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Silyl Nitronate Cycloadditions Catalyzed by Cu(II)-Bisoxazoline

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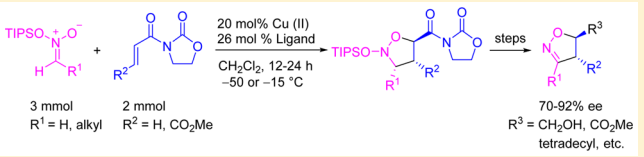
Supporting Information

ABSTRACT: $Cu(OTf)_2$ and chiral BOX ligand-catalyzed 1,3-dipolar cycloadditions of triisopropylsilyl nitronates with α,β-unsaturated carboximides produced chiral isoxazolines in high yields, high enantioselectivities, and complete diastereoselectivities. These chiral isoxazoline products were further converted into structurally diversified derivatives, which demonstrated the utility of the new method of constructing isoxazolines. The transition-state structure of cycloaddition was proposed in the light of the relative and absolute configurations of the products.



INTRODUCTION

Silyl nitronate, being an activated form of nitronate, may act as a synthetic equivalent of nitrile oxide in 1,3-dipolar cycloadditions. Both silyl nitronate and nitrile oxide can be used to prepare chiral isoxazolines, which are valuable for organic synthesis.[1,2] Silyl nitronates react with olefins to produce *N*-silyloxy isoxazolidines, which can generate isoxazolines via spontaneous or acid-catalyzed desilanol reaction.[3] In comparison with nitrile oxide, silyl nitronate may exhibit better regio- and stereoselectivities in cycloadditions with olefins.[1] Intermolecular and intramolecular cycloadditions of silyl nitronates are documented. Few asymmetric cycloaddition reactions involving silyl nitronates were reported (Scheme 1a–c).[4] Unexceptionally, stereocontrol of the cycloaddition was realized through asymmetric induction by preexisting chiral centers. Much less attention has been paid to asymmetric intermolecular reactions of achiral olefins and achiral silyl nitronates.

Recently our group reported an unprecedented catalytic asymmetric synthesis of enantiomerically pure isoxazolines from triisopropylsilyl nitronates and 2-alkylacroleins.[5] The isoxazolines are characteristic of a masked chiral tertiary alcohol unit and could be useful for the synthesis of natural products. However, the acroleins used were uniformly 2-alkyl substituted acroleins. Acrolein itself as well as β-substituted acroleins did not go detectable reaction in the asymmetric cycloaddition under the catalysis of Corey's "oxazaborolidine-TfOH (1:1)" catalyst.[6] To further explore the utility of silyl nitronates in asymmetric synthesis and to circumvent the dipolarophile substrates limitation encountered previously, we hope to develop a new synthesis of chiral isoxazolines from silyl nitronates and α,β-unsaturated carboximides (Scheme 1d). It was anticipated that with the catalysis of a "$Cu(OTf)_2$-BOX" complex, silyl nitronates react with α,β-unsaturated carboximides to produce chiral isoxazolines of structural diversity in complete regioselectivity and high stereoselectivities. The strategy of chelating an α,β-unsaturated carboximide with a chiral Lewis acid to introduce chirality has been used in asymmetric synthesis. Evans' seminal work on "Cu(II)-BOX"-catalyzed asymmetric Diels–Alder reactions is representative.[7−10]

RESULTS AND DISCUSSION

We started to investigate the cycloadditions of *N*-acryloyl-2-oxazolidinone **2a** using triisopropylsilyl propylidenenitronate **1a** as the 1,3-dipole molecule (Table 1). In the absence of a catalyst, no cycloadduct was observed at −60 °C. In the presence of 10 mol % of $Cu(OTf)_2$ and 13 mol % of L-valinol derived bisoxazoline **5a**, the *N*-silyloxy isoxazolidine cycloadduct **3a** was produced smoothly, and the isoxazoline product **4a** was isolated in 74% overall yield (Table 1, entry 1) after the PTSA-catalyzed desilanol reaction of the corresponding cycloadduct **3a**.[3] The enantiomeric excess (ee) of **4a** was determined to be 85%. Next, the bisoxazoline ligands bearing a benzyl (**5b**), phenyl (**5c**), or *t*-butyl group (**5d**) were examined. While **5b** and **5c** produced lower ee (entries 2 and 3), **5d** delivered higher yield and ee for **4a**, though a longer reaction time was required (entry 4 vs 1). (1*R*,2*S*)-1-Amino-2-indanol derived bisoxazolines (**5e**, **5f**) were also tested. Both the yields and the ee's were disappointing (Table 1, entries 5 and 6). Influences of the catalyst loading and reaction temperature were also checked. When 20 mol % of $Cu(OTf)_2$ and 26 mol % of **5d** were used, the yield and ee were improved (entry 7 vs 4). When the reaction was carried out at −50 °C, similar ee and yield were obtained (entry 8 vs 7). The reaction results of **1b** also indicated that **5d** was superior to **5a** with respect to ee (entry 11 vs 10). Thus, **5d** was selected to investigate the scope of silyl nitronates.

Under the optimal conditions [20 mol % $Cu(OTf)_2$, 26 mol % of ligand **5d**, −50 °C], the triisopropylsilyl nitronates (**1a**–**1g**) from various aliphatic nitroalkanes were reacted with *N*-acryloyl-2-oxazolidinone **2a**. The results are shown in Scheme 2. The isoxazolidine cycloadduct (**3a**–**3g**) was isolated by silica gel chromatography. Subsequent PTSA treatments gave the

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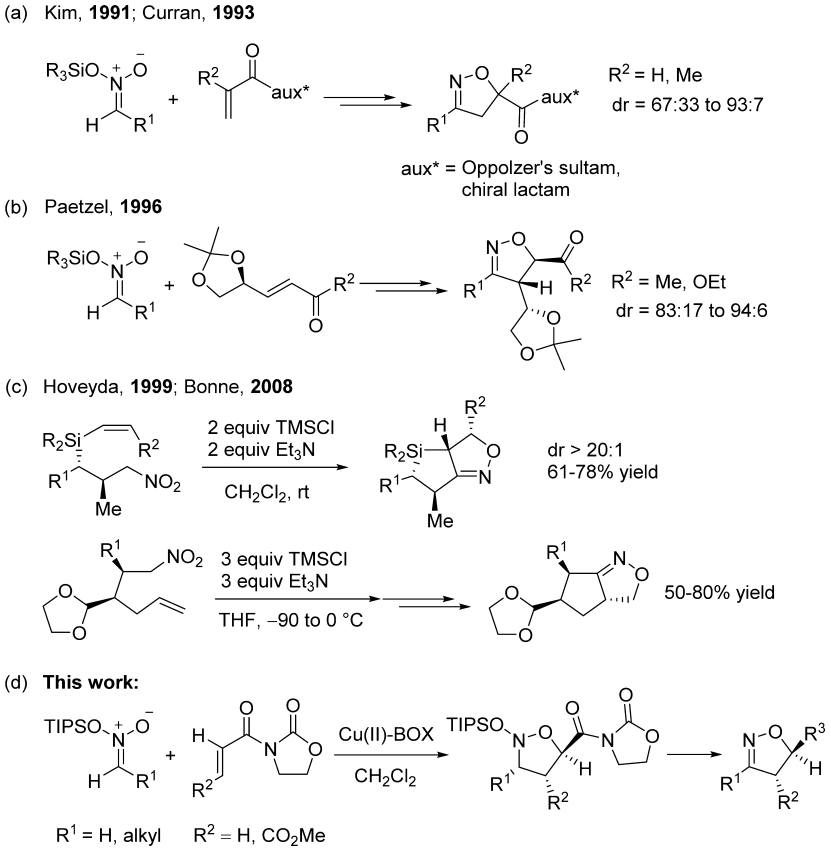
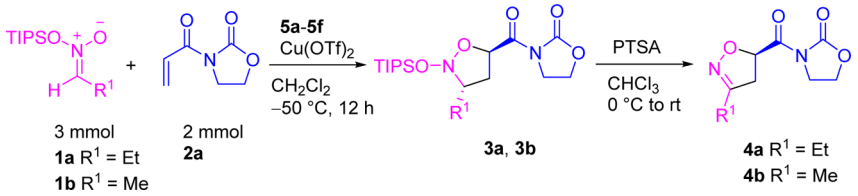
Scheme 1. Syntheses of Chiral Isoxazolines from Silyl Nitronates[a]



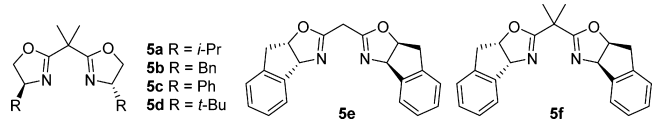
[a](a–c) Substrate controlled and (d) catalyst controlled.

Table 1. Screening of Bisoxazoline Ligands



entry	ligand	Cu mol %	t (°C)	yield (%)	ee (%)[a,b]
1	**5a**	10	−60	74	85 (**4a**)
2	**5b**	10	−60	65	46 (**4a**)
3	**5c**	10	−60	90	58 (**4a**)
4	**5d**[c]	10	−60	85	88 (**4a**)
5	**5e**	10	−60	24	60 (**4a**)
6	**5f**	10	−60	12	48 (**4a**)
7	**5d**	20	−60	90	92 (**4a**)
8	**5d**	20	−50	89	90 (**4a**)
9	**5d**	20	−40	74	86 (**4a**)
10	**5a**	20	−50	86	80 (**4b**)
11	**5d**	20	−50	86	88 (**4b**)

[a]Ee's were for **4a** or **4b**. Ee determined by chiral HPLC analysis using AD-H column. [b]Abs. configuration was (*R*). See Supporting Information. [c]Reaction time was 24 h.



isoxazolines (**4a**–**4g**) in good yields and ee. The chiral isoxazolidine **3b** (Scheme 2, R^1 = Me) was subjected to ^{1}H NMR analysis. A single diastereomer was observed. Single crystals of racemic **3b** were obtained.[11] X-ray diffraction (XRD)

