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Indium as a radical initiator in aqueous media: intermolecular alkyl radical addition to C=N and C=C bond

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Abstract—The carbon–carbon bond-forming method in aqueous media was investigated by using indium as a single-electron transfer radical initiator. The indium-mediated intermolecular alkyl radical addition to imine derivatives and electron-deficient C=C bond proceeded effectively.

1. Introduction

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] Therefore, the indium-mediated carbon–carbon bond-forming reactions in aqueous media have been of great importance.[3] Recently, numerous and useful indium-mediated allylation reactions of carbonyl compounds have been reported.[3] In contrast, the corresponding reaction of water-sensitive imine derivatives has not been widely studied; therefore, the development of indium-mediated reactions of imines in aqueous media has been a subject of current interest. Chan's group reported the first studies on the indium-mediated allylation of *N*-sulfonylimines in aqueous media.[4] These allylation reactions would proceed through an allylindium (I) intermediate which reacts with the *N*-sulfonylimines, thus, simple alkylation reactions are not investigated. As a part of our program directed toward the development of reactions of imines in aqueous media,[5] we report here in detail the aqueous-medium alkylation reactions of imine derivatives based on the alkyl radical addition to carbon–nitrogen double bond.[6a] This reaction is the first example of carbon–carbon bond-forming radical reaction using indium as a radical initiator in aqueous media.[7] As shown below, we also report the indium-mediated radical addition to electron-deficient carbon–carbon double bond in aqueous media.

Keywords: Indium; Radical; Water; Imine; Oxime ether; Hydrazone.
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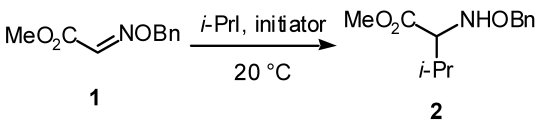
2. Results and discussion

2.1. Indium-mediated intermolecular carbon radical addition to glyoxylic imine derivatives

Among the different types of radical acceptors, the carbon–nitrogen double bond of imine derivatives has emerged as an excellent radical acceptor toward alkyl radicals, and thus numerous, powerful synthetic methods for the intramolecular carbon–carbon bond construction have been reported.[8] Recently, the several intermolecular radical reactions of imines were investigated in organic solvents mainly by the groups of Kim,[9] Bertrand,[10] Friestad,[11] as well as ourselves.[5,12] Our recent studies show that imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent water-resistant radical acceptors for the aqueous-medium reactions using triethylborane as a radical initiator.[5a]

On the basis of these results, we newly investigated the intermolecular radical addition to imine derivatives by using indium as a new radical initiator.[13] As a preliminary experiment, the substrate of choice was the glyoxylic oxime ether **1** since it has shown an excellent reactivity toward nucleophilic carbon radicals in our previous work on triethylborane-induced radical reactions.[12a,e] Additionally, we also expected that the direct comparison of indium-mediated reactions with triethylborane-induced reactions would lead to informative and instructive suggestions regarding indium as a single-electron transfer radical initiator.

In order to test the viability of indium as a radical initiator, the reaction of glyoxylic oxime ether **1** was investigated under the several reaction conditions (Scheme 1). To a



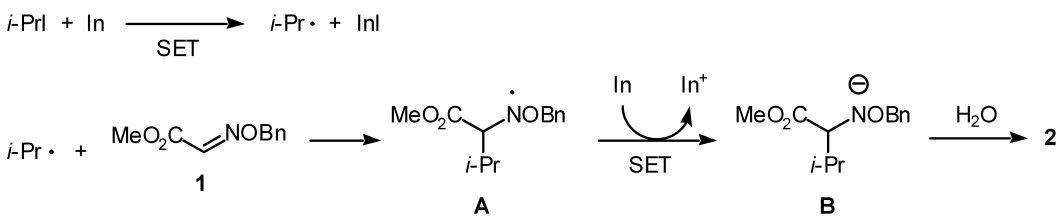
Scheme 1.

contrast, the indium-mediated alkyl radical addition to **3** gave selectively the desired *C*-monoalkylated products **4a**-**d** with no detection of *C*- and *N*-dialkylated products; thus, the indium was found to be a highly promising radical initiator for the radical reaction of hydrazones in aqueous media. The reaction of **3** with *i*-PrI proceeded smoothly to give 98% yield of the isopropylated product **4a** after being stirred for 1 h (Table 2, entry 1). In contrast, the reaction with *i*-PrBr did not take place because of the increase in bond

Table 1. Reaction of glyoxylic oxime ether **1**

Entry	Initiator	Solvent	Time (h)	Additive	Yield (%)
1[a]	In	H_2O:CH_2Cl_2 (4:1)	22	None	76
2[a]	In	CH_2Cl_2	24	None	No reaction
3[b]	In	H_2O:MeOH (2:1)	0.5	None	74
4[b]	In	H_2O:MeOH (2:1)	0.5	Galvinoxyl free radical	No reaction
5[c]	InI	H_2O:MeOH (2:1)	20	None	No reaction

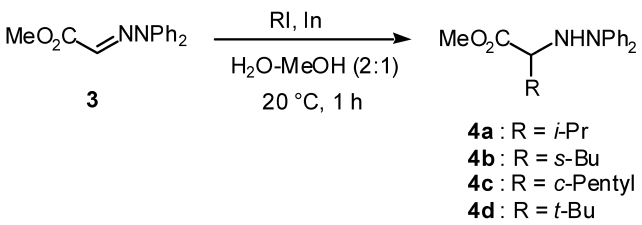
[a] Reactions were carried out with *i*-PrI (5 equiv.) and indium (7 equiv.).
[b] Reactions were carried out with *i*-PrI (4 equiv.×2) and indium (7 equiv.).
[c] Reaction was carried out with *i*-PrI (4 equiv.×2) and indium iodide (7 equiv.).



