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Asymmetric 1,3-Dipolar Cycloaddition Reactions of Benzonitrile Oxide Mediated by a Chiral Lewis Acid

Hidetoshi Yamamoto,*[a] Saori Hayashi,[a] Masashi Kubo,[a] Mayu Harada,[a] Masayuki Hasegawa,[a] Michihiko Noguchi,[b] Michinori Sumimoto,[a] and Kenzi Hori[a]

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In this paper we report on the asymmetric 1,3-dipolar cycloaddition reactions of nitrile oxides mediated by pybox/ytterbium triflates, -/magnesium bromide, and -/magnesium perchlorate. It was confirmed that the reactions proceed smoothly to give isoxazoline derivatives in high enantiomeric excesses with Mg^{2+} or Yb^{3+} complexes and acrylamide dipolarophiles bearing an oxazolidinone or imidazolidinone coordination auxiliary as well as a pybox ligand. In reactions with a dipolarophile bearing 4,4-dimethyloxazolidinone as the coordination auxiliary, an enantiomeric excess (59 % *ee*) of the corresponding cycloaddition product was achieved by using a slow addition technique to generate nitrile oxides in the presence of $Yb(OTf)_3$/ph-pybox. The cycloaddition reaction of a dipolarophile with an unsubstituted oxazolidinone group in the presence of $Yb(OTf)_3$/ph-pybox at a relatively high temperature (35 °C) produced a higher enantiomeric excess. A relatively low temperature (–78 °C) was required to obtain enantiomeric excesses such as 69 and 87 % *ee* in the reactions of a dipolarophile bearing an imidazolidinone group to afford cycloadducts in the presence of $MgBr_2$/ip-pybox.

Introduction

Nitrile oxides are chemical species that are very useful in organic synthesis, yielding five-membered heterocyclic compounds in 1,3-dipolar cycloaddition reactions with dipolarophiles such as alkenes, alkynes, aldehydes, ketones, and nitriles.[1] These heterocyclic compounds are not only useful as the basic backbones of biologically active substances such as pharmaceuticals and agrochemicals, but are also useful precursors. Cleavage of the oxygen–nitrogen bond in the ring leads to the formation of a variety of chiral chain compounds. As there is a demand for optically active compounds in most fields of organic synthesis, much effort has been made to develop methodologies for the asymmetric cycloaddition of nitrile oxides.[2] Although Lewis acids have been used to control reactions with spectacular success in many reactions, there are just a few reports of the successful use of Lewis acids in nitrile oxide cycloaddition reactions.[3,4]

As part of our investigation into the control of nitrile oxide cycloaddition reactions using Lewis acids we have already investigated the effects of added Lewis acids on the diastereoselectivity of the cycloaddition reactions between nitrile oxides and acrylamide dipolarophiles having an oxazolidinone chiral auxiliary.[5] In our preliminary studies, it was confirmed that nitrile oxide cycloaddition reactions proceeded smoothly even when magnesium and ytterbium salts were added. The diastereoselectivity of the cycloaddition reaction is significantly improved as a result of the coordination of the dipolarophile to the added Lewis acids. In subsequent studies we found that it is important to meet the following criteria in order for the Lewis acid to act effectively. 1) Dichloromethane or CH_3CN should be used as the solvent for magnesium salts, CH_2Cl_2 or THF for ytterbium salts. 2) Higher concentrations of substrate are preferable when using magnesium salts. 3) A reaction temperature ranging from 0 °C to room temperature should be used. It also became clear that to increase the selectivity of the reaction, the nitrile oxides should be added slowly.

In nitrile oxide cycloaddition reactions, for which effective catalysts have not yet been discovered, asymmetric cycloaddition using a chiral dipolarophile is still an effective method for synthesizing optically active isoxazoline compounds. However, in this type of method, new chiral centers are induced by using chiral centers in the dipolarophiles as chiral auxiliaries. In this method, chiral reactions require at least an equimolar amount of the optically active compound. Furthermore, the reaction as a whole requires two additional processes: introduction of the chiral auxiliary before the cycloaddition reaction and its removal afterwards. Therefore, in this paper we report the development of asym-

[a] Materials Science and Engineering, Graduate School of Science and Engineering, Yamaguchi University,
2-16-1 Tokiwadai, Ube 755-8611, Japan
Fax: +81-836-85-9201
E-mail: h-ymmt@yamaguchi-u.ac.jp
[b] Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University,
2-16-1 Tokiwadai, Ube 755-8611, Japan

metric nitrile oxide cycloaddition reactions using chiral Lewis acids.[6]

