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Oxidant-Triggered C_1-Benzylation of Isoquinoline by Iodine-Catalyzed Cross-Dehydrogenative-Coupling with Methylarenes

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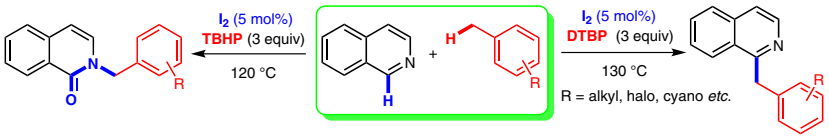

Advantages:
- **Oxidant-triggered C_1- or *N*-benzylation**
- **Metal- and additive-free conditions**
- **20 examples and up to 72% yield**

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Abstract A practical iodine-catalyzed oxidative functionalization of isoquinolines with methylarenes is developed, which can be triggered by the selected oxidants to produce C_1- or *N*-benzyl-substituted products selectively. This method utilizes readily available isoquinolines and methylarenes as starting materials and proceeds under metal-free conditions with broad substrate scope with respect to methylarenes, avoiding the usage of expensive metal catalysts and generation of halide and metal wastes.

Key words benzylation, Minisci reaction, iodine, isoquinoline, isoquinolinone

C_1-Substituted isoquinolines and tetrahydroisoquinolines are abundant in pharmaceutics and widely used as ligands in organic synthesis.[1] For example, natural products palaudine, papaverine, sevanine and coclaurine all contain C_1-benzyl-substituted (tetrahydro)isoquinoline motif (Figure 1), which feature narcotic, spasmolytic, dopaminergic, ion-channel modulating and cytotoxic properties.[2] Great efforts have been developed to construct these electron-deficient heterocycles, but the studies on the direct functionalization of the heterocyclic C(sp^2)–H bonds, especially under metal-free conditions, have been far less. Different from the easy alkylation of electron-rich arenes via Friedel–Crafts reaction, the similar alkylation of these heterocycles is unlikely due to their innate electron-deficient reactivity. In contrast, the addition of nucleophilic alkyl radicals to heterocycles, the Minisci reaction,[3,4] is well developed and widely used in organic synthesis. However, the disadvantages of the classic Minisci reaction include limited functionalized precursors (carboxylic acids or alkyl halides) and the addition of metal catalysts (Ag, for example) up to stoichiometric amounts. The recent progresses for the Minisci reaction have included the direct use of certain C(sp^3)–H bonds as radical sources, which, however, were confined to simple symmetric alkanes or ethers to suppress regioisomers.[5]

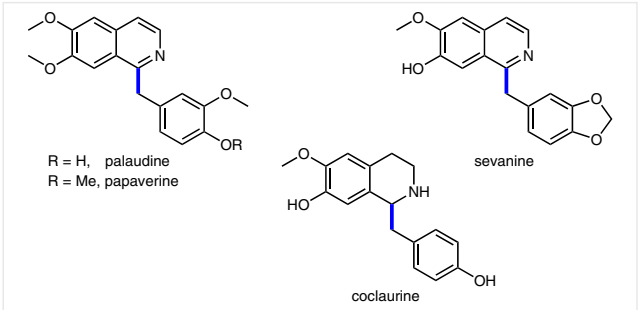
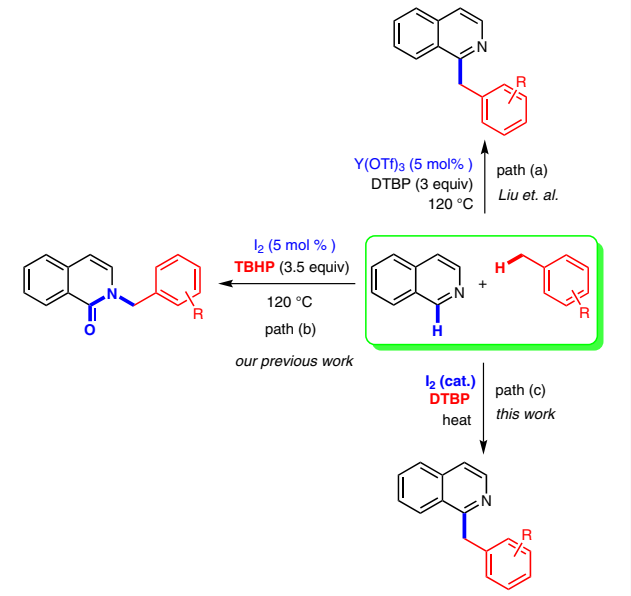