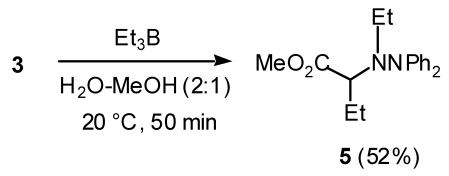
Scheme 2.

biphasic solution of **1** and *i*-PrI (5 equiv.) in H_2O–CH_2Cl_2 (4:1, v/v) was added indium (7 equiv.), and then the reaction mixture was stirred at 20 °C for 22 h. As expected, glyoxylic oxime ether **1** exhibits a good reactivity to give the desired isopropylated product **2** in 76% yield without formation of significant by-products such as a reduced product (Table 1, entry 1). When 1 equiv. of indium was used, **2** was obtained in only 8% yield and 72% yield of starting material **1** was recovered. In our recent studies, the triethylborane-induced reaction of **1** was usually run by using a large amount of alkyl iodides (more than 30 equiv.) to suppress the competitive reaction with ethyl radical generated from triethylborane.[12d,e] It is important to note that practically no reaction of **1** occurred in the absence of water (entry 2). These results suggest that water would be important for the activation of indium and for the proton-donor to the resulting amide anion (Scheme 2). In the case of monophasic reaction in H_2O–MeOH, the formation of isopropylated product **2** was observed after being stirred for only 0.5 h (entry 3). In the presence of galvinoxyl free radical as a radical scavenger, the reaction did not proceed effectively (entry 4). These results indicate that indium can serve as an initiator in aqueous media as well as triethylborane and thus, the reaction would proceed via the radical mechanism based on the single-electron transfer (SET) process from indium (Scheme 2). However, the reaction using indium (I) iodide instead of indium did not take place under similar reaction conditions (entry 5).

We next investigated the indium-mediated alkyl radical addition to glyoxylic hydrazone **3** (Scheme 3). In the case of the aqueous-medium reaction of **3** using triethylborane, the undesired *C*- and *N*-dialkylated product **5** was only obtained as a result of the additional *N*-alkylation (Scheme 4).[5a] In



Scheme 3.

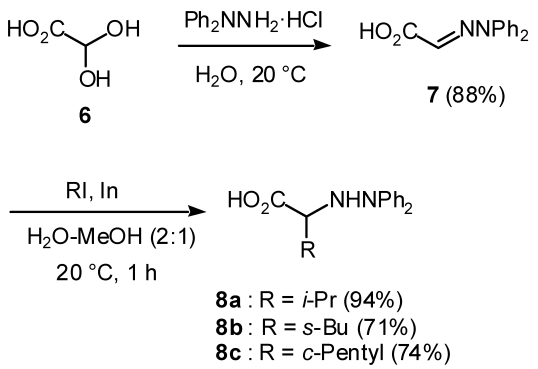


Scheme 4.

Table 2. Alkyl radical addition to glyoxylic hydrazone **3**[a]

Entry	RX	RX bond dissociation energy (kcal/mol)	Product	Yield (%)
1	*i*-PrI	53	**4a**	98
2	*i*-PrBr	68		No reaction
3	*s*-BuI		**4b**	90
4	*c*-Pentyl I		**4c**	79
5	*t*-BuI	49.5	**4d**	48
6	EtI	53.5		No reaction

[a] Reactions were carried out with RX (5 equiv.×2), indium (7 equiv.), and H_2O in MeOH at 20 °C for 1 h.

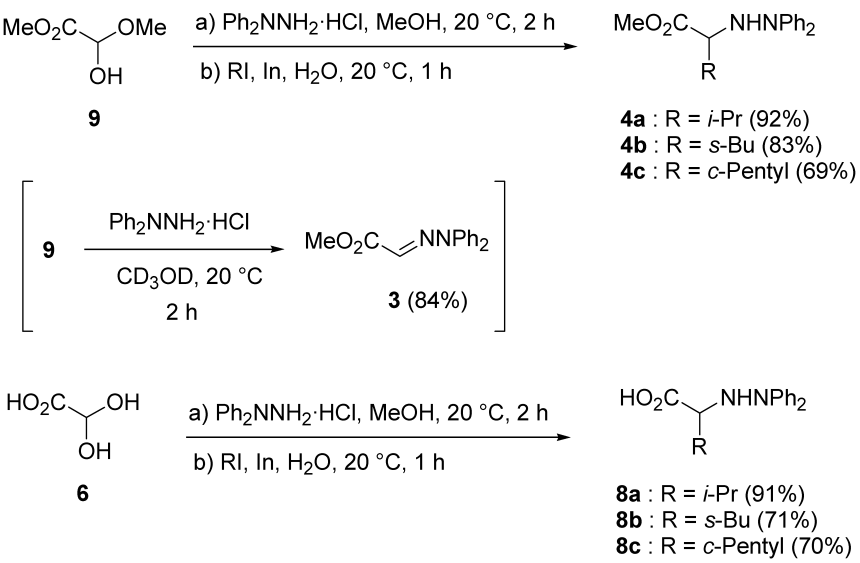


Scheme 5.

being stirred at 20 °C for 2 h. Subsequently, alkyl iodide, In, and H_2O were added to the reaction vessel to afford good yields of α-amino acid derivatives **4a-c** after the purification. The formation of hydrazone **3** was also confirmed in CD_3OD by ^1H NMR studies. The one-pot synthesis of α-amino acid derivatives using glyoxylic acid **6** was also studied. As expected, one-pot reaction proceeded effectively to give **8a-c** without interference of a free carboxyl group.

2.2. Indium-mediated intermolecular carbon radical addition to aldimine derivatives

To survey the scope and limitations of the present method, the alkylation reaction of aldimines was studied (Scheme 7).

