JOC The Journal of Organic Chemistry

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Asymmetric Synthesis of Amino-Bis-Pyrazolone Derivatives via an Organocatalytic Mannich Reaction

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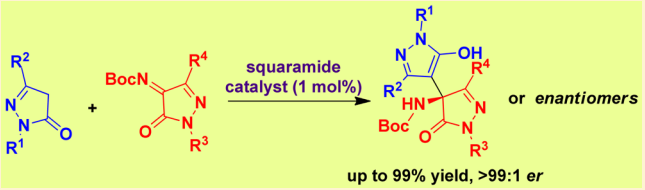
Supporting Information

ABSTRACT: A new series of *N*-Boc ketimines derived from pyrazolin-5-ones have been used as electrophiles in asymmetric Mannich reactions with pyrazolones. The amino-bis-pyrazolone products are obtained in excellent yields and stereoselectivities by employing a very low loading of 1 mol % of a bifunctional squaramide organocatalyst. Depending on the substitution at position 4 of the pyrazolones, the new protocol allows for the generation of one or two tetrasubstituted stereocenters, including a one-pot version combing the Mannich reaction with a base-mediated halogenation.



Pyrazoles and pyrazolones make up a privileged class of five-membered aza-heterocycles that have found wide applications as pharmaceuticals and agrochemicals, as well as synthetic scaffolds in combinatorial and medicinal chemistry, photographic couplers, and chelating agents in coordination chemistry.[1] The pyrazolone moiety is not a common feature of biologically active natural products, but a broad range of synthetic pyrazolone derivatives exhibit significant pharmacological activities. For example, pyrazolone derivatives are used as antipyretic drugs,[2] neuroprotective agents,[3] HIV-1 integrase inhibitors,[4] antibacterial agents,[5] etc. Because of the wide biological and synthetic applications, the synthesis of these 1,2-azoles has been a major focus of interest among synthetic organic chemists. In this context, the asymmetric synthesis of the structurally diverse pyrazole and pyrazolone derivatives, especially employing the reactivities of pyrazolin-5-one derivatives, remain at the forefront, thus leading to the discovery of new aza-heterocyclic compounds for further investigations.[6]

With the availability of many reactive centers, pyrazolin-5-ones are unique substrates with many possibilities of modification and manipulation for obtaining new valuable compounds (Figure 1). The well-established nucleophilic centers on pyrazolin-5-ones are available at the N-1,[7] C-4,[8] and 5-OH[9] positions, whereas the C-3 position is electrophilic.[10] The α,β-unsaturated pyrazolones bearing a γ-hydrogen have been used as vinylogous nucleophiles,[11] and those derived from aldol condensation with aldehydes served as very good Michael acceptors.[12] By knowing all these reactive sites of pyrazolin-5-one derivatives, we realized the synthesis of a new series of pyrazolin-5-one derivatives, i.e., *N*-Boc ketimines where the C-4 position can act as an acceptor. This new reactivity of the pyrazolin-5-one substrates can be utilized to develop new catalytic asymmetric transformations to generate a tetrasubstituted amino stereogenic center. To the best of our knowledge, there are only two reports in the literature that describe the formation of pyrazolones bearing a tetrasubstituted amino stereogenic center via the α-amination reaction of the 4-substituted pyrazolones (Scheme 1).[13] Alternatively, we herein report an enantioselective Mannich addition of pyrazolones to *N*-Boc ketimines derived from pyrazolin-5-ones to provide an efficient entry to amino-bis-pyrazolones bearing one or two tetrasubstituted stereogenic centers.

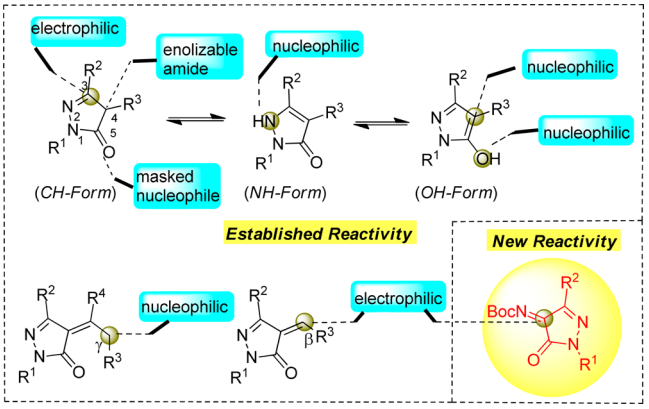


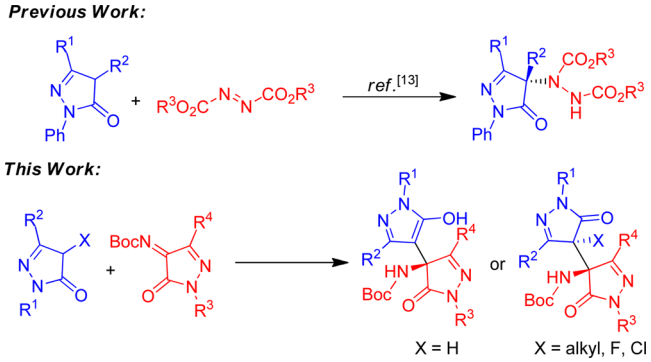
Figure 1. Reactive centers of pyrazolin-5-one derivatives.

Initially, we synthesized a new series of *N*-Boc ketimines starting with the base-catalyzed condensation reaction of pyrazolones **1** with nitrosobenzene to afford intermediate phenyl imines **2**, which were then hydrolyzed to afford ketones

Received: May 8, 2017
Published: May 25, 2017

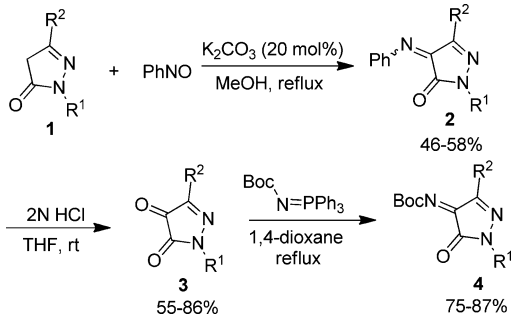
DOI: 10.1021/acs.joc.7b01113
J. Org. Chem. 2017, 82, 7050−7058

Scheme 1. Asymmetric Synthesis of N-Protected Amino-Pyrazolones



3 (Scheme 2). Ketones **3** were subsequently converted to the *N*-Boc ketimines **4** via an aza-Wittig reaction.

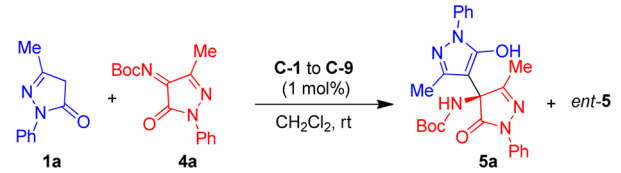
Scheme 2. Synthesis of Pyrazolone-Derived *N*-Boc Ketimines

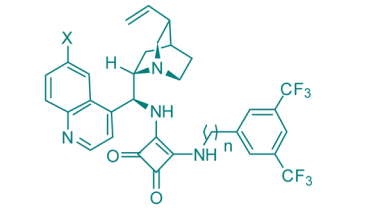


With the substrates in hand, we started the optimization studies by screening various bifunctional hydrogen-bonding organocatalysts[14] for the enantioselective addition of pyrazolone **1a** to imine **4a** in dichloromethane at room temperature to afford desired product **5a** (Table 1). It turned out that the reactions were generally very fast with 1 mol % squaramides **C-1**−**C-7**. The squaramide catalysts derived from quinine **C-2** and quinidine **C-5** gave the best enantioselectivities of products **5a** and *ent*-**5a**, respectively, with an excellent yield of 99%. However, a thiourea (**C-8**) and a cuperine catalyst (**C-9**) resulted in a slow reaction rate with poor er values.

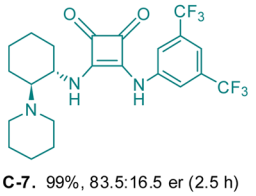
To further improve the yield and enantiomeric ratio, the reaction conditions were optimized by screening different solvents and additives and varying the temperature using catalyst **C-2** (Table 2). This time a one-pot addition/acylation reaction was performed to obtain enol acetate **6a**, whose enantiomers could be easily resolved by HPLC. After various solvents had been screened (entries 1−9), it was found that no other solvent provides er values better than those of dichloromethane. An increase in the er value of **6a** was observed when the temperature was decreased to −20 °C (entry 10). Moreover, the presence of 4 Å molecular sieves (MS) also led to an increase in enantioselectivity (entry 11). Further decreasing the temperature and the catalyst loading, however, led to a lower reaction rate and hence lower yields (entries 12 and 13). On the basis of these optimization studies, the best reaction condition for this transformation includes 1 mol % **C-2** in dichloromethane at −48 °C and 4 Å MS as an

Table 1. Catalyst Screening[a]

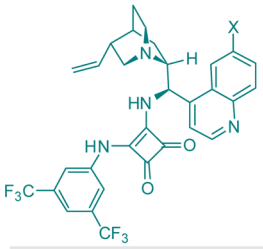




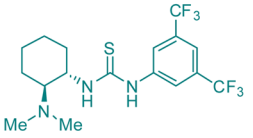
C-1. X = H, n = 0, 99%, 95:5 er (1.0 h)
C-2. X = OMe, n = 0, 99%, 95:5 er (1.0 h)
C-3. X = H, n = 1, 99%, 92.5:7.5 er (0.7 h)
C-4. X = OMe, n = 1, 99%, 92.5:7.5 er (0.7 h)



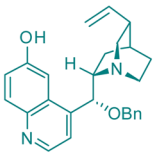
C-7. 99%, 83.5:16.5 er (2.5 h)



C-5. X = OMe, 99%, 95.5:4.5 er (1.0 h)
C-6. X = H, 99%, 5.5:94.5 er (1.0 h)



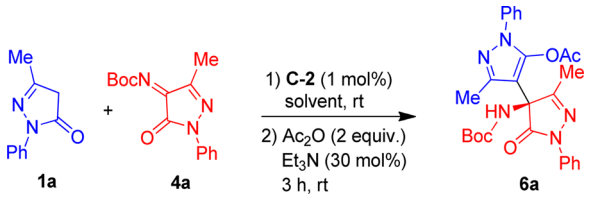
C-8. 94%, 54.5:45.5 er (24 h)



C-9. 94%, 45.5:54.5 er (12 h)

[a]Reaction conditions: 0.24 mmol of **1a**, 0.2 mmol of **4a**, and 1 mol % catalyst in 1.0 mL of CH_2Cl_2 at room temperature.