Figure 1 Examples of C_1-benzyl-substituted (tetrahydro)isoquinolines-fused natural products

Recently, a wonderful Y(OTf)$_3$-catalyzed C_1-benzylation of isoquinolines with methylarenes was discovered by Liu et al. (Scheme 1, path a).[6a] However, considering the costs of rare earth metal catalyst and difficulties to remove the trace transition metal impurities from the final products, especially for the late-stage functionalization of biologically active pharmaceuticals,[4c,7] a general method for the alkylation of heterocycles under metal-free conditions would be highly desired. In this context, an efficient alkylation of isoquinoline via metal-free oxidative decarbonylative coupling with aliphatic aldehydes had previously been developed by our group.[8a] This reaction was further developed by Guin group using dioxygen to replace peroxides as the radical initiator.[8b]

On the other hand, the use of molecular iodine or iodide anion as a catalyst is a promising strategy and has attracted increasing attention.[9] As our ongoing interests in the benzylic C(sp^3)–H bonds transformation for the functionalization of heterocycles,[10a–e] we recently reported the iodine-

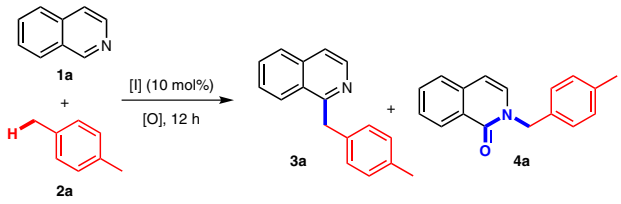


Scheme 1 The cross-dehydrogenative-coupling (CDC) of isoquinoline with methylarenes

catalyzed oxidative functionalization of isoquinoline with benzylic C–H bonds via N-alkylation and amidation cascade to provide isoquinolin-1(2*H*)-ones, with TBHP (*tert*-butyl hydroperoxide) as the oxidant (Scheme 1, path b).[10a] Unexpectedly, when using DTBP (di-*tert*-butyl peroxide) as the oxidant instead, the reaction switched to afford C_1-benzylated isoquinoline product predominantly.

With our previous studies on iodine-catalyzed oxidative functionalization of isoquinoline with benzylic C–H bonds to provide isoquinolin-1(2*H*)-ones in mind,[10a] we first tried the reaction of isoquinoline (**1a**) and *p*-xylene (**2a**) with DTBP as the oxidant in the presence of 5 mol% molecular iodine as catalyst, which produced the C_1-benzyl isoquinoline **3a** in 71% yield, and the yield of *N*-benzyl isoquinolinone **4a** was less than 2% as determined by GC (Table 1, entry 1). In contrast, the control reaction using TBHP as oxidant produced the *N*-benzyl isoquinolinone **4a** in 72% yield, and the C_1-benzyl isoquinoline **3a** could not be detected by GC (Table 1, entry 2). It seems that by simply switching the oxidants (and at the same time, the radical initiator), the reaction selectively generated the C_1 or *N*-benzyl-substituted products. So other oxidants such as aqueous hydroperoxide, potassium persulfate and benzoyl peroxide were tried but failed in this reaction (Table 1, entries 3–5). Next, other anionic iodine source (CuI, KI and TBAI) and cationic iodine (NIS, *N*-iodosuccinimide) as catalysts were examined. Among them, CuI was found to be totally inactive, KI gave lower yield, and KI and TBAI resulted in similar results as those obtained using molecular iodine (Table 1, entries 6–9). Later, the loading of molecular iodine and the influence of temperature were carefully evaluated (Table 1, entries 10–15). The blank control experiment failed to produce the target product, so we deduced that the molecular iodine played a crucial role in this transformation. Either decreasing the catalyst loading to 2.5 mol% or increasing to 10 mol% afforded lower yields, and 5 mol% was proved to be the optimal value. The yield also decreased rapidly when the reaction was run at lower temperatures of 120 °C and 110 °C, and no reaction took place at 100 °C, which might support our theory that the hemolytic cleavage of DTBP is the initial step for this reaction. No reaction occurred in the absence of iodine catalyst. It is worth noting that this reaction can also be conducted in other solvents such as chlorobenzene, with excess *p*-xylene (10 equiv) added as reactant, but leading to decreased yields (Table 1, entry 16).

