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Palladium-Catalyzed Diastereoselective Synthesis of 3-Arylbutanoic Acid Derivatives

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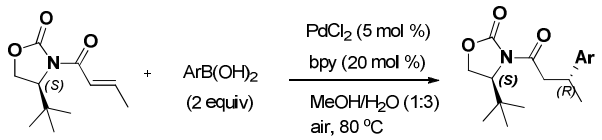
Supporting Information Placeholder



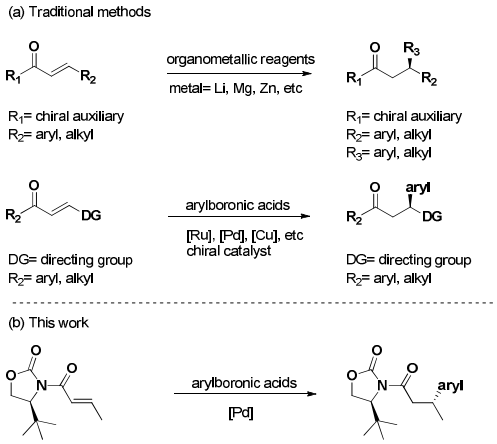
ABSTRACT: The first palladium-catalyzed diastereoselective conjugate addition of arylboronic acids to chiral imides is reported. The catalytic system employing 4-(tert-butyl)oxazolidin-2-one as the chiral auxiliary in a mixed solvent system of MeOH/H_2O (1:3) under an air atmosphere provides the optically active 3-arylbutanoic acid derivatives in excellent yields with high diastereoselectivity.

■ INTRODUCTION

Optically active 3-arylbutanoic acids and their derivatives are important intermediates for the synthesis of bioactive aromatic sesquiterpenes, diterpenes and a class of versatile building blocks in organic synthesis, which are structural moieties that are found in many pharmaceuticals and bioactive compounds[1]. Thus far, several types of asymmetric methods for the synthesis of the carboxylic acid derivatives have been developed. Asymmetric hydrogenation of α,β-unsaturated carboxylic acid derivatives has been developed as an efficient method[2] for the construction of chiral 3-arylbutanoic acid derivatives with good yields and high enantioselectivities. However, the high cost of most commercially available chiral ligands and high reaction pressure prohibited the use of the asymmetric hydrogenation method. Enzymatic processes[3], organocatalytic methods[4] and the Mitsunobu reaction[5] of chiral secondary benzylic alcohols have also been described as other protocols.

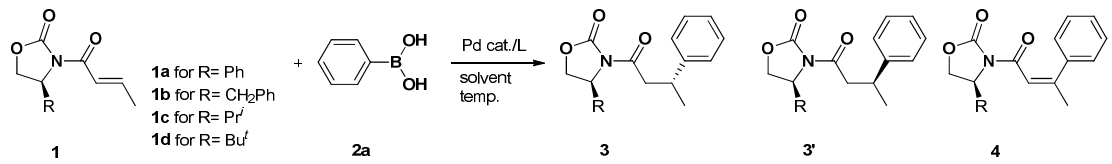
Moreover, asymmetric conjugate addition has been described as an effective method for the construction of these moieties, such as the conjugate addition of organometallic reagents to α,β-unsaturated esters and amides with chiral auxiliary groups[6] and rhodium[7]-, palladium[8]- or cuprum[9]-catalyzed asymmetric conjugate arylation of electron-deficient olefins with chiral ligands using organoboron reagents as nucleophiles. Unfortunately, excess organometallic reagents, a low reaction temperature, or the high cost of chiral catalysts restrict the potential applications of these reactions.

Scheme 1. Different Methods of Asymmetric Conjugate Addition.



In light of the importance of 3-arylbutanoic acids in organic synthesis, we became interested in other routes to synthesize their intermediates. To the best of our knowledge, the synthesis of optically active 3-arylbutanoic acid derivatives using α,β-unsaturated chiral imides as the acceptors and arylboronic acids as the donators has not been reported. Herein, we report an efficient and practical palladium-catalyzed

Table 1. Screening Reaction Conditions[a].



entry	1	catalyst	ligand	solvent	temp(°C)	conv.(%)[b]	**4**[b](%)	dr[c](**3/3'**)
1	1a	$Pd(OAc)_2$	2,2'-bipyridine	MeOH	80	>99	26	59:41
2	1a	$Pd(OAc)_2$	2,2'-bipyridine	MeOH/H_2O(3:1)	80	>99	6	73:27
3	1a	$Pd(OAc)_2$	2,2'-bipyridine	MeOH/H_2O(1:1)	80	>99	-	69:31
4	1a	$Pd(OAc)_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	73:27
5	1a	$Pd(OAc)_2$	2,2'-bipyridine	MeOH/H_2O(1:5)	80	>99	-	71:29
6	1a	$Pd(OAc)_2$	2,2'-bipyridine	H_2O	80	>99	-	63:37
7[d]	1a	$Pd(OAc)_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	13	72:28
8	1a	$Pd(OAc)_2$	2,2'-bipyridine	^{t}BuOH/H_2O(1:3)	80	>99	-	73:27
9	1a	$Pd(OAc)_2$	2,2'-bipyridine	NMP/H_2O(1:1)	80	>99	9	77:23
10	1a	$Pd(OAc)_2$	2,2'-bipyridine	NMP/H_2O(1:3)	80	>99	-	79:21
11	1a	$PdCl_2$	2,2'-bipyridine	NMP/H_2O(1:3)	80	>99	-	78:22
12	1a	$PdCl_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	78:22
13[e]	1a	$PdCl_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	50	>99	-	78:22
14	1a	$Pd(CF_3COO)_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	76:24
15	1a	$PdCl_2$	4,4'-dinitro-2,2'-bipyridine	MeOH/H_2O(1:3)	80	trace	trace	trace
16	1a	$PdCl_2$	[2,2'-bipyridine]-3,3'-diol	MeOH/H_2O(1:3)	80	62	-	67:33
17	1a	$PdCl_2$	dimethyl [2,2'-bipyridine]-4,4'-dicarboxylate	MeOH/H_2O(1:3)	80	97	-	71:29
18	1a	$PdCl_2$	1,10-phenanthroline	MeOH/H_2O(1:3)	80	>99	-	67:33
19	1a	$PdCl_2$	2,9-dimethyl-1,10-phenanthroline	MeOH/H_2O(1:3)	80	40	32	50:50
20	1a	$PdCl_2$	6,6'-dimethyl-2,2'-bipyridine	MeOH/H_2O(1:3)	80	trace	17	trace
21	1b	$PdCl_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	75:25
22	1c	$PdCl_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	74:26
23[f]	1d	$PdCl_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	86:14
24	1d	$Pd(OAc)_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	82:17
25	1d	$Pd(CF_3COO)_2$	2,2'-bipyridine	MeOH/H_2O(1:3)	80	>99	-	84:16
26	1d	$Pd(OAc)_2$	2,2'-bipyridine	NMP/H_2O(1:3)	80	>99	-	85:15

