

## Making Fe(BPBP)-catalyzed C–H and C=C oxidations more affordable†

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The limited availability of catalytic reaction components may represent a major hurdle for the practical application of many catalytic procedures in organic synthesis. In this work, we demonstrate that the mixture of isomeric iron complexes [Fe(OTf)<sub>2</sub>(*mix*-BPBP)] (*mix*-**1**), composed of  $\Lambda$ - $\alpha$ -[Fe(OTf)<sub>2</sub>(*S,S*-BPBP)] (*S,S*-**1**),  $\Delta$ - $\alpha$ -[Fe(OTf)<sub>2</sub>(*R,R*-BPBP)] (*R,R*-**1**) and  $\Delta/\Lambda$ - $\beta$ -[Fe(OTf)<sub>2</sub>(*R,S*-BPBP)] (*R,S*-**1**), is a practical catalyst for the preparative oxidation of various aliphatic compounds including model hydrocarbons and optically pure natural products using hydrogen peroxide as an oxidant. Among the species present in *mix*-**1**, *S,S*-**1** and *R,R*-**1** are catalytically active, act independently and represent ca. 75% of *mix*-**1**. The remaining 25% of *mix*-**1** is represented by mesomeric *R,S*-**1** which nominally plays a spectator role in both C–H and C=C bond oxidation reactions. Overall, this mixture of iron complexes displays the same catalytic profile as its enantiopure components that have been previously used separately in sp<sup>3</sup> C–H oxidations. In contrast to them, *mix*-**1** is readily available on a multi-gram scale via two high yielding steps from crude *DL*/*meso*-2,2'-bipyrrrolidine. Next to its use in C–H oxidation, *mix*-**1** is active in chemospecific epoxidation reactions, which has allowed us to develop a practical catalytic protocol for the synthesis of epoxides.

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## Introduction

Selective oxidation of hydrocarbons is still a challenging task in modern organic synthesis,<sup>1</sup> while the oxidative modification of functionalized molecules poses to chemists even more complex selectivity issues.<sup>2</sup> Only a limited number of intelligently designed homogeneous catalysts, answering this selectivity call, are available.<sup>3</sup> One of them is the single site catalyst  $\Lambda$ - $\alpha$ -[Fe(*S,S*-BPBP)(MeCN)<sub>2</sub>](SbF<sub>6</sub>)<sub>2</sub> (*S,S*-**1SbF<sub>6</sub>**) reported by White *et al.* (BPBP = *N,N'*-bis(2-picolyl)-2,2'-bipyrrrolidine) (Fig. 1, Scheme 1).<sup>3a,4</sup> This catalyst was shown to be predictive and outstandingly selective in challenging aliphatic C–H oxidations of numerous and structurally diverse natural compounds using hydrogen peroxide as a convenient oxidant. Moreover, enantiopure *R,R*- and *S,S*-**1SbF<sub>6</sub>** complexes are now commercially available, but at a price per gram at least 6-fold higher than for instance the Ru-based Grubbs I catalyst. This clearly indicates that the value of the optically pure BPBP

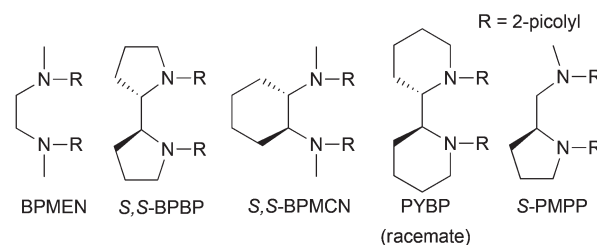


Fig. 1 Structurally related tetradentate ligands applied in preparative Fe-catalyzed C–H and C=C oxidation reactions with H<sub>2</sub>O<sub>2</sub>.

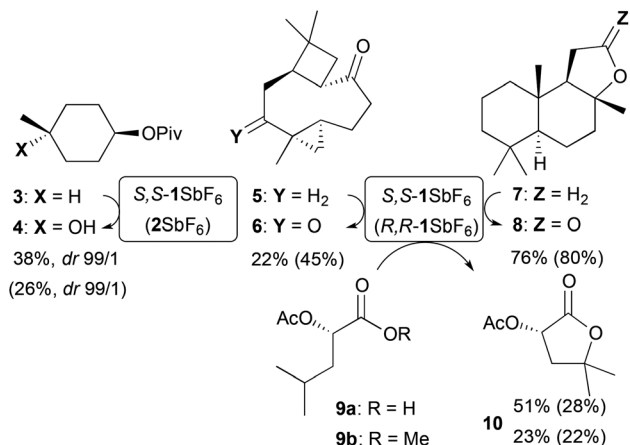
ligand has a dominant share in the production costs of this iron catalyst.

The *S,S*-**1SbF<sub>6</sub>** complex was reported as a superior C–H oxidation catalyst compared to its predecessor – racemic  $\Delta/\Lambda$ - $\alpha$ -[Fe(BPMEN)(MeCN)<sub>2</sub>](SbF<sub>6</sub>)<sub>2</sub>, **2SbF<sub>6</sub>** (BPMEN = *N,N'*-dimethyl-*N,N'*-bis(2-picolyl)-ethylene-1,2-diamine, Fig. 1) based on an achiral and readily accessible ligand. For instance, in the oxidation of **3**, both catalysts were comparably active (41 vs. 42% substrate was converted using **2SbF<sub>6</sub>** and *S,S*-**1SbF<sub>6</sub>**, respectively), while the reaction chemoselectivity towards **4** significantly varied (62% against 90% using **2SbF<sub>6</sub>** and *S,S*-**1SbF<sub>6</sub>**, respectively) (Scheme 1).<sup>3a</sup> The formation of by-products as observed with **2SbF<sub>6</sub>** was attributed to Fenton-type processes, even though the obtained tertiary alcohol **4**, in fact, was diastereopure (dr > 99/1) with both catalysts. The reactivity of

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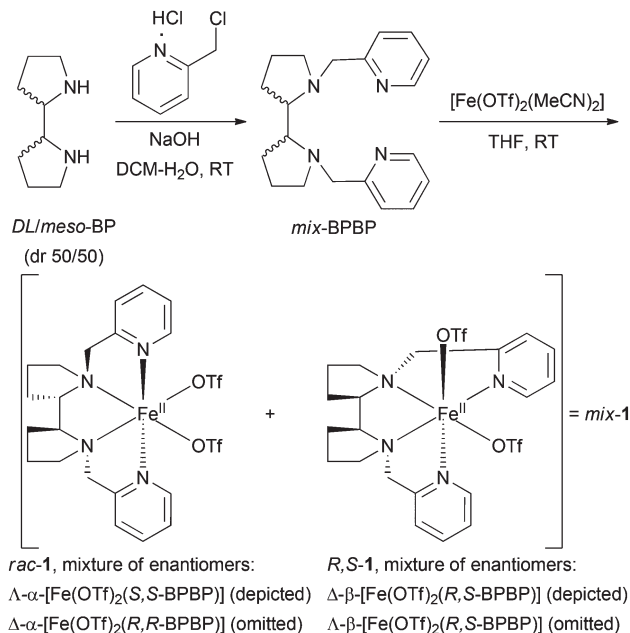


