Enantioselective synthesis of pyrazolone α-aminonitrile derivatives via an organocatalytic Strecker reaction

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General Methods and Materials:
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. 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 catalysts C1 to C5 and C-7 to C-8 were synthesized using known literature procedures.

General Procedures:
General procedure for the synthesis of pyrazolone derived aryl ketimines 2a-g-p (Scheme 1): Nitrosoarene 5 (1.0 equiv.) and K$_2$CO$_3$ (0.2 equiv.) were added to a solution of pyrazolone derivative 6 (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 products 2a-g-p.

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R'NO
5 + K2CO3 (0.2 equiv.)
MeOH (0.6 M)
reflux, 3 - 4.5 h

2a. R1 = Ph, R2 = Ph, R3 = CH$_3$ (48%)
2g. R1 = 2-Me$_2$C$_6$H$_3$, R2 = Ph, R3 = CH$_3$ (4)
2h. R1 = Ph, R2 = 4-ClC$_6$H$_4$, R3 = CH$_3$ (4)
2i. R1 = Ph, R2 = 2-ClC$_6$H$_4$, R3 = CH$_3$ (46)
2j. R1 = Ph, R2 = 4-Me$_2$C$_6$H$_3$, R3 = CH$_3$ (4)
2k. R1 = Ph, R2 = Me, R3 = CH$_3$ (82%)
2l. R1 = Ph, R2 = Ph, R3 = Et (46%)
2m. R1 = Ph, R2 = Ph, R3 = n-Pr (48%)
2n. R1 = Ph, R2 = Ph, R3 = i-Pr (58%)
2o. R1 = Ph, R2 = Ph, R3 = t-Bu (49%)
2p. R1 = R2 = R3 = Ph (56%)
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Scheme 1

Procedure for the synthesis of pyrazolone-derived ketone 7 (Scheme 2): The ketimine 2a (20 mmol) was dissolved in THF (0.13 M) and a 2.0 N HCl solution (20 mL) was added to the reaction mixture 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 MgSO₄. 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 7.

![Scheme 2](image)

General procedure for the synthesis of pyrazolone derived aryl ketimines 2c-f (Scheme 3): A mixture of pyrazolone-derived ketone 7 (1.0 equiv.) and aniline derivative (1.0 equiv.) in EtOH (2.0 M) was refluxed for 5 hours. In the case of 2e, p-TSA (30 mol%) was added as catalyst. 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, 3:1) to afford the desired product 2c-f.

![Scheme 3](image)

General procedure for the synthesis of pyrazolone derived N-Boc ketimine 2b (Scheme 4): The tert-butyl(triphenylphosphoranylidene)acetate (1.1 equiv.) was added to a solution of the pyrazolone-derived ketone 7 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 product 2b.

![Scheme 4](image)

General procedure for the organocatalytic enantioselective Strecker synthesis of 3 and ent-3 (Scheme 5): In a 10 mL reaction tube equipped with a magnetic stirring bar, the imine 2 (1 equiv., 0.2 mmol), catalyst C-2 or C-5 (5 mol%) were stirred in dichloroethane (4.5 mL) at room temperature. After 10 minutes, trimethylsilyl cyanide 1a (1.5 equiv. 0.45 mmol) was added and the stirring was continued for 4 days at room temperature. The crude product was
directly purified by flash column chromatography (n-hexane/EtOAc, 4:1) to afford the products 3 or ent-3.

Scheme 5

Procedure for the deprotection of the 4-methoxyphenyl group (Scheme 6): The α-amino nitrile ent-3e (64 mg, 0.2 mmol) was dissolved in CH$_3$CN/H$_2$O (1:1, 4 mL). Periodic acid (182 mg, 0.8 mmol, 4 equiv.) and sulfuric acid (0.4 mL) were added and the mixture was stirred until completion of the reaction in 1 h. Diethyl ether was added to the solution, the phases were separated and the aqueous phase was extracted twice with diethyl ether. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The crude product was directly purified by flash column chromatography (n-hexane/EtOAc, 6:4) to afford the product 4.

