Asymmetric Synthesis of α-Amino Acids Based on Carbon Radical Addition to Glyoxylic Oxime Ether

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The first asymmetric synthesis of α-amino acids based on diastereoselective carbon radical addition to glyoxylic imine derivatives is reported. The addition of an isopropyl radical, generated from *i*-PrI, Bu_3SnH, and Et_3B in CH_2Cl_2 at 25 °C, to achiral glyoxylic oxime ether **1** proceeded regioselectively at the imino carbon atom of the oxime ether group to give an excellent yield of the C-isopropylated product **2**. The competitive reaction using glyoxylic oxime ether **1** and aldoxime ether **4** showed that the reactivity of the glyoxylic oxime ether toward nucleophilic carbon radicals was enhanced by the presence of a neighboring electron-withdrawing substituent. Thus, the alkyl radical addition to glyoxylic oxime ether **1** proceeded smoothly even at −78 °C, in contrast to the unactivated aldoxime ether **4**. A high degree of stereocontrol in the carbon radical addition to the glyoxylic oxime ether was achieved by using Oppolzer's camphorsultam as a chiral auxiliary. The stannyl radical-mediated reaction of the camphorsultam derivative **6** with an isopropyl radical at −78 °C afforded a 96:4 diastereomeric mixture, **7a**, of the C-isopropylated product. The reductive removal of the benzyloxy group of the major diastereomer (*R*)-**7a**, by treatment with $Mo(CO)_6$ and the subsequent removal of the sultam auxiliary by standard hydrolysis, afforded the enantiomerically pure D-valine (*R*)-**12** without any loss of stereochemical purity. To evaluate the new methodology, a variety of alkyl radicals were employed in the addition reaction which gave the alkylated products **7** with excellent diastereoselectivity, allowing access to a wide range of enantiomerically pure natural and unnatural α-amino acids. Even in the absence of Bu_3SnH, treatment of **6** with alkyl iodide and Et_3B at 20 °C gave the C-alkylated products **7** with moderate diastereoselectivities. The use of Et_2Zn as a radical initiator, instead of Et_3B, was also effective for the radical reaction. The enantioselective isopropyl radical addition to **1** using (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) and $MgBr_2$ gave excellent chemical yield of the valine derivative **2** in 52% ee.

Introduction

The control of stereochemistry in free radical mediated reactions has been of great importance to organic synthesis.[1] Hence, in recent years, a high degree of stereocontrol in radical reactions has been achieved, mainly in the radical conjugate addition to the carbon−carbon double bond of α,β-unsaturated carbonyl compounds, the radical allyl-transfer reaction using allylstannane, the reduction of alkyl halides using tributyltin hydride, and so on.[2−9] Asymmetric induction, particularly in the carbon−carbon bond-forming radical reactions of acyclic systems, is a subject of current interest.[1] We are interested in the stereocontrol of carbon−carbon bond-forming reactions based on the intermolecular carbon radical addition to a carbon−nitrogen double bond of acyclic imine derivatives.

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.[10] However, studies on the radical reaction of oxime ethers have concentrated on intramolecular reactions,[10] and the difficulty in achieving the intermolecular con-

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struction of a carbon−carbon bond has remained unresolved.[11−13] Therefore, stereoselective carbon−carbon bond formation based on the intermolecular carbon radical addition to oxime ethers is a challenging and promising task. Hart's group reported the first studies on intermolecular alkyl radical additions to unhindered *O*-benzylformaldoxime ethers.[11a] Recently, intermolecular radical-mediated acylation using an α-sulfonyl oxime ether has been reported by Kim's group.[12] In the course of our investigations of the intramolecular radical reaction of oxime ethers,[14] we have succeeded in the development of new efficient carbon−carbon bond-forming reactions based on intermolecular radical additions to BF_3-activated aldoxime ethers.[15] This procedure is particularly useful for the synthesis of a variety of primary amines because of the exceptional tolerance of the functional groups, such as aromatic heterocycle, alcohol, acetal, ester, and amide moieties. We report here, in detail, the diastereofacial stereocontrol in the carbon radical addition to Oppolzer's camphorsultam derivatives of glyoxylic oxime ethers.[16] This reaction is the first reported example of stereocontrol in the intermolecular carbon radical addition to glyoxylic imine derivatives and is a convenient method for preparing a wide range of enantiomerically enriched α-amino acids.[17,18]

Results and Discussion

Carbon Radical Addition to Glyoxylic Oxime Ethers. Glyoxylic imine derivatives are convenient starting materials for the synthesis of natural and unnatural α-amino acids and related compounds through ene reactions, cycloadditions, or the nucleophilic additions of organometallic reagents or enolate anion equivalents.[19,20] Because glyoxylic imines have three electrophilic centers, the nucleophilic addition of traditional organometallic reagents takes place nonregioselectively at the imino carbon and nitrogen atoms of the carbon−nitrogen double bond, to give a mixture of C- and N-alkylated products.[21] The few known examples of the regioselective nucleophilic addition of organometallic reagents to the imino carbon atom of glyoxylic imines are limited to methods using allyl zinc, stannane, or boron reagents and alkenyl/aryl boronic acids.[22−24] These reactions proceed under mild conditions to give the corresponding α-amino acids in high yield with high levels of stereoselectivity; however, it is important to note that aliphatic α-amino acids would not be readily synthesized by applying these methods. Thus, we have explored the intermolecular carbon radical addition to glyoxylic oxime ethers as an alternative synthetic route to allow ready access to a wide range of aliphatic α-amino acids (Figure 1).[25]

Prior to exploring issues of stereocontrol, we investigated the regioselectivity in the intermolecular carbon radical addition to achiral glyoxylic oxime ether **1**.[26] At first, we examined the addition of an isopropyl radical to oxime ether **1** (Scheme 1). The reaction was run in dichloromethane at 25 °C for 5 min by the use of *i*-PrI

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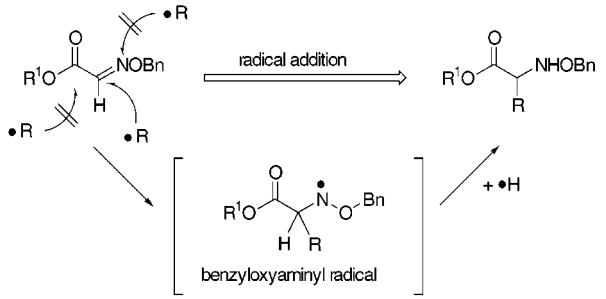
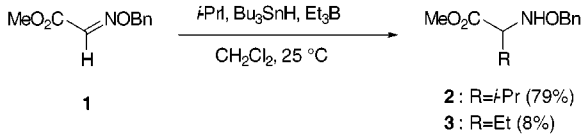


Figure 1. Radical addition to glyoxylic oxime ether.

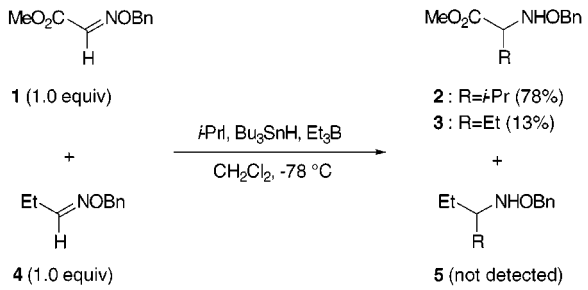
Scheme 1



(5.0 equiv), Bu_3SnH (2.5 equiv), and commercially available 1.0 M solution of Et_3B in hexane (5.0 equiv) as a radical initiator. As expected, the radical addition took place regioselectively at the imino carbon to give the desired C-isopropylated product **2** in 79% yield.[27] This is a representative example of an aliphatic α-amino acid derivative, which would be difficult to prepare by the nucleophilic addition involving organometallic reagents.[21−24] Only an 8% yield of the C-ethylated product **3** was formed as the result of a competitive reaction with the ethyl radical generated from Et_3B and O_2. We could not detect N-alkylated products, which may be formed by the Michael-type addition reaction of an alkyl radical to the imino nitrogen atom of oxime ether **1**. These results suggest that the radical addition to glyoxylic oxime ethers is not only a highly promising approach to the synthesis of α-amino acids but also complements the nucleophilic addition of organometallic reagents.

