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Synthesis of Enantiopure (*S*)-Indolylglycine by Organocatalyzed Friedel–Crafts Alkylation of Indole

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Tritylsulfenyl- and 2-nitrophenylsulfenyl-substituted glyoxyl imines were used in chiral phosphoric acid catalyzed Friedel–Crafts (FC) reactions with indole. High yields and *ee* values ranging from 86 % for Nps-protected (*S*)-indolylglycine to 88 % for Trs-protected (*R*)-indolylglycine were obtained. On a preparative scale, a FC product with 99.5 % *ee* and 71 % yield was readily obtained by crystallization of the reaction mixture. Removal of the Nps protecting group under mild acidic conditions did not affect the stereochemical integrity of the α-carbon atom and (*S*)-indolylglycine was afforded in ≥98 % *ee*.

Introduction

Indolylglycines have attracted much attention as nonproteinogenic amino acids in drug development, natural product synthesis and in peptide mimetics.[1] The total synthesis of biologically important bis(indole) alkaloids such as the dragmacidins and hamacanthins rely on indolylglycine and indolylglycinol units.[2,3] Although indolylglycine itself and a few of its derivatives are commercially available, no enantioselective synthesis of unprotected indolylglycine or its analogues can be found in the literature. Friedel–Crafts-type synthetic methods are the path of choice to prepare these aromatic amino acids and takes advantage of the excellent nucleophilic properties of the indole 3-position. With glyoxylic acid derived imines as counterparts in racemic Friedel–Crafts reactions, catalysts ranging from simple Brønsted acids, such as TFA, to lanthanide triflates or complexed palladium readily introduce the amino acid functionality. Even catalyst-free reactions are reported, although the indole N–H or even water can take the role of the Brønsted catalyst.[1,4] Several enantioselective syntheses of *N*-substituted indolylglycine are reported, and they use chiral amine auxiliaries in the imine part,[5,6] enzymatic resolution[7] or chiral Lewis acidic silanes.[8] Johannsen described the only catalytic process towards *N*-tosyl-substituted indolylglycines reported; the Lectka Cu^{I}Tol-binap system was used.[9]

Stimulated by the rapidly increasing number of applications of enantioselective organocatalyzed reactions involving iminium ions,[10] we explored the use of binolphosphoric acids as Brønsted activators in the Friedel–Crafts substitution of the indole 3-position. Several recent reports describe highly enantioselective indole alkylation reactions with imines or equivalents thereof, but an approach to indolylglycine has not yet appeared.[11] An important limitation of almost all examples mentioned here is the presence of undesirable substituents on both the indole nitrogen atom and on the amine functionality. Only a few publications describing deprotection of these Friedel–Crafts products to simple 3-alkylamino-substituted indoles can be found in the literature.[11a]

The reactive nature of the indole moiety and its 3-substituent renders chemoselective removal of substituents from the amine difficult; for example, removal of the methoxyphenyl group under oxidative conditions would harm the indole ring, and strongly hydrogenolytic conditions would cleave the C–N bond in the substituent. Also, strong base or acid can easily destroy the stereocentre. Reducing-metal conditions, successfully applied to remove tosyl or benzenesulfonyl substituents from 3-alkylaminoindoles,[11a] cannot be applied safely for sensitive amino acids such as indolylglycine. *N*-Sulfenyl-protected amines seemed suitable for this purpose, because the N–S bond can be hydrolyzed under mild acidic conditions.[12] Both the 2-nitrophenylsulfenyl (Nps) and the triphenylmethylsulfenyl (Trs) groups are known in the literature, and they are used in particular as *N*-protecting groups in amino acid chemistry.[13] Previously, we introduced the Nps and Trs groups as stabilizing and protecting substituents in the binolphosphoric acid cata-

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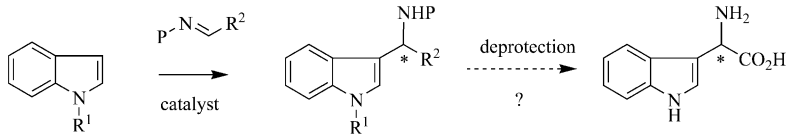


lyzed Pictet–Spengler reaction, which revealed their excellent behaviour in iminium-ion chemistry.[14] The required glyoxylic imine precursors **1**[15] and **2** were readily prepared by condensation of methyl glyoxylate with 2-nitrophenyl sulfenamide (Nps-NH_2) and with triphenylmethyl sulfenamide (Trs-NH_2).

