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Short Communication

Development of green and low-cost chiral oxidants for asymmetric catalytic hydroxylation of enals

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ABSTRACT

A novel type of chiral oxidants are developed for efficient and enantioselective β-hydroxylation reaction of enals. The chiral oxidants can be easily obtained from readily available and inexpensive substituted benzoic acids and chiral prolinols. A commercially accessible and inexpensive achiral NHC catalyst is used for this catalytic approach. β-Hydroxyl esters bearing various substituents and substitution patterns are afforded as the final products in moderate to excellent yields and enantioselectivities.

Oxidation reactions are among the most basic and significant transformations in organic synthesis [1]. Oxidants play the key roles in various oxidation reactions. Therefore, it is always important and interesting to develop novel oxidants for different oxidative processes.

Asymmetric oxidation reactions can be realized by various chiral catalysts in the presence of stoichiometric amount of achiral oxidants [2]. On the other hand, it is also possible to get molecules oxidized in enantioselective fashion by chiral oxidants with or without the catalysis of achiral catalysts. The latter approach is particularly attractive in cases that the chiral catalysts are extremely expensive and the chiral oxidants are easily accessible with low costs.

N-Heterocyclic carbene (NHC) organocatalytic reactions have been developed as powerful approaches for the preparation of various chiral functional molecules in the past 20 years [3]. Among the diverse transformations enabled by NHC catalysts, oxidative processes are frequently involved [4]. To date, a variety of organic molecules have been used as efficient oxidants for NHC-catalyzed chiral or achiral reactions through either electron-pair-transfer or single-electron-transfer (SET) pathways (Fig. 1a) [5]. For instance, quinone [6] and TEMPO [7] have been initially used by Studer and co-workers for the generation of acylazolium intermediate from adduct of an aldehyde substrate and an NHC catalyst. Nitro [8] and nitroso [9] group-containing molecules have been frequently used in the SET oxidative reactions with NHC organic catalysts. Phthalimide-derived redox active esters have been used by Ohmiya and co-workers for the preparation of various ketone molecules through NHC-catalyzed radical reactions [10]. Phenazine [11], Togni's regent [12] and polyhalides [13] have also been applied in the oxidation of various Breslow intermediates [14] generated from aldehydes and NHCs for asymmetric reactions. It is worth to note that most of the oxidants used in NHC organocatalytic reactions are achiral molecules. The development of efficient and inexpensive chiral oxidants for asymmetric transformations enabled by inexpensive achiral NHC catalysts is still attractive and challenging.

The asymmetric β-hydroxylation of enals can be realized by chiral NHC organic catalysts in the presence of achiral nitroarene oxidants, as independently disclosed by Rovis and us (Fig. 1b, catalytic systems # 1 & 2) [15]. However, from a cost point of view, both of the chiral NHC organic catalysts and the achiral nitro-containing oxidants used in these protocols are expensive. We have previously reported that an arylsulfonamide-derived chiral oxidant can be used for enal β-hydroxylation reaction under the catalysis of an inexpensive achiral NHC catalyst (Fig. 1b, catalytic systems # 3) [16]. This approach is attractive since the arylsulfonamide-derived chiral oxidant can easily be made from an arylsulfonyl chloride and the commercially available chiral Jørgensen-Hayashi amino catalyst [17].

Herein, we report that a new type of chiral oxidants derived from substituted benzoic acids can be used for the enantioselective β-hydroxylation of enals in the presence of a catalytic amount of the

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inexpensive achiral NHC catalyst (Fig. 1b, catalytic system # 4). Noteworthy, the newly developed chiral oxidant can be easily made from the readily available carboxylic acid and diphenylprolinol with much lower costs.

First of all, a variety of chiral oxidants were synthesized through dehydrative coupling reactions between carboxylic acids and chiral alcohols/amines and were then evaluated for the asymmetric β-hydroxylation of cinnamaldehyde **1a** under the catalysis of the achiral NHC catalyst **A** (Scheme 1) [18]. The chiral esters obtained from 2-nitrobenzoic acid and chiral alcohols could give the desired product **3a** in poor yields and er values (**2a**-**2d**). Switching the chiral ester fragment into linear chiral amides could not improve either the product yields or optical purities (**2e**-**2h**). However, promising improvements on the product er values were observed when using the oxidants bearing chiral pyrroline moieties (**2i** and **2j**) and the product **3a** could be afforded in up to 80:20 er when using **2j** as the chiral oxidant. The optical purity of the target product **3a** dropped when the nitro group was installed on the *meta*- or *para*-position of phenyl ring of the oxidant molecules (**2k**-**2l**). Various substituents on the 2-nitrobenzene ring of **2j** were then examined in order to further improve the reaction outcome (**2m**-**2r**). Electron-withdrawing groups existed on the *p*-position of the 2-nitrobenzene ring of **2j** gave the product **3a** in generally poor yields with moderate enantioselectivities (**2m**-**2p**). To our delight, installing an electron-donating group on the *p*-position of the 2-nitrobenzene ring of **2j** resulted in obvious improvements on both of the reaction yields and enantioselectivities (**2q** and **2r**). Therefore, the chiral amide **2r** was selected as the reaction oxidant for further condition optimizations for the enal β-hydroxylation reaction (Table 1).

