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Asymmetric peroxidation of prochiral allylic and benzylic compounds with *tert*-butyl hydroperoxide and chiral bisoxazoline–copper complexes †

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Abstract

The first enantioselective peroxidation of prochiral allylic and benzylic C–H compounds by the use of chiral bisoxazoline–copper(I) complexes, generated in situ from the ligands **3** and **4a**–**d**, and *t*-BuOOH as oxidant is reported. Cyclohexene **1**, cyclopentene **5**, α-angelica lactone **7**, allylbenzene **9** and 2-phenylbutane **11** were converted into the optically active allylic and benzylic *tert*-butyl peroxides **2**, **6**, **8**, **10a** and **12** in good yields and ee values of 4–20%. Oxidations of 1-substituted 1-cyclohexenes **13a**–**c** led to mixtures of regioisomeric peroxides **16a**–**c**, **17a**–**c** and **18a**–**c** with different regio- and enantioselectivities, depending on the 1-substituent and the ligand used. The highest ee values (up to 84%) were observed for (*S*)-3-*tert*-butylperoxy-1-methyl-1-cyclohexene **17a**.

1. Introduction

The direct enantioselective oxidation of C–H bonds is still one of the most difficult problems in oxidation chemistry. In the last few years significant progress has been achieved in this type of transformation, especially in the asymmetric Kharasch–Sosnovsky reaction (Eq. 1), i.e. the enantioselective allylic acyloxylation of olefins. By using *tert*-butyl hydroperoxide (in the presence of carboxylic acids) or peresters as oxidants and chiral (*S*)-proline- or bis- and trisoxazoline–copper complexes, optically active allylic esters with ee values of up to 60% (oxidant: *t*-BuOOH)[2] and up to 93% (oxidant: $PhCO_3t$-Bu)[3] were obtained.

* Corresponding author.

† Dedicated to Prof. Dr. Ernst Schmitz (Berlin) on the occasion of his 70th birthday.

‡ See References.[1]

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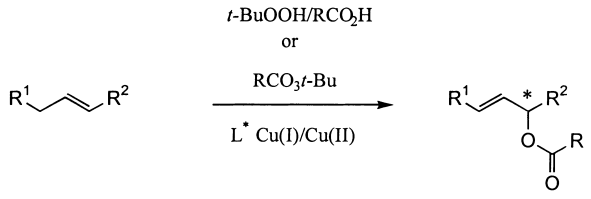

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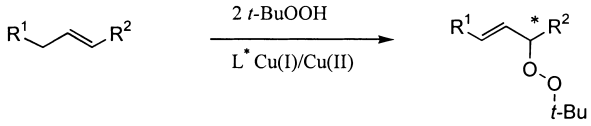

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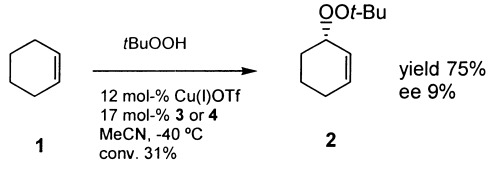
By contrast, the direct (nonenzymatic) asymmetric introduction of a peroxy group in prochiral C–H substrates remains to date an unsolved problem in peroxide chemistry. No example of an asymmetric variant of the Kharasch reaction, i.e. the copper-catalyzed allylic peroxidation of olefins to optically active peroxides (Eq. 2), has been hitherto reported, although the corresponding racemic peroxidation has been known for a long time.[4]

We have recently demonstrated that allylic peroxides may serve as synthetically useful substrates, namely for the further highly diastereoselective functionalization of the double bond (epoxidation and bishydroxylation).[5] Thus, if such a peroxidation could be performed asymmetrically, this would open the way to interesting new optically active functionalized peroxides.

2. Results and discussion

First attempts to achieve an asymmetric induction in the peroxidation of cyclohexene **1** with *t*-BuOOH (solvent: MeCN, temp.: 25–70°C) were made by employing chiral copper complexes, generated[6] in situ from (*S*)-amino acids (pro, phe, val, leu, ile, ala and *trans*-OH-pro). Indeed, the obtained peroxide **2** was optically active, but had ee values of at most 4%. The application of copper complexes derived from Cu(I)OTf and chiral bisoxazoline ligands **3** and **4a**,**b**, which have been successfully used in asymmetric acyloxylation reactions,[3a] allowed the oxidations to be carried out at lower temperatures and led to an increase of the ee value of **2** to 8–9% (Eq. 3).



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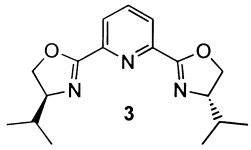

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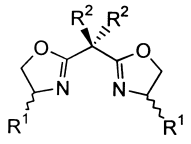
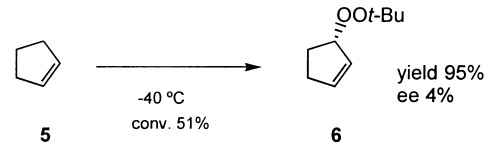


4a-d

a: (*S,S*) R^1= *t*Bu, R^2= Me
b: (*S,S*) R^1= Ph, R^2= Me
c: (*R,R*) R^1= Bn, R^2= Me
d: (*S,S*) R^1= Ph, R^2= H



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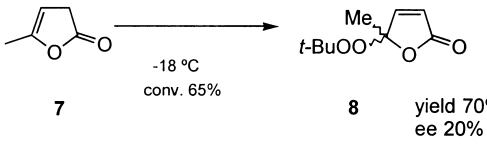

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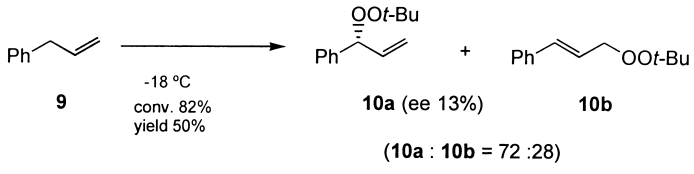

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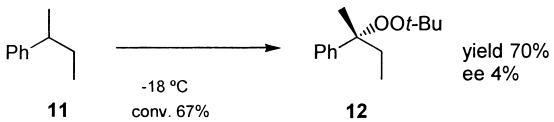

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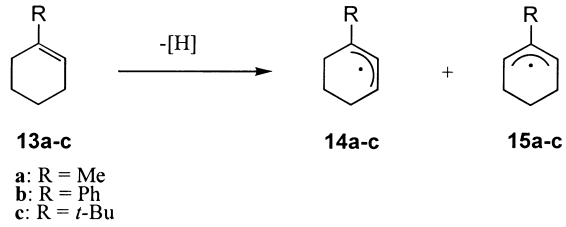
Similarly, cyclopentene **5**, α-angelica lactone **7**, allylbenzene **9** and racemic 2-phenylbutane **11** were oxidized with *t*-BuOOH in the presence of Cu(I)OTf/**3**.[7] The optically active peroxides **6**, **8**, **10a** and **12** were isolated in good yields and with ee values in the range of 4 to 20% (Eqs. 4–7).

Oxidation of 1-substituted cyclohexenes **13a–c** with the oxidant *t*-BuOOH and Cu(I)OTf/**3** or **4a–d** led to mixtures of isomeric peroxides **16a–c**, **17a–c** and **18a–c** (Eqs. 8 and 9, Table 1), which are the products of the intermediate regioisomeric allylic radicals **14a–c** (**16a–c** and **17a–c**) and **15a–c** (**18a–c**), formed by the initial radical attack on the different allylic positions of the substrates. The optically active isomeric peroxides **16a**,**b 17a–c** and **18b** were separated by flash chromatography and characterized by elemental analysis, NMR spectroscopy and optical rotation measurements. The isomers **16c** and **18a**,**c** were identified directly in the reaction mixtures (comparison with the racemic samples[1] by GC–MS and ^{1}H NMR).



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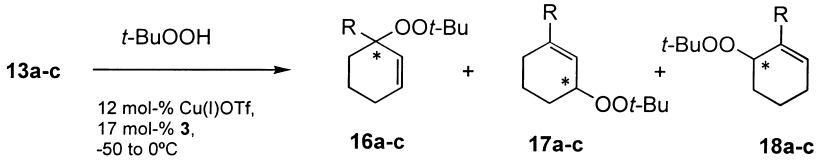

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The influence of the reaction conditions (ligand, solvent, temperature) on the regio- and enantioselectivity of the peroxidation is evident from the results obtained in the oxidation of 1-methylcyclohexene **13a**. Low dependence of the product ratio (**16a**+**17a**):**18a** (between 68:32 and 74:26), representing the regioselectivity of the formation of the allylic radicals **14a** and **15a**, was observed in the temperature range from −48°C to 0°C. Products of the CH_3-group attack were only detected in traces. In contrast, the isomer ratio **16a**:**17a** (products of radical **14a**) is influenced both by the chiral ligand and by the reaction temperature. Using the ligand **3**, the formation of the regioisomer **16a** was favoured over **17a** at lower temperatures (entries 1–7 of Table 1).

The highest ee values were obtained by employing the tridentate ligand **3**, but the ees of the regioisomers **16a**, **17a** and **18a** differ significantly. Whilst the peroxide **18a** was obtained almost racemic (except entry 5, ee 10%), **16a** had a max. 32% ee, but unexpectedly high ee values of up to 84% were observed for the regioisomer **17a** (the ee value of **17a** showed a stronger dependence on the temperature compared with the isomer **16a**). Surprisingly, the regioisomeric peroxides **16a** and **17a** were obtained with opposite configurations.

The use of the bidentate bisoxazoline ligands **4a–d**, which have been shown to give comparable or better enantioselectivities in the corresponding acyloxylation reaction (compared with ligand **3**),[3] led to drastically lower ee values (ee<10%) in the peroxidation of **13a** (Table 1, entry 8; only **4a** is shown, **4b–d** gave analogous results).

The highest ee values were observed when the reactions were carried out in acetone or MeCN as solvent, while the use of CH_2Cl_2 resulted in a decreased enantioselectivity (entry 6).

Attempts were made to diminish the amounts of Cu(I)OTf and of the expensive enantiomerically pure ligand **3**, but they resulted in lower ee values of the allylic peroxides **16a** and **17a**. This disadvantage was compensated by the addition of molecular sieves to tie up the water formed by the decomposition of *t*-BuOOH, which may destroy the active catalyst.[3c,8] This led to comparable ee values by employing only 1 mol% Cu(I)OTf and 1.5 mol% **3** (less than one twelfth of the initial amount, entry 7 of Table 1), but lower conversions were observed.

