Free-Radical Reaction of Imine Derivatives in Water

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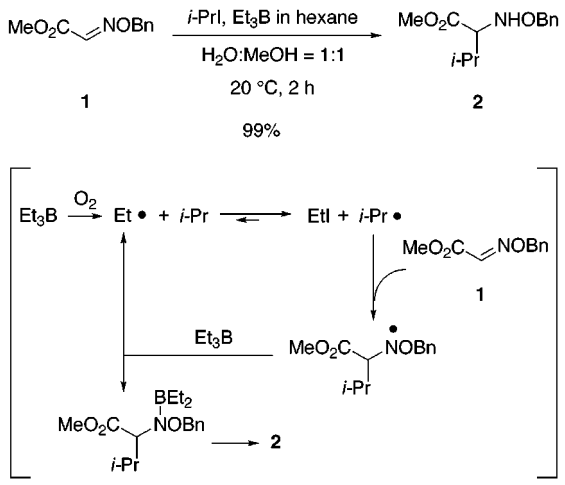
The use of water as a solvent has generated considerable interest from both economical and environmental points of view.[1] Particularly, the carbon−carbon bond formation in aqueous media is a challenging problem.[2]

The carbon−nitrogen double bond of imine derivatives has emerged as a radical acceptor, and thus numerous, synthetically useful carbon−carbon bond-forming reactions are available.[3] However, the reactions of water-sensitive imines have generally been performed in organic solvents under anhydrous reaction conditions.[4,5] In principle, the reactions of a strictly neutral species such as uncharged free radicals are not affected by the presence of water.[6] We now report the results of experiments to prove the utility of imine derivatives in the aqueous-medium radical reactions. As shown below, the screening of several imines shows that oxime ethers, oximes, hydrazones, and nitrones may participate in the aqueous-medium radical reactions involving the construction of the carbon−carbon bond. Another remarkable feature of this reaction is that employment of a water-resistant radical species successfully integrated a multistep chemical reaction into a one-pot reaction, thus providing a convenient method for preparing α-amino acid derivatives in water.

Results and Disscusion

Among the different types of imines, the oxime ethers are well-known to be excellent radical acceptors.[7] We first investigated the aqueous-medium radical addition to glyoxylic oxime ether **1** because it had shown good reactivity in organic solvents (Scheme 1).[8,9] To a solution of oxime ether **1** in water/methanol (1:1, v/v) were added isopropyl iodide (30 equiv) and a commercially available 1.0 M solution of triethylborane in hexane (5 equiv),[3] and then the biphasic reaction mixture was stirred vigorously at 20 °C for 2 h. ^{1}H NMR measurement of the crude product showed almost quantitative conversion of **1** to the adduct **2**. The α-amino acid derivative **2** was obtained in 99% yield after purification by preparative TLC. It is noteworthy that triethylborane worked well as a radical initiator and a terminator to trap the intermediate aminyl radical even in the biphasic reaction to give a chain-propagating ethyl radical.

Scheme 1



We next chose the imine derivatives **3**−**6** as a model substrate and investigated several reaction conditions for an ethyl radical addition (Figure 1, Table 1). Oxime ether **3** having a free carboxyl group showed high solubility in water, and the biphasic reaction using a solution of triethylborane in hexane proceeded within 10 min. After concentration of the reaction mixture at reduced pressure,^{1}H NMR measurement of the crude product showed almost quantitative formation of the ethylated product

(1) Garner, P. P.; Parker, D. T.; Gajewski, J. J.; Lubineau, A.; Angé, J.; Queneau, Y.; Beletskaya, I. P.; Cheprakov, A. V.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Kobayashi, S. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998.

(2) For reviews, see: (a) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (b) Lubineau, A.; Angé, J.; Queneau, Y. *Synthesis* **1994**, 741. (c) Li, C. J. *Tetrahedron* **1996**, *52*, 5643.

(3) For reviews, see: (a) Naito, T. *Heterocycles* **1999**, *50*, 505. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

(4) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Enders, D.; Reinhold, U. *Tetrahedron Asymmetry* **1997**, *8*, 1895. (c) Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999.

(5) For some examples of reactions of imines in water, see: (a) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463. (d) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19.