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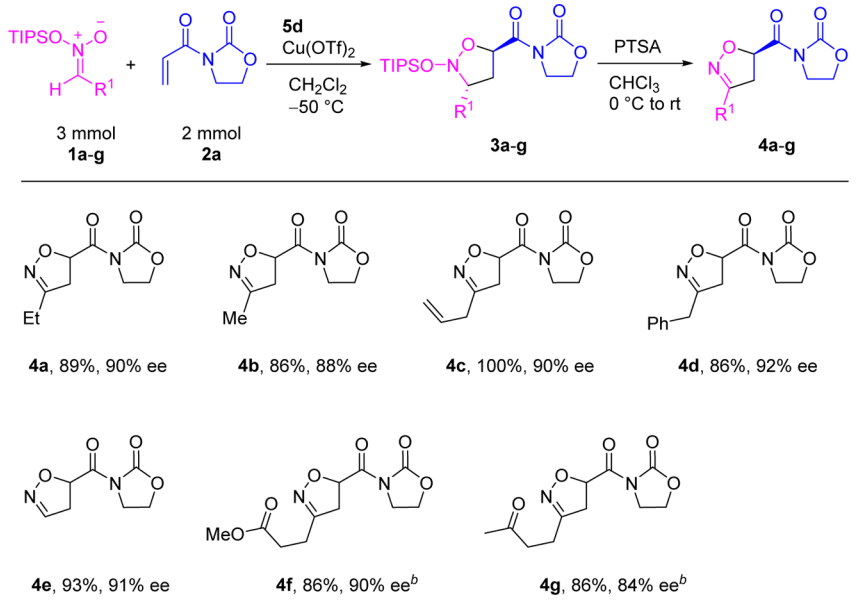
Scheme 2. Cycloadditions of TIPS Nitronates with Carboximide 2a[a,b]

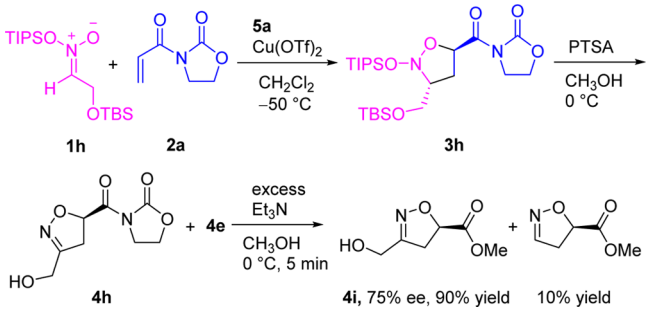


[a]Ee determined by chiral HPLC analysis. [b]**5a** was used instead of **5d**. Reaction time was 24 h.

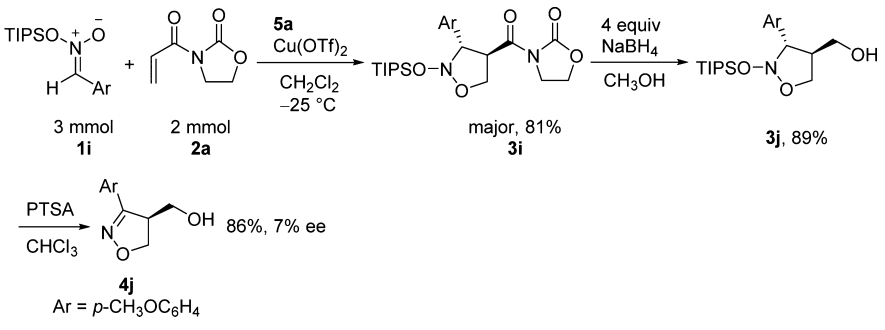
analysis verified the methyl and the carboximide group were *trans* configured, indicating a perfect *endo* selectivity.[11] An alkene, phenyl, ester, or ketone moiety in the nitronate substrate was well tolerated, as evidenced by the good ee and yields of **4c**, **4d**, **4f**, and **4g**. Notably, nitromethane derived TIPS nitronate **1e** gave isoxazoline **4e** in 91% ee and 93% yield. For the less reactive nitronates **1f** and **1g**, ligand **5a** was used instead of **5d**.

When 2-nitroethanol derived nitronate **1h** was reacted with **2a**, the cycloadduct **3h** was produced smoothly (Scheme 3) and isolated by silica gel chromatography. When PTSA or CSA (up to 1.0 equiv) in CH_2Cl_2 or $CHCl_3$ or concentrated HCl in THF was used to catalyze the desilanol reaction of **3h** in a temperature range of 0 °C to rt, **4e** was obtained as the major product with various amounts of **4h**. Upon silica gel chromatography, **4h** will be further converted into **4e**. Careful experiments confirmed that the isoxazoline **4h** was prone to eliminate formaldehyde to give **4e** under acidic conditions. Due to the instability of **4h** under acidic conditions, we sought to prepare it under basic conditions. At 0 °C, **3h** was treated with PTSA in methanol. Desilanol was accomplished with concomitant removal of the TBS protection group. **4h** and **4e** were produced in a ratio of 90:10. When the crude product in methanol was chromatographed on silica gel deactivated with Et_3N, **4i** was isolated in a good yield, which was fairly stable at rt, but may slowly eliminate formaldehyde over standing. Removal of methanol under high vacuum followed by chromatography of crude **4h** and **4e** on Et_3N deactivated silica gel gave **4h** as a white solid in 60% yield. Practically, **4h** was *in situ* reacted with excess Et_3N in methanol at 0 °C. As a result, the 2-oxazolidinone moiety was removed, and the hydroxymethyl group was reserved, and **4i** was isolated in 90% yield and 75% ee (Scheme 3).[12] The reactivity of a phenylnitromethane derived nitronate **1i** was also tested. **1i** was reacted

Scheme 3. Cycloaddition of Nitronate 1h with Carboximide 2a



Scheme 4. Cycloaddition of TIPS *p*-Anisylidenenitronate



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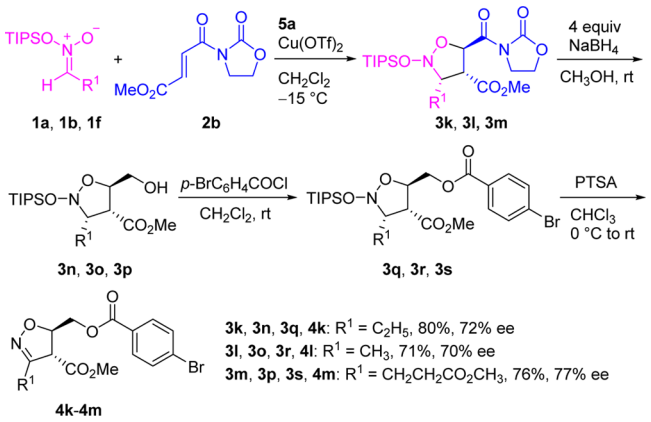
with **2a** at −25 °C using "Cu(OTf)$_2$-**5a**" complex as the catalyst (Scheme 4). Unfortunately, two regioisomeric isoxazolidines were obtained in a ratio of 95:5. The predominant cycloadduct **3i** was isolated in 81% yield and further converted via the isoxazolidine **3j** into the corresponding isoxazoline **4j**, which was shown to have an ee of only 7%.

To expand the substrate scope of the dipolarophile, cinnamic acid, crotonic acid, or fumaric acid monoester derived 2-oxazolidinone was used for the cycloadditions. Even at rt, *N*-cinnamoyl- or *N*-crotonoyl-2-oxazolidinone did not react with **1a**. At−15 °C, fumaric acid monoester derived 2-oxazolidinone (**2b**) reacted with TIPS nitronates smoothly (Scheme 5).

Scheme 5. Asymmetric Cycloadditions of Carboximide 2b



Interestingly, the reactivity of the isoxazolidine cycloadduct **3k**−**3m** bearing an ester group at the 4-position of the ring was quite different from the isoxazolidines with no substituent at the 4-position. When **3k**−**3m** (Scheme 5) was treated with PTSA (up to 1.0 equiv) in $CHCl_3$, the corresponding isoxazoline **4k**−**4m** was isolated in only 50% yield. The remaining starting material was not converted. Alternatively, the desilanol reaction of **3k**−**3m** was achieved in three sequential steps. $NaBH_4$ reduction (4 equiv) selectively removed the oxazolidinone moiety from **3k**−**3m**, while the ester group remained intact.[13] The newly formed hydroxy group in **3n**−**3p** was protected with a *p*-bromobenzoyl group to avoid possible lactonization between the hydroxy group and the adjacent ester group. Finally, treatment of **3q**−**3s** with PTSA gave the isoxazoline product **4k**−**4m** in a good overall yield. **4k**−**4m** were used for ee determination, which ranged from 70% to 77%. A single crystal of isoxazoline **4l** was used for XRD analysis. The absolute configuration was determined as (4*R*,5*R*).[14] The *trans* configuration of the *p*-bromobenzoxymethyl group and the ester group was confirmed.[14]

Based on the reported stereochemical analyses of "*α*,*β*-unsaturated carboximide-Cu(OTf)$_2$-BOX" complexes in asymmetric Diels−Alder reactions[7] and the crystal structures of **4l** and racemic **3b**,[11,14] we proposed the following transition-state structure for asymmetric cycloadditions of **2a** and **2b** (Figure 1). The *α*,*β*-unsaturated carboximide adopts an *s-cis* conformation and coordinates to the "Cu(OTf)$_2$-BOX" catalyst in a bidentate way. The four surrounding atoms chelate to the Cu(II) cation in a distorted square planar geometry, allowing the C$_\alpha$-*Re* face of the dipolarophile more accessible. The TIPS nitronate approached the dipolarophile from the *Re* face in an *endo* manner, delivering the isoxazolidine cycloadduct with a (5*R*) configuration and *cis*-configured R^1 and R^2 groups.

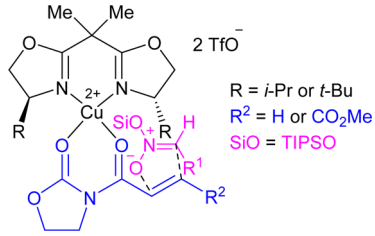


Figure 1. Suggested transition-state structure for cycloaddition.

The chiral isoxazolines prepared in our method could be useful starting materials for organic syntheses. [(5*S*)-5-Tetradecyl-2-isoxazolin-3-yl]methanol **4r**, a potential precursor for the synthesis of phytosphingosine,[15] was prepared in five steps from isoxazoline **4i** (Scheme 6). THP protection of the hydroxy group of **4i** and DIBAL-H reduction of the ester group of **4n** delivered the aldehyde intermediate **4o**. PhLi-mediated Wittig reaction of **4o** followed by catalytic hydrogenation of **4p** introduced the long alkyl chain into the isoxazoline core structure. Removal of THP group of **4q** furnished **4r**. The ee (82%) of **4r** was slightly higher than that of **4i**, which implicated a good tolerance of the reaction conditions to the chiral center.