Results and Discussion

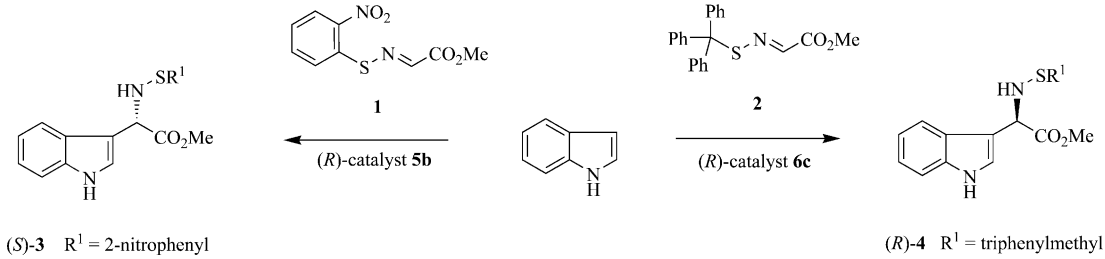
Reaction of Nps-imine **1** with indole catalyzed by unsubstituted (*R*)-binolphosphoric acid **5a** gave clean production of Nps-protected indolylglycine **3** in good yield and with a promising 30%*ee* (Scheme 1, Table 1). Chloroform was selected as the solvent for a preliminary optimization study with **1**, and next, a series of (*R*)-binolphosphoric acids **5**, (*R*)-octahydrobinol phosphoric acids **6** and (*R*)-vapol **7** as a nonbinol-derived catalyst were screened (Table 1). Remarkably low *ee* values were obtained from the generally very selective 3,5-bis(trifluoromethyl)phenyl and 2,4,6-triisopropylphenyl-substituted catalysts **5d** and **5g**, respectively. 3,3′-Triphenylsilyl catalyst **5b** gave the highest *ee* and although 3,3′-(4-biphenyl)-substituted catalyst **5c** showed comparable *ee* values, the triphenylsilyl catalyst was chosen for further optimization in view of its availability.[16] The (*S*) configuration at the newly formed asymmetric carbon centre was deduced from an X-ray structure obtained from **3**, which easily crystallized in an enantiopure form (see below).

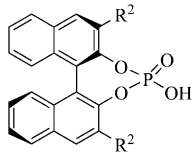
The Friedel–Crafts reaction between bulky tritylsulfenyl imine **2** (Scheme 1) and indole was also readily catalyzed by binolphosphoric acids, but it displayed a completely different catalyst preference in comparison with 2-nitrophenylsulfenyl imine **1**. Triphenylsilyl catalyst **5b** and 3,3′-bi-

Table 1. Catalyst screening and reaction optimization.[a]

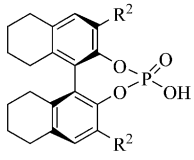
Entry	Catalyst	Solvent	*t* [h]	*T* [°C]	*ee* [%]	MS [Å]
		(*S*)-**3** R^2 = 2-nitrophenyl				
1	**5a**	$CHCl_3$	1	r.t.	30	
2	**5b**	$CHCl_3$	48	r.t.	69	
3	**5c**	$CHCl_3$	90	50	68	
4	**5d**	$CHCl_3$	0.5	r.t.	2	
5	**5e**	$CHCl_3$	0.5	r.t.	49	
6	**5f**	$CHCl_3$	48	50	62	
7	**5g**	$CHCl_3$	48	50	4	
8	**6a**	$CHCl_3$	6	r.t.	35	
9	**6b**	$CHCl_3$	18	50	53	
10	**6c**	$CHCl_3$	24	r.t.	5	
11	**7**	$CHCl_3$	24	50	61	
12	**5b**	PhH	48	r.t.	69	
13	**5b**	PhH	24	r.t.	78	5
14	**5b**[b]	PhH[c]	24	0	86	5
		(*R*)-**4** R^2 = triphenylmethyl				
15	**5a**	CH_2Cl_2	1	r.t.	0	
16	**5b**	CH_2Cl_2	48[d]	reflux	–	
17	**5c**	CH_2Cl_2	48[e]	r.t.	15	
18	**5d**	CH_2Cl_2	2	r.t.	21	
19	**5e**	CH_2Cl_2	1	r.t.	36	
20	**5f**	CH_2Cl_2	48[e]	r.t.	46	
21	**5g**	CH_2Cl_2	24	r.t.	72	
22	**6a**	CH_2Cl_2	4	r.t.	0	
23	**6b**	CH_2Cl_2	24	r.t.	21	
24	**6c**	CH_2Cl_2	4	r.t.	77	
25	**7**	CH_2Cl_2	2	r.t.	–12	
26	**6c**	PhH	10	r.t.	88	3
27	**6c**	CH_2Cl_2	10	r.t.	88	3
28	**6c**[b]	CH_2Cl_2	24	0	88	3