To learn about the intermolecular reactivity of oxime ether **1** with nucleophilic carbon radicals, we carried out competitive reactions employing two types of oxime ethers, **1** and **4** (Scheme 2). Treatment of a 1:1 mixture of glyoxylic oxime ether **1** and aldoxime ether **4**[15] with *i*-PrI (1.1 equiv), Bu_3SnH (1.1 equiv), and Et_3B (1.1 equiv) in CH_2Cl_2 at −78 °C for 30 min gave the isopropylated product **2** (78% yield) and the ethylated product **3**[15] (13% yield) with no detection of the other possible adduct, **5**. Thus, the addition of an alkyl radical to **4** did not take place, and 90% of the starting compound **4** was recovered. In our more recent studies, we also found that the alkyl radical addition to aldoxime ether **4** proceeded smoothly in the presence of $BF_3{\cdot}OEt_2$ to give the alkylated benzyloxyamines in high yields.[15] These results show that the reactivity of glyoxylic oxime ether **1** toward nucleophilic carbon radicals is enhanced by the neighboring electron-withdrawing substituent, which would lower the LUMO energy of the oxime ether as a radical acceptor.[28] Thus, the alkyl radical addition to glyoxylic oxime ether **1** proceeded smoothly even at −78 °C, in contrast to the unactivated aldoxime ether **4**.

Scheme 2



Diastereoselective Carbon Radical Addition to Camphorsultam Derivative of Glyoxylic Oxime Ether. Recent reports elucidate that control of the stereochemistry is possible in free radical reactions, even those found in acyclic systems.[1−9] Of the chiral auxiliaries used in acyclic systems, Oppolzer's camphorsultam, which is commercially available in both enantiomers and is easily removed after use, has been employed extensively in ionic and thermal cycloaddition reactions.[30−33] We selected Oppolzer's camphorsultam derivative of glyoxylic oxime ether **6** as a radical acceptor which would be flexible enough to allow access to a wide range of natural and unnatural α-amino acids. Additionally, camphorsultam derivative **6** was recently used in the asymmetric synthesis of α-allylated α-amino acids by using allyl zinc reagents.[22] Therefore, we also expected that the direct comparison of the radical reactions of **6** with the related ionic reactions would lead to informative and instructive suggestions regarding stereoselection in the addition reactions.

Compound **6** was readily prepared by treatment of oxime ether **1** with the commercially available (1*R*)-(+)-2,10-camphorsultam in the presence of trimethyl aluminum in boiling dichloroethane in 90% yield as a single *E* isomer (Scheme 3).[29] The reaction of **6** with *i*-PrI, Bu_3SnH, and Et_3B in CH_2Cl_2 at 20 °C proceeded smoothly to give an 86:14 diastereomeric mixture of the desired

(26) Glyoxylic oxime ether **1** was prepared by the treatment of commercially available methyl 2-hydroxy-2-methoxyacetate with benzyloxyamine hydrochloride in the presence of sodium acetate in methanol. Oxime ether **1** was obtained as a single *E* isomer with respect to the geometry of the oxime ether group. See: ref 15b.

(27) For the complete reaction, the excesses of reagents were employed. The reactions were run without any special precautions such as drying, degassing, or purification of solvents and reagents. The reaction would proceed as follows: (1) The stannyl radical, generated from Bu_3SnH and Et_3B, reacted with *i*-PrI to generate an isopropyl radical. (2) The isopropyl radical then intermolecularly attacked glyoxylic oxime ether **1** to afford the intermediate benzyloxyaminyl radical as shown in Figure 1.

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Scheme 3

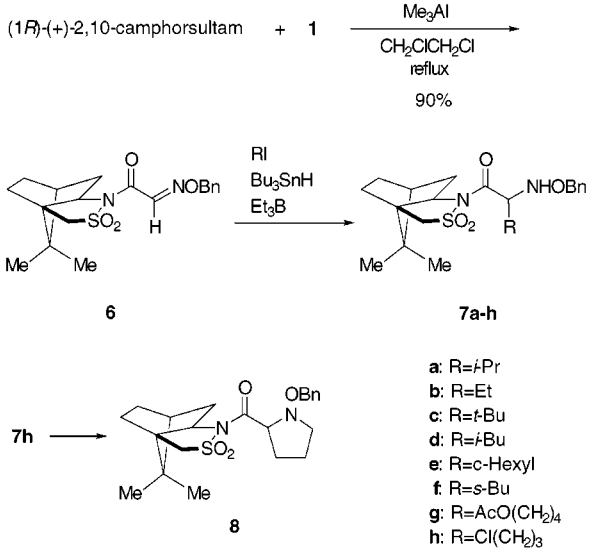


Table 1. Isopropyl Radical Addition to 6 by using Et_3B[a]

entry	Lewis acid[b]	solvent	*T* (°C)	yield[c] (%)	selectivity[d]
1		CH_2Cl_2	+20	76	86:14
2		CH_2Cl_2	−78	73	94:6
3		toluene	−78	74	93:7
4		Et_2O	−78	71	96:4
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	80	96:4
6	Et_2AlCl	CH_2Cl_2	−78	57	90:10
7	$Zn(OTf)_2$	CH_2Cl_2	−78	81	94:6
8	$Zn(OTf)_2$	CH_2Cl_2, THF	−78	73	91:9
9	$Yb(OTf)_3$	CH_2Cl_2	−78	74	92:8
10	$Yb(OTf)_3$	CH_2Cl_2, THF	−78	72	86:14

[a] All reactions were carried out with *i*-PrI (5.0 equiv), Bu_3SnH (2.5 equiv), and Et_3B (5.0 equiv). [b] 2 equiv of Lewis acid was used. [c] Isolated yields of major diastereomer **7a**; A small amount of the ethylated product **7b** was also obtained. [d] Diastereoselectivities were determined by ^1H NMR analysis.

C-alkylated product **7a** accompanied by a small amount of the C-ethylated product **7b** (Table 1, entry 1). Diastereoselectivity was determined by ^1H NMR analysis of the alkylated products obtained after rough purification to remove the tin residue from the reaction mixture. Diastereomer **7a** could be separated and purified by preparative TLC to afford the pure major isomer in 76% yield. To optimize the reaction conditions, we then investigated the effect of temperature, solvent, and Lewis acid on the reaction. The degree of stereoselectivity was shown to be dependent on the reaction temperature; thus, changing the temperature from +20 to −78 °C led to a moderate increase in diastereoselectivity to 94:6 (Table 1, compare entry 1 with entry 2). The replacement of CH_2Cl_2 with Et_2O as a solvent led to higher selectivity (Table 1, entry 4). These diastereoselectivities were comparable to or better than that obtained by the known addition of allyl zinc reagents to glyoxylic oxime ether **6**.[22] Curran has shown that high levels of stereoselectivity can be obtained in the reaction of chiral α-carbonyl radicals derived from camphorsultam.[8] We have now demonstrated that high stereoselectivity can be achieved in radical additions to the α-imino carbon atom on a camphorsultam derivative of oxime ether **6**. Although the addition of Lewis acids as an additive did not dramatically influence the degree of stereoselectivity, the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 slightly enhanced chemical yields (Table 1, entry 5). We have reported that $BF_3{\cdot}OEt_2$ is an effective Lewis acid for the activation of the carbon−nitrogen double bond of oxime ethers in radical reactions.[15] The current observations suggest that oxime ether **6** would be activated by $BF_3{\cdot}OEt_2$. Additionally, CH_2Cl_2 and toluene were found to be most effective as solvents for the present radical reaction.

