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Enantioselective Synthesis of Dialkylated α-Hydroxy Carboxylic Acids through Asymmetric Phase-Transfer Catalysis

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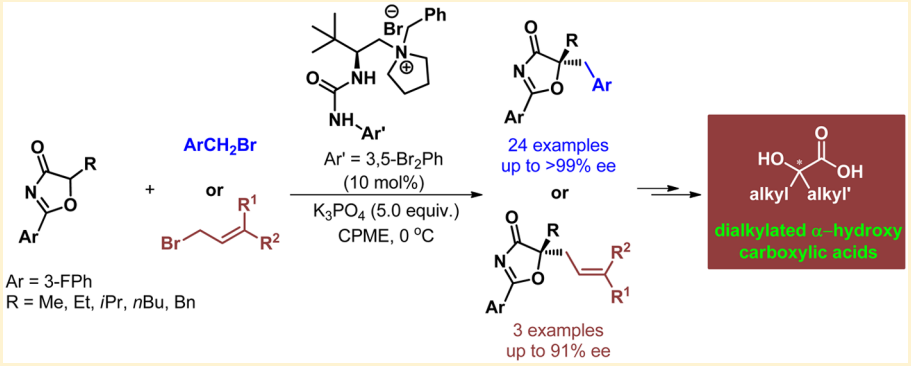
Supporting Information



ABSTRACT: In the presence of an *L*-*tert*-leucine-derived urea−ammonium salt as phase-transfer catalyst, a highly enantioselective alkylation of 5*H*-oxazol-4-ones with various benzyl bromides and allylic bromides has been developed to furnish catalytic asymmetric synthesis of biologically important dialkylated α-hydroxy carboxylic acids with a broad scope. This is the first example of an *L*-amino acid-derived urea−ammonium salt being used as a phase-transfer catalyst with excellent catalytic efficiency.

Enantiomeric pure dialkylated α-hydroxy carboxylic acids (HCAs), containing a tertiary hydroxy stereogenic center and an easily modified carboxylic acid, are versatile and powerful intermediates to access various chiral molecules with biological importance.[1] For example (Figure 1), α-methyl-α-benzyl HCA can be conveniently transformed to microbicide

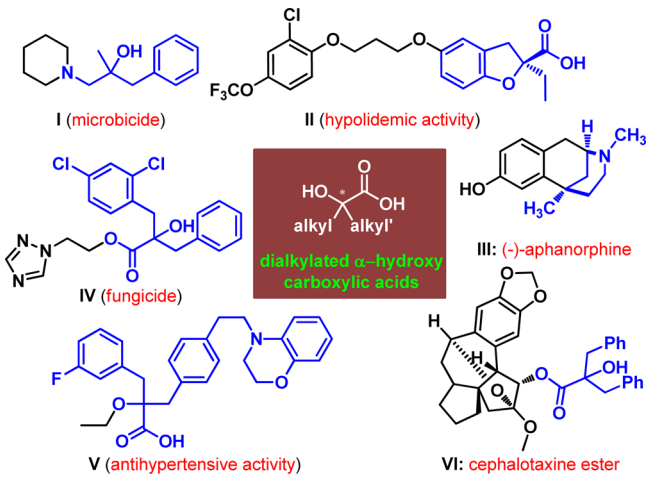


Figure 1. Representative dialkylated HCAs.

I,[1a] and α-ethyl-α-benzyl HCA has been demonstrated as a precursor to produce compound **II** with significant hypolidemic activity.[1b] α-Methyl-α-allyl HCA has been successfully employed as a key motif to accomplish asymmetric total synthesis of alkaloid (−)-aphanorphine (**III**).[1c] Furthermore, α,α-dibenzyl HCAs are found as the main frameworks of bioactive non-natural products **IV** and **V** and the side chain of natural product **VI** (cephalotaxine ester).[1d−f] In this context, stereoselective construction of these valuable entities has attracted numerous interest of chemists over the past few decades. To date, several efficient protocols,[1b,c,2,3] including kinetic resolution[2] and the employment of chiral auxiliaries,[1c,3] have been described. However, a catalytic asymmetric variant still remains elusive.[1b]

In 2004, the Trost group[4] creatively introduced 5*H*-oxazol-4-ones as α-alkyl-α-hydroxy ester surrogates in an asymmetric allylic alkylation, leading to a convenient pathway to furnish asymmetric synthesis of HCAs. Since then, 5*H*-oxazol-4-ones have been utilized as nucleophiles in a variety of asymmetric reactions to provide various HCA derivatives with biological targets. For instance, in 2010, Misaki, Sugimura, and co-workers presented a chiral guanidine-catalyzed aldol reaction of 5*H*-

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oxazol-4-ones to afford α-methyl-α,β-dihydroxy esters.[5a] Subsequently, the same research group described an asymmetric 1,4-addition of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds, and the obtained adducts could be conveniently converted to γ,γ-disubstituted butenolides.[5b] Ye et al. revealed an asymmetric Michael addition of 5*H*-oxazol-4-ones to α,β-unsaturated ketones.[6] To achieve highly stereoselective synthesis of α-alkylisoserine derivatives, Wang[7a] and our[7b] groups individually accomplished asymmetric Mannich reactions of 5*H*-oxazol-4-ones.[6] Other well-established examples include 1,4-conjugate addition to nitroolefins,[8a,b] vinyl sulfones[8c] and enones,[8d] transition metal-catalyzed allylic alkylation,[8e] and α-sulfenylation.[8f] Nevertheless, to the best of our knowledge, asymmetric phase-transfer alkylation and allylic alkylation of 5*H*-oxazol-4-ones, which can produce the desirable chiral dialkylated HCAs, has never been reported and represents a formidable task for their easily hydrolyzed imide groups under basic conditions. As an extension of our recent interest in developing organocatalytic asymmetric methodologies to construct chiral tertiary alcohols,[7b,8b,c,f,9] especially through exploring 5*H*-oxazol-4-one paticipating highly stereoselective asymmetric reactions,[7b,8b,c,f] we report here an unprecedented enantioselective alkylation of 5*H*-oxazol-4-ones through asymmetric phase-transfer catalysis to provide chiral dialkylated HCAs in satisfactory yields.

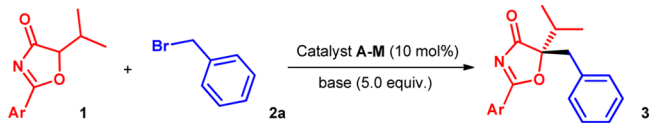
In our initial study, alkylation of 5*H*-oxazol-4-one **1a** and benzyl bromide **2a** was chosen as the model reaction to probe the feasible reaction conditions (Table 1). First, the reaction was carried out at 25 °C with 5.0 equiv of Cs_2CO_3 as base and employing 10 mol % of *L-tert*-leucine-derived thiourea−tertiary amine **A** (Figure 2) as catalyst, whose efficacy has been verified by our group and others.[8b,9,10] It was discovered that the desired alkylation product **3a** was obtained in 33% yield after 35 h with 40% ee (entry 1). In 2013, Zhao and co-workers developed *L*-α-amino acid-derived thiourea−ammonium salts as novel phase-transfer catalysts (PTCs) to successively address asymmetric aza-Henry reactions and the addition of mercaptans to imines in high enantioselectivities.[11] These achievements prompted us to attempt thiourea−ammonium **B** as PTC, but product **3a** with only 5% ee was achieved (entry 2). Although no success has yet been established utilizing *L*-amino acid-derived thiourea−ammonium salts as a catalyst, we still looked forward to improving the enantioselectivity through modifying the brønsted acid moiety of the catalyst. Thus, urea−ammonium salt **C** was evaluated, and to our delight, the enantioselectivity was dramatically improved (75% ee, entry 3).

Subsequently, we evaluated urea−ammonium salts **D** and **E** derived from other *L*-α-amino acids, but their distinct side chains could not give better results (entries 4 and 5). Catalyst **F**, featuring a pyrrolidine-formed ammonium salt, could slightly improve the ee value of **3a** to 77% (entry 6). A screening of solvents (entries 7−10) proved that cyclopentyl methyl ether (CPME) was the best (entry 10). When K_3PO_4 was utilized as base, **3a** with 81% ee was achieved (entry 11). The lower temperature was found to improve the enantioselectivity (entries 12−13), and the ee value of **3a** reached 87% when the temperature was 0 °C (entry 13).

Our previous investigations indicated that the aryl group on the 2-position of 5*H*-oxazol-4-ones often affects the enantioselective outcomes.[8b,f] Therefore, a series of 5*H*-oxazol-4-ones were tested under the established reaction conditions (see the Supporting Information for details). It was found that the alkylation product **3b**, from 5*H*-oxazol-4-one **1b** with a fluoro group at the *meta* position of the phenyl ring, could be obtained with the best enantioselectivity (90% ee, entry 14). Although excellent enantioselectivity was obtained, 40% yield of **3b** prompted us to improve the reactivity by increasing the amount of **2a** (entries 15−17). The survey indicated that 15.0 equiv of benzyl bromide **2a** could produce **3b** in moderate yield with slightly decreased ee value (entry 16). We then examined other PTCs (entries 18−24), such as **G**−**I** bearing different benzyl groups on ammonium moieties (entries 18−20) and **J**−**M** with different urea substituents (entries 21−24); catalyst **K** was observed to present the best results, affording product **3a** in 71% yield with 91% ee within 48 h (entry 22). Disappointingly, urea−tertiary amine **N**, the precursor of **K**, could not contribute a better enantioselective result than **K** (entry 26), representing an opposite stereoselective tendency compared to thiourea−tertiary amine **A** and thiourea−ammonium salt **B** (entries 1−2).

