Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1901–1907

TETRAHEDRON

Carbon–carbon bond construction on solid support: triethylborane-induced radical reactions of oxime ethers

Hideto Miyabe,† Azusa Nishimura, Yumi Fujishima and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

Received 19 December 2002; accepted 24 January 2003

Abstract—The triethylborane-induced solid-phase radical reaction was studied. The solid-phase radical reaction of oxime ether anchored to Wang resin proceeded smoothly to give the α-amino acid derivatives. The carbon–carbon bond-forming radical reaction of TentaGel OH resin-bound glyoxylic oxime ether proceeded even in aqueous media.

1. Introduction

Combinatorial chemistry has became a core technology for the rapid development of novel lead compounds in the pharmaceutical industry and for the optimization of therapeutic efficacy.[1] In recent years, a variety of reactions has been performed on solid-phase. However, the carbon–carbon bond-forming solid-phase reactions are less common than the carbon–heteroatom bond-forming solid-phase reactions.[1] Therefore, the extension of carbon–carbon bond-forming radical reactions to solid-phase reactions would allow further progress in combinatorial organic synthesis.[2–10]

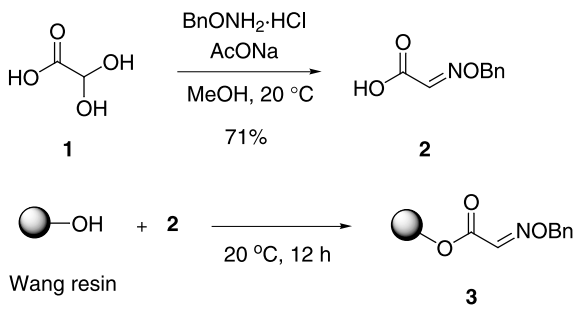
Some recent reports have shown that radical cyclizations could be performed on solid supports by using AIBN or SmI_2 as a radical initiator.[2–5] Sibi's group has reported the first studies on the solid-phase intermolecular radical reaction using allyl stannanes and AIBN.[9] We have also demonstrated that triethylborane has the potential to induce intermolecular radical reactions on solid support, and employment of triethylborane, particularly at low reaction temperature, facilitated the control of stereochemistry in solid-phase radical reaction.[11] We report here in detail the triethylborane-induced solid-phase radical reactions of oxime ethers.[11a] Among the different types of radical acceptors containing a carbon–nitrogen double bond, the oxime ethers are well known to be excellent radical acceptors because of the extra stabilization of the intermediate alkoxyaminyl radical provided by the lone pair on the adjacent oxygen atom. As shown below, we also report the novel carbon–carbon bond formation based on solid-phase radical reactions in aqueous media.

2. Results and discussion

2.1. Intermolecular carbon radical addition to glyoxylic oxime ethers in organic solvent

The preparation of glyoxylic oxime ether **3** anchored to a polymer support was shown in Scheme 1. The glyoxylic oxime ether **2** was prepared from glyoxylic acid **1**. We investigated several reaction conditions for attachment of the glyoxylic oxime ether **2** to Wang resin (Table 1).[12] Among them, the glyoxylic oxime ether **2** was attached to Wang resin by the treatment with DCC in the presence of DMAP in CH_2Cl_2 at 20°C for 12 h to give the resin-bound glyoxylic oxime ether **3** in 72% loading level (entry 1). The loading level of the Wang resin-bound glyoxylic oxime ether **3** was determined to be 0.83 mmol/g by quantification of nitrogen by elemental analysis.

In order to test the viability of triethylborane as a radical initiator on solid support, we first investigated the addition



Scheme 1.

Keywords: radical reactions; solid-phase reactions; amino acids; oxime ethers.

* Corresponding author. Tel.: +81-78-441-7554; fax: +81-78-441-7556; e-mail: taknaito@kobepharma-u.ac.jp

† Present address: Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan.

