Stannyl Radical Addition-Cyclization of Oxime Ethers Connected with Olefins

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Stannyl radical addition-cyclization of oxime ethers connected with olefin moieties was studied. The radical reactions proceeded effectively by the use of triethylborane as a radical initiator to provide the functionalized pyrrolidines *via* a carbon–carbon bond-forming process.

Key words radical reaction; stannyl radical; oxime ether; cyclization; triethylborane

Free radical-mediated cyclization has developed as a powerful method for preparing various types of cyclic compounds *via* carbon–carbon bond-forming processes.[2—5] Although a number of extensive investigations into radical reactions were reported in recent years, the majority of them employ methods utilizing typical radical precursors such as halides, selenides, and xanthates.[2—5] One drawback in traditional procedures using such radical precursors is loss of the inherent functional groups.[6,7] Our laboratory is interested in developing the effective and convenient methods for the synthesis of highly functionalized cyclic compounds.[8—21] Particularly, strategies involving the radical addition-cyclization reactions offer the advantage of the formation of multiple carbon–carbon and carbon–heteroatom bonds in a single operation. We recently reported the carbon tandem radical addition-cyclization of oxime ethers connected with the α,β-unsaturated carbonyl group.[22—24] As a part of our program directed toward the development of radical addition-cyclization reactions, we now describe full details of the heteroatom radical addition-cyclization reaction of substrates having two different radical acceptors such as olefin and oxime ether moieties (Chart 1).[25] This investigation is the first example of the stannyl radical-mediated reaction between oxime ethers connected with olefin moieties.

Results and Discussion

We first investigated the reaction of oxime ether **1**, which was prepared as shown in Chart 2. α-Chloroacetaldoxime ether **2** was prepared from chloroacetaldehyde and *O*-benzylhydroxyamine hydrochloride.[26] The reaction of **2** with allylamine gave the secondary amine **3** in 76% yield. The amine **3** was protected as the *N*-Boc derivative **1** in quantitative yield as an *E*/*Z* mixture in a 3 : 2 ratio. In our recent studies on the radical reaction of oxime ethers, we have observed no remarkable effect of the geometry of the starting oxime ether group on either the chemical yield or stereoselectivity by employing geometrically pure *E* and *Z*-isomers.[10] Thus, oxime ether **1** was subjected to the following radical reactions without the separation of *E*/*Z*-isomers.

At first, we examined the stannyl radical addition-cyclization reaction of oxime ether **1** (Chart 3). Treatment of **1** with Bu_3SnH in the presence of AIBN (1.0 eq) in boiling benzene for 15 min gave the cyclic product **4**[27] in 31% yield accompanied with 65% yield of the starting material **1** (Table 1, entry 1). The reaction using AIBN as a radical initiator proceeded slowly to give the product **4** in 84% yield, after being stirred in boiling benzene for 2 h (entry 2). The reaction using 0.4 eq of AIBN also proceeded smoothly to give the cyclic product **4** in 81% yield (entry 3). The reaction pathway is that the stannyl radical initially reacted with olefin moiety of **1** to form intermediate alkyl radical which attacked intramolecularly the oxime ether group as in 5-*exo*-*trig* radical cyclization (Chart 4).

We next examined the stannyl radical addition-cyclization reaction of oxime ether **1** by using triethylborane as a radical initiator. In contrast to the reaction using AIBN, the reaction using triethylborane (2.5 eq) proceeded smoothly to give the

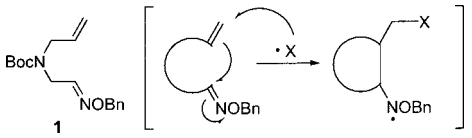

Chart 1

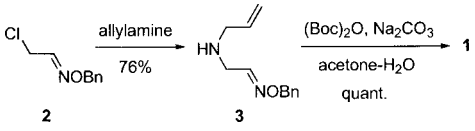

Chart 2

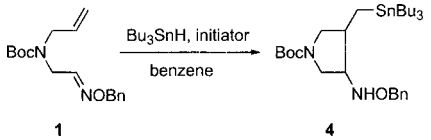

Chart 3

Table 1. Stannyl Radical Addition-Cyclization of Oxime Ether **1**[a]

Entry	Initiator	*T* (°C)	Time (min)	Yield (%)[b]
1	AIBN (1.0 eq)	reflux	15	31 (65)
2	AIBN (1.0 eq)	reflux	120	84
3	AIBN (0.4 eq)	reflux	120	81
4	Et_3B (2.5 eq)	reflux	15	82
5	Et_3B (0.2 eq)	reflux	15	27 (61)
6	Et_3B (5.0 eq)	20	120	37 (57)
7	Et_2Zn (2.5 eq)	reflux	15	73
8	9-BBN (2.5 eq)	reflux	15	trace

a) Reactions were carried out with Bu_3SnH in benzene. *b*) Yields of isolated product; yields in parentheses are for the recovered starting material **1**.

