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Switching of Enantioselectivity in the Catalytic Addition of Diethylzinc to Aldehydes by Regioisomeric Chiral 1,3-Amino Sulfonamide Ligands

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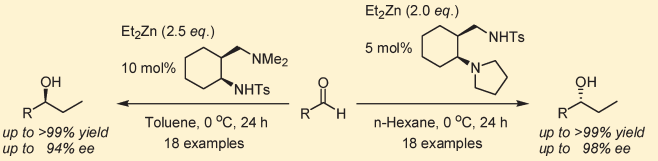
Supporting Information

ABSTRACT: Twenty chiral 1,3-amino sulfonamides of two classes (**2a**−**i** and **3a**−**k**) have been prepared from (−)-*cis*-2-benzamidocyclohexanecarboxylic acid (**1**) and studied as ligands for catalytic enantioselective addition of Et_2Zn to a variety of aromatic and aliphatic aldehydes. The ligands **2** and **3** are regioisomers in which the position of the amine and sulfonamide groups is exchanged. Each class of ligands with the same chirality was shown to afford *sec*-alcohols with the opposite stereochemistry. Structural surveys revealed that the combination of tertiary amino and *p*-toluenesufonylamido groups works most effectively for the reaction. Through optimization of the structural and reaction conditions, the best ligands quantitatively provided both enantiomeric secondary alcohols in good to excellent enantioselectivity of up to 94% and 98% ee for (*S*)- and (*R*)-enantiomers, respectively.



INTRODUCTION

Lately, catalytic asymmetric carbon−carbon bond formation has become a fundamental and most important subject. The enantioselective addition of Et_2Zn to aldehydes is one of the most intensely investigated reactions and serves as a test for new catalysts.[1] This reaction efficiently affords enantiomeric secondary alcohols as well as enantioselective hydrogenation of corresponding ketones catalyzed by heterogeneous catalysis.[2] The design and development of efficient chiral ligands for this purpose is an interesting challenge, and many research groups have studied various kinds of bidentate ligands, such as amino alcohols,[3] diols,[4] and amino thiols/disulfides,[5] as well as diamines and their derivatives.[6] Various types of effective chiral ligands have been reported; however, the structural characteristics still need to be explored to achieve high adaptability toward a wide range of aldehydes.

There have been many reports of 1,2-difunctionalized chiral ligands for asymmetric addition of Et_2Zn to aldehydes because of their wide availability. In contrast, the development of 1,3-difunctionalized chiral ligands is a less explored research area despite the formation of more stable six-membered chelates with the zinc atom in the transition state.[7]

In general asymmetric syntheses, it is believed that a family of structurally related chiral catalysts with identical chirality affords only one enantiomer of the product. On the other hand, some recent reports have demonstrated the switching of enantioselectivity using a common chiral source. The switching of chirality is achieved by changing the solvent, temperature, metal ions, additives, position of the substituents, and so on.[8] This method is particularly powerful in cases where the chiral source is derived from a natural product for which only one enantiomer is available. Previously, we have developed a number of 1,3-amino phenols and 1,3-amino alcohols as chiral bidentate and tridentate ligands, which are effective for enantioselective ethylation,[9] phenylethynylation,[10] and arylation of aldehydes,[11] respectively. In the course of our studies, the 1,3-amino alcohol ligands showed switching of enantioselectivity by control of the bulkiness around the functional groups of ligands.[9c,11b] The 1,3-amino alcohol ligands are derived from an enantiomer of cyclic β-amino acids, easily prepared by optical resolution,[12] and commercially available.

On the other hand, β-amino acids can be easily derivatized into 1,3-diamines, which have rarely been studied as chiral ligands for the addition of Et_2Zn to aldehydes.[13] Asami et al. studied some chiral 1,2-diamine ligands and reported that improvement of selectivity was achieved by converting an aliphatic amino group to an aromatic one because of the higher acidity of the latter.[14] Their results prompted us to attempt a systematic synthesis of chiral 1,3-amino sulfonamides as chiral ligands and to investigate their applicability for the enantioselective addition of Et_2Zn to a broad range of aromatic and aliphatic aldehydes. As the sulfonamide nitrogen proton is more acidic than aromatic amine protons, it forms a more stable covalent bond with Et_2Zn. In addition, sulfonamides, which are rather stable under various reaction conditions, allow simple synthetic procedures and the application of a wide range of reactions. To the best of our knowledge, however, only a few applications of amino sulfonamides in the enantioselective addition of Et_2Zn to aldehydes have been reported.[15] In this study, we report two regioisomeric classes of 1,3-amino sulfonamides with

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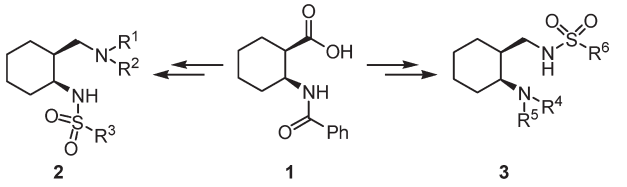
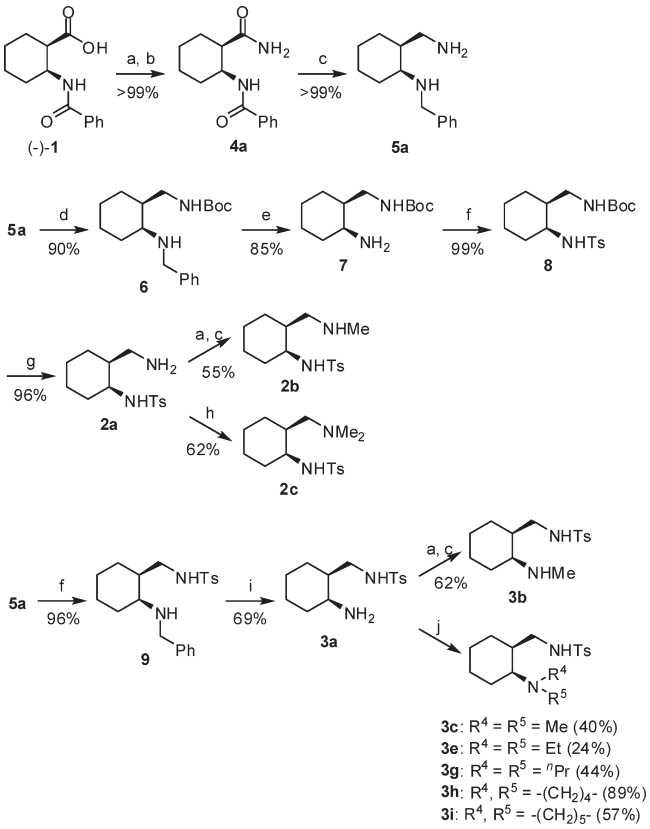
Scheme 1. Derivation to 1,3-Amino Sulfonamides 2 and 3 from (−)-*cis*-2-Benzamidocyclohexanecarboxylic Acid



Scheme 2. Synthetic Routes of 1,3-Amino Sulfonamides 2a−c, 3a−c, 3e, and 3g−i[a]



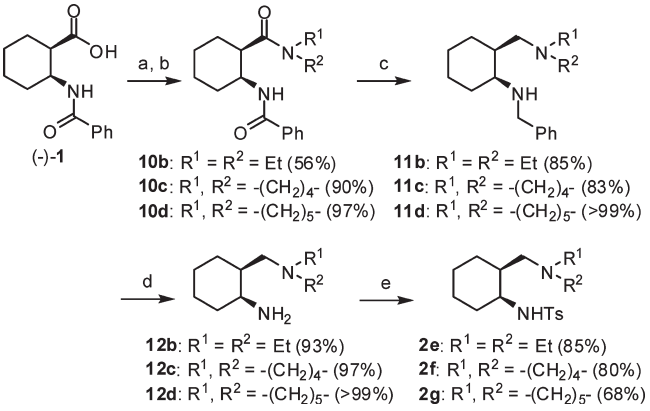
[a] Reagents and conditions: (a) $ClCO_2Et$, TEA, $CHCl_3$, 0 °C to rt; (b) add 28% NH_3 aq, rt; (c) $LiAlH_4$, THF, 0 °C to reflux; (d) Boc_2O, cat. thiourea, toluene, 70 °C; (e) H_2 (1 atm), cat. Pd−C, MeOH, reflux; (f) TsCl, TEA, $CHCl_3$, 0 °C to reflux; (g) 6 N HCl aq, THF, rt; (h) 37% HCHO aq, $NaBH_4$, 20% H_2SO_4 aq−THF, rt; (i) H_2 (1 atm), cat. Pd−C, EtOH, 70 °C; (j) (di)iodoalkane (MeI for **3c**, EtI for **3e**, ^{n}PrI for **3g**, 1, 4-diiodobutane for **3h**, 1,5-diiodopentane for **3i**), K_2CO_3, THF, rt or reflux. Abbreviations used: TEA = triethylamine; THF = tetrahydrofuran.

identical chirality to show a complete switching of stereoselectivity for the addition of Et_2Zn to aldehydes.

RESULTS AND DISCUSSION

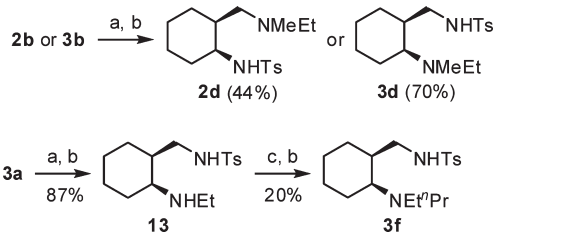
Synthesis of Enantiopure 1,3-Amino Sulfonamides. From (−)-*cis*-2-benzamidocyclohexanecarboxylic acid ((−)-**1**), asymmetric diamines with two different amino groups, i.e., cyclohexylamino (^{sec}C-amino) and cyclohexylmethylamino (^{prim}C-amino) groups, can be easily derived. During the transformation, one of

Scheme 3. Synthetic Route of 1,3-Amino Sulfonamides 2e−g[a]



[a] Reagents and conditions: (a) $ClCO_2Et$, TEA, $CHCl_3$, 0 °C to rt; (b) add HNR^1R^2, rt; (c) $LiAlH_4$, THF, 0 °C to reflux; (d) H_2 (1 atm), cat. Pd−C, EtOH, 70 °C; (e) TsCl, TEA, cat. DMAP, $CHCl_3$, 0 °C to reflux. Abbreviation used: DMAP = 4-dimethylaminopyridine.

Scheme 4. Synthetic Routes of 1,3-Amino Sulfonamides 2d, 3d, and 3f[a]



[a] Reagents and conditions: (a) AcCl, TEA, $CHCl_3$, 0 °C to rt; (b) $LiAlH_4$, THF, 0 °C to reflux; (c) CH_3CH_2COCl, TEA, $CHCl_3$, 0 °C to rt.

the amino groups was sulfonated with *p*-toluenesulfonyl chloride, methanesulfonyl chloride, or trifluoromethanesulfonic anhydride. The remaining amino group was modified to a secondary or tertiary amino group by alkylation or reduction of the preceding amido group. As a result, two families of regioisomeric 1,3-amino sulfonamides were synthesized in a direct manner. They have a rather simple structure with only amino and sulfonamido groups in the *cis*-1,2-position on a cyclohexane ring, as shown in Scheme 1. The 1,3-amino sulfonamides **2a**−**i** have a ^{prim}C-amino group, and **3a**−**k** have a ^{sec}C-amino group. Synthetic routes of the enantiopure 1,3-aminosulfonamides **2a**−**i**, **3a**−**k**, and their derivatives are shown in Schemes 2−7.

Structural Survey of 1,3-Amino Sulfonamides. The effects of amino and sulfonamido groups were systematically investigated in the catalytic enantioselective addition of Et_2Zn to benzaldehyde. The results are shown in Table 1 for **2a**−**i** and Table 2 for **3a**−**k**.

It is apparent that the tertiary amine ligands gave higher yields than the primary and secondary amine ligands for both **2** (entries 3−7 vs entries 1 and 2, Table 1) and **3** (entries 3−9 vs entries 1 and 2, Table 2). It appears that an appropriate basicity is necessary for the reaction to efficiently proceed, as is seen for amino alcohol ligands.[3] From comparisons among ^{prim}C-tertiary

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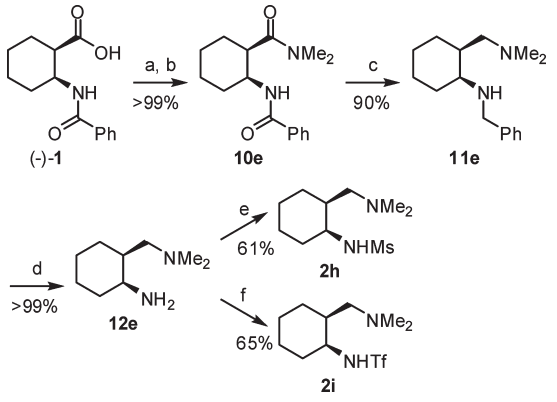
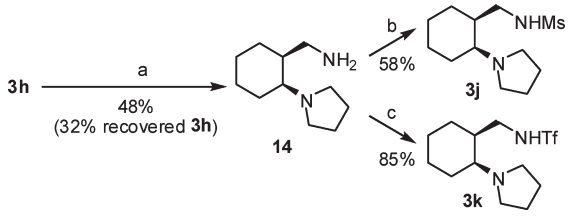
Scheme 5. Synthetic Routes of Diamine 11e and 1,3-Amino Sulfonamides 2h and 2i[a]



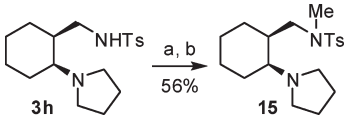
[a] Reagents and conditions: (a) $ClCO_2Et$, TEA, $CHCl_3$, 0 °C to rt; (b) add 50% $HNMe_2$ aq, rt; (c) $LiAlH_4$, THF, 0 °C to reflux; (d) H_2 (1 atm), cat. Pd−C, EtOH, 70 °C; (e) MsCl, TEA, $CHCl_3$, 0 °C to reflux; (f) Tf_2O, TEA, $CHCl_3$, −40 °C to rt.

Scheme 6. Synthetic Routes of 1,3-Amino Sulfonamides 3j and 3k[a]



[a] Reagents and conditions: (a) sodium naphthalenide, DME, −78 °C to rt; (b) MsCl, TEA, DCM, 0 °C to rt; (c) Tf_2O, TEA, DCM, −22 °C. Abbreviations used: DME = 1,2-dimethoxyethane; DCM = dichloromethane.

Scheme 7. Synthetic Route of 1,3-Amino Sulfonamide 15[a]



[a] Reagents and conditions: (a) NaH, DMF, 0 °C to rt. (b) add MeI, rt

amino sulfonamides **2c**−**g**, smaller alkyl groups on the amine nitrogen atom appear to be effective for both better yield and enantioselectivity. In particular, **2c** gave the best results, with moderate yield and good ee values (entry 3, Table 1). On the other hand, from comparisons among ^{sec}C-tertiary amino sulfonamides **3c**−**i**, the ligands **3e** and **3h** with moderately large substituents on the amine nitrogen atom worked better than the others, and **3h** was chosen for further study because of higher synthetic yield of the ligand. As reported previously, the substituent structure of a tertiary amine affected both yield and enantioselectivity.[3e,6d,9c] The effect of the sulfonamido group was also investigated for *p*-toluenesulfonamides (**2c** and **3h**), methanesulfonamides (**2h** and **3j**), and trifluoromethanesulfonamides (**2i** and **3k**). The latter two types of sulfonamides afforded a product in much lower yields than the *p*-toluenesulfonamides in both ligands **2** and **3** (entries 3, 8, and 9 in Table 1, and entries 8, 10, and 11 in Table 2). Despite the favorable steric and electronic effects of their sulfonamide groups, the reason of the present result is not clear at present.

The results demonstrated that the present 1,3-amino sulfonamide ligands are effective for the catalysis of benzaldehyde alkylation with Et_2Zn. In addition, they also showed that ^{prim}C-amino sulfonamide ligands **2** produced (*S*)-1-phenylpropan-1-ol (Table 1), whereas most ^{sec}C-amino sulfonamide ligands **3** produced the corresponding (*R*)-enantiomer despite having the same chirality (Table 2). It is noteworthy that the enantioselectivity is switched by exchanging the positions of two functional groups. As the best ^{prim}C-amino and ^{sec}C-amino sulfonamide ligands, **2c** and **3h** were chosen respectively considering the ability and availability of the ligands. Subsequently, the reaction conditions for these ligands were examined for optimization.

