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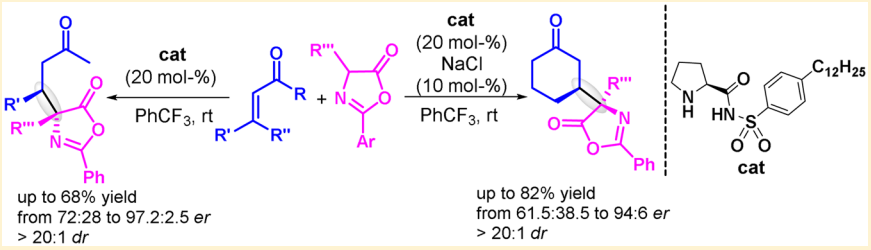
Organocatalytic Enantioselective Conjugate Addition of Azlactones to Enolizable Linear and Cyclic Enones

Chao-Ming Wang, Jun-An Xiao, Jing Wang, Sha-Sha Wang, Zhao-Xu Deng,† and Hua Yang*

College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, P. R. China

Supporting Information



ABSTRACT: Highly diastereo- and enantioselective conjugate additions of azlactones to enolizable cyclic and linear enones were conducted 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 attention had been paid to develop stereoselective accesses to diverse α,α-disubstituted α-amino acids.[6] As an intrinsic hurdle arises from the demanding steric effect of a quaternary stereocenter, the enantioselective synthesis of an α,α-disubstituted α-amino acid is still an ever-standing challenge in synthetic and medicinal chemistry.[7]

As is 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 elegant enantioselective conjugate additions of azlactone to α,β-unsaturated trichloromethyl ketones catalyzed by quinine-derived thiourea. However, the more reactive trichloromethyl ketone was a prerequisite, and the replacement of the methyl or phenyl ketone proved to be inactive.[10] Zhang et al. employed quinine-derived thiourea catalysts to realize the conjugate addition between azlactone and chalcone, in which *o*-hydroxyl chalcone was the only 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]

Unfortunately, despite these encouraging advances, the unmodified and enolizable benzalacetones and cyclohexenones with less electrophilicity remained elusive and unsuccessful in terms of the organocatalytic enantioselective conjugate addition of azlactones. It can be rationalized that these enolizable enones could readily undergo enolization under the organocatalytic conditions, leading to a reduction in the electrophilicity and a decrease in the efficacy of activating enones as the Micheal acceptor. The Amarante group described a conjugate addition of azlactone to benzalacetone catalyzed by (±)-camphorsulfonic acid, resulting in a racemic Micheal adduct.[13] It is worth noting that the only success in the enantioselective conjugate addition of azlactone to benzalacetone was achieved by Peters and co-workers who used a chiral mono or bis-palladacycle as the organometallic catalyst.[14] Our continuous interest in 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 prolinosulfonamide organocatalyst (Hua Cat), in which water was found to have a 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

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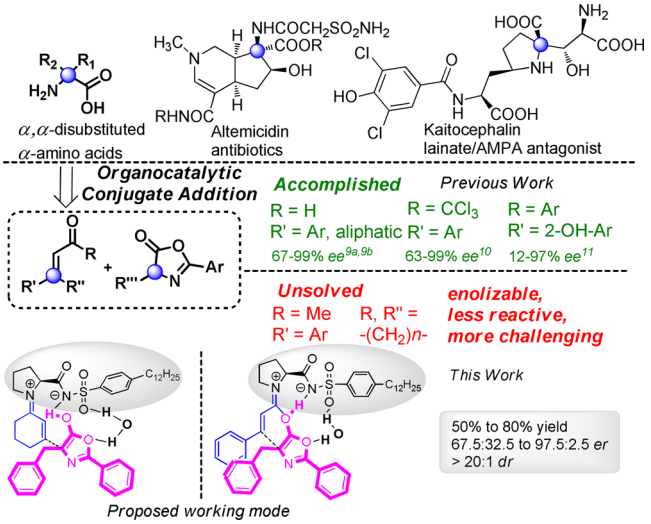
organocatalytic conjugate addition of azlactone leading to α,α-disubstituted α-amino acids.

