Proline-Derived *N*-Sulfonylcarboxamides: Readily Available, Highly Enantioselective and Versatile Catalysts for Direct Aldol Reactions

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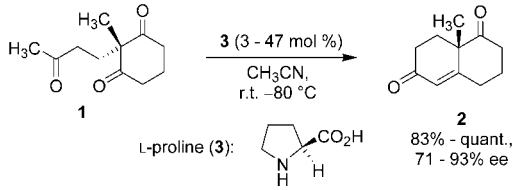
Abstract: Proline catalysis of the asymmetric direct aldol reaction involves both the secondary amine function and the carboxyl group of the amino acid. *N*-Sulfonylcarboxamides are known to be of similar acidity as carboxylic acids, and three *N*-arylsulfonyl derivatives of L-proline amide were synthesized as functionalized and versatile derivatives of L-Pro. Their catalytic performance was evaluated in the direct aldol addition of acetone to 4-nitrobenzaldehyde. Significantly improved reactivities and enantioselectivities were achieved in various solvents at low catalyst loadings (5–10 mol %) and at room temperature, with ees ranging up to 98%, whereas L-proline itself afforded a maximum ee of 80% (in DMSO). Thus, *N*-arylsulfonyl derivatives of proline amide represent a novel class of highly enantioselective catalysts for direct aldol reactions. Furthermore, the *N*-arylsulfonyl substituent suggests possibilities for incorporation into larger catalyst assemblies (including immobilization) without affecting the catalytically active functional groups.

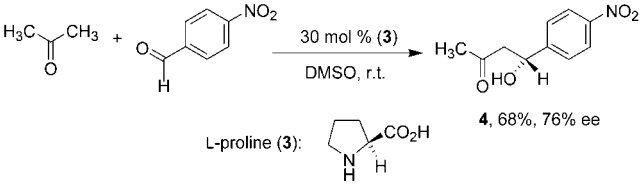
Keywords: aldol reaction; amino acids; asymmetric catalysis; organic catalyis; sulfonamides

Introduction

The aldol reaction is one of the most important C–C bond forming reactions in organic synthesis. In recent years, much effort has been spent on developing catalytic asymmetric versions.[1] A number of different approaches have been taken to solve this synthetically most important problem, such as the chiral Lewis acid-catalyzed Mukaiyama reaction of silyl enol ethers,[2] catalysis by Lewis bases,[3] the development of bifunctional Lewis acid/Brønsted base catalysts,[4] and application of aldolases or antibodies.[5] In the 1970s, the Hajos–Parrish–Eder–Sauer–Wiechert reaction was discovered, i.e., the proline (**3**)-catalyzed intramolecular asymmetric aldol cyclodehydration of the achiral trione **1** to the unsaturated Wieland–Miescher ketone **2** (Scheme 1).[6,7] Surprisingly, the catalytic potential of proline (**3**) in asymmetric aldol reactions was not explored further until recent years, when List et al. reported pioneering studies on *inter*molecular aldol reactions.[8,9] For example, acetone can be added to a variety of aldehydes, affording the corresponding aldols in good yields and enantiomeric purities. The case of 4-nitrobenzaldehyde as acceptor is shown in Scheme 2. In this example, the product aldol **4** was obtained in 68% isolated yield and with 76% ee.[8] The remarkable chemo- and enantioselectivities observed by List et al. triggered massive further research activities in the field of proline-catalyzed aldol, Mannich, Michael and related reactions.[10,11]



Scheme 1.



Scheme 2.

