JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

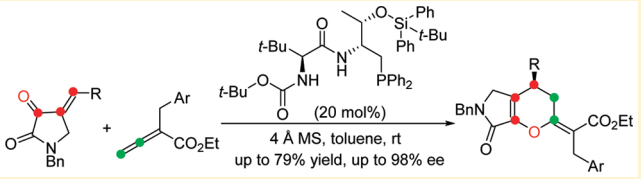
Phosphine-Catalyzed Enantioselective [2+4] Cycloaddition to Synthesize Pyrrolidin-2-one Fused Dihydropyrans Using α-Substituted Allenoates as C_2 Synthons

Chang Wang, Hao Jia, Cheng Zhang, Zhenzhen Gao, Leijie Zhou, Chunhao Yuan, Yumei Xiao, and Hongchao Guo*

Department of Applied Chemistry, China Agricultural University, Beijing 100193, China

Supporting Information

ABSTRACT: A bifunctional phosphine-catalyzed highly enantioselective [2+4] cycloaddition of α-substituted allenoates with (*E*)-1-benzyl-4-olefinicpyrrolidine-2,3-diones has been achieved, giving pyrrolidin-2-one fused dihydropyran derivatives in moderate to good yields with excellent enantioselectivities (up to 98% ee). This reaction provides a useful catalytic asymmetric access to dihydropyran structural motifs.



INTRODUCTION

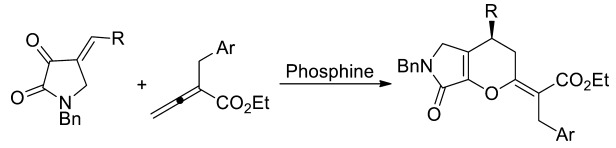
In the past decade, chiral phosphine-catalyzed asymmetric annulation reactions have attracted considerable attention in synthetic organic chemistry due to their wide application as a powerful approach to create structurally diverse and bioactive chiral cyclic compounds.[1] A variety of asymmetric annulation reactions promoted by nucleophilic chiral phosphines have been achieved.[2−7] Among these phosphine-promoted asymmetric annulation reactions, the reactions involving electron-deficient allenes are probably the most studied reactions.[1] In the presence of phosphine catalyst, these electron-deficient allenes can function as one-, two-, three-, or four-carbon synthons undergoing various annulations with electrophilic reagents such as electron-deficient alkenes, imines or dipolar species, to construct complex functionalized carbocycles or heterocycles.[1]

Chiral heterocycles fused dihydro- or tetrahydropyran structures are important building blocks of many biologically active molecules.[8] As a result, developing efficient synthetic methods to access such optically active structures is of great significance. Among several synthetic methods for dihydro- or tetrahydropyran motifs, Lewis base-catalyzed asymmetric [2+4] annulation reactions of allenes being used as C_2 synthons with α,β-unsaturated carbonyl compounds as C_4 synthons have been demonstrated to be a powerful tool.[9−15] With the use of cinchona alkaloid-derived chiral tertiary amines as chiral catalyst, a few asymmetric [2+4] annulation reactions of allenoates functioning as C_2 synthons have been reported, providing several simple accesses to functionalized dihydropyran derivatives in moderate to excellent yields with excellent enantioselectivities.[9−12] Tong and Borhan developed asymmetric [2+4] annulation of allenoates with α,β-unsaturated ketone.[9] Shi and Wei achieved asymmetric [2+4] annulation of allenic esters with β,γ-unsaturated α-ketoesters or α-ketophosphonatesh.[10] Cheng and Li presented enantioselective [2+4] annulation of allenoates with 2-olefinic benzofuran-3-ones or 3-olefinic oxindoles.[11] Xu achieved asymmetric [2+4] annulation of allene ketones with 2,3-dioxopyrrolidine derivatives.[12] In comparison, under chiral phosphines catalysis, only limited asymmetric [2+4] annulation reactions have been realized.[13,14] Lu described asymmetric [2+4] annulation of allene ketones and β,γ-unsaturated α-keto esters, α-cyano-α,β-unsaturated ketones or 3-aroylcoumarins.[13] Our group developed asymmetric [2+4] annulation of α-substituted allenoates and thiazolone-derived alkenes.[14] With our continuing interests in chiral phosphine-catalyzed enantioselective cycloaddition,[16] herein we report an enantioselective reaction of α-substituted allenoates with (*E*)-1-benzyl-4-olefinicpyrrolidine-2,3-diones to access pyrrolidin-2-one fused dihydropyran structures catalyzed by a bifunctional chiral phosphine (Scheme 1).

RESULTS AND DISCUSSION

As shown in Table 1, the reaction conditions were investigated by treating (*E*)-1-benzyl-4-benzylidenepyrrolidine-2,3-dione **1a** and ethyl 2-benzylbuta-2,3-dienoate **2a** with different chiral

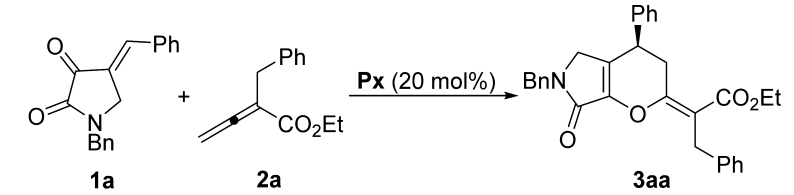
Scheme 1. Phosphine-Catalyzed [2+4] Annulation of α-Substitued Allenoates Using α-Substituted Allenoates as C_2 Synthons

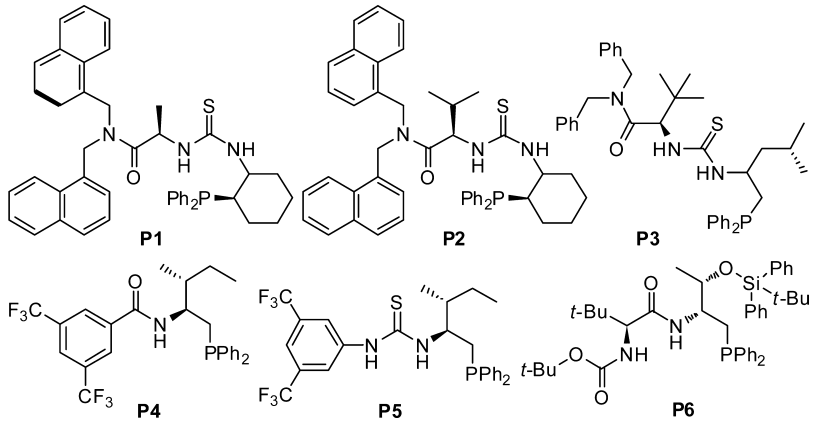


Received: November 3, 2016
Published: December 19, 2016

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

Table 1. Screening of the Reaction Conditions[a]





entry	Px	solvent	T/°C	t/h	yield (%)	ee (%)[b]
1	**P1**	toluene	25	72	trace	
2	**P2**	toluene	25	72	trace	
3	**P3**	toluene	25	72	trace	
4	**P4**	toluene	25	1.5	67	44
5	**P5**	toluene	25	72	trace	
6	**P6**	toluene	25	1	50	95
7	**P6**	CH_2Cl_2	25	8	45	65
8	**P6**	THF	25	2.5	48	48
9[c]	**P6**	toluene	25	5	73	95
10[c]	**P6**	toluene	0	24	58	95
11[c]	**P6**	toluene	40	5	63	93
12[c]	**P6**	toluene	60	1.5	60	92
13[c,d]	**P6**	toluene	25	6	49	94

[a]Unless otherwise stated, all reactions were carried out with **1a** (0.05 mmol), **2a** (0.075 mmol), and catalyst (0.01 mmol) in solvent (1 mL). [b]Determined by chiral HPLC analysis. [c]In the presence of 4 Å MS (25 mg). [d]0.005 mmol of catalyst was used.

