Chiral Organometallic Reagents, Part 26[+]

Highly Enantiomerically Enriched α-Haloalkyl Grignard Reagents

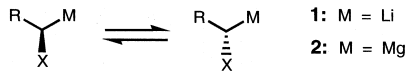
Reinhard W. Hoffmann,* Peter G. Nell, Roland Leo, and Klaus Harms**[a]**

Abstract: α-Chloro- and α-bromoalkyl Grignard reagents **11** and **30** with >97% *ee* (enantiomeric excess) were generated by a sulfoxide/magnesium exchange reaction from the enantiomerically and diastereomerically pure sulfoxides **25** and **27**. The resulting α-haloalkyl Grignard reagents are configurationally stable at −78°C. Racemization sets in at or above −60°C, especially when the solution contains bromide ions. In the absence of halide ions, the configurational stability extends up to −20°C, when chemical decomposition commences.

Keywords: carbenoids · Grignard reagents · racemization

Introduction

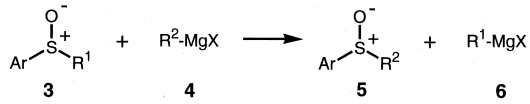
α-Heterosubstituted organolithium compounds **1** are chiral d[1] synthons. Of these, it is mainly the α-oxygenated and α-amino-substituted representatives which are used in stereoselective synthesis,[2] since these compounds are configurationally stable at or above −78°C for extended periods of time (Scheme 1).



Scheme 1.

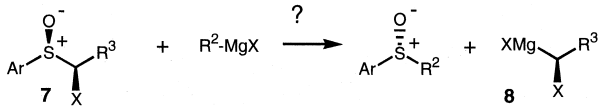
In contrast to the former, the configurational stability of α-arylthio- or α-arylseleno-alkyllithium compounds is so low[3] that racemization or epimerization occurs during the time needed to generate these lithium compounds and to trap them with electrophiles. There are indications[4, 5, 6] that the corresponding α-heterosubstituted Grignard reagents **2** would have a substantially higher configurational stability. Yet, there are hitherto no practical routes to generate species such as **2** in an enantiomerically pure form.[5, 6] We report here on the generation of α-haloalkylmagnesium compounds **2** (X = Br and X = Cl) with high enantiomeric purity by a sulfoxide/magnesium exchange reaction[7] from diastereomerically and enantiomerically pure α-haloalkyl sulfoxides. With the enantiomer-enriched α-haloalkylmagnesium compounds **2** in hand, we were able to obtain direct information on their rates of racemization under conditions relevant to the preparative use of such compounds.

The sulfoxide/magnesium exchange reaction has been known for a long time.[8] It has mainly been used to generate structurally modified sulfoxides **5**. Fewer examples concern the generation of Grignard reagents **6** (Scheme 2).[9, 10, 11]



Scheme 2.

The thermodynamic driving force for the reaction presumably stems from the higher stability of the generated Grignard reagent R^1MgX (**6**) over the one (**4**) used as the reagent. In this context, it is notable that sulfoxide/magnesium exchange reactions have been reported in which the R^1 residue is an α-haloalkyl moiety.[12, 13] This suggested a possible route for the generation of enantiomerically enriched α-haloalkyl Grignard reagents **8** from enantiomerically and diastereomerically pure α-haloalkyl sulfoxides **7**. This appeared highly attractive, since Satoh and Takano[13] had carried out several sulfoxide/magnesium exchange reactions at temperatures as low as −78°C (Scheme 3).



Scheme 3.

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[+] Part 25: See ref. [1].

[**] Correspondence regarding X-ray structure analysis.

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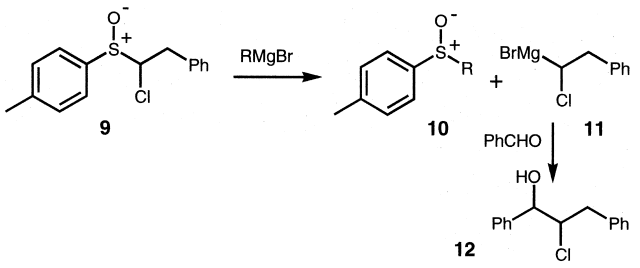
Results and Discussion

Initial experiments were carried out with the racemic diastereomer mixture of the sulfoxides **9**.[9] The sulfoxide/magnesium exchange reaction on **9** was tested with a number of Grignard reagents at low temperatures (Scheme 4).

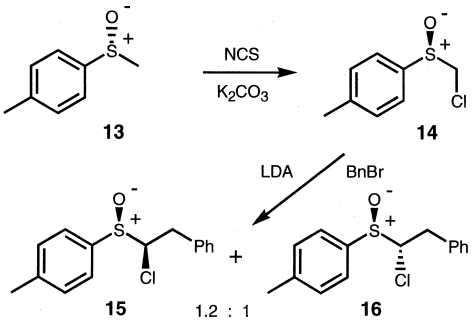


Scheme 4.

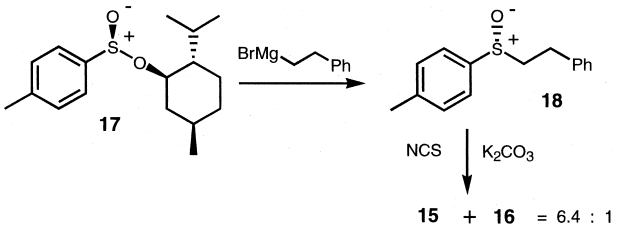
The reaction of **9** with ethylmagnesium bromide over a period of 5 h at $-78\,^{\circ}C$ led to the formation of 99% of the exchanged sulfoxide **10** (R = Et). The new Grignard reagent, *rac*-**11** was trapped with benzaldehyde to furnish 66% of the chlorohydrin **12** as a diastereomer mixture. Similar experiments indicated that isopropylmagnesium chloride is about equally as effective, whereas *tert*-butylmagnesium chloride did not initiate sulfoxide/magnesium exchange over a period of 14 h at $-78\,^{\circ}C$; however, it did at room temperature. Additional Grignard reagents, with which sulfoxide/magnesium exchange could be achieved at $-60\,^{\circ}C$ were $CH_2{=}CH$-MgX, C_6H_5MgX, and CH_3MgX.

