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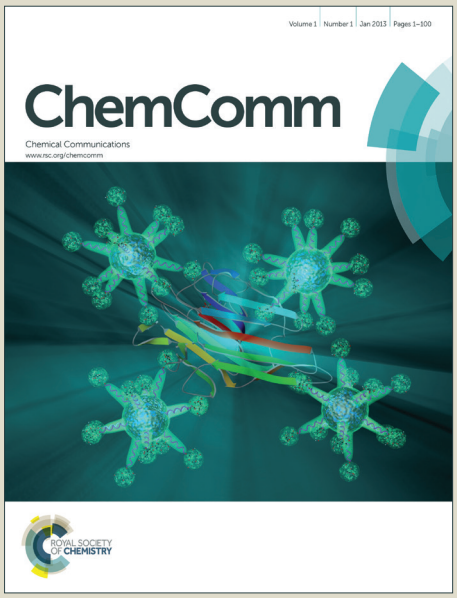


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# $C_1$-Benzyl and Benzoyl Isoquinoline Synthesis through Direct Oxidative Cross-Dehydrogenative Coupling with Methyl Arenes†

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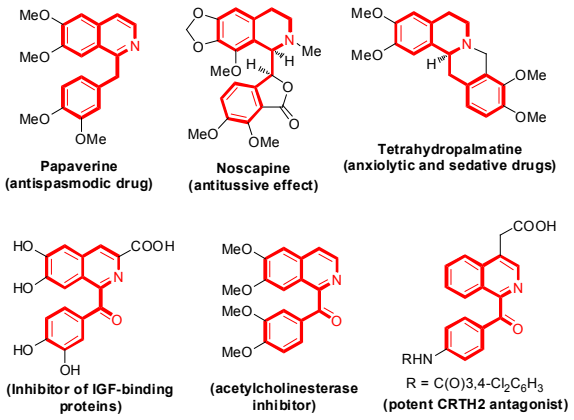
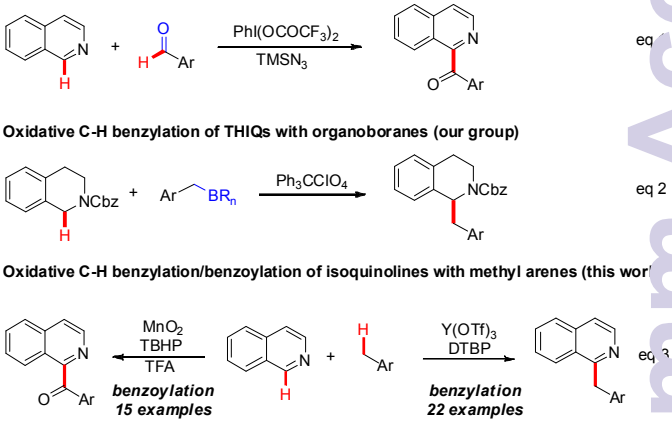
**An oxidative cross-dehydrogenative coupling (CDC) of isoquinolines with methyl arenes has been developed, allowing for facile synthesis of a broad range of structurally diverse $C_1$-benzyl and -benzoyl isoquinolines. The direct use of readily available methyl arenes as coupling partners avoids unproductive steps for preactivating functional group installation, and is thereby attractive. The method exhibits excellent chemoselectivity, affording exclusive benzylated products in the presence of DTBP and catalytic amount of $Y(OTf)_3$, and yielding benzoylated ones with TBHP and catalytic amount of $MnO_2$.**

$C_1$-Substituted isoquinolines and tetrahydroisoquinolines (THIQs) represent ubiquitous structural motifs in numerous biologically active natural products and synthetic pharmaceuticals.[1] Among them, $C_1$-benzyl and benzoyl substituted moieties are the most commonly encountered and serve as key intermediates in the synthesis and biosynthesis of other types of alkaloids (Scheme 1).[2] The direct C–H functionalization of nitrogen-containing heterocycles has emerged as efficient and robust alternatives to traditional synthetic strategies.[3] Antonchick developed a $PhI(OCOCF_3)_2/TMSN_3$ mediated benzoylation system, allowing the oxidative CDC of isoquinolines with diverse aryl aldehydes in good to excellent yields (Scheme 2, eq 1).[4a] Our group reported a trityl ion-mediated metal-free oxidative C–H benzylation of THIQs with a number of benzyl boronates (Scheme 2, eq 2).[5a] Albeit high efficiency, preactivating factors in coupling partners were prerequisite for the reactions, with the carbonyl moiety for the former, and the boronate for the latter.




