# *meta*-Selective Substitution of Phenols with Indoles via One-Pot Oxidative Dearomatization–Michael Addition–Aromatization

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Dedicated to Professors Xiyan Lu and Lixin Dai

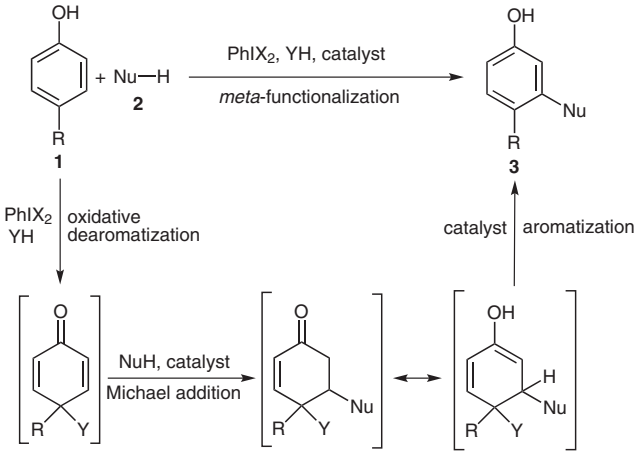
**Abstract:** An oxidative coupling strategy involving hypervalent organoiodine-induced oxidative dearomatization of 4-substituted phenols, Brønsted acid catalyzed Michael addition with indoles, and aromatization has been developed. The one-pot reaction provides an efficient access to the *meta*-indole-substituted phenol derivatives.

**Key words:** aromatic substitution, biaryls, cross-coupling reaction, oxidation, regioselectivity

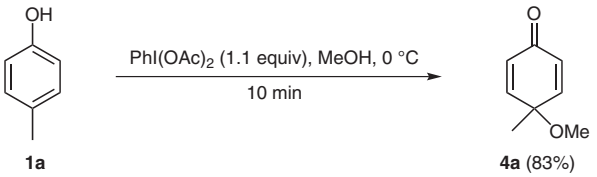
Selective substitution on the aryl-ring carbons is the most commonly used procedure for the preparation of functionalized aromatic organic compounds.[1] As the electron-rich aromatic systems, phenols and phenol ethers are high reactive toward electrophilic aromatic substitutions, and the electron-donating hydroxy and alkoxy groups direct the electrophilic substitutions to the *ortho*/*para* positions. Compared with the normal *ortho*/*para* selectivity, the *meta*-selective functionalization of phenols or phenol derivatives remains a challenge and an elusive problem.[2]

Hypervalent organoiodine-induced phenolic oxidation leads to a variety of synthetically useful compounds.[3] Except the formation of various benzoquinones from hydroquinones, the oxidation of the 4-substituted phenols in the presence of an appropriate internal or external nucleophile gives rise to the corresponding cyclohexadienones.[4] As the important intermediates, the resulting cyclohexadienones have found widespread use in the synthesis of natural and unnatural biologically active compounds.[5] Our planned strategy, based on a formal *meta*-functionalization of 4-substituted phenols, involves the in situ oxidative dearomatization of 4-substituted phenols, the Michael addition of the generated electrophilic cyclohexadienones, and the aromatization of the resulting Michael adducts (Scheme 1).

Because of the importance of arylindoles,[6] indoles were chosen as the coupling partners. To begin our study, we chose *p*-cresol and indole as the standard substrates to search for the suitable reaction conditions and the potential catalysts. To implement this oxidative coupling strategy, the first key point was the species of the first nucleophilic reagent (YH). It should be high reactive toward the oxidative dearomatization of the 4-substituted phenols and less reactive to the Michael addition of the generated cyclohexadienones. Additionally, the Y group should be a good leaving group to promote the following aromatization of the resulting Michael adducts. We examined the oxidation of *p*-cresol in the presence of various nucleophiles with (diacetoxyiodo)benzene as the oxidant. After the optimization of reaction conditions, the methoxylation of *p*-cresol with 1.1 equivalents of $PhI(OAc)_2$ in methanol gave the best result (Equation 1).[7]




**Scheme 1** *meta*-Functionalization of 4-substituted phenols




**Equation 1**

Although the obtained 4-methoxy-4-methylcyclohexa-2,5-dienone (**4a**) was stable, to simplify the procedure, one-pot oxidative coupling reaction was investigated. *p*-Cresol was treated with 1.1 equivalents of $PhI(OAc)_2$ in MeOH at 0 °C. After 10 minutes, indole and catalyst were added. A variety of Lewis acids and Brønsted acids were examined as catalysts. While no coupling reaction was

