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INTERMOLECULAR CARBON RADICAL ADDITION TO CYCLIC NITRONE

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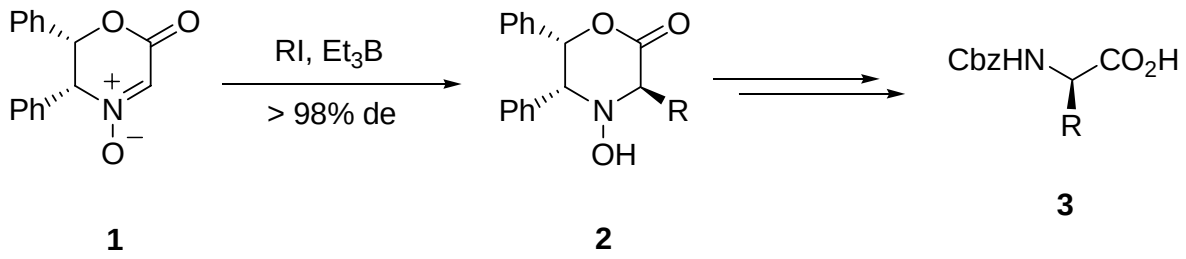
Abstract – The intermolecular radical addition to chiral glyoxylic nitrone was studied. The ethyl radical addition to nitrone by using triethylborane proceeded smoothly to give the desired ethylated product with moderate diastereoselectivities accompanying with the ethylated nitrone and the diethylated product. The radical reaction of nitrone took place even in aqueous media. The investigation of optimal reaction conditions and the reaction pathway were described.

INTRODUCTION

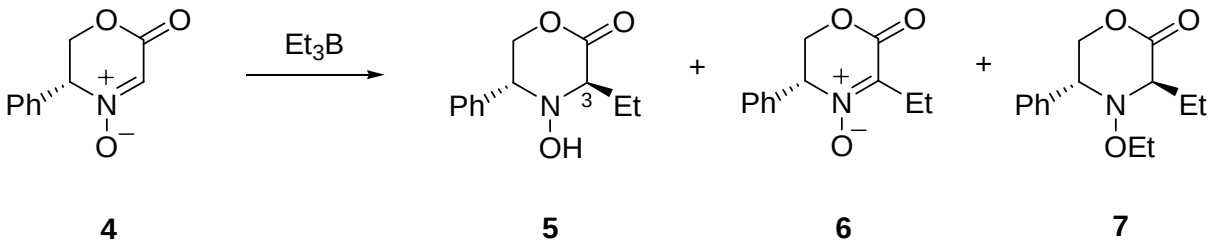
The carbon-nitrogen double bonds of imine derivatives are of great interest as radical acceptors in synthetic organic chemistry. The reductive radical addition to C=N bonds is important due to the prevalence of organic compounds in nature that contain the amine functional group. Compared with the extensive investigations into radical cyclization of imine derivatives,[1,2] the intermolecular radical addition to imines has not been widely studied. Therefore, the studies on intermolecular carbon-carbon bond-forming radical reactions of various imines have been recently demonstrated by several groups.[3-10] Nitrone is well-known to be a reactive substrate for 1,3-dipolar cycloaddition reactions, nucleophilic additions of organometallic reagents, and so on.[11,12] Although nitrone has also evolved as a useful trap for short-lived reactive free radicals,[13] the synthetically useful radical reactions of nitrone are not available until now.[14,15] As a part of our program directed toward the screening of reactive imino radical acceptors, we have recently reported the highly diastereoselective radical addition to chiral nitrone **1** for the asymmetric synthesis of α-amino acids **3** (Scheme 1).[16] In this paper, we describe full details of radical addition to simple nitrone **4** and the reaction pathway.[17]



