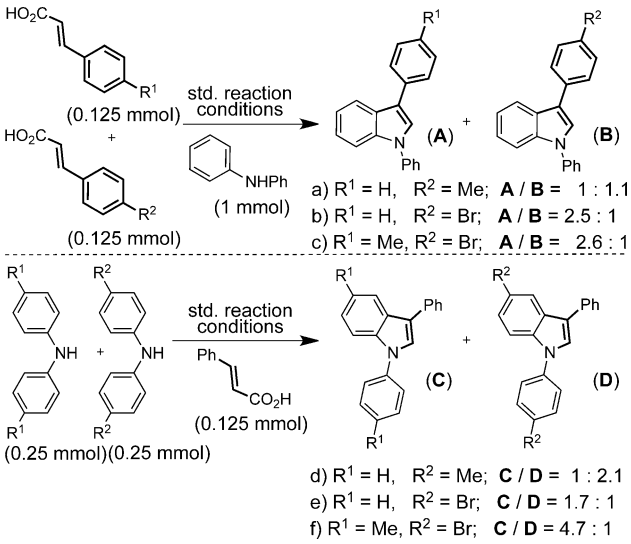
Presence of nitrogen and sulfur atoms in heterocyclic substrates may lead to the strong co-ordination of the heteroatom with metal catalysts, which can cause catalyst poisoning or C–H functionalization at an undesired position. This limits the applicability of C–H activation reactions in heterocycle-based drug discovery. Efforts were made to overcome these limitations in directed C–H functionalizations of heterocycles.[13] Notably, under the present reaction conditions, various 3-(hetero-aryl)-*N*-phenylindoles (**5d**–**h**) were successfully synthesized with complete selectivity and in synthetically useful yields (Table 2). The decrease in yields for **5d**–**h** was due to the incomplete conversion of the starting materials. Efforts to incorporate ArNHR (R = H, Me, Et, *i*Pr, Ts, Ac) in place of ArNH(Ar′), gave low yields of the desired products.

Series of competition experiments have were carried out between electronically different acrylic acids and diphenylamines to understand the reactivity and reaction mechanism of 1,3-disubstituted indole synthesis.[14] Based on these competition experiments and the results in Tables 1 and 2, we found that electron-rich acrylic acids and electron-rich diarylamines were cyclized preferentially over neutral and electron-deficient analogues (Scheme 2).

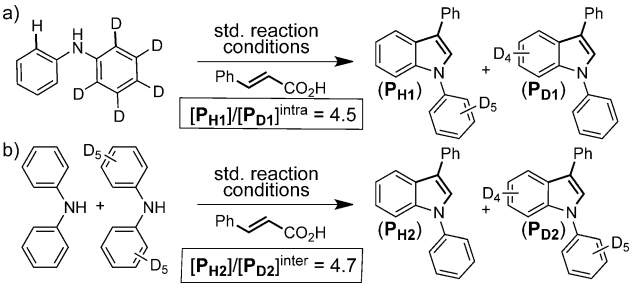
To probe the reaction mechanism, intra- and intermolecular competition experiments with deuterium-labeled diphenylamines were also carried out (Scheme 3). Cyclization on the undeuterated arene ring was observed preferentially with respect to the [D_5]aryl moiety in [D_5]diphenylamine ($[P_{H1}]/[P_{D1}] = 4.5$; Scheme 3a). Additionally, intermolecular competition between [D_{10}]- and simple (undeuterated) diphenylamine also gave the product distribution values of 4.7 ($[P_{H2}]/[P_{D2}]$, Scheme 3b).[14] These higher values indicate that C–H bond cleavage is irreversible and may be involved in the turnover-limiting step.[14]

Isolation of the intermediate **IV** (Scheme 4) was difficult due to its effective annulation in the presence of trifluoroacetic acid (TFA) to give 2-quinolinone **VIII**.[9] In the absence of TFA, *ortho*-olefinated intermediate **IV** underwent decarboxylative coupling to produce 1,3-diarylindole **V** instead of 2-quinolinone **VIII**.

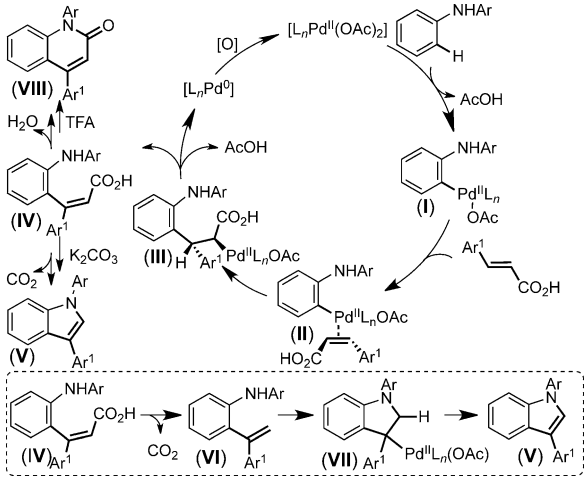
Based on these findings, *ortho*-palladation of diarylamine is proposed for the generation of intermediate **I** (Scheme 4), which is an irreversible step. Interaction of **I** with α,β-unsaturated acids will lead to species **II**. Subsequently, β-migratory in-



Scheme 2. Competition experiments.[11]



Scheme 3. Deuterium labeling studies[11]



Scheme 4. Proposed mechanism.

sertion followed by β-hydride elimination will form *ortho*-olefinated intermediate **IV**. Next, **IV** will undergo decarboxylation to give α, α'-disubstituted olefinated intermediate **VI**, which has been detected from the reaction mixture. In the presence of palladium, another catalytic cycle will be operative at **VI** to give intermediate **VII**, which can then undergo β-hydride elimination to provide indole **V**.

In summary, a palladium-catalyzed C–C and C–N bond formation between diarylamines and α,β-unsaturated acids has been discovered for the synthesis of indoles. Exclusive formation of 3-substituted indoles was achieved under basic conditions (K_2CO_3). The present method complements our recently developed strategy for 2-quinolinone synthesis.[9] The versatility and the generality of the method was demonstrated by preparing a variety of *N*-arylindoles with aromatic, aliphatic, and heterocyclic substituents. Preliminary mechanistic understanding was presented based on competition experiments and deuterium labeling studies.

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Keywords: amines · carboxylic acids · C–H activation · indoles · palladium

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[11] See the Supporting Information for a detailed description.

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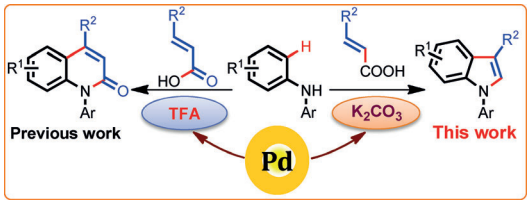

A basic diversion: A palladium-catalyzed C–H activation strategy is successfully employed for exclusive synthesis of 27 different 3-substituted indoles from α,β-unsaturated carboxylic acids and diarylamines under basic conditions in yields up to 89%. Mechanistic studies revealed an *ortho*-palladation–π-coordination–β-migratory insertion–β-hydride elimination reaction sequence.

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