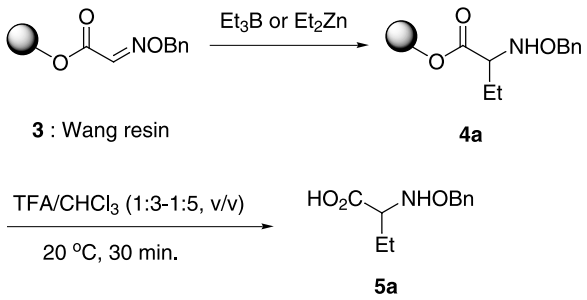
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00154-6

Table 1. Attachment of glyoxylic oxime ether **2** to Wang resin

Entry	Reagents	Solvent	Loading level (%)[a]
1	DCC, DMAP	CH_2Cl_2	72
2	2,6-Dichlorobenzoyl chloride, py	DMF	32
3	MSNT, MeIm[b]	THF–CH_2Cl_2	54

Reactions were carried out at 20°C for 12 h.
[a] The loading levels were determined by quantification of nitrogen by elemental analysis.
[b] MSNT—1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole. MeIm—1-methylimidazole.

of an ethyl radical, generated from triethylborane and O_2, to the oxime ether **3** (Scheme 2). The reaction of **3** was run with a commercially available triethylborane (1.0 M solution in hexane) in CH_2Cl_2 at 20°C for 1 h (Table 2, entry 1). The resin **4a** was then filtered and washed successively with CH_2Cl_2, AcOEt followed by MeOH, and the subsequent cleavage of the resin with TFA/$CHCl_3$ gave the crude ethylated α-amino acid **5a** as a TFA salt. Purification of the resulting α-amino acid **5a** was accomplished by a combination of Amberlite IR-120B and the preparative TLC to afford the amino acid **5a**. The replacement of CH_2Cl_2 with a nonpolar aromatic solvent such as toluene was also effective for triethylborane-induced solid-phase radical reactions to give the ethylated products **5a** in 83% yield from **3** (entry 2). Triethylborane worked well as an effective radical initiator for the solid-phase radical reaction even at low reaction temperature (entries 3 and 4). Ryu and Komatsu reported that diethylzinc–air system can serve as an initiator as well as triethylborane.[13] As expected, the radical reaction using a commercially available 1.0 M solution of diethylzinc in hexane was effective to give good yields of the ethylated products **5a** even at low reaction temperature (entries 5–7). These results indicate that both triethylborane and diethylzinc work well as an effective radical initiator for the solid-phase radical reactions without interference of polystyrene skeleton of the resin.



Scheme 2.

Table 2. Ethyl radical addition to oxime ether **3**

Entry	Initiator	Solvent	T (°C)	Yield (%)[a]
1[b]	Et_3B	CH_2Cl_2	20	71
2[b]	Et_3B	Toluene	20	83
3[b]	Et_3B	CH_2Cl_2	−78	61
4[b]	Et_3B	Toluene	−78	69
5[c]	Et_2Zn	CH_2Cl_2	20	72
6[c]	Et_2Zn	Toluene	20	81
7[c]	Et_2Zn	CH_2Cl_2	−78	89

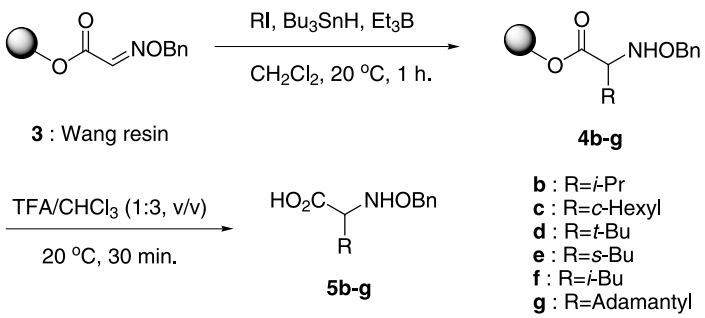
[a] Yields of isolated product **5a** from **3**.
[b] Reactions were carried out with Et_3B in hexane (3.6 equiv.).
[c] Reactions were carried out with Et_2Zn in hexane (5 equiv.).

