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# Reactions of Alkyl Radicals with Oxime Ether: One-Pot Synthesis of α-Amino Acids

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**Abstract**—The addition of water-resistant carbon radicals to glyoxylic oxime ether provided a new method for the one-pot synthesis of α-amino acids via a carbon–carbon bond formation. The reaction of 2-hydroxy-2-methoxyacetic acid methyl ester with benzyloxyamine and an alkyl radical gave the protected α-amino acids via the stannyl radical-mediated reaction. In the absence of $Bu_3SnH$, the predominant formation of the desired alkylated products was also observed by using RI and $Et_3B$ in boiling toluene. $Et_2Zn$ could serve as an initiator of these radical reactions as well as $Et_3B$. 

## Introduction

Integration of multi-step chemical reactions into a one-pot reaction is of great significance from both economical and ecological points of view. Moreover, multi-component reactions facilitate the rapid construction of compound libraries from simple building blocks, as exemplified by the recent progress in the field of combinatorial chemistry.[1]

The reaction of imines with *C*-nucleophiles provides a useful route for preparing a variety of amines.[2] The reactions are generally carried out by using moisture-sensitive organometallic reagents, except for a few outstanding examples.[3] These methods necessitate strictly anhydrous reaction conditions and additional protection-deprotection steps. The imine derivative has emerged as a radical acceptor, and thus numerous synthetically useful reactions are available.[4] However, the radical reactions of water-sensitive imines have generally been performed under anhydrous reaction conditions. In principle, the reactions of strictly neutral species such as uncharged free radicals are not affected by the presence of water.[5] Therefore, employment of a moisture-resistant radical species would eliminate the cumbersome operations involved in conventional ionic reactions and successfully integrate a multi-step reaction into a one-pot reaction. In this paper, we describe full details of the one-pot synthesis of α-amino acid derivatives based on a moisture-resistant carbon radical addition to glyoxylic oxime ether generated from 2-hydroxy-2-methoxyacetic acid methyl ester and benzyloxyamine.[6,7]

## Results and Discussion

### One-pot synthesis of α-amino acids

In recent years, much attention has been paid to the development of concise and flexible synthetic approaches to α-amino acids, allowing facile incorporation of functional groups and structural variability. Multi-step synthetic routes to α-amino acids are available;[8] however, the development of one-pot procedures remains a challenge in organic synthesis.[9] We have recently reported the first asymmetric synthesis of α-amino acids based on a diastereoselective carbon radical addition to glyoxylic oxime ether.[10] This reaction is particularly useful because there currently exists no general synthetic method for the construction of a wide range of aliphatic α-amino acids using glyoxylic imines as the starting material.[11] We next started synthetic studies on a novel one-pot approach to α-amino acids via the condensation of an α-keto acid derivative with alkoxyamine, followed by the addition of an alkyl radical to the resulting oxime ether.

We first investigated the one-pot reaction using commercially available 2-hydroxy-2-methoxyacetic acid methyl ester **1**, benzyloxyamine **2** and triethylborane as an ethyl radical source in $CH_2Cl_2$ (Scheme 1). Condensation of 2-hydroxy-2-methoxyacetic acid methyl ester **1** with benzyloxyamine **2** proceeded smoothly in the presence of $MgSO_4$ to give the glyoxylic oxime ether **6** after being stirred at 25°C for 24 h. To the reaction vessel was added $Et_3B$ and then the reaction mixture was stirred at 25°C for

*Keywords*: radical addition; oxime ether; atom-transfer; one-pot; α-amino acids.