Table 2. Isopropyl Radical Addition to 6

		product **7a**		product **7b**	
entry	method[a]	yield (%)[b]	selectivity[c]	yield (%)[b]	selectivity[c]
1	A	28	94:6	48	93:7
2	B	66	80:20		
3	C	no reaction			

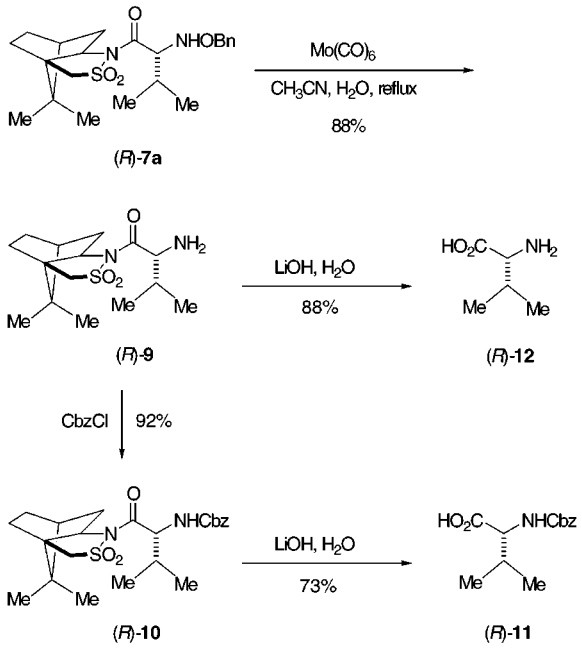
[a] Methods A−C. Reagents and conditions: Method A, *i*-PrI (5.0 equiv), $(Me_3Si)_3SiH$ (2.5 equiv), Et_3B (5.0 equiv), CH_2Cl_2, −78 °C.; Method B, *i*-PrI (3.5 equiv), Bu_3SnH (2.2 equiv), AIBN (0.2 equiv), toluene, reflux.; Method C, *i*-PrI (3.5 equiv), Bu_3SnH (2.2 equiv), 9-BBN (5.0 equiv), CH_2Cl_2, 20 °C. [b] Isolated yields of major diastereomer **7a**,**b**. [c] Diastereoselectivities were determined by ^1H NMR analysis.

Next, we examined the addition of an isopropyl radical to **6** under different reaction conditions. Treatment of **6** with *i*-PrI (5.0 equiv) and Et_3B (5.0 equiv) in the presence of $(Me_3Si)_3SiH$ (2.5 equiv) gave a 94:6 diastereomeric mixture of **7a** in 28% combined yield along with a significant amount of the ethylated product **7b** (Table 2, entry 1). From the result, it was ascertained that the use of Bu_3SnH is effective to achieve successful alkylation. Low diastereoselectivity was observed in the reaction of **6** with *i*-PrI and Bu_3SnH in the presence of AIBN (0.2 equiv) in boiling toluene to afford an 80:20 diastereomeric mixture of **7a** in 66% yield (Table 2, entry 2). Because 9-BBN has been reported to potentially induce a stannyl radical-mediated reaction,[34] we attempted the reaction using *i*-PrI, Bu_3SnH, and 9-BBN as a radical initiator, which however, did not proceed (Table 2, entry 3). Thus, both the stannyl radical-mediated generation of an alkyl radical from Et_3B and a low reaction temperature are important for obtaining high selectivity.

The absolute configuration at the newly formed stereocenter of the major product of mixture **7a** was determined to be *R* by converting the diastereomerically pure major isomer of **7a** into the authentic *N*-Cbz-D-valine **11** (Scheme 4).[35] The reductive cleavage of the N−O bond of (*R*)-**7a** by treatment with $Mo(CO)_6$ in boiling CH_3CN/H_2O gave the amine hydrochloride (*R*)-**9** in 88% yield.[36] The amine was protected as the *N*-Cbz derivative (*R*)-**10** in 92% yield by treatment with CbzCl. Mild hydrolysis of (*R*)-**10** with LiOH in THF/H_2O afforded the enantiomerically pure *N*-Cbz-D-valine (*R*)-**11** in 73% yield, which was found to be identical to an authentic sample, upon comparison of their spectral data and optical rotations.[35] D-Valine (*R*)-**12** itself was also obtained by the reductive removal of the benzyloxy group of (*R*)-**7a** followed by the subsequent removal of the sultam auxiliary by standard hydrolysis without any loss of stereochemical purity. It is noteworthy that the absolute stereochemical couse of the radical addition to the oxime ether **6** is the same as that for the allylation by the addition of zinc reagents to **6**.[22]

(34) Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron Lett.* **1998**, *39*, 5437−5438.
(35) (a) Oki, K.; Suzuki, K.; Tuchida, S.; Saito, T.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2554−2558. (b) Sarges, R.; Witkop, B. *J. Am. Chem. Soc.* **1965**, *87*, 2020−2027.
(36) (a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna. A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354. (b) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401−1406.

Scheme 4



Scheme 5

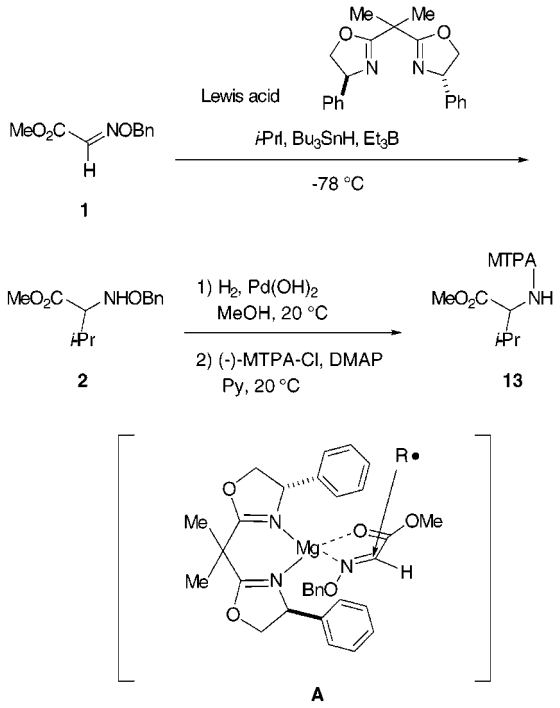


Table 3. Diastereoselective Alkyl Radical Addition to 6[a]

entry	RI	Lewis acid[b]	solvent	product (% yield[c])	selectivity[d]
1	EtI		Et_2O	**7b** (54)	96:4
2	EtI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**7b** (80)	95:5
3	*t*-BuI		Et_2O	**7c** (25)[e]	>98:2
4	*t*-BuI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**7c** (83)[e]	>98:2
5	*i*-BuI		Et_2O	**7d** (39)[e]	97:3
6	*i*-BuI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**7d** (83)[e]	97:3
7	c-HexylI		Et_2O	**7e** (74)[e]	96:4
8	c-HexylI	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**7e** (86)[e]	96:4
9	*s*-BuI		CH_2Cl_2	**7f** (69)[e]	>98:2
10	$AcO(CH_2)_4I$		CH_2Cl_2	**7g** (41)[f]	>98:2
11	$Cl(CH_2)_3I$		CH_2Cl_2	**8** (15)[f]	>98:2

[a] All reactions were carried out with RX (5.0 equiv), Bu_3SnH (2.5 equiv), and Et_3B (5.0 equiv) at −78 °C. [b] 2 equiv of Lewis acid was used. [c] Isolated yields of major diastereomer (*R*)-**7b**−**8**. [d] Diastereoselectivities were determined by ^1H NMR analysis. [e] A small amount of the ethylated product **7b** was also obtained. [f] A substantial amount of the ethylated product **7b** was obtained in 55% (entry 10) and 69% (entry 11) yields, respectively.

Excellent chemical yield and high diastereoselectivity were also obtained in the addition of different radical precursors to **6** (Table 3).[37] The reaction was run in CH_2Cl_2 or Et_2O at −78 °C for 30 min by the use of RI (5.0 equiv), Bu_3SnH (2.5 equiv), and commercially available 1.0 M solution of Et_3B in hexane (5.0 equiv). Not only did the secondary alkyl radicals, such as *sec*-butyl and cyclohexyl radicals, work well, but the bulky *tert*-butyl in CH_2Cl_2 radical also worked well (Table 3, entries 3−9). Modest chemical yields were obtained in reactions using functionalized primary alkyl radicals such as 4-acetoxybutyl and 3-chloropropyl radicals because of the competitive formation of a significant amount of the ethylated byproduct **7b** (Table 3, entries 10 and 11). Expecting that the addition of radicals generated from multifunctionalized precursors would yield products that would serve as more synthetically useful building blocks, we investigated the reaction employing bifunctional halides as alkyl radical precursors. As was expected from the nature of the radical reaction, alkyl iodides containing an ester moiety or a chlorine atom underwent the addition reactions to give the corresponding functionalized α-amino acid derivatives (*R*)-**7g** and (*R*)-**8** in 41 and 15% yields, respectively (Table 3, entries 10 and 11). In the case of 1-chloro-3-iodopropane, the proline derivative (*R*)-**8** was obtained as a result of the concomitant intramolecular *N*-alkylation of (*R*)-**7h** which was formed as an intermediate.

