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Synthesis of Amino-Functionalized Sulfonimidamides and Their Application in the Enantioselective Henry Reaction

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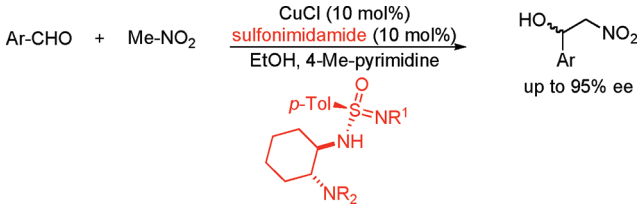

Amino-functionalized sulfonimidamides have been prepared by aziridinium ring-opening reactions and nucleophilic substitutions of sulfonimidoyl chlorides. Whereas the former reactions afford separable diastereomeric products, the latter provide single stereoisomers. Application of the resulting stereochemically homogeneous sulfonimidamides as ligands in asymmetric copper-catalyzed Henry reactions of aromatic aldehydes with nitromethane led to products with enantioselectivities up to 95% ee in good yields.

Introduction

Sulfonimidamides, the aza-analogues of sulfonamides, were first described in the 1960s by Levchenko et al.[1] Since then, the main interest for these compounds centered around their bioactivity[2] and their use as chiral nitrene precursors in metal-catalyzed nitrogen transfer reactions. In the latter context, aziridinations of olefins,[3] iminations of sulfides and sulfoxides,[3a,4] and CH aminations[5] have been studied by Malacria, Dodd, Müller, and others. In all of those reactions sulfonimidamides served as reagents being applied in stoichiometric quantities. Surprisingly, to the best of our knowledge, applications of sulfonimidamides as chiral ligands in asymmetric metal catalysis have not yet been described. The only example of a sulfonimidamide being part of a catalytic system involves a proline-derived organocatalyst, which we recently reported to promote solvent-free asymmetric aldol reactions leading to products with high enantioselectivities.[6]

On the basis of our expertise in sulfoximine chemistry[7] we hypothesized that the inherent stereogenic center at sulfur and the two nitrogens of a sulfonimidoyl amino moiety could be useful for the design and generation of effective ligands for asymmetric metal catalysis. For evaluating this assumption, amino-substituted sulfonimidamides such as **A** appeared suitable because they combined the well-known features of

(1) Levchenko, E. S.; Derkach, N. Y.; Kirsanov, A. V. *Zh. Obshch. Khim.* **1962**, *32*, 1208.

(2) See, for example: (a) Ray, E. J.; Toth, J. E. CA 2085297 A1, 1993. (b) Cathers, B. E. Dissertation, University of Kansas, Lawrence, KS, **1996**. (c) Toth, J. E.; Grindey, G. B.; Ehlhardt, W. J.; Ray, J. E.; Boder, G. B.; Bewley, J. R.; Klingerman, K. K.; Gates, S. B.; Rinzel, S. M.; Schultz, R. M.; Weir, L. C.; Worzalla, J. F. *J. Med. Chem.* **1997**, *40*, 1018. (d) Lang, H. J.; Jansen, H.-W.; Schwark, J.-R.; Kleemann, H.-W.; Jung, O.; Schafer, H.-L.; Linz, W.; Kramer, W.; Scholkens, B.; Falk, E. WO 9746226 A2, 1997. (e) Kleemann, H.-W.; Brendel, J.; Schwark, J.-R.; Weichert, A.; Lang, H. J.; Albus, U.; Scholz, W. EP 771788 A2, 1997. (f) Cathers, B. E.; Schloss, J. V. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1527. (g) Saxena, A.; Agrawal, V. K.; Khadikar, P. V. *Oxid. Commun.* **2003**, *26*, 9. (h) Paulini, R.; Breuninger, D.; von Deyn, W.; Bastiaans, H. M. M.; Beyer, C.; Anspaugh, D. D.; Oloumi-Sadeghi, H. WO 156336 A1, **2009**.

(3) For copper catalyses, see: (a) Leca, D.; Toussaint, A.; Mareau, C.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 3573. (b) Di Chenna, P. H.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503. (c) For rhodium catalyses, see: Fruit, C.; Robert-Peillard, F.; Bernardinelli, G.; Müller, P.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3484.

(4) Collet, F.; Dodd, R. H.; Dauban, P. *Org. Lett.* **2008**, *10*, 5473.

(5) (a) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (b) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343. (c) Rashatasakhan, P.; Harmata, M. *Chemtracts* **2006**, *19*, 143.

(6) Worch, C.; Bolm, C. *Synlett* **2009**, 2425.

(7) For reviews on the use of sulfoximines in metal catalysis, see: (a) Harmata, M. *Chemtracts* **2003**, *16*, 660. (b) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *32*, 482. (c) Bolm, C. In *Asymmetric Synthesis with Chemical and Biological Methods*; Enders, D., Jäger, K.-E., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p 149. (d) Worch, C.; Mayer, A. C.; Bolm, C. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008; p 209. (e) For a review on chiral sulfur-containing ligands in catalysis, see: Pellissier, H. *Tetrahedron* **2007**, *63*, 1297.

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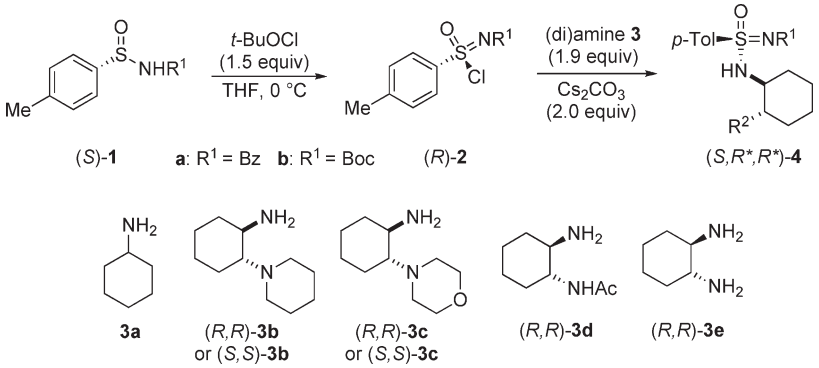
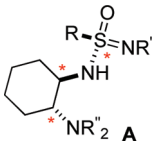
SCHEME 1. Synthesis of Sulfonimidamides 4 via Sulfonimidoyl Chlorides 2



vicinal *trans*-cyclohexanediamines with a still unexplored sulfonimidoyl amino group.



Following this concept a strategy for the synthesis of such compounds was developed, and subsequently the resulting products were tested in enantioselective copper-catalyzed nitroaldol reactions.

Results and Discussion

Syntheses of the Sulfonimidamides. Amino-substituted sulfonimidamides of type **A** have three stereogenic centers, and for obtaining them as single stereoisomers two preparative routes were devised. Method A involved couplings of sulfonimidoyl chlorides **2** with amino components **3** (Scheme 1). All chiral reaction partners were readily available in enantiomerically pure form, and stereospecific couplings led to isomerically homogeneous products. More specifically, stereoselective oxidative chlorinations of enantiopure sulfinamides (*S*)-**1**[8,9e] with *tert*-butylhypochlorite at 0 °C gave enantiopure sulfonimidoyl chlorides **2**,[9,10] which were directly (without isolation) converted into **4** by treatment with (di)amines **3** in the presence of Cs_2CO_3 at room temperature. (Di)amines **3** were either commercially available, or both enantiomers of the chiral derivatives were accessible by efficient resolution protocols of the racemic diamines.[11,12]

TABLE 1. Substrate Scope in the Synthesis of Sulfonimidamides 4 Starting from (*S*)-1

entry	sulfinamide	amine	sulfonimidamide	yield (%)
1[a]	(*S*)-**1a**	**3a**	(*S*)-**4a**	80
2[a]	(*S*)-**1b**	**3a**	(*S*)-**4b**	92
3	(*S*)-**1a**	(*S*,*S*)-**3b**	(*S*,*S*,*S*)-**4c**	48
4	(*S*)-**1a**	(*R*,*R*)-**3b**	(*S*,*R*,*R*)-**4d**	60
5	(*S*)-**1b**	(*S*,*S*)-**3b**	(*S*,*S*,*S*)-**4e**	43
6[b]	(*S*)-**1b**	(*R*,*R*)-**3b**	(*S*,*R*,*R*)-**4f**	48
7	(*S*)-**1a**	(*S*,*S*)-**3c**	(*S*,*S*,*S*)-**4g**	74
8	(*S*)-**1a**	(*R*,*R*)-**3c**	(*S*,*R*,*R*)-**4h**	78
9	(*S*)-**1b**	(*S*,*S*)-**3c**	(*S*,*S*,*S*)-**4i**	51
10	(*S*)-**1b**	(*R*,*R*)-**3c**	(*S*,*R*,*R*)-**4j**	59
11	(*S*)-**1a**	(*R*,*R*)-**3d**	(*S*,*R*,*R*)-**4k**	74
12[c]	(*S*)-**1a**	(*R*,*R*)-**3e**	(*S*,*R*,*R*)-**4l**	69

[a]In analogy *rac*-**1a** and *rac*-**1b** have been applied. [b]Use of 1.7 equiv of diamine. [c]Use of 3 equiv of diamine.

The substrate scope of this approach (method A) was wide, and the results for transformations starting from (*S*)-**1** are summarized in Table 1. In general, amino-substituted sulfonimidamides **4** were obtained in satisfactory to high yields, and commonly *N*-benzoyl-protected sulfinamide **1a** gave better results than sulfinamide **1b** having a *N*-Boc protecting group.

The well-studied stereochemistry of such reaction sequence (oxidative chlorination and subsequent attack of a nucleophile at sulfur) suggested a high stereospecificity with inversion of configuration at the stereogenic sulfur (via a retention-inversion pathway).[9d,e] Accordingly, all reactions between (*S*)-**1** and enantiopure diamines **3b-e** provided single diastereomers (Table 1, entries 3−12). Epimers were never observed. Furthermore, the reaction between (*S*)-**1a** and cyclohexylamine (**3a**) led to a single enantiomer (> 99% ee) as proven by HPLC analysis (Table 1, entry 1).[13] In the conversion of (*R*,*R*)-1,2-cyclohexanediamine (**3e**), a 3-fold excess of the diamine was used (instead of the commonly used 1.9 equiv) in order to prevent the formation of the corresponding biscoupled product (entry 12). In this manner, sulfonimidamide **4l** with a free amino functionality was accessed, offering the possibility for further derivatization at this position.

