HHS Public Access

Author manuscript

European J Org Chem. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

European J Org Chem. 2014 December ; 2014(35): 7803–7805. doi:10.1002/ejoc.201403220.

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

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Abstract

An asymmetric epoxidation of trisubstituted α,β-unsaturated esters is described. The oxidation utilizes a pseudo-C_2-symmetric iron(II) catalyst [Fe(L*)$_2$(CH_3CN)(OTf)](OTf) and peracetic acid as oxidant, yielding the α,β-epoxyesters in high enantiomeric purity (up to 99% ee).

Keywords

iron; asymmetric epoxidation; α, β-unsaturated ester

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 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]

Bio-inspired iron complexes, in particular, caught our attention, due to its low-cost, abundant 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.

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This catalyst has been proven effective in the asymmetric epoxidation of β,β-disubstituted enones, which is sterically congested at the β-carbon and thus hitherto inaccessible.[8] Nevertheless, the utilization of enantioenriched epoxy ketones is relatively narrow compared to epoxy esters, which can be readily converted to other functional groups such as epoxy carboxylic acid, amides and alcohols. And given such exciting results from those of β,β-disubstituted enones, we turn 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], which is used to access a wide range of carbonyl adjacent olefins, including α,β-unsaturated esters.

Unlike the majority of epoxidation on α,β-unsaturated esters, which generally employed disubstituted trans-alkenes, we started with the less reported trisubstituted (E)-alkene. An initial trial with -$C(CH_3)_2$(iPr) ester (Table 1) using similar conditions reported in preceding work[7] gave valuable result. Upon a brief optimization of the reaction conditions, we found performing the reaction at −20 °C significantly deteriorates the yield and enantioselectivity (entry 4), while raising the temperature to 20 °C produces a lower yield but similar selectivity. Two equivalents of peracetic acid are also observed to be the most desirable condition (entry 2). In addition, stirring the complex formation and epoxidation reactions at 1200 rpm is important in providing ideal results in terms of yields and enantioselectivities. Prompt addition of oxidant is also desirable presumably due to the short lifetime of the iron-oxo species.

Realizing that the -$C(CH_3)_2$(*i*Pr) ester generates better results than *t*-butyl ester (Table 2, entries 1 and 2), we further screened a variety of alkoxy moieties on the ester, which could serve as an auxiliary group for improving stereochemical induction. Subsequent screening of different esters revealed the importance of the alkoxy group on the enantioselectivity of the reaction. As a general trend, tertiary alcohol based esters (entries 1, 2, 3 and 5) perform better than secondary alcohol based esters (entries 4, 6 and 7), due to higher steric hindrance. Among them, –$C(CH_2)_2$(*t*Bu) ester (entry 3) provided optimum result with respect to both yield and ee.

Our exploration of the substrate scope revealed that either -$C(CH_2)_2$(*t*Bu) or –$C(CH_2)_2$(*i*Pr) esters could be used to induce high enantioselectivity. While in some cases –$C(CH_2)_2$(*t*Bu) ester gave higher yield and ee (Scheme 1, **4a** and **2c**), it would generate lower yield than its –$C(CH_2)_2$(*i*Pr) analogue (**4b** and **4e**) if the starting ester had lower solubility in acetonitrile. Nevertheless, high ee's were still maintained even in such cases. Enantioselectivities are remarkably high for substrates with a large naphthyl group at the β-position (**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 system, it is not applicable to substrates bearing an alkyl, furyl, thienyl group at the β position of the ester.

In summary, we report a highly enantioselective epoxidation of trisubstituted α,β-unsaturated esters catalyzed by a chiral iron-phenanthroline complex using peracetic acid as oxidant. This oxidation can enantioselectively target trans-α-methylcinnamic acid esters, of which $–C(CH_2)_2(t\text{Bu})$ and $–C(CH_2)_2(i\text{Pr})$ 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

To a flame-dried test tube charged with ligand L* (10.3 mg, 0.016 mmol) and stir-bar under nitrogen was added a solution of $Fe(OTf)_2$ (0.32 mL, 0.008 mmol, 0.025 M in CH_3CN) followed by CH_3CN (0.32 mL), resulting in a light yellow solution. The complex was stirred vigorously (1200 rpm) for 2–3 hours at room temperature. Another dry test tube was charged with the substrate (0.15 mmol) and flushed with nitrogen. The iron complex (0.6 mL, 0.0075 mmol) in CH_3CN from the first test tube was added via 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 reaction via microsyringe at once, yielding a near black solution. The reaction was stirred at this temperature for 2 hours and 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 over 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIH (2R01GM068433). We would like to thank Dr. Yasuhiro Nishikawa for his preliminary experimental results. We would like to thank Dr. Antoni Jurkiewicz, and Dr. Jin Qin for their assistance in NMR spectroscopy and mass spectrometry, respectively.

