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FULL PAPER

Enantiopure *cis*- and *trans*-2-(2-Aminocyclohexyl)phenols: Effective Preparation, Solid-State Characterization, and Application in Asymmetric Organocatalysis

Mustafa A. Tezeren,[a,b] Tolga A. Yeşil,[a,b] Yunus Zorlu,[c,d] Tahir Tilki,[b] and Erkan Ertürk*[a]

Abstract: Effective synthesis of *cis*- and *trans*-2-(2-methoxyphenyl)cyclohexylamine as well as their multigram-scale optical resolution by diastereomeric salt formation with dibenzoyl tartaric acid have been described. Assignment of absolute configurations to the enantiomers has been made by X-ray crystallography. Starting from the resolved precursor, diverse aminoalkylphenols (AAPs) having primary, secondary, and tertiary amine group as well as a quaternary ammonium phenol have been prepared as potential bifunctional organocatalysts based on the cyclohexane backbone. We furthermore report herein that AAPs carrying a primary amine and a phenolic hydroxyl group can catalyze the direct aldol reaction with high activity and setereoselectivity, and thus up to 97% yield, 90:10 *syn/anti* diastereomeric ratio, and 80% enantiomeric excess can be achieved.

Introduction

Over the past two decades, organocatalysis, the use of small organic molecules as catalysts, has had a tremendous impact in chemical synthesis. Usually, organocatalysts offer practically favorable advantages over metal-based ones, such as being non-toxic, air- and water-tolerant, inexpensive as well as easy to synthesize and handle. Furthermore, they have also proven to be complementary to metal-based catalysts, by enabling the synthesis of important target structures via unique activation modes, which is not possible using metal catalysts.[1] In particular, the development of novel chiral bifunctional motifs that bear Lewis and/or Brønsted basic and acidic functional groups for a simultaneous activation of both nucleophilic and electrophilic substrates (e.g. combination of a tertiary amine group with a thiourea moiety in a catalyst for the non-covalent organocatalysis) has been one of the major endeavors in the field.[2] Another remarkable facet of the field is aminocatalysis that employs chiral primary amines having an additional Lewis- or Brønsted-acidic moiety.[3] Recent studies demonstrated that chiral bifunctional primary amines can be more efficient and selective in aminocatalysis, e.g. in enantioselective functionalization of carbonyl compounds, compared to their secondary amine counterparts.[3,4]

Despite impressive progress in asymmetric organocatalysis, bifunctional organocatalysts that bear an amine and phenolic hydroxyl group (amine-phenol organocatalyst) remain relatively unexplored. The well-known examples of this class are the demethylated derivatives of cinchona alkaloids that have been reported to effect some reactions with high degree of activity and enantioselectivity, such as [4+2] cycloaddition reactions,[5a] the Morita-Baylis-Hillman reactions,[5b] the aza Morita-Baylis-Hillman reactions,[5c–e] conjugate additions to α,β-unsaturated systems,[5f–o] enantioselective addition to the activated carbonyl compounds,[5p–r] enantioselective transamination,[5s] and some other asymmetric transformations as well.[5t–v] The Betti base[6] and its derivatives[7] are the further prominent representatives of the chiral aminoalkylphenols (AAPs) which served as chiral ligands in the enantioselective addition reactions of diethylzinc[6a,7a] as well as as hydrogen-bond donor organocatalysts for the hetero Diels-Alder reaction[7b] of ethyl glyoxylate with Danishefsky's diene and the asymmetric acyl-Strecker reaction.[7c] In addition, Maruoka and co-workers recently developed a binaphthyl-based axially chiral secondary amine-phenol bifunctional organocatalyst for the highly *anti*-diastero- and enantioselective Mannich reaction.[8] A remarkable 7:1 *anti*/*syn* diastereomeric ratio and a 98% enantiomeric excess (*ee*) were achieved in their striking work. Nevertheless, AAPs have not been examined extensively so far though they seem to be promising structural motif for asymmetric (organo)catalysis. Because of these intriguing facts on AAPs, we were involved in effective synthesis of the enantiopure 1,4-AAPs based on the cyclohexane backbone (**1** and **2**) as well as in their use as organocatalyst (Figure 1). Additionally, closer inspection of the

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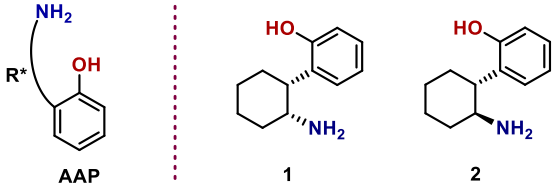
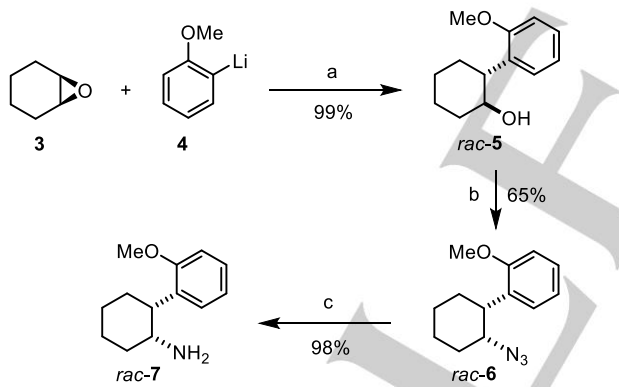


Figure 1. Structure of chiral 1,4-aminoalkylphenols (1,4-AAPs).

structure of 1,4-AAPs revealed that the distances between the hydrogen bond-donating phenolic **H** atom and the hydrogen bond-accepting **N** atom are larger than those of 1,2- and 1,3-AAPs, which was expected to provide an ideal spatial pocket for simultaneous activation of the both (electrophilic and nucleophilic) substrates. On the other hand, 1,4-AAPs rather tend to form intermolecular hydrogen bonding between O**H** and **N**H_2 functionalities whereas 1,2- and 1,3-AAPs are generally prone to form stronger intramolecular hydrogen bonding; this can result in a higher activity of 1,4-AAPs as organocatalyst.

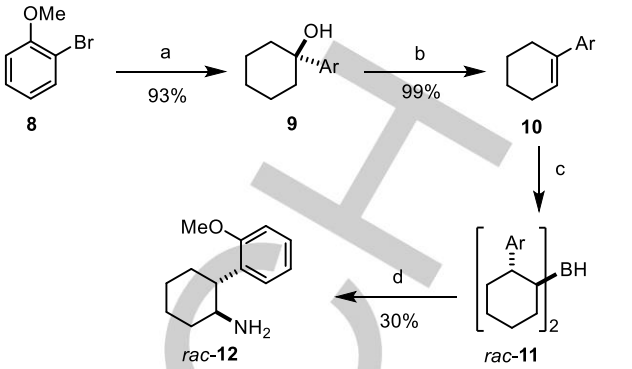
Results and Discussion

The racemic synthesis of the *cis*-AAP **1** started with the ring-opening of cyclohexene oxide (**3**) with *ortho*-lithioanisole (**4**) in the presence of $BF_3{\cdot}OEt_2$, as described in our previous report (Scheme 1).[9] The ring-opened product *rac*-**5** could be easily prepared in almost quantitative yield (99%). The Mitsunobu reaction of the *trans*-alcohol *rac*-**5** with diphenylphosphoryl azide ($(PhO)_2P(O)N_3$) gave racemic *cis*-2-(2-methoxyphenyl)-cyclohexyl azide (*rac*-**6**) in good yield (65%). Upon treatment with lithium aluminum hydride in diethyl ether, the azide *rac*-**6** could be converted into the *cis*-amine *rac*-**7** with a yield of 97%. Thus, the protected form of the racemic AAP **1** could be prepared in an effective manner. It should be noted that a similar synthetic route to *rac*-**7** has already been reported in the literature.[10]



Scheme 1. Preparation of racemic *cis*-2-(2-methoxyphenyl)cyclohexylamine (*rac*-**7**). *Reagents and conditions:* (a) **4** (3.00 equiv), $BF_3{\cdot}OEt_2$ (2.50 equiv), THF, −78 °C, 1 h; (b) $(PhO)_2P(O)N_3$ (1.50 equiv), DEAD (1.30 equiv), PPh_3 (1.50 equiv), THF −20 °C → rt, 16 h; (c) $LiAlH_4$ (3.00 equiv), Et_2O, 0 °C → rt, 16 h.

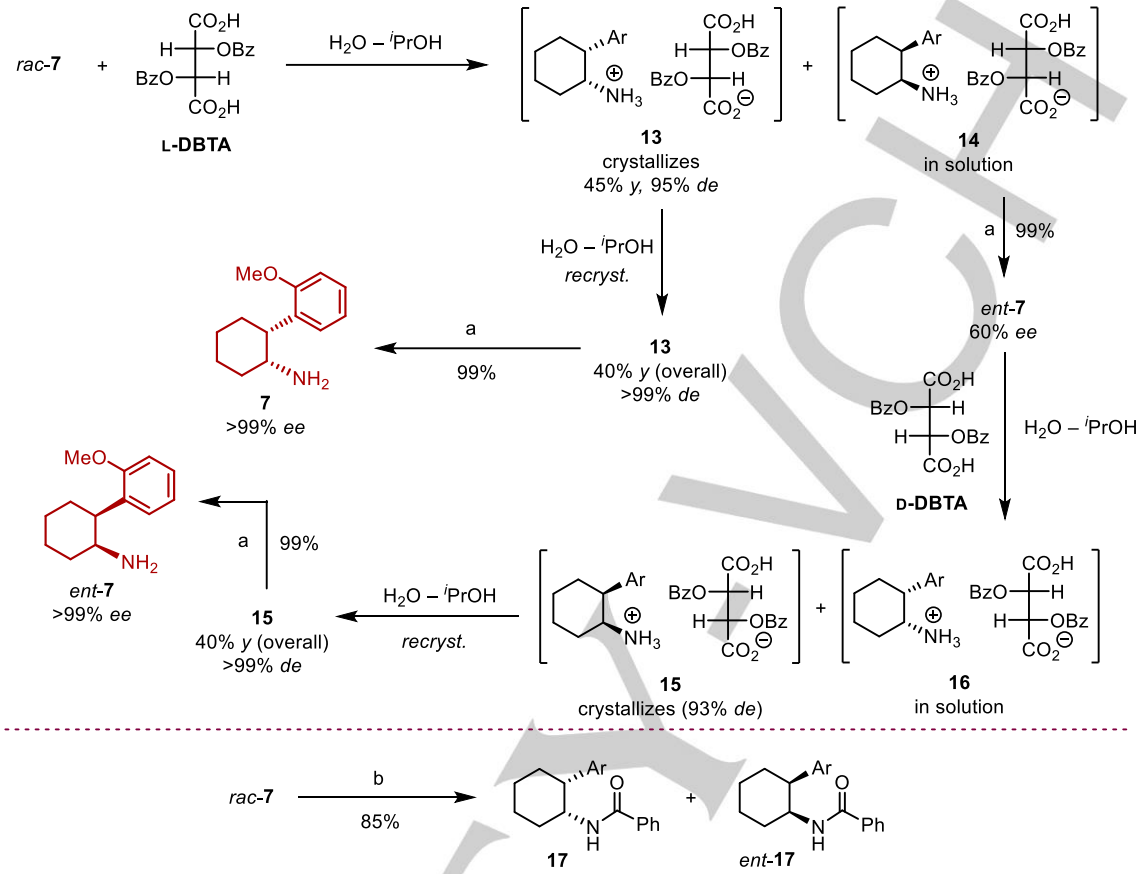
For the racemic synthesis of the *trans*-AAP **2**, 1-(2-methoxyphenyl)cyclohexene (**10**) was choosen to be as the intermediate, which could be prepared through the Grignard reaction between *ortho*-methoxyphenyl magnesium bromide and cylohexanone and the subsequent acid-catalyzed dehydration (Scheme 2). The olefin compound **10** was then subjected to hydroboration —which led to formation of the dialkylborane *rac*-**11**— and the subsequent amination with hydroxylamine-*O*-sulfonic acid. This simple procedure "hydroboration-amination



Scheme 2. Preparation of racemic *trans*-2-(2-methoxyphenyl)cyclohexylamine (*rac*-**12**). Ar = *ortho*-methoxyphenyl. *Reagents and conditions:* (a) (1) Mg, THF (2) Cyclohexanone (1.00 equiv), THF, 0 °C → rt, 3 h; (b) $AcOH/H_2SO_4$ (5:1), 0 °C → rt, 3 h; (c) $NaBH_4$ (0.40 equiv), $BF_3{\cdot}OEt_2$ (0.55 equiv), Diglyme, 0 °C → rt, 3 h; (d) H_2NOSO_3H (1.10 equiv), 100 °C, 3 h.

cascade" that was originally developed by H. C. Brown and co-workers enabled us to synthesize the racemic *trans*-amine **12** in 30% yield.[11] Thus, we accomplished the synthesis of racemic *cis*- and *trans*-2-(2-methoxyphenyl)cyclohexylamines, *rac*-**7** and *rac*-**12**, respectively. It should be mentioned that similar synthetic pathways to racemic *cis*- and *trans*-2-phenylcyclohexanamines were reported by Gotor and co-workers who then subjected those compounds to the enzymatic kinetic resolution by using *Candida antarctica* lipase A (CAL-A) and CAL-B in the presence of some esters as the acylating agents, thereby providing moderate selectivity for *cis*-2-phenylcyclohexanamines with CAL-A (E = 34) as well as high selectivity for *trans*-2-phenylcyclohexanamines (E > 200) with CAL-B.[12] It was also reported that enantiopure primary amines could be obtained via the asymmetric hydroboration of alkenes with monoisopinocamphenylborane ($IpcBH_2$) and the subsequent amination with hydroxylamine-*O*-sulfonic acid.[13] However, a brief literature survey indicated that this chiral auxiliary technique was inadequate for providing enantiopure 2-aryl-cyclohexanamines.[13]

