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Organocatalytic Enantioselective Conjugate Addition of Azlactones to Enolizable Linear and Cyclic Enones

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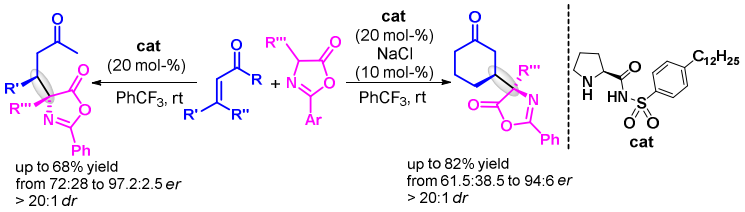


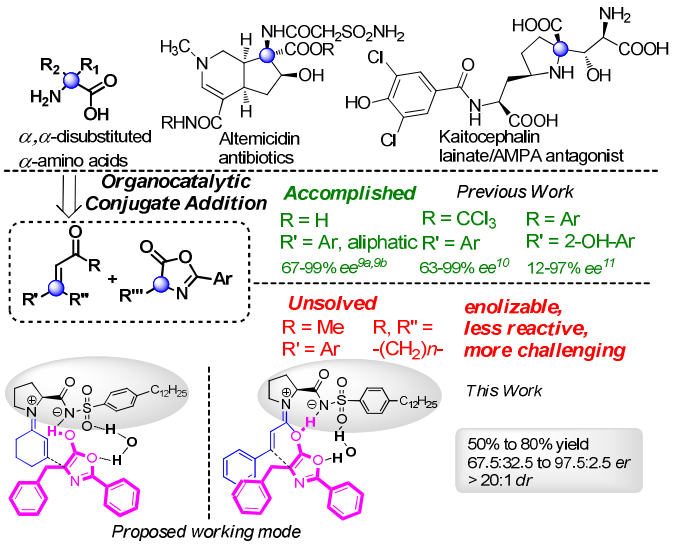
ABSTRACT: Highly diastereo- and enantioselective conjugate additions of azlactones with enolizable cyclic and linear enones were realized by employing proline aryl sulfonamide as the organocatalyst in trifluorotoluene. The conjugate adducts bearing contiguous quaternary and tertiary stereocenters were obtained in moderate to good yields with excellent diastereoselectivities and moderate to good enantioselectivities. This developed protocol filled in the substrate gap for the organocatalytic conjugate addition of azlactone to enones.

α,α-Disubstituted *α*-amino acids are nonproteinogenic modified amino acids, in which *α*-substituents could severely restrict the conformational freedom of peptides containing such residues. As a consequence, these amino acids are frequently being used as probes to investigate the biologically active conformation and clarify the secondary structure of peptides.[1] Moreover, *α,α*-disubstituted *α*-amino acids are present in many biologically active compounds such as (+)-LY-354740,[2] altemicidin,[3] kaitocephalin,[4] and sphingofungin[5]. Given the biological importance of *α,α*-disubstituted *α*-amino acids, considerable synthetic interests have been attracted to develop stereoselective accesses to diverse *α,α*-disubstituted *α*-amino acids.[6] As the

intrinsic hurdle arises from the demanding steric effect of quaternary stereocenter, the enantioselective synthesis of α,α-disubstituted α-amino acid is still an ever-standing challenge in synthetic and medicinal chemistry.[7]

As well known, azlactone, as a class of versatile building blocks for the masked amino acid, can serve as a facile Micheal donor.[8] Among all the established methodologies accessing α,α-disubstituted α-amino acids, the organocatalytic conjugate addition of azlactone to α,β-unsaturated enone or enal proved to be quite straightforward, atom-economic, and operationally accessible, which has progressively occupied the mainstream in the synthetic efforts of α,α-disubstituted α-amino acids.[9] Wang and co-workers reported an elegant enantioselective conjugate additions of azlactone to α,β-unsaturated trichloromethyl ketones catalyzed by quinine-derived thiourea. However, the more reactive trichloromethyl ketone was prerequisite and the replacement of methyl or phenyl ketone proved inactive.[10] Zhang *et al.* employed quinine-derived thioureas catalysts to realize the conjugate addition between azlactone and chalcone, in which only *o*-hydroxyl chalcone was the competent substrate to furnish the regioselective C-2 attack product.[11] Very recently, Ye and co-workers demonstrated 1,6-conjugate addition of azlactones to cyclic dienones catalyzed by primary amine catalysts with excellent enantio- and diastereoselectivities.[12]

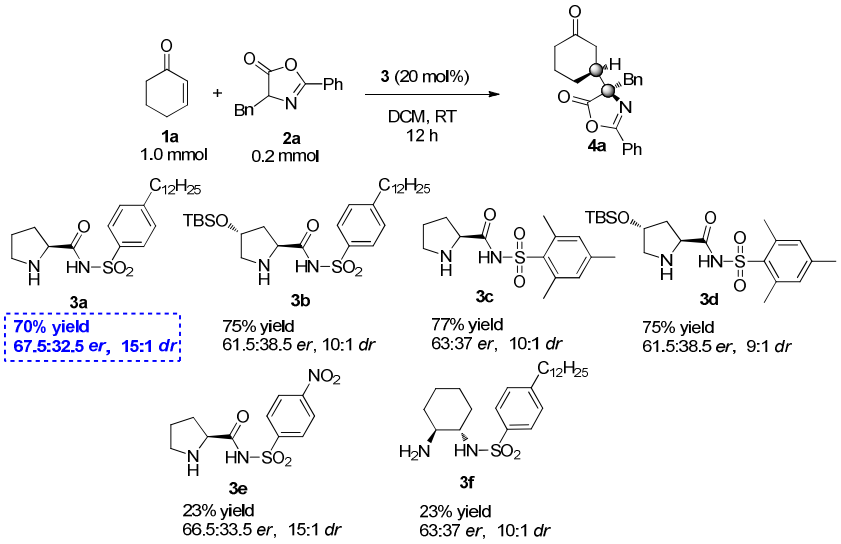
Scheme 1. Synthetic Profiles of Organocatalytic Conjugate Addition of Azlactone



Unfortunately, despite these encouraging advances, the unmodified and enolizable

benzalacetones and cyclohexenones with less electrophilicity still remained elusive and unsuccessful for the organocatalytic enantioselective conjugate addition of azlactones. It can be rationalized that these enolizable enones could readily undergo the enolization under the organocatalytic conditions, leading to the reduction in the electrophilicity and the decrease in the efficacy of activating enones as Micheal acceptor. Amarante group described a conjugate addition of azlactone to benzalacetone catalyzed by (±)-camphorsulfonic acid, resulting in racemic Micheal adduct.[13] It is worth noting that only single success of the enantioselective conjugate addition of azlactone to benzalacetone was achieved by Peters and co-workers with the employment of chiral mono or bis-palladacycle as the organometallic catalyst.[14] Our continuous interests in the organocatalyzed enone chemistry[15] stimulated us to face this challenge filling in the substrate gap with the enolizable enones. Herein, we describe the enantioselective conjugate addition of azlactones to cyclic enones and linear enones catalyzed by prolinosulphonamide organocatalyst (**Hua Cat**), in which water was found to show beneficial effect on the enantioselectivity as depicted in the working mode in Scheme 1. Certainly, this reported approach would address the drawback of the existing organocatalytic conjugate addition of azlactone leading to *α, α*-disubstituted *α*-amino acid.

