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Resolution of Racemic 2-Aminocyclohexanol Derivatives and Their Application as Ligands in Asymmetric Catalysis†

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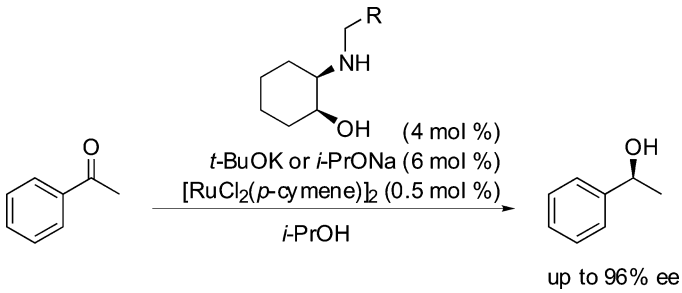

A preparatively easy and efficient protocol for the resolution of racemic 2-aminocyclohexanol derivatives is described, delivering both enantiomers with >99% enantiomeric excess (ee) by sequential use of (*R*)- and (*S*)-mandelic acid. A simple aqueous workup procedure permits the isolation of the amino alcohols in analytically pure form and the almost quantitative recovery of mandelic acid. Debenzylation of enantiopure *trans*-2-(*N*-benzyl)amino-1-cyclohexanol by hydrogenation and subsequent derivatization give access to a broad variety of diversely substituted derivatives. Furthermore, the corresponding cis isomers are readily available. Applications of these optically active aminocyclohexanols in catalyzed asymmetric phenyl transfer reactions to benzaldehydes and transfer hydrogenations of aryl ketones lead to products with up to 96% ee.

Introduction

The β-amino alcohol functional motif is one of the most important pharmacophores[1] because of its ubiquity in biologically active compounds,[2] such as antibiotics, alkaloids, enzyme inhibitors, and β-blockers.[3] Among the latter class, (*S*)-propranolol is, for example, a well-known antihypertensive drug,[4] whereas the (*R*)-enantiomer has a contraceptive effect,[5] one of the myriad of examples unambiguously demonstrating the need for enantiomeric purity in pharmaceuticals. Furthermore, chiral amino alcohols have successfully been used as auxiliaries[6] or ligands[7] in asymmetric synthesis. With the appearance of exceedingly effective systems for transfer hydrogenations,[8] additions of diorganozincs to aldehydes,[9] or borane reductions of ketones,[10] for example, the desire for efficient procedures for the preparation of optically pure amino alcohol derivatives has considerably increased. Many existing synthetic routes rely on the derivatization of the available pool of amino acids, inherently limiting the number of accessible analogues.[11] Alternative approaches toward β-amino alcohols utilize Sharpless' asymmetric aminohydroxylation[12] and stereoselective

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additions of several nucleophiles to α-aminocarbonyls,[13] nitroalkenes,[14] imines,[15] epoxides,[11a,16] aziridines,[11a,17] or cyclic sulfates.[18] Moreover, novel syntheses of vicinal amino alcohols by enantioselective direct catalytic Mannich-type reactions were recently reported by Trost, List, Barbas, and Shibasaki.[19] Our ongoing research in the fields of the catalytic enantioselective aryl transfer to aldehydes,[20] asymmetric sulfoxidation,[7h,q−s] and desymmetrization of meso anhydrides[21] is accompanied by the interest in efficient syntheses of enantiopure β-amino alcohols to enable an extensive ligand screening for the above-mentioned reactions. In the anhydride opening project, two pseudoenantiomeric cinchona alkaloids with β-amino alcohol units (quinine and quinidine) proved to be highly stereoselective mediators in the nucleophilic alcoholysis,[22] and it has been shown that the absolute configuration of the resulting hemiester correlates with the configuration of the hydroxyl-bearing stereocenter of the alkaloid.[23] This relationship was also found in the diethylzinc addition to aldehydes,[24] which is of particular interest for our studies because of the mechanistic analogies of the stereocontrol

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in aryl transfer reactions. Particularly promising in such processes are vicinal amino alcohols with a low degree of conformational freedom and a combination of a secondary alcohol moiety and an easily modifiable amino functionality. Considering that vicinal diamine derivatives with a cyclohexane backbone have very frequently been used in asymmetric catalysis,[7a−e,25] we wondered about the potential application of the corresponding β-amino alcohols. As a starting point, facile access to a variety of 2-aminocyclohexanol derivatives was required. Encouraged by the successful use of fractional crystallization procedures of diastereomeric ammonium salts of dehydroabietic acid[26] or enantiopure binaphthol and boric acid,[27] we focused on the development of a resolution protocol of 2-aminocyclohexanol derivatives with inexpensive and quantitatively recoverable (*R*)- and (*S*)-mandelic acid. Ease and efficiency in large-scale applications were envisaged as potential preparative advantages of such an approach.

Results and Discussion

For the preparation of optically active *trans*-2-aminocyclohexanols, three general approaches are available: (1) ring-opening reactions of cyclohexene oxide by a chiral amine resulting in diastereomers which can be separated; (2) enantioselective opening of the meso epoxide by an appropriate nucleophile in the presence of a chiral catalyst; and (3) resolutions of racemic compounds or related precursors. For example, as early as in 1985, Overman described the aminolysis of bicyclic epoxides with an aluminum amide stemming from enantiomerically enriched methylbenzylamine and trimethylaluminum.[28] The resulting two diastereomeric amino alcohols could be easily separated by simple flash chromatography on silica gel. Unfortunately, however, the amount of immediately available pure optically active material remained limited by this proceeding. Also, the destruction of the chiral auxiliary during the deprotection of the amino group, which was necessary for providing the more modifiable free 2-aminocyclohexanol, appeared unfavorable for a general large-scale access to the desired product. Alternatively, Nugent and Jacobsen reported highly enantioselective ring-opening reactions of cyclohexene oxide by azidosilanes catalyzed by chiral Zr(IV)/trialkanolamine and Cr(III)/salen complexes, respectively.[29] Although the utility of these protocols is unquestionable and enantiomeric excesses (ee's) of up to 93% were obtained, they do not reach the initially demanded criteria of enantiomeric purity, and furthermore, they suffer from the necessity of an additional reduction step. A direct aminolysis of meso epoxides in the presence of catalytic amounts of $Sc(OTf)_3$ and an enantiomerically pure 2,2′-bipyridine leading to amino alcohols in high yields with up to 97% ee was recently introduced by Schneider,[30] and finally, Collin reported on enantioselective ring openings by aromatic amines catalyzed by lanthanide iodo binaphtholates.[31] However, only in the latter protocol, a high enantioselectivity (up to 91% ee) has been observed for the cyclohexane-derived substrate.

Despite these advances in asymmetric synthetic approaches toward enantiomerically enriched 2-aminocyclohexanols, the great majority of methods for generating enantiopure derivatives is based on resolution processes of racemic starting materials. Surprisingly, enzymatic approaches[32] have only scarcely been applied for cyclic β-amino alcohol syntheses on a useful laboratory scale, which is probably due to the often preparatively demanding proceedings and the comparatively high amounts of enzymes needed. Frequently, even excellent protocols such as the enantioselective acylation of tertiary 2-aminocyclohexanols by means of *Pseudomonas cepacia*, recently introduced by Gotor and Rebolledo, are restricted to a narrow spectrum of substrates suitable for further derivatizations.[32a] Nonenzymatic approaches for the kinetic resolution of cyclic amino alcohols are, for example, Sharpless' asymmetric *N*-oxide formation and the organocatalytic acylation reaction of Kawabata.[33] By running the reaction to 60−70% conversion, both systems lead to high enantiomeric excesses of up to >99% in the remaining amino alcohol. However, the yield of the recovered substrate and the enantiopurity of the product are moderate. *All of these comments reveal that the classical resolution methodology is nowadays still a valuable alternative for the preparation of 2-aminocyclohexanols, even in an economic respect.*

In view of the highly selective aryl transfer systems developed by Pericàs and Chen involving tertiary amino alcohol ligands,[34] we were initially interested in the synthesis of enantiopure *trans*-2-pyrrolidinylcyclohexanol (**1**), for which a resolution process by means of boric acid and (*R*)- or (*S*)-binaphthol was recently reported by Periasamy.[27] However, this protocol requires a 3-fold repetition of the entire procedure, including binaphthol borate complex formation and salt liberation, to obtain the product with 99% ee.[35] Taking into account the low overall yield and the costs of the chiral resolving agent, we found that this resolution appeared less attractive for the large-scale synthesis of **1**.[36a] In our preliminary experiments, L-tartaric acid was tested as a resolving agent, but its bisammonium salt proved to be

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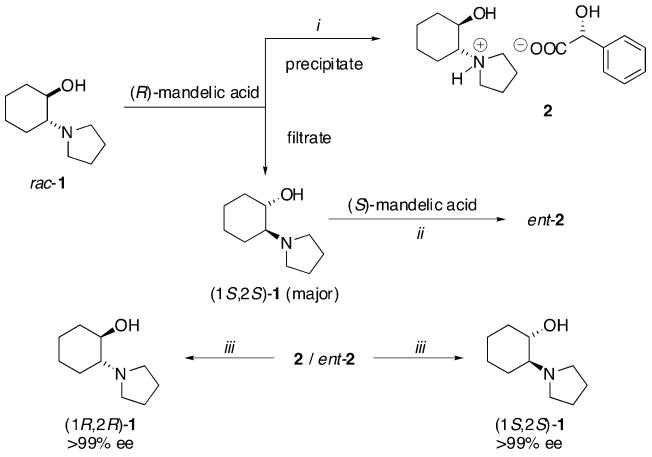
(35) Determined by optical rotation. In this context, it should be mentioned that the resolution of the corresponding methyl ether needs only one crystallization step; see ref 27a.