Table 2. Optimization of the Reaction Conditions[a]



entry	solvent	temp	time (h)	yield (%)[b]	er[c]
1	CH_2Cl_2	rt	2.5	94	95:5
2	$ClCH_2CH_2Cl$	rt	2.5	94	94:6
3	$CHCl_3$	rt	2.5	91	90.5:9.5
4	toluene	rt	5	95	76.5:23.5
5	xylene	rt	6	93	81:19
6	Et_2O	rt	1.5	92	77:23
7	THF	rt	0.3	94	91:9
8	1,4-dioxane	rt	1.5	92	80.5:19.5
9	MTBE	rt	1.5	96	79:21
10	CH_2Cl_2	−20 °C	5	82	96.5:3.5
11[d]	CH_2Cl_2	−20 °C	6	93	97:3
12[d,e]	CH_2Cl_2	−78 °C	24	90	94:6
13[d,e,f]	CH_2Cl_2	−48 °C	18	95	98:2
14[d,e]	CH_2Cl_2	−48 °C	24	99	98.5:1.5

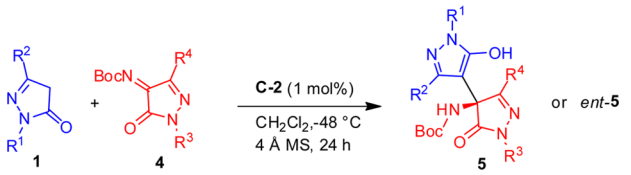
[a]Reaction conditions: 0.20 mmol of **1a**, 0.22 mmol of **4a**, 1 mol % of **C-2** in 1.0 mL of solvent. [b]Yield of isolated product **6a** after column chromatography. [c]The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [d]50 mg of 4 Å molecular sieves were used. [e]Yield of the nonacylated product **5a**. [f]0.5 mol % of **C-2** was used.

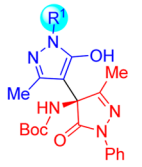
DOI: 10.1021/acs.joc.7b01113
J. Org. Chem. 2017, 82, 7050−7058

additive, providing desired product **5a** in 99% yield and 98.5:1.5 er (entry 14).

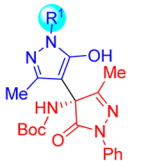
After the optimization, we then focused on the substrate scope for the squaramide **C-2**-catalyzed Mannich addition of pyrazolones **1** to imines **4** (Table 3). The variation in the N

Table 3. Substrate Scope with Catalysts C-2 and C-5[a]

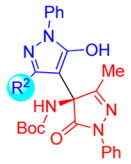




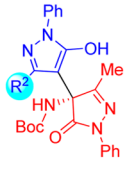
5a. R^1 = Ph, 99%, 98.5:1.5 er[b]
5b. R^1 = 2-ClC_6H_4, 91%, 93.5:6.5 er
5c. R^1 = 4-ClC_6H_4, 99%, 93:7 er
5d. R^1 = 4-MeC_6H_4, 96%, 95:5 er
5e. R^1 = Me, 89%, 91:9 er



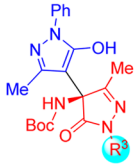
ent-5a. R^1 = Ph, 99%, 96:4 er[b]
ent-5b. R^1 = 2-ClC_6H_4, 92%, 91:9 er
ent-5c. R^1 = 4-ClC_6H_4, 99%, 93:7 er
ent-5d. R^1 = 4-MeC_6H_4, 95%, 94.5:5.5 er
ent-5e. R^1 = Me, 89%, 92.5:7.5 er



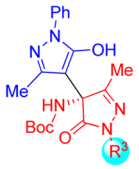
5f. R^2 = Et, 95%, 94.5:5.5 er
5g. R^2 = *n*-Pr, 96%, 92:8 er
5h. R^2 = *i*-Pr, 85%,93:7 er
5i. R^3 = CF_3, 71%, er ND



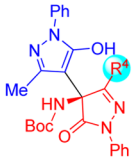
ent-5f. R^2 = Et, 96%, 92:8 er
ent-5g. R^2 = *n*-Pr, 97%, 93:7 er
ent-5h. R^2 = *i*-Pr, 86%, 94.5:5.5 er
ent-5i. R^3 = CF_3, 69%, er ND



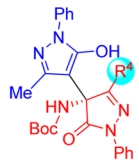
5j. R^3 = 4-ClC_6H_4, 99%, 94.5:5.5 er
5k. R^3 = 4-MeC_6H_4, 99%, >99:1 er



ent-5j. R^3 = 4-ClC_6H_4, 99%, 94:6 er
ent-5k. R^3 = 4-MeC_6H_4, 99%, 95:5 er



5l. R^4 = Et, 92%, 98-5:1.5 er[b]
5m. R^4= *i*-Pr, 95%, 98-5:1.5 er[b]
5n. R^4 = *t*-Bu, 67%, 80:20 er (rt, 5 d)
5o. R^4 = Ph, 93%, 87:13 er (rt, 2 d)



ent-5l. R^4 = Et, 93%, >99:1 er[b]
ent-5m. R^4 = *i*-Pr, 95%, 98:2 er[b]
ent-5n. R^4 = *t*-Bu, 62%, 81.5:18.5 er (rt, 5 d)
ent-5o. R^4 = Ph, 92%, 80.5:19.5 er (rt, 2 d)

[a]Reaction conditions: 0.20 mmol of **1**, 0.22 mmol of **4**, 1 mol % of **C-2** or **C-5**, 50 mg 4 Å MS in 1.0 mL of CH_2Cl_2 at −48 °C. [b]er values of the acylated product.

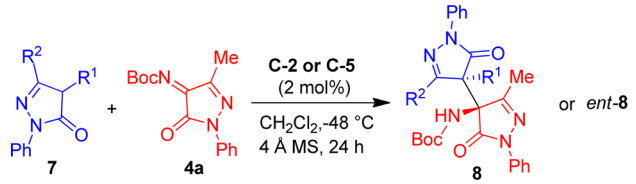
substituent (R^1) of **1** showed that the aryl group-bearing electron-withdrawing and electron-donating group led to the formation of the corresponding adducts **5b−d** in high yields with very good er values. An *N*-methyl group is also well tolerated to provide the desired product **5e** in 89% yield with a good er of 91:9. Various alkyl substituents (R^2) at the C-3 position of pyrazolone **1** also worked very well in terms of er values of the products **5f−h**, but with the increase in steric bulk, the yield decreased to some extent. A pyrazolone bearing a trifluoromethyl group at the C-3 position led to the formation of the desired product **5i** in 71% yield; however, the er could not be determined by HPLC.

The imines **4** bearing an electron-withdrawing and electron-donating group (R^3) at the N-1 position also reacted well to provide high enantioselectivities of the desired products **5j** and **5k**. It was further observed that the imines bearing ethyl and isopropyl substituents (R^4) at the C-3 position worked well to provide very good yields and excellent enantioselectivities for **5l** and **5m**. However, an increase in steric bulk (R^4 = *t*-Bu and Ph) at this position leads to low reactivity even at room temperature and resulted in lower er values for **5n** and **5o**.

The substrate scope was also tested with the catalyst **C-5**, which worked in a similar fashion to provide the enantiomeric products *ent*-**5a−o** with the same yields and enantiomeric ratios.

Furthermore, we have tested the applicability of this transformation to the generation of two adjacent tetrasubstituted stereocenters by using C-3 alkyl-substituted pyrazolones **7** as nucleophiles (Scheme 3). With 2 mol % of catalysts

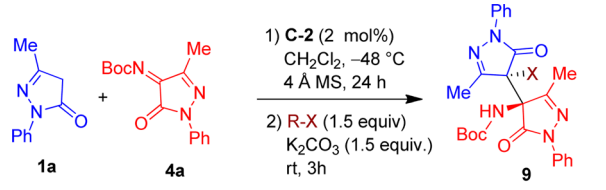
Scheme 3. Asymmetric Synthesis of Bis-Pyrazolones Bearing Two Adjacent Tetrasubstituted Stereocenters



C-2 and **C-5**, the corresponding bis-pyrazolone products **8** and *ent*-**8**, respectively, were obtained with good yields and enantioselectivities as well as excellent diastereoselectivities (>20:1 dr).

The one-pot organocatalytic 1,2-addition and base-mediated halogenation also worked successfully, leading to the formation of fluoro- and chloro-substituted amino-bis-pyrazolone products **9a** and **9b** bearing two contiguous tetrasubstituted stereocenters (Scheme 4). In both cases, good yields and excellent stereoselectivities were achieved.