Scheme 6

Analytical data:

5-Methyl-2-phenyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (2a). Red solid; mp = 102-104 °C; IR (Capillary): 3060, 2287, 2084, 1937, 1664, 1587, 1488, 1412, 1360, 1297, 1132, 998, 911, 831, 744, 687 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.88–7.86 (m, 2H, ArH), 7.45–7.23 (m, 7H, ArH), 7.22–7.19 (m, 1H, ArH), 2.35 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 152.7, 151.2, 150.8, 146.3, 137.7, 129.0 (2C), 128.7 (2C), 125.6, 121.8 (2C), 118.5 (2C), 118.4, 12.4; MS (EI): m/z 262.9 M$^+$; HRMS Calcd for [C$_{16}$H$_{13}$N$_3$O + H]$^+$: 264.1131, found: 264.1131.
tert-Butyl (3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene)carbamate (2b).
Orange solid; mp = 173-175 °C; IR (Capillary): 2979, 2319, 2110, 1722, 1596, 1482, 1369, 1250, 1143, 843, 759 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.84-7.82 (m, 2H, ArH), 7.42-7.40 (m, 2H, ArH), 2.28 (s, 3H, Me), 1.64 (s, 9H, t-Bu); ¹³C NMR (151 MHz, CDCl₃): 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 Calcd for [C₁₅H₁₇N₃O₃ + Na]⁺: 310.1162, found: 310.1161.

4-((4-Fluorophenyl)imino)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2c). Red solid; mp = 98-100 °C; IR (Capillary): 3076, 2674, 2345, 2110, 1906, 1694, 1490, 1310, 1231, 1117, 1013, 840, 758, 688, 660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.87-7.84 (m, 2H, ArH), 7.60-7.57 (m, 2H, ArH), 7.41-7.37 (m, 2H, ArH), 7.22-7.20 (m, 1H, ArH), 7.13-7.12 (m, 2H, ArH), 2.31 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 163.2, 152.0, 151.5, 151.1, 142.0, 137.7, 129.0 (2C), 126.1 (2C), 125.7, 118.6 (2C), 115.7 (2C), 12.4; MS (EI): m/z 280.9 M⁺; Elemental Analysis (CHN): calculated for [C₁₆H₁₂N₃OF]: C = 68.32%, H = 4.30%, N = 14.94%, found C = 68.15%, H = 4.52%, N = 16.63%.

4-((4-Chlorophenyl)imino)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2d). Red solid; mp = 118-120 °C; IR (Capillary): 3470, 2972, 2287, 2089, 1887, 1732, 1587, 1484, 1368, 1214, 1084, 1018, 836, 757 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.86 (d, J = 8.1 Hz, 2H, ArH), 7.42-7.37 (m, 6H, ArH), 7.22 (t, J = 7.4 Hz, 1H, ArH), 2.33 (s, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃): δ 152.8, 151.2, 150.8, 144.5, 137.5, 134.7, 129.0 (2C), 128.9 (2C), 125.7, 123.9 (2C), 118.5 (2C), 12.4; MS (EI): m/z 296.8 M⁺; Elemental Analysis (CHN): calculated for [C₁₆H₁₂N₃ClO]: C = 64.54%, H = 4.06%, N = 14.11%, found C = 64.73%, H = 4.25%, N = 14.05%.

4-((4-Trifluoromethylphenyl)imino)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2e). Red solid; mp = 155-157 °C; IR (Capillary): 3081, 2653, 2295, 2176, 2111, 2060, 2015, 1926, 1893, 1702, 1592, 1492, 1416, 1309, 1155, 1106, 1058, 840, 755, 692 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.84-7.81 (m, 2H, ArH), 7.66 (d, J = 8.3 Hz, 2H, ArH), 7.40-7.36 (m, 2H, ArH), 7.24-7.18 (m, 3H, ArH), 2.34 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃): δ
154.2, 150.7, 150.3, 149.6, 137.4, 129.2, 129.1 (2C), 126.1 (2C), 125.9, 120.0 (2C), 118.5, 118.4 (2C), 12.3; $^{13}$F NMR (376 MHz, CDCl$_3$); δ –62.4; MS (EI): m/z 331.1 M$^+$; Elemental Analysis (CHN): calculated for [C$_{17}$H$_{12}$N$_3$OF$_3$]: C = 61.63%, H = 3.65%, N = 12.68%, found C = 61.63%, H = 3.64%, N = 12.69%.