(8) For the preparation of enantiopure sulfinamides **1a** and **1b**, see: (a) Backes, B. J.; Dragoli, D. R.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 5472. (b) Dong, Z.; Pyne, S. G. *Sulfur Lett.* **2002**, *25*, 37. (c) Savile, C. K.; Magloire, V. P.; Kazlauskas, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 2104.

(9) For oxidative chlorinations of sulfinamides with *t*-BuOCl, see: (a) Johnson, C. R.; Wamsgans, A. *J. Org. Chem.* **1979**, *44*, 2278. (b) Harmata, M. *Tetrahedron Lett.* **1989**, *30*, 437. (c) Kluge, R.; Hocke, H.; Schulz, M.; Schilke, F. *Phosphorous, Sulfur Silicon Relat. Elem.* **1999**, *149*, 179. (d) Reggelin, M.; Junker, B. *Chem.—Eur. J.* **2001**, *7*, 1232. (e) Worch, C.; Atodiresei, I.; Raabe, G.; Bolm, C. *Chem.—Eur. J.* **2010**, *16*, 677.

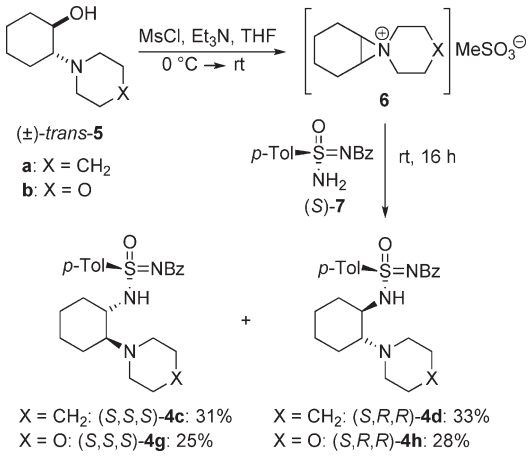
(10) For alternative oxidative chlorination methods of sulfinamides see, for example: Mancheño, O. G.; Bolm, C. *Beilstein J. Org. Chem.* **2007**, *3*, 25 and references therein.

(11) Enantiopure **3b** and **3c** were obtained by resolution of the corresponding racemic *trans*-diamines with mandelic acid following a similar protocol as described in (a) Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2320. (b) Schiffers, I.; Bolm, C. *Org. Synth.* **2008**, *85*, 106. (c) For the synthesis of racemic *trans*-**3b** and *trans*-**3c** and an alternative method for obtaining the diamines enantiomerically pure, see: Gonzalez-Sabin, J.; Gotor, V.; Rebolledo, F. *Chem.—Eur. J.* **2004**, *10*, 5788.

(12) In the graphic presentations of this article we follow the suggestions by Maehr for stereochemical notations. For a summary, see: Maehr, H. *J. Chem. Educ.* **1985**, *62*, 114.

(13) Suitable HPLC conditions for the ee analysis of sulfonimidamide **4b** could not be found.

SCHEME 2. Aziridinium Route to Amino-Substituted Sulfonimidamides



As alternative for the synthesis of amino-substituted sulfonimidamides, an aziridinium ring-opening sequence[14] involving the use of enantiomerically pure *N*-benzoyl-protected sulfonimidamide (*S*)-**7** (method B) was developed (Scheme 2). In contrast to method A, which provided single, isomerically pure products, method B led to diastereomers, which had to be separated. Advantages of this approach were the formation of two products in a single synthetic transformation and the availability of a wide range of racemic *trans*-aminoalcohols, which could easily be prepared in a single step from cyclohexene oxide.

Method B was used for the synthesis of amino-substituted sulfonimidamides (*S*,*S*,*S*)-**4c**, (*S*,*R*,*R*)-**4d**, (*S*,*S*,*S*)-**4g**, and (*S*,*R*,*R*)-**4h**. In one-pot reactions racemic *trans*-piperidinyl- and *trans*-morpholinyl-substituted aminoalcohols **5a** and **5b**, respectively, were first mesylated, and treatment of the resulting intermediates with enantiopure sulfonimidamide (*S*)-**7** gave amino-substituted sulfonimidamides **4c**/**4d** and **4g**/**4h** as ca. 1:1 pairs of diastereomers in acceptable overall yields. The intermediacy of aziridinium salts **6** guaranteed that only *trans*-products were generated, and in both cases the diastereomers could easily be separated by flash chromatography providing stereochemically homogeneous samples.[15]

Catalytic Application in the Henry Reaction. Henry reactions are nitroaldol-type additions of nitroalkanes to aldehydes generating products that often are versatile intermediates for organic synthesis. Transformations of the resulting β-nitroalkanes include, for example, reductions to the respective aminoalcohols,[16] Nef-oxidations to aldehydes, ketones or carboxylic acids,[17] and substitutions of the nitro group with carbon or heteroatom nucleophiles.[18] Of particular interest are catalytic and asymmetric versions of Henry reactions. Along these lines, various metal-based systems and organocatalytic approaches have recently been developed.[19] Since some catalysts involved 1,2-cyclohexanediamine-derived compounds,[20] we hypothesized that sulfonimidamides **4** could affect these transformations.[21] In order to test this idea, copper-catalyzed additions of nitromethane to *p*-nitrobenzaldehyde (**8a**) and benzaldehyde (**8b**) in the presence of sulfonimidamide (*S*,*R*,*R*)-**4d** were examined. First, the effects of the base, solvent, temperature, and copper source on the formations of products **9** were studied (Table 2).

In a typical experiment, the copper source and the sulfonimidamide were combined in dichloromethane, and the resulting mixture was kept at room temperature overnight to allow complex formation. For the subsequent catalysis, the solvent was changed (to the one listed in Table 2). Without preformation of the complex the yield of **9** was significantly lower (for example, compare Table 2, entries 8 and 9). Changing the catalyst amount from 10 to 5 mol % affected the yield negatively and the ee deceased (Table 2, entry 2 vs entry 3). In general, alcohols were the most suitable solvents, and the best results were achieved when the reactions were carried out in ethanol (compare entries 1, 8, 15−17). In this solvent, the yields reached the 80−90% range, and an ee of 88% (for **9b**) was observed (Table 2, entry 22). Lowering the reaction temperature from ambient temperature to 0 °C led to a decrease in both yield and enantioselectivity (entry 4). At 40 °C the ee (of product **9a**) was only 54% (Table 2, entry 5). Consequently, the subsequent experiments were performed at ambient temperature. Among the bases, pyridine and 4-methylpyrimidine gave the best results, with the latter being superior to the former. A screening of various copper sources using **8b** as substrate showed that all salts, except CuCN, were effective leading to good enantioselectivities. With CuCl the highest ee (83%) and a yield of 82% was achieved (Table 2, entry 8). Finally it was shown that neither lowering nor raising the concentration affected the results positively (Table 2, entries 19 and 20). Although a higher dilution led to a slight increase in enantioselectivity, the yield dropped from 82% to 62% (Table 2, entries 8 vs 20). An important observation was made when the reaction was performed (organocatalytically) with 10 mol % of (*S*,*R*,*R*)-**4d** in absence of a metal. In this case, the other enantiomer was preferentially formed. Albeit under these conditions the yield (20%) and the ee (8%) of **9b** were low (Table 2, entry 21), the result indicated that the previously performed

(14) (a) Periasamy, M.; Seenivasaperumal, M.; Padmaja, M.; Rao, V. D. *ARKIVOC* **2004**, *viii*, 4. (b) Anaya de Parrodi, C.; Juaristi, E. *Synlett* **2006**, 2699 and references therein.

(15) Attempts to use *N*-Boc-protected sulfonimidamide **7b** in combination with aminoalcohol **5a** or sulfonimidamide **7a** with a dibenzylated aminoalcohol remained unsuccessful, and complex product mixtures were formed.

(16) (a) Poupart, M.-A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356. (b) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.

(17) (a) Narayana, C.; Reddy, N. K.; Kabalka, G. W. *Synth. Commun.* **1992**, *22*, 2587. (b) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Syntheses*; Wiley-VCH: Weinheim, Germany, 1997. (c) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234. (d) For a review on Nef oxidations, see: Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.

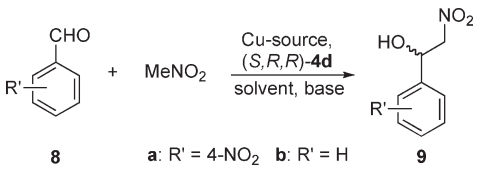
(18) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423.

(19) For recent reviews on Henry reactions, see: (a) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. (b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561. (c) Wang, A. X. In *Name Reactions for Homologations*; Li, J. J., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; p 404.

(20) For recent applications of catalysts with a 1,2-cyclohexanediamino skeleton in asymmetric Henry reactions, see: (a) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978. (b) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616. (c) Constable, E. C.; Zhang, G.; Housecroft, C. E.; Neuburger, M.; Schaffner, S.; Woggon, W.-D. *New J. Chem.* **2009**, *33*, 1064. (d) Zhang, G.; Yashima, E.; Woggon, W.-D. *Adv. Synth. Catal.* **2009**, *351*, 1255. (e) Kowalczyk, R.; Kwiatkowski, P.; Skarzewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753 and references therein.

(21) For the use of a sulfonamide-based *vicinal* diamine type ligand in a Henry reaction, see: Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903.

