

N-Arenesulfonyl-2-aminomethylpyrrolidines – Novel Modular Ligands and Organocatalysts for Asymmetric Catalysis

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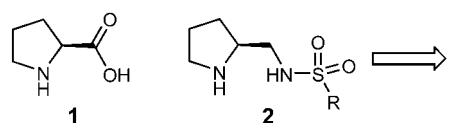
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Abstract: A novel series of (*S*)-*N*-arenesulfonyl-2-aminomethylpyrrolidines were prepared in high overall yield starting from *N*-Boc-L-proline. The mono-sulfonyldiamines were evaluated as organocatalysts in the asymmetric α -amination of propanal using diethyl azodicarboxylate (DEAD) as the amine source. The initially formed α -aminated aldehyde was reduced *in situ* to the corresponding *N*-aminooxazolidinone, which was obtained in moderate to high yield in up to 87% ee.

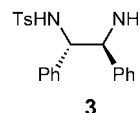
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Asymmetric organocatalysis, using simple enantiomerically pure amino acid catalysts, has emerged as a powerful tool and alternative to organic processes typically catalyzed by either chiral metal complexes or enzymes and other biocatalysts. In particular, the use of proline (**1**) as the organocatalyst has been highly successful in asymmetric organic transformations involving enamine chemistry.^[1,2] Currently there are an extensive number of reports on reactions catalyzed by proline, and the common theme in most of the cases is processes showing high reactivity and stereoselectivity. However, the rather poor solubility of proline in many solvents has resulted in the use of sub-stoichiometric amounts of the catalyst, often up to 30 mol %, which effectively reduce the turnover number. This drawback has emphasized the need for further development of novel organocatalysts with better solubility properties.^[3] We envisioned the use of mono-*N*-sulfonyl derivatives of chiral diamines to be proper alternatives to proline. Such compounds, here exemplified by **2**, can easily be reached by a few simple transformations starting from proline. Although compound **2** is a diamine, it fulfils all the criteria necessary to work as an organocatalyst in reactions where proline normally is used. The secondary amine allows for a reversible formation of the enamine intermediate present in proline-catalyzed reactions, and the sulfonyl group on the primary amine would effectively increase its acidity to facilitate required proton transfers. Fur-

thermore, significantly better solubility properties can be expected by choosing a proper R group on the sulfonyl moiety. In fact, both acidity and solubility can be fine-tuned by varying the R group and hence a modular catalyst system can be obtained.

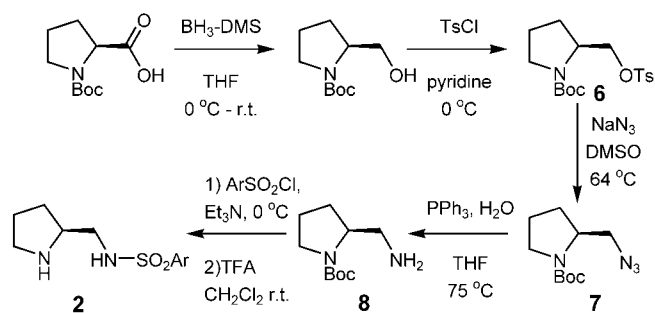


In addition, to be potentially useful as an organocatalyst the mono-sulfonyl diamine **2** can be expected to serve as a ligand for transition metal catalysts. Ruthenium complexes based on similar mono-sulfonyldiamines, e.g., TsDPEN (**3**), have been shown to be powerful and selective catalysts in asymmetric reduction of ketones under transfer-hydrogenation conditions.^[4,5] We have previously developed dipeptide-like ligands based on amino acids and amino alcohols for this particular process and, based on our results using these catalysts,^[6] along with the successful catalysts developed by Noyori and co-workers,^[5] we envisioned ligand **2** to be of potential use.



Herein we present the preparation of a novel class of pyrrolidines and the preliminary results obtained using these compounds in asymmetric catalysis.

The preparation of mono-sulfonyl-2-aminopyrrolidines was carried out according to the route depicted in Scheme 1.^[7] Reduction of *N*-Boc-protected L-proline with borane-dimethyl sulfide smoothly generated the corresponding (*S*)-prolinol in 95% yield. Treating the protected prolinol with tosyl chloride resulted in the formation of the sulfonyl ester **6** in high yield. Initially we intended to directly transform compound **6** into the desired mono-sulfonyl-2-aminomethylpyrrolidine derivative by substituting the tosylate by an appropriate sulfonamide. This substitution was, however, unsuccessful and we obtained no formation of the wanted compound.