With the optimized reaction conditions in hand, we examined the reaction scope, and the results are summarized in Table 2. First, we attempted enantioselective alkylation of 5*H*-oxazol-4-one **1b** with a variety of benzyl bromides in the presence of 10 mol % of catalyst **K** at 0 °C and in CPME as

Table 1. Optimization of Reaction Conditions[a]



entry	1	cat.	solvent	*T* (h)[b]	yield (%)[c]	ee (%)[d]
1	**1a**	**A**	toluene	35	33	40
2	**1a**	**B**	toluene	35	54	5
3	**1a**	**C**	toluene	35	47	75
4	**1a**	**D**	toluene	35	48	73
5	**1a**	**E**	toluene	35	42	70
6	**1a**	**F**	toluene	35	50	77
7	**1a**	**F**	CH_2Cl_2	35	37	62
8	**1a**	**F**	Et_2O	35	32	69
9	**1a**	**F**	MTBE	35	55	79
10	**1a**	**F**	CPME	35	51	80
11	**1a**	**F**	CPME	35	56	81
12	**1a**	**F**	CPME	72	48	85
13	**1a**	**F**	CPME	72	43	87
14	**1b**	**F**	CPME	72	40	90
15[e]	**1b**	**F**	CPME	48	34	88
16[f]	**1b**	**F**	CPME	24	63	88
17[g]	**1b**	**F**	CPME	24	71	85
18[f]	**1b**	**G**	CPME	24	67	79
19[f]	**1b**	**H**	CPME	24	60	86
20[f]	**1b**	**I**	CPME	24	63	86
21[f]	**1b**	**J**	CPME	17	60	91
22[f]	**1b**	**K**	CPME	48	71	91
23[f]	**1b**	**L**	CPME	17	63	67
24[f]	**1b**	**M**	CPME	24	50	81
25[f]	**1b**	**N**	CPME	24	57	85

[a]Unless otherwise noted, the reaction was carried out with 0.05 mmol of **1**, 0.25 mmol of **2a** (5.0 equiv), 0.25 mmol of base, and 0.005 mol of catalyst in 0.5 mL of solvent. Entries 1−10, Cs_2CO_3 was used as base; entries 11−26, K_3PO_4 was used as base. Entries 1−11, *T* = 25 °C; entry 12, *T* = 10 °C; entries 13−26 *T* = 0 °C. Entries 1−13, **3a** was product; entries 14−26, **3b** was product. [b]The reaction time was determined on TLC analysis until **1** was exhausted. [c]Isolated yield after silica gel column chromatography. [d]Determined by HPLC analysis. [e]Used 10.0 equiv of **2a**. [f]Used 15.0 equiv of **2a**. [g]Used 20.0 equiv of **2a**.

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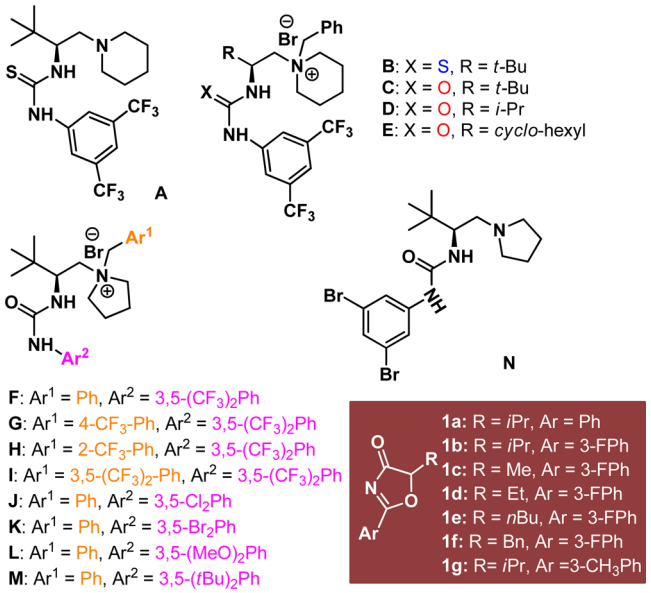


Figure 2. Structures of catalysts (**A**–**N**) and 5*H*-oxazol-4-ones (**1a**–**g**).

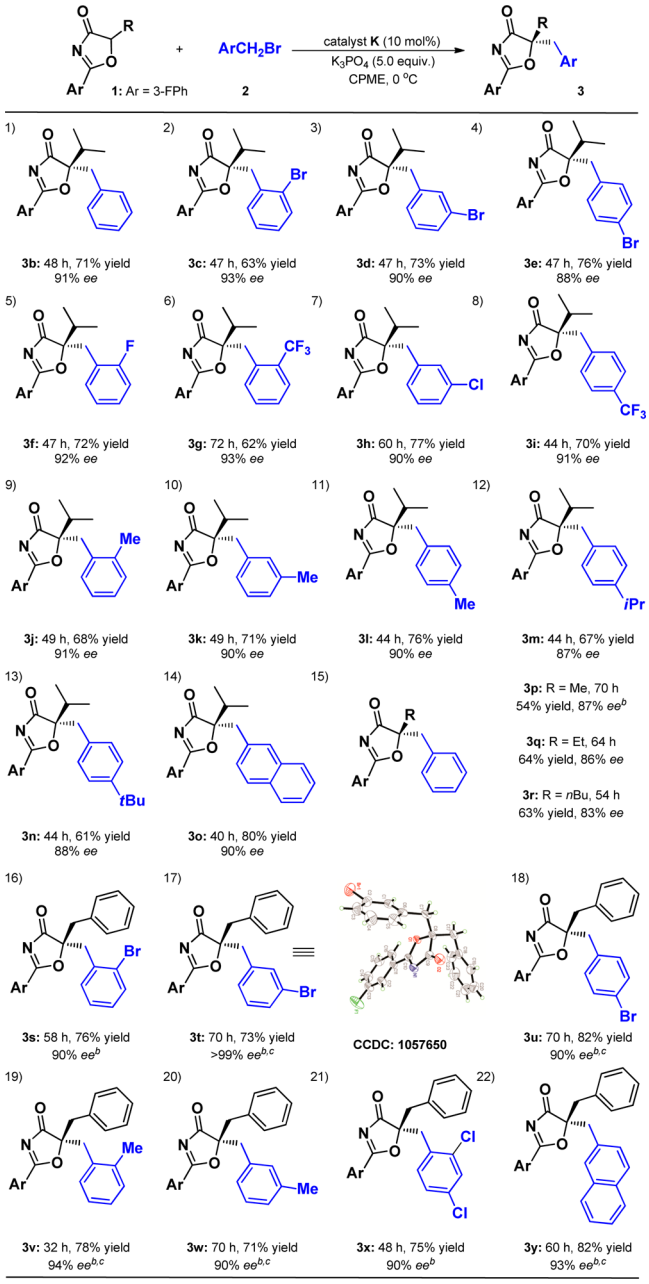
solvent (Table 2, entries 1–14). The corresponding products **3b**–**o** were obtained in 62–80% yield with 87–93% ee within 44–72 h. Next, 5*H*-oxazol-4-ones **1c**–**e** were subjected to alkylation with benzyl bromide **2a**, producing adducts **3p**–**r** with slightly decreased ee values (entry 15, 83–87% ee), probably due to less steric hindrance of methyl, ethyl, and *n*-butyl on the 5-position of 5*H*-oxazol-4-ones.

Subsequently, we engaged in surveying alkylations of 5-benzyl-substituted 5*H*-oxazol-4-one **1f** to several benzyl bromides to access the intriguing but challenging chiral dibenzylated HCAs (Table 2, entries 16–22). It was found that the corresponding products **3s**–**y** were achieved in 71–82% yields with good to excellent enantioselectivities. Importantly, ee values of **3t**–**w** and **3y** could be improved to 90 to >99% ee after a single recrystallzation.

Then, 5*H*-oxazol-4-one **1g**, bearing a *meta*-methyl-substituted phenyl group on the 2-position was reacted respectively with allylic bromide, crotyl bromide, and 3-methylcrotyl bromide under the established reaction conditions (Scheme 1); three corresponding allylic alkylation products **5a**–**c** were obtained in 61–87% yields with 87–91% ee within 41–78 h. The absolute configurations of alkylation products **3** and allylic alkylation products **5** were assigned based on X-ray crystallographic analysis of a single crystal of **3t** (Table 2, entry 17).[12]

To elucidate the enantioselective outcome of this asymmetric alkylation, a favored transition-state model is proposed as shown in Figure 3 (left). After abstraction of 5-hydrogen from 5*H*-oxazol-4-ones, the formed enolates of 5*H*-oxazol-4-ones should bind to the R_4N^+ arm of the catalyst via electrostatic interaction. The better enantioselectivity of urea catalyst than thiourea catalyst indicates that urea would simultaneously interact with the enolate of 5*H*-oxazol-4-one via hydrogen bonding for its higher acidity and the reasonably longer N–H bond. Then, the *tert*-butyl group of the catalyst would produce steric hindrance to the 5-substituent of 5*H*-oxazol-4-one (see disfavored transition state, Figure 2, right), which finally affords the obtained alkylated products with the observed enantioselective results. In light of bulkier substituents on the 5-position of 5*H*-oxazol-4-ones yielding better enantioselective results, the devised transition-state model can be further demonstrated.

Table 2. Asymmetric Alkylation of 5*H*-oxazol-4-ones 1 to Various Benzyl Bromides 2[a]



[a]All reactions were carried out with 0.1 mmol of **1**, 1.5 mmol of **2**, 0.5 mmol of K_3PO_4, and 0.01 mmol of catalyst **K** in 1.0 mL of CPME at 0 °C. Isolated yields. Ee values were determined by chiral HPLC analysis. [b]Used 10 mol % of catalyst **F**. [c]The ee values were obtained after a single recrystallization. Initial data: **3t**: ee = 85%; **3u**: ee = 85%; **3v**: ee = 89%; **3w**: ee = 85%; **3y**: ee = 84%.