Various achiral NHC catalysts were examined for this transformation (Table 1, entries 1-5). The reactions were carried out in toluene with 150 mol% of K_2CO_3 used as the base in presence of the chiral oxidant **2r**. NHC catalysts bearing electron-rich *N*-aryl groups worked well for this reaction (entries 1, 2, 4, 5), while the NHC catalyst bearing an electron-deficient *N*–C_6F_5 group [19] gave only trace amount of the desired product (entry 3). Then NHC catalyst **B** [20] was selected to test the effect of base and solvent on the asymmetric enal β-hydroxylation reaction (entries 6-11). Strong inorganic bases were not suitable for this catalytic process with little formation of the target products (*e.g.*, entry 6, Cs_2CO_3). The yield of **3a** was increased to 53% when using Na_2CO_3 as the base without erosion on the product er value (entry 7). Organic bases generally gave the product **3a** in poor yields, although the optical purities were not affected (*e.g.*, entries 8 and 9). Switching the reaction solvents into various organic solvents cannot further improve the reaction outcome

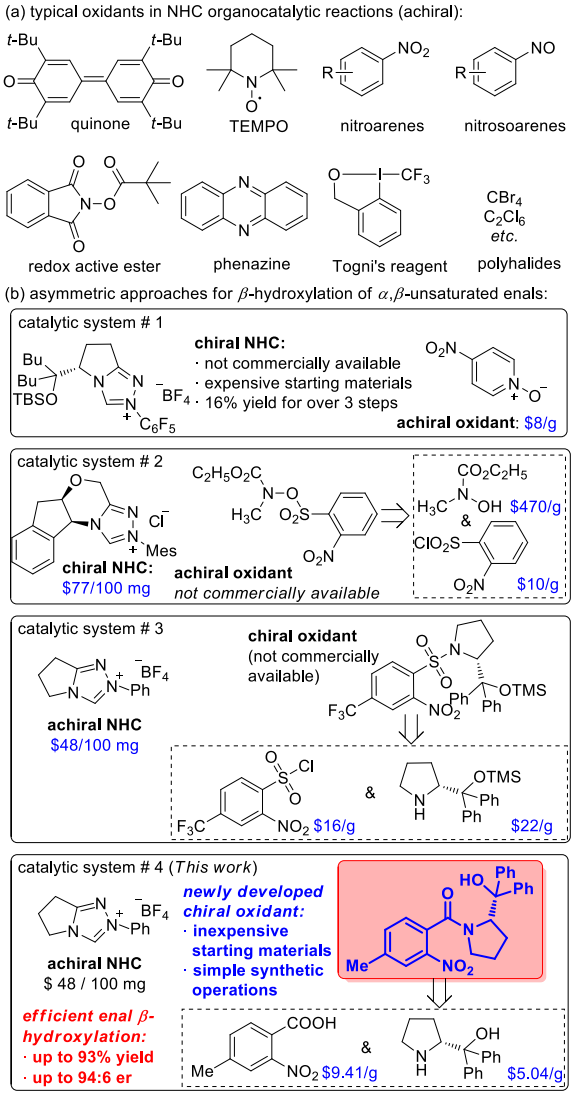
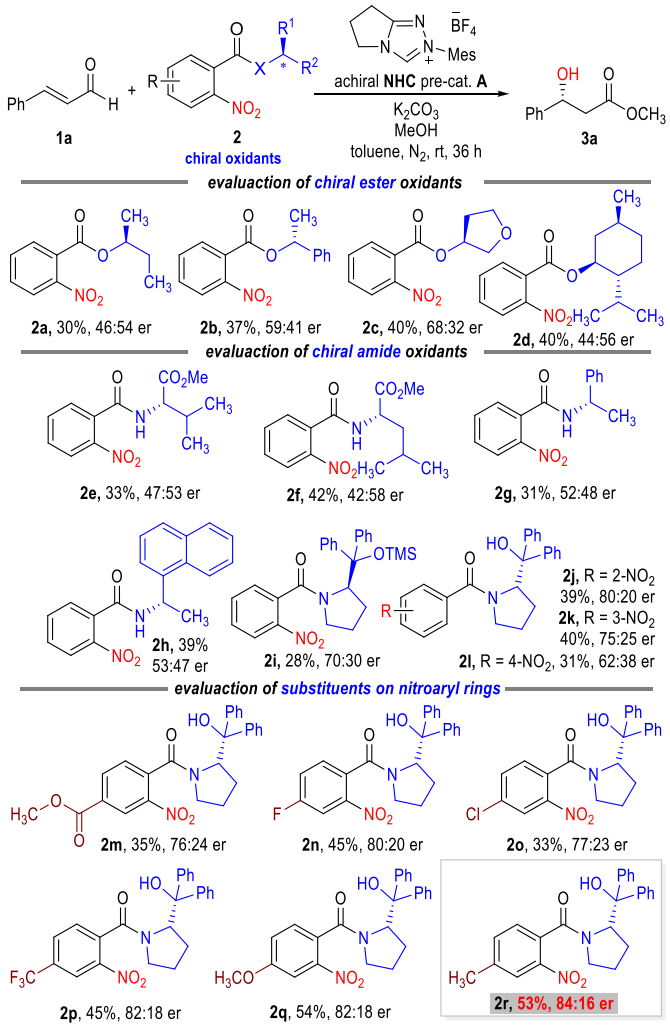
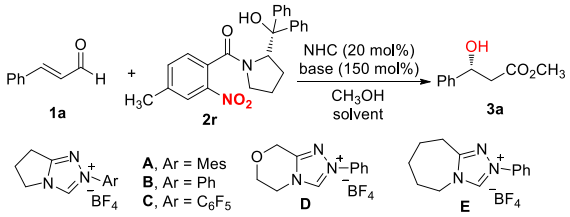


