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Zirconium cation coordination in the borohydride-mediated synthesis of β-hydroxy-*N*-alkoxylamines

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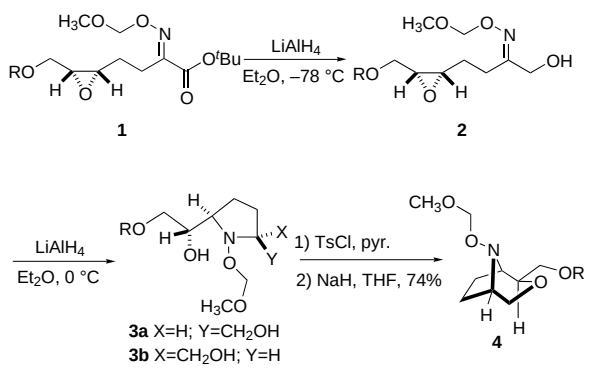
Abstract—Hydride reductions of oxime ethers to hydroxylamine derivatives are facilitated by the participation of neighboring hydroxyl groups. Precomplexation with zirconium cation in ether–methylene chloride solutions is effective for selective C=N bond reduction. The course for stereochemical control is dictated by Lewis acid coordination complexes of *E*- and *Z*-oximino ethers which lead to the preferred diastereofacial delivery of external hydride. © 2001 Elsevier Science Ltd. All rights reserved.

Methodology for the synthesis of amino alcohols has long been an important area of interest in natural products chemistry and pharmaceutical sciences. More recently, technologies for asymmetric synthesis and the use of chiral Lewis acids have accentuated the importance of novel amino alcohols as auxiliaries and ligands for catalysis and reagent-based chemistry.[1] Although derivatives of *N*-hydroxylamine have similar potential, these substances have received less attention. In fact, syntheses via reductive amination (C=N reduction), as broadly utilized in the synthesis of amino alcohols, often results in concomitant N–O bond cleavage.[2,3] Narasaka has reported on the stereoselective formation of *syn*-1,3-hydroxy-*N*-(benzylhydroxyl)amines from the treatment of individual *E*- and *Z*-oximino benzyl ethers with sodium methoxide and $LiAlH_4$.[4] Kibayashi and co-workers[5] have described the use of $LiAlH_4$, as well as other aluminum hydrides, for predominant formation of primary 1,2-*anti*-alkoxy amines via reductions of α-alkoxy oximes. Earlier efforts had also shown that the catalytic hydrogenation of pure *E*- and *Z*-α-hydroxy ketoximes yielded *anti*-1,2-amino alcohols regardless of oxime geometry.[6] Previous efforts from our laboratories have described the triacetoxyborohydride reductions of α- and β-hydroxy *E*- and *Z*-oximino ethers for stereoselective production of 1,2- and 1,3-*N*-benzyloxy amino alcohols.[7,8] In this study, we report our observations for the chemoselective reduction of the imino (C=N) bond in a series of oximino ethers using zirconium tetrachloride–sodium borohydride reagent. Our studies have provided good yields of *O*,*N*-disubstituted hydroxylamines, and have suggested a facilitating role for Lewis acid coordination.

Our strategies for alkaloid synthesis have focused on pyrrolidine and piperidine ring cyclization events utilizing the nucleophilic character of *N*-alkoxylamines.[9] For example, the lithium aluminum hydride reduction of **1** is selective for the *tert*-butyl ester at −78°C, and subsequent hydride delivery to the oximino ether **2** at 0°C directly leads to pyrrolidine formation.[10] Unfortunately the yields of *cis* and *trans*-**3ab** (1:1 ratio) are variable within the range 25–50% with the production of over-reduced materials.[11] While assignments of relative stereochemistry can often be challenging in these systems, the pure *cis*-**3a** was cleanly transformed to the bridged hydroxylamine derivative **4** (Scheme 1).[12]

Our search for a more effective reduction of the oximino ether C=N functionality was inspired by previ-



Scheme 1. Reductive cyclization (R = Si^{t}BuMe$_2$).