Table 1 Optimization of the CDC of Isoquinoline with *p*-Xylene[a]

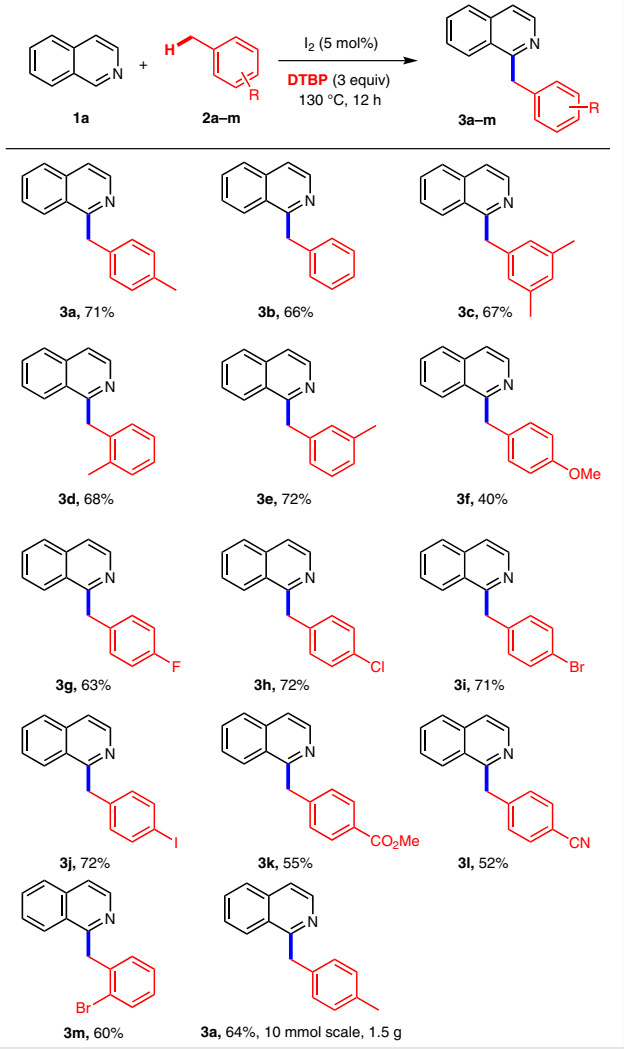


Entry	[I] (mol%)	[O] (equiv)	Temp (°C)	Yield (%)[b] **3a** (**4a**)
1	**I_2 (5)**	**DTBP (3)**	**130**	**71 (<2)**
2	I_2 (5)	TBHP (3)	130	0 (72)
3	I_2 (5)	H_2O_2 (3)	130	0
4	I_2 (5)	$K_2S_2O_8$ (3)	130	0
5	I_2 (5)	BPO (3)	130	0
6	CuI (10)	DTBP (3)	130	0
7	KI (10)	DTBP (3)	130	50
8	TBAI (10)	DTBP (3)	130	71
9	NIS(10)	DTBP (3)	130	70
10	I_2 (0)	DTBP (3)	130	trace
11	I_2 (2.5)	DTBP (3)	130	66
12	I_2 (10)	DTBP (3)	130	62
13	I_2 (5)	DTBP (3)	120	50
14	I_2 (5)	DTBP (3)	110	45
15	I_2 (5)	DTBP (3)	100	<2
16[c]	I_2 (5)	DTBP (3)	130	54

[a] Conditions: **1a** (0.4 mmol), catalyst (mol%), oxidant (equiv), in *p*-xylene (**2a**, 1.0 mL), reacted for 12 h under air atmosphere unless otherwise noted.
[b] Isolated yields of **3a**, the yield of **4a** is given in parentheses.
[c] A mixture of solvents *p*-xylene (10 equiv) and chlorobenzene (1.0 mL) was used.