To exhibit the synthetic utility of this work, we explored several transformations from alkylation products (Scheme 2). First, the hydrolysis of **3s** employing NaOH as the base smoothly afforded amide **6** in 86% yield (Scheme 2, eq 1). Then, amide **6** was able to be reduced to amine **7** in 81% yield without compromising the ee value. It is worth mentioning that both chiral dibenzylated α-hydroxyl amides and dibenzylated α-hydroxyl amines are significant structural motifs presenting in

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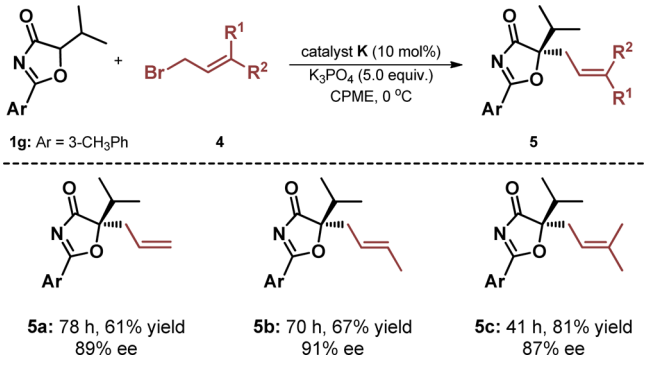
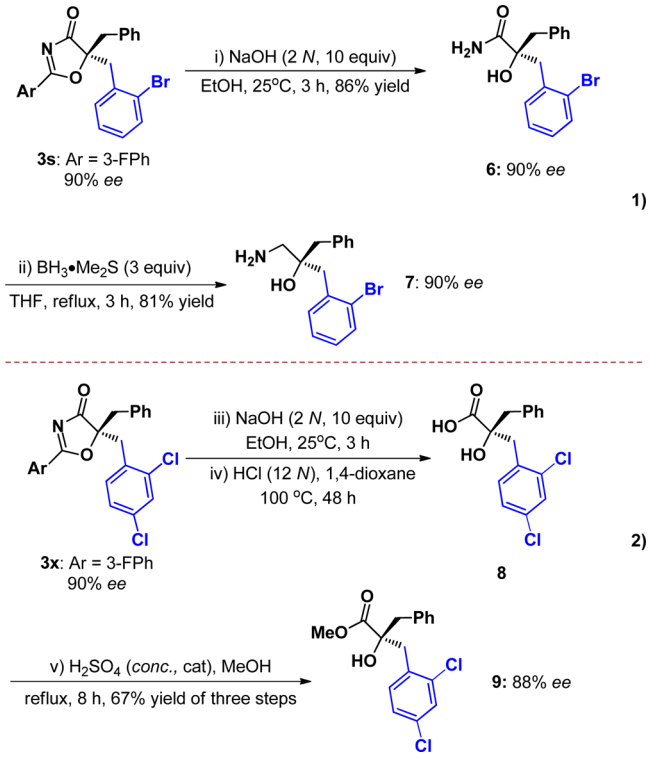
Scheme 1. Enantioselective Allylic Alkylation of 5*H*-oxazol-4-one 1g



Scheme 2. Transformations of Alkylation Products



many biologically active molecules.[13] Subsequently, through the sequence of hydroxylation by NaOH, acidification, and esterification, adduct **3x** was transformed to ester **9** in 67% yield with maintained enantiomeric purity (Scheme 2, eq 2). Obviously, this strategy could be readily adopted in asymmetric synthesis of fungicide **IV**.

In summary, we have developed a highly enantioselective catalytic synthesis of dialkylated HCAs with a broad scope. By employing an *L*-*tert*-leucine-derived urea−ammonium salt as phase-transfer catalyst, 5*H*-oxazol-4-ones could work with various benzyl bromides and allylic bromides to afford the biologically important alkylated and allylic alkylated adducts with 83 to >99% ee. This is the first successful example demonstrating the excellent catalytic efficiency of *L*-amino acid-derived urea−ammonium salts. We believe that this work should help to further develop novel *L*-amino acid-based bifunctional PTCs to deal with challenging and unprecedented reactions.

EXPERIMENTAL SECTION

General Procedure. 5*H*-Oxazol-4-ones **1** (0.1 mmol, 1.0 equiv), urea−ammonium salt **K** (6.2 mg, 0.01 mmol, 0.1 equiv) and K_3PO_4 (0.5 mmol, 5.0 equiv) were dissolved in CPME (1.0 mL) in a 4.0 mL sample vial and stirred at 0 °C for 30 min. Then, benzyl bromide **2** (1.5 mmol, 15.0 equiv) was added. The reaction mixtures were stirred and maintained at 0 °C, and the reaction progress was monitored by TLC. Upon complete consumption of **1**, the reaction mixtures were directly loaded onto a short silica gel column, followed by separation with flash chromatography using gradient elution with petroleum ether/ethyl acetate (15:1 to 8:1). After removal of solvent under vacuum, corresponding adducts **3** were obtained.

*(S)-1-Benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-3,3-dimethylbutyl)piperidin-1-ium Bromide (**B**).* White powder; mp 179.0−181.3 °C; 204 mg (0.5 mmol), 65.3% yield (final step); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.51−7.49 (m, 3H), 7.31 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 7.3 Hz, 1H), 7.12 (s, 2H), 6.55 (d, J = 9.5 Hz, 1H), 4.79 (d, J = 14.1 Hz, 1H), 4.61 (s, 1H), 4.39 (d, J = 14.1 Hz, 1H), 4.08 (d, J = 12.8 Hz, 1H), 3.73 (d, J = 12.0 Hz, 1H), 3.59 (s, 1H), 2.84 (s, 1H), 2.72 (d, J = 10.7 Hz, 2H), 2.45 (d, J = 12.3 Hz, 1H), 1.98 (d, J = 8.0 Hz, 4H), 1.50 (s, 1H), 0.82 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.0, 155.4, 150.7, 140.9, 135.8, 132.6, 132.2, 131.8, 131.3, 128.9 (two peaks), 127.7, 125.2, 122.7, 122.4, 121.6, 117.9 (two peaks), 116.0, 57.7, 56.1, 55.3, 53.9, 35.7, 35.4, 26.6, 26.2, 23.3, 22.1, 21.7; HRMS (ESI) m/z 546.2372 (M − Br^-), calcd for $C_{27}H_{34}F_6N_3S$ 546.2378.

*(S)-1-Benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3-dimethylbutyl)piperidin-1-ium Bromide (**C**).* White powder; mp 129.8−131.2 °C; 233 mg (0.5 mmol), 76.5% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.07 (s, 2H), 7.87 (d, J = 9.8 Hz, 1H), 7.55−7.41 (m, 6H), 4.89 (d, J = 13.0 Hz, 1H), 4.80 (d, J = 13.0 Hz, 1H), 4.26 (t, J = 9.7 Hz, 1H), 4.08−4.00 (m, 2H), 3.83−3.68

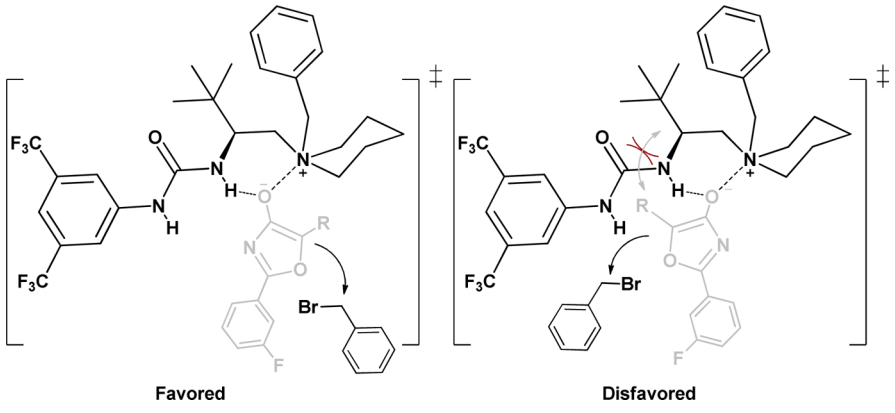


Figure 3. Proposed reaction mechanism.

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(m, 2H), 3.24−3.07 (m, 2H), 2.16 (s, 3H), 1.92 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 141.3, 133.5, 132.0, 131.6, 131.1 (d, J = 10.5 Hz), 129.4, 128.8, 126.4, 125.2, 121.6, 118.0, 115.1, 66.7, 60.2, 57.3 (two peaks), 52.4, 36.7, 26.5, 20.8, 20.3 (two peaks); HRMS (ESI) m/z 530.2601 (M − Br$^-$), calcd for $C_{27}H_{34}F_6N_3O$ 530.2606.

*(S)-1-Benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3-methylbutyl)piperidin-1-ium Bromide (**D**).* White powder; mp 203.5−205.9 °C; 245 mg (0.5 mmol), 82.3% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.06 (s, 2H), 7.86 (d, J = 9.7 Hz, 1H), 7.52−7.41 (m, 6H), 4.87 (d, J = 13.1 Hz, 1H), 4.79 (d, J = 13.1 Hz, 1H), 4.46−4.43 (m, 1H), 3.99−3.82 (m, 3H), 3.43−3.22 (m, 3H), 2.14 (d, J = 13.4 Hz, 2H), 1.94 (s, 4H), 1.52−1.40 (m, 1H), 1.06 (t, J = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 141.2, 133.2, 132.3, 131.9, 131.6, 131.2 (d, J = 37.2 Hz), 129.4, 128.7, 126.2, 125.1, 121.5, 117.9, 114.9, 65.7, 60.8, 58.5, 58.0, 48.8, 33.38, 20.7, 20.2 (two peaks), 19.5, 17.1; HRMS (ESI) m/z 516.2446 (M − Br$^-$), calcd for $C_{26}H_{32}F_6N_3O$ 516.2449.

*(S)-1-Benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-cyclohexylethyl)piperidin-1-ium Bromide (**E**).* White powder; mp 101.9−103.2 °C; 199 mg (0.5 mmol), 62.5% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.00 (s, 2H), 7.77 (d, J = 9.6 Hz, 1H), 7.46−7.34 (m, 6H), 4.82 (d, J = 13.1 Hz, 1H), 4.71 (d, J = 13.1 Hz, 1H), 4.37−4.35 (m, 1H), 3.92 (dd, J = 13.9, 10.3 Hz, 1H), 3.76 (d, J = 9.3 Hz, 2H), 3.36 (d, J = 14.2 Hz, 1H), 3.23−3.16 (m, 2H), 2.10−2.06 (m, 1H), 1.86 (s, 3H), 1.75−1.65 (m,5H), 1.54−1.51 (m, 2H), 1.37−1.24 (m, 2H), 1.17−1.00 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 141.3, 133.3, 132.5, 132.0, 131.6, 131.1, 129.5, 126.3, 125.2, 121.6, 118.0, 115.0, 65.8, 61.1, 58.2 (two peaks), 48.8, 43.4, 29.8, 27.6, 25.9 (two peaks), 20.8, 20.2 (two peaks); HRMS (ESI) m/z 556.2758 (M − Br$^-$), calcd for $C_{29}H_{36}F_6N_3O$ 556.2762.

