



Efficient and C2-selective arylation of indoles, benzofurans, and benzothiophenes with iodobenzenes in water at room temperature



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ABSTRACT

A mild, efficient, and C2-selective palladium-catalyzed arylation reaction of indoles, benzofurans, and benzothiophenes with iodobenzenes at room temperature has been developed. The methodology allows the use of water, the most environmentally friendly solvent, as the reaction solvent with the addition of Tween 80 (2% w/w) to increase the solubility of starting materials. The protocol demonstrated wide substrate scope and good yields were obtained for all the 32 examples evaluated (52–93%).

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1. Introduction

Functionalized indoles, benzofurans, and benzothiophenes serve as important building blocks of natural products and biologically active unnatural molecules.¹ Among the known methods in the functionalization of indoles, benzofurans, and benzothiophenes, C–H activation/arylation reactions have attracted tremendous interests due to their high atom efficiency.² However, the reported methods always suffered from low regio-selectivities (C-2 over C-3) when no directing groups were pre-installed and/or high reaction temperatures (100–150 °C), which significantly limited the substrate scope and functional group tolerance. Several C2-selective arylation reactions of indoles using boronic acids or trifluoroborate salts as arylation agents at room temperature were developed, whereas in these conditions acetic acid had to be used as the solvent/co-solvent and oftentimes the trifluoroborates were not commercially available.³ Recently Larrosa has reported the C2-arylation of *N*-alkylated indoles at room temperature using more readily available iodobenzenes as arylation agents.⁴ However, when free indoles were used as the substrates, the arylation reactions required higher temperature (50 °C).⁴ C2-selective arylations of benzofurans and benzothiophenes were less extensively reported

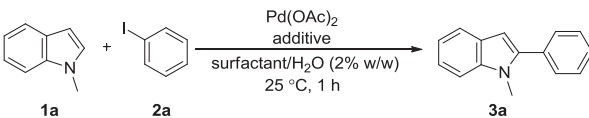
compared with indoles, and elevated reaction temperatures (>100 °C) were always required for the limited cases in literature.^{2a,e,h} Herein, we report a mild, efficient, and C2-selective arylation reaction of indoles, benzofurans, and benzothiophenes at room temperature with a wide scope of substrates. To the best of our knowledge, this is the first time the C2-selective arylation of benzofurans and benzothiophenes with iodobenzenes could be achieved at room temperature. In addition, our methodology allows the use of water as the reaction solvent, which makes it even more attractive in the aspect of reducing the hazardous organic waste.⁵ To develop organic reactions in aqueous solution has been one of the research focuses in our group.⁶ A challenge for aqueous reactions is the poor solubility of starting materials, and adding surfactants to water has been a widely used strategy to improve solubility.⁷ Among the surfactants used, polysorbates (also called Tweens) offer cheap and environmentally friendly choices⁸ and we focused our solvents on the Tweens/water micelle system.

2. Result and discussion

We started our exploration of the C–H arylation using 1-methyl-1*H*-indole (**1a**) and iodobenzene (**2a**) as starting materials and Tween 80/water (2% w/w) micelle as the solvent (Table 1). To our delight, our initial attempt using Pd(OAc)₂ as the catalyst and AgOAc as the additive at room temperature led to the formation of C2-arylation product (**3a**) in 39% conversion (Table 1, entry 1).

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Table 1
Optimization of the Pd-catalyzed direct arylation conditions of *N*-methylindole (**1a**) with iodobenzene (**2a**)^a



Entry	Pd(OAc) ₂ (mol %)	Surfactant	Additive	Conv. (%) ^c
1	2.5	Tween 80	AgOAc	39
2	2.5	Tween 80	K ₂ CO ₃	4
3	2.5	Tween 80	CF ₃ COOAg	85
4 ^b	2.5	Tween 80	Ag ₂ O+TFA	24
5	2.5	Tween 20	CF ₃ COOAg	81
6	2.5	Tween 40	CF ₃ COOAg	83
7	2.5	Tween 60	CF ₃ COOAg	73
8	2.5	Tween 85	CF ₃ COOAg	68
9	5	Tween 80	CF ₃ COOAg	97
10	5	none	CF ₃ COOAg	38

^a Conditions: *N*-methylindole **1a** (1 mmol), iodobenzene **2a** (2 mmol), additive (1.5 mmol), 2% of surfactant/H₂O (w/w, 2 ml).

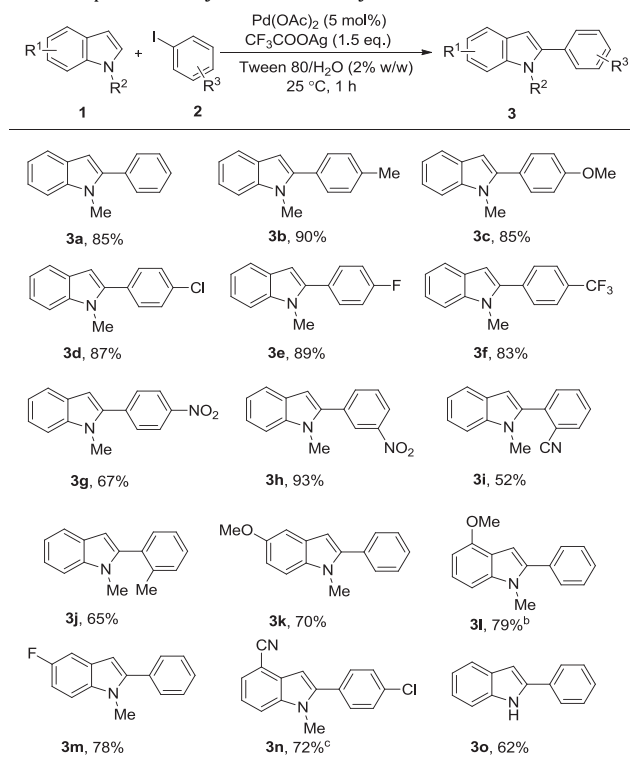
^b 0.75 equiv of Ag₂O followed by 1.5 equiv of trifluoroacetic acid.