Except the above synthesis of **4r**, several conversions of isoxazoline **4a** were conducted (Scheme 7). The imide group of **4a** was easily converted into an ester group in **4s** under similar conditions converting **4h** into **4i** (Scheme 7a).[16] $NaBH_4$ reduction of **4a** gave **4t** in 85% yield (Scheme 7b). When the hydroxy group of **4t** was protected with THP or TBS, the already existing chiral center in **4u** or **4x** could induce perfect diastereoselectivity in either HMPA-mediated lithiation at the 4-position followed by methylation with MeI (Scheme 7c,d)[17] or nucleophilic additions to the C═N double bond (Scheme 7e,f).[18]

■ CONCLUSION

In summary, we investigated "Cu(OTf)$_2$-BOX"-catalyzed cycloadditions of TIPS nitronates with *α*,*β*-unsaturated carboximides. Chiral isoxazolines were prepared in good yields and good to excellent ee. One chiral isoxazoline was easily converted into a potential precursor for phytosphingosine. The newly constructed chiral center at the 5-position of the isoxazoline ring could help efficiently build new chiral center at 3- or 4-poistion of the ring in high diastereoselectivities. Accordingly, chiral isoxazolines and isoxazolidines bearing novel structures were obtained. This new method well complements our previous synthesis of chiral isoxazolines.[5]

■ EXPERIMENTAL SECTION

All glassware for reactions using anhydrous solvents were dried under high vacuum (<0.1 Torr) using a heat gun. General Schlenk techniques were applied for addition and transfer operations. Commercial reagents and solvents were used as received unless otherwise noted. Toluene, THF, or benzene was distilled over sodium benzophenone ketyl under N_2. CH_2Cl_2 was distilled over CaH_2 under N_2. CH_3OH was distilled over Mg turnings. Thin-layer chromatography (TLC) was performed on precoated silica gel (0.2−0.25 mm thick) plates with fluorescent indicator 254 nm. The plate was visualized with 254 nm UV lamp, PMA or $KMnO_4$ stain. Column chromatography was performed on 200−300 mesh silica gel.

^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts of ^{1}H NMR and ^{13}C NMR were referred to TMS (δ = 0) and chloroform (δ = 77.16), respectively. The following abbreviations were used to denote the multiplicity of each

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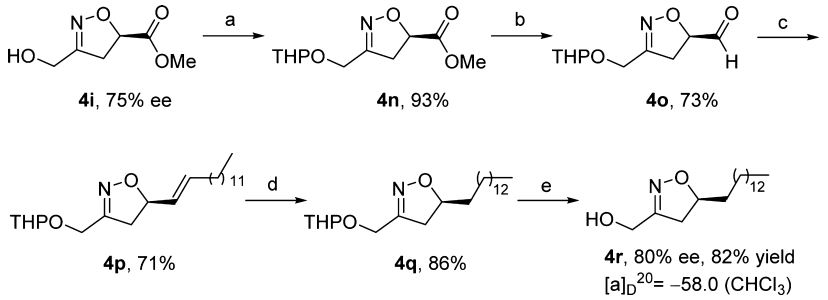
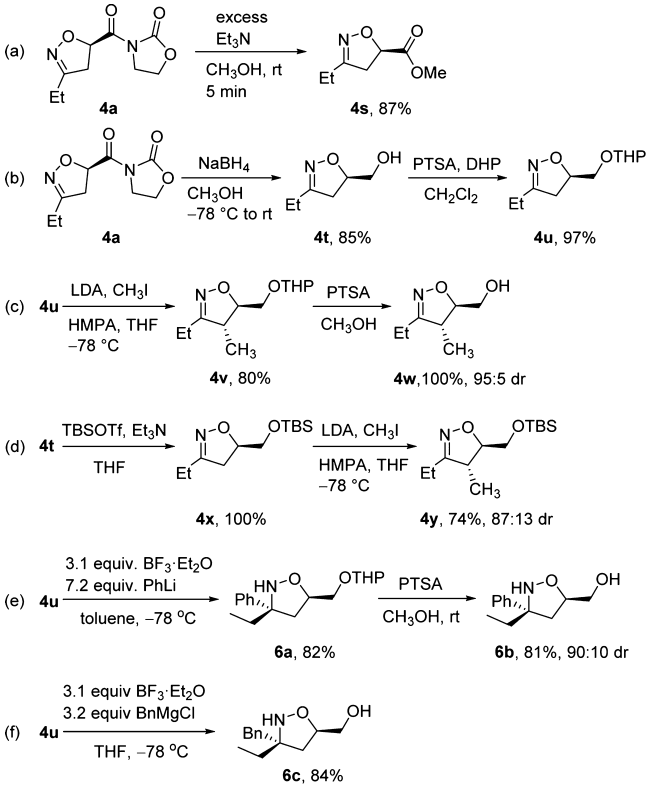
Scheme 6. Synthesis of [(5*S*)-5-Tetradecyl-2-isoxazolin-3-yl]methanol[a]



[a]Reagents and conditions: (a) PTSA, DHP, THF, 93%; (b) DIBAL-H, −60 °C, CH_2Cl_2, 73%; (c) PhLi, triphenyltridecylphosphonium bromide, THF, 71%; (d) Pd/C, H_2, CH_3OH, 86%; (e) PTSA, CH_3OH, 82%.

Scheme 7. Conversions of Chiral Isoxazolines



peak: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet). HPLC was performed at room temperature. Specific rotation was measured using the 589 nm D-line of sodium lamp and a quartz cell with 10 cm path length. XRD experiment was conducted using Mo Kα radiation. Nitronates **1a**−**1i** were prepared in known methods.[5]

***p*-Methoxyphenyl Triisopropylsilyl-*aci*-nitromethane (1i).** Light yellow oil (1.6 g, 99% yield), R_f = 0.45 (20:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, J = 8.9 Hz, 2H), 7.02 (s, 1H), 6.92 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H), 1.39−1.35 (m, 3H), 1.13 (d, J = 7.4 Hz, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 160.0, 128.9, 122.3, 115.3, 114.0, 55.2, 17.9, 12.6; IR (cm^{-1}): 2945, 2893, 2867, 2842, 1695, 1604, 1578, 1573, 1511, 1464, 1429, 1304, 1256, 1174, 1161, 1105, 1032, 936, 882, 835, 795, 726, 693, 523; MS (ESI): calcd for $C_{17}H_{29}NO_3Si$ [M + H]$^+$ 324.1995, found 324.1989.

General Procedures for the Cycloadditions of 2a. A dry 50 mL Schlenk tube was charged with **5d** (153 mg, 0.52 mmol), $Cu(OTf)_2$ (144 mg, 0.4 mmol), and anhydrous CH_2Cl_2 (12 mL). The mixture was stirred at rt for about 2 h until it became clear. Then it was cooled to −50 °C. After stirring for 30 min at −50 °C, the α,β-unsaturated carboximide **2a** (2.0 mmol) was added followed by silyl nitronate (3.0 mmol) in anhydrous CH_2Cl_2 (3 mL). The mixture was stirred at −50 °C overnight. The isoxazolidine cycloadduct was purified by silica gel chromatography.

To a solution of the isoxazolidine cycloadduct (1.5 mmol) in $CHCl_3$ (5 mL) was added *p*-TsOH·H_2O (40 mol %) at 0 °C. The mixture was stirred at rt for 4 h or longer. The isoxazoline product was purified by silica gel chromatography and used for HPLC analysis.

Note: All racemic products were prepared from 1 mmol of the α,β-unsaturated carboximide and 2 mmol of silyl nitronate in ca. 100% yield at rt without using any catalyst. The ee of the chiral isoxazoline was determined by HPLC.

(±)-*endo*-3-[(3-Methyl-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl)carbonyl]-2-oxazolidinone [(±)-3b]. Colorless oil (745 mg, 100% yield), R_f = 0.47 (2:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.78 (dd, J = 10.2, 3.2 Hz, 1H), 4.47−4.43 (m, 2H), 4.06−4.01 (m, 2H), 3.49−3.43 (m, 1H), 2.68 (dd, J = 22.2, 11.6 Hz, 1H), 2.26−2.20 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H), 1.25−1.18 (m, 3H), 1.10−1.07 (m, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 171.0, 153.1, 77.3, 67.4, 62.7, 42.6, 36.9, 18.07, 18.02, 14.3, 12.1; IR (cm^{-1}): 2945, 2891, 2866, 1782, 1770, 1708, 1454, 1386, 1276, 1205, 1039, 985, 912, 885, 759, 684, 607, 514; MS (ESI): calcd for $C_{17}H_{32}N_2O_5Si$ [M + H]$^+$ 373.2159, found 373.2161.

3-[(3*R*,5*R*)-(3-*t*-Butyldimethylsilyloxymethyl-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl)carbonyl]-2-oxazolidinone (3h). Colorless oil (944 mg, 94% yield), R_f = 0.48 (3:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −107 (c 0.250, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.80 (dd, J = 10.2, 3.4 Hz, 1H), 4.49−4.44 (m, 2H), 4.07−4.02 (m, 3H), 3.69 (dd, J = 10.0, 7.4 Hz, 1H), 3.57−3.49 (m, 1H), 2.80−2.72 (m, 1H), 2.37−2.32 (m, 1H), 1.25−1.15 (m, 3H), 1.08−1.06 (m, 18H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 170.7, 153.2, 73.6, 62.8, 62.1, 42.5, 34.4, 25.8, 17.99, 17.95, 12.0, −5.3, −5.4; IR (cm^{-1}): 2947, 2930, 2867, 1786, 1708, 1465, 1388, 1259, 1222, 1101, 1042, 838, 800, 781, 676; MS (ESI): calcd for $C_{23}H_{46}N_2O_6Si_2$ [M + H]$^+$ 503.2973, found 503.2970.

(3-*p*-Methoxyphenyl-*N*-triisopropylsilyloxy-2-isoxazolidin-4-yl)methanol (3j). Colorless oil (437 mg, 89% yield), R_f = 0.58 (1:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J = 8.7 Hz, 2H), 8.65 (d, J = 8.7 Hz, 2H), 4.57 (dd, J = 9.0, 7.6 Hz, 1H), 4.09 (d, J = 10.3 Hz, 1H), 4.02 (dd, J = 7.4, 6.1 Hz, 1H), 3.80 (s, 3H), 3.79−3.75 (m, 1H), 3.69−3.63 (m, 1H), 3.46−3.37 (m, 1H), 0.99−0.96 (m, 3H), 0.91−0.85 (m, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 159.8, 132.1, 125.8, 113.4, 77.7, 71.0, 63.1, 55.4, 45.4, 17.7, 11.9; IR (cm^{-1}): 3438, 2945, 2867, 1613, 1516, 1465, 1252, 1177, 1037, 884, 676, 586, 553; MS (ESI): calcd for $C_{20}H_{35}NO_4Si$ [M + H]$^+$ 382.2414, found 382.2413.

3-{[(3*S*,4*R*,5*R*)-4-Methoxycarbonyl-3-(2-methoxycarbonylethyl)-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl]carbonyl}-2-oxazolidinone (3m). Colorless oil (959 mg, 95% yield), R_f = 0.38 (1:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −109 (c 0.500, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.48 (d, J = 2.5 Hz, 1H), 4.46−4.42 (m, 2H), 4.03−3.99 (m, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 3.63 (dd, J = 7.5, 2.5 Hz, 1H), 3.50 (dd, J = 14.6, 7.2 Hz, 1H), 2.65−2.47 (m, 2H), 2.31−2.12 (m, 2H), 1.21−1.12 (m, 3H), 1.09−1.04 (m, 18H); ^{13}C{^{1}H}

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NMR (100 MHz, $CDCl_3$) δ: 173.3, 169.8, 169.2, 152.5, 79.3, 75.0, 62.5, 52.1, 51.8, 49.1, 42.8, 31.7, 22.5, 17.9, 17.8, 12.1; IR (cm^{-1}): 2949, 2893, 2868, 1789, 1737, 1701, 1465, 1388, 1273, 1222, 1201, 1116, 883, 808, 680; MS (ESI): calcd for $C_{22}H_{38}N_2O_9Si$ $[M + H]^+$ 503.2425, found 503.2416.