Fig. 1. Typical oxidants for NHC organocatalytic reactions and β-hydroxylation of enals.



Scheme 1. Evaluation of carboxylic acid-derived chiral oxidants. All reactions were carried out at room temperature using **1a** (0.1 mmol), **2** (0.1 mmol), Pre-cat **A** (20 mol%), K_2CO_3 (150 mol%), 40 μL CH_3OH and 2 mL toluene under N_2 atmosphere for 36 h. Estimated *via* ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard. Enantiomeric ratios were determined *via* HPLC analysis on a chiral stationary phase; the absolute configuration was determined by comparing the optical rotation of **3a** with literature values.

Table 1
Condition optimizations.[a]

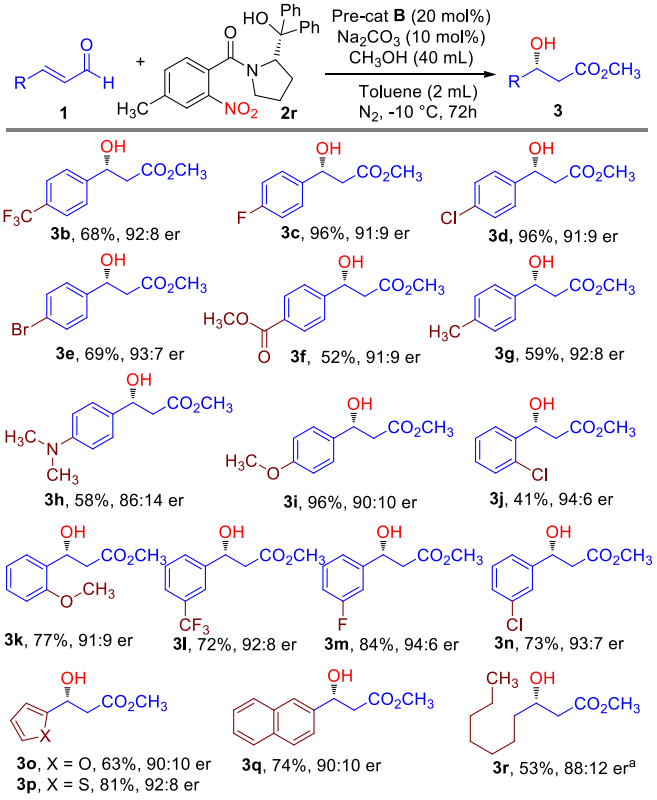


Entry	NHC	Base	Solvent	Yield (%)[b]	er[c]
1	**A**	K_2CO_3	Toluene	44	85:15
2	**B**	K_2CO_3	Toluene	44	86:14
3	**C**	K_2CO_3	Toluene	<5	–
4	**D**	K_2CO_3	Toluene	29	81:19
5	**E**	K_2CO_3	Toluene	42	82:18
6	**B**	Cs_2CO_3	Toluene	46	89:11
7	**B**	Na_2CO_3	Toluene	53	86:14
8	**B**	DBU	Toluene	19	86:14
9	**B**	DIEA	Toluene	23	87:13
10	**B**	Na_2CO_3	CH_2Cl_2	50	87:13
11	**B**	Na_2CO_3	THF	39	81:19
12[d]	**B**	Na_2CO_3	Toluene	73	88:12
13[e]	**B**	Na_2CO_3	Toluene	89 (88)[f]	91:9