Table 1. Organocatalyst Screening[a]



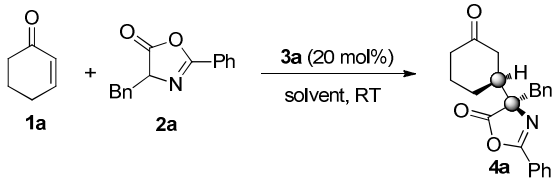
Initially, the conjugate addition between cyclohexenone (**1a**) and azlactone **2a**

was used as a model reaction to screen the reaction parameters. Based on our previous success on the organocatalytic enone chemistry, we speculated that amino acid sulphonamide should effectively activate enone through the formation of iminium ion to promote this reaction. Accordingly, various sulphonamides **3a-3e** derived from secondary amino acids were evaluated respectively. Gratifyingly, the desired product **4a** could be obtained in 70% yield along with 15:1 *dr* and 67.5:32.5 *er* upon using 20 mol% of *p*-dodecyl-*N*-arylsulphoprolinamide (**3a**) in DCM at room temperature (Table 1). The employment of TBS-4-hydroxyprolinamide **3b** and *tri*methyl analogues (**3c** and **3d**) all gave slightly lower enantioselectivity. The introduction of electron-withdrawing group onto the phenyl moiety (**3e**) remarkably slowed down the reaction without affecting the level of enantioselectivity. On the other hand, primary amine catalyst **3f** afforded poor yield, possibly due to the decomposition of azlactone promoted by the primary amino group.[16] As a consequence, prolinasulphonamide **3a** was chosen as the optimum catalyst for this transformation.

Subsequently, other reaction parameters including reaction medium and additive were further optimized by using **3a** as the organocatalyst. The results are summarized in Table 2. Firstly, various commonly used solvents were screened and the less polar solvent was appropriate for this reaction (Table 2, entries 1-10). In view of both reactivity and enantioselectivity, trifluorotoluene proved to be the optimal reaction medium (entry 8). Then, a series of additives was investigated. The addition of base such as trimethylamine or K_2CO_3 dramatically lowered the levels of chemical yield and enantioselectivity (Table 2, entries 11-12). However, the acidic additives including $PhCO_2H$ or NH_4Cl did not obviously affect this transformation (entries 13 & 14). Interestingly, removal of water by adding 4Å MS significantly decreased the enantioselectivity and diastereoselectivity, suggesting that water is crucial to the enantioselectivity in this reaction. However, the addition of water (1 equiv. or 10 equiv.) was unable to further enhance the diastereoselectivity and enantioselectivity (entries 15-17). Interestingly, the addition neutral inorganic salt could slightly enhance enantioselectivity (entries 18-21). Ultimately, adding 10 mol% of NaCl afforded 93:7 *er* with good yield (80%) (Table 2, entry 18). As a result, the optimal conditions were

finalized as 20 mol% of **3a** with 10 mol% NaCl in trifluorotoluene at room temperature.

Table 2. Optimization of Reaction Conditions[a]



Entry	solvent	Additive (10 mol%)	Yield (%)	er	dr
1	THF	-	70	87.5:12.5	12:1
2	DMF	-	62	62:38	>20:1
3	DMSO	-	74	64:36	5:1
4	2-Me-THF	-	63	88.5:11.5	>20:1
5	Toluene	-	77	89:11	15:1
6	Et_2O	-	22	87.5:12.5	15:1
7	Dioxane	-	90	86:14	>20:1
8	**Trifluorotoluene**	**-**	**86**	**90:10**	**>20:1**
9	MeOH	-	25	67.5:32.5	15:1
10	CH_3CN	-	46	78:22	10:1
11	Trifluorotoluene	Et_3N	31	53.5:46.5	>20:1
12	Trifluorotoluene	K_2CO_3	35	67.5:32.5	5:1
13	Trifluorotoluene	PhCOOH	77	87.5:12.5	>20:1
14	Trifluorotoluene	NH_4Cl	76	86.5:13.5	15:1
15[b]	Trifluorotoluene	4Å MS	20	65:35	5:1
16[c]	Trifluorotoluene	H_2O	90	90:10	>20:1
17[d]	Trifluorotoluene	H_2O	86	90:10	>20:1
18	**Trifluorotoluene**	**NaCl**	**80**	**93:7**	**>20:1**
19	Trifluorotoluene	KCl	76	91:9	>20:1
20	Trifluorotoluene	NaBr	72	91:5:8.5	>20:1
21	Trifluorotoluene	NaI	65	87.5:12.5	>20:1

[a] Unless otherwise noted, the reaction was carried out at 0.2 mmol scale in CH_2Cl_2 (1 mL) with a molar

ratio of **1a**/**2a** = 5:1 at RT for 24 h.

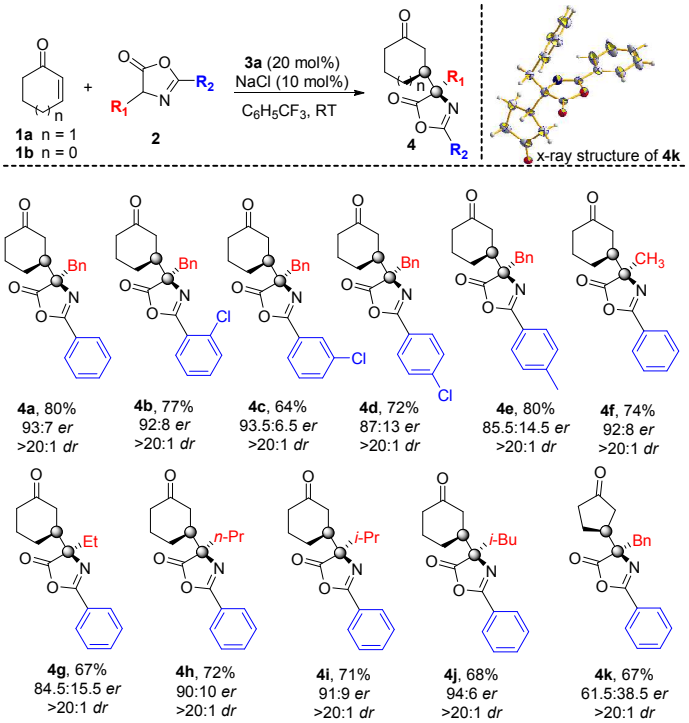
[b] 100 mg 4Å MS was added.