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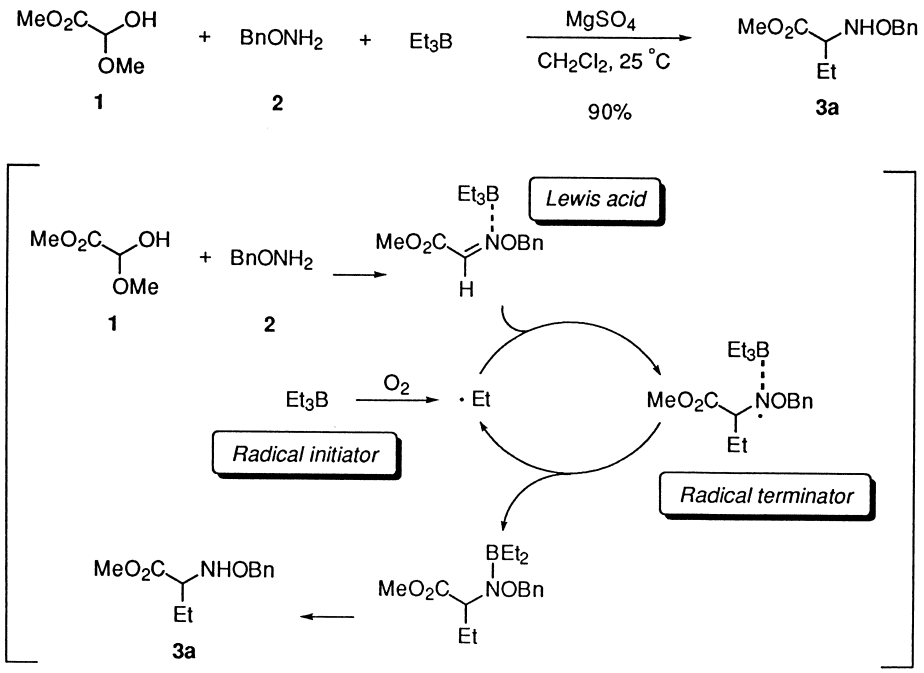
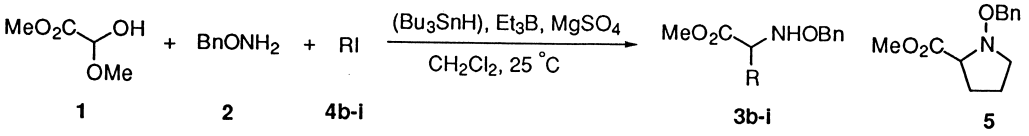



**Scheme 1.**

15 min. This simple one-pot reaction would proceed as indicated in Scheme 1 to afford the α-amino acid derivative **3a** in 90% yield. A similar result was obtained in the absence of $MgSO_4$ because triethylborane and the alkyl radical are stable even in aqueous media.[5] In this reaction, triethylborane acts not only as a radical initiator but also a Lewis acid and a radical terminator to trap the intermediate benzyloxyaminyl radical; thus a radical reaction cycle proceeds through the regeneration of the ethyl radical. It is also important to note that the radical addition to glyoxylic oxime ether takes place regioselectively at the imino carbon atom on the oxime ether group to give *C*-ethylated product **3a**, because the related addition of organometallic reagents is frequently plagued by the Michael-type addition to give *N*-alkylated products.

We then extended the radical reaction to the one-pot synthesis of α-amino acids by using different radical precursors, allowing structural variety (Table 1). Reactions were run both in the presence of $Bu_3SnH$ (method I) and in the absence of $Bu_3SnH$ (method II). In the case of method II, the radical reaction proceeded via a route involving the iodine atom-transfer process between the alkyl iodide and the ethyl radical generated from triethylborane. Both

**Table 1.** One-pot synthesis of α-amino acid derivatives **3b**–**h** and **5** in $CH_2Cl_2$ (**b**: R = *i*-Pr, **c**: R = *t*-Bu, **d**: R = *i*-Bu, **e**: R = *s*-Bu, **f**: R = *c*-Hexyl, **g**: R = Adamantyl, **h**: R = $(CH_2)_4OAc$, **i**: R = $(CH_2)_3Cl$)



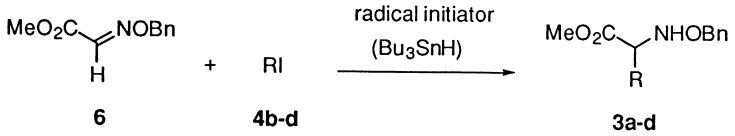

| Entry | RI | Method[a] | Product[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 | *i*-PrI | I | **3b** | 74 |
| 2 | *i*-PrI | II | **3b** | 52 |
| 3 | *t*-BuI | I | **3c** | 86 |
| 4 | *t*-BuI | II | **3c** | 85 |
| 5 | *i*-BuI | I | **3d** | 49 |
| 6 | *s*-BuI | I | **3e** | 71 |
| 7 | *s*-BuI | II | **3e** | 64 |
| 8 | *c*-Hexyl I | I | **3f** | 72 |
| 9 | *c*-Hexyl I | II | **3f** | 60 |
| 10 | Adamantyl I | II | **3g** | 73 |
| 11 | $AcO(CH_2)_4I$ | I | **3h** | 57 |
| 12 | $Cl(CH_2)_3I$ | I | **5** | 46 |

[a] Method I: Reaction was carried out with 2-hydroxy-2-methoxyacetic acid methyl ester (1 equiv.), $BnONH_2$ (1 equiv.), RI (5 equiv.), $Bu_3SnH$ (2.5 equiv.), and $Et_3B$ in hexane (2.5 equiv.) under $N_2$ at 25°C.; Method II: Reaction was carried out with 2-hydroxy-2-methoxyacetic acid methyl ester (1 equiv.), $BnONH_2$ (1 equiv.), RI (10 equiv.), and $Et_3B$ in hexane (5 equiv.) under $N_2$ at 25°C.

