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Note

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

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

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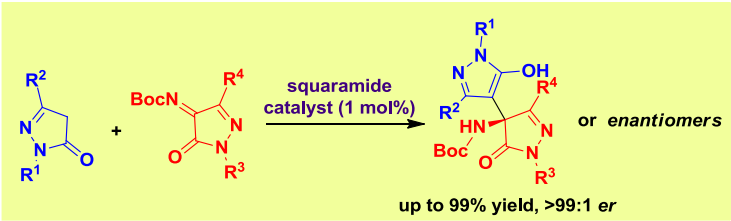
ABSTRACT: A new series of *N*-Boc ketimines derived from pyrazolin-5-ones have been used as electrophiles in asymmetric Mannich reactions with pyrazolones. The amino-bis-pyrazolone products are obtained in excellent yields and stereoselectivities by employing a very low loading of 1 mol% of a bifunctional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



Pyrazoles and pyrazolones, are a privileged class of five-membered aza-heterocycles that find 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 the pyrazolone derivatives are used as antipyretic drugs,[2] neuroprotective agents[3] HIV-1 integrase inhibitors[4], antibacterial agent,[5] etc. Due to 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-hetereocyclic 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 in order to obtain 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 which describe the formation of pyrazolones bearing a tetrasubstituted amino stereogenic center *via* the α-amination reaction of the 4-sustituted 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.

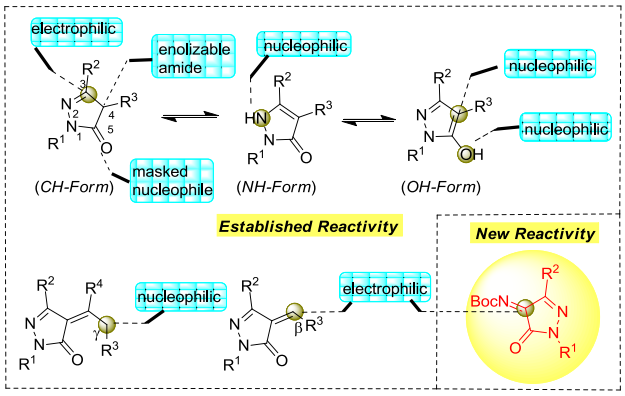
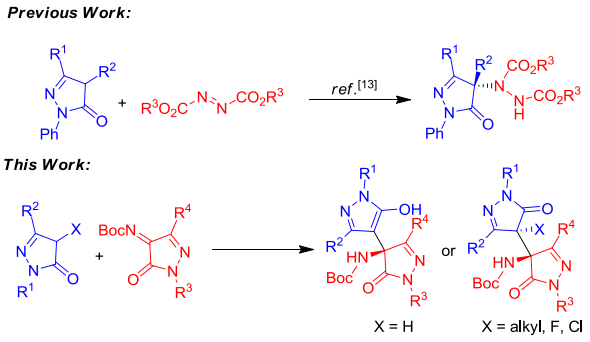


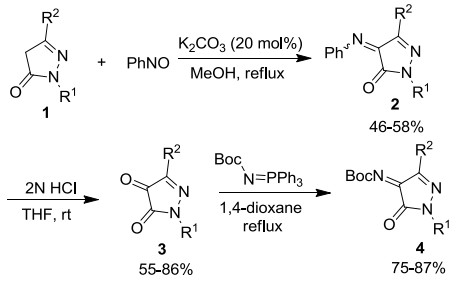
Figure 1. Reactive centers of pyrazolin-5-one derivatives.

Scheme 1. Asymmetric synthesis of *N*-protected amino-pyrazolones.