*(S)-1-benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3-dimethylbutyl)pyrrolidin-1-ium bromide (**F**).* White powder; mp 102.3−104.5 °C; 212 mg (0.5 mmol), 71.4% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.08 (s, 2H), 7.80 (d, J = 9.3 Hz, 1H), 7.52−7.41 (m, 6H), 4.80 (d, J = 12.8 Hz, 1H), 4.62 (d, J = 12.8 Hz, 1H), 4.47−4.31 (m, 1H), 4.15−4.02 (m, 1H), 3.98−3.74 (m, 2H), 3.67−3.42 (m, 3H), 2.38 (s, 2H), 2.05 (s, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 141.3, 132.8, 132.6 (two peaks), 132.0, 131.6, 131.2, 129.6, 127.0, 125.2, 121.6, 118.0, 115.1, 62.3 (two peaks), 61.4, 61.0, 53.1, 36.3, 26.5, 21.5, 20.6; HRMS (ESI) m/z 516.2446 (M − Br$^-$), calcd for $C_{26}H_{32}F_6N_3O$ 516.2449.

*(S)-1-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-3,3-dimethylbutyl)-1-(4-(trifluoromethyl)benzyl)pyrrolidin-1-ium Bromide (**G**).* White powder; mp 115.3−117.1 °C; 241 mg (0.5 mmol), 72.8% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.00 (s, 2H), 7.71−7.62 (m, 5H), 7.37 (s, 1H), 4.91−4.80 (m, 2H), 4.27 (t, J = 10.0 Hz, 1H), 4.03−3.86 (m, 3H), 3.54−3.40 (m, 3H), 2.30−2.23 (m, 1H), 2.20−2.14 (m, 1H), 2.02 (s, 2H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 141.2, 133.5, 133.0, 132.5, 132.1, 131.6, 131.1 (two peaks), 126.4 (two peaks), 125.1, 121.5, 117.9, 115.2, 62.2, 61.8, 61.5, 60.4, 53.3, 36.3, 26.4, 21.2, 20.6; HRMS (ESI) m/z 584.2320 (M − Br$^-$), calcd for $C_{27}H_{31}F_9N_3O$ 584.2323.

*(S)-1-(2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-3,3-dimethylbutyl)-1-(2-(trifluoromethyl)benzyl)pyrrolidin-1-ium Bromide (**H**).* White powder; mp 96.8−98.4 °C; 251 mg (0.5 mmol), 75.6% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.05 (d, J = 11.5 Hz, 3H), 7.85 (d, J = 6.2 Hz, 1H), 7.80−7.77 (m, 1H), 7.63 (p, J = 8.0 Hz, 2H), 7.43 (s, 1H), 5.21 (d, J = 14.2 Hz, 1H), 5.11 (d, J = 14.2 Hz, 1H), 4.33−4.21 (m, 2H), 4.16−4.11 (m, 1H), 4.04−3.96 (m, 1H), 3.69 (d, J = 13.7 Hz, 1H), 3.29−3.22 (m, 1H), 3.16−3.10 (m, 1H), 2.44−2.37 (m, 1H), 2.25−2.15 (m, 1H), 2.08−1.95 (m, 2H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 141.2, 136.1, 132.6 (two peaks), 132.0, 131.5 (two peaks), 128.0 (two peaks), 125.2 (three peaks), 118.1, 63.7, 60.5 (two peaks), 53.3, 36.4, 26.4, 20.8 (two peaks); HRMS (ESI) m/z 584.2319 (M − Br$^-$), calcd for $C_{27}H_{31}F_9N_3O$ 584.2323.

*(S)-1-(3,5-Bis(trifluoromethyl)benzyl)-1-(2-(3-(3,5-bis-(trifluoromethyl)phenyl)ureido)-3,3-dimethylbutyl)pyrrolidin-1-ium Bromide (**I**).* White powder; mp 214.5−216.2 °C; 300 mg (0.5 mmol), 82.1% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.15 (s, 2H), 8.04 (s, 2H), 8.01 (s, 1H), 7.72 (d, J = 9.8 Hz, 1H), 7.42 (s, 1H), 5.21 (d, J = 13.4 Hz, 1H), 5.10 (d, J = 13.4 Hz, 1H), 4.38−4.32 (m, 1H), 4.26−4.13 (m, 2H), 4.09−4.00 (m, 1H), 3.69−3.65 (m, 1H), 3.47−3.38 (m, 2H), 2.50−2.33 (m, 2H), 2.29−2.17 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 141.0, 133.9, 133.4, 133.1 (three peaks), 132.6, 132.1, 131.7, 131.2, 130.1, 125.0 (two peaks), 124.3, 121.5, 120.7, 118.0, 115.4, 62.5, 61.6, 61.0, 60.5, 53.4, 36.3, 26.4 (two peaks), 21.1, 20.6; HRMS (ESI) m/z 652.2194 (M − Br$^-$), calcd for $C_{28}H_{30}F_{12}N_3O$ 652.2197.

*(S)-1-Benzyl-1-(2-(3-(3,5-dichlorophenyl)ureido)-3,3-dimethylbutyl)pyrrolidin-1-ium Bromide (**J**).* White powder; mp 207.0−209.2 °C; 176 mg (0.5 mmol), 66.8% yield (final step); ^{1}H NMR (300 MHz, CD_3OD_SPE) δ 7.91 (s, 1H), 7.65−7.63 (m, 2H), 7.57−7.53 (m, 3H), 7.49 (d, J = 1.8 Hz, 2H), 7.03 (t, J = 1.7 Hz, 1H), 4.72 (d, J = 13.3 Hz, 1H), 4.65 (d, J = 13.3 Hz, 1H), 4.35 (d, J = 9.3 Hz, 1H), 3.71−3.45 (m, 6H), 2.21−2.01 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD_SPE) δ 155.6, 141.7, 134.8, 132.7, 130.5, 129.2, 128.0, 121.6, 116.4, 78.1, 62.9, 61.8, 61.1, 60.8, 52.9, 35.9, 25.0, 21.2, 20.5; HRMS (ESI) m/z 448.1918 (M − Br$^-$), calcd for $C_{24}H_{32}Cl_2N_3O$ 448.1922.

*(S)-1-Benzyl-1-(2-(3-(3,5-dibromophenyl)ureido)-3,3-dimethylbutyl)pyrrolidin-1-ium Bromide (**K**).* White powder; mp 205.9−208.2 °C; 237 mg (0.5 mmol), 76.9% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.84 (d, J = 10.0 Hz, 1H), 7.75 (s, 2H), 7.57−7.43 (m, 5H), 7.22 (s, 1H), 4.79 (d, J = 13.3 Hz, 1H), 4.58 (d, J = 13.3 Hz, 1H), 4.38 (t, J = 9.7 Hz, 1H), 4.07 (s, 1H), 3.92−3.70 (m, 2H), 3.62−3.41 (m, 3H), 2.44−2.18 (m, 2H), 2.07 (s, 2H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 142.0, 132.7, 131.2, 129.7, 127.3, 127.0, 122.7, 119.9, 62.2 (two peaks), 61.7, 61.1, 53.0, 36.3, 26.6, 21.5, 20.5; HRMS (ESI) m/z 536.0908 (M − Br$^-$), calcd for $C_{24}H_{32}{}^{79}Br_2N_3O$ 536.0912.

*(S)-1-Benzyl-1-(2-(3-(3,5-dimethoxyphenyl)ureido)-3,3-dimethylbutyl)pyrrolidin-1-ium Bromide (**L**).* White powder; mp 83.5−85.9 °C; 199 mg (0.5 mmol), 76.9% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (s, 1H), 7.71 (d, J = 10.0 Hz, 1H), 7.47 (dt, J = 13.4, 6.9 Hz, 5H), 6.83 (d, J = 2.2 Hz, 2H), 6.09 (t, J = 2.2 Hz, 1H), 4.81 (d, J = 13.3 Hz, 1H), 4.60 (d, J = 13.3 Hz, 1H), 4.38 (t, J = 9.8 Hz, 1H), 4.11−3.98 (m, 1H), 3.91−3.80 (m, 1H), 3.78−3.66 (m, 7H), 3.58−3.45 (m, 3H), 2.34 (s, 1H), 2.18 (s, 1H), 2.08−1.95 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 156.0, 141.5, 132.8, 131.0, 129.5, 127.2, 96.8, 95.1, 62.5, 62.1, 61.2 (two peaks), 55.4, 52.9, 36.3, 26.6, 21.5, 20.6; HRMS (ESI) m/z 440.2908 (M − Br$^-$), calcd for $C_{26}H_{38}N_3O_3$ 440.2913.

*(S)-1-Benzyl-1-(2-(3-(3,5-di-tert-butylphenyl)ureido)-3,3-dimethylbutyl)pyrrolidin-1-ium Bromide (**M**).* White powder; mp 198.4−201.2 °C; 161 mg (0.5 mmol), 56.5% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.76 (d, J = 9.6 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.45−7.39 (m, 5H), 7.05 (s, 1H), 4.82 (d, J = 13.2 Hz, 1H), 4.65 (d, J = 13.2 Hz, 1H), 4.43−4.36 (m, 1H), 4.11 (s, 1H), 3.88−3.80 (m, 2H), 3.63−3.50 (m, 3H), 2.37 (s, 1H), 2.21 (s, 1H), 1.99 (s, 2H), 1.29 (s, 18H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 151.2, 139.0, 132.9, 131.0, 129.5, 127.3, 116.5, 113.5, 62.4, 60.9 (two peaks), 52.8, 36.3, 34.9, 31.9, 31.5, 29.7, 29.4, 26.6, 22.7, 21.5, 20.7, 14.1; HRMS (ESI) m/z 492.3951 (M − Br$^-$), calcd for $C_{32}H_{50}N_3O$ 492.3954.

