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Oxidative coupling between C(sp^2)–H and C(sp^3)–H bonds of indoles and cyclic ethers/cycloalkanes†

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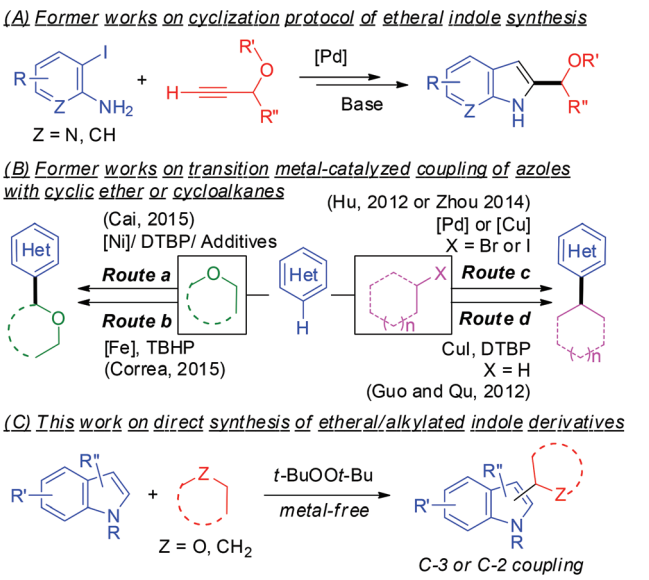
Cross-dehydrogenative-coupling (CDC) between C–H/C–H bonds of indoles and cyclic ethers/cycloalkanes is made viable through a simple transition-metal-free pathway. With the aid of only di-*tert*-butyl peroxide, a number of inactive cyclic ethers and cycloalkanes can be directly coupled with indole derivatives in satisfactory yields.

Direct cross-dehydrogenative-coupling (CDC) reactions of two different C–H bonds under oxidative conditions have emerged as one of the most effective and straightforward strategies for constructing C–C bonds in organic synthesis.[1] This approach is highly desirable as the direct engagement of naturally abundant C–H starting materials together can circumvent the pre-functionalization/preactivation of substrates and therefore lead to a better atom economy.[2] Yet, the challenges of CDC reactions are low reactivity and selectivity, owing to the high dissociation energy and the ubiquity of C–H bonds, respectively. Transition metal complexes are employed to overcome these difficulties[3] and the development of new catalyst systems for more efficient transformations is indeed a central theme in modern organic synthesis.

The indolyl framework is a common sub-unit in various pharmaceutically attractive and naturally occurring products.[4] Particularly, the relevant indolyl motifs exhibit unique anti-inflammatory and phosphodiesterase inhibitory activities.[5] Therefore, facile convergent approaches for accessing an array of C-3 or C-2 alkylated indole derivatives are in high demand. Nevertheless, the reported procedures are sometimes cumbersome and/or require costly catalysts/substrates (Scheme 1A).[6] In fact, the direct C–C bond construction of α-substituted cyclic ethers (*e.g.* five- or six-membered ring) or cycloalkanes to the C-3 or C-2 position of indoles is still rare by virtue of the low reactivity of these C–H bonds. The transition-metal-catalyzed C–C bond formation of ethers/cycloalkanes with heterocycles *via* cross-dehydrogenative-coupling (CDC) reactions has received considerable attention and advanced remarkably (Scheme 1B).[7] However, C–C coupling of indoles with ethers/cycloalkanes is far less explored.[8] In 2015, Cai reported a nickel-catalyzed regioselective CDC of inactive C(sp3)–H bonds with indole derivatives.[9] Regiospecific C-3 or C-2 coupling of indoles with 1,4-dioxane was shown with the aid of a $Ni(acac)_2$ or NiF_2 complex (Scheme 1B). Apart from the transition metal-catalyzed pathway, the CDC reaction would be further attractive if this reaction can proceed in a metal-free manner.[10] Nevertheless, a simple metal-free oxidative coupling between



Scheme 1 Selected examples of preparation of ethereal azoles.

