Asymmetric Syntheses of 2-(1-Aminoethyl)phenols

by **E. Peter Kündig***, **Candice Botuha**, **Gilles Lemercier**, **Patrick Romanens**, **Lionel Saudan**, and **Sylvie Thibault**

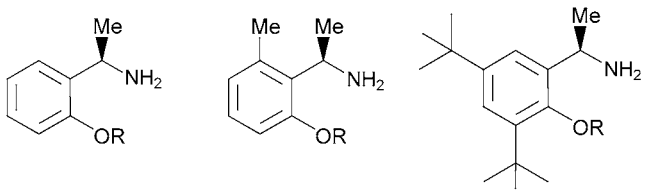
Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, CH-1211 Geneva 4

Three different routes were probed for the synthesis of enantiomerically enriched 2-(1-aminoethyl)phenols and their methyl ethers. The first route centers on diastereoselective nucleophile addition to chiral imines. The second route has as key steps the enantioselective reduction of a ketone followed by nucleophilic substitution, and the third route involves a diastereoselective imine reduction. The efficiency of the approach depends on the substrate substitution pattern. All three methods work well for the parent compound 2-(1-aminoethyl)phenol (**1**) but the third route is the most efficient, providing the compound with >96% enantiomer excess in three steps with an overall yield of 71%. Conversely, for the *ortho*-methyl analogue **2**, the first method is best. For the *t*-Bu-substituted analogue **3**, only moderate enantiomeric enrichment was achieved.

Introduction. – Enantiomerically pure chiral α-amino alcohols have been extensively used as chiral auxiliaries in asymmetric synthesis. They are abundant naturally occurring compounds (*e.g.*, norephedrine, ephedrine), or they are readily obtained from α-amino acids. The presence of two different functionalities gives access to a large variety of chiral derivatives such as oxazolidines [1], dihydrooxazoles [2], oxazolidinones [3], formamidines [4], and 1,3,2-oxazaphospholidines [5]. All these groups have found widespread use as chiral auxiliaries and chiral building blocks. Moreover, chiral α-amino alcohols are ligands in their own right or are building blocks for chiral ligands for transition-metal-mediated and catalyzed processes [6][7].

β-Amino alcohols on the other hand, while being important constituents of several antibiotics [8] and other biologically active natural products [9], have not seen extensive use as chiral auxiliaries or ligands [10][11] (for examples of chiral β-amino alcohols as ligands for asymmetric synthesis, see [5][12]). The prime reason would appear to be the lack of natural sources of these compounds. As part of a project aimed at the use of chiral 2-(1-aminoalkyl)phenols as precursors to new ligands and reagents [13], we present the results of a study of different asymmetric approaches to the synthesis of the (1-arylethyl)amines **1**–**3** (the (*R*)-enantiomers are shown in the *Figure*). We here describe three different routes that are complementary with respect to yield, selectivity, and efficiency.

Chiral enantiomerically pure benzylamines are generally obtained either by enzymatic [14] or chemical resolution [15] of racemic mixtures, or by asymmetric synthesis with either a chiral organometallic catalyst [16] or chiral reagents [17][18]. For [(2-methoxyphenyl)alkyl]amines or [(2-hydroxyphenyl)alkyl]amines (=2-(aminoalkyl)phenols), most syntheses have relied on chemical resolution [13d][19][20]. These methods allowed to obtain the products with high enantiomer excess (ee), but in the case of **1**, they were often of low efficiency because multiple recrystallizations were required. For example, amine (*R*)-**1a** was obtained in 28% yield and an ee >98% after



(*R*)-**1a** R = Me (*R*)-**2a** R = Me (*R*)-**3a** R = Me
(*R*)-**1b** R = H (*R*)-**2b** R = H (*R*)-**3b** R = H

Figure. *Chiral 2-(1-aminoethyl)phenols* **1b**, **2b** *and* **3b**, *and their methyl ethers* **1a**, **2a**, *and* **3a**

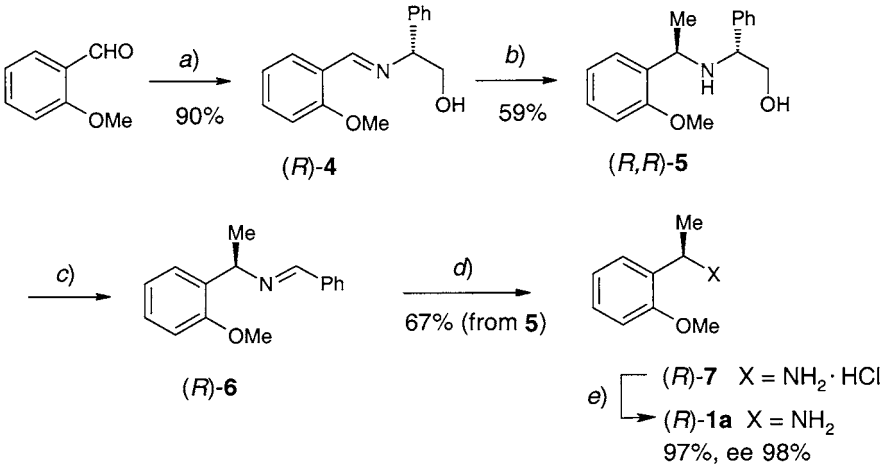
five recrystallizations [19a]. Three asymmetric syntheses have been reported: in early work, (*R*)-**1a** was prepared *via* Rh-catalyzed asymmetric hydrosilylation of a ketoxime with 16.5% ee [16d]. More recently, (*R*)-**1a** and (*R*)-**1b** were synthesized in up to 77% ee *via* nucleophilic addition of MeLi to chiral oxime ethers [21]. The synthesis of amine (*S*)-**1a** by ring opening of a chiral 1,3-oxazolidine with an organomagnesium reagent [22] is an efficient process, and this is an alternative route to those detailed in this report.

Recently, chiral non-racemic benzylamines possessing *o*-hydroxy or *o*-methoxy groups have found applications as chiral auxiliaries [23], chiral building blocks [13], or as ligands for transition-metal catalysts [24][25]. Moreover, (*S*)-**1a** has been reported to be a notably effective chiral auxiliary for the diastereoselective *Lewis* acid mediated allylation of tricyclic *N*-acyl-*N*,*O*-acetals [26].

Amines **2** were chosen to probe the influence of aromatic substituents on the conformation of the benzylic center. In ligands and auxiliaries containing a dihydrooxazine ring derived from **2**, and in metal chelates of ligand **2**, the aromatic Me group will enforce a pseudoaxial disposition of the benzylic Me group to avoid $A^{(1,3)}$ strain [27]. Chiral amines **3** may be of interest as ligands or ligand building blocks with the 3,5-di(*tert*-butyl) groups in place to guide incoming reagents to the chiral part of the molecule [28][29].

Results and Discussion. – 1. *[1-(2-Methoxyphenyl)ethyl]amine* ((*R*)-**1a**) *and [1-(2-Methoxy-6-methylphenyl)ethyl]amine* ((*S*)-**2a**) via *Diastereoselective Imine Alkylation* [30]: *Method A*. The amines (*R*)-**1a** and (*S*)-**2a** were synthesized by means of a method previously described for the preparation of chiral non-racemic benzylamines *via* alkylation of a chiral imine [31][32]. The synthetic route adopted by us for amine (*R*)-**1a** is shown in *Scheme 1*. Condensation of (*R*)-phenylglycinol (=(*βR*)-*β*-aminobenzeneethanol) with 2-methoxybenzaldehyde provided imine derivative (*R*)-**4**. Slow addition of MeLi to a THF solution of (*R*)-**4** at $-78°$ gave amino alcohol (*R*,*R*)-**5** as an orange oil. To achieve a high conversion (85% by GC) and chiral induction, the dark blue mixture was stirred at $-78°$ for 24 h and subsequently at $-30°$ for another 24 h. As judged by GC and ^{1}H-NMR analysis of the crude mixture, a single diastereoisomer was formed. Purification on deactivated silica gel gave amino alcohol (*R*,*R*)-**5** in 59%

Scheme 1



a) (*R*)-Phenylglycinol, 4 Å molecular sieves, EtOH, r.t. *b*) MeLi, THF, −78° to −30°. *c*) 1. $Pb(OAc)_4$, K_2CO_3, MeOH, 0°; 2. aq. Na_2CO_3 soln. *d*) 1. Aq. AcOH soln., THF, r.t.; 2. aq. NaOH soln. *e*) Aq. NaOH soln., Et_2O.

yield. Oxidative cleavage of the latter was performed by using a slight modification[1]) of a literature procedure [33]. Imine (*R*)-**6** was directly hydrolyzed in aq. AcOH/THF to provide the crude amine (*R*)-**1a** (ee 96%). Purification by formation of the HCl salt (*R*)-**7** and recrystallization gave amine (*R*)-**1a** in 67% yield (from (*R*,*R*)-**5**) and with an ee of 98%[2]) after basic extractive workup. The absolute configuration of amine (*R*)-**1a** was established by ^{1}H-NMR correlation of the amides obtained with both enantiomers of *Mosher*'s acid [34] as described for other chiral amines [35].

The same reaction sequence, when applied to 2-methoxy-6-methylbenzaldehyde (**8**) [36] and (*S*)-phenylglycinol, afforded *via* (*S*)-**9**, (*S*,*S*)-**10**, and (*S*)-**11** the highly enantiomerically enriched amine (*S*)-**2a**[3]) (*Scheme 2*).

The sequence of *Schemes 1* and *2* was successfully applied on a 30-g scale of imine derivative (*R*)-**4** and a 12-g scale of imine derivative (*S*)-**9** and provided with high enantiomeric excess 6 g (34% over five steps) of amine (*R*)-**1a** and 2.4 g (46% over four steps) of amine (*S*)-**2a**, respectively. Nevertheless, scale-up of this approach is hampered by the high-dilution conditions required in the alkylation step (0.05M), and the purification of the amino alcohol (*R*,*R*)-**5** by chromatography (silica gel) prior to the oxidative cleavage. Moreover, application of this methodology to the synthesis of enantiomerically enriched amine **3a** was not successful. A very poor yield was obtained for the diastereoselective addition step. We, therefore, turned to other approaches.

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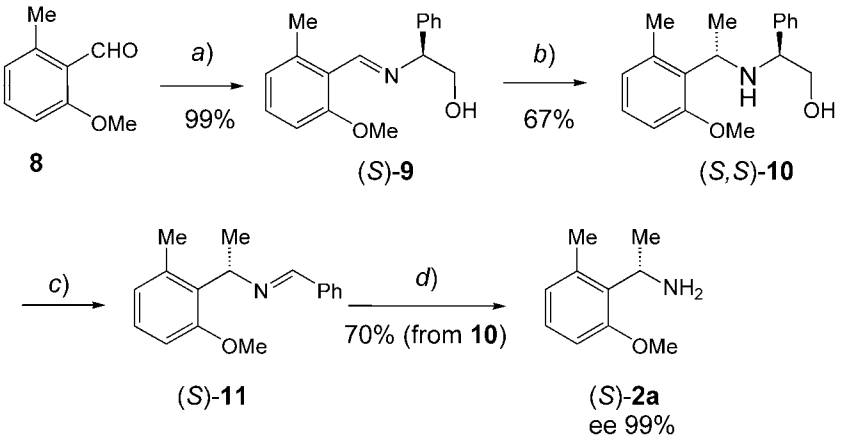
[1]) Simultaneous addition of a soln. of (*R*,*R*)-**5** and of $Pb(OAc)_4$ in MeOH to a suspension of K_2CO_3 in MeOH gave the lowest amount of oxazolidine formed between the amino alcohol and formaldehyde (see *Exper. Part* and [33]).

[2]) The ee was determined by GC on a chiral stationary phase after formation of the trifluoroacetamide **16** (see below and *Exper. Part*).

[3]) The ee was determined by HPLC on a chiral stationary phase after formation of the naphthalene-1-carboxamide with naphthalene-1-carbonyl chloride (see *Exper. Part*).

Scheme 2



a) (*S*)-Phenylglycinol, 4 Å molecular sieves, EtOH, r.t. *b*) MeLi, THF, −78°, 48 h. *c*) 1. $Pb(OAc)_4$, K_2CO_3, MeOH, 0°; 2. aq. Na_2CO_3 soln. *d*) 1. Aq. HCl soln., CH_2Cl_2, r.t.; 2. aq. NaOH soln.

