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Selective C3–C3 Oxidative Cross-Coupling between Unactivated Anilines and Indoles

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Abstract: A selective C3–C3 oxidative cross-coupling between unactivated anilines and indoles catalyzed by copper bromide together with iodobenzene diacetate as the oxidant is described. This methodology provides a novel approach to biaryl synthesis.

Keywords: aromatic substitution; biaryls; C–C coupling; oxidation; regioselectivity

As the important polyaryl compounds, arylindoles appear as basic skeltons in a wide range of biochemical, biological and medicinal compounds.[1] The regioselective formation of aryl-aryl bonds between aryl moieties and indoles has received considerable attention over the past decades.[2] From atom- and step-economic points of view, the direct oxidative cross-coupling reactions between two different C–H bonds of aromatic molecules without recourse to extra chemical activation are quite attractive processes in the synthesis of polyaryl compounds.[3] The purpose of this communication is to document the selective *C3–C3* oxidative cross-coupling between unactivated anilines and indoles catalyzed by copper bromide together with iodobenzene diacetate as the oxidant.

Recently, because of the economic attractiveness and the potential in industrial applications, copper catalysis has attracted significant interest in organic synthesis.[4] Since the pioneering studies by Yu's group[5] and others, copper salts or complexes have proved to be effective in various C–H activation reactions.[6,7] To realize the transition metal-catalyzed regioselective C–H functionalization, a nitrogen- or oxygen-containing functional group is normally required to act as the directing group. In most of cases, the new carbon-carbon or carbon-heteroatom bond is selectively formed at the *ortho* position. Interestingly, when we investigated the oxidative cross-coupling between unfunctionalized aniline derivatives and indoles, we isolated a C3–C3 cross-coupling product **2a** (Figure 1)[8] from the reaction of *N*-Ts protected *p*-toluidine **1a** and free indole with $Cu(OAc)_2$ as the catalyst and $PhI(OAc)_2$ as the oxidant in PivOH, albeit only in 2% yield [Eq. (1)].

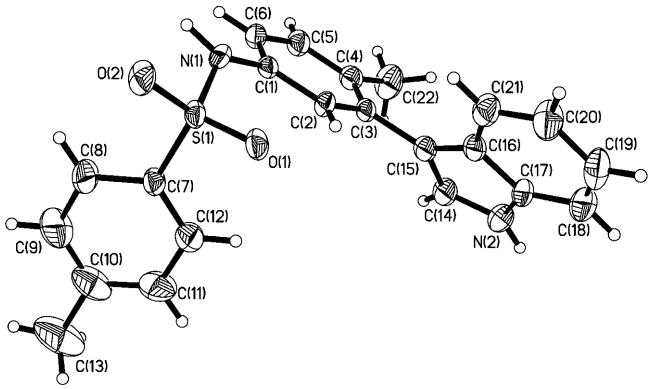
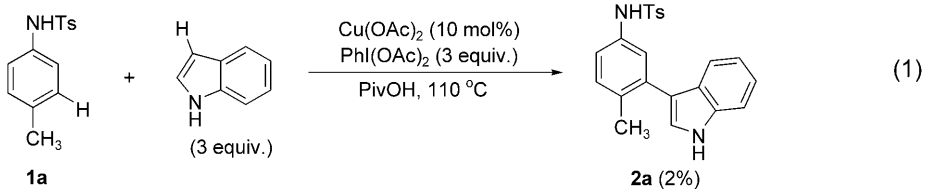
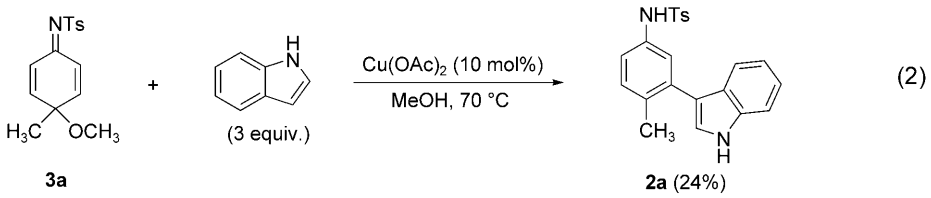


Figure 1. X-ray diffraction structure of **2a**.