Results and Discussion

Lewis Acid Mediated Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides

Effective Lewis acids for nitrile oxide cycloaddition reactions are magnesium and ytterbium salts.[5] We therefore selected pybox, which is used in Diels–Alder reactions, as a ligand to produce chiral Lewis acids.[7] We performed cycloaddition reactions between benzonitrile oxide and the three dipolarophiles **1a**–**c** shown in Figure 2. Nine chiral Lewis acids were used as catalysts: combinations of the three Lewis acids and the three pybox ligands (Figure 1). At the same time, the effects of temperature dependence as well as the rate of addition of triethylamine were examined.

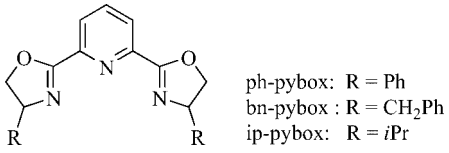
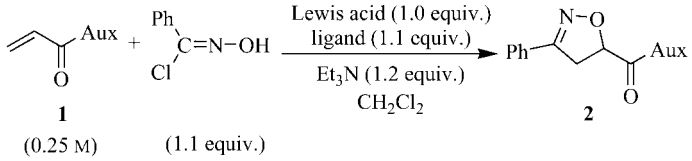


Figure 1. Chiral ligands tested in the cycloaddition reactions.

Figure 2 summarizes the enantiomeric excesses obtained for the cycloaddition reactions which are dependent on the reaction conditions. The upper and lower lines show the results at 0 °C and at room temperature, respectively. The results for the slow addition of triethylamine are in the right-hand columns and those for fast addition are in the left-hand columns. The slow and fast rates of addition are detailed in Figure 2. In the reaction with dipolarophile **1a**, linked to an unsubstituted oxazolidinone,[8] the highest enantiomeric excess of the resulting cycloaddition product was obtained when the chiral Lewis acid derived from $Yb(OTf)_3$ and ph-pybox was used (Figure 2). The reaction proceeded with a higher enantiomeric excess at room temperature than at 0 °C, but the rate of triethylamine addition showed no observable effects. In the reaction with dipolarophile **1b**, which incorporates a 4,4-dimethyloxazolidinone, although the chiral Lewis acid prepared from $Yb(OTf)_3$ and ph-pybox similarly gave the highest enantiomeric excess of the cycloaddition product, the rate of addition of the triethylamine was more important than the reaction temperature for the selectivity. Finally, in the reaction with the dipolarophile bearing the *N*-isopropylimidazolidinone moiety, unlike the other reactions, the highest enantiomeric excess was obtained when using the chiral Lewis acid derived from magnesium bromide and ip-pybox.



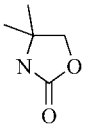
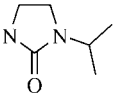
Aux	Ligand	$MgBr_2$		$Mg(ClO_4)_2$		$Yb(OTf)_3$	
1a: Aux^1 = 	(*R*)-ph-pybox	I 8 (*S*)	II 17 (*S*)	2 (*R*)	6 (*R*)	27 (*R*)	19 (*R*)
		III 5 (*S*)	IV 10 (*S*)	3 (*R*)	2 (*S*)	43 (*R*)	42 (*R*)
	(*S*)-bn-pybox	-	-	0	0	8 (*S*)	17 (*S*)
		-	-	1 (*S*)	1 (*S*)	5 (*S*)	25 (*S*)
	(*S*)-ip-pybox	-	-	14 (*S*)	28 (*S*)	-	1 (*R*)
		-	-	15 (*S*)	31 (*S*)	-	-
1b: Aux^2 = 	(*R*)-ph-pybox	I 2 (*S*)	II 1 (*S*)	1 (*S*)	1 (*S*)	25 (*R*)	45 (*R*)
		III 6 (*S*)	IV 2 (*S*)	1 (*S*)	1 (*S*)	34 (*R*)	43 (*R*)
	(*S*)-bn-pybox	1 (*S*)	1 (*S*)	1 (*S*)	1 (*S*)	24 (*S*)	29 (*S*)
		2 (*S*)	3 (*S*)	1 (*S*)	1 (*S*)	26 (*S*)	30 (*S*)
	(*S*)-ip-pybox	2 (*S*)	2 (*S*)	1 (*R*)	1 (*S*)	22 (*S*)	38 (*S*)
		7 (*S*)	3 (*S*)	2 (*S*)	2 (*S*)	35 (*S*)	36 (*S*)
1c: Aux^3 = 	(*R*)-ph-pybox	I 3 (*R*)	II 11 (*R*)	2 (*R*)	4 (*R*)	35 (*S*)	7 (*S*)
		III 14 (*R*)	IV 13 (*R*)	11 (*R*)	12 (*R*)	5 (*R*)	7 (*R*)
	(*S*)-bn-pybox	6 (*S*)	12 (*S*)	6 (*S*)	6 (*S*)	28 (*S*)	26 (*S*)
		14 (*S*)	10 (*S*)	10 (*S*)	6 (*S*)	22 (*S*)	26 (*S*)
	(*S*)-ip-pybox	43 (*S*)	44 (*S*)	28 (*S*)	29 (*S*)	20 (*S*)	8 (*S*)
		23 (*S*)	20 (*S*)	28 (*S*)	27 (*S*)	8 (*S*)	22 (*S*)

