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

Shaobo Duan,^{†,¶} Sanliang Li,^{†,¶} Xinyi Ye,[‡] Nuan-Nuan Du,[†] Choon-Hong Tan,^{†,‡} and Zhiyong Jiang^{*,†}

[†]Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Kaifeng, Henan 475004, P. R. China

[‡]Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link 637371, Singapore

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.

E nantiomeric 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 resolution² and the employment of chiral auxiliaries,^{1c,3} have been described. However, a catalytic asymmetric variant still remains elusive.^{1b}

In 2004, the Trost group⁴ creatively introduced 5*H*-oxazol-4ones 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 5H-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 5H-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 5H-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 sulfenvlation.^{8f} Nevertheless, to the best of our knowledge, asymmetric phase-transfer alkylation and allylic alkylation of 5H-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 5H-oxazol-4-ones through asymmetric phase-transfer catalysis to provide chiral dialkylated HCAs in satisfactory yields.

In our initial study, alkylation of 5H-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 Cs₂CO₃ 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 acidderived thiourea-ammonium salts as a catalyst, we still looked forward to improving the enantioselectivity through modifying the brønsted acid moiety of the catalyst. Thus, ureaammonium 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 K₃PO₄ 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 5H-oxazol-4-ones often affects the enantioselective outcomes.^{8b,f} Therefore, a series of 5H-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 5H-oxazol-4-one **1b** with a fluoro

Table 1. Optimization of Reaction Conditions^a

Ŷ	L	Br				
N I	+			st A-IVI (10 mo	¹⁷⁰⁾ ► N, T	
Ar	1	1	ba 2a	se (5.0 equiv.)	Ar	3
entry	1	cat.	solvent	$T(h)^b$	yield $(\%)^c$	ee (%) ^d
1	1a	Α	toluene	35	33	40
2	1a	В	toluene	35	54	5
3	1a	С	toluene	35	47	75
4	1a	D	toluene	35	48	73
5	1a	Е	toluene	35	42	70
6	1a	F	toluene	35	50	77
7	1a	F	CH_2Cl_2	35	37	62
8	1a	F	Et ₂ O	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	н	CPME	24	60	86
20 ^f	1b	Ι	CPME	24	63	86
21 ^{<i>f</i>}	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	М	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. ^cIsolated 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.

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 thioureatertiary 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 *SH*-oxazol-4-one **1b** with a variety of benzyl bromides in the presence of 10 mol % of catalyst K at 0 $^{\circ}$ C and in CPME as



Figure 2. Structures of catalysts (A-N) and 5H-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 5benzyl-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



Table 2. Asymmetric Alkylation of 5H-oxazol-4-ones 1 to

^{*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 = 85%; **3y**: ee = 84%.

of SH-oxazol-4-ones yielding better enantioselective results, the devised transition-state model can be further demonstrated.

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 amides presenting in

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



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, *5H*-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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₇H₃₄F₆N₃S 546.2378.

(*S*)-1-Benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3dimethylbutyl)piperidin-1-ium Bromide (**C**). White powder; mp 129.8–131.2 °C; 233 mg (0.5 mmol), 76.5% yield (final step); ¹H NMR (300 MHz, CDCl₃) 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







(m, 2H), 3.24–3.07 (m, 2H), 2.16 (s, 3H), 1.92 (s, 3H), 1.09 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₇H₃₄F₆N₃O 530.2606.

(5)-1-Benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3methylbutyl)piperidin-1-ium Bromide (**D**). White powder; mp 203.5–205.9 °C; 245 mg (0.5 mmol), 82.3% yield (final step); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₆H₃₂F₆N₃O 516.2449.

(S)-1-Benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2cyclohexylethyl)piperidin-1-ium Bromide (**E**). White powder; mp 101.9–103.2 °C; 199 mg (0.5 mmol), 62.5% yield (final step); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₉H₃₆F₆N₃O 556.2762.

(S)-1-benzyl-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3dimethylbutyl)pyrrolidin-1-ium bromide (F). White powder; mp 102.3–104.5 °C; 212 mg (0.5 mmol), 71.4% yield (final step); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₆H₃₂F₆N₃O 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); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₇H₃₁F₉N₃O 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); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₇H₃₁F₉N₃O 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); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₈H₃₀F₁₂N₃O 652.2197.

