Selected Papers

Catalytic Asymmetric Synthesis of Isoxazoline-*N*-oxides through Conjugate Addition–Cyclization under Phase-Transfer Conditions

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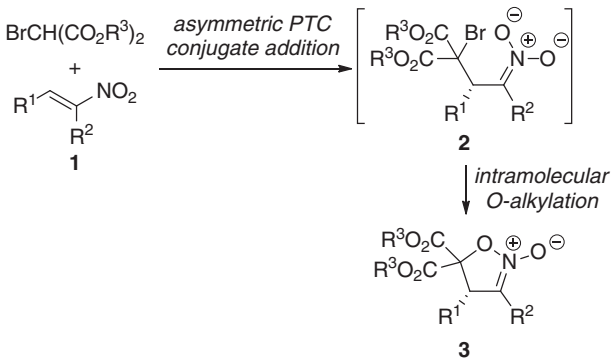
Catalytic asymmetric synthesis of various isoxazoline-*N*-oxides having a tetrasubstituted carbon has been accomplished by asymmetric phase-transfer conjugate addition of bromomalonate to nitroolefins and subsequent ring-closing *O*-alkylation. The obtained isoxazoline-*N*-oxide was readily converted to the corresponding oxime, isoxazoline, and lactam without loss of optical purity.

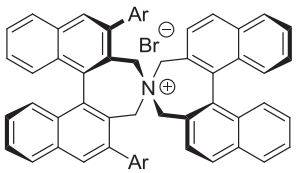
Isoxazoline-*N*-oxides are the synthetic equivalent of isoxazoline, and serve as versatile building blocks for complex molecules,[1] biologically active compounds and natural products.[2] While a number of synthetic methods have been developed to date,[3] there is still a need to expand synthetic approaches for their preparation. For instance, chiral isoxazoline-*N*-oxides are known to be synthesized by using optically pure starting material[4] or stoichiometric amounts of a chiral reagent;[5] however, general methods for their preparation based on catalytic asymmetric reaction are quite rare.[6] In this context, we have been interested in the development of a catalytic asymmetric synthesis of chiral isoxazoline-*N*-oxides under phase-transfer conditions.[7,8] The asymmetric conjugate addition of bromomalonate to nitroolefins **1** promoted by a chiral phase-transfer catalyst would give optically enriched nitronates **2**, which could be immediately converted to isoxazoline-*N*-oxides **3** by an intramolecular *O*-alkylation (Scheme 1). Here we wish to report the efficient asymmetric synthesis of isoxazoline-*N*-oxides based on the asymmetric phase-transfer conjugate addition.



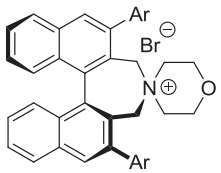
Scheme 1. Asymmetric synthesis of isoxazoline-*N*-oxides by asymmetric phase-transfer conjugate addition and intramolecular *O*-alkylation.

Results and Discussion

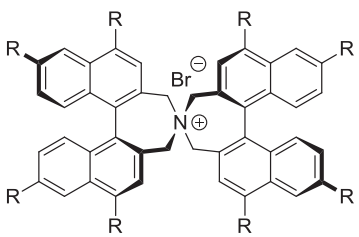
We first examined the synthesis of isoxazoline-*N*-oxides by the reaction between dialkyl bromomalonate and 1-phenyl-2-nitropropene (**1a**) using 1 mol % of (*R*,*R*)-**4a**[9] (Chart 1) as catalyst and K_2CO_3 in THF (Table 1). Attempted reaction of dimethyl bromomalonate and **1a** gave the desired isoxazoline-*N*-oxide in 68% yield with 56% ee (Entry 1). While use of diethyl bromomalonate improved the yield, a similar level of enantioselectivity was observed (Entry 2). A sterically more hindered diisopropyl bromomalonate was not as effective as



(*R*,*R*)-**4a** (Ar = 3,4,5-$F_3C_6H_2$)
(*S*,*S*)-**4b** (Ar = 3,5-*t*-$Bu_2C_6H_3$)
(*S*,*S*)-**4c** (Ar = 3,5-[3,5-$(CF_3)_2C_6H_3]_2C_6H_3$)
(*S*,*S*)-**4d** (Ar = 2-naphthyl)



(*S*)-**4e** (Ar = 3,4,5-$F_3C_6H_2$)



(*S*,*S*)-**4f** (R = 2,4,6-$Me_3C_6H_2$)
(*S*,*S*)-**4g** (R = 3,5-$Ph_2C_6H_3$)
(*S*,*S*)-**4h** (R = $SiMe_3$)
(*S*,*S*)-**4i** (R = $SiEt_3$)
(*S*,*S*)-**4j** (R = $SiMe_2Ph$)
(*S*,*S*)-**4k** (R = $SiMe_2Oct$)

Chart 1.

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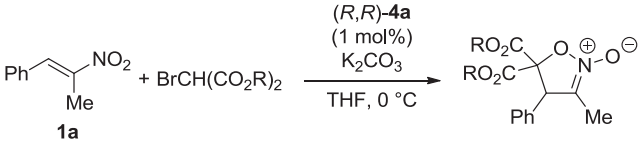
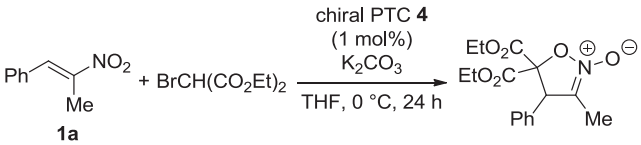
Table 1. Asymmetric Synthesis of Isoxazoline-*N*-oxide with **1a** and Dialkyl Bromomalonate Catalyzed by (*R*,*R*)-**4a**[a)]



Entry	R	Time/h	Yield/%[b)]	Ee/%[c)]
1	Me	24	68	56
2	Et	7.5	95	58
3	*i*-Pr	24	74	42
4	Bn	24	84	56

a) The reaction of **1a** (1 equiv) with dialkyl bromomalonate (1 equiv) was carried out in THF in the presence of (*R*,*R*)-**4a** (0.01 equiv) and K_2CO_3 (2 equiv) at 0 °C. b) Isolated yield. c) Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

Table 2. Asymmetric Synthesis of Isoxazoline-*N*-oxide with **1a** and Diethyl Bromomalonate Catalyzed by Chiral PTC **4**[a)]



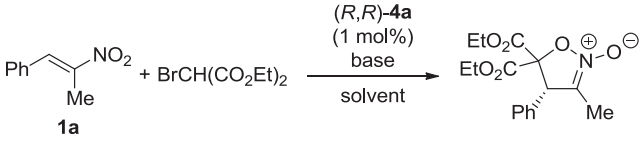
Entry	PTC	Yield/%[b)]	Ee/%[c)]	Config
1[d)]	(*R*,*R*)-**4a**	95	58	*S*
2	(*S*,*S*)-**4b**	87	46	*R*
3	(*S*,*S*)-**4c**	92	56	*R*
4	(*S*,*S*)-**4d**	73	30	*R*
5	(*S*)-**4e**	76	0	—
6	(*S*,*S*)-**4f**	65	47	*R*
7	(*S*,*S*)-**4g**	61	43	*R*
8	(*S*,*S*)-**4h**	55	17	*R*
9	(*S*,*S*)-**4i**	72	47	*R*
10	(*S*,*S*)-**4j**	59	36	*R*
11	(*S*,*S*)-**4k**	48	36	*R*

a) The reaction of **1a** (1 equiv) with diethyl bromomalonate (1 equiv) was carried out in THF in the presence of chiral PTC **4** (0.01 equiv) and K_2CO_3 (2 equiv) at 0 °C for 24 h. b) Isolated yield. c) Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.). d) The reaction was performed for 7.5 h.

other primary alkyl esters in terms of both yield and enantioselectivity (Entry 3). Accordingly, diethyl bromomalonate was chosen for further investigation. Intensive catalyst screening revealed that (*R*,*R*)-**4a** was the most efficient catalyst for the present reaction (Table 2).

