Synthetic Methods Hot Paper

DOI: 10.1002/anie.201308701

Catalytic Enantioselective Oxidative Cross-Coupling of Benzylic Ethers with Aldehydes**

Zhilin Meng, Shutao Sun, Huiqing Yuan, Hongxiang Lou, and Lei Liu**

Abstract: *The first one-pot enantioselective oxidative coupling of cyclic benzylic ethers with aldehydes has been developed. A variety of benzylic ethers were transformed into the corresponding oxygen heterocycles with high enantioselectivity. Mechanistic experiments were conducted to determine the nature of the reaction intermediates. The application of this strategy to coupling reactions with other nucleophiles besides aldehydes was also explored.*

The nucleophilic addition to a prochiral cyclic oxocarbenium ion provides a powerful and efficient strategy for the synthesis of α-substituted oxygen heterocycles, which are common structural motifs in complex natural products and biologically active molecules.[1] Although various reliable methods have been developed for diastereoselective additions to oxocarbenium ions, only a few catalytic enantioselective variants have been reported.[2] Jacobsen et al. described an innovative thiourea-catalyzed asymmetric addition of silyl ketene acetals to 1-chloroisochroman-derived oxocarbenium ions through an anion binding protocol.[3a] Schaus and co-workers disclosed a highly enantioselective addition of boronate esters to chromene acetals that was catalyzed by a chiral Brønsted acid together with an achiral Lewis acid.[3b] Recently, Watson et al. reported the enantioselective copper(I)-catalyzed addition of arylacetylene to oxocarbenium ions that were derived from isochroman acetals.[3c] In all of these reactions, oxocarbenium ions are generated in situ through the acid-mediated collapse of cyclic acetals; however, these methods suffer from extra steps[4] that are required for substrate construction.

On the other hand, the formation of oxocarbenium ions can be initiated by the selective oxidation of a C–H bond adjacent to an oxygen atom. This strategy provides excellent opportunities to access a target compound from readily accessible precursors with a minimal amount of intermediary refunctionalizations and with high atom economy.[4b,5] The cross-dehydrogenative coupling (CDC) of two C–H bonds is a particularly elegant process.[6,7] The majority of such CDC reactions involve the functionalization of the C–H bond in the α-position of an amine nitrogen atom,[8] whereas only few precedents focus on the coupling of a C–H bond in the α-position of an ethereal oxygen atom, probably because of the higher oxidation potential of the latter.[9] Recently, García Mancheño and co-workers described the α-alkylation of aldehydes with isochromans by C–H activation in the presence of a TEMPO-derived oxoammonium salt (2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate), $Cu(OTf)_2$, and Ac_2O.[9j] However, the development of the corresponding catalytic asymmetric variants of such transformations is highly challenging, mainly because the C–H oxidation process often requires harsh reaction conditions; therefore, the oxidants are often incompatible with the chiral catalyst system. To the best of our knowledge, a catalytic enantioselective CDC reaction of benzylic ethers has not been reported to date.[10] Given the importance of O-heterocyclic motifs in biologically relevant molecules and the fact that the asymmetric alkylation of aldehydes[11–13] would afford heterocycles with multiple stereogenic centers, we herein describe the first enantioselective oxidative cross-coupling of cyclic benzylic ethers with aldehydes.

First, the coupling of commercially available isochroman and pentanal was investigated in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and an amine catalyst. However, the desired product was not observed when the two coupling partners, DDQ, and the MacMillan catalyst **A**·TFA were mixed together (Table 1, entry 1). According to mechanistic studies on the DDQ-mediated ether oxidation,[14] we reasoned that the generated oxocarbenium ion was not stable enough to be captured by the chiral enamine. Therefore, protic additives, such as H_2O and MeOH, were employed in the hope of increasing the stability of the intermediate by formation of the corresponding ether dimer or by acetal formation.[15] However, these additives had no effect on the coupling (entry 2). Precedent reports that the counterion of the generated oxocarbenium ion was crucial to its electrophilicity[16] encouraged us to investigate the influence of metal-salt additives. Although $LiClO_4$ scarcely promoted the reaction (entry 3), the desired product **3a** was observed in 12% yield with 26% *ee* when both $LiClO_4$ and H_2O were present together with catalyst **A**·TFA (entry 4). Free amine **A** was inferior to its TFA salt in terms of conversion and *ee* (entry 5). Several different addition procedures were tested, and finally we were pleased to find that the reaction

