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Asymmetric 1,3-Dipolar Cycloaddition of Nitrones with an Electron-Withdrawing Group to Allylic Alcohols Utilizing Diisopropyl Tartrate as a Chiral Auxiliary

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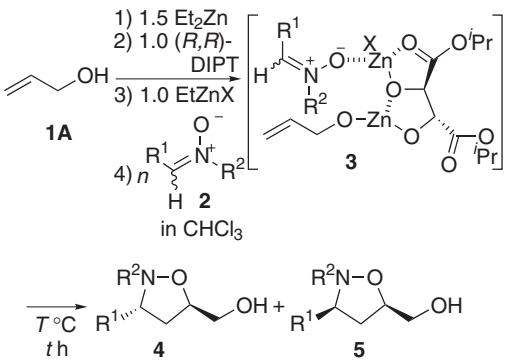
The asymmetric 1,3-dipolar cycloaddition of nitrones possessing an electron-withdrawing group to allylic alcohols was achieved by the use of diisopropyl (*R*,*R*)-tartrate as a chiral auxiliary to afford the corresponding isoxazolidines with high regio-, diastereo-, and enantioselectivity. In the case of nitrones possessing an electron-withdrawing cyano or *t*-butoxycarbonyl group, 1,3-dipolar cycloaddition to 2-propen-1-ol occurred to produce the corresponding 3,5-*trans*-isoxazolidines with high enantioselectivity. To the contrary, nitrones possessing an amide moiety afforded the corresponding optically active 3,5-*cis*-isoxazolidines with completely opposite diastereoselectivity. A catalytic asymmetric 1,3-dipolar cycloaddition of nitrones possessing the *N*,*N*-diisopropylamide moiety to allylic alcohols was achieved to afford di- or trisubstituted isoxazolidines with excellent enantioselectivity of up to over 99% ee. The present asymmetric 1,3-dipolar cycloaddition was applied to the synthesis for the (2*S*,4*R*)-4-hydroxyornithine derivative.

Cycloaddition reactions have drawn much attention in synthetic organic chemistry, since these processes can create contiguous carbon stereocenters at once.[1] The development of an asymmetric Diels–Alder reaction using chiral Lewis acids was a landmark achievement in this area.[2] In contrast, asymmetric 1,3-dipolar cycloadditions have been scarcely discovered, mainly due to the fact that complexation of 1,3-dipoles to Lewis acids, which are effective catalysts for the Diels–Alder reaction, alters the electronic character and reactivity of dipolar species.[3] Asymmetric 1,3-dipolar cycloadditions of nitrones to olefins are used to prepare isoxazolidines that are key synthetic intermediates for the synthesis of optically active nitrogen-containing substances such as γ-amino alcohols. Recently, several enantioselective methods for this reaction have been developed.[4,5]

A novel chiral multinucleating system utilizing tartaric acid ester as a chiral auxiliary was developed in our laboratory and it has been successfully applied to the asymmetric 1,3-dipolar cycloaddition of nitrile oxides.[6] These promising results tempted us to apply this strategy to the enantioselective 1,3-dipolar cycloaddition of nitrones. Herein, we describe the enantioselective 1,3-dipolar cycloaddition of nitrones bearing an electron-withdrawing group such as a cyano, ester, or amide group to allylic alcohols utilizing diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT] as a chiral auxiliary to afford the corresponding isoxazolidines with high regio-, diastereo-, and enantioselectivities.[7]

Results and Discussion

Firstly, the enantioselective 1,3-dipolar cycloaddition of the nitrone **2a** possessing a cyano group to 2-propen-1-ol (**1A**) was examined. When **1A** was treated with 1.0 molar amounts of diethylzinc, (*R*,*R*)-DIPT, additional diethylzinc, and **2a** successively, the corresponding isoxazolidine could not be obtained. This result seemed to be due to the weak Lewis acidity of the ethylzinc moiety of the speculative intermediate **3** (X = Et), to which the nitrone could not effectively coordinate. In order to increase the Lewis acidity, the chlorozinc intermediate **3** (X = Cl) was tried in an attempt to generate it alternatively. After several attempts, using ethylzinc chloride prepared from diethylzinc and anhydrous zinc chloride (1/1) in situ[8] was found to be effective to produce the corresponding 3,5-*trans*-isoxazolidines **4Aa** with high enantioselectivity (Entry 1, Table 1). The 1,3-dipolar cycloaddition of the nitrone **2b** (E/Z = 3.4/1 in $CDCl_3$) possessing a *t*-butoxycarbonyl group also proceeded to give the corresponding 3,5-*trans*-isoxazolidine **4Ab** with high enantioselectivity (Entry 2).[9]



(1)

To our surprise, the nitrone **2c** possessing a *N*,*N*-dibenzylamide moiety afforded the 3,5-*cis*-isoxazolidine **5Ac** with completely opposite diastereoselectivity and moderate enantioselectivity. Since this reaction proceeded smoothly even at 0 °C, we used this substrate for optimization of a catalytic

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Table 1. Asymmetric 1,3-Dipolar Cycloaddition of Nitrones **2a–2c** to 2-Propen-1-ol (**1A**)[a]

Entry	R^1	R^2	**2**	*n*	*T*/°C	*t*/h	**4** or **5**	Yield of **4**/%	ee/%	Yield of **5**/%	ee/%
1[b]	CN	Ph	**a**[c]	3.0	45→25	43 + 21	**Aa**	42	94[d]	trace	—
2	$CO_2{}^tBu$	Me	**b**[e]	2.0	60	22	**Ab**	68	92[f]	—	—
3	$CONBn_2$	Ph	**c**[c]	1.0	0	24	**Ac**	trace	—	85	50[g]

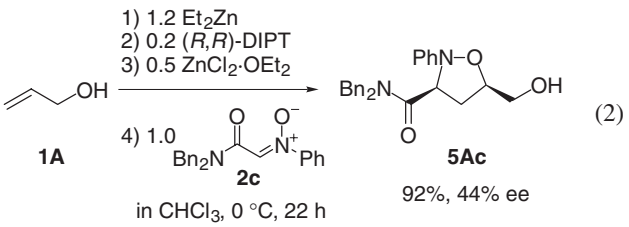
a) X = Cl. b) A solution of the nitrone **2a** in $CHCl_3$ was slowly added to the reaction mixture at 45 °C over a period of 43 h, and the mixture was stirred at 25 °C for 21 h. c) Only *Z*-form. d) Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OB-H). e) $E/Z = 3.4/1$ (in $CDCl_3$). f) Enantioselectivity was determined by ^1H NMR analysis of the corresponding (*R*)-MTPA ester. g) Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H).

Table 2. Catalytic Asymmetric 1,3-Dipolar Cycloaddition of the Nitrones **2** to γ-Substituted Allylic Alcohols **1**

Entry	R^4	**1**	R^2	R^3	**2**[a]	*x*	*y*	*z*	*m*	**5**	Yield/%	ee/%
1[b]	H	**A**	Ph	Bn	**c**	1.0	1.6	1.4	1.0	**Ac**	70	64[c]
2[b]	H	**A**	Ph	^{i}Pr	**d**	1.0	1.6	1.4	1.0	**Ad**	69	98[c]
3[b]						1.9	2.1	1.9	1.5		73	92[c]
4[d]						1.9	2.1	1.9	1.5		83	88[c]
5[b]	H	**A**	Bn	^{i}Pr	**e**	1.0	1.6	1.4	1.0	**Ae**	20	78[e]
6[b]	Me	**B**	Ph	^{i}Pr	**d**	1.0	1.6	1.4	1.0	**Bd**	24	99[c]
7[b]						1.9	2.1	1.9	1.5		51	>99[c]
8[d]						1.9	2.1	1.9	1.5		64	>99[c]
9[b]						2.9	3.1	2.9	2.5		57	99[c]
10[d]	^{n}Pr	**C**	Ph	^{i}Pr	**d**	1.4	1.6	1.4	1.0	**Cd**	48	>99[e]
11[d]	CO_2Me	**D**	Ph	^{i}Pr	**d**	2.0	2.2	2.0	1.6	**Dd**	63	97[c]

a) Only *Z*-form. b) Reaction was carried out on a 0.5 mmol scale of **2** in 9 mL of $CHCl_3$, and the solid nitrones **2c**–**2e** were added in portions to the reaction mixture over a period of 2 h. c) Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). d) Reaction was carried out on a 1.5 mmol scale of **2d** in 12 mL of $CHCl_3$, and the solid nitrone **2d** was added in portions to the reaction mixture over a period of 3 h. e) The product was isolated as the corresponding acetate and its enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H).

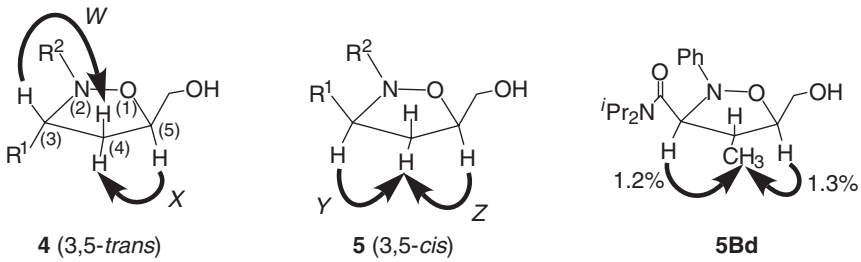
process. That is, when asymmetric 1,3-dipolar cycloaddition of **2c** was carried out by using a 0.2 molar amount of (*R*,*R*)-DIPT in the presence of anhydrous zinc chloride species produced from an ethylzinc species in situ as the following equation, the 3,5-*cis*-isoxazoline **5Ac** was obtained with the enantioselectivity of 44% ee. Unfortunately, the enantioselectivity was not reproducible.



(2)

Several attempts using a 0.2 molar amount of (*R*,*R*)-DIPT, especially paying attention to anhydrous conditions and the molar amounts of the reagents, showed that the generation of the zinc halide species in situ from the ethylzinc species and iodine[10] was crucial to realize extremely anhydrous conditions to obtain reproducible results (Table 2). Furthermore, the use of pyridine *N*-oxide as an additive was important to obtain reproducibly high enantioselectivity by dissolving the precipitate (probably a highly aggregated zinc complex containing (*R*,*R*)-DIPT), which appears in the progress of the catalytic reaction. With respect to the influence of substituents on the amide nitrogen of the nitrone, we found that excellent enantioselectivity is achieved by employing a bulky *N*,*N*-diisopropylamide group to afford the 3,5-*cis*-isoxazolidine **5Ad** with 98% ee (Table 2, Entry 2). The reaction of the *N*-benzyl nitrone **2e** gave the *cis*-cycloadduct **5Ae** diastereoselectively in lower chemical yield, but still with good enantioselectivity (Entry 5).

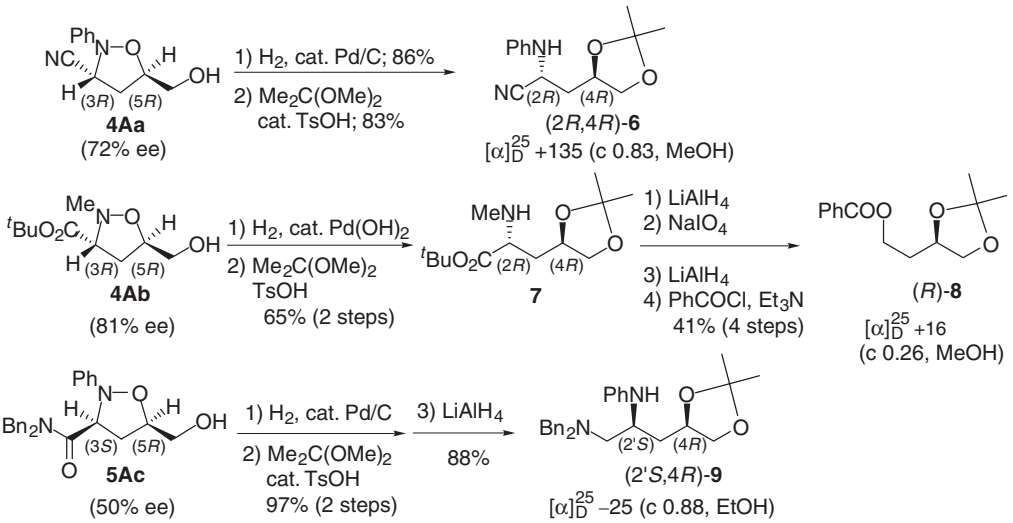
In the reaction of (*E*)-2-buten-1-ol (**1B**), the 3,5-*cis*-cycloadduct **5Bd** was formed with high levels of regio-, diastereo-, and enantioselectivity, but the chemical yield was low compared with the case of **1A** (Entries 2 and 6). The yield of this process could be improved by using larger amounts of **1B** together with the proper amounts of diethylzinc, iodine, and pyridine *N*-oxide (Entries 7 and 9). Furthermore, the concentration of the reactants was found to improve the efficiency of the reaction; a reaction employing 0.95 mmol of **1B** and 0.5 mmol of **2d** in 9 mL of $CHCl_3$ afforded the corresponding cycloadduct **5Bd** in 51% yield (Entry 7), while a reaction performed on 1.5 mmol scale of **2d** in 12 mL of $CHCl_3$ resulted in a higher chemical yield of 64% with complete enantioselectivity (Entry 8). (*E*)-2-Hexen-1-ol (**1C**) reacted to generate the corresponding cycloadduct **5Cd** with enantioselectivity higher than 99% ee (Entry 10). Enantioselectivity of the cycloaddition reaction of 2-propen-1-ol (**1A**) was lower when an excess amount of **1A** was employed, especially at higher concentrations (Entries 3 and 4). To broaden the scope of the present method, the reaction of γ-functionalized allylic alcohols was next examined. It was found that asymmetric 1,3-dipolar cycloaddition of the nitrone **2d** to methyl (*E*)-4-hydroxy-2-butenoate (**1D**) proceeded smoothly to give the corresponding trisubstituted isoxazolidine **5Dd** with complete regio- and diastereoselectivity and excellent enantioselectivity (Entry 11).



