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. 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. At first, Hajos, Parrish, Eder, Sauer and Wiechert employed proline for the catalysis of an intramolecular aldol reaction. Since the work of List, Lerner and Barbas, who studied the proline catalyzed direct intermolecular aldol reaction, a series of investigations have demonstrated that proline may efficiently catalyze Michael, Mannich, \( \alpha \)-amination, and \( \alpha \)-amination reactions. The aim of this work was to develop proline-based catalysts with improved catalytic properties for aldol reactions.

The pyrrolidinyl 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. Both the secondary amine of the pyrrolidino 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. 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 carboxylic 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. However, in the aldol reaction the tetrazole derivative did not lead to an increase in enantioselectivity compared to proline. When our work was in progress, Ley and Berkessel 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.

\((2S,4R)-3\)-Butoxycarbonyl-4-benzyloxy-L-proline (1) was coupled with methanesulfonamide and \( p \)-toluenesulfonamide using 4-((dimethylamino)pyridine (DMAP) 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 (1S)-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-\((N\)-Methanesulfonfyl\)aminomethyl\)pyrrolidine (15) was also prepared as depicted in Scheme 3. \((S\)-Butoxycarbonyl-L-prolinol (12), obtained from the corresponding proline, was converted into azide 13. Reduction of the azide group by \( \text{H}_2 \) in the presence of 10% \( \text{Pd/C} \), 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. 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.
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) H₂, 10% Pd/C, dioxane, r.t., 24 h, 89% for 4a and 72% for 4b; (d) (1S)-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 (1R)-10-camphorsulfonamide or (1S)-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 Et₃N (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 (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 derivatve 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 aci-dity 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 Berkes 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 the transition state proposed for proline itself, a similar framework from the carbonyl activation 15.15

Preparation of the Protected Acyl Sulphonamides 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 CH2Cl2 (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 CHCl3–MeOH (9:1) as eluents to give 2a,b and 9a–d, respectively.

(2S,4R,7R)-tert-Butyl 4-(Benzoxyl)-2-(methylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (2a)

Colorless oil (251 mg, 63%); [α]D25 = 60.0 (c = 1.0, CHCl3).

1H NMR (200 MHz, CDCl3); δ = 1.44 [br s, 9 H, C(CH3)3], 2.05–2.60 (m, 2 H, CH2CH), 3.25 (s, 3 H, SO2CH3), 3.40–3.90 (m, 3 H, CH2CH), 4.15 (m, 1 H, CHN), 4.25–4.60 (m, 3 H, CH2PH, OCH), 7.10–7.48 (m, 5 H, Ph), 9.80 (m, 0.4 H, NH), 10.35 (m, 0.6 H, NH).

13C NMR (50 MHz, CDCl3); δ = 15.5, 37.0, 50.0, 51.5, 59.0, 70.7, 71.1, 75.7, 81.5, 127.5, 127.7, 127.8, 137.4, 154.2, 156.0, 157.2, 172.1.

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-Benzoxypyrrolyl 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 F254) 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. Et2O was treated with CaCl2 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 P2O5 at 1–2 mm Hg, 48 h at r.t.) and were within ±0.4% of theoretical values.

13C NMR (50 MHz, CDCl3): δ = 24.3, 28.2, 30.8, 41.1, 47.2, 60.4, 81.6, 154.6, 171.3.


Found: C, 54.00; H, 6.52; N, 9.20.

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

White solid (277 mg, 72%); mp 213–215 °C; [α]D 25 −91.2 (c = 1.0, CHCl3).

1H NMR (200 MHz, CDCl3): δ = 1.48 [br s, 9 H, C(CH3)3], 1.70–2.10 (m, 2 H, CH2CH2), 2.43 (s, 3 H, CH3), 3.30–3.60 (m, 2 H, CH2N), 3.71 (d, J = 2.2 Hz, 1 H, OH), 4.25–4.55 (m, 2 H, CH2N), OCH3), 7.32 (d, J = 7.4 Hz, 2 H, C6H4), 7.94 (d, J = 7.8 Hz, 2 H, C6H4).

13C NMR (50 MHz, CDCl3): δ = 19.5, 19.8, 24.2, 24.9, 26.4, 26.9, 28.2, 30.5, 42.9, 47.1, 48.4, 48.8, 50.0, 53.5, 58.4, 59.1, 81.4, 156.0, 172.0, 217.3.

Found: C, 54.42; H, 6.57; N, 7.60.

Anal. Calcd for C20H32N2O6S (428.54): C, 56.05; H, 7.53; N, 6.54.

13C NMR (50 MHz, CD3OD): δ = 19.5, 21.7, 22.4, 24.9, 26.4, 26.9, 28.2, 30.5, 32.3, 38.9, 40.9, 41.3, 50.0, 53.5, 58.4, 59.1, 81.4, 146.3, 155.5, 156.1, 173.1.

Found: C, 55.40; H, 6.72; N, 7.70.

Anal. Calcd for C20H32N2O6S (428.54): C, 56.05; H, 7.53; N, 6.54.

