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Asymmetric Organocatalytic Friedel–Crafts Hydroxyalkylation of Indoles Using Electrophilic Pyrazole-4,5-diones

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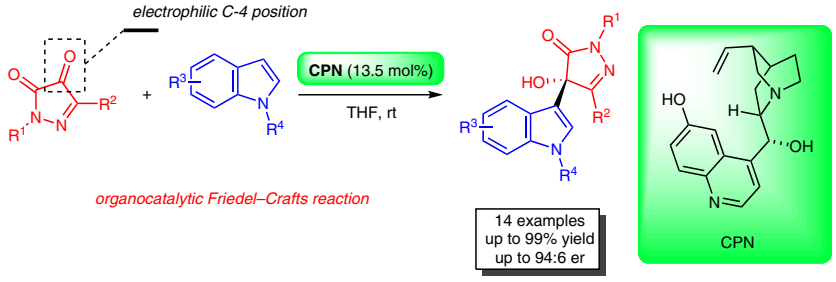

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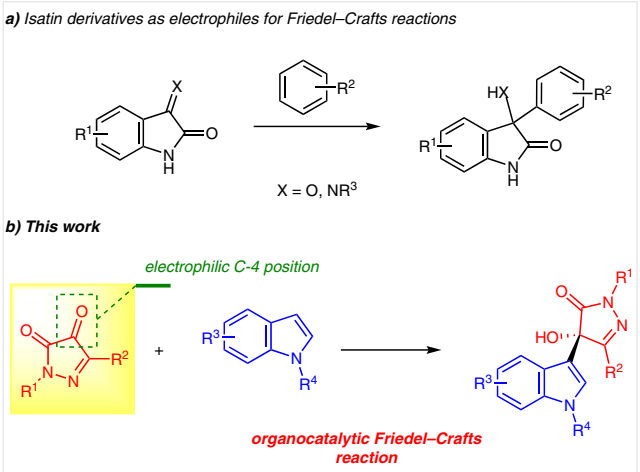
Abstract The electrophilic reactivity of a series of novel pyrazole-4,5-dione derivatives in the organocatalytic Friedel–Crafts reaction with various substituted indoles has been tested. The disclosed procedure catalyzed by a cinchona alkaloid derivative allows the conjugation of two very important aza-heterocyclic scaffolds to generate a new class of indolylpyrazolones bearing a tetrasubstituted stereocenter in excellent yields (up to 99%) and with enantioselectivities of up to 94:6 er.

Key words Friedel–Crafts, organocatalysis, pyrazolones, indoles, tetrasubstituted stereocenter

The Friedel–Crafts (F–C) reaction is undoubtedly one of the most important transformations in organic synthesis for the formation of C–C bonds. This electrophilic aromatic substitution represents a remarkable tool for the functionalization of aromatic compounds. Moreover, the application of this reaction with ketones or ketimines as electrophiles can lead to the formation of a tetrasubstituted stereocenter, a challenging task in the field of asymmetric organic synthesis.[1]

Since the turn of the millennium, the field of organocatalysis has emerged as an efficient approach in asymmetric synthesis, counting on versatile applicability in terms of activation modes of substrates and functional group tolerance. Moreover, organocatalysis offers many advantages such as mild reaction conditions as well as lower catalyst toxicity compared to transition metal complexes.[2] Consequently, with the advent of organocatalysis a plethora of efficient methodologies for the stereoselective F–C alkylation has been developed.[3]

Within this context, isatins (Scheme 1 a, X = O) and their derivatives are considered privileged substrates for this kind of transformation, due to the formation of the oxindole moiety bearing a tetrasubstituted stereocenter, a scaffold frequently found in natural products and bioactive compounds in general.[4] Inspired by the structure of isatin derivatives, our group recently developed the synthesis of a new series of *N*-aryliminopyrazolones, which possess some similarity with isatin ketimines **2**.[5] Pyrazoles and pyrazolones are an important class of aza-heterocycles with promising applications as dyes and chelating agents as well as in medicinal and agrochemical industries.[6]



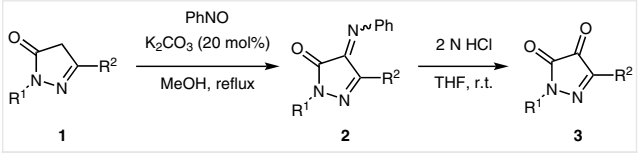
Scheme 1 Application of novel electrophiles in the Friedel–Crafts hydroxyalkylation of indoles

Moreover, the structure of pyrazolones **1** has been intensively explored, due to the extensive tautomerism that can be controlled by solvents, additives, and substituents.[7] For these unique properties, the reactivity of pyrazolones can be easily tuned and make these compounds powerful substrates for several organic transformations. One of most used reactivity of **1** is the nucleophilic methylene at C4

position for additions to nitroalkenes,[8] α,β-unsaturated carbonyl compounds,[9] as well as malononitriles.[10] The peculiar reactivity of the novel series of electrophilic iminopyrazolones **2** is the electrophilic C4 position, which to the best of our knowledge has never been investigated before. Consequently, we envisioned to use the corresponding pyrazole-4,5-diones **3** as electrophiles in the Friedel–Crafts hydroxyalkylation of indole derivatives.

This procedure would not only combine two important aza-heterocyclic scaffolds leading to new molecular structures bearing a quaternary stereocenter, but also demonstrate the applicability of these electrophilic pyrazolones **3**, which have not been employed so far.

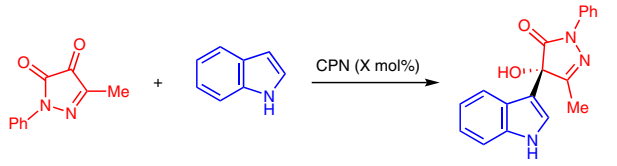
Pyrazole-4,5-diones **3** could be easily prepared starting from the corresponding pyrazolin-5-ones **1** by reaction with nitrosobenzene (Scheme 2). The resulting imines **2** could be hydrolyzed in the presence of aqueous 2 M HCl to afford the desired pyrazole-4,5-diones **3**.



