DOI: 10.1002/ejoc.200800622

Diastereoselective Synthesis of Heteroaromatic Glycine Derivatives

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Keywords: Aromatic heterocycles / Electrophilic substitution / Sulfinimine / Diastereoselectivity / Glycine derivatives

A TMSOTf promoted addition of an *N*-*tert*-butanesulfinyl α-imino ester to five-membered aromatic heterocycles furnishes optically active heteroaromatic glycine derivatives with moderate-to-good yield in diastereomeric ratios up to 99 %. The absolute configuration of two of the addition products were solved by X-ray analysis.

Introduction

Chiral nonracemic *N*-sulfinyl imines (sulfinimines) have proven to be an extremely versatile class of imines for asymmetric synthesis, especially through nucleophilic addition reactions in the asymmetric synthesis of amines, α-amino acids, β-amino carbonyl compounds (aldehydes, ketones, acids), and aziridines.[1] The chiral and electron-withdrawing sulfinyl group activates the C=N bond for nucleophilic addition with high and predictable asymmetric induction and is easily removed in the product.

N-Sulfinylimino esters **1** (see Figure 1) have been described in the literature as a chiral glycine cation equivalent for the asymmetric synthesis of α-amino acids.[2] Excellent diastereoselective results have been reported by using Grignard and dialkylzinc reagents,[2,3] or by the addition of ketene acetals in combination with Lewis acids[4] to **1**. Recent results involving transition-metal catalysts expand the utility of **1** as a chiral glycine cation equivalent. Addition of arylboronic acids, either catalyzed by cationic Pd^{II}[5] or Rh^{I},[6] demonstrates efficient and highly diastereoselective synthesis of arylglycines. The rhodium-catalyzed C–C bond-forming hydrogenation coupling of conjugated alkynes and **1** to β,γ-unsaturated α-amino acid esters,[7] and the diastereoselective Pd/In-mediated catalytic allylation of **1** to 2-arylallyl-α-amino acids[8] are both impressive examples of utilizing **1** as a chiral glycine cation equivalent.

We have previously shown that optically active **1a** reacts as a dienophile in the aza-Diels–Alder reaction with both activated and nonactivated dienes in the presence of Lewis acids.[9] The heterocyclic adducts were obtained in modest

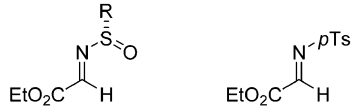

Figure 1. Glycine reagents.

yields and in diastereoselectivities ranging from poor for the activated Danishefsky-type dienes to excellent for unactivated acyclic dienes (up to 99 %*de*).

In this communication, we report our results for the reactions of **1a** with aromatic heterocycles bearing one heteroatom in the presence of a Lewis acid catalyst.

Results and Discussion

Initially, a mixture of furan (**3a**, 1 equiv.), **1a** (1 equiv.), and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1 equiv.) in dry dichloromethane was stirred overnight at –78 °C under an argon atmosphere. Instead of the expected aza-Diels–Alder reaction, nucleophilic addition of the furan α-carbon atom to the imine carbon atom took place as shown in Scheme 1. A similar result was previously reported by Jørgensen et al. for *N*-tosyl glyoxylate imine ethyl ester (**2**; see Figure 1) in the presence of an optically active BINAP–$CuClO_4$ catalyst.[10] In their case, the addition product was isolated in 25–30 % yield and up to 54 %*ee*. In our case, a 5:1 mixture of epimers **4a** and **5a**, partly separable by flash chromatography, was obtained in 56 % (total yield of isomers). The absolute configuration of the major diastereomer was determined by chemical correlation (cleavage of the sulfinyl group[6] and acetylation) to the known acetamido compound **6** (see Scheme 1).[11]

Encouraged by the result with **3a**, a series of aromatic heterocycles **3b**–**e** were tested in the presence of **1a** and a stoichiometric amount of TMSOTf. The results are presented in Table 1. Electron-rich pyrrole **3b** (Table 1, En-

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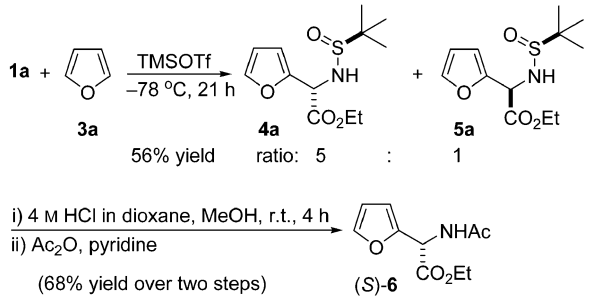