The screening of solvents revealed that the coupling product was only formed in alcohols, and methanol was the best choice. While the reaction in methanol afforded product **2a** in 7% yield, one of the by-products was identified as *N*-Ts-4-methoxy-4-methylcyclohexa-2,5-dienimine **3a**. When compound **3a** was treated with indole and $Cu(OAc)_2$, the generation of product **2a** was observed [Eq. (2)]. Moreover, the control experiments indicated that compound **3a** could be



(1)

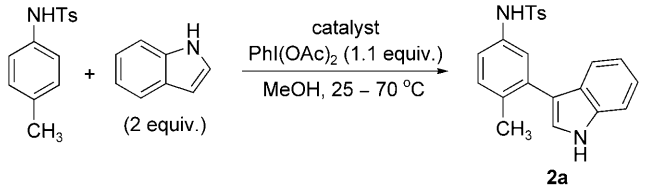


generated from the reaction of substrate **1a** with $PhI(OAc)_2$ in MeOH in the absence of $Cu(OAc)_2$ and indole.

Since indole also showed a reactivity towards $PhI(OAc)_2$, the coupling reaction was then carried out in a stepwise way. Before indole and catalyst were added, substrate was premixed with $PhI(OAc)_2$ in MeOH at 25 °C for 15 min. To improve the yields, various ratios of *p*-toluidine and indole as well as iodobenzene diacetate were examined. The best yield was obtained when the ratio of *p*-toluidine/indole/iodobenzene diacetate was 1:2:1.1. Various copper salts were examined as the catalysts for the coupling reaction (Table 1). $Cu(OTf)_2$, $CuCl_2$ and $CuBr_2$ proved to be the best catalysts. $Cu(OAc)_2$, CuCl, and CuI showed lower catalytic activities. While no reaction was observed in the absence of copper catalyst, 5 mol% $CuBr_2$ was sufficient to achieve 87% conversion after 1 h.

These conditions are compatible with a range of substrates as shown in Scheme 1. The desired cross-coupling products were obtained in good to excellent yields with excellent C3–C3 selectivities. The reaction was found to tolerate a variety of different groups with different electronic demands on the indole rings, both electron-donating and electron-withdrawing groups. Only a trace amount of product was detected from the reaction of *N*-acetylindole. An electron-withdrawing protecting group on the nitrogen atom of *p*-toluidine was essential to the coupling reaction. While *N*-Ts-, *N*-Ms-, N-Bz-, or *N*-Ac-*p*-toluidine was a suitable substrate, the reaction of *N*-Bn-*p*-toluidine was complicated and did not afford any coupling product. Additionally, the C-4 substitution of *N*-tosylaniline had a strong influence on the coupling reaction. *N*-Ts-4-(trifluoromethyl)benzenamine showed no reactivity toward $PhI(OAc)_2$. When *N*-tosylaniline was employed, no corresponding coupling product **2w** was detected. The ^1H NMR of the crude reaction mixture indicated the formation of *p*-quinone monosulfonimide.[9] Moreover, reactions of 4-methoxy-, 4-chloro-, and 4-bromo-substituted *N*-tosylaniline derivatives also only afforded *p*-quinone monosulfonimides as the product. 4-Butyl- and 4-phenyl-*N*-tosylaniline derivatives were found to be effective partners and the desired products **2q–2t** were isolated in moderate to good yields. When the *ortho*- and *para*-positions of the *N*-tosylaniline were blocked with methyl groups, the cross-coupling reaction still occurred and gave rise to the product **2u** in 50% yield.

