4-Substituted Prolyl Sulfonamides as Enantioselective Organocatalysts for Aldol Reactions

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Abstract: A series of prolyl and 4-substituted prolyl sulfonamides were prepared and were evaluated as organocatalysts of asymmetric aldol reaction. Using prolyl methanesulfonamide, 4-benzyloxy-prolyl methanesulfonamide and toluenesulfonamide and 4-hydroxy-prolyl toluenesulfonamide the aldol product was obtained in much higher enantiomeric excess (ee) in comparison to that observed using proline itself. In addition, these new catalysts may be used in lower sub-stoichiometric amounts than proline, because of their improved solubility in organic solvents.

Key words: aldol reactions, amino acids, asymmetric catalysis, catalysis, sulfonamides

Organocatalysis is a rapidly expanding field of asymmetric catalysis that promises interesting applications for the synthesis of a variety of enantiomerically pure chemical products.[1] Small organic molecules from the chiral pool may efficiently catalyze numerous classical organic reactions. Among the organocatalysts reported so far, the natural amino acid proline has found wide applications for the catalysis of enantioselective transformations.[2] At first, Hajos, Parrish, Eder, Sauer and Wiechert employed proline for the catalysis of an intramolecular aldol reaction.[3] Since the work of List, Lerner and Barbas,[4] who studied the proline catalyzed direct intermolecular aldol reaction, a series of investigations have demonstrated that proline may efficiently catalyze Michael,[5] Mannich,[6] α-amination,[7] and α-aminoxylation reactions.[8] The aim of this work was to develop proline-based catalysts with improved catalytic properties for aldol reactions.[9]

The pyrrolidine ring of proline seems to be a suitable template for the construction of new organocatalysts. It has been proposed that the asymmetric aldol reaction catalyzed by proline occurs via an enamine mechanism.[4] Both the secondary amine of the pyrrolidine ring and the carboxylic acid functionalities are required for the catalytic activity. In medicinal chemistry bioisosteric replacements in lead substances have frequently been utilized in order to retain or enhance potencies and to simultaneously improve pharmacokinetics properties.[10] Among the carboxylic acid bioisosters, the acyl sulfonamide functionality was selected in order to replace the carboxylic acid group of proline. The rationale behind our design was to replace the carboxyl group of proline with a group, which fulfills the following two criteria: (a) it contains an acidic hydrogen with a pK_a value similar to that of the carboxyl group, and (b) it allows for structural elongations and modifications.

Very recently, it has been demonstrated that a proline-derived tetrazole successfully catalyzes asymmetric Mannich, *O*-nitroso aldol/Michael and aldol reactions.[11–13] However, in the aldol reaction the tetrazole derivative did not lead to an increase in enantioselectivity compared to proline.[14] When our work was in progress, Ley[13] and Berkessel[15] reported an aldol reaction catalyzed by prolyl methane- and *p*-toluenesulfonamide. Thus, the present article focuses on our results obtained with 4-substituted-prolyl sulfonamides.

(2*S*,4*R*)-*tert*-Butoxycarbonyl-4-benzyloxy-L-proline (**1**) was coupled with methanesulfonamide and *p*-toluenesulfonamide using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a coupling reagent in the presence of an equivalent amount of 4-(dimethylamino)pyridine (DMAP)[16] to produce derivatives **2a,b** (Scheme 1). Removal of the Boc protecting group from **2a,b** by treatment with HCl in MeOH produced derivatives **3a,b**, respectively. In addition, 4-hydroxy derivatives **5a,b** were prepared after catalytic hydrogenation of compounds **2a,b** and Boc removal. Reaction of **4a** with (1*S*)-10-camphorsulfonyl chloride in the presence of *N*-methylmorpholine (NMM) and anhydrous THF afforded the protected sulfonate **6**, which was converted to the deprotected derivative **7** (Scheme 1). Prolyl sulfonamides **10a**–**d** were prepared in a similar manner starting from *tert*-butoxycarbonyl-L-proline (**8**) (Scheme 2). The enantiomer of **10b**, compound **11**, was also prepared.

(*S*)-2-[(*N*-Methanesulfonyl)aminomethyl]pyrrolidine (**15**) was also prepared as depicted in Scheme 3. *tert*-Butoxycarbonyl-L-prolinol (**12**), obtained from the corresponding proline,[17] was converted into azide **13**.[18] Reduction of the azide group by H_2 in the presence of 10% Pd/C, followed by treatment with methanesulfonyl chloride and deprotection, led to derivative **15**.

The aldol reaction serves as an excellent comparison of prolyl sulfonamides with proline, since it has been thoroughly investigated by Barbas and coworkers using proline as the catalyst.[19] Therefore, the reaction of 4-nitrobenzaldehyde with acetone was used as a model reaction to test the efficacy of our new catalysts against proline itself. The results obtained using prolyl sulfonamides as catalysts are summarized in Table 1.

