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The First Asymmetric Halogen/Metal-Exchange Reaction: Desymmetrization of Alcohols with Enantiotopic Bromoarene Substituents

Daniel Sälinger and Reinhard Brückner*[a]

Abstract: Desymmetrizations of the prochiral bis(bromoaryl)alcohols **1** and **4** were effected by treatment with iPr$_2$Mg and enantiomerically pure lithium alkoxides. The resulting arylmagnesium compounds were quenched with various electrophiles. The absolute and (if relevant) relative configurations of the resulting products were determined. The best *ee*/yield combination was obtained for the protonolysis furnishing monobromoalcohol (*R*)-**2** (53% *ee*, 51% yield). The latter was converted into (*R*)-orphenadrine, an antihistaminic and anticholinergic drug.

Keywords: asymmetric synthesis · bromine/magnesium exchange · desymmetrization · kinetic resolution · orphenadrine

Introduction

The generation of enantiomerically pure compounds by the desymmetrization of prochiral substrates is very appealing.[1] This is particularly true when the substrate is *meso*-configured because then it can be accessed by a "bidirectional synthesis".[2] Whatever (asymmetric) transformation effects such a desymmetrization, it may—yet need not—produce higher *ee* values than if the same transformation were used for resolving a racemic substrate kinetically.[3] In the following we reveal the first desymmetrizations of prochiral dihalides by asymmetric halogen/metal-exchange reactions.

For our prime substrate, the bis(bromoaryl)carbinol **1**, Scheme 1 depicts how four Br/Mg-exchange reactions are involved in the process. Under appropriate conditions (see below), monomagnesium compound *pre*-**2** arises mainly as the *R* isomer. This is because the *pro*-*S* bromoarene moiety of substrate **1** reacts faster [$\rightarrow$*pre*-(*R*)-**2**] than the *pro*-*R* moiety [$\rightarrow$*pre*-(*S*)-**2**]. Accordingly, the *ee* of monomagnesium compound *pre*-**2** should equal 100% $\times$ $(k_{fast}-k_{slow})/(k_{fast}+k_{slow})$—independent of time. However, we found that its *ee* increased with time. This must be the consequence of a second pair of Br/Mg-exchange reactions.[4] It consumes the major enantiomer *pre*-(*R*)-**2** of the monomagnesium compound more slowly (namely with rate constant k'_{slow}) than the minor enantiomer *pre*-(*S*)-**2** (which reacts with rate constant k'_{fast}). Functionalizing the resulting mixture of monomagnesium [*pre*-(*R*)- and some *pre*-(*S*)-**2**] and dimagnesium compounds (*pre*-**3**) with an electrophile at an appropriate point in time rendered substituted mono(bromoaryl)carbinols **2** preferentially as the *R* enantiomers; the corresponding difunctionalized diarylcarbinols **3** arose as side-products. Scheme 2 shows analogous desymmetrizing functionalizations of bis(bromoaryl)carbinol **4** without detail. While we consider substrates **1** and **4** essentially as model substrates, we are conscious of the importance of non-racemic diarylcarbinols **2** as intermediates for the preparation of biologically active compounds.[5] For this reason, we showed that compound (*R*)-**2** (E = H) can be carried on to the antihistaminic and anticholinergic drug (*R*)-orphenadrine[6] (see Scheme 8).

In principle transition-metal catalysts or metalating reagents other than organomagnesium compounds are suitable for desymmetrizing substrates like bis(bromoaryl)carbinols **1** or **4**. Nonetheless such reactions seem to have been barely studied: we are unaware of *any* previous desymmetrizing halogen/metal-exchange reactions of enantiotopic halide groups.[7]

As a start we chose Br/Mg-exchange reactions as our tool because they are slower than Br/Li-exchange reactions and can be accelerated by a ligand. The chemistry of iPrMgCl·LiX (X = Cl, OtBu)[8] or R$_2$Mg·LiCl (R = iPr, sBu)[9] developed by Knochel et al. or the reagents Et$_2$Mg·MOR (MOR = LiOtBu, KOMe, KOPh) from Richey's laboratory[10] illustrate this point. The assumption that mixtures of Grignard reagents or dialkylmagnesium compounds with

[a] Dipl.-Chem. D. Sälinger, Prof. Dr. R. Brückner
Institut für Organische Chemie und Biochemie
Universität Freiburg, Albertstr. 21, 79104 Freiburg (Germany)
Fax: (+49) 761-203-6100
http://www.chemie.uni-freiburg.de/orgbio/brueck/w3br/
E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de

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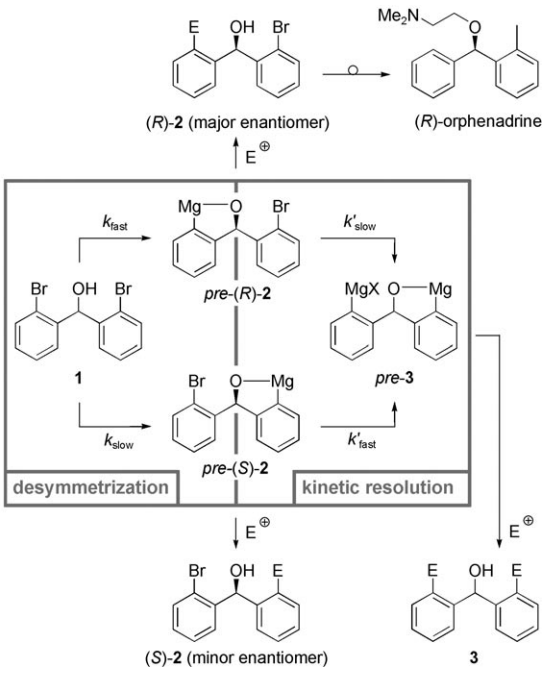
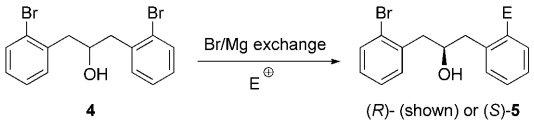


Scheme 1. Concept: Br/Mg-exchange reactions in prochiral dibromoalcohols—e.g., **1**—induced by treatment with iPr$_2$Mg and LiOR$_{enantiopure}$; products of subsequent electrophilic substitutions. The assignment of (*R*) and (*S*) to **2** is only appropriate under the proviso that substituent E has a lower Cahn–Ingold–Prelog priority than Br.

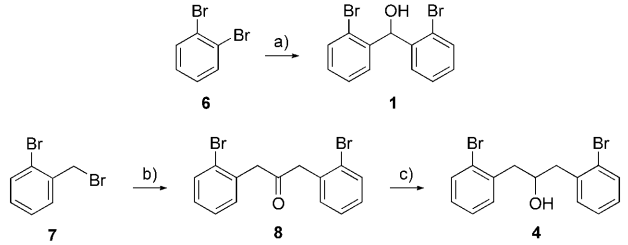
enantiomerically pure alkoxides or phenoxides—sufficiently strongly binding ones, that is, preferably chelating alkoxides or phenoxides—might undergo asymmetric Br/Mg-exchange reactions spurred our investigation. Enabling our substrates to "two-point binding" to the magnesiating reagent, we provided them with an OH group. We assumed that under the reaction conditions the latter would turn into an oxide ligand which would direct a RMg(OR*) counterpart intramolecularly to the transition state of the Br/Mg-exchange reaction. We employed dialkylmagnesium reagents for this purpose because Grignard reagents might be more inclined to undergo the Br/Mg-exchange step intermolecularly.



Scheme 2. Desymmetrization of prochiral alcohol **4** by the strategy of Scheme 1. The assignment of (*R*) and (*S*) to **5** is only appropriate under the proviso that substituent E has a lower Cahn–Ingold–Prelog priority than Br.

Results and Discussion

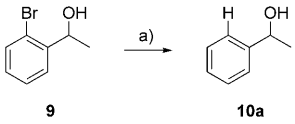
Syntheses of dibromoalcohols 1 and 4: Dibromoalcohol **1**[12,13] is accessible from 2-bromobenzaldehyde in at least 40% yield by a benzoin condensation and oxidation/benzilic acid rearrangement/decarboxylation[12] or in at least 34% yield by the addition of 2-bromophenylmagnesium bromide.[13] We improved the yield of the latter approach to 86% by making this Grignard reagent from 1,2-dibromobenzene (**6**) and iPrMgCl·LiCl (as described for a different context[8]) rather than Mg turnings (Scheme 3).[13] The chain-extended bis(bromoaryl)alcohol **4** (Scheme 3) was obtained from 2-bromobenzyl bromide (**7**) and diiron nonacarbonyl[14] via the known ketone **8**[11] (87% yield) and a subsequent reduction with $NaBH_4$ (96% yield). The syntheses of **1** and **4** were carried out on a 10 g scale.



Scheme 3. Syntheses of dibromoalcohols **1** and **4**. a) **6** (1.2 equiv), iPrMgCl·LiCl (1.1 equiv), THF, −15 °C, 4 h; 2-bromobenzaldehyde (1.0 equiv), 16 h; 86%. b) **7** (1.8 equiv), $Fe_2(CO)_9$ (1.0 equiv), toluene, 30 °C, 21 h; 87% (ref.:[11] 71%). c) $NaBH_4$ (1.1 equiv), AcOEt/MeOH 3:1, 0 °C, 3 h; 96%.

Ligand-accelerated Br/Mg-exchange reactions in a model alcohol: How to accelerate the desired kind of Br/Mg-exchange reaction was tested at room temperature using iPr$_2$Mg as the magnesiating reagent, the (*ortho*-bromophenyl)ethanol **9** as a model substrate, and diethyl ether as the solvent (Table 1). As desired, iPr$_2$Mg alone effected no Br/

Table 1. Reagent and ligand effects on the rate of Br/Mg-exchange reactions in model alcohol **9**. a) Reagent (in Et_2O) and ligand see Table, addition of **9** in Et_2O at 0 °C, 10 min; RT, 6 h; aq. NH_4Cl.



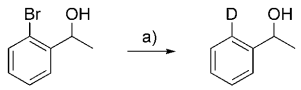
Entry	Reagent	Ligand (1.4 equiv)	Yield[a] [%]	
			9	**10a**
1		–	99	<1
2		TMEDA[b]	103	1
3		$LiO(CH_2)_2NMe_2$[c]	<1	96
4	iPr$_2$Mg (1.1 equiv)	$NaO(CH_2)_2NMe_2$[c]	20	71
5		$KO(CH_2)_2NMe_2$[c]	56	43
6		$MgIO(CH_2)_2NMe_2$[c]	91	<1
7		LiOPh[d]	3	68
8		LiO_2CtBu[d]	57	34
9		$LiNH\text{-}SO_2Ph$[d]	92	2
10	iPrMgCl (2.2 equiv)	$LiO(CH_2)_2NMe_2$[c]	101	<1
11[e]			97	3

[a] Determined by GLC analysis[16] of the crude product using biphenyl as an internal standard. [b] Tetramethylethylenediamine. [c] $HO(CH_2)_2NMe_2$ was deprotonated with nBuLi, NaH, KH, or MeMgI (each 1.0 equiv). [d] Deprotonation of the conjugated acid with nBuLi (1.0 equiv). [e] 2.8 equiv of $LiO(CH_2)_2NMe_2$ were used.

Mg exchange after 6 h (entry 1). No acceleration was observed in the presence of tetramethylethylenediamine (TMEDA; entry 2). This let sparteine[15] or related diamines appear as unlikely candidates for behaving differently. The Li salt of 2-(dimethylamino)ethan-1-ol sped up the Br/Mg exchange of substrate **9** considerably: after only 30 minutes, protonolysis delivered 96% of the bromine-free alcohol **10a** (entry 3). This let us consider enantiomerically pure chelating Li-alkoxides as prime ligands for the desymmetrizing Br/Mg-exchange reactions to be studied later on. Non-lithium alkoxides $MO(CH_2)_2NMe_2$ were inferior as ligands to $LiO(CH_2)_2NMe_2$ or prevented a Br/Mg exchange at all (entries 4–6). Lithium phenoxide also accelerated the Br/Mg-exchange reaction (entry 7), which suggested to screen enantiomerically pure Li-phenoxides for the desymmetrizing Br/Mg-exchange reactions to be described below. Less accelerating ligands were LiO_2CtBu (entry 8) and $LiNH\text{-}SO_2Ph$ (entry 9). As a comparison between entry 3 and entries 10 and 11 of Table 1 shows, the use of iPr_2Mg and $LiO(CH_2)_2NMe_2$ instead of *i*PrMgCl and $LiO(CH_2)_2NMe_2$ is mandatory for a Br/Mg exchange in **9**—as implied by the "two-point binding" concept mentioned above.

Deprotonation of model alcohol **9** by iPr_2Mg and $LiO(CH_2)_2NMe_2$ precedes the Br/Mg exchange under the proviso that the reactants are combined at −40 °C (Table 2, entry 2) rather than 0 °C (entry 1). This was shown by quenching the reaction mixture with deuteromethanol and determining the molecular mass of the resulting debrominated alcohol **10a** by GLC/MS: generated at −40 °C, **10a** was almost fully deuterated while it was only 82% deuterated when generated at 0 °C. This means, that at −40 °C iPr_2Mg and $LiO(CH_2)_2NMe_2$ deprotonate substrate **9** before the Br/Mg exchange takes place. This keeps the C–Mg bonds resulting from the substrate from undergoing protonolysis other than by the small fraction of protiomethanol in the deuteromethanol used as the quenching reagent. At 0 °C, however, Br/Mg exchange already occurs while some OH groups are still unaltered. This order of events subjects 18% of the initially formed C–Mg bonds to protonolysis. This led to a 18:82 mixture of protio- and deutero-**10a** after the persisting arylmagnesium intermediate was destroyed by adding deuteromethanol.

Table 2. Determination of the order of deprotonation vs. Br/Mg-exchange reaction in model alcohol **9**. a) iPr_2Mg (1.1 equiv) in Et_2O, $LiO(CH_2)_2NMe_2$ (1.4 equiv), addition of **9** in Et_2O at T_{add}, 10 min; RT, 30 min; MeOD (>99.5% D, 3.0 equiv).



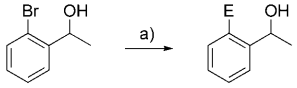
9 [D]-**10a**

Entry	T_{add} [°C]	Yield[a] [%]		D[b] [%]
		9	[D]-**10a**	
1	0	<1	96	82
2	−40	<1	101	96

[a] Determined by GLC analysis[16] of the crude product with biphenyl as internal standard. [b] Deuterium incorporation (determined by GLC/MS) in [D]-**10a**.

Our ability to establish the C–Mg bond in substrate **9** in the absence of intact OH groups allowed to scavenge the arylmagnesium intermediate with external electrophiles (Table 3) without losing sizable amounts of material through protonolysis (→**10a**). Formylation with DMF rendered aldehyde **10b** in 74% yield. Hydroxyalkylation with pivaldehyde gave alcohol **10c** in only 44% yield but with a diastereoselectivity (d.s.) of 92:8 in diethyl ether or in 90% yield albeit only with a d.s. of 62:38 in THF. Knochel et al. prepared this alcohol in a similar fashion [**9**, $iPr_2Mg{\cdot}LiCl$ (1.05 equiv), THF/dioxane 9:1, room temperature, 24 h; pivaldehyde; 90%, d.s. 50:50], but the Br/Mg-exchange reaction was slow and no diastereoselectivity occurred.[9] Cu-catalyzed alkylations with methyl iodide or allyl bromide converted the magnesiated substrate into compounds **10d** (85%) and **10e** (79%), respectively. Iodinolysis furnished 84% of iodoalcohol **10f**.

Table 3. Functionalizations other than deuteration (see Table 2) of model alcohol **9** after Br/Mg-exchange reaction. a) iPr_2Mg (1.1 equiv) in Et_2O, $LiO(CH_2)_2NMe_2$ (1.4 equiv), addition of **9** in Et_2O at −40 °C, 10 min; RT, 30 min; addition of electrophile.



