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Regiocontrol in Nucleophilic Ring Opening of Chiral Epoxides of Chemoenzymatic Origin

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Abstract: Homochiral *cis* epoxides derived from enzymatically asymmetrized *tris*(hydroxymethyl)methane equivalents (THYM*) are regioselectively opened by carbon based-nucleophiles (alkyl groups or cyanides) and halides in the presence of Lewis acids. *Enantio-* and *diastereodivergent* synthesis of branched triols is reported.

The epoxidation of a double bond and the subsequent nucleophilic ring-opening are one of the most popular method to functionalize a carbon-carbon double bond,[1] allowing in addition the possibility to introduce two new chiral centres at a time in a stereocontrolled manner. This versatile strategy has been largely used in the synthesis of a great number of natural products.[1a]

It is well known that the nucleophilic opening of the oxirane ring (made possible by ring-strain and by the presence of a basic oxygen in the heterocycle) is facilitated by the electrophilic assistance of Lewis acids. When additional functional groups are present in an unsimmetrically substituted epoxide, they usually direct the regiochemistry of the attack and their influence can be enforced or contrasted by the addition of coordinating species.[2]

Carbon-carbon bond forming during the opening of an oxiranic ring has been known for a long time. Formerly Grignard reagents, usually with the aid of copper catalysts, were employed, as well as alkyllithium reagents.[1, 3] Better results were obtained shifting to organocopper reagents, such as "lower order" cuprates ('Gilman reagents') or, even better, "higher order, mixed" cuprates,[3, 4] that seem to be more reactive towards disubstituted epoxides and to minimise the side reactions (rearrangement or elimination). For these type of reactions the solvent of choice seems to be ethyl ether, that is less effective than other ethereal solvents in solvating lithium cation, which is fundamental in assisting ring opening by coordination of the oxirane oxygen. The attack usually occurs at the most accessible, that is at the less hindered, site, despite differences in the electrophilicity of the two oxiranic carbon atoms.[4] Lewis acid catalysts, like $BF_3{\cdot}Et_2O$,[5] are known to influence both reactivity and regioselectivity.

Another straightforward method to form a new carbon-carbon bond consists in the nucleophilic oxirane ring opening by cyanide reagents.[1b] Several conditions were employed at times to obtain β-hydroxy nitriles. Alkali metal cyanides can be used, both in protic[2c, 6a-d] or aprotic[2a,c, 6b, c, e] medium, in the presence[2a, c, 6b, c] or in the absence of added metal derivatives. Diethylaluminum cyanide[6b, 7] (sometimes formed *in situ*[7b-d]) has also been used, as well as hydrogen cyanide.[8] Cyanotrimethylsilane[2a, 7b-d] is used both in combination with diethylaluminum chloride to generate *in situ* diethylaluminum cyanide (see above) and in combination with other metal derivatives, in order to obtain *O*-trimethylsilyl β-hydroxy nitriles. A major drawback is endowed in the ambident character of cyanotrimethylsilane: depending on the employed catalyst, *O*-protected β-hydroxy nitriles or isonitriles (precursors of β-amino alcohols[9a]) are formed.[6c, 7c, 9b, c]

A large variety of heteroatoms-based nucleophiles has also been employed in the opening of the oxi-

ranic ring.[1] Among them, halide ions appear to have a noticeable affinity for epoxides and are often encountered as by products, when different nucleophiles (organocopper derivatives,[5b] reducing agents[10]) are expected to react. Conversion of epoxides to halohydrins has been performed using several methods. A large variety of metal or ammonium halides under different conditions has been used,[2a, c, 6b, 11, 12] as well as hydrogen halides,[13] and molecular halogens in the presence of titanium tetraisopropoxide.[14] Several of these methods are compatible with additional functional groups in the oxirane and show appreciable degree of regio- and stereoselectivity: in particular, 2,3-epoxy- and 3,4-epoxy-1-ols (both unprotected and protected) usually show a pronounced regioselectivity for the C-3 and the C-4 attack, respectively.

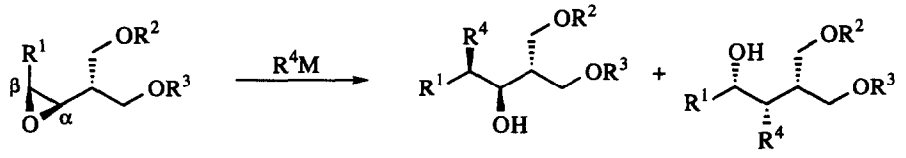
In connection with our ongoing studies on the exploitation of chiral building blocks having a chemoenzymatic origin,[10] we report here on the regioselective ring opening of oxiranes **1**[10, 15] using both C-nucleophiles [organometallic reagents (Scheme 1) and cyanides (Scheme 3)] and halides (Scheme 3). Tables 1, 2, and 3 report the most significant results of this study.

A perusal of Table 1, which reports the most relevant data on organocopper nucleophiles, indicates that "lower order, simple" cuprate like lithium dimethylcuprate resulted completely unreactive towards diprotected epoxide **1b** (entry 7). The addition of a Lewis acid,[5] that is known to affect both the reactivity and the regiochemistry of the attack of organocopper reagents to epoxides, enhanced the reactivity of the epoxide, but chemical yields were still not quite satisfactory (entry 9). Moreover, the presence of halide ions had to be absolutely avoided, in order to suppress the formation of halohydrins[16] (entry 8): it is apparent that halide ions are by far better nucleophiles in the attack to our oxiranes than hydride[10] or carbanion species. This fact rules out the possibility to employ other Lewis acids, such as titanium(IV) chloride or magnesium bromide, and rules out also the possibility to employ Grignard reagents in the presence of copper(I) salts.[17] Moreover, the presence of ligands like dimethyl sulfide[17b] usually employed to solubilize the copper reagents should depress the reactivity of the oxiranic ring, through competition in lithium coordination.[3a]

"Higher order, mixed" cuprates $[(Alkyl)_2Cu(CN)Li_2]$ gave positively better chemical and stereochemical results, especially in the presence of boron trifluoride etherate (entries 2, 5, 6, 14 - 17), provided that a moderate excess of reagents is employed (see Table 1): oxiranes possessing a longer R^1 chain (entries 14 - 17) gave a somewhat lesser yield, but an almost complete regiochemistry in favour of the alcohol **2**, deriving from attack to the less hindered site.

The major drawback of this reactions was the competitive formation of variable amounts of reduction products (alkenes **4**), which seem to depend more on the length of the alkyl moiety in the cuprate reagent (R^4)

Scheme 1



1 **2** **3**

	R^1	R^2	R^3		R^1	R^2	R^3
a	Me	PMBOM	BOM	**f**	Pr	PMBOM	BOM
b	Me	TIPS	PMP	**g**	Pr	TIPS	PMP
c	Me	PMBOM	H	**h**	Bu	PMBOM	BOM
d	Me	TIPS	H	**i**	Bu	TIPS	PMP
e	Me	TIPS	Ac				

Ac = CH_3CO; BOM = $PhCH_2OCH_2$; PMBOM = 4-$MeOC_6H_4CH_2OCH_2$; PMP = 4-$MeOC_6H_4$; TIPS = $(i\text{-}Pr)_3Si$

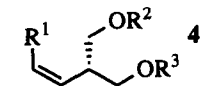
than on the length of oxirane chain (R^1) (*cfr* entries 2 and 5). Stereoselective deoxygenation of epoxides to olefins has been reported using lower valent tungsten halides,[18] as well as other metals or metal derivatives. As for protecting groups in the two hydroxymethyl branches of oxiranes **1**, both acetalic (BOM, PMBOM) and ethereal (PMP, TIPS) protections resulted equally suitable for this type of reaction. Monoprotected epoxides **1c** (entry 10) and **1d** (entries 11 - 12) gave no encouraging results: since in some case[17a] it has been reported that steric effects can be even more important than the presence of a free hydroxy group in directing the regioselectivity of the ring opening and since troublesome could arise from possible base catalyzed isomerization of the epoxide itself,[17a] reaction of monoprotected epoxides with organocuprates was not further explored.

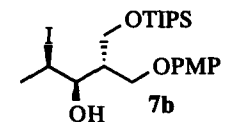
As already reported, methyl group is an almost "dummy"[3b] group: $Me_2Cu(CN)Li_2$ formed significant amounts of alcohol **2a** (R^4 = Me) only when reacted with **1a** (entry 5), while both $Pr_2Cu(CN)Li_2$ and $Bu_2Cu(CN)Li_2$ gave acceptable to good results with any of the epoxides employed.