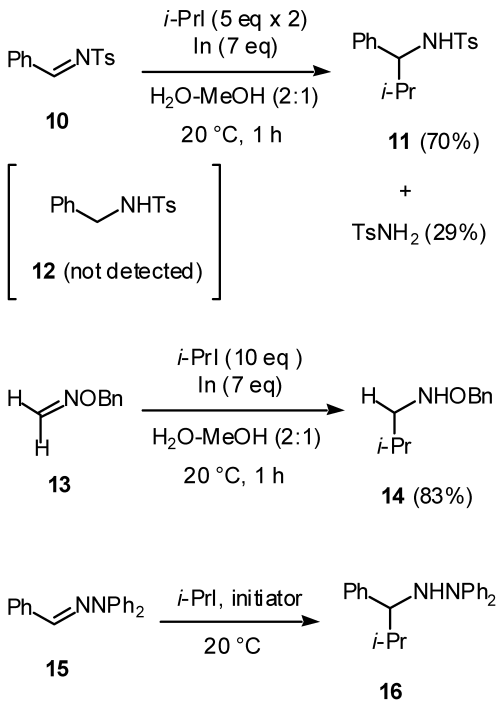


Scheme 6.

dissociation energy of *i*-PrBr (entry 2). Not only a secondary alkyl radicals but also the *tert*-butyl radical worked well to give **4b-d** in good yields after being stirred for 1 h (entries 3–5). However, primary ethyl iodide did not work because primary alkyl radicals are unstable and less nucleophilic radicals (entry 6). These results indicate that indium works as an effective radical initiator for generation of secondary and tertiary alkyl radicals from alkyl iodides.

We next investigated the reaction of hydrazone **7** having a free carboxyl group (Scheme 5). The glyoxylic hydrazone **7** was prepared from glyoxylic acid **6** and *N*,*N*-diphenylhydrazine hydrochloride in 88% yield. The indium-mediated reaction of **7** also proceeded in H_2O–MeOH without any problem to afford the good yields of products **8a-c**.

Integration of multi-step chemical reactions into one-pot reactions has attracted significant attention as an environmentally benign method.[14] The tolerance of the imine derivatives to the aqueous media prompted us to examine a one-pot reaction for the synthesis of α-amino acid derivatives in aqueous media (Scheme 6). Condensation of 2-hydroxy-2-methoxyacetic acid methyl ester **9** with *N*,*N*-diphenylhydrazine hydrochloride proceeded smoothly without any additive in MeOH to give hydrazone **3** after



Scheme 7.

At first, we investigated the indium-mediated radical addition to *N*-sulfonylimine **10** prepared from benzaldehyde. The monophasic reaction of *N*-sulfonylimine **10** in H_2O–MeOH (2:1, v/v) proceeded effectively to give the desired isopropylated product **11** in 70% yield, accompanied with 29% of $TsNH_2$ as a hydrolysis product after being stirred for only 1 h. In our recent studies on zinc-mediated radical reaction of *N*-sulfonylimines, the competitive reduction of *N*-sulfonylimine giving **12** was observed as a significant side reaction.[5d] Therefore, it should be note that the indium-mediated radical reaction did not give the reduced product **12**. The indium-mediated radical addition to sterically less hindered formaldoxine ether **13** proceeded smoothly to give product **14** in 83% yield. In contrast, the reactivity of hydrazone **15**, prepared from benzaldehyde, is not high (Table 3). We have recently reported that the triethylborane-induced radical addition to aldoxime ethers proceeded effectively in the presence of $BF_3{\cdot}OEt_2$. Thus, the triethylborane-induced radical addition to **15** was also investigated under general reaction conditions which have been already established in the reaction of aldoxime ethers (entries 1 and 2). However, the triethylborane-induced radical addition to **15** did not take place probably due to basic diphenylamino group. In the case of indium-mediated reactions, the monophasic reaction of **15** in 1 M HCl–MeOH (2:1, v/v) gave the desired product **16**, accompanied with starting material **15** (entries 3 and 4). The biphasic reaction of **15** in H_2O–CH_2Cl_2 (4:1, v/v) proceeded slowly to give **16** in 54% yield after being stirred for 2 days (entry 5).

Table 3. Reaction of hydrazone **15**

Entry	Initiator	Solvent	Time (h)	Yield (%)
1[a]	Et_3B	CH_2Cl_2	0.5	No reaction
2[b]	Et_3B	CH_2Cl_2	0.5	No reaction
3[c]	In	1 M HCl:MeOH (2:1)	1	34 (59)[d]
4[c]	In	1 M HCl:MeOH (2:1)	7	38 (54)[d]
5[e]	In	H_2O: CH_2Cl_2 (4:1)	48	54

[a] Reaction was carried out with *i*-PrI (30 equiv.) and Et_3B (5 equiv.).
[b] Reaction was carried out with *i*-PrI (30 equiv.) and Et_3B (5 equiv.) in the presence of $BF_3{\cdot}OEt_2$ (2 equiv.).
[c] Reactions were carried out with *i*-PrI (5 equiv.×2) and indium (7 equiv.).
[d] Yields in parentheses are for starting material **15**.
[e] Reaction was carried out with *i*-PrI (5 equiv.) and indium (7 equiv.).

2.3. Indium-mediated intermolecular carbon radical addition to electron-deficient C=C bond

To test the utility of indium as a single-electron transfer radical initiator, we next investigated the indium-mediated alkyl radical addition to compounds **17**-**20** having electron-deficient C=C bond (Fig. 1). Compounds **18** and **19** were readily prepared as shown in Scheme 8. The reaction of **21** with acryloyl chloride gave the **18** in 88% yield. Compound **19** was prepared by the reaction of **22** with acryloyl chloride followed by *N*-crotylation.