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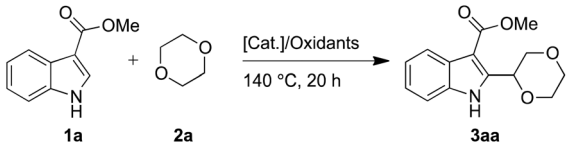
Table 1 Initial screening of CDC reaction between 1,4-dioxane and indole **1a**[a]



1a **2a** **3aa**

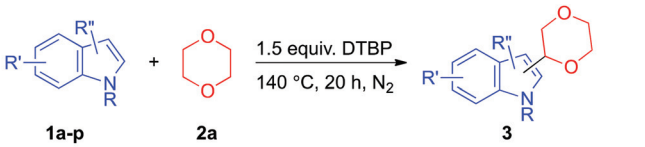
Entry	[Cat.] (10 mol%)	Oxidants (equiv.)	Yield[b] (%)
1	—	DTBP (1.5)	69
2	—	TBPB (1.5)	45
3	—	TBHP (1.5)	0
4	—	$K_2S_2O_8$ (1.5)	0
5	—	BPO (1.5)	0
6	—	DTBP (0)	0
7	$Pd(OAc)_2$	DTBP (1.5)	68
8	CuI	DTBP (1.5)	69
9	KI	DTBP (1.5)	65
10	Bu_4NI	DTBP (1.5)	35
11	—	DTBP (1.0)	61
12	—	DTBP (2.0)	58
13	—	**DTBP (1.5)**	**78**[c]
14	—	DTBP (1.5)	74[c,d]
15	—	DTBP (1.5)	61[e]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2 mL), [Cat.] (10% mol) and oxidant (0.75 mmol) were stirred at 140 °C in air for 20 hours. (DTBP = di-*tert*-butyl peroxide, TBPB = *tert*-butylperoxybenzoate, TBHP = *tert*-butyl hydroperoxide (70% in aqueous solution), BPO = benzoyl peroxide.) [b] Isolated yield. [c] Under a nitrogen atmosphere. [d] 120 °C was used. [e] 1 mL of **2a** was used.

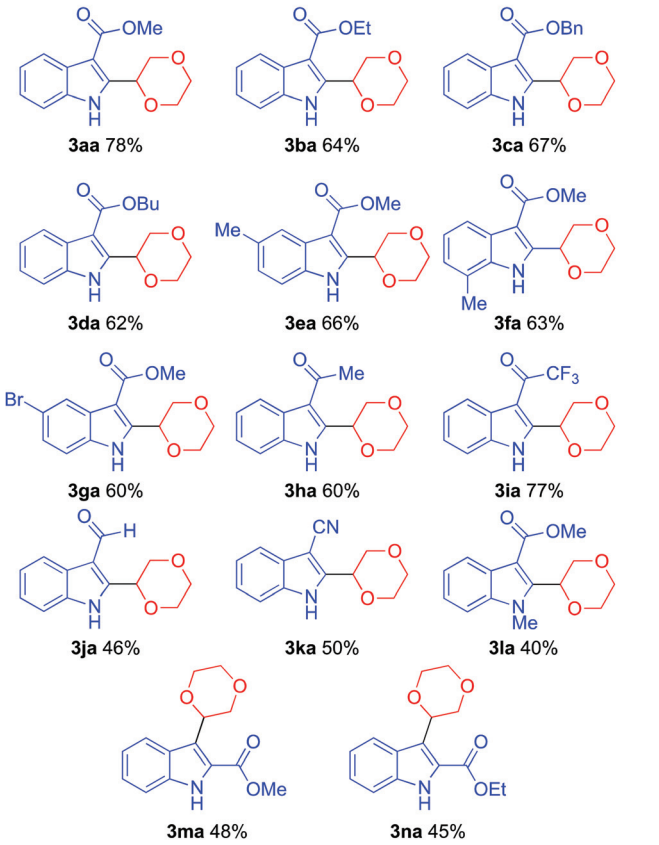
indoles and ethers/cycloalkanes remains sporadically studied. Cai showed that di-*tert*-butyl peroxide (DTBP) mediated oxidative coupling of isochroman with indole derivatives.[11] Tian and Li reported a KO*t*-Bu-mediated coupling of indoles and [60]fullerene with high regioselectivity at the C-3 position of indoles.[12] Continuing our research interest on metal-free coupling reactions,[13] C–H functionalization of heteroarene[14] and CDC reaction of *ortho*-acylaniline synthesis,[15] herein we demonstrate a metal-free protocol for coupling of cyclic ethers or cycloalkanes with the C-3 or C-2 position of indole derivatives using di-*tert*-butyl peroxide (DTBP) as the oxidant (Scheme 1C).