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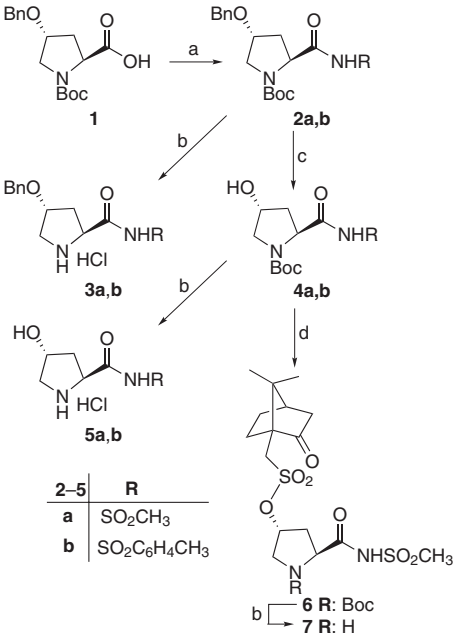
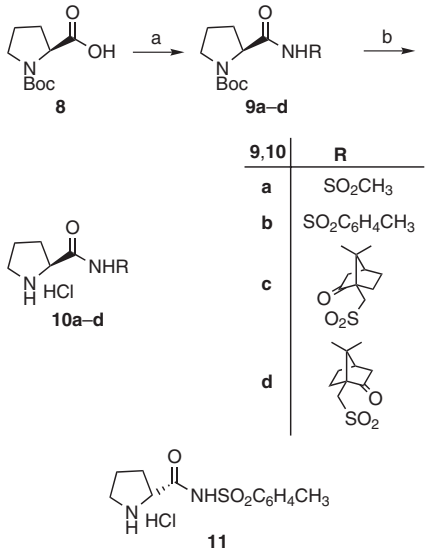
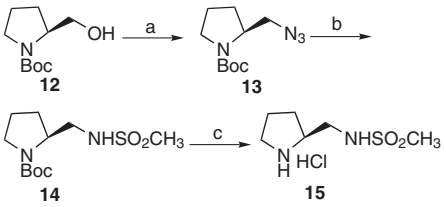


Scheme 1 *Reagents and conditions*: (a) Methanesulfonamide or *para*-toluenesulfonamide, DCC, DMAP, r.t., 18 h, 63% for **2a** and 80% for **2b**; (b) 5 N HCl–MeOH, r.t., 1 h, 85–95%; (c) H_2, 10% Pd/C, 1,4-dioxane, r.t., 24 h, 89% for **4a** and 72% for **4b**; (d) (1*S*)-10-camphorsulfonyl chloride, NMM, THF, 0 °C, 30 min, r.t., 18 h, 89%.



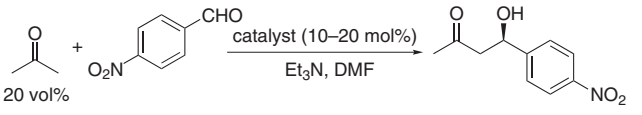
Scheme 2 *Reagents and conditions*: (a) Methanesulfonamide or *para*-toluenesulfonamide or (1*R*)-10-camphorsulfonamide or (1*S*)-10-camphorsulfonamide, DCC, DMAP, r.t., 18 h, 58–67%; (b) 5 N HCl–MeOH, r.t., 1 h, 94–96%.

Under the conditions employed, using both 4-benzyloxy derivatives **3a** and **3b** the product of the aldol reaction was isolated in the same chemical yield but in significantly higher ee (entries 1–4) than those observed using proline itself or proline hydrochloride in the presence of Et_3N (entries 15 and 16). However, among the derivatives **5a** and **5b** containing the hydroxyl group at the 4-position, only the *para*-toluenesulfonamide derivative led to a product of high ee (entry 6). 4-Camphorsulfonyloxy derivative **7**



Scheme 3 *Reagents and conditions*: (a) (i) MsCl, Et_3N, CH_2Cl_2, r.t., 3 h, 100% (ii) NaN_3, DMF, 60 °C, 18 h, 55%; (b) (i) H_2, 10% Pd/C, THF, r.t., 2 h, 100% (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min, r.t., 24 h, 63%; (c) 5 N HCl–MeOH, r.t., 1 h, 96%.

Table 1 Direct Asymmetric Aldol Reaction of Acetone and 4-Nitrobenzaldehyde Using Various Proline-Based Catalysts.



Entry	Catalyst	Catalyst loading (%)	Yield (%)[a]	ee (%)[b]
1	**3a**	20	61	88
2	**3a**	10	63	89
3	**3b**	20	60	89
4	**3b**	10	62	87
5	**5a**	20	58	50
6	**5b**	20	63	90
7	**5b**	10	63	89
8	**7**	20	22	63
9	**10a**	20	81	85
10	**10b**	20	62	76
11	**10c**	20	47	63
12	**10d**	20	78	60
13	**11**	20	58	74[c]
14	**15**	20	12	23
15	L-Pro[d]	20	63	69
16	L-Pro·HCl	20	60	63

[a] Isolated yields after column chromatography.
[b] The ee was determined by HPLC on a Daicel Chiralpak AD-RH column.
[c] (*S*)-Enantiomer of the aldol product.
[d] In the absence of Et_3N.

(entry 8) produced product in low yield and moderate ee. Methanesulfonamide and *para*-toluenesulfonamide derivatives **10a** and **10b** (entries 9 and 10) led to 85% and 76% ee, respectively, while sulfonamides **10c** and **10d** based on the bulky chiral (*R*)- or (*S*)-camphor moiety (entries 11 and 12) led to results similar to those obtained by using proline. The enantiomer of **10b**, compound **11**, (entry 13)

produced the (*S*)-aldol product in similar yield and ee. A dramatic decrease in both yield and ee was observed, when derivative **15** (entry 14) was tested, indicating the importance of the presence of the carbonyl group. Comparing the results obtained by using acyl sulfonamide **10a** and simple sulfonamide **15**, it is obvious that the presence of the carbonyl group is necessary, possibly contributing to the acidity of the sulfonamide hydrogen. It should be noticed that the rather poor solubility of proline in many solvents requires its use in catalytic amounts up to 30 mol%. Prolyl sulfonamides exhibit better solubility properties allowing the employment of low sub-stoichiometric amounts. For example, catalysts **3a**, **3b** and **5b** were used in 10 mol% amount (entries 2, 4 and 7, respectively) without affecting the isolated yield and the enantiopurity of the aldol product.