4-((4-Methoxyphenyl)imino)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2f). Red solid; mp = 111-113 °C; IR (Capillary): 2929, 2661, 2340, 2092, 1906, 1686, 1499, 1253, 1113, 1012, 837, 755 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.95 – 7.91 (m, 4H, ArH), 7.43 – 7.41 (m, 2H, ArH), 7.22 – 7.19 (m, 1H, ArH), 6.97 – 6.89 (m, 2H, ArH), 3.88 (s, 3H, OCH$_3$), 2.32 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 162.2, 152.4, 151.6, 148.9, 148.0, 129.4 (2C), 129.0 (2C), 125.4, 118.7 (2C), 114.0 (2C), 55.6, 12.5; MS (EI): m/z 292.8 M$^+$; Elemental Analysis (CHN): calculated for [C$_{17}$H$_{15}$N$_3$O$_2$]: C = 69.61%, H = 5.15%, N = 14.33%, found C = 69.58%, H = 5.16%, N = 14.41%.

5-Methyl-2-phenyl-4-(o-tolylimino)-2,4-dihydro-3H-pyrazol-3-one (2g). Red solid; mp = 71-73 °C; IR (Capillary): 3389, 2920, 2648, 2325, 2093, 1906, 1712, 1594, 1481, 1307, 1151, 1036, 843, 758 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.89 – 7.87 (m, 2H, ArH), 7.41 – 7.38 (m, 2H, ArH), 7.30 – 7.17 (m, 5H, ArH), 2.37 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 152.2, 151.3, 150.6, 145.4, 137.7, 130.8, 129.2, 129.0 (2C), 128.6, 125.8, 125.6, 118.5, 118.4 (2C), 18.2, 12.4.; MS (EI): m/z 276.9 M$^+$; HRMS Calcd for [C$_{17}$H$_{15}$N$_3$O + Na]$^+$: 300.1107, found: 300.1107.

2-(4-Chlorophenyl)-5-methyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (2h). Red solid (83 mg, 95%); mp = 121-123 °C; IR (Capillary): 3461, 2993, 2678, 2338, 2093, 1902, 1716, 1577, 1479, 1305, 1105, 994, 820 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.85 – 7.83 (m, 2H, ArH), 7.44 – 7.31 (m, 7H, ArH), 2.32 (s, 3H, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 152.2, 151.2, 151.1, 146.2, 136.3, 129.1 (2C), 129.0, 128.7 (2C), 122.03, 122.01, 119.4 (2C), 118.8, 12.4; MS (EI): m/z 296.8 M$^+$; HRMS Calcd for [C$_{16}$H$_{12}$N$_3$OCl + H]$^+$: 298.0742, found: 298.0742.
2-(2-Chlorophenyl)-5-methyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (2i). Red solid; mp = 119-120 °C; IR (Capillary): 3460, 2999, 2332, 2090, 1904, 1737, 1366, 1216, 1061, 885, 739 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.51 – 7.47 (m, 3H, ArH), 7.44 – 7.39 (m, 3H, ArH), 7.35 – 7.31 (m, 3H, ArH), 2.33 (s, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃): δ 151.9, 151.4, 150.9, 146.1, 130.7, 130.1, 129.3, 129.1, 128.7 (2C), 128.6, 127.7, 122.9 (2C), 118.9, 12.5; MS (EI): m/z 296.7 M⁺; Elemental Analysis (CHN): calculated for [C₁₆H₁₂N₃OCl]: C = 64.54%, H = 4.06%, N = 14.11%, found C = 64.52%, H = 4.01%, N = 14.32%.

5-Methyl-4-(phenylimino)-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one (2j). Red solid; mp = 75-77 °C; IR (Capillary): 3354, 2934, 2702, 2339, 2092, 1907, 1690, 1497, 1306, 1129, 993, 774, 683 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.75 (d, J = 8.5 Hz, 2H, ArH), 7.44 – 7.39 (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, CH₃), 2.33 (s, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃): 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 Calcd for [C₁₇H₁₅N₃O + Na]⁺: 300.1107, found: 300.1107.