[a] Reaction conditions: **1** or **2** (0.05 mmol), indole (1.1 equiv.), catalyst (2 mol-%) and optionally powdered MS (75 mg) in 0.5 mL of solvent (MS = molecular sieves). The reaction was continued until >95% conversion. Isolated yields were >85%. [b] 5 mol-%. [c] Mixture of PhH/PhMe, 4:1. [d] No conversion. [e] <10% Conversion.





5a: R^2 = H
5b: R^2 = $Si(Ph)_3$
5c: R^2 = 4-biphenyl
5d: R^2 = 3,5-bis(CF_3)phenyl
5e: R^2 = 4-nitrophenyl
5f: R^2 = 9-anthryl
5g: R^2 = 2,4,6-triisopropylphenyl



6a: R^2 = H
6b: R^2 = Ph
6c: R^2 = $CH(Ph)_2$

7 (*R*)-vapolphosphoric acid (vaulted biphenanthrol phosphoric acid)[17]

Scheme 1.

phenyl catalyst **5c**, previously found as most successful with the 2-nitrophenyl substituent, were virtually incapable of catalyzing the reaction. Only 3,3′-benzhydryl-substituted octahydrobinol phosphoric acid **6c** was acceptable as a catalyst with respect to *ee* values (77%) and conversion rate, and thus, it was selected for further optimization studies. Surprisingly, all catalysts except vapol-phosphate[17] gave product **4** with the (*R*) configuration at the newly formed centre. This is opposite to Nps-product **3**, which was obtained without exception with the (*S*) configuration. Obviously, the substituent on sulfur in combination with the 3,3′-R groups on the binol ring system determine the binding of the imine to the catalyst and not the configuration of the binolphosphoric acid [exclusively catalysts with the (*R*) configuration were used during this investigation]. In a recent publication, Terada and coworkers described an inversion of the sense of enantioselection during indole alkylation by different 3,3′-substitution on the (*R*)-binaphthyl ring system. Calculations gave some insight into the 3D structures that are responsible for these observations.[18]

Further optimization studies showed that both reactions were insensitive towards solvent changes. Addition of powdered molecular sieves and replacement of chloroform by benzene as the solvent gave a significant improvement in both the reaction time and the enantiomeric excess. Imine **1** showed a slight preference for 5 Å (Table 1, Entry 13; 78%*ee*) over 3-Å molecular sieves (73%*ee*). Surprisingly, 4-Å molecular sieves almost completely inhibited the reaction with the 2-nitrophenylsulfenyl-substituted imine **1**. Lowering the temperature to 0 °C further increased of the *ee* value to 86%, although increasing the catalyst loading to 5 mol-% was necessary to obtain acceptable reaction times. In the tritylsulfenyl reaction with imine **2**, an optimum *ee* value of 88% was reached upon combination of dichloromethane with 3-Å molecular sieves. Again, 4-Å molecular sieves showed a strong inhibitory effect on the reaction. These *ee* values were reproducible on a preparative scale: starting from **1** (2 mmol) and catalyst **5b** (2 mol-%), amino ester **3** was obtained in 97% yield and 79%*ee*. Enantiopure product was obtained by two simple crystallizations from EtOAc/petroleum ether mixtures: (*S*)-**3** (Figure 1): 71% yield based on **1**, >99.5%*ee*. *N*-STr amino ester **4** was obtained from **1** (3 mmol) in 88% yield and 88%*ee* (63% yield and >99.5%*ee* after crystallization).