Next, we addressed the synthesis of enantiomerically and diastereomerically pure α-chloroalkyl-sulfoxides **9**. Following earlier an precedent, (*R*)-methyl-*p*-tolyl-sulfoxide (**13**) was chlorinated with *N*-chlorosuccinimide (NCS) in the presence of potassium carbonate to give **14**. This reaction is known to proceed with essentially complete inversion of the configuration at the sulfur center (Scheme 5).[14]

Subsequent benzylation at the α-position[15] led to a 74% yield of a 1.2:1 mixture of the α-chloroalkyl sulfoxides **15** and **16**. Separation of the two diastereomers was possible by MPLC or HPLC on a reversed-phase column. The less abundant diastereomer crystallized. This allowed the assignment of its absolute and relative configuration as **16** by X-ray crystal structure analysis. It would be preferable, however, to have a route, which would give one of the diastereomers in high excess over the other one. Therefore, we tested an alternative route that employed the sulfoxide **18** (Scheme 6)



Scheme 5.



Scheme 6.

which was generated in a standard fashion[9] from the universal menthyl sulfinate **17**. Sulfoxide **18** was crystalline and had an *ee* of >99% by HPLC analysis. Chlorination of the latter with *N*-chlorosuccinimide and potassium carbonate furnished[9] a 6.4:1 mixture of **15** and **16**. We were able to crystallize **15** from this mixture (acetone) to eventually furnish 56% of diastereomerically pure **15** with >97% *ee* (determined by HPLC).

We then investigated the stereochemical course of the sulfoxide/magnesium exchange reaction on the sulfoxide **15**. The reaction with ethylmagnesium bromide was carried out in a two-compartment reaction vessel[16] at $-78\,^{\circ}C$. The formation of the sulfoxide **10** (R = Et) was monitored by TLC and the reaction was found to be complete in less than 5 min. Addition of three equivalents of benzaldehyde and an equivalent amount of Me_2AlCl[6] led to the formation of the chlorohydrin **12** in 77% yield. The chlorohydrins were formed with high simple diastereoselectivity as a 90:10 diastereomer mixture. In order to determine the enantiomeric excess of the chlorohydrins, the latter were converted to the epoxides **20** in 90% yield (*cis*/*trans* 88:12). By the use of $[Eu(hfc)_3]$ (hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate) as a chiral shift reagent, the enantiomeric purity of the *cis*-epoxide **20** was shown to be $93 \pm 3\%$ (Scheme 7).[6]

This finding established that enantiomerically enriched α-chloroalkyl Grignard reagents **11** can be generated by the sulfoxide/magnesium exchange reaction and that these Grignard reagents are configurationally stable for at least 3 h at temperatures below $-60\,^{\circ}C$.

Moreover, the sulfoxide **19** formed in the sulfoxide/magnesium exchange reaction was isolated in 86% yield and 97% *ee* (HPLC) ($[\alpha]_D^{22} = +198$ ($c = 1.00$, acetone); ref.:[9]: $[\alpha]_D^{25} = +202.6$). Since the absolute configuration of the starting sulfoxide **15** is known (see above), the optical rotation of the sulfoxide **19** obtained establishes that the sulfoxide/magnesium exchange reaction proceeded as expected with

Abstract in German: *α-Chlor- und α-bromalkyl Grignard Reagenzien **11** und **30** mit >97% ee wurden durch eine Sulfoxid/Magnesium-Austauschreaktion aus enantiomeren- und diastereomerenreinen Sulfoxiden **25** und **27** freigesetzt. Die so entstandenen α-Haloalkyl-Grignard-Reagenzien sind bei −78°C konfigurativ stabil. Eine Razemisierung setzt oberhalb von −60°C ein, besonders dann, wenn Bromid-Ionen zugegen sind. In Abwesenheit von Halogenid-Ionen reicht die konfigurative Stabilität bis etwa −20°C, der Zersetzungstemperatur solcher Reagenzien.*

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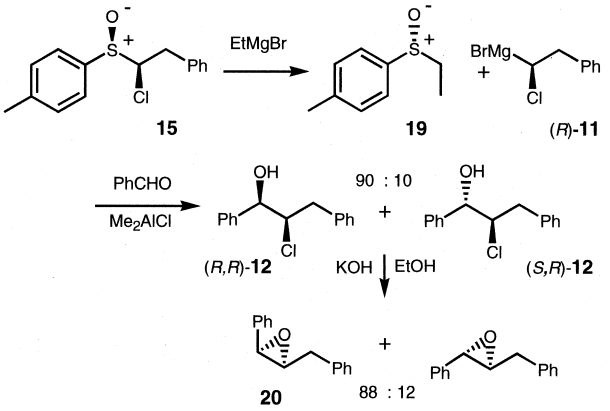
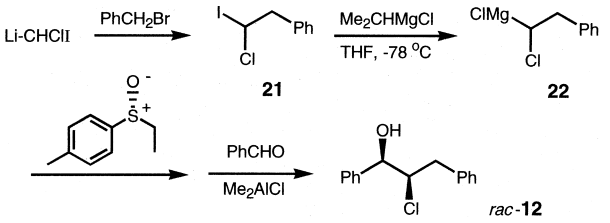


Scheme 7.

inversion of configuration at the stereogenic sulfoxide center. Finally, as the absolute configuration of the epoxide **20** is also known,[6] these findings establish that the sulfoxide/magnesium exchange proceeded with retention of configuration at the chlorine-bearing carbon atom.