Proline (**3**) is a very attractive catalyst because it is readily available in both enantiomeric forms, it is nontoxic, and typically no stringent reaction conditions such as low temperatures, inert atmosphere, etc. are required. On the other hand, fine-tuning of the catalytic properties of proline by derivatization is difficult: the five-membered pyrrolidine ring, and both the free carboxyl and the secondary amine function proved essential for effective catalysis.[8] However, *N*-substituted

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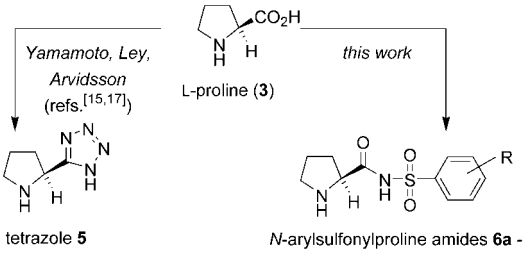
proline amides derived from β-amino alcohols are an exception because they promote catalytic asymmetric aldol reactions with high enantioselectivities.[12] By the same token, diamine catalysts derived from proline, in conjunction with Brønsted acids, were found to catalyze aldol reactions with moderate to good enantioselectivities and yields, albeit until now with a fairly narrow substrate spectrum.[13] Small peptides harbouring proline were synthesized and assessed as well, but the enantioselectivities compared to the "simple" proline-catalyzed reaction could not be improved.[14] Very recently, both Yamamoto et al.[15a] and Ley et al.[15b] exchanged the carboxylic acid function of proline for a tetrazole. The latter heterocycle is of similar acidity as carboxylic acids, and has frequently been employed as a "bio-isoster" of carboxylic acids.[16] The pyrrolidinyltetrazole **5** (Scheme 3) thus obtained was employed in asymmetric Mannich and aldol reactions quite successfully, with enantiomeric excesses ranging up to 99% ee.[15] However, in the aldol reaction shown in Scheme 2, Arvidsson and Hartikka observed only a minor increase in activity, but no improvement in enantioselectivity for the tetrazole **5** compared to L-proline (**3**).[17]

Unfortunately, the nature of the tetrazole group prevents further optimization of the catalytic properties of **5**, e.g., by attaching substituents of varying electronic and steric properties. We reasoned that *N*-sulfonylation of proline amide (as in **6**, Scheme 3) will as well result in a functional group of sufficient acidity, and will at the same time allow electronic and steric fine-tuning of the resulting catalyst by variation of substituents on the aryl residue. In fact, the acylsulfonamide group has frequently been used – just as tetrazole – in medicinal chemistry as a "bio-isoster" of carboxylic acids.[18] However, to the best of our knowledge, there appear to be no publications on the synthesis and characterization of *N*-sulfonylated *proline* amides. We herein report the synthesis of proline-amide derived acylsulfonamides as a new, versatile and readily accessible class of catalysts for the asymmetric direct aldol reaction. As a first test for catalytic efficiency, the addition of acetone to 4-nitrobenzaldehyde was performed, and significantly improved enantiomeric excesses compared to proline (up to 98% ee) were observed.



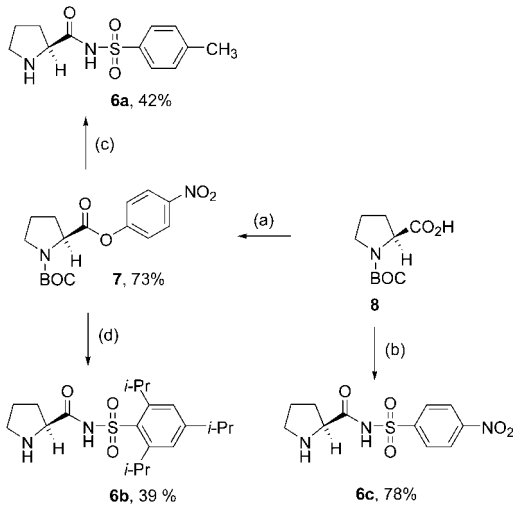
Scheme 3.

Results and Discussion

To study the steric and electronic effects of the *N*-sulfonyl substituent, we synthesized *N*-tosylproline amide (**6a**), the 2,4,6-tris(*iso*-propyl)benzenesulfonamide **6b** and the 4-nitrobenzenesulfonamide **6c**, as summarized in Scheme 4. The preparation of the catalysts **6a** and **6b** was easily achieved by treating the 4-nitrophenyl ester **7** of BOC-L-proline **8** with the corresponding sulfonamides **9a**, **b** under basic conditions. However, this procedure failed in the case of 4-nitrobenzenesulfonamide as nucleophile. Various reaction conditions were tested, but none of them afforded more than traces of the desired acylsulfonamide **6c**. Finally, by treating a mixture of BOC-L-proline **8** and 4-nitrobenzenesulfonamide **9c** with an excess of DMAP and EDCI in 1,2-dichloroethane/*tert*-butyl alcohol (1:1) as solvent, the product **6c** was formed in 78% yield.