Scheme 4. One-Pot Organocatalytic 1,2-Addition and Base-Mediated Halogenation Reaction[a]



[a]NFSI represents *N*-fluorobenzenesulfonimide and NCS *N*-chlorosuccinimide.

DOI: 10.1021/acs.joc.7b01113
J. Org. Chem. 2017, 82, 7050−7058

The absolute configuration of products **5**, **8**, and **9** obtained with catalyst **C-2** could be assigned by analogy to the X-ray crystal structures of products **6a** and **8a**.[15]

In conclusion, we have synthesized pyrazolone-derived *N*-Boc ketimines and utilized these new electrophiles in the organocatalytic asymmetric Mannich-type addition of pyrazolone derivatives. With a low loading of squaramides **C-2** and **C-5**, both enantiomers of the corresponding amino-bis-pyrazolones with one and two tetrasubstituted stereocenters were synthesized in good to excellent yields and stereoselectivities for a wide range of substrates. In addition, the one-pot organocatalytic enantioselective Mannich addition and base-mediated diastereoselective α-halogenation also worked efficiently to provide the corresponding bis-pyrazolones bearing two adjacent tetrasubstituted halo and amino stereogenic centers.

EXPERIMENTAL SECTION

General Method. All reactions were performed in oven-dried glassware. Analytical TLC was performed using a SIL G-25 UV254 instrument from Machery & Nagel and visualized with ultraviolet radiation at 254 nm. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on a Varian Innova 400 or Innova 600 instrument. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million, with coupling constants given in hertz. The following abbreviations are used for spin multiplicity: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad signal. The assignment of the exact numbers of carbon atoms in the bis-amino-pyrazolone products was not possible; hence, only the number of signals seen in the ^{13}C NMR spectra is written. It is assumed that this problem is due to a possible keto−enol tautomerization or the restricted rotation. Mass spectra were recorded with the SSQ 7000 spectrometer from Finnigan at 70 eV, whereas HRMS data (ESI) were collected with a ThermoFisher Scientific LTQ-Orbitrap XL apparatus. IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer. Analytical HPLC was performed either on a Hewlett-Packard 1050 series instrument or on an Agilent 1100 instrument using chiral stationary phases. Analytical SFC was performed on a Thar SFC Waters Method Station II instrument using chiral stationary phases. The diastereomeric ratio was determined by the ^{1}H NMR and HPLC analysis of the isolated product. Optical rotation values were measured on a PerkinElmer 241 polarimeter. Melting points were measured on an LLG MPM-H2 melting point instrument.

Unless specified, the starting materials and reagents were purchased directly from the commercial suppliers and used without further purification. Squaramides **C-1**−**C-7**[16] and benzyl cuperine **C-9**[17] were synthesized using known literature procedures.

General Procedure for the Synthesis of Pyrazolone-Derived Phenyl Ketimines 2. Nitrosobenzene (25.0 mmol, 1.0 equiv) and K_2CO_3 (0.2 equiv) were added to a solution of pyrazolone derivative **1** (25.0 mmol, 1.0 equiv) in MeOH (0.6 M) at room temperature. The reaction mixture was then refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed three times with water and once with brine and then dried over anhydrous $MgSO_4$. After evaporation of ethyl acetate under reduced pressure, the crude product was purified by flash column chromatography (*n*-pentane/diethyl ether, 3:1) to afford ketimine product **2**.

*5-Methyl-2-phenyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (**2a**).* Red solid: 3.16 g, 48%; mp 102−104 °C; IR (capillary) 3060, 2287, 2084, 1937, 1664, 1587, 1488, 1412, 1360, 1297, 1132, 998, 911, 831, 744, 687 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88−7.86 (m, 2H, ArH), 7.45−7.23 (m, 7H, ArH), 7.22−7.19 (m, 1H, ArH), 2.35 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.7, 151.2, 150.8, 146.3, 137.7, 129.0 (2C), 128.7 (2C), 125.6, 121.8 (2C), 118.5 (2C), 118.4, 12.4; MS (EI) *m*/*z* 262.9 M$^+$; HRMS (ESI) [M + H]$^+$ calcd for $C_{16}H_{14}N_3O$ *m*/*z* 264.1131, found *m*/*z* 264.1131.

*2-(4-Chlorophenyl)-5-methyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (**2b**).* Red solid: 3.64 g, 49%; mp 121−123 °C; IR (capillary) 3461, 2993, 2678, 2338, 2093, 1902, 1716, 1577, 1479, 1305, 1105, 994, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.83 (m, 2H, ArH), 7.44−7.31 (m, 7H, ArH), 2.32 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 151.2, 151.1, 146.2, 136.3, 129.1 (2C), 129.0, 128.7 (2C), 122.03, 122.01, 119.4 (2C), 118.8, 12.4; MS (EI) *m*/*z* 296.8 M$^+$; HRMS (ESI) [M + H]$^+$ calcd for $C_{16}H_{13}N_3OCl$ *m*/*z* 298.0742, found *m*/*z* 298.0742.

*5-Methyl-4-(phenylimino)-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one (**2c**).* Red solid: 3.32 g, 48%; mp 75−77 °C; IR (capillary) 3354, 2934, 2702, 2339, 2092, 1907, 1690, 1497, 1306, 1129, 993, 774, 683 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H, ArH), 7.44−7.42 (m, 2H, ArH), 7.38−7.36 (m, 2H, ArH), 7.34−7.31 (m, 1H, ArH), 7.20−7.19 (m, 2H, ArH), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.8, 151.1, 150.6, 146.3, 135.3, 135.2, 129.5 (2C), 129.1, 128.7 (2C), 128.6, 121.8, 118.4 (2C), 21.1, 12.4; MS (EI) *m*/*z* 276.9 M$^+$; HRMS (ESI) [M + Na]$^+$ calcd for $C_{17}H_{15}N_3ONa$ *m*/*z* 300.1107, found *m*/*z* 300.1107.

*5-Ethyl-2-phenyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (**2d**).* Red solid: 3.19 g, 46%; mp 94−96 °C; IR (capillary) 3460, 2970, 2663, 2336, 2094, 1912, 1728, 1589, 1479, 1341, 1225, 1117, 1037, 919, 836, 755 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92−7.90 (m, 2H, ArH), 7.45−7.32 (m, 6H, ArH), 7.22−7.20 (m, 2H, ArH), 2.76 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 1.40 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.6, 152.3, 151.3, 146.4, 137.7, 129.0 (2C), 128.7 (2C), 128.5, 125.5, 121.7, 118.4 (2C), 118.3, 20.2, 10.6; MS (EI) *m*/*z* 276.8 M$^+$; HRMS (ESI) [M + Na]$^+$ calcd for $C_{17}H_{15}N_3ONa$ *m*/*z* 300.1107, found *m*/*z* 300.1109.

*5-Isopropyl-2-phenyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (**2e**).* Red solid: 4.22 g, 58%; mp 77−79 °C; IR (capillary) 3398, 2959, 2707, 2340, 2093, 1709, 1593, 1467, 1334, 1256, 1102, 977, 835, 747, 685 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92−7.91 (m, 2H, ArH), 7.45−7.39 (m, 4H, ArH), 7.34−7.31 (m, 3H, ArH), 7.22−7.19 (m, 1H, ArH), 3.22−3.18 [m, 1H, $CH(CH_3)_2$], 1.42 [d, *J* = 7.0 Hz, 6H, $CH(CH_3)_2$]; ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.5, 152.0, 151.3, 146.5, 137.8, 129.0 (2C), 128.7 (2C), 128.4, 125.5, 121.4 (2C), 118.4 (2C), 27.1, 20.1 (2C); MS (EI) *m*/*z* 290.9 M$^+$; HRMS (ESI) [M + Na]$^+$ calcd for $C_{18}H_{17}N_3ONa$ *m*/*z* 314.1264, found *m*/*z* 314.1264.

*5-(tert-Butyl)-2-phenyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (**2f**).* Red solid: 3.74 g, 49%; mp 95−97 °C; IR (capillary) 2957, 2340, 2095, 1925, 1717, 1590, 1479, 1375, 1304, 1213, 1108, 963, 839, 689 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H, ArH), 7.45−7.39 (m, 4H, ArH), 7.31 7.29 (m, 1H, ArH), 7.24−7.19 (m, 3H, ArH), 1.51 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 152.0, 150.8, 146.7, 137.7, 128.9 (2C), 128.7 (2C), 127.8, 125.4, 120.3 (2C), 118.3 (2C), 35.1, 28.1 (3C); MS (EI) *m*/*z* 304.9 M$^+$; HRMS (ESI) [M + H]$^+$ calcd for $C_{19}H_{20}N_3O$ *m*/*z* 306.1601, found *m*/*z* 306.1602.

*2,5-Diphenyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (**2g**).* Red solid: 4.55 g, 56%; mp 176−178 °C; IR (capillary) 3449, 3026, 2682, 2338, 2092, 1896, 1714, 1592, 1482, 1399, 1307, 1142, 925, 838, 687 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32−8.30 (m, 2H, ArH), 7.99−7.97 (m, 2H, ArH), 7.51−7.42 (m, 7H, ArH), 7.35−7.21 (m, 3H, ArH), 7.26−7.23 (m, 1H, ArH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.1, 150.7, 147.1, 146.9, 137.6, 130.8, 129.0 (2C), 128.8 (3C), 128.7 (2C), 128.2, 128.1 (2C), 125.9, 120.6 (2C), 118.7 (2C); MS (EI) *m*/*z* 324.8 M$^+$. Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52%; H, 4.65%; N, 12.91%. Found: C, 77.69%; H, 4.71%; N, 13.08%.

