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Synthesis of chiral sulfinamido-sulfonamides and their evaluation as ligands for the enantioselective ethylation of aldehydes

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ABSTRACT

A family of chiral sulfinamido-sulfonamide ligands have been synthesized from sulfinimines and has been evaluated as ligands for the enantioselective addition of diethylzinc to aldehydes with $Ti(O^iPr)_4$. The structure of these diamino compounds has been systematically modified to optimize the results.

1. Introduction

Nowadays, processes based on asymmetric metal catalysis involving chiral sulfur-containing ligands are common within the plethora of methods available to produce chiral molecules. However, the amount of successful reactions developed for these types of ligands is still significantly smaller than for other ligands based on P, N or O complexation.[1]

Within this context, sulfoxides and sulfoximines have been applied, with excellent to moderate success, to catalytic enantioselective reductions and carbon–carbon bond forming reactions such as cycloadditions, aldol reactions, allylic substitutions, and alkylation of carbonyl compounds.[2] In contrast, sulfinimines and sulfinamides, compounds of established versatility in asymmetric synthesis based on chiral auxiliaries,[3] have been less exploited in enantioselective catalysis and only recently, some examples have been described of their use as ligands in asymmetric transfer hydrogenation,[4a] cycloadditions,[4b] allylic alkylations,[4c] additions to C=O/C=N,[4d,e] Pauson–Khand reaction[4f] or even in organocatalysis.[4g,h]

The asymmetric addition of organozinc reagents to aldehydes is a well-known reaction for the testing and optimization of new ligands and numerous experimental and theoretical studies have been developed on this process.[5] In the field of enantioselective catalysis, there is a growing interest on the design and evaluation of bifunctional catalysts, where a simultaneous Lewis acid/base system activates both nucleophilic and electrophilic reaction counterparts.[6] In this context, the addition of diethylzinc to aldehydes, developed by Ohno and Kobayashi[7] that relies on using a catalytic amount of a bis-sulfonamide and a stoichiometric amount of $Ti(O^iPr)_4$ offers a good opportunity for testing ligands containing various heteroatoms available for metal coordination. Herein we wish to report our recent investigations on the synthesis and evaluation of a novel class of enantiopure *N*-sulfinyl diamino compounds **I** (Fig. 1) as chiral ligands in the enantioselective alkylation of aldehydes.

In the last years, we have been involved in the synthesis of enantiopure vicinal diamino compounds from chiral sulfinimines.[8] This methodology provides a broad number of sulfinamides (**I**) and also would allow us to change easily groups R–R^4 in order to optimize their steric and electronic environments and thus forming efficient metal complexes that could yield high enantioselectivities for the alkylation. This report reveals some key structural features required for the success of this new family of ligands. As it will be explained in detail below, a combination of factors such as the

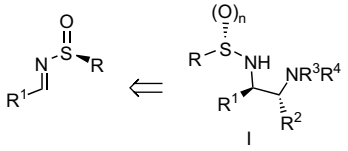

Figure 1. General skeleton of the sulfinamide ligands **I**.

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presence of two nitrogens with different coordinating capabilities and the relative configuration of the stereocenters in the ligands among others have shown an important influence in the enantiocontrol of the process.

2. Results and discussion

2.1. Synthesis of ligands

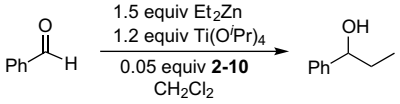
Most ligands employed in this study are described here for first time (see Experimental section) and have been synthesized through methodologies previously reported by us. The general synthetic approach is depicted in Scheme 1. The stepwise [3+2] cycloaddition between enantiopure sulfinimines (**1**) and *N*-benzylidene glycine-derived enolate stands as a very efficient and direct route to enantiopure imidazolidines **2**,[8b] our main intermediate in this synthetic approach. Initially, we chose *p*-tolyl sulfinimine **1a** (R^1=^{i}Pr) as starting material, since excellent diastereoselectivity is accomplished in the cyclization step; however sulfinimines **1b** with a naphthyl group (R^1) as well as **1c** and **1d** incorporating mesityl and 2-methoxy-1-naphthyl groups in the sulfinyl moiety (R) were also considered for this study. *N*-Sulfinyl imidazolidine **2a** was smoothly reduced preserving the imidazolidine ring by treatment with $NaBH_4$/LiI to afford hydroxymethyl imidazolidine **3a**. Alternatively, simultaneous reduction of the ester and reductive opening of the aminal took place with $LiAlH_4$ thus rendering *N*-sulfinyl diaminoalcohol **4a**[8b] in good yield that could be further protected to render silyl ether **4b**.[8a]

N-Sulfinyl diaminoesters **5** were prepared from **2** by using H_3PO_4 in THF[8c] and reaction of the primary amine in **5** with different reagents provided a new assembly of compounds in one synthetic step. Thus, treatment of **5** with 1,1-diphenylmethan imine or 1,4-dibromobutane rendered **6a** and **6b**, respectively, in good yields.[8c] On the other hand, a wide variety of sulfonamides **7a**–**m** were synthesized by reaction with different commercially available sulfonyl chlorides. Further transformations of sulfinamido-sulfonamides **7** such as oxidation of the sulfinyl group and reduction of the ester led us to bis-sulfonamides **8a**,**b** and hydroxymethyl sulfonamide **9**. Moreover, the hydroxyl group of **9** was protected to silyl ether **10**. As shown, a wide collection of compounds were obtained with the aim of testing them as chiral ligands.

2.2. Enantioselective addition of Et_2Zn to aldehydes

Preliminary studies on the enantioselective alkylation of aldehydes were focused on the ethylation of benzaldehyde. To our disappointment, standard conditions using 2.0 equiv of Et_2Zn and 0.05 equiv of chiral ligands **2**–**5** only yielded variable small amounts of racemic 1-phenylpropanol (5–48%) and high proportions of benzaldehyde, benzoic acid, probably generated during work-up, and benzylic alcohol.[9,2i]

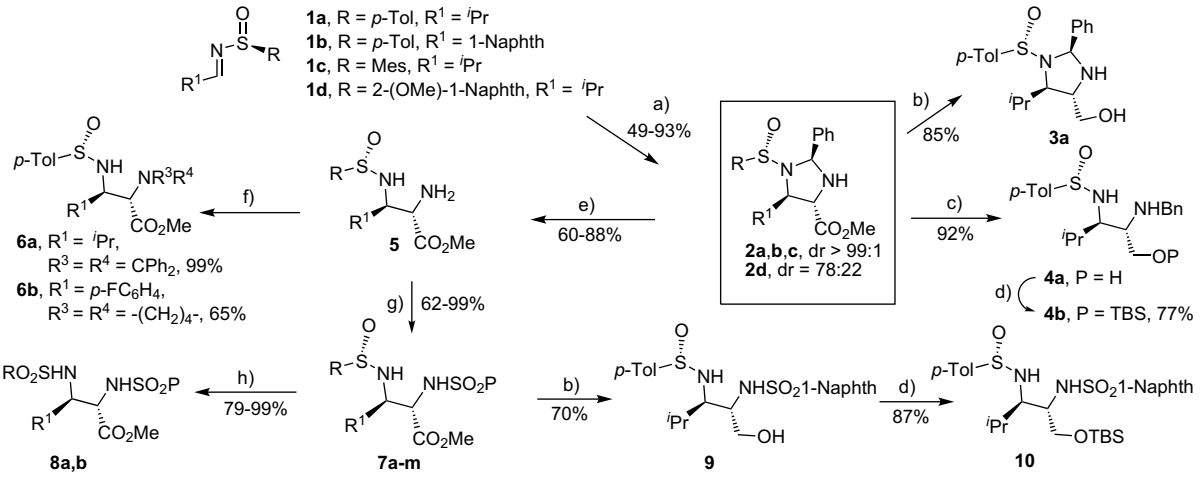
On the contrary, when the reactions of diethylzinc and benzaldehyde were conducted in CH_2Cl_2 with Ti(O^iPr)$_4$ (Scheme 2) and using sulfinamides **2**–**5**, excellent conversions to 1-phenylpropanol were obtained but the low enantiomeric excesses (<10%) confirmed that an effective asymmetric catalyst was not formed in these reactions.



Scheme 2. Diethylzinc addition onto benzaldehyde.

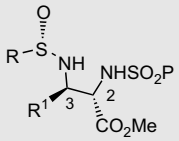
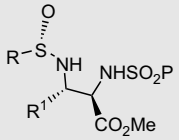
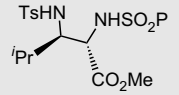
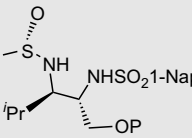
At this point we planned to examine the influence of different groups on the nitrogen atom at C-2 and we submitted to the reaction conditions *N*-benzyhydryl, pyrrolidine and sulfonamido derivatives **6a**, **6b**, and **7a**. From these experiments we observed that sulfonamide **7a** provided a slightly better conversion (71%) and ee (20%) than diamino esters **6a** and **6b** (ee<5%) and therefore, we focused on optimizing this result (Table 1). Based on earlier studies in this matter,[10] we evaluated the effect of changing the order of addition of the reagents on the enantioselectivity. Certainly, we noticed a significant enhancement of the enantiocontrol to a 40% ee when diethylzinc was firstly added over **7a** and then the titanium alkoxide (Table 1, entry 2). In fact, we examined the ^{1}H NMR spectrum of an equimolecular mixture of sulfonamido ligand **7a** with Ti(O^iPr)$_4$ in $CDCl_3$ and no significant variations occurred for proton signals of **7a**. Consequently, it looks likely that **7a** would react initially with diethylzinc through deprotonation of the sulfonamide moiety and then would be transferred to titanium in a subsequent step.[11]

Encouraged by these results, we screened a battery of sulfonamides **7b**–**m** under the optimized conditions. The outcome is summarized in Table 1 (entries 3–16). As shown, neither the use of methyl sulfonamide or variation of *p*-substituents on the aromatic ring had a significant impact on the enantioselectivity (entries 3, 5,



Scheme 1. Synthesis of chiral ligands from sulfinimines. Reagents and conditions: (a) methyl (*E*)-*N*-benzylideneglycinate, LDA, $BF_3{\cdot}OEt_2$, THF, −78 °C. (b) $NaBH_4$, LiI, THF, 0 °C to rt. (c) $LiAlH_4$, Et_2O, 0 °C to rt. (d) TBSCl, ImH, DMAP, CH_2Cl_2, 0 °C to rt. (e) H_3PO_4, THF/H_2O, rt. (f) Ph_2C=NH or 1,4-dibromobutane, $NaHCO_3$. (g) PSO_2Cl, Et_3N or $^iPr_2EtN$, CH_2Cl_2, 0 °C to rt. (h) *m*-CPBA, CH_2Cl_2, 0 °C to rt.