The *N*-tosylated proline amide **6a** afforded crystals suitable for X-ray structural analysis. The result is shown in Figure 1. The pyrrolidine function is protonated whereas the *N*-acylsulfonamide group is deprotonated. This is in accord with the high acidity of the *N*-acylsulfonamide proton which may replace the carboxylic proton of proline in the catalytic cycle. The partial double bond character of the carboxamide linkage [CO–N] is nicely reflected by the almost perfect co-planarity of C_α(proline)–C(O)–N–S. The torsion angle of these four atoms is 178.2°, and the maximum deviation from the best plane is 1.3 pm (N atom).

The novel catalysts **6a** – **c** were tested in the direct aldol reaction between *p*-nitrobenzaldehyde and acetone as shown in Scheme 2. Our initial reaction conditions



(a) DCC, 4-nitrophenol, pyridine; according to ref.[20]
(b) 4-nitrobenzenesulfonamide (**9c**), DMAP, EDCI, *t*-BuOH/1,2-dichloroethane; according to ref.[22]
(c) *p*-toluenesulfonamide (**9a**), NaH, DMF;
(d) 2,4,6-tris(*i*-propylbenzene)sulfonamide (**9b**), NaH, DMF.

Scheme 4.

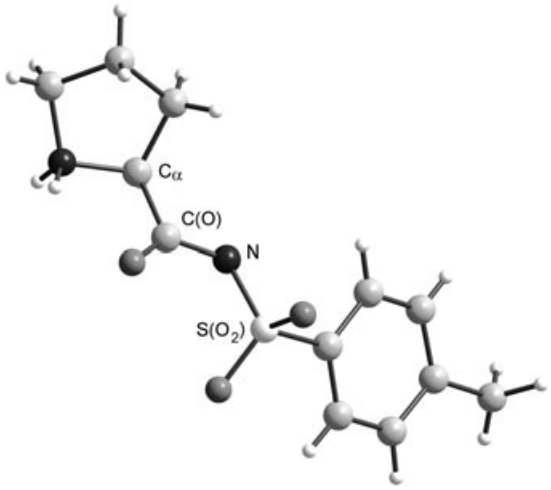
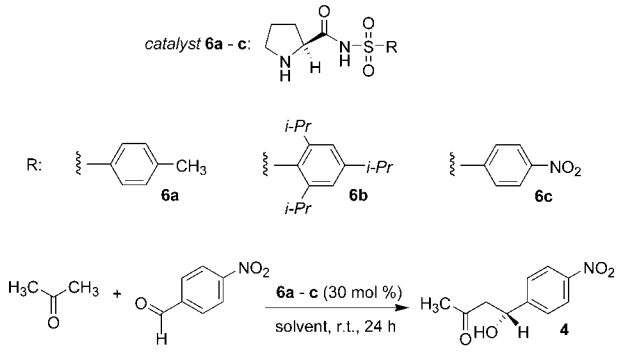


Figure 1. X-ray crystal structure of the proline *N*-sulfonylcarboxamide **6a**.

were the same as reported for proline catalysis, which means a large excess of ketone (27 equivalents), 30 mol % of the catalyst relative to the aldehyde, and stirring at room temperature. The results are summarized in Table 1.

We were pleased to see that with all of the three new catalysts **6a** – **c** enantioselectivity was significantly improved relative to the proline-catalyzed reaction (typically > 90% ee, proline: 76% ee[8]). Almost full conversion was reached after 24 hours. A solvent screening was performed, and the results are summarized in Table 1. Best yields and enantiomeric excesses (up to 93%)

Table 1.