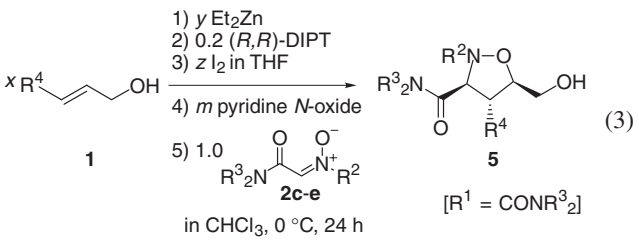
4 (3,5-*trans*) **5** (3,5-*cis*) **5Bd**

R^1	R^2		*W*/%	*X*/%		*Y*/%	*Z*/%
CN	Ph	**4Aa**	5.3	3.4	**5Aa**	4.5	5.1
$CO_2{}^tBu$	Me	**4Ab**	3.0	3.8	**5Ab**	3.1	4.1
$CONBn_2$	Ph	**4Ac**	6.8	5.5	**5Ac**	5.8	6.6
CON^iPr_2	Ph		--	--	**5Ad**	4.7	6.3

Fig. 1.



Scheme 1.

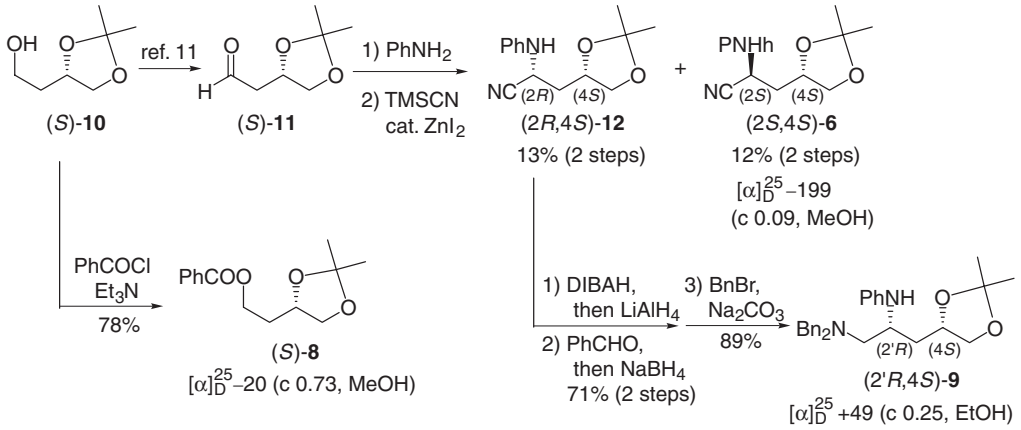


(3)

The relative stereochemistry of the cycloadducts **4Aa**, **5Aa**, **4Ab**, **5Ab**, **4Ac**, **5Ac**, **5Ad**, and **5Bd** was determined by NOE analysis (Fig. 1). The NOEs between *trans*-vicinal protons on C_3–C_4 and C_4–C_5 were scarcely observed.

Furthermore, the absolute configuration of the isoxazolidines **4Aa**, **4Ab**, and **5Ac** was confirmed to be (3*R*,5*R*), (3*R*,5*R*), and (3*S*,5*R*), respectively, by the chemical correlation between their derivatives and the stereochemically unambiguous authentic samples: The obtained cycloadduct **4Aa** (72% ee), **4Ab** (81% ee), and **5Ac** (50% ee) were transformed to the compounds (2*R*,4*R*)-**6**, (*R*)-**8**, and (2′*S*,4*R*)-**9**, respectively (Scheme 1). Authentic samples of (2*S*,4*S*)-**6**, (*S*)-**8**, and (2′*R*,4*S*)-**9** were prepared from (*S*)-**10**, which was originally derived from (*S*)-malic acid[11] (Scheme 2). The specific optical rotations of the obtained derivatives (2*R*,4*R*)-**6**, (*R*)-**8**, and (2′*S*,4*R*)-**9** were opposite to those of the authentic samples of (2*S*,4*S*)-**6**, (*S*)-**8**, and (2′*R*,4*S*)-**9**, respectively. The absolute configurations of the products **5Ad**, **5Ae**, **5Bd**, and **5Cd** were tentatively determined to also be 3*S*,5*R*. Furthermore, the absolute configuration of **5Dd** was determined by X-ray crystallography as follows: The enantiomerically pure **5Dd**, obtained by recrystallization from AcOEt, was treated with (*R*)-1-(1-naphthyl)ethyl isocyanate to give the corresponding adduct **13**. The absolute stereochemistry of **13** was determined to be 3*S*,4*R*,5*R* by X-ray crystallographic analysis of its single crystal as shown in Fig. 2.

The stereochemical outcome of the asymmetric 1,3-dipolar cycloaddition of nitrone might be rationalized by the transition state shown in Fig. 3. In the case of $R^1 < R^2$, the *endo*-transition state must be preferred due to the steric congestion between the R^2 group on nitrogen and the ester moiety of the tartrate ligand caused in the *exo*-transition state leading to formation of the 3,5-*trans*-isoxazolidine **4**. In addition, coordination of the carbonyl oxygen to zinc in the reaction using *Z*-**2b** activated the *endo*-transition state (Fig. 4) in contrast to the case of



Scheme 2.

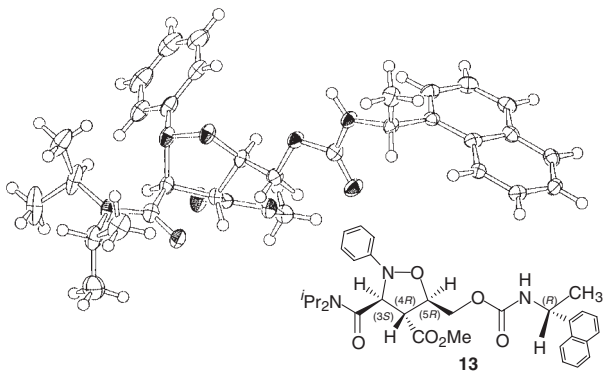


Fig. 2.

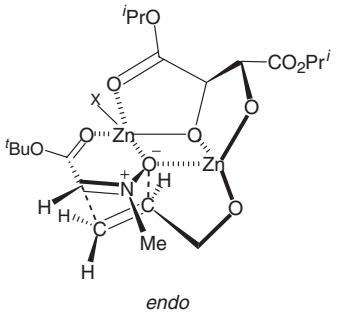


Fig. 4.

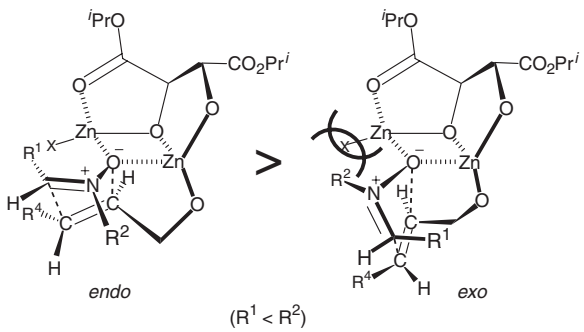


Fig. 3.

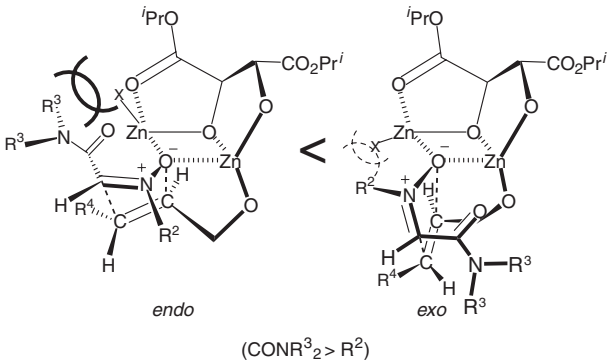
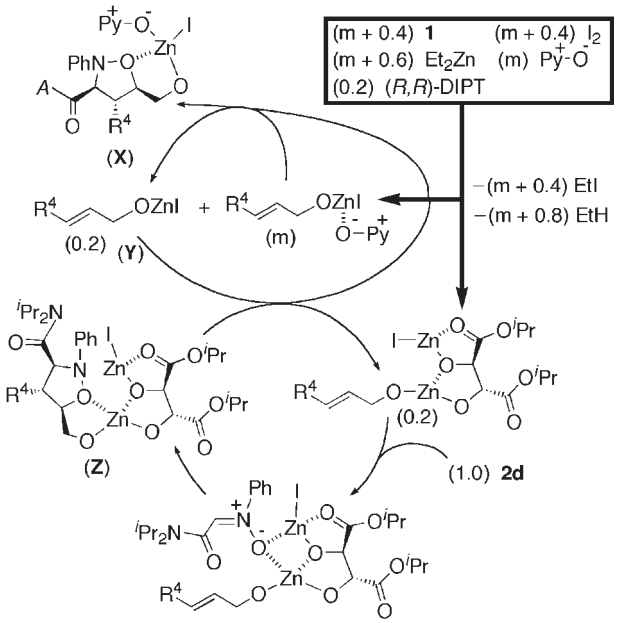


Fig. 5.

E-**2b**, which cannot form a chelating complex. Higher reaction temperatures might accelerate the isomerization of *E*-**2b** to *Z*-**2b**[12] prior to cycloaddition, which would then give the *trans*-(3*R*,5*R*)-isoxazolidine **4Ab** diastereo- and enantioselectively. On the other hand, in the case where $R^1 > R^2$, there is significant steric repulsion between R^1 and the ester moiety in DIPT, especially in the *endo* mode of reaction with **2c** and **2d**, which possesses a bulky amide moiety (Fig. 5). As a result, the *cis*-3,5-isoxazolidine **5** is preferentially formed via an *exo*-transition state.[13] Although difference in enantiofacial selectivity between the amide-substituted nitrones **2c** and **2d** still remains puzzling, it might be a result of the steric congestion of the *N*,*N*-diisopropylamide moiety that prevents aggregation of the intermediary metal-substrate complex **3**, even under concentrated conditions. Ultimately, the reaction might proceed through an ideal monomeric complex in which the *exo*-transition state (Fig. 5) is more favored.

Although the exact reaction course in the catalytic reaction of the amide-substituted nitrones is not yet clear, a plausible catalytic cycle is shown in Scheme 3 to rationalize the proper molar amounts of each reagent we found, x:y:z:$m = (m + 0.4)$:$(m + 0.6)$:$(m + 0.4)$:m (Table 2, Entries 3, 4, and 7–11). In order to realize the catalytic cycle, the zinc-bridging chiral salt (**Z**) must be replaced by the zinc salt (**Y**) of **1** being free from pyridine *N*-oxide to afford the zinc salt complex of **5** (**X**). The reason why enantioselectivity was decreased in the case using excess amounts of 2-propen-1-ol under condensed conditions (Table 2, Entries 3 and 4) is not yet clear; the non-catalytic 1,3-dipolar cycloaddition reaction to free zinc salt of 2-propen-1-ol (**Y**) might proceed competitively to lower the enantioselectivity.



Scheme 3.

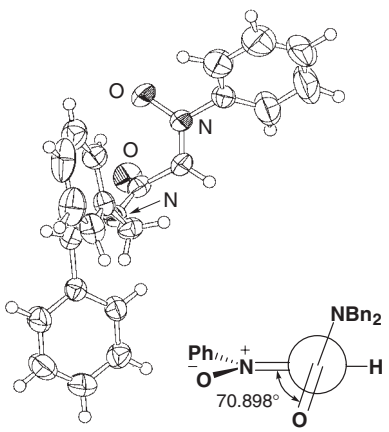


Fig. 6. ORTEP diagram of **2c**.

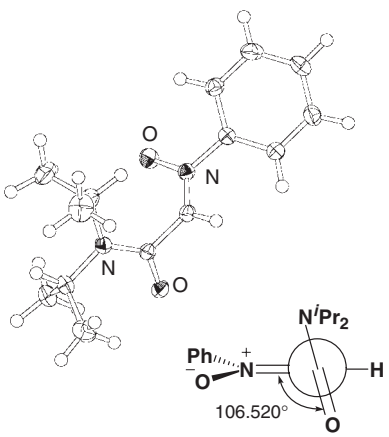


Fig. 7. ORTEP diagram of **2d**.