(6) Triethylborane can be applied to the radical reactions in water. For discussion of triethylborane-mediated radical reactions in aqueous media, see: (a) Yamazaki, O.; Togo, H.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2519. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604. (c) Nakamura, T.; Yorimitsu, H.: Shinokubo, H.: Oshima, K. *Synlett* **1998**, 1351. Alkyl radical can be generated via sonication of alkyl iodide in the presence of Zn/CuI in water. See: (d) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149. (e) Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 441. (f) Erdmann, P.; Schäfer, J.; Springer, R.; Zeitz, H.-G.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 638.

(7) For some examples of the radical reaction of oxime ethers, see: (a) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. (b) Iserloh, U.; Curran, D. P. *J. Org. Chem.* **1998**, *63*, 4711. (c) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877. (d) Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202.

(8) Because the glyoxylic oxime ether is activated by an electron-withdrawing substituent, it has high reactivity toward nucleophilic carbon radicals. See: (a) Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun.* **1997**, 1789. (b) Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174. (c) Miyabe, H.; Yoshioka, N.; Ueda, M.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3659. (d) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465. (e) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. For the complete reaction and selective alkylation, the excesses of reagents were employed. For example, treatment of oxime ether **1** with isopropyl iodide (1 equiv) and a commercially available 1.0 M solution of triethylborane in hexane (1 equiv) in water gave the isopropylated adduct **2** (13%) accompanied by the ethylated adduct (13%) and the recovered oxime ether **1** (70%).

(9) Bertrand's group recently reported their studies on the radical addition to glyoxylic imines. See: (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780. (b) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (c) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189.

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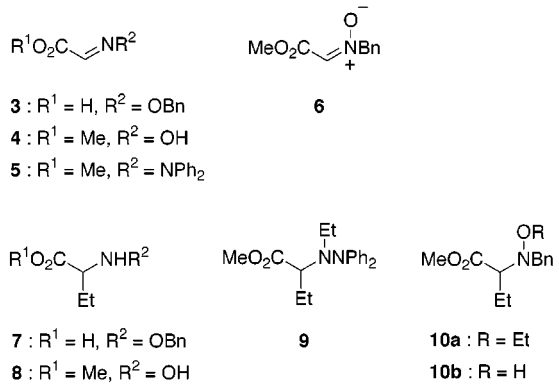


Figure 1. Imine derivatives **3**−**6** and ethylated products **7**−**10**.

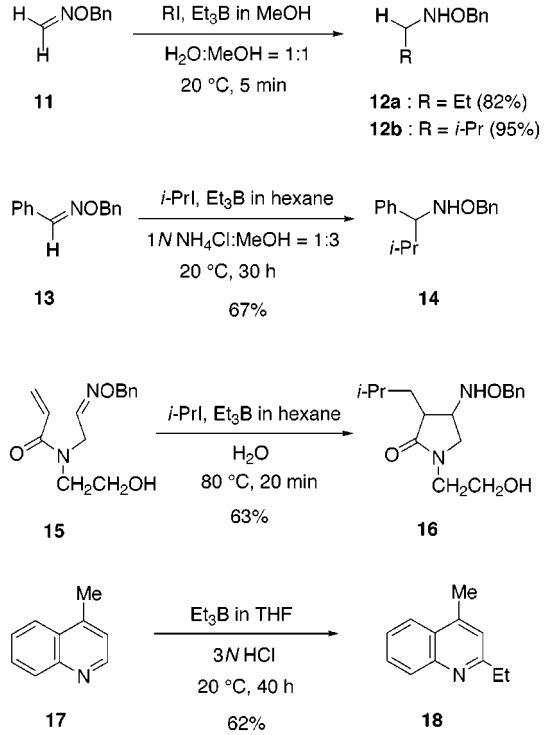
Table 1. Ethyl Radical Addition to Glyoxylic Imines 3−6

entry	substrate	solvent	product	time (min)	yield (%)
1[a]	**3**	H_2O	**7**	10	99[d]
2[a]	**3**	H_2O/MeOH, 1:1	**7**	30	99[d]
3[b]	**3**	H_2O	**7**	10	99[d]
4[a]	**4**	H_2O	**8**	10	17 (82)[d]
5[a]	**4**	H_2O	**8**	120	36 (63)[d]
6[a]	**4**	H_2O	**8**	1200	44 (54)[d]
7[a]	**5**	H_2O	**9**	120	71 (28)[d]
8[c]	**5**	H_2O/MeOH, 1:5	**9**	50	52[e]
9[a]	**6**	H_2O/MeOH, 1:1	**10a**/**10b**, 0.8:1	10	16 (83)[d]
10[a]	**6**	H_2O/MeOH, 1:1	**10a**/**10b**, 3.7:1	1200	80 (2)[e]

[a] Reaction was carried out with Et_3B in hexane (5 equiv) at 20 °C. [b] Reaction was carried out with Et_3B in THF (5 equiv) at 20 °C. [c] Reaction was carried out with Et_3B in hexane (10 equiv) at 20 °C. [d] Yields based on ^1H NMR. Yields in parentheses are for the recovered starting material. [e] Isolated yields.