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Table 2. ^{1}H-NMR Data for Oxime Ether **1** in C_6D_6

	Et_3B (none)	Et_3B (0.2 eq)	Et_3B (0.4 eq)	Et_3B (0.6 eq)
$BC\underline{H}_2CH_3$ of Et_3B		3.69	3.71	3.72
Benzylic H of (*E*)-**1**	5.02 (2H, s)	5.00 (2H, s)	4.99 (2H, s)	4.98 (2H, s)
Benzylic H of (*Z*)-**1**	5.06 (2H, s)	5.04 (2H, s)	5.03 (2H, s)	5.02 (2H, s)
Imino H of (*E*)-**1**	7.34 (1H, s)	7.31 (1H, s)	7.29 (1H, s)	
Imino H of (*Z*)-**1**	6.66 (1H, s)	6.61 (1H, s)	6.59 (1H, s)	6.58 (1H, s)
Methylene H of (*E*,*Z*)-**1**	3.4—4.3 (4H, m)	3.4—4.3 (4H, m)	3.4—4.3 (4H, m)	3.4—4.3 (4H, m)
$-CH=C\underline{H}_2$ of (*E*,*Z*)-**1**	4.8—5.0 (2H, m)	4.8—5.0 (2H, m)	4.8—5.0 (2H, m)	4.8—5.0 (2H, m)
$-C\underline{H}=CH_2$ of (*E*,*Z*)-**1**	5.53 (1H, m)	5.53 (1H, m)	5.53 (1H, m)	5.53 (1H, m)
Aromatic H of (*E*,*Z*)-**1**	7.0—7.3 (5H, m)	7.0—7.3 (5H, m)	7.0—7.3 (5H, m)	7.0—7.3 (5H, m)

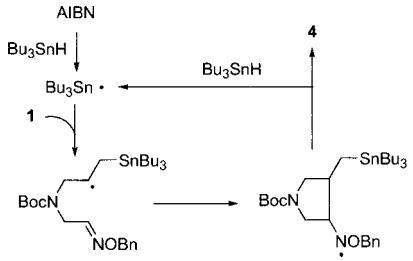

Chart 4

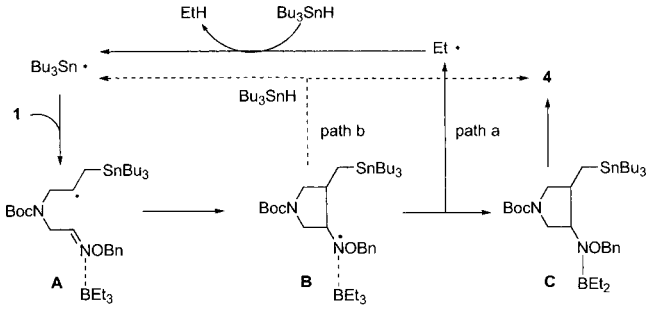

Chart 5

cyclic product **4** in 82% yield, after being stirred in boiling benzene for only 15 min (entry 4). However, the use of a catalytic amount of triethylborane (0.2 eq) was less effective for the radical cyclization (entry 5). The reaction using triethylborane (5.0 eq) proceeded moderately even at 20 °C (entry 6). These results indicate that triethylborane exhibits an excellent reactivity as a radical initiator and triethylborane acts as not only a radical initiator but also a Lewis acid and a radical terminator. Thus, the rationale of the major reaction pathway is that the stannyl radical adds to the olefin moiety of **1** to form intermediate alkyl radical **A**, which attacked intramolecularly the triethylborane-activated oxime ether group to form the benzyloxyaminyl radical **B** (Chart 5). The benzyloxyaminyl radical **B** would be trapped by triethylborane as a radical terminator to give the product **C** and an ethyl radical (path a); therefore, more than a stoichiometric amount of triethylborane is required.[28—30] Alternative catalytic reaction pathway involving stannyl radical as a chain carrier (path b) would be less important for this reaction, because of the high reactivity of triethylborane as a trapping reagent toward a key intermediate aminyl radical **B**. Recently, Ryu and Komatsu reported that diethylzinc-air system can serve as an initiator of tin hydride-mediated radical reaction as well as triethylborane.[31] In order to test the viability of diethylzinc, we also investigated the reaction of oxime ether **1** using a commercially available 1.0 M solution of diethylzinc. Diethylzinc also worked well as an effective radical initiator at high temperature to give the product **4** in 73% yield, after being stirred in boiling benzene for 15 min (entry 7). The use of 9-BBN[32] as a radical initiator was less effective for the reaction of **1** (entry 8).

The ^{1}H-NMR spectra data of the *E*/*Z*-mixture of oxime ether **1** obtained in the presence of triethylborane are shown in Table 2. The upper field shift of the chemical shifts for the hydrogens of the oxime ether moiety (benzylic H and imino H) and the downfield shifts of the chemical shift for the hydrogens of triethylborane ($BC\underline{H}_2CH_3$) were observed. These

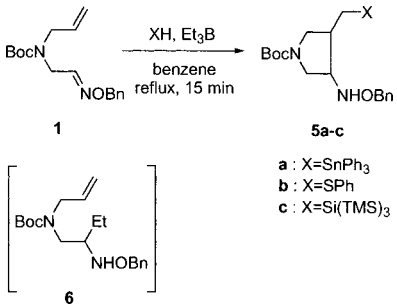

Chart 6

Table 3. Heteroatom Radical Addition-Cyclization of Oxime Ether **1**[a]

Entry	Initiator	XH	Time (min)	Product	Yield (%)[b]
1	Et_3B (2.5 eq)	Ph_3SnH	15	**5a**	81
2	Et_3B (2.5 eq)	PhSH	15	**5b**	24 (54)
3	AIBN (1.0 eq)	PhSH	180	**5b**	76
4	Et_3B (2.5 eq)	Ph_2PH	15		Complex mixture
5	Et_3B (2.5 eq)	Et_3SiH	15	**6**	32 (39)
6	Et_3B (2.5 eq)	$(TMS)_3SiH$	15	**5c**	79

a) Reactions were carried out in boiling benzene. *b*) Yields of isolated product; yields in parentheses are for the recovered starting material **1**.

results suggest that triethylborane was captured by the oxime ether group of **1**.

