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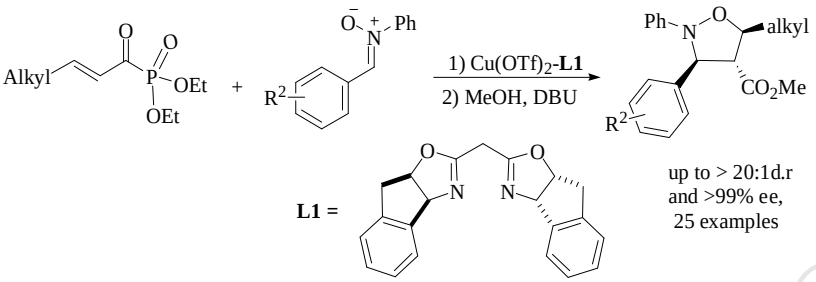

Cu(II)-Catalyzed Enantioselective 1,3-Dipolar Cycloaddition of Nitrones with α, β-Unsaturated Acyl Phosphonates

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Abstract

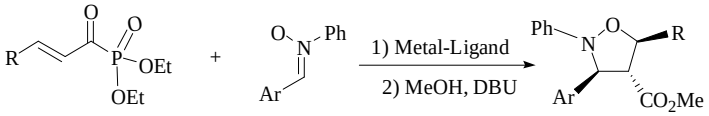
A highly enantioselective 1, 3-dipolar cycloaddition of nitrone with α, β-unsaturated acyl phosphonate was developed for the first time by using a chiral indane-bis(oxazoline)-copper(II) complex. The reaction proceeded smoothly under mild conditions to provide isoxazolidines with multi-stereocenters in good yields with high to excellent diastereo- (>20:1 dr) and enantioselectivities (up to 99% ee). The resulting products were readily converted to multi-functional isoxazolidines or γ-amino alcohol compounds.

Keywords: Dipolar cycloaddition; nitrone; isoxazolidine; α, β-unsaturated acyl phosphonate

1. Introduction

The asymmetric 1, 3-dipolar cycloaddition reactions provide efficient and reliable access to enantiomerically enriched five-membered heterocyclic systems.[1.] In particular, the 1, 3-dipolar cycloaddition of nitrones to electron-deficient alkenes or alkynes afford one powerful method for the construction of highly substituted isoxazolidine rings.[2] which is usually the core framework of many biologically active compounds and readily converted into β- or γ-amino alcohols and others. Since the pioneering works of Scheeren[3] and Jørgensen[4] in 1994, a plenthora of chiral metal complexes and organocatalysts have been successfully developed for the catalytic asymmetric 1, 3-DC of nitrones. Generally, the dipolarophiles are always limited to N-alkenoyl derivatives of oxazolidinone,[5] thiazolidinethione,[6] pyrrolidinone,[7] and pyrazolidinone,[8] as well as alkylidene malonate,[9] pyridinyl N-oxide,[10] α-hydroxy enones,[11] and so on.[12]

On the other hand, α, β-unsaturated acyl phosphonates as a class of useful synthon have been applied in enantioselective Michael addition and cycloaddition reaction.[13] The existing phosphonates have strong electron-withdrawing nature, coordination ability with metal and easy transformation to other functional group. However, to the best of our knowledge, α, β-unsaturated acyl phosphonates as dipolarophiles have never been used in catalytic asymmetric 1,3-DC of nitrones. In our ongoing research and continuing interest in the development of concise and efficient catalytic asymmetric methods,[14] we recently explored a highly diastereo- and enantioselective 1,3-dipolar cycloaddition of nitrones with α, β-unsaturated acyl carboxylates catalyzed by an indane-BOX–Ni(II) complex.[15] As a result, we envisioned that the reaction of α, β-unsaturated acyl phosphonates with nitrones could proceed smoothly to afford optical isoxazolidine products in good diastereo- and enantioselectivities in the presence of appropriate Lewis acid catalyst(**Scheme** 1). We herein report our investigations on this process.



1 **2** **3**

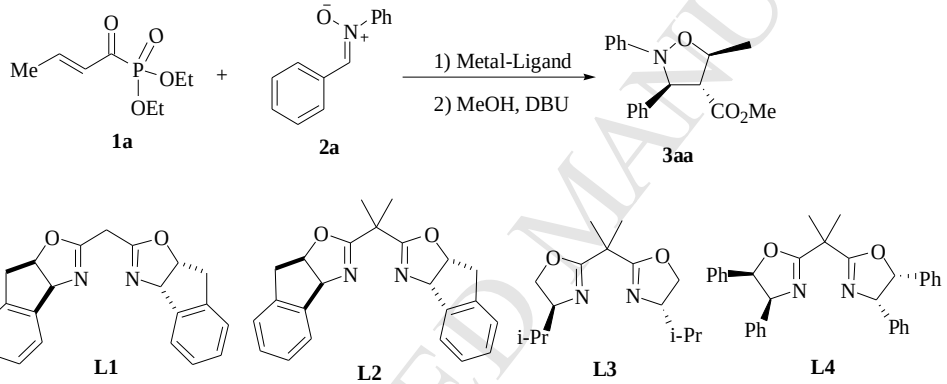
Scheme 1

2. Results and discussion

Initially, *β*-Me substituted unsaturated acyl phosphonate **1a** and nitrone **2a** as model

substrates were used for the condition optimization. The results are illustrated in **Table 1** (detailed results see ST1). The reaction was first carried out in CH_2Cl_2 at 0°C for 12 hours using a 11mol% bisoxazoline **L1** and 10 mol% metal salt as catalyst,[15] in most cases the desired product **3aa** was obtained in moderate yields and *ee* values. Gratifyingly, the indane-BOX **L1**-$Cu(OTf)_2$ complex offered a high yield of product **3aa** with excellent diastereo- and enantioselectivity (entry 4, 82% yield, endo/exo > 20:1, and 96% ee). Subsequently, other bisoxazoline (BOX) ligands were examined, and **L2** also gave rise to almost the same enantioselectivity and reactivity as **L1**, albeit other ligands furnished lower yields or *ee* values (entries 6-8). Moreover, a series of solvents were screened. Notably, the reaction was completed in $CHCl_3$ within 1 hour, and afforded **3aa** in 94% yield with 98% *ee*, exhibiting excellent reactivity and enantioselectivity. The next attempt to increase the temperature to room temperature resulted in a slight decrease in the enantioselectivity to 95% *ee* (entry 14). Pleasingly, the catalyst loading could be reduced to 5mol% without any loss of the stereoselectivity and reactivity (entry 15, detailed screening results see ST1). Therefore, the optimal reaction condition was identified as following: 5 mol% **L1**-$Cu(OTf)_2$, $CHCl_3$ as solvent and 0°C.