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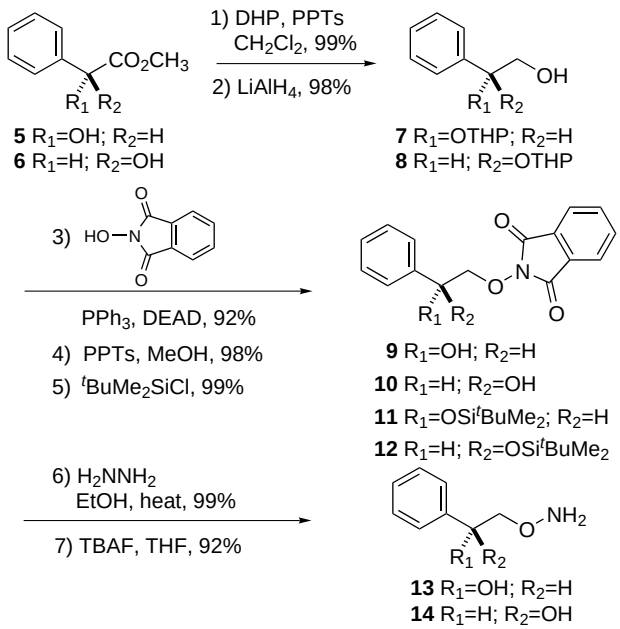
ous reports of Itsuno and co-workers,[13] describing a powerful hydride reagent prepared from zirconium tetrachloride and $NaBH_4$, which readily reduced nitriles, amides, and more reactive carbonyl derivatives. In combination with (*S*)-valinol, the asymmetric reduction of aryl ketoxime *O*-methyl ethers to 1-phenylethylamines (C=N and N–O bond reductions) was accomplished with enantioselectivity generally in the range of 55–75% ee.[13b]

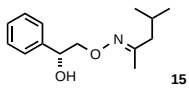
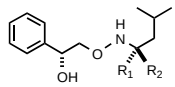
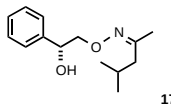
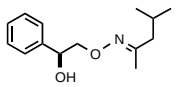
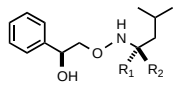
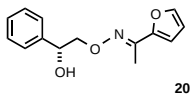
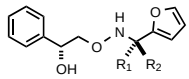
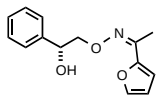
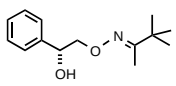
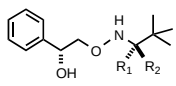
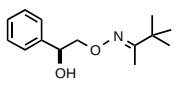
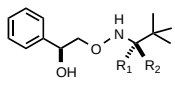
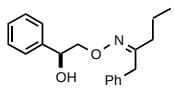
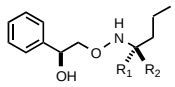
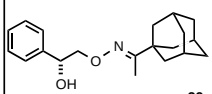
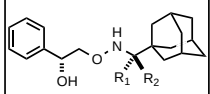
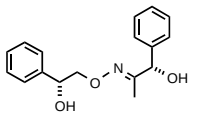
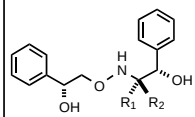
To incorporate a chirality control element, we prepared the optically active hydroxylamines **13** and **14** beginning with (*R*)- and (*S*)-mandelate esters **5** and **6** as shown in Scheme 2.

