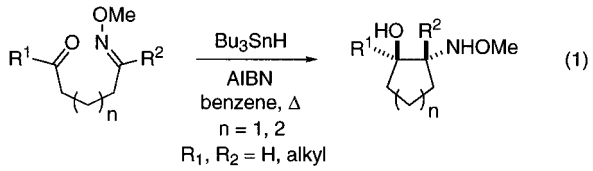
Diastereoselective Synthesis of β-Amino Alcohols via Bu_3SnH-Mediated Reductive Cyclization of Carbonyl−Oxime Ethers

Jordi Tormo, David S. Hays, and Gregory C. Fu*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received August 25, 1997

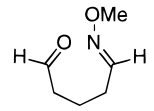
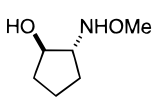
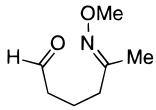
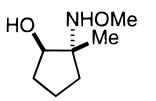
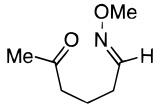
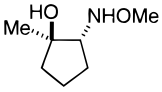
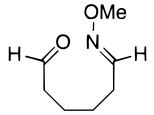
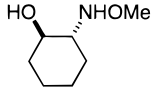
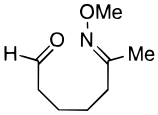
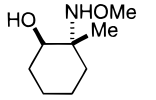
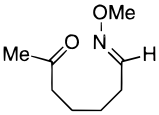
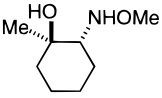
The reductive cyclization of carbonyl−oxime ethers to β-amino alcohols can be accomplished both electrochemically[1] and with inorganic reducing agents such as zinc[2] and SmI_2.[3−5] Naito recently observed that Bu_3SnH also mediates this transformation, providing heterocycles[6] and a carbocycle.[7] As part of our investigation of the chemistry of Bu_3SnH,[8,9] we have undertaken a systematic study of its capacity to effect reductive cyclizations.[8a,b] In this paper, we report that carbonyl−oxime ethers can be coupled by Bu_3SnH to generate an array of carbocycles (eq 1), and we establish that these cyclizations proceed with moderate to excellent trans stereoselection.



(1)

Treatment of any of a variety of carbonyl−oxime ethers with 1.5−2.5 equiv of Bu_3SnH in refluxing benzene (AIBN as the initiator) provides the desired β-amino alcohol in good yield (Table 1).[10] We have found that aldehyde−aldoximes (entries 1 and 4), aldehyde−ketoximes (entries 2 and 5), and ketone−aldoximes (entries 3 and 6) cyclize under these conditions. In contrast, under even more vigorous conditions (refluxing toluene, 4.5 equiv of Bu_3SnH) we observe essentially no reaction in the case of ketone−ketoximes (eq 1, $R^1 = R^2 =$ Me, *n* = 1 or 2), coupling of which would produce a ring that contains adjacent quaternary carbons. The stereoselectivity in favor of *trans*-β-amino alcohol is high when a five-membered ring is being formed (entries 1−3) and moderate when a six-membered ring is being formed (entries 4−6).[11]

Table 1. Diastereoselective Reductive Cyclization of Carbonyl−Oxime Ethers by Bu_3SnH

entry	substrate	major product	yield[a]	trans : cis[a]
1			73%	18 : 1
2			68%	>180 : 1
3			84%	7 : 1
4			67%	3 : 1
5			44%	7 : 1
6			70%	2 : 1

[a] Average of two runs.

Bu$_3$SnH likely effects reductive cyclization of carbonyl−oxime ethers through the pathway illustrated in Figure 1. The Bu_3Sn radical adds to the carbonyl group, generating the ketyl radical, which then adds to the pendent oxime ether to produce the nitrogen radical. In the irreversible final step, the nitrogen radical abstracts a hydrogen atom from Bu_3SnH, providing the β-amino alcohol and the chain-carrying Bu_3Sn radical.