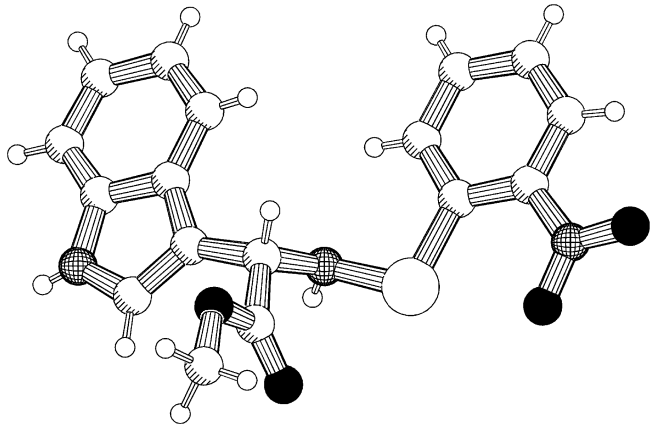
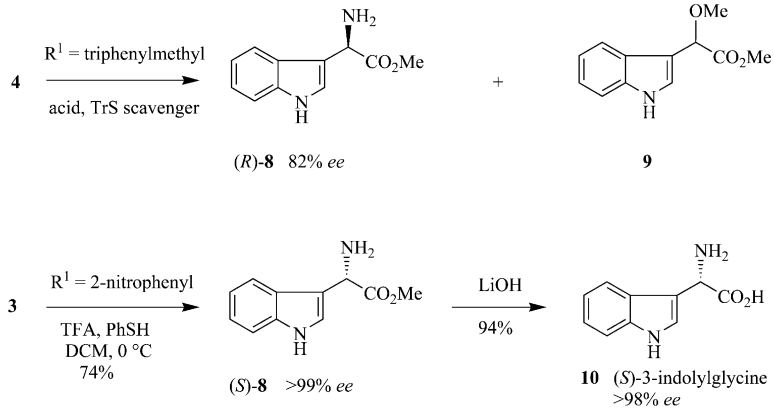


Figure 1. X-ray structure of (*S*)-**3**.

Deprotection of tritylsulfenylindolylglycine **4** turned out to be complicated owing to a combination of the electron-donating properties of the indole ring and the shielding effect of the trityl substituent on the sulfur atom (Scheme 2). Standard conditions with the use of hydrochloric acid in methanol gave deaminated racemic methyl 2-methoxyindoloacetate (**9**) (77%) and amino ester (*R*)-**8** (14% yield, 82%*ee*). Triphenylmethylsulfenyl scavengers such as ethanethiol or thiophenol in combination with trifluoroacetic acid or hydrochloric acid[14] gave the corresponding 2-mercaptoindoloacetics in low yield together with unidentified decomposition products. Undesirable reaction conditions such as tributyltin hydride/AIBN were not investigated.

Removal of the 2-nitrophenylsulfenyl substituent in **3** was readily accomplished under acidic conditions and amino ester (*S*)-**8** was obtained in 74% yield with complete retention of configuration of the stereocentre. Hydrolysis of the methyl ester cleanly afforded unprotected (*S*)-(3)-indolylglycine (**10**) with good *ee* and yield.



Scheme 2. Deprotection.

Conclusions

We developed a practical, organocatalytic Friedel–Crafts process with catalyst loadings as low as 2 mol-% for the synthesis of Trs- and Nps-protected indolylglycine. The alkylation products of indole were obtained with opposite configuration depending on the sulfur substituent when binolphosphoric acids with the (*R*) configuration were used exclusively. Only two recrystallization steps were required to obtain the enantiomerically pure compounds in good yield. Unprotected (*S*)-indolylglycine (**10**; ≥98% *ee*) was readily prepared by mild, acid catalyzed removal of the 2-nitrophenylsulfenyl substituent followed by ester saponification.