We first started our investigation by using indole **1a** and 1,4-dioxane (**2a**) as the model substrates (Table 1). A screening of oxidants showed that no reaction occurred when commonly used oxidants such as *tert*-butyl hydroperoxide (TBHP), benzoyl peroxide (BPO) and potassium persulfate ($K_2S_2O_8$) were employed (Table 1, entries 3–5). To our delight, di-*tert*-butyl peroxide (DTBP) and *tert*-butylperoxybenzoate (TBPB) gave the desired product **3a** in 69% and 45% yields, respectively (entries 1 and 2). There were no improvements when CuI, KI, Bu_4NI or $Pd(OAc)_2$ was added as the catalyst (entries 7–10). Control experiments revealed that the reaction did not proceed without DTBP, which suggested the crucial importance of peroxide in this transformation (entry 6). Increasing the amount of DTBP or lowering the reaction temperature led to the decrease of the product yield (entries 11 *vs.* 12 *vs.* 14). The

Table 2 Cross-dehydrogenative-coupling reaction of 1,4-dioxane with various indoles[a]



1a-p **2a** **3**

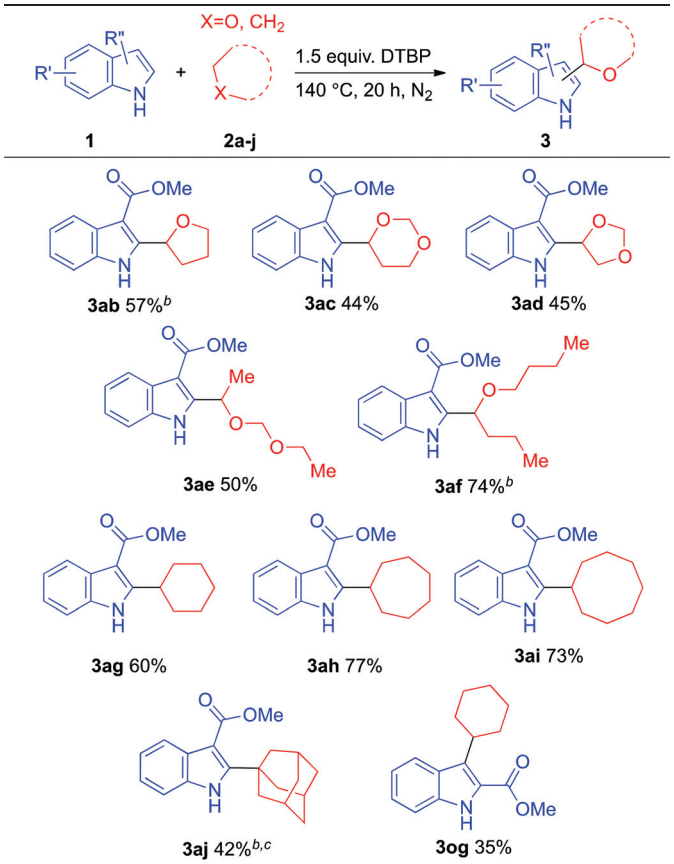


[a] Reaction conditions: substituted indoles **1a–1p** (0.5 mmol), 1,4-dioxane (**2a**) (2 mL), and DTBP (0.75 mmol, 1.5 equiv.) were stirred at 140 °C under N_2 for 20 hours. Isolated yields are reported. Reaction times are not optimized for each substrate.

optimal stoichiometry of DTBP employed was 1.5 equivalents with respect to **2a** (entry 1). The best yield was obtained under a nitrogen atmosphere (entry 13).

With the optimized reaction conditions in hand, we next tested the scope of this transformation (Table 2). A series of unprotected N–H indole derivatives coupled well with 1,4-dioxane to give the corresponding products in good yields. When the bulkiness of the ester-substituted group was increased, the yield of the desired product decreased (*e.g.*, product **3aa** *vs.* product **3da**). To the best of our knowledge, there have been no successful examples of indoles containing ketone and cyano groups in the oxidative C–C coupling with cyclic ethers. Gratifyingly, the reaction protocol displayed a good functional group tolerance, and bromo (*e.g.*, product **3ga**), keto (*e.g.*, product **3ha**, **3ia**), and cyano groups (*e.g.*, product **3ka**) were found compatible under these conditions.