Effects of Solvent, Temperature, and Amounts of Chiral Ligand and Et_2Zn. The solvent effect was first screened using five solvents, as shown in Table 3. For both ligands, better results were obtained in less polar solvents such as *n*-hexane, cyclohexane, and toluene as reported previously.[3−7] An especially large decrease in the yield was observed for tetrahydrofuran (THF), presumably due to its coordinative property toward Et_2Zn. For further improvement in the chemical yield and enantiomeric excess, other conditions, such as reaction temperature and the amounts of Et_2Zn and chiral ligand, were investigated using toluene and *n*-hexane as the best solvents for **2c** and **3h**, respectively.

As shown in Table 4 for **2c**, the reaction proceeded slowly at −25 °C to give a low yield of only 11%, whereas the reaction conducted at room temperature afforded yield comparable with the result when the reaction was conducted at 0 °C. However, the enantioselectivity of (*S*)-**17a** was lowered at room temperature, and **2c** afforded the best results at 0 °C. In addition, benzyl alcohol, produced by a competitive side-reaction of benzaldehyde, was also isolated in the reaction at room temperature. Similarly, the reaction at 0 °C afforded (*R*)-**17a** in the highest selectivity and moderate yield for **3h** as seen in Table 5. Therefore, the reaction temperature for the both ligands **2c** and **3h** was fixed to 0 °C for further optimization.

The amount of Et_2Zn also affected the reaction. A higher amount of the reagent, up to 2.5 equiv of Et_2Zn, gave a better result for **2c** of >90% yield and 83% ee (entry 6, Table 4); however, additional Et_2Zn lowered the yield because of enhancement of the undesirable reduction to benzyl alcohol (entry 7, Table 4). For **3h**, a similar tendency was observed, although 2.0 equiv of Et_2Zn was sufficient to obtain better results of >99% yield and 91% ee (entry 7, Table 5).

Finally, optimization of the amount of chiral ligand revealed this factor to be crucial as well. Although more than 10 mol % of **2c** was effective, less chiral ligand loading was found to lower the yield (entries 6 vs entries 8 and 9, Table 4). On the other hand, it was found that only 5 mol % of **3h** was sufficient to obtain the highest selectivity in a quantitative yield (entry 8, Table 5).

Effect of Sulfonylamide Proton. By introducing the sulfonamide moiety, we expected stable covalent bond formation between Et_2Zn and the sulfonamide nitrogen due to its highly acidic proton. In order to confirm the effect of the sulfonylamide proton, we also studied two more ligands, **11e** and **15**, as references. The diamine **11e**, the counterpart of **2c**, has a secondary amino proton instead of the sulfonylamide proton on a ^{sec}C-amino nitrogen. In contrast, a new 1,3-amino sulfonamide **15** without a sulfonylamide proton was prepared by *N*-methylation of **3h**. As seen in Scheme 8, the addition of Et_2Zn to

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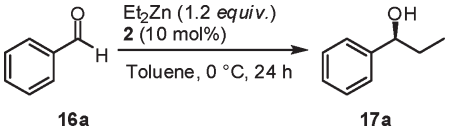
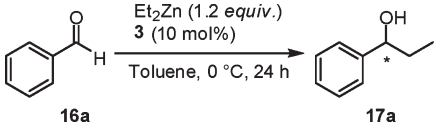
Table 1. Investigation of 1,3-Amino Sulfonamides 2 as Chiral Ligand in the Catalytic Asymmetric Addition of Diethylzinc to Benzaldehyde[a]



entry	1,3-Aminosulfonamide ligand		R^1	R^2	R^3	Yield[b] (%)	Ee[c] (%)	*Config.*[d]
1		**2a**	H	H	4-MeC_6H_4	trace	—	—
2		**2b**	H	Me	4-MeC_6H_4	trace	—	—
3		**2c**	**Me**	**Me**	**4-MeC_6H_4**	**62**	**87**	***S***
4		**2d**	Me	Et	4-MeC_6H_4	34	80	*S*
5		**2e**	Et	Et	4-MeC_6H_4	31	72	*S*
6		**2f**	—$(CH_2)_4$—		4-MeC_6H_4	36	88	*S*
7		**2g**	—$(CH_2)_5$—		4-MeC_6H_4	24	61	*S*
8		**2h**	Me	Me	Me	31	73	*S*
9		**2i**	Me	Me	CF_3	15	69	*S*

[a] All reactions were conducted with PhCHO (0.5 mmol), Et_2Zn (1 M in *n*-hexane, 600 μL; 0.6 mmol) and toluene (1.75 mL) as a solvent in the presence of **2** (10 mol %) at 0 °C for 24 h. [b] Yields based on PhCHO. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] Absolute configurations were determined by comparison of the HPLC elution order with that of the literature data.

Table 2. Investigation of 1,3-Amino Sulfonamides 3 as Chiral Ligand in the Catalytic Asymmetric Addition of Diethylzinc to Benzaldehyde[a]



entry	1,3-Aminosulfonamide ligand		R^4	R^5	R^6	Yield[b] (%)	Ee[c] (%)	*Config.*[d]
1		**3a**	H	H	4-MeC_6H_4	29	22	*S*
2		**3b**	H	Me	4-MeC_6H_4	trace	—	—
3		**3c**	Me	Me	4-MeC_6H_4	46	78	*R*
4		**3d**	Me	Et	4-MeC_6H_4	50	77	*R*
5		**3e**	Et	Et	4-MeC_6H_4	48	91	*R*
6		**3f**	Et	^{n}Pr	4-MeC_6H_4	52	84	*R*
7		**3g**	^{n}Pr	^{n}Pr	4-MeC_6H_4	47	74	*R*
8		**3h**	**—$(CH_2)_4$—**		**4-MeC_6H_4**	**52**	**90**	***R***
9		**3i**	—$(CH_2)_5$—		4-MeC_6H_4	28	89	*R*
10		**3j**	—$(CH_2)_4$—		Me	39	90	*R*
11		**3k**	—$(CH_2)_4$—		CF_3	37	67	*R*

[a] All reactions were conducted with PhCHO (0.5 mmol), Et_2Zn (1 M in *n*-hexane, 600 μL; 0.6 mmol) and toluene (1.75 mL) as a solvent in the presence of **3** (10 mol %) at 0 °C for 24 h. [b] Yields based on PhCHO. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] Absolute configurations were determined by comparison of the HPLC elution order with that of the literature data.

benzaldehyde in the presence of **11e** afforded 1-phenylpropan-1-ol in low chemical yield and very low enantioselectivity (48% and 11% ee, respectively). On the other hand, **15** gave a nearly racemic alcohol with only 8% yield. These results support the expected potential of a highly acidic proton of the sulfonamido group. The mechanism in enantioselectivity will be mentioned later.

Scope and Limitation of Substrates. The scope and limitation of the substrates were investigated using **2c** and **3h** under the optimum conditions, the results of which are summarized in Table 6. The electronic effect of a substituent was studied using substituted benzaldehydes (entries 2−5 and 8 for **2c**; entries 22−25 and 28 for **3h**). When 4-nitrobenzaldehyde was used, the products were so complex that the expected *sec*-alcohol was not detectable for both ligands (entry 2; entry 22). Other benzaldehydes with electron-withdrawing groups (4-trifluoromethyl and 4-chloro groups), however, gave the corresponding alcohols quantitatively (entries 3 and 5; entries 23 and 25), whereas electron-donating groups (4-methoxy and 4-methyl groups) lowered the yield (entries 4 and 8; entries 24 and 28). The chemical yield apparently depends on the electrophilicity of the carbonyl carbon atom of the substrates.

The effect of substituent position was observed for chlorobenzaldehydes and tolualdehydes. For chlorobenzaldehyde, only 2-chlorobenzaldehyde gave notably decreased yields (entries 5 and 6 vs entry 7; entries 25 and 26 vs entry 27). In contrast, little difference was observed for the three positional isomers of tolualdehydes (entries 8−10; entries 28−30). Given that chloro and methyl groups have comparable steric demand, the lower yield for 2-chlorobenzaldehyde may be attributed to

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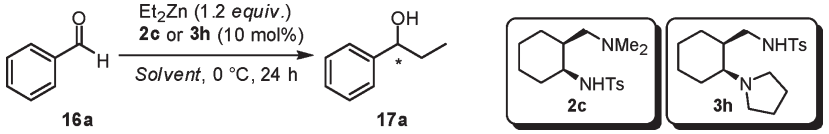
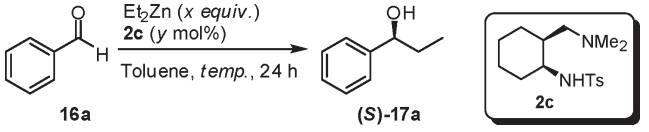
Table 3. Investigation of Reaction Solvents in the Catalytic Asymmetric Addition of Diethylzinc to Benzaldehyde Using 2c or 3h as Chiral Ligands[a]



conducted with **2c**					conducted with **3h**				
entry	solvent	yield[b] (%)	ee[c] (%)	config[d]	entry	solvent	yield[b] (%)	ee[c] (%)	config[d]
1	*n*-hexane	65	85	*S*	**6**	***n*-hexane**	**73**	**90**	***R***
2	cyclohexane	53	84	*S*	7	cyclohexane	68	90	*R*
3	**toluene**	**62**	**87**	***S***	8	toluene	52	90	*R*
4	THF	3	22	*S*	9	THF	4	47	*R*
5	DCM	44	82	*S*	10	DCM	46	90	*R*

[a] All reactions were conducted with PhCHO (0.5 mmol), Et_2Zn (1 M in *n*-hexane, 600 μL; 0.6 mmol), and solvent (1.75 mL) in the presence of **2c** or **3h** (10 mol %) at 0 °C for 24 h. [b] Yields based on PhCHO. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] Absolute configurations were determined by comparison of the HPLC elution order with that of the literature data.

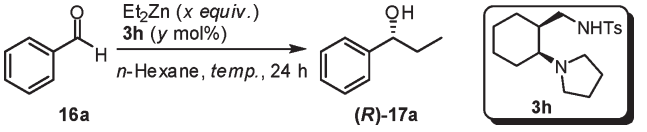
Table 4. Optimization of Reaction Temperatures and Loading Amount of Diethylzinc and Chiral Ligands 2c in the Catalytic Asymmetric Addition of Diethylzinc to Benzaldehyde[a]



entry	temp (°C)	Et_2Zn (equiv)	chiral ligand (mol %)	yield[b] (%)	ee[c] (%)
1	−25	1.2	10	11	75 (*S*)
2	0	1.2	10	62	87 (*S*)
3	rt	1.2	10	65[d]	78 (*S*)
4	0	1.5	10	67	83 (*S*)
5	0	2.0	10	74	83 (*S*)
6	**0**	**2.5**	**10**	**91**	**83** (*S*)
7	0	3.0	10	76[d]	83 (*S*)
8	0	2.5	20	95	83 (*S*)
9	0	2.5	5	82	82 (*S*)

[a] All reactions were conducted with PhCHO (0.5 mmol), Et_2Zn (1 M in *n*-hexane, *x* equiv), and toluene or *n*-hexane (1.75 mL) as a solvent in the presence of **2c** (*y* mol %) for 24 h. [b] Yields based on PhCHO. [c] Enantiomeric excesses were determined by chiral HPLC analysis, and absolute configurations were determined by comparison of the HPLC elution order with that of the literature data. [d] Benzyl alcohol was also obtained (entry 3, 10% yield; entry 7, 9% yield).

Table 5. Optimization of Reaction Temperatures and Loading Amount of Diethylzinc and Chiral Ligands 3h in the Catalytic Asymmetric Addition of Diethylzinc to Benzaldehyde[a]



entry	temp (°C)	Et_2Zn (equiv)	chiral ligand (mol %)	yield[b] (%)	ee[c] (%)
1	−25	1.2	10	48	89 (*R*)
2	0	1.2	10	73	90 (*R*)
3	rt	1.2	10	87	86 (*R*)
4	0	1.5	10	85	90 (*R*)
5	0	2.0	10	99	91 (*R*)
6	0	2.5	10	96	91 (*R*)
7	0	2.0	15	>99	91 (*R*)
8	**0**	**2.0**	**5**	**>99**	**91** (*R*)
9	0	2.0	1	91	90 (*R*)

[a] All reactions were conducted with PhCHO (0.5 mmol), Et_2Zn (1 M in *n*-hexane, *x* equiv), and toluene or *n*-hexane (1.75 mL) as a solvent in the presence of **3h** (*y* mol %) for 24 h. [b] Yields based on PhCHO. [c] Enantiomeric excesses were determined by chiral HPLC analysis, and absolute configurations were determined by comparison of the HPLC elution order with that of the literature data.

the electrostatic repulsive interaction between the nucleophilic ethyl group and the electron-rich chlorine atom around the reaction site.

The addition of Et_2Zn was also studied for conjugated and nonconjugated aliphatic aldehydes (entries 15−20; entries 35−40). It was shown that as the degree of conjugation decreased, the product yield significantly dropped while the selectivity increased (entries 15−17; entries 35−37). The reaction rate was largely suppressed for nonconjugated aldehydes, and the reaction did not proceed at all for 1-decanal (**16t**) (entries 17−20; entries 37−40). However, the enantioselectivity was high, especially for α-branched cyclohexanecarbaldehyde (94% and 98% ee for entries 18 and 38, respectively). These results indicate that this reaction is sensitive to the steric factor of the α-position of carbonyl group and gives lower yield and higher selectivity for more crowded substrates; si and re attacks of the Et group toward a carbonyl carbon atom for the reactions of ligands **2c** and **3h** occurred to give (*S*)- and (*R*)-alcohols, respectively. In most cases, higher selectivity was obtained for **3h**.