Figure 2. Enantiomer excess in Lewis acid mediated 1,3-dipolar cycloaddition of benzonitrile oxide. Reagents and conditions: I. 0 °C, 12 h; Et_3N was added all at once; II. 0 °C, 12 h; Et_3N was added at the rate of 0.29 equiv./0.5 h; III. room temp., 3 h; Et_3N was added all at once; IV. room temp., 3 h; Et_3N was added at the rate of 0.29 equiv./0.5 h. Enantiomer excesses were determined by HPLC (Chiralcel OJ, Daicel Co.).

Like dipolarophile **1a**, the triethylamine addition rate had no observable effect, but in this case a lower temperature is more effective for obtaining the cycloaddition product in a higher enantiomeric excess.

Rate of Generation of Nitrile Oxide

In preliminary experiments, we found that the rate of addition of triethylamine, which is closely related to the concentration of nitrile oxide[9] in the reaction mixture, is an important factor in reactions with dipolarophile **1b**, so we investigated the effects of the rate of addition of triethylamine in detail. In the presence of $Yb(OTf)_3$ and ph-pybox, 0.29 equiv. of triethylamine was added every 30 min to a mixture of dipolarophile **1b** and benzohydroximoyl chloride and the mixture was allowed to react at room temperature for 3 h. This reaction produced the objective isoxazoline **2b** in an enantiomeric excess of 43% (Table 1). In this case, the addition of triethylamine took 90 min. In another experiment, 0.12 equiv. of triethylamine was added every 12 min, that is, it took 108 min to add the triethylamine. This change increased the enantiomeric excess significantly to 59%. Further control of the addition rate (0.06 equiv. every 5 min) did not improve the enantiomeric excess.

Cycloaddition Temperature

The cycloaddition temperature was found to have a significant effect on the enantiomeric excess in the reactions with both dipolarophile **1a** with the unsubstituted oxazolidinone moiety and dipolarophile **1c** with the imidazolidinone group. The reaction was performed at 35 °C in the presence of $Yb(OTf)_3$/ph-pybox as the enantiomeric excess of the cycloaddition reaction with **1a** in the presence of $Yb(OTf)_3$/ph-pybox was found to be higher at room temperature (42, 43% *ee*) than at 0 °C (19, 27% *ee*). As dimerization of the nitrile oxide proceeds relatively quickly, the cycloaddition product yield is not necessarily very high, but the enantiomeric excess was found to be 69%, which is significantly higher than that achieved at lower temperatures. In order to make sure that the reactions proceed stereoselectively, the temperature was kept low which is usually useful to identify the configuration of the species that contribute to the reaction and to effectively use energy differences between transition states. However, higher selectivity was obtained at a higher temperature and this phenomenon is a contradiction of common sense. On the other hand, reducing the reaction temperature increases the enantiomeric excess of the cycloaddition reaction with **1c** to 87% at –78 °C in the presence of $MgBr_2$/ip-pybox. As the ligand exchange rate on the magnesium salt is slower than on ytterbium salts, it is necessary to form chiral magnesium complexes at a suitable temperature (see Conditions I in Table 2).