7 (Table 1, entry 1). The biphasic reaction also proceeded in aqueous methanol without any problem (entry 2). The monophasic reaction using a commercially available solution of triethylborane in THF gave a similar good result (entry 3). Although oxime **4**, hydrazone **5**, and nitrone **6** also acted as radical acceptors in water, their reactivities were quite different from those of oxime ethers **1** and **3**.[10] Reactions of water-soluble oxime **4** were run in water by using the solution of triethylborane in hexane (entries 4 and 5), and more than half of the starting material remained even after being stirred for 20 h. In the case of hydrazone **5**,[11] the diethylated product **9** was obtained as a result of the additional *N*-ethylation. Although hydrazone **5** was insoluble in water, good conversion was observed in the reaction using a stirred suspension of **5** in water alone (entry 7). The reaction of hydrazone **5** in a mixed-solvent system such as aqueous methanol proceeded to give the diethylated product **9** in 52% yield within 50 min accompanied with unidentified complex products (entry 8). Although the aqueous-medium radical reaction of nitrone **6**[12] took long reaction time, a 3.7:1 mixture of the diethylated product **10a** and monoethylated product **10b** was obtained in 80% combined yield (entry 10).

Scheme 2



Subsequently, the aqueous-medium radical reactions of a variety of nonglyoxylic imine derivatives were tested (Scheme 2). The ethyl radical addition to formaldoxime ether **11**[13] proceeded smoothly at 20 °C by using a solution of triethylborane in MeOH to give a good yield of alkylated product **12a**. In the case of isopropyl radical addition using isopropyl iodide, the product **12b** was also obtained with excellent chemical efficiency. In our recent studies, the activation of an oxime ether group with BF_3·OEt_2 was found to be essential to achieve the intermolecular radical reaction of unactivated aldoxime ethers such as benzaldehyde *O*-benzyloxime **13** in an organic solvent.[14] It is important to note that the aqueous-medium radical addition to **13** proceeded with the activation of 1 N NH_4Cl to give alkylated product **14** in 67% yield, whereas the reaction of **13** in H_2O/MeOH (1:3, v/v) did not take place. To test the intramolecular reactivity of the oxime ether group, we next investigated the tandem radical cyclization of oxime ether **15**. Treatment of oxime ether **15** with triethylborane and isopropyl iodide in water at 80 °C gave the cyclized product **16** in 62% yield via two carbon−carbon bond-forming steps.[15] The radical alkylation of a heteroaromatic compound having a nitrogen atom was also studied in acidic aqueous solution. Treatment of a solution of lepidine **17** in 3 N HCl with a solution of triethylborane in THF gave the ethylated product **18** in 62% yield.

In the field of combinatorial chemistry, integration of a multistep chemical reaction into a one-pot reaction has

(10) Oxime ether **3** and oxime **4** showed high solubility in water; however, hydrazone **5** and nitrone **6** were insoluble in water.

(11) For some examples of the radical reaction of hydrazones, see: (a) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603. (b) Tauh, P.; Fallis, A. G. *J. Org. Chem.* **1999**, *64*, 6960.

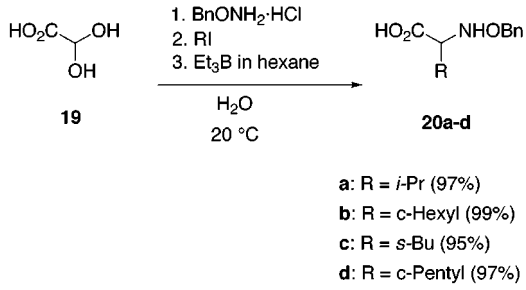
(12) Nitrones have evolved as a useful trap for short-lived reactive free radicals. See: Becker, D. A. D. *J. Am. Chem. Soc.* **1996**, *118*, 905.