Scheme 2 Synthesis of pyrazole-4,5-dione derivatives

With the substrates in hand, 3-methyl-5-phenyl-1*H*-pyrazole-4,5-dione (**3a**) was chosen as a model substrate for an initial test reaction with indole (**4a**) catalyzed by the benzyl-protected cupreine **A** (Scheme 3). To our delight the reaction showed promising outcomes providing the desired indolylpyrazolone **5a** in excellent yield (93%) and moderate enantioselectivity (75.5:24.5 er). Encouraged by this result, a series of organocatalysts were screened in order to improve the enantiocontrol. Initially, cinchona alkaloid derivatives **B**–**F** were tested and cupreine **B** provided the best results in terms of yield and er value (95% yield, 75.5:24.5 er). Afterwards, other classes of organocatalysts such as thioureas **G**, **H**, **N**, thiocarbamate **K**, squaramides **I**, **J**, as well as the the quinine dimers **L** and **M** were tested. Unfortunately, in all the implemented cases, the enantioselectivities could not be improved and therefore cupreine **B** was selected as the best catalyst. Subsequently, we focused on the optimization of the reaction conditions to evaluate the effects of solvents, the presence of additives, the catalyst loading, and temperature on the reaction outcomes. The screening of the solvents with different polarities revealed THF as the best one providing the desired compound in 95% yield and with 75.5:25.5 enantiomeric ratio (Table 1, entries 1–10). Furthermore, the variation of the temperature to –20 °C and 40 °C as well as the addition of 4Å MS (entry 16) caused a decrease of the er value (entries 11 and 17). To our delight, it was possible to increase the enantioselectivity by using absolute THF, achieving **5a** with 90:10 er (entry 12). Finally, the change of the catalyst loading (entries 13–15) allowed us to identify the best reaction conditions by using 13.5 mol% of catalyst **B** in THF at room temperature, affording the product **5a** in excellent yield and enantioselectivity (99% yield, 94:6 er, entry 14).

Table 1 Optimization of the Reaction Conditions

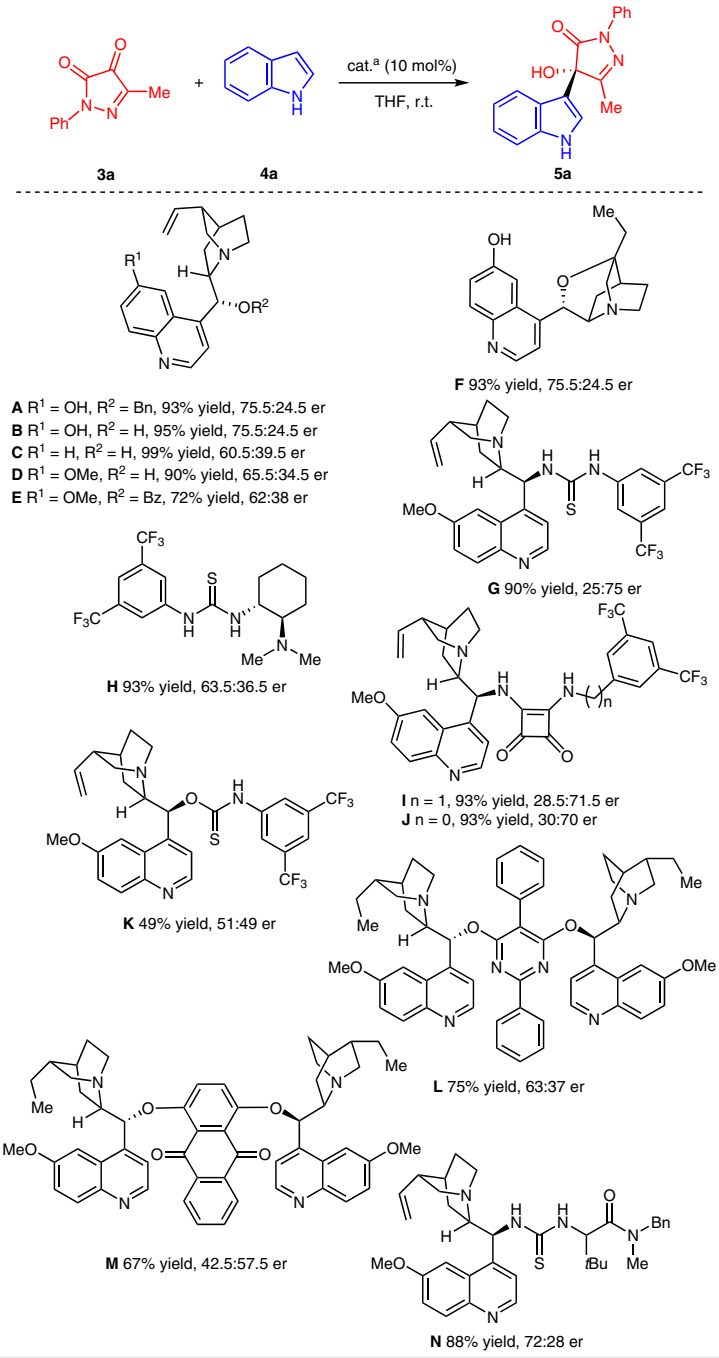


Entry[a]	Solvent	Temp (°C)	Catalyst (mol%)	Yield (%)[b]	er[c]
1[d]	THF	r.t.	10	98	74:26
2[d]	CH_2Cl_2	r.t.	10	90	53:47
3[d]	DCE	r.t.	10	95	54:46
4[d]	$CHCl_3$	r.t.	10	95	61.5:38.5
5[d]	toluene	r.t.	10	98	69.5:30.5
6[d]	1,4-dioxane	r.t.	10	80	50:50
7[d]	MTBE	r.t.	10	97	63.5:36.5
8[d]	Et_2O	r.t.	10	99	70.5:28.5
9[d]	hexane	r.t.	10	97	54:46
10	THF	r.t.	10	95	75.5:24.5
11	THF	–20	10	82	63.5:36.5
12	THF[e]	r.t.	10	90	90:10
13	THF[e]	r.t.	5	95	87.5:12.5
14	THF[e]	r.t.	13.5	99	94:6
15	THF[e]	r.t.	15	99	93:7
16[f]	THF[e]	r.t.	13.5	99	88:12
17	THF[e]	40	13.5	99	80:20
18[g]	THF[e]	r.t.	13.5	93	70.5:29.5

[a] Unless otherwise stated, the reaction conditions were: to a solution of pyrazolone **3a** (0.2 mmol) and catalyst **B** (0.02 mmol) in THF (1 mL) was added the indole (**4a**; 0.3 mmol, 1.5 equiv) and the mixture was stirred for 24 hours.
[b] Yield of the isolated product after chromatography.
[c] Enantiomeric ratio (er) values measured by HPLC with a chiral stationary phase.
[d] Indole (0.2 mmol, 1.0 equiv) and solvent (3 mL) were used.
[e] Absolute THF was used.
[f] Additive: 4 Å MS.
[g] Additive: $PhCO_2H$ (3.2 mg, 0.027 mmol, 13.5 mol%).