Stereoselectivity and Transition States. Catalytic enantioselective addition of Et_2Zn to aldehydes using 1,2-amino alcohols as a chiral ligand was extensively studied by Noyori et al., who explained that the reaction occurred via the 5/4/4 tricyclic transition state.[1d,16] On the basis of this mechanism, we have proposed the *anti*-6/4/4 tricyclic mechanism to explain the

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Scheme 8. Reactivity Comparison of Diamine 11e and 1,3-Amino Sulfonamide 15 with 1,3-Amino Sulfonamides 2c and 3h

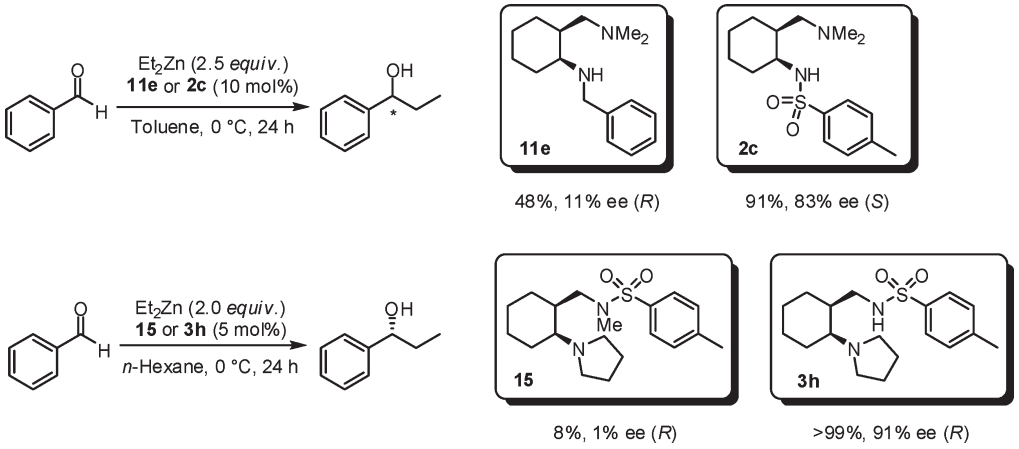
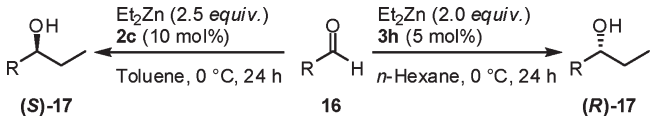


Table 6. Scope and Limitation of Substrates in the Catalytic Asymmetric Addition of Diethylzinc to Aldehydes Using 2c or 3h as Chiral Ligands[a]



conducted with **2c**					conducted with **3h**				
entry	R of aldehyde **16** (compd no.)	product	yield[b] (%)	ee[c] (%)	entry	R of aldehyde **16** (compd no.)	product	yield[b] (%)	ee[c] (%)
1	Ph (**16a**)	**17a**	91	83 (*S*)	21	Ph (**16a**)	**17a**	>99	91 (*R*)
2	4-$NO_2C_6H_4$ (**16b**)	**17b**	—[e]	—	22[d]	4-$NO_2C_6H_4$ (**16b**)	**17b**	—[e]	—
3	4-$CF_3C_6H_4$ (**16c**)	**17c**	>99	82 (*S*)[f]	23	4-$CF_3C_6H_4$ (**16c**)	**17c**	>99	86 (*R*)[f]
4	4-$MeOC_6H_4$ (**16d**)	**17d**	69	82 (*S*)	24[g]	4-$MeOC_6H_4$ (**16d**)	**17d**	95	83 (*R*)
5	4-ClC_6H_4 (**16e**)	**17e**	>99	82 (*S*)	25	4-ClC_6H_4 (**16e**)	**17e**	98	90 (*R*)
6	3-ClC_6H_4 (**16f**)	**17f**	>99	82 (*S*)	26	3-ClC_6H_4 (**16f**)	**17f**	98	90 (*R*)
7	2-ClC_6H_4 (**16g**)	**17g**	89	81 (*S*)	27	2-ClC_6H_4 (**16g**)	**17g**	89	90 (*R*)
8	4-MeC_6H_4 (**16h**)	**17h**	79	80 (*S*)	28	4-MeC_6H_4 (**16h**)	**17h**	96	92 (*R*)
9	3-MeC_6H_4 (**16i**)	**17i**	82	82 (*S*)	29	3-MeC_6H_4 (**16i**)	**17i**	97	91 (*R*)
10	2-MeC_6H_4 (**16j**)	**17j**	78	83 (*S*)	30	2-MeC_6H_4 (**16j**)	**17j**	94	90 (*R*)
11	1-naphthyl (**16k**)	**17k**	79[h]	78 (*S*)	31[g]	1-naphthyl (**16k**)	**17k**	94	86 (*R*)
12	2-naphthyl (**16l**)	**17l**	93	80 (*S*)	32[g]	2-naphthyl (**16l**)	**17l**	98	90 (*R*)
13	2-furyl (**16m**)	**17m**	67	76 (*S*)	33[g]	2-furyl (**16m**)	**17m**	71	78 (*R*)
14	2-thienyl (**16n**)	**17n**	88	85 (*S*)	34[g]	2-thienyl (**16n**)	**17n**	91	82 (*R*)
15	PhC≡C (**16o**)	**17o**	84	31 (*S*)	35[g]	PhC≡C (**16o**)	**17o**	95	46 (*R*)
16	(*E*)-PhCH=CH (**16p**)	**17p**	68	63 (*S*)	36[g]	(*E*)-PhCH=CH (**16p**)	**17p**	61	75 (*R*)
17	$Ph(CH_2)_2$ (**16q**)	**17q**	41	87 (*S*)	37	$Ph(CH_2)_2$ (**16q**)	**17q**	60	91 (*R*)
18	Cy (**16r**)	**17r**	49	94 (*S*)	38	Cy (**16r**)	**17r**	65	98 (*R*)
19	$CH_3(CH_2)_4$ (**16s**)	**17s**	12	86 (*S*)	39	$CH_3(CH_2)_4$ (**16s**)	**17s**	30	93 (*R*)
20	$CH_3(CH_2)_8$ (**16t**)	**17t**	nr[i]	—	40	$CH_3(CH_2)_8$ (**16t**)	**17t**	nr[i]	—

[a] All reactions were conducted with RCHO (0.5 mmol), Et_2Zn (1 M in hexane) and toluene or *n*-hexane as a solvent in the presence of **2c** (10 mol %) or **3h** (5 mol %) at 0 °C for 24 h. Otherwise mentioned, the aldehydes were added to the reaction systems as solutions in corresponding solvent. [b] Yields based on RCHO. [c] Enantiomeric excesses were determined by chiral HPLC analysis, and absolute configurations were determined by comparison of the HPLC elution order with that of the literature data. [d] The aldehyde was added to the reaction system as a solution in toluene because of solubility problems. [e] Isolation of the desired product was failed because a complex mixture of the products was obtained. [f] Enantiomeric excess and absolute configuration were determined by ^1H NMR analysis of the (*R*)-(+)-MTPA ester of **17c** (Mosher's ester method). [g] The aldehyde was added to the reaction system as a solution in mixed solvent (hexane/toluene = 3:1) because of solubility problems. [h] Primary alcohol formed by reduction of the corresponding aldehyde was also obtained (9% yield). [i] No reaction.

stereochemistry of the main product of enantioselective ethylation using chiral 1,3-amino alcohols as ligands.[9c] From the effect of sulfonamide mentioned above, its role is expected to correspond to that of the OH group of an amino alcohol ligand in the

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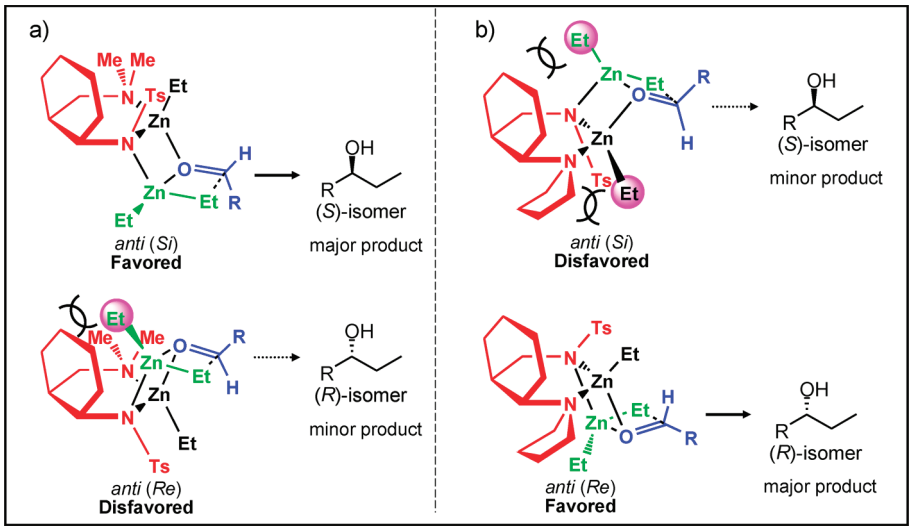

Figure 1. Expected transition states for the enantioselective addition of diethylzinc to aldehydes by the use of **2c** (a) and **3h** (b).

reaction to form a covalent bond with a zinc ion. Considering the similarity of the present ligands with the known 1,2- and 1,3-amino alcohols, the transition state of the reaction catalyzed by regioisomeric 1,3-amino sulfonamides was speculated to explain the stereochemistry of the major product and the switching of enantioselectivity.

The *anti*-6/4/4 tricyclic transition states for the catalytic ethylation promoted by **2c** are shown in Figure 1a, considering that the major products were (*S*)-1-phenylpropan-1-ols. When the transition state is *anti*(*re*), the cyclohexyl group of **2c** and the Et group of Et_2Zn create steric repulsion. The *anti*(*si*) form appears to be more favorable because of the flexibility of the *p*-toluenesulfonyl group on the sulfonamide N atom. Hence, when an amino group becomes more bulky, the enantioselectivity decreases (entries 3−5, Table 1) because the substituent on the amine nitrogen atom causes greater repulsion with the cyclohexyl group.

On the other hand, for the chiral ligand **3h**, the *anti*(*si*) form is less stable than the *anti*(*re*) form because of the steric repulsion between the cyclohexyl group and the Et group of Et_2Zn, as well as that between the pyrrolidine ring and the Et group on a Zn atom chelated by two nitrogen atoms (Figure 1b). The higher yields observed for **3h** are attributed to the more favorable transition state for the *anti*(*re*) form of **3h** than that of the *anti*(*si*) form of **2c**. In addition, the energy difference between the two transition forms of **3h** is apparently larger than that of **2c**. This leads to the higher enantioselectivity observed for **3h** (Tables 3 and 6). The position of the functional groups and the size of alkyl substituents on the amine nitrogen atom are shown to be important regulators for enantioselectivity, as seen in comparisons among **3e** and **3h**, **2e** and **2f**, as well as **3c**, **3g**, and **3i**.

CONCLUSIONS

Starting from commercially available enantiopure *cis*-2-benzamidocyclohexanecarboxylic acid, two regioisomeric classes of 1,3-aminosulfonamides were prepared and studied as chiral ligands for catalytic enantioselective addition of Et_2Zn to aldehydes. It was shown that the stereochemistry of the product is inverted by switching the positions of amino and sulfonamido groups despite the identical chirality. Under optimum conditions, chiral ligand **2c** provided (*S*)-alcohols in excellent yields and selectivity (up to >99% yield and 94% ee), whereas **3h** afforded (*R*)-alcohols with higher performance (up to >99% and 98% ee) to a variety of aromatic and aliphatic aldehydes. These results will help us further design regioisomeric chiral catalysts for enantiodivergent asymmetric reactions.

EXPERIMENTAL SECTION

General and Materials. All ^1H NMR and ^{13}C NMR (with complete proton decoupling) spectra were recorded on a 400 or a 500 MHz spectrometer. Chemical shifts of ^1H NMR are given in ppm relative to tetramethylsilane (δ = 0.0) as an internal standard, and those of ^{13}C NMR are given relative to the residual solvent peak (δ = 77.16) in $CDCl_3$ solution. The coupling constants *J* are given in hertz (Hz). Mass spectra were recorded using electrospray ionization mass spectrometry (ESI MS). IR spectra are reported in reciprocal centimeters (cm^{-1}). Enantiomeric excess determination was conducted by HPLC with chiral columns. Optical rotations were measured with a polarimeter. Melting points are reported uncorrected.

All commercially available substrates were used as received unless noted. Dry hexane, cyclohexane, toluene, and 1,2-dimethoxyethane (DME) were prepared by distillation from sodium grains and stored over sodium wire under N_2 atmosphere. Dry dichloromethane (DCM) was prepared by distillation from CaH_2 and stored over MS 4Å under N_2 atmosphere. Dry *N*,*N*-dimethylformamide (DMF) was prepared by distillation under reduced pressure and stored over MS 4Å under N_2 atmosphere. Dry tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone as a moisture indicator under N_2 atmosphere before use. All liquid aldehydes were freshly distilled under reduced pressure, and solid aldehydes were purified by silica gel column chromatography before use. (−)-*cis*-2-Benzamidocyclohexanecarboxylic acid ((−)-**1**) was prepared according to the literature procedure.[12a]

Analytical thin layer chromatography was performed on precoated aluminum sheets silica gel 60 F_{254} plates and visualized by UV lamp (254 nm), staining with phosphomolybdic acid or ninhydrin. Silica gel (B−5F, 45 μm) was used for preparative thin layer chromatography (PTLC), and silica gel (silica gel 60N, spherical, neutral, 100−210 μm) was used for column chromatography.

***N*-[(1*S*,2*R*)-2-Carbamoylcyclohexyl]benzamide (4a).** To a solution of (−)-**1** (2.47 g, 10.0 mmol) and triethylamine (TEA)

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(1.54 mL, 11.1 mmol) in $CHCl_3$ (20 mL) was added ethyl chloroformate (950 μL, 10.0 mmol) dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. To the reaction mixture was added 28% NH_3 aq (10.0 mL, 148 mmol) under vigorous stirring, and stirring was continued for 15 h at room temperature. The reaction mixture was neutralized by addition of 6 M HCl aq, and then the solvents were removed under reduced pressure. The residue was diluted by EtOAc (50 mL), and the organic solution was washed with 1 M HCl aq (30 mL × 2) and 1 M NaOH aq (30 mL × 2), and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dried in vacuo to give the diamide **4a** (2.46 g, 10.0 mmol, >99% yield) as a white powder. The diamide was directly used in the next reaction without further purification. The analytical sample was prepared by purification of the product on silica gel PTLC (EtOAc/hexane = 1:1). Mp: 133−134 °C. $[\alpha]_D^{23} = -15.6$ (*c* 0.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78−7.76 (m, 2H), 7.50−7.40 (m, 4H), 6.01−5.85 (br, 1H), 5.65−5.45 (br, 1H), 4.34 (ddd, J_1 = 8.8 Hz, J_2 = J_3 = 4.4 Hz, 1H), 4.35 (ddd, J_1 = J_2 = J_3 = 4.4 Hz, 1H), 2.11−2.03 (m, 1H), 1.93−1.87 (m, 1H), 1.87−1.80 (m, 1H), 1.72−1.70 (m, 2H), 1.57−1.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 166.9, 134.8, 131.5, 128.7, 127.1, 48.7, 44.3, 29.5, 27.9, 23.7, 22.6. IR (KBr): ν_{max} 3392, 3276, 3192, 2936, 2845, 1672, 1649, 1623, 1579, 1553, 1414, 655 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{14}H_{18}N_2O_2 + Na]^+$: 269.1260, found 269.1263.

(1*S*,2*S*)-2-(Aminomethyl)-*N*-benzylcyclohexanamine (5a). To a suspension of $LiAlH_4$ (3.04 g, 80.1 mmol) in dry THF (30 mL), a solution of **4a** (2.46 g, 10.0 mmol) in dry THF (20 mL) was added dropwise at 0 °C under N_2 atmosphere. After completion of addition, the reaction mixture was refluxed for 96 h. The reaction was quenched by addition of ion-exchanged water (3 mL), 15% NaOH aq (3 mL) and ion-exchanged water (9 mL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was evaporated under reduced pressure, and the residue was dissolved in 1 M HCl aq (50 mL). The aqueous solution was washed with EtOAc (30 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous layer was extracted with $CHCl_3$ (30 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1:10) to afford the diamine **5a** (2.18 g, 10.0 mmol, >99% yield) as a white powder. Mp: 48−49 °C. $[\alpha]_D^{21}$ = +48.3 (*c* 0.47, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.29 (m, 4H), 7.24−7.21 (m, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.67 (d, *J* = 13.0 Hz, 1H), 2.86−2.82 (m, 2H), 2.57 (dd, J_1 = 12.5 Hz, J_2 = 6.5 Hz, 1H), 1.81−1.77 (m, 1H), 1.66−1.51 (m, 3H), 1.45−1.36 (m, 3H), 1.36−1.28 (m, 2H), 1.28−1.20 (br, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.3, 128.4, 128.2, 126.8, 54.5, 51.3, 43.3, 28.5, 26.1, 24.2, 21.9. IR (KBr): ν_{max} 3276, 2920, 2858, 1492, 1462, 1447, 862, 749, 699 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{14}H_{22}N_2 + H]^+$: 219.1856, found 219.1859.

***tert*-Butyl [(1*S*,2*S*)-2-(Benzylamino)cyclohexyl]methylcarbamate (6).** To a mixture of **5a** (800 mg, 3.66 mmol) and thiourea (27.9 mg, 0.366 mmol) in toluene (15 mL), Boc_2O (799 mg, 3.66 mmol) was added and the reaction mixture was stirred for 30 min at 70 °C (vigorous emission of CO_2 was observed). The mixture was filtered through filter paper to remove thiourea and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1:10) to give the carbamate **6** (1.05 g, 3.30 mmol, 90% yield) as a white powder. Mp: 42−43 °C. $[\alpha]_D^{23}$ = +39.9 (*c* 0.27, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.0 Hz, 2H), 7.31 (dd, J_1 = J_2 = 7.5 Hz, 2H), 7.26−7.23 (m, 1H), 5.74 (br s, 1H), 3.78 (d, *J* = 12.5 Hz, 1H), 3.73 (d, *J* = 12.5 Hz, 1H), 3.27−3.22 (m, 1H), 3.19−3.14 (m, 1H), 2.80 (ddd, J_1 = 7.0 Hz, J_2 = J_3 = 3.4 Hz, 1H), 1.83−1.78 (m, 2H), 1.56−1.50 (m, 2H), 1.44 (s, 9H), 1.42−1.27 (m, 5H), 1.24 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 140.8, 128.5, 128.4, 127.0, 56.2, 51.7, 42.4, 38.9, 28.6, 28.3, 26.6, 23.7, 22.3. IR (KBr): ν_{max} 3348, 3323, 2929, 2852, 1675, 1534, 1496, 1364, 1278, 1174 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{19}H_{30}N_2O_2 - C_4H_8 + H]^+$: 263.1754, found 263.1751.

