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1,3-Dipolar Cycloaddition of Chirally Modified Vinylboronic Ester with Nitrile Oxides

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Abstract—Chiral modified vinylboronic ester **1**, derived from D-(+)-mannitol, reacted with nitrile oxides to afford optically active isoxazolines. The regioselectivity was excellent and moderate stereoselectivity (up to 60% d.e.) was achieved. The configuration of new chiral centres in all the isoxazoline products was established by NMR analysis or X-ray analysis.

Introduction

Vinylboronic ester derivatives are accessible and widely employed species for building a large number of important molecules.[1] Recently several groups have explored their application in asymmetric reactions, especially in asymmetric 1,3-dipolar cycloaddition reaction to prepare chiral Δ^2-isoxazolines, an important class of heterocycles.[2–8] Wallace and others have shown boronic esters to be an excellent group for inducing the regioselectivity of 1,3-dipolar cycloaddition reactions of 1,2-disubstituted vinylboronic esters with nitrile oxides.[9,10] This was further confirmed in our laboratory, but we also found that a chirally modified vinylboronic ester, in which optically active pinanediol was part of the boronic ester group, was not effective to control the stereoselectivity in asymmetric 1,3-dipolar cycloaddition reactions.[11]

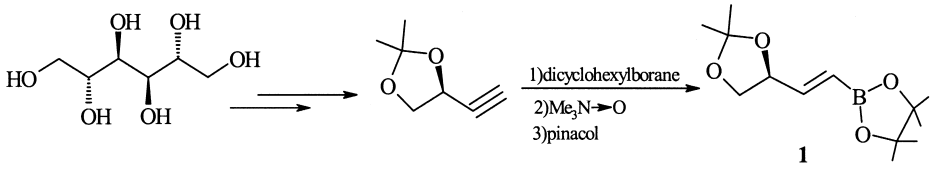
As part of our recent studies of the application of vinylboronic esters in 1,3-dipolar cycloaddition reactions, we synthesized optically active vinylboronic ester **1**, and carried out its asymmetric 1,3-dipolar cycloaddition with nitrile oxides, which allow the preparation of chiral isoxazolines, precursors for various classes of amino sugars.

Results and Discussion

The chirally modified vinyl pinacol boronic ester **1** was readily prepared by hydroboration of D-(+)-mannitol derived alkyne with dicyclohexylborane, selective oxidation of the resulted alkenylborane with trimethylamine oxide, and then transesterification of the intermediate dicyclohexylboronate with pinacol (Scheme 1).[12–14]

The asymmetric 1,3-dipolar cycloaddition reaction of vinylboronic ester **1** with aryl hydroximinoyl chloride **2** was initially carried out in THF at 0°C, by using Et_3N to generate the nitrile oxide. As expected, the reaction proceeded smoothly in a highly regioselective manner. Four isoxazoline products were obtained, comprising *erythro*- and *threo*-Δ^2-isoxazolines **3** and **3′** as the major products, together with (4*S*,5*S*,1′*R*)- and (4*R*,5*R*,1′*R*)-4-hydroxy-Δ^2-isoxazolines **4** and **4′** as the minor products (Scheme 2, Table 1).

From previous studies,[3,4,11] we could conclude that Δ^2-isoxazolines **3** and **3′** were the products which boronic ester group was lost from the resulting 4-boronic ester substituted Δ^2-isoxazoline intermediates in the cycloaddition reaction, while the 4-hydroxy-Δ^2-isoxazolines **4**



Scheme 1.

Keywords: 1,3-dipolar cycloaddition; vinylboronic ester; Δ^2-isoxazolines; 4-hydroxy-Δ^2-isoxazolines.
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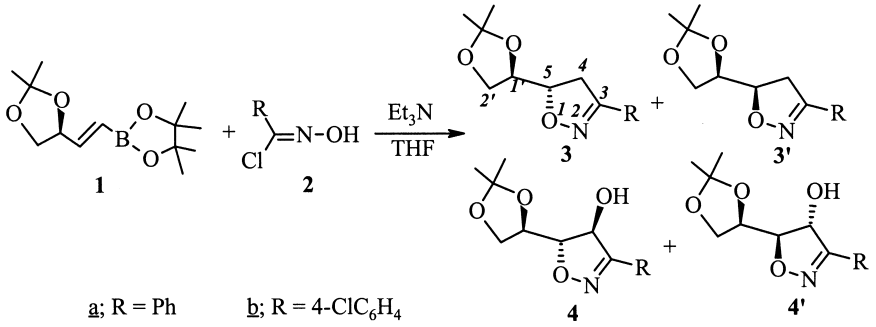


Scheme 2.