(*S*)-1-Benzyl-1-(2-(3-(3,5-dichlorophenyl)ureido)-3,3dimethylbutyl)pyrrolidin-1-ium Bromide (*J*). White powder; mp 207.0–209.2 °C; 176 mg (0.5 mmol), 66.8% yield (final step); ¹H NMR (300 MHz, CD₃OD_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); ¹³C NMR (75 MHz, CD₃OD_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 C₂₄H₃₂Cl₂N₃O 448.1922.

(S)-1-Benzyl-1-(2-(3-(3,5-dibromophenyl)ureido)-3,3dimethylbutyl)pyrrolidin-1-ium Bromide (K). White powder; mp 205.9–208.2 °C; 237 mg (0.5 mmol), 76.9% yield (final step); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₄H₃₂⁷⁹Br₂N₃O 536.0912.

(5)-1-Benzyl-1-(2-(3-(3,5-dimethoxyphenyl)ureido)-3,3dimethylbutyl)pyrrolidin-1-ium Bromide (L). White powder; mp 83.5–85.9 °C; 199 mg (0.5 mmol), 76.9% yield (final step); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₆H₃₈N₃O₃ 440.2913.

(5)-1-Benzyl-1-(2-(3-(3,5-di-tert-butylphenyl)ureido)-3,3dimethylbutyl)pyrrolidin-1-ium Bromide (**M**). White powder; mp 198.4–201.2 °C; 161 mg (0.5 mmol), 56.5% yield (final step); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₃₂H₅₀N₃O 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); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₂₆⁷⁹Br₂N₃O 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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₁₉H₁₉FNO₂ 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 (**3***c*). Colorless oil; 24.5 mg (0.1 mmol), 63% yield; 93% ee; $[\alpha]_{D}^{22}$ -41.41 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₉H₁₈⁸¹BrFNO₂ 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₉H₁₈BrFNO₂ 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₉H₁₈⁸¹BrFNO₂ 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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, I = 3.2 Hz); HRMS (ESI) m/z 330.1317 (M + H⁺), calcd for C19H18F2NO2 330.1306. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. \times 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₀H₁₇F₄NO₂Na 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₉H₁₈CIFNO₂ 346.1010. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2propanol = 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(5*H*)-*one* (**3i**). Colorless oil; 27 mg (0.1 mmol), 70% yield; 91% ee; $[\alpha]_{D}^{2D}$ +111.60 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₀H₁₇F₄NO₂ 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 (**3***j*). Colorless oil; 22 mg (0.1 mmol), 68% yield; 91% ee; $[\alpha]_{D}^{22}$ +67.91 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₀H₂₁FNO₂ 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₀H₂₁FNO₂ 326.1556. The ee was

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determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. \times 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 (**3***l*). Colorless oil; 25 mg (0.1 mmol), 76% yield; 90% ee; $[\alpha]_{D}^{22}$ +108.77 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₀H₂₁FNO₂ 326.1556. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2propanol = 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(5*H*)-one (**3m**). Colorless oil; 24 mg (0.1 mmol), 67% yield; 87% ee; $[\alpha]_{D}^{22}$ +105.57 (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₂H₂₅FNO₂ 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₃H₂₇FNO₂ 368.2026. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2propanol = 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-2ylmethyl)oxazol-4(5H)-one (**3o**). Colorless oil; 29 mg (0.1 mmol), 80% yield; 90% ee; $[\alpha]_{D^2}^{22}$ +136.14 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₃H₂₁FNO₂ 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; $[\alpha]_{\rm D}^{22}$ +46.03 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₇H₁₄FNO₂Na 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(5*H*)-one (**3q**). Colorless oil; 19 mg (0.1 mmol), 64% yield; 86% ee; $[\alpha]_{D}^{22}$ +44.26 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₈H₁₇FNO₂ 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 (**3***r*). Colorless oil; 20 mg (0.1 mmol), 63% yield; 83% ee; $[\alpha]_D^{22} + 42.65$ (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₀H₂₁FNO₂ 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₃H₁₈BrFNO₂ 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).

