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Iron-Catalyzed Asymmetric Epoxidation of β,β-Disubstituted Enones

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Abstract

The combination of $Fe(OTf)_2$ and novel phenanthroline ligands enables the catalytic asymmetric epoxidation of acyclic β,β-disubstituted enones which have been heretofore inaccessible substrate classes. The reactions provide highly enantioenriched α,β-epoxyketones (up to 92% ee) which are further converted to functionalized β-ketoaldehydes with an all-carbon quaternary center.

The catalytic asymmetric epoxidation of olefins presents a powerful strategy for the synthesis of chiral molecules. Thus, numerous efforts have been dedicated to achieving more efficiency with less expensive and environmentally benign catalysts and oxidants as well as the applicability to a variety of substrate classes.[1] Among various useful methods, the development of an iron-catalyzed asymmetric epoxidation should provide us with many advantages, as iron is the most abundant transition metal on the earth and relatively non-toxic.[2, 3, 4] In addition, understanding the mechanism of iron-catalyzed oxidations, which play important roles in biological metabolism, may lead to new insights in biocatalysis and a resulting drug design.[5] Actually, the biomimetic asymmetric epoxidation of styrene derivatives with iron porphyrin complexes was first reported in 1999,[6,7] although it has drawbacks such as the difficult synthesis of the required chiral porphyrin ligands. After studies to pursue non-heme iron catalysts which could be easily prepared and modified, Beller and co-workers reported that the best results have been from iron-catalyzed asymmetric epoxidation of stilbene derivatives with excellent enantioselectivity.[4c, d] However, the high selectivity was obtained only for one specific substrate with 10 mol% catalyst loading. Therefore, it is apparent that iron has yet to be fully introduced in asymmetric epoxidations.

Obviously, the extension of the accessible substrate classes for catalytic asymmetric epoxidation has been desirable. To the best of our knowledge, a general method for the catalytic asymmetric epoxidation of *acyclic* β,β-disubstituted enones is still lacking, probably due to the stereocongestion at the β-carbon in the Weitz-Scheffer type epoxidation, which is commonly employed to access α,β-epoxy carbonyl compounds (Scheme 1, eq 1).[1d, 8] In the case of acyclic enones, a β-substituent (R^3 group) increases the steric repulsion not only between the β-carbon and nucleophile but also between the R^3 group and the acyl group, which causes the substrate to break conjugation to avoid repulsion. As a result, electrophilicity of the double bond in acyclic β,β-disubstituted enones is thought to be lower than that in cyclic or β-non-substituted enones.[9] In contrast, the deconjugation described above should increase reactivity toward electrophilic epoxidation (eq. 2).[9c, i] Herein is a

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Supporting Information Available: Experimental procedures, characterization of compounds **L1-6**, **1a-m**, **1o**, **2a-n**, **3a**, **3l**, **3o**, **4a** and including these ^1H NMR and ^{13}C NMR spectra and HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

solution to the catalytic asymmetric epoxidation of acyclic β,β-disubstituted enones with a newly designed iron complex.

We initially investigated the epoxidation of the readily available (*E*)-dypnone (**1a**) as a model substrate with a variety of complexes consisting of iron metals and phenanthroline ligands attached to binaphthyl moieties (Table 1). After preliminary screening of reaction conditions, peracetic acid as a terminal oxidant was recognized as being crucial to afford epoxides.[10] When **1a** was reacted with 5 mol % of $FeCl_2$ and monophenanthroline ligand (**L1**) in the presence of peracetic acid solution in acetonitrile, the epoxidation resulted in only low conversion of starting material and low selectivity (entry 1). Replacing $FeCl_2$ with $Fe(OTf)_2$ led to a significant improvement in terms of reactivity and enantioselectivity (entry 2). Thus, we turned our attention to the effects of the several monophenanthroline ligands. Introduction of a methyl group on the 2′-position in binaphthyl group dramatically diminished reactivity as well as selectivity (entry 3). To our delight, we found that the introduction of a phenyl group on the 3,8-positions in the phenanthroline moiety, which is expected to restrict the rotation of the bond between binaphthyl group and phenanthroline moiety, resulted in increased enantioselectivity significantly (entry 4). After testing various of ligands bearing aromatic groups on the phenanthroline rings (entry 4–7), we identified **L5** as the ligand providing the excellent yield and enantioselectivity (entry 6). Study of the ligand-metal ratio implied that an iron complex coordinated by two phenanthroline ligands induces high enantioselectivity (entries 6, 8 and 9). Furthermore, catalyst loading was successfully lowered to 2.5 mol % with only a slight decrease of yield and selectivity (entry 10). It should be noted that only one diastereomer of epoxide was observed during the course of this study, while Weitz-Scheffer type epoxidation of trisubstituted α,β-carbonyl compounds often suffered from low diastereocontrol.[9e, g, 11] In addition, this diastereospecific epoxide formation in our catalytic system implies a concerted pathway unlike the stepwise mechanism proposed previously.[12n]

