Use of Prolyl Sulfonimidamides in Solvent-Free Organocatalytic Asymmetric Aldol Reactions

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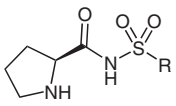
Abstract: Prolyl-substituted sulfonimidamides have been synthesized and applied as organocatalysts in solvent-free asymmetric aldol reactions.

Keywords: aldehyde, aldol reaction, amino acids, ketone, organocatalysis, sulfonimidamide

Much effort has been devoted to the development of catalytic asymmetric aldol reactions.[1] Various proline derivatives proved applicable as organocatalysts, and their reaction behavior has been thoroughly investigated.[2] In 2004, Berkessel described the synthesis of *N*-sulfonylated proline amides **1**–**3** and their use as catalysts for the enantioselective addition of acetone to 4-nitrobenzaldehyde (Figure 1).[3] Subsequently, Ley applied compounds **4** and **5** in catalytic asymmetric Mannich-type reactions and aldol additions of ketones to 4-nitrobenzaldehyde.[4] Kokotos tested a series of related 4-substituted prolyl sulfonamides and a dipeptide derived from proline, phenylalanine and sulfonamide on their effectiveness in organocatalytic aldol reactions.[5]



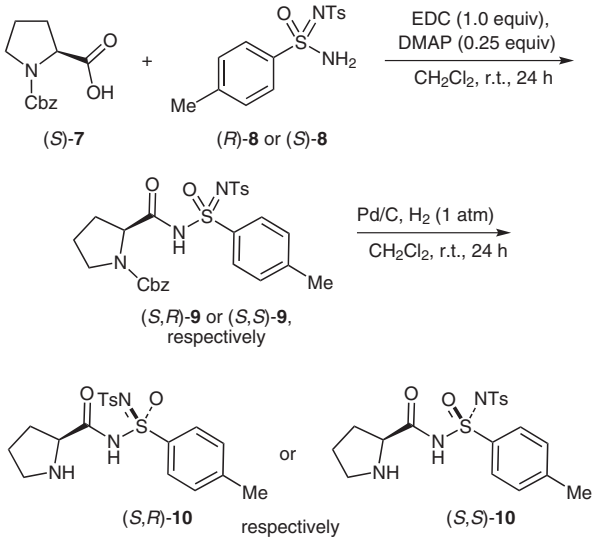
1 R = 4-MeC_6H_4
2 R = 2,4,6-*i*-$Pr_3C_6H_2$
3 R = 4-$NO_2C_6H_4$
4 R = Me
5 R = Ph
6 R = $C_{12}H_{25}C_6H_4$

Figure 1 Selected prolyl-substituted sulfonamides

Almost all of these procedures required a large excess of ketone (27 equiv or 20 vol%),[6] which represents a significant limitation for potential applications. Recently, this problem was addressed by the introduction of prolyl sulfonamide **6** (Figure 1).[7] In this case, only five equivalents of ketone were required and, in asymmetric aldol reactions, products with excellent enantioselectivities were obtained in very high yields.

As sulfonimidamides are the aza-analogues of sulfonamides, we hypothesized that these compounds could also have a potential in organocatalysis. The additional stereogenic center at the sulfur could then be beneficial for controlling the stereoselectivity in asymmetric processes. To the best of our knowledge, sulfonimidamides have never been applied as organocatalysts, and thus we expected promising findings to open new research opportunities. Here, we report our first results illustrating the concept by describing the synthesis and use of prolyl sulfonimidamides **10**.

The synthesis of **10** started from *N*-carbobenzyloxy (Cbz) protected L-proline (**7**), which was coupled with enantiopure *N*-tosyl-protected sulfonimidamide **8**[8] to give acylsulfonimidamide **9** (Scheme 1).[9] Removal of the Cbz-group by catalyzed hydrogenolysis led to prolyl sulfonimidamides **10** in good yields (>80%). In this manner both diastereomers (*S*,*R*)-**10** and (*S*,*S*)-**10** were accessible starting from (*R*)-**8** and (*S*)-**8**, respectively.