(13) The radical addition to formaldoxime ether **11** in organic solvents, see: (a) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. (b) Bhat, B.; Swayze, E. E.; Wheeler, P.; Dimock, S.; Perbost, M.; Sanghvi, Y. S. *J. Org. Chem.* **1996**, *61*, 8186.

(14) (a) Miyabe, H.; Shibata, R.; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631. (b) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569. (c) Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431. (d) Russell, G. A.; Lijuan, W.; Rajaratnam, R. *J. Org. Chem.* **1996**, *61*, 8988.

(15) The radical alkylation was generally performed in the presence of TFA or BF_3·OEt_2 in an organic solvent. See: Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700.

Scheme 3



attracted significant attention as a rapid synthetic method of creating a compound library from simple building blocks.[16] Finally, the tolerance of the aqueous media prompted us to examine a one-pot radical reaction for the synthesis of α-amino acids in water (Scheme 3). Conventional condensation of glyoxylic acid hydrate **19** with benzyloxyamine hydrochloride proceeded smoothly in water. Subsequently, alkyl iodide (RI) and triethylborane were added to the reaction vessel to afford excellent yields of α-amino acid derivatives **20a**−**d** after the purification. It should be noted that the one-pot reactions in water were much more effective compared to the reactions in an organic solvent such as toluene and CH_2Cl_2.[8c,d] Moreover, the present method is more convenient and milder than methods employing other multicomponent routes to α-amino acids such as the Strecker and Ugi syntheses.

In conclusion, we have demonstrated that imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent radical acceptors for the aqueous-medium radical reactions. Furthermore, the carbon radical addition to imine derivatives presents new opportunities for the carbon−carbon bond formation in water. Employment of a water-resistant radical species would eliminate the cumbersome operations and protection-deprotection step involved in conventional ionic reactions.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI, CI, or SIMS 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). Integrative fractions of ^{1}H NMR of the compounds obtained as an a:b mixture of *E*/*Z* isomers and/or rotamers were described as a/bH. The NMR yields were calculated from the peak ratio due to both the products and starting material in the ^{1}H NMR of almost pure crude product obtained by concentration of the reaction mixture.

Isopropyl Radical Addition to Oxime Ether 1. To a solution of oxime ether **1**[14c] (50 mg, 0.26 mmol) in H_2O/MeOH (1:1, 10 mL) were added *i*-PrI (0.78 mL, 7.8 mmol) and Et_3B (1.0 M in hexane, 1.3 mL, 1.3 mmol) at 20 °C. After the mixture was stirred at the same temperature for 2 h, the solvent was evaporated at reduced pressure. The resulting residue was diluted with saturated aqueous $NaHCO_3$ 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 preparative TLC (hexane/AcOEt, 12:1) afforded **2**[14c] (61 mg, 99%) as a colorless oil.

(16) For reviews, see: (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) *Chem. Rev.* **1997**, *97*, 347−510 (Special Issue). (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643.

2-(Benzyloxyimino)ethanoic Acid (3). To a solution of glyoxylic acid monohydrate (5.0 g, 54 mmol) in MeOH (250 mL) were added benzyloxyamine hydrochloride (13.0 g, 82 mmol) and AcONa (8.9 g, 109 mmol) under a nitrogen atmosphere at 20 °C. After the mixture was stirred at the same temperature for 12 h, the solvent was evaporated at reduced pressure, and the resulting residue was added to water and CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by recrystallization (AcOEt/hexane) afforded oxime ether (6.88 g, 71%) as a 2:1 mixture of *E*/*Z*-oxime. ^{1}H NMR ($CDCl_3$): δ 7.50 (2/3H, s), 7.29 (5H, s), 7.27 (1/3H, s), 5.18 (4/3, s), 4.89 (2/3, s). ^{13}C NMR ($CDCl_3$): δ 165.6, 142.5, 136.0, 135.5, 128.6, 128.43, 128.41, 128.29, 128.25, 77.6, 77.5. HRMS: calcd for $C_9H_9NO_3$ (M^+), 179.0582; found, 179.0569.