Scheme 1. Synthetic Profiles of Organocatalytic Conjugate Addition of Azlactone



Initially, the conjugate addition between cyclohexenone (**1a**) and azlactone **2a** was used as a model reaction to screen the reaction parameters. On the basis of our previous success with organocatalytic enone chemistry, we speculated that amino acid sulfonamide should effectively activate enone through the formation of iminium ion to promote this reaction. Accordingly, various sulfonamides **3a**–**3e** derived from secondary amino acids were evaluated. Gratifyingly, desired product **4a** could be obtained in 70% yield along with 15:1 dr and 67.5:32.5 er upon using 20 mol % *p*-dodecyl-*N*-arylsulfoprolinamide (**3a**) in DCM at room temperature (Table 1). The employment of TBS-4-hydroxyprolinamide **3b** and trimethyl analogues (**3c** and **3d**) all gave slightly lower enantioselectivities. The introduction of an electron-withdrawing group onto the phenyl moiety (**3e**) remarkably slowed the reaction without affecting the level of enantioselectivity. On the other hand, primary amine catalyst **3f** afforded a poor yield, possibly because of the decomposition of azlactone promoted by the primary amino group.[16] As a consequence, prolinasufhonamide **3a** was chosen as the optimal catalyst for this transformation.

Subsequently, other reaction parameters, including the reaction medium and additive, were further optimized by using **3a** as the organocatalyst. The results are summarized in Table 2. First, 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 were investigated. The addition of base such as trimethylamine or K_2CO_3 dramatically lowered the levels of chemical yield and enantioselectivity (Table 2, entry 11 or 12, respectively). However, the acidic additives, including $PhCO_2H$ and NH_4Cl, didn't obviously affect this transformation (entries 13 and 14, respectively). Interestingly, removal of water by adding 4 Å molecular sieves (MS) significantly decreased the enantioselectivity and diastereoselectivity, suggesting that water is crucial to the enantioselectivity in this reaction. However, the addition of water (1 or 10 equiv) could not further enhance the diastereoselectivity or enantioselectivity (entries 15–17). Interestingly, the addition of a neutral inorganic salt could slightly influence enantioselectivity (entries 18–21). Ultimately, adding 10 mol % NaCl afforded 93:7 er with good yield (80%) (Table 2, entry 18). As a result, the optimal conditions were finalized as 20 mol % **3a** with 10 mol % NaCl in trifluorotoluene at room temperature.

Having established the optimized reaction conditions, we next studied the substrate scope of the title reaction, and the results are summarized in Table 3. First, the substituent effects on R_2 were evaluated; it was found that the *ortho*- and *meta*-substituted azlactones provided comparable levels of chemical yield and enantioselectivity (**4b** and **4c**), while the presence of a

