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Zinc-mediated carbon radical addition to glyoxylic imines in aqueous media for the synthesis of α-amino acids

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The addition of carbon radicals to glyoxylic imines was studied using zinc dust as a radical initiator. The zinc-mediated radical reaction of glyoxylic oxime ethers and hydrazones proceeded smoothly to give the alkylated products *via* a carbon–carbon bond-forming process in aqueous media. The reaction of the oxime ethers and hydrazones having an Oppolzer's camphorsultam group provided the corresponding alkylated products, which could be converted into enantiomerically pure α-amino acids. The diastereoselectivities observed in the reaction of hydrazones were better than those obtained in the reaction of oxime ethers.

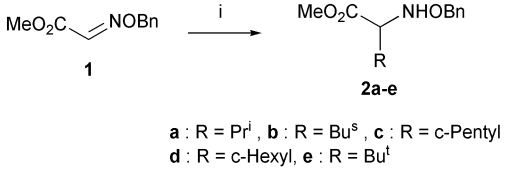
Introduction

The use of water as a solvent has generated considerable interest from both economical and environmental points of view.[1] Particularly, carbon–carbon bond-formation in aqueous media is a challenging problem.[2] Thus, zinc-mediated carbon–carbon bond-forming reactions in aqueous media have attracted considerable interest.[3] Among the various types of known zinc-mediated reactions,[3] radical reactions have captured much recent attention because of their exceptional tolerance to functional groups.[4]

The carbon–nitrogen double bond of imine derivatives has emerged as a radical acceptor.[5] However, the reactions of water-sensitive imines have generally been performed in anhydrous organic solvents. Therefore, zinc-mediated radical reactions of imine derivatives in aqueous media have not been widely studied to date. Our recent studies show that *N*-sulfonylimines are excellent radical acceptors for the aqueous-medium reactions using zinc as a single-electron transfer radical initiator.[6] We have a program directed toward the development of environmentally benign synthetic reactions in aqueous media.[7,8] As part of this, we report here, for the first time in detail, zinc-mediated radical addition to water-resistant glyoxylic oxime ethers and hydrazones.[9] We also report the diastereoselective radical reaction of the oxime ether and hydrazone incorporating Oppolzer's camphorsultam.[10]

Results and discussion

Among the different types of imines, the oxime ethers are well-known to be excellent radical acceptors.[5] As a preliminary experiment we first examined the zinc-mediated radical addition to glyoxylic oxime ether **1**, because it has shown high reactivity toward radical addition reactions in our recent studies (Scheme 1).[7] To a suspension of oxime ether **1**, metallic unactivated Zn and Pr^{i}I in MeOH was added dropwise sat. aqueous NH_4Cl at 20 °C and then the reaction mixture was stirred vigorously at 20 °C for 15 min (Table 1, entry 1). ^{1}H NMR measurement of the crude product showed an almost quantitative conversion of **1** to the desired **2a**. The product **2a** was isolated in 96% yield after purification by preparative TLC. It is important to note that no reaction of **1** occurred in H_2O–MeOH (Table 1, entry 2). These results suggest that aqueous NH_4Cl is important for the activation of unactivated Zn. In contrast, the reaction with Pr^{i}Br did not take place because of the larger bond dissociation energy of the C–Br bond (Table 1, entry 3). Secondary and tertiary alkyl radicals worked well to give **2b–d** after a 15 min reaction time (Table 1, entries 4–7). These reactions are expected to proceed through the radical pathway based on a single-electron transfer (SET) from zinc, as reported previously (Scheme 2).[4]

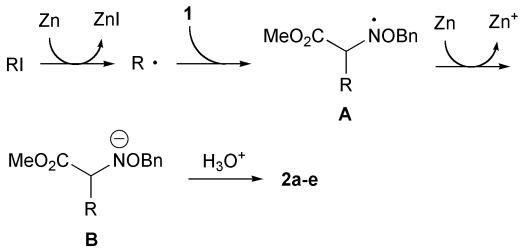


Scheme 1 Reagents and conditions: i) RX (5 eq.), Zn (7 eq.), 20 °C, 15 min.