Table 1. Optimization of the reaction conditions.[a]



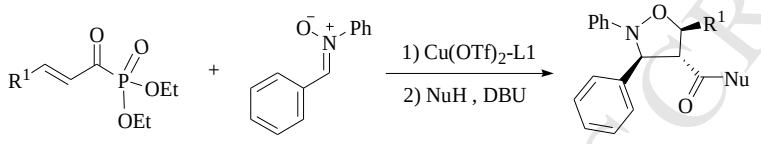
Entry	Metal	Ligand	Solvent	Yield(%)[b]	ee (%)[c]
1	$Ni(ClO_4)_2 \cdot 6H_2O$	**L1**	DCM	39	33
2	$Mg(ClO_4)_2 \cdot 6H_2O$	**L1**	DCM	51	31
3	$Cu(ClO_4)_2 \cdot 6H_2O$	**L1**	DCM	71	87
4	$Cu(OTf)_2$	**L1**	DCM	82	96
5	$Zn(OTf)_2$	**L1**	DCM	53	56
6	$Cu(OTf)_2$	**L2**	DCM	78	96
7	$Cu(OTf)_2$	**L3**	DCM	77	57
8	$Cu(OTf)_2$	**L4**	DCM	77	35
9	$Cu(OTf)_2$	**L1**	$CHCl_3$	94	98
10	$Cu(OTf)_2$	**L1**	DCE	80	95
11	$Cu(OTf)_2$	**L1**	AcOEt	84	97
12	$Cu(OTf)_2$	**L1**	Toluene	45	96
13	$Cu(OTf)_2$	**L1**	THF	74	97
14[d]	$Cu(OTf)_2$	**L1**	$CHCl_3$	95	95
15[e]	$Cu(OTf)_2$	**L1**	$CHCl_3$	94	98

[a] Unless otherwise noted, reactions were conducted with Ligand–metal (1.1 :1, 10 mol%), **1a** (0.3 mmol), and **2a** (0.25 mmol) in solvent (2.0 mL) at 0°C for 1~12h. [b] Isolated yields. [c] Unless otherwise stated, *dr* > 20:1, as

determined by ^{1}H NMR spectroscopy and chiral HPLC. [d] at rt. [e] 5 mol% **L1**-Cu(OTf)$_2$.

With the optimized condition in hand, we next investigated the scope of unsaturated acyl phosphonates in this reaction, as shown in **Table 2**. Various *β*-alkylated unsaturated acyl phosphonates were evaluated. All the reactions proceeded to completion within 1 hour, giving the cycloadducts **3** in high yields with excellent enantioselectivities (entries 1-4). Unfortunately, in the case of *β*-phenyl substituted unsaturated acyl phosphonate the reaction didn't occurred, even prolonging the reaction time to 48h and elevating the reaction temperature to rt (entry 5). Moreover, other nucleophiles including ethanol, benzyl alcohol, and *p*-Bromobenzylamine were examined, more higher reactivity and equal excellent enantioselectivity were exhibited (entries 6-8).

Table 2. **The scope of unsaturated acyl phosphonates and nucleophiles.**



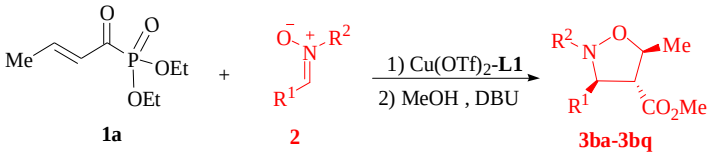
1 **2a** **3ab-3ai**

Entry	**R^1**	NuH	Time(h)	Yield (%)[b]	Ee (%)[c]
1	Et	MeOH	1	87(**3ab**)	98
2	*n*-Pr	MeOH	1	90(**3ac**)	99
3	*iso*-Pr	MeOH	1	82(**3ad**)	98
4	*n*-Hexyl	MeOH	1	94(**3ae**)	>99
5	Ph	MeOH	48	-(**3af**)	-
6	Me	EtOH	1	95(**3ag**)	97
7	Me	BnOH	1	92(**3ah**)	96
8	Me	*p*-BrC$_6$H$_4$NH$_2$	1	93(**3ai**)	95

[a] Unless otherwise noted, reactions were performed with **L1**–Cu(OTf)$_2$ (1.1 :1, 5 mol%), **1** (0.3 mmol), and **2a** (0.25 mmol) in $CHCl_3$ (2.5 mL) at 0□ for the indicated time. [b] Yields of isolated products. [c] The *ee* value was determined by chiral HPLC analysis, only one diastereomer was detected by ^{1}H NMR.

Next, the substrate scope was further extended by variation of nitrones, as summarized in **Table 3**. A series of different substituted phenyl group **2b-n** were first investigated. In most cases the reaction was completed within 1 h, and afforded the desired products **3ba~na** in good to excellent yields. Moreover excellent diastereo- and enantio- selectivity was observed for almost all tested substrates (>20:1 *dr*, 93-98%*ee*, entries 1~13). However, only 2-methoxyl phenyl substituted substrate **2la** afforded one couple of diastereomers with 16:9 dr value (93% *ee* for major isomer, and 71% *ee* for minor isomer, respectively). Furthermore, other aryl substituted nitrones including 2-naphthyl and 2-furyl group were also suitable substrates, giving the adducts in 97% ee values. Even styryl group was also well tolerated in this reaction, leading to **3qa** in good yield with 95% *ee* value (entry 16). Unfortunately, N-phenyl nitrone with methyl group and N-methyl nitrone as substrates the reaction didn't occurred even with an increase of the reaction temperature to rt for 72 h(entries 17 and 18).

Table 3. **The scope of nitrones.**[a]



Entry	R^1	R^2	Time(h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	4-MeC_6H_4	Ph	1	82(**3ba**)	>20:1	98
2	4-MeOC_6H_4	Ph	1	87(**3ca**)	>20:1	96
3	4-Cl C_6H_4	Ph	1	80(**3da**)	>20:1	98
4	4-Br C_6H_4	Ph	1	75(**3ea**)	>20:1	98
5	4-CNC_6H_4	Ph	1	93(**3fa**)	>20:1	98
6	4-NO_2 C_6H_4	Ph	1	96(**3ga**)	>20:1	97
7	3-Me C_6H_4	Ph	1	91(**3ha**)	>20:1	98
8	3-F C_6H_4	Ph	1	86(**3ia**)	>20:1	98
9	3-Br C_6H_4	Ph	1	75(**3ja**)	>20:1	96
10	3-CF_3 C_6H_4	Ph	1	60(**3ka**)	>20:1	96
11[d]	2-MeO C_6H_4	Ph	10	66(**3la**)	16:9	93% (major isomer)
12	2-F C_6H_4	Ph	1	91(**3ma**)	>20:1	94
13	3,4-di-Br C_6H_4	Ph	1	80(**3na**)	>20:1	97
14	2-naphthyl	Ph	1	95(**3oa**)	>20:1	97
15	2-furyl	Ph	1	88(**3pa**)	>20:1	97
16	C_6H_5-CH=CH-	Ph	10	64(**3qa**)	>20:1	95
17	Me	Ph	72	-	-	-
18	Ph	Me	72	-	-	-

[a] Unless otherwise noted, reactions were performed with **L1**–Cu(OTf)$_2$ (1.1 :1, 5 mol%), **1a** (0.3 mmol), and **2** (0.25 mmol) in $CHCl_3$ (2.5 mL) at 0□ for the indicated time. [b] Isolated yields. [c] Only one diastereomer was detected by ^{1}H NMR except for special statement. [d] The *ee* value was determined by chiral HPLC analysis.