Ley et al. reported that the product of the aldol reaction between acetone and 4-nitrobenzaldehyde was isolated in 52% yield and 87% ee, using catalyst **10a** (20% catalyst loading) and DMSO as the reaction solvent.[13] Higher yields but lower ee values were observed using other reaction solvents instead of DMSO.[13] According to Berkessel et al., catalyst **10b** (30% catalyst loading) led to the product of the same aldol reaction in 98% yield and 93% ee, when DMSO or acetone was used as the solvent.[15] Slightly higher ee values but lower yields were observed when they used 5–10% catalyst loading and prolonged reaction time.[15]

In the case of proline-catalyzed aldol reaction, the enantioselectivity has been explained with a metal free version of a Zimmerman–Traxler type transition state (Figure 1, **A**).[4] Computational studies have led to a better understanding of the catalytic mechanism.[20] In accordance with the transition state proposed for proline itself, a similar framework may be proposed for prolyl sulfonamides (Figure 1, **B**). In this case the N-substituent of sulfonamide possesses a position enhancing *re*-facial attack.

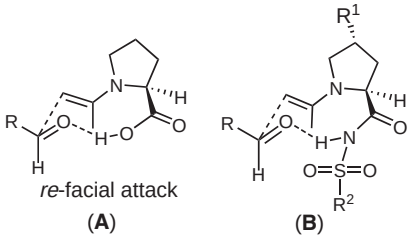


Figure 1 Transition state of the proline (**A**) and the prolyl sulfonamide (**B**) catalyzed aldol reaction.

In conclusion, a series of prolyl sulfonamides has been prepared and it has been demonstrated that some of them efficiently catalyze the aldol reaction. 4-Benzyloxyprolyl and 4-hydroxyprolyl sulfonamides **3a**,**b** and **5b** represent attractive alternatives to proline offering: (a) higher enantioselectivity (up to 20%) in comparison to proline, (b) a decrease of the required catalytic amount (10%) in comparison to proline (20–30%) and (c) better solubility in organic solvents.

Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a Perkin Elmer 841 polarimeter using a 10 cm cell. NMR spectra were recorded on a Varian Mercury 200 MHz spectrometer. Where rotamers are apparent and resolved, peaks for major and minor rotamers are reported. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70–230 or 230–400 mesh) for column chromatography were purchased from Merck. Visualisation of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin stains. THF and 1,4-dioxane were freshly distilled from sodium-benzophenone ketyl radical under an Ar atmosphere and immediately prior to use. Et_2O was treated with $CaCl_2$ and stored over Na. All other solvents and chemicals were of reagent grade and used without further purification. Elemental analyses were obtained in a Perkin-Elmer 2400 instrument from vacuum-dried samples (over P_2O_5 at 1–2 mm Hg, 48 h at r.t.) and were within ±0.4% of theoretical values.

Preparation of the Protected Acyl Sulfonamides 2a,b and 9a–d; General Procedure

To a solution of Boc-L-HyPro(Bn)-OH (**1**) or Boc-L-Pro-OH (**8**) (1.00 mmol) in anhyd CH_2Cl_2 (16 mL) were added the corresponding sulfonamide (1 mmol) followed by DCC (206 mg, 1.00 mmol) and DMAP (122 mg, 1.00 mmol). The mixture was stirred for 18 h. The dicyclohexylurea was filtered off, the solvent was removed and the residue was purified by column chromatography using initially a mixture of EtOAc–petroleum ether (1:1) and subsequently a mixture of $CHCl_3$–MeOH (9:1) as eluents to give **2a**,**b** and **9a**–**d**, respectively.

(2*S*,4*R*)-*tert*-Butyl 4-(Benzyloxy)-2-(methylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (2a)

Colorless oil (251 mg, 63%); $[\alpha]_D^{25}$ –60.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 [br s, 9 H, $C(CH_3)_3$], 2.05–2.60 (m, 2 H, C*H*$_2$CH), 3.25 (s, 3 H, SO_2CH_3), 3.40–3.90 (m, 2 H, CH_2N), 4.15 (m, 1 H, CHN), 4.25–4.60 (m, 3 H, C*H*$_2$Ph, OCH), 7.10–7.48 (m, 5 H, Ph), 9.80 (m, 0.4 H, NH), 10.35 (m, 0.6 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.1, 33.4, 33.5, 40.9, 41.3, 49.0, 51.9, 59.0, 70.7, 71.1, 75.7, 81.5, 127.5, 127.7, 128.3, 137.4, 154.2, 156.0, 157.2, 172.1.

Anal. Calcd for $C_{18}H_{26}N_2O_6S$ (398.47): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.50; H, 6.70; N, 6.90.