[c] H_2O (1 equiv.) was added.

[d] H_2O (10 equiv.) was added.

Having established the optimized reaction conditions, we next studied the substrate scope of the title reaction and the results are summarized in Table 3. Firstly, the substituent effects on R_2 were evaluated and it was found that the *ortho*- and *meta*-substituted azlactones provided the comparable levels of chemical yield and enantioselectivity (**4b** and **4c**) while the presence of *para*-substituent slightly lowered the enantioselectivity (**4d** and **4e**). Pleasingly, various R_1 substituting groups (Me, Et, *n*-Pr, *i*-Pr and *i*-Bu, **4f**-**4j**) were well tolerated, in which *iso*-butyl analogue afforded the superior level of enantioselectivity (94:6 *er*, **4j**). Lastly, the cyclic enone was extended to cyclopentenone and the chemical yield and enantioselectivity of the corresponding adduct **4k** were dramatically eroded (67% yield, 61.5:38.5 *er*), whose structure was unambiguously assigned by single crystal X-ray diffraction.

Table 3. Substrate Scope for the Conjugate Addition of Cyclic Enones[a]

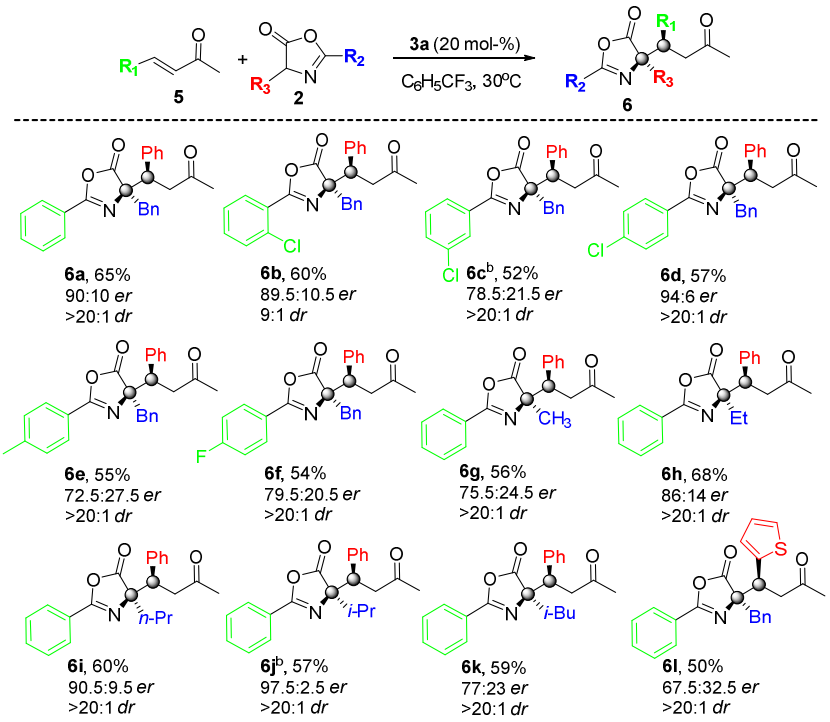


[a] Unless otherwise noted, the reaction was carried out at 0.2 mmol scale in $C_6H_5CF_3$ (1 mL) with a molar

ratio of **1**/**2** = 5:1 at RT for 48 h.

Subsequently, we moved forward to extend this protocol to the unmodified linear *α, β*-unsaturated enone -- 4-phenyl-3-buten-2-one, less reactive Micheal acceptor (Table 4). Encouragingly, the conjugate addition of azlactone **2** to 4-phenyl-3-buten-2-one did proceed to afford the corresponding adduct **6a** in 65% yield with moderate enantioselectivity and excellent diastereoselectivity (90:10 *er* and >20:1 *dr*) at 30°C. Furthermore, at higher temperature, the level of enantioselectivity was severely eroded although the chemical yield was improved. Differently, the addition of NaCl did not show any beneficial effect on the enantioselectivity. Thereafter, the reliability and feasibility of the linear substrates were also evaluated. As shown in Table 4, the *meta*-substitution slightly decreased the level enantioselectivity (**6c**) while *ortho*- and *para*-substitution patterns showed negligible effect on the enantioselectivity (**6b** and **6d**). However, the diastereoselectivity was obviously affected by the *ortho*-substituent (**6b**). The introduction of electron-donating group obviously reduced the level of enantioselectivity (**6e**). Variation of R_3 (**6g-6k**) demonstrated that *iso*-propyl group gave the superior level of enantioselectivity (97.5:2.5 *er*). At last, the electron-rich 4-(thienyl)-3-buten-2-one also furnished the corresponding product **6l** in moderate yield albeit with lower enantioselectivity. The absolute configuration of **6a** was established through the comparison of its specific rotation with the reported data in the literature.[14a]

Table 4. Extension of the Conjugate Addition of Azlactone to Linear Enones[a]

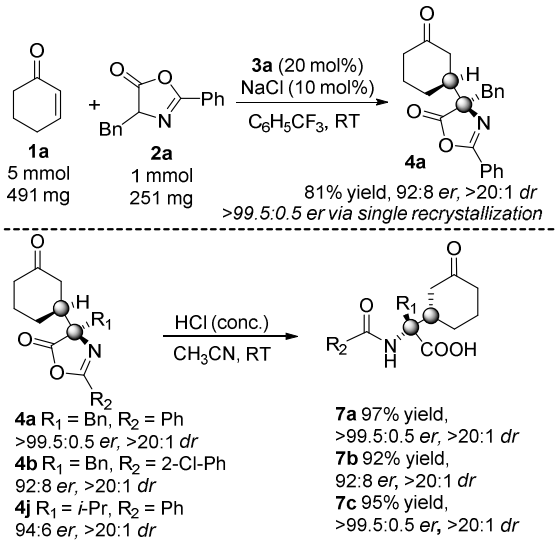


[a] Unless otherwise noted, the reaction was carried out at 0.2 mmol scale in $C_6H_5CF_3$ (1 mL) with a molar ratio of **5**/**2** = 5:1 at 30°C for 72 h.

[b] Performed at 30°C for 96 h.

Finally, large-scale reaction of this transformation was performed by using 1 mmol of **2a** and the corresponding adduct **4a** was obtained in good yield (81%) and good stereoselectivity (92:8 *er* and >20:1 *dr*) (Scheme 2). Pleasingly, the level of enantiopurity for **4a** was readily enhanced to >99.5:0.5 *er via* single recrystallization. To demonstrate the utility of this methodology, further transformation of the obtained adduct was subsequently proceeded and **4a**, **4b**, and **4j** were treated with concentrated hydrochloric acid at room temperature respectively, furnishing the corresponding *α*-cyclohexanone-substituted *α*-amino acid **7a-7c** in good yield and stereoselectivity.