TABLE 2. Evaluation of Reaction Conditions in Copper-Catalyzed Henry Reactions with Sulfonimidamide 4d as Ligand[a]



8 **a**: R' = 4-NO_2 **b**: R' = H **9**

entry	RCHO	solvent	base (equiv)	Cu source	time (h)	yield (%)[b]	ee (%)[c]
1[d]	**8a**[e]	MeOH	pyridine (1.37)	CuCl	17	83	60 (*R*)
2[d]	**8a**[e]	EtOH	pyridine (1.37)	CuCl	4	93	61 (*R*)
3[d,f]	**8a**[e]	EtOH	pyridine (1.37)	CuCl	4	90	47 (*R*)
4[d,g]	**8a**[e]	EtOH	pyridine (1.37)	CuCl	16.5	64	45 (*R*)
5[h]	**8a**[e]	EtOH	pyridine (1.37)	CuCl	4	88	54 (*R*)
6	**8a**[e]	EtOH	4-Me-pyrimidine (1.37)	CuCl	4	85	66 (*R*)
7	**8b**	EtOH	4-Me-pyrimidine (1.37)	CuCl	25	76	82 (*R*)
8	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuCl	21	82	83 (*R*)
9[i]	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuCl	19	32	74 (*R*)
10	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuI	25	72	62 (*R*)
11	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuBr	21	62	79 (*R*)
12	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuOAc	21	74	75 (*R*)
13	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuCN	18.5	40	10 (*R*)
14	**8b**	EtOH	4-Me-pyrimidine (1.18)	$(CuOTf)_2 \cdot Tol$	25	50	51 (*R*)
15	**8b**	$MeNO_2$	4-Me-pyrimidine (1.18)	CuCl	21	58	42 (*R*)
16	**8b**	*i*-PrOH	4-Me-pyrimidine (1.18)	CuCl	18	50	81 (*R*)
17	**8b**	PhOEt	4-Me-pyrimidine (1.18)	CuCl	25	4	70 (*R*)
18	**8b**	EtOH	4-Me-pyrimidine (0.5)	CuCl	21	48	82 (*R*)
19[j]	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuCl	21	64	82 (*R*)
20[k]	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuCl	19.5	62	88 (*R*)
21	**8b**	EtOH	4-Me-pyrimidine (1.18)	---	17.5	20	8 (*S*)
22[l]	**8b**	EtOH	4-Me-pyrimidine (1.18)	CuCl	19.5	66	88 (*R*)

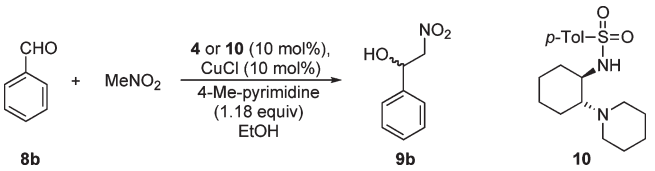
[a]Method: CuCl (10 mol %) and sulfonimidamide (*S*,*R*,*R*)-**4d** (11 mol %) were stirred at rt in CH_2Cl_2 (0.5 M) overnight. After removal of the solvent, the solid was redissolved in the indicated solvent (0.6 mL) and $MeNO_2$ (3 mmol, 10 equiv), base, and aldehyde **8a** or **8b** (0.3 mmol) were added. Then, the mixture was stirred at room temperature for the indicated period of time. [b]Yield after flash chromatography. [c]Enantiomeric ratios were determined by HPLC analysis using a Chiralcel OD-H column. Absolute configurations of the major enantiomers are given in parentheses. [d]CuCl−ligand complex preformation within 3 h. [e]Use of 0.5 mmol of the aldehyde. [f]Use of 5 mol % of CuCl and 5.5 mol % of (*S*,*R*,*R*)-**4d**. [g]Reaction performed at 0 °C. [h]Reaction performed at 40 °C. [i]No CuCl−ligand complex preformation. [j]1 M concentration. [k]0.25 M concentration. [l]Use of 10 mol % of (*S*,*R*,*R*)-**4d**.

copper catalyses could have been affected by the 10% excess of the sulfonimidamides with respect to the copper loading (use of 11 and 10 mol %, respectively). This assumption was confirmed by an experiment with equimolar amounts of CuCl and (*S*,*R*,*R*)-**4d**, which led to product **9b** with a slightly increased ee (88 vs 83%; Table 2, entries 22 and 8).

Using the optimized reaction conditions (complex preformation, EtOH as solvent, ambient temperature, 4-Me-pyrimidine as base, metal-to-ligand ratio of 1:1), sulfonimidamides **4a**−**l** were applied in the nitroaldol reaction between benzaldehyde (**8b**) and nitromethane. The results are summarized in Table 3.

Cyclohexylamine-derived sulfonimidamides (*S*)-**4a** and (*S*)-**4b** were almost inactive, leading to **9b** in very low yields (Table 3, entries 1 and 2). Presumably, the lack of the second nitrogen on the cyclohexane ring did not allow sufficient complexation of the metal to the ligands. This hypothesis was supported by the observation that with (*S*)-**4a** and (*S*)-**4b** no color change occurred during the initial complex formation phase, in contrast to the reaction behavior of diamine-derived sulfonimidamides, where the originally colorless solution turned green upon complex formation. It is also noteworthy that the application of (*S*,*R*,*R*)-**4k** having an amide nitrogen at the cyclohexane ring gave a catalyst with only moderate activity and low enantioselectivity (Table 3, entry 11). Also in this case the coordinating ability might have been too low to provide a high-activity copper catalyst. Sulfonimidamide (*S*,*R*,*R*)-**4l** having a primary amino group at the cyclohexane ring led to a catalyst with reasonable enantioselectivity, providing **9b** with 39% ee in 37% yield (Table 3, entry 12). Compared to the system with sulfonimidamide (*S*,*R*,*R*)-**4k** this one showed improved properties, but both could not compete with catalysts bearing diamine-derived sulfonimidamides **4c**−**j** having tertiary amino groups at the cyclohexane ring. Those proved to be the best ligands for the copper catalysis, providing products with good to high enantioselectivities in moderate to high yields (Table 3, entries 3−10). In general, the use of benzoyl-protected sulfonimidamides afforded products in higher yields and with slightly better enantioselectivities than their Boc-protected counterparts. Comparing the effects of ligands with piperidinyl and morpholinyl substituents [sulfonimidamides **4c**−**f** (Table 3, entries 3−6) versus **4g**−**j** (entries 7−10)], the latter proved more effective, suggesting that the higher basicity of the nitrogen improved the catalyst performance. Overall, the most effective ligand was (*S*,*R*,*R*)-**4h** leading to (*R*)-**9b** with 95% ee in 79% yield (Table 3, entry 8). Interestingly, its diastereomer (*S*,*S*,*S*)-**4g** gave the product with almost the same ee (92%), but the absolute configuration was opposite and the yield only moderate (47%; Table 3, entry 7). This result showed that the direction of asymmetric induction was determined by the two stereogenic centers at the cyclohexyl moiety and that the sulfonimidoyl amino group had a supporting effect for the catalyst activity and selectivity. The impact of the sulfur part of the ligand was further demonstrated by the application of sulfonamide-based

TABLE 3. Screening of Sulfonimidamides 4a−l in the Henry Reaction between Benzaldehyde (8b) and Nitromethane[a]



8b **9b** **10**

entry	sulfonimidamide	yield (%)[b]	ee (%)[c]
1	(*S*)-**4a**	11	0
2	(*S*)-**4b**	3	nd
3	(*S*,*S*,*S*)-**4c**	68	81 (*S*)
4[d]	(*S*,*R*,*R*)-**4d**	66	88 (*R*)
5	(*S*,*S*,*S*)-**4e**	40	55 (*S*)
6	(*S*,*R*,*R*)-**4f**	28	64 (*R*)
7	(*S*,*S*,*S*)-**4g**	47	92 (*S*)
8	(*S*,*R*,*R*)-**4h**	79	95 (*R*)
9	(*S*,*S*,*S*)-**4i**	69	77 (*S*)
10	(*S*,*R*,*R*)-**4j**	41	85 (*R*)
11	(*S*,*R*,*R*)-**4k**	34	4 (*S*)
12	(*S*,*R*,*R*)-**4l**	37	39 (*R*)
13	(*R*,*R*)-**10**	66	12 (*R*)

[a]Method: CuCl (10 mol %) and sulfonimidamide **4** (or sulfonamide **10**; 10 mol %) were stirred at rt in CH_2Cl_2 (3.4 mL) overnight. After removal of the solvent, the solid was redissolved in EtOH (1.2 mL), and $MeNO_2$ (10 equiv), 4-methylpyrimidine (1.18 equiv), and benzaldehyde (**8b**, 0.6 mmol, 1 equiv) were added. Stirring at ambient temperature overnight was followed by solvent evaporation and flash chromatography (see Experimental Section for details). [b]Yield after flash chromatography. [c]Enantiomeric ratios were determined by HPLC analysis; nd = not determined. Absolute configurations of the major enantiomers are given in parentheses. [d]Use of 0.3 mmol of **8b**.

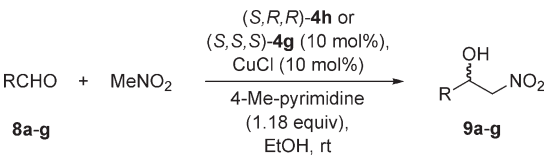
cyclohexanediamine **10**,[22] which led to a copper catalyst with good activity (66% yield in the formation of **9b**) but low enantioselectivity (12% ee; Table 3, entry 13). Clearly, the sulfonimidamides were superior to the analogous sulfonamide.

In order to evaluate the substrate scope, various aldehydes were applied under the optimized conditions in reactions with nitromethane using the (*S*,*R*,*R*)-**4h**/CuCl catalyst system. In addition, three of these Henry-type reactions were also performed with (*S*,*S*,*S*)-**4g** as ligand. The results are shown in Table 4.

All reactions with aromatic aldehydes (Table 4, entries 1−9) led to products with high ee values ranging from 88% to 95%. In contrast, aliphatic cyclohexylcarbaldehyde (**8g**, entry 10) reacted sluggishly, giving a mixture of unidentified products. The best results were achieved in catalyses with sulfonimidamide (*S*,*R*,*R*)-**4h**/CuCl. Compared to those obtained in analogous reactions with the diastereomeric ligand (*S*,*S*,*S*)-**4g**, the ee values and yields of the products were superior in all cases. Nevertheless, also with (*S*,*S*,*S*)-**4g** the product ees were high (88−92%), and noteworthy, applying this ligand instead of (*S*,*R*,*R*)-**4h** provided access to the enantiomeric series of the products. This aspect is particularly valuable because both sulfonimidamides (*S*,*R*,*R*)-**4h** and (*S*,*S*,*S*)-**4g** can be obtained in a single synthetic transformation by the aziridinium route (Scheme 2).

