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Enantioselective Epoxidation of β,β-Disubstituted Enamides with a Manganese Catalyst and Aqueous Hydrogen Peroxide

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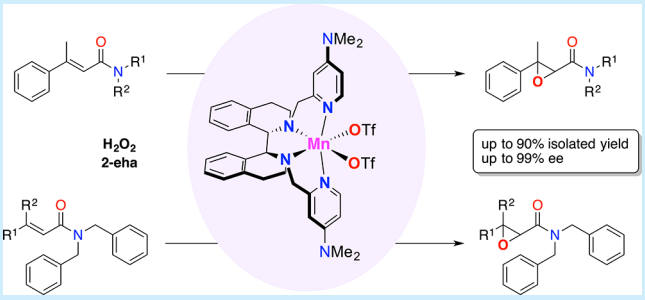
Supporting Information

ABSTRACT: Enantioselective epoxidation of β,β-disubstituted enamides with aqueous hydrogen peroxide and a novel manganese catalyst is described. Epoxidation is stereospecific and proceeds fast under mild conditions. Amides are disclosed as key functional groups to enable high enantioselectivity.



Chiral epoxides are useful building blocks for a number of transformations of interest in organic synthesis.[1] Because of that, methods for asymmetric epoxidation have been actively investigated and are currently known, covering a large range of olefin typology.[2] Still, a few classes of substrates such as acyclic β,β-disubstituted enones constitute standing problems. Methods for epoxidizing asymmetrically β-unsubstituted and β-monosubstituted α,β-unsaturated carbonyl compounds are very well stablished[2e,f,3] because of their importance in synthetic organic chemistry,[4] but the introduction of a second substituent at the β position of acyclic systems makes asymmetric epoxidation notoriously difficult. Weitz−Scheffer-type epoxidation, which is the common methodology for asymmetric epoxidation of enones, is not suitable because the β-carbon of the olefin is sterically protected and also because steric congestion between the β substituent and the carbonyl moiety promotes fast epimerization at this carbon after peroxide attack, producing diastereomeric mixtures.[5] Two previous successful examples operate in β-trifluoromethyl-β,β-disubstituted chalcones and rely on phase-transfer catalysts[6] (Scheme 1a). In this specific class of substrates, the electrophilicity of the olefin is accentuated by the strong electron-withdrawing character of the trifluoromethyl group. Both (*Z*)- and (*E*)-β-trifluoromethyl-substituted enones produce the same epoxide, in which the carbonyl and the CF_3 are *trans* to each other (Scheme 1a). Electrophilic oxidations may offer valuable alternatives, but examples remain scarce and exhibit limited substrate scope (Scheme 1b,c).[7,8]

Biologically inspired reactions based on iron and manganese coordination complexes as catalysts and peroxides (especially hydrogen peroxide) produce electrophilic oxidants and are interesting because of the availability of these metals and hydrogen peroxide combined with their low environmental impact.[3c,9] The structural versatility of this class of catalysts[10] makes them a potential solution for the asymmetric epoxidation of classes of olefins that remain a problem.[11] Herein we disclose a novel manganese catalyst that enables highly enantioselective epoxidation of β,β-disubstituted enamides employing aqueous hydrogen peroxide as the oxidant (Scheme 2). The combination of epoxide and amide groups makes these products valuable chiral building blocks that are currently unavailable by other methods.[9v,w,12,13]

Asymmetric epoxidation of β,β-disubstituted model substrates **S1** and **S2** (Table 1) was initially tested with a series of complexes $\mathbf{L^{N4}M}$ of general formula $[M(CF_3SO_3)_2(L^{N4})]$ (M = Fe, Mn) based on chiral tetradentate bis(amino)bis(pyridine) ligands (L^{N4}) (Figure 1). The study was initially focused on bipyrrolidine-based complexes bearing electron-donating groups on the pyridine (^{Me2N}pdp),[9n,14] and complexes bearing bulky triisopropylsilyl (tips) substituents[15] (^{tips}pdp), all of which have found recent use in asymmetric oxidation reactions. In addition, a new catalyst based on a chiral 1,1′,2,2′,3,3′,4,4′-octahydro-1,4′-biisoquinoline[16] (Ohq) was also considered.