Table 1. Organocatalyst Screening

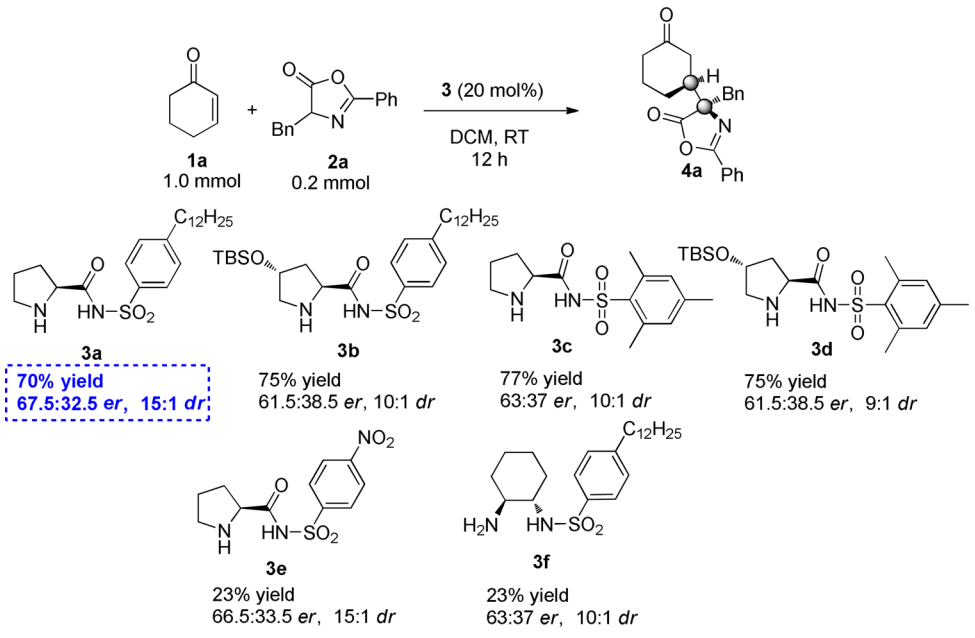


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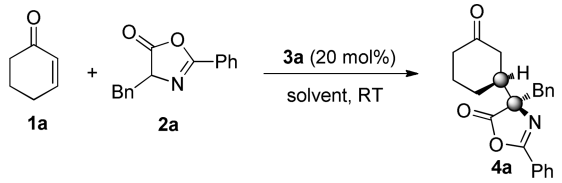
Table 2. Optimization of Reaction Conditions[a]



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	4 Å 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 conducted at a 0.2 mmol scale in CH_2Cl_2 (1 mL) with a **1a**:**2a** molar ratio of 5:1 at rt for 24 h. [b]With 100 mg of 4 Å MS added. [c]H_2O (1 equiv) was added. [d]H_2O (10 equiv) was added.

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**, respectively)] were well tolerated, in which isobutyl 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); the structure was unambiguously assigned by single-crystal X-ray diffraction.

Subsequently, we moved forward to extend this protocol to the unmodified linear α,β-unsaturated enone, 4-phenyl-3-buten-2-one, a 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 (90:10 er) and excellent diastereoselectivity (>20:1 dr) at 30 °C. Furthermore, at higher temperatures, the level of enantioselectivity was severely eroded, although the chemical yield was improved. On the other hand, the addition of NaCl did not have any beneficial effect on enantioselectivity. Thereafter, the reliability and feasibility of the linear substrates were also evaluated. As shown in Table 4, *meta* substitution slightly decreased the enantioselectivity (**6c**) while *ortho* and *para* substitution patterns had a negligible effect on enantioselectivity (**6b** and **6d**). However, the diastereoselectivity was obviously affected by the *ortho* substituent (**6b**). The introduction of an electron-donating group obviously reduced the level of enantioselectivity (**6e**). Variation of R_3 (**6g**–**6k**) demonstrated that the isopropyl group gave a 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 data reported in the literature.[14a]

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 a single recrystallization. To demonstrate the utility of this methodology, further transformation of the obtained adduct subsequently proceeded, and **4a**, **4b**, and **4j** were treated with concentrated hydrochloric acid at room temperature, furnishing the corresponding α-cyclohexanone-substituted α-amino acids **7a**–**7c**, respectively, in good yield and stereoselectivity.

In summary, we developed organocatalytic asymmetric conjugate additions of azlactones to enolizable α,β-unsaturated cyclic and linear enones in good yields and stereoselectivities by 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 toward 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 or 500 MHz. The chemical shifts were recorded in parts per million 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 (hertz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts are reported in parts per million from the tetramethylsilane with the solvent resonance as an internal standard. Infrared spectra (IR) were recorded by FT-IR apparatus. High-resolution mass spectroscopy (HRMS) was performed on TOF MS ES+ mass spectrometer, and acetonitrile was used to dissolve the sample. Column chromatography was conducted 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 a 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, 1 equiv) and triethylamine (1.02 g, 10.0 mmol, 2 equiv) in THF (10 mL) while it was being cooled on ice. After the addition, the mixture was warmed to room temperature and stirred overnight. The resulting solution was concentrated *in vacuo*. And the residue was purified via flash silica gel chromatography (1:19 MeOH/DCM) to give sulfonamide **3f** as a colorless oil (1.72 g, 4.1 mmol, 82% yield): $[\alpha]_D^{20}$ = +27.6 (c = 1 in CH_2Cl_2); IR (KBr) ν 3568, 3268, 2927, 1595, 1458, 1326, 1160, 833 cm^{-1}; ^{1}H 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,