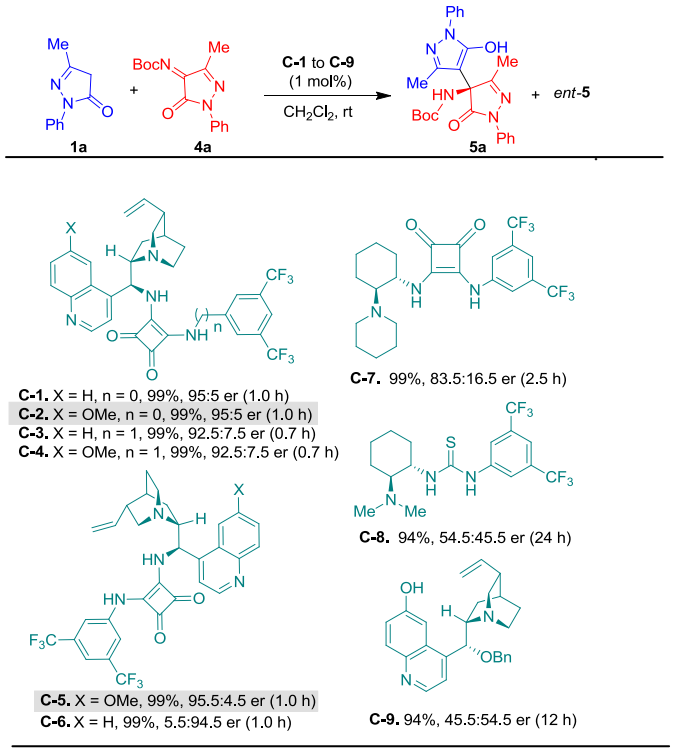
Initially, we synthesized a new series of *N*-Boc ketimines starting with the base catalyzed condensation reaction of pyrazolones **1** with nitrosobenzene to afford the intermediate phenyl imines **2**, which were then hydrolyzed to afford the ketones **3** (Scheme 2). The ketones **3** were subsequently 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 our hand, we started the optimization studies by screening various bifunctional hydrogen-bonding organocatalysts[14] for the enantioselective addition of pyrazolone **1a** to the imine **4a** in dichloromethane at room temperature to afford the desired product **5a** (Table 1). It turned out that the reactions were generally very fast with 1 mol% of squaramides **C-1** to **C-7**. The squaramide catalysts derived from quinine **C-2** and quinidine **C-5** gave the best enantioselectivities of the 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.

Table 1. Catalyst screening.[a]



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

To further improve the yield and enantiomeric ratio, the optimization of the reaction conditions was carried out by screening different solvents, additives and varying the temperature using catalyst **C-2** (Table 2). This time a one-pot addition/acylation reaction was carried out in order to obtain the enolacetate **6a**, whose enantiomers could be easily resolved by HPLC. After screening various solvents (entries 1-9), it was found that no other solvent provide better er-values than dichloromethane. An increase in the er-value of **6a** was observed by lowering the temperature to –20 ˚C (entry 10). Moreover, the presence of 4 Å molecular sieves (MS) also led to an increase in the enantioselectivity (entry 11). Further lowering of the temperature and the reducing catalyst loading, however, led to a lower reaction rate and hence lower yields (entries 12 and 13). Based on these optimization studies, best reaction condition for this transformation include 1 mol% of **C-2** in dichloromethane at -48 ˚C and 4 Å MS as an additive, providing the desired product **5a** with 99% yield and 98.5:1.5 *er* (entry 14).

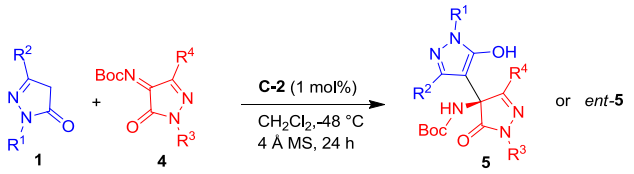
Table 2. Optimization of the reaction conditions.[a]

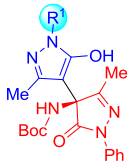
Entry	Solvent	Temp.	Time (h)	Yield (%) [b]	er [c]
1	CH_2Cl_2	rt	2.5	94	95:5
2	$ClCH_2CH_2Cl$	rt	2.5	94	94:6
3	$CHCl_3$	rt	2.5	91	90.5:9.5
4	toluene	rt	5	95	76.5:23.5
5	xylene	rt	6	93	81:19
6	Et_2O	rt	1.5	92	77:23
7	THF	rt	0.3	94	91:9
8	1,4-dioxane	rt	1.5	92	80.5:19.5
9	MTBE	rt	1.5	96	79:21
10	CH_2Cl_2	-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 non-acylated product **5a**. [f] 0.5 mol% of **C-2** was used.