Having identified a suitable catalyst, solvent screening was then carried out (Table 3). Among ethereal solvents used, a less polar solvent such as *t*-butyl methyl ether (TBME) showed higher enantioselectivity (Entry 4). We then screened a variety of aromatic solvents (Entries 5–8), and mesitylene was found to be a suitable solvent in terms of enantioselectivity (Entry 8). In an attempt to further improve enantioselectivity, lowering temperature was effective, although a longer reaction time was required (Entry 9). Use of 70% aqueous Cs_2CO_3 as a stronger

Table 3. Asymmetric Synthesis of Isoxazoline-*N*-oxide with **1a** and Diethyl Bromomalonate Catalyzed by (*R*,*R*)-**4a**[a)]



Entry	Base	Solvent	Conditions		Yield	Ee
			Temp/°C	Time/h	/%[b)]	/%[c)]
1	K_2CO_3	THF	0	7.5	95	58
2	50% K_2CO_3 aq.	Et_2O	0	8.5	84	63
3	50% K_2CO_3 aq.	CPME	0	12	88	65
4	50% K_2CO_3 aq.	TBME	0	11	70	67
5	50% K_2CO_3 aq.	anisole	0	15	71	59
6	50% K_2CO_3 aq.	PhCl	0	24	79	54
7	50% K_2CO_3 aq.	toluene	0	7.5	94	64
8	50% K_2CO_3 aq.	mesitylene	0	7.5	83	70
9	50% K_2CO_3 aq.	mesitylene	−20	24	80	77
10	70% Cs_2CO_3 aq.	mesitylene	−20	2	70	79
11	70% Cs_2CO_3 aq.	mesitylene	−30	8	97	81
12	70% Cs_2CO_3 aq.	mesitylene	−35	12	95	83
13	70% Cs_2CO_3 aq.	mesitylene	−40	12	29	77

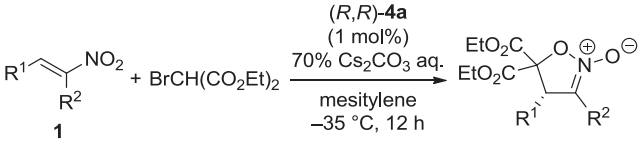
a) The reaction of **1a** (1 equiv) with diethyl bromomalonate (1 equiv) was carried out in a solvent in the presence of (*R*,*R*)-**4a** (0.01 equiv) and a base. b) Isolated yield. c) Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

base successfully increased the reaction rate without loss of enantioselectivity (Entry 10). When the reaction was performed at −35 °C for 12 h, the desired product was obtained in excellent yield with good enantioselectivity (Entry 12).

With the optimal reaction conditions, the catalytic asymmetric synthesis of isoxazoline-*N*-oxides with several other nitroolefins **1** was examined (Table 4). The reaction of nitroolefin **1** having a primary alkyl group (R^2 = Et or Bu) at the α-position gave the corresponding isoxazoline-*N*-oxide with good enantioselectivity (Entries 2 and 3). On the other hand, the reaction of sterically demanding nitroolefin **1** (R^2 = *i*-Pr) proceeded slowly to give the product in lower yield and enantioselectivity (Entry 4). We then investigated the effects of the β-substituent on nitroolefin **1**. The reaction of **1** having either electron-deficient or electron-rich phenyl group gave the corresponding isoxazolines in good yield and enantioselectivity (Entries 6–8). Use of **1** with heteroaromatic or alkyl substituent resulted in decreased enantioselectivity (Entries 9–11). Interestingly, the reaction of nitroolefin **1** having an ethoxycarbonyl group at the β-position did not provide the isoxazoline-*N*-oxide, giving a considerable amount of oxime epoxide **5** in racemic form (Entry 12). A possible reaction pathway for the formation of **5** is shown in Scheme 2.

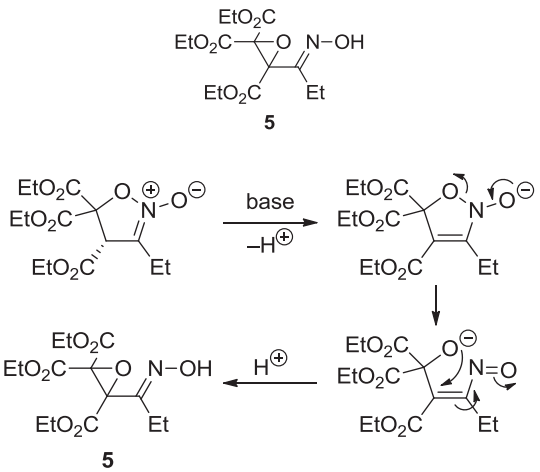
The absolute stereochemistry of the obtained isoxazoline-*N*-oxide (Table 4, Entry 6) was confirmed to be *S* by X-ray crystallographic analysis (Figure 1). Based on the observed stereochemistry, a plausible transition state model can be proposed as shown in Figure 2. The chiral ammonium enolate, which is generated from diethyl bromomalonate and chiral phase-transfer catalyst (*R*,*R*)-**4a** under basic conditions, approaches the *Si* face of nitroolefin.

Table 4. Asymmetric Synthesis of Isoxazoline-*N*-oxide with **1** and Diethyl Bromomalonate Catalyzed by (*R*,*R*)-**4a**[a]



Entry	R^1	R^2	Yield/%[b]	Ee/%[c),d)]
1	Ph	Me	95	83 (99)
2	Ph	Et	92	86
3	Ph	Bu	56	86
4[e)]	Ph	*i*-Pr	63	77
5	Ph	Ph	97	81 (99)
6[e)]	4-Br-C_6H_4	Et	84	85 (97)
7	4-NO_2-C_6H_4	Et	90	87
8[f)]	4-MeO-C_6H_4	Et	84	87
9[e)]	2-furyl	Et	85	78
10	3-pyridyl	Et	36	72
11	Bu	Et	63	77
12	CO_2Et	Et	73[g)]	—

a) The reaction of **1** (1 equiv) with diethyl bromomalonate (1 equiv) was carried out in mesitylene in the presence of (*R*,*R*)-**4a** (0.01 equiv) and 70% Cs_2CO_3 aq. at −35 °C for 12 h. b) Isolated yield. c) Determined by HPLC analysis using chiral column (Chiralpak AD-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd.). d) Enantiomeric excesses in parentheses were obtained after a single recrystallization from cold ethanol. e) The reaction was performed for 24 h. f) The reaction was performed for 36 h. g) Oxime epoxide **5** was obtained instead of the expected isoxazoline-*N*-oxide.



Scheme 2. A possible reaction pathway for the formation of oxime epoxide **5**.

The obtained isoxazoline-*N*-oxide was a useful intermediate in organic synthesis and readily converted to the corresponding oxime, isoxazoline, and lactam (Scheme 3). When isoxazoline-*N*-oxide **6** was treated with Pd/C in MeOH under H_2 atmosphere, oxime **7** was obtained in excellent yield with complete retention of stereochemistry. Treatment of **7** with methanesulfonyl chloride and triethylamine in dichloromethane gave isoxazoline **8** in excellent yield without loss of optical purity.[10] Selective reduction of one ester group in **8** with lithium tri(*t*-butoxy)aluminium hydride gave mono-alcohol **9** exclusively.[11] The *O*-benzylation of **9** afforded benzyl ether **10**, which was then converted to lactam **11** through diastereoselective reduction of the C=N bond,[6] the N–O bond cleavage and lactamization. The relative stereochemistry of **9** and **11** was determined by X-ray crystallographic analysis as shown in Figure 3 and Figure 4, respectively.

