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

Dhevalapally B. Ramachary and Carlos F. Barbas, III*

The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

carlos@scripps.edu

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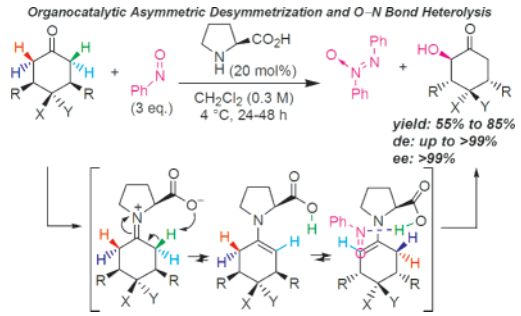
ABSTRACT



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 enzymatic[1] and nonenzymatic[2] 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.

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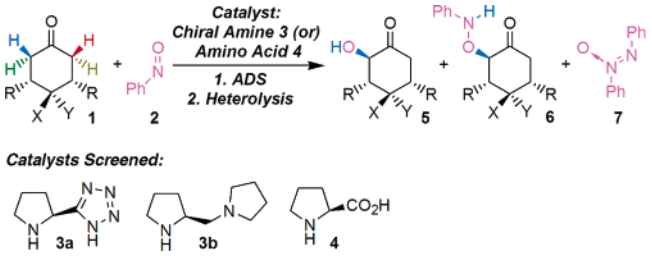
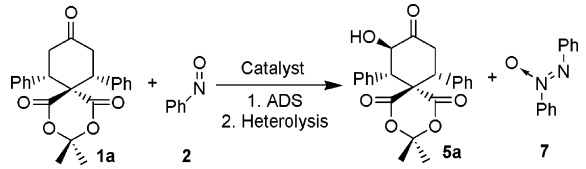
Scheme 1. Direct Organocatalytic Tandem Asymmetric Desymmetrization/O−N Bond Heterolysis



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]PF_6 solvents (Table 1, entries 1 and 2). The bifunctional catalyst diamine **3b**/TFA[6] 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 CH_3CN 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 ($CHCl_3$ and CH_2Cl_2) 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 de (Table 1, entries 7 and 8). The optimal conditions for L-proline **4** catalysis were 4 °C in CH_2Cl_2 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).

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_3CN	1.5	25	24	42	>99
5[f]	**4**	$CHCl_3$	1.5	25	24	50	>99
6[f]	**4**	CH_2Cl_2	1.5	25	24	60	>99
7	**3a**	CH_2Cl_2	1.5	25	44	72	>99
8	**3a**	CH_3CN	1.5	25	20	51	>99
9	**4**	**CH_2Cl_2**	**3.0**	**4**	**24**	**85**	**>99**
10	**3a**	CH_2Cl_2	3.0	4	24	76	>99
11[g]	**4**	**CH_2Cl_2**	**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%).

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) Bogevig, 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) Córdova, 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.

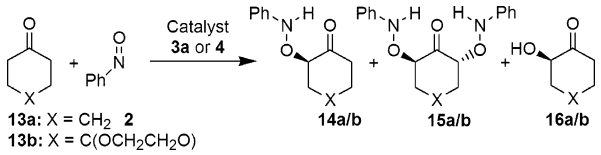
(5) All prochiral spirotriones **1** were prepared using the newly developed "organo-click chemistry" technique; see: Ramachary, D. B.; Barbas, C. F., III. *Chem. Eur. J.* **2004**, *10*, 5323−5331.

(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.; Anebouselvy, 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**, *16*, 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]

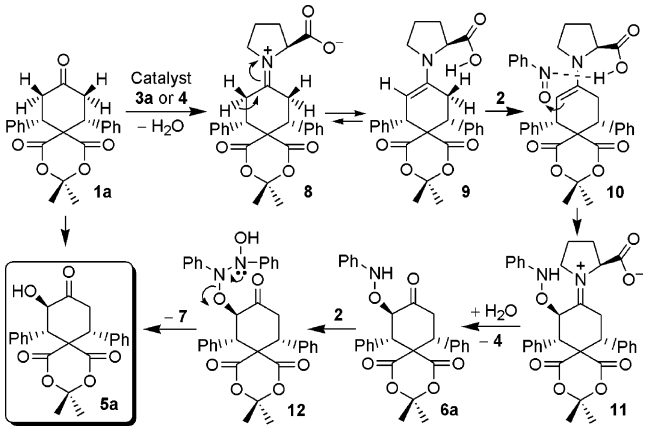


entry	substrate	catalyst	solvent	Ph−N=O (equiv)	T (°C)	t (h)	yield (%)[b] 14a/b	15a/b	16a/b	ee (%)[c] 16a/b
1[d]	**13a**	**3a**	DMSO	0.33	25	1	50	20	6	99
2	**13a**	**4**	CH_2Cl_2	3.0	25	1	2		43	99
3	**13a**	**4**	CH_2Cl_2	3.0	4	24	5		75	99
4	**13b**	**4**	CH_2Cl_2	3.0	4	30			40	98

[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**.