Scheme 2. Large-scale Experiment and Synthetic Transformation of Adduct **4**



In summary, we developed organocatalytic asymmetric conjugate additions of azlactones to enolizable α,β-unsaturated cyclic and linear enones in good yields and stereoselectivities employing proline aryl sulfonamide as the catalyst. The resulting adducts bearing two contiguous quaternary and tertiary stereocenters were efficiently constructed, which could serve as the precursors for α,α-disubstituted α-amino acids. Noticeably, the less reactive enones towards organocatalytic conjugate addition of azlactone were finally tackled, which would significantly complement the versatility of this methodology.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Infrared spectra (IR) were measured by FT-IR apparatus. High resolution mass

spectroscopy (HRMS) was recorded on TOF MS ES+ mass spectrometer and acetonitrile was used to dissolve the sample. Column chromatography was carried out on silica gel (200-300 mesh). Catalyst **3a**,[17a] **3b**-**3d**,[15b] **3e**,[17b] azlactone **2**,[14a, 17c] and *α, β*-unsaturated enone **5**[17d] were prepared according to the reported protocol.

Preparation of catalyst 3f. A solution of *p*-dodecylbenzenesulfonyl chloride (1.72 g. 5.0 mmol, 1 equiv, *sold as mixture of isomers*) in anhydrous THF (25 mL) was added dropwise to the mixture of (1*R*, 2*R*)-1,2-cyclohexane-1,2-diamine (0.57 g, 5.0 mmol, 1equiv) and triethylamine (1.02 g, 10.0 mmol, 2 equiv) in THF (10 mL) with ice-cooling. After the addition, the mixture was warmed to room temperature and stirred overnight. The result solution was concentrated *in vacuo*. And the residue was purified *via* flash silica gel chromatography (MeOH/DCM = 1/19) to give sulphonamide **3f** as colorless oil (1.72 g, 4.1 mmol, yield 82%); $[\alpha]_D^{20}$ = +27.6 (c = 1 in CH_2Cl_2); IR (KBr) ν 3568, 3268, 2927, 1595, 1458, 1326, 1160, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, *major isomer*) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.26-7.32 (m, 2H), 2.65-2.74 (m, 1H), 2.53-2.60 (m, 1H), 2.40 (td, *J* = 10.4, 3.6 Hz, 1H), 1.94 (d, *J* = 12.4 Hz, 1H), 1.52-1.71 (m, 7H), 1.03-1.31 (m, 20H), 0.72-0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, *major isomer*) δ 151.8, 138.3, 128.4, 128.3, 127.7, 127.0, 60.6, 54.8, 46.1, 36.8, 35.3, 32.6, 31.7, 29.6, 29.2, 27.1, 25.0, 24.8, 22.6, 20.6, 14.0; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{24}H_{43}N_2O_2S$ 423.3045, found 423.3036;

General procedures for synthesis of compound 4a-4k.

Azlactone (0.2 mmol, 1 equiv), cyclic enone (1.0 mmol, 5 equiv), NaCl (1.17 mg, 0.02 mmol, 0.1 equiv) and catalyst (0.04 mmol, 0.2 equiv) were dissolved in trifluorotoluene (1.0 mL) at room temperature. After completion of the reaction (monitored by TLC), organic solvent was removed *in vacuo*. Then the residue was purified *via* flash chromatography (petroleum ether/ethyl acetate =

19/1-9/1) to yield the corresponding product.

General procedures for the synthesis of compound 6a-6l.

Azlactone (0.2 mmol, 1 equiv), linear enone (1.0 mmol, 5 equiv) and catalyst (0.04 mmol, 0.2 equiv) were dissolved in trifluorotoluene (1.0 mL) at 30°C. After completion of the reaction (monitored by TLC), organic solvent was removed *in vacuo*. Then the residue was purified *via* flash chromatography (petroleum ether/ethyl acetate = 19/1-9/1) to yield the corresponding product.

Characterization Data for the Micheal Adducts 4a−4k and 6a-6l.

(*R*)-4-benzyl-4-((*S*)-3-oxocyclohexyl)-2-phenyloxazol-5(4*H*)-one 4a

White solid (55.6 mg, 0.160 mmol, yield 80%, > 20:1 *dr*, 93:7 *er*); m.p. 137-138°C; $[\alpha]_D^{20}$ = +106.8 (c = 1 in CH_2Cl_2); IR (KBr) ν 2937, 1816, 1710, 1656, 1450, 1320, 961, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.81-7.83 (m, 2H), 7.52-7.56 (m, 1H), 7.41-7.45 (m, 2H), 7.10-7.18 (m, 5H), 3.28 (d, *J* = 13.2 Hz, 1H), 3.15 (d, *J* = 13.2 Hz, 1H), 2.41-2.54 (m, 4H), 2.25-2.34 (m, 1H), 2.13-2.21 (m, 2H), 1.60-1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.6, 178.6, 160.5, 133.8, 132.8, 130.2, 128.7, 128.2, 127.9, 127.4, 125.3, 44.5, 42.3, 41.0, 40.9, 25.6, 24.4; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{21}NO_3Na$ 370.1419, found 370.1405; HPLC analysis: (CHIRALCEL OD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 10.4 min (major), 18.5 min (minor).

(*R*)-4-benzyl-2-(2-chlorophenyl)-4-((*S*)-3-oxocyclohexyl)oxazol-5(4*H*)-one 4b

White solid (58.8 mg, 0.154 mmol, yield 77%, > 20:1 *dr*, 92:8 *er*); m.p. 106-107°C; $[\alpha]_D^{20}$ = +103.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3031, 2952, 1814, 1711, 1667, 1479, 1305, 1083, 957, 877 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.46 (m, 2H), 7.17-7.32 (m, 7H), 3.31 (d, *J* = 12.8 Hz, 1H), 3.19 (d, *J* = 13.2 Hz, 1H), 2.50-2.56 (m, 3H), 2.42-2.46 (m, 1H), 2.27-2.34 (m, 1H), 2.20-2.22 (m, 2H), 1.61-1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.3, 178.2, 159.4, 133.7, 133.5, 132.7, 131.0,

130.8, 130.3, 128.3, 127.5, 126.8, 125.3, 58.4, 44.2, 42.3, 41.0, 40.9, 25.6, 24.4, 18.4; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}NO_3NaCl$ 404.1029, found 404.1013; HPLC analysis: (CHIRALCEL OD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 5.6 min (major), 8.2 min (minor).