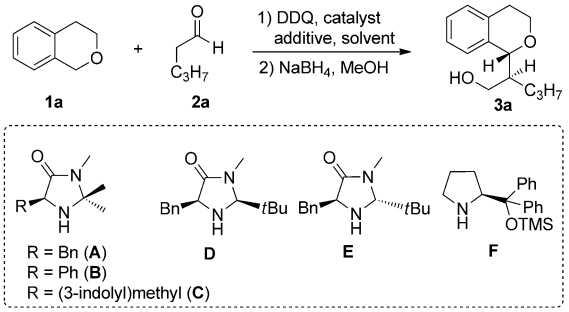
[*] Z. Meng, S. Sun, Prof. Dr. H. Lou, Prof. Dr. L. Liu
Department of Natural Products Chemistry
Key Lab of Chemical Biology of Ministry of Education
School of Pharmaceutical Sciences, Shandong University
Jinan 250012 (P. R. China)
E-mail: louhongxiang@sdu.edu.cn
leiliu@sdu.edu.cn

Prof. Dr. H. Yuan
Department of Biochemistry and Molecular Biology
School of Medicine, Shandong University
Jinan 250012 (P. R. China)

[**] We are grateful to Dr. Paul E. Floreancig (University of Pittsburgh) for helpful suggestions on this manuscript. Financial support from the National Science Foundation of China (21202093 and 30925038) and a Young Scientist Foundation Grant of Shandong Province (BS2013YY001) is greatly appreciated.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201308701.

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



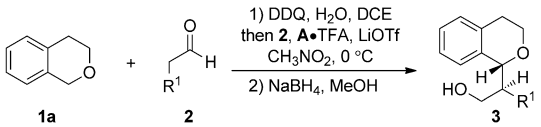
Entry	Amine	Additive	Method[b]	d.r.[c]	Yield[d] [%]	*ee*[e] [%]
1[f]	**A**·TFA	–	a	n.d.	< 5	n.d.
2[g]	**A**·TFA	–	a	n.d.	< 5	n.d.
3[f]	**A**·TFA	$LiClO_4$	a	n.d.	< 5	n.d.
4	**A**·TFA	$LiClO_4$	a	60:40	12	26
5	**A**	$LiClO_4$	a	58:42	7	19
6	**A**·TFA	$LiClO_4$	b	67:33	65	63
7	**A**·HCl	$LiClO_4$	b	57:43	35	32
8	**A**·DCA	$LiClO_4$	b	62:38	55	50
9	**B**·TFA	$LiClO_4$	b	58:42	68	17
10	**C**·TFA	$LiClO_4$	b	69:31	18	35
11	**D**·TFA	$LiClO_4$	b	57:43	51	65
12	**E**·TFA	$LiClO_4$	b	63:37	21	50
13	**F**·TFA	$LiClO_4$	b	n.d.	< 5	n.d.
14	**A**·TFA	LiOAc	b	n.d.	< 5	n.d.
15	**A**·TFA	$Mg(ClO_4)_2$	b	51:49	63	0
16	**A**·TFA	LiOTf	b	63:37	67	80
17	**A**·TFA	$Yb(OTf)_3$	b	61:39	69	66
18[h]	**A**·TFA	LiOTf	b	70:30	72	89
19[h]	**A**·TFA	–	b	n.d.	< 5	n.d.
20[h]	**A**	LiOTf	b	66:24	59	43
21[h,i]	**A**·TFA	LiOTf	b	72:28	69	96