(36) (a) Current prices for 5 g (17.5 mmol) of (*R*)- and (*S*)-1, 1′-bi-2-naphthol (99% ee) from the 2005−2006 Aldrich catalogue (Germany/Austria) are 227.60 and 206.90 euro, respectively. (b) Current prices for 5 g (33 mmol) of (*R*)- and (*S*)-mandelic acid (99% ee) from the same supplier are 22.30 and 11.80 euro, respectively.

SCHEME 1 [a]



[a] Conditions: (i) (*R*)-mandelic acid (0.5 equiv), ethyl acetate, −20 °C, 14 h, 92% of **2**, based on the amount of mandelic acid; (ii) (*S*)-mandelic acid (0.8 equiv), ethyl acetate, room temperature, 2 h, 94% of *ent*-**2**, based on the amount of mandelic acid; (iii) recrystallization from ethyl acetate (see Table 1) then 2 N aq HCl, ethyl acetate extraction to recover mandelic acid (99.6%), then 5 N aq NaOH, diethyl ether extraction, 95%.

unsuitable for the fractional crystallization because of its low solubility and an insufficient diastereomeric excess (de) in the initial precipitate. Next, (*R*)-mandelic acid was applied, but after heating a solution containing a mixture of racemic **1** and 1 equiv of the enantiopure acid[36b] in ethyl acetate to reflux and subsequently cooling to room temperature, no crystallization occurred. Because it is known that occasionally the resolution of a base proceeds more efficiently if only half of an equivalent of the acid is used (method of half quantities),[37] this stoichiometry was applied here as well and the formation of diastereomerically enriched ammonium salt precipitate **2** in high yield was observed (Scheme 1). The ^{13}C NMR spectrum of this material indicated an 18:82 ratio of diastereomers.[38a] For more highly enriched mixtures, this method of calculation becomes imprecise and therefore HPLC separation conditions for the 4-methoxybenzoic acid ester of *trans*-2-pyrrolidinylcyclohexanol (*rac*-**1**) were elaborated.[38b] A sample of the amino alcohol liberated from the initial precipitate and transformed into its 4-methoxybenzoic acid ester showed an enantiomeric excess of 65%, which is in good agreement with the NMR data. Subsequently, this HPLC analysis was used for the determination of the diastereomeric enrichment after each recrystallization step and for each compound subjected to the resolution step.

The filtrate of the first precipitation reaction contained an inversed 80:20 ratio of the enantiomeric amino alcohol as the major isomer, and treatment with 0.8 equiv of (*S*)-mandelic acid delivered the enantiomeric ammonium salt *ent*-**2** (Scheme 1). The collected mandelic acid salts crystallized in good yields from boiling ethyl acetate within the cooling period to room temperature. Thereby, the diastereomeric excess could be increased to >99% by just two recrystallizations (Table 1).

A simple workup sequence of aqueous HCl and NaOH extractions permits on one hand the almost quantitative recovery of the mandelic acid[39] and on the other hand the isolation of enantiopure **1** and *ent*-**1** in 95% yield and in analytically pure form. The possibilities of derivatization in view of a potential ligand screening in a catalytic reaction were, however, strictly limited with **1**, and an optimization of the resolution protocol for each analogue did not appear attractive. Therefore, the easily modifiable *trans*-2-(*N*-benzyl)amino-1-cyclohexanol (*rac*-**3**) was selected as the next substrate. For the synthesis of such racemic amino alcohols by nucleophilic ring opening of epoxides with the corresponding amines, a wide variety of promoters are available.[40,41] However, often, the highly active catalysts are not commercially available or are expensive, and the ring-opening product usually has to be purified chromatographically. Consequently, the solvent-free reaction of a small excess of cyclohexene oxide with benzylamine in a sealed steel bomb for 6 h at 240 °C proved to be the most efficient method for the preparation of the starting material (particularly in view of a large-scale synthesis).[42] The resolution protocol previously optimized for the pyrrolidinyl derivative could directly be applied in the resolution of *rac*-**3** delivering the corresponding (*R*)-mandelic acid salt **4** with 59% de in the initial precipitate

(37) For a highly efficient example, see: Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

(38) (a) Based on the integration of the distinctly separated signals of the hydroxyl bearing carbon atom in the amino alcohol moiety of the two ammonium salt diastereomers: ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.8 (major), 70.1 ppm. (b) The ester derivative was prepared by treatment of a cooled solution of the amino alcohol in CH_2Cl_2 with 6 equiv of the corresponding benzoyl chloride. After the reaction mixture had been stirred subsequently for 1 h at room temperature, a workup sequence of aqueous HCl and Na_2CO_3 extractions yielded the desired product in analytically pure form.

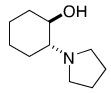
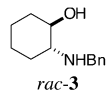
(39) The recovered mandelic acid was pure by NMR and showed an identical value for optical rotation in comparison to the starting material; see Experimental Section.

(40) These include, for example, metal salts: (a) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661 [$LiBF_4$, $LiClO_4$, $NaClO_4$, $Mg(ClO_4)_2$, $CaCl_2$]. (b) Chakraborti, A. K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597 [LiBr]. (c) Rodríguez, J. R.; Navarro, A. *Tetrahedron Lett.* **2004**, *45*, 7495 [$InBr_3$]. Transition metal halides: (d) Swamy, N. R.; Goud, T. V.; Reddy, S. M.; Krishnaiah, P.; Venkateswarlu, Y. *Synth. Commun.* **2004**, *34*, 727 [$ZrCl_4$]. (e) Chakraborti, A. K.; Kondaskar, A. *Tetrahedron Lett.* **2003**, *44*, 8315 [$ZrCl_4$]. (f) Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Yadav, J. S. *Synthesis* **2003**, 2298 [VCl_3]. (g) Chandrasekhar, S.; Ramachandar, T.; Prakash, J. S. *Synthesis* **2000**, 1817 [$TaCl_5$]. (h) Sundararajan, G.; Vijayakrishna, K.; Varghese, B. *Tetrahedron Lett.* **2004**, *45*, 8253 [$CoCl_2$]. (i) Iqbal, J.; Pandey, A. *Tetrahedron Lett.* **1990**, *31*, 575 [$CoCl_2$]. (j) Pachon, L. D.; Gamez, P.; vanBrussel, J. J. M.; Reedijk, J. *Tetrahedron Lett.* **2003**, *44*, 6025 [$ZnCl_2$]. Rare-earth metal halides: (k) Fu, X. L.; Wu, X. H. *Synth. Commun.* **1997**, *27*, 1677 [$SmCl_3$]. (l) Weghe, P. V.; Collin, J. *Tetrahedron Lett.* **1995**, *36*, 1649 [$SmI_2(THF)_2$]. (m) Reddy, L. R.; Reddy, M. A.; Bhanumathi, N.; Rao, K. R. *Synthesis* **2001**, 831 [$CeCl_3 \cdot 7H_2O$]. Metal triflates: (n) Augé, J.; Leroy, F. *Tetrahedron Lett.* **1996**, *37*, 7715 [LiOTf]. (o) Cepanec, I.; Litvic, M.; Mikuldas, Bartolincic, A.; Vinkovic, V. *Tetrahedron* **2003**, *59*, 2435 [$Ca(OTf)_2$]. (p) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287 [$Sn(OTf)_2$, $Cu(OTf)_2$]. (q) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49 [$Bi(OTf)_3$]. (r) Ref 30 and literature cited therein [$Sc(OTf)_3$]. (s) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597 [$Yb(OTf)_3$]. (t) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 575 [$Yb(OTf)_3$, $Nd(OTf)_3$, $Gd(OTf)_3$]. Metal alkoxides: (u) Sagawa, S.; Abe, H.; Hase, Y.; Inaba, T. *J. Org. Chem.* **1999**, *64*, 4962 [$Ti(O^iPr)_4$]. (v) Rampalli, S.; Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **2000**, 1201 [DIPAT (diisopropoxyaluminium trifluoroacetate)]. Metal amides: (w) Carre, M. C.; Houmounou, J. P.; Caubere, P. *Tetrahedron Lett.* **1985**, *26*, 3107 [R_2NMgBr]. (x) Yamada, J.; Yumoto, M.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *32*, 4255 [R'_3PbNR_2]. (y) Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J. G.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1201 [$(R^1R^2N)_2Cu(CN)Li_2$]. (z) Harris, C. E.; Fisher, G. B.; Beardsley, D.; Lee, L.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7746 [R_2NLi and aminoborane].

(41) For novel concepts of mediated epoxide aminolyses, see: (a) Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 726. (b) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narasaiah, A. V. *Tetrahedron Lett.* **2003**, *44*, 1047. (c) Harrak, Y.; Pujol, M. D. *Tetrahedron Lett.* **2002**, *43*, 819. (d) For novel concepts of epoxide aminolyses in the absence of any catalyst, see: Azizi, N.; Saidi, M. R. *Org. Lett.* **2005**, *7*, 3649 and references therein.

(42) A small amount of solvent (e.g., methanol or dichloromethane) is necessary to transfer the reaction mixture into a flask. After evaporation of the solvent and drying of the residue in high vacuum, the product was isolated quantitatively in analytically pure form (0.35 mol scale).