Reactions of **17**-**19** with *i*-PrI and indium were carried out in H_2O–MeOH at 20 °C (Scheme 9). In the case of substrate **17a**, the product **24a** was obtained only in 20% yield, probably due to the competitive polymerization of **17a**. In contrast, the radical addition to substrate **17b** having a

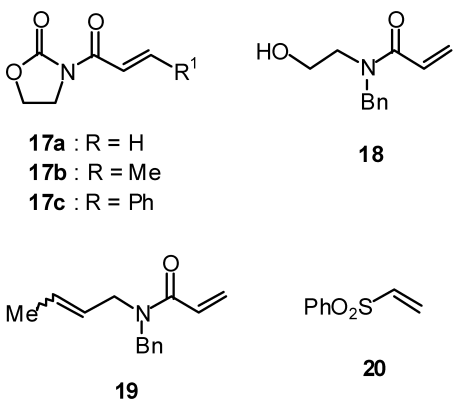
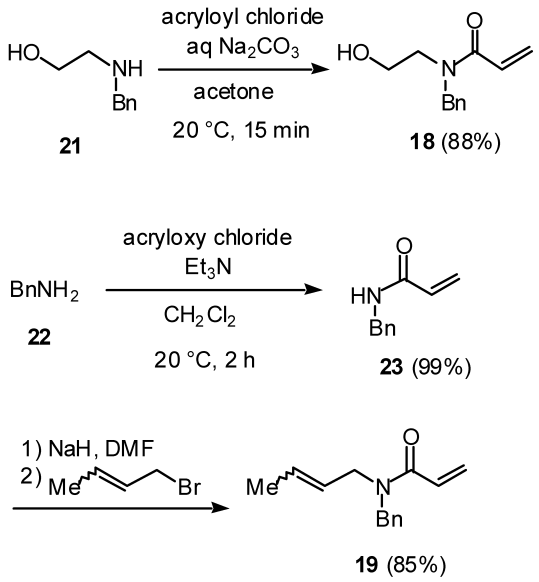
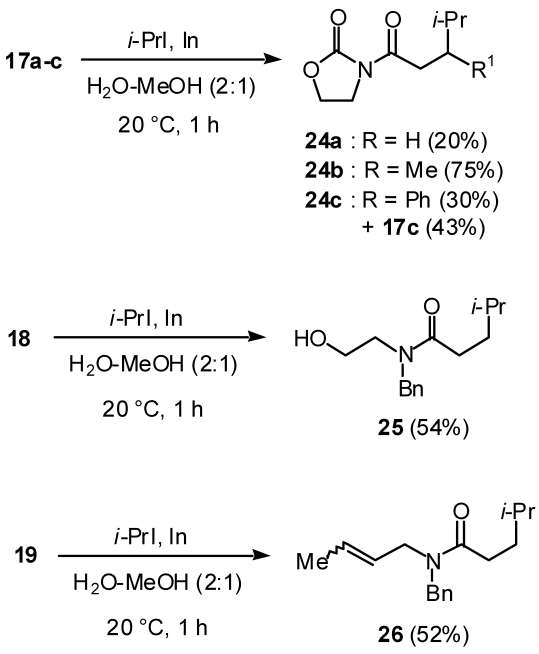


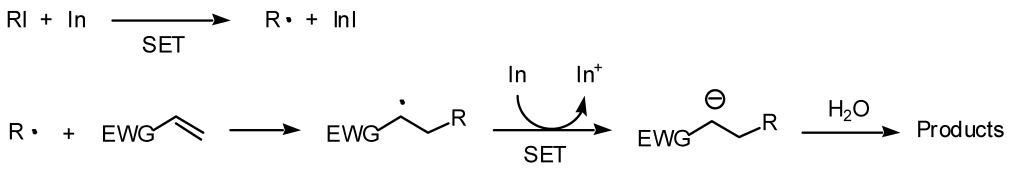
Figure 1.



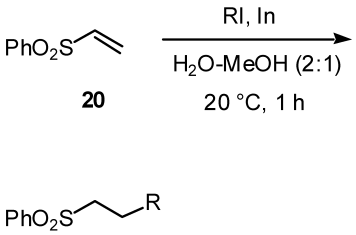
Scheme 8.



Scheme 9.



Scheme 10.



27a : R = *i*-Pr (86%)
27b : R = *s*-Bu (81%)
27c : R = *c*-Pentyl (80%)
27d : R = *t*-Bu (61%)

Scheme 11.

methyl group gave the desired product **24b** in 75% yield. In the case of substrate **17c** having a phenyl group, the radical reaction proceeded slowly to give 30% yield of the desired product **24c**, accompanied with 43% yield of starting material **17c**, after being stirred for 1 h. The reactions of **18** having a hydroxyl group and **19** having an additional olefin moiety also produced the isopropylated products **25** and **26** respectively. These reactions would proceed via the single-electron transfer process from indium as shown in Scheme 10.

We finally studied the radical addition to phenyl vinyl sulfone **20** (Scheme 11). To a solution of phenyl vinyl sulfone **20** and RI (5 equiv.) in MeOH were added indium (7 equiv.) and H_2O, and then the reaction mixture was stirred at 20 °C for 30 min. As expected, phenyl vinyl sulfone **20** exhibits a good reactivity to give the desired alkylated products **27a**-**d** in good yields with no detection of by-products such as a reduced product.

In general, free radical synthetic methods largely relied on toxic organotin chemistry; therefore, the development of tin-free reactions including SET processes from indium has been of great importance in radical chemistry.

3. Conclusion

We have demonstrated that indium has the potential to induce the radical reaction in aqueous media. The reaction of imine derivatives proceeded effectively, providing the one-pot synthesis of α-amino acids. Since the known examples of indium-mediated carbon–carbon bond-forming reactions in aqueous media are mainly limited to allylation reactions, it is noteworthy that newly-found reaction involves the alkylation of imine derivatives and electron-deficient olefins.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 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 $60F_{254}$).

