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An efficient ketone-catalyzed asymmetric epoxidation using hydrogen peroxide (H_2O_2) as primary oxidant

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Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

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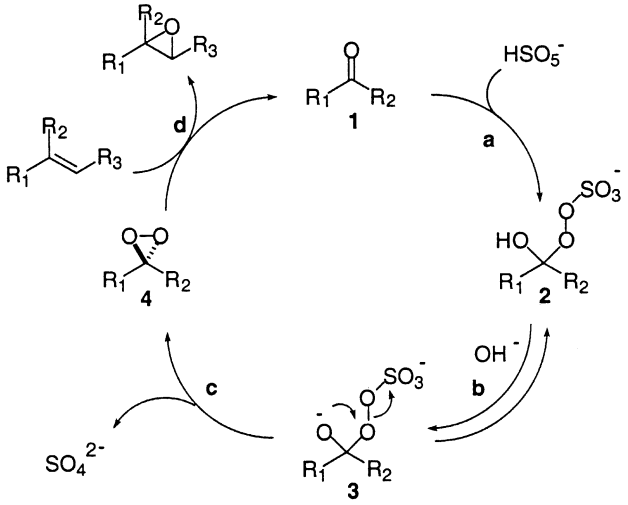
Abstract—High enantioselectivities have been obtained for asymmetric epoxidation of olefins using a fructose-derived chiral ketone (**5**) as catalyst and hydrogen peroxide as primary oxidant.

Epoxides are very important building blocks in organic synthesis.[1] Dioxiranes, either isolated, or generated in situ, have been shown to be extremely versatile epoxidation reagents.[2–6] The reaction is rapid, mild, and a variety of efficient protocols for this type of epoxidation have been developed. Thus far, the efficient generation of dioxiranes primarily uses potassium peroxomonosulfate ($KHSO_5$) as oxidant (Scheme 1).[7,8] Its effectiveness in the formation of dioxiranes is probably due to the fact that sulfate is a good leaving group, which facilitates the ring closure of intermediate **3** to form dioxirane **4**. Nevertheless, the formation of dioxiranes for a synthetic purpose using substantially different oxidants is largely unexplored. It is particularly of interest whether oxidants with poorer leaving groups than sulfate are capable of efficiently generating dioxiranes.[9] Herein we wish to report our detailed studies in this area.[10]

Among oxidants hydrogen peroxide (H_2O_2) is quite unique. It has a high active oxygen content and its reduction product is water.[11] We decided to test whether hydrogen peroxide itself, or its activated form, could serve as oxidants to produce dioxiranes. Our investigation started with *trans*-β-methylstyrene as substrate and chiral ketone **5** as catalyst.[6] When a solution of the olefin (1 mmol), ketone **5** (0.3 mmol), hydrogen peroxide (30%, 0.5 mL, 5 mmol) in CH_3CN (2 mL)-aqueous buffer ($AcOH–K_2CO_3$) (the buffer pH was adjusted to 10.3 by adding HOAc to 0.1 M K_2CO_3) (1 mL) was stirred at room temperature for 2 h, a 40% conversion was obtained. Analysis of the epoxide product, using chiral GC (Chiraldex G-TA), showed 86% ee! The fact that the epoxide was formed with good enantioselectivity suggested that the dioxirane was the likely epoxidizing agent.[12] However, when the reaction was carried out in other solvents, such as DMF, THF, CH_2Cl_2, EtOH, or dioxane, instead of CH_3CN, only trace amounts of the epoxide (<1%) were detected by GC, suggesting that hydrogen peroxide itself could not effectively generate the dioxirane and that CH_3CN played a role. It is highly likely that in the case of CH_3CN, the actual oxidant responsible for the formation of the dioxirane was peroxyimidic acid **9** (Scheme 2).[13] The reaction pH was found to be a very important parameter and the optimal pH for both conversion and ee was determined to be around 11.0. It was found that K_2CO_3 was an effective base to control the reaction pH. Fig. 1 shows the reaction results with different concentrations of K_2CO_3. High conversion could be obtained when the proper concentrations of K_2CO_3 were used, with over 90% ee obtained when [K_2CO_3] was above 0.6 M (increasing the concentration of K_2CO_3 slightly increased the ee of the epoxide product).[14,15]



Scheme 1.