Table 1
Enantioselective addition of Et_2Zn onto benzaldehyde using $Ti(O^iPr)_4$ and ligands **7**–**10**, according to Scheme 2

Entry	Ligand[a]		Conversion[b] (%)	(*S*:*R*)[c]	ee (%)
1		**7a**, R=*p*-Tol, R^1=^{i}Pr, P=*p*-Tol	71	60:40[d]	20
2		**7a**, R=*p*-Tol, R^1=^{i}Pr, P=*p*-Tol	100	70:30	40
3		**7b**, R=*p*-Tol, R^1=^{i}Pr, P=Me	76	72:28	44
4		**7c**, R=*p*-Tol, R^1=^{i}Pr, P=2,4,6-(^{i}Pr)$_3$-C_6H_2	100	80:20	60
5		**7d**, R=*p*-Tol, R^1=^{i}Pr, P=*p*-NO_2-C_6H_4	50	72:28	44
6		**7e**, R=*p*-Tol, R^1=^{i}Pr, P=2,4-NO_2-C_6H_4	64	47:53	6
7		**7f**, R=*p*-Tol, R^1=^{i}Pr, P=*p*-Br-C_6H_4	76	72:28	44
8		**7g**, R=*p*-Tol, R′=^{i}Pr, P=*p*-MeO-C_6H_4	100	73:27	46
9		**7h**, R=*p*-Tol, R^1=^{i}Pr, P=3,5-Cl_2-2-OH-C_6H_4	70	55:45	10
10		**7i**, R=*p*-Tol, R^1=^{i}Pr, P=1-Naphth	100	84:16	68
11		**7i**, R=*p*-Tol, R^1=^{i}Pr, P=1-Naphth	100	87:13[e]	74
12		**7j**, R=*p*-Tol, R^1=^{i}Pr, P=*D*-Camphor	66	59:41	18
13		**7j′**, R=*p*-Tol, R^1=^{i}Pr, P=*L*-Camphor	100	60:40	20
14		**7k**, R=*p*-Tol, R^1=1-Naphth, P=1-Naphth	91	65:35	30
15		**7l**, R=Mes, R^1=^{i}Pr, P=1-Naphth	100	87:13	74
16		**7m**, R=2-(OMe)-1-Naphth, R^1=^{i}Pr, P=1-Naphth	100	75:25	50
17		**7m′**, R=2-(OMe)-1-Naphth, R^1=^{i}Pr, P=1-Naphth	100	42:58	16
18		**8a**, P=*p*-Tol	100	50:50	0
19		**8b**, P=1-Naphth	82	52:48	4
20		**9**, P=H	91	50:50	0
21		**10**, P=TBS	80	53:47	6

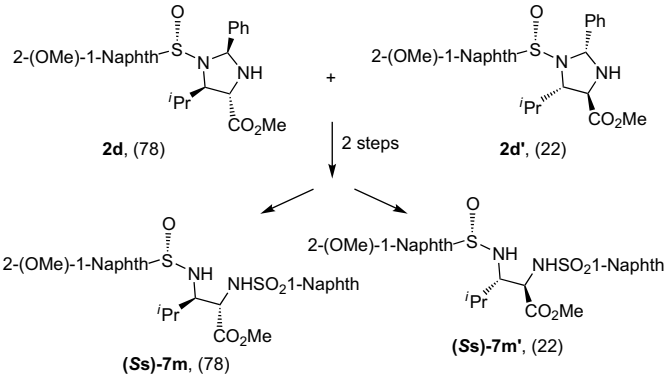
[a] To a solution of **7**–**10** in CH_2Cl_2 was added: (1) Et_2Zn; (2) $Ti(O^iPr)_4$; (3) PhCHO.
[b] Conversions were determined by ^{1}H NMR of the crude.
[c] Enantiomeric ratio determined by chiral HPLC (Chiralcel OD).
[d] Sequence of addition of the reactants over **7a** in CH_2Cl_2: (1) $Ti(O^iPr)_4$; (2) Et_2Zn; (3) PhCHO.
[e] When the amount of $Ti(O^iPr)_4$ was reduced to 0.8 equiv, the selectivity slightly improved to 87:13 (*S*:*R*).[14]

7, and 8). In contrast, the introduction of several electron-withdrawing groups on aromatic sulfonamides caused a drastic decrease in the enantiocontrol (entry 6). The presence of an *o*-phenol[12] group or a chiral camphor[13] moiety at the sulfonamides, successfully employed in other examples of enantioselective sulfonamido ligands had a negative effect in the present study (entries 9, 12, and 13). The best enantioselectivities were achieved for 2,4,6-triisopropylbenzene and 1-naphthyl sulfonamides (entries 4, 10, and 11) being (*S*)-1-phenylpropanol the major enantiomer. Likely both sulfonamides contain in their structure an optimal combination of electron-donating effects and conformational rigidity required for an effective chiral metal catalyst.[14]

With the aim of improving the enantioselectivity of these sulfinamide-sulfonamido ligands, we carried out further modifications of their structure. Therefore we tested the effect of the nature of R^1, however changing from ^{i}Pr to naphthyl group (**7k**) had a negative impact on the ee (entry 14). In addition, the ester moiety was replaced for either a hydroxymethyl or a silyloxymethyl group in the search of an additional point of coordination to the metal[15] (**9** and **10**) but racemic 1-phenylpropanol was recovered in both experiments (Table 1, entries 20 and 21).

Interestingly, the experimental evidences showed a crucial cooperation between sulfinyl and sulfonyl functionalities to reach enantiocontrol in the alkylation process since suppressing the sulfur chiral atom by oxidation to the sulfonamide led to bis-sulfonamides **8a** and **8b** that provided racemic 1-phenylpropanol when tested under the same conditions (entries 18 and 19). Subsequently, we tried to vary the nature of the sulfinyl group (R) with mixed results. While (*S*)-mesityl sulfoxide slightly improved the enantioselectivity, (*S*)-2-methoxy-1-naphthyl sulfoxide had the opposite effect[16] (entries 15 and 16).

To clarify the role of the chiral sulfinamide in the enantiocontrol of the reaction, we tested (S_s)-**7m′** thus comparing both diastereomeric ligands isomers (2*S*,3*R*,S_s)-**7m** and (2*R*,3*S*,S_s)-**7m′** (Scheme 3). These compounds were prepared from the two



Scheme 3. Synthesis of (2*S*,3*R*,S_s)-**7m** and (2*R*,3*S*,S_s)-**7m′**.

Table 2
Enantioselective addition of Et_2Zn to RCHO using ligand **7i**[a]

Entry	R	Conversion[b] (%)	(*S*:*R*)	ee (%)
1	4-ClC_6H_4	100	77:23[c]	54
2	3,4-$(MeO)_2C_6H_3$	26	63:37[c]	26
3	1-Naphth	85	75:25[d]	50

[a] 1.5 equiv Et_2Zn, 1.2 equiv $Ti(O^iPr)_4$, 0.05 equiv **7i**, CH_2Cl_2, rt, 24 h.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR of (+)-MPA esters.
[d] Determined by HPLC (Chiralcel OD).

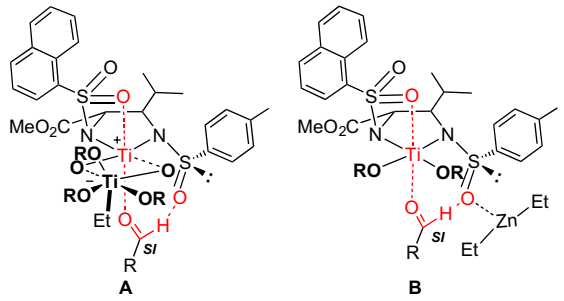


Figure 2. Proposed stereochemical outcome for ligand **7i**.

diastereofacial isomers **2d** and **2d′** obtained in the initial [3+2] cyclization step, after selective aminal removal, sulfonylation, and separation.[17] By changing the relative configuration of the carbon skeleton relative to the chiral sulfinamide (2*R*,3*S*,S_s)-**7m′** the enantioselectivity of the ethylation of benzaldehyde dramatically dropped to a 16% ee isolating (*R*)-1-phenylpropanol as the major isomer (Table 1, compare entries 16 and 17). This result reveals that the sulfinamide exerts a high influence but it is not the only stereogenic center that controls the stereochemical pathway of the reaction existing a reinforcing/non-reinforcing combination of configurations of the stereocenters in the ligands.

Finally, other aldehydes have been tested in the alkylation using ligand **7i**, however the enantioselectivities were always lower than when benzaldehyde was used. The results are gathered in Table 2.

In order to rationalize the stereochemical outcome of the alkylation, and based on prior studies in this area,[18] we propose the formation of a bimetallic catalytic species where ligand (**7i**) coordinates to the titanium atom arranging its substituents in an *anti* disposition and placing the sulfonamide and the sulfinamide in opposite faces of the complex, which in turn would provide a stereoelectronic discrimination at the metal that should be responsible of the different behavior of ligands **7a**,**i** (sulfinamido-sulfonamide) and **8a**,**b** (bis-sulfonamide). In this scenario, it seems plausible that coordination of the sulfonamide through one of the oxygen atoms to titanium would block the β-face of the complex, leaving the α-face accessible for coordination of the aldehyde. The lack of enantioselectivity of the bis-sulfonamido ligands **8a** and **8b** (*S*:*R*, 50:50) along with the change in the magnitude and sense of the enantioselectivity encountered for **7m′** (*S*:*R*, 42:58) reveals the crucial role of the chiral sulfinamide moiety in the catalytic process. Consequently, the addition of the ethyl group onto the *si* face of benzaldehyde, delivered either from a second titanium atom[18b,7b] **A** or directly from $ZnEt_2$ **B**,[15,19] would be guided by coordination with the sulfinamide group. Additionally, a hydrogen bond between the sulfinamide and the aldehyde would contribute to organize the approach of the reagents (Fig. 2).[20]

3. Conclusions

A large amount of research has been devoted to the understanding of the role of sulfonamides as chiral ligands, however the use of enantiopure sulfinamides in enantioselective catalysis is still under examination. The synthesis and evaluation of a number of sulfinamido-sulfonamide compounds as ligands for the enantioselective alkylation of aldehydes with Et_2Zn and $Ti(O^iPr)_4$ have been carried out in our laboratory. The systematic study of the structural requirements to create enantioselective metal species has entailed testing a broad collection of chiral diamino derivatives as ligands easily available from chiral sulfinamides through the methodology developed in our group. Further investigations toward the applications of these compounds in new asymmetric processes are now underway in our laboratory.

4. Experimental

4.1. General

Reagents and solvents were handled by using standard syringe techniques. All reactions were carried out under an argon atmosphere. Crude products were purified by flash chromatography on Merck 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on Merck (Kieselgel 60 F_{254}) silica gel plates. Throughout this section, the volume of solvents is reported in mL/mmol of starting material. Infrared spectra (IR) were obtained on a Perkin–Elmer 681 and on a Perkin–Elmer Spectrum one. ^1H and ^{13}C NMR spectra were recorded at 200 MHz, 300 MHz, 400 MHz or 500 MHz using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm) unless otherwise noted. Melting points were determined on a Reichert Kofler microscope and are uncorrected. Optical rotations were measured at 20 °C using a sodium lamp and in $CHCl_3$ solution. HPLC was carried out on Daicel Chiralcel-OD chiral column (5% ^{i}PrOH/hex, 1 mL/min, 250 nm). Low resolution mass spectra were recorded by direct injection using the electronic impact technique with an ionization energy of 70 eV or using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative modes. High resolution mass spectra were recorded in an Accurate Mass Q-TOF, LC/MS, Agilent technologies 6520. Elemental analyses were carried out at Instituto de Química Orgánica General, CSIC.

4.2. Synthesis of chiral ligands

Compounds **2ab**, **4ab**, **5ab**, and **6b** were prepared following procedures previously reported.[8a–c] Sulfinimines **1c** and **1d** were prepared from the corresponding (*S*)-sulfinamide following a reported procedure.[21] New compounds are described below.