Solvent	ee (Yield) [%] of the Aldol Product **4**, Catalyst			
	6a	**6b**	**6c**	L-proline (**3**)
DMSO	93 (98)	92 (98)	92 (73)	72 (98)[a] 76[b]
methanol	54 (62)	70 (97)	69 (40)	37 (87)[a] -
THF	93 (73)	90 (62)	86 (98)	69 (92)[a] 60[b]
acetone	93 (98)	71 (98)	90 (98)	67 (97)[a] 67[b]
chloroform	85 (58)	76 (95)	88 (54)	59 (97)[a] 61[b]

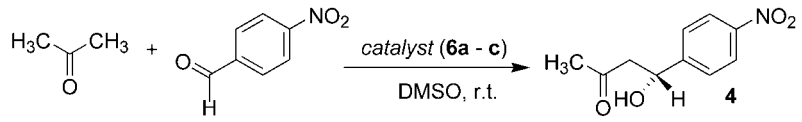
[a] This work.
[b] Enantiomeric excesses reported in ref.[9]

were obtained in polar aprotic solvents such as DMSO, acetone or THF, whereas protic solvents like methanol led to a decrease both in enantioselectivity and conversion. Also in chloroform, the enantioselectivity and the conversion were lower. With the sterically more demanding acylsulfonamide **6b**, only small changes in the catalytic properties compared to catalyst **6a** were observed. Catalyst **6c**, carrying an electron-withdrawing *p*-nitrobenzene group, also showed quite comparable catalytic properties. In the latter case, conversions in DMSO and methanol were slower, but the enantioselectivities were almost identical to those observed with catalyst **6a** and **6b**. Overall, the trends in the solvent effects observed for the three novel catalysts **6a** – **c** are comparable to those reported for L-proline (**3**).[9] In contrast to L-proline (**3**), all three catalysts **6a** – **c** are completely soluble in the solvents tested. In some cases, this can be an important factor for achieving practical rates of substrate conversion, as has been reported for the soluble tetrazole-derivatized proline catalyst **5** (Scheme 3).[15b]

Next, we studied the influence of catalyst loading (Table 2). For this series of experiments, DMSO was used exclusively as solvent. Besides 30 mol % (as summarized in Table 1 and in line 1, Table 2), the aldol addition of acetone to *p*-nitrobenzaldehyde was also studied at 10 mol % and 5 mol % catalyst loading. Under these conditions, differences in reaction rates became clearly visible: Even at 5 mol %, the tris(*iso*-propyl)benzenesulfonamide **6b** effected almost complete conversion (91%) after 72 h. The *N*-tosylated proline amide **6a** was somewhat slower (45% conversion after 72 h, 5 mol %), and the nitro-substituted catalyst **6c** only gave 10% conversion after this period of time. L-Proline (**3**) itself falls in between the sulfonamides **6a** and **6c**. However, whereas our sulfonamide catalysts showed continuous increase in conversion over the entire reaction time, conversion appeared to level off at *ca.* 40% (10 mol % **3**) and 17% (5 mol % **3**) in the case of L-proline (**3**). We furthermore observed that the enantioselectivity of the aldol reaction generally increased with decreasing catalyst concentration. Enantiomeric excesses up to 98% were achieved by the 4-nitrobenzenesulfonamide **6c**, and the fastest catalyst (**6b**) still afforded 95% ee at 91% conversion with as little as 5 mol % of catalyst. Finally, it should be pointed out that the enantiomeric excesses observed for the aldol product **4** did not change significantly over the entire reaction period of 72 h (Table 2). As mentioned already, all experiments were run at room temperature, as no significant improvement of enantioselectivity was observed upon lowering the reaction temperature to 0 °C.

List and Houk have recently proposed a *one*-proline enamine mechanism, in which the carboxylic acid proton fulfils a number of crucial roles in the catalytic cycle.[19] In the transition state (**IIIa**, Scheme 5), the aldehyde **II** is attacked by the intermediate enamine **I**, gen-