2. *[1-(2-Methoxyphenyl)ethyl]amine* ((*S*)-**1a**), *[1-(2-Methoxy-6-methylphenyl)-ethyl]amine* ((*S*)-**2a**), *and {1-[3,5-Di(*tert*-butyl)-2-methoxyphenyl]ethyl}amine* ((*S*)-**3a**) via *Enantioselective Ketone Reduction: Method B.* In this second approach, amines (*S*)-**1a**, (*S*)-**2a**, and (*S*)-**3a** were synthesized by using as key step the enantioselective reduction of a prochiral ketone by the *Corey–Bakshi–Shibita* (*CBS*) method [37–39]. The chiral benzyl alcohol was next substituted in a stereospecific S_N2 reaction with inversion of configuration by an N-nucleophile (*Schemes 3* and *5*).

Thus, alcohol (*R*)-**14** was obtained in 99% yield and 96% ee[4]) from ketone **12** following a known procedure by using oxazaborolidine (*S*)-**13** (20 mol-%) in THF (0.4M) [40] (*Scheme 3*). Treatment of (*R*)-**14** with diphenyl phosphorazidate (DPPA) and 1,8-diazabicylo[5.4.0]undec-7-ene (DBU) in a THF solution at room temperature gave the azide (*S*)-**15** in 59% yield [41]. Hydrogenation of the latter over Pd/C gave amine (*S*)-**1a** in 78% yield and with 93% ee[5]). The erosion of the ee from alcohol (*R*)-**14** to the amine (*S*)-**1a** is ascribed to the activated benzylic center in these compounds [42]. Recrystallization of the trifluoroacetamide (*S*)-**16** of amine (*S*)-**1a** from hexane/AcOEt gave, after hydrolysis (K_2CO_3/MeOH/H_2O), the amine (*S*)-**1a** with an ee $\geq$98%[6]).

The same reaction sequence was used for the preparation of amines (*S*)-**2a** and (*S*)-**3a** starting from the ketones **21** and **20**. The former was prepared following a literature

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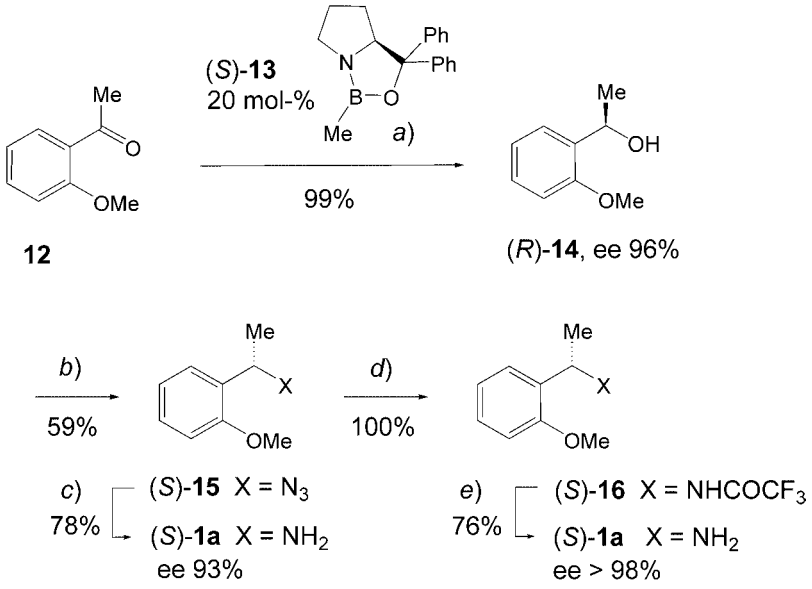
4) The ee was determined by ^{1}H- and ^{19}F-NMR after formation of the *Mosher* ester with (*R*)-*Mosher* chloride (see *Exper. Part*).

5) The ee was determined by GC on a chiral stationary phase after formation of the trifluoroacetamide **16** (see *Exper. Part*).

6) The ee was determined by GC on a chiral stationary phase after formation of the trifluoroacetamide **16** (see *Exper. Part*).

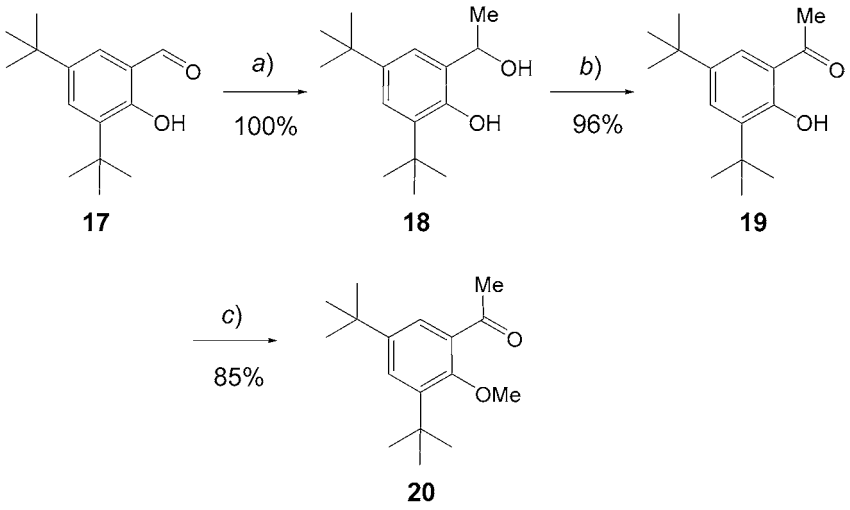
Scheme 3



a) $BH_3 \cdot THF$, THF, r.t. *b*) DPPA, DBU, THF, r.t. *c*) H_2 (1 atm), Pd/C, EtOH, r.t. *d*) CF_3COOH, THF. *e*) 1. Recryst. from hexane; 2. K_2CO_3, MeOH.

procedure in three steps from 2,3-dimethylanisole [36] and the latter from **17** *via* **18** and **19** as shown in *Scheme 4*. Alternatively, **19** is now accessible *via* an efficient $TiCl_4$-mediated phenol acetylation [43].

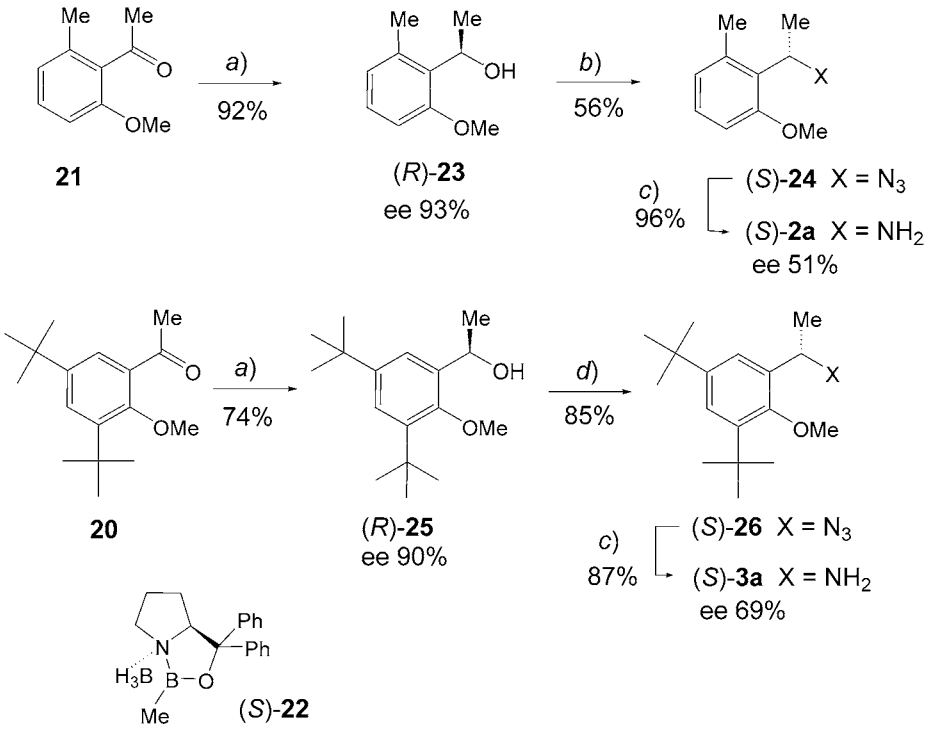
Scheme 4



a) MeMgBr, Et_2O, reflux. *b*) MnO_2, hexane, reflux. *c*) Me_2SO_4, K_2CO_3.

The enantioselective reduction of ketones **20** and **21** turned out to be more difficult than that of 2-methoxyacetophenone. Treatment of ketones **20** and **21** with borane·THF complex in the presence of oxazaborolidine (*S*)-**13** (20 mol-%) in THF (0.2M) at room temperature gave the alcohols **23** and **25** with low enantioselectivity (**23**: 100% yield, 43% ee; **25**: 81% yield, 9% ee). Increasing the concentration (1M) resulted in only a small improvement for alcohol **25** (86% yield, 31% ee). Better results were achieved by using the preformed BH_3·oxazaborolidine complex (*S*)-**22** in dry CH_2Cl_2 at $-20°$ (0.7–1M) [44]. With a catalytic amount (5 mol-%) of (*S*)-**22**, alcohol (*R*)-**23** was obtained from ketone **21** in 92% yield with 93% ee (*Scheme 5*). When applied to ketone **20**, alcohol (*R*)-**25** was obtained in 74% yield with 90% ee. A stoichiometric amount of the BH_3·oxazaborolidine complex (*S*)-**22** was required for the reduction of ketone **19** to give alcohol (*R*)-**18** (55% yield, 98% ee). The absolute configuration of alcohols (*R*)-**23**, (*R*)-**18**, and (*R*)-**25** as shown above, were determined by NMR correlation after formation of the ester derived from *Mosher*'s acid [45].

Scheme 5



a) (*S*)-**22** (5 mol-%), BH_3·Me_2S, CH_2Cl_2, $-20°$. *b*) DPPA, DBU, THF, r.t. *c*) H_2 (1 atm), Pd/C, EtOH, r.t. *d*) 4-NO_2-DPPA, DBU, THF, r.t.

The reaction of alcohols (*R*)-**23** (93% ee) and (*R*)-**25** (90% ee) with DPPA and DBU in THF solution at room temperature was very slow. The azides (*S*)-**24** and (*S*)-**26** were isolated in only 56 and 53% yield, respectively, and after long reaction times (24 h for (*R*)-**23**, 72 h for (*R*)-**25**). Partial racemization was observed, as amines (*S*)-**2a** and

(*S*)-**3a** were obtained with a lower ee after hydrogenation of the azides: (*S*)-**2a** (51% ee), and (*S*)-**3a** (77% ee). A better yield (85%) but slightly lower selectivity (69% ee) was obtained for azide (*S*)-**26** when the reaction was carried out with the more-reactive bis(4-nitrophenyl) phosphorazidate (4-NO_2-DPPA) [46] (*Scheme 5*).

This methodology was successfully applied to the synthesis of enantiomerically enriched (*S*)-**1a** in an overall yield of 35% (5 steps). Despite the partial racemization observed during the synthesis of amine (*S*)-**1a** by this *Method B*, scale-up was easier than in the synthesis by *Method A* because the individual steps can be run at higher concentrations. Nevertheless, it should be pointed out that the route *via* enantioselective aryl alkyl ketones is limited because the selectivity drops for bulky alkyl groups. Resolution is thus the method of choice for ^{i}Pr or ^{t}Bu analogs [13d]. Moreover, the serious erosion of enantiomer purity of (*S*)-**2a** and (*S*)-**3a** obtained *via* this route makes *Method B* of very limited use for these amines.

Amine (*R*)-**1a** was demethylated by treatment with $AlBr_3$ [47] in benzene to provide the aminophenol (*R*)-**1b** in 70% yield and 98% ee[7]). The use of BBr_3, previously successfully applied to the *tert*-butyl analog [13d], resulted here in partial racemization. This procedure with $AlBr_3$ could not be applied successfully for the demethylation of (*S*)-**3a** because it resulted in partial loss of *tert*-butyl groups from the aromatic ring.

3. *2-(1-Aminoethyl)phenols (*R*)-***1b***, (*S*)-***2b***, and (*R*)-***3b*** via *Diastereoselective Imine Reduction: Method C. Hogeveen* and co-workers have reported the highly diastereoselective reduction (Pd/H_2) of chiral imines derived from *ortho*-methoxyacetophenone and α-methylbenzylamine [48]. High diastereoselectivity was also reported for the reductive amination of the imine derived from *ortho*-hydroxyacetophenone with $NaBH_4$ [25]. This approach could be a rapid and efficient route for the preparation of 2-(1-aminoethyl)phenols (*R*)-**1b**, (*S*)-**2b**, and (*R*)-**3b**, provided that a selective removal of the chiral auxiliary could be found. The synthetic route to (1-aminoethyl)phenols (*R*)-**1b**, (*S*)-**2b**, and (*R*)-**3b** *via* this approach is shown in *Schemes 6–9*.