[a]Reaction conditions: under an air atmosphere, chiral amide (0.5 mmol), phenylboronic acid (**2**) (1 mmol), $PdCl_2$ (0.025 mmol), 2,2'-bipyridine (0.1 mmol), MeOH (1 mL), H_2O (3 mL), time (12 h), in a sealed Schlenk tube at 80 °C. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]The diastereoselective ratio (dr value) was determined according to the ^{1}H NMR peak areas of α-H in **3** and **3'** from the reaction mixture of **1** with **2a**. [d]2,2'-bipyridine (0.05 mmol) was used, 83% conversion. [e]Reacted for 18 h, 87% conversion. [f]Isolated yield: 3 (74%), 3' (2%).

diastereoselective synthesis of 3-arylbutanoic acid derivatives via the reaction of arylboronic acids with α,β-unsaturated chiral imides (Scheme 1), where oxazolidinones act as chiral auxiliaries. Oxazolidinone auxiliaries, popularized by David Evans, have been used as chiral auxiliaries in many stereoselective transformations.[10]

■ RESULTS AND DISCUSSION

Initially, (S)-4-phenyloxazolidin-2-one was chosen as the chiral auxiliary for optimization of the reaction, which was installed on (E)-2-butenoyl chloride to give the corresponding (S,E)-3-(but-2-enoyl)-4-phenyloxazolidin-2-one[11] (**1a**). A mixture of the imide **1a** (1 equiv), phenylboronic acid **2a** (2 equiv), $Pd(OAc)_2$ (0.05 equiv) and 2,2'-bipyridine (0.2 equiv) in MeOH at 80 °C was stirred for 12 h in a sealed Schlenk tube. The reaction was found to proceed to nearly full conversion (>99%), and the conjugate addition products **3** and **3'** were obtained in a 47% yield, together with a 26% yield of the oxidative Heck[12] product **4** (based on imide **1a**). Conjugate addition products **3** and **3'** could be isolated by column chromatography using hexane/ethyl acetate (7:1) as the eluent. When 2,2'-bipyridine (0.1 equiv) was used, oxidative Heck product (13%) was found and the reaction could not give full conver-

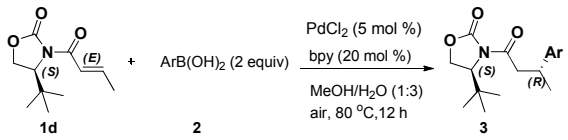
sion (entry 7). Then, the effect of various solvents was investigated.[13] As shown in Table 1, the addition of H_2O switched the outcome fully to the conjugate addition products **3** and **3'** (entries 2-6). Other solvents such as EtOH, ^{i}PrOH, ^{t}BuOH and hexafluoroisopropyl alcohol were used respectively to give the reaction in slightly lower diastereoselective ratio (entry 8). NMP was also suitable for the reaction (entries 9-10).. In NMP/H_2O (1:3), the reaction gave a higher diastereoselective ratio (entry 10). Water demonstrated an important effect in the switching process between oxidative Heck and conjugate addition reactions (entries 1-3). $PdCl_2$ showed a similar activity in NMP/H_2O (1:3) compared to $Pd(OAc)_2$ (entries 10 and 11), and it could improve diastereoselective ratio in MeOH/H_2O (1:3) (entries 4 and 12). $Pd(CF_3COO)_2$ showed moderate activity (entry 14). Since the isolation of **3** and **3'** by column chromatography was difficult when using $PdCl_2$/NMP as the catalyst system, $PdCl_2$ was chosen as the catalyst, and MeOH/H_2O (1:3) was chosen as the solvent.

Although lowering the reaction temperature to 50 °C did not alter the diastereoselective ratio (entry 12 vs. entry 13), the conversion deteriorated significantly even if the reaction proceeded for 18 h. Other ligands[14] such as 4,4'-dinitro-2,2'-bipyridine, [2,2'-bipyridine]-3,3'-diol, 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, and 6,6'-dimethyl-2,2'-bipyridine (entries 15-20) were also screened, and all afforded the product in a poor diastereoselective ratio. Phosphorus ligands such as PPh_3, PCy_3, S-phos and X-phos didn't work in this reaction. Other Evans-oxazolidinones were also investigated as the chiral auxiliaries.[15] (*S*)-4-Benzyloxazolidin-2-one (**b**), (*S*)-4-iso-propyloxazolidin-2-one (**c**), and (*S*)-4-*tert*-butyloxazolidin-2-one (**d**) were installed on (E)-2-butenoyl chloride to give the corresponding chiral imides (**1b-d**), as shown in Table 1. The reaction of **1d** with phenylboronic acid **2** gave the highest diastereoselective ratio of **3a/3'a** (86:14), using $PdCl_2$ as the catalyst in the presence of 2,2'-bipyridine in a mixed solvent of MeOH/H_2O (1:3) at 80 °C under air atmosphere (entry 23). The desired product **3a** with a R-configuration could easily be isolated by column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent in a 74% yield.

Catalysts and solvents were also screened based on compound **1d** (R = Bu^t), switching the palladium source from $PdCl_2$ to $Pd(OAc)_2$ or $Pd(CF_3COO)_2$ lead to slightly lower of the *dr* value (entries 24-25). When NMP/H_2O was used as solvent instead of MeOH/H_2O, nearly similar result was obtained (entry 26). These results following a similar pattern when **1a** (R = Ph) was used.