4.2. Indium-mediated reaction of glyoxylic oxime ether 1 in $H_2O-CH_2Cl_2$

To a micro tube containing **1**[12e] (50 mg, 0.259 mmol), *i*-PrI (0.13 mL, 1.30 mmol), indium (257 mg, 1.813 mmol), and CH_2Cl_2 (0.1 mL) was added dropwise H_2O (0.4 mL) at 20 °C. After being stirred at the same temperature for 22 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1) afforded **2**[12e] (46.6 mg, 76%) as a colorless oil.

4.3. Indium-mediated reaction of glyoxylic oxime ether 1 in $H_2O-MeOH$

To a micro tube containing **1** (50 mg, 0.259 mmol), *i*-PrI (0.10 mL, 1.036 mmol), indium (257 mg, 1.813 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 15 min, *i*-PrI (0.10 mL, 1.036 mmol) was added to the reaction mixture. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1) afforded **2** (45.1 mg, 74%) as a colorless oil.

4.3.1. (*E*)-(*N*,*N*-Diphenylhydrazono)acetic acid (7). To a solution of glyoxylic acid monohydrate **6** (1 g, 10.8 mmol) in H_2O (100 mL) was added *N*,*N*-diphenylhydrazine hydrochloride (2.4 g, 10.8 mmol) at 20 °C. After being stirred at the same temperature for 30 min, the product was crystallized out from the reaction mixture. Crystals were filtered and washed with H_2O. Purification of crystals by flash chromatography ($CHCl_3$/MeOH 30:1) afforded **7** (2.3 g, 88%). Colorless crystals. Mp 209–210 °C (AcOEt). IR ($CHCl_3$) 3022, 1741, 1592, 1547, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.49–6.16 (10H, m), 6.49 (1H, s). ^{13}C NMR ($CDCl_3$) δ 166.2, 141.7, 130.1, 126.7, 123.2. HRMS Calcd for $C_{14}H_{12}N_2O_2$ (M^+) 240.0898, found 240.0887. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.04; H, 5.13; N, 11.68.

4.4. General procedure for alkyl radical addition to glyoxylic hydrazones 3 and 7

To a micro tube containing **3**[5a] or **7** (0.197 mmol), RX (0.985 mmol), indium (196 mg, 1.38 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, RX (0.985 mmol) was added to the reaction mixture. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1 or hexane/AcOEt 30:1 2-fold development) afforded **4a-c** and **4d**.

4.4.1. Methyl 2-(*N*,*N*-diphenylhydrazino)-3-methylbutanoate (4a). Colorless crystals. Mp 43–43.5 °C (hexane). IR ($CHCl_3$) 3012, 1731, 1589, 1489 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.98 (10H, m), 4.40 (1H, br s), 3.45 (3H, s), 3.41 (1H, d, J=6.3 Hz), 2.03–1.96 (1H, m), 1.07 (3H, d, J=6.6 Hz), 0.97 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 173.8, 148.0, 129.0, 122.7, 120.9, 67.7, 51.2, 30.5, 19.2, 18.8. HRMS Calcd for $C_{18}H_{22}N_2O_2$ (M^+) 298.1680, found 298.1696. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.70; H, 7.44; N, 9.28.

4.4.2. Methyl 2-(*N*,*N*-diphenylhydrazino)-3-methylpentanoate (4b). 1:1 Mixture of diastereomers with regard the *sec*-butyl group. A colorless oil. IR ($CHCl_3$) 3029, 3010, 2965, 1730, 1589 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.98 (10H, m), 4.41 (1H, br s), 3.53–3.50 (1H, br m), 3.47 (3H, s), 1.84–1.72 (1H, m), 1.66–1.52 (1H, m), 1.38–1.16 (1H, m), 1.04–0.87 (6H, m). ^{13}C NMR ($CDCl_3$) δ 174.1, 169.9, 148.2, 148.1, 129.0, 122.7, 121.0, 66.1, 66.0, 51.3, 51.2, 37.4, 37.0, 26.0, 25.9, 15.5, 15.3, 11.7, 11.4. HRMS Calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1836, found 312.1847.

4.4.3. Methyl 2-(*N*,*N*-diphenylhydrazino)-2-cyclopentylethanoate (4c). Colorless crystals. Mp 52.5–53 °C (AcOEt/hexane). IR ($CHCl_3$) 2953, 1732, 1589, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–7.00 (10H, m), 4.28 (1H, br s), 3.42 (3H, s), 3.42 (1H, br m), 2.13–2.02 (1H, m), 1.98–1.88 (1H, m), 1.66–1.28 (7H, m). ^{13}C NMR ($CDCl_3$) δ 174.3, 148.0, 129.0, 122.7, 120.9, 66.9, 51.3, 41.6, 30.0, 29.0, 25.1, 24.9. HRMS Calcd for $C_{20}H_{24}N_2O_2$ (M^+) 324.1836, found 324.1836. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.05; H, 7.45; N, 8.62.

4.4.4. Methyl 2-(*N*,*N*-diphenylhydrazino)-3,3-dimethylbutanoate (4d). A white solid. IR ($CHCl_3$) 2955, 1729, 1589, 1498 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.32–6.98 (10H, m), 4.35 (1H, br s), 3.36 (3H, s), 3.36 (1H, br d), 1.03 (9H, s); ^{13}C NMR ($CDCl_3$) δ 174.0, 148.5, 129.1, 122.9, 121.3, 71.4, 51.0, 34.2, 27.0; HRMS Calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1836, found 312.1840.

4.4.5. 2-(*N*,*N*-Diphenylhydrazino)-3-methylbutanoic acid (8a). Colorless crystals. Mp 111–113 °C (AcOEt/hexane). IR ($CHCl_3$) 2968, 1711, 1590, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.30–6.99 (10H, m), 3.04 (1H, d, J=5.4 Hz), 2.09–2.03 (1H, m), 1.07 (3H, d, J=6.9 Hz), 1.03 (3H, d, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 178.4, 148.1, 129.2, 123.2, 121.2, 67.0, 30.3, 19.0, 18.8. HRMS Calcd for $C_{17}H_{20}N_2O_2$ (M^+) 284.1523, found 284.1529. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.73; H, 7.01; N, 9.86.