*(S)-1-(3,5-Dibromophenyl)-3-(3,3-dimethyl-1-(pyrrolidin-1-yl)-butan-2-yl)urea (**N**).* White powder; mp 175.5−177.5 °C; 154 mg (0.5 mmol), 68.9% yield (final step); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 2H), 7.19 (s, 1H), 5.11 (s, 1H), δ 3.46 (s, 1H), 3.28 (s, 1H), 2.80−2.56 (m, 6H), 1.86 (s, 4H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 142.6, 127.1, 122.8, 120.4, 59.4, 54.4, 34.0, 26.6, 23.6; HRMS (ESI) m/z 446.0438 (M + H$^+$), calcd for $C_{17}H_{26}{}^{79}Br_2N_3O$ 446.0443.

*(R)-(+)-5-Benzyl-2-(3-fluorophenyl)-5-isopropyloxazol-4(5H)-one (**3b**).* Colorless oil; 22 mg (0.1 mmol), 71% yield; 91% ee; $[\alpha]_D^{22}$ +39.23 (c 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.7 Hz, 1H), 7.75−7.71 (m, 1H), 7.46 (td, J = 8.0, 5.5 Hz, 1H), 7.34 (ddd, J = 10.1, 5.5, 1.7 Hz, 3H), 7.15−7.11 (m, 5H), 3.32 (d, J = 13.9 Hz, 1H), 3.20 (d, J = 13.9 Hz, 1H), 2.37−2.28 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

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192.5, 184.3, 164.2, 160.9, 133.4, 130.6 (d, J = 7.9 Hz), 130.0, 128.3, 127.7 (d, J = 8.2 Hz), 127.3, 125.6 (d, J = 3.1 Hz), 122.0, 121.7, 116.5, 116.2, 94.3, 39.8, 34.0, 16.6 (d, J = 2.4 Hz); HRMS (ESI) m/z 312.1408 (M + H^+), calcd for $C_{19}H_{19}FNO_2$ 312.1400. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 11.0 min (major) and 13.0 min (minor).

*(R)-(−)-5-(2-Bromobenzyl)-2-(3-fluorophenyl)-5-isopropyloxazol-4(5H)-one (**3c**).* Colorless oil; 24.5 mg (0.1 mmol), 63% yield; 93% ee; $[\alpha]_D^{22}$ −41.41 (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 1H), 7.77−7.74 (m, 1H), 7.43 (td, J = 8.0, 5.5 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H), 7.31 (td, J = 8.3, 1.9 Hz, 1H), 7.19 (dd, J = 7.7, 1.5 Hz, 1H), 7.11 (dd, J = 10.8, 4.2 Hz, 1H), 6.94 (td, J = 7.8, 1.6 Hz, 1H), 3.81 (d, J = 13.8 Hz, 1H), 3.28 (d, J = 13.8 Hz, 1H), 2.42−2.32 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 184.6, 163.7, 161.2, 133.3, 132.8, 131.5, 130.5 (d, J = 7.9 Hz), 129.0, 127.6, 127.4, 125.8, 122.2, 122.0 (d, J = 21.3 Hz), 116.7, 116.5, 94.3, 39.2, 34.3, 16.6; HRMS (ESI) m/z 392.0493 (M + H^+), calcd for $C_{19}H_{18}{}^{81}BrFNO_2$ 392.0484. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 9.0 min (major) and 11.2 min (minor).

*(R)-(+)-5-(3-Bromobenzyl)-2-(3-fluorophenyl)-5-isopropyloxazol-4(5H)-one (**3d**).* Colorless oil; 28 mg (0.1 mmol), 73% yield; 90% ee; $[\alpha]_D^{22}$ +53.41 (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.87 (m, 1H), 7.75 (ddd, J = 9.0, 2.4, 1.5 Hz, 1H), 7.49 (td, J = 8.0, 5.5 Hz, 1H), 7.36 (tdd, J = 8.3, 2.6, 0.9 Hz, 1H), 7.30 (d, J = 1.6 Hz, 1H), 7.26−7.25 (m, 1H), 7.24−7.22 (m, 1H), 7.04 (dt, J = 15.4, 7.7 Hz, 2H), 3.29 (d, J = 13.9 Hz, 1H), 3.15 (d, J = 13.9 Hz, 1H), 2.32 (dt, J = 13.7, 6.8 Hz, 1H), 1.14 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 184.3, 163.8, 161.38, 135.68, 133.1, 130.6, 129.9, 128.5, 127.5 (d, J = 8.2 Hz), 125.6 (d, J = 3.2 Hz), 122.1, 116.5, 116.3, 93.8, 39.4, 33.9, 16.6 (d, J = 2.3 Hz); HRMS (ESI) m/z 390.0508 (M + H^+), calcd for $C_{19}H_{18}BrFNO_2$ 390.0505. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95:5; flow rate 0.5 mL/min; 25 °C; 254 nm; retention time, 17.3 min (minor) and 19.1 min (major).

*(R)-(+)5-(4-Bromobenzyl)-2-(3-fluorophenyl)-5-isopropyloxazol-4(5H)-one (**3e**).* Colorless oil; 29 mg (0.1 mmol), 76% yield; 88% ee; $[\alpha]_D^{22}$ +121.45 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.7 Hz, 1H), 7.77−7.74 (m, 1H), 7.49 (td, J = 8.0, 5.5 Hz, 1H), 7.37 (ddd, J = 8.3, 5.0, 1.8 Hz, 1H), 7.28 (dd, J = 4.8, 3.1 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 3.28 (d, J = 14.0 Hz, 1H), 3.16 (d, J = 14.0 Hz, 1H), 2.31 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.3, 184.3, 163.8, 161.3, 132.4, 131.5 (d, J = 16.5 Hz), 130.7 (d, J = 7.9 Hz), 127.4, 125.7, 122.5, 122.2 (d, J = 21.3 Hz), 121.5, 116.5, 116.2, 93.9, 39.1, 34.1, 16.56; HRMS (ESI) m/z 392.0485 (M + H^+), calcd for $C_{19}H_{18}{}^{81}BrFNO_2$ 392.0484. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 6.8 min (minor) and 8.0 min (major).

*(R)-(+)-5-(2-Fluorobenzyl)-2-(3-fluorophenyl)-5-isopropyloxazol-4(5H)-one (**3f**).* Colorless oil; 23 mg (0.1 mmol), 72% yield; 92% ee; $[\alpha]_D^{22}$ +69.20 (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.85 (m, 1H), 7.74 (ddd, J = 9.0, 2.4, 1.5 Hz, 1H), 7.45 (td, J = 8.0, 5.5 Hz, 1H), 7.33 (tdd, J = 8.3, 2.6, 0.9 Hz, 1H), 7.15 (td, J = 7.5, 1.6 Hz, 1H), 7.09 (tdd, J = 7.3, 5.3, 1.7 Hz, 1H), 6.94 (td, J = 7.5, 1.0 Hz, 1H), 6.86 (t, J = 9.1 Hz, 1H), 3.58 (d, J = 13.9 Hz, 1H), 3.13 (dd, J = 13.9, 1.2 Hz, 1H), 2.35 (dt, J = 13.7, 6.9 Hz, 1H), 1.15 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 184.5, 163.7, 162.5, 161.2, 160.0, 131.9 (d, J = 3.7 Hz), 130.6 (d, J = 7.8 Hz), 129.3 (d, J = 8.3 Hz), 127.6 (d, J = 8.2 Hz), 125.6 (d, J = 3.2 Hz), 124.2 (d, J = 3.6 Hz), 122.1, 121.9 (d, J = 21.3 Hz), 120.6 (d, J = 15.4 Hz), 116.5, 116.3, 115.3, 115.1, 93.9, 34.0, 32.7 (d, J = 2.0 Hz), 16.6 (d, J = 3.2 Hz); HRMS (ESI) m/z 330.1317 (M + H^+), calcd for $C_{19}H_{18}F_2NO_2$ 330.1306. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 10.4 min (major) and 12.4 min (minor).

*(R)-(+)-2-(3-Fluorophenyl)-5-isopropyl-5-(2-(trifluoromethyl)-benzyl)oxazol-4(5H)-one (**3g**).* Colorless oil; 24 mg (0.1 mmol), 62% yield; 93% ee; $[\alpha]_D^{22}$ +28.37 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, J = 6.4 Hz, 1H), 7.65−7.62 (m, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.41 (td, J = 8.0, 5.5 Hz, 1H) 7.35−7.27 (m, 3H), 7.20 (t, J = 7.3 Hz, 1H), 3.81−3.78 (m, 1H), 3.36 (d, J = 14.4 Hz, 1H), 2.40−2.30 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 184.8, 163.7, 161.2, 132.0 (d, J = 15.1 Hz), 131.6, 130.6 (d, J = 7.8 Hz), 129.8, 129.5, 127.5, 127.2 (d, J = 8.2 Hz), 126.3 (d, J = 5.7 Hz), 125.5 (d, J = 3.1 Hz), 123.0, 122.2, 122.0, 116.6, 116.3, 93.7, 36.1, 34.8, 16.5 (d, J = 9.8 Hz); HRMS (ESI) m/z 402.1082 (M + Na^+), calcd for $C_{20}H_{17}F_4NO_2Na$ 402.1093. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 6.5 min (major) and 7.5 min (minor).