Next, X-ray crystallographic analysis was carried out on single-crystal grown in an acetonitrile solution of $Fe(OTf)_2$ and two equivalent of *rac*-**L3**. As illustrated in Figure 1, an octahedral, mononuclear [Fe(**L3**)$_2$(CH_3CN)(OTf)](OTf) was identified in which two homo-chiral phenanthroline ligands coordinate the iron center in a *cis* topology to construct a pseudo C_2-symmetric iron complex. Although the bidentate phenanthroline ligands can, in principle, adopt many possible diastereomers on the iron center, including the hetero- or homo-combination of *rac*-**L3**, only the diastereomer shown above was selectively crystallized.[13] This selective complexation can be explained by the π–π interactions between the naphthyl groups and diphenyl phenanthroline. However the relationship between this selective formation of iron-ligand complex and enantioselectivities, as well as the actual structure of the catalyst in the reaction medium, is still unclear.[12]

With optimized conditions in hand, we next examined the scope of substrates using $Fe(OTf)_2$-**L5** complex (Table 2). The epoxidations of β,β-disubstituted enones having different electronic characters on the phenacyl groups proceeded smoothly with good yield and with excellent enantioselectivities (entries 1–5). Sterically different types of aromatic substituents were also tolerated (entries 6–8). While an electron-deficient aromatic group on the β-position had no influence on the epoxidation (entry 9), an electron-rich group such as naphthyl group on the β-position showed the deleterious effect on the yield of the product, probably due to the instability of the epoxide obtained under the acidic condition, although the high enantioselectivity was still maintained (entry 10). On the other hand, the substrate bearing an alkyl substituent on the β-position turned out to have inferior reactivity and selectivity compared to aromatic substrates (entry 11). The substrate with an ethyl group as the R^3 substituent kept the high enantiomeric excess (entry 12). Notably, a single

diastereomer was obtained even in employing (Z)-dypnone with poor enantioselectivity. This fact could further support the reaction proceeds via a concerted pathway (entry 13).

Gratifyingly, we realized this chiral iron-phenanthroline system can also be applied not only to α,β-enones but also to a non-activated olefin such as trans-α-methyl stilbene with good enantioselectivity (Scheme 2, eq. 1).[14] With this result in hand, we conducted an intermolecular competition reaction to prove the nature of the active oxidant (eq. 2).[15] A competitive reaction of electron-deficient alkene **1a** and electron-rich one **1n** shows a 2.4:1 preference for the latter with comparable enantioselectivities, confirming the electrophilic nature of the active oxidant.

The utility of chiral α,β-epoxyketones was demonstrated as shown in Scheme 3. The obtained α,β-epoxyketones (**2a** and **2l**) were converted into β-ketoaldehydes (**3a** and **3l**) bearing all-carbon quaternary centers without significant loss of enantiomeric excess by utilizing the Lewis acid-mediated rearrangement (Scheme 3, eq. 1).[16] Unlike the substrate having a phenacyl group, the iron-catalyzed epoxidation of alkyl substituted substrate **1o** gave the rearranged product **3o** as a major compound concomitant with the corresponding epoxide (eq. 2). Eventually, the pure rearranged product **3o** could be successfully obtained in 35% yield over two steps by treatment of the mixture with $BF_3{\cdot}OEt_2$ at room temperature. Furthermore, the chiral α,β-epoxyketones can be transformed to 2-isoxazolidines,[17] which are important intermediates in the preparation of a variety of compounds with 1,3-difunctional groups such as β-hydroxy ketones[18] and γ-amino alcohols.[19] The treatment of **2a** with hydroxylamine hydrochloride in the presence of pyridine furnished a highly substituted 2-isoxazoline **4a** in optically pure form (eq.3).[20]