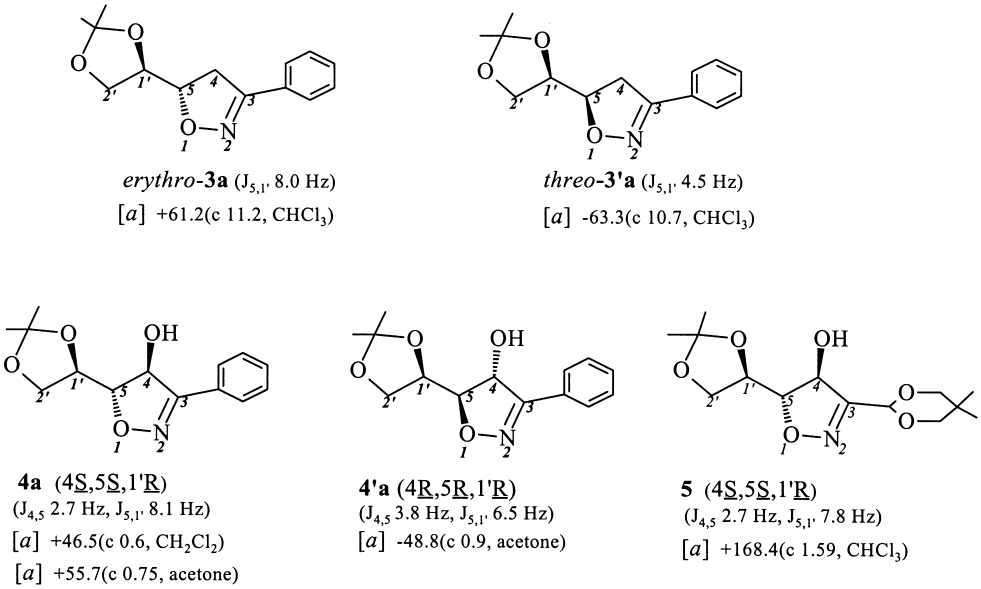
Table 1. Results of cycloaddition of chirally modified vinylboronic ester **1** with aryl hydroximinoyl chloride **2**

Entry	R	Diastereomer ratio[a] (yield %[b])	
		3/**3**′	**4**/**4**′
1	*a*; R=Ph	75/25(52)	80/20(44)
2	*b*; R=4-ClC$_6$H$_4$	77/23(50)	70/30(45)

[a] Based on the isolated yields.
[b] Isolated yields.

and **4**′ were the products which 4-boronic ester substituted Δ^2-isoxazoline intermediates were oxidized. Moderate stereoselectivity was obtained in each pair of diastereoisomers, the 4,5-*erythro* isomer was always dominant.

The diastereomers of *erythro*/*threo*-Δ^2-isoxazoline **3**/**3**′ or (4*S*,5*S*,1′*R*)/(4*R*,5*R*,1′*R*)-4-hydroxy-Δ^2-isoxazoline **4**/**4**′ could be separated by careful silica gel column chromatography. The structures of Δ^2-isoxazolines **3** and **3**′ were unambiguously ascertained from their spectroscopic data. The coupling constants between H-5 and H-1′ in their 300 MHz ^{1}H NMR were significantly different, $J_{5,1'}$=8.0 Hz in *erythro*-Δ^2-isoxazoline **3a** while $J_{5,1'}$=4.5 Hz in *threo*-Δ^2-isoxazoline **3**′**a**. Because the configuration of C-1′ in the cycloadducts was known from D-(+)-mannitol, the absolute configuration of C-5 was *S* in compound **3** and *R* in compound **3**′. Jäger and others have also prepared *erythro*/*threo*-**3a**/**3**′**a** and reported their spectroscopic data.[15,17] In their reports, the coupling constant between H-5 and H-1′ and other spectral data of compounds **3a** and **3**′**a** were completely in agreement with our results. With respect to the oxidized products in the regioselective 1,3-dipolar cycloaddition reaction, retention of the configuration of the *trans*-1,2-disubstituted alkene **1** as the dipolarophile upon cycloaddition requires H-4 and H-5 in the cycloadducts should be in a *trans* relationship. So only two diastereoisomers of *trans*-4,5-disubstituted-4-hydroxy-Δ^2-isoxazolines should result. The coupling constants in our experiments, $J_{4,5}$=2.7 Hz in **4a** and $J_{4,5}$=3.8 Hz in **4**′**a**, which were indicative of a *trans*-stereochemistry between H-4 and H-5, supported our analysis. The absolute configuration of the major oxidized product **4a** was inferred from the close agreement of the chemical shift and coupling constants of the key H-4, H-5 and H-1′signals in the 300 MHz ^{1}H NMR spectrum with the related compound **5**, which $J_{4,5}$=2.7 Hz, $J_{5,1'}$=8.1 Hz in compound **4a** while $J_{4,5}$=2.7 Hz, $J_{5,1'}$=7.8 Hz in compound **5**. Further support for this assignment was afforded by comparison of the specific rotation of compound **4a** with compound **5** (Scheme 3).[16] Further support for the structure of (4*S*,5*S*,1′*R*)-**4a** comes from the X-ray analysis



Scheme 3.