13C NMR (50 MHz, CDCl3): δ = 0.87 (s, 3 H, CH3), 1.01 (s, 3 H, CH3), 1.44 [br s, 9 H, C(CH3)3], 1.65–2.52 (series of m, 11 H, 5 × CH2, CH3), 3.00–3.90 (m, 4 H, CH2SO2, CH2N), 4.38 (m, 1 H, CHN).


Found: C, 45.05; H, 7.20; N, 9.60.

1H NMR (200 MHz, CDCl3): δ = 0.87 (s, 3 H, CH3), 1.01 (s, 3 H, CH3), 1.44 [br s, 9 H, C(CH3)3], 1.65–2.52 (series of m, 11 H, 5 × CH2, CH3), 3.00–3.90 (m, 4 H, CH2SO2, CH2N), 4.38 (m, 1 H, CHN).

Found: C, 45.19; H, 6.90; N, 9.08.

(2S,4R)-tert-Butyl 4-Hydroxy-2-(tosylcarbamoyl)pyrroline-1-carboxylate (4a)

White solid (279 mg) and used without additional purification. The product was evaporated. The intermediate mesylate was obtained in quantitative yield as a yellowish oil (279 mg) and used without additional purification. The solvent was removed under reduced pressure. Subsequently, H2O (10 mL) and NaN3 (195 mg, 3.00 mmol) was added. The reaction mixture was stirred for 3 h. The solvent was removed, H2O (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 KHSO4 and H2O and dried (Na2SO4), and the solvent was evaporated. The product was purified by column chromatography using a mixture of CHCl3–MeOH (9:1) as eluent to give 6 as a colorless oil (464 mg, 89%); [α]D 25 −91.2 (c = 1.0, MeOH).

1H NMR (200 MHz, CDCl3): δ = 0.75–2.80 (series of m, 24 H, 5 × CH2, CH3, 4 × CH2, CH3), 3.00 (d, J = 16 Hz, 1 H, CH3SO2), 3.10–3.30 (m, 3 H, SO2CH3), 3.58 (d, J = 16 Hz, 1 H, CHHSO2), 3.65–4.48 (m, 3 H, CHN, CHN), 5.29 (m, 1 H, OCH), 7.50 (m, 0.5 H, NH), 7.68 (m, 0.5 H, NH).

13C NMR (50 MHz, CDCl3): 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, 50.0, 53.7, 58.0, 60.0, 77.2, 78.9, 82.2, 155.6, 167.6, 214.4.

Found: C, 47.52; H, 6.32; 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-t-prolinol (12) (201 mg, 1.00 mmol) in anhyd CH2Cl2 (4 mL) were added Et3N (0.21 mL, 1.50 mmol) and methanesulfonyl chloride (116 mL, 1.50 mmol). The reaction mixture was stirred for 3 h. The solvent was removed, H2O (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 KHSO4 and H2O and dried (Na2SO4), 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 NaN3 (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, H2O (10 mL) was added and the product was then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na2SO4), and the solvent was evaporated. The product was purified by column chromatography using a mixture of EtOAc–petroleum ether (7:3)
as eluent to give 13 as a colorless oil (125 mg, 55%); \([\alpha]_D^{25} -50.0 \text{ (c = 1.0, CHCl}_3)\); \([\text{Lit.}^{21}\] \([\alpha]_D^{25} -49.5 \text{ (c = 1.16, CHCl}_3)\).

1H NMR (200 MHz, CDCl3); \(\delta = 1.48 \text{ [s, 9 H, C(CH}_3}])_3\), 1.72–2.08 (m, 4 H, CH2CH2CH2, 3.10–3.08 (m, 4 H, CH2NHSO2CH2N), 3.92 (m, 1 H, CH). Anal. Caled for C13H19ClN2O4S (334.82): C, 46.63; H, 5.72; N, 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. Caled for C13H19ClN2O4S (334.82): C, 46.63; H, 5.72; N, 60.6, 72.0, 78.0, 78.3, 129.0, 129.1, 129.5, 138.7, 169.5.

(2S,AR)-4-(Benzylxyl)-N-(methylsulfonfyl)pyrrolidine-2-carboxamide Hydrochloride (3b)

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

1H NMR (200 MHz, CD3OD); \(\delta = 1.96 \text{ (m, 1 H, CHHCH)}, 2.43 \text{ (s, 3 H, CH)}, 2.72 \text{ (m, 1 H, CH/HCH)}, 3.34–3.58 \text{ (m, 2 H, CH2N)}, 4.30–4.52 (m, 2 H, CHN, OCH), 4.56 (s, 2 H, CH2Ph), 7.20–7.47 (m, 7 H, Ph, CH2), 7.93 (d, \(J = 8.0 \text{ Hz, 2 H, CH}_2\)).

13C NMR (50 MHz, CD3OD); \(\delta = 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. Caled for C5H12N2O4S (410.91): C, 55.54; H, 5.64; N, 6.82. Found: C, 55.70; H, 6.00; N, 6.70.

(2S,AR)-4-Hydroxy-N-(methylsulfonfyl)pyrrolidine-2-carboxamide Hydrochloride (5a)

White, sticky solid (hyperscopic) (232 mg, 95%); \([\alpha]_D^{25} -11.0 \text{ (c = 1.0, MeOH)}\).