General Procedure for the Synthesis of Pyrazolone-Derived Ketones 3. Ketimine **2** (10 mmol) was dissolved in THF (0.13 M), and an aqueous HCl (2.0 N) solution (25 mL) was added to it at room temperature. The progress of the reaction was monitored via TLC. After completion of the reaction, the mixture was diluted with water. The organic layer was extracted three times with dichloromethane, and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to afford the desired product **3**.

DOI: 10.1021/acs.joc.7b01113
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*3-Methyl-1-phenyl-1H-pyrazole-4,5-dione (**3a**).* Red solid: 1.58 g, 84%; mp 119−121 °C; IR (capillary) 3083, 2078, 1765, 1722, 1591, 1492, 1434, 1416, 1370, 1279, 1151, 1086, 1039, 972, 913, 849, 763, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H, ArH), 7.44−7.40 (m, 2H, ArH), 7.26−7.22 (m, 1H, ArH), 2.18 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6, 149.2, 144.5, 137.0, 129.3 (2C), 126.3, 117.8 (2C), 11.1; MS (EI) *m*/*z* 188.1 M^+; HRMS (ESI) $[M]^+$ calcd for $C_{10}H_8N_2O_2$ *m*/*z* 188.0580, found *m*/*z* 188.0583.

*1-(4-Chlorophenyl)-3-methyl-1H-pyrazole-4,5-dione (**3b**).* Red solid: 1.71 g, 77%; mp 157−159 °C; IR (capillary) 3106, 2060, 1772, 1714, 1591, 1491, 1432, 1402, 1369, 1309, 1284, 1166, 1090, 1048, 1006, 855, 825, 736, 687 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H, ArH), 7.41 (d, *J* = 8.4 Hz, 2H, ArH), 2.23 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.3, 149.1, 144.8, 135.5, 131.6, 129.4 (2C), 118.9 (2C), 11.2; MS (EI) *m*/*z* 222.1 M^+; HRMS (ESI) $[M]^+$ calcd for $C_{10}H_7N_2O_2Cl$ *m*/*z* 222.0192, found *m*/*z* 222.0191.

*1-(4-Methylphenyl)-3-methyl-1H-pyrazole-4,5-dione (**3c**).* Red solid: 1.11 g, 55%; mp 116−119 °C; IR (capillary) 3192, 2349, 2099, 1703, 1507, 1368, 1220, 1117, 819, 674 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.73−7.71 (m, 2H, ArH), 7.24−7.22 (m, 2H, ArH), 2.36 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.9, 149.05, 144.4, 136.3, 134.6, 129.8 (2C), 117.9 (2C), 21.1, 11.1; MS (EI) *m*/*z* 202.1 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_2Na$ *m*/*z* 225.0634, found *m*/*z* 225.0633.

*3-Ethyl-1-phenyl-1H-pyrazole-4,5-dione (**3d**).* Red solid: 1.68 g, 83%; mp 128−130 °C; IR (capillary) 3351, 2962, 2094, 1707, 1478, 1353, 1094, 748 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.90−7.87 (m, 2H, ArH), 7.47−7.46 (m, 2H, ArH), 7.28−7.26 (m, 1H, ArH), 2.62−2.58 (m, 2H, CH_2CH_3), 1.33−1.31 (m, 3H, CH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.8, 149.4, 148.5, 137.1, 129.3 (2C), 126.4, 117.9 (2C), 19.5, 9.8; MS (EI) *m*/*z* 202.1 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_2Na$ *m*/*z* 225.0634, found *m*/*z* 225.0632.

*3-Isopropyl-1-phenyl-1H-pyrazole-4,5-dione (**3e**).* Red solid: 1.73 g, 80%; mp 51−53 °C; IR (capillary) 3337, 2968, 2092, 1710, 1067, 1085, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.89−7.87 (m, 2H, ArH), 7.46−7.46 (m, 2H, ArH), 7.27−7.24 (m, 1H, ArH), 2.97−2.92 [m, 1H, $CH(CH_3)_2$], 1.33 [d, *J* = 7.0 Hz, 6H, $CH(CH_3)_2$]; ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.7, 151.4, 149.3, 137.0, 129.2 (2C), 126.3, 117.8 (2C), 27.0, 19.1 (2C); MS (EI) *m*/*z* 216.2 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{12}H_{13}N_2O_2$ *m*/*z* 217.0971, found *m*/*z* 217.0968.

*3-tert-Butyl-1-phenyl-1H-pyrazole-4,5-dione (**3f**).* Red solid: 1.98 g, 86%; mp 80−82 °C; IR (capillary) 3454, 2961, 2328, 2089, 1738, 1593, 1488, 1385, 1212, 1126, 1043, 942, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.90−7.88 (m, 2H, ArH), 7.46−7.43 (m, 2H, ArH), 7.28−7.25 (m, 1H, ArH), 1.37 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.3, 153.1, 148.9, 137.1, 129.2 (2C), 126.3, 117.8 (2C), 33.9, 27.1 (3C); MS (EI) *m*/*z* 230.2 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{13}H_{14}N_2O_2Na$ *m*/*z* 253.0947, found *m*/*z* 253.0947.

*1,3-Diphenyl-1H-pyrazole-4,5-dione (**3g**).* Red solid: 2.07 g, 83%; mp 165−166 °C; IR (capillary) 3452, 2926, 2332, 2097, 1729, 1590, 1482, 1390, 1143, 912, 747 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.19−8.17 (m, 2H, ArH), 7.99−7.97 (m, 2H, ArH), 7.53−7.48 (m, 5H, ArH), 7.32−7.29 (m, 1H, ArH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.1, 148.9, 141.2, 137.0, 132.0, 129.4 (2C), 129.3 (2C), 127.3 (2C), 126.7, 126.6, 118.1 (2C); MS (EI) *m*/*z* 250.1 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{15}H_{10}N_2O_2Na$ *m*/*z* 273.0634, found *m*/*z* 273.0634.

General Procedure for the Synthesis of Pyrazolone-Derived *N*-Boc Ketimine 4. *tert*-Butyl(triphenylphosphoranylidene)acetate (1.1 equiv) was added to a solution of the pyrazolone-derived ketone **3** (0.5 mmol) in 1,4-dioxane (0.2 M) at room temperature, and the mixture was refluxed for 3−3.5 h. After the completion of the reaction, the solvent was removed under reduced pressure and the crude product was directly purified by flash column chromatography (*n*-pentane/diethyl ether, 1:1) to afford the desired *N*-Boc ketimine **4**.

*tert-Butyl (3-Methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)carbamate (**4a**).* Orange solid: 1.09 g, 76%; mp 173−175 °C; IR (capillary) 2979, 2319, 2110, 1722, 1596, 1482, 1369, 1250, 1143, 843, 759 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H, ArH), 7.42−7.40 (m, 2H, ArH), 7.24−7.21 (m, 1H, ArH), 2.28 (s, 3H, Me), 1.64 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 153.9, 150.2, 150.0, 137.0, 129.1 (2C), 126.0, 118.3 (2C), 85.4, 28.1 (3C), 12.1; MS (EI) *m*/*z* 286.9 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{15}H_{17}N_3O_3Na$ *m*/*z* 310.1162, found *m*/*z* 310.1161.

*tert-Butyl [1-(4-Chlorophenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]carbamate (**4b**).* Orange solid: 1.13 g, 70%; mp 148−150 °C; IR (capillary) 2980, 2315, 2115, 1735, 1482, 1368, 1239, 1145, 836, 759 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H, ArH), 7.37 (d, *J* = 8.5 Hz, 2H, ArH), 2.29 (s, 3H, Me), 1.63 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7, 153.6, 150.6, 150.0, 135.6, 131.2, 129.2 (2C), 119.4 (2C), 85.6, 28.1 (3C), 12.1; MS (EI) *m*/*z* 320.9 M^+; HRMS (ESI) $[M + K]^+$ calcd for $C_{15}H_{16}N_3O_3ClK$ *m*/*z* 360.0512, found *m*/*z* 360.0513.

*tert-Butyl [1-(4-Methylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]carbamate (**4c**).* Orange solid: 1.13 g, 75%; mp 170−172 °C; IR (capillary) 2986, 1727, 1612, 1517, 1440, 1368, 1313, 1249, 1147, 1036, 988, 880, 818, 772 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H, ArH), 7.21 (d, *J* = 8.3 Hz, 2H, ArH), 2.35 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.63 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8, 153.9, 149.9, 149.8, 135.7, 134.5, 129.6 (2C), 118.3 (2C), 85.3, 28.0 (3C), 21.0, 12.0; MS (EI) *m*/*z* 301.7 M^+. Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77%; H, 6.36%; N, 13.94%. Found: C, 63.44%; H, 6.55%; N, 13.52%.

*tert-Butyl (3-Ethyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)carbamate (**4d**).* Orange solid: 1.13 g, 75%; mp 103−105 °C; IR (capillary) 2972, 2339, 2103, 1717, 1595, 1483, 1349, 1250, 1141, 839, 762 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86−7.84 (m, 2H, ArH), 7.43−7.30 (m, 2H, ArH), 7.24−7.21 (m, 1H, ArH), 2.68 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 1.64 (s, 9H, *t*-Bu), 1.35 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 154.1, 153.6, 150.3, 137.1, 129.1 (2C), 126.0, 118.4 (2C), 85.3, 28.1 (3C), 20.2, 10.2; MS (EI) *m*/*z* 301.2 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{16}H_{19}N_3O_3Na$ *m*/*z* 324.1319, found *m*/*z* 324.1318.

