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Masked Oxo Sulfinimines (*N*-Sulfinyl Imines) in the Asymmetric Synthesis of Proline and Pipecolic Acid Derivatives

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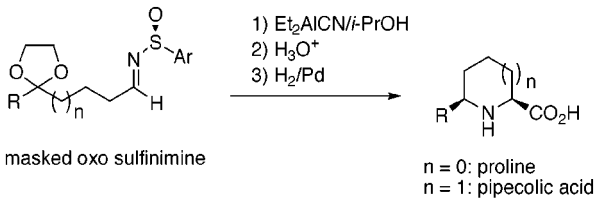
ABSTRACT

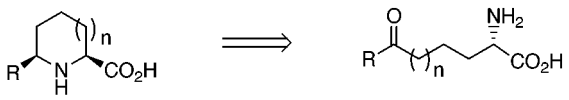


On addition of Et_2AlCN/*i*-PrOH, masked oxo sulfinimines give α-amino nitriles that afford oxo α-amino acids on hydrolysis. These amino acids cyclize and are reduced to cis proline and cis pipecolic acids derivatives in high ee and good yield. This new procedure avoids many of the limitations related to the preparation of oxo amino acids from proteinogenic amino acids.

There is considerable current interest in the synthesis of cyclic α-amino acids because of the effect these acids, once incorporated into proteins, have on biological activity.[1] In this context the asymmetric synthesis of proline and pipecolic acid (homoproline) and their derivatives is of importance because they are key constituents of bioactive molecules and are useful building blocks for asymmetric synthesis.[2−4] In peptides these cyclic amino acids confer rigidity on the protein, which influences cell recognition events.[5] Replacement of proteinogenic amino acids with cyclic amino acids has been used in structure−reactivity studies and in the search for new peptidomimetics that have improved pharmacological profiles as well as resistance to the protease enzymes.[6]

An attractive strategy for the asymmetric syntheses of cis 5-substituted prolines **1**[7] and cis 6-substituted pipecolates **2**[8] is cyclization/reduction of oxo α-amino acids,[9] which has been exploited by Lubell,[7a,8b] Rapoport,[7d] and others (Scheme 1).[9,10] However, this approach is limited because most oxo

Scheme 1



α-amino acids are derived from proteinogenic amino acids, making access to both enantiomers difficult.[9] In addition, tedious protection/deprotection chemistry is frequently required. As part of our continuing studies of functionalized sulfinimines[11,12] we describe herein preliminary results of a

(1) For a review, see Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

(2) For reviews on α-amino acids, see (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, UK, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(3) For reviews on the applications of amino acids to asymmetric synthesis, see (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (c) Remuzon, P. *Tetrahedron* **1996**, *52*, 13803. (d) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633.

(4) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106.

(5) For leading references, see (a) Burgess, K.; Ho, K.-K.; Pal, B. *J. Am. Chem. Soc.* **1995**, *117*, 3808. (b) Beausoleil, E.; Lubell, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 12902. (c) Hayashi, T.; Asai, T.; Ogoshi, H. *Tetrahedron Lett.* **1997**, *38*, 3039.

(6) For example, see Smith, A. B., III; Benowitz, A. B.; Sprengeler, P. A.; Barbosa, J.; Guzman, M. C.; Hirschmann, R.; Schweiger, E. J.; Bolin, D. R.; Nagy, Z.; Campbell, R. M.; Cox, D. C.; Olson, G. L. *J. Am. Chem. Soc.* **1999**, *121*, 9286.

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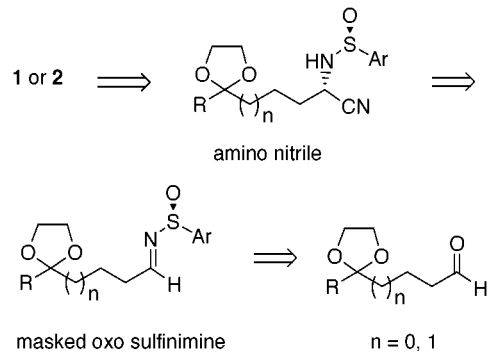
simple method for the asymmetric synthesis of proline and pipecolic acid derivatives via masked oxo sulfinimines (*N*-sulfinyl imines).

Our general approach, outlined in Scheme 2, involves the synthesis of a masked oxo sulfinimine from a masked oxo aldehyde. The sulfinimine-mediated asymmetric Strecker synthesis is used to generate an α-amino nitrile with the desired absolute stereochemistry followed by hydrolysis and reduction to give amino acids **1** and **2**.