Scheme 1. Radical Addition to Nitrone **1**

RESULTS AND DISCUSSION

The radical addition reaction of nitrone **4** using triethylborane as an ethyl radical source was studied under the several reaction conditions (Scheme 2, Table 1).[18] To a solution of nitrone **4** in CH_2Cl_2 was added 1.0 M solution of Et_3B in hexane (5 equiv), and then the reaction mixture was stirred at 25 ^oC for 5 min. As expected, the radical reaction proceeded smoothly to give a 78:22 diastereomeric mixture of the desired ethylated product **5** in 46% yield, accompanying with 15% yield of the ethylated nitrone **6** and 9% yield of the diethylated product **7** (Table 1, entry 1). We were able to separate and purify each diastereomeric isomers 3*R*-**5** and 3*S*-**5** by PTLC. Thus, the absolute configuration of the minor product **5** could be determined to be *S* by X-ray analysis (Figure 1). Changing the temperature from 25 to –78 ^oC did not show significant effect in the diastereoselectivity (entry 2). Although the replacement of CH_2Cl_2 with benzene as a solvent did not lead to good diastereoselectivities (entry 3), changing the temperature from 25 ^oC to reflux in benzene led to an effective increase in the yield of the desired ethylated compound **5**. Treatment of **4** with Et_3B in boiling benzene for 1 min gave a 71:29 diastereomeric mixture of **5** in 63% yield (entry 4). The ratio of undesired ethylated nitrone **6** to the desired ethylated compound **5** was also dependent on the amount of Et_3B. The reaction using only 1 equiv of Et_3B in boiling benzene afford a significant amount of **6** (Table 1, entry 5).



Scheme 2. Radical Addition to Nitrone **4** by Using Et_3B

Table 1. Ethyl Radical Addition to Nitrone **4** by Using Et_3B[a]

Entry	Equivalent of Et_3B	Solvent (10 mL)	*T* (^oC)	Time (min)	Selectivity[b] 3*R*-**5** : 3*S*-**5**	Yield (%)[c] **5**	**6**	**7**
1	5	CH_2Cl_2	25	5	78 : 22	46 (14)	15	9
2	5	CH_2Cl_2	-78	60	80 : 20	32 (9)	14	13
3	5	benzene	25	5	73 : 27	49 (12)	15	10
4	5	benzene	reflux	1	71 : 29	63 (2)	9	14
5	1	benzene	reflux	1	71 : 29	59 (12)	19	nd

[a] All Reactions of nitrone **4** (50 mg, 0.26 mmol) were carried out in CH_2Cl_2 or benzene (10 mL). [b] Diastereoselectivities were determined by ^1H NMR analysis. [c] Isolated yields. Yields in parentheses are for the recovered starting nitrone **4**.