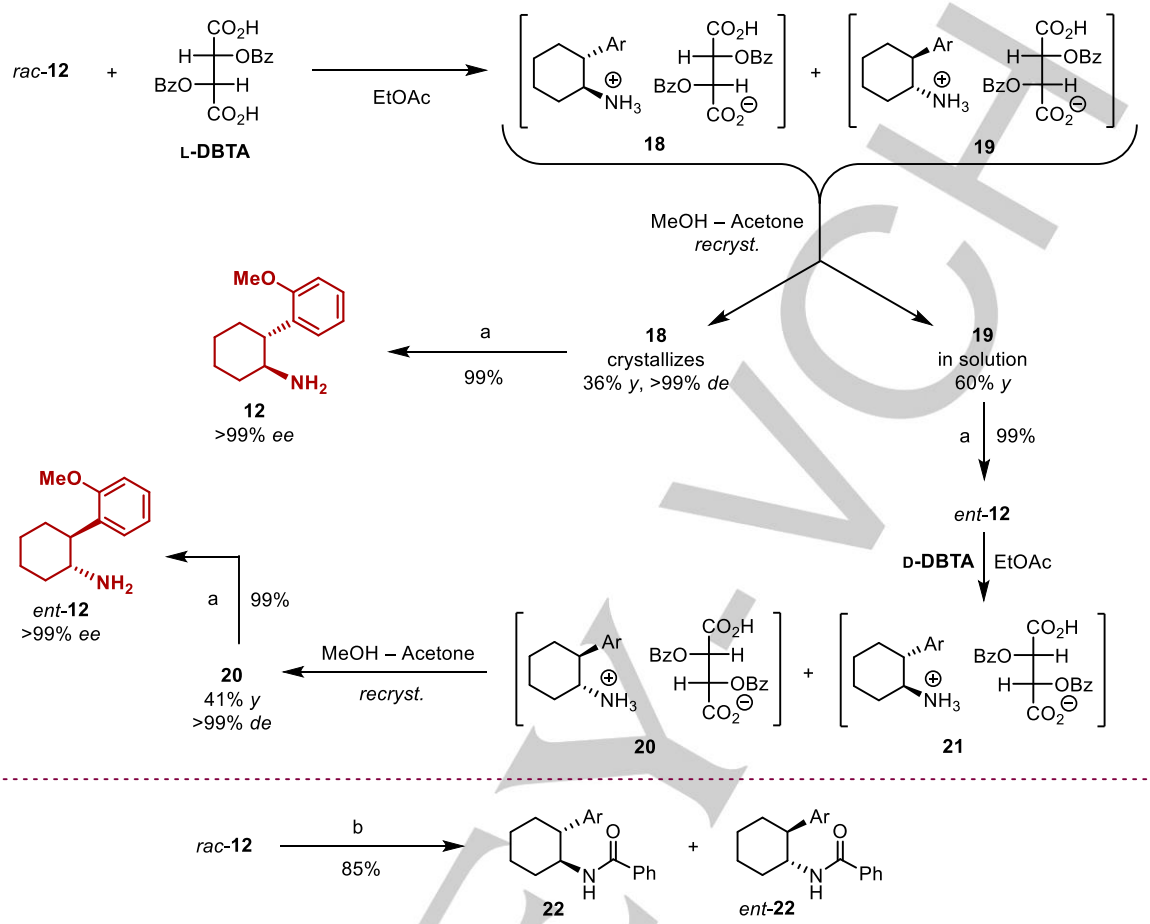
Over recent decades, a dramatic increase in the development of catalytic enantioselective methods has been observed, which allow access to chiral compounds in their enantiopure forms in an efficient and step-economic manner. Nevertheless, resolution by diastereomeric salt formation is still one of the most favorable technique for this purpose.[14] There have been also many cases in which this classical technique of resolution has proven to be particularly effective for preparing enantiopure chiral compounds on a large scale.[15] Accordingly, we started looking for a suitable acidic resolving agent, for the resolution of the racemic *cis*-amine *rac*-**7**. L-Tartaric acid (L-TA), (*R*)-(+)-mandelic acid, (1*S*)-(+)-10-camphorsulfonic acid, and dibenzoyl-L-tartaric acid (L-DBTA) were the resolving agents of choice. In the first setting, equimolar amounts of *rac*-**7** and all 4 selected resolving agent candidates were mixed in 50% aqueous ethanol in consecutive experiments, hoping for the formation of a crystalline salt. All of these attempts by using 50% aqueous EtOH as the solvent failed.[16] After extensive examination of the above-mentioned chiral acids with unary as well as binary solvent systems, an effective resolution of



Scheme 3. Resolution of racemic *cis*-2-(2-methoxyphenyl)cyclohexylamine (*rac*-**7**). Ar = *ortho*-methoxyphenyl. *Reagents and conditions:* (a) $NaOH_{(aq)}$ (4 N), DCM; (b) PhCOCl (2.00 equiv), $NaOH_{(aq)}$ (4 N), DCM, 15 min.

rac-**7** could eventually be achieved with L-DBTA as the resolving agent and 2-propanol–water mixture as the binary solvent system (Scheme 3). Addition of *rac*-**7** solution in 2-propanol into the suspension of L-DBTA in water instantaneously delivered the ammonium tartarate salt **13** as white crystals in 45% yield (with respect to total amount of *rac*-**7**) and 95% diastereomeric excess. Note that, **7** was converted into its benzamide derivatives **17** and *ent*-**17** (at the bottom of Scheme 3) so that the diastereomeric excess of **13** (as well as **14** and **15**), or rather the enantiomeric excess of **7** could be determined by HPLC on a chiral column. A further recrystallization of **13** (95% *de*) from the 2-propanol–water mixture (^{i}PrOH–H_2O, approx. 50:50, v/v) afforded diastereomerically pure **13** in 40% overall yield, based on the amount of the starting *rac*-**7**. Treatment of **13** (>99% *de*) with aqueous NaOH (4.0 N) followed by extraction with DCM furnished the chiral amine **7** in enantiomerically pure form (>99% *ee*), in quantitative yield. The combined filtrates that predominantly contained **14** were evaporated under reduced pressure, treated with 4.0 N NaOH, and exracted with DCM, thus liberating enantiomerically enriched *ent*-**7** (60% *ee*) from L-DBTA. Then, treatment of *ent*-**7** (60% *ee*) with equimolar amount of dibenzoyl-D-tartaric acid (D-DBTA) and recrystallization of the resulting D-DBTA salt (**15**) from the 2-propanol–water mixture (^{i}PrOH–H_2O, approx. 50:50, v/v) as described above afforded **15** in diastereomerically pure form (>99% *de*) and high overall yield (40% *y* with respect to starting amount of *rac*-**7**). The enantiomerically pure amine *ent*-**7** was liberated from the D-DBTA salt **15** by addition of 4.0 N NaOH and a subsequent extraction with DCM, in quantitative yield as a colorless oil.

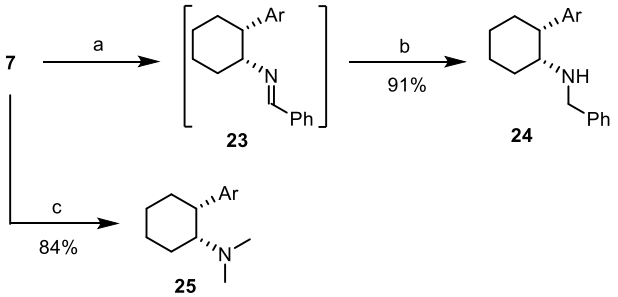
As a consequence of the remarkable success in the optical resolution of *rac*-**7** by employing dibenzoyl tartaric acid, we immediately turned our attention to resolution of the racemic *trans*-amine (*rac*-**12**) by using the same resolving agents (Scheme 4). However, it was relatively complicated: Mixing *rac*-**12** with L-DBTA in 2-propanol–water mixture simply did not form any crystalline salt. Therefore, we first prepared a diastereomeric mixture of **18** and **19**, by treatment of *rac*-**12** with L-DBTA in EtOAc and subsequent removal of EtOAc. Then, we sought after a suitable recrystallization solvet or solvent mixture for separation of the diastereomers **18** and **19** from each other. Pleasingly, we found out that a methanol-acetone mixture is an excellent binary solvent system for this purpose: After a single recrystallization from methanol–acetone (ca. 1:2, v/v), **18** was obtained as a white crystalline product in 36% yield and >99% *de*. The diastereomeric



Scheme 4. Resolution of racemic *trans*-2-(2-methoxyphenyl)cyclohexylamine (*rac*-**12**). Ar = *ortho*-methoxyphenyl. *Reagents and conditions:* (a) $NaOH_{(aq)}$ (4 N), DCM ; (b) PhCOCl (2.00 equiv), $NaOH_{(aq)}$ (4 N), DCM, 15 min.

excess of **18** as well as enantiopurity of **12** and *ent*-**12** in turn were determined by their derivatization to the benzamide **22** and *ent*-**22**, and the subsequent chiral HPLC analysis thereof (on the bottom of Scheme 4). The enantiopure amine **12** was isolated in quantitative yield by treatment of **18** with 4.0 aqueous NaOH and extraction with DCM consecutively. The filtrate was evaporated under reduced pressure, treated with 4.0 N aqueous NaOH solution, and extracted with DCM, thus obtaining enantiomerically enriched *ent*-**12** in 60% *ee*. Then, *ent*-**12** (60% *ee*) was treated with an equimolar amount of dibenzoyl-D-tartaric acid (D-DBTA) in EtOAc, which was followed by removal of the solvent by rotary evaporation under reduced pressure. The residue containing predominantly the diastereomer **20** was recrystallized from methanol/acetone (ca. 1:2, v/v), which delivered the diastereomerically pure **20** in 41% yield, with respect to starting *rac*-**12**. Treatment of **20** with 4.0 N aqueous NaOH and subsequent extraction with DCM as usual produced the enantiopure amine *ent*-**12** as a colorless oil in quantitative yield.

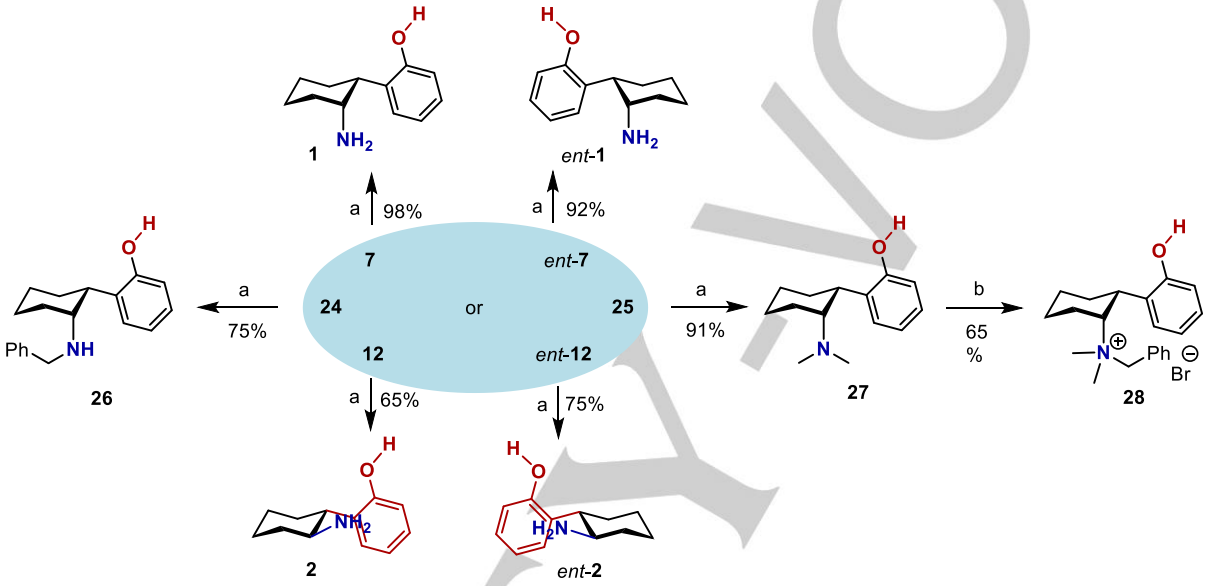
After the preparation of the enantiopure *cis*- and *trans*-2-(2-methoxyphenyl)cyclohexylamines, we turned our attention to modify the substituents attached to the amino group in order to add some diversity to our work. Starting from **7**, secondary and tertiary amines **24** and **25** could be easily accessed in good yields



Scheme 5. Synthesis of the di- and trisubstituted cyclohexylamines **24** and **25**. Ar = *ortho*-methoxyphenyl. *Reagents and conditions:* (a) PhCHO (1.00 equiv), $MgSO_4$, DCM, rt, 16 h; (b) $NaBH_3CN$ (2.00 equiv), AcOH (4.00 equiv), MeCN, 0 °C → rt, 16 h; (c) $HCHO_{(aq)}$ (5.00 equiv), $NaBH_3CN$ (2.00 equiv), AcOH (5.00 equiv), MeCN, 0 °C → rt, 16 h.

by exploiting the conventional organic transformations, as illustrated in Scheme 5.

At this stage, a suitable procedure for the demethylation of the chiral anisoles **7**, *ent*-**7**, **12**, *ent*-**12**, as well as **24** and **25** was needed in order to synthesize the corresponding AAPs as potential organocatalysts (Sheme 6). Ethanethiol–sodium *tert*-butoxide couple in DMF did not appear to be suitable for the demethylation of these substrates; instead, it formed unidentified side products. To our delight, boron tribromide (BBr_3) in DCM was found to work sufficiently well, delivering the corresponding phenols in high yields. Thus, the effective preparation of both enantiomers of *cis*- and *trans*-2-(2'-aminocyclohexyl)phenols (**1**, *ent*-**1**, **2**, *ent*-**2**) as well as the secondary- and tertiary-aminoalkylphenols **26** and **27** was established. Additionally, the quaternarization of AAP **27** was successfully achieved by refluxing it with benzyl bromide in acetonitrile, providing the quaternary ammonium salt **28** possessing a phenolic hydroxyl group.



Scheme 6. Enantiopure AAPs. *Reagents and conditions:* (a) BBr_3 (3.00 equiv), DCM, 0 °C → rt, 6 h; (b) BnBr (1.10 equiv), MeCN, reflux, 24 h.

Single crystals of *cis*-AAP **1** and the *trans*-AAP **2** suitable for X-ray crystallography could also be obtained in our studies. So, we were able to determine the absolute configurations of the AAPs **1** and **2**. The X-ray crystal structures of the both isomers (**1** and **2)** with the atom numbering schemes are shown in Figure 2. Suitable crystals of **1** for single-crystal X-ray analysis were grown from methanol whereas single crystals of **2** for single-crystal X-ray analysis were obtained from benzene at room temperature. The AAP **1** (Fig. 2A) crystallizes in the hexagonal $P6_1$ space group whereas the trans AAP **2** (Fig. 2B) crystallizes in the monoclinic $P2_1$ space group. These are the first crystal structures according to the results of the Cambridge Structural Database (CSD) survey. The hydrogen atoms in the *cis*-AAP **1** and the *trans*-AAP **2** occupy the *cis*- and *trans*-positions relative to the C(1)–C(6) bond, respectively (Fig. 2). To highlight similarities and contrasts between the *cis*-AAP **1** and the *trans*-AAP **2** some equivalent bond lengths and angles are tabulated in Table S2. The bond distances and angles are in good aggreement, but the overall conformations around the C(6)-C(7) bond are quite different (Fig. 2C), i.e. the torsion angles of C(1)–C(6)–C(7)–C(8) in *cis*-AAP **1** and *trans*-AAP **2** are −73.8(9)° and −142.9(3)°, respectively. It is worth mentioning that self-assembly of *cis*-isomer (**1**) results in the formation of honeycomb-like hexagonal porous molecular network along the *c*-axis (Fig. 2D). In contrast, *trans*-isomer (**2**) exhibit highly dense-packed nonporous structure (Fig. 2E).