TABLE 1. Resolution of Racemic *trans*-2-Aminocyclohexanols *rac*-1 and *rac*-3 by Means of Mandelic Acid[a]

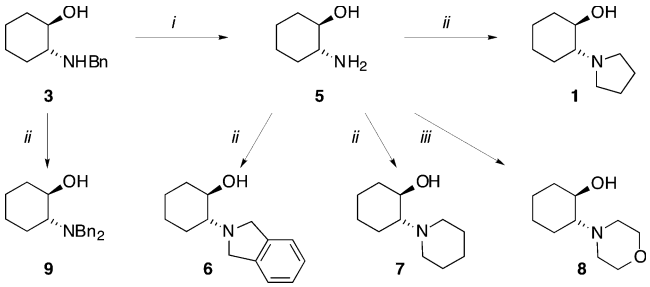
entry	substrate	(*R*)-mandelic acid salt from the initial precipitation				(*S*)-mandelic acid salt obtained from the filtrate			
		salt	recrystallization step	yield (%)[b]	ee (%)[c]	salt	recrystallization step	yield (%)[b]	ee (%)[c]
1			-	92	65		-	94	62
2		**2**	1	81	92	*ent*-**2**	1	78	98
3	*rac*-**1**		2	89	>99[d]		2	85	>99[e]
4			-	90	59		-	77	96
5		**4**	1	78	93	*ent*-**4**	1	79	>99[f]
	rac-**3**								
6			2	85	>99[g]		-	-	-

[a] The resolution experiments were performed using first 0.5 equiv of (*R*)-mandelic acid for a 0.5 M solution of the amino alcohol in ethyl acetate, delivering the corresponding ammonium salt and a filtrate. Treatment of the latter fraction with an equimolar amount of (*S*)-mandelic acid based on the enantiomeric ratio resulted in the formation of the corresponding (*S*)-salt. [b] The yield of the initial precipitate formation relates to the amount of mandelic acid used. [c] Enantiomeric excesses of amino alcohol samples liberated from their corresponding mandelic acid salts were determined by HPLC analysis using a chiral stationary phase. [d] Yields enantiopure (1*R*,2*R*)-**1**. [e] Yields enantiopure (1*S*,2*S*)-**1**. [f] Yields enantiopure (1*R*,2*R*)-**3**. [g] Yields enantiopure (1*S*,2*S*)-**3**.

(Table 1, entry 4). Analogously, the enantiomeric ammonium salt *ent*-**4** was obtained in 77% yield[43a] by treatment of the filtrate with 1 equiv[43b] of (*S*)-mandelic acid (entry 4). In the latter case, only a single recrystallization followed by aqueous workup led to highly enantiomerically enriched (1*R*,2*R*)-**3** in good yield. The absolute configurations of the aminocyclohexanols were determined by comparison of their senses of optical rotation with those reported in the literature,[44] and to our surprise, it was observed that liberation of the (*R*)-mandelic acid salts **2** and **4** led to the corresponding products (1*R*,2*R*)-**1** and (1*S*,2*S*)-**3**, respectively, with opposite absolute configurations at the stereogenic centers. This unexpected stereochemical outcome was additionally confirmed by converting **3** into **1** by hydrogenation[44c] and alkylation (Scheme 2). The same reaction sequence was also applicable for the syntheses of other *trans*-2-aminocyclohexanols with tertiary amino groups. Such products were then tested for their capabilities to serve as chiral ligands in the asymmetric phenyl transfer reaction.

The series of catalyzed aryl transfer reactions was carried out under the previously optimized reaction conditions with 10 mol % of amino alcohol, *p*-chlorobenzaldehyde (**10a**) as the test substrate, and a 2:1 mixture of diethylzinc and diphenylzinc as the phenyl source.[20] First, pyrrolidinylcyclohexanol **1** stemming from the initial resolution experiments was subjected to the test reaction and led to a catalytically active system. Unfortunately, the enantioselectivity in the formation of diarylmethanol **11a** was very low (Table 2, entry 1). Applying dihydroisoindolyl derivative **6** was even worse, whereas aminocyclohexanols **7**−**9** delivered product **11a** in high yields (up to 99%, entry 5) and with improved enantioselectivity. However, compared to our previous catalyses,[20] the ee values remained only moderate (Table 2).

SCHEME 2 [a]



[a] Conditions: (i) H_2 (1 atm), Pd/C, MeOH, room temperature, 2 h, 97%; (ii) K_2CO_3, MeCN, 80 °C, 3−18 h; for **1**, 1,4-dibromobutane, 68%; for **6**, α,α′-dibromo-*o*-xylene, 84%; for **7**, 1,5-dibromopentane, 85%; for **9**, benzyl bromide, 88%; (iii) Et_3N, DMSO, 2-bromoethyl ether, room temperature, 60 h, 76%.

For the diethylzinc addition to aldehydes, it has been shown that open-chain tertiary β-amino alcohols with an anti configuration (corresponding to a cis disubstitution pattern in the zinc chelate) are usually better ligands than the corresponding syn stereoisomers.[24,45] Therefore, we converted first the racemic *N*-benzyl amino alcohol **3** into the cis analogue *rac*-**13**, following a protocol published by Johnson and Schubert.[46] As indicated in Scheme 3, the corresponding *N*-benzoyl amide **12** was treated with thionyl chloride to give an oxazolinium intermediate that was hydrolyzed by refluxing the concentrated residue with aqueous 6 N HCl, yielding an 8:1 mixture of cis/trans isomers, which could be easily separated by column chromatography. Then, the resolution protocol was successfully applied on *rac*-**13** delivering enantiopure (1*R*,2*S*)-**13** in 67% overall yield[43a] from the (*S*)-mandelic acid salt after two recrystallizations of the initial precipitate.[47] However, owing to the simpler access

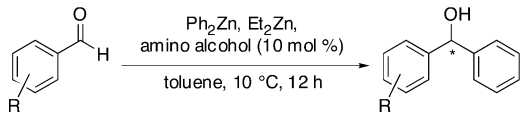
(43) (a) Based on the amount of mandelic acid. (b) According to the amount of the corresponding major enantiomer of the amino alcohol.

(44) (a) For optical rotatory power of **1**, see: ref 27 and 32a. (b) For **3**, see: Nishida, A.; Shirato, F.; Nakagawa, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3789. (c) The sense of optical rotation of the deprotected *trans*-2-aminocyclohexanol verified additionally the absolute configuration determined for the *N*-benzyl derivative; see: ref 26, 28, and 32d. In this context, it should be noted that as early as 1932 the two enantiomers of racemic *trans*-2-aminocyclohexanol (*rac*-**5**) were separated by the use of fractional crystallizations of the corresponding diastereomeric D-tartaric acid ammonium salts; see: Godchot, M. M. M.; Mousseron, M. *Bull. Soc. Chim.* **1932**, *51*, 1277. However, in this protocol, the isolated amount of the initial precipitate is low (20−25%) and yields are neither given for the recrystallizations nor given for the liberation of the highly water-soluble amino alcohol.

(45) For an exception, see, e.g.: Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108.

(46) (a) Johnson, W. S.; Schubert, E. N. *J. Am. Chem. Soc.* **1950**, *72*, 2187. (b) Koga applied this method for the epimerization of the *N*-cyclopropyl aminocyclohexanol, which had been enantiomerically enriched via the corresponding (*S*)-mandelic acid ester: Koga, Y.; Kihara, Y.; Okada, M.; Inoue, Y.; Tochizawa, S.; Toga, K.; Tachibana, K.; Kimura, Y.; Nishi, T.; Hidaka, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1471.

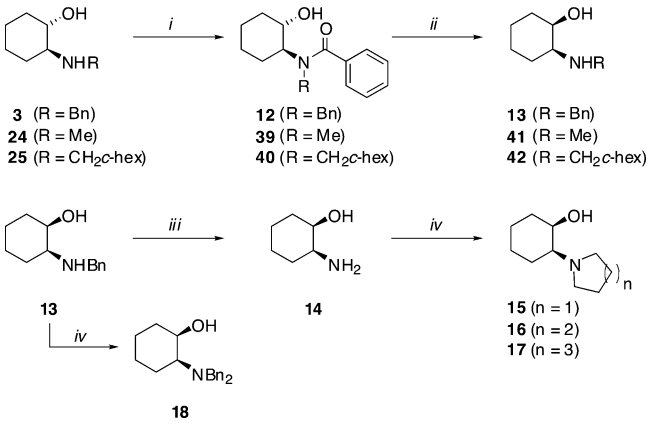
TABLE 2. Enantiopure Tertiary 2-Aminocyclohexanol Derivatives as Ligands in the Asymmetric Phenyl Transfer Reaction[a]



entry	amino alcohol	aldehyde	yield (%)[b]	ee (%)[c]
1	(1*S*,2*S*)-**1**	*p*-chlorobenzaldehyde (**10a**)	79	12 (*S*)
2	(1*R*,2*R*)-**6**	*p*-chlorobenzaldehyde (**10a**)	59	6 (*R*)
3	(1*R*,2*R*)-**7**	*p*-chlorobenzaldehyde (**10a**)	95	27 (*R*)
4	(1*R*,2*R*)-**8**	*p*-chlorobenzaldehyde (**10a**)	82	44 (*R*)
5	(1*R*,2*R*)-**9**	*p*-chlorobenzaldehyde (**10a**)	99	25 (*R*)
6	(1*R*,2*S*)-**15**	*p*-chlorobenzaldehyde (**10a**)	75	60 (*R*)
7	(1*R*,2*S*)-**16**	*p*-chlorobenzaldehyde (**10a**)	68	80 (*R*)
8	(1*S*,2*R*)-**17**	*p*-chlorobenzaldehyde (**10a**)	73	65 (*S*)
9	(1*S*,2*R*)-**18**	*p*-chlorobenzaldehyde (**10a**)	67	16 (*S*)
10	(1*S*,2*R*)-**16**	*p*-methylbenzaldehyde (**10b**)	74	87 (*S*)
11	(1*S*,2*R*)-**16**	*p*-methoxybenzaldehyde (**10c**)	80	87 (*S*)
12	(1*S*,2*R*)-**16**	*o*-bromobenzaldehyde (**10d**)	84	79 (*S*)

[a] All reactions were performed on a 0.25 mmol scale using 10 mol % of amino alcohol, 0.65 equiv of diphenylzinc, and 1.3 equiv of diethylzinc in toluene at 10 °C for 12 h. [b] After column chromatography. [c] Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase.

