JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

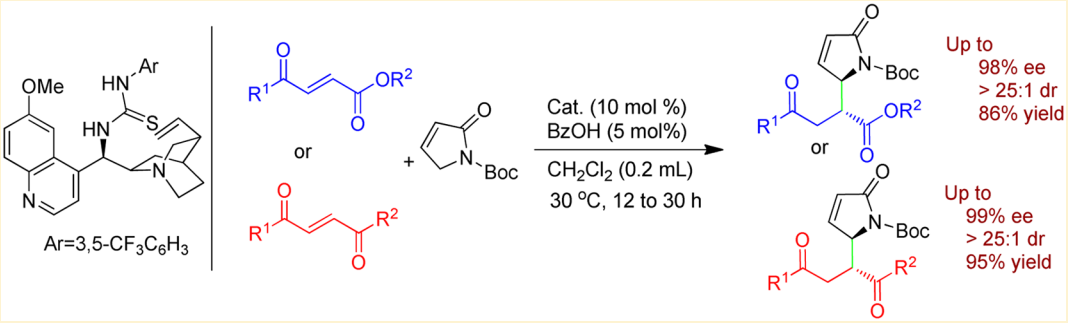
Organocatalytic Enantioselective Direct Vinylogous Michael Addition of α,β-Unsaturated γ-Butyrolactam to β-Acyl Acrylates and 1,2-Diacylethylenes

Yi-Ru Chen,[†,§] Utpal Das,[‡,§] Meng-Hsien Liu,[†] and Wenwei Lin*[,†]

[†]Department of Chemistry, National Taiwan Normal University, Taipei 11677, Taiwan, Republic of China

[‡]Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune-411 008, India

Supporting Information



ABSTRACT: A highly efficient Michael addition of α,β-unsaturated γ-butyrolactam to various β-acyl acrylates and ene-diones to provide synthetically useful compounds was developed. The products were obtained with high diastereo- and enantioselectivities (up to >25:1 dr and 99% ee) containing adjacent tertiary stereocenters.

α,β-Unsaturated γ-butyrolactam derivatives (5-substituted 3-pyrrolidin-2-ones) belong to a family of structurally diverse natural or non-natural compounds with remarkable biological activities which also signify their importance in organic chemistry (Figure 1).[1] Consequently, chemists have paid much attention to the synthesis of 5-substituted butyrolactam derivatives. In this regard, α,β-unsaturated γ-butyrolactam **1** and its silyloxypyrrole derivatives have been employed extensively as direct precursors for the synthesis of these important heterocyclic systems.[2]

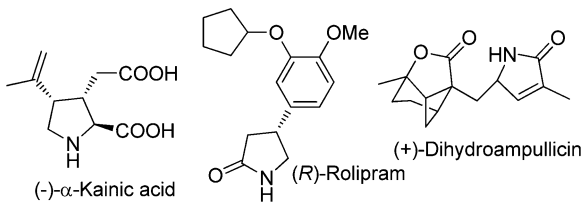


Figure 1. Selected natural and non-natural products containing a γ-butyrolactam unit.

The γ-deprotonation pathway of **1** leading to a dienolate intermediate followed by its relay vinylogous process with electrophiles is well developed.[3−6] In addition, metal- and organo-catalyzed α- and β-functionalization of this dienolate are also known.[7−9] We have recently reported an enantio- and diastereoselective organocatalytic vinylogous Michael reaction [VM] of γ-substituted β,γ-butenolides with 3-aroyl acrylates **2** and 1,2-diaroylethylenes **3**.[10] In continuation of our interest in vinylogous reactivity, we herein report an unprecedented asymmetric VM reaction at the γ-position of the activated dienolate generated from α,β-unsaturated γ-butyrolactam **1** with **2** and **3** catalyzed by a bifunctional thiourea catalyst.

We initially performed a base-catalyzed VM reaction between our model substrates α,β-unsaturated γ-butyrolactam **1** and ethyl 3-benzoyl acrylate **2a** in chloroform. When using 10 mol % DABCO at room temperature, the desired racemic product was obtained in good diastereoselectivity (6:1) and in 57% yield (Table 1, entry 1).

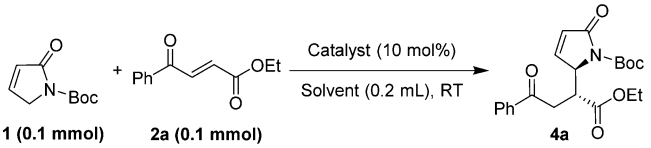
For the optimization of the enantio- and diastereoselective protocol, several bifunctional organocatalysts (**I**−**IX**, 10 mol %; Figure 2)[11,12] were screened to evaluate their ability to promote the VM reaction between **1** and **2a** at room temperature in chloroform (entries 2−9, Table 1).

Our initial studies were carried out using naturally available cinchona alkaloids **I**−**III** for the model reaction. As presented in Table 1 (entries 2−4), the reaction worked well in terms of chemical yields (78−85%) and diastereoselectivities (>11:1) albeit with moderate enantioselectivities (41−49%). Considering the fact that the catalyst **IV** has been utilized as effective bifunctional organocatalyst for VM reaction in our previous work,[10] we switched catalysts from cinchona alkaloids to their derivatives **IV** and **V**. However, the reactions ended up with

Received: November 28, 2014
Published: January 6, 2015

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985−1992

Table 1. Studies and Optimization of the Reaction Conditions



1 (0.1 mmol) 2a (0.1 mmol) 4a

entry	cat.	solvent	t (day)	yield[a] (%)	dr[b]	ee (%)[c]
1	DABCO	$CHCl_3$	1.5	57	6:1	racemic
2	**I**	$CHCl_3$	1.5	78	>25:1	49[d]
3	**II**	$CHCl_3$	1.5	82	11:1	45
4	**III**	$CHCl_3$	1.5	85	15:1	41
5	**IV**	$CHCl_3$	2.0	95	1.5:1	5
6	**V**	$CHCl_3$	1.5	97	2:1	14
7	**VI**	$CHCl_3$	7.0	64	>25:1	95[d]
8	**VII**	$CHCl_3$	7.0	57	>25:1	96[d]
9	**VIII**	$CHCl_3$	7.0	71	>25:1	96
10	**IX**	$CHCl_3$	7.0	47	>25:1	89
11[e]	**VIII**	$CHCl_3$	4.0	67	>25:1	96
12[e]	**VIII**	CH_2Cl_2	2.0	65	>25:1	96
13[e]	**VIII**	EtOAc	2.0	66	>25:1	94
14[e]	**VIII**	toluene	2.5	72	2:1	93
15[e]	**VIII**	THF	2.5	70	3:1	88
16[e,f]	**VIII**	CH_2Cl_2	1.0	78	>25:1[j]	89
17[e,g]	**VIII**	CH_2Cl_2	1.0	84	11:1	96
18[e,g,h]	**VIII**	CH_2Cl_2	0.5	90	>25:1	96
19[h,i]	**VIII**	CH_2Cl_2	**1.0**	**86 (78)**[j]	**>25:1**	**96**

[a]Determined by ^{1}H NMR using Ph_3CH as internal standard. [b]Determined by ^{1}H NMR. [c]Determined by HPLC analysis (major isomer **4a**). [d]ee of ***ent*-4a**. [e]20 mol % catalyst was used. [f]4 Å MS was used. [g]10 mol % benzoic acid was used. [h]**2a** (0.12 mmol) was used. [i]10 mol % catalyst and 5 mol % benzoic acid were used. [j]Isolated yield of major diastereomer **4a**.