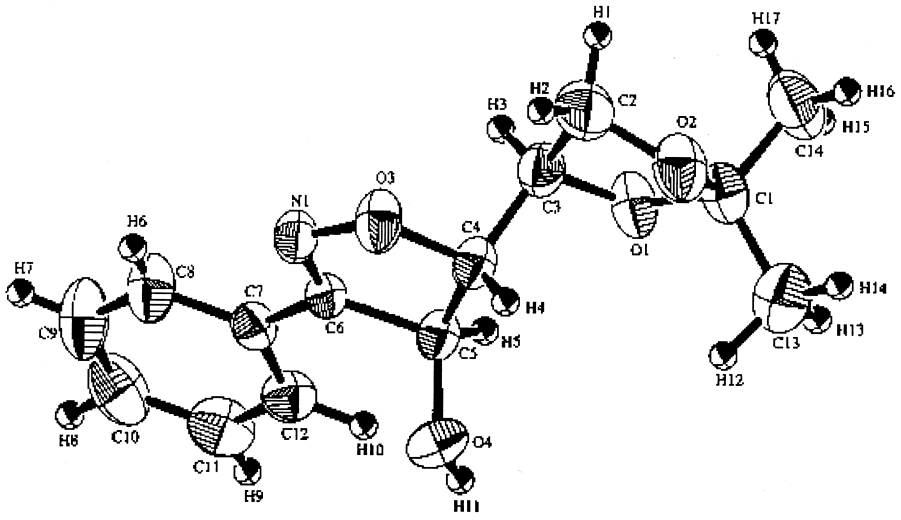


Figure 1. X-ray analysis of **4a**.

(Fig. 1). Since the structure of compound **4a** has been well established, according to our preliminary analysis, the minor oxidized product must be compound **4′a**. The ^{1}H NMR spectrum of this material was well resolved, and its analysis confirmed the indicated stereochemistry. The coupling constant between H-5 and H-1′ in compound **4′a** ($J_{5,1'}$=6.5 Hz) was slightly smaller than that in compound **4a** ($J_{5,1'}$=8.1 Hz), the other coupling constants and the chemical shifts for the key signals were very close. Another indication for this assignment was comparison of the specific rotation of compound **4′a** with **4a**.

4-Hydroxy-Δ^2-isoxazolines **4** and **4′** were obtained as the major products when oxidizing agent *tert*-butyl hydroperoxide was added during the completion of the cycloaddition. In Wallace's work and our previous paper,[11] sodium percarbonate was found to be a good reagent to generate the nitrile oxides and to oxidize the 4-substituted boronic ester cycloaddition intermediate in 1,3-dipolar cycloaddition reaction of 1,2-disubstituted vinylboronic ester with nitrile oxide. So in the cycloaddition of vinylboronic ester **1** with aryl hydroximinoyl chloride **2**, we employed sodium percarbonate in place of triethylamine to generate the cycloaddition. As expected, 4-hydroxy-Δ^2-isoxazolines **4** and **4′** were obtained as the major products, Δ^2-isoxazolines **3** and **3′** were not detected in the crude reaction mixture by TLC analysis. The regioselectivity was excellent, but the diastereoselectivity still fell in the range of 52–58% (Table 2, Scheme 4).

Table 2. Results of cycloaddition reaction by using $Na_2CO_3 \cdot 1.5H_2O_2$

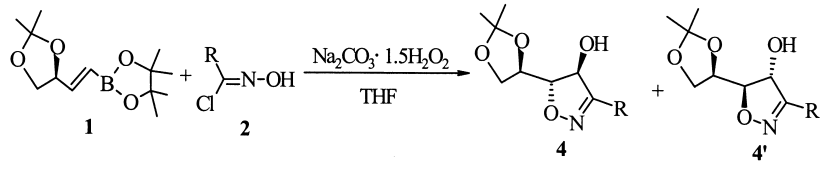
Entry	R	Ratio of **4**/**4′**[a]	Overall yield (%)[b]
1	*a*; R=Ph	77:23	90
2	*b*; R=4-ClC_6H_4	78:22	82
3	*c*; R=4-MeC_6H_4	79:21	87
4	*d*; R=4-$MeOC_6H_4$	76:24	60
5	*e*; R=2,4-$Cl_2C_6H_4$	76:24	73

[a] Based on the isolated yields.
[b] Isolated yields.