Having the optimal conditions in hand, the asymmetric conjugate addition of a variety of arylboronic acids with diverse substituents on the benzene rings was evaluated for reaction with **1d** under the standard conditions, as shown in Table 2. Most of the major adducts **3a-t** were obtained in good yields (63-86%) with high diastereoselectivity. Arylboronic acids with electron-withdrawing substituents on the benzene rings (entries 12, 13, 16 and 19) gave higher diastereoselectivity (>9:1) compared to those with electron-donating substituents (entries 2-5). When (4-hydroxyphenyl)-boronic acid was used (entry 5), the reaction could proceed with 95% conversion, but the isolation of **3e** by column chromatography was difficult. Meanwhile, **3q** bearing a methylol group could be isolated in a 75% yield (entry 17). For ortho-substituted arylboronic acids, high diastereoselectivity was also observed (entries 2 and 9), except for those with bigger steric substituents in the *ortho*-position, such as (2-(trifluoromethyl)phenyl)-boronic acid (entry 6) and [1,1'-biphenyl]-2-ylboronic acid (entry 23).

Table 2. Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to Chiral Imide.



1d 2 3

entry	Ar	conv.(%)[b]	dr[c]	yield(%)[d]
1	Ph	>99	86:14	**3a** 74
2	*o*-MeC_6H_4	95	82:18	**3b** 72
3	*m*-MeC_6H_4	90	83:17	**3c** 73
4	*p*-MeC_6H_4	90	78:22	**3d** 72
5	*p*-HOC_6H_4	95	71:29	**3e** -
6	*o*-$CF_3C_6H_4$	0	-	-
7[e]	*m*-$CF_3C_6H_4$	95	88:12	**3g** 80
8	*p*-$CF_3C_6H_4$	95	88:12	**3h** 82
9	*o*-ClC_6H_4	90	87:13	**3i** 71
10	*m*-ClC_6H_4	>99	84:16	**3j** 75
11	*p*-ClC_6H_4	>99	85:15	**3k** 69
12[e]	*m*-CNC_6H_4	95	91:9	**3l** 79
13	*p*-CNC_6H_4	98	90:10	**3m** 86
14[e]	3,4-difluoroC_6H_3	98	88:12	**3n** 75
15	*m*-$MeOC_6H_4$	98	89:11	**3o** 80
16	*p*-$NH_2COC_6H_4$	98	93:7	**3p** 82
17	*p*-$OHCH_2C_6H_4$	98	87:13	**3q** 75
18	*p*-$MeO_2CC_6H_4$	98	87:13	**3r** 80
19	*p*-$CHOC_6H_4$	98	91:9	**3s** 74
20[e]	*m*-$NO_2C_6H_4$	85	87:13	**3t** 63
21[e]	2-furanyl	83	83:17	**3u** 62
22	3-thienyl	>99	83:17	**3v** 74
23	2-phenyl	0	-	-

[a]Reaction conditions: under an air atmosphere, chiral amide (**1d**) (0.5 mmol), phenylboronic acid (**2**) (1 mmol), $PdCl_2$ (0.025 mmol), 2,2'-bipyridine (0.1 mmol), MeOH (1 mL), H_2O (3 mL), time (12 h), in a sealed Schlenk tube at 80 °C. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]The diastereoselective ratio (dr value) was determined according to the ^{1}H NMR peak areas of α-H in **3** and **3'** from the reaction mixture of **1d** with **2**. [d]Isolated yield. [e]The reaction time is 24 h.

Arylboronic acids with some functional groups including imides, halogens, esters, and methylol were tolerated under the

optimal conditions. For hetero-arylboronic acids, such as furan-2-ylboronic acid, thiophen-3-ylboronic acid, the reaction also worked well (entries 21 and 22). And all of the major diastereomers **3** could be easily isolated by column chromatography except for **3e**. Therefore, the present method can easily afford diverse 3-arylbutanoic acid derivatives.

In addition, a single crystal of **3m** was prepared to further confirm the absolute configuration, and its structure was unambiguously confirmed by X-ray diffraction analysis (Figure 1). The X-ray diffraction analysis indicated that the conjugate addition intends to form the product with the R-configuration.[16]

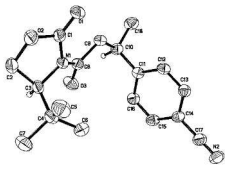
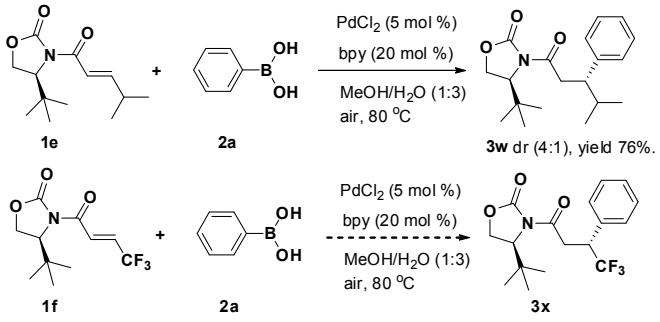


Figure 1. X-ray structure of **3m**.

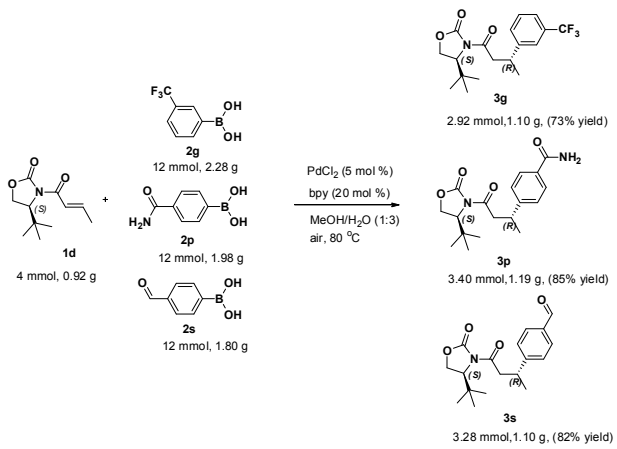
The steric and electronic effect of the group on the alkenyl carbon was further surveyed. As shown in scheme 2, when compound **1e** with isopropyl on the alkenyl carbon reacted with phenylboronic acid **2a** under the optimal conditions, lower dr value (80:20) with fully conversion and none oxidative Heck product was obtained compared to **1d** (86:14). When the methyl group was changed to trifluromethyl group (**1f**), although the reaction could give fully conversion, about 50% oxidative Heck product was detected according to crude ^{1}H NMR. The optically active **3x** could not be isolated by column chromatography, and the dr value was difficult to be confirmed due to the complex crude ^{1}H NMR.