Recently, we prepared a number of enantiopure chiral alcohols of type **29** in order to develop 2-(2-hydroxyaryl)alcohols (HAROLs) as chiral ligands and hydrogen-bond donor organocatalysts (Scheme 7).[17] We reasoned that **29** might be a useful starting material for the synthesis of linear types of 1,4-AAPs that are based on cyclohexane backbone (**1**, *ent*-**1**, **2**, *ent*-**2**). The classical Mitsunobu reaction of the alcohol **29** by employing phthalimide delivered **30** in 75% yield. Enantiopurity of the stereo-inversed phthalimide **30** was checked by HPLC on a chiral column and determined to be >99%. Subsequent aminolysis of **30** with hydrazine hydrate provided the amine **31**. However, demethylation of **31** proved to be somewhat complicated: In contrast to the counterparts **7** and **12** that are based on cyclohexane backbone, demethylation of **31** by employing BBr_3 unexpectedly did not deliver the desired AAP (**33**). Formation of various by-products was observed. On the other hand, the ethanethiol–sodium *tert*-butoxide couple in DMF yielded the formamide derivative **32** (78%), which could be formed via a base-catalyzed formylation of the intermediate **33** with DMF.[18] Saponification of the formamide **32** gave the linear AAP **33** with a yield of 90%. The demethylation of **31** with NaSEt was also tried

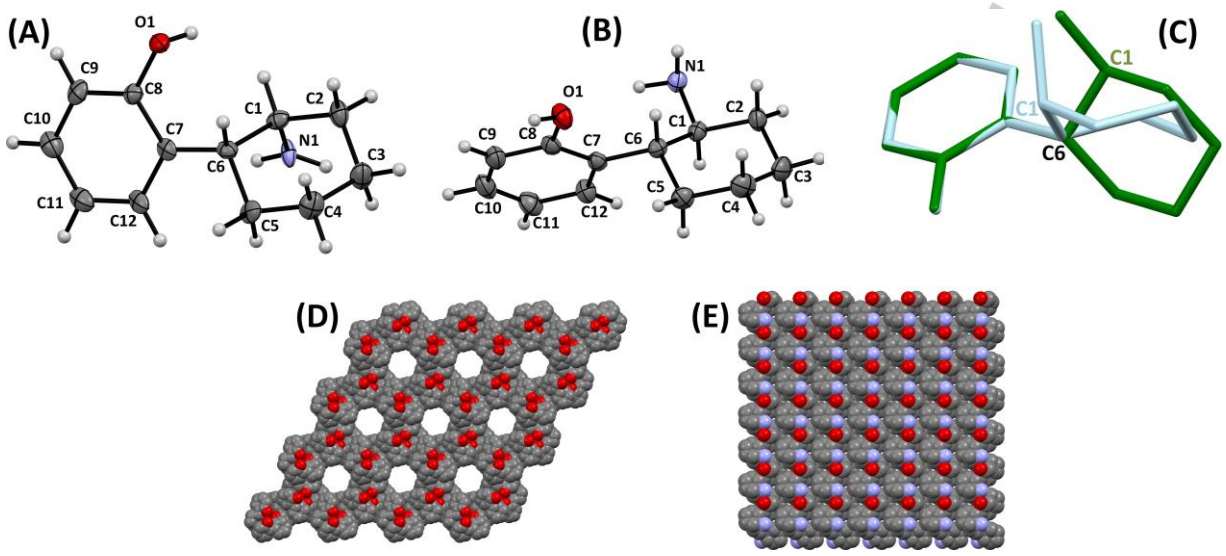
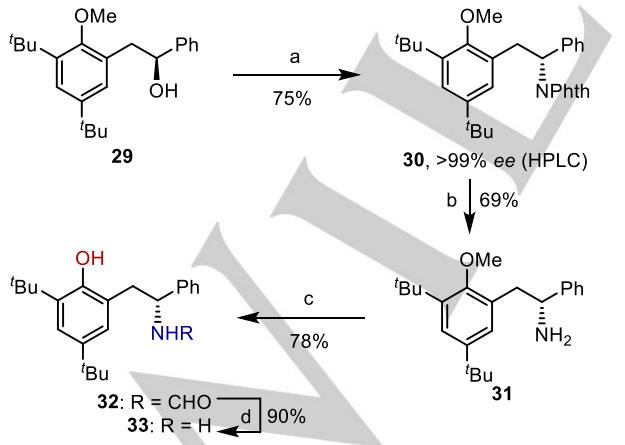


Figure 2. X-ray crystal structures of (A) the AAP **1** (*cis*) and (B) the AAP **2** (*trans*). Displacement ellipsoids are drawn at the 50% probability level. (C) Superimposed crystal structures of **1** (light blue) and **2** (green). (D) Schematic representation of honeycomb-like porous molecular structures of **1**. (E) Schematic representation for higly-dense crystal packing of **2**.

in hexamethylphosphoramide (HMPA) and *N*-methyl-2-pyrrolidone (NMP) as the solvents, in order to obtain **33** directly. However, the former gave rise to the formation the AAP **33** in 28% yield whereas the latter provided only traces of **33**. Note that the AAP **33** is not stable enough for chromatographic separation on silica gel; it rapidly undergoes decomposition on it. But, its reason as well as mechanism was not further investigated.

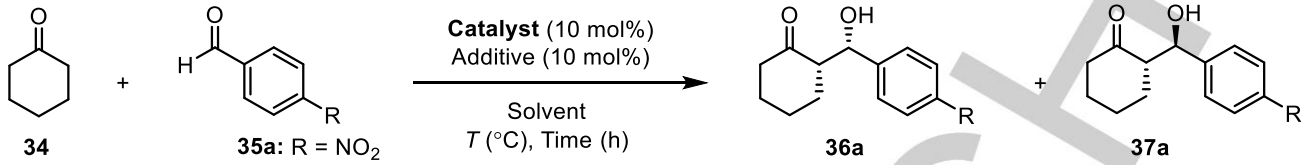
Next, our novel enantiopure AAPs were employed in the asymmetric enamine catalysis to examine their organocatalytic performances (Table 1). Because a number of chiral primary amines exhibited high activity and stereoselectivity in enamine



Scheme 7. Synthesis of the enantiopure linear AAP **33**. R^1 = ^{t}Bu, NPhth = Phthalimido. *Reagents and conditions:* (a) Ph_3P (4.00 equiv), HNPhth (3.00 equiv), DIAD (4.00 equiv), THF, 0 °C, 12 h; (b) $H_2NNH_2{\cdot}H_2O$ (10.00 equiv), EtOH, reflux, 6h; (c) EtSH (8.00 equiv), NaO^{t}Bu (3.00 equiv), DMF, 120 °C, 2 h; (d) NaOH, MeOH, reflux, 2 h.

catalysis in previous studies,[4f,g,j–l] the aldol reaction between cyclohexanone (**34**) and 4-nitrobenzaldehyde (**35a**) served as the test reaction. Almost all the reaction factors were tested carefully in order to identify the best reaction conditions in terms of reaction yield and stereoselectivity.[19] In addition to AAPs **1**, **2**, and **33**, their *O*-protected forms **7**, **12**, and **31** were also employed as the potential catalysts. In the absence of any additives, all the *cis*- and *trans*-cylohexanamine compounds performed the aldol condensation with a similar activity and stereoselectivity, producing the diasteromers **36a** and **37a** with yields in the range of 24–32% (in favor of the *syn*-diastereomer **36a**) and up to 60% *ee* (Table 1, entries 1–4). Among the acidic additives examined, benzoic acid was the best in terms of the stereoselectivity and it dramatically enhanced the reaction yields (up to 97% *y*), albeit the diastero- and enantioselectivities could only be increased fairly under neat conditions (entries 5–8). Comparison of the enantioselectivities observed with the *cis*-AAP **1** and **7** as the catalyst underpins the bifunctional behavior of the AAP **1** (entries 5 and 6). Based on the first screening, the *cis*-AAP **1** was determined to effect the reaction with the highest level of stereoselectivities (see, Supporting Informations). Additionally, a high solvent effect on the stereochemical outcome of the reaction was observed so that toluene and THF achieved the most remarkable values (entries 9 and 10). THF provided the highest diastereomeric ratio in favor of the *syn*-diastereomer (**36a**/**37a** = 91:9), but led to modest yield and enantioselectivities (46% *ee* for **36a** and 48% *ee* for **37a**, entry 10). It is noteworthy that there have been only a few catalytic systems that effect aldol reaction with *syn*-selectivity.[20] On the other hand, toluene resulted in a significant enhancement in both diastereo- and enantioselectivity (86% *y*; **36a**/**37a** =70:30; 64% *ee* for **36a** and 78% *ee* for **37a**; entry 9). When the reaction temperature was decreased from

Table 1. Enantioselective aldol condensation between cyclohexanone (**34**) and 4-nitrobenzaldehyde (**35a**) catalyzed by chiral AAPs.[a]



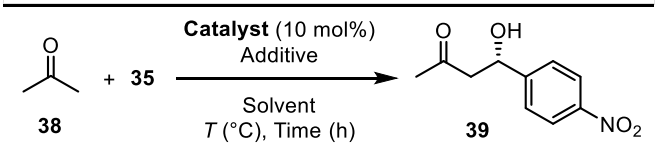
Entry	Catalyst	Additive	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	36a : 37a *(syn/anti)*[c]	*ee*[d] for 36a (%)	*ee*[d] for 37a (%)
1	**7**	—	—	rt	48	29	63:37	16	46
2	**1**	—	—	"	"	27	60:40	19	44
3	**12**	—	—	"	"	24	59:41	28	58
4	**2**	—	—	"	"	32	53:47	20	60
5	**7**	Benzoic acid	—	"	"	94	63:37	44	44
6	**1**	"	—	"	"	84	60:40	54	54
7	**12**	"	—	"	"	97	61:39	8	24
8	**2**	"	—	"	"	97	62:38	6	6
9	**1**	"	Toluene	"	36	86	70:30	64	78
10	**1**	"	THF	"	"	24	91:9	46	48
11	**1**	"	Toluene	0	"	24	73:27	70	80
12	**31**	"	"	rt	24	87	58:42	8	8
13	**33**	"	"	"	"	0	–	–	–

[a] Reactions were performed with 4-nitrobenzaldehyde (0.25 mmol) and cyclohexanone (2.0 mmol) in the solvent (0.5 mL). [b] Combined yield of the isolated isomers **36a** and **37a**. [c] Diastereomeric ratio (**36a**/**37a**) was determined by HPLC analysis. [d] Enantiomeric excesses (*ee*) were determined by HPLC analysis on a chiral phase: Chiralpak AD-H; *n*-hexane/^{i}PrOH (85:15), 1 mL/min; 254 nm (UV–vis); t_R = 15.1 min (*ent*-**36a**), t_R = 16.9 min (**36a**), t_R = 18.6 min (**37a**), t_R = 24.6 min (*ent*-**37a**).

room temperature to 0 °C, higher diastereo- and enantioselectivities were achieved (**36a/37a** = 73:27, 70% and 80% *ee*, respectively; entry 11). It was interesting to see that the linear AAP **33** did not show catalytic activity (entry 13), while its *O*-protected form **31** could catalyze the reaction with high yield and low stereoselectivities (entry 12). The inactivity of the linear AAP **33** might be attributed to the potential but very strong intramolecular hydrogen bonding between the amine N and the phenolic H atoms, which could not be true regarding the cyclohexane-based AAPs **1** and **2**. This entirely different behavior of **1** and **33** in catalytic activity is reminiscent of the importance of the cyclohexane framework in bifunctional organocatalysts. Note that there have been numerous cases in the literature, where bifunctional organocatalysts incorporating cyclohexane backbone have exhibited higher catalytic activities and selectivities, which is mainly due to their diminished ability to build aggregates via intermolecular hydrogen bonding than their linear analogues.[21]

Catalytic activity of the AAP **1** and its *O*-protected form **7** were also explored for the aldol reaction between acetone (**38**) and 4-nitrobenzaldehyde (**35a**) (Table 2). All individual factors were basically screened. Remarkably, it was observed that 2,4,6-triisopropylbenzoic acid (TRIBA) that is sterically more demanding than benzoic acid affected the stereochemical outcome of the reaction, compared to benzoic acid (entries 3 and 4). To the best of our knowledge, this is the first report showing the advantageous effect of TRIBA. More remarkably, the *O*-protected AAP **7** exhibited a slightly higher catalytic activity and enantioselectivity than AAP **1** (entries 4 and 5). The best result in terms of enantiomeric excess was obtained in the presence of **7** as the catalyst and TRIBA as the additive at 0 °C (up to 62% *ee*). Extending the reaction time enabled the formation of the aldol product **39** in high yield (85% *y* after 192 h, entry 6). It should be noted that TRIBA was also employed in the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde. However, it did not

Table 2. Enantioselective aldol condensation catalyzed by the chiral primary amines **1** and **7**.[a]

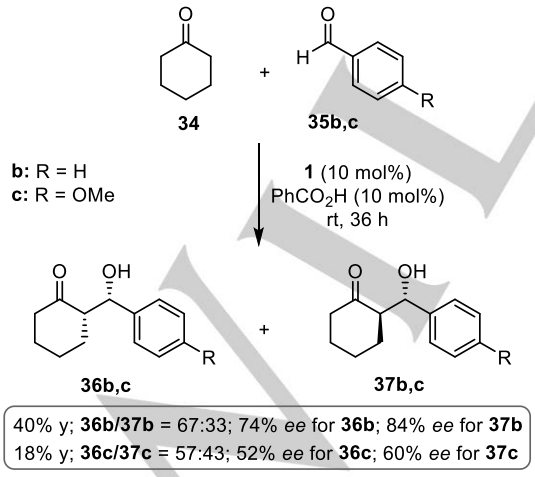


Entry	Catalyst	Reaction conditions	Yield[b] (%)	*ee*[c] (%)
1	**1**	TRIBA (10 mol%), solvent-free, rt, 66 h	42	40
2	**1**	TRIBA (10 mol%), Toluene (0.25 mL), rt, 66 h	21	42
3	**1**	TRIBA (20 mol%), Toluene (0.1 mL), 0 °C, 60 h	19	55
4	**1**	BA (20 mol%), Toluene (0.1 mL), 0 °C, 92 h	19	52
5	**7**	BA (20 mol%), Toluene (0.1 mL), 0 °C, 90 h	23	58
6	**7**	TRIBA (20 mol%), Toluene (0.1 mL), 0 °C, 192 h	85	62

[a] 0.25 mmol (1.00 equiv) **35a** and 2.0 mmol (8.00 equiv) **38** were employed. [b] Isolated yield of the NMR-pure product. [c] Enantiomeric excesses (*ee*) were determined by HPLC analysis on a chiral phase: Chiralpak AS-H; *n*-hexane/^{i}PrOH (85:15), 1 mL/min; 254 nm (UV–vis); t_R = 25.1 min (*ent*-**39**), t_R = 32.4 min (**39**).

bring about any improvement in the stereoselectivity (Supp Info., Table S3, entries 59 and 60).

Last, cyclohexanone (**34**) was reacted with benzaldehyde (**35b**) and *p*-anisaldehyde (**35c**), in the presence of **1** and benzoic acid (Scheme 8). As expected, the aldol products **36b**/**37b** and **36c**/**37c** were obtained in lower yields, 40% and 18% yields



Scheme 8. AAP **1** catalyzed aldol reaction of cyclohexanone (**34**) with benzaldehyde (**35b**) and *p*-anisaldehyde (**35c**). *8.00 equiv of cyclohexanone were used in the absence of any solvents.*

respectively. Diastereomeric ratio (**36b**/**37b** = 67:33) and *ee* values for **36b** (74% *ee*) and **37b** (84% *ee*) were determined to be comparable with those of **36a** and **37a** whereas these values for **36c** and **37c** were lower (**36c/37c** = 57:43, 52% *ee* and 60% *ee* respectively). This indicates that the AAP **1** catalyzed aldol reactions of cyclohexanone with benzaldehyde and *p*-nitrobenzaldehyde proceed via similar pathways. Finally, some plausible transition states that are dictated by the stereochemical outcome of the reactions can be proposed (Figure 2): Benzaldehyde (**35b**) can form a hydrogen bond with phenolic hydroxyl group; additionally, a π···π interaction between the aromatic rings of **1** and the aldehyde can take place (TS-I). On the other hand, the contribution of benzoic acid must be also taken into account because higher *syn/anti* ratio as well as higher enantiomeric excesses were observed in the presence of benzoic acid, which suggests that benzoic acid not only accelerates the formation of the enamine, but also participates in the stereo-determinig step. Accordingly, in TS-II benzoic acid is estimated to be able to build a supramolecular catalyst through multiple hydrogen bondings. Furthermore, the lower *syn/anti* ratio and enantiomeric excesses obtained in the aldol reaction of *p*-anisaldehyde (**35c**) might be attributed to lower (or no) contribution of π···π interaction between the aromatic rings of the catalyst **1** and *p*-anisaldehyde. This might be due to the similar electron distributions of aromatic rings of the phenol moiety and *p*-anisaldehyde.