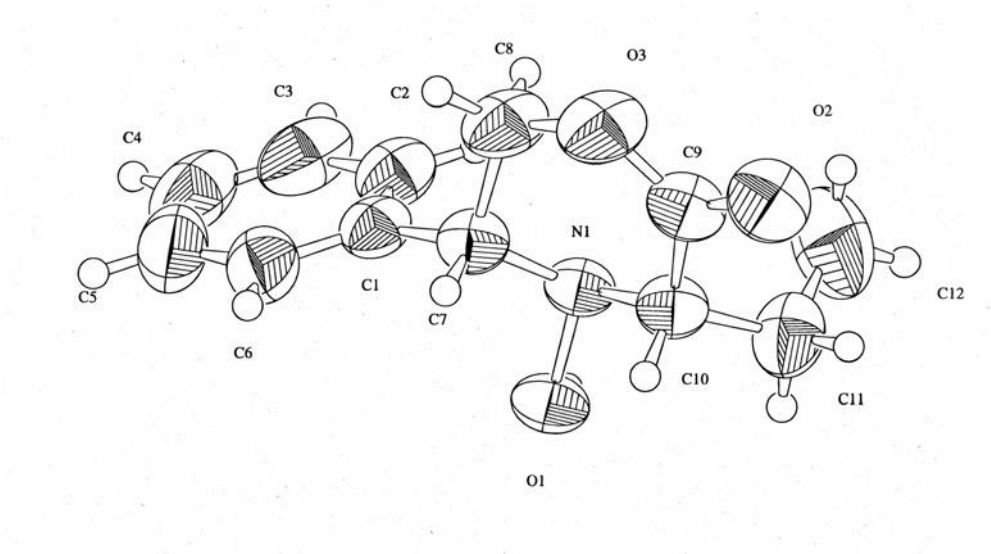
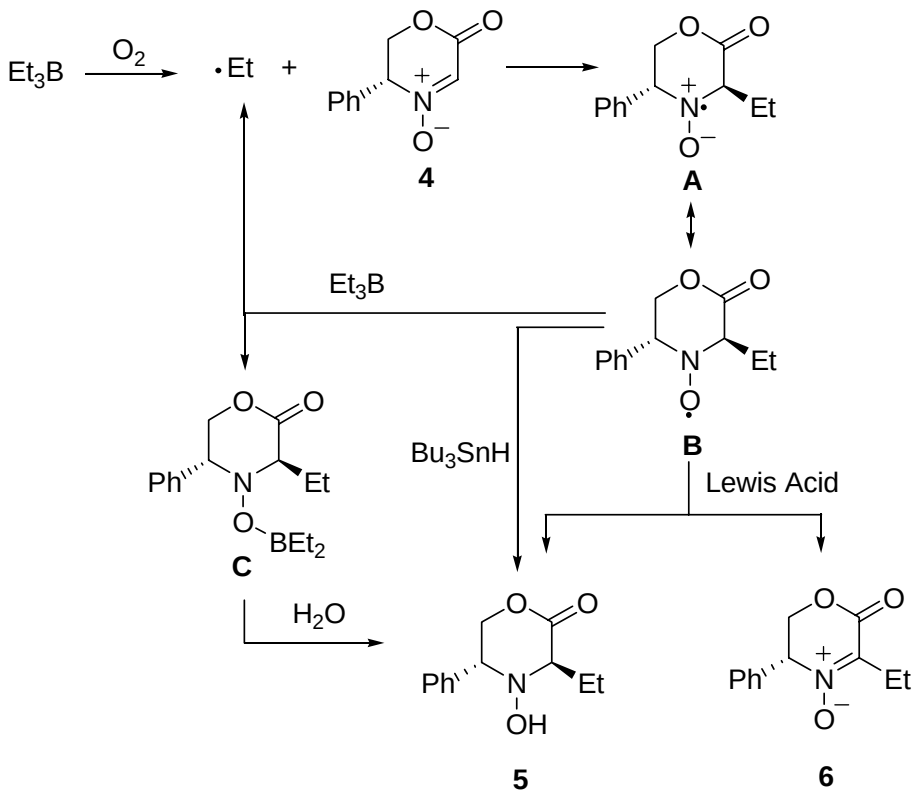


Figure 1. X-Ray Analysis of 3*S*-**5**

As shown in Scheme 3, the ethylated nitrone **6** would be obtained as a result of disproportionation reaction of the intermediate radical **B**, which was generated by the ethyl radical addition to nitrone **4**. These results indicate that Et_3B worked as not only a radical initiator but also a radical terminator to trap the intermediate radical **B** to give an adduct **C** and a chain-propagating ethyl radical, therefore a large amount of Et_3B is required for the selective formation of the desired ethylated product **5**.[19] However, the reaction of intermediate radical **B** with Et_3B is a slow process; thus, the formation of *C*- and *O*-diethylated product **7** may result from the accumulation of the nitroxide radical **B** in reaction mixture due to the persistent radical effect.



