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Synergistic Interplay of a Non-Heme Iron Catalyst and Amino Acid Coligands in H_2O_2 Activation for Asymmetric Epoxidation of α-Alkyl-Substituted Styrenes**

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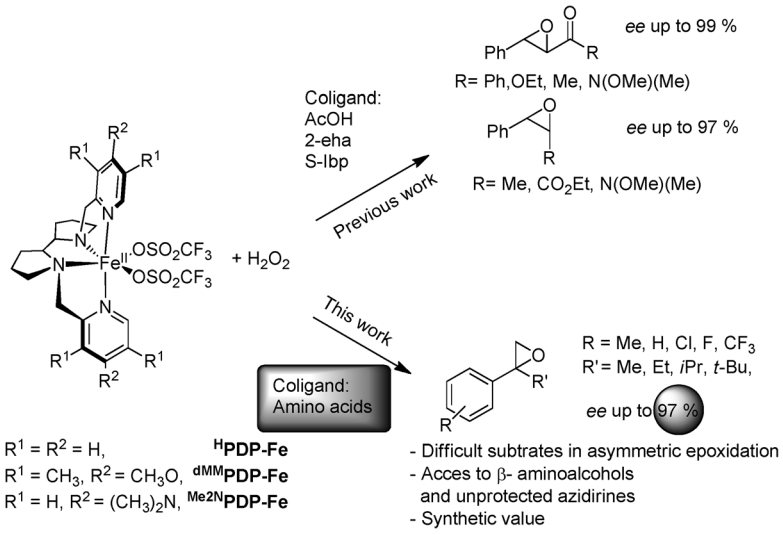
Abstract: *Highly enantioselective epoxidation of α-substituted styrenes with aqueous H_2O_2 is described by using a chiral iron complex as the catalyst and N-protected amino acids (AAs) as coligands. The amino acids synergistically cooperate with the iron center in promoting an efficient activation of H_2O_2 to catalyze epoxidation of this challenging class of substrates with good yields and stereoselectivities (up to 97% ee) in short reaction times.*

Biologically inspired catalysts are currently explored with the aim to produce selective oxidation reactions. The quest for catalytic methodologies that provide novel reactivities and selectivities that could complement those attained with traditional oxidants, or that could represent a more efficient alternative constitute major reasons of interest for this approach.[1] Among oxidations, asymmetric epoxidation is a reaction of broad interest in synthetic organic chemistry because of the synthetic value of chiral epoxides.[2] Recently we reported that iron complexes with electron-rich aminopyridine ligands catalyze highly stereoselective epoxidation of enones and *cis*-β-substituted styrenes with H_2O_2 (Scheme 1, 2-eha = 2-ethylhexanoic acid, S-Ibp = *S*-ibuprofen).[3] In these experiments, carboxylic acids were also key elements for controlling O–O breakage and epoxidation stereoselectivity. The system could therefore be adapted to cover novel families of substrates just by employing other carboxylic acids, without requiring preparation of novel chiral iron catalysts. We reasoned that this variability could be an important aspect because the activity and reaction mechanisms of iron complexes when reacting with peroxides are very dependent on the nature of aminopyridine ligands.[1] With these considerations in mind, we focused our attention on amino acids (AAs) as putative coligands for the system. While their large structural diversity finds wide use in organocatalytic epoxidation methodologies,[2c,d,4] the compatibility of amino acids with metal-catalyzed oxidations has few but notable precedents.[5]

Herein we show that synergistic cooperation between a non-heme iron coordination complex and amino acid coligands allows for efficient activation of hydrogen peroxide leading to highly stereoselective epoxidation reactions in short reaction times. Remarkable aspects of the current system are: a) the use of iron as the metal catalyst and aqueous H_2O_2 as oxidant, reagents that are attractive because of their availability and low environmental impact.[6–8] b) The use of amino acids as a versatile source of chirality. c) The highly stereoselective epoxidation of α-substituted styrenes, a class of substrates that remain very challenging for other asymmetric epoxidation methods.[9] Furthermore the present system can be considered a remarkable approach towards the mimicking of selective oxidation reactions taking place in non-heme iron-dependent oxygenases because a number of these enzymes rely in controlled breakage of the O–O bond, and amino acids are common biological iron ligands and provide a main element of chirality regulating stereoselectivity in the enzymatic transformations.



