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An amine sulfonamide organocatalyst for promoting direct, highly enantioselective α-aminoxylation reactions of aldehydes and ketones

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Abstract—A novel, pyrrolidine sulfonamide-based organocatalyst has been developed and used to catalyze direct, efficient α-aminoxylation reactions of aldehydes and ketones with excellent regio- and enantioselectivities. Unlike L-proline, the new catalyst exhibits high activity and enantioselectivity when used in a variety of organic solvents.

The development of efficient, stereoselective catalytic reactions, which can be used to construct optically active α-hydroxy carbonyl compounds, has continued to attract considerable synthetic interest. A number of diastereoselective and enantioselective methods for the synthesis of these substances have been reported. Most employ indirect approaches, requiring preformation of enolates and enolate equivalents from the corresponding ketones and aldehydes.[1] From the viewpoint of economy, direct α-aminoxylation reactions of aldehydes and ketones are more attractive. Recently, an elegant enantioselective α-oxidation reaction of tin enolates with nitrosobenzene has been developed by Yamomoto and his co-workers.[2] Based on the observations, MacMillan, Zhong, Cordova, and Hayashi, independently uncovered direct, nitrosobenzene based, proline-catalyzed enantioselective α-aminoxylation reactions of aldehydes and ketones.[3,4]

Inspired by the pioneering work of List, Barbas, III and Learner,[5] proline has received considerable attention in recent years as the foundation of small organic molecule-based organocatalysts for asymmetric synthesis.[6] Surprisingly, however, relatively few efficient organocatalysts other than chiral amino acids have been probed for use in asymmetric organic transformations including α-aminoxylations.[3,4,6–14] As a result of this deficiency, we have recently initiated an investigation aimed at designing novel small organic catalysts capable of promoting highly stereoselective organic reactions on a number of structurally diverse organic substrates.[15–17] In this communication, we report the results of a study, which has led to the development of a novel (*S*)-pyrrolidine sulfonamide based organocatalyst for direct α-aminoxylation reactions of aldehydes and ketones with high regio- and enantioselectivities (>97% ee) in good yields.

The carboxylic acid proton in proline plays a critical role in enhancing the reactivity and stereoselectivity of proline based catalyst.[4,18] In contrast, L-prolinamide is known to be ineffective in catalyzing reactions (Fig. 1).[18] The acidity of NH protons in L-prolinamide is much less than that of a carboxyl group in proline and, as a result, the significant difference in catalytic activity between these two substances is likely due to their different acidity. We hypothesized that increasing the acidity of the NH amide protons would lead to a significant enhancement in the catalytic activity of L-prolinamide. It is known that the pK_a of trifluoromethanesulfonamide in water is 6.3, which is comparable to that

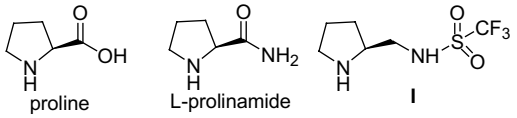

Figure 1. A pyrrolidine sulfonamide-based organocatalyst **I**.

Keywords: Asymmetric catalysis; Aldehydes; Ketones; α-Aminoxylation; Pyrrolidine sulfonamide.
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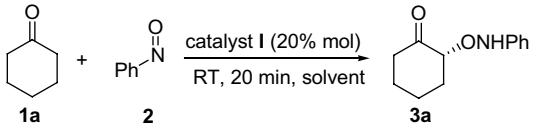
of acetic acid (pK_a of 4.76).[19] However, in DMSO, trifluoromethanesulfonamide has an even greater acidity (pK_a of 9.7) than that of acetic acid (pK_a 12.3).[19] With these observations in mind, we envisioned that incorporation of trifluoromethanesulfonamide moiety into a pyrrolidine system would create a new class of amine–sulfonamide bifunctional organocatalysts that could function in the same way as proline in catalyzing organic reactions.

The first generation catalyst in this family, **I** (Fig. 1) contains a primary trifluoromethanesulfonamide group linked to a chiral pyrrolidine backbone. The pyrrolidine sulfonamide **I** is readily prepared from (*S*)-2-amino-1-*N*-Cbz-pyrrolidine by using a known reaction sequence (see Supplementary data).[20] Preliminary studies showed that **I** effectively catalyzed nitrosobenzene induced α-aminoxylation reactions of aldehydes and ketones with comparable and, in some cases, even greater activity and efficiency than does proline.