In conclusion, we have described a systematic study of the Bu_3SnH-mediated reductive cyclization of carbonyl−oxime ethers to generate carbocycles. We have determined which families of substrates are susceptible to intramolecular coupling, and we have established that these compounds cyclize to generate *trans*-β-amino alcohols with moderate to excellent stereoselectivity. The investigation of other Bu_3SnH-mediated reductive cyclizations, as well as the development of catalytic variants of these processes, is currently underway.

(1) Shono, T.; Kise, N.; Fujimoto, T.; Yamanami, A.; Nomura, R. *J. Org. Chem.* **1994**, *59*, 1730−1740.
(2) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821−2824.
(3) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabe, M. *J. Org. Chem.* **1995**, *60*, 6010−6011. See also: Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447−7448.
(4) Al/Hg (oxime): Camps, P.; Font-Bardía, M.; Muñoz-Torrero, D.; Solans, X. *Liebigs Ann.* **1995**, 523−535.
(5) For early work on the addition of radicals to oxime ethers, see: (a) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631−1633. (b) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633−1634.
(6) (a) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205−2206. (b) Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624−626.
(7) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253−256.
(8) (a) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283−7284. (b) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4−5. (c) Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751−6752. (d) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949−6950.
(9) For reviews of the chemistry of Bu_3SnH, see: (a) Neumann, W. P. *Synthesis* **1987**, 665−683. (b) RajanBabu, T. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995.
(10) 1,2-Reduction of the carbonyl group is the predominant side reaction.
(11) For a review, see: Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996; Chapter 2. See also: Giese, B.; Kopping, B.; Goebel, T.; Dickhaut, J.; Thoma, G., Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301−856.

S0022-3263(97)01574-0 CCC: $15.00
Published on Web 01/09/1998

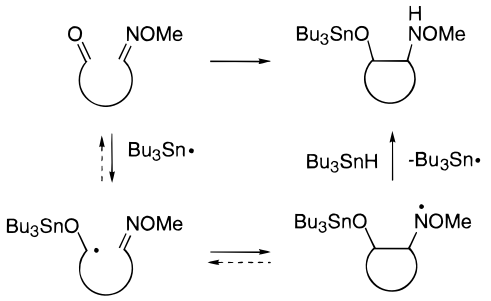


Figure 1. Probable radical-chain mechanism for reductive cyclization of carbonyl−oxime ethers by Bu_3SnH.

Experimental Section

General. Bu_3SnH (Gelest) was distilled prior to use, and AIBN (Kodak) was used as received. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. All yields and diastereoselectivities that are reported in Table 1 are the average of two runs.

Method A: *trans*-2-(*N*-methoxyamino)-1-cyclopentanol (Table 1, Entry 1). A solution of Bu_3SnH (240 μL, 0.88 mmol) and AIBN (19 mg, 0.12 mmol) in benzene (0.5 mL) was added to a stirred solution of the carbonyl−oxime ether (76 mg, 0.59 mmol) in benzene (6 mL) at rt. The reaction mixture was heated to reflux and stirred for 17 h. After cooling to rt, the mixture was concentrated, and the crude product was purified by flash chromatography on silica gel (1% → 40% Et_2O/pentane), which afforded the desired β-amino alcohol as a colorless oil (58 mg, 73%).

The diastereoselectivity was assessed by GC analysis of the unpurified reaction mixture. ^{1}H NMR ($CDCl_3$) δ 5.59 (br s, 1H), 4.21 (m, 1H), 3.57 (s, 3H), 3.34 (m, 1H), 2.19−1.55 (m, 5H), 1.39−1.20 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 77.2, 69.0, 62.4, 33.1, 27.5, 21.2. FTIR (neat) 3383, 3264, 1032 cm^{-1}. HRMS (EI, *m/e*) calcd for $C_6H_{13}NO_2$ (M^+) 131.0946, found 131.0946.