[b] A small amout of the ethylated product **3a** was also obtained.

[c] Isolated yields.

**Table 2.** Alkyl radical addition to **6** (**a**: R=Et, **b**: R=*i*-Pr, **c**: R=*t*-Bu, **d**: R=*i*-Bu)




**6** **4b-d** **3a-d**

| Entry | Reagents (equiv.) | *T* (°C) | Solvent | Product (% yield)[a] |
|---|---|---|---|---|
| 1 | *i*-PrI (3.5), $Bu_3SnH$ (2.2), AIBN (0.2) | Reflux | Toluene | **3b** (39%) |
| 2 | *i*-PrI (5.0), $Bu_3SnH$ (2.5), $Et_3B$ (0.2) | 25 | $CH_2Cl_2$ | **3b** (trace)+**3a** (trace) |
| 3 | *i*-PrI (3.5), $Bu_3SnH$ (2.2), V-70 (0.5) | 25 | Toluene | No Reaction |
| 4 | *i*-PrI (5.0), $Et_3B$ (5.0) | 25 | $CH_2Cl_2$ | **3b** (65%)+**3a** (17%) |
| 5 | *t*-BuI (5.0), $Et_3B$ (5.0) | 25 | $CH_2Cl_2$ | **3c** (74%)+**3a** (9%) |
| 6 | *i*-BuI (5.0), $Et_3B$ (5.0) | 25 | $CH_2Cl_2$ | **3d** (6%)+**3a** (69%) |

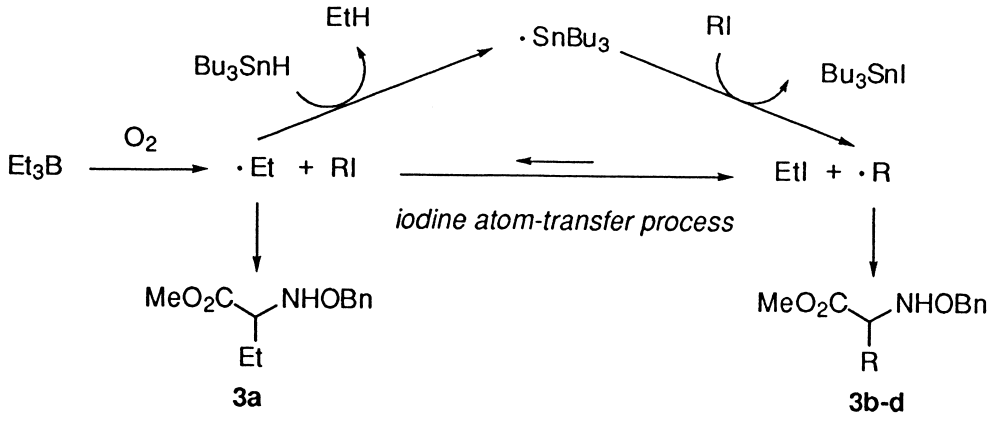
[a] Yields of isolated product.

methods were effective for the one-pot reactions using secondary and tertiary alkyl iodides, although the stannyl radical-mediated reactions proceeded with slightly higher efficiency (Table 1, entries 1–4 and 6–10). In contrast, the use of $Bu_3SnH$ was essential for the successful one-pot reaction with the unstable primary alkyl radicals (Table 1, entries 5, 11 and 12). Expecting that the addition of functionalized radicals would make the products more useful building blocks, we investigated the reaction employing bifunctional halides as an alkyl radical precursor. As was expected from the nature of the radical reaction, alkyl iodides containing an ester moiety or a chlorine atom underwent smooth radical addition reactions to give the correspondingly functionalized α-amino acid derivatives (Table 1, entries 11 and 12). In the case of 1-chloro-3-iodopropane **4i**, the proline derivative **5** was obtained by the concomitant intramolecular *N*-alkylation of **3i** which was preformed by the one-pot reaction of the chloropropyl radical. In all cases, the competitive formation of the ethylated products **3a** was observed as a result of the addition of the ethyl radical generated from triethylborane.

