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Cross-dehydrogenative coupling of secondary benzylic ethers with indoles and pyrroles

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ABSTRACT

Current studies on cross-dehydrogenative coupling of benzylic ethers for new C–C bond construction predominantly focus on primary ether moieties. Oxidative cross-coupling of secondary benzylic ethers remains elusive. Herein, we describe the first cross-dehydrogenative coupling of secondary benzylic ethers with indoles and pyrroles for tertiary ether construction. A broad range of α-aryl substituted isochromans react with a variety of electronically varied indoles and pyrroles smoothly under mild metal-free conditions in high efficiency. In addition, the catalytic asymmetric variant was preliminarily explored, and corresponding tertiary ether was obtained in 69% ee.

Cross-dehydrogenative coupling (CDC) of two readily available C—H components for C—C bond construction under oxidative conditions has been regarded as one of the most straightforward and economical approaches for increasing molecular complexity and functional group content with minimal waste generation [1,2]. During the past decade, considerable progress has been achieved in the CDC reactions involving benzylic ether substrates [3,4]. However, existing studies always focused on the manipulation of methylene C—H bonds of primary benzylic ethers for corresponding secondary ether preparation [4]. To the best of our knowledge, a CDC reaction of secondary benzylic ethers involving the functionalization of methine C—H bonds for tertiary ether synthesis has never been established to date, which might be ascribed to the increased steric hindrance of both the substrate and highly substituted oxocarbenium intermediate.

α-Substituted isochromans are common structural motifs in a number of natural products and synthetic pharmaceuticals with diverse biological activities [5]. In particular, isochromans having α-tetrasubstituted stereocenters show antioxidative, anticancer, antibacterial, antifungal, antiviral, and antidepressive activities [6]. Inspired by the significance of the skeletons in modern pharmacology, considerable efforts have been made to their preparation, and current syntheses mainly rely on the *O*-heterocycle construction strategy involving cyclization reactions of prefunctionalized alcohol substrates [7]. On the other hand, indole and pyrrole moieties are also key skeletons in numerous molecules possessing a wide range of pharmaceutical activities [8]. Considering that structurally diverse α-monosubstituted isochromans can be readily prepared by a number of methods, the CDC of the secondary ethers with indoles and pyrroles would be highly desired for rapid construction of α,α-disubstituted isochroman-based libraries for biologically active small molecule discovery.

Initially, the CDC of α-PMP (4-methoxyphenyl) substituted isochroman **1a** and indole **2a** was selected as the model reaction for optimization (Table 1). The oxidation was conducted prior to the introduction of **2a** to avoid the direct quench between oxidant and nucleophile. Several commonly employed reagents for ether oxidations were applied to the CDC reaction. ^{t}BuOOH and PhI$(OAc)_2$ did not promote the oxidation, and all the starting **1a** was recovered (entries 1 and 2, Table 1). Ph_3CClO_4 effected the oxidation, and all the **1a** was consumed (entry 3, Table 1). However, no expected **3a** was detected, and a ring opening byproduct was observed [9]. TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl) oxo-ammonium effected the coupling, and the expected **3a** was obtained in 16% yield (entry 4, Table 1). When DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) was used as the oxidant, the CDC reaction proceeded smoothly in CH_2Cl_2 at room temperature in 85% yield (entry 5, Table 1). The solvent effect on the reaction efficiency was also examined, and obvious loss of efficiency was observed when the reaction was conducted in toluene and ethyl acetate (entries 6 and 7, Table 1). When THF was used as the solvent, all the starting **1a** was consumed, but no discriminable

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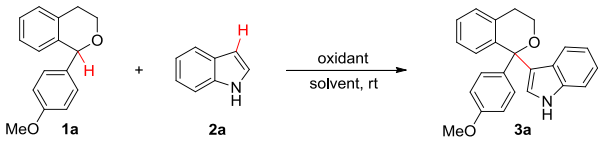
Table 1
Reaction condition optimization.[a]



Entry	Oxidant	Solvent	Yield[b] (%)
1	^{t}BuOOH	CH_2Cl_2	<5
2	$PhI(OAc)_2$	CH_2Cl_2	<5
3	Ph_3CClO_4	CH_2Cl_2	<5
4	$TEMPO^+BF_4^-$	CH_2Cl_2	16
5	DDQ	CH_2Cl_2	85
6	DDQ	toluene	50
7	DDQ	EtOAc	61
8	DDQ	THF	<5
9[c]	DDQ	CH_2Cl_2	<5

[a] General conditions: **1a** (0.1 mmol), oxidant (0.12 mmol) in solvent (1.0 mL) at rt for 0.5 h followed by **2a** (0.15 mmol) at rt for 3 h.
[b] Isolated yield.
[c] **2a** was added prior to DDQ.