(*R*)-4-benzyl-2-(3-chlorophenyl)-4-((*S*)-3-oxocyclohexyl)oxazol-5(4*H*)-one 4c

Colorless oil (48.9 mg, 0.128 mmol, yield 64%, > 20:1 *dr*, 93.5:6.5 *er*); $[\alpha]_D^{20}$ = +100.2 (c = 1 in CH_2Cl_2); IR (KBr) ν 3620, 2950, 1817, 1712, 1654, 1293, 1048, 891 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.48-7.58 (m, 1H), 7.29-7.39 (m, 2H), 7.10-7.17 (m, 5H), 3.28 (d, *J* = 13.2 Hz, 1H), 3.15 (d, *J* = 13.2 Hz, 1H), 2.38-2.52 (m, 4H), 2.26-2.34 (m, 1H), 2.09-2.20 (m, 1H), 1.61-1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.5, 178.1, 159.5, 134.9, 133.6, 132.9, 130.2, 130.1, 128.3, 127.8, 127.5, 127.0, 126.0, 44.4, 42.3, 41.0, 40.9, 25.6, 24.4; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}NO_3NaCl$ 404.1029, found 404.1011; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 8.8 min (minor), 13.3 min (major).

(*R*)-4-benzyl-2-(4-chlorophenyl)-4-((*S*)-3-oxocyclohexyl)oxazol-5(4*H*)-one 4d

White solid (55.0 mg, 0.144 mmol, yield 72%, > 20:1 *dr*, 87:13 *er*); m.p. 133-134°C; $[\alpha]_D^{20}$ = +95.4 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 2943, 1817, 1712, 1653, 1312, 1091, 960，876 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.10-7.16 (m, 5H), 3.27 (d, *J* = 13.2 Hz, 1H), 3.14 (d, *J* = 13.2 Hz, 1H), 2.41-2.53 (m, 4H), 2.26-2.32 (m, 1H), 2.12-2.20 (m, 2H), 1.60-1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.3, 178.2, 159.7, 139.2, 133.7, 130.2, 129.2, 129.1, 128.2, 127.4, 123.7, 44.4, 44.3, 40.97, 40.93, 25.6, 24.4, 18.5; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}NO_3NaCl$ 404.1029, found 404.1012; HPLC analysis: (CHIRALCEL

AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 10.1 min (minor), 17.3 min (major).

(*R*)-4-benzyl-4-((*S*)-3-oxocyclohexyl)-2-(p-tolyl)oxazol-5(4*H*)-one 4e

White solid (57.8 mg, 0.160 mmol, yield 80%, > 20:1 *dr*, 85.5:14.5 *er*); m.p. 142-143 °C; $[\alpha]_D^{20}$ = +90.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3404, 2962, 1814, 1710, 1656, 1444, 1178, 1045, 957, 879 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.11-7.17 (m, 5H), 3.26 (d, *J* = 13.2 Hz, 1H), 3.13 (d, *J* = 13.2 Hz, 1H), 2.43-2.55 (m, 3H), 2.40 (s, 3H), 2.12-2.18 (m, 2H), 1.62-1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.8, 178.7, 160.6, 143.5, 133.9, 130.2, 129.5, 128.2, 127.8, 127.3, 122.5, 44.5, 42.3, 41.0, 40.9, 25.6, 24.4, 21.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{23}H_{23}NO_3Na$ 384.1576, found 384.1579; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 8.9 min (minor), 14.9 min (major).

(*R*)-4-methyl-4-((*S*)-3-oxocyclohexyl)-2-phenyloxazol-5(4*H*)-one 4f

White solid (40.2 mg, 0.148 mmol, yield 74%, > 20:1 *dr*, 92:8 *er*); m.p. 106-108°C; $[\alpha]_D^{20}$ = +110.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3743, 2946, 1818, 1710, 1653, 1452, 1003, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99-8.01 (m, 2H), 7.58-7.62 (m, 1H), 7.49-7.52 (m, 2H), 2.35-2.45 (m, 5H), 2.22-2.32 (m, 1H), 2.05-2.17 (m, 1H), 1.46-1.69 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.7, 179.7, 160.6, 133.0, 128.9, 128.0, 125.5, 71.3, 44.9, 42.0, 40.9, 25.2, 24.4, 21.5; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}NO_3$ 272.1287, found 272.1283; HPLC analysis: (CHIRALCEL AS-H, 3.0% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 17.0 min (minor), 22.7 min (major).

(*R*)-4-ethyl-4-((*S*)-3-oxocyclohexyl)-2-phenyloxazol-5(4*H*)-one 4g

Colorless oil (38.3 mg, 0.134 mmol, yield 67%, > 20:1 *dr*, 84.5:15.5 *er*); $[\alpha]_D^{20}$ = +85.2 (c = 0.5 in

CH_2Cl_2); IR (KBr) ν 2932, 1815, 1713, 1655, 1451, 1291, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 2.34-2.45 (m, 3H), 2.32-2.44 (m, 1H), 2.11-2.16 (m, 1H), 1.91-2.06 (m, 3H), 1.49-1.68 (m, 2H), 1.30-1.35 (m, 1H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.7, 179.3, 160.8, 132.9, 128.9, 128.0, 125.4, 76.0, 44.0, 42.1, 41.0, 27.8, 25.4, 24.4, 8.0; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{17}H_{19}NO_3Na$ 308.1263, found 308.1270; HPLC analysis: (CHIRALCEL OD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 6.6 min (major), 10.5 min (minor).

(*R*)-4-((*S*)-3-oxocyclohexyl)-2-phenyl-4-propyloxazol-5(4*H*)-one 4h

Colorless oil (43.1 mg, 0.144 mmol, yield 72%, > 20:1 *dr*, 90:10 *er*); $[\alpha]_D^{20}$ = +109.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 2959, 1810, 1714, 1654, 1291, 1021, 945, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 2.63-2.67 (m, 1H), 2.38-2.44 (m, 2H), 2.21-2.33 (m, 2H), 2.03-2.08 (m, 1H), 1.90 (td, *J* = 13.0, 4.5 Hz, 1H), 1.74-1.84 (m, 2H), 1.58-1.67 (m, 1H), 1.43-1.51 (m, 1H), 1.10-1.29 (m, 4H), 0.89 (t, *J* = 8.0 Hz,, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.0, 179.7, 160.6, 132.9, 128.9, 128.0, 125.5, 76.0, 44.3, 42.2, 41.1, 36.7, 25.7, 24.3, 17.0, 13.8; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{18}H_{21}NO_3Na$ 322.1419, found 322.1404; HPLC analysis: (CHIRALCEL OD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 6.0 min (major), 9.3 min (minor).