Chiral Lewis Acid-Catalyzed Enantioselective Carbon Radical Addition to Glyoxylic Oxime Ether. We next investigated the enantioselective radical addition to oxime ether **1** in the presence of chiral Lewis acids (Scheme 5). Several combinations of chiral ligands and Lewis acids were initially evaluated. The isopropyl radical addition to **1** was run in CH_2Cl_2 at −78 °C by using *i*-PrI, Bu_3SnH, and Et_3B in the presence of chiral ligand and Lewis acid, and then the enantiomeric purity of **2** was checked by chiral column chromatography (Chiral Pack OJ column) eluting with ethanol/hexane (15:85, v/v). The results obtained by using (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) as a chiral ligand are shown in Table 4. Excellent chemical yield and moderate enantioselectivity were obtained when a stoichiometric amount of a chiral ligand and $MgBr_2$ in CH_2Cl_2 was employed (Table 4, entry 4). In this combination, the replacement of CH_2Cl_2 with toluene or diethyl ether as a solvent led to lower selectivity (Table 4, entries 5 and 6). The absolute configuration at the stereocenter of the major enantiomer was determined to be *R* by converting the adduct **2** into the MTPA derivative **13**. Hydrogenolysis of the benzyloxyamino group of **2** in the presence of $Pd(OH)_2$ in MeOH followed by *N*-acylation of the resulting crude amine with (*R*)-2-methoxy-2-(trifluoromethyl)-phenylacetyl ((−)-MTPA) chloride afforded the MTPA derivative **13**. A *re* face radical addition to complex **A** accounts for the observed absolute configuration of the product **2**.

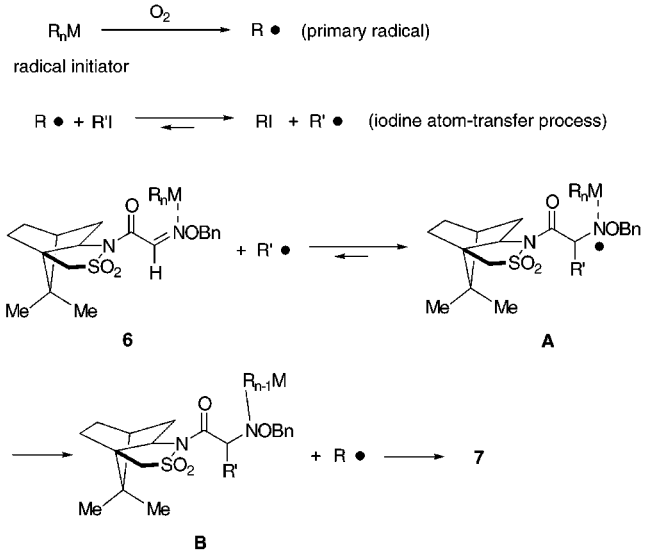
(37) The absolute configuration of major products **7b**−**g** and **8** was assigned to have *R*-configuration since their ^1H NMR data were similar to that of (*R*)-**7a**.

Table 4. Enantioselective Isopropyl Radical Addition to 1[a]

entry	Lewis acid[b]	solvent	yield (%)[c]	ee (%)[d]	config
1	$Zn(OTf)_2$	CH_2Cl_2	73	10	*R*
2	$Yb(OTf)_3$	CH_2Cl_2	92	24	*R*
3	$Mg(OTf)_2$	CH_2Cl_2	85	2	*R*
4	$MgBr_2$	CH_2Cl_2	97	52	*R*
5	$MgBr_2$	Et_2O	98	13	*R*
6	$MgBr_2$	toluene	98	10	*R*

[a] All reactions were carried out with *i*-PrI (10 equiv), Bu_3SnH (5 equiv), and Et_3B (10 equiv). [b] 1 equiv amounts of Lewis acid and of chiral ligand were used. [c] Isolated yields. [d] Stereoselectivities were determined by chiral HPLC analysis using Chiralcel OJ (Daicel Chemical Industries, LTD.) eluting with ethanol/hexane (15:85, v/v).

Scheme 6



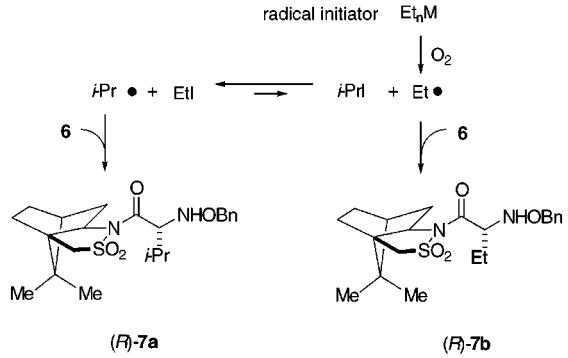
Carbon Radical Addition in the Absence of Tin Hydride. Free radical synthetic methods largely relied on toxic organomercury or organotin chemistry. From economical and ecological points of view, we next investigated the radical addition to oxime ether **6** in the absence of Bu_3SnH (Scheme 6).[38] Recently, Ryu and Komatsu reported that a diethylzinc−air system can serve as an initiator of tin hydride-mediated radical reaction.[39] To test the viability of Et_3B and Et_2Zn, we first investigated the simple addition of an ethyl radical, generated from Et_3B or Et_2Zn and O_2, to oxime ether **6** (Table 5). In the absence of Bu_3SnH, treatment of **6** with Et_3B (5.0 equiv) in CH_2Cl_2 at 20 °C for 5 min gave an 89:11 diastereomeric mixture of **7b** in 82% yield (Table 5, entry 1). Changing the temperature from +20 to −78 °C led to a moderate increase in diastereoselectivity to 94:6 (Table 5, compare entry 1 with entry 2). The replacement of CH_2Cl_2 with toluene as a solvent was also effective for the reaction (Table 5, entry 3). A commercially available 1.0 M solution of Et_2Zn in hexane was added to a solution of oxime ether **6** in CH_2Cl_2, and then the reaction mixture was stirred at 20 °C for 5 min. A

Table 5. Ethyl Radical Addition to 6[a]

				product **7b**	
entry	initiator	solvent	*T* (°C)	yield (%)[b]	selectivity[c]
1	Et_3B	CH_2Cl_2	+20	82	89:11
2	Et_3B	CH_2Cl_2	−78	99	94:6
3	Et_3B	toluene	−78	98	93:7
4	Et_3Zn	CH_2Cl_2	+20	76	79:21
5	Et_3Zn	CH_2Cl_2	−78	84	92:8
6	Et_2Zn	toluene	+20	83	69:31
7	Et_2Zn	toluene	−78	99	86:14
8	Me_2Zn	CH_2Cl_2	−78	no reaction (71)[d]	
9	Me_2Zn	toluene	+20	no reaction (73)[d]	
10	Me_2Zn	toluene	−78	no reaction (99)[d]	

[a] All reactions were carried out with radical initiator (5.0 equiv). [b] Combined yields of diastereomers. [c] Diastereoselectivities were determined by ^1H NMR analysis. [d] Yields in parentheses are for the recovered starting material.

Scheme 7



79:21 diastereomeric mixture of **7b** was obtained in 76% yield (Table 5, entry 4). Although the use of Et_2Zn led to a small decrease in diastereoselectivity, it is noteworthy that the reaction proceeded even at −78 °C (Table 5, entries 5 and 7). These observations suggest that Et_2Zn acts as well as Et_3B in its utility as a radical initiator, Lewis acid, and radical terminator. Surprisingly, the reaction using Me_2Zn did not take place and the starting compound **6** was recovered (Table 5, entries 8−10).