In summary, chirally modified vinylboronic ester **1** was a very reactive group to prepare optically active 4-hydroxy-Δ^2-isoxazolines *via* 1,3-dipolar cycloaddition reaction. Compared with Wallace's work, which achieved excellent stereoselectivity by building camphorsultam into vinylboronic ester.[9,10] We obtained only moderate diastereoselectivity. But because of the ready accessibility of optically active vinylboronic ester **1** from D-(+)-mannitol and all the isoxazalines in our system could be isolated in optical purity, it provides a short and efficient method to prepare these functionalized isoxazoline rings. These, after reduction or suitable ring cleavage, may lead to interesting chiral building blocks for synthesis of various important amino sugars.[15,16]

Experimental

Melting points were determined on a Digital Melting Apparatus WRS-1A. NMR spectra were recorded as $CDCl_3$ solutions on a VXL-300 instrument. The ^{1}H NMR (300 MHz) chemical shifts are reported as δ values in ppm relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin–Elmer 983 FT-IR



Scheme 4.

spectrometer. Mass spectral measurements were performed on a Fining 4021 or Fining MAT 8403 gas chromatography/mass spectrometer at 70 eV. Elemental analyses were carried out on a MOD-1106 elemental analyzer. All solvents were purified and dried by standard techniques just before use. All reactions were monitored by thin layer chromatography (TLC) using silica gel GF254. Products were purified by chromatography on silica gel manufactured in Qingdao Marine Chemical Factory, eluting with the solvent mixture of petroleum ether (bp 60–90°C) and ethyl acetate. Optical rotations were measured using a Shanghai WZZ-1S automatic polarimeter.

General procedures

1,3-Dipolar cycloaddition reaction of vinylboronic ester 1 with nitrile oxides which initiated by Et_3N. To a 0°C cooled solution of vinylboronic ester **1** (136 mg, 0.535 mmol) and aryl hydroximinoyl chloride **2** (0.74 mmol) in THF (10 mL), was dropped slowly a solution of Et_3N (760 mg, 0.75 mmol) by a syringe. The resulting mixture was stirred at 0°C to room temperature until the starting material of vinylboronic ester **1** disappeared as followed by TLC. The reaction suspension was filtered by celite and the solid was washed with THF (2×10 mL). After condensation of the combined organic phase, the residue was subjected to flash chromatography on silica gel column. The first elution (ethyl acetate: petroleum 1:15) afforded the optically pure diastereoisomers Δ^2-isoxazoline **3** and **3′**, the optically pure diastereoisomers 4-hydroxy-Δ^2-isoxazoline **4** and **4′** were obtained after the second elution (ethyl acetate: petroleum 1:4).

3a: MS *m/z* 249 (M^++2, 8), 248 (M^++1, 46), 247 (M^+, 1), 232 (26), 190 (22), 146 (20), 115 (18), 101 (100), 77 (28), 43 (96). IR (cm^{-1}): 2986, 2920, 1594, 1565, 1448, 1371, 1356, 1264, 1204, 1153, 1049, 859, 764. 300 MHz ^{1}H NMR ($CDCl_3$): 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.35 (dd, *J*=6.6, 16.9 Hz, 1H, H-4β), 3.45 (dd, *J*=10.1, 16.8 Hz, 1H, H-4α), 3.95 (dd, *J*=4.2, 8.0 Hz, 1H, H-2′ β), 4.15 (m, 2H, H-1′, H-2′ α), 4.65 (ddd, *J*=7.8, 8.0, 10.0 Hz, 1H, H-5), 7.44 (m, 3H, ArH), 7.70 (m, 2H, ArH). HRMS: $C_{14}H_{17}NO_3$ Calcd 247.1209, Found: 247.1193

3′a: MS *m/z* 249 (M^++ 2, 10), 248 (M^++ 1, 60), 247 (M^+, 1), 232 (30), 190 (29), 146 (22), 115 (19), 101 (100), 77 (27), 43 (94). IR (cm^{-1}): 3030, 2987, 2932, 1599, 1569, 1448, 1372,1357, 1256, 1214, 1153, 1075, 862, 761. 300 MHz ^{1}H NMR ($CDCl_3$): 1.38 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.26 (dd, *J*=8.0, 16.7 Hz, 1H, H-4β), 3.42 (dd, *J*=11.1, 16.8 Hz, 1H, H-4α), 3.92 (dd, *J*=6.3, 8.6 Hz, 1H, H-2′ β), 4.13 (dd, *J*=7.0, 8.7 Hz, 1H, H-2′ α), 4.36 (ddd, *J*=4.7, 6.4, 6.5 Hz, 1H, H-1′), 4.83 (ddd, *J*=4.5, 8.1, 11.0 Hz, 1H, H-5), 7.42 (m, 3H, ArH), 7.68 (m, 2H, ArH). HRMS: $C_{14}H_{17}NO_3$ Calcd: 247.1209, Found: 247.1194.