An analysis of the envisioned structures of the complexes $[M(CF_3SO_3)_2(^{Me2N}Ohq)]$ reveals several stereogenic elements. First, each of the isoquinoline rings contains one stereogenic carbon and one stereogenic nitrogen center. In addition, the paddlewheel-like structure of the biisoquinoline may be regarded as an element of axial chirality.[17] Finally, the complexes are chiral at the metal (Δ and Λ).[10] In principle, metalation may result in multiple isomers. Remarkably, only a single complex is observed in the ^{1}H NMR spectrum of ^{Me2N}**Ohq-Fe**, and according to the number of signals it exhibits twofold symmetry.

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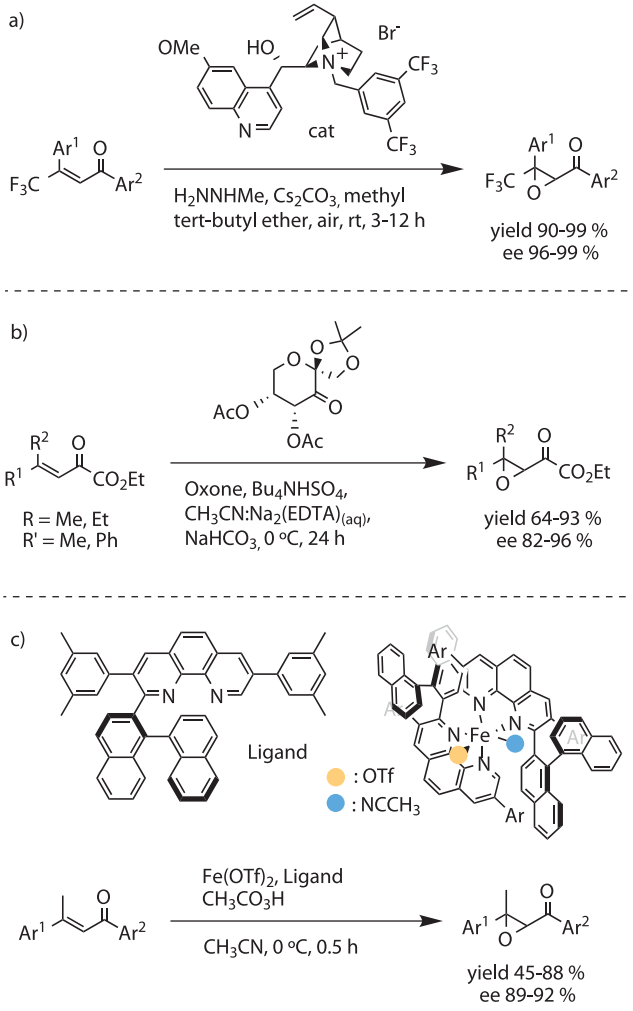
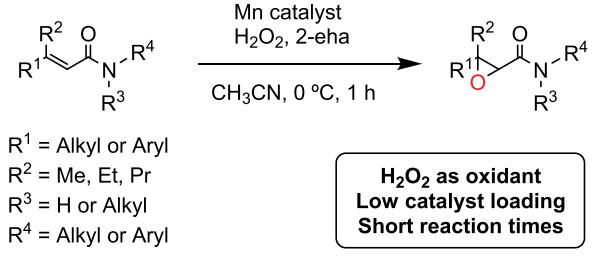
Scheme 1. Previous Examples of Asymmetric Epoxidation of *β,β*-Disubstituted Enones



Scheme 2. Characteristics of the Current System

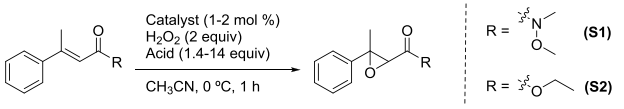


The crystal structure of ^{Me2N}**Ohq-Mn** is shown in Figure 1 and is consistent with the ^{1}H NMR spectrum of the iron analogue, further supporting the above analysis. The complex adopts an octahedral coordination geometry with a characteristic C_2-symmetric *cis-α* topology,[10] in which the two pyridine rings are *trans* to each other and two labile triflate ligands are *cis*- ligated.