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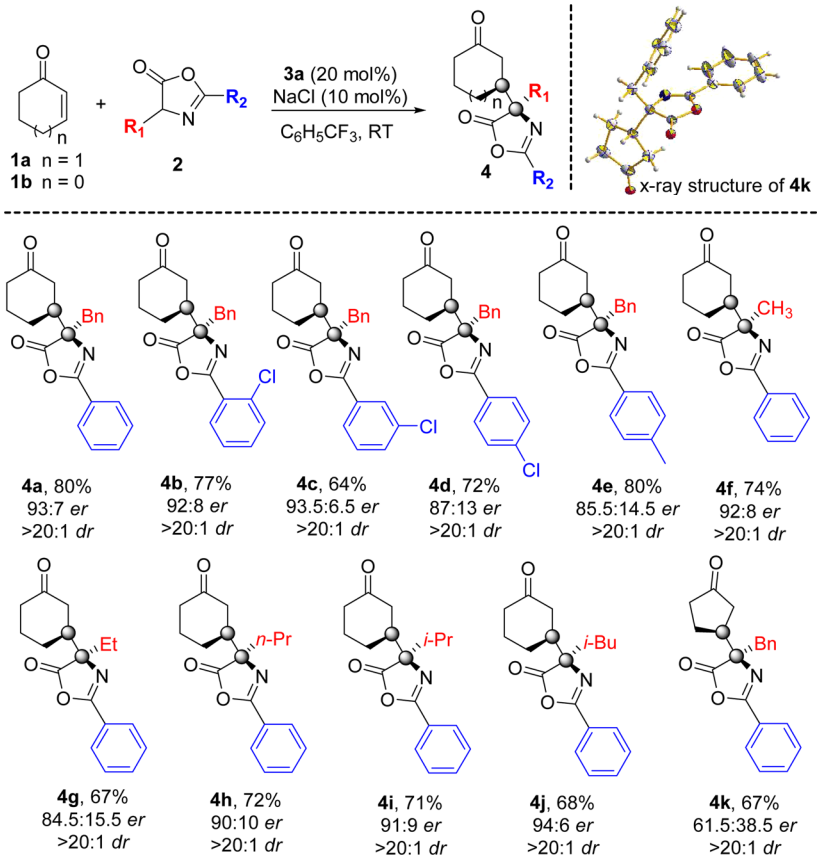
Table 3. Substrate Scope for the Conjugate Addition of Cyclic Enones[a]



[a]Unless otherwise noted, the reaction was conducted at a 0.2 mmol scale in $C_6H_5CF_3$ (1 mL) with a **1**:**2** molar ratio of 5:1 at rt for 48 h.

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 Procedure for the Synthesis of Compounds 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 a 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), the organic solvent was removed *in vacuo*. Then the residue was purified via flash chromatography (19:1 to 9:1petroleum ether/ethyl acetate) to yield the corresponding product.

General Procedures for the Synthesis of Compounds 6a–6l. Azlactone (0.2 mmol, 1 equiv), linear enone (1.0 mmol, 5 equiv), and a 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), the organic solvent was removed *in vacuo*. Then the residue was purified via flash chromatography (19:1 to 9:1 petroleum ether/ethyl acetate) to yield the corresponding product.