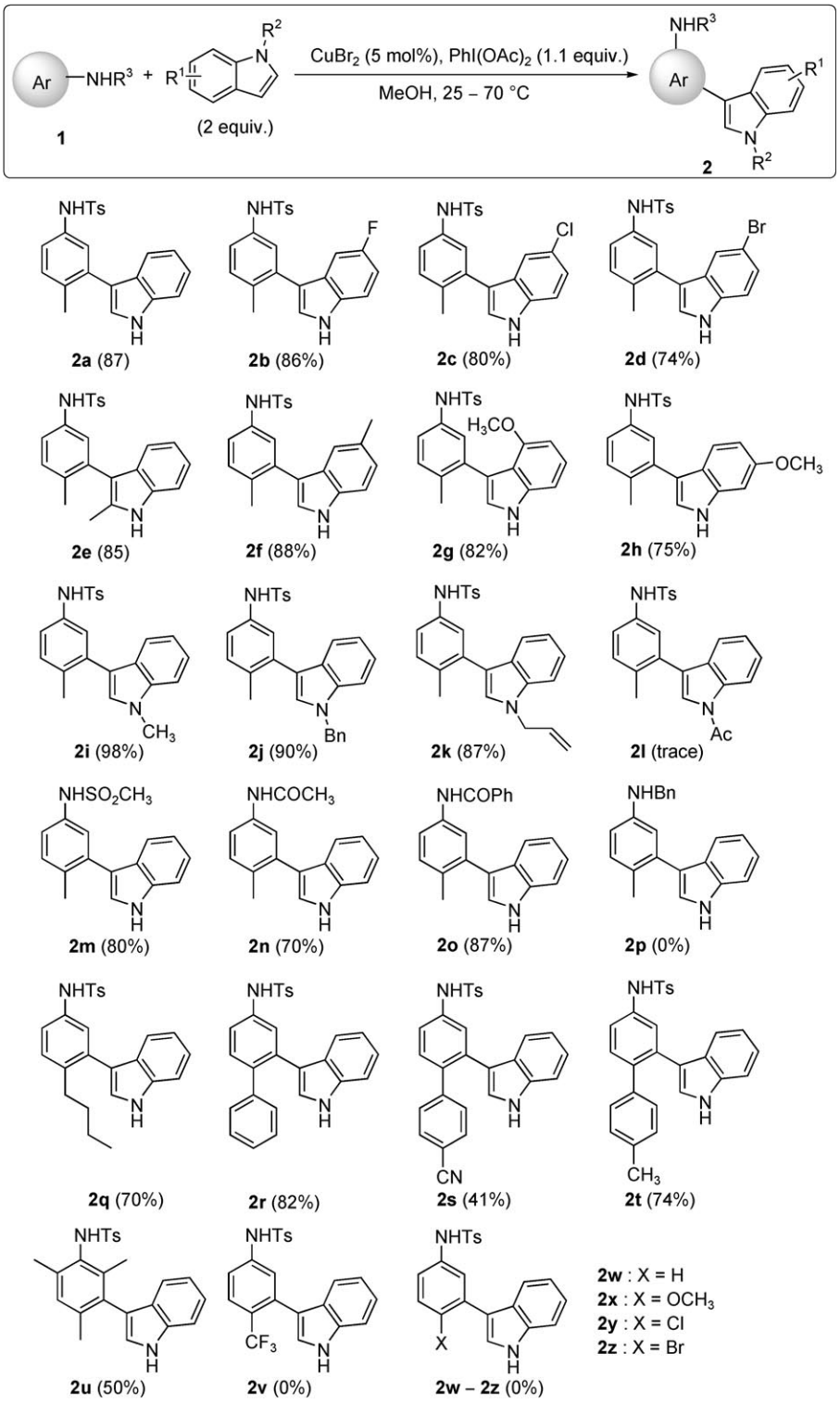
Table 1. Selection of the copper catalyst.



Entry	Catalyst	Yield [%][a]
1	$Cu(OAc)_2$ (10 mol%)	13
2	$Cu(OTf)_2$ (10 mol%)	90
3	$CuCl_2$ (10 mol%)	87
4	CuCl (10 mol%)	68
5	$CuBr_2$ (10 mol%)	89
6	CuI (10 mol%)	20
7	$CuBr_2$ (5 mol%)	87
8	$CuBr_2$ (1 mol%)	33
9	no	0

[a] Isolated yield based on **1a**.