Table 1 Zinc-mediated radical additions to oxime ether **1**[a]

Entry	RX	Solvent	Product	Yield (%)[b]
1	Pr^{i}I	Sat. NH_4Cl : MeOH (2 : 1)	**2a**	96
2	Pr^{i}I	H_2O : MeOH (2 : 1)		No reaction
3	Pr^{i}Br	Sat. NH_4Cl : MeOH (2 : 1)		No reaction
4	Bu^{s}I	Sat. NH_4Cl : MeOH (2 : 1)	**2b**	42
5	*c*-Pentyl I	Sat.NH_4Cl : MeOH (2 : 1)	**2c**	53
6	*c*-Hexyl I	Sat. NH_4Cl : MeOH (2 : 1)	**2d**	68
7	Bu^{t}I	Sat. NH_4Cl : MeOH (2 : 1)	**2e**	57

[a] Reactions were carried out with RX (5 eq.) and zinc (7 eq.) at 20 °C for 15 min. [b] Isolated yields.



Scheme 2 Possible reaction pathway.

We next investigated diastereoselective radical additions to oxime ether **3** which has camphorsultam as a chiral auxiliary (Scheme 3). In our previous study, the radical addition to oxime ether **3** proceeded with good diastereoselectivity using triethylborane as a radical initiator.[10a] Additionally, we recently

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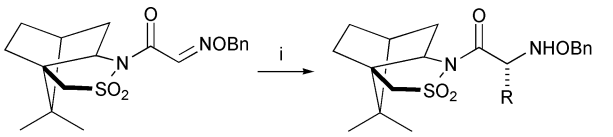


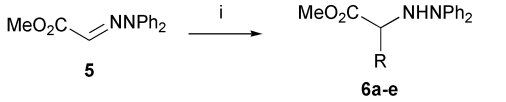
3 **4**

a : R = Pr^i , **c** : R = c-Pentyl, **e** : R = Bu^t

Scheme 3 Reagents and conditions: i) RI, Zn (7 eq.).

reported the indium-mediated radical addition to **3** in aqueous media.[8a,8b] Therefore, we expected that the comparison of zinc-mediated reactions with indium-mediated reactions would lead to insight into radical initiators such as triethylborane, indium and zinc. The biphasic reaction of **3** with an isopropyl radical in aqueous NH_4Cl–CH_2Cl_2 (2 : 1, v/v) proceeded smoothly to give **4a** in 63% yield, after being stirred for only 0.5 h (Table 2, entry 1). In the case of the indium-mediated reaction, the isopropylated product **4a** was obtained in 44% yield after being stirred in H_2O–CH_2Cl_2 for 72 h.[8b] These results indicate that zinc exhibits good reactivity as a radical initiator, although the zinc-mediated reactions need to be carried out under the acidic reaction conditions using sat. aqueous NH_4Cl. The diastereomeric ratio of **4a** was determined by ^{1}H NMR and was assumed to be 77% de. This is lower than the de obtained in the previous indium-mediated reactions.[8b] The major product could be easily isolated by preparative TLC. Based on our previous work,[10a] the absolute configuration at the newly formed stereocenter of the major product **4a** was assumed to be *R*.[11] The monophasic reaction of **3** in aqueous NH_4Cl–MeOH (2 : 1, v/v) proceeded slowly to give **4a** in 20% yield with 67% de (Table 2, entry 2). The reaction also proceeded effectively in the absence of organic cosolvent to give **4a** in 64% yield with 75% de (Table 2, entry 3). Lowering the temperature from 20 to 0 °C led to a moderate increase in diastereoselectivity, to 83% de (Table 2, entry 4). We have observed no remarkable effect of additive on either the chemical yield or stereoselectivity by employing CTAB, SDS and $Yb(OTf)_3$ (Table 2, entries 5–7). Not only the secondary cyclopentyl radical but also the bulky tertiary butyl radical worked well under similar reaction conditions to give the corresponding adducts **4c** and **4e** in good yields (Table 2, entries 8 and 9).

We next investigated zinc-mediated alkyl radical additions to glyoxylic hydrazone **5** (Scheme 4). The zinc-mediated reaction



5 **6a-e**

a : R = Pr^i , **b** : R = Bu^s , **c** : R = c-Pentyl
d : R = c-Hexyl, **e** : R = Bu^t

Scheme 4 Reagents and conditions: i) RI (5 eq. × 2), Zn (7 eq.), 20 °C, 1 h.