4.4.6. 2-(*N*,*N*-Diphenylhydrazino)-3-methylpentanoic acid (8b). 1:1 Mixture of diastereomers with regard the *sec*-butyl group. Colorless crystals. Mp 112–114 °C (AcOEt/hexane). IR ($CHCl_3$) 2967, 1710, 1590, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.99 (10H, m), 3.57 (1/2H, d, J=4.5 Hz), 3.55 (1/2H, d, J=4.5 Hz), 1.86–1.81 (1H, m), 1.59–1.54 (1H, m), 1.38–1.26 (1H, m), 1.05–0.87 (6H, m). ^{13}C NMR ($CDCl_3$) δ 177.2, 148.2, 148.1, 129.3, 123.4, 121.2, 121.1, 65.3, 65.1, 37.1, 36.8, 26.0, 25.9, 15.4, 11.8, 11.6. HRMS Calcd for $C_{18}H_{22}N_2O_2$ (M^+) 298.1680, found 298.1660. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.53; H, 7.42; N, 9.39.

4.4.7. 2-(*N*,*N*-Diphenylhydrazino)-2-cyclopentylethanoic acid (8c). A white solid. IR ($CHCl_3$) 3009, 2959, 1714, 1590, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.30–6.98 (10H, m), 3.44 (1H, d, J=8.1 Hz), 2.16–2.04 (1H, m), 1.94–1.23 (8H, m). ^{13}C NMR ($CDCl_3$) δ 178.2, 129.2, 122.3, 121.2, 117.8, 66.2, 41.3, 29.8, 29.1, 25.1, 25.0. HRMS s for $C_{19}H_{22}N_2O_2$ (M^+) 310.1180, found 310.1167.

4.5. General procedure for the one-pot synthesis of α-amino acid derivatives

To a solution of 2-hydroxy-2-methoxyacetic acid methyl ester **9** or glyoxylic acid monohydrate **6** (0.25 mmol) in MeOH (0.3 mL) was added *N,N*-diphenylhydrazine hydrochloride (55 mg, 0.25 mmol) at 20 °C. After being stirred at the same temperature for 2 h, RI (1.25 mmol) and indium (1.75 mmol) were added to the reaction mixture, and then H_2O (0.3 mL) was added dropwise to the reaction mixture at 20 °C over 5 min. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **4a-c** and **8a-c**.

4.5.1. 4-Methyl-*N*-(2-methyl-1-phenylpropyl)benzenesulfonamide (11). To a micro tube containing **10** (50 mg, 0.193 mmol), *i*-PrI (0.096 mL, 0.965 mmol), indium (191 mg, 1.35 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.40 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, *i*-PrI (0.096 mL, 0.965 mmol) was added to the reaction mixture. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1, 2-fold development) afforded **10** (41 mg, 70%). Colorless crystals. Mp 136.5–138 °C (AcOEt/hexane). IR ($CHCl_3$) 3030, 1495, 1327, 1159 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.52–6.95 (9H m), 5.66 (1H, br s), 4.04–3.99 (1H, m), 2.31 (3H, s), 1.95–1.88 (1H, m), 0.95 (3H, d, J=6.6 Hz), 0.72 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 142.5, 139.8, 137.5, 128.9, 127.8, 126.9, 126.8, 126.7, 64.1, 34.2, 21.2, 19.2, 18.7.

HRMS Calcd for $C_{17}H_{20}NO_2S$ ([M−H]$^+$) 302.1214, found 302.1218. Anal. Calcd for $C_{17}H_{21}NO_2S{\cdot}1/2H_2O$: C, 66.50; H, 7.03; N, 4.56; S, 10.44. Found: C, 66.37; H, 6.94; N, 4.50; S, 10.74.

4.5.2. 2-Methyl-*N*-(phenylmethoxy)-1-propanamine (14). To a micro tube containing **13** (50 mg, 0.37 mmol), *i*-PrI (3.7 mL, 3.7 mmol), indium (366 mg, 2.59 mmol), and MeOH (0.4 mL) was added dropwise H_2O (0.80 mL) at 20 °C over 5 min. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1) afforded **14** (55 mg, 83%). A colorless oil. IR ($CHCl_3$) 3011, 2959, 1496, 1469, 1454 cm^{-1}. ^{1}H 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.

4.5.3. 2-(2-Methyl-1-phenylpropyl)-1,1-diphenylhydrazine (16). To a micro tube containing hydrazone **15** (50 mg, 0.183 mmol) in CH_2Cl_2 (0.1 mL) were added *i*-PrI (0.182 mL, 1.83 mmol), indium (182 mg, 1.28 mmol) and H_2O (0.4 mL) at 20 °C. After being stirred at the same temperature for 2 days, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane 7-fold development) afforded **16** (31.0 mg, 54%). A colorless oil. IR ($CHCl_3$) 3018, 2963, 1590, 1494 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.23–6.87 (15H, m), 3.64 (1H, d, J=5.4 Hz), 2.14–1.98 (1H, m), 1.18–1.15 (1H, br m), 0.83 (3H, d, J=7.0 Hz), 0.69 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 148.2, 140.2, 129.0, 128.7, 127.7, 127.1, 122.3, 120.7, 67.6, 31.1, 19.9, 18.4. HRMS Calcd for $C_{22}H_{24}N_2$ (M$^+$) 316.1938, found 316.1944.