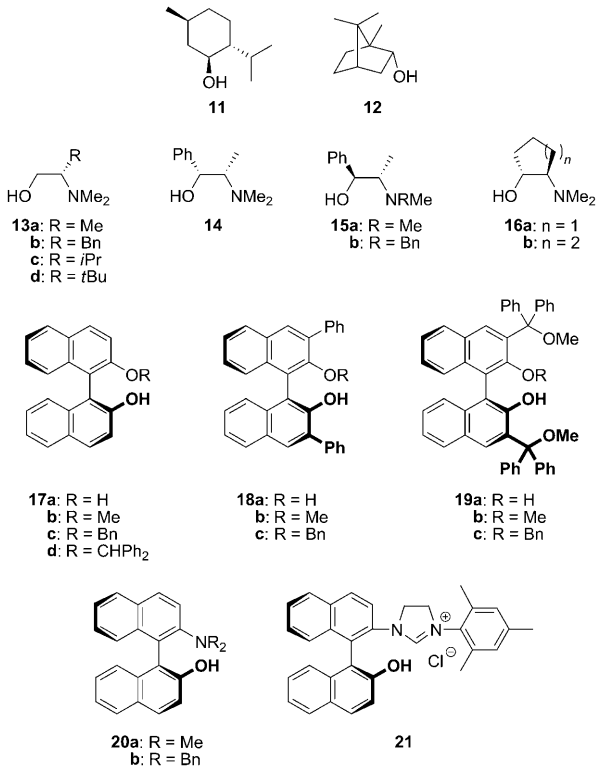
9 **10b-f**

10b: E = CHO
c: E = CH(OH)*t*Bu
d: E = Me
e: E = CH_2–CH=CH_2
f: E = I

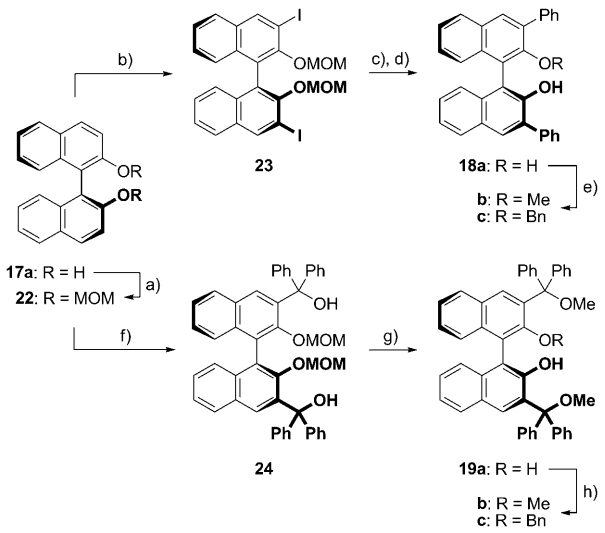
10	Electrophile, conditions	Yield[a] [%]
b[b]	DMF (1.6 equiv), 0 °C → RT, 13 h	74
c	*t*BuCHO (1.4 equiv), −70 °C → RT, 2.5 h	44, d.s. 92:8[c]
c[b]	*t*BuCHO (1.4 equiv), 0 °C → RT, 15 h	90, d.s. 62:38[c]
d	CuCN·2LiCl (10 mol%), MeI (1.6 equiv), 0 °C → RT, 15 h	85
e	CuCN·2LiCl (10 mol%), allyl bromide (1.4 equiv), 0 °C → RT, 1.5 h	79
f	I_2 (1.5 equiv) in THF, −20 °C, 5 min; RT, 10 min	84

[a] Isolated yield after flash chromatography. [b] Br/Mg exchange in THF. [c] Easily separated by flash chromatography.

Ligand syntheses: We studied 25 Li salts as ligands in our investigation. They were obtained from alcohols **11**–**16** or phenols **17**–**21** (Scheme 4) by deprotonation with a stoichiometric amount of *n*BuLi. Alcohols **11** and **12** as well as aminoalcohol **14** and (*S*)-2,2′-dihydroxy-1,1′-binaphthalene [(*S*)-BINOL (**17a**)] were purchased. Aminoalcohols **13a**,[17] **13b**,[18] **13c**,[19] **13d**,[20] **15a**,[21] **15b**,[22] **16a**,[23] and **16b**[24] were prepared according to literature procedures, and (*S*)-BINOL-monoethers **17b**[25,26] and **17c**,**d** as well.[26] NHC precursor **21** is an elaborated 2-amino-2′-hydroxy-1,1′-binaphthalene (NOBIN) and was obtained by our recently developed synthesis[27] in 55% overall yield, avoiding the lengthier previous synthesis.[28] The (*S*)-BINOL-based monoethers **18b** and **18c**, the equally (*S*)-BINOL-based triethers **19b** and **19c**, and (*S*)-*N*,*N*-dibenzyl-NOBIN (**20b**) are new



Scheme 4. Alcohols **11**–**16** and naphthols **17**–**21**, the Li salts of which were examined as a ligand in desymmetrizing Br/Mg exchange of prochiral alcohols **1** and **4**.



Scheme 5. Syntheses of ligands **18a**–**c** and **19a**–**c**. a) NaH (3.0 equiv), THF, 0°C, 1 h; RT, 1 h; MOMCl [$(MeO)_2CH_2$ (3.9 equiv), AcCl (3.0 equiv), $ZnBr_2$ (2.0 mol%), RT, 1 h], 0°C; RT, 4 h; 92% (ref.:[29] 100% with purified MOMCl). b) *n*BuLi (3.0 equiv), TMEDA (2.8 equiv), Et_2O, RT, 6 h; THF, 1 h; I_2 (3.1 equiv), −40°C; RT, 2 h; 84% (ref.:[29] 88% without TMEDA). c) $PhB(OH)_2$ (2.6 equiv), Na_2CO_3 (5.3 equiv), $[Pd(PPh_3)_4]$ (5.4 mol%), DME, H_2O, reflux, 8 h. d) Conc. H_2SO_4, THF/MeOH (5:3), RT, 21 h; 89% over the 2 steps. e) DIAD (1.1 equiv), PPh_3 (1.1 equiv), MeOH or BnOH (1.5 equiv), THF, RT, 25 h; 93%. f) *n*BuLi (3.1 equiv), TMEDA (3.1 equiv), Et_2O, T, 6 h; benzophenone (3.6 equiv) in THF, 0°C; RT, 14 h; 85% (ref.:[30] 95% without TMEDA). g) $HC(OMe)_3$ (9.0 equiv), conc. H_2SO_4 (0.50 equiv), CH_2Cl_2/MeOH (1:1), RT, 1.5 h; 94%. h) DIAD (1.1 equiv), PPh_3 (1.1 equiv), MeOH or BnOH (1.5 equiv), THF, RT 27 h; 86% (**19b**) or 77% (**19c**). MOM = MeO-CH_2; DIAD = diisopropylazodicarboxylate.

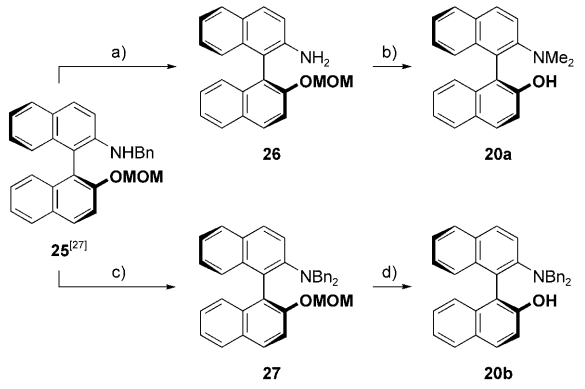
compounds. They were synthesized as detailed below—as were the known compounds **18a**[29] and **19a**[30] and, on a new route, the equally known compound[31] (*S*)-*N*,*N*-dimethyl-NOBIN (**20a**).

The syntheses of BINOL-ethers **18b**,**c** and **19b**,**c** began with the methoxymethylation of (*S*)-BINOL (**17a**) with in situ prepared[32] chloromethyl methyl ether (Scheme 5). This rendered 92% of the bis(methoxymethyl ether **22**.[29] Bis(*ortho*-lithiation) of **22** with *n*BuLi/TMEDA followed by iodination provided diiodide **23**[29] in 84% yield (in the absence of TMEDA, these steps furnished only 49% of **23** rather than 88% as reported[29]). A 1:2 Suzuki coupling between diiodide **23** and 2.6 equiv of $PhB(OH)_2$ followed by removal of the MOM groups through transacetalization with methanol/H_2SO_4 led to the phenylated binaphthol **18a** in 89% yield over the two steps. This was more efficient than the Suzuki route using the dibromide akin to **23** and twice as much $[Pd(PPh_3)_4]$ (→85% yield[29]) followed by a transacetalization (→ 89% yield[29]). Monomethylation or -benzylation of binaphthol **18a** under Mitsunobu conditions[26] provided the new BINOL-derived ethers **18b** and **18c**, respectively, in 93% yield in both cases.

The transformation of the bis(MOM ether) **22** of (*S*)-BINOL into the triethers **19b**,**c** (Scheme 5) began with a bis(*ortho*-lithiation) with *n*BuLi/TMEDA (see above) followed by a double hydroxyalkylation with benzophenone. The resulting dihydroxy-bisacetal **24**[30] (85% yield) was deprotected and reprotected at different positions in the presence of methanol, trimethylorthoformate, and H_2SO_4. This led to the disubstituted binaphthol **19a** in 94% yield, and therefore working better than described[30] for separate deprotection (aq. HCl, Δ) and reprotection (MeOH, trifluoroacetic acid) steps (74% yield[30] overall). Mitsunobu conditions[26] were again appropriate for effecting the monoalkylations leading to the triethers **19b** (86%) and **19c** (77%) selectively.

Our accesses to the *N*-alkylated (*S*)-NOBIN derivatives **20a** and **20b** started from *N*-benzyl-*O*-MOM-protected (*S*)-NOBIN (**25**; Scheme 6), which stemmed from a three-step synthesis from (*S*)-BINOL published recently (76% overall yield).[27] Debenzylation of **25** gave the primary amine **26** in 97% yield. It was carried on by a one-pot Eschweiler–Clarke methylation[34]/MOM ether deprotection sequence providing (*S*)-*N*,*N*-dimethyl-NOBIN (**20a**; 85% yield) in a different manner than originally reported.[31] Benzylation of the secondary amine **25** provided the *O*-protected (*S*)-*N*,*N*-dibenzyl-NOBIN **27**[33] in 91% yield. Cleavage of the acetal moiety delivered 85% of the new dibenzylaminoalcohol **20b**.

Ligand screening: The best conditions found in Et_2O for deprotonating the model alcohol **9** first (−40°C, 10 min) and

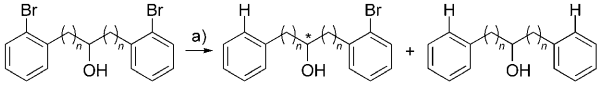


Scheme 6. Syntheses of ligands **20a** and **20b**. a) H_2 (1 atm), Pd/C (5.7 mol%), EtOAc, 60°C, 7 h; 97%. b) Aq. CH_2O, HCO_2H, reflux, 9 h; 85%. c) BnBr (1.6 equiv), K_2CO_3 (1.6 equiv), MeCN, reflux, 10 h; 91% (ref.:[33] ≧91%). d) Aq. HCl, MeOH, reflux, 7 h; 85%.

effecting the Br/Mg exchange thereafter (RT, 6 h) by treatment with a mixture of iPr$_2$Mg (1.1 equiv) and LiO-(CH$_2$)$_2$NMe$_2$ (1.4 equiv) were applied to the prochiral alcohols **1** and **4** with a single modification (Table 4): the achiral ligand LiO(CH$_2$)$_2$NMe$_2$ was substituted by an enantiomerically pure ligand, which was derived from each of the enantiomerically pure alcohols **11**–**16** and naphthols **17**–**21** and a stoichiometric amount of nBuLi. Each experiment was terminated by quenching with a satd. aq. solution of NH_4Cl. This allowed to quantify the yield of the monomagnesium derivative of substrates **1** or **4** by a GLC analysis of the yield of the corresponding protonation product, that is, **2a** or **5a**. The yields of the dimagnesium derivatives of substrates **1** or **4** were determined by GLC analogously, namely by determining the yield of the corresponding bromine-free alcohols **3a** or **28**. These data are not included in Table 4 since it suffices to summarize that the combined yields **1** + **2a** + **3a** or **4** + **5a** + **28** were usually between 90 and 100%; this implies that the material balance was usually fine. Work-up of the respective reaction mixture by flash chromatography on silica gel delivered the mentioned protonation products **2a** or **5a** in mixtures with dibromoalcohol **1** or with dibromoalcohol **4** and dibenzylmethanol (**28**), respectively. Thereupon their enantiomeric ratios could be assessed by chiral HPLC.

In essence the outcome of these experiments (Table 4) was the following: alcohol **1** was desymmetrized best in the presence of the monoalkylated BINOLates Li-**17c** (28% *ee*, entry 14), Li-**17b** (23% *ee*, entry 13), and Li-**17d** (19% *ee*, entry 15) or the NOBIN-derived naphthoxide Li-**21** (20% *ee*, entry 24). Alcohol **4** revealed lower highest *ee* values in the desymmetrization experiments, two-digit percentages resulting from the same group of ligands: BINOLate Li-**17b** → 17% *ee* (entry 13); BINOLate Li$_2$-**17a** → 15% *ee* (entry 12); NOBIN-derived naphthoxide Li-**21** → 15% *ee* (entry 24). It would be premature to attribute this difference to the greater conformational flexibility of the transition state of the Br/Mg exchange taking place in substrate **4** versus **1** although such an interpretation would be plausible.

Table 4. Desymmetrization of alcohols **1** and **4** in the presence of the oxyanions derived from the respective ligand **11**–**21** and an equimolar amount of nBuLi (best yields and highest *ee* values in gray). a) iPr$_2$Mg (1.1 equiv) in Et$_2$O, lithiated ligand (1.4 equiv), addition of **1** in Et$_2$O or of **4** in THF at −40°C, 10 min; RT, 6 h; aq. NH_4Cl.



1: n = 0 **4**: n = 1 | **2a**: n = 0 **5a**: n = 1 | **3a**: n = 0 **28**: n = 1

Entry	Ligand	**2a**		**5a**	
		Yield[a] [%]	*ee*[b] [%]	Yield[a] [%]	*ee*[b] [%]
1	**11**	36	7 (*S*)	20	<1
2	**12**	43	<1	36	<1
3	**13a**	59	8 (*S*)	53	4 (*S*)
4	**13b**	39	1 (*S*)	38	2 (*R*)
5	**13c**	71	4 (*S*)	45	1 (*S*)
6	**13d**	41	2 (*S*)	44	2 (*S*)
7	**14**	49	3 (*S*)	40	4 (*S*)
8	**15a**	39	14 (*S*)	54	5 (*R*)
9	**15b**	41	7 (*S*)	15	7 (*R*)
10	**16a**	44	12 (*R*)	19	8 (*S*)
11	**16b**	20	<1	18	2 (*S*)
12	**17a**[c]	37	6 (*S*)	51	15 (*S*)
13	**17b**	60	23 (*R*)	31	17 (*S*)
14	**17c**	33	28 (*R*)	33	11 (*S*)
15	**17d**	38	19 (*R*)	39	12 (*R*)
16	**18a**[c]	14[d]	8 (*R*)[d]	43	4 (*S*)
17	**18b**	10	<1	11	<1
18	**18c**	9	1 (*R*)	17	<1
19	**19a**[c]	50[d]	3 (*S*)[d]	16	<1
20	**19b**	39[d]	6 (*S*)[d]	–[e]	–[e]
21	**19c**	10	<1	20	<1
22	**20a**	26	7 (*R*)	31	2 (*R*)
23	**20b**	17	3 (*R*)	28	<1
24	**21**	10	20 (*S*)	31	15 (*S*)
25	**21**[c]	37	5 (*S*)	36	2 (*R*)
26	**17b**[f]	27	<1		
27	**21**[f,g]	9	12 (*S*)		
28	**21**[c,f,g]	20	8 (*S*)		

[a] Determined by GLC analysis[16] of the crude product using biphenyl as an internal standard. [b] Determined by HPLC analysis[35,36] after flash chromatography. Absolute configurations are given in parentheses. [c] 2.0 equiv of nBuLi relative to the ligand were used. [d] This reaction was conducted in toluene because the reaction mixture was insoluble in Et$_2$O. [e] Initially, a clear solution formed; at RT it turned into a gel within a few minutes. Therefore, we did not continue the experiment by cooling and adding **4**. [f] Only a catalytic amount of ligand (20 mol%) was used. [g] 2.2 equiv of iPr$_2$Mg were used.

In some cases, desymmetrization with a given ligand led to different absolute configurations in products **2a** and **5a** (see entries 8, 9, 10, 13, and 14).

While substrate **1** delivered the monomagnesium derivative in the presence of 1.4 equiv of ligand Li-**17b** with 23% *ee* (Table 4, entry 13[37]), using 20 mol% of Li-**17b** gave only racemic product (entry 26). However, using 20 mol% of the NOBIN-derived naphthoxide Li-**21** as a ligand, protonation product **2a** revealed up to 12% *ee* (entries 27 and 28). This was less than when 1.4 equiv of the same naphthoxide were employed (→ 20% *ee*, entry 24) but is intriguing because it indicates that a *catalytic* asymmetric Br/Mg-exchange reac-

tion might be feasible. Unfortunately, the reaction was rather slow even if more *i*Pr_2Mg (2.2 instead of 1.1 equiv) was used.