Table 1. Ring opening of epoxides **1** using organocopper reagents (Scheme 1)

	Subs	R^1	R^2, R^3	R^4M[a]	Lewis Acid[b]	T, °C (t, h)	Yield,[c] %	Regioisom. ratio[d] 2 : 3
1	**1a**	Me	PMBOM, BOM	$Bu_2CuCNLi_2$	-	-78(1.5) → -45 (2)	70 (84)	91 : 9
2	**1a**	Me	PMBOM, BOM	$Bu_2CuCNLi_2$	$BF_3{\cdot}Et_2O$	-78 (2.5)	69[e]	94 : 6
3	**1a**	Me	PMBOM, BOM	$Bu_2CuCNLi_2$[f]	$BF_3{\cdot}Et_2O$[g]	-78 (20) → rt (4)	7 (21)	> 99 : 1
4	**1a**	Me	PMBOM, BOM	$Me_2Cu(CN)Li_2$	-	-78 (1.5) → rt (6)	-[h]	-
5	**1a**	Me	PMBOM, BOM	$Me_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (1.5)	69 (85)[e]	88 : 12
6	**1b**	Me	TIPS, PMP	$Bu_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (1.5)	72[i]	93 : 7
7	**1b**	Me	TIPS, PMP	Me_2CuLi	-	-40 (1) → rt (96)	-[l]	-
8	**1b**	Me	TIPS, PMP	Me_2CuLi[m, n]	$BF_3{\cdot}Et_2O$	-78 (10) → -20 (2)	-[o]	-
9	**1b**	Me	TIPS, PMP	Me_2CuLi[m, p]	$BF_3{\cdot}Et_2O$	-70 (5)	27 (40)	88 : 12
10	**1c**	Me	PMBOM, OH	$Me_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (20) → rt (4)	-[l]	-
11	**1d**	Me	TIPS, OH	$Bu_2Cu(CN)Li_2$	-	-78 (15) → rt (2)	-[q]	-
12	**1d**	Me	TIPS, OH	Me_2CuLi	-	-40 (1) → rt (96)	37 (46)	61 : 39
13	**1f**	Pr	PMBOM, BOM	$Me_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (2) → -20 (24)	-[l]	-
14	**1f**	Pr	PMBOM, BOM	$Bu_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (0.75)	57[r]	> 99 : 1
15	**1g**	Pr	TIPS, PMP	$Bu_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (0.75)	52[s]	> 99 : 1
16	**1h**	Bu	PMBOM, BOM	$Pr_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (0.75)	52[t]	> 99 : 1
17	**1i**	Bu	TIPS, PMP	$Pr_2Cu(CN)Li_2$	$BF_3{\cdot}Et_2O$	-78 (0.75)	49[u]	> 99 : 1

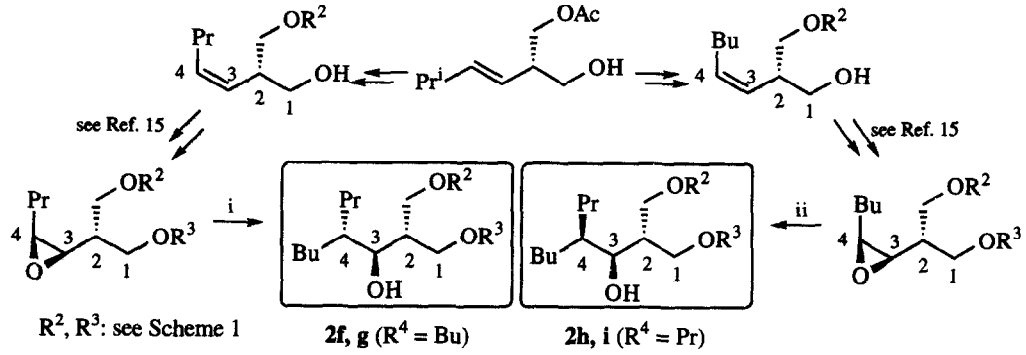
[a] A fivefold to tenfold excess of copper reagent was usually employed. [b] A twofold excess of Lewis acid was usually employed. 'Direct addition': organometallic reagent + epoxide + $BF_3{\cdot}Et_2O$ or organometallic reagent + $BF_3{\cdot}Et_2O$ + epoxide (see ref. 5a). 'Reversed addition': epoxide + $BF_3{\cdot}Et_2O$ + organometallic reagent. [c] Isolated total yield; yield in parentheses is referred to unrecovered substrate. [d] Products identification rests on ^1H and ^{13}C NMR spectra, with the aid of DEPT, COSY, and HETCOR experiments. Products ratio was usually determined by weighing isolated regioisomers. [e] Alkene **4a** was obtained as a by-product (21% and 8% for entries 2 and 5, respectively). [f] 1.4 eq of copper reagent were used. [g] 1.4 eq of Lewis acid were used. [h] Unidentified by-products were formed. [i] Alkene **4b** was obtained as a by-product (18%). [l] No reaction was observed. [m] Reversed addition.





[n] CuI was used in copper reagent preparation. [o] Iodohydrin **7b** (see Scheme 3) was obtained as the only product [59% (91%, based on unrecovered substrate), regioisomeric ratio > 99 : 1]. [p] CuSCN was used in copper reagent preparation. [q] Only traces of addition product were observed, along with unidentified by-products. [r] Alkene **4f** was obtained as a by-product (25%). [s] Alkene **4g** was obtained as a by-product (22%). [t] Alkene **4h** was obtained as a by-product (16%). [u] Alkene **4i** was obtained as a by-product (35%).

Scheme 2



i: $Bu_2Cu(CN)Li_2$, $BF_3{\cdot}Et_2O$, dry Et_2O, -78°C, 45 min. ii: $Pr_2Cu(CN)Li_2$, $BF_3{\cdot}Et_2O$, dry Et_2O, -78°C, 45 min.

This fact, along with the possibility to synthesise epoxides **1** in an *enantio-* and *diastereodivergent*[15] manner, implies that both **2** and any of its seven stereoisomeric forms can be in principle obtained starting from THYM* [asymmetrized *tris*(hydroxymethyl)methane].[10, 15] Actually, during this work both epoxides **1** and their enantiomers were used at times, but for sake of semplicity the same enantiomeric form is always shown. In the opening products **2**, the stereochemical relationship between chiral carbon atoms 2 and 3 (Scheme 2) was maintained fixed, while the relationship between carbon atoms 3 and 4 was varied: this goal was achieved simply by 'reverting' the order of introduction of the two alkyl chains (R^1, R^4) on carbon 4.

In order to test the feasibility of the introduction of a "functionalized" carbon-chain we studied also cyanide-based nucleophilic reactions (Scheme 3) and the most relevant data are reported in Table 2.

It is apparent that cyanide ring opening requires, not unexpectedly, both temperature equal or above room temperature and prolonged reaction times. When reaction conditions reported in Table 2 were applied, chemical yields are usually moderate, while regioselectivity, still depending on steric effects, was almost complete. Other different sets of reaction conditions (namely potassium cyanide in the presence of lithium perchlorate in acetonitrile,[6c] or potassium cyanide in the presence of ammonium chloride in methanol-water,[6c] or tetrabutylammonium cyanide in methanol-water,[6c] or cyanotrimethylsilane in the presence of titanium tetraisopropoxide in acetonitrile[9d]) were tried on diprotected epoxide **1b**, but even after prolonged (48 h) refluxing no formation of product was observed. When monoprotected epoxide **1d** was subjected to the same reaction conditions used in entries 1 and 3 (entry 5), only decomposition of substrate occurred. As already observed using organocopper reagents, when halide ions in aprotic solvents are present, competitive formation of halohydrin is observed in at least comparable yield to cyanohydrin (entry 4). In the last case,

Scheme 3

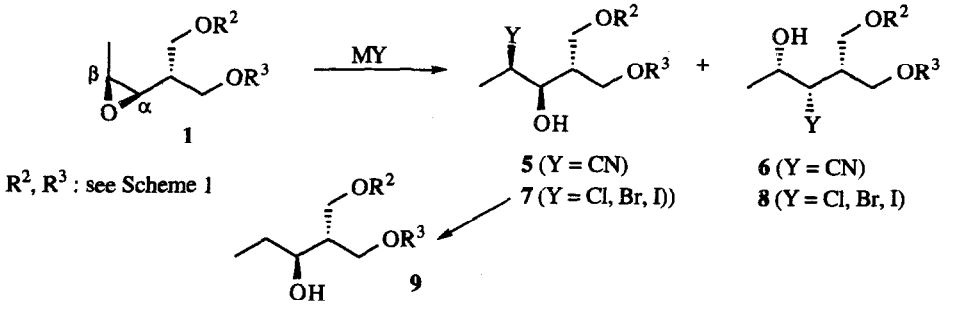
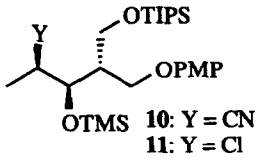


Table 2. Ring opening of epoxides **1** using cyanides (Scheme 3, Y = CN)

	Subs	R^2, R^3	MY (Solvent)	T, °C (t, h)	Yield,[a] %	Regioisom. ratio[b] 5 : 6
1	**1a**	PMBOM, BOM	LiCN (THF)[c]	Reflux (48)	63	> 99 : 1
2	**1a**	PMBOM, BOM	Et_2AlCN (CH_2Cl_2)[d]	-78 → rt (48)	57	94 : 6
3	**1b**	TIPS, PMP	LiCN (THF)[c]	Reflux (48)	65	> 99 : 1
4	**1b**	TIPS, PMP	TMSCN, Et_2AlCl (Toluene)[e]	rt (56)	23[f]	> 99 : 1[f]
5	**1d**	TIPS, OH	LiCN (THF)[c]	Reflux (48)	-[g]	-

[a] Isolated total yield; yield in parentheses is referred to unrecovered substrate. [b] Products identification rests on ^1H and ^{13}C NMR spectra, with the aid of DEPT, COSY, and HETCOR experiments. Products ratio was usually determined by weighing isolated regioisomers. [c] Ref. 6e. [d] Ref. 7e. [e] Ref. 6c. [f] Yield and regioisomeric ratio refer to *O*-silylated cyanohydrin **10**, that was isolated as the only detectable regioisomer, along with *O*-silylated chlorohydrin **11** as a by-product (25%). [g] Substrate disappeared, but no expected product was detected.