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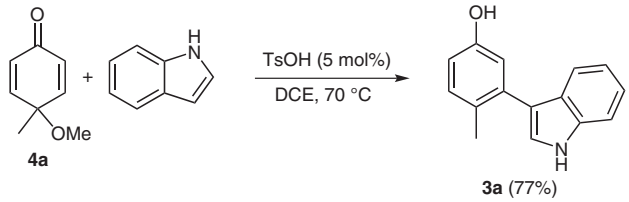
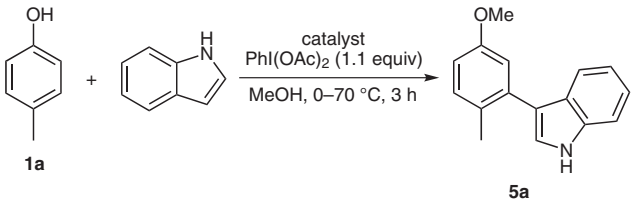
observed in the absence of an acid catalyst, several Brønsted acids proved to be effective in the coupling reaction (Table 1). 4-Methylbenzenesulfonic acid (TsOH) was the best catalyst, and 5 mol% TsOH were sufficient to achieve 75% conversion. Interestingly, the isolated product was not the expected 3-(1*H*-indol-3-yl)-4-methylphenol (**3a**), but 3-(5-methoxy-2-methylphenyl)-1*H*-indole (**5a**). As a control experiment the isolated 4-methoxy-4-methylcyclohexa-2,5-dienone (**4a**) was treated with indole and TsOH in DCE under the same conditions. The reaction gave rise to 3-(1*H*-indol-3-yl)-4-methylphenol (**3a**) as the major product in 77% yield (Equation 2).




**Equation 2**

A hypothesized pathway for the formation of 3-(5-methoxy-2-methylphenyl)-1*H*-indole (**5a**) is proposed as shown in Scheme 2. The oxidative dearomatization of *p*-cresol with iodobenzene diacetate in the presence of methanol generates 4-methoxy-4-methylcyclohexa-2,5-dienone (**4a**), which is ready to undergo a Brønsted acid catalyzed Michael addition with indole to form an intermediate **I**. Because the reaction is carried out in methanol, the intermediate **I** is first attacked by methanol to form intermediate **II** before the aromatization takes place to afford 3-(1*H*-indol-3-yl)-4-methylphenol (**3a**). After a Brønsted acid catalyzed aromatization of the resulting intermediate, 3-(5-methoxy-2-methylphenyl)-1*H*-indole (**5a**) is yielded as the final product.

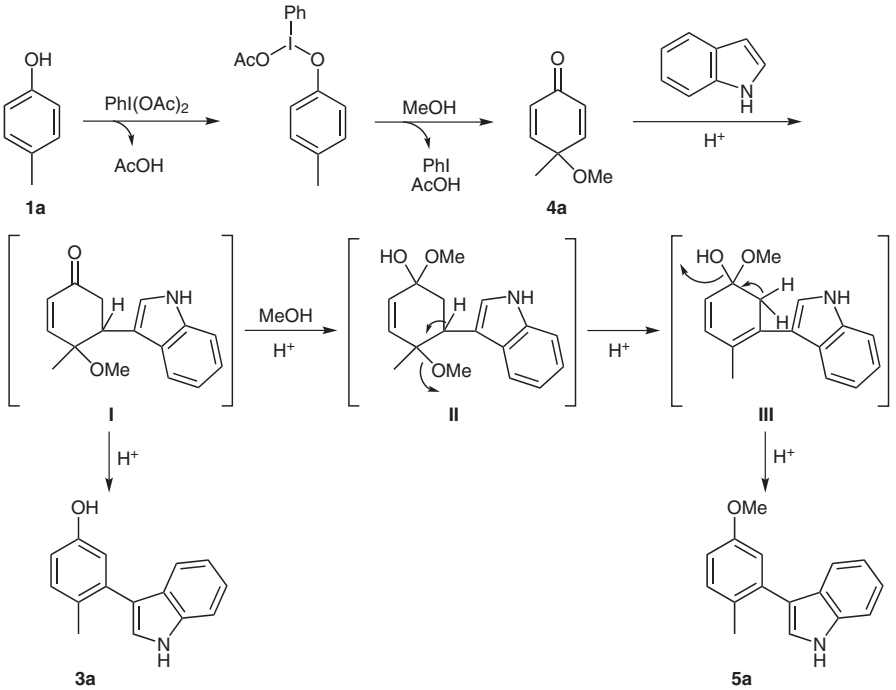
**Table 1** Conditions Screening for the Oxidative Coupling Reaction of *p*-Cresol (**1a**) with Indole[a]