4.5.4. *N*-(2-Hydroxyethyl)-*N*-(phenylmethyl)propenoylamide (18). To a solution of *N*-benzylethanolamine **21** (1.0 g, 6.6 mmol) in acetone (30 mL) were added a solution of Na_2CO_3 (1.4 g, 13.2 mmol) in H_2O (2 mL) and acryloyl chloride (0.80 mL, 9.9 mmol) at 0 °C. After being stirred at 20 °C for 15 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 1:5) afforded **18** (1.18 g, 88%). After characterization by ^{1}H NMR and HRMS, unstable **18** was immediately subjected to radical reaction. The presence of rotamers (8:5) precluded a comprehensive assignment of all proton resonances. A colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.37–7.17 (5H, m), 6.83–6.36 (2H, m), 5.72 (1H, dd, J=9.6, 2.4 Hz), 4.71 (10/13H, s), 4.68 (16/13H, s), 3.78–3.60 (4H, m). HRMS Calcd for $C_{12}H_{15}NO_2$ (M$^+$) 205.1102, found 205.1101.

4.5.5. *N*-(Phenylmethyl)propenoylamide (23). To a solution of benzylamine (300 mg, 2.8 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.39 mL, 2.8 mmol) and acryloyl chloride (0.27 mL, 3.36 mmol) at 0 °C. After being stirred at 20 °C for 2 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 2:1) afforded **23** (447 mg, 99%). A white solid. IR ($CHCl_3$) 3441, 1671 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.34–7.26 (5H, m), 6.33 (1H, dd, J=16, 1.8 Hz), 6.11 (1H, dd, J=16, 10 Hz), 5.68 (1H, dd, J=10, 1.8 Hz), 4.52 (2H, d, J=5.8 Hz). ^{13}C NMR ($CDCl_3$) δ 165.4, 138.0, 130.6, 128.7, 127.8, 127.5, 126.7, 43.6. HRMS Calcd for $C_{10}H_{11}NO$ (M$^+$) 161.0840, found 161.0843.

4.5.6. *N*-2-Butenyl-*N*-(phenylmethyl)-2-propenoylamide (19). To a solution of amide **23** (50 mg, 0.31 mmol) in DMF (1.5 mL) was added NaH (60% oil suspension, 75 mg, 1.86 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at 0 °C for 30 min, crotyl bromide (0.064 mL, 0.62 mmol) was added to the reaction mixture at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with Et_2O. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 3:1) afforded **19** (57 mg, 85%). The presence of rotamers (2:3 (*Z*-isomer), 5:7 (*E*-isomer)) precluded a comprehensive assignment of ^{1}H and ^{13}C NMR. A colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.35–7.17 (5H, m), 6.63–6.39 (2H, m), 5.74–5.33 (3H, m), 4.63 (10/17H (*Z*)+10/17H (*E*), br s), 4.56 (14/17H (*E*), br s), 4.11 (4/17H (*Z*), br d, J=6.6 Hz), 3.99 (10/17H (*E*), br d, J=5.7 Hz), 3.92 (6/17H (*Z*), br d, J=6.3 Hz), 3.81 (14/17H (*E*), br d, J=4.5 Hz), 1.71–1.59 (3H, m). ^{13}C NMR ($CDCl_3$) δ 166.2, 137.2, 136.6, 129.0, 128.5, 128.2, 127.9, 127.5, 127.3, 127.2, 127.0, 126.1, 125.5, 125.3, 125.2, 124.9, 49.8, 49.5, 48.3, 48.2, 48.1, 47.3, 43.5, 41.7, 17.3 (2C), 12.6, 12.5. HRMS Calcd for $C_{14}H_{17}NO$ (M$^+$) 215.1310, found 215.1319.

4.6. General procedure for the radical addition to 17-19

To a micro tube containing **17**-**19** (0.20 mmol), *i*-PrI (0.10 mL, 1.0 mmol), indium (199 mg, 1.4 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, *i*-PrI (0.10 mL, 1.0 mmol) was added to the reaction mixture. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2:1) afforded **24a**-**c**, and purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **25** and **26**.

4.6.1. 3-(4-Methylpentanoyl)-2-oxazolidine (24a). A colorless oil. IR ($CHCl_3$) 3027, 2960, 1783, 1701 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.41 (2H, t, J=8.4 Hz), 4.01 (2H, t, J=8.4 Hz), 2.92 (2H, t, J=7.7 Hz), 1.63–1.50 (3H, m), 0.92 (6H, d, J=6.2 Hz). ^{13}C NMR ($CDCl_3$) δ 173.8, 153.5, 61.9, 42.5, 33.2, 33.1, 27.6, 22.3. HRMS Calcd for $C_9H_{15}NO_3$ (M$^+$) 185.1051, found 185.1060.

4.6.2. 3-(3,4-Dimethylpentanoyl)-2-oxazolidine (24b). A

colorless oil. IR ($CHCl_3$) 2963, 1781, 1697 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.41 (2H, t, J=8.3 Hz), 4.02 (2H, t, J=8.3 Hz), 2.95 (1H, dd, J=16.2, 5.1 Hz), 2.74 (1H, dd, J=16.2, 9.3 Hz), 2.04–1.94 (1H, m), 1.69–1.58 (1H, m), 0.91 (3H, d, J=6.6 Hz), 0.87 (3H, d, J=6.6 Hz) 0.89 (3H, d, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 173.4, 153.4, 61.8, 42.5, 39.4, 35.0, 32.1, 19.9, 18.1, 15.6. HRMS Calcd for $C_{10}H_{17}NO_3$ (M^+) 199.1207, found 199.1203.

4.6.3. 3-[(4-Methyl-3-phenyl)pentanoyl]-2-oxazolidine (24c). A colorless oil. IR ($CHCl_3$) 3028, 2963, 2927, 1780, 1701, 1494, 1481 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.31–7.14 (5H, m), 4.37–4.15 (2H, m), 3.91–3.73 (2H, m), 3.53 (1H, dd, J=16.5, 10.2 Hz), 3.21 (1H, dd, J=16.5, 4.8 Hz), 2.98 (1H, ddd, J=10.2, 8.2, 4.8 Hz), 1.96–1.85 (1H, m), 0.99 (3H, d, J=6.6 Hz), 0.75 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 172.6, 153.5, 143.0, 128.4, 128.0, 126.3, 61.9, 48.5, 42.5, 38.6, 33.2, 20.7, 20.5. HRMS Calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1363, found 261.1368.