**Scheme 1** Comparison of the catalytic performances of  $1\text{SbF}_6$  and  $2\text{SbF}_6$  in C–H oxidation reactions with hydrogen peroxide.<sup>3a,4a,5</sup>

enantiopure  $S,S$ - $1\text{SbF}_6$  catalyst was illustrated in a seminal report about catalytic hydroxylations of complex molecules.<sup>3a</sup> However, no examples of chiral induction from the catalyst to the product were provided, as all optically pure alcohol products retained the initial configuration of their chiral precursors.<sup>3a</sup>

Subsequent reports indicated the importance of catalyst–substrate topology matching in the case of hyper-functionalized molecule oxidations with  $R,R$ - and  $S,S$ - $1\text{SbF}_6$ , where, *e.g.* in the oxidation of **5** to diketone **6**, the main product yield varied from 22 to 45% depending on the employed Fe catalyst enantiomer (Scheme 1).<sup>4a</sup> In contrast, the oxidation of (–)-ambroxide **7** – another complex substrate – proceeded smoothly with both  $R,R$ - and  $S,S$ - $1\text{SbF}_6$ , yielding 80 and 76% of (+)-sclareolide, respectively. In the synthesis of  $S$ - $\alpha$ -acetoxy isocapro lactone **10** from  $S$ - $\alpha$ -acetoxy isocaproic acid **9a**, the use of  $S,S$ - $1\text{SbF}_6$  was clearly beneficial compared to  $R,R$ - $1\text{SbF}_6$ . On the other hand, the oxidation of the corresponding esterified substrate **9b** led to the same lactone **10** and the yield did not depend on the catalyst chirality (Scheme 1).<sup>5</sup> More reports confirmed that only structurally enhanced analogues of  $1\text{SbF}_6$  or **1**, in which the catalyst bite angle was affected, can feasibly alter the substrate-imposed regio- and chemoselectivity in C–H oxidations.<sup>6</sup>

We envisioned that the most costly, tricky and low yielding step in the synthesis of enantiopure  $1\text{SbF}_6$  catalysts, *i.e.* the resolution of the crude  $DL/meso$ -2,2'-bipyrrrolidine mixture,<sup>7,8</sup> might be avoided if the catalyst is used for certain C–H oxidation reactions that occur without serious topological restrictions on the catalyst–substrate interaction and where catalyst-to-substrate stereo-induction is not involved. We therefore set out to evaluate the catalytic properties of a mixture of iron triflate complexes,  $[\text{Fe}(\text{OTf})_2(\text{mix-BPBP})]$  (*mix-1*), derived from a mixture of the BPBP ligand diastereomers, *i.e.* using a non-resolved mixture of BPBP ligands (Scheme 2). The ferrous triflate  $S,S$ -BPBP complex  $\Lambda$ - $\alpha$ - $[\text{Fe}(\text{OTf})_2(S,S\text{-BPBP})]$  ( $S,S$ -**1**) is a part of it and has previously been reported to catalyze hydrocarbon oxidation processes, *e.g.* C–H oxidations,<sup>3b,6b</sup>



**Scheme 2** Two-step preparation of *mix-1* starting from crude  $DL/meso$ -2,2'-bipyrrrolidine.

stereoselective olefin epoxidation,<sup>9</sup> and dihydroxylation reactions.<sup>3f</sup> The use of triflate instead of antimony hexafluoride counterions could further decrease the catalyst cost without largely altering its activity and selectivity.<sup>6b</sup>

## Results and discussion

A  $DL/meso$ -2,2'-bipyrrrolidine mixture (dr *ca.* 50/50) is available on a multi-gram scale.<sup>7a,b</sup> In our study, this mixture was converted in two steps into the target catalyst *mix-1* with an overall yield of 57–66%, containing *rac-1* (equimolar mixture of  $S,S$ - and  $R,R$ -**1**, 65–75%) and  $\Delta/\Lambda$ - $\beta$ - $[\text{Fe}(\text{OTf})_2(R,S\text{-BPBP})]$  ( $R,S$ -**1**, 25–35%) (Scheme 2; see ESI†).

The X-ray crystal structure of enantiopure  $S,S$ -**1** was previously reported.<sup>3f</sup> The  $S,S$ -BPBP ligand wraps around the Fe-center in a *cis*- $\alpha$  coordination topology, causing the exchangeable triflates to be chemically equivalent, positioned *cis* to each other and *trans* to the pyrrolidine nitrogen donors. The  $R,S$ -BPBP ligand in the racemic  $R,S$ -**1** complex, obtained in an independent manner (see ESI†), adopts the alternative *cis*- $\beta$  coordination topology in the solid state, where the labile *cis*-sites, occupied by triflates, are not equivalent (Fig. 2). One labile site is positioned in a position *trans* to a pyrrolidine nitrogen donor atom, while the second one is located *trans* to a pyridine nitrogen donor.

Such a structural disparity, in principle, might raise certain selectivity issues if both catalyst structures are present in *mix-1*.<sup>10</sup> In addition, the enantiopure catalyst performance can be affected by the presence of its antipode if (poly)nuclear clusters are involved in catalysis or are responsible for catalyst deactivation.<sup>11</sup>

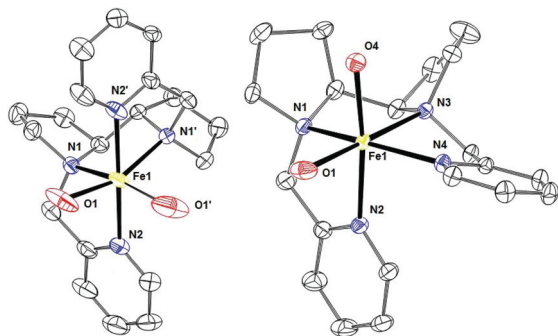
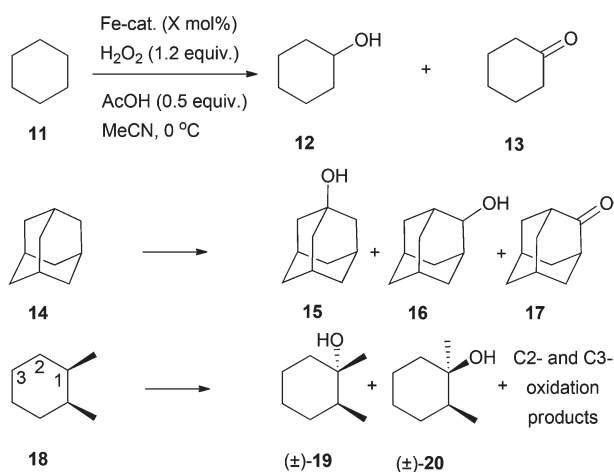


Fig. 2 Molecular structures of *S,S*-1 (left)<sup>3f</sup> and *R,S*-1 (right,  $\Delta$ -isomer), drawn with displacement ellipsoids at the 50% probability level. Of the triflate groups, only the coordinated oxygen atoms are shown, and hydrogen atoms are omitted for clarity.