The set of catalysts were applied in the asymmetric epoxidation of the synthetically versatile Weinreb amide **S1**. In a standard reaction, 2 equiv of aqueous hydrogen peroxide was delivered by syringe pump during 30 min to an acetonitrile solution of the substrate, the catalyst (1−2 mol %), and a carboxylic acid (2-ethylhexanoic acid (2-eha), 1.4−14 equiv) at 0 °C under air, and after this time, the catalysis was further stirred for another 30 min. The results are collected in Table 1. Epoxidation of **S1** with the electron-rich catalysts ^{Me2N}**pdp-Fe** and ^{Me2N}**pdp-Mn** proceeds in good yields (73−74%) with good enantioselectivities, with the manganese catalyst being more enantioselective (70 and 77% ee, respectively; entries 1 and 2). Use of sterically hindered ^{tips}**pdp-Fe** and ^{tips}**pdp-Mn** produced less satisfactory yields (25 and 57%, respectively) and enantioselectivities (−57 and −32% ee, respectively) (entries 3 and 4). This observation led us to explore alternative catalysts obtained by introducing modifications to the nature of the chiral diamine backbone while preserving the electron-rich nature of the ligands. Toward this end, the novel bis(isoquinoline)-based and electron-rich catalysts ^{Me2N}**Ohq-Mn** (entry 5) and ^{Me2N}**Ohq-Fe** (entry 6) were then considered.

While ^{Me2N}**Ohq-Fe** performs worse than ^{Me2N}**pdp-Fe** in terms of yield and enantioselectivity (compare Table 1, entries 1 and 5), the data reveal excellent performance of ^{Me2N}**Ohq-Mn** in terms of enantioselectivity at the expense of providing a modest yield of epoxide (59% yield, 82% ee; entry 6). Epoxidation was then tested by replacing 2-eha by different

Table 1. Epoxidation of *β,β*-Disubstituted Model Substrates[a]



entry	substrate	catalyst	acid[b]	conv. (yield) (%)[c]	ee (%)[d]
1	**S1**	^{Me2N}**pdp-Fe**	2-eha	90 (73)	70
2		^{Me2N}**pdp-Mn**	2-eha	86 (74)	77
3		^{tips}**pdp-Fe**	2-eha	52 (25)	−57
4		^{tips}**pdp-Mn**	2-eha	100 (57)	−32
5		^{Me2N}**Ohq-Fe**	2-eha	83 (53)	68
6		^{Me2N}**Ohq-Mn**	2-eha	70 (59)	82
7		^{Me2N}**Ohq-Mn**	pva	100 (79)	69
8		^{Me2N}**Ohq-Mn**	eba	95 (78)	77
9		^{Me2N}**Ohq-Mn**	aca	27 (25)	69
10		^{Me2N}**Ohq-Mn**	chca	92 (73)	65
11[e]		^{Me2N}**Ohq-Mn**	2-eha	82 (80)	88
12	**S2**	^{Me2N}**Ohq-Mn**	2-eha	57 (52)	59
13		^{Me2N}**Ohq-Fe**	2-eha	93 (55)	38

[a]For experimental details, see the Supporting Information. [b]Abbreviations: 2-eha, 2-ethylhexanoic acid; pva, pivalic acid; eba, 2-ethylbutanoic acid; chca, cyclohexyl carboxylic acid; aca, 1-adamantanecarboxylic acid. [c]Epoxide yields and substrate conversions were determined by ^{1}H NMR analyses. [d]Determined by HPLC with a chiral stationary phase. [e]The reaction was conducted at −40 °C using 3 equiv of 2-eha.