Once we had identified the best reaction conditions and in order to prove the general applicability of the disclosed protocol, the scope of the reaction was investigated (Scheme 4). We started by changing the substituents R^1 and R^2 on the pyrazolone substrates **5a**–**g**. Despite the slightly decreased er values due to the presence of a methyl group or a Cl-substituent on the aromatic ring, the reactivity was not influenced (**5b**, **c**). Then, the steric hindrance of R^2 was

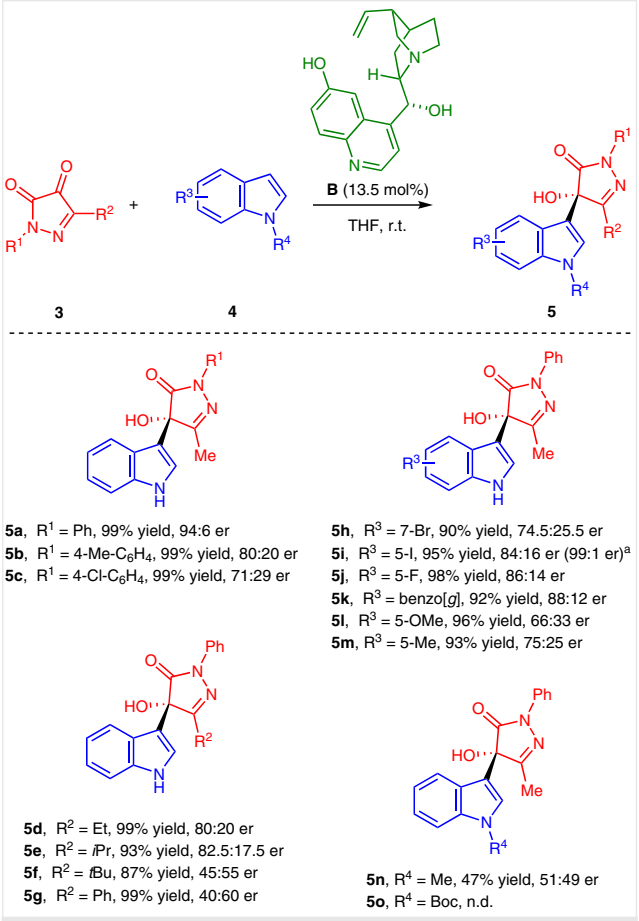
sequentially increased from ethyl to *tert*-butyl. Because of the bulkiness of the substituents the yield was marginally reduced down to 87% for *tert*-butyl (**5f**), but interestingly in this last case we could observe an inversion of the stereoselectivity in favor of the other enantiomer. Similarly, the change to a phenyl group showed the same outcome (**5g**). These results may be explained with the high steric hindrance adjacent to the electrophilic site, which causes a distortion in the orientation of the reagents in the transition state. Furthermore, N-substituted indoles with Me and Boc groups **5n**,**o** were probed. A dramatic decrease of the reactivity was observed with *N*-methylindole, achieving the corresponding product in only 47% yield in its racemic form (**5n**). Instead, in the reaction using the more hindred



Scheme 3 Catalyst screening for the Friedel–Crafts reaction. [a] Unless otherwise stated, the reaction conditions were: to a solution of pyrazolone **3a** (0.2 mmol) and catalyst (0.02 mmol) in THF (1 mL) was added indole (**4a**; 0.3 mmol, 1.5 equiv) and the mixture was stirred for 24 h.

N-Boc-indole, the formation of the corresponding product could not be observed. Subsequently, various substituted indole derivatives bearing electron-withdrawing as well as electron-donating groups **5h–m** were tested. Although in these cases a general decrease of the enantioselectivity could be detected (up to 88:12 er), the yields remained excellent (up to 98%) irrespective of the electronic and steric nature of the substituents.

The absolute configuration was determined to be *S* by comparison of the electronic circular dichroism (ECD) spectrum of compound **5i** and its calculated enantiomeric counterpart (Figure 1).



5a, R^1 = Ph, 99% yield, 94:6 er
5b, R^1 = 4-Me-C_6H_4, 99% yield, 80:20 er
5c, R^1 = 4-Cl-C_6H_4, 99% yield, 71:29 er

5h, R^3 = 7-Br, 90% yield, 74.5:25.5 er
5i, R^3 = 5-I, 95% yield, 84:16 er (99:1 er)[a]
5j, R^3 = 5-F, 98% yield, 86:14 er
5k, R^3 = benzo[*g*], 92% yield, 88:12 er
5l, R^3 = 5-OMe, 96% yield, 66:33 er
5m, R^3 = 5-Me, 93% yield, 75:25 er

5d, R^2 = Et, 99% yield, 80:20 er
5e, R^2 = *i*Pr, 93% yield, 82.5:17.5 er
5f, R^2 = *t*Bu, 87% yield, 45:55 er
5g, R^2 = Ph, 99% yield, 40:60 er

5n, R^4 = Me, 47% yield, 51:49 er
5o, R^4 = Boc, n.d.

Scheme 4 Substrate scope. *Reagents and conditions*: To a solution of pyrazolone **3** (0.2 mmol) and catalyst **B** (8.3 mg, 0.027 mmol) in THF (1 mL) was added the indole 4 (0.3 mmol, 1.5 equiv) and the mixture was stirred for 24 hours. [a] er of the mother solution after recrystallization (cyclohexane/acetone).