Scheme 3 Catalytic oxidation of cyclohexane (**11**), adamantane (**14**) and *Z*-1,2-dimethylcyclohexane (**18**). Reaction conditions: Fe-cat./H<sub>2</sub>O<sub>2</sub>/substrate/AcOH *x* : 120 : 100 : 50, where *x* = 0.050–4.00, at 0 °C.

We have compared the easily accessible BPBP iron complex mixture *mix*-1 and its separate components (*S,S*-, *R,R*- and *R,S*-1) as catalysts for aliphatic C–H oxidations firstly using the set of cyclohexane (**11**), adamantane (**14**), and *Z*-1,2-dimethylcyclohexane (**18**) as benchmark substrates to reveal the relations between the catalyst composition and its performance (Scheme 3).

There are several slightly different catalytic protocols reported in the literature, which involve Fe(BPBP) complexes for alkane oxidation reactions. The initially developed protocol utilizes 5–25 mol% of *S,S*-1SbF<sub>6</sub>.<sup>3a,4,5</sup> The catalyst amount was further optimized and lowered to 1–3 mol% for *S,S*-1 and several structurally related Fe-complexes.<sup>3b,6b,12</sup> Both reaction protocols operate under formal substrate limiting (preparative) conditions, and use hydrogen peroxide as an oxidant and acetic acid as an additive. Following the latter protocol, we found only very minor deviations in the catalyst activity, oxidizing the benchmark substrates in the presence of 1 mol% of either *S,S*-1 or *mix*-1 (Table 1).

Table 1 Alkane hydroxylation with **1** and **2**/H<sub>2</sub>O<sub>2</sub>/AcOH<sup>a</sup>

Substrate	Fe-cat.	Main products, yield <sup>b</sup> [%]	Remarks
<b>11</b>	<i>S,S</i> -1	13/12	(K/A) <sup>c</sup>
	<i>mix</i> -1	27/3.0	8.9
	<b>2</b>	26/2.9	9.0
	<i>R,S</i> -1	11/4.6	2.4
<b>14</b>	<i>S,S</i> -1	0.3/0.3	—
	<i>mix</i> -1	15/16/17	(3°/2°) <sup>d</sup>
	<b>2</b>	19/0.5/2.2	21
	<i>R,S</i> -1	16/0.7/1.6	21
<b>18</b>	<i>S,S</i> -1	8.1/0.7/0.8	16
	<i>mix</i> -1	0.2/0.1/0.1	—
	<b>2</b>	(±)-19/(±)-20	(RC, %) <sup>e</sup>
	<i>R,S</i> -1	43/0.3	>99
		41/0.2	>99
		22/0.2	>99
		0.1/0.2	—

<sup>a</sup> Reaction conditions: Fe-cat./H<sub>2</sub>O<sub>2</sub>/substrate/AcOH 1:120:100:50, 0 °C. <sup>b</sup> Determined by GC. <sup>c</sup> Ketone over alcohol product ratio, K/A = [mol **13**]/[mol **12**]. <sup>d</sup> 3°/2° = 3 × [mol **15**]/([mol **16**] + [mol **17**]). <sup>e</sup> Retention of configuration, RC, % = 100 × [mol (±)-19]/([mol (±)-19] + [mol (±)-20]).

Cyclohexanone (**13**) was formed as the main product in 26–27% substrate-based yield in the oxidation of **11**, regardless of the used catalyst. Adamantane oxidation provided the tertiary alcohol **15** in 19 and 16% yield with both *S,S*-1 and *mix*-1 catalysts, respectively. The latter substrate is poorly soluble in the reaction medium, which might make the catalyst activity interpretation under preparative conditions within the standard reaction period (16 min) less accurate. *E*-1,2-Dimethylcyclohexanol **19** was obtained from **18** in 43 and 41% yield using *S,S*- and *mix*-1, respectively, in accordance with the previous reports.<sup>3b,6b</sup>

Remarkably, the product distribution obtained with *S,S*-1 and *mix*-1 in these oxidations was almost identical. For instance, in the oxidation of cyclohexane (**11**) the molar ratio between ketone **13** and alcohol **12** products (K/A) was found to be 8.9–9.0 for both catalysts. Thus, the mixed catalyst can substitute enantiopure *S,S*-1 in certain transformations, where the formation of carbonyl compounds is desired.

Another property of **1** is its ability to preferentially oxidize tertiary in the presence of secondary C–H bonds, which is illustrated by the 3°/2° ratio in adamantane (**14**) oxidation. The corresponding value was 21 for the 3°/2° regioselectivity for both catalysts, *i.e.* the different catalytic sites present in *mix*-1 act coherently also in this case. From a mechanistic point of view, such a high 3°/2° value indicates that the rate limiting step in alkane oxidation by **1**/H<sub>2</sub>O<sub>2</sub> is hydrogen abstraction from a substrate molecule.<sup>3c,13</sup>

The regioselectivity of this step is firstly determined by the difference of the homolytic dissociation energy of the different C–H bonds in the substrate, while the steric accessibility of these C–H bonds is less crucial. The formed transient tertiary carboradicals nearly instantly get converted into the corresponding alcohols, thereby retaining the configuration of their

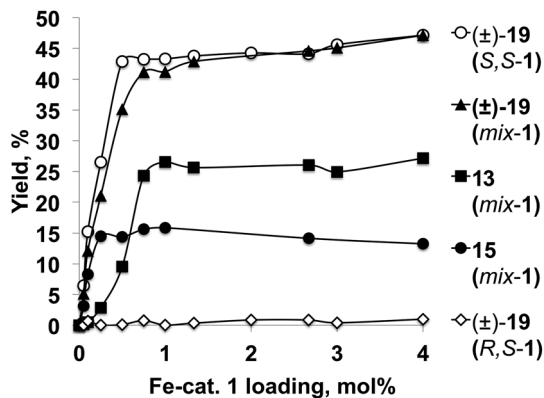


Fig. 3 GC yield of cyclohexanone (**13**), 1-adamantanol (**15**) and ( $\pm$ )-*E*-1,2-dimethylcyclohexanol (( $\pm$ )-**19**) vs. Fe-catalyst **1** loading in catalytic oxidations of corresponding substrates. Fe-cat./alkane/H<sub>2</sub>O<sub>2</sub>/AcOH *x*: 100 : 120 : 50, where *x* = 0.050–4.0, at 0 °C.