2,5-Dimethyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (2k). Red wax; IR (CDCl₃): 3339, 2932, 2666, 3340, 2904, 1906, 1705, 1440, 1307, 1218, 1056, 935, 735 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.41 – 7.24 (m, 5H, ArH), 3.28 (s, 3H, CH₃), 2.20 (s, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃): δ 153.0, 152.7, 149.1, 146.3, 128.7 (2C), 122.1 (2C), 115.3, 31.7, 12.2; MS (EI): m/z 201.1 M⁺; HRMS Calcd for [C₁₁H₁₁N₃O + Na]⁺: 224.0794, found: 224.0794.
5-Ethyl-2-phenyl-4-(phenylimino)-2,4-dihydro-3\textit{H}-pyrazol-3-one (2l). Red solid; mp = 94-96 °C; IR (Capillary): 3460, 2970, 2663, 2336, 2094, 1728, 1589, 1479, 1341, 1225, 1117, 1037, 919, 836, 755 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{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, CH\textsubscript{2}CH\textsubscript{3}), 1.40 (t, J = 7.5 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}): δ 154.6, 152.3, 151.3, 146.4, 137.7, 129.0 (2C), 128.7 (2C), 128.6, 125.6, 121.7, 118.4 (2C), 118.3, 20.2, 10.6; MS (EI): m/z 276.8 M\textsuperscript{+}; HRMS Calcd for [C\textsubscript{17}H\textsubscript{15}N\textsubscript{3}O + Na\textsuperscript{+}]: 300.1107, found: 300.1109.

2-Phenyl-4-(phenylimino)-5-propyl-2,4-dihydro-3\textit{H}-pyrazol-3-one (2m). Red Solid; mp = 55-58 °C; IR (Capillary): 3351, 2944, 2338, 2092, 1905, 1703, 1478, 1314, 1101, 894, 753 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): 7.89 – 7.87 (m, 2H, ArH), 7.44 – 7.38 (m, 4H, ArH), 7.35 – 7.30 (m, 3H, ArH), 7.22 – 7.19 (m, 1H, ArH), 2.71 – 2.69 (m, 2H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.89 – 1.83 (m, 2H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.09 (t, J = 7.4 Hz, 3H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}): δ 153.7, 152.5, 151.26, 146.4, 137.7, 129.0 (2C), 128.7 (2C), 128.6, 125.6, 121.6 (2C), 118.5 (2C), 28.6, 20.1, 14.1; MS (EI): m/z 290.9 M\textsuperscript{+}; Elemental Analysis (CHN): calculated for [C\textsubscript{18}H\textsubscript{17}N\textsubscript{3}O]: C = 74.20%, H = 5.88%, N = 14.42%, found C = 74.03%, H = 5.70%, N = 14.44%.

5-Isopropyl-2-phenyl-4-(phenylimino)-2,4-dihydro-3\textit{H}-pyrazol-3-one (2n). Red solid; mp = 77-79 °C; IR (Capillary): 3398, 2959, 2707, 2340, 2093, 1709, 1593, 1467, 1334, 1256, 1102, 977, 835, 747, 685 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{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, CH(CH\textsubscript{3})) \textsuperscript{2}; \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}): δ 157.5, 152.0, 151.3, 146.5, 137.8, 129.0 (2C), 128.7 (2C), 128.6, 125.6, 121.6 (2C), 118.5 (2C), 28.6, 20.1, 14.1; MS (EI): m/z 290.9 M\textsuperscript{+}; HRMS Calcd for [C\textsubscript{18}H\textsubscript{17}N\textsubscript{3}O + Na\textsuperscript{+}]: 314.1264, found: 314.1264.

5-(\textit{tert}-Butyl)-2-phenyl-4-(phenylimino)-2,4-dihydro-3\textit{H}-pyrazol-3-one (2o). Red solid; mp = 95-97 °C; IR (Capillary): 2957, 2340, 2095, 1925, 1717, 1590, 1479, 1375, 1304, 1213, 1108, 963, 839, 689 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{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, CH(CH\textsubscript{3})) \textsuperscript{2}; \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{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\textsuperscript{+}; HRMS Calcd for [C\textsubscript{18}H\textsubscript{17}N\textsubscript{3}O + Na\textsuperscript{+}]: 314.1264, found: 314.1264.
$^{13}$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 Calcd for [C$_{19}$H$_{19}$N$_3$O + H]$^+$: 306.1601, found: 306.1602.

