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Influence of hydroperoxides on the enantioselectivity of metal-catalyzed asymmetric Baeyer–Villiger oxidation and epoxidation with chiral ligands

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Abstract—Chiral hydroperoxides have a significant influence on the enantioselectivity of the metal-catalyzed asymmetric Baeyer–Villiger oxidation of cyclic ketones and the epoxidation of allylic alcohols, when chiral ligands are employed. If both the ligand and the hydroperoxide are enantiopure, the ligand determines the formation of the preferred product enantiomer in both reactions.

1. Introduction

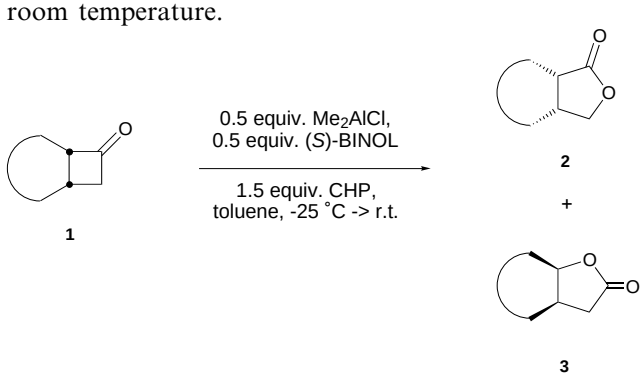
Asymmetric epoxidation has gained its place among the most powerful synthetic methods to obtain chiral intermediates.[1] Metal-catalyzed Baeyer–Villiger oxidation has not yet reached this highly developed level; however, some promising new developments have recently been reported.[2] For both types of reactions, much effort has been expended in finding the right combination of metal and chiral ligand to catalyze these oxidations efficiently. To date, the hydroperoxides tested were mainly restricted to the commercially available *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CHP).

In the course of our search for new methods of asymmetric catalysis, we have examined the influence of hydroperoxides in oxidative transformations, viz the Baeyer–Villiger oxidation of cyclic ketones and the epoxidation of allylic alcohols. Two different substrates were investigated for each reaction to allow more general conclusions.

2. Results and discussion

We have recently reported on a new variant of the asymmetric Baeyer–Villiger oxidation, mediated by a chiral Lewis acid that is based on aluminium (Scheme 1).[3] The combination of BINOL and an appropriate aluminium compound (1:1 ratio of ligand and metal precursor) were found to give optically active lactones from the racemic cyclobutanones **1**. In part, this system proved to be more efficient than the other metal-based ones known to date.[2,3]

The experiments to examine the influence of the hydroperoxide were carried out in toluene in the presence of 0.5 equivalents of Me_2AlCl and 0.5 equivalents of enantiopure BINOL. The reaction mixture was stirred overnight and allowed to warm from −25°C to room temperature.



Scheme 1.

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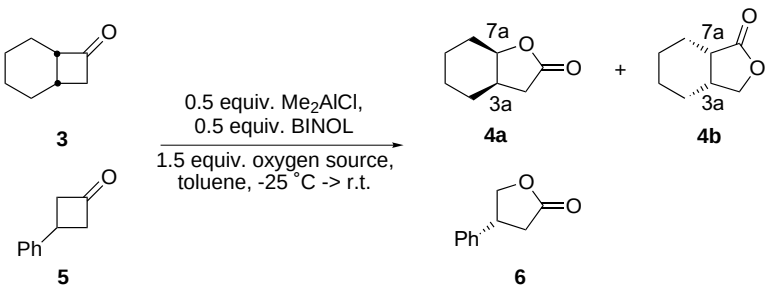
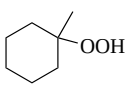
Based on the results shown in Table 1, no general trend may be deduced, as long as an achiral hydroperoxide is employed. Although trityl hydroperoxide (TrOOH,[4] entry 4) was the best oxygen source in the case of lactone **6**, the two regioisomeric products **4a** and **4b** were formed with the lowest enantioselectivity under these conditions. Furthermore, the lowest **4a**:**4b** ratio was not observed with the smallest hydroperoxide, TBHP, but with the sterically more demanding 1-methylcyclohexyl hydroperoxide.[5] In contrast, the bulkiest hydroperoxide, TrOOH, led to the highest **4a**:**4b** ratio.

