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Catalytic Asymmetric Epoxidation of α-Branched Enals

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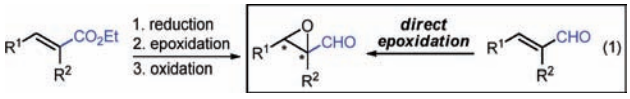
Abstract: An asymmetric catalytic epoxidation of α-branched, α,β-unsaturated aldehydes is presented. A highly synergistic combination of a primary cinchona-based amine and a chiral phosphoric acid was found to promote the reaction with excellent enantiocontrol for α-monosubstituted and α,β-disubstituted enals.

Ever since Sharpless's pioneering studies on the enantioselective epoxidation of allylic alcohols in the 1980s,[1] advances in catalytic olefin epoxidation have defined the current state of the art in asymmetric synthesis. Breakthrough discoveries have not only tackled important substrate classes such as unfunctionalized olefins but also identified entirely new catalyst motifs.[2] Very recently, initiated by a seminal finding by Jørgensen et al.,[3] aminocatalysis has provided powerful methodologies for the epoxidation of α,β-unsaturated aldehydes and ketones, including substrate classes that had been inaccessible to enantioselective epoxidation catalysis before.[4] Despite these advances, however, a general method for the direct catalytic asymmetric epoxidation of α-*branched*, α,β-unsaturated aldehydes is still lacking.[5] Such a reaction would provide enantioenriched α-substituted epoxyaldehydes, which find numerous and specific applications in organic synthesis.[6] Herein we describe a general solution to this problem. We have identified new salts that consist of a chiral primary ammonium cation and a chiral phosphate anion that catalyze the epoxidation of a variety of branched enals with superb enantioselectivity.

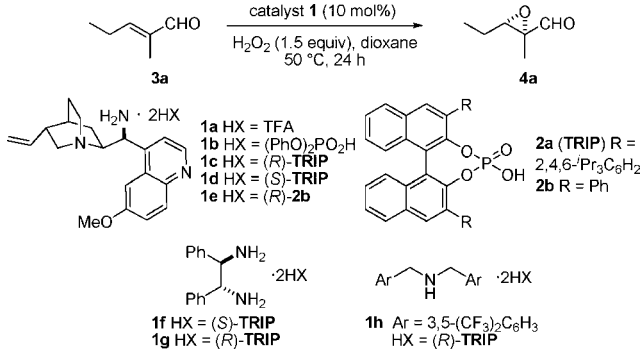
While several approaches exist for the generation of racemic α-substituted, α,β-epoxyaldehydes,[7] catalytic enantioselective variants invariably utilize substrates of higher or lower oxidation state.[8] For example, one of the most widely used routes to α-substituted, α,β-epoxyaldehydes is based on the Sharpless epoxidation of allylic alcohols.[1] However, since the starting material is commonly at the carbonyl or carboxyl oxidation level, this approach suffers from moderate step, atom, and redox economy[9] (eq 1).



Encouraged by our previous success in establishing primary amine salts in asymmetric iminium ion catalysis,[10] we have recently introduced cinchona alkaloid-derived primary ammonium salts as powerful catalysts for the epoxidation of cyclic and acyclic enones.[4c,d,11] Recent reports[7a,12] have furthermore demonstrated the utility of primary aminocatalysis also for the activation of α-branched enals. With this background in mind, we became interested in exploring our previously used catalyst system consisting of a primary cinchona alkaloid-derived amine and trifluoroacetic acid (**1a**) in the epoxidation of α-*branched*, α,β-unsaturated aldehydes.

We began our investigation by testing the epoxidation of commercially available (*E*)-2-methylpent-2-enal (**3a**) with catalyst

Table 1. Catalyst Screening[a]



entry	catalyst	conv (%)[b]	dr[b]	er[c]
1	**1a**	38	75:25	93:7
2	**1b**	58	87:13	95:5
3	**1c**	50	94:6	99.5:0.5
4	**1d**	35	74:26	36:64
5	**1e**	84	96:4	99.5:0.5
6[d]	**1e**	*100*	*92:8*	*98.5:1.5*[e]
7	**1f**	25	75:25	14:86
8	**1g**	32	81:19	6.5:93.5
9	**1h**	2		0