*(R)-(+)-5-(3-Chlorobenzyl)-2-(3-fluorophenyl)-5-isopropyloxazol-4(5H)-one (**3h**).* Colorless oil; 27 mg (0.1 mmol), 77% yield; 90% ee; $[\alpha]_D^{22}$ +73.47 (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 1H), 7.77−7.73 (m, 1H), 7.48 (td, J = 8.0, 5.5 Hz, 1H), 7.38−7.33 (m, 1H), 7.14 (s, 1H), 7.09 (td, J = 5.4, 2.2 Hz, 2H), 7.05−7.01 (m, 1H), 3.30 (d, J = 13.9 Hz, 1H), 3.16 (d, J = 13.9 Hz, 1H), 2.31 (dq, J = 13.7, 6.9 Hz, 1H), 1.14 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 184.3, 163.8, 161.3, 135.3, 134.0, 130.7 (d, J = 7.8 Hz), 130.2, 129.6, 128.1, 127.5, 125.6 (d, J = 3.1 Hz), 122.2, 122.1 (d, J = 21.3 Hz), 116.5, 116.3, 93.8, 39.4, 34.0, 16.6 (d, J = 2.9 Hz); HRMS (ESI) m/z 346.1012 (M + H^+), calcd for $C_{19}H_{18}ClFNO_2$ 346.1010. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95:5; flow rate 0.5 mL/min; 25 °C; 254 nm; retention time, 17.7 min (minor) and 19.1 min (major).

*(R)-(+)-2-(3-Fluorophenyl)-5-isopropyl-5-(4-(trifluoromethyl)-benzyl)oxazol-4(5H)-one (**3i**).* Colorless oil; 27 mg (0.1 mmol), 70% yield; 91% ee; $[\alpha]_D^{22}$ +111.60 (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.48 (m, 1H), 7.37 (m, 3H), 7.28 (s, 2H), 3.38 (d, J = 13.8 Hz, 1H), 3.25 (d, J = 13.8 Hz, 1H), 2.38−2.26 (m, 1H), 1.16 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 184.4, 163.8, 161.3, 137.6, 130.8 (d, J = 7.8 Hz), 130.4, 129.8, 129.5, 127.4 (d, J = 8.2 Hz), 125.8, 125.4 (dd, J = 37.0, 3.4 Hz), 122.6, 122.3, 122.1, 116.4, 116, 93.8, 39.5, 34.2, 16.6 (d, J = 1.9 Hz); HRMS (EI) m/z 379.1198 (M^+), calcd for $C_{20}H_{17}F_4NO_2$ 379.1195. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95:5; flow rate 0.5 mL/min; 25 °C; 254 nm; retention time, 21.4 min (minor) and 23.0 min (major).

*(R)-(+)-2-(3-Fluorophenyl)-5-isopropyl-5-(2-methylbenzyl)oxazol-4(5H)-one (**3j**).* Colorless oil; 22 mg (0.1 mmol), 68% yield; 91% ee; $[\alpha]_D^{22}$ +67.91 (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.44 (td, J = 8.0, 5.5 Hz, 1H), 7.32 (td, J = 8.3, 2.0 Hz, 1H), 7.08 (d, J = 6.9 Hz, 1H), 7.02−6.92 (m, 3H), 3.44 (d, J = 14.1 Hz, 1H), 3.25 (d, J = 14.1 Hz, 1H), 2.44−2.29 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 184.2, 163.7, 161.2, 137.0, 131.8, 130.5 (dd, J = 19.0, 9.4 Hz), 127.7 (d, J = 8.4 Hz), 127.4, 125.9, 125.4 (d, J = 3.1 Hz), 121.9, 121.7, 116.4, 116.1, 94.7, 36.3, 34.4, 19.8, 16.7 (d, J = 2.0 Hz); HRMS (ESI) m/z 326.1566 (M + H^+), calcd for $C_{20}H_{21}FNO_2$ 326.1556. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 9.5 min (major) and 13.1 min (minor).

*(R)-(+)-2-(3-Fluorophenyl)-5-isopropyl-5-(3-methylbenzyl)oxazol-4(5H)-one (**3k**).* Colorless oil; 23 mg (0.1 mmol), 71% yield; 90% ee; $[\alpha]_D^{22}$ +80.11 (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.85 (m, 1H), 7.76−7.73 (m, 1H), 7.49−7.44 (m, 1H), 7.36−7.32 (m, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.94−6.92 (m, 3H), 3.29 (d, J = 13.8 Hz, 1H), 3.14 (d, J = 13.8 Hz, 1H), 2.36−2.28 (m, 1H), 2.14 (s, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 184.2, 163.7, 161.3, 137.7, 133.2, 130.8, 130.6 (d, J = 7.9 Hz), 128.0 (dd, J = 25.2, 11.4 Hz), 126.9, 125.5 (d, J = 3.1 Hz), 121.9, 121.7, 116.4, 116.2, 94.3, 39.8, 33.9, 21.1, 16.6; HRMS (ESI) m/z 326.1563 (M + H^+), calcd for $C_{20}H_{21}FNO_2$ 326.1556. The ee was

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determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 10.6 min (major) and 12.6 min (minor).

*(R)-(+)-2-(3-Fluorophenyl)-5-isopropyl-5-(4-methylbenzyl)oxazol-4(5H)-one (**3l**).* Colorless oil; 25 mg (0.1 mmol), 76% yield; 90% ee; $[\alpha]_D^{22}$ +108.77 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.77−7.73 (m, 1H), 7.47 (td, *J* = 8.0, 5.5 Hz, 1H), 7.34 (ddd, *J* = 10.1, 7.9, 2.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 3.28 (d, *J* = 14.0 Hz, 1H), 3.15 (d, *J* = 14.0 Hz, 1H), 2.31 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.19 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 184.2, 163.7, 161.3, 136.8, 130.6 (d, *J* = 7.8 Hz), 130.1 (d, *J* = 15.9 Hz), 129.8, 129.0, 127.8 (d, *J* = 8.3 Hz), 125.6 (d, *J* = 3.1 Hz), 121.9, 121.7 116.5, 116.2, 94.4, 39.4, 33.9, 20.9, 16.6; HRMS (ESI) *m*/*z* 326.1562 (M + H^+), calcd for $C_{20}H_{21}FNO_2$ 326.1556. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 6.1 min (minor) and 7.3 min (major).

*(R)-(+)-2-(3-Fluorophenyl)-5-isopropyl-5-(4-isopropylbenzyl)-oxazol-4(5H)-one (**3m**).* Colorless oil; 24 mg (0.1 mmol), 67% yield; 87% ee; $[\alpha]_D^{22}$ +105.57 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.46 (td, *J* = 8.0, 5.6 Hz, 1H), 7.34 (td, *J* = 8.3, 1.9 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 3.28 (d, *J* = 13.9 Hz, 1H), 3.16 (d, *J* = 13.9 Hz, 1H), 2.74 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.32 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.09 (ddd, *J* = 19.2, 13.7, 6.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 184.2, 163.7, 161.2, 147.9, 130.5 (d, *J* = 10.4 Hz), 129.9, 127.9, 126.3, 125.5 (d, *J* = 3.1 Hz), 121.9, 121.7, 116.4, 116.2, 94.4, 39.5, 33.8, 33.6, 23.8, 16.6 (d, *J* = 3.8 Hz); HRMS (ESI) *m*/*z* 354.1871 (M + H^+), calcd for $C_{22}H_{25}FNO_2$ 354.1869. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95:5; flow rate 0.5 mL/min; 25 °C; 254 nm; retention time, 13.7 min (minor) and 15.2 min (major).

*(R)-(+)-5-(4-(tert-Butyl)benzyl)-2-(3-fluorophenyl)-5-isopropyloxazol-4(5H)-one (**3n**).* Colorless oil; 22 mg (0.1 mmol), 61% yield; 88% ee; $[\alpha]_D^{22}$ +7.25 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.72 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.46 (td, *J* = 8.0, 5.5 Hz, 1H), 7.36−7.33 (m, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 3.29 (d, *J* = 13.9 Hz, 1H), 3.16 (d, *J* = 13.9 Hz, 1H), 2.32 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.16 (s, 9H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 184.3, 163.7, 161.2, 150.1, 130.5 (d, *J* = 7.8 Hz), 130.2, 129.7, 127.9 (d, *J* = 8.2 Hz), 125.5 (d, *J* = 3.1 Hz), 125.1, 121.8, 121.6, 116.4, 116.2, 94.4, 39.5, 34.3, 33.8, 31.1, 16.6 (d, *J* = 5.0 Hz); HRMS (ESI) *m*/*z* 368.2029 (M + H^+), calcd for $C_{23}H_{27}FNO_2$ 368.2026. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 12.4 min (major) and 13.8 min (minor).

*(R)-(+)-2-(3-Fluorophenyl)-5-isopropyl-5-(naphthalen-2-ylmethyl)oxazol-4(5H)-one (**3o**).* Colorless oil; 29 mg (0.1 mmol), 80% yield; 90% ee; $[\alpha]_D^{22}$ +136.14 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.74−7.60 (m, 5H), 7.41−7.26 (m, 5H), 3.50 (d, *J* = 13.9 Hz, 1H), 3.37 (d, *J* = 13.9 Hz, 1H), 2.37 (dq, *J* = 13.7, 6.9 Hz, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 184.3 (d, *J* = 3.1 Hz), 163.7, 161.2, 133.1, 132.4, 130.9, 130.5 (d, *J* = 7.9 Hz), 129.0, 127.7, 125.9, 125.6, 122.0, 121.8, 116.4, 116.2, 94.3, 39.9, 34.1, 16.6 (d, *J* = 4.1 Hz); HRMS (ESI) *m*/*z* 362.1563 (M + H^+), calcd for $C_{23}H_{21}FNO_2$ 362.1556. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 8.6 min (minor) and 11.0 min (major).

*(S)-(+)-5-Benzyl-2-(3-fluorophenyl)-5-methyloxazol-4(5H)-one (**3p**).* Colorless oil; 15 mg (0.1 mmol), 54% yield; 87% ee; $[\alpha]_D^{22}$ +46.03 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.90 (m, 1H), 7.78 (ddd, *J* = 9.0, 2.4, 1.6 Hz, 1H), 7.48 (td, *J* = 8.0, 5.5 Hz, 1H), 7.36 (tdd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 7.23−7.17 (m, 5H), 3.22 (d, *J* = 14.2 Hz, 1H), 3.18 (d, *J* = 14.2 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 183.8 (d, *J* = 3.0 Hz), 163.7, 161.3, 133.4, 130.6 (d, *J* = 7.8 Hz), 123.0, 128.4, 127.9 (d, *J* = 8.2 Hz), 127.5, 125.7 (d, *J* = 3.1 Hz), 122.1, 121.9, 116.6, 116.4, 88.5, 42.9, 21.8; HRMS (ESI) *m*/*z* 306.0911 (M + Na^+), calcd for $C_{17}H_{14}FNO_2Na$ 306.0906. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 19.5 min (major) and 26.6 min (minor).