To survey the scope and limitations of the triethylborane-promoted radical addition-cyclization of oxime ether **1**, we next investigated the reaction using different radical precursors (Chart 6). High chemical yield was also observed in the addition-cyclization of oxime ether **1** using triphenyltin hydride to give the cyclic product **5a** in 81% yield (Table 3, entry 1). The combination of triethylborane and thiophenol was less effective for the sulfanyl radical addition-cyclization reaction, presumably due to the formation of an unidentified

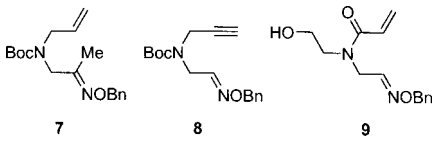

Chart 7

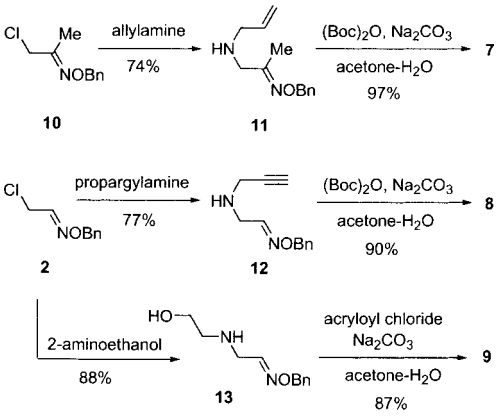

Chart 8

complex from triethylborane and thiophenol (entry 2). Thus, the cyclic product **5b** was obtained in only 24% yield accompanied with 54% yield of the starting material **1**. In contrast, the reaction of **1** with thiophenol is known to proceed slowly by using AIBN as a radical initiator to give the product **5b** in 76% yield, after being stirred in boiling benzene for 3 h (entry 3).[33] The combination of triethylborane and diphenylphosphine also did not give the good result (entry 4). The use of the less reactive triethylsilane led to the predominant formation of the ethylated product **6** as a result of the competitive intermolecular addition of an ethyl radical, generated from triethylborane, to oxime ether group (entry 5). In contrast to triethylsilane, the reaction using the more reactive tris(trimethylsilyl)silane proceeded smoothly to give the cyclic product **5c** in 79% yield (entry 6).

We next investigated the reaction of different types of oxime ethers **7**—**9** (Chart 7). Preparation of oxime ethers **7**—**9** is shown in Chart 8. Ketoxime ether **10** was prepared from chloroacetone and *O*-benzylhydroxyamine hydrochloride. The reaction of **10** with allylamine gave the secondary amine **11** in 74% yield. The amine **11** was protected as the *N*-Boc derivative **7** in 97% yield. Treatment of α-chloroacetaldoxime ether **2** with propargylamine gave the secondary amine **12**, which was protected as the *N*-Boc derivative **8**. The reaction of **2** with 2-aminoethanol gave the secondary amine **13** in 88% yield. Treatment of amine **13** with acryloyl chloride in the presence of Na_2CO_3 in acetone–H_2O gave oxime ether **9** in 87% yield.

At first, we examined the stannyl radical addition-cyclization of ketoxime ether **7** by using triethylborane as a radical initiator. However, ketoxime ethers (*E*)-**7** and (*Z*)-**7** did not work under similar reaction conditions (Chart 9). We next examined the reaction of oxime ether **8** having the propargyl group.[34—36] Treatment of an *E*/*Z* mixture of **8** with triethylborane in the presence of Bu_3SnH gave the cyclic product **14** in 61% yield, after being stirred in boiling benzene for 15 min. Additionally, the reaction of the cyclic product **14** with hydrogen chloride in ethanol resulted in protodestannylation, leading to product **15** in 91% yield. The reaction using tris(trimethylsilyl)silane proceeded smoothly to give the cyclic product **16** in 63% yield, although the reaction using triethylsilane led to the predominant ethylation. We finally examined the reaction of oxime ether **9** having an electron-deficient carbon–carbon double bond. Treatment of **9** with triethylborane in the presence of Bu_3SnH gave the cyclic product **17** in 82% yield, after being stirred in boiling benzene for 15 min. This observation indicates that the stannyl radical adds to electron-deficient carbon–carbon double bonds as well as isolated carbon–carbon double bonds when triethylborane was used as a radical initiator.