SCHEME 3[a]



[a] Conditions: (i) benzoyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temperature, 16 h, 95−99%; (ii) $SOCl_2$, CH_2Cl_2, 0 °C to room temperature, 4 h, then 6 N aq HCl, reflux, 6 h, 75−85%; (iii) H_2 (1 atm), Pd/C, MeOH, room temperature, 2 h, 98%; (iv) K_2CO_3, MeCN, 80 °C, 18 h; for **15**, 1,4-dibromobutane, 50%; for **16**, 1,5-dibromopentane, 61%; for **17**, 1,6-dibromohexane, 54%; for **18**, benzyl bromide, 54%.

to the starting material for the resolution (vide supra), the epimerization of optically active (1*R*,2*R*)-**3** was preferred and (1*S*,2*R*)-**13** was synthesized in 76% yield over two steps. Next, a set of enantiopure *cis*-2-aminocyclohexanol derivatives with tertiary amino groups was prepared by double alkylation of deprotected **14** (Scheme 3), and these products were also tested in the asymmetric catalytic aryl transfer reaction, as shown in Table 2 (entries 6−12).

As expected, the *cis*-pyrrolidinyl amino alcohol **15** proved to be superior in terms of enantioselectivity over its trans isomer (Table 2, entry 6 vs 1). A comparable improvement in ee was also observed for the piperidinyl analogue **16**, although this was accompanied by a decrease in activity (entry 7). Enlarging the ring size of the amino moiety had, unfortunately, no positive impact on the selectivity, and in the case of *N*-dibenzyl ligand **18**, the yield and ee were even worse than those achieved with its trans isomer (entry 9 vs 5). Because amino alcohol **16** led to the best result in the test reaction (80% ee, entry 7), the scope of the asymmetric phenyl transfer to aldehydes was briefly examined. *p*-Methylbenzaldehyde (**10b**) and *p*-methoxybenzaldehyde (**10c**) reacted smoothly under the standard conditions giving the corresponding alcohols **11b** and **11c**, respectively, both with 87% ee (entries 10 and 11). When the 2-bromo-substituted aldehyde (**10d**), which is known to be a challenging substrate for this kind of transformation, was subjected to the reaction, diarylmethanol **11d** was obtained with an increased yield and only a slightly lower enantiomeric excess (79% ee, entry 12).

TABLE 3. Additive Effects in the Asymmetric Phenyl Transfer onto Aldehyde 10a in the Presence of Amino Alcohol 16[a]

entry	protocol	additive	yield (%)[b]	ee (%)[c]
1	A	MAO	52	*rac*
2	A	DiMPEG	69	11
3	B	-	76	63
4	B	DiMPEG	72	72
5	C	DiMPEG	62	49

[a] All reactions were run on a 0.25 mmol scale using aldehyde **10a**. Method A: use of 10 mol % of (1*S*,2*R*)-**16** and 10 mol % of additive, 0.65 equiv of diphenylzinc and 1.3 equiv of diethylzinc in toluene at 10 °C for 12 h. Method B: use of 10 mol % of (1*S*,2*R*)-**16** and 10 mol % of additive, 1 equiv of triphenylborane and 3 equiv of diethylzinc in toluene at 10 °C for 12 h. Method C: use of 10 mol % of (1*S*,2*R*)-**16** and 10 mol % of DiMPEG (M_w = 2000 g/mol), 2.4 equiv of phenylboronic acid and 7.2 equiv of diethylzinc in toluene (first at 60 °C for 12 h, then at 10 °C for 12 h). [b] After column chromatography. [c] Enantiomer ratios were determined by HPLC analysis using a chiral stationary phase.

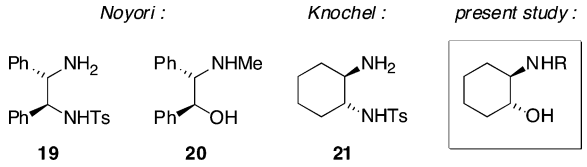
Noyori and Pericàs have shown that for the diethylzinc addition the absolute configuration of the product alcohol correlates with the configuration of the stereogenic hydroxyl-bearing carbon of the amino alcohol.[24] Consistently, we observed in all experiments that 2-aminocyclohexanols with (*S*)-configuration at C1 generate (*S*)-diarylmethanols, whereas the (*R*)-aminocyclohexanols led to the opposite product enantiomer.

Because a beneficial influence of a small quantity of DiMPEG (dimethylpoly(ethylene glycol)) in the reaction mixture on the enantioselectivity had been revealed in previous studies,[20a,e] the effect of additives in the presence of three different phenyl sources was studied (Table 2, entry 7 vs Table 3). As shown in Table 3, the addition of MAO (methylaluminoxane) resulted in the formation of a racemic product (entry 1), whereas DiMPEG led only in the reaction with triphenylborane to an increased enantiomeric excess (entry 3 vs 4).

Next, the potential of 2-aminocyclohexanol derivatives to act as ligands in asymmetric transfer hydrogenations of aryl ketones was studied. Noyori reported in 1995 that a chiral Ru(II) complex, formed by heating a mixture of $[RuCl_2(mesitylene)]_2$ and (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (**19**) in 2-propanol, acts as a highly enantioselective catalyst

(47) The mandelic acid ammonium salts of the *cis*-amino alcohols showed a lower solubility, compared to that of their trans analogues. For their resolution (and for large scales of all mentioned recrystallizations in general), 1−5 vol % of ethanol could be added to the refluxing ethyl acetate to achieve more rapidly the complete dissolution of the starting material without affecting the results of the process significantly.

leading at room temperature to (*S*)-1-phenylethanol (**23a**) with 97% ee in 95% yield within 15 h.[48]



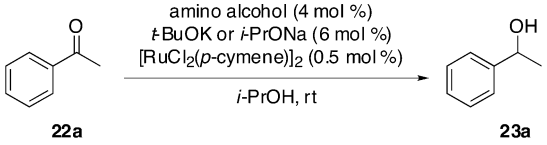
In the following year, the same authors observed an even higher acceleration of the catalysis by using *N*-methylated amino alcohol **20**.[48c] By using this compound, **23a** was obtained with 92% ee in 94% yield in only 1 h. At the same time, Knochel introduced several monosulfonamides of (1*R*,2*R*)-1,2-diaminocyclohexane, among which the 1-naphthylsulfonyl derivative showed a slightly higher enantioselectivity in comparison to the monotosylated diamine **21** (92% ee vs 89% ee).[49] In this respect, the simple access to a variety of secondary amino cyclohexanols by reductive amination of **5** appeared promising for the development of an efficient alternative system.

As standard reaction conditions for the transfer hydrogenation, 1 mmol of acetophenone (**22a**) was reduced by using 0.5 mol % of $[RuCl_2(p\text{-cymene})]_2$ in the presence of 4 mol % of the amino alcohol and 6 mol % of *t*-BuOK or *i*-PrONa in 2-propanol as the solvent and hydrogen source (Table 4). First, the benzyl derivative (1*S*,2*S*)-**3** was tested, which yielded (*S*)-1-phenylethanol (**23a**) with 54% ee in 3 h (96% conversion of **22a**) (entry 1). The unprotected analogue (1*S*,2*S*)-**5** showed a lower enantioselectivity. This result is in agreement with observations by Noyori for the corresponding primary amino alcohol.[48c] With regard to the highly selective ligand **20**, *N*-methyl-substituted aminocyclohexanol (1*S*,2*S*)-**24** was prepared by resolution of the racemate with (*R*)-mandelic acid affording the enantiopure material after three recrystallizations in 46% overall yield.[50] By its application in the test reaction, a 94% conversion of **22a** to the product alcohol was achieved within 1 h, and the product had 68% ee (entry 3). In comparison to the results previously reported for *N*-methylnorephedrin,[48c] Frost and Mendonça observed higher enantioselectivities with the ligand derived from the reductive amination of norephedrin with cyclohexanecarboxaldehyde.[51] Thus, aminocyclohexanol (1*S*,2*S*)-**25** was synthesized, delivering, in the catalysis, **23a** with 76% ee (entry 4). Because this result was a significant improvement by a simple derivatization, the impact of the substituent was examined in more detail in the following set of experiments. The results are summarized in Table 4.

With *N*-neopentyl compound **26**, a decreased activity accompanied by a low enantiomeric excess was observed (Table 4, entry 5).[52] The use of *N*-benzyl derivatives **27**−**31**, which were diversely substituted on the phenyl ring, indicated that electronic and steric effects at the aryl moiety of the ligand had only a marginal influence on the enantioselectivity (entries 6−10). Interestingly, applying the catalyst prepared by combining $[RuCl_2(benzene)]_2$ and *N*-3-phenylpropyl ligand **32** resulted in a decrease of the reaction rate compared to the *p*-cymene system, although the former precatalyst is known to be the most active one (entries 11 and 12). This behavior might be due to the replacement of the η^6-benzene group by the phenyl substituent of the ligand during the catalyst formation, leading to a complex in which the η^6-arene group is covalently bound to the amino alcohol unit, analogously to the ruthenium catalyst with a norephedrine-based ligand that was recently described by Wills.[53] However, this assumption could not be rigorously proven.