*(S)-(+)-5-benzyl-5-ethyl-2-(3-fluorophenyl)oxazol-4(5H)-one (**3q**).* Colorless oil; 19 mg (0.1 mmol), 64% yield; 86% ee; $[\alpha]_D^{22}$ +44.26 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.79−7.77 (m, 1H), 7.48 (td, *J* = 8.0, 5.5 Hz, 1H), 7.35 (ddd, *J* = 8.3, 5.0, 1.8 Hz, 2H), 7.22−7.08 (m, 5H), 3.20 (s, 2H), 2.13−1.98 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 184.4, 163.8, 161.3, 133.4, 130.6 (d, *J* = 7.9 Hz), 130.0, 128.4, 127.8, 127.4, 125.7 (d, *J* = 3.1 Hz), 122.2, 122.0 (d, *J* = 21.3 Hz), 116.6, 116.3, 92.2, 42.0, 28.9, 7.4; HRMS (ESI) *m*/*z* 298.1244 (M + H^+), calcd for $C_{18}H_{17}FNO_2$ 298.1243. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 14.9 min (major) and 17.9 min (minor).

*(S)-(+)-5-Benzyl-5-butyl-2-(3-fluorophenyl)oxazol-4(5H)-one (**3r**).* Colorless oil; 20 mg (0.1 mmol), 63% yield; 83% ee; $[\alpha]_D^{22}$ +42.65 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.7 Hz, 1H), 7.79−7.76 (m, 1H), 7.48 (td, *J* = 8.0, 5.5 Hz, 1H), 7.36 (td, *J* = 8.3, 1.8 Hz, 1H), 7.18−7.15 (m, 5H), 3.24−3.17 (m, 2H), 2.07−1.94 (m, 2H), 1.34−1.18 (m, 5H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 184.2, 163.8, 161.3, 133.3, 130.6 (d, *J* = 7.8 Hz), 123.0, 128.3, 127.8, 127.4, 125.7 (d, *J* = 3.1 Hz), 122.1, 121.9, 116.6, 116.3, 91.8, 42.3, 35.5, 25.0, 22.5, 13.7; HRMS (ESI) *m*/*z* 326.1554 (M + H^+), calcd for $C_{20}H_{21}FNO_2$ 326.1556. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 11.1 min (major) and 13.0 min (minor).

*(S)-(−)-5-Benzyl-5-(2-bromobenzyl)-2-(3-fluorophenyl)oxazol-4(5H)-one (**3s**).* White crystal; mp 83.8−85.1 °C; 33 mg (0.1 mmol), 76% yield; 90% ee; $[\alpha]_D^{22}$ −97.20 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81−7.78 (m, 1H), 7.67 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 1H), 7.46−7.38 (m, 2H), 7.32−7.25 (m, 2H), 7.25−7.13 (m, 6H), 7.02 (td, *J* = 7.8, 1.7 Hz, 1H), 3.70 (d, *J* = 14.2 Hz, 1H), 3.41−3.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 184.1 (d, *J* = 3.0 Hz), 163.6, 161.1, 133.3, 133.0 (d, *J* = 5.5 Hz), 131.8, 130.5 (d, *J* = 7.8 Hz), 130.0, 129.2, 128.4, 127.5 (dd, *J* = 16.2, 11.8 Hz), 125.7, 122.1, 121.9, 116.6, 116.4, 91.4, 77.3, 77.0, 76.7, 41.8, 40.9; HRMS (ESI) *m*/*z* 438.0506 (M + H^+), calcd for $C_{23}H_{18}BrFNO_2$ 438.0505. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 24.9 min (major) and 32.0 min (minor).

*(S)-(+)-5-Benzyl-5-(3-bromobenzyl)-2-(3-fluorophenyl)oxazol-4(5H)-one (**3t**).* White crystal; mp 95.0−96.3 °C; 32 mg (0.1 mmol), 73% yield; 85% ee (>99% ee after a single recrystallization); $[\alpha]_D^{22}$ +12.9 (*c* 1.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.38 (td, *J* = 8.0, 5.7 Hz, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.19 (s, 1H), 7.12 (s, 5H), 7.02 (dt, *J* = 15.1, 7.6 Hz, 2H), 3.27−3.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 184.1 (d, *J* = 3.1 Hz), 164.2, 160.9, 135.4, 133.1 (d, *J* = 10.4 Hz), 130.7 (d, *J* = 6.0 Hz), 130.1 (d, *J* = 3.6 Hz), 128.6 (d, *J* = 6.0 Hz), 127.5, 125.5 (d, *J* = 3.1 Hz), 122.3, 122.0, 116.5, 116.2, 91.0, 41.9, 41.3; HRMS (ESI) *m*/*z* 438.0504 (M + H^+), calcd for $C_{23}H_{18}BrFNO_2$ 438.0505. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 29.2 min (major) and 30.8 min (minor).

*(S)-(+)-5-Benzyl-5-(4-bromobenzyl)-2-(3-fluorophenyl)oxazol-4(5H)-one (**3u**).* White crystal; mp 138.8−140.5 °C; 36 mg (0.1 mmol), 82% yield; 85% ee (90% ee after a single recrystallization); $[\alpha]_D^{22}$ +26.25 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78−7.75 (m, 1H), 7.66−7.62 (m, 1H), 7.47−7.40 (m, 1H), 7.36−7.29 (m, 3H), 7.21−7.12 (m, 5H), 7.06−7.02 (m, 2H), 3.33−3.18 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 184.0 (d, *J* = 3.1 Hz), 164.1, 160.8, 132.9, 132.2, 131.6 (d, *J* = 4.5 Hz), 130.7 (d, *J* = 7.9 Hz), 123.0, 128.5, 127.4, 125.5 (d, *J* = 3.1 Hz), 122.3, 122.0, 121.7, 116.4, 116.1, 91.1, 42.0, 41.0; HRMS (ESI) *m*/*z* 438.0523 (M + H^+), calcd for

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$C_{23}H_{18}BrFNO_2$ 438.0505. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 16.5 min (minor) and 18.8 min (major).

*(S)-(−)-5-Benzyl-2-(3-fluorophenyl)-5-(2-methylbenzyl)oxazol-4(5H)-one (**3v**).* White crystal; mp 89.3−91.2 °C; 29 mg (0.1 mmol), 78% yield; 89% ee (94% ee after a single recrystallization); $[\alpha]_D^{22}$ −15.04 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 1H), 7.62 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.42 (td, *J* = 8.0, 5.5 Hz, 1H), 7.32 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.19−7.14 (m, 6H), 7.03 (dd, *J* = 9.6, 2.9 Hz, 3H), 3.40−3.25 (m, 4H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 183.8 (d, *J* = 3.1 Hz), 164.0, 137.1, 133.2, 131.7, 130.6, 130.0, 128.4, 127.5 (t, *J* = 5.3 Hz), 126.0, 125.4 (d, *J* = 3.2 Hz), 122.1, 121.8, 116.4, 116.0, 91.9, 42.0, 38.2, 19.8; HRMS (ESI) *m*/*z* 374.1562 (M + H^+), calcd for $C_{24}H_{21}FNO_2$ 374.1556. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 16.5 min (major) and 17.9 min (minor).

*(S)-(+)-5-Benzyl-2-(3-fluorophenyl)-5-(3-methylbenzyl)oxazol-4(5H)-one (**3w**).* White crystal; mp 89.7−91.5 °C; 26 mg (0.1 mmol), 71% yield; 85% ee (90% ee after a single recrystallization); $[\alpha]_D^{22}$ +7.65 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.67−7.63 (m, 1H), 7.43 (td, *J* = 8.0, 5.5 Hz, 1H), 7.34−7.28 (m, 1H), 7.15 (s, 5H), 7.10−7.04 (m, 1H), 6.97 (d, *J* = 7.6 Hz, 3H), 3.34−3.19 (m, 4H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 183.9 (d, *J* = 3.1 Hz), 164.0, 160.8, 137.9, 133.1 (d, *J* = 15.4 Hz), 130.6, 130.0, 128.3, 127.6, 127.0, 125.4 (d, *J* = 3.1 Hz), 122.0, 121.7, 116.4, 116.1, 91.4, 41.8, 21.2; HRMS (ESI) *m*/*z* 374.1557 (M + H^+), calcd for $C_{24}H_{21}FNO_2$ 374.1556. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95:5; flow rate 0.5 mL/min; 25 °C; 254 nm; retention time, 102.1 min (minor) and 107.4 min (major).

*(S)-(−)-5-Benzyl-5-(2,4-dichlorobenzyl)-2-(3-fluorophenyl)oxazol-4(5H)-one (**3x**).* White crystal; mp 106.7−108.2 °C; 32 mg (0.1 mmol), 75% yield; 90% ee; $[\alpha]_D^{22}$ −21.13 (*c* 2.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.43 (td, *J* = 8.0, 5.5 Hz, 1H), 7.36−7.29 (m, 2H), 7.21−7.11 (m, 7H), 3.63 (d, *J* = 14.2 Hz, 1H), 3.38−3.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 184.2 (d, *J* = 3.1 Hz), 164.1, 160.8, 135.8, 134.2, 132.8 (d, *J* = 5.6 Hz), 130.7 (d, *J* = 7.9 Hz), 130.1 (d, *J* = 9.9 Hz), 129.5, 128.5, 127.4 (dd, *J* = 16.5, 11.6 Hz), 125.7 (d, *J* = 3.2 Hz), 122.4, 122.1, 116.6, 116.3, 91.2, 41.9, 37.9; HRMS (EI) *m*/*z* 427.0539 (M^+), calcd for $C_{23}H_{16}NO_2FCl_2$ 427.0542. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 12.7 min (major) and 15.5 min (minor).

