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Organocatalytic Enantioselective Dehydrogenative α-Alkylation of Aldehydes with Benzylic Compounds

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The highly enantioselective cross-dehydrogenative coupling of aldehydes with benzylic compounds has been developed as an efficient and rapid protocol for synthesis of enantioriched α-alkylated aldehydes.

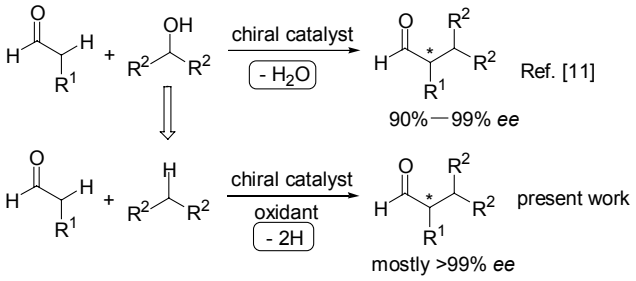
Keywords organocatalytic, alkylation, aldehyde, benzylic, coupling

Introduction

In recent years, transition-metal catalyzed direct cross-dehydrogenative coupling (CDC) of two C—H bonds has attracted considerable attention owing to its green, low-cost, and environmentally friendly nature in efficient construction of C—C bonds.[1] In this context, much effort has been directed toward the enantioselective version of CDC reactions. However, such asymmetric reactions remain a great challenge given the absence of binding sites in hydrocarbon substrates and the incompatibility of chiral catalysts with oxidants.[2] Thus the enantioselective oxidative C—C bond formation is still in its infancy and needs extensive exploration.

The direct, catalytic, and asymmetric functionalization of aldehydes in high stereoselectivity represents a remarkble challenge in asymmetric catalysis.[3] For instance, alkylation of aldehydes at the α position using the organometallic methods often required preformed metal enolates and stoichiometric amounts of chiral auxiliaries, where many undesirable side reactions may occur.[4] Moreover, the catalytic enantioselective intermolecular α-alkylation of aldehydes has been regarded as "the Holy Grail" reaction in asymmetric aminocatalysis.[5,6] We recently reported the highly enantioselective intermolecular α-alkylation of aldehydes with alcohols by a diarylprolinol silyl ether under Brønsted acid, Lewis acid or acid-free conditions.[7] Encouraged by this result and the recent reports on the highly enantioselective β-functionalization of simple aldehydes,[8] we envisage that coorporation of diarylprolinol silyl ether catalyst with an suitable oxidant may offer an efficient catalytic system to effect a highly enantioselective cross-dehydrogenative coupling of aldehydes with benzylic compounds when the C—O bond is changed to a C—H bond (Scheme 1). The obvious advantage is that the desired enantioriched α-alkylated aldehydes can be directly produced from aldehydes with benzylic compounds through an oxidative C—H functionalization process. Although this transformation has been recently studied by Cozzi and coworkers,[9] their system has the drawback of high catalyst loading (20 mol% MacMillan catalyst), low temperature (−25 ℃), moderate enantioselectivity (10%—86% *ee*) as well as tedious operation. Thus the required harsh conditions and unsatisfactory *ee* value limited the overall sustainability and applicability. Recently, anodic oxidation was applied to the enantioselective coupling of aldehydes and xanthene by use of 20—50 mol% of the MacMillan catalyst and the products were also afforded in low enantioselectivity (10%—68% *ee*).[10] Despite the obviously green and atom-economic advantage, this reaction still remains a formidable challenge and the highly enantioselective version is rare.[11] As a continuation of our interest in developing highly enantioselective organocatalytic reactions,[7,12] herein we report the highly enantioselective

Scheme 1 Enantioselective cross-dehydrogenative coupling of aldehydes with benzylic compounds



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cross-dehydrogenative coupling of aldehydes with benzylic compounds by cooperative catalysis of diarylprolinol silyl ether with an oxidant, leading to a variety of enantioriched α-alkylated aldehydes in high optical purity at room temperature under very mild conditions.