In comparison to published data from Henry reactions with related copper catalysts,[20d,21] the system reported here compares well, despite the fact that superior enantioselectivities could not be reached. This aspect as well as attempts to decrease the metal/ligand loading (of 10 mol %) will be addressed in subsequent studies, which shall focus on further ligand modifications.

TABLE 4. Substrate Scope in the Copper-Catalyzed Nitroaldol Reaction[a]



8a-g **9a-g**

entry	aldehyde **8**; R =	sulfonimidamide	yield of **9** (%)[b]	ee (%)[c]
1	4-(NO_2)-C_6H_4- (**8a**)	(*S*,*R*,*R*)-**4h**	82 (**9a**)	88 (*R*)
2	C_6H_5- (**8b**)	(*S*,*R*,*R*)-**4h**	79 (**9b**)	95 (*R*)
3	C_6H_5- (**8b**)	(*S*,*S*,*S*)-**4g**	47 (**9b**)	92 (*S*)
4	4−Cl-C_6H_4- (**8c**)	(*S*,*R*,*R*)-**4h**	61 (**9c**)	90 (*R*)
5	2-(MeO)-C_6H_4- (**8d**)	(*S*,*R*,*R*)-**4h**	83 (**9d**)	95 (*R*)
6	2-(MeO)-C_6H_4- (**8d**)	(*S*,*S*,*S*)-**4g**	63 (**9d**)	92 (*S*)
7	2-Me-C_6H_4- (**8e**)	(*S*,*R*,*R*)-**4h**	72 (**9e**)	92 (*R*)
8	1-naphthyl- (**8f**)	(*S*,*R*,*R*)-**4h**	70 (**9f**)	93 (*R*)
9	1-naphthyl- (**8f**)	(*S*,*S*,*S*)-**4g**	48 (**9f**)	88 (*S*)
10	cyclohexyl- (**8g**)	(*S*,*R*,*R*)-**4h**	nd (**9g**)	

[a]For reaction conditions, see Experimental Section. [b]Yield after flash chromatography; nd = not determined. [c]Enantiomeric ratios were determined by HPLC analysis. Absolute configurations of the major enantiomers are given in parentheses.

In summary, we developed two synthetic routes for the preparation of enantiopure amino-functionalized sulfonimidamides. Whereas single isomeric products are obtained using a nucleophilic substitution route, diastereomeric products, which can readily be separated, are formed in a reaction sequence involving an aziridinium ring opening as key step. Both approaches lead to stereochemically homogeneous products in good to high yields. We have further shown that the resulting amino-functionalized sulfonimidamides are promising chiral ligands in the asymmetric copper-catalyzed Henry reactions between aromatic aldehydes and nitromethane. In combination with copper chloride they catalytically lead to products with up to 95% ee in good to high yields. By applying diastereomeric ligands, both enantiomers of the products are accessible with almost the same enantioselectivities. Compared to a reaction with an analogous sulfonamide-based catalyst, the sulfonimidamides proved superior. Since this is, to the best of our knowledge, the first asymmetric metal catalysis with complexes bearing chiral sulfonimidamides as ligands, we regard the results as a promising starting point, which will eventually guide us to further discoveries.

Experimental Section

General. All reactions were carried out in oven-dried flasks under an inert atmosphere of argon using Schlenk technique. THF and CH_2Cl_2 were dried over Na/benzophenone and CaH_2, respectively, and freshly distilled before using. For the Henry reactions EtOH of p.A. grade was used. All liquid aldehydes except *o*-tolylaldehyde were distilled prior to use. *p*-Tolylsulfinamide,[8,23] piperidinyl-, morpholinyl-, and acetyl-substituted

(22) (a) Bisai, A.; Prasad, B. A.; Bhanu; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 7935. (b) Corrigendum: Bisai, A.; Prasad, B. A.; Bhanu; Singh, V. K. *Tetrahedron Lett.* **2006**, *47*, 1487.

(23) (a) For the preparation of racemic *p*-tolylsulfinamide see, for example: Krasnova, L. B.; Yudin, A. K. *J. Org. Chem.* **2004**, *69*, 2584. (b) For the preparation of enantiopure (*S*)-*p*-tolylsulfinamide, see: Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403 and references therein.

diamines (**3b**,[11] **3c**,[11] and **3d**,[24] respectively), and aminoalcohols **5**[11,25] were prepared analoguosly to literature procedures. (1*R*,2*R*)-1,2-Cyclohexanediamine was purchased with a 99% purity. *tert*-Butylhypochlorite was prepared according to literature procedures and stored at −20 °C.[26] Absolute configurations of β-nitroalcohols **9** were assigned comparing the measured optical rotations to literature values.[27] Flash chromatography was done on silica gel 60 (40−63 μm; F254 plates). Analysis of TLCs was done either using UV light (254 nm) or $KMnO_4$ stain. NMR spectra were recorded at 400 or 300 MHz (^{1}H NMR) and 100 or 75 MHz (^{13}C NMR). Chemical shifts are given in ppm relative to TMS (δ = 0 ppm) or solvent residual peaks ($CDCl_3$; ^{1}H, δ = 7.26 ppm; ^{13}C, δ = 77.0 ppm) as internal standards. Coupling constants *J* are given in Hz, and coupling patterns are described as bs = broad singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, etc. $[\alpha]_D$ values are given in $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$; concentration *c* is listed in $g \cdot (100\ mL)^{-1}$. Melting points were determined in open capillaries and are uncorrected.

(*S*)-*N*-(4-Tolylsulfinyl)-benzamide [(*S*)-1a][9e]. (*S*)-4-Toluenesulfinamide (860 mg, 5.540 mmol, 1 equiv) was dissolved in dry THF (22 mL) and cooled to −78 °C. Immediately after addition of *n*-BuLi (7.6 mL, 12.16 mmol, 1.6 M in hexane, 2.2 equiv) benzoic anhydride (1.504 g, 6.648 mmol, 1.2 equiv) was added at −78 °C. Stirring was continued for additional 2 h at the same temperature and subsequently for 22 h at room temperature. The reaction was stopped by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL), and the thereby formed white precipitate was dissolved by addition of CH_2Cl_2. The phases were separated, and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. To the yellow oil was added diethylether (5 mL), and then the ether was removed again in vacuum. This procedure was repeated until the oil solidified. The solid was filtered and washed with diethylether, affording (*S*)-**1a** as a white solid (985 mg, 3.798 mmol, 69%, >99% ee). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H), 7.35 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.56 (tt, J_1 = 1.3 Hz, J_2 = 7.6 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.79−7.84 (m, 2H), 8.53 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 124.7, 127.8, 128.7, 130.0, 131.5, 133.0, 140.6, 142.5, 167.2; mp 122−124 °C; IR (KBr) ν 3158, 3070, 1672, 1450, 1403, 1242, 1088, 1053, 1026, 882, 805, 780, 700 cm^{-1}; MS (EI, 70 eV) *m*/*z* 259 ([M], 83%), 211 (5%), 139 (33%), 108 (63%), 105 (100%), 77 (37%). Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.48; H, 5.19; N, 5.34. $[\alpha]^{21}_D$ +106.4 (*c* 0.51, $CHCl_3$); HPLC (Chiralcel OD-H, 20 °C, 210 nm, 95/5 Heptan/*i*-PrOH, 1.0 mL/min) t_R = 26.2 min (*R*), 34.5 min (*S*).

***rac*-*N*-(4-Tolylsulfinyl)-benzamide (*rac*-1a)[10].** Prepared in analogy to (*S*)-**1a** starting from *rac*-4-toluenesulfinamide (1.0 g, 6.442 mmol). The product was purified by recrystallization from ethylacetate (100 mL) to afford *rac*-**1a** (1.17 g, 4.512 mmol, 70%) as a white solid, mp (decomp) 107 °C.

(*S*)-*tert*-Butyl-(4-tolylsulfinyl)-carbamate [(*S*)-1b][9e]. (*S*)-4-Toluenesulfinamide (1.510 g, 9.728 mmol, 1 equiv) was dissolved in dry THF (40 mL) and cooled to −78 °C. Immediately after addition of *n*-BuLi (15.20 mL, 24.320 mmol, 1.6 M in hexane, 2.5 equiv), di-*tert*-butyl dicarbonate (3.240 g, 14.845 mmol, 1.5 equiv) was added at −78 °C. Stirring was continued for additional 20 min at the same temperature and then for 2 h at 0 °C. The reaction was stopped by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL), and the thereby formed white precipitate was dissolved by addition of water. The solution was diluted with CH_2Cl_2, and the phases were separated. The aqueous phase was extracted four times with CH_2Cl_2, and the combined organic phases were washed with brine. The solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The raw material was purified by flash chromatography (silica gel, pentane/ethylacetate = 2:1) to afford (*S*)-**1b** (1.925 g, 8.043 mmol, 83%, >99% ee) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 2.42 (s, 3H), 6.66 (bs, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 28.1, 83.5, 124.6, 129.9, 140.5, 142.3, 152.3 (1 qC not observed); mp 107−112 °C; IR (KBr) ν 3135, 1712, 1412, 1367, 1238, 1151, 1093, 1063, 812, 709 cm^{-1}; MS (EI, 70 eV) *m*/*z* 199 ([M − C_4H_8]$^+$, 79%), 139 (52%), 108 (25%), 57 (100%). Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49. Found: C, 56.25; H, 6.81; N, 5.41. $[\alpha]^{21}_D$ +110.3 (*c* 1.0, $CHCl_3$); HPLC (Chiralcel OG, 20 °C, 210 nm, 95/5 Heptan/*i*-PrOH, 1.0 mL/min) t_R = 12.8 min (*S*), 18.3 min (*R*).