^c Conversions measured by HPLC.

Encouraged by the result, we started to evaluate the effects of different additives to the reaction including K₂CO₃, CF₃COOAg, and Ag₂O plus TFA (Table 1, entries 2–4). Among them, CF₃COOAg provided the best conversion (85%) to the desired product **3a** (Table 1, entry 3). Tweens of different sizes were also explored (Table 1, entries 5–8) and they all resulted in similar or lower conversions than Tween 80. Increasing the catalyst loading from 2.5 mol % to 5 mol % accelerated the reaction to provide 97% conversion within 1 h (Table 1, entry 9). In comparison, removal of Tween 80 from the reaction mixture gave a much decreased conversion (38%, Table 1, entry 10) at otherwise the same reaction condition, and this was believed to be due to the insolubility of starting materials without the micelle formation of the surfactant in water.

With the optimized reaction condition of C2-selective arylation of indoles developed, the substrate scope was examined. As shown in Table 2, iodobenzenes with a variety of different substitutions were well tolerated for the reaction. Both electron-withdrawing and electron-donating substitutions were tolerated at the *para*-position of the iodobenzene, providing C2-arylation products in good isolated yields (67–90%, **3b–g**). Substitution at the *meta*-position also demonstrated high reactivity to afford the desired product (**3h**) in high yield (93%). Increasing the steric hindrance of the iodobenzene by introducing *ortho*-substitutions resulted in lower yields (52% and 65% for **3i** and **3j**, respectively). These results suggested the reactivities of iodobenzenes for the C2-arylation reaction were sensitive to steric rather than electronic effects. The scope of indole substrates was also evaluated, and the reaction showed good tolerability for different substitutions including both electron-withdrawing and electron-donating groups (**3j–n**). The electron-withdrawing substituent at the 4-position of the indole (**3n**) resulted in a much slower arylation reaction compared with the electron-donating substituent (**3l**) and a much longer reaction time was required (3 days for **3n** and 3 h for **3l**). It was noteworthy that for the free indole substrate (**3o**) high yield (62%) was also obtained at room temperature whereas elevated temperature was required in the reported procedure.⁴ In addition, the high C2-selectivity of our arylation reactions was striking and there was no C3-arylation product observed in all the tested substrates, even for the steric hindered ones (**3i** and **3j**). The mechanistic studies of palladium-catalyzed arylation of indoles had been reported and the palladium migration from the 3-position to the 2-position of the indole–palladium(II) intermediate was the key to give C2-selectivity.⁹ Our aqueous condition must have strongly favored

Table 2
Substrate scope of Pd-catalyzed direct C–H arylation of indoles^a



^a Unless otherwise stated, the reaction was conducted with **1** (1 mmol), **2** (2 equiv.), CF₃COOAg (1.5 equiv.) and Pd(OAc)₂ (0.05 equiv.) in Tween 80/H₂O (2 mL, 2% w/w) at room temperature for 1 hour. Isolated yields.

^b Reaction runs for 3 hours. ^c Reaction runs for 3 days.

the C3→C2 migration of palladium to provide the high C2-selectivity of the arylation products.

We then expanded the substrate scope to benzofurans, which are less electron-rich than indoles. As expected, the C–H arylation reactions of benzofurans were much slower (Table 3) compared with indoles, and extended reaction time (overnight) was required for the reaction to be completed. In addition, TFA had to be used to accelerate the arylation reactions.¹⁰ The substituted iodobenzenes were well tolerated and generally good isolated yields of C2-arylation products were obtained at room temperature (**5a–e**), although *para*-CF₃ iodobenzene was less effective and a prolonged reaction time was required for high yield (**5e**). On the other hand, both electron-withdrawing and electron-donating substitutions on benzofurans were tolerated. Prolonged reaction times were required for the full conversions to **5f** and **5g**, due to poor solubility of starting materials in the reaction mixtures. Again, our arylation condition for benzofurans was highly C2-selective, and there was no C3-arylation product observed for all cases.

We further expanded the substrate scope to benzothiophenes, which are even less electron-rich. To our delight, both substituted iodobenzenes and substituted benzothiophenes were well-tolerated and high yields of desired C2-arylation products were obtained at room temperature, albeit more prolonged reaction time was required (Table 4). Electron-withdrawing substitutions on the iodobenzene made the reactions less efficient and extremely slow, but good yields could still be obtained (**7b** and **7e**).

3. Conclusion

In summary, we have developed a mild, efficient, and highly C2-selective palladium-catalyzed arylation reaction of indoles,

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