[a] Reaction conditions, unless otherwise specified: **1a** (0.2 mmol), **2a** (0.6 mmol), DDQ (0.2 mmol), catalyst (0.04 mmol), H_2O (0.22 mmol), additives, DCE (2.0 mL), RT, 48 h. [b] Method a: Catalyst and **2a** were added before DDQ oxidation. Method b: Catalyst and **2a** were added after completion of the DDQ oxidation process. [c] Determined by ^{1}H NMR spectroscopy. [d] Combined yield of the two isolated diastereomers. [e] Determined by HPLC analysis on a chiral stationary phase. [f] The reaction was performed without H_2O. [g] H_2O or MeOH were added. [h] CH_3NO_2 was used as the solvent for the nucleophilic-addition step. [i] Nucleophilic addition at 0 °C. Bn = benzyl, n.d. = not determined, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

proceeded most efficiently when the C–H oxidation was performed prior to the addition of the nucleophile, rather than when the nucleophile was added prior to the oxidation.[17] Whereas the C–H oxidation process was facilitated by $LiClO_4$, presumably because the additive activates DDQ by increasing its reduction potential, the involvement of $LiClO_4$ after oxidation resulted in higher enantioselectivity (entry 6). An extensive screen of the Brønsted acid and the chiral imidazolidinones **B**–**E** and pyrrolidine **F** revealed that the phenylalanine-derived catalyst **A**·TFA provided the highest levels of enantiofacial discrimination (entries 6–13). The influence of the additives was further explored, with LiOTf providing the highest enantioselectivity (entries 6 and 14–17). H_2O was superior to a range of other protic additives, including MeOH, *i*PrOH, PhOH, AcOH, and CF_3CH_2OH, in terms of enantioselectivity (Table S3, Supporting Information). The efficiency of the reaction was also highly dependent on the solvent. Extensive screening documented that the C–H oxidation proceeded most efficiently in 1,2-dichloroethane (DCE), whereas the nucleophilic addition worked best in CH_3NO_2 in terms of yield and enantioselectivity (entry 18; see also the Supporting Information). Variation of the reaction temperature indicated that the optimal *ee* value and reaction efficiency were achieved when the reaction was conducted at 0 °C (entry 21; see also the Supporting Information).

With the optimized conditions for the one-pot reaction in hand, the scope of the enantioselective oxidative coupling of isochroman with various aldehydes was extensively investigated (Table 2). In general, the reactions proceeded smoothly to generate the desired alkylation products in good yields (62–79 %) with excellent enantioselectivities (90–96 % *ee*). A variety of functional groups, such as olefins, electronically varied aryl moieties, silyl ethers, and benzyl ethers, were tolerated in this process, demonstrating the capacity of this method in creating diversely functionalized molecules.

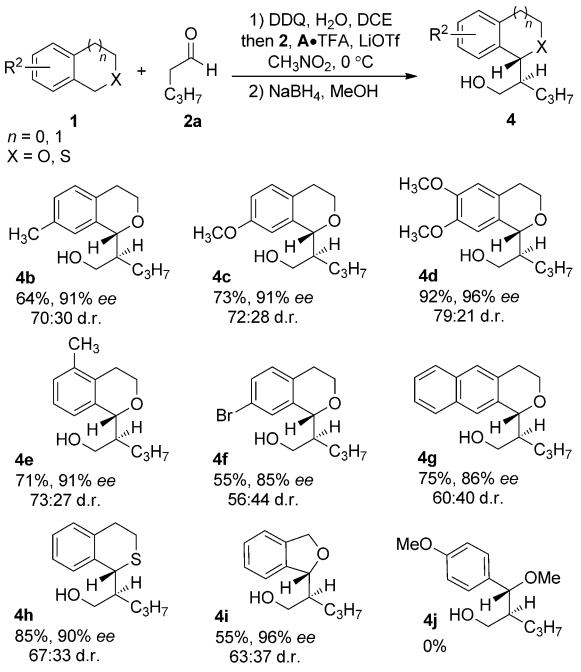
Table 2: Variation of the aldehyde.[a]



Entry	R^1	3	d.r.[b]	Yield[c] [%]	*ee*[d] [%]
1	*n*-propyl	**3a**	72:28	69	96
2	Me	**3b**	69:31	66	93
3	*n*-pentyl	**3c**	78:22	75	95
4	8-nonenyl	**3d**	77:23	67	92
5	Bn	**3e**	73:27	79	96
6	*m*-BrC_6H_4-CH_2	**3f**	64:36	62	92
7	*p*-$MeOC_6H_4$-CH_2	**3g**	75:25	73	95
8	C_4H_8OBn	**3h**	71:29	63	90
9	C_4H_8OTBS	**3i**	70:30	65	94