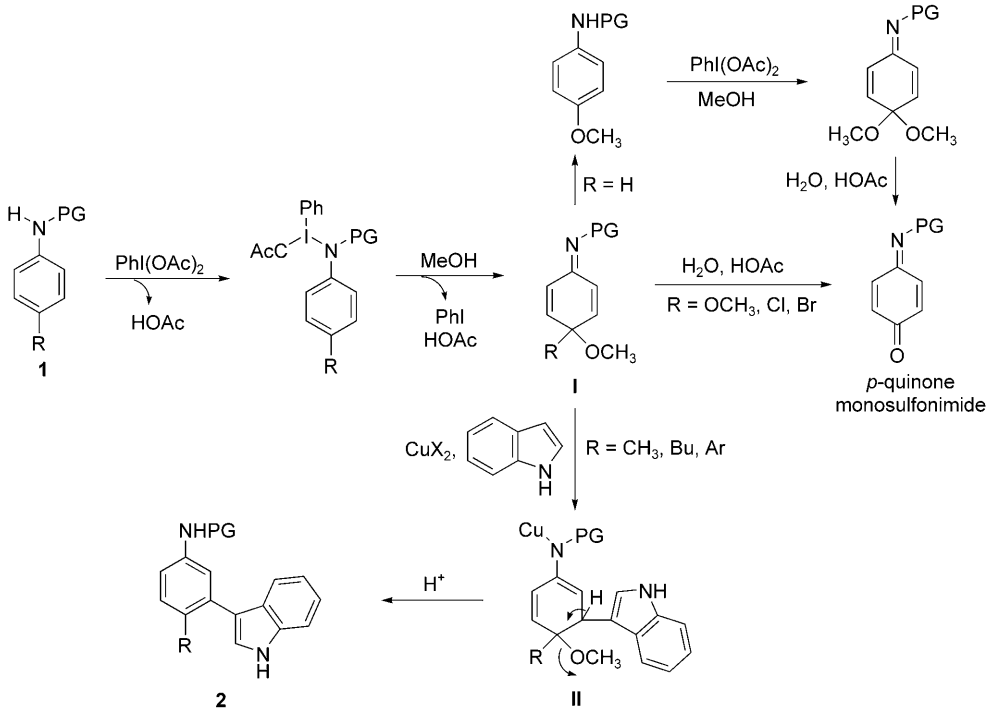
Compared with the normal *ortho*/*para* substitution, a *meta*-selective functionalization of aromatic molecular remains a big challenge and an elusive problem.[10] Gaunt and co-workers have developed an efficient copper-catalyzed *meta*-selective C–H bond arylation of anilide with Ph_2IOTf.[11] A *meta*-C–H bond cupration was proposed to be the key step. However, our experimental results indicated that the obtained C3–C3 coupling product **2** might not be formed *via* a similar metal-catalyzed cross-coupling pathway. Although, so far, we cannot be certain of the precise mechanism of this selective C3–C3 cross-coupling, the first step of the reaction is most likely the oxidative dearomatization of the aniline derivative by iodobenzene diacetate to form the intermediate **I** (Scheme 2). When the C-4 substitution is a strong electron-withdrawing group (CF_3), the substrate is electron-poor and does not show reactivity toward the oxidant. When the C-4 substitution is methoxy, chloro, or bromo, the corresponding intermediate is sensitive to the generated AcOH. In the presence of a trace of water in the solvent, these intermediates hydrolyze to form the unreactive *p*-quinone monosulfonimide. In the case of *N*-tosylaniline, the formed intermediate will undergo an aromatization to form 4-methoxy-*N*-tosylaniline followed by a further oxidation to yield



Scheme 1. Reactions of indoles with anilines.

the *p*-quinone monosulfonimide. When the C-4 substitution is an alkyl or an aryl group, the intermediate **I** is stable and reactive to the copper-catalyzed addition with indoles. After an acid-catalyzed rearomatization of the resultant intermediate **II**, the selective C3−C3 cross-coupling product of aniline with indole is formed.

In conclusion, we have developed a selective C3−C3 oxidative cross-coupling between unactivated anilines and indoles catalyzed by copper bromide togeth-



Scheme 2. Tentative mechanism for the oxidative coupling of anilines and indoles.

er with iodobenzene diacetate as the oxidant. This methodology provides a novel approach to biaryl synthesis. Besides optimization for a 'greener' procedure, currently studies are underway to extend its scope, to explore its reaction mechanism and to disclose possible synthetic applications.

Experimental Section

Typical Experimental Procedure

$PhI(OAc)_2$ (177 mg, 0.55 mmol) was added into the solution of *N*-Ts-*p*-toluidine (131 mg, 0.5 mmol) in MeOH (2 mL) at 25 °C. After 15 min, the reaction mixture was treated with indole (117 mg, 1 mmol) and $CuBr_2$ (6 mg, 0.025 mmol), and then was allowed to warm up to 70 °C. Upon completion by TLC, the reaction was quenched with saturated $NaHCO_3$, and extracted by ethyl acetate (100 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to give the product **2a** as a white solid; yield: 164 mg (87%); mp 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.45$ (s, 1H), 7.64 (d, $J = 7.8$ Hz, 2H), 7.29 (d, $J = 7.8$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 1H), 7.08–7.15 (m, 4H), 7.01–7.03 (m, 3H), 6.91 (s, 1H), 2.25 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.0$, 136.0, 135.8, 134.2, 134.0, 131.4, 129.8, 127.5, 126.9, 124.5, 123.6, 122.2, 120.7, 120.0, 119.7, 116.0, 111.7, 21.6, 20.4; IR (KBr): $\nu = 3412$, 3262, 2923, 1608, 1492, 1457 cm^{-1}; HR-MS: $m/z = 399.1140$, calcd. for $C_{22}H_{20}N_2NaO_2S$ ($[M+Na]^+$): 399.1143.

Acknowledgements

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[8] CCDC 786145 contains the supplementary crystallographic data of compound **2a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336033.

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