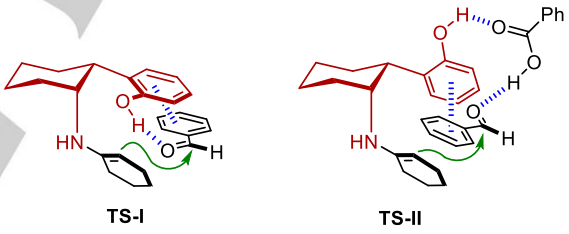


Figure 2. Plausible transition states for the *syn*-selective aldol reaction catalyzed by the AAP **1**.

Conclusions

In summary, we have achieved effective racemic synthesis of both *cis*- and *trans*-2-(2-methoxyphenyl)cyclohexylamine as well as their multigram-scale resolution via diastereomeric salt formation, thus delivering the enantiomerically pure precursors for aminoalkylphenols (AAPs) based on cyclohexane framework. Diverse AAPs bearing primary, secondary, and tertiary amine group, as well as a quaternary ammonium phenol have been prepared, in their enantiopure form in an effective manner. In addition, primary AAPs were evaluated as organocatalysts in the direct aldol reaction, thereby exhibiting good catalytic activity and providing *syn*-aldol product predominantly with good enantioselectivity. As far as we know, this is one of the rare examples of catalytic systems that provide *syn*-aldol product selectively.[20] 2-Aryl-substituted cyclic amines are also of great importance due to their diverse pharmacological properties.[12,22]

Therefore, we believe that the methdology disclosed herein can also become a general and useful technique for the preparation of enantiopure 2-aryl-substituted cycloalkylamines.

Experimental Section

General Remarks. All air-sensitive reactions were performed under an inert atmosphere of dry nitrogen (N_2) using oven-dried glassware. All reagents and solvents were transferred using gas-tight syringe and cannula techniques under N_2. Reactions were monitored by thin layer chromatography (TLC) on aluminum sheets that were pre-coated with silica gel *SIL G/UV*$_{254}$ from MN GmbH & Co., in which the spots were visualized in UV-light (λ = 254 nm) and/or by staining with phosphomolybdic acid solution in EtOH (10%, w/v). Chromatographic separations were performed using silica gel (MN-silicagel 60, 230-400 mesh). All melting points were determined in open glass capillary tube by means of a BÜCHI Melting Point B-540 apparatus and values are uncorrected. Infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer, $\tilde{\nu}_{max}$ in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H and ^{13}C NMR spectra were recorded on a 500 MHz or 600 MHz NMR spectrometer. Chemical shifts δ are reported in parts per million (ppm) relative to the residual protons in the NMR solvent ($CHCl_3$: δ 7.26) and carbon resonance of the solvent ($CDCl_3$: δ 77.00). NMR peak multiplicities were given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra were recorded on a gas chromatography with mass sensitive detector from Agilent Technologies 6890N Network GC System (EI, 70 eV) using Standard Method (column: HP-5MSI, 30 m, 0.25 mm ID, 0.25 µm film tickness; inlet: 300 °C (split modus); det: 300 °C; He, 1 mL/min (constant flow modus); oven: 40 °C (5 min), 5 °C/min, 280 °C (5 min)). High resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained with MeOH on a Bruker micrOTOF-Q. The specific rotations ([α]) were measured on a Optical Activity Ltd. AA-65 polarimeter using 1 mL cell with a 1.0 dm path length and the sample concentrations are given in g/100 mL unit. Tetrahydrofuran (THF), diethyl ether (Et_2O), and diglyme were freshly distilled from sodium/benzophenone prior to use under nitrogen atmosphere. *N,N*-dimethylformamide (DMF) and anisole were distilled under reduced pressure from calcium hydride (CaH_2). Acetonitrile (MeCN), dichloromethane (DCM), triethylamine (TEA), and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) were dried by distillation over CaH_2 under N_2. Some reagents, such as boron trifluoride-diethyl ether complex ($BF_3{\cdot}OEt_2$), ^{n}BuLi (2.5 M or 1.7 M solution in hexane), EtSH, $LiAlH_4$, PPh_3, $NaBH_4$, $NaBH_3CN$, diethyl azodicarboxylate (DEAD), diphenyl phosphoryl azide ($(PhO)_2P(O)N_3$), and 2-bromoanisole were purchased from commercial suppliers and used as received. Hydroxylamine-*O*-sulfonic acid (H_2NOSO_3H),[23] 2,4,6-triisopropylbenzoic acid (TRIBA)[24] and L-DBTA[25] were prepared according to procedures given in literature.

***trans*-2-(2-Methoxyphenyl)cyclohexanol (*rac*-5).**[9] An oven-dried 1 L round-bottomed Schlenk flask, capped with a glass stopper and equipped with a magnetic stirring bar, was evacuated under heating with a blow-drier for 15 min. After the flask was cooled down to ambient temperature, dry nitrogen was back-filled and the glass stopper was replaced with a rubber septum, under a positive pressure of nitrogen. The flask was charged with anisole (9.8 mL, 9.7 g, 90.0 mmol, 3.00 equiv) and TMEDA (2.1 g, 2.7 mL, 18.0 mmol, 0.60 equiv), which was succeeded by the addition of dry THF (180 mL) as the solvent. After the mixture was cooled in an ice-bath, 36 mL of 2.50 M solution of ^{n}BuLi in hexanes (90.0 mmol, 3.00 equiv of ^{n}BuLi) were drop-wise added to the mixture. The mixture was then stirred for 2 h while the temperature was allowed to rise to ambient temperature. After cooling the reaction mixture down to −78 °C in an acetone-dry ice bath, cyclohexene oxide (**3**) (3.6 g, 3.45 mL, 30.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (10.80 g, 9.30 mL, 75.0 mmol, 2.50 equiv) were added sequentially. The reaction mixture was stirred at −78 °C for 1 h and quenched with saturated $NaHCO_3$ solution (180 mL). THF was removed by rotary evaporation under reduced pressure and the aqueous residue was extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The residue was then purified by silica gel column chromatography eluting with hexanes/EtOAc (9:1) to afford *rac*-**5** (6.12 g, 29.7 mmol, 99%) as a colorless solid. Mp: 52–54 °C. TLC: R_f = 0.11 (silica gel; hexanes/EtOAc, 9:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3372 (m), 3103 (w), 3073 (w), 3012 (w), 2919 (s), 2661 (w), 2008 (w),1911 (w), 1876 (w), 1756 (w) 1599 (s), 1585 (s), 1492 (s), 1463 (s), 1438 (s),1326 (m), 1290 (m), 1240a (s), 1191 (m), 1126 (m), 1090 (w), 1051 (s), 961 (m), 824 (w), 746 (s), 730 (s), 577 (w), 565 (w). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23 (m, 1 H), 7.20 (m, 1 H), 6.97 (dt, *J* = 7.5, 1.0 Hz, 1 H), 6.89 (dd, *J* = 8.2, 1.0 Hz, 1 H), 3.83 (s, 3 H), 3.77–3.71 (m, 1 H), 2.98-3.04 (m, 1 H), 2.16–2.12 (m, 1 H), 1.86–1.73 (m, 4 H), 1.54–1.33 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.6 (C), 131.5 (C), 127.3 (CH), 127.2 (CH), 120.9 (CH), 110.7 (CH), 73.8 (CH), 55.4 (CH_3), 45.0 (CH), 35.1 (CH_2), 32.3 (CH_2), 26.1 (CH_2), 25.1 (CH_2). GCMS: t_R = 28.19 min, *m/z* (%) = 206 ($[M]^+$, 73), 188 ($[M-18]^+$, 7), 173 ($[M-33]^+$, 43), 147 (23), 134 (7), 121 (100), 107 (9), 91 (47), 77 (10). HRMS (ESI): ($[M+Na]^+$) calcd for $C_{13}H_{18}O_2Na$: 229.1199; found: 229.1196.

***cis*-1-(2-Azidocyclohexyl)-2-methoxybenzene (*rac*-6).** An oven-dried 250 mL round-bottomed Schlenk flask, capped with a glass stopper and equipped with a magnetic stirring bar, was charged with *rac*-**5** (5.175 g, 25.0 mmol, 1.00 equiv) and triphenylphosphine (PPh_3) (9.825 g, 37.5 mmol, 1.50 equiv). After dry THF (100 mL) was added into the reaction flask by means of a gas-tight syringe, the reaction system was slightly evacuated and back-filled with dry N_2, at least three times. The glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen and the flask was cooled down to −78 °C in an acetone-dry ice bath. Then, DEAD (14.16 g, 14.8 mL, 32.5 mmol, 1.30 equiv) and $(PhO)_2P(O)N_3$ (10.3 g, 8.1 mL, 37.5 mmol, 1.50 equiv) were added at −78 °C sequentially, using syringes. The reaction mixture was then stirred for 16 h while the temperature was allowed to rise to ambient temperature. THF was removed by rotary evaporation under reduced pressure. The yellow residue was filtered through a column filled with silica gel, by using a hexanes/EtOAc (95:5) mixture as the mobile phase. Purification by flash chromatography (hexanes) on silica gel gave *rac*-**6** (3.76 g, 16.3 mmol, 65%) as a colorless oil. TLC: R_f = 0.22 (silica gel, hexanes). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 2935 (s), 2102 (s), 1601 (w), 1492 (s), 1239 (s), 1031 (w), 753 (s). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.21 (m, 2H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 4.05 (d, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 3.22 (dt, *J* = 12.9, 2.9 Hz, 1H), 2,06–1.99 (m, 2 H), 1,91–1.87 (m, 1H), 1,80–1.70 (m, 1H), 1,61–1.54 (m, 3H), 1,48–1.36 (m, 1H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 156.6 (C), 131.2 (C), 128.1 (CH), 127.6 (CH), 120.5 (CH), 109.9 (CH), 62.0 (CH), 55.3 (CH_3), 39.5 (CH), 30.7 (CH_2), 26.3 (CH_2), 25.0 (CH_2), 20.4 (CH_2). HRMS (ESI): ($[M-N_2+H]^+$) calcd for $C_{13}H_{18}NO$: 204.1383; found: 204.1403.

***cis*-2-(2-Methoxyphenyl)cyclohexylamine (*rac*-7).**[10] Oven-dried 250 mL and 500 mL round-bottomed schlenk flasks, capped with a glass stoppers and equipped with a magnetic stirring bars, were evacuated under heating with a blow-drier for 15 min. After the flasks were cooled down to ambient temperature, dry nitrogen was back-filled and the glass stoppers were replaced with rubber septums, under a positive pressure of nitrogen. The 500 mL flask was charged with $LiAlH_4$ (1.71 g, 45.0 mmol, 3.00 equiv) and dry Et_2O (120 mL) was added into the flask by means of a gas-tight syringe. In the 250 mL Schlenk flask was prepared a solution of *rac*-**6** (3.5 g, 15.0 mmol, 1.00 equiv) in dry Et_2O (120 mL) which was then drop-wise added to the suspension of $LiAlH_4$ in Et_2O present in the 500 mL flask, by using cannula technique. The resulting mixture was stirred for 16 h while the temperature was allowed to rise to ambient temperature. After

the reaction mixture was carefully poured into 10.0 N NaOH (250 mL), the organic phase was separated by means of a separatory funnel, the aqueous residue was extracted twice with Et_2O (2 × 50 mL) and the organic phases were combined. *Purification process for rac-**7** without performing any column chromatography:* The combined organic phases in Et_2O were treated with aqueous HCl (37%, 3 × 100 mL). After the resulting aqueous and ethereal phases were separated by means of a separatory funnel, the aqueous phase was extracted with Et_2O (100 mL). The pH value of the aqueous phase was adjusted to 13–14 with 4.0 N NaOH and the resulting suspension was extracted with DCM (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After drying the residue under high vacuum (10^{-2} mbar) overnight, *rac*-**7** (3.0 g, 14.7 mmol, 98%) was obtained as a colorless oil in high purity for the next step. TLC: R_f = 0.36 (silica gel; hexanes/EtOAc/TEA/MeOH, 8:1.4:0.4:0.2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3440 (br), 3190 (w), 2941 (w), 1736 (s), 1699 (s), 1600 (w), 1529 (w), 1493 (w), 1285 (s), 1244 (s), 1128 (s), 1026 (s), 710 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.21 (m, 2H), 6.96 (td, J = 7.5, 1.0 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 4.05 (d, J = 2.5 Hz, 1H), 3.83 (s, 3H), 3.22 (dt, J = 12.9, 2.9 Hz, 1H), 2.06–1.99 (m, 2 H), 1.91–1.87 (m, 1H), 1.80–1.70 (m, 1H), 1.48–1.36 (m, 1H), 1.61–1.54 (m, 3H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 156.6 (C), 131.2 (C), 128.1 (CH), 127.6 (CH), 120.5 (CH), 109.9 (CH), 62.0 (CH), 55.3 (CH_3), 39.5 (CH), 30.7 (CH_2), 26.3 (CH_2), 25.0 (CH_2), 20.4 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{13}H_{20}NO$: 206.1539; found: 206.1551.

1-(2-Methoxyphenyl)cyclohexanol (9).[26] An oven-dried 500 mL three-neck round-bottom flask, capped with a glass stopper as well as equipped with a reflux condenser, a dropping funnel with a pressure equalizing arm and a magnetic stirring bar, was evacuated under heating with a blow-drier for 15 min. After the flask was cooled down to ambient temperature, dry nitrogen was back-filled and the glass stopper was replaced with a rubber septum, under a positive pressure of nitrogen. The flask was charged with magnesium turnings (2.92 g, 120.0 mmol, 1.20 equiv) and activated under heating with a blow-drier for 15 min. After the flask was cooled down to ambient temperature, a few piece small iodine crystals were added into the flask, under positive pressure of N_2 and activation process of magnesium was completed by gentle heating with a blow-drier for a very short time. After the flask was cooled down to ambient temperature, dry THF (60 mL) was added with a gas-tight syringe. A solution of *o*-bromoanisole (**8**) (20.6 g, 13.8 mL, 110.0 mmol, 1.10 equiv) in dry THF (60 mL) that was prepared by mixing them simply in the separatory funnel was drop-wise added with magnetic stirring into the reaction flask at such a rate that overheating of the reaction mixture was prevented. After the addition was completed, the mixture was refluxed for 3 h in order to drive the formation of the Grignard reagent to completion and cooled down to ambient temperature. After the reaction mixture was cooled to 0 °C in an ice-bath, a solution of cyclohexanone (9.86 g, 10.4 mL, 100.0 mmol, 1.00 equiv) in dry THF (30 mL) that was prepared in another Schlenk flask under N_2 was drop-wise added. The ice bath was removed, the resulting mixture was stirred at ambient temperature for 3 h. It was then quenched with saturated NH_4Cl solution, THF was removed removed by rotary evaporation under reduced pressure, and the aqueous residue was extracted with Et_2O (3 × 75 mL) sequentially. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 19.2 g (93 mmol, 93%) of the title compound (**9**) as a colorless oil that became a solid upon standing in time. Mp: 53–54 °C. TLC: R_f = 0.35 (silica gel; hexanes/EtOAc, 9:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3547 (s), 3445 (s), 2930 (s), 2856 (s), 1599 (s), 1582 (s), 1464 (s), 1390 (s), 1342 (w), 1230 (s), 1179 (s), 1027 (s), 967 (s), 929 (w), 906 (w), 854 (w), 753 (s), 635 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (dd, J = 7.7, 1.7 Hz, 1H), 7.25–7.19 (m, 1H), 6.95 (td, J = 7.6, 1.2 Hz, 1H), 6.92 (dd, J = 8.2, 0.9 Hz, 1H), 3.89 (s, 3H), 2.07–1.97 (m, **2H), 1.92–1.67 (m, 5H), 1.63–1.54 (m, 2H), 1.29–1.21 (m, 1H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 157.2 (C), 136.5 (C), 127.9 (CH), 125.8 (CH), 121.0 (CH), 111.4 (CH), 73.1 (C), 55.3 (CH_3), 36.7 (CH_2), 26.0 (CH_2), 22.0 (CH_2).**

1-(Cyclohexen-1-yl)-2-methoxybenzene (10).[27] A 100 mL round-bottomed flask was charged with **9** (19.2 g, 93.0 mmol, 1.00 equiv) and AcOH (18.5 mL). After the mixture was cooled in an ice-bath, H_2SO_4 (3.7 mL) was drop-wise added and it was then stirred for 3 h while the temperature was allowed to rise to ambient temperature. The reaction mixture was then quenched with a mixture of Et_2O and saturated aqueous $NaHCO_3$ solution (600 mL, 1:1, v/v), the organic phase was separated and the aqueous layer was extracted with Et_2O (2 × 150 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (3 × 150 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The residue was purified by silica gel column chromatography eluting with hexanes (100%) to afford 17.5 g (92 mmol, 99%) of the title compound (**10**) as a colorless oil. TLC: R_f = 0.60 (silica gel; hexanes, 100%). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 2929 (s), 2834 (s), 1597 (w), 1489 (s), 1435 (s), 1246 (s), 1117 (s), 1029 (s), 918 (w), 791 (w), 751 (s), 648 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (ddd, J = 8.2, 7.5, 1.8 Hz, 1H), 7.14 (dd, J = 7.4, 1.8 Hz, 1H), 6.92 (td, J = 7.4, 1.1 Hz, 1H), 6.87 (dd, J = 8.2, 0.8 Hz, 1H), 5.78 (tt, J = 3.7, 1.7 Hz, 1H), 3.82 (s, 3H), 2.39–2.35 (m, 2H), 2.23–2.18 (m, 2H), 1.79–1.68 (m, 4H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 156.2 (C), 137.1 (C), 133.4 (C), 129.1 (CH), 127.2 (CH), 125.7 (CH), 120.1 (CH), 110.3 (CH), 55.0 (CH_3), 28.4 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 21.8 (CH_2).