(2*S*,4*R*)-*tert*-Butyl 4-(Benzyloxy)-2-(tosylcarbamoyl)pyrrolidine-1-carboxylate (2b)

Colorless oil (380 mg, 80%); $[\alpha]_D^{25}$ –64.7 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 [br s, 9 H, $C(CH_3)_3$], 2.05 (m, 1 H, CH*H*CH), 2.20–2.50 (m, 4 H, C*H*HCH, CH_3), 3.25–3.77 (m, 2 H, CH_2N), 4.10 (m, 1 H, CHN), 4.20–4.60 (m, 3 H, OCH, C*H*$_2$Ph), 7.09–7.50 (m, 7 H, Ph, C_6H_4), 7.73–8.08 (m, 2 H, C_6H_4), 10.00 (m, 0.6 H, NH), 10.60 (m, 0.4 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 21.3, 27.6, 27.9, 32.7, 33.4, 48.8, 51.6, 58.8, 59.9, 70.5, 70.9, 75.6, 76.1, 80.8, 81.4, 127.3, 127.5, 127.9, 128.1, 129.2, 135.5, 137.7, 144.5, 144.7, 154.0, 156.1, 157.2, 169.4, 170.7.

Anal. Calcd for $C_{24}H_{30}N_2O_6S$ (474.57): C, 60.74; H, 6.37; N, 5.90. Found: C, 60.80; H, 6.30; N, 5.85.

(*S*)-*tert*-Butyl 2-(Methylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (9a)

Colorless oil (170 mg, 58%); $[\alpha]_D^{25}$ –125.2 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 [br s, 9 H, $C(CH_3)_3$], 1.75–2.20 (m, 3 H, C*H*$_2$CH*H*CH), 2.42 (m, 1 H, C*H*HCH), 3.20 (s, 3 H, SO_2CH_3), 3.30–3.60 (m, 2 H, CH_2N), 4.30 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.3, 28.2, 30.8, 41.1, 47.2, 60.4, 81.6, 156.4, 171.3.

Anal. Calcd for $C_{11}H_{20}N_2O_5S$ (292.35): C, 45.19; H, 6.90; N, 9.58. Found: C, 45.05; H, 7.20; N, 9.60.

(*S*)-*tert*-Butyl 2-(Tosylcarbamoyl)pyrrolidine-1-carboxylate (9b)

White solid (220 mg, 60%); mp 201–203 °C; $[\alpha]_D^{25}$ –117.5 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 [br s, 9 H, $C(CH_3)_3$], 1.70–2.25 (m, 4 H, CH_2CH_2CH), 2.40 (s, 3 H, CH_3), 3.10–3.60 (m, 2 H, CH_2N), 4.10 (m, 1 H, CH), 7.30 (d, *J* = 8.7 Hz, 2 H, C_6H_4), 7.90 (d, *J* = 8.7 Hz, 2 H, C_6H_4), 9.58 (m, 0.3 H, NH), 10.70 (m, 0.7 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5, 24.2, 24.8, 28.1, 30.5, 33.7, 47.1, 49.0, 60.2, 61.0, 81.5, 128.2, 129.3, 135.7, 144.7, 157.1, 169.3.

Anal. Calcd for $C_{17}H_{24}N_2O_5S$ (368.45): C, 55.42; H, 6.57; N, 7.60. Found: C, 55.40; H, 6.72; N, 7.70.

(2*S*)-*tert*-Butyl 2-{[((1*R*,4*S*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyl]carbamoyl}pyrrolidine-1-carboxylate (9c)

Colorless oil (262 mg, 61%); $[\alpha]_D^{25}$ –91.8 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 1.44 [br s, 9 H, $C(CH_3)_3$], 1.65–2.52 (series of m, 11 H, 5 × CH_2, CH), 3.00–3.90 (m, 4 H, CH_2SO_2, CH_2N), 4.38 (m, 1 H, CHN).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5, 19.8, 24.2, 24.9, 26.4, 26.9, 28.2, 30.5, 42.5, 42.9, 47.1, 48.4, 48.8, 50.0, 53.5, 58.4, 59.1, 81.4, 156.0, 172.0, 217.3.

Anal. Calcd for $C_{20}H_{32}N_2O_6S$ (428.54): C, 56.05; H, 7.53; N, 6.54. Found: C, 56.40; H, 7.52; N, 6.60.

(2*S*)-*tert*-Butyl 2-{[((1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyl]carbamoyl}pyrrolidine-1-carboxylate (9d)

Colorless oil (286 mg, 67%); $[\alpha]_D^{25}$ –51.3 (*c* = 1.2, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.47 [br s, 9 H, $C(CH_3)_3$], 1.60–2.58 (series of m, 11 H, 5 × CH_2, CH), 3.10–3.95 (m, 4 H, CH_2SO_2, CH_2N), 4.30 (m, 1 H, CHN).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5, 19.7, 24.4, 25.0, 26.7, 27.2, 28.4, 30.5, 42.4, 42.7, 47.1, 48.4, 48.5, 50.2, 53.5, 58.5, 59.2, 81.6, 156.3, 172.4, 217.5.

Anal. Calcd for $C_{20}H_{32}N_2O_6S$ (428.54): C, 56.05; H, 7.53; N, 6.54. Found: C, 56.35; H, 7.55; N, 6.59.