***rac*-*tert*-Butyl-(4-tolylsulfinyl)-carbamate (*rac*-1b)[10].** Prepared in analogy to (*S*)-**1b** starting from *rac*-4-toluenesulfinamide (651 mg, 4.191 mmol), 2.5 equiv of *n*-BuLi and 1.4 equiv of di-*tert*-butyl dicarbonate. Flash chromatography (silica gel, pentane/ethylacetate = 2:1) afforded *rac*-**1b** (635 mg, 2.653 mmol, 63%) as a white solid, mp 90−93 °C.

(*S*)-*N*-Benzoyl-4-toluenesulfonimidamide [(*S*)-7][9e]. To a solution of (*S*)-*N*-(4-tolylsulfinyl)-benzamide (**1a**, 501 mg, 1.932 mmol, 1 equiv) in dry THF (25 mL), *t*-BuOCl[26] (328 μL, 2.900 mmol, 1.5 equiv) was added dropwise at 0 °C. After stirring for 2 h at 0 °C, an aqueous solution of NH_3 (10 mL, 25 wt %) was added at 0 °C, and stirring was continued for 45 min at room temperature. Subsequently, water (15 mL) was added, the phases were separated, and the aqueous phase was extracted four times with ethylacetate. The combined organic phases were washed with brine, and the aqueous phase was extracted once with ethylacetate. All organic phases were combined and dried over $MgSO_4$. After removal of the solvent under reduced pressure, raw material **7** (514 mg, 1.874 mmol, 97%) was obtained as a white solid, which was sufficiently pure for further reactions. An analytical sample was purified by flash chromatography (silica gel, pentane/ethylacetate = 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 6.37 (bs, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.35−7.41 (m, 2H), 7.49 (tt, J_1 = 7.3 Hz, J_2 = 1.4 Hz, 1H), 7.88−7.93 (m, 2H), 8.09−8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 126.5, 127.9, 129.3, 129.7, 132.2, 135.2, 138.1, 144.3, 173.3; mp 140−144 °C; IR (KBr) ν 3164, 3066, 1599, 1572, 1551, 1324, 1297, 1219, 1151, 1095, 978, 839, 806, 716 cm^{-1}; MS (EI, 70 eV) *m*/*z* 275 ([M + H]$^+$, 2%), 197 (7%), 108 (100%), 104 (29%). Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.28; H, 5.14; N, 10.21. $[\alpha]^{21}_D$ +69.9 (*c* 1.0, $CHCl_3$); HPLC (Chiralcel OJ, 20 °C, 210 nm, 85/15 Heptan/*i*-PrOH, 0.7 mL/min) t_R = 37.4 min (*R*), 54.5 min (*S*).

General Procedure for the Synthesis of Sulfonimidamides 4. Nucleophilic Substitution Route. Under an inert atmosphere of argon *t*-BuOCl[26] (0.578 mmol, 1.5 equiv) was added dropwise to a solution of sulfinamide **1** (0.386 mmol, 1 equiv) in dry THF (3 mL) at 0 °C. After stirring for 2 h at 0 °C, (di)amine **3** (0.733 mmol, 1.9 equiv) and Cs_2CO_3 (0.771 mmol, >99%, 2 equiv) were added at 0 °C, and subsequently the solution was stirred overnight at room temperature. The reaction was stopped by addition of water (5 mL), and the phases were separated. The aqueous phase was extracted three times with CH_2Cl_2, and the combined organic phases were washed with brine. After drying over $MgSO_4$ and removal of the solvent under reduced pressure, the product was purified by flash chromatography on silica gel.

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(25) See for example: Chakraborti, A. K.; Rudrawar, S.; Kondaskar, A. *Eur. J. Org. Chem.* **2004**, 3597.
(26) (a) *t*-BuOCl reacts violently when exposed to light or in contact with rubber. For safety instructions, see: Teeter, H. M.; Bell, E. W. *Org. Synth.* **1952**, *32*, 20. (b) For a convenient preparation of *t*-BuOCl using NaOCl, see: Mintz, M. J.; Walling, C. *Org. Synth.* **1969**, *49*, 9.
(27) Selvakumar, S.; Sivasankaran, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156.

(*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-cyclohexylamide [(*S*)-4a]. Prepared according to the general procedure by starting from sulfinamide (*S*)-**1a** (250 mg, 0.964 mmol), amine **3a** (210 μL, 1.832 mmol), and Cs_2CO_3 (628 mg, 1.928 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 2:2:0.3) yielded product (*S*)-**4a** (273 mg, 0.766 mmol, 80%, >99% ee) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11−1.38 (m, 4H), 1.40−1.56 (m, 2H), 1.56−1.67 (m, 2H), 1.67−1.78 (m, 1H), 2.00−2.12 (m, 1H), 2.41 (s, 3H), 3.17−3.29 (m, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.33−7.40 (m, 2H), 7.43−7.49 (m, 1H), 7.63−7.75 (m, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 8.09−8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 24.5, 24.6, 25.1, 33.1, 34.6, 34.7, 51.9, 127.0, 127.8, 129.2, 129.6, 131.9, 135.6, 137.4, 143.9, 172.5; mp 88−90 °C; IR (KBr) ν 2930, 2854, 1605, 1573, 1448, 1317, 1291, 1239, 1173, 1144, 1094, 1066, 990, 945, 809, 710 cm^{-1}; MS (EI, 70 eV) *m*/*z* 357 ([M], 1%), 313 (9%), 211 (19%), 155 (21%), 146 (28%), 139 (17%), 108 (100%), 105 (75%). Anal. Calcd for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.79; N, 7.86. Found: C, 67.09; H, 6.93; N, 7.74. $[\alpha]^{24}_D$ +123.6 (*c* 1.0, $CHCl_3$); HPLC (Chiralcel AD-H, 20 °C, 230 nm, 90:10 heptane/*i*-PrOH, 0.5 mL/min) t_R = 39.0 min (*S*), 55.15 min (*R*).

***rac*-*N*-Benzoyl-4-toluenesulfonimid-*N*′-cyclohexylamide (*rac*-4a).** Prepared according to the general procedure by starting from racemic sulfinamide **1a** (100 mg, 0.386 mmol), amine **3a** (84 μL, 0.733 mmol), and Cs_2CO_3 (251 mg, 0.772 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 2:2:0.3) yielded product *rac*-**4a** (114 mg, 0.320 mmol, 83%) as a white solid, mp 105 °C; the spectroscopic data are in agreement with those reported for (*S*)-**4a**.

(*S*)-*N*-*tert*-Butyloxycarbonyl-4-toluenesulfonimid-*N*′-cyclohexylamide [(*S*)-4b]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1b** (250 mg, 0.979 mmol), amine **3a** (213 μL, 1.860 mmol), and Cs_2CO_3 (638 mg, 1.958 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 2:2:0.3) afforded product (*S*)-**4b** (319 mg, 0.905 mmol, 92%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07−1.45 (m, 14H), 1.45−1.63 (m, 3H), 1.65−1.75 (m, 1H), 1.95−2.06 (m, 1H), 2.43 (s, 3H), 3.06−3.18 (m, 1H), 6.35 (d, *J* = 4.9 Hz, 1H), 7.26−7.37 (d, *J* = 8.2 Hz, 2H), 7.81−7.88 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 24.6, 25.1, 28.1, 33.2, 34.5, 51.4, 80.1, 127.7, 129.5, 137.0, 143.5, 157.0; mp 122−124 °C; IR (KBr) ν 2974, 2931, 2857, 1668, 1450, 1363, 1272, 1160, 1074, 1033, 991, 903, 860, 816, 786, 756 cm^{-1}; MS (EI, 70 eV) *m*/*z* 353 ([M], 2%), 297 (6%), 279 (54%), 235 (35%), 215 (23%), 197 (42%), 171 (44%), 154 (21%), 139 (34%), 108 (100%), 98 (92%), 57 (67%). Anal. Calcd for $C_{18}H_{28}N_2O_3S$: C, 61.33; H, 8.01; N, 7.95. Found: C, 61.07; H, 8.14; N, 7.82. $[\alpha]^{24}_D$ +62.4 (*c* 1.0, $CHCl_3$).

***rac*-*N*-*tert*-Butyloxycarbonyl-4-toluenesulfonimid-*N*′-cyclohexylamide (*rac*-4b).** Prepared according to the general procedure starting from sulfinamide *rac*-**1b** (100 mg, 0.392 mmol), amine **3a** (90 μL, 0.744 mmol), and Cs_2CO_3 (255 mg, 0.783 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 2:2:0.3) afforded product *rac*-**4b** (130 mg, 0.369 mmol, 94%) as a white solid, mp 110−115 °C; the spectroscopic data are in agreement with those reported for (*S*)-**4b**.

(*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*S*,2*S*)-2-piperidin-1-yl-cyclohexyl]amide [(*S*,*S*,*S*)-4c]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1a** (250 mg, 0.964 mmol), diamine (*S*,*S*)-**3b** (334 mg, 1.832 mmol), and Cs_2CO_3 (628 mg, 1.928 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 4:1:0.5) afforded product (*S*,*S*,*S*)-**4c** (205 mg, 0.466 mmol, 48%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97−1.31 (m, 3H), 1.33−1.53 (m, 3H), 1.56−1.88 (m, 7H), 2.13−2.57 (m, 9H), 2.60−2.81 (m, 1H), 7.27−7.41 (m, 4H), 7.42−7.52 (m, 1H), 7.88−7.98 (m, 2H), 8.12−8.27 (m, 2H), 1 NH not observed; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 23.1, 24.2, 24.8, 25.2, 26.4, 33.4, 49.5, 53.8, 67.8, 127.4, 127.8, 129.5, 129.6, 131.7, 136.1, 136.3, 143.7, 1qC not observed; mp 127−128 °C; IR (KBr) ν 2932, 2856, 1602, 1572, 1312, 1292, 1258, 1095, 810, 781, 708 cm^{-1}; MS (EI, 70 eV) *m*/*z* 320 ([M − C_7H_5NO], 2%), 229 (1%), 181 (100%), 164 (7%). Anal. Calcd for $C_{25}H_{33}N_3O_2S$: C, 68.30; H, 7.57; N, 9.56. Found: C, 68.21; H, 7.58; N, 9.30. $[\alpha]^{22}_D$ +146.6 (*c* 0.75, $CHCl_3$).