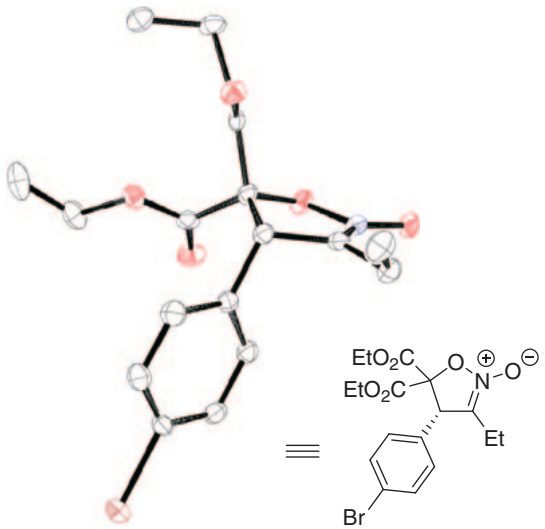


Figure 1. X-ray structure of isoxazoline-*N*-oxide.

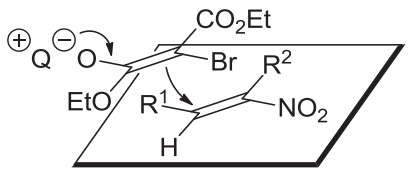
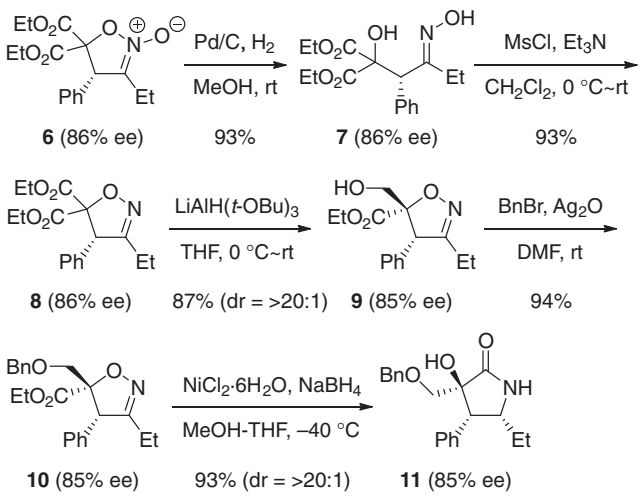


Figure 2. Plausible transition state model.



Scheme 3. Transformation of isoxazoline-*N*-oxide **6**.

Conclusion

In summary, we have developed an efficient asymmetric synthesis of isoxazoline-*N*-oxides by asymmetric phase-transfer conjugate addition and subsequent ring-closing *O*-alkylation. The obtained isoxazoline-*N*-oxide was readily converted to useful building blocks in organic synthesis such as the corresponding oxime, isoxazoline, and lactam.

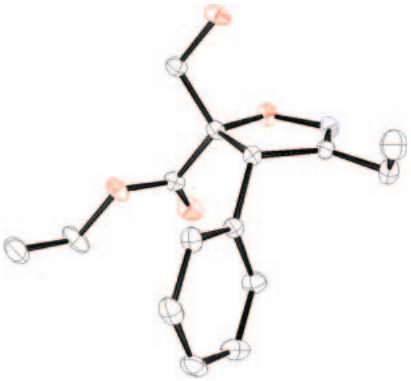


Figure 3. X-ray structure of isoxazoline **9**.

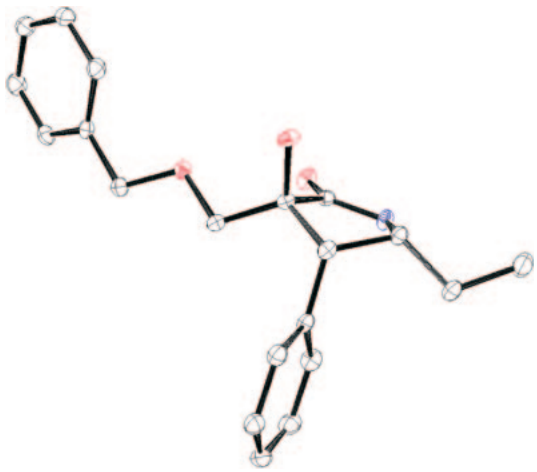


Figure 4. X-ray structure of lactam **11**.

Experimental

Infrared (IR) spectra were recorded on a Nicolet MAGNA560. ^{1}H NMR spectra were measured on Bruker AV500 (500 MHz) and Bruker AV300 (300 MHz) spectrometers. Data were reported as follows: chemical shifts in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on Bruker AV500 (125 MHz) and Bruker AV300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using Daicel Chiralpak AD-H and Chiralcel OD-H 4.6 mm × 25 cm columns. High-resolution mass spectra (HRMS) were performed on a Thermo Fisher Scientific LTQ Orbitrap XL and a JEOL JMS-700 MStation. Optical rotations were measured on a JASCO P-1020 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. Flash column chromatography was performed with silica gel 60 (Merck 1.09386.9025, 230–400 mesh) or using a Biotage Isolera with prepacked silica cartridges (10 g). In experiments requiring dry solvent, tetrahydrofuran (THF) and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. as "Dehydrated." Commercially available reagents were used as received. Nitroolefins[12–16] and phase-transfer catalysts (*R*,*R*)-**4a**,[9] (*S*,*S*)-**4b**,[17] (*S*,*S*)-**4c**,[17] (*S*,*S*)-**4d**,[17] (*S*)-**4e**,[18] (*S*,*S*)-**4f**,[17] (*S*,*S*)-**4g**,[19] (*S*,*S*)-**4h**,[20] (*S*,*S*)-**4i**,[20] (*S*,*S*)-**4j**,[20] and (*S*,*S*)-**4k**[20] were synthesized according to literature procedures and used after column chromatography on silica gel.

General Procedure for Asymmetric Synthesis of Isoxazoline-*N*-oxides with 1-Phenyl-2-nitropropene (1a) and Dialkyl Bromomalonates. To a suspension of (*R*,*R*)-**4a** (2.2 mg, 0.0025 mmol), 1-phenyl-2-nitropropene (**1a**) (40.8 mg, 0.25 mmol) and dialkyl bromomalonate (0.25 mmol) in THF (0.33 mL) at 0 °C was added K_2CO_3 (69.1 mg, 0.5 mmol). After stirring for 24 h at 0 °C, the reaction mixture was quenched with saturated NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel to give the corresponding cyclic nitronate. The product was identified by NMR spectroscopy. The enantiomeric excess of the product was determined by HPLC using a chiral column.

Dimethyl (*S*)-3-Methyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 1, Entry 1): $[\alpha]_D^{20}$ 1.55 (*c* 1.0, $CHCl_3$; 56% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.33 (3H, m, Ar–*H*), 7.27–7.19 (2H, m, Ar–*H*), 5.29 (1H, d, $J = 1.5$ Hz, Ar–C*H*), 3.89 (3H, s, $-CO_2CH_3$), 3.26 (3H, s, $-CO_2CH_3$), 1.92 (3H, d, $J = 1.5$ Hz, $-C(=N)CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 164.2, 132.7, 129.1, 128.9, 128.8, 112.7, 84.4, 57.1, 54.0, 52.7, 11.1; IR (neat): 2956, 1752, 1665, 1454, 1390, 1335, 1277, 1212, 1094, 1045 cm^{-1}; HRMS (ESI): Calcd for $C_{14}H_{16}NO_6$: 294.0978 ($[M + H]^+$), Found: 294.0972 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL min^{-1}, retention time: 11.3 (*R*) and 14.5 min (*S*).