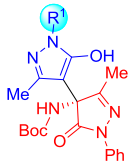
After the optimization, we then focused towards the substrate scope for the squaramide **C-2** catalyzed Mannich addition of the pyrazolones **1** to the imines **4** (Table 3). The variation in the *N*-substituent (R^1) of **1** showed that the aryl group bearing electron-withdrawing and electron-donating group led to the formation of the corresponding adducts **5b-d** in high yields and very good er-values. A *N*-methyl group is also well tolerated to provide the desired product **5e** in 89% yield and good er of 91:9. Various alkyl substituents (R^2) at the C-3 position of the pyrazolone **1** also worked very well in terms of er-values of the products **5f-h**, but 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.

Table 3. Substrate scope with catalyst **C-2** and **C-5**.[a]

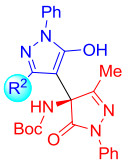




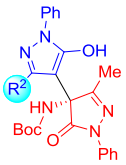
5a. R^1 = Ph, 99%, 98.5:1.5 er[b]
5b. R^1 = 2-ClC_6H_4, 91%, 93.5:6.5 er
5c. R^1 = 4-ClC_6H_4, 99%, 93:7 er
5d. R^1 = 4-MeC_6H_4, 96%, 95:5 er
5e. R^1 = Me, 89%, 91:9 er



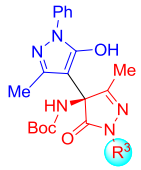
ent-5a. R^1 = Ph, 99%, 96:4 er[b]
ent-5b. R^1 = 2-ClC_6H_4, 92%, 91:9 er
ent-5c. R^1 = 4-ClC_6H_4, 99%, 93:7 er
ent-5d. R^1 = 4-MeC_6H_4, 95%, 94.5:5.5 er
ent-5e. R^1 = Me, 89%, 92.5:7.5 er



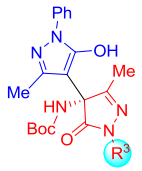
5f. R^2 = Et, 95%, 94.5:5.5 er
5g. R^2 = *n*-Pr, 96%, 92:8 er
5h. R^2 = *i*-Pr, 85%,93:7 er
5i. R^3 = CF_3, 71%, er ND



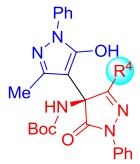
ent-5f. R^2 = Et, 96%, 92:8 er
ent-5g. R^2 = *n*-Pr, 97%, 93:7 er
ent-5h. R^2 = *i*-Pr, 86%, 94.5:5.5 er
ent-5i. R^3 = CF_3, 69%, er ND



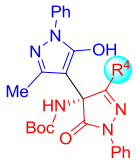
5j. R^3 = 4-ClC_6H_4, 99%, 94.5:5.5 er
5k. R^3 = 4-MeC_6H_4, 99%, >99:1 er



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)

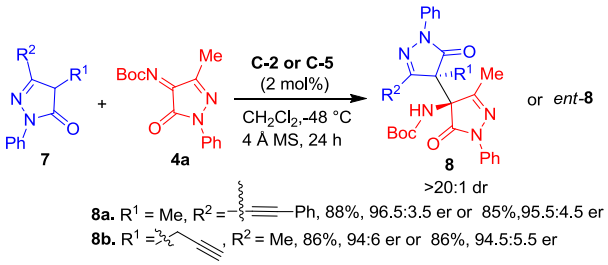
[a] Reaction conditions: 0.20 mmol of **1**, 0.22 mmol of **4**, 1 mol% of **C-2** or **C-5**, 50 mg 4 Å MS in 1.0 mL of CH_2Cl_2 at -48 °C. [b] er-values of acylated product.