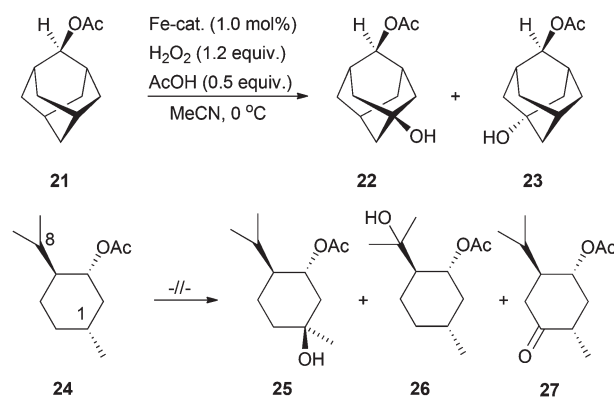
precursor, which was confirmed for the oxidation of **18**. In this case, **19** was obtained as a single diastereomer (RC > 99%) using either the *S,S*-**1** or *mix*-**1** catalyst. Overall, these experiments show that *mix*-**1** retains the most important intrinsic C–H bond oxidation characteristics of its separate single site congener *S,S*-**1**.

Based on the experiments with 1 mol% loading of *mix*-**1** and *S,S*-**1**, a nearly equal catalytic behaviour of all components (*S,S*-, *R,R*- and *R,S*-**1**) in the mixed catalyst might be assumed. Yet, catalytic experiments carried out with pure *R,S*-**1** demonstrated its complete inertness (Table 1). It was found that increasing the loading of *mix*-**1** from 1 to 4 mol% had almost no effect on the formation of the main product in the oxidation of both **11** and **14** (Fig. 3). In the case of **18**, the yield in ( $\pm$ )-**19** rose slightly from 41 to 47% and did not improve after more oxidant was added. Actually, the mixed catalyst loading can be lowered to 0.75 mol% for the oxidation of **11** and **18** and even to 0.25 mol% in the case of **14** without substantially affecting the product yield (Fig. 3). Yet, minor changes were observed in the product distribution upon changing the catalyst loading. In the oxidation of **11**, the K/A ratio rose from 6.6 to 15 when increasing the loading of *mix*-**1** from 0.75 to 4.0 mol%. The 3°/2° value in the oxidation of **14**, on the other hand, dropped from 26 to 20, using 0.25 and 4.0 mol% of *mix*-**1**, respectively. This trend implies a certain overoxidation of the respective minor product **12** and major product **15** at higher catalyst loadings. In the oxidation of **18**, we found a persistently high product diastereopurity with the *mix*-**1** catalyst within a broad range of catalyst loadings. When the catalyst loading was reduced to 0.050 mol%, the tertiary alcohol ( $\pm$ )-**19**, formed in *ca.* 5% yield, was still diastereopure (dr 97/3). Such a high retention of the configuration (RC 97%) at extremely low catalyst concentrations rules out the participation of free OH-radicals in alkane oxidations carried out with *mix*-**1**.

The observed relation between the catalyst activity and its loading supports the idea of bi- or multimolecular pathways of catalyst deactivation.<sup>3b,6b,14,15</sup> Several reports have proposed

that non-heme iron catalysts containing tetradentate polyamine ligands (TPA,<sup>16</sup> BPMEN<sup>17</sup> and *S,S*-BPBP<sup>3b,6b,15</sup>) can oxidatively dimerize in the presence of oxidants and acetic acid forming binuclear oxo-bridged dimers [Fe<sup>III</sup><sub>2</sub>L<sub>2</sub>(O)OAc]<sup>3+</sup>, which represent either inert or resting states of the catalyst. Investigating the catalytic reaction mixtures containing *R,S*- or *S,S*-**1** by ESI-MS analysis, we found a clear difference in the fate of these catalysts: while ESI-MS analysis of *S,S*-**1** at the end of the oxidation of **13** (*S,S*-**1**/**13**/H<sub>2</sub>O<sub>2</sub>/AcOH 1:100:120:50) showed the iron-containing ions [Fe<sub>2</sub>L<sub>2</sub>(O)OAc]<sup>3+</sup>, [Fe<sub>2</sub>L<sub>2</sub>(O)OAc](OTf)<sup>2+</sup> and [Fe<sub>2</sub>L<sub>2</sub>(O)OAc](OTf)<sub>2</sub><sup>+</sup> with respective *m/z* values of 277.1005 (calcd 277.1033), 490.1337 (calcd 490.1369) and 1129.2134 (calcd 1129.2139), no iron-containing ions were identified in the reaction carried out with *R,S*-**1**. The ligand recovery protocol described by White *et al.*<sup>15</sup> was applied to both reaction mixtures and allowed for the isolation of unchanged *S,S*-BPBP in 79% yield (95% originally reported) and the anticipated *R,S*-BPBP in 74% yield. Using the same reaction and recovery protocol, the *mix*-BPBP ligand was recovered in 69% yield and an improved dr (from 75/25 to 85/15), *i.e.* the share of *rac*-BPBP ligand slightly increased. Only the *rac*-BPBP ligand (dr > 98/2, 58–63% yield) was recovered from precipitates formed after diluting the product mixtures obtained with *mix*-**1**/H<sub>2</sub>O<sub>2</sub> using diethyl ether as an anti-solvent (see ESI†). This experiment confirmed that *rac*-BPBP remains bound to Fe after catalysis and it is insoluble in diethyl ether in this state, while *R,S*-**1** under the same conditions dissociates liberating ether-soluble oxidized *R,S*-BPBP. In addition, *S,S*-BPBP, being coordinated to iron, is more oxidatively robust than its diastereomer: no oxidized ligand was identified in ESI-MS traces of catalytic oxidations utilizing H<sub>2</sub>O<sub>2</sub> in a larger excess (*S,S*-**1**/**18**/H<sub>2</sub>O<sub>2</sub>/AcOH 1:100:1000:50). In contrast, only ions with *m/z* 337.2148 (calcd for [L + O – H]<sup>+</sup> 337.2023) were observed after catalysis with *R,S*-**1** under these conditions.