[(3*S*,4*R*,5*R*)-3-Ethyl-4-methoxycarbonyl-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl]methanol (3n). Colorless oil (651 mg, 98% yield), R_f = 0.40 (2:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −148 (*c* 0.600, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.14−5.11 (m, 1H), 3.88−3.70 (m, 2H), 3.68 (s, 3H), 3.35−3.29 (m, 1H), 3.22 (dd, *J* = 8.7, 4.4 Hz, 1H), 1.96 (br, 1H), 1.89−1.73 (m, 2H), 1.19−1.11 (m, 3H), 1.08−1.03 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 171.6, 82.1, 78.6, 62.4, 51.8, 47.6, 20.8, 18.05, 18.04, 12.3; IR (cm^{-1}): 3444, 2945, 2866, 1739, 1463, 1435, 1386, 1224, 1172, 1055, 1001, 972, 883, 827, 810, 682; MS (ESI): calcd for $C_{17}H_{35}NO_5Si$ $[M + H]^+$ 362.2363, found 362.2355.

[(3*S*,4*R*,5*R*)-4-Methoxycarbonyl-3-methyl-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl]methanol (3o). Colorless oil (448 mg, 92% yield), R_f = 0.39 (2:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −133 (*c* 0.500, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.17−5.15 (m, 1H), 3.93−3.88 (m, 1H), 3.74−3.68 (m, 1H), 3.71 (s, 3H), 3.62 (dq, *J* = 9.3, 6.9 Hz, 1H), 3.23 (dd, *J* = 9.4, 5.2 Hz, 1H), 1.79−1.76 (m, 1H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.19−1.14 (m, 3H), 1.09−1.06 (m, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 171.5, 81.9, 71.4, 61.8, 51.7, 48.4, 17.9, 17.8, 13.1, 12.1; IR (cm^{-1}): 3458, 2945, 2893, 2866, 1743, 1388, 1224, 1001, 883, 827, 810, 684, 665; MS (ESI): calcd for $C_{16}H_{33}NO_5Si$ $[M + H]^+$ 348.22062, found 348.21987.

3-{[(3*S*,4*R*,5*R*)-4-Methoxycarbonyl-3-(2-methoxycarbonylethyl)-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl]methanol (3p). Colorless oil (142 mg, 87% yield), R_f = 0.28 (2:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −136 (*c* 0.550, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.09 (m, 1H), 3.82−3.78 (m, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.42−3.36 (m, 1H), 3.21−3.18 (m, 1H), 2.57−2.41 (m, 2H), 2.29 (s, 1H), 2.17−2.01 (m, 2H), 1.15−1.07 (m, 3H), 1.04−1.00 (m, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.4, 171.1, 82.0, 75.3, 61.9, 51.7, 51.5, 47.1, 31.6, 22.7, 17.76, 17.75, 12.1; IR (cm^{-1}): 3446, 2955, 2926, 2853, 1738, 1733, 1438, 1261, 1202, 1023, 890; MS (ESI): calcd for $C_{19}H_{37}NO_7Si$ $[M + H]^+$ 420.2418, found 420.2412.

[(3*S*,4*R*,5*R*)-3-Ethyl-4-methoxycarbonyl-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl]methyl *p*-Bromobenzoate (3q). Colorless oil (902 mg, 92% yield), R_f = 0.32 (10:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −94.0 (*c* 0.250, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86−7.84 (d, *J* = 8.5 Hz, 2H), 7.59−7.56 (d, *J* = 8.6 Hz, 2H), 5.41−5.38 (m, 1H), 4.53−4.44 (m, 2H), 3.70 (s, 3H), 3.45−3.39 (m, 1H), 3.15−3.12 (dd, *J* = 8.8, 4.6 Hz, 1H), 1.92−1.80 (m, 2H), 1.25−1.13 (m, 3H), 1.10−1.04 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 170.8, 165.5, 131.8, 131.2, 128.7, 128.4, 79.2, 77.9, 64.5, 51.9, 48.4, 20.5, 17.94, 17.93, 12.27, 12.24; IR (cm^{-1}): 2945, 2891, 2866, 1730, 1591, 1463, 1269, 1228, 1118, 1103, 1012, 885, 817, 756, 682; MS (ESI): calcd for $C_{24}H_{38}BrNO_6Si$ $[M + H]^+$ 544.1730, found 544.1724.

[(3*S*,4*R*,5*R*)-4-Methoxycarbonyl-3-methyl-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl]methyl *p*-Bromobenzoate (3r). Colorless oil (333 mg, 98% yield), R_f = 0.31 (10:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −89.0 (*c* 0.900, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.4 Hz, 2H), 7.57−7.55 (m, 2H), 5.40 (dd, *J* = 8.8, 4.9 Hz, 1H), 4.54−4.45 (m, 2H), 3.72 (m, 1H), 3.71−3.68 (m, 1H), 3.10 (dd, *J* = 9.4, 5.5 Hz, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.20−1.15 (m, 3H), 1.09−1.05 (m, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 170.8, 165.6, 131.9, 131.3, 128.7, 128.5, 79.1, 70.9, 64.2, 52.0, 49.5, 18.0, 17.9, 13.1, 12.1; IR (cm^{-1}): 2954, 2893, 2866, 1728, 1591, 1463, 1269, 1228, 1118, 827, 813, 682; MS (ESI): calcd for $C_{23}H_{36}BrNO_6Si$ $[M + H]^+$ 530.1574, found 530.1568.

3-{[(3*S*,4*R*,5*R*)-4-Methoxycarbonyl-3-(2-methoxycarbonylethyl)-*N*-triisopropylsilyloxy-2-isoxazolidin-5-yl]methyl *p*-Bromobenzoate (3s). Colorless oil (244 mg, 94% yield), R_f = 0.41 (5:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −81.0 (*c* 0.500, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 5.35 (q, *J* = 4.4 Hz, 2H), 4.48−4.38 (qd, *J* = 12.2, 3.5 Hz, 2H), 3.66 (s, 3H), 3.60 (s, 3H), 3.52 (q, *J* = 7.4 Hz, 1H), 3.12 (dd, *J* = 8.6, 4.4 Hz, 2H), 2.57−2.42 (m, 2H), 2.24−2.00 (m, 2H), 1.19−1.07 (m, 3H), 1.04−1.00 (m, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 173.4, 170.5, 165.5, 131.8, 131.2, 128.5, 128.4, 79.3, 74.8, 64.3, 52.0, 51.6, 48.0, 31.5, 22.6, 17.88, 17.87, 12.1; IR (cm^{-1}): 2948, 2925, 2896, 2867, 1738, 1722, 1717, 1591, 1436, 1398, 1383, 1366, 1267, 1173, 1124, 1102, 1069, 1012, 884, 817, 756, 682, 469; MS (ESI): calcd for $C_{26}H_{40}BrNO_8Si$ $[M + H]^+$ 602.1785, found 602.1775.

3-[(5*R*)-3-Ethyl-2-isoxazolin-5-yl]carbonyl-2-oxazolidinone (4a). White solid (378 mg, 89% yield), mp 121−122 °C, ee = 90%, R_f = 0.30 (1:3 hexanes/AcOEt). $[\alpha]_D^{20}$ = −139 (*c* 0.500, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.92 (dd, *J* = 11.4, 6.1 Hz, 1H), 4.51−4.47 (m, 2H), 4.07−4.01 (m, 2H), 3.36 (dd, *J* = 17.3, 11.4 Hz, 1H), 3.15 (dd, *J* = 17.3, 6.1 Hz, 1H), 2.40−2.34 (m, 2H), 1.17 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.5, 159.3, 153.3, 76.5, 63.0, 42.5, 40.6, 20.8, 10.7; IR (cm^{-1}): 1778, 1770, 1699, 1475, 1388, 1367, 1274, 1266, 1118, 1039, 979, 914, 856, 759, 684; MS (ESI): calcd for $C_9H_{12}N_2O_4$ $[M + H]^+$ 213.0875, found 213.0874; HPLC (Daicel AD-H column, *n*-hexane:*i*-PrOH = 75:25, Flow rate = 1 mL/min, λ = 210 nm.): t_{major} = 18.4 min, t_{minor} = 25.5 min.

3-[(5*R*)-3-Methyl-2-isoxazolin-5-yl]carbonyl-2-oxazolidinone (4b). White solid (342 mg, 86% yield), mp 144−145 °C, ee = 88%, R_f = 0.30 (1:3 hexanes/AcOEt). $[\alpha]_D^{20}$ = −132 (*c* 0.500, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.93 (dd, *J* = 11.4, 6.0 Hz, 1H), 4.51−4.47 (m, 2H), 4.08−4.01 (m, 2H), 3.40−3.32 (m, 1H), 3.19−3.13 (m, 1H), 2.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.5, 154.8, 153.3, 76.7, 63.0, 42.5, 42.3, 12.6; IR (cm^{-1}): 1761, 1714, 1477, 1444, 1394, 1278, 1234, 1213, 1128, 908, 875, 758, 725, 704; MS (ESI): calcd for $C_8H_{10}N_2O_4$ $[M + H]^+$ 199.0719, found 199.0726; HPLC (Daicel AD-H column, *n*-hexane:*i*-PrOH = 80:20, Flow rate = 1 mL/min, λ = 210 nm.): t_{major} = 31.9 min, t_{minor} = 40.4 min.

[(5*R*)-3-Methyl-2-isoxazolin-5-yl]methanol.[19] The title compound was obtained from **4b** by reduction with $NaBH_4$. Comparison of the specific rotation confirmed the absolute configuration was (*R*). $[\alpha]_D^{20}$ = −158 (*c* 0.250, $CHCl_3$); lit. $[\alpha]_D^{27}$ = −170 (*c* 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.65−4.59 (m, 1H), 3.71 (dd, *J* = 12.1, 2.9 Hz, 1H), 3.53 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.94 (dd, *J* = 17.1, 10.6 Hz, 1H), 2.80 (dd, *J* = 17.0, 7.6 Hz, 1H), 2.66 (s, 1H), 1.95 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 156.0, 80.3, 63.5, 40.0, 13.0.

