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Diastereoselective Intermolecular Radical Addition to Nitrones

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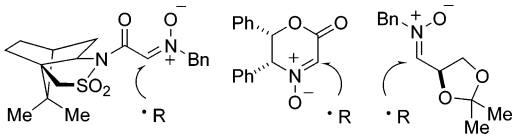

The intermolecular radical addition to chiral nitrones **2**, **4**, **5**, and **16** was studied. The isopropyl radical addition to Oppolzer's camphorsultam derivative **2** of glyoxylic nitrone proceeded with excellent diastereoselectivity to give the desired isopropylated product **3a** accompanied by the diisopropylated product **3b**. A high degree of stereocontrol in the reaction of cyclic nitrone **4** was achieved. The ethyl radical addition to nitrone **4** with triethylborane afforded the desired ethylated product **9a** accompanied by the diethylated product **10a** and the ethylated nitrone **11a**. To evaluate the utility of cyclic nitrone **4**, several alkyl radicals were employed in the addition reaction, which afforded the alkylated products **9b**−**d** with excellent diastereoselectivities. In the presence of $Mg(ClO_4)_2$, the ethyl radical addition to BIGN **16** afforded selectively syn isomers. In contrast, the alkyl radical addition to **16** took place even in the absence of Lewis acid to give anti isomers.

Introduction

The carbon−nitrogen double bond has attracted significant attention as an excellent radical acceptor.[1] Compared with the extensive investigations into radical cyclization of imine derivatives,[2,3] the intermolecular radical addition to imines has not been widely studied. Therefore, the development of intermolecular carbon−carbon bond-forming radical reactions of imines is a subject of current interest.[4]

Hart's group reported the first study on the intermolecular alkyl radical addition to the sterically less hindered formaldoxime ether.[5] Recently, the intermolecular radical-mediated acylation using α-sulfonyl oxime ethers has been reported by the research group of Kim.[6] We have also reported that the intermolecular radical addition reactions to a wide range of aldoxime ethers proceeded smoothly in the presence of $BF_3{\cdot}OEt_2$.[7] Additionally, Bertrand's and our groups have independently reported the diastereofacial control in intermolecular radical addition to glyoxylic imine derivatives for the synthesis of α-amino acids.[8,9] More recently,

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(1) For reviews, see: (a) Miyabe, H.; Miyata, O.; Naito, T. *J. Synth. Org. Chem.*, *Jpn.* **2002**, *60*, 1087. (b) Naito, T. *Heterocycles* **1999**, *50*, 505. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (d) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* (*N.Y.*) **1996**, *48*, 301.

(2) For our examples of the radical cyclization of oxime ethers and hydrazones, see: (a) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 2003. (b) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835. (c) Miyabe, H.; Nishiki, A.; Naito, T. *Chem. Pharm. Bull.* **2003**, *51*, 100. (d) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun.* **2001**, 831. (e) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. (f) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397.

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(4) For reviews, see: (a) Miyabe, H.; Ueda, M.; Naito, T. *Synlett.* **2004**, 1140. (b) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (b) Miyabe, H.; Naito, T. *J. Synth. Org. Chem.*, *Jpn.* **2001**, *59*, 35.

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Friestad's group reported the diastereo- and enantioselective radical additions to acylhydrazone.[10,11]

Nitrones are well-known to be reactive substrates for the 1,3-dipolar cycloaddition reaction, nucleophilic addition of organometallic reagents, and so on.[12,13] Although nitrones have also evolved as a useful trap for short-lived reactive radicals,[14] synthetically useful radical reactions of nitrones are not available.[15] We have investigated the viability of nitrones as radical acceptors and recently reported the highly diastereoselective radical addition to chiral nitrone for the asymmetric synthesis of α-amino acids.[16] As a part of our program directed toward the screening of reactive imino radical acceptors,[17,18] we now describe full details of a radical reaction of chiral nitrones.

Results and Discussion

Diastereoselective Radical Addition to Nitrone Bearing Oppolzer's Camphorsultam. As a preliminary experiment, we investigated the radical addition to glyoxylic nitrone **2**, because its reactivity toward the nucleophilic carbon radical would be enhanced by the neighboring electron-withdrawing substituent (Scheme 1). The auxiliary of choice was Oppolzer's camphorsultam, since it had shown good characteristics in our previous work on radical reactions of oxime ether and hydrazone.[9]

SCHEME 1

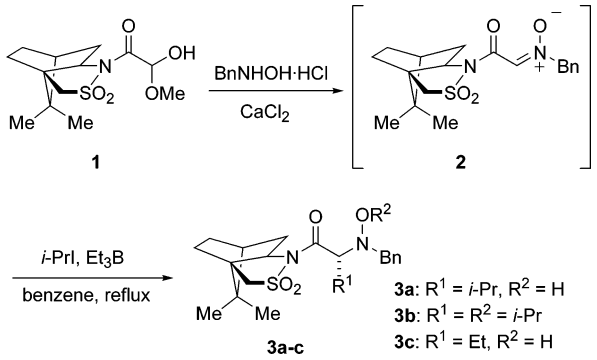

TABLE 1. Isopropyl Radical Addition to Nitrone 2

entry	conditions	yield (%)[a] 3a	3b	3c	selectivity of 3a[b]
1[c]	*i*-PrI (30 equiv) in benzene	28	7	16	>95% de
2[c]	*i*-PrI (90 equiv) in benzene	43	12	9	>95% de
3[d]	*i*-PrI: benzene (3:1)	47	18	7	>95% de

[a] Isolated yield. [b] Diastereoselectivities were determined by ^{1}H NMR analysis. [c] Reactions of **2** were carried out with *i*-PrI (30 or 90 equiv) and Et_3B (5.0 equiv) in boiling benzene. [d] Reaction of **1** was carried out with Et_3B (5.0 equiv) in boiling *i*-PrI−benzene (3:1, v/v).

Condensation of hemiacetal **1**[19] with *N*-benzylhydroxylamine proceeded in the presence of $CaCl_2$ to give the unstable nitrone **2** as an *E*/*Z* mixture after being stirred at 20 °C for 24 h. The nitrone **2** could not be easily isolated and hence was used in a crude state, after simple filtration to remove $CaCl_2$. To avoid the use of the commonly used toxic tin reagents, we have explored tin-free, iodine atom-transfer reactions.[11,13] Et_3B was used as a radical initiator for isopropyl radical addition to **2**; formation of the ethylated byproduct **3c** was shown to be dependent on the reaction temperature. Thus, changing the temperature from 20 °C to reflux in benzene led to a decrease in the ratio of ethylated byproduct **3c** to the desired isopropylated products **3a** and **3b**. A similar trend has been observed in our recent studies on the radical reaction of oxime ethers.[20] The reaction with isopropyl iodide (30 equiv) in boiling benzene proceeded within 30 min to give the isopropylated product **3a** in 28% yield, accompanied by a 7% yield of the *C*- and *O*-diisopropylated product **3b** and a 16% yield of the ethylated product **3c** (Table 1, entry 1). A high degree of diastereoselectivity was attained even at the high reaction temperature. The diastereomeric purity of **3a** was found to be not less than 95% de by ^{1}H NMR analysis.[21] As the best result, the predominant formation of desir-

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(13) For 1,3-dipolar cycloaddition reactions of chiral nitrones prepared from L-phenylananine and glyoxylic acid, see: (a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun.* **1996**, 1861. (b) Tamura, O.; Kuroki, T.; Sakai, Y.; Takizawa, J.; Yoshino, J.; Morita, Y.; Mita, N.; Gotanda, K.; Sakamoto M. *Tetrahedron Lett.* **1999**, 40, 895. (c) Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Commun.* **2003**, 2678.