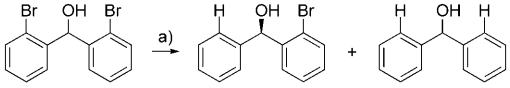
It is clear that the quality and practicability of asymmetric Br/Mg-exchange reactions are not measured by *ee* values alone but need to take the yields into account. In this regard we considered the results of Table 4 as merely orienting: they suggested to pursue our study with a monoalkyl naphthoxide Li-**17** as the most promising ligand and to search for useful *ee*/yield pairs through variations of the reaction conditions, to which we subjected substrate **1**. We came to consider the methylated BINOLate Li-**17b** as the most promising ligand included in Table 4 rather than the benzylated analogue Li-**17c** in spite of the slightly lower *ee* observed in the desymmetrization of the prochiral alcohol **1** under the screening conditions, because we encountered the inverse relationship under improved conditions (see Table 6, entries 11 vs. 10).

Refinement of the Br/Mg exchange of substrate 1 in the presence of ligand 17b and subsequent functionalizations: Substrate **1** (contrary to **4**) behaved in accordance to Scheme 1 such that higher conversions allowed for a more extensive kinetic resolution whereby the *ee* increased. This, of course, occurred at the expense of a decreased yield of the monomagnesiated product **2a**, which implied finding a compromise between yield and *ee* optimization (see Tables 5 and 6). In fact, higher conversions of **1** could not be achieved by prolonged reaction times (alone) but only by a larger amount of metalation reagent. This was because the Br/Mg-exchange reaction came virtually to a standstill after some hours.

Varying the temperature of the Br/Mg exchange, our initial choice of "room temperature" proved to be optimal since it led to 54% monomagnesiation and 29% *ee* (Table 5, entry 2). An exchange temperature of 0°C not only slowed down the reaction but lowered the *ee* to 17% at best (entries 4–6). Heating the reaction mixture to 40°C left the *ee* almost unaltered compared with conducting the Br/Mg-exchange at 20°C (entry 8 vs. 2: 28% vs. 29%).

The initially chosen solvent Et_2O was suboptimal. Entry 2 of Table 6 reveals 54% yield and 29% *ee* as the best combined result and entry 3 32% as the maximum *ee* value. In the more polar solvent THF, the Br/Mg-exchange reaction delivered an almost racemic product (4% *ee*, entry 4). In contrast, significantly improved enantioselectivities were obtained in the unpolar solvent toluene: 42% yield/44% *ee* was the best combined result (entry 6) and 51% the highest *ee* value achieved at all (entry 7). Gratifyingly, we learnt to avoid the inconvenience imposed by the latter experiments—namely to remove the solvent Et_2O required for making *i*Pr_2Mg, and redissolve the residue in toluene: the addition of a solution of substrate **1** in benzene to a solution of *i*Pr_2Mg and naphthoxide Li-**17b** in Et_2O simplified the procedure considerably. Moreover, it led to an improved yield/*ee* pair (58%/52%, entry 9) and a slightly increased maximum *ee* value (53%, entry 10). As shortly mentioned above, the related naphthoxide Li-**17c** performed not as well under the same conditions (22% yield/42% *ee*, entry 11).

Table 5. Optimization of the temperature for Br/Mg exchange. a) *i*Pr_2Mg (1.1–2.2 equiv) in Et_2O, Li-**17b** (1.4 equiv), addition of **1** in Et_2O at −40°C, 10 min; T_{exch}, 6 h; aq. NH_4Cl.

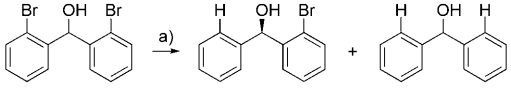


1 (*R*)-**2a** **3a**

Entry	*i*Pr_2Mg [equiv]	T_{exch} [°C]	Yield[a] [%] (*R*)-**2a**	**3a**	*ee*[b] [%]
1	1.1	20	60	9	23
2	1.4		54	19	29
3	1.7		25	53	32
4	1.4	0	18	1	3
5	1.7		43	6	17
6	2.2		42	50	17
7	1.1	40	22	5	9
8	1.4		49	18	28

[a] Determined by GLC analysis[16] of the crude product using biphenyl as an internal standard. [b] Determined by HPLC analysis[35] after flash chromatography.

Table 6. Optimization of the solvent for Br/Mg exchange. a) *i*Pr_2Mg (1.1–1.7 equiv) in Et_2O, Li-**17b** (1.4 equiv), RT, 15 min; (removal of Et_2O in vacuo; solvent, RT, 15 min;) addition of **1** in solvent at −40°C, 10 min; RT, 6 h; aq. NH_4Cl.



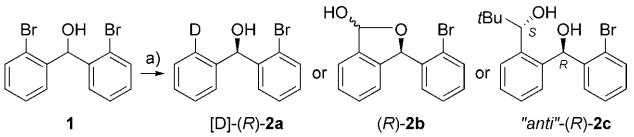
1 (*R*)-**2a** **3a**

Entry	*i*Pr_2Mg [equiv]	Solvent	Yield[a] [%] (*R*)-**2a**	**3a**	*ee*[b] [%]
1	1.1	Et_2O	60	9	23
2	1.4		54	19	29
3	1.7		25	53	32
4	1.1	THF	32	4	4[c]
5	1.1	toluene	19	1	12[c]
6	1.4		42	20	44
7	1.7		14	84	51
8	1.1	Et_2O/benzene 1:1[d]	44	7	29
9	1.4		58	27	52
10	1.7		18	54	53
11[e]	1.7		22	65	42

[a] Determined by GLC analysis[16] of the crude product using biphenyl as an internal standard. [b] Determined by HPLC analysis[35] after flash chromatography. [c] (*S*)-**2a**. [d] A solution of **1** in pure benzene was added. [e] Li-**17c** instead of Li-**17b** was employed as a ligand.

Starting from the best Br/Mg-exchange conditions of Table 6 (entry 9), the organomagnesium derivative of **1** was trapped with the electrophiles compiled in Table 7. Quenching with deuteromethanol (>99.5% D) led to the deuterated alcohol [D]-(*R*)-**2a** (58% yield, 52% *ee*) with virtually complete deuterium incorporation (97% D). As discussed for the equally complete deuterium incorporation into

Table 7. Desymmetrization of alcohol **1** and functionalization of its monomagnesium derivative. a) iPr$_2$Mg (1.4 equiv) in Et$_2$O, Li-**17b** (1.4 equiv), addition of **1** in benzene at −40 °C, 10 min; RT, 6 h; addition of electrophile.



1 [D]-(*R*)-**2a** (*R*)-**2b** "*anti*"-(*R*)-**2c**

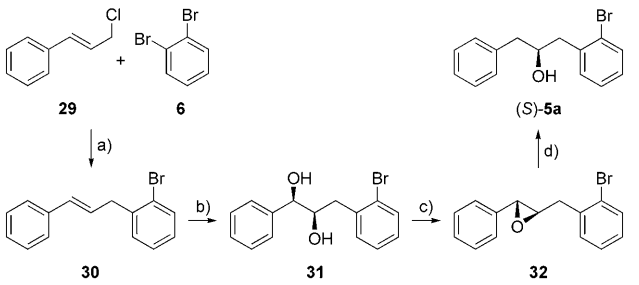
(*R*)-**2**	Electrophile	Conditions	Yield [%]	*ee*[a] [%]
[D]-**a**	MeOD[b]	RT, 30 min	58[c] (97% D[d])	52
b	DMF	THF,[e] 0 °C → RT, 16 h	42	49
"*anti*"-**c**	*t*BuCHO		39[f] (d.s. 66:34[g])	51 (58[h])

[a] Determined by HPLC analysis[35,38,39] after flash chromatography. [b] >99.5% D. [c] Determined by GLC analysis[16] of the crude product using biphenyl as an internal standard. [d] Deuterium incorporation (determined by GLC/MS). [e] Removal of the initial solvent mixture (Et$_2$O/benzene) in vacuo and dissolution of the residue in THF. [f] Combined yield of both diastereomers. The minor diastereomer was impure after separation by flash chromatography; its yield was determined by ^{1}H NMR spectroscopy employing 2,4,6-tribromotoluene as an internal standard. [g] Isomer ratio determined by ^{1}H NMR analysis of the crude product. [h] *ee* of the minor diastereomer (see discussion in the text).

model alcohol **9** by the Br/Mg-exchange/deuterolysis sequence of Table 2 this means that magnesiation of the prochiral alcohol **1** occurs *after* the complete deprotonation of all OH groups as expected. Consequently, none of the organomagnesium intermediate suffers protonation before it has an opportunity to react with an added electrophile. Quenching with DMF provided lactol (*R*)-**2b** (42%, 49% *ee*), quenching with pivaldehyde a mixture of two separable diastereomeric diols (*R*)-**2c** (d.s. 66:34, 39%). The relative configuration in the major diastereomer was established to be "*anti*" (as visualized at the top of Table 7) by X-ray crystallography of a racemic sample.[40] "*anti*"-(*R*)-**2c** was shown to possess 51% *ee*. Interestingly, the minor diastereomer revealed a somewhat higher *ee* value, namely 58%. If this deviation is real, we find the following rationalization conceptionally intriguing: since the (*R*)-arylmagnesium/(*S*)-BINOLate complex and the (*S*)-arylmagnesium/(*S*)-BINOLate complex are diastereomers they may exhibit different "*anti*"/"*syn*" selectivities in their additions to pivaldehyde. Accordingly, *different* relative amounts of (*R*)- and (*S*)-configured diarylcarbinol moieties might be incorporated into the "*anti*"- versus "*syn*"-product—which, of course, would be tantamount to their having different enantiomeric compositions.

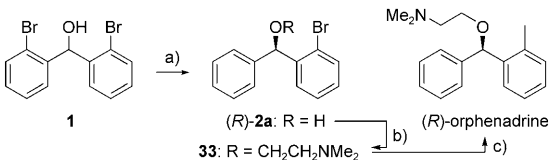
Absolute configuration of the desymmetrization products: The absolute configuration of the monobromoalcohol **2a** emerging from the desymmetrization of dibromoalcohol **1** recorded as entry 13 of Table 4 follows from its specific rotation, which was $[\alpha]_D^{20} = +10.3$ ($c = 1.53$ in $CHCl_3$). Since (*S*)-**2a** is levorotatory,[41] our dextrorotatory specimen of **2a** is rightfully assigned as (*R*)-**2a**.

The absolute configuration of monobromoalcohol **5a** obtained from the desymmetrizations of dibromoalcohol **4** (Table 4) was determined by HPLC comparison with an authentic sample of its (*S*)-configured enantiomer. The latter was synthesized with 91% *ee* as shown in Scheme 7, starting with the allylation of 2-bromophenylmagnesium bromide[8] by cinnamyl chloride (**29**). The resulting diarylpropene **30** was subjected to an asymmetric Sharpless dihydroxylation.[42] It rendered diol **31** with predictable configurations. It was converted into epoxide **32** with retention of the configuration of both C–O bonds.[43] Reduction with DIBAH opened the heterocycle at the benzylic position[44] and gave the desired alcohol (*S*)-**5a**. The *S* enantiomer of compound **5a** eluted prior to the *R* enantiomer under the HPLC conditions used in our co-injection experiment, which allowed to assess the configuration of a non-racemic specimen of **5a** prepared from **4**.



Scheme 7. Synthesis of monobromoalcohol (*S*)-**5a**. a) **6** (1.3 equiv), iPrMgCl·LiCl (1.2 equiv), THF, −15 °C, 4 h; **29** (1.0 equiv), CuCN·2LiCl (11 mol%), 12 h. b) $K_2OsO_2(OH)_4$ (0.5 mol%), $(DHQD)_2PHAL$ (1 mol%), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), tBuOH/H_2O/Et$_2$O (15:15:1), 0 °C, 22 h; 79% over the 2 steps (91% *ee*). c) $MeC(OMe)_3$ (1.6 equiv), Me_3SiCl (1.6 equiv), CH_2Cl_2, RT, 6 h; K_2CO_3 (1.9 equiv), MeOH, RT, 4 h; 84%. d) DIBAH (2.8 equiv), CH_2Cl_2, −40 °C, 4 h; 67%.

Synthesis of (*R*)-orphenadrine: Orphenadrine[6] (see Scheme 8) is an antihistaminic and anticholinergic drug. To date, it has been synthesized three times: as a racemic mixture without[45] or with an ensuing resolution[46] or by a Ru-catalyzed asymmetric hydrogenation.[47] We synthesized (*R*)-orphenadrine following the desymmetrization of dibromoalcohol **1** (Scheme 8). The resulting monobromoalcohol **2a** (51%, 52% *ee*) was etherified with β-(dimethylamino)ethyl chloride[48] to give aminoether **33** in 78% yield. Br/Li ex-



Scheme 8. Synthesis of (*R*)-orphenadrine. a) iPr$_2$Mg (1.4 equiv) in Et$_2$O, Li-**17b** (1.4 equiv), addition of **1** (1.0 equiv) in benzene at −40 °C, 10 min; RT, 6 h; 51%, 52% *ee*. b) Cl-CH_2CH_2-NMe_2·HCl (2.0 equiv), KOH (10 equiv), DMSO, RT, 16 h; 78%. c) nBuLi (1.2 equiv), THF, −78 °C, 1 h; MeI (1.3 equiv), 2 h; → −60 °C; Et$_2$NH (49 equiv); 66%.

change and methylation accomplished (*R*)-orphenadrine for the third time (66% yield).

Conclusion

The first *asymmetric* halogen/metal-exchange reactions were accomplished using $i\mathrm{Pr_2Mg}$ as a magnesiating reagent in the presence of stoichiometric amounts of enantiopure Li-alkoxides or Li-phenoxides. Due to a concomitant kinetic resolution, the desymmetrizing Br/Mg exchange afforded up to 53% *ee* (in the presence of naphthoxide Li-**17b**). $i\mathrm{Pr_2Mg}$ combined with other Li salts, non-Li alkoxides or tetramethylethylenediamine underwent significantly slower Br/Mg-exchange reactions, as did *i*PrMgCl in the presence of LiO-$(CH_2)_2NMe_2$. The arylmagnesium intermediate *pre*-**2** was trapped with a number of electrophiles. Its protonolysis and two follow-up reactions provided the antihistaminic and anticholinergic drug (*R*)-orphenadrine. In one instance, a *catalytic* amount of the naphthoxide Li-**21** (20 mol%) induced an asymmetric induction (8 and 12% *ee*), albeit with very little yields (20 and 9%, respectively). While else we used stoichiometric amounts of the additive, the latter was not consumed such that our best ligand, naphthoxide Li-**17b**, could be recovered in up to 99% yield.

Experimental Section

General information: Reactions were performed in oven-dried (110°C) glassware under N_2. Products were purified by flash chromatography[49] (column diameter, filling height, fraction volume, and eluents are given in parentheses; which fractions contained the isolated product is indicated in each description as "fractions *xx–yy*") on Merck silica gel 60 (0.040–0.063 mm). Yields refer to analytically pure samples. ^{1}H NMR (TMS as internal standard in $CDCl_3$): Varian Mercury VX 300, Bruker AM 400, and Bruker DRX 500. Integrals agree with the given assignments. ^{13}C NMR [$CDCl_3$ ($\delta = 77.10$)]: Bruker AM 400 and Bruker DRX 500. Assignments of ^{1}H and ^{13}C NMR resonances refer to the IUPAC nomenclature except within substituents (where primed numbers are used). Chiral HPLC: G. Fehrenbach, Institut für Organische Chemie und Biochemie, Universität Freiburg. GLC/MS: Dr. J. Wörth, C. Warth, Institut für Organische Chemie und Biochemie, Universität Freiburg. Combustion analyses: E. Hickl, Institut für Organische Chemie und Biochemie, Universität Freiburg. IR spectra: Perkin–Elmer Paragon 1000. Optical rotations α_{exp} were measured with a Perkin-Elmer polarimeter 341 MC at 589 nm [and at 365 nm for "*anti*"-(*R*)-**2c**] and 20°C; specific rotations were calculated from the average of five measurements of α_{exp} in a given solution of the respective sample.