Experimental Section

General: All reactions were carried out in flame-dried glassware with magnetic stirring under an atmosphere of nitrogen. Solvents were dried and distilled by standard procedures. Powdered molecular sieves (Aldrich) were dried at 200 °C and 0.1 mbar. Flash chromatography was performed by using silica gel (Biosolve 60 Å). 400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR spectra were obtained with a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts (δ) are given in ppm downfield from tetramethylsilane. ^{13}C NMR chemical shifts were calibrated to internal $CDCl_3$ (δ = 77 ppm). Optical rotations ($[\alpha]_D^{25}$) were measured with a Perkin–Elmer 241 polarimeter. HPLC was performed by using LKB equipment (2150 HPLC-pump and 2140 rapid spectral detector) and a Daicel Chiralcel OD- or an AD-column with the use of 2-propanol/heptane as the eluent. Chromatograms were measured at 254 nm. Chromatograms were processed by using Borwin software version 1.22 (build 0.3). (*R*)-3,3′-Bis(triphenylsilyl)-1,1′-binaphthyl phosphate **5b** was prepared according to MacMillan.[16] (*R*)-3,3′-Bis[3,5-bis-(trifluoromethyl)phenyl]-1,1′-binaphthyl phosphate **5d**, (*R*)-3,3′-bis(4-nitrophenyl)-1,1′-binaphthyl phosphate **5e**, 3,3′-bis(9-anthryl)-1,1′-binaphthyl phosphate **5f**, 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl phosphate **5g** and 3,3′-diphenyl-octahydro-1,1′-binaphthyl phosphate **6b** were prepared according to Akiyama et al.;[19] (*R*)-3,3′-bis(*p*-biphenylyl)-1,1′-binaphthyl phosphate **5c** was prepared according to Terada et al.;[20,21] (*R*)-1,1′-binaphthyl phosphate **5a**, (*R*)-VAPOL **7**, triphenylmethanesulfenamide and 2-nitrobenzenesulfenyl chloride were obtained from Aldrich.

(*R*)-3,3′-Bis(benzhydryl)-octahydro-1,1′-binaphthyl Phosphate 6c: (*R*)-3,3′-Bis(benzhydryl)-octahydro-1,1′-binaphthol (**11**) was prepared by reaction of (*R*)-octahydro-1,1′-binaphthol[22] with benzhydryl chloride.[23] Phosphorylation of **11** (0.120 g, 0.19 mmol) was performed with $POCl_3$ (37 mL, 0.40 mmol) in pyridine (0.6 mL) over 1 h at 90 °C. After cooling to room temperature, water (0.12 mL) was added and heating was continued at 95 °C for 1.5 h. After evaporation of the pyridine, hydrochloric acid (6 M, 3 mL) was added and heating was continued for 2 h at 110 °C. Pure **6c** (0.120 g, 0.174 mmol, 92%) was obtained by extraction with DCM and drying of the solid residue at 50 °C/0.05 mbar. M.p. 204–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.0–7.25 (m, 20 H), 6.63 (s, 2 H), 6.16 (s, 2 H), 2.4–2.75 (m, 6 H), 2.2 (m, 4 H), 1.4–1.8 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 143.8, 143.4, 135.9, 134.5, 133.0, 130.8, 129.9, 128.9, 128.2, 127.0, 126.0, 49.60, 29.71, 29.28, 22.45 ppm. HRMS (FAB): *m*/*z* calcd. for $C_{46}H_{42}O_4P$ [M + H] 689.2818; found 689.2821.

2-Nitrobenzenesulfenamide (*o*-Nitrophenylsulfenamide, Nps-NH$_2$):[15a] 2-Nitrobenzenesulfenyl chloride (18.0 g, 0.10 mol) was added in portions to a stirred homogeneous mixture of NH_4OH (25%, 150 mL), THF (300 mL) and MeOH (55 mL) at 0 °C. After stirring for 2 h at room temperature, saturated NH_4Cl and diethyl ether were added. The layers were separated, the organic layer was dried with Na_2SO_4 and the solvents were evaporated. The remaining solid was dissolved in hot EtOAc and after cooling, diethyl ether was added slowly, followed by PE 40/65. 2-Nitrobenzenesulfenamide (14.95 g, 88%) was obtained in two fractions. Note: Small amounts of a less-polar compound can cocrystallize. M.p. 120–124 °C (ref.[15a] 122–125 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 1.0, 8.3 Hz, 1 H), 8.15 (dd, *J* = 1.2, 8.3 Hz, 1 H), 7.70 (m, 1 H), 7.26 (m, 1 H), 2.74 (br. s, 2 H) ppm.