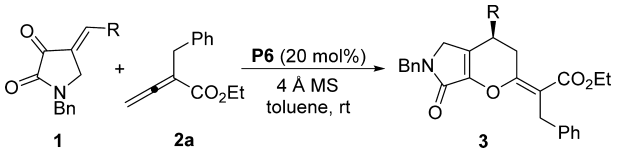
phosphines **P1** − **P6** in toluene at room temperature. Based on our previous work, thiourea- or amino acid-modified chiral phosphines were selected as the catalyst candidates. The results showed that thiourea-modified catalysts **P1**−**P3** and **P5** were noneffective, giving only trace of the desired product **3aa** in 72 h, in contrast, amino acid-modified phosphine **P4** and **P6** are much more efficient in terms of yield and enantioselectivity (entries 1−6). In particular, the commercially available catalyst **P6** delivered the product in 50% yield with 95% ee (entry 6). Then, the catalytic reactivity and enantioselectivity of the phosphine **P6** was further tested in CH_2Cl_2 and THF (entries 7−10). However, the results showed that using **P6** as the catalyst in toluene is still the best conditions (entries 7−8 vs 6). To our delight, the product **3aa** was obtained with 73% yield and 97% ee after 5 h when 25 mg of 4 Å molecule sieves was used as the additive (entry 9). Lowering reaction temperature deteriorated the reactivity (entry 10), and increasing reaction temperature impaired both the reactivity and enantioselectivity (entries 11−12). Decreasing the amount of catalyst to 10 mol % did not worsen enantioselectivity, albeit leading to lower 49% yield (entry 13). According to the above screening, the optimal conditions were: in toluene at room temperature in the presence of molecular sieves and 20 mol% of chiral phosphine **P6**. Under the optimal conditions, at the 0.5 mmol of scale, the reaction still worked efficiently to give the product **3aa** in 75% yield and 95% ee. Compared with the reaction at 0.05 mmol, there was no loss on yield and enantioselectivity.

With the optimized reaction conditions in hand, the scope of (*E*)-1-benzyl-4-olefinic pyrrolidine-2,3-dione **1** with various substituents was then explored, as shown in Table 2. In all cases, both electron-rich (Me or MeO, entries 1−2) and electron-deficient (F, Cl, Br or CF_3, entries 3−10) substituent-substituted aryl groups were tolerated to afford the corresponding products in moderate to high yields (49−79% yield) with excellent enantioselectivities (89−96% ee). The fused aromatic group substituted substrate **1l** is also a suitable partner for the reaction, and it affords the desired product **3la** with high yield (74% yield) and excellent enantioselectivity (93% ee, entry 11).

Different allenoates with various substituents were also tested under the optimized conditions (Table 3). When R was aryl group substituted by electron-withdrawing group, generally, the corresponding products were obtained in good yields (66−79% yield) with excellent enantioselectivities (93−96% ee, entries 6,

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

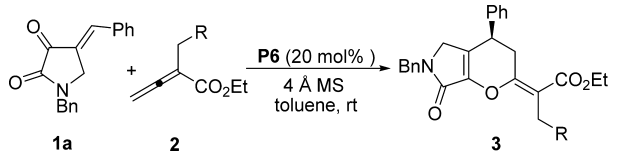
Table 2. Substrate Scope of Pyrrolidine-2,3-diones[a]



entry	R in **1**	*t*/h	**3**	yield (%)	ee (%)[b]
1	4-MeC_6H_4 (**1b**)	3.5	**3ba**	79	95
2	4-OMeC_6H_4 (**1c**)	4.5	**3ca**	65	95
3	4-FC_6H_4 (**1d**)	3	**3da**	64	95
4	2-ClC_6H_4 (**1e**)	3	**3ea**	49	89
5	3-ClC_6H_4 (**1f**)	4	**3fa**	63	91
6	4-ClC_6H_4 (**1g**)	4	**3ga**	67	94
7	3-BrC_6H_4 (**1h**)	3	**3ha**	51	92
8	4-BrC_6H_4 (**1i**)	3	**3ia**	78	96
9	4-$CF_3C_6H_4$ (**1j**)	4	**3ja**	51	96
10	3,4-$Br_2C_6H_3$ (**1k**)	5.5	**3ka**	47	93
11	2-naphthyl (**1l**)	4.5	**3la**	74	93

[a]All reactions were carried out with **1** (0.05 mmol), **2** (0.075 mmol), 4 Å MS (25 mg), and catalyst (0.01 mmol) in toluene (1 mL) at rt. [b]Determined by chiral HPLC analysis.

Table 3. Substrate Scope of α-Substituted Allenoates[a]



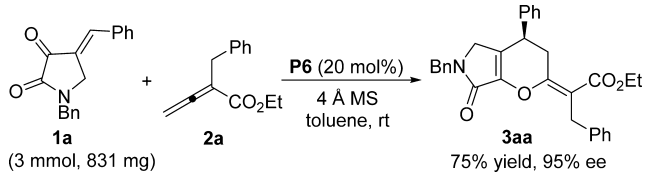
entry	R in **2**	*t*/h	**3**	yield (%)	ee (%)[b]
1	2-MeC_6H_4 (**2b**)	24	**3ab**	36	98
2	3-MeC_6H_4 (**2c**)	3	**3ac**	55	93
3	4-MeC_6H_4 (**2d**)	24	**3ad**	34	95
4	3-OMeC_6H_4 (**2e**)	2.5	**3ae**	74	96
5	3,5-$OMe_2C_6H_3$ (**2f**)	3	**3af**	67	96
6	4-FC_6H_4 (**2g**)	2	**3ag**	79	96
7	4-ClC_6H_4 (**2h**)	2	**3ah**	74	95
8	2-BrC_6H_4 (**2i**)	5	**3ai**	40	98
9	3-BrC_6H_4 (**2j**)	3	**3aj**	76	94
10	4-BrC_6H_4 (**2k**)	2	**3ak**	77	94
11	3-$CF_3C_6H_4$ (**2l**)	2.5	**3al**	72	93
12	4-$CF_3C_6H_4$ (**2m**)	2.5	**3am**	66	94
13	2-naphthyl (**2n**)	1.5	**3an**	71	94
14	H (**2o**)	48	**3ao**	trace	-

[a]All reactions were carried out with **1** (0.05 mmol), **2** (0.075 mmol), 4 Å MS (25 mg), and catalyst (0.01 mmol) in toluene (1 mL) at rt. [b]Determined by chiral HPLC analysis.

7, 9−12). Interestingly, when R was 2-bromophenyl group, the desired product was obtained with extremely excellent enantioselectivity (98% ee), albeit with lower 40% yield (entry 8). It seems that the reactivity was impaired when R was aryl substituted by electron-rich groups (34−74% yield), but it retains good enantioselectivity (93−98% ee, entries 1−5). The 2-naphthyl substituted allenoate was also compatible substrate, and the cycloadduct **3an** was obtained in 71% yield with 94% ee (entry 13). Unfortunately, the alkyl-substituted allenoate did not work (entry 14).

As shown in Scheme 2, the reaction on the gram scale still worked efficiently to give the product **3aa** in 75% yield with 95% ee, demonstrating the reaction to be a practical tool for synthesis of pyrrolidin-2-one-fused dihydropyran derivatives.

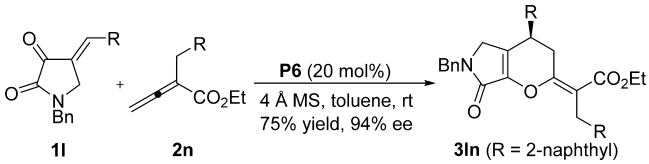
Scheme 2. Preparation of 3aa on the Gram Scale



Compared with the reaction at 0.05 mmol of scale, there was no significant loss on yield and enantioselectivity.

