

Direct Amino Acid-Catalyzed Asymmetric Desymmetrization of *meso*-Compounds: Tandem Aminoxylation/O–N Bond Heterolysis Reactions

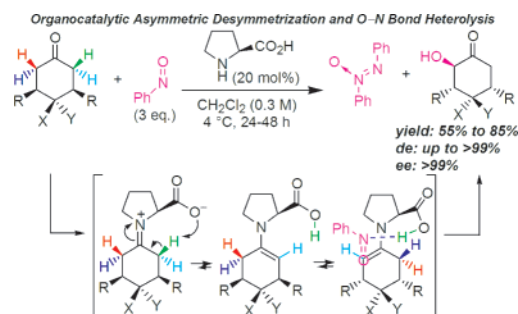
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Received February 4, 2005

ABSTRACT



A practical organocatalytic process for the synthesis of optically active, highly substituted α -hydroxy-ketones was achieved through asymmetric desymmetrization (ADS) of prochiral ketones. The ADS and O–N bond reduction reaction of prochiral ketone with nitrosobenzene in the presence of a catalytic amount of chiral amine or amino acid produced the tandem ADS/O–N bond reduced products as single diastereomers with good yields and excellent enantiomeric excesses.

The asymmetric desymmetrization (ADS) of highly substituted prochiral *meso*-compounds represents a powerful synthetic tool for the expedient synthesis of two or more contiguous stereogenic centers in a single operation. The ADS of *meso*-compounds by enzymatic¹ and nonenzymatic² methods has proven to be a versatile and powerful strategy. ADS of *meso*-compounds allows many stereocenters to be established in a single symmetry-breaking transformation. The most typical nonenzymatic ADS methods involve the

addition of stoichiometric amounts of heteronucleophiles to prochiral cyclic anhydrides using a catalytic chiral source.³

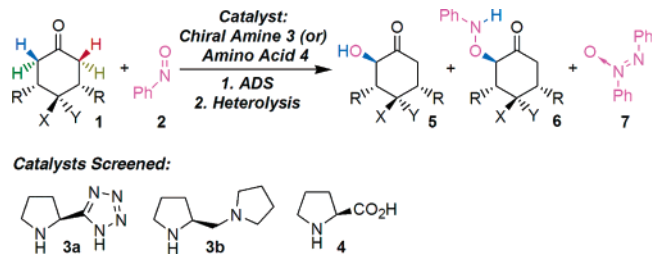
Here we describe a novel ADS of highly substituted *meso*-ketones **1** using organocatalytic highly diastereo- and enantioselective α -hydroxylation through tandem aminoxylation/O–N bond heterolysis with nitrosobenzene **2**. Nitrosobenzene **2** plays a dual role: it furnishes chiral α -hydroxy ketones **5** through enantioselective oxidation of prochiral ketones **1** and reduces O–N bonds to result in α -aminoxy products **6** under amine **3** or amino acid **4** catalysis as shown in Scheme 1.

(1) (a) For an overview of enzymatic ADS, see: Wong, C.-H.; Whitesides, G. M. In *Enzymes in Synthetic Organic Chemistry*; Baldwin, J. E., Magnus, P. D., Eds.; Elsevier: Oxford, 1994. (b) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354.

(2) For a review of nonenzymatic ADS, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765–1784.

(3) For references to important ADS literature, see: (a) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131–3134. (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965–2983.

Scheme 1. Direct Organocatalytic Tandem Asymmetric Desymmetrization/O–N Bond Heterolysis



Our tandem approach complements previous α -aminoxylation of simple ketones catalyzed by L-proline.⁴

We initiated our studies of the ADS/O–N bond reduction reaction by screening a number of known and novel organocatalysts for the α -hydroxylation of highly substituted spirotrione **1a**⁵ by nitrosobenzene **2**. Representative results are shown in Table 1. L-Proline **4** catalyzed the formation of α -hydroxy ketone **5a** in very poor yields in DMSO and [bmim]PF₆ solvents (Table 1, entries 1 and 2). The bifunctional catalyst diamine **3b**/TFA⁶ also generated **5a** in very poor yields in DMSO (Table 1, entry 3). In contrast to this result, L-proline **4** afforded **5a** as a single diastereomer in CH₃CN with >99% enantiomeric excess (ee); however, the yield of **5a** was moderate (42%, Table 1, entry 4). Interestingly, L-proline catalysis in aprotic/nonpolar solvents (CHCl₃ and CH₂Cl₂) provided **5a** in good yields with >99% ee and diastereomeric excess (de) (Table 1, entries 5 and 6). Tetrazole-based catalyst **3a**⁷ also furnished the α -hydroxy ketone **5a** in moderate to good yields with excellent ee and