4.2.1. (+)-(S)-2,4,6-Trimethyl-N-[(1E)-2-methylpropyliden]-benzenesulfinamide, ***1c***

From (+)-(*S*)-2,4,6-trimethylbenzenesulfinamide[22] (430 mg, 2.4 mmol), isobutyraldehyde (0.21 mL, 2.4 mmol), and $Ti(OEt)_4$ (2.5 mL, 11.7 mmol), following the reported procedure[21] (4 h) and after purification by column chromatography (30% CH_2Cl_2/hex to CH_2Cl_2), sulfinimine **1c** was obtained as a colorless oil (585 mg, 92%). Data for **1c**: R_f 0.34 (20% EtOAc/hex). $[\alpha]_D^{20}$ +328.8 (*c* 1.01). ^1H NMR (300 MHz) δ 1.14 (d, 3H, *J*=3.7 Hz, Me ^{i}Pr), 1.16 (d, 3H, *J*=3.7 Hz, Me ^{i}Pr), 2.26 (s, 3H, Me Ar), 2.43 (s, 6H, Me Ar×2), 2.73 (m, 1H, CH ^{i}Pr), 6.82 (s, 2H, Ar–H), 8.16 (d, 1H, *J*=5.1 Hz, CH=N). ^{13}C NMR (75 MHz) δ 18.7 (2C), 18.8, 18.9, 20.9, 34.7, 130.7 (2C), 135.1, 138.2 (2C), 141.5, 172.0 (C=N). IR (film): 2966, 2926, 2871, 1616, 1600, 1569, 1463, 1380, 1291, 1089, 1050, 851, 711, 677, 620 cm^{-1}. HRMS (ESI) *m*/*z* for $C_{13}H_{19}NNaOS$ $[M+Na]^+$ calcd: 260.1085, found: 260.1079.

4.2.2. (+)-(S)-N-[(1E)-2-Methylpropyliden]-2-methoxy-1-naphthylsulfinamide, ***1d***

From (−)-(*S*)-2-methoxy-1-naphthylsulfinamide[21a] (480 mg, 2.17 mmol), isobutyraldehyde (0.2 mL, 2.17 mmol), and $Ti(OEt)_4$ (2.3 mL, 10.85 mmol), following the reported procedure[21] (6 h) and after purification by column chromatography (60% CH_2Cl_2/hex to CH_2Cl_2), sulfinimine **1d** was obtained as a yellow solid (520 mg, 87%). Data for **1d**: R_f 0.27 (5% EtOAc/CH_2Cl_2). Mp: 118–120 °C. $[\alpha]_D^{20}$ +259.4 (*c* 0.72). ^1H NMR (300 MHz) δ 1.13 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.17 (d, 3H, *J*=7.1 Hz, Me ^{i}Pr), 2.76 (m, 1H, CH ^{i}Pr), 3.98 (s, 3H, OMe), 7.26 (d, 1H, *J*=9.0 Hz, Ar–H), 7.36 (m, 1H, Ar–H), 7.48 (m, 1H, Ar–H), 7.78 (d, 1H, *J*=8.1 Hz, Ar–H), 7.94 (d, 1H, *J*=9.3 Hz, Ar–H), 8.38 (d, 1H, *J*=5.4 Hz, CH=N), 8.48 (d, 1H, *J*=8.5 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 18.9, 19.1, 34.8, 56.7, 113.1, 121.8, 122.1, 124.3, 127.8, 128.7, 129.2, 131.3, 134.6, 157.1, 172.3. IR (KBr): 2967, 2931, 2865, 2841, 1619, 1592,

1562, 1506, 1467, 1428, 1336, 1272, 1251, 1149, 1134, 1065, 1024, 982, 896, 811, 747 cm^{-1}. HRMS (ESI) *m/z* for $C_{30}H_{34}N_2NaO_4S_2$ $[2M+Na]^+$ calcd: 573.1858, found: 573.1854. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.06; H, 5.98; N, 5.12; S, 11.48.

4.2.3. (+)-Methyl [(2S,4S,5R,S_s)-5-isopropyl-1-(mesitylsulfinyl)-2-phenylimidazolidin-4-yl]carboxylate, **2c**

From LDA [$^i Pr_2NH$ (0.57 mL, 4.07 mmol) and *n*-BuLi (0.15 mL, 3.45 mmol)], methyl (*E*)-*N*-benzylideneglycinate (556 mg, 3.14 mmol), **1c** (372 mg, 1.57 mmol), and 4.25 equiv of $BF_3 \cdot OEt_2$ (0.85 mL), in THF following the reported procedure[8b] (15 min), was obtained **2c** after column chromatography (CH_2Cl_2 to 40% Et_2O/CH_2Cl_2) as a yellow oil (380 mg, 58%). Data for **2c**: R_f 0.36 (20% Et_2O/CH_2Cl_2). $[\alpha]_D^{20}$ +94.6 (*c* 1.6). ^1H NMR (300 MHz) δ 0.28 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 0.79 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 1.15 (m, 1H, CH $^i Pr$), 2.22 (br s, 10H, Me Ar×3+NH), 3.82 (s, 4H, H-4+OMe), 3.93 (dd, 1H, *J*=8.8, 2.7 Hz, H-5), 5.77 (s, 1H, H-2), 6.74 (s, 2H, Ar–H), 7.24–7.38 (m, 3H, Ar–H), 7.51–7.54 (m, 2H, Ar–H). ^{13}C NMR (75 MHz) δ 19.1, 19.2, 19.3, 20.9 (2C), 32.9, 52.5, 63.5, 67.1, 80.4, 127.3 (4C), 128.2 (5C), 134.5, 140.5, 140.7, 172.7 (C=O). IR (film): 3335, 2956, 1739, 1602, 1455, 1435, 1206, 1092, 901, 700 cm^{-1}. HRMS (ESI) *m/z* for $C_{23}H_{31}N_2O_3S$ $[M+H]^+$ calcd: 415.2055, found: 415.2068.

4.2.4. Methyl [(2S,4S,5R,S_s)-5-isopropyl-1-(2-methoxy-1-naphthylsulfinyl)-2-phenylimidazolidin-4-yl]carboxylate, **2d** and methyl [(2R,4R,5S,S_s)-5-isopropyl-1-(2-methoxy-1-naphthylsulfinyl)-2-phenylimidazolidin-4-yl]carboxylate, **2d′**

From LDA [$^i Pr_2NH$ (0.034 mL, 0.31 mmol) in THF and *n*-BuLi (0.13 mL, 0.21 mmol)], methyl (*E*)-*N*-benzylideneglycinate (33 mg, 0.19 mmol), **1d** (26 mg, 0.09 mmol), and 3.25 equiv of $BF_3 \cdot OEt_2$ (0.039 mL, 0.31 mmol), following the reported procedure[8b] (1 h), a 78:22 inseparable mixture of **2d**:**2d′** was obtained after column chromatography (60% Et_2O/hex to Et_2O) as a yellow oil (20 mg, 49%). Data for **2d** from the mixture: ^1H NMR (300 MHz) δ 0.25 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 0.65 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 1.04 (m, 1H, CH $^i Pr$), 3.76 (d, 1H, *J*=3.4 Hz, H-4), 3.85 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.14 (dd, 1H, *J*=8.8, 3.4 Hz, H-5), 5.92 (s, 1H, H-2), 7.19–7.49 (m, 7H, Ar–H), 7.61–7.93 (m, 4H, Ar–H). ^{13}C NMR (100 MHz) δ 19.1, 19.3, 33.0, 52.5, 56.4, 64.0, 68.5, 80.7, 112.3, 122.8, 124.2, 126.1, 127.0 (2C), 127.5, 127.7, 127.8, 128.0 (2C), 128.4, 128.5, 134.2, 140.9, 156.3, 172.7 (C=O). HRMS (ESI) *m/z* for $C_{25}H_{29}N_2O_4S$ $[M+H]^+$ calcd: 453.1848, found: 453.1873. Partial data for **2d′** from the mixture: ^1H NMR (300 MHz) δ 3.89 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.20 (s, 1H, H-2).

4.2.5. (+)-[(2S,4S,5R,S_s)-5-Isopropyl-2-phenyl-1-(p-tolylsulfinyl)-imidazolidin-4-yl]methanol, **3a**

From **2a** (108 mg, 0.279 mmol), LiI (112 mg, 0.838 mmol), and $NaBH_4$ (32 mg, 0.838 mmol), following the reported procedure[8b] (3 h) and after chromatographic purification (40–80% EtOAc/hex), **3a** was obtained as a white solid (85 mg, 85%). Compound **3a** was further crystallized in Et_2O/hex (1:1). Data for **3a**: R_f 0.26 (5% MeOH/CH_2Cl_2). Mp: 105–106 °C. $[\alpha]_D^{20}$ +56.6 (*c* 2.62). ^1H NMR (300 MHz)-selective decouplings δ 0.36 (d, 3H, *J*=6.0 Hz, Me $^i Pr$), 0.67 (d, 3H, *J*=6.5 Hz, Me $^i Pr$), 0.74 (m, 1H, CH $^i Pr$), 2.39 (s, 3H, Me *p*-Tol), 2.88 (br s, 1H), 3.28 (dd, 1H, *J*=4.7, 2.8 Hz, H-4), 3.49 (dd, 1H, *J*=5.9, 2.9 Hz, H-5), 3.64 (dd, 1H, *J*=11.4, 4.8 Hz, CH_2OH), 3.75 (dd, 1H, *J*=11.4, 7.3 Hz, CH_2OH), 5.72 (s, 1H, H-2), 7.25–7.62 (m, 9H, Ar–H). ^{13}C NMR (75 MHz) δ 17.4 (Me $^i Pr$), 19.7 (Me $^i Pr$), 21.4 (Me *p*-Tol), 31.6 (CH $^i Pr$), 59.8 (C–O), 61.8 (C–N), 63.0 (C–N), 80.8 (C-2), 125.2 (2C), 127.1 (2C), 128.6, 128.6 (2C), 129.5 (2C), 139.7, 140.3, 141.8. IR (KBr): 3401, 2960, 2927, 2869, 1641, 1490, 1450, 1385, 1201, 1085, 1046, 1013, 916, 812, 745, 699 cm^{-1}. HRMS (ESI) *m/z* for $C_{20}H_{27}N_2O_2S$ $[M+H]^+$ calcd: 359.1793, found: 359.1803.

4.2.6. (+)-Methyl [(2R,3R,S_s)-2-amino-3-(mesitylsulfinylamino)-4-methyl]pentanoate, **5c**

From **2c** (264 mg, 0.64 mmol) and aqueous H_3PO_4 (0.5 M, 5.1 mL, 2.55 mmol), following the reported procedure[8c] (18 h) and after chromatographic purification (CH_2Cl_2 to 10% EtOH/CH_2Cl_2), **5c** was obtained as a colorless oil (125 mg, 60%). Data for **5c**: R_f 0.34 (5% EtOH/CH_2Cl_2). $[\alpha]_D^{20}$ +136.9 (*c* 1.69). ^1H NMR (300 MHz) δ 1.00 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 1.08 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 1.60 (s, 2H, NH_2), 1.87 (m, 1H, CH $^i Pr$), 2.24 (s, 3H, Me Ar), 2.53 (s, 6H, Me Ar), 3.50 (dd, 1H, *J*=7.6, 2.7 Hz, H-3), 3.62 (d, 1H, *J*=2.7 Hz, H-2), 3.72 (s, 3H, OMe), 4.47 (d, 1H, *J*=7.6 Hz, NH), 6.81 (s, 2H, Ar–H). ^{13}C NMR (75 MHz) δ 19.3, 19.5, 19.8, 20.7, 30.6, 51.9, 51.9, 55.4, 63.3, 130.6 (2C), 135.9 (2C), 138.7, 140.2, 174.9 (C=O). IR (film): 3233, 2958, 2926, 1739, 1602, 1436, 1225, 1071, 851, 755 cm^{-1}. HRMS (ESI) *m/z* for $C_{16}H_{27}N_2O_3S$ $[M+H]^+$ calcd: 327.1742, found: 327.1737.