Experimental

Unless otherwise noted, commercial reagents were used as received and all reactions were carried out directly in air atmosphere. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditons. High Resolution Mass (HRMS) spectra were obtained using Finnigan MAT95XP GC/HRMS (Thermo Electron Corporation). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer ($CDCl_3$ as solvent). Enantioselectivities were determined by HPLC analysis employing a Daicel Chiracel column at 25 ℃. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm. Concentration is denoted as *c* and was calculated as grams per deciliters (g/100 mL) using chloroform as solvent. Absolute configuration of the products was determined by comparison with known compounds.

A typical reaction procedure is as follows: To a 5 mL vial equipped with a magnetic stirring bar, were added $CHCl_3$ (2 mL) and benzylic compound **2a** (0.2 mmol). Then catalyst **I** (0.02 mmol) and DDQ (0.24 mmol) were added before addition of aldehyde **1** (0.8 mmol). The resulting solution was stirred at room temperature for 12 h. Then the mixture was filtered through celite to remove any precipitate. The filtration was evacuated and the resulting mixture was dissolved in EtOH (5 mL). $NaBH_4$ was then cautiously added to the solution. The mixture was stirred at room temperature for 0.5 h and was quenched with 1 mol/L HCl. The organic phase was separated and the aqueous solution was extracted with ethyl acetate (10 mL×3). The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting oil was purified by preparative chromatography or column chromatography (hexane/ethyl acetate＝4∶1) to afford the desired product **3**. The enantiomeric excess was determined by HPLC using chiral AD-H or AS-H columns. The absolute configuration of the products was determined by optical rotation in comparison with the literature reported values.[7,9,10] (*R*)-2-(9*H*-xanthen-9-yl)propan-1-ol (**3a**): yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.26—7.22 (m, 4H), 7.10—7.07 (m, 4H), 4.22 (d, J= 4.5 Hz, 1H), 3.53—3.46 (m, 1H), 3.45—3.43 (m, 1H), 2.01—1.98 (m, 1H), 1.25 (br s , 1H), 0.64 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.4, 153.1, 129.7, 128.75, 127.7, 127.5, 125.1, 123.3, 122.9, 122.5, 116.3, 116.2, 64.9, 45.1, 40.2, 12.0; HRMS (ESI) calcd for $C_{16}H_{17}O_2$ 241.1229 $[M+H]^+$, found 241.1230 $[M+H]^+$.

Results and Discussion

The reaction of butyraldehyde **1a** and xanthene **2a** was selected as the model reaction to define the suitable oxidant in the presence of 10 mol% diarylprolinol silyl ether **I**.[13] Our preliminary results showed that the commonly used metal oxidants such as Fe(III) and Cu(II) salts as well as IBX cannot afford satisfactory results (Table 1, Entries 1—4). When O_2 was employed as oxidant, only trace of product was found in the presence of catalyst **I**, however, catalyst **II** can afford 58% yield, abeit no enantioselectivity was observed (Table 1, Entries 5—6). Inspired by the recent success on DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as an oxidant in implementing oxidative cross coupling reactions,[14] we tried DDQ as oxidant to perform this reaction. To our delight, this reaction proceeded smoothly to give the desired product **3a** in moderate yield and moderate *ee* in CH_2Cl_2 (Table 1, Entry 7). This encouraged us to investigate the other solvents. Gratifyingly, 42% yield and 94% *ee* was given when nitromethane was used as solvent (Table 1, Entry 8). The best result was obtained in $CHCl_3$, affording 62% yield and 92% *ee* (Table 1, Entry 9). However, other solvents such as toluene and THF were not effective and low chemical yields were obtained (Table 1, Entries 10—11). The yield becomes lower when the amount of DDQ was increased to 1.5 equiv. (Table 1, Entry 12). Performing this reaction at 0 ℃ also resulted in lower yield (Table 1, Entry 13). Addition of an acid to the mixture was not beneficial for this reaction (Table 1, Entry 14). In sharp contrast, catalyst **II** without any trifluoromethyl group only gave 27% yield and 57% *ee*, indicative of the importance of the trifluoromethyl group in catalyst **I** in terms of reactivity and enantioselectivity (Table 1, Entry 15). In addition, when the MacMillan catalyst **III** was used, 55% yield and 70% *ee* was obtained (Table 1, Entry 16).