Scheme 1.

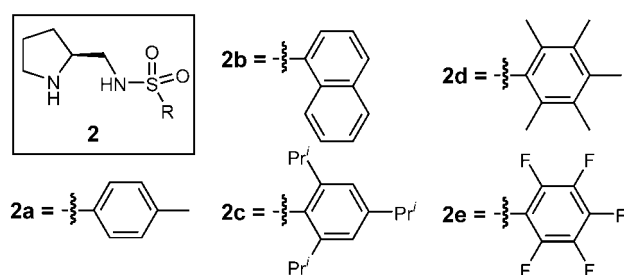


Figure 1.

The poor reactivity of tosylate **6** can most likely be traced to steric hindrance, and we decided to use a less hindered nucleophile for the substitution. Displacing the tosylate with sodium azide in dry DMSO gave *N*-Boc-(*S*)-2-azidomethylpyrrolidine (**7**) in 90% yield. The azide was readily reduced to the mono-protected diamine **8** using the Staudinger protocol.^[8] Compound **8** served as the common intermediate in the preparation of the five mono-sulfonyl-2-aminomethylpyrrolidines presented in Figure 1. Thus, treating diamine **8** with the appropriate arenesulfonyl chloride followed by removal of the carbamate using trifluoroacetic acid gave compounds **2a–e** in good overall yields.

With the mono-sulfonyl-2-aminomethylpyrrolidines **2a–e** in hand, we decided to investigate the catalytic properties of these compounds in the α -amination of aldehydes using diethyl azodicarboxylate (DEAD) as the amine source (Scheme 2).^[9] This protocol has previously been used by Jørgensen and co-workers who showed that *L*-proline efficiently catalyzed the reaction.^[1c,10] In an initial experiment, propanal was treated with DEAD and catalyst **2a** (1 mol %) and the reaction mixture was stirred for 3 h. The reaction was quenched with

Table 1. Asymmetric α -amination of aldehydes.^[a]

Entry	R	Catalyst	Time [h]	Yield [%] ^[b]	ee [%] ^[c,d]
1	Me	2a	9	58 ^c	87 (<i>R</i>)
2	Me	2b	4	54	86 (<i>R</i>)
3	Me	2c	9	55	83 (<i>R</i>)
4	Me	2d	24	70	82 (<i>R</i>)
5	Me	2e	24	19	68 (<i>R</i>)
6	Et	2a	23	77	85 (<i>R</i>)
7	<i>n</i> -C ₅ H ₁₁	2a	47	88	80 (<i>R</i>)
8	<i>i</i> -Pr	2a	2	18	61 (<i>R</i>)

[a] For reaction conditions, see experimental section.

[b] Yields determined by GLC.

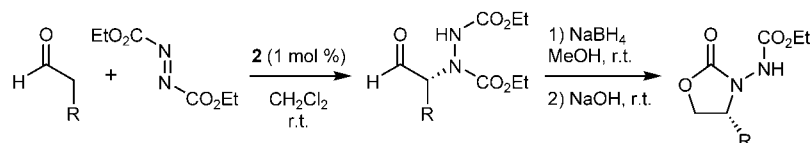
[c] Enantiomeric excess determined by GLC analysis.

[d] In analogy with the *L*-proline-catalyzed reaction we obtained the same absolute configuration of the major product enantiomer, as determined by GLC analysis.

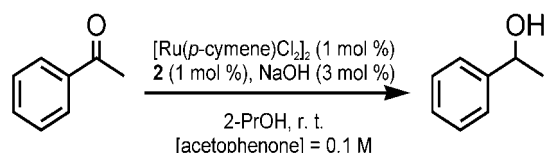
[e] Yield of isolated product.

sodium borohydride and the formed *N*-aminooxazolidinone was obtained in 58% yield and 87% ee (entry 1, Table 1). Screening the other *N*-arylsulfonyl-2-aminomethylpyrrolidines as catalysts in the same reaction gave similar results with the only exception being catalyst **2e** which generated the oxazolidinone product in somewhat lower enantioselectivity (entry 5, Table 1). Furthermore, we used catalyst **2a** in the reaction between other alkyl aldehydes and DEAD. Linear substrates gave yields and selectivity in the same range as obtained with propanal (entries 6 and 7), whereas the reaction with a branched substrate resulted in poor yield and lower enantioselectivity (entry 8). Comparing the obtained results with reactions performed using *L*-proline as the catalyst show that these novel mono-sulfonyldiamines are only slightly inferior in inducing asymmetry.^[11] On the other hand, the fact that reasonably high selectivity was obtained makes these compounds interesting as potential organocatalysts in other asymmetric transformations, for instance, the analogues α -amination of ketones.^[1c,10c]