Table 1. Optimization of Direct Organocatalytic Tandem ADS and O–N Bond Heterolysis of Highly Substituted Prochiral Spirotrione **1a**^a

entry	catalyst (20 mol %)	solvent (0.3 M)	Ph–N=O (equiv)	T (°C)	t (h)	product (5a) yield (%) ^b	ee ^c (%)
1 ^d	4	DMSO	1.5	25	54	<3	
2 ^d	4	(bmim)PF ₆	1.5	25	54	<2	
3 ^d	3b /TFA ^e	DMSO	1.5	25	54	<2	
4 ^f	4	CH ₃ CN	1.5	25	24	42	>99
5 ^f	4	CHCl ₃	1.5	25	24	50	>99
6 ^f	4	CH ₂ Cl ₂	1.5	25	24	60	>99
7	3a	CH ₂ Cl ₂	1.5	25	44	72	>99
8	3a	CH ₃ CN	1.5	25	20	51	>99
9	4	CH₂Cl₂	3.0	4	24	85	>99
10	3a	CH ₂ Cl ₂	3.0	4	24	76	>99
11 ^g	4	CH₂Cl₂	0.5	4	24	30	>99

^a Reactions were carried out in solvent (0.3 M) with indicated equivalents of nitrosobenzene relative to the prochiral ketone **1a** in the presence of 20 mol % catalyst. ^b Yield refers to the column-purified product. ^c Ee determined by CSP-HPLC analysis. ^d Unreacted prochiral ketone **1a** (80–85%) was isolated. ^e 1:1 mixture of **3b** and trifluoroacetic acid. ^f Unreacted prochiral ketone **1a** (30–40%) was isolated. ^g Aminoxy ketone **6a** (15%) was isolated along with unreacted prochiral ketone **1a** (70%).

de (Table 1, entries 7 and 8). The optimal conditions for L-proline **4** catalysis were 4 °C in CH₂Cl₂ with 3 equiv of nitrosobenzene **2** and furnished α -hydroxy ketone **5a** in 85% yield, >99% ee, and de (Table 1, entry 9).⁸ In these tandem reactions, product **5a** was accompanied by *trans*-azoxybenzene **7** and unreacted prochiral spirotrione **1a**, and no α -aminoxy ketone **6a** was observed (Table 1).

The proposed mechanism for stereospecific synthesis of chiral alcohol **5a** through reaction of prochiral spirotrione **1a** and nitrosobenzene **2** is illustrated in Scheme 2. Chiral L-pyrrolidine-tetrazole **3a** or L-proline **4** catalyze the diastereospecific in situ generation of enamine **9** from spirotrione **1a**. Subsequent (*Re*-face)⁴ⁿ nucleophilic addition to nitrosobenzene **2** furnishes the α -aminoxy ketone **6a**, which immediately undergoes addition to excess nitrosobenzene **2** followed by rearrangement of intermediate **12** into α -hydroxy

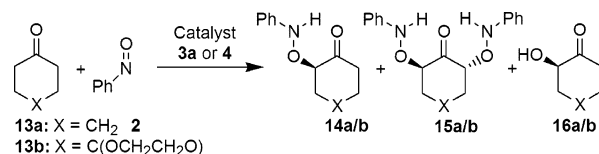
(4) (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809. (c) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374–5378. (d) Bøgevig, A.; Sundeen, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112. (e) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1115. (f) Merino P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995–2997. (g) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293–8296. (h) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966–5973. (i) Córdoba, A.; Sundén, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673–3684. (j) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963. (k) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317–3321. (l) Wang, W.; Wang, J.; Hao, Li.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 7235–7238. (m) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435. (n) Cheong, P. H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912–13913.

(5) All prochiral spirotriones **1** were prepared using the newly developed “organo-click chemistry” technique; see: Ramachary, D. B.; Barbas, C. F., III. *Chem. Eur. J.* **2004**, *10*, 5323–5331.