Scheme 1 Synthesis of sulfonimidamides (*S*,*R*)-**10** and (*S*,*S*)-**10**

As a test reaction for the catalytic potential of sulfonimidamides **10**, the aldol addition of cyclohexanone (**11**) to 4-nitrobenzaldehyde (**12a**) was chosen (Table 1). In order to investigate whether there was any catalytic activity, the first experiments were carried out at room temperature with 20 mol% of a diastereomeric mixture (ca. 1:1) of (*S*,*R*)-**10** and (*S*,*S*)-**10** derived from L-proline and *rac*-**8**. To our delight, addition product **13a** was obtained in 86% yield with a very good *anti*/*syn* ratio (95:5) and an ee of 95% (Table 1, entry 1). The major isomer of **13a** had (2*S*,1′*R*)-configuration. No solvent was required[10] but, unfortunately, even with a large excess of ketone (30 equiv) the reaction time was long (8 d). Increasing the reaction temperature to 30 °C improved the catalyst performance

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to give **13a** in 84% yield after only two days (Table 1, entry 2). It is worth noting that the stereoselectivity remained almost unaffected (*anti*/*syn* = 95:5, 92% ee). When diastereomerically pure (*S*,*R*)-**10** was applied as catalyst under the same reaction conditions, both the de and the ee slightly increased to 94 and 95%, respectively (Table 1, entry 3). Diastereomeric sulfonimidamide (*S*,*S*)-**10** proved to be less effective (see Table 2). Varying the catalyst loading from 20 to 10, 7, and 5 mol% (Table 1, entries 4–6) indicated an optimum at 10 mol% of (*S*,*R*)-**10**, which gave **13a** with 96% de and 98% ee in 92% yield. However, the aldehyde-to-ketone ratio had an effect on the catalyst performance (Table 1, entries 4, 7–9). Taking all factors (substrate amount, stereoselectivity and product yield) into account, the best result was obtained with 10 mol% of (*S*,*R*)-**10** and five equivalents of ketone **11** (entry 8).

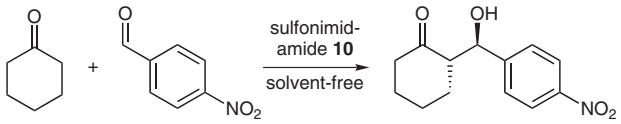
Next, the application of other aldehydes was tested (Table 2),[11] and the catalytic activities of diastereomeric sulfonimidamides (*S*,*R*)-**10** and (*S*,*S*)-**10** were compared. In all cases, the former diastereomer gave higher yields and better stereoselectivities than the latter. Although the differences were usually only minor, in conversions of 4-chlorobenzaldehyde (**12d**), for example, the Δde and Δee reached values of 18 and 11%, respectively (Table 2, entries 7 and 8). Apparently, the stereogenic center at sulfur influenced the stereochemical result of the catalysis, and a fine-tuning of the sulfonimidamide structure was important.

With respect to the substrate tolerance, the following conclusions can be drawn: The electron-withdrawing nitro group in the substituted benzaldehydes **12a–c** has a positive effect on the catalysis and, in general, very good diastereo- and enantioselectivities are achieved for the formation of the corresponding products **13a–c** (Table 2, entries 1–6). The strongest substrate activation is observed when the nitro group is in the *para* position of the aromatic system (as in **12a**).[12] Use of benzaldehydes **12b** and **12c** having *meta* and *ortho* nitro groups, respectively, require longer reaction times for achieving good yields. The same is true for conversions of 4-chlorobenzaldehyde (**12d**) and benzaldehyde (**12e**), with the latter being the least reactive substrate. Although in both cases the stereoselectivities are acceptable, the yields are only moderate (Table 2, entries 7–10). In all cases the major isomers had (2*S*,1′*R*)-configuration.

