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SHORT COMMUNICATION

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Iron(II)-Catalyzed Asymmetric Epoxidation of Trisubstituted α,β-Unsaturated Esters

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The asymmetric epoxidation of trisubstituted α,β-unsaturated esters was developed. The oxidation utilizes a pseudo-C_2-symmetric iron(II) catalyst [Fe(L*)$_2$(CH$_3$CN)(OTf)](OTf) (Tf = trifluoromethylsulfonyl) and peracetic acid as oxidant and yields α,β-epoxy esters with high enantiomeric purity (up to 99 % *ee*).

Introduction

The oxidation reaction is one of the most powerful and fundamental transformations in organic chemistry. Among oxidation reactions, epoxidation of alkenes has been extensively studied, as subsequent ring opening of epoxides affords versatile building blocks for the synthesis of more complex molecules. Pioneering contributions to asymmetric epoxidation, such as Katsuki–Sharpless epoxidation[1] and Jacobsen epoxidation,[2] have involved the use of chiral metal complexes.

Since then, methods for epoxidation have flourished, including those towards electron-deficient olefins, which are less reactive to electrophilic oxidants. Approaches to these targets are typically nucleophilic and generally execute through a Weitz–Scheffer-type mechanism. Examples of such systems include chiral ligand--metal peroxides,[3] phase-transfer catalysts,[4] and polyamino acid catalysts.[5] However, no single method can serve as the ultimate solution for the epoxidation of electron-deficient systems.[6]

Bioinspired iron complexes, in particular, caught our attention, owing to their low cost, abundance, and environmentally benign nature. In fact, many iron catalysts have been developed in the past, including heme and non-heme biomimetic systems.[7] Our interest in β,β-disubstituted enones and α,β-unsaturated esters prompted our development of a non-heme phenanthroline-based ligand for the epoxidation of unsaturated carbonyl compounds. This catalyst has been proven to be effective in the asymmetric epoxidation of β,β-disubstituted enones, which are sterically congested at the β carbon and thus have been hitherto inaccessible.[8] Nevertheless, the utilization of enantioenriched epoxy ketones is relatively narrow compared to epoxy esters, which can be readily converted into other functional groups such as epoxy carboxylic acid, amides, and alcohols. Given such exciting results as those obtained with β,β-disubstituted enones, we turned our attention to α,β-unsaturated esters, from which derivations are expected to be fruitful.

Examples of other systems that target α,β-unsaturated esters are yttrium-chiral biphenyldiol,[9] chiral dioxirane,[10] and chiral Mn–salen complexes.[11] More recently, Cussó et al. reported a chiral Fe–bipyrrolidine catalyst[12] that was used to access a wide range of carbonyl-adjacent olefins, including α,β-unsaturated esters.

Results and Discussion

Unlike the majority of epoxidations of α,β-unsaturated esters, which generally employ disubstituted *trans*-alkenes, we started with the less reported trisubstituted (*E*)-alkene. An initial trial with the –C(CH$_3$)$_2$(*i*Pr) ester (Table 1) by using conditions similar to those reported in preceding work[7] gave valuable results. Upon brief optimization of the reaction conditions, we found performing the reaction at –20 °C significantly deteriorated the yield and enantioselectivity (Table 1, entry 4), whereas raising the temperature to 20 °C produced a lower yield but similar selectivity. Two equivalents of peracetic acid were also observed to be the most desirable conditions (Table 1, entry 2). In addition, stirring the complex formation and epoxidation reactions at 1200 rpm was important to provide ideal results in terms of yields and enantioselectivities. Prompt addition of the oxidant was also desirable, presumably owing to the short lifetime of the iron–oxo species.