Condensation of (*R*)-α-methylbenzylamine (99% ee) with *ortho*-hydroxyacetophenone (**27**) afforded the corresponding imine derivative (*R*)-**28**. Addition of $NaBH_4$ to a MeOH suspension of (*R*)-**28** and $CeCl_3 \cdot 7\,H_2O$ at $-90°$ provided a diastereoisomer mixture of amine (*R*,*R*)-**29** and (*S*,*R*)-**29** in a ratio of 96.5 : 3.5 (93% de). Recrystallization of the (*R*,*R*)-**29** · HCl salt in H_2O followed by basic extractive workup afforded amine (*R*,*R*)-**29** in 82% yield and with a de $>96\%$. Selective cleavage of the N–C benzylic bond bearing the less-substituted aromatic ring was achieved by Pd-catalyzed hydrogenolysis. Several conditions were tested with amine (*R*,*R*)-**29**, as shown in the *Table* (*cf. Scheme 7*). A poor conversion was observed with Pd/C with either H_2 gas or under H-transfer conditions ($NH_4(HCO_2)$; *Entries 1* and *2*). Fortunately, the conversion was improved by using *Pearlman*'s catalyst ($Pd(OH)_2/C$) under acidic conditions (MeOH/AcOH) [49]. The highest yield was obtained under H_2 pressure (4 atm) at room temperature, and this provided (*R*)-**1b** in 89% yield with an ee $>96\%$ (cleavage b, *Entry 4*). Increasing the temperature resulted in an internal benzylic cleavage of amine **1b** (*Entry 5*).

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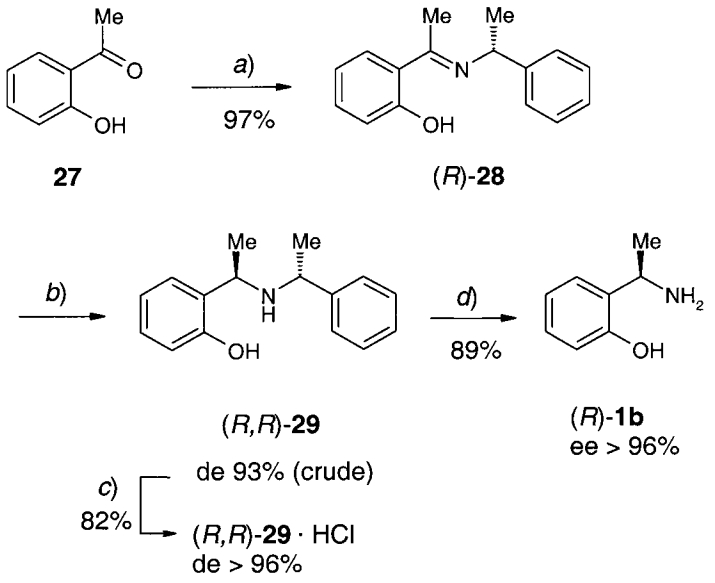
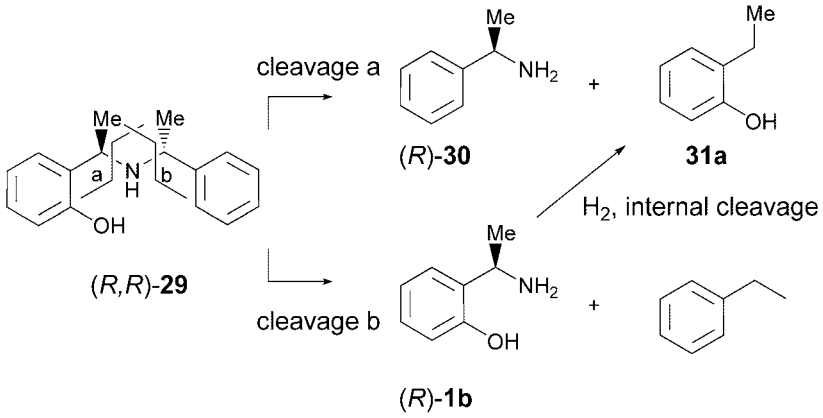
[7]) The ee was determined by GC after formation of the bis-*Mosher* ester (see *Exper. Part*).

Scheme 6



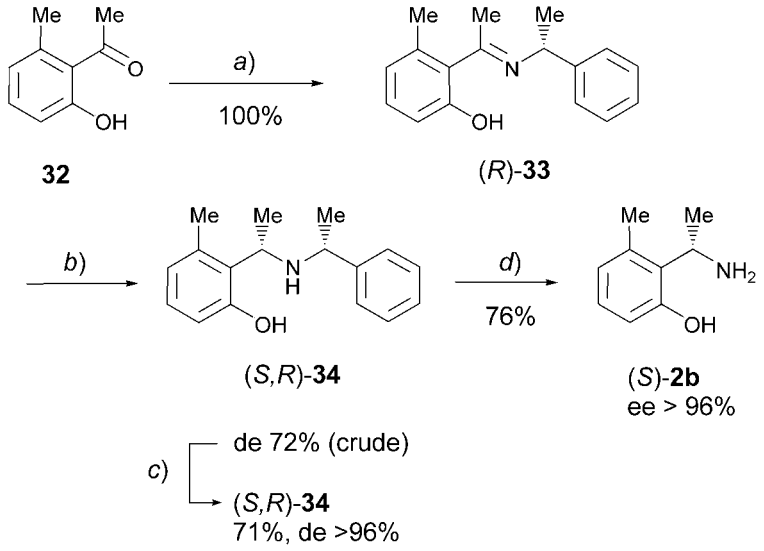
a) (α*R*)-α-Methylbenzylamine, cat. TsOH, toluene, reflux. *b*) $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$, MeOH, $-90°$ to r.t. *c*) 1.5N HCl in Et_2O recryst. from H_2O. *d*) 1. 1M NaOH; 2. H_2 (4 atm), $Pd(OH)_2$/C, MeOH, AcOH, r.t.

Scheme 7



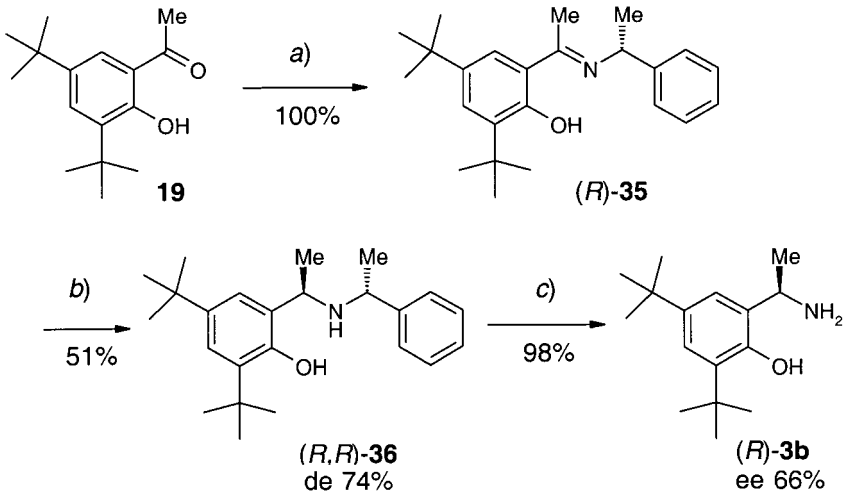
The imine derivatives (*R*)-**33** and (*R*)-**35** were obtained from the condensation of (*R*)-α-methylbenzylamine with 2-hydroxy-6-methylacetophenone (**32**) [36b] and 3,5-di(*tert*-butyl)-2-hydroxyacetophenone (**19**), respectively (*Schemes 8* and *9*, resp.). Their reduction occurred with substantially lower diastereoselectivities than that of imine derivative (*R*)-**28**. With $NaBH_4/CeCl_3$ in MeOH at $-90°$, the reduction of (*R*)-**33** gave a mixture of diastereoisomers (*S,R*)-**34** and (*R,R*)-**34** in a ratio of 59 : 41 (18%

Scheme 8



a) (α*R*)-α-Methylbenzylamine, cat. TsOH, toluene, reflux. *b*) $NaBH_4$, MeOH, −78° to r.t. *c*) FC (SiO_2). *d*) $NH_4(HCO_2)$, $Pd(OH)_2$/C, MeOH, AcOH, reflux.

Scheme 9



a) (α*R*)-α-Methylbenzylamine, cat. TsOH, toluene, reflux. *b*) $NaBH_4$, AcOH, THF, −78° to r.t., then FC (SiO_2). *c*) H_2 (4 atm), $Pd(OH)_2$/C, MeOH, AcOH.

de). The same reaction with imine derivative (*R*)-**35** afforded a mixture of (*R,R*)-**36** and (*S,R*)-**36** in a ratio of 79 : 21 (58% de). For (*R*)-**35**, the use of $NaBH_4$ in AcOH [25] as reducing agent improved the diastereoselectivity somewhat (to 70% de). Purifica-

Table. *Effect of Catalysts and Hydrogen Sources on the Selectivity of the N–C Cleavage of (*R,R*)-***29***[a])*

Entry	Hydrogen source	Conditions	(*R*)-**1b**/(*R*)-**30**/**31a**[b])	Yield of **1b** [%]
1	$NH_4(HCO_2)$ (6 equiv.)	20°, 40 h	42 : 17 : 41	–[c])
2	$NH_4(HCO_2)$ (6 equiv.)	70°, 2 h	51 : 6 : 43	–[c])
3	H_2 (1 atm)[d])	70°, 16 h	70 : 0 : 30	65[e])
4	H_2 (4 atm)	20°, 48 h	83 : 6 : 11	89[f])
5	H_2 (4 atm)	70°, 20 h	0 : 23 : 77	–[c])

[a]) Reactions run with 2 mmol of substrate and $Pd(OH)_2$/C (20 wt-%) in MeOH/AcOH. [b]) Ratio measured with the crude mixture by GC (see *Exper. Part*). [c]) Not determined. [d]) 40 mol-% of $Pd(OH)_2$/C. [e]) Isolated yield after purification by distillation. [f]) Isolated yield after acid–base extractive workup.

tion by chromatography (silica gel) afforded amino alcohol (*R*,*R*)-**36** in 51% yield with a diastereomer ratio of 87 : 13 (74% de) (*Scheme 9*).

The reduction of imine derivative (*R*)-**33** with $NaBH_4$ in MeOH gave (*S,R*)-**34** and (*R,R*)-**34** in a 86 : 14 ratio (72% de; *Scheme 8*). Here, the two diastereoisomers could be separated by chromatography (silica gel) to afford the highly diastereoisomerically enriched amino alcohol (*S*,*R*)-**34** (de > 96%) in a yield of 71%. Hydrogenolysis of (*S*,*R*)-**34** and (*R*,*R*)-**36** in the presence of *Pearlman*'s catalyst under H-transfer hydrogenation conditions and under 4 atm of H_2, respectively, afforded the desired amines (*S*)-**2b** in 76% yield with an ee > 96% and (*R*)-**3b** in 98% yield and 66% ee (*Schemes 8* and *9*).

The absolute configuration of amines **2a** and **3a** and aminophenols **2b** and **3b** were confirmed by using the ^{1}H-NMR correlation of the amides obtained with both enantiomers of *Mosher*'s acid as described for amine **1** [34][35].

In conclusion, we have described three different approaches for the synthesis of enantiomerically enriched benzylamines bearing *ortho*-methoxy or *ortho*-hydroxy groups. For **1b**, *Method C*, based on earlier work by *Hogeveen* and co-workers [48] and by *Palmieri* [25] is most efficient. In our hands, it provided (*R*)-**1b** (> 96% ee) in three steps in an overall yield of 71%. For enantiomerically enriched amines **2**, the route based on *Pridgen*'s diastereoselective alkylation (*Method A*) proved to be best, and it afforded (*S*)-**2a** (99% ee) in a four-step sequence in 46% yield. Problems persist to date for the obtention of highly enantiomerically enriched **3**, however; (*R*)-**3b** was obtained with only 66% ee by *Method C* and (*S*)-**3a** in 69% ee *via Method B*. The methods detailed in this report should prove useful in the synthesis of new chiral auxiliaries for asymmetric synthesis and of chiral ligands based on 2-(1-aminoethyl)phenols.

