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Di-*tert*-butyl Peroxide (DTBP)-Mediated Oxidative Cross-Coupling of Isochroman and Indole Derivatives

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Abstract: A metal-free C–C bond formation method *via* the oxidative cross-coupling reaction of isochroman and indole derivatives was established. Various α-fuctionalized cyclic ethers were achieved in satisfactory yields using di-*tert*-butyl peroxide (DTBP) as the oxidant. This method is also a potentially efficient strategy for the construction of cyclic ether-containing targets.

Keywords: C–C bond formation.; C–H activation; α-fuctionalized cyclic ethers; metal-free conditions

Introduction

Progress in methods for the selective functionalization of C–H bonds has enabled the efficient construction of a tremendous variety of organic compounds of relevance in materials science and medicinal chemistry.[1] Among them, recently developed dehydrogenative cross-coupling (CDC) reactions for the formation of various C–C and C–heteroatom bonds have attracted much attention.[2] Pioneered by the study of Zhao and Li in 2008,[3] great progress has been achieved in this area. Privileged palladium,[4a–c] copper,[4d–f] and iron[4g–i] catalysts were employed owing to the highly desirable atom-economy. However, most of the reactions were catalyzed by metal salts in combination with stoichiometric oxidants such as TBHP, DTBP and DDQ.[4a–i] More recently, organocatalysis has proven to be an alternative to these transition metal-mediated oxidative couplings involving C(sp^3)–H bond cleavage.[5] Since the oxidative couplings of glycine derivatives[6] and *N*-aryltetrahydroisoquinolines[6] have been well documented, further explorations were turned to other cyclic derivatives such as isochroman, 1,3-dithiane and cyclohexane.[7]

α-Substituted ethers are common structural motifs that widely exist in natural products and pharmaceuticals with diverse biological activities.[8] 1-Substituted isochromans have been demonstrated to have unique pharmacological activities, similar to the more complicated bioactive compounds.[8a,9] Consequently, functionalization of C(sp^3)–H bonds adjacent to the oxygen atom of isochroman or analogous heterocyclic skeletons represents an interesting topic in formal C–H bond activation reactions. Some recent developments have been achieved as follows:[10a–f] Li's group developed a CDC pathway to realize the functionalization of *N*-arylated tetrahydroisoquinolines employing copper(I) bromide as the catalyst and *tert*-butyl hydroperoxide as the oxidant in 2005.[10a] Later, Pan's group demonstrated an iron-catalyzed esterification of inactive C(sp^3)–H bonds in 1,4-dioxane with carboxylic acids.[10b] Very recently, Liu's group reported the selective direct construction of diverse α-functionalized ethers by use of the trityl ion and a Lewis acid catalyst at ambient temperature.[10c]

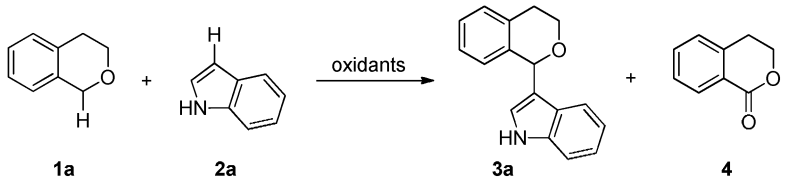
Radical-based reactions lead to mostly spontaneous processes in natural systems ranging from protein damage to aging and diseases.[11] Thus exploring the metal-free approach to develop radical reactions[12] could be conceived as a more "natural" strategy for the synthesis of complicated pharmaceutical compounds, whose syntheses traditionally rely on transition metal-catalyzed reactions. Inspired by that, we are engaged in discovering the C(sp^3)–H bond functionalization of isochroman in the absence of metal catalysts or high-pressure oxygen. To our delight, the use of DTBP (di-*tert*-butyl peroxide) allows the easy assembly of the C(sp^3)–C(sp^2) bond from isochroman and indole derivatives. This C–H functionalization strategy to synthesize 3-(isochroman-1-yl)-indoles can be regarded as an efficient and practical alternative for the formation of α-substituted ethers.