Finally, the carbonyl component was varied. Starting from cyclopentanone (**14**) and 4-nitrobenzaldehyde (**12a**), hydroxy ketone **15** was obtained in 73% yield under the standard conditions (Scheme 2). Although the diastereoselectivity was only very moderate (36% de), the enantioselectivity was high (95% ee). Again, the major isomer had (2*S*,1′*R*)-configuration.[13]

In summary, we have prepared prolyl-substituted sulfonimidamides and demonstrated their applicability as organocatalysts in solvent-free asymmetric aldol reactions. In additions of cyclic ketones to aromatic aldehydes, the stereoselectivities are good to excellent, and the products are formed in moderate to very good yields. The excess of ke-

Table 1 Optimization of the Aldol Addition of Cyclohexanone (**11**) to 4-Nitrobenzaldehyde (**12a**)[a]

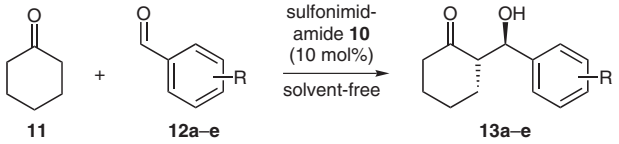


11 **12a** **13a**

Entry	Sulfonimidamide **10**	Catalyst loading (mol%)	Ketone (equiv)	Time (d)	Temp (°C)	Yield (%)[b]	*anti*/*syn* rato[c]	ee (*anti*) (%)[d]
1	(*S*,*S*) + (*S*,*R*)	20	30	8	~20	86	95:5	95
2	(*S*,*S*) + (*S*,*R*)	20	30	2	30	84	95:5	92
3	(*S*,*R*)	20	30	2	30	74	97:3	95
4	(*S*,*R*)	10	30	2	30	92	98:2	98
5	(*S*,*R*)	7	30	2	30	82	95:5	96
6	(*S*,*R*)	5	30	2	30	75	89:11	95
7	(*S*,*R*)	10	10	2	30	85	96:4	96
8	(*S*,*R*)	10	5	2	30	88	97:3	96
9	(*S*,*R*)	10	2	2	30	55	95:5	94

[a] All reactions were performed solvent-free on a 0.30 mmol scale.
[b] Determined after column chromatography.
[c] Ascertained from ^{1}H NMR of the crude reaction mixture.
[d] The enantiomeric ratios were determined by HPLC using a Chiralpak AD-H column (heptane–*i*-PrOH, 90:10, 1.0 mL/min). The major product had (2*S*,1′*R*)-configuration.

Table 2 Reaction of Cyclohexanone (**11**) and Various Aromatic Aldehydes **12a–e**[a]

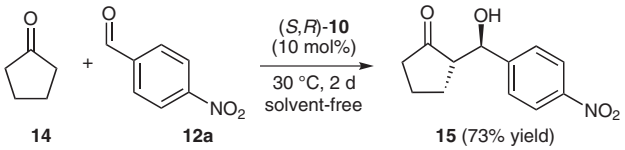


11 **12a–e** **13a–e**

Entry	Sulfonimidamide **10**	R	Aldehyde **12**	Time (d)	Product[b]	Yield (%)[c]	*anti*/*syn* ratio[d]	ee (*anti*) (%)[e]
1	(*S*,*R*)	4-NO_2	**12a**	2	**13a**	84	96:4	95
2	(*S*,*S*)	4-NO_2	**12a**	2	**13a**	80	94:6	93
3	(*S*,*R*)	3-NO_2	**12b**	3	**13b**	81	96:4	97
4	(*S*,*S*)	3-NO_2	**12b**	3	**13b**	72	96:4	96
5	(*S*,*R*)	2-NO_2	**12c**	4	**13c**	74	94:6	98
6	(*S*,*S*)	2-NO_2	**12c**	4	**13c**	55	92:8	93
7	(*S*,*R*)	4-Cl	**12d**	4	**13d**	40	91:9	89
8	(*S*,*S*)	4-Cl	**12d**	4	**13d**	31	87:13	78
9	(*S*,*R*)	H	**12e**	4	**13e**	22	92:8	96
10	(*S*,*S*)	H	**12e**	4	**13e**	35	87:13	90

[a] All reactions were performed solvent-free at 30 °C, on a 0.60 mmol scale utilizing 10 mol% of sulfonimidamide **10** and 5 equiv of cyclohexanone (**11**).
[b] The major isomers had (2*S*,1′*R*)-configuration.
[c] Determined after column chromatography.
[d] Ascertained from ^{1}H NMR of the crude reaction mixture.
[e] Determined by HPLC using columns with chiral stationary phases.

tone could be limited to five equivalents. By studying the diastereomeric catalysts it was shown that the stereogenic center at the sulfur atom of the sulfonimidamide unit had only a minor impact on the formation of the products.