*tert-Butyl (3-Isopropyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)carbamate (**4e**).* Orange solid: 1.37 g, 87%; mp 114−116 °C; IR (capillary) 2975, 2306, 2115, 1728, 1597, 1497, 1369, 1251, 1150, 1045, 980, 845, 749, 684 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 2H, ArH), 7.45−7.40 (m, 2H, ArH), 7.23 (t, *J* = 7.4 Hz, 1H, ArH), 3.12−3.02 [m, 1H, $CH(CH_3)_2$], 1.64 (s, 9H, *t*-Bu), 1.37 [d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$]; ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 157.0, 153.0, 150.2, 137.1, 129.0 (2C), 125.8, 118.3 (2C), 85.1, 28.0 (3C), 27.4, 19.7 (2C); MS (EI) *m*/*z* 315.7 M^+. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74%; H, 6.71%; N, 13.32%. Found: C, 64.63%; H, 6.60%; N, 13.19%.

*tert-Butyl (3-tert-Butyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)carbamate (**4f**).* Orange solid: 1.39 g, 84%; mp 111−113 °C; IR (capillary) 2975, 1727, 1597, 1493, 1371, 1309, 1249, 1147, 1049, 968, 845, 748, 685 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 2H, ArH), 7.44−7.40 (m, 2H, ArH), 7.23 (t, *J* = 7.4 Hz, 1H, ArH), 1.64 (s, 9H, *t*-Bu), 1.43 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 158.4, 152.4, 150.0, 137.1, 129.0 (2C), 125.8, 118.2 (2C), 84.9, 34.9, 28.1 (3C), 27.8 (3C); MS (EI) *m*/*z* 329.7 M^+. Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63%; H, 7.04%; N, 12.76%. Found: C, 65.35%; H, 7.07%; N, 12.77%.

*tert-Butyl [5-Oxo-1,3-diphenyl-1H-pyrazol-4(5H)-ylidene]-carbamate (**4g**).* Orange solid: 1.43 g, 82%; mp 176−178 °C; IR (capillary) 2982, 2293, 2107, 1731, 1595, 1493, 1369, 1325, 1239, 1145, 1060, 984, 930, 846, 749, 684 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.3 Hz, 2H, ArH), 7.95 (d, *J* = 7.7 Hz, 2H, ArH), 7.54−7.44 (m, 5H, ArH), 7.27 (t, *J* = 8.4 Hz, 1H, ArH), 1.67 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 152.8, 149.9, 146.8, 137.0, 131.2, 129.1 (2C), 128.8 (2C), 128.1, 127.4 (2C), 126.2, 118.5 (2C), 85.3, 28.0 (3C); MS (EI) *m*/*z* 349.7 M^+. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75%; H, 5.48%; N, 12.03%. Found: C, 68.54%; H, 5.29%; N, 11.87%.

General Procedure for the Synthesis of 5 and *ent*-5. In a 10 mL reaction tube equipped with a magnetic stirring bar, imine **4** (1.1 equiv, 0.22 mmol), catalyst **C-2** or **C-5** (2 mol %), and 4 Å molecular sieves (50 mg) were stirred in dichloromethane (1.0 mL) at −48 °C. After 10 min, pyrazolone **1** (1.0 equiv. 0.2 mmol) was added and the

DOI: 10.1021/acs.joc.7b01113
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stirring was continued for 24 h at the same temperature. The reaction mixture was kept at room temperature for 1 h, and the crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to afford product **5** or *ent*-**5**.

*tert-Butyl (S)-(5-Hydroxy-3,3′-dimethyl-5′-oxo-1,1′-diphenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5a**).* Colorless solid: 91 mg, 99%; mp 143−145 °C; $[\alpha]_D^{24}$ = −56.0 (*c* = 0.5, $CHCl_3$); IR (capillary) 2974, 2322, 2093, 1730, 1473, 1366, 1210, 744 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.99−7.91 (m, 2H, ArH), 7.54−7.52 (m, 2H, ArH), 7.47−7.40 (m, 4H, ArH), 7.32 (t, *J* = 7.4 Hz, 1H, ArH), 7.20 (t, *J* = 7.4 Hz, 1H, ArH), 2.15 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 1.43 (s, 6H, *t*-Bu), 1.27 (s, 3H, *t*-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.1, 162.1, 161.3, 155.9, 146.8, 139.4, 136.3, 130.4, 130.0, 129.9, 128.3, 126.3, 123.0, 120.0, 119.1, 94.9, 81.7, 66.4, 28.6, 13.5, 11.7; MS (EI) *m*/*z* 461.0 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{25}H_{27}N_5O_4Na$ *m*/*z* 484.1955, found *m*/*z* 484.1951.

*tert-Butyl (S)-[1-(2-Chlorophenyl)-5-hydroxy-3,3′-dimethyl-5′-oxo-1′-phenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**5b**).* Colorless solid: 90 mg, 91%; mp 150−152 °C; $[\alpha]_D^{24}$ = −38.0 (*c* = 0.5, $CHCl_3$); 93.5:6.5 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 148 bar, 230 nm] t_R = 5.35 min (minor), t_R = 8.51 min (major); IR (capillary) 2976, 2927, 2099, 1713, 1598, 1483, 1393, 1362, 1312, 1254, 1159, 1088, 1061, 1028, 938, 837, 749, 691 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.94−7.91 (br m, 2H, ArH), 7.64−7.61 (m, 1H, ArH), 7.55−7.41 (m, 5H, ArH), 7.22 (t, *J* = 7.4 Hz, 1H, ArH), 2.12 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.42−1.27 (br m, 9H, *t*-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.1, 163.3, 162.2, 161.4, 155.9, 146.6, 139.4, 134.3, 133.4, 132.8, 131.8, 131.7, 129.9, 129.2, 126.4, 126.1, 120.1, 119.2, 93.7, 81.7, 66.5, 28.5, 13.3, 11.6; MS (ESI) *m*/*z* 495.2 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{25}H_{27}N_5O_4Cl$ *m*/*z* 496.1746, found *m*/*z* 496.1734.

*tert-Butyl (S)-[1-(4-Chlorophenyl)-5-hydroxy-3,3′-dimethyl-5′-oxo-1′-phenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**5c**).* Colorless solid: 98 mg, 99%; mp 148−150 °C; $[\alpha]_D^{24}$ = +134.0 (*c* = 0.5, $CHCl_3$); 93:7 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 150 bar, 236 nm] t_R = 8.22 min (minor), t_R = 8.78 min (major); IR (capillary) 2977, 2928, 2080, 1708, 1628, 1595, 1561, 1489, 1396, 1364, 1312, 1253, 1158, 1090, 1049, 1013, 933, 887, 830, 753, 690 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.92−7.90 (br m, 2H, ArH), 7.59−7.56 (m, 2H, ArH), 7.48−7.39 (m, 4H, ArH), 7.23−7.19 (m, 1H, ArH), 2.11 (s, 6H, $2CH_3$), 1.43−1.25 (m, 9H, *t*-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.2, 162.5, 161.4, 156.0, 147.8, 139.4, 135.6, 133.3, 130.4, 129.9, 126.3, 124.1, 120.1, 119.2, 94.7, 81.7, 66.5, 28.5, 13.5, 11.9; MS (ESI) *m*/*z* 495.2 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{25}H_{27}N_5O_4Cl$ *m*/*z* 496.1746, found *m*/*z* 496.1744.

*tert-Butyl (S)-[5-Hydroxy-3,3′-dimethyl-5′-oxo-1′-phenyl-1-(p-tolyl)-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**5d**).* Colorless solid: 91 mg, 96%; mp 144−146 °C; $[\alpha]_D^{24}$ = −92.0 (*c* = 0.5, $CHCl_3$); 95:5 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 152 bar, 209 nm] t_R = 16.71 min (minor), t_R = 19.12 min (major); IR (capillary) 2977, 2926, 2107, 1715, 1596, 1492, 1395, 1363, 1309, 1277, 1255, 1159, 1118, 1077, 1049, 1023, 970, 937, 888, 817, 755, 691 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.98−7.91 (br m, 2H, ArH), 7.43−7.39 (m, 4H, ArH), 7.28 (d, *J* = 8.2 Hz, 2H, ArH), 7.22−7.19 (m, 1H, ArH), 2.36 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.43 (s, 6H *t*-Bu), 1.27 (s, 3H, *t*-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.1, 162.1, 161.3, 155.9, 146.2, 139.4, 138.7, 133.7, 130.9, 129.9, 126.3, 126.1, 123.4, 120.1, 119.1, 94.7, 81.7, 66.5, 28.6, 21.1, 13.4, 11.5; MS (ESI) *m*/*z* 475.3 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{26}H_{30}N_5O_4$ *m*/*z* 476.2292, found *m*/*z* 476.2294.

*tert-Butyl (S)-(5-Hydroxy-1,3,3′-trimethyl-5′-oxo-1′-phenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5e**).* Colorless solid: 71 mg, 89%; mp 207−209 °C; $[\alpha]_D^{24}$ = −90.0 (*c* = 0.5, $CHCl_3$); 91:9 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 149 bar, 230 nm] t_R = 3.30 min (minor), t_R = 3.95 min (major); IR (capillary) 3182, 2976, 2932, 2093, 1714, 1595, 1493, 1393, 1362, 1306, 1255, 1159, 1073, 1028, 953, 885, 837, 755, 690 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.94−7.87 (m, 2H, ArH), 7.43−7.40 (m, 2H, ArH), 7.20 (t, *J* = 7.5 Hz, 1H, ArH), 3.40 (s, 3H, CH_3), 2.14−2.02 (m, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.43 (s, 6H, *t*-Bu), 1.26 (s, 3H, *t*-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.2, 162.9, 161.4, 155.9, 143.8, 139.4, 129.9, 126.3, 126.1, 120.1, 119.1, 93.9, 81.6, 66.5, 30.4, 28.5, 28.4, 13.2, 11.2; MS (EI) *m*/*z* 399.2 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{26}N_5O_4$ *m*/*z* 400.1979, found *m*/*z* 400.1979.