Because it was shown by Andersson for a 2-azanorbornyl-3-methanol ligand that introducing a methyl substituent in the

TABLE 4. 2-Aminocyclohexanol Derivatives as Ligands in the Ruthenium-Catalyzed Transfer Hydrogenation of Acetophenone (22a)[a]



entry	ligand	time (h)	conversion (%)[b]	ee (%)[c]
1	(1*S*,2*S*)-**3**	3	96	54 (*S*)
2	(1*S*,2*S*)-**5**	2	97	47 (*S*)
3	(1*S*,2*S*)-**24**	1	94	68 (*S*)
4	(1*S*,2*S*)-**25**	2.5	91	76 (*S*)
5	(1*R*,2*R*)-**26**	3	47	29 (*R*)
6	(1*R*,2*R*)-**27**	1	94	51 (*R*)
7	(1*S*,2*S*)-**28**	2.5	44	43 (*S*)
8	(1*R*,2*R*)-**29**	2	94	47 (*R*)
9	(1*R*,2*R*)-**30**	5	90	46 (*R*)
10	(1*R*,2*R*)-**31**	5.5	95	44 (*R*)
11	(1*R*,2*R*)-**32**	1	96	56 (*R*)
12	(1*R*,2*R*)-**32**	1	72[d]	38 (*R*)[d]
13	(1*S*,2*S*)-**35**	19	68	*rac*
14	(1*R*,2*R*)-**36**	24	-	-
15	(1*S*,2*S*)-**37**	10	36	44 (*S*)
16	(1*S*,2*S*)-**38**	1	83	*rac*
17	(1*R*,2*S*)-**13**	1	94	89 (*R*)
18	(1*R*,2*S*)-**14**	2	95	58 (*R*)
19	(1*S*,2*R*)-**41**	1	94	81 (*S*)
20	(1*R*,2*S*)-**42**	2	92	87 (*R*)
21	(1*S*,2*R*)-**43**	1	94	92 (*S*)

[a] All reactions were performed on a 1 mmol scale in 2-propanol (0.1 M with respect to acetophenone) at room temperature using 0.5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 4 mol % of amino alcohol ligand, and 6 mol % of *t*-BuOK or *i*-PrONa (0.1 M in 2-propanol). [b] Several aliquots were taken in periods of 30−60 min. For a completed reaction, the product could also be isolated after column chromatography in 96% yield with respect to the measured conversion. [c] Enantiomer ratios were determined by GC analysis using a chiral stationary phase. [d] $[RuCl_2(benzene)]_2$ instead of $[RuCl_2(p\text{-cymene})]_2$ was used.

(48) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. For the improved protocol by use of a 5:2 formic acid/triethylamine mixture in place of 2-propanol, see: (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (c) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233.

(49) Püntener, K.; Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8165.

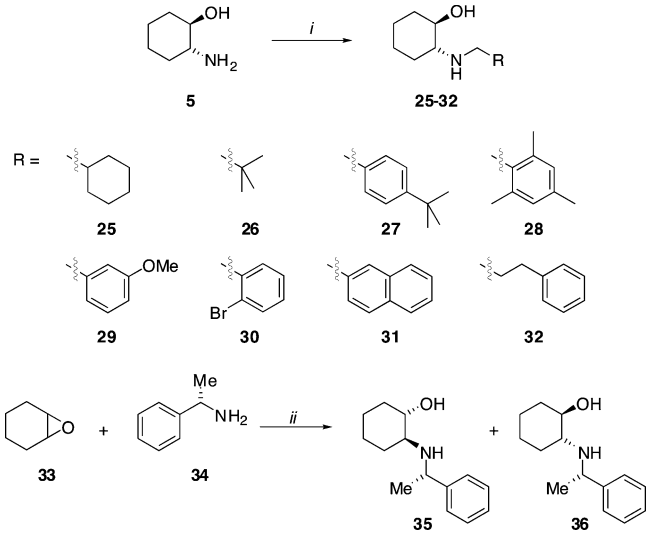
(50) Because of the fact that a highly efficient one-step resolution protocol for the racemic compound by means of di-*p*-toluoyltartaric acid has been developed by Lu, we first tried to obtain the enantiopure compound following the described procedure which led, however, in our hands to the methylamino alcohol **24** with only 87% ee. Recrystallization of the tartaric acid salt from ethanol furnished no increase in the enantiomeric excess. For the protocol, see: (a) Lu, X.; Xu, Z.; Tang, G. *Org. Process Res. Dev. J.* **2001**, *5*, 184. For a similar procedure, see: (b) Pracejus, H.; Pracejus, G.; Costisella, B. *J. Prakt. Chem.* **1987**, *329*, 235.

(51) Frost, C. G.; Mendonça, P. *Tetrahedron: Asymmetry* **2000**, *11*, 1845.

(52) In this context, it should be mentioned that the mandelic acid salt of *trans*-2-(*N*-*tert*-butyl)amino-1-cyclohexanol (35% de by NMR) could not be diastereomerically enriched by recrystallization from ethyl acetate.

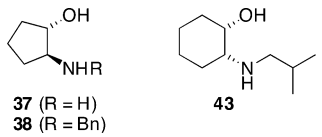
(53) (a) Cheung, F. K.; Hayes, A. M.; Hannedouche, J.; Yim, A. S. Y.; Wills, M. *J. Org. Chem.* **2005**, *70*, 3188. (b) Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2005**, *7*, 5489. (c) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986.

SCHEME 4 [a]



[a] Conditions: (i) aldehyde, MeOH, room temperature, 4 h then $NaBH_4$ or $NaCNBH_3$ (see Experimental Section), 0 °C to room temperature, 1 h; for **25**, cyclohexanecarboxaldehyde, 78%; for **26**, pivalaldehyde, 62%; for **27**, 4-*tert*-butylbenzaldehyde, 69%; for **28**, mesitylaldehyde, 77%; for **29**, 3-methoxybenzaldehyde, 81%; for **30**, 2-bromobenzaldehyde, 75%; for **31**, 2-naphthaldehyde, 70%; for **32**, 3-phenylpropionaldehyde, 74%; (ii) sealed steel bomb, 240 °C, 10 h, 46% (**35**), 40% (**36**).

carbinol position had a significant influence on the enantioselectivity and the activity of the catalysts,[54] diastereomeric aminocyclohexanols **35** and **36** with an α-methylbenzyl moiety were prepared. The ring opening of cyclohexene oxide (**33**) with (*S*)-1-phenylethylamine (**34**)[28,50b] using the improved solvent-free procedure mentioned already for the *N*-benzyl derivative gave a straightforward access to these products (Scheme 4). Unfortunately, however, both led to complexes with significantly reduced activity and selectivity (entries 13 and 14). Finally, aminocyclopentanol (1*S*,2*S*)-**37** and its *N*-benzyl-substituted derivative (1*S*,2*S*)-**38** were tested in this set of trans ligands. The latter was obtained in enantiomerically pure form after three recrystallizations and liberation from the (*S*)-mandelic acid salt in 58% yield.[43a,55] In contrast to the cyclohexane analogues, **38** led to a racemate in the test reaction whereas the corresponding deprotected (1*S*,2*S*)-*trans*-2-amino-1-cyclopentanol (**37**) afforded enantiomerically enriched 1-phenylethanol, although both ee and conversion were low (entries 15 vs 2 and 16 vs 3).



In Noyori's studies, 2-amino-1,2-diphenylethanol **20** with a threo configuration (corresponding to a trans orientation in cyclic systems) showed a considerably higher enantioselectivity and acceleration in the asymmetric transfer hydrogenation than the corresponding erythro ligand.[48c] On the other hand, Wills obtained 91% ee for the reduction of acetophenone at room temperature using rigid *cis*-1-amino-2-indanol.[56] Thus, optically active *trans*-2-aminocyclohexanols **3**, **24**, and **25** were selected and converted into their corresponding cis isomers **13**, **41**, and **42**, respectively (Scheme 3). Alternatively, enantiopure (1*S*,2*R*)-**41** was prepared by resolution with (*R*)-mandelic acid in 61% yield after two recrystallizations of the initial ammonium salt precipitate, followed by the aqueous workup.[43a] Applying the latter compound in the test reaction led to a result that was superior to those obtained in the entire trans ligand series (Table 4, entry 19), and also, the *N*-cyclohexylmethyl-substituted derivative **42** showed the same extent of increased enantioselectivity (entry 20). With *N*-benzyl amino alcohol **13**, 1-phenylethanol (**23a**) was obtained with 89% ee, and the isobutyl-substituted derivative **43**, which was synthesized from (1*S*,2*R*)-**13** by hydrogenation and reductive amination to imitate the structural features of ligand **42** in an open-chain analogue, delivered a slightly higher enantiomeric excess (92%, entries 17 and 21). These results encouraged us to investigate the transfer hydrogenation promoted by **13** in more detail. The results are summarized in Table 5.

TABLE 5. Temperature Dependence of the Ruthenium-Catalyzed Transfer Hydrogenation of Acetophenone (22a) Using Amino Alcohol 13[a]

entry	temperature (°C)	time	conversion (%)	ee (%)[b]
1	0	1 h	15	93
2		3 h	44	95
3		9 h	48	96
4		24 h	50	95
5	10	1 h	81	93
6		3 h	95	94
7		5 h	95	90
8	25	0.5 h	79	90
9		1 h	94	89
10		1.5 h	95	88
11		2 h	96	87
12	25[c]	1 h	66	89
13		2 h	76	89
14		3 h	82	89
15		10 h	91	89
16	50	10 min	89	87
17		20 min	97	86
18		30 min	97	84
19		90 min	97	78

[a] All reactions were performed on a 1 mmol scale in 2-propanol (0.1 M with respect to acetophenone) at room temperature using 0.5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 4 mol % of amino alcohol **13**, and 6 mol % of *t*-BuOK (0.1 M in 2-propanol). [b] Enantiomer ratios were determined by GC analysis using a chiral stationary phase. [c] 0.25 mol % of $[RuCl_2(p\text{-cymene})]_2$ was used.