In addition to the enantioselective α -amination of aldehydes, we have employed the series of (*S*)-*N*-arylsulfonyl-2-aminomethylpyrrolidines as ligands in the ruthenium-catalyzed transfer hydrogenation of acetophenone. The reductions were carried out using the following conditions: substrate-ruthenium-ligand-base in a 100:1:1:3 ratio, with 0.2 M concentration of acetophene-



Scheme 2.



Scheme 3.

Table 2. Asymmetric ruthenium-catalyzed transfer hydrogenation of acetophenone.^[a]

Entry	Ligand	Time [h]	Conversion [%] ^[b]	ee [%] ^[c]
1	2a	4	26	33 (<i>S</i>)
2	2b	3	12	61 (<i>S</i>)
3	2c	3	8	54 (<i>S</i>)
4	2d	4	15	41 (<i>S</i>)
5	2e	4	18	31 (<i>R</i>)

^[a] For reaction conditions, see experimental section.^[b] Conversion determined by GLC.^[c] Enantiomeric excess determined by GLC analysis.

none in 2-propanol. The pre-catalyst was prepared by initially drying a mixture of $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.5 mol %) and the mono-sulfonyldiamine (1 mol %) under vacuum for 15 minutes followed by addition of oxygen-free 2-propanol. The solution was heated to 80 °C for 20 minutes and thereafter cooled to room temperature. Acetophenone and sodium hydroxide (3 mol %) were added to the reaction vessel and the progress of the reaction was monitored by analyzing small samples using GLC methods. The results obtained after 3–4 hours reaction time using the different catalysts are presented in Table 2. The catalytic activity was rather poor irrespective of the ligand structure, and the obtained enantioselectivity ranged from 31% ee up to 61% ee. Prolonging the reaction time did not increase conversion, which suggests that the catalysts were decomposing during the first period of the reaction. Interestingly, in the transfer hydrogenation using the ruthenium catalyst derived from ligand **2e**, the opposite stereoisomer of 2-phenylethanol was obtained as the major isomer. The reason for this switch in enantioselectivity is presently unknown, but the electronic nature of the *N*-arenesulfonyl group in compound **2e** is certainly quite different in comparison to the other ligands used in this study. This could perhaps influence the stereochemical outcome of the hydride transfer. The poor conversion and enantioselectivity obtained with these compounds as ligands support the statement by Noyori that the “presence of an NH_2 terminus in the ligand structure is crucially important” for a successful reduction.^[4c]

In conclusion, we have successfully prepared a novel series of modular (*S*)-*N*-arylsulfonyl-2-aminomethylpyrrolidines starting from L-proline. The synthetic protocol is rather straightforward and allows for the introduction of various sulfonyl groups at a late stage in the synthesis, thereby facilitating the formation of com-

pounds with different electronic and structural properties. The obtained compounds were employed as organocatalysts in the asymmetric α -amination of aldehydes and as ligands for ruthenium in the asymmetric transfer hydrogenation of prochiral ketones. The best catalytic results were acquired in the former reaction, where the isolated *N*-aminooxazolidinone formed after reduction of the initial amination product, was obtained in up to 87% enantioselectivity.

Experimental Section

N-Boc-(*S*)-prolinol^[7]

A solution of *N*-Boc-(*S*)-proline (4.94 g, 23 mmol) in THF (35 mL) was stirred under nitrogen and cooled to 0 °C, when $\text{BH}_3\text{-DMS}$ (4.38 mL, 46 mmol) was carefully added. The reaction mixture kept at 0 °C for an additional 5 h and then left to warm up overnight. Water (~80 mL) was carefully added to quench the reaction. Ethyl acetate (500 mL) was added and the organic phase was washed with saturated aqueous solutions of NaCl (80 mL), NaHCO_3 (80 mL), H_2O (2×80 mL) and finally NaCl (80 mL). The organic phase was evaporated under reduced pressure to yield the crude alcohol, which was purified by flash chromatography on a silica gel column (eluent: pentane:EtOAc:EtOH, 88:6:6). The yield was 4.37 g (95%). ^1H NMR (400 MHz, CDCl_3 , 25 °C): δ = 1.47 (s, 9H), 1.53 (m, 1H), 1.80 (m, 2H), 2.00 (m, 1H), 3.32 (m, 1H), 3.44 (m, 1H), 3.59 (m, 2H), 3.96 (b, 1H), 4.71 (m, 1H).

