Catalytic Asymmetric Cross-Dehydrogenative Coupling of 2*H*-Chromenes and Aldehydes

Xinhui Pan,[a,c,+] Xigong Liu,[a,+] Shutao Sun,[a] Zhilin Meng,[a] and Lei Liu*[,a,b]

ABSTRACT The first catalytic asymmetric cross-dehydrogenative coupling of 2*H*-chromenes with aldehydes using *o*-chloranil (3,4,5,6-tetrachloro-1,2-benzoquinone) as an oxidant has been described. The organocatalytic process is tolerated with a broad range of structurally and electronically 2*H*-chromenes and aldehydes with good yield and high enantiocontrol.

KEYWORDS asymmetric catalysis, C–H functionalization, 2*H*-chromene, aldehyde, oxidation

Introduction

The cross-dehydrogenative coupling (CDC) reactions of two readily available C–H substrates have been regarded as an economic and straightforward strategy for the construction of new C–C bonds whereby the only loss is H_2 formally.[1] However, the development of corresponding catalytic asymmetric variants is challenging, mainly because of the incompatibility of the harsh oxidative conditions with the chiral catalyst system.[2] Since the pioneering studies of the groups of Li and Cozzi, impressive advances have been achieved for the asymmetric CDC of electron-rich amines and diarylmethanes, especially *N*-arylated tetrahydroisoquinolines and xanthenes.[3,4] In contrast, enantioselective CDC of corresponding ether substrates has remained elusive, probably owning to their increased oxidation potentials and lack of suitable sites on oxocarbenium ion intermediates for coordination to chiral catalysts. To the best of our knowledge, only two examples of enantioselective CDC of ethers have been reported to date.[5,6] In 2014, our group disclosed the first catalytic asymmetric bimolecular CDC of cyclic benzylic ethers with aldehydes with excellent enantiocontrol (Figure 1a).[5] In 2018, Scheidt and co-workers described an elegant $Cu(OTf)_2$-catalyzed enantioselective intramolecular CDC of allylic ethers with appended β-ketoesters, furnishing substituted tetrahydropyrones with high yields and enantioselectivity (Figure 1b).[6] Therefore, developing a catalytic asymmetric CDC process of other types of ether skeletons would still be an attractive project to pursue.

Enantiopure α-substituted 2*H*-chromenes and their analogs are commonly encountered in numerous biologically active natural products and synthetic pharmaceuticals exhibiting antipsychotic, antibacterial, antifungal, antiviral, anticancer, antioxidative, antidepressive, antihypertensive, and antidiabetic activities.[7,8] Direct and enantioselective C–H functionalization of 2*H*-chromene skeletons with diverse carbon components represents an ideal strategy that streamlines the synthetic planning for both complex target molecules and their analogues for lead discovery.[9] In this context, the Floreancig group documented the first and only example of enantioselective oxidative C–H functionalization of 2*H*-chromene with allyl phenyl dimethylsilane through asymmetric ion-pairing catalysis (Figure 1c).[10] Despite great innovation and good enantioselectivity, the method suffered from high loading of chiral thiophosphoric acid and limited scope of both 2*H*-chromene and allylsilane components. As part of our ongoing interest in enantioselective oxidative C–H functionalization, we herein communicate the first catalytic asymmetric CDC of 2*H*-chromenes with aldehydes using

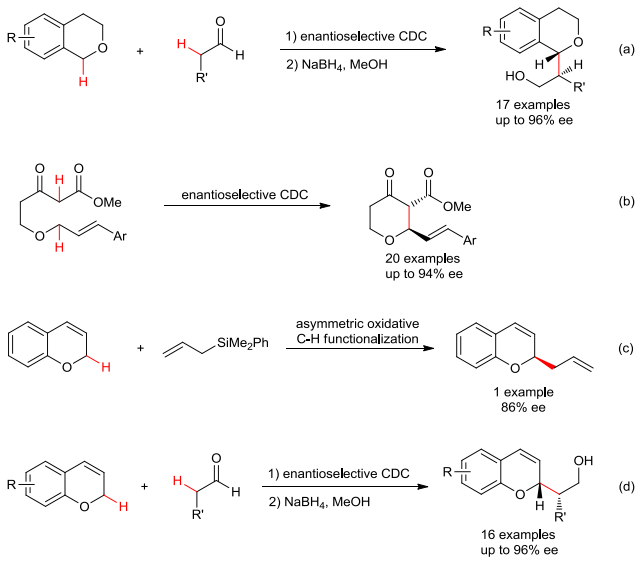

Figure 1 Overview of catalytic asymmetric oxidative C–H functionalization of ethers.