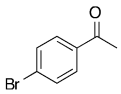
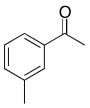
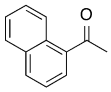
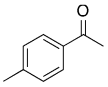
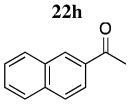
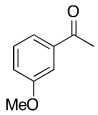
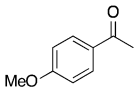
First, the influence of the temperature was studied, revealing that the reaction at 0 °C afforded 1-phenylethanol with up to 96% ee. Unfortunately, a concomitant reduction in the turnover rate was observed and the conversion did not exceed 50% (Table 5, entries 1−4). In contrast to most other experiments, no considerable loss in product enantiomeric excesses with extended reaction times was observed at 0 °C (as well as in the transfer hydrogenation of acetophenone with 0.5 mol % ruthenium at room temperature; entries 12−15). A significantly

(54) (a) Alonso, D. A.; Nordin, S. J. M.; Roth, P.; Tarnai, T.; Andersson, P. G. *J. Org. Chem.* **2000**, *65*, 3116. (b) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580.

(55) The absolute configuration was determined by comparison of the sense of optical rotation of the corresponding deprotected derivative **37** with that reported in the literature; see ref 32d. Additionally, the assigned configuration was confirmed by the stereochemical outcome of the transfer hydrogenation (Table 4, entry 16).

(56) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.

TABLE 6. Substrate Scope for the Ruthenium-Catalyzed Transfer Hydrogenation by Use of Amino Alcohol 13 as the Ligand[a]

entry	arylketone	time (h)	conv. (%)	ee (%)[b]	entry	arylketone	time (h)	conv. (%)	ee (%)[b]
1		3	73	77	11		1	81	82
2	**22b**	6	79	76	12	**22g**	2	85	81
3		1	93	90	13		3	60	85
4	**22c**	2	94	89	14	**22h**	6	61	85
5		1	86	85	15		2	95	85
6	**22d**	3	89	81		**22i**			
7		1	95	91	16		2	90	77
8	**22e**	2	96	89	17	**22j**	6	94	77
9		3	50	87					
10	**22f**	20	52	87					

[a] All reactions were performed on a 1 mmol scale in 2-propanol (0.1 M with respect to the aryl ketone) at room temperature using 0.5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 4 mol % of amino alcohol (1*R*,2*S*)-**13**, and 6 mol % of *t*-BuOK (0.1 M in 2-propanol). [b] Enantiomer ratios were determined by GC or HPLC analysis using a chiral stationary phase. All products **23b**−**f** had an (*R*)-configuration.

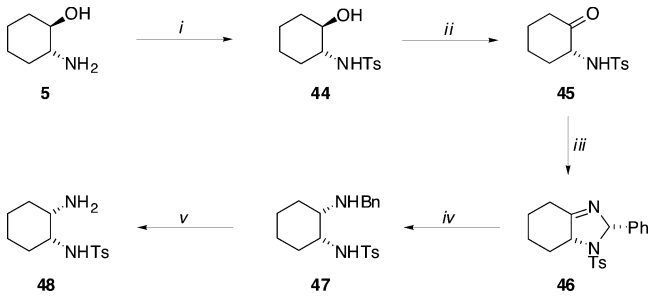
higher acceleration could be achieved at 10 °C, which led to only a slight decrease in selectivity in comparison to the reaction at 0 °C (entries 5−7). Finally, a complete conversion within 20 min was achieved at 50 °C, delivering enantiomeric excesses which were comparable to the results achieved at room temperature (entries 16 and 17 vs 11).

For a more thorough study, various alkyl aryl ketones were chosen as substrates and reduced under the standard transfer hydrogenation conditions. It is known that both rate and selectivity are sensitive to the steric crowding of the substrates as well as to the electronic properties of the aryl substituents. The results which are summarized in Table 6 are in agreement with the trends reported for other systems.[8e,54a,56] Thus, meta-substituted substrates (entries 3 and 7) gave better results than ortho- or nonsubstituted derivatives (entries 1 and 16). *p*-Methoxyacetophenone (**22f**) is known to be a challenging substrate for this transformation, giving low reaction rates with only moderate enantioselectivities.[8e,54a,56] Interestingly, by using **13** as a ligand, the enantiomeric excesses remained high, but the conversion ceased at 52% (entries 9 and 10).

Also, the stereochemical outcome of all transfer hydrogenation experiments was in agreement with Noyori's observations, confirming that the sense of asymmetric induction is determined by the configuration of the stereogenic hydroxy-bearing carbon (vide supra), whereas the orientation of the amino group affects the extent of enantioselection.

Because in the aminocyclohexanol ligand series the cis isomers were found to be superior in terms of enantioselectivity in comparison to their trans analogues, we wondered about the potential of the monotosylated diaminocyclohexyl derivative **48**, the cis pendant of Knochel's ligand **21**.[49] The *N*-benzyl-protected racemic compound *rac*-**47** was already described in 1979 by

SCHEME 5[a]



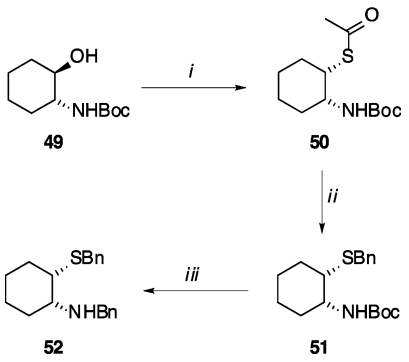
[a] Conditions: (i) tosyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temperature, 16 h, 97%; (ii) CrO_3/H_2SO_4, acetone, room temperature, 30 min, 98%; (iii) benzaldehyde, aq NH_3, EtOH, room temperature, 2 h, 92%; (iv) $LiAlH_4$, THF, room temperature, 2 h; (v) H_2 (1 atm), Pd/C, MeOH, room temperature, 2 h, 96%.

Bäckvall and Sharpless, who elaborated a simple protocol for its synthesis starting from *N*-tosyl-*trans*-aminocyclohexanol **44**,[57] which was easily available in optically pure form in the present study by treatment of (1*R*,2*R*)-**5** with *p*-toluenesulfonyl chloride in the presence of triethylamine. As shown in Scheme 5, the overall reaction sequence involves a Jones oxidation of (1*R*,2*R*)-**44** to the corresponding ketone **45**, followed by imidazoline formation with benzaldehyde and aqueous ammonia giving **46**, which was then converted into **47** by LAH reduction.[58] Finally, debenzylation by Pd/C-catalyzed hydrogenation (1 atm of H_2)

(57) Bäckvall, J.-E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953.

(58) The absolute configurations of imidazoline **46** and *cis*-diamine **47** were determined by NOE experiments verifying the previous assignment for *rac*-**47** by Bäckvall and Sharpless; see ref 57.

SCHEME 6 [a]



[a] Conditions: (i) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temperature, 2.5 h, 94%, then KSAc, DMF, reflux, 16 h, 93%; (ii) $LiAlH_4$, Et_2O, 0 °C to room temperature, 1 h, 65%, then benzyl bromide, K_2CO_3, MeCN, 80 °C, 8 h, 60%; (iii) TFA, CH_2Cl_2, room temperature, 4 h, 60%, then benzaldehyde, MeOH, room temperature, 3 h followed by $NaBH_4$, room temperature, 2 h, 60%.

for 1−2 h at room temperature afforded the desired product **48** in 75% yield over five steps.

Unfortunately, applying **48** in the transfer hydrogenation of acetophenone (**22a**) under standard reaction conditions did not lead to any conversion, and even after 24 h, no traces of the product could be observed (by GC analysis).[59] Nevertheless, on the basis of the efficient resolution protocol, the synthetic route depicted in Scheme 5 presents a novel approach among a narrow spectrum of available methods for the preparation of enantiopure *cis*-diaminocyclohexyl derivatives containing different protecting groups at each amino function.[60] Such valuable building blocks are of particular interest for the synthesis of pharmacologically active substances such as σ-receptor agonists,[61a] spasmolytics,[61b] and highly potent inhibitors of cyclin-dependent kinases,[61c] and efforts aiming on the application of **47** or **48** in this field are currently in progress.

Finally, the observed decisive role of the relative configuration in such disubstituted cyclohexane derivatives on their efficiency in acting as ligands prompted us to synthesize *N*,*S*-dibenzylamino sulfide, (1*S*,2*R*)-**52** (Scheme 6). Although *N*,*S*-chelates have been widely used in asymmetric catalysis,[25a] there are only a few reports on the application of β-amino thiols, especially described as ligands in the asymmetric addition of diethylzinc,[62] alkenylzinc,[63] or alkyllithium[64] reagents to aldehydes. Their great potential to serve as highly enantioselective ligands in the iridium-catalyzed transfer hydrogenation of prochiral ketones was first evaluated in 2000 by van Leeuwen, who synthesized cysteine-based amino sulfides.[65] Andersson screened a set of diversely substituted monocyclic amino thioethers, which were derived from the ring opening of aziridines with sulfur nucleophiles, followed by separation of the enantiomers by chiral HPLC.[66] He found that use of the trans isomer of **52** in combination with $[IrCl(COD)]_2$ gave a highly efficient catalyst for the transfer hydrogenation affording 1-phenylethanol (**23a**) with 70% ee. A third contribution in this field was recently published by Lemaire, who used the regioselective and stereospecific ring opening of a chiral thiirane for the preparation of various amino thiol ligands.[67] In the latter investigation, $[RuCl_2(p\text{-cymene})]_2$ was superior to $[IrCl(COD)]_2$ as a precatalyst and led to the best results with respect to activity as well as enantioselectivity.