***trans*-2-(2-Methoxyphenyl)cyclohexylamine (*rac*-12).**[28] An oven-dried 250 mL three-neck round bottomed flask, capped with a glass stopper and equipped with a magnetic stir bar, reflux condenser and dropping funnel, was evacuated under heating with a blow-drier for 15 min and back-filled with dry nitrogen. After the flask was cooled down to room temperature, the alkene **10** (28.24 g, 27.9 mL, 150.0 mmol, 1.00 equiv), dry diglyme (75 mL), and $NaBH_4$ (2.27 g, 60.0 mmol, 0.40 equiv) were sequentially added into the flask, under positive pressure of N_2. To the cooled reaction mixture in an ice-bath was drop-wise added $BF_3{\cdot}OEt_2$ (11.71 g, 10.2 mL, 82.5 mmol, 0.55 equiv) via dropping funnel over a period of 15 minutes and it was then stirred for 3 h while the temperature was allowed to rise to ambient temperature. A solution of $H_2N\text{-}OSO_3H$ (18.7 g, 165.0 mmol, 1.10 equiv) in dry THF (100 mL) that was prepared in a 100 mL Schlenk flask under N_2 was introduced into the 250 mL flask via cannula technique over a period of 1h. The mixture was then heated to 100 °C and stirred at this temperature for 3 h. After the temperature was allowed to cool down to ambient temperature, aqueous HCl (45 mL, 37%) was drop-wise added to the reaction mixture. The mixture was poured into water (500 mL) and extracted with Et_2O (3 × 150 mL). 45 g NaOH (pellets) were portionswise added to the aqueous residue under ice-cooling, which was followed by extraction with Et_2O (3 × 150 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc/TEA/MeOH, 7:2:0.5:0.5) gave 9.24 g (50 mmol, 30%) of the title compound (*rac*-**12**) as a colorless oil. TLC: R_f = 0.62 (silica gel; hexanes/EtOAc/TEA/MeOH, 7:2:0.5:0.5). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3367 (br), 2999 (w), 2853 (s), 2054 (w), 1771 (w), 1599 (s), 1492 (s), 1361 (w), 1240 (s), 1130 (w), 1029 (s), 965 (w), 822 (w), 753 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23–7.15 (m, 2H), 6.94 (td, J = 7.5, 1.0 Hz, 1H), 6.87 (dd, J = 8.2, 0.9 Hz, 1H), 3.81 (s, 3H), 2.85 (br, 2H), 2.04–1.97 (m, 1H), 1.83–1.75 (m, 3H), 1.48–1.20 (m, 4H), 1.08 (br s, 1H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 157.7 (C), 133.0 (C), 126.9 (2 × CH, corresponds two CH groups, which was determined by HSQC NMR experiment.), 120.9 (CH), 110.7 (CH), 55.5 (CH_3), 55.5 (2 × CH, they could be determined by HSQC NMR because these ^{13}C signals had very low intensities.) 36.1 (CH_2), ca. 33.0 (CH_2, this ^{13}C peak had very low intensity

and was only be determined by HSQC NMR experiment.) 26.6 (CH_2), 25.9 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{13}H_{20}NO$: 206.1539; found: 206.1548.

(2*R*,3*R*)-2,3-Bis(benzoyloxy)butanedioic Acid (1*R*,2*R*)-2-(2-Methoxyphenyl)cyclohexylamine Salt (13). A 250 L two-necked, round-bottomed flask equipped with a magnetic stir bar and a reflux condenser was charged with dibenzoyl-L-tartaric acid (**L-DBTA**) (5.37 g, 15.0 mmol, 1.00 equiv) and distilled water (60 mL). After the resulting suspension was heated to the reflux temperature, a solution of *rac*-**7** (3.08 g, 15.0 mmol, 1.00 equiv) in 2-propanol (30 mL) was drop-wise added with vigorous stirring, during which a crystalline product precipitated. The mixture was then stirred for 2 h while the temperature was allowed to down to ambient temperature. The colorless crsytals formed were filtered off, washed with Et_2O (2 × 15 mL), and dried under reduced pressure to give the ammonium salt **13** in 45% yield (with respect to the amount of *rac*-**7**, 3.83, 6.8 mmol) and 98.6% diastereomeric excess. For the second recrystallization, the diastereomerically enriched ammonium salt **13** (98.6% *de*) was dissolved in boiling 2-propanol (20 mL) and 20 mL of distilled water were drop-wise added to the solution with vigorous stirring, whereupon crystals began to precipitate. The precipitation continued while the reaction mixture was allowed to cool down to ambient temperature, with vigorous strirring, over 2 h. The product was separated by filtration, washed with Et_2O (2 × 15 mL), and dried under reduced pressure overnight, thereby giving the diastereomerically pure ammonium salt **13** in 40% yield (3.38 g, 6.0 mmol) with respect to the amount of *rac*-**7**, as a white powder. Mp: 118–121 °C. $[\alpha]_D^{28}$ = −132 (c = 0.5, MeOH). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3580 (w), 3190 (s), 2941 (s), 2530 (w), 1736 (s), 1600 (s), 1493 (s), 1329 (s), 1266 (s), 1122 (s), 1025 (s), 852 (w), 760 (s), 709 (s). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.97–7.92 (m, 4H), 7.64–7.61 (t, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 4H), 7.29–7.20 (m, 1H), 7.16–7.08 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 5.65 (s, 2H), 3.77 (s, 3H), 3.49 (d, *J* = 2.7 Hz, 1H), 3.19 (d, *J* = 13.4 Hz, 1H), 2.13 (qd, *J* = 13.2, 3.1 Hz, 1H), 1.96 (d, *J* = 13.6 Hz, 1H), 1.74 (d, *J* = 12.3 Hz, 1H), 1.68–1.56 (m, 1H), 1.53–1.28 (m, 4H). ^{13}C NMR (APT, 125 MHz, DMSO-d_6): δ = 168.3 (C), 165.3 (C), 157.3 (C), 133.8 (C), 130.1 (C), 129.7 (CH), 129.1 (CH), 129.0 (C), 128.6 (CH), 128.1 (CH), 121.1 (CH), 111.3 (CH), 72.4 (CH_3), 55.9 (CH), 49.6 (CH), 38.1 (CH), 29.6 (CH_2), 25.8 (CH_2), 23.8 (CH_2), 19.2 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{31}H_{34}NO_9$: 564.2228; found: 564.2234.

(1*R*,2*R*)-2-(2-Methoxyphenyl)cyclohexylamine (7). The ammonium salt **13** (3.38 g, 6.0 mmol) was treated with 4.0 N NaOH solution (100 mL) and the resulting aqueous mixture was extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After drying the residue under high vacuum (10^{-2} mbar) overnight, enantiopure **7** (1.224 g, 5.96 mmol, 99% *y*, >99% *ee*) was obtained as a pale yellow oil. $[\alpha]_D^{25}$ = –92 (c = 0.5, $CHCl_3$).

(2*S*,3*S*)-2,3-Bis(benzoyloxy)butanedioic Acid (1*S*,2*S*)-2-(2-Methoxyphenyl)cyclohexylamine Salt (15). All the filtrates that were obtained during the separation of **13** were combined and organic solvents were evaporated under reduced pressure. The remaining aqueous slurry was treated with 4.0 N NaOH (100 mL) and extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo, thereby affording enantiomerically enriched *ent*-**7** (1.7 g, 8.3 mmol, 60% *ee*) as a colorless oil. It was dissolved in ^{i}PrOH (16.5 mL) and drop-wise added to a suspension of dibenzoyl-D-tartaric acid (**D-DBTA**) (2.97 g, 8.3 mmol, 1.00 equiv) in distilled water (33 mL) at reflux temperature, following the same procedure described for the separation of **13**. The mixture was then stirred for 2 h while the temperature was allowed to down to ambient temperature. The colorless crsytals formed were filtered off, washed with Et_2O (2 × 15 mL), and dried under reduced pressure to give 3.50 g of the ammonium salt **15** in 41% yield (with respect to the amount of starting *rac*-**7**, 6.21 mmol) and 93% *de*. For the second recrystallization, the diastereomerically enriched ammonium salt **15** (93% *de*) was dissolved in boiling 2-propanol (20 mL) and 20 mL of distilled water were drop-wise added to the solution with vigorous stirring, whereupon crystals began to precipitate. The precipitation continued while the reaction mixture was allowed to cool down to ambient temperature, with vigorous strirring, over 2 h. The product was separated by filtration, washed with Et_2O (2 × 15 mL), and dried under reduced pressure overnight, thereby furnishing the diastereomerically pure ammonium salt **15** in 40% yield (3.38 g, 6.0 mmol) with respect to the amount of *rac*-**7**, as a white powder. Mp: 119–122 °C. $[\alpha]_D^{28}$ = +135 (c = 0.5, MeOH). FTIR (KBr): It was determined to be identical with that of 13. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.96 (d, J = 7.9 Hz, 4H), 7.63 (t, J = 7.4 Hz, 2H), 7.50 (t, J = 7.7 Hz, 4H), 7.28 – 7.21 (m, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 5.66 (s, 2H), 3.77 (s, 3H), 3.50 (d, J = 2.5 Hz, 1H), 3.19 (d, J = 13.4 Hz, 1H), 2.13 (qd, J = 13.2, 2.9 Hz, 1H), 1.97 (d, J = 13.8 Hz, 1H), 1.74 (d, J = 12.3 Hz, 1H), 1.62 (dd, J = 12.3, 9.1 Hz, 1H), 1.52 – 1.26 (m, 4H). ^{13}C NMR (APT, 125 MHz, DMSO-d_6): δ = 168.4 (C), 165.4 (C), 157.3 (C), 133.8 (C), 130.2 (C), 129.7 (CH), 129.1 (CH), 129.0 (C), 128.6 (CH), 128.2 (CH), 121.1 (CH), 111.2 (CH), 72.7 (CH_3), 55.9 (CH), 49.6 (CH), 38.1 (CH), 29.6 (CH_2), 25.9 (CH_2), 23.8 (CH_2), 19.3 (CH_2).

(1*S*,2*S*)-2-(2-Methoxyphenyl)cyclohexylamine (*ent*-7). The ammonium salt **15** (3.38 g, 6.0 mmol) was treated with 4.0 N NaOH solution (100 mL) and the resulting aqueous mixture was extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After drying the residue under high vacuum (10^{-2} mbar) overnight, enantiopure *ent*-**7** (1.224 g, 5.96 mmol, 99% *y*, >99% *ee*) was obtained as a pale yellow oil. $[\alpha]_D^{25}$ = +90 (c = 0.5, $CHCl_3$). *Derivatization and Enantiomeric Excess Determination:* ***cis*-*N*-2-(2-Methoxyphenyl)cyclohexylbenzamide (*rac*-17).** A 50 mL one-necked, round-bottomed flask equipped with a magnetic stirr bar was charged with 205 mg of *rac*-**7** (1.0 mmol, 1.00 equiv), 12 mL of DCM, and 4 mL of 4.0 N aqueous NaOH. 163 µL of benzoyl chloride (197 mg, 1.4 mmol, 1.40 equiv) were drop-wise added with stirring, at ambient temperature. After the two-phase reaction mixture was stirred at ambient temperature for 15 min, the aqueous phase was removed by pulling with a pipette. The organic phase was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 263 mg (0.85 mmol, 85% *y*) of the title compound (*rac*-**17**) as a white solid. Mp: 150–151 °C. TLC: R_f = 0.15 (silica gel; hexanes/EtOAc, 9:1). HPLC: Daicel Chiralpak OD-H (4.60 mm ID × 250 mm column length); *n*-hexane/^{i}PrOH (85:15), 1.0 mL/min; 254 nm (UV–vis); t_R = 6.2 min (**17**), t_R = 7.3 min (*ent*-**17**). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3429 (s), 3028 (w), 2927 (s), 2873 (m), 2063 (w), 1808 (w), 1641 (s), 1577 (s), 1491 (s), 1439 (m), 1239 (s), 1100 (m), 1034 (m), 922 (m), 832 (m), 756 (s), 512 (m). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.73 (d, *J* = 9.1 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.11–7.07 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 4.47 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.78 (s, 3H), 3.27 (dt, *J* = 13.7, 3.2 Hz, 1H), 2.40–2.30 (m, 1H), 1.85–1.76 (m, 2H), 1.68–1.56 (m, 2H), 1.38–1.51 (m, 3H). ^{13}C NMR (APT, 150 MHz, DMSO-d_6): δ = 168.2 (C=O), 160.0 (C), 138.0 (C), 135.1 (C), 133.8 (CH), 131.1 (CH), 130.1 (CH), 130.0 (CH), 129.9 (CH), 123.3 (CH), 113.7 (CH), 58.4 (CH_3), 53.6 (CH), 36.6 (CH_2), 29.1 (CH_2), 28.4 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{20}H_{24}NO_2$: 310.1802; found: 310.1798. *Determination of the diastereomeric excesses of the **13** and **15** could be carried out as described as follows:* The separated salt **13** or **15** (500 mg, 0.89 mmol, 1.00 equiv) was mixed with 12 mL of DCM and 4 mL of 4.0 N aqueous NaOH solution with stirring, in a flask. Benzoyl chloride (120 µL, 1.03 mmol, 1.40 equiv) was added to the two-phase mixture, with stirring, at ambient temperature. After the mixture was stirred at ambient temperature for 15 min, the aqueous upper phase was removed by pulling with a pipette. The

organic phase was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 185 mg (0.60 mmol, 85% *y*) of the benzamide derivative **17** or *ent*-**17** as a white solid.