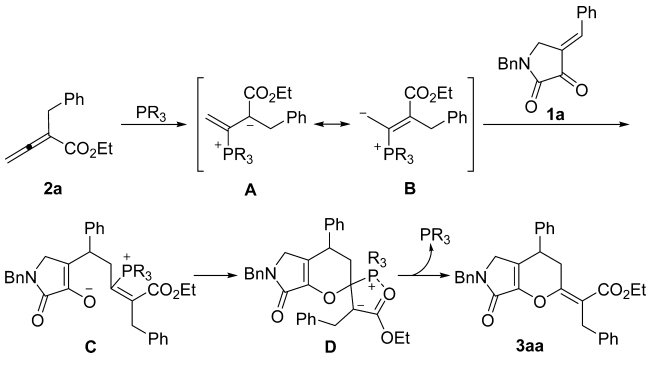
To determine the absolute configuration of the cycloadducts, a easily crystallized compound **3ln** was prepared in 75% yield and 94% ee through the reaction of (*E*)-1-benzyl-4-(naphthalen-2-ylmethylene)pyrrolidine-2,3-dione (**1l**) with ethyl 2-(naphthalen-2-ylmethyl)buta-2,3-dienoate (**2n**) under the standard reaction conditions (Scheme 3). By the X-ray crystallography of the product **3ln**, the absolute configuration of the cycloadducts was assigned as (*R*)-configuration (see the details in Supporting Information).[17]

Scheme 3. Preparation of 3ln for the Determination of Absolute Configuration



On the basis of previous reports,[1] a plausible mechanism for the formation of dihydropyran derivatives **3aa** was proposed in Scheme 4. The β-phosphonium intermediate **B** formed through

Scheme 4. A Plausible Reaction Mechanism



conjugate addition of the phosphine to the allenoate **2a**, undergoes Michael addition to α,β-unsaturated enone **1a** to give the enolate intermediate **C**. Subsequent intramolecular conjugate addition leads to the intermediate **D**, which eliminates tertiary phosphine to produce the product **3aa**. With respect to the excellent *E*-selectivity for the exocyclic double bond of tetrahydropyrano[2,3-*c*]pyrrol-7(2H)-one **3**, the electrostatic interaction between the phosphorus atom and the carbonyl of the β-phosphonium enoate might play a key role.[16a] The bulky phosphonium group stays away from the puckered bicyclic structure, thus helping rotation of the carbonyl also away from the rest of the molecule. As a consequence, the product with (*E*)-configuration of the

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

exocyclic double bond is obtained when the phosphine catalyst is expelled.

CONCLUSIONS

In conclusion, we have developed a bifunctional chiral phosphine catalyzed enantioselective [2+4] cycloaddition of α-substituted allenoates with (*E*)-1-benzyl-4-olefinicpyrrolidine-2,3-diones, and the reaction worked smoothly under mild conditions to afford moderate to good yields of pyrrolidin-2-one fused dihydropyran derivatives with excellent enantioselectivity. The reaction tolerated a wide range of allenoates and enones.

EXPERIMENTAL SECTION

General Information. All reactions were performed under N_2 atmospheres in oven-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents were purified and dried according to standard methods prior to use. Organic solutions were concentrated under reduced pressure on a rotary evaporator or an oil pump. Reactions were monitored through thin layer chromatography (TLC) on silica gel−precoated glass plates. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. Flash column chromatography was performed using flash silica gel (200−300 mesh). Infrared spectra were recorded using an FT-IR spectrophotometer and are reported as cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a 300 MHz NMR instrument (referenced internally to Me_4Si). ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet; d = doublet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), and integral. Data for ^{13}C NMR spectra are reported in terms of chemical shift. Optical rotation was obtained on a polarimeter. Accurate mass measurements were performed on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. Melting points were determined on a melting apparatus. HPLC analysis was performed on high performance liquid chromatography, UV detection monitored at 254 nm, using an IA column with hexane and *i*-PrOH as the eluent. 4-Olefinicpyrrolidine-2,3-diones **1** were prepared according to the literature procedure.[17] α-Substitued allenoates **2** were synthesized according to literature procedure.[6e]

General Procedure for Preparation of Racemic Products 3 by [2+4] Annulation of 4-Olefinicpyrrolidine 1 with α-Substitued Allenoates 2. Under nitrogen atmosphere, to a mixture of 4-olefinicpyrrolidine-2,3-diones **1** (0.1 mmol, 27.8 mg) and additive 4 Å MS (50 mg) in 1 mL of toluene in a Schlenk tube, α-substitued allenoates **2** (1.5 eq., 0.15 mmol, 30.5 mg) followed with catalyst $PMePh_2$ (20 mol %, 0.02 mmol, 4.0 mg) were added at 40 °C. The resulting mixture was stirred until the starting material was completely consumed (monitored by TLC) and then was concentrated to dryness. The residue was purified through flash column chromatography (EtOAc/PE 1:3) to afford the corresponding racemic cycloaddition product.

General Procedure for Asymmetric [2+4] Annulation. Under nitrogen atmosphere, to a mixture of 4-olefinicpyrrolidine-2,3-diones **1** (0.05 mmol, 13.9 mg) and additive 4 Å MS (25 mg) in 1 mL of toluene in a Schlenk tube, α-substisuted allenotes **2** (1.5 eq., 0.075 mmol, 15.2 mg) followed with catalyst **P6** (20 mol %, 0.01 mmol, 7.25 mg) were added at room temperature. The resulting mixture was stirred until the starting material was completely consumed (monitored by TLC) and then was concentrated to dryness. The residue was purified through flash column chromatography (EtOAc/PE 1:3) to afford the corresponding cycloaddition product **3**.

General Procedure for Preparation of 3aa on the Gram Scale. Under nitrogen atmosphere, to a mixture of 4-olefinicpyrrolidine-2,3-diones **1** (3 mmol, 831 mg) and the additive 4 Å MS (1.5 g) in 60 mL of toluene in a Schlenk bottle, α-substisuted allenotes **2** (1.5 eq., 4.5 mmol, 910 mg) followed with the catalyst **P6** (20 mol %, 0.6 mmol, 435 mg) were added at room temperature. The resulting mixture was stirred until the starting material was completely consumed (monitored by TLC) and then was concentrated to dryness. The residue was purified through flash column chromatography (EtOAc/PE 1:3) to afford the corresponding annulation product **3**.

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3aa**).* Faint yellow semisolid (17.5 mg, 73% yield). $[\alpha]^{25}_D$ = −42.6 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 7.28−7.22 (m, 6H), 7.22−7.13 (m, 2H), 7.01 (dd, *J* = 7.2, 2.1 Hz, 2H), 4.80 (d, *J* = 15.0 Hz, 1H), 4.45 (d, *J* = 15.0 Hz, 1H), 4.05 (qd, *J* = 7.1, 1.2 Hz, 2H), 4.00−3.86 (m, 2H), 3.77 (t, *J* = 6.2 Hz, 1H), 3.59 (d, *J* = 1.9 Hz, 2H), 3.53−3.38 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.2, 163.4, 157.1, 143.3, 140.05, 139.99, 136.5, 128.59, 128.56, 128.5, 127.81, 127.75, 127.4, 127.1, 127.0, 125.5, 124.8, 115.8, 60.2, 47.1, 46.3, 37.2, 31.6, 31.5, 13.7; IR (film) ν_{max} 3029, 2925, 1703, 1513, 1495, 1453, 1386, 1244, 1182, 1143, 1099, 1031, 991, 787, 741, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{30}NO_4^+$ $[M + H]^+$ 480.2169, found 480.2166. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 9.2 min (minor), 14.3 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-(p-tolyl)-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ba**).* Faint yellow semisolid (19.5 mg, 79% yield). $[\alpha]^{25}_D$ = −45.2 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 7.32−7.28 (m, 2H), 7.28−7.19 (m, 4H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 4.83 (d, *J* = 15.0 Hz, 1H), 4.48 (d, *J* = 15.0 Hz, 1H), 4.10 (qd, *J* = 7.1, 1.6 Hz, 2H), 4.04−3.91 (m, 2H), 3.77 (t, *J* = 6.3 Hz, 1H), 3.62 (s, 2H), 3.59−3.38 (m, 2H), 2.34 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.3, 163.5, 157.3, 143.1, 140.0, 137.0, 136.8, 136.5, 129.2, 128.6, 128.5, 127.79, 127.75, 127.4, 126.9, 125.5, 125.1, 115.6, 60.1, 47.1, 46.2, 36.8, 31.6, 31.6, 20.7, 13.7; IR (film) ν_{max} 3029, 2923, 1704, 1514, 1495, 1453, 1385, 1245, 1186, 1144, 1100, 1031, 989, 819, 751, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{32}NO_4^+$ $[M + H]^+$ 494.2326, found 494.2323. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 9.4 min (minor), 15.5 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(4-methoxyphenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ca**).* Faint yellow semisolid (16.6 mg, 65% yield). $[\alpha]^{25}_D$= −56.7 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 3H), 7.32−7.27 (m, 3H), 7.27−7.16 (m, 4H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 4.80 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.08 (qd, *J* = 7.2, 2.0 Hz, 2H), 4.02−3.88 (m, 2H), 3.75 (t, *J* = 6.2 Hz, 1H), 3.60 (s, 2H), 3.47 (qd, *J* = 15.1, 6.3 Hz, 2H), 2.32 (s, 3H),