2,5-Diphenyl-4-(phenylimino)-2,4-dihydro-3H-pyrazol-3-one (2p). Red solid; mp = 176-178 °C; IR (Capillary): 3449, 3026, 2682, 2338, 2092, 1896, 1714, 1592, 1482, 1399, 1307, 1142, 925, 838, 687 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 8.32 – 8.30 (m, 2H, ArH), 7.99 – 7.97 (m, 2H, ArH), 7.51 – 7.42 (m, 7H, ArH), 7.35 – 7.21 (m, 3H, ArH), 7.26 – 7.23 (m, 1H, ArH); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 152.1, 150.7, 147.1, 146.9, 137.6, 130.8, 129.0 (2C), 128.8 (3C), 128.7 (2C), 128.2, 128.1 (2C), 125.9, 120.6 (2C), 118.7 (2C); MS (EI): $m/z$ 324.8 M$^+$; Elemental Analysis (CHN): Calcd for [C$_{21}$H$_{15}$N$_3$O]: C = 77.52%, H = 4.65%, N = 12.91%, found C = 77.69%, H = 4.71%, N = 13.08%.

3-Methyl-1-phenyl-1H-pyrazole-4,5-dione (7). Red solid; 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 Calcd for [C$_{10}$H$_8$N$_2$O$_2$]: 188.0580, found: 188.0583.

(R)-3-Methyl-5-oxo-1-phenyl-1-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3a). Reddish brown wax (83 mg, 95%); [α]$_D$ = –11.5 (c = 0.6, CH$_2$Cl$_2$); 95.5:4.5 er; HPLC: tR 11.08 min (major), 12.44 min (minor), 230 nm, n-heptane/i-PrOH, 97:3, 0.7 mL/min, Chiralpak IC column; IR (CHCl$_3$): 3329, 2916, 2314, 2098, 1732, 1467, 1369, 1222, 747 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.85 – 7.83 (m, 2H, ArH), 7.46 – 7.44 (m, 2H, ArH), 7.30 – 7.26 (m, 1H, ArH), 7.22 – 7.20 (m, 2H, ArH), 6.96 (t, J = 7.4 Hz, 1H, ArH), 6.70 – 6.69 (m, 2H, ArH), 4.71 (s, 1H, NH), 2.35 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 164.7, 154.7, 141.9, 136.9, 129.9 (2C), 129.3 (2C), 126.6, 122.7, 119.2 (2C), 116.6 (2C), 112.4, 62.4, 14.5; MS (EI): $m/z$ 289.9 M$^+$; HRMS Calcd for [C$_{17}$H$_{14}$N$_3$O + Na]$^+$: 313.1060, found: 313.1061.
(S)-3-Methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3a). Reddish brown wax (75 mg, 86%); [α]D²⁴ = –10.0 (c = 0.5, CHCl₃); HPLC: tR 11.21 min (minor), 12.51 min (major), 230 nm, n-heptane/i-PrOH, 97:3, 0.7 mL/min, Chiralpak IC column.

**tert-Butyl (R)-(4-cyano-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)carbamate (3b).** White Solid (93 mg, 83%); mp = 150 – 152 °C [α]D²⁴ = –10.0 (c = 0.5, CHCl₃); 62:38 er; HPLC: tR 7.73 min (minor), 8.23 min (major), 254 nm, n-heptane/i-PrOH, 7:3, 0.5 mL/min, Chiralpak IA column; IR (Capillary): 3306, 2980, 2335, 2106, 1715, 1599, 1498, 1364, 1278, 1155, 880, 753 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.86 (d, J = 8.1 Hz, 2H, ArH), 7.44 – 7.41 (m, 2H, ArH), 7.26 – 7.24 (m, 1H), 5.98 (s, 1H, NH), 2.30 (s, 3H, CH₃), 1.39 (br s, 9H, t-Bu); ¹³C NMR (151 MHz, CDCl₃): δ 164.1, 153.1, 137.2, 129.2 (2C), 126.3 (2C), 119.2 (2C), 111.1, 83.6, 58.9, 28.1 (3C), 13.7; MS (EI): m/z 314.2 M⁺; HRMS Calcd for [C₁₆H₁₈N₄O₃ + Na]⁺: 337.1271, found: 337.1269.