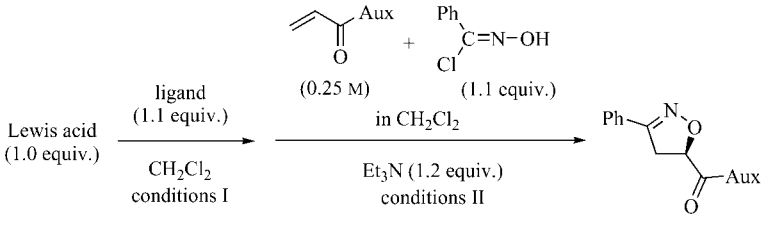
Absolute Configuration

The absolute configuration of the isoxazolines **2a**–**c** was identified by reductive removal of the coordination auxiliary Aux[1–3] with L-Selectride®[10] followed by comparison of the retention time in HPLC analysis of the isoxazolin-5-ylmethanol **3** with that of the authentic (*S*)-**3** (Table 3).[5b]

Table 1. Effect of rate of addition of triethylamine on the generation rate of nitrile oxide in the cycloaddition reactions between benzonitrile oxide and **1b**.

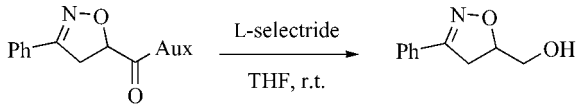
Aux	Lewis acid	Ligand	Conditions	Addition rate of Et_3N	% Yield	% *ee*
Aux[2]	$Yb(OTf)_3$	(*R*)-ph-pybox	room temp., 3 h	0.29 equiv./30 min	77	43 (*R*)
Aux[2]	$Yb(OTf)_3$	(*R*)-ph-pybox	room temp., 3 h	0.12 equiv./12 min	100	59 (*R*)
Aux[2]	$Yb(OTf)_3$	(*R*)-ph-pybox	room temp., 3 h	0.06 equiv./5 min	94	54 (*R*)

Table 2. Effect of cycloaddition temperature on nitrile oxide cycloaddition reactions of **1a** and **1c**.



Aux	Lewis acid	Ligand	Conditions I	Conditions II	% Yield	% *ee*
Aux[1]	$Yb(OTf)_3$	(*R*)-ph-pybox	room temp., 3 h	35 °C, 1 h	35	69 (*R*)
Aux[3]	$MgBr_2$	(*S*)-ip-pybox	0 °C, 6 h	0 °C, 6 h	80	38 (*S*)
Aux[3]	$MgBr_2$	(*S*)-ip-pybox	–40 °C, 6 h	–40 °C, 24 h	63	75 (*S*)
Aux[3]	$MgBr_2$	(*S*)-ip-pybox	–60 °C, 6 h	–60 °C, 24 h	64	61 (*S*)
Aux[3]	$MgBr_2$	(*S*)-ip-pybox	–78 °C, 6 h	–78 °C, 24 h	50	69 (*S*)
Aux[3]	$MgBr_2$	(*S*)-ip-pybox	–40 °C, 6 h	–78 °C, 24 h	53	87 (*S*)

Table 3. Reductive cleavage of isoxazoline **2** to isoxazolin-5-ylmethanol **3**.



2 **3**

Aux	**2**	Conditions	% Yield	(*S*)-**3**/(*R*)-**3**
Aux[1]	54:46	0 °C, 1 h	100	54:46
Aux[2]	68:32	0 °C, 4 h	75	64:36
Aux[3]	74:26	0 °C, 2 h; room temp., 2 h	70	73:27

Density Functional Theory (DFT) Calculations

Density functional theory (DFT) calculations at the B3LYP/6-31G* level of theory were used to optimize the geometry of two Mg^{2+}/(*S*)-ip-pybox complexes, Mg^{2+}/(*S*)-ip-pybox/**1a** and Mg^{2+}/(*S*)-ip-pybox/**1c**, using the Gaussian 03 program.[11] As shown in Figure 3, the Mg^{2+} ion in the two complexes adopts a distorted trigonal bipyramidal molecular geometry as the N(oxazoline)–Mg–N(oxazoline) angles were calculated to be 148.2 and 146.1° for **4a** and **4c**, respectively. The N(oxazoline)–Mg and N(pyridine)–Mg bond lengths in **4a** were turned out to be 2.221 and 2.160 Å and those in **4c** to be 2.233 and 2.169 Å, respectively.