Next, we turned to functionalized substrates investigating the performance of *mix*-**1** (Scheme 4 and Table 2). For instance, the oxidation of 2-adamantyl acetate (**21**) with methyltrifluoromethyl dioxirane is known to provide a mixture of two diastereomeric *Z*-**22** and *E*-**23** alcohols in *ca.* 2.5:1



Scheme 4 Catalytic oxidation of 2-adamantyl acetate (**21**) and L-(-)-menthyl acetate (**24**) with **1** and hydrogen peroxide.

Table 2 Oxidation of functionalized substrates by 1<sup>a</sup>

Substrate	Fe-cat.	Main products, yield <sup>b</sup> [%]	Remarks
21	<i>S,S</i> -1	22 + 23/(rSM, %) <sup>c</sup> 34 <sup>e</sup> /(35)	<i>Z/E</i> <sup>b,d</sup> 2.6
	<i>R,R</i> -1	30 <sup>e</sup> /(42)	2.0
	<i>mix</i> -1	35 <sup>e</sup> /(38)	2.2
24	<i>S,S</i> -1	25/26/27 22/2.1/1.5	C1/C8 <sup>f,g</sup> 10
	<i>R,R</i> -1	21/1.9/1.6	10
	<i>mix</i> -1	19/1.9/1.6 [16/1.4/1.1] <sup>e</sup>	10

<sup>a</sup> See Table 1. <sup>b</sup> See Table 1. <sup>c</sup> rSM – recovered starting material (21).

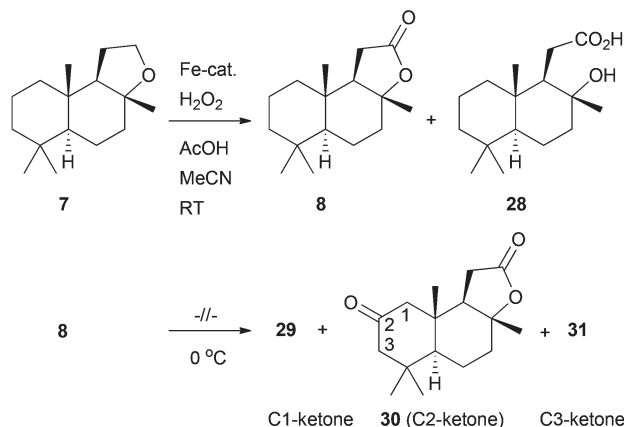
<sup>d</sup> *Z/E* = [mol 22]/[mol 23]. <sup>e</sup> Isolated yield. <sup>f</sup> C1/C8 = [mol 25]/[mol 26].

<sup>g</sup> Determined by <sup>1</sup>H NMR.

ratio.<sup>18</sup> This ratio was found to be 2.6, 2.0 and 2.2 : 1 using the *S,S*-, *R,R*- and *mix*-1 catalysts, respectively, while the total isolated yield of these products did not depend on the catalyst choice and was *ca.* 30–35% for each of these catalysts. The unreacted substrate was recovered in 35, 42 and 38% after oxidations with *S,S*-, *R,R*- and *mix*-1, respectively. The hydroxylation of L-menthyl acetate 24 was also carried out with *mix*-1 and with its separate components, following the standard reaction protocol. One major (25) and two minor (26 and 27) reaction products were identified in this process (Scheme 4, Table 2). The optically pure Fe catalysts, *S,S*-1 and *R,R*-1, turned out to be slightly more active, yielding 21–22% of the main product 25, while the mixed catalyst (1 mol%) afforded 19%. The isomeric alcohols 25 and 26 were formed in a 10 : 1 ratio irrespective of the employed catalyst, which is in agreement with the distribution previously obtained with *S,S*-1SbF<sub>6</sub>.<sup>3a,15</sup> The observed regioselectivity is driven by the distinct steric accessibility of electronically similar tertiary C–H bonds at the C1 and C8 carbons in 24 (Scheme 4).<sup>3a</sup> Interesting, the reaction between 24 and ozone, a small and electrophilic oxidant, demonstrated the inverted regioselectivity providing mainly 26.<sup>19</sup>

The plausible ketone product 27 has been initially overlooked (tests with *S,S*-1SbF<sub>6</sub>)<sup>3a</sup> and was just recently detected and characterized among the oxidation products of 24 (tests with *S,S*-1, *R,R*-1 and *S,S*-1SbF<sub>6</sub>); however, the formation of 26 was not mentioned.<sup>6b</sup> A large-scale oxidation of 24 (10 g) using cheap *mix*-1 allowed us to confirm that indeed both by-products are formed in this reaction and that their amounts are comparable (26 : 27 = 1.3 : 1 (isolated yields) or 1.1 : 1 (GC yields)).

(–)-Ambroxide (7) is another substrate that attracted our attention. Despite the numerous sites available for oxidation, this terpenoid was shown to form the corresponding lactone (+)-sclareolide (8) in a high isolated yield of 80% using *R,R*-1SbF<sub>6</sub> in an “iterative reaction protocol”, where the catalyst and reagents are added to 7 in three equal portions with the ultimate component ratio 1SbF<sub>6</sub>/7/H<sub>2</sub>O<sub>2</sub>/AcOH of 15 : 100 : 360 : 150 (Scheme 1 and 5).<sup>4a</sup> This oxidation is considered as regiospecific as 19% of the reactant (7) was



Scheme 5 Catalytic oxidation of (–)-ambroxide 7 and (+)-sclareolide 8.

recovered, rising the reaction mass balance and selectivity up to 99%. When the oxidant was delivered by a syringe pump to the reaction mixture, the reported reaction selectivity towards lactone 8 was 57, 66 and 58% with *R,R*-1SbF<sub>6</sub>, *R,R*-1 and *S,S*-1, respectively (Fe-cat./7/H<sub>2</sub>O<sub>2</sub>/AcOH 3 : 100 : 260 : 150), and no remaining 7 was observed.<sup>6b</sup> Under the latter conditions and in our hands, the *R,R*-1, *S,S*-1 and *mix*-1 catalyst afforded 70, 66 and 67% of 8, respectively (GC yield), while the substrate conversion was complete. Subsequently, we set up a 1.5 g oxidation of 7 and isolated both products of this reaction: the lactone (8, 54%) and the hydroxy acid (28, 29%) using a casual “pH switching” separation technique (see ESI†).