Our synthetic approach started from *N*-Boc-protected amino alcohol (1*R*,2*R*)-**49** because its corresponding mesylate is known to react with appropriate nucleophiles under inversion of configuration at C1 (Scheme 6).[60b] However, direct introduction of a thioether functionality by treatment of mesylated (1*R*,2*R*)-**49** with deprotonated thiols remained unsuccessful. For example, when NaSMe was used, the racemic trans product was obtained, which obviously resulted from a formation of a *meso*-aziridine intermediate by intramolecular attack on the mesylate by the amino moiety followed by ring opening by the thiolate. In contrast, the nucleophilic substitution with potassium thioacetate worked smoothly, and *cis*-amino thioacetate **50** could be isolated in high yield. Subsequently, the reaction sequence was easily completed by LAH reduction to the corresponding amino thiol, which was then *S*-benzylated, Boc-deprotected, and converted into the desired *N*,*S*-dibenzyl derivative **52** by reductive amination.[68]

Examination of its applicability in the transfer hydrogenation under standard conditions revealed that *N*,*S*-dibenzyl derivative **52** strongly accelerated the iridium-catalyzed reaction, leading to 93% conversion of **22a** within 15 min at room temperature (TOF = 372 mol h^{-1}, Table 7, entry 4), albeit its enantioselectivity was lower than that of the literature system. The situation changed significantly when $[RuCl_2(p\text{-cymene})]_2$ was used for the catalyst generation. Although the activity was still very high, the reaction rate decreased noticeably in comparison with the rate of the Ir-catalyzed reaction, and a considerable increase in enantioselectivity was observed (entries 1−3).

The sense of asymmetric induction in the latter reaction was identical to the results obtained with the *cis*-amino alcohol ligands. On the other hand, iridium catalysis in the presence of the same ligand afforded the opposite product enantiomer. This

(59) (a) During the course of our investigations, Wills reported on the importance of 1,2-anti disubstitution in monotosylated diamine ligands for the ruthenium-catalyzed transfer hydrogenation; see: Hayes, A.; Clarkson, G.; Wills, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2079. (b) In this context, it should be mentioned that also enantiopure monotosylated *cis-exo*- and *cis-endo*-norbornane diamines, prepared by sequential introduction of the two amino moieties into the corresponding chiral hemiesters, did not accelerate the transfer hydrogenation reaction. However, in this preceded study, even the use of the trans analogue with N-substitution in the endo position resulted in no conversion; see ref 23b.

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(68) To circumvent the final benzylation step, we tried to apply the reaction sequence on the Boc-protected *N*-benzyl amino alcohol, but the attempted nucleophilic substitution of the corresponding mesylate failed.

TABLE 7. Transfer Hydrogenation of Acetophenone (22a) in the Presence of *N*,*S*-Dibenzylamino Sulfide (1*S*,2*R*)-52[a]

entry	catalyst precursor	time (min)	conversion (%)	ee (%)[b]
1		15	42	75 (*S*)
2	$[RuCl_2(p\text{-cymene})]_2$	30	83	81 (*S*)
3		60	95	80 (*S*)
4		15	93	48 (*R*)
5	$[IrCl(COD)]_2$	30	97	45 (*R*)
6		60	97	44 (*R*)

[a] All reactions were performed on a 1 mmol scale in 2-propanol (0.1 M with respect to acetophenone) at room temperature using 0.5 mol % of catalyst precursor, 4 mol % of amino sulfide (1*S*,2*R*)-**52**, and 6 mol % of *t*-BuOK (0.1 M in 2-propanol). [b] Enantiomer ratios were determined by GC analysis using a chiral stationary phase.

seems to indicate that the iridium-catalyzed reduction proceeds via a different mechanistic pathway, which would confirm van Leeuwen's suggestion of a direct hydrogen transfer path for the Ir(I)/amino thiol combination,[65] instead of the hydridic route proposed for the Ru(II)/amino alcohol catalysis by Noyori.[69]

Conclusions

The elaboration of an efficient protocol for the resolution of racemic *trans*-2-(*N*-benzyl)amino-1-cyclohexanol by means of mandelic acid delivering both enantiomers with >99% ee has been reported. Deprotection by hydrogenation leads to the easily modifiable free amino alcohol **5**, which gives access to a broad variety of diversely substituted derivatives and their corresponding cis isomers. These optically active amino alcohols have been applied as ligands in asymmetric phenyl transfer reactions to aldehydes leading to enantioselectivities of up to 87% ee. In transfer hydrogenations of aryl ketones, secondary alcohols with up to 96% ee have been obtained. In addition, it was demonstrated that enantiopure *trans*-2-aminocyclohexanol **5** is a valuable building block for the synthesis of an optically active *cis*-diaminocyclohexane and a chiral *cis*-amino thiol derivative. The latter compound showed an impressive activity in the iridium-catalyzed transfer hydrogenation reaction. Currently, we are focusing our efforts on applications of the amino alcohols in other asymmetric catalyses, and on the basis of preliminary promising results, we are confident to be able to report on these projects soon.

Experimental Section

General. Solvent purification, suppliers, instruments, and the general procedures for the resolution of racemic 2-aminocyclohexanol derivatives (GP-1), the liberation of the amino alcohols from their mandelic acid salts (GP-2), the deprotection of *N*-benzyl amino derivatives (GP-3), the double alkylation (GP-4), the reductive amination (GP-5), the epimerization to the *cis*-amino alcohols (GP-6), and the protocols for the asymmetric phenyl transfer and the transfer hydrogenation are described in the Supporting Information.

(*R*)-Mandelic Acid Salt of (1*R*,2*R*)-*trans*-2-(Pyrrolidin-1′-yl)-cyclohexanol (2). The title compound was synthesized according to GP-1a by reaction of racemic amino alcohol **1** (14.08 g, 83.21 mmol) with (*R*)-mandelic acid (6.33 g, 41.60 mmol, 0.5 equiv). Two recrystallizations afforded the diastereomerically pure salt as a colorless solid: 8.82 g (66%, based on the amount of mandelic acid); mp 109 °C; $[\alpha]_D^{25} = -86.0$ ($c = 2.05$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15−1.38 (4 H, m), 1.69−1.93 (8 H, m), 2.01−2.08 (1 H, m), 2.83−2.91 (1 H, m), 3.14 (4 H, br s), 3.54 (1 H, dt, $J = 4.7$, 10.4 Hz), 4.93 (1 H, s), 7.20 (1 H, tt, $J = 1.1$, 7.1 Hz), 7.28 (2 H, t, $J = 7.1$ Hz), 7.50 (2 H, d, $J = 7.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 24.0, 24.4, 24.7, 34.6, 68.4, 69.9, 74.3, 126.4, 127.0, 127.9, 142.5, 179.2; IR (KBr) $\nu = 3388$, 3188, 2937, 2897, 2863, 2542, 2453, 1617, 1455, 1361, 1198, 1090, 1061, 745 cm^{-1}; MS (EI, DIP, positive ions) *m*/*z* 169 (16), 152 (17), 110 (100), 107 (64), 97 (16), 84 (22), 79 (44), 77 (31), 51 (12); MS (EI, DIP, negative ions) *m*/*z* 151 (100), 134 (39). Anal. Calcd for $C_{18}H_{27}NO_4$ (321.41): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.39; H, 8.51; N, 4.33.

According to GP-1b, the opposite ammonium salt enantiomer *ent*-**2** was prepared starting from amino alcohol (1*S*,2*S*)-**1** (1.74 g, 10.30 mmol, er = 80:20), isolated from the filtrate of the above reaction, and (*S*)-mandelic acid (1.25 g, 8.24 mmol, 0.8 equiv, that is, 1.0 equiv according to the appropriate amino alcohol enantiomer). Two recrystallizations afforded the diastereomerically pure salt as a colorless solid: 1.68 g (62%, based on the amount of mandelic acid); $[\alpha]_D^{25} = +85.3$ ($c = 1.55$, $CHCl_3$).

(*R*)-Mandelic Acid Salt of (1*S*,2*S*)-*trans*-2-(*N*-Benzyl)amino-1-cyclohexanol (4). The title compound was synthesized according to GP-1a by reaction of racemic amino alcohol **3** (82.12 g, 0.40 mol) with (*R*)-mandelic acid (30.43 g, 0.20 mol, 0.5 equiv). Two recrystallizations afforded the diastereomerically pure salt as a colorless solid: 42.66 g (60%, based on the amount of mandelic acid); mp 148.5 °C; $[\alpha]_D^{25} = -2.0$ ($c = 3.90$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95−1.34 (4 H, m), 1.57−1.74 (3 H, m), 1.90 (1 H, d, $J = 12.9$ Hz), 2.55 (1 H, dt, $J = 5.1$, 12.7 Hz), 3.03 (1 H, dt, $J = 4.9$, 12.2 Hz), 3.45 (1 H, AB-system, $J = 12.6$ Hz), 3.90 (1 H, AB-system, $J = 12.9$ Hz), 4.91 (1 H, s), 7.15−7.35 (8 H, m), 7.49 (1 H, s), 7.52 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 24.0, 26.4, 33.8, 48.2, 62.3, 70.1, 74.1, 126.4, 127.1, 127.8, 128.7, 128.9, 129.7, 130.8, 141.8, 178.2; IR (KBr) $\nu = 3373$, 3036, 2938, 2860, 1605, 1555, 1491, 1447, 1426, 1372, 1085, 1064, 1042 cm^{-1}; MS (EI, DIP, positive ions) *m*/*z* 206 (7), 205 (45), 146 (100), 132 (11), 120 (15), 114 (18), 107 (37), 106 (14), 91 (77), 79 (10); MS (EI, DIP, negative ions) *m*/*z* 151 (100), 134 (69). Anal. Calcd for $C_{21}H_{27}NO_4$ (357.44): C, 70.56; H, 7.61; N, 3.92. Found: C, 70.83; H, 7.52; N, 3.88.

According to GP-1b, the opposite ammonium salt enantiomer *ent*-**4** was prepared starting from amino alcohol (1*R*,2*R*)-**3** (9.95 g, 48.47 mmol, er = 77:23), isolated from the filtrate of the above reaction, and (*S*)-mandelic acid (5.68 g, 37.32 mmol, 0.77 equiv, that is, 1.0 equiv according to the appropriate amino alcohol enantiomer). One recrystallization afforded the diastereomerically pure salt as a colorless solid: 8.46 g (61%, based on the amount of mandelic acid); $[\alpha]_D^{25} = +1.3$ ($c = 2.15$, $CHCl_3$).