Scheme 3. Reaction Pathway of Radical Reaction of Nitrone **4**

Table 2. Concentration Effect of Nitrone **4** on Radical Addition Reaction[a]

Entry	Solvent	*T* (°C)	Time (min)	Selectivity[b] 3*R*-**5** : 3*S*-**5**	Yield (%)[c] **5**	**6**	**7**
1	CH_2Cl_2 (1 mL)	25	5	77 : 23	66 (6)	3	6
2	CH_2Cl_2 (5 mL)	25	5	77 : 23	58 (3)	12	4
3	CH_2Cl_2 (10 mL)	25	5	78 : 22	46 (14)	15	9
4	benzene (1 mL)	25	5	75 : 25	71 (13)	nd	11
5	benzene (10 mL)	25	5	73 : 27	49 (12)	15	10
6	benzene (100 mL)	25	5	73 : 27	31 (27)	20	8
7	benzene (1 mL)	reflux	1	70 : 30	71 (7)	4	5
8	benzene (10 mL)	reflux	1	71 : 29	63 (2)	9	4
9	benzene (100 mL)	reflux	1	69 : 31	40 (12)	15	nd

[a] All reactions of **4** (50 mg, 0.26 mmol) were carried out with Et_3B (5 equiv.) in CH_2Cl_2 or benzene. [b] Diastereoselectivities were determined by ^1H NMR analysis. [c] Isolated yields. Yields in parentheses are for the recovered starting nitrone **4**.

The ratio of the desired ethylated product **5** to the ethylated nitrone **6** was also dependent on the concentration of the substrate **4** (Table 2). Under the high dilution conditions, the yield of the desired product **5** diminished and the yield of the undesired product **6** increased. Good results were obtained by the use of 1 mL of CH_2Cl_2 or benzene for 0.26 mmol of substrate **4** at 25 °C (entries 1 and 4). Treatment of **4** in CH_2Cl_2 (1 mL) for 5 min gave a 77:23 diastereomeric mixture of **5** in 66% yield (entry 1), which is better than that obtained by the reaction in CH_2Cl_2 (10 mL) (entry 3). The reaction of **4** proceeded smoothly in benzene (1 mL) at 25 °C to afford **5** in 71% yield without the formation of the undesired product **6** (entry 4). In contrast, the reaction in benzene (100 mL) gave 31% yield of **5** and 20% yield of **6**, accompanying with 27% yield of starting nitrone **4** (entry 6). When the reaction was carried out in refluxing benzene, a similar trend was observed (entries 7-9).

Table 3. Radical Addition to Nitrone **4** in The Presence of Lewis Acids[a]

Entry	Lewis acid	*T* (°C)	Time (min)	Selectivity[b] 3*R*-**5** : 3*S*-**5**	Yield (%)[c] **5**	**6**
1	$BF_3{\cdot}OEt_2$	25	15	48 : 52	30	8
2	Bu_2BOTf	25	25	61 : 39	33	39
3	MAD	25	25	56 : 44	38	19
4	$BF_3{\cdot}OEt_2$	-78	30	52 : 48	20	9
5	Bu_2BTOf	-78	25	-	trace	30
6	MAD	-78	60	62 : 38	19	16
7	TMSOTf	-78	60	61 : 39	41	27
8	$MgBr_2$	-78	40	-	decomposed	

[a] All reaction of **4** (50 mg, 0.26 mmol) were carried out with Et_3B (5 equiv.) in CH_2Cl_2 (10 mL). [b] Diastereoselectivities were determined by ^1H NMR analysis. [c] Isolated yields. Yields in parentheses are for the recovered starting nitrone **4**.

To suppress the formation of the diethylated product **7**, several Lewis acids were screened (Table 3). As expected, the undesired product **7** was not formed in the presence of Lewis acid. In the presence of $BF_3{\cdot}OEt_2$, 30% yield of **5** as a 48:52 diastereomeric mixture was obtained without the formation of **7** (entry 1). However, the addition of Lewis acid led to a decease in the ratio of the desired ethylated product **5** to the ethylated nitrone **6**. In the case of Bu_2BOTf, 33% yield of **5** and 39% yield of **6** were obtained (entry 2). In the case of MAD (Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), 38% yield of **5** and 19% yield of **6** were obtained (entry 3). These results indicate that the intermediate radical **B** was not effectively trapped by Et_3B as a result of the competitive coordination of Lewis acid and Et_3B

to oxygen atom of **B**. Thus, the disproportionation reaction of the intermediate radical **B** was a significant side reaction. Additionally, the addition of Lewis acids influenced the degree of stereoselectivity. Good diastereoselectivities were not observed even at low reaction temperature (entries 4-8).