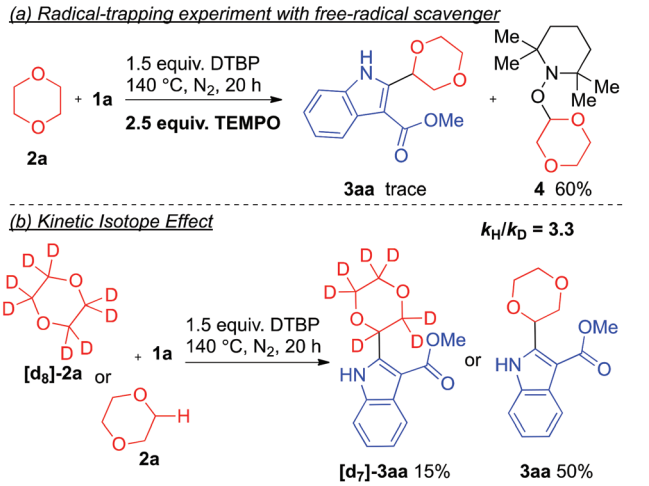
Table 3 Cross-dehydrogenative-coupling reaction of indoles with various ethers and cycloalkanes[a]



[a] Reaction conditions: substituted indole **1a** or **1o** (0.5 mmol), ether or cycloalkane **2a–j** (2 mL), and DTBP (0.75 mmol, 1.5 equiv.) were stirred at 140 °C under N_2 for 20 hours. Isolated yields are reported. Reaction times are not optimized for each substrate. [b] 2.0 mmol of DTBP was used. [c] 5 equivalents of **1j** were used with 2 mL of xylene as a solvent.

Surprisingly, the aldehyde group remained intact under these reaction conditions with moderate yield (*e.g.*, product **3ja**). *N*-Protected indole derivatives were suitable substrates for this reaction with a lower yield possibly due to the steric effect (*e.g.*, product **3la**). Apart from the C–C bond formation at the C-2 position of indoles, C-3 target products could also be afforded under this protocol (*e.g.*, products **3oa** and **3pa**).

We next turned our attention to extend the substrate scope regarding the ether coupling partner and the results are compiled in Table 3. Apart from 1,4-dioxane, other ethereal entities were tested. Cyclic ethers such as tetrahydrofuran (**2b**), 1,3-dioxane (**2c**), and 1,3-dioxolane (**2d**) coupled smoothly with moderate yields (*e.g.*, products **3ab**, **3ac**, and **3ad**). Acyclic ethers including diethoxymethane (**2e**) and dibutyl ether (**2f**) also underwent the coupling and gave the corresponding coupled products **3ae** and **3af** in 50% and 74% isolated yields, respectively. In order to evaluate the scope of this system, we attempted to use cycloalkanes as the coupling partners instead of cyclic ethers. When cyclohexane was used, the desired coupling product was obtained in 60% yield (*e.g.*, product **3ah**). Cycloheptane and cyclooctane were also feasible coupling partners to yield the desired products (*e.g.*, products **3ah** and **3ai**). It is noteworthy that the bulky adamantane also underwent the target reaction (*e.g.*, product **3aj**).



Scheme 2 Control experiments for the CDC reaction of 1,4-dioxane with indole **1a**.

To verify whether the reaction proceeded through a radical pathway, a radical trapping experiment was conducted. When 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was added, a drastic suppression of the reaction resulted and only a trace amount of the desired product **3aa** was detected whereas the 1,4-dioxane-TEMPO coupling product was isolated (Scheme 2a). These results suggested that this reaction likely proceeds *via* a free-radical intermediate. Meanwhile, a kinetic isotopic effect (KIE) experiment was also performed for probing the dependence of C–H bond cleavage (Scheme 2b). As is depicted, a significant KIE was observed with k_H/k_D = 3.3. This result indicated that the –C–H bond cleavage of 1,4-dioxane could be the kinetically-dependent rate-limiting step of this reaction. Based on the reported literature,[8] it is believed that a *tert*-butoxyl radical was generated by homolytic cleavage through thermal decomposition of di-*tert*-butyl peroxide. Then, the *tert*-butoxyl radical undergoes a hydrogen abstraction of the α-proton adjacent to the oxygen atom of the cyclic ether to afford an ether radical. The radical species further undergoes addition to the indole derivative, followed by SET leading to the oxidative coupling final product.

Conclusions

In summary, we have demonstrated an effective metal-free method for a cross-dehydrogenative-coupling reaction between indole derivatives and ethers/cycloalkanes. The usage of rich feedstock starting materials (*e.g.* non-prefunctionalized simple cyclic ethers and cycloalkanes), good compatibility of functional groups (*e.g.* bromo, keto, nitrile, ester, N–H amino and

aldehyde) and particularly without the need of transition metal catalysts underline the advantage of this straightforward protocol. This also shows the first examples of the CDC reaction between indole derivatives and cycloalkanes under metal-free reaction conditions.

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