Scheme 2. Steric and Electronic Effect of the Group on the Alkenyl Carbon.



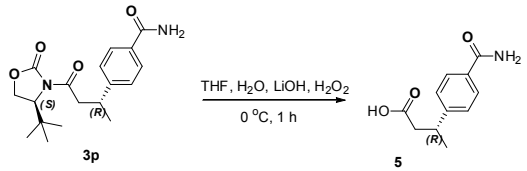
Gram-scale experiments were also performed to find that optically pure **3g, 3p,** and **3s** were obtained with high yields (73-85%), as shown in Scheme 3, and the diastereoselective ratios (dr values) of the desired products were essentially in agreement with those figures shown in Table 2 (entries 7, 16 and 19). The results showed that the present method was also practical and effective for commercial production.

Scheme 3. Palladium-Catalyzed Synthesis of 3g, 3p, and 3s on a Gram-Scale under the Standard Conditions.



Optically active 3-arylbutanoic acids could be obtained by the hydrolysis of the corresponding chiral imides. When **3p** was hydrolyzed in the mixed solvent of THF and water in the presence of H_2O_2 and LiOH at 0 °C for 1 h, **5** was obtained with 97.6% ee value in an 85% yield (Scheme 4).

Scheme 4. Hydrolysis of 3p Leading to 5.



■CONCLUSION

In summary, we have developed a convenient, efficient and practical palladium-catalyzed method for the diastereoselective synthesis of optically active 3-arylbutanoic acid derivatives. The protocol relies on the use of easily available substrates, cheap ligands and recoverable chiral auxiliary groups. The notable advantage of this method is that it is simple and compatible with a variety of functional groups (halide, cyano, ester, amide, methylol, etc.). Moreover, the desired optically active 3-arylbutanoic acid derivatives could be obtained in excellent yields with a high diastereoselectivity. Therefore, the present method provides a novel and valuable strategy for the synthesis of diverse optically active 3-arylbutanoic acid derivatives.

■EXPERIMENTAL SECTION

Unless otherwise stated, all reactions were carried out under air atmosphere. All commercial materials and solvents were used directly without further purification. NMR spectra were obtained on Bruker AVANCE III systems using $CDCl_3$ or $(CD_3)_2SO$ as solvent, TMS as internal standard substance, at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR. High-resolution mass spectra (HRMS) were obtained on Q-TOF spectrometer using Agilent 6450 spectrometer. Column chromatography was performed on silica gel (300-400 mesh ASTM) using the reported eluents. Thin-layer chromatography (TLC) was carried out on 4×15 cm plates with a layer thickness of 0.2 mm (silica gel 60 F254). Moreover, the structure of 3m was confirmed by single-crystal X-ray analysis.

General procedure for the preparation of 1. n-Butyl lithium (33 mmol, 1.1 equiv) was added to a solution of the chiral 4-substituted 1,3-oxazolidin-2-one (30 mmol, 1 equiv) in THF (120 mL) at -78 °C. After 15 min of stirring at -78 °C, (E)-2-butenoyl chloride (33 mmol, 1.1 equiv) was added in dropwise. The mixture was stirred at -78 °C for a further 30 min then at 0 °C for 15 min, the reaction was quenched with saturated NH_4Cl aqueous solution and the resultant slurry was concentrated in *vacuo*. The residue was diluted with EA and washed with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the crude product. The crude product was purified by silica flash column chromatography.

(S,E)-3-(but-2-enoyl)-4-phenyloxazolidin-2-one (**1a**, 6.5 g, yield 94%): White solid, mp 72-73 °C. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.29-7.39 (m, 6H), 7.04-7.13 (m, 1H), 5.47 (dd, *J* = 8.4, 3.6 Hz, 1H), 4.68 (t, *J* = 8.8 Hz,1H), 4.25 (dd, *J* = 8.8, 4.0 Hz, 1H), 1.93 (dd, *J* = 6.8, 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.5, 153.7, 147.3, 139.1, 129.2, 128.6, 125.9, 121.7, 69.9, 57.7, 18.5; LC-MS (ESI, *m/z*): $[M+H]^+$ 232.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C13H14NO3 232.0974; Found 232.0967.

(S,E)-4-benzyl-3-(but-2-enoyl)oxazolidin-2-one (**1b**, 6.8 g, yield 93%): White solid, mp 76-77 °C. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.21-7.35 (m, 7H), 4.73 (m, 1H), 4.18 (m, 2H), 3.34 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.80 (dd, *J* = 13.2, 9.6 Hz, 1H), 1.98 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.0, 153.5, 147.0, 135.4, 129.5, 129.0, 127.3, 121.9, 66.1, 55.3, 37.9, 18.6; LC-MS (ESI, *m/z*): $[M+H]^+$ 246.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C14H16NO3 246.1130; Found 246.1124.

(S,E)-3-(but-2-enoyl)-4-isopropyloxazolidin-2-one (**1c**, 5.6 g, yield 95%): White solid, mp 50-51 °C. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 (m, 1H), 7.15 (m, 1H), 4.49 (m, 1H), 4.28 (t, *J* = 8.8 Hz, 1H), 4.22 (dd, *J* = 7.2, 3.2 Hz, 1H), 2.40(m, 1H), 1.95 (dd, *J* = 6.8, 1.6 Hz, 3H), 0.92 (dd, *J* = 17.6, 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.3, 154.7, 146.8, 121.9, 65.2, 60.8, 35.9, 25.6, 18.5; GC-MS (EI, *m/z*): $[M]^+$ 197.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C10H16NO3 198.1130; Found 198.1129.