**Scheme 1** Representative $C_1$-Benzyl and Benzoyl Isoquinolines.




**Scheme 2** $C_1$-Benzyl and Benzoyl Isoquinoline Synthesis through Oxidative C–H Cleavage.

The direct oxidative C–H functionalization of methyl arenes has recently emerged as an efficient and economic approach to deliver increases in molecular complexity and functional group content.[6,7] We envisioned that utilizing readily available and inexpensive methyl arenes as surrogates for the benzylation and benzoylation of isoquinolines would not require traditional reagents like benzyl boronates and aryl aldehydes with preactivating functional groups, and thus avoid unproductive steps for the installation of these factors. Herein, we facile synthesis of $C_1$-benzyl and benzoyl substituted

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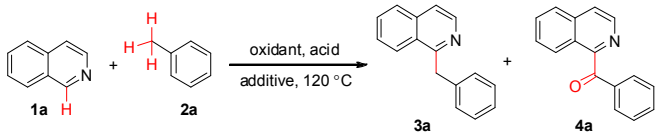
**Table 1** Reaction condition optimization[a]



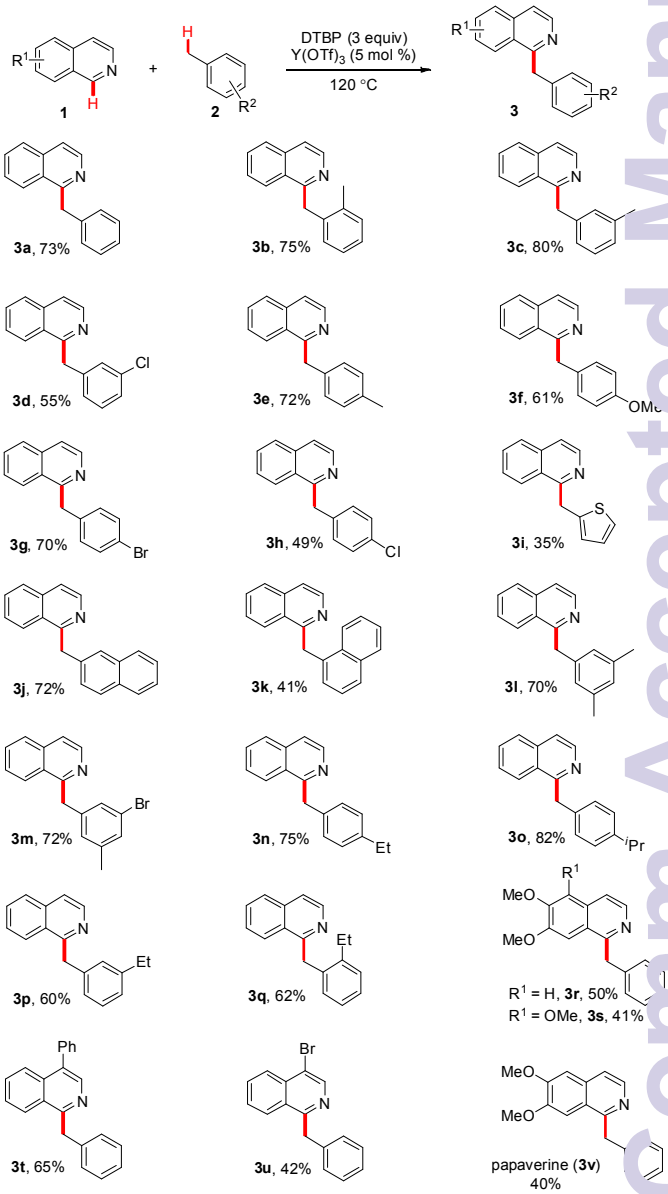

| Entry | Oxidant | Acid | Yield[b] (%, **3a**) | Yield[b] (%, **4a**) |
|---|---|---|---|---|
| 1 | DTBP | — | < 5 | < 5 |
| 2 | DTBP | TFA | 22 | 18 |
| 3 | DTBP | $Cu(OTf)_2$ | 31 | < 5 |
| 4 | DTBP | $La(OTf)_3$ | 50 | < 5 |
| 5 | DTBP | $Sc(OTf)_3$ | 46 | < 5 |
| 6 | DTBP | $Yb(OTf)_3$ | 54 | < 5 |
| 7 | DTBP | $In(OTf)_3$ | 45 | < 5 |
| 8 | DTBP | $Bi(OTf)_3$ | 63 | < 5 |
| 9 | DTBP | $Y(OTf)_3$ | 75 | < 5 |
| 10 | TBHP | $Y(OTf)_3$ | 11 | 41 |
| 11 | $H_2O_2$ | $Y(OTf)_3$ | < 5 | < 5 |
| 12 | DCP | $Y(OTf)_3$ | 70 | < 5 |
| 13 | $K_2S_2O_8$/TBAB | — | < 5 | < 5 |
| 14 | PIFA/$TMSN_3$ | — | < 5 | < 5 |
| 15 | TBHP | TFA | 10 | 50 |
| 16[c] | TBHP | TFA | < 5 | 66 |
| 17[d] | TBHP | TFA | < 5 | 68 |
| 18[e] | TBHP | TFA | n.d. | 42 |
| 19[f] | TBHP | TFA | n.d. | 45 |

[a]General conditions: **1a** (0.2 mmol), **2a** (1.8 mmol), oxidant (0.6 mmol for DTBP; 1.0 mmol for TBHP), acid (0.01 mmol for $Y(OTf)_3$; 0.2 mmol for TFA), and additive (0.02 mmol) at 120 °C for 12-24 h, unless stated otherwise. [b]Isolated yield. [c]$MnO_2$ as the additive. [d]$Mn(OAc)_3{\cdot}2H_2O$ as the additive. [e]$Mn(OAc)_2{\cdot}4H_2O$ as the additive. [f]$MnO_2$ (30 mol %). DTBP = di-tert-butyl peroxide. TBHP = tert-butyl hydroperoxide. DCP = dicumyl peroxide. TBAB = tert-n-butylammonium bromide. n.d. = not determined.

isoquinolines through a direct oxidative C–H functionalization using methyl arenes as the coupling partners (Scheme 2, eq 3).