(2*R*,3*R*)-2,3-Bis(benzoyloxy)butanedioic Acid (1*S*,2*R*)-2-(2-Methoxyphenyl)cyclohexylamine Salt (18). A solution of dibenzoyl-L-tartaric acid (**L-DBTA**) (19.35 g, 54.0 mmol, 1.00 equiv) in EtOAc (150 mL) was added to a solution of *rac*-**12** (11.1 g, 54.0 mmol, 1.00 equiv) in EtOAc (150 mL) with stirring and the homogeneous mixture was stirred at ambient temperature for 15 min. The solvent was removed by rotary evaporation in vacuo. The residue consisting of the ammonium salts **18** and **19** was then suspended in acetone (300 mL). Upon heating at reflux temperature with stirring, complete dissolution was observed. MeOH (170 mL) was drop-wise added to the homogeneous solution at reflux temperature, whereupon the homogeneous mixture became turbid. The mixture was then stirred for 2 h with vigorous stirring as the temperature was allowed to down to ambient temperature. The precipitated salt was isolated by filtration, washed with Et_2O (2 × 15 mL), and and dried under reduced pressure overnight. The diastereomerically pure ammonium salt **18** was obtained in 36% yield (10.96 g, 19.44 mmol) as a white powder. Mp: 179–180 °C. $[\alpha]_D^{22}$ = −64 (c = 0.5, MeOH). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = It was determined to be identical with that of reported for **13**. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.95 (d, *J* = 7.3 Hz, 4H), 7.63 (t, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 4H), 7.24–7.20 (m, 2H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.90 (t, *J* = 6.5 Hz, 1H), 5.66 (s, 2H), 3.76 (s, 3H), 3.39–3.34 (m, 1H), 2.93 (br, 1H), 2.04 (br s, 1H), 1.65–1.62 (m, 3H), 1.54–1.13 (m, 4H). ^{13}C NMR (APT, 150 MHz, DMSO-d_6): δ = 170.9 (C), 168.0 (C), 160.3 (C), 136.5 (CH), 132.8 (C), 132.3 (CH), 131.8, 131.1 (CH), 123.9 (CH), 114.5 (CH), 75.1 (CH), 58.5 (CH_3), 33.9 (CH_2), 33.8 (CH), 28.4 (CH_2), 27.1 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{31}H_{34}NO_9$: 564.2228; found: 564.2234.

(1*S*,2*R*)-2-(2-Methoxyphenyl)cyclohexylamine (12). The ammonium salt **18** (10.96 g, 19.44 mmol) was treated with 4.0 N NaOH solution (100 mL) and the resulting aqueous mixture was extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After drying the residue under high vacuum (10^{-2} mbar) overnight, enantiopure **12** (3.94 g, 19.2 mmol, 99% *y*, >99% *ee*) was obtained as a colorless oil. $[\alpha]_D^{23}$ = +48 (c = 0.5, $CHCl_3$).

(2*S*,3*S*)-2,3-Bis(benzoyloxy)butanedioic Acid (1*R*,2*S*)-2-(2-Methoxyphenyl)cyclohexylamine Salt (20). All the filtrates that were saved during the separation of **18** were combined and organic solvents such as MeOH, acetone, and Et_2O were evaporated under reduced pressure. The residue was treated with 100 mL of 4.0 N NaOH and extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo, thereby affording enantiomerically enriched *ent*-**12** (7.15 g, 34.8 mmol, 65% *y*) as a colorless oil. A 250 mL one-necked, round-bottomed flask equipped with a magnetic stir bar was charged with *ent*-**12** (7.15 g, 34.8 mmol, 1.00 equiv) and EtOAc (97 mL). A solution of dibenzoyl-D-tartaric acid (**D-DBTA**) (12.47 g, 34.8 mmol, 1.00 equiv) in EtOAc (97 mL) was added with stirring in one portion and the resulting homogeneous mixture was stirred at ambient temperature for 15 min. The solvent was removed by rotary evaporation in vacuo. The residue consisting of the ammonium salts **20** and **21** was then suspended in acetone (198 mL). Upon heating at reflux temperature with stirring, complete dissolution was observed. MeOH (130 mL) was drop-wise added to the solution at reflux temperature, whereupon the homogeneous mixture became turbid. The mixture was then stirred for 2 h with vigorous stirring as the temperature was allowed to down to ambient temperature. The precipitated salt was isolated by filtration, washed with Et_2O (2 × 15 mL), and and dried under reduced pressure overnight. The diastereomerically pure ammonium salt **20** was obtained in 41% yield (12.47 g, 22.1 mmol), with respect to the molar amount of the starting *rac*-**12**, as a white powder. Mp: 179–180 °C. $[\alpha]_D^{21}$ = +78 (c = 0.5, MeOH). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.98–7.94 (m, 4H), 7.66–7.62 (m, 2H), 7.51 (t, *J* = 7.8 Hz, 4H), 7.24–7.15 (m, 2H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 7.3 Hz, 1H), 5.67 (s, 2H), 3.77 (s, 3H), 3.34 (t, *J* = 9.4 Hz, 1H), 2.93 (s, 1H), 2.04 (t, *J* = 11.5 Hz, 2H), 1.77 (s, 1H), 1.63 (d, *J* = 10.6 Hz, 4H), 1.47 (d, *J* = 9.7 Hz, 1H), 1.38–1.15 (m, 3H). ^{13}C NMR (APT, 150 MHz, DMSO-d_6): δ = 168.4 (C), 165.4 (C), 157.7 (C), 133.8 (CH), 130.1 (C), 129.7 (CH), 129.1 (CH), 128.5, 121.2 (CH), 111.9 (CH), 72.6 (CH), 55.8 (CH_3), 31.2 (CH_2), 31.1 (CH), 25.8 (CH_2), 24.5 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{31}H_{34}NO_9$: 564.2228; found: 564.2234.

(1*R*,2*S*)-2-(2-Methoxyphenyl)cyclohexylamine (*ent*-12). The ammonium salt **20** (12.47 g, 22.1 mmol) was treated with 4.0 N NaOH solution (100 mL) and the resulting aqueous mixture was extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After drying the residue under high vacuum (10^{-2} mbar) overnight, enantiopure *ent*-**12** (3.59 g, 21.9 mmol, 99% *y*, >99% *ee*) was obtained as a colorless oil. $[\alpha]_D^{25}$ = −44 (c = 0.5, $CHCl_3$). *Derivatization and Enantiomeric Excess Determination:* ***trans*-*N*-2-(2-Methoxyphenyl)cyclohexylbenzamide (*rac*-22).** *rac*-**22** was prepared from *rac*-**12**, by following the same procedure that was described for the synthesis of *rac*-**17**. Mp: 145–146 °C. TLC: R_f = 0.23 (silica gel; hexanes/EtOAc, 9:1). HPLC: Daicel Chiralcel OD-H (4.60 mm ID × 250 mm column length); *n*-hexane/^{i}PrOH (85:15), 1.0 mL/min; 254 nm (UV–vis); t_R = 7.4 min (*ent*-**22**), t_R = 8.2 min (**22**). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3345 (m), 3288 (m), 2915 (m), 2833 (w), 1629 (s), 1558 (m), 1492 (s), 1325 (m), 1243 (s), 1098 (m), 1027 (m), 870 (w), 750 (m), 695 (m). ^{1}H NMR(600 MHz, DMSO-d_6): δ = 7.96 (d, *J* = 8.9 Hz, 1H), 7.60–7.55 (m, 2H), 7.44–7.39 (m, 1H), 7.36–7.32 (m, 2H), 7.20 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.09–7.05 (m, 1H), 6.88 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.80 (td, *J* = 7.5, 0.9 Hz, 1H), 4.23 (d, *J* = 8.7 Hz, 1H), 3.78 (s, 3H), 3.22–3.11 (m, 1H), 1.96–1.90 (m, 1H), 1.87–1.75 (m, 2H), 1.72 (d, *J* = 12.0 Hz, 1H), 1.53–1.25 (m, 4H). ^{13}C NMR (APT, 150 MHz, DMSO-d_6): δ = 165.1 (C=O), 156.9 (C), 134.9 (C), 132.0 (C), 130.7 (CH), 128.0 (CH), 127.0 (CH), 126.8 (CH), 120.2 (CH), 110.5 (CH), 55.3 (CH_3), 50.4 (CH), 33.5 (CH_2), 26.00 (CH_2), 25.3 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{20}H_{24}NO_2$: 310.1802; found: 310.1800. *Determination of the diastereomeric excesses of the **18** and **20** was carried out by following the procedure that was described for **13** and **15** above.*

***N*-[(1*R*,2*R*)-2-(2-Methoxyphenyl)cyclohexyl]-*N*-benzylamine (24).** An oven-dried 25 mL Schlenk flask equipped with a magnetic stir bar was charged with the enantiopure amine **7** (410 mg, 2.0 mmol, 1.00 equiv). The flask was capped with a glass stopper, evacuated for 15 min, and back-filled with dry N_2. Dry DCM (10 mL), anhydrous MgSO4, and benzaldehyde (205 µL, 212 mg, 2.0 mmol, 2.00 equiv) were added sequentially and the resulting heterogeneous mixture was stirred at ambient temperature for 16 hours. The mixture was then filtered, the solid was washed with DCM (3 × 10 mL), the filtrate was concentrated by rotary evaporation in vacuo, thus delivering a light yellow oil which was employed in the next step directly. The intermediate **23** was not subjected to column chromatography because it was rapidly decomposed on silica gel. Thereafter, the crude **23** (ca. 590 mg, 2.0 mmol, 1.00 equiv) was taken into an oven-dried 25 mL Schlenk tube and it was then evacuated for 15 minutes. After dry nitrogen was back-filled and the glass stopper was replaced with a rubber septum under a positive pressure of nitrogen, dry MeCN (14 mL) was added.The resulting solution was cooled in an ice-bath and $NaBH_3CN$ (250 mg, 4.0 mmol, 2.00 equiv) were added to the solution in one portion under positive pressure of N_2. The resulting mixture was stirred for 15 minutes in the ice-bath. After AcOH (460 µL, 8.0 mmol, 4.00 equiv) was drop-wise added at 0 °C, the mixture was stirred for 2 h while the temperature was allowed to rise to ambient temperature. After diluting with 50 mL of a DCM–MeOH mixture (DCM/MeOH, 49:1, v/v), it was extracted with 1.0 N NaOH (2 × 50

mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification by flash column chromatography (silica gel, hexanes/EtOAc/TEA, 9:0.8:0.2) afforded 537 mg (1.82 mmol, 91%) of the title compound (**24**) as a colorless oil. TLC: R_f = 0.27 (silica gel; hexanes/EtOAc/TEA, 9:0.8:0.2). $[\alpha]_D^{28}$ = −176 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3436 (br), 2929 (s), 2853 (s), 1599 (w), 1491 (s), 1627 (s), 1289 (w), 1238 (s), 1103 (w), 1030 (s), 786 (w), 753 (s), 698 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 – 7.09 (m, 5H), 6.96 – 6.89 (m, 3H), 6.82 – 6.78 (m, 1H), 3.67 (s, 3H), 3.63 (d, J = 13.9 Hz, 1H), 3.36 (d, J = 13.9 Hz, 1H), 3.23 (dt, J = 13.2, 3.0 Hz, 1H), 3.03 (d, J = 2.9 Hz, 1H), 2.14 (qd, J = 12.8, 3.5 Hz, 1H), 1.95 – 1.86 (m, 2H), 1.78 – 1.66 (m, 1H), 1.55 – 1.35 (m, 4H), 1.21 (s, 1H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 157.1 (C), 141.3 (C), 132.7 (C), 128.0 (CH), 127.9 (CH), 127.7 (CH), 126.9 (CH), 126.2 (CH), 120.2 (CH), 110.2 (CH), 55.1 (CH_3), 53.2 (CH), 51.4 (CH_2), 40.5 (CH), 29.7 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 20.0 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{20}H_{26}NO$: 296.2009; found: 296.1981.

(1*R*,2*R*)-*N*,*N*-Dimethyl-2-(2-methoxyphenyl)cyclohexylamine (25). An oven-dried 25 mL Schlenk flask equipped with a magnetic stir bar was charged with the enantiopure amine **7** (410 mg, 2.0 mmol, 1.00 equiv). The flask was capped with a glass stopper, evacuated for 15 min, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of N_2. Dry MeCN (10 mL), 745 µL of 37% aqueous formaldehyde (10.0 mmol HCHO, 5.00 equiv) were added sequentially and the resulting mixture was stirred at ambient temperature for 15 minutes. After $NaBH_3CN$ (250 mg, 4.0 mmol, 2.00 equiv) was added to the reaction mixture, the resulting mixture was stirred for 15 minutes at ambient temperature. Finally, AcOH (570 µL, 10.0 mmol, 5.00 equiv) was added into the Schlenk tube and the mixture was stirred at ambient temperature for 2 hours. After diluting with 50 mL of the DCM–MeOH mixture (DCM/MeOH, 49:1, v/v), it was extracted with 1.0 N NaOH (2 × 50 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification by flash column chromatography on silica gel by applying gradient elution (the first eluent: hexanes/EtOAc, 9:1 (750 mL); the second eluent: hexanes/EtOAc/TEA, 9:0.8:0.2) gave 392 mg (1.7 mmol, 84%) of the title compound (**25**) as a colorless oil. TLC: R_f = 0.22 (silica gel; hexanes/EtOAc/TEA, 9:0.8:0.2). $[\alpha]_D^{28}$ = +6 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3430 (br), 2935 (s), 2762 (s), 1599 (s), 1490 (s), 1366 (w), 1341 (w), 1290 (w), 1238 (s), 1109 (w), 1038 (s), 888 (w), 749 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.15 (td, *J* = 8.0, 1.6 Hz, 1H), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (dd, *J* = 8.1, 0.8 Hz, 1H), 3.53 (dt, *J* = 6.5, 4.3 Hz, 1H), 3.82 (s, 3H), 2.43 (dt, *J* = 8.7, 4.3 Hz, 1H), 2.06 (s, 6H), 2.03–1.92 (m, 2H), 1.90–1.75 (m, 2H), 1.66–1.58 (m, 1H), 1.56–1.47 (m, 1H), 1.47–1.34 (m, 2H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 157.1 (C), 133.2 (C), 129.8 (CH), 126.4 (CH), 120.0 (CH), 110.2 (CH), 65.7 (CH), 55.3 (CH_3), 44.6 (CH_3), 36.7 (CH), 29.4 (CH_2), 28.7 (CH_2), 24.1 (CH_2), 23.0 (CH_2). HRMS (ESI): ($[M+H]^+$) calcd for $C_{15}H_{24}NO$: 234.1852; found: 234.1841.