Table 3. Solid-phase synthesis of α-amino acids **5b–g**

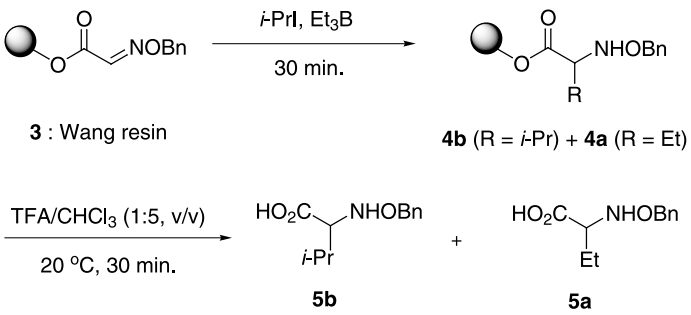
Entry	RI	Solvent	Product[a]	Yield (%)[b]
1	*i*-Pr I	CH_2Cl_2	**5b**	66
2	*i*-Pr I	Toluene	**5b**	42
3	*c*-Hexyl I	CH_2Cl_2	**5c**	61
4	*t*-Bu I	CH_2Cl_2	**5d**	78
5	*s*-Bu I	CH_2Cl_2	**5e**	71
6	*i*-Bu I	CH_2Cl_2	**5f**	24
7	Adamantyl I	CH_2Cl_2	**5g**	28

All reactions were carried out with RI (7.1 equiv.), Bu_3SnH (2.1 equiv.), and Et_3B in hexane (1.1 equiv.).
[a] The ethylated product **5a** was obtained in 5–30% yields.
[b] Yields of isolated products **5b–g** from **3**.

We next investigated the reaction using different radical precursors in the presence of tributyltin hydride (Scheme 3). The isopropyl radical addition to **3** was carried out with isopropyl iodide, tributyltin hydride and triethylborane in CH_2Cl_2 at 20°C for 1 h (Table 3, entry 1). The isopropylated α-amino acid derivative **5b** was obtained in 66% yield from **3** after cleavage of the resin followed by purification, accompanied with a small amount of the ethylated product **5a**, which was formed by the competitive reaction with the ethyl radical generated from triethylborane. Not only secondary alkyl radicals such as isopropyl, cyclohexyl and *sec*-butyl radicals but also a bulky *tert*-butyl radical worked well under similar reaction conditions, allowing facile incorporation of structural variability (entries 1–5). The unstable primary alkyl radicals such as isobutyl radical and a more bulky adamantyl radical were less effective for the



Scheme 3.



Scheme 4.

Table 4. Isopropyl radical addition to **3** via iodine atom-transfer process

Entry	*i*-Pr I (equiv.)	Solvent	*T* (°C)	Yield (%)[a]	Ratio (**5b/5a**)
1	30	CH_2Cl_2	20	73	2.0:1
2	30	Toluene	20	69	2.4:1
3	30	Toluene	80	79	3.1:1
4	60	Toluene	80	71	5.7:1

All reactions were carried out with Et_3B in hexane (5.0 equiv.).
[a] Combined yields of products **5b** and **5a**.

present solid-phase intermolecular radical reaction (entries 6 and 7). The solid-phase radical reaction will be particularly useful because the often tedious work-up to remove excess tin residues from the reaction mixture is eliminated in the solid-phase methodology by washing of the resin with solvents.

2.2. Tin-free radical addition to glyoxylic oxime ethers

The development of tin-free radical reactions has generated considerable interest from both economical and environmental points of view. Thus, we next investigated the isopropyl radical addition to oxime ether **3** in the absence of tributyltin hydride under the iodine atom-transfer reaction conditions (Scheme 4).[14,15]

The isopropyl radical addition to **3** was carried out with isopropyl iodide (30 equiv.) and triethylborane (5 equiv.) in the absence of tributyltin hydride in CH_2Cl_2 at 20°C for 30 min (Table 4, entry 1). After cleavage of the resin followed by purification, a 2.0:1 mixture of the desired isopropylated amino acid **5b** and the undesired ethylated amino acid **5a** was obtained in 73% combined yield. We recently reported that the solution-phase radical reaction of glyoxylic oxime ethers gave the desired alkylated amino acids selectively under the similar iodine atom-transfer reaction conditions. In contrast, in the case of the solid-phase radical reaction, the addition of ethyl radical, generated from triethylborane, competed with iodine atom-transfer process to give a significant amount of the ethylated product **5a**. Although the precise reason for the preferential ethylation was unclear, triethylborane presumably concentrated on solid-support as Lewis acid and gave a large amount of ethyl radical around the surface of resin (Fig. 1). In the studies on solution-phase radical reaction, we recently found that the selectivity was largely dependent on the reaction temperature and solvent, and the high selectivities were obtained by using toluene as solvent and at high reaction temperature.[14c] The replacement of CH_2Cl_2 with toluene did not lead to good selectivities comparable to that obtained in solution-phase radical reaction (entries 2 and 3). The reaction using isopropyl iodide (60 equiv.) and triethylborane (5 equiv.) in toluene at 80°C gave a 5.7:1 mixture of **5b** and **5a** in 71% combined yield (entry 4). In these reactions, triethylborane acts as not only a radical initiator but also a terminator to trap the intermediate benzyloxyaminyl radical. Thus, the radical reaction cycle involving the regeneration of the ethyl radical proceeds by this quite simple procedure which does not require the use of moisture-sensitive irritant tin hydride.[14b] Additionally, the newly-found solid-phase radical reactions are run without any special precautions such as drying, degassing and purification of solvents and reagents and are thus readily adaptable to parallel synthesis.