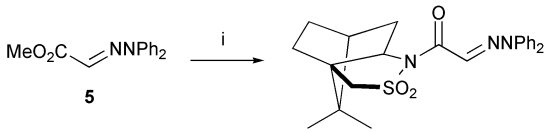
Table 3 Zinc-mediated radical additions to hydrazone **5**[a]

Entry	RX	Solvent	Product	Yield (%)[b]
1	Pr^{i}I	Sat. NH_4Cl : MeOH (2 : 1)	**6a**	92
2	Pr^{i}I	H_2O : MeOH (2 : 1)		No reaction
3	Bu^{s}I	Sat. NH_4Cl : MeOH (2 : 1)	**6b**	89
4	*c*-Pentyl I	Sat. NH_4Cl : MeOH (2 : 1)	**6c**	63 (30)
5	*c*-Hexyl I	Sat. NH_4Cl : MeOH (2 : 1)	**6d**	89 (10)
6	Bu^{t}I	Sat. NH_4Cl : MeOH (2 : 1)	**6e**	95

[a] Reactions were carried out with RI (5 eq. × 2) and zinc (7 eq.) at 20 °C. [b] Isolated yields; yields in parentheses are for the recovered starting material **5**.

of **5** with Pr^{i}I in aqueous NH_4Cl–MeOH proceeded smoothly to give 92% yield of **6a** after being stirred for 1 h (Table 3, entry 1). In contrast, no reaction took place in H_2O–CH_2Cl_2 (Table 3, entry 2). The zinc-mediated reaction of **5** with other radical precursors also proceeded to give the good yields of the products **6b–e** (Table 3, entries 3–6). These chemical yields were better than those obtained in the reaction of oxime ether **1**. In our previous study on the radical addition to hydrazone **5** using triethylborane the undesired *C*- and *N*-dialkylated products were obtained as a result of additional *N*-alkylation.[12] In contrast, the zinc-mediated radical addition to **5** proceeded selectively to give the desired *C*-monoalkylated products **6a–e** with no detection of *C*- and *N*-dialkylated products. A similar trend was observed in the reaction of **5** using indium.[8a] Thus, zinc and indium were found to be highly promising radical initiators for the radical reactions of hydrazones in aqueous media. Additionally, this methodology can be applied to the large-scale synthesis of α-amino acid derivatives. The isopropyl radical addition to 1 g of hydrazone **5** afforded the desired product **6a** in 91% yield.

The task of controlling the stereochemistry in radical additions to glyoxylic hydrazones is an achievable one. Therefore, we finally investigated the diastereoselective radical addition to hydrazone **7**, having the camphorsultam group as a chiral auxiliary. We expected that the bulky diphenyl amino group on the imino nitrogen atom of **7** would enhance the diastereoselectivities. The hydrazone **7** was easily prepared in 92% yield by condensation of glyoxylic hydrazone **5** with (1*R*)-(+)-2,10-camphorsultam in the presence of trimethylaluminum (Scheme 5).



5 **7**

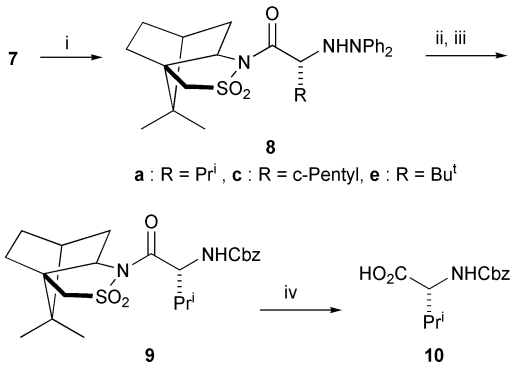
Scheme 5 Reagents and conditions: i) Me_3Al, (1*R*)-(+)-2,10-camphorsultam, CH_2ClCH_2Cl, reflux, 92%.