Removal of Benzyl Group from the Protected Acyl Sulfonamides 2a,b; General Procedure

To a stirred solution of **2a,b** (1.00 mmol) in anhyd 1,4-dioxane (15 mL), 10% Pd/C (50 mg) was added. The reaction mixture was stirred under H_2 for 24 h at r.t. After filtration through a pad of Celite, the solvent was removed and the residue was purified by column chromatography using a mixture of $CHCl_3$–MeOH (9:1) as eluent to give **4a,b**.

(2*S*,4*R*)-*tert*-Butyl 4-Hydroxy-2-(methylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (4a)

White solid (foam) (274 mg, 89%); mp 92–94 °C; $[\alpha]_D^{25}$ –97.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 [br s, 9 H, $C(CH_3)_3$], 1.95–2.50 (m, 2 H, CH_2CH), 3.10–3.75 (m, 5 H, SO_2CH_3, CH_2N), 4.20–4.60 (m, 2 H, CHN, OCH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3, 37.8, 39.0, 40.9, 41.3, 54.9, 58.2, 60.2, 69.0, 69.7, 81.4, 81.7, 154.6, 155.8, 173.5.

Anal. Calcd for $C_{11}H_{20}N_2O_6S$ (308.35): C, 42.85; H, 6.54; N, 9.08. Found: C, 42.90; H, 6.50; N, 9.20.

(2*S*,4*R*)-*tert*-Butyl 4-Hydroxy-2-(tosylcarbamoyl)pyrrolidine-1-carboxylate (4b)

White solid (277 mg, 72%); mp 213–215 °C; $[\alpha]_D^{25}$ –91.2 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 [br s, 9 H, $C(CH_3)_3$], 1.70–2.10 (m, 2 H, CH_2CH), 2.43 (s, 3 H, CH_3), 3.30–3.60 (m, 2 H, CH_2N), 3.71 (d, *J* = 2.2 Hz, 1 H, OH), 4.25–4.55 (m, 2 H, CHN, OCH), 7.32 (d, *J* = 7.4 Hz, 2 H, C_6H_4), 7.94 (d, *J* = 7.8 Hz, 2 H, C_6H_4).

^{13}C NMR (50 MHz, CD_3OD): δ = 21.5, 28.2, 28.6, 38.9, 39.9, 55.7, 55.9, 60.2, 60.4, 69.8, 70.6, 81.8, 129.1, 129.4, 130.4, 130.6, 137.6, 146.3, 155.5, 156.1, 173.1.

Anal. Calcd for $C_{17}H_{24}N_2O_6S$ (384.45): C, 53.11; H, 6.29; N, 7.29. Found: C, 53.12; H, 6.30; N, 7.32.

(2*S*,4*R*)-*tert*-Butyl 4-{[(1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyloxy}-2-(methylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (6)

To a stirred solution of **4a** (308 mg, 1.00 mmol) in anhyd THF (12 mL) were added NMM (0.28 mL, 2.50 mmol) and (1*S*)-(+)-camphor-10-sulfonyl chloride (315 mg, 1.25 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at r.t. for 3 h. NMM (75 μL, 0.67 mmol) and (1*S*)-(+)-camphor-10-sulfonyl chloride (150 mg, 0.60 mmol) were then added and the stirring was continued at r.t. for 18 h. The solvent was removed, H_2O (15 mL) was added and the product was then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ and H_2O and dried (Na_2SO_4), and the solvent was evaporated. The product was purified by column chromatography using a mixture of $CHCl_3$–MeOH (9:1) as eluent to give **6** as a colorless oil (464 mg, 89%); $[\alpha]_D^{25}$–2.2 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.75–2.80 (series of m, 24 H, 5 × CH_3, 4 × CH_2, CH), 3.00 (d, *J* = 16 Hz, 1 H, C*H*HSO_2), 3.10–3.30 (m, 3 H, SO_2CH_3), 3.58 (d, *J* = 16 Hz, 1 H, CH*H*SO_2), 3.65–4.48 (m, 3 H, CHN, CH_2N), 5.29 (m, 1 H, OCH), 7.50 (m, 0.5 H, NH), 7.68 (m, 0.5 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5, 26.3, 26.7, 28.1, 28.4, 32.3, 34.5, 41.0, 42.3, 42.5, 46.5, 48.0, 53.0, 57.8, 60.0, 77.2, 78.9, 82.2, 155.6, 167.6, 214.4.

Anal. Calcd for $C_{21}H_{34}N_2O_9S_2$ (522.63): C, 48.26; H, 6.56; N, 5.36. Found: C, 48.52; H, 6.32; N, 5.60.

***N*-Boc-(*S*)-2-azidomethylpyrrolidine (13)**

To an ice-cold solution of *N*-Boc-L-prolinol (**12**) (201 mg, 1.00 mmol) in anhyd CH_2Cl_2 (4 mL) were added Et_3N (0.21 mL, 1.50 mmol) and methanesulfonyl chloride (116 μL, 1.50 mmol). The reaction mixture was stirred for 3 h. The solvent was removed, H_2O (7 mL) was added and the product was then extracted with EtOAc (3 × 5 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ and H_2O and dried (Na_2SO_4), and the solvent was evaporated. The intermediate mesylate was obtained in quantitative yield as a yellowish oil (279 mg) and used without additional purification. Thus, the mesylate was dissolved in anhyd DMF (5 mL) and NaN_3 (195 mg, 3.00 mmol) was added. The reaction mixture was heated to 60 °C for 18 h, allowed to cool to r.t. and the solvent was removed under reduced pressure. Subsequently, H_2O (10 mL) was added and the product was then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The product was purified by column chromatography using a mixture EtOAc–petroleum ether (7:3)

as eluent to give **13** as a colorless oil (125 mg, 55%); $[\alpha]_D^{25}$ –50.0 (*c* = 1.0, $CHCl_3$); [Lit.[21] $[\alpha]_D^{25}$ –49.5 (*c* = 1.16, $CHCl_3$)].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, $C(CH_3)$], 1.72–2.08 (m, 4 H, CH_2CH_2CH), 3.10–3.68 (m, 4 H, CH_2NHSO_2, CH_2N), 3.92 (m, 1 H, CH).