The absolute configuration of the cycloadduct **3ai** was determined to be (**3*S***, **4*R***, **5*S***) by X-ray diffraction analysis, as illustrated in **Fig 1.**[16] The absolute configuration of other cycloadducts were also assigned by analogy. Based on the observed stereochemistry in this study we believe that the dipolarophile (unsaturated acyl phosphonate) firstly coordinates to the Cu(II)-BOX complex through a 1, 4-coordinate pattern and is hence activated, as illustrated in **Fig 1.** Subsequently nitrone preferentially approaches the dipolarophile from the *Re*-face of the double bond due to the steric hindrance between the *Si*-face indane moiety of ligand and the C-aryl group of nitrone, leading to the major(**3*S***, **4*R***, **5*S***)-configured isoxazolidine product. The detailed mechanism remains to be further investigated.

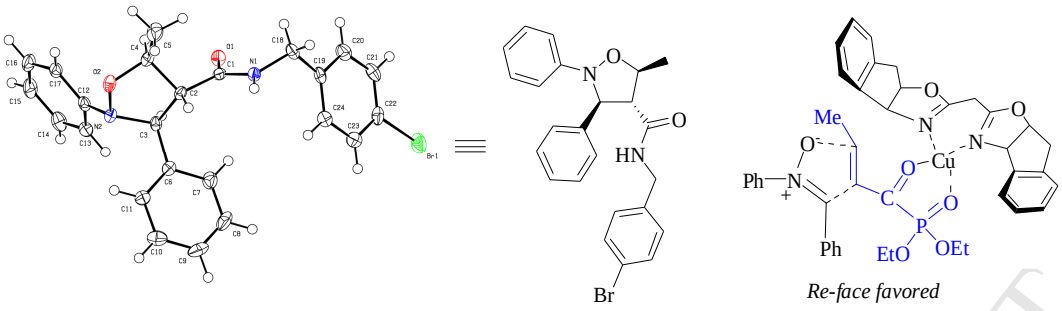
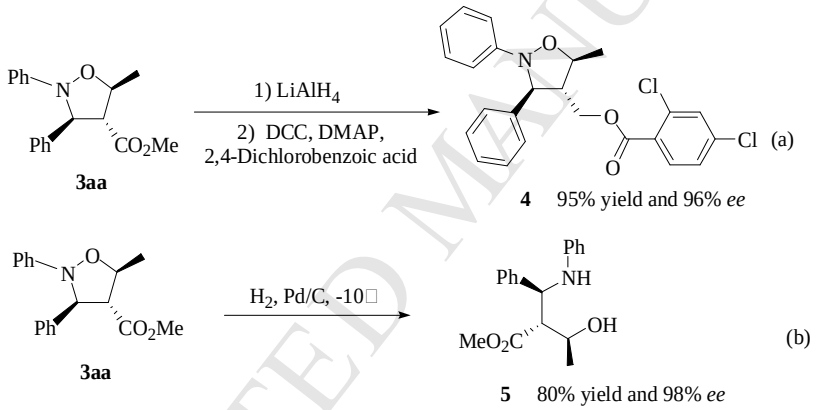


Fig.1 The absolute configuration of **3ai** and the possible transition model

To show the practicality of the present method, the resulting isoxazolidines could be further transformed to useful compounds. For example, treatment of **3aa** (98%ee) with $LiAlH_4$ led to the formation of corresponding alcohol, then which was reacted with 2, 4-dichlorobenzoic acid in the presence of DCC/DMAP to afford the corresponding ester **4** in almost quantitative yield (**Scheme 2**(a)).[17] When **3aa** was hydrogenated by Pd/C in AcOEt, chiral γ-amino alcohol **5** was obtained in good yield without any loss of diastereo- and enantioselectivity (**Scheme 2**(b)).[18]



Scheme 2. The transformation of isoxazolidine 3aa

3. Conclusion

In summary, we have developed an asymmetric 1, 3-dipolar cycloadditions of nitrones with unsaturated acyl phosphonate for the first time. Under the catalysis of indane-bis(oxazoline)-$Cu(OTf)_2$ the reaction can proceed to completion within 1h in most cases, providing the isoxazolidines in high to excellent diastereo- and enantiosectivities. N-phenyl substitution in nitrone is important for the reactivity and stereoselectivity of the reaction. The synthetic application of this methodology was illustrated by the facile transformation of the cycloadduct into other isoxazolidine derivative and amino alcohol with maintained enantiopurity. This work well complements our previous report in the chiral Lewis acid-catalyzed asymmetric 1, 3-dipolar cycloaddition of nitrones.[15]

4. Experimental Section

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX300 instrument in $CDCl_3$

solution with TMS as internal standard. Optical rotations were measured on a PerkineElmer 341 LC polarimeter. Infrared spectra were obtained on a Nicolet AVATAR 330 FT-IR spectrometer. The enantiomeric excesses of (R)- and (S)-enantiomer were determined by HPLC analysis over a chiral column((Daicel Chiralcel OD-H, AD-H or AS-H; eluted with hexane/isopropyl alcohol; UV detector). All anhydrous solvents were purified and dried by standard techniques before use. The *β*-alkylated unsaturated acyl phosphontes were prepared according to the reported methods in the literature.[19] The *C*-aryl-*N*-phenyl nitrones were synthesized according to the literature's procedure.[17]

4.2 General procedure for the asymmetric 1,3-dipolar cycloaddition of unsaturated acyl phosphonates to nitrones

To a solution of ligand **L1** (0.011 mmol) in chloroform (1.0 mL) was added $Cu(OTf)_2$ (0.01 mmol) under nitrogen. The reaction mixture was stirred for 1h at room temperature before unsaturated acyl phosphonate **1** (0.25 mmol) was added. After stirring for15 min. the resulting mixture was cooled to 0^oC, and then a solution of nitrone **2** (0.2 mmol) in chloroform (1.0 mL) was added. The reaction proceeded to completion at 0^oC (monitored by TLC), alcohol or amine (0.5 mL) and DBU (100μL) were directly added to the reaction mixture, and stirred for another 1 hour at room temperature. Saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL × 3). The organic layer was combined, and washed (brine), dried(anhydrous Na_2SO_4), and concentrated to give the crude product, which was purified by flash column chromatography on silica gel (eluted with ethyl acetate/petroleum ether (1/20, v/v) to afford the desired product **3**.