Further (+)-sclareolide oxidation leading to a mixture of (+)-oxo-sclareolides (29, 30, 31) was shown to be sensitive to the catalyst topology.<sup>4a</sup> In our hands, the C2–30 and C3–31 oxo-products formed equally in 33, 37 and 34% combined yield using either *S,S*-, *R,R*- or *mix*-1 with 1/8/H<sub>2</sub>O<sub>2</sub>/AcOH 3 : 100 : 360 : 150 (Scheme 5, Table 3). Thus, no notable difference in the reaction regioselectivity was found. The *R,R*-1SbF<sub>6</sub> catalyst at 3 mol% loading was reported to afford 43% of an equimolar ketone mixture in this transformation.<sup>6b</sup> Also a

Table 3 Oxidation of functionalized substrates by 1<sup>a,b</sup>

Substrate	Fe-cat.	Main products, Yield <sup>c</sup> [%]	TON <sup>e</sup>
7 <sup>a</sup>	<i>S,S</i> -1	8/28 66 (50) <sup>d</sup> /nd	29.3
	<i>R,R</i> -1	70 (51) <sup>d</sup> /nd	31.1
	<i>mix</i> -1	67 (54) <sup>d</sup> /29 <sup>d</sup>	29.8
8 <sup>b</sup>	<i>S,S</i> -1	29/30/31 8/17/16	TON <sup>e</sup> 18.2
	<i>R,R</i> -1	5/20/17	18.7
	<i>mix</i> -1	7/18/16	18.2

Reaction conditions: Fe-cat./H<sub>2</sub>O<sub>2</sub>/substrate/AcOH. <sup>a</sup> 3 : 260 : 100 : 150, RT. <sup>b</sup> 3 : 360 : 100 : 150. <sup>c</sup> Determined by GC. <sup>d</sup> Isolated yield. <sup>e</sup> TON = [mol epoxide]/([mol *S,S*-1] + [mol *R,R*-1]). The amount of *R,S*-1 (inert part) in *mix*-1 was determined to be *ca.* 25% and was not considered calculating the TON values.

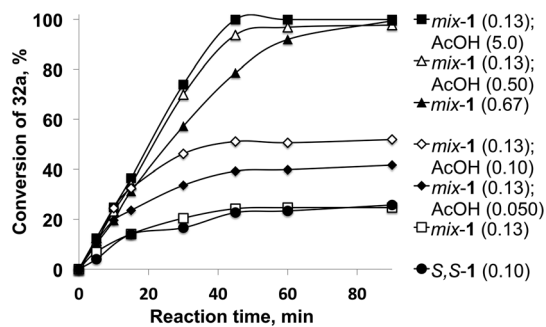


Fig. 4 Kinetic profiles of *Z*-cyclooctene (**32a**) oxidation with **1** catalysts at 0 °C. Fe-cat./**32a**/H<sub>2</sub>O<sub>2</sub>/AcOH *x* : 100 : 150 : *y*, where *x* and *y* are given in parentheses in the legend; *y* is omitted for the experiments carried out without AcOH. The oxidant addition was complete at 60 min.

Table 4 Alkene epoxidation with **1**/H<sub>2</sub>O<sub>2</sub>/AcOH<sup>a</sup>

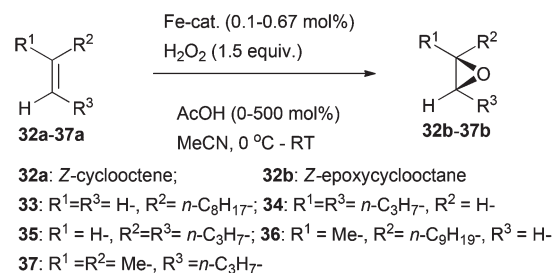
Alkene	Fe-cat. (mol%)	AcOH, mol%	Yield <sup>b</sup> [%]/Conv. <sup>b</sup> [%]	TON <sup>c</sup>
<b>32a</b>	<i>S,S</i> - <b>1</b> (0.50)	0	97/99	194
	<i>R,R</i> - <b>1</b> (0.50)	0–50	<1/<3	—
	<i>mix-1</i> (0.50)	0.050	97/99	194
	<i>mix-1</i> (0.67)	0	95/99	190
	<i>S,S</i> - <b>1</b> (0.10)	0	26/26	260
	<i>mix-1</i> (0.13)	0	24/25	240
	<i>mix-1</i> (0.13)	0.50	92 <sup>d</sup> /98	920
<b>33a</b>	<i>mix-1</i> (0.13)	0.50	29/29	290
	<i>mix-1</i> (0.52)	2.0	89 <sup>d</sup> /95	223
<b>34a</b>	<i>mix-1</i> (0.26)	1.0	92 <sup>d</sup> /99	460
<b>35a</b>	<i>mix-1</i> (0.26)	1.0	95 <sup>d</sup> /99	475
<b>36a</b>	<i>mix-1</i> (0.26)	1.0	89 <sup>d</sup> /98	445
<b>37a</b>	<i>mix-1</i> (0.26)	1.5	90 <sup>d</sup> /99	450

<sup>a</sup> Reaction conditions: alkene (1.0 mmol), H<sub>2</sub>O<sub>2</sub> (1.5 mmol over 60 min), AcOH, Fe-cat., MeCN (5 mL), 0 °C, 90 min. <sup>b</sup> Determined by GC. <sup>c</sup> TON = [mol epoxide]/([mol *S,S*-**1**] + [mol *R,R*-**1**]). The amount of *R,S*-**1** (inert part) in *mix-1* was determined to be ca. 25% and was not considered calculating the TON values. <sup>d</sup> Isolated yield.

small amount of the C1–29 ketone (ca. 5–8%) was always formed.

The synthetic accessibility of the *mix-1* catalyst is comparable to that of the structurally related  $\Delta/\Lambda$ - $\alpha$ -[Fe(OTf)<sub>2</sub>-(BPMEN)] **2**<sup>20</sup> derived from an achiral ligand and to recently reported  $\Delta/\Lambda$ - $\alpha$ -[Fe(*rac*-PYBP)(MeCN)<sub>2</sub>](ClO<sub>4</sub>)<sub>2</sub><sup>21</sup> catalysts, which are among the most easily synthesized and highly active non-heme Fe-catalysts for alkene epoxidations (Fig. 1). Optimizing the reaction conditions for *mix-1* it was found that *Z*-cyclooctene (**32a**) is smoothly converted into its epoxide **32b** within 90 min using *mix-1*/**32a**/H<sub>2</sub>O<sub>2</sub>/AcOH (0.13–0.67) : 100 : 150 : (0–0.50) (Fig. 4, Table 4). No AcOH is required to complete the oxidation using 0.67 mol% of *mix-1* and just 0.5 mol% AcOH turned out to be sufficient to reach full conversion of **32a** with 0.13 mol% of the mixed catalyst. In the latter case, the oxidant was introduced over either 60 or 6 min, showing very little difference in product yield (92 and 95%, respectively).