Results and Discussion

We initiated our study by investigating the C(sp^3)–C(sp^2) coupling between isochroman **1a** and indole **2a** to generate **3a**. We tried to use molecular oxygen as the terminal oxidant at first. Thus ideally, water would be only by-product. However, only a 15% yield the desired product was observed and the yield was not improved obviously though screening of previously developed conditions.[5a] (Table 1, entries 2–4) The low yield and long reaction time indicated the limited reaction efficiency. Then, chemical oxidants such as TBHP, DTBP and DDQ were tested for the reaction. After a brief survey of plausible conditions (Table 1, entries 5–9), the desired product **3a** was obtained in 76% yield along with isochroman-1-one (**4**) as the by-product using DTBP as the single oxidant under solvent-free conditions. Solvents were screened to further optimize the reaction. However, we found no significant increase of the yield in the presence of DCE, even slight decreases were observed in PhCl and MeCN (Table 1, entries 10–12). It was also found that a lower reaction temperature (Table 1, entry 13) and smaller amount of DTBP (Table 1, entry 14) diminished the yields to 47% and 53%, respectively. Besides, increasing the amount of DTBP also did not show any significant improvement (Table 1, entry 15). Eventually we chose 1.2 equivalents of DTBP without solvent as the optimized conditions for the procedure. In order to examine the effect of oxygen, we conducted the reaction under an atmosphere of argon which did not affect the yield (Table 1, entry 17).

With the optimized conditions in hand, we next examined the substrate scope for the reaction. Various indole derivatives were smoothly coupled with isochroman, giving the target products in moderate to good yields. Generally, as is shown in Table 2, indoles bearing electron-withdrawing (Table 2, **3k–m**, **3p–s**) and eletron-neutral (Table 2, **3d**) groups gave good yields. Electron-donating groups such as methyl and methoxy were tolerated (Table 2, **3b** and **3c**), but led to lower yields as compared to the electron-deficient indole substrates. It is worth noting that under our standard conditions, substituents on the 1- and 2-positions of indoles had a significant influence on the reaction. Instead, when indoles were substituted on the 6- and 7-positions, the electronic effect of the substituents played a lesser role on reaction yields,

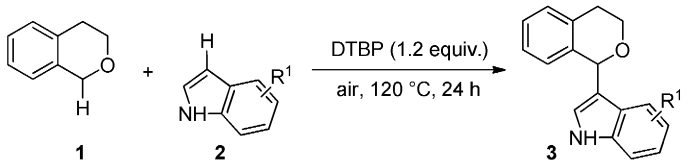
Table 1. Optimization of the reaction conditions.[a]