Diisopropoxyl (*S*)-3-Methyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 1, Entry 3): $[\alpha]_D^{20}$ 1.00 (*c* 1.0, $CHCl_3$; 42% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.31 (3H, m, Ar–*H*), 7.30–7.20 (2H, m, Ar–*H*), 5.25 (1H, d, $J = 1.4$ Hz, Ar–C*H*), 5.19–5.11 (1H, m, $-CO_2CH(CH_3)_2$), 4.64–4.56 (1H, m, $-CO_2CH(CH_3)_2$), 1.88 (3H, d, $J = 1.4$ Hz, $-C(=N)CH_3$), 1.33 (3H, d, $J = 6.3$ Hz, $-CO_2CH(CH_3)_2$), 1.27 (3H, d, $J = 6.2$ Hz, $-CO_2CH(CH_3)_2$), 0.99 (3H, d, $J = 6.3$ Hz, $-CO_2CH(CH_3)_2$), 0.64 (3H, d, $J = 6.2$ Hz, $-CO_2CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 163.3, 133.1, 129.3, 129.0, 128.9, 113.5, 84.2, 71.4, 70.5, 56.6, 21.4, 21.24, 21.17, 20.6, 11.1; IR (neat): 2983, 2936, 1742, 1665, 1377, 1277, 1211, 1102 cm^{-1}; HRMS (ESI): Calcd for $C_{18}H_{24}NO_6$: 350.1604 ($[M + H]^+$), Found: 350.1585 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL min^{-1}, retention time: 16.6 (*R*) and 20.7 min (*S*).

Dibenzyl (*S*)-3-Methyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 1, Entry 4): $[\alpha]_D^{20}$ 0.97 (*c* 1.0, $CHCl_3$; 56% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.14 (13H, m, Ar–*H*), 6.94–6.87 (2H, m, Ar–*H*), 5.32 (1H, d, $J = 12.2$ Hz, $-CO_2CH_2Ph$), 5.26 (1H, d, $J = 1.4$ Hz, Ar–C*H*), 5.16 (1H, d, $J = 12.2$ Hz, $-CO_2CH_2Ph$), 4.67 (1H, d, $J = 12.2$ Hz, $-CO_2CH_2Ph$), 4.42 (1H, d, $J = 12.2$ Hz, $-CO_2CH_2Ph$),

1.88 (3H, d, $J = 1.4$ Hz, –C(=N)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 163.6, 134.3, 133.7, 132.6, 129.2, 129.0, 128.9, 128.6 (two peaks overlap), 128.5, 128.4, 128.3, 128.1, 113.0, 84.5, 68.8, 67.9, 57.0, 11.1; IR (neat): 3064, 3033, 2957, 1746, 1665, 1498, 1454, 1378, 1334, 1276, 1202, 1089 cm^{-1}; HRMS (ESI): Calcd for $C_{26}H_{24}NO_6$: 446.1604 ([M + H]$^+$), Found: 446.1626 ([M + H]$^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/EtOH = 4:1, flow rate 1.0 mL min^{-1}, retention time: 17.9 (*R*) and 19.3 min (*S*).

General Procedure for Asymmetric Synthesis of Isoxazoline-*N*-oxides with Nitroolefin 1 and Diethyl Bromomalonate. To a suspension of (*R*,*R*)-**4a** (0.9 mg, 0.001 mmol), diethyl bromomalonate (23.9 mg, 0.1 mmol) and nitroolefin (0.1 mmol) in mesitylene (0.33 mL) at −35 °C was added 70% Cs_2CO_3 solution (0.12 mL). After stirring for 12 h at −35 °C, the reaction mixture was quenched with saturated NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel to give the corresponding cyclic nitronate. The product was identified by NMR spectroscopy. The enantiomeric excess of the product was determined by HPLC using a chiral column.

Diethyl (*S*)-3-Methyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 1): $[\alpha]_D^{20}$ 2.28 (*c* 1.0, $CHCl_3$; 83% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.32 (3H, m, Ar–*H*), 7.27–7.19 (2H, m, Ar–*H*), 5.27 (1H, s, Ar–C*H*), 4.38 (1H, dq, $J = 11.1$, 7.3 Hz, –$CO_2CH_2CH_3$), 4.30 (1H, dq, $J = 11.1$, 7.3 Hz, –$CO_2CH_2CH_3$), 3.78 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 3.66 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 1.90 (3H, d, $J = 1.4$ Hz, –C(=N)CH_3), 1.31 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$), 0.84 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 163.8, 133.0, 129.14, 129.09, 128.9, 113.1, 84.4, 63.4, 62.3, 56.9, 13.8, 13.4, 11.1; IR (neat): 2984, 1747, 1664, 1457, 1369, 1262, 1208, 1095, 1045 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{20}NO_6$: 322.1284 ([M + H]$^+$), Found: 322.1285 ([M + H]$^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL min^{-1}, retention time: 10.7 (*R*) and 12.1 min (*S*).

Diethyl (*S*)-3-Ethyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (6) (Table 4, Entry 2): $[\alpha]_D^{20}$ 2.58 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.32 (3H, m, Ar–*H*), 7.28–7.22 (2H, m, Ar–*H*), 5.26 (1H, s, Ar–C*H*), 4.39 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 4.29 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 3.78 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 3.68 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 2.49 (1H, dqd, $J = 15.3$, 7.6, 0.9 Hz, –C(=N)CH_2CH$_3$), 2.15 (1H, dqd, $J = 15.3$, 7.6, 1.3 Hz, –C(=N)CH_2CH$_3$), 1.32 (3H, t, $J = 7.2$ Hz, –$CO_2CH_2CH_3$), 1.02 (3H, t, $J = 7.6$ Hz, –C(=N)CH$_2$CH_3), 0.84 (3H, t, $J = 7.2$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 163.8, 133.2, 129.2, 129.1, 128.9, 117.6, 84.5, 63.4, 62.3, 55.8, 19.2, 13.8, 13.4, 9.3; IR (neat): 2982, 1746, 1654, 1457, 1368, 1279, 1227, 1205, 1093, 1039 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{22}NO_6$: 336.1440 ([M + H]$^+$), Found: 336.1442 ([M + H]$^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL min^{-1}, retention time: 17.2 (*S*) and 20.2 min (*R*).

Diethyl (*S*)-3-Butyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 3): $[\alpha]_D^{20}$ 2.15 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.32 (3H, m, Ar–*H*), 7.28–7.22 (2H, m, Ar–*H*), 5.26 (1H, s, Ar–C*H*), 4.38 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 4.29 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 3.78 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 3.68 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 2.45 (1H, dt, $J = 15.1$, 7.5 Hz, –C(=N)CH_2CH$_2$), 2.05 (1H, dt, $J = 14.3$, 7.1 Hz, –C(=N)CH_2CH$_2$), 1.50–1.22 (4H, m, –C(=N)CH$_2$(CH_2)$_2$CH$_3$), 1.31 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$), 0.854 (3H, t, $J = 7.2$ Hz, –C(=N)(CH$_2$)$_3$CH_3), 0.846 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 163.8, 133.2, 129.13, 129.07, 128.8, 116.9, 84.5, 63.3, 62.3, 56.0, 27.0, 25.2, 22.2, 13.8, 13.5, 13.4; IR (neat): 2961, 2934, 1746, 1653, 1457, 1369, 1278, 1208, 1095, 1041 cm^{-1}; HRMS (ESI): Calcd for $C_{19}H_{26}NO_6$: 364.1752 ([M + H]$^+$), Found: 364.1755 ([M + H]$^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 20:1, flow rate 1.0 mL min^{-1}, retention time: 22.6 (*S*) and 26.8 min (*R*).