3b: MS *m/z* 284 (M^++ 3, 10), 282 (M^++ 1, 30), 281 (M^+, 9), 266 (19), 224 (15), 180 (11), 101 (94), 43 (100). IR (cm^{-1}): 3059, 2988, 2925, 1597, 1491, 1382, 1371, 1256, 1147, 1093, 1077, 903, 834. 300 MHz ^{1}H NMR ($CDCl_3$): 1.34 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.34 (dd, *J*=6.8, 16.9 Hz, 1H, H-4β), 3.41 (dd, *J*=10.2, 16.9 Hz, 1H, H-4α), 3.95 (dd, *J*=4.3, 8.2 Hz, 1H, H-2′ β), 4.12 (m, 2H, H-1′, H-2′ α), 4.66 (ddd, *J*=6.9, 6.9, 9.9 Hz, 1H, H-5), 7.38 (m, 2H, ArH), 7.60 (m, 2H, ArH). HRMS: Calcd. for $C_{14}H_{16}NO_3{}^{35}Cl$: 281.0819, Found: 281.0832, Calcd. for $C_{14}H_{16}NO_3{}^{37}Cl$: 283.0790, Found: 281.0803.

3′b: MS *m/z*: 284 (M^++ 3, 11), 282 (M^++ 1, 49), 281 (M^+, 1), 266 (26), 224 (25), 180 (14), 115 (16), 101 (100), 43 (69). IR (cm^{-1}): 3060, 2989, 2926, 1598, 1492, 1382, 1372, 1257, 1094, 1077, 904, 836. 300 MHz ^{1}H NMR ($CDCl_3$): 1.36 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.23 (dd, *J*=8.1, 16.8 Hz, 1H, H-4β), 3.38 (dd, *J*=11.0, 16.8 Hz, 1H, H-4α), 3.90 (dd, *J*=6.3, 8.6 Hz, 1H, H-2′ β), 4.10 (dd, *J*=6.85, 8.7 Hz, 1H, H-2′ α), 4.34 (ddd, *J*=4.5, 6.4, 6.4 Hz, 1H, H-1′), 4.83 (ddd, *J*=4.4, 7.9, 11.0 Hz, 1H, H-5), 7.39 (m, 2H, ArH), 7.60 (m, 2H, ArH). HRMS: Calcd. for $C_{14}H_{16}NO_3{}^{35}Cl$: 281.0819, Found: 281.0835, Calcd. for $C_{14}H_{16}NO_3{}^{37}Cl$: 283.0790, Found: 281.0782.

4a: $[\alpha]_D^{20}$=+46.5 (*c* 0.60, CH_2Cl_2). MS *m/z* 265 (M^++ 2, 9), 264 (M^++ 1, 56), 248 (34), 160 (5), 115 (5), 104 (34), 101 (100), 73 (24), 43 (97). IR (cm^{-1}): 3304, 3070, 2992, 1569, 1450, 1373, 1382, 1256, 1217.9, 1143, 1074.7, 1056, 904, 833. 300 MHz ^{1}H NMR ($CDCl_3$): 1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.75 (s, OH), 3.88 (ddd, *J*=4.38, 6.32, 8.14 Hz, 1H, H-1′), 3.96 (dd, *J*=4.3, 8.8 Hz, 1H, H-2′ β), 4.08 (dd, *J*=6.9, 8.8 Hz, 1H, H-2′ α), 4.38 (dd, *J*=2.7, 8.1 Hz, 1H, H-5), 5.45 (m, 1H, H-4), 7.30 (m, 3H, ArH), 7.77 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): 24.97 (CH_3), 26.80 (CH_3), 67.01 (C-2′), 73.49 (C-1′), 78.95 (C-5), 88.60 (C-4), 110.08 (C-4′), 127.21, 127.70, 128.86, 130.46 (Ar), 157.73 (C-3). Anal.: $C_{14}H_{17}NO_4$ Calcd: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.81; H, 6.58; N, 5.10