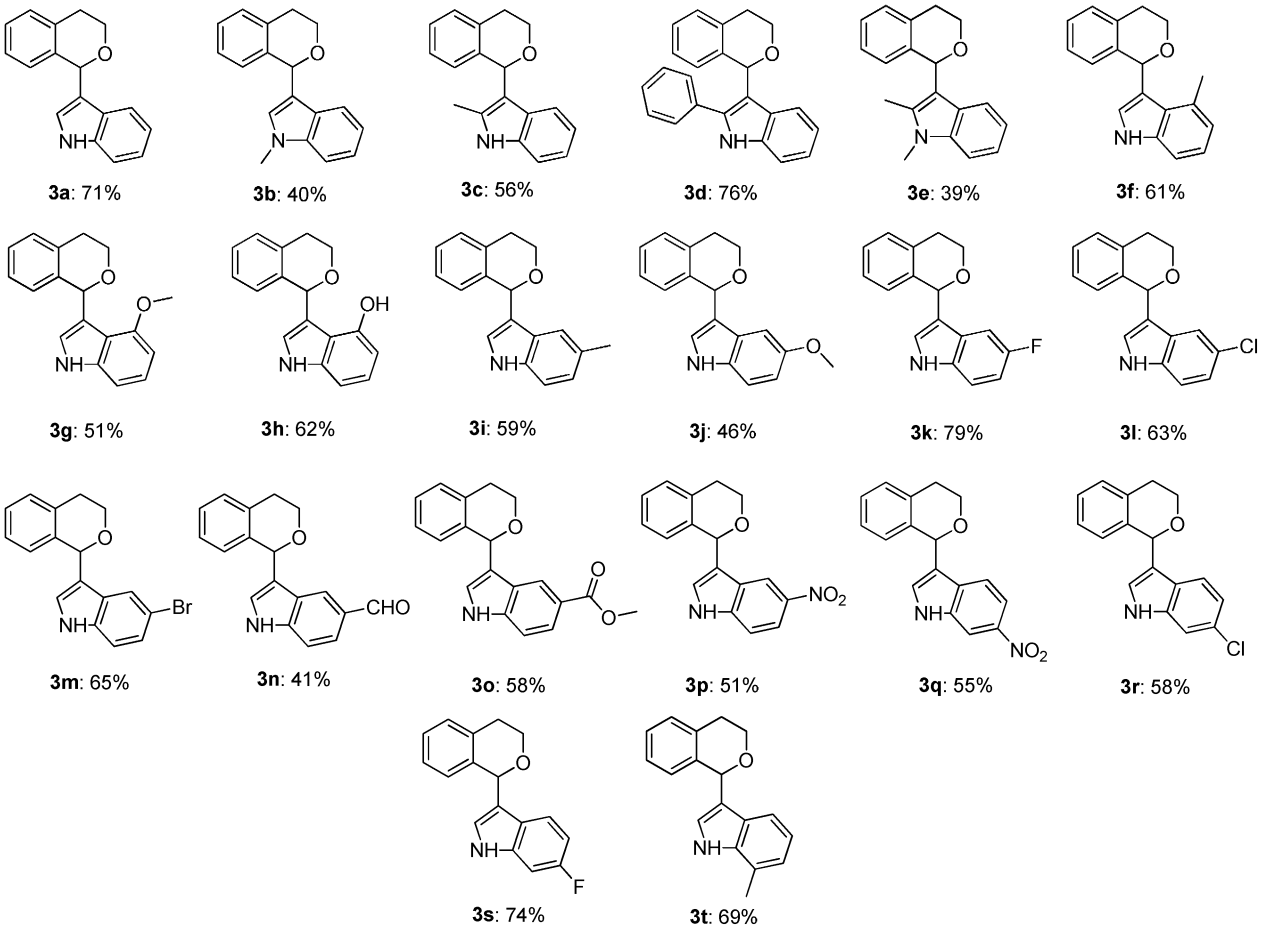
Entry	Oxidant	Solvent	Temp. [°C]	Time [h]	Yield of **3a**[b] [%]	Yield of **4**[b] [%]
1	–	–	120	24	0	0
2	O_2	MeCN	120	24	3	0
3	O_2	MeCN/DCE	120	72	12[c]	5[c]
4	O_2	MeCN/DCE	140	72	15[c]	10[c]
5	TBHP (1.2 equiv.)	–	120	24	0[d]	0[d]
6	TBHP (1.2 equiv.)	–	120	24	34[e]	0[e]
7	DTBP (1.2 equiv.)	–	120	24	76	5
8	DDQ (1.5 equiv.)	–	120	24	1	16
9	BPO (1.2 equiv.)	–	120	24	0	0
10	DTBP (1.2 equiv.)	DCE	120	24	71	7
11	DTBP (1.2 equiv.)	PhCl	120	24	58	0
12	DTBP (1.2 equiv.)	MeCN	120	24	47	0
13	DTBP (1.2 equiv.)	–	80	24	40	0
14	DTBP (0.5 equiv.)	–	120	24	53	0
15	DTBP (3 equiv.)	–	120	24	9	58
16	DTBP (1.2 equiv.)	–	120	36	78	4
17	DTBP (1.2 equiv.)	–	120	24	70[f]	5[f]

[a] *Reaction conditions:* isochroman (1.2 mmol) and indole (1 mmol).
[b] GC yield.
[c] Under the conditions of mixed solvent: MeCN/DCE (5:1).
[d] TBHP (70% in water).
[e] TBHP (~5.5 M in decane).
[f] Reaction conducted under an argon atmosphere.

Table 2. DTBP-mediated oxidative coupling of isochroman with indoles.[a]



1 2 3



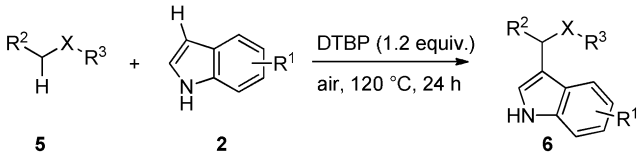
[a] *Reaction conditions:* isochroman (1.2 mmol), indoles (1 mmol) and 1.2 mmol DTBP at 120 °C in 24 h. Isolated yields.

namely, the target products bearing strong electron-withdrawing and electron-donating groups tended to show small distinctions on yields (Table 2, **3s** *vs.* **3t**).