Methyl 2-(Hydroxyimino)ethanoate (4). To a solution of methyl 2-hydroxy-2-methoxyacetate (5.0 g, 41.6 mmol) in MeOH (50 mL) were added hydroxylamine hydrochloride (4.3 g, 62.4 mmol) and AcONa (6.8 g, 83.3 mmol) under nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 2 h, the reaction mixture was filtered and evaporated at reduced pressure. Purification of the residue by a combination of flash column chromatography (hexane/AcOEt, 1:1) and recrystallization from hexane afforded **4** (3.7 g, 86%) as a white solid. IR ($CHCl_3$): 3268, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.59 (1H, s), 3.87 (3H, s). ^{13}C NMR ($CDCl_3$): δ 162.6, 141.7, 52.5. HRMS: calcd for $C_3H_5NO_3$ (M^+), 103.0269; found, 103.0265.

***N*-Benzyl-α-Methoxycarbonylnitrone (6).** To a solution of methyl 2-hydroxy-2-methoxyacetate (0.94 g, 7.8 mmol) in Et_2O (80 mL) were added *N*-benzylhydroxylamine (0.96 g, 7.8 mmol) and calcium chloride (0.87 g, 7.8 mmol) under nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 3 h, the reaction mixture was filtered through a pad of Celite diatomaceous earth, and then the filtrate was concentrated at reduced pressure. Purification of the residue by recrystallization from petroleum ether afforded an *E*/*Z* mixture of **6** (0.65 g, 43%) as a white solid. IR ($CHCl_3$): 3014, 1731, 1698, 1558, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.55−7.33 (5H, m), 7.22 (8/13H, s), 7.06 (5/13H, s), 5.71 (16/13H, s), 5.00 (10/13H, s), 3.81 (24/13H, s), 3.78 (15/13H, s). ^{13}C NMR ($CDCl_3$): δ 161.3, 160.4, 133.2, 131.5, 129.53, 129.49, 129.2, 129.1, 128.8, 128.6, 126.5, 124.8, 73.3, 66.4, 52.1, 51.8. HRMS: calcd for $C_{10}H_{11}NO_3$ (M^+), 193.0738; found, 193.0721.

2-(Benzyloxyamino)butanoic Acid (7). To a solution of 2-(benzyloxyimino)ethanoic acid **3** (50 mg, 0.28 mmol) in H_2O (10 mL) was added Et_3B (1.0 M in hexane, 1.4 mL, 1.4 mmol) at 20 °C. After being stirred at the same temperature for 10 min, the reaction mixture was concentrated at reduced pressure. ^{1}H NMR measurement of the resulting residue showed almost quantitative formation of the ethylated product **7** (Table 1, entry 1). ^{1}H NMR (CD_3OD): δ 7.34−7.26 (5H, m), 4.68 (2H, s), 3.50 (1H, br t, J = 10.2 Hz), 1.58 (2H, m), 0.95 (3H, t, J = 7.4 Hz). ^{13}C NMR (CD_3OD): δ 177.2, 138.9, 129.4, 129.1, 128.7, 76.9, 66.1, 23.6, 10.7. HRMS: calcd for $C_{11}H_{15}NO_3$ (M^+), 209.1051; found, 209.1064.

Methyl 2-(Hydroxylamino)butanoate (8). To a solution of methyl 2-(hydroxyimino)ethanoate **4** (50 mg, 0.49 mmol) in H_2O (10 mL) was added Et_3B (1.0 M in hexane, 2.4 mL, 2.4 mmol) at 20 °C. After being stirred at the same temperature for 10, 120, or 1200 min, the reaction mixture was concentrated at reduced pressure. Yield was determined by ^{1}H NMR measurement of the resulting residue without purification (Table 1, entries 4−6). IR ($CHCl_3$): 3583, 2955, 1736, 1461 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.78 (3H, s), 3.60 (1H, t, J = 6.8 Hz), 1.73−1.58 (2H, m), 0.97 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 174.2, 66.4, 51.9, 22.5, 10.2. HRMS: calcd for $C_5H_{11}NO_3$ (M^+), 133.0738; found, 133.0725.

Carboxylic acid **8** was purified by preparative TLC (hexane/AcOEt, 2:1, 2-fold development).

Methyl 2-(*N*′-Ethyl-*N*,*N*-diphenylhydrazino)butanoate (9). To a solution of methyl 2-(diphenylaminoimino)ethanoate **5**[14c] (50 mg, 0.20 mmol) in H_2O/MeOH (1:5, 10 mL) was added Et_3B (1.0 M in hexane, 2.0 mL, 2.0 mmol) at 20 °C. After being stirred at the same temperature for 50 min, the reaction mixture was concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt, 5:1, 2-fold development) afforded **9**[14c] (29 mg, 52%) as a colorless oil (Table 1, entry 8).