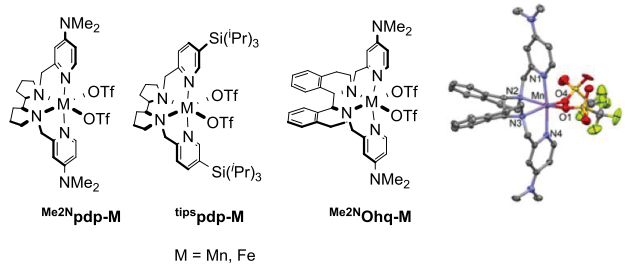


Figure 1. Structures of the $[M(CF_3SO_3)_2(L^{N4})]$ catalysts and ORTEP diagram (50% probability level) of (*S,S*)-^{Me2N}**Ohq-Mn**.

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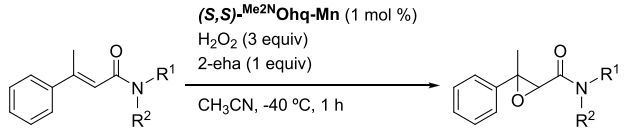
Table 2. Epoxidation of *β,β*-Disubstituted Enamides Using (*S,S*)-^{Me2N}Ohq-Mn[a]



entry	R^1	R^2	enamide	conv. (yield) (%)[b]	ee (%)[c]	isolated yield (%)
1[d,e]	Me	Me	**S3**	100 (80)	94	72
2[d]	Et	Et	**S4**	95 (87)	96	78[f]
3[d]	*i*-Pr	*i*-Pr	**S5**	90 (87)	97	87
4[d]	Bn	Bn	**S6**	99 (90)	99[g]	90
5	Pip[h]	–	**S7**	96 (43)	93	25[i]
6	Ph	Ph	**S8**	52 (0)	–	–
7	Ph	Cy	**S9**	94 (90)	84	83
8	*i*-Pr	H	**S10**	96 (87)	89	78
9[e]	Bn	H	**S11**	100 (87)	92	62
10[e]	Ph	H	**S12**	100 (57)	90	57
11[e]	Adam[j]	H	**S13**	72 (38 + 43[k])	82/84	30 + 43[k]

[a]For experimental details, see the Supporting Information. [b]Epoxide yields and substrate conversions were determined by ^{1}H NMR analyses. [c]Determined by HPLC with a chiral stationary phase. [d]5 equiv of 2-eha. [e]4 equiv of H_2O_2. [f]84:16 *E:Z*. [g]An absolute configuration of (2*R*,3*S*) was determined by X-ray crystallography. [h]Piperidine. [i]Isolated on a 1 mmol scale. [j]1-adamantyl. [k]Product **EO13** (Figure 2).

carboxylic acids (entries 7−10). However, none of these improved the enantioselectivity provided by 2-eha. More effectively, lowering the temperature of the reaction to −40 °C and using 3 equiv of H_2O_2 proved to be effective in improving the yield (80%) while delivering high enantioselectivity (88% ee) (entry 11). Most remarkably, the reactions proceeded stereospecifically, and epimerized epoxides were not detected. It is noteworthy that epoxidation of ester **S2** (entries 12 and 13) proceeds with lower yields and ee's, irrespective of the catalyst (^{Me2N}**Ohq-Mn** or ^{Me2N}**Ohq-Fe**), suggesting that the amide moiety is key in eliciting high enantioselectivity.