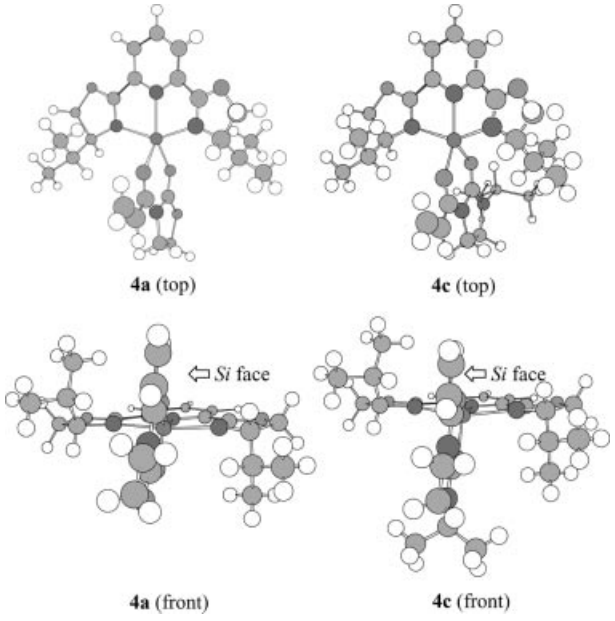


Figure 3. Structures of the Mg^{2+}/(*S*)-ip-pybox/**1a** (**4a**) and Mg^{2+}/(*S*)-ip-pybox/**1c** complexes (**4c**).

The front view of **4a** clearly shows that the orientation of the isopropyl groups is closely related to the face selectivity of the nitrile oxides that react with the C=C bond of the acrylamide. The *Si* face of the dipolarophile is less crowded than the *Re* face because of the orientation of the isopropyl groups in ip-pybox. Reaction at the *Si* face produces the (*S*)-isoxazoline, as mentioned previously. Although **4c** has geometrical features similar to those of **4a**, a better enantiomeric excess was obtained for **4c**. It is considered that this difference is a result of the difference in the N(oxazoline)–Mg–N(oxazoline) angle in the trigonal bipyramidal molecular geometry, that is, the smaller angle in **4c** brings the isopropyl group closer to the C=C moiety and shields the *Re* face more effectively.

Conclusions

To summarize, we have investigated asymmetric nitrile oxide cycloaddition reactions using a chiral Lewis acid for the synthesis of optically active isoxazoline compounds. As a result, we have found that in reactions with a dipolarophile having 4,4-dimethyloxazolidinone as a coordination auxiliary, a high enantiomeric excess of the corresponding cycloaddition product is obtained by adding triethylamine slowly to generate nitrile oxide in the presence of Yb(OTf)$_3$/ph-pybox. We have also discovered that higher enantiomeric excesses are obtained in cycloaddition reactions with dipolarophiles having an unsubstituted oxazolidinone group when the reaction is performed at relatively high temperatures in the presence of Yb(OTf)$_3$/ph-pybox and in reactions with dipolarophiles having imidazolidinone groups when the reaction is performed at relatively low temperatures in the presence of $MgBr_2$/ip-pybox. Nitrile oxides are chemical species with a relatively high reactivity and their cycloaddition reactions proceed quickly even at –78 °C. Nitrile oxides also react to form dimers. The abovementioned reactions are therefore the result of competitive processes involving reactions to which the Lewis acid contributes and reactions to which the Lewis acid does not contribute. In this paper, we have reported on chiral induction using a chiral Lewis acid. In this reaction, the reaction rate is hardly increased at all by the addition of a Lewis acid, so it is not easy to reduce the amount of Lewis acid used. We are currently investigating reactions that involve only a catalytic amount of a chiral Lewis acid.

Experimental Section

General: All commercially available reagents were used without further purification. Reaction solvents were dried by standard methods before use. ^{1}H NMR spectra were recorded at 270 MHz and ^{13}C NMR spectra at 67.8 MHz with a JEOL EX-270 spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in parts per million (δ, in ppm) downfield from tetramethylsilane. HPLC analysis was performed using a Shimadzu LC-10A system with a UV/VIS detector and Chiralcel OD-H (Daicel Co.) column. Optical rotations were measured with a JASCO DIP-140 digital polarimeter. Electron-impact mass spectra (EIMS) were recorded at 70 eV with a direct inlet and chemical ionization mass spectra (CIMS) were obtained with methane (ionized at 200 eV) as the carrier gas. The progress of the reactions was monitored by TLC (silica gel 60 F_{254}, Merck). Chromatographic purification was performed with Wakogel C-200 (100–200 mesh, Wako Pure Chemical Industries) and/or silica gel 60 (230–400 mesh, Merck).