***tert*-Butyl [(1*S*,2*S*)-2-Aminocyclohexyl]methylcarbamate (7).** A mixture of **6** (993 mg, 3.12 mmol) and 10% Pd−C (99.2 mg, catalytic amount) in MeOH (20 mL) was refluxed for 16 h under H_2 atmosphere (1 atm). After completion of the reaction, the catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc to 25% NH_3 aq/MeOH/$CHCl_3$ = 1:10:100) to yield the carbamate **7** (606 mg, 2.65 mmol, 85% yield) as a white powder. Mp: 43−44 °C. $[\alpha]_D^{22}$ = +5.9 (*c* 0.41, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.02 (br s, 1H), 3.24−3.19 (m, 1H), 3.08−3.07 (m, 1H), 3.01−2.96 (m, 1H), 1.67−1.56 (m, 3H), 1.55−1.50 (m, 2H), 1.44 (s, 9H), 1.41−1.35 (m, 2H), 1.34−1.31 (m, 1H), 1.29−1.20 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 48.0, 43.0, 41.5, 33.8, 28.6, 25.0, 24.8, 20.7. IR (KBr): ν_{max} 3346, 3253, 2929, 2860, 1693, 1547, 1364, 1274, 1254, 1177, 1139 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{12}H_{24}N_2O_2 + Na]^+$: 251.1730, found 251.1728.

***tert*-Butyl [(1*S*,2*S*)-2-(4-Methylphenylsulfonamido)cyclohexyl]methylcarbamate (8).** To a solution of **7** (588 mg, 2.58 mmol) and TEA (430 μL, 3.09 mmol) in $CHCl_3$ (10 mL), tosyl chloride (540 mg, 2.83 mmol) was added and the reaction mixture was refluxed for 5 h. The reaction was quenched by addition of 1 M NaOH aq (5 mL), and then organic layer was washed with 1 M NaOH aq (10 mL × 2), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:3 to EtOAc) to furnish the carbamate **8** (971 mg, 2.54 mmol, 98% yield) as a white powder. Mp: 58−59 °C. $[\alpha]_D^{22}$ = +5.4 (*c* 0.94, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.17 (br s, 1H), 5.12 (app. d, *J* = 9.5 Hz, 1H), 3.53−3.51 (m, 1H), 3.23−3.18 (m, 1H), 2.88−2.82 (m, 1H), 2.45 (s, 3H), 1,75−1.61 (br, 2H), 1.45 (s, 9H), 1.34−1.16 (m, 5H), 1.06−0.98 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 143.6, 138.0, 129.9, 127.1, 50.0, 42.3, 41.0, 30.3, 28.6, 25.0, 24.6, 21.7, 21.2. IR (KBr): ν_{max} 3394, 3285, 2931, 1691, 1511, 1456, 1332, 1250, 1161, 1093, 669 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{19}H_{30}N_2O_4S + Na]^+$: 405.1819, found 405.1821.

***N*-[(1*S*,2*S*)-2-(Aminomethyl)cyclohexyl]-4-methylbenzenesulfonamide (2a).** To a solution of **8** (950 mg, 2.48 mmol) in THF (10 mL), 6 M HCl aq (10 mL) was added and the mixture was stirred for 3 h at room temperature. After completion of the reaction, the solvents were removed under reduced pressure, and the residue was dissolved in 1 M NaOH aq (30 mL). The cloudy aqueous solution was extracted with $CHCl_3$ (20 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1:10) to yield the 1,3-aminosulfonamide **2a** (672 mg, 2.38 mmol, 96% yield) as a white powder. Mp: 124−125 °C. $[\alpha]_D^{23}$ = +47.4 (*c* 0.14, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 3.48 (ddd, J_1 = 5.5 Hz, J_2 = J_3 = 2.5 Hz, 1H), 2.86 (dd, J_1 = 12.5 Hz, 8.5 Hz, 1H), 2.49 (dd, J_1 = 12.5 Hz, J_2 = 3.5 Hz, 1H), 2.42 (s, 3H), 1.60−1.55 (m, 1H), 1.54−1.43 (m, 4H), 1.40−1.33 (m, 4H), 1.32−1.29 (m, 1H), 1.27−1.20 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.02, 138.5, 129.7, 127.1, 77.4, 53.0, 44.0, 41.4, 30.5, 26.4, 23.9, 21.6. IR (KBr): ν_{max} 3341, 3371, 2927, 1313, 1155, 1093, 665, 553 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{14}H_{22}N_2O_2S + H]^+$: 283.1475, found 283.1480.

4-Methyl-*N*-{(1*S*,2*S*)-2-[(methylamino)methyl]cyclohexyl}benzenesulfonamide (2b). To a solution of **2a** (141 mg, 0.500 mmol) and TEA (76.5 μL, 0.549 mmol) in dry THF (10 mL), ethyl chloroformate (52.0 μL, 0.548 mmol) was added dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. When the reaction completed,

the reaction mixture was filtered through filter paper and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry THF (2 mL) and this solution was added dropwise to a suspension of $LiAlH_4$ (56.9 mg, 1.50 mmol) in dry THF (5 mL) at 0 °C under N_2 atmosphere. The mixture was refluxed for 24 h and the reaction was quenched by addition of ion-exchanged water (57.0 μL), 15% NaOH aq (57.0 μL) and ion-exchanged water (170 μL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M HCl aq (10 mL). The aqueous solution was washed with EtOAc (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous solution was extracted with $CHCl_3$ (10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to afford the 1,3-aminosulfonamide **2b** (81.6 mg, 0.275 mmol, 55% yield) as a white powder. Mp: 79−80 °C. $[\alpha]_D^{23}$ = +43.9 (*c* 0.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.35 (ddd, J_1 = 7.5 Hz, J_2 = J_3 = 3.4 Hz, 1H), 2.85 (dd, J_1 = 11.8 Hz, J_2 = 4.3 Hz, 1H), 2.42 (s, 3H), 2.33−2.29 (m, 4H), 1.70−1.62 (m, 2H), 1.57−1.50 (m, 2H), 1.45−1.37 (br, 3H), 1.34−1.26 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 138.7, 129.6, 127.0, 54.5, 54.1, 38.0, 36.7, 30.3, 27.8, 23.1, 22.7, 21.6. IR (KBr): ν_{max} 3299, 2931, 2848, 1450, 1326, 1312, 1301, 1288, 1158, 1093, 815, 670, 553 cm^{-1}. HRMS (ESI$^+$): *m*/*z* calcd for $[C_{15}H_{24}N_2O_2S + H]^+$: 297.1631, found 297.1635.

***N*-{(1*S*,2*S*)-2-[(Dimethylamino)methyl]cyclohexyl}-4-methylbenzenesulfonamide (2c).** To a mixture of 37% HCHO aq (600 μL, 21.6 mmol) and 20% H_2SO_4 aq (560 μL) in THF (2.8 mL), a solution of **2a** (141 mg, 0.500 mmol) in THF (5 mL) and $NaBH_4$ (150 mg, 3.97 mmol) were simultaneously added portionwise over 15 min. After completion of addition, the reaction mixture was stirred for 2 h at room temperature. When the reaction completed, the reaction mixture was basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy solution was extracted with $CHCl_3$ (10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to give the 1,3-aminosulfonamide **2c** (96.2 mg, 0.310 mmol, 62% yield) as a white powder. Mp: 122−123 °C. $[\alpha]_D^{23}$ = +45.7 (*c* 0.14, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 3.35 (ddd, J_1 = 11.0 Hz, J_2 = J_3 = 3.8 Hz, 1H), 2.91 (dd, J_1 = J_2 = 12.0 Hz, 1H), 2.41 (s, 3H), 2.17 (s, 6H), 1.91 (app. d, *J* = 13.0 Hz, 1H), 1.84−1.81 (m, 1H), 1.74−1.70 (m, 1H), 1.64−1.62 (m, 1H), 1.56−1.48 (m, 1H), 1.45−1.11 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.6, 139.4, 129.6, 126.9, 61.0, 55.5, 45.7, 33.6, 30.1, 29.9, 24.9, 21.6, 20.9. IR (KBr): ν_{max} 3442, 2938, 1330, 1162, 1088, 662, 575, 552 cm^{-1}. HRMS (ESI$^+$): *m*/*z* calcd for $[C_{16}H_{26}N_2O_2S + H]^+$: 311.1788, found 311.1790.

***N*-{[(1*S*,2*S*)-2-(Benzylamino)cyclohexyl]methyl}-4-methylbenzenesulfonamide (9).** To a solution of **5a** (800 mg, 3.66 mmol) and TEA (560 μL, 4.01 mmol) in $CHCl_3$ (15 mL), tosyl chloride (698 mg, 3.66 mmol) was added and the reaction mixture was refluxed for 15 h. The reaction was quenched by addition of 1 M NaOH aq (5 mL), and the organic layer was washed with 1 M NaOH aq. (10 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:1 to MeOH/$CHCl_3$ = 1:10) to produce the sulfonamide **9** (1.30 g, 3.50 mmol, 96% yield) as a white powder. Mp: 89−90 °C. $[\alpha]_D^{23}$ = +13.6 (*c* 0.17, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.26−7.17 (m, 7H), 3.64 (s, 2H), 3.04 (dd, J_1 = 12.0 Hz, J_2 = 8.0 Hz, 1H), 2.85 (dd, J_1 = 12.3 Hz, J_2 = 4.3 Hz, 1H), 2.67 (ddd, J_1 = 7.5 Hz, J_2 = J_3 = 3.6 Hz, 1H), 2.33 (s, 3H), 1.83−1.81 (m, 1H), 1.54−1.51 (m, 1H), 1.39−1.34 (m, 3H), 1.31−1.27 (m, 2H), 1.25−1.18 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 140.0, 137.4, 129.6, 128.7, 128.3, 127.3, 127.1, 57.3, 51.6, 45.6, 37.2, 27.8, 26.8, 23.1, 22.4, 21.6. IR (KBr): ν_{max} 2925, 2862, 1458, 1448, 1328, 1290, 1162, 1094, 1081, 824, 740, 702, 662, 576, 553 cm^{-1}. HRMS (ESI$^+$): *m*/*z* calcd for $[C_{21}H_{28}N_2O_2S + Na]^+$: 395.1764, found 395.1767.

***N*-{[(1*S*,2*S*)-2-Aminocyclohexyl]methyl}-4-methylbenzenesulfonamide (3a).** A mixture of **9** (1.24 g, 3.33 mmol) and 10% Pd−C (377 mg, catalytic amount) in EtOH (10 mL) was stirred for 36 h at 70 °C under H_2 atmosphere (1 atm). After completion of the reaction, the catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc to 25% NH_3 aq/MeOH/$CHCl_3$ = 1:10:100) to yield the 1,3-aminosulfonamide **3a** (646 mg, 2.29 mmol, 69% yield) as a white powder. Mp: 144−145 °C. $[\alpha]_D^{23}$ = +13.0 (*c* 0.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.08 (br s, 1H), 3.03 (dd, J_1 = 12.3 Hz, J_2 = 7.8 Hz, 1H), 2.88 (dd, J_1 = 12.3 Hz, J_2 = 4.3 Hz, 1H), 2.42 (s, 3H), 1.70−1.68 (m, 1H), 1.55−1.34 (m, 7H), 1.27−1.24 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 137.4, 129.7, 127.2, 49.9, 46.3, 39.5, 33.4, 25.5, 24.3, 21.6, 21.0. IR (KBr): ν_{max} 3370, 3305, 3054, 2932, 2891, 2854, 1598, 1448, 1323, 1304, 1282, 1160, 1095, 1051, 1039, 962, 924, 823 808, 775, 757, 658, 553 cm^{-1}. HRMS (ESI$^+$): *m*/*z* calcd for $[C_{14}H_{22}N_2O_2S + H]^+$: 283.1475, found 283.1478.

4-Methyl-*N*-{[(1*S*,2*S*)-2-(methylamino)cyclohexyl]methyl}benzenesulfonamide (3b). To a solution of **3a** (141 mg, 0.500 mmol) and TEA (76.5 μL, 0.549 mmol) in dry THF (10 mL), ethyl chloroformate (52.0 μL, 0.548 mmol) was added dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. When the reaction completed, the reaction mixture was filtered through filter paper and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry THF (2 mL) and this solution was added dropwise to a suspension of $LiAlH_4$ (56.9 mg, 1.50 mmol) in dry THF (5 mL) at 0 °C under N_2 atmosphere. The mixture was refluxed for 24 h and the reaction was quenched by addition of ion-exchanged water (57.0 μL), 15% NaOH aq (57.0 μL) and ion-exchanged water (170 μL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M HCl aq (10 mL). The aqueous solution was washed with EtOAc (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous solution was extracted with $CHCl_3$ (10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to afford the 1,3-aminosulfonamide **3b** (91.3 mg, 0.308 mmol, 62% yield) as a colorless viscous liquid. $[\alpha]_D^{21}$ = +14.9 (*c* 0.40, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.12 (dd, J_1 = 12.0 Hz, J_2 = 8.0 Hz, 1H), 2.92 (dd, J_1 = 12.0 Hz, J_2 = 4.0 Hz, 1H), 2.58 (ddd, J_1 = 7.5 Hz, J_2 = J_3 = 3.6 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 1.96−1.88 (m, 1H), 1.53−1.47 (m, 3H), 1.43−1.33 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 137.4, 129.6, 127.2, 60.8, 45.7, 36.5, 34.3, 27.5, 27.2, 23.0, 22.8, 21.6. IR (neat): ν_{max} 3288, 2927, 2857, 1450, 1324, 1160, 1095, 815, 551 cm^{-1}. HRMS (ESI$^+$): *m*/*z* calcd for $[C_{15}H_{24}N_2O_2S + H]^+$: 297.1631, found 297.1634.

Typical Procedure for the Synthesis of 1,3-Aminosulfonamides 3c, 3e, 3g−i. To a mixture of **3a** (141 mg, 0.500 mmol) and K_2CO_3 (180 mg, 1.30 mmol) in THF (5 mL), MeI (134 μL, 2.15 mmol) was added and the mixture was stirred for 96 h at room temperature. The mixture was filtered through filter paper and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to furnish the 1,3-aminosulfonamide **3c** (61.4 mg, 0.198 mmol, 40% yield) as a white powder.

***N*-{[(1*S*,2*S*)-2-(Dimethylamino)cyclohexyl]methyl}-4-methylbenzenesulfonamide (3c).** Mp: 108−109 °C. $[\alpha]_D^{22}$ = +42.1 (*c* 0.38, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.0 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 3.19 (dd, J_1 = J_2 = 11.3 Hz, 1H), 2.94 (dd,

J_1 = 12.0 Hz, J_2 = 4.5 Hz, 1H), 2.43 (s, 3H), 2.37−2.35 (m, 1H), 2.21 (s, 6H), 2.05 (app. d, J = 12.0 Hz, 1H), 1.70 (app. d, J = 10.0 Hz, 2H), 1.59 (app. d, J = 13.5 Hz, 1H), 1.41−1.32 (m, 2H), 1.20−1.09 (m, 2H), 1.07−0.98 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 137.4, 129.6, 127.2, 68.3, 43.6, 43.5, 32.8, 29.6, 25.8, 24.4, 21.7, 20.1. IR (KBr): ν_{max} 3445, 2925, 1328, 1163, 1096, 664, 572, 553 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{16}H_{26}N_2O_2S + H]^+$: 311.1788, found 311.1794.