Experimental Part

1. *General*. Reactions were carried out under N_2, and the glassware was heat-dried prior to use. Solvents for reactions were purified before use as follows: THF and Et_2O were distilled from Na/benzophenone-ketyl (= diphenylketyl). CH_2Cl_2 and hexane were distilled from CaH_2, and toluene and benzene from Na under N_2. Commercially available, solid chemicals were usually used without further purifiation, liquids were generally freshly distilled. Chemicals were purchased from *Fluka* and *Aldrich*. The 2-methoxybenzaldehyde was washed with sat. aq. $NaHCO_3$ soln. and distilled from anh. $MgSO_4$. The oxazaborolidine (*S*)-**13**, *o*-methoxyacetophenone (**12**), (+)-(α*R*)-α-methylbenzylamine, 4-(*tert*-butyl)cyclohexanone, 3,5-di(*tert*-butyl)-2-hydroxybenzaldehyde (**17**), (−)-(*R*)-2-amino-2-phenylethanol (= (−)-(β*R*)-β-aminobenzeneethanol) [50], 2-methoxy-6-methylbenzaldehyde (**8**) [36b], borane–oxazaborolidine complex (*S*)-**22** [41], 1-(2-methoxy-6-methylphenyl)etha-

none (**21**) [36b], and 4-NO_2-DPPA [46], were prepared by literature methods. MeLi was titrated following *Gilman*'s method prior to use [51]. $Pb(OAc)_4$ was placed under vacuum (0.2 mbar) for 30 min prior to use. Hydrogenolysis was performed on a *Parr* apparatus No. *3916*. Molecular sieves (4 Å) were activated at 160° under vacuum (0.4 mbar) for 16 h. Flash column chromatography (FC): in air; silica gel *Merck 60*; the eluents were distilled prior to use. GC: *Hewlett-Packard 6890* chromatograph with FID detector; silicon capillary column from *Macherey-Nagel: Permabond OV-1-0.25* (25 m × 0.32 mm i.d.) or *Lipodex E* (octakis(2,6-di-*O*-pentyl-3-*O*-butyryl)-γ-cyclodextrin; 25 m × 0.25 mm i.d.); *Chirasil DEX-CB* capillary column; carrier gas He (80 kPa); t_R in min. HPLC: *Daicel Chiralpack-AD* and *Chiracel-OD* anal. columns; *Jasco PU-980* chromatograph with UV detector; t_R in min. M.p.'s: *Büchi 510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter; 10-cm cell. IR Spectra: films on NaCl windows or KBr press disks; *Perkin-Elmer FT-IR-1650* instrument; ν in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker 300*, *400* or *500* or *Varian XL-200* spectrometers; δ in ppm, J in Hz. MS: at 70 eV; *Varian-CH4* or *-SM1* instrument; in m/z (rel. %). Elemental analyses were performed by Dr. *H. J. Eder*, Service de Microchimie, Département de Chimie Pharmaceutique, Université de Genève.

2. *Enantiomerically Enriched* **1a** *and* **1b**: *Method A. (−)-(βR)-β-{[(1E)-(2-Methoxyphenyl)methylene]-amino}benzeneethanol* ((R)-**4**). A soln. of (−)-(*βR*)-β-aminobenzeneethanol (22.2 g, 161.93 mmol) and 2-methoxybenzaldehyde (22.0 g, 161.76 mmol) in EtOH (300 ml) was stirred for 26 h at r.t. with activated 4 Å molecular sieves. This mixture was filtered through a pad of *Celite* and the filtrate evaporated. The white residue obtained was washed with hexane and dried under vacuum: (*R*)-**4** (37.20 g, 90%). White solid. M.p. 62–63°. $[\alpha]_D^{20} = -8.4$ ($c = 2.19$, EtOH). IR ($CHCl_3$): 3593, 3030, 2939, 2887, 2841, 1635, 1601, 1488, 1466, 1438, 1383, 1287, 1251. ^1H-NMR (C_6D_6, 400 MHz): 1.73 (br. *s*, 1 H); 3.22 (*s*, 3 H); 3.8–4.0 (*m*, 2 H); 4.42 (*dd*, $J = 8.1$, 4.1, 1 H); 6.48 (*d*, $J = 8.5$, 1 H); 6.91 (*t*, $J = 7.6$, 1 H); 7.10–7.24 (*m*, 4 H); 7.46 (*d*, $J = 7.6$, 2 H); 8.43 (*dd*, $J = 7.6$, 1.8, 1 H); 9.03 (*s*, 1 H). ^{13}C-NMR (C_6D_6, 50 MHz): 54.9; 68.2; 77.6; 111.1; 120.9; 125.1; 127.3 (2); 127.8; 128.0; 128.6 (2); 132.1; 142.0; 158.2; 159.3. MS: 254 (2, $[M-H]^+$), 224 (100), 209 (19), 180 (8), 91 (35), 77 (19). HR-MS: 254.1180 ($[M-H]^+$, $C_{16}H_{16}NO_2^+$; calc. 254.1181). Anal. cal. for $C_{16}H_{17}NO_2$ (255.32): C 75.27, H 6.71; found: C 75.01, H 6.72.

(−)-(βR)-β-{[(1R)-1-(2-Methoxyphenyl)ethyl]amino}benzeneethanol ((*R,R*)-**5**). A soln. of (*R*)-**4** (28.90 g, 113.21 mmol) in THF (2 l) under N_2 was cooled to −78°, 1.52M MeLi in Et_2O (300 ml, 456 mmol) was added dropwise. The resulting dark-blue soln. was stirred at −78° for 24 h, the temperature allowed to reach −30° within 6 h, and the mixture stirred at −30° for 20 h. The reaction was quenched by addition of sat. aq. NH_4Cl soln. (250 ml) at −30°. The resulting yellow mixture was brought to r.t., the org. phase separated and evaporated, the residue taken up in Et_2O (200 ml), and the soln. washed with sat. aq. $NaHCO_3$ soln. (100 ml). The combined aq. phase was extracted with Et_2O (3 × 100 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the crude orange oil (32 g) purified by FC (SiO_2, hexane/Et_2O 1:2 + 1% MeOH/sat. NH_3): (*R,R*)-**5** (18.19 g, 59%). Orange oil. $[\alpha]_D^{20} = -32.1$ ($c = 2.10$, CH_2Cl_2). IR (CH_2Cl_2): 3612, 3443, 3344, 3029, 2964, 2872, 2838, 1600, 1586, 1492, 1464, 1403, 1369, 1278. ^1H-NMR ($CDCl_3$, 400 MHz): 1.41 (*d*, $J = 6.4$, 3 H); 2.75 (br. *s*, 2 H); 3.53 (*dd*, $J = 10.3$, 7.4, 1 H); 3.69 (*s*, 3 H); 3.7–3.8 (*m*, 2 H); 4.13 (*q*, $J = 6.4$, 1 H); 6.78 (*d*, $J = 8.4$, 1 H); 6.92 (*t*, $J = 7.4$, 1 H); 7.2–7.3 (*m*, 7 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 21.1; 50.8; 55.0; 61.6; 65.6; 110.6; 120.6; 127.2 (2); 127.3; 127.8; 128.3 (2); 133.1; 141.5; 156.9. MS: 240 (46, $[M-CH_2OH]^+$), 135 (100), 106 (24), 91 (9), 77 (11). HR-MS: 240.1382 ($[M-CH_2OH]^+$, $C_{16}H_{18}NO^+$; calc. 240.1388).

(−)-[(1R)-1-(2-Methoxyphenyl)ethyl]amine Hydrochloride ((*R*)-**7**). A white suspension of anh. K_2CO_3 (55.02 g, 398.11 mmol) and MeOH (135 ml) was cooled to 0° with an ice bath. A soln. of (*R,R*)-**5** (17.82 g, 65.67 mmol) in CH_2Cl_2 (250 ml) and a soln. of $Pb(OAc)_4$ (34.73 g, 78.34 mmol) in CH_2Cl_2 (250 ml) were simultaneously added dropwise within 12 min. After additional 3 min, the mixture was hydrolyzed with sat. aq. Na_2CO_3 soln. (300 ml). The mixture was filtered through *Celite* and washed with CH_2Cl_2 (2 × 100 ml) and sat. aq. Na_2CO_3 soln. (2 × 50 ml). The org. phase was washed with sat. aq. Na_2CO_3 soln. (250 ml). The combined aq. phase was extracted with CH_2Cl_2 (2 × 100 ml) and the combined org. phase dried (K_2CO_3) and evaporated: imine derivative (*R*)-**6** as an orange oil (15.46 g). The crude (*R*)-**6** in THF (200 ml) was directly hydrolyzed in 30% aq. AcOH soln. (200 ml) for 20 h at r.t. The mixture was concentrated and the aq. phase extracted with Et_2O (3 × 100 ml). The combined org. phase was washed with 30% aq. AcOH soln. (2 × 100 ml). The combined aq. phase was cooled to 0° and neutralized by addition of 6M aq. NaOH. The neutral aq. phase was washed with Et_2O (100 ml), cooled, and basified (pH 14) by addition of 6M NaOH. The basified aq. phase was extracted with Et_2O (4 × 100 ml). The combined org. phase was dried (K_2CO_3) and evaporated and the residue purified by bulb-to-bulb distillation (80°/0.1 mbar): crude free amine (*R*)-**1a** (7.87 g, 52.1 mmol). Colorless oil. This was taken up in Et_2O (220 ml) and treated at 0° dropwise with 1.37N HCl in Et_2O (48 ml, 65.76 mmol). The mixture was stirred for 30 min at r.t. and the solvent evaporated to give a solid (9.70 g). This was dissolved in CH_2Cl_2

(110 ml) and treated with hexane (220 ml). The precipitated white solid was filtered off, washed with hexane (50 ml), and dried under vacuum: (*R*)-**7** (8.30 g, 67% from (*R,R*)-**5**). M.p. 174–175°. $[\alpha]_D^{20} = -36.1$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 2972, 1605, 1496, 1465, 1384, 1292, 1252, 1084, 1029. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.69 (*d*, *J* = 6.6, 3 H); 3.83 (*s*, 3 H); 4.69 (*q*, *J* = 6.6, 1 H); 6.87 (*d*, *J* = 8.0, 1 H); 6.95 (*t*, *J* = 7.5, 1 H); 7.31 (*td*, *J* = 8.0, 1.4, 1 H); 7.38 (*dd*, *J* = 7.5, 1.4, 1 H); 8.6 (br. *s*, 3 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 18.5; 47.2; 55.4; 110.6; 120.9; 125.9; 127.6; 129.9; 156.7. MS: 151 (3, $[M - HCl]^+$), 136 (100), 121 (27), 107 (16), 91 (10), 77 (13). Anal. calc. for $C_9H_{14}ClNO$ (187.6690): C 57.60, H 7.52, N 7.46; found: C 57.72, H 7.52, N 7.44.

*(+)-[(1*R*)-1-(2-Methoxyphenyl)ethyl]amine* ((*R*)-**1a**). To a suspension of (*R*)-**7** (8.02 g, 42.77 mmol) in Et_2O (200 ml) at 0°, 6N aq. NaOH (100 ml) was added, and the mixture was stirred at r.t. for 30 min. The aq. phase was extracted with Et_2O (3 × 50 ml) and the combined org. phase dried (K_2CO_3) and evaporated: (*R*)-**1a** (6.82 g, 97%; 98% ee by GC of trifluoroacetamide (*R*)-**16**). Colorless oil. $[\alpha]_D^{20} = +19.8$ (c = 2.22, EtOH). IR ($CHCl_3$): 3187, 3021, 3007, 2965, 2838, 1599, 1585, 1490, 1464, 1438, 1285, 1243. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.40 (*d*, *J* = 6.8, 3 H); 1.90 (*s*, 2 H); 3.84 (*s*, 3 H); 4.35 (*q*, *J* = 6.8, 1 H); 6.86 (*d*, *J* = 8, 1 H); 6.94 (*m*, 1 H); 7.21–7.33 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 23.0; 45.9; 55.0; 110.4; 120.6; 125.6; 127.5; 135.4; 156.6. MS: 151 (1, M^+), 150 (3), 138 (9), 136 (100), 121 (19), 107 (7), 77 (6). HR-MS: 151.0997 (M^+, $C_9H_{13}NO^+$; calc. 151.0997).

The absolute configuration was confirmed to be (*R*) by comparison with literature data [19a].