4.2.7. Methyl [(2S,3R,S_s)-2-amino-4-methyl-3-(2-methoxy-1-naphthylsulfinylamino)]pentanoate, **5d** and methyl [(2R,3S,S_s)-2-amino-4-methyl-3-(2-methoxy-1-naphthylsulfinylamino)]-pentanoate, **5d′**

From a 78:22 mixture of **2d**:**2d′** (13 mg, 0.03 mmol) and aqueous H_3PO_4 (0.5 M, 0.21 mL, 0.11 mmol), following the reported procedure[8c] (6 h), a 78:22 mixture of **5d**:**5d′** was obtained as a colorless oil (9 mg, 70%) that was used without further purification. Data for **5d** from the mixture: R_f 0.26 (5% EtOH/CH_2Cl_2). ^1H NMR (300 MHz) δ 1.07 (d, 3H, *J*=6.6 Hz, Me $^i Pr$), 1.20 (d, 3H, *J*=6.6 Hz, Me $^i Pr$), 1.94 (m, 1H, CH $^i Pr$), 3.48 (s, 3H, OMe), 3.54 (m, 1H, H-3), 3.62 (d, 1H, *J*=2.9 Hz, H-2), 4.08 (s, 3H, OMe), 5.89 (d, 1H, *J*=7.1 Hz, NH), 7.30 (dd, 1H, *J*=9.0, 2.0 Hz, Ar–H), 7.37 (dd, 1H, *J*=8.1, 1.0 Hz, Ar–H), 7.53 (dt, 1H, *J*=7.1, 1.5 Hz, Ar–H), 7.79 (d, 1H, *J*=8.3 Hz, Ar–H), 7.90 (d, 1H, *J*=9.3 Hz, Ar–H), 8.53 (d, 1H, *J*=8.8 Hz, Ar–H). Partial data for **5d′** from the mixture: ^1H NMR (300 MHz) δ 0.99 (d, 3H, *J*=6.6 Hz, Me $^i Pr$), 0.98 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 6.21 (d, 1H, *J*=8.5 Hz, NHSO), 8.61 (d, 1H, *J*=8.5 Hz, Ar–H).

4.2.8. (+)-Methyl [(2S,3R,S_s)-N-(diphenylmethylene)-4-methyl-3-(p-tolylsulfinylamino)]pentanoate, **6a**

To a solution of **5a**[8c] (86 mg, 0.288 mmol) in CH_2Cl_2 (10 mL/mmol), 1.15 equiv of Ph_2C=NH was added (0.06 mL, 0.331 mmol). The mixture was stirred at room temperature until the disappearance of **5a** monitored by TLC (22 h). The solvent was removed under reduced pressure and the crude was purified by column chromatography (20–50% Et_2O/hex) to render **6a** as a white solid (133 mg, 99%). Data for **6a**: R_f 0.41 (Et_2O). Mp: 47 °C. $[\alpha]_D^{20}$ +2.2 (*c* 1.55). ^1H NMR (300 MHz) δ 0.75 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 0.88 (d, 3H, *J*=6.8 Hz, Me $^i Pr$), 1.65 (m, 1H, CH $^i Pr$), 2.38 (s, 3H, Me *p*-Tol), 3.72 (m, 1H, H-3), 3.74 (s, 3H, OMe), 4.23 (d, 1H, *J*=2.2 Hz, H-2), 5.16 (d, 1H, *J*=9.7 Hz, NHSO), 7.10 (m, 2H, Ar–H), 7.28 (m, 4H, Ar–H), 7.40 (m, 4H, Ar–H), 7.60 (m, 4H, Ar–H). ^{13}C NMR (75 MHz) δ 19.3 (Me $^i Pr$), 19.7 (Me $^i Pr$), 21.3 (Me *p*-Tol), 31.7 (CH $^i Pr$), 52.3, 63.9, 67.2, 125.9 (2C), 127.2 (2C), 128.1 (2C), 128.6 (2C), 128.9 (2C), 129.4 (2C), 130.0, 130.7, 136.3, 139.0, 141.0, 143.3, 171.8 (C=O, C=N). IR (KBr): 3304, 2956, 1742, 1624, 1443, 1197, 1089, 1067, 695 cm^{-1}. HRMS (ESI) *m/z* for $C_{27}H_{31}N_2O_3S$ $[M+H]^+$ calcd: 463.2055, found: 463.2073. Anal. Calcd for $C_{27}H_{30}N_2O_3S$: C, 70.10; H, 6.54; N, 6.06; S, 6.93. Found: C, 69.89; H, 6.62; N, 5.87; S, 7.21.

4.2.9. General procedure for the synthesis of sulfonamides

To a solution of 1.0 equiv of amine **5** in anhydrous CH_2Cl_2 (3 mL/mmol) was added 1.0–1.5 equiv of PSO_2Cl and 2.0–2.5 equiv of Et_3N or $^i Pr_2EtN$. The mixture was stirred from 0 °C to room temperature and was monitored by TLC until completion. Then, it was hydrolyzed with a 50% aqueous solution of K_2CO_3 (15 mL/mmol) and extracted with CH_2Cl_2 (3×10 mL/mmol). The combined organic phases were washed with a saturated solution of NaCl (10 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and the solvent was

evaporated under reduced pressure. The crude was purified by chromatography on silica gel using the appropriate mixture of eluents. *Note*: careful attention should be paid to the presence of water in the reaction since traces of sulfonic acid can led to epimerization of the sulfinamide moiety in **7**. Azeotropic co-evaporation with anhydrous cyclohexane of substrate and pure PSO_2Cl prior to use prevent this process.

4.2.10. (+)-Methyl [(2S,3R,S_s)-4-methyl-3-(p-tolylsulfinylamino)-2-(p-tolylsulfonylamino)]pentanoate, **7a**

From **5a** (31 mg, 0.10 mmol), Et_3N (0.029 mL, 0.21 mmol, 2.0 equiv), and *p*-$TolSO_2Cl$ (20 mg, 0.10 mmol), following the general procedure (6 h) and after chromatographic purification (20–30% EtOAc/hex), **7a** was obtained as a white solid (44 mg, 93%). Data for **7a**: R_f 0.12 (10% EtOAc/CH_2Cl_2). Mp: 62 °C. $[\alpha]_D^{20}$ +6.3 (*c* 0.87). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.94 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 1.81 (m, 1H, CH ^{i}Pr), 2.38 (s, 3H, Me *p*-Tol), 2.41 (s, 3H, Me *p*-Tol), 3.35 (td, 1H, *J*=8.3, 3.4 Hz, H-3), 3.49 (s, 3H, OMe), 4.06 (d, 1H, *J*=9.3 Hz, NHSO), 4.09 (dd, 1H, *J*=9.9, 3.4 Hz, H-2), 5.85 (d, 1H, *J*=9.3 Hz, NHTs), 7.24–7.30 (m, 4H, Ar–H), 7.51 (d, 2H, *J*=8.0 Hz, Ar–H), 7.73 (d, 2H, *J*=8.3 Hz, Ar–H). ^{1}H NMR (C_6D_6, 300 MHz) δ 0.69 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 0.80 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 1.71 (m, 1H, CH ^{i}Pr), 1.84 (s, 3H, *p*-Tol), 1.92 (s, 3H, *p*-Tol), 3.10 (s, 3H, OMe), 3.40 (td, 1H, *J*=7.3, 4.2 Hz, H-3), 4.07 (d, 1H, J=9.0 Hz, NH–SO), 4.31 (dd, 1H, *J*=8.1, 4.1 Hz, H-2), 6.61 (d, 1H, *J*=8.8 Hz, NH–Ts), 6.75 (d, 2H, *J*=8.1 Hz, Ar–H), 6.84 (d, 2H, *J*=8.3 Hz, Ar–H), 7.60 (d, 2H, *J*=8.3 Hz, Ar–H), 7.86 (d, 2H, *J*=8.1 Hz, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8 (Me ^{i}Pr), 19.8 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 21.5 (Me *p*-Tol), 29.8 (CH ^{i}Pr), 52.6 (OMe), 57.4 (C–N), 61.8 (C–N), 125.7 (2C), 127.3 (2C), 129.6 (4C), 136.8, 140.7, 141.8, 143.7, 170.9 (C=O). IR (KBr): 3275, 2959, 2920, 1747, 1598, 1435, 1338, 1163, 1092, 1035, 814, 775, 667 cm^{-1}. HRMS (ESI) *m*/*z* for $C_{21}H_{29}N_2O_5S_2$ $[M+H]^+$ calcd: 453.1518, found: 453.1528.

4.2.11. (−)-Methyl [(2S,3R,S_s)-4-methyl-2-(methylsulfonylamino)-3-(p-tolylsulfinylamino)]pentanoate, **7b**

From **5a** (38 mg, 0.13 mmol), ^{i}Pr$_2$EtN (0.043 mL, 0.25 mmol), and $MeSO_2Cl$ (0.01 mL, 0.13 mmol), following the general procedure (4 h) and after chromatographic purification (10–30% EtOAc/CH_2Cl_2), **7b** was obtained as a colorless oil (35 mg, 73%). Data for **7b**: R_f 0.21 (30% EtOAc/CH_2Cl_2). $[\alpha]_D^{20}$ −8.7 (*c* 0.77). ^{1}H NMR (300 MHz) δ 0.90 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 0.97 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 1.83 (m, 1H, CH ^{i}Pr), 2.39 (s, 3H, Me *p*-Tol), 2.99 (s, 3H, Me–Ms), 3.42 (td, 1H, *J*=8.3, 2.7 Hz, H-3), 3.77 (s, 3H, OMe), 4.27 (dd, 1H, *J*=9.8, 2.9 Hz, H-2), 4.42 (d, 1H, *J*=8.3 Hz, NHSO), 5.94 (d, 1H, *J*=9.7 Hz, NHMs), 7.27 (d, 2H, *J*=8.1 Hz, Ar–H), 7.49 (d, 2H, *J*=8.3 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 19.0 (Me ^{i}Pr), 19.6 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 30.0 (CH ^{i}Pr), 41.6 (Me–Ms), 52.9 (OMe), 57.8 (C–N), 61.4 (C–N), 125.8 (2C), 129.5 (2C), 140.4, 141.7, 171.7 (C=O). IR (film): 3271, 2959, 2927, 2876, 1746, 1436, 1327, 1216, 1142, 1087, 1055, 813, 754 cm^{-1}. MS (ES): 775 $[2M+Na]^+$ (100%), 399 $[M+Na]^+$, 377 $[M+1]^+$.

4.2.12. (+)-Methyl [(2S,3R,S_s)-4-methyl-3-(p-tolylsulfinylamino)-2-(2,3,6-triisopropylphenylsulfonylamino)]pentanoate, **7c**

From **5a** (30 mg, 0.10 mmol), Et_3N (0.028 mL, 0.20 mmol), and 2,4,6-(^{i}Pr)$_3C_6H_2SO_2Cl$ (31 mg, 0.10 mmol), following the general procedure (26 h) and after chromatographic purification (5–20% EtOAc/hex), **7c** was obtained as a colorless oil (56 mg, 99%). Data for **7c**: R_f 0.23 (50% Et_2O/hex). $[\alpha]_D^{20}$ +53.4 (*c* 0.98). ^{1}H NMR (300 MHz) δ 0.76 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.95 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.23 (d, 6H, *J*=6.8 Hz, Me ^{i}Pr Ar), 1.24 (d, 6H, *J*=6.8 Hz, Me ^{i}Pr Ar), 1.30 (d, 6H, *J*=6.8 Hz, Me ^{i}Pr Ar), 1.76 (m, 1H, CH ^{i}Pr), 2.38 (s, 3H, Me *p*-Tol), 2.87 (m, 1H, CH Ar), 3.38 (ddd, 1H, *J*=8.3, 7.1, 4.4 Hz, H-3), 3.44 (s, 3H, OMe), 4.11 (m, 2H, 2CH Ar), 4.23 (dd, 1H, *J*=9.3, 4.4 Hz, H-2), 4.27 (d, 1H, *J*=8.0 Hz, NHSO), 6.15 (d, 1H, *J*=9.5 Hz, $NHSO_2$), 7.14 (s, 2H, Ar–H), 7.26 (d, 2H, *J*=8.0 Hz, Ar–H), 7.54 (d, 2H, *J*=8.0 Hz, Ar–H). ^{13}C NMR (75 MHz)-HSQC δ 18.3 (Me ^{i}Pr), 19.6 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 23.5 (CH ^{i}Pr Ar), 23.6 (CH ^{i}Pr Ar), 24.7 (2Me ^{i}Pr), 24.9 (2Me ^{i}Pr), 29.8 (CH ^{i}Pr), 30.0 (2Me ^{i}Pr), 34.2 (CH ^{i}Pr Ar), 52.3 (OMe), 56.5 (C–N), 61.0 (C–N), 123.6 (2C), 125.7 (2C), 129.5 (2C), 132.9, 140.9, 141.8, 150.2 (2C), 152.8, 171.1 (C=O). IR (film): 3275, 2956, 2927, 2869, 1747, 1598, 1461, 1429, 1327, 1255, 1197, 1161, 1147, 1085, 1056, 879, 811 cm^{-1}. HRMS (ESI) *m*/*z* for $C_{29}H_{45}N_2O_5S_2$ $[M+H]^+$ calcd: 565.2770, found: 565.2788.