In an exploratory study, the reaction of cyclohexanone **1a** with nitrosobenzene **2** in the presence of 20 mol% of catalyst **I** at room temperature was carried out in different solvents. The results revealed that **I** exhibited a high catalytic efficiency in its promotion of high yielding 62–85%, α-aminoxylation reactions, that proceeded with excellent enantioselectivities (>99% ee) and high regioselectivities (Table 1). Independent of the solvent used, the reactions were completed in 20 min and they afforded *O*-addition product **3a** exclusively. In contrast, solvents had a significant effect on proline-catalyzed α-aminoxylation reaction yields and enantioselectivities.[3a,b,d] Based on this exploratory study, DMSO was selected as a solvent for the studies described below.

To demonstrate the generality of direct α-aminoxylations catalyzed by **I**, reactions of a variety of ketone substrates with nitrosobenzene in DMSO at room temperature were explored. The results of reactions of

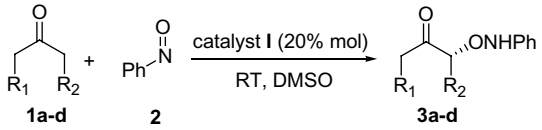
Table 1. Effect of solvents on the asymmetric α-aminoxylation reactions[a]

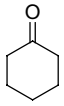
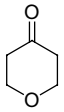
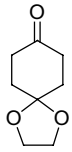
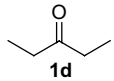


Entry	Solvent	% Yield[b]	% ee[c]
1	DMSO	84	>99
2	$CHCl_3$	85	>99
3	DMF	62	>99
4	THF	77	>99
5	CH_3CN	66	>99
6	EtOAc	76	>99

[a] Reaction conditions: A solution of **2** (2 equiv) in DMSO was added by a syringe pump over 10 min to a solution of **1a** (1 equiv) and **I** (0.2 equiv) in DMSO and the reaction was continued for an additional 10 min (see Supplementary data).
[b] Isolated yields.
[c] Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralpak AD).

Table 2. Catalyst **I** catalyzed direct α-aminoxylation reactions of different ketones



Entry	Product	% Yield[a]	% ee[b]
1	 **1a**	84	>99
2	 **1b**	86	>99
3	 **1c**	94	98
4	 **1d**	71	97

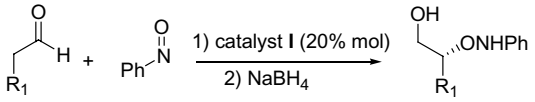
[a] Isolated yields.
[b] ee Determined by chiral HPLC analysis (Chiralpak AD or AS-H).

four cyclic and acyclic ketones promoted by 20 mol% **I** are given in Table 2. These processes took place smoothly to give *O*-addition products exclusively in good yields and with high enantioselectivities. As with cyclohexanone, cyclic ketones **1b**,**c**, and acyclic ketone **1d** gave adducts **3b**–**d** in high yields (86%, 94% and 71%, respectively) with excellent enantioselectivities (>99%, 98% and 97%, respectively). The effect of catalyst loading on reaction efficiency was also studied using **1a** and **2** as an example. Remarkably, a catalyst loading as low as 1.0 mol% still led to significantly fast reaction without any loss of enantioselectivity (>99% ee).[21]

α-Aminoxylation reactions of nitrosobenzene with aldehydes, catalyzed by **I**, were probed next. Under the same reaction conditions described above, efficient reaction occurred within 0.5 h following slow addition of nitrosobenzene (Table 3). Owing to their instability, the aldehyde *O*-addition products were reduced by $NaBH_4$ in situ to produce the more stable 2-aminoxy alcohols **3e**–**i** prior to purification and characterization.[3b] Again, reactions resulted in efficient (66–81%), highly regio- and enantioselective (>99% ee) formation of *O*-addition products (Table 3).