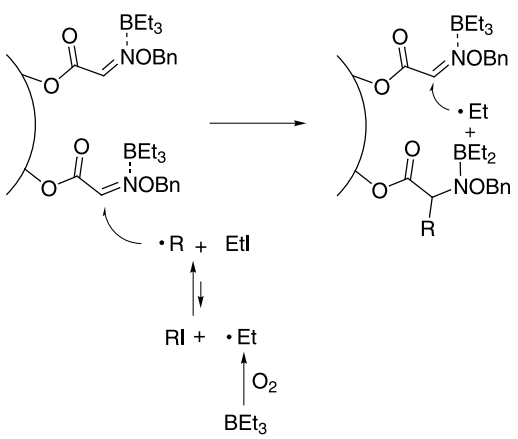
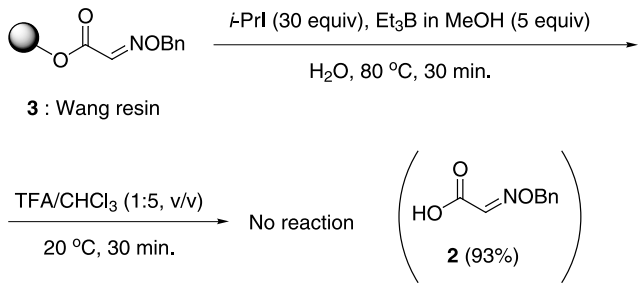


Figure 1. Radical reaction of oxime ether anchored to resin.

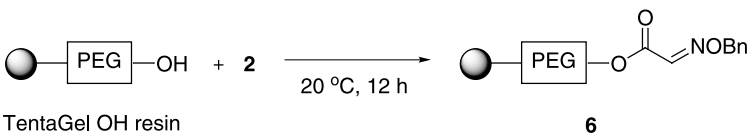
2.3. Solid-phase radical reaction in aqueous media

The development of new efficient methods for carbon–carbon bond formation in aqueous media is a challenging problem. We recently reported that oxime ether, oxime, hydrazone and nitrone could participate in the aqueous medium radical reactions involving the construction of the carbon–carbon bond.[16] We next investigated the radical addition to Wang resin-bound oxime ether **3** in water (Scheme 5). However, the reaction of oxime ether **3** did not take place and the glyoxylic oxime ether **2** was recovered in 93% yield after cleavage of the resin, because the Wang resin-bound substrate **3** did not swell in water.

Thus, we next investigated the reaction of oxime ether **6** anchored to TentaGel OH resin, which has polyethyleneglycol (PEG) chains and can swell in a wide range of



Scheme 5.



Scheme 6.

Table 5. Attachment of glyoxylic oxime ether **2** to TentaGel OH resin

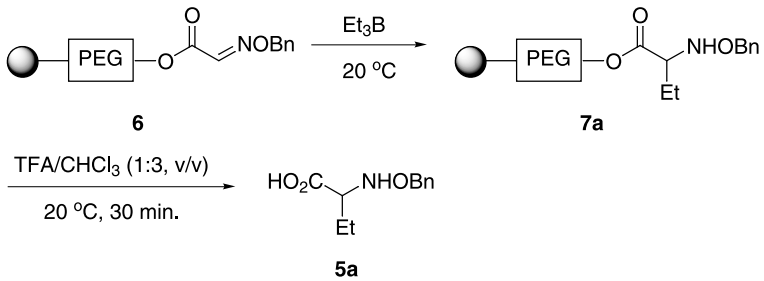
Entry	Reagents	Solvent	Loading level (%)[a]
1	DCC, DMAP	CH_2Cl_2	45
2	2,6-Dichlorobenzoyl chloride, Py	DMF	90
3	MSNT, Melm[b]	THF–CH_2Cl_2	59

