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Regio- and Stereoselective Direct *N*-Alkenylation of Indoles via Pd-Catalyzed Aerobic Oxidation

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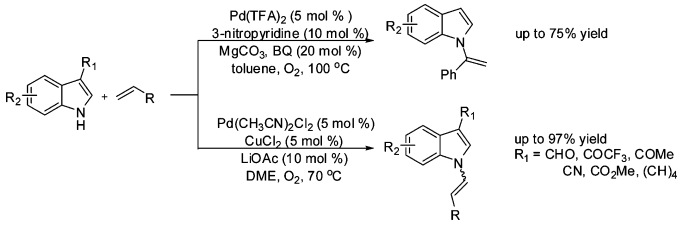
ABSTRACT



With two different sets of Pd catalyst systems in hand, indoles, whether bearing a C3-substituent or not, can be directly alkenylated on their nitrogen atoms using a sterically and electronically diverse array of alkenes, in which the high regio- and stereoselectivity are dependent on the nature of the alkenes used. This process proceeds in generally good yields and is compatible with a broad range of functional groups.

The rapid progress in the metal-catalyzed oxidative cross-coupling (e.g., C−H functionalization) has allowed chemists to consider straightforward constructions of C−C and C−X (X = heteroatoms) bonds from inexpensive and readily available substrates, opening a new door to the ideal chemical synthesis.[1] When the substrates have more than one possible reaction site, however, control of the selectivity in these transformations remains the important but challenging issue. Thus, an effective strategy to address the selective issue in the metal-catalyzed oxidative cross-coupling is a highly attractive goal for the advancement of chemical synthesis.

The prevalence of indoles in natural products and bioactive compounds has prompted the development of indole chemistry.[2] Recently, by using Pd catalysts, a number of useful methods have been developed for the selective C−H functionalization of indoles, such as C−H arylation,[3] alkenylation,[4] cyanation,[5] amination,[6] trifluoromethylation,[7] carbonylation,[8] and alkylation.[9] Although most of these reported methods employed N-substituted indoles as starting materials to achieve the direct functionalization of C−H bonds on either the C-2 or C-3 position of indoles, a few of these methods enabled free N−H indoles to undergo selective

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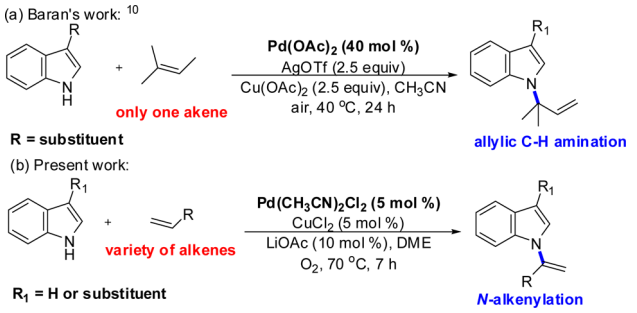
C−H functionalization.[4,8,9] In contrast to the significant advance in the C−H functionalization of indoles, only one example of the metal-catalyzed oxidative cross-coupling for the *N*-functionalization of indoles has been reported to date (Scheme 1a).[10] Recently, in the mechanistic studies on the norbornene-mediated 2-alkylation of free N−H indoles, the reaction of stoichiometric $Pd(OAc)_2$ with free N−H indole and norbornene was observed to proceed via amino-palladation of norbornene to form a palladacycle complex.[9b] Herein, we report that the *N*-alkenylation of free N−H indoles can be achieved by Pd-catalyzed oxidative cross-coupling between indoles and alkenes using readily available dioxygen as an oxidant (Scheme 1b).[11] The *N*-alkenylated indoles are ubiquitous structural motifs in numerous natural products and small molecule pharmaceuticals,[12] and versatile synthetic intermediates.[13] In fact, the conventional methods for the syntheses of *N*-alkenylated indoles, such as the addition to alkynes[14] and the cross-coupling between indoles and vinyl(pseudo)halides,[15] usually require prefunctionalized starting materials, strong bases, and inconvenient separation of a mixture of *E* and *Z* isomers, thereby adding to the cost and reducing the scope of substrates.

A series of elegant studies on the oxidative coupling of alkenes with amides[16] provided useful starting points for our investigation of the direct N-alkenylation of indoles.

Scheme 1. Pd-Catalyzed Oxidative Cross-Coupling Reactions of Indoles with Alkenes



Nevertheless, our target reaction is quite different from the oxidative coupling of alkenes with amides, in which free N−H indoles have several accessible reaction positions. To obtain a high level of regioselectivity, the catalyst system for the direct N-alkenylation of indoles must suppress the indole C−H alkenylation. In the Pd-catalyzed C−H alkenylation reactions of free N−H indoles, carboxylic acids are essential for a high level of efficiency for the following reasons: (1) carboxylic acids are helpful for generating more electrophilic Pd species by facilitating dissociation of an anionic ligand from a Pd precatalyst;[17] (2) carboxylic acids can retard the activation of N−H via formation of a hydrogen bond between the N−H moiety and carboxylic acid. Therefore, we reasoned that the direct N-alkenylation of indoles would take place in the absence of Brønsted acids.