The stereochemical feature of this reaction can be rationalized in terms of steric control in the conformationally restricted nitrone **4** (Figure 2). In the absence of Lewis acid, the radical addition to the less hindered *re* (top) face is favored, presumably due to steric interactions with the phenyl group in nitrone **D**, which prevents addition to *si* (bottom) face. In the presence of Lewis acid, the steric repulsion between Lewis acids and phenyl group in **E** led to a decrease in diastereoselectivity.

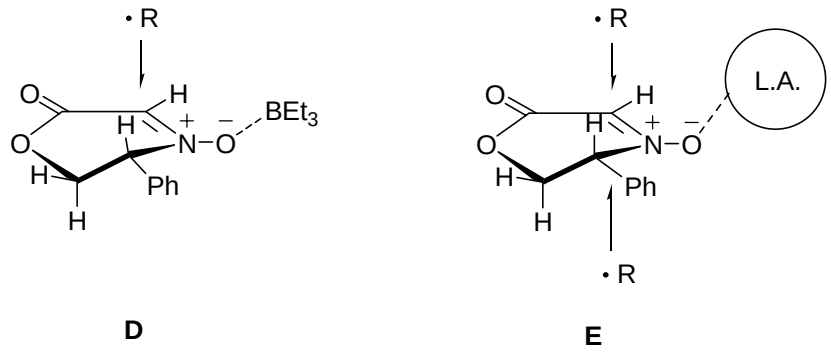
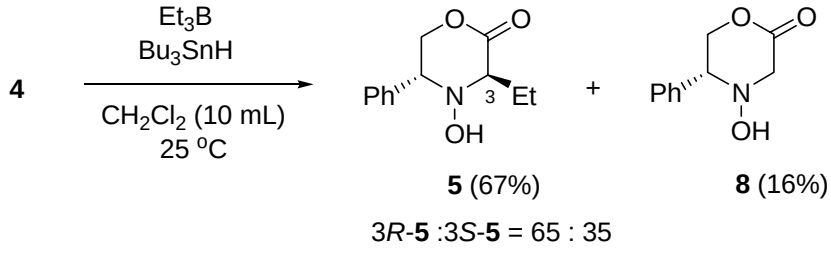


Figure 2. Stereochemical Feature

To suppress the formation of undesired ethylated nitrone **6**, we next employed Bu_3SnH as a hydride atom donor (Scheme 4). As expected, the yield of **6** diminished as a result of the predominant reaction of intermediate radical **B** with Bu_3SnH to give a 65:35 diastereomeric mixture of the desired ethylated product **5** in 67% yield, accompanying with 16% yield of product **8** as a result of the reduction of nitrone **4** with Bu_3SnH.

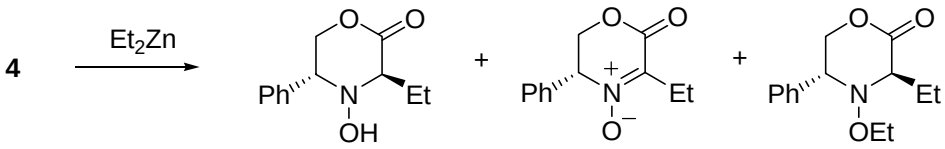


Scheme 4. Radical Addition to Nitrone **4** in the Presence of Bu_3SnH

We next investigated the reaction of nitrone **4** using Et_2Zn as an ethyl radical source under the similar reaction conditions (Table 4).[20] Et_2Zn worked well. Although the use of Et_2Zn led to a decrease in diastereoselectivity due to coordination of Et_2Zn as a Lewis acid, the formation of the ethylated nitrone **6** was not observed at 25 °C, because the reaction of intermediate radical **B** with Et_2Zn is a quick process