General Procedure for Lewis Acid Mediated Asymmetric Nitrile Oxide Cycloaddition: A mixture of Lewis acid (0.125 mmol) and pybox (0.138 mmol) in dry dichloromethane (0.2 mL) was stirred at room temperature for 3 h under N_2. A solution of dipolarophile

(0.125 mmol) and benzohydroximoyl chloride (21.4 mg, 0.138 mmol) in dichloromethane (0.3 mL) was added and stirred for 20 min at the same temperature. Triethylamine (21.0 μL, 0.151 mmol) was then added and the mixture stirred (Figure 2 and Table 1). The mixture was diluted with ethyl acetate (5 mL) and filtered though Celite® 545. The filtrate was evaporated under reduced pressure and the residue was purified by chromatography on silica gel with hexane/ethyl acetate as eluent to afford the corresponding isoxazoline **2**. The enantiomeric excess was measured by HPLC analysis. Hexane/2-propanol (1:1, v/v) was used as eluent and the flow rate was 0.8 mL/min.

3-[(4,5-Dihydro-3-phenylisoxazol-5-yl)carbonyl]oxazolidin-2-one (2a):[6a,6b] The reaction was performed using $Yb(OTf)_3$ (77.5 mg, 0.125 mmol), (*R*)-ph-pybox (50.8 mg, 0.138 mmol), dipolarophile **1a** (17.7 mg, 0.125 mmol), benzohydroximoyl chloride (21.4 mg, 0.138 mmol), and triethylamine (21.0 μL, 0.151 mmol, addition rate: 0.29 equiv./0.5 h) in dichloromethane (0.5 mL) at 0 °C for 12 h to afford isoxazoline **2a** (20.0 mg, 60%) after purification by chromatography. Colourless prisms (from AcOEt/hexane). $[\alpha]_D^{27}$ = –23.5 (*c* = 0.23, $CHCl_3$)[7] [19.0% *ee*, (*R*) rich]; m.p. 173.1–174.0 °C. ^{1}H NMR ($CDCl_3$): δ = 3.60 (dd, *J* = 17.2, 6.3 Hz, 1 H, one of 4-H), 3.82 (dd, *J* = 17.2, 11.6 Hz, 1 H, the other of 4-H), 4.00–4.16 (m, 2 H, 4′-H), 4.50–4.56 (m, 2 H, 5′-H), 6.14 (dd, *J* = 11.6, 6.3 Hz, 1 H, one of 5-H), 7.40–7.43 (m, 3 H, Ph), 7.67–7.70 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 38.89 (C-4), 42.52 (C-4′), 63.02 (C-5′), 77.81 (C-5), 126.93, 128.77, and 130.49 (each Ph), 153.38 (C-3), 155.95 (C-2′), 169.18 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3000, 2950, 2940, 1765 (C=O), 1720 (C=O), 1475, 1445, 1385, 1365, 1355, 1280, 1240, 1220, 1200, 1115, 1035, 985, 970, 915, 880, 865, 770, 760, 715, 695 cm^{-1}. EIMS: *m*/*z* (%) = 260 (11) $[M]^+$, 232 (13), 146 (100), 118 (36), 115 (12), 104 (25), 103 (12), 90 (14), 87 (13), 77 (61), 51 (20), 43 (19), 42 (20). $C_{13}H_{12}N_2O_4$ (260.24): calcd. C 60.00, H 4.65, N 10.76; found C 59.80, H 4.66, N 10.74. HPLC analysis [Daicel chiralcel OD-H, hexane/*i*PrOH (1:1 v/v), 0.8 mL/min]: 30 [(5*S*)-**2a**], 50 min [(5*R*)-**2a**].