A number of oximino ethers were prepared from **13** and **14** using mild dehydration conditions, and *E*- and *Z*-isomers were separated by flash or preparative thin-layer silica gel chromatography. The determination of oxime configuration was based on ^{13}C and ^{1}H NMR data. The assignments of chemical shifts for α-carbons located *syn* to the *N*-alkoxy substituent were consistently observed upfield relative to the corresponding *E*-isomers due to steric compression. In addition, the proton signals for α-methylene (methyl) units located *syn* with respect to the oximino ether appeared at slightly lower field compared to the *anti* arrangement.[14] Representative examples have been compiled in Table 1. The search for conditions to permit the selective C=N reduction of these compounds proved challenging. In most cases, these oxime derivatives were simply inert to the common assortment of borane and borohydride reagents. More powerful hydrides and DIBAL gave uncontrolled over-reduction.[15] Notably, the use of zirconium tetraborohydride[16] at 0°C for 6–24 h typically provided 70–75% yields of the desired *N*-alkoxyamines, although 10–20% yields of recovered starting oxime were often obtained with these mild conditions.[17] The choice of a methylene chloride–diethyl ether solvent mixture (1:1 by volume) was crucial for success, as other solvents led to problems of insolubility or very slow reactions. Proton NMR analysis of crude product mixtures demonstrated modest diastereofacial selectiv-



Scheme 2. Synthesis of homochiral *N*-alkoxyamines.

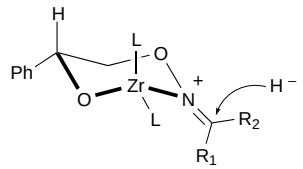
Table 1. Zirconium borohydride reductions

Entry	Oximino Ether	Yield[a]	Product	Isomer Ratio (*anti*/*syn*)[b]
1	 **15**	70%	 **16a** R_1 = H, R_2 = CH_3 **16b** R_1 = CH_3, R_2 = H	67 : 33
2	 **17**	58%		36 : 64
3	 **18**	76%	 **19a** R_1 = CH_3, R_2 = H **19b** R_1 = H, R_2 = CH_3	70 : 30
4	 **20**	73%	 **21a** R_1 = H, R_2 = CH_3 **21b** R_1 = CH_3, R_2 = H	50 : 50
5	 **22**	61%		50 : 50
6	 **23**	80%	 **24a** R_1 = H, R_2 = CH_3 **24b** R_1 = CH_3, R_2 = H	72 : 28
7	 **25**	65%	 **26a** R_1 = CH_3, R_2 = H **26b** R_1 = H, R_2 = CH_3	77 : 23
8	 **27**	70%	 **28a** R_1 = Bn, R_2 = H **28b** R_1 = H, R_2 = Bn	50 : 50
9	 **29**	33%	 **30a** R_1 = H, R_2 = CH_3 **30b** R_1 = CH_3, R_2 = H	67 : 33
10	 **31**	76%	 **32a** R_1 = H, R_2 = CH_3 **32b** R_1 = CH_3, R_2 = H	33 : 67

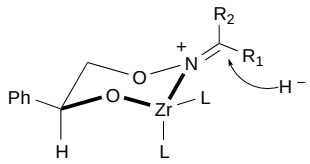
[a] All yields are for chromatographically pure products. [b] Ratios determined by integration of methyl signals in ^{1}H NMR data and HPLC analysis.

ity, which was generally dependent upon the configuration of the neighboring secondary alcohol. For example, diastereomeric *E*-oximes **15**, **18**, **23**, **25**, as well as **29**, (Table 1), gave an abundance of *anti*-products versus *syn*-isomers.[18] Thus, the change in stereochemistry of the resident *R*-hydroxyl in **15** and **23** compared to the *S*-configuration in **18** and **25** brought about a commensurate reversal in the diastereofacial selectivity for hydride addition to the imino bond. We have also briefly examined the role of oxime geometry via reductions of pure *E*- and *Z*-isomers **15**/**17**, and **20**/**22**. The case of the furan derivatives (entries 4/5) cleanly gave the acid-sensitive amino alcohols **21ab** without over-reduction, however little stereoselectivity was observed. On the other hand, *Z*-**17** gave the *syn*-diastereomer **16b** as the major reduction product. This reaction retains the overall sense of facial selectivity noted for the analogous *E*-oxime **15**. Preferential formation of the *syn*-diastereomer **32b** was also observed in the reduction of the *E*-oximino ether **31** (entry 10) as the additional feature of α-hydroxylation undoubtedly played a significant role in the generation of 1,2-*syn*-stereochemistry.[19] In contrast, reductions with sodium cyanoborohydride under acidic conditions gave approximately 1:1 ratios of products (**21ab** decomposed under acidic conditions).