(*R*)-4-isopropyl-4-((*S*)-3-oxocyclohexyl)-2-phenyloxazol-5(4*H*)-one 4i

Colorless oil (42.5 mg, 0.142 mmol, yield 71%, > 20:1 *dr*, 91:9 *er*); $[\alpha]_D^{20}$ = +105.8 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 2967, 1810, 1714, 1655, 1451, 1321, 1291, 1042, 937, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.01-8.04 (m, 2H), 7.58-7.62 (m, 1H), 7.53-7.50 (m, 2H), 2.67-2.63 (m, 4H), 2.44-2.38 (m, 2H), 2.33-2.01 (m, 1H), 1.90 (td, *J* = 13, 4.5 Hz, 1H), 1.84-1.74 (m, 2H), 1.67-1.58 (m,

1H), 1.51-1.43 (m, 1H), 1.46-1.36 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.0, 179.2, 160.8, 132.9, 128.9, 128.0, 125.4, 78.4, 41.4, 41.3, 41.1, 31.4, 25.5, 24.5, 16.6, 16.5; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for 322.1419, found 322.1407; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 8.3 min (major), 13.7 min (minor).

(*R*)-4-isobutyl-4-((*S*)-3-oxocyclohexyl)-2-phenyloxazol-5(4*H*)-one 4j

Colorless oil (42.6 mg, 0.136 mmol, yield 68%, > 20:1 *dr*, 94:6 *er*); $[\alpha]_D^{20}$ = +106.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3364, 2957, 1811, 1714, 1653, 1454, 1291, 1041, 952 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01-8.03 (m, 2H), 7.60 (td, J = 7.2, 1.2 Hz, 1H), 7.49-7.53 (m, 2H), 2.36-2.50 (m, 3H), 2.20-2.31 (m, 2H), 2.06-2.13 (m, 1H), 1.97-2.04 (m, 2H), 1.78 (dd, J = 7.2 Hz, 1H), 1.52-1.64 (m, 2H), 1.37-1.47 (m, 1H), 0.90 (d, J = 8.0 Hz, 3H), 0.85 (d, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.8, 179.8, 160.3, 132.9, 128.9, 128.0, 125.5, 74.8, 45.5,43.5, 41.7, 41.0, 25.3, 24.8, 24.4, 24.2, 23.1; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{19}H_{23}NO_3Na$ 336.1576, found 336.1585; HPLC analysis: (CHIRALCEL OD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 13.2 min (major), 14.7min (minor).

(*R*)-4-benzyl-4-((*S*)-3-oxocyclopentyl)-2-phenyloxazol-5(4*H*)-one 4k

White solid (44.6 mg, 0.134 mmol, yield 67%, > 20:1 *dr*, 61.5:38.5 *er*); m.p. 116-117°C; $[\alpha]_D^{20}$ = +56.5 (c = 1 in CH_2Cl_2); IR (KBr) ν 2963, 1817, 1738, 1651, 1494, 1452, 976, 884 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82-7.84 (m, 2H), 7.52-7.56 (m, 1H), 7.41-7.45 (m, 2H), 7.13-7.17 (m, 5H), 3.34 (d, J = 13.2 Hz, 1H), 3.16 (d, J = 13.2 Hz, 1H), 2.85-2.94 (m, 1H), 2.12-2.47 (m, 5H), 1.94-2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.2, 178.7, 160.7, 133.9, 132.9, 130.1, 128.7, 128.2, 127.9, 127.4, 125.2, 75.9, 43.1, 41.8, 39.4, 38.2, 24.3; HRMS (TOF-ES+) m/z: $[M+Na]^+$

calcd for $C_{21}H_{19}NO_3Na$ 356.1263, found 356.1251; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 8.6 min (minor), 10.7 min (major).

(*R*)-4-benzyl-4-((*R*)-3-oxo-1-phenylbutyl)-2-phenyloxazol-5(4*H*)-one 6a[14a]

White solid (51.7 mg, yield 65%, > 20:1 *dr*, 90:10 *er*); m.p. 115-116°C; $[\alpha]_D^{20}$ = -19.6 (c = 1 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.48-7.52 (m, 1H), 7.40-7.46 (m, 2H), 7.08-7.23 (m, 10H), 3.98 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.26-3.31 (m, 3H), 3.18 (d, *J* = 13.2 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.2, 177.9, 160.5, 138.1, 134.0, 132.6, 130.3, 129.2, 128.7, 128.3, 128.2, 127.7, 127.3, 125.5, 78.2, 46.7, 44.5, 41.9, 30.7; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 8.1 min (minor), 9.9 min (major).

(*R*)-4-benzyl-2-(2-chlorophenyl)-4-((*R*)-3-oxo-1-phenylbutyl)oxazol-5(4*H*)-one 6b

White solid (51.8 mg, 0.120 mmol, yield 60%, 9:1 *dr*, 89.5:10.5 *er*); m.p. 116-117°C; $[\alpha]_D^{20}$ = -14.4 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3031, 2935, 1823, 1718, 1651, 1474, 1321, 1097, 1036, 963, 888, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.53 (td, *J* = 7.6, 1.2 Hz, 1H), 7.39-7.43 (m, 3H), 7.31 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.06-7.16 (m, 7H), 4.73 (q, *J* = 4.8 Hz, 1H), 3.21 (d, *J* = 13.2 Hz, 1H), 3.09-3.21 (m, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.4, 177.3, 160.7, 136.1, 133.8, 132.7, 130.4, 130.2, 128.8, 128.7, 128.1, 127.8, 127.3, 126.7, 125.4, 45.2, 41.7, 41.3, 30.2, 30.1, 29.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{26}H_{22}NO_3NaCl$ 454.1186, found 454.1166; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254nm), t_R = 8.1 min (minor), 14.8 min (major).

(*R*)-4-benzyl-2-(3-chlorophenyl)-4-((*R*)-3-oxo-1-phenylbutyl)oxazol-5(4*H*)-one 6c

Yellow oil (44.8 mg, 0.104 mmol, yield 52%, > 20:1 *dr*, 78.5:21.5 *er*); $[\alpha]_D^{20}$ = -9.6 (c = 0.5 in

CH_2Cl_2); IR (KBr) ν 2928, 1815, 1716, 1654, 1293, 1095, 970, 891 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.50 (td, *J* = 7.6, 1.2 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.22-7.25 (m, 1H), 7.09-7.14 (m, 8H), 3.96 (q, *J* = 4.4 Hz, 1H), 3.12-3.32 (m, 4H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.6, 177.7, 160.8, 140.4, 134.0, 133.8, 132.7, 130.3, 129.6, 129.3, 128.7, 128.2, 127.9, 127.7, 127.6, 127.4, 125.3, 77.9, 46.3, 44.4, 41.8, 30.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{26}H_{22}NO_3NaCl$ 454.1186, found 454.1174; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 7.8 min (minor), 9.3 min (major).