10: Y = CN
11: Y = Cl

since trimethylsilyl cyanide is used, a fully protected diol is obtained.

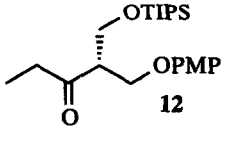
Positively milder conditions were required for halide ring opening of epoxides **1** (Scheme 3, Table 3): optically active halohydrins, which are useful intermediates in organic synthesis,[11f, 14] were obtained in moderate to very good chemical yields, with complete diastereoselectivity and generally very high regioselectivity. The same electronic and steric effects that have been above discussed operate also in this case, so that nucleophilic attack at the β-position is favoured and regioisomer **7** is usually observed as the main or the only product.

Conditions described by Murai[11c-d] and by Bonini[11f] gave the best results, avoiding protecting groups deblocking, that is usually a major problem when strong Lewis acids, like Et_2AlCl, are used alone (entry 1). Nevertheless a Lewis acid was necessary to perform the reaction: neither diprotected epoxides **1a - b** reacted

Table 3. Ring opening of epoxides **1** using halides as nucleophiles (Scheme 3)

	Subs	R^2, R^3	Y	MY (Solvent)	T, °C (t, h)	Yield,[a] %	Regioisom. ratio[b] 7 : 8
1	**1a**	PMBOM, BOM	Cl	Et_2AlCl (Et_2O)	0 (1) → rt (3)	-[c]	-
2	**1a**	PMBOM, BOM	I	MgI_2 (Toluene)[d]	-78 (1) → 0	83 (93)	92 : 8
3	**1b**	TIPS, PMP	Cl	Et_2AlCl (CH_2Cl_2)[e]	rt (20)	-[c]	-
4	**1b**	TIPS, PMP	Cl	Et_2NH·HCl, Et_2AlCl (CH_2Cl_2)[e]	rt (20)	86	93 : 7
5	**1b**	TIPS, PMP	Br	$MgBr_2$ (Et_2O)	rt (48)	66[f]	90 : 10
6	**1b**	TIPS, PMP	I	MgI_2 (Toluene)[d]	-78 (1) → 0	99	> 99 : 1
7	**1d**	TIPS, H	Cl	Et_2NH·HCl, (*i*-PrO)$_4$Ti (CH_2Cl_2)[g]	Reflux (10)	71	> 99 : 1
8	**1d**	TIPS, H	Br	Et_2NH·HBr, (*i*-PrO)$_4$Ti (CH_2Cl_2)[g]	rt (20)	88	> 99 : 1
9	**1d**	TIPS, H	I	ZnI_2 (DME)	0 (3)	-[h]	-
10	**1e**	TIPS, Ac	Cl	Et_2AlCl (CH_2Cl_2)	-60 → rt (20)	75	> 99 : 1

[a] Isolated total yield; yield in parentheses is referred to unrecovered substrate. [b] Products identification rests on ^1H and ^{13}C NMR spectra (with the aid of DEPT, COSY, and HETCOR experiments) and, in some case, on chemical correlation. Products ratio was usually determined by weighing isolated regioisomers. [c] Extensive decomposition of substrate was observed, probably through *O*-protecting groups deblocking. [d] Ref. 11g. [e] Ref. 11d. [f] Ketone **12** was detected as a by-product (27%). [g] Ref. 11c. [h] No reaction was observed.



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with alkylammonium halides in the absence of diethylaluminum chloride nor monoprotected epoxide **1d** reacted in the absence of titanium tetraisopropoxide. Despite reported data on glycidyl tosylates,[9d] titanium tetraisopropoxide was completely ineffective in ring opening of diprotected epoxides. Regioselectivity seems to be independent of the halide employed (entries 7 and 8). Freshly prepared magnesium iodide is superior to commercial magnesium bromide or zinc iodide with regard to both chemical and regiochemical yields (*cfr* entries 5, 6 and 9). When commercial magnesium bromide etherate was employed (entry 5), substantial amounts of rearranged ketone **12** were observed.[10] The stereochemistry of the main products was unequivocally confirmed by converting halohydrins **7** to the corresponding starting epoxides **1**. Finally, dehalogenation[10] of halohydrins **7** to triols **9** (Scheme 3) resulted in a regioselective formal reductive ring opening of epoxides **1**.

We wish to thank M.U.R.S.T. and C.N.R. (Progetto Finalizzato Chimica Fine) for financial assistance.

EXPERIMENTAL

General. - NMR spectra were recorded as $CDCl_3$ solutions on a Varian Gemini 200 spectrometer using tetramethylsilane (^1H NMR) or $CDCl_3$ (^{13}C NMR) as internal standard; chemical shifts (δ) are in ppm, coupling constants (J) are in Hz; a * means that the value was obtained through double resonance experiments.

'Usual workup' means that the given reaction mixture was extracted (Et_2O, CH_2Cl_2, or AcOEt), the organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure.

Tetrahydrofuran (THF) was always freshly distilled from K / Ph_2CO; CH_2Cl_2, Et_2O, toluene, benzene, and *N, N*-dimethylformamide (DMF) were purchased as dry solvents from Aldrich and stored over 4 Å molecular sieves. All reactions requiring dry conditions were run under an inert atmosphere (N_2 or He).

TLC analyses were carried out on silica gel plates, which were developed by spraying a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming. R_f were measured after an elution of 7 - 9 cm. Column chromatographies were run following the method of 'flash chromatography',[17] using 230 - 400 mesh silica gel (Merck).

t-Butylhydroperoxide is abbreviated as TBHP, vanadyl acetylacetonate as $VO(acac)_2$, diethyl azodicarboxylate as DEAD, and petroleum ether (b. p. 40 - 60°C) as PE.

All compounds gave satisfactory spectroscopic and analytical data: a selection of the latter data is reported in Table 7.

Synthesis of optically active epoxides **1a - e** through a chemoenzymatic route has been already reported in Ref. 10 and Ref. 15.

Reductive dehalogenation of halohydrins **7** has already been reported in Ref. 10, as well as their conversion to starting epoxides.

Synthesis of diprotected cis epoxide 1f. - Monoprotected *cis* epoxide 2-(4-methoxybenzyloxymethoxy)-3,4-epoxyheptan-1-ol[15] (1.0 mmol) was dissolved in dry CH_2Cl_2 (8 ml) at 0°C and added with *i*-Pr_2NEt (4.0 mmol) and (benzyloxymethoxymethyl)chloride (3.4 mmol). Cooling bath was removed and the reaction mixture was stirred at r. t. for 15 h; Et_2NH (1 mmol) was added, then reaction mixture was diluted with brine and subjected to usual workup (Et_2O). After chromatographic purification (PE / Et_2O 7 : 3, containing 0.5% of Et_3N), pure **1f** (89%) was obtained as a colorless oil. ^1H NMR: 0.99 (t, J 6.8 Hz, 3 H, *Me*CH_2), 1.38 - 1.63 (m, 4 H, MeCH_2CH_2), 1.76 - 1.87 (m, 1 H, CH_2CHCH_2), 2.93 - 3.03 (m, 2 H, 2 x C*H*O), 3.63 - 3.86 (m, 4 H, 2 x CH_2O), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, CH_2Ar), 4.61 (s, 2 H, CH_2Ph), 4.72 (s, 2 H, CH_2OCH_2Ar), 4.78 (s, 2 H, CH_2OBzl), 6.85 - 6.90 (m, 2 H, Ar*H*), 7.24 - 7.36 (m, 7 H, Ar*H*).