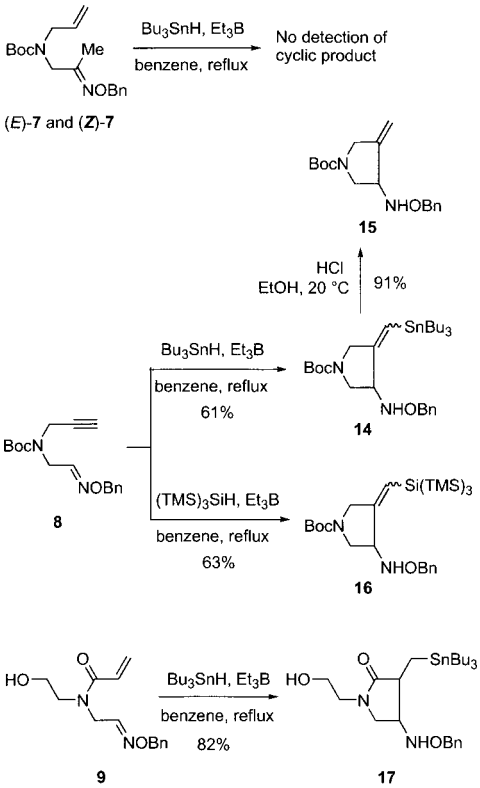

Chart 9

In conclusion, we have demonstrated the radical addition-cyclization of oxime ethers connected with olefin moieties. The reaction of oxime ethers with stannyl radical proceeded smoothly by the use of triethylborane as a radical initiator to provide the functionalized pyrrolidines.

Experimental

General Melting point is uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at 200, 300, or 500 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI or CI methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Flash column chromatography was performed using E. Merck Kieselgel 60 (230—400 mesh).

***N*-(2-Propenyl)aminoethanal *O*-Benzyloxime (3)** To allylamine (16.6 g, 290 mmol) was added chloroacetaldehyde *O*-benzyloxime (**2**) (17.8 g, 96.3 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 h, the reaction mixture was added to saturated aqueous $NaHCO_3$ and AcOEt. The layers were separated, and the aqueous phase was extracted with AcOEt. The combined organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$/MeOH 30 : 1) afforded **3** (14.9 g, 76%) as a yellow oil and a 3 : 2 mixture of *E*/*Z*-oxime. IR ($CHCl_3$) cm^{-1}: 1644, 1496. ^{1}H-NMR ($CDCl_3$) δ: 7.49 (3/5H, t, J=5.3 Hz), 7.38—7.24 (5H, m), 6.79 (2/5H,

t, J=4.4 Hz), 5.95—5.74 (1H, m), 5.22—5.10 (2H, m), 5.10 (4/5H, s), 5.07 (6/5H, s), 3.54 (4/5H, t, J=4.4 Hz), 3.35 (6/5H, t, J=5.3 Hz), 3.25—3.19 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 151.5, 149.0, 137.6, 137.4, 136.0, 135.9, 128.2 (2C), 128.0 (2C), 127.7, 127.6, 116.2 (2C), 75.8, 75.6, 51.9, 51.5, 47.2, 44.0. HR-MS m/z: 205.1355 (Calcd for $C_{12}H_{17}N_2O$ ($M+H^+$): 205.1340).

***N*-(*tert*-Butoxycarbonyl)-*N*-(2-propenyl)aminoethanal *O*-Benzyloxime (1)** To a solution of **3** (4.83 g, 23.7 mmol) in acetone (100 ml) was added a solution of Na_2CO_3 (4.27 g, 40.3 mmol) in H_2O (15 ml) under a nitrogen atmosphere at room temperature. After di-*tert*-butyl dicarbonate (7.39 g, 35.5 mmol) was added dropwise at 0 °C, the reaction mixture was stirred at room temperature for 20 h. After the reaction mixture was filtered through a pad of Celite, the filtrate was concentrated at reduced pressure. The resulting residue was diluted with water and then extracted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash column chromatography (AcOEt/hexane 1 : 8) afforded **1** (7.20 g, quantitative yield) as a colorless oil and a 3 : 2 mixture of *E*/*Z*-oxime. IR ($CHCl_3$) cm^{-1}: 1687. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.24 (3/5H+5H, m), 6.69 (2/5H, br t, J=4.4 Hz), 5.85—5.60 (1H, m), 5.18—5.03 (2H, m), 5.10 (4/5H, s), 5.07 (6/5H, s), 4.13—3.70 (4H, br m), 1.44 (9H, br s). ^{13}C-NMR ($CDCl_3$) δ: 155.0 (2C), 150.2 (br), 146.7, 137.5, 137.3, 133.3, 133.2, 128.2, 128.1, 127.8, 127.7, 116.8 (br), 80.1, 80.0, 76.0, 75.7, 50.2, 49.0, 45.0, 41.6, 28.1, 27.2. Some carbon peaks were missing due to overlapping. HR-MS m/z: 305.1857 (Calcd for $C_{17}H_{25}N_2O_3$ ($M+H^+$): 305.1864).