3-[(5*R*)-3-Allyl-2-isoxazolin-5-yl]carbonyl-2-oxazolidinone (4c). White solid (448 mg, 100% yield), mp 91−92 °C, ee = 90%, R_f = 0.42 (1:3 hexanes/AcOEt). $[\alpha]_D^{20}$ = −141 (*c* 0.500, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.93 (dd, *J* = 11.4, 6.1 Hz, 1H), 5.86−5.76 (m, 1H), 5.22−5.16 (m, 2H), 4.51−4.47 (m, 2H), 4.09−3.98 (m, 2H), 3.35 (dd, *J* = 17.4, 11.5 Hz 1H), 3.19−3.11 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.4, 156.7, 153.3, 131.6, 118.8, 76.7, 63.0, 42.5, 40.5, 31.6; IR (cm^{-1}): 1774, 1718, 1477, 1394, 1274, 1232, 1217, 1124, 1041, 979, 914, 877, 758, 731, 700; MS (ESI): calcd for $C_{10}H_{12}N_2O_4$ $[M + H]^+$ 225.0875, found 225.0877; HPLC (Daicel AD-H column, *n*-hexane:*i*-PrOH = 75:25, Flow rate = 1 mL/min, λ = 210 nm.): t_{major} = 23.3 min, t_{minor} = 29.1 min.

3-[(5*R*)-3-Benzyl-2-isoxazolin-5-yl]carbonyl-2-oxazolidinone (4d). White solid (472 mg, 86% yield), mp 148−149 °C, ee = 92%, R_f = 0.42 (1:3 hexanes/AcOEt). $[\alpha]_D^{20}$ = −126 (*c* 0.500, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34−7.21 (m, 5H), 5.91 (dd, *J* = 11.4, 6.2 Hz, 1H), 4.48−4.43 (m, 2H), 4.07−3.94 (m, 2H), 3.70 (s, 2H), 3.24 (dd, *J* = 17.5, 11.5 Hz, 1H), 3.02 (dd, *J* = 17.5, 6.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.3, 157.1, 153.3, 135.2, 128.9, 128.8, 127.2, 76.8, 62.9, 42.5, 40.3, 33.6; IR (cm^{-1}): 1770, 1716, 1479, 1386, 1273, 1226, 1205, 1114, 1035, 902, 758, 717, 698; MS (ESI): calcd for $C_{14}H_{14}N_2O_4$ $[M + H]^+$ 275.1032, found 275.1028; HPLC (Daicel AD-H column, *n*-hexane:*i*-PrOH = 75:25, Flow rate = 1 mL/min, λ = 210 nm.): t_{major} = 22.4 min, t_{minor} = 32.1 min.

3-[(5*R*)-2-Isoxazolin-5-yl]carbonyl-2-oxazolidinone (4e). White solid (343 mg, 93% yield), mp 122−123 °C, ee = 91%, R_f = 0.35 (1:5 hexanes/AcOEt). $[\alpha]_D^{20}$ = −128 (*c* 0.500, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.18 (s, 1H), 5.95 (dd, *J* = 11.5, 6.2 Hz, 1H), 4.53−4.49 (m, 2H), 4.12−4.00 (m, 2H), 3.46−3.38 (m, 1H), 3.31−3.24 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.1, 153.4, 145.3, 75.2, 63.0, 42.5, 39.4; IR (cm^{-1}): 1795, 1770, 1705, 1473, 1384, 1373, 1292, 1230, 1045, 908, 817, 745; MS (ESI): calcd for $C_7H_8N_2O_4$ $[M + H]^+$ 185.0562, found 185.0554; HPLC (Daicel AD-

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H column, *n*-hexane:*i*-PrOH = 70:30, Flow rate = 1 mL/min, λ = 210 nm.): t_{minor} = 37.2 min, t_{major} = 44.8 min.

3-[(5*R*)-3-(2-Methoxycarbonylethyl)-2-isoxazolin-5-yl]-carbonyl-2-oxazolidinone (4f). White solid (448 mg, 83% yield), mp 95−96 °C, ee = 90%, R_f = 0.36 (1:4 hexanes/AcOEt). $[\alpha]_D^{20}$ = −103 (*c* 0.500, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93 (dd, *J* = 11.4, 6.1 Hz, 1H), 4.50−4.46 (m, 2H), 4.07−3.99 (m, 2H), 3.68 (s, 3H), 3.37 (dd, *J* = 17.4, 11.4 Hz, 1H), 3.18 (dd, *J* = 17.3, 6.1 Hz, 1H), 2.66−2.64 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 172.6, 169.3, 157.0, 153.3, 76.9, 63.0, 51.9, 42.6, 41.2, 30.4, 22.8; IR (cm^{-1}): 1782 1759, 1712, 1475, 1444, 1392, 1344, 1276, 1234, 1211, 1272, 1128, 1039, 977, 962, 904, 873, 769, 721, 702; MS (ESI): calcd for $C_{11}H_{14}N_2O_6$ [M + H]$^+$ 271.0930, found 271.0923; HPLC (Daicel AD-H column, *n*-hexane:*i*-PrOH = 65:35, Flow rate = 1 mL/min, λ = 210 nm.): t_{major} = 24.9 min, t_{major} = 35.7 min.

3-[(5*R*)-3-(3-Oxobutyl)-2-isoxazolin-5-yl]carbonyl-2-oxazolidinone (4g). White solid (437 mg, 86% yield), mp 147−148 °C, ee = 84%, R_f = 0.33 (AcOEt). $[\alpha]_D^{20}$ = −79.8 (*c* 0.500, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.92 (dd, *J* = 11.4, 6.1 Hz, 1H), 4.50−4.46 (m, 2H), 4.06−4.00 (m, 2H), 3.37 (dd, *J* = 17.4, 11.4 Hz, 1H), 3.16 (dd, *J* = 17.4, 6.0 Hz, 1H), 2.84−2.80 (m, 2H), 2.58−2.54 (m, 2H), 2.17 (s, 3H); ^{13}C{ ^{1}H} NMR (100 MHz, $CDCl_3$) δ: 206.9, 169.4, 157.5, 153.3, 76.8, 63.0, 42.5, 41.6, 39.4, 30.0, 21.5; IR (cm^{-1}): 788, 1703, 1627, 1471, 1425, 1384, 1365, 1328, 1269, 1220, 1201, 1157, 1111, 1035, 904, 858, 823, 752, 682, 567; MS (ESI): calcd for $C_{11}H_{14}N_2O_5$ [M + H]$^+$ 255.0981, found 255.0980; HPLC (Daicel AD-H column, *n*-hexane:*i*-PrOH = 50:50, Flow rate = 1 mL/min, λ = 210 nm.): t_{major} = 15.2 min, t_{minor} = 31.5 min.

[(5*R*)-3-Hydroxymethyl-2-isoxazolin-5-yl]carboxylic Acid Methyl Ester (4i). To a solution of **3h** (3.5 g, 7.0 mmol) in MeOH (30 mL) was added *p*-TsOH·H_2O (300 mg, 1.57 mmol, 0.22 equiv) at 0 °C. The mixture was stirred at 0 °C for 2 h before Et_3N (0.5 mL) was added. The mixture was stirred for a further 5 min, then the solvent was removed under high vacuum. The crude product was purified by column chromatography.

3-[(5*R*)-3-Hydroxymethyl-2-isoxazolin-5-yl]carbonyl-2-oxazolidinone (4h). White solid (129 mg, 60% yield), mp 142−143 °C, R_f = 0.36 (AcOEt). $[\alpha]_D^{20}$ = −115 (*c* 0.250, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.02 (dd, *J* = 11.5, 6.1 Hz, 1H), 4.52−4.41 (m, 4H), 4.08−4.03 (m, 2H), 3.48 (dd, *J* = 17.6, 11.5 Hz, 1H), 3.32 (dd, *J* = 17.6, 6.1 Hz, 1H), 2.45 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 169.7, 159.1, 153.9, 77.0, 63.6, 56.2, 42.8, 39.8; IR (cm^{-1}): 3434, 2925, 1747, 1695, 1470, 1393, 1372, 1234, 1039, 1024, 859, 761; MS (ESI): calcd for $C_8H_{10}N_2O_5$ [M + H]$^+$ 215.0668, found 215.0664. Note: **4h** was labile under normal silica gel chromatography conditions.

[(5*R*)-3-Hydroxymethyl-2-isoxazolin-5-yl]carboxylic Acid Methyl Ester (4i). Colorless oil (1.01 g, 90% yield), ee = 75%, R_f = 0.25 (1:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −133 (*c* 0.600, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.06 (dd, *J* = 10.3, 8.0 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 3.37−3.34 (m, 2H), 2.53 (t, *J* = 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 170.8, 158.5, 77.4, 57.4, 52.8, 39.2; IR (cm^{-1}): 3367, 2956, 1741, 1438, 1332, 1290, 1224, 1151, 1029, 864, 752, 648; MS (ESI): calcd for $C_6H_9NO_4$ [M + H]$^+$ 160.0610, found 160.0606.

[(5*R*)-3-Benzoyloxymethyl-2-isoxazolin-5-yl]carboxylic Acid Methyl Ester. The chiral 3-isoxazolinylmethanol **4i** was esterized with benzoyl chloride (2.0 equiv) in CH_2Cl_2 at rt for 1 h using Et_3N (3.0 equiv) and DMAP (1.0 equiv). The corresponding benzoic acid ester was purified by silica gel chromatography and used for HPLC analysis. Colorless oil (242 mg, 92% yield), R_f = 0.40 (1:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 8.16 Hz, 2H), 7.59−7.57 (m, 1H), 7.47−7.43 (m, 2H), 5.13 (s, 2H), 5.11−5.06 (m, 1H), 3.79 (s, 3H), 3.39−3.36 (d, *J* = 9.5 Hz, 2H). HPLC (Daicel AD-H column, *n*-hexane:*i*-PrOH = 95:5, Flow rate = 1 mL/min, λ = 240 nm.): t_{major} = 29.8 min, t_{minor} = 32.8 min.

(3-*p*-Methoxyphenyl-2-isoxazolin-4-yl)methanol (4j). Colorless oil (204 mg, 86% yield), ee = 7%, R_f = 0.45 (1:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −10.0 (*c* 0.250, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.58 (dd, *J* = 8.4, 3.9 Hz, 1H), 4.45 (t, *J* = 9.0 Hz, 1H), 3.89−3.82 (m, 2H), 3.84 (s, 3H), 3.77−3.74 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 161.0, 157.3, 128.5, 120.8, 114.2, 72.6, 61.3, 55.2, 50.9; IR (cm^{-1}): 3422, 2958, 2932, 2875, 1727, 1608, 1516, 1463, 1351, 1256, 1177, 1040, 835, 601; MS (ESI): calcd for $C_{11}H_{13}NO_3$ [M + H]$^+$ 208.0974, found 208.0972.