We next investigated the isopropyl radical addition to oxime ether **6** using *i*-PrI and Et_3B or Et_2Zn in the absence of Bu_3SnH (Scheme 7). Treatment of **6** with *i*-PrI (10 equiv) and Et_3B (2.5 equiv) in the absence of Bu_3SnH gave a 93:7 diastereomeric mixture of **7a** in 35% combined yield, along with a significant amount of the ethylated product **7b** (Table 6, entry 1). The formation of the isopropylated product **7a** was found to be dependent on the reaction temperature. Thus, changing the temperature from −78 °C to +20 °C led to an effective increase in the yield of **7a** (Table 6, entry 2). These results indicate that the reaction proceeded effectively at 20 °C via a route involving the iodine atom-transfer process between the isopropyl iodide and the ethyl radical generated from Et_3B;[40] the predominant addition of the more nucleophilic and stable isopropyl radical was observed. Although the reaction proceeded with moderate diastereoselectivity, the major diastereomer (*R*)-**7a** could be easily isolated by preparative TLC. Therefore, this radical reaction has a tremendous practical advantage over the stannyl radical-induced reaction, which requires tedious workup to remove the tin residues from the reaction

(38) We recently reported that the treatment of **1** with RI and Et_3B is an effective method for the synthesis of α-amino acids when the stable tertiary and secondary alkyl radicals were employed. In this reaction, Et_3B acts multiply as a radical initiator, a Lewis acid, and a radical terminator by trapping the intermediate benzyloxyaminyl radical. Therefore, more than a stoichiometric amount of Et_3B is required. See: ref 17b.

(39) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335−6336.

(40) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403−409. (b) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143−147.

Table 6. Isopropyl Radical Addition to 6 via Iodine Atom-Transfer Process[a]

				product **7a**		product **7b**	
entry	initiator	solvent	*T* (°C)	yield (%)[b]	selectivity[c]	yield (%)[b]	selectivity[c]
1	Et_3B	CH_2Cl_2	−78	35	93:7	53	92:8
2	Et_3B	CH_2Cl_2	+20	78	87:13	13	87:13
3	Et_3B	toluene	−78	51	90:10	41	90:10
4	Et_3B	toluene	+20	78	89:11	16	89:11
5	Et_3Zn	CH_2Cl_2	−78	19	95:5	66	95:5
6	Et_2Zn	CH_2Cl_2	+20	75	88:12	18	88:12
7	Et_2Zn	toluene	−78	26	95:5	65	94:6
8	Et_2Zn	toluene	+20	64	86:14	19	86:14

[a] All reactions were carried out with *i*-PrI (10 equiv) and radical initiator (2.5 equiv). [b] Combined yields of diastereomers. [c] Diastereoselectivities were determined by ^{1}H NMR analysis.

Scheme 8

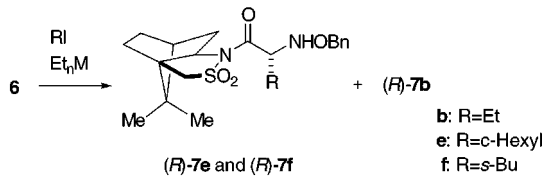


Table 7. Alkyl Radical Addition to 6 via Iodine Atom-Transfer Process[a]

entry	RX	initiator	solvent	product	yield (%)[b]	selectivity[c]
1	c-HexylI	Et_3B	CH_2Cl_2	**7e**	63	87:13
2	*s*-BuI	Et_3B	CH_2Cl_2	**7f**	74	87:13
3	c-HexylI	Et_3B	toluene	**7e**	69	80:20
4	*s*-BuI	Et_3B	toluene	**7f**	76	86:14
5	c-HexylI	Et_2Zn	toluene	**7e**	57	81:19
6	*s*-BuI	Et_2Zn	toluene	**7f**	65	83:17

[a] All reactions were carried out with RX (10 equiv) and radical initiator (2.5 equiv) in toluene at 20 °C. [b] The ethylated product **7b** was also obtained in 10−25 yields. [c] Combined yields of diastereomers. [d] Diastereoselectivities were determined by ^{1}H NMR analysis.

mixture. The replacement of CH_2Cl_2 with a nonpolar aromatic solvent such as toluene was also effective for the reaction (Table 6, entries 3 and 4). It is noteworthy that similar trends were observed in the reaction using Et_2Zn (Table 6, entries 5−8).

To evaluate the generality of the radical reaction, we investigated the reaction using different radical precursors, such as *sec*-butyl and cyclohexyl iodides, which afforded the alkylated respective products **7e** and **7f** with moderate diastereoselectivities (Scheme 8, Table 7). The reactions were run at 20 °C for 10 min by the use of RI (10 equiv) and 1.0 M solution of Et_3B in hexane (2.5 equiv) or 1.0 M solution of Et_2Zn in hexane (2.5 equiv).

Curran has suggested that in imides derived from camphorsultam, dipole−dipole interactions control the C(O)−N rotamer population and is responsible for the observed stereoselection in radical reactions.[8] In our reaction, the rotamer having the carbonyl group anti to the sulfonyl group would be favored in order to minimize dipole−dipole interactions between these groups (Figure 2). As suggested by the studies on the camphorsultam derivative of glyoxylic acid,[33] it is expected that the sterically more stable s-cis planar conformation between the carbonyl group and the oxime ether group would be favored. Therefore, the anti and s-cis planar rotamer **A** should be preferred over rotamers **B**−**D**, and the radical addition to the *re* (bottom) face is favored, presumably due to steric interactions with the axial oxygen of the sulfonyl group, which effectively prevents addition to the *si* face.

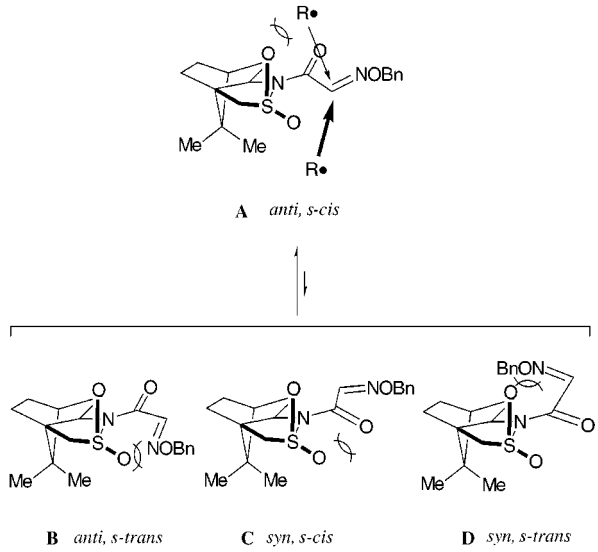


Figure 2. Radical addition to camphorsultam derivative of glyoxylic oxime ether.

Conclusions

We have succeeded in the asymmetric synthesis of α-amino acids based on the intermolecular carbon radical addition to Oppolzer's camphorsultam derivatives of the glyoxylic oxime ether with excellent diastereoselectivities. The new methodology provides a synthetic approach to a wide range of enantiomerically pure natural and unnatural α-amino acids, including aliphatic α-amino acids. Therefore, the free radical-mediated carbon−carbon bond-forming reaction complements the nucleophilic addition of organometallic reagents.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI, CI, or SIMS methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Medium-pressure column chromatography was performed using Lobar grösse B (E. Merck 310−25, Lichroprep Si60). Flash column chromatography was performed using E. Merck Kieselgel 60 (230−400 mesh).

[3a*S*-[1(*E*),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[[(phenylmethoxy)imino]acetyl]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide (6). To a solution of (1*R*)-(+)-2,10-camphorsultam (1.0 g, 4.6 mmol) and glyoxylic oxime ether **1** (1.33 g, 6.9 mmol) in CH_2ClCH_2Cl (40 mL) was added Me_3Al (1.0 M in hexane, 6.9 mL, 6.9 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 5 h, the reaction mixture was diluted with 1 N HCl and

then extracted with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 4:1) afforded **6** (1.56 g, 90%) as colorless crystals: mp 133−134 °C (Et_2O/hexane); $[\alpha]^{27}_D$ +88.9 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 2962, 1693, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (1H, s), 7.42−7.28 (5H, m), 5.32 (2H, s), 3.98 (1H, dd, *J* = 5.2, 7.4 Hz), 3.52, 3.45 (each 1H, d, *J* = 13.7 Hz), 2.20−2.02 (2H, m), 1.98−1.82 (3H, m), 1.48−1.29 (2H, m), 1.16, 0.97 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 159.0, 140.8, 135.8, 128.5, 128.4, 128.3, 78.2, 65.1, 52.9, 48.8, 47.7, 44.5, 38.1, 32.7, 26.2, 20.7, 19.7; HRMS calcd for $C_{19}H_{25}N_2O_4S$ (M^+ + H) 377.1543, found 377.1538. Anal. Calcd for $C_{19}H_{24}N_2O_4S$: C, 60.62; H, 6.43; N, 7.44; S, 8.52. Found: C, 60.42; H, 6.34; N, 7.34; S, 8.67.