Preparation of a solution of $i\mathrm{Pr_2Mg}$ in $\mathrm{Et_2O}$: *i*PrBr (12.0 mL, 15.7 g, 128 mmol) was added portionwise within 1–1.5 h to a suspension of Mg turnings (3.14 g, 129 mmol, 1.01 equiv) in Et_2O (60 mL). The dark grey suspension was heated under reflux for further 3–4 h. After cooling to 0°C, first diglyme (7.20 mL, 6.75 g, 50.3 mmol, 0.393 equiv) in Et_2O (9 mL) and then dioxane (6.60 mL, 6.80 g, 77.2 mmol, 0.603 equiv) in Et_2O (6 mL) were added dropwise with a syringe pump within 75 and 50 min, respectively. The white suspension was stirred at −10°C for 14–16 h and then filtered with suction under nitrogen. The clear and colorless filtrate was concentrated in a stream of nitrogen by ca. 50%, which was usually accompanied by the formation of a small amount of a white precipitate. The concentration of $i\mathrm{Pr_2Mg}$ was determined by titration with salicylic aldehyde phenylhydrazone[50] (typically 0.8–1.0 M, 25–30% yield). The solution could be stored in a refrigerator for a few weeks.

Preparation of the Li-salts used as ligands (general procedure)

a) "Large-scale" preparation as a supply for several reactions: *n*BuLi (1 or 2 equiv, ca. 2.5 M in hexanes) was added dropwise to an ice-cooled solution of the respective alcohol [2-(dimethylamino)ethanol or alcohols **11**–**20**] in THF (0.2–1 M). After 30 min, the cooling bath was removed and stirring continued for another 30 min. The solvent was removed in a stream of nitrogen. The residue was dried *in vacuo* at 100°C for 4 h, powdered, and used without further purification or analysis.

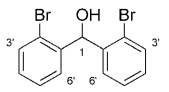
b) "Small-scale" preparation directly in the reaction vessel: *n*BuLi (1 or 2 equiv, ca. 0.8 M in hexanes or, when using a substoichiometric amount of ligand, ca. 0.25 M) was added dropwise to an ice-cooled solution of the respective acidic compound (phenol, pivalic acid, benzenesulfonamide, or alkohol **21**) in THF (1 mL). After 15 min, the cooling bath was removed and stirring continued for another 15 min. The solvent was removed in a stream of nitrogen. The residue was dried in vacuo at room temperature for 15 min and used immediately.

NaO-CH_2CH_2-NMe_2: 2-(Dimethylamino)ethanol (0.120 mL, 106 mg, 1.19 mmol, 1.66 equiv) was added dropwise to an ice-cooled suspension of NaH (17.2 mg, 0.717 mmol) in THF (2 mL). After 15 min, the cooling bath was removed. After stirring at room temperature for further 15 h, the solvent was removed in a stream of nitrogen. The residue was dried in vacuo at 100°C for 2 h and used immediately.

KO-CH_2CH_2-NMe_2: 2-(Dimethylamino)ethanol (70 μL, 62 mg, 0.70 mmol) was added dropwise to an ice-cooled suspension of KH (28.2 mg, 0.703 mmol, 1.0 equiv) in THF (2 mL). After 15 min, the cooling bath was removed. After stirring at RT for further 60 min, the solvent was removed in a stream of nitrogen. The residue was dried in vacuo at RT for 15 min and used immediately.

IMgO-CH_2CH_2-NMe_2: MeMgI (2.1 M in Et_2O, 0.330 mL, 0.69 mmol, 0.99 equiv) was added dropwise to an ice-cooled solution of 2-(dimethylamino)ethanol (70 μL, 62 mg, 0.70 mmol) in THF (1 mL). After 15 min, the cooling bath was removed. After stirring at RT for further 15 min, the solvent was removed in a stream of nitrogen. The residue was dried in vacuo at RT for 15 min and used immediately.

Bis(2-bromophenyl)methanol (1): At −20°C, 1,2-dibromobenzene (**6**) (6.00 mL, 11.5 g, 48.8 mmol, 1.18 equiv) was added dropwise to *i*PrMgCl·LiCl (1.79 M in THF, 25.0 mL, 44.8 mmol, 1.08 equiv) within 5 min.



The mixture was stirred at −15°C for 4 h. At −30°C 2-bromobenzaldehyde (5.00 mL, 7.66 g, 41.4 mmol) was added dropwise within 15 min and the mixture was stirred at −15°C for further 16 h. The reaction was quenched by the addition of EtOH (1 mL). After removal of the cooling bath, satd. aq. NH_4Cl (30 mL) and H_2O (30 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O (3× 15 mL). The combined organic phases were washed with brine (15 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure, flash chromatography (10×14 cm, 100 mL, cyclohexane/EtOAc 95:5, from fraction 32 80:20) and drying in vacuo at 60°C for 6 h provided the title compound (fractions 31–45, 12.2 g, 86%) as a colorless solid. M.p. 80–81°C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS): $\delta = 2.60$ (d, $J_{1\text{-OH},1} = 4.1$ Hz, 1-OH), 6.39 (d, $J_{1,1\text{-OH}} = 3.8$ Hz, 1-H), 7.17 (ddd, $J_{4',3'} = 7.9$, $J_{4',5'} = 6.9$, $J_{4',6'} = 2.2$ Hz, 2×4′-H), 7.30 (ddd, $J_{5',6'} = 7.7$, $J_{5',4'} = 6.9$, $J_{5',3'} = 1.2$ Hz, 2×5′-H), 7.32 (dd, $J_{6',5'} = 7.7$, $J_{6',4'} = 2.2$ Hz, 2×6′-H), 7.57 ppm (dd, $J_{3',4'} = 7.9$, $J_{3',5'} = 1.0$ Hz, 2×3′-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 74.19$ (C-1), 123.84 (2×C-2′), 127.57 (2×C-4′)*, 128.64 (2×C-5′)*, 129.36 (2×C-6′)*, 132.92 (2×C-3′)*, 140.88 ppm (2×C-1′); * assignment interchangeable; IR (film): $\tilde{\nu} = 3600$, 3070, 2930, 1590, 1570, 1465, 1440, 1365, 1330, 1300, 1285, 1270, 1195, 1180, 1160, 1120, 1050, 1035, 1025, 1015 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{10}Br_2O$ (139.9): C 45.65, H 2.95; found: C 45.65, H 2.92.

Br/Mg exchange with prochiral alcohols 1 or 4 (general procedure)

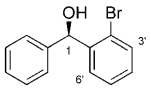
a) Reactions in $\mathrm{Et_2O}$, $\mathrm{Et_2O/THF}$ or $\mathrm{Et_2O/benzene}$: $i\mathrm{Pr_2Mg}$ (ca. 0.8–1.0 M in Et_2O, 1.1–2.2 equiv) was added quickly to the solvent-free powdered

respective Li salt (0.2 or 1.4 equiv), which was stirred vigorously. After 15 min, the mixture was cooled to −40 °C and a solution of the alcohol **1** or **4** (171 or 185 mg, respectively, 0.50 mmol) and, if a protonolysis or a deuterolysis was to follow, biphenyl (ca. 30 mg, ca. 0.20 mmol) in Et_2O or THF (so much that the total volume of the reaction was ca. 1.6 mL) or benzene (so much that Et_2O/benzene 1:1) was added dropwise within 4 min. 10 min later, the cooling bath was replaced by an ice (0 °C), water (RT), or oil bath (40 °C). After 6 h, the reaction was quenched by the addition of the electrophile.

b) Reactions in toluene or THF: iPr$_2$Mg (ca. 0.8–1.0 M in Et_2O, 1.1–2.2 equiv) was added quickly to the solvent-free powdered Li-**17b** (1.4 equiv), which was stirred vigorously. After 15 min, Et_2O was removed first in a stream of nitrogen and then in vacuo (RT, 5 min). The residue was dissolved in toluene or THF (1 mL). After another 15 min, the mixture was cooled to −40 °C and a solution of alcohol **1** (171 mg, 0.50 mmol) and biphenyl (ca. 30 mg, ca. 0.20 mmol) in toluene or THF (0.6 mL) was added dropwise within 4 min. 10 min later, the cooling bath was replaced by water bath at RT and the mixture was stirred for further 6 h.

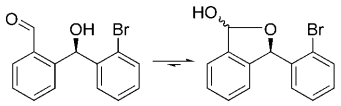
H$^+$ as an electrophile (→ **2a or 5a**; see below for analytical data): Satd. aq. NH_4Cl (3 mL) was added to the reaction mixture. The phases were separated and the aqueous phase was extracted with Et_2O (3×2 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure provided a crude product which was analyzed by GLC.[16] Further purification by flash chromatography (2.5×15 cm, 20 mL, cyclohexane/EtOAc 95:5) provided a mixture of dibromoalcohol **1** and monobromoalcohol **2a** or a mixture of dibromoalcohol **4**, monobromoalcohol **5a**, and dibenzylmethanol (**28**), which were analyzed by chiral HPLC.,[35,36]

D$^+$ as an electrophile (→ [D]-**2a** or [D]-**5a**): The reaction mixture was diluted with THF (1 mL) and MeOD (>99.5 % D, 80 μL, 65 mg, 2.0 mmol, 4.0 equiv) was added. After 30 min, satd. aq. NH_4Cl (3 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3×2 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure provided a crude product, which was analyzed by GLC.[16] Further purification by flash chromatography (2.5×15 cm, 20 mL, cyclohexane/EtOAc 95:5) provided a mixture of dibromoalcohol **1** and monobromoalcohol **2a** or a mixture of dibromoalcohol **4**, monobromoalcohol **5a**, and dibenzylmethanol (**28**), which was analyzed by chiral HPLC.[35,36]



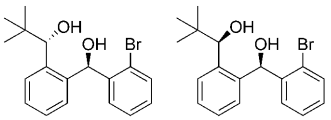
(*R*)-(2-Bromophenyl)phenylmethanol [(*R*)-2a]:[41] iPr$_2$Mg (0.84 M in Et_2O, 6.5 mL, 5.5 mmol, 1.4 equiv) was added quickly to the solvent-free powdered Li-**17b** (1.63 g, 5.32 mmol, 1.38 equiv), which was stirred vigorously. After 20 min, the mixture was cooled to −40 °C and a solution of alcohol **1** (1.32 g, 3.86 mmol) in benzene (6.5 mL) was added dropwise within 12 min. 10 min later, the cooling bath was removed. After further 10 min, a water bath was applied (RT). After 6 h, the reaction was quenched by the addition of satd. aq. NH_4Cl (8 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and double flash chromatography (8×20 cm, 100 mL, cyclohexane/EtOAc 97:3, from fraction 33 96:4, from fraction 43 95:5 and 5×22 cm, 50 mL, cyclohexane/EtOAc 96:4, from fraction 42 95:5) provided the title compound (fractions 65–89 and fractions 46–70, 521 mg, 51 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ=2.33 (br s, OH), 6.21 (s, 1-H), 7.15 (ddd, $J_{4',3'}=J_{4',5'}=7.9$, $J_{4',6'}=1.8$ Hz, 4′-H), 7.27–7.42 (m, 6×ArH), 7.54 (dd, $J_{6',5'}=7.9$, $J_{6',4'}=1.0$ Hz, 6′-H)*, 7.58 (dd, $J_{3',4'}=7.9$, $J_{3',5'}=1.6$ Hz, 2×3′-H)*; * assignment interchangeable.

(1*RS*,3*R*)-3-(2-Bromophenyl)-1,3-dihydroisobenzofuran-1-ol and (*R*)-2-[(2-bromophenyl)(hydroxy)methyl]benzaldehyde {98:2 mixture, in which the major constituent [(*R*)-**2b**] is a 63:37 mixture of 2 diastereomers} Alcohol **1** (170 mg, 0.497 mmol) was converted to the arylmagnesium compound following the general procedure. The solvent was removed in vacuo at RT. The residue was dissolved in THF (1.5 mL) and cooled to



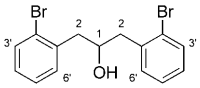
0 °C. DMF (60 μL, 57 mg, 0.78 mmol, 1.6 equiv) was added and the cooling bath was removed. After 16 h, the reaction was quenched by the addition of satd. aq. NH_4Cl (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (3×20 cm, 20 mL, cyclohexane/EtOAc 90:10, from fraction 45 85:15) provided the title compound (fractions 36–49, 60.9 mg, 42 %) as a colorless solid. M.p. 128–130 °C; $[\alpha]_D^{20} = +118$ (c=1.16 in $CHCl_3$); 49 % *ee* (by chiral HPLC[38]); ^{1}H NMR [400 MHz, $CDCl_3$/TMS, sample contained the two lactol diastereomers (L1 and L2, respectively) in a 63:37 ratio and ca. 2 % hydroxyaldehyde]: δ=3.33 (d, ^3J=7.6 Hz, L2-OH), 3.63 (m, L1-OH), 6.65 [d, ^3J=8.0 Hz, L1-CH(-O)$_2$], 6.66 (s, L1-CH-O), 6.76 [m, possibly interpretable as d, ^3J=7.6 Hz, L2-CH(-O)$_2$], 6.88 (m, possibly interpretable as s, L2-CH-O), 7.12–7.19 and 7.22–7.40 and 7.46–7.50 (3×m, 7×L1/2-ArH), 7.60 (dd, ^3J=7.0, ^4J=1.3 Hz, L1-HC=CBr), 7.60 (m, possibly interpretable as dd, ^3J=8.0, ^4J=1.2 Hz, L2-HC=CBr), 10.18 ppm (s, hydroxyaldehyde-CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ=83.58 and 84.16 (CH-O), 101.42 and 101.64 [CH(-O)$_2$], 122.25, 122.52, 122.57, 122.62, 123.04, 123.12, 127.93, 128.07, 128.55, 128.60, 129.42, 129.54, 129.62, 129.83, 132.84, 133.05, 138.55, 138.88, 140.47, 140.87, 142.06, 142.19 ppm; IR (film): $\tilde{\nu}$=3380, 3060, 2915, 1770, 1730, 1680, 1565, 1555, 1465, 1435, 1340, 1245, 1215, 1175, 1105, 1025, 995, 915, 785, 770, 750 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{11}BrO_2$ (291.1): C 57.76, H 3.81; found: C 57.75, H 3.55.

(*S*)-1-{2-[(*R*)-(2-Bromophenyl)hydroxymethyl]phenyl}-2,2-dimethylpropan-1-ol ["*anti*"-(*R*)-2c] and (*R*)-1-{2-[(*R*)-(2-Bromophenyl)hydroxymethyl]phenyl}-2,2-dimethylpropan-1-ol ["*syn*"-(*R*)-2c]: Alcohol **1** (171 mg,

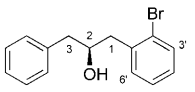


0.500 mmol) was converted to the arylmagnesium compound following the general procedure. The solvent was removed in vacuo at RT. The residue was dissolved in THF (1.5 mL) and cooled to 0 °C. Pivaldehyde (80 μL, 61 mg, 0.71 mmol, 1.4 equiv) was added and the ice bath was removed. After 16 h, the reaction was quenched by the addition of satd. aq. NH_4Cl (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (3×20 cm, 20 mL, cyclohexane/EtOAc 90:10, from fraction 25 80:20, from fraction 50 70:30) provided a mixture of diol "*anti*"-(*R*)-**2c** and ligand **17b** (fractions 22–35, 52.4 mg "*anti*"-(*R*)-**2c**, 30 %) and separately diol "*syn*"-(*R*)-**2c** (fractions 43–54, 15.7 mg, 9 %[51]) as a colorless oil. Ligand **17b** could be removed from diol "*anti*"-(*R*)-**2c** by flash chromatography only after selective *O*-methylation [MeI (10 equiv), K_2CO_3 (3 equiv), acetone (1 mL per 100 mg of the mixture), RT, 20 h] as 2,2′-dimethoxy-1,1′-binaphthalene. "*anti*"-(*R*)-**2c** (major diastereomer): m.p. 89–90 °C; $[\alpha]_D^{20} = \approx 0$, $[\alpha]_{365}^{20} = -0.6$ (c=1.22 in $CHCl_3$); 51 % *ee* (by chiral HPLC[39]); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ=1.02 [s, C(CH$_3$)$_3$], 1.51 (br s, OH), 2.44 (br s, OH), 4.63 (s, C*H*tBu), 6.47 (s, C*H*Ar$_2$), 7.13 (ddd, ^3J=8.0, ^3J=7.2, ^4J=2.0 Hz, ArH), 7.18 (dd, ^3J=7.8, ^4J=1.9 Hz, ArH), 7.21–7.26 (m, ArH), 7.33 (m, 2×ArH), 7.51–7.54 (m, ArH), 7.56 (dd, ^3J=8.0, ^4J=1.3 Hz, ArH), 7.60 ppm (m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.34 [C(*C*H$_3$)$_3$], 36.51 [*C*(CH$_3$)$_3$], 71.42 (*C*HAr$_2$), 76.55 (*C*HtBu), 123.73, 126.20, 127.40, 127.60, 127.96, 128.21, 129.06, 129.62, 133.13, 139.37, 139.71, 142.73 ppm; IR (film): $\tilde{\nu}$=3420, 3065, 2955, 2870, 1820, 1565, 1480, 1465, 1440, 1395, 1360, 1295, 1220, 1175, 1115,

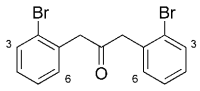
1095, 1000, 955, 915, 820, 770, 750 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{21}BrO_2$ (349.3): C 61.90, H 6.06; found: C 61.81, H 5.68. "*syn*"-(*R*)-**2c** (minor diastereomer): ^1H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 0.97$ [s, $C(CH_3)_3$], 1.58 (br s, OH), 2.70 (br s, OH), 5.07 (s, C*H*tBu), 6.50 (s, C*H*Ar_2), 6.97 (d, $^3J = 7.8$ Hz, ArH), 7.19 (dd, $^3J = {}^3J = 7.5$ Hz, 2×ArH), 7.29–7.37 (m, 2×ArH), 7.46 (dd, $^3J = 7.8$, $^4J = 1.5$ Hz, ArH), 7.59 ppm (m, possibly interpretable as dd, $^3J = {}^3J = 6.6$ Hz, 2×ArH).