Synthesis of diprotected cis epoxide 1g. - Monoprotected *cis* epoxide 2-(triisopropylsilyloxymethoxy)-3,4-epoxyheptan-1-ol[15] (1.0 mmol) was dissolved in dry CH_2Cl_2 (13 ml) and added with Ph_3P (1.5 mmol), 4-methoxyphenol (3.0 mmol), and DEAD (1.5 mmol). The reaction mixture was stirred ad r. t. for 15 h, then it was diluted with brine and subjected to usual workup (Et_2O). After chromatographic purification (PE / Et_2O 9 : 1, containing 0.5% of Et_3N), pure **1g** (81%) was obtained as a colorless oil. ^1H NMR: 1.00 - 1.70 (m, 28 H, *Me*CH_2CH_2 & 3 x *Me*$_2$*CH*Si), 1.84 - 1.95 (m, 1 H, CH_2CHCH_2), 2.98 - 3.11 (m, 2 H, 2 x C*H*O), 3.77 (s, 3 H, *Me*O), 3.93 (app d, J 5.1 Hz, 2 H, CH_2O), 4.14 (app d, J 5.2 Hz, 2 H, CH_2O), 6.78 - 6.90 (m, 4 H, Ar*H*).

Synthesis of (Z)-2-(4-methoxybenzyloxymethoxy)-1-(triisopropylsilyloxy)-3-octene. - It was obtained as a colourless oil from THYM* [as described in Ref. 15 for (*Z*)-2-(4-methoxybenzyloxymethoxy)-1-(triisopropylsilyloxy)-3-heptene] in 76% overall yield (two steps, that is modified Swern oxidation and Wittig condensation) after chromatographic purification (PE / Et_2O 95 : 5, containing 0.5% of Et_3N). ^1H NMR: 0.86-1.19 (m, 5 H, *Me*CH_2), 1.30-1.38 (m, 2 H, MeCH$_2$CH_2), 2.04-2.10 (m, 2 H, CH_2CH=), 2.75-2.91 (m, 1 H, C*H*CH=), 3.58 & 3.70 (AB part of an ABX system, J 9.7 & 6.1 & 5.6 Hz, 2 H, CH_2O), 3.68 (app d, J 5.5 Hz, 2 H, CH_2O), 3.81 (s, 3 H, *Me*O), 4.52 (s, 2 H, CH_2Ar), 4.73 (s, 2 H, OCH_2O), 5.28-5.59 (m, 2 H, C*H*=C*H*), 6.86-6.91 (m, 2 H, Ar*H*), 7.26-7.34 (m, 2 H, Ar*H*).

Synthesis of diprotected epoxide 1h. - A solution of (*Z*)-2-(4-methoxybenzyloxymethoxy)-1-(triisopropylsilyloxy)-3-octene (1 mmol) in THF (30 ml) was cooled to 0°C and 7 ml of a 0.5 M solution of TBAF in THF (3.5 mmol) were added. After stirring 1.5 h at r.t., brine (40 ml) and water (40 ml) were added and, after usual work-up (Et_2O) and chromatography (PE / Et_2O 7 : 3, containing 0.5% of Et_3N), pure monoprotected alkene (98%) was obtained as a colourless oil. H NMR: 0.87-0.94 (m, 3 H, *Me*CH_2), 1.25-1.39 (m, 4 H, MeCH_2CH_2), 2.04-2.15 (m, 2 H, CH_2CH=), 2.87-3.03 (m, 1 H, C*H*CH=), 3.54-3.78 (m, 4 H, 2 x CH_2O), 5.13-5.24 (m, 1 H, CH-C*H*=), 5.54-5.66 (m, 1 H, CH_2-C*H*=), 6.85-6.92 (m, 2 H, Ar*H*), 7.25-7.32 (m, 2 H, Ar*H*).

The alkene was epoxidized using TBHP in the presence of VO(acac)$_2$, as described in Ref. 15 (reaction time: 10 h). After column chromatography (PE / Et_2O 1 : 2, containing 0.5% of Et_3N) the epoxide was obtained as a colourless oil (68%). ^1H NMR: 0.92 (t, J 7.0 Hz, 3 H, *Me*CH_2), 1.36-1.59 (m, 6 H, MeC$H_2CH_2CH_2$), 1.77-1.87 (m, 1 H, CH_2CHCH_2), 2.93-2.98 (m, 2 H, 2 x C*H*O), 3.72 (app d, J 5.0 Hz, 2 H, CH_2O), 3.83 (s, 3 H, *Me*O), 3.87 & 3.96 (AB part of an ABX system, J 10.9 & 4.6 & 4.5 Hz, 2 H, CH_2O), 4.53 (s, 2 H, CH_2Ar), 4.73 (s, 2 H, OCH_2O), 6.85-6.92 (m, 2 H, Ar*H*), 7.23-7.29 (m, 2 H, Ar*H*).

The monoprotected epoxide was treated with (benzyloxymethoxymethyl)chloride and *i*-Pr$_2$NEt in dry CH_2Cl_2 as above described for **1f** to give diprotected epoxide **1h** (86%) as a colourless oil. ^1H NMR: 0.93 (t, J 6.9 Hz, 3 H, *Me*CH_2), 1.22 - 1.65 (m, 6 H, MeC$H_2CH_2CH_2$), 2.94 - 2.99 (m, 2 H, 2 x C*H*O), 1.77-1.93 (m, 1 H, CH_2CHCH_2), 3.68 & 3.74 (AB part of an ABX system, J 9.6 & 6.3 & 5.5 Hz, 2 H, CH_2O), 3.82 (app d, J 6.5 Hz, 2 H, CH_2O), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, CH_2Ar), 4.61 (s, 2 H, CH_2Ph), 4.72 (s, 2 H, CH_2OCH$_2$Ar), 4.79 (s, 2 H, CH_2OBzl), 6.85 - 6.90 (m, 2 H, Ar*H*), 7.24 - 7.36 (m, 7 H, Ar*H*).

Synthesis of diprotected epoxide 1i. - A solution of (*Z*)-2-(4-methoxybenzyloxymethoxy)-1-(triisopropylsilyloxy)-3-octene (1 mmol) in CH_2Cl_2 (15 ml) was added with 0.87 ml of a 0.2 M pH 7 phosphate buffer and 0.87 ml of *t*-BuOH and treated with 2 mmol of DDQ at r.t.. After 2 h, a saturated aqueous solution of $NaHCO_3$ was added. Usual work-up (Et_2O) and chromatography (PE / Et_2O 80: 20) afforded pure monoprotected alkene (80%) as a colourless oil. ^1H NMR: 0.86 - 0.93 (m, 3 H, *Me*CH_2), 1.06 - 1.08 (m, 21 H, 3 x *Me*$_2$*CH*Si), 1.29 - 1.38 (m, 4 H, MeCH_2CH_2), 2.04 - 2.14 (m, 2 H, CH_2CH=), 2.08 - 2.99 (m, 1 H, C*H*CH=), 3.63 - 3.84 (m, 4 H, 2 x CH_2O), 5.04 - 5.16 (m, 1 H, CHC*H*=), 5.48 - 5.61 (m, 1 H, CH_2C*H*=).

The alkene was epoxidized using TBHP in the presence of VO(acac)$_2$, as described in Ref. 15 (reaction time: 15 h). After column chromatography (PE / Et_2O 1 : 1, containing 0.5% of Et_3N) the epoxide was ob-

Table 4. ^{1}H NMR data for regioisomers **2**.