Reactions were carried out at 20°C for 12 h.
[a] The loading levels were determined by quantification of nitrogen by elemental analysis.
[b] MSNT—1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole. Melm—1-methylimidazole.

solvents from toluene to water (Scheme 6). Several reaction conditions for attachment of the glyoxylic oxime ether **2** to TentaGel OH resin were investigated (Table 5).[12] TentaGel OH resin-bound glyoxylic oxime ether **6** was prepared in 90% loading level by the treatment with 2,6-dichlorobenzoyl chloride in the presence of pyridine in DMF at 20°C for 12 h (entry 2).

To test the reactivity of TentaGel OH resin-bound oxime ether **6** in aqueous media, we investigated the addition of an ethyl radical to **6** in H_2O–MeOH (2:1, v/v) (Scheme 7). The biphasic reaction using a hexane solution of triethylborane in aqueous media did not take place to give the recovered glyoxylic oxime ether **2** in 81% after cleavage of the resin (Table 6, entry 1). In the case of monophasic reactions using a solution of triethylborane in THF or MeOH, the formation of ethylated product **5a** was observed after being stirred for only 15 min (entries 2 and 3). The radical reaction of **6** also proceeded in CH_2Cl_2 by using a solution of triethylborane in hexane (entry 4).

We finally investigated the alkyl radical addition to oxime ether **6** in H_2O–MeOH (2:1, v/v) under the iodine atom-transfer reaction conditions (Scheme 8). The isopropyl radical addition to **6** was carried out with isopropyl iodide (60 equiv.) and triethylborane in MeOH (10 equiv.) at 20°C (Table 7, entry 1). However, the reaction proceeded but less effectively to give a 2.9:1 mixture of the desired isopropylated amino acid **5b** and the undesired ethylated amino acid **5a** in 23% combined yield, after cleavage of the resin followed by purification. The formation of isopropylated product **5b** was shown to be dependent on the reaction temperature; thus, changing the temperature from 20 to 70°C led to a increase in the chemical yield and the ratio of the isopropylated product **5b** and the ethylated product **5a** (entry 2). Although the ratios for the *sec*-butylated product **5e** and cyclopentylated product **5h** were moderate, the radical reactions of **6** were found to proceed even in aqueous media (entries 3–6).



Scheme 7.

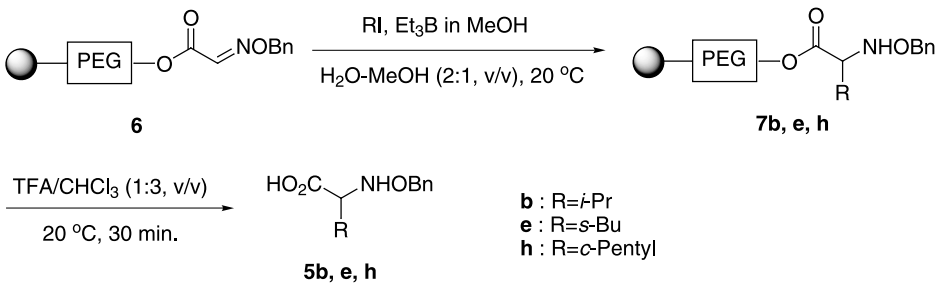
Table 6. Ethyl radical addition to **6** in aqueous media

Entry	Solvent	Et_3B	Yield (%)[a]
1[b]	H_2O–MeOH (2:1, v/v)	in hexane	No reaction (81)
2[b]	H_2O–MeOH (2:1, v/v)	in THF	66
3[b]	H_2O–MeOH (2:1, v/v)	in MeOH	79
4[c]	CH_2Cl_2	in hexane	57

[a] Isolated yields; yields in parentheses are for the recovered glyoxylic oxime ether **2**.
[b] Reactions were carried out with Et_3B (10 equiv.) at 20°C for 15 min.
[c] Reaction was carried out with Et_3B (3.6 equiv.) at 20°C for 1 h.