(S,E)-3-(but-2-enoyl)-4-(tert-butyl)oxazolidin-2-one (**1d**, 5.9 g, yield 94%): Yellow oil. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 (m, 1H), 7.17 (m, 1H), 4.51 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.28 (m, 2H), 1.97 (dd, *J* = 6.8, 1.6 Hz, 3H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.0, 154.1, 146.6, 121.9, 63.3, 58.8, 28.5, 18.5, 18.0, 14.7; GC-MS (EI, *m/z*): $[M]^+$ 211.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H18NO3 212.1287; Found 212.1283.

(S)-4-(tert-butyl)oxazolidin-2-one (7.8g, yield 70% over two steps): White solid, mp 115-116 °C. (L)-tert-leucine (10.00 g, 76.23 mmol) was added to a flask was charged with $NaBH_4$ (158 mmol, 6.92 g) and THF (250 mL), then a solution of iodine (76.2 mmol, 19.40 g) in dry THF (40 mL) was added dropwise to the flask over 30 min at 0 °C. After evolution of hydrogen gas ceased, the reaction mixture was heated to reflux for 20 h and then cooled to 0 °C. Methanol was added until the mixture become clear, then the solvent was removed with rotary evaporator to obtain a white paste, which was then dissolved to 20% aqueous KOH (150 mL). The solution was stirred for 4 h at 50℃ and extracted with DCM (3 ×100 mL). The organic layers were combined, dried over $MgSO_4$ and then concentrated in vacuo to get a colorless oil (9.6 g), which was dissolved in DCM (250 mL), Et_3N (152 mmol, 21.1 mL) was added dropwise. Then the mixture was cooled to 0 °C, and a solution of triphosgene (25 mmol, 12.6 g) in DCM (100 mL) was added dropwise. After stirring at this temperature for 30 min, the mixture was allowed to warm to room temperature and stirred for 3 h. Then saturate NH_4Cl water (100 mL) and CH_2Cl_2 (100 mL) was added, and the mixture was stirred for 5 h. Then the aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the residue was recrystalized in DCM/petroleum ether (v/v = 1:50), which afforded pure (S)-4-tert-butyloxazolidin-2-one as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.81 (br s, 1H), 4.36 (t, *J* = 8.8 Hz, 1H), 4.18 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.60 (m, 1H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.6, 66.6, 61.5, 33.3, 24.8; GC-MS (EI, *m/z*): $[M]^+$ 143.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C7H14NO2 144.1025; Found 144.1021.

(S,E)-4-(tert-butyl)-3-(4-methylpent-2-enoyl)oxazolidin-2-one (**1e**, 0.44g, yield 92%): Yellow oil. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.24 (dd, *J* = 15.6, 1.2 Hz, 1H), 7.11 (dd, *J* = 15.2, 6.8 Hz, 1H), 4.52 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.28 (m, 2H), 2.55 (m, 1H), 1.10 (dd, *J* = 6.8, 1.2 Hz, 6H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.7, 157.7, 154.7, 117.9, 65.2, 60.9, 35.9, 31.5, 25.6, 21.31, 21.28; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C13H22NO3 240.1600; Found 240.1601.

(S,E)-4-(tert-butyl)-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one (**1f**, 0.44g, yield 92%): Yellow oil. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95 (m, 1H), 6.86 (m, 1H), 4.51 (dd, *J* = 5.4, 2.0 Hz, 1H), 4.28 (m, 2H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.8, 154.1, 132.0 (q, *J* = 35.4 Hz), 127.8 (q, *J* = 6.2 Hz), 126.1 (q, *J* = 288.9 Hz), 65.6, 61.3, 36.0, 25.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H15F3NO3 266.1004; Found 266.1001.

General procedure for the synthesis of 3. A mixture of chiral amide (**1d**) (0.5 mmol, 1 equiv), boronic acid (2) (1.0 mmol, 2 equiv), $PdCl_2$ (0.025 mmol, 0.05 equiv), 2,2'-bipyridine (0.1 mmol, 0.2 equiv) in MeOH (1 mL) and H_2O (3 mL) was sealed in a Schlenk tube, then stirred at 80 °C for 12 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed subsequently with 2N HCl aqueous solution and 2N NaOH aqueous solution. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the crude product, which was purified by silica flash column chromatography.

(S)-4-(tert-butyl)-3-((R)-3-phenylbutanoyl)oxazolidin-2-one (**3a**, 106 mg, yield 74%): White solid, mp 65-66 °C. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 (m, 4H), 7.17 (m, 1H), 4.38 (d, *J* = 1.6 Hz, 1H), 4.20 (m, 2H), 3.54 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.40 (m,

1H), 3.02 (dd, *J* = 16.0, 6.8 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 0.75(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 154.7, 145.7, 128.4, 127.1, 126.3, 65.2, 60.8, 42.9, 36.3, 35.5, 25.4, 22.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for C17H23NNaO3 312.1576; Found 312.1575.

(S)-4-(tert-butyl)-3-((S)-3-phenylbutanoyl)oxazolidin-2-one (**3'a**, 2 mg, yield 2%): Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 (m, 4H), 7.19 (m, 1H), 4.31 (dd, J = 7.6, 1.6 Hz, 1H), 4.20 (dd, J = 9.2, 1.6Hz, 1H), 4.03 (dd, J = 9.2, 7.6Hz, 1H), 3.39(m, 2H), 3.02 (m, 1H), 1.34 (d, J = 6.8Hz, 3H), 0.88(s, 9H).

(S)-4-(tert-butyl)-3-((R)-3-(o-tolyl)butanoyl)oxazolidin-2-one (**3b**, 109 mg, yield 72%): White solid, mp 55-56 °C. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27 (d, *J* = 9.6 Hz, 1H), 7.16 (7, *J* = 7.2 Hz, 1H), 7.07(m, 2H), 4.38 (d, *J* = 1.6 Hz, 1H), 4.22 (m, 2H), 3.68 (m, 1H), 3.57 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.04 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.38(s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.72(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.2, 154.7, 144.0, 135.6, 130.4, 126.3, 126.0, 125.3, 65.1, 60.8, 42.0, 35.6, 31.3, 25.4, 21.9, 19.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C18H25NO3 304.1913; Found 304.1910.