Table 2 Zinc-mediated radical additions to oxime ether **3**

Entry	RI	Solvent	Additive/eq.	Time/h	Yield (%)[d]	de (%)[e]
1[a]	Pr^{i}I	Sat. NH_4Cl : CH_2Cl_2 (2 : 1)	None	0.5	63	77
2[a]	Pr^{i}I	Sat. NH_4Cl : MeOH (2 : 1)	None	0.5	20	67
3[a]	Pr^{i}I	Sat. NH_4Cl	None	0.5	64	75
4[b]	Pr^{i}I	Sat. NH_4Cl	None	1	56	83
5[a]	Pr^{i}I	Sat. NH_4Cl	CTAB (0.2)	1	56	73
6[a]	Pr^{i}I	Sat. NH_4Cl	SDS (0.2)	1	47	72
7[a]	Pr^{i}I	Sat. NH_4Cl	$Yb(OTf)_3$ (1.0)	1	30	68
8[c]	*c*-Pentyl I	Sat. NH_4Cl	None	2	74	78
9[a]	Bu^{t}I	Sat. NH_4Cl	None	1	81	73

[a] Reactions were carried out with RI (5 eq.) and zinc (7 eq.) at 20 °C. [b] Reaction was carried out with Pr^{i}I (5 eq.) and zinc (7 eq.) at 0 °C. [c] Reaction was carried out with *c*-pentyl I (5 eq. × 2) and zinc (7 eq.) at 20 °C. [d] Isolated yields. [e] Diastereoselectivities were determined by ^{1}H NMR analysis.

The diastereoselective radical addition to hydrazone **7** was examined under several reaction conditions (Scheme 6). The biphasic reaction of **7** with an isopropyl radical in aqueous NH_4Cl–CH_2Cl_2 (4 : 1, v/v) proceeded slowly to give **8a** in 73% yield after being stirred for 22 h (Table 4, entry 1). Some starting material was also recoverd in 7% yield. As expected, the diastereoselectivity observed in the reaction of hydrazone **7** was better than that obtained in the reaction of oxime ether **3**, although the reaction of hydrazone **7** was slower than the reaction of oxime ether **3**. In contrast to the reaction of achiral hydrazone **5**, the monophasic reaction of **7** in aqueous NH_4Cl–MeOH (2 : 1, v/v) did not proceed effectively (Table 4, entry 2). In the absence of organic cosolvent, the product **8a** was obtained in 26% yield with 83% de after being stirred in sat. aqueous NH_4Cl for 48 h (Table 4, entry 3). This is in contrast to the reaction of oxime ether **3**. The major diastereomer **8a** could be easily isolated by preparative TLC. The absolute configuration at the newly formed stereocenter of major product **8a** was determined to be *R* by conversion into the known α-amino acid **10**. Thus, the stereochemical course of the diastereoselective radical addition to hydrazone **7** was found to be the same as that for the reaction of oxime ether **3**. The cleavage of the N–N bond of diastereomerically pure product **8a** was successfully achieved by hydrogenolysis in the presence of Pearlman catalyst and camphorsulfonic acid (CSA). Subsequently, protection with CbzCl and hydrolysis using 1 M LiOH gave *N*-Cbz-D-valine **10** in 61% yield from **8a** without any loss of optical purity. The cyclopentyl radical addition also worked well (Table 4, entry 4). In the case of *tert*-butyl radical addition, 84% yield of the desired product **8e** was obtained as a single diastereomer (Table 4, entry 5).



Scheme 6 Reagents and conditions: i) RI, Zn (7 eq.), 20 °C; ii) H_2, $Pd(OH)_2$/C, CSA, MeOH, 20 °C; iii) CbzCl, Na_2CO_3, acetone–H_2O, 0 °C (84%, 2 steps); iv) 1 M LiOH, THF, 20 °C (73%).

As shown in Fig. 1, the rotamer having the carbonyl group *anti* to the sulfonyl group would be favored in order to minimize dipole–dipole interactions between these groups. As suggested by the studies on the camphorsultam derivatives of glyoxylic acid,[13] it is expected that the sterically more stable *s-cis* planar conformation between the carbonyl group and the diphenylhydrazino group would be favored. This would lead to alkyl radical attack from α-face which is not hindered by the S–O group.