(R)-4-((4-Fluorophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (3c). Yellowish brown wax (69 mg, 75%); [α]D²⁴ = –18.0 (c = 0.5, CH₂Cl₂); 97.0:3.0 er; HPLC: tR 8.27 min (minor), 15.32 min (major), 230 nm, n-heptane/i-PrOH, 8:2, 1.0 mL/min, Chiralpak AD column; IR (CHCl₃): 3343, 3052, 2257, 2090, 1724, 1600, 1501, 1363, 1227, 1115, 783 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.79 – 7.76 (m, 2H, ArH), 7.44 – 7.40 (m, 2H, ArH), 6.93 – 6.89 (m, 2H, ArH), 6.77 – 6.74 (m, 2H), 6.74 (m, 2H), 4.52 (s, 1H, NH), 2.33 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 164.8, 159.2, 154.3, 137.6, 136.8, 129.3 (2C), 126.6, 120.3 (2C), 119.2 (2C), 116.6 (2C), 112.4, 63.0, 14.5; MS (EI): m/z 308.0 M⁺; HRMS Calcd for [C₁₇H₁₃N₄OF + Na]⁺: 331.0966, found: 331.0966.
(S)-4-((4-Fluorophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3c). Yellowish brown wax (64 mg, 69%); [α]D^21 = −4.0 (c = 0.5, CH2Cl2); 96.9:3.1 er; HPLC: tR 8.27 min (major), 15.33 min (minor), 230 nm, n-heptane/i-PrOH, 8:2, 1.0 mL/min, Chiralpak AD column.

(R)-4-((4-Chlorophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (3d). Light brown wax (78 mg, 80%); [α]D^21 = −4.0 (c = 0.5, CH2Cl2); 94.4:5.6 er; HPLC: tR 6.35 min (minor), 13.32 min (major), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column; IR (CHCl3): 3305, 2919, 2318, 2100, 1728, 1599, 1473, 1371, 1180, 1089, 812 cm⁻¹; ¹H NMR (600 MHz, CDCl3): δ 7.84 – 7.72 (m, 2H, ArH), 7.47 – 7.44 (m, 2H, ArH), 7.31 – 7.28 (m, 1H, ArH), 7.15 – 7.14 (m, 2H, ArH), 6.62 – 6.60 (m, 2H, ArH), 4.87 (s, 1H, NH), 2.34 (s, 3H, CH3); ¹³C NMR (151 MHz, CDCl3): δ 164.6, 154.5, 140.5, 136.8, 129.8 (2C), 129.3 (2C), 127.8, 126.7, 119.2 (2C), 117.8 (2C), 112.1, 62.3, 14.4; MS (EI): m/z 323.9 M⁺, HRMS Calcd for [C₁₇H₁₃N₄OCl + Na]⁺: 347.0670, found: 347.0671.

(S)-4-((4-Chlorophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3d). Light brown wax (77 mg, 79%); 94.4:5.6 er; HPLC: tR 6.35 min (major), 13.35 min (minor), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.

(R)-4-((4-Trifluoromethylphenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (3e). Light brown wax (88 mg, 82%); [α]D^21 = −15.0 (c = 0.4, CH2Cl2); 85.5:15.5 er; HPLC: tR 10.35 min (major), 13.81 min (minor), 254 nm, n-heptane/i-PrOH, 9:1, 1.0 mL/min, Chiralpak IA column; IR (CHCl3): 3351, 2324, 2085, 1722, 1615,
1530, 1495, 1362, 1321, 1262, 1160, 1100, 1065, 1011, 941, 908, 827, 755, 688 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.87 – 7.84 (m, 2H, ArH), 7.48 – 7.44 (m, 2H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.32 – 7.28 (m, 1H, ArH), 6.59 (d, J = 8.4 Hz, 2H, ArH), 5.38 (s, 1H, NH), 2.33 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 164.4, 154.5, 144.9, 136.8, 129.4 (2C), 127.2 (2C), 126.9, 124.2, 123.7, 119.2 (2C), 114.7, 114.4, 111.7, 61.7, 14.2; MS (EI): m/z 358.4 M⁺, HRMS Calcd for [C₁₈H₁₅N₄O₃ + K⁺]: 397.0673, found: 397.0607.

(S)-4-((4-Trifluoromethylphenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3e). Light brown wax (86 mg, 80%); 89:11 er; HPLC: tR 10.31 min (minor), 13.75 min (major), 254 nm, n-heptane/i-PrOH, 9:1, 1.0 mL/min, Chiralpak IA column.