3. Conclusion

We have demonstrated that triethylborane can be applied to the solid-phase radical reaction. The reaction of TentaGel OH resin-bound glyoxylic oxime ether is the first example of solid-phase radical reaction in aqueous media. Furthermore, the radical addition to glyoxylic oxime ethers



Scheme 8.

Table 7. Alkyl radical addition to **6** in aqueous media

Entry	RI (equiv.)	T (°C)	Product	Yield (%)[a]	Ratio (**5b**,**e**,**h**/**5a**)
1	*i*-Pr I (60)	20	**5b**	23 (54)	2.9:1
2	*i*-Pr I (60)	70	**5b**	69	5.7:1
3	*s*-Bu I (60)	70	**5e**	52	3.2:1
4	*s*-Bu I (120)	70	**5e**	73	3.3:1
5	*c*-Pentyl (60)	70	**5h**	43	3.2:1
6	*c*-Pentyl (120)	70	**5h**	68	3.4:1

All reactions were carried out with RI and Et_3B (10 equiv.) for 1 h.
[a] Combined yields of products **5b**,**e**,**h** and **5a**.; yields in parentheses are for the recovered glyoxylic oxime ether **2**.

anchored to a polymer support provides direct access to unnatural α-amino acids as useful building blocks exemplified by the recent progress in the fields of combinatorial chemistry and drug discovery.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and at 50 or 125 MHz, respectively. Mass spectra were obtained by EI or CI methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$).

4.1.1. 2-(Benzyloxyimino)ethanoic acid (2).[17] To a solution of glyoxylic acid monohydrate (5.0 g, 54 mmol) in MeOH (250 mL) were added *O*-benzyloxyamine hydrochloride (13.0 g, 82 mmol) and AcONa (8.9 g, 109 mmol) under a nitrogen atmosphere at 20°C. After the reaction 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 colorless crystals (2:1 mixture of *E*/*Z*-oxime). IR ($CHCl_3$) 1716, 1597, 1497 cm^{-1}. ^1H 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.

4.1.2. Wang resin-bound oxime ether (3). To a suspension of Wang resin[12] (0.83 mmol/g, 25 g) in CH_2Cl_2 (200 mL) were added oxime ether **2** (14.9 g, 83 mmol), DCC (21.4 g, 104 mmol) and DMAP (1.27 g, 10 mmol) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 1 h and then stood for 11 h, the resin was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried at reduced pressure.

4.1.3. General procedure for ethyl radical addition to oxime ether 3. To a suspension of oxime ether **3** (0.83 mmol/g, 274 mg, 0.28 mmol) in CH_2Cl_2 or toluene (3.0 mL) was added Et_3B (1.0 M in hexane, 1.0 mL, 1.0 mmol) or Et_2Zn (1.0 M in hexane, 1.4 mL, 1.4 mmol) under a nitrogen atmosphere at 20 or −78°C. After the reaction mixture was stirred at the same temperature for 15 min–1 h, the resin was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried at reduced pressure. To a flask with the resulting resin **4a** was added TFA/$CHCl_3$ (1:3–1:5, v/v, 4.0 mL) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with MeOH/$CHCl_3$ (1:11, v/v, 60 mL), and the filtrate was concentrated at reduced pressure. Purification of the residue by Amberlite IR-120B (eluting with MeOH) followed by preparative TLC (MeOH/$CHCl_3$ 1:10, v/v) afforded the α-amino acid derivative **5a** as a white powder. IR (Nujol) 1603, 1573 cm^{-1}. ^1H 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=11.1 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.

4.1.4. General procedure for the alkyl radical addition to oxime ether 3

To a suspension of oxime ether **3** (0.83 mmol/g, 274 mg, 0.28 mmol) in CH_2Cl_2 or toluene (3.0 mL) were added RI (2.0 mmol), Bu_3SnH (0.16 mL, 0.6 mmol) and Et_3B (1.0 M in hexane, 0.30 mL, 0.30 mmol) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 1 h, the resin was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried at reduced pressure. To a flask with the resulting resin **4b–g** was added TFA/$CHCl_3$ (1:3, v/v, 4.0 mL) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with MeOH/$CHCl_3$ (1:11, v/v, 60 mL), and the filtrate was concentrated at reduced pressure. Purification of the residue by Amberlite IR-120B (eluting with MeOH) followed by preparative TLC

(MeOH/$CHCl_3$ 1:10, v/v) afforded the α-amino acid derivatives **5b–g**.