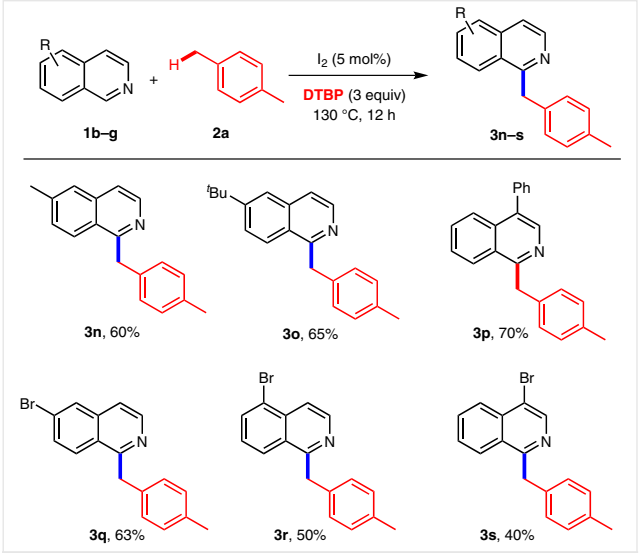
The generality of this iodine-catalyzed cross-dehydrogenative-coupling of isoquinoline with benzylic C–H bonds was subsequently investigated. The substrate scope for the methylarene moiety is listed in Scheme 2. Methylarenes bearing electron-donating or electron-withdrawing substituents were successfully transformed into the desired C_1-benzylated isoquinolines in high yields, such as methyl (**2c**–

e), methoxy (**2f**), halo (**2g–j** and **2m**), methoxycarbonyl (**3k**) and cyano group (**2l**). Among them, 1-methoxy-4-methylbenzene (**2f**) gave a much lower yield of 40%, which might be caused by the loss of molecular iodine during the electrophilic iodination of election-rich arene. To our delight, both the *m*-xylene (**2d**) and *o*-xylene (**2e**) reacted with isoquinoline readily and good yields were realized, which indicated that there was no obvious steric hindrance effect for this CDC reaction. Gratifyingly, the reaction could be satisfactorily performed on a 1-gram scale of isoquinoline, providing **3a** in a slightly lower yield of 64%. For all of these substrate tested, the *N*-benzyl isoquinolinone product **4** was not detected by GC–MS, so the reaction shows high chemoselectivity.



Scheme 2 The influence of methylarenes on iodine-catalyzed CDC. *Reagents and conditions*: **1a** (0.4 mmol), I_2 (5 mol %), DTBP (1.2 mmol, 3 equiv), in methylarene **2a–m** (1.0 mL) was reacted for 12 h under air atmosphere unless otherwise noted; isolated yields.

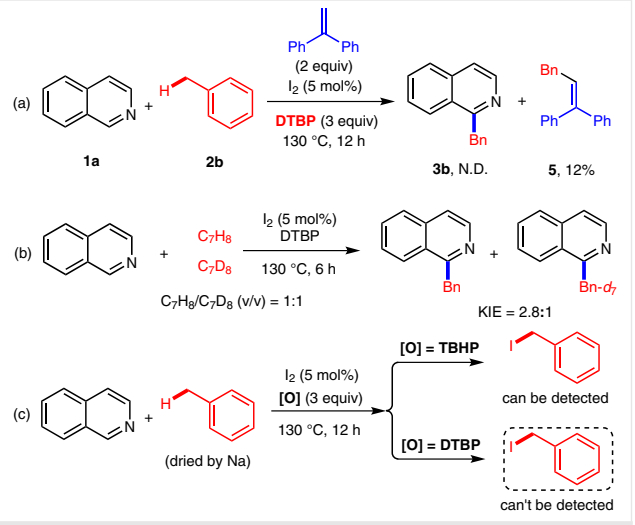
Encouraged by the exciting results obtained through the CDC of isoquinoline (**1a**) with different methylarenes, application of this iodine-catalyzed CDC to other substituted isoquinolines was investigated next (Scheme 3). Isoquinolines **1b–g** substituted at different positions turned out to be suitable substrates for this transformation. Among them, 4-bromoisoquinoline resulted in a much lower yield, due to the generation of debromination by-product. It is a pity that the CDC of quinoline and *p*-xylene provided 2-(4-methylbenzyl)quinoline in a much lower yield of 18%, which might be due to its decreased reactivity compared with isoquinoline.



Scheme 3 The influence of isoquinolines on the iodine-catalyzed CDC. *Reagents and conditions*: azaarene **1b–g** (0.4 mmol), I_2 (5 mol %), DTBP (1.2 mmol, 3 equiv), in *p*-xylene (**2a**, 1.0 mL) was reacted for 12 h under air atmosphere unless otherwise noted; isolated yields.