***N*-{[(1*S*,2*S*)-2-(Diethylamino)cyclohexyl]methyl}-4-methylbenzenesulfonamide (3e).** The 1,3-sulfonamide **3e** (39.8 mg, 0.118 mmol, 24% yield) was obtained as a white powder according to the typical procedure using **3a** (141 mg, 0.500 mmol), K_2CO_3 (180 mg, 1.30 mmol) and EtI (4.02 mL, 50.0 mmol) under reflux. Mp: 104−105 °C. $[\alpha]_D^{23}$ = +28.3 (c 0.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (br s, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 3.20 (dd, J_1 = J_2 = 11.5 Hz, 1H), 2.92 (dd, J_1 = 11.5 Hz, J_2 = 3.5 Hz, 1H), 2.69 (dq, J_1 = 14.0 Hz, 7.0 Hz, 2H), 2.58 (dq, J_1 = 13.5 Hz, J_2 = 7.0 Hz, 2H), 2.51 (app. d, J = 11.5 Hz, 1H), 2.43 (s, 3H), 2.33−2.31 (m, 1H), 1.71−1.66 (m, 2H), 1.55 (app. d, J = 14.0 Hz, 1H), 1.42−1.33 (m, 2H), 1.21−1.08 (m, 3H), 0.97 (dd, J_1 = J_2 = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 137.5, 129.6, 127.2, 63.0, 43.7, 41.4, 32.9, 30.0, 26.2, 24.2, 21.7, 20.6, 10.4. IR (KBr): ν_{max} 3444, 2976, 2927, 2867, 1327, 1160, 1092, 823, 661, 563, 553 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{18}H_{30}N_2O_2S + H]^+$: 339.2101, found 339.2103.

***N*-{[(1*S*,2*S*)-2-(Dipropylamino)cyclohexyl]methyl}-4-methylbenzenesulfonamide (3g).** The 1,3-sulfonamide **3g** (81.4 mg, 0.222 mmol, 44% yield) was obtained as a white powder according to the typical procedure using **3a** (141 mg, 0.500 mmol), K_2CO_3 (180 mg, 1.30 mmol) and ^{n}PrI (4.86 mL, 50.0 mmol) under reflux. Mp: 74−75 °C. $[\alpha]_D^{23}$ = +11.0 (c 0.17, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.20 (dd, J_1 = J_2 = 11.3 Hz, 1H), 2.93 (dd, J_1 = 11.5 Hz, J_2 = 4.5 Hz, 1H), 2.52−2.44 (m, 4H), 2.43 (s, 3H), 2.32 (ddd, J_1 = 7.0 Hz, J_2 = J_3 = 3.5 Hz, 1H), 1.73−1.70 (m, 1H), 1.64 (app. d, J = 10.5 Hz, 1H), 1.55 (app. d, J = 13.5 Hz, 1H), 1.49−1.32 (m, 7H), 1.19−1.10 (m, 3H), 0.86 (t, J = 7.3 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 137.5, 129.6, 127.2, 64.0, 51.4, 43.6, 33.1, 29.9, 26.2, 24.4, 21.6, 20.6, 18.9, 12.0. IR (KBr): ν_{max} 3279, 2951, 2930, 2869, 2851, 1456, 1426, 1329, 1157, 1092, 1059, 816, 670, 550 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{20}H_{34}N_2O_2S + H]^+$: 367.2414, found 367.2416.

4-Methyl-*N*-{[(1*S*,2*S*)-2-(pyrrolidin-1-yl)cyclohexyl]methyl}benzenesulfonamide (3h). The 1,3-sulfonamide **3h** (150 mg, 0.446 mmol, 89% yield) was obtained as a white powder according to the typical procedure using **3a** (141 mg, 0.500 mmol), K_2CO_3 (180 mg, 1.30 mmol) and 1,4-diiodobutane (75.5 μL, 0.577 mmol) under reflux. Mp: 118−119 °C. $[\alpha]_D^{23}$ = +16.0 (c 0.38, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.23 (dd, J_1 = J_2 = 11.5 Hz, 1H), 2.97 (dd, J_1 = 12.0 Hz, J_2 = 5.0 Hz, 1H), 2.62−2.61 (m, 2H), 2.43 (s, 3H), 2.41−2.40 (m, 2H), 2.31 (ddd, J_1 = 8.0 Hz, J_2 = J_3 = 4.0 Hz, 1H), 2.24−2.21 (m, 1H), 1.82−1.72 (m, 4H), 1.68−1.66 (m, 2H), 1.56 (app. d, J = 14.0 Hz, 1H), 1.40 (dddd, J_1 = J_2 = 13.5 Hz, J_3 = J_4 = 3.0 Hz, 1H), 1.36−1.33 (m, 1H), 1.25−1.09 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 137.5, 129.6, 127.1, 67.7, 52.0, 43.4, 34.3, 29.2, 25.7, 25.6, 23.1, 21.6, 20.3. IR (KBr): ν_{max} 3445, 2938, 2867, 1320, 1161, 1144, 1092, 822, 661, 568, 553 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{18}H_{28}N_2O_2S + H]^+$: 337.1944, found 337.1945.

4-Methyl-*N*-{[(1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl]methyl}benzenesulfonamide (3i). The 1,3-sulfonamide **3i** (99.1 mg, 0.283 mmol, 57% yield) was obtained as a white powder according to the typical procedure using **3a** (141 mg, 0.500 mmol), K_2CO_3 (180 mg, 1.30 mmol) and 1,5-diiodopentane (85.5 μL, 0.575 mmol) under reflux. Mp: 123−124 °C. $[\alpha]_D^{23}$ = +21.1 (c 0.38, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.96 (br s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.18 (dd, J_1 = J_2 = 11.5 Hz, 1H), 2.91 (dd, J_1 = 12.0 Hz, J_2 = 3.5 Hz, 1H), 2.50 (br s, 4H), 2.43 (s, 3H), 2.35−2.33 (m, 1H), 2.22 (ddd, J_1 = 12.5 Hz, J_2 = J_3 = 3.5 Hz, 1H), 1.72−1.54 (m, 7H), 1,46 (br s, 2H), 1.42−1.29 (m, 2H), 1.18−1.07 (m, 2H), 1.06−0.96 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 137.6, 129.6, 127.1, 66.7, 51.5, 43.9, 32.5, 30.1, 26.5, 26.1, 24.6, 23.6, 21.7, 20.6. IR (KBr): ν_{max} 3446, 2936, 2919, 2859, 1328, 1315, 1161, 1145, 1096, 661, 567, 550 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{19}H_{30}N_2O_2S + H]^+$: 351.2101, found 351.2104.

Typical Procedure for the Synthesis of Diamides 10b−d. To a solution of (−)-**1** (495 mg, 2.00 mmol) and TEA (310 μL, 2.23 mmol) in $CHCl_3$ (5 mL), ethyl chloroformate (190 μL, 2.00 mmol) was added dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. To the reaction mixture, Et_2NH (420 μL, 4.06 mmol) was added under stirring, and stirring was continued for 15 h at room temperature. The solvents were removed under reduced pressure, and the residue was diluted by EtOAc (10 mL), and the organic solution was washed with 1 M HCl aq (10 mL × 2) and 1 M NaOH aq (10 mL × 2) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dried in vacuo to give the diamide **10b** (339 mg, 1.12 mmol, 56% yield) as a white powder. The diamide was directly used in the next reaction without further purification.

***N*-[(1*S*,2*R*)-2-(Diethylcarbamoyl)cyclohexyl]benzamide (10b).** The analytical sample was prepared by purification of the product on silica gel PTLC (EtOAc/hexane = 1:1). Mp: 117−118 °C. $[\alpha]_D^{20}$ = +54.0 (c 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 6.8 Hz, 1H), 7.42 (dd, J_1 = J_2 = 7.6 Hz, 2H), 7.24 (br d, J = 4.8 Hz, 1H), 4.24−4.21 (m, 1H), 3.41−3.24 (m, 4H), 3.02−2.99 (m, 1H), 2.52−2.48 (m, 1H), 1.94 (app. q, J = 9.3 Hz, 1H), 1.68−1.62 (m, 3H), 1,59−1.41 (m, 3H), 1.18 (t, J = 6.8 Hz, 3H), 1.05 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 167.3, 135.1, 131.4, 128.7, 127.1, 48.1, 42.3, 40.9, 40.5, 29.4, 26.3, 23.5, 22.1, 15.1, 13.3. IR (KBr): ν_{max} 3377, 2979, 2933, 2874, 1655, 1620, 1489, 1463, 1073, 710, 691 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{18}H_{26}N_2O_2 + Na]^+$ 325.1888, found 325.1884.

***N*-[(1*S*,2*R*)-2-(Pyrrolidine-1-carbonyl)cyclohexyl]benzamide (10c).** The diamide **10c** (541 mg, 1.80 mmol, 90% yield) was obtained as a white powder according to the typical procedure using (−)-**1** (495 mg, 2.00 mmol), TEA (310 μL, 2.23 mmol), ethyl chloroformate (190 μL, 2.00 mmol) and pyrrolidine (330 μL, 4.11 mmol). The analytical sample was prepared by purification of the product on silica gel PTLC (EtOAc/hexane = 1:1). Mp: 94−95 °C. $[\alpha]_D^{18}$ = +54.6 (c 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.42 (dd, J_1 = J_2 = 7.6 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 4.25−4.20 (m, 1H), 3.54−3.37 (m, 4H), 2.92−2.89 (m, 1H), 2.51−2.48 (m, 1H), 1.98−1.89 (m, 3H), 1.88−1.81 (m, 2H), 1.69−1.53 (m, 4H), 1.49−1.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 167.2, 135.0, 131.4, 128.6, 127.1, 47.7, 46.7, 45.9, 43.1, 29.4, 26.3, 25.6, 24.3, 23.4, 22.2. IR (KBr): ν_{max} 3419, 2932, 1646, 1620, 1523, 1486, 1448, 754, 714 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{18}H_{24}N_2O_2 + Na]^+$ 323.1730, found 323.1737.

***N*-[(1*S*,2*R*)-2-(Piperidine-1-carbonyl)cyclohexyl]benzamide (10d).** The diamide **10d** (610 mg, 1.94 mmol, 97% yield) was obtained as a white powder according to the typical procedure using (−)-**1** (495 mg, 2.00 mmol), TEA (310 μL, 2.23 mmol), ethyl chloroformate (190 μL, 2.00 mmol) and piperidine (590 μL, 5.97 mmol). The analytical sample was prepared by purification of the product on silica gel PTLC (EtOAc/hexane = 1:1). Mp: 76−77 °C. $[\alpha]_D^{23}$ = +42.7 (c 0.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J = 7.0 Hz, 2H), 7.48 (tt, J_1 = 7.3 Hz, J_2 = 1.7 Hz, 1H), 7.43−7.40 (m, 2H), 7.08 (br d, J = 7.0 Hz, 1H), 4.28−4.25 (m, 1H), 3.57−3.46 (m, 2H), 3.43−3.38 (m, 2H), 3.08 (ddd, J_1 = 7.5 Hz, J_2 = J_3 = 4.5 Hz, 1H), 2.42−2.40 (m, 1H), 1.95−1.91 (m, 1H), 1.71−1.62

(m, 8H), 1.61−1.43 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 167.0, 135.1, 131.3, 128.6, 127.1, 48.0, 47.0, 42.9, 40.8, 29.5, 26.9, 26.5, 25.8, 24.7, 23.1, 22.8. IR (KBr): ν_{max} 3326, 2935, 2856, 1633, 1579, 1529, 1488, 1442, 1256, 1223, 715 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{19}H_{26}N_2O_2 + Na]^+$ 337.1886, found 337.1887.

Typical Procedure for the Synthesis of Diamines 11b−d. To a suspension of $LiAlH_4$ (213 mg, 5.60 mmol) in dry THF (5 mL) was added dropwise a solution of **10b** (339 mg, 1.12 mmol) in dry THF (5 mL) at 0 °C under N_2 atmosphere. After completion of addition, the reaction mixture was refluxed for 96 h. The reaction was quenched by addition of ion-exchanged water (210 μL), 15% NaOH aq (210 μL), and ion-exchanged water (630 μL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M HCl aq (10 mL). The aqueous solution was washed with EtOAc (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous solution was extracted with $CHCl_3$ (10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 1:10) to afford the diamine **11b** (261 mg, 0.952 mmol, 85% yield) as a pale yellow oil.

(1*S*,2*S*)-*N*-Benzyl-2-[(diethylamino)methyl]cyclohexanamine (11b). $[\alpha]_D^{18}$ = +21.0 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.6 Hz, 2H), 7.30 (dd, $J_1 = J_2$ = 7.6 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.70 (d, *J* = 13.2 Hz, 1H), 2.82 (ddd, J_1 = 6.4 Hz, $J_2 = J_3$ = 3.2 Hz, 1H), 2.53−2.42 (m, 5H), 2.25 (dd, J_1 = 12.8 Hz, J_2 = 7.2 Hz, 1H), 1.82−1.69 (m, 2H), 1.61−1.55 (m, 3H), 1.50−1.47 (m, 1H), 1.40−1.34 (m, 3H), 1.32−1.26 (m, 1H) 0.99 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 128.3, 128.2, 126.7, 55.5, 54.3, 51.5, 47.6, 38.0, 28.9, 27.1, 24.4, 22.3, 11.9. IR (neat): ν_{max} 2968, 2926, 2853, 2796, 2362, 1495, 1453, 1200, 1176, 1069, 740, 698 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{18}H_{30}N_2 + H]^+$ 275.2482, found 275.2481.

(1*S*,2*S*)-*N*-Benzyl-2-(pyrrolidin-1-ylmethyl)cyclohexanamine (11c). The diamine **11c** (406 mg, 1.49 mmol, 83% yield) was obtained as a pale yellow oil according to the typical procedure using **10c** (541 mg, 1.80 mmol) and $LiAlH_4$ (342 mg, 9.00 mmol). $[\alpha]_D^{19}$ = +14.6 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.6 Hz, 2H), 7.29 (dd, $J_1 = J_2$ = 7.6 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 3.84 (d, *J* = 13.6 Hz, 1H), 3.73 (d, *J* = 13.6 Hz, 1H), 2.84 (ddd, J_1 = 6.4 Hz, $J_2 = J_3$ = 3.2 Hz, 1H), 2.57 (dd, J_1 = 12.0 Hz, J_2 = 3.0 Hz, 1H), 2.52−2.42 (m, 4H), 2.41 (dd, J_1 = 12.0 Hz, J_2 = 7.6 Hz, 1H), 1.88−1.84 (m, 1H), 1.73−1.68 (m, 5H), 1.62−1.52 (m, 3H), 1.44−1.38 (m, 2H), 1.36−1.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 128.3, 128.1, 126.7, 57.5, 55.7, 54.7, 51.3, 38.5, 28.8, 27.0, 24.0, 23.5, 22.3. IR (neat): ν_{max} 2926, 2785, 1453, 737, 698 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{18}H_{28}N_2 + H]^+$ 273.2325, found 273.2326.

(1*S*,2*S*)-*N*-Benzyl-2-(piperidin-1-ylmethyl)cyclohexanamine (11d). The diamine **11d** (450 mg, 1.57 mmol, >99% yield) was obtained as a pale yellow oil according to the typical procedure using **10d** (493 mg, 1.57 mmol) and $LiAlH_4$ (298 mg, 7.85 mmol). $[\alpha]_D^{23}$ = +30.8 (*c* 0.18, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.31 (ddd, $J_1 = J_2$ = 7.3 Hz, J_3 = 1.0 Hz, 2H), 7.23 (dd, *J* = 7.3 Hz, 1H), 3.84 (d, *J* = 13.5 Hz, 1H), 3.72 (d, *J* = 13.5 Hz, 1H), 2.87−2.75 (br, 1H), 2.40 (dd, J_1 = 12.5 Hz, J_2 = 8.0 Hz, 1H), 2.40−2.30 (br, 4H), 2.13 (dd, J_1 = 12.5 Hz, J_2 = 6.5 Hz, 1H), 1.91−1.82 (br, 1H), 1.71−1.67 (m, 2H), 1.63−1.58 (m, 1H), 1.55−1.51 (m, 5H), 1.49−1.25 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.5, 128.3, 128.2, 126.7, 60.6, 55.5, 55.1, 51.5, 36.9, 29.0, 27.4, 26.3, 24.8, 24.5, 22.3. IR (neat): ν_{max} 2929, 2852, 2796, 1453, 698 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{19}H_{30}N_2 + H]^+$ 287.2482, found 287.2482.