We have rationalized these stereochemical results by the consideration of Lewis acid activation for external hydride additions as illustrated in **33** and **34**. This analysis accounts for the observed preference in formation of the 1,5-*anti*-products arising from the *E*-oximino ethers as the chirality of the secondary alcohol is communicated through the six-membered chair-like chelation complex. In similar fashion, the 1,5-*syn*-amino alcohol **16b** produced via reduction of *Z*-oxime **17** reflects this same mode of addition as presented in **33** ($R_1 = CH_3$ and R_2 = isobutyl).[20]



33 (L = BH_4)



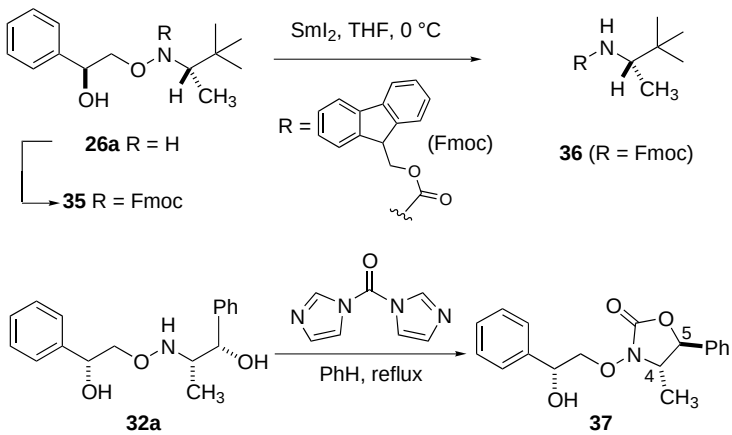
34 (L = BH_4)

Our assignments of stereochemistry rest upon two independent sets of experiments. In the first case, the reduction of *E*-oximino ether **25** was followed by careful separation and purification of the major amino alcohol product (^{1}H NMR δ 1.12 for the methyl doublet). Nitrogen acylation with 9-fluorenylmethyl chloroformate (Fmoc-Cl) provided the Fmoc amide **35**, which underwent facile N–O bond cleavage upon treatment with samarium iodide in THF at 0°C. The optical rotation of the resulting homochiral amide **36** ($[\alpha]_D^{25}$ +21 (*c* 0.30, $CHCl_3$)) was compared with data obtained for the pair of enantiomeric Fmoc amides prepared as standards from optically pure *R*- and *S*-2-amino-3,3-dimethylbutanes.[21] Thus, the major product of the oxime reduction **26a** corresponded with the *S*-configuration of authentic Fmoc amide **36** ($[\alpha]_D^{25}$ +23 (*c* 0.95, $CHCl_3$)), whereas similar reactions of the minor isomer **26b** (^{1}H NMR δ 1.17 for the methyl doublet) led to the analogous *R*-Fmoc amide ($[\alpha]_D^{25}$ −22 (*c* 0.94, $CHCl_3$)). As a result, the characteristic appearance of chemical shifts for the methyl doublets of our amino alcohols consistently provided recognition of *anti*- and *syn*-products for the entries of Table 1.

The complexity of the additional hydroxyl group in the example of entry 10 raised some concern regarding these assignments. Therefore, we sought corroborative evidence via formation of oxazolidinone **37** formed from the major diastereomer **32a** via treatment with 1,1′-carbonyldiimidazole in benzene (Scheme 3). The planar nature of the five-membered ring in **37** introduces eclipsing interactions of the phenyl and methyl substituents with C_4 and C_5 methine hydrogens, respectively. The ^{1}H NMR data suggests a shielding environment in **37**. Although vicinal coupling constants were not diagnostic for the assignment of *cis*- and *trans*-disubstituted oxazolidinone diastereomers, the observed chemical shifts of H_4 (δ 3.79) and H_5 (δ 4.99) are substantially upfield compared to the corresponding *cis*-4,5-disubstituted oxazolidinone.[22]