*(+)-2,2,2-Trifluoro-*N*-[(1*R*)-1-(2-methoxyphenyl)ethyl]acetamide* ((*R*)-**16**). To a soln. of (*R*)-**1a** (32.8 mg, 216.9 μmol) in THF (2 ml) was added $(CF_3CO)_2O$ (250 μl, 1.79 mmol). The resulting soln. was stirred for 30 min at r.t. and then evaporated. The residue was dissolved with CH_2Cl_2, the soln. filtered over a short column (1 × 4 cm, SiO_2), the column washed with CH_2Cl_2 (5 ml), and the solvent evaporated: (*R*)-**16** (46.1 mg, 85%). White solid. Chiral GC *Lipodex E*, H_2, 50 kPa, 120° isotherm; trifluoroacetamide: t_R 15.9 ((−)-(*S*)-**16**; 0.8%); 17.5 ((+)-(*R*)-**16**; 99.2%); ee 98%. M.p. 127–128°. $[\alpha]_D^{20} = +138.1$ ($c = 1.00$, CH_2Cl_2). IR ($CHCl_3$): 3422, 3028, 2980, 2841, 1720, 1603, 1588, 1533, 1494, 1465, 1241, 1169. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.53 (*d*, *J* = 6.9, 3 H); 3.92 (*s*, 3 H); 5.22 (*q*, *J* = 6.9, 1 H); 6.96 (*t*, *J* = 7.8, 2 H); 7.2–7.3 (*m*, 2 H); 7.6 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 21.0; 48.8; 55.3; 111.3; 115.9 (*q*, *J* = 36); 121.1; 128.4; 129.2; 155.9 (*q*, *J* = 36); 156.9. MS: 247 (46, M^+), 232 (79), 151 (6), 150 (58), 135 (25), 119 (12), 109 (11), 108 (11), 107 (100), 105 (18), 91 (30), 77 (28). HR-MS: 247.0805 (M^+, $C_{11}H_{12}NO_2F_3^+$; calc. 247.0820). Anal. calc. for $C_{11}H_{12}F_3NO_2$: C 53.44, H 4.89, N 5.67; found: C 53.45, H 4.93, N 5.66.

*(−)-2-[(1*R*)-1-Aminoethyl]phenol* ((*R*)-**1b**). A soln. of (*R*)-**1a** (0.2 g, 1.32 mmol) in benzene (18 ml) was added under N_2 at r.t. to a soln. of $AlBr_3$ (1.23 g, 4.6 mmol) in benzene (15 ml). The mixture was stirred for 20 h at r.t. and then added to a sat. $NaHCO_3$ soln. at 0° and stirred for 1 h. The mixture was extracted with AcOEt (2 × 10 ml), the combined org. phase washed with H_2O, dried (K_2CO_3), and evaporated, and the residue purified by bulb-to-bulb distillation: (*R*)-**1b** (126 mg, 70%; 98% ee by GC (*OV17*, He, 100° for 1 min then 10°/min to 250°; (*R,R*)-*Mosher* amide). White solid. M.p. 83°. $[\alpha]_D^{20} = -12.1$ ($c = 0.60$, EtOH). IR (KBr): 3448, 2979, 1594, 1447, 1275, 1150, 1110, 1180, 1040, 1000, 922, 748. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.49 (*d*, *J* = 6.6, 3 H); 4.33 (*q*, *J* = 6.6, 1 H); 6.7–7.2 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 23.6; 51.6; 117.0; 119.0; 127.2; 127.9; 128.5; 157.5. MS: 138 (3, $[M + 1]^+$), 137 (36, M^+), 122 (72), 120 (100), 92 (19), 91 (68), 77 (19), 65 (15), 51 (12). Anal. calc. for $C_8H_{11}NO$: C 70.05, H 8.08, N 10.21; found: C 70.06, H 8.04, N 10.08.

3. *Enantiomerically Enriched* **1a**: *Method B. (+)-(α*R*)-2-Methoxy-α-methylbenzenemethanol* ((*R*)-**14**). To 1M oxazaborolidine (*S*)-**13** in toluene (40 ml, 0.04 mol) in THF (200 ml) 1M $BH_3 \cdot$ THF in THF (120 ml, 0.12 mol) was added. Within 1 h, 1-(2-methoxyphenyl)ethanone (**12**; 27.58 ml, 0.1 mol) in THF (250 ml) was added slowly. After 4 h, the reaction was stopped by adding MeOH (200 ml). The mixture was stirred for an additional 30 min and then evaporated. The residue was dissolved in Et_2O, the soln. washed with 1N HCl, sat. aq. Na_2CO_3 soln., and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (SiO_2, cyclohexane/AcOEt 70:30): (*R*)-**14** (30.3 g, 99%; 96% ee by ^{1}H-NMR, integration of C*H*OH signal of the corresponding (*R,R*)-*Mosher* ester). Colorless oil. $[\alpha]_D^{20} = +25.6$ ($c = 1.94$, $CHCl_3$) ([40]: $[\alpha]_D^{20} = +32.3$ ($c = 2.00$, $CHCl_3$)). IR ($CHCl_3$): 3602, 3444, 3018, 2975, 2939, 2839, 1601, 1587, 1491, 1465, 1438, 1400, 1366, 2968, 1287, 1239, 1210. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.53 (*d*, *J* = 6.5, 3 H); 2.30 (br. *s*, 1 H); 3.88 (*s*, 3 H); 5.12 (*q*, *J* = 6.5, 1 H); 6.90 (*d*, *J* = 8.1, 1 H); 6.98 (*m*, 1 H); 7.2–7.3 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 22.7; 55.1; 66.4; 110.3; 120.9; 126.0; 128.2; 133.3; 156.4. MS: 152 (46, M^+), 138 (16), 137 (100), 121 (25), 109 (52), 107 (83), 105 (18), 94 (22), 91 (21), 77 (49). HR-MS: 152.0831 (M^+, $C_9H_{12}O_2^+$; calc. 152.0837).

*(−)-1-[(1*S*)-1-Azidoethyl]-2-methoxybenzene* ((*S*)-**15**). Diphenylphosphoryl azide (= diethyl phosphorazidate = DPPA; 15.6 ml, 0.072 mol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 10.8 ml, 0.072 mol) were added dropwise to a stirred soln. of (*R*)-**14** (9.15 g, 0.060 mol) in THF (300 ml) at r.t. The mixture was stirred for 12 h and then evaporated. H_2O (100 ml) was added to the residue, the soln. extracted with Et_2O (3 × 100 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified by FC

(SiO_2, pentane/Et_2O 80:20): (*S*)-**15** (6.3 g, 59%). Yellow oil. $[\alpha]_D^{20} = -11.9$ ($c = 2.12$, $CHCl_3$). IR ($CHCl_3$): 3019, 2101, 1491, 1464, 1287, 1247, 1223. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.51 (*d*, *J* = 6.8, 3 H); 3.86 (*s*, 3 H); 5.08 (*q*, *J* = 6.8, 1 H); 6.92 (*d*, *J* = 8.2, 1 H); 7.01 (*t*, *J* = 7.5, 1 H); 7.2–7.4 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 20.0; 54.9; 55.3; 110.5; 120.7; 126.5; 128.9; 129.0; 156.4. MS: 177 (10, M^+), 136 (10), 135 (100), 119 (6), 105 (20), 91 (12), 77 (18). HR-MS: 177.0897 (M^+, $C_9H_{11}N_3O^+$; calc. 177.0902).

(−)-[(1S)-1-(2-Methoxyphenyl)ethyl]amine ((*S*)-**1a**). A mixture of (*S*)-**15** (6.3 g, 35.5 mmol), EtOH (130 ml), and the Pd/C catalyst (*Degussa* type *101 NE/W*, 0.6 g) was purged with H_2 (3×), stirred under H_2 (1 atm) at r.t. for 12 h, and then filtered through a pad of *Celite*. Evaporation gave crude (*S*)-**1a** as a yellow oil. Purification by bulb-to-bulb distillation at 120°/2 Torr afforded pure (*S*)-**1a** (4.21 g, 78%). Colorless oil. Chiral GC (*Lipodex E*, H_2, 50 kPa, 120° isotherm; trifluoroacetamide) t_R 16.3 ((−)-(*S*)-**16**; 96.5%), 17.9 ((+)-(*R*)-**16**; 3.5%); 93% ee. Enantiomerically pure amine (*S*)-**1a** (3.19 g, 76%) was obtained by recrystallization of (*S*)-**16** in hexane/AcOEt followed by hydrolysis by K_2CO_3 in MeOH. $[\alpha]_D^{20} = -18.2$ ($c = 2.19$, EtOH). Chiral GC (*Lipodex E*, H_2, 50 kPa, 120° isotherm; trifluoroacetamide) t_R 12.7 ((−)-(*S*)-**16**; >98%), (*R*)-enantiomer not detected; ee > 98%.

4. *Enantiomerically Enriched* **1b**: *Method C. (−)-2-{1-{[(1R)-1-Phenylethyl]imino}ethyl}phenol* ((*R*)-**28**). A mixture of 1-(2-hydroxyphenyl)ethanone (**27**; 4.08 g, 30.0 mmol), (+)-(α*R*)-α-methylbenzylamine (3.63 g, 30.0 mmol; >99% ee), TsOH (0.400 g, 3.0 mmol) and 4 Å molecular sieves (20 g) in dry toluene (40 ml) was heated to reflux for 16 h. The soln. was filtered through a pad of *Celite*, and the filtrate was evaporated: crude (*R*)-**28** (6.93 g, 29 mmol). Yellow oil. The product was used without further purification. $[\alpha]_D^{20} = -275$ ($c = 0.45$, CH_2Cl_2). IR ($CHCl_3$): 3069, 3030, 2974, 2927, 1612, 1579, 1498, 1449, 1376, 1302, 1239, 1161, 1134, 1083. ^{1}H-NMR (C_6D_6, 400 MHz): 1.29 (*d*, *J* = 6.6, 3 H); 1.54 (*s*, 3 H); 4.37 (*q*, *J* = 6.6, 1 H); 6.59 (*m*, 1 H); 6.9–7.2 (*m*, 8 H); 16.29 (br. *s*, 1 H). ^{13}C-NMR (C_6D_6, 100 MHz): 13.8; 25.0; 58.5; 116.9; 118.5; 119.8; 126.1; 126.8; 127.3; 127.6; 128.1; 128.5; 132.1; 144.6; 163.7; 170.1. MS: 239 (41, M^+), 148 (6), 135 (36), 121 (21), 105 (100), 91 (11), 77 (28). HR-MS: 239.1324 (M^+, $C_{16}H_{17}NO^+$; calc. 239.1310).

(+)-2-{(1R)-1-{[(1R)-1-Phenylethyl]amino}ethyl}phenol ((*R*,*R*)-**29**). $NaBH_4$ (2.28 g, 60 mmol) was added in one portion to a mixture of (*R*)-**28** (6.93 g, 29 mmol), $CeCl_3 \cdot 7\,H_2O$ (5.60 g, 15 mmol), and MeOH (100 ml) at −90°. The temp. was allowed to rise slowly to r.t. (12 h), and CH_2Cl_2 (400 ml) was added, followed by sat. aq. NH_4Cl soln. (400 ml). The soln. was extracted with CH_2Cl_2 and the combined org. phase dried ($MgSO_4$) and evaporated. The resulting crude oily product was diluted in Et_2O (200 ml) and the hydrochloride salt precipitated by adding 1.5M HCl in Et_2O (1 equiv.). The white precipitate was washed with H_2O and dried: (*R*,*R*)-**29** · HCl/(*S*,*R*)-**29** · HCl 20:1 (by ^{1}H-NMR; integration of Me*C*H signals). The white solid was recrystallized in H_2O: (*R*,*R*)-**29** · HCl (6.60 g, 82%; >96% de, the other diastereoisomer was not detected). M.p. 139–141°. $[\alpha]_D^{20} = +56$ ($c = 1.15$, MeOH). IR (KBr): 3377, 3228, 2977, 2811, 2522, 1624, 1507, 1450, 1382, 1291, 1255, 1189, 1065. ^{1}H-NMR ((D_6)DMSO, 400 MHz): 1.43 (*d*, *J* = 6.9, 3 H); 1.55 (*d*, *J* = 6.7, 3 H); 3.96 (br. *s*, 1 H); 4.14 (br. *s*, 1 H); 6.7–6.9 (*m*, 2 H); 7.13 (*m*, 1 H); 7.30 (*s*, 5 H); 7.47 (*d*, *J* = 6.6, 1 H); 9.60 (br. *s*, 1 H); 9.80 (br. *s*, 2 H). ^{13}C-NMR ((D_6)DMSO, 100 MHz): 19.9; 20.9; 50.3; 56.1; 115.9; 119.6; 123.2; 128.1 (2); 128.2; 128.9 (2); 129.0; 129.7; 137.1; 155.0. MS: 241 (13, $[M - HCl]^+$), 226 (24), 136 (3), 122 (34), 120 (51), 106 (100), 91 (26), 77 (26). HR-MS: 241.1450 (M^+, $C_{16}H_{19}NO^+$; calc. 241.1466).