Guided by the above hypothesis, we screened a variety of reaction parameters to optimize reaction conditions using the reaction of methyl indole-3-carboxylate (**1a**) with styrene (**2a**) as a model system (Table 1). **1a** was chosen as a representative substrate in the model reaction to preclude the complication arising from the reaction on the C3 position of indole. Three critical reaction parameters have a remarkable effect on the reaction outcomes. First, a weak base was necessary for the model reaction to occur probably because bases were required to abstract the proton from indole N−H and therefore trigger the reaction.[18] The effect of bases on the reaction was also observed to depend on the amounts of bases and their counter cations (entries 7, 8). The best result was obtained when 10 mol % LiOAc was used (entry 3). Second, when the reaction was carried out in polar solvents such as DMF, DMSO, the starting material was not completely converted; this may be due to their strong coordination to prevent palladium from interacting with indole and styrene. Although apolar toluene resulted in partial decomposition to generate a partial unidentifiable product, we were pleased to find that using weak coordinating DME as the solvent gave a satisfactory 82% yield. Finally, a catalytic amount of $CuCl_2$ (5 mol %) as a cocatalyst significantly improve the yield of the cross-coupling reaction of **1a** with

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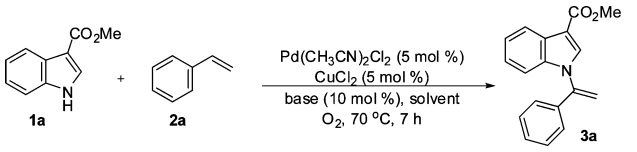
Table 1. Reaction Optimization[a]



entry	solvent	base	yield (%)[b]
1	DMF	LiOAc	30
2	DMSO	LiOAc	0
3	DME	LiOAc	89(82)[c]
4	DME	none	0
5	dioxane	LiOAc	43
6	toluene	LiOAc	40
7	DME	NaOAc	23
8	DME	KOAc	4
9[d]	DME	LiOAc	12
10[e]	DME	LiOAc	9
11[f]	DME	LiOAc	77
12[g]	DME	LiOAc	13

[a] Reaction conditions: a mixture of methyl indole-3-carboxylate (0.4 mmol), styrene (3 equiv), $Pd(CH_3CN)_2Cl_2$ (5 mol %), $CuCl_2$ (5 mol %), and base (10 mol %) in solvent (2 mL) at 70 °C for 7 h under 1 atm of O_2. [b] Yield determined with GC by using dodecane as an internal standard. [c] Yield of isolated product. [d] In the absence of $CuCl_2$. [e] Benzoquinone (1.0 equiv) was used instead of $CuCl_2$. [f] $Cu(OAc)_2$ (5 mol %) was used instead of $CuCl_2$. [g] Under N_2.

2a (entry 3 vs 9). A control experiment showed that the cross-coupling failed completely when the reaction was carried out in the absence of a Pd catalyst.

Under the optimized reaction conditions, a sterically and electronically diverse array of alkenes (Scheme 2) could be used for the direct N-alkenylation of indoles. Styrenes bearing a variety of substituents, as well as 2-vinylnaphthalene, were observed to afford exclusively 1,1-disubstituted products (Markovnikov-type adducts) in good-to-excellent yields (**3a**−**3i**). The regioselectivity was also observed in the reaction of indole with unactivated vinyl cyclohexane (**3j**). We reasoned that the regioselectivity for Markovnikov-type adducts could result from the stability of the partial positive charge on the benzylic carbon that was produced in the aminopalladation of the double bond. Cyclic alkenes were suitable substrates in this reaction to afford the regular product as well as olefin isomerizations (**3k** and **3l**). Interestingly, allylic ethers afforded *Z*-configuration products (anti-Markovnikov-type adducts) with exclusive selectivity (**3o**−**3t**). However, when moving oxo-functionality away from the allylic position in ethers, the selectivity for *Z*-configuration products decreased rapidly (**3u**). A proposal was made to rationalize the high selectivity in the reactions of allylic ethers (Scheme 3). The oxygen atom of the allylic ether coordinates to Pd center and undergoes cis-aminopalladation[19] to form the C−N bond on the terminal position of the alkene and then β-H