Characterization Data for Micheal Adducts 4a–4k and 6a–6l. *(R)-4-Benzyl-4-[(S)-3-oxocyclohexyl]-2-phenyloxazol-5(4H)-one* ***4a.*** White solid (55.6 mg, 0.160 mmol, 80% yield, >20:1 dr, 93:7 er): mp 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% 2-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(4H)-one ***4b.*** White solid (58.8 mg, 0.154 mmol, 77% yield, >20:1 dr, 92:8 er): mp 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% 2-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(4H)-one ***4c.*** Colorless oil (48.9 mg, 0.128 mmol, 64% yield, >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% 2-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(4H)-one ***4d.*** White solid (55.0 mg, 0.144 mmol, 72% yield, >20:1 dr, 87:13 er): mp 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,

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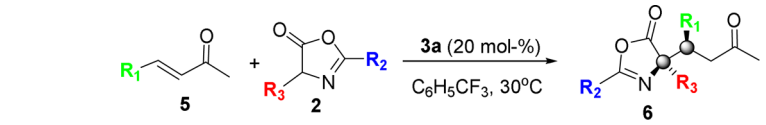
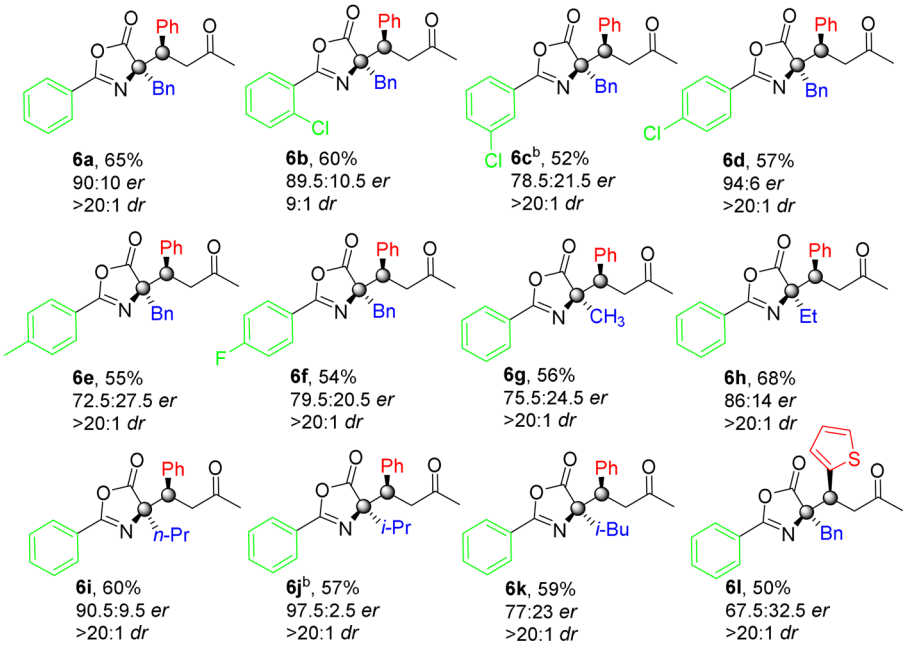
Table 4. Extension of the Conjugate Addition of Azlactone to Linear Enones[a]