General Procedure I (Demethylation of Anisoles): 2-[(1′*R*,2′*R*)-2′-Aminocyclohexyl]phenol (1). An oven-dried 50 mL Schlenk tube equipped with a magnetic stir bar was charged with the enantiopure amine **7** (1.03 g, 5.0 mmol, 1.00 equiv). The tube was capped with a glass stopper, evacuated for 15 min, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of N_2. Dry DCM (30 mL) was added to the tube by means of syringe and the resulting mixture was cooled in an ice-bath. Boron tribromide (1.45 mL, 3.76 g, 15.0 mmol, 3.00 equiv) was drop-wise added to the ice-cooled mixture and it was stirred for 6 hours while the temperature was allowed to rise to ambient temperature. The pH value of the reaction mixture was adjusted to 9–9.5, by a drop-wise addition of an aqueous saturated $NaHCO_3$ solution. The organic phase separated and the aqueous phase was shaken with DCM (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The crude product was dissolved with Et_2O (75 mL) and it was extracted with 5% HCl (3 × 50 mL). The combined aqueous fractions were again extracted with Et_2O (75 mL). After the pH value of the aqueous phase was adjusted to 9–9.5 with 4.0 N NaOH, the resulting suspension was extracted with DCM (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After drying the residue under high vacuum (10^{-2} mbar) overnight, the title compound (**1**) (0.94 g, 4.9 mmol, 98% *y*, >99% *ee*) was obtained as a colorless solid. Mp: 153–156 °C. TLC: R_f = 0.15 (silica gel; hexanes/EtOAc/TEA/MeOH, 8:1.4:0.4:0.2). $[\alpha]_D^{25}$ = +36 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3343 (w), 3064 (w), 2931 (s), 2573 (w), 1890 (w), 1597 (s), 1453 (s), 1277 (s), 1247 (s), 1137 (w), 1047 (w), 984 (w), 959 (w), 837 (w), 753 (s), 459 (w). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.01–6.90 (m, 2H), 6.63 (ddd, *J* = 8.6, 7.8, 1.1 Hz, 2H), 5.93 (br, 2H), 3.21 (d, *J* = 2.6 Hz, 1H), 2.74 (dt, *J* = 12.9, 2.8 Hz, 1H), 2.07 (qd, *J* = 12.8, 3.3 Hz, 1H), 1.80–1.57 (m, 4H), 1.48–1.25 (m, 3H). ^{1}H NMR (500 MHz, $CDCl_3$): δ =7.10 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 6.97 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.74 (td, *J* = 7.4, 1.3 Hz, 1H), 3.45 (d, *J* = 2.7 Hz, 1H), 2.65 (dt, *J* = 13.0, 3.0 Hz, 1H), 2.19 (ddd, *J* = 26.5, 13.0, 3.7 Hz, 1H), 1.91–1.84 (m, 1H), 1.84–1.75 (m, 1H), 1.73–1.63 (m, 2H), 1.60–1.39 (m, 3H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 156.7(C), 131.5 (CH), 131.0 (C), 128.2 (CH), 119.1 (CH), 118.7 (CH), 52.0 (CH), 50.4 (CH), 34.5 (CH_2), 26.6 (CH_2), 24.9 (CH_2), 19.1 (CH_2). HRMS (ESI): ($[M+H]^+$) cald for $C_{12}H_{18}NO$: 192.1383; found: 192.1386. X-ray structural data of **1** (**CCDC 1848756**): Colorless crystals of **1**, suitable for X-ray crystallography, were obtained by crystallization from MeOH. $C_{12}H_{17}NO$; formula weight 191.27; crystal size 0.05 × 0.06 × 0.48 mm; crystal system hexagonal; space group $P\,6_1$; unit cell dimensions a = 16.5654(18) Å, b = 16.5654(18) Å, c = 7.7871(13) Å; α = 90°, β = 90°, γ = 120°; Z = 6; D_{calcd} 1.030 g cm^{-3}; absorption coefficient 0.065 mm; wavelength 0.71073 Å; T = 173(2) K; θ range for data collection = 2.98 to 25.00°; 9384/1990 collected/unique reflections (R(int) = 0.1918); final R indices [I > 2σ(I)] R_1 = 0.0858, wR_2 = 0.1792; R indices (all data) R_1 = 0.1882, wR_2 = 0.2154; largest diff. peak and hole 0.192 and −0.235 e $Å^{-3}$.

2-[(1′*S*,2′*S*)-2′-Aminocyclohexyl]phenol (*ent*-1). Mp: 153–156 °C. TLC: R_f = 0.38 (silica gel; hexanes/EtOAc/TEA/MeOH, 4:0.8:0.3:0.3). $[\alpha]_D^{25}$ = −36 (c = 0.5, $CHCl_3$).

2-[(1′*R*,2′*S*)-2′-Aminocyclohexyl]phenol (2). Following the general procedure I as described above, 2-[(1′*R*,2′S)-2-aminocyclohexy]phenol (**12**) (821 mg, 4.0 mmol, 1.00 equiv) was treated with BBr_3 (1.15 mL, 3.0 g, 12.0 mmol, 3.00 equiv) in 20 mL DCM in an ice-bath. The temperature allowed to rise to ambient temperature as the mixture was stirred for 6 h under N_2. The pH value was adjusted to 9–9.5, by drop-wise addition of an aqueous saturated $NaHCO_3$ solution. The organic phase separated and the aqueous phase was shaken with DCM (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc/TEA/MeOH, 3:1:0.5:0.5) afforded 500 mg (2.6 mmol, 65%) of the title compound (**2**) as a colorless solid. Mp: 177–178 °C. TLC: R_f = 0.49 (silica gel; hexanes/EtOAc/TEA/MeOH, 3:1:0.5:0.5). $[\alpha]_D^{23}$ = −72 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3343 (w), 3064 (w), 2931 (s), 2573 (w), 1890 (w), 1597 (s), 1453 (s), 1277 (s), 1247 (s), 1137 (w), 1047 (w), 984 (w), 959 (w), 837 (w), 753 (s), 459 (w). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.09 (dd, J = 7.6, 1.5 Hz, 1H), 6.98 (td, J = 7.9, 1.6 Hz, 1H), 6.75 (ddd, J = 15.0, 7.8, 1.1 Hz, 2H), 4.32 (s, 2H), 2.74 (td, J = 10.6, 3.9 Hz, 1H), 2.67 – 2.60 (m, 1H), 1.91 – 1.85 (m, 1H), 1.74 – 1.68 (m, 2H), 1.66 – 1.61 (m, 1H), 1.42 (tt, J = 12.7, 6.2 Hz, 1H), 1.36 – 1.17 (m, 3H). ^{13}C NMR (APT, 150 MHz, DMSO-d_6): δ = 155.8 (C), 131.3 (C), 127.0 (CH), 126.5 (CH), 119.0 (CH), 115.8 (CH), 54.0 (CH), 45.5 (CH), 36.0 (CH_2), 32.1 (CH_2), 26.2 (CH_2), 25.4 (CH_2). HRMS (ESI): ($[M+H]^+$) cald for $C_{12}H_{18}NO$: 192.1383; found: 192.1388. X-ray structural data of **2** (**CCDC 1848757**): Colorless crystals of **2**, suitable for X-ray crystallography, were obtained by crystallization

from benzene. $C_{12}H_{17}NO$; formula weight 191.27; crystal size 0.12 × 0.15 × 0.50 mm; crystal system monoclinic; space group $P\ 2_1$; unit cell dimensions a = 7.5222(5) Å, b = 7.0571(5) Å, c = 10.4522(7) Å; α = 90°, β = 95.961(4)°, γ = 90°; Z = 2; D_{calcd} 1.151 g cm^{-3}; absorption coefficient 0.073 mm; wavelength 0.71073 Å; T = 300(2) K; θ range for data collection = 1.96 to 25.00°; 7973/1922 collected/unique reflections (R(int) = 0.1478); final R indices [I > 2σ(I)] R_1 = 0.0561, wR_2 = 0.1485; R indices (all data) R_1 = 0.0609, wR_2 = 0.1521; largest diff. peak and hole 0.268 and −0.208 e Å^{-3}.

2-[(1′*S*,2′*R*)-2′-Aminocyclohexyl]phenol (*ent*-2). Mp: 177–178 °C. TLC: R_f = 0.49 (silica gel; hexanes/EtOAc/TEA/MeOH, 3:1:0.5:0.5). $[\alpha]_D^{23}$ = +72 (c = 0.5, $CHCl_3$).

2-[(1′*R*,2′*R*)-2′-Benzylaminocyclohexyl]phenol (26). Following the general procedure I as described above, **24** (295 mg, 1.0 mmol, 1.00 equiv) was treated with BBr_3 (290 µL, 752 mg, 3.00 mmol, 3.00 equiv) in 10 mL DCM in an ice-bath. The temperature allowed to rise to ambient temperature as the mixture was stirred for 6 h under N_2. The pH value was adjusted to 9–9.5, by drop-wise addition of of an aqueous saturated $NaHCO_3$ solution. The organic phase separated and the aqueous phase was shaken with DCM (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (Hexanes/EtOAc/TEA, 9:0.8:0.2) afforded 210 mg (0.75 mmol, 75%) of the title compound (**26**) as a colorless oil. TLC: R_f = 0.29 (silica gel; hexanes/EtOAc/TEA, 9:0.8:0.2). $[\alpha]_D^{28}$ = −94 (c = 0.5, $CHCl_3$). ^{1}H NMR(500 MHz, $CDCl_3$): δ = 13.51 (br, 1H), 7.41–7.31 (m, 4H), 7.31–7.25 (m, 1H), 7.11 (ddd, J = 8.0, 7.3, 1.7 Hz, 1H), 6.96 (dd, J = 7.5, 1.7 Hz, 1H), 6.89 (dd, J = 8.0, 1.2 Hz, 1H), 6.72 (td, J = 7.4, 1.3 Hz, 1H), 3.84–3.70 (m, 2H), 3.19 (d, J = 2.4 Hz, 1H), 2.66 (dt, J = 13.0, 3.0 Hz, 1H), 2.12–2.04 (m, 1H), 1.92–1.79 (m, 2H), 1.69–1.53 (m, 3H), 1.50–1.32 (m, 2H). ^{13}C NMR(APT, 125 MHz, $CDCl_3$): δ = 157.1 (C), 138.0 (C), 131.5 (CH), 130.8 (C), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.8 (CH), 118.8 (CH), 118.5 (CH), 57.4 (CH), 53.1 (CH_2), 51.9 (CH), 29.6 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 19.8 (CH_2). HRMS (ESI): ([M+H]$^+$) calcd for $C_{19}H_{24}NO$: 282.1852; found: 282.1860.

2-[(1′*R*,2′*R*)-2′,2′-Dimethylaminocyclohexyl]phenol (27). Following the general procedure I as described above, **25** (233 mg, 1.0 mmol, 1.00 equiv) was treated with BBr_3 (290 µL, 752 mg, 3.00 mmol, 3.00 equiv) in 10 mL DCM in an ice-bath. The temperature allowed to rise to ambient temperature as the mixture was stirred for 6 h under N_2. The pH value was adjusted to 9–9.5, by the drop-wise addition of of an aqueous saturated $NaHCO_3$ solution. The organic phase separated and the aqueous phase was shaken with DCM (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc/TEA, 9:0.8:0.2) afforded 200 mg (0.91 mmol, 91%) of the title compound (**27**) as a colorless oil. TLC: R_f = 0.19 (silica gel; hexanes/EtOAc/TEA, 9:0.8:0.2). $[\alpha]_D^{28}$ = −10 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 2933 (s), 2600 (br), 1843 (br), 1605 (s), 1472 (s), 1236 (s), 1104 (w), 1029 (s), 974 (s), 881 (s), 834 (w), 752 (s), 563 (w), 526 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (dd, J = 7.7, 0.7 Hz, 1H), 7.11–7.06 (m, 1H), 6.84 (dd, J = 8.0, 1.3 Hz, 1H), 6.77 (td, J = 7.7, 1.4 Hz, 1H), 3.55 (dd, J = 8.1, 4.0 Hz, 1H), 2.70 (ddd, J = 11.5, 4.7, 3.4 Hz, 1H), 2.30 (s, 6H), 2.27 (ddd, J = 7.1, 4.6, 2.8 Hz, 1H), 1.91–1.83 (m, 1H), 1.82–1.72 (m, 2H), 1.66–1.52 (m, 2H), 1.51–1.44 (m, 1H), 1.43–1.32 (m, 1H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 158.1 (C), 129.6 (CH), 127.9 (C), 127.6 (CH), 118.6 (CH), 118.3 (CH), 68.1 (CH), 42.5 (CH_3), 40.5 (CH), 31.2 (CH_2), 26.1 (CH_2), 23.5 (CH_2), 22.4 (CH_2). HRMS (ESI): ([M+H]$^+$) calcd for $C_{14}H_{22}NO$: 220.1696; found: 220.1703.

(1*R*,2*R*)-*N*,*N*-Dimethyl-*N*-benzyl-2-(2'-hydroxyphenyl)cyclohexylammonium bromide (28). An oven-dried 25 mL Schlenk tube was charged with **27** (439 mg, 2.0 mmol, 1.00 equiv). The tube was for 15 minutes and back-filled with N_2. Dry MeCN (10 mL) and benzyl bromide (1.19 mL, 1.71 g, 10.0 mmol, 5.00 equiv) were added sequentially and the resulting mixture was refluxed at 90 °C for 24 h. The precipitate was filtered off, washed with EtOAc (2 × 5 mL), and dried under high vacuum (10^{-2} mbar) overnight, thereby furnishing the title compound **28** (508 mg, 1.3 mmol, 65%) as a colorless solid. Mp: 212–214 °C. TLC: R_f = 0.23 (silica gel; $CHCl_3$/MeOH, 9:1). $[\alpha]_D^{28}$ = +26 (c = 0.5, MeOH). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3056 (s), 2937 (s), 2660 (w), 2526 (w), 240a4 (w), 1599 (s), 1498 (s), 1454 (s), 1336 (s), 1262 (s), 1214 (s), 1097 (s), 998 (s), 964 (w), 858 (s), 765 (s), 727 (s), 670 (w), 641 (w), 515 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.71 (br s, 1H), 7.76 (dd, J = 8.2, 1.1 Hz, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.35–7.29 (m, 3H), 7.29–7.26 (m, 2H), 7.20–7.14 (m, 1H), 6.88–6.81 (m, 1H), 4.87 (d, J = 12.5 Hz, 1H), 4.73–4.58 (m, 3H), 2.86 (s, 3H), 2.67 (s, 3H), 2.36–2.28 (m, 2H), 2.20 (d, J = 9.5 Hz, 1H), 2.12–2.04 (m, 1H), 1.93–1.77 (m, 2H), 1.73 (d, J = 13.5 Hz, 1H), 1.54 (d, J = 9.9 Hz, 1H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 154.4 (s), 133.3 (CH), 130.3 (CH), 130.3 (CH), 129.1 (CH), 128.8 (CH), 127.3 (C), 126.4 (C), 119.9 (CH), 118.2 (CH), 65.3 (CH_2), 47.8 (CH_3), 46.8 (CH_3), 32.8 (CH_2), 29.7 (CH), 25.5 (CH_2), 21.7 (CH_2), 19.1 (CH_2). HRMS (ESI): ([M−Br+H]$^+$) calcd for $C_{21}H_{29}BrNO$: 390.1427, found: 310.2067.