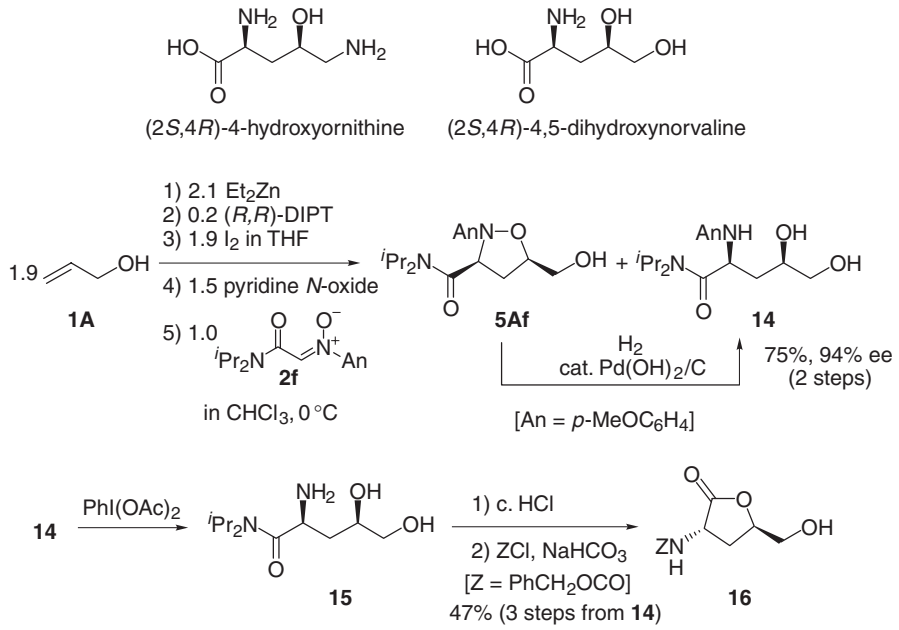
X-ray crystallographic analysis of the amide-substituted nitrones **2c** (Fig. 6) and **2d** (Fig. 7) showed that the stereochemistry at the C=N bond is *Z*, and the amide moiety and C=N bond are twisted with dihedral angles (O=C–C=N) of 70.898° (**2c**) and 106.520° (**2d**), respectively. This suggests that the nitrones **2c** and **2d** did not act as an electron-deficient 1,3-dipole even in the solution, and thus **2d** could react with the electron-deficient olefin **1D**.

γ-Hydroxy-α-amino acid is an important skeleton found in 4-hydroxyornithine and 4,5-dihydroxynorvaline: (2*S*,4*R*)-4-Hydroxyornithine is a nonprotenogenic amino acid that is widely found in nature and is a key component of Biphenomycin A and B.[14] (2*S*,4*R*)-4,5-Dihydroxynorvaline is a key component of Polyoxin E.[15] The isoxazolidines produced in the present asymmetric 1,3-dipolar cycloaddition potentially contain the γ-hydroxy-α-amino acid skeleton. Therefore, the present method was next applied to the synthesis of 4-hydroxyornithine derivatives (Scheme 4).[16] Since the isoxazolidines from the *N*-phenyl-substituted nitrone **2d** seemed to be difficult to deprotect, the phenyl group was replaced by a *p*-methoxyphenyl (An) group. The 1,3-dipolar cycloaddition of the nitrone **2f** possessing a *p*-methoxyphenyl group on nitrogen, whose stereochemistry was suggested to be only *Z* from the ^{1}H NMR spectrum by comparison with **2d**, to 2-propen-1-ol (**1A**) was carried out. Surprisingly, the NMR spectrum of the crude products showed that not only the desired isoxazolidine **5Af**, but also the reduced γ-amino alcohol **14** was produced, probably due to the electron-donating *p*-methoxy group introduced on an aromatic ring that made the N–O bond labile as shown in Scheme 5. Further, the isoxazolidine **5Af** was too unstable to be purified by TLC or column chromatography on silica gel. Thus, the crude mixture was subjected to hydrogenolysis to afford the 4,5-dihydroxy-α-amino acid derivative **14** in 75% yield with a selectivity of 94% ee. Removal of the *p*-methoxyphenyl group on nitrogen in **14**, followed by lactonization and protection of the free amino group by a benzyloxycarbonyl (Z) group furnished the γ-lactone **16**, which is a key intermediate for the synthesis of protected (2*S*,4*R*)-4-hydroxyornithine.[16a] The ^{1}H NMR and IR spectra and the specific rotation of **16** were identical to the data reported in the literatures.[17]

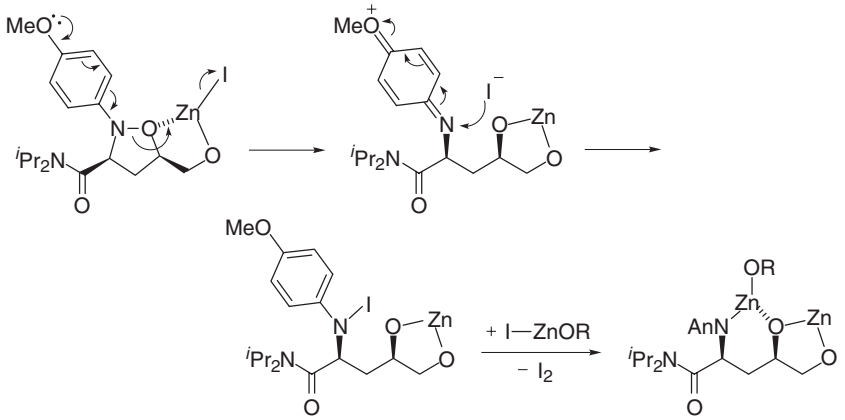
In conclusion, we have established an efficient regio-, diastereo-, and enantioselective 1,3-dipolar cycloaddition of nitrone to allylic alcohols by using (*R*,*R*)-DIPT as a chiral auxiliary. This reaction provides a simple and attractive approach to highly functionalized isoxazolidines with almost complete enantioselectivity. The ready availability of both (*R*,*R*)- and (*S*,*S*)-tartaric acid esters allows these methods to be applied to the preparation of either enantiomer of the target substances.

Experimental

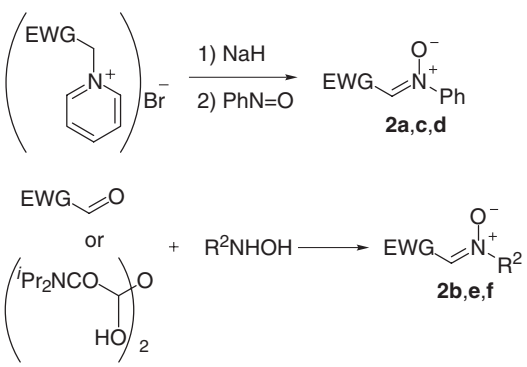
The ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-GX 400, Lambda 400, and Lambda 300 NMR spectrometers. The chemical shifts were determined in the δ-scale relative to TMS ($\delta = 0$ ppm) as an internal standard. The IR spectra were measured on JASCO FT/IR-230 and JASCO IR A-1 spectrometers. The MS spectra were recorded with Hitachi M-80 and JEOL SX-102A mass spectrometers. THF and Et_2O were freshly distilled from sodium diphenylketyl. $CHCl_3$ was passed through aluminium oxide (Merck 1076) twice and stored over MS 3A before use. All other solvents were distilled and stored over drying agents. Thin-layer chromatography (TLC) and flash column chromatography were performed by using Merck silica gel 60 PF_{254} (Art. 7749) and Cica-Merck silica gel 60 (No. 9385-5B), respectively.



Scheme 4.



Scheme 5.



Scheme 6.

Nitrones possessing electron-withdrawing groups were synthesized from *N*-substituted pyridinium salts and nitrosobenzene in the presence of a base[18] for **2a**, **2c**, and **2d**, and/or from glyoxylic acid derivatives and *N*-substituted hydroxylamines for **2b**, **2e**, and **2f** (Scheme 6).

***N*-(Cyanomethyl)pyridinium Bromide.** To 10.94 g (91.2 mmol) of bromoacetonitrile was added 44 mL (544 mmol) of pyridine at 0 °C, and the mixture was kept at this temperature for 30 min with stirring. The precipitated solid was filtered off and thoroughly washed with Et_2O to afford the desired product. Recrystallization from EtOH gave white crystals in 92% (16.66 g) yield. mp 162 °C (from EtOH). IR (KBr) 3140, 3050, 2930, 2880, 2250, 1620, 1570, 1480, 1400, 1380, 1350, 1300, 1230, 1205, 1180, 960, 935, 860, 810, 760, 670 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 6.01 (2H, s), 8.27 (2H, dd, $J = 6.59$, 7.81 Hz), 8.74 (1H, tt, $J = 1.22$, 7.81 Hz), 9.21 (2H, dd, $J = 1.22$, 6.59 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.6, 114.1, 128.5, 145.4, 147.5. Anal. Found: C, 42.38; H, 3.49; N, 13.95%. Calcd for $C_7H_7BrN_2$: C, 42.24; H, 3.54; N, 14.07%.

***N*-(Cyanomethylene)aniline *N*-Oxide (2a).** To a mixture of *N*-(cyanomethyl)pyridinium bromide (3.98 g, 20 mmol), nitrosobenzene (2.14 g, 20 mmol), and sodium hydride (60% dispersion in mineral oil) (0.80 g, 20 mmol), THF (50 mL) was added at 0 °C, and the resulting mixture was stirred for 1 h at 0 °C.[18] The reaction was quenched by the addition of a saturated aq NH_4Cl solution, and the mixture was extracted several times with ethyl

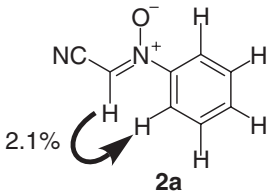


Fig. 8.

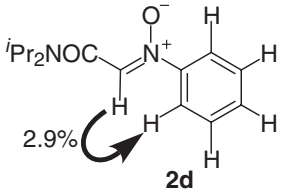


Fig. 9.

acetate. The combined extracts were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/AcOEt = 5/1, v/v) to give **2a** in 61% yield (1.77 g) as a single isomer. mp 102.0–102.5 °C (from CH_2Cl_2/hexane). IR (KBr) 3140, 3080, 2230, 1515, 1478, 1378, 1300, 1190, 1155, 1090, 1010, 878, 760, 720, 675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, s), 7.50–7.55 (2H, m), 7.60 (1H, tt, J = 1.22, 7.33 Hz), 7.72 (2H, dd, J = 1.22, 8.54 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.6, 112.5, 121.2, 129.7, 132.6, 146.4. Anal. Found: C, 65.64; H, 3.85; N, 19.11%. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17%. The stereochemistry of the nitrone **2a** in a $CDCl_3$ solution was determined by NOE measurement to be Z as shown in Fig. 8.

In a similar manner, the nitrones **2c** and **2d** were prepared from the corresponding pyridinium salts.

***N*-[(Dibenzylcarbamoyl)methylene]aniline *N*-Oxide (2c):** Yield: 50%. mp 123–123.5 °C (from AcOEt/hexane). IR (KBr) 3055, 2959, 1645, 1605, 1552, 1485, 1470, 1451, 1432, 1367, 1307, 1281, 1234, 1204, 1170, 1081, 1041, 955, 926, 910, 894, 765, 749, 734, 711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (2H, s), 4.73 (2H, s), 7.18 (2H, d, J = 6.59 Hz), 7.29–7.38 (8H, m), 7.42–7.51 (3H, m), 7.60 (1H, s), 7.63–7.65 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.1, 50.6, 121.5, 127.2, 127.5, 127.86, 127.94, 128.0, 128.8, 128.9, 129.3, 131.0, 135.7, 136.7, 147.0, 162.2. Anal. Found: C, 76.62; H, 5.71; N, 8.06%. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13%.

Single crystals were obtained by recrystallization from AcOEt/hexane. Crystal data: $C_{22}H_{20}N_2O_2$, FW 344.41, monoclinic, $P2_1/c$, a = 18.278(2) Å, b = 10.037(2) Å, c = 10.1438(7) Å, β = 93.990(7)°, V = 1856.4(3) $Å^3$, Z = 4. D_{calcd} = 1.232 g cm^{-3}. R = 0.042 (R_w = 0.057) for 1785 reflections with $I > 3.00\sigma(I)$ and 316 variable parameters.