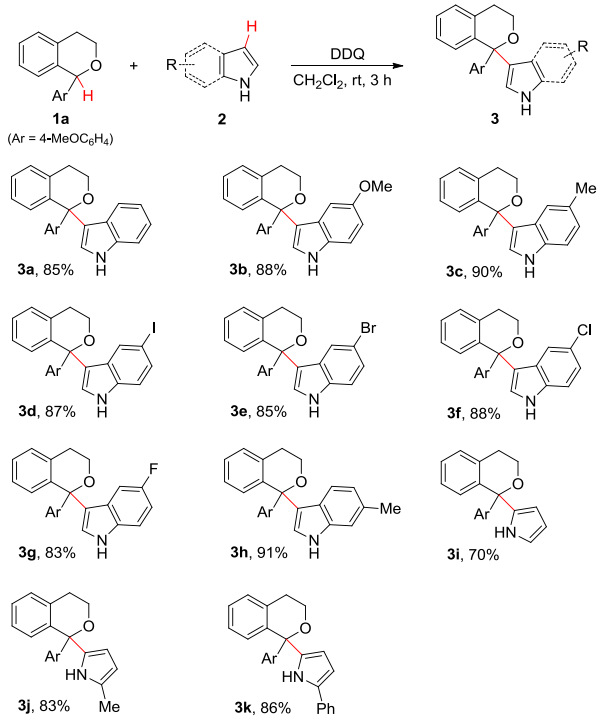
product was isolated (entry 8, Table 1). Performing the oxidation after the introduction of indole **2a** also failed to provide any expected **3a**, which might be ascribed to the incompatibility of indole with DDQ (entry 9, Table 1).

The scope of oxidative cross-coupling of α-PMP (*p*-methoxy phenyl) substituted isochroman **1a** with diverse indole components was next explored (Scheme 1). The CDC efficiency proved to be unsusceptible to the electronic substituent properties on indoles, as demonstrated by the generation of isochromans **3a**–**3g** bearing α-tetrasubstituted stereocenters in 83–90% yield. Indole **2h** with a methyl substituent at the 6-position was a suitable coupling partner, and corresponding **3h** was isolated in 91% yield. Pyrroles were also found to be competent components under the standard conditions. Simple pyrrole **2i**, 2-methyl substituted **2j**, and 2-phenyl substituted **2k** participated in the CDC reaction smoothly, furnishing respective **3i**–**3k** with up to 86% yield.

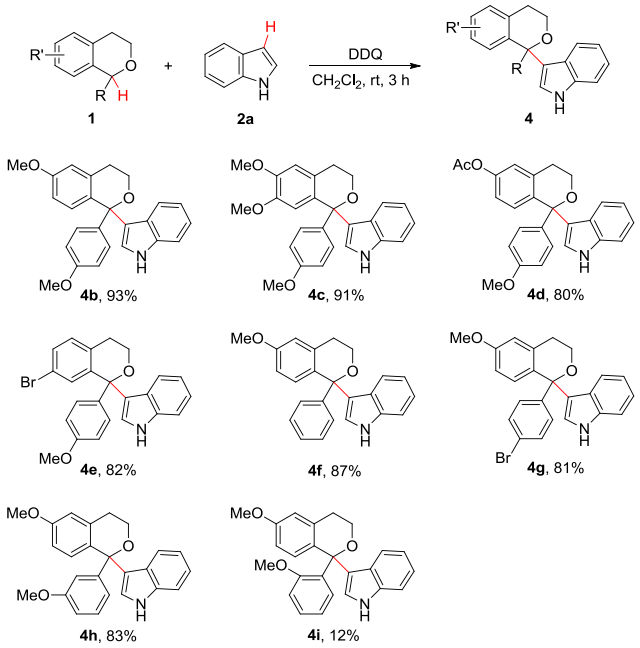
The scope with respect to α-substituted isochromans was further investigated (Scheme 2). Isochromans **1b**–**1e** bearing either electron-donating or -withdrawing groups at C_6 or C_7 position were well compatible with the standard CDC reaction conditions, providing the expected tertiary ethers **4b**-**4e** in good yields. Besides the PMP moiety, simple phenyl (**1f**) and electron-deficient aryl (**1g**) groups at the α-position of isochroman were well tolerated in 87% and 81% yields, respectively. Isochroman **1h** bearing an α-aryl group with a substituent at the meta-position was also a suitable substrate. An extremely obvious loss of efficiency was observed for isochroman **1i** bearing a 2-methoxyphenyl group at the α-position, which might be ascribed to the increased steric hindrance of both the ether substrate and highly substituted oxocarbenium intermediate. The mild CDC condition exhibits good functional group compatibility, with halogens and acetate tolerated for further manipulations.