Realizing that the –C(CH$_3$)$_2$(*i*Pr) ester generated better results than the *tert*-butyl ester (Table 2, entries 1 and 2), we further screened a variety of alkoxy moieties on the ester that could serve as an auxiliary group for improving stereochemical induction. Subsequent screening of different esters

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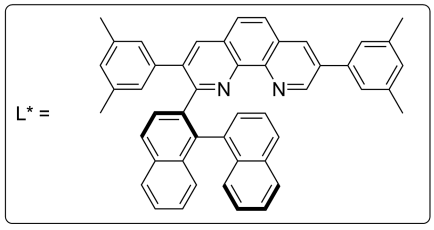
Table 1. Optimizing reaction conditions for the epoxidation of α,β-unsaturated esters.[a]



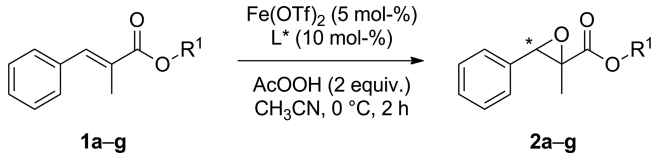
Entry	AcOOH [equiv.]	Temperature [°C]	Yield[b] [%]	*ee*[c] [%]
1	1.8	0	42	92
2	2	0	58	94
3	2.2	0	51	86
4	2	–20	32	66
5	2	20	38	92
6[d]	2	0	43	78
7[e]	2	0	57	86
8[f]	2	0	54	95

[a] Unless otherwise stated, reactions were performed in CH_3CN (0.6 mL) and stirred at 1200 rpm. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction was performed in 0.3 mL of CH_3CN. [e] Reaction was performed in 1.2 mL of CH_3CN. [f] $Fe(OTf)_2$ (10 mol-%. Tf = trifluoromethylsulfonyl) and L* (20 mol-%) were used.

revealed the importance of the alkoxy group on the enantioselectivity of the reaction. As a general trend, tertiary alcohol based esters (Table 2, entries 1–3 and 5) performed better than secondary alcohol based esters (Table 2, entries 4, 6, and 7), owing to higher steric hindrance. Among them, –$C(CH_2)_2$(*t*Bu) ester (Table 2, entry 3) provided an optimum result with respect to both yield and enantioselectivity.

Our exploration into the substrate scope revealed that either the –$C(CH_2)_2$(*t*Bu) or –$C(CH_2)_2$(*i*Pr) ester could be used to induce high enantioselectivity. Whereas in some cases the –$C(CH_2)_2$(*t*Bu) ester gave a higher yield and *ee* (Table 3, **4a** and **2c**), it provided a lower yield than its –$C(CH_2)_2$(*i*Pr) analogue (see compounds **4b** and **4e**) if the starting ester had lower solubility in acetonitrile. Nevertheless, high *ee* values were still maintained even in such cases. Enantioselectivities were remarkably high for substrates with a large naphthyl group at the β position (see compounds **4e**, **4g**, and **4j**). In terms of reactivity, the epoxidation of *para*-substituted phenyl olefins gave a higher yield of the epoxide product than *meta*- and *ortho*-substituted ones. Although this catalytic system works well for phenyl and naphthyl systems, it is not applicable to substrates bearing an alkyl, furyl, or thienyl group at the β position of the ester.

Table 2. Asymmetric epoxidation of α,β-unsaturated esters catalyzed by chiral Fe–phenanthroline catalyst.[a]



Entry[a]	R^1	Yield [%][b]	*ee* [%][c]
1	*t*Bu	49	90
2	$C(CH_3)_2$(*i*Pr)	58	94
3	$C(CH_3)_2$(*t*Bu)	69	95
4	*i*Pr	30	70
5	$C(Et)_3$	43	90
6	$CH(tBu)_2$	26	76
7	cyclododecanyl	18	63

[a] All reactions were performed on a 0.15 mmol scale by using $Fe(OTf)_2$ (5 mol-%), ligand (10 mol-%), peracetic acid (32 wt.-% in dilute acetic acid, 2 equiv.) in CH_3CN (0.6 mL) at 0 °C and quenched after 2 h. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase.

Conclusions

In summary, we developed a highly enantioselective epoxidation of trisubstituted α,β-unsaturated esters catalyzed by a chiral iron–phenanthroline complex by using peracetic acid as the oxidant. This oxidation enantioselectively targets *trans*-α-methylcinnamic acid esters, of which the –$C(CH_2)_2$(*t*Bu) and –$C(CH_2)_2$(*i*Pr) esters gave ideal results. The enantioselectivity was remarkably high for substrates bearing a large group at the β position and was maintained even in cases of lower yields.