(entries 1 and 2). The reaction in CH_2Cl_2 at 25 °C gave a 54:46 diastereomeric mixture of the desired ethylated product **5** without the formation of undesired products **6** and **7** (entry 1). The formation of undesired products **6** was observed by performed the reaction at -78 °C (entry 3).

Table 4. Ethyl Radical Addition to Nitrone **4** by Using Et_2Zn[a]

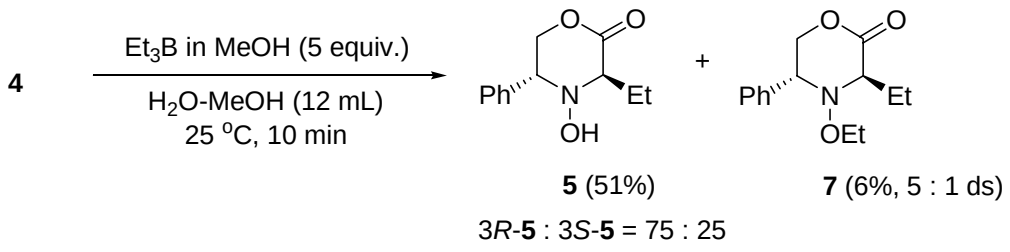


5 **6** **7**

Entry	Solvent	*T* (°C)	Time (min)	Selectivity[b] 3*R*-**5** : 3*S*-**5**	Yield (%)[c] **5**	**6**	**7**
1	CH_2Cl_2	25	10	54 : 46	49	nd	nd
2	benzene	25	10	57 : 43	42	nd	10
3	CH_2Cl_2	-78	10	50 : 50	37	10	nd

[a] All reaction of **4** (50 mg, 0.26 mmol) were carried out with Et_2Zn (5 equiv.) in CH_2Cl_2 or benzene (10 mL). [b] Diastereoselectivities were determined by ^1H NMR analysis. [c] Isolated yields.

The use of water as a solvent has generated considerable interest from both economical and environmental points of view.[21] Particularly, the carbon-carbon bond formation in aqueous media is a challenging problem.[22,23] We finally investigated the reaction of **4** in aqueous media (Scheme 5). To a solution of **4** in H_2O/MeOH was added a solution of Et_3B in MeOH (5 equiv), and then the reaction mixture was stirred at 25 °C for 10 min. The radical reaction smoothly proceeded to give a 75:25 diastereomeric mixture of the desired ethylated product **5** in 51% yield, accompanying with 6% yield of the diethylated product **7**.



Scheme 5. Radical Addition to Nitrone **4** in Aqueous Media

In conclusion, we have demonstrated that nitrone is an excellent radical acceptor for intermolecular carbon-carbon bond-forming radical reactions even in the presence of water. In addition to intermolecular

radical reaction of oxime ethers, hydrazones, and *N*-sulfonylimines, the radical reactions of nitrones disclosed a broader aspect of the utility of imine derivatives as a radical acceptor for the synthesis of various types of amino compounds.

EXPERIMENTAL

General.

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200, 300 or 500 MHz and at 50, 75 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}). Flash column chromatography was performed using E. Merck Kieselgel 60 (230-400 mesh).

Et_3B-mediated ethyl radical addition to nitrone 4 (Table 1 and 2).

To a solution of nitrone **4** (50 mg, 0.26 mmol) in CH_2Cl_2 or benzene (1, 5, 10, or 100 mL) was added Et_3B (1.0 M in hexane, 1.31 mL, 1.31 mmol or 0.26 mL, 0.26 mmol) at –78 °C, +25 °C or reflux. After being stirred at the same temperature for 1, 5 or 60 min, the reaction mixture was concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1, 2-fold developments) afforded the desired ethylated product *R*-**5**, *S*-**5**, the ethylated nitrone **6** and diethylated product **7**, respectively.