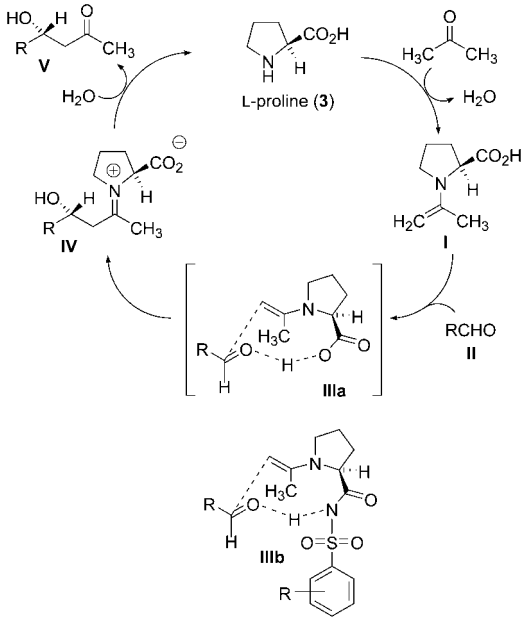
Table 2.



Catalyst Loading [mol %]	Reaction Time [h]	ee (Yield) [%] of the Aldol Product **4**, Catalyst			
		6a	**6b**	**6c**	L-proline (**3**)
30	24	93 (98)	92 (98)	92 (73)	72 (98)
10	24	95 (29)	95 (70)	≥ 97 (8)	75 (41)
10	48	96 (69)	97 (96)	98 (15)	73 (42)
10	72	94 (96)	95 (99)	98 (25)	76 (43)
5	24	94 (15)	95 (39)	> 97 (3)	80 (14)
5	48	94 (30)	94 (72)	> 97 (5)	77 (17)
5	72	95 (45)	95 (91)	98 (10)	76 (17)

erated from the ketone and L-proline (**3**). In this bimolecular complex, the carboxylic acid proton enables hydrogen bonding between the reaction partners. As the result, the iminium-aldol intermediate is generated stereoselectively (**IV**, *re*-facial attack, Scheme 5). The hydrolysis of the intermediate **IV** releases the aldol adduct **V** (Scheme 5).[8] We assume that in the sulfonamide-catalyzed reaction, the acidic NH-proton replaces the carboxylic proton (transition state **IIIb**, Scheme 5), and the same probably holds for the tetrazole-derivatized proline catalysts.[15,17]

The origin of the improved enantioselectivity observed with the acylsulfonamide catalysts **6a** – **c** may be explained by a better shielding of one of the enantiotopic faces of the aldehyde by the aryl ring (Scheme 5). It may also be speculated that "tighter" hydrogen bonding in the transition state **IIIb** accounts for the better stereoselection observed. However, the evaluation of more and structurally diverse acylsulfonamides is necessary to shed further light on the mechanism of enantioselection.



Scheme 5.

The catalysts **6a** – **c** provide high enantioselectivities in low-boiling solvents, and the use of pure acetone is not necessary. Furthermore, there is no need for low temperatures to obtain high enantioselectivities, as seen in other proline amide-catalyzed reactions.[12] Thus, the sulfonamides **6a – c** provide practical advantages over L-proline (**3**) and other proline-derived amides. It is hoped that further optimization of the sulfonamide moiety will lead to catalysts which are able to promote reactions in which L-proline (**3**) itself gives only modest or poor results, such as Michael additions, or aldol reactions with α-non-branched aldehydes.[8c]

Conclusion

In summary, we have introduced the new class of proline-derived acylsulfonamide catalysts for the asymmetric direct aldol reaction. Compared to L-proline (**3**), the enantioselectivity could be improved to 98% ee while maintaining high activity at low catalyst loadings. The novel catalysts are readily available and they do not need inert reaction conditions. The sulfonamide part can be varied in a broad fashion. It is thus expected that the catalytic properties can be further tuned for individual applications. This may be especially interesting in cases where L-proline (**3**) itself affords only modest results, e.g., in aldol reactions of α-unbranched aldehydes, Michael reactions etc. Furthermore, the sulfonamide moiety may be employed as a linker for immobilization on solid support, or as an attachment point for further catalytically competent or stereo-differentiating groups.