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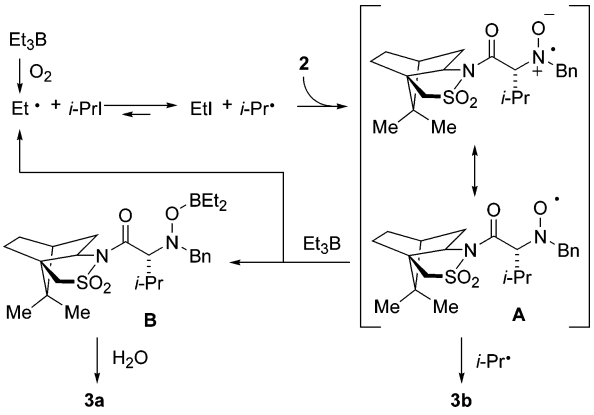
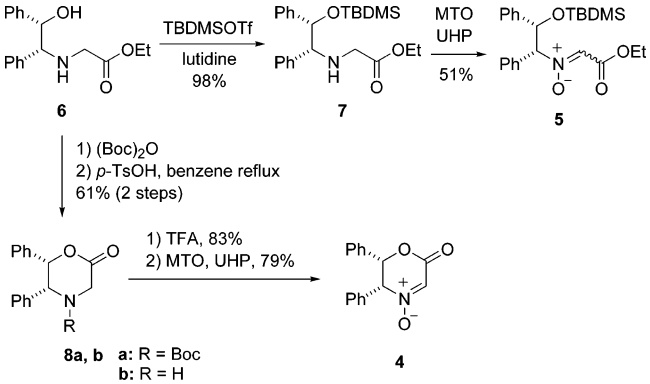
(20) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413.

SCHEME 2



SCHEME 3



ably isopropylated products **3a** and **3b** was achieved in the reaction by using *i*-PrI−benzene (3:1, v/v) as a solvent (entry 3). Treatment of nitrone **2** with Et_3B in boiling *i*-PrI−benzene (3:1, v/v) for 30 min gave the product **3a** in 47% yield as a single diastereomer (entry 3).

In this reaction, Et_3B worked as not only a radical initiator but also a chain transfer agent to trap the intermediate radical **A** to give an adduct **B** and a chain-propagating ethyl radical. Therefore, an excess amount of Et_3B was required for the present reaction (Scheme 2).[22,23]

Diastereoselective Radical Addition to Cyclic and Acyclic Nitrones. For the synthesis of various types of α-amino acids, we next investigated the reaction of cyclic nitrone **4** (Scheme 3). For comparison, the reaction of acyclic nitrone **5** was also studied. The acyclic nitrones **2** and **5** exist as a mixture of *E*- and *Z*-isomers concerning the geometry of the C−N double bond, which were easily isomerized. In marked contrast to acyclic nitrones, the cyclic nitrone **4** has the advantage of increased rigidity and stability.

As shown in Scheme 3, the nitrones **4** and **5** were prepared. The amino alcohol **6**, which was prepared from (1*S*,2*R*)-diphenylaminoethanol,[24] was protected as the TBDMS derivative **7** in 98% yield. Next, the oxidation of secondary amine **7** to nitrone **5** was investigated under several reaction conditions. Methyltrioxorhenium(VII) (MTO)-catalyzed oxidation of **7** with a urea−hydrogen peroxide complex (UHP) was effective for preparing the conjugated nitrone **5** as an *E*/*Z* mixture.[25] According to Williams' method,[24] the amino alcohol **6** was protected as the *N*-Boc derivative, which was then treated with *p*-TsOH in benzene at reflux to give the morpholinone **8a** in 61% yield from **6**. Deprotection of the *N*-*tert*-butoxycarbonyl group followed by oxidation with MTO and UHP gave the cyclic nitrone **4**.[26]

SCHEME 4

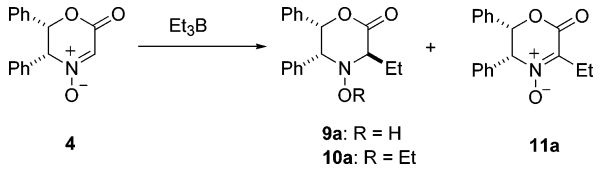


TABLE 2. Ethyl Radical Addition to Cyclic Nitrone 4

entry	solvent	*T* (°C)	yield (%)[a] **9a**	**10a**	**11a**	selectivity of **9a**[b]
1[c]	CH_2Cl_2	+20	50	32	trace	>95% de
2[c]	CH_2Cl_2	−78	36	22	14	>95% de
3[c]	benzene	reflux	55	15	trace	>95% de
4[d]	benzene	+20	50	trace	trace	>95% de
5[d]	CH_2Cl_2	−78	64	trace	16	>95% de

[a] Isolated yield. [b] Diastereoselectivities were determined by ^1H NMR analysis. [c] Reactions of **4** were carried out with Et_3B (5.0 equiv) in the presence of 20 mL of O_2 under N_2 atmosphere. [d] Reactions of **4** were carried out with Bu_3SnH (1.2 equiv) and Et_3B (5.0 equiv) in the presence of 20 mL of O_2 under N_2 atmosphere.

The addition of an ethyl radical to cyclic nitrone **4** was studied by using Et_3B (5.0 equiv) as an ethyl radical source under several reaction conditions (Scheme 4). At first, the reaction was carried out in the presence of 20 mL of O_2 under N_2 atmosphere (Table 2). As expected, the reaction of **4** in CH_2Cl_2 proceeded smoothly at 20 °C to give the desired product **9a** in 50% yield and the diethylated product **10a** in 32% yield (entry 1). Changing the reaction temperature from 20 to −78 °C led to an increase in the formation of undesired nitrone **11a** (entry 2). In contrast, treatment of **4** with Et_3B in boiling benzene afforded the desired product **9a** in 55% yield, along with 15% yield of the diethylated product **10a** (entry 3). A high degree of diastereoselectivity was obtained even at the elevated reaction temperature. The undesired nitrone **11a** would be obtained as a result of a disproportionation reaction of intermediate radical **C** (Scheme 5). To suppress the formation of the undesired products **10a** and **11a**, Bu_3SnH was employed as a hydride atom donor (entries 4 and 5). In the presence of Bu_3SnH, the formation of **10a** was diminished remarkably leading to 64% yield of **9a** after being stirred in

(21) The absolute configuration of **3a** was determined to be *R* by conversion into amino acid derivatives: reductive cleavage of the N−O bond with Zn in acidic condition followed by hydrogenolysis of the benzyl group afforded the known amino acid derivative. See ref 9e.

(22) The reaction of nitroxide radical with triethylborane is presumably a slow process and the formation of diisopropylated product **3b** may result from the accumulation of the nitroxide radical in the reaction mixture due to the persistent radical effect.