A similar transition-state model **II** to that used to rationalize proline-catalyzed α-aminoxylation reactions of ketones and aldehydes can be used to explain the regio- and stereochemical courses of the processes catalyzed by **I** (Fig. 2).[3b–d] In this model, the enamine formed by reaction of (*S*)-pyrrolidine sulfonamide **I** with the enolizable ketone or aldehyde is attacked by nitrosobenzene from the less hindered *Si* face through a chair

Table 3. Catalyst **I** catalyzed direct α-aminoxylation of different aldehydes



Entry	R_1	% Yield[a]	% ee[b]
1	*i*-Pr, **1e**	81	>99
2	CH_3, **1f**	66	>99
3	*n*-Pr, **1g**	73	>99
4	*n*-Bu, **1h**	74	>99
5	$PhCH_2$, **1i**	79	>99

[a] Isolated yields.
[b] ee Determined by chiral HPLC analysis (Chiralpak AD or AS-H).

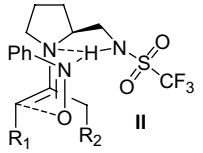


Figure 2. Proposed transition-state model for α-aminoxylation reactions.

transition state to afford the *O*-addition product enantioselectively. The CF_3SO_2-group may also play a role in controlling the stereochemistry of the process by offering further interference for attack at the *Re* face. A detailed study probing this proposal is under current investigation.

In conclusion, a novel pyrrolidine sulfonamide catalyst **I**, which promotes direct, highly efficient α-aminoxylation reactions of aldehydes and ketones with nitrosobenzene, has been developed. This catalyst displays excellent levels of enantioselectivity for reactions of ketones (>97% ee) and aldehydes (>99% ee). Furthermore, it also exhibits high catalytic activities and enantioselectivities when used in a wide variety of organic solvents. Further efforts to evaluate the scope of the α-aminoxylation reactions described above and to explore other organic transformations using new types of catalysts are underway.[17]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.029.

References and notes

1. Reviews of hydroxylation: (a) Davis, F. A.; Chen, B. C. In *Houben Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffman, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1995; Vol. E 21, p 4497; (b) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919–934.
2. (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039; (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360–5361.
3. Aldehydes as substrates: (a) Brown, F. J.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250; Ketones as substrates: (c) Bøgevig, A.; Sunden, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112; (d) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1115.
4. During the manuscript preparation, Yamamoto and coworkers reported a pyrrolidine tetrazole catalyzed the reaction: Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374–5378.
5. List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
6. For a review of proline-catalyzed asymmetric transformations, see: List, B. *Tetrahedron* **2002**, *58*, 5573–5590.
7. For a review of amino acids and peptides as catalysts, see: Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495.
8. For a review on amine-catalyzed reactions, see: France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985–3012.
9. For a general review on organocatalysis, see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748, and references cited therein.
10. For a review on Shi ketone-based epoxidation catalyst, see: Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000, and reference cited therein.
11. For examples using MacMillan catalyst, see: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875; (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371; (d) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173; (e) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458–2459; (f) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895; (g) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1193; (h) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109.
12. For results from Jørgenson and his group, see: (a) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331–8338; (b) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661–665; (c) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583–2591; (d) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151–4157; (e) Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498–1501; (f) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955–4957.
13. For examples using Jacobsen thiourea catalyst, see: (a) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103; (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10013.

14. For Other examples, see: (a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146; (b) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394–12395; (c) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; (d) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986.
15. We recently reported a L-prolinamide catalyzed a-selenenylation of aldehydes: Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817–2820.
16. This catalyst can catalyze the Mannich-type reactions: Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.*, accepted for publication. doi:10.1016/j.tetlet.2004.08.032.
17. We have found this catalyst can efficiently facilitate the asymmetric Aldol and Michael addition reactions.
18. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5261.
19. (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463; (b) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *41*, 3305–3313; (c) Bordwell, F. G.; Algrim, D. *J. Org. Chem.* **1976**, *41*, 2507–2508.
20. Recently we have developed a more efficient 3-step synthesis of the catalyst from commercially available *N*-Cbz-L-prolinamide instead of 6-step from *N*-Cbz-L-Proline reported in the patent: Burch, R. M.; Patch, R. J.; Shearer, B. G.; Perumattam, J. J.; Natalie, K. J., Jr. WO Patent 9203415, 1992.
21. 20 mol% **I**: 15 min, 84% yield, >99% ee; 10 mol% **I**: 30 min, 80% yield, >99% ee; 5 mol% **I**: 50 min, 72% yield, >99% ee; 2 mol% **I**: 2.5 h, 70% yield, >99% ee; 1 mol% **I**: 6.5 h, 64% yield, >99% ee.