(3*S*, 4*R*, 5*S*)-Methyl 5-methyl-2, 3-diphenylisoxazolidine-4-carboxylate (**3aa**)

Colorless oil, 94% yield. $[\alpha]_D^{20}$ =–103.91 (c = 0.66, CH_2Cl_2); 98% *ee*, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 4.52 min, t (minor) = 5.90 min]; IR(cm^{-1}): 2953, 2925, 1736, 1598, 1487, 1198, 1030, 755, 697. ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.43 – 7.22 (m, 5H), 7.04 – 6.90 (m, 3H), 5.17 (d, *J* = 7.0 Hz, 1H), 4.44 (dq, *J* = 9.1, 6.0 Hz, 1H), 3.70 (d, *J* = 5.5 Hz, 3H), 3.20 (dd, *J* = 9.1, 7.1 Hz, 1H), 1.52 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.51, 151.37, 141.50, 128.64, 128.57, 127.36, 126.03, 121.19, 113.64, 77.32, 73.26, 65.24, 52.08, 17.12. ESI-HRMS: Calcd for $C_{18}H_{20}NO_3^+$ ([M+H^+]): 298.1438; Found: 298.1439.

(3*S*, 4*R*, 5*S*)-Methyl-5-ethyl-2,3-diphenylisoxazolidine-4-carboxylate (**3ab**)

Colorless oil, 87% yield. $[\alpha]_D^{20}$ = –102.79 (c = 0.90, CH_2Cl_2); 98% ee, determined by HPLC

analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 4.38 min, t (minor) = 6.45 min]; IR(cm^{-1}): 2925, 2848, 1736, 1597, 1487, 1265, 755, 737, 698. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.41 – 7.33 (m, 2H), 7.32 – 7.19 (m, 3H), 7.01 – 6.88 (m, 3H), 5.12 (d, *J* = 6.8 Hz, 1H), 4.29 (td, *J* = 7.7, 4.8 Hz, 1H), 3.68 (s, 3H), 3.22 (dd, *J* = 8.6, 6.9 Hz, 1H), 1.93 – 1.75 (m, 2H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.06, 151.41, 141.57, 128.76, 128.71, 127.48, 126.17, 121.41, 113.98, 82.54, 73.45, 63.49, 52.18, 25.35, 10.12. ESI-HRMS: Calcd for $C_{19}H_{22}NO_3^+$ ([M+H^+]): 312.1594; Found: 312.1591.

(3*S*, 4*R*, 5*S*)-Methyl-2,3-diphenyl-5-propylisoxazolidine-4-carboxylate (**3ac**)

Colorless oil, 90% yield. $[\alpha]_D^{20}$ = –83.22 (c = 0.59, CH_2Cl_2); 99% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm; t (major) = 4.72 min, t (minor) = 10.15 min]; IR(cm^{-1}): 2930, 2849, 1737, 1598, 1488, 1244, 1197, 1174, 755, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 7.26 – 7.20 (m, 2H), 7.01 – 6.86 (m, 3H), 5.11 (d, *J* = 6.9 Hz, 1H), 4.38 – 4.28 (m, 1H), 3.69 (s, 3H), 3.26 – 3.16 (m, 1H), 1.84 – 1.73 (m, 2H), 1.66 – 1.51 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.01, 151.45, 141.59, 128.76, 128.70, 127.48, 126.16, 121.36, 113.89, 81.27, 73.38, 63.97, 52.18, 34.39, 19.33, 13.84. ESI-HRMS: Calcd for $C_{20}H_{24}NO_3^+$ ([M+H^+]): 326.1751; Found: 326.1748.

(3*S*, 4*R*, 5*S*)-Methyl-5-isopropyl-2, 3-diphenylisoxazolidine-4-carboxylate (**3ad**)

Colorless oil, 82% yield. $[\alpha]_D^{20}$ = –83.33 (c = 0.63, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, n-hexane/i-PrOH = 90:10, 0.5 mL/min, 220 nm; t (major) = 8.14 min, t (minor) = 9.88 min]; IR(cm^{-1}): 2960, 2920, 1738, 1598, 1488, 1260, 1198, 1028, 755, 697. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 2H), 7.42 – 7.17 (m, 5H), 7.01 – 6.88 (m, 3H), 5.05 (d, *J* = 6.5 Hz, 1H), 4.27 – 4.11 (m, 1H), 3.67 (s, 3H), 3.28 (dd, *J* = 8.3, 6.6 Hz, 1H), 2.03 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.78, 151.24, 141.46, 128.73, 128.71, 127.50, 126.14, 121.51, 114.17, 86.37, 74.12, 61.72, 52.13, 30.55, 18.61, 18.30. ESI-HRMS: Calcd for $C_{20}H_{24}NO_3^+$ ([M+H^+]): 326.1751; Found: 326.1746.

(3S, 4R, 5S)-Methyl-5-hexyl-2,3-diphenylisoxazolidine-4-carboxylate (**3ae**)

Colorless oil, 94% yield. $[\alpha]_D^{20}$ = –75.90 (c = 0.98, CH_2Cl_2); 99% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, n-hexane/i-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major)

= 4.16 min, t (minor) = 5.77 min]; IR(cm^{-1}): 2930, 2857, 1738, 1598, 1488, 1197, 1171, 754, 725, 697, 674. ^{1}H NMR (300 MHz, DMSO) δ 7.55 – 7.48 (m, 2H), 7.42 –7.34 (m, 2H), 7.33 – 7.20 (m, 4H), 7.00 – 6.89 (m, 3H), 5.11 (d, *J* = 6.9 Hz, 1H), 4.32 (ddd, *J* = 8.8, 7.5, 5.0 Hz, 1H), 3.70 (s, 3H), 3.21 (dd, *J* = 8.9, 6.9 Hz, 1H), 1.87 – 1.73 (m, 2H), 1.69 – 1.30 (m, 8H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.03, 151.48, 141.60, 128.78, 128.72, 127.49, 126.16, 121.36, 113.87, 81.49, 73.42, 63.96, 52.20, 32.30, 31.51, 29.02, 25.96, 22.40, 13.90. ESI-HRMS: Calcd for $C_{23}H_{30}NO_3^+$ ([M+H^+]): 368.222; Found: 368.2217.

(3S, 4R, 5S)-Ethyl-5-methyl-2, 3-diphenylisoxazolidine-4-carboxylate (**3ag**)

Colorless oil, 95% yield. $[\alpha]_D^{20}$ = –94.59 (c = 1.09, CH_2Cl_2); 97% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, n-hexane/i-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 8.66 min, t (minor) = 10.57 min]; IR(cm^{-1}): 2987, 1732, 1598, 1488, 1267, 1186, 1029, 754, 738, 697. ^{1}H NMR (300 MHz, CDCl3) δ 7.58 –7.48 (m, 2H), 7.42 – 7.18 (m, 5H), 7.04 – 6.86 (m, 3H), 5.15 (d, J = 7.0 Hz, 1H), 4.41 (dt, J = 11.8, 6.0 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.23 – 3.09 (m, 1H), 1.50 (d, J = 5.9 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 170.17, 151.57, 141.72, 128.77, 128.68, 127.46, 126.19, 121.30, 113.81, 77.49, 73.41, 65.49, 61.17, 17.30, 13.94. ESI-HRMS: Calcd for $C_{19}H_{22}NO_3^+$ ([M+H^+]): 312.1594; Found: 312.1591.