Treatment of (*R*,*R*)-**29** · HCl with 1M aq. NaOH afforded the free amine (*R*,*R*)-**29** (5.54 g, quant.). Colorless oil $[\alpha]_D^{20} = +69$ ($c = 0.11$, $CHCl_3$; >96% ee) [25]: $[\alpha]_D^{20} = +142$ ($c = 1.66$, $CHCl_3$)). IR ($CHCl_3$): 3322, 3005, 2988, 2927, 2869, 2730, 2638, 1588, 1487, 1452, 1406, 1377, 1257, 1193, 1144, 1106, 1029. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.43 (*d*, *J* = 6.8, 3 H); 1.51 (*d*, *J* = 6.8, 3 H); 3.69 (*q*, *J* = 6.8, 1 H); 3.77 (*q*, *J* = 6.8, 1 H); 6.78 (*m*, 2 H); 6.9–7.4 (*m*, 7 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 22.9; 23.4; 55.3; 56.1; 116.7; 119.1; 126.2 (2); 126.5; 127.4; 128.2 (2); 128.7 (2); 143.5; 157.5. MS: 241 (6, M^+), 227 (10), 226 (39), 122 (16), 120 (16), 106 (37), 105 (29), 92 (33), 91 (100), 79 (11), 77 (13). HR-MS: 241.15 (M^+, $C_{16}H_{19}NO^+$; calc. 241.1466).

The absolute configuration was assigned (*R*,*R*) by comparison with ^{1}H-NMR literature data [25].

(−)-2-[(1R)-1-Aminoethyl]phenol ((*R*)-**1b**): *Best Procedure.* A mixture of (*R*,*R*)-**29** (5 g, 21 mmol), MeOH (210 ml), AcOH (4 equiv., 4.8 ml, 84 mmol), and $Pd(OH)_2$/C (20 wt-%, 2.1 g) was purged with H_2 (3×), stirred under H_2 (4 atm) at r.t. for 48 h, and then passed through a pad of *Celite*. The filtrate was evaporated: (*R*)-**1b**/(*R*)-**30**/**31a** 83:6:11 (by GC (*OV1*, H_2). The mixture was treated with 1N aq. HCl (100 ml) and extracted with Et_2O (2 × 100 ml). The aq. phase (pH 1) was basified with 2N NaOH and extracted with Et_2O (2 × 100 ml). The combined org. phase (pH 9) was dried (Na_2SO_4) and evaporated: (*R*)-**1b** (2.57 g, 89%; >96% ee by ^{1}H-NMR, integration of MeCH signal of the corresponding (*R*,*S*)-*Mosher* amide; the other diastereoisomer was not detected). $[\alpha]_D^{20} = -18$ ($c = 1.85$, $CHCl_3$).

5. *Enantiomerically Enriched* **2a**: *Method A. (+)-(βS)-β-{[(1E)-(2-Methoxy-6-methylphenyl)methylene]amino}benzeneethanol* ((*S*)-**9**). A soln. of (+)-(β*S*)-β-aminobenzeneethanol (5.90 g, 43.03 mmol) and 2-

methoxy-6-methylbenzaldehyde (**8**; 5.90 g, 39.30 mmol) in EtOH (250 ml) was stirred for 26 h at r.t. with activated 4 Å molecular sieves. The mixture was filtered through a pad of *Celite* which was washed with EtOH (3 × 20 ml). The solvent was evaporated and the residue washed with hexane and dried under vacuum: (*S*)-**9** (11.50 g, 99%). White solid. M.p. 58–60°. $[\alpha]_D^{20} = +18.8$ ($c = 0.69$, EtOH). IR (CH_2Cl_2): 3592, 3065, 3030, 2964, 2927, 2873, 2841, 1639, 1597, 1579, 1492, 1470, 1442, 1390, 1340, 1290. ^{1}H-NMR (400 MHz, C_6D_6): 2.70 (*s*, 3 H); 3.25 (*s*, 3 H); 3.86 (*m*, 2 H); 4.38 (*m*, 1 H); 6.41 (*d*, $J = 8.3$, 1 H); 6.79 (*d*, $J = 7.6$, 1 H); 7.0–7.3 (*m*, 5 H); 7.47 (*d*, $J = 7.1$, 2 H); 9.01 (*s*, 1 H). ^{13}C-NMR (50 MHz, C_6D_6): 21.7; 55.7; 67.9; 77.9; 108.3; 123.7; 123.8; 126.9; 127.3; 127.4; 128.5; 130.3; 130.3; 139.6; 140.9; 159.4; 160.9. MS: 269 (40, M^+), 238 (100), 222 (11), 147 (18), 133 (17), 121 (4), 91 (38), 77 (23). HR-MS: 269.1408 (M^+, $C_{17}H_{19}NO_2^+$; calc. 269.1415).

(+)-(βS)-β-[[(1S)-1-(2-Methoxy-6-methylphenyl)ethyl]amino}benzeneethanol ((*S*,*S*)-**10**). A soln. of (*S*)-**9** (11.50 g, 42.71 mmol) in THF (350 ml) under N_2 was cooled to −78°, and 1.6M MeLi in Et_2O (106 ml, 170 mmol) was added dropwise within 1.3 h under stirring. The resulting purple mixture was stirred at −78° for 48 h. The reaction was stopped by addition of sat. aq. NH_4Cl soln. (150 ml). The resulting yellow mixture was allowed to warm to r.t. and the org. phase evaporated. Et_2O (80 ml) was added and the soln. washed with sat. aq. $NaHCO_3$ soln. (50 ml). The combined aq. phase was extracted with Et_2O (3 × 50 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue recrystallized in hexane/AcOEt: (*S*,*S*)-**10** (8.23 g, 67% from (*S*)-**9**). White solid. M.p. 123–124°. $[\alpha]_D^{20} = +16.9$ ($c = 0.93$, CH_2Cl_2). IR (CH_2Cl_2): 3615, 3343, 3029, 2965, 2932, 2869, 2838, 1598, 1581, 1473, 1453, 1405, 1366, 1289, 1247. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.44 (*d*, $J = 7.0$, 3 H); 2.24 (*s*, 3 H); 3.5–3.6 (*m*, 2 H); 3.59 (*s*, 3 H); 3.6–3.7 (*m*, 1 H); 4.12 (*q*, $J = 7.0$, 1 H); 6.53 (*d*, $J = 8.0$, 1 H); 6.68 (*d*, $J = 8.0$, 1 H); 6.98 (*t*, $J = 8.0$, 1 H); 7.0–7.1 (*m*, 2 H); 7.1–7.2 (*m*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.0; 20.1; 51.7; 54.7; 62.3; 65.3; 108.9; 123.0; 127.0; 128.0; 130.6; 136.3; 141.9; 157.9. MS: 270 (14, $[M - Me]^+$), 254 (80), 238 (4), 149 (100), 134 (16), 119 (38), 106 (45), 91 (49), 77 (23). HR-MS: 270.1490 ($[M - Me]^+$, $C_{17}H_{20}NO_2^+$; calc. 270.1494).

(−)-[(1S)-1-(2-Methoxy-6-methylphenyl)ethyl]amine ((*S*)-**2a**). A suspension of anh. K_2CO_3 (22.50 g, 160 mmol) in MeOH (60 ml) was cooled to 0°. A soln. of (*S*,*S*)-**10** (7.73 g, 27.11 mmol) in CH_2Cl_2 (100 ml) and a soln. of $Pb(OAc)_4$ (15.02 g, 33.89 mmol) in CH_2Cl_2 (100 ml) were added dropwise to the suspension at the same time within 10 min. After an additional 3 min, the reaction was stopped by addition of sat. aq. Na_2CO_3 soln. (150 ml). The brown-red mixture was filtered through a pad of *Celite*. CH_2Cl_2 (100 ml) was added, and the mixture was washed with sat. aq. Na_2CO_3 soln. (2 × 30 ml). The org. phase was extracted once more with sat. aq. Na_2CO_3 soln. The org. phase was dried (K_2CO_3) and evaporated to afford the imine (*S*)-**11** as a yellow oil which solidified under vacuum (10^{-2} mbar). The solid was washed with hexane: (*S*)-**11** (5.30 g) as a white solid. (*S*)-**11** was directly hydrolyzed for 15 h by 0.05N HCl (400 ml) in CH_2Cl_2 (150 ml) at r.t. The soln. was decanted and the org. phase washed with 0.05N HCl (70 ml). The combined aq. phase was extracted with Et_2O (2 × 20 ml) and neutralized with 6N NaOH. The resulting aq. phase was extracted with Et_2O (3 × 20 ml) and basified (pH 9) with 6N NaOH and extracted with Et_2O (3 × 20 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the crude yellow oil purified by bulb-to-bulb distillation at 60°/0.4 mbar: (−)-(*S*)-**2a** (2.38 g, 70% from (*S*,*S*)-**10**). White solid. Chiral HPLC (corresponding *N*-[(1*S*)-1-(2-methoxy-6-methylphenyl)ethyl]-naphthalene-1-carboxamide; *Chiracel OD-H*, 10% ^{i}PrOH/hexane, 1 ml/min, λ 300 nm): t_R 12 min ((+)-(*R*); 0.5%), ((−)-(*S*); 99.5%)); 99% ee. $[\alpha]_D^{20} = -27.0$ ($c = 1.21$, EtOH). IR (CCl_4): 3390, 3068, 2936, 2836, 1581, 1472, 1365, 1259, 1245. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.47 (*d*, $J = 6.8$, 3 H); 2.33 (*s*, 3 H); 2.38 (br. *s*, 2 H); 3.85 (*s*, 3 H); 4.31 (*q*, $J = 6.8$, 1 H); 6.7–6.8 (*m*, 2 H); 7.08 (*m*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.1; 22.2; 47.0; 55.1; 109.4; 123.2; 126.9; 132.7; 135.6; 158.2. MS: 151 (10), 150 (100, $[M - Me]^+$), 135 (24), 121 (12), 91 (8), 77 (6). HR-MS: 165.1152 (M^+, $C_{10}H_{15}NO^+$; calc. 165.1153).

6. *Enantiomerically Enriched* **2a**: *Method B. (+)-(αR)-2-Methoxy-α,6-dimethylbenzenemethanol* ((*R*)-**23**). To a soln. of borane–oxazaborolidine complex (*S*)-**22** (265 mg, 0.913 mmol) in CH_2Cl_2 (0.5 ml; previously dried over 4 Å molecular sieves) under N_2, 10M $BH_3 \cdot SMe_2$ (1.70 ml, 18.27 mmol) was added. The mixture was cooled to −20°, and 1M **21** (3 g, 18.27 mmol) in CH_2Cl_2 (18.3 ml; previously dried over 4 Å molecular sieves) was added *via* a syringe pump within 5 h. After 36 h, MeOH (10 ml) was added to the soln. at −20°. The mixture was then warmed to r.t. and evaporated. The residue was purified by FC (SiO_2, cyclohexane/AcOEt 70:30: (*R*)-**23** (2.78 g, 92%; 93% ee by ^{1}H-NMR, integration of Me-Ar signal of the corresponding (*R*,*R*)-*Mosher* ester). Colorless oil. $[\alpha]_D^{20} = +27.6$ ($c = 1.30$, $CHCl_3$). IR ($CHCl_3$): 3021, 2927, 1583, 1223. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.52 (*d*, $J = 6.7$, 3 H); 2.31 (*s*, 3 H); 3.6 (br. *s*, 1 H); 3.88 (*s*, 3 H); 5.06 (*q*, $J = 6.7$, 1 H); 6.77–6.80 (*m*, 2 H); 7.10 (*t*, $J = 7.8$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.5; 23.0; 55.3; 67.2; 109.1; 123.5; 126.4; 130.9; 135.4; 157.4. MS: 166 (74, M^+), 164 (65), 151 (100), 149 (97), 212 (90), 91 (84). HR-MS: 166.0984 (M^+, $C_{10}H_{14}O_2^+$; calc. 166.0993).