(3*R*,5*R*)-3-Ethyl-4-hydroxy-5-phenyl-2-morpholinone (*R*-5) colorless crystals: mp 73-77 °C (benzene). IR ($CHCl_3$) 3577, 2966, 1743 cm^{-1}. ^{1}H NMR δ 7.42-7.32 (5H, m), 5.51-5.46 (1H, m), 4.92-4.84 (1H, m), 4.65 (1H, dd, *J*=11.5, 5.0 Hz), 4.42 (1H, dd, *J* = 9.5, 5.0 Hz), 3.69-3.63 (1H, m), 2.15-1.85 (2H, m), 1.11 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 170.6, 135.9, 128.9, 128.5, 127.7, 67.1, 66.9, 60.2, 23.3, 11.2. HRMS: Calcd for $C_{12}H_{15}NO_3$ (M^+): 221.1051, Found: 221.1071. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.10; H, 6.86; N, 6.08. $[\alpha]^{17}_D$ +33.0 (*c* 1.01, $CHCl_3$).

(3*S*,5*R*)-3-Ethyl-4-hydroxy-5-phenyl-2-morpholinone (*S*-5) colorless crystals: mp 122-127 °C (benzene/hexane). IR ($CHCl_3$) 3574, 3381, 3019, 2975, 1741 cm^{-1}. ^{1}H NMR δ 7.44-7.34 (5H, m), 5.11 (1H, br s), 4.25-4.18 (2H, m), 4.05 (1H, t, *J* = 7.5 Hz), 3.72 (1H, t, *J* = 4.3 Hz), 2.18-2.02 (2H, m), 1.07 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 169.7, 136.1, 129.1, 128.8, 127.8, 70.0, 69.5, 67.1, 22.9, 9.3. HRMS: Calcd for $C_{12}H_{15}NO_3$ (M^+): 221.1051, Found: 221.1069. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.84; H, 6.75; N, 6.33. $[\alpha]^{18}_D$ -58.1 (*c* 1.21, $CHCl_3$). Crystal data of ***S*-5**: $C_{12}H_{15}NO_3$, space group MONOCLINIC, $p2_1$ with *a* = 9.415 (2), *b* = 6.8150 (9), *c* = 9.817 (1) Å, *V* = 605.3 (1) Å^3, final *R* value 0.0312 for 1194 reflections.

(5*R*)-3-Ethyl-5, 6-dihydro-5-phenyl-2*H*-1,4-oxadin-2-one 4-oxide (6)

a colorless oil: IR ($CHCl_3$) 3013, 1721, 1549 cm^{-1}. ^1H NMR δ 7.44-7.31 (5H, m), 5.11 (1H, t, *J* = 4.0 Hz), 4.82 (1H, dd, *J* = 12.5, 4.0 Hz), 4.68 (1H, dd, *J* = 12.5, 4.0 Hz), 2.87-2.75 (2H, m), 1.18 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 158.8, 140.9, 132.3, 129.7, 129.3, 127.0, 70.8, 66.9, 19.3, 9.2. HRMS: Calcd for $C_{12}H_{13}NO_3$ (M^+): 219.0895, Found: 219.0909.