Scheme 1.

try 1), known to be more active than **3a** in aromatic electrophilic substitution,[12] afforded only one addition product (pure according to ^{1}H NMR spectroscopy) at –78 °C after 17.5 h, which was identified as **4b** and isolated in 92% yield. The absolute configuration of **4b** was assumed to be (S_S,2*S*) by comparison with results obtained by using two equivalents of **1a** (Table 1, Entry 7) discussed below. This result deviates from the result obtained by Johannsen where chiral copper(I)/Tol-BINAP-catalyzed addition of tosyl imine **2** to **3b** gave the pyrrole *N*-addition product as the main product.[13] Furthermore, Johannsen also reported the catalyzed addition of **2** to *N*-methylpyrrole to give approximately a 1:1 mixture of the 2- and 3-substituted products in 84 and 56%*ee*, respectively.

Thiophene (**3c**) is known to be somewhat less reactive than **3a** toward electrophiles, and much less reactive than **3b**.[12] This we indeed observed in the reaction between **1a** and **3c**, where no reaction took place at –78 °C (Table 1, Entry 2), but at –20 °C, a mixture of epimers **4c** was formed in a 1:1.5 ratio and isolated in 40% combined yield (Table 1, Entry 3). The configuration of the major compound of **4c** was not determined.

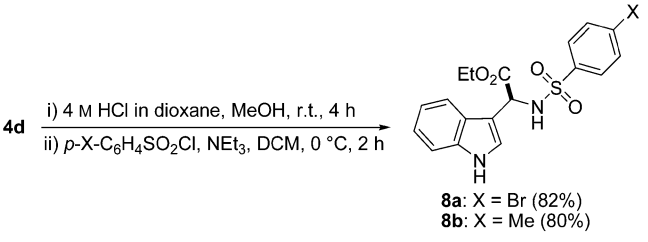
The preferred site for electrophilic substitution at indole (**3d**) is known to be C-3 rather than C-2, in contrast to **3b**.[12] The reaction between **1a** and **3d** at –78 °C for 17 h afforded a mixture of isomers, from which the major 3-substituted indole derived amino acid **4d** was isolated pure by flash chromatography in 82% yield as a solidified foam (Table 1, Entry 4). Comparable results are also reported for the chiral copper(I)–Tol-BINAP-catalyzed addition of **2** to a variety of 5-substituted indole derivatives.[13] There, the indoles reacted exclusively at the 3-position giving the *N*-tosyl addition products in high yields (61–89%) and enantioselectivities (78–97%*ee*). Enantiopure products were available after one recrystallization. In an attempt to determine the absolute configuration by X-ray analysis, **4d** was transformed into **8a** (see Scheme 2). Recrystallization of **8a** from a mixture of 1-chloropentane and *n*-hexane afforded crystals of sufficient quality for X-ray analysis. The absolute configuration of **8a** was determined to be (2*S*),[14] and thus, **4d** should have the (S_S,2*S*) configuration. Because the *N*-tosyl 3-substituted indole amino acid ethyl ester **8b** had previously been reported with high *ee* (96%) without assignment of the configuration,[13] **8b** was prepared from **4d** (see Scheme 2). Comparison of our data for the optical

Table 1. Addition of **1a** (1 equiv.) to aromatic compounds **3b**–**f** (1–2 equiv.) promoted by TMSOTf (1 equiv.) in dry CH_2Cl_2 under an argon atmosphere.

Entry	Substrate	Conditions	Addition product[a]	Yield [%][b]
1	**3b**	–78 °C, 17.5 h	**4b**	92
2	**3c**	–78 °C, 17.5 h	No reaction	–
3	**3c**	–20 °C, 20 h	**4c** ratio: 1 : 1.5[c]	40[d]
4	**3d**	–78 °C, 17 h	**4d**	82
5	**3e**	–78 °C, 20 h	No reaction	–
6	**3f**	–20 °C, 20 h	**4f** : **5f** ratio: 1 : 2.6	65[d]
7[e]	**3b**	–78 °C, 20 h	**7**	77

[a] The product ratio was determined by ^{1}H NMR (400 MHz) spectroscopic analysis of the crude product. [b] Isolated yield. [c] Relative configuration was not determined. [d] Total yield of isolated isomers. [e] Two equivalents of **1a** and TMSOTf were added to one equivalent **3b**.

rotation {$[\alpha]_D^{rt}$ = +105.6 (c = 1, $CHCl_3$)} with the literature data {$[\alpha]_D^{20}$ = +102 (c = 1, $CHCl_3$)}[13] verifies that the gentle acidic removal of the sulfinyl group[6] and the following tosylation proceeded without notable racemization.