General procedure for zirconium borohydride reductions of *N*-alkoxyl oximino ethers

To a flame-dried flask equipped with a stirbar under



32a **37**

Scheme 3. Derivatives for stereochemical assignments.

argon was added $ZrCl_4$ (1.5 mmol), $NaBH_4$ (6.0 mmol) and diethyl ether (12 mL). After 10 min, CH_2Cl_2 (15 mL) was added dropwise until the mixture became an evenly dispersed, fine suspension. The mixture was allowed to stir overnight under argon at room temperature. Upon cooling to −10°C, a solution of oximino ether (1.5 mmol) in Et_2O (3 mL) was slowly added. After 30 min, the reaction was allowed to warm to 0°C, and was maintained at 0°C with continuous stirring for 24 h. The reaction was then quenched by the dropwise addition of water. This mixture was first acidified with 10% aqueous HCl followed by stirring for 40 min. The subsequent addition of 25% aqueous NH_4OH was followed by the separation of the aqueous phase and extraction with Et_2O (3×20 mL) permitted recovery of the amino alcohol products. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was generally purified by flash chromatography or by preparative TLC techniques (0.50 mm×20 cm×20 cm plates: EtOAc/hex). Yields of diastereomers and recovered starting oxime accurately accounted for the quantity of starting reactant. Ratios of diastereomers were evaluated by integration of selected ^1H NMR signals, and subsequently by analytical HPLC separations.

In summary, the partial (C=N) reduction of oximino ethers can be accomplished without N–O bond cleavage, providing novel *N*-alkoxyamine derivatives. Studies suggest that the in situ generation of zirconium borohydride facilitates formation of an activated chelation complex due to the presence of a neighboring hydroxyl group. Modest diastereofacial selectivity is observed based upon the configuration of the resident secondary alcohol.