3-[(4,5-Dihydro-3-phenylisoxazol-5-yl)carbonyl]-4,4-dimethyloxazolidin-2-one (2b):[6a,6b] The reaction was performed using $Yb(OTf)_3$ (77.5 mg, 0.125 mmol), (*R*)-ph-pybox (50.8 mg, 0.138 mmol), dipolarophile **1b** (21.1 mg, 0.125 mmol), benzohydroximoyl chloride (21.4 mg, 0.138 mmol), and triethylamine (21.0 μL, 0.151 mmol, addition rate: 0.29 equiv./1 min) in dichloromethane (0.5 mL) at room temperature for 3 h to afford isoxazoline **2b** (32.2 mg, 89%) after purification by chromatography. Colourless prisms (from CH_2Cl_2/hexane). $[\alpha]_D^{28}$ = –30.8 (*c* = 1.59, $CHCl_3$) [34.0% *ee*, (*R*) rich]; m.p. 214.4–214.8 °C. ^{1}H NMR ($CDCl_3$): δ = 1.59 and 1.62 (s, each 3 H, 2 × 4′-CH_3), 3.54 (dd, *J* = 17.2, 6.3 Hz, 1 H, one of 4-H), 3.79 (dd, *J* = 17.2, 11.6 Hz, 1 H, the other of 4-H), 4.12 (s, 2 H, 5′-H), 6.07 (dd, *J* = 11.6, 6.3 Hz, 1 H, 5-H), 7.38–7.43 (m, 3 H, Ph), 7.67–7.71 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.33 and 24.78 (4′-Me), 38.94 (C-4), 60.74 (C-4′), 75.89 and 78.74 (C-4 and C-5′), 126.90, 128.72, 129.00, and 130.37 (each Ph), 153.84 and 155.72 (C-3 and C=O), 170.04 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 1790 (C=O), 1710, 1690 (C=O), 1370, 1350, 1300, 1250, 1230, 1180, 1090, 1030, 900, 890, 840, 760, 700 cm^{-1}. EIMS: *m*/*z* (%) = 288 (2) $[M]^+$, 260 (13), 146 (100), 118 (27), 104 (15), 100 (18), 77 (33), 55 (12), 43 (21), 42 (12). $C_{15}H_{16}N_2O_4$ (288.11): calcd. C 62.49, H 5.59, N 9.72; found C 62.20, H 5.56, N 9.50. HPLC analysis [Daicel chiralcel OD-H, hexane/*i*PrOH (1:1 v/v), 0.8 mL/min]: 10 [(5*S*)-**2b**], 30 min [(5*R*)-**2b**].

1-[(4,5-Dihydro-3-phenylisoxazol-5-yl)carbonyl]-3-(1-methylethyl)-imidazolidin-2-one (2c):[6c] The reaction was performed using $MgBr_2$ (23.0 mg, 0.125 mmol), (*S*)-ip-pybox (42.2 mg, 0.138 mmol), dipolarophile **1c** (22.8 mg, 0.125 mmol), benzohydroximoyl chloride (21.4 mg, 0.138 mmol), and triethylamine (21.0 μL, 0.151 mmol, addition rate: 0.29 equiv./0.5 h) in dichloromethane (0.5 mL) at 0 °C for 12 h to afford isoxazoline **2c** (27.0 mg, 72%) as colourless needles (from CH_2Cl_2/hexane) after purification by chromatography. $[\alpha]_D^{24}$ = 22.0 (*c* = 1.00, $CHCl_3$)[5] [45.8% *ee*, (*S*) rich]; m.p. 112.3–113.0 °C. ^{1}H NMR ($CDCl_3$): δ = 1.21 (d, *J* = 6.9 Hz, 6 H, CH_3), 3.42–3.48 (m, 2 H, 4′-H), 3.56 (dd, *J* = 17.2, 6.6 Hz, 1 H, one of 4-H), 3.78 (dd, *J* = 17.2, 11.6 Hz, 1 H, the other of 4-H), 3.77–3.97 (m, 2 H, 5′-H), 4.23 (septet, *J* = 6.9 Hz, 1 H, CH), 6.24 (dd, *J* = 11.6, 6.6 Hz, 1 H, 5-H), 7.36–7.42 (m, 3 H, Ph), 7.66–7.70 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.53, 19.66, 36.28, 39.35, 39.66, 44.08, 78.17, 126.93, 128.66, 129.04, 130.19, 153.47, 155.81, 169.50 ppm. IR (KBr): $\tilde{\nu}$ = 3050, 2970, 2870, 1720, 1680, 1590, 1560, 1470, 1440, 1410, 1380, 1360, 1290, 1260, 1240, 1220, 1200, 1120, 1070, 980, 900, 860, 760, 720, 690 cm^{-1}. CIMS: *m*/*z* (%) = 303 (17), 302 (100) $[M + 1]^+$, 284 (32), 237 (12), 199 (12), 198 (33), 185 (15), 174 (28), 165 (12), 145 (13), 129 (76), 128 (30), 113 (57), 104 (14). $C_{16}H_{19}N_3O_3$ (301.34): calcd. C 63.77, H 6.36, N 13.94; found C 63.45, H 6.25, N 13.68. HPLC analysis [Daicel chiralcel OJ, hexane/*i*PrOH (1:1 v/v), 1.2 mL/min]: 14 [(5*S*)-**2c**], 32 min [(5*R*)-**2c**].