(S)-4-(tert-butyl)-3-((R)-3-(m-tolyl)butanoyl)oxazolidin-2-one (**3c**, 110 mg, yield 73%): Yellow oil. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.17 (t, *J* = 7.6 Hz, 1H), 7.08 (m, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 2.0 Hz, 1H), 4.20 (m, 2H), 3.54 (dd, *J* = 16, 7.6 Hz, 1H), 3.37 (m, 1H), 3.01 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.31 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 3H), 0.76(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.0, 154.7, 145.6, 137.9, 128.4, 127.8, 127.1, 124.0, 65.2, 60.8, 42.8, 36.3, 35.6, 25.4 22.3, 21.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C18H25NO3 304.1913; Found 304.1909.

(S)-4-(tert-butyl)-3-((R)-3-(p-tolyl)butanoyl)oxazolidin-2-one (**3d**, 109 mg, yield 72%): Yellow oil. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.17 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.38 (d, *J* = 2.0 Hz, 1H), 4.22 (m, 2H), 3.49 (dd, *J* = 15.6, 7.2 Hz, 1H), 3.35 (m, 1H), 3.03 (dd, *J* = 16.0, 8.8 Hz, 1H), 2.30 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.77(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.0, 154.7, 142.7, 135.8, 129.1, 126.9, 65.2, 60.8, 43.0, 36.0, 35.7, 25.5, 22.3, 21.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C18H25NO3 304.1913; Found 304.1912.

(S)-4-(tert-butyl)-3-((R)-3-(3-(trifluoromethyl)phenyl)butanoyl)oxazolidin-2-one (**3g**, 142 mg, yield 80%): White solid, mp 50-51 °C. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.42 (m, 4H), 4.37 (d, *J* = 2.0 Hz, 1H), 4.23 (m, 2H), 3.59 (dd, *J* = 16.4, 8.0 Hz, 1H), 3.51 (m, 1H), 2.99 (dd, *J* = 16.0, 6.0 Hz, 1H), 1.35 (d, *J* = 7.2 Hz, 3H), 0.72(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 154.6, 146.6, 130.7 (q, *J* = 31.5 Hz), 130.6, 128.9, 124.0 (d, *J* = 3.8 Hz), 123.3 (d, *J* = 3.7 Hz), 125.7 (q, *J* = 270.5 Hz), 65.2, 60.8, 42.8, 36.2, 35.5, 25.3, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C18H22F3NO3 358.1630; Found 358.1628.

(S)-4-(tert-butyl)-3-((R)-3-(4-(trifluoromethyl)phenyl)butanoyl)oxazolidin-2-one (**3h**, 146 mg, yield 82%): White solid, mp 86-87 °C. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 4.37 (d, *J* = 1.6 Hz, 1H), 4.25 (m, 2H), 3.58 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.48 (m, 1H), 3.02 (dd, *J* = 16.0, 6.4 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 0.72(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 154.7, 149.8, 128.7 (q, *J* = 32.1 Hz), 127.5, 127.1 (q, *J* = 270.1 Hz), 125.4 (q, *J* = 3.6 Hz), 65.2, 60.8, 42.6, 36.3, 35.5, 25.3, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C18H22F3NO3 358.1630; Found 358.1626.

(S)-4-(tert-butyl)-3-((R)-3-(2-chlorophenyl)butanoyl)oxazolidin-2-one (**3i**, 115 mg, yield 71%): White solid, mp 89-90 °C. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34 (m, 2H), 7.22 (m, 1H), 7.12 (m, 1H), 4.39 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.23 (m, 2H), 3.92 (m, 1H), 3.42 (dd, *J* = 16.8, 6.8 Hz, 1H), 3.21 (dd, *J* = 16.8, 7.2 Hz, 1H), 1.32 (d, *J* = 7.2 Hz, 3H), 0.79(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 154.7, 142.9, 133.7, 129.7, 127.4, 127.2, 127.1, 65.3, 60.9, 41.8, 35.7, 32.1, 25.5, 21.0; HRMS (ESI) m/z calcd for C17H23ClNO3 $[M + H]^+$ 324.1366, found 324.1365.

(S)-4-(tert-butyl)-3-((R)-3-(3-chlorophenyl)butanoyl)oxazolidin-2-one (**3j**, 122 mg, yield 75%): Yellow oil. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27 (s, 1H), 7.17 (m, 3H), 4.38 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.25 (m, 2H), 3.53 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.39 (m, 1H), 2.98 (dd, *J* = 16.4, 6.8 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 0.76(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.6, 154.6, 147.8, 134.2, 129.7, 127.3, 126.5, 125.3, 65.2, 60.8, 42.7, 36.1, 35.6, 25.4, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C17H23NO3Cl 324.1366; Found 324.1365.

(S)-4-(tert-butyl)-3-((R)-3-(4-chlorophenyl)butanoyl)oxazolidin-2-one (**3k**, 111 mg, yield 69%): White solid, mp 64-65 °C. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.23 (m, 4H), 4.37 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.21 (m, 2H), 3.50 (dd, *J* = 16.0, 6.8 Hz, 1H), 3.39 (m, 1H), 2.97 (dd, *J* = 16.0, 6.4 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.76(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.7, 154.7, 144.2, 132.0, 128.5, 128.5, 65.2, 60.8, 42.9, 35.8, 35.5, 25.4, 22.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C17H23NO3Cl 324.1366; Found 324.1366.

3-((R)-4-((S)-4-(tert-butyl)-2-oxooxazolidin-3-yl)-4-oxobutan-2-yl)benzonitrile (**3l**, 124 mg, yield 79%): Yellow oil. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.50 (m, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 4.31 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.18 (m, 2H), 3.41 (m, 2H), 2.95 (dd, *J* = 15.6, 5.6 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 0.68(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 154.7, 147.2, 131.7, 131.0, 130.2, 129.3, 118.9, 112.4, 65.3, 60.2, 42.8, 35.8, 35.5, 25.44, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C18H23N2O3 315.1709; Found 315.1708.

4-((R)-4-((S)-4-(tert-butyl)-2-oxooxazolidin-3-yl)-4-oxobutan-2-yl)benzonitrile (**3m**, 135 mg, yield 86%): White solid, mp 90-91 °C. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.59 (dd, *J* = 6.4, 1.6 Hz, 2H), 7.40 (dd, *J* = 6.4, 1.6 Hz, 2H), 4.37 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.21 (m, 2H), 3.53 (m, 2H), 3.03 (dd, *J* = 16, 6 Hz, 1H),

1.34 (d, J = 6.8 Hz, 3H), 0.75(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 154.7, 151.4, 132.3, 128.0, 119.0, 110.2, 65.3, 60.8, 42.6, 36.3, 35.5, 25.4, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2O_3$ 315.1709; Found 315.1707.