With few exceptions, chiral hydroperoxides have so far been reported to give only moderate enantioselectivities in asymmetric oxidations.[6] We have developed an effective method to obtain enantiopure (*S*)-(1-phenyl)ethyl hydroperoxide by enzymatic kinetic resolution[7] and demonstrated that it serves as an efficient chiral oxygen source in various asymmetric oxidations.[8a] Moreover, a TADDOL-based hydroperoxide was recently reported,[8b] with which highly efficient asymmetric oxidations have been achieved. Consequently, the opportunity presented itself to examine the stereoselectivity of a combination of a chiral hydroperoxide with each enantiomer of BINOL in the asymmetric Baeyer–Villiger oxidation (Scheme 1). The incentive was to assess whether any cooperative effects operate between the two chiral components, that is, the optically active hydroperoxide and the optically active ligand simultaneously coordinated to the metal catalyst, and to identify which stereogenic center is responsible for the formation of the preferred enantiomer of the oxidation product. Clearly, entries 5 and 6 in Table 1 reveal that the absolute configurations for the products **4** and **6** are determined by the chirality of the ligand. Furthermore, the enantiomeric excess of the oxidation products differ in both experiments, which implicates cooperative effects between the chiral ligand and the chiral hydroperoxide as a result of matched and mismatched combinations. This is also supported by the marked change in the **4a**:**4b** ratio from 11.2:1 to 4.5:1. Conse-

Table 1. Aluminium-promoted Baeyer–Villiger oxidation of **3** and **5** using different hydroperoxides



Entry	Oxygen source	BINOL	E.e. of **4a** [%][a]	E.e. of **4b** [%][a]	Ratio **4a**:**4b**[b,c]	E.e. of **6** [%][a]
1	TBHP	(*S*)	27 (3a*R*,7a*R*)	95 (3a*R*,7a*S*)	3.3	64 (*S*)
2		(*S*)	36 (3a*R*,7a*R*)	94 (3a*R*,7a*S*)	2.1	58 (*S*)
3	CHP	(*S*)	34 (3a*R*,7a*R*)	96 (3a*R*,7a*S*)	2.7	71 (*S*)
4	TrOOH	(*S*)	22 (3a*R*,7a*R*)	80 (3a*R*,7a*S*)	4.5	75 (*S*)
5[d]		(*S*)	5 (3a*R*,7a*R*)	89 (3a*R*,7a*S*)	11.2	60 (*S*)
6[d]		(*R*)	18 (3a*S*,7a*S*)	92 (3a*S*,7a*R*)	4.5	51 (*R*)
7[e]		(*S*)	11 (3a*R*,7a*R*)	89 (3a*R*,7a*S*)	8.3	56 (*S*)

[a] Determined by GC using a chiral column.

[b] Calculated from area percentages.

[c] Full conversion of the starting material in each case.

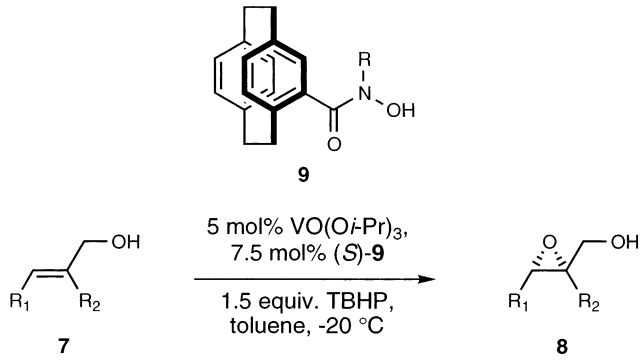
[d] (*S*)-(1-phenyl)ethyl hydroperoxide with >99% e.e. was used.

[e] Oxidant was racemic.

quently, the enantiomeric excess achieved with the racemic (1-phenyl)ethyl hydroperoxide (entry 7) falls, after complete oxidation, between the e.e. values of the experiments with the pure enantiomers in entries 5 and 6.