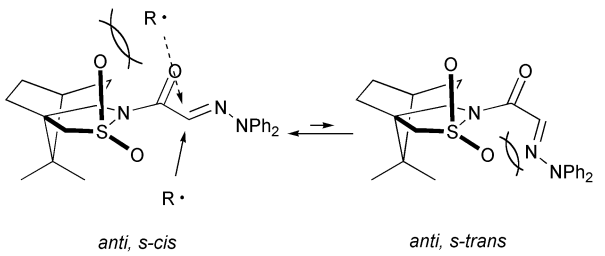


Fig. 1 Stereochemical feature.

In conclusion, we have established the diastereoselective zinc-mediated alkyl radical addition to imine derivatives such as oxime ethers and hydrazones in aqueous media. The reactions proceeded with good diastereoselectivities, providing access to potentially a large range of α-amino acids.

Experimental

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 500, 300, and 200 MHz and at 125, 75, and 50 MHz, respectively; chemical shifts are measured in ppm. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained using the EI method. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F254). Flash column chromatography was performed using E. Merck Kieselgel 60 (230–400 mesh). Optical rotations were recorded on a Jasco polarimeter with a path length of 1 cm; concentrations are quoted in mg (2 mL). $[\alpha]_D$ values were measured in 10^{-1} deg cm^2 g^{-1}.

General procedure for alkyl radical addition to glyoxylic oxime ether 1

To a micro tube containing **1** (50 mg, 0.26 mmol), RI (1.3 mmol), zinc (119 mg, 1.82 mmol) and MeOH (0.2 mL) was added dropwise aqueous sat. NH_4Cl (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 10 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 a reduced pressure. Purification of the residue by preparative TLC (hexane–AcOEt, 10 : 1) afforded **2a–e**[14] in the yields shown in Table 1.

General procedure for alkyl radical addition to chiral oxime ether 3

To a micro tube containing **3** (50 mg, 0.13 mmol), RI (0.65 mmol), zinc (59.5 mg, 0.91 mmol) and cosolvent (0.2 mL) was added dropwise aqueous sat. NH_4Cl (0.4 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 a reduced pressure. Purification of the residue by preparative TLC (hexane–AcOEt, 3 : 1) afforded **4a–e**[10a] in the yields shown in Table 2.

Table 4 Zinc-mediated radical additions to hydrazone **7**[a]

Entry	RI/eq.	Solvent	Time	Product	Yield (%)[b]	de (%)[c]
1	Pr^iI (5.0)	Sat. NH_4Cl : CH_2Cl_2 (4 : 1)	22	**8a**	73 (7)	86
2	Pr^iI (5.0 × 4)	Sat. NH_4Cl : MeOH (2 : 1)	4	**8a**	4 (86)	—
3	Pr^iI (10)	Sat. NH_4Cl	48	**8a**	26 (68)	83
4	*c*-Pentyl I (5.0)	Sat. NH_4Cl : CH_2Cl_2 (4:1)	22	**8c**	58 (40)	86
5	Bu^tI (5.0)	Sat. NH_4Cl : CH_2Cl_2 (4 : 1)	22	**8e**	84	>95

[a] Reactions were carried out with RI and zinc (7 eq.) at 20 °C. [b] Isolated yields; yields in parentheses are for the recovered starting material **7**. [c] Diastereoselectivities were determined by ^1H NMR analysis.

General procedure for alkyl radical addition to glyoxylic hydrazone 5

To a micro tube containing **5** (50 mg, 0.2 mmol), RI (2.0 mmol), zinc (92 mg, 1.4 mmol) and MeOH (0.2 mL) was added dropwise aqueous sat. NH_4Cl (0.4 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 a reduced pressure. Purification of the residue by preparative TLC (hexane–AcOEt, 5 : 1) afforded **6a–e** in the yields shown in Table 3.

2-(2,2-Diphenylhydrazino)-3-methylbutanoic acid methyl ester (6a). 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%.

2-(2,2-Diphenylhydrazino)-3-methylpentanoic acid methyl ester (6b). A 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.

α-(2,2-Diphenylhydrazino)cyclopentaneacetic acid methyl ester (6c). 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%.