Diethyl (*S*)-3-Isopropyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 4): $[\alpha]_D^{20}$ 2.21 (*c* 1.0, $CHCl_3$; 77% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (5H, m, Ar–*H*), 5.15 (1H, s, Ar–C*H*), 4.38 (1H, dq, $J = 10.6$, 7.2 Hz, –$CO_2CH_2CH_3$), 4.28 (1H, dq, $J = 10.6$, 7.1 Hz, –$CO_2CH_2CH_3$), 3.79 (1H, dq, $J = 11.1$, 7.0 Hz, –$CO_2CH_2CH_3$), 3.72 (1H, dq, $J = 11.0$, 6.9 Hz, –$CO_2CH_2CH_3$), 2.81 (1H, m, –C(=N)CH(CH$_3$)$_2$), 1.31 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$), 1.15 (3H, d, $J = 7.0$ Hz, –C(=N)CH(CH_3)$_2$), 0.88 (3H, d, $J = 7.0$ Hz, –C(=N)CH(CH_3)$_2$), 0.85 (3H, t, $J = 7.0$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 163.6, 133.9, 129.2, 129.1, 128.8, 120.9, 84.9, 63.4, 62.3, 55.3, 27.0, 18.5, 18.1, 13.9, 13.4; IR (neat): 2978, 2938, 1747, 1651, 1457, 1369, 1247, 1087, 1038 cm^{-1}; HRMS (ESI): Calcd for $C_{18}H_{24}NO_6$: 350.1597 ([M + H]$^+$), Found: 350.1598 ([M + H]$^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL min^{-1}, retention time: 13.5 (*S*) and 12.1 min (*S*).

Diethyl (*S*)-3,4-Diphenyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 5): $[\alpha]_D^{20}$ 2.51 (*c* 1.0, $CHCl_3$; 81% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.76 (2H, m, Ar–*H*), 7.36–7.24 (8H, m, Ar–*H*), 5.76 (1H, s, Ar–C*H*), 4.40 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 4.31 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 3.80 (1H, dq, $J = 10.8$, 7.2 Hz, –$CO_2CH_2CH_3$), 3.72 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 1.32 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$), 0.90 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 163.5, 133.9, 129.7, 129.1, 129.0, 128.9, 128.7, 126.9, 125.0, 115.4, 84.8, 63.5, 62.5, 55.4, 13.8, 13.4; IR (neat): 2983, 1747, 1626, 1494, 1448, 1370, 1298, 1233, 1094, 1061, 1041 cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{22}NO_6$: 384.1440 ([M + H]$^+$), Found: 384.1442 ([M + H]$^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/EtOH = 4:1, flow rate 0.5 mL min^{-1}, retention time: 19.1 (*S*) and 24.3 min (*R*).

Diethyl (*S*)-4-(4-Bromophenyl)-3-ethyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 6): $[\alpha]_D^{20}$ 2.12 (*c* 1.0, $CHCl_3$; 85% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (2H, dd, $J = 8.5$, 2.2 Hz, Ar–*H*), 7.14 (2H, dd, $J = 8.5$,

2.2 Hz, Ar–*H*), 5.23 (1H, s, Ar–C*H*), 4.38 (1H, dq, $J = 10.7$, 7.1 Hz, $-CO_2CH_2CH_3$), 4.29 (1H, dq, $J = 10.7$, 7.1 Hz, $-CO_2CH_2CH_3$), 3.85 (1H, dq, $J = 10.7$, 7.2 Hz, $-CO_2CH_2CH_3$), 3.75 (1H, dq, $J = 10.7$, 7.1 Hz, $-CO_2CH_2CH_3$), 2.48 (1H, dqd, $J = 15.2$, 7.7, 0.9 Hz, $-C(=N)CH_2CH_3$), 2.14 (1H, dqd, $J = 15.3$, 7.7, 1.3 Hz, $-C(=N)CH_2CH_3$), 1.32 (3H, t, $J = 7.1$ Hz, $-CO_2CH_2CH_3$), 1.02 (3H, t, $J = 7.6$ Hz, $-C(=N)CH_2CH_3$), 0.92 (3H, t, $J = 7.2$ Hz, $-CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 163.6, 132.3, 132.1, 130.8, 123.4, 116.9, 84.2, 63.5, 62.5, 55.2, 19.1, 13.8, 13.5, 9.3; IR (neat): 2981, 1747, 1654, 1488, 1368, 1280, 1227, 1205, 1093, 1040, 1012 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{21}BrNO_6$: 414.0546 ($[M + H]^+$), Found: 414.0547 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 40:1, flow rate 0.7 mL min^{-1}, retention time: 33.2 (*R*) and 35.5 min (*S*).

Crystal Structure Analysis of Diethyl (*S*)-4-(4-Bromophenyl)-3-ethyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide: Single crystals of diethyl (*S*)-4-(4-bromophenyl)-3-ethyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-oxide for X-ray diffraction experiments were recrystallized from EtOH. The data were collected at -177 °C on a Rigaku R-AXIS RAPID IP area detector with graphite-monochromated Mo Kα radiation ($\lambda = 0.71075$ Å). The crystal structure was solved by direct methods using SIR92[21] and expanded using DIRDIF99 Fourier techniques.[22] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement[23] on F^2 was based on 4145 observed reflections and 306 variable parameters. Crystallographic data for (c): $C_{17}H_{20}BrNO_6$, colorless block, $0.5 \times 0.4 \times 0.3$ mm^3, orthorhombic, $P2_12_12_1$, $a = 10.0497(2)$, $b = 10.3362(3)$, $c = 17.5284(5)$ Å, $V = 1820.77(8)$ Å^3, $D_{calcd} = 1.511$ g cm^{-3}, $Z = 4$, $2\theta_{max} = 55.0°$, $\mu = 22.962$ cm^{-1}. A total of 17820 reflections were measured. $R = 0.024$, and $Rw = 0.041$ for all reflections. All calculations were performed using the CrystalStructure3.8[24] crystallographic software package. CCDC-796797 contains the supplementary crystallographic data for this paper. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-796797 for the title compound. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Diethyl (*S*)-3-Ethyl-4-(4-nitrophenyl)-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 7): $[\alpha]_D^{20}$ 1.85 (*c* 1.0, $CHCl_3$; 87% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (2H, dd, $J = 8.8$, 2.2 Hz, Ar–*H*), 7.49 (2H, dd, $J = 8.8$, 2.2 Hz, Ar–*H*), 5.38 (1H, s, Ar–C*H*), 4.40 (1H, dq, $J = 10.8$, 7.1 Hz, $-CO_2CH_2CH_3$), 4.31 (1H, dq, $J = 10.7$, 7.1 Hz, $-CO_2CH_2CH_3$), 3.85 (1H, dq, $J = 10.8$, 7.1 Hz, $-CO_2CH_2CH_3$), 3.75 (1H, dq, $J = 10.8$, 7.1 Hz, $-CO_2CH_2CH_3$), 2.51 (1H, dqd, $J = 15.2$, 7.7, 0.8 Hz, $-C(=N)CH_2CH_3$), 2.14 (1H, dqd, $J = 15.2$, 7.7, 1.3 Hz, $-C(=N)CH_2CH_3$), 1.33 (3H, t, $J = 7.1$ Hz, $-CO_2CH_2CH_3$), 1.03 (3H, t, $J = 7.6$ Hz, $-C(=N)CH_2CH_3$), 0.92 (3H, t, $J = 7.1$ Hz, $-CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 163.4, 148.3, 140.7, 130.2, 124.0, 116.3, 84.1, 63.7, 62.7, 55.1, 19.1, 13.8, 13.5, 9.3; IR (neat): 2983, 2941, 1747, 1655, 1607, 1525, 1351, 1279, 1229, 1205, 1095, 1040, 1014 cm^{-1}; HRMS (ESI): Calcd for $C_{17}H_{21}N_2O_8$: 381.1291 ($[M + H]^+$), Found: 381.1292 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 4:1, flow rate 1.0 mL min^{-1}, retention time: 13.1 (*S*) and 19.2 min (*R*).