Scheme 1.

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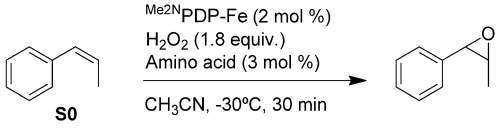
(*S*,*S*)-^{Me2N}PDP-Fe (2 mol%, Scheme 1) and amino acid coligand (3 mol%) in acetonitrile solution at −30°C, over which 1.8 equivalents of H_2O_2 were delivered by syringe pump over 30 min (Table 1). This substrate was chosen to compare the efficiency of amino acids with respect to simple organic acids as co-catalyst.[3]

The initial screening involved the use of a range of amino acids, and also an analysis of the nature of the *N*-protecting group in reaction performance. Since both the amino acid and the iron catalyst are chiral, each amino acid was tested with both (*S*,*S*)-^{Me2N}PDP-Fe (3rd–4th columns in Table 1) and (*R*,*R*)-^{Me2N}PDP-Fe (5–6th columns in Table 1). The first significant observation is that proline is not a valid acid partner (Table 1, entry 1), presumably because the unprotected amine poisoned the catalyst by chelation. However, when the amine site was protected, the reaction took place with moderate to excellent yields and good enantioselectivities (entries 2–4). No major side product was detected. Boc as a protecting group provides the highest enantioselectivities of the series. Moreover, when the reaction was carried out using ^{dMM}PDP-Fe (Scheme 1), a catalyst which has less-electron-donating groups in the pyridine rings, moderate yields were obtained and the enantioselectivities decrease (Table 1 entry 6). In the same vein, the use of the simplest ^{H}PDP-Fe (Scheme 1) produced poor yields and stereoselectivities (Table 1, entry 7), thus illustrating the important role of the electronic properties of the aminopyridine ligand in the activation of H_2O_2 and in the O-delivering step. Then, a series of Boc-protected amino acids were tested, resulting in an improvement of the enantioselectivity up to 81 and 80% *ee* using *N*-Boc-*t*-Leu-OH (entry 8) and *N*-Boc-ILeu-OH (entry 10), respectively. Since both the iron catalyst and the amino acid coligand are chiral, matching–mismatching effects resulting from combination of the respective chiralities were also evaluated by using the two enantiomeric *R*,*R* and *S*,*S* forms of the catalyst (compare columns 4 and 6 in Table 1). Without exception when the same amino acid was employed in combination with the two enantiomeric forms of the iron catalyst, the opposite epoxide enantiomer was obtained as major product. In addition, as a general trend, small differences in yields and stereoselectivities were observed for each of these pair of reactions. A different picture was however observed when the *N*-Npha-ILeu-OH derivative was employed (entry 13). This amino acid not only

Table 1: Screening of amino acids in asymmetric epoxidation reaction (Table continued on next page).[a]