*tert-Butyl (S)-(3-Ethyl-5-hydroxy-3′-methyl-5′-oxo-1,1′-diphenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5f**).* Colorless solid: 90 mg, 95%; mp 144−146 °C; $[\alpha]_D^{24}$ = +24.0 (*c* = 0.5, $CHCl_3$); 94.5:5.5 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 156 bar, 241 nm] t_R = 6.73 min (minor), t_R = 7.53 min (major); IR (capillary) 2965, 1711, 1599, 1480, 1365, 1366, 1162, 7438 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.92 (br s, 2H, ArH), 7.58−7.56 (m, 2H, ArH), 7.51−7.48 (m, 2H, ArH), 7.45−7.32 (m, 2H, ArH), 7.37−7.35 (m, 1H, ArH), 7.22 (t, *J* = 7.4 Hz, 1H, ArH), 2.56−2.46 (m, 2H, CH_2CH_3), 2.12 (s, 3H, CH_3), 1.43 (br s, 6H, *t*-Bu), 1.29 (br s, 3H, *t*-Bu), 1.11 (t, *J* = 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (151 MHz, CD_3OD) δ 173.4, 162.8, 161.7, 155.9, 152.2, 139.4, 136.4, 130.4, 129.9, 128.5, 126.4, 123.6, 120.1, 119.1, 94.2, 81.7, 66.5, 28.5, 19.9, 13.4, 12.7; MS (EI) *m*/*z* 475.2 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{26}H_{29}N_5O_4Na$ *m*/*z* 498.2098, found *m*/*z* 498.2112.

*tert-Butyl (S)-(5-Hydroxy-3′-methyl-5′-oxo-1,1′-diphenyl-3-propyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5g**).* Colorless solid: 94 mg, 96%; mp 144−146 °C; $[\alpha]_D^{24}$ = +4.0 (*c* = 0.5, $CHCl_3$); 92:8 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 148 bar, 229 nm] t_R = 6.16 min (minor), t_R = 6.91 min (major); IR (capillary) 2965, 2087, 1709, 1471, 1170, 734 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.97−7.95 (m, 2H, ArH), 7.58−7.55 (m, 2H, ArH), 7.52−7.48 (m, 2H, ArH), 7.46−7.42 (m, 2H, ArH), 7.39−7.35 (m, 1H, ArH), 7.22 (t, *J* = 7.5 Hz, 1H, ArH), 2.45−2.31 (m, 2H, $CH_2CH_2CH_3$), 2.10 (s, 3H, CH_3), 1.55−1.47 (m, 2H, $CH_2CH_2CH_3$), 1.41 (br s, 6H, *t*-Bu), 2.38 (br s, 3H, *t*-Bu), 0.74 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (151 MHz, CD_3OD) δ 173.3, 162.9, 161.8, 155.8, 150.6, 139.4, 136.3, 130.4, 129.0, 129.9, 128.5, 126.3, 123.5, 119.8, 118.9, 94.3, 81.7, 66.7, 28.5, 28.4, 24.2, 22.7, 14.1, 13.3; MS (EI) *m*/*z* 489.0 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{27}H_{31}N_5O_4Na$ *m*/*z* 512.2268, found *m*/*z* 512.2250.

*tert-Butyl (S)-(5-Hydroxy-3-isopropyl-3′-methyl-5′-oxo-1,1′-diphenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5h**).* Colorless solid: 83 mg, 85%; mp 151−153 °C; $[\alpha]_D^{24}$ = +8.9 (*c* = 0.5, $CHCl_3$); 93:7 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 149 bar, 230 nm] t_R = 4.54 min (minor), t_R = 5.65 min (major); IR (capillary) 3230, 2960, 2281, 2286, 1723, 1580, 1356, 1165, 911, 728 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.90 (br s, 2H, ArH), 7.56−7.40 (m, 4H, ArH), 7.46−7.37 (m, 3H, ArH), 7.23 (t, *J* = 7.4 Hz, 1H, ArH), 3.02−2.98 [m, 1H, $CH(CH_3)_2$], 2.15−2.12 (m, 3H, CH_3), 1.42 (br s, 6H, *t*-Bu), 1.30 (br s, 3H, *t*-Bu), 1.19 [d, *J* = 6.9 Hz, 3H, $CH(CH_3)_2$], 1.15 [d, *J* = 6.9 Hz, 3H, $CH(CH_3)_2$]; ^{13}C NMR (151 MHz, CD_3OD) δ 173.5, 162.7, 161.8, 156.4, 155.8, 139.4, 136.3, 130.7, 129.9, 128.8, 126.4, 124.4, 120.2, 119.1, 93.3, 81.6, 66.6, 28.5, 26.6, 21.4, 21.3, 13.4; MS (EI) *m*/*z* 489.0 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{27}H_{31}N_5O_4Na$ *m*/*z* 512.2268, found *m*/*z* 512.2251.

*tert-Butyl (S)-[5-Hydroxy-3′-methyl-5′-oxo-1,1′-diphenyl-3-(trifluoromethyl)-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**5i**).* Brown solid: 73 mg, 71%; mp 132−134 °C; $[\alpha]_D^{24}$ = +114.0 (*c* = 0.5, $CHCl_3$); IR (capillary) 2976, 2926, 2097, 1700, 1597, 1563, 1494, 1367, 1305, 1231, 1153, 1121, 1057, 1029, 1006, 917, 836, 756, 728, 692 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.87 (d, *J* = 8.1 Hz, 2H, ArH), 7.70 (d, *J* = 8.1 Hz, 2H, ArH), 7.47−7.39 (m, 4H, ArH), 7.33−7.29 (m, 1H, ArH), 7.21−7.18 (m, 1H, ArH), 2.08 (s, 3H, CH_3), 1.44−1.29 (m, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 160.7, 155.8, 139.9, 139.7, 138.2, 130.2, 129.9, 129.6, 127.8, 126.0, 124.4, 124.0, 122.8, 120.4, 88.2, 81.6, 30.7, 28.6, 13.2; MS (ESI) *m*/*z* 538.2 $[M + Na]^+$; HRMS (ESI) $[M + Na]^+$ calcd for $C_{25}H_{24}N_5O_4F_3Na$ *m*/*z* 538.1673, found *m*/*z* 538.1663.

*tert-Butyl (S)-[1′-(4-Chlorophenyl)-5-hydroxy-3,3′-dimethyl-5′-oxo-1-phenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**5j**).* Colorless solid: 98 mg, 99%; mp 141−143 °C; $[\alpha]_D^{24}$ = −102.0 (*c* = 0.5, $CHCl_3$); 94.5:5.5 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 149 bar, 219 nm] t_R = 9.46 min (minor), t_R = 10.45 min (major); IR (capillary) 2977, 2927, 2098, 1716, 1601, 1488,

DOI: 10.1021/acs.joc.7b01113
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1394, 1362, 1308, 1159, 1084, 1013, 968, 937, 887, 831, 757, 731, 685 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.99−7.93 (m, 2H, ArH), 7.54 (d, J = 7.9 Hz, 2H, ArH), 7.48−7.45 (m, 2H, ArH), 7.42 (d, J = 8.6 Hz, 2H, ArH), 7.34−7.32 (m, 1H, ArH), 2.13 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.43 (s, 6H, t-Bu), 1.29−1.25 (m, 3H, t-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.0, 152.3, 161.6, 156.0, 147.0, 138.2, 136.4, 131.2, 130.4, 129.9, 128.3, 123.0, 121.2, 120.4, 95.0, 81.7, 66.3, 28.5, 13.6, 11.7; MS (EI) m/z 495.3 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{25}H_{27}N_5O_4Cl$ m/z 496.1746, found m/z 496.1743.

*tert-Butyl (S)-[5-Hydroxy-3,3′-dimethyl-5′-oxo-1-phenyl-1′-(p-tolyl)-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**5k**).* Colorless solid: 94 mg, 99%; mp 141−142 °C; $[\alpha]_D^{24}$ = −70.0 (c = 0.5, $CHCl_3$); >99:1 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 150 bar, 254 nm] t_R = 11.82 min (minor), t_R = 12.16 min (major); IR (capillary) 2977, 2925, 2087, 1715, 1611, 1491, 1395, 1363, 1309, 1278, 1254, 1159, 1121, 1176, 1020, 969, 937, 889, 818, 758, 729, 686 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.84−7.76 (br m, 2H, ArH), 7.57−7.55 (m, 2H, ArH), 7.49−7.47 (m, 2H, ArH), 7.35−7.33 (m, 1H, ArH), 7.24 (d, J = 8.2 Hz, 2H, ArH), 2.34 (s, 3H, CH_3), 2.14−2.10 (m, 6H, $2CH_3$), 1.43 (s, 6H, t-Bu), 1.23−1.27 (m, 3H, t-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.0, 162.0, 161.3, 155.9, 155.3, 146.9, 136.9, 136.4, 136.3, 130.4, 130.3, 128.3, 123.1, 120.3, 119.2, 95.0, 81.7, 66.4, 28.6, 21.0, 13.4, 11.5; MS (EI) m/z 475.2 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{26}H_{30}N_5O_4$ m/z 476.2292, found m/z 476.2288.