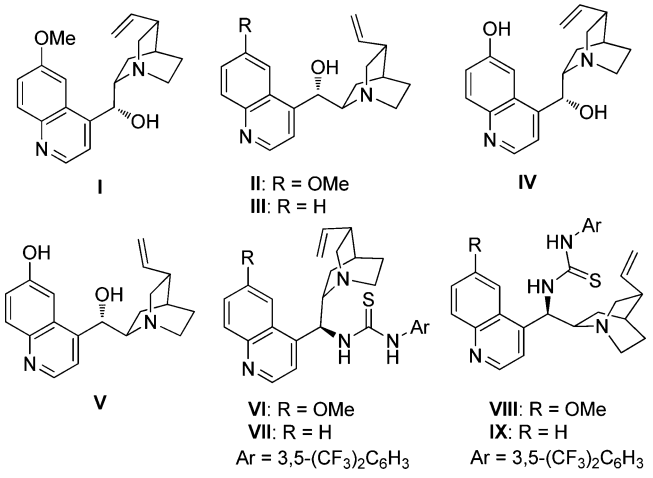


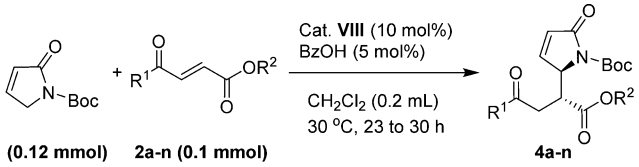
Figure 2. Catalysts screened for direct vinylogous Michael addition.

very poor enantio- and diastereoselectivities albeit with very good chemical yields (entries 5 and 6). Further screening of quinine-derived thiourea catalyst **VI** showed excellent ability in regulating the stereoinduction (95% ee and >25:1 dr), but prolonged reaction time was needed for completion of the reaction (entry 7). The results indicate that stereoinduction of the product **4a** is significantly enhanced by the thiourea moiety of the catalysts. Encouraged by these results, the thiourea catalysts **VII**–**IX** were then examined (entries 8–10). When the reaction was catalyzed by **VII** or **VIII**, excellent stereoselectivities of 4a (96% ee and >25:1 dr) were obtained in both cases (entries 8 and 9). However, the quinidine-derived thiourea catalyst **VIII** provided higher yield of 4a (71%). The enantioselectivity and chemical yield dropped significantly (89% ee and 47% yield) when the reaction was catalyzed by the cinchonine-derived catalyst (**IX**; entry 10). These results indicate that the thiourea catalyst **VIII** is the best catalyst (entry 9) in terms of chemical yield and enantioselectivity. Moreover, a significant improvement of reaction time (4 days) was observed on increasing the catalyst loading to 20 mol % of **VIII** (entry 11). Subsequently, investigation of other solvents was carried out with 20 mol % of **VIII**. We noticed that by using dichloromethane or ethyl acetate as solvent, the reaction was completed within 2 days with >25:1 dr and excellent enantioselectivities (96% and 94% ee; entries 12 and 13). However, use of solvents such as toluene or tetrahydrofuran resulted in poor diastereocontrol and also in slightly diminished enantioselectivities (entries 14 and 15). Next, the effects of additives were also investigated (entries 16–18). The reaction worked well in the presence of 4 Å MS but with considerable loss of enantioselectivity (89% ee; entry 16) whereas by using 10 mol % of benzoic acid as an additive, loss of diastereoselectivity was observed (11:1 dr; entry 17). To our delight, a higher yield and stereoselectivity (91% yield, >25:1 dr and 96% ee) were observed using 1.2 equiv of **1**, 20 mol % of catalyst **VIII**, and 10 mol % of benzoic acid (entry 18). Further lowering of catalyst and additive loading (10 mol % **VIII** and 5 mol % benzoic acid) turned out to be beneficial as the product was obtained without any loss of stereoselectivities (entry 19).

After establishing the optimized reaction conditions, the scope and limitations of the direct VM reactions of α,β-unsaturated γ-butyrolactam **1** with different 3-acyl acrylates (**2a**–**n**) were investigated. A wide range of 3-acyl acrylates (**2a**–**n**) and α,β-unsaturated γ-butyrolactam **1** were converted to the corresponding products (**4a**–**n**) having adjacent tertiary stereogenic centers with very good to excellent enantio- and diastereoselectivities and in high chemical yields (Table 2). As presented in Table 2, the reaction can tolerate electron-withdrawing or electron-donating R^1 substituents (entries 2–8). However, the *ortho*-bromo-substituent on the aromatic ring (**2d**) resulted in a slight decrease in enantioselectivity (89% ee, entry 4). Moreover, Michael acceptor (**2e** or **2f**) bearing 4-chloro or 4-nitro substituent on phenyl ring also provided the corresponding product (**4e** or **4f**, entries 5 and 6) in high diastereoselectivity and good yield albeit with diminished enantioselectivity (83%) of **4f**. Electron-donating R^1 substituents on the aromatic ring also afforded the products in excellent diastereo- (>25:1) and enantioselectivities (97% ee; entries 7 and 8). Notably, our optimized reaction conditions worked well even in case of fused-ring and heteroaromatic substrates furnishing the corresponding products in very high stereoselectivities (>18:1 dr; 93% and 96% ee; entries 9 and 10). We have also evaluated Michael addition of α,β-unsaturated γ-butyrolactam **1** to Michael acceptor containing different ester groups, such as methyl 3-benzoyl acrylate (**2k**) and isopropyl 3-benzoyl acrylate (**2l**). As presented in entries 11 and 12, the corresponding products **4k** and **4l** were obtained with very high stereoselectivities (>16:1 dr and 95% ee) along with high chemical yields. After the successful use of various 3-aroyl acrylates as described above, other aliphatic α,β-unsaturated keto-esters (entries 13 and 14) were evaluated under the present optimized protocol. Interestingly, the corresponding

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985–1992

Table 2. Substrate Scope for the Direct VM Addition of α,β-Unsaturated γ-Butyrolactam 1 with Various 3-Acyl Acrylates 1a−n



entry	R^1	R^2	2	4[a] (%)	dr[b]	ee[c] (%)
1	C_6H_5	Et	**2a**	**4a** (78)	>25:1	96
2	4-BrC_6H_4	Et	**2b**	**4b**[13] (83)	>25:1	95
3	3-BrC_6H_4	Et	**2c**	**4c** (70)	>25:1	96
4	2-BrC_6H_4	Et	**2d**	**4d** (80)	>25:1	89
5	4-ClC_6H_4	Et	**2e**	**4e** (71)	>25:1	96
6	4-$NO_2C_6H_4$	Et	**2f**	**4f** (70)	>25:1	83
7	4-MeC_6H_4	Et	**2g**	**4g** (79)	>25:1	97
8	4-$MeOC_6H_4$	Et	**2h**	**4h** (81)	>25:1	97
9	2-naphthyl	Et	**2i**	**4i** (76)	18:1	93
10	2-thienyl	Et	**2j**	**4j** (76)	>25:1	96
11	4-MeC_6H_4	Me	**2k**	**4k** (78)	16:1	98
12	4-BrC_6H_4	^{i}Pr	**2l**	**4l** (77)	>25:1	95
13	Me	Et	**2m**	**4m** (86)	13:1	93
14	^{t}Bu	Et	**2n**	**4n** (75)	12:1	95

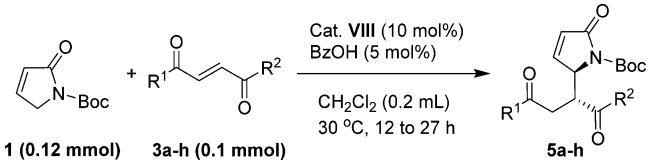
[a]Isolated yield of major diastereomer. [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis.

products were obtained in good enantioselectivities and diastereoselectivities with high product yields.