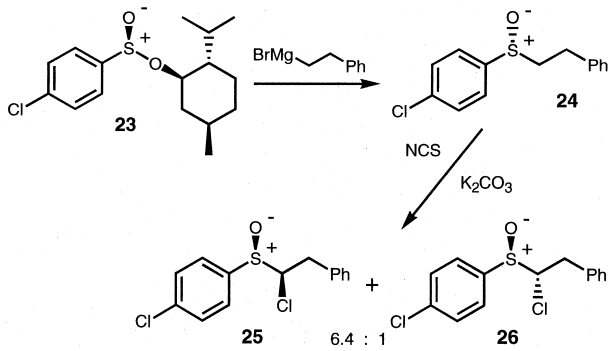
This statement is only valid if other mechanistic scenarios can be excluded. For instance, the α-chloroalkyl Grignard reagents **11** could be thought to racemize rapidly at −78 °C, and, in the presence of one equivalent of the chiral sulfoxide **9**, diastereomeric complexes could be formed, in which the combination of (*R*)-**19** and (*R*)-**11** might greatly predominate. To exclude this possibility, the following set of experiments was carried out: Racemic 1-chloro-1-iodo-2-phenylethane (*rac*-**21**) was prepared by benzylation of chloroiodomethyllithium (Scheme 8).[17, 18]



Scheme 8.

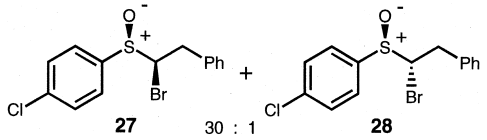
Treatment of **21** with *i*PrMgCl at −78 °C in THF for two hours[19] generated the racemic reagent **22** by a chemoselective iodine/magnesium exchange reaction. One equivalent of the (*R*)-sulfoxide **19** was added and, after stirring for 10 min at −78 °C, the mixture was quenched by the addition of benzaldehyde/Me_2AlCl. This resulted in the formation of the chlorohydrin **12** as a racemate in 94% yield. This clearly shows that the presence of the chiral sulfoxide does not affect the stereochemical course of the overall reaction sequence.

These results establish that the α-chloroalkyl Grignard reagent **11** of high enantiomeric purity can be generated by a sulfoxide/magnesium exchange reaction on enantiomerically and diastereomerically pure α-chloroalkyl-sulfoxide **15** (and probably also on **16**). As the purification of **15** by multiple crystallizations was tedious and implied loss of material, we wanted to use a sulfoxide system which, we hoped, would have a higher tendency to crystallize. We envisaged that this would apply to the *p*-chlorophenyl sulfoxides **25** and **26**. The precursor *p*-chlorophenyl sulfoxide **24** was generated from the menthyl sulfinate[20] **23** in 82% yield. Chlorination as before furnished a 6.4:1 mixture of the α-chloroalkyl sulfoxides **25** and **26** (Scheme 9).



Scheme 9.

Unfortunately, three recrystallizations were required in order to reach enantiomerically and diastereomerically pure **25**, in yields which did not exceed 55%. The structure of the (*R*,*R*)-**25** diastereomer was secured by X-ray crystal structure analysis. The precursor sulfoxide **24** could also be converted into the α-bromoalkyl sulfoxides **27** and **28** by bromination in



the presence of silver nitrate,[21] which prevented racemization. The sulfoxides **27** and **28** were generated in a ≈30:1 ratio. Chromatography, followed by crystallization from acetone, furnished enantiomerically and diastereomerically pure **27** (44%), the structure of which was again secured by X-ray structure analysis.

The sulfoxide/magnesium exchange on the α-chloroalkyl-sulfoxide **25** was carried out as before with ethyl magnesium bromide followed by trapping with benzaldehyde/dimethylaluminum chloride, to furnish 99% of the sulfoxide **29** with 99% *ee*. Chlorohydrins **12** were obtained in 56% yield as a 94:6 diastereomer mixture. After conversion to the epoxide **20**, the latter showed an *ee* of >98% (Scheme 10).

The α-chloroalkylmagnesium *chloride* **22** could be generated in similar manner by treatment of the α-chloroalkyl sulfoxide **25** with ethylmagnesium chloride (Scheme 11). Grignard reagent **22** was used to establish the stereochemistry of further transformations: trapping of (*R*)-**22** with trifluoroiodoethane generated 1-chloro-1-iodo-2-phenylethane (**21**) in 74% yield. The latter, on reaction with isopropylmagnesium chloride regenerated the Grignard reagent (*R*)-**22**. This was evident from trapping with benzaldehyde/dimethylaluminium chloride, followed by conversion of the chlorohydrins to the epoxide **20**. The latter was obtained in >97% *ee* as the enantiomer shown in Scheme 11.

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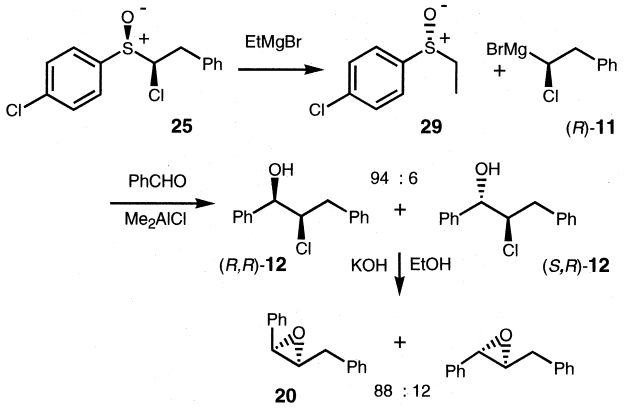
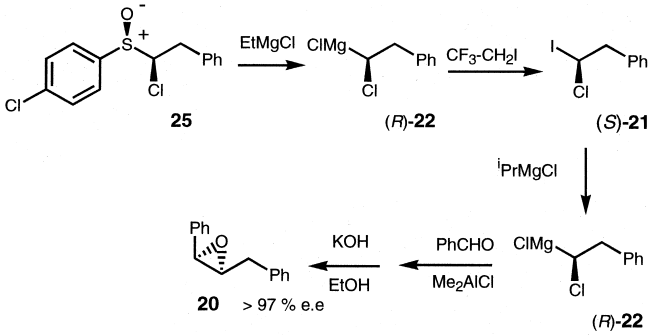