Initially, the oxidative CDC of isoquinoline **1a** with toluene **2a** was selected as the model reaction for optimization (Table 1). No reaction was observed when DTBP was employed as the oxidant without any acid (Table 1, entry 1). According to our previous observations in the C–H benzylation of *N*-acyl THIQs (Scheme 2, eq 2),[5a] we envisioned that an acid additive might be beneficial for enhancing the electrophilicity of isoquinolines. To our delight, acidic additives proved to be crucial to the efficiency and selectivity of the coupling. The reaction with 1 equiv of TFA afforded an equivalent of benzylated **3a** and benzoylated **4a** in a total yield of 40% (Table 1, entry 2). Employing catalytic amount of Lewis acids (5 mol %) was beneficial to suppressing the benzoylation process with a considerable amount of **1a** recovered when $Cu(OTf)_2$, $La(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, or $In(OTf)_3$ was used (Table 1, entries 3-7). Finally, $Y(OTf)_3$ was found to be the optimal choice for the benzylation reaction in terms of the reaction efficiency (Table 1, entries 3-9). Extensive examination of other types of peroxides identified DTBP to be optimal (Table 1, entries 9-12). Previously reported oxidation systems for CDC of isoquinolines with aryl aldehydes were uneffective for the reaction (Table 1, entries 13 and 14).[4]

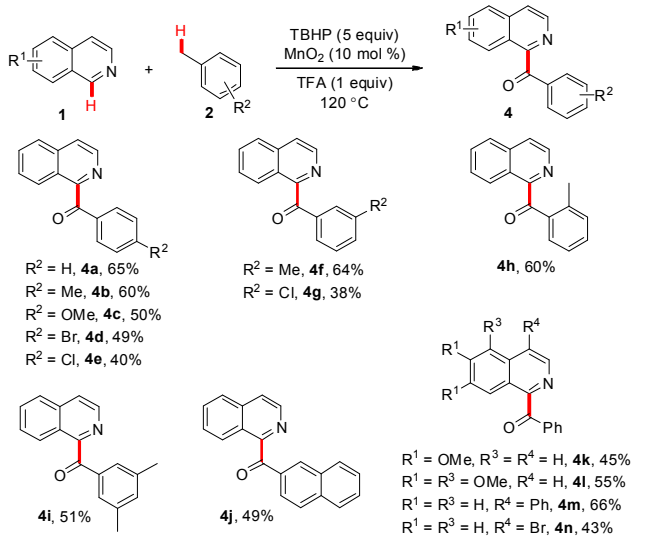
When either TFA or TBHP was employed as the component, a considerable amount of benzoylated isoquinoline **4a** was isolated (Table 1, entries 2 and 10). The observation prompted us to further explore the optimized condition for benzoylation of isoquinoline with toluene. The coupling in the presence of TFA and TBHP afforded **4a** in 52% yield (Table 1, entry 15). An extensive exploration of the additive revealed that catalytic amount of manganese-based candidates were beneficial for improving the reaction efficiency, with 66% yield for $MnO_2$, and 68% yield for $Mn(OAc)_3{\cdot}2H_2O$ (Table 1, entries 16-18). Increasing the loading of the additive delivered a compromised yield (Table 1, entry 19). While $Mn(OAc)_3$ excelled $MnO_2$ in terms of the yield, the use of the latter for further study would be more attractive based on economic and environmental issues.