## Optimization of reaction conditions

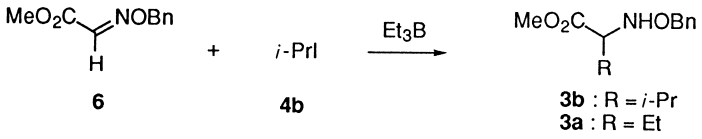
To learn the reaction pathway, we first examined the isopropyl radical addition to glyoxylic oxime ether **6** under several reaction conditions (Table 2). As shown in our previous reports,[6b,10b] the reaction of **6** with *i*-PrI (5 equiv.), $Bu_3SnH$ (2.5 equiv.), and triethylborane (5 equiv.) proceeded smoothly in $CH_2Cl_2$ at 25°C to give the desired isopropylated product **3b** in 79% yield accompanied with 8% yield of the ethylated product **3a**, which was formed by a competitive reaction with the ethyl radical generated from triethylborane. Although treatment of **6** with *i*-PrI and $Bu_3SnH$ in the presence of AIBN (0.2 equiv.) in boiling toluene gave the isopropylated product **3b** in 39% yield, the reaction using triethylborane (0.2 equiv.) or V-70 (0.5 equiv.) as a radical initiator did not take place at 25°C (Table 2, entries 1–3).[12] These results support the multiple roles of triethylborane as a Lewis acid, a radical initiator, and a terminator; therefore, more than a stoichiometric amount of triethylborane is required.

Since the radical reactions including atom- and group-transfer processes have been a subject of current interest from the ecological point of view,[13] the reactions involving an iodine atom-transfer process using triethylborane (5 equiv.) and alkyl iodides (5 equiv.) were also examined in the absence of $Bu_3SnH$. The isopropyl radical addition reaction proceeded smoothly at 25°C to give a good yield of alkylated products **3b** and **3a** with slightly low selectivity compared with that obtained by the stannyl radical-induced radical addition (Table 2, entry 4). Although the addition of the most stable tertiary alkyl radical such as *tert*-butyl radical led to higher selectivity to give an excellent yield of **3c**, the reaction with the unstable primary isobutyl radical gave




**Scheme 2.**

**Table 3.** Effect of solvent and reaction temperature on the isopropyl radical addition to **6** (reaction was carried out with *i*-PrI (5 equiv.) and $Et_3B$ in hexane (5 equiv.) under $N_2$)




| Entry | Solvent | *T* (°C) | Time (min) | Yield (%)[a] | |
|---|---|---|---|---|---|
| | | | 15 | **3b** | **3a** |
| 1 | $CH_2Cl_2$ | 25 | 15 | 65 | 17 |
| 2 | $CH_2Cl_2$ | −78 | 180 | 42 | 44 |
| 3 | $CH_2Cl_2$ | −78 | 15 | 42 | 46 |
| 4 | $Et_2O$ | 25 | 15 | 62 | 18 |
| 5 | $CH_2ClCH_2Cl$ | 25 | 15 | 46 | 23 |
| 6 | MeCN | 25 | 15 | 59 | 34 |
| 7 | MeOH | 25 | 15 | 41 | 37 |
| 8 | MeOH | reflux | 15 | 47 | 38 |
| 9 | Toluene | 25 | 15 | 66 | 27 |
| 10 | Toluene | reflux | 1 | 70 | 13 |

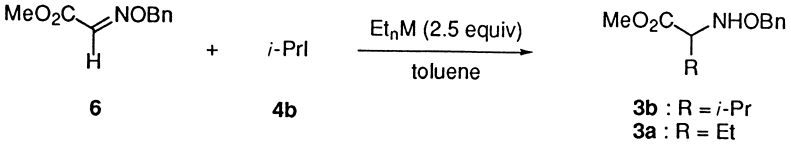
[a] Yields of isolated product.

significant amounts of the ethylated product **3a** (Table 2, entries 5 and 6). These observations suggest that the radical reaction through a route involving the iodine atom-transfer process is an effective method when the stable tertiary and secondary alkyl radicals are employed (Scheme 2). This reaction has a tremendous practical advantage over the stannyl radical-induced reaction which requires tedious work-up to remove the tin-residues from the reaction mixture.

In order to optimize the reaction conditions of the radical addition reaction via the iodine atom-transfer process, we then investigated the reaction by varying the reaction temperature, solvent, and the radical initiator. The isopropyl radical addition reaction to glyoxylic oxime ether **6** was run by using *i*-PrI (5 equiv.) and triethylborane (5 equiv.) to give the alkylated products **3b** and **3a** (Table 3). The formation of the isopropylated product **3b** in $CH_2Cl_2$ was shown to be dependent on the reaction temperature; thus, changing the temperature from 25 to −78°C led to a decrease in the ratio of the isopropylated product **3b** to the ethylated product **3a** (Table 3, entries 1–3). The reaction time did not influence the degree of selectivity. The replacement of $CH_2Cl_2$ with $Et_2O$, $CH_2ClCH_2Cl$, MeCN, or MeOH as a solvent led to low chemical yield of the isopropylated product **3b** (Table 3, entries 4–8). Effect of the reaction temperature was observed in the reaction using toluene as a solvent, and the best result was obtained in the reaction carried out in boiling toluene (Table 3, entries 9 and 10). These results indicate that the isopropyl radical addition reaction proceeded effectively in boiling toluene via a route involving the iodine atom-transfer process between the isopropyl iodide and ethyl radical, and the predominant addition of the more nucleophilic and stable isopropyl radical was observed.