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SCHEME 5

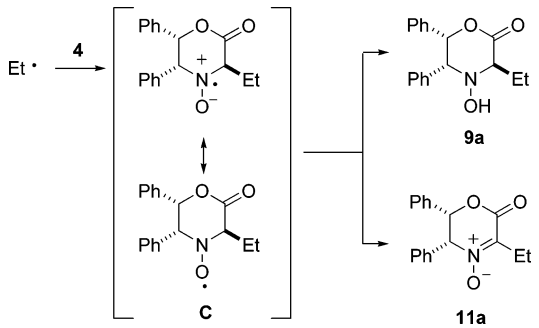
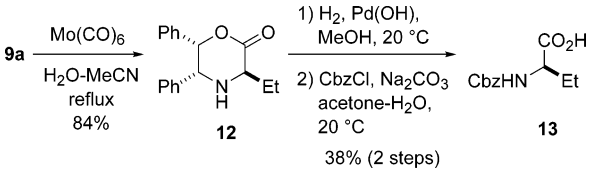


TABLE 3. Effect of Oxygen on Ethyl Radical Addition to Cyclic Nitrone 4

				yield (%)[a,b]		
entry	solvent	T (°C)	O_2 (equiv)	**9a**	**10a**	**11a**
1[c]	CH_2Cl_2	+20	0.05	65	9	trace
2[c]	CH_2Cl_2	+20	5	40	18	trace
3[c]	CH_2Cl_2	+20	50	26	38	trace

[a] Isolated yield. [b] Diastereoselectivities of **9a** and **10a** were >95% de. [c] Reactions of **4** were carried out with Et_3B (5.0 equiv) under Ar atmosphere.

SCHEME 6



CH_2Cl_2 at −78 °C for 2 h, though the ethylated nitrone **11a** was still obtained in 16% yield (entry 5).[27]

We next examined the effect of oxygen on the ratio of ethylated product **9a** to diethylated product **10a**. After a solution of **4** in CH_2Cl_2 was strictly degassed, Et_3B was added to the reaction mixture under Ar and O_2 atmosphere (Table 3). In the presence of a catalytic amount of O_2, the radical reaction gave ethylated product **9a** in 65% yield along with only 9% yield of diethylated product **10a** (entry 1). On the other hand, the undesired formation of **10a** dramatically increased in the presence of an excess amount of oxygen probably due to the accumulation of ethyl radical generated from Et_3B and O_2 (entries 2 and 3). These results indicated that the radical chain process proceeded effectively in the presence of a catalytic amount of O_2 as a result of the suppressed formation of the undesired diethylated product **10a**.

The absolute configuration of **9a** was assigned to be *R* by converting the product **9a** into authentic *N*-Cbz-amino acid **13**.[28] The reductive cleavage of the N−O bond of **9a** with $Mo(CO)_6$ gave the amine **12** in 84% yield. Subsequent hydrogenolysis of **12** in the presence of $Pd(OH)_2$ followed by treatment with CbzCl afforded the enantiomerically pure (*R*)-*N*-Cbz-amino acid **13** without any loss of optical purity (Scheme 6).

(27) The stannyl radical, which is generated by the reduction of nitroxide radical with tin hydride, is known to dimerize to form the corresponding ditin compound. See: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; translated by J. Lomas; John Wiley & Sons: New York, 1995.

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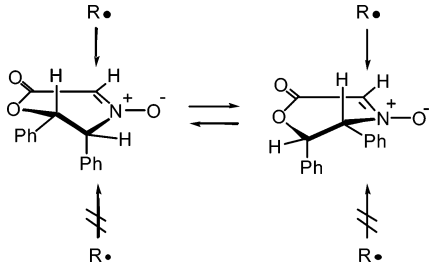


FIGURE 1. Stereochemical feature of radical addition to nitrone **4**.

SCHEME 7

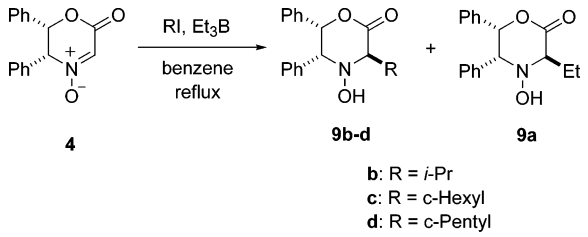


TABLE 4. Alkyl Radical Addition to Cyclic Nitrone 4

			yield (%)[a]		selectivity
entry	conditions	product	**9b−d**	**9a**	of **9b−d**[b]
1[c]	*i*-PrI (90 equiv) in benzene	**9b**	60	18	>95% de
2[d]	*i*-PrI:benzene (3:1)	**9b**	82	trace	>95% de
3[d]	c-Hexyl I:benzene (3:1)	**9c**	72	3	>95% de
4[d]	c-Pentyl I:benzene (3:1)	**9d**	72	12	>95% de

[a] Isolated yield; a small amount of alkylated nitrones was formed. [b] Diastereoselectivities were determined by ^1H NMR analysis. [c] Reaction of **4** was carried out with *i*-PrI (90 equiv) and Et_3B (2.5 equiv) in boiling benzene. [d] Reactions of **4** were carried out with Et_3B (2.5 equiv) in boiling RI−benzene (3:1, v/v).

The stereochemical features of this reaction can be rationalized in terms of steric control as shown in Figure 1. The alkyl radical addition takes place predominantly from the less hindered *re*-face to avoid the steric interaction with the phenyl group.

Next, we explored the alkyl radical addition to nitrone **4** under the iodine atom-transfer reaction conditions (Scheme 7). The isopropyl radical addition to nitrone **4** proceeded smoothly by using isopropyl iodide (90 equiv) and Et_3B (2.5 equiv) in boiling benzene, to give the desired isopropylated product **9b** in 60% yield, accompanied by an 18% yield of the ethylated product **9a** (Table 4, entry 1). The predominant formation of the isopropylated product **9b** was observed in the reaction with Et_3B (2.5 equiv) in boiling RI−benzene (3:1, v/v), although a trace amount of **9a** was formed (entry 2). Excellent diastereoselectivities were observed in the reactions with cyclohexyl and cyclopentyl radicals (entries 3 and 4).

The reaction of acyclic nitrone **5** was studied by using triethylborane as an ethyl radical source (Scheme 8). In the case of acyclic nitrone **5**, the predominant formation of diethylated product **15** was observed in organic solvents (Table 5, entries 1 and 2). To a solution of **5** in benzene was added a 1.0 M solution of Et_3B in hexane (5.0 equiv) and then the reaction mixture was stirred at 20 °C. The diethylated product **15** was obtained in 61% yield with 34% de, accompanied by a 14% yield of the

SCHEME 8

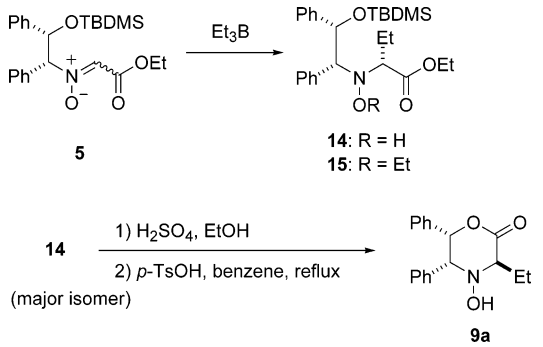


TABLE 5. Ethyl Radical Addition to Acyclic Nitrone 5[a]

entry	solvent	Lewis acid	T (°C)	yield (%)[b,c] **14**	**15**
1	benzene	none	20	14 (22% de)	61 (34% de)
2	CH_2Cl_2	none	20	15 (31% de)	53 (31% de)
3	H_2O−EtOH	none	20	44 (30% de)	27 (21% de)
4[d]	CH_2Cl_2	$TiCl_4$	20	8 (27% de)	0
5[d]	CH_2Cl_2	$Cu(OTf)_2$	20	13 (23% de)	43 (33% de)
6[d]	CH_2Cl_2	$Cu(OTf)_2$	−78	16 (20% de)	54 (4% de)

[a] Reactions of **5** were carried out with Et_3B (5.0 equiv). [b] Isolated yield of diastereomeric mixture. [c] Diastereoselectivities were determined by ^1H NMR analysis. [d] Lewis acid (1.0 equiv) was employed.