Diethyl (*S*)-3-Ethyl-4-(4-methoxyphenyl)-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 8): $[\alpha]_D^{20}$ 2.42 (*c* 1.0, $CHCl_3$; 87% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (2H, d, $J = 8.6$ Hz, Ar–*H*), 6.86 (2H, d, $J = 8.5$ Hz, Ar–*H*), 5.21 (1H, s, Ar–C*H*), 4.37 (1H, dq, $J = 10.7$, 7.1 Hz, $-CO_2CH_2CH_3$), 4.28 (1H, dq, $J = 10.6$, 7.1 Hz, $-CO_2CH_2CH_3$), 3.83 (1H, dq, $J = 10.7$, 7.1 Hz, $-CO_2CH_2CH_3$), 3.80 (3H, s, $-OCH_3$), 3.73 (1H, dq, $J = 10.6$, 7.2 Hz, $-CO_2CH_2CH_3$), 2.47 (1H, dq, $J = 15.2$, 7.6 Hz, $-C(=N)CH_2CH_3$), 2.15 (1H, dq, $J = 15.2$, 7.6 Hz, $-C(=N)CH_2CH_3$), 1.31 (3H, t, $J = 7.1$ Hz, $-CO_2CH_2CH_3$), 1.02 (3H, t, $J = 7.6$ Hz, $-C(=N)CH_2CH_3$), 0.91 (3H, t, $J = 7.1$ Hz, $-CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 163.9, 160.1, 130.4, 124.9, 117.7, 114.2, 84.6, 63.3, 62.3, 55.3, 55.2, 19.2, 13.9, 13.6, 9.3; IR (neat): 2981, 2362, 1747, 1653, 1611, 1514, 1458, 1368, 1252, 1228, 1206, 1179, 1094, 1036 cm^{-1}; HRMS (ESI): Calcd for $C_{18}H_{24}NO_7$: 366.1544 ($[M + H]^+$), Found: 366.1547 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 0.8 mL min^{-1}, retention time: 23.0 (*R*) and 24.9 min (*S*).

Diethyl (*R*)-3-Ethyl-4-(furan-2-yl)-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 9): $[\alpha]_D^{20}$ 1.91 (*c* 1.0, $CHCl_3$; 78% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (1H, d, $J = 1.3$ Hz, Ar–*H*), 6.38 (2H, app d, $J = 1.3$ Hz, Ar–*H*), 5.47 (1H, t, $J = 1.2$ Hz, Ar–C*H*), 4.37 (1H, dq, $J = 10.7$, 7.2 Hz, $-CO_2CH_2CH_3$), 4.29 (1H, dq, $J = 10.8$, 7.2 Hz, $-CO_2CH_2CH_3$), 4.04 (1H, dq, $J = 10.7$, 7.2 Hz, $-CO_2CH_2CH_3$), 3.95 (1H, dq, $J = 10.7$, 7.2 Hz, $-CO_2CH_2CH_3$), 2.45 (1H, dqd, $J = 15.2$, 7.6, 1.0 Hz, $-C(=N)CH_2CH_3$), 2.22 (1H, dqd, $J = 15.2$, 7.6, 1.4 Hz, $-C(=N)CH_2CH_3$), 1.31 (3H, t, $J = 7.2$ Hz, $-CO_2CH_2CH_3$), 1.07 (3H, t, $J = 7.2$ Hz, $-CO_2CH_2CH_3$), 1.03 (3H, t, $J = 7.6$ Hz, $-C(=N)CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 163.9, 146.1, 143.5, 114.8, 111.1, 111.0, 83.1, 63.5, 62.7, 49.7, 19.1, 13.8, 13.7, 9.0; IR (neat): 3123, 2984, 2941, 1745, 1659, 1464, 1368, 1301, 1281, 1240, 1208, 1096, 1039, 1013 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{20}NO_7$: 326.1233 ($[M + H]^+$), Found: 326.1234 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 254 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL min^{-1}, retention time: 9.5 (*S*) and 12.6 min (*R*).

Diethyl (*S*)-3-Ethyl-4-(pyridin-3-yl)-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 10): $[\alpha]_D^{20}$ 1.86 (*c* 1.0, $CHCl_3$; 72% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (1H, dd, $J = 4.7$, 1.3 Hz, Ar–*H*), 8.54 (1H, d, $J = 1.9$ Hz, Ar–*H*), 7.62 (1H, ddd, $J = 7.9$, 1.9, 1.9 Hz, Ar–*H*), 7.33 (1H, dd, $J = 7.9$, 4.8 Hz, Ar–*H*), 5.30 (1H, s, Ar–C*H*), 4.40 (1H, dq, $J = 10.8$, 7.1 Hz, $-CO_2CH_2CH_3$), 4.31 (1H, dq, $J = 10.7$, 7.1 Hz, $-CO_2CH_2CH_3$), 3.84 (1H, dq, $J = 10.9$, 7.2 Hz, $-CO_2CH_2CH_3$), 3.76 (1H, dq, $J = 10.8$, 7.1 Hz, $-CO_2CH_2CH_3$), 2.51 (1H, dq, $J = 15.2$, 7.6 Hz, $-C(=N)CH_2CH_3$), 2.15 (1H, dqd, $J = 15.3$, 7.7, 1.1 Hz, $-C(=N)CH_2CH_3$), 1.33 (3H, t, $J = 7.1$ Hz, $-CO_2CH_2CH_3$), 1.04 (3H, t, $J = 7.6$ Hz,

–C(=N)CH_2CH_3), 0.89 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 163.5, 150.5, 150.3, 136.3, 129.4, 123.7, 116.4, 84.2, 63.6, 62.7, 53.2, 19.1, 13.8, 13.5, 9.4; IR (neat): 2984, 2941, 1747, 1652, 1591, 1577, 1429, 1368, 1278, 1094, 1040 cm^{-1}; HRMS (ESI): Calcd for $C_{16}H_{21}N_2O_6$: 337.1392 ($[M + H]^+$), Found: 337.1394 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 254 nm, hexane/2-propanol = 4:1, flow rate 1.0 mL min^{-1}, retention time: 10.9 (*R*) and 14.8 min (*S*).

Diethyl (*S*)-4-Butyl-3-ethyl-4,5-dihydroisoxazole-5,5-dicarboxylate 2-Oxide (Table 4, Entry 11): $[\alpha]_D^{20}$ 1.55 (*c* 1.0, $CHCl_3$; 77% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.42–4.20 (4H, m, –$CO_2CH_2CH_3$), 4.04 (1H, t, $J = 6.0$ Hz, Bu–C*H*), 2.51 (1H, dq, $J = 15.1$, 7.5 Hz, –C(=N)CH_2CH_3), 2.28 (1H, dqd, $J = 15.1$, 7.5, 1.1 Hz, –C(=N)CH_2CH_3), 1.75–1.50 (2H, m, –CH_2–), 1.45–1.25 (4H, m, –CH_2–), 1.33 (3H, t, $J = 7.1$ Hz, –CH_3), 1.31 (3H, t, $J = 7.1$ Hz, –CH_3), 1.15 (3H, t, $J = 7.6$ Hz, –C(=N)CH_2CH_3), 0.90 (3H, t, $J = 7.0$ Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 164.9, 118.5, 84.2, 63.1, 62.7, 49.1, 28.5, 27.9, 22.7, 19.2, 14.0, 13.8, 13.7, 9.3; IR (neat): 2960, 2936, 2874, 1747, 1653, 1458, 1369, 1277, 1230, 1088, 1037 cm^{-1}; HRMS (ESI): Calcd for $C_{15}H_{26}NO_6$: 316.1754 ($[M + H]^+$), Found: 316.1755 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H, 235 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL min^{-1}, retention time: 12.7 (*R*) and 14.0 min (*S*).