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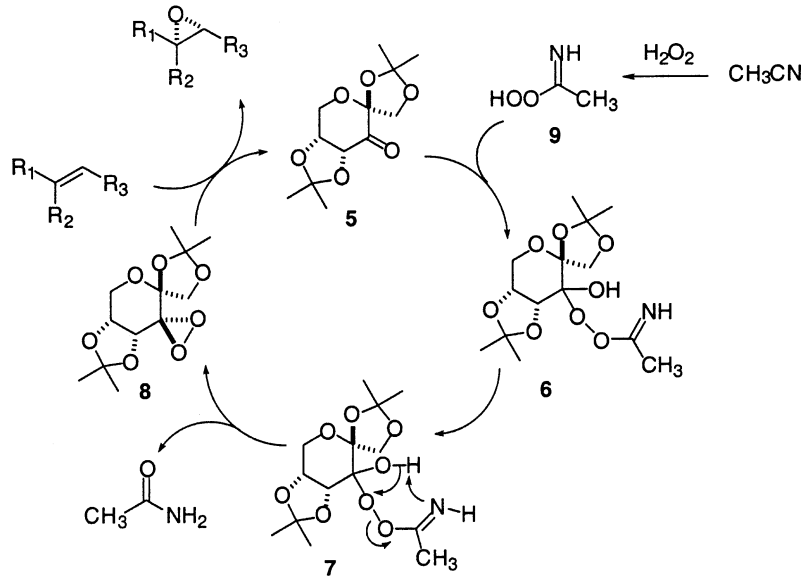


Scheme 2.

After the determination of the optimal reaction pH, the scope of this epoxidation system was investigated. As shown in Table 1, a variety of *trans*- and trisubstituted olefins can be effectively epoxidized giving good yields and ee's. It was found that the H_2O_2–CH_3CN system provided similar enantioselectivities to Oxone. The catalyst loading is somewhat substrate dependent and it can be reduced to as low as 10 mol% in some cases (Table 1, entry 7). It was found that the solvent was also very important for the reactions. For substrates with poor solubility like *trans*-stilbene (Table 1, entry 4), the epoxidation did not give a high conversion when CH_3CN was used as the organic solvent (Table 1, method A). However, a good conversion could be obtained by running the epoxidation in a mixed solvent of CH_3CN–DMM (1:2, v/v) (Table 1, method B). Further studies showed that a mixed solvent such as CH_3CN–EtOH–CH_2Cl_2 was beneficial for olefins with poor solubility (Table 1, method C, entries 4–9). These mixed solvent systems increase the utility of the current epoxidation method.[16]

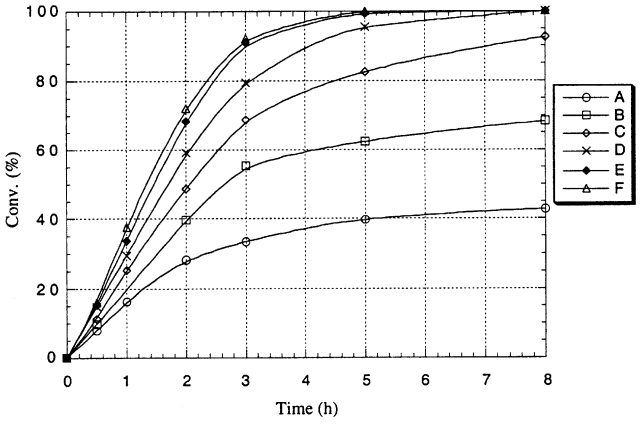
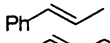
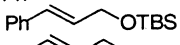
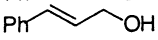
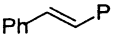
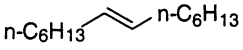
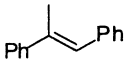
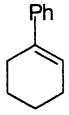
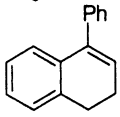
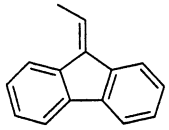
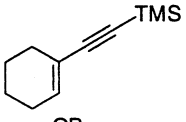
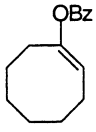
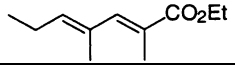