*(S)-(+)-5-Benzyl-2-(3-fluorophenyl)-5-(naphthalen-2-ylmethyl)-oxazol-4(5H)-one (**3y**).* White crystal; mp 134.6−135.1 °C; 34 mg (0.1 mmol), 82% yield; 84% ee (93% ee after a single recrystallization); $[\alpha]_D^{22}$ +28.17 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76−7.61 (m, 6H), 7.44−7.28 (m, 5H), 7.21−7.11 (m, 5H), δ 3.51−3.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 183.9 (d, *J* = 3.1 Hz), 164.0, 160.7, 133.2 (d, *J* = 3.6 Hz), 132.5, 130.6, 130.0, 129.1, 128.4, 127.7, 126.0 (d, *J* = 14.6 Hz), 125.5 (d, *J* = 3.1 Hz), 122.1, 121.8, 116.4, 116.1, 91.5, 41.9 (d, *J* = 4.0 Hz); HRMS (ESI) *m*/*z* 410.1570 (M + H^+), calcd for $C_{27}H_{21}FNO_2$ 410.1556. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 23.0 min (minor) and 24.7 min (major).

*(R)-(+)-5-Allyl-5-isopropyl-2-(m-tolyl)oxazol-4(5H)-one (**5a**).* Colorless oil; 16 mg (0.1 mmol), 61% yield; 89% ee; $[\alpha]_D^{22}$ +27.73 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−8.01 (m, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 5.61 (ddt, *J* = 17.2, 10.1, 7.3 Hz, 1H), 5.17 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.07 (d, *J* = 10.1 Hz, 1H), 2.75 (dd, *J* = 14.1, 7.5 Hz, 1H), 2.64 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.44 (s, 3H), 2.24 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 185.8, 138.9, 135.9, 130.5, 129.7 128.8, 127.1, 125.7, 120.7, 93.0, 38.0, 33.5, 21.2, 16.4; HRMS (ESI) *m*/*z* 258.1487 (M + H^+), calcd for $C_{16}H_{20}NO_2$ 258.1494. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 17.1 min (major) and 19.4 min (minor).

*(R, E)-(+)-5-(But-2-en-1-yl)-5-isopropyl-2-(m-tolyl)oxazol-4(5H)-one (**5b**).* Colorless oil; 18 mg (0.1 mmol), 67% yield; 91% ee; $[\alpha]_D^{22}$ +61.01 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−7.96 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 5.58 (dq, *J* = 12.9, 6.4 Hz, 1H), 5.23 (dtd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 2.66 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.56 (dd, *J* = 14.2, 7.1 Hz, 1H), 2.44 (s, 3H), 2.21 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.52 (d, *J* = 6.2 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 185.8, 138.9, 135.8, 131.5, 130.5, 128.9, 127.1, 125.8, 122.0, 93.4, 36.9, 33.5, 21.3, 18.0, 16.4; HRMS (ESI) *m*/*z* 272.1645 (M + H^+), calcd for $C_{17}H_{22}NO_2$ 272.1651. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95:5; flow rate 0.5 mL/min; 25 °C; 254 nm; retention time, 48.8 min (major) and 54.0 min (minor).

*(R)-(+)-5-Isopropyl-5-(3-methylbut-2-en-1-yl)-2-(m-tolyl)oxazol-4(5H)-one (**5c**).* Colorless oil; 23 mg (0.1 mmol), 81% yield; 87% ee; $[\alpha]_D^{22}$ +55.68 (*c* 1.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02−7.98 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 4.98−4.94 (m, 1H), 2.73 (dd, *J* = 14.6, 7.8 Hz, 1H), 2.57 (dd, *J* = 14.6, 7.3 Hz, 1H), 2.44 (s, 3H), 2.24 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.58 (d, *J* = 17.0 Hz, 6H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 185.75, 138.85, 137.5, 135.7, 130.5, 128.8, 127.0, 125.8, 115.2, 93.8, 33.5, 32.4, 25.8, 21.2, 18.0, 16.5; HRMS (ESI) *m*/*z* 286.1808 (M + H^+), calcd for $C_{18}H_{24}NO_2$ 286.1807. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time, 14.3 min (major) and 16.4 min (minor).

*(S)-(−)-2-Benzyl-3-(2-bromophenyl)-2-hydroxypropanamide (**6**).* To a solution of 3s (87.6 mg, 0.2 mmol) in EtOH (1.0 mL) was added NaOH aqueous solution (2.0 *N*, 1.0 mL). The resulting mixture was stirred for 3 h at 25 °C. Then, the reaction mixture was diluted with water. The mixture was extracted three times with ethyl acetate (5 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Then, the reaction mixtures were loaded onto a short silica gel column, followed by gradient elution with DCM/MeOH mixture (100:1−50:1 ratio) to afford **6** in 86% yield (57.4 mg, white powder); mp 148.4−150.0 °C; 90% ee; $[\alpha]_D^{22}$ −16.93 (*c* 0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 1H), 7.33 (m, 6H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.04 (dd, *J* = 10.9, 4.4 Hz, 1H), 6.31 (s, 1H), 5.45 (s, 1H), 3.30 (dt, *J* = 14.0, 12.2 Hz, 3H), 2.89 (d, *J* = 13.5 Hz, 1H), 2.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 135.7, 135.3, 132.7, 132.4, 130.6, 128.6 (two peaks), 127.6, 127.2, 125.9, 79.9, 45.2, 42.8; HRMS (ESI) *m*/*z* 356.0263 (M + Na^+), calcd for $C_{16}H_{16}NO_2BrNa$ 356.0262. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time, 9.3 min (major) and 10.5 min (minor).

*(S)-(−)-1-Amino-2-benzyl-3-(2-bromophenyl)propan-2-ol (**7**).* A solution of 57.4 mg (0.17 mol) of **6** in 1 mL of anhydrous THF was heated to reflux under N_2, and 38.7 mg (0.51 mmol) of borane dimethyl sulfide complex was added. A gas evolved, and the mixture was refluxed for 3 h, cooled to room temperature, and treated with methanol. Then, the solvent was removed, and the residue was chromatographed on silica gel using 50:1 methanol-DCM as eluent to afford **7** in 81% yield (44.1 mg, a white crystal); mp 87.8−89.3 °C; 90% ee; $[\alpha]_D^{22}$ −6.20 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.29−7.17 (m, 6H), 7.03 (td, *J* = 7.8, 1.6 Hz, 1H), 3.03 (d, *J* = 13.9 Hz, 1H), 2.92 (d, *J* = 13.9 Hz, 1H), 2.81 (s, 2H), 2.68 (d, *J* = 12.9 Hz, 1H), 2.58 (d, *J* = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (two peaks), 133.1, 132.7, 130.6, 128.1, 127.9, 127.0, 126.4, 125.8, 73.8, 47.3, 45.2, 43.5; HRMS (ESI) *m*/*z* 320.0652 (M + H^+), calcd for $C_{16}H_{19}NOBr$ 320.0650. The ee was determined by HPLC analysis. CHIRALCEL OD-H (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time, 12.0 min (minor) and 14.7 min (major).

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(S)-(−)-Methyl 2-Benzyl-3-(2,4-dichlorophenyl)-2-hydroxypropanoate (9). (a) To a solution of **3x** (85.6 mg, 0.2 mmol) in EtOH (1.0 mL) was added NaOH aqueous solution (2.0 *N*, 1.0 mL). The resulting mixture was stirred for 3 h at 25 °C. Then, the reaction mixture was diluted with water. The mixture was extracted three times with ethyl acetate (5 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Then, the reaction mixtures were loaded onto a short silica gel column, followed by gradient elution with DCM/MeOH mixture (100:1−50:1 ratio) to afford 2-benzyl-3-(2,4-dichlorophenyl)-2-hydroxypropanamide in 89% yield (76.2 mg). (b) A solution of 2-benzyl-3-(2,4-dichlorophenyl)-2-hydroxypropanamide (76.2 mg, 0.18 mmol) was dissolved in 1,4-dioxane (0.2 mL). HCl (12 *N*, 4.0 mL) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was heated at 100 °C for 48 h. Then, the solution was cooled and extracted three times with ethyl acetate (5 mL). The combined organic layers were washed with saturated aqueous NaCl and dried over Na_2SO_4. After being concentrated, crude 2-benzyl-3-(2,4-dichlorophenyl)-2-hydroxypropanoic acid **8** was obtained. Subsequently, crude 2-benzyl-3-(2,4-dichlorophenyl)-2-hydroxypropanoic acid **8** was diluted with methanol (4.0 mL), and H_2SO_4 (conc. 0.1 mL) was added to the stirred solution. After stirring at 70 °C for 12 h, the reaction mixture was cooled to room temperature and diluted with water. Then, the mixture was extracted with EtOAc (5 mL × 3), and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/EtOAc = 10:1) to afford **9** in 75% yield (45.8 mg, white powder); mp 79.1−81.2 °C; 88% ee; $[\alpha]_D^{22}$ −5.80 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 7.8 Hz, 2H), 7.30−7.27 (m, 1H), 7.25−7.23 (m, 2H), 7.21−7.15 (m, 3H), 3.69 (s, 3H), 3.36 (d, J = 14.0 Hz, 1H), 3.25 (s, 1H), 3.20 (s, 1H), 3.09 (s, 1H), 2.98 (d, J = 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 135.4 (two peaks), 133.3(two peaks), 132.4, 130.2, 129.2, 128.2, 126.9 (two peaks), 78.2, 52.6, 45.0, 40.8; HRMS (EI) m/z 338.0482 (M^+), calcd for $C_{17}H_{16}O_3Cl_2$ 338.0477. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90:10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time, 6.0 min (minor) and 6.8 min (major).

■ ASSOCIATED CONTENT

Supporting Information

General information, optimization of reaction conditions, specific synthesis of chiral PTC **F**, copies of HPLC spectra, crystallographic data of **3t** and catalyst **K**, and copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01081.

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Notes

The authors declare no competing financial interest.

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