(5)-(+)-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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, SH), 7.02 (dt, *J* = 15.1, 7.6 Hz, 2H), 3.27–3.12 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₃H₁₈BrFNO₂ 438.0505. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2propanol = 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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 $C_{23}H_{18}BrFNO_2$ 438.0505. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. \times 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); $[\alpha]_{D^2}^{20}$ -15.04 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₄H₂₁FNO₂ 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 (**3**w). 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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₄H₂₁FNO₂ 374.1556. The ee was determined by HPLC analysis. CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2propanol = 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(5*H*)-*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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₃H₁₆NO₂FCl₂ 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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₇H₂₁FNO₂ 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* (**5***a*). Colorless oil; 16 mg (0.1 mmol), 61% yield; 89% ee; $[\alpha]_D^{22}$ +27.73 (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₆H₂₀NO₂ 258.1494. The ee was determined by HPLC analysis.

CHIRALPAK IC (4.6 mm i.d. \times 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).

(\hat{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; [α]_D²² +61.01 (c 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₇H₂₂NO₂ 272.1651. The ee was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2propanol = 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-*IsopropyI*-5-(3-*methylbut*-2-*en*-1-*yI*)-2-(*m*-tolyl)*oxazol*-4(5*H*)-*one* (5*c*). Colorless oil; 23 mg (0.1 mmol), 81% yield; 87% ee; $[\alpha]_{D}^{22}$ +55.68 (*c* 1.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₈H₂₄NO₂ 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; $[\alpha]_{\rm D}^{22}$ –16.93 $(c \ 0.60, \ CHCl_3); \ ^1H \ NMR \ (300 \ MHz, \ CDCl_3) \ \delta \ 7.45 \ (d, \ J = 8.0 \ Hz,$ 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); ¹³C NMR (75 MHz, CDCl₂) 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 C16H16NO2BrNa 356.0262. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2propanol = 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 N2, 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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₁₉NOBr 320.0650. The ee was determined by HPLC analysis. CHIRALCEL OD-H (4.6 mm i.d. \times 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 (Na2SO4), 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)-2hydroxypropanamide (76.2 mg, 0.18 mmol) was dissolved in 1,4dioxane (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 Na2SO4. After being concentrated, crude 2-benzyl-3-(2,4-dichlorophenyl)-2-hydroxypropanoic acid 8 was obtained. Subsequently, crude 2-benzyl-3-(2,4dichlorophenyl)-2-hydroxypropanoic acid 8 was diluted with methanol (4.0 mL), and H₂SO₄ (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 \times 3), and the combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated. The obtained crude product was purified by SiO₂ 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; $[\alpha]_{\rm D}^{22}$ –5.80 (c 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.35 (d, I = 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); ¹³C NMR (75 MHz, CDCl₃) 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/2propanol = 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.Sb01081.

AUTHOR INFORMATION

Corresponding Author

*E-mail: chmjzy@henu.edu.cn.