Figure 1. Plot of the conversion of *trans*-β-methylstyrene against time (h). The curves presented are: (**A**) 0.05 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.1), (**B**) 0.1 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.3), (**C**) 0.4 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.6), (**D**) 0.6 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.7), (**E**) 0.8 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.8), (**F**) 1.0 M K_2CO_3 in 4×10^{-4} M of EDTA (pH 11.9). (The pH indicated above is the pH of the K_2CO_3 solution. The pH varied upon adding other reaction components as well as the reaction time. This variation became smaller when higher concentration of K_2CO_3 was used.)

In the present epoxidation system, acetonitrile (CH_3CN) serves not only as a solvent but also as a reagent to react with H_2O_2 to form the peroxyimidic acid. It would be interesting to know whether other nitriles could also be used for the epoxidation. To this end, a variety of nitriles were investigated (Table 2). These nitriles were used either alone or with other organic solvents. As shown in Table 2, CH_3CN and CH_3CH_2CN give the best results. Other H_2O_2 activators such as DCC were also investigated (Table 2, entries 18–20),[17] however, low conversions were obtained. Some epoxidation occurred with oxidants such as $NaBO_3$, $Na_2CO_3{\cdot}1.5H_2O_2$, mCPBA, CH_3COOOH.[18] Only trace amounts of epoxides were obtained when NaClO and $NaClO_2$ were used. Among all those oxidants tested, it is clear that peroxyimidic acids generated from nitriles such as acetonitrile are effective oxidants to react with ketones to generate dioxiranes. The efficient formation of the dioxirane with this class of oxidant could be due to the fact the nitrogen of the peroxyimidic acid acts as an internal base to facilitate the generation of the dioxirane (Scheme 2).

In summary, we have shown that dioxiranes can be generated in situ using a combination of nitrile and H_2O_2 as oxidant. Among the nitriles tested, acetonitrile is particularly effective and inexpensive. Peroxyimidic acid **9** is postulated to be the active oxidant. A few appealing features of the current epoxidation system are worth mentioning. High yields and ee's were obtained for a number of olefins. The epoxidation was carried out under mild conditions using inexpensive hydrogen peroxide as primary oxidant. Also, the amount of salts introduced and volume of solvent required were significantly reduced compared to our previous procedures using Oxone. In addition, the current

Table 1. Asymmetric epoxidation of olefins catalyzed by ketone **5** using H_2O_2 and CH_3CN

Entry	Substrate	Method[a]	Cat (mol%)	Time (h)	Yield (%)[b]	ee (%)
1		A	15	12	93	92[c]
2		A	30	24	75	93[d]
3		A	30	16	71	89[d]
4		B	30	24	77	99[d]
		C	30	24	90	98[d]
		D	30	1.5	78	99
5		C	30	10	97	92[e]
6		B	30	24	68	97[d]
		C	30	24	94	95[d]
7		A	10	6	90	96[c]
		D	30	2	94	98
8		C	30	16	88	89[d]
9		C	30	16	77	92[d]
10		A	30	4	93	95[f]
11		A	15	5.5	75	96[d]
12		A	30	3.5	76	95[g]

[a] Method A: The reactions were carried out at 0°C (bath temperature) with substrate (1.0 mmol), ketone **5** (0.1–0.3 mmol), and H_2O_2 (4.0 mmol) in CH_3CN (1.5 mL)-2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1.5 mL). Method B: The reactions were carried out at 0°C (bath temperature) with substrate (1.0 mmol), ketone **5** (0.3 mmol), and H_2O_2 (4.0 mmol) in CH_3CN–DMM (1:2, v/v) (6.0 mL)-2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1.5 mL). For entries 4 and 6, the reactions were carried out at 0°C for 10 h then at rt for 14 h. Method C: The reactions were carried out at 0°C (bath temperature) with substrate (1.0 mmol), ketone **5** (0.3 mmol), and H_2O_2 (4.0 mmol) in CH_3CN–EtOH–CH_2Cl_2 (1:1:2, v/v) (2.0 mL)-2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1.5 mL). For entries 4 and 6, the reactions were carried out at 0°C for 12 h then at rt for 12 h. Method D: The reactions were carried out with substrate (1 equiv.), ketone (0.3 equiv.), Oxone (1.38 equiv.), and K_2CO_3 (5.8 equiv.) in CH_3CN–DMM–0.05 M $Na_2B_4O_7.10H_2O$ of aqueous EDTA (4×10^{-4} M) solution (1:2:2, v/v). The reactions were run at 0°C for entry 4 and −10°C for entry 7 (taken from Ref. 6c).