(*R*)-2-[2'-(3'',5''-di-*tert*-butyl-2''-methoxyphenyl)-1'-phenylethyl]isoindoline-1,3-dione (30). A 1 L, round-bottomed, oven-dried Schlenk flask equipped with a magnetic stir bar was charged with (*S*)-(−)-2-(3,5-di-*tert*-butyl-2-methoxyphenyl)-1-phenylethanol (**29**) (3.4 g, 10.0 mmol, 1.00 equiv), triphenylphosphine (PPh_3, 10.5 g, 40.0 mmol, 4.00 equiv) and phthalimide (PhthNH, 4.4 g, 30.0 mmol, 3.00 equiv). The reaction flask was evacuated for 15 minutes and back-filled with dry N_2 and its content was dissolved by the addition of dry THF (400 mL). Diisopropyl azodicarboxylate (DIAD, 7.9 mL, 8 g, 40.0 mmol, 4.00 equiv) was drop-wise added to the ice-cooled reaction mixture. The mixture was then stirred for 16 h while the temperature was allowed to rise to ambient temperature. Purification by flash column chromatography (silica gel; Hexane/EtOAc, 9:1) afforded 3.52 g (7.5 mmol, 75%) of the title compound (**30**) as a colorless oil. TLC: R_f = 0.26 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{22}$ = +140 (c = 0.5, $CHCl_3$). HPLC: Daicel Chiralpak AD-H (4.60 mm ID × 250 mm column length); *n*-hexane/^{i}PrOH (98:2), 0.5 mL/min; 254 nm (UV–vis); t_R = 17.1 min (*ent*-**30**), t_R = 19.4 min (**30**). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 2959 (br), 1771 (s), 1713 (s), 1603 (m), 1478 (s), 1386 (s), 1331 (s), 1229 (s), 1158 (m), 1124 (s), 1087 (s), 1010 (s), 883 (m), 757 (s), 720 (s), 667 (w), 530 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78–7.72 (m, 2H), 7.68–7.60 (m, 4H), 7.41–7.34 (m, 2H), 7.33–7.28 (m, 1H), 7.15 (td, J = 8.1, 1.7 Hz, 1H), 7.09 (dd, J = 7.4, 1.5 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.74 (td, J = 7.4, 0.9 Hz, 1H), 5.85 (dd, J = 10.9, 5.1 Hz, 1H), 3.93 (dd, J = 13.5, 10.9 Hz, 1H), 3.84 (s, 3H), 3.61 (dd, J = 13.5, 5.1 Hz, 1H). ^{13}C NMR (APT, 125 MHz, $CDCl_3$): δ = 168.3 (C), 157.8 (C), 139.9 (C), 133.8 (CH), 131.8 (C), 130.8 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 127.7 (C), 126.4 (C), 123.1 (CH), 120.3 (CH), 110.3 (CH), 55.3 (CH_3), 54.1 (CH), 32.4 (CH_3). HRMS: ([M+H]$^+$) calcd for $C_{31}H_{36}NO_3$: 470.2690, found: 470.2668.

(*R*)-2-(3',5'-di-*tert*-butyl-2'-methoxyphenyl)-1-phenylethan-1-amine (31). A 250 mL, round-bottomed, oven-dried Schenk flask equipped with a magnetic stir bar was charged with **30** (2.82 g, 6.0 mmol, 1.00 equiv) and capped wih a glass stopper. The flask was evacuated for 15 min and back-filled with N_2. After addition of ethanol (90 mL) as the solvent, hydrazine hydrate ($H_2NNH_2{\cdot}H_2O$) (2.9 mL, 3 g, 60.0 mmol, 10.00 equiv) was drop-wise added into the flask, under a positive pressure of N_2. The reaction mixture was then heated to 90 °C and stirred at this temperature for 6 h. After the reaction mixture was cooled to the room temperature, diethyl ether (50 mL) was added to the mixture and it was filtered in order to separate from the white precipitate. The filtrate was dried over Na_2SO_4,

filtered, and concentrated by rotary evaporation in vacuo. This procedure was repeated one more time. Thus, the title compound **31** (1.41 g, 4.15 mmol, 69%) was obtained as a colorless solid. Mp: 85–86 °C. TLC: R_f = 0.25 (silica gel; hexanes/EtOAc/TEA, 9.2:0.4:0.4). $[\alpha]_D^{26}$ = −4 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3370 (s), 3305 (w), 2962 (s), 2862 (s), 1989 (w), 1951 (w), 1728 (w), 1589 (m), 1361 (s), 1224 (s), 1111 (s), 1000 (s), 844 (s), 756 (s), 697 (s). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.25–7.18 (m, 2H), 6.92 (d, *J* = 1.9 Hz, 1H), 4.28 (dd, *J* = 8.3, 5.4 Hz, 1H), 3.79 (s, 3H), 3.01 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.94 (dd, *J* = 13.6, 8.6 Hz, 1H), 1.63 (br, 2H), 1.40 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.3 (C), 146.2 (C), 145.5 (C), 141.9 (C), 131.7 (C), 128.4 (CH), 126.9 (CH), 126.5 (CH), 126.4 (CH), 122.6 (CH), 61.6 (CH_3), 56.5 (CH), 42.0 (CH_2), 35.26 (C), 34.34 (C), 31.46 (CH_3), 31.23 (CH_3). HRMS: ([M+H]$^+$) calcd for $C_{23}H_{34}NO$: 340.2635, found: 340.2627.

(*R*)-*N*-[2-(3',5'-di-*tert*-butyl-2'-hydroxyphenyl)-1-phenyl]ethylformamide (32). An oven-dried 50 mL Schlenk tube, capped with a glass stopper and equipped with a magnetic stir bar, was evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of dry N_2. Dry DMF (7.5 mL) and EtSH (881 µL, 732 mg, 11.78 mmol, 8.00 equiv) were mixed in the tube. To the cooled reaction mixture in an ice-bath was added NaO^{t}Bu (423 mg, 4.41 mmol, 3.00 equiv) at once and it was stirred at 0 °C for 30 minutes. Then, the anisole **31** (500 mg, 1.47 mmol, 1.00 equiv) was added into the Schlenk tube at 0 °C and the reaction tube was heated to 120 °C and stirred at this temperature for 3 hours. Conversion of the starting material **31** was followed by TLC. After cooling down to 0 °C, pH value of the reaction mixture was adjusted to 9–10, by the addition of 1.0 N HCl. The organic components were extracted with Et_2O (3 × 75 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc, 7:3) gave 407 mg (1.15 mmol, 78%) of the title compound (**32**) as a colorless solid. Mp: 68–70 °C. TLC: *Rf* = 0.41 (silica gel; hexanes/EtOAc, 7:3). $[\alpha]_D^{26}$ = +28 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3297 (br s), 2958 (s), 2869 (m), 1646 (br,s), 1525 (m), 1480 (s), 1362 (s), 1221 (s), 1121 (w), 879 (w), 759 (m) , 699 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.35–7.29 (m, 3H), 7.21–7.18 (m, 2H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.09 (s, 1H), 6.42 (s, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 4.82 (ddd, *J* = 8.8, 5.4, 3.2 Hz, 1H), 3.48 (dd, *J* = 14.0, 3.1 Hz, 1H), 2.85 (dd, *J* = 14.0, 9.4 Hz, 1H), 1.65 (d, *J* = 3.1 Hz, 1H), 1.45 (s, 9H), 1.11 (s, 9H). ^{13}C-NMR (APT, 125 MHz,$CDCl_3$): δ = 162.0 (CH), 151.3 (C), 141.1 (C), 139.7 (C), 135.8 (C), 128.8 (CH), 128.1 (CH), 127.1 (CH), 125.7 (CH), 122.5 (CH), 122.4 (C), 55.6 (CH), 38.6 (CH_2), 34.9 (C), 33.9 (C), 31.4 (CH_3), 29.9 (CH_3). HRMS: ([M+H]$^+$) calcd for $C_{23}H_{32}NO_2$: 354.2428, found: 354.2402.

(*R*)-2-(2'-amino-2'-phenylethyl)-4,6-di-*tert*-butylphenol (33). The formamide **32** (232 mg, 0.66 mmol, 1.00 equiv) was dissolved in 3 mL MeOH and 3 mL of 10% sodium hydroxide solution in MeOH (w/w) were added to this solution. The resulting homogenous mixture was refluxed for 2 h under N_2, with magnetic stirring. Conversion of the formamide **32** was followed by TLC. Methanol was removed by rotary evaporation under reduced pressure. To the oily residue was added water (ca. 5 mL) and then, 20 mL of 20% hydrochloric acid were drop-wise added to the mixture. The resulting homogenous mixture was extracted with Et_2O (2 × 50 mL), organic phase was discharged. pH value of the aqueous phase was adjusted to 9 by adding saturated sodium bicarbonate solution under ice cooling. Organic component of the resulting slurry was extracted with DCM (2 × 50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The title compound (**33**) was obtained as a beige colored solid (193 mg, 0.59 mmol, 90%). Mp: 241–242 °C. TLC: R_f = 0.55 (silica gel; hexanes/EtOAc/TEA/MeOH, 4:0.5:0.25:0.25). $[\alpha]_D^{21}$ = −98 (c = 0.5, $CHCl_3$). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3458 (br), 2955 (s), 1605 (m), 1536 (m), 1479 (s), 1361 (s), 1296 (w), 1194 (s), 1121 (s), 879 (w), 758 (m) , 698 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, J = 6.9 Hz, 2H), 7.16–7.03 (m, 4H), 6.20 (s, 1H), 4.42 (d, *J* = 6.3 Hz, 1H), 3.66 (d, *J* = 11.6 Hz, 1H), 3.04–2.98 (m, 1H), 1.35 (s, 9H), 1.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.5 (C), 144.3 (C), 139.4 (C), 131.4 (CH), 131.2 (CH), 130.1 (CH), 129.0 (CH), 125.2 (CH), 59.1 (CH), ca. 40.0 (CH_2, this signal was missing, but, it was determined by HSQC experiment.) 37.6 (C), 36.5 (C), 34.0 (CH_3), 32.7 (CH_3). Two substituted aromatic carbon atoms did not give resolved ^{13}C peaks, thus they were missing. HRMS: ([M+H]$^+$) calcd for $C_{22}H_{32}NO$: 326.2478, found: 326.2479.

(2*S*,1'*S*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (36a) and (2*S*,1'*R*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (37a) (Table 1, entry 9). The AAP **1** (4.8 mg, 25 µmol, 10 mol%) and benzoic acid (3.1 mg, 25 µmol, 10 mol%) were placed in a 5 mL vial and they are dissolved in 0.5 mL toluene. After cyclohexanone (207 µL, 196 mg 2.0 mmol, 8.00 equiv) was added into the vial, the homogenous mixture was stirred for 15 minutes. 4-Nitrobenzaldehyde (37 mg, 0.25 mmol, 1.00 equiv) was added in one portion and the mixture was stirred at rt for 36 h, in the closed vial. The progress of the reaction was monitored by TLC. The title products **36a** and **37a** were obtained by column chromatography on silica gel. A 70:30 syn/anti ratio (**36a**:**37a**) as well as 64% *ee* for **36a** and 78% *ee* for **37a** were determined by HPLC on a chiral column. R_f (**36a**)= 0.42 (silica gel; hexanes/EtOAc, 7:3). R_f (**37a**)= 0.41 (silica gel; hexanes/EtOAc, 7:3). HPLC**:** Daicel Chiralpak AD-H (4.60 mm ID × 250 mm column length); *n*-hexane/^{i}PrOH (85:15), 1.0 mL/min; 254 nm (UV–vis); t_R = 15.1 min (*ent*-**36a**), t_R = 16.9 min (**36a**), t_R = 18.6 min (**37a**), t_R = 24.6 min (*ent*-**37a**).

(*S*)-4-Hydroxy-4-(4-nitrophenyl)-2-butanone (39) (Table 2, entry 6). The primary amine **7** (5.1 mg, 25 µmol, 10 mol%) and 2,4,6-triisopropylbenzoic acid (12.5 mg, 50 µmol, 20 mol%) were placed in a 5 mL vial and they are suspended in 0.1 mL toluene. After acetone (150 µL, 118 mg, 2.0 mmol, 8.00 equiv) was added into the vial, the resulting homogenous mixture was cooled to 0 °C in a cooling bath and stirred for 15 minutes. 4-Nitrobenzaldehyde (37 mg, 0.25 mmol, 1.00 equiv) was added in one portion and the mixture was stirred at 0 °C for 192 h, in the closed vial. The progress of the reaction was monitored by TLC. The title product **39** was isolated by column chromatography on silica gel, in 85% yield and 62% *ee*. R_f = 0.41 (silica gel; hexanes/EtOAc, 6:4). HPLC**:** Daicel Chiralpak AS-H (4.60 mm ID × 250 mm column length); *n*-hexane/^{i}PrOH (85:15), 1.0 mL/min; 254 nm (UV–vis); t_R = 25.1 min (*ent*-**39**), t_R = 32.4 min (**39**).

(2*S*,1'*S*)-2-[Hydroxy(phenyl)methyl]cyclohexanone (36b) and (2*R*,1'*S*)-2-[Hydroxy(phenyl)methyl]cyclohexanone (37b) (Scheme 8). The AAP **1** (4.8 mg, 25 µmol, 10 mol%) and benzoic acid (3.1 mg, 25 µmol, 10 mol%) were placed in a 5 mL vial. After cyclohexanone (207 µL, 196 mg 2.0 mmol, 8.00 equiv) was added into the vial, the homogenous mixture was stirred for 15 minutes. Then, benzaldehyde (27 mg, 0.25 mmol, 1.00 equiv) was added in one portion and the mixture was stirred at rt for 36 h, in the closed vial. The progress of the reaction was monitored by TLC. The title products **36b** and **37b** were obtained by column chromatography on silica gel (82 mg, 10 µmol, 40%). R_f (**36b**)= 0.44 (silica gel; hexanes/EtOAc, 8:2). R_f (**37b**)= 0.39 (silica gel; hexanes/EtOAc, 8:2). HPLC**:** Daicel Chiralpak AS-H (4.60 mm ID × 250 mm column length); *n*-hexane/^{i}PrOH (90:10), 0.5 mL/min; 220 nm (UV–vis); t_R = 20.6 min (**36b**), t_R = 25.5 min (*ent*-**36b**), t_R = 27.5 min (*ent*-**37b**), t_R = 28.5 min (**37b**).

***syn*-2-[Hydroxy(4-methoxyphenyl)methyl]cyclohexanone (36c) and *anti*-2-[Hydroxy(4-methoxyphenyl)methyl]cyclohexanone (37c) (Scheme 8).** The AAP **1** (4.8 mg, 25 µmol, 10 mol%) and benzoic acid (3.1 mg, 25 µmol, 10 mol%) were placed in a 5 mL vial. After cyclohexanone (207 µL, 196 mg 2.0 mmol, 8.00 equiv) was added into the vial, the

homogenous mixture was stirred for 15 minutes. Then, *p*-anisaldehyde (34 mg, 0.25 mmol, 1.00 equiv) was added in one portion and the mixture was stirred at rt for 36 h, in the closed vial. The progress of the reaction was monitored by TLC. The title products **36c** and **37c** were obtained by column chromatography on silica gel (42 mg, 4.5 µmol, 18%). R_f (**36c**)= 0.38 (silica gel; hexanes/EtOAc, 7:3). R_f (**37c**)= 0.35 (silica gel; hexanes/EtOAc, 7:3). HPLC**:** Daicel Chiralpak AS-H (4.60 mm ID × 250 mm column length); *n*-hexane/^{i}PrOH (90:10), 0.5 mL/min; 220 nm (UV–vis); t_R = 25.7 min (**36c**, minor), t_R = 29.5 min (**36c**, major), t_R = 42.4 min (**37c**, major), t_R = 43.8 min (**37c**, minor).

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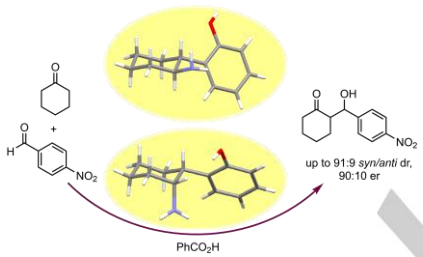
FULL PAPER

Effective preparation of enantiopure *cis*- and *trans*-2-(2-aminocyclohexyl)phenols, novel 1,4-aminoalkylphenols, as well as their performance as chiral organocatalyst are presented.



Asymmetric Catalysis

*Mustafa A. Tezeren, Tolga A. Yeşil, Yunus Zorlu, Tahir Tilki, Erkan Ertürk**

Page No. – Page No.

Enantiopure *cis*- and *trans*-2-(2-Aminocyclohexyl)phenols: Effective Preparation, Solid-State Characterization, and Application in Asymmetric Organocatalysis