(3S, 4R, 5S)-Benzyl-5-methyl-2,3-diphenylisoxazolidine-4-carboxylate (**3ah**)

Colorless oil, 92% yield. $[\alpha]_D^{20}$ = –87.5 (c = 0.84, CH_2Cl_2); 96% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, n-hexane/i-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 5.44 min, t (minor) = 6.88 min]; IR(cm^{-1}): 2918, 1734, 1598, 1454, 1265, 1176, 1029, 754, 738, 696. ^{1}H NMR (300 MHz, CDCl3) δ 7.52 – 7.44 (m, 2H), 7.38 – 7.17 (m, 10H), 7.01 – 6.87 (m, 3H), 5.15 (d, J = 7.0 Hz, 1H), 5.12 (s, 2H), 4.44 (dq, J = 9.0, 6.0 Hz, 1H), 3.22 (dd, J = 9.0, 7.0 Hz, 1H), 1.47 (d, J = 6.0 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ 170.07, 151.49, 141.56, 135.16, 128.82, 128.71, 128.47, 128.29, 128.00, 127.50, 126.21, 121.39, 113.86, 77.52, 73.51, 66.92, 65.48, 17.32. ESI-HRMS: Calcd for $C_{24}H_{24}NO_3^+$ ([M+H^+]): 374.1751; Found: 374.1746.

(3S, 4R, 5S)-N-(4-bromobenzyl)-5-methyl-2, 3-diphenylisoxazolidine-4-carboxamide (3ai)

White solid, 174-176 oC, 93% yield. $[\alpha]_D^{20}$ = –76.27 (c = 0.51, CH_2Cl_2); 95% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, n-hexane/i-PrOH = 80:20, 1.0 mL/min, 254 nm; t (minor) = 4.99 min, t (major) = 6.00 min]; IR(cm^{-1}): 3290, 2920, 2336, 1646, 1564, 1487, 1070, 792, 750, 696. ^{1}H NMR (300 MHz, CDCl3) δ 7.44 –7.37 (m, 4H), 7.36 –7.27 (m, 3H), 7.26 –7.17

(m, 2H), 7.01 – 6.96 (m, 2H), 6.94 – 6.87 (m, 3H), 5.84 (t, J = 5.7 Hz, 1H), 4.97 (d, J = 8.3 Hz, 1H), 4.44 (dq, *J* = 9.4, 6.0 Hz, 1H), 4.35 (dd, *J* = 14.9, 6.2 Hz, 1H), 4.20 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.80 (dd, *J* = 9.3, 8.4 Hz, 1H), 1.38 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.42, 152.02, 141.20, 136.61, 131.63, 129.18, 128.87, 128.76, 127.76, 126.12, 121.45, 121.37, 113.89, 77.87, 74.98, 68.18, 42.86, 16.49. ESI-HRMS: Calcd for $C_{24}H_{24}BrN_2O_2^+$ ([M+H$^+$]): 451.1016; Found: 451.1016.

(3S, **4R**, **5S)-Methyl-5-methyl-2-phenyl-3-(*p*-tolyl)isoxazolidine-4-carboxylate** (**3ba**)

Colorless oil, 82% yield. $[\alpha]_D^{20}$ = –98.03 (c = 0.92, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 5.37 min, t (minor) = 8.97 min]; IR(cm^{-1}): 2952, 2926, 1737, 1598, 1488, 1198, 1177, 1030, 820, 758, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.27 – 7.15 (m, 4H), 7.01 – 6.97 (m, 3H), 5.09 (d, *J* = 7.2 Hz, 1H), 4.41 (dq, *J* = 9.1, 6.0 Hz, 1H), 3.68 (s, 3H), 3.16 (dd, *J* = 9.1, 7.2 Hz, 1H), 2.35 (s, 3H), 1.50 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.70, 151.59, 138.59, 137.18, 129.38, 128.74, 126.12, 121.29, 113.87, 77.40, 73.32, 65.45, 52.15, 20.92, 17.29. ESI-HRMS: Calcd for $C_{19}H_{22}NO_3^+$ ([M+H$^+$]): 312.1594; Found: 312.1590.

(3S, **4R**, **5S)-Methyl-3-(4-methoxyphenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate** (**3ca**)

Colorless oil, 87% yield. $[\alpha]_D^{20}$ = –94.84 (c = 1.15, CH_2Cl_2); 96% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (minor) = 6.62 min, t (major) = 7.41 min]; IR(cm^{-1}): 2950, 2932, 1736, 1596, 1513, 14888, 1247, 1174, 1031, 834, 758, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 2H), 7.28 – 7.18 (m, 2H), 7.03 – 6.85 (m, 5H), 5.07 (d, *J* = 7.2 Hz, 1H), 4.42 (tt, *J* = 11.9, 5.9 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.15 (dd, *J* = 8.9, 7.4 Hz, 1H), 1.50 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.69, 159.02, 151.57, 133.55, 128.74, 127.41, 121.35, 114.11, 113.95, 77.37, 73.13, 65.44, 55.12, 52.14, 17.33. ESI-HRMS: Calcd for $C_{19}H_{22}NO_4^+$ ([M+H$^+$]): 328.1543; Found: 328.1539.

(3S, 4R, 5S)-Methyl-3-(4-chlorophenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3da**)

White solid, m.p. 45−46 ^{o}C, 80% yield. $[\alpha]_D^{20}$ = –101.26 (c = 0.56, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 5.49 min, t (minor) = 7.44 min]; IR(cm^{-1}): 2953, 2927, 1736, 1598, 1489, 1268, 1222, 1090, 1015, 831, 756, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 2H), 7.37 – 7.30

(m, 2H), 7.28 – 7.19 (m, 2H), 6.99 – 6.87 (m, 3H), 5.12 (d, *J* = 6.9 Hz, 1H), 4.41 (dq, *J* = 9.2, 5.9 Hz, 1H), 3.69 (s, 3H), 3.12 (dd, *J* = 8.9, 7.1 Hz, 1H), 1.49 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.44, 151.21, 140.22, 133.30, 128.86, 127.63, 121.56, 113.81, 77.45, 72.69, 65.29, 52.30, 17.28. ESI-HRMS: Calcd for $C_{18}H_{19}NO_3^+$ ([M+H$^+$]): 332.1048; Found: 332.1051.