In summary, we have demonstrated the applicability of a novel series of electrophilic pyrazole-4,5-diones **3** in the organocatalytic Friedel–Crafts hydroxyalkylation of indoles **4** catalyzed by cupreine **B**. The novel indolylpyrazolones **5** bearing two important aza-heterocyclic scaffolds and a

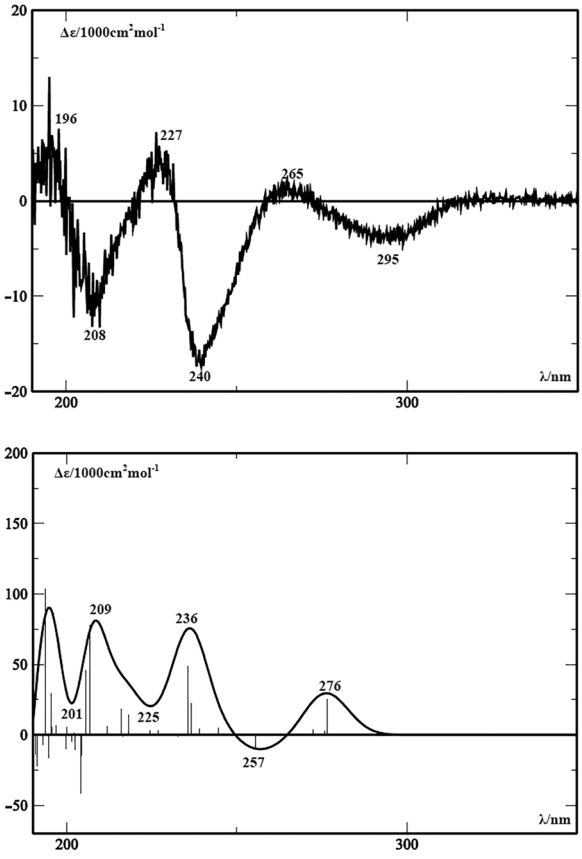


Figure 1 Experimental (top) and calculated [bottom, TD-DFT/CAM-B3LYP/6-311++(3df,3pd), SDD//MP2/6-31+G*, SDD] electronic circular dichroism spectra (ECD) of compound **5i**. The calculation was performed assuming the configuration *R* at chiral center C4. The measured and the calculated spectrum appear roughly like image and mirror image and we therefore conclude that the absolute configuration of **5i** is *S*.[11]

tetrasubstituted stereocenter were obtained with good enantioselectivity (up to 94:6) and in excellent yields (up to 99%).

Unless otherwise noted, all commercially available compounds were used without further purification. For preparative column chromatography SIL G-25 UV252 from Macherey & Nagel, particle size 0.040–0.063 nm (230–240 mesh, flash) was used. Visualization of the developed TLC plates was performed with UV irradiation (254 nm) or by staining with ninhydrin stain (0.5% EtOH solution). Optical rotations were measured on a PerkinElmer 241 polarimeter. Mass spectra were recorded on a Finnigan SSQ7000 (EI 70 eV) spectrometer and high-resolution mass spectra on a Thermo Fisher Scientific Orbitrap XL spectrometer. IR spectra were recorded on a PerkinElmer FT-IR Spectrum 100 using an ATR unit. ^{1}H and ^{13}C spectra were recorded at ambient temperature on Varian Mercury 300, Inova 400, Varian VNMRS-400, or Varian VNMRS-600 spectrometer with TMS as an internal standard. Analytical HPLC was performed on a Hewlett-Packard 1100

Series instrument using chiral stationary phases (Daichel AD, AS, IA, OD, OJ, Chiralpak IC, or Whelk. M columns). Cupreine (CPN) was synthesized following a reported procedure.[12]

Pyrazole-4,5-diones 3; General Procedure

Pyrazol-4,5-diones **3** were synthesized following the procedure previously developed by our group.[5b] To a solution of pyrazolone **1** (25 mmol, 1 equiv) and K_2CO_3 (0.2 equiv) in MeOH (0.66 M) was added dropwise nitrosobenzene (1 equiv) and the mixture was stirred at reflux for 3 h. The reaction was quenched by adding EtOAc and brine. The organic phase was separated and the aqueous phase extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The products **2** were isolated after flash chromatography on silica gel (pentane/EtOAc 8:2).

To a solution of **2** in THF (0.5 M, 30 mL) was added dropwise aq 2 M HCl (15 mL) and the mixture was stirred for 35 min. The reaction mixture was concentrated under reduced pressure to remove the THF and then EtOAc was added. The organic phase was separated and the aqueous phase extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The pyrazolone-4,5-diones **3** were isolated after flash chromatography on silica gel (pentane/EtOAc 8:2).

All analytical data are consistent with literature values.

(*S*)-Indolylpyrazol-3-ones 5; General Procedure

To a solution of the pyrazolone **3** (0.2 mmol, 1 equiv) and CPN (cuperine B, 8.3 mg, 13.5 mol%) in absolute THF (1 mL, 0.2 M) was added the indole **4** (0.3 mmol, 1.5 equiv) and the solution was stirred at r.t. for 24 h. The product was isolated after flash column chromatography.

(*S*)-4-Hydroxy-4-(1*H*-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5a)

Yield: 61 mg (99%); colorless solid; mp 179 °C (dec.); $[\alpha]_D^{20}$ –90.4 (*c* 1.0, acetone); R_f = 0.35 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/EtOH (7:3), 1.0 mL/min, λ = 254.4; t_R (minor) = 4.0 min, t_R (major) = 2.7 min; 94:6 er.

IR (ATR): 3839, 3359, 3232, 2919, 2341, 2098, 1934, 1685, 1370, 1093, 1093, 922, 829, 740 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.93 (d, *J* = 7.9 Hz, 2 H, CH_{ar}), 7.48–7.36 (m, 5 H, CH_{ar}), 7.21 (t, *J* = 7.3 Hz, 1 H, CH_{ar}), 7.11 (t, *J* = 7.8 Hz, 1 H, CH_{ar}), 6.97 (t, *J* = 7.4 Hz, 1 H, CH_{ar}), 2.07 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, CD_3OD): δ = 175.2, 164.9, 139.4, 138.6, 129.9 (2 C), 126.3, 125.3, 124.9, 123.0 (2 C), 120.65, 120.0, 119.7, 112.8, 111.2, 80.3, 13.4.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 306.1 (26), 205.1 (100, $[M]^+ = [C_{18}H_{15}N_3O_2]^+$), 278.2 (10), 261.1 (14), 260.0 (71), 145.1 (11), 144.0 (61), 117.1 (20), 116.1 (13), 57.2 (13).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{18}H_{15}N_3O_2Na]^+$: 328.1057; found: 328.1042.

(*S*)-4-Hydroxy-4-(1*H*-indol-3-yl)-5-methyl-2-(*p*-tolyl)-2,4-dihydro-3*H*-pyrazol-3-one (5b)

Yield: 63 mg (99%); colorless solid; mp 177–178 °C (dec.); $[\alpha]_D^{20}$ –179.5 (*c* 1.0, acetone); R_f = 0.32 (pentane/EtOAc 6:4).

HPLC: Chiralpak IA, *n*-heptane/*i*-PrOH (8:2), 0.5 mL/min, λ = 230.4; t_R (minor) = 13.2 min, t_R (major) = 7.6 min; 80:20 er.