Chloroacetone *O*-Benzyloxime (10) To a solution of chloroacetone (10.0 g, 108 mmol) in H_2O–MeOH (200 ml, 1 : 1, v/v) was added *O*-benzylhydroxylamine hydrochloride (17.3 g, 108 mmol) under a nitrogen atmosphere at room temperature. After being stirred at room temperature for 30 h, MeOH was evaporated at reduced pressure. The resulting residue was extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure to afford **10** (20.3 g, 95%) as a yellow oil and an 8 : 1 mixture of *E*/*Z*-oxime. *E*-Isomer: IR ($CHCl_3$) cm^{-1}: 1644. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.25 (5H, m), 5.11 (2H, s), 4.05 (2H, s), 1.98 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 153.4, 137.5, 128.3, 127.9, 127.7, 75.9, 45.8, 12.4. HR-MS m/z: 197.0621 (Calcd for $C_{10}H_{12}ClNO$ (M^+): 197.0607).

***N*-(2-Propenyl)aminoacetone *O*-Benzyloxime (11)** Following the same procedure as for **3**, compound **11** was obtained from **10** in 74% yield as a yellow oil and an 8 : 1 mixture of *E*/*Z*-oxime. *E*-Isomer: IR ($CHCl_3$) cm^{-1}: 3331. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.26 (5H, m), 5.86 (1H, m), 5.22—5.02 (2H, m), 5.10 (2H, s), 3.29 (2H, s), 3.21 (1H, t, J=1.4 Hz), 3.18 (1H, t, J=1.4 Hz), 1.90 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 156.0, 138.1, 136.4, 128.1, 127.8, 127.5, 116.0, 75.4, 52.6, 51.5, 13.2. HR-MS m/z: 219.1497 (Calcd for $C_{13}H_{19}N_2O$ ($M+H^+$): 219.1496).

***N*-(*tert*-Butoxycarbonyl)-*N*-(2-propenyl)aminoacetone *O*-Benzyloxime (7)** Following the same procedure as for **1**, compounds *E*-**7** and *Z*-**7** were obtained from **11** in 87% and 10% yields, respectively, both as colorless oils. *E*-**7**: IR ($CHCl_3$) cm^{-1}: 1686. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.26 (5H, m), 5.68 (1H, br m), 5.12—4.97 (2H, m), 5.09 (2H, s), 3.95—3.62 (4H, br m), 1.84 (3H, s), 1.46 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 155.8, 154.9, 138.2, 133.2, 128.3, 127.9, 127.7, 116.7, 80.0, 75.6, 49.4, 48.5, 28.4, 12.4. HR-MS m/z: 319.2013 (Calcd for $C_{18}H_{27}N_2O_3$ ($M+H^+$): 319.2020). *Z*-**7**: IR ($CHCl_3$) cm^{-1}: 1692. ^{1}H-NMR ($CDCl_3$) δ: 7.37—7.26 (5H, m), 5.74 (1H, br m), 5.17—5.02 (2H, m), 5.05 (2H, s), 4.15 (2H, br m), 3.82—3.67 (2H, br m), 1.83 (3H, s), 1.45 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 156.8, 155.3, 137.9, 133.1, 128.3, 127.9, 127.7, 117.5, 80.3, 75.7, 50.2, 44.5, 28.3, 17.1. HR-MS m/z: 319.2010 (Calcd for $C_{18}H_{27}N_2O_3$ ($M+H^+$): 319.2020).

***N*-(2-Propynyl)aminoethanal *O*-Benzyloxime (12)** To propargylamine (9.00 g, 164 mmol) was added chloroacetaldehyde *O*-benzyloxime (**2**) (10.0 g, 54.5 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 h, the reaction mixture was added to saturated aqueous $NaHCO_3$ and AcOEt. The layers were separated, and the aqueous phase was extracted with AcOEt. The combined organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$/MeOH 30 : 1) afforded **12** (8.46 g, 77%) as a yellow oil and a 3 : 2 mixture of *E*/*Z*-oxime. IR ($CHCl_3$) cm^{-1}: 3307. ^{1}H-NMR ($CDCl_3$) δ: 7.50 (3/5H, t, J=5.3 Hz), 7.34—7.25 (5H, m), 6.80 (2/5H, t, J=4.4 Hz), 5.11 (4/5H, s), 5.08 (6/5H, s), 3.63 (4/5H, d, J=4.4 Hz), 3.45 (6/5H, d, J=5.3 Hz), 5.41 (2H, m), 2.23 (1H, br t, J=2.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 150.9, 148.5, 137.6, 137.3, 128.3 (2C), 128.1 (1C), 127.8 (3C), 81.4, 81.3, 75.9, 75.7, 71.8 (2C), 46.7 (2C), 37.9, 37.4. HR-MS m/z: 203.1204 (Calcd for $C_{12}H_{15}N_2O$ ($M+H^+$): 203.1184).

***N*-(*tert*-Butoxycarbonyl)-*N*-(2-Propynyl)aminoethanal *O*-Benzyloxime (8)** Following the same procedure as for **1**, compound **8** was obtained from **12** in 90% yield as a colorless oil and a 3 : 2 mixture of *E*/*Z*-oxime. IR ($CHCl_3$) cm^{-1}: 1690. ^{1}H-NMR ($CDCl_3$) δ: 7.41 (3/5H, t, J=5.6 Hz), 7.36—7.26 (5H, m), 6.80 (2/5H, br t, J=4.4 Hz), 5.13 (4/5H, s), 5.08 (6/5H, s), 4.27—3.88 (4H, m), 2.21 (2/5H, t, J=2.5 Hz), 2.18 (3/5H, t, J=2.4 Hz), 1.45 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 154.5, 154.4, 149.7 (br), 146.3, 137.5, 137.3, 128.2 (2C), 128.1, 127.8 (2C), 127.7. 80.9, 80.8, 79.0, 78.7, 76.0, 75.8, 72.1, 71.7, 45.0, 42.9, 36.9, 35.9, 28.1 (2C). HR-MS m/z: 303.1712 (Calcd for $C_{17}H_{23}N_2O_3$ ($M+H^+$): 303.1707).