4.2.13. (+)-Methyl (2S,3R,S_s)-[4-methyl-2-(p-nitrophenylsulfonylamino)-3-(p-tolylsulfinylamino)]pentanoate, **7d**

From **5a** (25 mg, 0.08 mmol), Et_3N (0.023 mL, 0.17 mmol, 2.0 equiv), and *p*-$NO_2C_6H_4SO_2Cl$ (19 mg, 0.08 mmol, 1.0 equiv), following the general procedure (1.5 h) and after chromatographic purification (20–30% EtOAc/hex), **7d** was obtained as a white solid (40 mg, 98%). Data for **7d**: R_f 0.28 (50% EtOAc/hex). Mp: 75–76 °C. $[\alpha]_D^{20}$ +74.9 (*c* 0.39). ^{1}H NMR (300 MHz) δ 0.82 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.95 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.83 (m, 1H, CH ^{i}Pr), 2.38 (s, 3H, Me *p*-Tol), 3.35 (tdd, 1H, *J*=8.8, 3.9, 1.5 Hz, H-3), 3.48 (s, 3H, OMe), 4.16 (dd, 1H, *J*=9.0, 3.9 Hz, H-2), 4.28 (br s, 1H, NHSO), 6.65 (br s, 1H, $NHSO_2$), 7.27 (d, 2H, *J*=8.0 Hz, Ar–H), 7.48 (d, 2H, *J*=8.3 Hz, Ar–H), 8.06 (d, 2H, *J*=8.0 Hz, Ar–H), 8.32 (d, 2H, *J*=8.3 Hz, Ar–H). ^{13}C NMR (75 MHz)-HSQC δ 18.5 (Me ^{i}Pr), 19.8 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 29.5 (CH ^{i}Pr), 52.7 (OMe), 57.5 (C-2), 61.1 (C-3), 124.1 (2C), 125.7 (2C), 128.5 (2C), 129.6 (2C), 139.8, 142.0, 145.9, 150.0, 170.4 (C=O). IR (KBr): 3435, 2956, 2920, 1748, 1606, 1531, 1432, 1350, 1309, 1168, 1091, 1053, 854, 735 cm^{-1}. HRMS (ESI) *m*/*z* for $C_{20}H_{26}N_3O_7S_2$ $[M+H]^+$ calcd: 484.1212, found: 484.1223.

4.2.14. (+)-Methyl [(2S,3R,S_s)-2-(2,4-dinitrophenylsulfonylamino)-4-methyl-3-(p-tolylsulfinylamino)]pentanoate, **7e**

From **5a** (23 mg, 0.08 mmol), Et_3N (0.021 mL, 0.16 mmol), and 2,4-$(NO_2)_2C_6H_3SO_2Cl$ (21 mg, 0.08 mmol), following the general procedure (32 h) and after chromatographic purification (5–15% EtOAc/hex), **7e** was obtained as a yellow oil (26 mg, 64%). Data for **7e**: R_f 0.26 (50% EtOAc/hex). $[\alpha]_D^{20}$ −65.8 (*c* 0.83). ^{1}H NMR (300 MHz) δ 1.04 (ap t, 6H, *J*=7.7, 6.8 Hz, Me ^{i}Pr), 1.91 (m, 1H, CH ^{i}Pr), 2.39 (s, 3H, Me *p*-Tol), 3.51 (s, 3H, OMe), 3.58 (td, 1H, *J*=6.7, 2.2 Hz, H-3), 4.14 (d, 1H, *J*=6.9 Hz, H-2), 4.46 (d, 1H, *J*=7.5 Hz, NHSO), 6.88 (d, 1H, *J*=9.4 Hz, $NHSO_2$), 7.28 (d, 2H, *J*=8.4 Hz, Ar–H), 7.49 (d, 2H, *J*=8.2 Hz, Ar–H), 8.28 (d, 1H, *J*=8.6 Hz, Ar–H), 8.51 (ddd, 1H, *J*=8.6, 2.2, 0.4 Hz, Ar–H), 8.77 (d, 1H, *J*=2.3 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 19.1 (Me ^{i}Pr), 19.6 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 30.1 (CH ^{i}Pr), 52.9 (OMe), 58.8 (C–N), 61.6 (C–N), 121.0, 125.5 (2C), 127.1, 129.7 (2C), 132.0, 140.2, 140.5, 142.1, 147.9, 149.7, 170.6 (C=O). IR (film): 3304, 3101, 2956, 2920, 1743, 1602, 1551, 1539, 1432, 1350, 1172, 1049, 811, 746 cm^{-1}. HRMS (ESI) *m*/*z* for $C_{20}H_{25}N_4O_9S_2$ $[M+H]^+$ calcd: 529.1063, found: 529.1082.

4.2.15. (+)-Methyl [(2S,3R,S_s)-2-(p-bromophenylsulfonylamino)-4-methyl-3-(p-tolylsulfinylamino)]pentanoate, **7f**

From **5a** (28 mg, 0.09 mmol), Et_3N (0.026 mL, 0.19 mmol), and *p*-$BrC_6H_4SO_2Cl$ (24 mg, 0.09 mmol), following the general procedure (5 h) and after chromatographic purification (20–50% EtOAc/hex), **7f** was obtained as a white solid (40 mg, 82%). Data for **7f**: R_f 0.34 (50% EtOAc/hex). Mp: 65 °C. $[\alpha]_D^{20}$ +28.7 (*c* 0.54). ^{1}H NMR (300 MHz) δ 0.83 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.94 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.81 (m, 1H, CH ^{i}Pr), 2.38 (s, 3H, Me *p*-Tol), 3.34 (td, 1H, *J*=8.3, 3.7 Hz, H-3), 3.50 (s, 3H, OMe), 4.10 (dd, 1H, *J*=9.0, 3.7 Hz, H-2), 4.24 (d, 1H, *J*=8.3 Hz, NHSO), 6.24 (d, 1H, *J*=9.0 Hz, $NHSO_2$), 7.25 (d, 2H, *J*=8.1 Hz, Ar–H), 7.49 (d, 2H, *J*=8.1 Hz, Ar–H), 7.62 (d, 2H, *J*=8.5 Hz, Ar–H), 7.72 (d, 2H, *J*=8.7 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 18.6 (Me ^{i}Pr), 19.8 (Me ^{i}Pr), 21.3 (Me *p*-Tol), 29.6 (CH ^{i}Pr), 52.6 (OMe), 57.4 (C–N), 61.5 (C–N), 125.7 (2C), 127.7, 128.8 (2C), 129.5 (2C), 132.1 (2C), 139.0, 140.4, 141.8, 170.6 (C=O). IR (KBr): 3435, 3297, 2956, 1748, 1575, 1468, 1432, 1389, 1342, 1166,

1091, 1067, 1010, 813, 739, 610 cm^{-1}. HRMS (ESI) *m/z* for $C_{40}H_{50}Br_2N_4NaO_{10}S_4$ $[2M+Na]^+$ calcd: 1057.0654, found: 1057.0678.

4.2.16. (+)-Methyl [(2S,3R,S_s)-4-methyl-2-(p-methoxyphenylsulfonylamino)-3-(p-tolylsulfinylamino)]pentanoate, **7g**

From **5a** (20 mg, 0.07 mmol), Et_3N (0.019 mL, 0.14 mmol), and *p*-$MeOC_6H_4SO_2Cl$ (14 mg, 0.07 mmol), following the general procedure (21 h) and after chromatographic purification (20–40% EtOAc/hex), **7g** was obtained as a yellow oil (22 mg, 70%). Data for **7g**: R_f 0.16 (50% EtOAc/hex). $[\alpha]_D^{20}$ +30.8 (*c* 0.94). ^{1}H NMR (300 MHz) δ 0.84 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.93 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 1.80 (m, 1H, CH ^{i}Pr), 2.37 (s, 3H, Me *p*-Tol), 3.34 (td, 1H, *J*=8.1, 3.4 Hz, H-3), 3.51 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.08 (m, 2H, H-2, NHSO), 5.85 (d, 1H, *J*=9.3 Hz, $NHSO_2$), 6.94 (d, 2H, *J*=8.8 Hz, Ar–H), 7.25 (d, 2H, *J*=8.3 Hz, Ar–H), 7.50 (d, 2H, *J*=8.1 Hz, Ar–H), 7.77 (d, 2H, *J*=8.5 Hz, Ar–H). ^{13}C NMR (75 MHz)-DEPT δ 18.7 (Me ^{i}Pr), 19.8 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 29.8 (CH ^{i}Pr), 52.7 (C–O), 55.6 (C–O), 57.4 (C–N), 61.8 (C–N), 114.1 (2C), 125.7 (2C), 129.5 (2C), 129.6 (2C), 131.3, 140.8, 141.8, 163.0, 171.0 (C=O). IR (film): 3268, 3166, 2962, 2927, 1747, 1597, 1498, 1441, 1338, 1260, 1158, 1094, 1030, 893, 835, 813, 756, 670 cm^{-1}. MS (ES): 959 $[2M+Na]^+$, 491 $[M+Na]^+$ (100%), 469 $[M+1]^+$.

4.2.17. (+)-Methyl [(2S,3R,S_s)-2-(3,5-dichloro-2-hydroxyphenylsulfonylamino)-4-methyl-3-(p-tolylsulfinylamino)]pentanoate, **7h**

From **5a** (40 mg, 0.13 mmol), Et_3N (0.037 mL, 0.27 mmol), and 3,5-Cl_2-2-(OH)$C_6H_2SO_2Cl$ (36 mg, 0.13 mmol), following the general procedure (26 h) and after chromatographic purification (5–30% EtOAc/CH_2Cl_2), **7h** was obtained as a colorless oil (68 mg, 97%). Data for **7h**: R_f 0.20 (80% EtOAc/hex). $[\alpha]_D^{20}$ +77.9 (*c* 0.57). ^{1}H NMR (300 MHz) δ 0.81 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.95 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.83 (m, 1H, CH ^{i}Pr), 2.38 (s, 3H, Me *p*-Tol), 3.36 (ap tdd, 1H, *J*=8.1, 3.9 Hz, H-3), 3.54 (s, 3H, OMe), 4.14 (m, 1H, H-2), 4.32 (d, 1H, *J*=8.3 Hz, NHSO), 6.86 (d, 1H, *J*=7.6 Hz, $NHSO_2$), 7.27 (d, 2H, *J*=8.1 Hz, Ar–H), 7.49 (d, 2H, *J*=8.1 Hz, Ar–H), 7.52 (d, 1H, *J*=2.4 Hz, Ar–H), 7.60 (d, 1H, *J*=2.4 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 18.4 (Me ^{i}Pr), 19.7 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 29.6 (CH ^{i}Pr), 52.8 (OMe), 57.4 (C–N), 60.8 (C–N), 124.0, 124.6, 125.8 (2C), 126.8, 126.9, 129.5 (2C), 134.2, 139.5, 141.9, 149.5, 170.4 (C=O). IR (film): 3304, 3079, 2964, 1748, 1468, 1436, 1338, 1212, 1164, 1085, 811, 755 cm^{-1}. HRMS (ESI) *m/z* for $C_{20}H_{25}Cl_2N_2O_6S_2$ $[M+H]^+$ calcd: 523.0531, found: 523.0518.