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 enatioselectivities of **5l** and **5m**. However, an increase of 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 of **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 level of yields and enantiomeric ratios.

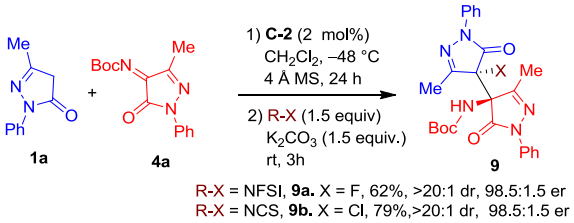
Furthermore, we have tested the applicability of this transformation to generate two adjacent tetrasubstituted stereocenters by using C-3 alkyl substituted pyrazolones **7** as nucleophiles (Scheme 3). With 2 mol% of the catalysts **C-2** and **C-5** the corresponding bis-pyrazolone products **8** and *ent*-**8** were obtained with good yields and enantioselectivities as well as excellent diastereselectivities (>20:1 dr).

Scheme 3. Asymmetric synthesis of *bis*-pyrazolones bearing two adjacent tetrasubstituted stereocenters.



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 tetra-substituted 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. (NFSI: *N*-fluorobenzenesulfonimide, NCS: *N*-chlorosuccinimide)



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

CONCLUSION

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 the squaramide **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 were carried out using SIL G-25 UV254 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 Varian Innova 400 or Innova 600 instruments. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were reported in parts per million (ppm), with coupling constants given in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet and 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 are 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 spectrometer SSQ 7000 from Finnigan at 70 eV, whereas HRMS data (ESI) were collected with a ThermoFisher Scientific LTQ-Orbitrap XL apparatus. IR spectra were taken on a PerkinElmer Spectrum 100 FT-IR spectrometer. Analytical HPLC was carried out either on a Hewlett-Packard 1050 series instrument or Agilent 1100 instrument using chiral stationary phases. Analytical SFC was carried out on a Thar SFC Waters Method Station II instrument using chiral stationary phases. The diasteromeric ratio was determined by the ^{1}H NMR

and HPLC analysis of the isolated product. Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. Melting points were measured on a 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. The squaramides **C1** to **C7**[16] and the 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 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed three times with water, 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 the 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}; ^1H 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/z*: $[M + H]^+$ calcd for $C_{16}H_{14}N_3O$ 264.1131, found 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}; ^1H 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/z*: $[M + H]^+$ calcd for $C_{16}H_{13}N_3OCl$ 298.0742, found 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/z*: [M + Na]$^+$ calcd for $C_{17}H_{15}N_3ONa$ 300.1107, found 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, $CDCl_3$) 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, C*H*$_2$CH$_3$), 1.40 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$); ^{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/z*: [M + Na]$^+$ calcd for $C_{17}H_{15}N_3ONa$ 300.1107, found 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, C*H*(CH$_3$)$_2$), 1.42 (d, *J* = 7.0 Hz, 6H, CH(C*H*$_3$)$_2$); ^{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/z*: [M + Na]$^+$ calcd for $C_{18}H_{17}N_3ONa$ 314.1264, found 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/z*: [M + H]$^+$ calcd for $C_{19}H_{20}N_3O$ 306.1601, found 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, 687cm^{-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. The ketimine **2** (10 mmol) was dissolved in THF (0.13 M) and the aqueous HCl (2.0 N) solution (25 mL) was added to it at room temperature. The progress of the reaction was monitored on 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**.