[a] Reactions were carried out at room temperature using **1a** (0.1 mmol), **2r** (0.1 mmol), NHC (20 mol%), base (150 mol%), 40 μL CH_3OH and 2 mL solvent under N_2 atmosphere for 36 h.
[b] Estimated *via* ^1H NMR analysis of crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard.
[c] Enantiomeric ratio were determined *via* HPLC analysis on a chiral stationary phase.
[d] 0.1 mmol Na_2CO_3 and 0.2 mmol **1a** were used.
[e] Reactions were carried out at −10 °C using 0.2 mmol **1a** and 0.1 mmol Na_2CO_3 for 72 h.
[f] Isolated yield after purification *via* column chromatography was given in parenthesis.

(*e.g.*, entries 10 and 11). Interestingly, both of the reaction yield and enantioselectivity could be effectively increased when using a less amount of basic additives (entry 12). Finally, the chiral product **3a** could be obtained in a good isolated yield and er value when carrying out the reaction at −10 °C with an excess amount of cinnamaldehyde **1a** used (entry 13).

With an optimal reaction condition at hand, we next examined the reaction scope using various enal substrates (Scheme 2). Both electron-withdrawing and electron-donating groups were well tolerated on the *p*-position of the phenyl ring of the cinnamaldehyde substrate, with the chiral *β*-hydroxyl ester products afforded in generally moderate to excellent yields and good optical purities (**3b**-**3i**). Noteworthy, installing a strong electron-donating dimethylamino group on the *p*-position resulted in a significant drop on the product er value (**3h**). Substituents on the *o*-position of the phenyl ring of the cinnamaldehyde could give the target products in better enantioselectivities, although the yields varied according to the electron densities of the reaction substrates (**3j** & **3k**). Various functional groups were also well tolerated on the *m*-position of the phenyl rings and could give the corresponding products in good yields and good to excellent enantioselectivities (**3l**-**3n**). To our delight, the phenyl group on the enal substrate **1a** could also be replaced with a furanyl group, although the yield and enantioselectivity of the reaction were slightly dropped (**3o**). However, replacing the phenyl group on **1a** with a thiophenyl group or a naphthyl group resulted in better yields and optical purities of the desired *β*-hydroxyl ester products (**3p** & **3q**). Noteworthy, the *β*-phenyl group on the enal **1a** could also be switched to an alkyl group, although the product **3r** could only be afforded in a moderate yield and enantioselectivity under the current reaction condition.



Scheme 2. Substrate scope. All reactions were carried out at −10 °C using **1a** (0.2 mmol), **2r** (0.1 mmol), **B** (20 mol%), Na_2CO_3 (100 mol%), 40 μL CH_3OH and 2 mL toluene under N_2 atmosphere for 72 h. Isolated yield based on **2r** after purification *via* column chromatography. Enantiomeric ratios were determined *via* HPLC analysis on a chiral stationary phase. [a] Determined *via* HPLC analysis on chiral stationary phase after derivatization (Supporting information).

It is worth noting that the enal *β*-hydroxylation reaction can be carried out at gram scales with retention of the product isolated yield and enantioselectivity (Fig. 2). Moreover, the chiral *β*-hydroxyl ester product **3a** obtained through this approach can be efficiently reduced to give the chiral di-alcohol **4** without erosion on the optical purity.

In summary, we have reported a green and practical useful approach for the enantioselective *β*-hydroxylation reaction of enals. A class of easily accessible and inexpensive chiral oxidants has been developed to achieve chiral *β*-hydroxyl ester products in moderate to excellent yields and optical purities. Readily available and inexpensive achiral NHC catalysts were used for this catalytic oxidative approach. It will definitely be attractive to broaden the application scope of this new type of chiral oxidants to extensive asymmetric oxidative processes. Investigations within this direction are in progress in our laboratories.

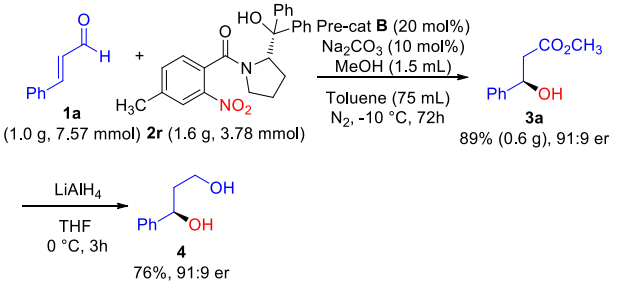


Fig. 2. A gram-scale reaction and synthetic application of the chiral product **3a**.

Declaration of competing interest

The authors declare no financial interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gresc.2021.05.002.

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