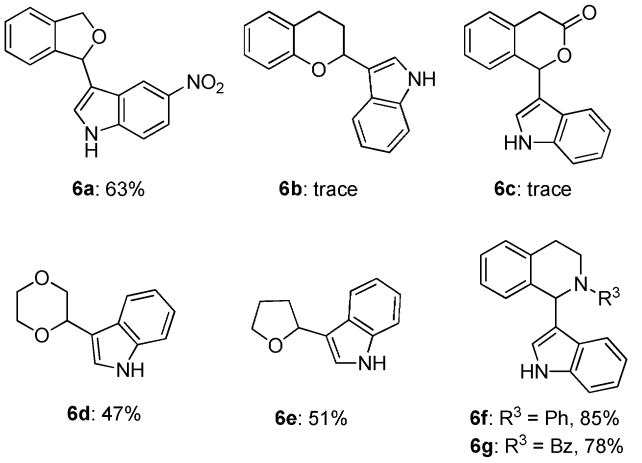
To further extend the substrate scope, we subsequently turned our attention to investigate ethers and the analogous heterocycles (Table 3). Besides isochroman, other saturated cyclic ethers including 1, 3-dihydroisobenzofuran (**5a**), 1, 4-dioxane (**5d**) and THF (**5e**) were compatible with the reaction, though lower yields were obtained. Chroman (**5b**) and isochroman-3-one (**5c**) were not good substrates for the reaction, and only traces of the products were detected. Besides ether candidates, the scope was further extended to *N*-substituted tetrahydroisoquinolines (**5f** and **5g**). To our delight, the cross-couplings of **5f** and **5g** under our standard conditions afforded the desired products **6f** and **6g** in 85% and 78% yields, respectively.

To gain some insight into the mechanism of this transformation, control experiments were carried out. As is shown in Scheme 1, we first conducted the reaction without indole, which resulted in **4** in 59% yield. Then, 4 equivalents of TEMPO were added to the reaction as a radical inhibitor. As expected, no desired product was observed, indicating that a radical process is involved in the transformation. Meanwhile, the coupling between indole (**2a**) with isochroman (**1a**) under an argon atmosphere resulted in no significant decrease of the yield suggesting that oxygen is not essential for the procedure. When the reaction was run under argon without DTBP, neither **3a** or **4** was detected.

Table 3. Scope of cyclic ethers and heteroatom-containing components.[a]