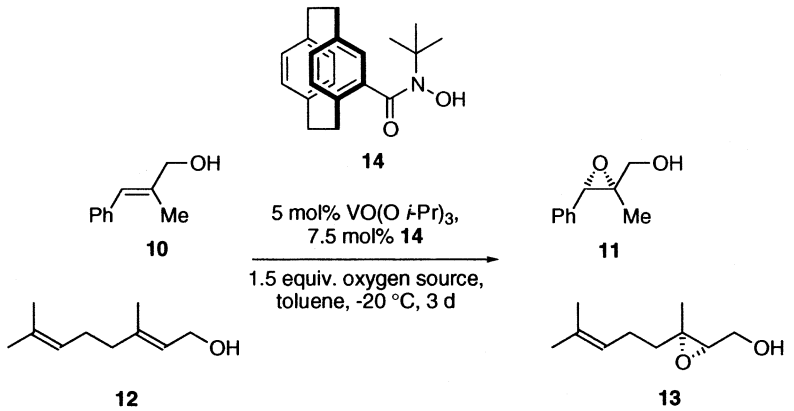
In order to gain more insight into the generality of the findings, we extended our studies to the vanadium-catalyzed epoxidation of allylic alcohols **7**. We have reported earlier that the catalyst formed from $VO(O\textit{i}\text{-}Pr)_3$ and the chiral hydroxamic acids **9** with a [2.2]paracyclophane scaffold gave epoxides **8** with up to 71% e.e. (Scheme 2) by asymmetric oxidation.[9,10]

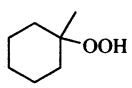
A survey of various achiral hydroperoxides revealed that the presence of aryl groups in the oxygen source is detrimental to the enantiomeric excess (Table 2, entries 1–4). Exchange of the aryl substituents with methyl groups dramatically increased the enantioselectivity in the epoxidation of geraniol **12** from 9% e.e. (*R*,*R*) to 42% e.e. (*S*,*S*) for the corresponding epoxide **13**. Again, it was the chiral ligand which determined the absolute configuration of the epoxide for both substrates, when a combination of chiral ligand and chiral hydroperox-



Scheme 2.

Table 2. Vanadium-catalyzed epoxidation of **10** and **12** using different hydroperoxides



Entry	Oxygen source	Ligand **14**	ee of **11** [%][a]	Yield of **11** [%]	ee of **13** [%][b]	Yield of **13** [%]
1	TBHP	(*S*)	72 (2*S*,3*S*)	81	42 (2*S*,3*S*)	88
2		(*S*)	51 (2*S*,3*S*)	80	30 (2*S*,3*S*)	86
3	CHP	(*S*)	46 (2*S*,3*S*)	86	20 (2*S*,3*S*)	93
4	TrOOH	(*S*)	42 (2*S*,3*S*)	70	9 (2*R*,3*R*)	42
5[c]		(*S*)	33 (2*S*,3*S*)	86	39 (2*S*,3*S*)	91
6[c]		(*R*)	63 (2*R*,3*R*)	90	27 (2*R*,3*R*)	93
7[d]		(*S*)	49 (2*S*,3*S*)	88	33 (2*S*,3*S*)	93

[a] Determined by HPLC using a chiral column (Chiracel OD, hexane : *i*-PrOH = 97:3).

[b] Determined by ^{1}H-NMR shift experiments ($Eu(tfc)_3$).

[c] (*S*)-(1-phenyl)ethyl hydroperoxide with > 99% ee was used.

[d] Oxidant was racemic.

ide was used (entries 5 and 6). Substrate **10** showed a remarkable difference in the enantioselectivity (63 versus 33% e.e.) with respect to the matched versus the mismatched combination. In agreement with our findings for the Baeyer–Villiger oxidation, the use of racemic (1-phenyl)ethyl hydroperoxide (entry 7) gave a value between the ones of the experiments with the single enantiomer in entries 5 and 6. In addition, the e.e. value of the remaining hydroperoxide, which was employed in 1.5-fold excess, was determined to be less than 5% after the reaction[11] for both substrates, which indicates that no kinetic resolution of the racemic hydroperoxide had taken place. This confirms that both diastereomeric combinations of the chiral ligand and the chiral hydroperoxide react at about the same rates. Significantly, again the more effective combination, analogous to the Baeyer–Villiger oxidation, cannot be predicted: either substrate shows a better selectivity for the opposite enantiomer combination.

In conclusion, we have demonstrated that the choice of the hydroperoxide as oxygen source has a pronounced influence on the stereochemical outcome of the metal-catalyzed asymmetric Baeyer–Villiger oxidation of cyclic ketones, as well as the epoxidation of allylic alcohols. For the combination of chiral ligands with chiral hydroperoxides, the ligand dominates the formation of the preferred enantiomer of the oxidation product. A significant cooperative effect has been found, but it is difficult to predict a priori which combination may be the more successful. The outcome strictly depends on the substrate used.