α-(2,2-Diphenylhydrazino)cyclohexaneacetic acid methyl ester (6d). A white solid. IR ($CHCl_3$) 2932, 1731, 1589, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.30–6.98 (10H, m), 4.35 (1H, br s), 3.43 (3H, s), 3.41 (1H, br d), 1.96–1.92 (1H, m), 1.78–1.59 (5H, m), 1.27–1.09 (5H, m). ^{13}C NMR ($CDCl_3$) δ 174.1, 148.1, 129.0, 122.8, 121.0, 67.5, 51.3, 40.1, 29.8, 29.4, 26.2, 26.1. HRMS calcd for $C_{21}H_{26}N_2O_2$ (M^+) 338.2037, found 338.2015.

2-(2,2-Diphenylhydrazino)-3,3-dimethylbutanoic acid methyl ester (6e). 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.

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[(2*E*)-(diphenylhydrazono)acetyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (7). To a solution of (1*R*)-(+)-2,10-camphorsultam (1.0 g, 4.6 mmol) and **5** (1.8 g, 7.0 mmol) in CH_2ClCH_2Cl (60 mL) was added Me_3Al (1.0 M in hexane, 7.1 mL, 7.0 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 10 h, the reaction mixture was diluted with 36% potassium sodium (+)-tartrate and then extracted with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$ and concentrated at a reduced pressure. Purification by flash chromatography ($CHCl_3$–hexane, 10 : 1) afforded **7** (1.23 g, 61%). Colorless crystals. mp 226–227 °C (AcOEt–hexane). $[\alpha]_D^{21}$ +51 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3010, 2964, 1676, 1536, 1486 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45–7.21 (10H, m), 7.11 (1H, s), 4.01 (1H, dd, $J = 8$, 5.5 Hz), 3.41, 3.37 (each 1H, d, $J = 13.5$ Hz), 2.15–2.08 (2H, m), 1.91–1.86 (3H, m), 1.45–1.34 (2H, m), 1.14, 0.95 (each 3H, s). ^{13}C NMR ($CDCl_3$) δ 162.1, 129.9, 124.6, 65.4, 53.1, 48.6, 47.7, 44.8, 38.5, 32.9, 26.5, 21.0, 19.9. HRMS calcd for $C_{24}H_{27}N_3O_3S$ (M^+) 437.1772, found: 437.1773. Anal. calcd for $C_{24}H_{27}N_3O_3S$: C, 65.88; H, 6.22; N, 9.60; S, 7.33%. Found: C, 65.62; H, 6.19; N, 9.59; S, 7.49%.

General procedure for alkyl radical addition to chiral hydrazone 7

To a micro tube containing **7** (50 mg, 0.11 mmol), RI (0.55 mmol), zinc (50.3 mg, 0.77 mmol) and CH_2Cl_2 (0.1 mL) was added dropwise aqueous sat. NH_4Cl (0.4 mL) at 20 °C over 5 min. After being stirred at the same temperature for 22 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 a reduced pressure. Purification of the residue by preparative TLC (hexane–AcOEt, 3 : 1) afforded **8a–c** in the yields shown in Table 4.

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[(2*R*)-1-oxo-2-(2,2-diphenylhydrazino)-3-(methyl)butyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*)-8a]. Colorless crystals. Mp 145.5–146.5 °C (AcOEt–hexane). $[\alpha]_D^{23}$ +20.1 (*c* 1.00, $CHCl_3$). IR ($CHCl_3$) 3010, 2966, 1691, 1589, 1492 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.28–7.15 (10H, m), 4.59 (1H, br s), 4.17 (1H, br s), 3.64 (1H, dd, $J = 7.5$, 5 Hz), 3.42, 3.38 (each 1H, d, $J = 13.5$ Hz), 2.18–2.14 (1H, m), 1.97–1.82 (5H, m), 1.39–1.28 (2H, m), 1.16, 0.90 (each 3H, d, $J = 7$ Hz), 1.07, 0.93 (each 3H, s). ^{13}C NMR ($CDCl_3$) δ 173.6, 149.1, 129.0, 122.8, 121.5, 67.8, 65.0, 52.9, 48.5, 47.8, 44.4, 38.4, 32.8, 32.1, 26.4, 20.7, 20.6, 19.9, 16.3. HRMS calcd for $C_{27}H_{35}N_3O_3S$ (M^+) 481.2397, found 481.2402. Anal. calcd for $C_{27}H_{35}N_3O_3S$: C, 67.33; H, 7.32; N, 8.72; S, 6.66%. Found: C, 67.30; H, 7.40; N, 8.62; S, 6.88%.