(6) The **3b**/trifluoroacetic acid (TFA) catalyst system was shown to be highly effective in the asymmetric aldol and Michael reactions. Due to the insolubility of salt **3b**/TFA in other solvents, we used only DMSO as a solvent in our tandem ADS/O–N bond heterolysis studies. For details of catalyst **3b**/TFA in asymmetric catalysis, see: (a) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527–2530. (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423. (c) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369–4372. (d) Ramachary, D. B.; Anebousely, K.; Chowdari, N. S.; Barbas, C. F., III. *J. Org. Chem.* **2004**, *69*, 5838–5849. (e) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177. (f) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267. (g) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199–201.

(7) (a) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558–560. (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986. (c) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96. (d) Hartikka, A.; Arvidsson, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834. (e) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808–1809. (f) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541–3544. (g) For application in total synthesis of BIRT-377, see: Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867–870.

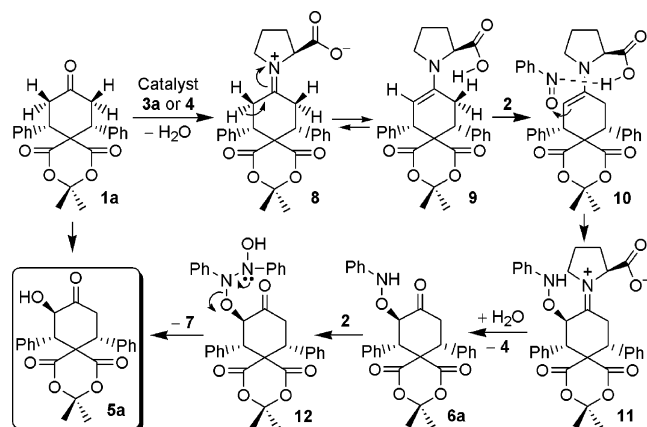
(8) Relative stereochemistry of product **5a** was established by NMR analysis of the 3,5-dinitrobenzoate derivative of **5a** (eq S1, see Supporting Information).

Table 2. Direct Organocatalytic Tandem Aminoxylation and O–N Bond Heterolysis of Cyclohexanones **13a/b**^a

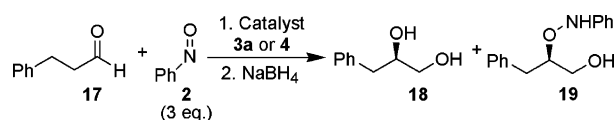
entry	substrate	catalyst	solvent	Ph–N=O (equiv)	T (°C)	t (h)	yield (%) ^b			ee (%) ^c 16a/b
							14a/b	15a/b	16a/b	
1 ^d	13a	3a	DMSO	0.33	25	1	50	20	6	99
2	13a	4	CH ₂ Cl ₂	3.0	25	1	2		43	99
3	13a	4	CH ₂ Cl ₂	3.0	4	24	5		75	99
4	13b	4	CH ₂ Cl ₂	3.0	4	30			40	98

^a Reactions were carried out in solvent (0.3 M) with indicated equivalents of nitrosobenzene relative to the cyclohexanone in the presence of 30 mol % catalyst. ^b Yield refers to the column-purified product. ^c Ees of product were determined by CSP-HPLC analysis of the 3,5-dinitrobenzoate derivative of **16a/b**. ^d Performed with 5 mol % L-pyrrolidine-tetrazole **3a**.

ketone **5a** and *trans*-azoxybenzene **7**.⁹ The key intermediate **6a** was isolated when 0.5 equiv of **2** was used (Table 1, entry 11).

Scheme 2. Proposed Reaction Mechanism

This method for *in situ* reduction of O–N bonds was further applied to simple ketones and aldehydes. As shown in Tables 2 and 3, simple ketones and aldehydes were

Table 3. Direct Organocatalytic Tandem Aminoxylation and O–N Bond Heterolysis of 3-Phenyl Propanal **17**

catalyst	solvent	T (°C)	t (h)	yield (%)		ee (%) 18
				18	19	
4	CH ₃ CN	4	18	20		>99
3a	CH ₃ CN	24	1.5	35	35	>99

Table 4. Chemically Diverse Libraries of α-Hydroxy Ketones^a

entry	substrate	product	yield (%) ^b	ee (%) ^c
1			76	99
2			71	>99
3			63	99
4			71	>99
5			55	98
6 ^d			<5	–
7 ^e			26	>99 (cis) >99 (trans)