Scheme 2.

In order to explore the feasibility of the reaction further, **1a** was treated with pyridine (**3e**) and anisole (**3f**) in the presence of TMSOTf. As expected, reactions with **3e** did not afford addition products at all at –78 °C (Table 1, Entry 5) or at room temperature (20 h reaction time). This result is consistent with the knowledge that the dominance of electrophilic substitution, which typifies benzene chemistry, is not apparent in the chemistry of pyridines.[12] For **3f**, no reaction was observed at –78 °C (17 h reaction time), but at –20 °C a mixture of epimers **4f** and **5f** was formed in a 1:2.6 ratio (65% combined yield; Table 1, Entry 6). The isomers were partly separable by flash chromatography. The ^{1}H NMR spectrum of minor isomer **4f** was in accordance with the data reported for the (R_S,2*R*) enantiomer obtained from cationic Pd^{II} catalyzed addition of *p*-methoxyphenylboronic acid to *ent*-**1a** (*ent* = enantiomer).[5] The major isomer should then have (S_S,2*R*) configuration.

The excellent result obtained for **3b** by addition of one equivalent of **1a** and TMSOTf (Table 1, Entry 1) prompted us to investigate if we were able to introduce two glycine units into the pyrrole ring. Indeed, we were pleased to observe that addition of two equivalents of **1a** and TMSOTf afforded only one addition product with two glycine groups (according to ^{1}H NMR spectroscopy) in 77% yield (Table 1, Entry 7) and a minor amount of **4b**. The NMR spectra of the former product indicated C_2 symmetry in the molecule. This was also confirmed by X-ray analysis (see Figure 2).[14] Here, the absolute configuration of product **7** was determined to be (S_S,2*S*) in both glycine parts of the molecule. From this result we also assume (S_S,2*S*) configuration in the mono glycine pyrrole product **4b** (Table 1, Entry 1).

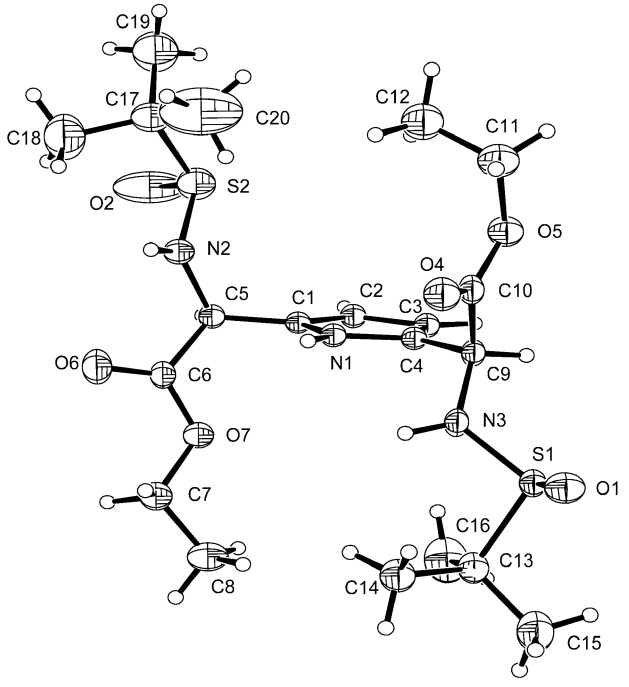
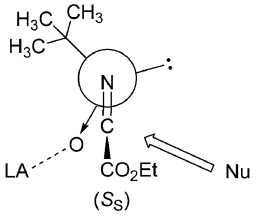


Figure 2. X-ray structure of **7**.[14]

The stereochemical outcome of the addition reactions of **1a** to **3a**, **3b**, and **3d** can be rationalized according to the open-transition-state model (see Scheme 3) proposed by others from calculations on related sulfinimines with and without a Lewis acid (LA) present.[15] This model also confirms the model proposed for the reaction of sulfinimines with Grignard reagents in the presence of BF_3·ether[2] and the stereochemical outcome observed for the Lewis acid promoted addition of silyl nucleophiles.[16]



Scheme 3. Stereochemical model.