We next investigated the isopropyl radical addition using *i*-PrI and triethylborane or diethylzinc as a radical initiator (Table 4). Recently, Ryu and Komatsu reported that a diethylzinc-air system can serve as an initiator of tin hydride-mediated radical reaction.[14] Therefore, the iodine atom-transfer reaction using diethylzinc in the absence of $Bu_3SnH$ is a new subject of considerable interest. The

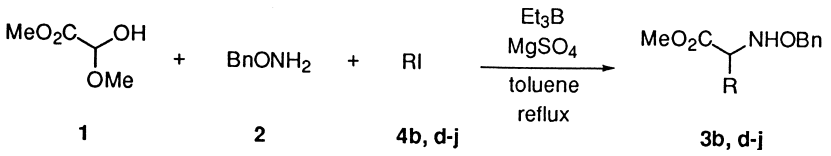
**Table 4.** Isopropyl radical addition to **6** using $Et_3B$ or $Et_2Zn$ (reaction was carried out with $Et_nM$ in hexane (2.5 equiv.) under $N_2$)




| Entry | $Et_nM$ | *i*-PrI (equiv.) | *T* (°C) | Time (min) | Yield (%) of **3b**[a] | Ratio (**3b**/**3a**)[b] |
|---|---|---|---|---|---|---|
| 1 | $Et_3B$ | 5 | Reflux | 1 | 78 | 7.6 |
| 2 | $Et_3B$ | 5 | Reflux | 30 | 75 | 7.0 |
| 3 | $Et_3B$ | 10 | Reflux | 1 | 85 | 10.6 |
| 4 | $Et_3B$ | 20 | Reflux | 1 | 88 | 14.4 |
| 5 | $Et_3B$ | 30 | Reflux | 1 | 87 | 32.1 |
| 6 | $Et_2Zn$ | 5 | 25 | 1 | 52 | 3.1 |
| 7 | $Et_2Zn$ | 5 | 25 | 30 | 51 | 4.5 |
| 8 | $Et_2Zn$ | 10 | 25 | 1 | 58 | 6.8 |
| 9 | $Et_2Zn$ | 20 | 25 | 1 | 67 | 12.4 |
| 10 | $Et_2Zn$ | 30 | 25 | 1 | 68 | 19.0 |

[a] Yields of isolated product.
[b] Based on $^1H$ NMR.

**Table 5.** One-pot synthesis of α-amino acid derivatives in boiling toluene (reaction was carried out with 2-hydroxy-2-methoxyacetic acid methyl ester (1 equiv.), $BnONH_2$ (1 equiv.), RI (30 equiv.), and $Et_3B$ in hexane (2.5 equiv.) under $N_2$. **b**: R=*i*-Pr, **d**: R=*i*-Bu, **e**: R=*s*-Bu, **f**: R=*c*-Hexyl, **j**: R=*c*-Pentyl)




1 2 4b, d-j 3b, d-j

| Entry | RI | Product | Yield (%) of **3b**–**k**[a] | Ratio (**3b**–**k**/**3a**)[b] |
|---|---|---|---|---|
| 1 | *i*-PrI | **3b** | 88 | >10 |
| 2 | *i*-BuI | **3d** | 29 (+30% yield of **3a**) | 1 |
| 3 | *s*-BuI | **3e** | 94 | >10 |
| 4 | *c*-Hexyl I | **3f** | 83 | >10 |
| 5 | *c*-Pentyl I | **3j** | 76 | >10 |

[a] Yields of isolated product.
[b] Based on $^1H$ NMR.

reactions using triethylborane were run in boiling toluene (Table 4, entries 1–5). The ratio of **3b** to **3a** was dependent on the equivalent of *i*-PrI; thus, the best selectivity was obtained when 30 equiv. of *i*-PrI were employed. A similar trend was observed in the isopropyl radical addition using *i*-PrI and diethylzinc as a radical initiator (Table 4, entries 6–10). In the case of diethylzinc, the reaction carried out in boiling toluene gave a mixture of *C*- and *N*-alkylated products as a result of the competitive Michael-type addition of diethylzinc; thus, the reaction was carried out in toluene at 25°C. Although chemical yields and selectivities were slightly lower than that obtained by using triethylborane, diethylzinc was found to serve as an initiator of these radical reactions as well as triethylborane.