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[(2*S*)-1-oxo-2-(2,2-diphenylhydrazino)-3-(methyl)butyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*S*)-8a]. A yellow solid. $[\alpha]_D^{23}$ +34.5 (*c* 1.15, $CHCl_3$). IR ($CHCl_3$) 3018, 2966, 1685, 1589, 1493 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27–7.12 (10H, m), 4.57 (1H, br s), 4.05 (1H, d, $J = 4.5$ Hz), 3.75 (1H, dd, $J = 7.4$, 4.2 Hz), 3.41, 3.34 (each 1H, d, $J = 13.8$ Hz), 2.20–2.09 (1H, m), 1.92–1.70 (5H, m), 1.36–1.26 (2H, m), 1.13, 1.00 (each 3H, d, $J = 6.9$ Hz), 0.88, 0.85 (each 3H, s). ^{13}C NMR ($CDCl_3$) δ 173.8, 148.7, 129.0, 122.7, 121.1, 66.9, 65.6, 53.0, 48.2, 47.6, 44.5, 38.5, 33.0, 30.1, 26.3, 21.0, 19.8, 16.9. HRMS calcd for $C_{27}H_{35}N_3O_3S$ (M^+) 481.2397, found 481.2404.

(3a*R*,6*S*,7a*S*)-1-[(2*R*)-2-Cyclopentyl-2-(2,2-diphenylhydrazino)-acetyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*)-8c]. A colorless oil. $[\alpha]_D^{24}$ +39.5 (*c* 1.04, $CHCl_3$). IR ($CHCl_3$) 2961, 1692, 1589, 1493 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.97 (10H, m), 4.60 (1H, br s), 4.28 (1H, br s), 3.66 (1H, t, $J = 6.3$ Hz), 3.43, 3.37 (each 1H, d, $J = 13.5$ Hz), 2.30–2.22 (1H, m), 1.98–1.26 (15H, m), 1.08, 0.93 (each 3H, s). ^{13}C NMR ($CDCl_3$) δ 174.0, 149.1, 128.9, 122.7, 121.4, 65.6, 65.1, 53.0, 48.3, 47.7, 44.4, 43.3, 38.3, 32.8, 29.2, 27.9, 26.4, 25.5, 25.4, 20.6, 19.9. HRMS calcd for $C_{29}H_{37}N_3O_3S$ (M^+) 507.2553, found 507.2565.

((3a*R*,6*S*,7a*S*)-1-[(2*S*)-2-Cyclopentyl-2-(2,2-diphenylhydrazino)acetyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*S*)-8c]. A yellow solid. IR ($CHCl_3$) 2959, 1691, 1589, 1493 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27–6.96 (10H, m), 4.42 (1H, br s), 4.15 (1H, br d, $J = 6.3$ Hz), 3.82–3.77 (1H, m), 3.41, 3.34 (each 1H, d, $J = 13.8$ Hz), 2.35–2.28 (1H, m), 1.94–1.25 (15H, m), 0.86, 0.80 (each 3H, s). HRMS calcd for $C_{29}H_{37}N_3O_3S$ (M^+) 507.2554, found 507.2548.

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[(2*R*)-3,3-dimethyl-1-oxo-2-(2,2-diphenylhydrazino)butyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*)-8e]. A colorless oil. $[\alpha]_D^{24}$ +50.6 (*c* 1.11, $CHCl_3$). IR ($CHCl_3$) 2958, 1685, 1589, 1467 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29–6.97 (10H, m), 4.63 (1H, br s), 4.11 (1H, s), 3.66 (1H, t, J = 6.3 Hz), 3.43, 3.37 (each 1H, d, J = 13.5 Hz), 2.05–2.01 (2H, br m), 1.93–1.81 (3H, br m), 1.35–1.20 (3H, br m), 1.08 (12H, m), 0.93 (each 3H, s). ^{13}C NMR ($CDCl_3$) δ 174.1, 149.3, 128.7, 122.6, 121.4, 69.3, 65.9, 53.2, 47.6, 47.5, 44.5, 38.6, 35.8, 33.2, 27.1, 26.4, 20.6, 20.0. HRMS calcd for $C_{28}H_{37}N_3O_3S$ (M^+) 495.2554, found 495.2546.