o-chloranil as the oxidant (Figure 1d). A broad range of 2*H*-chromene and aldehyde components were well tolerated with the organocatalytic process with excellent enantiocontrol and good functional group compatibility.

Results and Discussion

Initially, the CDC of 2*H*-chromene **1a** and pentanal **2a** was selected as the model reaction using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as an oxidant for the search of a suitable chiral catalyst (Table 1). While chiral imidazolidinone **A** failed to promote the CDC reaction, expected **3a** was isolated in 40% yield and 25% ee when salt **A**·TFA was employed as the catalyst (entries 1 and 2, Table 1). A systematic investigation of the combination of chiral amine catalysts **B**-**F** and Brønsted acids identified phenylalanine-derived catalyst **B**·TFA to be optimal in terms of selectivities and yields (entries 2-12, Table 1). Next, a series of benzoquinone oxidants bearing electron-withdrawing substitutions were evaluated. While the CDC with *p*-chloranil (tetrachloro-1,4-benzoquinone) and fluoranil (tetrafluoro-1,4-benzoquinone) did not provide any expected **3a**, *o*-chloranil proved to be an ideal oxidant for the process, furnishing **3a** in 80% yield and 61% ee (entries 3 and 13-15, Table

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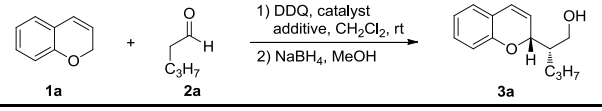
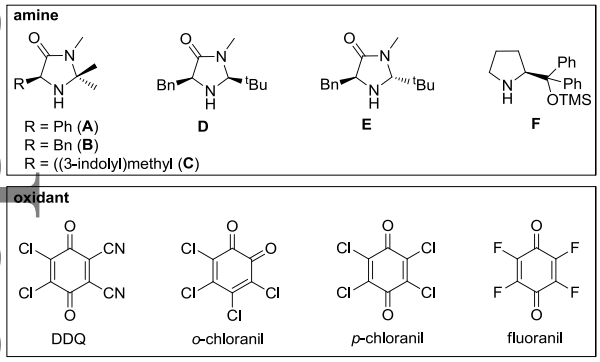
Table 1 Reaction condition optimization.[a]