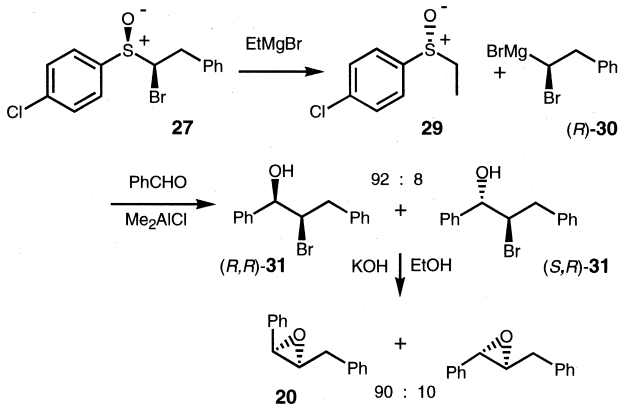
Scheme 10.



Scheme 11.

This indicates that both the trapping of the Grignard reagent **22** with trifluoroiodoethane[22] and the iodine/magnesium exchange reaction on **21** proceeded without significant loss of stereochemical integrity. Since these two steps proceed with overall retention of configuration, it is tempting to assume that each of these steps occurs with retention of configuration.

Finally, the α-bromoalkyl Grignard reagent **30** was generated from the α-bromoalkyl sulfoxide **27** (Scheme 12): the bromohydrins **31** were obtained as a 92:8 mixture of diastereomers. Upon closure to the epoxides, the resulting **20** had an *ee* of merely 85% despite the fact that the starting sulfoxide **27** had an *ee* of 99%, which was reflected in the enantiomeric purity of the coproduct, sulfoxide **29** (99% *ee*, HPLC). Apparently, the α-bromoalkyl Grignard reagent has suffered partial racemization under the reaction conditions used. We ascribed this racemization to a nucleophilic substitution at **30** by an external bromide[11, 23, 24] that is present as a result of the use of ethylmagnesium *bromide*. Indeed, when the reaction was repeated with ethylmagnesium *chloride*, the bromohydrin **31** obtained in a 96:4 diastereomer ratio gave, on treatment with potassium hydroxide, the epoxide *cis*-**20** with an *ee* of 97%.



Scheme 12.

Configurational stability of 1-chloro-2-phenylethylmagensium compounds: The foregoing results proved that the α-chloroalkyl and the α-bromoalkyl Grignard reagents **11** and **30** can be generated at $-78\,^{\circ}C$ in a highly enantiomerically enriched form. This is also valid for the corresponding α-phenylthio-alkyl Grignard reagent.[25] Information on the configurational stability of such Grignard reagents is a key prerequisite for their application in stereoselective synthesis. We therefore explored the limits of the configurational stability of the α-chloroalkyl Grignard reagent **11**. The latter has been generated with 1.3 equivalents of the starting Grignard reagent with respect to the sulfoxide **15** in the sulfoxide/magnesium exchange reaction. The resulting α-chloroalkyl Grignard reagent **11** was trapped with benzaldehyde/dimethylaluminium chloride and the yield of the resulting chlorohydrins was recorded (Table 1). The *syn*/*anti* ratio of the chlorohydrins—though not of immediate interest in the present context—is also given in Table 1.[18] The chlorohydrins **12** were converted to the epoxides **20** and the *ee* values of the major *cis*-epoxide are listed in the last column of the table.

Table 1. Racemization studies of the Grignard reagent **11**.

Entry	Grignard reagent (1.3 equiv)	Reaction T [°C]	t [min]	Chlorohydrin **12** yield [%]	*syn*/*anti*	*ee* [%][a]
1	EtMgBr	−50	15	70	89:11	64
2	EtMgCl	−50	15	69	91:9	89
3	iPr$_2$Mg	−50	15	83	84:16	92
4	EtMgBr	−50	5	71	89:11	91
5	EtMgBr	−50	10	48	91:9	78
6	EtMgBr	−50	20	70	87:13	60
7	EtMgBr	−78	15	56	94:6	93
8	EtMgBr	−40	15	58	84:16	17
9	iPr$_2$Mg	−50	60	56	77:23	93
10	iPr$_2$Mg	−40	15	62	84:16	94
11	iPr$_2$Mg	−30	15	46	77:23	92
12	iPr$_2$Mg	−20	15	48	69:31	91
13	iPr$_2$Mg + 1 equiv MgBr$_2$	−50	15	84	89:11	88
14	iPr$_2$Mg + 2 equiv MgBr$_2$	−50	15	88	91:9	84
15	iPr$_2$Mg + 1 equiv MgI$_2$	−50	15	60	96:4	15

[a] Determined at the stage of epoxide **20**.