(3S, 4R, 5S)-Methyl-3-(4-bromophenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3ea**)

Colorless oil, 75% yield. $[\alpha]_D^{20}$ = –82.79 (c = 0.61, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 11.36 min, t (minor) = 15.99 min]; IR(cm^{-1}): 2921, 2850, 1736, 1597, 1488, 1266, 1199, 1072, 1011, 823, 755, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.44 – 7.37 (m, 2H), 7.29 – 7.20 (m, 2H), 6.99 – 6.89 (m, 3H), 5.11 (d, *J* = 7.0 Hz, 1H), 4.47 – 4.35 (m, 1H), 3.70 (s, 3H), 3.11 (dd, *J* = 9.1, 7.0 Hz, 1H), 1.50 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.41, 151.17, 140.72, 131.81, 128.85, 127.95, 121.56, 121.39, 113.78, 77.44, 72.71, 65.23, 52.30, 17.26. ESI-HRMS: Calcd for $C_{18}H_{19}BrNO_3^+$ ([M+H$^+$]): 376.0543; Found: 376.0540.

(3S, 4R, 5S)-Methyl-3-(4-cyanophenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3fa**)

Colorless oil, 93% yield. $[\alpha]_D^{20}$ = –88.13 (c = 1.12, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 9.81 min, t (minor) = 12.72 min]; IR(cm^{-1}): 2920, 2850, 2228, 1736, 1597, 1488, 1222, 1202, 1021, 840, 760, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 4H), 7.31 – 7.21 (m, 2H), 7.00 – 6.90 (m, 3H), 5.24 (d, *J* = 6.7 Hz, 1H), 4.43 (dq, *J* = 11.9, 5.9 Hz, 1H), 3.72 (s, 3H), 3.11 (dd, *J* = 9.0, 6.8 Hz, 1H), 1.51 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.18, 150.81, 147.18, 132.57, 128.98, 126.99, 121.79, 118.48, 113.67, 111.45, 77.51, 72.56, 65.04, 52.48, 17.22. ESI-HRMS: Calcd for $C_{19}H_{19}N_2O_3^+$ ([M+H$^+$]): 323.139; Found: 323.1385.

(3S, 4R, 5S)-Methyl-5-methyl-3-(4-nitrophenyl)-2-phenylisoxazolidine-4-carboxylate (**3ga**)

Yellow solid, m.p. 71-72 ^{o}C, 96% yield. $[\alpha]_D^{20}$ = – 100.49 (c = 1.03, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 9.91 min, t (minor) = 12.86 min]; IR(cm^{-1}): 2928, 2850, 1736, 1598, 1521, 1488, 1347, 1222, 856, 755, 697. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 – 8.11 (m, 2H), 7.80 – 7.66 (m, 2H), 7.31 – 7.22 (m, 2H), 7.08 – 6.86 (m, 3H), 5.29 (d, *J* = 6.6 Hz, 1H), 4.45 (dq, *J* = 11.9, 5.9 Hz, 1H), 3.73 (s, 3H), 3.13 (dd, *J* = 8.9, 6.8 Hz, 1H), 1.52 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.14, 150.73, 149.15, 147.35, 129.00, 127.15, 123.98, 121.85, 113.69, 77.54, 72.37,

65.04, 52.51, 17.24. ESI-HRMS: Calcd for $C_{18}H_{19}N_2O_5^+$ ([M+H$^+$]): 343.1288; Found: 343.1284.

(3S, 4R, 5S)-Methyl-5-methyl-2-phenyl-3-(*m*-tolyl)isoxazolidine-4-carboxylate (**3ha**)

Colorless oil, 91% yield. $[\alpha]_D^{20}$ = –84.65 (c = 1.14, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 8.20 min, t (minor) = 10.06 min]; IR(cm^{-1}): 2923, 2851, 1737, 1597, 1488, 1436, 1346, 1221, 1176, 1138, 758, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 1H), 7.31 – 7.19 (m, 4H), 7.14 – 7.07 (m, 1H), 7.02 – 6.87 (m, 3H), 5.11 (d, *J* = 7.1 Hz, 1H), 4.41 (dd, *J* = 9.1, 5.9 Hz, 1H), 3.69 (s, 3H), 3.23 – 3.12 (m, 1H), 2.36 (s, 3H), 1.50 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.68, 151.60, 141.58, 138.46, 128.76, 128.57, 128.26, 126.70, 123.25, 121.28, 113.77, 77.47, 73.45, 65.42, 52.17, 21.30, 17.22. ESI-HRMS: Calcd for $C_{19}H_{22}NO_3^+$ ([M+H$^+$]): 312.1594; Found: 312.1591.

(3S, 4R, 5S)-Methyl-3-(3-fluorophenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3ia**)

Colorless oil, 86% yield. $[\alpha]_D^{20}$ = –110.16 (c = 0.63, CH_2Cl_2); 98% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 11.02 min, t (minor) = 12.12 min]; IR(cm^{-1}): 2918, 2849, 1737, 1596, 1487, 1451, 1222, 1139, 1030, 789, 760, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 5H), 7.02 – 6.89 (m, 4H), 5.16 (d, *J* = 6.8 Hz, 1H), 4.47 – 4.35 (m, 1H), 3.71 (s, 3H), 3.15 (dd, *J* = 9.1, 6.9 Hz, 1H), 1.50 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.46, 163.05 (d, *J* = 246.4 Hz), 151.18, 144.40 (d, *J* = 7.0 Hz), 130.27 (d, *J* = 8.2 Hz), 128.88, 121.71 (d, *J* = 2.8 Hz), 121.54, 114.43 (d, *J* = 21.2 Hz), 113.72, 113.20 (d, *J* = 22.5 Hz), 77.49, 72.71 (d, *J* = 1.9 Hz), 65.19, 52.34, 17.23. ESI-HRMS: Calcd for $C_{18}H_{19}FNO_3^+$ ([M+H$^+$]): 316.1343; Found: 316.1340.

(3S, 4R, 5S)-Methyl-3-(3-bromophenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3ja**)

Colorless oil, 75% yield. $[\alpha]_D^{20}$ = – 77.49 (c = 1.04, CH_2Cl_2); 97% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 8.88 min, t (minor) = 9.42 min]; IR(cm^{-1}): 2917, 2849, 1736, 1596, 1488, 1260, 1091, 1019, 796, 755, 694. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 1H), 7.48 – 7.39 (m, 2H), 7.30 – 7.19 (m, 3H), 7.00 – 6.90 (m, 3H), 5.14 (d, *J* = 6.9 Hz, 1H), 4.40 (dq, *J* = 9.2, 6.0 Hz, 1H), 3.70 (s, 3H), 3.14 (dd, *J* = 9.1, 6.9 Hz, 1H), 1.50 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.37, 151.16, 144.13, 130.68, 130.31, 129.22, 128.91, 124.83, 122.88, 121.57, 113.70, 77.52, 72.63, 65.22, 52.36, 17.22. ESI-HRMS: Calcd for $C_{18}H_{19}BrNO_3^+$ ([M+H$^+$]): 376.0543; Found: 376.0543.