Experimental Section

General

BOC-L-proline (**8**) was purchased from Novabiochem, 2,4,6-tris(isopropyl)benzenesulfonamide (**9b**) was purchased from Lancaster, tosylamide (**9a**) and 4-nitrobenzensulfonamide (**9c**) were purchased from Fluka, Amberlyst-15 resin was purchased from Supelco. L-Proline (**3**) was purchased from EGA

Chemie. All commercially available chemicals were used without further purification. BOC-proline 4-nitrophenyl ester (**7**) was synthesized from BOC-proline and *p*-nitrophenol in 73% yield according to a literature procedure.[20] Solvents were distilled prior to use and dried, if necessary, using standard techniques.[21] NMR spectra were recorded on a Bruker AC300 NMR spectrometer, FT-IR spectra were recorded on a Perkin Elmer FT-IR 1600 instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Elemental analysis was performed on a Vario EL elementar CHN-apparatus. HPLC analysis was carried out on Merck-Hitachi HPLC equipment using HPLC grade solvents from Fisher Scientific.

N-Toluenesulfonyl-L-proline Amide 6a

To a solution of *p*-toluenesulfonamide (**9a**, 1.00 g, 5.8 mmol) in 20 mL of absolute DMF was added sodium hydride (268 mg, 60% dispersion in mineral oil, 6.69 mmol). After stirring for 0.5 h at ambient temperature, L-proline (4-nitrophenyl) ester, (**7**, 1.50 g, 4.46 mmol), dissolved in 5 mL of absolute DMF, was added. The yellow solution was stirred overnight at ambient temperature and then poured onto crushed ice. The pH was adjusted to 3 by addition of citric acid. The aqueous layer was extracted with ethyl acetate (3×20 mL). The organic layer was washed with water (5×20 mL), dried over magnesium sulfate and concentrated under vacuum. The semi-solid residue was triturated with ether (10 mL), and the resulting colourless solid was collected by filtration to afford the BOC-protected *N*-sulfonylcarboxamide; yield: 1.00 g (61%). Deprotection was performed using 50% TFA in dichloromethane (10 mL) for one hour at room temperature. After rotary evaporation, TFA salts were removed by triturating the residue with 10 mL of methanol (saturated with ammonia). The acylsulfonamide **6a** was obtained as a colourless powder; yield: 693 mg (42% overall); mp 217 °C. Recrystallization from methanol gave colourless crystals suitable for X-ray analysis. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 1.64-1.86$, 2.06–2.16 (m, 4H), 2.30 (s, 3H), 2.99–3.07, 3.11–3.19 (m, 2H), 3.78–3.83 (m, 1H), 7.17–7.20 (m, 2H), 7.65–7.67 (m, 2 H), NH-protons not visible; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 20.87$ (q), 23.36 (t), 29.08 (t), 45.31 (t), 61.88 (d), 126.84 (d), 128.16 (d), 139.97 (s), 142.42 (s), 171.27 (s); IR (CsI): $\tilde{\nu} = 3088$ 1619, 1586 1403, 1326, 1241, 1128, 1085, 1046 947, 872, 811, 709, 646, 555 cm^{-1}; elemental analysis: calcd. for $C_{12}H_{16}N_2O_3S$: C 53.71, H 6.01, N 10.44; found: C 53.37, H 6.05, N 10.30.

N-2,4,6-Tris-(isopropylbenzene)sulfonyl-L-proline Amide 6b

In analogy to the preparation of **6a**, 2,4,6-tris(isopropylbenzene)sulfonamide (**9b**, 2.00 g, 7.06 mmol) was reacted with sodium hydride (325 mg, 60% dispersion in mineral oil, 8.14 mmol) and L-proline 4-nitrophenyl ester (**7**, 1.83 g, 5.43 mmol). Work-up as described above afforded the BOC-protected *N*-sulfonylcarboxamide; yield: 1.45 g (55%). Deprotection and removal of TFA salts as described for **6a** afforded **6b** as a colourless powder; yield: 1.45 mg (39% overall); mp 220 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 1.13$ (br. s, 18H), 1.70–1.90, 2.11–2.18 (both m, 4H), 2.77–2.86 (m, 1H), 3.01–3.18 (m, 2H), 3.76–3.81 (m, 1H), 4.49–4.58 (m, 2H), 7.01 (s, 2 H), NH protons not visible; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 23.52$ (t), 23.62 (t), 24.70 (q), 24.76 (q), 28.08 (d), 29.02 (t), 33.30 (d), 45.19 (t), 61.82 (d), 122.12 (d), 139.30 (s), 148.60 (s), 149.07 (s), 170.92 (s), (number of signals higher than expected due to amide rotamers); IR (CsI): $\tilde{\nu} = 2961$, 1586, 1464, 1379, 1323, 1276, 1126, 1043, 996, 881, 822, 765, 688, 655, 556, 463 cm^{-1}; an analytically pure sample was obtained by recrystallization from methanol; elemental analysis: calcd. for $C_{17}H_{32}N_2O_3S$: C 63.12, H 8.48, N 7.36; found: C 62.80, H 8.45, N 7.28.