Experimental Section

General Procedure for the Asymmetric Epoxidation of Unsaturated Esters: A solution of $Fe(OTf)_2$ (0.32 mL, 0.008 mmol, 0.025 M in CH_3CN) and CH_3CN (0.32 mL) were sequentially added to a flame-dried test tube charged with ligand L* (10.3 mg, 0.016 mmol) and a stir bar under a nitrogen atmosphere, which resulted in a light yellow solution. The complex was stirred vigorously (1200 rpm) for 2–3 h at room temperature. Another dry test tube was charged with the substrate (0.15 mmol) and was flushed with nitrogen. The iron complex (0.6 mL, 0.0075 mmol) in CH_3CN from the first test tube was added by syringe, and the vessel was cooled to 0 °C for 10 min with vigorous stirring (1200 rpm). Peracetic acid (63 μL, 32 wt.-% in dilute acetic acid, 0.3 mmol) was added to the mixture by microsyringe at once, which yielded a near-black solution. The mixture was stirred at this temperature for 2 h and was then quenched with 10% $Na_2S_2O_3$ in 1:1 saturated $NaHCO_3/H_2O$ (3 mL). The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/CH_2Cl_2 = 1:1) to furnish the epoxide. The column was flushed with ethyl acetate (100%) to elute the ligand.

Acknowledgments

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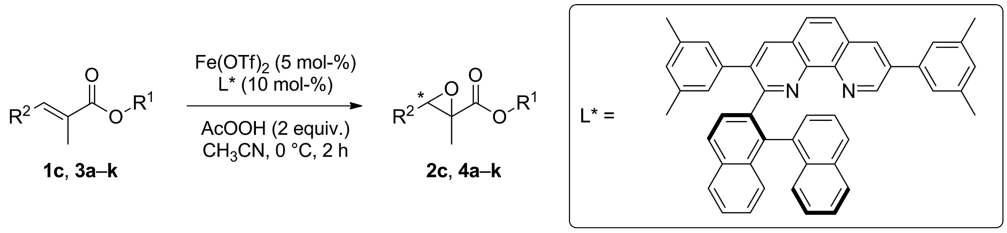
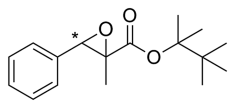
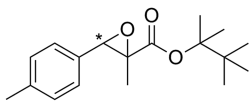
Table 3. Substrate scope of epoxidation.[a,b,c]

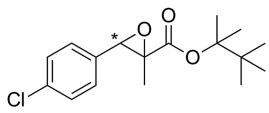




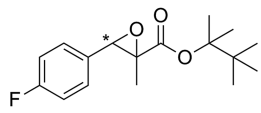
2c
69 %
95 % *ee*



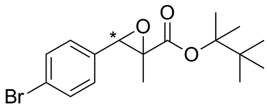
4a
65 %
93 % *ee*



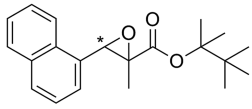
4b
48 %
96 % *ee*



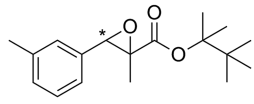
4c
30 %
95 % *ee*



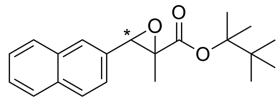
4d
34 %
95 % *ee*



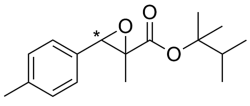
4e
61 %
98 % *ee*



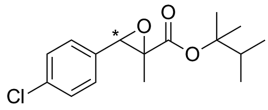
4f
24 %
94 % *ee*



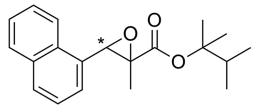
4g
38 %
99 % *ee*



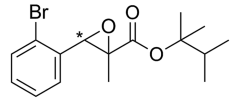
4h
46 %
93 % *ee*



4i
64 %
94 % *ee*



4j
62 %
98 % *ee*



4k
16 %
93 % *ee*

[a] All reactions were performed on a 0.15 mmol scale by using $Fe(OTf)_2$ (5 mol-%), ligand (10 mol-%), substrate (0.15 mmol), and peracetic acid (32 wt.-% in dilute acetic acid, 2 equiv.) in CH_3CN (0.6 mL) at 0 °C and quenched after 2 h. [b] Yields of the isolated products are given. [c] The *ee* values were determined by HPLC on a chiral stationary phase.

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