Conclusions

In conclusion, a simple method for preparation of heteroaromatic glycine derivatives from TMSOTf-promoted addition of an *N*-*tert*-butanesulfinyl α-imino ester to aromatic heterocycles has been presented. The addition products were obtained in moderate-to-good yields and in diastereoselectivities up to 99%. Acidic cleavage of the sulfinyl group occurred without notable racemization.

Experimental Section

General: All reactions were performed under an argon atmosphere. Dichloromethane and pyridine were distilled from calcium hydride. Sulfinimine **1a** was prepared according to the literature.[2] TLC was performed on Merck silica gel 60 F_{254} plates by using UV light at 312 nm and a 5% alcoholic molybdophosphoric acid for detection. Silica gel for flash chromatography was purchased from Merck. Optical rotations were measured with a Perkin–Elmer 243B Polarimeter. Enantiomeric excesses were determined by HPLC analysis by using Daicels column Chiralpak AD (250 × 4.6 mm). ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Advance DPX instrument (400 and 100 MHz, respectively) from solutions of $CDCl_3$. The chemical shifts are referenced to TMS. The ^{1}H and ^{13}C NMR signals were assigned by 2D correlation techniques (COSY, HSQC). IR spectra were recorded with a Thermo Nicolet FTIR NEXUS instrument, and only the strongest and structurally most important peaks are listed. Elemental analyses were performed at the Mikroanalytisches labor Beller, Göttingen, Germany. Melting points were determined with a Büchi 535 apparatus and are uncorrected.

General Procedure for the Addition of Ethyl (S_S)-[(*tert*-Butylsulfinyl)-imino]acetate (1a) to Aromatic Heterocycles: The aromatic heterocycle (1 mmol) was dissolved with stirring in dry CH_2Cl_2 (8 mL) and cooled to the temperature shown in Table 1 given for the specific reaction. A solution of **1a** in dry CH_2Cl_2 (1.13–1.24 M, 1 mmol) and TMSOTf (180 μL, 1 mmol) were added by syringe. After the specified reaction time (see Table 1), the reaction was

quenched by addition of phosphate buffer (8 mL, pH = 7), warmed to room temperature and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. The crude product was analyzed by ^1H NMR spectroscopy to determine the diastereomeric ratio and, thereafter, purified by flash chromatography.

Ethyl (S_S,2*S*)-2-[(*tert*-Butylsulfinyl)amino](2-furyl)acetate (4a) and Ethyl (S_S,2*R*)-[(*tert*-Butylsulfinyl)amino](2-furyl)acetate (5a): Addition of **1a** to **3a** according to the general procedure afforded a 5:1 mixture of **4a**/**5a**, which were partly separable by flash chromatography (EtOAc/hexane, 1:2). The mixture was isolated as a pale yellow oil (total yield 0.153 g, 56%). Analytical data of the mixture **4a** and **5a**: IR (thin film, NaCl): $\tilde{\nu}$ = 3287, 2980, 1743, 1475, 1367, 1280, 1219, 1076, 1014 cm^{-1}. $C_{12}H_{19}NO_4S$ (273.10): calcd. C 52.73, H 7.01, N 5.12, S 11.73; found C 52.62, H 7.02, N 5.08, S 11.46. Data for **4a**: HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm): t_R = 12.4 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 1.7, 0.8 Hz, 1 H, 5-H), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1 H, 4-H), 6.34 (app dt, *J* = 3.2, 0.7 Hz, 1 H, 3-H), 5.13 (d, *J* = 5.4 Hz, NCH), 4.46 (br. d, *J* = 5.2 Hz, 1 H, NH), 4.28 (dq, *J* = 10.7, 7.2 Hz, 1 H, OCH_2), 4.24 (dq, *J* = 10.7, 7.1 Hz, 1 H, OCH_2), 1.26 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.23 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.40 (CO_2Et), 149.6 (2-C), 143.09 (5-C), 110.5 (4-C), 108.9 (3-C), 62.6 (OCH_2), 56.2 (CMe_3), 52.2 (NCH), 22.47 (CMe_3), 14.0 (OCH_2CH_3) ppm. HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm) of racemic **4a**: t_R = 7.8, 12.4 min. Data for **5a**: HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm): t_R = 10.9 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 1.9, 0.8 Hz, 1 H, 5-H), 6.39 (app dt, *J* = 3.3, 0.7 Hz, 1 H, 3-H), 6.36 (dd, *J* = 3.2, 1.8 Hz, 1 H, 4-H), 5.15 (d, *J* = 8.6 Hz, 1 H, NCH), 4.32 (br. d, *J* = 7.8 Hz, 1 H, NH), 4.25 (dq, *J* = 10.7, 7.1 Hz, 1 H, OCH_2), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1 H, OCH_2), 1.26 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.22 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.45 (CO_2Et), 149.7 (2-C), 143.08 (5-C), 110.7 (4-C), 108.8 (3-C), 62.2 (OCH_2), 57.0 (CMe_3), 53.8 (NCH), 22.45 (CMe_3), 14.0 (OCH_2CH_3) ppm. HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm) of racemic **5a**: t_R = 9.5, 10.9 min.