1H NMR (200 MHz, CD3OD); \(\delta = 2.17 \text{ (m, 1 H, CHHCH)}, 2.47 \text{ (m, 1 H, CH/HCH)}, 3.20–3.45 (m, 5 H, SO2CH2CH2N), 4.45–4.67 \text{ (m, 2 H, CHN, OCH)}.

13C NMR (50 MHz, CD3OD); \(\delta = 38.5, 39.4, 41.6, 54.0, 55.0, 55.3, 59.4, 60.5, 70.6, 70.9, 169.9.

MS (EI): \(m/z\) (%) = 209 (22) [M + H].

Anal. Caled for C3H7N2O4S (244.70): C, 29.45; H, 5.35; N, 11.45. Found: C, 29.30; H, 5.61; N, 11.48.

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

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

1H NMR (200 MHz, CD3OD); \(\delta = 1.94 \text{ (m, 1 H, CHHCH)}, 2.34–2.58 \text{ (m, 4 H, CH2CH2CH2N), 3.22–3.45} \text{ (m, 2 H, CH2N)}, 4.40–4.66 \text{ (m, 2 H, CHN, OCH)}.

13C NMR (50 MHz, CD3OD); \(\delta = 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. Caled for C23H25ClN2O4S (437.09): C, 44.93; H, 5.34; N, 8.73. Found: C, 45.01; H, 5.70; N, 8.70.

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

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

1H NMR (200 MHz, CD3OD); \(\delta = 0.90 \text{ (s, 3 H, CH)}, 1.09 \text{ (s, 3 H, CH)}, 1.40–2.95 \text{ (series of m, 9 H, 4 × CH2CH2), 3.25–3.38} \text{ (m, 4 H, CH2HOSO2CH2N), 3.60–3.84} \text{ (m, 3 H, CH2HOSO2CH2N), 4.60 \text{ (m, 1 H, CHN), 5.61} \text{ (m, 1 H, OCH)}}.

13C NMR (50 MHz, CD3OD); \(\delta = 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. Caled for C23H25ClN2O4S (437.09): C, 41.87; H, 5.93; N, 6.10. Found: C, 42.00; H, 6.30; N, 6.08.

(5)-N-(Methylsulfonfyl)pyrrolidine-2-carboxamide Hydrochloride (10a)

Pale yellow, sticky solid (hyperscopic) (217 mg, 95%); \([\alpha]_D^{25} -11.2 \text{ (c = 0.5, MeOH)}\).
Pale yellow, sticky solid (hygroscopic) (286 mg, 94%; [α]D 25 + 43.5 (c = 0.57, MeOH).

1H NMR (200 MHz, CD3OD): δ = 1.10–2.15 (m, 4 H, CH2CH2CH), 2.43 (s, 3 H, CH3), 3.20–3.40 (m, 2 H, CH2N), 3.95 (d, J = 15 Hz, 1 H, CH), 7.41 (d, J = 8.2 Hz, 2 H, C6H4), 7.92 (d, J = 8.2 Hz, 2 H, C6H4).

13C NMR (50 MHz, CD3OD): δ = 21.6, 24.7, 30.3, 34.7, 47.4, 61.5, 129.4, 130.7, 137.2, 146.8, 168.4.

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

Anal. Calc. for C15H25ClN2O4S (364.89): C, 49.37; H, 6.91; N, 13.0; Cl, 11.0; S, 0.57, MeOH).

Pale yellow, sticky solid (hygroscopic) (510 mg, 94%); [α]D 25 + 43.5 (c = 0.57, MeOH).

1H NMR (200 MHz, CD3OD): δ = 1.10–2.15 (m, 4 H, CH2CH2CH), 2.43 (s, 3 H, CH3), 3.20–3.40 (m, 2 H, CH2N), 3.95 (d, J = 15 Hz, 1 H, CH), 7.41 (d, J = 8.2 Hz, 2 H, C6H4), 7.92 (d, J = 8.2 Hz, 2 H, C6H4).

13C NMR (50 MHz, CD3OD): δ = 21.6, 24.7, 30.3, 34.7, 47.4, 61.5, 129.4, 130.7, 137.2, 146.8, 168.4.

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

Anal. Calc. for C15H25ClN2O4S (364.89): C, 49.37; H, 6.91; N, 13.0; Cl, 11.0; S, 0.57, MeOH).

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,6 or 7 or 10a–d or 15 (10–20 mol%) and an equivalent amount of Et3N. The resulting mixture was stirred at r.t. for 18–24 h. Following aqueous workup with sat. NH4Cl solution and extraction several times with EtOAc, the combined organic layers were dried (Na2SO4), 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 aldon product as a yellowish oil. HPLC [Daicel Chiralpak AD-RH, CH3CN–H2O (30:70), flow rate 0.5 mL/min, λ = 254 nm]: tR (major) = 15.99 min, tR (minor) = 19.61 min.

1H NMR (200 MHz, CDCl3): δ = 2.21 (s, 3 H), 2.83 (m, 2 H), 3.56 (m, 1 H), 7.25 (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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