The synthetic flexibility of this VM addition using α,β-unsaturated γ-butyrolactam **1** was also expanded to various ene-diones (**3a−h**). The optimization of this process was quickly realized (see Supporting Information for details) with generally high chemical yields and good to excellent enantio- and diastereoselectivities (Table 3). Michael acceptors bearing neutral, electron-rich, or electron-deficient aryl groups (**3a−d**) worked well to provide the corresponding products (**5a−d**) in good stereocontrol and yields, except in case of **5b** (entries 1−4). Importantly, enantioselectivity of **5b**[13] was improved up to >99% ee by single recrystallization (entry 2). In the case of a Michael acceptor **3e** (entry 5) having unsymmetrical substitution pattern, both the regioisomers (**5e**[13] and **5e′**) were afforded with good stereocontrol (>25:1 dr, 91% and 97% ee). Notably, the method demonstrated good tolerance to the Michael acceptor **3f** and **3g** containing both aliphatic and aromatic functional groups with excellent regioselectivities and stereoselectivities (entries 6 and 7). The reaction of the substrate **3h** bearing two *t*-butyl substituents also proceeded excellently (>25:1 dr, 99% ee, 56% yield) when diethyl ether was used as solvent (entry 8). The structure of **5b**[13] was determined by single-crystal X-ray data analysis and the absolute configurations of other adducts (**4** and **5**) were assigned analogously.

The potential of the catalytic protocol was further elaborated by performing a gram-scale synthesis of **4j**. Accordingly, treatment of 4.8 mmol of **1** with 4.0 mmol of **2j** under the optimized conditions furnished the corresponding product **4j** in 88% yield (1.38 g) with 97% ee (Scheme 1). We have also demonstrated reversal of stereoselectivity in the case of compound **5f**. Thus, ***ent*-5f** was obtained as the single regioisomer in 83% yield, 94% ee, and >25:1 dr by using the pseudoenantiomeric catalyst **VI** under the same optimized reaction condition (Scheme 2).

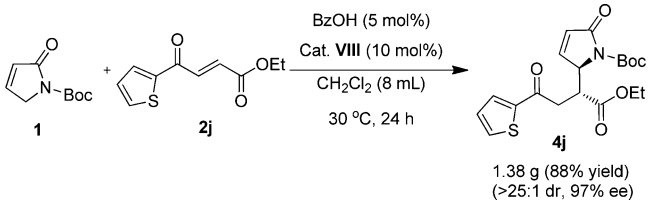
Table 3. Substrate Scope for the Direct VM Addition of α,β-Unsaturated γ-Butyrolactam 1 with Various Ene-diones 3a−h



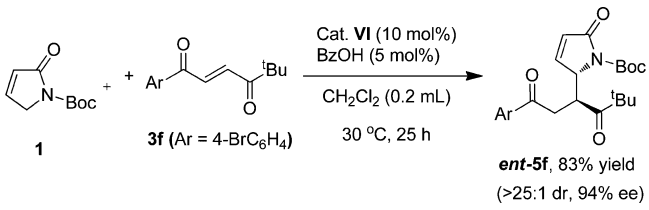
entry	R^1	R^2	3	5[a] (%)	dr[b]	ee[c] (%)
1	C_6H_5	C_6H_5	**3a**	**5a** (95)	>25:1	94
2	4-BrC_6H_4	4-BrC_6H_4	**3b**	**5b** (78)	>25:1	83 (99)[d]
3	4-ClC_6H_4	4-ClC_6H_4	**3c**	**5c** (71)	>25:1	92
4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**3d**	**5d** (89)	>25:1	95
5	4-BrC_6H_4	4-$MeOC_6H_4$	**3e**	**5e**[e] (80)	>25:1	91
6	4-BrC_6H_4	^{t}Bu	**3f**	**5f**[13] (80)	>25:1	97
7	4-BrC_6H_4	Me	**3g**	**5g** (75)	10:1	95
8[f]	^{t}Bu	^{t}Bu	**3h**	**5h** (56)	>25:1	99

[a]Isolated yield of major diastereomer. [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis. [d]>99% ee after single recrystallization. [e]The combined yield of regioisomers, major:minor = 1.7:1, for minor isomer (**5e′**) dr >25:1, 97% ee. [f]Diethyl ether (0.2 mL) was used (when using CH_2Cl_2 (0.2 mL), **5h** was obtained with 99% ee, 5:1 dr, and 52% NMR yield in 10 days).

Scheme 1. Gram-Scale Synthesis of 4j



Scheme 2. Organocatalytic Approach to *ent*-5f



In summary, we have demonstrated an efficient protocol using quinidine-derived bifunctional catalyst for the direct asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam **1** to various β-acyl acrylates **2** and ene-diones **3**. The reactions proceeded well, furnishing the corresponding products in high yields (up to 95%) and excellent stereoselectivities (up to >25:1 dr and 99% ee). A possible catalytic activation mode,[14] gram-scale synthesis, and reversal of enantioselectivity were also demonstrated.

EXPERIMENTAL SECTION

α,β-Unsaturated γ-butyrolactam **1**,[5a] β-acyl acrylates **2**,[15,16] ene-diones **3**,[15] and the catalysts **IV−V**[5a] and **VI−IX**[17] were prepared according to the reported literature. All reagents were used as purchased from

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985−1992

commercial suppliers without further purification. Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (δ 77.0 ppm) for ^{13}C NMR. Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis. High resolution mass spectra (HRMS) were recorded using MALDI (TOF analyzer) and ESI (TOF analyzer). The X-ray diffraction measurements were carried out at 298 K on a CCD area detector system equipped with a graphite monochromator and a Mo−Kα fine-focus sealed tube (k = 0.71073 Å). Analytical thin layer chromatography (TLC) was performed using precoated silica gel plate (0.2 mm thickness). Compounds were purified by flash-chromatography.

Typical Procedure for the Preparation of 5-Substitued-pyrrol-2(5*H*)-one Derivatives 4 and 5 (Table 2 and Table 3). In a glass vial, a mixture of benzoic acid (0.6 mg, 5 mol %), α,β-unsaturated γ-butyrolactam **1** (22.0 mg, 0.12 mmol), catalyst **VIII** (5.9 mg, 10 mol %), and **2** or **3** (0.1 mmol) were dissolved in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred for the indicated time at room temperature (30 °C) and was monitored by TLC and ^{1}H NMR data analysis. After complete consumption of **2** or **3**, the reaction mixture was directly purified by flash chromatography to obtain the desired product **4** or **5**.