Triethyl 3-[(*E*)-1-(Hydroxyimino)propyl]oxirane-2,2,3-tricarboxylate (5) (Table 4, Entry 12): ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (1H, br, N–O*H*), 4.36–4.15 (6H, m, –$CO_2CH_2CH_3$), 2.57 (1H, dq, $J = 15.2$, 7.4 Hz, –C(=N)CH_2CH_3), 2.44 (1H, dq, $J = 15.1$, 7.4 Hz, –C(=N)CH_2CH_3), 1.32 (3H, t, $J = 7.1$ Hz, –CH_2CH_3), 1.30 (3H, t, $J = 7.6$ Hz, –CH_2CH_3), 1.28 (3H, t, $J = 7.6$ Hz, –CH_2CH_3), 1.14 (3H, t, $J = 7.6$ Hz, –CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 162.9, 162.8, 153.6, 64.8, 64.7, 63.1, 63.0, 62.7, 19.9, 13.9, 13.8 (two peaks overlap), 9.4; IR (neat): 3462, 2986, 2942, 1758, 1559, 1466, 1446, 1370, 1253, 1066, 1023 cm^{-1}; HRMS (ESI): Calcd for $C_{14}H_{22}NO_8$: 332.1338 ($[M + H]^+$), Found: 332.1340 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 230 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL min^{-1}, retention time: 8.3 and 9.0 min.

Diethyl 2-Hydroxy-2-[(*S*)-2-(hydroxyimino)-1-phenylbutyl]malonate (7). To a solution of **6** (200 mg, 0.60 mmol) in MeOH (8 mL) was stirred for 3 h in the presence of 5% palladium on activated carbon (80 mg) at room temperature under H_2 atmosphere. The resulting mixture was filtered to remove the catalyst, and the filtrate was concentrated. Purification of the residue by column chromatography on silica gel (ethyl acetate/hexane = 1:1 as eluent) gave the title compound **7** (188 mg, 0.56 mmol, 93% yield). $[\alpha]_D^{20}$ 1.68 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.34 (2H, m, Ar–*H*), 7.32–7.27 (3H, m, Ar–*H*), 7.12 (1H, br, O*H*), 4.90 (1H, br, O*H*), 4.63 (1H, s, Ar–C*H*), 4.31 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 4.27 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 4.08 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 4.04 (1H, dq, $J = 10.7$, 7.2 Hz, –$CO_2CH_2CH_3$), 2.54 (1H, dq, $J = 13.5$, 7.6 Hz, –C(=N)CH_2CH_3), 1.86 (1H, dq, $J = 13.5$, 7.6 Hz, –C(=N)CH_2CH_3), 1.31 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$), 1.09 (3H, t, $J = 7.2$ Hz, –$CO_2CH_2CH_3$), 1.00 (3H, t, $J = 7.6$ Hz, –C(=N)CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 167.8, 162.3, 134.0, 130.4, 128.3, 128.0, 82.3, 62.5, 62.4, 53.0, 21.5, 14.0, 13.8, 9.8; IR (neat): 3427, 2980, 2366, 2340, 1741, 1462, 1452, 1367, 1262, 1220, 1149, 1040 cm^{-1}; HRMS (FAB): Calcd for $C_{17}H_{24}NO_6$: 338.1604 ($[M + H]^+$), Found: 338.1596 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 230 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL min^{-1}, retention time: 14.5 (*R*) and 19.3 min (*S*).

Diethyl (*S*)-3-Ethyl-4-phenyl-4,5-dihydroisoxazole-5,5-dicarboxylate (8). To a solution of **7** (33.7 mg, 0.1 mmol) and Et_3N (21.2 mg, 0.21 mmol) in CH_2Cl_2 (0.5 mL) was added MsCl (11.4 mg, 0.1 mmol) dropwise at 0 °C under argon atmosphere, and the cooling bath was then removed.[10] The reaction mixture was stirred overnight at room temperature and poured into water. After extraction with ethyl acetate, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5:1 as eluent) to give the title compound **8** (29.8 mg, 0.933 mmol, 93% yield). $[\alpha]_D^{20}$ 3.01 (*c* 1.0, $CHCl_3$; 86% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.31 (3H, m, Ar–*H*), 7.18–7.16 (2H, m, Ar–*H*), 5.19 (1H, s, Ar–C*H*), 4.35 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 4.26 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 3.78 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 3.68 (1H, dq, $J = 10.7$, 7.1 Hz, –$CO_2CH_2CH_3$), 2.34 (1H, dq, $J = 15.1$, 7.8 Hz, –C(=N)CH_2CH_3), 2.13 (1H, dq, $J = 15.4$, 7.8 Hz, –C(=N)CH_2CH_3), 1.30 (3H, t, $J = 7.1$ Hz, –$CO_2CH_2CH_3$), 1.12 (3H, t, $J = 7.5$ Hz, –C(=N)CH_2CH_3), 0.81 (3H, t, $J = 7.2$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 165.0, 162.2, 132.8, 129.3, 128.8, 128.6, 91.6, 62.9, 61.9, 61.3, 19.9, 13.9, 13.4, 10.6; IR (neat): 2980, 1768, 1742, 1462, 1452, 1368, 1268, 1228, 1201, 1128, 1081, 1050 cm^{-1}; HRMS (FAB): Calcd for $C_{17}H_{22}NO_5$: 320.1498 ($[M + H]^+$), Found: 320.1491 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 230 nm, hexane/2-propanol = 9:1, flow rate 0.5 mL min^{-1}, retention time: 14.1 (*S*) and 18.9 min (*R*).

Ethyl (4*S*,5*S*)-3-Ethyl-5-(hydroxymethyl)-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (9). To a solution of **8** (11.6 mg, 0.036 mmol) in THF (0.5 mL) was added LiAlH(O*t*-Bu)$_3$ (1.0 M in THF solution, 180 µL, 0.180 mmol) dropwise at 0 °C, and the cooling bath was then removed.[11] The reaction mixture was stirred for 11 h at room temperature and poured into ice-cooled 1 M HCl. After neutralization with $NaHCO_3$ the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane = 1:2 as eluent) to give the title compound **9** (8.7 mg, 0.031 mmol, 87% yield). $[\alpha]_D^{20}$ 0.68 (*c* 0.5, $CHCl_3$; 85% ee); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.28 (3H, m, Ar–*H*), 7.14–7.12 (2H, m, Ar–*H*), 4.43 (1H, s, Ar–C*H*), 3.92 (1H, dd, $J = 11.8$, 5.8 Hz, –CCH_2OH), 3.86 (1H, dd, $J = 11.8$, 8.5 Hz, –CCH_2OH), 3.74 (2H, q, $J = 7.2$ Hz, –$CO_2CH_2CH_3$), 2.54 (1H, dd, $J = 8.2$, 6.4 Hz, –CCH_2O*H*), 2.34 (1H, dq, $J = 15.1$, 7.8 Hz, –C(=N)CH_2CH_3), 2.12 (1H, dq, $J = 14.6$, 7.6 Hz, –C(=N)CH_2CH_3), 1.11 (3H, t, $J = 7.5$ Hz, –C(=N)CH_2CH_3), 0.84 (3H, t, $J = 7.2$ Hz, –$CO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 161.9, 133.7, 129.0, 128.7, 128.4, 92.1, 65.5, 61.5, 61.3, 20.1, 13.5, 10.7; IR (neat): 3349, 2979, 2927, 1745,

1461, 1453, 1371, 1277, 1244, 1129, 1096, 1076, 1055, 1040 cm^{-1}; HRMS (FAB): Calcd for $C_{15}H_{20}NO_4$: 278.1392 ($[M + H]^+$), Found: 278.1388 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 230 nm, hexane/2-propanol = 9:1, flow rate 1.0 mL min^{-1}, retention time: 14.0 (4*S*,5*S*) and 18.9 min (4*R*,5*R*).