Anal. Calcd for $C_{10}H_{18}N_4O_2$ (226.28): C, 53.08; H, 8.02; N, 24.76. Found: C, 53.30; H, 8.00; N, 24.90.

N-Boc-(*S*)-2-(methanesulfonyl)methylpyrrolidine (14)

To a stirred solution of azide **13** (120 mg, 0.53 mmol) in anhyd THF (5 mL), 10% Pd/C (50 mg) was added. The reaction mixture was stirred under H_2 for 2 h at r.t. After filtration through a pad of Celite, the solvent was removed and H_2O (5 mL) was added. The pH of the aqueous phase was lowered to 2 with 1 M $KHSO_4$. The aqueous layer was washed with EtOAc (2 × 5 mL), and the pH was then adjusted to 13 with Na_2CO_3 (sat. solution). After extraction with EtOAc (6 × 5 mL), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate amine was obtained in quantitative yield as a yellowish oil (106 mg) and used without additional purification. Hence, *N*-Boc-(*S*)-aminomethylpyrrolidine (106 mg, 0.53 mmol) was dissolved in anhyd CH_2Cl_2 (4 mL), the solution was cooled to 0 °C and Et_3N (0.22 mL, 1.59 mmol) and methanesulfonyl chloride (82 μL, 1.06 mmol) were added. The mixture was stirred for 24 h at r.t. and then the solvent was removed under reduced pressure, H_2O (5 mL) was added and the product was then extracted with EtOAc (3 × 7 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ and H_2O and dried (Na_2SO_4), and the solvent was evaporated. The product was purified by column chromatography using a mixture of EtOAc–petroleum ether (8:2) as eluent to give **14** as a yellowish oil (175 mg, 63%); $[\alpha]_D^{25}$ –17.1 (*c* = 0.7, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 [br s, 9 H, $C(CH_3)_3$], 1.60–2.12 (m, 4 H, CH_2CH_2CH), 2.90 (s, 3 H, SO_2CH_3), 3.05–3.55 (m, 4 H, CH_2NHSO_2, CH_2N), 3.94 (m, 1 H, CH), 5.05 (m, 0.3 H, NH), 5.97 (m, 0.7 H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.7, 28.4, 29.3, 39.8, 47.2, 47.9, 56.8, 80.2, 156.2.

Anal. Calcd for $C_{11}H_{22}N_2O_4S$ (278.37): C, 47.46; H, 7.97; N, 10.06. Found: C, 47.41; H, 7.90; N, 10.12.

Removal of Boc Group from the Protected Acyl Sulfonamides 2a,b, 4a,b, 6, 9a–d, and from *N*-Boc-(*S*)-2-(methanesulfonyl)methylpyrrolidine (14); General Procedure

The *tert*-butoxycarbonyl groups of **2a,b**, **4a,b**, **6**, **9a–d**, and **14** (1.00 mmol) were removed by treatment with 5 N HCl in MeOH (7 mL, 35 mmol) for 1 h at r.t. After evaporation under reduced pressure to a small volume (1 mL), anhyd Et_2O was added (5 mL) and the precipitated product was afforded through decantation.

(2*S*,4*R*)-4-(Benzyloxy)-*N*-(methylsulfonyl)pyrrolidine-2-carboxamide Hydrochloride (3a)

White solid (285 mg, 85%); mp 190–192 °C; $[\alpha]_D^{25}$ +1.7 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 2.19 (m, 1 H, CH*H*CH), 2.71 (m, 1 H, C*H*HCH), 3.30 (s, 3 H, CH_3), 3.36–3.65 (m, 2 H, CH_2N), 4.36–4.55 (m, 2 H, CHN, OCH), 4.59 (s, 2 H, CH_2Ph), 7.23–7.45 (m, 5 H, Ph).

^{13}C NMR (50 MHz, CD_3OD): δ = 35.6, 36.4, 41.6, 52.4, 52.7, 59.5, 60.6, 72.0, 78.0, 78.3, 129.0, 129.1, 129.5, 138.7, 169.5.

MS (FAB): *m*/*z* (%) = 299 (78) [M + H$^+$].

Anal. Calcd for $C_{13}H_{19}ClN_2O_4S$ (334.82): C, 46.63; H, 5.72; N, 8.37. Found: C, 46.30; H, 5.99; N, 8.38.

(2*S*,4*R*)-4-(Benzyloxy)-*N*-tosylpyrrolidine-2-carboxamide Hydrochloride (3b)

White solid (352 mg, 94%); mp 187–189 °C; $[\alpha]_D^{25}$ +12.9 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 1.96 (m, 1 H, CH*H*CH), 2.43 (s, 3 H, CH_3), 2.72 (m, 1 H, C*H*HCH), 3.34–3.58 (m, 2 H, CH_2N), 4.30–4.52 (m, 2 H, CHN, OCH), 4.56 (s, 2 H, CH_2Ph), 7.20–7.47 (m, 7 H, Ph, C_6H_4), 7.93 (d, *J* = 8.0 Hz, 2 H, C_6H_4).