N-Boc-(*S*)-2-(4-toluenesulfonyloxy)methylpyrrolidine (**6**)

To an ice-cold solution of *N*-Boc-(*S*)-prolinol (4.37 g, 21.7 mmol) in pyridine (23 mL) was added 4-toluenesulfonyl chloride (4.94 g, 25.9 mmol). The reaction mixture was stirred for 6 h and then diluted with diethyl ether (200 mL). The organic phase was washed with 10% HCl (3×75 mL), NaHCO_3 (3×75 mL) and NaCl (2×75 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was subjected to flash chromatography on silica gel (eluent: pentane:EtOAc 3:2). The yield was 6.47 g (84%). ^1H NMR (400 MHz, CDCl_3 , 60 °C): δ = 1.44 (s, 9H), 1.78 (m, 3H), 1.96 (m, 1H), 2.42 (s, 3H), 3.18 (m, 3H), 3.32 (b, 1H), 3.86 (b, 1H), 7.28 (m, 2H), 7.73 (d, J = 8.2 Hz, 2H).

N-Boc-(*S*)-2-azidomethylpyrrolidine (**7**)^[8b]

N-Boc-(*S*)-2-(4-toluenesulfonyloxy)methylpyrrolidine (4.38 g, 12.3 mmol) was dissolved in dry DMSO (130 mL) and sodium azide (4.81 g, 74.0 mmol) was added. The reaction mixture was heated to 64 °C for 19 h, allowed to cool to room temperature and diluted with diethyl ether (250 mL). The organic phase was washed with H_2O (3×200 mL) and NaCl (100 mL), dried with Na_2SO_4 and the solvent was evaporated. The crude product (2.53 g, 90%), was not further purified and was stored in the refrigerator until it was further used. ^1H NMR (400 MHz, CDCl_3 ,

25 °C): δ = 1.47 (s, 9H), 1.86 (m, 4H), 3.37 (m, 4H), 3.80–4.00 (b, 1H).

***N*-Boc-(*S*)-2-aminomethylpyrrolidine (**8**)^[8b]**

N-Boc-(*S*)-2-azidomethylpyrrolidine (0.46 g, 2.0 mmol) was dissolved in anhydrous THF (17 mL) and triphenylphosphine (1.1 g, 4.1 mmol) followed by H₂O (0.08 mL, 4.2 mmol) were added. The reaction mixture was heated to reflux until all starting material had been consumed (about 2 h). The organic solvent was then removed under reduced pressure and the remaining oil was dissolved in diethyl ether (45 mL). The pH was adjusted to around 2 with 1 M HCl and vigorous stirring and the aqueous phase was washed with diethyl ether (2 × 20 mL). The pH of the aqueous phase was adjusted to 13 using 2 M NaOH, and extracted with CH₂Cl₂ (6 × 20 mL). The organic phase was dried with Na₂SO₄ and concentrated under reduced pressure to afford the crude product (0.30 g, 74%). The crude was not further purified. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.40 (s, 9H), 1.49 (m, 2H), 1.75 (m, 4H), 2.62 (m, 1H), 2.77 (b, 1H), 3.26 (m, 2H), 3.75 (m, 2H).

General Preparation of Compounds **2a–e, Exemplified for the Synthesis of (*S*)-2-[(*N*-4-Toluenesulfonyl)aminomethyl]pyrrolidine (**2a**)**

N-Boc-(*S*)-2-aminomethylpyrrolidine (0.53 g, 2.62 mmol) was dissolved in triethylamine (4.6 mL), the solution was cooled to 0 °C and 4-toluenesulfonyl chloride (0.62 g, 3.26 mmol) was added. The reaction mixture was stirred for 2 h, diluted with diethyl ether (100 mL) and washed with 10% HCl (40 mL), NaHCO₃ (2 × 40 mL) and NaCl (2 × 40 mL). The organic phase was dried with Na₂SO₄ and purified by flash chromatography on silica gel (3:1 pentane: EtOAc) to afford the *N*-Boc-derivative; yield: 0.48 g (53%).