Based on these results, we finally examined the one-pot synthesis of α-amino acids via a route involving the iodine atom-transfer process (Table 5). The radical reactions were run in toluene at reflux by using excessive amount of alkyl iodide and triethylborane. As expected, the one-pot reaction proceeded smoothly to give a good yield of alkylated products **3b**, **3f**, **3g**, and **3k** with excellent selectivities, when secondary alkyl iodides were employed (Table 5, entries 1 and 3–5). The reaction using primary alkyl iodides was less effective because of a competitive reaction with the ethyl radical generated from triethylborane (Table 5, entry 2).

## Conclusion

We have demonstrated that the use of a moisture-resistant radical species provides direct access to various types of α-amino acids from 2-hydroxy-2-methoxyacetic acid methyl ester. The advantages of this procedure are that the tedious isolation of the intermediate glyoxylic oxime ethers is unnecessary and aliphatic alkyl iodides having functional groups participate readily as reagents.

## Experimental

### General

$^1H$ and $^{13}C$ NMR spectra were measured using Varian Gemini-200 (200 and 50 MHz, respectively) instrument in $CDCl_3$. Chemical shifts ($\delta$ scale) are relative to TMS as internal reference. IR spectra were measured with a Perkin–Elmer 1600 FTIR machine and mass spectra were taken by Hitachi M-4100 spectrometer. For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Triethylborane proved to be an effective radical initiator in the presence of trace amount of oxygen.[5]

### The one-pot synthesis of methyl 2-(benzyloxyamino)-butanate (3a)[15] (Scheme 1)

To a solution of 2-hydroxy-2-methoxyacetic acid methyl ester **1** (80 mg, 0.67 mmol) in $CH_2Cl_2$ (1 mL) were added benzyloxyamine **2** (82.4 mg, 0.67 mmol) in $CH_2Cl_2$ (0.5 mL) and $MgSO_4$ (10 mg) under a nitrogen atmosphere at 25°C. After being stirred at the same temperature for 1 day, $Et_3B$ (1.0 M in hexane, 1.68 mL, 1.68 mmol) was added to the reaction mixture. After being stirred at the same temperature for 15 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 (hexane/AcOEt 12:1) afforded the α-amino acid derivatives **3a** as a colorless oil. IR ($CHCl_3$) 2954, 1728, 1605, 1496, 1455 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.37–7.25 (5H, m), 4.69 (2H, s), 3.74 (3H, s), 3.53 (1H, br t, $J$=6.6 Hz), 1.53 (2H, m), 0.91 (3H, t, $J$=7.4 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.4, 137.6, 128.3, 128.1, 127.6, 76.0, 64.9, 51.7, 22.7, 10.3. HRMS: Calcd for $C_{12}H_{17}NO_3$ ($M^+$): 223.1207, Found: 223.1227.

### General procedure for the one-pot synthesis of α-amino acids by using $Bu_3SnH$ (Method I in Table 1)

To a solution of 2-hydroxy-2-methoxyacetic acid methyl ester **1** (80 mg, 0.67 mmol) in $CH_2Cl_2$ (1 mL) were added benzyloxyamine **2** (82.4 mg, 0.67 mmol) in $CH_2Cl_2$ (0.5 mL) and $MgSO_4$ (10 mg) under a nitrogen atmosphere at 25°C. After being stirred at the same temperature for 1 day, RI **4** (3.35 mmol), $Bu_3SnH$ (0.45 mL, 1.68 mmol), and $Et_3B$ (1.0 M in hexane, 1.68 mL, 1.68 mmol) were added to the reaction mixture. After being stirred at the same temperature for 15 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 (hexane/AcOEt 15:1, 2-fold development) followed by preparative TLC (chloroform) afforded the α-amino acid derivatives **3**.

### General procedure for the one-pot synthesis of α-amino acids in the absence of $Bu_3SnH$ (Method II in Table 1)

To a solution of 2-hydroxy-2-methoxyacetic acid methyl ester **1** (80 mg, 0.67 mmol) in $CH_2Cl_2$ (1 mL) were added benzyloxyamine **2** (82.4 mg, 0.67 mmol) in $CH_2Cl_2$ (0.5 mL) and $MgSO_4$ (10 mg) under a nitrogen atmosphere at 25°C. After the reaction mixture was stirred at the same temperature for 1 day, RI **4** (6.7 mmol) and $Et_3B$ (1.0 M in hexane, 3.35 mL, 3.35 mmol) were added. After being stirred at the same temperature for 15 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 under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 15:1) afforded the α-amino acid derivatives **3**.

### Isopropyl radical addition to glyoxylic oxime ether 6 by using AIBN (Table 2, entry 1)

To a solution of glyoxylic oxime ether **6** (100 mg, 0.52 mmol) in toluene (10 mL) were added *i*-PrI **4b** (0.18 mL, 1.8 mmol), $Bu_3SnH$ (0.31 mL, 1.14 mmol), and AIBN (17 mg, 0.104 mmol) at reflux. After the reaction mixture was stirred at the same temperature for 5 min, the reaction mixture was diluted with $H_2O$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1, 2-fold development) afforded the α-amino acid derivatives **3b** (48 mg, 39%).