With the optimized conditions in hand, we next examined the substrate scope using various aldehydes and xanthene **2a** (Table 2, Entries 1—8). Satisfyingly, in all cases the desired products were obtained in moderate yields with good to excellent enantioselectivities (Table 2, Entries 1—8), making this methodology highly valuable considering the biochemical and pharmaceutical importance of xanthene derivatives.[15] Propionaldehyde reacted to give 52% yield and 88% *ee* (Table 2, Entry 1). Bulky aldehydes such as isovaleraldehyde is reactive enough to provide product **3h**, albeit with lower yield and lower enantioselectivity (Table 2, Entry 8). For substrate 9*H*-thioxanthene **2b**, lower enantioselectivities were observed, propionaldehyde and butylaldehyde

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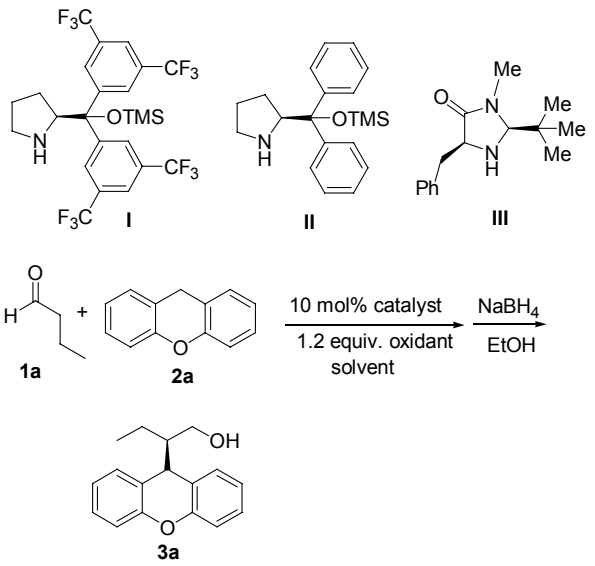
Table 1 Optimizations for enantioselective cross-dehydrogenative coupling of aldehyde **1a** with **2a**



Entry[a]	Oxidant	Solvent	Catalyst	Yield[b]/%	*ee*[c]/%
1	CAN	CH_2Cl_2	**I**	Trace	—
2	$FeCl_3$	CH_2Cl_2	**I**	Trace	—
3	$Cu(OAc)_2$	CH_2Cl_2	**I**	Trace	—
4	IBX	CH_2Cl_2	**I**	Trace	—
5[d]	O_2	CH_2Cl_2	**I**	Trace	—
6[d]	O_2	CH_2Cl_2	**II**	58	0
7	DDQ	CH_2Cl_2	**I**	50	72
8	DDQ	$MeNO_2$	**I**	42	94
9	DDQ	$CHCl_3$	**I**	62	92
10	DDQ	Toluene	**I**	18	—
11	DDQ	THF	**I**	17	—
12[e]	DDQ	$CHCl_3$	**I**	51	—
13[f]	DDQ	$CHCl_3$	**I**	29	—
14[g]	DDQ	$CHCl_3$	**I**	23	—
15	DDQ	$CHCl_3$	**II**	27	57
16	DDQ	$CHCl_3$	**III**	55	70

[a] Reactions were performed with **1a** (0.8 mmol), **2a** (0.2 mmol) and **I** (0.02 mmol) in 2 mL solvent at room temperature. [b] Isolated yield by column chromatography. [c] *ee* was determined by chiral HPLC on a chiral stationary phase. [d] 20 mol% catalyst and 20 mol% TfOH was used. [e] 1.5 equiv. DDQ was used. [f] 0 ℃ for 12 h. [g] 10 ml% 4-$NO_2C_6H_5CO_2H$ was added.

reacted to afford products in 77% *ee* and 74% *ee*, respectively (Table 2, Entries 9—10). This cooperative system could be extended to substrate 1,3,5-cycloheptatriene **2c**, where good yields and high enantioselectivities still could be obtained (58% yield and 91% *ee* for butylaldehyde, 47% yield and 90% *ee* for valeraldehyde) (Table 2, Entries 11—12). The absolute configuration of the products **3** was determined by optical rotation in comparison with the reported values.[7,9,10]

A plausible catalytic cycle is given in Scheme 2. Condensation of aldehyde **1** with catalyst **I** gives (*E*)-enamine **4**. Concurrently, the benzylic compound **2** was oxidized *in situ* by DDQ to form carbocation **5**. Subsequent nucleophilic attack on the carbocation **5** by enamine **4** from the *Si* face affords the intermediate **6** since the *Re* face was efficiently shielded by the bulky silyl ether group. Hydrolysis of **6** afforded product **3** with the regeneration of catalyst **I**.

