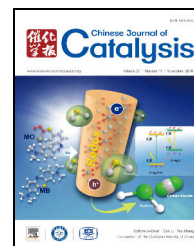


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Communication

Selective arylation/annulation cascade reactions of 2-alkynylanilines with diaryliodonium salts

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ABSTRACT

An efficient Cu catalyzed selective arylation/annulation cascade reaction of 2-alkynylanilines with diaryliodonium salts was developed. This reaction was selective to *N*-arylation instead of *C*-arylation, which provides a simple synthetic method for *N*-aryl indoles.

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Diaryliodonium salts are used in versatile organic transformations because of their highly electron-deficient nature and excellent leaving-group ability [1]. As mild, nontoxic, and selective reagents, they are competent arylating agents in organic synthesis [2,3], especially in constructing C–C [4–13] and C–X [14–17] bonds. Among these, nucleophilic substitution reactions between diaryliodonium salts with nitrogen nucleophiles have received much attention [18–21]. Recently, Guant's group [7] reported aromatic electrophile equivalents generated from the combination of diaryliodonium salts and copper catalysts via the intermediacy of Cu(III)–aryl species. These active species were considered to be responsible for the high activity of the diaryliodonium salts in Cu catalyzed reactions.

Indoles are one of the most ubiquitous heterocycles found in nature. Owing to their significant biological activity, indoles are central structural motifs in making numerous pharmacologi-

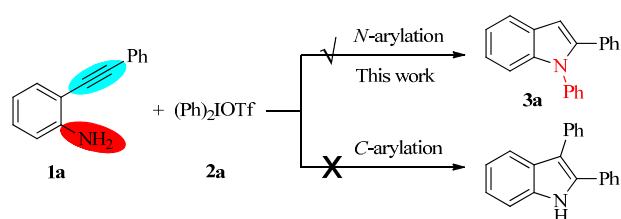
cally important compounds [22]. Consequently, much attention has been paid to their preparation, which is a major research area in organic synthesis and many methods have been developed [23]. Meanwhile, the cyclization of 2-alkynylaniline derivatives has long been exploited for the construction of indoles [24,25].

Although diaryliodonium salts have been applied to a number of arylation reactions with substrates possessing single nucleophilic group, the selective arylation of the substrates with two or more nucleophilic groups is still a challenging subject [4,6]. For example, it was disclosed that although *C*-arylation and *N*-arylation can be achieved by diaryliodonium salts, the selectivity is still a challenge. The key to solving this is how to exploit the difference in the nucleophilic groups. Here, we reported an example of a selective *N*-arylation reaction of 2-alkynylanilines with diaryliodonium salts where subse-

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Scheme 1. Reaction of 2-alkynylaniline (**1a**) and diphenyliodonium salt (**2a**).

quently the untouched *C*-nucleophile behaved as another reactive site to complete arylation-annulation cascade reactions to afford *N*-aryl indoles [26–28] (Scheme 1).

We first examined the reaction of 2-(phenylethynyl)aniline (**1a**) and diphenyliodonium triflate (**2a**). First, to overcome the possible competition of *N*-arylidindoles and *C*-arylation, 1,2-dichloroethane (DCE) was placed on the top of the solvent list because it has been demonstrated to favor *N*-arylation [4]. No reaction occurred when the metal catalyst was omitted. A Cu catalyst system has been shown to be effective in both the arylation and annulation of 2-alkynylanilines [29]. Both copper(I) and copper(II) salts were effective for this reaction, and the use of 10 mol% Cu(OCOC₈H₁₇)₂ (copper 2-ethylhexoate) gave the desired product **3a** in 93% yield. Meanwhile, the use of CuCl, CuBr, CuI, CuSCN and Cu(OTf)₂ resulted in decreased yields (Table 1, entries 1–8). Then the screening of the base exhibited that *N,N*-diisopropylethylamine (DIPEA) was more effective than the other bases (Et₃N, K₂CO₃, KOtBu and K₃PO₄, Table 1, entries 9–12). The influence of the solvent on the reac-

Table 1
Optimization of the reaction conditions.