(+)-2-[(1S)-1-Azidoethyl]-1-methoxy-3-methylbenzene ((*S*)-**24**). DPPA (0.724 ml, 3.3 mmol) followed by DBU (0.473 ml, 3.3 mmol) were added at r.t. to a soln. of (*R*)-**23** (464 mg, 2.8 mmol) in THF (8 ml). The mixture was stirred at r.t. for 24 h. To the dark red soln., H_2O (6 ml) and CH_2Cl_2 (6 ml) were added. The org. phase was washed with H_2O (2 × 15 ml), dried ($MgSO_4$), and evaporated and the residue purified by FC (SiO_2, cyclohexane/AcOEt 80:20): (*S*)-**24** (300 mg, 56%). Colorless oil. $[\alpha]_D^{20} = +2.66$ ($c = 1.24$, $CHCl_3$; 51% ee). IR ($CHCl_3$): 3020, 2936, 2839, 2116, 1583, 1489, 1472, 1373, 1262, 1206. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.58 (*s*, *J* = 7.1, 3 H); 2.41 (*s*, 3 H); 3.86 (*s*, 3 H); 5.17 (*q*, *J* = 7.1, 1 H); 6.80 (*d*, *J* = 7.6, 1 H); 7.18 (*t*, *J* = 7.6, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.3; 20.0; 54.4; 55.5; 109.0; 120.9; 123.5; 126.6; 137.2; 157.9. MS: 191 (14, M^+), 150 (11), 149 (100), 133 (12), 119 (19), 91 (20), 77 (13). HR-MS: 191.1074 (M^+, $C_{10}H_{13}N_3O^+$; calc. 191.1058).

(−)-[(1S)-1-(2-Methoxy-6-methylphenyl)ethyl]amine ((*S*)-**2a**). A mixture of (*S*)-**24** (160 mg, 0.83 mmol), EtOH (6 ml), and the Pd/C catalyst (*Degussa* type *101 NE/W*, 10 mg) was purged with H_2 (3 ×), stirred under H_2 (1 atm) at r.t. for 4 h, and then filtered through a pad of *Celite*. Evaporation gave a yellow oil, which was purified by bulb-to-bulb distillation at 60°/0.4 mbar: (*S*)-**2a** (132 mg, 96%). Chiral HPLC (*N*-[(1*S*)-1-(2-methoxy-6-methylphenyl)ethyl]naphthalene-1-carboxamide; *Chiracel OD-H*, 10% ^{i}PrOH/hexane, 1 ml/min, λ 300 nm): t_R 12 ((+)-(*R*); 24.5%); 18 ((−)-(*S*); 75.4%); 51% ee. $[\alpha]_D^{20} = -14.5$ ($c = 1.75$, EtOH).

7. *Enantiomerically Enriched* **2b**: *Method C*. *(+)-3-Methyl-2-{(1E)1-{[(1R)-1-phenylethyl]imino}-ethyl]phenol* ((*R*)-**33**). A mixture of 1-(2-hydroxy-6-methylphenyl)ethanone (**32**; 1.80 g, 12 mmol), (+)-(αR)-α-methylbenzylamine (1.45 g, 12 mmol; > 99% ee), a catalytic amount of TsOH (0.200 g), and 4 Å molecular sieves (10 g) in dry toluene (20 ml) was refluxed for 20 h. The soln. was filtered through a pad of *Celite*, and the filtrate was evaporated: crude (*R*)-**33** (3.03 g, 12 mmol). Pale yellow solid. The product was used without further purification. $[\alpha]_D^{20} = +157$ ($c = 0.35$, EtOH). IR (CCl_4): 2966, 1605, 1450, 1366, 1288. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.64 (*d*, *J* = 6.5, 3 H); 2.33 (*s*, 3 H); 2.42 (*s*, 3 H); 4.89 (*q*, *J* = 6.5, 1 H); 6.65 (*d*, *J* = 7.4, 1 H); 6.81 (*d*, *J* = 8.1, 1 H); 7.12 (*t*, *J* = 7.8, 1 H); 7.26 (*m*, 2 H); 7.3–7.4 (*m*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.8; 23.4; 25.1; 58.9; 115.5; 121.9; 123.0; 126.4; 126.8; 128.7; 130.6; 136.9; 144.2; 160.3; 170.8. MS: 253 (25, M^+), 238 (11), 162 (6), 149 (20), 134 (10), 133 (6), 106 (11), 105 (100), 91 (4), 79 (18), 77 (26). HR-MS: 253.1457 (M^+, $C_{17}H_{19}NO^+$; calc. 253.1466).

(+)-3-Methyl-2-{(1S)-1-{[(1R)-1-phenylethyl]amino}ethyl]phenol ((*S,R*)-**34**). To a soln. of **33** (506 mg, 2 mmol) in MeOH (10 ml) at −78° was added $NaBH_4$ (152 mg, 4 mmol). The mixture was allowed to warm to r.t. and stirred for 12 h. The mixture was cooled to 0°, and sat. NH_4Cl soln. (5 ml) was added followed by CH_2Cl_2 (5 ml). The aq. phase was extracted with CH_2Cl_2 (5 ml) and the combined org. phase dried ($MgSO_4$) and evaporated: crude (*S,R*)-**34**/(*R,R*)-**34** 2.6:1 (by ^{1}H-NMR). Purification by FC (SiO_2, pentane/Et_2O/Et_3N 4:1:3) afforded (*S,R*)-**34** (362 mg, 71%; > 96% de by ^{1}H-NMR, integration of Me-Ar signal). $[\alpha]_D^{20} = +18$ ($c = 0.75$, $CHCl_3$). IR ($CHCl_3$): 2970, 2922, 2855, 2744, 1605, 1583, 1465, 1444, 1378, 1272, 1234, 1108. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.40 (*d*, *J* = 6.7, 3 H); 1.50 (*d*, *J* = 6.7, 3 H); 2.22 (*s*, 3 H); 3.89 (*q*, *J* = 6.7, 1 H); 4.36 (*q*, *J* = 6.7, 1 H); 6.60 (*d*, *J* = 7.5, 1 H); 6.69 (*d*, *J* = 8.0, 1 H); 7.03 (*t*, *J* = 8.0, 1 H); 7.26–7.36 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.4; 19.8; 21.3; 50.9; 54.3; 115.2; 121.1; 125.1; 126.3 (2); 127.4; 127.9; 128.6 (2); 135.4; 143.4; 157.9. MS: 255 (31, M^+), 240 (60), 134 (68), 120 (15), 106 (100), 91 (32), 79 (31). HR-MS: 255.1627 (M^+, $C_{17}H_{21}NO^+$; calc. 255.1623).

A pure sample of (*R,R*)-**34** (55 mg, 11%) was also obtained. M.p. 115–117°. $[\alpha]_D^{20} = +55$ ($c = 1.23$, $CHCl_3$). IR ($CHCl_3$): 2970, 2922, 2855, 2744, 1605, 1583, 1465, 1444, 1378, 1272, 1234, 1108. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.31 (*d*, *J* = 6.7, 3 H); 1.43 (*d*, *J* = 6.8, 3 H); 1.92 (*s*, 3 H); 3.68 (*q*, *J* = 6.8, 1 H); 3.90 (*q*, *J* = 6.7, 1 H); 6.59 (*d*, *J* = 7.4, 1 H); 6.72 (*d*, *J* = 8.0, 1 H); 7.05 (*t*, 1 H); 7.15 (*m*, 2 H); 7.3–7.4 (*m*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.0; 20.7; 23.4; 51.1; 55.3; 114.9; 121.2; 124.0; 126.3 (2); 127.5; 127.8; 128.8 (2); 135.9; 143.6; 158.2. MS: 255 (22, M^+), 241 (7), 240 (39), 136 (51), 135 (25), 134 (52), 133 (15), 120 (13), 106 (91), 105 (100), 91 (36), 77 (34). HR-MS: 255.1629 (M^+, $C_{17}H_{21}NO^+$; calc. 255.1623).

(+)-[(1S)-1-(2-Hydroxy-6-methylphenyl)ethyl]amine ((*S*)-**2b**). Hydrogenolysis of (*S,R*)-**34** (1.02 g, 4 mmol) was performed in refluxing MeOH (40 ml) with AcOH (960 mg, 16 mmol), ammonium formate (2.27 g, 24 mmol), and $Pd(OH)_2$/C (20 wt.-%, 400 mg). The reaction was stopped after 24 h. The mixture was filtered through a pad of *Celite* and the filtrate evaporated. The residue was dissolved in Et_2O, the soln. washed with sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and evaporated, and the residue recrystallized from hexane: (*S*)-**2b** (460 mg, 76%; > 96% ee by ^{1}H-NMR, integration of Me-Ar signal of the corresponding (*S,R*)-*Mosher* amide). M.p. 110–112°. $[\alpha]_D^{20} = +64$ ($c = 0.9$, $CHCl_3$). IR ($CHCl_3$): 3009, 2966, 2866, 2766, 1583, 1466, 1383, 1273, 1214, 1072. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.43 (*d*, *J* = 6.6, 3 H); 2.25 (*s*, 3 H); 4.65 (*q*, *J* = 6.6, 1 H); 6.61 (*d*, *J* = 7.5, 1 H); 6.70 (*d*, *J* = 7.5, 1 H); 7.02 (*t*, *J* = 7.5, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.3; 21.4; 47.7; 115.5; 121.1; 125.8; 127.9; 135.1; 158.1. MS: 151 (50, M^+), 136 (63), 134 (100), 119 (23), 105 (21), 91 (61), 77 (20). HR-MS: 151.0954 (M^+, $C_9H_{13}NO^+$; calc. 151.0997).

8. *Enantiomerically Enriched* **3a**: *Method B. (±)-3,5-Di(*tert*-butyl)-2-hydroxy-α-methylbenzenemethanol* (**18**). MeMgBr (3M) in Et_2O (8.33 ml, 25.0 mmol) was added within 30 min to a stirred soln. of **17** (2.34 g, 10.0 mmol) in Et_2O (40 ml). The soln. was refluxed for 16 h. Sat. NH_4Cl soln. (100 ml) was added and the product extracted with Et_2O (3 × 40 ml). The combined org. phase was washed with H_2O and brine, dried ($MgSO_4$), and evaporated: pure **18** (2.50 g, 100%). Colorless crystals. M.p. 62–64°. IR ($CHCl_3$): 3591, 3374, 2964, 2869, 1480, 1445, 1362, 1249, 1228, 1009, 881, 767. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.34 (*s*, 9 H); 1.48 (*s*, 9 H); 1.65 (*d*, *J* = 6.8, 3 H); 2.47 (br. *d*, *J* = 3.4 , 1 H); 5.06 (*q*, *J* = 6.6, 1 H); 6.89 (*d*, *J* = 2.4, 1 H); 7.30 (*d*, *J* = 2.4 , 1 H); 8.20 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 23.0; 29.7; 31.6; 34.2; 35.1; 73.0; 121.2; 123.5; 136.0; 141.2; 152.5. MS: 250 (3, M^+), 233 (33), 217 (100), 57 (26). HR-MS: 250.1927 (M^+, $C_{16}H_{26}O_2^+$; calc. 250.1932).

*1-[3,5-Di(*tert*-butyl)-2-hydroxyphenyl]ethanone* (**19**). A soln. of **18** (2.50 g, 10.0 mmol), MnO_2 (2.61 g, 30.0 mmol), and hexane (40 ml) was refluxed for 16 h. The soln. was filtered through a pad of *Celite* and the filtrate evaporated: **19** (2.38 g, 96%). Pale yellow oil. IR ($CHCl_3$): 3530, 2964, 2871, 1630, 1466, 1434, 1329, 1240, 1203, 1185, 1105, 974, 880, 822. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.35 (*s*, 9 H); 1.45 (*s*, 9 H); 2.67 (*s*, 3 H); 7.59 (*q*, *J* = 2.5, 2 H); 13.01 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 27.0; 29.3; 31.3; 34.2; 35.0; 118.6; 124.3; 131.3; 137.9; 140.0; 160.0; 205.2. MS: 248 (21, M^+), 233 (100), 57 (12). HR-MS: 248.1774 (M^+, $C_{16}H_{24}O_2^+$; calc. 248.1776).

*1-[3,5-Di(*tert*-butyl)-2-methoxyphenyl]ethanone* (**20**). A soln. of **19** (496 mg, 2.0 mmol), Me_2SO_4 (3.0 ml, 31 mmol), K_2CO_3 (5.0 g, 36 mmol), and acetone (20 ml) was refluxed for 4 h. After addition of 2N aq. NaOH (100 ml), the product was extracted with CH_2Cl_2 (3 × 50 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the crude product purified by FC (SiO_2, Et_2O/cyclohexane 1:4): **20** (449 mg, 85%). Colorless crystals. M.p. 84–86°. IR ($CHCl_3$): 2965, 2870, 1678, 1595, 1477, 1425, 1364, 1266, 1244, 1102, 1008, 891. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.33 (*s*, 9 H); 1.43 (*s*, 9 H); 2.65 (*s*, 3 H); 3.74 (*s*, 3 H); 7.32 (*d*, *J* = 2.5, 1 H); 7.48 (*d*, *J* = 2.5, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 29.8; 30.8; 31.3; 34.5; 35.2; 63.1; 124.1; 127.3; 134.1; 142.2; 145.5; 156.6; 203.6. MS: 262 (16, M^+), 247 (100), 57 (22). HR-MS: 262.1935 (M^+, $C_{17}H_{26}O_2^+$; calc. 262.1932).