### Isopropyl radical addition to glyoxylic oxime ether 6 by using $Et_3B$ (Table 3)

To a solution of glyoxylic oxime ether **6** (100 mg, 0.52 mmol) in $CH_2Cl_2$, $Et_2O$, $CH_2ClCH_2Cl$, $CH_3CN$, MeOH, or toluene (10 mL) were added *i*-PrI **4b** (0.26 mL, 2.6 mmol) and $Et_3B$ (1.0 M in hexane, 2.6 mL, 2.6 mmol) at 25°C, −78°C, or reflux. After the reaction mixture was stirred at the same temperature for 1, 15, or 180 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 under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 12:1, 2-fold development) afforded the α-amino acid derivatives **3a** and **3b**.

### Isopropyl radical addition to glyoxylic oxime ether 6 by using $Et_3B$ (Table 4, entries 1–5)

To a solution of glyoxylic oxime ether **6** (100 mg, 0.52 mmol) in toluene (10 mL) were added *i*-PrI **4b** (5, 10, 20, or 30 equiv.) and $Et_3B$ (1.0 M in hexane, 1.3 mL, 1.3 mmol) at reflux. After the reaction mixture was stirred at the same temperature for 1 or 30 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 under reduced pressure. Selectivity was determined by $^1H$ NMR analysis of the crude products. Purification of the residue by preparative TLC (hexane/AcOEt 12:1) afforded the α-amino acid derivatives **3a** and **3b**.

### Isopropyl radical addition to glyoxylic oxime ether 6 by using $Et_2Zn$ (Table 4, entries 6–10)

To a solution of glyoxylic oxime ether **6** (100 mg, 0.52 mmol) in toluene (10 mL) were added *i*-PrI **4b** (5, 10, 20, or 30 equiv.) and $Et_2Zn$ (1.0 M in hexane, 1.3 mL, 1.3 mmol) at 25°C. After the reaction mixture was stirred at the same temperature for 1 or 30 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 under reduced pressure. Selectivity was determined by $^1H$ NMR analysis of the crude products. Purification of the residue by preparative TLC (hexane/AcOEt 12:1) afforded the α-amino acid derivatives **3a** and **3b**.

### General procedure for the one-pot synthesis of α-amino acids by using $Et_3B$ in boiling toluene (Table 5)

To a solution of 2-hydroxy-2-methoxyacetic acid methyl ester **1** (80 mg, 0.67 mmol) in toluene (1 mL) were added benzyloxyamine **2** (82.4 mg, 0.67 mmol) in toluene (0.5 mL) and $MgSO_4$ (10 mg) under a nitrogen atmosphere at 25°C. After the reaction mixture was stirred at the same temperature for 1 day, RI **4** (6.7 mmol) and $Et_3B$ (1.0 M in hexane, 3.35 mL, 3.35 mmol) were added to the reaction mixture at reflux. After being stirred at the same temperature for 1 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 under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 15:1) afforded the α-amino acid derivatives **3**.

**Methyl 2-(benzyloxyamino)-3-methylbutanate (3b).** Colorless oil. IR ($CHCl_3$) 2958, 1742, 1605, 1496, 1454 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.35–7.26 (5H, m), 4.67 (1H, d, $J$=12.5 Hz), 4.66 (1H, d, $J$=12.5 Hz), 3.75 (3H, s), 3.36 (1H, br m), 1.78 (1H, m), 0.91 (3H, d, $J$=7.0 Hz), 0.89 (3H, d, $J$=6.5 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.5, 137.8, 128.6, 128.2, 127.7, 76.0, 69.6, 51.7, 29.2, 19.3, 19.3. HRMS: Calcd for $C_{13}H_{19}NO_3$ ($M^+$): 237.1363, Found: 237.1371.

**Methyl 2-(benzyloxyamino)-3,3-dimethylbutanate (3c).** Colorless oil. IR ($CHCl_3$) 2956, 1728, 1605, 1496, 1455 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.34–7.26 (5H, m), 4.65 (2H, s), 3.74 (3H, s), 3.31 (1H, br s), 0.90 (9H, s). $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.5, 137.9, 128.7, 128.2, 127.7, 75.8, 72.1, 51.5, 33.1, 27.0. HRMS: Calcd for $C_{14}H_{21}NO_3$ ($M^+$): 251.1521, Found: 251.1530.