IR (ATR): 337, 3274, 2917, 2254, 1690, 1621, 1512, 1416, 1367, 1287, 1243, 1179, 1100, 1036, 988, 916, 817, 736, 676 cm^{-1}.

^1H NMR (600 MHz, acetone-d_6): δ = 10.47 (s, 1 H, NH), 7.87 (d, *J* = 8.6 Hz, 2 H, CH_{ar}), 7.56 (d, *J* = 8.1 Hz, 1 H, CH_{ar}), 7.48 (d, *J* = 2.7 Hz, 1 H, CH_{ar}), 7.45 (d, *J* = 8.2 Hz, 1 H, CH_{ar}), 7.25 (d, *J* = 8.5 Hz, 2 H, CH_{ar}), 7.13 (t, *J* = 7.8 Hz, 1 H, CH_{ar}), 7.02–6.98 (m, 1 H, CH_{ar}), 5.93 (s, 1 H, OH), 2.34 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.4, 163.1, 138.1, 137.1, 134.9, 130.1 (2 C), 125.3, 124.8, 122.75, 120.4, 120.0, 119.0 (2 C), 112.7, 111.9, 79.5, 20.9, 13.6.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 319.1 (37, $[M]^+ = [C_{19}H_{17}N_3O_2]^+$), 274.1 (24), 146.1 (15), 145.1 (18), 144.0 (100), 133.0 (11), 117.1 (26), 116.1 (25), 107.2 (11), 106.1 (24), 105.1 (30), 91.1 (28), 89.1 (26), 79.2 (11), 77.2 (15), 71.2 (17), 65.2 (18).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{19}H_{17}N_3O_2Na]^+$: 342.1213; found: 342.1209.

(*S*)-2-(4-Chlorophenyl)-4-hydroxy-4-(1*H*-indol-3-yl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (5c)

Yield: 61 mg (99%); pale orange solid; mp 198 °C (dec.); $[\alpha]_D^{20}$ –118.5 (*c* 1.0, acetone); R_f = 0.48 (pentane/EtOAc 6:4).

HPLC: Chiralpak IA, *n*-heptane/EtOH (7:3), 1.0 mL/min, λ = 230.4; t_R (minor) = 8.6 min, t_R (major) = 5.9 min; 71:29 er.

IR (ATR): 3364, 3234, 2322, 2222, 2115, 1691, 1494, 1416, 1365, 1288, 1203, 1134, 1091, 1010, 974, 918, 823, 743, 674 cm^{-1}.

^1H NMR (600 MHz, acetone-d_6): δ = 10.50 (br s, 1 H, NH), 8.01 (d, *J* = 8.7 Hz, 2 H, CH_{ar}), 7.56 (d, *J* = 8.1 Hz, 1 H, CH_{ar}), 7.50–7.44 (m, 4 H, CH_{ar}), 7.14 (t, *J* = 7.8 Hz, 1 H, CH_{ar}), 7.01 (t, *J* = 7.8 Hz, 1 H, CH_{ar}), 5.99 (s, 1 H, OH), 2.12 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.65, 163.8, 138.25, 138.1, 129.9, 129.7 (2 C), 125.3, 124.9, 122.8, 120.5, 120.2 (2 C), 120.1, 112.75, 111.6, 79.6, 13.6.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 341.2 (13), 339.1 (48, $[M]^+ = [C_{20}H_{19}N_3O_2]^+$), 296.2 (13), 294.2 (41), 145.2 (15), 144.1 (100), 126.2 (12), 125.1 (12), 117.2 (46), 116.1 (15).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{18}H_{14}ClN_3O_2Na]^+$: 362.0667; found: 362.0663.

(*S*)-5-Ethyl-4-hydroxy-4-(1*H*-indol-3-yl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5d)

Yield: 63 mg (99%); colorless solid; mp 168–169 °C (dec.); $[\alpha]_D^{20}$ –24.0 (*c* 1.0, acetone); R_f = 0.3 (pentane/EtOAc 7:3).

HPLC: Chiralpak IA, *n*-heptane/*i*-PrOH (8:2), 0.7 mL/min, λ = 254.4; t_R (minor) = 13.3 min, t_R (major) = 11.4 min; 80:20 er.

IR (ATR): 3348, 3058, 2975, 2932, 2481, 2323, 2080, 1697, 1595, 1496, 1345, 1229, 1111, 1051, 1011, 913, 819, 747, 687 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.96 (d, *J* = 7.9 Hz, 2 H, CH_{ar}), 7.47–7.43 (m, 2 H, CH_{ar}), 7.41–7.36 (m, 3 H, CH_{ar}), 7.23 (t, *J* = 7.3 Hz, 1 H, CH_{ar}), 7.11 (t, *J* = 7.7 Hz, 1 H, CH_{ar}), 6.98–6.94 (m, 1 H, CH_{ar}), 2.58 (dt, *J* = 17.4, 7.4 Hz, 1 H, $CHHCH_3$), 2.38–2.30 (m, 1 H, $CHHCH_3$), 1.20 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (151 MHz, CD_3OD): δ = 175.5, 168.65, 139.6, 138.6, 129.9 (2 C), 126.3, 125.2, 124.8, 123.0, 120.6, 120.0 (2 C), 119.5, 112.8, 111.5, 80.5, 21.8, 9.8.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 320.1 (12), 319.1 (25, $[M]^+ = [C_{19}H_{17}N_3O_2]^+$), 275.1 (11), 274.1 (34), 146.0 (15), 145.0 (37), 144.0 (100), 119.0 (23), 117.1 (30), 116.1 (28), 92.1 (23), 91.1 (24), 89.1 (21), 77.1 (29), 65.2 (12), 51.2 (11).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for [$C_{19}H_{17}N_3O_2Na$]$^+$: 342.1213; found: 342.1213.

(*S*)-4-Hydroxy-4-(1*H*-indol-3-yl)-5-isopropyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5e)

Yield: 62 mg (93%); colorless solid; mp 170–172 °C (dec.); $[\alpha]_D^{20}$ –150.8 (*c* 1.0, acetone); R_f = 0.35 (pentane/EtOAc 7:3).

HPLC: Chiralpak IA, *n*-heptane/EtOH (7:3), 0.7 mL/min, λ = 254.4; t_R (minor) = 11.9 min, t_R (major) = 11.0 min; 82.5:17.5 er.