***trans*-2-(*N*-Methoxyamino)-2-methyl-1-cyclopentanol (Table 1, entry 2)** was prepared by method A (0.03 M), which afforded 14 mg (26%) of the pure trans isomer and a mixture of the trans isomer contaminated with the product of 1,2-reduction of the aldehyde (30 mg, 57%; 2.8:1) as colorless oils. The diastereoselectivity was assessed by GC analysis of the unpurified reaction mixture. ^{1}H NMR ($CDCl_3$) δ 5.42 (br s, 1H), 4.04 (t, 1H, J = 7.5), 3.53 (s, 3H), 2.08−1.98 (m, 1H), 1.72−1.48 (m, 6H), 1.15 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 78.4, 67.5, 63.1, 34.2, 31.8, 19.1, 18.1. FTIR (neat) 3390, 3235, 1054 cm^{-1}. HRMS (EI, *m/e*) calcd for $C_7H_{15}NO_2$ (M^+) 145.1103, found 145.1103.

Method B: 2-(*N*-Methoxyamino)-1-methyl-1-cyclopentanol (Table 1, Entry 3). A solution of Bu_3SnH (230 μL, 0.86 mmol) and AIBN (19 mg, 0.11 mmol) in benzene (0.5 mL) was added to a stirred solution of the carbonyl−oxime ether (82 mg, 0.57 mmol) in benzene (6 mL) at rt. The reaction mixture was heated to reflux, and additional AIBN (19 mg, 0.11 mmol) was added four times at 5 h intervals. After 30 h (total), a solution of Bu_3SnH (76 μL, 0.27 mmol) and AIBN (19 mg, 0.11 mmol) in benzene (0.5 mL) was added to the reaction mixture. After an additional 10 h of reflux, another solution of Bu_3SnH (76 μL, 0.27 mmol) and AIBN (19 mg, 0.11 mmol) in benzene (0.5 mL) was added. After an additional 10 h of reflux, the reaction mixture was cooled to room temperature, concentrated, and purified by flash chromatography on silica gel (1% → 30% Et_2O/pentane), which afforded 60 mg (73%) of the trans isomer and 9 mg (11%) of the cis isomer (colorless oils). ***trans* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.62 (br s, 1H), 3.53 (s, 3H), 3.41 (t, 1H, J = 4.5), 2.41 (br s, 1H), 2.05−1.52 (m, 6H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 80.5, 69.3, 61.8, 39.2, 26.9, 22.2, 19.7. FTIR (neat) 3384, 1041 cm^{-1}. HRMS (FAB, *m/e*) calcd for $C_7H_{15}NO_2$ (M^+) 145.1103, found 145.1103. ***cis* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.75 (br s, 1H), 3.55 (s, 3H), 3.18 (t, 1H, J = 9.4), 2.88 (br s, 1H), 1.98−1.25 (m, 6H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 77.6, 68.2, 62.1, 40.4, 28.2, 27.7, 20.9. FTIR (neat) 3384, 1045 cm^{-1}. HRMS (EI, *m/e*) calcd for $C_7H_{15}NO_2$ (M^+) 145.1103, found 145.1103.

2-(*N*-Methoxyamino)-1-cyclohexanol (Table 1, entry 4) was prepared by method A (0.10 M), which afforded 41 mg (50%) of the trans isomer and 14 mg (17%) of the cis isomer as colorless oils. ***trans* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.92 (br s, 1H), 3.54 (s, 3H), 3.42 (m, 1H), 3.11 (br s, 1H), 2.65 (m, 1H), 2.07−1.85 (m, 2H), 1.75−1.67 (m, 2H), 1.32−1.17 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 72.8, 65.6, 62.7, 34.0, 28.9, 24.9, 24.4. FTIR (neat) 3384, 3293, 1043 cm^{-1}. HRMS (FAB, *m/e*) calcd for $C_7H_{15}NO_2$ (M^+) 145.1103, found 145.1103. ***cis* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.53 (br s, 1H), 4.05 (br s, 1H), 3.56 (s, 3H), 2.98−2.91 (m, 1H), 2.59 (br s, 1H), 1.98−1.23 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 66.2, 62.9, 61.6, 30.7, 24.2, 23.9, 20.0. FTIR (neat) 3384, 1039 cm^{-1}. HRMS (FAB, *m/e*) calcd for $C_7H_{15}NO_2$ (M^+) 145.1103, found 145.1103.