The latter observation led us to explore a series of *β,β*-disubstituted enamides (Table 2). Effectively, their epoxidation with (*S,S*)-^{Me2N}**Ohq-Mn** proceeds in good to excellent yields with extraordinarily high enantioselectivity. Epoxidation of *N,N*-dimethylamide **S3** provides the corresponding epoxide in 72% isolated yield with 94% ee (entry 1). Moreover, an increase in the size of the *N*-alkyl groups in the order Me to Et to *i*-Pr (**S3**−**S5**) translates into a systematic increase in the enantioselectivity (94 to 97% ee) while also improving the product yield (72 to 87%) (entries 1−3). Somewhat along this trend, the highest enantioselectivity of the series was obtained for dibenzyl-substituted **S6** (99% ee, 90% yield; entry 4). Piperidine-substituted **S7** is also epoxidized with high enantioselectivity (90% ee) but modest product yield (25%) (entry 5). Instead, the oxidation of *N,N*-diphenyl-substituted amide **S8** (entry 6) produces multiple nonidentified products. On the other hand, *N*-cyclohexyl-*N*-phenyl-substituted **S9** is epoxidized in good yield (83%) and enantioselectivity (84% ee) (entry 7). Moreover, this system can also be applied to monosubstituted enamides (entries 8−11). Oxidation of isopropyl (**S10**) and benzyl enamide (**S11**) provides the corresponding epoxides in satisfactory yields (78 and 62%, respectively) and enantioselectivities (88 and 92% ee, respectively). Epoxidation of phenyl enamide **S12** also proceeds with high enantioselectivity (90% ee) in moderate yield (57%).

Finally, the sterically congested adamantyl-substituted **S13** is oxidized to the corresponding epoxide (30% yield, 82% ee) and the epoxide where the adamantane has been also hydroxylated (**EO13**) (43% yield, 84% ee) (Figure 2). In this case, the sterically congested olefinic site competes for the oxidizing species with the tertiary C−H bonds of adamantane.

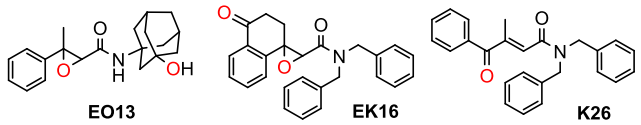


Figure 2. Oxidation products in which oxidation of an aliphatic C−H bond is observed.

The versatility of the reaction was then further evaluated in the epoxidation of *β,β*-disubstituted dibenzyl enamides having different substituents at the *β* position (Table 3). The crowded nature of the olefin in these substrates makes them particularly challenging. Epoxidation of enamides where the *β*-methyl group has been replaced by larger substituents such as ethyl (**S14**) or isopropyl (**S15**) proceeds with different outcomes. The former is epoxidized with high enantiomeric excess (99% ee) and yield (84%) (entry 1). However, for the bulkier isopropyl substituted **S15**, the yield dropped substantially (33%, 85% ee; entry 2), presumably reflecting the increase in steric constraints in the olefin, which prevents attack by the catalyst. Cyclic *β,β* substituents are also well-tolerated: substrate **S16** (entry 3) containing the 3,4-dihydronaphthyl substituent is epoxidized with high ee (91%) and yield (62%), but epoxidation occurs in combination with oxidation of a benzylic methylenic site, producing epoxide **EK16** (Figure 2). Substituents in the aromatic ring also have distinct effects. While *ortho* substitution (**S17**) completely inhibits the activity of the catalyst (entry 4), *meta* and *para* substituents are well-tolerated, and epoxide products are obtained in good yields (64 and 74%, respectively) with excellent enantioselectivity (98 and 99% ee, respectively) (entries 5 and 6). Presumably, *ortho* substituents exert steric protection of the olefinic site that prevents its oxidation. Epoxidation of substrates having substituents with different electronic characters on the phenyl group (**S19**−**S22**) proceeded smoothly in good yields with excellent enantioselectivity (97−99% ee; entries 6−9). Nonetheless, the large naphthyl group at the *β* position in **S23** had a