3. Experimental

3.1. General information

^{1}H NMR spectra were recorded on a Varian VXR 300 (300 MHz) or a Varian Inova 400 (400 MHz). The chemical shifts are referred to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity, coupling constants, integration. ^{13}C NMR spectra were recorded on a Varian VXR 300 (75 MHz), a Varian Inova 400 (100 MHz) or a Varian Unity 500 (125 MHz) with complete proton decoupling. The chemical shifts are referenced to the solvent used. IR spectra were recorded on a Perkin Elmer spectrometer (PE 1720X, PE 1760 FT). Melting points were determined on a Büchi B-540 and are uncorrected. Optical rotation values α were determined on a Perkin Elmer polarimeter PE-241. All reactions were carried out under an argon gas atmosphere. Dichloromethane was distilled from CaH_2 under N_2, toluene was distilled from Na under an argon atmosphere; NEt_3 and pyridine were distilled from KOH and stored under argon. Anhydrous DMF was purchased from Fluka and used without further purification.

3.2. Synthesis of (*S*)-*N*-(1,1-dimethylethyl)-*N*-hydroxy-[2.2]paracyclophane-4-carboxylic amide 14

A solution of oxalyl chloride in dichloromethane (0.5 M, 3 mL, 1.50 mmol) was slowly added to a suspension of (*S*)-[2.2]paracyclophane-4-carboxylic acid[12] (252 mg, 1.00 mmol) and DMF (two drops) in dichloromethane (2 mL). The resulting mixture was stirred for 1 h at ambient temperature (ca. 20°C) wherein a light red solution was obtained. The solvent and excess oxalyl chloride were removed in vacuo. The remaining carboxylic chloride was dissolved in dichloromethane (5 mL) and slowly added to a solution of *tert*-butylhydroxylamine (115 mg, 1.30 mmol) and NEt_3 (0.40 mL, 2.88 mmol) in dichloromethane (5 mL) at −70°C. The mixture was then allowed to warm to ambient temperature and stirred for an additional 4 h. Upon completion, aqueous hydrochloric acid (2 M, 10 mL) was added. The aqueous layer was extracted with MTBE (2×20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) and dried over $MgSO_4$. Removal of the solvent provided the crude product, which was purified by flash column chromatography (silica, petroleum ether:MTBE, 2:1), followed by recrystallization from hexane to give (*S*)-**14** as white fibers (145 mg, 45%): mp 146°C; R_f 0.41 (petroleum ether:MTBE, 2:1); $[\alpha]_D^{25} = +73.6$ (*c* 0.5, $CHCl_3$); IR (KBr) 3180, 2928, 2852, 1604, 1558, 1499, 1475, 1454, 1430, 1383, 1364, 1203, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 2.86–3.03 (m, 4H), 3.08–3.27 (m, 4H), 6.38 (dd, $J=8.0$, 1.6 Hz, 1H), 6.41 (d, $J=7.7$ Hz, 1H), 6.45 (d, $J=1.6$ Hz, 1H), 6.53–6.61 (m, 3H), 7.13 (dd, $J=8.0$, 1.6 Hz, 1H), 8.80 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2, 33.9, 35.4, 35.6, 35.8, 61.8, 131.6, 132.0, 132.5, 132.6, 133.1, 133.3, 135.0, 135.1, 138.4, 139.3, 139.5, 139.7, 168.9; HPLC (Chiralcel OD, hexane:*i*-PrOH, 98:2, 0.6 mL/min, 25°C): $t_R = 38.3$ min (*S*) and 48.4 min (*R*). Anal. calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 77.96; H, 7.52; N, 4.25%.

3.3. Asymmetric Baeyer–Villiger oxidation

3.3.1. Synthesis of reactants. (±)-*cis*-Bicyclo[4.2.0]octan-7-one **3**[13] and 3-phenylcyclobutanone **5**[14] are accessible by means of [2+2]-cycloaddition of dichloroketene to an appropriate olefin and subsequent dehalogenation.

3.3.2. (±)-*cis*-Bicyclo[4.2.0]octan-7-one 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04–1.26 (m, 3H), 1.39–1.48 (m, 1H), 1.52–1.59 (m, 2H), 1.94–1.98 (m, 1H), 2.13–2.19 (m, 1H), 2.44–2.50 (m, 2H), 3.11–3.18 (m, 1H), 3.26–3.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 22.2, 22.3, 22.4, 29.3, 52.0, 56.4, 209.7; GC: Lipodex B (25 m×0.25 mm) with pre-column (3 m×0.25 mm), 60 kPa N_2, either 120°C isotherm with $t_R = 5.9$ min or 120°C, 2°C/min, 150°C, 5 min with $t_R = 4.9$ min.