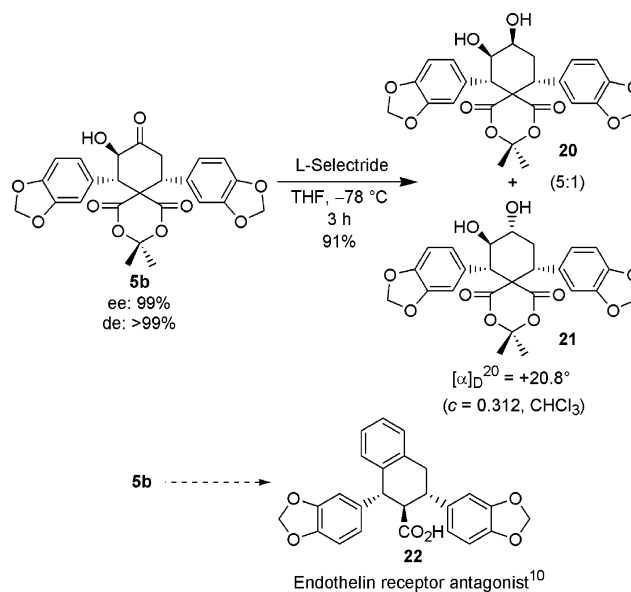
^a All reactions were carried out in CH₂Cl₂ (0.3 M) with 3.0 equiv of nitrosobenzene relative to the prochiral ketones **1b–g** in the presence of 20 mol % L-proline at 4 °C and were complete in 48 h. ^b Yield refers to the column-purified product. ^c Ees of product were determined by CSP-HPLC analysis. ^d Reaction was performed at 24 °C for 7 days under L-proline catalysis. ^e Reaction was performed at 24 °C for 69 h under L-Pyrrolidine-tetrazole **3a** catalysis.

transformed into enantiomerically pure α -hydroxy ketones **16a** and **16b** or 1,2-diols **18** in moderate to good yields using 3 equiv of nitrosobenzene under organocatalysis. The intermediacy of aminoxylated products is supported in the heterolysis of the O–N bond of **14a** following treatment with **2** (eq S2, see Supporting Information).

The scope of the diastereo- and enantioselective tandem ADS/O–N bond reduction was investigated. A series of 1,2,3-trisubstituted prochiral spirotriones **1b–g**⁵ were reacted with excess nitrosobenzene **2** catalyzed by 20 mol % L-proline **4** at 4 °C in CH₂Cl₂ (Scheme 1 and Table 4). With one exception, the hydroxy-spirotriones **5** were obtained as single diastereomers with good yields and excellent ees. The reaction of prochiral ketone **1f** with nitrosobenzene **2** furnished the hydroxy-ketone **5f** as single isomer, in good yield and excellent ee (Table 4, entry 5). Interestingly, ketone **1g** did not furnish the expected hydroxy-ketone **5g** under these conditions; however, ketone **5g** was generated in 1.5:1 dr with very poor yields at 24 °C after a longer reaction time (Table 4, entry 6). Under L-pyr-tetrazole **3a** catalysis at 24 °C, a moderate yield of **5g** was obtained with 1.5:1 dr and >99% ee of each isomer (Table 4, entry 7). L-Selectride reduction of **5b** furnished the chiral diols **20** and **21** in a 5:1 ratio with 91% yield (Scheme 3). Chiral hydroxy-ketone **5b** will serve as a suitable synthon for the synthesis of endothelin receptor antagonist **22**¹⁰ as shown in Scheme 3.

In summary, we have developed methods for the ADS and O–N bond reduction of prochiral ketones **1** with nitrosobenzene **2** under amino acid catalysis. The tandem reaction proceeds in good yield with >99% ee and >99% de using L-proline as the catalyst. Furthermore, we have demonstrated that the *in situ*-generated α -aminoxyl ketones

Scheme 3. Application of ADS/O–N Bond Heterolysis Products



6 undergo O–N bond reduction with **2** to yield α -hydroxy ketones **5**. Further work is in progress to utilize this novel ADS/O–N bond reduction reaction.

Acknowledgment. This study was supported in part by the National Institutes of Health [CA27489] and the Skaggs Institute for Chemical Biology.

Supporting Information Available: Experimental procedures, compound characterization, and analytical data (¹H NMR, ¹³C NMR, and HRMS) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) For preparation of azoxybenzene **7** from reaction of nitrosobenzene **2** with phenylhydroxylamine, see: Becker, A. R.; Sternson, L. A. *J. Org. Chem.* **1980**, *45*, 1708–1710.

(10) Xiang, J. N.; Nambi, P.; Ohlstein, E. H.; Elliott, J. D. *Bioorg. Med. Chem.* **1998**, *6*, 695–700.