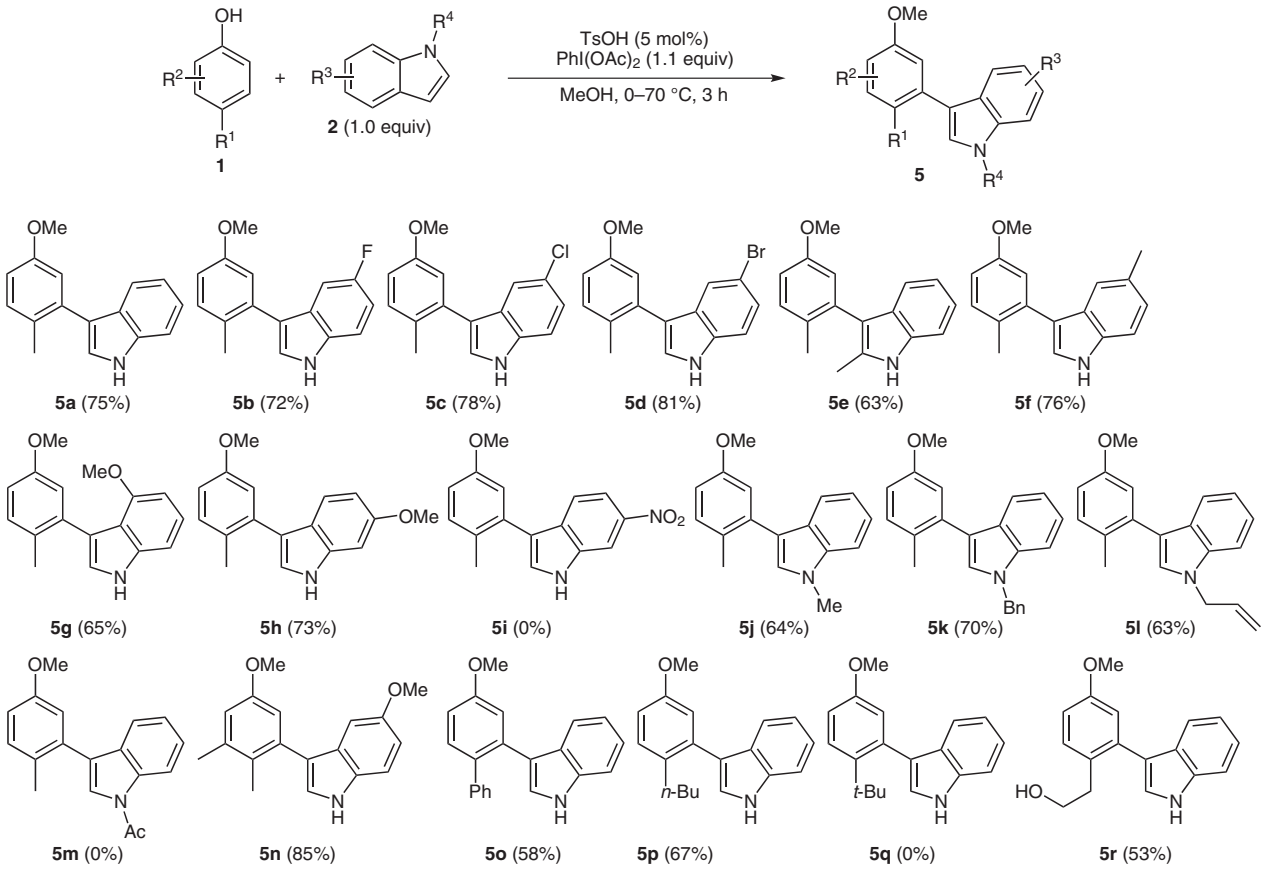

| Entry | Catalyst (equiv) | Yield of **5a** (%)[b] |
|---|---|---|
| 1 | MeCOOH (0.1) | 0 |
| 2 | PhCOOH (0.1) | 30 |
| 3 | 4-$MeOC_6H_4COOH$ (0.1) | 28 |
| 4 | 4-$O_2NC_6H_4COOH$ (0.1) | 32 |
| 5 | $CF_3COOH$ (0.1) | 69 |
| 6 | $CF_3SO_3H$ (0.1) | 67 |
| 7 | 4-$MeC_6H_4SO_3H$ (0.1) | 76 |
| 8 | 4-$MeC_6H_4SO_3H$ (0.05) | 75 |
| 9 | 4-$MeC_6H_4SO_3H$ (0.01) | 53 |

[a] *Reaction conditions*: *p*-cresol (**1a**, 0.50 mmol), $PhI(OAc)_2$ (0.55 mmol), indole (0.50 mmol), catalyst (as noted), solvent (2.0 mL).
[b] Isolated yield based on *p*-cresol (**1a**).

The oxidative coupling reaction conditions are compatible with a range of substrates as shown in Scheme 3. The reaction was found to tolerate a variety of different groups




**Scheme 2** Possible mechanism for the oxidative coupling reactions of *p*-cresol (**1a**) with indole




**Scheme 3** Oxidative coupling reaction of 4-substituted phenols with indoles

with different electronic demands on the indole rings involving electron-donating and electron-withdrawing groups. *N*-Alkyl-protected indoles were suitable substrates while no product was detected from the reaction of *N*-acetyl indole. 4-Butyl- and 4-phenylphenols were found to be the effective coupling partners, but the reaction of 4-*tert*-butylphenol was complicated. When 3,4-dimethylphenol was employed, the corresponding coupling product **5n** was isolated in 85% yield. When 4-hydroxyphenethyl acetate was used as the substrate, the reaction accompanied the oxidative coupling with the deacetylation to provide 4-(2-hydroxyethyl)-3-(1*H*-indol-3-yl)phenol (**5r**) in 53% yield.

In summary, we have developed an oxidative coupling strategy between 4-substituted phenols and indoles to provide a new access to the *meta*-indole-substituted phenol derivatives. The desired carbon–carbon bond formation proceeds under mild conditions to generate the coupling products in good yields. Current studies have also been carried to extend its scope, to explore its reaction mechanism and possible synthetic applications.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

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