| Entry | [Cu] | Base | Solvent | Yield ^a (%) |
|-----------------|---|--------------------------------|---------------------------------|------------------------|
| 1 | — | DIPEA | DCE | <5 |
| 2 | CuCl | DIPEA | DCE | 56 |
| 3 | CuBr | DIPEA | DCE | 61 |
| 4 | CuI | DIPEA | DCE | 67 |
| 5 | CuSCN | DIPEA | DCE | 67 |
| 6 | CuBF ₄ (MeCN) ₄ | DIPEA | DCE | 80 |
| 7 | Cu(OTf) ₂ | DIPEA | DCE | 61 |
| 8 | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | DCE | 93 |
| 9 | Cu(OCOC ₈ H ₁₇) ₂ | Et ₃ N | DCE | 69 |
| 10 | Cu(OCOC ₈ H ₁₇) ₂ | K ₂ CO ₃ | DCE | <5 |
| 11 | Cu(OCOC ₈ H ₁₇) ₂ | KO ^t Bu | DCE | 26 |
| 12 | Cu(OCOC ₈ H ₁₇) ₂ | K ₃ PO ₄ | DCE | <5 |
| 13 | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | Toluene | 69 |
| 14 | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | CH ₂ Cl ₂ | 56 |
| 15 | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | CHCl ₃ | 35 |
| 16 | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | THF | 20 |
| 17 ^b | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | DCE | 22 |
| 18 ^c | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | DCE | 48 |
| 19 ^d | Cu(OCOC ₈ H ₁₇) ₂ | DIPEA | DCE | 43 |

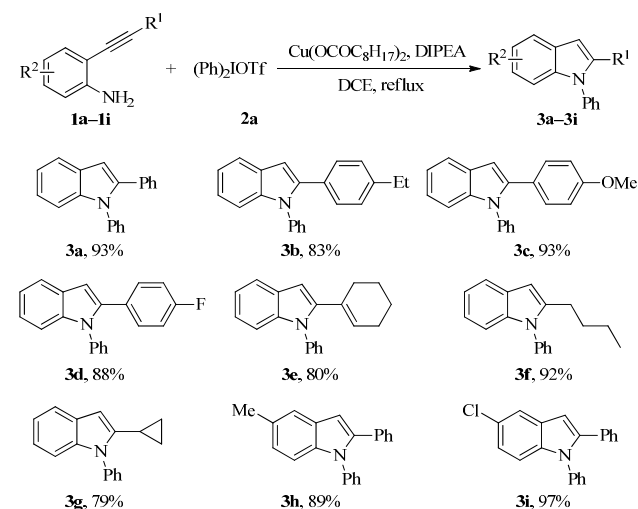
Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] (10 mol%), base (0.4 mmol), solvent (2.0 mL), 1 h. ^a Isolated yields. ^b Diphenyliodonium chloride used. ^c Diphenyliodonium hexafluorophosphate used. ^d Diphenyliodonium tetrafluoroborate used.

tion was also examined. The result showed that DCE was the best choice while a decreased yield of the desired product was observed in solvents such as toluene, CH₂Cl₂, CHCl₃ and THF (Table 1, entries 13–16). The counter-ions of the diphenyliodonium salt were also evaluated. The result showed that diphenyliodonium triflate was superior to diphenyliodonium chloride, diphenyliodonium hexafluorophosphate and diphenyliodonium tetrafluoroborate (Table 1, entries 17–19).

With these optimized reaction conditions in hand, we next elucidated the substrate scope of the cascade reaction. First, various *o*-alkynylanilines **1** with diphenyliodonium triflate (**2a**) were employed in the reaction. The results are compiled in Scheme 2. Generally, the reactions proceeded smoothly to afford the corresponding indoles **3** in isolated yields of 79%–97%. The reaction went well when R¹ = aryl group while the electronic nature of the substituent on the benzene ring of R¹ was varied. Both electron-withdrawing and electron-donating groups were tolerated. Notably, it was found that alkynes bearing alkenyl (R¹ = alkenyl group) or alkyl groups (R¹ = alkyl group) on the alkyne terminus were also compatible, providing the products **3e–3g** in good to excellent yields of 79%–92%. Substitution with 4-Me or 4-Cl functionalities on the parent aryl ring also afforded **3h** and **3i** in high yields of 89% and 97%, respectively.

The scope of the reaction was also investigated by varying the diaryliodonium triflate. The results are summarized in Scheme 3. Interestingly, the sterically demanding di(*o*-methylphenyl)iodonium triflate **2b** gave product **4b** in good yield (82%). Higher yields (**4c–4f**) were obtained with less sterically demanding diaryliodonium triflates. Also, the substituent nature of R¹ has some influence on the reaction (**4f** vs **4g**). Substrates with substituent on the benzene ring (**1h**) reacted with diaryliodonium triflate to afford **4h** with good to excellent yields (82% and 98%, respectively).

The reaction of **1a** and unsymmetric diaryliodonium salt **2i** was also evaluated. Aryl with a lesser steric effect could be transferred to **1a**, and **4i** was obtained in 80% yield (Scheme 4).



Scheme 2. Synthesis of *N*-phenyl indoles (**3a–3i**). Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Cu(OCOC₈H₁₇)₂ (10 mol%), DIPEA (0.4 mmol), solvent (2.0 mL), 1 h.

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