(*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-piperidin-1-yl-cyclohexyl]amide [(*S*,*R*,*R*)-4d]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1a** (100 mg, 0.386 mmol), diamine (*R*,*R*)-**3b** (134 mg, 0.733 mmol), and Cs_2CO_3 (251 mg, 0.771 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 4:1:0.5) afforded product (*S*,*R*,*R*)-**4d** (102 mg, 0.232 mmol, 60%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99−1.31 (m, 5H), 1.38−1.94 (m, 10H), 2.22−2.45 (m, 6H), 2.64−2.79 (m, 2H), 3.32−3.44 (m, 1H), 7.25−7.40 (m, 4H), 7.40−7.48 (m, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 8.08−8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 23.1, 24.2, 24.6, 25.2, 26.1, 32.7, 49.3, 53.0, 68.0, 127.5, 127.7, 129.3, 129.4, 131.5, 136.4, 138.8, 143.3; mp (decomp) 156 °C; IR (KBr) ν 2933, 2857, 1617, 1575, 1450, 1313, 1283, 1223, 1142, 935, 904, 801, 711, 683 cm^{-1}; MS (EI, 70 eV) *m*/*z* 440 ([M], 2%), 320 (6%), 181 (100%), 164 (37%), 124 (21%), 105 (32%), 96 (21%), 84 (31%); HRMS calcd for $C_{25}H_{33}N_3O_2S$ ([M]) 439.2288, found 439.2288. $[\alpha]^{24}_D$ −31.8 (*c* 1.0, $CHCl_3$).

(*S*)-*N*-*tert*-Butyloxycarbonyl-4-toluenesulfonimid-*N*′-[(1*S*,2*S*)-2-piperidin-1-yl-cyclohexyl]amide [(*S*,*S*,*S*)-4e]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1b** (250 mg, 0.979 mmol), diamine (*S*,*S*)-**3b** (339 mg, 1.860 mmol) and Cs_2CO_3 (638 mg, 1.958 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 4:2:0.5) afforded product (*S*,*S*,*S*)-**4e** (183 mg, 0.420 mmol, 43%) as a light-brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94−1.24 (m, 3H), 1.28−1.57 (m, 17H), 1.58−1.83 (m, 3H), 2.06−2.24 (m, 5H), 2.39−2.49 (m, 4H), 2.58 (dt, J_1 = 4.1 Hz, J_2 = 10.6 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 22.7, 24.1, 24.6, 25.2, 26.2, 28.0, 33.1, 45.9, 49.1, 52.9, 67.4, 79.7, 127.4, 129.4, 135.8, 143.3, 156.7; mp 107−108 °C; IR (KBr) ν 2935, 2855, 2806, 1666, 1450, 1364, 1279, 1251, 1162, 1142, 1089, 961, 890, 867 cm^{-1}; MS (EI, 70 eV) *m*/*z* 436 ([M + H]$^+$ 2%), 362 (16%), 319 (37%), 181 (100%), 165 (56%), 137 (26%), 124 (35%), 84 (45%); HRMS calcd for $C_{23}H_{37}N_3O_3S$ ([M]) 435.2550, found 435.2538. $[\alpha]^{24}_D$ +69.4 (*c* 0.5, $CHCl_3$).

(*S*)-*N*-*tert*-Butyloxycarbonyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-piperidin-1-yl-cyclohexyl]amide [(*S*,*R*,*R*)-4f]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1b** (300 mg, 1.175 mmol), diamine (*R*,*R*)-**3b** (363 mg, 1.991 mmol, 1.7 equiv), and Cs_2CO_3 (766 mg, 2.350 mmol, 2.0 equiv). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 4:1:0.5) afforded product (*S*,*R*,*R*)-**4f** (246 mg, 0.565 mmol, 48%) as a light-brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84−1.24 (m, 3H), 1.31−1.50 (m, 13H), 1.61 (quint, *J* = 5.4 Hz, 4H), 1.66−1.85 (m, 3H), 2.20−2.34 (m, 3H), 2.38 (s, 3H), 2.59 (quint., *J* = 5.4 Hz, 2H), 3.18 (td, *J* = 4.0 Hz, *J* = 10.6 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 1 NH not observed; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 22.8, 24.1, 24.5, 25.2, 25.9, 28.1, 32.1, 49.2, 53.0, 67.6, 79.6, 127.5, 129.1, 138.1, 143.1, 157.2; mp 126−128 °C; IR (KBr) ν 2968, 2930, 2855, 2807, 1655, 1450, 1366, 1277, 1243, 1142, 1095, 904, 869 cm^{-1}; MS (EI, 70 eV) *m*/*z* 436 ([M], 6%), 362 (5%), 319 (13%), 181 (100%), 164 (21%); HRMS calcd for $C_{23}H_{37}N_3O_3S$ ([M]) 435.2550, found 435.2540. $[\alpha]^{24}_D$ −30.9 (*c* 1.0, $CHCl_3$).

(*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*S*,2*S*)-2-morpholin-4-yl-cyclohexyl]amide [(*S*,*S*,*S*)-4g]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1a** (150 mg, 0.578 mmol), diamine (*S*,*S*)-**3c** (203 mg, 1.099 mmol), and Cs_2CO_3 (377 mg, 1.157 mmol). Flash chromatography (silica gel, pentane/diethylether = 1:1) afforded product (*S*,*S*,*S*)-**4g** (189 mg, 0.428 mmol, 74%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00−1.27 (m, 3H), 1.36−1.49 (m, 1H), 1.60−1.70 (m, 1H),

1.70−1.79 (m, 1H), 1.80−1.88 (m, 1H), 2.24−2.39 (m, 5H), 2.41 (s, 3H), 2.43−2.51 (m, 1H), 2.72 (dt, J_1 = 4.1 Hz, J_2 = 10.6 Hz, 1H), 3.75−3.81 (m, 4H), 7.30 (d, J = 8.2 Hz, 2H), 7.35−7.41 (m, 2H), 7.44−7.50 (m, 1H), 7.93 (d, J = 8.2 Hz, 2H), 8.16−8.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 23.2, 24.1, 25.1, 33.4, 48.4, 53.8, 67.1, 67.2, 127.0, 127.7, 129.3, 129.6, 131.8, 135.8, 136.3, 143.9, 172.2; mp 178−180 °C; IR (KBr) ν 2934, 2860, 1606, 1572, 1450, 1291, 1259, 1114, 1019, 922, 812, 750, 717 cm^{-1}; MS (EI, 70 eV) m/z 441 ([M], 1%), 398 (1%), 354 (1%), 321 (2%), 183 (100%), 166 (14%). Anal. Calcd for $C_{24}H_{31}N_3O_3S$: C, 65.28; H, 7.08; N, 9.52. Found: C, 65.14; H, 7.04; N, 9.47. $[\alpha]^{24}_D$ +169.5 (c 1.0, $CHCl_3$).

(*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-morpholin-4-yl-cyclohexyl]amide [(*S*,*R*,*R*)-4h]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1a** (511 mg, 1.971 mmol), diamine (*R*,*R*)-**3c** (690 mg, 3.744 mmol), and Cs_2CO_3 (1.284 g, 3.941 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 2:1:0.5) afforded product (*S*,*R*,*R*)-**4h** (678 mg, 1.535 mmol, 78%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94−1.32 (m, 4H), 1.48−1.60 (m, 1H), 1.71−1.82 (m, 1H), 1.82−1.95 (m, 2H), 2.23−2.33 (m, 1H), 2.33−2.50 (m, 6H), 2.66−2.79 (m, 2H), 3.43 (td, J = 4.0 Hz, J = 10.7 Hz, 1H), 3.77 (t, J = 4.5 Hz, 4H), 7.30 (d, J = 8.4 Hz, 2H), 7.33−7.42 (m, 2H), 7.43−7.50 (m, 1H), 7.88−7.95 (m, 2H), 8.08−8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 23.0, 24.1, 25.2, 32.5, 48.2, 53.0, 67.0, 67.2, 127.3, 127.8, 129.2, 129.4, 131.7, 135.8, 138.3, 143.6, 172.6; mp 106−108 °C; IR (KBr) ν 2932, 2861, 1615, 1577, 1451, 1311, 1279, 1224, 1172, 1140, 1114, 1067, 1015, 940, 905, 803, 718 cm^{-1}; MS (EI, 70 eV) m/z 442 ([M], 1%), 399 (1%), 355 (1%), 321 (2%), 231 (1%), 183 (100%), 166 (14%), 105 (10%). Anal. Calcd for $C_{24}H_{31}N_3O_3S$: C, 65.28; H, 7.08; N, 9.52. Found: C, 65.12; H, 7.06; N, 9.38. $[\alpha]^{24}_D$ −39.2 (c 1.0, $CHCl_3$).

(*S*)-*N*-*tert*-Butyloxycarbonyl-4-toluenesulfonimid-*N*′-[(1*S*,2*S*)-2-morpholin-4-yl-cyclohexyl]amide [(*S*,*S*,*S*)-4i]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1b** (200 mg, 0.783 mmol), diamine (*S*,*S*)-**3c** (274 mg, 1.488 mmol), and Cs_2CO_3 (510 mg, 1.567 mmol). Flash chromatography (silica gel, pentane/diethylether = 1:1 to elute nonpolar byproducts, pentane/diethylether/Et_3N = 2:1:0.5 to elute the product) afforded product (*S*,*S*,*S*)-**4i** (175 mg, 0.400 mmol, 51%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97−1.40 (m, 4H), 1.41 (s, 9H), 1.56−1.87 (m, 4H), 2.15−2.30 (m, 4H), 2.37−2.48 (m, 4H), 2.63 (dt, J_1 = 4.2 Hz, J_2 = 10.6 Hz, 1H), 3.57−3.69 (m, 4H), 6.88 (bs, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 22.9, 24.1, 25.1, 28.1, 33.2, 48.1, 53.0, 67.0, 67.0, 80.0, 127.4, 129.7, 136.3, 143.8, 1 qC not observed; mp 150−153 °C; IR (KBr) ν 2974, 2935, 2858, 2821, 1664, 1452, 1363, 1279, 1252, 1139, 1111, 1089, 1067, 1017, 960, 894, 865, 783, 753 cm^{-1}; MS (EI, 70 eV) m/z 438 ([M], 1%), 419 (1%), 364 (9%), 321 (13%), 183 (100%), 166 (36%); HRMS calcd for $C_{22}H_{36}N_3O_4S$ ([M + H]$^+$) 438.2421, found 438.2407. $[\alpha]^{24}_D$ +89.7 (c 1.0, $CHCl_3$).