*(R)-tert-Butyl-2-((R)-1-ethoxy-1,4-dioxo-4-phenylbutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**4a**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 30.2 mg, 78% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C) δ/ppm: 7.87 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 7.17 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.19 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.17−5.16 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.21−4.15 (m, 1H), 3.20 (dd, J = 17.7 Hz, 9.0 Hz, 1H), 2.75 (dd, J = 17.7 Hz, 4.1 Hz, 1H), 1.58 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C) δ/ppm: 196.9, 171.8, 168.9, 148.9, 148.0, 136.2, 133.4, 128.6, 128.0, 127.9, 83.9, 62.0, 61.5, 40.8, 33.2, 28.0, 14.1; IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1776, 1728, 1686; HRMS (ESI) for $C_{21}H_{25}NO_6Na$, [M + Na]$^+$ (410.1580) found: 410.1588.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 240 nm, *n*- Hexane:IPA = 90:10, flow rate: 1.0 mL/min, t_R (major) = 13.71 min; t_R (minor) = 19.07 min] ee 96%.

*(R)-tert-Butyl-2-((R)-4-(4-bromophenyl)-1-ethoxy-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**4b**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 38.7 mg, 83% isolated yield. $[\alpha]^{25}_D$ = 148.2 (c = 0.653, CH_2Cl_2). R_f 0.45 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.73 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.14 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.20 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.21−5.12 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.21−4.16 (m, 1H), 3.16 (dd, J = 17.8 Hz, 9.0 Hz, 1H), 2.68 (dd, J = 17.8 Hz, 4.1 Hz, 1H), 1.58 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 195.9, 171.7, 168.8, 148.8, 147.8, 134.9, 131.9, 129.5, 128.7, 128.0, 84.0, 61.9, 61.6, 40.8, 33.1, 28.0, 14.1. IR $\tilde{\nu}$ (KBr) cm^{-1}): 1783, 1736. HRMS (ESI) for $C_{21}H_{24}NO_6NaBr$, [M + Na]$^+$ (488.0685) found: 488.0678.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 240 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 9.13 min; t_R (minor) = 11.46 min] ee 95%.

*(R)-tert-Butyl-2-((R)-4-(3-bromophenyl)-1-ethoxy-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**4c**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 27 h, 32.6 mg, 70% isolated yield. $[\alpha]^{25}_D$ = 135.2 (c = 0.405, CH_2Cl_2). R_f 0.38 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 26 °C) δ/ppm: 8.00 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.15 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.21 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.21−5.14 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.21−4.16 (m, 1H), 3.18 (dd, J = 18.0 Hz, 9.0 Hz, 1H), 2.69 (dd, J = 18.0 Hz, 4.0 Hz, 1H), 1.59 (s, 9H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 26 °C) δ/ppm: 195.7, 171.6, 168.8, 148.9, 147.8, 138.0, 136.3, 131.0, 130.2, 128.1, 126.5, 123.0, 84.0, 61.9, 61.6, 40.8, 33.3, 28.0, 14.1. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1780, 1732, 1688. HRMS (ESI) for $C_{21}H_{24}NO_6NaBr$, [M + Na]$^+$ (488.0685) found: 488.0688.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 240 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 8.36 min; t_R (minor) = 10.34 min] ee 96%.

*(R)-tert-Butyl-2-((R)-4-(2-bromophenyl)-1-ethoxy-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**4d**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 37.3 mg, 80% isolated yield. $[\alpha]^{25}_D$ = 97.2 (c = 0.525, CH_2Cl_2). R_f 0.43 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ/ppm: 7.59 (d, J = 7.7 Hz, 1H), 7.37−7.28 (m, 3H), 7.12 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 6.17 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 5.18−5.16 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.20−4.17 (m, 1H), 3.10 (dd, J = 18.3 Hz, 8.8 Hz, 1H), 2.77 (dd, J = 18.3 Hz, 4.0 Hz, 1H), 1.60 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) δ/ppm: 200.6, 171.5, 168.8, 148.9, 147.8, 140.7, 133.5, 131.9, 128.6, 128.1, 127.5, 118.5, 84.0, 61.8, 61.6, 40.7, 37.3, 28.0, 14.2. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1783, 1734. HRMS (MALDI) for $C_{21}H_{24}NO_6NaBr$, [M + Na]$^+$ (488.0679) found: 488.0680.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 219 nm, *n*-Hexane:IPA = 90:10, flow rate: 1.0 mL/min, t_R (minor) = 15.29 min; t_R (major) = 20.73 min] ee 89%.

*(R)-tert-Butyl-2-((R)-4-(4-chlorophenyl)-1-ethoxy-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**4e**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 30 h, 30.0 mg, 71% isolated yield. $[\alpha]^{25}_D$ = −176.5 (c = 0.49, CH_2Cl_2). R_f 0.45 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.81 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.15 (dd, J = 6.2 Hz, 2.2 Hz, 1H), 6.20 (dd, J = 6.2 Hz, 2.2 Hz, 1H), 5.18−5.14 (m, 1H), 4.24 (q, J = 7.3 Hz, 2H), 4.21−4.15 (m, 1H), 3.17 (dd, J = 18.0 Hz, 8.8 Hz, 1H), 2.69 (dd, J = 18.0 Hz, 4.0 Hz, 1H), 1.58 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C) δ/ppm: 195.8, 171.7, 168.8, 148.9, 147.9, 140.0, 134.6, 129.4, 129.0, 128.0, 84.0, 61.9, 61.6, 40.9, 33.2, 28.1, 14.1. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1778, 1728. HRMS (ESI) $C_{21}H_{24}NO_6NaCl$, [M + Na]$^+$ (444.1190) found: 444.1180.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 245 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 8.36 min; t_R (minor) = 10.34 min] ee 96%.

*(R)-tert-Butyl-2-((R)-1-ethoxy-4-(4-nitrophenyl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**4f**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 30.3 mg, 70% isolated yield. $[\alpha]^{25}_D$ = 128.2 (c = 0.215, CH_2Cl_2). R_f 0.28 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.30 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.14 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.22 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.21−5.19 (m, 1H), 4.30−4.20 (m, 3H), 3.25 (dd, J = 18.0 Hz, 9.1 Hz, 1H), 2.74 (dd, J = 18.0 Hz, 4.0 Hz, 1H), 1.59 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 195.7, 171.5, 168.7, 150.5, 148.9, 147.6, 140.7, 129.1, 128.3, 123.9, 84.1, 61.8, 40.9, 33.7, 28.0, 14.1. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1778, 1736, 1695. HRMS (ESI) for $C_{21}H_{24}N_2O_8Na$, [M + Na]$^+$ (455.1430) found: 455.1434.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 259 nm, *n*-Hexane:IPA = 85:15 flow rate: 1.0 mL/min, t_R (major) = 28.83 min; t_R (minor) = 41.07 min] ee 83%.