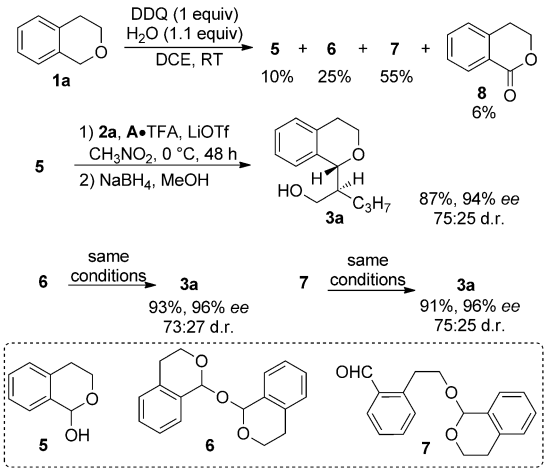
[a] Reaction conditions: **1a** (0.2 mmol), DDQ (0.2 mmol), H_2O (0.22 mmol), DCE (2.0 mL), RT, 16 h; then addition of **2** (0.6 mmol), **A**·TFA (0.04 mmol), LiOTf (0.2 mmol) in CH_3NO_2 at 0 °C for 30–48 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Combined yield of the two isolated diastereomers. [d] Determined by HPLC analysis on a chiral stationary phase.

Good yields and high enantioselectivities were also observed for the functionalization of a variety of cyclic benzylic ethers, although oxidation and nucleophilic addition proceeded more readily with electron-rich substrates than with electron-neutral starting materials (Scheme 1). A bromo substituent (**4f**) was compatible with the oxidation system, which will be beneficial for further diversification. Isothiochroman **1h** and phthalan **1i** were also found to be suitable substrates for the oxidative cross-coupling (**4h** and **4i**). The desired product was not observed when the acyclic benzylic ether **1j** was subjected to the reaction conditions, and benzaldehyde was isolated as the major product.



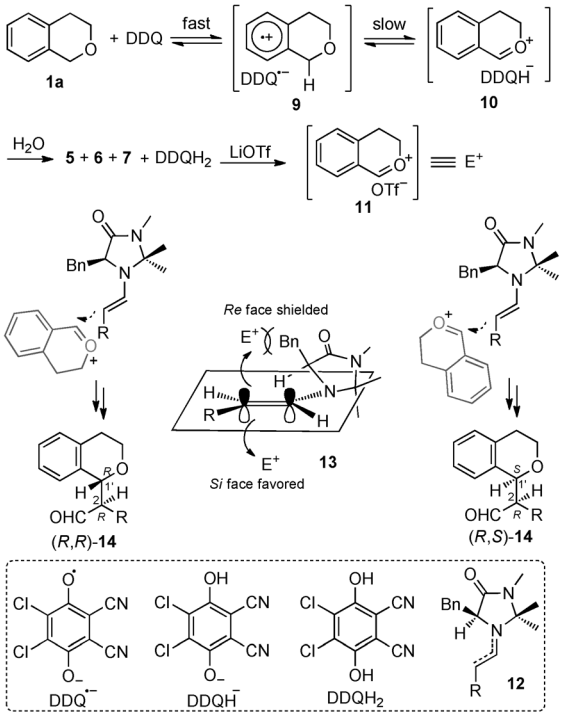
Scheme 1. Variation of the benzylic ether.

The reaction mixture was analyzed upon completion of the oxidation step to determine the identity of the precursors for nucleophilic addition process: ^{1}H NMR analysis of the crude reaction mixture indicated formation of hemiacetal **5** (10%), oxydiisochroman **6** (23%, d.r. = 1:1), aldehyde **7** (57%), and lactone **8** (6%), accompanied by a minute amount of unreacted isochroman (4%; Scheme 2). When isolated **5**, **6**, and **7** were each resubjected to the standard reaction conditions, **3a** was formed in very good yields with excellent *ee*. The enantioselectivity was comparable to that observed for the reaction starting from isochroman **1a** (Table 2, entry 1), which indicates that **5**, **6**, and **7** should be intermediates of the enantioselective one-pot cross-coupling reaction.