IR (ATR): 3347, 2968, 2926, 2324, 2109, 1923, 1698, 1595, 1495, 1345, 1225, 1095, 1051, 962, 920, 806, 745, 683 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.97 (d, *J* = 8.6 Hz, 2 H, CH_{ar}), 7.49–7.35 (m, 4 H, CH_{ar}), 7.31–7.19 (m, 2 H, CH_{ar}), 7.09 (t, *J* = 7.6 Hz, 1 H, CH_{ar}), 6.93 (t, *J* = 7.3 Hz, 1 H, CH_{ar}), 2.75 [hept, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$], 1.30 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, CD_3OD): δ = 175.4, 171.5, 139.5, 138.5, 129.9 (2 C), 126.3, 125.1, 124.8, 122.9, 120.6, 120.0 (2 C), 119.2, 112.8, 111.7, 80.9, 29.3, 21.2, 20.7.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 334.1 (12), 333.1 (29, [M]$^+$ = [$C_{20}H_{19}N_3O_2$]$^+$), 288.1 (28), 145.0 (37), 144.0 (100), 119.0 (26), 117.0 (31), 116.0 (29), 92.1 (21), 91.1 (19), 89.1 (17), 77.1 (30).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for [$C_{20}H_{19}N_3O_2Na$]$^+$: 356.1369; found: 356.1369.

(*R*)-5-(*tert*-Butyl)-4-hydroxy-4-(1*H*-indol-3-yl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5f)

Yield: 60 mg (87%); colorless solid; mp 196 °C (dec.); $[\alpha]_D^{20}$ +14.2 (*c* 1.0, acetone); R_f = 0.35 (pentane/EtOAc 7:3).

HPLC: Chiralpak IA, *n*-heptane/EtOH (7:3), 0.7 mL/min, λ = 254.4; t_R (minor) = 11.6 min, t_R (major) = 9.9 min; 45:55 er.

IR (ATR): 3344, 2928, 2321, 2069, 1702, 1595, 1493, 1366, 1227, 1101, 913, 838, 745, 686 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.96 (d, *J* = 7.9 Hz, 2 H, CH_{ar}), 7.52 (s, 1 H, CH_{ar}), 7.45 (t, *J* = 7.9 Hz, 2 H, CH_{ar}), 7.37 (d, *J* = 8.2 Hz, 1 H, CH_{ar}), 7.23 (t, *J* = 7.5 Hz, 1 H, CH_{ar}), 7.12 (d, *J* = 8.1 Hz, 1 H, CH_{ar}), 7.07 (t, *J* = 7.6 Hz, 1 H, CH_{ar}), 6.89 (t, *J* = 7.5 Hz, 1 H, CH_{ar}), 1.16 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (151 MHz, CD_3OD): δ = 175.5, 172.35, 139.5, 138.5, 129.95 (2 C), 126.3, 124.9, 124.7, 122.8, 120.5, 120.0 (2 C), 118.7, 112.8, 112.5, 81.3, 37.3, 29.1 (3 C).

MS (EI$^+$, 70 eV): *m*/*z* (%) = 348.1 (24), 347.1 (82, [M]$^+$ = [$C_{20}H_{19}N_3O_2$]$^+$), 333.1 (16), 302.1 (24), 292.1 (13), 291.1 (63), 145.1 (16), 144.1 (100), 117.1 (10).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for [$C_{21}H_{21}N_3O_2Na$]$^+$: 370.1526; found: 370.1526.

(*R*)-4-Hydroxy-4-(1*H*-indol-3-yl)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (5g)

Yield: 73 mg (99%); pale pink solid; mp 230 °C (dec.); $[\alpha]_D^{20}$ +10.1 (*c* 1.0, acetone); R_f = 0.38 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 1.0 mL/min, λ = 254.4; t_R (minor) = 7.0 min, t_R (major) = 13.1 min; 40:60 er.

IR (ATR): 3781, 3702, 3354, 3020, 2632, 2280, 2226, 2024, 1737, 1683, 1597, 1494, 1427, 1371, 1223, 1142, 1072, 899, 817, 748, 685 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 710.45 (br s, 1 H, NH), 8.17–8.13 (m, 2 H, CH_{ar}), 8.07 (d, *J* = 8.2 Hz, 2 H, CH_{ar}), 7.63 (d, *J* = 8.1 Hz, 1 H, CH_{ar}), 7.56 (d, *J* = 1.6 Hz, 1 H, CH_{ar}), 7.48 (t, *J* = 7.8 Hz, 2 H, CH_{ar}), 7.40 (t, *J* = 8.6 Hz, 4 H, CH_{ar}), 7.25 (t, *J* = 7.5 Hz, 1 H, CH_{ar}), 7.08 (t, *J* = 7.5 Hz, 1 H, CH_{ar}), 6.94 (t, *J* = 7.7 Hz, 1 H, CH_{ar}), 6.28 (s, 1 H, OH).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.8, 159.6, 139.5, 138.1, 137.9, 131.3, 131.1, 129.8 (2 C), 129.3, 128.0, 125.8, 125.0, 124.75, 124.6, 122.7, 120.3, 120.1 (2 C), 119.2, 112.6, 112.6, 79.4.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 367.2 (100, [M]$^+$ = [$C_{27}H_{17}N_3O_2$]$^+$), 322.2 (54).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for [$C_{23}H_{17}N_3O_2Na$]$^+$: 390.1213; found: 390.1208.

(*S*)-4-(7-Bromo-1*H*-indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5h)

Yield: 69 mg (90%); pale orange solid; mp 187–189 °C (dec.); $[\alpha]_D^{20}$ –86.4 (*c* 1.0, acetone); R_f = 0.37 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 1.0 mL/min; λ = 254.4; t_R (minor) = 7.6 min, t_R (major) = 6.3 min; 74.5:25.5 er.

IR (ATR): 3267, 3119, 3062, 2972, 2660, 2222, 2094, 1687, 1594, 1553, 1493, 1430, 1363, 1294, 1204, 1085, 973, 885, 820, 746, 692 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 10.69 (s, 1 H, NH), 7.97 (d, *J* = 8.6 Hz, 2 H, CH_{ar}), 7.60–7.56 (m, 2 H, CH_{ar}), 7.45 (t, *J* = 7.9 Hz, 2 H, CH_{ar}), 7.37 (d, *J* = 7.6 Hz, 1 H, CH_{ar}), 7.21 (t, *J* = 7.4 Hz, 1 H, CH_{ar}), 6.98 (t, *J* = 7.9 Hz, 1 H, CH_{ar}), 6.07 (s, 1 H, OH), 2.12 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.3, 163.0, 139.4, 136.4, 129.7 (2 C), 126.8, 125.8, 125.5, 125.5, 121.9, 119.7, 118.9 (2 C), 113.3, 105.5, 79.4, 13.6.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 384.0 (2, [M]$^+$ = [$C_{18}H_{14}BrN_3O_2$]$^+$), 225.1 (14), 224.0 (57), 223.0 (16), 222.0 (55), 197.0 (13), 196.0 (15), 195.0 (14), 194.0 (14), 144.0 (14), 143.0 (29), 132.0 (15), 120.1 (10), 119.1 (100), 116.1 (25), 115.1 (42), 114.1 (21), 92.2 (45), 91.1 (57), 89.1 (15), 88.1 (12), 77.2 (94), 55.3 (26), 64.2 (21), 63.2 (15).