***N*-[(Diisopropylcarbamoyl)methylene]aniline *N*-Oxide (2d):** Yield: 47%. mp 119–121 °C (from AcOEt/hexane). IR (KBr) 3060, 2973, 2933, 1624, 1558, 1484, 1368, 1330, 1295, 1206, 1158, 1139, 1088, 1043, 983, 775, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, d, J = 6.59 Hz), 1.52 (6H, d, J = 6.83 Hz), 3.58 (1H, hept, J = 6.83 Hz), 3.89 (1H, hept, J = 6.59 Hz), 7.44–7.49 (3H, m), 7.46 (1H, s), 7.72–7.75 (2H, m). ^1H NMR (400 MHz, C_6D_6) δ 1.08 (6H, d, J = 6.59 Hz), 1.57 (6H, d, J = 6.59 Hz), 3.18 (1H, hept, J = 6.59 Hz), 3.82 (1H, hept, J = 6.59 Hz), 6.81–6.88 (3H, m), 7.02 (1H, s), 7.40 (2H, d, J = 7.56 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.5, 46.3, 50.7, 121.4, 128.1, 129.2, 130.7, 147.2, 160.2. Anal. Found: C, 67.52; H, 8.13; N, 11.21%. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28%.

Crystal data: $C_{14}H_{20}N_2O_2$, FW 248.32, monoclinic, $P2/c$, a = 12.446(1) Å, b = 8.3599(9) Å, c = 15.236(2) Å, β = 116.0870(6)°, V = 1423.8(3) $Å^3$, Z = 4. D_{calcd} = 1.158 g cm^{-3}. R = 0.045 (R_w = 0.065) for 2278 reflections with $I > 3.00\sigma(I)$ and 163 variable parameters.

The stereochemistry of the nitrone **2d** in a C_6D_6 solution was determined to also be Z by NOE measurement as shown in Fig. 9.

***N*-[(*t*-Butoxycarbonyl)methylene]methylamine *N*-Oxide (2b).** Under an oxygen atmosphere, ozone-containing oxygen was bubbled into a CH_2Cl_2 (30 mL) solution of *t*-butyl acrylate (7.3 mL, 50 mmol) for 4 h at −78 °C. After the color of the solution changed to blue, extra oxygen was bubbled until the solution became colorless again, and dimethyl sulfide (5.5 mL, 75 mmol) was added. The reaction mixture was gradually warmed to room temperature and stirred overnight. After the evaporation of excess dimethyl sulfide and CH_2Cl_2, a crude *t*-butyl glyoxylate was dissolved in CH_2Cl_2 (60 mL), and *N*-methylhydroxylamine hydrochloride (4.18 g, 50 mmol) and triethylamine (7.7 mL, 55 mmol) were added to the solution at rt. After stirring for 4.5 h, water was added and extracted with Et_2O. The combined extracts were washed with water and brine, and then dried over $MgSO_4$. The solid residue obtained by evaporation of the solvent was recrystallized from AcOEt and hexane to give **2b** (2.140 g) in 27% yield (E/Z = 3.4/1, determined by ^1H NMR spectrum in $CDCl_3$[19]) in two steps. mp 57.8–58.0 °C (from AcOEt/hexane; mixture of (*E*)- and (*Z*)-isomers). IR (KBr) 3131, 2976, 1708, 1567, 1479, 1421, 1403, 1371, 1233, 1161, 1108, 980, 845, 812, 774, 742 cm^{-1}. ^1H NMR of (*E*)-isomer (300 MHz, $CDCl_3$) δ 1.51 (9H, s), 4.14 (3H, s), 7.16 (1H, s). ^{13}C NMR of (*E*)-isomer (100 MHz, $CDCl_3$) δ 28.1, 51.7, 82.7, 128.9, 160.3. ^1H NMR of (*Z*)-isomer (300 MHz, $CDCl_3$) δ 1.51 (9H, s), 3.81 (3H, s), 7.03 (1H, s). ^{13}C NMR of (*Z*)-isomer (100 MHz, $CDCl_3$) δ 28.1, 55.9, 82.3, 127.4, 158.8. Anal. Found: C, 52.56; H, 8.23; N, 8.71%. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80%.

***N*-[(Diisopropylcarbamoyl)methylene]benzylamine *N*-Oxide (2e).** Under an oxygen atmosphere, ozone-containing oxygen was bubbled into a CH_2Cl_2 (100 mL) solution of *N*,*N*,*N*′,*N*′-tetraisopropylfumaramide (3.61 g, 12.8 mmol) for 2 h at −78 °C. After the color of the solution changed to blue, extra oxygen was bubbled until the color of the solution became colorless again, followed by addition of dimethyl sulfide (3.7 mL, 38.3 mmol). After warming to room temperature, the resulting solution was allowed to stand overnight. The solvent was removed in vacuo and a yellow oil was obtained as the crude product of *N*,*N*-diisopropylglyoxylamide (2.61 g). To the crude product in CH_2Cl_2 (30 mL) were added *N*-benzylhydroxylamine hydrochloride (2.73 g, 16.6 mmol) and triethylamine (4.62 mL, 33.2 mmol) at rt, and the mixture was kept for 3 h at rt with stirring. The mixture was filtered and the filtrate was concentrated. The residue was partitioned between AcOEt and water. The resulting organic extract was successively washed with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by column chromatography (hexane/AcOEt = 1/1, v/v) afforded the desired product **2e** (1.34 g, 20% in 2 steps) as a single isomer. mp 102.5–104 °C (from AcOEt/hexane). IR (KBr) 3036, 2974, 2944, 1636, 1497, 1457, 1439, 1409, 1371, 1338, 1309, 1209, 1193, 1158, 1043, 988, 964, 950, 819, 781, 743, 702, 670, 656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (6H, d, J = 6.83 Hz), 1.42 (6H, d, J = 6.83 Hz), 3.51 (1H, hept, J = 6.83 Hz), 3.72

(1H, hept, $J = 6.83$ Hz), 4.93 (2H, s), 6.94 (1H, s), 7.39–7.52 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.3, 46.1, 50.4, 70.3, 128.7, 129.1, 129.2, 129.5, 132.2, 160.3. Anal. Found: C, 68.39; H, 8.52; N, 10.77%. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68%.

***N*-[(Diisopropylcarbamoyl)methylene]-4-methoxyaniline *N*-Oxide (2f).** Under an oxygen atmosphere, ozone-containing oxygen was bubbled into a CH_2Cl_2 (150 mL) solution of *N*,*N*-(diisopropyl)crotonamide (14.04 g, 89 mmol) for 4 h at -78 °C. After the color of the solution changed to blue, extra oxygen was bubbled until the color of the solution became colorless again, and dimethyl sulfide (9.8 mL, 133 mmol) was added. After warming to room temperature, the resulting solution was allowed to stand overnight. The CH_2Cl_2 solution was washed with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave crude *N*,*N*-diisopropylglyoxylamide. After the crude amide was stored in a freezer overnight, a precipitated solid product was filtrated off and washed by Et_2O to give *N*,*N*-diisopropylglyoxylamide 1/2 hydrate [2,2′-oxybis(2-hydroxy-*N*,*N*-diisopropylacetamide)] (3.01 g) in 23% yield. The filtrate was concentrated in vacuo, followed by treatment with a few drops of water and one drop of acetic acid to give additional *N*,*N*-diisopropylglyoxylamide 1/2 hydrate. mp 112.0–112.5 °C (from Et_2O). IR (KBr) 3363, 2973, 2937, 1646, 1421, 1375, 1320, 1139, 1109, 1044, 1011, 933, 890 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (6H, d, $J = 6.79$ Hz), 1.19 (6H, d, $J = 6.79$ Hz), 1.37 (6H, d, $J = 6.79$ Hz), 1.41 (6H, d, $J = 6.79$ Hz), 3.45 (2H, hept, $J = 6.79$ Hz), 4.20 (2H, hept, $J = 6.79$ Hz), 5.50 (2H, d, $J = 9.54$ Hz), 5.59 (2H, d, $J = 9.54$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 19.9, 20.1, 20.5, 46.3, 47.8, 86.0, 166.4. Crystal data (Fig. 10): $C_{16}H_{32}N_2O_5$, FW 332.44, orthorhombic, *Pbcn*, $a = 11.843(1)$ Å, $b = 12.021(1)$ Å, $c = 13.607(1)$ Å, $V = 1937.1(3)$ Å^3, $Z = 4$. $D_{calcd} = 1.140$ g cm^{-3}. $R = 0.042$ ($R_w = 0.054$) for 1379 reflections with $I > 3.00\sigma(I)$ and 105 variable parameters.

To a mixture of *N*-(*p*-methoxyphenyl)hydroxylamine (743 mg, 5.34 mmol) and *N*,*N*-diisopropylglyoxylamide 1/2 hydrate (839 mg, 5.34 mmol) in CH_2Cl_2 (8 mL) was added a drop of acetic acid. After stirring for 7 h, evaporation of the solvent and separation of the residue by column chromatography (hexane/AcOEt = 1/1, v/v) afforded the nitrone **2f** (962 mg) in 65% yield. mp 134.5–135.0 °C (from Et_2O). IR (KBr) 3039, 2968, 2933, 1629, 1601, 1502, 1473, 1444, 1370, 1330, 1303, 1250, 1027, 845 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (6H, d, $J = 6.59$ Hz), 1.51 (6H, d, $J = 6.83$ Hz), 3.55–3.62 (1H, m), 3.85 (3H, s), 3.85–3.93 (1H, m), 6.93 (2H, d, $J = 9.03$ Hz), 7.39 (1H, s), 7.68 (2H, d, $J = 9.03$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.5, 46.2, 50.7, 55.7, 114.1, 122.7, 127.1, 140.3, 160.4, 161.3. Anal. Found: C, 64.74; H, 8.09; N, 10.12%. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.72; H, 7.97; N, 10.06%.

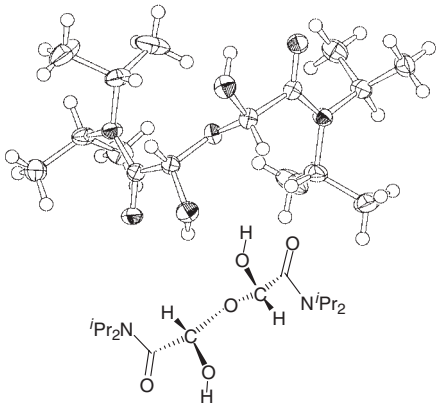


Fig. 10.

1,3-Dipolar Cycloaddition for the Syntheses of Racemic Addition Products 4Aa and 5Aa. To a CH_2Cl_2 (3 mL) solution of 2-propen-1-ol (**1A**) (51 mg, 0.89 mmol) was added ethylmagnesium bromide (0.88 mmol, 0.85 mL of 1.03 M solution in THF) at 0 °C under a nitrogen atmosphere. After stirring for 30 min at 0 °C, a CH_2Cl_2 (3 mL) solution of *N*-(cyanomethylene)aniline *N*-oxide (**2a**) (128 mg, 0.88 mmol) was added, and the resulting solution was stirred for 23 h at 25 °C.[9a] The reaction was quenched by the addition of a saturated aq NH_4Cl solution, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by TLC (SiO_2, hexane/AcOEt = 2/1, v/v, twice) to afford the *trans*-isoxazolidine **4Aa** (9 mg, 5%) and *cis*-isomer **5Aa** (59 mg, 33%).

In a similar manner, the racemic isoxazolidines **4Ab** and **5Ab** were prepared from the corresponding nitrones **2b**.

***trans*-5-(Hydroxymethyl)-2-phenylisoxazolidine-3-carbonitrile (4Aa):** mp 68.5 °C (from Et_2O/hexane). IR (KBr) 3422, 2957, 2238, 1598, 1492, 1454, 1267, 1214, 1045, 855, 763 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3/C_6D_6 = 1/1$) δ 1.78 (1H, brs), 2.11 (1H, ddd, $J = 6.44$, 8.24, 12.81 Hz), 2.24 (1H, ddd, $J = 1.83$, 7.63, 12.81 Hz), 3.31–3.39 (2H, m), 3.95 (1H, dd, $J = 1.83$, 8.24 Hz), 4.12–4.18 (1H, m), 6.95–7.01 (3H, m), 7.18–7.24 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9, 54.7, 64.0, 77.3, 116.9, 117.0, 124.5, 129.2, 146.5. HRMS (EI) Found: *m*/*z* 204.0903. Calcd for $C_{11}H_{12}N_2O_2$: 204.0899.

***cis*-5-(Hydroxymethyl)-2-phenylisoxazolidine-3-carbonitrile (5Aa):** An oil. IR (neat) 3412, 2925, 2242, 1597, 1490, 1454, 1033, 762, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (1H, brs), 2.60 (1H, ddd, $J = 2.75$, 6.10, 12.82 Hz), 2.70 (1H, ddd, $J = 8.55$, 8.55, 12.82 Hz), 3.78 (1H, dd, $J = 4.88$, 12.51 Hz), 3.95 (1H, dd, $J = 2.74$, 12.51 Hz), 4.39–4.43 (1H, m), 4.63 (1H, dd, $J = 2.75$, 8.55 Hz), 7.06–7.10 (3H, m), 7.31–7.35 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 55.5, 62.1, 78.1, 115.9, 117.9, 124.0, 129.3, 147.4. MS (EI) *m*/*z* 205 ($M^+ + 1$, 21.06%), 204 (M^+, 100.00), 147 (52.69), 131 (47.26), 130 (28.56), 118 (25.48), 108 (29.61), 104 (64.23), 91 (50.15), 77 (33.18).