Ethyl (2*S*)-(Acetylamino)(2-furyl)acetate [(*S*)-6]: A mixture of **4a** and **5a** (ratio 5:1, 37 mg, 0.135 mmol) was dissolved with stirring in methanol (1 mL) and treated with 4.0 M HCl in dioxane (0.170 mL, 5.0 equiv. HCl) at room temperature for 4 h.[6] The reaction mixture was concentrated in vacuo, and the crude amine hydrochloride (white solid) was dissolved with stirring in dry pyridine (1 mL) and cooled to 0 °C. Acetic acid anhydride (55 µL, 0.58 mmol) was added by syringe, and the mixture was stirred for 4 h at 0 °C before being diluted with diethyl ether (20 mL) and washed with water (4 mL) and 10% $CuSO_4$ (aq. 10 mL). The combined aqueous phase was extracted with diethyl ether (20 mL). The combined organic layer was washed successively with water (10 mL), saturated $NaHCO_3$ (aq. 10 mL), and brine (10 mL) and then dried ($MgSO_4$). The solvent was removed to yield a residue, which was purified by flash chromatography (EtOAc/hexane, 1:1). Acetamido compound (*S*)-**6** was obtained as a yellow oil (19.3 mg, 68%), which solidified in the freezer. $[\alpha]_D^{r.t.}$ = +96.4 (*c* = 1.2, abs. EtOH) {ref.[11] for (*R*)-**6**: $[\alpha]_D^{20}$ = –69.6 (*c* = 1, EtOH)}. HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm) 64%*ee*, t_R = 8.5 (*R*), 9.5 (*S*) min. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 1.7, 1.0 Hz, 1 H, 5-H), 6.40 (br. d, *J* = 6 Hz, 1 H, NH), 6.37–6.35 (m, 2 H, 3-H/4-H), 5.75 (d, *J* = 7.9 Hz, 1 H, NCH), 4.25 (dq, *J* = 10.8, 7.2 Hz, 1 H, OCH_2), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1 H, OCH_2), 2.05 (s, 3 H, Ac), 1.25 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3) ppm.

Ethyl (S_S,2*S*)-[(*tert*-Butylsulfinyl)amino](1*H*-pyrrol-2-yl)acetate (4b): Addition of **1a** to **3b** according to the general procedure afforded pure **4b** according to NMR spectroscopic analysis. Flash chromatography (EtOAc/hexane, 3:2) of the crude product gave **4b** (0.249 g, 92% yield) as a pale yellow oil. $[\alpha]_D^{20}$ = +137.2 (*c* = 1.3, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.74 (br. s, 1 H, pyrrole NH), 6.77 (app td, *J* = 2.6, 1.6 Hz, 1 H, 5-H), 6.18–6.14 (m, 2 H, 3-H/4-H), 5.16 (br. d, *J* = 6.0 Hz, 1 H, NCH), 4.47 (br. d, *J* = 6.0 Hz, 1 H, NH), 4.27 (dq, *J* = 10.8, 7.2 Hz, 1 H, OCH_2), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1 H, OCH_2), 1.28 (t, *J* = 7.1 Hz, OCH_2CH_3), 1.26 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (CO_2Et), 126.2 (2-C), 118.8 (5-C), 108.7 (3-C or 4-C), 107.8 (3-C or 4-C), 62.3 (OCH_2), 56.3 (CMe_3), 54.7 (NCH), 22.7 (CMe_3), 14.1 (OCH_2CH_3) ppm. IR (thin film, NaCl): $\tilde{\nu}$ = 3279, 2981, 1736, 1473, 1367, 1229, 1180, 1098 cm^{-1}. $C_{12}H_{20}N_2O_3S$ (272.12): calcd. C 52.92, H 7.40, N 10.29, S 11.77; found C 52.74, H 7.41, N 10.06, S 11.49.