[b] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization.

[c] Enantioselectivity was determined by chiral GC (Chiraldex G-TA).

[d] Enantioselectivity was determined by chiral HPLC (Chiracel OD).

[e] The epoxide was opened (NaOMe–MeOH), and the resulting alcohol was converted to its acetate; enantioselectivity was determined by ^1H NMR shift analysis of the resulting acetate with $Eu(hfc)_3$.

[f] Enantioselectivity was determined by chiral GC (Chiraldex B-TA) after desilylation with TBAF.

[g] Enantioselectivity was determined by chiral HPLC (Chiracel OB).

study shows that oxidants other than peroxysulfates can be used to efficiently generate dioxiranes.

1. Experimental

The general experimental information is similar to those recently described.[6c] Hydrogen peroxide (H_2O_2) is potentially explosive although no incidents occurred by our experience, care must be taken in handling this compound. In the epoxidation reaction, EDTA is used to minimize the decomposition of H_2O_2 catalyzed by any trace metals. All the epoxides in Table 1 are known compounds and give satisfactory spectroscopic characterization. The corresponding references for these epoxides are included.

1.1. Representative epoxidation procedures

1.1.1. Method A. To a solution of *trans*-β-methylstyrene (0.118 g, 1.0 mmol) and ketone **5** (0.0387 g, 0.15 mmol) in CH_3CN (1.5 mL) was added a solution of 2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1.5 mL) followed by H_2O_2 (30%, 0.4 mL, 4 mmol) at 0°C. Upon stirring at 0°C for 12 h, the reaction mixture was extracted with hexane, washed with 1 M aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (silica gel

Table 2. Asymmetric epoxidation of *trans*-β-methylstyrene with 10–30 mol% ketone **5**, H_2O_2, and various nitriles and activators

Entry	nitrile	Conv.(%)	ee (%)
1[a]	CH_3CN	73	92
2[a]	CH_3CH_2CN	52	94
3[a]	$CH_3CH_2CH_2CN$	13	95
4[a]	*t*-BuCN	0.6	nd
5[a]	PhCN	14	91
6[a]	CCl_3CN	9	6
7[b]	CH_3CN	94	93
8[b]	CH_3CH_2CN	92	94
9[b]	$CH_3CH_2CH_2CN$	27	94
10[b]	*t*-BuCN	4	93
11[b]	CCl_3CN	11	13
12[b]	$HOCH_2CN$	0.7	26
13[b]	CH_3OCH_2CN	13	68
14[b]	PhCN	50	92
15[b]	*o*-F-PhCN	17	84
16[b]	*o*-CH_3O-PhCN	1	91
17[b]	F_5-PhCN	7	12
18[c]	DCC	17	93
19[c]	$(MeO)_2CO$	2	93
20[c]	$(t\text{-BuOCO})_2O$	8	70

[a] The reactions were carried out at 0°C (bath temperature) with substrate (0.5 mmol), ketone **5** (0.05 mmol), and 30% H_2O_2 (2 mmol) in RCN (0.75 mL) and 2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (0.75 mL). The conversion and ee were determined by chiral GC (Chiraldex G-TA) after the reaction mixture was stirred for 10 h.

[b] The reactions were carried out at 0°C (bath temperature) with substrate (0.5 mmol), ketone **5** (0.05 mmol), and 30% H_2O_2 (2 mmol) in RCN–EtOH–CH_2Cl_2 (1:1:1 v/v, 0.75 mL) and 2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (0.75 mL). The conversion and ee were determined by chiral GC (Chiraldex G-TA) after the reaction mixture was stirred for 10 h.