(5*R*)-4-Ethoxy-3-ethyl-5-phenyl-2-morpholinone (7)

a colorless oil (5:1mixture of diasteromers): IR ($CHCl_3$) 2979, 1736, 1455 cm^{-1}. ^1H NMR δ 7.46-7.32 (5H, m), 4.66-4.58 (1H, m), 4.44-4.34 (1H, m), 4.30-4.21 (1H, m), 3.66-3.56 (3H, m), 2.15-1.82 (2H, m), 1.15 (15/6H, t, *J* = 7.5 Hz), 1.09 (3/6H, t, *J* = 7.5 Hz) 1.01 (15/6H, br t, *J* = 7.5 Hz), 0.98 (3/6H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 173.1, 170.9, 138.3, 128.8, 128.7, 128.62, 128.58, 128.5, 128.2, 127.8, 127.7, 127.0, 75.0, 68.5, 67.4, 64.2, 53.5, 33.0, 32.2, 13.9, 11.3, 8.8, 8.0. HRMS: Calcd for $C_{14}H_{19}NO_3$ (M^+): 249.1364, Found: 249.1376.

Et_3B-mediated ethyl radical addition to nitrone 4 in the presence of Lewis acid (Table 3).

To a solution of nitrone **4** (50 mg, 0.26 mmol) and Lewis acid (0.26 mmol) in CH_2Cl_2 (10 mL) was added Et_3B (1.0 M in hexane, 1.31 mL, 1.31 mmol) at –78 °C or +25 °C. After being stirred at the same temperature for 15-60 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 of the residue by preparative TLC (hexane/AcOEt 3:1, 2-fold developments) afforded the desired ethylated product *R*-**5**, *S*-**5** and the ethylated nitrone **6**, respectively.

Et_3B-mediated ethyl radical addition to nitrone 4 in the presence of Bu_3SnH.

To a solution of nitrone **4** (50 mg, 0.26 mmol) in CH_2Cl_2 (10 mL) were added Et_3B (1.0 M in hexane, 1.31 mL, 1.31 mmol) and Bu_3SnH (0.085 mL, 0.31 mmol) at 25 °C. After being stirred at the same temperature for 5 min, the reaction mixture was concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1, 2-fold developments) afforded the ethylated product **5** (39.0 mg, 67%, diastereomeric ratio 65:35), diethylated product **7** (18.1 mg, 28%) and reduction product **8** (8.1 mg, 16%).

(5*R*)-4-Hydroxy-5-phenyl-2-morpholinone (8)

colorless crystals: mp 95-97 °C (hexane/AcOEt). IR ($CHCl_3$) 3572, 1748 cm^{-1}. ^1H NMR δ 7.44 -7.34 (5H, m), 5.52 (1H, br s), 4.43-4.26 (2H, m), 4.13, 3.66 (each 1H, d, *J* = 17 Hz), 3.96 (1H, t, *J* = 8 Hz). ^{13}C NMR ($CDCl_3$) δ 167.1, 135.0, 128.9, 128.8, 127.8, 69.6, 66.6, 58.9. HRMS: Calcd for $C_{10}H_{11}NO_3$ (M^+) 193.0738, Found: 193.0742. $[\alpha]^{21}_D$ -124.2 (*c* 1.11, $CHCl_3$).

Et_2Zn-mediated ethyl radical addition to nitrone 4.

To a solution of nitrone **4** (50 mg, 0.26 mmol) in CH_2Cl_2 or benzene (10 mL) was added Et_2Zn (1.0 M in

hexane, 1.31 mL, 1.31 mmol) at –78 °C or +25 °C. After being stirred at the same temperature for 10 min, the reaction mixture was diluted with saturated aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3:1, 2-fold developments) afforded the desired ethylated product *R*-**5**, *S*-**5**, the ethylated nitrone **6** and diethylated product **7,** respectively.

Et_3B-mediated ethyl radical addition to nitrone 4 in aqueous media.

To a solution of nitrone **4** (50 mg, 0.26 mmol) in H_2O-MeOH (1:2, 12 mL) was added Et_3B (1.0 M in hexane, 1.31 mL, 1.31 mmol) at 25 °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. Purification of the residue by preparative TLC (hexane/AcOEt 3:1, 2-fold developments) afforded the desired ethylated product **5** (29.6 mg, 51%, diastereomeric ratio 70:30) and the diethylated product **7** (3.6 mg, 6%), respectively.

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