Ethyl [(*tert*-Butylsulfinyl)amino](thien-2-yl)acetate (4c): Addition of **1a** to **3c** according to the general procedure afforded a 1:1.5 mixture of epimeric **4c**. Purification of the crude product by flash chromatography (EtOAc/hexane, 1:2) afforded **4c** (0.116 g, 40%) as a colorless oil. IR (thin film, NaCl): $\tilde{\nu}$ = 3283, 3237, 2980, 1740, 1474, 1366, 1189, 1074, 1020, 705 cm^{-1}. $C_{12}H_{19}NO_3S_2$ (289.08): calcd. C 49.80, H 6.62, N 4.84; found C 49.86, H 6.80, N 4.80. Data for the major epimer: R_F (EtOAc) = 0.45. HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm): t_R = 13.3 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 5.1, 1.3 Hz, 1 H, 5-H), 7.09 (app dt, *J* = 3.6, 1.1 Hz, 1 H, 3-H), 6.99 (dd, *J* = 5.1, 3.6 Hz, 1 H, 4-H), 5.32 (dd, *J* = 5.2, 0.9 Hz, 1 H, NCH), 4.66 (br. d, *J* = 5 Hz, 1 H, NH), 4.28 (dq, *J* = 10.8, 7.2 Hz, 1 H, OCH_2), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1 H, OCH_2), 1.29 (s, 9 H, *t*Bu), 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (CO_2Et), 140.7 (2-C), 127.1 (4-C), 126.2 (3-C), 126.0 (5-C), 62.6 (OCH_2), 56.8 (NCH), 56.3 (CMe_3), 22.6 (CMe_3), 14.0 (OCH_2CH_3) ppm. Data for the minor epimer: R_F (EtOAc) = 0.52. HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm): t_R = 11.5 min. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 5.1, 1.3 Hz, 1 H, 5-H), 7.13 (app dt, *J* = 3.6, 1.0 Hz, 1 H, 3-H), 6.98 (dd, *J* = 5.1, 3.6 Hz, 1 H, 4-H), 5.36 (dd, *J* = 7.1, 0.8 Hz, 1 H, NCH), 4.37 (br. d, *J* = 7.1 Hz, 1 H, NH), 4.24 (dq, *J* = 10.7, 7.1 Hz, 1 H, OCH_2), 4.22 (dq, *J* = 10.7, 7.1 Hz, 1 H, OCH_2), 1.27 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.23 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (CO_2Et), 139.8 (2-C), 127.1 (4-C), 126.5 (3-C), 126.1 (5-C), 62.2 (OCH_2), 57.1 (CMe_3), 54.6 (NCH), 22.5 (CMe_3), 14.0 (OCH_2CH_3) ppm.

Ethyl (S_S,2*S*)-[(*tert*-Butylsulfinyl)amino](1H-indol-3-yl)acetate (4d): Addition of **1a** to **3d** according to the general procedure afforded a complex mixture of isomers. Purification of the crude product by flash chromatography (EtOAc/hexane, 3:2) afforded **4d** (0.140 g, 82%) as a white foam. Analytical data for **4d**: $[\alpha]_D^{r.t.}$ = +146.8 (*c* = 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (br. s, 1 H, indol NH), 7.65 (app d, *J* = 8 Hz, 1 H, 4-H), 7.38 (app dt, *J* = 8.2, 0.9 Hz, 1 H, 7-H), 7.23–7.18 (m, 2 H, 2-H/6-H), 7.12 (ddd, *J* = 8.1, 7.1, 0.9 Hz, 1 H, 5-H), 5.33 (app dd, *J* = 4.6, 0.4 Hz, 1 H, NCH), 4.51 (br. d, *J* = 4.6 Hz, 1 H, NH), 4.25 (dq, *J* = 10.7, 7.1 Hz, 1 H, OCH_2), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1 H, OCH_2), 1.21 (s, 9 H, *t*Bu), 1.19 (t, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9 (CO_2Et), 136.6 (7a-C), 125.6 (3a-C), 124.0 (C-2 or C-6), 122.5 (C-2 or C-6), 120.0 (5-C), 119.7 (4-C), 111.8 (3-C), 111.4 (7-C), 62.0 (OCH_2), 55.8 (CMe_3), 54.3 (NCH), 22.7 (CMe_3), 14.1 (OCH_2CH_3) ppm. IR (KBr tablet): $\tilde{\nu}$ = 3406, 3250, 3059, 2979, 1732, 1458, 1367, 1232, 1185, 1052, 744 cm^{-1}. $C_{16}H_{22}N_2O_3S$

(322.14): calcd. C 59.60, H 6.88, N 8.69, S 9.95; found C 59.22, H 6.99, N 8.46, S 9.69.