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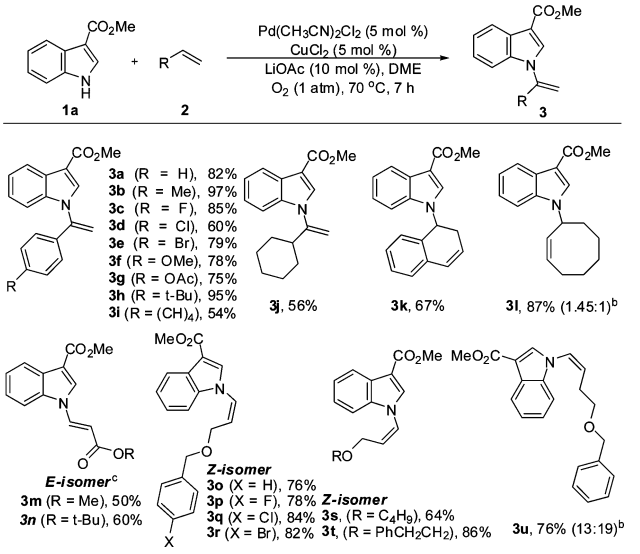
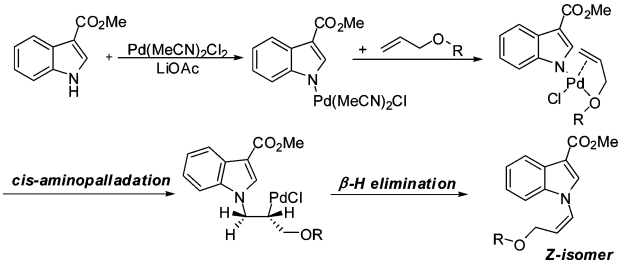
Scheme 2. Scope of Alkenes in the Direct N-Alkenylation of Indole[a]



[a] Reaction conditions: a mixture of methyl indole-3-carboxylate (0.4 mmol), alkenes (3 equiv), $Pd(CH_3CN)_2Cl_2$ (5 mol %), $CuCl_2$ (5 mol %), and LiOAc (10 mol %) in DME (2 mL) at 70 °C for 7 h under 1 atm of O_2; isolated yields. [b] The ratio of isomers was determined by ^1H NMR spectroscopy; ratio in parentheses is isomer shown/all other observed isomers. [c] Reaction conditions: a mixture of methyl indole-3-carboxylate (0.4 mmol), methyl acrylate (3 equiv), Pd(TFA)2 (5 mol %), $Cu(OAc)_2$ (5 mol %), in toluene (2 mL) at 100 °C for 24 h under 1 atm of O_2; isolated yields.

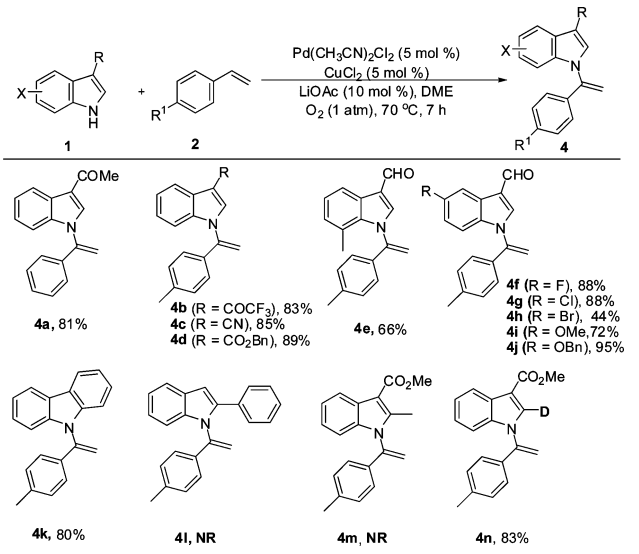
Scheme 3. Possible Reaction Pathway for the *N*-Alkenylation of Indole with Allylic Ether



elimination to generate the stereoselective *Z*-configuration product. In the case of electron-deficient methyl acrylate, the standard conditions did not work well. However, by using $Pd(TFA)_2$ (5 mol %)/$Cu(OAc)_2$ (5 mol %) as a combination catalyst and toluene as the solvent, the reaction of electron-deficient acylates occurred in the absence of base to form *E*-configuration products (**3m** and **3n**), presumably because alkenes are able to bind to the Pd center for activation under the modified reaction conditions.

The substituent effects of 3-substitued indoles on the reaction were also examined using 4-methylstyrene as a coupling partner (Scheme 4). Similar to the methyl carboxylate group, a variety of electron-withdrawing substituents on the 3-position of indoles, such as formyl (**4e**−**4j**), acyl (**4a**, **4b**), and cyano (**4c**) groups, provided good yields. An array of substituents on the benzene ring of indoles, such as

Scheme 4. Scope of 3-Substituted Indoles in the Direct N-Alkenylation of Indole[a]



[a] Reaction conditions: indole (0.4 mmol), styrene (3 equiv), Pd-$(CH_3CN)_2Cl_2$ (5 mol %), CuCl2 (5 mol %), and LiOAc (10 mol %) in DME (2 mL) at 70 °C for 7 h under O_2; isolated yields.