General Procedure for Bu_3SnH-Mediated Radical Addition to Camphorsultam Derivative 6. To a solution of **6** (100 mg, 0.27 mmol) in CH_2Cl_2 (20 mL) were added Lewis acid (0.53 mmol), alkyl iodide (1.33 mmol), Bu_3SnH (0.18 mL, 0.66 mmol), and Et_3B (1.0 M in hexane, 1.33 mL, 1.33 mmol) under a nitrogen atmosphere at −78 °C. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The diastereoselectivity was determined by the ^1H NMR analysis of the diastereomeric mixtures obtained after rough purification (hexane/AcOEt 11:1) to remove the tin residues from the reaction mixture. Further careful purification by preparative TLC afforded the alkylated products (*R*)-**7a**−**h** and their diastereomers.

Isopropyl Radical Addition to 6 Using $(Me_3Si)_3SiH$. To a solution of **6** (100 mg, 0.27 mmol) in CH_2Cl_2 (20 mL) were added *i*-PrI (0.13 mL, 1.35 mmol), $(Me_3Si)_3SiH$ (0.21 mL, 0.66 mmol), and Et_3B (1.0 M in hexane, 1.33 mL, 1.33 mmol) under a nitrogen atmosphere at −78 °C. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification was performed using the protocol described in the general procedure.

Isopropyl Radical Addition to 6 Using AIBN. To a boiling solution of **6** (100 mg, 0.27 mmol) and *i*-PrI (0.09 mL, 0.945 mmol) in toluene (10 mL) was added a solution of Bu_3SnH (0.18 mL, 0.59 mmol) and AIBN (9 mg, 0.054 mmol) in toluene (5 mL) under a nitrogen atmosphere. After being heated at reflux for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification was performed using the protocol described in the general procedure.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[3-methyl-1-oxo-2-[(phenylmethoxy)amino]butyl]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-7a].** Further careful purification by preparative TLC (hexane/AcOEt 8:1) afforded the alkylated products (*R*)-**7a** as colorless crystals and (*S*)-**7a** as a white solid, respectively:[41] mp 83−84 °C (Et_2O/hexane); $[\alpha]^{29}_D$ +103.6 (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 3288, 2966, 1692, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.24 (5H, m), 6.22 (1H, d, *J* = 11.0 Hz), 4.69, 4.63 (each 1H, d, *J* = 14.0 Hz), 4.17−4.10 (1H, br m), 3.99 (1H, br t, *J* = 6.0 Hz), 3.49, 3.48 (each 1H, d, *J* = 14.0 Hz), 2.15−2.03 (2H, m), 1.95−1.83 (4H, m), 1.48−1.30 (2H, m), 1.13, 0.97 (each 3H, s), 1.01, 0.86 (each 3H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.3, 138.0, 128.8, 128.1, 127.5, 75.6, 68.1, 65.1, 53.1, 48.4, 47.8, 44.6, 38.5, 32.9, 30.3, 26.5, 20.7, 20.0, 17.9; HRMS calcd for $C_{22}H_{33}N_2O_4S$ (M^+ + H) 421.2159, found 421.2150. Anal. Calcd for $C_{22}H_{32}N_2O_4S$: C, 62.83; H, 7.67; N, 6.66; S, 7.62. Found: C, 62.67; H, 7.60; N, 6.38; S, 7.68.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[1-oxo-2-[(phenylmethoxy)amino]butyl]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-7b].** Further careful purification by preparative TLC (hexane/AcOEt 11:1) afforded the alkylated products (*R*)-**7b** as colorless crystals and (*S*)-**7b** as a white solid, respectively:[41] mp 99−100 °C (Et_2O/hexane); $[\alpha]^{28}_D$ +107.4 (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3271, 2966, 1693, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.24 (5H, m), 6.18 (1H, br d, *J* = 10.5 Hz), 4.71, 4.66 (each 1H, d, *J* = 12.0 Hz), 4.27 (1H, br m), 3.97 (1H, br t, *J* = 6.5 Hz), 3.50, 3.47 (each 1H, d, *J* = 14.0 Hz), 2.09 (2H, br d, *J* = 6.5 Hz), 1.93−1.86 (3H, m), 1.72−1.35 (4H, m), 1.13, 0.97 (each 3H, s), 0.95 (3H, t, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 174.1, 137.9, 128.6, 128.1, 127.6, 75.8, 65.0, 64.4, 53.1, 48.6, 47.8, 44.6, 38.3, 32.8, 26.4, 24.0, 20.7, 19.9, 10.5; HRMS calcd for $C_{21}H_{31}N_2O_4S$ (M^+ + H) 407.2002, found 407.1997. Anal. Calcd for $C_{21}H_{30}N_2O_4S$: C, 62.04; H, 7.44; N, 6.89; S, 7.89. Found: C, 62.12; H, 7.58; N, 6.71; S, 7.92.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[3,3-dimethyl-1-oxo-2-[(phenylmethoxy)amino]butyl]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-7c].** Further careful purification by preparative TLC (hexane/AcOEt 11:1) afforded the alkylated products (*R*)-**7c** as a colorless oil and (*S*)-**7c** as a white solid, respectively:[41] $[\alpha]^{29}_D$ +87.2 (*c* 3.37, $CHCl_3$); IR ($CHCl_3$) 3291, 2962, 1687, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.23 (5H, m), 6.20 (1H, br d, *J* = 9.5 Hz), 4.69, 4.60 (each 1H, d, *J* = 12.0 Hz), 4.12 (1H, br d, *J* = 9.5 Hz), 4.01 (1H, br t, *J* = 6.0 Hz), 3.49 (2H, br s), 2.16−2.02 (2H, br m), 1.94−1.83 (3H, m), 1.43−1.32 (2H, m), 1.13 (3H, s), 0.98 (9H, s), 0.96 (3H, s); ^{13}C NMR ($CDCl_3$) δ 174.8, 138.2, 128.8, 128.0, 127.4, 75.3, 69.6, 65.5, 53.3, 47.8, 47.7, 44.6, 38.6, 34.7, 33.0, 27.0, 26.5, 20.6, 20.0; HRMS calcd for $C_{23}H_{35}N_2O_4S$ (M^+ + H) 435.2315, found 435.2307.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[4-methyl-1-oxo-2-[(phenylmethoxy)amino]pentyl]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-7d].** Further careful purification by preparative TLC (hexane/AcOEt 11:1) afforded the alkylated products (*R*)-**7d** as a colorless oil and (*S*)-**7d** as a white solid, respectively:[41] $[\alpha]^{27}_D$ +48.6 (*c* 6.70, $CHCl_3$); IR ($CHCl_3$) 3270, 2962, 1693, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.24 (5H, m), 6.15 (1H, br m), 4.69, 4.66 (each 1H, d, *J* = 12.0 Hz), 4.42−4.35 (1H, br m), 3.97 (1H, t, *J* = 6.0 Hz), 3.48, 3.47 (each 1H, d, *J* = 14.0 Hz), 2.07 (2H, br m), 1.94−1.83 (3H, m), 1.78 (1H, m), 1.43−1.18 (4H, m), 1.13, 0.97 (each 3H, s), 0.86 (6H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.7, 138.0, 128.7, 128.1, 127.5, 75.8, 65.0, 61.9, 53.0, 48.6, 47.8, 44.6, 39.2, 38.2, 32.8, 26.4, 25.2, 23.4, 21.3, 20.8, 19.9; HRMS calcd for $C_{23}H_{35}N_2O_4S$ (M^+ + H) 435.2315, found 435.2292.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-1-[Cyclohexyl[(phenylmethoxy)-amino]acetyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-7e].** Further careful purification by preparative TLC (hexane/AcOEt 11:1) afforded the alkylated products (*R*)-**7e** as a colorless oil and (*S*)-**7e** as a colorless oil, respectively:[41] $[\alpha]^{30}_D$ +85.4 (*c* 4.00, $CHCl_3$); IR ($CHCl_3$) 3275, 2931, 1691, 1453 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.24 (5H, m), 6.21 (1H, br m), 4.68, 4.62 (each 1H, d, *J* = 11.5 Hz), 4.15 (1H, br m), 3.98 (1H, br t, *J* = 6.5 Hz), 3.49, 3.47 (each 1H, d, *J* = 14.0 Hz), 2.07 (2H, m), 1.95−1.84 (3H, m), 1.78−1.02 (13H, m), 1.13, 0.97 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 174.2, 138.1, 128.7, 128.1, 127.5, 75.6, 68.0, 65.1, 53.1, 48.4, 47.7, 44.6, 40.0, 38.5, 32.8, 29.9, 28.7, 26.5, 26.3, 26.2, 26.0, 20.6, 20.0; HRMS calcd for $C_{25}H_{37}N_2O_4S$ (M^+ + H) 461.2471, found 461.2479.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[3-methyl-1-oxo-2-[(phenylmethoxy)amino]pentyl]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-7f].** Further careful purification by preparative TLC (hexane/AcOEt (10:1), 2-fold development) afforded the alkylated products (*R*)-**7f** as a colorless oil and as a 1:1 diastereomeric mixture concerning the chiral carbon on the *sec*-butyl group: $[\alpha]^{28}_D$ +84.2 (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 3300, 2966, 1691, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−7.20 (5H, m), 6.25 (1H, br s), 4.67 ($^1/_2$H, d, *J* = 12.0 Hz), 4.66 ($^1/_2$H, d, *J* = 12.0 Hz), 4.63 (1H, d, *J* = 12.0 Hz), 4.29, 4.18 (each $^1/_2$H, br m), 3.98 (1H, br t, *J* = 6.5 Hz), 3.47 (2H, m), 2.18−1.98 (2H, br m), 1.98−1.82 (3H, br m), 1.82−1.23 (5H, m) 1.12, 0.96 (each 3H, br s), 0.87, 0.81 (each $^3/_2$H, t, *J* = 7.5 Hz), 0.82, 0.76 ($^3/_2$H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.3, 174.0, 138.0, 137.9, 128.6, 128.0, 127.4, 75.53, 75.45, 67.6, 66.3, 65.0, 64.9, 52.9, 48.4, 48.3, 47.6, 44.4,