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (101 MHz, $CDCl_3$) δ 167.6, 163.9, 157.7, 143.4, 140.4, 137.4, 137.1, 136.9, 129.6, 129.0, 128.8, 128.2, 128.1, 127.8, 127.2, 125.9, 125.6, 115.9, 60.5, 47.4, 46.6, 37.1, 32.0, 31.9, 21.1, 14.1; IR (film) ν_{max} 3029, 2925, 1704, 1640, 1495, 1453, 1385, 1245, 1186, 1144, 1101, 1031, 989, 819, 751, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{32}NO_5^+$ $[M + H]^+$ 510.2275, found 510.2267. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 9.4 min (minor), 16.0 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(4-fluorophenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3da**).* Faint yellow semisolid (15.9 mg, 64% yield). $[\alpha]^{25}_D$ = −34.4 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 7.31−7.18 (m, 5H), 7.01−6.90 (m, 4H), 4.83 (d, J = 14.9 Hz, 1H), 4.50 (d, J = 15.0 Hz, 1H), 4.09 (qd, J = 7.1, 1.4 Hz, 2H), 4.03−3.88 (m, 2H), 3.79 (t, J = 5.9 Hz, 1H), 3.71−3.58 (m, 2H), 3.57−3.37 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.2, 163.3, 161.6 (d, J = 246.4 Hz), 156.7, 143.4, 139.9, 136.4, 135.8 (d, J = 3.3 Hz), 128.6, 128.5, 128.4, 127.81, 127.75, 127.4, 125.5, 124.3, 116.2, 115.4 (d, J = 21.5 Hz), 60.2, 47.0, 46.3, 36.5, 31.6, 31.5, 13.7; IR (film) ν_{max} 2927, 1703, 1604, 1509, 1495, 1453, 1386, 1366, 1244, 1195, 1159, 1099, 1031, 989, 840, 752, 702 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}FNO_4^+$ $[M + H]^+$ 498.2075, found 498.2071. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 11.2 min (minor), 18.7 min (major).

*(S,E)-Ethyl 2-(6-Benzyl-4-(2-chlorophenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ea**).* Faint yellow semisolid (12.6 mg, 49% yield). $[\alpha]^{25}_D$ = −33.5 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.36 (m, 3H), 7.35−7.30 (m, 4H), 7.29−7.25 (m, 4H), 7.18 (dd, J = 7.8, 1.7 Hz, 1H), 7.10 (td, J = 7.5, 1.4 Hz, 1H), 6.82 (dd, J = 7.7, 1.7 Hz, 1H), 4.83 (d, J = 15.0 Hz, 1H), 4.53 (d, J = 15.0 Hz, 1H), 4.36 (t, J = 5.4 Hz, 1H), 4.13−4.03 (m, 2H), 4.02−3.85 (m, 2H), 3.77 (dd, J = 15.0, 4.6 Hz, 1H), 3.72−3.59 (m, 2H), 3.25 (dd, J = 15.0, 6.4 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.3, 156.3, 144.2, 134.0, 137.2, 136.5, 132.9, 129.5, 128.6, 128.5, 128.3, 128.1, 127.8, 127.7, 127.4, 127.0, 125.5, 123.4, 116.5, 60.2, 47.2, 46.3, 33.6, 31.7, 29.7, 13.7; IR (film) ν_{max} 2928, 2367, 2345, 1704, 1495, 1453, 1387, 1366, 1243, 1195, 1147, 1100, 1036, 990, 750, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}ClNO_4^+$ $[M + H]^+$ 514.1780, found 514.1779. The product was analyzed by HPLC to determine the enantiomeric excess: 89% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 9.9 min (minor), 11.6 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(3-chlorophenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3fa**).* Faint yellow semisolid (16.2 mg, 63% yield). $[\alpha]^{25}_D$ = −34.0 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.34 (m, 3H), 7.34−7.31 (m, 2H), 7.30−7.26 (m, 3H), 7.26−7.17 (m, 3H), 7.11 (t, J = 1.8 Hz, 1H), 6.91 (dt, J = 7.1, 1.6 Hz, 1H), 4.87 (d, J = 15.0 Hz, 1H), 4.48 (d, J = 15.0 Hz, 1H), 4.09 (qd, J = 7.1, 1.4 Hz, 2H), 3.97 (q, J = 14.5 Hz, 2H), 3.78 (t, J = 6.0 Hz, 1H), 3.71−3.59 (m, 2H), 3.50 (qd, J = 15.1, 6.0 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.2, 156.3, 143.6, 142.1, 139.8, 136.4, 134.4, 129.9, 128.5, 127.9, 127.8, 127.45, 127.37, 127.2, 125.5, 125.2, 123.6, 116.2, 60.2, 47.0, 46.3, 36.9, 31.6, 31.2, 13.6; IR (film) ν_{max} 3029, 2926, 1704, 1597, 1495, 1453, 1386, 1366, 1245, 1195, 1144, 1100, 1031, 990, 785, 752, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}ClNO_4^+$ $[M + H]^+$ 514.1780, found 514.1781. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 11.2 min (minor), 22.4 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(4-chlorophenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ga**).* Faint yellow semisolid (17.2 mg, 67% yield). $[\alpha]^{25}_D$ = −41.6 (c 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H), 7.31−7.27 (m, 3H), 7.27−7.20 (m, 3H), 6.99−6.90 (m, 2H), 4.82 (d, J = 14.9 Hz, 1H), 4.50 (d, J = 15.0 Hz, 1H), 4.10 (qd, J = 7.1, 1.5 Hz, 2H), 4.02−3.88 (m, 2H), 3.77 (t, J = 5.9 Hz, 1H), 3.70−3.56 (m, 2H), 3.57−3.34 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.2, 156.5, 143.5, 139.9, 138.6, 136.4, 132.9, 128.7, 128.6, 128.5, 128.3, 127.82, 127.75, 127.4, 125.6, 123.9, 116.2, 60.2, 46.9, 46.3, 36.6, 31.6, 31.2, 13.7; IR (film) ν_{max} 3029, 2927, 1703, 1493, 1453, 1385, 1366, 1244, 1188, 1144, 1099, 1030, 1015, 989, 828, 749, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}ClNO_4^+$ $[M + H]^+$ 514.1780, found 514.1777. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 11.6 min (minor), 20.2 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(3-bromophenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ha**).* Faint yellow semisolid (14.2 mg, 51% yield). $[\alpha]^{25}_D$= −41.8 (c 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ7.43−7.38 (m, 1H), 7.38−7.34 (m, 2H), 7.34−7.31 (m, 3H), 7.31−7.24 (m, 5H), 7.23−7.11 (m, 2H), 6.95 (d, J = 7.7 Hz, 1H), 4.86 (d, J = 14.9 Hz, 1H), 4.48 (d, J = 15.0 Hz, 1H), 4.09 (qd, J = 7.2, 1.3 Hz, 2H), 3.97 (q, J = 14.5 Hz, 2H), 3.77 (t, J = 6.0 Hz, 1H), 3.72−3.57 (m, 2H), 3.57−3.40 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.2, 156.3, 143.6, 142.4, 139.8, 136.4, 130.3, 130.2, 130.1, 128.5, 127.9, 127.8, 127.4, 125.6, 125.5, 123.6, 122.6, 116.2, 60.2, 47.0, 46.3, 36.8, 31.6, 31.2, 13.7; IR (film) ν_{max} 3029, 2980, 1702, 1594, 1568, 1494, 1453, 1429, 1386, 1366, 1244, 1195, 1143, 1100, 1074, 1030, 990, 738, 700 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}BrNO_4^+$ $[M + H]^+$ 558.1274, found 558.1274. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 11.6 min (minor), 23.0 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(4-bromophenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ia**).* Faint yellow semisolid (21.8 mg, 78% yield). $[\alpha]^{25}_D$= −38.9 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ7.41−7.28 (m, 7H), 7.25 (d, J = 7.8 Hz, 3H), 7.18 (dd, J = 12.4, 5.3 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.78 (d, J = 14.9 Hz, 1H), 4.46 (d, J = 14.9 Hz, 1H), 4.12−4.01 (m, 2H), 4.00−3.85 (m, 2H), 3.73 (t, J = 5.9 Hz, 1H), 3.66−3.55 (m, 2H), 3.52 (dd, J = 15.0, 5.8 Hz, 1H), 3.36 (dd, J = 15.0, 6.2 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.2, 156.6, 143.5, 139.9, 139.1, 136.4, 131.7, 128.7, 128.6, 128.5, 127.85, 127.75, 127.5, 125.6, 123.9, 121.0, 116.2, 60.3, 47.0, 46.3, 36.6, 31.6, 31.2, 13.7; IR (film) ν_{max} 3029, 2927, 1703, 1639, 1489, 1453, 1407, 1385, 1366, 1244, 1185, 1143, 1100, 1074, 1031, 1011, 989, 750, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}BrNO_4^+$ $[M + H]^+$ 558.1274, found 558.1273. The product was analyzed by HPLC to determine