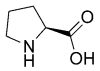
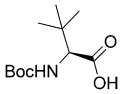
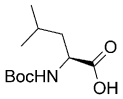
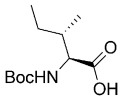
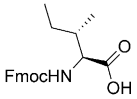
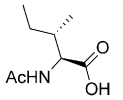
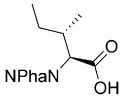
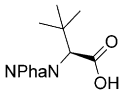
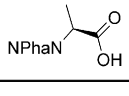
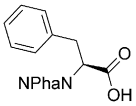
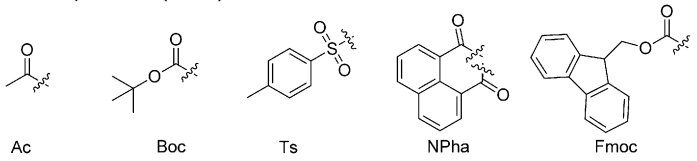
Catalyst Entry	Amino acid		(*S*,*S*′)-^{Me2N}PDPFe[b] Conv. (Yield) [%]	*ee* [%]	(*R*,*R*′)-^{Me2N}PDPFe[b] Conv. (Yield) [%]	*ee* [%]
1		Pro-OH	–	–	n.d.	n.d.
2		*N*-Ts-Pro-OH	47 (30)	63	87 (69)	76
3		*N*-Fmoc-Pro-OH	100 (75)	74	96 (77)	77
4		*N*-Boc-Pro-OH	100 (87)	79	95 (90)	77
5[c]		*N*-Boc-Pro-OH	100 (90)	76	n.d.	n.d.
6[d]		*N*-Boc-Pro-OH	50 (40)	32	n.d.	n.d.
7[e]		*N*-Boc-Pro-OH	55(27)	17	n.d.	n.d.
8		*N*-Boc-*t*-Leu-OH	100 (93)	80	100 (91)	81
9		*N*-Boc-Leu-OH	100 (89)	71	100 (89)	75
10		*N*-Boc-Ileu-OH	100 (96)	80	100 (83)	73
11		*N*-Fmoc-Ileu-OH	100 (84)	78	100 (84)	74
12		*N*-Ac-Ileu-OH	100 (89)	78	100 (82)	74
13		*N*-Npha-Ileu-OH	79 (51)	49	100 (81)	87
14		*N*-Npha-*t*-Leu-OH	72 (57)	70	100 (89)	85
15		*N*-Npha-Ala-OH	92 (74)	70	100 (87)	76

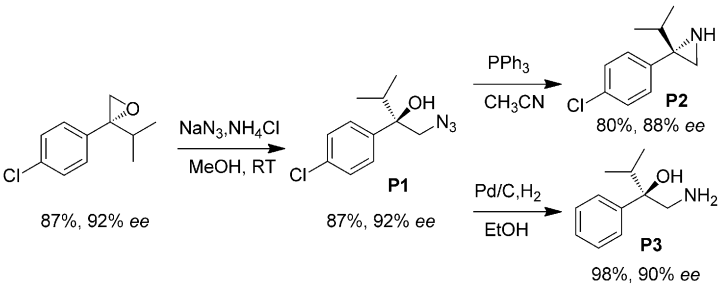
Table 1: (Continued)

Catalyst Entry	Amino acid		(*S*,*S*′)-^{Me2N}PDPFe[b] Conv. (Yield) [%]	*ee* [%]	(*R*,*R*′)-^{Me2N}PDPFe[b] Conv. (Yield) [%]	*ee* [%]
16		*N*-Npha-Phe-OH	98 (79)	68	100 (84)	74

[a] Reaction conditions are ^{Me2N}PDP-Fe (2 mol%), H_2O_2 (1.8 equiv) and amino (3 mol%), *cis*-β-methylstyrene (**S0**, 0.11 M) in CH_3CN at −30 °C during 30 min. [b] Conversion and yield were calculated using an internal standard. The *ee* values were determined by chiral GC. [c] 1.4 equiv of *N*-Boc-Pro-OH. [d] ^{dMM}PDP-Fe as catalyst.[3] [e] ^{H}PDP-Fe as catalyst. n.d.: not determined. See Supporting Information for a complete list of the amino acids tested. All the amino acids have *S* configuration. The absolute configuration of the epoxide obtained with (*S*,*S*′)-^{Me2N}PDPFe was determined as (*1R*,*2S*) by comparison of optical rotation data with that from the literature,[10] in the case of (*R*,*R*′)-^{Me2N}PDPFe the configuration of the epoxide is (*1S*,*2R*).



provides the best stereoselection among the series (up to 87% *ee*) but also a pronounced difference in epoxide yield and *ee* values responding to matching–mismatching between chiralities of *N*-Npha-ILeu-OH and of the iron complex ^{Me2N}PDP-PFe were observed (81 vs 51% in yield and 87 vs 49% in *ee*). We interpreted this large difference as a signature that this amino acid effectively helps in defining the structure of the active site. For comparison, when the reaction is performed in the absence of amino acid, epoxide was obtained in modest 20% yield and 46% *ee*.[3]



Scheme 2.