(41) The characterization data of the minor diasteromers (*S*)-**7a**−**e** are given in the Supporting Information.

38.4, 38.3, 36.6, 36.2, 32.6, 27.0, 26.3, 24.4, 20.5, 20.4, 19.8, 15.9, 14.0, 11.5, 11.3; HRMS calcd for $C_{23}H_{35}N_2O_4S$ ($M^+ + H$) 435.2315, found 435.2297.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-1-[6-Acetyloxy-1-oxo-2-[(phenylmethoxy)amino]hexyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-7g].** Further careful purification by preparative TLC (hexane/AcOEt (5:1), 2-fold development) afforded the alkylated products (*R*)-**7g** as a colorless oil: $[\alpha]^{31}_D$ +64.9 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3300, 2963, 1727, 1693, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.23 (5H, m), 6.18 (1H, br d, J = 10.5 Hz), 4.69, 4.65 (each 1H, d, J = 12.0 Hz), 4.28 (1H, m), 4.04−3.93 (3H, m), 3.49, 3.47 (each 1H, d, J = 13.0 Hz), 2.11−1.28 (13H, m), 2.03 (3H, s), 1.12, 0.97 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 174.0, 171.1, 137.9, 128.7, 128.2, 127.6, 75.8, 65.0, 64.2, 63.1, 53.0, 48.7, 47.8, 44.6, 38.2, 32.8, 30.1, 28.1, 26.4, 22.5, 21.0, 20.7, 19.9; HRMS calcd for $C_{25}H_{37}N_2O_6S$ ($M^+ + H$) 493.2370, found 493.2393.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[1-oxo-[2-[*N*-(phenylmethoxy)pyrrolidinyl]]]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-8].** In the case of product (*R*)-**8**, the reaction mixture was stirred at −78 °C for 30 min and then stirred at room temperature for an additional 30 h. Further careful purification by preparative TLC (hexane/AcOEt (6:1), 2-fold development) afforded the alkylated product (*R*)-**8** as a yellow solid: $[\alpha]^{27}_D$ +131.0 (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 2964, 1703, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.23 (5H, m), 4.86, 4.81 (each 1H, d, J = 11.0 Hz), 4.40 (1H, dd, J = 8.0, 10.0 Hz), 3.97 (1H, dd, J = 5.0, 7.0 Hz), 3.49, 3.48 (each 1H, d, J = 14.0 Hz), 3.28 (1H, m), 2.97 (1H, m), 2.41 (1H, m), 2.14−2.00 (2H, m), 1.97−1.83 (4H, m), 1.81 (1H, m), 1.68 (1H, m), 1.47−1.32 (2H, m), 1.13, 0.97 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 171.7, 137.9, 128.6, 128.2, 127.6, 75.7, 69.8, 65.1, 56.1, 53.1, 48.6, 47.8, 44.6, 38.2, 32.8, 27.7, 26.4, 21.2, 20.7, 19.9; HRMS calcd for $C_{22}H_{31}N_2O_4S$ ($M^+ + H$) 419.2001, found 419.2024.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-1-[(2-Amino-3-methyl-1-oxo)-butyl]hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide Monohydrochloride [(*R*)-9].** To a solution of (*R*)-**7a** (120 mg, 0.286 mmol) in H_2O (0.29 mL) and MeCN (4.3 mL) was added $Mo(CO)_6$ (52.8 mg, 0.20 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 2 h, the reaction mixture was concentrated at reduced pressure. The resulting residue was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and water. The organic phase was extracted with 1 N HCl. The aqueous phase was concentrated at reduced pressure to afford (*R*)-**9** (88 mg, 88%) as a white powder: $[\alpha]^{29}_D$ +61.3 (*c* 1.06, MeOH); IR ($CHCl_3$) 3423, 1654 cm^{-1}; ^1H NMR (CD_3OD) δ 4.29 (1H, br d, J = 4.5 Hz), 3.99 (1H, dd, J = 5.0, 7.5 Hz), 3.80, 3.69 (each 1H, d, J = 13.7 Hz), 2.46 (1H, m), 2.16−1.85 (5H, m), 1.55−1.32 (2H, m), 1.14, 1.03 (each 3H, s), 1.12, 0.98 (each 3H, d, J = 7.0 Hz); ^{13}C NMR (CD_3OD) δ 169.5, 66.4, 59.6, 53.6, 50.2, 48.9, 46.1, 39.1, 33.5, 31.7, 27.3, 21.2, 20.1, 19.5, 16.4; HRMS calcd for $C_{15}H_{27}N_2O_3S$ ($M^+ + H$) 315.1740, found 315.1721.

[3a*S*-[1(*S),3aα,6α,7a*β*]]-Hexahydro-8,8-dimethyl-1-[3-methyl-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]butyl]-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide [(*R*)-10].** To a solution of (*R*)-**9** (168 mg, 0.48 mmol) in acetone (2 mL) was added a solution of Na_2CO_3 (153 mg, 1.44 mmol) in H_2O (1 mL) under a nitrogen atmosphere at room temperature. After a solution of CbzCl (119 mg, 0.70 mmol) in acetone (0.5 mL) was added dropwise at 0 °C, the reaction mixture was stirred at room temperature for 1 h. After the reaction mixture was concentrated at reduced pressure, the resulting residue was diluted with water and then extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 6:1 to 4:1) afforded (*R*)-**10** (197 mg, 92%) as colorless crystals: mp 169−170 °C (AcOEt/Et_2O/hexane); $[\alpha]^{29}_D$ +62.0 (*c* 1.50, MeOH); IR ($CHCl_3$) 3435, 2966, 1725, 1697, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.29 (5H, m), 5.35 (1H, br d, J = 9.0 Hz), 5.08, 5.14 (each 1H, br d, J = 12.0 Hz), 4.94 (1H, br dd, J = 3.0, 9.0 Hz), 3.91 (1H, br t, J = 6.0 Hz), 3.49, 3.47 (each 1H, br d, J = 14.0 Hz), 2.29 (1H, br m), 2.08 (1H, dd, J = 7.5, 13.5 Hz), 2.03−1.85 (3H, br m), 1.46−1.32 (2H, m), 1.13, 0.97 (each 3H, s), 1.04, 0.80 (each 3H, d, J = 7.0 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, 61.60; H, 7.24; N, 6.25; S, 7.34.