4.6.4. *N*-(2-Hydroxyethyl)-4-methyl-*N*-(phenylmethyl)-pentanoylamide (25). The presence of rotamers (3:1) precluded a comprehensive assignment of all proton resonances. A colorless oil. IR ($CHCl_3$) 3393, 3008, 2960, 1626, 1469 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40–7.17 (5H, m), 4.67 (2/4H, s), 4.61 (6/4H, s), 3.75–3.69 (2H, m), 3.56 (6/4H, t, J=4.5 Hz), 3.42 (2/4H, t, J=4.5 Hz), 2.59 (1H, br s), 2.48 (2/4H, t, J=7.5 Hz), 2.38 (6/4H, t, J=7.5 Hz), 1.62–1.53 (3H, m), 0.98 (3H, d, J=6.3 Hz), 0.86 (3H, d, J=6.3 Hz). ^{13}C NMR ($CDCl_3$) δ 176.3, 174.3, 137.9, 136.4, 129.0, 128.6, 127.9, 127.8, 127.3, 126.3, 62.3, 60.1, 52.7, 50.0, 49.0, 48.5, 34.3, 34.1, 31.3, 27.9, 27.8, 22.4, 22.3. HRMS Calcd for $C_{15}H_{23}NO_2$ (M^+) 249.1727, found 249.1725.

4.6.5. *N*-(2-Butenyl)-4-methyl-*N*-phenylmethylpentanoylamide (26). The presence of rotamers (1:1 (*Z*-isomer), 2:3 (*E*-isomer)) precluded a comprehensive assignment of ^1H and ^{13}C NMR. A colorless oil. IR ($CHCl_3$) 3019, 2960, 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.15 (5H, m), 5.65–5.31 (2H, m), 4.57 (4/7H (*Z*)+4/7H (*E*), br s), 4.49 (6/7H (*E*), br s), 4.05 (2/7H (*Z*), br d, J=7.2 Hz), 3.93 (4/7H (*E*), br d, J=5.7 Hz), 3.85 (2/7H (*Z*), br d, J=6.6 Hz), 3.74 (6/7H (*E*), br d, J=5.1 Hz), 2.40–2.30 (2H, m), 1.72–1.54 (6H, m), 0.92 (24/7H, d, J=5.7 Hz), 0.85 (18/7H, d, J=5.7 Hz). ^{13}C NMR ($CDCl_3$) δ 173.6, 137.9, 137.1, 129.0, 128.8, 128.5, 128.2, 127.6, 127.4, 127.1, 126.4, 126.3, 125.9, 125.6, 50.2, 49.9, 48.5, 48.1, 47.8, 47.2, 43.8, 41.6, 34.3, 31.3, 31.2, 29.7, 27.9, 27.8, 22.4, 22.3, 17.7, 17.6, 12.9. HRMS Calcd for $C_{17}H_{25}NO$ (M^+) 259.1935, found 259.1937.

4.7. General procedure for the radical addition to 20

To a micro tube containing **20** (95% of purity, 50 mg, 0.282 mmol), RI (1.41 mmol), indium (280 mg, 1.97 mmol), and MeOH (0.2 mL) was added dropwise H_2O (0.8 mL) at 20 °C over 5 min. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The organic phase was washed, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **27a-d**.

4.7.1. 3-Methylbutyl phenyl sulfone (27a). A white solid. IR ($CHCl_3$) 2961 1469, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.55 (5H, m), 3.11–3.06 (2H, m), 1.63–1.58 (3H, m), 0.87 (6H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 139.1, 133.5, 129.2, 127.9, 54.6, 30.9, 27.1, 21.9. HRMS Calcd for $C_{11}H_{16}O_2S$ (M^+) 212.0870, found 212.0879.

4.7.2. 3-Methylpentyl phenyl sulfone (27b). A colorless oil. IR ($CHCl_3$) 3028, 2964, 1587, 1464, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.55 (5H, m), 3.17–3.00 (2H, m), 1.79–1.07 (5H, m), 0.85–0.80 (6H, m). ^{13}C NMR ($CDCl_3$) δ 139.1, 133.5, 129.2, 128.0, 54.4, 33.4, 28.8, 28.7, 18.6, 11.0. HRMS Calcd for $C_{12}H_{18}O_2S$ (M^+) 226.1026, found 226.1027.

4.7.3. 2-Cyclopentylethyl phenyl sulfone (27c). Colorless crystals. Mp 68–69 °C (AcOEt/hexane). IR ($CHCl_3$) 3028, 2954, 1587, 1448 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.55 (5H, m), 3.13–3.07 (2H, m), 1.74–1.69 (5H, m), 1.58–1.50 (4H, m), 1.08–1.02 (2H, m). ^{13}C NMR ($CDCl_3$) δ 139.2, 133.6, 129.2, 128.0, 55.7, 38.7, 32.2, 28.5, 25.0. HRMS Calcd for $C_{13}H_{18}O_2S$ (M^+) 238.1026, found 238.1024. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.43; H, 7.47; S, 13.73.

4.7.4. 3,3-Dimethylbutyl phenyl sulfone (27d). Colorless crystals. Mp 60–60.5 °C (AcOEt/hexane). IR ($CHCl_3$) 3027, 2962, 1587, 1476, 1448, 1303, 1150 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.93–7.56 (5H, m), 3.09–3.04 (2H, m), 1.63–1.57 (2H, m), 0.87 (9H, s). ^{13}C NMR ($CDCl_3$) δ 139.2, 133.6, 129.2, 128.0, 52.9, 35.6, 30.0, 28.9. HRMS Calcd for $C_{12}H_{18}O_2S$ (M^+) 226.1026, found 226.1011. Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02; S, 14.17. Found: C, 63.64; H, 7.86; S, 13.93.

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