In summary, we have developed the first iron-catalyzed asymmetric epoxidation of acyclic β,β-disubstituted enones. Essential for success was the use of the iron complex consisting of $Fe(OTf)_2$ and two equivalents of carefully designed phenanthroline ligand. X-ray crystallography revealed a pseudo *C*-2 symmetric iron/ligand complex. Moreover, the construction of the chiral all-carbon quaternary center was also realized by the Lewis acid mediated rearrangement of the obtained chiral epoxides. Furthermore, this work provides a new strategy for designing pseudo C_2-symmetric orthophenanthroline ligand-based catalysts, which should have a vast potential for transition metal catalyzed organic synthesis in general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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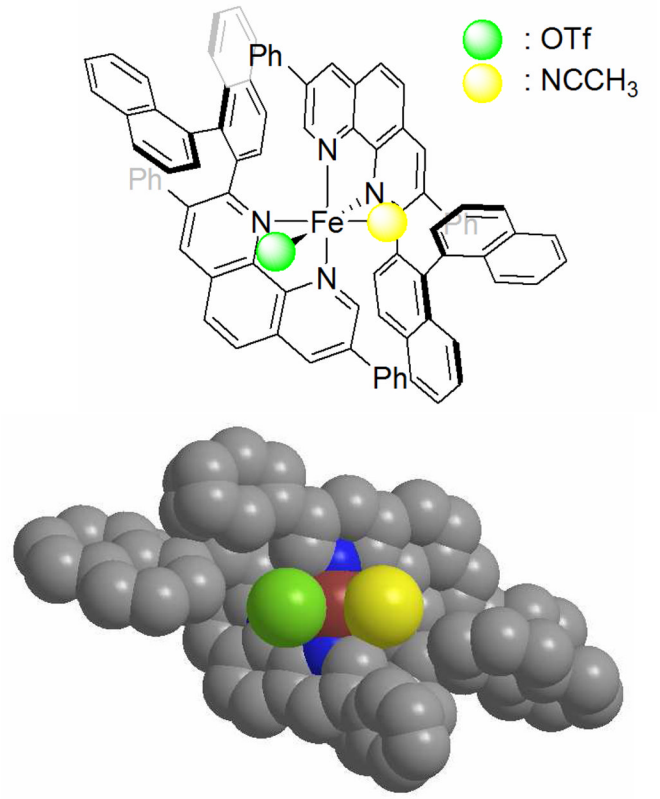
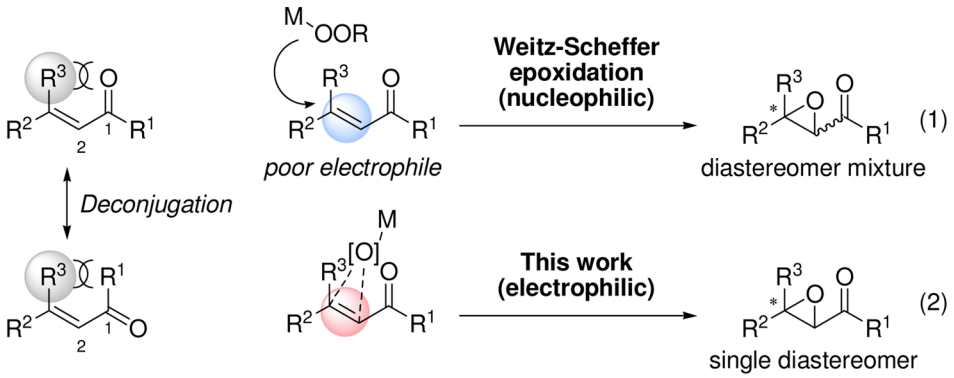
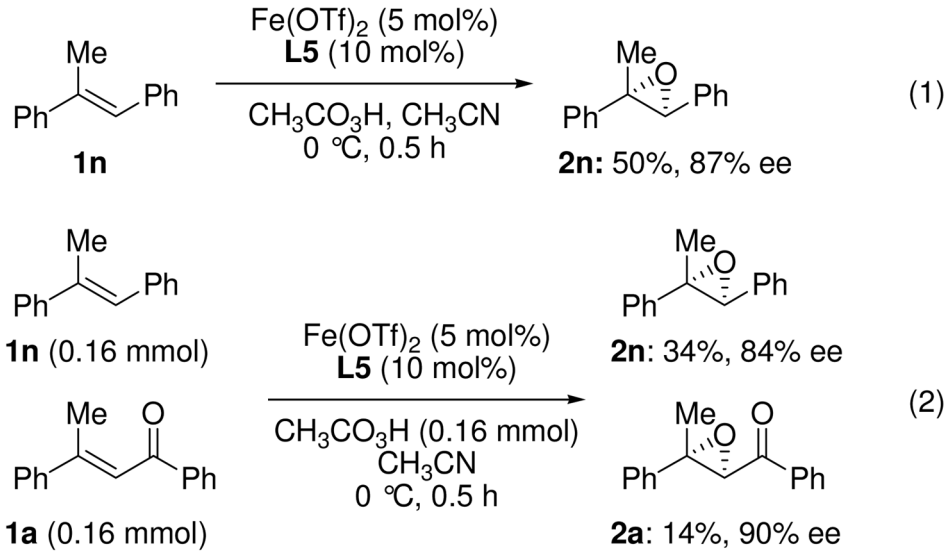