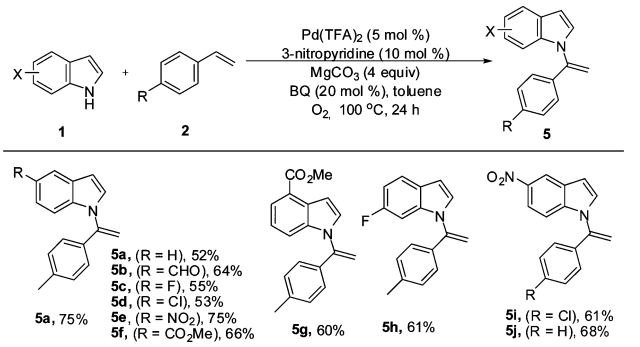
methyl (**4e**), fluoride (**4f**), chloride (**4g**), bromide (**4h**), and methoxyl (**4i**, **4j**), were observed to have little influence on the reactivity and selectivity of the N-alkenylation. Carbazoles, which could undergo Pd-catalyzed oxidative cross-coupling with alkenes in the presence of a Ag salt as an oxidant,[16l] proved to be suitable substrates under our standard conditions (**4k**). When the introduction of a methyl group occupied the C-2 position, no expected product was detected (**4m**). However, when deuterium was put into the C-2 position, ssswe obtained the deuterium fully incorporated product (**4n**). To investigate whether N-alkenylation of functionalized pyrroles could occur, pyrrole-2-carboxaldehyde, pyrrole-2-trifluoroacetyl, methyl pyrrole-2-carboxylate, and pyrrole-2-carbontrile were subjected to the optimized reaction conditions, but this results in only slight decomposition of the starting material without the desired products.

When expanding the substrate scope to indoles lacking a 3-substituent, we found that the standard reaction conditions did not afford the desired N-alkenylation products, instead leading to decomposition of these indoles. Considering that the reaction conditions established above for electron-deficient methyl acrylate avoided competition for binding to the Pd center between methyl acrylate and other components by using noncoordinating toluene and removing the base from the reaction system, we reasoned that these indoles had a stronger ability to coordinate to Pd than the indole bearing electron-withdrawing groups on C3, impeding coordination of alkenes to the Pd center.

(20) When the **5a** product under the standard conditions was stirred for 24 h at 100 °C, the product decomposition was 32%.

(21) BQ is a well-known oxidant and electron carrier in the Pd-catalyzed oxidation reactions; for selective examples: (a) Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506. (b) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.

Scheme 5. Scope of Simple Indoles[a]



[a] Reaction conditions: a mixture of indole (0.4 mmol), styrene (5 equiv), $Pd(TFA)_2$ (5 mol %), 3-nitropyridine (10 mol %), BQ (20 mol %), and $MgCO_3$ (4.0 equiv) in toluene (2 mL) was stirred under 1 atm of O_2 at 100 °C for 24 h; isolated yields.

Gratifyingly, the *N*-alkenylation of unsubstituted free N−H indole could be achieved in 52% yield (Scheme 5, **5a**) along with oxidative decomposition of some of the product,[20] when the reaction of indole with 5 equiv of 4-methylstyrene was conducted in toluene (2 mL) at 100 °C under 1 atm of O_2 using $Pd(TFA)_2$ (5 mol %)/3-nitropyridine (10 mol %)[3a]/1,4-benzoquinone (20 mol %)[21] as a catalyst system and insoluble $MgCO_3$ as a base. As shown in Scheme 5, a variety of indoles lacking the 3-substituent could undergo the N-alkenylation with good selectivity in reasonable yields. Some functional substituents such as F, Cl, CHO, NO_2, and CO_2Me were compatible under current conditions. Unfortunately, the presence of the electron-donating 5-OMe group reduced the yield (< 20%), suggesting that the 5-OMe group made the parental pyrrole moiety more nucleophilic and therefore impeded the interaction of palladium with styrene. It is noteworthy that the alkenylation occurred exclusively at the N-position of the indoles without any side product from C2, or C3-alkenylation of indole.

In conclusion, two different sets of protocols have been developed for the direct N-alkenylations of indoles bearing or lacking 3-substituents with alkenes. These two protocols complement each other to cover a broad range of substrate scope for both of the coupling partners, and allow this aerobic oxidative cross-coupling to proceed with excellent selectivity in generally good yields. The ongoing work is to investigate the origins of regioselectivity of indoles and alkene-dependent stereoselectivity in this oxidative cross-coupling reaction.

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Supporting Information Available. Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.