Under the standard conditions, a gram-scale CDC reaction of **1e** with **2a** proceeded smoothly without obvious loss of reaction efficiency, thus demonstrating the practicability of the method (Scheme 3).

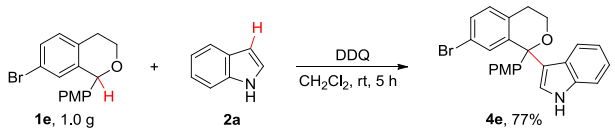
Catalytic asymmetric CDC reaction has received considerable attentions during the past decades [10,11]. However, to our knowledge, a catalytic asymmetric CDC process leading to quaternary carbon center has never been reported to date. Accordingly, the catalytic enantioselective variant of the reaction was then explored and the preliminary result was shown in Scheme 4. Performing the oxidation of **1a** with DDQ and MeOH additive at room temperature, followed by chiral phosphoric acid **5** catalyzed indole addition at −78 °C provided the expected **3a** in 71% yield and 69% ee [12]. Although the optimization of the reaction was not exclusively optimized, the result provided a proof-of-concept for the development of catalytic asymmetric tertiary ether synthesis.



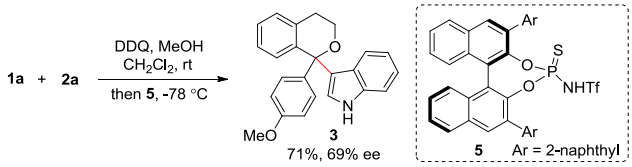
Scheme 1. Scope of indole and pyrrole moieties.



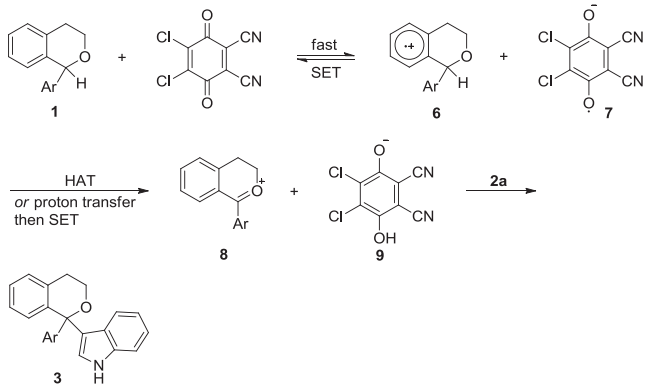
Scheme 2. The scope of α-substituted isochroman.



Scheme 3. A gram-scale experiment.



Scheme 4. Catalytic asymmetric CDC reaction development.



Scheme 5. A proposed reaction mechanism.

The CDC reaction was completely blocked by 1 equivalent of the radical inhibitor TEMPO, thus implying that a radical intermediate might be involved in the process. According to mechanistic studies on DDQ-mediated primary benzylic ether oxidation, a plausible mechanism for CDC of secondary ethers with indoles was suggested (Scheme 5) [13]. We envisioned that secondary ether **1** underwent a single electron transfer (SET) to DDQ affording radical cation **6** together with DDQ radical anion **7**. **6** might either undergo a hydrogen atom transfer (HAT) to **7** or a proton abstraction by **7** followed by another SET giving 1,1-disubstituted oxocarbenium intermediate **8**. A subsequent nucleophilic attack of indole **2a** onto **8** provided the expected isochroman **3** with an α-tetrasubstituted stereocenter.

In summary, the first CDC reaction of secondary benzylic ethers for tertiary ether construction is described. The metal-free oxidative cross-coupling of a broad range of α-aryl substituted isochromans with electronically varied indole and pyrrole components proceeded smoothly at ambient temperature in high efficiency, thus allowing for rapid preparation of a library of isochromans bearing structurally diverse α-aryl-heteroaryl substituent patterns for subsequent biologically active small molecule discovery. The catalytic asymmetric variant was preliminarily explored, and corresponding tertiary ether was obtained in 69% ee. The systematic study on the catalytic asymmetric variant development would be reported in a due course.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.03.032.

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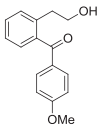
9  was isolated as the byproduct.
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