Scheme 2 Plausible catalytic cycle for enantioselective cross-dehydrogenative coupling of aldehydes with benzylic compounds

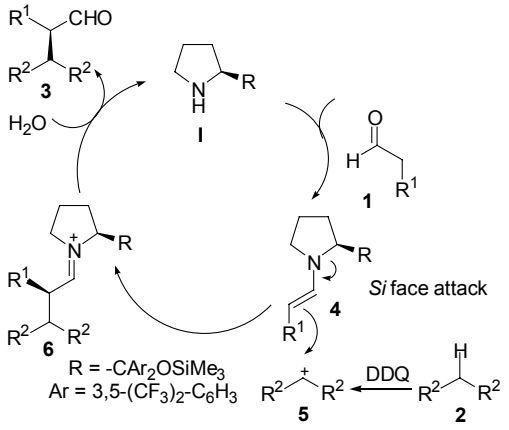
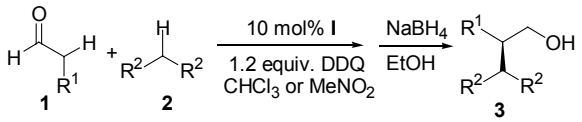
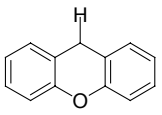
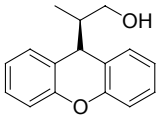
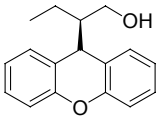
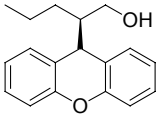
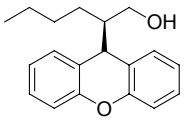
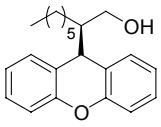
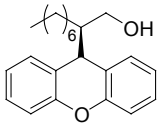
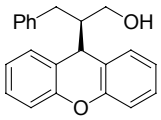
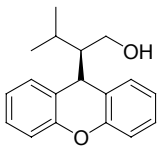
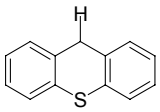
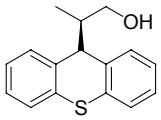
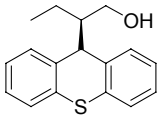
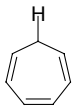
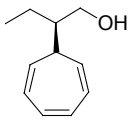
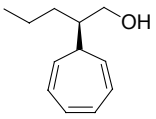


Table 2 Enantioselective cross-dehydrogenative coupling of aldehydes with benzylic compounds



Entry[a]	Substrate	Product	Yield[b]/%	*ee*[c]/%
1	 **2a**	 **3a**	52	88
2	**2a**	 **3b**	57	92
3	**2a**	 **3c**	51	94

Continued

Entry[a]	Substrate	Product	Yield[b]/%	*ee*[c]/%
4	**2a**	 **3d**	47	95
5	**2a**	 **3e**	42	92
6	**2a**	 **3f**	44	92
7	**2a**	 **3g**	57	83
8	**2a**	 **3h**	36	58
9	 **2b**	 **3i**	46	77
10	**2b**	 **3j**	51	74
11	 **2c**	 **3k**	58	91
12	**2c**	 **3l**	47	90

[a] Reactions were performed with **1** (0.8 mmol), **2** (0.2 mmol) and **I** (0.02 mmol) in 2 mL solvent at room temperature. [b] Isolated yield by column chromatography. [c] *ee* was determined by chiral HPLC on a chiral stationary phase.

Conclusions

In summary, we have developed the highly enantioselective cross-dehydrogenative coupling of aldehydes with benzylic compounds catalyzed by diarylprolinol silyl ether. DDQ proved to be an efficient and compatible oxidant. This method provides an efficient and rapid protocol for synthesis of enantioriched α-alkylated aldehydes in high optical purity, and many of the desired α-alkylated aldehydes were obtained in good to high enantioselectivities. Additionally, the simple room temperature operations and use of non-metal oxidant should make this methodology attractive for synthesis of optically pure α-alkylated aldehydes.

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