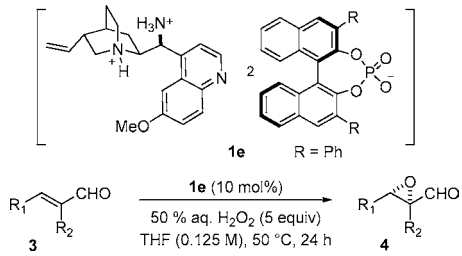
[a] See Supporting Information for full details. [b] Determined by GC. [c] Determined by GC analysis on a chiral stationary phase. [d] With THF as solvent and 5 equiv of H_2O_2. [e] The absolute configuration (2*R*,3*S*) of **4a** was assigned by comparing the optical rotation of the corresponding alcohol to the literature value.[15]

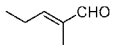
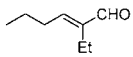
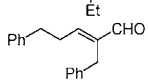
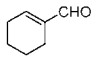
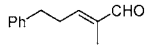
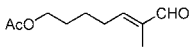
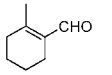
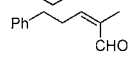
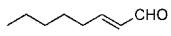
salt **1a** and aqueous hydrogen peroxide (Table 1, entry 1). The desired product was obtained with moderate conversion as a 25:75 *cis*/*trans* mixture of diastereomers but with an encouraging enantiomer ratio (er) of 93:7 for the major *trans*-diastereomer. A screen of acid cocatalysts (see Supporting Information (SI)) showed that an achiral phosphoric acid had a positive influence on conversion and selectivity (entry 2). Cognizant of the potential role of an asymmetric counterion in such systems,[4b−d,10,13] we tested the chiral phosphoric acid (*R*)-**2a** (**TRIP**) as the cocatalyst. This resulted in a dramatic case of "matched" chiral induction, whereby the major diastereomer was generated in essentially enantiopure form (er = 99.5:0.5, entry 3). Notably, this synergism was lost when the opposite enantiomer of the phosphoric acid (*S*)-**TRIP** was used: catalyst salt **1d** furnished the product with completely reversed but only modest enantioselectivity (entry 4). A further screen of phosphoric acids **2**, bearing various 3,3′-substituents, identified the bis-phenyl-substituted analogue **2b** as the optimal cocatalyst in terms of both activity and stereoselectivity (entry 5). Using the most effective catalyst **1e**, we further optimized the reaction parameters to achieve full conversion (entry 6). We also tested various simpler achiral and chiral amines in combination with **TRIP**,[14] including the chiral catalyst pair that we employed for the epoxidation of cyclic enones[4c] (entries 7 and 8), but none of the combinations provided satisfactory levels of enantiocontrol. Similarly, our previ-

ous system utilizing a secondary amine catalyst[4b] failed to give any conversion (entry 9).

With the optimal conditions in hand, we examined the scope of our new epoxidation (Table 2). It is noteworthy that the required (*E*)-configured α,*β*-disubstituted enals **3** could be easily prepared via redox-neutral[9] methodologies from aldehyde precursors via Grubbs olefin cross-metathesis[16] and aldol condensation.[17] We were pleased to find excellent enantioselectivity regardless of the α-substituent (entries 1−3). The same level of enantiocontrol was seen for cyclic substrate **3d** (entry 4) and enals bearing different functional groups (entries 5 and 6). In all cases, the *trans*-diastereomer was favored with good to excellent selectivity. Tetrasubstituted olefins appear to be a current limitation of our method, as enal **3g** (entry 7) did not afford the desired product, giving decomposition products via Baeyer−Villiger reaction instead. We also tested (*Z*)-**3e** in the reaction. This starting material also gave preferentially the *trans*-product, although the reaction rate and selectivity were compromised (entry 8, see SI for further details). Intriguingly, the current catalyst system proved unsuitable for α-*unbranched*, α,*β*-unsaturated aldehydes (entry 9). While we currently do not have an explanation for this reactivity, the result underscores the intricate complementarity that must be achieved between the steric and electronic requirements of the substrate and those of the catalyst to obtain a viable catalytic system.