14 **12a** **15** (73% yield)
(*anti*/*syn* = 68:32, 95% ee)

Scheme 2 Catalytic use of sulfonimidamide (*S*,*R*)-**10** in the reaction of cyclopentanone (**14**) and 4-nitrobenzaldehyde (**12a**)

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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References and Notes

(1) Selected reviews: (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (b) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (c) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502.
(2) For recent reviews, see: (a) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493. (b) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 575.
(3) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141.
(4) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.
(5) (a) Bellis, E.; Vasilatou, K.; Kokotos, G. *Synthesis* **2005**, 2407. (b) Tsandi, E.; Kokotos, C. G.; Kousidou, S.; Ragoussis, V.; Kokotos, G. *Tetrahedron* **2009**, *65*, 1444.
(6) For the use of a ketone/aldehyde ratio of 3:1, see: Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417.
(7) Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649.
(8) (a) Di Chenna, P. H.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503. (b) Fruit, C.; Robert-Peillard, F.; Bernardinelli, G.; Müller, P.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3484.
(9) **Syntheses of (2*S*)-benzyl 2-(N-tosyl-4-tolylsulfonimidoylcarbamoyl)pyrrolidine-1-carboxylates 9; General Procedure:** To a solution of Cbz-L-proline (L-**7**, 374 mg, 1.50 mmol), sulfonimidamide **8** (487 mg, 1.50 mmol) and DMAP (46 mg, 0.375 mmol) in CH_2Cl_2 (9 mL), was added EDC (233 mg, 263 μL, 1.50 mmol). After stirring of the reaction mixture at room temperature for 24 h, EtOAc (30 mL) was added. The resulting mixture was then sequentially washed with 1 M HCl (10 mL) and half-saturated brine (10 mL). Drying the organic phase over $MgSO_4$ and concentration under reduced pressure gave white solids that were used without further purification.

For analytical data of (*S*,*R*)-**9** and (*S*,*R*)-**9** see Supporting Information.

Syntheses of (2*S*)-*N*-(*N*-tosyl-4-tolylsulfonimidoyl)pyrrolidine-2-carboxamides 10; General Procedure: To a solution of (2*S*)-benzyl 2-(*N*-tosyl-4-tolylsulfonimidoyl-carbamoyl)pyrrolidine-1-carboxylate (**9**; 800 mg, 1.44 mmol) in CH_2Cl_2 (32 mL), was added 10% Pd/C (86 mg). The mixture was stirred for 24 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite® and silica and rinsed with CH_2Cl_2–MeOH (9:1, 30 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2–MeOH, 9:1). Products **10** were isolated as white solids.

For analytical data of (*S*,*R*)-**10** and (*S*,*R*)-**10** see Supporting Information.

(10) The use of solvents such as dimethylsulfoxide, methanol, tetrahydrofuran, and dichloromethane led to low catalyst activity and stereoselectivity.

(11) **Aldol Reaction; General Procedure:** A vial was charged with sulfonimidamide **10** (10 mol%), ketone (5.0 equiv, 3.0 mmol) and aldehyde (1.0 equiv, 0.6 mmol) and sealed. The mixture was stirred at 30 °C for the indicated period of time. After the addition of ethyl acetate (5 mL) the reaction mixture was filtered thought a pad of silica gel, then the solvent was removed in vaccuo, and purified by column chromatography on silica gel to afford the corresponding aldol products.

(12) In an unoptimized ball milling experiment (at 400 rpm) the aldol reaction between ketone **11** (5 equiv) and aldehyde **12a** catalyzed by 10 mol% of (*S,R*)-**10** led to 35% conversion of **12a** after 5.3 h, giving **13a** with 66% ee (*anti*/*syn*, 88:12) in 31% yield. For recent guiding reviews in this area, see: (a) Rodriguez, B.; Rantanen, T.; Bruckmann, A.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2213. (b) Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131.

(13) The catalyst performance in the reaction of acetone and 4-nitrobenzaldehyde was poor. The product was isolated after 6 d at 30 °C with 49% ee in 23% yield.