The *N*-Boc-derivative (0.48 g, 1.29 mmol) was dissolved in a 1:1 mixture of trifluoroacetic acid and dichloromethane (8 mL) and the solution was stirred for 2 h at ambient temperature, at which time the solvent was evaporated under reduced pressure. The pH was adjusted to 8 with aqueous NaHCO₃ and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with Na₂SO₄ and the solvent was evaporated at reduced pressure to afford the pure title compound; yield: 0.31 g (90%). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.38 (m, 1H), 1.68 (m, 3H), 2.40 (s, 3H), 2.95 (m, 4H), 3.31 (b, 1H), 4.22 (b, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 143.2, 137.1, 129.8, 127.1, 58.0, 46.7, 46.1, 28.8, 25.5, 21.6.

(*S*)-2-[*N*-(1-Naphthalenesulfonyl)aminomethyl]-pyrrolidine (2b**)**

Compound **2b** was obtained in 61% yield from **8** (two steps). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.25 (m, 1H), 1.59 (m, 3H), 2.74 (m, 3H), 2.92 (m, 1H), 3.18 (m, 1H), 4.51 (b, 2H), 7.48 (m, 3H), 7.90 (m, *J* = 8.0 Hz, 1H), 8.02 (m, *J* = 5.2 Hz, 1H), 8.21 (m, *J* = 7.2 Hz, 1H), 8.67 (d, *J* = 8.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 135.0, 134.2, 134.0,

129.2 (2C), 129.0, 128.2, 126.9, 124.6, 124.2, 57.3, 47.1, 46.1, 28.8, 25.6.

(*S*)-2-[*N*-(2,4,6-Triisopropylbenzenesulfonyl)aminomethyl]pyrrolidine (2c**)**

Compound **2c** was obtained in 55% yield from **8** (two steps). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.22 (s, 3H), 1.23 (s, 3H), 1.24 (s, 3H), 1.26 (s, 9H), 1.40 (m, 1H), 1.69 (m, 3H), 2.78 (m, 1H), 2.88 (m, 2H), 3.35 (m, 1H), 3.80 (b, 2H), 4.15 (m, 2H), 7.14 (s, 2H); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 152.5, 150.3, 132.4, 123.7, 57.1, 46.7, 46.2, 34.2, 29.7, 29.1, 25.9, 25.0, 23.6.

(*S*)-2-(*N*-Pentamethylbenzenesulfonylaminomethyl)-pyrrolidine (2d**)**

Compound **2d** was obtained in 57% yield from **8** (two steps). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 1.36 (m, 1H), 1.68 (m, 3H), 2.24 (s, 6H), 2.28 (s, 3H), 2.58 (m, 1H), 2.60 (s, 6H), 2.75 (m, 1H), 2.88 (m, 2H), 3.29 (m, 1H); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 139.3, 134.8, 134.3, 126.0, 57.0, 46.9, 46.4, 29.1, 26.2, 19.0, 17.9, 17.1.

(*S*)-2-(*N*-Pentafluorobenzenesulfonylaminomethyl)-pyrrolidine (2e**)**

Compound **2e** was obtained in 15% yield from **8** (two steps). ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 0.85 (m, 1H), 1.69 (m, 2H), 1.97 (m, 1H), 2.99 (t, 1H), 3.34 (d, 1H), 3.60 (m, 1H), 3.90 (m, 2H), 5.77 (b, 1H); ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 146.7, 144.3, 142.4, 132.6, 51.6, 51.5, 48.9, 29.4, 24.5.

General Procedure for the α -Amination Exemplified for the Formation of (4-Methyl-2-oxooxazolidin-3-yl)carbamic Acid Ethyl Ester^[10]

Propanal (0.11 mL, 1.5 mmol) and diethyl azodicarboxylate (0.16 mL, 1.0 mmol) were suspended in dichloromethane (2.5 mL). The catalyst **2** (0.01 mmol) was added and the reaction mixture was stirred until the yellow colour disappeared (3 h) at which time MeOH (2.5 mL) and NaBH₄ (50 mg, 1.32 mmol) were added. After 20 min, 0.5 M NaOH (2.5 mL) was added and the mixture was stirred for 2 h when the organic solvents were evaporated. The aqueous phase was extracted with EtOAc and the organic phase was dried with Na₂SO₄. Evaporation of the solvent yielded the *N*-aminooxazolidinone. The enantiomeric excess was determined using GLC using the following conditions (CP Chirasil DEX CB), oven: 250 °C 30 min R_t; major (1): 15.4 min, minor (2): 15.6 min.