Typical Procedure for the Synthesis of Diamine 12b−d. A mixture of **11b** (261 mg, 0.952 mmol) and 10% Pd−C (26.1 mg, catalytic amount) in EtOH (5 mL) was stirred for 24 h at 70 °C under H_2 atmosphere (1 atm). After completion of the reaction, the catalyst was removed by filtration through Celite under reduced pressure, and the filtrate was concentrated under reduced pressure. The residue was dried in vacuo to yield the diamine **12b** (163 mg, 0.885 mmol, 93% yield) as a pale yellow oil. The diamine was directly used in the next reaction without further purification.

(1*S*,2*S*)-2-[(Diethylamino)methyl]cyclohexanamine (12b). The analytical sample was prepared by purification of the product on silica gel PTLC (MeOH/$CHCl_3$ = 1:10). $[\alpha]_D^{20}$ = +10.5 (*c* 0.11, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.09−3.09 (m, 1H), 2.57−2.51 (m, 2H), 2.43−2.35 (m, 3H), 2.15 (dd, J_1 = 12.5 Hz, J_2 = 5.0 Hz, 1H), 1.66−1.62 (m, 2H), 1.56−1.20 (m, 9H), 1.00 (t, *J* = 6.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5, 48.2, 47.5, 38.7, 33.7, 25.8, 25.3, 21.2, 11.8. IR (neat): ν_{max} 2965, 2927, 2854, 2798, 1455, 1383, 1200, 1092, 757 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{11}H_{24}N_2 + H]^+$ 185.2012, found 185.2016.

(1*S*,2*S*)-2-(Pyrrolidin-1-ylmethyl)cyclohexanamine (12c). The diamine **12c** (264 mg, 1.45 mmol, 97% yield) was obtained as a yellow oil according to the typical procedure using **11c** (406 mg, 1.49 mmol) and 10% Pd−C (40.6 mg, catalytic amount). The analytical sample was prepared by purification of the product on silica gel PTLC (MeOH/$CHCl_3$ = 1:10). $[\alpha]_D^{20}$ = +20.5 (*c* 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.11−3.10 (m, 1H), 2.51−2.42 (m, 5H), 2.21 (dd, J_1 = 12.0 Hz, J_2 = 7.0 Hz, 1H), 1.76−1.73 (m, 4H), 1.71−1.62 (m, 3H), 1.54−1.50 (m, 2H), 1.47−1.43 (m, 2H), 1.35−1.23 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 62.4, 54.8, 48.4, 40.0, 33.8, 30.4, 25.8, 25.3, 23.6. IR (neat): ν_{max} 3356, 2926, 2854, 2854, 2787, 1448 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{11}H_{22}N_2 + H]^+$ 183.1856, found 183.1855.

(1*S*,2*S*)-2-(Piperidin-1-ylmethyl)cyclohexanamine (12d). The diamine **12d** (279 mg, 1.42 mmol, >99% yield) was obtained as a brownish wet powder according to the typical procedure using **11d** (408 mg, 1.42 mmol) and 10% Pd−C (40.8 mg, catalytic amount). The analytical sample was prepared by purification of the product on silica gel PTLC (MeOH/$CHCl_3$ = 1:10). $[\alpha]_D^{22}$ = +24.0 (*c* 1.12, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10−3.10 (m, 1H), 2.39 (br s, 2H), 2.32 (dd, J_1 = 12.5 Hz, J_2 = 9.0 Hz, 1H), 2.26 (br s, 2H), 2.13 (br s, 2H), 2.07 (dd, J_1 = 12.5 Hz, J_2 = 6.3 Hz, 1H), 1.81−1.75 (m, 1H), 1.66−1.60 (m, 2H), 1.57−1.54 (m, 6H), 1.42−1.39 (m, 4H), 1.33−1.31 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 61.6, 55.3, 48.6, 37.2, 33.1, 29.8, 26.2, 24.9, 24.6, 21.5. IR (neat): ν_{max} 3414, 2928, 2854, 2781, 1557, 1456, 1380, 1359, 1348, 1297, 1285, 1156, 1119, 1039, 997, 813, 729 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{12}H_{24}N_2 + H]^+$ 197.2012, found 197.2015.

Typical Procedure for the Synthesis of 1,3-Amino Sulfonamides 2e−g. To a solution of **12b** (143 mg, 0.776 mmol), TEA (220 μL, 1.58 mmol) and DMAP (9.5 mg, 0.078 mmol) in $CHCl_3$ (10 mL) was added tosyl chloride (296 mg, 1.55 mmol) at 0 °C and, the reaction mixture was refluxed for 72 h. The reaction was quenched by addition of 1 M NaOH aq (5 mL), and the organic layer was washed with 1 M NaOH aq (10 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to produce the 1,3-amino sulfonamide **2e** (223 mg, 0.660 mmol, 85% yield) as a white powder.

***N*-{(1*S*,2*S*)-2-[(Diethylamino)methyl]cyclohexyl}-4-methylbenzenesulfonamide (2e).** Mp: 72−73 °C. $[\alpha]_D^{23}$ = +44.0 (*c* 0.60, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.34 (ddd, J_1 = 11.5 Hz, $J_2 = J_3$ = 3.9 Hz, 1H), 3.02 (dd, $J_1 = J_2$ = 12.5 Hz, 1H), 2.77 (dd, J_1 = 12.5 Hz, J_2 = 2.3 Hz, 1H), 2.66 (dq, J_1 = 14.0 Hz, J_2 = 7.0 Hz, 2H), 2.41 (s, 3H), 2.28 (dq, J_1 = 13.6 Hz, J_2 = 6.8 Hz, 2H), 1.93−1.90 (m, 1H), 1.77−1.74 (m, 1H), 1.67−1.63 (m, 1H), 1.51 (app. dq, J_1 = 13.5 Hz, J_2 = 3.5 Hz, 1H), 1.43−1.39 (m, 2H), 1.34−1.31 (m, 1H), 1.24−1.20 (m, 1H), 1.16−1.11 (m, 1H), 1.06 (dd, $J_1 = J_2$ = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 139.7, 129.5, 126.9, 55.7, 54.5, 46.8, 33.0, 30.5, 29.8, 25.2, 21.6, 20.6, 11.6. IR (KBr): ν_{max} 3439,

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3063, 2975, 2935, 2898, 2859, 2816, 1471, 1450, 1427, 1332, 1304, 12881162, 1092, 823, 662, 575, 551 cm^{-1}. HRMS (ESI^+): m/z calcd for $[C_{18}H_{30}N_2O_2S + H]^+$ 339.2101, found 339.2106.

4-Methyl-*N*-[(1*S*,2*S*)-2-(pyrrolidin-1-ylmethyl)cyclohexyl] benzenesulfonamide (2f). The 1,3-aminosulfonamide **2f** (360 mg, 1.07 mmol, 80% yield) was obtained as a white powder according to the typical procedure using **12c** (244 mg, 1.34 mmol), TEA (380 μL, 2.73 mmol), DMAP (16.4 mg, 0.134 mmol) and tosyl chloride (511 mg, 2.68 mmol). Mp: 73−74 °C. $[\alpha]_D^{23}$ = +33.1 (*c* 0.17, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.0 Hz, 2H), 3.38 (ddd, J_1 = 10.5 Hz, J_2 = J_3 = 4.3 Hz, 1H), 3.21 (dd, J_1 = J_2 = 12.0 Hz, 1H), 2.52−2.46 (br, 2H), 2.42 (s, 3H), 2.40−2.32 (br, 2H), 2.05 (dd, J_1 = 12.5 Hz, J_2 = 2.5 Hz, 1H), 1.89−1.85 (m, 1H), 1.79−1.75 (m, 4H), 1.74−1.69 (m, 1H), 1.67−1.62 (m, 1H), 1.59−1.53 (m, 1H), 1.44−1.40 (m, 2H), 1.33−1.29 (m, 1H), 1.27−1.23 (m, 1H), 1.21−1.11 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.6, 139.6, 129.5, 126.8, 57.3, 55.6, 54.2, 34.9, 30.3, 30.0, 24.9, 23.6, 21.6, 20.9. IR (KBr): ν_{max} 3443, 2935, 2892, 2874, 2843, 2804, 1445, 1328, 1307, 1284, 1164, 1094, 1082, 817, 661, 573, 553 cm^{-1}. HRMS (ESI^+): m/z calcd for $[C_{18}H_{28}N_2O_2S + H]^+$ 337.1944, found 337.1945.

4-Methyl-*N*-[(1*S*,2*S*)-2-(piperidin-1-ylmethyl)cyclohexyl] benzenesulfonamide (2g). The 1,3-aminosulfonamide **2g** (239 mg, 0.682 mmol, 68% yield) was obtained as a white powder according to the typical procedure using **12d** (196 mg, 1.00 mmol), TEA (290 μL, 2.08 mmol), DMAP (12.2 mg, 0.0999 mmol) and tosyl chloride (381 mg, 2.00 mmol). Mp: 89−90 °C. $[\alpha]_D^{23}$ = +30.2 (*c* 0.45, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 7.75 (d, J = 7.0 Hz, 2H), 7.26 (d, J = 7.5 Hz, 2H), 3.32 (ddd, J_1 = 11.5 Hz, J_2 = J_3 = 4.3 Hz, 1H), 2.89 (dd, J_1 = J_2 = 12.5 Hz, 1H), 2.62−2.34 (br, 2H), 2.41 (s, 3H), 2.32−2.10 (br, 2H), 2.01 (app. d, J = 12.5 Hz, 1H), 1.90−1.88 (m, 1H), 1.77−1.73 (m, 1H), 1.67−1.60 (m, 5H), 1.56−1.48 (m, 1H), 1.48−1,42 (br, 2H), 1.39−1.38 (m, 2H), 1.33−1.30 (m, 1H), 1.27−1.18 (m, 1H), 1.16−1.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ142.5, 139.6, 129.5, 126.8, 60.1, 55.7, 55.0, 32.4, 30.3, 29.8, 26.2, 25.2, 24.3, 21.6, 20.6. IR (KBr): ν_{max} 3445, 2926, 2850, 2816, 2786, 1451, 1439, 1325, 1310, 1285, 1154, 1112, 1099, 814, 661, 572, 548 cm^{-1}. HRMS (ESI^+): m/z calcd for $[C_{19}H_{30}N_2O_2S + H]^+$ 351.2101, found 351.2102.

Typical Procedure for the Synthesis of 1,3-Amino Sulfonamides 2d and 3d. To a solution of **2b** (88.9 mg, 0.300 mmol) and TEA (83.5 μL, 0.600 mmol) in dry THF (5 mL) was added acetyl chloride (42.5 μL, 0.596 mmol) dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. When the reaction completed, the reaction mixture was filtered through filter paper, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry THF (2 mL), and this solution was added dropwise to a suspension of $LiAlH_4$ (34.2 mg, 0.900 mmol) in dry THF (5 mL) at 0 °C under N_2 atmosphere. The mixture was refluxed for 24 h, and the reaction was quenched by addition of ion-exchanged water (35.0 μL), 15% NaOH aq (35.0 μL) and ion-exchanged water (105 μL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M HCl aq (10 mL). The aqueous solution was washed with EtOAc (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous solution was extracted with $CHCl_3$ (10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to afford the 1,3-amino sulfonamide **2d** (42.8 mg, 0.132 mmol, 44% yield) as a white powder.

***N*-((1*S*,2*S*)-2-{[Ethyl(methyl)amino]methyl}cyclohexyl)-4-methylbenzenesulfonamide (2d).** Mp: 104−105 °C. $[\alpha]_D^{17}$ = +35.7 (*c* 0.14, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 3.35 (ddd, J_1 = 10.5 Hz, J_2 = J_3 = 5.5 Hz, 1H), 3.01 (dd, J_1 = J_2 = 12.3 Hz, 1H), 2.54−2.50 (m, 1H), 2.42 (s, 3H), 2.30−2.29 (m, 1H), 2.17 (s, 3H), 1.98 (app. d, J = 12.5 Hz, 1H), 1.89−1.87 (m, 1H), 1.75−1.72 (m, 1H), 1.64−1.62 (m, 1H), 1.55−1.47 (m, 1H), 1.46−1.39 (m, 2H), 1.34−1.20 (m, 3H), 1.10 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 139.5, 129.6, 126.9, 58.6, 55.6, 51.9, 41.7, 33.2, 30.2, 29.9, 25.0, 21.6, 20.8, 12.4. IR (KBr): ν_{max} 3427, 2929, 2850, 1329, 1162, 1091, 663, 575, 553 cm^{-1}. HRMS (ESI^+): m/z calcd for $[C_{17}H_{28}N_2O_2S + H]^+$ 325.1944, found 325.1947.

***N*-({(1*S*,2*S*)-2-[Ethyl(methyl)amino]cyclohexyl}methyl)-4-methylbenzenesulfonamide (3d).** The 1,3-aminosulfonamide **3d** (68.1 mg, 0.210 mmol, 70% yield) was obtained as a white powder according to the typical procedure using **3b** (88.9 mg, 0.300 mmol), TEA (83.5 μL, 0.600 mmol), acetyl chloride (42.5 μL, 0.596 mmol) and $LiAlH_4$ (34.2 mg, 0.900 mmol). Mp: 113−114 °C. $[\alpha]_D^{23}$ = +34.5 (*c* 0.35, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.45 (br s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.19 (dd, J_1 = J_2 = 11.5 Hz, 1H), 2.92 (dd, J_1 = 11.5 Hz, J_2 = 4.3 Hz, 1H), 2.67 (dq, J_1 = 13.0 Hz, J_2 = 7.0 Hz, 1H), 2.43 (s, 3H), 2.40−2.34 (m, 2H), 2.31−2.28 (m, 1H), 2.18 (s, 3H), 1.71 (app. d, J = 9.0 Hz, 2H), 1.57 (app. d, J = 14.0 Hz, 1H), 1.42−1.32 (m, 2H), 1.21−1.09 (m, 3H), 1.04 (dd, J_1 = J_2 = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 137.4, 129.6, 127.2, 65.6, 47.8, 43.7, 38.0, 32.9, 29.8, 26.0, 24.2, 21.6, 20.4, 11.2. IR (KBr): ν_{max} 3446, 2972, 2930, 2868, 2785, 1452, 1402, 1326, 1161, 1142, 1092, 1037, 824, 807, 787, 768, 662, 576, 562, 553 cm^{-1}. HRMS (ESI^+): m/z calcd for $[C_{17}H_{28}N_2O_2S + H]^+$ 325.1944, found 325.1945.

***N*-{[(1*S*,2*S*)-2-(Ethylamino)cyclohexyl]methyl}-4-methylbenzenesulfonamide (13).** To a solution of **3a** (141 mg, 0.500 mmol) and TEA (140 μL, 1.01 mmol) in dry THF (5 mL) was added acetyl chloride (71.5 μL, 1.00 mmol) dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. When the reaction completed, the reaction mixture was filtered through filter paper, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry THF (2 mL), and this solution was added dropwise to a suspension of $LiAlH_4$ (56.9 mg, 1.50 mmol) in dry THF (5 mL) at 0 °C under N_2 atmosphere. The mixture was refluxed for 24 h, the reaction was quenched by addition of ion-exchanged water (57.0 μL), 15% NaOH aq (57.0 μL) and ion-exchanged water (170 μL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M HCl aq (10 mL). The aqueous solution was washed with EtOAc (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous solution was extracted with $CHCl_3$ (10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to afford the sulfonamide **13** (136 mg, 0.438 mmol, 87% yield) as a colorless viscous liquid. $[\alpha]_D^{21}$ = +16.1 (*c* 0.24, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.13 (dd, J_1 = 11.8 Hz, J_2 = 8.3 Hz, 1H), 2.92 (dd, J_1 = 12.0 Hz, J_2 = 3.4 Hz, 1H), 2.67 (ddd, J_1 = 8.0 Hz, J_2 = J_3 = 3.6 Hz, 1H), 2.67−2.60 (m, 1H), 2.58−2.52 (m, 1H), 2.42 (s, 3H), 1.93−1.85 (m, 1H), 1.53−1.47 (m, 3H), 1.39−1.26 (m, 5H), 1.09 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 137.5, 129.6, 127.1, 77.4, 58.9, 45.8, 41.8, 36.4, 28.2, 27.2, 22.9, 21.6, 15.6. IR (neat): ν_{max} 3285, 2927, 2859, 1326, 1161, 1095, 816, 661, 552 cm^{-1}. HRMS (ESI^+): m/z calcd for $[C_{16}H_{26}N_2O_2S + H]^+$ 311.1788, found 311.1784.