1a 2a 3a

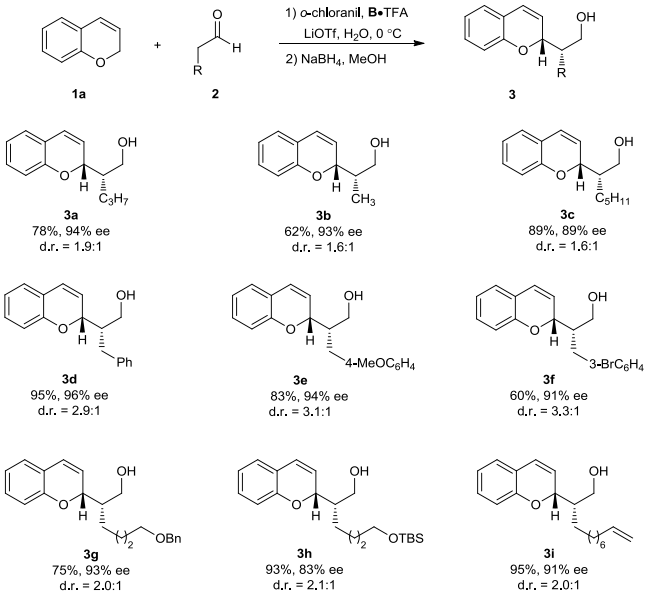
Entry	Amine	Additive	d.r.[b]	Yield (%)[c]	ee (%)[d]
1	**A**	—	n.d.	< 5	n.d.
2	**A**·TFA	—	1.7:1	40	25
3	**B**·TFA	—	1.9:1	80	52
4	**C**·TFA	—	1.2:1	65	40
5	**D**·TFA	—	1.5:1	70	47
6	**E**·TFA	—	1.4:1	70	48
7	**F**·TFA	—	n.d.	< 5	n.d.
8	**F**	—	n.d.	< 5	n.d.
9	**B**·HCl	—	1.7:1	58	40
10	**B**·DCA	—	1.5:1	57	46
11	**B**·HCOOH	—	1.3:1	55	40
12	**B**·AcOH	—	1.4:1	59	45
13[e]	**B**·TFA	—	n.d.	< 5	n.d.
14[f]	**B**·TFA	—	n.d.	< 5	n.d.
15[g]	**B**·TFA	—	1.9:1	80	61
16[g,h]	**B**·TFA	—	1.9:1	70	66
17[g,h]	**B**·TFA	$LiClO_4$	1.7:1	40	58
18[g,h]	**B**·TFA	LiOAc	n.d.	< 5	n.d.
19[g,h]	**B**·TFA	LiOTf	1.9:1	64	77
20[g,h]	**B**·TFA	H_2O	1.9:1	61	76
21[g,h]	**B**·TFA	LiOTf/H_2O	1.9:1	80	87
22[g,h,i]	**B**·TFA	LiOTf/H_2O	1.9:1	78	94
23[g,h,j]	**B**·TFA	LiOTf/H_2O	1.9:1	76	94



[a] Reaction conditions, unless otherwise specified: a solution of **1a** (0.2 mmol) and DDQ (0.19 mmol) in CH_2Cl_2 (2.0 mL) was stirred at rt for 0.5 h, followed by amine catalyst (0.04 mmol), **2a** (0.8 mmol), and additive (1.5 equiv) at rt for 12-24 h. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield of the two diastereomers. [d] Determined by chiral HPLC analysis. [e] *p*-Chloranil instead of DDQ as an oxidant. [f] Fluoranil instead of DDQ as an oxidant. [g] *o*-Chloranil instead of DDQ as an oxidant. [h] Reaction at 0 °C. [i] 30 equiv of H_2O added. [j] 40 equiv of H_2O added. n.d. = not determined, TFA = trifluoroacetic acid, DCA = dichloroacetic acid, Ac = acyl, Tf = trifluoromethanesulfonyl, Bn = benzyl, TMS = trimethylsilyl.

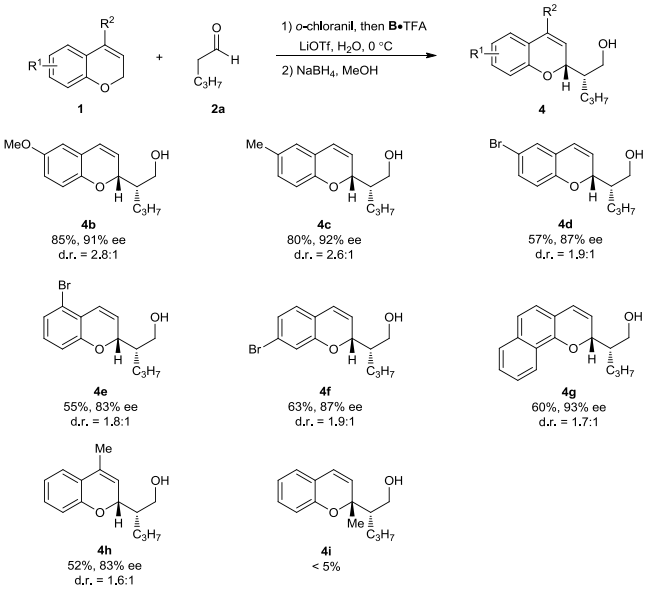
1). The enantioselectivity was further increased to 66% by lowering the temperature to 0 °C (entry 16, Table 1). A range of additives were then introduced to the system, and either LiOTf or H_2O was found to be beneficial for improving the enantiocontrol, giving **3a** in 77% ee and 76% ee, respectively (entries 17-20, Table 1). Synchronous presence of LiOTf and H_2O led to **3a** in 80% yield and 87% ee (entry 21, Table 1). The amount of H_2O was crucial to the enantioselectivity, and increasing the H_2O additive from 1.5 equiv to 30 equiv afforded **3a** in 78% yield and 94% ee (entries 22 and 23, Table 1).