Remarkably, the reported non-heme iron complexes of BPMEN and *rac*-PYBP require substantial amounts of AcOH



Scheme 6 Catalytic oxidation of substituted alkenes with Fe catalysts and hydrogen peroxide.

(up to 70% v/v) to maintain high levels of their catalytic activity in alkene epoxidations and to suppress diol formation.<sup>16,22,23</sup> In numbers,  $\Delta/\Lambda$ - $\alpha$ -[Fe(*rac*-PYBP)(MeCN)<sub>2</sub>](ClO<sub>4</sub>)<sub>2</sub> (0.10 mol%) was reported to afford **32b** in 10 and 72% yield in the presence of 50 and 500 mol% of AcOH, respectively, approaching the activity of *mix-1* in the presence of only 0.5 mol% of AcOH.

The *R,S*-**1** complex was inert in preparative epoxidations just like in C–H oxidations, while the structurally related  $\beta$ -[Fe(OTf)<sub>2</sub>(6-Me<sub>2</sub>-BPMCN)] catalyst was reported to be active in olefin *syn*-dihydroxylation reactions under oxidant limiting conditions.<sup>22b</sup>

Subsequent epoxidation of several substituted alkenes using *mix-1*/alkene/H<sub>2</sub>O<sub>2</sub>/AcOH 0.13 : 100 : 150 : 0.5 resulted in incomplete substrate conversions (Scheme 6, Table 4). This issue for the oxidation of **34a–37a** was solved by increasing the amount of *mix-1* and AcOH. 1-Decene (**33a**) was found to be the least reactive substrate with hydrogen peroxide among the tested unfunctionalized alkenes. Its complete conversion into epoxide **33b** required more elevated loadings of the *mix-1* catalyst and acetic acid (0.52 and 2.0 mol%, respectively). The epoxidation of this substrate turned out to be challenging also for the reported Fe(*rac*-PYBP) catalyst, where 500 mol% (5 equiv. to **33a**) of AcOH and 0.50 mol% of Fe(*rac*-PYBP) were necessary to drive the reaction to completion.<sup>21</sup>

Based on these observations, more electron-rich internal alkenes are more readily oxidized by *mix-1*/H<sub>2</sub>O<sub>2</sub> than terminal ones. Subsequently, binary mixtures of 1-decene and model alkene substrates were oxidized using the catalytic system *mix-1*/H<sub>2</sub>O<sub>2</sub>/1-decene/alkene/AcOH 1 : 300 : 200 : 200 : 8 to probe the regioselectivity of *mix-1* in the oxidation of olefins. In this experiment, the reaction progress was monitored along with the gradual delivery of hydrogen peroxide into the system, *i.e.* over 1 h. In all cases, we observed simultaneous oxidation of both alkenes at every stage of H<sub>2</sub>O<sub>2</sub> addition; however, 1-decene was always consumed at a lesser extent. The most pronounced reactivity difference was found oxidizing *Z*-cyclooctene and 1-decene (**32a**/**33a**), where the epoxide **32b**/**33b** ratio decreased from 8.6 to 5.8 and 4.5 : 1 at combined substrate conversions of 11, 52 and 70%, respectively.

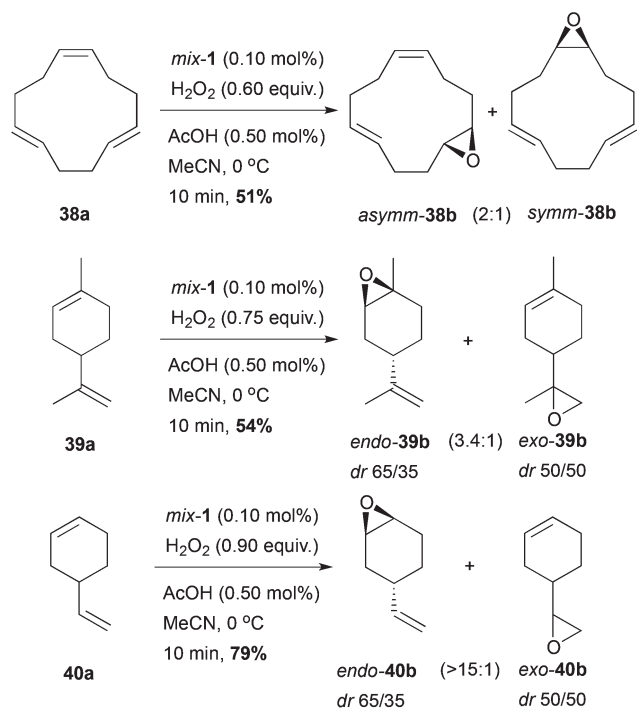
The oxidation of *E*-4-octene and 1-decene (**34a**/**33a**) turned out to be the least regioselective with the **34b**/**33b** product distribution changed from 3.1 to 2.1 and 2.0 : 1 at combined substrate conversions of 13, 57 and 69%. As a measure of

regioselectivity, here we consider the approximate ratio of an epoxy alkene and **33b** at 50% combined conversion of both competing alkene substrates. Thus, the following alkene reactivity order depending on the C=C bond substitution pattern can be drawn: mono-<E-di<Z-di<gem-di<tri-<<cyclic 1.0 : 2.2 : 3.1 : 3.3 : 3.5 : 5.8, based on the oxidation of **33a**, **34a**, **36a**, **35a**, **37a** and **32a**, respectively.

The reactivity trend is applicable to the prediction of the product distribution in random couples of alkenes. For instance, the equimolar mixture of *Z*-(**35a**) and *E*-4-octene (**34a**) tested under the same conditions yielded the corresponding epoxides **35b** and **34b** in a 1.5 *Z/E* ratio at 48% total conversion of the substrates, which is in agreement with the determined reactivity order. The geminal disubstituted alkene (2-methylundecene-2, **36a**) and *Z*-**35a** turned out to be comparably active being oxidized as a mixture, producing 1.0–1.1 **36b** epoxide for every *Z*-**35b** epoxide molecule.

Based on these data it was concluded that the *mix-1* catalyst is unable to efficiently distinguish disubstituted alkenyl moieties under the applied epoxidation conditions. Indeed, the epoxidation of *E,E,Z*-1,5,9-cyclododecatriene (**38a**) with 0.6 equiv. of H<sub>2</sub>O<sub>2</sub> yielded 51% (85% monoepoxide selectivity) of the 1:2 mixture of the corresponding epoxy *E,E*-(*symm*-**38b**) and *E,Z*-5,9-cyclododecadiene (*asymm*-**38b**) (Scheme 7).