(3-*p*-Methoxyphenyl-2-isoxazolin-4-yl)methyl *p*-Bromobenzoate. The 4-isoxazolinylmethanol **4j** was esterized with *p*-bromobenzoyl chloride (2.0 equiv) in CH_2Cl_2 at rt for 1 h using Et_3N (3.0 equiv) and DMAP (1.0 equiv). The corresponding *p*-bromobenzoic acid ester was purified by silica gel chromatography and used for HPLC analysis. Colorless oil (139 mg, 99% yield), R_f = 0.57 (2:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.61−4.57 (m, 2H), 4.48−4.43 (m, 1H), 4.29−4.24 (m, 1H), 4.11−4.05 (m, 1H), 3.83 (s, 3H). HPLC (Daicel OJ-H column, *n*-hexane:*i*-PrOH = 40:60, Flow rate = 1 mL/min, λ = 254 nm.): t_{major} = 23.4 min, t_{minor} = 30.3 min.

General Procedures for the Cycloadditions of 2b. A dry 50 mL Schlenk tube was charged with **5a** (139 mg, 0.52 mmol), $Cu(OTf)_2$ (144 mg, 0.4 mmol), and anhydrous CH_2Cl_2 (12 mL). The mixture was stirred at rt for about 2 h until it became clear. Then it was cooled to −15 °C. After stirring for 30 min at −15 °C, **2b** (2.0 mmol) was added, followed by silyl nitronate (3.0 mmol) in anhydrous CH_2Cl_2 (3 mL). The mixture was stirred at −15 °C overnight. The cycloadduct (**3k−3m**) was purified by silica gel chromatography.

To a solution of the cycloadduct (**3k−3m**) in CH_3OH was added $NaBH_4$ (4 equiv) at rt. The mixture was stirred at rt for 2 h before the solvent was removed under high vacuum. The crude product (**3n−3p**) was purified by silica gel chromatography.

To a solution of the reduction product (**3n−3p**) in CH_2Cl_2 was added Et_3N, DMAP, and *p*-BrC_6H_4COCl. The mixture was stirred at rt for 2 h before the solvent was removed under high vacuum. The crude product (**3q−3s**) was purified by silica gel chromatography.

To a solution of the above benzoate (**3q−3s**) in $CHCl_3$ was added *p*-TsOH·H_2O. The mixture was stirred at rt for 4 h before the solvent was removed under high vacuum. The crude product (**4k−4m**) was purified by silica gel chromatography.

[(4*R*,5*R*)-3-Ethyl-4-methoxycarbonyl-2-isoxazolin-5-yl]-methyl *p*-Bromobenzoate (4k). Colorless oil (329 mg, 89% yield), ee = 72%, R_f = 0.42 (2:1 hexanes/AcOEt); $[\alpha]_D^{20}$ = −111 (*c* 2.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 5.20−5.16 (m, 1H), 4.46 (d, *J* = 4.5 Hz, 2H), 3.98−3.96 (d, *J* = 7.1 Hz, 1H), 3.78 (s, 3H), 2.60−2.51 (m, 1H), 2.41−2.31 (m, 1H), 1.87 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 168.4, 165.5, 156.6, 131.9, 131.3, 128.7, 128.4, 80.7, 64.8, 57.2, 53.1, 20.7, 10.8; IR (cm^{-1}): 1737, 1728, 1591, 1483, 1456, 1435, 1379, 1269, 1203, 1174, 1122, 1103, 1068, 1012, 891, 848, 756, 682; MS (ESI): calcd for $C_{15}H_{16}BrNO_5$ [M + H]$^+$ 370.0290, found 370.0289; HPLC (Daicel OJ-H column, *n*-hexane:*i*-PrOH = 70:30, Flow rate = 1 mL/min, λ = 254 nm.): t_{major} = 17.2 min, t_{minor} = 22.1 min.

[(4*R*,5*R*)-4-Methoxycarbonyl-3-methyl-2-isoxazolin-5-yl]-methyl *p*-Bromobenzoate (4l). Colorless oil (285 mg, 80% yield), ee = 70%, R_f = 0.42 (2:1 hexanes/AcOEt); $[\alpha]_D^{20}$ = −103 (*c* 1.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 5.20−5.16 (m, 1H), 4.46 (dd, *J* = 4.4, 1.7 Hz, 2H), 3.92 (d, *J* = 7.4 Hz, 1H), 3.79 (s, 3H), 2.09 (s, 3H); ^{13}C{ ^{1}H} NMR (100 MHz, $CDCl_3$) δ: 168.2, 165.5, 152.1, 132.0, 131.3, 128.7, 128.4, 80.8, 64.8, 58.4, 53.1, 12.1; IR (cm^{-1}): 1739, 1726, 1589, 1436, 1398, 1269, 1205, 1174, 1122, 1103, 1012, 885, 848, 756, 682; MS (ESI): calcd for $C_{14}H_{14}BrNO_5$ [M + H]$^+$ 356.0134, found 356.0130; HPLC (Daicel OJ-H column, *n*-hexane:*i*-PrOH = 70:30, Flow rate = 1 mL/min, λ = 254 nm.): t_{major} = 22.6 min, t_{minor} = 31.6 min.

[(4*R*,5*R*)-4-Methoxycarbonyl-3-(2-methoxycarbonylethyl)-2-isoxazolin-5-yl]methyl *p*-Bromobenzoate (4m). Colorless oil (347 mg, 81% yield), ee = 77%, R_f = 0.31 (2:1 hexanes/AcOEt); $[\alpha]_D^{20}$ = −132 (*c* 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88−7.86 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 5.21−5.17 (m, 1H), 4.45−4.44 (m, 2H), 4.02 (d, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.67

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(s, 3H), 2.80−2.66 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 172.7, 168.2, 165.5, 154.4, 132.0, 131.4, 128.7, 128.3, 80.9, 64.6, 57.7, 53.2, 52.0, 30.4, 22.6; IR (cm^{-1}): 2954, 1737, 1732, 1591, 1485, 1436, 1398, 1271, 1203, 1174, 1122, 1105, 1068, 1012, 889, 848, 756, 682; MS (ESI): calcd for $C_{17}H_{18}BrNO_7$ $[M + H]^+$ 428.0345, found 428.0348; HPLC (Daicel OJ-H column, *n*-hexane:*i*-PrOH = 40:60, Flow rate = 1 mL/min, λ = 254 nm.): t_{major} = 23.9 min, t_{minor} = 32.8 min.

[(5*R*)-3-(2-Tetrahydropyranyloxymethyl)-2-isoxazolin-5-yl]-carboxylic Acid Methyl Ester (4n). To a solution of **4i** (782 mg, 4.9 mmol) in THF (6 mL) was added DHP (1.47 mL, 14.7 mmol, 3 equiv) and PTSA (15 mg, 0.08 mmol, 0.016 equiv) at rt. The mixture was stirred overnight at rt. Then the mixture was concentrated and purified by silica gel column chromatography.

4n: Colorless oil (1.11 g, 93% yield), R_f = 0.37 (2:1 hexanes/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.03 (dd, J = 9.4, 7.6 Hz, 1H), 4.63−4.61 (m, 1H), 4.44 (dd, J = 13.0, 3.8 Hz, 1H), 4.31 (dd, J = 12.9, 5.1 Hz, 1H), 3.83−3.81 (m, 1H), 3.78 (s, 3H), 3.54−3.49 (m, 1H), 3.37−3.33 (m, 2H), 1.80−1.68 (m, 2H), 1.59−1.49 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 170.76, 170.74, 156.43, 156.35, 98.78, 98.76, 62.55, 61.38, 61.34, 52.8, 39.6, 39.5, 30.4, 25.3, 19.39, 19.38; IR (cm^{-1}): 2949, 2870, 1743, 1438, 1354, 1328, 1284, 1217, 1122, 1078,1066, 1033, 970, 904, 869, 815, 754; MS (ESI): calcd for $C_{11}H_{17}NO_5$ $[M + Na]^+$ 266.1004, found 266.1002.

(5*R*)-3-(2-Tetrahydropyranyloxymethyl)-2-isoxazolin-5-yl]-carboxaldehyde (4o). A 50 mL dried Schlenk tube was charged with **4n** (1.01 g, 4.2 mmol) and anhydrous CH_2Cl_2 (10 mL) under a N_2 atmosphere. The mixture was stirred at rt for 10 min and then cooled to −65 °C. DIBAL-H (1.2 M in hexanes, 5.2 mL, 1.5 equiv) was added dropwise via syringe in 30 min. After completion of the addition, the mixture was stirred at −65 °C overnight. Several droplets of MeOH and 10 mL sat. aq. NH_4Cl solution were added. After extraction by CH_2Cl_2, drying over Na_2SO_4, and solvent concentration in vacuum, the crude product was purified by silica gel chromatography.

4o: Colorless oil (644 mg, 73% yield), R_f = 0.31 (1:2 hexanes/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.73−9.72 (m, 1H), 4.99−4.87 (m, 1H), 4.64−4.56 (m, 1H), 4.47−4.29 (m, 2H), 3.85−3.80 (m, 1H), 3.54−3.52 (m, 1H), 3.32−3.25 (m, 1H), 3.16−3.10 (m, 1H), 1.82−1.70 (m, 2H), 1.61−1.53 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 200.1, 199.8, 157.05, 157.00, 98.7, 98.4, 98.2, 98.0, 82.7, 77.5, 62.4, 62.3, 62.2, 62.0, 61.4, 61.2, 61.1, 37.1, 37.0, 36.88, 36.84, 36.5, 30.2, 30.1, 25.1, 25.0, 19.2, 19.1, 19.0; IR (cm^{-1}): 3396, 2941, 2870, 1735, 1456, 1440, 1328, 1201, 1120, 1074, 1033, 970, 904, 869, 815; MS (ESI): calcd for $C_{10}H_{15}NO_4$ $[M + Na]^+$ 236.0899, found 236.0892. Note: **4o** existed as a mixture with its hydrate. NMR signals could not be definitely assigned.

Triphenyltridecylphosphonium Bromide.[20] To a 50 mL round-bottom flask was added 1-bromotridecane (2.29 g, 8.6 mmol), PPh_3 (2.28 g, 8.6 mmol) and toluene (15 mL). After refluxing for 3 days under N_2, the solvent was removed under high vacuum. The crude product was treated with Et_2O (50 mL), and the solids were collected by filtration in a glovebox. The product was dried under high vacuum. White solid (2.57 g, 57% yield). R_f = 0.45 (5:1 CH_2Cl_2/MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87−7.66 (m, 15H), 3.84−3.79 (m, 2H), 1.61−1.60 (m, 4H), 1.21−1.17 (m, 18H), 0.85 (t, J = 6.6 Hz, 3H).