1,3-Bis(2-bromophenyl)propan-2-ol (4):[52] $NaBH_4$ (0.984 g, 26.0 mmol, 1.07 equiv) was added to an ice-cooled solution of ketone **8** (8.94 g, 24.3 mmol) in EtOAc (150 mL) and MeOH (50 mL). After 3 h, the reaction was quenched by the addition of acetone (50 mL), NH_4Cl (10 g) and $MgSO_4$ (10 g). After stirring at RT for 3 h, the solids were filtered off and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (30 mL) and stirred vigorously with aqueous NaOH solution (10%, 30 mL) for 8 h to hydrolyze remaining amounts of boronic acid esters. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (4×10 cm, 50 mL, cyclohexane/EtOAc 80:20) provided the title compound (fractions 3–17, 8.59 g, 96%) as a colorless solid. M.p. 95–96 °C; ^1H NMR (500 MHz, $CDCl_3$/TMS): $\delta = 1.59$ (d, $J_{1\text{-}OH,1} = 3.1$ Hz, 1-OH), AB signal ($\delta_A = 2.90$, $\delta_B = 3.10$, $J_{AB} = 13.7$ Hz, in addition split by $J_{H(A),1} = 8.6$, $J_{H(B),1} = 4.2$ Hz, 2×2-H_2), 4.28 (ttd, $J_{1,2\text{-}H(A)} = 8.6$, $J_{1,2\text{-}H(B)} = 4.2$, $J_{1,1\text{-}OH} = 3.1$ Hz, 1-H), 7.09 (ddd, $J_{4',3'} = 8.0$, $J_{4',5'} = 7.3$, $J_{4',6'} = 1.8$ Hz, 2×4′-H), 7.24 (ddd, $J_{5',6'} = 7.5$, $J_{5',4'} = 7.3$, $J_{5',3'} = 1.2$ Hz, 2×5′-H), 7.30 (dd, $J_{6',5'} = 7.5$, $J_{6',4'} = 1.7$ Hz, 2×6′-H), 7.54 ppm (dd, $J_{3',4'} = 8.0$, $J_{3',5'} = 1.4$ Hz, 2×3′-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 43.57$ (2×C-2), 70.65 (C-1), 124.89 (2×C-2′), 127.34 (2×C-4′)*, 128.21 (2×C-5′)*, 131.84 (2×C-3′)**, 132.93 (2×C-6′)**, 137.93 ppm (2×C-1′); *,** assignments interchangeable; IR (film): $\tilde{\nu} = 3690$, 3600, 3435, 3060, 3015, 2960, 2930, 2850, 2250, 1955, 1920, 1595, 3570, 1470, 1440, 1390, 1360, 1335, 1325, 1300, 1260, 1205, 1160, 1120, 1110, 1060, 1030, 945, 935, 915, 900, 880, 870, 845, 830, 805, 775 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{14}Br_2O$ (367.9): C 48.68, H 3.81; found: C 48.75, H 3.87.



(*S*)-1-(2-Bromophenyl)-3-phenylpropan-2-ol [(*S*)-5a]: DIBAH (1.0 M in hexanes, 1.0 mL, 1.0 mmol, 2.8 equiv was added at −40 °C to a solution of epoxide **32** (102 mg, 0.353 mmol) in CH_2Cl_2 (3 mL). After 4 h, the reaction was quenched at −40 °C by the addition of MeOH (0.5 mL) and aqueous HCl (1 M, 4 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (2×20 cm, 20 mL, cyclohexane/EtOAc 95:5, from fraction 12 90:10) provided the title compound (fractions 22–28, 69.0 mg, 67%) as a colorless solid. M.p. 48–50 °C; $[\alpha]_D^{20} = +28.7$ ($c = 1.13$ in $CHCl_3$); 91% *ee* (by chiral HPLC[36]); ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.61$ (s, OH), AB signal ($\delta_A = 2.79$, $\delta_B = 2.90$, $J_{AB} = 13.8$ Hz, in addition split by $J_{H(A),2} = 8.3$, $J_{H(B),2} = 4.4$ Hz, 3-H_2), AB-Signal ($\delta_A = 2.87$, $\delta_B = 3.07$, $J_{AB} = 13.9$ Hz, in addition split by $J_{H(A),2} = 8.1$, $J_{H(B),2} = 4.3$ Hz, 1-H_2), 4.18 (dddd, $J_{2,1\text{-}H(A)} \approx J_{2,3\text{-}H(A)} \approx 8.2$, $J_{2,1\text{-}H(B)} \approx J_{2,3\text{-}H(B)} \approx 4.4$ Hz, 2-H), 7.08 (ddd, $J_{4',3'} = 8.1$, $J_{4',5'} = 7.2$, $J_{4',6'} = 2.0$ Hz, 4′-H), 7.20–7.33 (m, 7×ArH), 7.54 ppm (dd, $J_{3',4'} = 8.0$, $J_{3',5'} = 1.1$ Hz, 3′-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 43.50$ (C-1)*, 43.75 (C-3)*, 72.13 (C-2), 124.94, 126.62, 127.44, 128.25, 128.62, 129.52, 131.89, 133.02, 138.22 (C-1′)**, 138.35 ppm (3-C_{Ar})**; *,** assignments interchangeable; IR (film): $\tilde{\nu} = 3570$, 3415, 3060, 3025, 2925, 1565, 1495, 1470, 1440, 1220, 1030, 915, 770, 750, 700 cm^{-1}; HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{15}H_{15}BrO$ [M^+]: 290.03063; found: 290.03110 (+1.6 ppm).



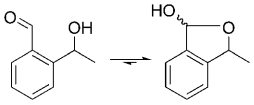
1,3-Bis(2-bromophenyl)propan-2-one (8):[11] A suspension of $[Fe_2(CO)_9]$[14] (25.3 g, 69.5 mmol) and benzyl bromide **7** (31.3 g, 125 mmol, 1.80 equiv) in toluene (70 mL) was treated with ultrasound for 30 min and then stirred at 30 °C for 29 h. The mixture was diluted with toluene and filtered with suction. Removal of the solvent under reduced pressure, recrystallization from MeOH and flash chromatography of the concentrated mother liquor (6×10 cm, 100 mL, cyclohexane/EtOAc 98:2, from fraction 32 80:20) provided the title compound [fractions 25–32, 11.1 g total, 87%[53] (ref.:[11] 71%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 3.96$ (s, 2×CH_2), 7.14 (ddd, $J_{4,3} \approx J_{4,5} \approx 7.5$, $J_{4,6} = 2.1$ Hz, 2×4-H), 7.21–7.32 (m, 2×5-H, 2×6-H), 7.57 ppm (d, $J_{3,4} = 8.1$ Hz, 2×3-H).

Br/Mg exchange with alcohol 9 (general procedure): *i*Pr_2Mg (ca. 0.8–1.0 M in Et_2O, 1.1 equiv) or *i*PrMgCl (ca. 1.9 M in Et_2O, 2.2 equiv) was added quickly to TMEDA or the solvent-free powdered respective metal salt (1.4 or 2.8 equiv), which was stirred vigorously. At this point, nothing happened if the solvent was to stay Et_2O. However, if the subsequent reaction was to be performed in THF, Et_2O was removed first in a stream of nitrogen and then *in vacuo* (RT, 5 min); the residue then was dissolved in THF (0.6 mL). After 15 min, the mixture was cooled to the indicated temperature. A solution of alcohol **9** (100 mg, 0.50 mmol) and, if a protonolysis or a deuterolysis was to follow, biphenyl (ca. 30 mg, ca. 0.20 mmol) in Et_2O (so much that the total volume of the reaction was ca. 1.6 mL) or THF (1 mL) was added dropwise within 4 min. 10 min later, the cooling bath was replaced by a RT water bath. After the indicated time, the Br/Mg exchange was stopped by the addition of the electrophile.

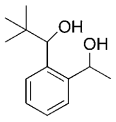
H^+ as an electrophile (→ 10a): Satd. aq. NH_4Cl (2 mL) was added to a sample (ca. 0.2 mL) of the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic phases were dried over $MgSO_4$. After concentrating the solution under reduced pressure, its composition was analyzed by GLC.[16]

D^+ as an electrophile (→ [D]-10a): The reaction mixture was diluted with THF (1 mL) and MeOD (>99.5% D, 60 μL, 49 mg, 1.5 mmol, 3.0 equiv) was added. After 30 min, satd. aq. NH_4Cl (4 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was analyzed by GLC[16] and GLC/MS.

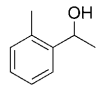
3-Methyl-1,3-dihydroisobenzofuran-1-ol and 2-(1-hydroxyethyl)benzaldehyde [99:1 mixture, in which the major constituent **(10b)** is a 54:46 mixture of 2 diastereomers]:[54] Alcohol **9** (100 mg, 0.497 mmol) was converted to the arylmagnesium compound following the general procedure. The reaction mixture was cooled to 0 °C and DMF (60 μL, 57 mg, 0.78 mmol, 1.6 equiv) was added. The cooling bath was removed and after further 13 h, the reaction was quenched by the addition of satd. aq. NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (2×5 cm, 20 mL, cyclohexane/EtOAc 90:10, from fraction 12 80:20) provided the title compound (fractions 7–14, 55.4 mg, 74%) as a colorless oil. ^1H NMR [300 MHz, $CDCl_3$/TMS, sample contained the two lactol diastereomers (L1 and L2, respectively) in a 54:46 ratio and ca. 1% hydroxyaldehyde]: $\delta = 1.49$ and 1.58 (2×d, 2×$^3J = 6.5$ Hz, L1/2-CH_3), 2.99 (br s, L1/2-OH), 5.26 (q, $^3J = 6.5$ Hz, L2-CH-O), 5.51 (q, $^3J = 6.5$ Hz, L1-CH-O), 6.41 [s, L2-CH(-O)$_2$], 6.48 [s, L1-CH(-O)$_2$], 7.21 (d, $^3J = 7.2$ Hz, L1/2-ArH), 7.32–7.44 (m, 3×L1/2-ArH), 7.60–7.64 (m, 3×hydroxyaldehyde-ArH), 7.83–7.86 (m, hydroxyaldehyde-ArH), 10.14 ppm (s, hydroxyaldehyde-CHO).



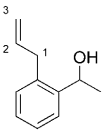
1-[2-(1-Hydroxyethyl)phenyl]-2,2-dimethylpropan-1-ol (10c, initially a 92:8 mixture of diastereomers):[9] Alcohol **9** (99.9 mg, 0.497 mmol) was converted to the arylmagnesium compound following the general procedure. The reaction mixture was cooled



to −70 °C and pivaldehyde (80 μL, 61 mg, 0.71 mmol, 1.4 equiv) was added. The reaction was allowed to warm to RT within 2.5 h. The reaction was quenched by the addition of satd. aq. NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3× 5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (1.5× 10 cm, 10 mL, cyclohexane/EtOAc 90:10, from fraction 27 80:20) provided the title compound (fractions 12–26, 41.3 mg, 40 % and fractions 30–35, 3.8 mg, 4 %; d.s. 92:8) as two separable diastereomers as colorless oils. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 0.99$ [s, C-$(CH_3)_3$], 1.47 (d, $^3J = 6.5$ Hz, CH_3), 1.76 (brs, OH), 1.83 (brs, OH), 4.80 (s, C*H*tBu), 5.35 (q, $^3J = 6.2$ Hz, C*H*Me), 7.29 (m, 2× ArH), 7.45 (dd, $^3J = 7.3$, $^4J = 1.6$ Hz, ArH), 7.59 (dd, $^3J = 7.6$, $^4J = 1.8$ Hz, ArH); minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 0.95$ [s, $C(CH_3)_3$], 1.52 (d, $^3J = 6.5$ Hz, CH_3), 1.91 (brs, OH), 2.03 (brs, OH), 4.90 (s, *t*BuC*H*), 5.28 (q, $^3J = 6.3$ Hz, MeC*H*), 7.28–7.33 (m, 2× ArH), 7.48–7.53 ppm (m, 2× ArH).

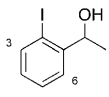


1-(2-Methylphenyl)ethan-1-ol (10 d):[55] Alcohol **9** (100 mg, 0.497 mmol) was converted to the arylmagnesium compound following the general procedure. The reaction mixture was cooled to 0 °C and CuCN·2 LiCl (1.0 M in THF, 50 μL, 50 μmol, 10 mol %) and methyl iodide (50 μL, 0.11 g, 0.80 mmol, 1.6 equiv) were added. The cooling bath was removed and after further 15 h, the reaction was quenched by the addition of satd. aq. NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3× 5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (1.5× 5 cm, 20 mL, cyclohexane/EtOAc 88:12) provided the title compound (fractions 1–4, 57.6 mg, 85 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS, sample contained 8.6 % 1-phenylethan-1-ol which were subtracted before the yield calculation): $\delta = 1.47$ (d, $^3J = 6.3$ Hz, CH_3), 1.70 (brs, OH), 2.35 (s, $ArCH_3$), 5.13 (q, $^3J = 6.4$ Hz, CH-O), 7.12–7.30 (m, 3× ArH), 7.51 ppm (d, $^3J = 7.5$ Hz, ArH).

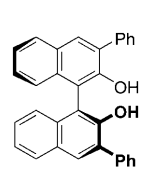


1-(2-Allylphenyl)ethan-1-ol (10 e):[56] Alcohol **9** (99.9 mg, 0.497 mmol) was converted to the arylmagnesium compound following the general procedure. The reaction mixture was cooled to 0 °C and CuCN·2 LiCl (1.0 M in THF, 50 μL, 50 μmol, 10 mol %) and allyl bromide (60 μL, 84 mg, 0.69 mmol, 1.4 equiv) were added. The cooling bath was removed and after further 1.5 h, the reaction was quenched by the addition of satd. aq. NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3× 5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (1.5× 5 cm, 20 mL, cyclohexane/EtOAc 88:12) provided the title compound (fractions 1–4, 63.8 mg, 79 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS, sample contained 7.1 % 1-phenylethan-1-ol which were subtracted before the yield calculation): $\delta = 1.48$ (d, $^3J = 6.4$ Hz, CH_3), 1.73 (brs, OH), 3.46 (dd, $J_{1,2} = 6.0$, $J_{1,3\text{-H}(Z)} = 1.2$ Hz, 1-H_2), 4.98 (ddt, $J_{3,2} = 17.1$, $J_{gem} \approx J_{3,1} \approx 1.8$ Hz, 3-H^Z), 5.07 (dd, $J_{3,2} = 10.1$, $J_{gem} = 1.6$ Hz, 3-H^E), 5.16 (q, $^3J = 6.4$ Hz, CH-O), 5.99 (ddt, $J_{2,3\text{-H}(Z)} = 17.1$, $J_{2,3\text{-H}(E)} = 10.1$, $J_{2,1} = 6.0$ Hz, 2-H), 7.13–7.30 (m, 3× ArH), 7.54 ppm (dd, $^3J = 7.6$, $^4J = 1.6$ Hz, ArH).