[(1*R*)-2-Methyl-1-[[(3a*R*,6*S*,7a*S*)-tetrahydro-8,8-dimethyl-2,2-dioxide-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]carbonyl]-propyl]carbamic acid 2,2-dioxide phenylmethyl ester (9). A suspension of 20% $Pd(OH)_2/C$ (208 mg) in MeOH (5 mL) was stirred under a hydrogen atmosphere (1 atm) at 20 °C for 45 min. To this suspension was added a solution of (*R*)-**8a** (100 mg, 0.20 mmol) and 10-camphorsulfonic acid (100 mg, 0.40 mmol) in MeOH (10 mL). After being stirred under a hydrogen atmosphere at the same temperature for 30 min, the reaction mixture was filtered and the filtrate was concentrated at a reduced pressure to afford the crude amine. To a solution of the resulting crude amine in acetone (5 mL) was added a solution of Na_2CO_3 (106 mg, 1.00 mmol) in H_2O (2 mL) under a nitrogen atmosphere at 20 °C. After a solution of benzyloxycarbonyl chloride (0.9 mL, 0.60 mmol) in acetone (1 mL) was added to the reaction mixture at 20 °C, the reaction mixture was stirred at the same temperature for 5 h. After the reaction mixture was concentrated at a reduced pressure, the resulting residue was diluted with CH_2Cl_2 and water and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at a reduced pressure. Purification by preparative TLC (hexane–AcOEt, 4 : 1) afforded **9** (75.1 mg, 84%). Colorless crystals. Mp 169–170 °C (AcOEt–hexane). $[\alpha]_D^{29}$ +62 (*c* 1.50, $CHCl_3$). IR ($CHCl_3$) 3010, 2966, 1691, 1589, 1492 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41–7.29 (5H, m), 5.35 (1H, br d, J = 9 Hz), 5.14, 5.08 (each 1H, br d, J = 12 Hz), 4.94 (1H, br dd, J = 9, 3 Hz), 3.91 (1H, br t, J = 6 Hz), 3.49, 3.47 (each 1H, br d, J = 14 Hz), 2.29 (1H, br m), 2.08 (1H, dd, J = 13.5), 2.03–1.85 (4H, br m), 1.46–1.32 (2H, m), 1.13, 0.97 (each 3H, s), 1.04, 0.80 (each 3H, d, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 171.9, 156.0, 136.4, 128.5, 128.2, 128.1, 67.1, 64.9, 59.1, 53.0, 48.6, 47.8, 44.6, 38.4, 32.8, 32.0, 26.5, 20.6, 19.9, 19.8, 15.9. HRMS calcd for $C_{23}H_{32}N_2O_5S$ (M^+) 448.2030, found 448.2031. Anal. calcd for $C_{23}H_{32}N_2O_5S$: C, 61.61; H, 7.14; N, 6.25; S, 7.14%. Found: C, 61.6; H, 7.24; N, 6.25; S, 7.34%.

***N*-[(Phenylmethoxy)carbonyl]-D-valine (10).** A solution of **9** (174 mg, 0.39 mmol) in 1 N LiOH–THF (1:4, 10 mL) was stirred at room temperature for 4 h. After the reaction mixture was concentrated at a reduced pressure, the resulting residue was diluted with water, acidified to a pH between 4 and 5 with diluted HCl, then extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at a reduced pressure. Purification of the residue by flash column chromatography (hexane–AcOEt, 1 : 2) afforded **10** (71 mg, 73%). A colorless oil. $[\alpha]_D^{27}$ +5.6 (*c* 1.78, $CHCl_3$). IR ($CHCl_3$) 3438, 1715, 1456 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.39–7.28 (5H, m), 5.27 (1H, br m), 5.12, 5.11 (each 1H, br d, J = 12 Hz), 4.34 (1H, br m), 2.22 (1H, br m), 1.00, 0.93 (each 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 176.2, 156.4, 136.2, 128.6, 128.3, 128.2, 67.2, 58.9, 31.0, 19.0, 17.4. HRMS calcd for $C_{13}H_{17}N_2O_4$ (M^+) 251.1157, found 251.1152.

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