The effect of the substituent in the 1-position of substituted cyclohexenes on the regio- and enantioselectivity of the peroxidation became more apparent when 1-phenylcyclohexene **13b** and 1-*tert*-butylcyclohexene **13c** were oxidized by the *t*-BuOOH/Cu(I)OTf/**3** combination (Table 1). Analogous regioisomeric peroxides **16b**,**c**, **17b**,**c** and **18b**,**c** were formed, but in contrast to the oxidation of 1-methylcyclohexene **13a**, the isomers **17b** and **17c** were obtained as the main products. This is probably a consequence of the increasing size of the *R* substituent (Ph, *t*-Bu) which influences the regioselectivities of both the hydrogen atom and the peroxy-group transfer. Additionally, lower ee values were found for the peroxides **17b** and **17c** compared to the analogous methyl-substituted isomer **17a** (in the case of the

Table 1
Enantioselective allylic oxidation of 1-substituted 1-cyclohexenes **13a–c** with *t*-BuOOH in the presence of Cu(I)OTf and chiral bisoxazoline ligands **3** and **4a**

entry[a]	ligand	educt	T [°C][b]	t [d]	conv. [%][c]	yield **16**+**17**+**18** [%][d] (**16**/**17**/**18**)[e]	products: ee [%][f] (configuration)[g]
1	**3**	**13a**	0	14	82	72 (35/33/32)	**16a**: 19.6 (*R*) **17a**: 32 (*S*) **18a**: 0
2	**3**	**13a**	-36	23	44	52 (51/23/26)	**16a**: 23 (*R*) **17a**: 66 (*S*) **18a**: 0
3	**3**	**13a**	-40	20	40	89 (53/19/28)	**16a**: 28 (*R*) **17a**: 70 (*S*) **18a**: 0
4[h]	**3**	**13a**	-40	13	19	50 (49/19/32)	**16a**: 27 (*R*) **17a**: 75 (*S*) **18a**: 0
5[i]	**3**	**13a**	-48	20	29	54 (57/17/26)	**16a**: 32 (*R*) **17a**: 84 (*S*) **18a**: 10
6[j]	**3**	**13a**	-48	17	26	60 (56/18/26)	**16a**: n.d. **17a**: 40 (*S*) **18a**: 0
7[h,k]	**3**	**13a**	-45	17	9	75 (51/18/31)	**16a**: n.d. **17a**: 68 (*S*) **18a**: 0
8	**4a**	**13a**	-40	18	73	64 (20/48/32)	**16a**: 7 (*R*) **17a**: 5 (*S*) **18a**: 5
9	**3**	**13b**	-20[l]	23	61	98 (28/55/17)	**16b**: -[m] (+)[n] **17b**: 4 (-)[n] **18b**: 0
10	**3**	**13c**	0	14	69	73 (5/75/15)	**16c**: -[m] **17c**: 8 (*S*) **18c**: -[m]
11	**3**	**13c**	-20[l]	27	76	67 (4/81/15)	**16c**: -[m] **17c**: 16 (*S*) **18c**: -[m]

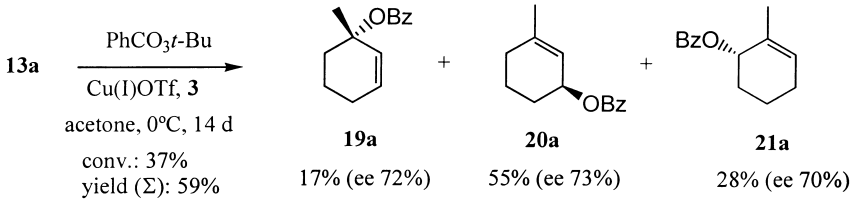
[a] Cu(I)OTf: 12 mol-%, **3** or **4**: 17 mol-% (relative to the oxidant); solvent: MeCN. [b] 0°C (± 1°C): a refrigerator was used; -36/-48°C (± 2°C): a freezer was used. [c] Conversion of the oxidant. [d] Isolated mixture of the regioisomers relative to conversion. [e] Product ratio, determined by GC (**13a,c**) or ^{1}H NMR (**13b**) analysis. [f] **17a**, **18a**: determined by chiral GC (column: FS-Hydrodex β-PM); **16a, 17c**: determined by chiral GC (FS-Hydrodex β-PM) after reduction with DIBAH; **17b**, **18b**: determined by chiral HPLC (Chiralcel OD). [g] **16a**, **17a, 17c**: determined after reduction (DIBAH) to the corresponding allylic alcohols by optical rotation measurements. [h] Solvent: acetone. [i] Solvent: acetone/MeCN (1/1). [j] Solvent: CH_2Cl_2. [k] 1 mol-% Cu(I)OTf and 1.5 mol-% **3** were used (addition of molecular sieves 3A). [l] No oxidation products detected at -40°C after 14d. [m] Separation of the enantiomers on chiral GC or HPLC column was not achieved. [n] Sign of optical rotation, the configuration could not be determined because the reduction with DIBAH failed.

regioisomers **16b**,**c** and **18c**, separation of the enantiomers on chiral GC and HPLC columns was not achieved).

Since the allylic and benzylic peroxides were obtained here for the first time in optically active form, the determination of their configuration was necessary. Determination of the specific rotations allows only a tentative assignment of the configurations by supposing the same sign of rotation for the allylic peroxides and the corresponding allylic alcohols. This supposition was previously made for optically active benzylic alcohols and hydroperoxides,[9,10] but a rigorous configurational assignment required an independent chemical correlation. Since it has been shown that the reduction of optically active hydroperoxides and endoperoxides with aluminium hydrides proceeds under retention of the configuration,[11] the allylic and benzylic *tert*-butyl peroxides **2**, **6**, **10a**, **12**, **16a**, **17a** and **17c** were reduced with diisobutyl aluminium hydride (DIBAH) to the corresponding optically active alcohols (Table 2). Under the reduction conditions (nonpolar solvent, 30–60°C), decomposition or racemization of the optically active peroxides did not occur (determined by GC and $[\alpha]_D$ measurements). The application of $LiAlH_4$ as reductant was not successful, because partial reduction of the double bond was also observed. The configuration of the isolated allylic alcohols was easily determined by optical rotation measurements or by comparison with authentic samples of known enantiomeric purity by GC analysis on a chiral column (see Experimental section). From Table 2 it is evident that the isolated allylic alcohols and the introduced peroxides show, indeed, the same sign of optical rotation. Reduction of the peroxides **16b**,**c**, **17b** and **18b**,**c** was not achieved even by raising the reaction temperature to 110°C (at higher temperature decomposition occurred); therefore, their configuration could not be determined unequivocally.

The above reduction method was also applied for the determination of the ee values of those optically active allylic peroxides for which the separation of the peroxide enantiomers was not achieved on chiral GC or HPLC columns.

At first sight, the asymmetric peroxidation seems to proceed analogously to the known acyloxylation reaction, but on comparison of the results for the peroxidation reaction of 1-methylcyclohexene **13a** (Table 1) with those of the corresponding benzoyloxylation (Eq. 10), remarkable differences become evident: (i) comparable ratios were observed for the products of the radicals **14a** and **15a**, but opposite regioselectivities were found for the peroxides **16a**/**17a** and the benzoates **19a**/**20a** derived from the same radical **14a**; (ii) different ee values were observed for the analogous regioisomers **16a**/**19a**, **17a**/**20a** and **18a**/**21a**; (iii) more significantly, the tertiary peroxide **16a** and the corresponding ester **19a** had opposite configurations, thus (*R*)-(+)-**16a** was obtained in the peroxidation of **13a** with both (*S*,*S*)-configured ligands **3** and **4a**, while (*S*)-(−)-**19a** was formed preferentially in the benzoyloxylation of **13a** with the oxidant $PhCO_3t$-Bu in the presence of Cu(I)OTf/**3** (in agreement with the findings of Pfaltz et al.[3a] and Andrus et al.[3b]); (iv) a stronger ligand influence on the regio- and enantioselectivities was observed in the peroxidation reaction. Consequently, we conclude that the transfer steps of the peroxy group and the acyloxy group are different.



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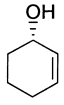
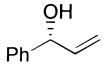
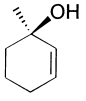
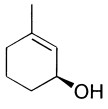
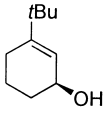
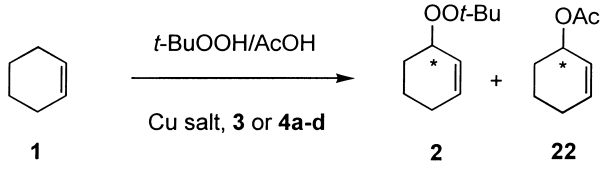
The peroxidation and the acyloxylation are competitive reactions when mixtures of the oxidant *t*-BuOOH and carboxylic acids are employed in the presence of the chiral bisoxazoline–copper complexes.

Table 2
Reduction of optically active allylic and benzylic peroxides to optically active allylic and benzylic alcohols with DIBAH

	peroxide ee [%]	peroxide $[\alpha]_D$ (c)/ T [°C][a]	reduction conditions	allylic alcohol	yield[b] [%]	ee [%] (config.)	$[\alpha]_D^{25}$ (c)
2	9[c]	-14.4 (1.43)/ 25	*n*-hexane 30°C, 10 h		70	8[c] (*S*)[d]	n.d.[e]
6	-[f]	-4.0 (1.23)/ 26	*n*-hexane 40°C, 10 h		62	4[g] (*S*)[h]	-3.2 (1.22)[a]
10a	-[f]	n.d.[e]	*n*-hexane 40°C, 24 h		50	13[c] (*R*)[d]	n.d.[e]
12	-[f]	+3.5 (0.19)/ 24[i]	*n*-hexane 60°C, 8 h		54[j]	4[c] (*R*)[d]	n.d.[e]
16a	-[f]	+27.5 (1.42)/ 25	benzene 55°C, 24 h		37	28[c] (*R*)[h]	+25.9 (0.30)[k]
17a	70[c]	n.d.[l]	*n*-hexane 40°C, 24 h		75	50[c] (*S*)[d]	n.d.[e]
17c	-[f]	-9.2 (0.44)/ 27	*n*-hexane 50°C, 10 h		73	8[c] (*S*)[h]	-5.2 (0.57)[a]
17c	-[f]	-20.0 (1.93)/ 22	*n*-hexane 50°C, 10 h		73	16[c] 17[g] (*S*)[d]	n.d.[e]

[a] Solvent: $CHCl_3$. [b] Isolated pure material. [c] Determined by chiral GC analysis (FS-Hydrodex β-PM). [d] Determined by chiral GC (comparison with an authentic sample of known configuration). [e] Not determined. [f] Separation of the enantiomers on chiral GC or HPLC columns was not achieved. [g] Determined by ^{19}F NMR spectroscopy [de value of the (*S,S*) Mosher ester[12]]. [h] Determined from the sign of optical rotation. [i] Solvent: CH_2Cl_2. [j] GC analysis. [k] Solvent: Et_2O. [l] A sample of **17a** (ee 66%, entry 2 of Table 1) showed $[\alpha]_D^{25}$ -40.7 (c 1.33, $CHCl_3$).