Given the arbitrarily chosen temperature of $-50\,^{\circ}C$, it can be seen that racemization is already occurring at this temperature. The extent of racemization depends on the nature of the Grignard reagent used for the sulfoxide/magnesium exchange: the least racemization occurs with diisopropylmagnesium while the highest is with ethylmagnesium bromide (see Table 1; entries 1–3). Racemization with ethylmagnesium bromide was followed for periods of 5–20 min at $-50\,^{\circ}C$ (Table 1; entries 1 and 4–6): racemization of **11** is minimal at

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−78 °C and almost complete after 15 min at −40 °C (Table 1; entries 7 and 8). When the α-chloroalkyl Grignard reagent **11** is generated from **15** with diisopropylmagnesium, there appears to be some initial racemization of <10%; however, **11**, generated in this manner, is configurationally stable for 15 min at temperatures ranging up to −20 °C, above which decomposition occurs (Table 1; entries 9–12). The addition of magnesium bromide induces racemization (Table 1; entries 13 and 14) although the effect is not as marked as with ethylmagnesium bromide of similar concentration (see Table 1; entry 1). Magnesium iodide leads to rapid racemization (see Table 1; entry 15).

These observations suggest that the α-chloroalkyl Grignard reagent **11** is racemized by the influence of external halide ions, most likely in a S_N2-type halide exchange process, a mechanism that has already been suggested.[11, 23, 26]

From a preparative point of view, the following qualitative conclusions may be drawn: the α-chloroalkyl Grignard reagent **11** is configurationally stable in THF for periods of >15 min at temperatures up to −20 °C, provided that the solution does not contain magnesium halides. In the presence of magnesium *bromide* or if ethyl magnesium *bromide* is used as the reagent, there is significant racemization over a period of 15 min at −50 °C. With ethylmagnesium *chloride* at −50 °C, the racemization reaches merely 10% over 15 min. At −60 °C or below, racemization of the α-chloroalkyl Grignard reagent **11** remains slow—if it is occurring at all—irrespective of the way **11** has been generated.

Experimental Section

All temperatures quoted are not corrected. Reactions with organometallic compounds were carried out in dried solvents under nitrogen or argon. ^{1}H NMR, ^{13}C NMR: Bruker ARX-200, AC-300. Flash chromatography: silica gel 60 (40–63 μm; E. Merck AG, Darmstadt). Preparative HPLC: column with LiChrosorb RP18 (7 μm; Knauer, Berlin).

(*S*-*R*,1-*R*) and (*S*-*R*,1-*S*)-*p*-Tolyl-1-chloro-2-phenylethyl sulfoxide (15 and 16): A solution of *n*-butyllithium in hexane (2.05 M, 6.3 mL, 13 mmol) was added dropwise at −20 °C to a solution of diisopropylamine (1.32 g, 13 mmol) in THF (20 mL). The mixture was stirred for 15 min at 0 °C and cooled to −78 °C. A solution of (−)-(*R*)-*p*-tolyl-chloromethyl-sulfoxide (**14**)[9] (1.90 g, 10 mmol) in THF (10 mL) was added dropwise. After further stirring for 30 min, benzyl bromide (2.22 g, 13 mmol) was added dropwise and stirred for a further 20 min at −78 °C. Saturated aqueous NH_4Cl solution (5 mL) was added and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (2 × 10 mL). The solution was dried over $MgSO_4$ and concentrated to give a 1.2:1 mixture of the diastereomeric sulfoxides **15** and **16** (2.05 g, 74%). The diastereomers were separated by preparative HPLC with methanol/water = 3:7.

Major diastereomer (−)-(*R*,*R*)-15: Colorless crystals from acetone; m.p. 77–78 °C; $[\alpha]_D^{20} = -91.8$ ($c = 2.0$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3H), 2.73 (dd, $J = 14.3$ and 9.7 Hz, 1H), 3.64 (dd, $J = 14.3$ and 4.5 Hz, 1H), 4.68 (dd, $J = 9.8$ and 4.5 Hz, 1H), 7.23–7.37 (m, 7H), 7.59 (d, $J = 8.2$ Hz, 2H), cf. the data in ref. [9]; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 21.5, 37.1, 76.5, 125.8, 127.4, 128.8, 129.5, 129.6, 134.9, 135.6, 142.5.

Minor diastereomer (*S*,*R*)-16: m.p. 62 °C (acetone). The structure was secured by X-ray crystal structure analyses; see below.

Alternative method: To a solution of (+)-(*R*)-*p*-tolyl-2-phenylethyl sulfoxide (**18**)[9] (1.22 g, 5.0 mmol) in anhydrous dichloromethane (10 mL), were added potassium carbonate (400 mg) and subsequently *N*-chlorosuccinimide (1.32 g, 10.0 mmol). The suspension was stirred for five days. Diethyl ether (50 mL) was added and the solution was washed with 4% aqueous sodium iodide solution (50 mL) and 10% aqueous sodium thiosulfate solution (50 mL). The organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate 4:1) furnished a 6.4:1 mixture of **15** and **16** (1.02 g; 73%). Recrystallization from acetone gave enantiomerically and diastereomerically pure **15** (781 mg; 56%).

(1*R*,2*R*)-1,3-Diphenyl-2-chloro-1-hydroxypropane (12): In the top compartment of a two-compartment reaction vessel,[16] was placed a solution of (−)-(*R*,*R*)-*p*-tolyl-1-chloro-2-phenylethyl-sulfoxide (**15**, 97% *ee*, 50.0 mg, 0.18 mmol) in anhydrous THF (3 mL). The lower compartment was charged with a solution of ethylmagnesium bromide in THF (0.11 M, 2.28 mL). After cooling to −78 °C, the top solution was slowly added to the lower compartment. After 2 h, a precooled mixture of a solution of benzaldehyde (31.8 mg, 0.30 mmol) in anhydrous THF (2 mL) and dimethylaluminum chloride in hexane (1.0 M, 0.30 mL, 0.30 mmol) was added. The mixture was stirred for 12 h at −60 °C and then a saturated aqueous solution of NH_4Cl (1 mL) was added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic extracts were washed with water (2 × 5 mL) and brine (2 × 5 mL). The solution was dried (Na_2SO_4) and concentrated. Flash chromatography (petroleum ether/ethyl acetate 10:1 to methanol) furnished **12** (34 mg; 77%) as a colorless oil and (+)-(*R*)-*p*-ethyltolyl sulfoxide (**19;** 26 mg; 86%). $[\alpha]_D^{22} = +198$ ($c = 1.00$, acetone; lit.:[9] $[\alpha]_D^{25} =$ +202.6.). Enantiomeric purity by HPLC = 97%. Compound **12** was obtained as a 9.4:1 *syn*/*anti* mixture (by ^{1}H NMR spectroscopy). Elemental analysis (%) calcd. for $C_{15}H_{15}ClO$ (246.7): C 73.02, H 6.13; found: C 72.96, H 5.83.