Methyl 2-(2-Nitrophenylsulfenimino)acetate (1):[15b,15c] A solution of NpsNH_2 (0.680 g, 4.0 mmol), methyl glyoxylate methanol hemiacetal (0.528 g, 4.4 mmol) and PPTS (10 mg) in EtOAc (15 mL) was heated at reflux for 4 h. PE 40/65 (7.5 mL) and silica gel (0.5 g) were added and after stirring for 5 min the mixture was filtered through Celite. The solids were washed with EtOAc/PE (2:1, 3 × 10 mL) and the solvents were evaporated. Crystallization from EtOAc/PE mixtures gave imine **1** (0.785 g, 3.27 mmol, 82%). M.p. 120–121 °C (ref.[15] 120 °C). ^{1}H NMR (400 MHz, $CDCl_3$): 4:1 mixture of rotamers: imine protons at 8.28 (major) and 8.02 ppm. In the literature[15] these rotamers are ascribed to the existence of *E*/*Z* isomers. Instead, a high temperature experiment in DMSO clearly shows rotamers: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, 3:1 mixture of rotamers): δ = 8.52 (s, major), 8.37 (m, 2 H, Ar), 8.17 (s, 1 H, minor), 7.96 (m, 1 H Ar), 7.57 (m, 1 H Ar), 3.87 (s, 3 H, minor), 3.83 (s, 3 H, major) ppm. Upon increasing the temperature to 80 °C a single rotamer is left: δ = 8.4 (br., 1 H, imine), 8.35 (m, 2 H), 7.93 (m, 1 H), 7.56 (m, 1 H), 3.87 (s, 3 H) ppm. After cooling to room temperature, the initial 3:1 ratio reformed.

Methyl 2-(Triphenylmethanesulfenimino)acetate (2): Triphenylmethanesulfenamide (1.746 g, 6.0 mmol), methyl glyoxylate methanol hemiacetal (0.720 g, 6.6 mmol), PPTS (76.4 mg, 0.30 mmol) and $MgSO_4$ (1.25 g, 10 mmol) were stirred in dichloromethane (10 mL) for 3 h at room temperature. The mixture was filtered through silica and washed with a 1:1 mixture of EtOAc and PE 60/80 to remove the catalyst. Evaporation and trituration of the solid residue gave imine **2** (1.86 g, 5.14 mmol, 86%). M.p. 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (br., 1 H, imine), 7.2–7.4 (15 H, Ar), 3.81 (br., 3 H, CH_3) ppm. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 80 °C): δ = 7.78 (s, 1 H), 7.3–7.4 (m, 9 H); 7.2 (m, 6 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.1, 126.7, 127.2, 127.9, 130.5 ppm, S-*C*Ph$_3$ and carbonyl not observed due to line broadening. HRMS (FAB): calcd. for $C_{22}H_{20}NO_2S$ [M + H] 362.1208; found 362.1219.

Catalytic Experiments with Methyl 2-(2-Nitrophenylsulfenimino)-acetate (1): Indole (6.5 mg, 0.055 mmol) and methyl 2-(2-nitrophenylsulfenimino)acetate (**1**; 12.0 mg, 0.050 mmol) and molecular sieves if appropriate, were mixed with $CHCl_3$ (0.5 mL), and the catalyst (0.002 mmol, 2 mol-%) was added to the stirred suspension. The progress of the reaction was monitored with TLC on silica (PE/EtOAc, 1:1). After disappearance of the starting material, the reaction mixture was diluted with DCM (0.5 mL) and PE (1 mL) and immediately applied to a silica column packed with PE/EtOAc (2:1). If racemate had precipitated from the reaction mixture, this was first dissolved by adding more DCM and heating. Product **3** was obtained in 92–97% yield. Spectroscopic data: see synthesis of **3**. HPLC (OD-column; heptane/2-propanol, 75:25; 0.8 mL min^{-1}): t_R = 19.4 (minor), 27.8 min.

Catalytic Experiments with Methyl 2-Tritylsulfeniminoacetate (2): The same conditions described for the nitrophenyl derivative were

applied for purification (silica; PE/EtOAc, 3:1). Spectroscopic data: see synthesis of **4**. HPLC (AD-column; heptane/2-propanol, 80:20; 1 mL min^{-1}): t_R = 4.9 (major), 8.7 min.