6a, 65%
90:10 *er*
>20:1 *dr*

6b, 60%
89.5:10.5 *er*
9:1 *dr*

6c[b], 52%
78.5:21.5 *er*
>20:1 *dr*

6d, 57%
94:6 *er*
>20:1 *dr*

6e, 55%
72.5:27.5 *er*
>20:1 *dr*

6f, 54%
79.5:20.5 *er*
>20:1 *dr*

6g, 56%
75.5:24.5 *er*
>20:1 *dr*

6h, 68%
86:14 *er*
>20:1 *dr*

6i, 60%
90.5:9.5 *er*
>20:1 *dr*

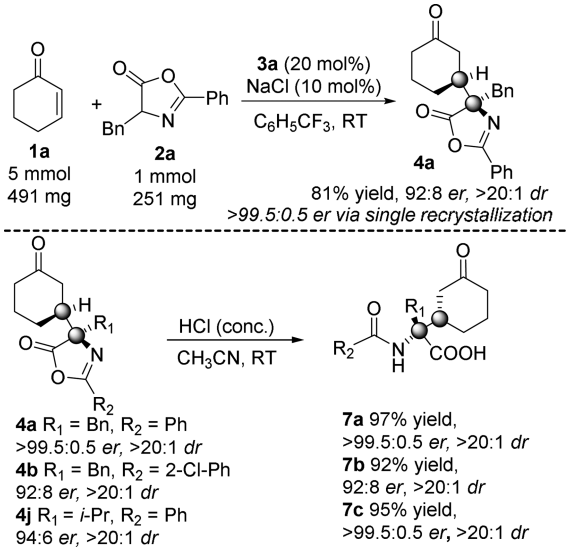
6j[b], 57%
97.5:2.5 *er*
>20:1 *dr*

6k, 59%
77:23 *er*
>20:1 *dr*

6l, 50%
67.5:32.5 *er*
>20:1 *dr*

[a]Unless otherwise noted, the reaction was conducted at a 0.2 mmol scale in $C_6H_5CF_3$ (1 mL) with a **5**:**2** molar ratio of 5:1 at 30 °C for 72 h. [b]Performed at 30 °C for 96 h.

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



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% 2-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(4H)-one ***4e***. White solid (57.8 mg, 0.160 mmol, 80% yield, > 20:1 dr, 85.5:14.5 er): mp 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}; ^{1}H 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% 2-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(4H)-one ***4f***. White solid (40.2 mg, 0.148 mmol, 74% yield, >20:1 dr, 92:8 er): mp 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}; ^{1}H 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% 2-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(4H)-one ***4g***. Colorless oil (38.3 mg, 0.134 mmol, 67% yield, >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}; ^{1}H 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% 2-propanol/

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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(4H)-one ***4h***. Colorless oil (43.1 mg, 0.144 mmol, 72% yield, >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% 2-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(4H)-one ***4i***. Colorless oil (42.5 mg, 0.142 mmol, 71% yield, >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% 2-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(4H)-one ***4j***. Colorless oil (42.6 mg, 0.136 mmol, 68% yield, >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}; ^1H 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% 2-propanol/hexanes, 1.0 mL/min, UV 254 nm) t_R = 13.2 min (major), 14.7 min (minor).

(R)-4-Benzyl-4-[(S)-3-oxocyclopentyl]-2-phenyloxazol-5(4H)-one ***4k***. White solid (44.6 mg, 0.134 mmol, 67% yield, >20:1 dr, 61.5:38.5 er): mp 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}; ^1H 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% 2-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(4H)-one ***6a***.[14a] White solid (51.7 mg, 65% yield, >20:1 dr, 90:10 er): mp 115−116 °C; $[\alpha]_D^{20}$ = −19.6 (c = 1 in CH_2Cl_2); ^1H 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% 2-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(4H)-one ***6b***. White solid (51.8 mg, 0.120 mmol, 60% yield, 9:1 dr, 89.5:10.5 er): mp 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}; ^1H 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% 2-propanol/hexanes, 1.0 mL/min, UV 254 nm) t_R = 8.1 min (minor), 14.8 min (major).

(R)-4-Benzyl-2-(3-chlorophenyl)-4-[(R)-3-oxo-1-phenylbutyl]-oxazol-5(4H)-one ***6c***. Yellow oil (44.8 mg, 0.104 mmol, 52% yield, >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% 2-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(4H)-one ***6d***. Yellow oil (49.2 mg, 0.114 mmol, 57% yield, >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% 2-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(4H)-one ***6e***. White solid (45.2 mg, 0.110 mmol, 55% yield, >20:1 dr, 72.5:27.5 er): mp 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% 2-propanol/hexanes, 1.0 mL/min, UV 254 nm) t_R = 8.2 min (minor), 10.0 min (major).