***N*-({(1*S*,2*S*)-2-[Ethyl(propyl)amino]cyclohexyl}methyl)-4-methylbenzenesulfonamide (3f).** To a solution of **13** (129 mg, 0.416 mmol) and TEA (116 μL, 0.833 mmol) in dry THF (5 mL) was added propanoyl chloride (72.5 μL, 0.831 mmol) dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. When the reaction completed, the reaction mixture was filtered through filter paper, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry THF (2 mL), and this solution was added dropwise to a suspension of $LiAlH_4$ (47.4 mg, 1.25 mmol) in dry THF (5 mL) at 0 °C under N_2

atmosphere. The mixture was refluxed for 24 h, the reaction was quenched by addition of ion-exchanged water (47.5 μL), 15% NaOH aq (47.5 μL) and ion-exchanged water (140 μL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M HCl aq (10 mL). The aqueous solution was washed with EtOAc (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous solution was extracted with $CHCl_3$ (10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel PTLC ($MeOH/CHCl_3$ = 1:10) to afford the sulfonamide **3f** (29.3 mg, 0.0832 mmol, 20% yield) as a white powder. Mp: 37−38 °C. $[\alpha]_D^{17}$ = +13.8 (*c* 0.21, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.20 (dd, $J_1 = J_2$ = 11.3 Hz, 1H), 2.92 (dd, J_1 = 11.5 Hz, J_2 = 4.0 Hz, 1H), 2.69−2.59 (m, 1H), 2.50 (br s, 1H), 2.47 (br s, 1H), 2.43 (s, 3H), 2.40 (br s, 1H), 2.31 (br s, 1H), 1.73−1.71 (m, 1H), 1.66 (app. d, *J* = 11.0 Hz, 1H), 1.56 (app. d, *J* = 13.0 Hz, 1H), 1.49−1.37 (m, 2H), 1.35−1.32 (m, 2H), 1.26−1.21 (m, 1H), 1.19−1.11 (m, 3H), 0.97 (dd, $J_1 = J_2$ = 6.8 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 137.4, 129.5, 127.2, 63.4, 50.4, 43.6, 42.3, 33.0, 29.9, 26.2, 24.2, 21.6, 20.5, 19.1, 12.0, 10.2. IR (KBr): ν_{max} 3440, 3278, 2963, 2928, 2870, 1330, 1161, 1094, 662, 565, 553 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{19}H_{32}N_2O_2S + H]^+$ 353.2257, found 353.2256.

***N*-[(1*S*,2*R*)-2-(Dimethylcarbamoyl)cyclohexyl)]benzamide (10e).** To a solution of (−)-**1** (1.24 g, 5.00 mmol) and TEA (770 μL, 5.53 mmol) in $CHCl_3$ (10 mL) was added ethyl chloroformate (480 μL, 5.06 mmol) dropwise at 0 °C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. To the reaction mixture was added 50% Me_2NH aq (5.00 mL, 75.5 mmol) under vigorous stirring, and stirring was continued for 15 h at room temperature. The reaction mixture was neutralized by addition of 6 M HCl aq, and then the solvents were removed under reduced pressure. The residue was diluted by EtOAc (20 mL), and the organic solution was washed with 1 M HCl aq (10 mL × 2) and 1 M NaOH aq (10 mL × 2), and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dried in vacuo to give the diamide **10e** (1.37 g, 5.00 mmol, >99% yield) as a colorless viscous liquid. The diamide was directly used in the next reaction without further purification. The analytical sample was prepared by purification of the product on silica gel PTLC (EtOAc/hexane = 1:1). $[\alpha]_D^{18}$ = +43.5 (*c* 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.50−7.46 (m, 1H), 7.42 (dd, $J_1 = J_2$ = 7.2 Hz, 2H), 7.12 (br d, *J* = 6.0 Hz, 1H), 4.30−4.24 (m, 1H), 3.10 (ddd, $J_1 = J_2 = J_3$ = 3.9 Hz, 1H), 3.05 (s, 3H), 2.91 (s, 3H), 2.47−2.40 (m, 1H), 1.99−1.91 (m, 1H), 1.72−1.54 (m, 4H), 1.51−1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 167.0, 134.9, 131.4, 128.6, 127.1, 47.7, 41.0, 37.6, 35.7, 29.4, 26.1, 23.1, 22.7. IR (neat): ν_{max} 3341, 2931, 1644, 1520, 1486, 753, 714 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{16}H_{22}N_2O_2 + Na]^+$ 297.1574, found 297.1578.

(1*S*,2*S*)-*N*-Benzyl-2-[(dimethylamino)methyl]cyclohexanamine (11e). To a suspension of $LiAlH_4$ (949 mg, 25.0 mmol) in dry THF (20 mL) was added a solution of **10e** (1.37 g, 5.00 mmol) in dry THF (10 mL) dropwise at 0 °C under N_2 atmosphere. After completion of addition, the reaction mixture was refluxed for 96 h. The reaction was quenched by addition of ion-exchanged water (950 μL), 15% NaOH aq (950 μL) and ion-exchanged water (2.85 mL) again at 0 °C, and then the cloudy reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1 M HCl aq (20 mL). The aqueous solution was washed with EtOAc (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous solution was extracted with $CHCl_3$ (20 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ = 1:10) to afford the diamine **11e** (1.11 g, 4.50 mmol, 90% yield) as a pale yellow oil. $[\alpha]_D^{19}$ = +5.1 (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.31 (dd, $J_1 = J_2$ = 7.2 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 3.82 (d, *J* = 12.8 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 2.81 (ddd, J_1 = 6.4 Hz, $J_2 = J_3$ = 3.2 Hz, 1H), 2.32 (dd, J_1 = 12.4 Hz, J_2 = 6.8 Hz, 1H), 2.22 (dd, J_1 = 12.4 Hz, J_2 = 7.6 Hz, 1H), 2.20 (s, 6H), 1.82−1.80 (m, 1H), 1.73−1.66 (m, 1H), 1.63−1.47 (m, 4H), 1.43−1.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 128.3, 128.2, 126.8, 60.8, 55.6, 51.6, 46.3, 37.6, 29.0, 26.7, 24.1, 22.3. IR (neat): ν_{max} 3027, 2925, 2817, 2763, 2360, 1457, 1030, 747, 698 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{16}H_{26}N_2 + H]^+$ 247.2169, found 247.2169.

(1*S*,2*S*)-2-[(Dimethylamino)methyl]cyclohexanamine (12e). A mixture of **11e** (1.11 g, 4.50 mmol) and 10% Pd−C (111 mg, catalytic amount) in EtOH (20 mL) was stirred for 24 h at 70 °C under H_2 atmosphere (1 atm). After completion of the reaction, the catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was dried in vacuo to yield the diamine **12e** (703 mg, 4.50 mmol, >99% yield) as a pale yellow oil. The diamine was directly used in the next reaction without further purification. The analytical sample was prepared by purification of the product on silica gel PTLC ($MeOH/CHCl_3$ = 1:10). $[\alpha]_D^{23}$ = +19.0 (*c* 0.90, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.10−3.09 (m, 1H), 2.27 (dd, J_1 = 12.4 Hz, J_2 = 8.4 Hz, 1H), 2.20 (s, 6H), 2.03 (dd, J_1 = 12.0 Hz, J_2 = 6.8 Hz, 1H), 1.65−1.63 (m, 3H), 1.55−1.39 (m, 3H), 1.35−1.22 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.4, 47.8, 46.1, 38.5, 33.7, 25.4, 25.2, 20.9. IR (neat): ν_{max} 2929, 2856, 2817, 2765, 1459, 1447, 1262, 1029, 849, 835, 755 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_9H_{20}N_2 + Na]^+$ 179.1519, found 179.1520.

***N*-{(1*S*,2*S*)-2-[(Dimethylamino)methyl]cyclohexyl}methanesulfonamide (2h).** To a solution of **12e** (156 mg, 1.00 mmol) and TEA (280 μL, 2.00 mmol) in $CHCl_3$ (5 mL) was added mesyl chloride (155 μL, 2.00 mmol) at 0 °C, and the reaction mixture was refluxed for 15 h. The reaction was quenched by addition of 1 M NaOH aq (2 mL), and the organic layer was diluted with $CHCl_3$ (10 mL), then washed with 1 M NaOH aq (10 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel PTLC ($MeOH/CHCl_3$ = 1:10) to produce the 1,3-aminosulfonamide **2h** (144 mg, 0.614 mmol, 61% yield) as a viscous yellow liquid. $[\alpha]_D^{21}$ = +28.7 (*c* 0.22, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 3.56 (ddd, J_1 = 10.0 Hz, $J_2 = J_3$ = 5.0 Hz, 1H), 2.94 (s, 3H), 2.93 (dd, $J_1 = J_2$ = 12.5 Hz, 1H), 2.24 (s, 6H), 2.13−2.10 (m, 1H), 1.99 (dd, J_1 = 13.0 Hz, J_2 = 3.5 Hz, 1H), 1.79−1.77 (m, 1H), 1.72−1.66 (m, 2H), 1.58−1.52 (m, 2H), 1.43−1.30 (m, 3H), 1.27−1.25 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.8, 45.6, 41.6, 34.7, 31.7, 30.5, 29.4, 24.3, 22.7. IR (neat): ν_{max} 3297, 2932, 2858, 2774, 1457, 1326, 1153, 1029, 1009 cm^{-1}. HRMS (ESI^+): *m*/*z* calcd for $[C_{10}H_{22}N_2O_2S + H]^+$ 235.1475, found 235.1480.

***N*-{(1*S*,2*S*)-2-[(Dimethylamino)methyl]cyclohexyl}trifluoromethanesulfonamide (2i).** To a solution of **12e** (156 mg, 1.00 mmol) and TEA (155 μL, 1.11 mmol) in $CHCl_3$ (5 mL) was added Tf_2O (180 μL, 1.10 mmol) at −40 °C, and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of 1 M NaOH aq (2 mL), and the organic layer was diluted with $CHCl_3$ (10 mL), then washed with 1 M NaOH aq (10 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel PTLC ($MeOH/CHCl_3$ = 1:10) to produce the 1,3-aminosulfonamide **2i** (186 mg, 0.645 mmol, 65% yield) as a white powder. Mp: 77−78 °C. $[\alpha]_D^{23}$ = +28.8 (*c* 0.29, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 9.33 (br s, 1H), 3.65 (ddd, J_1 = 12.0 Hz, $J_2 = J_3$ = 4.5 Hz, 1H), 3.15 (dd, $J_1 = J_2$ = 13.0 Hz, 1H), 2.33−2.22 (br, 1H), 2.29 (s, 6H), 2.11 (app. ddd, J_1 = 13.0 Hz, J_2 = 2.5 Hz, J_3 = 1.5 Hz, 1H), 1.96−1.95 (m, 1H), 1.77−1.74 (m, 1H), 1.63 (dddd, $J_1 = J_2 = J_3$ = 7.8 Hz, J_4 = 4.0 Hz, 1H),

1.60−1.51 (m, 2H), 1.44−1.41 (m, 1H), 1.31 (ddddd, $J_1 = J_2 = J_3 =$ 13.5 Hz, $J_4 = J_5 =$ 3.8 Hz, 1H), 1.16 (ddddd, $J_1 = J_2 = J_3 =$ 13.0 Hz, $J_4 = J_5 =$ 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 120.3 (q, J_{C-F} = 320 Hz), 60.6, 57.7, 45.0, 32.8, 30.2, 30.0, 25.2, 20.1. IR (KBr): ν_{max} 3444, 2952, 1477, 1282, 1207, 1196, 1179, 1156, 1079, 945, 877, 614 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{10}H_{19}F_3N_2O_2S + H]^+$ 289.1192, found 289.1193.

[(1*S*,2*S*)-2-(Pyrrolidin-1-yl)cyclohexyl]methanamine (14). To a solution of **3h** (505 mg, 1.50 mmol) in dry DME (5 mL) was added sodium naphthalenide (1 M in DME, freshly prepared by the reaction between sodium metal (230 mg, 10.0 mmol) and naphthalene (1.41 g, 11.0 mmol) in dry DME (10.0 mL) at room temperature for 2 h under N_2 atmosphere; 7.50 mL, 7.50 mmol) dropwise via a syringe at −78 °C. After completion of addition, the green reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched by addition of ion-exchanged water (1 mL), and the solvents were removed under reduced pressure. The residue was dissolved in 1 M HCl aq (15 mL). The aqueous solution was washed with Et_2O (10 mL × 2) and basified by addition of 6 M NaOH aq (pH >11). The resulting cloudy aqueous layer was extracted with $CHCl_3$ (20 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to afford the diamine **14** (130 mg, 0.713 mmol, 48% yield) as a pale yellow oil and the starting material **3h** was recovered (159 mg, 0.473 mmol, 32% recovery). $[\alpha]_D^{21}$ = −13.5 (*c* 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.99 (dd, J_1 = 12.8 Hz, J_2 = 4.8 Hz, 1H), 2.72 (dd, J_1 = 12.5 Hz, J_2 = 4.5 Hz, 1H), 2.53−2.44 (m, 4H), 2.05 (ddd, J_1 = 11.0 Hz, $J_2 = J_3$ = 3.8 Hz, 1H), 1.98−1.92 (m, 1H), 1.87−1.85 (m, 1H), 1.75−1.73 (m, 6H), 1.49 (br s, 2H), 1.41−1.26 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 67.6, 52.3, 40.6, 38.6, 27.4, 27.2, 25.6, 23.2, 20.2. IR (neat): ν_{max} 3373, 2925, 2864, 2779, 1493, 1473, 1451, 1376, 1147, 1129, 914, 889 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{11}H_{22}N_2 + H]^+$: 183.1856, found 183.1856.

***N*-{[(1*S*,2*S*)-2-(Pyrrolidin-1-yl)cyclohexyl]methyl}methanesulfonamide (3j).** To a solution of **14** (54.7 mg, 0.300 mmol) and TEA (50.5 μL, 0.363 mmol) in dry DCM (5 mL) was added mesyl chloride (27.5 μL, 0.355 mmol) at 0 °C, and then the reaction mixture was allowed to warm to room temperature and stirred for 15 h. The reaction was quenched by addition of 1 M NaOH aq (2 mL), and the organic layer was diluted with DCM (10 mL), then washed with 1 M NaOH aq (10 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to produce the 1,3-aminosulfonamide **3j** (45.3 mg, 0.174 mmol, 58% yield) as a white powder. Mp: 84−85 °C. $[\alpha]_D^{23}$ = +2.8 (*c* 0.28, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (br s, 1H), 3.53 (dd, $J_1 = J_2$ = 12.5 Hz, 1H), 3.09 (dd, J_1 = 12.5 Hz, J_2 = 5.5 Hz, 1H), 2.90 (s, 3H), 2.67 (br s, 2H), 2.48 (br s, 2H), 2.39−2.38 (m, 1H), 2.29 (app. d, J = 12.0 Hz, 1H), 1.84−1.76 (m, 6H), 1.66 (app. d, J = 13.0 Hz, 1H) 1.51−1.43 (m, 3H), 1.34−1.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 67.8, 52.2, 43.4, 39.6, 35.0, 29.1, 26.0, 25.6, 23.1, 20.3. IR (KBr): ν_{max} 3259, 2947, 2916, 2870, 2848, 2780, 1314, 1307, 1166, 1154, 1132, 1059, 520 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{12}H_{24}N_2O_2S + H]^+$ 261.1631, found 261.1632.