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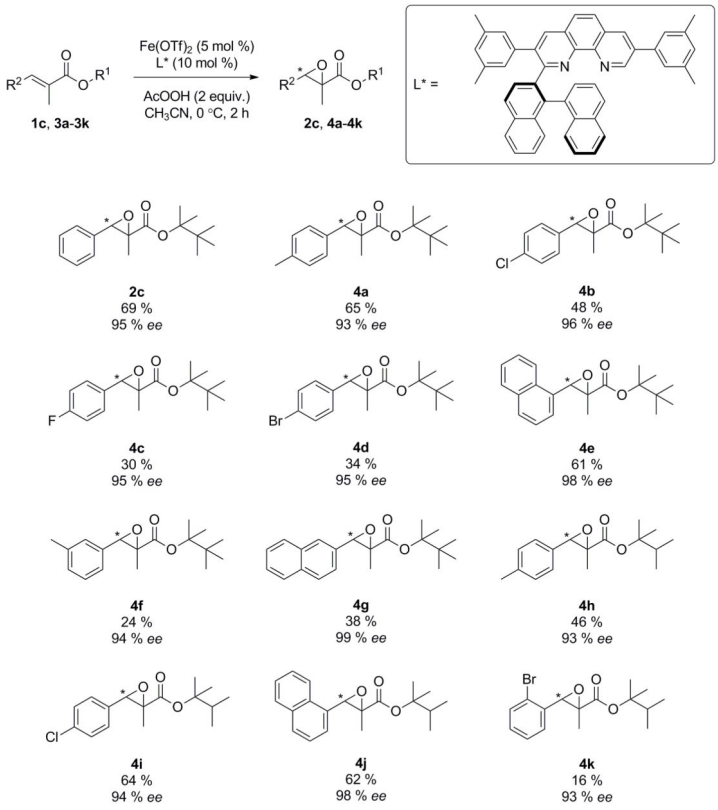
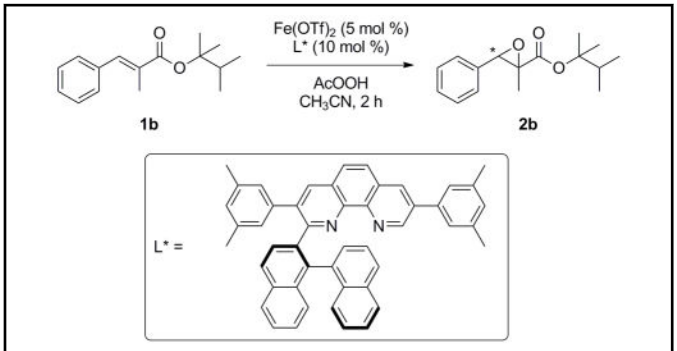


Scheme 1.

Substrate scope of epoxidation. [a] [b] [c] [a] All reactions were carried out on a 0.15 mmol scale using $Fe(OTf)_2$ (5 mol %), ligand (10 mol %), substrate (0.15 mmol), peracetic acid (32 wt. % in dilute acetic acid, 2 equiv) in CH_3CN (0.6 mL) at 0 °C and quenched after 2 hours. [b] Isolated yields. [c] Determined by HPLC on a chiral stationary phase.

Table 1

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



Entry	AcOOH (equiv.)	Temperature (° C)	Yield (%)[e]	ee (%)[f]
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[b]	2	0	43	78
7[c]	2	0	57	86
8[d]	2	0	54	95

[a] Unless otherwise stated, reactions are performed in 0.6 ml CH_3CN and stirred at 1200 revolutions per minute (rpm).

[b] Reaction performed in 0.3 mL CH_3CN.

[c] Reaction performed in 1.2 mL CH_3CN.

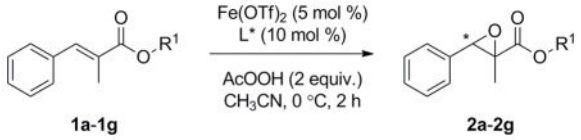
[d] $Fe(OTf)_2$ (10 mol %) and L* (20 mol %) were used.

[e] Isolated yields.

[f] Determined by HPLC on a chiral stationary phase.

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 carried out on a 0.15 mmol scale of 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 hours.

[b] Isolated yields.

[c] Determined by HPLC on a chiral stationary phase.