4.1.5. 2-(Benzyloxyamino)-3-methylbutanoic acid (5b). A white powder. IR (Nujol) 1603, 1574 cm^{-1}. ^1H 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.

4.1.6. 2-(Benzyloxyamino)-2-cyclohexylethanoic acid (5c). A white powder. IR (Nujol) 1603, 1574 cm^{-1}. ^1H 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.

4.1.7. 2-(Benzyloxyamino)-3,3-dimethylbutanoic acid (5d). A white powder. IR (Nujol) 1604, 1574 cm^{-1}. ^1H NMR (CD_3OD) δ 7.36–7.28 (5H, m), 4.65 (2H, s), 3.31 (1H, br m), 0.94 (9H, s). ^{13}C NMR (CD_3OD) δ 177.2, 139.1, 129.7, 129.1, 128.6, 76.5, 73.2, 33.3, 27.5. HRMS: calcd for $C_{13}H_{19}NO_3$ (M^+): 237.1364, Found: 237.1344.

4.1.8. 2-(Benzyloxyamino)-3-methylpentanoic acid (5e). 1:1 Diastereomeric mixture. A white powder. IR (Nujol) 1603, 1573 cm^{-1}. ^1H 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.

4.1.9. 2-(Benzyloxyamino)-4-methylpentanoic acid (5f). A white powder. IR (Nujol) 1602, 1573 cm^{-1}. ^1H NMR (CD_3OD) δ 7.36–7.29 (5H, m), 4.68 (2H, s), 3.59 (1H, t, *J*= 10.7 Hz), 1.69 (1H, m), 1.34 (2H, m), 0.90 (3H, d, *J*= 11.0 Hz), 0.81 (3H, d, *J*=11.0 Hz). ^{13}C NMR (CD_3OD) δ 177.8, 138.9, 129.4, 129.1, 128.6, 76.8, 63.2, 39.5, 26.0, 23.0, 22.7. HRMS: calcd for $C_{13}H_{19}NO_3$ (M^+): 237.1364, Found: 237.1348.

4.1.10. 2-(Benzyloxyamino)-2-adamantylethanoic acid (4g). A white powder. IR (Nujol) 1605, 1575 cm^{-1}. ^1H NMR (CD_3OD) δ 7.38–7.24 (5H, m), 4.62 (2H, s), 3.13 (1H, br s), 2.00–1.26 (15H, m). ^{13}C NMR (CD_3OD) δ 176.6, 139.1, 129.6, 129.1, 128.6, 76.5, 74.2, 40.3, 37.8, 35.6, 29.6. HRMS: calcd for $C_{19}H_{25}NO_3$ (M^+): 315.1833, Found: 315.1825.

4.1.11. General procedure for isopropyl radical addition to oxime ether 3. To a suspension of oxime ether **3** (0.83 mmol/g, 274 mg, 0.28 mmol) in CH_2Cl_2 or toluene (3.0 mL) were added *i*-PrI (30 or 60 equiv.) and Et_3B (1.0 M in hexane, 1.4 mL, 1.4 mmol) under a nitrogen atmosphere at 20 or 80°C. After the reaction mixture was stirred at the same temperature for 30 min, the resin was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried at reduced pressure. To a flask with the resulting resin **4** was added TFA/$CHCl_3$ (1:5, v/v, 4.0 mL) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with MeOH/$CHCl_3$ (1:11, v/v, 60 mL), and the filtrate was concentrated at reduced pressure. Purification of the residue by Amberlite IR-120B (eluting with MeOH) followed by preparative TLC (MeOH/$CHCl_3$ 1:10, v/v) afforded the α-amino acid derivatives **5b** and **5a**.

4.1.12. TentaGel OH resin-bound oxime ether (6). To a suspension of TentaGel OH resin[12] (0.26 mmol/g, 0.50 g) in DMF (2.5 mL) were added oxime ether **2** (107 mg, 0.60 mmol), 2,6-dichlorobenzoyl chloride (0.086 mL, 0.60 mmol) and pyridine (0.08 mL, 0.99 mmol) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 1 h and then stood for 11 h, the resin was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried at reduced pressure.