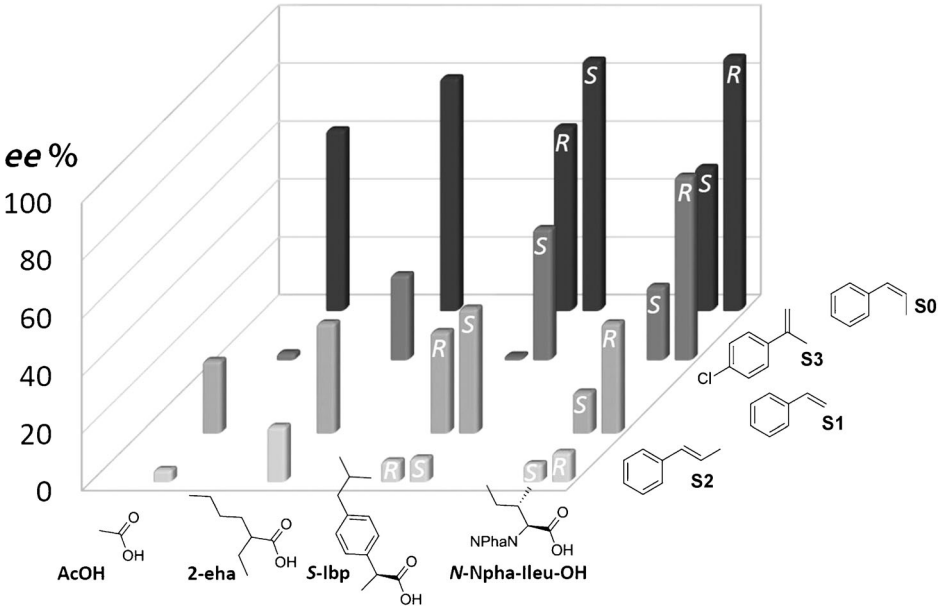
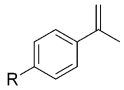
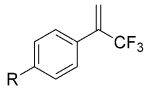
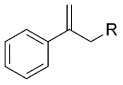
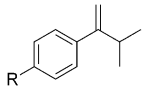
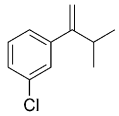
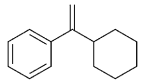
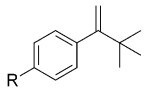
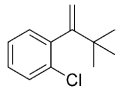


Figure 1. The stereoselectivity on epoxidation of structurally different styrenes with *R*,*R* and *S*,*S* forms of ^{Me2N}PDP-Fe using different carboxylic acids. See supporting information for details of the reactions. *R* and *S* inside the bars refer to the chirality of ^{Me2N}PDP-Fe. When chirality is not specified, *S*,S-^{Me2N}PDP-Fe was employed as the catalyst.

The benefits of using *N*-Npha-ILeu-OH and *N*-Npha-*t*-Leu-OH as acid coligand partners in asymmetric epoxidations catalyzed by ^{Me2N}PDP-Fe was then tested against different families of substrates (Figure 1 and Table S2). Styrenes **S1**–**S4** differing in the substitution patterns at the olefinic site were chosen because these are recognized as a challenge for iron asymmetric epoxidation catalysis.[6f] Furthermore results were compared with those obtained with other carboxylic acids which had previously proved to be excellent in the epoxidation of aromatic and cyclic aliphatic enones, as well as in *cis*-aromatic olefins.[3] Most interesting from this analysis was the observation that an α-substituted styrene (**S3**) was epoxidized with values of stereoselectivity substantially better than any of the carboxylic acids previously studied. α-Alkyl substituted styrenes are particularly challenging for asymmetric catalysis because of the difficulty to differentiate between the enantiotopic faces of these substrates.[11] To our knowledge good levels of *ee* values in their epoxidation is limited to chloroperoxidase (up to 89% *ee*)[9a] and Shi's organocatalysts (up to 88% *ee*).[9b] Therefore, catalytic epoxidation of a series of this class of substrates was evaluated under optimized conditions using *N*-Npha-ILeu-OH.