4′a: $[\alpha]_D^{20}$=−48.8 (*c* 0.90, acetone). MS *m/z* 265 (M^++ 2, 2), 264 (M^++ 1, 12), 263 (M^+, 5), 248 (36), 162 (5), 145 (6), 131 (6), 104 (46), 101 (100), 73 (29), 43 (91). IR (cm^{-1}): 3311, 3061, 2991, 2921, 1600, 1451, 1372, 1263, 1215, 1155, 1090, 916, 838, 694. 300 MHz ^{1}H NMR ($CDCl_3$): 1.32 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.24 (s, OH), 3.93 (dd, *J*=6.5, 8.6 Hz, 1H, H-2′ β), 4.08 (dd, *J*=6.8, 8.6 Hz, 1H, H-2′ α), 4.32 (ddd, *J*=2.2, 4.2, 6.5 Hz, 1H, H-1′), 4.50 (m, 1H, H-5), 5.45 (d, *J*=3.8 Hz, 1H, H-4), 7.40 (m, 3H, ArH), 7.78 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): 25.26 (CH_3), 26.09 (CH_3), 65.28 (C-2′), 75.39 (C-1′), 79.14 (C-5), 87.72 (C-4), 110.16 (C-4′), 127.14, 127.74, 128.83, 130.32 (Ar), 157.76 (C-3). Anal.: $C_{14}H_{17}NO_4$ Calcd: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.82; H, 6.71; N, 5.33

4b: $[\alpha]_D^{20}$=+21.0 (*c* 0.65, CH_2Cl_2). MS *m/z* 299 (M^++ 2, 6), 297 (M^+, 18), 281 (26), 240 (2), 138 (29), 111 (8), 102 (12), 101 (100.00), 73 (21). IR (cm^{-1}): 3252, 2987, 2935, 1597, 1496, 1372, 1245, 1216, 1093, 1060, 1038, 1014, 901, 842. 300 MHz ^{1}H NMR ($CDCl_3$): 1.32 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.08 (s, OH), 3.90 (ddd, *J*=4.4, 6.3, 8.4 Hz, 1H, H-1′), 4.00 (dd, *J*=4.3, 8.9 Hz, 1H, H-2′ β), 4.12 (dd, *J*=6.3, 8.9 Hz, 1H, H-2′ α), 4.41 (dd, *J*=2.7, 8.2 Hz, 1H, H-5), 5.44 (d, *J*=2.3 Hz, 1H, H-4), 7.35 (m, 2H, ArH), 7.71 (m, 2H, ArH). Anal.: $C_{14}H_{16}NO_4Cl$ Calcd: C, 56.47; H, 5.38; N, 4.70. Found: C, 56.17; H, 5.39; N, 4.53.

4′b: $[\alpha]_D^{20}$=−46.6 (*c* 0.70, acetone). MS *m/z* 299 (M^++ 2, 9), 297 (M^+, 27), 283 (10), 281 (28), 138 (22), 111 (9), 101 (100), 73 (20), 43 (77). IR (cm^{-1}): 3243, 2987, 2935, 1597,

1496, 1372, 1213, 1092, 1058, 1037, 901, 842. 300 MHz ^{1}H NMR ($CDCl_3$): 1.31 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.21 (s, OH), 3.92 (dd, *J*=6.2, 8.2 Hz, 1H, H-2′ β), 4.08 (dd, *J*=6.9, 8.3 Hz, 1H, H-2′ α), 4.34 (m, 1H, H-1′), 4.50 (dd, *J*=3.5, 7.2 Hz, 1H, H-5), 5.38 (d, *J*=3.14 Hz, 1H, H-4), 7.34 (m, 2H, ArH), 7.70 (m, 2H, ArH). $C_{14}H_{16}NO_4Cl$ Calcd: C, 56.47; H, 5.38; N, 4.70. Found: C, 56.43; H, 5.42; N, 4.50.

1,3-Dipolar cycloaddition reaction of vinylboronic ester 1 with nitrile oxides initiated by sodium percarbonate. To a solution of vinylboronic ester **1** (330 mg, 1.30 mmol) and aryl hydroximinoyl chloride (1.8 mmol) in THF (20 mL), was added sodium percarbonate (570 mg, 3.63 mmol) in one portion. The resulting suspension was stirred at room temperature until the starting material of vinylboronic ester **1** disappeared as followed by TLC. The reaction mixture was filtered by celite and the solid was washed with THF (2×20 mL). After condensation of the combined organic phase, the residue was subjected to flash chromatography on silica gel column with a mixture of ethyl acetate and petroleum (1/4) as the eluent, the optically pure diastereoisomer 4-hydroxy-Δ^2-isoxazoline **4** and **4**′ were obtained.