4.1.13. General procedure for ethyl radical addition to oxime ether 6 in H_2O–MeOH. To a suspension of oxime ether **6** (0.23 mmol/g, 300 mg, 0.07 mmol) in H_2O–MeOH (2:1, v/v, 3.0 mL) was added Et_3B (1.0 M in THF or 1.0 M in MeOH, 0.70 mL, 0.07 mmol) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 15 min, the resin was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried at reduced pressure. To a flask with the resulting resin **7a** was added TFA/$CHCl_3$ (1:5, v/v, 4.0 mL) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with MeOH/$CHCl_3$ (1:11, v/v, 60 mL), and the filtrate was concentrated at reduced pressure. Purification of the residue by Amberlite IR-120B (eluting with MeOH) followed by preparative TLC (MeOH/$CHCl_3$ 1:10, v/v) afforded the α-amino acid derivative **5a**.

4.1.14. General procedure for alkyl radical addition to oxime ether 6 in H_2O–MeOH. To a suspension of oxime ether **6** (0.23 mmol/g, 300 mg, 0.07 mmol) in H_2O–MeOH (2:1, v/v, 6.0 mL) were added RI (60 or 120 mmol) and Et_3B (1.0 M in MeOH, 0.70 mL, 0.07 mmol) under a nitrogen atmosphere at 20 or 80°C. After the reaction mixture was stirred at the same temperature for 1 h, the resin was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried at reduced pressure. To a flask with the resulting resin **7** was added TFA/$CHCl_3$ (1:5, v/v, 4.0 mL) under a nitrogen atmosphere at 20°C. After the reaction mixture was stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with MeOH/$CHCl_3$ (1:11, v/v, 60 mL), and the filtrate was concentrated at reduced pressure. Purification of the residue by Amberlite IR-120B (eluting with MeOH) followed by preparative TLC (MeOH/$CHCl_3$ 1:10, v/v) afforded the α-amino acid derivatives **5b**, **5e**, **5h**, and **5a**.

Acknowledgements

We wish to thank Grant-in Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Science Research

Promotion Fund of the Japan Private School Promotion Foundation for research grants.

References

1. For reviews, see: (a) Brown, R. C.; D, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) *Chem. Rev.* **1997**, *97*, whole issue of No. 2, pp 347–510. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643. (d) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (e) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (f) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (g) *Acc. Chem. Res.* **1996**, *29*, whole issue of No. 3, pp 112–170. (h) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527.
2. Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, 61.
3. (a) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678. (b) Du, X.; Armstrong, R. W. *Tetrahedron Lett.* **1998**, *39*, 2281.
4. (a) Berteina, S.; De Mesmaeker, A. *Tetrahedron Lett.* **1998**, *39*, 5759. (b) Berteina, S.; Wendeborn, S.; De Mesmaeker, A. *Synlett* **1998**, 1231.
5. Watanabe, Y.; Ishikawa, S.; Takao, G.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 3411.
6. Caddick, S.; Hamza, D.; Wadman, S. N. *Tetrahedron Lett.* **1999**, *40*, 7285.
7. Zhu, X.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 157.
8. Enholm, E. J.; Gallagher, M. E.; Jiang, S.; Batson, W. A. *Org. Lett.* **2002**, *2*, 1443.
9. Sibi, M. P.; Chandramouli, S. V. *Tetrahedron Lett.* **1997**, *38*, 8929.
10. Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. J. *Am. Chem. Soc.* **2000**, *122*, 2966.
11. (a) Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174. (b) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387. (c) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443. (d) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun.* **2001**, 831.
12. Wang and TentaGel OH resins purchased from Novabiochem were used in all experiments.
13. Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335.
14. (a) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (b) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **1999**, 465. (c) Miyabe, H.; Yamakawa, K.; Yoshioka, N.; Naito, T. *Tetrahedron* **1999**, *55*, 11209.
15. For related examples, see: (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Stella, L. *Synlett* **1998**, 780. (b) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189.
16. (a) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043. (b) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059. (c) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. (d) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131. (e) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454.
17. Kolasa, T.; Sharma, S. K.; Miller, M. J. *Tetrahedron* **1988**, *44*, 5431.