Author Contributions

[¶]S.D. and S.L. made equal contributions to this work

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Riiburi, P. JPS6267069(A), 19870326. (b) Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-q.; Hernandez, M.; Wright, S. D.; M?ller, D. E.; Heck, J. V.; Meinke, P. T. J. Med. Chem. 2005, 48, 5589. (c) Pansare, S. V.; Kulkarni, K. G. RSC Adv. 2013, 3, 19127. (d) Erik, R.; Karl Heinz, B.; Wilhelm, B.; Paul, R. Ger. Offen. 1984, DE 3235935A1 19840329. (e) Braj Bhushan, L.; Vidya Bhushan, L.; Channaveerappa Bajji, A.; Shivaramayya, K.; Ranga Madhavan, G.; Ramanujam, R.; Chakrabarti, R. PCT Int. Appl. 2000, WO 2000066572A1 20001109. (f) Jean-Pierre, R.; Nina, R.; Julie, B. PCT Int. Appl. 2010, WO 2010103405A2 20100916. (g) Wolf Dieter, V.; Gerhard, S.; Manfred, H. U.S. 1978, US 4076937A 19780228. (h) Sitachitta, N.; Williamson, R. T.; Gerwick, W. H. J. Nat. Prod. 2000, 63, 197. For a selected book: (i) Coppola, G. M.; Schuster, H. F. α-Hydroxy Acids in Enantioselective Synthesis; VCH: Weinheim, 1997. (2) (a) Moorlag, H.; Kellogg, R. M. J. Org. Chem. 1990, 55, 5878. (b) Moorlag, H.; Kellogg, R. M. Tetrahedron: Asymmetry 1991, 2, 705. (c) O'Hagan, D.; Zaidi, N. A. Tetrahedron: Asymmetry 1994, 5, 1111. (3) (a) Ojima, I.; Miyazawa, Y.; Kumagai, M. J. Chem. Soc., Chem. Commun. 1976, 927. (b) Terashima, S.; Jew, S.-s. Tetrahedron Lett. 1977, 18, 1005. (c) Díez, E.; Dixon, D. J.; Ley, S. V. Angew. Chem., Int. Ed. 2001, 40, 2906. (d) Ley, S. V.; Díez, E.; Dixon, D. J.; Guy, R. T.; Michel, P.; Nattrass, G. L.; Sheppard, T. D. Org. Biomol. Chem. 2004, 2, 3608.

(4) Trost, B. M.; Dogra, K.; Franzini, M. J. Am. Chem. Soc. 2004, 126, 1944.

(5) (a) Misaki, T.; Takimoto, G.; Sugimura, T. J. Am. Chem. Soc. 2010, 132, 6286. (b) Misaki, T.; Kawano, K.; Sugimura, T. J. Am. Chem. Soc. 2011, 133, 5695.

(6) Huang, H.; Zhu, K.; Wu, W.; Jin, Z.; Ye, J. Chem. Commun. 2012, 48, 461.

(7) (a) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. Angew. Chem., Int. Ed. 2012, 51, 7523. (b) Han, Z.; Yang, W.; Tan, C.-H.; Jiang, Z. Adv. Synth. Catal. 2013, 355, 1505.

(8) (a) Trost, B. M.; Hirano, K. Angew. Chem., Int. Ed. 2012, 51, 6480. (b) Qiao, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. Org. Lett. 2013, 15, 2358. (c) Liu, Q.; Qiao, B.; Chin, K. F.; Tan, C.-H.; Jiang, Z. Adv. Synth. Catal. 2014, 356, 3777. (d) Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. J. Am. Chem. Soc. 2014, 136, 17869. (e) Chen, W.; Hartwig, J. F. J. Am. Chem. Soc. 2014, 136, 377. (f) Xu, M.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. Tetrahedron 2014, 70, 8696.

(9) (a) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. Angew. Chem., Int. Ed. **2012**, 51, 10069. (b) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W.; Tan, D.; Huang, K.-W.; Jiang, Z. Angew. Chem., Int. Ed. **2013**, 52, 6666.

(10) (a) Gao, Y.; Ren, Q.; Wang, L.; Wang, J. Chem. - Eur. J. 2010, 16, 13068. For a selected review, see: (b) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. Org. Biomol. Chem. 2013, 11, 7051.

(11) (a) Wang, H.-Y.; Chai, Z.; Zhao, G. *Tetrahedron* 2013, *69*, 5104.
(b) Wang, H.-Y.; Zhang, J.-X.; Cao, D.-D.; Zhao, G. *ACS Catal.* 2013, 3, 2218.

(12) CCDC1057650 (3t) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data_request/cif.

(13) For biologically active molecules containing dibenzylated α -hydroxyl amides as chiral scaffolds, see: (a) Howard, T. Eur. Pat. Appl. 1988, EP 253503A2 19880120. (b) Wolfgang, S.; Carsten, M.; Anja, S.; Ulrike, F.; Andrea, R.; Thomas Andrew, K.; Ralf, W. U.S. Pat. Appl. 2009, US 20090075989A1 20090319. For biologically active molecules containing dibenzylated α -hydroxyl amines as chiral scaffolds, see: (c) Herve, G.; Jean Francois, G.; Claude, C. F.; Marcel, C.; Charlotte, D.; Jacques, W. *Eur. J. Med. Chem.* 1979, 14, 165.

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