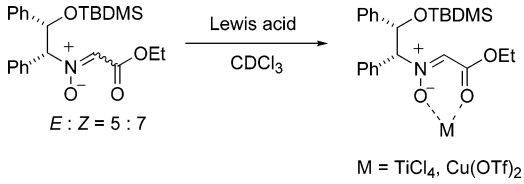


FIGURE 2. Isomerization of *E*- and *Z*-isomers.

ethylated product **14** (entry 1). A similar result was obtained in the reaction of **5** in CH_2Cl_2 (entry 2). In contrast to acyclic nitrone **2**, the acyclic nitrone **5** was stable even in aqueous media. The radical addition to **5** in H_2O−MeOH gave 44% yield of ethylated product **14** and 27% yield of diethylated product **15** (entry 3). The absolute configuration of **14** was assigned to be *R* by converting the major diastereoisomer of **14** into cyclic product **9a**. Deprotection of the TBDMS group followed by lactonization with *p*-TsOH gave the cyclic (*R*)-product **9a**. The acyclic nitrone **5** existed as an *E*/*Z* mixture with a ratio of 5:7 in $CDCl_3$, which was determined by ^1H NMR. Isomerization of the *E*-isomer led exclusively to the *Z*-isomer in the presence of $TiCl_4$ or $Cu(OTf)_2$ as observed by ^1H NMR (Figure 2).[29] An improvement in the diastereoselectivity was expected in the presence of these Lewis acids; however, only moderate diastereoselectivities were obtained (entries 4−6).

Diastereoselective Radical Addition to BIGN. *N*-Benzyl-2.3-*O*-isopropylidene-D-glyceraldehyde nitrone (BIGN) **16** is known to be a reactive substrate for 1,3-dipolar cycloaddition reactions[30] and nucleophilic additions of organometallic reagents.[31] However, radical reaction of **16** has not been explored. We finally studied the diastereoselective radical addition to BIGN **16** (Scheme 9). In the absence of Lewis acid, the ethyl radical addition to **16** in CH_2Cl_2 proceeded smoothly to give an 85:15 anti/syn mixture of diethylated product **18a** in 46% yield (Table 6, entry 1). The reaction of **16** in boiling benzene proceeded with better chemical efficiency (entry 2). In marked contrast to the radical reaction giving the anti isomer, selective formation of the syn isomer was reported in the reaction of **16** with Grignard reagents.[31b] Therefore, the effect of Lewis acid on anti/syn selectivity was investigated. As expected, the selective formation of syn isomer **18a** was observed in the presence of $Mg(ClO_4)_2$ (entry 3).

SCHEME 9

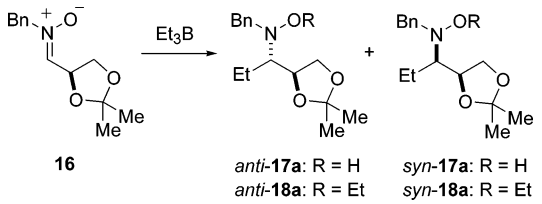


TABLE 6. Radical Addition to Acyclic Nitrone 16

entry	solvent	Lewis acid	T (°C)	yield (%)[a] **17a**	**18a**	selectivity of **18a**[b] anti:syn
1[c]	CH_2Cl_2	none	20	trace	46	85:15
2[c]	benzene	none	reflux	18	54	82:18
3[d]	CH_2Cl_2	$Mg(ClO_4)_2$	0	trace	47	3:97

[a] Isolated yield. [b] Selectivities of anti and syn isomers were determined by ^1H NMR analysis. [c] Reactions of **16** were carried out with Et_3B (5.0 equiv). [d] Reaction of **16** was carried out with Et_3B (5.0 equiv) in the presence of $Mg(ClO_4)_2$ (1.0 equiv).

In the absence of Lewis acid, dipole−dipole interaction controls the rotamer population and is responsible for the observed stereoselection in radical reaction (Figure 3). Thus, the rotamer **B** having the N−O bond moiety anti to the acetal oxygen atom would be favored in order to minimize the dipole−dipole interaction between these moieties. The syn selectivity observed in the reaction with $Mg(ClO_4)_2$ can be explained by invoking a favorable conformer **C**.

The alkyl radical addition to **16** was carried out in the absence of Lewis acid (Scheme 10). The isopropyl radical addition to **16** also proceeded by using *i*-PrI and Et_3B to give the isopropylated product **17b** and the diisopropylated product **18b** with high diastereoselectivity, respectively. Excellent anti selectivity was also achieved in the reactions with a cyclopentyl radical. It is important to note that anti selectivity in the reaction of **16** with Grignard reagent has been difficult to achieve.

(29) Tamura's group reported that tandem transesterification, *E*,*Z*-isomerization, and cycloaddition of nitrones proceeded in the presence of titanium tetraisopropoxide. See: (a) Tamura, O.; Yamaguchi, T.; Noe, K.; Sakamoto, M. *Tetrahedron Lett.* **1993**, *34*, 4009. (b) Tamura, O.; Okabe, T.; Yamaguchi, T.; Gotanda, K.; Noe, K.; Sakamoto, M. *Tetrahedron* **1995**, *51*, 107.

(30) Merino, P.; Mates, J. A.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Romeo, G.; Iannazzo, D.; Romeo, R. *Tetrahedron*: *Asymmetry* **2002**, *13*, 173.

(31) (a) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3489. (b) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301. (c) Merino, P.; del Alamo, E. M.; Bona, M.; Franco, S.; Merchan, F. L.; Tejero, T.; Vieceli, O. *Tetrahedron Lett.* **2000**, *41*, 9239. (d) Merino, P.; Franco, S.; Merchan, F. L.; Revuelta, J.; Tejero, T. *Tetrahedron Lett.* **2002**, *43*, 459.

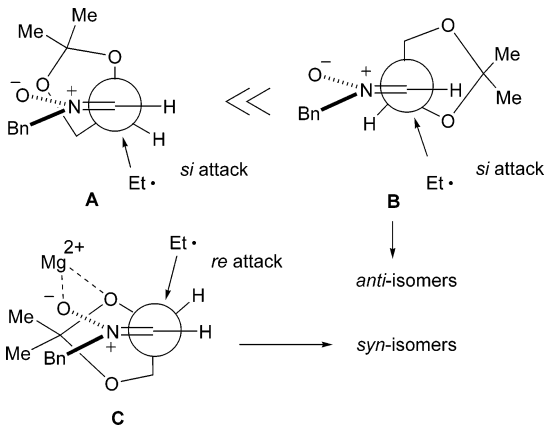
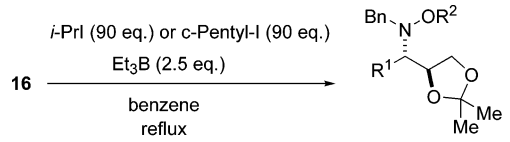


FIGURE 3. Stereochemical feature of radical addition to nitrone **16**.