Scheme 1 The scope of aldehydes.



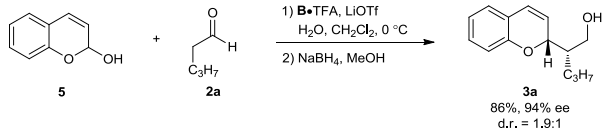
With the optimized reaction conditions in hand, the scope of aldehyde components was extensively examined (Scheme 1). Generally, the organocatalytic enantioselective CDC of 2*H*-chromene **1a** with a wide range of aldehydes proceeded smoothly, furnishing the corresponding expected α-alkylated 2*H*-chromenes **3a**-**3j** in good yields (60−95%) with excellent enantioselectivities (92% ee on average) and moderate diastereocontrol. Notably, the protocol showed excellent functional group tolerance, with commonly encountered moieties such as aryl (**3d**-**3f**), benzyl ethers (**3g**), silyl ethers (**3h**), and alkenes (**3i**) tolerated, thus demonstrating the capacity in creating diverse α-substituted 2*H*-chromenes.

Scheme 2 The scope of 2*H*-chromenes.



The scope of 2*H*-chromenes was next investigated (Scheme 2). 2*H*-chromenes **1b** and **1c** bearing electron-donating substitutions at the C6 position participated in the enantioselective CDC with **2a** efficiently, generating corresponding **4b** and **4c** with 91% and 92% ee, respectively. 2*H*-Chromenes bearing electron-withdrawing moiety at C6 position were well tolerated with the standard conditions, though slightly decreased efficiency was observed, which might be ascribed to the increased oxidation potential of **1d**. 2*H*-Chromenes **1e** and **1f** bearing substitutions at C5 and C7 positions were found to be competent substrates with good enentiocontrol. 2*H*-Benzo[*h*]chromene **1g** also proved to be suitable component for the asymmetric coupling reaction, further demonstrating the tolerance of diverse substituent patterns on 2*H*-chromenes. The substitution effect on the dihydropyran ring was next examined. The asymmetric CDC of C4-methyl substituted **1h** proceeded smoothly. The attempt to construct quaternary carbon center from C2-methyl substituted **1i** failed, which might be ascribed to the increased steric hindrance on the ether substrate.

Scheme 3 Control experiment.



During the course of the enantioselective CDC process, TLC analysis suggested the formation of a considerable amount of an intermediate, which was verified to be hemiacetal **5** (Scheme 3). Subjecting **5** to the standard CDC conditions in the absence of oxidation elements afforded comparable ee and yield to those starting from 2*H*-chromene **1a**, thus implying the intermediacy of **5** in the asymmetric CDC process.

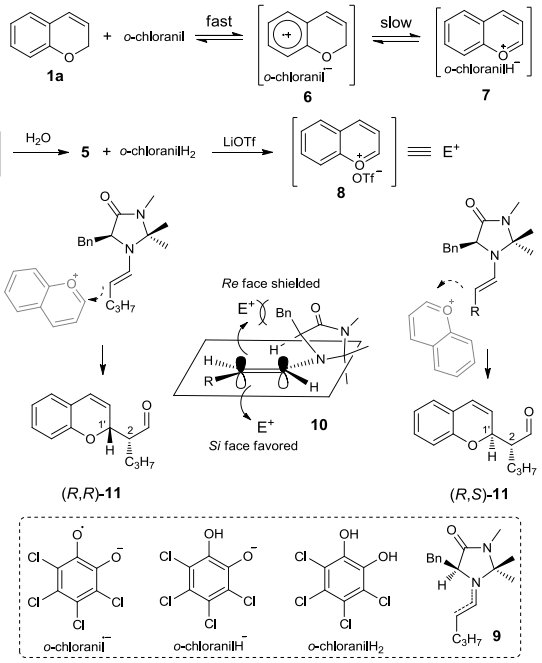


Figure 2 Stereochemical analysis.