Methyl *N*-(2-Nitrobenzenesulfenyl)(3-indolyl)glycinate [(*S*)-3]: A solution of **1** (0.480 g, 2.0 mmol), indole (0.257 g, 2.2 mmol), 5-Å molecular sieves (3.0 g) and triphenylsilyl catalyst **5b** (34.6 mg, 0.04 mmol, 2 mol-%) in benzene (20 mL) was stirred under an atmosphere of N_2 at room temperature for 24 h. DCM (20 mL) and silica (3 g) were added. The mixture was stirred for 5 min and PE 60/80 (30 mL) was added. The mixture was immediately applied to a silica column packed with PE/EtOAc (2:1). Elution with PE/EtOAc (2:1 → 3:2) gave pure (*S*)-**3** (0.691 g, 1.94 mmol, 97%) as a solid. This product had an *ee* value of 79.3%. The crude product was stirred with EtOAc and filtered to give racemic **3**. Evaporation of the filtrate and crystallization by dissolving the residue in hot EtOAc followed by the addition of PE gave (*S*)-**3** with 96–99% *ee*. Recrystallization of this product from EtOAc/PE gave enantiopure product. Repeating this process with the filtrate gave a total yield of 0.505 g (71%) of enantiopure (*S*)-**3** (>99.5% *ee*). M.p. 142.5–143 °C; m.p. (racemate) 172.5–174 °C. HPLC: (OD-column; heptane/2-propanol, 75:25; 0.8 mL min^{-1}): (*S*)-enantiomer not observed. $[a]_D$ = +106 (c = 0.54, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (dd, J = 1, J = 8.3 Hz, 1 H), 8.22 (br. s, 1 H), 8.11 (d, J = 7.5 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.53 (m, 1 H), 7.42 (d, J = 8.3 Hz, 1 H), 7.20–7.26 (m, 4 H), 4.92 (d, J = 7.5 Hz, 1 H), 3.78 (s, 3 H), 3.73 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 144.8, 142.7, 136.4, 133.6, 125.64, 125.61, 124.9, 124.7, 123.3, 122.9, 120.5, 119.0, 112.6, 111.5, 60.5, 52.6 ppm. HRMS (FAB): calcd. for $C_{17}H_{16}N_3O_4S$ [M + H] 358.0862; found 358.0863. $C_{17}H_{15}N_3O_4S$ (357.38): calcd. C 57.13, H 4.23, N 11.76; found C 57.18, H 4.27, N 11.75.

X-ray Crystal Structure Analysis of [(*S*)-3]: $C_{17}H_{15}N_3O_4S$, formula weight: 357.38 g mol^{-1}, crystal size 0.16 × 0.12 × 0.04 mm, T = 208(2) K, λ = 0.71073 Å, orthorhombic, $P2_12_12_1$, a = 7.4639(2) Å, b = 14.686(6) Å, c = 14.867(8) Å, V = 1629.6(12) Å^3, Z = 4, $D_{calcd.}$ = 1.457 Mg m^{-3}, μ = 0.227 mm^{-1}, F(000) = 744; final R indices [$I > 2\sigma(I)$] R_1 = 0.0568, wR_2 = 0.0769, R indices (all data): R_1 = 0.0876, wR_2 = 0.0849, absolute structure parameter: 0.00(10), largest diff. peak and hole: 0.267 and –0.303 e Å^{-3}. CCDC-660890 [for (*S*)-**3**] contains 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.

Methyl *N*-(Triphenylmethanesulfenyl)(3-indolyl)glycinate [(*R*)-4]: A mixture of **2** (1.085 g, 3.0 mmol), indole (0.369 g, 3.15 mmol), 3-Å molecular sieves (4.5 g) and benzhydryl catalyst **6c** (41.3 mg, 0.06 mmol, 2 mol-%) in CH_2Cl_2 (30 mL) was stirred under an atmosphere of N_2 at room temperature for 24 h. PE 60/80 (50 mL) and silica (4 g) were added, and the suspension was directly applied to a silica column packed with PE/EtOAc (3:1). The product was obtained as a syrup (88% *ee*), which was crystallized from EtOAc and some PE to remove racemic **4**. The filtrate was dissolved in a small amount of EtOAc, and the enantiopure product [(*R*)-**4**, 0.907 g, 1.90 mmol, 63%] was crystallized by the addition of PE. M.p. 142–144 °C; M.p. (racemate) 88–95 °C. HPLC (AD-column; heptane/2-propanol, 80:20; 1 mL min^{-1}): t_R = 4.9 (major), 8.7 min. (*S*) enantiomer not observed (>99.5% *ee*). $[a]_D$ = –122 (c = 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (br. s, 1 H), 7.0–7.45 (m, 19 H), 6.93 (d, J = 2.5 Hz, 1 H), 4.38 (d, J = 6.0 Hz, 1 H), 3.7 (s, 3 H), 3.62 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 144.3, 136.1, 130.1, 128.0, 126.9, 125.6, 123.2, 122.5, 120.0, 119.5, 112.9, 111.4, 70.46, 60.75, 52.29 ppm. HRMS (FAB): calcd. for $C_{30}H_{27}N_2O_2S$ [M + H] 479.1789; found 479.1797.