SCHEME 10



17b: R^1 = *i*-Pr, R^2 = H (14% yield, 90 : 10)
18b: $R^1 = R^2$ = *i*-Pr (40% yield, >95 : 5)
17c: R^1 = c-Pentyl, R^2 = H (11% yield, 93 : 7)
18c: $R^1 = R^2$ = c-Pentyl (30% yield, >95 : 5)

Conclusion

We have demonstrated that nitrones are excellent radical acceptors for intermolecular carbon−carbon bond-forming radical reactions. In addition to intermolecular radical reaction of oxime ethers, hydrazones, and *N*-sulfonylimines, the diastereoselective reaction of nitrones disclosed a broader aspect of the utility of imino radical acceptors for the synthesis of various types of amino compounds.

Experimental Section

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[[oxide(phenylmethyl)imino]acetyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (2). To a solution of *N*-benzylhydroxylamine (20 mg, 0.16 mmol) and hemiacetal **1** (50 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added $CaCl_2$ (27 mg, 0.24 mmol) under N_2 atmosphere at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated at reduced pressure to afford nitrone **2** as a colorless oil (*E*:*Z* = 1:2). After characterization by ^{1}H and ^{13}C NMR spectra, unstable **2** was immediately subjected to radical reaction. ^{1}H NMR ($CDCl_3$) δ 7.54−7.22 (5H, m), 5.18 (2/3H, s), 5.01 (1/3H, s), 4.22−3.88 (3H, m), 3.54−3.38 (2H, m), 2.34−1.76 (5H, m), 1.50−1.20 (2H, m), 1.15, 0.97 (each 6/3H, s), 1.08, 0.95 (each 3/3H, s); ^{13}C NMR ($CDCl_3$) δ 158.3, 156.6, 133.1, 131.5, 129.7, 129.5, 129.2, 129.0, 128.8, 128.6, 126.8, 124.7, 73.7, 67.9, 65.0, 64.8, 53.0, 52.9, 48.8, 48.7, 47.9, 47.8, 44.6, 44.5, 38.3, 38.0, 32.8, 32.7, 26.5, 26.4, 20.7, 19.8.

General Procedure for Radical Reaction of 2. To a solution of **2** (0.16 mmol) in benzene (5 mL) or *i*-PrI−benzene (4 mL, 3:1, v/v) were added *i*-PrI (0.48 mL, 4.8 mmol or 1.4 mL, 14 mmol) and Et_3B (1.0 M in hexane, 0.80 mL, 0.80 mmol) in the presence of 20 mL of O_2 under N_2 atmosphere at reflux. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1) afforded **3a**−**c**.

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[3-methyl-1-oxo-2-[hydroxy(phenylmethyl)amino]butyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (3a). A colorless oil. IR ($CHCl_3$) 3568, 2966, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40−7.21 (5H, m), 5.70 (1H, br s), 4.21 (1H, d, J = 14 Hz), 4.04 (1H, t, J = 6.5 Hz), 3.93 (1H, d, J = 8.5 Hz), 3.81 (1H, d, J = 14 Hz), 3.53, 3.49 (2H, ABq, J = 14 Hz), 2.51−2.43 (1H, m), 2.16 (2H, br d, J = 6 Hz), 1.99−1.85 (3H, m), 1.49−1.35 (2H, m), 1.21, 1.10 (each 3H, d, J = 7 Hz), 1.16, 0.99 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 174.5, 138.5, 128.6, 128.1, 126.9, 73.3, 65.2, 61.6, 53.3, 48.0, 47.7, 44.6, 38.5, 33.0, 30.5, 26.4, 20.7, 20.3, 20.0, 19.3; HRMS calcd for $C_{22}H_{32}N_2O_4S$ (M^+) 420.2081, found 420.2087. $[\alpha]^{18}_D$ +17.4 (*c* 1.04, $CHCl_3$).

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[3-methyl-1-oxo-2-[1-methylethoxy(phenylmethyl)amino]butyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (3b). A colorless oil. IR ($CHCl_3$) 2967, 2928, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40−7.21 (5H, m), 4.23−4.12 (1H, br m), 4.18, 4.04 (each 1H, d, J = 14 Hz), 4.07−4.01 (1H, br m), 3.47−3.45 (2H, ABq, J = 14 Hz), 3.40−3.30 (1H, br m), 2.24−2.06 (3H, m), 1.95−1.85 (3H, m), 1.48−1.36 (2H, m), 1.26, 1.04 (each 3H, d, J = 7 Hz), 1.15, 0.96 (each 3H, s), 1.00, 0.64 (each 3H, d, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 139.7, 130.2, 127.8, 126.8, 73.8, 72.9, 65.5, 57.4, 53.2, 47.7, 44.4, 38.6, 33.0, 31.3, 29.7, 26.5, 20.60, 20.57, 20.5, 20.3, 20.0, 19.8; HRMS calcd for $C_{25}H_{38}N_2O_4S$ (M^+) 462.2550, found 462.2547. $[\alpha]^{17}_D$ +73.3 (*c* 0.60, $CHCl_3$).

(3a*R*,6*S*,7a*S*)-Hexahydro-8,8-dimethyl-1-[1-oxo-2-[hydroxy(phenylmethyl)amino]butyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide (3c). Colorless crystals. Mp 126−129 °C (AcOEt/hexane). IR ($CHCl_3$) 3569, 2966, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42−7.21 (5H, m), 5.77 (1H, br s), 4.09 (1H, dd, J = 7.5, 5.5 Hz), 4.08, 3.95 (each 1H, d, J = 14 Hz), 3.98 (1H, t, J = 6.5 Hz), 3.51, 3.46 (2H, ABq, J = 14 Hz), 2.14−1.82 (7H, m), 1.50−1.30 (2H, m), 1.15, 0.98 (each 3H, s), 1.10 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 174.1, 137.9, 128.9, 128.2, 127.1, 69.3, 64.9, 61.5, 53.0, 48.4, 47.8, 44.5, 38.3, 32.8, 26.4, 23.8, 20.7, 19.9, 10.5; HRMS calcd for $C_{21}H_{30}N_2O_4S$ (M^+) 406.1924, found 406.1921. Anal. Calcd for $C_{21}H_{30}N_2O_4S$: C, 62.04; H, 7.44; N, 6.89; S, 7.89. Found: C, 62.17; H, 7.62; N, 6.88; S, 7.95. $[\alpha]^{19}_D$ +20.0 (*c* 0.69, $CHCl_3$).

Ethyl Radical Addition to 4 (Table 2, entries 1−3). To a solution of nitrone **4** (50 mg, 0.19 mmol) in CH_2Cl_2 or benzene (5 mL) was added Et_3B (1.0 M in hexane, 0.94 mL, 0.94 mmol) in the presence of 20 mL of O_2 under N_2 atmosphere at +20 or −78 °C or reflux. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1, 2-fold developments) afforded **9a**−**11a**.