**Methyl 2-(benzyloxyamino)-4-methylpentanate (3d).** Colorless oil. IR ($CHCl_3$) 2959, 1736, 1603, 1496, 1455 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.34–7.27 (5H, m), 4.68 (2H, s), 3.74 (3H, s), 3.64 (1H, br t, $J$=7.0 Hz), 1.65 (1H,

m), 1.33 (2H, m), 0.88 (3H, d, $J$=6.5 Hz), 0.84 (3H, d, $J$=6.5 Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2, 137.9, 128.5, 128.2, 127.8, 76.1, 62.2, 51.9, 38.6, 25.1, 22.7, 22.1. HRMS: Calcd for $C_{14}H_{21}NO_3$ ($M^+$): 251.1520, Found: 251.1529.

**Methyl 2-(benzyloxyamino)-3-methylpentanate (3e).** Colorless oil. IR ($CHCl_3$) 2967, 2935, 1733, 1496, 1455 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.37–7.25 (5H, m), 4.67 (1H, m), 4.66 (1H, m), 3.74 (3H, m), 3.48 (1H, m), 1.68–1.05 (3H, m), 0.88–0.80 (6H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ 174.6, 174.4, 137.8, 128.51, 128.45, 128.1, 127.6, 75.8, 68.0, 67.6, 51.6, 51.5, 35.7, 35.3, 26.2, 25.8, 15.4, 15.2, 11.2, 10.9. HRMS: Calcd for $C_{14}H_{21}NO_3$ ($M^+$): 251.1521, Found: 251.1544.

**Methyl 2-(benzyloxyamino)-2-cyclohexylethanate (3f).** Colorless oil. IR ($CHCl_3$) 2932, 1733, 1604, 1496, 1452 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.35–7.26 (5H, m), 4.66 (2H, s), 3.74 (3H, s), 3.40 (1H, br m), 1.81–0.88 (11H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ 174.6, 137.9, 128.6, 128.2, 127.7, 75.9, 69.0, 51.7, 38.6, 29.8, 29.7, 26.1, 26.0, 25.9. HRMS: Calcd for $C_{16}H_{23}NO_3$ ($M^+$): 277.1676, Found: 277.1698.

**Methyl 2-(benzyloxyamino)-2-(1-adamantyl)ethanate (3g).** Colorless oil. IR ($CHCl_3$) 2909, 1731 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.34–7.28 (5H, m), 4.64 (2H, s), 3.74 (3H, s), 3.20 (1H, br m), 1.93–1.33 (15H, s). $^{13}$C NMR ($CDCl_3$) $\delta$ 173.9, 137.8, 128.5, 128.0, 127.5, 75.5, 72.9, 51.2, 39.0, 36.6, 35.0, 28.1. HRMS: Calcd for $C_{20}H_{27}NO_3$ ($M^+$): 329.1989, Found: 329.2006.

**Methyl 6-acetoxy-2-(benzyloxyamino)hexanate (3h).** Colorless oil. IR ($CHCl_3$) 2956, 1734, 1496, 1454 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.39–7.28 (5H, m), 4.68 (2H, s), 4.01 (2H, t, $J$=6.3 Hz), 3.75 (3H, s), 3.56 (1H, br t, $J$=6.4 Hz), 2.03 (3H, s), 1.74–1.23 (6H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ 174.3, 170.9, 137.6, 128.4, 128.1, 127.7, 76.0, 63.9, 63.3, 51.8, 29.0, 28.0, 22.3, 20.3. HRMS: Calcd for $C_{16}H_{23}NO_5$ ($M^+$): 309.1575, Found: 309.1588.

**Methyl 2-(benzyloxyamino)-2-cyclopentylethanate (3j).** Colorless oil. IR ($CHCl_3$) 2955, 1734, 1454 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.39–7.21 (5H, m), 4.66 (2H, s), 3.73 (3H, s), 3.39 (1H, br d, $J$=8.8 Hz), 1.97–1.15 (9H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ 174.5, 137.6, 128.4, 128.0, 127.5, 75.7, 68.1, 51.5, 39.7, 29.9, 28.9, 24.8, 24.7. HRMS: Calcd for $C_{15}H_{21}NO_3$ ($M^+$): 263.1521, Found: 263.1527.

***N*-Benzyloxyproline methyl ester (5).** Colorless oil. IR ($CHCl_3$) 2955, 1740, 1496, 1454 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$ 7.36–7.23 (5H, m), 4.82 (2H, s), 3.73 (3H, s), 3.72 (1H, m), 3.32 (1H, m), 2.91 (1H, m), 2.15 (1H, m), 1.96–1.79 (3H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ 173.0, 137.5, 128.5, 128.2, 127.7, 75.6, 68.8, 55.9, 51.8, 25.8, 20.9. HRMS: Calcd for $C_{13}H_{17}NO_3$ ($M^+$): 235.1208, Found: 235.1195.

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