Figure 1.

X-ray structure of [Fe(**L3**)$_2$(CH$_3$CN)(OTf)](OTf) is shown as CPK model. Thermal ellipsoids correspond to 50 % probability. Hydrogen atoms and non-coordinating molecules are omitted for clarity. Triflate group and CH$_3$CN are replaced by a green atom and a yellow atoms for clarity, respectively. See supporting information for details. C: gray, N: blue, Fe: red.

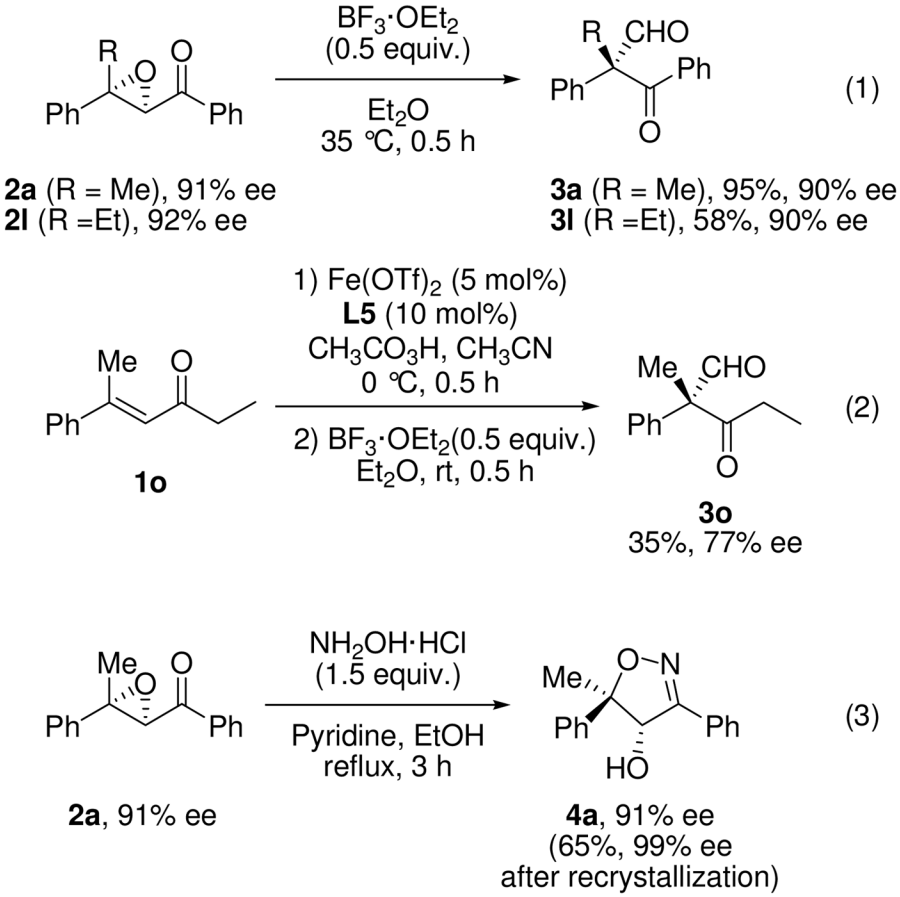


Scheme 1.
The epoxidation of acyclic β,β-disubstituted carbonyl compounds.



Scheme 2.

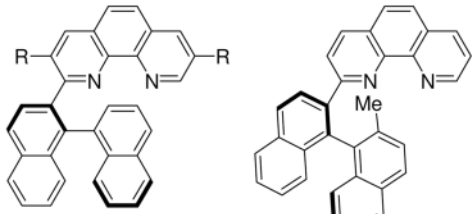
The asymmetric epoxidation with a non-activated olefin and a competitive experiment using electron-rich and electron-deficient olefins.



Scheme 3.
The transformations of optically active α,β-epoxyketones.

Table 1

Screening of reaction conditions



				2a	
entry	**metal**	**ligand L (R)**	**x**	**% yield[a]**	**% ee[b]**
1	$FeCl_2$	**L1** (R=H)	10	17	3
2	$Fe(OTf)_2$	**L1** (R=H)	10	95	57
3	$Fe(OTf)_2$	**L2**	10	<5	17
4	$Fe(OTf)_2$	**L3** (R=Ph)	10	93	83
5	$Fe(OTf)_2$	**L4** (R=*o*-Tol)	10	72	75
6	**$Fe(OTf)_2$**	**L5 (R=*m*-xylyl)**	**10**	**88 (80)**	**91**
7	$Fe(OTf)_2$	**L6** (R=*m*-$Et_2C_6H_3$)	10	64	86