[c] The reactions were carried out at 0°C (bath temperature) with substrate (1.0 mmol), ketone **5** (0.3 mmol), activator (4.0 mmol), and 30% H_2O_2 (4 mmol) in EtOH–CH_2Cl_2 (1:1 v/v, 1.5 mL) and 2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1.5 mL). The conversion and ee were determined by chiral GC (Chiraldex G-TA) after the reaction mixture was stirred for 10 h.

was buffered with 1% Et_3N in hexane, using hexane/ether 1/0–50/1 as eluent) to afford the epoxide product as a colorless oil (0.124 g, 93% yield, 92% ee) (Table 1, entry 1).

1.1.2. Method B. To a solution of *trans*-stilbene (0.180 g, 1.0 mmol) and ketone **5** (0.0774 g, 0.30 mmol) in CH_3CN–DMM (1:2, v/v) (6.0 mL) was added a solution of 2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1.5 mL) followed by H_2O_2 (30%, 0.4 mL, 4 mmol) at 0°C. Upon stirring at 0°C for 10 h and rt for 14 h, the reaction mixture was extracted with hexane, washed with 1 M aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (silica gel was buffered with 1% Et_3N in hexane, using hexane/ether 50/1 as eluent) to afford the epoxide product as a white solid (0.151 g, 77% yield, 99% ee) (Table 1, entry 4).

1.1.3. Method C. To a solution of 1-phenyl-3,4-dihydronaphthalene (0.206 g, 1.0 mmol) and ketone **5** (0.0774 g, 0.30 mmol) in CH_3CN–EtOH–CH_2Cl_2 (1:1:2, v/v) (2.0 mL) was added a solution of 2.0 M K_2CO_3 in 4×10^{-4} M of EDTA (1.5 mL) followed by H_2O_2 (30%, 0.4 mL, 4 mmol) at 0°C. Upon stirring at 0°C for 16 h, the reaction mixture was extracted with hexane, washed with 1 M aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography (silica gel was buffered with 1% Et_3N in hexane, using hexane/ether 50/1 as eluent) to afford the epoxide product as a white solid (0.196 g, 88% yield, 89% ee) (Table 1, entry 8).

1.1.4. (*R,R*)-*trans*-β-Methylstyrene oxide (Table 1, entry 1).[6c] $[\alpha]^{25}_D=+44.7$ (*c* 0.47, $CHCl_3$); ^1H NMR δ 7.38–7.23 (m, 5H), 3.58 (d, *J*=2.6 Hz, 1H), 3.04 (qd, *J*=5.1, 2.6 Hz, 1H), 1.47 (d, *J*=5.1 Hz, 3H).

1.1.5. (*R,R*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-3-phenyloxirane (Table 1, entry 2).[6c] $[\alpha]^{25}_D=+40.0$ (*c* 0.47, CH_2Cl_2); ^1H NMR δ 7.40–7.20 (m, 5H), 3.97 (dd, *J*=12.0, 3.0 Hz, 1H), 3.82 (dd, *J*=12.0, 3.9 Hz, 1H), 3.80 (d, *J*=1.8 Hz, 1H), 3.14 (ddd, *J*=3.9, 3.0, 1.8 Hz, 1H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H).

1.1.6. (*R,R*)-3-Phenyloxiranemethanol (Table 1, entry 3).[6e] $[\alpha]^{25}_D=+46.0$ (*c* 0.55, $CHCl_3$). ^1H NMR δ 7.40–7.25 (m, 5H), 4.06 (ddd, *J*=12.6, 5.1, 2.1 Hz, 1H), 3.94 (d, *J*=2.1 Hz, 1H), 3.82 (ddd, *J*=12.6, 7.8, 3.9 Hz, 1H), 3.24 (m, 1H), 1.78 (m, 1H).

1.1.7. (*R,R*)-*trans*-Stilbene oxide (Table 1, entry 4).[6c] $[\alpha]^{25}_D=+357.2$ (*c* 1.10, benzene). ^1H NMR δ 7.44–7.31 (m, 10H), 3.88 (s, 2H).