(S)-4-(tert-butyl)-3-((R)-3-(3,4-difluorophenyl)butanoyl)oxazolidin-2-one (**3n**, 122 mg, yield 75%): White solid, mp 51-52 °C. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.07 (m, 3H), 4.39 (dd, J = 7.2, 1.6 Hz, 1H), 4.23 (m, 2H), 3.50 (dd, J = 16.4, 8.0 Hz, 1H), 3.38(m, 1H), 2.97 (dd, J = 16.0, 6.4 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H), 0.77(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.4, 154.7, 150.7 (dd, J = 129.2, 12.8 Hz), 148.4 (dd, J = 127.6, 12.5 Hz), 142.8 (t, J = 4.8 Hz), 122.9 (dd, J = 5.9, 3.5 Hz), 117.0 (d, J = 14.8 Hz), 116.0 (d, J = 16.9 Hz), 65.3, 60.8, 43.0, 35.5, 29.7, 25.4, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}F_2NO_3$ 326.1568; Found 326.1568.

(S)-4-(tert-butyl)-3-((R)-3-(3-methoxyphenyl)butanoyl)oxazolidin-2-one (**3o**, 127 mg, yield 80%): Yellow oil. Eluent: petroleum ether/ethyl acetate (6:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.20 (t, J = 8.0 Hz, 1H), 6.86 (m, 2H), 6.71 (m, 1H), 4.39 (dd, J = 7.6, 1.6 Hz, 1H), 4.20 (m, 2H), 3.78 (s, 3H), 3.56 (dd, J = 16.0, 7.6 Hz, 1H), 3.37(m, 1H), 3.00 (dd, J = 16, 7.2 Hz, 1H), 1.32 (d, J = 7.2 Hz, 3H), 0.76(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 159.7, 154.7, 147.4, 129.4, 119.4, 112.8, 111.8, 65.2, 60.9, 55.2, 42.7, 36.5, 35.6, 25.4, 22.3; ; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}NO_4$ 320.1862; Found 320.1860.

4-((R)-4-((S)-4-(tert-butyl)-2-oxooxazolidin-3-yl)-4-oxobutan-2-yl)benzamide (**3p**, 136 mg, yield 82%): White solid, mp 145-146 °C. Eluent: petroleum ether/ethyl acetate (1:2). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.74 (dd, J = 6.4, 1.6 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.04 (br s, 1H), 5.57 (br s, 1H), 4.37(dd, J = 7.6, 2.0 Hz, 1H), 4.20 (m, 2H), 3.52(m, 2H), 3.03 (dd, J = 16.0, 6.4 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H), 0.75(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 169.4, 154.7, 150.2, 131.5, 127.6, 127.4, 65.3, 60.9, 42.7, 36.1, 35.6, 25.4, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{24}N_2O_4$ 333.1814; Found 333.1813.

(S)-4-(tert-butyl)-3-((R)-3-(4-(hydroxymethyl)phenyl)butanoyl)oxazolidin-2-one (**3q**, 120 mg, yield 75%): Yellow oil. Eluent: petroleum ether/ethyl acetate (1:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27 (d, J = 4.0 Hz, 4H), 4.63 (s, 2H), 4.37(dd, J = 7.6, 1.6 Hz, 1H), 4.20 (m, 2H), 3.49 (dd, J = 15.6, 7.2 Hz, 1H), 3.38 (m, 1H), 3.03 (dd, J = 15.6, 6.8 Hz, 1H), 1.90 (br s, 1H), 1.32 (d, J = 7.2 Hz, 3H), 0.76(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 154.7, 145.2, 139.0, 127.2, 127.2, 65.2, 65.1, 60.8, 42.9, 36.0, 35.6, 25.5, 22.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}NO_4$ 320.1862; Found 320.1860.

methyl 4-((R)-4-((S)-4-(tert-butyl)-2-oxooxazolidin-3-yl)-4-oxobutan-2-yl)benzoate (**3r**, 139 mg, yield 80%): White solid, mp 109-110 °C. Eluent: petroleum ether/ethyl acetate (2:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 4.37(dd, J = 7.2, 1.6 Hz, 1H), 4.24 (m, 2H), 3.90 (s, 3H), 3.50 (m, 2H), 3.05 (dd, J = 16.0, 6.4 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H), 0.75(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 167.2, 154.7, 151.2, 129.8, 128.3, 127.1, 65.3, 60.8, 52.0, 42.7, 36.2, 35.6, 25.4, 22.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}NO_5$ 348.1811; Found 348.1809.

4-((R)-4-((S)-4-(tert-butyl)-2-oxooxazolidin-3-yl)-4-oxobutan-2-yl)benzaldehyde (**3s**, 118 mg, yield 74%): White solid, mp 86-87 °C. Eluent: petroleum ether/ethyl acetate (1:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.97 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H),4.38 (dd, J = 5.6, 1.6 Hz, 1H), 4.23 (m, 2H), 3.55 (m, 2H), 3.05 (dd, J = 16.0, 6 Hz, 1H), 1.36 (d, J = 6.8 Hz, 3H), 0.74(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 192.0, 171.4, 154.7, 153.1, 134.9, 130.0, 127.8, 65.3, 60.8, 42.6, 36.4, 35.5, 25.4, 22.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}NO_4$ 318.1705; Found 318.1703.