***N*-(2-Hydroxyethyl)aminoethanal *O*-Benzyloxime (13)** To 2-aminoethanol (10 ml, 166 mmol) was added chloroacetaldehyde *O*-benzyloxime (**2**) (10.0 g, 54.5 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was added to saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash column chromatography ($CHCl_3$/MeOH 30 : 1 to $CHCl_3$/MeOH 15 : 1) afforded *N*-(2-hydroxyethyl)aminoethanal *O*-benzyloxime (9.96 g, 88%) as colorless crystals and a 3 : 2 mixture of *E*/*Z*-oxime: mp 58.5—60 °C (AcOEt/hexane). IR ($CHCl_3$) cm^{-1}: 3600—3300. ^{1}H-NMR ($CDCl_3$) δ: 7.49 (3/5H, t, J=5.2 Hz), 7.38—7.25 (5H, m), 6.79 (2/5H, t, J=4.4 Hz), 5.10 (4/5H, s), 5.07 (6/5H, s), 3.65—3.57 (2H, m), 3.56 (4/5H, d, J=4.4 Hz), 3.38 (6/5H, d, J=5.2 Hz), 2.78—2.70 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 151.3, 149.0, 137.6, 137.4, 128.3, 128.2, 128.0, 127.8, 76.1, 75.8, 60.8, 60.7, 51.0, 50.6, 47.7, 44.4. Some carbon peaks were missing due to overlapping. HR-MS m/z: 209.1271 (Calcd for $C_{11}H_{17}N_2O_2$ ($M+H^+$): 209.1289). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45, Found: C, 63.43; H, 7.76; N, 13.50.

***N*-[2-(Benzyloxyimino)ethyl]-*N*-(2-hydroxyethyl)-2-propenamide (9)** To a solution of **13** (5.00 g, 24.0 mmol) in acetone (100 ml) was added a solution of Na_2CO_3 (5.09 g, 48.0 mmol) in H_2O (20 ml) at 20 °C. After acryloyl chloride (2.92 ml, 36.0 mmol) was added dropwise at 0 °C, the reaction mixture was stirred at the same temperature for 90 min. After the solvent was evaporated at reduced pressure, the resulting residue was diluted with water and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by flash columun chromatography (hexane/AcOEt 1 : 3) afforded **9** (5.47 g, 87%) as a colorless oil and a 3 : 1 mixture of *E*/*Z*-oxime. The presence of rotamers and *E*/*Z*-isomers precluded a comprehensive assignment of all proton and carbon resonances. IR ($CHCl_3$) cm^{-1}: 3600—3300, 1647, 1611. ^{1}H-NMR ($CDCl_3$) δ: 7.50 (1/4H, t, J=5.1 Hz), 7.43 (1/4H, t, J=4.8 Hz), 7.40—7.25 (5H, m), 6.80—6.25 (5/2H, m), 5.72—5.64 (1H, m), 5.12 (1H, br d, J=7.2 Hz), 5.05 (1H, br d, J=7.5 Hz), 4.31 (1H, dd, J=6.0, 4.2 Hz), 4.12 (1H, br d, J=4.8 Hz), 3.80—3.40 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 168.1, 167.7, 167.4, 167.2, 149.1, 148.4, 147.1, 145.7, 137.5, 137.1, 129.7, 129.3, 128.7, 128.6, 128.5, 128.43, 128.36, 128.33, 128.25, 128.1, 128.0, 127.7, 127.5, 127.3, 126.9, 76.7, 76.3, 76.2, 76.0, 61.2, 61.1, 60.2, 60.0, 51.0, 50.8, 50.5, 50.4, 48.4, 45.6, 45.4, 43.3. HR-MS m/z: 262.1318 (Calcd for $C_{14}H_{18}N_2O_2$ (M^+): 262.1317).

General Procedure for Radical Reaction Using AIBN To a boiling solution of **1** (100 mg, 0.345 mmol) in benzene (5 ml) was added portionwise a solution of Bu_3SnH or PhSH (0.380 mmol) and AIBN (0.345 mmol) in benzene (2 ml) under a nitrogen atmosphere over 15 min. The reaction mixture was heated at reflux for 2—3 h, and then the solvent was evaporated at reduced pressure. The resulting residue was diluted with water and then extracted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (AcOEt/hexane) afforded **4** or **5b** as colorless oils.