4.2.18. (+)-Methyl [(2S,3R,S_s)-4-methyl-2-(1-naphthylsulfonylamino)-3-(p-tolylsulfinylamino)]pentanoate, **7i**

From **5a** (34 mg, 0.11 mmol), Et_3N (0.032 mL, 0.23 mmol), and 1-naphthalene sulfonyl chloride (27 mg, 0.11 mmol), following the general procedure (7.5 h) and after chromatographic purification (20–30% EtOAc/hex), **7i** was obtained as a white solid (48 mg, 86%). Data for **7i**: R_f 0.27 (50% EtOAc/hex). Mp: 67 °C. $[\alpha]_D^{20}$ +91.9 (*c* 0.48). ^{1}H NMR (300 MHz) δ 0.62 (d, 3H, *J*=6.9 Hz, Me ^{i}Pr), 0.82 (d, 3H, *J*=6.9 Hz, Me ^{i}Pr), 1.63 (m, 1H, CH ^{i}Pr), 2.36 (s, 3H, Me *p*-Tol), 3.15 (s, 3H, OMe), 3.27 (td, 1H, *J*=8.5, 4.1 Hz, H-3), 4.04 (dd, 1H, *J*=9.3, 4.0 Hz, H-2), 4.17 (d, 1H, *J*=8.4 Hz, NHSO), 6.51 (d, 1H, *J*=9.2 Hz, $NHSO_2$), 7.23 (d, 2H, *J*=7.3 Hz, Ar–H), 7.47 (d, 2H, *J*=8.1 Hz, Ar–H), 7.50–7.74 (m, 3H, Ar–H), 7.93 (d, 1H, *J*=8.1 Hz, Ar–H), 8.05 (d, 1H, *J*=8.3 Hz, Ar–H), 8.23 (d, 1H, *J*=7.5 Hz, Ar–H), 8.72 (d, 1H, *J*=8.7 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 18.3 (Me ^{i}Pr), 19.6 (Me ^{i}Pr), 21.3 (Me *p*-Tol), 29.6 (CH ^{i}Pr), 52.2 (OMe), 57.3 (C–N), 60.9 (C–N), 124.0, 124.8, 125.7 (2C), 126.9, 128.4, 128.9, 129.5 (2C), 129.6, 134.1, 134.4 (2C), 134.8, 140.4, 141.8, 170.6 (C=O). IR (KBr): 3282, 2956, 2920, 2869, 1744, 1432, 1331, 1262, 1201, 1134, 1085, 1046, 767, 755 cm^{-1}. HRMS (ESI) *m/z* for $C_{24}H_{29}N_2O_5S_2$ $[M+H]^+$ calcd: 489.1518, found: 489.1532.

4.2.19. (+)-Methyl {[(2S,3R,S_s)-2-[(1S,4R)-7,7-dimethyl-2-oxabicyclo[2.2.1]heptan-1-yl-methylsulfonylamino]-4-methyl-3-(p-tolylsulfinylamino)}pentanoate, **7j**

From **5a** (28 mg, 0.09 mmol), Et_3N (0.026 mL, 0.19 mmol), and (1*S*)-(+)-camphor-10-sulfonyl chloride (29 mg, 0.11 mmol), following the general procedure (4 d) and after chromatographic purification (CH_2Cl_2 to 40% EtOAc/CH_2Cl_2), **7j** was obtained as a yellow oil (27 mg, 62%). Data for **7j**: R_f 0.14 (40% EtOAc/hex). $[\alpha]_D^{20}$ +24.4 (*c* 0.81). ^{1}H NMR (400 MHz) δ 0.99 (s, 3H, Me camphor), 1.00 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 1.01 (s, 3H, Me camphor), 1.03 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 1.44 (m, 1H, camphor) 1.84 (m, 1H, CH ^{i}Pr), 1.95 (d, 1H, *J*=18.4 Hz, H-3′ camphor), 2.05 (m, 3H, camphor), 2.14 (t, 1H, *J*=4.3 Hz, H-4′ camphor), 2.39 (s, 3H, Me *p*-Tol), 2.47 (ddd, 1H, *J*=18.7, 4.7, 2.5 Hz, H-3′ camphor), 3.00 (d, 1H, *J*=15.2 Hz, CH_2S), 3.59 (ddd, 1H, *J*=8.9, 7.4, 2.3 Hz, H-3), 3.70 (d, 1H, *J*=14.8 Hz, CH_2S), 3.75 (s, 3H, CO_2Me), 4.06 (d, 1H, *J*=7.4 Hz, NHSO), 4.45 (dd, 1H, *J*=9.8, 2.3 Hz, H-2), 6.99 (d, 1H, *J*=10.1 Hz, $NHSO_2$), 7.25 (d, 2H, *J*=7.8 Hz, Ar–H), 7.60 (d, 2H, *J*=8.6 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 19.4, 19.5, 19.6, 20.1, 21.4, 27.1, 27.8, 30.1, 42.9, 43.1, 48.9, 52.6, 52.8, 58.9, 59.7, 62.5, 126.0 (2C), 129.4 (2C), 141.5 (2C), 172.0 (C=O), 184.0 (C=O). IR (film): 3279, 2961, 1742, 1452, 1435, 1393, 1373, 1334, 1257, 1216, 1141, 1090, 1055, 935, 812, 755, 663 cm^{-1}. HRMS (ESI) *m/z* for $C_{24}H_{37}N_2O_6S_2$ $[M+H]^+$ calcd: 513.2093, found: 513.2108.

4.2.20. (+)-Methyl {[(2S,3R,S_s)-2-[(1R,4S)-7,7-dimethyl-2-oxabicyclo[2.2.1]heptan-1-yl-methylsulfonylamino]-4-methyl-3-(p-tolylsulfinylamino)}pentanoate, **7j′**

From **5a** (18 mg, 0.06 mmol), Et_3N (0.02 mL, 0.14 mmol), and (1*R*)-(+)-camphor-10-sulfonyl chloride (18 mg, 0.07 mmol), following the general procedure (2 h) and after chromatographic purification (20–40% EtOAc/hex), **7j′** was obtained as a colorless oil (30 mg, 97%). Data for **7j′**: R_f 0.27 (50% EtOAc/hex). $[\alpha]_D^{20}$ +36.3 (*c* 1.45). ^{1}H NMR ($CDCl_3$, 500 MHz)-COSY δ 0.74 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.85 (s, 3H, Me camphor), 0.98 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.05 (s, 3H, Me camphor), 1.44 (ddd, 1H, *J*=12.9, 9.3, 3.7 Hz, camphor) 1.74 (m, 1H, CH ^{i}Pr), 1.88 (ddd, 1H, *J*=14.1, 9.3, 4.9 Hz, camphor), 1.93 (d, 1H, *J*=18.6 Hz, H-3′ camphor), 2.03 (m, 1H, camphor), 2.10 (t, 1H, *J*=4.4 Hz, camphor), 2.34 (dd, 1H, *J*=4.4, 3.4 Hz, H-4′ camphor), 2.39 (s, 3H, Me *p*-Tol), 2.44 (ddd, 1H, *J*=14.7, 11.7, 3.9 Hz, camphor), 2.96 (d, 1H, *J*=14.9 Hz, CH_2S), 3.38 (ddd, 1H, *J*=8.8, 6.8, 4.6 Hz, H-3), 3.50 (d, 1H, *J*=14.9 Hz, CH_2S), 3.77 (s, 3H, OMe), 4.34 (dd, 1H, *J*=8.1, 4.6 Hz, H-2), 4.50 (d, 1H, *J*=8.6 Hz, NHSO), 6.40 (d, 1H, *J*=8.3 Hz, $NHSO_2$), 7.28 (d, 2H, *J*=8.1 Hz, Ar–H), 7.53 (d, 2H, *J*=8.1 Hz, Ar–H). ^{13}C NMR ($CDCl_3$, 100 MHz)-HSQC δ 18.0, 19.7, 19.8, 19.9, 21.4 (*p*-Tol), 24.9 (camphor), 27.0 (camphor), 29.8 (CH ^{i}Pr), 42.6 (camphor), 42.8 (camphor), 48.5 (camphor), 50.3 (CH_2S), 52.8 (OMe), 57.6 (C-2), 58.6 (camphor), 60.6 (C-3), 125.9 (2C), 129.5 (2C), 140.2, 141.8, 171.9 (C=O), 216.3 (C=O). IR (film): 3291, 2959, 1744, 1451, 1436, 1334, 1141, 1052, 813 cm^{-1}. HRMS (ESI) *m/z* for $C_{24}H_{37}N_2O_6S_2$ $[M+H]^+$ calcd: 513.2093, found: 513.2113.

4.2.21. (+)-Methyl [(2S,3R,S_s)-3-naphthyl-2-(1-naphthylsulfonylamino)-3-(p-tolylsulfinylamino)]propanoate, **7k**

From **5b** (64 mg, 0.17 mmol), Et_3N (0.063 mL, 0.45 mmol), and 1-naphthalene sulfonyl chloride (57 mg, 0.25 mmol), following the general procedure (24 h) and after chromatographic purification (5–20% EtOAc/CH_2Cl_2), **7k** was obtained as a white solid (65 mg, 68%). Data for **7k**: R_f 0.28 (20% EtOAc/CH_2Cl_2). Mp: 98–100 °C. $[\alpha]_D^{20}$ +123.4 (*c* 0.73). ^{1}H NMR (500 MHz) δ 2.17 (s, 3H, Me *p*-Tol), 3.14 (s, 3H, OMe), 4.36 (t, 1H, *J*=6.6 Hz), 5.37 (t, 1H, *J*=6.6 Hz), 5.47 (d, 1H, *J*=7.6 Hz, NHSO), 6.88 (d, 1H, *J*=7.6 Hz, $NHSO_2$), 6.91 (d, 3H, *J*=8.3 Hz, Ar–H), 7.06 (d, 1H, *J*=6.4 Hz, Ar–H), 7.24 (m, 2H, Ar–H), 7.29 (d, 2H, *J*=8.3 Hz, Ar–H), 7.33 (t, 1H, *J*=7.0 Hz, Ar–H), 7.41 (d, 1H, *J*=8.1 Hz, Ar–H), 7.45 (d, 1H, *J*=8.6 Hz, Ar–H), 7.56 (td, 1H, *J*=6.9, 1.0 Hz, Ar–H), 7.64 (m, 2H, Ar–H), 7.86 (d, 1H, *J*=8.1 Hz, Ar–H), 7.91 (m, 2H, Ar–H), 8.66 (d, 1H, *J*=8.6 Hz, Ar–H). ^{13}C NMR (75 MHz)

δ 21.1, 52.4, 60.4, 60.8, 122.1, 123.8, 124.6, 124.9, 125.2, 125.6, 125.8 (2C), 126.1, 126.7, 127.9, 128.2, 128.3, 128.7, 128.7, 129.1 (2C), 129.4, 129.5, 133.1, 133.2, 133.9, 134.0, 134.3, 139.3, 141.2, 169.5 (C=O). IR (KBr): 3435, 3059, 2947, 2355, 1749, 1624, 1506, 1434, 1335, 1162, 1086, 771 cm^{-1}. HRMS (ESI) *m/z* for $C_{31}H_{29}N_2O_5S_2$ $[M+H]^+$ calcd: 573.1518, found: 573.1531. Anal. Calcd for $C_{31}H_{28}N_2O_5S_2$: C, 65.01; H, 4.93; N, 4.89; S, 11.20. Found: C, 65.30; H, 5.20; N, 5.18; S, 10.97.