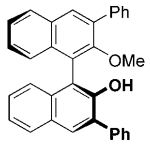
1-(2-Iodophenyl)ethan-1-ol (10 f):[57] Alcohol **9** (99.6 mg, 0.495 mmol) was converted to the arylmagnesium compound following the general procedure. The reaction mixture was cooled to −20 °C and I_2 (189 mg, 0.745 mmol, 1.50 equiv) in THF (1.5 mL) was added dropwise within 15 min. After 5 min, the cooling bath was removed and after further 10 min, the reaction was quenched by the addition of satd. aq. NH_4Cl (2 mL) and saturated aqueous $Na_2S_2O_3$ (1 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3× 5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (2× 10 cm, 20 mL, cyclohexane/EtOAc 98:2) provided the title compound (fractions 22–39, 98.5 mg, 84 %) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 1.46$ (d, $^3J = 6.5$ Hz, CH_3), 1.97 (brs, OH), 5.07 (q, $^3J = 6.0$ Hz, CH-O), 6.96 (ddd, $J_{4,3} \approx J_{4,5} \approx 7.6$, $J_{4,6} = 1.6$ Hz, 4-H), 7.38 (dd, $J_{5,6} \approx J_{5,4} \approx 7.5$ Hz, 5-H), 7.56 (dd, $J_{6,5} = 7.8$, $J_{6,4} = 1.6$ Hz, 6-H), 7.80 ppm (dd, $J_{3,4} = 7.9$, $J_{3,5} = 1.2$ Hz, 3-H).



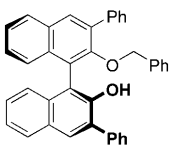
(*S*)-3,3′-Diphenyl-1,1′-bi-2-naphthol (18 a):[29] A solution of Na_2CO_3 (7.31 g, 69.0 mmol, 5.26 equiv) in H_2O (30 mL) was added to a suspension of diiodide **23** (8.22 g, 13.1 mmol), $PhB(OH)_2$ (4.10 g, 33.6 mmol, 2.56 equiv), and $[Pd(PPh_3)_4]$ (814 mg, 0.704 mmol, 5.38 mol %) in DME (50 mL). The mixture was degassed by introducing a stream of nitrogen for 15 min and then heated under reflux for 8 h. After cooling, the mixture was diluted with Et_2O (100 mL), filtered through Celite, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was dissolved in a mixture of THF (50 mL) and MeOH (30 mL) and conc. H_2SO_4 (4 mL) was added. After 21 h, the reaction mixture was diluted with Et_2O (180 mL), $NaHCO_3$ (15 g) and $MgSO_4$ (15 g) were added, the mixture was stirred for 1.5 h, and the solids were filtered off. Removal of the solvent under reduced pressure and flash chromatography (8× 20 cm, 100 mL, cyclohexane/EtOAc 92:8) provided the title compound (fractions 19–35, 5.09 g, 89 %) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 5.34$ (s, 2× OH), 7.23 (d, $^3J = 9.1$ Hz, 2× ArH), 7.31 (ddd, $^3J = {}^3J = 8.3$, $^4J = 1.5$ Hz, 2× ArH), 7.36–7.43 (m, 4× ArH), 7.49 (dd, $^3J = 8.4$, $^3J = 7.1$ Hz, 2× ArH), 7.73 (dd, $^3J = 8.5$, $^4J = 1.5$ Hz, 2× ArH), 7.92 (d, $^3J = 7.8$ Hz, 2× ArH), 8.02 ppm (s, 2× *H*C=CPh).



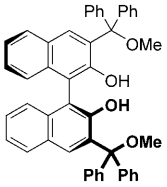
(*S*)-1-(2-Methoxy-3-phenylnaphthalen-1-yl)-3-phenylnaphthalen-2-ol (18 b): Methanol (0.180 mL, 142 mg, 4.44 mmol, 1.47 equiv) and DIAD (0.650 mL, 663 mg, 3.28 mmol, 1.09 equiv) were added to a solution of diol **18 a** (1.32 g, 3.02 mmol) and PPh_3 (870 mg, 3.32 mmol, 1.10 equiv) in THF (11 mL). The mixture was stirred at RT for 25 h. Removal of the solvent under reduced pressure and flash chromatography (7× 20 cm, 100 mL, cyclohexane/EtOAc 98:2) provided the title compound (fractions 32–43, 1.27 g, 93 %) as a colorless solid. Melting range 81–106 °C; $[\alpha]_D^{20} = +0.95$ ($c = 1.40$ in $CHCl_3$); >99 *ee*;[58] ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.17$ (s, OCH_3), 5.31 (s, OH), 7.18 (d, $^3J = 8.3$ Hz, ArH), 7.25–7.50 (m, 11× ArH), 7.73–7.76 (m, possibly interpretable as d, $^3J = 7.1$ Hz, 4× ArH), 7.89 (d, $^3J = 8.0$ Hz, ArH), 7.93 (d, $^3J = 8.2$ Hz, ArH), 7.96 ppm (s, *H*C=CPh), 8.03 (s, *H*C=CPh); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 60.86$ (OCH_3), 116.38, 123.08, 123.83, 124.94, 125.48, 125.69, 126.69, 127.03, 127.55, 127.70, 128.28, 128.34, 128.43, 128.56, 129.16, 129.47, 129.74, 130.22, 130.54, 131.34, 131.65, 133.38, 133.61, 135.51, 137.96, 138.46, 148.84 (*C*OMe), 155.21 ppm (COH); IR (film): $\tilde{\nu} = 3530$, 3055, 3010, 2935, 1805, 1715, 1620, 1600, 1495, 1455, 1445, 1425, 1405, 1360, 1310, 1250, 1220, 1190, 1150, 1130, 1075, 1040, 1015, 985, 955, 895, 855, 820, 780, 750, 730, 700 cm^{-1}; HRMS (EI, 70 eV): *m/z*: calcd for $C_{33}H_{24}O_2$ [M^+]: 452.177630; found: 452.177703 (+0.2 ppm).



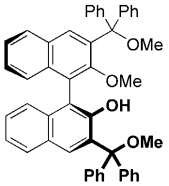
(*S*)-1-[2-(Benzyloxy)-3-phenylnaphthalen-1-yl]-3-phenylnaphthalen-2-ol (18 c): Benzyl alcohol (0.460 mL, 481 mg, 4.45 mmol, 1.47 equiv) and DIAD (0.650 mL, 663 mg, 3.28 mmol, 1.09 equiv) were added to a solution of diol **18 a** (1.32 g, 3.02 mmol) and PPh_3 (869 mg, 3.31 mmol, 1.10 equiv) in THF (11 mL). The mixture was stirred at RT for 25 h. Removal of the solvent under reduced pressure and flash chromatography (7× 20 cm, 100 mL, cyclohexane/



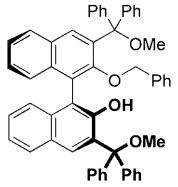
EtOAc 98:2) provided the title compound (fractions 31–45, 1.55 g, 93%) as a colorless solid. Melting range 68–87 °C; $[\alpha]_D^{20} = +96.2$ ($c = 1.16$ in $CHCl_3$); >99 *ee*;[58] ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = AB signal ($\delta_A = 4.16$, $\delta_B = 4.30$, $J_{AB} = 10.1$ Hz, OCH_2), 5.39 (s, OH), 6.36–6.39 (m, 2× ArH), 6.97 (tt, $^3J = 8.2$, $^4J = 1.7$ Hz, 2×*p*-C_6H_4-*H*), 7.05 (tt, $^3J = 6.3$, $^4J = 1.3$ Hz, *p*-C_6H_4-*H*), 7.19 (ddd, $^3J = 8.5$, $^4J = ^4J = 0.7$ Hz, ArH), 7.25 (ddd, $^3J = ^3J = 8.5$ Hz, $^4J = 1.4$, ArH), 7.30–7.35 (m, 2× ArH), 7.36–7.43 (m, 3× ArH), 7.43–7.49 (m, 5× ArH), 7.64–7.67 (m, 2× ArH), 7.75–7.78 (m, 2× ArH), 7.89 (d, $^3J = 8.1$ Hz, ArH), 7.96 (d, $^3J = 8.2$ Hz, ArH), 7.97 (s, *H*C=CPh); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 75.16$ (OCH_2), 116.47, 123.80, 124.15, 125.07, 125.81, 125.83, 126.74, 126.99, 127.62, 127.66, 127.68, 127.95, 128.19, 128.26, 128.37, 128.40, 128.52, 129.18, 129.73, 130.20, 130.86, 131.38, 131.52, 133.50, 133.68, 136.00, 136.58, 138.04, 138.40, 149.09 (*C*OMe), 153.80 ppm (COH); IR (film): $\tilde{\nu}$ = 3530, 3055, 2985, 1740, 1715, 1620, 1600, 1495, 1455, 1420, 1375, 1360, 1305, 1245, 1220, 1185, 1150, 1130, 1075, 1050, 1005, 895, 850, 785, 750, 730, 700 cm^{-1}; HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{39}H_{28}O_2$ [M^+]: 528.208930; found: 528.208202 (−1.4 ppm).



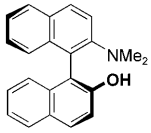
(*S*)-3,3′-Bis(methoxydiphenylmethyl)-1,1′-bi-2-naphthol (19a):[30] A solution of conc. H_2SO_4 (0.500 mL, 0.883 g, 9.01 mmol, 0.495 equiv) in MeOH (180 mL) was added to a solution of diol **24** (13.4 g, 18.2 mmol) and trimethyl orthoformate (18.0 mL, 17.5 g, 165 mmol, 9.04 equiv) in CH_2Cl_2 (180 mL) and the mixture was stirred at RT. After 1.5 h, the reaction was quenched by the addition of NEt_3 (6.00 mL, 4.38 g, 43.3 mmol, 2.38 equiv). Removal of the solvent under reduced pressure and flash chromatography (7×20 cm, 100 mL, cyclohexane/EtOAc 90:10 + 1% NEt_3, from fraction 41 80:20 + 1% NEt_3, from fraction 61 70:30 + 1% NEt_3) provided the title compound (fractions 14–78, 11.6 g, 94%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 3.29$ (s, 2×CH_3), 6.98 (d, $^3J = 8.2$ Hz, 2× ArH), 7.11 (ddd, $^3J = ^3J = 8.4$, $^4J = 1.2$ Hz, 2× ArH), 7.20 (ddd, $^3J = ^3J = 7.9$, $^4J = 1.0$ Hz, 2× ArH), 7.28–7.40 (m, 12× ArH), 7.45–7.51 (m, 8× ArH), 7.64 (s, 2×*H*C=C-CPh_2OMe), 7.65 (d, $^3J = 6.2$ Hz, 2× ArH), 8.44 ppm (s, 2× OH).



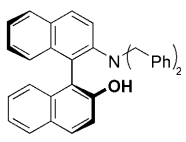
(*S*)-1-[2-Methoxy-3-(methoxydiphenylmethyl)naphthalen-1-yl]-3-(methoxydiphenylmethyl)-2-naphthol (19b): MeOH (0.200 mL, 158 mg, 4.94 mmol, 1.53 equiv) and DIAD (0.700 mL, 714 mg, 3.53 mmol, 1.09 equiv) were added to a solution of diol **19a** (2.19 g, 3.23 mmol) and PPh_3 (941 mg, 3.59 mmol, 1.11 equiv) in THF (20 mL) and the mixture was stirred at RT for 27 h. KOH (1.78 g, 31.7 mmol, 9.82 equiv) in H_2O (1 mL) was added and the mixture stirred at RT for further 19 h. The reaction was quenched by the addition of satd. aq. KH_2PO_4 (24 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (7×20 cm, 100 mL, cyclohexane/EtOAc 98:2) provided the title compound (fractions 35–53, 1.93 g, 86%) as a colorless solid. M.p. 170–173 °C (decomp.); $[\alpha]_D^{20} = -163$ ($c = 2.66$ in $CHCl_3$); >99 *ee*;[58] ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.33–2.33 (m, possibly interpretable as s, CH_3), 3.17 (s, CH_3), 3.26 (s, CH_3), 6.87 (d, $^3J = 8.5$ Hz, ArH), 7.07–7.40 (m, 19× ArH), 7.47–7.49 (m, possibly interpretable as dd, $^3J = 8.3$, $^4J = 1.8$ Hz, 2× ArH), 7.52–7.54 (m, possibly interpretable as dd, $^3J = 8.6$, $^4J = 1.3$ Hz, 2× ArH), 7.61–7.66 (m, 4× ArH), 7.87 (d, $^3J = 8.1$ Hz, ArH), 8.35 (s, *H*C=C-CPh_2OMe)*, 8.82 ppm (s, OH)*; * assignment interchangeable; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.53 ($AlkOCH_3$), 53.05 ($AlkOCH_3$), 59.22 ($ArOCH_3$), 86.29 (Ar_3C), 90.59 (Ar_3C), 118.60, 123.48, 124.09, 124.56, 124.69, 126.22, 126.51, 126.62, 126.79, 127.60, 127.71, 127.76, 127.93, 128.01, 128.12, 128.27, 128.35, 128.39, 128.61, 128.71, 128.90, 129.19, 129.93, 130.17, 130.48, 133.42, 133.53, 136.98, 140.50, 140.68, 143.33, 143.56, 151.90 (OC_{Ar}), 155.54 ppm (OC_{Ar}); IR (film): $\tilde{\nu}$ = 3295, 3060, 2940, 2825, 1625, 1600, 1495, 1450, 1425, 1400, 1335, 1310, 1280, 1220, 1150, 1105, 1060, 1035, 1000, 945, 910, 890, 850, 815, 750, 700 cm^{-1}; HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{48}H_{36}O_3$ [M−MeOH$^+$]: 660.266445; found: 660.266802 (+0.5 ppm).



(*S*)-1-[2-(Benzyloxy)-3-(methoxydiphenylmethyl)naphthalen-1-yl]-3-(methoxydiphenylmethyl)-2-naphthol (19c): Benzyl alcohol (0.480 mL, 502 mg, 4.64 mmol, 1.55 equiv) and DIAD (0.650 mL, 663 mg, 3.28 mmol, 1.09 equiv) were added to a solution of diol **19a** (2.04 g, 3.00 mmol) and PPh_3 (884 mg, 3.37 mmol, 1.12 equiv) in THF (18 mL) and the mixture was stirred at RT for 27 h. KOH (1.79 g, 31.9 mmol, 10.6 equiv) in H_2O (1 mL) was added and the mixture was stirred at RT for further 19 h. The reaction was quenched by the addition of satd. aq. KH_2PO_4 (26 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (7×20 cm, 100 mL, cyclohexane/EtOAc 98:2) provided the title compound (fractions 37–58, 1.78 g, 77%) as a colorless solid. M.p. range 84–117 °C; $[\alpha]_D^{20} = -110$ ($c = 3.01$ in $CHCl_3$); >99 *ee*;[58] ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.12$ (s, CH_3), 3.13 (s, CH_3), AB signal ($\delta_A = 3.72$, $\delta_B = 4.09$, $J_{AB} = 11.4$ Hz, CH_2), 5.89 (dd, $^3J = 7.0$, $^4J = 0.9$ Hz, 2× ArH), 6.78–6.83 (m, 3× ArH), 6.94 (dddd, $^3J = ^3J = 7.3$, $^4J = ^4J = 1.1$ Hz, *p*-C_6H_4-*H*), 7.04–7.11 (m, 2× ArH), 7.13–7.25 (m, 14× ArH), 7.27–7.37 (m, 4× ArH), 7.39–7.42 (m, 2× ArH), 7.51 (m, 2× ArH), 7.54–7.59 (m, 4× ArH), 7.91 (dd, $^3J = 8.1$, $^4J = 0.5$ Hz, ArH), 8.45 (s, *H*C=C-CPh_2OMe)*, 8.72 ppm (s, OH)*; * assignment interchangeable; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.17 (CH_3), 52.91 (CH_3), 72.97 (CH_2), 86.27 (Ar_3C), 90.29 (Ar_3C), 118.36, 123.35, 124.68, 124.92, 124.97, 125.13, 126.15, 126.30, 126.46, 126.54, 126.71, 126.80, 127.12, 127.40, 127.62, 127.70, 127.79, 127.94, 128.06, 128.19, 128.22, 128.78, 128.97, 129.09, 129.16, 129.92, 130.27, 130.49, 133.39, 133.60, 137.74, 137.92, 140.48, 141.19, 142.65, 142.70, 151.73 (OC_{Ar}), 153.76 ppm (OC_{Ar}); IR (film): $\tilde{\nu}$ = 3295, 3060, 3025, 2940, 2825, 2250, 1955, 1710, 1625, 1600, 1495, 1450, 1425, 1365, 1335, 1310, 1280, 1255, 1220, 1195, 1150, 1105, 1060, 1035, 1000, 945, 930, 905, 890, 850, 815, 750, 720, 700 cm^{-1}; HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{54}H_{40}O_3$ [M−MeOH$^+$]: 736.297745; found: 736.297300 (−0.6 ppm).