^{13}C NMR (50 MHz, CD_3OD): δ = 21.6, 36.4, 52.6, 60.5, 72.0, 78.2, 129.0, 129.1, 129.4, 129.5, 130.7, 137.1, 138.6, 146.8, 168.2.

MS (FAB): *m*/*z* (%) = 375 (100) [M + H$^+$].

Anal. Calcd for $C_{19}H_{23}ClN_2O_4S$ (410.91): C, 55.54; H, 5.64; N, 6.82. Found: C, 55.70; H, 6.00; N, 6.70.

(2*S*,4*R*)-4-Hydroxy-*N*-(methylsulfonyl)pyrrolidine-2-carboxamide Hydrochloride (5a)

White, sticky solid (hygroscopic) (232 mg, 95%); $[\alpha]_D^{25}$ –11.0 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 2.17 (m, 1 H, CH*H*CH), 2.47 (m, 1 H, C*H*HCH), 3.20–3.45 (m, 5 H, SO_2CH_3, CH_2N), 4.45–4.67 (m, 2 H, CHN, OCH).

^{13}C NMR (50 MHz, CD_3OD): δ = 38.5, 39.4, 41.6, 54.0, 55.0, 55.3, 59.4, 60.5, 70.6, 70.9, 169.9.

MS (ESI): *m*/*z* (%) = 209 (22) [M + H$^+$].

Anal. Calcd for $C_6H_{13}ClN_2O_4S$ (244.70): C, 29.45; H, 5.35; N, 11.45. Found: C, 29.30; H, 5.61; N, 11.48.

(2*S*,4*R*)-4-Hydroxy-*N*-tosylpyrrolidine-2-carboxamide Hydrochloride (5b)

White solid (302 mg, 94%); mp 123–125 °C; $[\alpha]_D^{25}$ +3.4 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 1.94 (m, 1 H, CH*H*CH), 2.34–2.58 (m, 4 H, CH_3, C*H*HCH), 3.22–3.45 (m, 2 H, CH_2N), 4.40–4.66 (m, 2 H, CHN, OCH), 7.40 (d, *J* = 8.0 Hz, 2 H, C_6H_4), 7.91 (d, *J* = 8.4 Hz, 2 H, C_6H_4).

^{13}C NMR (50 MHz, CD_3OD): δ = 21.6, 39.3, 55.1, 60.4, 70.9, 129.3, 130.7, 137.2, 146.6, 168.7.

MS (FAB): *m*/*z* (%) = 285 (100) [M + H$^+$].

Anal. Calcd for $C_{12}H_{17}ClN_2O_4S$ (320.79): C, 44.93; H, 5.34; N, 8.73. Found: C, 45.01; H, 5.70; N, 8.70.

(3*R*,5*S*)-5-(Methylsulfonylcarbamoyl)pyrrolidin-3-yl [(1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methanesulfonate Hydrochloride (7)

White solid (422 mg, 92%); mp 165–166 °C; $[\alpha]_D^{25}$ +31.6 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 0.90 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.40–2.95 (series of m, 9 H, 4 × CH_2, CH), 3.25–3.38 (m, 4 H, C*H*HSO_2, CH_3SO_2), 3.60–3.84 (m, 3 H, CH*H*SO_2, CH_2N), 4.60 (m, 1 H, CHN), 5.61 (m, 1 H, OCH).

^{13}C NMR (50 MHz, CD_3OD): δ = 19.7, 19.9, 26.4, 27.7, 37.5, 41.6, 43.4, 44.1, 47.3, 49.2, 53.5, 59.3, 60.7, 80.9, 169.2, 216.5.

MS (FAB): *m*/*z* (%) = 423 (50) [M + H$^+$].

Anal. Calcd for $C_{16}H_{27}ClN_2O_7S_2$ (458.98): C, 41.87; H, 5.93; N, 6.10. Found: C, 42.00; H, 6.30; N, 6.08.

(*S*)-*N*-(Methylsulfonyl)pyrrolidine-2-carboxamide Hydrochloride (10a)

Pale yellow, sticky solid (hygroscopic) (217 mg, 95%); $[\alpha]_D^{25}$ –11.2 (*c* = 0.5, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 1.95–2.25 (m, 3 H, CH_2CH*H*CH), 2.47 (m, 1 H, C*H*HCH), 3.31 (s, 3 H, SO_2CH_3), 3.35–3.50 (m, 2 H, CH_2N), 4.36 (m, 1 H, CH).

^{13}C NMR (50 MHz, CD_3OD): δ = 24.8, 30.4, 41.5, 47.5, 61.7, 169.7.

MS (FAB): *m*/*z* (%) = 193 (100) [M + H^+].

Anal. Calcd for $C_6H_{13}ClN_2O_3S$ (228.70): C, 31.51; H, 5.73; N, 12.25. Found: C, 31.44; H, 6.02; N, 12.27.