We examined examples of α-methylstyrene derivatives (Table 2, entries 1–3). In these cases the yields obtained were

Table 2: Substrate scope on the asymmetric epoxidation.[a]

Entry	Substrate	Yield [%]	Npha-I-Leu-OH (*ee*) [%]
			
1	R = Cl (S3)	90	63
2	R = NO_2 (S4)	94	66
3	R = CF_3 (S5)	88	50
			
4	R = H (S6)	ca. 20 (5)	84
5	R = Cl (S7)	16 (16)	87
			
6	R = Me(S8)	78	80
7	R = OAc (S9)	80	83
8	R = OPiv (S10)	83	81
9	R = Ph (S11)	70	80
			
10	R = H (S12)	60	91
11	R = Cl (S13)	87	92
12	R = F (S14)	85	91
13	R = CF_3 (S15)	77	84
			
14	S16	90	97[b]
			
15	S17	52	75
			
16	R = Me (S18)	79	93
17	R = H (S19)	85	91
18	R = Cl (S20)	80	94
19	R = F (S21)	85	96
			
20	S22	57	92
			
21	S23	–	–

[a] Reaction conditions are (*R*,*R*)-^{Me2N}PDP-Fe (2 mol%), H_2O_2 (1.8 equiv), and *N*-Npha-ILeu-OH (3 mol%) in CH_3CN at −30°C during 30 min. The *ee* values and configuration are determined by chiral GC. [b] The *ee* values are determined by ^{1}H NMR with europium tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] (see Supporting Information for details). Absolute configuration of epoxides at entries 10 and 11 are (*R*) and were determined by comparing optical rotation with that described in the literature.[9b]

excellent (88–94%), but enantioselectivities were moderate (50–66% *ee*). On the other hand, replacing the α-methyl by a trifluoromethyl group (entries 4–5) the enantioselectivity increased up to 87%, although in this case yields were small (5–16%), presumably reflecting the poor reactivity of this electron-deficient olefin with an electrophilic reagent. Most interestingly, when the α position of styrenes was modified by sterically more demanding groups such as ethyl, isopropyl, and *tert*-butyl the enantioselectivities increased up to 97% *ee* (entries 6–20), although the cyclohexyl derivate substrate **S17** provided a more modest *ee* value (75%). The system tolerates *o*, *m*- and *p*- substitutions in the aromatic ring, and also different functional groups, such as nitro, esters, and halides. On the other hand, epoxidation of α,α′-dialkyl substrates provided very low enantioselectivities (16% *ee* for 2-methyl-hept-1-ene; not shown) and pyridine heterocycles inhibit the catalysis (entry 21).

To illustrate the utility of this methodology, epoxide resulting from epoxidation of **S13** (Scheme 2) was transformed into azido-alcohol **P1** with no erosion of the enantioselectivity (yield 87%, 92% *ee*), which can then be converted into unprotected aziridine **P2** through a Staudinger reaction (80%, 88% *ee*),[12] which can be regarded as an entry into chiral amines. Alternatively, reduction of the azide using palladium under hydrogen conditions (see Scheme 2) provide the corresponding chiral 1,2-amino alcohol **P3** (yield 98%, 90% *ee*), which can be seen as a precursor for the synthesis of oxazolines, among other interesting products.[13]

In summary, the present work shows the use of amino acids as suitable coligands in epoxidation reactions with aqueous H_2O_2 using bioinspired non-heme iron catalysts,[14] extending the substrate scope of these systems to the challenging terminal olefins. The present approach is appealing as it provides proof of concept that the versatility of these systems can be extended straightforwardly towards novel classes of substrates without requiring an elaborate development of novel chiral catalysts.

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Keywords: amino acids · asymmetric catalysis · bioinspired catalysis · epoxidation · non-heme iron complexes

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