(*R*,*R*)-12: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.78$ (br s, 1H), 2.93 (dd, $J =$ 14.2 and 9.0 Hz, 1H), 3.11 (dd, $J = 14.1$ and 5.2 Hz, 1H), 4.33 (ddd, $J = 9.0$, 5.4, and 5.4 Hz, 1H), 4.76 (d, $J = 5.5$ Hz, 1H), 7.17–7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 41.0$, 69.8, 75.8, 126.5, 128.15, 128.22, 128.49, 128.53, 129.2, 137.4, 140.2.

(*S*,*R*)-12: The following signals could be recorded: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.89$ (s, 1H), 3.10 (dd, 1H), 3.24 (dd, $J = 15.2$ and 6.7 Hz, 1H), 4.45 (ddd, $J = 8.7$, 5.6, and 5.6 Hz, 1H), 5.00 (d, $J = 4.4$ Hz, 1H), 7.17–7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.8$, 68.3, 76.8, 125.8. 125.9, 126.2, 126.6, 127.2, 128.1, 128.2.

Synthesis of epoxide 20 from the *syn*/*anti* mixture of 12: A solution of potassium hydroxide in ethanol (0.4 M, 0.4 mL, 0.16 mmol) was added dropwise at 0 °C into a solution of **12** (18 mg, 0.08 mmol) in ethanol (2 mL). After stirring for 12 h, ammonium chloride was added (≈100 mg). The solution was concentrated and the residue then partitioned between aqueous saturated NH_4Cl solution (5 mL) and *tert*-butyl methyl ether (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 10 mL) and the combined organic phases were washed with brine (2 × 5 mL). The organic phases were dried (Na_2SO_4) and concentrated to give epoxide **20** (15 mg, 90%) as a colorless oil. The *cis*/*trans* ratio was determined by ^{1}H NMR spectroscopy to be 88:12. For the spectral data of *cis*-**20** see ref. [6]. The enantiomeric purity of *cis*-**20** was determined to 93% *ee* as described in ref. [6].

trans-**20**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.01$ (d, $J = 5.8$ Hz, 2H), 3.20 (td, $J = 5.4$ and 2.0 Hz, 1H), 3.70 (d, $J = 2.0$ Hz, 1H), 7.20–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 38.7$, 58.5, 62.8, 125.6, 125.9, 126.7, 127.7, 128.4, 128.6, 129.0, 137.0, 137.4.

1-Chloro-1-iodo-2-phenylethane (21): A solution of *n*-butyllithium in hexane (1.49 M, 18.8 mL, 38.0 mmol) was added at −30 °C to a solution of hexamethyldisilazane (7.26 g, 45.0 mmol) in THF (15 mL). The resulting solution was placed in the top compartment of a two-compartment reaction vessel.[16] The lower compartment was charged with a solution of chloroiodomethane (5.29 g, 30.0 mmol) in THF (30 mL). After cooling to −105 °C the solution of the lithium hexamethyldisilazide was slowly added to the lower compartment. After 30 min, a precooled (−105 °C) solution of benzyl bromide (6.41 g, 37.5 mmol) in THF (5 mL) was added slowly over 30 min. The mixture was allowed to reach 0 °C over 10 h. Saturated aqueous NH_4Cl solution (25 mL), 20% aqueous $Na_2S_2O_3$ solution (5 mL), and petroleum ether (10 mL) were added. The phases were separated and the aqueous phase was extracted with petroleum ether (3 × 15 mL). The combined organic phases were washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation at 1.0 mbar (50 °C) furnished **21** (1.93 g; 24%) as a colorless liquid, which was stored over

copper powder. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.58$ (dd, $J = 14.4$ and 7.2 Hz, 1H), 3.69 (dd, $J = 14.4$ and 6.5 Hz, 1H), 5.82 (dd, $J = 6.9$ and 6.9 Hz, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.5$, 52.7, 126.1, 127.9, 129.4, 137.1; elemental analysis (%) calcd for C_8H_8ClI (266.5): C 36.05, H 3.03; found: C 36.20, H 3.13.

Reaction of 21 with isopropylmagnesium bromide in the presence of sulfoxide 19: A solution of isopropylmagnesium bromide in diethyl ether (1.74 M, 0.86 mL, 1.49 mmol) was added at $-78\,^\circ$C to a precooled solution of 1-chloro-1-iodo-2-phenylethane (**21**, 330 mg, 1.24 mmol) in THF (8 mL). After stirring for 1 h, a solution of (+)-(*R*)-ethyl-tolyl-sulfoxide (**19**; 94% *ee*; 313 mg, 1.86 mmol) in THF (1 mL) was added. After stirring for 10 min, a solution of benzaldehyde (158 mg, 1.49 mmol) and of dimethylaluminum chloride in hexane (1.0 M, 1.49 mL, 1.49 mmol) in THF (1 mL) were added. The mixture was stirred for 1 h at $-78\,^\circ$C followed by 30 min at $-40\,^\circ$C. Saturated aqueous NH_4Cl solution (2 mL) was added and the mixture was worked-up as described for **12** above to furnish 2-chloro-1-hydroxy-1,3-diphenylpropane (**12;** 288 mg; 94%) as a colorless oil. After conversion to **20** as described above, the enantiomeric excess was <1%.