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

the enantiomeric excess: 96% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 12.0 min (minor), 22.0 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-(4-(trifluoromethyl)-phenyl)-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ja**).* Faint yellow semisolid (14.0 mg, 51% yield). $[\alpha]^{25}_D$ = −44.8 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.49 (d, *J* = 8.1 Hz, 2H), 7.40−7.29 (m, 5H), 7.29−7.23 (m, 3H), 7.23−7.15 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.80 (d, *J* = 14.9 Hz, 1H), 4.47 (d, *J* = 15.0 Hz, 1H), 4.05 (qd, *J* = 7.0, 1.1 Hz, 2H), 4.00−3.87 (m, 2H), 3.84 (t, *J* = 5.7 Hz, 1H), 3.70−3.51 (m, 3H), 3.38 (dd, *J* = 15.0, 6.2 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.0, 163.1, 156.2, 144.1, 143.7, 139.8, 136.4, 129.4 (q, *J* = 32.3 Hz), 128.6, 128.5, 127.8, 127.7, 127.5, 127.4, 125.5 (q, *J* = 4.5 Hz), 123.6 (q, *J* = 270.4 Hz), 123.3, 116.5, 60.2, 49.6, 46.3, 37.0, 31.6, 31.0, 13.6; IR (film) ν_{max} 2926, 2345, 1704, 1603, 1495, 1454, 1420, 1366, 1326, 1244, 1166, 1121, 1068, 1018, 990, 847, 747, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{29}F_3NO_4^+$ $[M + H]^+$ 548.2043, found 548.2039. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 10.7 min (minor), 18.9 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(3,4-dibromophenyl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3ka**).* Faint yellow semisolid (14.9 mg, 47% yield). $[\alpha]^{25}_D$ = −30.1 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 4.3, 1.8 Hz, 2H), 7.34 (d, *J* = 2.4 Hz, 2H), 7.33−7.29 (m, 4H), 7.29−7.24 (m, 2H), 7.21 (ddd, *J* = 9.5, 4.0, 2.0 Hz, 1H), 6.79 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.84 (d, *J* = 14.9 Hz, 1H), 4.49 (d, *J* = 14.9 Hz, 1H), 4.10 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.96 (q, *J* = 14.4 Hz, 2H), 3.74 (t, *J* = 5.7 Hz, 1H), 3.66−3.53 (m, 3H), 3.38 (dd, *J* = 15.1, 6.2 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.0, 163.1, 155.9, 143.8, 141.2, 139.7, 136.3, 133.7, 132.2, 128.54, 128.48, 127.9, 127.8, 127.5, 127.1, 125.6, 124.9, 123.4, 123.0, 116.6, 60.3, 46.9, 46.3, 36.3, 31.6, 30.9, 13.7; IR (film) ν_{max} 3029, 2928, 1702, 1639, 1568, 1489, 1454, 1407, 1386, 1366, 1245, 1185, 1143, 1101, 1074, 1031, 1011, 989, 750, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{28}Br_2NO_4^+$ $[M + H]^+$ 636.0380, found 636.0380. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 13.2 min (minor), 24.6 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-4-(naphthalen-2-yl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-phenylpropanoate (**3la**).* Faint yellow semisolid (19.6 mg, 74% yield). $[\alpha]^{25}_D$ = −70.9 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−7.72 (m, 3H), 7.57−7.48 (m, 3H), 7.43−7.36 (m, 3H), 7.36−7.31 (m, 3H), 7.30−7.25 (m, 4H), 7.21 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.88 (d, *J* = 14.9 Hz, 1H), 4.48 (d, *J* = 14.9 Hz, 1H), 4.13−3.94 (m, 5H), 3.76−3.53 (m, 4H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.2, 163.5, 157.1, 143.4, 140.0, 137.5, 136.5, 133.1, 132.4, 128.6, 128.5, 127.9, 127.8, 127.4, 127.3, 126.1, 125.9, 125.8, 125.5, 124.9, 124.7, 115.8, 60.2, 47.2, 46.3, 37.3, 31.7, 31.3, 13.6; IR (film) ν_{max} 3029, 2981, 2345, 1703, 1634, 1602, 1495, 1453, 1387, 1366, 1245, 1197, 1180, 1143, 1100, 1031, 990, 859, 821, 752, 702 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{32}NO_4^+$ $[M + H]^+$ 530.2326, found 530.2321. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 12.4 min (minor), 27.6 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(o-tolyl)-propanoate (**3ab**).* Faint yellow semisolid (8.9 mg, 36% yield). $[\alpha]^{25}_D$ = −48.9 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (ddd, *J* = 8.4, 6.5, 3.4 Hz, 5H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.28−7.22 (m, 2H), 7.19−7.13 (m, 2H), 7.13−7.09 (m, 4H), 4.83 (d, *J* = 14.9 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.03 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.97 (d, *J* = 5.1 Hz, 2H), 3.85 (t, *J* = 6.2 Hz, 1H), 3.65 (d, *J* = 1.4 Hz, 2H), 3.51 (d, *J* = 6.2 Hz, 2H), 2.42 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.4, 163.4, 156.2, 143.4, 140.1, 137.7, 136.5, 136.1, 129.6, 128.6, 128.5, 127.9, 127.8, 127.4, 127.2, 127.0, 125.5, 125.3, 124.6, 115.2, 60.1, 47.1, 46.3, 37.3, 31.6, 28.9, 19.4, 13.6; IR (film) ν_{max} 3029, 2926, 2345, 1703, 1641, 1605, 1494, 1453, 1386, 1366, 1271, 1243, 1195, 1143, 1100, 1030, 989, 762, 738, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{32}NO_4^+$ $[M + H]^+$ 494.2326, found 494.2322. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 12.4 min (minor), 20.8 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(m-tolyl)-propanoate (**3ac**).* Faint yellow semisolid (13.6 mg, 55% yield). $[\alpha]^{25}_D$ = −41.9 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.29 (m, 2H), 7.29−7.21 (m, 5H), 7.21−7.10 (m, 1H), 7.02 (td, *J* = 8.9, 8.3, 4.3 Hz, 3H), 4.82 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.07 (qd, *J* = 7.1, 1.7 Hz, 2H), 4.00−3.84 (m, 2H), 3.78 (t, *J* = 6.2 Hz, 1H), 3.60 (s, 2H), 3.56−3.39 (m, 2H), 2.34 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.3, 163.4, 156.9, 143.3, 140.1, 139.8, 137.2, 136.6, 129.4, 128.6, 128.5, 127.8, 127.7, 127.4, 127.1, 127.0, 126.2, 125.6, 124.7, 115.9, 60.1, 47.1, 46.2, 37.3, 31.6, 31.5, 21.1, 13.7; IR (film) ν_{max} 3029, 2925, 2345, 1703, 1640, 1605, 1495, 1453, 1386, 1366, 1270, 1243, 1193, 1143, 1100, 1031, 989, 762, 738, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{32}NO_4^+$ $[M + H]^+$ 494.2326, found 494.2321. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 9.9 min (minor), 16.6 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(p-tolyl)-propanoate (**3ad**).* Faint yellow semisolid (8.4 mg, 34% yield). $[\alpha]^{25}_D$ = −30.1 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.29 (m, 3H), 7.27−7.24 (m, 5H), 7.22 (s, 2H), 7.11−7.01 (m, 4H), 4.81 (d, *J* = 14.9 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.07 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.99−3.83 (m, 2H), 3.77 (t, *J* = 6.3 Hz, 1H), 3.60 (s, 2H), 3.55−3.37 (m, 2H), 2.32 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.3, 163.4, 156.9, 143.3, 140.1, 136.9, 136.6, 134.8, 128.6, 128.50, 128.47, 127.9, 127.8, 127.4, 127.1, 127.0, 124.7, 116.0, 60.1, 47.1, 46.2, 37.2, 31.5, 31.2, 20.7, 13.7; IR (film) ν_{max} 3029, 2925, 1703, 1639, 1513, 1495, 1453, 1386, 1366, 1244, 1182, 1143, 1099, 1031, 991, 787, 741, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{32}NO_4^+$ $[M + H]^+$ 494.2326, found 494.2320. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 9.5 min (minor), 15.1 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(3-methoxyphenyl)propanoate (**3ae**).* Faint yellow semisolid (18.9 mg, 74% yield). $[\alpha]^{25}_D$ = −46.1 (*c* 1.16, CH_2Cl_2). ^{1}H