4c: $[\alpha]_D^{20}$=+44.8 (*c* 1.87, CH_2Cl_2). MS *m*/*z* 278 (M^++ 1, 6), 277 (M^+, 25), 262 (36), 176 (7), 118 (52), 101 (100), 91 (18), 73 (26). IR (cm^{-1}): 3404, 3050, 2989, 2925, 1612, 1517, 1374, 1217, 1075, 1059, 892, 843. 300 MHz ^{1}H NMR ($CDCl_3$): 1.31 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.35 (s, 3H, $ArCH_3$), 3.62 (s, OH), 3.88 (ddd, *J*=4.4, 6.3, 8.2 Hz, 1H, H-1′), 3.96 (dd, *J*=4.3, 8.8 Hz, 1H, H-2′ β), 4.08 (dd, *J*=6.3, 8.8 Hz, 1H, H-2′ α), 4.37 (dd, *J*=2.7, 8.2 Hz, 1H, H-5), 5.43 (d, *J*=2.6 Hz, 1H, H-4), 7.14 (m, 2H, ArH), 7.64 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$+acetone-d_6): 21.57 (CH_3), 25.26 (CH_3), 26.99 ($ArCH_3$), 67.19 (C-2′), 74.14 (C-1′), 78.91 (C-5), 88.73 (C-4), 110.09 (C-4′), 125.87, 127.45, 129.71, 140.56 (Ar), 158.13 (C-3). Anal.: $C_{15}H_{19}NO_4$ Calcd C, 64.98; H, 6.86; N, 5.05. Found: C, 64.54; H, 6.93; N, 5.00.

4′c: $[\alpha]_D^{20}$=−57.3 (*c* 0.80, acetone). MS *m*/*z* 278 (M^++ 1, 3), 277 (M^+, 15), 262 (27), 174 (3), 118 (43), 101 (100), 91 (19), 73 (24), 43 (64). IR (cm^{-1}): 3270, 2990, 2920, 1517, 1455, 1381, 1370, 1265, 1211, 1084, 1056, 1022, 949, 857, 822. 300 MHz ^{1}H NMR ($CDCl_3$): 1.32 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.36 (s, 3H, $ArCH_3$), 3.10 (s, OH), 3.92 (dd, *J*=6.6, 8.5 Hz, 1H, H-2′β), 4.08 (dd, *J*=6.9, 8.5 Hz, 1H, H-2′ α), 4.34 (m, 1H, H-1′), 4.49 (dd, *J*=4.0, 7.9 Hz, 1H, H-5), 5.41 (m, 1H, H-4), 7.19 (m, 2H, ArH), 7.66 (m, 2H, ArH). Anal.: $C_{15}H_{19}NO_4$ Calcd C, 64.98; H, 6.86; N, 5.05. Found: C, 64.84; H, 6.84; N, 4.78.

4d: $[\alpha]_D^{20}$=+30.2 (*c* 1.25, CH_2Cl_2). MS *m*/*z* 294 (M^++ 1, 24), 293 (M^+, 60), 278 (19), 192 (4), 176 (6), 149 (6), 134 (84), 101 (92), 73 (33), 43 (100). IR (cm^{-1}): 3217, 2995, 2990, 2851 1609, 1518, 1375, 1263, 1181, 1076, 889, 834. 300 MHz ^{1}H NMR ($CDCl_3$): 1.32 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.25 (s, OH), 3.82 (s, 3H, OCH_3), 3.89 (ddd, *J*=4.1, 6.0, 8.0 Hz, 1H, H-1′), 4.00 (dd, *J*=4.3, 8.8 Hz, 1H, H-2′ β), 4.11 (dd, *J*=6.3, 8.8 Hz, 1H, H-2′ α), 4.38 (dd, *J*=2.5, 8.3 Hz, 1H, H-5), 5.44 (d, *J*=2.4 Hz, 1H, H-4), 6.89 (m, 2H, ArH), 7.72 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): 25.05 (CH_3), 26.92 (CH_3), 55.38 (OCH_3), 67.18 (C-2′), 73.53 (C-1′), 79.40 (C-5), 88.39 (C-4), 110.08 (C-4′), 114.30, 120.09, 128.85, 161.30 (Ar), 157.50 (C-3). Anal.: $C_{15}H_{19}NO_5$ Calcd C, 61.43; H, 6.48; N, 4.78. Found: C, 61.31; H, 6.52; N, 4.67.