(*S*)-*N*-Tosylpyrrolidine-2-carboxamide Hydrochloride (10b)
Pale yellow, sticky solid (hygroscopic) (286 mg, 94%); $[\alpha]_D^{25}$ +5.3 (*c* = 0.57, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 1.10–2.15 (m, 4 H, CH_2CH_2CH), 2.43 (s, 3 H, CH_3), 3.20–3.40 (m, 2 H, CH_2N), 4.27 (m, 1 H, CH), 7.41 (d, *J* = 8.0 Hz, 2 H, C_6H_4), 7.92 (d, *J* = 8.2 Hz, 2 H, C_6H_4).

^{13}C NMR (50 MHz, CD_3OD): δ = 21.6, 24.7, 30.3, 34.7, 47.4, 61.5, 129.4, 130.7, 137.2, 146.8, 168.4.

MS (FAB): *m*/*z* (%) = 269 (100) [M + H^+].

Anal. Calcd for $C_{12}H_{17}ClN_2O_3S$ (304.79): C, 47.29; H, 5.62; N, 9.19. Found: C, 47.02; H, 5.98; N, 9.25.

(2*S*)-*N*-{[(1*R*,4*S*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyl}pyrrolidine-2-carboxamide Hydrochloride (10c)
Pale yellow, sticky solid (hygroscopic) (350 mg, 96%); $[\alpha]_D^{25}$ –35.1 (*c* = 0.58, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 0.89 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.40–2.58 (series of m, 11 H, 5 × CH_2, CH), 3.10 (d, *J* = 14 Hz, 1 H, C*H*HSO_2), 3.25–3.53 (m, 2 H, CH_2N), 3.95 (d, *J* = 15 Hz, 1 H, CH*H*SO_2), 4.44 (m, 1 H, CHN).

^{13}C NMR (50 MHz, CD_3OD): δ = 19.8, 19.9, 24.9, 26.3, 27.8, 30.2, 43.4, 44.0, 46.0, 47.6, 51.7, 59.7, 61.8, 169.6, 217.7.

MS (ESI): *m*/*z* (%) = 329 (100) [M + H^+].

Anal. Calcd for $C_{15}H_{25}ClN_2O_4S$ (364.89): C, 49.37; H, 6.91; N, 7.68. Found: C, 49.55; H, 7.28; N, 7.80.

(2*S*)-*N*-{[(1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyl}pyrrolidine-2-carboxamide Hydrochloride (10d)
Pale yellow, sticky solid (hygroscopic) (346 mg, 95%); $[\alpha]_D^{25}$ +39.6 (*c* = 0.50, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 0.89 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.18–2.59 (series of m, 11 H, 5 × CH_2, CH), 3.20–3.50 (m, 3 H, CH_2N, C*H*HSO_2), 3.92 (d, *J* = 15.4 Hz, 1 H, CH*H*SO_2), 4.36 (m, 1 H, CHN).

^{13}C NMR (50 MHz, CD_3OD): δ = 19.7, 19.9, 25.0, 26.4, 27.9, 30.3, 43.4, 43.6, 44.0, 47.6, 51.1, 59.8, 61.9, 170.4, 217.5.

Anal. Calcd for $C_{15}H_{25}ClN_2O_4S$ (364.89): C, 49.37; H, 6.91; N, 7.68. Found: C, 49.50; H, 7.27; N, 7.78.

(*S*)-2-[(*N*-Methanesulfonyl)aminomethyl]pyrrolidine Hydrochloride (15)
White, sticky solid (hygroscopic) (206 mg, 96%); $[\alpha]_D^{25}$ –11.0 (*c* = 1.0, MeOH).

^{1}H NMR (200 MHz, CD_3OD): δ = 1.79 (m, 1 H, C*H*HCH), 1.95–2.58 (m, 3 H, CH_2CH*H*CH), 3.02 (s, 3 H, SO_2CH_3), 3.20–3.55 (m, 4 H, CH_2NHSO_2, CH_2N), 3.73 (m, 1 H, CH).

^{13}C NMR (50 MHz, CD_3OD): δ = 24.1, 28.3, 39.6, 44.3, 46.6, 61.8.

MS (ESI): *m*/*z* (%) = 179 (100) [M + H^+].

Anal. Calcd for $C_6H_{15}ClN_2O_2S$ (214.71): C, 33.56; H, 7.04; N, 13.05. Found: C, 33.40; H, 7.40; N, 13.12.

Aldol Reactions between 4-Nitrobenzaldehyde and Acetone; General Procedure
To a mixture of anhyd DMF (1.60 mL) and anhyd acetone (0.40 mL) were added 4-nitrobenzaldehyde (30 mg, 0.20 mmol) followed by the catalysts **3a**,**b** or **5a,b** or **7** or **10a**–**d** or **15** (10–20 mol%) and an equivalent amount of Et_3N. The resulting mixture was stirred at r.t. for 18–24 h. Following aqueous workup with sat. NH_4Cl solution and extraction several times with EtOAc, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The product was purified by column chromatography using a mixture of EtOAc–petroleum ether (1:1) as eluent to give the pure aldol product as a yellowish oil. HPLC [Daicel Chiralpak AD-RH, CH_3CN–H_2O (30:70), flow rate 0.5 mL/min, λ = 254 nm]: t_R (major) = 15.99 min, t_R (minor) = 19.61 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 2.83 (m, 2 H), 3.56 (d, *J* = 3.2 Hz, 1 H), 5.25 (m, 1 H), 7.52 (d, *J* = 7.0 Hz, 2 H), 8.20 (d, *J* = 7.0 Hz, 2 H).

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