(3S,4R,5S)-Methyl-5-methyl-2-phenyl-3-(3-(trifluoromethyl)phenyl)isoxazolidine-4-carboxylate (**3ka**)

Colorless oil, 60% yield. $[\alpha]_D^{20}$ = –80.97 (c = 0.83, CH_2Cl_2); 96% ee, determined by HPLC analysis [Daicel Chiralcel AS-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 6.94 min, t (minor) = 9.98 min]; IR(cm^{-1}): 2919, 2849, 1737, 159, 1489, 1328, 1167, 1125, 1073 1016, 800, 758, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.77 – 7.70 (m, 1H), 7.60 – 7.45 (m, 2H), 7.31 – 7.21 (m, 2H), 7.01 – 6.91 (m, 3H), 5.24 (d, *J* = 6.8 Hz, 1H), 4.44 (dq, *J* = 9.1, 6.0 Hz, 1H), 3.72 (s, 3H), 3.14 (dd, *J* = 9.1, 6.8 Hz, 1H), 1.51 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.33, 151.11, 142.91, 131.11 (q, *J* = 32.3 Hz), 129.60, 129.22, 128.93, 124.39 (q, *J* = 3.7 Hz), 123.88 (dd, *J* = 544.8, 272.5 Hz), 123.00 (q, *J* = 3.7 Hz), 121.66, 113.71, 77.52, 72.76, 65.22, 52.36, 17.17. ESI-HRMS: Calcd for $C_{19}H_{19}F_3NO_3^+$ ([M+H$^+$]): 366.1312; Found: 366.1309.

(3S, **4R**, **5S)-Methyl-3-(2-methoxyphenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate** (**3la**)

Colorless oil, 66% yield. $[\alpha]_D^{20}$ = + 32.18 (c = 1.13, CH_2Cl_2); 93% ee for major isomer, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm; t (major) = 11.50 min, t (minor) = 12.19 min, t (major) = 12.94 min, t (minor) = 18.49 min]; IR(cm^{-1}): 2927, 1739, 1599, 1490, 1437, 1244, 1209, 1048, 753, 694.^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.76 – 7.70 (m, 0.9H), 7.64 – 7.59 (m, 1H), 7.31 – 7.15 (m, 5H), 7.02 – 6.83 (m, 10H), 5.48 (d, *J* = 6.1 Hz, 0.9H), 5.30 (d, *J* = 9.5 Hz, 1H), 4.75 (dq, *J* = 8.5, 6.1 Hz, 1H), 4.36 (dq, *J* = 9.2, 6.0 Hz, 0.9H), 3.84 (s, 3H), 3.78 (s, 2.7H), 3.67 (s, 2.7H), 3.39 (dd, *J* = 9.4, 8.7 Hz, 1H), 3.26 (s, 3H), 3.03 – 2.94 (m, 0.9H), 1.42 (d, *J* = 6.1 Hz, 5.7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.60, 169.88, 156.13, 155.90, 151.57, 150.31, 129.85, 128.81, 128.71, 128.68, 128.39, 126.55, 126.02, 121.90, 120.97, 120.81, 120.62, 115.84, 113.47, 109.98, 109.74, 78.42, 75.78, 69.38, 65.23, 64.99, 58.77, 55.28, 54.97, 51.94, 51.25, 17.87, 16.96. ESI-HRMS: Calcd for $C_{19}H_{22}NO_4^+$ ([M+H$^+$]): 328.1543; Found: 328.1539.

(3S, 4R, 5S)-Methyl-3-(2-fluorophenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3ma**)

Colorless oil, 91% yield. $[\alpha]_D^{20}$ = – 88.89 (c = 0.36, CH_2Cl_2); 93% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 9.96 min, t (minor) = 12.50 min]; IR(cm^{-1}): 2919, 2849, 1740, 1598, 1489, 1221, 1175, 1032, 756, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 1H), 7.33 – 7.22 (m, 3H), 7.21 – 7.14 (m,

1H), 7.13 – 6.90 (m, 4H), 5.51 (d, *J* = 6.3 Hz, 1H), 4.42 (dq, *J* = 9.0, 5.9 Hz, 1H), 3.69 (s, 3H), 3.14 (dd, *J* = 8.9, 6.4 Hz, 1H), 1.49 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.62, 159.75 (d, *J* = 245.7 Hz), 151.03, 129.07 (d, *J* = 8.2 Hz), 128.86, 128.59 (d, *J* = 13.2 Hz), 128.01 (d, *J* = 3.9 Hz), 124.54 (d, *J* = 3.4 Hz), 121.48, 115.21 (d, *J* = 21.3 Hz), 113.69, 78.07, 67.62, 64.52, 52.24, 17.10. ESI-HRMS: Calcd for $C_{18}H_{19}FNO_3^+$ ([M+H$^+$]): 316.1343; Found: 316.1339.

(3S, 4R, 5S)-Methyl-3-(3,4-dibromophenyl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3na**)

Colorless oil, 80% yield. $[\alpha]_D^{20}$ = – 69.17 (c = 1.08, CH_2Cl_2); 97% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 12.91 min, t (minor) = 14.20 min]; IR(cm^{-1}): 2917, 2849, 1736, 1597, 1488, 1260, 1014, 796, 757, 694. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.87 – 7.80 (m, 1H), 7.66 – 7.57 (m, 1H), 7.38 – 7.21 (m, 3H), 7.01 – 6.89 (m, 3H), 5.11 (d, *J* = 6.8 Hz, 1H), 4.40 (dq, *J* = 12.0, 5.9 Hz, 1H), 3.71 (s, 3H), 3.11 (dd, *J* = 8.9, 7.0 Hz, 1H), 1.50 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.21, 150.93, 142.85, 133.90, 131.39, 128.96, 126.43, 125.15, 123.72, 121.74, 113.69, 77.50, 72.03, 65.07, 52.44, 17.23. ESI-HRMS: Calcd for $C_{18}H_{18}Br_2NO_3^+$ ([M+H$^+$]): 453.9648; Found: 453.9643.

(3S, 4R, 5S)-Methyl-5-methyl-3-(naphthalen-2-yl)-2-phenylisoxazolidine-4-carboxylate (**3oa**)

White solid, 76-78 ^{o}C, 95% yield. $[\alpha]_D^{20}$ = –74.17 (c = 0.76, CH_2Cl_2); 97% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 6.37 min, t (minor) = 12.99 min]; IR(cm^{-1}): 2917, 2848, 1736, 1598, 1488, 1260, 1222, 1198, 817, 759, 751, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.92 – 7.79 (m, 3H), 7.68 – 7.61 (m, 1H), 7.53 – 7.43 (m, 2H), 7.30 – 7.19 (m, 2H), 7.08 – 6.99 (m, 2H), 6.98 – 6.88 (m, 1H), 5.32 (d, *J* = 7.1 Hz, 1H), 4.47 (dq, *J* = 11.9, 6.0 Hz, 1H), 3.69 (s, 3H), 3.26 (dd, *J* = 9.0, 7.3 Hz, 1H), 1.53 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.66, 151.61, 138.95, 133.30, 132.87, 128.87, 128.82, 127.90, 127.57, 126.18, 125.90, 124.98, 124.18, 121.45, 113.87, 77.58, 73.72, 65.39, 52.30, 17.33. HPLC analysis (Chiralcel AD-H, n-hexane/i-PrOH = 90:10, 1.0 mL/min, t_r (major) = 6.369 min, t_r (minor) = 12.991 min, 97%ee). ESI-HRMS: Calcd for $C_{22}H_{22}NO_3^+$ ([M+H$^+$]): 348.1594; Found: 348.1591.