Methyl 3-Indolylglycinate [(*S*)-8]: TFA (0.385 mL, 5.0 mmol) was added to a solution of (*S*)-**3** (0.357 g, 1.0 mmol) and PhSH (0.308 mL, 3.0 mmol) in DCM (15 mL) at 0 °C. After stirring for 1 h PE (15 mL) was added, and the reaction mixture was directly applied to a silica column. Elution with PE/EtOAc (5:1 and 1:1), EtOAc containing 3% TEA and finally EtOAc/MeOH (95:5) afforded (*S*)-**8** (0.151 g, 0.74 mmol, 74%) as colourless crystals after crystallization from EtOAc/PE. M.p. 114–115 °C; m.p. (racemate) 118 °C.[24] $[a]_D$ = +163 (c = 0.51, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (br., 1 H); 7.74 (d, J = 8.0 Hz, 1 H); 7.39 (d, J = 8.1 Hz, 1 H), 7.23 (d, J = 1.5 Hz, 1 H), 7.15–7.25 (m, 2 H), 4.96, (br., 1 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 136.4, 125.4, 122.7, 122.4, 120.0, 119.0, 114.2, 111.6, 52.43, 51.54 ppm. The *ee* was determined by integration of the methyl ester signals in the ^{1}H NMR spectrum taken from a 2-mg sample after addition of 8 mg (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle alcohol).[14,25] From a racemic mixture the methyl esters appeared at δ = 3.70 and 3.67 ppm. Only the methyl ester at δ = 3.67 ppm was observed (>99% *ee*).

Methyl (3-Indolyl)glycinate [(*R*)-8] and Methyl 2-Methoxyindoloacetate (9): Concentrated HCl (0.1 mL) was added to a solution of (*R*)-**4** (48.0 mg, 0.10 mmol) in a mixture of THF (3 mL) and MeOH (2 mL) at 0 °C. After stirring for 2 h at 0 °C and 30 min at room temperature, an excess amount of a saturated solution of Na_2CO_3 was added, and the products were extracted with EtOAc. Chromatography (PE/EtOAc, 3:1; then EtOAc; then EtOAc/MeOH, 88:12) gave (*R*)-**8** and racemic **9**. (*R*)-**8**: 2.9 mg, 0.014 mmol, 14%, glass. $[a]_D$ = –126 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (br., 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.40 (d, J = 8.1 Hz, 1 H), 7.1–7.3 (m, 3 H), 4.96, (br., 1 H), 3.74 (s, 3 H) ppm. The *ee* was determined as described for (*S*)-**8**: 3.70 ppm (major) and 3.67 ppm (82% *ee*). **9**: 19.0 mg, 0.077 mmol, 77%, solid, m.p. 124–126 °C. $[a]_D$ = 0 (c = 0.2, $CHCl_3$). HPLC (AD; 2-propanol/heptane, 80:20): 0% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (br. s, 1 H), 7.81, (d, J = 8.0 Hz, 1 H); 7.15–7.40 (m, 4 H); 5.16 (s, 1 H); 3.76 (s, 3 H); 3.56 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 136.1, 125.6, 123.9, 122.5, 120.1, 119.5, 111.15, 56.77, 52.08 ppm. HRMS (FAB): calcd. for $C_{12}H_{14}NO_3$ [M + H] 220.0996; found 220.0967.

3-(Indolyl)glycine [(*S*)-10]: LiOH·H_2O (25.2 mg, 0.60 mmol) in water (0.4 mL) was added to a solution of (*S*)-**8** (61.5 mg, 0.30 mmol) in MeOH (1.5 mL). After stirring at room temperature for 2 h, acetic acid (45 μL, 0.8 mmol) was added, and the mixture was kept at 4 °C overnight. Filtration and drying in vacuo gave (*S*)-**10** (53.6 mg, 0.282 mmol, 94%). M.p. 204–206 °C; m.p. (racemate) 221 °C (decomp.).[24] $[a]_D$ = +111 (c = 0.20, H_2O). HPLC (Chirobiotic T; methanol/water, 60:40): t_R = 4.20 (major), 5.85 min; ≥98% *ee*. ^{1}H NMR (400 MHz, D_2O): δ = 7.58 (d, J = 8.0 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 1 H), 7.40 (s, 1 H), 7.19 (m, 1 H), 7.10 (m, 1 H), 5.03 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 169.6, 136.5, 126.5, 125.0, 121.6, 120.1, 118.9, 111.8, 111.7, 51.59 ppm.

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