(*R*)-4-benzyl-2-(4-chlorophenyl)-4-((*R*)-3-oxo-1-phenylbutyl)oxazol-5(4*H*)-one 6d

Yellow oil (49.2 mg, 0.114 mmol, yield 57%, > 20:1 *dr*, 94:6 *er*); $[\alpha]_D^{20}$ = -17.4 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 2925, 1815, 1712, 1650, 1493, 1319, 1095, 969, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72-7.74 (m, 2H), 7.52-7.56 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.16-7.21 (m, 4H), 7.11-7.15 (m, 5H), 3.98 (q, *J* = 4.4 Hz, 1H), 3.16-3.34 (m, 4H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.7, 177.7, 160.7, 136.8, 133.8, 133.6, 132.7, 130.6, 130.2, 128.7, 128.5, 128.2, 127.7, 127.4, 125.3, 78.0, 46.0, 44.4, 41.9, 30.6; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{26}H_{22}NO_3NaCl$ 454.1186, found 454.1182; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 8.2 min (minor), 11.5 min (major).

(*R*)-4-benzyl-4-((*R*)-3-oxo-1-phenylbutyl)-2-(p-tolyl)oxazol-5(4*H*)-one 6e

white solid (45.2 mg, 0.110 mmol, yield 55%, > 20:1 *dr*, 72.5:27.5 *er*); m.p. 127-129°C; $[\alpha]_D^{20}$ = -16.0 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3032, 1812, 1716, 1659, 1496, 1296, 969, 890, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73-7.74 (m, 2H), 7.51-7.54 (m, 1H), 7.39-7.43 (m, 2H), 7.11-7.16 (m, 7H), 6.98-7.00 (d, *J* = 8.0 Hz, 2H), 3.96 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.18-3.33 (m, 4H), 2.24 (s, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.2, 177.9, 160.5, 137.3, 135.0, 134.1, 132.5, 130.3,

129.0, 128.6, 128.1, 127.7, 127.2, 125.6, 78.3, 46.5, 44.6, 42.0, 30.7, 21.0; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{27}H_{26}NO_3$ 412.1913, found 412.1897; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254nm), t_R = 8.2 min (minor), 10.0 min (major).

(*R*)-4-benzyl-2-(4-fluorophenyl)-4-((*R*)-3-oxo-1-phenylbutyl)oxazol-5(4*H*)-one 6f

Yellow oil (44.8 mg, 0.108 mmol, yield 54%, > 20:1 *dr*, 79.5:20.5 *er*); $[\alpha]_D^{20}$ = -7.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 2923, 1811, 1714, 1658, 1510, 1229, 1160, 968, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.48-7.52 (m, 1H), 7.36-7.40 (m, 2H), 7.17-7.21 (m, 2H), 7.08-7.12 (m, 5H), 6.81-6.87 (m, 2H), 3.97 (q, *J* = 4.4 Hz, 1H), 3.13-3.31 (m, 4H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.9, 177.8, 162.1 (d, $^1J_{C-F}$ = 245 Hz), 160.7, 134.0, 133.9, 132.7, 130.8 ($^3J_{C-F}$= 8 Hz), 130.2, 128.7, 128.2, 127.7, 127.3, 125.4, 115.2(d, $^2J_{C-F}$ = 21 Hz), 78.2, 45.9, 44.5, 41.9, 30.6, 29.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{26}H_{22}NO_3FNa$ 438.1481, found 438.1463; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 7.8 min (minor), 10.7 min (major).

(*R*)-4-Methyl-4-((*R*)-3-oxo-1-phenylbutyl)-2-phenyloxazol-5(4*H*)-one 6g[14a]

white solid (36.0 mg, 0.112 mmol, yield 56%, > 20:1 *dr*, 75.5:24.5 *er*); m.p. 93-94°C; $[\alpha]_D^{20}$ = -84.0 (c = 0.5 in CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.89-7.90 (m, 2H), 7.56-7.59 (m, 1 H), 7.45-7.49 (m, 2H), 7.13-7.20 (m, 5 H), 3.81 (dd, *J* = 7.5, 6.5 Hz, 1H), 3.18-3.20 (m, 2H), 2.10 (s, 3 H,), 1.58 (s, 3 H); HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 5.9 min (minor), 7.1 min (major).

(*R*)-4-ethyl-4-((*R*)-3-oxo-1-phenylbutyl)-2-phenyloxazol-5(4*H*)-one 6h[14b]

Colorless oil (45.5 mg, 0.136 mmol, yield 68%, > 20:1 *dr*, 86:14 *er*); $[\alpha]_D^{20}$ = -97.2 (c = 0.5 in CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88-7.90 (m, 2 H), 7.55-7.56 (m, 1 H), 7.44-7.48 (m, 2H),

7.13-7.19 (m, 5 H), 3.81 (t, J = 6.8 Hz, 1H), 3.15 (d, J = 6.8 Hz, 2H), 2.06 (s, 3 H), 2.00 (q, J = 7.6 Hz, 2H), 0.82 (t, J = 7.6 Hz, 3H); HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 5.4 min (minor), 6.6 min (major).

(*R*)-4-((*R*)-3-oxo-1-phenylbutyl)-2-phenyl-4-propyloxazol-5(4*H*)-one 6i[14b]

Colorless oil (41.8 mg, 0.120 mmol, yield 60%, > 20:1 *dr*, 90.5:9.5 *er*); $[\alpha]_D^{20}$ = -120.0 (c = 0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89-7.92 (m, 2 H), 7.56-7.61 (m, 1 H), 7.46-7.50 (m, 2H), 7.15-7.20 (m, 5 H), 3.81 (dd, J = 7.6, 6.0 Hz, 1 H), 3.17-3.19 (m, 2 H), 2.08 (s, 3 H), 1.93-1.97 (m, 2 H), 1.14-1.28 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254nm), t_R = 5.0 min (minor), 6.2 min (major).

(*R*)-4-isopropyl-4-((*R*)-3-oxo-1-phenylbutyl)-2-phenyloxazol-5(4*H*)-one 6j

white solid (39.8 mg, 0.114 mmol, yield 57%, > 20:1 *dr*, 97.5:2.5 *er*); m.p. 113-114°C; $[\alpha]_D^{20}$ = -145.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 2968, 1813, 1724, 1654, 1450, 1289, 923, 881 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89-7.91 (m, 2H), 7.57-7.60 (m, 1H), 7.46-7.49 (m, 2H), 7.22-7.24 (m, 2H), 7.12-7.17 (m, 3H), 3.99 (dd, J = 11.0, 3.5 Hz, 1H), 3.28 (dd, J = 17.0, 11.5 Hz, 1H), 2.96 (dd, J = 17.0, 3.5 Hz, 1H), 2.30-2.37 (m, 1H), 2.04 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.3, 177.7, 160.6, 137.7, 132.6, 129.4, 128.7, 128.1, 127.8, 127.6, 125.6, 79.5, 44.3, 43.5, 32.1, 30.8, 17.6, 15.6; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{23}NO_3Na$ 372.1576, found 372.1563; HPLC analysis: (CHIRALCEL AD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 4.6 min (minor), 5.4 min (major).