Methyl 2-(*N*-Benzyl-*N*-ethoxyamino)butanoate (10a) and Methyl 2-(*N*-Benzyl-*N*-hydroxylamino)butanoate (10b). To a solution of *N*-benzyl-α-methoxycarbonylnitrone **6** (50 mg, 0.26 mmol) in H_2O/MeOH (1:1, 10 mL) was added Et_3B (1.0 M in hexane, 1.3 mL, 1.3 mmol) at 20 °C. After being stirred at the same temperature for 10 or 1200 min, the reaction mixture was concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt, 5:1, 2-fold development) afforded **10a** and **10b** as a colorless oil (Table 1, entries 9 and 10).

10a. IR ($CHCl_3$): 2976, 1604, 1495, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.40−7.22 (5H, m), 3.99 (1H, d, J = 13.3 Hz), 3.91 (1H, d, J = 13.3 Hz), 3.75 (3H, s), 3.52−3.35 (3H, m), 1.89−1.74 (2H, m), 0.95 (3H, t, J = 7.4 Hz), 0.91 (3H, t, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 172.1, 137.6, 129.8, 127.9, 127.1, 70.2, 69.1, 59.3, 51.3, 22.9, 13.6, 10.4. HRMS: calcd for $C_{14}H_{21}NO_3$ (M^+), 251.1520; found, 251.1517.

10b. IR ($CHCl_3$): 3572, 2954, 1737, 1496, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.38−7.23 (5H, m), 5.56 (1H, br s), 3.96 (2H, s), 3.76 (3H, s), 3.40 (1H, t, J = 7.0 Hz), 1.94−1.79 (2H, m), 0.98 (3H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 173.0, 137.2, 129.2, 128.3, 127.3, 70.0, 61.1, 51.5, 22.9, 10.3. HRMS: calcd for $C_{12}H_{17}NO_3$ (M^+), 223.1207; found, 223.1201.

***O*-Benzyl-*N*-propylhydroxylamine (12a).** To a solution of oxime ether **11**[13] (50 mg, 0.37 mmol) in H_2O/MeOH (1:1, 10 mL) was added Et_3B (1.0 M in MeOH, 1.85 mL, 1.85 mmol) at 20 °C. After the mixture was stirred at the same temperature for 5 min, the solvent was evaporated at reduced pressure. The resulting residue was diluted with saturated aqueous $NaHCO_3$ 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 column chromatography (hexane/AcOEt, 8:1) afforded **12a**[14c] (50 mg, 82%) as a colorless oil.

***O*-Benzyl-*N*-(2-methylpropyl)hydroxylamine (12b).** To a solution of oxime ether **11** (50 mg, 0.37 mmol) in H_2O/MeOH (1:1, 10 mL) were added *i*-PrI (1.1 mL, 11.1 mmol) and Et_3B (1.0 M in MeOH, 1.85 mL, 1.85 mmol) at 20 °C. After the mixture was stirred at the same temperature for 5 min, the solvent was evaporated at reduced pressure. The resulting residue was diluted with saturated aqueous $NaHCO_3$ 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 column chromatography (hexane/AcOEt, 8:1) afforded **12b** (66 mg, 99%) as a colorless oil. IR ($CHCl_3$): 3011, 2959, 1496, 1469, 1454 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.38−7.25 (5H, m), 4.70 (2H, s), 2.74 (2H, d, J = 6.8 Hz), 1.88 (1H, m), 0.91 (6H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 137.9, 128.3, 127.6, 75.9, 59.8, 25.8, 20.5. HRMS: calcd for $C_{11}H_{17}NO$ (M^+), 179.1309; found, 179.1328.