3-Methyl-1-phenyl-1H-pyrazole-4,5-dione (***3a***): red solid; 1.58g, 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}; ^{1}H 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/z*: [M]$^{+}$ calcd for $C_{10}H_8N_2O_2$ 188.0580, found 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}; ^{1}H 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/z*: [M]$^{+}$ calcd for $C_{10}H_7N_2O_2Cl$ 222.0192, found 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}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_2Na$ 225.0634, found 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}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_2Na$ 225.0634, found 225.0632.

3-Isopropyl-1-phenyl-1H-pyrazole-4,5-dione (***3e***): red solid; 1.73, 80%; mp = 51 – 53 ˚C; IR (capillary) 3337, 2968, 2092, 1710, 1067, 1085, 755 cm^{-1}; ^{1}H 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/z*: $[M + H]^+$ calcd for $C_{12}H_{13}N_2O_2$ 217.0971, found 217.0968.

3-(tert-Butyl)-1-phenyl-1H-pyrazole-4,5-dione (***3f***): red solid; 1.98, 86%; mp = 80 – 82 ˚C; IR (capillary) 3454, 2961, 2328, 2089, 1738, 1593, 1488, 1385, 1212, 1126, 1043, 942, 753 cm^{-1}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{13}H_{14}N_2O_2Na$ 253.0947, found 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}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{15}H_{10}N_2O_2Na$ 273.0634, found 273.0634.

General procedure for the synthesis of pyrazolone-derived *N*-Boc ketimine 4. The *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 hours. After 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%; 173-175 °C; IR (capillary) 2979, 2319, 2110, 1722, 1596, 1482, 1369, 1250, 1143, 843, 759 cm^{-1}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{15}H_{17}N_3O_3Na$ 310.1162, found 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}; ^{1}H 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/z*: $[M + K]^+$ calcd for $C_{15}H_{16}N_3O_3ClK$ 360.0512, found 360.0513.

tert-Butyl (1-(4-methylphenyl)-3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)-carb-amate (***4c***): 1.13 g, 75%; orange solid; mp = 170-172 °C; IR (capillary) 2986, 1727, 1612, 1517, 1440, 1368, 1313, 1249, 1147, 1036, 988, 880, 818, 772 cm^{-1}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{16}H_{19}N_3O_3Na$ 324.1319, found 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, 2 H, 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 (3 C); 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 (2 C), 128.1, 127.4 (2C), 126.2, 118.5 (2C), 85.3, 28.0 (3 C); 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, the 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 minutes, pyrazolone **1** (1.0 equiv. 0.2 mmol) was added and the stirring was continued for 24 hours at the same temperature. The reaction mixture was kept at room temperature for 1 hour and the crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 1:1) to afford the products **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/z*: $[M + Na]^+$ calcd for $C_{25}H_{27}N_5O_4Na$ 484.1955, found 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/z*: $[M + H]^+$ calcd for $C_{25}H_{27}N_5O_4Cl$ 496.1746, found 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/z*: $[M + H]^+$ calcd for $C_{25}H_{27}N_5O_4Cl$ 496.1746, found: 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/z*: $[M + H]^+$ calcd for $C_{26}H_{30}N_5O_4$ 476.2292, found 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}; ^{1}H 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/z*: $[M + H]^+$ calcd for $C_{20}H_{26}N_5O_4$ 400.1979, found 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}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{26}H_{29}N_5O_4Na$ 498.2098, found 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}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{27}H_{31}N_5O_4Na$ 512.2268, found: 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}; ^{1}H 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, C*H*$(CH_3)_2$), 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(C$H_3)_2$), 1.15 (d, *J* = 6.9 Hz, 3H, CH(C$H_3)_2$); ^{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/z*: $[M + Na]^+$ calcd for $C_{27}H_{31}N_5O_4Na$ 512.2268, found 512.2251.

tert-Butyl (S)-(5-hydroxy-3'-methyl-5'-oxo-1,1'-diphenyl-3-(trifluoromethyl)-1',5'-dihy-dro-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}; ^{1}H 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/z*: $[M + Na]^+$ calcd for $C_{25}H_{24}N_5O_4F_3Na$ 538.1673, found 538.1663.