**Scheme 3** $C_1$-Benzyl Isoquinoline Synthesis. Reaction conditions: **1** (0.2 mmol), **2** (1.8 mmol), DTBP (0.6 mmol), and $Y(OTf)_3$ (0.01 mmol) at 120 °C for 12-24 h.

The scope of the benzylation of isoquinolines with methyl arenes was explored (Scheme 3). Mono-substituted toluene derivatives bearing electron-donating and -withdrawing functional groups like methyl, methoxy, chloride, and bromide were well compatible with the oxidation system diversifications (**3b-3h**). Notably, the reaction effic

not sensitive to the substituent pattern of the methyl arenes. Methyl heteroarene (**2i**) and methyl naphthalenes (**2j** and **2k**) were suitable components. Di-substituted toluene moieties proved to be effective coupling partners (**2l** and **2m**). With respect to the methyl arenes containing more than one benzyl methyl groups (**2b**, **2c**, **2e**, **2l**, and **2m**), the exclusive formation of mono-arylated product was observed, with the other methyl group intact. The reaction exhibited overwhelming regioselectivity at the less sterically hindered methyl group when two types of benzylic C–H bonds were present in methyl arenes, as demonstrated by the substrates bearing an ethyl or isopropyl substituent at the 2-, 3-, or 4-position of toluene (**3n-3q**). The substituent effect on isoquinolines was also investigated, with electron-rich and -deficient substrates tolerated in moderate efficiency (**3r-3u**). The direct benzylation of isoquinolines with methyl arenes allowed for the facile preparation of papaverine (**3v**), an opium alkaloid antispasmodic drug.

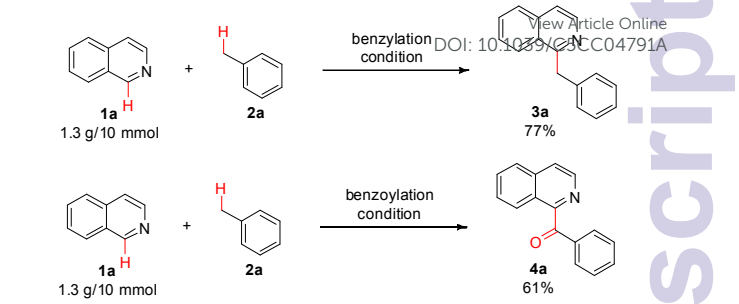



**Scheme 4** $C_1$-Benzoyl Isoquinoline Synthesis. Reaction conditions: **1** (0.2 mmol), **2** (1.8 mmol), TBHP (1.0 mmol), TFA (0.2 mmol), and $MnO_2$ (0.02 mmol) at 120 °C for 12-24 h.

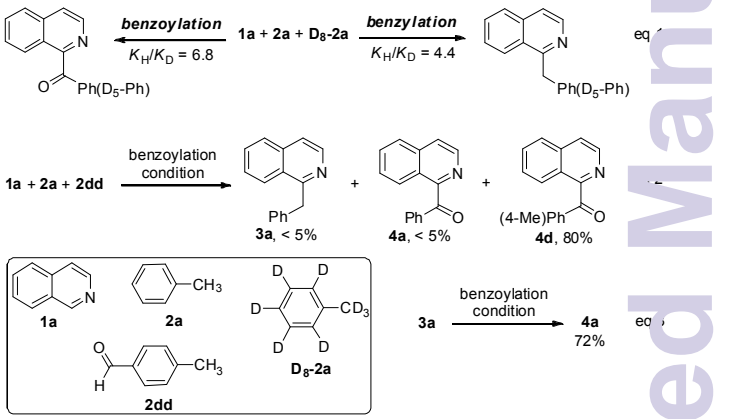
The scope of benzoylation of isoquinolines was next examined in the presence of TBHP and catalytic amount of $MnO_2$ (Scheme 4). Similarly to the benzylation process, a broad range of toluene derivatives bearing both electron-donating and -withdrawing functional groups with different substitution were tolerated (**4a-4j**), though decreased yields were observed for the latter ones (**4d**, **4e**, and **4g**). Substituted isoquinolines bearing a variety of functional groups participated in the benzoylation reaction in moderate yields (**4k-4n**).