	R^4	CH_2CHCH_2 (1 H)[a]	$CHOH$ (1 H)[a]	CH_2OR^2 (2 H)[a] CH_2OR^3 (2 H)[a]	Others
2a	Me	2.06[b] (4.9)	3.38-3.48[c]	3.71-3.93[d]	0.91 (d, J 6.8 Hz, 3 H, *Me*CH), 1.02 (d, J 6.6 Hz, 3 H, *Me*CH), 1.79 (app sextuplet, J 6.7 Hz, 1 H, Me_2CH), 2.75-2.83 (m, 1 H, O*H*), 3.80 (s, 3 H, *Me*O), 4.53 (s, 2 H, CH_2Ar), 4.60 (s, 2 H, CH_2Ph), 4.74 (s, 2 H, CH_2OCH_2Ar), 4.75 (s, 2 H, CH_2OBzl), 6.85-6.90 (m, 2 H, Ar*H*), 7.25-7.34 (m, 7 H, Ar*H*).
2a	Bu	2.04-2.12[c]	3.44-3.53[c] [3.47, dd, J 3.8 & 7.9 Hz][e]	3.71-3.94[d]	0.86-1.46 (m, 12 H, $MeCH_2CH_2CH_2CHMe$), 1.54-1.80 (m, 1 H, C*H*Me), 2.80 (d, J 5.8 Hz, 1 H, O*H*), 3.80 (s, 3 H, *Me*O), 4.53 (s, 2 H, CH_2Ar), 4.60 (s, 2 H, CH_2Ph), 4.74 (s, 2 H, CH_2OCH_2Ar), 4.75 (s, 2 H, CH_2OBzl), 6.85-6.89 (m, 2 H, Ar*H*), 7.26-7.34 (m, 7 H, Ar*H*).
2b	Me	2.05-2.18[c]	3.56[f] (8.7) [dd, J 2.7 & 8.2 Hz][e]	3.95 & 4.19[g] (10.1, 4.0, 2.6); 4.14 & 4.20[g] (9.7, 0.6, 11.8)	0.92 (d, J 6.8 Hz, 6 H, 2 x *Me*CH), 1.02-1.05 (m, 21H, 3 x Me_2CHSi), 1.76-1.93 (m, 1 H, Me_2CH), 3.37-3.38 (m, 1 H, O*H*), 3.77 (s, 3 H, *Me*O), 6.83 (bs, 4 H, Ar*H*).
2b	Bu	2.07-2.17[c]	3.69-3.69[c] [3.63, dd, J 2.5 & 8.7 Hz][e]	3.95 & 4.23[g] (9.8, 3.8, 3.3); 4.13 & 4.22[g] (9.1, 3.9, 8.9)	0.87-1.90 (m, 34 H, $MeCH_2CH_2CH_2CHMe$ & 3 x Me_2CHSi), 3.52 (d, J 2.8 Hz, 1 H, O*H*), 3.77 (s, 3 H, *Me*O), 6.83-6.84 (m, 4 H, Ar*H*).
2f	Bu	2.08[b] (5.3)	3.65-3.70[c] [J* 4.8 & 5.1 Hz]	3.70 & 3.77[g] (11.1, 5.8, 5.8); 3.86 & 3.90[g] (9.7, 4.5, 5.6)	0.84 (t, J 5.1 Hz, 3 H, *Me*CH_2), 0.90 (t, J 4.9 Hz, 3 H, *Me*CH_2), 1.20-1.60 (m, 11 H, $CH_2CH_2CH_2CHCH_2CH_2$), 3.71 (d, J 5.2 Hz, O*H*), 3.80 (s, 3 H, *Me*O), 4.53 (s, 2 H, CH_2Ar), 4.60 (s, 2 H, CH_2Ph), 4.73 (s, 2 H, CH_2OCH_2Ar), 4.76 (s, 2 H, CH_2OBzl), 6.84-6.91 (m, 2 H, Ar*H*), 7.24-7.36 (m, 7 H, Ar*H*).
2g	Bu	2.05-2.18[c]	3.81-3.93[c] [3.85* & 3.94*, J* 9.9, 3.7, 4.3]; 4.10-4.29[h] [4.16* & 4.26*, J*$_{gem}$ 9.6 Hz; 4.20*, J* 9.7 Hz]		0.89 (t, J 7.9 Hz, 3 H, *Me*CH_2), 0.90 (t, J 6.6 Hz, 3 H, *Me*CH_2), 1.00-1.35 (m, 32 H, $CH_2CH_2CH_2CHCH_2CH_2$ & x Me_2CHSi), 3.18 (d, J 3.3 Hz, 1 H, O*H*), 3.77 (s, 3 H, *Me*O), 6.84 (bs, 4 H, Ar*H*).
2h	Pr	2.08[b] (5.1)	3.65-3.73[c] [J* 4.6 & 4.7 Hz]	3.70 & 3.76[g] (9.9, 6.4, 4.9); 3.86 & 3.90[g] (9.6, 4.4, 5.4)	0.89 (t, J 6.5 Hz, 3 H, *Me*CH_2), 0.91 (t, J 6.6 Hz, 3 H, *Me*CH_2), 1.21-1.60 (m, 11 H, $CH_2CH_2CH_2CHCH_2CH_2$), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, CH_2Ar), 4.60 (s, 2 H, CH_2Ph), 4.72 (s, 2 H, CH_2OCH_2Ar), 4.76 (s, 2 H, CH_2OBzl), 6.85-6.89 (m, 2 H, Ar*H*), 7.24-7.35 (m, 7 H, Ar*H*.
2i	Pr	2.10[b] (3.9)	3.77-3.93[c] [3.79* & 3.90*, J* 9.6, 3.3, 4.0]; 4.10-4.27[h] [4.15* & 4.23*, J*$_{gem}$ 9.2 Hz; 4.18*, J* 9.9 Hz]		0.88 (t, J 6.6 Hz, 3 H, *Me*CH_2), 9.92 (t, J 6.6 Hz, 3 H, *Me*CH_2), 1.00-1.58 (m, 32 H, $CH_2CH_2CH_2CHCH_2CH_2$ & 3 x Me_2CHSi), 3.17 (d, J 3.3 Hz, 1 H, O*H*), 3.77 (s, 3 H, *Me*O), 6.79-6.89 (m, 4 H, Ar*H*).

[a] Coupling constants J (Hz) are reported in parentheses; a * means that the value was obtained through double resonance experiments. [b] Apparent sextuplet. [c] Multiplet. [d] Multiplet, 4 H. [e] Exchange with D_2O. [f] Apparent doublet. [g] AB Part of an ABX system. [h] Multiplet, 3 H, CH_2O (AB part of an ABX system) & C*H*OH.

tained as a colourless oil (60%). ^{1}H NMR: 0.89 - 0.96 (m, 3 H, *Me*CH_2), 1.03 - 1.60 (m, 27 H, $MeCH_2CH_2CH_2$ & 3 x Me_2CHSi), 1.60 - 1.80 (m, 1 H, CH_2CHCH_2), 2.94 - 3.01 (m, 2 H, 2 x C*H*O), 3.78 - 4.01 (m, 4 H, 2 x CH_2O).

The monoprotected epoxide was treated with 4-methoxyphenol, Ph_3P, and DEAD in CH_2Cl_2 as above described for **1g** to give diprotected epoxide **1i** (75%) as a colourless oil. ^{1}H NMR: 0.89 - 1.62 (m, 30 H,

Table 5. ^{1}H NMR data for regioisomers **3**.

	R^4	CH_2CHCH_2 (1 H)	CHOH (1 H)	CH_2OR^2 (2 H) CH_2OR^3 (2 H)	Others
3a	Me	1.96-2.10[a]	3.94-4.00[a]	3.61-3.65[b]	0.95 (d, J 7.1 Hz, 3 H, *Me*CH), 1.20 (d, J 6.3 Hz, 3 H, *Me*CHOH), 1.50-1.70 (m, 1 H, CHC*H*CH), 3.80 (s, 3 H, *Me*O), 4.53 (s, 2 H, CH_2Ar), 4.60 (s, 2 H, CH_2Ph), 4.73 (s, 2 H, CH_2OCH_2Ar), 4.76 (s, 2 H, CH_2OBzl), 6.86-6.90 (m, 2 H, Ar*H*), 7.21-7.36 (m, 7 H, Ar*H*).
3a	Bu	2.02-2.18[a]	3.92-4.10[a]	3.52-3.79[b]	0.90 (d, J 6.3 Hz, 3 H, *Me*CH_2), 1.20 (d, J 6.5 Hz, 3 H, *Me*CH), 1.20-1.40 (m, 6 H, MeC$H_2CH_2CH_2$), 1.50-1.60 (m, 1 H, CHC*H*CH), 3.53 (d, J 2.3 Hz, 1 H, O*H*), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, CH_2Ar), 4.60 (s, 2 H, CH_2Ph), 4.73 (s, 2 H, CH_2OCH_2Ar), 4.77 (s, 2 H, CH_2OBzl), 6.85-6.90 (m, 2 H, Ar*H*), 7.24-7.34 (m, 7 H, Ar*H*).
3b	Me	2.10-2.21[a]	3.95-4.05[a]	3.83-3.88[b]	0.96 (d, J 7.0 Hz, 3 H, *Me*CH), 1.20 (d, J 6.3 Hz, 3 H, *Me*CHOH), 1.70-1.83 (m, 1 H, CHC*H*CH), 1.07-1.11 (m, 21 H, 3 x Me_2CHSi), 3.77 (s, 3 H, *Me*O), 6.82 (bs, 4 H, Ar*H*).
3b	Bu	2.05-2.25[a]	3.83-4.07[c]		0.88-0.94 (m, 3 H, *Me*CH_2), 1.03-1.10 (m, 21 H, 3 x Me_2CHSi), 1.22 (d, J 6.5 Hz, 3 H, *Me*CH), 1.53-1.64 (m, 1 H, CHC*H*CH), 3.55 (d, J 1.5 Hz, 1 H, O*H*), 3.77 (s, 3 H, *Me*O), 6.83 (bs, 4 H, Ar*H*).

[a] Multiplet. [b] Multiplet, 4 H. [c] Multiplet, 5 H.

MeCH_2CH_2 CH_2 & 3 x Me_2CHSi), 1.81 - 1.97 (m, 1 H, CH_2CHCH_2), 2.98 - 3.11 (m, 2 H, 2 x CHO), 3.77 (s, 3 H, *Me*O), 3.94 (app d, J 5.0 Hz, 2 H, CH_2O), 4.14 (app d, J 5.8 Hz, 2 H, CH_2O), 6.78 - 6.90 (m, 4 H, Ar*H*).