Ethyl Radical Addition to 4, Using Bu_3SnH (Table 2, entries 4 and 5). To a solution of nitrone **4** (50 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) were added Bu_3SnH (0.060 mL, 0.23 mmol) and Et_3B (1.0 M in hexane, 0.94 mL, 0.94 mmol) in the presence of 20 mL of O_2 under N_2 atmosphere at +20 or −78 °C. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1, 3-fold developments) afforded **9a**−**11a**.

Ethyl Radical Addition to 4 under Ar and O_2 Atmosphere (Table 3). A solution of nitrone **4** (50 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was degassed. To the mixture was added Et_3B (1.0 M in hexane, 0.94 mL, 0.94 mmol) in the presence of 0.05, 5, or 50 equiv of O_2 under Ar atmosphere at +20 °C. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1) afforded **9a**−**11a**.

(3*R*,5*R*,6*S*)-3-Ethyl-4-hydroxy-5,6-diphenyl-2-morpholinone (9a). Colorless crystals. Mp 174−176 °C (AcOEt/hexane). IR ($CHCl_3$) 3572, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32−7.14 (10H, m), 6.17 (1H, d, J = 3.5 Hz), 4.95 (1H, br s), 4.85 (1H, d, J = 3.5 Hz), 3.60 (1H, t, J = 4.5 Hz), 2.15−2.00 (2H, m), 1.05 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.5, 135.8, 131.4, 130.7, 128.4, 128.3, 127.7, 125.4, 78.6, 68.7, 64.3, 22.0, 9.6; HRMS calcd for $C_{18}H_{19}NO_3$ (M^+) 297.1364, found 297.1364. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.45; H, 6.41; N, 4.72. $[\alpha]^{26}_D$ −7.0 (*c* 1.00, $CHCl_3$).

(3*R*,5*R*,6*S*)-4-Ethoxy-3-ethyl-5,6-diphenyl-2-morpholinone (10a). A colorless oil. IR ($CHCl_3$) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.14 (6H, m), 6.16 (1H, br d, J = 3.5 Hz), 4.86 (1H, d, J = 3.5 Hz), 4.04−3.90 (2H, m), 3.56 (1H, t, J = 4.5 Hz), 2.10−1.96 (2H, m), 1.26 (3H, t, J = 7.5 Hz), 1.06 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 170.8, 136.0, 132.1, 130.7, 128.3, 128.1, 127.6, 125.4, 78.8, 68.4, 65.6, 63.4, 21.9, 14.1, 9.8; HRMS calcd for $C_{20}H_{23}NO_3$ (M^+) 325.1676, found 325.1688. $[\alpha]^{29}_D$ −59.1 (*c* 1.10, $CHCl_3$).

(5*R*,6*S*)-3-Ethyl-5,6-dihydro-5,6-diphenyl-2*H*-1,4-oxadin-2-one 4-Oxide (11a). Colorless crystals. Mp 158−160 °C (AcOEt/hexane). IR ($CHCl_3$) 3033, 1721, 1549 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32−7.15 (6H, m), 7.03 (2H, m), 6.82 (2H, m), 6.05 (1H, d, J = 3.3 Hz), 5.15 (1H, d, J = 3.3 Hz), 3.02−2.80 (2H, m), 1.26 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 159.6, 140.6, 132.5, 129.4, 129.2, 128.9, 128.5, 128.3, 127.6, 126.0, 78.1, 77.2, 19.1, 9.1; HRMS calcd for $C_{18}H_{17}NO_3$ (M^+) 295.1207, found 295.1222. Anal. Calcd for $C_{18}H_{17}NO_3 \cdot {}^1/_4H_2O$: C, 72.10; H, 5.88; N, 4.67. Found: C, 72.18; H, 5.85; N, 4.71. $[\alpha]^{27}_D$ +573.0 (*c* 1.01, $CHCl_3$).

General Procedure for Alkyl Radical Addition to 4. To a solution of nitrone **4** (50 mg, 0.19 mmol) in RI−benzene (5 mL, 3:1, v/v) was added Et_3B (1.0 M in hexane, 0.47 mL, 0.47 mmol) in the presence of 20 mL of O_2 under N_2 atmosphere at reflux. After being stirred at the same temperature for 30 min, the reaction mixture was concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2:1) afforded the alkylated products **9b**−**d** and the ethylated product **9a**.

(3*R*,5*R*,6*S*)-4-Hydroxy-3-isopropyl-5,6-diphenyl-2-morpholinone (9b). Colorless crystals. Mp 104−106 °C (AcOEt/hexane). IR ($CHCl_3$) 3569, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27−7.14 (10H, m), 5.98 (1H, d, J = 3 Hz), 4.98 (1H, br s), 4.76 (1H, d, J = 3 Hz), 3.63 (1H, d, J = 3 Hz), 2.46 (1H, m), 1.21, 1.15 (each 3H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 170.0, 135.4, 131.2, 130.7, 128.4, 128.3, 127.9, 125.7, 79.2, 70.6, 69.7, 31.0, 19.5, 18.7; HRMS calcd for $C_{19}H_{21}NO_3$ (M^+) 311.1521, found 311.1530. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.38; H, 6.81; N, 4.56. $[\alpha]^{28}_D$ +51.6 (*c* 0.61, $CHCl_3$).

(3*R*,5*R*,6*S*)-3-Cyclohexyl-4-hydroxy-5,6-diphenyl-2-morpholinone (9c). Colorless crystals. Mp 152−155 °C (AcOEt/hexane). IR ($CHCl_3$) 3569, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28−7.11 (10H, m), 5.94 (1H, d, J = 3.5 Hz), 4.94 (1H, br s), 4.73 (1H, d, J = 3.5 Hz), 3.66 (1H, d, J = 2.5 Hz), 2.15−1.16 (11H, m); ^{13}C NMR ($CDCl_3$) δ 170.3, 135.4, 131.4, 130.6, 128.4, 128.2, 127.9, 125.8, 79.2, 70.8, 69.8, 41.6, 29.7, 29.5, 26.7, 26.2; HRMS calcd for $C_{22}H_{25}NO_3$ (M^+) 351.1833, found 351.1833. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.89; H, 7.09; N, 3.95. $[\alpha]^{28}_D$ +19.7 (*c* 0.60, $CHCl_3$).

(3*R*,5*R*,6*S*)-3-Cyclopentyl-4-hydroxy-5,6-diphenyl-2-morpholinone (9d). Colorless crystals. Mp 161−164 °C (AcOEt/hexane). IR ($CHCl_3$) 3569, 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27−7.16 (10H, m), 6.18 (1H, d, J = 3.5 Hz), 5.10 (1H, br s), 4.80 (1H, d, J = 3.5 Hz), 3.68 (1H, d, J = 5.5 Hz), 2.60−2.51 (1H, m), 2.08−1.40 (8H, m); ^{13}C NMR ($CDCl_3$) δ 170.6, 136.0, 132.3, 130.4, 128.4, 128.3, 127.7, 125.6, 78.3, 69.1, 66.9, 41.5, 30.4, 29.4, 25.4, 24.9; HRMS calcd for $C_{21}H_{23}NO_3$ (M^+) 337.1677, found 337.1701. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.48; H, 6.82; N, 4.14. $[\alpha]^{28}_D$ +17.5 (*c* 1.00, $CHCl_3$).