Scheme 2



The masked oxo aldehydes **4** were readily prepared by DIBAL-H reduction, at −78 °C, of the corresponding esters **3**, which were obtained using literature procedures (Scheme 3, Table 1).[13] The masked sulfinimines **7** were generated as previously described in one-pot by treating commercially available (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (**5**) with LiHMDS at −78 °C followed by the aldehyde.[14] Alternatively, 5,5-(ethylenedioxy)-5-phenylpentanal (**4d**) and 3,3-(ethylenedioxy)-3-phenylpropanal (**4e**) were treated with (*S*)-(+)-*p*-toluenesulfinamide (**6**), also commercially available, and 5 equiv of $Ti(OEt)_4$ in CH_2Cl_2 to give **7d** and **7e** in 80% and 57% yield, respectively.[15] The somewhat lower yield for **7e** by this method compared to the one-pot procedure may reflect some deprotection of the ketal under the Lewis acid conditions (Table 1; entry 8).

Scheme 3

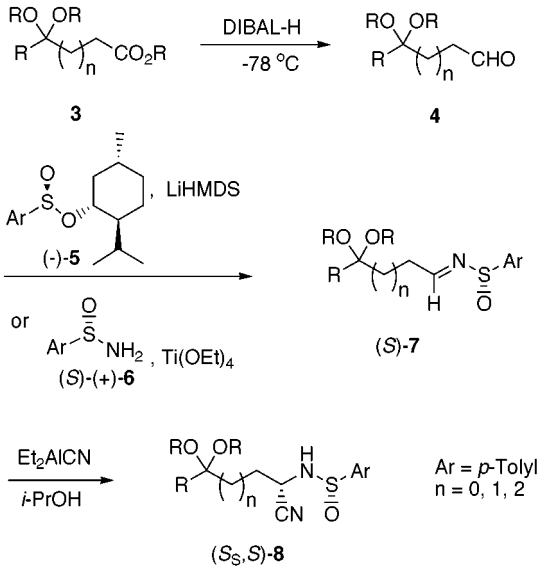
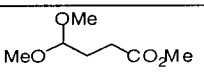
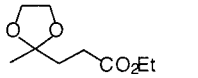
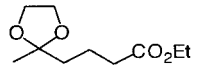
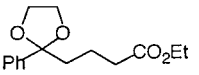
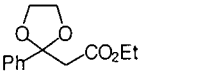


Table 1. Synthesis of Masked Oxo Sulfinimines **7** and Amino Nitriles **8**

entry	**3**	**4**	% Yields[a] (*S*)-**7**	(*S*S,*S*)-**8** (% de)
1	**a**		74	58 (*R*)[b] 83 (84)[c]
2	**b**		92	54 88 (90)
3	**c**		98	61 74 (82)
4				95 (95)[e]
5	**d**		65	80[d] 85 (84)
6				90 (91)[e]
7				89 (93)[f]
8	**e**		82	68 (57)[d] 82 (74)
9				80 (75)[e]

[a] Isolated yields of major product. [b] Prepared from *R*-(−)-**6**. [c] (*R*S,*R*) configuration. [d] Prepared from (*S*)-(+)-**6**. [e] 5.0/3.0 equiv of Et_2AlCN/*i*-PrOH was used. [f] 2.4/1.3 equiv of Et_2AlCN/*i*-PrOH was used.

(7) For leading references to the synthesis of 5-substituted prolines, see (a) Belokon, Y. N.; Bulychev, A. G.; Pavolov, V. A.; Fedorova, E. B.; Tsyryapkin, V. A.; Bakhmutov, V. A.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2075. (b) Beausoleil, E.; L'Archeveque, B.; Belec, L.; Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447. (c) Li, H.; Sakamoto, T.; Kikugawa, Y. *Tetrahedron Lett.* **1997**, *38*, 6677. (d) Turner, S. C.; Zhai, H. B.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861.

(8) For leading references to 6-substitued pipecolic acids, see: (a) ref 3d. (b) Swarbrick, M. E.; Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 1993.

(9) For leading references to the synthesis of oxo α-amino acids, see (a) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438. (b) Golubev, A. S.; Sewald, N.; Burger, K. *Tetrahedron* **1996**, *52*, 14757.