***t*-Butyl *trans*-5-(Hydroxymethyl)-2-methylisoxazolidine-3-carboxylate (4Ab):** An oil. IR (neat) 3422, 2977, 2926, 2875, 1735, 1458, 1369, 1227, 1158, 848, 780, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.01 (1H, brs), 2.37 (1H, ddd, $J = 7.15$, 8.99, 12.29 Hz), 2.50 (1H, ddd, $J = 6.97$, 8.07, 12.29 Hz), 2.79 (3H, s), 3.24 (1H, brs), 3.58 (1H, dd, $J = 4.59$, 12.10 Hz), 3.80 (1H, dd, $J = 2.93$, 12.10 Hz), 4.20–4.29 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 34.6, 44.8, 63.2, 70.2, 77.5, 82.0, 169.2. MS (EI) *m*/*z* 218 (M^++1, 1.37%), 217 (M^+, 12.30), 161 (13.83), 141 (5.70), 116 (100.00), 98 (16.12), 86 (12.91), 57 (86.29), 42 (66.37), 41 (53.48), 32 (52.23), 31 (96.33), 29 (84.76).

***t*-Butyl *cis*-5-(Hydroxymethyl)-2-methylisoxazolidine-3-carboxylate (5Ab):** mp 67.6–68.0 °C (from Et_2O/hexane). IR (KBr) 3283, 2972, 2935, 2867, 1737, 1458, 1370, 1281, 1236, 1157, 1088, 1063, 1006, 966, 857, 830, 748, 705, 676 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.38 (1H, ddd, $J = 5.37$, 6.10, 12.69 Hz), 2.64 (1H, dt, $J = 12.69$, 8.78 Hz), 2.74 (3H, s), 2.78 (1H, brs), 3.38–3.40 (1H, m), 3.64 (1H, dd, $J = 4.88$, 11.95 Hz), 3.73 (1H, dd, $J = 2.44$, 11.95 Hz), 4.28–4.33 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 34.0, 44.4, 64.0, 69.7, 76.8, 82.0, 170.0. Anal. Found: C, 55.07; H, 8.80; N,

6.38%. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45%.

Stoichiometric Asymmetric 1,3-Dipolar Cycloaddition of the Nitrone 2a to 2-Propen-1-ol (1A) (Table 1, Entry 1). To a $CHCl_3$ (3 mL) solution of 2-propen-1-ol (**1A**) (29 mg, 0.50 mmol) was added diethylzinc (0.75 mmol, 0.75 mL of 1.0 M solution in hexane) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. To the solution, a $CHCl_3$ (3 mL) solution of (*R*,*R*)-DIPT (117 mg, 0.50 mmol) was added, and the mixture was stirred for 1 h. Ethylzinc chloride (0.50 mmol), prepared from diethylzinc (0.25 mmol, 0.25 mL of 1.0 M solution in hexane) and Et_2O–zinc chloride (1/1) (0.25 mmol, 0.115 mL of 2.2 M solution in CH_2Cl_2),[8] was added to the solution. The reaction mixture was warmed to 45 °C and a $CHCl_3$ (5 mL) solution of *N*-(cyanomethylene)aniline *N*-oxide (**2a**) (219 mg, 1.50 mmol) was added over a period of 43 h. The resulting solution was stirred at 25 °C for 21 h. The reaction was quenched by the addition of a saturated aq NH_4Cl solution, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by TLC (SiO_2, hexane/AcOEt = 2/1, v/v, twice) to afford the *trans*-isoxazolidine **4Aa** (43 mg, 42%) in 94% ee. $[\alpha]_D^{25}$ +96 (*c* 0.47, MeOH).

Stoichiometric Asymmetric 1,3-Dipolar Cycloaddition of the Nitrone 2b to 2-Propen-1-ol (1A) (Table 1, Entry 2). To a $CHCl_3$ (3 mL) solution of 2-propen-1-ol (**1A**) (29 mg, 0.50 mmol) was added diethylzinc (0.75 mmol, 0.75 mL of 1.0 M solution in hexane) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. To the solution, a $CHCl_3$ (3 mL) solution of (*R*,*R*)-DIPT (117 mg, 0.50 mmol) was added, and the mixture was stirred for 1 h. Ethylzinc chloride (0.50 mmol), prepared from diethylzinc (0.25 mmol, 0.25 mL of 1.0 M solution in hexane) and Et_2O–zinc chloride (1/1) (0.25 mmol, 0.115 mL of 2.2 M solution in CH_2Cl_2),[8] was added and the mixture was stirred for 10 min. A $CHCl_3$ (3 mL) solution of *N*-[(*t*-butoxycarbonyl)methylene]methylamine *N*-oxide (**2b**) (160 mg, 1.00 mmol) was added, and the reaction mixture was warmed to 60 °C and stirred for 22 h. The reaction was quenched by the addition of a saturated aq NH_4Cl solution, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by TLC (SiO_2, hexane/AcOEt = 2/1, v/v, twice) to afford the isoxazolidine **4Ab** (74 mg, 68%). $[\alpha]_D^{25}$ +51 (*c* 0.62, MeOH). The enantioselectivity was determined by ^{1}H NMR analysis after transforming to its MTPA ester to be 92% ee, as shown in the following.

Transformation of 2-Isoxazolidine 4Ab to the Corresponding MTPA Esters. To a mixture of the isoxazolidine **4Ab** (14 mg, 0.064 mmol), triethylamine (13 mg, 0.128 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2 (1.5 mL) was added (*R*)-α-methoxy-(α-trifluoromethyl)phenylacetyl chloride (MTPACl) (24 mg, 0.097 mmol) in CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. After stirring for 1.5 h, water was added, and the resulting solution was extracted with AcOEt. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by TLC on silica gel (hexane/AcOEt = 3/1, v/v) gave the corresponding MTPA esters of **4Ab** (26 mg) in 93% yield.

***t*-Butyl (3*R*,5*R*)- and (3*S*,5*S*)-5-[(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetoxy]methyl-2-methylisoxazolidine-3-carboxylate:** An oil (mixture of diastereomers). IR (neat) 2979, 1751, 1452, 1369, 1274, 1168, 1124, 1025, 848, 767, 721 cm^{-1}. ^{1}H NMR of major (3*R*,5*R*)-isomer, (400 MHz, C_6D_6) δ 1.30 (9H, s), 1.72–1.79 (1H, m), 2.30–2.37 (1H, m), 2.65 (3H, s), 2.88–2.98 (1H, m), 3.43 (3H, s), 3.76–3.85 (2H, m), 4.07–4.16 (1H, m), 7.02–7.12 (3H, m), 7.69 (2H, d, J = 7.56 Hz). ^{13}C NMR of major (3*R*,5*R*)-isomer, (100 MHz, $CDCl_3$) δ 28.0, 35.2, 44.8, 55.5, 65.8, 69.6, 74.1, 82.1, 84.7, 127.4, 128.5, 129.7, 132.1, 166.3, 168.9. ^{1}H NMR of minor (3*S*,5*S*)-isomer, (400 MHz, C_6D_6) δ 1.30 (9H, s), 1.72–1.79 (1H, m), 2.30–2.37 (1H, m), 2.68 (3H, s), 2.88–2.98 (1H, m), 3.41 (3H, s), 3.76–3.85 (1H, m), 4.07–4.16 (2H, m), 7.02–7.12 (3H, m), 7.69 (2H, d, J = 7.56 Hz). MS (EI) m/z 434 ($M^+ + 1$, 1.10%), 433 (M^+, 4.61), 418 (1.08), 377 (6.64), 332 (100.00), 189 (46.33), 98 (82.09), 91 (4.43), 77 (8.93), 65 (0.60), 57 (28.62).

Representative Procedure for a Catalytic Asymmetric 1,3-Dipolar Cycloaddition of the Amide-Substituted Nitrone 2d (Table 2, Entry 2). To a solution of 2-propen-1-ol (**1A**) (29 mg, 0.5 mmol) in 3 mL of $CHCl_3$ was added diethylzinc (1.0 M solution in hexane, 0.8 mL, 0.8 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. A solution of diisopropyl (*R*,*R*)-tartrate (23 mg, 0.1 mmol) in 3 mL of $CHCl_3$ was further added dropwise, and the resulting solution was kept for 10 min at the same temperature. Iodine (178 mg, 0.7 mmol) dissolved in 3 mL of THF was added to the resulting solution. After stirring for another 10 min, pyridine *N*-oxide (48 mg, 0.5 mmol) in 3 mL of $CHCl_3$ was added. Stirring was continued for 1 h, followed by the addition of the solid nitrone **2d** (124 mg, 0.5 mmol) over a period of 2 h. The resulting mixture was kept for 24 h at 0 °C and then treated with a saturated aq NH_4Cl solution. After warming to room temperature, the solvent was removed in vacuo and the residue was partitioned between AcOEt and water. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (hexane/AcOEt = 1/1, v/v) afforded the cycloadduct **5Ad** as a colorless solid (105 mg) in 69% yield. Optical purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/EtOH = 30/1, v/v) to be 98% ee.

Representative Procedure for a Catalytic Asymmetric 1,3-Dipolar Cycloaddition of the Amide-Substituted Nitrone 2d in Concentrated Method (Table 2, Entry 8). To a solution of (*E*)-2-buten-1-ol (**1B**) (655 mg, 2.85 mmol) in 4 mL of $CHCl_3$ was added diethylzinc (1.0 M solution in hexane, 3.15 mL, 3.15 mmol) at 0 °C under an argon atmosphere. After stirring for 10 min, a solution of diisopropyl (*R*,*R*)-tartrate (69 mg, 0.3 mmol) in 4 mL of $CHCl_3$ was further added dropwise, and the resulting solution was kept for 10 min at the same temperature. Iodine (723 mg, 2.85 mmol) dissolved in 5 mL of THF was added to the resulting solution. After stirring for another 10 min, pyridine *N*-oxide (214 mg, 2.25 mmol) in 4 mL of $CHCl_3$ was added. Stirring was continued for 1 h, followed by the addition of solid **2d** (372 mg, 1.5 mmol) over a period of 3 h. The resulting mixture was kept for 24 h at 0 °C and then treated with a saturated aq NH_4Cl solution. After warming to room temperature, the solvent was removed in vacuo, and the residue was partitioned between AcOEt and water. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by flash column chromatography (hexane/AcOEt = 2/1, v/v) and a subsequent preparative TLC ($CHCl_3$/MeOH = 30/1, v/v) afforded the cycloadduct **5Bd** (307 mg) in 64% yield as a white solid. Optical purity was determined to be >99% ee by HPLC analysis (Daicel Chiralcel OD-H, hexane/EtOH = 30/1, v/v).

In a similar manner, amide-substituted isoxazolidines were obtained from the corresponding allylic alcohols and nitrones.

(3*S*,5*R*)-*N*,*N*-Dibenzyl-5-(hydroxymethyl)-2-phenylisoxazolidine-3-carboxamide (5Ac): $[\alpha]_D^{25}$ −74 (*c* 1.40, EtOH; 64% ee).

mp 116.5–117.5 °C (from EtOH/hexane). IR (KBr) 3412, 3027, 2908, 1649, 1594, 1488, 1427, 1353, 1288, 1220, 1196, 1077, 1044, 1019, 960, 899, 817, 769, 751, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (1H, ddd, J = 8.30, 9.27, 12.44 Hz), 2.83 (1H, ddd, J = 1.95, 5.86, 12.44 Hz), 3.80–3.87 (1H, m), 3.82 (1H, brs), 4.02–4.08 (1H, m), 4.38–4.42 (1H, m), 4.49 (1H, d, J = 14.88 Hz), 4.50 (1H, d, J = 17.32 Hz), 4.70 (1H, dd, J = 1.95, 8.30 Hz), 4.80 (1H, d, J = 17.32 Hz), 4.91 (1H, d, J = 14.88 Hz), 6.91 (2H, d, J = 8.30 Hz), 6.97 (1H, t, J = 7.32 Hz), 7.19–7.42 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 49.5, 49.8, 62.0, 64.9, 78.7, 114.6, 122.7, 126.4, 127.6, 127.9, 128.2, 128.7, 128.9, 129.16, 129.22, 136.1, 136.6, 149.5, 171.7. Anal. Found: C, 74.59; H, 6.56; N, 6.85%. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96%.

***trans*-*N*,*N*-Dibenzyl-5-(hydroxymethyl)-2-phenylisoxazolidine-3-carboxamide (4Ac):**[20] mp 124 °C (from Et_2O/hexane). IR (KBr) 3457, 3056, 2926, 1642, 1596, 1494, 1473, 1451, 1429, 1362, 1298, 1271, 1205, 1077, 1039, 977, 961, 810, 764, 743, 698 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 1.00 (1H, brs), 1.77 (1H, dt, J = 11.95, 7.32 Hz), 2.81 (1H, ddd, J = 2.68, 7.32, 11.95 Hz), 3.28 (1H, dd, J = 6.10, 11.95 Hz), 3.35 (1H, dd, J = 3.66, 11.95 Hz), 4.15 (1H, d, J = 17.20 Hz), 4.25 (1H, d, J = 14.88 Hz), 4.51 (1H, dd, J = 2.68, 7.32 Hz), 4.60 (1H, d, J = 17.20 Hz), 4.62–4.68 (1H, m), 4.96 (1H, d, J = 14.88 Hz), 6.74–6.80 (1H, m), 6.95–7.20 (14H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 49.2, 49.8, 64.0, 64.6, 80.8, 115.1, 122.8, 126.5, 127.5, 127.8, 128.3, 128.7, 129.0, 129.2, 136.4, 136.8, 150.1, 170.2. Anal. Found: C, 74.50; H, 6.54; N, 6.83%. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96%.