Crystal Structure Analysis of Ethyl (4*S*,5*S*)-3-Ethyl-5-(hydroxymethyl)-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (9): Single crystals of **9** for X-ray diffraction experiments were recrystallized from EtOH. The data were collected at −177 °C on a Rigaku R-AXIS RAPID IP area detector with graphite-monochromated Mo Kα radiation ($\lambda = 0.71075$ Å). The crystal structure was solved by direct methods using SIR92[21] and expanded using DIRDIF99 Fourier techniques.[22] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement[23] on F^2 was based on 3087 observed reflections and 257 variable parameters. Crystallographic data for (c): $C_{15}H_{19}NO_4$, colorless prism, 0.5 × 0.4 × 0.3 mm^3, monoclinic, $P2_1$, $a = 9.0974(10)$, $b = 7.7565(9)$, $c = 10.9278(14)$ Å, $V = 724.14(15)$ $Å^3$, $D_{calcd} = 1.272$ g cm^{-3}, $Z = 2$, $2\theta_{max} = 54.9°$, $\mu = 0.921$ cm^{-1}. A total of 7136 reflections were measured. $R = 0.047$, and $Rw = 0.111$ for all reflections. All calculations were performed using the CrystalStructure3.8[24] crystallographic software package. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-794861 for compound **9**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Ethyl (4*S*,5*S*)-5-(Benzyloxymethyl)-3-ethyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (10). To a solution of **9** (35.0 mg, 0.126 mmol) in DMF (0.25 mL) was added Ag_2O (146 mg, 0.630 mmol) and BnBr (2.16 g, 12.6 mmol) at room temperature. The reaction flask was covered with aluminum foil and stirred for 11 h at room temperature. The mixture was filtered through a pad of celite, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20:1 to 4:1 as eluent) to give the title compound **10** (43.6 mg, 0.118 mmol, 94% yield). $[\alpha]_D^{20}$ 0.78 (*c* 0.5, $CHCl_3$; 85% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.25 (8H, m, Ar–*H*), 7.12–7.05 (2H, m, Ar–*H*), 4.69 (2H, s, ArCH_2O–), 4.27 (1H, s, Ar–C*H*), 3.90 (1H, d, $J = 10.7$ Hz, $ArCH_2OCH_2$), 3.86 (1H, d, $J = 10.7$ Hz, $ArCH_2OCH_2$), 3.73 (1H, dq, $J = 10.6$, 7.2 Hz, $–CO_2CH_2CH_3$), 3.68 (1H, dq, $J = 10.5$, 7.1 Hz, $–CO_2CH_2CH_3$), 2.32 (1H, dq, $J = 15.2$, 7.7 Hz, $–C(=N)CH_2CH_3$), 2.07 (1H, dq, $J = 15.3$, 7.7 Hz, $–C(=N)CH_2CH_3$), 1.07 (3H, t, $J = 7.5$ Hz, $–C(=N)CH_2CH_3$), 0.82 (3H, t, $J = 7.1$ Hz, $–CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 161.3, 137.8, 133.9, 128.9, 128.7, 128.4, 128.3, 127.8, 127.7, 92.7, 73.9, 72.9, 61.33, 61.31, 20.0, 13.5, 10.7; IR (neat): 3251, 2967, 2931, 2875, 1703, 1495, 1453, 1100, 1080 cm^{-1}; HRMS (FAB): Calcd for $C_{22}H_{26}NO_4$: 368.1862 ($[M + H]^+$), Found: 368.1876 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 215 nm, hexane/EtOH = 4:1, flow rate 0.5 mL min^{-1}, retention time: 14.7 (4*S*,5*S*) and 17.6 min (4*R*,5*R*).

(3*S*,4*S*,5*R*)-3-(Benzyloxymethyl)-5-ethyl-3-hydroxy-4-phenylpyrrolidin-2-one (11). To a solution of **10** (7.4 mg, 0.02 mmol) in a 3:1 mixture of MeOH/THF (0.3 mL) was added $NiCl_2$•$6H_2O$ (14.2 mg, 0.06 mmol) at −40 °C. After 10 min of stirring, $NaBH_4$ (7.4 mg, 0.20 mmol) was added portionwise. The stirring was maintained at −40 °C for 2 h, and the reaction was quenched with 5 M HCl. After the reaction mixture was poured into K_2CO_3 and 28% ammonia solution at 0 °C, the mixture was stirred for 1 h at 0 °C. The reaction mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (chloroform/methanol = 50:1 as eluent) to give the title compound **11** (6.1 mg, 0.019 mmol, 93% yield). $[\alpha]_D^{20}$ 0.43 (*c* 0.5, $CHCl_3$; 85% ee); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.23 (6H, m, Ar–*H*), 7.19–7.15 (2H, m, Ar–*H*), 7.11–7.08 (2H, m, Ar–*H*), 6.47 (1H, br, N*H*), 4.38 (1H, d, $J = 11.9$ Hz, ArCH_2O–), 4.21 (1H, d, $J = 11.9$ Hz, ArCH_2O–), 4.18–4.10 (1H, m, CH_3CH_2CH–), 3.56 (1H, d, $J = 10.2$ Hz, $ArCH_2OCH_2$), 3.60–3.45 (1H, br, O*H*), 3.46 (1H, d, $J = 5.5$ Hz, Ar–C*H*), 3.24 (1H, d, $J = 10.2$ Hz, $ArCH_2OCH_2$), 1.44–1.32 (1H, m, CH_3CH_2–), 1.30–1.18 (1H, m, CH_3CH_2–), 0.79 (3H, t, $J = 7.4$ Hz, CH_3CH_2–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 137.5, 135.7, 129.7, 128.3, 128.2, 127.6 (two peaks overlap), 127.3, 79.5, 73.6, 69.9, 57.4, 55.7, 23.6, 10.5; IR (neat): 3292, 3064, 3030, 2963, 2872, 1704, 1699, 1494, 1454, 1381, 1102 cm^{-1}; HRMS (FAB): Calcd for $C_{20}H_{24}NO_3$: 326.1756 ($[M + H]^+$), Found: 326.1763 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, 215 nm, hexane/EtOH = 4:1, flow rate 0.5 mL min^{-1}, retention time: 26.6 (3*S*,4*S*,5*R*) and 29.7 min (3*R*,4*R*,5*S*).

Crystal Structure Analysis of (3*S*,4*S*,5*R*)-3-(Benzyloxymethyl)-5-ethyl-3-hydroxy-4-phenylpyrrolidin-2-one (11): Single crystals of **11** for X-ray diffraction experiments were recrystallized from MeCN. The data were collected at −177 °C on a Rigaku R-AXIS RAPID IP area detector with graphite-monochromated Mo Kα radiation ($\lambda = 0.71075$ Å). The crystal structure was solved by direct methods using SIR92[21] and expanded using DIRDIF99 Fourier techniques.[22] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to N and O were refined isotropically. Other hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[23] on F^2 was based on 3447 observed reflections and 246 variable parameters. Crystallographic data for (c): $C_{20}H_{23}NO_3$, colorless platelet, 1.0 × 0.4 × 0.06 mm^3, monoclinic, $P2_1$, $a = 10.7063(3)$, $b = 7.2476(2)$, $c = 11.5374(5)$ Å, $\beta = 109.4732(11)°$, $V = 844.18(5)$ $Å^3$, $D_{calcd} = 1.280$ g cm^{-3}, $Z = 2$, $2\theta_{max} = 54.9°$, $\mu = 0.855$ cm^{-1}. $R = 0.029$, and $Rw = 0.082$ for all reflections. All calculations were performed using the CrystalStructure3.8[24] crystallographic software package. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-827004 for compound **9**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information

^{1}H and ^{13}C spectra for isoxazoline-*N*-oxides and compounds **5**–**11**. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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