(*S*)-*N*-*tert*-Butyloxycarbonyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-morpholin-4-yl-cyclohexyl]amide [(*S*,*R*,*R*)-4j]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1b** (200 mg, 0.783 mmol), diamine (*R*,*R*)-**3c** (274 mg, 1.488 mmol), and Cs_2CO_3 (510 mg, 1.567 mmol). Flash chromatography (silica gel, pentane/diethylether/Et_3N = 2:1:0.3) afforded product (*S*,*R*,*R*)-**4j** (203 mg, 0.464 mmol, 59%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79−0.95 (m, 1H), 1.02−1.30 (m, 3H), 1.35−1.56 (m, 10H), 1.63−1.82 (m, 2H), 1.82−2.00 (m, 1H), 2.19−2.32 (m, 1H), 2.31−2.51 (m, 5H), 2.63−2.79 (m, 2H), 3.30 (dt, J_1 = 3.6 Hz, J_2 = 10.6 Hz, 1H), 3.70−3.87 (m, 4H), 7.28 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H), 1 NH not observed; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 22.8, 24.1, 25.2, 28.2, 32.0, 48.2, 53.0, 66.9, 67.1, 80.1, 127.7, 129.3, 138.0, 143.5, 157.4; mp 143−145 °C; IR (KBr) ν 2932, 2860, 2812, 1650, 1452, 1366, 1279, 1250, 1161, 1140, 1112, 1018, 956, 906, 865, 813, 765, 736 cm^{-1}; MS (EI, 70 eV) m/z 438 ([M], 5%), 364 (10%), 321 (19%), 183 (100%), 166 (51%), 139 (27%), 126 (19%), 96 (25%), 57 (36%); HRMS calcd for $C_{22}H_{35}N_3O_4S$ ([M]) 437.2343, found 437.2349. $[\alpha]^{24}_D$ −23.4 (c 1.0, $CHCl_3$).

(*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-acetylamino cyclohexyl]amide [(*S*,*R*,*R*)-4k]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1a** (250 mg, 0.946 mmol), diamine (*R*,*R*)-**3d** (286 mg, 1.832 mmol), and Cs_2CO_3 (628 mg, 1.928 mmol). Flash chromatography (silica gel, pentane/ethylacetate = 1:3) afforded product (*S*,*R*,*R*)-**4k** (295 mg, 0.713 mmol, 74%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03−1.23 (m, 2H), 1.23−1.45 (m, 2H), 1.59−1.80 (m, 3H), 1.99 (s, 3H), 2.13−2.23 (m, 1H), 2.42 (s, 3H), 3.12−3.24 (m, 1H), 3.67−3.78 (m, 1H), 6.26 (d, J = 6.9 Hz, 1H), 7.06−7.17 (bs, 1H), 7.28−7.40 (m, 4H), 7.43−7.50 (m, 1H), 7.90 (d, J = 8.1 Hz, 2H), 8.07−8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 23.5, 24.4, 24.9, 32.6, 33.3, 53.1, 56.3, 127.2, 127.9, 129.3, 129.7, 132.0, 135.4, 137.6, 144.1, 171.2, 172.7; mp 80−83 °C; IR (KBr) ν 2934, 2859, 1627, 1571, 1544, 1447, 1315, 1282, 1239, 1141, 1092, 1067, 810, 712 cm^{-1}; MS (EI, 70 eV) m/z 414 ([M], 1%), 293 (1%), 203 (21%), 155 (88%), 139 (40%), 105 (100%), 96 (90%), 77 (39%); HRMS calcd for $C_{22}H_{27}N_3O_3S$ ([M]) 413.1768, found 413.1767. $[\alpha]^{24}_D$ +102.5 (c 0.5, $CHCl_3$).

(*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-amino-cyclohexyl]amide [(*S*,*R*,*R*)-4l]. Prepared according to the general procedure starting from sulfinamide (*S*)-**1a** (300 mg, 1.157 mmol) with (*R*,*R*)-1,2-cyclohexanediamine (*R*,*R*)-**3e** (396 mg, 3.471 mmol, 3 equiv) and Cs_2CO_3 (754 mg, 2.314 mmol). A first flash chromatography (silica pentane/diethylether = 1:3 to elute nonpolar byproducts, EtOH/acetone = 1:1 to elute the product) afforded a fraction of pure product (*S*,*R*,*R*)-**4l** (209 mg) as a yellow solid and an impure fraction of (*S*,*R*,*R*)-**4l**. A second chromatography of the impure fraction (silica gel, acetone/EtOH = 3:2, then acetone/EtOH = 1:1) afforded another 87 mg of pure product (*S*,*R*,*R*)-**4l** (overall, 296 mg, 0.797 mmol, 69%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99−1.27 (m, 4H), 1.51−1.67 (m, 3H), 2.00−2.07 (m, 1H), 2.42 (s, 3H), 2.65 (dt, J_1 = 10.2 Hz, J_2 = 3.8 Hz, 1H), 2.98 (dt, J_1 = 10.2 Hz, J_2 = 3.8 Hz, 1H), 4.12 (bs, 3H), 7.30 (d, J = 8.2 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.47 (tt, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 8.09−8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 24.5, 25.0, 32.2, 34.2, 55.1, 59.0, 127.0, 127.9, 129.4, 129.7, 132.1, 135.6, 138.0, 143.9, 173.0; mp 79−82 °C; IR (KBr) ν 2932, 2859, 1598, 1543, 1447, 1318, 1288, 1141, 1117, 1091, 902, 839, 808, 713 cm^{-1}; MS (EI, 70 eV) m/z 372 ([M], 2%), 251 (3%), 139 (18%), 113 (100%), 105 (32%), 96 (95%); HRMS calcd for $C_{20}H_{26}N_3O_2S$ ([M + H]$^+$) 372.1740, found 372.1742. $[\alpha]^{21}_D$ +83.04 (c 0.42, $CHCl_3$).

Synthesis of (*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*S*,2*S*)-2-piperidin-1-yl-cyclohexyl]amide [(*S*,*S*,*S*)-4c] and (*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-piperidin-1-yl-cyclohexyl]amide [(*S*,*R*,*R*)-4d] by the Aziridinium Route. Under an inert atmosphere of argon methanesulfonyl chloride (18 μL, 0.229 mmol, 1.2 equiv) was added dropwise to a solution of (±)-*trans*-2-piperidin-1-yl-cyclohexanol (35 mg, 0.191 mmol, 1 equiv) in dry THF (1.5 mL) at 0 °C. Subsequently the mixture was stirred for 5 min at 0 °C and then for 3 h at room temperature. After addition of triethylamine (133 μL, 0.959 mmol, 5 equiv) the solution was stirred for an additional 1 h, and then (*S*)-*N*-benzoyl-4-toluenesulfonimidamide [(*S*)-**7**, 157 mg, 0.572 mmol, 3 equiv] and water (0.2 mL) were added. After the solution was stirred overnight at room temperature, the phases were separated, and the aqueous phase was extracted three times with ethylacetate. The combined organic phases were washed with an aqueous solution of $NaHCO_3$ (5 wt %) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the products were purified by flash chromatography (silica gel, pentane/diethylether/Et_3N = 4:1:0.5). The first fraction afforded

(*S*,*S*,*S*)-**4c** (26 mg, 0.059 mmol, 31%) as a white solid, and the second fraction afforded (*S*,*R*,*R*)-**4d** (27 mg, 0.064 mmol, 33%) as a white solid.

The purities of (*S*,*S*,*S*)-**4c** and (*S*,*R*,*R*)-**4d** were equal to the ones obtained by the nucleophilic substitution route. For analytical data see the protocol of nucleophilic substitution pathway.

Synthesis of (*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*S*,2*S*)-2-morpholin-4-yl-cyclohexyl]amide [(*S*,*S*,*S*)-4g] and (*S*)-*N*-Benzoyl-4-toluenesulfonimid-*N*′-[(1*R*,2*R*)-2-morpholin-4-yl-cyclohexyl]-amide [(*S*,*R*,*R*)-4h] by the Azirdinium Route. Same procedure as for the synthesis of (*S*,*S*,*S*)-**4c** and (*S*,*R*,*R*)-**4d** using methanesulfonyl chloride (28.5 μL, 0.363 mmol, 1.2 equiv), (±)-*trans*-2-morpholin-4-yl-cyclohexanol (56 mg, 0.302 mmol, 1 equiv), triethylamine (210 μL, 1.511 mmol, 5 equiv), (*S*)-*N*-benzoyl-4-toluenesulfonimidamide [(*S*)-**7**, 166 mg, 0.605 mmol, 2 equiv), and water (0.2 mL). The stirring times were 1.5 and 2 h instead of 3 and 1 h. The first chromatography (silica gel, pentane/diethylether = 2:3) afforded (*S*,*R*,*R*)-**4h** (38 mg, 0.086 mmol, 28%) as a white solid and a mixture of (*S*,*S*,*S*)-**4g** and starting material (*S*)-**7**. A second chromatography (silica gel, pentane/acetone = 6:1) provided pure (*S*,*S*,*S*)-**4g** (34 mg, 0.077 mmol, 25%) as a white solid.

The purities of (*S*,*S*,*S*)-**4g** and (*S*,*R*,*R*)-**4h** were equal to the ones obtained by the nucleophilic substitution route. For analytical data see the protocol of nucleophilic substitution pathway.