(3*S*,5*R*)-5-(Hydroxymethyl)-*N*,*N*-diisopropyl-2-phenylisoxazolidine-3-carboxamide (5Ad): $[\alpha]_D^{25}$ −135 (*c* 1.04, EtOH; 98% ee). mp 120.5–121.5 °C (from AcOEt/hexane). IR (KBr) 3458, 1638, 1597, 1542, 1488, 1448, 1375, 1326, 1254, 1085, 1043, 891, 857 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, d, J = 6.60 Hz), 1.23 (3H, d, J = 6.97 Hz), 1.40 (3H, d, J = 6.97 Hz), 1.50 (3H, d, J = 6.60 Hz), 2.27 (1H, ddd, J = 8.07, 9.17, 12.47 Hz), 2.72 (1H, ddd, J = 2.20, 5.87, 12.47 Hz), 3.30–4.00 (1H, br), 3.40 (1H, hept, J = 6.97 Hz), 3.76 (1H, dd, J = 3.67, 12.47 Hz), 3.95 (1H, dd, J = 2.20, 12.47 Hz), 4.20 (1H, hept, J = 6.60 Hz), 4.32 (1H, dddd, J = 2.20, 3.67, 5.87, 9.17 Hz), 4.66 (1H, dd, J = 2.20, 8.07 Hz), 6.97 (1H, t, J = 7.34 Hz), 7.04 (2H, d, J = 7.70 Hz), 7.26 (2H, dd, J = 7.34, 7.70 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 20.40, 20.44, 20.8, 31.3, 46.6, 48.8, 62.0, 66.0, 78.5, 114.6, 122.6, 129.3, 149.9, 169.5. Anal. Found: C, 66.38; H, 8.68; N, 9.06%. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14%.

(3*S*,5*R*)-5-(Acetoxymethyl)-2-benzyl-*N*,*N*-diisopropylisoxazolidine-3-carboxamide (5Ae Acetate) (Table 2, Entry 5). Using 2-propen-1-ol (**1A**) (29 mg, 0.5 mmol), diethylzinc (1.0 M solution in hexane, 0.8 mL, 0.8 mmol), diisopropyl (*R*,*R*)-tartrate (23 mg, 0.1 mmol), iodine (178 mg, 0.7 mmol), pyridine *N*-oxide (48 mg, 0.5 mmol), and *N*-[(diisopropylcarbamoyl)methylene]benzylamine *N*-oxide (**2e**) (131 mg, 0.5 mmol), the isoxazolidine **5Ae** contaminated with by-products was obtained (91 mg) by TLC separation. However, since the impurity was not separable, **5Ae** was isolated as the corresponding acetate. To a CH_2Cl_2 (10 mL) solution of the crude product **5Ae** obtained above, triethylamine (0.058 mL, 0,42 mmol), a catalytic amount of 4-(dimethylamino)-pyridine, and Ac_2O (0.040 mL, 0.42 mmol) were added at rt under N_2. The resulting solution was kept at the same temperature overnight with stirring. The solvent was removed in vacuo, and the residue was partitioned between AcOEt and water. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (hexane/AcOEt = 2/1, v/v) afforded the desired acetate of the cycloadduct **5Ae** (36 mg) in 20% yield. $[\alpha]_D^{25}$ −22 (*c* 0.20, EtOH; 78% ee). An oil. IR (neat) 2966, 2931, 1741, 1640, 1497, 1444, 1370, 1287, 1238, 1136, 1042, 734, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, brd, J = 5.14 Hz), 1.04 (3H, d, J = 6.42 Hz), 1.32 (3H, d, J = 6.60 Hz), 1.33 (3H, d, J = 6.79 Hz), 2.07 (3H, s), 2.53 (1H, ddd, J = 8.07, 8.80, 12.47 Hz), 2.74 (1H, ddd, J = 3.85, 5.50, 12.47 Hz), 3.23–3.32 (1H, m), 3.52–3.72 (1H, m), 3.85 (1H, d, J = 12.29 Hz), 3.97–4.02 (1H, m), 4.09 (1H, d, J = 12.29 Hz), 4.27 (1H, dd, J = 7.70, 11.55 Hz), 4.40 (1H, dd, J = 3.67, 11.55 Hz), 4.56–4.57 (1H, m), 7.27–7.39 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 20.37, 20.42, 21.0, 29.7, 31.4, 46.1, 48.2, 61.3, 65.6, 66.0, 76.3, 127.9, 128.5, 129.8, 136.2, 167.5, 170.9. MS (EI) m/z 362 (M^+, 4.61%), 347 (19.49), 235 (11.78), 234 (81.31), 174 (19.23), 149 (9.05), 128 (7.86), 91 (100.00), 86 (12.37).

(3*S*,4*R*,5*R*)-5-(Hydroxymethyl)-*N*,*N*-diisopropyl-4-methyl-2-phenylisoxazolidine-3-carboxamide (5Bd): $[\alpha]_D^{25}$ −98 (*c* 3.02, EtOH; >99% ee). mp 91–92 °C (from AcOEt/hexane). IR (KBr) 3384, 2968, 2933, 2875, 1631, 1490, 1449, 1373, 1343, 1245, 1210, 1138, 1093, 1042, 758, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, J = 6.83 Hz), 1.195 (3H, d, J = 6.59 Hz), 1.197 (3H, d, J = 6.34 Hz), 1.426 (3H, d, J = 6.83 Hz), 1.431 (3H, d, J = 6.83 Hz), 2.97–3.06 (1H, m), 3.39–3.45 (1H, m), 3.40 (1H, dd, J = 1.95, 12.44 Hz), 3.70–3.95 (1H, br), 3.78 (1H, dd, J = 3.66, 12.44 Hz), 3.88–3.91 (1H, m), 4.17 (1H, d, J = 5.37 Hz), 4.35–4.41 (1H, m), 6.94 (1H, t, J = 7.32 Hz), 7.03 (2H, d, J = 8.54 Hz), 7.26 (2H, dd, J = 7.34, 8.54 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 20.3, 20.5, 20.6, 20.9, 42.6, 46.6, 48.4, 61.0, 75.6, 85.7, 114.2, 122.0, 129.1, 151.0, 169.4. Anal. Found: C, 67.21; H, 8.87; N, 8.61%. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74%.

(3*S*,4*R*,5*R*)-5-(Acetoxymethyl)-*N*,*N*-diisopropyl-2-phenyl-4-propylisoxazolidine-3-carboxamide (5Cd Acetate) (Table 2, Entry 10). Using (*E*)-2-hexen-1-ol (**1C**) (210 mg, 2.1 mmol), diethylzinc (1.0 M solution in hexane, 2.42 mL, 2.4 mmol), diisopropyl (*R*,*R*)-tartrate (69 mg, 0.3 mmol), iodine (534 mg, 2.1 mmol), pyridine *N*-oxide (144 mg, 1.5 mmol), and *N*-[(diisopropylcarbamoyl)methylene]aniline *N*-oxide (**2d**) (372 mg, 1.5 mmol), the crude isoxazolidine **5Cd** was obtained after extraction. To a CH_2Cl_2 (5 mL) solution of the crude cycloadduct **5Cd**, triethylamine (1.15 mL, 8.3 mmol), a catalytic amount of 4-(dimethylamino)pyridine, and Ac_2O (0.68 mL, 7.2 mmol) were added at room temperature under N_2. The resulting solution was kept at the same temperature overnight with stirring. The solvent was removed in vacuo, and the residue was partitioned between AcOEt and water. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by flash column chromatography (hexane/AcOEt = 2/1, v/v) afforded the desired cycloadduct **5Cd acetate** (291 mg, 48%) as a colorless solid. Optical purity was determined by HPLC analysis (Daicel Chiralcel OD-H, hexane/^{i}PrOH = 50/1, v/v). $[\alpha]_D^{25}$ −90 (*c* 2.91, EtOH; >99% ee). mp 81.9–83.5 °C (from AcOEt/hexane). IR (KBr) 2960, 1748, 1636, 1599, 1490, 1444, 1371, 1308, 1224, 1032, 972, 892, 775, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.07 Hz), 1.12 (3H, d, J = 6.59 Hz), 1.16 (3H, d, J = 6.59 Hz), 1.19–1.50 (10H, m), 2.12 (3H, s), 2.88–2.95 (1H, m), 3.39 (1H, hept, J = 6.59 Hz), 4.01 (1H, dt, J = 2.93, 7.07 Hz), 4.14 (1H, d, J = 5.86 Hz), 4.28 (1H, dd, J = 7.07, 12.20 Hz), 4.38 (1H, hept, J =

6.59 Hz), 4.45 (1H, dd, $J = 2.93$, 12.20 Hz), 6.98 (1H, t, $J = 7.32$ Hz), 7.06 (2H, d, $J = 7.81$ Hz), 7.28 (2H, dd, $J = 7.32$, 7.81 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.3, 20.4, 20.8, 20.9, 34.3, 46.5, 48.3, 48.7, 64.0, 75.9, 81.6, 114.5, 122.3, 129.1, 150.9, 168.5, 170.8. Anal. Found: C, 67.66; H, 8.90; N, 7.10%. Calcd for $C_{22}H_{34}N_2O_4$: C, 67.66; H, 8.78; N, 7.17%.

Methyl (3*S*,4*R*,5*R*)-5-(Hydroxymethyl)-3-(diisopropylcarbamoyl)-2-phenylisoxazolidine-4-carboxylate (5Dd): $[\alpha]_D^{25}$ −153 (*c* 0.96, EtOH; 100% ee). mp 123.3–124.8 °C (from AcOEt/hexane). IR (KBr) 3477, 2974, 1743, 1635, 1600, 1489, 1477, 1452, 1382, 1298, 1271, 1251, 1225, 1180, 1058, 1033, 922, 768, 729, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, d, $J = 6.59$ Hz), 1.26 (3H, d, $J = 6.59$ Hz), 1.30 (3H, d, $J = 6.59$ Hz), 1.42 (3H, d, $J = 6.59$ Hz), 3.46 (1H, hept, $J = 6.59$ Hz), 3.58 (3H, s), 3.81 (1H, brs), 3.92 (1H, dd, $J = 3.66$, 12.44 Hz), 4.06 (1H, dd, $J = 2.20$, 12.44 Hz), 4.19 (1H, hept, $J = 6.59$ Hz), 4.26 (1H, dd, $J = 2.20$, 6.34 Hz), 4.58 (1H, ddd, $J = 2.20$, 3.66, 6.34 Hz), 5.30 (1H, d, $J = 2.20$ Hz), 7.00 (1H, t, $J = 7.32$ Hz), 7.10 (2H, d, $J = 8.78$ Hz), 7.28 (2H, dd, $J = 7.32$, 8.78 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 20.2, 20.4, 20.8, 46.8, 49.1, 50.7, 52.6, 61.7, 67.7, 81.4, 115.4, 123.1, 129.2, 148.2, 167.9, 171.8. Anal. Found: C, 62.51; H, 7.85; N, 7.58%. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69%.

Transformation of 4Aa to (2*R*,4*R*)-6. To an EtOH (12 mL) solution of *trans*-isoxazolidine **4Aa** (167 mg, 0.82 mmol, 72% ee) was added 5% Pd/C (40 mg). The suspension was stirred at room temperature overnight under hydrogen at atmospheric pressure. After filtration of the catalyst, the filtrate was concentrated under reduced pressure and the residue was purified by TLC on SiO_2 (hexane/AcOEt = 1/1, v/v) to afford (2*R*,4*R*)-4,5-dihydroxy-2-(phenylamino)pentanonitrile (145 mg) in 86% yield. To a mixed solution of (2*R*,4*R*)-4,5-dihydroxy-2-(phenylamino)pentanonitrile (86 mg, 0.42 mmol) and a catalytic amount of TsOH·H_2O in 6 mL of dry DMF were added acetone (1.9 mL) and $Me_2C(OMe)_2$ (0.38 mL, 3.1 mmol) under N_2, followed by stirring at 0 °C overnight. The reaction was quenched by the addition of a saturated aq $NaHCO_3$ solution (1 mL), and the product was extracted by Et_2O. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (hexane/AcOEt = 2/1, v/v) afforded (2*R*,4*R*)-**6** (85 mg) in 83% yield.