(5*R*)-5-[(*E*)-1-Tetradecenyl]-3-(2-tetrahydropyranyloxymethyl)-2-isoxazoline (4p).[21] To a solution of triphenyltridecylphosphonium bromide (509 mg, 0.97 mmol, 1.1 equiv) in anhydrous THF (4 mL) was added dropwise phenyllithium (1.0 M in Et_2O, 2.9 mL) under a N_2 atmosphere. The solution was stirred at rt for 20 min and then cooled to −78 °C. A solution of the aldehyde **4o** (200 mg, 0.94 mmol) in anhydrous THF (2 mL) was added dropwise. The reaction mixture was stirred overnight, during which time it was allowed to warm to rt slowly. Water was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuum to give the crude product. The crude product was purified by silica gel chromatography.

4p: Colorless oil (257 mg, 71% yield), R_f = 0.48 (5:1 hexanes/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.66−5.59 (m, 1H), 5.51 (dd, J = 10.1, 8.8 Hz, 1H), 5.33 (dd, J = 19.2, 9.7 Hz, 1H), 4.65−4.63 (m, 1H), 4.45−4.43 (m, 1H), 4.31−4.25 (m, 1H), 3.86−3.81 (m, 1H), 3.55−3.50 (m, 1H), 3.23−3.13 (m, 1H), 2.78−2.70 (m, 1H), 2.14−2.02 (m, 2H), 1.81−1.51 (m, 6H), 1.39−1.24 (m, 20H), 0.86 (t, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 156.79, 156.76, 135.24, 135.20, 127.88, 127.86, 98.6, 76.8, 62.5, 62.4, 62.0, 41.68, 41.65, 32.0, 30.5, 30.4, 29.76, 29.73, 29.6, 29.58, 29.56, 29.4, 29.3, 27.7, 25.3, 22.7, 19.4, 19.3, 14.3; IR (cm^{-1}): 2924, 2852, 1465, 1440, 1327, 1261, 1201, 1122, 1087, 1035, 970, 904, 885, 815, 721; MS (ESI): calcd for $C_{23}H_{41}NO_3$ $[M + H]^+$ 380.3165, found 380.3160.

(5*S*)-5-Tetradecyl-3-(2-tetrahydropyranyloxymethyl)-2-isoxazoline (4q). To a solution of **4p** (100 mg, 0.27 mmol) in MeOH (8 mL) was added Pd/C (20 wt %, 20 mg). The mixture was placed under 1 atm of H_2 and well stirred for 30 h. The catalyst was filtered off, and the filtrate concentrated. The crude product was purified by column chromatography.

4q: Colorless oil (86 mg, 86% yield), R_f = 0.48 (4:1 hexanes/AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.64−4.63 (m, 1H), 4.61−4.56 (m, 1H), 4.42 (d, J = 12.6 Hz, 1H), 4.27 (d, J = 12.6 Hz, 1H), 3.87−3.81 (m, 1H), 3.55−3.50 (m, 1H), 3.08 (dd, J = 17.0, 10.2 Hz, 1H), 2.67 (dd, J = 17.0, 8.3 Hz, 1H), 1.83−1.49 (m, 8H), 1.41−1.24 (m, 24H), 0.87 (t, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 156.6, 98.6, 81.1, 62.5, 62.1, 40.5, 35.3, 32.0, 30.5, 29.82, 29.81, 29.7, 29.68, 29.66, 29.5, 29.4, 25.6, 25.4, 22.8, 19.4, 14.2; IR (cm^{-1}): 2924, 2852, 1465, 1440, 1354, 1328, 1201, 1132, 1122, 1078, 1064, 1035, 972, 906, 869, 815; MS (ESI): calcd for $C_{23}H_{43}NO_3$ $[M + H]^+$ 382.3321, found 382.3320.

[(5*S*)-5-Tetradecyl-2-isoxazolin-3-yl]methanol (4r). To a solution of **4q** (156 mg, 0.41 mmol) in MeOH (5 mL) was added PTSA (23 mg, 0.3 equiv) at 0 °C. The mixture was then warmed to rt and stirred for 2 h. The solvent was removed under vacuum, and the crude product was purified by silica gel chromatography.

4r: White solid (100 mg, 82% yield), mp 67−68 °C, R_f = 0.48 (4:1 hexanes/AcOEt); ee = 80%. $[\alpha]_D^{20}$ = −58.0 (c 0.750, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.64−4.56 (m, 1H), 4.38 (d, J = 5.8 Hz, 2H), 3.08 (dd, J = 17.0, 10.2 Hz, 1H), 2.65 (dd, J = 17.0, 8.3 Hz, 1H), 2.41 (t, J = 6.0 Hz, 1H), 1.76−1.66 (m, 1H), 1.56−1.49 (m, 1H), 1.41−1.24 (m, 24H), 0.87 (t, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 158.5, 81.4, 58.6, 40.1, 35.2, 32.0, 29.81, 29.81, 29.78, 29.76, 29.68, 29.64, 29.5, 29.4, 25.6, 22.8, 14.2; IR (cm^{-1}): 3211, 2918, 2846, 1463, 1425, 1055, 1016, 852, 813, 721, 684; MS (ESI): calcd for $C_{18}H_{35}NO_2$ $[M + H]^+$ 298.2746, found 298.2744.

[(5*S*)-5-Tetradecyl-2-isoxazolin-3-yl]methyl Benzoate. The chiral 3-isoxazolinylmethanol **4r** was esterized with benzoyl chloride (2.0 equiv) in CH_2Cl_2 (8 mL) at rt for 1 h using Et_3N (3.0 equiv) and DMAP (1.0 equiv). The corresponding benzoic acid ester was purified by silica gel chromatography and used for HPLC analysis.

^1H NMR (400 MHz, $CDCl_3$) δ: 8.06−8.03 (m, 2H, ArH), 7.61−7.57 (m, 1H), 7.46 (t, J = 7.8 Hz, 2H), 5.10 (s, 2H), 4.69−4.61 (m, 1H), 3.12 (dd, J = 17.0, 10.4 Hz, 1H), 2.69 (dd, J = 17.1, 8.4 Hz, 1H), 1.76−1.69 (m, 1H), 1.59−1.51 (m, 1H), 1.42−1.24 (m, 24H), 0.87 (t, J = 6.5 Hz, 3H). HPLC (Daicel OJ-H column, *n*-hexane:*i*-PrOH = 99:1, Flow rate = 1 mL/min, λ = 240 nm.): t_{major} = 13.0 min, t_{minor} = 15.2 min.

[(5*R*)-3-Ethyl-2-isoxazolin-5-yl)]carboxylic Acid Methyl Ester (4s). To a solution of **4a** (106 mg, 0.5 mmol) in CH_3OH (13 mL) was added Et_3N (0.5 mL) at rt. The mixture was stirred at rt for 5 min before the solvent was removed. The crude product was purified by silica gel chromatography.

4s: Colorless oil (68 mg, 87% yield), R_f = 0.56 (1:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −168 (c 0.750, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.98−4.93 (m, 1H), 3.76 (s, 3H), 3.21−3.18 (m, 2H), 2.36 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 171.1, 159.5, 76.9, 52.7, 40.9, 20.9, 10.8; IR (cm^{-1}): 2976, 1741, 1460, 1438, 1346, 1292, 1217, 1014, 866, 781, 754, 588; MS (ESI): calcd for $C_7H_{11}NO_3$ $[M + H]^+$ 158.0817, found 158.0818.

[(5*R*)-3-Ethyl-2-isoxazolin-5-yl)]methanol (4t).[19] To a solution of **4a** (184 mg, 0.87 mmol) in CH_3OH (10 mL) was added $NaBH_4$ (131 mg, 3.47 mmol, 4 equiv) at −78 °C. The mixture was warmed to rt and stirred overnight. The solvent was removed under vacuum. The

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crude product was purified by silica gel chromatography. The absolute configuration was confirmed to be (*R*) by comparison of the specific rotation.

4t: Colorless oil (95 mg, 85% yield), R_f = 0.53 (AcOEt); $[\alpha]_D^{20}$ = −132 (*c* 1.50, $CHCl_3$); lit. $[\alpha]_D^{20}$ = −160 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.67−4.61 (m, 1H), 3.74 (dd, *J* = 12.1, 3.2 Hz, 1H), 3.54 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.96 (dd, *J* = 16.9, 10.6 Hz, 1H), 2.82 (dd, *J* = 16.9, 7.5 Hz, 1H), 2.34 (s, 1H), 2.34 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 160.7, 80.1, 63.9, 38.5, 21.4, 11.0.

(5*R*)-3-Ethyl-5-(2-tetrahydropyranyloxy)-2-isoxazoline (4u). To a solution of **4t** (144 mg, 1.1 mmol), 3,4-dihydro-2*H*-pyran (0.2 mL, 2.2 mmol) in CH_2Cl_2 (10 mL) was added *p*-TsOH·H_2O (8 mg, 0.04 mmol). The mixture was stirred at rt for 12 h and then treated with sat. aq. $NaHCO_3$ (10 mL). The organic layer was separated, washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Purification by column chromatography gave the title compound.

4u: Yellow oil (229 mg, 97% yield), R_f = 0.51 (1:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.75−4.69 (m, 1H), 4.64−4.62 (m, 1H), 3.87−3.81 (m, 1H), 3.79−3.69 (m, 1H), 3.53−3.48 (m, 2H), 3.03−2.94 (m, 1H), 2.90−2.72 (m, 1H), 2.35 (q, *J* = 7.5 Hz, 2H), 1.81−1.67 (m, 6H), 1.56 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 159.8, 159.7, 99.3, 98.9, 78.5, 78.4, 68.7, 68.4, 62.4, 62.2, 39.4, 39.1, 30.57, 30.50, 25.44, 25.42, 21.3, 19.4, 19.3, 11.03, 11.01; IR (cm^{-1}): 2939, 2870, 1456, 1438, 1201, 1124, 1076, 1033, 970, 906, 869, 815; MS (ESI): calcd for $C_{11}H_{19}NO_3$ [M + Na]$^+$ 236.1263, found 236.1265.

(4*R*,5*R*)-3-Ethyl-4-methyl-5-(2-tetrahydropyranyloxymethyl)-2-isoxazoline (4v).[17d] To a solution of diisopropylamine (210 μL, 1.5 mmol) in anhydrous THF (4 mL) at 0 °C was added *n*-butyllithium in hexane (938 μL, 1.6 M, 1.5 mmol). The solution was stirred at −65 °C for 15 min, and HMPA (524 μL, 3.0 mmol) was added. After 30 min, **4u** (107 mg, 0.5 mmol) in 2 mL of anhydrous THF was added over 15 min. The mixture was stirred for 30 min at −65 °C, and then it was cooled to −78 °C. After 2 h, methyl iodide (125 μL, 2.0 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min and then warmed to rt. The mixture was quenched with sat. aq. NH_4Cl (6 mL) and extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to give a light yellow oil. The crude product was purified by column chromatography (2:1 hexanes/AcOEt) to give the title compound.