General Procedure for Ethyl Radical Addition to 5. To a solution of nitrone **5** (50 mg, 0.12 mmol) in benzene, CH_2Cl_2, or H_2O−EtOH (3:2, v/v) (5 mL) was added Et_3B (1.0 M in hexane, 0.59 mL, 0.59 mmol) in the presence of 20 mL of O_2 under N_2 atmosphere at 20 °C. After being stirred at the same temperature for 90 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **14**−**15**.

[(1*R*,2*S*)-*N*-(2-*tert*-Butyldimethylsilyloxy-1,2-diphenylethyl)-*N*-hydroxy]-2-ethylglycine Ethyl Ester (14). Major isomer: A colorless oil. IR ($CHCl_3$) 3556, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.18 (10H, m), 5.48 (1H, s), 5.32 (1H, d, J = 6.9 Hz), 4.05−3.91 (2H, m), 3.87 (1H, d, J = 6.9 Hz), 3.24 (1H, t, J = 6 Hz), 1.73−1.62 (2H, m), 1.18 (3H, t, J = 7.2 Hz), 0.68 (9H, s), 0.64 (3H, t, J = 7.5 Hz), −0.18, −0.30 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 173.2, 143.7, 136.4, 130.5, 127.5, 127.4, 127.0, 75.6, 74.9, 67.3, 60.3, 25.5, 21.4, 17.9, 14.0, 9.6, −4.7, −5.5; HRMS calcd for $C_{26}H_{40}NO_4Si$ ($M + H^+$) 458.2724, found 458.2721. $[\alpha]^{23}_D$ +56.2 (*c* 1.26, $CHCl_3$). Minor isomer: A colorless oil. IR ($CHCl_3$) 3581, 2958, 2931, 2857, 1703, 1472, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−6.84 (10H, m), 5.78 (1H, s), 5.61 (1H, d, J = 2.7 Hz), 4.15−4.00 (2H, m), 3.95 (1H, d, J = 2.7 Hz), 3.17 (1H, dd, J = 9.5, 5.5 Hz), 2.06−1.62 (2H, m), 1.16 (3H, t, J = 7.2 Hz), 1.00 (3H, t, J = 7.2 Hz), 0.90 (9H, s), −0.14, −0.16 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 174.0, 142.9, 135.5, 130.7, 127.5, 127.2, 127.0, 126.7, 126.6, 77.8, 73.8, 65.4, 60.2, 25.8, 23.6, 18.2, 14.1, 10.9, −4.9; HRMS calcd for $C_{26}H_{40}NO_4Si$ ($M + H^+$) 458.2724, found 458.2744. $[\alpha]^{22}_D$ +38.9 (*c* 1.47, $CHCl_3$).

[(1*R*,2*S*)-*N*-(2-*tert*-Butyldimethylsilyloxy-1,2-diphenylethyl)-*N*-ethoxy]-2-ethylglycine Ethyl Ester (15). A colorless oil (a 2:1 mixture of diastereoisomers). IR ($CHCl_3$) 2958, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−6.84 (10H, m), 5.29 (1H, d, J = 4.8 Hz), 4.31−4.00 (2 + 1/3 + 1H, m), 3.90−3.62 (4/3H, m), 3.52 (2/3H, dd, J = 9.6, 4.5 Hz), 3.27 (1/3H, t, J = 7.5 Hz), 2.04−1.72 (2H, m), 1.37 (6/3H, t, J = 6.9 Hz), 1.30 (6/3H, t, J = 6.9 Hz), 1.03 (3H, t, J = 6.9 Hz), 0.95 (9/3H, s), 0.89 (18/3H, s), 0.88 (6/3H, t, J = 7.5 Hz), 0.11, −0.34 (each 3/3H, s), 0.06, −0.30 (each 6/3H, s); ^{13}C NMR ($CDCl_3$) δ 171.6, 170.8, 142.9, 136.8, 136.0, 131.7, 131.3, 128.3, 127.7, 127.5, 127.3, 127.2, 127.1, 127.0, 126.82, 126.77, 126.6, 77.2, 76.7, 75.6, 74.9, 74.8, 71.2, 70.5, 67.6, 60.1, 59.8, 53.4, 25.8, 25.7, 23.4, 18.1, 18.0, 14.24, 14.20, 13.7, 10.8, 10.6, −3.8, −4.2, −5.1, −5.3; HRMS calcd for $C_{28}H_{43}NO_4Si$ (M^+) 485.2959, found 485.2940. $[\alpha]^{21}_D$ +68.5 (*c* 1.09, $CHCl_3$).

General Procedure for Ethyl Radical Addition to 16. To a solution of nitrone **16** (50 mg, 0.21 mmol) and $Mg(ClO_4)_2$ (47 mg, 0.21 mmol or none) in CH_2Cl_2 or benzene (5 mL) was added Et_3B (1.0 M in hexane, 1.1 mL, 1.1 mmol) in the presence of 20 mL of O_2 under N_2 atmosphere at 20 or −78 °C or reflux. After being stirred at the same temperature for 2−4 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 10:1, 2-fold developments) afforded **17a** and **18a**.

(3*S*,4*S*)-1,2,3-Trideoxy-3-[hydroxy(phenylmethyl)amino]-4,5-*O*-(1-methylethylidene)pentitol (*anti*-17a) and **(3*R*,4*S*)-1,2,3-Trideoxy-3-[hydroxy(phenylmethyl)amino]-4,5-*O*-(1-methylethylidene)pentitol (*syn*-17a).** A colorless oil (a 6:1 mixture of *anti*-**17a** and *syn*-**17a**). IR ($CHCl_3$) 3576, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.22 (5H, m), 5.20−4.94 (1H, br s), 4.50−4.40 (1/7H, m), 4.32 (6/7H, q, J = 7 Hz), 4.14−4.32 (4H, m), 2.83−2.74 (1/7H, m), 2.70−2.60 (6/7H, m), 1.92−1.56 (2H, m), 1.43, 1.39 (each 3/7H, s), 1.41, 1.36 (each 18/7H, s), 1.08 (18/7H, t, J = 7.5 Hz), 1.02 (3/7H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 138.3, 129.4, 128.3, 127.2, 108.7, 76.0, 69.7, 68.6, 60.1, 26.6, 25.5, 19.6, 12.1; HRMS calcd for $C_{15}H_{23}NO_3$ (M^+) 265.1677, found 265.1668. $[\alpha]^{18}_D$ −4.7 (*c* 0.96, $CHCl_3$).

(3*S*,4*S*)-1,2,3-Trideoxy-3-[ethoxy(phenylmethyl)amino]-4,5-*O*-(1-methylethylidene)pentitol (*anti*-18a). A colorless oil. IR ($CHCl_3$) 2984, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.22 (5H, m), 4.28 (1H, q, J = 7 Hz), 4.16 (1H, dd, J = 6.5, 8.5 Hz), 3.84 (2H, s), 3.77 (1H, dd, J = 7, 8.5 Hz), 3.39−3.28 (2H, m), 2.74 (1H, td, J = 7, 5 Hz), 1.79−1.68 (2H, m), 1.38, 1.36 (each 3H, s), 1.11 (3H, t, J = 7.5 Hz), 0.88 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 138.7, 129.5, 128.0, 127.0, 108.6, 76.1, 69.1, 68.4, 58.0, 26.6, 25.5, 20.3, 13.9, 12.3; HRMS calcd for $C_{17}H_{27}NO_3$ (M^+) 293.1989, found 293.1985. $[\alpha]^{23}_D$ −13.6 (*c* 1.88, $CHCl_3$).