(10) (a) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937. (b) Van Betsbrugge, J.; Van Den Nest, W.; Verheyden, P.; Tourwe, D. *Tetrahedron* **1998**, *54*, 1753.

(11) For a reviews on the chemistry of sulfinimines, see (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (b) Hua, D. H.; Chen, Y.; Millward, G. S. *Sulfur Rep.* **1999**, *21*, 211. (c) Zhou, P.; Chen, B.-C.; Davis, F. A. Syntheses and Reactions of Sulfinimines. In *Advances in Sulfur Chemistry*; Rayner, C. M., Ed.; JAL Press: Stamford, CT, 2000; Vol 2, pp 249−282.

(12) For leading references to sulfinimine (*N*-sulfinyl imine) chemistry, see Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627.

(13) References to oxo esters: **3a**: Simoneau, B.; Brassard, P. *Tetrahedron* **1988**, *44*, 1015. **3b**: Dowd, P.; Trivedi, B. K. *J. Org. Chem.* **1985**, *50*, 206. **3c**: Le-Hocine, M. B.; Khac, D. D.; Fetizon, M.; Prange, T. *Synth. Commun.* **1992**, *22*, 1871. **3d**: Hassarajani, S. A.; Dhotare, B.; Chattopadhyay, A.; Mamdapur, V. R. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1998**, *37B*, 80. **3e**: Lui, K.-H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 457.

(14) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.

The sulfinimine-mediated asymmetric Strecker synthesis involves addition of ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN], generated in situ by addition of *i*-PrOH to diethylaluminum cyanide (Et_2AlCN) to the sulfinimine.[16] Thus treatment of **7** (1.0 mmol) at −78 °C in THF with 1.5/1.0 equiv of Et_2AlCN/*i*-PrOH give amino nitriles **8** in good yield (54−68%) and de (74−95%). Interestingly the des for **8c** and **8d** were 82 and 84%, respectively (Table 1; entries 3 and 5), but improved to >90 when different ratios of Et_2AlCN/*i*-PrOH were used (Table 1; entries 4, 6, and 9). When these conditions were used with **7e**, there was no effect (entry 9) on the diastereoselectivity. Since the sulfinyl group controls the stereochemistry of cyanide addition to the C−N double bond of the sulfinimine, (*S*)-**7** is predicted to give amino nitrile **8** where the major diastereoisomer has the (S_S,*S*)-configuration. Likewise (*R*)-**7a** gives (R_S*R*)-**8** (Table 1; entry 1). The stereochemistry of the proline and pipecolic acid derivatives confirm these assignments. These results are summarized in Table 1.

Hydrolysis of the diastereomerically pure amino nitriles **8a**−**d** in refluxing 6 N HCl for 3−5 h accomplishes five operations in a single pot (Scheme 4). Hydrolysis removes the *N*-sulfinyl auxiliary with concomitant conversion of the nitrile to the acid. The protected oxo group is unmasked to give the intermediate oxo α-amino acid **9**, which cyclizes to give the iminium ion **10**. The aqueous mixture containing **10** was extracted with ethyl ether to remove *p*-toluenesulfinic acid and glycol byproducts, and the solvent was removed to give the crude imine salt **10**. The salt, dissolved in MeOH, was hydrogenated (H_2/10% Pd/C) for 8 h at atmospheric pressure, and the cyclic amino acids **11** were isolated using a Dowex-50 ion-exchange column. However, attempts to isolate 6-methyl-2-pipecolic acid (**11c**) and 6-phenyl-2-pipecolic acid (**11d**) in this manner resulted in poorer yields and/or decomposition. We found that these products could be obtained by first washing the HCl salt with acetone several times to remove the ethylene glycol byproducts which afforded (−)-**11c** in 85% yield. Further crystallization gave **11d** in 48% yield.

Hydrogenation is expected to occur from the least hindered direction, and the cis amino acids **11** were formed exclusively (Scheme 4).[17] The cis stereochemistry of **11b**−**d** was unambiguously assigned by comparison with authentic materials and with literature values. The enantiomeric purity of the products were determined to be >93% ee by comparison with literature values and making the Mosher amides (Table 2).[18] Because cyclization to an azetidine carboxylic acid is energetically unfavorable, hydrolysis of **8e** affords (*S*)-(+)-β-benzoylalanine (**12**)[19] in 95% yield (Table 2; entry 5).