General procedure for reaction of epoxides with 'higher order' cuprates $R_2Cu(CN)Li_2$. - CuCN (5 mmol) was suspended in dry Et_2O (20 ml) under an inert atmosphere (He) and cooled to -78°C., then 6.2 ml of a 1.6 M solution of *n*-BuLi in hexane (9.9 mmol) or 6.2 ml of a 1.6 M solution of MeLi in Et_2O (9.9 mmol) or 6.6 ml of a 1.5 M solution of *n*-PrLi in *n*-hexane (9.9 mmol) were added and the reaction mixture was allowed to reach -20°C. The reaction mixture was cooled again to -78°C and a solution of the epoxide (0.5 mmol) in dry Et_2O (10 ml) was added. After the appropriate reaction time at the temperature indicated in Table 1, 40 ml of 10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v) were added, the reaction mixture was stirred at room temperature until two clear layers separated and worked up as usual. After column chromatography, pure regioisomers **2** and **3** were isolated as colourless oils. Total reaction yields and products ratios can be found in Table 1 and ^{1}H NMR data of products can be found in Table 4 (regioisomers **2**), and Table 5 (regioisomers **3**).

General procedure for reaction of epoxides with 'higher order' cuprates $R_2Cu(CN)Li_2$ in the presence of boron trifluoride etherate. - The 'higher order' cuprate was prepared as described for the uncatalyzed process, then a solution of the epoxide (0.5 mmol) in dry Et_2O (10 ml) was added, followed by the addition of 2.5 ml of a 0.4 M solution of $BF_3{\cdot}Et_2O$ in dry Et_2O. After the appropriate reaction time at the temperature indicated in Table 1, 40 ml of 10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v) were added, the reaction mixture was stirred at room temperature until two clear layers separated and worked up as usual. After column chromatography, pure regioisomers **2** and **3**, as well as alkenes **4** were isolated as colourless oils. Total reaction yields and products ratios can be found in Table 1 and ^{1}H NMR data of products can be found in Table 4 (regioisomers **2**), Table 5 (regioisomers **3**), and Table 6 (alkenes **4**).

Table 6. ^{1}H NMR data for alkenes **4**.

	CH_2CHCH_2 (1 H)[a]	CH_2OR^2 (2 H)[a] CH_2OR^3 (2 H)[a]	CH=C*H*CH (1 H)[a]	CH_2CH=CH (1 H)[a]	Others
4a	2.91-3.08[b]	3.57 & 3.66[c] (10.3, 2.4, 5.6); 3.57 & 3.67[c] (10.2, 4.9, 3.0)	5.30-5.42[b] [J* 10.9 & 9.1 Hz]	5.57-5.73[b] [J* 10.9 & 6.5 Hz]	1.69 (dd, J 1.7 & 6.8 Hz, 3 H, *Me*), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, CH_2Ar), 4.60 (s, 2 H, CH_2Ph), 4.73 (s, 2 H, CH_2OCH_2Ar), 4.76 (s, 2 H, CH_2OBzl), 6.82-6.92 (m, 2 H, Ar*H*), 7.25-7.37 (m, 7 H, Ar*H*).
4b	2.93-3.09[b]	3.73 & 3.78[c] (9.5, 6.6, 4.5); 3.88 & 4.04[c] (9.0, 5.9, 6.3)	5.47-5.51[b] [J* 10.9 & 9.0 Hz]	5.56-5.71[b]	1.03-1.07 (m, 21 H, 3 x *Me*CHSi), 1.68 (dd, J 1.6 & 6.7 Hz, 3 H, *Me*), 3.77 (s, 3 H, *Me*O), 6.83 (bs, 5 H, Ar*H*).
4f	2.87-3.04[b]	3.57 & 3.64[c] (9.4, 2.6, 3.4); 3.58 & 3.66[c] (9.4, 5.9, 2.8)	5.29-5.40[b] [J* 10.7 & 9.3 Hz]	5.57[d] (10.7, 7.2)	0.92 (t, J 7.2 Hz, 3 H, *Me*CH_2), 1.25-1.60 (m, 2 H, MeC*H*$_2$), 1.99-2.13 (m, 2 H, C*H*$_2$CH=CH), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, C*H*$_2$Ar), 4.59 (s, 2 H, C*H*$_2$Ph), 4.72 (s, 2 H, C*H*$_2$OCH$_2$Ar), 4.76 (s, 2 H, C*H*$_2$OBzl), 6.82-6.91 (m, 2 H, Ar*H*), 7.25-7.36 (m, 7 H, Ar*H*).
4g	2.90-3.06[b]	3.73 & 3.79[c] (9.6, 6.4, 4.8); 3.87 & 4.04[c] (9.0, 5.9, 6.3)	5.36-5.62[f] [5.44*, J* 11.0 & 9.0 Hz; 5.58*, J* 11.0 & 6.5 Hz]		0.91 (t, J 7.3 Hz, 3 H, *Me*CH_2), 1.03-1.07 (m, 21 H, 3 x *Me*$_2$*CH*Si), 1.39 (app sextuplet, J 7.4 Hz, 2 H, MeC*H*$_2$), 2.01-2.12 (m, 2 H, C*H*$_2$CH=CH), 3.77 (s, 3 H, *Me*O), 6.82 (bs, 4 H, Ar*H*).
4h	2.91-3.04[b]	3.38-3.89[e]	5.28-5.38[b] [J* 0.7 & 9.2 Hz]	5.50-5.63 [J* 10.8 & 6.9 Hz]	0.86-0.93 (m, 3 H, *Me*CH_2), 1.20-1.39 (m, 4 H, MeC*H*$_2$C*H*$_2$), 2.05-2.15 (m, 2 H, C*H*$_2$CH=CH), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, C*H*$_2$Ar), 4.60 (s, 2 H, C*H*$_2$Ph), 4.72 (s, 2 H, C*H*$_2$OCH$_2$Ar), 4.76 (s, 2 H, C*H*$_2$OBzl), 6.85-6.89 (m, 2 H, Ar*H*), 7.25-7.35 (m, 7 H, Ar*H*).
4i	2.90-3.07[b]	3.73 & 3.79[c] (9.6, 6.5, 5.0); 3.87 & 4.04[c] (9.0, 5.9, 6.3)	5.35-5.61[f] [5.44*, J* 10.9 & 9.1 Hz; 5.59*, J* 10.9 & 6.6 Hz]		0.83-1.34 (m, 28 H, *Me*C*H*$_2$C*H*$_2$ & 3 x *Me*$_2$*CH*Si), 2.03-2.12 (m, 2 H, C*H*$_2$CH=CH), 3.77 (s, 3 H, *Me*O), 6.83 (bs, 4 H, Ar*H*).

[a] Coupling constants J (Hz) are reported in parentheses; a * means that the value was obtained through double resonance experiments. [b] Multiplet. [c] AB Part of an ABX system. [d] Doublet of triplet. [e] Multiplet, 4 H. [f] Multiplet, 2 H.

General procedure for reaction of epoxides with 'lower order' cuprate Me$_2$CuLi in the absence and in the presence of boron trifluoride etherate. - ^{1}H NMR data of products can be found in Table 4 (regioisomers **2**) and Table 5 (regioisomers **3**).

a) Cuprate from CuI, uncatalyzed. - A suspension of CuI (6 mmol) in dry Et_2O (20 ml) was cooled to -25°C, added with 7.4 ml of a 1.6 M solution of MeLi in Et_2O (11.8 mmol), and stirred for 30 min at the same temperature. An aliquot of this solution (5.5 ml, about 1.2 mmol of Me_2CuLi) was added to a solution of the epoxide (0.2 mmol) in dry Et_2O (1.5 ml) cooled at -40°C. The reaction mixture was stirred at -40°C for 1 h, the allowed to reach r.t. and stirred at the same temperature for four days.

When diprotected epoxide **1b** was used in this reaction, TLC analysis (PE / Et_2O) showed that no reaction had occurred, and starting material was recovered after quenching with 10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v) and usual workup.

When monoprotected epoxide **1d** was employed as substrate, quenching with 10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v), usual workup, and chromatographic purification (PE / Et_2O 6 : 4, con-

taining 0.5% of Et_3N) afforded **2d** and **3d** in low total yield (37%) and regioisomeric ratio (61 : 39), along with some unreacted epoxide **1d** (8%) (extensive deprotection of primary alcohol moiety had occurred).

b) Cuprate from CuI, catalyzed. - A solution of epoxide **1b** (0.2 mmol) in dry Et_2O (1.5 ml) was cooled to -78°C and added with 0.2 ml of a 1 M solution of $BF_3{\cdot}Et_2O$ in dry Et_2O (0.2 mmol). Then the solution of Me_2CuLi (prepared as above described for the uncatalyzed process) was added (5.5 ml, about 1.2 mmol of Me_2CuLi) and the reaction mixture was stirred at -78°C for 10 h and then at -20°C fort2 h. After quenching [10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v)], usual workup, and chromatography (PE / Et_2O 9 : 1, containing 0.5% of Et_3N), pure iodohydrin **7b** (Y = I) (59%, 91% based on unrecovered substrate) was obtained as a yellowish oil. Analytical and spectroscopic data for **7b** (Y = I) have already been reported.[10]

c) Cuprate from CuSCN, catalyzed. - A suspension of CuSCN (5 mmol) in dry Et_2O (15 ml) was cooled to -30°C, added with 6.2 ml of a 1.6 M solution of MeLi in Et_2O (10 mmol) and stirred at the same temperature for 30 min.