(+)-(*R*)-*p*-Chlorophenyl-2-phenylethyl-sulfoxide (24): A solution of 2-phenylethylmagnesium bromide in diethyl ether (2.0 M, 17.5 mL, 35.0 mmol) was concentrated in a vacuum to dryness. The residue was taken up in toluene (20 mL) and cooled to $-60\,^\circ$C. A solution of (−)-(1*R*,2*R*,4*S*)-menthyl-(*S*)-*p*-chlorophenylsulfinate[20] (5.00 g, 15.8 mmol) in toluene (35 mL) was added dropwise. The mixture was allowed to warm to $-20\,^\circ$C and a saturated aqueous solution of NH_4Cl (10 mL) was added. Addition of aqueous hydrochloric acid (2 M, 5 mL) clarified the solution. The phases were separated and the aqueous phase was extracted with diethyl ether (6×25 mL). The combined organic phases were washed with water (2×20 mL) and brine (2×20 mL), dried ($MgSO_4$), and concentrated. The residue was crystallized from acetone (≈ 5 mL) to give **24** (3.43 g, 82%) as colorless crystals. For analyses a sample was recrystallized twice from acetone. M.p. 72 °C; $[\alpha]_D^{20} = +105.5$ ($c = 1.27$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.81-3.15$ (m, 4H), 7.16–7.32 (m, 5H), 7.48–7.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.0$, 58.3, 125.4, 126.8, 128.5, 128.8, 129.5, 137.2, 138.5, 142.3; elemental analysis (%) calcd for $C_{14}H_{13}ClOS$ (264.8): C 61.03, H 7.36; found: C 60.73, H 7.39.

(*R*,*R*)-*p*-Chlorophenyl-1-chloro-2-phenylethyl sulfoxide (25 and 26): Potassium carbonate (0.62 g) and *N*-chlorosuccinimide (2.02 g, 37.8 mmol) were added to a solution of (+)-(*R*)-*p*-chlorophenyl-2-phenylethyl-sulfoxide (**24**, 2.00 g, 7.55 mmol) in anhydrous dichloromethane (20 mL). After the mixture had been stirred for five days, diethyl ether (50 mL) was added. The solution was washed with aqueous sodium iodide solution (4%, 50 mL) and aqueous $Na_2S_2O_3$ solution (10%, 50 mL). The combined organic phases were washed with brine (2×10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (petroleum ether/ethyl acetate, 10:1) furnished a mixture of **25** and **26** (1.47 g, 65%) as a colorless solid. The diastereomer ratio was determined by ^{1}H NMR spectroscopy to be 6.4:1. Crystallization from acetone ($3\times$) furnished colorless **25** (m.p. 113 °C). $[\alpha]_D^{20} = -82.4$ ($c = 1.53$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.72$ (dd, $J = 14.3$ and 9.5 Hz, 1H), 3.64 (dd, $J = 14.3$ and 4.8 Hz, 1H), 4.68 (dd, $J = 9.5$ and 4.8 Hz, 1H), 7.22–7.37 (m, 5H), 7.52–7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.1$, 76.3, 127.1, 127.6, 128.8, 129.3, 129.5, 135.1, 138.4. The absolute and relative configuration was secured by X-ray crystal structure analyses (see below).

The sulfoxide/magnesium exchange reaction of **25** with ethylmagnesium bromide was carried out as described for **15**.

(*S*)-1-Chloro-1-iodo-2-phenylethane (21) and reaction with isopropylmagnesium chloride: The bottom compartment of a two-compartment reaction vessel[16] was charged with ethylmagnesium chloride (1.78 M in THF, 0.35 mL, 0.62 mmol) and THF (4 mL) and the top compartment was charged with a solution of (*R*,*R*)-*p*-chlorophenyl-1-chloro-2-phenylethyl sulfoxide (**25**, 155 mg, 0.52 mmol) in THF (4 mL). After the apparatus had been cooled to $-78\,^\circ$C, the top solution was allowed to drip into the lower compartment. A solution of CF_3CH_2I (154 μL, 1.56 mmol) in THF (4 mL) was precooled to $-78\,^\circ$C and added after 10 min. After the mixture had been stirred for 10 h at $-20\,^\circ$C, saturated aqueous NH_4Cl solution (0.5 mL), water (2 mL), and aqueous $Na_2S_2O_3$ solution (10%, 3 mL) were added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3×15 mL). The combined organic phases were washed with brine (2×15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (petroleum ether/ether, 19:1) furnished **21** (103 mg; 74%) as a colorless oil. The spectral data of **21** are given above.

A solution of isopropylmagnesium chloride in diethyl ether (2.0 M, 65 μL, 0.13 mmol) in THF (2 mL) was placed in the lower compartment of a two compartment reaction vessel.[16] The top compartment was charged with the solution of the chloroiodo compound obtained above (26 mg, 0.10 mmol) in THF (2 mL). After the apparatus had been cooled to $-78\,^\circ$C the upper solution was allowed to drip into the lower solution. After stirring for 10 min at $-78\,^\circ$C, the mixture was allowed to react with benzaldehyde (0.20 mmol) and dimethylaluminum chloride, as described above for **12**. The resulting 2-chloro-1-hydroxy-1,3-diphenylpropane was converted to the epoxide, as described above, to give **20** with >97% *ee*.