***O*-Benzyl-*N*-(2-methyl-1-phenylpropyl)hydroxylamine (14).** To a solution of oxime ether **13**[14c] (50 mg, 0.24 mmol) and *i*-PrI (0.72 mL, 7.2 mmol) in 1 N NH_4Cl/MeOH (1:3, 10 mL) was added Et_3B (1.0 M in hexane, 1.2 mL, 1.2 mmol) three times at 20 °C. After the mixture was stirred at the same temperature for 30 h, the solvent was evaporated at reduced pressure. The resulting residue was diluted with saturated aqueous $NaHCO_3$ 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 preparative TLC (hexane/AcOEt, 15:1) afforded **14** (41 mg, 67%) as a colorless oil. IR ($CHCl_3$): 2964, 1495, 1454 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.32−7.16 (10H, m), 4.57 (1H, d, J = 11.4 Hz), 4.52 (1H, d, J = 11.4 Hz), 3.73 (1H, br d, J = 7.3 Hz), 1.98 (1H, m), 0.96 (3H, d, J = 6.8 Hz), 0.74 (3H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 141.0, 137.7, 128.4, 128.2, 128.1, 127.8, 127.6, 127.0, 76.4, 71.6, 30.8, 19.8, 18.9. HRMS: calcd for $C_{17}H_{21}NO$ (M^+), 255.1622; found, 255.1635.

Preparation of Oxime Ether (15). To 2-aminoethanol (10 mL, 166 mmol) was added chloroacetaldehyde *O*-benzyloxime (10 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 (10 g, 88%) as colorless crystals and a 3:2 mixture of *E*/*Z*-oxime. Mp 58.5−60 °C (AcOEt/hexane). IR ($CHCl_3$): 3600−3300 cm^{-1}. ^1H 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. HRMS: calcd for $C_{11}H_{17}N_2O_2$ ($M + H^+$), 209.1289; found, 209.1271. 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.

To a solution of *N*-(2-hydroxyethyl)aminoethanal *O*-benzyloxime (6.15 g, 29.6 mmol) in acetone (100 mL) was added a solution of Na_2CO_3 (6.28 g, 59.2 mmol) in H_2O (25 mL) at 20 °C. After acryloyl chloride (4.83 mL, 59.2 mmol) was added dropwise at 0 °C, the reaction mixture was stirred at the same temperature for 30 min. After the solvent was evaporated at reduced pressure, the resulting residue was diluted with water and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by flash column chromatography ($CHCl_3$/MeOH, 30:1) afforded **15** (6.72 g, 87%) as an oil. The presence of rotamers and *E*/*Z* isomers precluded a comprehensive assignment of all protons. IR ($CHCl_3$): 2936, 1647, 1611 cm^{-1}. ^1H NMR ($CDCl_3$): 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), 5.13 (1/2H, s), 5.11 (1/2H, s), 5.06 (1/2H, s), 5.04 (1/2H, s), 4.31 (1H, 2d, 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. HRMS: calcd for $C_{14}H_{18}N_2O_2$ (M^+), 262.1317; found, 262.1318.

Radical Cyclization of Oxime Ether (15). To a suspension of oxime ether **15** (100 mg, 0.382 mmol) in H_2O (3 mL) were added *i*PrI (1.14 mL, 11.5 mmol) and Et_3B (1.0 M in hexane, 1.15 mL, 1.15 mmol) at 80 °C. After being stirred at the same temperature for 20 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ 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 preparative TLC (AcOEt) afforded a trans/cis mixture of **16** (74 mg, 63%) as a colorless oil. IR ($CHCl_3$): 2959, 1674, 1670, 1489, 1467, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.40−7.25 (5H, m), 4.70 (4/3H, s), 4.69 (1/3H, d, J = 11.8 Hz), 4.66 (1/3H, d, J = 11.8 Hz), 3.79−3.23 (7H, m), 2.57 (1/3H, m), 2.34 (2/3H, m), 1.82−1.21 (3H, m), 0.928 (6/3H, d, J = 6.2 Hz), 0.926 (3/3H, d, J = 6.2 Hz), 0.911 (3/3H, d, J = 6.2 Hz), 0.908 (6/3H, d, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$): δ 176.7, 176.3, 137.3, 137.0, 128.64, 128.61, 128.4, 128.3, 128.1, 128.0, 76.7, 76.4, 60.5, 60.4, 59.6, 56.2, 51.24, 51.19, 46.0, 45.9, 44.1 42.8, 39.1, 32.5, 26.0, 25.8, 23.13, 23.09, 21.8, 21.7. HRMS: calcd for $C_{17}H_{26}N_2O_2$ (M^+), 306.1941; found, 306.1941.