N-4-Nitrobenzenesulfonyl-L-proline Amide 6c[22]

BOC-L-proline (**8**, 472 mg, 2.19 mmol), DMAP (803 mg, 6.57 mmol), EDCI (850 mg, 5.48 mmol), and 4-nitrobenzenesulfonamide (**9c**, 307 mg, 1.52 mmol) were dissolved in 20 mL of a 1:1 mixture of *tert*-butyl alcohol and 1,2-dichloroethane. The solution was stirred overnight at ambient temperature. Ethyl acetate (5 ml) and Amberlyst-15 (protonated form, 2.0 g) were added, and stirring was continued for 2 h. The mixture was passed through a plug of silica gel (1 cm) and washed with ethyl acetate. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (dichloromethane/methanol, 40:1) to give protected **6c** as a brown solid; yield: 400 mg (78%). Deprotection was performed using 50% TFA in dichloromethane (10 mL) for one hour at room temperature. After rotary evaporation, TFA salts were removed by triturating the residue with 10 mL of methanol (saturated with ammonia). The acylsulfonamide **6c** was obtained as a colourless solid; yield: 300 mg (66% overall); mp 198 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 1.67-1.87$ (m, 3H), 2.09–2.18 (m, 1H), 2.98–3.07 (m, 2H), 3.83–3.87 (m, 1H), 7.98–8.01 (m, 2H), 8.24–8.27 (m, 2H), NH-protons not visible; ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 23.31$ (t), 29.00 (t), 45.27 (t), 61.89 (d), 123.29 (d), 128.38 (d), 148.36 (s), 151.08 (s), 172.09 (s); IR (CsI): $\tilde{\nu} = 3114$, 1680, 1606, 1529, 1354, 1268, 1203, 1148, 836, 740, 614 cm^{-1}; an analytically pure sample was obtained by recrystallization from methanol; elemental analysis: calcd. for $C_{11}H_{13}N_2O_5S$: C 44.14, H, 4.38, N 14.04; found: C 44.02, H 4.34, N 13.97.

General Procedure for Aldol Reactions between 4-Nitrobenzaldehyde and Acetone

In a 10 mL test tube, 4-nitrobenzaldehyde (76 mg, 0.5 mmol) was dissolved in 5 mL of a 4:1 mixture of the solvent stated in Table 1 and acetone. Then the catalysts **6a** – **c** (30 mol %: **6a**: 40.3 mg; **6b**: 57.1 mg, **6c**: 44.9 mg) were added, and the resulting homogeneous solutions were stirred at 20 °C for 24 h. Samples of 100 μL were withdrawn, diluted with 1 mL dichloromethane, and conversion and enantiomeric excess was determined immediately by HPLC (Chiralcel-OJ, *n*-hexane/isopropanol, 9:1, 1.0 mL/min). Quantification was performed using integrated wavelengths from 240–261 nm. Conversion was determined by comparison to the peak areas of stock solutions of 4-nitrobenzaldehyde and the racemic aldol adduct **4** in dichloromethane (8.27 mmol/L each). Retention times: t_R [min]: 19.73 4-nitrobenzaldehyde; 31.52 *(R)*-4-hydroxy-4-

(4-nitrophenyl)butan-2-one **4**, 36.99 *(S)*-4-hydroxy-4-(4-nitrophenyl)butan-2-one *ent*-**4**.