(3S, 4R, 5S)-Methyl-3-(furan-2-yl)-5-methyl-2-phenylisoxazolidine-4-carboxylate (**3pa**)

Colorless oil, 88% yield. $[\alpha]_D^{20}$ = – 174.53 (c = 1.06, CH_2Cl_2); 97% ee, determined by HPLC

analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 10.91 min, t (minor) = 12.69 min]; IR(cm^{-1}): 2921, 2850, 1738, 1597, 1487, 1207, 1139, 1014, 796, 753, 737, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 1H), 7.32 – 7.23 (m, 2H), 7.13 – 7.05 (m, 2H), 7.00 – 6.91 (m, 1H), 6.43 – 6.31 (m, 2H), 5.25 (d, *J* = 6.3 Hz, 1H), 4.39 (dq, *J* = 8.8, 6.0 Hz, 1H), 3.67 (s, 3H), 3.43 (dd, *J* = 8.8, 6.3 Hz, 1H), 1.55 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.45, 153.00, 150.77, 142.59, 128.80, 121.82, 114.30, 110.29, 107.06, 77.39, 67.29, 60.79, 52.32, 17.32. ESI-HRMS: Calcd for $C_{16}H_{18}NO_4^+$ ([M+H$^+$]): 288.123; Found: 288.1227.

(3R, 4R, 5S)-Methyl-5-methyl-2-phenyl-3-((E)-styryl)isoxazolidine-4-carboxylate (**3qa**)

Colorless oil, 64% yield. $[\alpha]_D^{20}$ = –131.78 (c = 0.65, CH_2Cl_2); 95% ee, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 0.5 mL/min, 254 nm; t (major) = 14.43 min, t (minor) = 21.18 min]; IR(cm^{-1}): 2917, 2846, 1736, 1597, 1488, 1266, 1219, 968, 738, 694. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.37 – 7.23 (m, 5H), 7.10 – 7.02 (m, 2H), 7.00 – 6.91 (m, 1H), 6.82 – 6.73 (m, 1H), 6.49 – 6.35 (m, 1H), 4.70 (t, *J* = 6.9 Hz, 1H), 4.36 (dq, *J* = 12.1, 5.9 Hz, 1H), 3.70 (s, 3H), 3.14 – 2.99 (m, 1H), 1.51 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.48, 151.43, 136.19, 131.15, 128.79, 128.60, 128.44, 127.70, 126.45, 121.55, 114.16, 76.79, 72.22, 62.48, 52.20, 17.28. ESI-HRMS: Calcd for $C_{20}H_{22}NO_3^+$ ([M+H$^+$]): 324.1594; Found: 324.1595.

((3S,4S,5S)-5-methyl-2, 3-diphenylisoxazolidin-4-yl)methyl 2,4-dichlorobenzoate (**4**)

To a suspension of lithium aluminum hydride(60 mg, 0.3 mmol) in THF(2 mL)was added the cycloadduct **3aa** (60 mg, 0.2 mmol) at 0 ^{o}C, then the mixture was stirred at rt for 1 h. The reaction was quenched with water and the mixture was extracted with EtOAc (3 ×15 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the crude product which was used directly in the next step. To a solution of the crude reduction product in CH_2Cl_2 (2 mL) was added 1, 3-dicyclohexylcarbodiimide (49 mg, 0.24 mmol), 4-(dimethylamino)pyridine (12.2 mg, 0.1 mmol), and 2,4-dichlorobenzoic acid (27 mg, 0.3mmol). The mixture was allowed to stir at rt for 2 h. The solution was washed with hydrochloric acid (5 mL × 2, 0.5 M) and saturated aqueous $NaHCO_3$ (5mL × 2). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (ethyl acetate/petroleum ether, 1/10, v/v) to obtain the product **4** as a white solid. m.p. 74-76 ^{o}C, 95% yield. $[\alpha]_D^{20}$ = –53.04 (c =

1.24, CH_2Cl_2); 96% *ee*, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm; t (major) = 5.33 min, t (minor) = 7.51 min]; IR(cm^{-1}): 2917, 28497, 17347, 1586, 1487, 1281, 1242, 1101, 1049, 753, 698. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 –7.50 (m, 2H), 7.43 – 7.26 (m, 5H), 7.26 – 7.18 (m, 2H), 7.17 – 7.11 (m, 1H), 7.01 – 6.86 (m, 3H), 4.61 (d, *J* = 7.2 Hz, 1H), 4.45 (d, *J* = 4.9 Hz, 2H), 4.25 (dq, *J* = 8.9, 6.0 Hz, 1H), 2.72 – 2.59 (m, 1H), 1.49 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.03, 151.82, 141.79, 138.32, 134.77, 132.21, 130.77, 128.68, 127.38, 127.06, 126.77, 126.15, 121.11, 113.63, 76.37, 73.67, 62.63, 60.27, 16.94. ESI-HRMS: Calcd for $C_{24}H_{22}Cl_2NO_3^+$ ([M+H$^+$]): 442.0971; Found: 442.0969.

(2R, 3S)-Methyl-3-hydroxy-2-((S)-phenyl(phenylamino)methyl)butanoate (**5**)

To a stirred solution of **3aa** (90 mg, 0.3 mmol) in AcOEt (3 mL) was added Pd/C (10 *wt*%, 55 mg) at room temperature. After several times of purging with H_2, the reaction mixture was stirred at –10 ^{o}C for overnight under H_2 atmosphere (1atm). After **3aa** was consumed completely (monitored by TLC), the reaction mixture was filtered and concentrated. The residue was purified by column chromatography (ethyl acetate/petroleum ether, 1/5, v/v) to obtain the pure product **5** as a white solid. m.p. 123−124 ^{o}C, 80% yield. $[\alpha]_D^{20}$ = –52.74 (c = 0.62, CH_2Cl_2); 98% *ee*, determined by HPLC analysis [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm; t (minor) = 8.22 min, t (major) = 17.71 min]; IR(cm^{-1}): 3393, 2951, 1712, 1604, 1516, 1497, 1307, 1175, 748, 690. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.09 (m, 5H), 7.07 – 6.99 (m, 2H), 6.71 – 6.56 (m, 3H), 4.80 (d, *J* = 9.1 Hz, 1H), 4.31 – 4.15 (m, 3H) , 3.33 (s, 3H), 2.82 (t, *J* = 8.7 Hz, 1H), 1.16 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.72, 145.90, 140.11, 129.02, 128.37, 127.58, 126.70, 119.37, 115.61, 69.01, 60.99, 59.32, 51.36, 21.61. ESI-HRMS: Calcd. for $C_{18}H_{22}NO_3^+$ ([M+H$^+$]): 300.1594; Found: 300.1592.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at

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