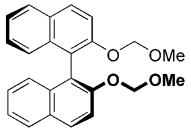


(*S*)-1-[2-(Dimethylamino)naphthalen-1-yl]-2-naphthol (20a):[31] A solution of amine **26** (1.28 g, 3.87 mmol) in HCO_2H (14 mL) and an aq. formaldehyde solution (37%, 14 mL) were heated under reflux for 9 h. After cooling, satd. aq. $NaHCO_3$ (200 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (6×5 cm, 100 mL, cyclohexane/EtOAc 90:10 + 1% NEt_3) provided the title compound (fractions 5–19, 1.03 g, 85%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 2.64$ (s, 2×CH_3), 7.02–7.22 (m, 4× ArH), 7.31 (m, possibly interpretable as dd, $^3J = ^3J = 7.4$ Hz, 2× ArH), 7.37 (d, $^3J = 8.9$ Hz, ArH), 7.50 (d, $^3J = 8.9$ Hz, ArH), 7.83 (d, $^3J = 8.5$ Hz, ArH), 7.85 (d, $^3J = 8.4$ Hz, ArH), 7.88 (d, $^3J = 8.8$ Hz, ArH), 7.95 ppm (d, $^3J = 9.1$ Hz, ArH).

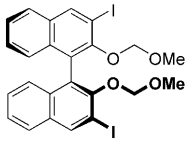


(*S*)-1-[2-(*N*,*N*-Dibenzylamino)naphthalen-1-yl]-2-naphthol (20b): Conc. aqueous HCl (0.5 mL) was added to a solution of methoxymethyl ether **27** (94.6 mg, 0.186 mmol) in MeOH (3 mL) and the mixture was heated under reflux for 7 h. After cooling,

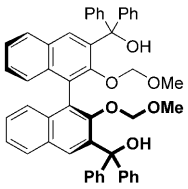
satd. aq. $NaHCO_3$ (4 mL) was added. The aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (2×15 cm, 20 mL, cyclohexane/EtOAc 95:5) provided the title compound (fractions 3–7, 73.6 mg, 85%) as a colorless solid. M.p. range 60–70°C; $[\alpha]_D^{20}=+113$ ($c=1.08$ in $CHCl_3$); >99 *ee*;[58] ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = AB signal ($\delta_A=3.91$, $\delta_B=3.96$, $J_{AB}=14.3$ Hz, 2×CH_2), 5.27 (br s, OH), 6.94 (dd, $^3J=7.5$, $^4J=3.4$ Hz, 4×ArH), 7.10–7.30 (m, 12×ArH), 7.37 (ddd, $^3J=8.1$, $^3J=6.8$, $^4J=1.4$ Hz, ArH), 7.39 (d, $^3J=8.8$ Hz, ArH), 7.45 (d, $^3J=9.0$ Hz, ArH), 7.85 (m, possibly interpretable as dd, $^3J=8.1$, $^4J=2.1$ Hz, 2×ArH), 7.89 ppm (d, $^3J=8.3$ Hz, ArH), 7.91 (d, $^3J=8.0$ Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=56.19$ (2×CH_2), 117.56, 118.13, 122.38, 123.34, 123.39, 124.89, 125.24, 125.62, 126.79, 126.89, 127.08, 127.30, 128.03, 128.14, 128.35, 129.01, 129.47, 129.72, 129.93, 130.69, 133.94, 134.30, 137.73, 149.43 (C_{Ar}N)*, 151.11 ppm (C_{Ar}O)*; * assignment interchangeable; IR (film): $\tilde{\nu}$=3520, 3060, 3030, 2925, 2850, 1810, 1620, 1595, 1505, 1495, 1455, 1430, 1380, 1270, 1220, 1175, 1145, 1130, 1070, 1030, 970, 960, 935, 915, 865, 815, 770, 745 cm^{-1}; HRMS (EI, 70 eV): *m*/*z*: calcd for $C_{34}H_{27}NO$ [M^+]: 465.209264; found: 465.209805 (+1.2 ppm).



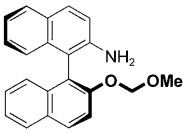
(*S*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthalene (22):[29] (*S*)-BINOL (**17a**, >99% *ee*) (9.90 g, 34.6 mmol) in THF (50 mL) was added dropwise to an ice-cooled suspension of NaH (60% in mineral oil, 4.15 g, 104 mmol, 3.01 equiv) in THF (180 mL). After 1 h, the ice bath was removed. After stirring at RT for 1 h, chloromethyl methyl ether [freshly prepared by the dropwise addition of acetyl chloride (7.40 mL, 8.14 g, 104 mmol, 3.01 equiv) to a suspension of $ZnBr_2$ (155 mg, 0.688 mmol, 1.99 mol%) in dimethoxymethane (12.0 mL, 10.3 g, 136 mmol, 3.93 equiv) at RT within 40 min and further stirring for 1 h] was added with ice-cooling. The ice bath was removed and after 4 h, the reaction was quenched by the addition of satd. aq. NH_4OH (25 mL) and satd. aq. NH_4Cl (25 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (8×20 cm, 100 mL, cyclohexane/EtOAc 90:10) provided the title compound (fractions 39–70, 11.9 g, 92%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta=3.14$ (s, 2×CH_3), AB signal ($\delta_A=4.97$, $\delta_B=5.07$, $J_{AB}=6.7$ Hz, 2×CH_2), 7.17 (dd, $^3J=^3J=8.5$ Hz, 2×ArH), 7.23 (d, $^3J=9.8$ Hz, 2×ArH), 7.34 (ddd, $^3J=^3J=6.7$, $^4J=1.3$ Hz, 2×ArH), 7.57 (d, $^3J=9.1$ Hz, 2×ArH), 7.87 (d, $^3J=8.2$ Hz, 2×ArH), 7.94 ppm (d, $^3J=9.1$ Hz, 2×ArH).



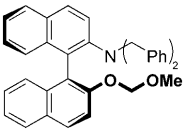
(*S*)-3,3′-Diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (23):[29] *n*BuLi (2.50 M in hexanes, 3.60 mL, 9.00 mmol, 2.98 equiv) was added to solution of methoxymethyl ether **22** (1.13 g, 3.02 mmol) and TMEDA (1.40 mL, 0.994 g, 8.55 mmol, 2.83 equiv) in Et_2O (52 mL). After 6 h, THF (33 mL) was added. 1 h later, the mixture was cooled to −40°C and I_2 (2.39 g, 9.42 mmol, 3.12 equiv) in THF (9.4 mL) was added. The cooling bath was removed. After 2 h, the reaction was quenched by the addition of satd. aq. K_2CO_3 (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic phases were washed with satd. aq. $Na_2S_2O_3$ (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (5×20 cm, 100 mL, cyclohexane/EtOAc 90:10) provided the title compound (fractions 6–11, 1.61 g, 84%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta=2.61$ (s, 2×CH_3), AB signal ($\delta_A=4.69$, $\delta_B=4.80$, $J_{AB}=5.6$ Hz, 2×CH_2), 7.17 (d, $^3J=8.5$ Hz, 2×ArH), 7.30 (dd, $^3J=^3J=7.6$ Hz, 2×ArH), 7.42 (dd, $^3J=7.8$, $^3J=7.0$ Hz, 2×ArH), 7.78 (d, $^3J=8.2$ Hz, 2×ArH), 8.54 ppm (s, 2×HC=CI).



(*S*)-3,3′-Bis(hydroxydiphenylmethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (24):[30] *n*BuLi (2.20 M in hexanes, 36.0 mL, 79.2 mmol, 3.08 equiv) was added to a solution of methoxymethyl ether **22** (9.64 g, 25.7 mmol) and TMEDA (12.0 mL, 9.24 g, 79.5 mmol, 3.09 equiv) in Et_2O (400 mL). After 6 h, THF (250 mL) and benzophenone (16.9 g, 92.7 mmol, 3.61 equiv) in THF (16 mL) were added with ice cooling. The cooling bath was removed and after 14 h, the reaction was quenched by the addition of satd. aq. NH_4Cl (250 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (8×20 cm, 100 mL, cyclohexane/EtOAc 92:8) provided the title compound (fractions 31–50, 16.1 g, 85%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta=2.81$ (s, 2×CH_3), AB signal ($\delta_A=3.78$, $\delta_B=3.82$, $J_{AB}=4.8$ Hz, 2×CH_2), 5.79 (s, 2×OH), 7.15–7.20 (m, 4×ArH), 7.25–7.36 (m, 20×ArH), 7.44 (d, $^3J=8.6$ Hz, 4×ArH), 7.62 ppm (d, $^3J=7.9$ Hz, 2×ArH).

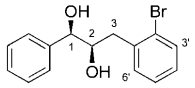


(*S*)-2-Amino-1-[2-(methoxymethoxy)-naphthalen-1-yl]naphthalene (26): A suspension of benzylamine **25** (1.85 g, 4.40 mmol) and Pd (10% on C, 265 mg, 0.249 mmol, 5.66 mol%) in EtOAc (8 mL) was heated under H_2 (1 atm) at 60°C for 7 h. Filtration over Celite, removal of the solvent under reduced pressure and flash chromatography (6×15 cm, 100 mL, cyclohexane/EtOAc 85:15) provided the title compound (fractions 15–27, 1.41 g, 97%) as a colorless solid. M.p. 127–129°C; $[\alpha]_D^{20}=-81.2$ ($c=1.54$ in $CHCl_3$); >99 *ee*;[58] ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta=3.16$ (s, CH_3), 3.51 (br s, NH_2), AB signal ($\delta_A=5.01$, $\delta_B=5.05$, $J_{AB}=6.8$ Hz, CH_2), 7.00 (m, possibly interpretable as d, $^3J=8.2$ Hz, ArH), 7.10 (d, $^3J=8.7$ Hz, ArH), 7.17 (m, 2×ArH), 7.22–7.28 (m, 2×ArH), 7.37 (ddd, $^3J=8.1$, $^3J=5.8$, $^4J=2.14$ Hz, ArH), 7.57 (d, $^3J=9.0$ Hz, ArH), 7.76 (dd, $^3J=7.8$, $^4J=1.5$ Hz, ArH), 7.78 (d, $^3J=8.8$ Hz, ArH), 7.88 (d, $^3J=8.1$ Hz, ArH), 7.96 ppm (d, $^3J=9.1$ Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=56.06$ (OCH_3), 95.31 (OCO), 113.72, 117.91, 118.19, 121.17, 122.21, 124.38, 124.57, 125.32, 126.39, 126.92, 128.00, 128.14, 128.18, 129.12, 129.94, 130.47, 133.63, 134.28, 142.20 (CN), 153.15 ppm (C_{Ar}O); IR (film): $\tilde{\nu}$= 3465, 3380, 3055, 3010, 2955, 2900, 2825, 1920, 1620, 1590, 1505, 1475, 1465, 1430, 1405, 1380, 1350, 1330, 1270, 1255, 1240, 1220, 1200, 1150, 1085, 1060, 1035, 1015, 965, 915, 865, 815, 770, 750 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{19}NO_2$ (329.4): C 80.22, H 5.81, N 4.25; found: C 79.90, H 5.74, N 4.02.

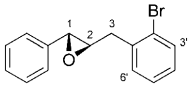


(*S*)-2-(*N*,*N*-Dibenzylamino)-1-[2-(methoxymethoxy)naphthalen-1-yl]naphthalene (27):[33] A suspension of benzylamine **25** (98.6 mg, 0.235 mmol), benzyl bromide (44.3 mg, 0.259 mmol, 1.10 equiv), and K_2CO_3 (35.8 mg, 0.259 mmol, 1.10 equiv) in MeCN (2 mL) was heated under reflux for 6 h. More benzyl bromide (20.0 mg, 0.117 mmol, 0.498 equiv) and K_2CO_3 (17.0 mg, 0.123 mmol, 0.523 equiv) were added and the mixture was heated under reflux for further 4 h. After cooling, the reaction mixture was diluted with H_2O (10 mL) and Et_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (2×5 cm, 20 mL, cyclohexane/EtOAc 98:2) provided the title compound (fractions 1–6, 110 mg, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta=3.09$ (s, CH_3), AB signal ($\delta_A=3.89$, $\delta_B=4.01$, $J_{AB}=14.4$ Hz, 2×NCH_2), AB signal ($\delta_A=4.98$, $\delta_B=5.06$, $J_{AB}=7.0$ Hz, OCH_2), 6.78 (d, $^3J=6.3$ Hz, 4×ArH), 7.01–7.23 (m, 9×ArH), 7.30–7.40 (m, 4×ArH), 7.58 (d, $^3J=$

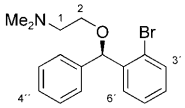
9.1 Hz, ArH), 7.83 (d, ^3J=8.5 Hz, 2×ArH), 7.90 (d, ^3J=8.2 Hz, ArH), 7.95 ppm (d, ^3J=9.1 Hz, ArH).



(1*R*,2*R*)-3-(2-Bromophenyl)-1-phenylpropane-1,2-diol (31): At −20 °C 1,2-dibromobenzene (**6**; 0.700 mL, 1.34 g, 5.69 mmol, 1.34 equiv) was added dropwise to *i*PrMgCl·LiCl (1.86 M in THF, 2.80 mL, 5.21 mmol, 1.23 equiv). After 4 h at −15 °C, *trans*-cinnamyl chloride (**29**; 0.620 mL, 646 mg, 4.23 mmol) and then CuCN·2 LiCl (0.97 M in THF, 0.50 mL, 0.50 mmol, 11 mol %) were added dropwise and the mixture was stirred at −15 °C for 12 h. The reaction was quenched by the addition of EtOH (0.2 mL). After removal of the cooling bath, satd. aq. NH_4Cl (6 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (1 mL) and added to a solution of $K_3Fe(CN)_6$ (4.19 g, 12.7 mmol, 3.00 equiv), K_2CO_3 (1.76 g, 12.7 mmol, 3.00 equiv), $MeSO_2NH_2$ (406 mg, 4.27 mmol, 1.01 equiv), $K_2OsO_2(OH)_4$ (7.9 mg, 21 μmol, 0.51 mol %), and $(DHQD)_2PHAL$ (34.0 mg, 43.6 μmol, 1.03 mol %) in *t*BuOH (15 mL)/H_2O (15 mL), which was cooled to 0 °C. After stirring at this temperature for 22 h, the reaction mixture was extracted with EtOAc (3×20 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (4×10 cm, 50 mL, cyclohexane/EtOAc 70:30) provided the title compound (fractions 9–18, 1.03 g, 79 % overall yield) as a colorless solid. M.p. 131–134 °C; $[\alpha]_D^{20}$=+15.7 (c=1.02 in $CHCl_3$); 91 % *ee* (by chiral HPLC[36]); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ=2.28 (d, $J_{2\text{-}OH,2}$=4.1 Hz, 2-OH)*, 2.80 (d, $J_{1\text{-}OH,1}$=4.2 Hz, 1-OH)*, AB signal (δ_A=2.79, δ_B=2.91, J_{AB}=13.9 Hz, in addition split by $J_{H(A),2}$=9.4, $J_{H(B),2}$=3.7 Hz, 3-H_2), 4.06 (dddd, $J_{2,3\text{-}H(A)}$=9.4, $J_{2,1}$=5.8, $J_{2,2\text{-}OH}$ ≈$J_{2,3\text{-}H(B)}$ ≈3.9 Hz, 2-H), 4.56 (dd, $J_{1,2}$=5.8, $J_{1,1\text{-}OH}$=4.2 Hz, 1-H), 7.07 (ddd, $J_{4',3'}$=7.8, $J_{4',5'}$=7.2, $J_{4',6'}$=2.0 Hz, 4′-H), 7.23 (ddd, $J_{5',6'}$=$J_{5',4'}$=7.6, $J_{5',3'}$=1.3 Hz, 5′-H), 7.27 (dd, $J_{6',5'}$=8.2, $J_{6',4'}$=2.0 Hz, 6′-H), 7.29–7.40 (m, 5×ArH), 7.51 ppm (dd, $J_{3',4'}$=8.1, $J_{3',5'}$=1.3 Hz, 3′-H); * assignment interchangeable; ^{13}C NMR (100 MHz, $CDCl_3$): δ=39.82 (C-3), 75.13 (C-1)*, 77.15 (C-2)*, 124.79, 126.94, 127.47, 128.24, 128.31, 128.63, 131.93, 132.97, 137.84, 140.85 ppm; * assignment interchangeable; IR (film): $\tilde{\nu}$=3425, 3210, 3060, 3025, 2955, 2925, 2900, 1470, 1450, 1440, 1365, 1330, 1290, 1195, 1175, 1120, 1090, 1070, 1035, 1025, 1015, 945, 915, 885, 860, 810, 770, 750, 720 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{15}BrO_2$ (307.2): C 58.65, H 4.92; found: C 58.88, H 5.01.