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

NMR (300 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 7.27 (d, J = 5.4 Hz, 1H), 7.26−7.20 (m, 5H), 7.17 (d, J = 8.0 Hz, 1H), 7.04−6.91 (m, 4H), 6.74 (dd, J = 8.2, 1.6 Hz, 1H), 4.80 (d, J = 14.9 Hz, 1H), 4.44 (d, J = 15.0 Hz, 1H), 4.07 (qd, J = 7.1, 1.3 Hz, 2H), 3.99−3.85 (m, 2H), 3.84−3.70 (m, 4H), 3.64−3.56 (m, 2H), 3.48 (dq, J = 15.2, 8.4, 7.1 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.3, 157.4, 143.3, 140.0, 137.2, 136.5, 133.7, 129.6, 128.8, 128.6, 128.5, 127.8, 127.4, 127.2, 127.0, 126.8, 126.1, 124.8, 114.0, 60.2, 47.1, 46.2, 37.1, 31.4, 30.5, 29.4, 13.5; IR (film) ν_{max} 3030, 2937, 1703, 1640, 1600, 1491, 1454, 1386, 1366, 1244, 1195, 1146, 1100, 1037, 990, 762, 738, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{32}NO_5^+$ $[M + H]^+$ 510.2275, found 510.2275. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 11.9 min (minor), 19.0 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(3,5-dimethoxyphenyl)propanoate (**3af**).* Faint yellow semisolid (18.1 mg, 67% yield). $[\alpha]^{25}_D$ = −45.4 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 3H), 7.27−7.25 (m, 1H), 7.25−7.18 (m, 5H), 7.00 (dd, J = 7.4, 2.0 Hz, 2H), 6.55 (d, J = 2.3 Hz, 2H), 4.78 (d, J = 15.0 Hz, 1H), 4.43 (d, J = 15.0 Hz, 1H), 4.08 (qd, J = 7.1, 1.1 Hz, 2H), 3.88 (s, 2H), 3.77 (s, 7H), 3.69−3.56 (m, 2H), 3.46 (qd, J = 15.0, 6.4 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.2, 163.4, 160.2, 157.4, 143.2, 142.4, 140.0, 136.5, 128.6, 128.5, 127.7, 127.4, 127.1, 127.0, 124.8, 115.5, 106.5, 98.2, 60.2, 54.9, 47.1, 46.2, 37.2, 31.9, 31.5, 13.8; IR (film) ν_{max} 2936, 2837, 2370, 1703, 1637, 1596, 1495, 1454, 1430, 1386, 1365, 1277, 1243, 1195, 1155, 1100, 1065, 1031, 990, 830, 738, 702 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{34}NO_6^+$ $[M + H]^+$ 540.2381, found 540.2375. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 13.3 min (minor), 20.3 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(4-fluorophenyl)propanoate (**3ag**).* Faint yellow semisolid (19.7 mg, 79% yield). $[\alpha]^{25}_D$ = −55.4 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 7.0 Hz, 3H), 7.27 (dd, J = 4.6, 1.7 Hz, 2H), 7.26−7.19 (m, 5H), 6.99 (dd, J = 7.6, 2.7 Hz, 2H), 6.96−6.90 (m, 2H), 4.80 (d, J = 15.0 Hz, 1H), 4.45 (d, J = 15.0 Hz, 1H), 4.06 (qd, J = 7.1, 1.4 Hz, 2H), 3.96−3.81 (m, 2H), 3.77 (t, J = 6.2 Hz, 1H), 3.69−3.52 (m, 2H), 3.46 (d, J = 6.2 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.4, 161.0 (d, J = 243.1 Hz), 157.3, 143.2, 140.0, 136.5, 135.7, 130.1, 130.0, 128.6, 128.5, 127.7, 127.3 (d, J = 21.1 Hz), 126.9, 124.8, 115.7, 114.5 (d, J = 21.1 Hz), 60.2, 47.1, 46.3, 37.2, 31.5, 30.9, 13.7; IR (film) ν_{max} 2927, 1703, 1604, 1510, 1496, 1453, 1386, 1367, 1244, 1195, 1159, 1099, 1031, 990, 840, 753, 702 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}FNO_4^+$ $[M + H]^+$ 498.2075, found 498.2071. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 10.9 min (minor), 16.1 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(4-chlorophenyl)propanoate (**3ah**).* Faint yellow semisolid (19.0 mg, 74% yield). $[\alpha]^{25}_D$ = −34.5 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.28 (m, 3H), 7.26 (s, 2H), 7.23 (d, J = 2.1 Hz, 5H), 7.21 (d, J = 1.8 Hz, 2H), 6.93 (ddd, J = 31.7, 6.9, 4.0 Hz, 2H), 4.79 (d, J = 15.0 Hz, 1H), 4.45 (d, J = 15.0 Hz, 1H), 4.06 (qd, J = 7.1, 1.2 Hz, 2H), 3.95−3.80 (m, 2H), 3.76 (t, J = 6.1 Hz, 1H), 3.60 (d, J = 2.0 Hz, 2H), 3.47 (d, J = 5.6 Hz, 2H), 1.13 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.0, 163.4, 157.6, 143.2, 139.9, 138.6, 136.5, 131.2, 130.9, 130.0, 128.6, 128.5, 128.0, 127.9, 127.7, 127.4, 127.2, 126.9, 124.9, 115.3, 60.2, 47.1, 46.2, 37. 1, 31.5, 31.0, 13.7; IR (film) ν_{max} 3028, 2927, 1703, 1492, 1453, 1385, 1365, 1244, 1188, 1143, 1100, 1030, 1015, 989, 827, 749, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}ClNO_4^+$ $[M + H]^+$ 514.1780, found 514.1781. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 12.0 min (minor), 18.1 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(2-bromophenyl)propanoate (**3ai**).* Faint yellow semisolid (11.2 mg, 40% yield). $[\alpha]^{25}_D$ = −36.6 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.3 Hz, 4H), 7.28 (d, J = 8.8 Hz, 2H), 7.25−7.19 (m, 3H), 7.18−7.11 (m, 3H), 7.10−7.03 (m, 1H), 4.83 (d, J = 14.9 Hz, 1H), 4.46 (d, J = 15.0 Hz, 1H), 4.11 (q, J = 6.9 Hz, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.86 (t, J = 6.2 Hz, 1H), 3.71−3.47 (m, 4H), 1.06 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.1, 163.3, 157.4, 143.3, 139.9, 138.9, 136.5, 132.2, 129.3, 128.6, 128.5, 127.8, 127.4, 127.2, 127.1, 127.0, 126.8, 124.8, 124.3, 114.1, 60.2, 47.1, 46.3, 37.1, 32.0, 31.4, 13.6; IR (film) ν_{max} 3030, 2925, 1704, 1641, 1595, 1568, 1495, 1453, 1388, 1366, 1244, 1143, 1100, 1031, 991, 762, 739, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}BrNO_4^+$ $[M + H]^+$ 558.1274, found 558.1268. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 10.2 min (minor), 14.4 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(3-bromophenyl)propanoate (**3aj**).* Faint yellow semisolid (21.3 mg, 76% yield). $[\alpha]^{25}_D$ = −37.1 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.37−7.25 (m, 10H), 7.16 (t, J = 7.8 Hz, 1H), 7.09−7.01 (m, 2H), 4.84 (d, J = 14.9 Hz, 1H), 4.48 (d, J = 15.0 Hz, 1H), 4.09 (qd, J = 7.1, 1.2 Hz, 2H), 3.93 (q, J = 14.5 Hz, 2H), 3.81 (t, J = 6.1 Hz, 1H), 3.65 (s, 2H), 3.61−3.44 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 166.9, 163.4, 157.7, 143.1, 142.4, 139.9, 136.4, 131.5, 129.4, 128.6, 128.5 127.9, 127.8, 127.4, 127.2, 126.9, 125.0, 121.8, 114.9, 60.3, 47.1, 46.3, 37.1, 31.5, 31.3, 13.7; IR (film) ν_{max} 3030, 2926, 1704, 1641, 1594, 1568, 1495, 1453, 1387, 1366, 1244, 1184, 1143, 1101, 1031, 990, 762, 739, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}BrNO_4^+$ $[M + H]^+$ 558.1274, found 558.1272. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 11.4 min (minor), 18.5 min (major).