General Procedure for the Catalytic Transfer Hydrogenation of Acetophenone

Compound **2** (0.01 mmol) and [RuCl₂(*p*-cymene)]₂ (0.0031 g, 0.005 mmol) were added to a dried reaction tube and the reaction vessel was put under vacuum for 1 h. The tube was filled

with N₂ (gas) and 2-PrOH (2.5 mL) was added. The mixture was heated to 80 °C for 20 min and then cooled to room temperature. Acetophenone (0.12 mL, 1 mmol) and 3 mol % NaOH (0.13 mL of 0.227 M solution in 2-PrOH) were added. Samples taken at various time-points were passed through a funnel of silica and washed with ethyl acetate. The solutions were analyzed by chiral GLC using the following conditions (CP Chiral DEX CB), oven: 110 °C 10 min, 80 °C/min to 200 °C, hold 5 min, R_t: acetophenone: 3.4 min, (R)-1-phenylethanol: 6.9 min and (S)-1-phenylethanol: 7.4 min.

Acknowledgements

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References and Notes

- [1] For reviews, see: a) B. List, *Synlett* **2001**, 1675–1686; b) B. List, *Tetrahedron* **2002**, 58, 5573–5590; c) R. O. Duthaler, *Angew. Chem. Int. Ed.* **2003**, 42, 975–978; d) A. Córdova, *Acc. Chem. Res.* **2004**, 37, 102–112.
- [2] For recent examples of the catalytic use of proline, see: a) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem. Int. Ed.* **2004**, 43, 1109–1112; b) Y. Hayashi, J. Yamaguchi, T. Suniya, M. Shoji, *Angew. Chem. Int. Ed.* **2004**, 43, 1112–1115.
- [3] a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, 43, 1272–1277; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 2458–2460.
- [4] For reviews, see: a) U. Matteoli, P. Frediani, M. Bianchi, C. Botteghi, S. Gladiali, *J. Mol. Catal.* **1981**, 12, 265–319; b) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, 92, 1051–1069; c) J.-E. Bäckvall, R. L. Chowdhury, U. Karlsson, G. Z. Wang, in: *Perspectives in Coordination Chemistry*, (Eds.: A. F. Williams, C. Floriani, A. E. Merbach), Helvetica Chimica Acta, Basel, **1992**, pp. 463–486; d) C. F. de Graauw, J. A. Peters, H. van Bekkum, J. Huskens, *Synthesis* **1994**, 1007–1017; e) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, 30, 97–102; f) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, 10, 2045–2061; g) J.-E. Bäckvall, *J. Organomet. Chem.* **2002**, 652, 105–111; h) K. Everaere, A. Mortreux, J.-F. Carpentier, *Adv. Synth. Catal.* **2003**, 345, 67–77; i) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, 345, 103–151.
- [5] a) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, 117, 7562–7563; b) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, 118, 2521–2522; c) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, 118, 4916–4917; d) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 285–288; e) S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 288–290.
- [6] a) I. M. Pastor, P. Västilä, H. Adolfsson, *Chem. Commun.* **2002**, 2046–2047; b) I. M. Pastor, P. Västilä, H. Adolfsson, *Chem. Eur. J.* **2003**, 9, 4031–4045; c) A. Bøgevig, I. M. Pastor, H. Adolfsson, *Chem. Eur. J.* **2004**, 10, 294–302.
- [7] G. Bartoli, M. Bosco, A. Giuliani, T. Mecozzi, L. Sambri, E. Torregiani, E. Marcantoni, *J. Org. Chem.*, **2002**, 67, 9111–9114.
- [8] The procedure was originally presented in: a) H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, 2, 635; we employed conditions used in: b) M. J. Soth, J. S. Nowick, *J. Org. Chem.* **1999**, 64, 276–281; c) A. Slaitas, E. Yeheskiely, *Eur. J. Org. Chem.* **2002**, 14, 2391–2399.
- [9] For a recent review, see: C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem.* **2004**, 1377–1385.
- [10] a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, 41, 1790–1793; b) B. List, *J. Am. Chem. Soc.* **2002**, 124, 5656–5657; c) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, 124, 6254–6255; d) H. Vogt, S. Vanderheiden, S. Bräse, *Chem. Commun.* **2003**, 2448–2449.
- [11] The L-proline (10 mol %) catalyzed α -amination of propanal with DEAD resulted in 67% yield and 93% ee. However, using a catalytic loading of 2 mol % L-proline gave the α -aminated product in 92% yield and 84% ee (see Ref.^[10a]).