This is shown in the oxidation of cyclohexene **1** with *t*-BuOOH/acetic acid resulting in both the peroxide **2** and the acetate **22** (Eq. 11).[13,14]



(11)

Table 3
Oxidation of cyclohexene **1** with *t*-BuOOH/acetic acid in the presence of bisoxazoline–copper complexes (ligands: **3** and **4a–d**)

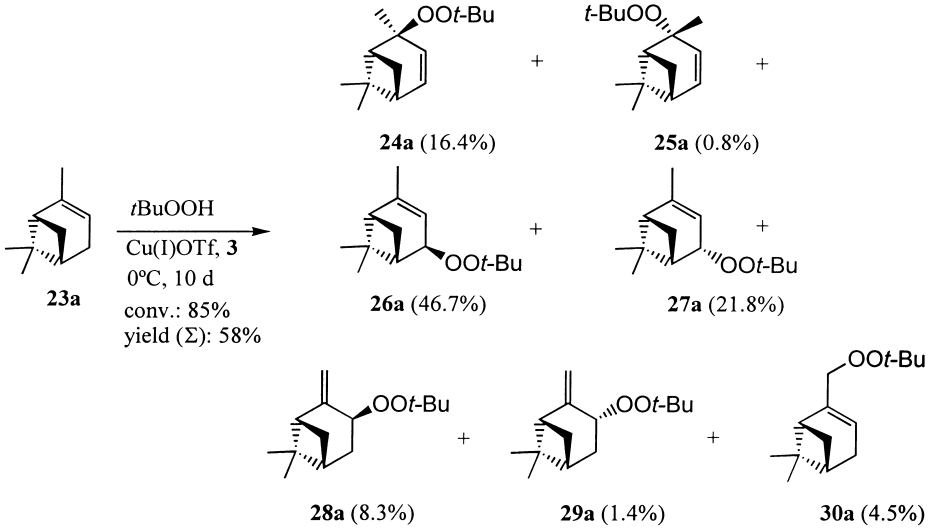
entry	Cu salt (amount [mol-%])[a]	ligand L* (amount [mol-%])[a]	conditions[b] (temp. [°C])	products (yields [%])[c]	ee [%][d] (config.)[e] of **22**[f]
1	Cu(I)OTf (5.0)	**3** (6.5)	A (65)	**22** (33) **2** (11)	59 (*S*)
2	$Cu(OAc)_2$ (5.0)	**3** (6.5)	A (65)	**22** (40) **2** (7)	38 (*S*)
3	$Cu(OAc)_2$ (5.0) Cu^0 (3.0)[g]	**3** (6.5)	A (25)	**22** (80) **2** (14)	34 (*S*)
4	Cu_2O (2.5)	**3** (6.5)	A (65)	**22** (71) **2** (23)	66 (*S*)
5	Cu_2O (2.5)	**3** (6.5)	B (65)	**22** (72) **2** (22)	41 (*S*)
6	Cu_2O (2.5)	**3** (6.5)	C (65)	**22** (38) **2** (24)	27 (*S*)
7	Cu_2O (2.5)	**3** (6.5)	D (65)	**22** (20) **2** (46)	15 (*S*)
8	Cu_2O (2.5)	**3** (6.5)	E (65)	**22** (15) **2** (76)	14 (*S*)
9	Cu_2O (2.5) Cu^0 (3.0)	**3** (13)	A (25)	**22** (32) **2** (14)	67 (*S*)
10	Cu_2O (2.5)	**4a** (6.5)	A (65)	**22** (20) **2** (70)	5 (*S*)
11	Cu_2O (2.5)	**4b** (6.5)	A (65)	**22** (36) **2** (40)	47 (*S*)
12	Cu_2O (2.5)	**4c** (6.5)	A (65)	**22** (27) **2** (26)	56 (*R*)
13	Cu_2O (2.5)	**4d** (6.5)	A (65)	**22** (33) **2** (24)	24 (*S*)

[a] Amounts relative to *t*-BuOOH. [b] Reaction time 24 h; temp. ± 3°C; molar ratios **1**/AcOH/*t*-BuOOH: A 5/2.5/1, B 5/4/1, C 5/2.5/2, D 5/2.5/3, E 5/2.5/4. [c] Isolated pure material relative to *t*-BuOOH consumed. Conversion of *t*-BuOOH >95% (exceptions: entry 7, 63%; entry 8, 36%). [d] Determined by chiral GC analysis (FS-Hydrodex β-PM). e) Determined by optical rotation measurements (see Experimental part), by comparing (chiral GC) with a sample (*S*)-**22** (ee 25%) prepared by an independent method,[15] and by hydrolysis of (*S*)-**22** to (*S*)-1-cyclohexen-3-ol. [f] The ee value of **2** was <4% in all experiments (chiral GC). [g] When Cu_2O was used, the actual amount of Cu in the filtered solution was 0.15 mol-% (determined by AES analysis).

The product ratio **2**:**22** depends on the chiral ligand, the reaction temperature and the ratio *t*-BuOOH:acetic acid used (Table 3). Preferential formation of the acetate **22** was observed with the ligand **3**, whilst a higher peroxide yield was obtained for the ligand **4a**. Peroxide **2** is favoured over acetate **22** by increased amounts of *t*-BuOOH and at lower temperatures (in the presence of CuOTf/**3**, exclusively peroxide **2** was observed at 0°C). Both isolated peroxide **2** and acetate **22** were optically active. While the ee value of the peroxide **2** was <4% in all cases, the acetate **22** was obtained with substantially higher ee values. The highest enantioselectivities for the acetoxylation of **1** (ee of **22**: 59–67%, entries 1, 4 and 9 of Table 3) were achieved under A conditions (excess substrate) by using Cu_2O or CuOTf in the presence of the ligand **3**. The addition of copper powder[2c] (entries 3 and 9) allowed a decrease in the reaction temperature from 65 to 25°C without a decrease of the conversion, but had no significant effect on the enantioselectivity. Increased concentrations of *t*-BuOOH or AcOH led to significantly decreased ee values of the acetate **22** (entries 5–8 of Table 3).

To examine the diastereoselectivity of the peroxidation reaction, both enantiomers of α-pinene, (−)-(1*S*,5*S*)-2-pinene **23a** and (+)-(1*R*,5*R*)-2-pinene **23b**, were chosen as chiral substrates and *t*-BuOOH as the oxidant in the presence of Cu(I)OTf and the chiral ligand **3** (Eq. 12). Oxidation of **23a** led to four regioisomeric pinene peroxides (products of the hydrogen atom abstraction from the allylic

CH_2 and CH_3 groups). Three of the isomers **24a**/**25a**, **26a**/**27a** and **28a**/**29a** were obtained as pairs of diastereoisomers. The isomeric peroxides **24a**–**28a** were separated by flash chromatography and their structure was proven by ^1H and ^{13}C NMR spectroscopy ($^1H,^1H$-COSY, $^1H,^1H$-NOESY, $^1H,^{13}C$-HETCOR and APT experiments). The minor isomers **29a** and **30a** were identified directly from the crude mixture (^1H NMR and GC–MS). The main product (1*S*,4*R*,5*S*)-4-*tert*-butylperoxy-2-pinene **26a** was isolated in 17% yield (relative to conversion).



(12)

The product ratio (GC) observed in the oxidation of **23a** demonstrates the preferential substitution at the 4-position (formation of **26a**, **27a**) of the pinene skeleton (ca. 69%). Nevertheless, in contrast to the corresponding acyloxylation of **23**,[16] substitution at the 2-positions **24a**, **25a** was also observed (ca. 17%). The introduction of the peroxy group occurred mainly *anti* to the dimethyl-substituted bridge (*exo* substitution), and the de values of the isomeric peroxides varied in the range from 36% up to 90%, which depended on the position of the peroxy group.

The regioselectivities of the peroxidation of the pinene **23a** are different from those observed in the oxidation of 1-methylcyclohexene **13a**. The predominant formation of the secondary peroxides **26a**, **27a** and the increased amounts of the substitution products **28a**–**30a** of the methyl group in the case of pinene **23a** may be the result of the sterically demanding dimethyl-substituted bridge.

The oxidation of the enantiomeric (+)-(1*R*,5*R*)-2-pinene **23b** under the same conditions (as described for **23a**) resulted in the analogous isomeric pinene peroxides **24b**–**30b** (enantiomers of **24a**–**30a**). The following product composition was observed by GC analysis: **24b** (20%), **25b** (1.5%), **26b** (42.1%), **27b** (20.5%), **28b** (7.8%), **29b** (1.2%) and **30b** (5.7%). Thus, no significantly different regio- and diastereoselectivities are displayed in the peroxidation of both enantiomers **23a** and **23b**. In the oxidation of pinene **23**, the substrate structure (steric hindrance by the dimethyl-substituted bridge) seems to be the determinant factor for the stereochemical course of the reaction compared with the stereodifferentiation by the chiral copper complex.