General Procedure for Radical Reaction Using Et_3B To a boiling solution of **1**, **7**, **8**, or **9** (0.345 mmol) and Bu_3SnH, Ph_3SnH, PhSH, Ph_2PH, Et_3SiH or $(TMS)_3SiH$ (0.380 mmol) in benzene (7 ml) was added portionwise a 1 M solution of Et_3B in hexane (0.862 ml, 0.862 mmol) under a nitrogen atmosphere over 15 min. The reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (AcOEt/hexane) afforded **4**—**6** or **14**—**18** as colorless oils. The presence of rotamers and isomers precluded a comprehensive assignment of all proton and carbon resonances.

3-(Benzyloxyamino)-*N*-(*tert*-butoxycarbonyl)-4-(tributylstannylmethyl)pyrrolidine (4) As a colorless oil and a 1 : 1 mixture of isomers: IR ($CHCl_3$) cm^{-1}: 1684. ^{1}H-NMR ($CDCl_3$) δ: 7.35 (5H, br m), 5.59 (1H, br s), 4.69 (2H, br s), 3.62—2.85 (5H, m), 2.38 (1/2H, br m), 2.19 (1/2H, br m), 1.60—1.38 (2H, m), 1.47 (9/2H, s), 1.46 (9/2H, s), 1.37—1.22 (6H, m), 0.92—0.81 (21H, m). HR-MS m/z: 539.2283 (Calcd for $C_{25}H_{43}N_2O_3Sn^{120}$ (M^+-t-Bu): 539.2293), 538.2296 (Calcd for

$C_{25}H_{43}N_2O_3Sn^{119}$ (M^+-t-Bu): 538.2305), and 537.2298 (Calcd for $C_{25}H_{43}N_2O_3Sn^{118}$ (M^+-t-Bu): 537.2287).

3-(Benzyloxyamino)-*N*-(*tert*-butoxycarbonyl)-4-(triphenylstannylmethyl)pyrrolidine (5a) As a colorless oil and a 1 : 1 mixture of isomers: IR ($CHCl_3$) cm^{-1}: 1684. ^{1}H-NMR ($CDCl_3$) δ: 7.64—7.17 (20H, m), 5.48 (1H, br s), 4.60—4.48 (2H, br m), 3.68—2.91 (5H, m), 2.58 (1/2H, br m), 2.37 (1/2H, br m), 1.72—1.40 (2H, m), 1.43 (9/2H, s), 1.38 (9/2H, s). HR-MS *m/z*: 656.2033 (Calcd for $C_{35}H_{40}N_2O_3Sn^{120}$ (M^+): 656.2059) and 654.2038 (Calcd for $C_{35}H_{40}N_2O_3Sn^{118}$ (M^+): 654.2053).

3-(Benzyloxyamino)-*N*-(*tert*-butoxycarbonyl)-4-(phenylthiomethyl)-pyrrolidine (5b) As a colorless oil and a 1 : 2 mixture of isomers: IR ($CHCl_3$) cm^{-1}: 1686. ^{1}H-NMR ($CDCl_3$) δ: 7.40—7.15 (10H, m), 5.60 (1H, br s), 4.68 (4/3H, s), 4.65 (2/3H, s), 3.70—2.80 (7H, m), 2.45 (2/3H, br m), 2.33 (1/3H, br m), 1.45 (9H, br s). ^{13}C-NMR ($CDCl_3$) δ: 154.4 (2C), 137.3, 137.2, 135.6, 135.5, 129.7, 129.5, 128.9, 128.4, 128.3, 127.9, 126.4, 126.3, 79.4, 79.3, 76.7, 76.5, 60.6, 60.1, 49.8, 49.6, 49.4, 49.2, 41.2, 40.4, 36.2, 31.8, 31.7, 28.4. Some carbon peaks were missing due to overlapping. HR-MS *m/z*: 414.1968 (Calcd for $C_{23}H_{30}N_2O_3S$ (M^+): 414.1976).

3-(Benzyloxyamino)-*N*-(*tert*-butoxycarbonyl)-4-[tris(trimethylsilyl)-silylmethyl]pyrrolidine (5c) As a colorless oil and a 1 : 2 mixture of isomers: IR ($CHCl_3$) cm^{-1}: 1686. ^{1}H-NMR ($CDCl_3$) δ: 7.40—7.20 (5H, br m), 5.53 (1H, br s), 4.69 (2H, br s), 3.67—2.93 (5H, m), 2.27 (2/3H, br m), 2.16 (1/3H, br m), 1.46 (9H, s), 1.02 (1H, m), 0.70 (1H, m), 0.18 (27H, s). HR-MS *m/z*: 552.3054 (Calcd for $C_{26}H_{52}N_2O_3Si_4$ (M^+): 552.3053) and 553.3149 (Calcd for $C_{26}H_{53}N_2O_3Si_4$ ($M+H^+$): 553.3130).

***O*-Benzyl-*N*-[1-[*N′*-(*tert*-butoxycarbonyl)-*N′*-(2-propenyl)]amino-2-butyl]hydroxylamine (6)** As a colorless oil: IR ($CHCl_3$) cm^{-1}: 1683. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.23 (5H, m), 5.76 (1H, br m), 5.12—5.01 (2H, br m), 4.68 (2H, s), 4.00—3.74 (2H, br m), 3.32—3.12 (2H, br m), 2.94 (1H, br m), 1.65—1.40 (2H, br m), 1.42 (9H, s), 0.95 (3H, t, J=7.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 155.7, 137.9, 134.0, 128.2 (2C), 127.7, 116.2, 79.6, 76.5, 61.5, 50.5, 48.1, 28.3, 23.0, 10.4. HR-MS *m/z*: 334.2233 (Calcd for $C_{19}H_{30}N_2O_3$ (M^+): 334.2255).