2-(*N*-Methoxyamino)-2-methyl-1-cyclohexanol (Table 1, entry 5) was prepared by method B (0.01 M), which afforded 26 mg (30%) of the trans isomer, a mixture of the trans isomer contaminated with the product of 1,2-reduction of the aldehyde (23 mg, 27%; 1:2.4), and 5 mg (5%) of the cis isomer as colorless oils. ***trans* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.52 (br s, 1H), 3.65 (dd, 1H, J = 12.5, 6.0), 3.54 (s, 3H), 2.79 (br s, 1H), 1.84−1.18 (m, 8H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 74.4, 63.4, 61.4, 34.0, 30.7, 24.5, 22.3, 14.9. FTIR (neat) 3405, 1048 cm^{-1}. HRMS (EI, *m/e*) calcd for $C_8H_{17}NO_2$ (M^+) 159.1259, found 159.1260. ***cis* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.59 (br s, 1H), 3.66 (br s, 1H), 3.56 (s, 3H), 2.87 (br s, 1H), 1.82−1.18 (m, 8H), 1.21 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 71.9, 63.2, 59.6, 30.9, 29.3, 21.7, 21.2, 21.1. HRMS (EI, *m/e*) calcd for $C_8H_{17}NO_2$ (M^+) 159.1259, found 159.1260.

2-(*N*-Methoxyamino)-1-methyl-1-cyclohexanol (Table 1, entry 6) was prepared by method B (0.10 M), which afforded 40 mg (47%) of the trans isomer and 19 mg (23%) of the cis isomer as pale yellow oils. ***trans* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.68 (br s, 1H), 3.54 (s, 3H), 3.29 (br s, 1H), 2.93 (dd, 1H, J = 12.0, 4.5), 1.87−1.14 (m, 8H), 1.16 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 73.2, 66.8, 62.1, 40.2, 27.7, 25.0, 23.4, 20.7. FTIR (neat) 3420, 3240, 1049 cm^{-1}. HRMS (EI, *m/e*) calcd for $C_8H_{17}NO_2$ (M^+) 159.1259, found 159.1259. ***cis* isomer:** ^{1}H NMR ($CDCl_3$) δ 5.68 (br s, 1H), 3.53 (s, 3H), 2.69 (dd, 1H, J = 9.0, 5.0), 2.67 (s, 1H), 1.78−1.24 (m, 8H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 71.0, 65.3, 62.3, 38.4, 28.6, 26.3, 24.5, 21.6. FTIR (neat) 3440, 1048 cm^{-1}. HRMS (EI, *m/e*) calcd for $C_8H_{17}NO_2$ (M^+) 159.1259, found 159.1259.

Independent Synthesis of *trans*-β-Amino Alcohols. Typical Procedure. A sealed tube charged with the cycloalkene oxide (4.0 mmol), methoxylamine hydrochloride (8.0 mmol), triethylamine (8.0 mmol), and water (1 mL) was heated at 110 °C for 7 h. After cooling to rt, Et_2O (10 mL) and 1 N KOH (10 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford the crude β-amino alcohol, which was purified by flash chromatography on silica gel. The reaction products were identical by ^{1}H and ^{13}C NMR with the major products of the Bu_3SnH-mediated reductive cyclizations.

Acknowledgment. Support has been provided by the Alfred P. Sloan Foundation, the American Cancer Society, the Camille and Henry Dreyfus Foundation, Eli Lilly, Firmenich, Glaxo Wellcome, the National Science Foundation (predoctoral fellowship to D.S.H.; Young Investigator Award to G.C.F., with funding from Procter & Gamble, Merck, Bristol-Myers Squibb, DuPont, Pfizer, Rohm & Haas, and Pharmacia & Upjohn), the Research Corporation, and the Spanish Ministry of Education (postdoctoral fellowship to J.T.). Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS, for partial support of this research.

Supporting Information Available: Experimental procedures for the synthesis of the carbonyl−oxime ether substrates, as well as compound characterization data (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971574Y