From our results obtained in the copper-catalyzed allylic peroxidation, it is evident that this reaction cannot be explained by a simple radical combination[4] or by trapping of carbenium ions formed by electron transfer[17a] from the corresponding allylic radical. Instead, in view of the formation of optically active peroxides with ee values up to 84%, a chiral copper complex must be involved in the peroxy-group transfer. It is well established that allylic radicals are formed initially,[17] but little is known on how the peroxy residue is transferred. For the similar acyloxylation reaction, the formation of a copper(III)

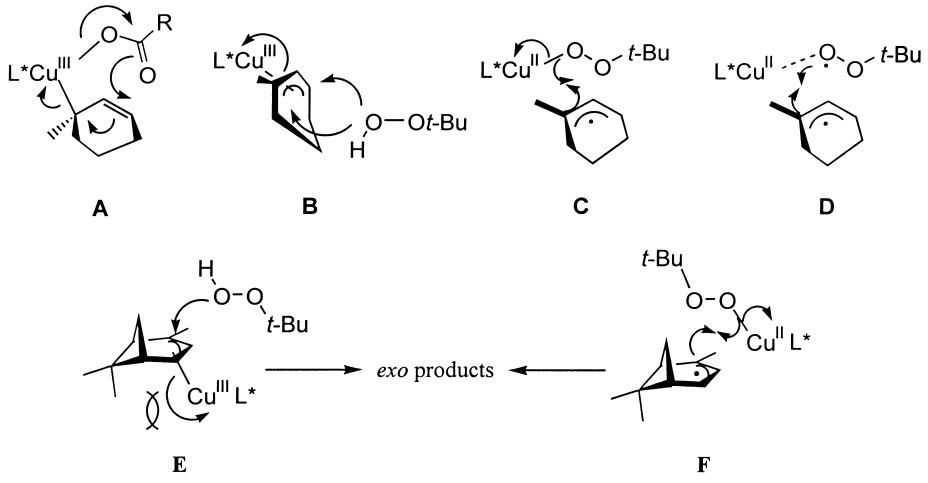


Figure 1. Possible transition states for the transfer of the acyloxy-group (**A**, according to Beckwith et al.[19]) and of the peroxy-group (**B**–**D**) in the oxidation of 1-methyl-1-cyclohexene (**13a**). Formation of *exo* products from α-pinene **23a** via *endo* coordinated copper(III) complex (**E**) or by homolytic *exo* substitution (**F**)

allyl species by the very fast reaction of copper(II) and the allylic radical (compare with Cohen and Meyerstein[18]) and the transfer of the acyloxy group in an intramolecular S_N2'-like pericyclic process was proposed by Beckwith et al.[19] (Fig. 1, transition state **A**), which is in agreement with the observed regio- and enantioselectivities.[3]

An analogous process is unlikely for the peroxidation reaction because of the significantly different regio- and enantioselectivities. The formation of the oppositely configured peroxides (*R*)-**16a** and (*S*)-**17a** in the peroxidation of 1-methylcyclohexene **13a** shows that the peroxy group has been introduced mainly from the same enantiotopic side of the substrate for both regioisomers. This result might imply the occurrence of an external nucleophilic attack of the hydroperoxide on an intermediate copper(III) allyl complex (Fig. 1, transition state **B**), analogous to the well-established mechanism of the palladium-catalyzed allylic substitution.[20] However, this mechanism is inconsistent with the prefered *exo* substitution observed in the peroxidation of α-pinene **23a**,**b**, because it would require *endo* coordination of the metal (Fig. 1, transition state **E**). Instead, the exclusive coordination on the *exo* side of the pinene was demonstrated in the case of an analogous palladium(II) complex.[21] Additionally, the formation of the secondary and tertiary peroxides **10a** and **16a** as the main regioisomers in the oxidation of allylbenzene **9** and 1-methylcyclohexene **13a** is in contrast to the preferred reaction of nucleophiles at the less substituted carbon atom of the allyl palladium complexes.[20]

As alternative pathways (Fig. 1, transition states **C**, **D** or **F**), we would like to propose the reaction of the allylic radicals with an intermediate alkylperoxy–copper(II) complex[22] [peroxy–copper(II) complexes have been isolated recently[23]] or with an alkylperoxy radical coordinated to the copper(II) centre (metal-coordinated peroxy radicals were detected by ESR spectroscopy[24]). Both pathways are in better agreement with the observed regio-, diastereo- and enantioselectivities of the peroxidation and they avoid the formation of an unstable copper(III) intermediate. In biochemical oxidations, e.g. for galactose oxidase, the participation of copper(III) complexes was likewise excluded;[25] instead, aryloxy radicals coordinated to the copper(II) centre were shown to be the active key intermediates (corresponding model complexes of aryloxy radicals and different metals were prepared by Wieghardt et al.[26]).

In summary, our results represent the first examples for the direct asymmetric peroxidation of prochiral C–H substrates, achieved by the use of chiral bisoxazoline–copper complexes. The new optically active peroxides were isolated in moderate to good yields, and side reactions (formation of alcohols, carbonyl

compounds or epoxides) were not observed in amounts worth mentioning. Although the ee values of the peroxides were rather modest (ee 4–32%) in most cases, high enantioselectivities were obtained in the asymmetric peroxidation of 1-methylcyclohexene **13a**, which yielded (*S*)-3-*tert*-butylperoxy-1-methyl-1-cyclohexene **17a** with ee values up to 84%. This is the first example for which a higher enantioselectivity was found in the peroxidation reaction compared with the corresponding acyloxylation (the benzoate **20a** was obtained with ee values of max. 73%).

3. Experimental

3.1. General

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) or a Varian Unity 500 (500 MHz) spectrometer with $CDCl_3$ as the solvent and hexamethyldisiloxane (HMDSO) as internal reference. Chemical shifts (δ) are given in ppm. GC analyses of the enantiomers were performed on a Chrompack CP 9000 gas chromatograph (FID) by the use of a chiral capillary column FS-Hydrodex β-PM (50 m×0.25 mm, Macherey-Nagel). Otherwise a Varian GC 3300 gas chromatograph (FID, 30 m DB 5 capillary column) or a Varian Saturn II GC–MS system was utilized. For the HPLC analyses of the enantiomers a Merck-Hitachi D-6000 apparatus (pump: L-6250) was used, equipped with a L-3000 diode array detector and a Knauer chiral detector (solvent: *n*-hexane:*i*-PrOH 1000:1; flow rate: 0.5 ml/min). Optical rotation measurements were carried out with a Perkin–Elmer polarimeter 341. The solvent MeCN and the olefins **1** and **5** (commercial products from Fluka) were distilled from CaH_2 prior use under an N_2 atmosphere. Acetone was distilled over P_4O_{10} and was stored over molecular sieves under N_2. *tert*-Butyl hydroperoxide (80% in di-*tert*-butyl peroxide) and *tert*-butyl perbenzoate (98%) were purchased from Fluka; the peroxide contents were determined by iodometric titration before use. The chiral bisoxazoline ligands **3**, **4a**,**b** and **4d** were commercially available from Aldrich and Fluka and were used without further purification. Copper(I) triflate [Cu(I)OTf·0.5C_6H_6] (90%) was obtained from Fluka. Silica gel for flash chromatography (Mallinckrodt Baker) was used for the chromatographic purifications. The reactions at lower temperatures were carried out by using a refrigerator (0±1°C) or a freezer (−20 to −50±2°C).

3.2. General procedure for the asymmetric peroxidation reactions

The oxidation of cyclohexene **1** is representative. A solution of 456 mg (1.48 mmol) (*S*,*S*)-2,6-bis-(4-isopropyl-2-oxazolin-2-yl)-pyridine **3** and 280 mg (1 mmol) [Cu(I)OTf·0.5(C_6H_6)] in 20 ml dry acetone was stirred at rt for 2 h under N_2. The catalyst solution was filtered over a Celite bed (Merck, particle size 0.1 mm) and the residue was washed with 2 ml acetone. Then 3.3 g (40 mmol) cyclohexene **1** was added and the mixture was degassed and then cooled to −45°C. Under N_2, a degassed solution of 0.904 g *t*-BuOOH (8 mmol, 80% solution in di-*tert*-butyl peroxide) in 2 ml acetone was added within 10 min with stirring. The reaction mixture was kept at −45°C for 17 days. The conversion of *t*-BuOOH (31%) was determined by iodometric titration. After the addition of 40 ml saturated aq. $NaHCO_3$, the mixture was extracted with Et_2O (3×30 ml). The combined organic layers were washed with ice-cold 1 N HCl and with brine and dried over $MgSO_4$. Removal of the solvent in vacuo (rt, ca. 50 mbar) gave the crude peroxide.

3.3. (S)-3-tert-Butylperoxy-1-cyclohexene **2**

Chromatographic purification (*n*-pentane:Et_2O 50:1) of the crude product (see above) yielded 160 mg (75% rel. to conv.) of the pure peroxide **2** {$[\alpha]_D^{25}$ −14.4 (c 1.43, $CHCl_3$); ee 9% (*S*)} as a colourless oil. The ee value was determined by chiral GC analysis [temp. 40°C–1 K/min–140°C; t_R 62.5 min (*R*), 62.8 min (*S*)]. The configuration of **2** (*S*) was determined by reduction with DIBAH to (*S*)-1-cyclohexen-3-ol (see below). ^{1}H NMR (300 MHz): 1.19 (s, 9H, *t*-Bu), 1.35 (m, 1H, CH_2), 1.71 (m, 4H, $2CH_2$), 2.05 (m, 1H, CH_2), 4.48 (m, 1H, OCH), 5.75 (m, 1H, CH_{olef}), 5.86 (m, 1H, CH_{olef}). ^{13}C NMR (75 MHz): 18.3, 25.2, 26.3, 26.7, 76.2, 79.4, 124.5, 132.8. GC–MS (EI): m/z 97 (65, $M^+-C_4H_9O$), 81 (100, $M^+-C_4H_9O_2$).