Table 2. Substrate Scope of the Epoxidation of α,*β*-Disubstituted Enals

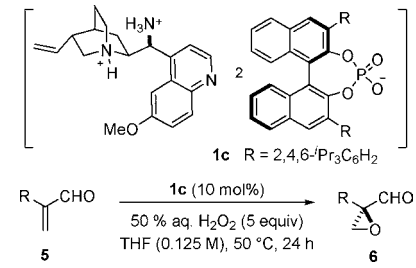


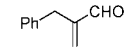
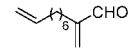
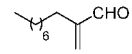
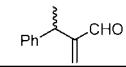
entry	substrate	product	yield, %[a]	dr[b]	er[c]
1		**4a**	43[d]	92:8	98.5:1.5
2[e]		**4b**	64	83:17	99:1
3		**4c**	77	90:10	99:1
4		**4d**	70	-	98.5:1.5
5		**4e**	75 (94)[f]	95:5	98.5:1.5
6		**4f**	66	93:7	99:1
7		**4g**	0	-	-
8[g]		**4e**	85[f]	76:24	85:15
9		**4h**	30[f]	95:5	64:36

[a] Isolated yield after reduction with $NaBH_4$. [b] Determined by NMR or GC analysis of the crude reaction mixture. [c] Determined by GC or HPLC analysis on a chiral stationary phase. [d] Complete conversion and no side products were observed; the reduced yield reflects the high volatility of the product. [e] *E*/*Z* ratio of the substrate =96:4. [f] GC yield. [g] *E*/*Z* ratio of the substrate =5:95.

We next turned our attention to the epoxidation of α-substituted *terminal* enals **5** (Table 3). To the best of our knowledge, there are no reports describing a direct enantioselective epoxidation for this substrate class, although Pihko et al. have recently developed a very useful non-asymmetric version.[7a] The combination of two chiral catalysts proved essential in this case, as achiral acid cocatalysts gave very poor enantioselectivity (er up to 63:37 for **6a**).[14] In comparison, catalyst pair **1e** afforded the epoxide **6a** with 91:9 er. Gratifyingly, the enantioselectivity could be further improved by using catalyst salt **1c**, which contains (*R*)-**TRIP** as a bulkier phosphoric acid (Table 3, entries 1−3). This catalyst salt could also be applied to the kinetic resolution of *β*′-substituted enal **5d** (entry 4). After 53% conversion under the reaction conditions, the (*R*)-enantiomer underwent a highly enantioselective epoxidation, while the (*S*)-enantiomer was recovered with a 97:3 er.

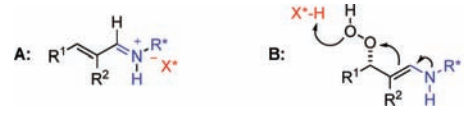
Table 3. Substrate Scope of the Epoxidation of α-Monosubstituted Enals



entry	substrate	product	yield, %[a]	er[b]
1		**6a**	78[c]	99:1 (63:37)[d]
2		**6b**	74	98.5:1.5
3		**6c**	78	99:1[e]
4		**6d**	53% conv.[f]	96:4[g] (5:1 dr)[f] (*S*)-**5d**: 97:3

[a] Isolated yield after reduction with $NaBH_4$. [b] Determined by GC on a chiral stationary phase. [c] Isolated yield of the aldehyde. [d] Using **1b** as the catalyst. [e] The absolute configuration (*R*) of **6c** was assigned by comparing the optical rotation of the corresponding alcohol to the literature value.[18] [f] Determined by GC analysis of the crude reaction mixture. [g] Refers to the major diastereomer; er (minor diastereomer) = 87:13.

Mechanistically, we believe that the primary cinchona-derived amine activates the enal substrates via iminium ion **A**, which undergoes conjugate addition by hydrogen peroxide and ring closure via enamine intermediate **B** (eq 2). Importantly, the chiral phosphoric acid provides additional enantiodiscrimination in both steps as a chiral counterion in **A** and as a Brønsted acid in **B**. This is supported by the dramatic match/mismatch observed when using the phosphoric acids (*R*)-**TRIP** and (*S*)-**TRIP** in the epoxidation of enals **3** (Table 1, entries 3 and 4), as well as the strong influence of the acid cocatalyst on the enantioselectivity of epoxidation of enals **5** (Table 3, entry 1).



(2)

In summary, we have developed a highly enantioselective catalytic epoxidation of α-branched, α,*β*-unsaturated aldehydes. Crucial to the success was the combination of a chiral primary cinchona-based amine and a chiral phosphoric acid. Employing the catalyst pair not only provided excellent enantiocontrol due to the

exceptional synergism of its two components but also allowed for rapid optimization for different substrates owing to its modular nature. The utility of our methodology is underscored by the numerous synthetic applications described for α-branched, α,*β*-epoxyaldehydes, which can now be accessed in a single step from readily available precursors.

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Supporting Information Available: Experimental procedures, compound characterization, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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