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for [$C_{18}H_{14}BrN_3O_2Na$]$^+$: 406.0162; found: 406.0161.

(*S*)-4-Hydroxy-4-(5-iodo-1*H*-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5i)

Yield: 82 mg (95%); pale orange solid; mp 190–191 °C (dec.); $[\alpha]_D^{20}$ –116.8 (*c* 1.0, acetone); R_f = 0.29 (pentane/EtOAc 6:4). The product was recrystallized from cyclohexane/acetone (99:1 er of the mother solution).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 0.5 mL/min, λ = 254.4; t_R (minor) = 6.4 min, t_R (major) = 5.5 min; 84:16 er.

IR (ATR): 3425, 3269, 3068, 2924, 2317, 2100, 1887, 1689, 1590, 1536, 1488, 1363, 1237, 1108, 975, 917, 878, 797, 760, 690, 671 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 10.67 (s, 1 H, NH), 8.12 (s, 1 H, CH_{ar}), 7.96 (d, *J* = 7.8 Hz, 2 H, CH_{ar}), 7.47–7.42 (m, 4 H, CH_{ar}), 7.33 (d, *J* = 8.4 Hz, 1 H, CH_{ar}), 7.21 (t, *J* = 7.3 Hz, 1 H, CH_{ar}), 6.03 (s, 1 H, OH), 2.16 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.4, 163.0, 139.3, 137.1, 131.1, 129.7 (2 C), 129.6, 128.2, 125.65, 125.5, 119.0 (2 C), 115.0, 111.3, 83.6, 79.4, 13.7.

MS (EI$^+$, 70 eV): *m*/*z* (%) = 431.0 (11, [M]$^+$ = [$C_{18}H_{14}IN_3O_2$]$^+$), 2431. (11), 144.1 (12), 143.1 (17), 142.1 (16), 127.0 (17), 119.1 (46), 116.1 (41), 115.1 (17), 92.1 (34), 91.1 (100), 89.2 (31), 88.1 (11), 77.3 (58), 65.3 (22), 64.2 (37), 63.2 (39), 62.2 (17).

HRMS (ESI$^+$): m/z [M + Na]$^+$ calcd for [$C_{18}H_{14}IN_3O_2Na$]$^+$: 454.0023; found: 454.0016.

(*S*)-4-(5-Fluoro-1*H*-indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5j)

Yield: 63 mg (98%); pale orange solid; mp 195–197 °C (dec.); $[\alpha]_D^{20}$ –106.5 (*c* 1.0, acetone); R_f = 0.29 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/EtOH (7:3), 1.0 mL/min, λ = 254.4; t_R (minor) = 6.9 min, t_R (major) = 5.5 min; 86:14 er.

IR (ATR): 3812, 3408, 3272, 3013, 2932, 2652, 2290, 2099, 1735, 1583, 1484, 1365, 1218, 1095, 979, 909, 755, 692 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 10.60 (s, 1 H), 7.98 (d, *J* = 8.1 Hz, 2 H), 7.53 (s, 1 H), 7.48–7.42 (m, 3 H), 7.36–7.32 (m, 1 H), 7.21 (t, *J* = 7.3 Hz, 1 H), 6.98–6.92 (m, 1 H), 6.01 (s, 1 H), 2.16 (s, 3 H).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.5, 163.1, 158.43 (d, $^1J_{C,F}$ = 232.8 Hz), 139.4, 134.7, 129.7 (2 C), 126.6, 125.7 (d, $^3J_{C,F}$ = 10.6 Hz), 125.5, 118.9 (2 C), 113.75 (d, $^3J_{C,F}$ = 9.8 Hz), 112.0 (d, $^4J_{C,F}$ = 4.7 Hz), 111.0 (d, $^2J_{C,F}$ = 26.4 Hz), 105.2 (d, $^2J_{C,F}$ = 24.6 Hz), 79.4, 13.6.

MS (EI$^+$, 70 eV): m/z (%) = 323.1 (22, [M]$^+$ = [$C_{18}H_{14}FN_3O_2$]$^+$), 278.1 (37), 163.0 (20), 162.0 (100), 135.1 (31), 134.1 (29), 132.1 (20), 119.1 (18), 108.1 (11), 107.1 (30), 92.1 (32), 91.1 (39), 77.2 (34), 65.2 (12), 64.2 (11), 51.2 (16).

HRMS (ESI$^+$): m/z [M + Na]$^+$ calcd for [$C_{18}H_{14}FN_3O_2Na$]$^+$: 346.0962; found: 346.0961.

(*S*)-4-(1*H*-Benzo[*g*]indol-3-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5k)

Yield: 65 mg (92%); pale orange oil; $[\alpha]_D^{20}$ –117.5 (*c* 1.0, acetone); R_f = 0.49 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 0.5 mL/min, λ = 230.4; t_R (minor) = 9.9 min, t_R (major) = 7.1 min; 88:12 er.

IR (ATR): 3328, 2093, 1702, 1597, 1496, 1366, 1280, 1220, 1101, 966, 907, 811, 753, 689 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 11.41 (s, 1 H, NH), 8.35 (d, *J* = 8.2 Hz, 1 H, CH_{ar}), 8.00 (d, *J* = 7.9 Hz, 2 H, CH_{ar}), 7.92 (d, *J* = 8.1 Hz, 1 H, CH_{ar}), 7.77 (d, *J* = 8.7 Hz, 1 H, CH_{ar}), 7.55–7.41 (m, 6 H, CH_{ar}), 7.21 (t, *J* = 7.3 Hz, 1 H, CH_{ar}), 6.03 (s, 1 H, OH), 2.17 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.7, 163.4, 139.5, 132.8, 131.3, 129.7 (2 C), 129.3, 126.4, 125.4, 125.0, 123.2, 122.7, 121.5, 121.3, 121.1, 120.4, 118.9 (2 C), 113.9, 79.6, 13.7.