(2*R*,4*R*)-4,5-Isopropylidenedioxy-2-(phenylamino)pentanonitrile ((2*R*,4*R*)-6): $[\alpha]_D^{25}$ +135 (*c* 0.83, MeOH). mp 54.3–55.0 °C (from hexane). IR (KBr) 3370, 2986, 2935, 2235, 1604, 1508, 1439, 1372, 1312, 1255, 1214, 1155, 1070, 753, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.48 (3H, s), 2.10 (1H, ddd, $J = 3.35$, 6.71, 14.34 Hz), 2.18 (1H, ddd, $J = 3.66$, 9.46, 14.34 Hz), 3.65 (1H, dd, $J = 6.41$, 8.54 Hz), 4.16 (1H, dd, $J = 6.41$, 8.54 Hz), 4.49–4.56 (2H, m), 4.65 (1H, d, $J = 9.76$ Hz), 6.71 (2H, d, $J = 8.54$ Hz), 6.87 (1H, t, $J = 7.33$ Hz), 7.26 (2H, dd, $J = 7.33$, 8.54 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 27.0, 36.6, 44.1, 69.1, 72.8, 110.2, 114.1, 118.9, 120.0, 129.5, 144.8. Anal. Found: C, 68.13; H, 7.38; N, 11.28%. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%.

Transformation of 4Ab to (*R*)-8. To an EtOH (2.5 mL) solution of the *trans*-isoxazolidine **4Ab** (106 mg, 0.49 mmol, 81% ee) was added 20% $Pd(OH)_2/C$ (21 mg). The suspension was stirred at room temperature for 24 h under hydrogen at atmospheric pressure. After filtration of the catalyst, the filtrate was concentrated under reduced pressure, and the resulting residue was used for the next step without further purification. To a solution of the above crude product and TsOH·H_2O (127 mg, 0.74 mmol) in 10 mL of dry DMF were added acetone (3.2 mL) and $Me_2C(OMe)_2$ (2.0 mL) under N_2, and the reaction mixture was stirred at rt overnight. The reaction was quenched by the addition of a saturated aq $NaHCO_3$ solution (1 mL) and extracted by Et_2O. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (AcOEt) afforded *t*-butyl (2*R*,4*R*)-4,5-isopropylidenedioxy-2-(methylamino)pentanoate (**7**) (82 mg) in 65% yield from **4Ab**.

***t*-Butyl (2*R*,4*R*)-4,5-Isopropylidenedioxy-2-(methylamino)-pentanoate (7):** $[\alpha]_D^{25}$ +1.5 (*c* 0.82, MeOH). An oil. IR (neat) 3421, 2982, 2926, 1715, 1364, 1222, 1151, 900, 850 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.41 (3H, s), 1.48 (9H, s), 1.62 (1H, ddd, $J = 5.14$, 8.80, 13.94 Hz), 1.71 (1H, brs), 1.95 (1H, ddd, $J = 4.77$, 7.52, 13.94 Hz), 2.36 (3H, s), 3.12 (1H, dd, $J = 4.77$, 8.80 Hz), 3.54 (1H, dd, $J = 6.97$, 8.07 Hz), 4.08 (1H, dd, $J = 5.87$, 8.07 Hz), 4.20–4.28 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 27.0, 28.1, 34.7, 37.6, 61.4, 69.8, 73.6, 81.2, 108.7, 174.4. MS (EI) *m/z* 259 (M^+, 2.23), 244 (8.69), 201 (1.44), 188 (94.44), 158 (100.00), 146 (10.63), 128 (21.85), 100 (99.86), 82 (52.09), 72 (12.16), 57 (32.55).

Under a nitrogen atmosphere, lithium tetrahydroaluminate (24 mg, 0.63 mmol) was added to an Et_2O (5 mL) solution of *t*-butyl (2*R*,4*R*)-4,5-isopropylidenedioxy-2-(methylamino)pentanoate (**7**) (82 mg, 0.32 mmol), and the suspension was stirred for 3 h at rt. The reaction was quenched by adding a saturated aq Na_2SO_4 solution (0.18 mL). The precipitate was then filtered off and washed with Et_2O. The filtrate was concentrated in vacuo to give crude (2*R*,4*R*)-1,2-*O*-isopropylidene-4-(methylamino)pentane-1,2,5-triol (66 mg). To a MeOH (3 mL) solution of the obtained alcohol was added $NaIO_4$ (149 mg, 0.70 mmol) in water (1.5 mL), and the solution was stirred for 40 min. The reaction product was extracted by CH_2Cl_2 and dried over Na_2SO_4. Evaporation of the solvent gave crude (*R*)-3,4-isopropylidenedioxybutanal ((*R*)-**11**) (39 mg). Under a nitrogen atmosphere, lithium tetrahydroaluminate (10 mg, 0.27 mmol) was added to an Et_2O (2 mL) solution of the aldehyde (*R*)-**11**, and the suspension was stirred for 1 h at −40 °C. The reaction was quenched by adding a saturated aq Na_2SO_4 solution (0.08 mL). The precipitate was then filtered off and washed with Et_2O. The filtrate was concentrated in vacuo to give crude (*R*)-**10** (27 mg). A mixture of the obtained alcohol (*R*)-**10** (27 mg), triethylamine (37 mg, 0.37 mmol), benzoyl chloride (39 mg, 0.28 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2 (3 mL) was stirred for 3 h under a nitrogen atmosphere at room temperature. To the solution was added water, and the resulting solution was extracted with AcOEt. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by TLC on silica gel (hexane/Et_2O = 3/1, v/v) gave (*R*)-4-(2-benzoyloxy)ethyl-2,2-dimethyl-1,3-dioxolane ((*R*)-**8**) (29 mg) in 41% yield in 4 steps.

(*R*)-4-(2-Benzoyloxy)ethyl-2,2-dimethyl-1,3-dioxolane ((*R*)-8): $[\alpha]_D^{25}$ +16 (*c* 0.26, MeOH). An oil. IR (neat) 2985, 2935, 2867, 1719, 1602, 1452, 1370, 1277, 1112, 1069, 713 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.40 (3H, s), 1.94–2.09 (2H, m), 3.61 (1H, dd, $J = 7.07$, 8.05 Hz), 4.09 (1H, dd, $J = 6.10$, 8.05 Hz), 4.22–4.39 (1H, m), 4.36 (1H, ddd, $J = 5.86$, 8.05, 11.22 Hz), 4.46 (1H, dt, $J = 11.22$, 5.86 Hz), 7.39–7.43 (2H, m), 7.51–7.56 (1H, m), 7.99–8.02 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 27.0, 33.0, 61.9, 69.5, 73.4, 109.0, 128.4, 129.6, 130.2, 133.0, 166.4. MS (CI) *m/z* 251 ($M^+ + 1$, 65.55%), 250 (M^+, 0.33), 235 (10.19), 193 (100.00), 154 (4.77), 145 (0.60), 105 (5.91), 77 (0.38), 71 (5.37).

Transformation of 5Ac to (2′*S*,4*R*)-9. To a solution of **5Ac** (554 mg, 1.38 mmol, 50% ee) in 7 mL of dry EtOH was added 68 mg of 5% Pd/C. The resulting mixture was stirred for 26 h under the normal pressure of a H_2 atmosphere at room temperature, and then the catalyst was filtered off. The solvent of the filtrate was removed in vacuo, and the resulting residue was used for the next step without further purification. To a solution of the above crude (2*S*,4*R*)-*N*,*N*-dibenzyl-4,5-dihydroxy-2-(phenylamino)pentanamide in 30 mL of dry DMF and 9.6 mL of acetone was added $Me_2C(OMe)_2$ (6 mL) under N_2. A catalytic amount of $TsOH \cdot H_2O$ was further added to the resulting mixture and kept for 14 h at room temperature. The solvent was removed in vacuo, and the residue was partitioned between Et_2O and water. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (hexane/AcOEt = 5/1, v/v) afforded (2*S*,4*R*)-*N*,*N*-dibenzyl-4,5-isopropylidenedioxy-2-(phenylamino)pentanamide (593 mg) in 97% yield.

To the solution of the obtained acetal (103 mg, 0.23 mmol) in 3 mL of Et_2O was added dropwise 47 mg (1.24 mmol) of $LiAlH_4$ at 0 °C under N_2. The resulting mixture was stirred for 1 h at 0 °C, and then was treated with a saturated aq Na_2SO_4 solution (0.36 mL). The insoluble substance was filtered off followed by washing with Et_2O, and the filtrate was concentrated in vacuo. Separation of the residue by preparative TLC (hexane/AcOEt = 6/1, v/v) afforded (2′*S*,4*R*)-**9** (88 mg) in 88% yield.

(*R*)-4-[(*S*)-3-(Dibenzylamino)-2-(phenylamino)propyl]-2,2-dimethyl-1,3-dioxolane ((2′*S*,4*R*)-9): $[\alpha]_D^{25}$ −25 (*c* 0.88, EtOH). mp 60.2–61.0 °C (from AcOEt/hexane). IR (KBr) 3356, 2986, 2946, 2873, 2816, 1601, 1529, 1496, 1449, 1382, 1327, 1258, 1208, 1144, 1042, 1015, 849, 741, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, s), 1.41 (3H, s), 1.67–1.80 (2H, m), 2.53 (1H, dd, J = 6.10, 12.93 Hz), 2.62 (1H, dd, J = 7.32, 12.93 Hz), 3.40 (1H, dd, J = 7.56, 7.81 Hz), 3.49–3.56 (1H, m), 3.50 (2H, d, J = 13.42 Hz), 3.68 (2H, d, J = 13.42 Hz), 3.93 (1H, dd, J = 5.86, 7.81 Hz), 3.92 (1H, brs), 4.03–4.10 (1H, m), 6.54 (2H, d, J = 7.56 Hz), 6.67 (1H, t, J = 7.32 Hz), 7.13 (2H, dd, J = 7.32, 7.56 Hz), 7.22–7.31 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 26.9, 37.3, 49.1, 57.6, 59.2, 69.8, 73.5, 108.8, 113.2, 117.2, 127.2, 128.3, 129.1, 129.2, 139.2, 148.0. Anal. Found: C, 77.99; H, 8.02; N, 6.44%. Calcd for $C_{28}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51%.

Transformation of (*S*)-3,4-Isopropylidenedioxybutanal ((*S*)-11) to (2*R*,4*S*)-12 and (2*S*,4*S*)-6. A CH_2Cl_2 (10 mL) solution of (*S*)-3,4-isopropylidenedioxybutanal ((*S*)-**11**) (135 mg, 0.94 mmol), obtained from (*S*)-**10**,[11] was treated with molecular sieves 3A, followed by the addition of aniline (0.091 mL, 0.94 mmol). After stirring for 4 h, the molecular sieves 3A were filtered off and the filtrate was concentrated in vacuo to give the crude corresponding imine. To the crude imine were added anhydrous zinc iodide (15 mg, 0.047 mmol) and trimethylsilyl cyanide (0.125 mL, 0.936 mmol) under a nitrogen atmosphere, and the reaction mixture was stirred overnight.[21] To the mixture was added excess CH_2Cl_2 in order to dissolve any undissolved materials. The solution was washed with a saturated aq $NaHCO_3$ solution, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by TLC (SiO_2, hexane/AcOEt = 3/1, v/v, twice) to afford (2*R*,4*S*)-**12** (29 mg, 13%) and (2*S*,4*S*)-**6** (27 mg, 12%, $[\alpha]_D^{25}$ −199 (*c* 0.09, MeOH)). The ^1H NMR spectrum of (2*R*,4*R*)-**6** obtained from **4Aa** was in accord with that of (2*S*,4*S*)-**6**, but not with that of (2*R*,4*S*)-**12**.

(2*R*,4*S*)-4,5-Isopropylidenedioxy-2-(phenylamino)pentanonitrile ((2*R*,4*S*)-12): $[\alpha]_D^{25}$ +106 (*c* 0.10, MeOH). mp 88 °C (from hexane). IR (KBr) 3388, 2989, 2228, 1606, 1519, 1380, 1155, 1140, 1059, 743, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.45 (3H, s), 2.14–2.18 (2H, m), 3.67 (1H, dd, J = 6.41, 8.24 Hz), 4.04 (1H, d, J = 8.54 Hz), 4.16 (1H, dd, J = 6.10, 8.24 Hz), 4.35–4.39 (1H, m), 4.44 (1H, dt, J = 8.54, 6.71 Hz), 6.75 (2H, d, J = 8.55 Hz), 6.89 (1H, t, J = 7.63 Hz), 7.26 (2H, dd, J = 7.63, 8.55 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 27.0, 37.7, 44.1, 68.9, 72.4, 110.0, 114.2, 119.2, 120.1, 129.5, 144.8. Anal. Found: C, 68.20; H, 7.38; N, 11.29%. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%.