3.3.3. 3-Phenylcyclobutanone 5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15–3.27 (m, 2H), 3.40–3.52 (m, 2H), 3.64 (quin, $J=8.2$ Hz, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 54.5, 126.3, 126.5, 128.5, 143.4, 206.4; GC: Lipodex B (25 m×0.25 mm) with pre-column (3 m×0.25 mm), 60 kPa N_2 at 140°C, 140°C, 15 min, 2°C/min, 160°C, 50 min with $t_R = 15.8$ min.

3.3.4. General procedure for the Baeyer–Villiger oxidation. A solution of Me_2AlCl in hexane (50 mol%) was injected into a solution of enantiopure BINOL (50 mol%) in dry toluene under an argon gas atmosphere. After

being stirred for 0.5×1 h at ambient temperature, the ketone was added to the suspension, which became more homogeneous after stirring for an additional 15 min. The mixture was cooled to −25°C before addition of hydroperoxide (1.5 equiv.) and then slowly allowed to warm to ambient temperature again. After stirring for 12 h, the mixture was treated with aqueous HCl (0.5 M) and the aqueous layer was extracted with MTBE. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and directly submitted to GC analysis.

When yields of isolated products were to be determined, 1–2 mmol of ketone was employed and the product was purified by flash column chromatography (silica, petroleum ether:MTBE, 2:1).

3.3.5. (±)-*cis*-Hexahydro-2(3*H*)-benzofuranone 4a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.34 (m, 2H), 1.43–1.54 (m, 2H), 1.58–1.77 (m, 3H), 2.03–2.12 (m, 1H), 2.25 (dd, $J=16.4$, 2.4 Hz, 1H), 2.35–2.45 (m, 1H), 2.62 (dd, $J=16.8$, 6.9 Hz, 1H), 4.52 (ddd, $J_1=J_2=J_3=4.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 22.6, 27.0, 27.6, 34.7, 37.3, 79.1, 177.6; GC: Lipodex B (25 m×0.25 mm) with pre-column (3 m×0.25 mm), 60 kPa N_2, either 120°C isotherm with $t_R=37.7$ min [(+)-(3a*R*,7a*R*)] and 41.0 min [(−)-(3a*S*,7a*S*)] or 120°C, 2°C/min, 150°C, 5 min with $t_R=17.6$ min [(+)-(3a*R*,7a*R*)] and 18.2 min [(−)-(3a*S*,7a*S*)].[15]

3.3.6. (±)-*cis*-Hexahydro-1(3*H*)-isobenzofuranone 4b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19–1.24 (m, 3H), 1.56–1.67 (m, 3H), 1.77–1.85 (m, 1H), 2.10–2.13 (m, 1H), 2.44–2.51 (m, 1H), 2.63–2.67 (m, 1H), 3.96 (dd, $J=9.1$, 1.4 Hz, 1H), 4.20 (dd, $J=8.8$, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 22.9, 23.4, 27.2, 35.4, 39.5, 71.7, 178.3; GC: Lipodex B (25 m×0.25 mm) with pre-column (3 m×0.25 mm), 60 kPa N_2, either 120°C isotherm with $t_R=24.6$ min [(−)-(3a*S*,7a*R*)] and 26.1 min [(+)-(3a*R*,7a*S*)] or 120°C, 2°C/min, 150°C, 5 min with $t_R=14.3$ min [(−)-(3a*S*,7a*R*)] and 14.7 min [(+)-(3a*R*,7a*S*)].[16]

3.3.7. (±)-4-Phenyltetrahydro-2-furanone 6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (dd, $J=17.3$, 9.1 Hz, 1H), 2.90 (dd, $J=17.3$, 8.5 Hz, 1H), 3.78 (quin, $J=8.2$ Hz, 1H), 4.24 (t, $J=8.6$ Hz, 1H), 4.64 (t, $J=8.5$ Hz, 1H), 7.21–7.24 (m, 2H), 7.26–7.31 (m, 1H), 7.34–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5, 40.9, 73.8, 126.5, 127.4, 128.8, 139.2, 176.1; GC: Lipodex B (25 m×0.25 mm) with pre-column (3 m×0.25 mm), 60 kPa N_2 at 140°C, 140°C, 15 min, 2°C/min, 160°C, 50 min with $t_R=65.0$ min [(+)-(*S*)] and 66.6 min [(−)-(*R*)].[17]