General Procedure for the Henry Reaction, Optimized Conditions. Under an inert atmosphere of argon CuCl (5.9 mg, 0.060 mmol, 0.1 equiv) and sulfonimidamide **4** (0.060 mmol, 0.1 equiv) were dissolved in dry CH_2Cl_2 (3.4 mL) and stirred overnight at room temperature. After removal of the solvent under reduced pressure, the resulting green solid was redissolved in EtOH (1.2 mL). Then, $MeNO_2$ (320 μL, 6.000 mmol, 10 equiv) and 4-methylpyrimidine (65 μL, 0.708 mmol, 1.18 equiv) were added. After addition of the aldehyde **8** (0.600 mmol, 1 equiv) the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and product **9** was purified by flash chromatography.

(*R*)-2-Nitro-1-(4-nitrophenyl)-ethanol [(*R*)-9a]. Obtained using sulfonimidamide (*S*,*R*,*R*)-**4h** (26.5 mg, 0.060 mmol) and aldehyde **8a** (90.7 mg, 0.600 mmol) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether = 1:1) afforded (*R*)-**9a** (105 mg, 0.495 mmol, 82%, 88% ee) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.19 (bs, 1H), 4.57 (dd, J_1 = 4.1 Hz, J_2 = 13.7 Hz, 1H) 4.61 (dd, J_2 = 13.7 Hz, J_3 = 8.1 Hz, 1H), 5.61 (dd, J_1 = 4.1 Hz, J_3 = 8.1 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 8.27 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.00, 80.6, 124.1, 126.8, 144.8, 1 qC not observed. $[\alpha]^{24}_D$ −30.4 (*c* 0.53, $CHCl_3$); HPLC (Chiralcel OD-H, 20 °C, 210 nm, 85:15 heptane/*i*-PrOH, 0.8 mL/min) t_R = 19.4 min (*R*), 24.6 min (*S*); the spectroscopic data are in agreement with those reported in the literature.[27]

(*R*)-2-Nitro-1-phenylethanol [(*R*)-9b]. Obtained using sulfonimidamide (*S*,*R*,*R*)-**4h** (26.5 mg, 0.060 mmol) and aldehyde **8b** (61 μL, 0.600 mmol) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether =4:1) afforded (*R*)-**9b** (79 mg, 0.473 mmol, 79%, 95% ee) as a colorless oil. $[\alpha]^{22}_D$ −47.1 (*c* 0.51, $CHCl_3$); for the spectroscopic data and the determination of the enantiomeric ratio, see the preparation of (*S*)-**9b**.

(*S*)-2-Nitro-1-phenylethanol [(*S*)-9b]. Obtained using sulfonimidamide (*S*,*S*,*S*)-**4g** (26.5 mg, 0.060 mmol) and aldehyde **8b** (61 μL, 0.600 mmol) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether = 4:1) afforded (*S*)-**9b** (47 mg, 0.281 mmol, 47%, 92% ee) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.97 (d, J_1 = 3.3 Hz, 1H, OH), 4.50 (dd, J_2 = 3.3 Hz, J_3 = 13.3 Hz, 1H), 4.60 (dd, J_3 = 13.3 Hz, J_4 = 9.4 Hz, 1H), 5.44 (td, J_1 = J_2 = 3.3 Hz, J_4 = 9.4 Hz, 1H), 7.32−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.0, 81.2, 125.9, 128.9, 129.0, 138.1. $[\alpha]^{23}_D$ +44.5 (*c* 0.52, $CHCl_3$); HPLC (Chiralcel OD-H, 20 °C, 210 nm, 85:15 heptane/*i*-PrOH, 0.8 mL/min) t_R = 12.5 min (*R*), 15.2 min (*S*); the spectroscopic data are in agreement with those reported in the literature.[27]

(*R*)-1-(4-Chlorophenyl)-2-nitro-ethanol [(*R*)-9c]. Obtained using sulfonimidamide (*S*,*R*,*R*)-**4h** (26.5 mg, 0.060 mmol) and aldehyde **8c** (84.3 mg, 0.600 mmol) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether = 3:1) afforded (*R*)-**9c** (74 mg, 0.367 mmol, 61%, 90% ee) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.00 (bs, 1H), 4.48 (dd, J_1 = 3.4 Hz, J_2 = 13.4 Hz, 1H), 4.57 (dd, J_2 = 13.4 Hz, J_3 = 9.2 Hz, 1H), 5.44 (dd, J_1 = 3.4 Hz, J_3 = 9.2 Hz, 1H), 7.31−7.41 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.3, 80.9, 127.3, 129.2, 134.8, 136.5. $[\alpha]^{22}_D$ −38.8 (*c* 0.55, $CHCl_3$); HPLC (Chiralcel OD-H, 20 °C, 210 nm, 85:15 heptane/*i*-PrOH, 0.8 mL/min) t_R = 11.7 min (*R*), 14.6 min (*S*); the spectroscopic data are in agreement with those reported in the literature.[27]

(*R*)-1-(2-Methoxyphenyl)-2-nitro-ethanol [(*R*)-9d]. Obtained using sulfonimidamide (*S*,*R*,*R*)-**4h** (26.5 mg, 0.060 mmol) and aldehyde **8d** (81.7 mg, 0.600 mmol) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether = 4:1) afforded (*R*)-**9d** (98 mg, 0.497 mmol, 83%, 95% ee) as a yellow oil. $[\alpha]^{22}_D$ −50.4 (*c* 0.54, $CHCl_3$); for the spectroscopic data and the determination of the enantiomeric ratio see the preparation of (*S*)-**9d**.

(*S*)-1-(2-Methoxyphenyl)-2-nitro-ethanol [(*S*)-9d]. Obtained using sulfonimidamide (*S*,*S*,*S*)-**4g** (26.5 mg, 0.060 mmol) and aldehyde **8d** (81.7 mg, 0.600 mmol) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether = 4:1) afforded (*S*)-**9d** (74 mg, 0.375 mmol, 63%, 92% ee) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.22 (d, J_1 = 6.2 Hz, 1H), 3.88 (s, 3H), 4.56 (dd, J_2 = 9.1 Hz, J_3 = 13.0 Hz, 1H), 4.64 (dd, J_3 = 13.0 Hz, J_4 = 3.3 Hz, 1H), 5.62 (m, J_1 = 6.2 Hz, J_2 = 9.1 Hz, J_4 = 3.3 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 7.01 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.33 (dt, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.44 (dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.4, 67.8, 79.8, 110.4, 121.0, 125.8, 127.1, 129.7, 155.8. $[\alpha]^{22}_D$ +47.8 (*c* 0.51, $CHCl_3$); HPLC (Chiralcel OD-H, 20 °C, 210 nm, 90:10 heptane/*i*-PrOH, 0.8 mL/min) t_R = 13.7 min (*R*), 16.0 min (*S*); the spectroscopic data are in agreement with those reported in the literature.[27]

(*R*)-1-(2-Methylphenyl)-2-nitro-ethanol [(*R*)-9e]. Obtained using sulfonimidamide (*S*,*R*,*R*)-**4h** (26.5 mg, 0.060 mmol) and aldehyde **8e** (71.5 μL, 0.600 mmol, 97%) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether = 4:1) afforded (*R*)-**9e** (78 mg, 0.430 mmol, 72%, 92% ee) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 2.76 (d, J_1 = 3.2 Hz, 1H), 4.43 (dd, J_2 = 2.6 Hz, J_3 = 13.5 Hz, 1H), 4.54 (dd, J_3 = 13.5 Hz, J_4 = 9.8 Hz, 1H), 5.68 (m, J_2 = 2.6 Hz, J_4 = 9.8 Hz, 1H), 7.16−7.22 (m, 1H), 7.23−7.30 (m, 2H), 7.49−7.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 67.9, 80.2, 125.5, 126.7, 128.6, 130.8, 134.3, 136.1. $[\alpha]^{22}_D$ −49.5 (*c* 0.51, $CHCl_3$); HPLC (Chiralcel OD-H, 20 °C, 210 nm, 85:15 heptane/*i*-PrOH, 0.8 mL/min, t_R = 10.0 min (*R*), 14.4 min (*S*); the spectroscopic data are in agreement with those reported in the literature.[27]

(*R*)-1-Naphthalen-1-yl-2-nitro-ethanol [(*R*)-9f]. Obtained using sulfonimidamide (*S*,*R*,*R*)-**4h** (26.5 mg, 0.060 mmol) and aldehyde **8f** (81.5 μL, 0.600 mmol) according to the general procedure. Flash chromatography (silica gel, pentane/diethylether = 4:1) afforded (*R*)-**9f** (91 mg, 0.419 mmol, 70%, 93% ee) as a colorless oil. $[\alpha]^{22}_D$ −24.7 (*c* 0.58, $CHCl_3$); for the spectroscopic data and the determination of the enantiomeric ratio see the preparation of (*S*)-**9f**.

(*S*)-1-Naphthalen-1-yl-2-nitro-ethanol [(*S*)-9f]. Obtained using sulfonimidamide (*S*,*S*,*S*)-**4g** (26.5 mg, 0.060 mmol) and aldehyde **8f** (81.5 μL, 0.600 mmol) according to the general procedure. Flash-chromatography (silica gel, pentane/diethylether =4:1) afforded (*S*)-**9f** (62 mg, 0.285 mmol, 48%, 88% ee) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.05 (bs, 1H), 4.62 (dd,

J_1 = 8.4 Hz, J_2 = 13.5 Hz, 1H) 4.67 (dd, J_2 = 13.5 Hz, J_3 = 3.8 Hz, 1H), 6.19−6.25 (m, 1H), 7.48−7.62 (m, 3H), 7.72−7.77 (m, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.89−7.93 (m, 1H), 8.02 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.2, 80.7, 121.7, 123.7, 125.4, 126.0, 126.9, 129.2, 129.2, 129.4, 133.4, 133.6. $[\alpha]^{21}_D$ +24.5 (*c* 0.53, $CHCl_3$); HPLC (Chiralcel OD-H, 20 °C, 210 nm, 85:15 heptane/*i*-PrOH, 0.8 mL/min, t_R = 15.3 min (*R*), 21.4 min (*S*); the spectroscopic data are in agreement with those reported in the literature.[27]

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