Ethyl (2*S*)-{[(4-Bromophenyl)sulfonyl]amino}(1*H*-indol-3-yl)acetate (8a): *N*-Sulfinyl indolylglycine derivative **4d** (0.233 g, 0.722 mmol) was dissolved with stirring in MeOH (6 mL) and treated with 4.0 M HCl in dioxane (0.900 mL, 3.60 mmol) at room temperature for 4 h.[6] The reaction mixture was concentrated under reduced pressure, and the precipitated amine hydrochloride was dissolved with stirring by addition of dry CH_2Cl_2 (2 mL) and triethylamine (0.320 mL, 2.30 mmol), and then cooled to 0 °C. A solution of 4-bromobenzenesulfonyl chloride (0.182 g, 0.712 mmol) in dry CH_2Cl_2 (3 mL) was cannulated into the mixture. The resultant mixture was stirred at 0 °C for 2 h and then warmed to room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc/hexane, 3:7 to 1:1) affording **8a** (0.256, 82% yield) as a white solid. M.p. 141–142 °C (abs EtOH). $[\alpha]_D^{rt.}$ = +101.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (br. s, 1 H, indol NH), 7.49 (app d, J = 8.8 Hz, 2 H, 4-BrC_6H_4, 2-H/6-H), 7.49–7.46 (m, 1 H, 4-H), 7.35 (app d, J = 8.8 Hz, 2 H, 4-BrC_6H_4, 3-H/5-H), 7.29 (dt, J = 8.2, 0.9 Hz, 1 H, 7-H), 7.19 (app ddd, J = 8.2, 7.1, 1.1 Hz, 1 H, 6-H), 7.09–7.05 (m, 2 H, 2-H/5-H), 5.67 (br. d, J = 7.3 Hz, 1 H, NH), 5.36 (app dd, J = 7.3, 0.4 Hz, 1 H, NCH), 4.13 (dq, J = 10.8, 7.1 Hz, 1 H, OCH_2), 4.03 (dq, J = 10.7, 7.1 Hz, 1 H, OCH_2), 1.14 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.2 (CO_2Et), 139.0 (4-BrC_6H_4, 1-C), 136.2 (7a-C), 131.6 (4-BrC_6H_4, 3-C/5-C), 128.5 (4-BrC_6H_4, 2-C/6-C), 127.2 (3a-C or 1-C in 4-BrC_6H_4), 124.9 (3a-C or 1-C in 4-BrC_6H_4), 123.7 (2-C), 122.9 (6-C), 120.5 (5-C), 119.0 (4-C), 111.4 (7-C), 110.1 (3-C), 62.3 (OCH_2), 53.2 (NCH), 13.9 (OCH_2CH_3) ppm. IR (KBr tablet): $\tilde{\nu}$ = 3408, 3251, 3129, 3058, 2998, 1731, 1575, 1471, 1458, 1420, 1344, 1304, 1197, 1168, 1101, 1087, 1009, 919, 830, 750 cm^{-1}. The absolute configuration of **8a** was corroborated by X-ray crystallographic analysis.[14]

Ethyl (2*S*)-1*H*-Indol-3-yl{[(4-methylphenyl)sulfonyl]amino}acetate (8b): *N*-Tosyl indolylglycine derivative **8b** was prepared according to the procedure described for the preparation of **8a**. Purification of the crude product by flash chromatography (EtOAc/hexane, 3:7 to 8:2) afforded **8b** (0.214 g, 80%) as a white solid. $[\alpha]_D^{rt.}$ = +105.6 (c = 1, $CHCl_3$) {ref.[13] 96% *ee*, $[\alpha]_D^{rt.}$ = +102 (c = 1, $CHCl_3$), absolute configuration was not given in the reference}. ^{1}H and ^{13}C NMR spectra were in accordance with the data reported in the literature.[13]