(3*R*,4*S*)-1,2,3-Trideoxy-3-[ethoxy(phenylmethyl)amino]-4,5-*O*-(1-methylethylidene)pentitol (*syn*-18a). A colorless oil. IR ($CHCl_3$) 2983, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.22 (5H, m), 4.54 (1H, ddd, J = 8, 6.5, 4.5 Hz), 4.05, 3.98 (2H, ABq, J = 13 Hz), 4.01, 3.80 (each 1H, d, J = 8 Hz), 3.53−3.41 (2H, m), 2.78 (1H, dt, J = 9, 4.5 Hz), 1.62−1.44 (2H, m), 1.41, 1.38 (each 3H, s), 1.00 (3H, t, J = 7 Hz), 0.95 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 138.6, 129.5, 128.0, 127.0, 107.7, 74.3, 69.1, 66.6, 66.4, 59.8, 26.4, 25.2, 19.4, 13.9, 11.9; HRMS calcd for $C_{17}H_{27}NO_3$ (M^+) 293.1989, found 293.1985. $[\alpha]^{21}_D$ +42.0 (*c* 1.41, $CHCl_3$).

General Procedure for Alkyl Radical Addition to 16. To a solution of nitrone **16** (50 mg, 0.21 mmol) in benzene (5 mL) were added RI (19 mmol) and Et_3B (1.0 M in hexane, 0.52 mL, 0.52 mmol) in the presence of 20 mL of O_2 under N_2 atmosphere at reflux. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 5:1) afforded **17b**,**c** and **18b**,**c**.

(3*S*,4*S*)-1,2,3-Trideoxy-3-[hydroxy(phenylmethyl)amino]-2-methyl-4,5-*O*-(1-methylethylidene)pentitol (*anti*-17b) and (3*R*,4*S*)-1,2,3-Trideoxy-3-[hydroxy(phenylmethyl)amino]-2-methyl-4,5-*O*-(1- methylethylidene)pentitol (*syn*-17b). A white solid oil (a 9:1 mixture of *anti*-**17b** and *syn*-**17b**). IR ($CHCl_3$) 3577, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.25 (5H, m), 4.64 (1H, br s), 4.47 (1/10H, q, J = 7 Hz), 4.46 (9/10H, q, J = 7 Hz), 4.16−4.11 (1H, m), 3.93−3.89 (3H, m), 2.67 (9/10H, dd, J = 7, 3.5 Hz), 2.63(1/10H, dd, J = 7, 4 Hz), 2.33−2.26 (1H, m), 1.42, 1.37 (each 3H, s), 1.11, 1.09 (each 27/10H, d, J = 7 Hz), 1.10, 1.08 (each 3/10H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 138.5, 129.2, 129.1, 128.6, 128.5, 128.3, 127.3, 108.4, 74.5, 74.4, 72.3, 68.7, 62.0, 61.9, 27.1, 26.7, 25.3, 21.4, 19.8; HRMS calcd for $C_{16}H_{25}NO_3$ (M^+) 279.1833, found 279.1834.

(2*S*,3*S*)-3-Cyclopentyl-3-[hydroxy(phenylmethyl)amino]-1,2-*O*-(1-methylethylidene)-1,2-propanediol (*anti*-17c) and (2*S*,3*R*)-3-Cyclopentyl-3-[hydroxy(phenylmethyl)-amino]-1,2-*O*-(1-methylethylidene)-1,2-propanediol (*syn*-17c). A white solid (a 9:1 mixture of *anti*-**17c** and *syn*-**17c**). IR ($CHCl_3$) 3574, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.22 (5H, m), 5.41 (1/10H, br s), 5.19 (9/10H, br s), 4.54−4.49 (1/10H, m), 4.47 (9/10H, q, J = 6.5 Hz), 4.10 (9/10H, dd, J = 8, 6.5 Hz), 3.94, 3.86 (18/10H, ABq, J = 13.5 Hz), 3.86−3.60 (2/10H+1H, m), 2.83 (1/10H, dd, J = 8.5, 5 Hz), 2.74 (9/10H, dd, J = 7, 6 Hz), 2.26−2.20 (1H, m), 1.94−1.85 (2H, m), 1.72−1.30 (6H, m), 1.43, 1.37 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 138.7, 129.3, 128.3, 127.2, 108.7, 74.9, 71.1, 68.5, 60.4, 39.5, 31.5, 30.5, 26.7, 25.4, 25.3, 24.2; HRMS calcd for $C_{18}H_{28}NO_3$ ($M + H^+$) 306.2068, found 306.2069.

(3*S*,4*S*)-1,2,3-Trideoxy-2-methyl-3-[1-methylethoxy-(phenylmethyl)amino]-4,5-*O*-(1-methylethylidene)pentitol (*anti*-18b). A colorless oil. IR ($CHCl_3$) 2974, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.22 (5H, m), 4.43−4.35 (1H, br m), 4.18−4.14 (1H, m), 3.86, 3.83 (2H, ABq, J = 13.5 Hz), 3.75−3.66 (1H, br m), 3.56−3.48 (1H, m), 2.61 (1H, br m), 2.33−2.25 (1H, m), 1.35, 1.33 (each 3H, s), 1.16, 1.08 (each 3H, d, J = 7 Hz), 0.95 (3H, br s), 0.90 (3H, d, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 138.4, 129.9, 128.0, 127.2, 121.3, 108.5, 74.4, 73.5, 69.5, 59.3, 26.6, 26.4, 25.5, 22.6, 21.5, 21.4, 19.8; HRMS calcd for $C_{19}H_{31}NO_3$ (M^+) 321.2303, found 321.2305. $[\alpha]^{18}_D$ −4.1 (*c* 1.58, $CHCl_3$).

(2*S*,3*S*)-3-Cyclopentyl-3-[cyclopentyloxy(phenylmethyl)-amino]-1,2-*O*-(1- methylethylidene)-1,2-propanediol (*anti*-18c). A colorless oil. IR ($CHCl_3$) 3032, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.24 (5H, m), 4.46−4.38 (1H, br m), 4.16 (1H, dd, J = 8.5, 6.5 Hz), 3.87, 3.72 (each 1H, d, J = 13.5 Hz), 3.84−3.78 (1H, br m), 3.76−3.70 (1H, br m), 2.88 (1H, t, J = 6.5 Hz), 2.25−2.15 (1H, br m), 2.00−1.20 (16H, m), 1.38, 1.37 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 138.9, 129.9, 129.8, 127.94, 127.92, 127.0, 121.3, 108.5, 82.9, 69.5, 69.3, 57.7, 39.8, 31.9, 31.6, 31.5, 30.6, 26.6, 25.6, 25.4, 24.1, 23.3, 23.1; HRMS calcd for $C_{23}H_{35}NO_3$ (M^+) 373.2615, found 373.2629. $[\alpha]^{16}_D$ −7.6 (*c* 1.24, $CHCl_3$).

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Supporting Information Available: Experimental procedure and characterization data for compounds **1**, **4**, **5**, **7**, **12**, **13**, and **16**, and ^1H and ^{13}C NMR spectra of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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