(S)-4-(tert-butyl)-3-((R)-3-(3-nitrophenyl)butanoyl)oxazolidin-2-one (**3t**, 105 mg, yield 63%): White solid, mp 90-91 °C. Eluent: petroleum ether/ethyl acetate (1:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.15 (t, J = 2.0 Hz, 1H), 8.07 (m, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 2.0 Hz, 1H), 4.38 (dd, J = 7.2, 1.6 Hz, 1H), 4.23 (m, 2H), 3.55 (m, 2H), 3.09 (dd, J = 19.2, 9.2 Hz, 1H), 1.38 (d, J = 6.8 Hz, 3H), 0.75 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 154.7, 148.4, 147.9, 133.5, 129.4, 122.1, 124.6, 65.4, 60.8, 42.9, 35.9, 35.6, 25.4, 21.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_2O_5$ 335.1607; Found 335.1606.**(S)-4-(tert-butyl)-3-((R)-3-(furan-2-yl)butanoyl)oxazolidin-2-one** (**3u**, 86 mg, yield 62%): Yellow oil. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.29 (dd, J = 2.0, 0.8 Hz, 1H), 6.26 (dd, J = 3.2, 2.0 Hz, 1H), 6.05 (d, J = 3.2 Hz, 1H), 4.43 (dd, J = 7.6, 2.0 Hz, 1H), 4.27 (m, 2H), 3.49 (m, 2H), 3.05 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.6, 158.7, 154.7, 140.9, 110.0, 104.0, 65.3, 61.0, 41.0, 35.8, 29.5, 25.6, 19.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{22}NO_4$ 280.1549; Found 280.1546.

(S)-4-(tert-butyl)-3-((R)-3-(thiophen-3-yl)butanoyl)oxazolidin-2-one (**3v**, 109 mg, yield 74%): Yellow oil. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.23 (dd, J = 5.2, 3.2 Hz, 1H), 7.06 (m, 2H), 4.40 (dd, J = 7.2, 1.6 Hz, 1H), 4.20 (m, 2H), 3.54 (m, 2H), 2.95 (m, 1H), 1.34 (d, J = 6.8 Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 154.6, 146.6, 126.9, 125.4, 119.7, 65.2, 60.8, 42.9, 35.6, 31.8, 25.5, 22.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{22}NO_3S$ 296.1320; Found 296.1320.

(S)-4-(tert-butyl)-3-((S)-4-methyl-3-phenylpentanoyl)oxazolidin-2-one (**3w**, 120 mg, yield 76%): White solid, mp 70-71 °C. Eluent: petroleum ether/ethyl acetate (7:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.23 (m, 4H), 7.14 (m, 1H), 4.28 (dd, J = 7.6, 1.6 Hz, 1H), 4.15 (m, 2H), 3.81 (m, 1H), 3.01 (m, 2H), 1.88 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H), 0.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.5, 154.7, 142.8, 128.6, 128.0, 65.0, 60.8, 49.0, 38.0, 35.3, 33.5, 25.2, 20.7, 20.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{28}NO_3$ 318.2069; Found 318.2071.

General procedure for the synthesis of (R)-3-(4-carbamoylphenyl)butanoic acid (5). LiOH (2 mmol, 48 mg), 30% aqueous H_2O_2 (5 mmol, 170 mg) were added to a mixture

of **3p** (0.5 mmol, 166 mg) in THF (20 mL) and H_2O (10 mL), the mixture was stirred at room temperature for 1 hour, TLC showed compound 3p was disappeared, then concentrated to remove THF, the residue was extracted with ethyl acetate for twice, then the water layer was acidification with $NaHSO_3$ to pH 5, extracted with ethyl acetate for three times, the combined organic layer was dried over $MgSO_4$, filtered and concentrated to get **5** as a white solid (98 mg, yield 85%).

(R)-3-(4-carbamoylphenyl)butanoic acid (**5**, 98 mg, yield 85%): White solid, mp 152-153 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.10 (br s, 1H), 7.90 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.28 (br s, 1H), 3.19 (m, 1H), 2.52 (d, *J* = 7.6 Hz, 2H), 1.21 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$, ppm) δ 173.1, 167.7, 149.4, 132.2, 127.5, 126.6, 41.8, 35.7, 21.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C11H14NO3 208.0974; Found 208.0971.

methyl 3-(4-carbamoylphenyl)butanoate. (**6**, 401 mg, yield 91% over two steps): White solid, mp 176-178 °C. A mixture of (E)-methyl but-2-enoate (200 mg, 2 mmol), (4-carbamoylphenyl)boronic acid (**2p**) (660 mg, 4 mmol), $PdCl_2$ (17.5 mg, 0.1 mmol), 2,2'-bipyridine (62.4 mg, 0.4 mmol) in MeOH (4 mL) and H_2O (12 mL) was sealed in a Schlenk tube, stirred at 80 °C for 12 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed subsequently with 2N HCl aqueous solution and 2N NaOH aqueous solution. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield crude product as a mixture of **6'** ((Z)-methyl 3-(4-carbamoylphenyl)but-2-enoate) and **6**, which was diluted with MeOH (10 mL), then Pd/C (10 mg) was added, the mixture was stirred under H_2 atmosphere at room temperature for 3 hours, the mixture was filtered through celit, concentrated and purified by silica flash column chromatography, eluted with petroleum ether/ethyl acetate(1:2), methyl 3-(4-carbamoylphenyl)butanoate (**6**) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.15 (b, 2H), 3.61 (s, 3H), 3.34 (m, 1H), 2.60 (m, 2H), 1.31 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.5, 169.4, 150.0, 131.6, 127.7, 127.0, 51.6, 42.3, 36.3, 21.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for C12H16NO3 222.1130; Found 222.1129.

3-(4-carbamoylphenyl)butanoic acid (***Rac*-5**, 182 mg, yield 88%): White solid, mp 152-153 °C. Methyl 3-(4-carbamoylphenyl)butanoate 6 (220mg, 1 mmol) was added to a solution of LiOH (72 mg, 3 mmol) in THF(10 mL) and H_2O (10 mL), the mixture was stirred at room temperature for 3 hours, TLC showed 3-(4-carbamoylphenyl)butanoate (6) was disappeared, then concentrated to remove THF, the residue was acidification with $NaHSO_3$ to pH 5, extracted with ethyl acetate for three times, dried over $MgSO_4$, filtered and concentrated to get *Rac*-**5** as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.10 (br s, 1H), 7.90 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.28 (br s, 1H), 3.19 (m, 1H), 2.52 (d, *J* = 7.6 Hz, 2H), 1.21 (d, *J* = 7.2 Hz, 3H). LC-MS (ESI, *m/z*): $[M+H]^+$ 208.1.

■ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

X-ray crystallography data, HPLC data and NMR spectra of the products (PDF)

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Notes

Any additional relevant notes should be placed here.

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