Ethyl (S_S,2*S*)-[(*tert*-Butylsulfinyl)amino](4-methoxyphenyl)acetate (4f) and Ethyl (S_S,2*R*)-[(*tert*-Butylsulfinyl)amino](4-methoxyphenyl)-acetate (5f): Addition of **1a** to **3f** according to the general procedure afforded a 1:2.6 mixture of **4f/5f**, which were partly separable by flash chromatography (EtOAc/hexane, 1:2). The mixture was isolated as a pale yellow oil (total yield: 0.201 g, 65%). Analytical data for **4f**: R_F (EtOAc) = 0.34. HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm): t_R = 20.9 min. ^{1}H NMR spectroscopic data was in accordance with data reported for the (R_S,2*R*)-enantiomer.[5] Analytical data for **5f**: R_F (EtOAc) = 0.44. $[\alpha]_D^{20}$ = –52.7 (c = 1, $CHCl_3$). HPLC (Chiralpak AD; *i*PrOH/hexane, 10:90; 1 mL min^{-1}; 230 nm): t_R = 22.2 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (app d, J = 8.8 Hz, 2 H, aryl), 6.88 (app d, J = 8.8 Hz, 2 H, aryl), 5.05 (br. d, J = 5.9 Hz, 1 H, NCH), 4.20 (dq, J = 10.8, 7.1 Hz, 1 H, OCH_2), 4.13 (dq, J = 10.8, 7.1 Hz, 1 H, OCH_2), 4.12 (br. d, J = 6 Hz, 1 H, NH), 3.80 (s, 3 H, OCH_3), 1.21 (s, 9 H, *t*Bu), 1.208 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5 (CO_2Et), 159.8 (aryl), 129.3 (aryl), 128.8 (aryl), 114.3 (aryl), 61.7 (OCH_2), 58.8 (NCH), 56.7 (CMe_3), 55.3 (OCH_3), 22.5 (CMe_3), 14.0 (OCH_2CH_3) ppm. IR (thin film, NaCl): $\tilde{\nu}$ = 3269, 3214, 2979, 1736, 1611, 1513, 1464, 1389, 1304, 1249, 1178, 1070, 1031, 836 cm^{-1}. $C_{15}H_{23}NO_4S$ (313.13): calcd. C 57.48, H 7.40, N 4.47, S 10.23; found C 57.08, H 7.53, N 4.43, S 10.23.

Diethyl (S_S,2*S*,2′*S*)-2,2′-(1*H*-Pyrrole-2,5-diyl)bis({[(*S*)-*tert*-butylsulfinyl]amino}acetate) (7): Addition of **1a** (2 equiv.) and TMSOTf (2 equiv.) to **3b** (1 equiv.) according to the general procedure afforded a mixture of **7** and a minor amount of **4b**. Purification of the crude product by flash chromatography (EtOAc) gave **7** (0.368 g, 77%) as a white solid. M.p. 103–104 °C (10% *i*PrOH in hexane). $[\alpha]_D^{rt.}$ = +162.4 (c = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (br. s, 1 H, pyrrole NH), 6.09 (d, J = 2.7 Hz, 2 H, 3-H/4-H), 5.11 (br. d, J = 6.0 Hz, 2 H, 2 × NCH), 4.41 (br. d, J = 6.0 Hz, 2 H, 2 × NH), 4.27 (dq, J = 10.7, 7.2 Hz, 2 H, OCH_2), 4.22 (dq, J = 10.7, 7.1 Hz, 2 H, OCH_2), 1.29 (t, J = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 1.26 (s, 18 H, 2 × *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 (2 × CO_2Et), 127.4 (2-C/5-C), 108.3 (3-C/4-C), 62.4 (2 × OCH_2), 56.3 (2 × CMe_3), 54.7 (2 × NCH), 22.6 (2 × CMe_3), 14.1 (2 × OCH_2CH_3) ppm. IR (KBr tablet): $\tilde{\nu}$ = 3444, 3275, 2981, 1739, 1474, 1367, 1299, 1233, 1186, 1057 cm^{-1}. $C_{20}H_{35}N_3O_6S_2$ (477.20): calcd. C 50.29, H 7.39, N 8.80, S 13.43; found C 50.09, H 7.50, N 8.68, S 13.29. The absolute configuration of **7** was corroborated by X-ray crystallographic analysis.[14]

Acknowledgments

We thank the Norwegian Research Council (Grant 160099 to T.A.) for generous financial support.

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688243 (for **7**) and -692534 (for **8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Received: June 24, 2008
Published Online: September 2, 2008