Scheme 2. Identification of the reaction intermediates.

A plausible mechanism for the reaction is illustrated in Scheme 3. Isochroman is oxidized by DDQ in a reversible process to form ion pair **10**.[14] H_2O and LiOTf are crucial for the reaction efficiency, as no reaction occurred in the absence of either of these additives (Table 1, entries 1, 3, and 19).



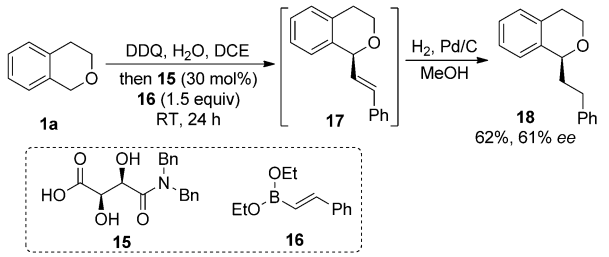
Scheme 3. Stereochemical analysis.

Therefore, we believe that **10** is too weak an electrophile to be attacked by the enamine **12**, so that no conversion into the desired product occurs in the absence of H_2O (Table 1, entry 3). However, when H_2O is added, it reacts with **10** to afford intermediates **5**, **6**, and **7**. As the combination of free amine **A** and LiOTf can enable the coupling reaction in the absence of TFA (Table 1, entry 20), we postulate that LiOTf should act as a Lewis acid to promote the breakdown of the intermediates **5**, **6**, and **7** into ion pair **11**, which is a better electrophile for subsequent nucleophilic attack in terms of yield and *ee*. In the predominant (*E*)-iminium ion **12**,[18a] the benzyl group on the imidazolidinone ring shields the *Re* face of the enamine (**13**), and the oxocarbenium ion will be attacked from the *Si* face of **12** to give **14** with *R* configuration at the C2 position.[18b] The configuration at the C1′ position depends on whether the attack occurs on the *Si* or *Re* face of the intermediate. The absolute and relative configurations of **14** were determined by X-ray diffraction analysis of the corresponding sulfonic and benzoic esters, respectively (see the Supporting Information).

The biological importance of isochroman derivatives prompted us to evaluate the biological activity of the products. Three randomly selected compounds (**3g**, **4d**, and **4f**) exhibited inhibitory activity in human prostate cancer

(PC3) cells with IC_{50} values in the range of 18.1–29.7 μM (see the Supporting Information). These preliminary results suggest that our isochroman derivatives are promising anticancer agents that are worthy of further exploration.

Further preliminary studies suggest that the one-pot strategy will also be applicable to the enantioselective functionalization of benzylic ethers with other classes of nucleophiles. Under the standard conditions, Brønsted acid **15** catalyzed the alkenylation of isochroman to afford **18** in 62% yield and 61% *ee* (Scheme 4).[3b–c]



Scheme 4. Application of the one-pot strategy to the enantioselective alkenylation of **1a**.

In summary, we have developed the first one-pot oxidative and enantioselective cross-coupling reaction of cyclic benzylic ethers with aldehydes. The reaction features high enantioselectivity, good yields, excellent functional-group tolerance, wide compatibility of structurally and electronically varied benzylic ethers, and proven biological activity of the products, making it applicable to structurally complex compounds and drug discovery. The successful identification of reaction intermediates and promising results with boronate esters suggest that the one-pot strategy outlined herein will serve as a guide for future efforts in the area of enantioselective C–H functionalization of cyclic benzylic ethers with other classes of nucleophiles. Ongoing studies focus on the expansion of the scope of the reaction with respect to variation of the electrophile and nucleophile and on the discovery of biologically important small molecules.

Received: October 6, 2013
Published online: November 25, 2013

Keywords: aldehydes · asymmetric catalysis · benzylic ethers · C–H functionalization · organocatalysis

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