Scheme 4

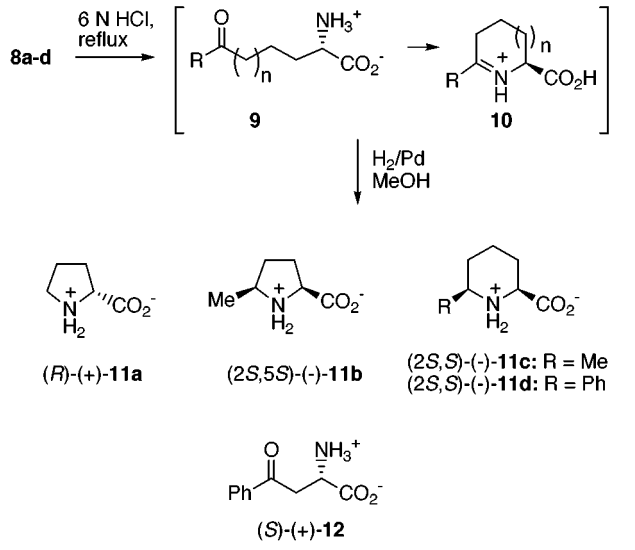


Table 2. Hydrolysis of Masked Oxo Sulfinimines **8** and **12**

entry	**8**	amino acids **11** and **12**	% yield (% ee)
1	(R_S,*R*)-(−)-**8a**	(*R*)-(+)-**11a**	77 (98)
2	(S_S,*S*)-(+)-**8b**	(2*S*,5*S*)-(−)-**11b**	80 (95)
3	(S_S,*S*)-(+)-**8c**	(2*S*,6*S*)-(−)-**11c**[a]	85 (97)
4	(S_S,*S*)-(+)-**8d**	(2*S*,6*S*)-(−)-**11d**[a]	48 (95)
5	(S_S,*S*)-(+)-**8e**	(*S*)-(+)-**12**	95 (93)

[a] Isolated as the hydrochloride salt.

In summary, masked oxo sulfinimines, in combination with the sulfinimine-mediated asymmetric Strecker synthesis, provide easy access to oxo α-amino acids, which are precursors of cis proline and pipecolic acid derivatives. Our procedure avoids many of the limitations associated with their preparation from proteinogenic amino acids, i.e., limited access to both enantiomers and extensive protection/deprotection chemistry. Masked oxo sulfinimines are examples of polyfunctionalized chiral building blocks in that they have at least one stereogenic center and more than one chemically

(15) (a) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403. (b) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50.

(16) For examples of the sulfinimine-mediated asymmetric Strecker synthesis, see (a) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. *J. Org. Chem.* **1996**, *61*, 440. (b) Davis, F. A.; Fanelli, D. L. *J. Org. Chem.* **1998**, *63*, 1981. (c) Davis, F. A.; Srirajan, V.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 6931. (d) Portonovo, P.; Liang, B.; Joullie, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 1451. (e) Davis, F. A.; Srirajan, V. *J. Org. Chem.* **2000**, *64*, 3248. (f) Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663. (g) Boisnard, S.; Neuville, L.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2000**, *2*, 2459. (h) Davis, F. A.; Lee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704.

(17) van der Werf, A.; Kellogg, R. M. *Tetrahedron Lett.* **1991**, *32*, 3727.

(18) References to cyclic amino acids (a) (*R*)-(+)-**11a**: Shiraiwa, T.; Shinjo, K.; Kurokawa, H. *Chem. Lett.* **1989**, 1413. (b) (5*S*,2*S*)-(−)-**11b**: Overberger, C. G.; David, K. H.; Morre, J. A. *Macromolecules* **1972**, *5*, 368. (c) (2*S*,6*S*)-(−)-**11c**: Berrien, J.-F.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1994**, *59*, 3769. (d) (2*S*,6*R*)-(−)-**11d**: ref 8b. (e) (*S*)-(+)-**11e**: ref 19.

(19) Golubev, A. S.; Sewald, N.; Burger, K. *Tetrahedron* **1996**, *52*, 14757.

(20) For leading references to sulfinimine-derived polyfunctionalized chiral building blocks, see (a) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041. (b) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. (c) ref 4.ed.

differentiated functional group.[20] The rich diversity of sulfinimine chemistry suggests that these building blocks will find useful applications in the concise asymmetric synthesis of novel amino derivatives.

Acknowledgment. This work was supported by the National Institutes of Health (GM57870).

Supporting Information Available: Experimental procedures, and spectroscopic data for compounds **4** to **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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