4.2.22. (+)-Methyl [(2S,3R,S_s)-3-(mesitylsulfinylamino)-4-methyl-2-(1-naphthylsulfonylamino)]pentanoate, **7l**

From **5c** (107 mg, 0.33 mmol), Et_3N (0.11 mL, 0.82 mmol), and 1-naphthalene sulfonyl chloride (112 mg, 0.49 mmol), following the standard procedure (20 h) and after chromatographic purification (10–40% EtOAc/hex), **7l** was obtained as a white solid (147 mg, 87%). Data for **7l**: R_f 0.14 (30% EtOAc/hex). Mp: 95 °C. $[\alpha]_D^{20}$ +115.9 (*c* 0.66). ^1H NMR (300 MHz) δ 0.76 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 0.96 (d, 3H, *J*=6.6 Hz, Me ^{i}Pr), 1.88 (m, 1H, CH ^{i}Pr), 2.25 (s, 3H, Me Ar), 2.46 (s, 6H, Me Ar), 3.09 (s, 3H, OMe), 3.37 (ddd, 1H, *J*=8.1, 6.3, 3.7 Hz, H-3), 4.12 (dd, 1H, *J*=9.3, 3.7 Hz, H-2), 4.36 (d, 1H, *J*=6.3 Hz, NHSO), 6.82 (m, 3H, $NHSO_2$+2Ar–H), 7.49 (m, 1H, Ar–H), 7.59 (m, 1H, Ar–H), 7.67 (m, 1H, Ar–H), 7.92 (d, 1H, *J*=8.1 Hz, Ar–H), 8.03 (d, 1H, *J*=8.3 Hz, Ar–H), 8.21 (dd, 1H, *J*=7.3, 1.2 Hz, Ar–H), 8.68 (d, 1H, *J*=7.8 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 19.0, 19.4 (2C), 20.8, 28.7 (2C), 51.9, 57.0, 63.2, 123.9, 124.7, 126.7, 128.1, 128.2, 128.7, 129.1, 130.8 (2C), 133.9, 134.1, 135.0, 136.5 (2C), 136.8, 140.8, 170.6 (C=O). IR (KBr): 3449, 2955, 2926, 1742, 1600, 1436, 1335, 1200, 1164, 1134, 1065, 1044, 982, 804, 772, 593 cm^{-1}. MS (ES): 1055 $[2M+Na]^+$, 539 $[M+Na]^+$ (100%), 517 $[M+1]^+$. Anal. Calcd for $C_{26}H_{32}N_2O_5S_2$: C, 60.44; H, 6.24; N, 5.42; S, 12.41. Found: C, 60.33; H, 6.18; N, 5.31; S, 12.24.

4.2.23. (+)-Methyl [(2S,3R,S_s)-4-methyl-3-(2-methoxynaphthylsulfinylamino)-2-(1-naphthylsulfonylamino)]pentanoate, **7m** and (−)-methyl [(2R,3S,S_s)-4-methyl-3-(2-methoxynaphthylsulfinylamino)-2-(1-naphthylsulfonylamino)]pentanoate, **7m′**

From a 78:28 mixture of **5d**:**5d′** (67 mg, 0.18 mmol), Et_3N (0.051 mL, 0.37 mmol), and 1-naphthalene sulfonyl chloride (46 mg, 0.20 mmol), following the general procedure (24 h) and after chromatographic purification (CH_2Cl_2 to 20% EtOAc/CH_2Cl_2), **7m** (75 mg, 73%) and **7m′** (23 mg, 22%) were obtained as yellow oils. Data for **7m**: R_f 0.11 (10% EtOAc/CH_2Cl_2). $[\alpha]_D^{20}$ +112.0 (*c* 1.29). ^1H NMR (300 MHz)-COSY δ 0.90 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 1.05 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 1.98 (m, 1H, CH ^{i}Pr), 3.04 (s, 3H, OMe), 3.45 (ddd, 1H, *J*=8.7, 5.6, 2.7 Hz, H-3), 4.00 (s, 3H, OMe), 4.20 (dd, 1H, *J*=10.0, 2.8 Hz, H-2), 5.65 (d, 1H, *J*=5.6 Hz, NHSO), 6.38 (d, 1H, *J*=10.0 Hz, $NHSO_2$), 7.27 (d, 1H, *J*=9.3 Hz, Ar–H), 7.33–7.48 (m, 3H, Ar–H), 7.51–7.60 (m, 2H, Ar–H), 7.77 (d, 1H, *J*=7.6 Hz, Ar–H), 7.85–7.92 (m, 2H, Ar–H), 8.01 (d, 1H, *J*=8.3 Hz, Ar–H), 8.18 (d, 1H, *J*=7.3, 1.2 Hz, Ar–H), 8.42 (d, 1H, *J*=8.5 Hz, Ar–H), 8.60–8.63 (m, 1H, Ar–H). ^{13}C NMR (75 MHz)-HSQC δ 19.5 (2C), 28.6, 51.9, 57.0, 57.5, 64.5, 113.6, 122.0, 124.0, 124.4, 124.6 (2C), 126.7, 127.9, 128.2, 128.3, 128.6, 128.7, 129.0, 129.2, 130.2, 133.5, 133.9, 134.2, 135.0, 155.1, 170.5 (C=O). IR (film): 3326, 2950, 1741, 1622, 1594, 1508, 1433, 1335, 1273, 1252, 1202, 1164, 1135, 1062, 806, 754 cm^{-1}. HRMS (ESI) *m/z* for $C_{28}H_{31}N_2O_6S_2$ $[M+H]^+$ calcd: 555.1624, found: 555.1656. Data for **7m′**: R_f 0.28 (70% EtOAc/hex). $[\alpha]_D^{20}$ −12.9 (*c* 0.82). ^1H NMR (300 MHz) δ 0.82 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 0.95 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 1.79 (m, 1H, CH ^{i}Pr), 2.84 (s, 3H, OMe), 3.59 (ddd, 1H, *J*=10.2, 6.0, 4.8 Hz, H-3), 4.15 (dd, 1H, *J*=8.6, 4.8 Hz, H-2), 4.25 (s, 3H, OMe), 6.13 (d, 1H, *J*=10.2 Hz, NHSO), 6.67 (d, 1H, *J*=8.6 Hz, $NHSO_2$), 7.37–7.42 (m, 2H, Ar–H), 7.50–7.60 (m, 3H, Ar–H), 7.69 (m, 1H, Ar–H), 7.81 (d, 1H, *J*=8.1 Hz, Ar–H), 7.92 (d, 1H, *J*=8.1 Hz, Ar–H), 7.97 (d, 1H, *J*=9.0 Hz, Ar–H), 8.05 (d, 1H, *J*=8.2 Hz, Ar–H), 8.25 (dd, 1H, *J*=7.3, 1.1 Hz, Ar–H), 8.46 (d, 1H, *J*=8.4 Hz, Ar–H), 8.70 (d, 1H, *J*=8.8 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 17.4, 19.9, 30.9, 51.8, 57.1, 57.6, 63.9, 113.7, 122.1, 124.0, 124.6, 124.8, 125.3, 126.8, 128.2, 128.4, 128.5, 128.5, 128.7, 128.8, 129.5, 130.6, 133.7, 134.0, 134.3, 135.0, 155.7, 170.4 (C=O). IR (film): 3435, 2955, 2925, 1745, 1621, 1506, 1464, 1331, 1198, 1165, 1038, 772, 589 cm^{-1}. HRMS (ESI) *m/z* for $C_{28}H_{31}N_2O_6S_2$ $[M+H]^+$ calcd: 555.1624, found: 555.1641.

4.2.24. General procedure for oxidation of sulfinamides to sulfonamides with m-CPBA

m-CPBA (1.3 equiv, 70%) was added at 0 °C to a solution of the sulfinamide in CH_2Cl_2 (15 mL/mmol). The reaction mixture was allowed to warm up slowly to room temperature and was monitored by TLC. Then, it was quenched with 1 M aqueous solution of $Na_2S_2O_4$ (3 mL/mmol), a saturated solution of $NaHCO_3$ (3 mL/mmol), and H_2O (3 mL/mmol), and was diluted with CH_2Cl_2 (8 mL/mmol). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL/mmol). The organic layer was washed with a saturated solution of NaCl (10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography.

4.2.25. (+)-Methyl [(2S,3R)-4-methyl-2,3-bis(p-tolylsulfonylamino)]pentanoate, **8a**

From **7a** (10 mg, 0.022 mmol) and *m*-CPBA (6.5 mg, 0.026 mmol), following the general procedure (1.5 h) and after chromatographic purification (10–20% EtOAc/hex), **8a** was obtained as a white solid (10 mg, 99%). Data for **8a**: R_f 0.15 (30% EtOAc/hex). Mp: 152 °C. $[\alpha]_D^{20}$ +54.8 (*c* 0.73). ^1H NMR (300 MHz) δ 0.57 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 0.88 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.83 (m, 1H, CH ^{i}Pr), 2.38 (s, 3H, Me *p*-Tol), 2.39 (s, 3H, Me *p*-Tol), 3.36 (td, 1H, *J*=9.0, 2.3 Hz, H-3), 3.44 (s, 3H, OMe), 4.02 (dd, 1H, *J*=9.3, 2.4 Hz, H-2), 4.66 (d, 1H, *J*=9.5 Hz, $NHSO_2$), 5.50 (d, 1H, *J*=8.8 Hz, $NHSO_2$), 7.24 (d, 2H, *J*=8.3 Hz, Ar–H), 7.26 (d, 2H, *J*=8.5 Hz, Ar–H), 7.66 (d, 2H, *J*=8.3 Hz, Ar–H), 7.67 (d, 2H, *J*=8.0 Hz, Ar–H). ^{13}C NMR (75 MHz) δ 18.6 (Me ^{i}Pr), 19.9 (Me ^{i}Pr), 21.5 (Me *p*-Tol), 29.7 (CH ^{i}Pr), 29.8 (Me *p*-Tol), 52.8 (OMe), 56.9 (C–N), 61.7 (C–N), 127.2 (2C), 127.3 (2C), 129.6 (2C), 129.7 (2C), 136.2, 137.6, 143.5, 143.8, 170.0 (C=O). IR (KBr): 3436, 2956, 2920, 1739, 1628, 1436, 1335, 1262, 1163, 1093, 1017, 802, 667, 551 cm^{-1}. HRMS (ESI) *m/z* for $C_{42}H_{56}N_4NaO_{12}S_4$ [2M+Na] calcd: 959.2675, found: 959.2665.