*(R)-tert-Butyl-2-((R)-1-ethoxy-1,4-dioxo-4-(p-tolyl)butan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**4g**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 31.7 mg, 79% isolated yield. $[\alpha]^{25}_D$ = 178.3 (c = 0.393, CH_2Cl_2). R_f 0.43 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ/ppm: 7.77 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.19 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.20−5.14 (m, 1H), 4.24 (q, J = 7.3 Hz, 2H), 4.18−4.14 (m, 1H), 3.17 (dd, J = 17.8 Hz, 9.3 Hz, 1H), 2.73 (dd, J =

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985−1992

17.8 Hz, 4.0 Hz, 1H), 2.40 (s, 3H), 1.58 (s, 9H), 1.28 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) δ/ppm: 196.5, 171.9, 169.0, 148.8, 148.1, 144.3, 133.7, 129.3, 128.1, 127.8, 83.9, 62.0, 61.4, 40.8, 33.0, 28.0, 21.6, 14.1. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1780, 1730, 1682. HRMS (ESI) $C_{22}H_{27}NO_6Na$, $[M + H]^+$ (424.1736) found: 424.1736.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 239 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 7.80 min; t_R (minor) = 9.37 min] ee 97%.

(R)-tert-Butyl-2-((R)-1-ethoxy-4-(4-methoxyphenyl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(4h)***. The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 27 h, 33.8 mg, 81% isolated yield. $[\alpha]^{25}_D$ = 158.6 (c = 0.515, CH_2Cl_2). R_f 0.25 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ/ppm: 7.85 (d, J = 8.8 Hz, 2H), 7.17 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.10 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.17−5.13 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.19−4.12 (m, 1H), 3.86 (s, 3H), 3.15 (dd, J = 17.7 Hz, 9.3 Hz, 1H), 2.71 (dd, J = 17.7 Hz, 3.8 Hz, 1H), 1.58 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 24 °C) δ/ppm: 195.3, 172.0, 169.0, 163.7, 148.8, 148.2, 130.3, 129.3, 127.8, 113.8, 83.9, 62.0, 61.5, 55.5, 40.8, 32.8, 28.0, 14.1. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1776, 1736, 1675. HRMS (ESI) $C_{22}H_{27}NO_7Na$, $[M + Na]^+$ (440.1685) found: 440.1677.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 270 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 11.40 min; t_R (minor) = 14.90 min] ee 97%.

(R)-tert-Butyl-2-((R)-1-ethoxy-4-(naphthalen-2-yl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(4i)***. The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 27 h, 33.2 mg, 76% isolated yield. $[\alpha]^{25}_D$ = 182.9 (c = 0.633, CH_2Cl_2). R_f 0.40 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.38 (s, 1H), 7.97−7.86 (m, 4H), 7.65−7.50 (m, 2H), 7.21 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 6.23 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 5.23−5.16 (m, 1H), 4.33−4.19 (m, 3H), 3.35 (dd, J = 17.6 Hz, 9.2 Hz, 1H), 2.89 (dd, J = 17.6 Hz, 3.8 Hz, 1H), 1.59 (s, 9H), 1.29 (t, 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 196.8, 171.9, 169.0, 148.9, 148.1, 135.7, 133.6, 132.4, 129.8, 129.6, 128.6, 128.5, 128.0, 127.8, 126.9, 123.6, 84.0, 62.0, 61.5, 41.0, 33.3, 28.1, 14.1. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1778, 1732, 1684. HRMS (ESI) $C_{25}H_{27}NO_6Na$, $[M + Na]^+$ (460.1730) found: 460.1725.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 235 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 9.99 min; t_R (minor) = 12.55 min] ee 93%.

(R)-tert-Butyl-2-((R)-1-ethoxy-1,4-dioxo-4-(thiophen-2-yl)butan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(4j)***. The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 23 h, 29.9 mg, 76% isolated yield. $[\alpha]^{25}_D$ = 163.3 (c = 0.453, CH_2Cl_2). R_f 0.28 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ/ppm: 7.70−7.64 (m, 2H), 7.16 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 7.11 (t, J = 4.4 Hz, 1H), 6.19 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 5.20−5.13 (m, 1H), 4.26−4.15 (m, 3H), 3.13 (dd, J = 17.2 Hz, 9.0 Hz, 1H), 2.70 (dd, J = 17.2 Hz, 3.9 Hz, 1H), 1.58 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) δ/ppm: 189.7, 171.7, 168.9, 148.8, 147.9, 143.2, 134.1, 132.2, 128.2, 128.0, 84.0, 61.9, 61.6, 40.8, 33.7, 28.0, 14.1. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1776, 1734, 1662. HRMS (ESI) $C_{19}H_{23}NO_6NaS$, $[M + Na]^+$ (416.1144) found: 416.1134.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 260 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 10.38 min; t_R (minor) = 11.78 min] ee 96%.

(R)-tert-Butyl-2-((R)-1-methoxy-1,4-dioxo-4-(p-tolyl)butan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(4k)***. The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 28 h, 30.2 mg, 78% isolated yield. $[\alpha]^{25}_D$ = 184.0 (c = 1.247, CH_2Cl_2). R_f 0.35 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.76 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.17 (dd, J = 6.2 Hz, 1.9 Hz, 1H), 6.18 (dd, J = 6.2 Hz, 1.9 Hz, 1H), 5.17−5.10 (m, 1H), 4.23−4.15 (m, 1H), 3.78 (s, 3H), 3.18 (dd, J = 18.0 Hz, 9.0 Hz, 1H), 2.75 (dd, J = 18.0 Hz, 3.8 Hz, 1H), 2.40 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 26 °C) δ/ppm: 196.4, 172.4, 168.9, 148.9, 148.1, 144.4, 133.7, 129.3, 128.1, 127.9, 83.9, 61.9, 52.5, 40.6, 33.1, 28.0, 21.6. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1774, 1739. HRMS (ESI) $C_{21}H_{25}NO_6Na$, $[M + Na]^+$ (410.1580) found: 410.1572.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 250 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 9.10 min; t_R (minor) = 10.93 min] ee 98%.

(R)-tert-Butyl-2-((R)-4-(4-bromophenyl)-1-isopropoxy-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(4l)***. The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 37.0 mg, 77% isolated yield. $[\alpha]^{25}_D$ = 159.6 (c = 0.63, CH_2Cl_2). R_f 0.33 (ethyl acetate/hexane: 1/2). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C) δ/ppm: 7.74 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.14 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 6.20 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 5.19−5.13 (m, 1H), 5.09 (sep, J = 6.0 Hz, 1H), 4.16−4.12 (m, 1H), 3.15 (dd, J = 17.7 Hz, 9.0 Hz, 1H), 2.67 (dd, J = 17.7 Hz, 3.8 Hz, 1H), 1.58 (s, 9H), 1.26 (t, J = 6.0 Hz, 6H) . ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C) δ/ppm: 196.0, 171.1, 168.9, 148.8, 147.9, 135.0, 131.9, 129.5, 128.7, 128.0, 83.9, 69.2, 61.9, 41.0, 33.1, 28.0, 21.7. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1783, 1730. HRMS (ESI) $C_{22}H_{26}NO_6NaBr$, $[M + Na]^+$ (502.0841) found: 502.0844.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 238 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 7.29 min; t_R (minor) = 9.09 min] ee 95%.