*(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(4-bromophenyl)propanoate (**3ak**).* Faint yellow semisolid (21.5 mg, 77% yield). $[\alpha]^{25}_D$ = −35.8 (*c* 1.16, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.17 (m, 12H), 7.01−6.81 (m, 2H), 4.79 (d, J = 15.0 Hz, 1H), 4.45 (d, J = 14.9 Hz, 1H), 4.06 (qd, J = 7.2, 1.3 Hz, 2H), 3.94−3.79 (m, 2H), 3.76 (t, J = 6.2 Hz, 1H), 3.68−3.52 (m, 2H), 3.47 (d, J = 5.8 Hz, 2H), 1.13 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$) δ 167.0,

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

163.3, 157.6, 143.1, 139.9, 139.1, 136.4, 130.8, 130.4, 128.6, 128.5, 127.7, 127.4, 127.2, 126.9, 124.9, 119.3, 115.2, 60.3, 47.1, 46.3, 37.1, 31.5, 31.1, 13.7. IR (film) ν_{max} 3030, 2927, 1704, 1487, 1453, 1387, 1366, 1244, 1184, 1143, 1102, 1073, 1031, 1012, 990, 801, 738, 701 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}BrNO_4^+$ $[M + H]^+$ 558.1274, found 558.1272. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 12.0 min (minor), 17.8 min (major).

(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(3-(trifluoromethyl)phenyl)propanoate (**3al**). Faint yellow semisolid (19.7 mg, 72% yield). $[\alpha]^{25}_D$ = −40.7 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.41 (m, 4H), 7.37−7.18 (m, 8H), 6.97 (dd, *J* = 6.6, 2.9 Hz, 2H), 4.80 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.07 (qd, *J* = 7.1, 1.3 Hz, 2H), 4.03−3.88 (m, 2H), 3.77 (t, *J* = 6.1 Hz, 1H), 3.69−3.54 (m, 2H), 3.54−3.42 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ 166.8, 163.3, 157.9, 143.1, 141.0, 140.4, 139.9, 137.7, 136.4, 132.2, 128.5(q, *J* = 10.5 Hz), 128.2, 127.8, 127.7, 127.4, 127.2, 126.9, 125.2 (q, *J* = 3.7 Hz), 124.9, 124.2 (q, *J* = 278.0 Hz), 122.4 (q, *J* = 3.8 Hz), 114.8, 60.3, 47.1, 46.3, 37.1, 31.4, 26.6, 13.6. IR (film) ν_{max} 3031, 2928, 1705, 1495, 1453, 1387, 1367, 1332, 1271, 1244, 1193, 1165, 1122, 1075, 1031, 990, 786, 744, 702 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{29}F_3NO_4^+$ $[M + H]^+$ 548.2043, found 548.2042. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 10.6 min (minor), 16.3 min (major).

(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(4-(trifluoromethyl)phenyl)propanoate (**3am**). Faint yellow semisolid (18.1 mg, 66% yield). $[\alpha]^{25}_D$ = −38.9 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.46 (m, 4H), 7.39−7.26 (m, 8H), 7.01 (dd, *J* = 6.6, 2.8 Hz, 2H), 4.84 (d, *J* = 14.9 Hz, 1H), 4.49 (d, *J* = 15.0 Hz, 1H), 4.16−4.06 (m, 2H), 4.04−3.92 (m, 2H), 3.82 (t, *J* = 6.1 Hz, 1H), 3.65 (s, 2H), 3.53 (dd, *J* = 6.2, 2.2 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 166.9, 163.4, 158.0, 144.2, 143.1, 139.8, 136.4, 128.9, 128.5 (q, *J* = 9.0 Hz), 128.0, 127.8, 127.7, 127.3 (q, *J* = 17.0 Hz), 126.9, 125.0, 124.7 (q, *J* = 3.8 Hz), 124.1(q, *J* = 270.3 Hz), 114.8, 60.3, 47.1, 46.3, 37.1, 31.5, 13.7. IR (film) ν_{max} 2928, 1704, 1641, 1496, 1454, 1367, 1326, 1273, 1244, 1164, 1118, 1067, 1019, 990, 820, 740, 701 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{29}F_3NO_4^+$ $[M + H]^+$ 548.2043, found 548.2040. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 11.5 min (minor), 16.1 min (major).

(R,E)-Ethyl 2-(6-Benzyl-7-oxo-4-phenyl-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(naphthalen-2-yl)propanoate (**3an**). Faint yellow semisolid (18.8 mg, 71% yield). $[\alpha]^{25}_D$ = −21.6 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 10.8 Hz, 2H), 7.41 (dd, J = 16.5, 7.8 Hz, 2H), 7.36−7.28 (m, 3H), 7.28−7.14 (m, 7H), 7.06−6.80 (m, 3H), 4.81 (d, *J* = 14.9 Hz, 1H), 4.45 (d, *J* = 14.9 Hz, 1H), 4.14−3.87 (m, 4H), 3.78 (t, *J* = 6.1 Hz, 1H), 3.70−3.53 (m, 2H), 3.50 (d, *J* = 6.2 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.3, 163.4, 157.4, 143.3, 140.0, 137.6, 136.5, 133.3, 131.8, 128.6, 128.5, 128.0, 127.7, 127.5, 127.41, 127.38, 127.3, 127.2, 127.1, 127.0, 126.9, 125.3, 124.7, 115.7, 60.2, 47.0, 46.2, 37.2, 31.8, 31.6, 13.8. IR (film) ν_{max} 3029, 2981, 2345, 1703, 1635, 1602, 1495, 1453, 1387, 1366, 1243, 1197, 1180, 1143, 1100, 1031, 990, 860, 821, 752, 738, 702 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{32}NO_4^+$ $[M + H]^+$ 530.2326, found 530.2325. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 12.5 min (minor), 19.6 min (major).

((R,E)-ethyl 2-(6-Benzyl-4-(naphthalen-2-yl)-7-oxo-3,4,6,7-tetrahydropyrano[2,3-c]pyrrol-2(5H)-ylidene)-3-(naphthalen-2-yl)propanoate) (**3ln**). white solid (21.7 mg, 75% yield), mp =62−68 °C. $[\alpha]^{25}_D$ = −39.5 (*c* 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.73 (m, 5H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.62−7.39 (m, 7H), 7.27 (dtd, *J* = 15.7, 8.3, 7.8, 5.9 Hz, 5H), 7.13 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.25−4.08 (m, 2H), 4.03 (ddt, *J* = 10.9, 7.3, 3.5 Hz, 2H), 3.93 (t, *J* = 6.0 Hz, 1H), 3.73−3.49 (m, 4H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$) δ 167.2, 163.5, 157.3, 143.4, 137.6, 137.4, 136.5, 133.3, 133.0, 132.3, 131.8, 128.5, 127.8, 127.50, 127.47, 127.41, 127.37, 127.3, 127.2, 126.9, 126.0, 125.8, 125.7, 125.3, 124.9, 124.8, 124.7, 115.8, 60.2, 47.1, 46.3, 37.3, 31.8, 31.4, 13.7. IR (film) ν_{max} 3029, 2980, 2345, 1703, 1634, 1602, 1495, 1476, 1453, 1387, 1366, 1270, 1243, 1198, 1180, 1143, 1100, 1031, 990, 860, 821, 752, 738, 701 cm^{-1}; HRMS (ESI) calcd for $C_{39}H_{34}NO_4^+$ $[M + H]^+$ 580.2443, found 580.2477. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (IA column, *i*-propanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm); t_R = 13.6 min (minor), 24.2 min (major).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02659.