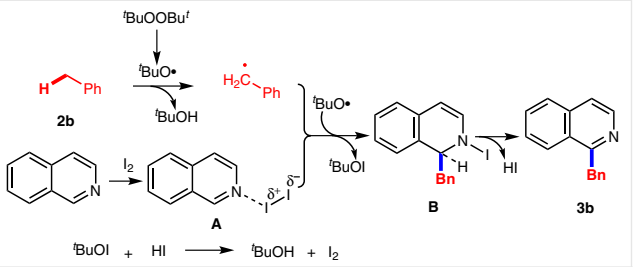
Based on our previous study on metal-free oxidative decarbonylative coupling of aliphatic aldehydes with azaarenes[8a] and literature reports,[3,6] we speculated that this reaction was also realized through a Minisci-type mechanism. To verify this speculation, several mechanistic experiments were designed. First, when 1,1-diphenylethene (2.0 equiv) as radical scavenger was added to prove the generation of benzyl radical, the reaction of isoquinoline and toluene failed to provide the C_1-benzylation product **3b**. Indeed, the corresponding oxidative benzyl radical addition product **5** was isolated in 12% yield (Scheme 4 a). Then, the preliminary kinetic isotope competition experiment of isoquinoline with toluene (C_7H_8) and deuterated toluene (C_7D_8) revealed that the KIE value was 2.8 (Scheme 4 b, see SI for details), which implied that the cleavage of the benzylic C–H bond to produce the benzyl radical was the rate-determining step. When TBHP was used as oxidant to produce *N*-benzyl isoquinolinone selectively, benzyl iodide could be detected by GC–MS (Scheme 4 c), thus a 'quaterna-

ry ammonium salt' intermediate was proposed. However, when the oxidant was switched to DTBP, no benzyl iodide can be detected. Thus, we speculated that the molecular iodine as catalyst might play a role of Lewis acid [9a] to activate the isoquinoline and accelerate the subsequent aromatization step. Since at the beginning of this reaction, only I_2 was added but no HI was generated yet; at the same time, in the presence of excess oxidant (DTBP), HI would be readily oxidized to I_2. So we proposed that the molecular iodine was more likely to act as the Lewis acid to activate the isoquinoline than HI.



Scheme 4 Mechanistic investigation on the iodine-catalyzed CDC

According to the above analysis, a plausible mechanism is proposed in Scheme 5, with the reaction of isoquinoline (**1a**) and toluene (**2b**) as an example. First, the homolytic cleavage of DTBP forms *tert*-butoxy radical, which abstracts the benzylic hydrogen atom of toluene to provide the benzyl radical. At the same time, molecular iodine as a Lewis acid coordinates with isoquinoline to increase its electrophilicity.[9a] Then, the benzyl radical adds to the activated electron-deficient isoquinoline (**A**) to afford the intermediate (**B**), which would eliminate the hydroiodide to afford the benzylated product **3b**. The molecular iodine can be regenerated by the oxidation of iodide anions by the peroxide or *tert*-butyl hypoiodite generated in situ.[9d]



Scheme 5 Proposed mechanism for the iodine-catalyzed CDC

In conclusion, we have developed an efficient and practical iodine-catalyzed cross-dehydrogenative-coupling of isoquinoline with benzylic C–H bonds via the Minisci-type mechanism. This reaction can selectively realize C_1- or N-benzylation of isoquinoline by choosing DTBP or TBHP as the oxidant, respectively. This method utilizes unfunctionalized isoquinoline and methylarenes as starting materials and proceeds under metal-free conditions with good yields, avoiding the usage of expensive metal catalysts and generation of halide and metal wastes, and thus is a practical pathway for the C_1-benzylation of isoquinolinone. Further application of this strategy to other functionalization of azaarenes is ongoing in our laboratory.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588331.

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(11) A general experimental procedure for this CDC is described as following: an oven-dried reaction vessel was charged with isoquinoline (**1a**, 0.4 mmol, 1 equiv), I_2 (0.02 mmol, 5.2 mg, 5 mol%), DTBP (di-*tert*-butyl peroxide, 1.2 mmol, 3 equiv) in *p*-xylene (1 mL) under air. The vessel was sealed and heated at 130 °C for 12 h, then cooled to r.t. The resulting mixture was transferred to a silica gel column and eluted with hexanes and EtOAc (12:1) to give 1-(4-methylbenzyl)isoquinoline (**3a**) in 71% yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 5.6 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.50–7.55 (m, 2 H), 7.17 (d, *J* = 7.3 Hz, 2 H), 7.05 (d, *J* = 7.4 Hz, 2 H), 4.63 (s, 2 H), 2.27 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.48, 142.11, 136.67, 136.49, 135.81, 129.88, 129.30, 128.59, 127.41, 127.28, 127.25, 125.94, 119.82, 41.76, 21.07.