X-Ray Crystal Structure of the Acylsulfonamide 6a

Crystals suitable for X-ray structural analysis were obtained by recrystallization from methanol. Crystal data for **6a**: $C_{12}H_{16}N_2O_3S$, M = 268.33, colourless platelet, 0.25 × 0.15 × 0.15 mm, orthorhombic, $a = 6.123(1)$, $b = 7.402$ (1), $c = 27.465(1)$ Å, $V = 1244.8(3)$ Å^3, space group $P2_12_12_1$, Z = 4, $\rho_{calcd} = 1.432$ g·cm^{-3}, $\mu = 0.262$ mm^{-1}, T = 293(2) K. 6188 reflections were measured, 2619 unique, 228 parameters, final residuals were R1 = 0.034 and ωR2 = 0.079 for 2368 observed reflections with $I > 2\sigma(I)$. Data were collected on a Nonius KappaCCD diffractometer ($2\theta_{max} = 54°$), $Mo_{K\alpha}$ radiation (λ=0.71073 Å), graphite monochromator, φ/ω-scans. The structure was solved using direct methods (SHELXS-97: G. M. Sheldrick, *Program for the Solution of Crystal Structures.* University of Göttingen, Germany, **1997**), followed by full-matrix least squares refinement (using all unique reflections) with anisotropic thermal parameters for C, N, O and S and isotropic parameters for H (SHELXL-97: G. M. Sheldrick, *Program for the Refinement of Crystal Structures.* University of Göttingen, Germany, **1997**).

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-237138. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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References

[1] C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.* **2004**, *33*, 65–75.
[2] T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.
[3] S. E. Denmark, K. T. Wong, R. A. Stavenger, *J. Am. Chem. Soc.* **1997**, *119*, 2333–2334.
[4] Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942–1943; *Angew. Chem. Int. Ed.* **1997**, *36*, 1871–1873.
[5] T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406–1430; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1375.
[6] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.
[7] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497.
[8] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; c) B. List, P. Pojarliev, C. Castello, *Org. Lett*. **2001**, *3*, 573–575.
[9] K. S. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.
[10] B. List, *Synlett* **2001**, *11*, 1675–1686.
[11] B. List, *Tetrahedron* **2002**, *58*, 5573–5590.
[12] Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263.
[13] a) S. Saito, M. Nakadai, H. Yamamoto, *Synlett* **2001**, *8*, 1245–1248; b) S. Saito, M. Nakadai, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167–8177.
[14] a) H. J. Martin, B. List, *Synlett* **2003**, 1901–1902; b) J. Kofoed, J. Nielsen; J.-L. Reymond, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445–2447.
[15] a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017–2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; b) A. J. A. Cobb, D. M. Shawn, S. V. Ley, *Synlett* **2004**, *3*, 558–560.
[16] R. J. Herr, *Bioorg. Med. Chem*. **2002**, *10*, 3379–3393.
[17] A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.
[18] a) V. L. Schuster, S. Itoh, S. W. Andrews, R. M. Burk, J. Chen, K. M. Kedzie, D. W. Gil, D. F. Woodward, *Mol. Pharm.* **2000**, *58*, 1511–1516; b) D. E. Uehling, K. H. Donaldson, D. N. Deaton, C. E. Hyman,. E. E. Sugg, D. G. Barrett, R. G. Hughes, B. Reitter, K. K. Adkinson, M. E. Lancaster, F. Lee, R. Hart, M. A.Paulik, B. W. Sherman, T. True, C . Cowan, *J. Med. Chem.* **2002**, *45*, 567–583.
[19] a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283; b) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16–17; c) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479; d) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839–5842; e) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557.
[20] K. Hohenlohe-Oehringen, L. Call, *Monatsh. Chem.* **1968**, *99*, 1289–1300.
[21] W. L. F. Armarego, D. D. Perrin, *Purification of laboratory chemicals*, 4th edn., Butterworth-Heinemann, Oxford, **2000**.
[22] C. F. Sturino, M. Labelle, *Tetrahedron Lett.* **1998**, *39*, 5891–5894.