*Reduction of **2** with DIBAH*: To a solution of 80 mg (0.47 mmol) **2** in 2 ml dry benzene (N_2), 1 ml (1 mmol) DIBAH (1 M in hexane, Aldrich) was added and the mixture was stirred at 30°C (4 h). After the completion of the reaction (TLC), water was added dropwise and the precipitate was filtered off and washed with ether. The filtrate was dried over $MgSO_4$ and the solvent was evaporated (rt, ca. 50 mbar). The crude product was purified by flash chromatography to yield 32 mg (70%) pure 1-cyclohexen-3-ol [ee 8% (*S*), chiral GC: temp. 40°C–1 K/min–140°C, t_R 35.6 min (*S*), 36.3 min (*R*)]. The configuration was determined by comparison with a sample of (*S*)-1-cyclohexen-3-ol (GC), obtained by hydrolysis of the corresponding (*S*)-acetate **22**.[2] The ^{1}H NMR data corresponded well with the reported data.[27]

3.4. (S)-3-tert-Butylperoxy-1-cyclopentene **6**

According to the general procedure, 10 g (146.8 mmol) cyclopentene **5** was oxidized with 3.25 g (28.8 mmol) *t*-BuOOH (80%) in the presence of 0.4 g (1.86 mmol) Cu(I)OTf and 0.84 g (2.8 mmol) bisoxazoline **3** in 30 ml acetone at −40°C (15 d, conv. of *t*-BuOOH: 51%). After work up and flash chromatography (*n*-pentane:Et_2O 25:1), 1.25 g (95% rel. to conv.) pure peroxide **6** {$[\alpha]_D^{26}$ −4.0 (c 1.23, $CHCl_3$), ee 4% (*S*)} was isolated. The ee value and the configuration were determined after reduction of **6** with DIBAH and transformation of the obtained 1-cyclopenten-3-ol to the corresponding Mosher ester (see later). ^{1}H NMR (300 MHz): 1.26 (s, 9H, *t*-Bu), 2.02 (m, 2H, CH_2), 2.28 (m, 1H, CH_2), 2.49 (m, 1H, CH_2), 5.09 (m, 1H, OCH), 5.86 (m, 1H, CH_{olef}), 6.11 (m, 1H, CH_{olef}). ^{13}C NMR (75 MHz): 26.5, 28.3, 79.7, 88.9, 129.0, 137.6.

*Reduction of **6***: As described for the reduction of **2**, 234 mg (1.5 mmol) **6** in 3 ml *n*-hexane was reacted with 2 ml (2 mmol) DIBAH (1M solution in hexane) at 40°C (10 h). After analogous work up and chromatography, 78 mg (62%) (*S*)-1-cyclopenten-3-ol {$[\alpha]_D^{25}$ −3.2 (c 1.22, $CHCl_3$)}[27a] was isolated. For the determination of the ee value, 12 mg (0.14 mmol) of the pure alcohol was treated with 38 μl (0.15 mmol) (*S*)-(+)-MTPA chloride (Fluka) in $CHCl_3$ at 0°C in the presence of pyridine according to the procedure of Mosher et al.[12] to yield 39 mg (88%) 1-cyclopenten-3-yl-[(*S*)-α-methoxy-α-trifluoromethylphenyl] acetate [de 4% (*S,S*), ^{19}F NMR analysis]. ^{19}F NMR (282.3 MHz): −70.97 (*S,S*), −70.87 (*R,S*) (external reference: CF_3CO_2H, δ −77 ppm). The ^{1}H NMR data corresponded with the published data.[12]

3.5. (+)-5-tert-Butylperoxy-2,5-dihydro-5-methyl-2-furanone **8**

According to the general procedure, 1.96 g (20 mmol) α-angelica lactone (**7**) was oxidized in 7 ml MeCN with 360 mg (4 mmol) *t*-BuOOH (98%), 140 mg (0.5 mmol) Cu(I)OTf and 228 mg (0.75 mmol) of the ligand **3** at −40°C (24 d, conv. of *t*-BuOOH: 65%). After usual work up and chromatography (*n*-pentane:Et_2O 10:1), 170 mg (70% rel. to conv.) pure **8** was obtained as a colourless oil {$[\alpha]_D^{25}$ +2.06 (c 0.26, $CHCl_3$), ee 20%}. The ee value was determined by chiral GC analysis (temp. 120°C; t_R 28.0 min,

29.0 min). Elemental analysis: calc. (found) C: 58.04 (58.10), H: 7.58 (7.40). ^{1}H NMR (300 MHz): 1.19 (s, 9H, *t*-Bu), 1.61 (s, 3H, CH_3), 6.12 (d, 1H, CH, *J* 5.5 Hz), 7.15 (d, 1H, CH, *J* 5.5 Hz). ^{13}C NMR (75 MHz): 20.7 (CH_3), 26.2 (CH_3), 81.4 (C), 110.1 (C), 123.6 (CH), 152.8 (CH), 169.9 (CO). IR (neat): ν (cm^{-1}) 1801 (C=O).

3.6. (R)-1-tert-Butylperoxy-1-phenyl-2-propene **10a**

Oxidation of 2.38 g (20 mmol) allylbenzene **9** with 360 mg (4 mmol) *t*-BuOOH (98%) in 7 ml MeCN in the presence of 140 mg (0.5 mmol) Cu(I)OTf and 228 mg (0.75 mmol) bisoxazoline **3** at −18°C (20 d, conv. of *t*-BuOOH: 82%) gave, after aqueous work up and chromatographic purification (*n*-pentane:Et_2O 40:1), 250 mg of a mixture of the isomeric peroxides **10a** and **10b** (ratio **10a**:**10b**=72:28, ^{1}H NMR analysis). Repeated chromatography (*n*-pentane:Et_2O 100:1) yielded 165 mg (49% rel. to conv.) pure **10a** [ee 13% (*R*)] as colourless oil. The ee value and the configuration of **10a** were determined by chiral GC analysis after reduction of **10a** to 1-phenyl-2-propen-1-ol (see later). The structure of the byproduct *trans*-3-*tert*-butylperoxy-1-phenyl-1-propene (**10b**) was determined directly from the crude mixture by ^{1}H NMR analysis.

10a: Elemental analysis: calc. (found) C: 75.70 (75.50), H: 8.74 (8.91). ^{1}H NMR (300 MHz): 1.22 (s, 9H, *t*-Bu), 5.21 (d, 1H, $CH_{2\,olef}$, *J* 11.3 Hz), 5.27 (ddd, 1H, CH_{2olef}, J_1 17.5 Hz, J_2 1.5 Hz, J_3 1.3 Hz), 5.35 (d, 1H, CHO, *J* 6.8 Hz), 6.04 (ddd, 1H, CH_{olef}, J_1 17.5 Hz, J_2 11.1 Hz, J_3 6.8 Hz), 7.29 (m, 5H, CH_{arom}). ^{13}C NMR (75 MHz): 26.5 (CH_3), 80.4 (OCH), 86.8 (C), 117.7 (CH_2), 127.5, 127.9, 128.3, 136.9, 139.3.

10b: ^{1}H NMR (300 MHz): 1.26 (s, 9H, *t*-Bu), 4.58 (d, 2H, CH_2, *J* 6.5 Hz), 6.3 (dt, 1H, CH_{olef}, J_1 15.9 Hz, J_2 6.6 Hz), 6.61 (d, 1H, CH_{olef}, *J* 16.0 Hz), 7.31 (m, 5H, CH_{arom}).

*Reduction of **10a***: Reduction of 309 mg (1.5 mmol) **10a** in 3 ml *n*-hexane with 2.5 ml (2.5 mmol) DIBAH (1 M solution in hexane) at 40°C (24 h) yielded, after work up and chromatography (see reduction of **2**), 101 mg (50%) (*R*)-1-phenyl-2-propen-1-ol (ee 13%). The ee value and the configuration were determined by chiral GC analysis [temp. 140°C; t_R 21.3 min (*R*), 21.7 min (*S*)] by comparing with racemic and (−)-(*S*)-1-phenyl-2-propen-1-ol (Fluka). The ^{1}H NMR data were in accordance with those of the authentic samples.

3.7. (R)-2-tert-Butylperoxy-2-phenylbutane **12**

2-Phenylbutane (2.684 g, 20 mmol) was oxidized in 7 ml MeCN at −18°C (20 d) by using 360 mg (4 mmol) *t*-BuOOH (98%), 140 mg (0.5 mmol) Cu(I)OTf and 228 mg (0.75 mmol) of the ligand **3** (conv. of *t*-BuOOH: 67%). Usual work up and chromatography (*n*-pentane:Et_2O 80:1) yielded 126 mg (70% rel. to conv.) pure peroxide **12** {$[\alpha]_D^{24}$ +3.54 (c 0.19, CH_2Cl_2), ee 4% (*R*)}. The ee value and the configuration were determined by reduction to 2-phenyl-2-butanol (see below). ^{1}H NMR (300 MHz, CD_3OD): 0.79 (t, 3H, CH_3, *J* 7.5 Hz), 1.27 (s, 9H, *t*-Bu), 1.62 (s, 3H, CH_3), 1.86 (m, 2H, CH_2), 7.02–7.44 (m, 5H, CH_{arom}). ^{13}C NMR (75 MHz, CD_3OD): 18.95, 24.35, 27.37, 34.48, 79.94, 85.11, 127.28, 127.79, 128.97, 146.73.

*Reduction of **12***: 89 mg (0.4 mmol) **12**, dissolved in 1 ml *n*-hexane, was reacted with 0.5 ml (0.5 mmol) DIBAH (1 M solution in hexane) at 60°C (8 h) to (*R*)-2-phenylbutanol (yield: 54%, GC). The ee value (4%) and the configuration (*R*) were determined by chiral GC analysis [temp.: 60°C–1 K/min–140°C; t_R 29.87 min (*S*), 32.78 min (*R*)] by comparing with an authentic sample [ee 62% (*R*)[28]].

3.8. Peroxidation of 1-methyl-1-cyclohexene **13a**

(a) (Entry 1 of Table 1): According to the general procedure, 1.952 g (20 mmol) **13a** was oxidized with 0.455 g *t*-BuOOH (4 mmol, 80%) in the presence of 228 mg (0.75 mmol) **3** and 140 mg (0.5 mmol) Cu(I)OTf at 0°C in 10 ml MeCN (14 d, conv. of *t*-BuOOH: 82%, iodometric titration) to yield, after work up and evaporation of the solvent in vacuo (rt, ca. 50 mbar), 220 mg (72% rel to conv.) of a mixture of the regioisomeric peroxides **16a**–**18a** (ratio **16a**:**17a**:**18a**=35:32:33, GC analysis). Separation by flash chromatography (*n*-hexane:EtOAc 50:1) afforded 62 mg (21%) pure 3-*tert*-butylperoxy-3-methyl-1-cyclohexene **16a** {$[\alpha]_D^{25}$ +19.1 (0.9, $CHCl_3$); ee 20% (*R*), chiral GC after reduction with DIBAH — see below} and a mixture of **17a** and **18a**. Repeated chromatography (*n*-hexane:EtOAc 400:1) of this mixture gave 50 mg (16%) pure 3-*tert*-butylperoxy-1-methyl-1-cyclohexene (**17a**) {$[\alpha]_D^{25}$ −22.9 (c 1.59, $CHCl_3$); ee 32% (*S*), chiral GC: temp. 80°C–2 K/min–140°C, t_R 26.17 min (*R*), 26.40 min (*S*)}. The configurations of **17a** and **18a** were determined by reduction to the corresponding allylic alcohols (see below). The peroxide **18a** was not isolated in pure form, the ee value was determined directly from the crude mixture (ee 0%, chiral GC: temp. 80°C–2 K/min–140°C; t_R 24.06 min, 24.30 min).