The epoxide **1b** (0.2 mmol) was dissolved in dry Et_2O (3 ml), cooled to -70°C, added with 0.2 ml of a 1 M solution of $BF_3{\cdot}Et_2O$ in dry Et_2O (0.2 mmol), and stirred at the same temperature for 15 min. An aliquot of the cuprate solution (1.8 ml, about 0.4 mmol of Me_2CuLi) was added and stirring continued at -70°C for 2 h. An additional aliquot of Me_2CuLi solution (1.8 ml) was added, and stirring continued for 3 h, then 10% aqueous NH_4OH / saturated aqueous NH_4Cl 1 : 9 (v / v) was added and reaction mixture was worked up as usual. After chromatographic purification, regioisomers **2b** and **3b** were obtained (27%, regioisomeric ratio 88 : 12) along with unreacted starting material (32%).

Reaction of epoxides 1a, b, d with lithium cyanide. - Lithium cyanide (1.00 mmol) was added to a solution of the epoxide (0.20 mmol) in dry THF (1 ml) and the reaction mixture was refluxed for two days. Water and dichloromethane were added and, after usual work-up and chromatographic separation (PE / Et_2O), **5a** [63%; R_f = 0.20 (PE / Et_2O 6 : 4)] and **5b** [65%; R_f = 0.45 (PE / Et_2O 1 : 1)] were isolated from diprotected epoxides **1a** and **1b**, while in the case of monoprotected epoxide **1d** only decomposition of substrate was observed.

5a: ^1H NMR: 1.31 (d, J 7.2 Hz, 3 H, *Me*CH), 2.12 (app sextuplet, J 5.5 Hz, 1 H, C*H*CH_2), 2.89 [dq, J 4.9 (d) & 7.1 (q) Hz], 3.68 (app d, J 5.3 Hz, 2 H, CHC*H*$_2$O), 3.73 - 3.86 (m, 3 H, CHC*H*$_2$O & C*H*OH), 3.80 (s, 3 H, *Me*O), 4.52 (s, 2 H, C*H*$_2$Ar), 4.60 (s, 2 H, C*H*$_2$Ph);,4.71 (s, 2 H, C*H*$_2$OCH$_2$Ar);,4.76 (s, 2 H, C*H*$_2$OBzl); 6.86 - 6.91 (m, 2 H, Ar*H*), 7.24 - 7.36 (m, 7 H, Ar*H*).

5b: ^1H NMR: 1.05 - 1.06 (m, 21 H, 3 x *Me*$_2$C*H*Si), 1.41 (d, J 7.2 Hz, 3 H, *Me*CH), 2.15 - 2.28 (m, 1 H, C*H*CH_2), 3.04 [dq, J 6.1 (d) & 7.1(q) Hz], 3.77 (s, 3 H, *Me*O), 3.94 - 3.99 (m, 1 H, C*H*OH), 3.96 & 4.07 (AB part of an ABX system, J 10.2 & 4.5 & 4.4 Hz, 2 H, C*H*$_2$O), 4.14 & 4.24 (AB part of an ABX system, J 9.5 & 5.8 & 6.1 Hz, C*H*$_2$O), 6.83 (s, 4 H, Ar*H*).

Reaction of epoxide 1b with trimethylsilyl cyanide in the presence of diethylaluminum chloride. - Epoxide **1b** (0.15 mmol) was dissolved in dry toluene (1 ml) and added with trimethylsilyl cyanide (0.40 mmol) and 0.1 ml of a 1.8 M solution of diethylaluminum chloride in toluene (0.18 mmol). Stirring at rt was continued for 56 h, then water was added. Usual work-up (Et_2O) and chromatographic purification (PE : Et_2O 95 : 5, containing 0.1% Et_3N) afforded *O*-silylated cyanohydrin **10** (23%; R_f = 0.71) along with *O*-silylated chlorohydrin **11** (25%; R_f = 0.30).

10: ^1H NMR: 0.17 (s, 9 H, 3x *Me*Si), 1.03 - 1.06 (m, 21 H, 3 x *Me*$_2$C*H*Si), 1.35 (d, J 7.2 Hz, 3 H, *Me*CH), 2.25 (app sextuplet, J 5.8 Hz, 1 H, C*H*CH_2), 3.01 - 3.17 (m, 1 H, C*H*CN; J_d* 5.4 Hz), 3.73-4.28 (m, 5 H, 2 x C*H*$_2$OR & C*H*O), 3.77 (s, 3 H, *Me*O), 6.82 - 6.83 (m, 4 H, Ar*H*).

11: ^1H NMR: 0.16 (s, 9 H, 3 x *Me*Si), 1.04 - 1.06 (m, 2 1H, 3 x *Me*$_2$C*H*Si), 1.53 (d, J 6.7 Hz, 3 H,

*Me*CH), 2.32 (app sextuplet, J 5.7 Hz, 1 H, C*H*CH$_2$), 3.77 (s, 3 H, *Me*O), 3.81(app dd, J 1.3 & 6.2 Hz, 2 H, C*H*$_2$O), 3.89 & 4.12 (AB part of an ABX system, J 9.3 & 6.5 & 4.9 Hz, 2 H, C*H*$_2$O), 4.00 (app t, J 5.2 Hz, 1 H, C*H*O), 4.23 [dq, J 5.3 (d) & 6.7 (q) Hz, C*H*Cl], 6.82 (s, 4 H, Ar*H*).

Reaction of epoxide 1a with diethylaluminum cyanide. - Epoxide **1a** (0.10 mmol) was dissolved in dry CH_2Cl_2 (2 ml), cooled to -78°C, and added with 0.50 ml of a 1 M solution of diethylaluminum cyanide in toluene (0.50 mmol). Reaction mixture allowed to slowly reach rt and stirred at the same temperature for 2 days. 1 N NaOH was added (1 ml) and reaction mixture was subjected to usual work-up (Et_2O) to give, after chromatographic purification (PE / Et_2O, containing 0.1% of Et_3N), pure **5a** and **6a** (57% overall yield; regioisomeric ratio 94 : 6).

6a: ^{1}H NMR: 1.40 (d, J 6.2 Hz, 3 H, *Me*CH), 2.25 - 2.35 (m, 1 H, C*H*CH$_2$), 2.93 (dd, J 2.6 & 5.9 Hz, 1H, C*H*CN), 3.49 (d, J 3.8 Hz, 1 H, O*H*; disappeared after D_2O exchange), 3.56 - 3.86 (m, 4 H, 2 x C*H*$_2$O), 3.80 (s, 3 H, *Me*O), 3.98 - 4.06 (m, 1 H, C*H*OH), 4.52 - 4.84 (m, 8 H, C*H*$_2$OC*H*$_2$Ar & C*H*$_2$OC*H*$_2$Ph), 6.86 - 6.91 (m, 2 H, Ar*H*), 7.26 - 7.35 (m, 7 H, Ar*H*).

Reaction of epoxide 1a, b, e with diethylaluminum chloride in the absence of added salts. - Diprotected epoxide **1a** (0.13 mmol) was dissolved in dry Et_2O (2 ml), cooled to 0°C, and added with 0.2 ml of a 1.8 M solution of diethylaluminum chloride in toluene (0.36 mmol). After 40' at the same temperature, extensive decomposition of substrate was observed.

Diprotected epoxide **1b** (0.10 mmol) was dissolved in dry CH_2Cl_2 (1 ml), cooled to 0°C, and added with 80 µl of a 1.8 M solution of diethylaluminum chloride in toluene (0.15 mmol). After stirring overnight at room temperature, extensive decomposition of substrate was observed.

Diprotected epoxide **1e** was subjected to the same reaction described for **1b**; after stirring overnight at room temperature water was added and reaction mixture was worked up as usual. Chromatographic purification (PE / Et_2O 7 : 3, containing 0.1% of Et_3N) afforded chlorohydrin **7e** (Y = Cl) as the only product (75%). ^{1}H NMR: 1.05 - 1.07 (m, 21 H, 3 x SiC*HMe*$_2$), 1.58 (d, J 6.6 Hz, 3 H, *Me*CH), 2.02 - 2.12 [m, 1 H, C*H*(CH$_2$OR)$_2$], 2.05 (s, 3 H, *Me*CO), 2.52 (d, J 4.2 Hz, 1 H, O*H*), 3.71 - 3.82 (m, 1 H, C*H*OH), 3.81 & 3.89 (AB part of an ABX system, J 10.2 & 4.4 & 4.7 Hz, 2 H, C*H*$_2$OSi), 4.22 & 4.41 (AB part of an ABX system, J 11.2 & 7.5 & 4.8 Hz, 2 H, C*H*$_2$OAc), 4.33 [dq, J 4.8 (d) & 6.6 (q) Hz, 1 H, C*H*Cl). ^{13}C NMR: 11.93 (Si*C*), 17.95 (CH*Me*$_2$), 20.92 & 21.81 (*Me*CO & *Me*CH), 43.78 [*C*H (CH$_2$OR)$_2$], 61.46 (*C*HCl), 61.76 & 61.83 (*C*H$_2$OAc & *C*H$_2$OSi), 74.63 (*C*HOH), 170.90 (*C*=O).