(R)-tert-Butyl-2-((R)-1-ethoxy-1,4-dioxopentan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(4m)***. The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 28.0 mg, 86% isolated yield. $[\alpha]^{25}_D$ = 91.1 (c = 0.325, CH_2Cl_2). R_f 0.25 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C) δ/ppm: 7.06 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 6.17 (dd, J = 6.2 Hz, 2.2 Hz, 1H), 5.13−5.06 (m, 1H), 4.30−4.17 (q, 7.2 Hz, 2H), 4.05−3.95 (m, 1H), 3.05 (dd, J = 18.0 Hz, 10.1 Hz, 1H), 2.41 (dd, J = 18.0 Hz, 3.9 Hz, 1H), 2.21 (s, 3H), 1.57 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C) δ/ppm: 205.1, 171.6, 168.8, 148.8, 147.8, 127.9, 83.9, 62.7, 61.5, 40.4, 37.6, 30.0, 28.0, 14.0. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1783, 1736, 1719. HRMS (ESI) $C_{16}H_{23}NO_6Na$, $[M + Na]^+$ (348.1423) found: 348.1426.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 236 nm, *n*-Hexane:IPA = 90:10, flow rate: 1.0 mL/min, t_R (major) = 11.49 min; t_R (minor) = 13.30 min] ee 93%.

(R)-tert-Butyl-2-((R)-1-ethoxy-5,5-dimethyl-1,4-dioxohexan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(4n)***. The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 30 h, 27.6 mg, 75% isolated yield. $[\alpha]^{25}_D$ = 147.6 (c = 0.36, CH_2Cl_2). R_f 0.33 (ethyl acetate/hexane: 1/2). ^{1}H NMR (400 MHz, $CDCl_3$, 26 °C) δ/ppm: 7.09 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.16 (d, J = 6.2 Hz, 1.8 Hz, 1H), 5.14−5.08 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.10−4.00 (m, 1H), 2.71 (dd, J = 18.0 Hz, 8.8 Hz, 1H), 2.24 (dd, J = 18.0 Hz, 3.9 Hz, 1H), 1.58 (s, 9H), 1.28 (t, J = 7.0 Hz, 3H), 1.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 26 °C) δ/ppm: 212.7, 171.9, 169.0, 148.8, 148.1, 127.8, 83.8, 62.0, 61.4, 44.0, 40.3, 31.3, 28.0, 26.4, 14.1. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1785, 1734. HRMS (ESI) $C_{19}H_{29}NO_6Na$, $[M + Na]^+$ (390.1893) found: 390.1884.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 236 nm, *n*-Hexane:IPA = 90:10, flow rate: 1.0 mL/min, t_R (major) = 6.46 min; t_R (minor) = 7.40 min] ee 95%.

(R)-tert-Butyl-2-((R)-1,4-dioxo-1,4-diphenylbutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate ***(5a)***. The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 16 h, 39.8 mg, 95% isolated yield. $[\alpha]^{27}_D$ = 2.4 (c = 0.5, CH_2Cl_2). mp: 124−125 °C. R_f 0.36 (ethyl acetate/hexane: 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.29 (d, J = 7.3 Hz, 2H),

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985−1992

7.87 (d, J = 7.3 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.60−7.50 (m, 3H), 7.43 (t, J = 7.7 Hz, 2H), 7.14 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 6.23 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 5.22 (dt, J = 10.2 Hz, 3.0 Hz, 1H), 5.05 (m, 1H), 3.51 (dd, J = 18.0 Hz, 10.2 Hz, 1H), 2.87 (dd, J = 18.0 Hz, 3.0 Hz, 1H), 1.63 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 199.3, 197.2, 168.5, 149.6, 147.9, 136.1, 135.7, 133.9, 133.5, 129.0, 128.9, 128.6, 128.1, 127.9, 84.1, 61.2, 42.3, 34.1, 28.2. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 1741, 1708, 1675. HRMS (ESI) $C_{25}H_{25}NO_5Na$, $[M + Na]^+$ (442.1630) found: 442.1623.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 243 nm, n-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 7.85 min; t_R (minor) = 10.44 min] ee 94%.

*(R)-tert-Butyl-2-((R)-1,4-bis(4-bromophenyl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5b**).* The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 12 h, 45.0 mg, 78% isolated yield. $[\alpha]^{27}_D$ = −25.9 (c = 0.5, CH_2Cl_2). mp: 154−155 °C. R_f 0.39 (ethyl acetate/hexane: 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.17 (d, J = 8.6 Hz, 2H), 7.76−7.69 (m, 4H), 7.58 (d, J = 8.6 Hz, 2H), 7.11 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.23 (d, J = 6.2 Hz, 1.8 Hz, 1H), 5.12 (dt, J = 10.6 Hz, 3.2 Hz, 1H), 5.02−4.96 (m, 1H), 3.44 (dd, J = 18.2 Hz, 10.6 Hz, 1H), 2.83 (dd, J = 18.2 Hz, 3.2 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 198.3, 196.2, 168.2, 149.8, 147.6, 134.6, 134.3, 132.4, 132.0, 130.4, 129.6, 129.4, 128.9, 128.2, 84.3, 61.0, 42.2, 34.2, 28.2. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1765, 1680. HRMS (ESI) $C_{25}H_{23}NO_5NaBr_2$, $[M + Na]^+$ (597.9841) found: 597.9842.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 243 nm, n-Hexane:IPA = 75:25, flow rate: 1.0 mL/min, t_R (major) = 8.33 min; t_R (minor) = 10.41 min] ee 83%.

*(R)-tert-Butyl-2-((R)-1,4-bis(4-chlorophenyl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5c**).* The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 23 h, 34.7 mg, 71% isolated yield. $[\alpha]^{27}_D$ = −25.7 (c = 0.5, CH_2Cl_2). mp: 154−155 °C. R_f 0.29 (ethyl acetate/hexane: 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.25 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 7.12 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 6.23 (d, J = 6.2 Hz, 2.0 Hz, 1H), 5.13 (dt, J = 10.3 Hz, 3.3 Hz, 1H), 5.02−4.96 (m, 1H), 3.45 (dd, J = 18.0 Hz, 10.3 Hz, 1H), 2.83 (dd, J = 18.0 Hz, 3.3 Hz, 1H), 1.62 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 26 °C) δ/ppm: 198.2, 196.0, 168.2, 149.8, 147.6, 140.6, 140.1, 134.3, 133.9, 130.4, 129.5, 129.4, 129.0, 128.2, 84.3, 61.0, 42.2, 34.3, 28.2. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1776, 1682. HRMS (ESI) $C_{25}H_{23}NO_5NaCl_2$, $[M + Na]^+$ (510.0851) found: 510.0849.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 260 nm, n-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 8.30 min; t_R (minor) = 10.52 min] ee 92%.