*(+)-(*α*R)-3,5-Di(*tert*-butyl)-2-methoxy-α-methylbenzenemethanol* ((*R*)-**25**). To a soln. of borane complex (*S*)-**22** (47 mg, 0.161 mmol) in CH_2Cl_2 (2 ml; previously dried over 4 Å molecular sieves) under N_2 10M $BH_3 \cdot SMe_2$ (0.328 ml, 3.28 mmol) was added. The mixture was cooled to −20° and 1M **20** (860 mg, 3.28 mmol) in CH_2Cl_2 (3.3 ml; previously dried over 4 Å molecular sieves) was added *via* a syringe pump over 5 h. After 12 h, MeOH (10 ml) was added to the soln. at −20°. The mixture was then warmed to r.t. and evaporated. The residue was purified by FC (SiO_2, cyclohexane/AcOEt 4:1): (*R*)-**25** (644 mg, 74%; 90% ee by ^{19}F-NMR, integration of CF_3–C of the corresponding (*R*,*R*)-*Mosher* ester). Oil. $[\alpha]_D^{20} = +24.7$ (*c* = 0.63, $CHCl_3$). IR ($CHCl_3$): 3454, 2965, 2869, 1478, 1228, 1122, 1090, 1011, 922. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.33 (*s*, 9 H); 1.41 (*s*, 9 H); 1.58 (*d*, *J* = 6.6, 3 H); 2.10 (br. *s*, 1 H); 3.82 (*s*, 3 H); 5.30 (*q*, *J* = 6.6, 1 H); 7.27 (*s*, 1 H); 7.32 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 24.0; 31.5; 32.2; 34.7; 35.3; 62.8; 64.6; 121.5; 123.8; 138.1; 141.7; 146.2; 154.5. MS: 264 (3, $[M+H]^+$), 246 (26), 232 (100), 57 (56). HR-MS: 264.2074 ($[M+H]^+$, $C_{17}H_{28}O_2^+$; calc. 264.2089).

*(+)-(*α*R)-3,5-Di(*tert*-butyl)-2-hydroxy-α-methylbenzenemethanol* ((*R*)-**18**). To a soln. of borane–oxazaborolidine complex (*S*)-**22** (80 mg, 0.275 mmol) in CH_2Cl_2 (0.25 ml; previously dried over 4 Å molecular sieves) under N_2, 10M $BH_3 \cdot SMe_2$ (0.05 ml, 0.5 mmol) was added. The mixture was cooled to −20° and 1M **19** (124 mg, 0.5 mmol) in CH_2Cl_2 (0.5 ml; previously dried over 4 Å molecular sieves) was added *via* a syringe pump over 5 h. After 4 h, MeOH (5 ml) was added to the soln. at −20°. The mixture was then warmed to r.t. and evaporated. The residue was purified by FC (SiO_2, Et_2O): (*R*)-**18** (0.069 g, 55%). Chiral HPLC (*Chiracel OJ*, 0.2% ^{i}PrOH/hexane, 0.3 ml/min, λ 210 nm): t_R 66.1 ((−)-(*S*); 1%), 80.1 ((+)-(*R*); 99.0%; 98% ee. $[\alpha]_D^{20} = +5.3$ (*c* = 1.2, $CHCl_3$).

(−)-1-[(1S)-1-Azidoethyl]-3,5-di(tert-butyl)-2-methoxybenzene ((*S*)-**26**). To a soln. of **25** (566 mg, 2.14 mmol) in THF (20 ml) was added 4-NO_2-DPPA (1.17 g, 3.21 mmol). The suspension was stirred at r.t. until the solid was dissolved. DBU (0.45 ml, 3.21 mmol) was added dropwise, and the yellow soln. was stirred for 2 h at r.t. H_2O (10 ml) and CH_2Cl_2 (10 ml) were added to the deep yellow soln., the org. phase was washed with H_2O (2 × 20 ml) and 2N HCl (2 × 20 ml), dried ($MgSO_4$), and evaporated and the residue purified by FC (SiO_2, cyclohexane/AcOEt 95:05): (*S*)-**26**. Pale yellow crystals (530 mg, 85%). M.p. 55–56°. $[\alpha]_D^{20} = -17.3$ (*c* = 1.25, $CHCl_3$). IR (CH_2Cl_2): 3597, 2965, 2869, 2173, 1590, 1489, 1297, 1188, 1010, 965. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.34 (*s*, 9 H); 1.42 (*s*, 9 H); 1.58 (*d*, *J* = 6.9, 3 H); 3.81 (*s*, 3 H); 5.03 (*q*, *J* = 6.9, 1 H); 7.23 (*d*, *J* = 2.5, 1 H); 7.33 (*d*, *J* = 2.5, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 21.4; 31.2; 31.5; 34.6; 35.4; 54.6; 63.1; 121.9; 124.3; 133.6; 142.0; 146.3; 154.7. MS: 289 (14, M^+), 247 (56), 231 (20), 57 (100). HR-MS: 289.2150 (M^+, $C_{17}H_{27}ON_3^+$; calc. 289.2154).

*(−)-{(1S)-1-[3,5-Di(*tert*-butyl)-2-methoxyphenyl]ethyl}amine* ((*S*)-**3a**). A mixture of (*S*)-**26** (450 mg, 1.55 mmol), EtOH (15 ml), and Pd/C catalyst (*Degussa* type *101 NE/W*, 30 mg) was purged with H_2 (3×), stirred under H_2 (1 atm) at r.t. for 12 h, and then filtered through a pad of *Celite*. Evaporation gave (*S*)-**3a**

(394 mg, 96%; 69% ee by ^{19}F-NMR, integration of CF_3–C of the corresponding (*S,R*)-*Mosher* amide). Colorless crystals. M.p. 77–78°. $[\alpha]_D^{20} = -13$ ($c = 0.3$, EtOH). IR ($CHCl_3$): 3220, 2965, 2869, 1477, 1430, 1362, 1228, 1208, 1119, 1009, 882. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.33 (*s*, 9 H); 1.41 (*s*, 9 H); 1.44 (*d*, $J = 6.6$, 3 H); 1.89 (br. *s*, 2 H); 3.80 (*s*, 3 H); 4.53 (*q*, $J = 6.6$, 1 H); 7.25 (*d*, $J = 2.5$, 1 H); 7.32 (*d*, $J = 2.5$, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 25.0; 31.2; 31.5; 34.7; 35.4; 44.3; 62.7; 121.1; 122.9; 140.2; 141.7; 146.0; 154.4. MS: 263 (8, M^+), 248 (100), 231 (23), 117 (10), 57 (62). HR-MS: 263.2237 (M^+, $C_{17}H_{29}ON^+$; calc. 263.2249).

9. *Enantiomerically Enriched* **3b**: *Method C. (–)-2,4-Di(*tert*-butyl)-6-{(1*E*)-1-[[(1*R*)-1-phenylethyl]-imino}ethyl}phenol* ((*R*)-**35**). A mixture of **19** (2.48 g, 10.0 mmol), (+)-(*R*)-α-methylbenzylamine (1.27 ml, 10.0 mmol), a catalytic amount of TsOH (0.095 g, 0.5 mmol) and 4 Å molecular sieves (5.0 g) in dry toluene (15 ml) was refluxed for 16 h. The soln. was filtered and evaporated: crude (*R*)-**35** (3.48 g, 99%). Yellow viscous oil. $[\alpha]_D^{20} = -155.0$ ($c = 1.04$, EtOH). IR ($CHCl_3$): 3689, 3201, 2964, 2869, 1611, 1478, 1450, 1390, 1362, 1248, 1212, 1095, 1023, 878, 700. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.32 (*s*, 9 H); 1.49 (*s*, 9 H); 1.66 (*d*, $J = 6.6$, 3 H); 2.35 (*s*, 3 H); 4.96 (*q*, $J = 6.6$, 1 H); 7.41–7.16 (*m*, 7 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 15.2; 25.4; 29.5; 31.5; 34.2; 35.2; 58.5; 118.0; 122.0; 126.4; 126.9; 127.0; 128.2; 128.6; 129.0; 137.6; 137.9; 144.6; 160.9; 171.1. MS: 351 (63, M^+), 336 (28), 232 (59), 204 (19), 105 (100), 57 (28). HR-MS: 351.2538 (M^+, $C_{24}H_{33}NO^+$; calc. 351.2562).

*(+)-2,4-Di(*tert*-butyl)-6-{(1*R*)-1-{[(1*R*)-1-phenylethyl]amino}ethyl}phenol* ((*R,R*)-**36**). $NaBH_4$ (1.15 g, 30 mmol) was slowly added to a soln. of AcOH (2 ml, 35 mmol) in THF (40 ml). The temp. of the soln. was kept at 10–20° while H_2 evolved (0.5 h). The soln. was then cooled to −78°, and (*R*)-**35** (3.5 g, 10 mmol) in THF (10 ml) was added in one portion and the temp. of the mixture was allowed to warm slowly to r.t. overnight. The soln. was evaporated, the residue taken up in CH_2Cl_2 (100 ml), the soln. washed with sat. Na_2CO_3 soln. (50 ml), dried ($MgSO_4$), and evaporated, and the 2.4:1 (by ^{1}H-NMR) mixture (*R,R*)-**36**/(*S,R*)-**36** purified by FC (SiO_2, pentane/CH_2Cl_2 1:1): (*R,R*)-**36** (1.8 g, 51%; 74% de). Colorless viscous oil. $[\alpha]_D^{20} = +35.0$ ($c = 2.1$, $CHCl_3$). IR ($CHCl_3$): 3674, 3084, 2964, 2868, 1602, 1479, 1444, 1362, 1264, 1224, 1109, 882. ^{1}H-NMR ($CDCl_3$, 400 MHz; mixture of inseparable diastereoisomers): 1.26–1.27 (2*s*, 9 H); 1.35–1.46 (*m*, 18 H); 1.54 (2*s*, 9 H); 3.65 (2*q*, $J = 6.8$, 6.5, each 1 H); 4.0 (2*q*, $J = 6.8$, 6.5, each 1 H); 6.62 (*d*, $J = 2.5$, 1 H); 6.75 (*m*, 1 H); 7.14–7.34 (*m*, 7 H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 22.5; 23.2; 29.6; 31.7; 34.1; 35.5; 50.8; 55.2; 57.0; 122.3; 123.3; 125.5; 126.4; 127.4; 128.6 (2); 135.8; 140.3; 143.8; 154.0. MS: 353 (34, M^+), 338 (15), 232 (38), 217 (100), 175 (16), 105 (39), 84 (40), 69 (12), 57 (44). HR-MS: 353.2695 (M^+, $C_{24}H_{35}NO^+$; calc. 353.2718).

*(–)-2-[(1*R*)-1-Aminoethyl]-4,6-di(*tert*-butyl)phenol* ((*R*)-**3b**). A mixture of **36** (1.41 g, 4 mmol), MeOH (40 ml), AcOH (960 mg, 16 mmol), and $Pd(OH)_2$/C (30 wt.-%, 850 mg) was purged with H_2 (3×), stirred under H_2 (4 atm) at r.t. for 16 h, and then passed through a pad of *Celite*. The filtrate was evaporated and the residue taken up in Et_2O (20 ml) and sat. $NaHCO_3$ soln. (20 ml). The aq. phase was extracted with Et_2O the combined org. phase dried ($MgSO_4$) and evaporated, and the residue purified by FC (pentane/Et_2O/Et_3N 95:5:3): (*R*)-**3b** (976 mg, 98%; 66% ee by ^{19}F-NMR, integration of CF_3–C signal of the corresponding (*R,S*)-*Mosher* amide). Pale yellow crystals. M.p. 80–82°. $[\alpha]_D^{20} = -3$ ($c = 2.15$, $CHCl_3$). IR ($CHCl_3$): 3689, 3392, 2964, 2869, 1601, 1480, 1440, 1362, 1223, 1161, 1129, 882. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.31 (*s*, 9 H); 1.44 (*s*, 9 H); 1.51 (*d*, $J = 6.6$, 3 H); 4.34 (*q*, $J = 6.6$, 1 H); 6.88 (*d*, $J = 2.5$, 1 H); 7.22 (*d*, $J = 2.5$, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 23.5; 29.7; 31.6; 34.2; 35.0; 52.4; 122.0; 122.8; 127.2; 136.6; 140.3; 154.1. MS: 249 (9, M^+), 232 (33), 217 (100), 175 (13), 105 (14), 77 (14), and 57 (35). HR-MS: 249.2091 (M^+, $C_{16}H_{27}NO^+$; calc. 249.2092).

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