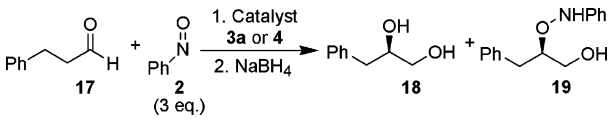
ketone **5a** and *trans*-azoxybenzene **7**.[9] The key intermediate **6a** was isolated when 0.5 equiv of **2** was used (Table 1, entry 11).

Scheme 2. Proposed Reaction Mechanism



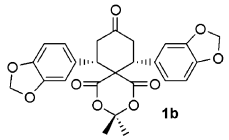
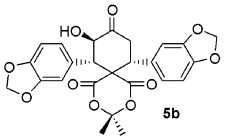
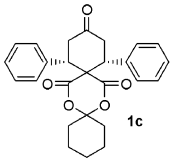
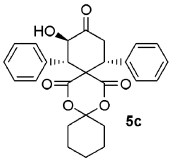
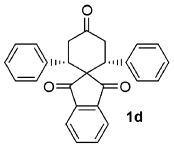
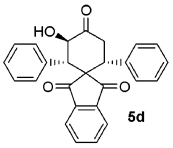
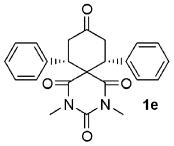
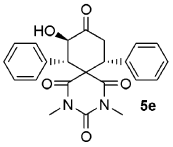
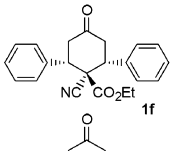
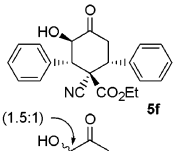
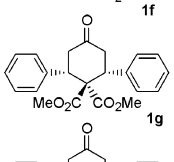
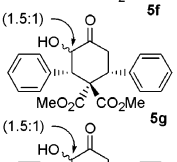
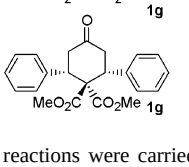
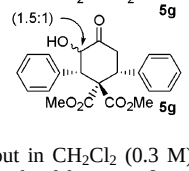
This method for *in situ* reduction of O−N bonds was further applied to simple ketones and aldehydes. As shown in Tables 2 and 3, simple ketones and aldehydes were

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



catalyst	solvent	T (°C)	t (h)	yield (%) 18	19	ee (%) 18
4	CH_3CN	4	18	20		>99
3a	CH_3CN	24	1.5	35	35	>99

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

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

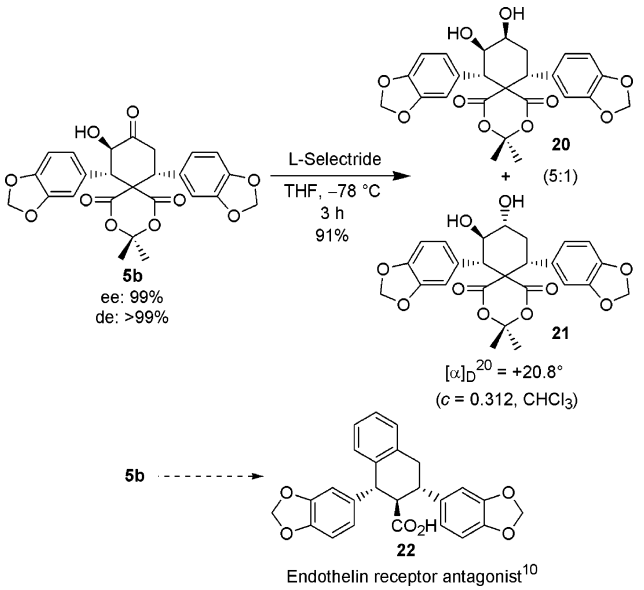
[a] All reactions were carried out in CH_2Cl_2 (0.3 M) with 3.0 equiv of nitrosobenzene relative to the prochiral ketones **1b−g** in the presence of 20 mol % L-proline at 4 °C and were complete in 48 h. [b] Yield refers to the column-purified product. [c] Ees of product were determined by CSP-HPLC analysis. [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 CH_2Cl_2 (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-aminoxy ketones **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.

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



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 (^{1}H NMR, ^{13}C NMR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050246E

(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.