3-(Benzyloxyamino)-*N*-(*tert*-butoxycarbonyl)-4-(tributylstannylmethylene)pyrrolidine (14) As a colorless oil and a 1 : 1 *E*/*Z* mixture: IR ($CHCl_3$) cm^{-1}: 1688. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.26 (5H, m), 6.07 (1/2H, br m), 5.45 (1H, br t, J=5.1 Hz), 5.49 (1/2H, br m), 4.72 (2H, s), 4.16—3.72 (3H, m), 3.66—3.48 (2H, m), 1.48 (9/2H, s), 1.47 (9/2H, s), 1.38—1.21 (6H, m), 0.98—0.83 (21H, m). HR-MS *m/z*: 594.2854 (Calcd for $C_{29}H_{50}N_2O_3Sn^{120}$ (M^+): 594.2841) and 592.2813 (Calcd for $C_{29}H_{50}N_2O_3Sn^{118}$ (M^+): 592.2835).

3-(Benzyloxyamino)-*N*-(*tert*-butoxycarbonyl)-4-[tris(trimethylsilyl)-silylmethylene]pyrrolidine (16) As a colorless oil and a single isomer: IR ($CHCl_3$) cm^{-1}: 1688. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.25 (5H, m), 5.76 (1H, br s), 5.37 (1H, br s), 4.71 (2H, s), 4.12—3.82 (3H, m), 3.63—3.47 (2H, m), 1.47 (9H, s), 0.20 (27H, s). ^{13}C-NMR ($CDCl_3$) δ: 154.5, 137.5, 128.5, 128.3, 127.9, 118.5, 79.4, 76.9, 65.4, 51.6, 49.6, 28.5, 1.1. One carbon peak was missing due to overlapping. HR-MS *m/z*: 550.2888 (Calcd for $C_{26}H_{50}N_2O_3Si$ (M^+): 550.2896).

4-(Benzyloxyamino)-3-(tributylstannylmethyl)-*N*-(2-hydroxyethyl)-2-pyrrolidinone (17) Major isomer (58% yield): as a colorless oil: IR ($CHCl_3$) cm^{-1}: 3368, 1674. ^{1}H-NMR ($CDCl_3$) δ: 7.40—7.25 (5H, m), 4.70 (2H, s), 3.72 (2H, t, J=5.1 Hz), 3.55 (1H, m), 3.46—3.26 (4H, m), 2.43 (1H, dt, J=5.7, 8.1 Hz), 1.52—1.41 (4H, m), 1.36—1.22 (6H, m), 0.92—0.81 (21H, m). ^{13}C-NMR ($CDCl_3$) δ: 177.4, 137.2, 128.4, 128.3, 128.0, 76.5, 63.5, 60.6, 50.9, 46.1, 43.9, 29.0, 27.3, 13.6, 9.7. One carbon peak was missing due to overlapping. HR-MS *m/z*: 554.2548 (Calcd for $C_{26}H_{46}N_2O_3Sn^{120}$ (M^+): 554.2528). Minor isomer (24% yield): as a colorless oil: IR ($CHCl_3$) cm^{-1}: 3368, 1675. ^{1}H-NMR ($CDCl_3$) δ: 7.40—7.25 (5H, m), 4.70 (2H, s), 3.72 (2H, t, J=5.4 Hz), 3.64 (1H, m), 3.51—3.26 (4H, m), 2.69 (1H, dt, J=7.5, 9.3 Hz), 1.55—1.40 (4H, m), 1.38—1.21 (6H, m), 0.92—0.81 (21H, m). ^{13}C-NMR ($CDCl_3$) δ: 177.1, 137.1, 128.5, 128.4, 128.0, 76.4, 60.6, 58.0, 51.0, 46.2, 43.2, 29.1, 27.3, 13.6, 9.9. One carbon peak was missing due to overlapping. HR-MS *m/z*: 554.2540 (Calcd for $C_{26}H_{46}N_2O_3Sn^{120}$ (M^+): 554.2528).

3-(Benzyloxyamino)-*N*-(*tert*-butoxycarbonyl)-4-methylenepyrrolidine (15) To a solution of **14** (20 mg, 0.034 mmol) in EtOH (1 ml) was added conc. HCl (0.1 ml) at room temperature. After being stirred at room temperature for 15 min, the reaction mixture was added to saturated aqueous $NaHCO_3$ and CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by preparative TLC (AcOEt/hexane 1 : 5) afforded **15** (9.3 mg, 91%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1689. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.29 (5H, m), 5.45 (1H, br s), 5.19 (1H, br s), 5.13 (1H, br s), 4.72 (2H, s), 4.17—3.84 (3H, m), 3.63—3.48 (2H, m), 1.47 (9H, s). HR-MS *m/z*: 305.1867 (Calcd for $C_{17}H_{25}N_2O_3$ ($M+H^+$): 305.1864).

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References and Notes

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