tert-Butyl (S)-(1'-(4-chlorophenyl)-5-hydroxy-3,3'-dimethyl-5'-oxo-1-phenyl-1',5'-dihy-dro-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, 1394, 1362, 1308, 1159, 1084, 1013, 968, 937, 887, 831, 757, 731, 685 cm^{-1}; ^{1}H 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/z*: $[M + H]^+$ calcd for $C_{25}H_{27}N_5O_4Cl$ 496.1746, found 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/z*: $[M + H]^+$ calcd for $C_{26}H_{30}N_5O_4$ 476.2292, found: 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, C*H*(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(C*H*$_3$)$_2$); ^{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/z*: $[M + Na]^+$ calcd for $C_{27}H_{31}N_5O_4Na$ 512.2268, found 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}; ^{1}H 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) 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/z*: $[M + Na]^+$ calcd for $C_{28}H_{33}N_5O_4Na$ 526.2424, found 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}; ^{1}H 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) 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/z*: $[M + H]^+$ calcd for $C_{30}H_{30}N_5O_4$ 524.2292, found 524.2290.

General procedure for the acylation of product 5. In a 10 mL reaction tube equipped with a magnetic stirring bar, the 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 hours 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/z*: $[M + Na]^+$ calcd for $C_{27}H_{29}N_5O_5Na$ 526.2061, found 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), 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/z*: $[M + Na]^+$ calcd for $C_{28}H_{31}N_5O_5Na$ 540.2217, found 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] tR 15.93 min (minor), 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, C*H*$(CH_3)_2$), 2.37 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.41 – 1.22 (br m, 9H, *t*-Bu, 3H, CH(C*H*$_3$)$_2$), 1.23 – 1.22 (m, 3H, CH(C*H*$_3$)$_2$); ^{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/z*: $[M + Na]^+$ calcd for $C_{29}H_{33}N_5O_5Na$ 554.2374, found 554.2374.

General procedure for the synthesis of 8 and *ent*-8. In a 10 mL reaction tube equipped with a magnetic stirring bar, the 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. After 10 minutes, pyrazolone **7** (1.0 equiv. 0.2 mmol) was added and the stirring was continued for 24 hours at the same temperature. The reaction mixture was kept at room temperature for 1 hour and the crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to afford the products **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] tR 12.00 min (minor), 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/z*: $[M + Na]^+$ calcd for $C_{33}H_{31}N_5O_4Na$ 584.2268, found 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] tR 10.60 min (minor), 12.92 min (major); IR (capillary) 3296, 2975, 2190, 1718, 1470, 1355, 1163, 878, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 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/z*: $[M + Na]^+$ calcd for $C_{28}H_{29}N_5O_4Na$ 522.2109, found 522.2112.

General procedure for the synthesis of 9. In a 10 mL reaction tube equipped with a magnetic stirring bar, the 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 minutes, pyrazolone **1a** (1.0 equiv. 0.2 mmol) was added and the stirring was continued for 24 hours at the same temperature. The reaction mixture was warmed to the room temperature. After 1 hour NFSI or NCS (1.5 equiv.) and K_2CO_3 (1.5 equiv.) were added and the reaction mixture was stirred for 3.5 hours at the room temperature. The crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to afford the products **9a** or 9**b**.

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 (***9b***): 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] tR 3.72 min (major), 5.09 min (minor); IR (capillary) 3379, 2931, 2083, 1717, 1493, 1369, 1247, 1157, 908, 831, 752, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) –179.94; MS (EI) *m/z*: 479.0 M^+; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{26}N_5O_4FNa$ 502.1861, found 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, $CDCl_3$) 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/z*: $[M + K]^+$ calcd for $C_{25}H_{26}N_5O_4ClK$ 534.1305, found 534.1305.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxxxxxxxxxxxxxx.

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.

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