1.1.8. (*R,R*)-2,3-Dihexyloxirane (Table 1, entry 5).[6c] $[\alpha]^{25}_D=+26.2$ (*c* 0.65, $CHCl_3$); ^1H NMR δ 2.66 (m, 2H), 1.60–1.20 (m, 20H), 0.89 (t, *J*=6.8 Hz, 6H).

1.1.9. (*R,R*)-*trans*-Methylstilbene oxide (Table 1, entry 6).[6c] $[\alpha]^{25}_D=+114.3$ (*c* 0.63, EtOH) ^1H NMR δ 7.52–7.24 (m, 10H), 3.96 (s, 1H), 1.47 (s, 3H).

1.1.10. (*R,R*)-1-Phenylcyclohexene oxide (Table 1, entry 7).[6c] $[\alpha]^{25}_D=+113.5$ (*c* 1.71, benzene); ^1H NMR δ 7.41–7.22 (m, 5H), 3.08 (m, 1H), 2.29 (ddd, *J*=14.7, 8.4, 5.4 Hz, 1H), 2.13 (dt, *J*=14.7, 5.4 Hz, 1H), 2.04 (m, 2H), 1.68–1.42 (m, 3H), 1.31 (m, 1H).

1.1.11. (*1S,2R*)-1-Phenyl-3,4-dihydronaphthalene oxide (Table 1, entry 8).[6c] $[\alpha]^{25}_D=-43.7$ (*c* 0.75, $CHCl_3$); ^1H NMR δ 7.49–6.98 (m, 9H), 3.63 (d, *J*=3.3 Hz, 1H), 2.95 (ddd, *J*=15.3, 13.2, 6.6 Hz, 1H), 2.70 (dd, *J*=15.3, 5.4 Hz, 1H), 2.49 (dddd, *J*=14.7, 6.6, 3.3, 1.8 Hz, 1H), 2.04 (ddd, *J*=14.7, 13.2, 5.4 Hz, 1H).

1.1.12. (*R*)-9-Ethylidenefluorene oxide (Table 1, entry 9).[19] $[\alpha]^{25}_D=+38.4$ (*c* 0.5, $CDCl_3$); ^1H NMR δ 7.74 (m, 2H), 7.47–7.35 (m, 3H), 7.34–7.22 (m, 3H), 3.88 (q, *J*=5.4 Hz, 1H), 1.70 (d, *J*=5.4 Hz, 3H).

1.1.13. (*R,R*)-1-(Trimethylsilylethynyl)cyclohexene oxide (Table 1, entry 10).[6i] $[\alpha]^{25}_D=+9.53$ (*c* 0.64, $CHCl_3$); ^1H NMR δ 3.31 (t, *J*=2.4 Hz, 1H), 2.10 (dt, *J*=15.2, 6.2 Hz, 1H), 1.99 (ddd, *J*=15.2, 7.5, 5.7 Hz, 1H), 1.88 (m, 2H), 1.44–1.16 (m, 4H), 0.14 (s, 9H).

1.1.14. (*R,R*)-1-Benzoyloxy-1,2-epoxycyclooctane (Table 1, entry 11).[6g] $[\alpha]^{25}_D=+7.03$ (*c* 0.91, $CHCl_3$); ^1H NMR δ 8.01 (m, 2H), 7.57 (tt, *J*=7.4, 1.6 Hz, 1H), 7.43 (m, 2H), 3.20 (ddd, *J*=10.0, 4.6, 0.8 Hz, 1H), 2.88 (m, 1H), 2.27 (ddd, *J*=13.1, 7.8, 4.5 Hz, 1H), 1.92–1.20 (m, 10H).

1.1.15. (*R,R*)-2-[(*E*)-2-(Ethoxycarbonyl)-2-methylvinyl]-3-ethyl-2-methyloxirane (Table 1, entry 12).[6d] $[\alpha]^{25}_{D}$= −96.79 (*c* 0.66, $CHCl_3$); ^{1}H NMR δ 6.83 (m, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 2.85 (t, *J*=6.3 Hz, 1H), 1.92 (d, *J*= 1.2 Hz, 3H), 1.77–1.50 (m, 2H), 1.39 (s, 3H), 1.29 (t *J*= 7.1 Hz, 3H), 1.08 (t, *J*=7.5 Hz, 3H).

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