Acknowledgements

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References

1. (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995; pp. 64–67 and 117–142; (b) For the preparation and use of 1,2-amino alcohols: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835.
2. (a) Hoffman, C.; Tanke, R. S.; Miller, M. J. *J. Org. Chem*. **1989**, *54*, 3750. Previous studies include: (b) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 395; (c) Landor, S. R.; Chan, Y. M.; Sonola, O. O.; Tatchell, A. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 493; (d) Brunner, H.; Becker, R.; Gauder, S. *Organometallics* **1986**, *4*, 739.
3. Several noteworthy studies have examined the nucleophilic addition of Grignard reagents, allylboranes and organolithium species to chiral imines and hydrazones: (a) Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc*. **1986**, *108*, 8265; (b) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc*. **1987**, *109*, 2224; (c) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun*. **1985**, 814.
4. (a) Narasaka, K.; Uraji, Y. *Chem. Lett*. **1984**, 147; (b) Narasaka, K.; Yamazaki, S.; Uraki, Y. *Chem. Lett*. **1984**, 2065; (c) Narasaka, K.; Uraki, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 525.
5. Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun*. **1987**, 746.
6. Harada, K.; Shion, S. *Bull. Chem. Soc. Jpn*. **1984**, *57*, 1040.
7. Williams, D. R.; Osterhout, M. H. *J. Am. Chem. Soc*. **1992**, *114*, 8750.
8. Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett*. **1993**, *34*, 3271.
9. Williams, D. R.; Osterhout, M. H.; McGill, J. M. *Tetrahedron Lett*. **1989**, *30*, 1327.
10. Benbow, J. W. Ph. D. Thesis, Indiana University, **1990**, pages 21–31. The starting ester **1** was prepared via the alkylation of the monoanion of *tert*-butyl pyruvate oximino ether followed by Sharpless asymmetric epoxidation of the *Z*-allylic alcohol (Williams, D. R.; Benbow, J. W. *Tetrahedron Lett*. **1990**, *31*, 5881).
11. Generally it is difficult to avoid concomitant reduction of the N–O bond, and substantial amounts of cyclized and uncyclized (N–H) amine side products are produced.
12. The 3-oxa-8-azabicyclo[3.2.1]octane skeleton of **4** was characterized as follows: $R_f=0.55$ in 50% EtOAc/hexanes; IR (neat) ν 2959, 2930, 2860, 1461, 1150–1073 (br) cm^{-1}; ^1H NMR (400 MHz) δ 4.79 (AB, $J_{AB}=7.8$ Hz, $\Delta\nu=19.9$ Hz, 2H), 3.89 (d, $J=10.9$ Hz, 1H), 3.85 (AB of ABX, $J_{AB}=10.2$ Hz, $J_{AX}=6.3$ Hz, $J_{BX}=5.5$ Hz, $\Delta\nu=45.0$ Hz, 2H), 3.51 (m, 1H), 3.45 (dd, $J=10.9$, 3.1 Hz, 1H), 3.39 (s, 3H), 2.16–1.92 (m, 2H), 1.90–1.86 (m, 2H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); MS (CI, NH_3), m/e (relative intensity) 317 (1), 260 (51), 256 (69), 230 (77), 172 (37), 89 (92), 82 (100); HRMS m/e calcd. For $C_{15}H_{31}NO_4Si$ (M^+) 317.2023, found 317.2033.
13. (a) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1548; (b) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1859.
14. Karabatsos, G. J.; His, N. *Tetrahedron* **1967**, *23*, 1079. See also: Ref. 5.
15. Reductions in THF with Red-Al®, lithium pyrrolidinoborohydride, and lithium diethylaminoborohydride gave only phenylethylene diol and primary amines. See: Singaram, B.; Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T. *Tetrahedron Lett*. **1992**, *33*, 4533 and Singaram, B.; Fuller, J. C.; Belisle, C. M.; Goralski, C. T. *Tetrahedron Lett*. **1994**, *35*, 5389. Use of lithium triethylborohydride and zinc borohydride resulted in no reaction, and reduction with tetra-*n*-butylammonium triacetoxyborohydride ($AcOH/CH_3CN$) proceeded at very slow rates for these substrates.
16. The appearance of sodium chloride precipitate occurs upon stirring $ZrCl_4$ and $NaBH_4$. Crystalline zirconium borohydride is essentially tetrahedral as the $Zr(\eta^3\text{-}BH_4)_4$ complex. For crystallography, see: Bird, P. H.; Churchill, M. R. *Chem. Commun*. **1967**, 403.
17. Recovered oximino ethers did not undergo C=N isomerization under these conditions.

18. Proton NMR spectra of our reduced products consistently exhibited well-defined pairs of methyl doublets in which the 1,5-*syn*-diastereomeric relationship produced a downfield chemical shift (δ) for the secondary methyl group relative to that of the 1,5-*anti* isomer. This recognition feature permitted an evaluation of isomer ratios of crude products by integration, subsequently confirmed by HPLC and/or separation and isolation of the individual amino alcohols.
19. Production of *syn*-**32b** follows a trend previously observed for triacetoxyborohydride reductions of α-hydroxy oximino ethers (see Ref. 9).
20. Our illustrations of facial selectivity in **33** and **34** may inadequately address fundamental mechanistic concerns. Note that 1 equiv. of borane (BH_3) is released upon complexation of the starting alcohols.
21. Authentic samples of pure *R*- and *S*-2-amino-3,3-dimethylbutanes were generously supplied by Dr. Clint D. Brooks, Abbott Laboratories, Abbott Park, Illinois, 60064.
22. These assignments of 4,5-*cis*- and *trans*-disubstituted oxazolidinones were consistent with NMR data obtained from a series of five-membered cyclic carbamates, including known standards prepared from (+)-pseudoephedrine and (−)-ephedrine. An X-ray crystallographic analysis of a derivative allowed unambiguous confirmation (see Ref. 9).