4.2.26. (+)-Methyl [(2S,3R)-4-methyl-2-(1-naphthylsulfonylamino)-3-(p-tolylsulfonylamino)]pentanoate, **8b**

From **7i** (27 mg, 0.055 mmol) and *m*-CPBA (16 mg, 0.066 mmol), following the general procedure (45 min) and after chromatographic purification (CH_2Cl_2 to 10% EtOAc/CH_2Cl_2), **8b** was obtained as a white solid (22 mg, 79%). Data for **8b**: R_f 0.27 (10% EtOAc/CH_2Cl_2). Mp: 198 °C. $[\alpha]_D^{20}$ +149.1 (*c* 0.44). ^1H NMR (500 MHz) δ 0.45 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 0.72 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 1.67 (m, 1H, CH ^{i}Pr), 2.37 (s, 3H, Me *p*-Tol), 3.13 (s, 3H, OMe), 3.28 (td, 1H, *J*=8.8, 2.4 Hz, H-3), 4.04 (br s, 1H, H-2), 4.92 (d, 1H, *J*=9.3 Hz, $NHSO_2$), 5.96 (br s, 1H, $NHSO_2$), 7.22 (d, 2H, *J*=8.3 Hz, Ar–H), 7.50 (t, 1H, *J*=7.8 Hz, Ar–H), 7.58 (t, 1H, *J*=7.3 Hz, Ar–H), 7.67 (m, 3H, Ar–H), 7.91 (d, 1H, *J*=7.8 Hz, Ar–H), 8.04 (d, 1H, *J*=8.3 Hz, Ar–H), 8.21 (d, 1H, *J*=7.3 Hz, Ar–H), 8.68 (d, 1H, *J*=8.8 Hz, Ar–H). ^{13}C NMR (125 MHz)-HSQC δ 18.4 (Me ^{i}Pr), 19.8 (Me ^{i}Pr), 21.5 (Me *p*-Tol), 29.6 (CH ^{i}Pr), 52.4 (OMe), 57.3, 61.5, 124.1, 124.6, 127.0, 127.2 (2C), 128.3, 128.6, 128.9, 129.6 (2C), 129.7, 134.1, 134.2, 134.6, 137.4, 143.5, 169.8 (C=O). IR (KBr): 3432, 3266, 2955, 2925, 1719, 1622, 1595, 1506, 1439, 1337, 1321, 1301, 1160, 1067, 952, 806, 773, 665, 591, 574, 545 cm^{-1}. HRMS (ESI) *m/z* for $C_{48}H_{56}N_4NaO_{12}S_4$ [2M+Na] calcd: 1031.2675, found: 1031.2657. Anal. Calcd for $C_{24}H_{28}N_2O_6S_2$: C, 57.12; H, 5.59; N, 5.55; S, 12.71. Found: C, 57.31; H, 5.71; N, 5.35; S, 12.48.

4.2.27. (+)-N-[(1S,2R,S_s)-1-(Hydroxymethyl)-3-methyl-2-(p-tolylsulfinylamino)butyl]-1-naphthylsulfonamide, **9**

A round-bottomed flask was charged with anhydrous THF (2 mL/mmol), LiI (29 mg, 0.215 mmol, 3.0 equiv), and $NaBH_4$ (8 mg, 0.215 mmol, 3.0 equiv). The resulting suspension was cooled to 0 °C and a solution of **7i** (35 mg, 0.072 mmol, 1.0 equiv) in anhydrous

THF (6 mL/mmol) was added dropwise and the reaction mixture was stirred at 0 °C (30 min) and then at room temperature monitored by TLC. When the reaction reached completion (2 d) the mixture was quenched with a 5% $NaHCO_3$ solution (2 mL/mmol) and diluted with CH_2Cl_2 (5 mL/mmol). The crude was filtered through Celite and the residue was washed with CH_2Cl_2 (3×8 mL/mmol). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×8 mL/mmol). The combined organic extracts were washed with a saturated NaCl solution (4 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was purified by column chromatography on silica gel (10–40% EtOAc/hex). Compound **9** was obtained as a white solid (26 mg, 70%). Data for **9**: R_f 0.22 (50% EtOAc/hex). Mp: 59 °C. $[\alpha]_D^{20}$ +99.3 (*c* 0.74). ^{1}H NMR (500 MHz) δ 0.27 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 0.40 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 1.43 (m, 1H, H-3), 2.35 (s, 3H, Me *p*-Tol), 2.67 (t, 1H, *J*=6.4 Hz, OH), 2.79 (ddd, 1H, *J*=9.9, 5.1 Hz, H-2), 3.13 (ddd, 1H, *J*=8.6, 5.1 Hz, H-1), 3.31 (m, 2H, CH_2), 4.27 (d, 1H, *J*=9.9 Hz, NHSO), 7.16 (d, 1H, *J*=8.6 Hz, $NHSO_2$), 7.23 (d, 2H, *J*=8.0 Hz, Ar–H), 7.45 (d, 2H, *J*=8.3 Hz, Ar–H), 7.52 (t, 1H, *J*=7.9 Hz, Ar–H), 7.62 (td, 1H, *J*=7.0, 1.0 Hz, Ar–H), 7.74 (ddd, 1H, *J*=8.5, 7.0, 1.3 Hz, Ar–H), 7.94 (d, 1H, *J*=8.0 Hz, Ar–H), 8.06 (d, 1H, *J*=8.3 Hz, Ar–H), 8.29 (dd, 1H, *J*=7.4, 1.0 Hz, Ar–H), 8.83 (d, 1H, *J*=8.6 Hz, Ar–H). ^{13}C NMR (125 MHz)-HSQC δ 16.6 (Me ^{i}Pr), 19.9 (Me ^{i}Pr), 21.4 (Me *p*-Tol), 29.7 (CH ^{i}Pr), 55.6 (C-1), 56.6 (C-2), 63.9 (CH_2), 124.2, 124.6, 126.1 (2C), 127.1, 127.9, 128.7, 129.2, 129.4 (2C), 130.0, 134.2, 134.5, 134.8, 138.8, 142.0. IR (KBr): 3435, 2925, 2852, 1740, 1628, 1594, 1508, 1461, 1330, 1200, 1162, 1134, 1085, 1040, 985, 806, 772, 677, 592 cm^{-1}. HRMS (ESI) *m/z* for $C_{23}H_{29}N_2O_4S_2$ $[M+H]^+$ calcd: 461.1569, found: 461.1568. Anal. Calcd for $C_{23}H_{28}N_2O_4S_2$: C, 59.97; H, 6.13; N, 6.08; S, 13.92. Found: C, 60.10; H, 5.96; N, 6.31; S, 13.81.

4.2.28. (+)-N-{(1S,2R,S$_s$)-1-[(tert-Butyldimethylsilyloxymethyl)-3-methyl-2-(p-tolylsulfinylamino)butyl]}-1-naphthylsulfonamide, ***10***

To a solution of **9** (8 mg, 0.016 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL/mmol), TBSCl (6 mg, 0.032 mmol, 2.0 equiv), imidazole (3 mg, 0.032 mmol, 2.0 equiv), and 0.05 equiv of DMAP were added. The reaction was stirred at room temperature until the disappearance of **9** by TLC. It was quenched with H_2O (10 mL/mmol) and the layers were separated. It was extracted with CH_2Cl_2 (2×10 mL) and the combined organic phases were washed with saturated solution of NaCl, dried over anhydrous Na_2SO_4, and the solvent was evaporated. Purification by column chromatography (10–30% EtOAc/hex) yielded **10** as a colorless oil (8 mg, 87%). Data for **10**: R_f 0.29 (30% EtOAc/hex). $[\alpha]_D^{20}$ +61.5 (*c* 0.39). ^{1}H NMR (300 MHz) δ −0.24 (s, 3H, Me TBS), −0.22 (s, 3H, Me TBS), 0.30 (d, 3H, *J*=6.8 Hz, Me ^{i}Pr), 0.57 (d, 3H, *J*=6.7 Hz, Me ^{i}Pr), 0.67 (s, 9H, ^{t}Bu TBS), 1.57 (m, 1H, H-3), 2.36 (s, 3H, Me *p*-Tol), 3.04 (dt, 1H, *J*=8.5, 5.4 Hz, H-2), 3.21 (m, 1H, H-1), 3.34 (m, 2H, CH_2), 4.08 (d, 1H, *J*=8.8 Hz, NHSO), 6.95 (d, 1H, *J*=9.0 Hz, $NHSO_2$), 7.23 (d, 2H, *J*=7.8 Hz, Ar–H), 7.49 (m, 3H, Ar–H), 7.60 (ddd, 1H, *J*=8.0, 6.8, 1.1 Hz, Ar–H), 7.73 (ddd, 1H, *J*=8.5, 6.8, 1.4 Hz, Ar–H), 7.93 (d, 1H, *J*=8.0 Hz, Ar–H), 8.05 (d, 1H, *J*=8.3 Hz, Ar–H), 8.29 (dd, 1H, *J*=7.3, 1.2 Hz, Ar–H), 8.81 (dd, 1H, *J*=8.8, 0.7 Hz, Ar–H). ^{13}C NMR (75 MHz) δ −5.8, 1.0, 16.6, 17.9, 20.0, 21.4, 25.6 (3C), 29.0, 54.5, 58.3, 63.9, 124.1, 125.1, 126.1 (2C), 127.0, 128.0, 128.5, 128.9, 129.3 (3C), 134.1, 134.2, 135.9, 139.9, 141.6. IR (film): 3287, 3056, 2955, 2927, 2854, 1506, 1463, 1387, 1328, 1258, 1213, 1162, 1106, 1044, 1015, 935, 837, 805, 771, 675 cm^{-1}. MS (ES): 1171 $[2M+Na]^+$ (100%), 597 $[M+Na]^+$, 575 $[M+1]^+$.

4.3. General procedure for the addition of diethylzinc to aldehydes

To a solution of 0.05 equiv of chiral ligand in CH_2Cl_2 (50 mL/mmol ligand) was added 1.5 equiv of Et_2Zn 1.0 M in hexane and the mixture was stirred at room temperature for 10 min. Then, 1.2 equiv of Ti(O^iPr)$_4$ were added and, after 30 min, 1.0 equiv of aldehyde. After 24 h, the reaction was quenched at 0 °C with 1 M aqueous solution of HCl (10 mL/mmol). The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL/mmol); the combined organic phase was washed with saturated solution of NaCl (10 mL/mmol) and was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude mixture was purified by chromatography on silica gel using CH_2Cl_2 as eluent. Enantiomeric ratios were determined by chiral HPLC. Conditions: Daicel Chiralcel OD, 95:5 hex/^{i}PrOH, 0.5 mL/min flow rate, λ=254 nm. For 1-phenyl-1-propanol: t_R (*R*): 7.61 min; t_R (*S*): 8.32 min. For 1-(1-naphthyl)-1-propanol: t_R (major): 13.22 min; t_R (minor): 21.87 min.

4.4. General procedure for the synthesis of methoxyphenylacetic esters

To a cold solution (0 °C) of 1.0 equiv of alcohol in CH_2Cl_2 (10 mL/mmol) were added 1.05 equiv of (+)-MPA, 1.0 equiv of DCC, and 0.05 equiv of DMAP. The mixture was allowed to reach room temperature and stirred until completion, monitored by TLC. The solvent was evaporated and the crude was filtered through a plug of silica gel.

4.4.1. (S)-[1-(RS)-(4-Chlorophenyl)propyl]methoxy(phenyl)acetate (Table 2, entry 1)

^{1}H NMR (300 MHz) δ 0.62 (t, 3H, *J*=7.3 Hz, Me), 0.82 (t, 3H, *J*=7.3 Hz, Me′), 1.68–1.86 (m, 4H, CH_2/CH_2′), 3.36 (s, 3H, OMe), 3.38 (s, 3H, OMe′), 4.75 (s, 1H, CHOMe), 4.78 (s, 1H, CHOMe′), 5.63 (t, 2H, *J*=6.8 Hz, CH–OCO/CH′–OCO), 6.89–7.44 (m, 18H, Ar–H/Ar–H′).

4.4.2. (S)-[1-(RS)-(3,4-Dimethoxyphenyl)propyl]methoxy(phenyl)-acetate (Table 2, entry 2)

^{1}H NMR (300 MHz) δ 0.64 (t, 3H, *J*=7.3 Hz, Me), 0.84 (t, 3H, *J*=7.5 Hz, Me′), 1.04–1.36 (m, 2H, CH_2), 1.63–1.93 (m, 2H, CH_2′), 3.36 (s, 6H, OMe/OMe′), 3.80 (s, 6H, OMe/OMe′), 3.84 (s, 6H, OMe/OMe′), 4.76 (d, 2H, *J*=6.8 Hz, CHOMe/CHOMe′), 5.62 (t, 2H, *J*=6.0 Hz, CH–OCO/CH′–OCO), 6.74–6.86 (m, 6H, Ar–H/Ar–H′), 7.26–7.43 (m, 10H, Ar–H/Ar–H′).

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