(1*R*,2*R*)-*trans*-2-(Pyrrolidin-1′-yl)cyclohexanol (1). According to GP-2, the title compound was obtained from the corresponding (*R*)-mandelic acid salt **2** (29.16 g, 86.42 mmol): 13.90 g (95%); colorless oil; ee = >99% [HPLC analysis of the 4-methoxybenzoic acid ester: Chiralpak AD at room temperature, *n*-heptane/2-propanol = 98:2, 0.6 mL/min, 254 nm, $t_1 = 16.0$ min, $t_2 = 20.4$ min (major)]; $[\alpha]_D^{25} = -68.7$ ($c = 1.10$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.31 (4 H, m), 1.70−1.80 (7 H, m), 2.07−2.15 (1 H, m), 2.41−2.51 (1 H, m), 2.53−2.61 (2 H, m), 2.65−2.74 (2 H, m), 3.35 (1 H, dt, $J = 4.7$, 9.6 Hz), 4.04 (1 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 23.7, 24.3, 25.4, 33.4, 47.3, 65.1, 70.8; IR (KBr) $\nu = 3454$, 2931, 2860, 2811, 1451, 1077 cm^{-1}; MS (EI, DIP) *m*/*z* 170 (10), 169 (51), 111 (10), 110 (100), 97 (20), 84 (23); HRMS calcd for $C_{10}H_{19}NO$ 169.1467, found 169.1467.

(1*S*,2*S*)-*trans*-2-(*N*-Benzyl)amino-1-cyclohexanol (3). According to GP-2, the title compound was obtained from the corresponding (*R*)-mandelic acid salt **4** (35.22 g, 98.53 mmol): 19.82 g (98%); colorless solid; mp 92 °C; ee = >99% [HPLC analysis: Chiralcel OB−H at room temperature, *n*-heptane/2-propanol = 98:2, 0.5 mL/min, 220 nm, $t_1 = 20.9$ min (major), $t_2 = 26.9$ min]; $[\alpha]_D^{25} =$

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+79.7 (c = 1.05, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91−1.06 (1 H, m), 1.12−1.33 (3 H, m), 1.64−1.76 (2 H, m), 1.94−2.04 (1 H, m), 2.09−2.20 (1 H, m), 2.29 (1 H, ddd, J = 3.9, 9.4, 13.4 Hz), 3.19 (1 H, dt, J = 4.9, 12.1 Hz), 3.67 (1 H, AB-system, J = 12.9 Hz), 3.93 (1 H, AB-system, J = 12.9 Hz), 7.20−7.29 (1 H, m), 7.30−7.35 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.1, 30.5, 33.4, 50.8, 63.1, 73.7, 127.0, 128.1, 128.4, 140.5; IR (KBr) ν = 3295, 3109, 3061, 3025, 2934, 2855, 1450, 1432, 1099, 1078 cm^{-1}; MS (EI, DIP) *m*/*z* 205 (51), 146 (100), 120 (15), 114 (19), 106 (14), 91 (75). Anal. Calcd for $C_{13}H_{19}NO$ (205.30): C, 76.06; H, 9.33; N, 6.82. Found: C, 76.41; H, 9.50; N, 6.79.

(1*R*,2*R*)-*trans*-2-(*N*-Benzoyl-*N*-benzyl)amino-1-cyclohexanol (12). The title compound was synthesized according to GP-6a by reaction of *N*-benzylamino alcohol (1*R*,2*R*)-**3** (9.27 g, 45.13 mmol) with benzoyl chloride (5.1 mL, 6.22 g, 44.23 mmol, 0.98 equiv) in the presence of Et_3N (19.0 mL, 13.79 g, 136.0 mmol, 3 equiv): 13.41 g (98%); colorless solid; mp 122.5 °C; $[\alpha]_D^{25}$ = −1.3 (c = 3.10, MeOH); ^{1}H NMR (400 MHz, CD_3OD) [mixture of two rotamers A/B = 80:20] δ 0.82−1.44 (8 H, m, A + B), 1.51−1.75 (6 H, m, A + B), 1.91−1.99 (1 H, m, A), 2.01−2.09 (1 H, m, B), 3.54 (1 H, dt, J = 3.7, 9.7 Hz, A), 3.67 (1 H, dt, J = 4.5, 9.9 Hz, A), 3.85 (1 H, br s, B), 4.05 (1 H, br s, B), 4.33 (1 H, d, J = 15.8 Hz, A), 4.57 (2 H, d, J = 4.5 Hz, B), 4.86 (4 H, s, A + B), 5.17 (1 H, d, J = 15.8 Hz, A), 7.16−7.53 (20 H, m, A + B); ^{13}C NMR (100 MHz, CD_3OD) δ 25.1 (A), 25.5 (B), 26.2 (A), 26.5 (B), 30.7 (B), 31.9 (A), 35.8 (A), 36.6 (B), 45.6 (A + B), 66.8 (A + B), 70.1 (A), 70.4 (B), 127.4 (B), 127.6 (A), 127.8 (A + B), 128.0 (A), 128.2 (B), 129.2 (A + B), 129.3 (A + B), 130.2 (B), 130.3 (A), 138.2 (A + B), 140.2 (A + B), 175.5 (A + B); IR (KBr) ν = 3368, 2932, 2860, 1604, 1444, 1075 cm^{-1}; MS (EI, DIP) *m*/*z* 309 (8), 212 (100), 105 (81), 91 (29), 77 (15). Anal. Calcd for $C_{20}H_{23}NO_2$ (309.40): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.48; H, 7.33; N, 4.51.

(1*S*,2*R*)-*cis*-2-(*N*-Benzyl)amino-1-cyclohexanol (13). The title compound was synthesized according to GP-6b by reaction of benzoyl amide (1*R*,2*R*)-**12** (13.96 g, 45.12 mmol) with thionyl chloride (12.4 mL, 20.40 g, 171.45 mmol, 3.8 equiv): 7.23 g (78%); colorless solid; $[\alpha]_D^{25}$ = +14.9 (c = 2.95, $CHCl_3$); analytical data were in accordance with those observed for the corresponding opposite product enantiomer derived from the resolution with (*S*)-mandelic acid (see Supporting Information).

(1*S*,2*S*)-*trans*-2-Amino-1-cyclohexanol (5). According to GP-3, the title compound was prepared by hydrogenation of (1*S*,2*S*)-**3** (6.33 g, 30.83 mmol): 3.45 g (97%); colorless solid; mp 68 °C; $[\alpha]_D^{25}$ = +41.8 (c = 1.19, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05−1.17 (1 H, m), 1.19−1.33 (3 H, m), 1.61−1.75 (2 H, m), 1.81−1.89 (1 H, m), 1.91−1.97 (1 H, m), 2.45 (1 H, ddd, J = 4.4, 9.1, 13.5 Hz), 2.75 (3 H, br s), 3.12 (1 H, dt, J = 4.8, 11.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.0, 33.9, 34.3, 57.0, 75.4; IR (KBr) ν = 3351, 3331, 3280, 3100, 2929, 2856, 1587, 1073 cm^{-1}; MS (EI, DIP) *m*/*z* 115 (29), 72 (16), 56 (100). Anal. Calcd for $C_6H_{13}NO$ (115.17): C, 62.57; H, 11.38; N, 12.16. Found: C, 62.57; H, 11.37; N, 11.95.

(1*R*,2*S*)-*cis*-2-Amino-1-cyclohexanol (14). According to GP-3, the title compound was prepared by hydrogenation of (1*R*,2*R*)-**13** (6.95 g, 33.85 mmol): 3.82 g (98%); colorless solid; mp 89.5 °C; $[\alpha]_D^{25}$ = −26.6 (c = 3.02, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.26−1.40 (2 H, m), 1.44−1.66 (5 H, m), 1.69−1.80 (1 H, m), 2.66−2.74 (1 H, m), 3.71−3.79 (1 H, m), 4.80 (3 H, br s); ^{13}C NMR (75 MHz, CD_3OD) δ 21.6, 24.2, 30.6, 32.1, 53.4, 71.2; IR (KBr) ν = 3352, 3329, 3108, 2930, 2857, 1580, 1072, 778, 645 cm^{-1}; MS (EI, DIP) *m*/*z* 115 (45), 72 (20), 56 (100). Anal. Calcd for $C_6H_{13}NO$ (115.17): C, 62.57; H, 11.38; N, 12.16. Found: C, 62.53; H, 11.10; N, 12.02.

(1*R*,2*S*)-*cis*-2-(Piperidin-1′-yl)cyclohexanol (16). The title compound was obtained according to GP-4 from the corresponding free amino alcohol (1*R*,2*S*)-**14** (990 mg, 8.6 mmol) and 1,5-dibromo pentane (97%, 1.2 mL, 0.71 g, 8.6 mmol, 1.0 equiv): 961 mg (61%); colorless solid; mp 108 °C; $[\alpha]_D^{25}$ = −22.4 (c = 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00−1.54 (11 H, m), 1.55−1.74 (2 H, m), 1.90−2.02 (2 H, m), 2.34−2.56 (4 H, m), 3.24 (1 H, br s), 3.92 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 24.2, 24.7, 25.1, 26.5, 30.4, 50.7, 64.2, 64.9; IR (KBr) ν = 3176, 2929, 2849, 2796, 2757, 1440, 1183, 1108, 984, 871 cm^{-1}; MS (EI, DIP) *m*/*z* 183 (33), 166 (1), 154 (2), 140 (5), 124 (100), 111 (6), 98 (16), 96 (6), 84 (5). Anal. Calcd for $C_{11}H_{21}NO$ (183.29): C, 72.08; H, 11.55; N, 7.64. Found: C, 72.32; H, 11.37; N, 7.58.

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Supporting Information Available: Full experimental details as well as copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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