(R)-4-Benzyl-2-(4-fluorophenyl)-4-[(R)-3-oxo-1-phenylbutyl]-oxazol-5(4H)-one ***6f***. Yellow oil (44.8 mg, 0.108 mmol, 54% yield, >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% 2-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(4H)-one ***6g***.[14a] White solid (36.0 mg, 0.112 mmol, 56% yield, >20:1 dr, 75.5:24.5 er): mp 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, 1H), 7.45−7.49 (m, 2H), 7.13−7.20 (m, 5H), 3.81 (dd, J = 7.5, 6.5 Hz, 1H), 3.18−3.20 (m, 2H), 2.10 (s, 3H), 1.58 (s, 3H); HPLC analysis

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(CHIRALCEL AD-H, 10% 2-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(4H)-one **6h**.[14b] Colorless oil (45.5 mg, 0.136 mmol, 68% yield, >20:1 dr, 86:14 er): $[\alpha]_D^{20}$ = −97.2 (c = 0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88−7.90 (m, 2H), 7.55−7.56 (m, 1H), 7.44−7.48 (m, 2H), 7.13−7.19 (m, 5H), 3.81 (t, J = 6.8 Hz, 1H), 3.15 (d, J = 6.8 Hz, 2H), 2.06 (s, 3H), 2.00 (q, J = 7.6 Hz, 2H), 0.82 (t, J = 7.6 Hz, 3H); HPLC analysis (CHIRALCEL AD-H, 10% 2-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(4H)-one **6i**.[14b] Colorless oil (41.8 mg, 0.120 mmol, 60% yield, >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, 2H), 7.56−7.61 (m, 1H), 7.46−7.50 (m, 2H), 7.15−7.20 (m, 5H), 3.81 (dd, J = 7.6, 6.0 Hz, 1H), 3.17−3.19 (m, 2H), 2.08 (s, 3H), 1.93−1.97 (m, 2H), 1.14−1.28 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); HPLC analysis (CHIRALCEL AD-H, 10% 2-propanol/hexanes, 1.0 mL/min, UV 254 nm) t_R = 5.0 min (minor), 6.2 min (major).

(R)-4-Isopropyl-4-[(R)-3-oxo-1-phenylbutyl]-2-phenyloxazol-5(4H)-one **6j**. White solid (39.8 mg, 0.114 mmol, 57% yield, >20:1 dr, 97.5:2.5 er): mp 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% 2-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(4H)-one **6k**.[14b] Colorless oil (42.9 mg, 0.118 mmol, 59% yield, >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% 2-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(4H)-one **6l**. White solid (40.3 mg, 0.100 mmol, 50% yield, >20:1 dr, 72:28 er): mp 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}; ^{1}H 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% 2-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 Michael adduct **4** (1 equiv) in CH_3CN (0.1 M) was added concentrated HCl (2.5 equiv). Then stirring was continued at room temperature until the starting material had been consumed. The solvent was removed *in vacuo*, and the resulting residue was purified via flash chromatography (1:19 MeOH/DCM) to yield the corresponding product **7**.

Product **7a** was prepared according to the general procedure using **4a** (69.4 mg, 0.2 mmol) to afford **7a** as a white solid (70.8 mg, 0.194 mmol, 97% yield, >20:1 dr, >99.5:0.5 er): mp 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}; ^{1}H 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% 2-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 the general procedure using **4b** (76.2 mg, 0.2 mmol) to afford **7b** as a white solid (73.6 mg, 0.184 mmol, 92% yield, >20:1 dr, 92:8 er): mp 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% 2-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 the general procedure using **4j** (47.0 mg, 0.15 mmol) to afford **7c** as a colorless oil (47.3 mg, 0.143 mmol, 95% yield, >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% 2-propanol/hexanes, 1.0 mL/min, UV 254 nm) t_R = 7.3 min (major), 8.0 min (minor).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01356.

^{1}H NMR and ^{13}C NMR spectra for compounds **3f**, **4a**−**4k**, **6a**−**6l**, and **7a**−**7c** and HPLC traces for compounds **4a**−**4k**, **6a**−**6l**, and **7a**−**7c** (PDF)

Crystallographic data of **4k** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Telephone: +86-731-88830833. E-mail: hyangchem@csu.edu.cn.

Present Address

†Z.-X.D.: Changjun Bilingual School, Changsha 410013, P. R. China.

Notes

The authors declare no competing financial interest.

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