Reaction of monoprotected epoxide 1d with zinc iodide. - Monoprotected epoxide **1d** (0.10 mmol) was dissolved in dry DME (1 ml), cooled to 0°C and added with ZnI_2 (0.25 mmol). After stirring 3 h at the same temperature, no reaction was observed.

Reaction of diprotected epoxides 1a, b with magnesium iodide. - A solution of the diprotected epoxide **1a** or **1b** (0.10 mmol) in dry toluene (2 ml) was cooled to -78°C and added with a ≈ 0.2 M MgI_2 solution in Et_2O / PhMe (0.20 mmol). After stirring 1 h at the same temperature, reaction mixture was allowed to reach room temperature and added with 1 ml of a 25% aqueous solution of Na_2SO_3. After usual workup and chromatographic purification (PE / Et_2O, containing 0.1% Et_3N), iodohydrins **7a** (Y = I) (87%) and **8a** (Y = I) (7%) were obtained from **1a**, while only iodohydrin **7b** (Y = I) (quantitative yield) was obtained from **1b**. Analytical and spectroscopic data for these iodohydrins have already been reported.[10]

Reaction of diprotected epoxide 1b with magnesium bromide. - A solution of **1b** (0.10 mmol) in dry Et_2O (2 ml) was cooled to -78°C and added with 26 mg of $MgBr_2{\cdot}Et_2O$ (0.10 mmol). Reaction mixture was

Table 7. Analytical data for some selected compounds.

	Formula	Calculated		Found			Formula	Calculated		Found	
		H%	C%	H%	C%			H%	C%	H%	C%
2a (R^4 = Me)	$C_{24}H_{34}O_6$	8.19	68.88	8.11	68.91	**4f**	$C_{25}H_{34}O_5$	8.27	72.44	8.26	72.66
2a (R^4 = Bu)	$C_{27}H_{40}O_6$	8.75	70.41	8.79	70.46	**4g**	$C_{24}H_{42}O_3Si$	10.41	70.88	10.50	71.01
2b (R^4 = Bu)	$C_{26}H_{48}O_4Si$	10.69	68.98	10.71	68.48	**4h**	$C_{26}H_{36}O_5$	8.47	72.87	8.45	72.99
2f (R^4 = Bu)	$C_{29}H_{44}O_6$	9.08	71.28	9.12	71.01	**4i**	$C_{25}H_{44}O_3Si$	10.54	71.37	10.56	71.36
2g (R^4 = Bu)	$C_{28}H_{52}O_4Si$	10.90	69.95	10.92	70.00	**5a** (Y = CN)	$C_{24}H_{31}NO_6$	7.27	67.11	7.30	66.99
2h (R^4 = Pr)	$C_{29}H_{44}O_6$	9.08	71.28	9.10	71.26	**5b** (Y = CN)	$C_{23}H_{39}NO_4Si$	9.32	65.52	9.26	66.02
2i (R^4 = Pr)	$C_{28}H_{52}O_4Si$	10.90	69.95	10.88	69.66	**7b** (Y = Cl)	$C_{22}H_{39}ClO_4Si$	9.12	61.30	9.06	61.75
4a	$C_{23}H_{30}O_5$	7.82	71.48	7.76	71.36	**7d** (Y = Cl)	$C_{15}H_{33}ClO_3Si$	10.24	55.44	10.18	55.10
4b	$C_{22}H_{38}O_3Si$	10.12	69.79	10.09	69.79						

allowed to reach room temperature and stirred at the same temperature for 2 days. Saturated aqueous NH_4Cl was added and the reaction mixture was subjected to usual workup and chromatographic purification (PE / Et_2O 8 : 2) to give bromohydrins **7b** (Y = Br) (60%) and **8b** (Y = Br) (7%), along with a substantial amount of ketone **12** (27%). Analytical and spectroscopic data for these bromohydrins and the ketone have already been reported.[10]

Reaction of diprotected epoxide 1b with diethylamine hydrochloride in the presence of diethylaluminum chloride. - Diethylamine hydrochloride (0.30 mmol) was suspended in dry CH_2Cl_2 (2 ml) and added with 80 µl of a 1.8 M solution of Et_2AlCl in toluene (0.15 mmol) at room temperature. After ageing at the same temperature for 15', reaction mixture was cooled to 0°C and a solution of **1b** (0.10 mmol) in dry CH_2Cl_2 (2 ml) was added. After stirring 20 h at room temperature, water was added. Usual workup and chromatography afforded chlorohydrins **7b** (Y = Cl) (80%) and **8b** (Y = Cl) (6%).

7b: ^{1}H NMR: 1.04 - 1.08 (m, 21 H, 3 x SiC*HMe*$_2$), 1.60 (d, J 6.7 Hz, 3 H, *Me*CH), 2.25 [app sextuplet, J 5.4 Hz, 1 H, C*H*(CH$_2$OR)$_2$], 2.72 (d, J 4.8 Hz, 1 H, O*H*), 3.77 (s, 3 H, *Me*O), 3.80 - 3.88 (m, 1 H, C*H*OH), 3.89 & 3.99 (AB part of an ABX system, J 10.1 & 4.9 & 4.5 Hz, 2 H, C*H*$_2$O), 4.10 & 4.23 (AB part of an ABX system, J 9.3 & 6.5 & 5.8 Hz, 2 H, C*H*$_2$O), 4.40 [dq, J 5.3 (d) & 6.7 (q) Hz, 1 H, C*H*Cl), 6.83 (s, 4 H, Ar*H*). ^{13}C NMR: 11.82 (Si*C*), 17.88 (CH*Me*$_2$), 21.75 (*Me*CH), 44.08 [*C*H (CH$_2$OR)$_2$], 55.68 (*C*HCl), 61.79 & 62.18 (2 x*C*H$_2$O), 65.75 (*Me*O), 75.25 (*C*HOH), 114.60 & 115.30 (Ar*C*H), 152.80 & 154.00 (Ar*C*).

8b: ^{1}H NMR: 1.07 - 1.08 (m, 21 H, 3 x SiC*HMe*$_2$), 1.34 (d, J 6.2 Hz, 3 H, *Me*CH), 2.43 - 2.60 [m, 1 H, C*H*(CH$_2$OR)$_2$], 3.52 (d, J 4.2 Hz, 1 H, O*H*), 3.77 (s, 3 H, *Me*O), 3.84 - 4.22 (m, 6 H, 2 x C*H*$_2$O & C*H*OH & C*H*Cl), 6.83 (s, 4 H, Ar*H*).

Reaction of monoprotected epoxide 1d with diethylamine hydrochloride or hydrobromide in the presence of titanium tetraisopropoxide. - Diethylamine hydrobromide (0.80 mmol) was added at room temperature to a solution of (*i*-PrO)$_4$Ti (0.40 mmol) in dry CH_2Cl_2 (2 ml) and the mixture was stirred at the same temperature for 30'. A solution of **1d** (0.27 mmol) in dry CH_2Cl_2 (3 ml) was added and stirring continued for 20 h, then an aqueous solution of tartaric acid was added. Usual workup and chromatography afforded bromohydrin **7d** (Y = Br) (88%) as the only detectable product. Analytical and spectroscopic data for this bromohydrin have already been reported.[10]

When diethylamine hydrochloride was used instead of hydrobromide, refluxing for 10 h was required in order to drive the reaction to completion. Chlorohydrin **7d** (Y = Cl) (71%) was obtained as the only detectable product. ^{1}H NMR: 1.03 - 1.10 (m, 21 H, 3 x C*HMe*$_2$), 1.59 (d, J 6.7 Hz, 3 H, *MeCH*), 1.89 - 2.01 [m, 1 H, C*H*(CH$_2$OR)$_2$], 3.84 - 3.89 (m, 5 H, C*H*$_2$OSi & C*H*$_2$OH & C*H*OH), 4.33 [dq, J 4.4 (d) & 6.7 (q), 1 H, C*H*Cl]. ^{13}C NMR: 11.82 (*C*HSi), 17.97 (*Me*$_2$CH), 21.81 (*Me*CH), 45.34 [*C*H(CH$_2$OR)$_2$], 61.69 (*C*HCl), 62.70 & 63.72 (*C*H$_2$OSi & *C*H$_2$OH), 75.13 (*C*HOH).

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