A better regioselectivity is expected in the oxidation of dienes containing *endo*- and *exo*-cyclic C=C bonds. The



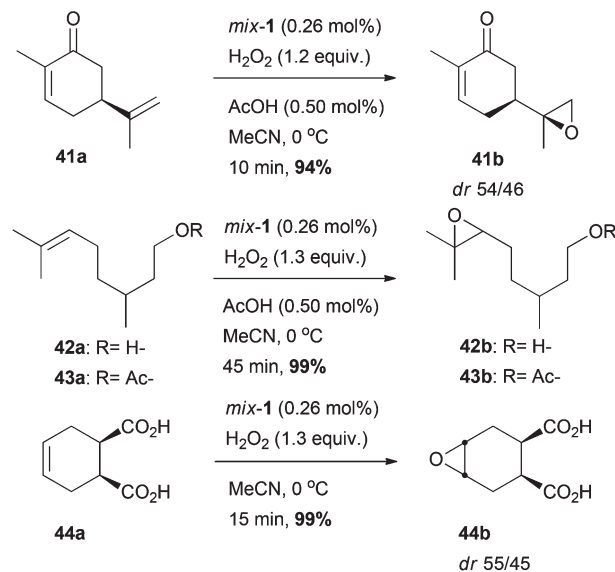
**Scheme 7** Catalytic oxidation of dienes with *mix-1* on a preparative scale. The isomeric monoepoxides were efficiently separated from by-products and unreacted dienes *via* vacuum distillation (**38b**, **39b**) and column chromatography (**40b**). Substrate based yields are indicated in all cases. The isomer ratio was determined by <sup>1</sup>H-NMR for **38b** and by GC for the epoxides **39b** and **40b**.

natural diene ( $\pm$ )-limonene **39a** bearing both highly reactive geminal di- and endocyclic tri-substituted C=C bonds was converted into a 1 : 3.4 mixture (54% yield) of 8,9-*exo*-(*exo*-**39b**) and 1,2-*endo*-cyclic (*endo*-**39b**) monoepoxides using *mix-1*/**39a**/H<sub>2</sub>O<sub>2</sub>/AcOH 1 : 1000 : 750 : 5. Much better regioselectivity was achieved oxidizing 4-vinyl-cyclohexene (**40a**) (a diene with isolated *Z*-disubstituted and terminal C=C bonds), where the endocyclic monoepoxide *endo*-**40b** was mainly formed (>15 : 1). In addition, the *endo*-monoepoxide can be obtained in a good yield of 79% using almost stoichiometric quantity of an oxidant (0.90 equiv.).

An excellent regioselectivity of the *mix-1*/H<sub>2</sub>O<sub>2</sub> system was observed oxidizing *S*-(+)-carvone (**41a**), where 8,9-epoxycarvone **41b** was the only regioisomer formed (94% isolate yield, Scheme 8). The conjugated electron-poor C=C bonds in **41a** and **41b** remain untouched by the oxidant as long as some starting material (**41a**) remains in solution. This allows the substrate conversion to go to completion without compromising on the reaction selectivity.

A brief study on the functional group tolerance was carried out showing that the utilized catalytic system can be successfully applied to the epoxidation of unsaturated primary alcohols and carboxylic acids (Scheme 8). For instance, the epoxidation of *S*-citronellol (**42a**) with *mix-1*/H<sub>2</sub>O<sub>2</sub> proceeded smoothly leading to quantitative epoxide **42b** formation. ( $\pm$ )-Citronellyl acetate **43a** was converted into the epoxide **43b** without any sign of the acetate group hydrolysis or 3° C-H hydroxylation processes.

Potentially chelating *cis*-1,2,3,6-tetrahydrophthalic acid (**44a**) was readily oxidized into a 1 : 1.2 mixture of the corresponding moderately stable epoxides using *mix-1* (0.26 mol%) and H<sub>2</sub>O<sub>2</sub> (1.3 equiv.).



**Scheme 8** Catalytic epoxidation of functionalized molecules with *mix-1*. The isomer ratio was determined by GC for **41b** and by <sup>1</sup>H-NMR for **44b**.

## Conclusions

A rapidly growing number of publications discussing the application of the promising small molecular catalyst Fe(BPBP) in various C–H and C=C bond oxidation processes is an evident sign of its appreciation by the scientific community. Despite the efforts at making this catalyst more efficient in several challenging C–H oxidations, its recently developed and more advanced alternatives are comparable or less accessible from a synthetic point of view and their showcase of preparative oxidations usually affords submillimolar product quantities. In contrast, the *mix-1* catalyst (*rac*-*R,S-1* ca. 75/25) presented here can be prepared on a multi-gram scale in two steps from a crude 2,2'-bipyrrrolidine mixture. The *R,S*-isomer component plays only a spectator role in both C–H and C=C bond oxidation reactions. The presence of this inactive catalyst isomer does not affect the overall reactivity and selectivity of the *mix-1* catalyst system. Most strikingly, the *mix-1* catalyst retained the most crucial selectivity properties of its optically pure components, e.g. a high ketone over alcohol ratio in methylene oxidations and high selectivity towards tertiary alcohols along with complete retention of the initial tertiary carbon center configuration in C–H oxidations. The *mix-1* catalyst is also applicable to the functionalization of more complex substrates, e.g. the transformation of (–)-ambroxide into (+)-sclareolide proceeds in a very similar manner with *mix-1* as with itself enantiopure *S,S*- and *R,R*-congeners. The *mix-1* catalyst is even useful in a challenging synthesis of oxo-sclareolides, in which the product distribution depends on the chiral catalyst shape. Importantly, the C–H oxidations mediated by this simple iron complex in combination with hydrogen peroxide have been proven to be scalable without compromising on the reaction selectivity.

Moreover, the *mix-1*/H<sub>2</sub>O<sub>2</sub> system is very promising in preparative epoxidation reactions, where the amount of acetic acid – a commonly used additive (or even a co-solvent) – can be remarkably reduced to less than 2 mol% or even totally eliminated. Under these conditions, a high catalyst activity (TON approaching 1000) is obtained in the oxidation of electron-rich olefins, where the epoxides are the only isolated products. A highly selective monoepoxidation of dienes is only possible if the substrate molecule bears electronically different C=C fragments. This *mix-1*/H<sub>2</sub>O<sub>2</sub> epoxidation system tolerates functional groups like primary alcohols and dicarboxylic acids.

Overall, we have shown the practical use of an easy to prepare iron complex in a range of challenging organic reactions, which now become much more affordable. We believe that our practical observations on the Fe(BPBP) complex reactivity will further contribute to the popularization of this promising catalyst and will further broaden its application in organic synthesis.

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