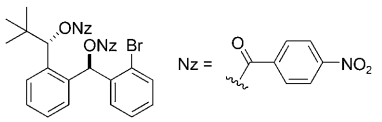


(1*R*,2*R*)-3-(2-Bromophenyl)-1,2-epoxy-1-phenylpropane (32): Me_3SiCl (0.200 mL, 171 mg, 1.58 mmol, 1.58 equiv) was added to a suspension of diol **31** (307 mg, 0.999 mmol) and trimethyl orthoacetate (0.200 mL, 189 mg, 1.57 mmol, 1.57 equiv) in CH_2Cl_2 (3.5 mL). After 6 h, the solvent was removed under reduced pressure. The residue was dissolved in MeOH (4 mL) and K_2CO_3 (265 mg, 1.92 mmol, 1.92 equiv) was added. After stirring at RT for 4 h, the reaction mixture was diluted with CH_2Cl_2 (8 mL) and the solids were filtered off. Removal of the solvent under reduced pressure and flash chromatography (2.5×10 cm, 20 mL, cyclohexane/EtOAc 95:5) provided the title compound (fractions 3–8, 241 mg, 84 % as a faintly yellowish oil. $[\alpha]_D^{20}$=+15.6 (c=1.08 in $CHCl_3$); 91 % *ee* (by chiral HPLC[36]); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ=AB signal (δ_A=3.16, δ_B=3.20, J_{AB}=13.7 Hz, in addition split by $J_{H(A),2}$=5.6, $J_{H(B),2}$=4.4 Hz, 3-H_2), 3.24 (ddd, $J_{2,3\text{-}H(A)}$=5.7, $J_{2,\ 3\text{-}H(B)}$=4.7, $J_{2,1}$=2.0 Hz, 2-H), 3.71 (d, $J_{1,2}$=1.9, 1-H), 7.11 (ddd, $J_{4',3'}$=8.0, $J_{4',5'}$=7.5, $J_{4',6'}$=1.9 Hz, 4′-H), 7.25–7.36 (m, 7×ArH), 7.56 ppm (dd, $J_{3',4'}$=8.0, $J_{3',5'}$=1.3 Hz, 3′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=38.63 (C-3), 58.67 (C-2)*, 61.64 (C-1)*, 124.81, 125.65, 127.71, 128.21, 128.53, 128.60, 131.30, 132.93, 136.59 (C-1′)**, 137.34 ppm (1-C_{Ar})**; *·** assignments interchangeable; IR (film): $\tilde{\nu}$=3060, 2980, 2922, 1565, 1496, 1470, 1440, 1350, 1290, 1220, 1070, 1025, 940, 915, 890, 860, 750 cm^{-1}; HRMS (EI, 70 eV): m/z: calcd for $C_{15}H_{13}BrO$ [M^+]: 288.01498; found: 288.01500 (+0.1 ppm).



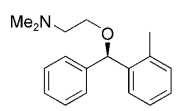
(*R*)-*N*-{2-[(2-Bromophenyl)phenylmethoxy]ethyl}-*N*,*N*-dimethylamine (33): A suspension of alcohol (*R*)-**2a** (320 mg, 1.21 mmol), the hydrochloride of 2-(*N*,*N*-dimethylamino)ethyl chloride (347 mg, 2.41 mmol, 1.99 equiv), and freshly ground KOH (692 mg, 12.3 mmol, 10.2 equiv) in DMSO (2.5 mL) was stirred at RT for 16 h. Aq. NaOH (1 M, 6 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were washed with aqueous NaOH solution (1 M, 2×5 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (2.5×5 cm, 20 mL, cyclohexane/EtOAc 70:30, from fraction 14 70:30 + 1 % NEt_3) provided the title compound (fractions 6–29, 315 mg, 78 %) as a colorless oil. $[\alpha]_D^{20}$=+23.1 (c=1.02 in $CHCl_3$); 52 % *ee* (by chiral HPLC[35]); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ=2.25 (s, 2×CH_3), 2.59 (m, possibly interpretable as t, ^3J=6.1 Hz, 1-H_2), 3.59 (t, ^3J=6.1 Hz, 2-H_2), 5.79 (s, OCH), 7.10 (ddd, $J_{4,3}$=8.0, $J_{4,5}$=7.3, $J_{4,6}$=1.8 Hz, 4′-H), 7.23 (tt, ^3J=8.6, ^4J=1.4 Hz, 4″-H), 7.28–7.32 (m, 3×ArH), 7.38–7.41 (m, 2×ArH), 7.52 (dd, $J_{3,4}$=7.9, $J_{3,5}$=1.3 Hz, 3′-H), 7.53 ppm (dd, $J_{6,5}$=7.8, $J_{6,4}$=1.8 Hz, 6′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=46.03 (2×CH_3), 58.99 (C-1), 67.68 (C-2), 82.14 (OCH), 123.61 (C-2′), 127.43, 127.62, 127.76, 128.33, 128.87, 129.00, 132.75, 140.82 (C-1′)*, 141.33 ppm (C-1″)*; * assignment interchangeable; IR (film): $\tilde{\nu}$=3065, 3030, 2945, 2865, 2820, 2770, 1570, 1495, 1455, 1270, 1185, 1160, 1100, 960, 920, 855, 755, 720, 700 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{20}BrNO$ (334.3): C 61.09, H 6.03, N 4.19; found: C 61.15, H 5.76, N 4.02.

***rac*-(*R*)-(2-Bromophenyl)-{2-[(*S*)-2,2-dimethyl-1-(4-nitrobenzoyloxy)propyl]phenyl}methyl 4-nitrobenzoate (34)**: NEt_3 (60 μL, 44 mg, 0.43 mmol, 3.0 equiv) and 4-nitrobenzoyl chloride (67.0 mg, 0.361 mmol, 2.53 equiv)



were added to an ice-cooled solution of diol "*anti*"-*rac*-**2c** (49.7 mg, 0.142 mmol) and DMAP (7.4 mg, 61 μmol, 43 mol %) in CH_2Cl_2 (1.5 mL). The resulting mixture was stirred at 0 °C for 4 h. Removal of the solvent under reduced pressure and flash chromatography (2×15 cm, 20 mL, cyclohexane/EtOAc 92:8) provided the title compound (fractions 5–9, 87.2 mg, 95 %) as a yellowish solid. Single crystals suitable for X-ray structure analysis were obtained from a solution in a little CH_2Cl_2 upon covering it with a layer of petroleum ether. M.p. 181–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ=1.20 [s, $C(CH_3)_3$], 5.94 (s, C*H*t Bu), 7.03 (dd, ^3J=7.7, ^4J=1.8 Hz, ArH), 7.22 (ddd, ^3J=^3J=7.6, ^4J=1.4 Hz, ArH), 7.27 (ddd, ^3J=^3J=7.5, ^4J=1.8 Hz, ArH), 7.39 (m, 2×ArH), 7.58 (m, 2×ArH), 7.73 (dd, ^3J=7.8, ^4J=1.4 Hz, ArH), 7.89 (s, C*H*Ar_2), 8.07 (m, 2×Ar_{Nz}H), 8.22–8.26 (m, 2×Ar_{Nz}H), 8.27–8.32 ppm (m, 4×Ar_{Nz}H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.52 [$C(CH_3)_3$], 37.14 [$C(CH_3)_3$], 75.86 (*C*HAr_2)*, 79.14 (*CH*t Bu)*, 123.57, 123.76, 125.13, 125.58, 127.78, 128.03, 128.43, 129.02, 130.63, 130.66, 130.90, 131.12, 133.34, 135.12, 135.86, 136.01, 136.71, 137.47, 150.51 (CNO_2), 150.86 (CNO_2), 162.71 (O-C=O), 163.39 ppm (O-C=O); * assignment interchangeable; IR (film): $\tilde{\nu}$=3110, 3075, 2970, 2870, 2255, 1735, 1730, 1605, 1525, 1480, 1465, 1440, 1410, 1395, 1360, 1345, 1320, 1265, 1170, 1095, 1025, 1015, 945, 910, 870, 855, 815, 780, 750, 740, 715 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{27}BrN_2O_8$ (647.5): C 59.36, H 4.20, N 4.33; found: C 59.41, H 4.42, N 4.21.

(*R*)-*N*,*N*-Dimethyl-*N*-{2-[1-(2-methylphenyl)-1-phenylmethoxy]ethyl}amine [(*R*)-orphenadrine]:[45] *n*BuLi (2.12 M in hexanes, 0.440 mL, 0.933 mmol, 1.18 equiv) was added to a solution of



bromide **33** (264 mg, 0.790 mmol) in THF (3 mL) at −78 °C. After 1 h, MeI (65 μL, 0.15 g, 1.0 mmol, 1.3 equiv) was added. After 2 h, the dry ice was removed from the cooling bath and the reaction was allowed to warm slowly. At −60 °C, the reaction was quenched by the addition of MeOH (0.5 mL) and Et_2NH (4.0 mL, 2.8 g, 39 mmol, 49 equiv). After removal of the cooling bath, aqueous NaOH solution (1 M, 8 mL) was added to the reaction mixture. The phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography (2.5×20 cm, 20 mL, cyclohexane/EtOAc 90:10 + 1% NEt_3, from fraction 21 80:20 + 1% NEt_3) provided the title compound (fractions 39–59, 140 mg, 66%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 2.26 (s, 3×CH_3), 2.59 (t, ^3J = 6.2 Hz, NCH_2), 3.57 (t, ^3J = 6.0 Hz, OCH_2), 5.53 (s, OCH), 7.10–7.36 (m, 8×ArH), 7.41–7.44 ppm (m, possibly interpretable as dd, ^3J = 6.7, ^4J = 2.1 Hz, ArH).

Acknowledgements

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[35] The *ee* of monobromoalcohol **2a** was determined by chiral HPLC (Chiralcel OD-H, *n*-heptane/EtOH 100:3, 0.8 mL min^{-1}, 40 °C isotherm, 230 nm): $t_{r,(R)}$ = 17.7 min, $t_{r,(S)}$ = 20.9 min (determined with racemic material).[59]

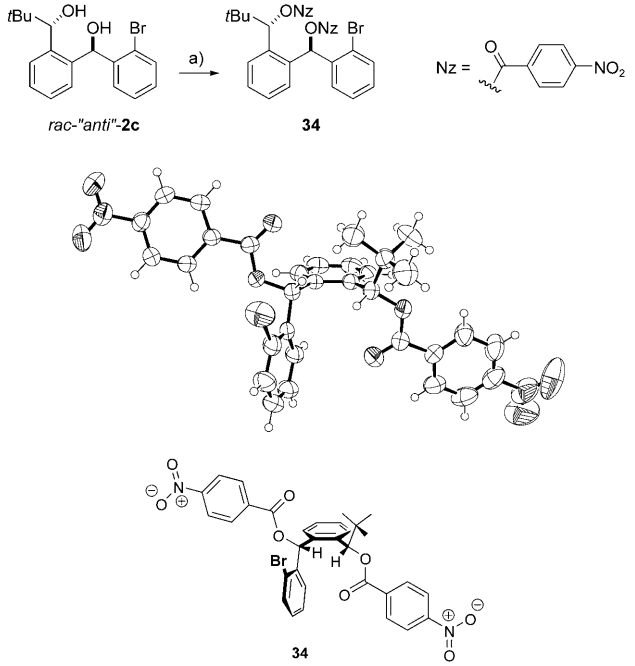
[36] The *ee* of monobromoalcohol **5a** was determined by chiral HPLC (Chiralcel OD-H, *n*-heptane/EtOH 100:2, 0.8 mL min^{-1}, 20 °C isotherm, 230 nm): $t_{r,(S)}$ = 17.9 min, $t_{r,(R)}$ = 19.7 min (determined with racemic material).[59]

[37] Ligand **17b** could be recovered in up to 99% yield after quenching the reaction with a saturated aqueous NH_4Cl solution by extracting the resulting mixture with CH_2Cl_2.

[38] The *ee* of lactol **2b** was determined by chiral HPLC (Chiralpak AD-H, *n*-heptane/*i*PrOH 95:5, 1.0 mL min^{-1}, 20 °C isotherm, 230 nm): $t_{r,\text{diastereomer 1},(S)}$ = 18.5 min, $t_{r,\text{diastereomer 1},(R)}$ = 20.1 min, $t_{r,\text{diastereomer 2},(S)}$ = 29.2 min, $t_{r,\text{diastereomer 2},(R)}$ = 31.9 min (determined with racemic material).[59]

[39] The *ee* of diol **2c** was determined by chiral HPLC (Chiralpak AD-H for "*anti*"-**2c**, Chiralpak IA for "*syn*"-**2c**, *n*-heptane/EtOH 95:5, 1.0 mL min^{-1}, 20 °C isotherm, 230 nm): $t_{r,\text{"anti"-2c},(S)}$ = 26.9 min, $t_{r,\text{"anti"-2c},(R)}$ = 40.1 min, $t_{r,\text{"syn"-2c},(R)}$ = 10.4 min, $t_{r,\text{"syn"-2c},(S)}$ = 22.7 min (determined with racemic material).[59]

[40] The relative configuration of the stereocenters in a racemic sample of the major diastereomer of this diol **2c** was elucidated after bis-*p*-nitrobenzoylation and crystallization (→ diester **34**) by an X-ray structure analysis[60] (Scheme 9).



Scheme 9. Structure elucidation of the major diastereomer of *rac*-*"anti"*-**2c** as bis-*p*-nitrobenzoate. a) *p*-O_2N-C_6H_4-COCl (2.5 equiv), NEt_3 (3.0 equiv), DMAP (43 mol%), CH_2Cl_2, 0 °C, 4 h; 95%. DMAP = 4-(dimethylamino)pyridine.

[41] For a 96% *ee* sample of (*S*)-**2a**, a specific rotation of $[\alpha]_D^{20} = -41.9$ ($c = 1.19$ in $CHCl_3$) is reported.[47] Since our specimen of (*R*)-**2a** possessed 23.4% *ee* according to HPLC, a $CHCl_3$ solution of a 96% *ee* sample should have exhibited $[\alpha]_D^{20} = +10.3 \times (96/23.4) = +42.3$. However, it must be remembered that this calculation is correct only with the provision that there is a linear correlation between the optical purity (determined via specific rotation) and the enantiomeric purity (determined by HPLC). This need not be true though: "Aussi on admet, et cette supposition classique n'a jamais été mise en doute, que la pureté optique $[\alpha]/[\alpha]_0$ est égale à la pureté énantiomérique $(R-S)/(R+S)$. Or, dans certains cas, ceci est tout à fait inexact." ("It is accepted as well—and this classical assumption has never been questioned—that the optical purity $[\alpha]/[\alpha]_0$ equals the enantiomeric purity $(R-S)/(R+S)$. However, in certain cases this is not exact.") (A. Horeau, *Tetrahedron Lett.* **1969**, *10*, 3121–3124). In support of this statement Horeau noticed a significant nonlinearity of the correlation of the optical with the enantiomeric purity of rather concentrated solutions (ca. 1.6 M) of a substituted nonracemic succinic acid in a nonpolar solvent ($CHCl_3$): the optical purity could be off by 15% *ee*. This deviation reflects the presence of (possibly diastereomeric) carboxylic acid dimers. Since alcohols vs. carboxylic acids are less prone to dimerize and since the solution of (*R*)-**2a** used to determine the specific rotation was considerably more diluted (ca. 0.06 M) than Horeau's, an extrapolation from $[\alpha]_D^{20}$ (23.4% *ee*) to $[\alpha]_D^{20}$ (96% *ee*) seems justifiable.

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[51] Diastereomer "*syn*"-(*R*)-**2c** remained impure after flash chromatography. Its yield was therefore determined by NMR analysis with 2,4,6-tribromotoluene as internal standard and no further analysis was made.

[52] The numbering shown in the formula does not match the IUPAC name of this compound. This discrepancy was chosen because it simplifies the written assignment of spectroscopically identical nuclei.

[53] The indicated yield refers to the following stoichiometry: $2\,ArCH_2Br + 2\,Fe_2(CO)_9 \rightarrow (ArCH_2)_2C{=}O + FeBr_2 + Fe_3(CO)_{12} + 5\,CO$ (see M. A. Bennett, H. Neumann, *Aust. J. Chem.* **1980**, *33*, 1251–1259).

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[58] Commercially available enantiopure (*S*)-BINOL (>99% *ee*) was used as the starting material.

[59] The peaks used for *ee* calculation did not exhibit shoulders. When the *ee* was determined by the same method for a racemic mixture, the two peak areas equalled each other with a discrepancy of <1%. Nevertheless, we cannot exclude that a given sample contained an impurity with the same retention time as one of the two respective enantiomers (see the Supporting Information for representative HPLC profiles).

[60] CCDC 707774 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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