Transformation of (2*R*,4*S*)-12 to (2′*R*,4*S*)-9. To a toluene (2 mL) solution of (2*R*,4*S*)-**12** (41 mg, 0.167 mmol) was added $^iBu_2AlH$ (1.0 M solution in toluene, 0.33 mL, 0.33 mmol) at −78 °C under N_2, and the mixture was kept at this temperature for 15 min with stirring. A solution of $LiAlH_4$ (41 mg, 1.08 mmol) in dry Et_2O was further added to the resulting solution and warmed to 0 °C over a period of 40 min. After stirring for another 1 h at the same temperature, the mixture was treated with a saturated aq Na_2SO_4 solution (0.38 mL). The insoluble substance was filtered off followed by washing with Et_2O, and the filtrate was concentrated in vacuo to give the crude product. To this crude product in 2 mL of MeOH, benzaldehyde (52 mg, 0.49 mmol) was added and stirred for 1 h at room temperature, followed by the addition of $NaBH_4$ (45 mg, 1.19 mmol). The mixture was kept for 1 h at the same temperature and then treated with H_2O. The mixture was extracted with AcOEt, and the organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (AcOEt/MeOH = 10/1, v/v) afforded (*S*)-4-[(*R*)-3-(benzylamino)-2-(phenylamino)propyl]-2,2-dimethyl-1,3-dioxolane (40 mg) in 71% yield.

A solution of sodium carbonate (21 mg, 0.20 mmol) in H_2O (0.1 mL) was added to the $CHCl_3$ (1.5 mL) solution of diamine (23 mg, 0.068 mmol) obtained above. To the solution, benzyl bromide (35 mg, 0.205 mmol) was further added and kept for 15 h with stirring at room temperature. The mixture was then treated with H_2O and extracted by AcOEt. The resulting organic extract was successively washed with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (hexane/AcOEt = 6/1, v/v) afforded the desired optically pure (2′*R*,4*S*)-**9** (26 mg) in 89% yield. $[\alpha]_D^{25}$ +49 (*c* 0.25, EtOH). The spectral data were identical with the (2′*S*,4*R*)-**9** obtained above.

(*S*)-4-(2-Benzoyloxy)ethyl-2,2-dimethyl-1,3-dioxolane ((*S*)-8). A mixture of (*S*)-3,4-isopropylidenedioxybutan-1-ol (27 mg, 0.18 mmol) ((*S*)-**10**) derived from (*S*)-malic acid,[11] triethylamine (37 mg, 0.37 mmol), benzoyl chloride (39 mg, 0.28 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2 (3 mL) was stirred for 3 h under a nitrogen atmosphere at room temperature. To the solution was added water, and the resulting solution was extracted with AcOEt. The combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification by TLC on silica gel (hexane/Et_2O = 3/1, v/v) gave (*S*)-**8** (36 mg) in 78% yield. $[\alpha]_D^{25}$ −20 (*c* 0.73, MeOH). The spectral data were identical with those of the (*R*)-**8** obtained above.

Methyl (3*S*,4*R*,5*R*)-3-(Diisopropylcarbamoyl)-5-{[(*R*)-1-(1-naphthyl)ethylcarbamoyloxy]methyl}-2-phenylisoxazolidine-4-carboxylate (13). To a mixed solution of **5Dd** (16 mg, 0.044 mmol) in 5 mL of CH_2Cl_2 and a catalytic amount of 4-(dimethylamino)pyridine was added (*R*)-1-(1-naphthyl)ethyl isocyanate (9 mg, 0.044 mmol) at room temperature under N_2. The re-

sulting solution was kept at the same temperature for 2 days with stirring. The solvent was removed in vacuo, and the residue was partitioned between AcOEt and water. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by preparative TLC (hexane/AcOEt = 2/1, v/v) afforded **13** as a while solid (20 mg) in 79% yield. mp 152.2–153.8 °C (from AcOEt). IR (KBr) 3349, 2999, 2969, 1727, 1636, 1597, 1517, 1488, 1443, 1373, 1344, 1302, 1236, 1126, 1071, 1057, 1007, 912, 798, 782, 768 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, $J = 6.34$ Hz), 1.23 (3H, d, $J = 6.83$ Hz), 1.37 (3H, d, $J = 6.83$ Hz), 1.43 (3H, d, $J = 6.83$ Hz), 1.66 (3H, d, $J = 6.83$ Hz), 3.41 (1H, hept, $J = 6.83$ Hz), 3.55 (3H, s), 4.15 (1H, hept, $J = 6.83$ Hz), 4.33 (1H, dd, $J = 2.93$, 6.34 Hz), 4.38 (1H, dd, $J = 7.81$, 12.44 Hz), 4.54–4.59 (2H, m), 5.19 (1H, d, $J = 2.93$ Hz), 5.29 (1H, d, $J = 7.56$ Hz), 5.66 (1H, dq, $J = 7.56$, 6.34 Hz), 7.01 (1H, t, $J = 7.32$ Hz), 7.10 (2H, d, $J = 8.05$ Hz), 7.26 (2H, dd, $J = 7.32$, 8.05 Hz), 7.45–7.65 (4H, m), 7.78 (1H, d, $J = 8.05$ Hz), 7.86 (1H, d, $J = 7.32$ Hz), 8.14 (1H, d, $J = 8.54$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.1, 20.6, 20.9, 21.8, 46.6, 46.8, 49.1, 51.7, 52.5, 64.4, 68.4, 79.0, 115.7, 122.2, 123.3, 125.3, 125.7, 126.4, 128.1, 128.8, 129.2, 130.8, 134.0, 138.8, 148.3, 155.2, 166.3, 171.6. Anal. Found: C, 68.28; H, 7.01; N, 7.33%. Calcd for $C_{32}H_{39}N_3O_6$: C, 68.43; H, 7.00; N, 7.48%.

A single crystal was obtained by recrystallization from AcOEt. Crystal data: $C_{32}H_{39}N_3O_6$, FW 561.68, monoclinic, $P2_1$, $a = 10.851(1)$ Å, $b = 7.030(1)$ Å, $c = 20.246(1)$ Å, $\beta = 103.751(1)°$, $V = 1500.2(3)$ Å^3, $Z = 2$. $D_{calcd} = 1.243$ g cm^{-3}. $R = 0.034$ ($R_w = 0.033$) for 3628 reflections with $I > 3.00\sigma(I)$ and 371 variable parameters.

(2*S*,4*R*)-4,5-Dihydroxy-*N*,*N*-diisopropyl-2-[(4-methoxyphenyl)amino]pentanamide (14). To a solution of 2-propen-1-ol (**1A**) (55 mg, 0.95 mmol) in 3 mL of $CHCl_3$ was added diethylzinc (1.0 M solution in hexane, 1.05 mL, 1.05 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 10 min. A solution of diisopropyl (*R*,*R*)-tartrate (24 mg, 0.10 mmol) in 3 mL of $CHCl_3$ was added dropwise, and the resulting solution was kept for 10 min at the same temperature. Iodine (241 mg, 0.95 mmol) dissolved in 3 mL of THF was added to the resulting solution. After stirring for another 10 min, pyridine *N*-oxide (71 mg, 0.75 mmol) in 3 mL of $CHCl_3$ was added. Stirring was continued for 1 h, followed by addition of solid **2f** (139 mg, 0.50 mmol) over a period of 2 h. The resulting mixture was kept for 24 h at 0 °C and then treated with a saturated aq NH_4Cl solution. After warming to room temperature, the solvent was removed in vacuo and the residue was partitioned between AcOEt and water. The organic extract was washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent gave crude products containing **5Af** (ca. 57%) and **14**. The mixture was dissolved in EtOH (3 mL) in the presence of 20% $Pd(OH)_2/C$ (68 mg) under a hydrogen atmosphere at rt for 48 h. The catalyst was filtered off using Celite. Evaporation of the solvent and separation of the residue by a preparative TLC (AcOEt/MeOH = 20/1, v/v) afforded **14** (127 mg) in 75% yield. Optical purity was determined to be 94% ee by HPLC analysis (Daicel Chiralcel OD-H, hexane/EtOH = 40/1, v/v). $[\alpha]_D^{25}$ −37 (*c* 1.27, EtOH). An oil. IR (neat) 3397, 2964, 2958, 2926, 1626, 1513, 1446, 1373, 1239, 1039, 713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, $J = 6.59$ Hz), 1.20 (3H, d, $J = 6.59$ Hz), 1.27 (3H, d, $J = 6.83$ Hz), 1.36 (3H, d, $J = 6.83$ Hz), 1.50–1.75 (2H, br), 1.78–1.82 (2H, m), 3.37–3.45 (1H, m), 3.52 (1H, dd, $J = 5.12$, 11.22 Hz), 3.65 (1H, dd, $J = 3.90$, 11.22 Hz), 3.74 (3H, s), 3.94–4.06 (2H, m), 4.27–4.30 (1H, m), 6.77 (4H, s). The signal of amine proton (N<u>H</u>) was not observed clearly. ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.5, 19.7, 20.0, 34.8, 45.3, 47.3, 54.6, 55.7, 65.6, 69.6, 113.6, 117.8, 139.4, 153.2, 171.0. MS (FAB$^+$) *m/z* 339 ($M^+ + 1$, 85.22%), 338 (M^+, 20.04), 307 (2.39), 263 (4.69), 210 (100.00), 146 (1.55), 134 (16.92), 107 (8.20), 77 (8.33), 43 (10.29).

(2*S*,4*R*)-2-(Benzyloxycarbonyl)amino-5-hydroxy-4-pentanolide (16). To a solution of **14** (35 mg, 0.10 mmol) in MeOH (0.2 mL) was slowly added $PhI(OAc)_2$ (66 mg, 0.21 mmol) in MeOH (4 mL) and AcOH (0.2 mL) at room temperature over a period of 30 min, and then a 1 M aqueous HCl solution was added.[22] After stirring for 30 min, $NaHSO_3$ (11 mg, 0.10 mmol) was added and the mixture was stirred for an additional 30 min. The solvent was evaporated under reduced pressure. To the resulting residue containing **15** was added a conc. HCl solution (3.9 mL) and ethylene glycol (0.8 mL), and the mixed solution was refluxed for 2 h. The solution was cooled to 0 °C and neutralized by the addition of solid $NaHCO_3$. To the resulting solution, THF (15 mL), a sat. aqueous $NaHCO_3$ solution (4 mL), and a THF (3 mL) solution of benzyloxycarbonyl chloride (88 mg, 0.52 mmol) were successively added at 0 °C. After stirring for 30 min at 0 °C and for 13 h at room temperature, the solution was extracted with AcOEt. The combined organic extracts were washed successively with water and brine, and then dried over Na_2SO_4. Evaporation of the solvent and separation of the residue by flash column chromatography (hexane/AcOEt = 1/2, v/v) afforded **16** (13 mg) in 47% yield. Recrystallization from $CHCl_3$ afforded white crystalline **16** (>99% ee by HPLC analysis using Daicel Chiralcel OD-H). $[\alpha]_D^{25}$ −44 (*c* 0.11, MeOH). mp 122.0–123.0 °C (from $CHCl_3$). [lit.:[17a] (2*S*,4*R*)-isomer; $[\alpha]_D^{25}$ −50.9 (*c* 0.48, MeOH). mp 123 °C. lit.:[17b] (2*R*,4*S*)-isomer; $[\alpha]_D^{25}$ +36.54 (*c* 0.26, MeOH). mp 120–122 °C. lit.:[17c] (2*S*,4*R*)-isomer; $[\alpha]_D^{25}$ −46 (*c* 1.3, MeOH). mp 120.5–121.9 °C.] IR (neat) 3408, 3320, 3062, 2950, 2924, 2872, 1784, 1684, 1537, 1288, 1266, 1203, 1092, 1044, 1019, 985, 933, 742, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.92–2.10 (1H, br), 2.30–2.42 (1H, m), 2.63–2.73 (1H, m), 3.70 (1H, dd, $J = 2.44$, 12.20 Hz), 3.94 (1H, dd, $J = 2.20$, 12.20 Hz), 4.57 (1H, dt, $J = 6.59$, 9.75 Hz), 4.65–4.75 (1H, m), 5.13 (2H, s), 5.31 (1H, brs), 7.31–7.38 (5H, m). ^1H NMR (400 MHz, acetone-d_6) δ 2.43 (1H, ddd, $J = 9.27$, 10.23, 12.43 Hz), 2.55 (1H, ddd, $J = 1.96$, 9.75, 12.43 Hz), 3.69 (1H, ddd, $J = 3.20$, 5.12, 11.95 Hz), 3.83 (1H, ddd, $J = 2.68$, 5.12, 11.95 Hz), 4.33 (1H, t, $J = 5.12$ Hz), 4.61–4.68 (2H, m), 5.09 (2H, s), 6.83 (1H, brs), 7.28–7.44 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 50.4, 64.3, 67.4, 78.1, 128.2, 128.3, 128.6, 135.9, 156.0, 175.5.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition numbers CCDC-602254, CCDC-602255, CCDC-193572, and CCDC-602256 for **2c**, **2d**, **13**, and the compound in Fig. 10, respectively. 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, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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13 The reaction using a *N*,*N*-dimethylamide-substituted nitrone instead of the *N*,*N*-dibenzylamide-substituted nitrone **2c** or *N*,*N*-diisopropylamide-substituted nitrone **2d** also gave the corresponding 3,5-*cis*-isoxazolidine diastereoselectively in 32% yield with the enantioselectivity of 61% ee under the same reaction conditions of Entry 1 in Table 2, which might imply that even the *N*,*N*-dimethylamide moiety is bulky enough to avoid the chelation to zinc metal to be subject to the *exo*-transition state in Fig. 5.

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