16a: ^{1}H NMR (300 MHz): 1.20 (s, 9H, *t*-Bu), 1.27 (s, 3H, CH_3), 1.40–2.10 (m, 6H, $3CH_2$), 5.57 (dm, 1H, CH_{olef}, *J* 10 Hz), 5.81 (dt, 1H, J_1 10 Hz, J_2 3.6 Hz). ^{13}C NMR (75 MHz): 19.4, 25.3, 25.5, 32.9, 77.2, 78.4, 130.6, 130.8. GC–MS (EI): m/z 95 (100, $M^+-C_4H_9O_2$).

17a: ^{1}H NMR (300 MHz): 1.20 (m, 1H, CH_2), 1.24 (s, 9H, *t*-Bu), 1.53 (m, 2H, CH_2), 1.68 (s, 3H, CH_3), 1.90 (m, 3H, $2CH_2$), 4.37 (m, 1H, CHO), 5.46 (m, 1H, CH_{olef}). ^{13}C NMR (75 MHz): 18.41 (CH_2), 23.94 (CH_3), 26.43 (CH_2), 26.51 (CH_3), 30.4 (CH_2), 77.01 (CHO), 79.74 (CO), 118.48 (CH), 142.23 (C). GC–MS (EI): m/z 95 (100, $M^+-C_4H_9O_2$).

18a (analysis of the mixture with **17a**): ^{1}H NMR (300 MHz): 1.25 (s, 9H, *t*-Bu), 1.78 (s, 3H, CH_3), 1.40–2.10 (m, 6H, $3CH_2$), 4.23 (m, 1H, CHO), 5.66 (m, 1H, CH_{olef}). ^{13}C NMR (75 MHz): 17.3, 21.7, 25.6, 27.0, 79.6, 83.2, 129.1, 130.7. GC–MS (EI): m/z 95 (100, $M^+-C_4H_9O_2$).

(b) (Entry 2 of Table 1): From the oxidation of 10 g (102.5 mmol) **13a** with 2.135 g (20.5 mmol) *t*-BuOOH, 1.168 g (3.84 mmol) **3** and 0.717 g (2.56 mmol) Cu(I)OTf in 80 ml MeCN at −36°C (23 d, conv. of *t*-BuOOH: 44%), 427 mg (52% rel. to conv.) of the crude peroxide mixture (ratio **16a**:**17a**:**18a**=51:22:27, GC) was obtained. Analogous chromatographic separation [see *(a)*] gave 130 mg (16%) pure peroxide **16a** {$[\alpha]_D^{26}$ +21.5 (c 1.39, $CHCl_3$); ee 23% (*R*)} and 65 mg (8%) **17a** {$[\alpha]_D^{25}$ −40.7 (c 1.33, $CHCl_3$); ee 66% (*S*)}. The regioisomer **18a** (ee 0%, chiral GC) was not isolated.

(c) (Entry 3 of Table 1): As described above, 1.952 g (20 mmol) **13a** was reacted with 452 mg (4 mmol) *t*-BuOOH, 228 mg (0.75 mmol) **3** and 140 mg (0.5 mmol) Cu(I)OTf in 10 ml MeCN at −40°C (20 d, conv. of *t*-BuOOH: 44%) to yield 144 mg (89% rel. to conv.) of the crude peroxide mixture (ratio **16a**:**17a**:**18a**=53:19:28). Chromatographic separation gave 52 mg (28%) pure **16a** {$[\alpha]_D^{25}$ +27.46 (c 1.42, $CHCl_3$); ee 28% (*R*)} and 22 mg (12%) **17a** [ee 70% (*S*)]. For the isomer **18a** an ee value of 0% was determined (GC analysis of the crude mixture).

(d) (Entry 5 of Table 1): Analogously, 1.952 g (20 mmol) **13a** was oxidized with 360 mg (4 mmol) *t*-BuOOH (>98%), 228 mg (0.75 mmol) **3** and 140 mg (0.5 mmol) Cu(I)OTf in 10 ml acetone:MeCN (1:1) at −48°C (20 d, conv. of *t*-BuOOH: 29%) to yield 57 mg (54% rel. to conv.) of the crude peroxide mixture (ratio **16a**:**17a**:**18a**=57:17:26, GC). The ee values of **17a** (84%) and **18a** (10%) were determined directly from the crude mixture by chiral GC analysis. The ee value of **16a** (32%) and the configurations of **16a** (*R*) and **17a** (*S*) were determined by chiral GC analysis of the mixture of allylic alcohols obtained by reduction of the crude peroxide mixture with DIBAH.

*Reduction of **16a** with DIBAH:* Likewise treatment of 90 mg (0.49 mmol) **16a** with 1 ml 1 M DIBAH as described above for **2** (55°C, 24 h) yielded, after usual work up and flash chromatography

(*n*-hexane:EtOAc 10:1), 20 mg (37%) pure 3-methyl-1-cyclohexen-3-ol {ee 28% (*R*); $[\alpha]_D^{25}$ +25.9 (c 0.3, Et_2O)[29]}. The ee was determined by chiral GC [temp. 80°C–2 K/min–140°C; t_R 18.3 min (*S*), 18.6 min (*R*)]. All spectroscopic data corresponded well with those reported.[29]

*Reduction of **17a** with DIBAH:* Analogous treatment of **17a** (313 mg, 1.7 mmol; ee 70%) in 3 ml *n*-hexane with 3 mmol DIBAH (40°C, h) as described for **16a** gave, after chromatographic purification (*n*-hexane:EtOAc 10:1), 143 mg (75%) pure 1-methyl-1-cyclohexen-3-ol [ee 50% (*S*)]. The ee was determined by chiral GC [temp.: 80°C–2 K/min–140°C; t_R 23.4 min (*S*), 24.4 min (*R*)]. The configuration was determined by comparing (chiral GC) with a sample of the (*S*) configured alcohol (ee 73%) obtained after hydrolysis of the benzoate (*S*)-**20a** with KOH/MeOH (see below). The analytic data were in agreement with the reported values.[29]

3.9. *Peroxidation of 1-phenyl-1-cyclohexene **13b***

Following the general procedure, 8.512 g (51.23 mmol) **13b** was oxidized in 30 ml MeCN with 1.16 g (10.25 mmol) *t*-BuOOH, 584 mg (1.92 mmol) **3** and 359 mg (1.28 mmol) Cu(I)OTf at −20°C (23 d, conv. of *t*-BuOOH: 61%). After column chromatography (*n*-pentane:Et_2O 10:1), 770 mg (98% rel. to conv.) of the crude peroxide mixture (ratio **16b**:**17b**:**18b**=28:55:17, ^{1}H NMR analysis) was obtained. 200 mg of this mixture was separated by flash chromatography (*n*-pentane:Et_2O 100:1) to yield 50 mg (25%) pure 3-*tert*-butylperoxy-3-phenyl-1-cyclohexene **16b** {$[\alpha]_D^{21}$ +0.17 (c 1.57, $CHCl_3$)}, 123 mg (62%) 3-*tert*-butylperoxy-1-phenyl-1-cyclohexene **17b** {$[\alpha]_D^{22}$ −0.24 (c 2.24, $CHCl_3$); ee 4%, chiral HPLC: Chiralcel OD, t_R 12.8 min (−), 14.2 min (+)} and 16 mg (8%) 3-*tert*-butylperoxy-2-phenyl-1-cyclohexene **18b** [ee 0%, chiral HPLC: Chiralcel OD, t_R 10.9 min (+), 12.3 min (−)].

16b: Elemental analysis: calc. (found) C: 78.04 (78.58), H 8.94 (9.21). ^{1}H NMR (300 MHz): 1.20 (s, 9H, *t*-Bu),1.50–2.10 (m, 6H, $3CH_2$), 5.96–6.08 (m, 2H, $2CH_{olef}$), 7.20–7.30 (m, 3H, CH_{arom}), 7.45 (d, 2H, CH_{arom}, *J* 7.4 Hz). ^{13}C NMR (75 MHz): 19.13 (CH), 25.16 (CH_2), 26.77 (CH_3), 34.85 (CH_2), 79.03 (C), 81.51 (C), 126.58 (CH), 126.78 (CH), 127.68 (CH), 129.83 (CH), 130.93 (CH), 145.20 (C). GC–MS (EI): m/z 158 (100, M^+−88).

17b: Elemental analysis: calc. (found) C: 78.04 (78.02), H: 8.94 (8.35). ^{1}H NMR (300 MHz): 1.28 (s, 9H, *t*-Bu), 1.70–2.50 (m, 6H,$3CH_2$), 4.61 (m, 1H, CHO), 6.13 (m, 1H, CH_{olef}), 7.27 (m, 2H, CH_{arom}), 7.33 (m, 1H, CH_{arom}), 7.41 (d, 2H, CH_{arom}, *J* 7.3 Hz). ^{13}C NMR (75 MHz): 18.98 (CH_2), 24.20 (CH_2), 26.54 (CH_3), 27.84 (CH_2), 77.25 (CH), 79.91 (C), 121.27 (CH), 125.48 (CH), 127.45 (CH), 128.21 (CH), 141.48 (C), 142.71 (C).

18b: ^{1}H NMR (300 MHz): 1.16 (s, 9H, *t*-Bu), 1.50–2.20 (m, 6H, $3CH_2$), 4.88 (m, 1H, CHO), 6.28 (m, 1H, CH_{olef}), 7.26–7.40 (m, 5H, CH_{arom}). ^{13}C NMR (75 MHz): 16.43 (CH_2), 26.16 (CH_2), 26.59 (CH_2), 26.64 (CH_3), 76.62 (CH), 79.49 (C), 126.08 (CH), 126.71 (CH), 128.05 (CH), 132.48 (CH), 134.22 (C), 141.18 (C).