A plausible mechanism for the CDC process is shown in Figure 2. 2*H*-Chromene **1a** was oxidized by *o*-chloranil in a reversible process to generate ion pair **7**.[11] H_2O and LiOTf are beneficial for improving the enantioselectivity. When H_2O is present in the system, **7** might be captured by H_2O affording hemiacetal **5**.[12] We postulate that LiOTf should act as a Lewis acid to promote the breakdown of the intermediate **5** into ion pair **8**, which is a better electrophile for subsequent nucleophilic attack in terms of enantiocontrol. In the predominant (*E*)-iminium ion **9**,[13] the benzyl group on the imidazolidinone ring shields the *Re* face of the enamine (**10**), and the oxocarbenium ion will be attacked from the *Si* face of **9** to give **11** with *R* configuration at the C2 position.[13b] The configuration at the C1' position depends on whether the attack occurs on the *Si* or *Re* face of the intermediate **8**. The absolute and relative configurations of products were determined by comparing the NMR spectra of CDC products with known compounds.[8b]

Conclusions

In summary, we have developed the first catalytic asymmetric CDC reaction of 2*H*-chromenes with aldehydes. The organocatalytic process is tolerated with a broad range of structurally and electronically 2*H*-chromenes and aldehydes with good yield and high enantiocontrol. Instead of commonly adopted DDQ, *o*-chloranil was used as the oxidant for the enantioselective oxidative C−H functionalization for the first time. The study on the catalytic asymmetric CDC of other types of ethers is being pursued and will be reported in due course.

Experimental

To a solution of 2*H*-chromene **1** (0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added *o*-chloranil (0.19 mmol, 0.95 equiv) at room temperature. The reaction was monitored by TLC and, upon starting material consumption, LiOTf (0.3 mmol, 1.5 equiv), **B**·TFA (0.04 mmol, 20 mol%), aldehyde **2** (0.8 mmol, 4.0 equiv), and H_2O (6.0 mmol, 30 equiv) were successively added at 0 °C. The reaction mixture was stirred at 0 °C until TLC analysis showed complete starting material consumption. The reaction mixture was then poured into the suspension of excess $NaBH_4$ (0.4 mmol, 2.0 equiv) in MeOH (1.0 mL) at 0 °C, and after stirring for 20 min, the solution was treated with saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O (10 mL × 3), and the combined organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum. The residue was purified by flash chromatography to give the desired product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

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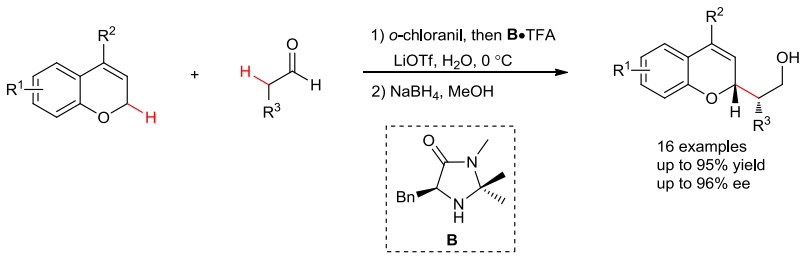

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The first catalytic asymmetric cross-dehydrogenative coupling of 2*H*-chromenes with aldehydes using *o*-chloranil as an oxidant has been described. The organocatalytic process is tolerated with a broad range of structurally and electronically 2*H*-chromenes and aldehydes with good yield and high enantiocontrol.

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