5 2 6

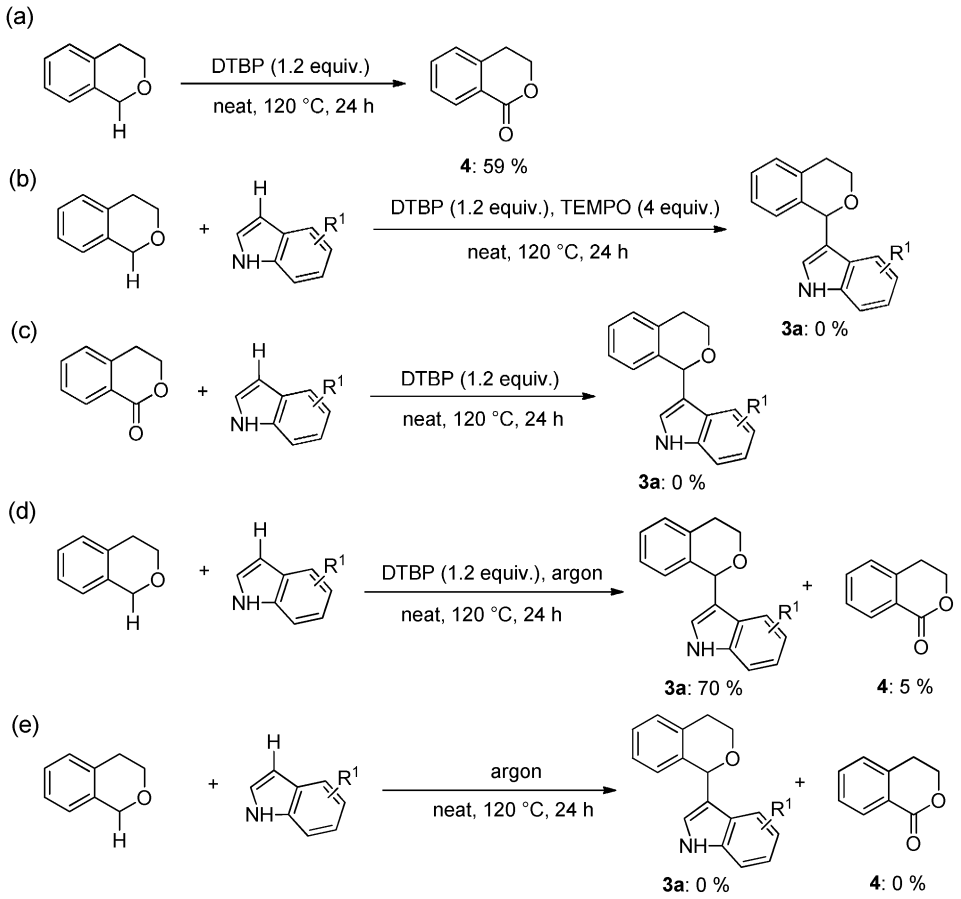


6a: 63% **6b**: trace **6c**: trace

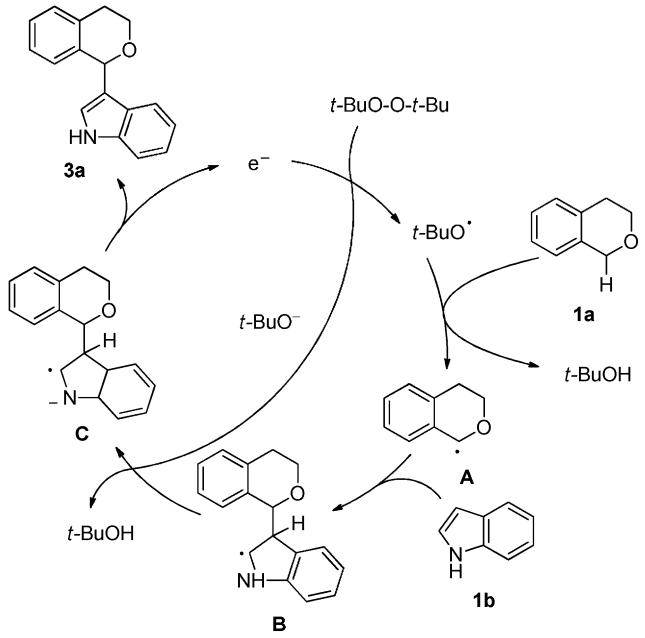
6d: 47% **6e**: 51% **6f**: R^3 = Ph, 85% **6g**: R^3 = Bz, 78%

[a] *Reaction conditions:* **5** (1.2 mmol), indoles (1 mmol) and 1.2 mmol DTBP at 120 °C in 24 h. Isolated yields.

According to the results above and recent reports,[6d,10d–g,13] a working hypothesis for the reaction pathway is depicted in Scheme 2. An electron-catalyzed formal C(sp^2)–C(sp^3) cross-coupling was involved in the process. The *tert*-butoxyl radical is first generated by the thermal decomposition of di-*tert*-butyl peroxide (DTBP). Then the isochroman-derived benzylic radical **A** is formed through hydrogen abstraction of the sp^3 C–H bond adjacent to the oxygen atom. After that, the benzylic radical **A** adds to indole at the C-3 position, and it is known that radicals readily react with indoles selectively at the C-3 position. Subsequently, the generated adduct radical **B** bearing an acidic NH proton is deprotonated by *tert*-butanolate in the chain. After deprotonation, the radical anion **C** is then formally liberating an electron to give the product **3a** and meanwhile reducing DTBP *via* electron transfer to give the *tert*-butoxyl radical and the *tert*-butanolate. The *tert*-butanolate acts as a base in the chain reaction and the *tert*-butoxyl radical formed in the process then sustains the chain.



Scheme 1. Control experiment for the oxidative coupling of isochroman with indoles.



Scheme 2. Proposed mechanism.

Conclusions

In summary, DTBP enables the assembly of new carbon-carbon bonds between isochroman and indole derivatives effectively *via* a metal-free cross-coupling process. The synthetically valuable procedure tolerates a broad range of substrates, which provides an alternative method for the preparation of various α-substituted cyclic ethers. Further studies in our laboratory are dedicated towards the exploitation of regio- and stereocontrol over the final cyclic ethers.

Experimental Section

General Procedure for DTBP-Mediated Oxidative Cross-Couplings of Isochroman and Indole Derivatives

Isochroman (**1**) (1.2 mmol), DTBP (1.2 mmol) and indole (**2**) (1 mmol) were sequentially added to a Schlenk tube with a magnetic stir bar. The resulting mixture was stirred at 120 °C for 24 h. After that, the reaction mixture was allowed to cool to ambient temperature, and then diluted with ethyl acetate, washed with water, dried over anhydrous Na_2SO_4. After the solvent had been removed under reduced pressure, the residue was purified by flash chromatography using PE-AcOEt (10:1–5:1, v/v) as the eluent to give 3-(isochroman-1-yl)-indoles (**3**). Other 3-indolyl cyclic ethers were prepared similarly.

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