^{1}H and ^{13}C{^{1}H}NMR spectra for all products (PDF)

X-ray crystallographic data for product **3ln** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hchguo@cau.edu.cn.

ORCID

Cheng Zhang: 0000-0002-8760-8152

Hongchao Guo: 0000-0002-7356-4283

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 21172253, 21372256, 21572264), Chinese Universities Scientific Fund (No. 2016TC021, 2016QC090), the National S&T Pillar Program of China (2015BAK45B01), Research Fund for the Doctoral Program of Higher Education of China (No. 20120008110038).

■ REFERENCES

(1) For recent reviews, see: (a) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927. (b) Li, W.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 1657. (c) Xiao, Y.; Guo, H.; Kwon, O. *Aldrichimica Acta* **2016**, *49*, 3. (d) Wang, T.; Han, X.; Zhong, F.; Yao, W.; Lu, Y. *Acc. Chem. Res.* **2016**, *49*, 1369 And references cited therein..

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641

(2) For selected example of [2+2] annulation, see: Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, *14*, 1784.
(3) For representative examples of [3+2] annulation, see: (a) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (b) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (c) Xiao, H.; Chai, Z.; Zheng, C. W.; Yang, Y. Q.; Liu, W.; Zhang, J. K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467. (d) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293. (e) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767. (f) Henry, C. E.; Xu, Q. H.; Fan, Y. C.; Martin, T. J.; Belding, L.; Dudding, T.; Kwon, O. *J. Am. Chem. Soc.* **2014**, *136*, 11890. (g) Sankar, M. G.; Garcia-Castro, M.; Golz, C.; Strohmann, C.; Kumar, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 9709.
(4) For a representative example of [3+3] annulation, see: Zhang, L.; Liu, H.; Qiao, G.; Hou, Z.; Liu, Y.; Xiao, Y.; Guo, H. *J. Am. Chem. Soc.* **2015**, *137*, 4316.
(5) For representative examples of [4+1] annulation, see: (a) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183. (b) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643. (c) Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803. For a review, see: (d) Chen, J.−R.; Hu, X.−Q.; Lu, L.−Q.; Xiao, W.-J. *Chem. Rev.* **2015**, *115*, 5301.
(6) For representative examples of [4+2] annulation, see: (a) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (b) Xiao, H.; Chai, Z.; Wang, H.; Wang, X.; Cao, D.; Liu, W.; Lu, Y.; Yang, Y.; Zhao, G. *Chem. - Eur. J.* **2011**, *17*, 10562. (c) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231. (d) Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2015**, *137*, 54. (e) Liu, H.; Liu, Y.; Yuan, C.; Wang, G.-P.; Zhu, S.-F.; Wu, Y.; Wang, B.; Sun, Z.; Xiao, Y.; Zhou, Q.-L.; Guo, H. *Org. Lett.* **2016**, *18*, 1302.
(7) For selected other examples, see: (a) Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2225. (b) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9725. (c) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 943. (d) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2525.
(8) (a) Maloney, K. N.; Hao, W.; Xu, J.; Gibbons, J.; Hucul, J.; Roll, D.; Brady, S. F.; Schroeder, F. C.; Clardy, J. *Org. Lett.* **2006**, *8*, 4067. (b) Ramakanth, S. Patent WO 2011-157682, 2011. (c) Emanuele, A. A.; Adams, N. E.; Chen, Y.-C.; Maurelli, A. T.; Garcia, G. A. *J. Antibiot.* **2014**, *67*, 379. (d) Abzianidze, V. V.; Prokofieva, D. S.; Chisty, L. A.; Bolshakova, K. P.; Berestetskiy, A. O.; Panikorovskii, T. L.; Bogachenkov, A. S.; Holder, A. A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5566.
(9) (a) Wang, X.; Fang, T.; Tong, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5361. (b) Ashtekar, K. D.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 5732.
(10) (a) Pei, C.-K.; Shi, M. *Tetrahedron: Asymmetry* **2011**, *22*, 1239. (b) Pei, C.-K.; Jiang, Y.; Shi, M. *Org. Biomol. Chem.* **2012**, *10*, 4355. (c) Pei, C.-K.; Jiang, Y.; Wei, Y.; Shi, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11328.
(11) (a) Wang, F.; Luo, C.; Shen, Y.-Y.; Wang, Z.-D.; Li, X.; Cheng, J.-P. *Org. Lett.* **2015**, *17*, 338. (b) Wang, F.; Li, Z.; Wang, J.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2015**, *80*, 5279.
(12) Zhang, S.; Luo, Y.-C.; Hu, X.-Q.; Wang, Z.-Y.; Liang, Y.-M.; Xu, P.-F. *J. Org. Chem.* **2015**, *80*, 7288.
(13) (a) Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2015**, *137*, 54. (b) Ni, H.; Yao, W.; Waheed, A.; Ullah, N.; Lu, Y. *Org. Lett.* **2016**, *18*, 2138. (c) Han, X.; Ni, H.; Chan, W.-L.; Gai, X.; Wang, Y.; Lu, Y. *Org. Biomol. Chem.* **2016**, *14*, 5059.
(14) Wang, C.; Gao, Z.; Zhou, L.; Yuan, C.; Sun, Z.; Xiao, Y.; Guo, H. *Org. Lett.* **2016**, *18*, 3418.
(15) For achiral Lewis base-catalyzed [2+4] annulation reactions of allenes, see: (a) Zhao, G.-L.; Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 4527. (b) Kumar, N. N. B.; Reddy, M. N.; Swamy, K. C. K. *J. Org. Chem.* **2009**, *74*, 5395. (c) Meng, X.; Huang, Y.; Zhao, H.; Xie, P.; Ma, J.; Chen, R. *Org. Lett.* **2009**, *11*, 991. (d) Sun, Y.-W.; Guan, X.-Y.; Shi, M. *Org. Lett.* **2010**, *12*, 5664. (e) Chen, X.-Y.; Wen, M.-W.; Ye, S.; Wang, Z.-X. *Org. Lett.* **2011**, *13*, 1138. (f) Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 1142. (g) Zhang, D.-H.; Shi, M. *ChemistryOpen* **2012**, *1*, 215. (h) Zheng, J.; Huang, Y.; Li, Z. *Org. Lett.* **2013**, *15*, 5064. (i) Li, E.; Chang, M.; Liang, L.; Huang, Y. *Eur. J. Org. Chem.* **2015**, *2015*, 710. (j) Gu, Y.; Li, F.; Hu, P.; Liao, D.; Tong, X. *Org. Lett.* **2015**, *17*, 1106. (k) Kumari, A. L. S.; Swamy, K. C. K. *J. Org. Chem.* **2015**, *80*, 4084. (l) Chang, M.; Wu, C.; Zheng, J.; Huang, Y. *Chem. - Asian J.* **2016**, *11*, 1512.
(16) (a) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (b) Jing, C.; Na, R.; Wang, B.; Liu, H.; Zhang, L.; Liu, J.; Wang, M.; Zhong, J.; Kwon, O.; Guo, H. *Adv. Synth. Catal.* **2012**, *354*, 1023. (c) Yu, H.; Zhang, L.; Yang, Z.; Li, Z.; Zhao, Y.; Xiao, Y.; Guo, H. *J. Org. Chem.* **2013**, *78*, 8427. (d) Yu, H.; Zhang, L.; Li, Z.; Liu, H.; Wang, B.; Xiao, Y.; Guo, H. *Tetrahedron* **2014**, *70*, 340. (e) Liu, Y.; Yang, W.; Wu, Y.; Mao, B.; Gao, X.; Liu, H.; Sun, Z.; Xiao, Y.; Guo, H. *Adv. Synth. Catal.* **2016**, *358*, 2867. (f) Wu, Y.; Liu, Y.; Yang, W.; Liu, H.; Zhou, L.; Sun, Z.; Guo, H. *Adv. Synth. Catal.* **2016**, *358*, 3517.
(17) Crystallographic data for **3ln** have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 1504063.

DOI: 10.1021/acs.joc.6b02659
J. Org. Chem. 2017, 82, 633−641