4v: Light yellow oil (91 mg, 80% yield), R_f = 0.41 (2:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.65−4.63 (m, 1H), 4.28−4.20 (m, 1H), 3.88−3.74 (m, 2H), 3.57−3.48 (m, 2H), 3.17−3.01 (m, 1H), 2.46−2.37 (m, 1H), 2.24−2.18 (m, 1H), 1.81−1.49 (m, 6H), 1.22−1.14 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 163.5, 163.4, 99.1, 98.8, 85.7, 85.6, 68.0, 67.5, 62.2, 62.1, 46.6, 46.0, 30.48, 30.44, 25.38, 25.37, 19.45, 19.43, 19.3, 19.2, 16.1, 10.6; IR (cm^{-1}): 2939, 2875, 1458, 1381, 1201, 1124, 1076, 1035, 975, 881, 871; MS (ESI): calcd for $C_{12}H_{21}NO_3$ [M + H]$^+$ 228.1600, found 228.1602.

[(4*R*,5*R*)-3-Ethyl-4-methyl-2-isoxazolin-5-yl]methanol (4w). To a solution of **4v** (62 mg, 0.27 mmol) in MeOH (5 mL) was added *p*-TsOH·H_2O (10 mg, 0.05 mmol). After stirring for 30 min at rt, the mixture was concentrated and purified by column chromatography.

4w: Light yellow oil (39 mg, 100% yield, dr = 95:5), R_f = 0.27 (1:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15−4.11 (m, 1H), 3.75 (dd, *J* = 12.1, 3.1 Hz, 1H), 3.57 (dd, *J* = 12.1, 4.6 Hz, 1H), 3.13−3.09 (m, 1H), 2.46 (s, 1H), 2.42−2.33 (m, 1H), 2.23−2.14 (m, 6H), 1.19−1.12 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.2, 87.3, 62.6, 45.2, 19.5, 15.9, 10.5; IR (cm^{-1}): 2972, 2927, 1689, 1477, 1411, 1365, 1247, 1165, 773; MS (EI): calcd for $C_7H_{13}NO_2$ [M] 143.0, found 143.0. Note: The mass spectrum was obtained on a Bruker 320 GC-MS equipment. HRMS data were not available.

(5*R*)-5-(*t*-Butyldimethylsilyloxymethyl)-3-ethyl-2-isoxazoline (4x).[22] To a solution of the **4t** (129 mg, 1.0 mmol) in anhydrous THF (8 mL) cooled in an ice-water bath was added DMAP (12 mg, 0.10 mmol) and Et_3N (309 μL, 2.2 mmol). TBSOTf (505 μL, 2.2 mmol) was then added dropwise, and the solution slowly warmed to ambient temperature. After 1 h, the mixture was cooled in an ice-water bath again, diluted with sat. NH_4Cl (5 mL), and extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography.

4x: Colorless oil (243 mg, 100% yield), R_f = 0.44 (5:1 hexanes/AcOEt). $[\alpha]_D^{20}$ = −47.0 (*c* 0.750, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.62−4.55 (m, 1H), 3.69−3.59 (m, 2H), 2.96−2.82 (m, 2H), 2.34 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 159.6, 79.9, 64.2, 38.7, 25.9, 21.3, 18.3, 11.0, −5.25, −5.28; IR (cm^{-1}): 2963, 2927, 2856, 1462, 1253, 1130, 1097, 970, 873, 837, 777, 669; MS (ESI): calcd for $C_{12}H_{25}NO_2Si$ [M + H]$^+$ 244.1733, found 244.1712.

(4*R*,5*R*)-5-(*t*-Butyldimethylsilyloxymethyl)-3-ethyl-4-methyl-2-isoxazoline (4y).[17d] To a solution of diisopropylamine (210 μL, 1.5 mmol) in anhydrous THF (4 mL) at 0 °C was added *n*-butyllithium in hexane (938 μL, 1.6 M, 1.5 mmol). The solution was stirred at −65 °C for 15 min, and HMPA (524 μL, 3.0 mmol) was added. After 30 min, the TBS ether **4x** (122 mg, 0.5 mmol) in 2 mL of anhydrous THF was added over 15 min. The mixture was stirred for 30 min at −65 °C, and then it was cooled to −78 °C. After 2 h, methyl iodide (125 μL, 2.0 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min and then warmed to ambient temperature, and the mixture was quenched with sat. aq. NH_4Cl (6 mL) and extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to give a light yellow oil. The crude product was purified by column chromatography (5:1 hexanes/AcOEt) to give the title compound.

4y: Light yellow oil (95 mg, 74% yield, dr = 87:13), R_f = 0.51 (5:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12−4.08 (m, 1H), 3.72 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.62 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.14−3.11 (m, 1H), 2.43−2.35 (m, 1H), 2.22−2.16 (m, 1H), 1.20−1.13 (m, 6H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 163.4, 87.2, 63.5, 46.1, 25.9, 19.5, 18.4, 16.5, 10.7, −5.2; IR (cm^{-1}): 2954, 2929, 2856, 1471, 1462, 1255, 1120, 1007, 837, 779; MS (ESI): calcd for $C_{13}H_{27}NO_2Si$ [M + H]$^+$ 258.1889, found 258.1896.

(3*R*,5*R*)-3-Ethyl-3-phenyl-5-(2-tetrahydropyranyloxymethyl)-2-isoxazolidine (6a).[18d] To a solution of **4u** (142 mg, 0.67 mmol) in anhydrous toluene (5 mL) cooled at −78 °C, BF_3·Et_2O (266 μL, 2.08 mmol) was added dropwise, and the resulting solution was stirred for 30 min at −78 °C. A solution of the PhLi (7.9 mL, 0.61 M in Et_2O, 4.82 mmol) was then added over 15 min. After complete consumption of the starting material (typically 2 h, monitored by TLC), the reaction was quenched with 15 mL sat. aq. $NaHCO_3$. The mixture was extracted with AcOEt (3 × 20 mL), and the combined extracts were washed with H_2O (3 × 15 mL), brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (2:1 hexanes/AcOEt) to give the title compound.

6a: Yellow oil (160 mg, 82% yield), R_f = 0.41 (2:1 hexanes/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46−7.22 (m, 5H), 5.60 (s, 1H), 4.69−4.66 (m, 1H), 4.21−4.18 (m, 1H), 3.95−3.81 (m, 2H), 3.64−3.51 (m, 2H), 2.70 (s, 1H), 2.32−2.14 (m, 1H), 1.84−1.80 (m, 4H), 1.56−1.54 (m, 4H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 143.3, 128.1, 126.4, 116.1, 98.8, 71.1, 62.1, 61.8, 30.5, 30.4, 25.4, 25.3, 19.1, 9.4; IR (cm^{-1}): 2937, 2872, 1448, 1350, 1136, 1124, 1076, 1066, 1031, 993, 972, 906, 869, 815, 761, 702; MS (ESI): calcd for $C_{17}H_{25}NO_3$ [M + H]$^+$ 292.1913, found 292.1907.

[(3*R*,5*R*)-3-Ethyl-3-phenyl-2-isoxazolidin-5-yl]methanol (6b). To a solution of **6a** (79 mg, 0.27 mmol) in MeOH (5 mL) was added PTSA (21 mg, 0.11 mmol). After stirring for 12 h at rt, the mixture was concentrated and purified by column chromatography. 46% of **6a** was recovered.

6b: Light yellow oil (25 mg, 45% yield, dr = 90:10), R_f = 0.47 (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45−7.23 (m, 5H), 4.11−4.06 (m, 1H), 3.80 (dd, *J* = 12.1, 2.8 Hz, 1H), 3.64 (dd, *J* = 12.1, 5.1 Hz, 1H), 2.66 (dd, *J* = 12.1,7.9 Hz, 1H), 2.15 (dd, *J* = 12.2, 8.1 Hz,

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1H), 1.92−1.78 (m, 2H), 0.73 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 142.8, 128.3, 126.9, 71.5, 63.7, 42.9, 33.2, 9.4; IR (cm^{-1}): 3388, 2968, 2933, 2877, 1494, 1446, 1381, 1321, 1051, 1031, 954, 873, 815, 761, 702; MS (ESI): calcd for $C_{12}H_{17}NO_2$ $[M + H]^+$ 208.1338, found 208.1332.

[(3*S*,5*R*)-3-Benzyl-3-ethyl-2-isoxazolidin-5-yl]methanol (6c).[18d] A stirred solution of **4u** (128 mg, 0.6 mmol) in anhydrous THF (2 mL) was cooled to −78 °C, and $BF_3{\cdot}Et_2O$ (238 μL, 1.86 mmol) was added dropwise. After 30 min at −78 °C, benzylmagnesium chloride (3.38 mL, 0.57 M in THF, 1.92 mmol) was added to the reaction mixture over 10 min. Following complete consumption of the starting material as indicated by TLC analysis (typically 3 h), excess reagents were quenched with 2 mL H_2O. The reaction mixture was moved to an ice-water bath, acidified by addition of 1 N HCl (1 mL), and stirred with gradual warming to rt. The crude reaction mixture was diluted with 10 mL AcOEt and then extracted with 0.1 N HCl (3 × 20 mL). The combined aqueous extracts were neutralized with sat. aq. K_2CO_3 and extracted with AcOEt (3 × 20 mL). Combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (AcOEt) to give the title compound.

6c: Yellow oil (104 mg, 84% yield), R_f = 0.39 (AcOEt); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32−7.22 (m, 5H), 4.12−4.07 (m, 1H), 3.71 (dd, J = 12.0, 2.9 Hz, 1H), 3.55 (dd, J = 12.0, 5.9 Hz, 1H), 2.91 (d, J = 13.7 Hz, 1H), 2.71 (d, J = 13.8 Hz, 1H), 2.21−2.16 (m, 1H), 1.73−1.68 (m,1H), 1.59−1.57 (m, 1H), 1.46−1.39 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 137.4, 130.6, 128.2, 126.6, 82.3, 68.1, 63.9, 40.4, 40.0, 19.2, 9.0; IR (cm^{-1}): 3394, 2966, 2937, 1494, 1454, 1381, 1091, 1053, 1031, 974, 812, 736, 702; MS (ESI): calcd for $C_{13}H_{19}NO_2$ $[M + H]^+$ 222.1494, found 222.1493.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02035.

Compound **4l** (CIF)
Racemic **3b** (CIF)
^1H and ^{13}C NMR spectra and HPLC charts (PDF)

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Notes

The authors declare no competing financial interest.

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(11) (±)-**3b**: CCDC1051808. See Supporting Information for details.

(12) To the best of our knowledge, using excess Et_3N in methanol to remove the oxazolidinone moiety has never been reported.

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(13) Following the $NaBH_4$ reduction step, PTSA treatment of the 5-hydroxymethyl isoxazolidine **3n**-**3p** in methanol furnished the corresponding 5-hydroxymethyl isoxazoline in a quantitative yield.
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