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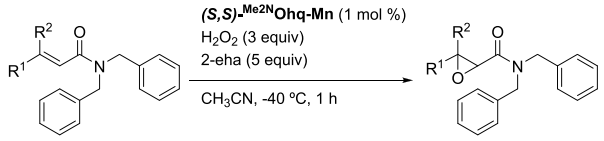
Table 3. Epoxidation of *β,β*-Dibenzyl Enamides Using (*S,S*)-^{Me2N}Ohq-Mn[a]



entry	R^1	R^2	enamide	conv. (yield, %)[b]	ee (%)[c]	isolated yield (%)
1[d]	Ph	Et	**S14**	100 (83)	99	84
2[e]	Ph	*i*-Pr	**S15**	92 (39)	85	33
3	DHN[f]	–	**S16**	100 (75)	91	62[g]
4	*o*-MePh	Me	**S17**	33 (3)	–	–
5	*m*-MePh	Me	**S18**	100 (76)	98	64
6[d]	*p*-MePh	Me	**S19**	100 (95)	99	74
7[d]	*p*-CF_3Ph	Me	**S20**	93 (65)	97	65
8[h]	*p*-MeOPh	Me	**S21**	95 (70)	98	57
9[d]	*p*-ClPh	Me	**S22**	100 (90)	99	83
10[d]	Naph[i]	Me	**S23**	86 (59)	99	–
11[e]	Cy	Me	**S24**	85 (20)	65	–
12	*i*-Pr	Me	**S25**	86 (52)	95	51
13	Bn	Me	**S26**	86 (42[j])	95	35[k]
14	Et	Ph	**S27**	40 (4)	–	–

[a]For experimental details, see the Supporting Information. [b]Epoxide yields and substrate conversions were determined by ^{1}H NMR analyses. [c]Determined by HPLC with a chiral stationary phase. [d]4 equiv of H_2O_2. [e]Acetic acid was used instead of 2-eha. [f]3,4-dihydronaphthyl. [g]Product **EK16** (Figure 2). [h]2 equiv of H_2O_2. [i]2-Naphthyl. [j]Benzylic ketone **K26** (Figure 2) was also obtained as product in 19% yield. [k]Isolated on a 1.5 mmol scale.

counterproductive effect on the yield of the product (entry 10). Finally, aliphatic enones also appear to be suitable substrates for the system, although some limitations arise. Cyclohexyl-substituted **S24** is epoxidized in modest yield (20%) and enantioselectivity (65%) (entry 11), presumably reflecting again a high steric demand at the olefin. Instead, less-demanding isopentyl (**S25**, entry 12) and benzyl (**S26**, entry 13) substituted enamides are epoxidized with high enantioselectivities (95 and 98% ee, respectively), albeit in moderate yields (51 and 35%, respectively). Benzylic oxidation (19%) to form **K26** (Figure 2) competes with olefin epoxidation in **S26**. Finally, *β*-ethyl-*β*-phenyl-substituted **S27**, in which the aromatic ring is *cis* with respect to the carbonyl moiety, proved to be unreactive.

In conclusion, highly enantioselective epoxidation of *β,β*-disubstituted enamides is accomplished with a novel manganese catalyst and hydrogen peroxide. The system operates under mild experimental conditions, is stereospecific, and affords highly enantiomerically enriched epoxides in moderate to excellent product yields, providing a reliable methodology for this class of substrates. The stereospecific nature of the reaction and the positive role of the carboxylic acid in the product yields and enantioselectivities are congruent with recent mechanistic studies in related catalysts, suggesting that a highly electrophilic Mn^V−oxo−carboxylate species is responsible for the epoxidation.[18] The positive role of the amide moiety in securing the high enantioselectivity, while yet not elucidated, provides a useful handle that may find utility in other oxidation reactions of difficult substrates.[13,15b,19] Furthermore, the work further extends the portfolio of highly enantioselective oxidation catalysts, showcasing the powerful reach of this class of systems to address standing problems in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00729.

Complete experimental details and characterization data (PDF)

Accession Codes

CCDC 1894831−1894832 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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