*tert-Butyl (S)-(3′-Ethyl-5-hydroxy-3-methyl-5′-oxo-1,1′-diphenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5l**).* Colorless solid: 87 mg, 92%; mp 136−138 °C; $[\alpha]_D^{24}$ = −146.0 (c = 0.5, $CHCl_3$); IR (capillary) 2977, 2934, 2321, 2097, 1715, 1597, 1490, 1392, 1367, 1306, 1248, 1159, 1075, 1044, 1021, 933, 888, 835, 755, 688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.83 (s, 1H, br s, OH), 8.90 (s, 1H, NH), 7.89 (d, J = 8.0 Hz, 2H, ArH), 7.55 (d, J = 8.0 Hz, 2H, ArH), 7.39−7.31 (m, 4H, ArH), 7.19−7.15 (m, 2H, ArH), 2.29−2.27 (m, 2H, CH_2CH_3), 1.77 (s, 3H, CH_3), 1.26 (s, 9H, t-Bu), 1.15−1.14 (m, 3H, CH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3, 164.2, 162.7, 154.3, 146.1, 137.8, 135.6, 129.2, 129.1, 126.5, 125.7, 121.0, 120.5, 119.2, 118.1, 95.2, 80.4, 69.9, 28.2, 20.9, 11.5, 9.9; MS (EI) m/z 475.3 M^+. Anal. Calcd for $C_{26}H_{29}N_5O_4$: C, 65.67%; H, 6.15%; N, 14.73%. Found: C, 65.54%; H, 6.17%; N, 14.43%.

*tert-Butyl (S)-(5-Hydroxy-3′-isopropyl-3-methyl-5′-oxo-1,1′-diphenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5m**).* Colorless solid: 93 mg, 95%; mp 145−147 °C; $[\alpha]_D^{24}$ = −186.2 (c = 0.6, $CHCl_3$); IR (capillary) 2974, 2931, 2107, 1715, 1597, 1490, 1369, 1305, 1249, 1160, 1078, 1023, 979, 899, 834, 755, 689, 660 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 8.02−7.94 (m, 2H, ArH), 7.57−7.55 (m, 2H, ArH), 7.51−7.48 (m, 2H, ArH), 7.46−7.43 (m, 2H, ArH), 7.37−7.34 (m, 1H, ArH), 7.23 (t, J = 7.4 Hz, 1H, ArH), 2.81−2.78 [m, 1H, $CH(CH_3)_2$], 1.98 (s, 3H, CH_3), 1.42 (s, 6H, t-Bu), 1.37−1.18 [m, 3H, t-Bu, 6H, $CH(CH_3)_2$]; ^{13}C NMR (151 MHz, CD_3OD) δ 173.0, 167.3, 163.0, 155.7, 146.1, 139.4, 139.4, 136.3, 130.5, 129.9, 128.4, 126.4, 123.1, 120.1, 119.1, 95.0, 81.6, 66.8, 29.6, 28.6, 28.4, 21.3, 21.2, 11.2; MS (EI) m/z 489.3 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{27}H_{31}N_5O_4Na$ m/z 512.2268, found m/z 512.2256.

*tert-Butyl (S)-(3′-tert-Butyl-5-hydroxy-3-methyl-5′-oxo-1,1′-diphenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5n**).* Colorless solid: 68 mg, 67%; mp 165−158 °C; $[\alpha]_D^{24}$ = −108.0 (c = 0.5, $CHCl_3$); 80:20 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 151 bar, 230 nm] t_R = 17.83 min (minor), t_R = 18.94 min (major); IR (capillary) 2977, 2932, 2097, 1713, 1595, 1492, 1393, 1362, 1305, 1254, 1158, 1073, 1029, 953, 885, 838, 794, 755, 690 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 8.04−7.94 (m, 2H, ArH), 7.58−7.57 (m, 2H, ArH), 7.52−7.49 (m, 2H, ArH), 7.46−7.43 (m, 2H, ArH), 7.38−7.36 (m, 1H, ArH), 7.24 (t, J = 7.5 Hz, 1H), 1.94 (s, 3H, CH_3), 1.42 (s, 6H, t-Bu), 1.34 (s, 3H, t-Bu), 1.31 (s, 6H, t-Bu), 1.26 (s, 3H, t-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.2, 167.7, 163.0, 155.6, 145.7, 139.3, 136.3, 130.5, 130.1, 129.9, 128.5, 126.4, 126.2, 123.3, 120.0, 119.0, 95.7, 81.5, 66.9, 37.0, 29.5, 29.3, 28.6, 28.4, 10.9; MS (EI) m/z 503.3 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{33}N_5O_4Na$ m/z 526.2424, found m/z 526.2419.

*tert-Butyl (S)-(5-Hydroxy-3-methyl-5′-oxo-1,1′,3′-triphenyl-1′,5′-dihydro-1H,4′H-[4,4′-bipyrazol]-4′-yl)carbamate (**5o**).* Colorless solid: 97 mg, 93%; mp 155−156 °C; $[\alpha]_D^{24}$ = −8.0 (c = 0.5, $CHCl_3$); 87:13 er; SFC [(*R*,*R*)-Whelk-O1 column, MeOH/CO_2, 4.00 mL/min, 148 bar, 230 nm] t_R = 12.68 min (minor), t_R = 13.45 min (major); IR (capillary) 2977, 2929, 2098, 1717, 1597, 1490, 1371, 1292, 1254, 1156, 1115, 1074, 1023, 949, 917, 878, 837, 796, 756, 688 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 8.12−8.03 (m, 4H, ArH), 7.56−7.54 (m, 2H, ArH), 7.49−7.42 (m, 7H, ArH), 7.33 (t, J = 7.5 Hz, 1H, ArH), 7.28−7.25 (m, 1H, ArH), 1.99 (s, 3H, CH_3), 1.31 (s, 6H, t-Bu), 1.14 (s, 3H, t-Bu); ^{13}C NMR (151 MHz, CD_3OD) δ 173.5, 162.5, 157.7, 155.8, 146.1, 139.3, 136.2, 131.9, 130.4, 130.0, 129.9, 128.4, 127.7, 126.7, 123.2, 120.3, 119.4, 95.5, 81.7, 65.8, 28.5, 28.3, 11.2; MS (EI) m/z 523.3 M^+; HRMS (ESI) $[M + H]^+$ calcd for $C_{30}H_{30}N_5O_4$ m/z 524.2292, found m/z 524.2290.

General Procedure for the Acylation of Product 5. In a 10 mL reaction tube equipped with a magnetic stirring bar, amino-bis-pyrazolone **5** (1 equiv, 0.1 mmol) was stirred in dichloromethane (1.0 mL) at room temprature followed by the addition of Ac_2O (2.0 equiv, 0.2 mmol) and triethylamine (0.3 equiv, 0.03 mmol). The stirring was continued for 3 h at room temperature, and the crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) to afford the enolacetate product **6**.

*(S)-4′-[(tert-Butoxycarbonyl)amino]-3,3′-dimethyl-5′-oxo-1,1′-diphenyl-4′,5′-dihydro-1H,1′H-[4,4′-bipyrazol]-5-yl Acetate (**6a**).* Colorless solid: 49 mg, 97%; mp 179−181 °C; 98.5:1.5 er; HPLC (chiralpak AD column, *n*-heptane/*i*-PrOH, 8:2, 1.0 mL/min, 254 nm) t_R = 9.90 min (minor), t_R = 15.67 min (major); IR (capillary) 3294, 2929, 1656, 1530, 1446, 1367, 1241, 1051, 752, 691 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.94−7.93 (m, 2H, ArH), 7.42−7.37 (m, 6H, ArH), 7.35−7.33 (m, 1H, ArH), 7.18−7.16 (m, 1H, ArH), 5.57 (br s, 1H, NH), 2.46 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.39 (s, 9H, t-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 166.7, 159.2, 153.8, 146.8, 141.5, 138.2, 137.3, 129.4, 129.0, 128.3, 125.1, 123.5, 118.7, 101.4, 64.5, 28.2, 20.1, 15.0, 14.2; MS (EI) m/z 503.0 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{27}H_{29}N_5O_5Na$ m/z 526.2061, found m/z 526.2064.

*(S)-4′-[(tert-Butoxycarbonyl)amino]-3′-ethyl-3-methyl-5′-oxo-1,1′-diphenyl-4′,5′-dihydro-1H,1′H-[4,4′-bipyrazol]-5-yl Acetate (**6l**).* Colorless wax: 50 mg, 97%; 98.5:1.5 er; HPLC (chiralpak IA column, *n*-heptane/*i*-PrOH, 7:3, 0.5 mL/min, 254 nm) t_R = 13.86 min (minor), t_R = 20.54 min (major); IR (capillary) 3278, 2970. 2325, 1719, 1591, 1477, 1358, 1155, 1050, 876, 751 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.98−7.99 (m, 2H, ArH), 7.42−7.38 (m, 6H, ArH), 7.34−7.32 (m, 1H, ArH), 7.18−7.16 (m, 1H, ArH), 5.57 (s, 1H, NH), 2.51−2.43 (m, 2H, CH_2CH_3), 2.43 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 1.37 (br s, 9H, t-Bu), 1.31 (d, J = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 166.7, 162.8, 146.6, 141.5, 138.4, 137.3, 129.4, 129.0, 128.3, 125.1, 101.8, 64.5, 28.4, 28.2, 21.5, 20.1, 15.0, 9.5; MS (EI) m/z 517.4 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{31}N_5O_5Na$ m/z 540.2217, found m/z 540.2211.