3.4. Asymmetric epoxidation

3.4.1. General procedure for the epoxidation of allylic alcohols. $VO(O$*i*$\text{-Pr})_3$ (5 mol%) and ligand **14** (7.5 mol%) were dissolved in dry toluene under an argon atmosphere. The resulting deep red solution was first stirred for 1 h at ambient temperature and then cooled to −20°C. Subsequently, the allylic alcohol was added via syringe, followed, after 15 min, by the hydroperoxide (1.5 equiv.). After stirring the mixture for 3 days, the reaction was quenched with aqueous Na_2SO_3 (1 M), and the mixture was extracted with MTBE. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The epoxide was purified by flash column chromatography on silica gel.

When the enantiomeric excess of the remaining (1-phenyl)ethyl hydroperoxide was to be determined, the crude reaction mixture was directly submitted to column chromatography without any work-up.

3.4.2. Procedure for the experiments with the shift reagent Eu(tfc)$_3$. Acetic anhydride (50 μL) was added to a solution of 2,3-epoxygeraniol **13** (30 mg) in dry pyridine (0.5 mL). The resulting mixture was stirred at ambient temperature for 2 h and then diluted with petroleum ether (0.5 mL). The formed acetate was purified by flash column chromatography (silica, petroleum ether:MTBE, 2:1, R_f 0.75). The enantiomeric excess was determined by ^{1}H NMR analysis of a solution of the acetate and $Eu(tfc)_3$ (8 mg) in C_6D_6 (1 mL) by integrating the signal at δ 1.04 ppm.

3.4.3. (±)-2,3-Epoxy-2-methyl-3-phenylpropan-1-ol 11. R_f 0.22 (petroleum ether:MTBE, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H), 2.18 (dd, $J=8.5$, 4.1 Hz, 1H), 3.76 (dd, $J=12.5$, 8.7 Hz, 1H), 3.86 (dd, $J=12.5$, 4.0 Hz, 1H), 4.22 (s, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 60.4, 64.0, 65.2, 126.6, 127.8, 128.3, 135.8; HPLC (Chiralcel OD, hexane:*i*-PrOH, 97:3, 0.8 mL/min, 25°C): $t_R=19.0$ min (2*S*,3*S*) and 26.3 min (2*R*,3*R*).

3.4.4. (±)-2,3-Epoxygeraniol 13. R_f 0.19 (petroleum ether:MTBE, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.43–1.52 (m, 1H), 1.61 (s, 3H), 1.64–1.72 (m, 1H), 1.69 (d, $J=1.1$ Hz, 3H), 1.96 (dd, $J=7.3$, 4.8 Hz, 1H), 2.09 (q, $J=8.0$ Hz, 2H), 2.98 (dd, $J=6.8$, 4.3 Hz, 1H), 3.64–3.72 (m, 1H), 3.79–3.87 (m, 1H), 5.06–5.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 17.6, 23.7, 25.7, 38.4, 61.1, 61.4, 62.9, 123.2, 132.0.

3.4.5. Acetate of (±)-2,3-epoxygeraniol 13. ^{1}H NMR (400 MHz, C_6D_6) δ 1.04 (s, 3H), 1.31–1.39 (m, 1H), 1.48 (s, 3H), 1.48–1.56 (m, 1H), 1.63 (d, $J=1.1$ Hz, 3H), 1.66 (s, 3H), 1.96–2.03 (m, 2H), 2.89 (dd, $J=6.6$, 4.4 Hz, 1H), 3.99 (dd, $J=12.1$, 6.6 Hz, 1H), 4.19 (dd, $J=12.1$, 4.4 Hz, 1H), 5.03–5.09 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 16.8, 17.6, 20.2, 23.9, 25.7, 38.5, 59.5, 59.8, 63.5, 123.9, 131.6, 169.7; ^{1}H NMR experiment with the shift reagent $Eu(tfc)_3$: δ 1.16 (2*S*,3*S*) and 1.19 (2*R*,3*R*).

3.4.6. (±)-(1-Phenyl)ethyl hydroperoxide. R_f 0.20 (petroleum ether:MTBE, 4:1); HPLC (Chiralcel OD-H, hexane:*i*-PrOH, 95:5, 0.5 mL/min, 20°C): $t_R=23.2$ min (*R*) and 28.4 min (*S*).

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