MS (EI$^+$, 70 eV): m/z (%) = 356.1 (25), 355.0 (100, [M]$^+$ = [$C_{22}H_{17}N_3O_2$]$^+$), 311.1 (21), 310.1 (91), 195.1 (10), 194.0 (44), 188.0 (10), 167.0 (57), 166.0 (15), 139.0 (16).

HRMS (ESI$^+$): m/z [M + Na]$^+$ calcd for [$C_{22}H_{17}N_3O_2Na$]$^+$: 378.1213; found: 378.1222.

(*S*)-4-Hydroxy-4-(5-methoxy-1*H*-indol-3-yl)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5l)

Yield: 64 mg (96%); pale orange oil; $[\alpha]_D^{20}$ –89.6 (*c* 1.0, acetone); R_f = 0.41 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 1.0 mL/min, λ = 254.4; t_R (minor) = 12.6 min, t_R (major) = 10.1 min; 66:34 er.

IR (ATR): 3343, 2925, 2329, 2094, 1703, 1625, 1591, 1489, 1442, 1360, 1291, 1217, 1088, 1030, 972, 909, 804, 757, 693 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 10.34 (s, 1 H, NH), 8.01 (d, *J* = 7.8 Hz, 2 H, CH_{ar}), 7.47–7.43 (m, 3 H, CH_{ar}), 7.34 (d, *J* = 9.0 Hz, 1 H, CH_{ar}), 7.20 (t, *J* = 7.4 Hz, 1 H, CH_{ar}), 7.02 (d, *J* = 2.4 Hz, 1 H, CH_{ar}), 6.79 (dd, *J* = 8.7, 2.4 Hz, 1 H, CH_{ar}), 5.93 (s, 1 H, OH), 3.61 (s, 3 H, OCH_3), 2.13 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.7, 163.3, 155.0, 139.45, 133.1, 129.7 (2 C), 125.6, 125.4, 125.25, 118.8 (2 C), 113.4, 113.0, 111.5, 101.7, 79.7, 55.5, 13.6.

MS (EI$^+$, 70 eV): m/z (%) = 336.0 (22), 335.0 (100, [M]$^+$ = [$C_{19}H_{17}N_3O_3$]$^+$), 291.1 (15), 290.1 (75), 174.0 (23), 147.0 (12).

HRMS (ESI$^+$): m/z [M + Na]$^+$ calcd for [$C_{19}H_{17}N_3O_3Na$]$^+$: 358.1262; found: 358.1168.

(*S*)-4-Hydroxy-5-methyl-4-(5-methyl-1*H*-indol-3-yl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5m)

Yield: 59 mg (93%); pale orange oil; $[\alpha]_D^{20}$ –121.5 (*c* 1.0, acetone); R_f = 0.46 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 1.0 mL/min, λ = 254.4; t_R (minor) = 9.5 min, t_R (major) = 6.9 min; 75:25.

IR (ATR): 3348, 2920, 1703, 1594, 1543, 1494, 1421, 1359, 1285, 1231, 1105, 972, 909, 800, 755, 692, 662 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 10.35 (s, 1 H, NH), 7.99 (d, *J* = 8.6 Hz, 2 H, CH_{ar}), 7.45 (t, *J* = 7.8 Hz, 2 H, CH_{ar}), 7.42 (d, *J* = 2.6 Hz, 1 H, CH_{ar}), 7.39 (s, 1 H, CH_{ar}), 7.33 (d, *J* = 8.3 Hz, 1 H, CH_{ar}), 7.21 (t, *J* = 7.4 Hz, 1 H, CH_{ar}), 6.97 (d, *J* = 8.3 Hz, 1 H, CH_{ar}), 5.90 (s, 1 H, OH), 2.32 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.7, 163.3, 139.5, 136.4, 129.7 (2 C), 129.2, 125.6, 125.4, 124.8, 124.4, 119.9, 119.0 (2 C), 112.4, 111.3, 79.6, 21.7, 13.7.

MS (EI$^+$, 70 eV): m/z (%) = 320.1 (21), 319.1 (100, [M]$^+$ = [$C_{20}H_{19}N_3O_2$]$^+$), 296.2 (13), 274.0 (43).

HRMS (ESI$^+$): m/z [M + Na]$^+$ calcd for [$C_{19}H_{17}N_3O_2Na$]$^+$: 342.1213; found: 342.1219.

4-Hydroxy-5-methyl-4-(1-methyl-1*H*-indol-3-yl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5n)

Yield: 30 mg (47%); pale orange solid; mp 178–179 °C (dec.); R_f = 0.52 (pentane/EtOAc 6:4).

HPLC: Chiralpak IC, *n*-heptane/*i*-PrOH (8:2), 1.0 mL/min, λ = 254.4; t_R (minor) = 16.8 min, t_R (major) = 9.2 min; 51:49 er.

IR (ATR): 3351, 3059, 2926, 1702, 1598, 1491, 1356, 1247, 1212, 1112, 966, 908, 825, 745, 693 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 7.97 (d, *J* = 7.8 Hz, 2 H, CH_{ar}), 7.59 (d, *J* = 7.9 Hz, 1 H, CH_{ar}), 7.46–7.41 (m, 3 H, CH_{ar}), 7.37 (s, 1 H, CH_{ar}), 7.20 (q, *J* = 7.4 Hz, 2 H, CH_{ar}), 7.03 (t, *J* = 7.7 Hz, 1 H, CH_{ar}), 5.90 (s, 1 H, OH), 3.85 (s, 3 H, NCH_3), 2.12 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, acetone-d_6): δ = 173.6, 163.3, 139.5, 138.5, 129.7 (2 C), 128.95, 125.8, 125.4, 122.7, 120.45, 120.35, 118.9 (2 C), 110.8, 110.7, 79.5, 33.0, 13.65.

MS (EI$^+$, 70 eV): m/z (%) = 320.1 (20), 319.1 (83, [M]$^+$ = [$C_{19}H_{13}N_3O_2$]$^+$), 275.1 (16), 274.1 (73), 171.1 (11), 159.1 (19), 158.1 (100), 144.0 (24), 131.1 (34), 130.1 (19), 119.0 (13), 92.1 (12), 91.1 (13), 77.1 (24).

HRMS (ESI$^+$): m/z [M + Na]$^+$ calcd for [$C_{19}H_{17}N_3O_2Na$]$^+$: 342.1213; found: 342.1212.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591860.

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