*(S)-4′-[(tert-Butoxycarbonyl)amino]-3′-isopropyl-3-methyl-5′-oxo-1,1′-diphenyl-4′,5′-dihydro-1H,1′H-[4,4′-bipyrazol]-5-yl Acetate (**6m**).* Colorless wax: 51 mg, 96%; 98.5:1.5 er; HPLC (chiralpak IA column, *n*-heptane/*i*-PrOH, 7:3, 0.5 mL/min, 254 nm) t_R = 15.93 min (minor), t_R = 17.10 min (major); IR (capillary) 3238, 2965. 2309, 1716, 1594, 1480, 1361, 1155, 871, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 2H, ArH), 7.43−7.39 (m, 6H, ArH), 7.35−7.33 (m, 1H, ArH), 7.19−7.16 (m, 1H, ArH), 5.74 (s, 1H, NH), 2.83−2.64 [m, 1H, $CH(CH_3)_2$], 2.37 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.41−1.22 [br m, 9H, t-Bu, 3H, $CH(CH_3)_2$], 1.23−1.22 [m, 3H, $CH(CH_3)_2$]; ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 166.6, 165.4, 153.9, 146.2, 141.6, 138.3, 137.3, 129.4, 129.0, 128.3, 125.0, 123.5, 118.6, 101.8, 53.6, 28.4, 28.2, 21.0, 20.8, 20.1, 14.9; MS (EI) m/z 531.4 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{29}H_{33}N_5O_5Na$ m/z 554.2374, found m/z 554.2374.

General Procedure for the Synthesis of 8 and *ent*-8. In a 10 mL reaction tube equipped with a magnetic stirring bar, imine **4a** (1.1 equiv, 0.22 mmol), catalyst **C-2** or **C-5** (2 mol %), and 4 Å molecular sieves (50 mg) were stirred in dichloromethane (1.0 mL) at −48 °C.

DOI: 10.1021/acs.joc.7b01113
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After 10 min, pyrazolone **7** (1.0 equiv, 0.2 mmol) was added and the stirring was continued for 24 h at the same temperature. The reaction mixture was kept at room temperature for 1 h, and the crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to afford product **8** or *ent*-**8**.

*tert-Butyl [(4S,4′S)-3′,4-Dimethyl-5,5′-dioxo-1,1′-diphenyl-3-(phenylethynyl)-1′,4,5,5′-tetrahydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]-carbamate (**8a**).* Colorless solid: 102 mg, 88%; mp 97−98 °C; $[\alpha]_D^{24}$ = −144.0 (*c* = 0.5, $CHCl_3$); 96.5:3.5 er; HPLC [(*S*,*S*)-Whelk-O1 column, *n*-heptane/*i*-PrOH, 9:1, 1.0 mL/min, 230 nm] t_R = 12.00 min (minor), t_R = 13.93 min (major); IR (capillary) 3333, 2979, 2209, 1720, 1483, 1359, 1147, 878, 748 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84−7.83 (m, 2H, ArH), 7.76−7.74 (m, 2H, ArH), 7.61−7.59 (m, 2H, ArH), 7.48−7.40 (m, 5H, ArH), 7.30−7.25 (m, 3H, ArH), 7.13−7.11 (m, 2H, ArH, NH), 2.35 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.39 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.8, 169.7, 155.6, 154.4, 143.6, 137.7, 136.8, 132.2, 130.4, 129.1, 128.9, 128.8, 126.7, 125.3, 120.7, 120.3, 119.3, 99.4, 79.3, 68.3, 52.9, 28.2, 16.4, 16.2; MS (ESI) *m*/*z* 584.2 $[M + Na]^+$; HRMS (ESI) $[M + Na]^+$ calcd for $C_{33}H_{31}N_5O_4Na$ *m*/*z* 584.2268, found *m*/*z* 584.2266.

*tert-Butyl [(4S,4′S)-3,3′-Dimethyl-5,5′-dioxo-1,1′-diphenyl-4-(prop-2-yn-1-yl)-1′,4,5,5′-tetrahydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]-carbamate (**8b**).* Colorless solid: 86 mg, 86%; mp 94−96 °C; $[\alpha]_D^{24}$ = +48.0 (*c* = 0.5, $CHCl_3$); 94:6 er; HPLC [(*S*,*S*)-Whelk-O1 column, *n*-heptane/*i*-PrOH, 9:1, 1.0 mL/min, 254 nm] t_R = 10.60 min (minor), t_R = 12.92 min (major); IR (capillary) 3296, 2975, 2190, 1718, 1470, 1355, 1163, 878, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82−7.80 (m, 2H, ArH), 7.77−7.75 (m, 2H, ArH), 7.43−7.40 (m, 2H, ArH), 7.38−7.35 (m, 2H, ArH), 7.26−7.23 (m, 1H, ArH), 7.19−7.17 (m, 1H, ArH), 3.21 (dd, *J* = 16.4, 2.6 Hz, 1H, CH_2), 2.84 (dd, *J* = 16.4, 2.6 Hz, 1H, CH_2), 2.30 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 1.97 (t, *J* = 2.6 Hz, 1H, CH), 1.37 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 169.7, 156.2, 155.4, 137.4, 136.8, 129.1, 129.0, 126.4, 125.6, 120.4, 119.1, 75.4, 72.6, 67.7, 57.2, 28.2, 20.1, 16.5, 14.7; MS (EI) *m*/*z* 499.3 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{29}N_5O_4Na$ *m*/*z* 522.2109, found *m*/*z* 522.2112.

General Procedure for the Synthesis of 9. In a 10 mL reaction tube equipped with a magnetic stirring bar, imine **4a** (1.1 equiv, 0.22 mmol), catalyst **C-2** (1 mol %), and 4 Å molecular sieves (50 mg) were stirred in dichloromethane (1.0 mL) at −48 °C. After 10 min, pyrazolone **1a** (1.0 equiv, 0.2 mmol) was added and the stirring was continued for 24 h at the same temperature. The reaction mixture was warmed to room temperature. After 1 h, NFSI or NCS (1.5 equiv) and K_2CO_3 (1.5 equiv) were added, and the reaction mixture was stirred for 3.5 h at room temperature. The crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to afford product **9a** or **9b**.

*tert-Butyl [(4R,4′S)-4-Fluoro-3,3′-dimethyl-5,5′-dioxo-1,1′-diphenyl-1′,4,5,5′-tetrahydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**9a**).* Colorless solid: 59 mg, 62%; mp 75−77 °C; $[\alpha]_D^{24}$ = +180.0 (*c* = 0.5, $CHCl_3$); 98.5:1.5 er; HPLC (chiralpak IC column, *n*-heptane/*i*-PrOH, 9:1, 1.0 mL/min, 230 nm) t_R = 3.72 min (major), t_R = 5.09 min (minor); IR (capillary) 3379, 2931, 2083, 1717, 1493, 1369, 1247, 1157, 908, 831, 752, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 4H, ArH), 7.43−7.33 (m, 4H, ArH), 7.27−7.24 (m, 1H, ArH), 7.20−7.16 (s, 1H, ArH), 2.34 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.39 (s, 9H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 164.7, 156.7, 154.0, 152.2, 137.5, 136.2, 129.2, 129.1, 126.7, 125.9, 119.8, 119.2, 89.7, 82.0, 69.0, 28.2, 15.7, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −179.94; MS (EI) *m*/*z* 479.0 M^+; HRMS (ESI) $[M + Na]^+$ calcd for $C_{25}H_{26}N_5O_4FNa$ *m*/*z* 502.1861, found *m*/*z* 502.1862.

*tert-Butyl [(4R,4′S)-4-Chloro-3,3′-dimethyl-5,5′-dioxo-1,1′-diphenyl-1′,4,5,5′-tetrahydro-1H,4′H-[4,4′-bipyrazol]-4′-yl]carbamate (**9b**).* Colorless solid: 78 mg, 79%; mp 83−85 °C; $[\alpha]_D^{24}$ = −170.0 (*c* = 0.5, $CHCl_3$); 98.5:1.5 er; HPLC (chiralpak IA column, *n*-heptane/*i*-PrOH, 7:3, 0.7 mL/min, 230 nm) t_R = 5.24 min (minor), t_R = 5.70 min (major); IR (capillary) 3354, 2932, 2101, 1718, 1595, 1490, 1369, 1259, 1157, 1064, 902, 826, 745, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81−7.80 (m, 2H, ArH), 7.77−7.75 (m, 2H, ArH), 7.44−7.41 (m, 2H, ArH), 7.38−7.35 (m, 2H, ArH), 7.28−7.25 (m, 1H, ArH), 7.20−7.18 (m, 1H, ArH), 2.42 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 1.40 (s, 9H, *t*-Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 166.7, 156.9, 153.2, 137.4, 136.4, 129.2, 129.1, 126.7, 125.9, 120.0, 119.2, 82.04, 68.3, 62.2, 29.8, 28.2, 16.5, 14.0; MS (EI) *m*/*z* 494.9 M^+; HRMS (ESI) $[M + K]^+$ calcd for $C_{25}H_{26}N_5O_4ClK$ *m*/*z* 534.1305, found *m*/*z* 534.1305.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01113.

Crystallographic data for **6a** (CIF)
Crystallographic data for **8a** (CIF)
NMR spectra, HPLC data, and X-ray crystal structures of **6a** and **8a** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Mrs. Cornelia Vermeeren for her help with the SFC measurements.

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DOI: 10.1021/acs.joc.7b01113
J. Org. Chem. 2017, 82, 7050−7058