(−)-(*R*,*R*)-*p*-Chlorophenyl-1-bromo-2-phenylethyl sulfoxide (27): To a solution of (+)-(*R*)-*p*-chlorophenyl-2-phenylethyl sulfoxide (**24**, 99% *ee*, 1.103 g, 4.17 mmol) in acetonitrile (12 mL) was added silver nitrate (1.701 g, 10.0 mmol) and pyridine (2.09 mL). The mixture was cooled to $-40\,^\circ$C. A solution of bromine (800 mg, 5.01 mmol) in acetonitrile (4 mL) was added slowly to control the exothermic reaction. After stirring for 60 min at $-40\,^\circ$C, the suspension was filtered. The filtrate was concentrated and the residue was purified by flash chromatography (pentane/ethyl acetate, 10:1). ^{1}H NMR analyses showed the product to be a 30:1 mixture of **27** and **28**. Recrystallization from acetone furnished **27** (621 mg, 44%) as colorless crystals. M.p. 72 °C; $[\alpha]_D^{20} = -74.4$ ($c = 1.21$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.88$ (dd, $J = 14.4$ and 9.4 Hz, 1H), 3.79 (dd, $J = 14.4$ and 5.2 Hz, 1H), 4.74 (dd, $J = 9.5$ and 5.2 Hz, 1H), 7.11–7.65 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.7$, 69.2, 127.2, 127.6, 128.9, 129.2, 129.4, 135.8, 138.1, 138.3; elemental analysis (%) calcd for $C_{14}H_{12}BrOS$ (342.0): C 48.93, H 3.52; found: C 48.88, H 3.52. The absolute and relative configuration was secured by X-ray crystal structure analysis, see below.

(*R*,*R*)-2-Bromo-1-hydroxy-1,3-diphenyl-propane (31): (*R*,*R*)-*p*-chlorophenyl-1-bromo-2-phenylethyl-sulfoxide (**27**, 50 mg, 0.15 mmol) and ethylmagnesium chloride (2.0 M in THF, 95 μL, 0.19 mmol) were allowed to react as described for the synthesis of **12**, to furnish 2-bromo-1-hydroxy-1,3-diphenylpropane (**31;** 30 mg; 69%) as a 96:4 *syn*/*anti* mixture. The ^{13}C and ^{1}H NMR data corresponded to those given in the literature.[6]

Representative procedure to monitor the racemization of 11: the lower chamber of a two-compartment reaction vessel[16] was charged with a solution of diisopropylmagnesium (0.8 M in THF, 260 μL, 0.21 mmol) and THF (2 mL). The top chamber was charged with a solution of (*R*,*R*)-*p*-chlorophenyl-1-chloro-2-phenylethyl sulfoxide (**25**, 48 mg, 0.16 mmol) in THF (2 mL). The system was cooled to the given temperature at which the contents of the top chamber were allowed to flow into the bottom chamber. After the indicated time, a precooled solution of benzaldehyde (51 mg, 0.48 mmol) and a solution of dimethylaluminum chloride in hexane (1.0 M, 480 μL, 0.48 mmol) in THF (2 mL) were added. The mixture was stirred for 20 min at the given temperature, and then saturated aqueous NH_4Cl solution (0.5 mL) and water (3 mL) were added. The phases were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3×7 mL). The combined organic phases were washed with brine (2×7 mL), dried (Na_2SO_4), and concentrated. The chlorohydrins **12** were isolated by flash chromatography (petroleum ether/ethyl acetate, 19:1). They were converted to the epoxides **20** for the determination of the enantiomeric purity.

Crystallographic data for 16, 25, and 27: The data were collected with an Enraf Nonius CAD 4 diffractometer with monochromatic $Cu_{K\alpha}$ radiation at 213 K. The structures were solved by direct methods (SHELXS-97) and refined against F^2 values (SHELXL-97).

16: $C_{15}H_{15}ClOS$, $M_r = 278.78$: crystal dimensions: $0.4 \times 0.2 \times 0.1$ mm, monoclinic, space group $P2_1$, $a = 768.5(2)$, $b = 500.6(1)$, $c = 1858.0(5)$ pm, $\beta = 97.94(2)^\circ$, $U = 707.9(3)$ Å^3, $\rho_{calcd} = 1.308$ g cm^{-3} for $Z = 2$, $F(000) = 292$, $\mu = 3.637$ mm^{-1}, $R1 = 0.0700$ (for 1210 reflections with $I > 2\sigma(I)$, $wR2 = 0.2106$ (all 1782 unique data), Flack parameter (absolute structure) $= -0.02(6)$.

25: $C_{14}H_{12}Cl_2OS$, $M_r = 299.20$: crystal dimensions: $0.3 \times 0.3 \times 0.1$ mm, triclinic space group $P1$, $a = 901.8(1)$, $b = 967.7(1)$, $c = 997.4(1)$ pm, $\alpha = 71.56(1)$, $\beta = 62.99(1)$, $\gamma = 62.95(1)^\circ$, $U = 683.9(1)$ Å^3, $\rho_{calcd} = 1.453$ g cm^{-3} for $Z = 2$, $F(000) = 308$, $\mu = 5.562$ mm^{-1}, $R1 = 0.0437$ (for 5367 reflections with $I > 2\sigma(I)$, $wR2 = 0.1226$ (all 5411 unique data), Flack parameter $= -0.008(14)$.

27: $C_{14}H_{12}BrClOS$, $M_r = 343.66$: crystal dimensions: $0.3 \times 0.24 \times 0.12$ mm, triclinic, space group $P1$, $a = 911.2(1)$, $b = 976.0(1)$, $c = 997.6(1)$ pm, $\alpha =$

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84.68(1), $\beta = 62.89(1)$, $\gamma = 63.40(1)^\circ$, $U = 699.2(1)$ Å^3, $\rho_{calcd} = 1.632$ g cm^{-3} for $Z = 2$, $F(000) = 344$, $\mu = 7.031$ mm^{-1}, empirical absorption correction, $R1 = 0.0523$ (for 5042 reflections with $I > 2\sigma(I)$), $wR2 = 0.1495$ (all 5147 unique data), Flack parameter = 0.00(3).

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-102492 (**16**, K. Harms, private communication), CCDC-146741 (**25**) and CCDC-146742 (**27**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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