4′d: $[\alpha]_D^{20}$=−55.20 (*c* 0.65, acetone). MS *m*/*z* 294 (M^++1, 14), 293 (M^+, 62), 278 (29), 192 (5), 176 (10), 161 (3), 149 (10), 134 (82), 101 (100), 73 (32), 43 (99). IR (cm^{-1}): 3473, 2998, 1607, 1595, 1514, 1382, 1253, 1183, 1051, 1012, 945, 874. 300 MHz ^{1}H NMR ($CDCl_3$): 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.10 (s, OH), 3.83 (s, 3H, OCH_3), 3.92 (dd, *J*=6.5, 8.6 Hz, 1H, H-2′ β), 4.10 (dd, *J*=6.9, 8.6 Hz, 1H, H-2′ α), 4.35 (m, 1H, H-1′), 4.50 (dd, *J*=4.1, 8.1 Hz, 1H, H-5), 5.44 (d, *J*=3.6 Hz, 1H, H-4), 6.80 (m, 2H, ArH), 7.75 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): 25.25 (CH_3), 26.13 (CH_3), 55.36 (OCH_3), 65.31 (C-2′), 75.33 (C-1′), 79.40 (C-5), 87.51 (C-4), 110.13 (C-4′), 114.28, 120.10, 128.70, 161.20 (Ar), 157.30 (C3). Anal. $C_{15}H_{19}NO_5$ Calcd C, 61.43; H, 6.48; N, 4.78. Found: C, 61.32; H, 6.63; N, 4.53.

4e: $[\alpha]_D^{20}$=+74.5 (*c* 0.60, CH_2Cl_2). MS *m*/*z* 333 (7), 332 (M^+, 3), 331 (10), 315 (20), 273 (1), 172 (19), 136 (6), 101 (100), 73 (19), 43 (59). IR (cm^{-1}): 3402, 3094, 2989, 2937, 1586, 1553, 1476, 1374, 1253, 1216, 1105, 1077, 1050, 871, 842. 300 MHz ^{1}H NMR ($CDCl_3$): 1.37 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.70 (s, OH), 4.05 (ddd, *J*=4.13, 5.67, 7.93 Hz, 1H, H-1′), 4.15 (m, 2H, H-2′), 4.46 (dd, *J*=3.5, 7.7 Hz, 1H, H-5), 5.73 (d, *J*=3.5 Hz, 1H, H-4), 7.32 (dd, *J*=2.1, 8.4 Hz, 1H, ArH), 7.48 (d, *J*=2.0 Hz, 1H, ArH), 7.66 (dd, *J*=8.4 Hz, 1H, ArH). Anal. $C_{14}H_{15}NO_4Cl_2$ Calcd C, 50.60; H, 4.52; N, 4.21. Found: C, 50.75; H, 4.74; N, 4.18.

4′e: $[\alpha]_D^{20}$=−97.0 (*c* 0.85, acetone). MS *m*/*z* 336 (2), 334 (12), 332 (M^+, 21), 331 (M^+−1, 100), 315 (34), 260 (58), 172 (6), 101 (68), 43 (21). IR (cm^{-1}): 3402, 3094, 2989, 2937, 1586, 1553, 1476, 1374, 1253, 1216, 1105, 1077, 1050, 871, 842. 300 MHz ^{1}H NMR ($CDCl_3$): 1.36 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.79 (s, OH), 3.97 (dd, *J*=6.3, 8.7 Hz, 1H, H-2′ β), 4.12 (dd, *J*=6.8, 8.5 Hz, 1H, H-2′ α), 4.39 (m, 1H, H-1′), 4.54 (dd, *J*=4.4, 4.4 Hz, 1H, H-5), 5.69 (d, *J*=4.5 Hz, 1H, H-4), 7.30 (dd, *J*=1.8, 8.4 Hz, 1H, ArH), 7.47 (d, *J*=1.6 Hz, 1H, ArH), 7.63 (dd, *J*=8.4 Hz, 1H, ArH). Anal. $C_{14}H_{15}NO_4Cl_2$ Calcd C, 50.60; H, 4.52; N, 4.21. Found: C, 50.54; H, 4.65; N, 4.30.

X-Ray diffraction study. X-Ray structure determination of **4a** $C_{14}H_{17}NO_4$: colourless crystal (0.20×0.20×0.30 mm, grown from diethyl ether and *n*-hexane), $C_{14}H_{17}NO_4$, M263.29, orthorhombic, space group $P2_12_12_1$(#19), *a*=11.314(1) Å, *b*=12.707(2) Å, *c*=9.411(2) Å, *V*=1353.1(4) Å^3, *Z*=4, *D*=1.292 g cm^{-3}, *F*(000)=560.00, *T*=293 K. A Rigaku AFC7R diffractometer (CCD area detector) and graphite monochromated Mo-Kα radiation, λ=0.34 Å, was used for all measurements. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 20 carefully centered reflections in the range $18.29<2\theta<21.79°$. The data was collected using the ω-2θ scan technique to a maximum 2θ value of 55.0°. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 235 mm. A total of 1808 reflections was collected. The intensities of

three representative reflection were measured after every 200 reflections. The structure was solved by direct methods using SHELXS86 and expanded using DIRDIF92. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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