3.10. *1*-tert-*Butyl-3*-tert-*butylperoxy-1-cyclohexene **17c***

(a) (Entry 11 of Table 1): Following the general procedure, 9.96 g (60 mmol) 1-*tert*-butyl-1-cyclohexene **13c** dissolved in 30 ml MeCN was oxidized with 1.365 g (12 mmol) *t*-BuOOH in the presence of 684 mg (2.25 mmol) **3** and 420 mg (1.5 mmol) Cu(I)OTf at −20°C (27 d, conv. of *t*-BuOOH: 76%). Chromatographic work up (*n*-pentane:Et_2O 10:1) gave 696 mg (67% rel. to conv.) of the peroxide mixture **16c**–**18c** (ratio **16c**:**17c**:**18c**=4:81:15, GC and ^{1}H NMR analyses). Repeated chromatography (*n*-pentane:Et_2O 100:1) yielded 316 mg (30%) pure **17c** {$[\alpha]_D^{22}$ −20.0 (c 1.93, $CHCl_3$); ee 16% (*S*), determined by chiral GC after reduction with DIBAH — see below}. The minor products **16c** and **18c**

were not isolated, they were identified from the crude mixture by comparing with the racemic products[1] (GC and ^{1}H NMR analyses). **17c**: Elemental analysis: calc. (found) C: 74.34 (74.34), H: 11.50 (10.98). ^{1}H NMR (300 MHz): 1.02 (s, 9H, *t*-Bu), 1.24 (s, 9H, *t*-Bu), 1.40–2.10 (m, 6H, $3CH_2$), 4.42 (m, 1H, CHO), 5.50 (m, 1H, CH_{olef}). ^{13}C NMR (75 MHz): 19.3 (CH_2), 24.7 (CH_2), 26.5 (CH_3), 26.9 (CH_2), 28.8 (CH_3), 35.5 (C), 77.7 (CH), 79.7 (C), 115.45 (CH), 152.8 (C). GC–MS (EI): m/z 137 (100, $M^+-C_4H_9O_2$).

(b) (Entry 10 of Table 1): The analogous oxidation of **13c** (3.32 g, 20 mmol) at 0°C (14 d, conv. of *t*-BuOOH: 69%) led to 226 mg (73% rel. to conv.) of the mixture of isomeric peroxides **16c**–**18c** (ratio **16c**:**17c**:**18c**=5:75:15), from which 180 mg (58%) pure **17c** {$[\alpha]_D^{27.5}$ −9.2 (c 0.44, $CHCl_3$); ee 8% (*S*), see above} was isolated by chromatography.

*Reduction of **17c**:* As described for the peroxide **2**, 215 mg (0.95 mmol) **17c** in 3 ml *n*-hexane was treated with 2 mmol DIBAH (50°C, 10 h). Chromatographic purification (*n*-hexane:EtOAc 10:1) yielded 107 mg (73%) 1-*tert*-butyl-1-cyclohexen-3-ol. Reduction of **17c** {$[\alpha]_D^{22}$ −20 (c 1.93, $CHCl_3$); exp. (a)} afforded the allylic alcohol with an ee value of 16% [chiral GC: temp. 150°C, t_R 15.3 min (*R*), 15.6 min (*S*)]. From the reduction of **17c** {$[\alpha]_D^{27.5}$ −9.2 (c 0.44, $CHCl_3$); exp. (b)}, 1-*tert*-butyl-1-cyclohexen-3-ol with 8% ee and $[\alpha]_D^{25}$ −5.2 (c 0.57, $CHCl_3$) was obtained.

3.11. Peroxidation of (−)-(1S,5S)-2-pinene **23a**

According to the general procedure, 1.36 g (10 mmol) **23a** was oxidized in a solvent mixture of MeCN:acetone (1:1) using 180 mg (2 mmol) *t*-BuOOH (98%), 70 mg (0.25 mmol) Cu(I)OTf and 114 mg (0.375 mmol) **3** at 0°C (10 d, conv. of *t*-BuOOH: 85%). After usual work up and chromatography (*n*-pentane:Et_2O 100:1), 100 mg (58% rel. to conv.) of the mixture of peroxides **24a**–**30a** [product composition: **24a** (16.4%), **25a** (0.8%), **26a** (46.7%), **27a** (21.8%), **28a** (8.3%), **29a** (1.4%), **30a** (4.5%); GC–MS analysis] was obtained. The main product **26a** was isolated in pure form as a colourless oil {yield: 32 mg, 17% rel. to conv.; $[\alpha]_D^{25}$ −0.1 (c 0.86, CH_2Cl_2)} by chromatographic separation (*n*-pentane:Et_2O 100:1). The other isomers were obtained as enriched samples of the following purities (GC analyses): **24a** (90%), **27a** (80%) and **28a** (60%). They were identified by ^{1}H and ^{13}C NMR spectroscopy (^{1}H,^{1}H-COSY, ^{1}H,^{1}H-NOESY, APT and ^{1}H,^{13}C-HETCOR experiments). The peroxides **25a** (comparison of the ^{1}H and GC–MS data with those of the isolated enantiomeric compound **25b**, see below), **29a** (GC–MS analysis) and **30a** (^{1}H NMR, ^{13}C NMR and GC–MS analysis) were identified directly from the crude mixture.

*(1*R*,2*S*,5*R*)-2-*tert*-Butylperoxy-3-pinene (**24a**):* ^{1}H NMR (500 MHz): 0.95 (s, 3H, CH_3, H-9), 1.19 (s, 9H, *t*-Bu), 1.35 (s, 3H, CH_3, H-8), 1.39 (s, 3H, CH_3, H-10), 1.77 (d, 1H, H-7_{exo}, *J* 8.8 Hz), 2.14 (q, 1H, H-5, *J* 6.2 Hz), 2.21 (td, 1H, H-1, J_1 6.3 Hz, J_2 2 Hz), 2.27 (dt, 1H, H-7_{endo}, J_1 9 Hz, J_2 5.7 Hz), 5.48 (dm, 1H, H-3, *J* 8.8 Hz), 6.33 (dd, 1H, H-4, J_1 9 Hz, J_2 6.5 Hz). ^{13}C NMR (100 MHz): 24.05 (C-9), 25.9 (C-10), 26.70 (*t*-Bu), 27.58 (C-8), 32.41 (C-7), 42.55 (C-5), 46.39 (C-6), 50.46 (C-1), 126.75 (C-3), 139.84 (C-4). GC–MS (EI): m/z 135 (3, $M^+-C_4H_9O_2$).

*(1*R*,2*R*,5*R*)-2-*tert*-Butylperoxy-3-pinene (**25a**):* ^{1}H NMR (500 MHz): 1.06 (s, 3H, CH_3), 1.19 (s, 9H, *t*-Bu), 1.30 (s, 3H, CH_3, H-9), 1.33 (s, 3H, CH_3), 1.40 (d, 1H, H-7_{exo}, *J* 9 Hz), 2.10–2.14 (m, 2H, H-1 and H-5), 2.47 (dt, 1H, H-7_{endo}, J_1 9 Hz, J_2 5.3 Hz), 5.68 (dd, 1H, H-3, J_1 9 Hz, J_2 1.5 Hz), 6.24 (dd, 1H, H-4, J_1 9 Hz, J_2 6.5 Hz). GC–MS (EI): m/z 135 (3, $M^+-C_4H_9O_2$).

*(1*S*,4*R*,5*S*)-4-*tert*-Butylperoxy-2-pinene (**26a**):* ^{1}H NMR (500 MHz): 0.87 (s, 3H, CH_3, H-9), 1.23 (s, 9H, *t*-Bu), 1.33 (s, 3H, CH_3, H-8), 1.40 (dt, 1H, H-7_{exo}, J_1 9 Hz, J_2 1.4 Hz), 1.71 (t, 3H, CH_3, H-10, *J* 1.5 Hz), 2.0 (td, 1H, H-1, J_1 5.1 Hz, J_2 1.3 Hz), 2.21 (dt, 1H, H-7_{endo}, J_1 9 Hz, J_2 5.6 Hz), 2.43 (m, 1H, H-5), 4.52 (m, 1H, H-4), 5.30 (m, 1H, H-3). ^{13}C NMR (100 MHz): 20.36 (C-9), 22.80 (C-10), 26.46 (*t*-Bu),

26.46 (C-8), 28.80 (C-7), 43.02 (C-5), 45.76 (C-6), 47.99 (C-1), 79.74 (C-O), 82.30 (C-4), 114.13 (C-3), 151.26 (C-2). GC–MS (EI): m/z 151 (1.5), 135 (5, $M^+-C_4H_9O_2$).

*(1S,4S,5S)-4-*tert*-Butylperoxy-2-pinene (**27a**):* ^{1}H NMR (500 MHz): 0.98 (s, 3H, CH_3, H-9), 1.23 (s, 9H, *t*-Bu), 1.30 (d, 1H, H-7$_{exo}$, *J* 8.8 Hz), 1.31 (s, 3H, CH_3, H-8), 1.71 (t, 3H, CH_3, H-10, *J* 1.8 Hz), 1.94 (t, 1H, H-1, *J* 5 Hz), 2.45 (dm, 1H, H-7$_{endo}$, *J* 9 Hz), 2.48 (m, 1H, H-5), 4.68 (m, 1H, H-4), 5.45 (m, 1H, H-3). ^{13}C NMR (100 MHz): 22.67 (C-9), 26.54 (*t*-Bu), 26.73 (C-8), 35.22 (C-7), 39.04 (C-6), 44.76 (C-5), 48.05 (C-1), 79.49 (CO), 84.58 (C-4), 115.87 (C-3), 148.71 (C-2). GC–MS (EI): m/z 151 (2), 135 (7, $M^+-C_4H_9O_2$).