Under the standard CDC conditions, benzylation and benzoylation reactions with **1a** on a 1.3 g (10 mmol) scale proceeded smoothly affording comparable yields (75% for **3a** and 61% for **4a**) to the smaller scale reactions (73% for **3a** and 65% for **4a**), demonstrating the capacity to apply the protocol to scaled up reactions (Scheme 5).

The reaction mechanism was next studied. The addition of 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (1 equiv) completely quenched the reaction of isoquinoline (**1a**) with toluene (**2a**), suggesting the radical nature of the mechanism.

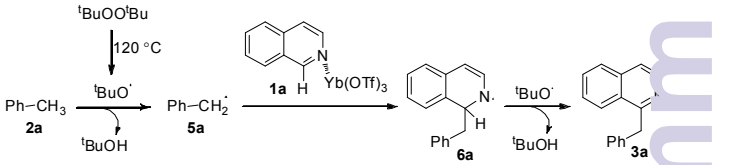



**Scheme 5** Gram Scale Reaction Exploration.




**Scheme 6** Mechanistic Studies.

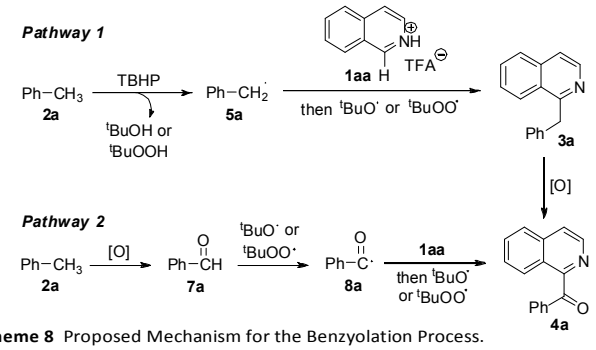
Intermolecular kinetic isotope effects ($K_H/K_D$ = 4.4 for benzylation; $K_H/K_D$ = 6.8 for benzoylation) were observed for the reaction of **1a** with an equivalent of toluene and deuterated toluene, indicating the involvement of the cleavage of the benzylic C–H bond in the rate-determining step (Scheme 6, eq 1). According to the above analysis, a plausible mechanism for the benzylation reaction was proposed in Scheme 7. Toluene (**2a**) is converted to benzyl radical **5a** in the presence of DTBP at 120 ºC. Isoquinoline (**1a**) can be activated by $Y(OTf)_3$ to facilitate the addition of **5a** onto **1a** giving radical **6a**, which then reacts with *tert*-butoxyl radical to yield **3a**.




**Scheme 7** Proposed Mechanism for the Benzylation Process.

In the course of the benzoylation reaction, the formation of a considerable amount of benzaldehyde and benzylated **3a** was detected by $^1$H NMR together with the benzoylated **4a**. Therefore, two possible sequences could be envisaged for the benzoylation process (Scheme 8). The first one involves an initial benzylation reaction, followed by an overoxidation of **3a** affording **4a**. Alternatively, toluene (**2a**) might be oxidized to benzaldehyde (**7a**) that undergoes a radical coupling with **1a** giving **4a**. Several control experiments were conducted to elucidate the nature of the mechanism. A crossover experiment involving a mixture of toluene (**2a**) and 4-methylbenzaldehyde (**2dd**) with **1a** gave exclusive benzoylated **4d**, suggesting feasibility of the second pathway given the generation

the reaction (Scheme 6, eq 2). **3a** can be oxidized to **4a**, indicating the first pathway might be viable (Scheme 6, eq 3).




**Scheme 8** Proposed Mechanism for the Benzyolation Process.

In conclusion, an oxidative CDC of isoquinolines with methyl arenes has been disclosed, allowing for facile synthesis of a broad range of structurally diverse $C_1$-benzyl and -benzoyl substituted isoquinolines, respectively. The direct use of readily available methyl arenes as coupling partners avoids unproductive steps for preactivating functional group installation, and is thereby attractive. The scaled-up reactions provided comparable efficiency to smaller scale reactions, demonstrating the capacity in real alkaloid synthesis.

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