8	$Fe(OTf)_2$	**L5** (R=*m*-xylyl)	5	73	78
9	$Fe(OTf)_2$	**L5** (R=*m*-xylyl)	15	25	53
10[c]	$Fe(OTf)_2$	**L5** (R=*m*-xylyl)	5	81	86

[a] Yields were determined using ^{1}H-NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. The value in parentheses represents isolated yield

[b] Determined by chiral HPLC analysis.

[c] 2.5 mol% of $Fe(OTf)_2$ was used.

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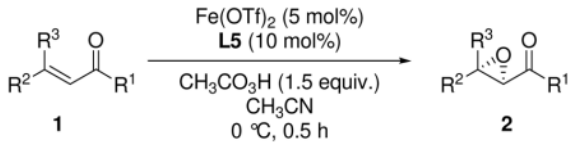
Table 2

Substrate scope of epoxidations



entry	R^1	R^2	R^3	% yield[a]	% ee[b]
1	**1a** Ph	Ph	Me	**2a** (80)	91
2	**1b** *p*-$MeOC_6H_4$	Ph	Me	**2b** (78)	90
3	**1c** *p*-MeC_6H_4	Ph	Me	**2c** (77)	92
4	**1d** *p*-FC_6H_4	Ph	Me	**2d** (78)	92
5	**1e** *p*-$CF_3C_6H_4$	Ph	Me	**2e** (70)	89
6	**1f** *m*-MeC_6H_4	Ph	Me	**2f** (67)	90
7	**1g** *o*-MeC_6H_4	Ph	Me	**2g** (61)	92
8	**1h** 2-Naphthyl	Ph	Me	**2h** (88)	90
9	**1i** Ph	*p*-ClC_6H_4	Me	**2i** (88)	92
10	**1j** Ph	2-Naphthyl	Me	**2j** (45)	92
11	**1k** Ph	*n*-C_3H_7	Me	**2k** (20)	50
12	**1l** Ph	Ph	Et	**2l** (72)	92
13	**1m** Ph	Me	Ph	**2m** (33)	6

[a] Isolated yields.

[b] Determined by chiral HPLC analysis.