(*R*)-4-isobutyl-4-((*R*)-3-oxo-1-phenylbutyl)-2-phenyloxazol-5(4*H*)-one 6k[14b]

Colorless oil (42.9 mg, 0.118 mmol, yield 59%, > 20:1 *dr*, 77:23 *er*); $[\alpha]_D^{20}$ = -44.4 (c = 0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89-7.92 (m, 2H), 7.57-7.61 (m, 1H), 7.47-7.51 (m, 2H),

7.14-7.18 (m, 5H), 3.75 (dd, J = 8.0, 5.6 Hz, 1H), 3.16-3.18 (m, 2H), 2.07 (s, 3H), 2.01 (dd, J = 14.0, 6.4 Hz, 1H), 1.92 (dd, J = 14.0, 6.0 Hz, 1H), 1.48-1.58 (m, 1H), 0.88 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H); HPLC analysis: (CHIRALCEL AD-H, 3.0% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 7.5 min (minor), 9.8 min (major).

(*R*)-4-benzyl-4-((*S*)-3-oxo-1-(thiophen-2-yl)butyl)-2-phenyloxazol-5(4*H*)-one 6l

white solid (40.3 mg, 0.100 mmol, yield 50%, > 20:1 *dr*, 72:28 *er*); m.p. 118-119°C; $[\alpha]_D^{20}$ = -6.0 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3036, 1811, 1714, 1657, 1451, 1294, 1095, 971, 890, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.74-7.76 (m, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H), 7.10-7.14 (m, 5H), 7.06 (d, J = 4.8 Hz, 1H), 6.93 (dd, J = 3.6, 0.8 Hz, 1H), 6.83 (dd, J = 5.2, 3.6 Hz, 1H), 4.33 (q, J = 4.4 Hz, 1H), 3.17-3.30 (m, 4H), 2,12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.7, 177.6, 161.4, 140.7, 133.9, 132.6, 130.2, 128.7, 128.2, 127.9, 127.4, 127.3, 126.6, 125.6, 125.3, 78.1, 45.9, 42.4, 41.7, 30.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{24}H_{21}NO_3SNa$ 426.1140, found 426.1152; HPLC analysis: (CHIRALCEL OD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 7.1 min (minor), 9.1 min (major).

General Procedure for Azlactone Opening

To a solution of the Michael adduct **4** (1eq) in CH_3CN (0.1 M) was added conc. HCl (2.5 eq). Then the stirring was maintained at room temperature until consumption of the starting material. The solvent was removed in *vacuo*. And the resulting residue was purified via flash chromatography (MeOH/DCM = 1/19) to yield the corresponding product **7.**

Product **7a** was prepared according to general procedure using **4a** (69.4 mg, 0.2 mmol) afforded **7a** as white solid (70.8 mg, 0.194 mmol, yield 97%, > 20:1 *dr*, > 99.5:0.5 *er*); m.p. 155-157°C; $[\alpha]_D^{20}$ = +40.2 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3369, 2925, 2534, 1704, 1618, 1524, 1214, 1100, 886, 796 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67-7.73 (m, 3H), 7.54 (t, J = 7.6 Hz, 1H), 7.45-7.49 (m,

2H), 7.14-7.22 (m, 3H), 7.08-7.10 (m, 2H), 3.59 (d, J = 13.6 Hz, 1H), 3.38 (d, J = 13.6 Hz, 1H), 2.44-2.60 (m, 2H), 2.32-2.40 (m, 1H), 2.16-2.20 (m, 1H), 2.10-2.11 (m, 1H), 1.99-2.03 (m, 1H), 1.40-1.48 (m, 2H), 1.23 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 210.4, 173.2, 166.6, 137.2, 135.5, 131.8, 130.3, 129.0, 128.5, 127.4, 127.0, 66.7, 44.0, 42.4, 41.1, 36.3, 26.7, 25.0; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{22}H_{23}NO_4Na$ 388.1525, found 388.1511; HPLC analysis: (CHIRALCEL AD-H, 15% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 5.8 min (major), 6.2 min (minor).

Product **7b** was prepared according to general procedure using **4b** (76.2 mg, 0.2 mmol) afforded **7b** as white solid (73.6 mg, 0.184 mmol, yield 92%, > 20:1 *dr*, 92:8 *er*); m.p. 149-151°C; $[\alpha]_D^{20}$ = +72.4 (c = 0.5 in CH_2Cl_2); IR (KBr) ν 3377, 2930, 2861, 1712, 1631, 1514, 1238, 868 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.75 (s, 1H), 7.35-7.49 (m, 3H), 7.20-7.27 (m, 5H), 3.55 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 12.8 Hz, 1H), 2.55-2.61 (m, 2H), 2.29-2.38 (m, 1H), 2.15-2.20 (m, 2H), 2.00-2.02 (m, 1H), 1.40-1.42 (m, 2H), 1.24-1.28 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 211.2, 172.8, 165.3, 138.2, 137.3, 131.4, 130.5, 130.3, 130.1, 129.1, 128.2, 127.6, 126.7, 67.6, 44.3, 43.3, 41.3, 37.4, 27.0, 25.1; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{22}H_{23}NO_4Cl$ 400.1316, found 400.1301; HPLC analysis: (CHIRALCEL AS-H, 25% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 8.7 min (major), 10.4 min (minor).

Product **7c** was prepared according to general procedure using **4j** (47.0 mg, 0.15 mmol) afforded **7c** as colorless oil (47.3 mg, 0.143 mmol, yield 95%, > 20:1 *dr*, > 99.5:0.5 *er*); $[\alpha]_D^{20}$ = +67.2 (c = 0.1 in CH_2Cl_2); IR (KBr) ν 3427, 2925, 2364, 1632, 1525, 1232, 1080 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.78-7.80 (m, 3H), 7.54-7.57 (m, 1H), 7.48-7.51 (m, 2H), 2.59-2.64 (m, 1H), 2.28-2.42 (m, 4H), 2.14-2.17 (m, 1H), 1.97-2.04 (m, 2H), 1.86 (q, J = 7.5 Hz, 1H), 1.51-1.58 (m, 1H), 1.39-1.45

(m, 1H), 1.28-1.36 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 210.5, 174.5, 165.8, 135.4, 131.8, 129.0, 127.3, 79.6, 65.5, 43.5, 41.1, 26.6, 24.9, 24.6, 24.5, 23.1; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{19}H_{25}NO_4Na$ 354.1681, found 354.1678; HPLC analysis: (CHIRALCEL AD-H, 15% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), t_R = 7.3 min (major), 8.0 min (minor).

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge *via* the internet at http://pubs.acs.org.

^{1}H NMR and ^{13}C NMR spectra for compounds **3f**, **4a-4k**, **6a-6l and 7a-7c**;

HPLC traces for compound **4a-4k, 6a-6l and 7a-7c.**

Crystallographic data of **4k** in CIF format.

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Notes

The authors declare no competing financial interest.

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