*(R)-tert-Butyl-2-((R)-1,4-bis(4-methoxyphenyl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5d**).* The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 15 h, 42.7 mg, 89% isolated yield. $[\alpha]^{27}_D$ = −42.3 (c = 0.5, CH_2Cl_2). mp: 151−152 °C. R_f 0.36 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.28 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.16 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.21 (dd, J = 6.2 Hz, 2.0 Hz, 1H), 5.16 (dt, J = 10.2 Hz, 3.3 Hz, 1H), 5.04−4.98 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.44 (dd, J = 18.0 Hz, 10.2 Hz, 1H), 2.79 (dd, J = 18.0 Hz, 3.3 Hz, 1H), 1.63(s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 197.7, 195.7, 168.6, 164.1, 163.7, 149.6, 148.3, 131.3, 130.4, 129.3, 128.7, 127.7, 114.2, 113.7, 84.0, 61.6, 55.5, 55.4, 42.0, 33.7, 28.2. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1743, 1704, 1671. HRMS (ESI) $C_{27}H_{29}NO_7Na$, $[M + Na]^+$ (502.1842) found: 502.1841.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 263 nm, n-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 14.40 min; t_R (minor) = 17.50 min] ee 95%.

*(R)-tert-Butyl-2-((R)-4-(4-bromophenyl)-1-(4-methoxyphenyl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5e**, major regioisomer).* The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 24 h, 42.3 mg, 80% combined isolated yield (**5e** + **5e′**). $[\alpha]^{27}_D$ = −49.0 (c = 0.5, CH_2Cl_2). mp: 168−169 °C. R_f 0.67 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.28 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.21 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.16 (dt, J = 10.2 Hz, 3.4 Hz, 1H), 5.04−5.02 (m, 1H), 3.91 (s, 3H), 3.45 (dd, J = 17.8 Hz, 10.2 Hz, 1H), 2.75 (dd, J = 17.8 Hz, 3.4 Hz, 1H), 1.63 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C) δ/ppm: 197.4, 196.4, 168.4, 164.3, 149.7, 148.0, 135.0, 131.9, 131.4, 129.6, 128.7, 128.6, 127.9, 114.3, 84.1, 61.6, 55.6, 42.1, 33.9, 28.2. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1741, 1704. HRMS (ESI) $C_{26}H_{26}NO_6NaBr$, $[M + Na]^+$ (550.0841) found: 550.0837.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 263 nm, n-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 11.55 min; t_R (minor) = 14.40 min] ee 91%.

*(R)-tert-Butyl-2-((R)-1-(4-bromophenyl)-4-(4-methoxyphenyl)-1,4-dioxobutan-2-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5e′**, minor regioisomer, inseparable mixture).* The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 24 h, 42.3 mg, 80% combined isolated yield (**5e** + **5e′**). R_f 0.61 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 8.17 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.15 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.23 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 5.11 (dt, J = 10.5 Hz, 3.3 Hz, 1H), 5.00−4.94 (m, 1H), 3.86 (s, 3H), 3.42 (dd, J = 17.6 Hz, 10.5 Hz, 1H), 2.86 (dd, J = 17.6 Hz, 3.3 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 198.7, 195.6, 168.4, 163.9, 149.8, 147.9, 134.5, 132.3, 130.5, 130.4, 129.2, 129.0, 128.0, 113.8, 84.2, 61.1, 55.5, 42.2, 34.1, 28.2.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK AD-H column, 267 nm, n-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (minor) = 14.2 min; t_R (major) = 17.6 min] ee 97%.

*(R)-tert-Butyl-2-((R)-1-(4-bromophenyl)-5,5-dimethyl-1,4-dioxohexan-3-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5f**).* The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 27 h, 38.3 mg, 80% isolated yield. $[\alpha]^{25}_D$ = 130.0 (c = 0.7, CH_2Cl_2). mp: 57−58 °C. R_f 0.32 (ethyl acetate/hexane: 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.69 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.13 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.22 (d, J = 6.2 Hz, 1.8 Hz, 1H), 4.92−4.87 (m, 1H), 4.71(dt, J = 9.8 Hz, 3.5 Hz, 1H), 3.19 (dd, J = 17.7 Hz, 9.8 Hz, 1H), 2.64 (dd, J = 17.7 Hz, 3.5 Hz, 1H), 1.59 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 26 °C) δ/ppm: 215.7, 196.3, 168.6, 149.4, 147.8, 134.9, 131.9, 129.5, 128.7, 128.1, 84.1, 60.8, 45.5, 41.9, 34.8, 28.2, 27.0. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1741, 1708. HRMS (ESI) $C_{23}H_{28}NO_5NaBr$, $[M + Na]^+$ (500.1049) found: 500.1053.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 254 nm, n-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (minor) = 8.45 min; t_R (major) = 10.08 min] ee 97%.

*(S)-tert-Butyl-2-((S)-1-(4-bromophenyl)-5,5-dimethyl-1,4-dioxohexan-3-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**ent-5f**).* The compound was prepared following the general procedure and was obtained as a colorless solid. Reaction time 25 h, 39.7 mg, 83% isolated yield. $[\alpha]^{27}_D$ = −135.6 (c = 0.5, CH_2Cl_2). mp: 68−69 °C. R_f 0.32 (ethyl acetate/hexane: 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.69 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.13 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.22 (d, J = 6.2 Hz, 1.8 Hz, 1H), 4.93−4.87 (m, 1H), 4.71(dt, J = 10.0 Hz, 3.5 Hz, 1H), 3.19 (d, J = 17.7 Hz, 10.0 Hz, 1H), 2.64 (dd, J = 17.7 Hz, 3.5 Hz, 1H), 1.59 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 215.8, 196.3, 168.6, 149.4, 147.9, 134.9, 131.9, 129.6, 128.7, 128.1, 84.1, 60.9, 45.5, 42.0, 34.8, 28.2, 27.0.

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985−1992

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 254 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 7.90 min; t_R (minor) = 9.37 min] ee 94%.

*(R)-tert-Butyl-2-((R)-1-(4-bromophenyl)-1,4-dioxopentan-3-yl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5g**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 27 h, 32.7 mg, 75% isolated yield. $[\alpha]^{25}_D$ = 129.2 (c = 0.228, CH_2Cl_2). R_f 0.30 (ethyl acetate/hexane: 2/3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ/ppm: 7.71 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.11 (dd, J = 6.2 Hz, 1.8 Hz, 1H), 6.21 (d, J = 6.2 Hz, 1.8 Hz, 1H), 4.97−4.95 (m, 1H), 4.26 (dt, J = 10.2 Hz, 3.1 Hz, 1H), 3.19 (dd, J = 18.1, 10.2 Hz, 1H), 2.70 (dd, J = 18.1 Hz, 3.1 Hz, 1H), 2.67 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 207.4, 196.4, 168.6, 149.1, 147.8, 134.6, 132.1, 129.5, 128.9, 128.0, 84.1, 60.4, 47.3, 34.1, 30.0, 28.2. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1780, 1715, 1682. HRMS (ESI) $C_{20}H_{22}NO_5NaBr$, $[M + Na]^+$ (458.0579) found: 458.0583.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 254 nm, *n*-Hexane:IPA = 80:20, flow rate: 1.0 mL/min, t_R (major) = 11.10 min; t_R (minor) = 15.82 min] ee 95%.