Effect of Cycloaddition Temperature: Under N_2, a mixture of $Yb(OTf)_3$ (77.5 mg, 0.125 mmol) and (*R*)-ph-pybox (50.8 mg, 0.138 mmol) in dry dichloromethane (0.2 mL) was stirred for 3 h at room temperature. A solution of dipolarophile **1a** (17.7 mg, 0.125 mmol) and benzohydroximoyl chloride (21.4 mg, 0.138 mmol) in dichloromethane (0.3 mL) was added and stirred for 20 min at 35 °C. Triethylamine (21.0 μL, 0.151 mmol) was added at a rate of 5 μL/min and stirred for 3 h at the same temperature. The mixture was diluted with ethyl acetate (5 mL) and filtered though Celite® 545. The filtrate was evaporated under a reduced pressure and the residue was purified by chromatography on silica gel with hexane/ethyl acetate (1:1 v/v) as eluent to afford isoxazoline **2a** (11.3 mg, 35%).

Under N_2, a mixture of $MgBr_2$ (23.0 mg, 0.125 mmol) and (*S*)-ip-pybox (42.2 mg, 0.138 mmol) in dry dichloromethane (0.2 mL) was stirred at –40 °C for 6 h. A solution of dipolarophile **1c** (22.8 mg, 0.125 mmol) and benzohydroximoyl chloride (21.4 mg, 0.138 mmol) in dichloromethane (0.3 mL) was added and the mixture was stirred for 20 min at the same temperature. Triethylamine (21.0 μL, 0.151 mmol) was added at a rate of 5 μL/min and stirred at –78 °C for 24 h. The mixture was diluted with ethyl acetate (5 mL) and filtered though Celite® 545. The filtrate was evaporated under a reduced pressure and the residue was purified by chromatography on silica gel with hexane/ethyl acetate (1:1 v/v) as eluent to afford isoxazoline **2c** (20.0 mg, 53%).

Reduction of Isoxazoline 2a to Isoxazolin-5-ylmethanol 3: L-Selectride® (1.0 M in THF, 0.12 mL, 0.12 mmol) was added to a solution of isoxazoline **2a** (7.8 mg, 0.03 mmol) in dry THF (0.3 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 1 h, water, 15% aq. NaOH, 35% H_2O_2 (each 0.5 mL) were successively added and then the mixture extracted with ethyl acetate (1 mL × 5). The combined extracts were dried with anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane/ethyl acetate (3:1 v/v) as eluent to give isoxazolin-5-ylmethanol **3** (5.3 mg, 100%) as a colorless solid. HPLC analysis [Daicel chiralcel OJ, hexane/*i*PrOH (4:1 v/v), 1.0 mL/min]: 11 [(5*R*)-**3**], 13 min [(5*S*)-**3**].[5b,10,12]

Reduction of Isoxazoline 2b to Isoxazolin-5-ylmethanol 3: L-Selectride® (1.0 M in THF, 0.23 mL, 0.23 mmol) was added to a solution of isoxazoline **2b** (16.5 mg, 0.057 mmol) in dry THF (0.57 mL)

at 0 °C under N_2. The mixture was stirred at 0 °C for 4 h, water, 15% aq. NaOH, 35% H_2O_2 (each 1 mL) were successively added and the mixture extracted with ethyl acetate (5 mL × 4). The combined extracts were dried with anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane/ethyl acetate (3:1 v/v) as eluent to give isoxazolin-5-ylmethanol **3** (7.6 mg, 75%) as a colorless solid.

Reduction of Isoxazoline 2c to Isoxazolin-5-ylmethanol 3: L-Selectride® (1.0 M in THF, 0.14 mL, 0.14 mmol) was added to a solution of isoxazoline **2c** (10.5 mg, 0.035 mmol) in dry THF (0.35 mL) at 0 °C under N_2. The mixture was stirred for 2 h at 0 °C and then for 2 h at room temperature. Water, 15% aq. NaOH, 35% H_2O_2 (each 0.5 mL) were successively added and extracted with ethyl acetate (2 mL × 4). The combined extracts were dried with anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane/ethyl acetate (3:1 v/v) as eluent to give isoxazolin-5-ylmethanol **3** (4.3 mg, 70%) as a colorless solid.

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