***N*-[(Phenylmethoxy)carbonyl]-D-valine [(*R*)-11].** A solution of (*R*)-**10** (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 reduced pressure, the resulting residue was diluted with water, acidified to a pH between 4 and 5 with diluted HCl, and then extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash column chromatography (hexane/AcOEt 1:2) afforded (*R*)-**11** (71 mg, 73%) as a colorless oil: $[\alpha]^{27}_D$ +5.6 (*c* 1.78, MeOH); IR ($CHCl_3$) 3438, 2968, 1715, 1466, 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 = 12.0 Hz), 4.34 (1H, br m), 2.22 (1H, br m), 1.00, 0.93 (each 3H, d, 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 $C_{13}H_{17}NO_4$ (M^+) 251.1157, found 251.1152.

D-Valine [(*R*)-12]. A solution of (*R*)-**9** (60 mg, 0.17 mmol) in 1 N LiOH-THF (1:4, 7 mL) was stirred at room temperature for 3 h. After the reaction mixture was concentrated at reduced pressure, the resulting residue was diluted with CH_2Cl_2 and extracted with water. After the aqueous phase was acidified to a pH between 4 and 5 with the diluted HCl, Amberlite IR-120B ion-exchange resin (200 mg) was added to the aqueous phase at room temperature. After being stirred at same temperature for 15 h, the reaction mixture was filtered. After the resin was washed well with water, a solution of the resin in 30% NH_3 (10 mL) was stirred at room temperature for 4 h. The reaction mixture was filtered, and the filtrate was concentrated at reduced pressure to afford (*R*)-**12** (17.6 mg, 88%) as a white powder: $[\alpha]^{28}_D$ −26.0 (*c* 0.97, 6 N HCl); IR (Nujol) 2890, 1605 cm^{-1}; ^1H NMR (D_2O) δ 3.05 (1H, d, J = 5.2 Hz), 1.92 (1H, m), 0.94, 0.87 (each 3H, d, J = 7.0 Hz); ^{13}C NMR (D_2O) δ 171.3, 64.8, 34.7, 22.0, 19.6; HRMS calcd for $C_5H_{12}NO_2$ ($M^+ + H$) 118.0867, found 118.0883.

Enantioselective Radical Addition to 1. To a solution of **1** (30 mg, 0.155 mmol) and (*R*)-(+)-2,2′-isopropylidenebis-(4-phenyl-2-oxazoline) (52 mg, 0.155 mmol) in CH_2Cl_2 (4 mL) were added Lewis acid (0.155 mmol), isopropyl iodide (0.155 mL, 1.55 mmol), Bu_3SnH (0.209 mL, 0.776 mmol), and Et_3B (1.0 M in hexane, 1.55 mL, 1.55 mmol) under a nitrogen atmosphere at −78 °C. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. After rough purification of the residue by preparative TLC (hexane/AcOEt 12:1) to remove the tin residues from the reaction mixture, further careful purification by preparative TLC ($CHCl_3$) afforded the alkylated product **2**.

(2*S*)-*N*-(3,3,3-Trifluoro-2-methoxy-1-oxo-2-phenylpropoxy)-D-valine Methyl Ester [(*R*)-13] and (2*S*)-*N*-(3,3,3-Trifluoro-2-methoxy-1-oxo-2-phenylpropoxy)-L-valine Methyl Ester [(*S*)-13]. A suspension of 20% $Pd(OH)_2$ (30 mg) in MeOH (1 mL) was stirred under a hydrogen atmosphere at 20 °C for 1 h. To this suspension was added a solution of **2** (100 mg, 0.42 mmol) in MeOH (2 mL). After being stirred under a hydrogen atmosphere at 20 °C for 3 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure to afford the crude amine. To a solution of the resulting crude amine in pyridine (0.5 mL) were added DMAP (12 mg, 0.1 mmol) and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (150 mg, 0.59 mmol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 15 min, the reaction mixture was extracted with AcOEt. The organic phase was washed with 3% HCl, water, and brine; dried over $MgSO_4$; and concentrated at reduced pressure. Purification of the residue by preparative TLC (AcOEt/hexane 1:3) afforded (*R*)-**13** (85 mg, 59%) as a

colorless oil and (*S*)-**13** (26 mg, 18%) as a colorless oil (*R*)-**13**: $[\alpha]^{27}_D$ −486 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 2969, 1740, 1698, 1514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60−7.50 (2H, m), 7.45−7.35 (3H, m), 4.59 (1H, m), 3.74 (3H, s), 3.39 (3H, br s), 2.23 (1H, m), 0.99, 0.94 (each 3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 166.1, 131.7, 129.4, 128.5, 127.9, 123.7 (q, J = 289 Hz, CF_3), 84.1 (q, J = 27 Hz, CF_3C), 57.0, 54.8, 52.1, 31.0, 18.9, 17.5; HRMS calcd for $C_{16}H_{21}F_3NO_4$ (M^+ + H) 248.1421, found 348.1427. (*S*)-**13**: $[\alpha]^{27}_D$ −2713 (*c* 2.50, $CHCl_3$); IR ($CHCl_3$) 2968, 1740, 1698, 1514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65−7.55 (2H, m), 7.50−7.35 (3H, m), 4.61 (1H, m), 3.76 (3H, s), 3.50 (3H, br s), 2.19 (1H, m), 0.87, 0.80 (each 3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 166.4, 132.9, 129.4, 128.3, 127.2, 123.4 (q, J = 289 Hz, CF_3), 83.9 (q, J = 29 Hz, CF_3C), 56.7, 55.6, 52.2, 31.1, 18.8, 17.4; HRMS calcd for $C_{16}H_{20}F_3NO_4$ (M^+ + H) 248.1421, found 348.1432.

Ethyl Radical Addition to 6 Using Et_3B or Et_2Zn. To a solution of **6** (50 mg, 0.133 mmol) in CH_2Cl_2 or toluene (3 mL) were added Et_3B or Et_2Zn (1.0 M in hexane, 0.664 mL, 0.664 mmol) under a nitrogen atmosphere at +20 or −78 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Diastereoselectivity was determined by ^1H NMR analysis of crude products. Purification of the residue by preparative TLC (hexane/AcOEt 4:1) afforded (*R*)-**7b** and (*S*)-**7b**.

General Procedure for Radical Addition to 6. To a solution of **6** (50 mg, 0.133 mmol) in CH_2Cl_2 or toluene (3 mL) were added RI (1.33 mmol) and Et_3B or Et_2Zn (1.0 M in hexane, 0.33 mL, 0.332 mmol) under a nitrogen atmosphere at +20 or −78 °C. After being stirred at the same temperature for 10 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. After the separation of the alkylated products **7a**,**e**,**f** and the ethylated product **7b** by preparative TLC (hexane/AcOEt 4:1, 2-fold development), diastereoselectivities were determined by ^1H NMR analysis. The pure diastereomers (*R*)-**7a**, (*R*)-**7e**, and (*R*)-**7f** could be also isolated by preparative TLC (hexane/AcOEt 4:1, 2-fold development).

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Supporting Information Available: Experimental procedures for the isopropyl radical addition to glyoxylic oxime ether **1** and the competitive reaction. The characterization data of the minor diastereomers (*S*)-**7a**−**e** and ^1H NMR data for **2**, **6**, (*R*)-**7a**−**g**, (*S*)-**7a**−**e**, and (*R*)-**8**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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