*(R)-tert-Butyl-2-oxo-5-((R)-2,2,7,7-tetramethyl-3,6-dioxooctan-4-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (**5h**).* The compound was prepared following the general procedure and was obtained as a colorless oil. Reaction time 24 h, 21.3 mg, 56% isolated yield. $[\alpha]^{27}_D$ = 2.6 (c = 0.41, CH_2Cl_2). R_f 0.53 (ethyl acetate/hexane: 1/4). ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C) δ/ppm: 7.09 (dd, J = 6.2 Hz, 2.2 Hz, 1H), 6.19 (dd, J = 6.2 Hz, 2.2 Hz, 1H), 4.84−4.79 (m, 1H), 4.62−4.54 (m, 1H), 2.69 (dd, J = 18.0 Hz, 9.3 Hz, 1H), 2.18 (dd, J = 18.0 Hz, 3.5 Hz, 1H), 1.60 (s, 9H), 1.30 (s, 9H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ/ppm: 216.0, 213.1, 168.7, 149.3, 147.9, 127.9, 83.9, 60.9, 45.4, 44.0, 41.6, 32.9, 28.2, 26.8, 26.2. IR $\tilde{\nu}$ (KBr) (cm^{-1}): 1785, 1743, 1708. HRMS (MALDI) $C_{21}H_{33}NO_5Na$, $[M + Na]^+$ (402.2251) found: 402.2265.

The enantiomeric excess was determined by HPLC analysis. [CHIRALPAK IB column, 233 nm, *n*-Hexane:IPA = 95:5, flow rate: 1.0 mL/min, t_R (major) = 5.68 min; t_R (minor) = 6.78 min] ee 99%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +886-2-77346131. E-mail: wenweilin@ntnu.edu.tw

Author Contributions

§Das, U. and Chen, Y.-R. made equal contributions to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Ministry of Science and Technology of the Republic of China (MOST 103-2113-M-003-009-MY3) for financial support.

■ REFERENCES

(1) For selected reviews on natural or non-natural compounds with remarkable biological activities, please see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139−165. (b) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3−99. (c) Trabocchi, A.; Guarna, F.; Guarna, A. *Curr. Org. Chem.* **2005**, *9*, 1127−1153. (d) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, *15*, 2670−2680. (e) Cheng, Y.; Huang, Z.-T.; Wang, M. X. *Curr. Org. Chem.* **2004**, *8*, 325−351. For selected recent literature, please see: (f) Lee, C.; Choi, E.; Cho, M.; Lee, B.; Oh, S. J.; Park, S.-K.; Lee, K.; Kim, H. M.; Han, G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4189−4192. (g) Choi, E.; Lee, C.; Cho, M.; Seo, J. J.; Yang, J. S.; Oh, S. J.; Lee, K.; Park, S.-K.; Kim, H. M.; Kwon, H. J.; Han, G. *J. Med. Chem.* **2012**, *55*, 10766−10770. (h) Yu, H.-J.; Shao, C.; Cui, Z.; Feng, C.-G.; Lin, G.-Q. *Chem.—Eur. J.* **2012**, *18*, 13274−13278.

(2) For reviews, please see: (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076−3154. (b) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, *10*, 1525−1542. (c) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531−3543. (d) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595−2615.

(3) For direct use of α,β-unsaturated γ-butyrolactams in racemic vinylogous reactions, please see: (a) Ramireddy, N.; Zhao, J. C.-G. *Tetrahedron Lett.* **2014**, *55*, 706−709. (b) Sartori, A.; Curti, C.; Battistini, L.; Burreddu, P.; Rassu, G.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Tetrahedron* **2008**, *64*, 11697−11705.

(4) For the selected recent literature in Mannich reaction, please see: (a) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666−3667. For the selected recent literature in Mannich reaction with β,γ-unsaturated butenolide, please see: (b) Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056−3059.

(5) For selected recent examples in Michael addition, please see: (a) Choudhury, A. R.; Mukherjee, S. *Org. Biomol. Chem.* **2012**, *10*, 7313−7320. (b) Huang, H.; Jin, Z.; Zhu, K.; Liang, X.; Ye, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3232−3235. (c) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, *13*, 6410−6413. (d) Zhang, Y.; Shao, Y.-L.; Xu, H.-S.; Wang, W. *J. Org. Chem.* **2011**, *76*, 1472−1474. (e) Feng, X.; Cui, H.-L.; Xu, S.; Wu, L.; Chen, Y.-C. *Chem.—Eur. J.* **2010**, *16*, 10309−10312. (f) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 9329−9331. For the selected recent example in Michael addition with α,β-unsaturated butenolide, please see: (g) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572−4573.

(6) For the selected recent example in aldol reaction, please see: (a) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Burreddu, P.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **2008**, *73*, 5446−5451. For the selected recent example in aldol reaction with silyloxy furans, please see: (b) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558−9560.

(7) For selected recent examples on α-position reactivity, please see: (a) Ma, Y.; Zhang, G.; Zhang, J.; Yang, D.; Wang, R. *Org. Lett.* **2014**, *16*, 5358−5361. (b) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 3300−3302. (c) Duan, Z.; Zhang, Z.; Qian, P.; Han, J.; Pan, Y. *RSC Adv.* **2013**, *3*, 10127−10130.

(8) For selected recent examples on β-position reactivity, please see: (a) Pace, V.; Rae, J. P.; Procter, D. J. *Org. Lett.* **2014**, *16*, 476−479. (b) Kuuloja, N.; Vaismaa, M.; Franzen, R. *Tetrahedron* **2012**, *68*, 2313−2318. (c) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788−791. (d) Pineschi, M.; Del Moro, F.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, *10*, 1244−1245.

(9) For the selected recent example on dual activation of β,γ-position, please see: Jiang, X.; Liu, L.; Zhang, P.; Zhong, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 11329−11333.

(10) Das, U.; Chen, Y.-R.; Tsai, Y.-L.; Lin, W. *Chem.—Eur. J.* **2013**, *19*, 7713−7717.

(11) For reviews on cinchona alkaloids in asymmetric catalysis, please see: (a) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *8*, 1229−1279. (b) Yeboah, E. M. O.; Yeboah, S. O.; Singh, G. S. *Tetrahedron* **2011**, *67*, 1725−1762. for a book, please see: (c) *Cinchona Alkaloids in Synthesis and Catalysis*; Song, C. E., Eds.; Wiley-VCH: Weinheim, 2009.

(12) For selected recent reviews on bifunctional catalysis, please see: (a) Connon, S. J. *Chem. Commun.* **2008**, *22*, 2499−2510. (b) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593−601. (c) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298−1310. (d) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, *4*, 490−508. (e) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*,

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985−1992

7051−7071. (f) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, 2633−2646. (g) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2014**, *20*, 358−368.

(13) CCDC 1033384 (***rac*-4b**), 1025579 (**5b**), 1025110 (**5e**), and 1024723 (***rac*-5f**) contain 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. Please see the Supporting Information for further details.

(14) For the detail of proposed activation mode, please see the Supporting Information.

(15) Bhella, S. S.; Elango, M.; Ishar, M. P. S. *Tetrahedron* **2009**, *65*, 240−246.

(16) Lu, H.-H.; Wang, X.-F.; Yao, C.-J.; Zhang, J.-M.; Wu, H.; Xiao, W.-J. *Chem. Commun.* **2009**, 4251−4253.

(17) Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658−3661.

DOI: 10.1021/jo5027047
J. Org. Chem. 2015, 80, 1985−1992