***N*-{[(1*S*,2*S*)-2-(Pyrrolidin-1-yl)cyclohexyl]methyl}trifluoromethanesulfonamide (3k).** To a solution of **14** (54.7 mg, 0.300 mmol) and TEA (50.5 μL, 0.363 mmol) in dry DCM (5 mL) was added Tf_2O (59.0 μL, 0.360 mmol) at −22 °C and the reaction mixture was stirred for 5 h at this temperature. The reaction was quenched by addition of 1 M NaOH aq (2 mL), and the organic layer was diluted with DCM (10 mL), then washed with 1 M NaOH aq (10 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to produce the 1,3-aminosulfonamide **3k** (80.2 mg, 0.255 mmol, 85% yield) as a white powder. Mp: 113−114 °C. $[\alpha]_D^{23}$ = +4.7 (*c* 0.38, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.53 (br s, 1H), 3.69 (dd, $J_1 = J_2$ = 12.0 Hz, 1H), 3.32 (dd, J_1 = 12.0 Hz, J_2 = 4.8 Hz, 1H), 2.85 (br s, 2H), 2.65 (br s, 2H), 2.58 (ddd, J_1 = 12.5 Hz, $J_2 = J_3$ = 3.0 Hz, 1H), 2.44 (app. dd, J_1 = 7.8 Hz, J_2 = 3.8 Hz, 1H), 1.88−1.78 (m, 6H), 1.69−1.59 (m, 2H), 1.51−1.44 (m, 2H), 1.41−1.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 120.7 (q, J_{C-F} = 321 Hz), 68.2, 51.4, 45.0, 33.4, 28.7, 25.6, 25.2, 22.9, 20.0. IR (KBr): ν_{max} 3446, 2933, 1284, 1272, 1236, 1208, 1173, 1150, 1137, 1081, 848, 615, 598 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{12}H_{21}F_3N_2O_2S + H]^+$ 315.1349, found 315.1354.

***N*,4-Dimethyl-*N*-{[(1*S*,2*S*)-2-(pyrrolidin-1-yl)cyclohexyl]methyl}benzenesulfonamide (15).** To a suspension of NaH (60% in oil; 60.0 mg, 1.50 mmol) in dry DMF (5 mL) was added **3h** (168 mg, 0.500 mmol) at 0 °C under N_2 atmosphere, and then the reaction mixture was allowed to warm to room temperature and stirred for 1 h. To the reaction mixture was added MeI (47.0 μL, 0.755 mmol), and the mixture was stirred for 15 h at room temperature. Ion-exchanged water (2 mL) was added to the mixture at 0 °C to destroy excess NaH, and the mixture was diluted with ion-exchanged water (10 mL). The solution was extracted with mixed organic solvent (EtOAc/hexane = 1:1; 10 mL × 3), and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel PTLC (MeOH/$CHCl_3$ = 1:10) to give the aprotic 1,3-aminosulfonamide **15** (98.1 mg, 0.280 mmol, 56% yield) as a white powder. Mp: 122−123 °C. $[\alpha]_D^{23}$ = −17.8 (*c* 0.57, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.52 (dd, $J_1 = J_2$ = 13.0 Hz, 1H), 2.79 (dd, J_1 = 13.5 Hz, J_2 = 2.3 Hz, 1H), 2.72 (s, 3H), 2.46 (br d, J = 3.0 Hz, 4H), 2.42 (s, 3H), 2.22−2.19 (m, 1H), 2.09−2.04 (m, 2H), 1.78−1.76 (m, 2H), 1.75−1.70 (m, 4H), 1.59−1.51 (m, 1H), 1.47−1.44 (m, 1H), 1.34−1.20 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 135.0, 129.8, 127.6, 66.9, 52.2, 47.0, 35.8, 35.4, 27.4, 26.2, 25.5, 23.3, 21.6, 19.8. IR (KBr): ν_{max} 2952, 2932, 2903, 2869, 2794, 1339, 1162, 930, 820, 753, 658, 577, 549 cm^{-1}. HRMS (ESI$^+$): m/z calcd for $[C_{19}H_{30}N_2O_2S + H]^+$ 351.2101, found 351.2105.

General Procedure for the Enantioselective Addition of Diethylzinc to Aldehydes Using 2c or 3h as Chiral Ligand. To a solution of **2c** (15.5 mg, 50.0 μmol, 10 mol %) or **3h** (8.4 mg, 25.0 μmol, 5 mol %) in dry toluene or hexane (750 μL) was added Et_2Zn (1 M in hexane; 1.25 mL, 1.25 mmol, 2.5 equiv or 1.00 mL, 1.00 mmol, 2.0 equiv) dropwise at 0 °C via a syringe under N_2 atmosphere, and the reaction mixture was stirred for 30 min. A solution of aldehyde (**16**; 0.500 mmol) in dry toluene or hexane (1 mL) was added dropwise to the mixture via a syringe, and the mixture was stirred for 24 h at 0 °C. The reaction was quenched by addition of 1 M HCl aq (2 mL), ion-exchanged water (10 mL) was added to the mixture, and the aqueous layer was extracted with EtOAc (10 mL × 3). The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by silica gel PTLC (EtOAc/hexane) to afford the corresponding enantio-enriched secondary alcohol (**17**). The ee value of the secondary alcohol was determined by chiral HPLC analysis or ^{1}H NMR analysis of the MTPA ester.[3a,d,9b,9c,14b,17,18]

1-Phenylpropan-1-ol (17a)[14b]. 91% yield, 83% ee (*S*) (conducted with **2c**) and >99% yield, 91% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OB-H, 2% IPA in hexane, 0.4 mL/min, 254 nm UV detector). Retention times: t_r = 29.5 min for (*S*)-isomer and t_r = 34.9 min for (*R*)-isomer. ^{1}H NMR (400 MHz): δ 7.36−7.24 (m, 5H), 4.57 (dd, $J_1 = J_2$ = 6.5 Hz, 1H), 2.00 (br s, 1H), 1.86−1.68 (m, 2H), 0.90 (dd, $J_1 = J_2$ = 7.4 Hz, 3H).

1-[4-(Trifluoromethyl)phenyl]propan-1-ol (17c)[18]. >99% yield, 82% ee (*S*) (conducted with **2c**) and >99% yield, 86% ee (*R*) (conducted with **3h**). The ee values were determined by ^{1}H NMR analysis of the (*R*)-(+)-MTPA esters (Mosher's ester method). ^{1}H NMR (400 MHz): δ7.57 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 4.59 (dd, $J_1 = J_2$ = 6.6 Hz, 1H), 2.77 (br s, 1H), 1.78−1.66 (m, 2H), 0.88 (dd, $J_1 = J_2$ = 7.4 Hz, 3H).

1-(4-Methoxyphenyl)propan-1-ol (17d)[3a]**.** 69% yield, 82% ee (*S*) (conducted with **2c**) and 95% yield, 83% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 2% IPA in hexane, 1.0 mL/min, 254 nm UV detector). Retention times: t_r = 22.9 min for (*R*)-isomer and t_r = 28.3 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 7.23 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.49 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 3.78 (s, 3H), 2.36 (br s, 1H), 1.84−1.62 (m, 2H), 0.90 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(4-Chlorophenyl)propan-1-ol (17e)[3a]**.** >99% yield, 82% ee (*S*) (conducted with **2c**) and 98% yield, 90% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 2% IPA in hexane, 0.8 mL/min, 254 nm UV detector). Retention times: t_r = 31.4 min for (*S*)-isomer and t_r = 33.6 min for (*R*)-isomer. ^{1}H NMR (400 MHz): δ 7.31 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 4.56 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 2.04 (br s, 1H), 1.85−1.62 (m, 2H), 0.89 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(3-Chlorophenyl)propan-1-ol (17f)[9b]**.** >99% yield, 82% ee (*S*) (conducted with **2c**) and 98% yield, 90% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OB-H, 5% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention times: t_r = 15.0 min for (*S*)-isomer and t_r = 17.6 min for (*R*)-isomer. ^{1}H NMR (400 MHz): δ7.35 (d, J = 2.1 Hz, 1H), 7.30−7.19 (m, 3H), 4.59 (dd, $J_1 = J_2$ = 6.6 Hz, 1H), 1.97 (br s, 1H), 1.87−1.63 (m, 2H), 0.92 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(2-Chlorophenyl)propan-1-ol (17g)[9b]**.** 89% yield, 81% ee (*S*) (conducted with **2c**) and 89% yield, 90% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OB-H, 2% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention times: t_r = 17.8 min for (*S*)-isomer and t_r = 20.2 min for (*R*)-isomer. ^{1}H NMR (400 MHz): δ 7.53 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 7.31 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 7.26 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 7.25 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 4.56 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 2.04 (br s, 1H), 1.86−1.64 (m, 2H), 0.98 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(4-Methylphenyl)propan-1-ol (17h)[9a]**.** 79% yield, 80% ee (*S*) (conducted with **2c**) and 96% yield, 92% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALPAK AD-H, 1% IPA in hexane, 1.0 mL/min, 254 nm UV detector). Retention times: t_r = 25.0 min for (*R*)-isomer and t_r = 29.3 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ7.23 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 4.54 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 2.36 (s, 3H), 2.08 (br s, 1H), 1.89−1.68 (m, 2H), 0.91 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(3-Methylphenyl)propan-1-ol (17i)[9b]**.** 82% yield, 82% ee (*S*) (conducted with **2c**) and 97% yield, 91% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OB-H, 5% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention times: t_r = 13.9 min for (*S*)-isomer and t_r = 16.4 min for (*R*)-isomer. ^{1}H NMR (400 MHz): δ 7.14 (dd, $J_1 = J_2$ = 7.6 Hz, 1H), 7.04−6.99 (m, 3H), 4.44 (dd, $J_1 = J_2$ = 6.4 Hz, 1H), 2.27 (s, 3H), 2.02 (br s, 1H), 1.75−1.61 (m, 2H), 0.82 (dd, $J_1 = J_2$ = 7.6 Hz, 3H).

1-(2-Methylphenyl)propan-1-ol (17j)[3a]**.** 78% yield, 83% ee (*S*) (conducted with **2c**) and 94% yield, 90% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALPAK AD-H, 1% IPA in hexane, 1.0 mL/min, 254 nm UV detector). Retention times: t_r = 20.7 min for (*R*)-isomer and t_r = 24.8 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 7.46 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.26−7.11 (m, 3H), 4.87 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 2.35 (s, 3H), 1.89 (br s, 1H), 1.79−1.67 (m, 2H), 0.99 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(Naphthalen-1-yl)propan-1-ol (17k)[3a]**.** 79% yield, 78% ee (*S*) (conducted with **2c**) and 94% yield, 86% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 10% IPA in hexane, 1.0 mL/min, 254 nm UV detector). Retention times: t_r = 9.2 min for (*S*)-isomer and t_r = 17.4 min for (*R*)-isomer. ^{1}H NMR (400 MHz): δ 8.10−8.08 (m, 1H), 7.91−7.76 (m, 2H), 7.63 (d, J = 6.9 Hz, 1H), 7.53−7.45 (m, 3H), 5.26 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 2.45 (br s, 1H), 2.07−1.86 (m, 2H), 1.03 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(Naphthalen-2-yl)propan-1-ol (17l)[3a]**.** 93% yield, 80% ee (*S*) (conducted with **2c**) and 98% yield, 90% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 10% IPA in hexane, 0.5 mL/min, 254 nm UV detector). Retention times: t_r = 22.4 min for (*S*)-isomer and t_r = 24.6 min for (*R*)-isomer. ^{1}H NMR (400 MHz): δ 7.88−7.82 (m, 3H), 7.75 (s, 1H), 7.55−7.45 (m, 3H), 4.71 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 2.63 (br s, 1H), 1.96−1.80 (m, 2H), 0.96 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-(Furan-2-yl)propan-1-ol (17m)[9c]**.** 67% yield, 76% ee (*S*) (conducted with **2c**) and 71% yield, 78% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 0.5% IPA in hexane, 1.5 mL/min, 230 nm UV detector). Retention times: t_r = 25.5 min for (*R*)-isomer and t_r = 29.4 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 7.29−7.28 (m, 1H), 6.25−6.24 (m, 1H), 6.15−6.14 (m, 1H), 4.51 (dd, $J_1 = J_2$ = 6.8 Hz, 1H), 2.14 (br s, 1H), 1.85−1.73 (m, 2H), 0.86 (dd, $J_1 = J_2$ = 7.2 Hz, 3H).

1-(Thiophen-2-yl)propan-1-ol (17n)[9c]**.** 88% yield, 85% ee (*S*) (conducted with **2c**) and 91% yield, 82% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 0.5% IPA in hexane, 1.5 mL/min, 230 nm UV detector). Retention times: t_r = 30.7 min for (*R*)-isomer and t_r = 35.9 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 7.24−7.20 (m, 1H), 6.94−6.92 (m, 2H), 4.76 (dd, $J_1 = J_2$ = 6.8 Hz, 1H), 2.65 (br s, 1H), 1.89−1.77 (m, 2H), 0.92 (dd, $J_1 = J_2$ = 7.6 Hz, 3H).

1-Phenylpent-1-yn-3-ol (17o)[17a]**.** 84% yield, 31% ee (*S*) (conducted with **2c**) and 95% yield, 46% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 5% IPA in hexane, 1.0 mL/min, 254 nm UV detector). Retention times: t_r = 11.6 min for (*R*)-isomer and t_r = 33.4 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 7.48−7.37 (m, 2H), 7.34−7.28 (m, 3H), 4.56 (dd, $J_1 = J_2$ = 6.9 Hz, 1H), 3.22 (br s, 1H), 1.88−1.76 (m, 2H), 1.08 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

***(E)*-1-Phenylpent-1-en-3-ol (17p)**[14b]**.** 68% yield, 63% ee (*S*) (conducted with **2c**) and 61% yield, 75% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 5% IPA in hexane, 1.0 mL/min, 254 nm UV detector). Retention times: t_r = 14.6 min for (*R*)-isomer and t_r = 25.5 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 7.45−7.23 (m, 5H), 6.59 (d, J = 15.9 Hz, 1H), 6.24 (dd, J_1 = 15.9 Hz, J_2 = 6.6 Hz, 1H), 4.87 (ddd, $J_1 = J_2 = J_3$ = 6.6 Hz, 1H), 1.87 (br s, 1H), 1.74−1.63 (m, 2H), 0.99 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-Phenylpentan-3-ol (17q)[3a]**.** 41% yield, 87% ee (*S*) (conducted with **2c**) and 60% yield, 91% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis (CHIRALCEL OD-3, 2% IPA in hexane, 1.5 mL/min, 254 nm UV detector). Retention times: t_r = 15.8 min for (*R*)-isomer and t_r = 27.6 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 7.33−7.28 (m, 2H), 7.24−7.17 (m, 3H), 3.59−3.54 (m, 1H), 2.84−2.79 (m, 1H), 2.71−2.66 (m, 1H), 1.86−1.71 (m, 2H), 1.58−1.47 (m, 2H), 1.42 (br s, 1H), 0.95 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

1-Cyclohexylpropan-1-ol (17r)[3d]**.** 49% yield, 94% ee (*S*) (conducted with **2c**) and 65% yield, 98% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis of the benzoates (CHIRALPAK AD-H, 1% IPA in hexane, 0.3 mL/min, 254 nm UV detector). Retention times: t_r = 18.7 min for (*R*)-isomer and t_r = 21.7 min for (*S*)-isomer. ^{1}H NMR (400 MHz): δ 3.31−3.26 (m, 1H), 1.82−1.11 (m, 14H), 0.95 (dd, $J_1 = J_2$ = 7.5 Hz, 3H).

Octan-3-ol (17s)[17b]**.** 12% yield, 86% ee (*S*) (conducted with **2c**) and 30% yield, 93% ee (*R*) (conducted with **3h**). The ee values were determined by chiral HPLC analysis of the benzoates (CHIRALCEL OD-3, hexane, 0.5 mL/min, 254 nm UV detector). Retention times: t_r = 21.1 min for (*S*)-isomer and t_r = 22.4 min for (*R*)-isomer. ^{1}H NMR (500 MHz): δ 3.55−3.49 (m, 1H), 1.63 (br s, 1H), 1.54−1.22 (m, 10H), 0.93 (dd, $J_1 = J_2$ = 7.5 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H).

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H NMR and ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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