*(1R,3S,5R)-3-*tert*-Butylperoxy-2(10)-pinene (**28a**):* ^{1}H NMR (500 MHz): 0.65 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.25 (s, 9H, *t*-Bu), 1.23–1.27 (m, 2H, CH_2), 1.55 (d, 1H, CH_2, *J* 9.8 Hz), 1.92 (m, 1H, CH), 2.35 (m, 1H, CH_2), 2.45 (m, 1H, CH), 4.61 (d, 1H, CHO, *J* 6.5 Hz), 4.92 (s, 1H, CH_2, H-10), 5.13 (s, 1H, CH_2, H-10). ^{13}C NMR (100 MHz): 21.85 (CH_3), 25.85 (CH_3), 26.29 (CH_3), 27.85 (CH_2), 34.05 (CH_2), 39.51 (CH), 50.58 (CH), 78.42 (CH), 114.88(CH_2), 121.6 (C). GC–MS (EI): m/z 135 (11, $M^+-C_4H_9O_2$).

*(1R,5S)-10-*tert*-Butylperoxy-2-pinene (**30a**):* ^{1}H NMR (500 MHz): 1.28 (s, 3H, CH_3), 2.09 (m, 3H), 2.21–2.26 (m, 3H), 2.39 (m, 1H), 4.28 (dq, 1H, OCH_2, J_1 10.5 Hz, J_2 1.4 Hz), 4.33 (dq, 1H, OCH_2, J_1 10.4 Hz, J_2 1.4 Hz), 5.53 (m, 1H, CH). ^{13}C NMR (100 MHz): 26.15 (CH_3), 31.20 (CH_2), 31.51 (CH_2), 40.73 (CH), 44.13 (CH), 78.26 (OCH_2), 122.58 (CH). GC–MS (EI): m/z 135 (11, $M^+-C_4H_9O_2$).

3.12. Peroxidation of (+)-(1R,5R)-2-pinene (23b)

Analogous oxidation (as described for **23a**) of 1.36 g (10 mmol) **23b** at 0°C afforded, after chromatography (see above), 120 mg (63% rel. to conv.) of the mixture of isomeric pinene peroxides **24b**–**30b**. [Product composition: **24b** (20.1%), **25b** (1.5%), **26b** (42.1%), **27b** (20.5%), **28b** (7.8%), **29b** (1.2%), **30b** (5.7%); GC–MS analysis.] The products were identified by comparing the ^{1}H NMR and GC–MS data with those of the enantiomeric compounds **24a**–**30a**. A sample (ca. 1 mg) of the minor isomer **25b** (purity: 90%) was obtained by flash chromatography (*n*-pentane:Et_2O 100:1), the ^{1}H NMR and GC–MS data were in accordance with those of the enantiomer **25a** (see above).

3.13. General procedure for the enantioselective acyloxylation reactions

(a) Without addition of copper (entry 4 of Table 3 is representative): Copper(I) oxide (0.05 mmol, 7.5 mg) and 44 mg (0.13 mmol) of the ligand **3** were stirred for 12 h at 30°C in 5 ml MeCN under N_2. [When Cu(I)OTf or $Cu(OAc)_2$ were used, they were likewise treated for 2 h at rt.] After filtration over a Celite bed (Merck, particle size 0.1 mm), and washing of the residue with 3 ml MeCN, the clear filtrate was concentrated to 5 ml (rt, ca. 7 mbar). To the obtained catalyst solution, 821 mg (10 mmol) cyclohexene (**1**) and then 300 mg (5 mmol) acetic acid were added (N_2). Within 10 min, a solution of mg (2 mmol) *t*-BuOOH (80%) dissolved in 2 ml MeCN was added dropwise under stirring at rt. The temperature was raised to 65°C (±3°C) and stirring was continued for 24 h (N_2). After cooling to rt, iodometric titration showed the complete conversion of *t*-BuOOH. The solvent and the excess olefin (**1**) were removed in vacuo (rt, ca. 50 mbar). The residue was purified by flash chromatography (*n*-hexane:EtOAc 25:1) to yield 40 mg (23%) pure **2** [ee ≈3% (*S*), chiral GC]. As the second (main) fraction, 200 mg (71%) 3-acetoxy-1-cyclohexene (**22**) [ee 66% (*S*)] was isolated. The ee value of **22** was determined by chiral GC [temp. 40°C–1 K/min–140°C; t_R 58.8 min (*R*), 59.3 min (*S*)]. The configuration of **22** was determined by chiral GC by comparing with a sample of (*S*)-**22** prepared by the method of Muzart[15] {ee 25%, $[\alpha]_D^{20}$ −53 (c 1.95, $CHCl_3$) and by optical rotation measurement of a sample of (*S*)-**22** (ee 63%), showing

$[\alpha]_D^{25}$ −109 (c 1.59, $CHCl_3$).[30] Additionally, the hydrolysis of (*S*)-**22** gave (−)-(*S*)-1-cyclohexen-3-ol (see below). The spectroscopic data (^{1}H NMR, MS, IR) of **22** are in agreement with the published data.[30]

(b) Oxidations in the presence of copper(0) (entry 9 of Table 3 is representative): After analogous preparation of the catalyst solution from 7.5 mg (0.05 mmol) Cu_2O and 72 mg (0.24 mmol) **3** in 5 ml MeCN as described under (a), 4 mg (0.06 mmol) copper powder were added (N_2). Under stirring at rt, 827 mg (10 mmol) cyclohexene (**1**) and 300 mg (5 mmol) acetic acid were added. After dropwise addition of 2 mmol *t*-BuOOH (dissolved in 2 ml MeCN) within 10 min, stirring was continued for 24 h. Analogous work up and chromatography yielded 90 mg (32%) pure **22** [ee 67% (*S*), chiral GC]. GC analysis of the reaction mixture showed the formation of **2** (15%) and 1-cyclohexen-3-one (5%) as byproducts.

*Hydrolysis of (S)-**22**:* By adopting Muzart's method,[2b] 70 mg (0.5 mmol) (*S*)-**22** (ee 63%, chiral GC) were treated with 4 ml of a 4 M KOH solution in MeOH at 0°C (2 h). After complete conversion of **22** (TLC), the solvent was removed in vacuo (rt, ca. 50 mbar) and the residue extracted with Et_2O (3×30 ml). The collected organic phases were washed with 1 ml ice-cold 1 N HCl, then with 2 ml brine and dried over $MgSO_4$. After evaporation of the solvent and chromatographic purification (*n*-pentane:Et_2O 5:1), 20 mg (41%) pure 1-cyclohexen-3-ol {ee 57% (*S*), $[\alpha]_D^{25}$ −68.2 (c 1.0, $CHCl_3$)[27]} were isolated. The ee value was determined by chiral GC (see above, reduction of peroxide **2**). The ^{1}H NMR data were in agreement with the published values.[27]

3.14. Enantioselective benzoyloxylation of 1-methyl-1-cyclohexene **13a**

To the catalyst solution, prepared by stirring 56 mg (0.2 mmol) Cu(I)OTf and 91.3 mg (0.3 mmol) **3** in 7 ml acetone at rt for 2 h (N_2), 1.7 g **13a** was added and the mixture was degassed. At 0°C, a solution of 783 mg *tert*-butyl perbenzoate (4 mmol, 98%) in 2 ml acetone was added with stirring over a period of 1 h. The reaction mixture was allowed to stand for 14 d at 0°C (conv. of $PhCO_3t$-Bu: 37%, iodometric titration). The excess perester was destroyed by treatment with 10 ml saturated aq. KI and 4 ml 2 M HCl. After addition of 20 ml saturated aq. $NaHCO_3$, the mixture was decolourized by treating with 37% $NaHSO_3$ and then extracted with Et_2O (3×30 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was evaporated. Chromatographic purification (*n*-hexane:EtOAc 10:1) of the residue yielded 90 mg (59% rel. to conv.) of a mixture of the isomeric benzoates **19a**–**21a** (ratio **19a**:**20a**:**21a**=17:52:31, ^{1}H NMR analysis). The ee values and the configurations[31] of the benzoates were determined directly from the mixture by chiral HPLC analysis (comparison with the corresponding racemic compounds).

*3-Methyl-1-cyclohexen-3-yl benzoate (**19a**):* ee 66% (*S*); [HPLC, Chiralcel OD; t_R 16.3 min (*S*), 28.9 min (*R*)]; ^{1}H NMR (300MHz): 1.63 (s, 3H, CH_3), 1.60–2.05 (m, 6H, $3CH_2$), 5.80 (m, 1H, CH_{olef}), 6.20 (dm, 1H, CH_{olef}), 7.30 (m, 2H, CH_{arom}), 7.40 (m, 1H, CH_{arom}), 7.97 (d, 2H, CH_{arom}, *J* 7.2 Hz).

*1-Methyl-1-cyclohexen-3-yl benzoate (**20a**):* ee 64% (*S*); [HPLC, Chiralcel OJ; t_R 18.0 min (*R*), 19.3 min (*S*)]; ^{1}H NMR (300 MHz): 1.72 (s, 3H, CH_3), 1.60–2.05 (m, 6H, $3CH_2$), 5.50 (m, 1H, OCH), 5.60 (m, 1H, CH_{olef}), 7.40 (t, 2H, CH_{arom}, *J* 7.2 Hz), 7.50 (m, 1H, CH_{arom}), 8.00 (d, 2H, CH_{arom}, *J* 7.5 Hz).

*2-Methyl-1-cyclohexen-3-yl benzoate (**21a**):* ee 70% (*S*); [HPLC, Chiralcel OD; t_R 15.2 min (*S*), 17.5 min (*R*)]; ^{1}H NMR (300 MHz): 1.70 (s, 3H, CH_3), 1.60–2.05 (m, 6H, $3CH_2$), 5.45 (m, 1H, OCH), 5.70 (m, 1H, CH_{olef}), 7.40 (m, 2H, CH_{arom}), 7.50 (m, 1H, CH_{arom}), 8.00 (m, 2H, CH_{arom}).

Because in the case of **19a** and **20a** no baseline separation was achieved (chiral HPLC), 80 mg of the mixture of the optically active benzoates was hydrolyzed (24 h, rt) with KOH/MeOH as described for **22** to yield, after chromatographic purification (*n*-pentane:Et_2O 5:1), 20 mg (48%) of a mixture of the corresponding allylic alcohols (*S*)-3-methyl-1-cyclohexen-3-ol (ee 72%, chiral GC, conditions: see

reduction of **16a**), (*S*)-1-methyl-1-cyclohexen-3-ol (ee 73%, chiral GC) and (*S*)-2-methyl-1-cyclohexen-3-ol (ee not determined, no separation on the chiral GC column).

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