2-Ethyl-4-methylquinoline (18). To a solution of lepidine (50 mg, 0.35 mmol) in 3 N HCl (10 mL) was added Et_3B (1.0 M in THF, 1.75 mL, 1.75 mmol) five times at 20 °C. After being stirred at the same temperature for 40 h, the reaction mixture was neutralized by $NaHCO_3$ 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 preparative TLC (hexane/AcOEt, 2:1) afforded **18** (37 mg, 62%) as a colorless oil. IR ($CHCl_3$): 3016, 2972, 1605, 1562, 1508 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.04 (1H, br m), 7.94 (1H, dd, J = 8.4, 1.2 Hz), 7.67 (1H, ddd, J = 8.4, 7.0, 1.2 Hz), 7.49 (1H, ddd, J = 8.4, 7.0, 1.5 Hz), 7.15 (1H, br s), 2.95 (2H, q, J = 7.8 Hz), 2.67 (3H, s), 1.39 (3H, t, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 163.6, 147.6, 144.2, 129.2, 128.9, 126.7, 125.3, 123.4, 121.4, 32.1, 18.6, 19.9. HRMS: calcd for $C_{12}H_{13}N$ (M^+), 171.1047; found, 171.1053.

General Procedure for the One-Pot Synthesis of α-Amino Acid Derivatives. To a solution of glyoxylic acid monohydrate (50 mg, 0.54 mmol) in H_2O (10 mL) was added *O*-benzylhydroxylamine hydrochloride (86 mg, 0.54 mmol) at 20 °C. After the reaction mixture was stirred at the same temperature for 3 h, RI (16.2 mmol) and Et_3B (1.0 M in hexane, 2.7 mL, 2.7 mmol) were added. After the reaction mixture was stirred at the same temperature for 1 h, the solvent was evaporated at reduced pressure. Purification of the residue by flash column chromatography ($CHCl_3$/MeOH, 10:1) afforded **20a**−**d** as a white powder.

2-(Benzyloxyamino)-3-methylbutanoic Acid (20a). ^{1}H NMR (CD_3OD): δ 7.38−7.26 (5H, m), 4.67 (2H, s), 3.30 (1H, br m), 1.90−1.70 (1H, m), 0.94 (6H, d, J = 10.1 Hz). ^{13}C NMR (CD_3OD): δ 177.2, 139.0, 129.5, 129.1, 128.6, 76.7, 70.6, 29.9, 19.7. HRMS: calcd for $C_{12}H_{17}NO_3$ (M^+), 223.1207; found, 223.1221.

2-(Benzyloxyamino)-2-cyclohexylethanoic Acid (20b). ^{1}H NMR (CD_3OD): δ 7.34−7.26 (5H, m), 4.65 (2H, s), 3.31 (1H, m), 1.35−0.78 (11H, m). ^{13}C NMR (CD_3OD): δ 177.2, 139.0, 129.5, 129.1, 128.6, 76.7, 70.1, 39.5, 30.72, 30.66, 27.1, 27.0. HRMS: calcd for $C_{15}H_{21}NO_3$ (M^+), 263.1520; found, 263.1505.

2-(Benzyloxyamino)-3-methylpentanoic Acid (20c) as a Diastereomeric Mixture. ^{1}H NMR (CD_3OD): δ 7.38−7.26 (5H, m), 4.65 (2H, s), 3.42 (1H, br m), 1.68−1.38 (2H, m), 1.26−1.11 (1H, m), 0.87 (6H, m). ^{13}C NMR (CD_3OD): δ 177.4, 177.1, 139.0, 129.5, 129.1, 128.6, 76.1, 69.1, 68.6, 36.8, 36.2, 27.3, 26.9, 16.0, 15.7, 11.8, 11.5. HRMS: calcd for $C_{13}H_{19}NO_3$ (M^+), 237.1364; found, 237.1354.

2-(Benzyloxyamino)-2-cyclopentylethanoic Acid (20d). ^{1}H NMR (CD_3OD): δ 7.38−7.20 (5H, br m), 4.68 (2H, s), 3.40−3.32 (2H, br m), 1.99−1.18 (8H, br m). ^{13}C NMR (CD_3OD): δ 177.3, 138.4, 129.2, 128.8, 128.4, 76.5, 69.0, 40.5, 30.6, 29.9, 25.6, 25.5. HRMS: calcd for $C_{14}H_{19}NO_3$ (M^+), 249.1364; found, 249.1355.

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Supporting Information Available: Spectra for compounds **1**−**20e**. This material is available free of charge via the internet at http://pubs.acs.org.

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