(R)-4-((4-Methoxyphenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (3f). Brown wax (58 mg, 60%); [α]D²⁴ = −16.7 (c = 0.6, CH₂Cl₂); 97.6:2.4 er; HPLC: tR 8.05 min (minor), 17.36 min (major), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column; IR (CHCl₃): 3276, 2910, 2343, 2088, 1731, 1475, 1205, 1056, 789 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.79 – 7.77 (m, 2H, ArH), 7.43-7.41 (m, 2H, ArH), 7.26-7.24 (m, 1H, ArH), 6.85 (d, J = 9.0 Hz, 2H, ArH), 6.77 (d, J = 8.9 Hz, 2H, ArH), 4.35 (s, 1H, NH), 3.73 (s, 3H, OCH₃), 2.33 (s, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃): δ 165.2, 156.7, 154.5, 136.8, 134.4, 129.2 (2C), 126.5, 122.2 (2C), 119.2 (2C), 114.9 (2C), 112.7, 63.6, 55.6, 14.7; MS (EI): m/z 319.9 M⁺; HRMS Calcd for [C₁₈H₁₆N₄O₂ + Na⁺]: 343.1165, found: 343.1166.

(S)-4-((4-Methoxyphenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3f). Brown wax (57 mg, 59%); 96.4:3.6 er; HPLC: tR 8.07 min (major), 17.32 min (minor), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.
(R)-4-((2-Methylphenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (3g). Brown wax (35 mg, 38%); [α]D 24 = −26.7 (c = 0.6, CH2Cl2); 93.5:6.5 er; HPLC: tR 5.27 min (minor), 6.37 min (major), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column; IR (CHCl3): 3325, 2969, 2334, 2098, 1737, 1600, 1365, 1216, 1053, 906, 750 cm⁻¹; ¹H NMR (600 MHz, CDCl3): δ 7.97 – 7.85 (m, 2H, ArH), 7.47 – 7.44 (m, 2H, ArH), 7.30 – 7.27 (m, 1H, ArH), 7.15 (d, J = 7.2 Hz, 1H, ArH), 7.05 – 7.02 (m, 1H, ArH), 6.89 – 6.86 (m, 1H, ArH), 6.44 (dd, J = 8.0, 1.1 Hz, 1H, ArH), 4.41 (s, 1H, NH), 2.32 (s, 3H, CH3); ¹³C NMR (151 MHz, CDCl3): δ 164.8, 154.8, 140.2, 137.0, 131.4, 129.3 (2C), 127.6, 126.6, 125.9, 122.3, 119.2 (2C), 113.2, 112.6, 62.3, 17.7, 14.5; MS (EI): m/z 303.9 M⁺; HRMS Calcd for [C18H16N4O + Na]⁺: 327.1216, found: 327.1219.

(S)-4-((2-Methylphenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3g). Brown wax (34 mg, 37%); 92.0:8.0 er; HPLC: tR 5.27 min (major), 6.37 min (minor), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.

(R)-1-(4-Chlorophenyl)-3-methyl-5-oxo-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3h). Light brown solid (76 mg, 78%); mp = 131-134 °C; [α]D 24 = −8.2 (c = 0.6, CH2Cl2); 97.5:2.5 er; HPLC: 8.74 min (minor), tR 26.88 min (major), 214 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, ChiralCel AD column; IR (CHCl3): 3322, 3040, 2320, 2061, 1717, 1605, 1491, 1356, 1254, 1157, 1089, 1011, 830, 751 cm⁻¹; ¹H NMR (600 MHz, CDCl3): δ 7.82 – 7.79 (m, 2H, ArH), 7.41 – 7.39 (m, 2H, ArH), 7.22 – 7.20 (m, 2H, ArH), 6.98 – 6.96 (m, 1H, ArH), 6.69 – 6.67 (m, 2H, ArH), 4.64 (s, 1H, NH), 2.35 (s, 3H, CH3); ¹³C NMR (151 MHz, CDCl3): δ 164.6, 155.1, 141.8, 135.5, 131.8, 130.0 (2C), 129.4 (2C), 122.9, 120.2 (2C), 116.7 (2C), 112.2, 62.4, 14.5; MS (EI): m/z 323.9 M⁺, HRMS Calcd for [C17H13N4OCl + H]⁺: 325.0851, found: 325.0846.
(S)-1-(4-Chlorophenyl)-3-methyl-5-oxo-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3h). Light brown solid (76 mg, 78%); 97.0:3.0 er; HPLC: tR 8.70 min (major), 26.63 min (minor), 214 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.

(R)-1-(2-Chlorophenyl)-3-methyl-5-oxo-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3i). White Solid (85 mg, 87%); mp = 128-130 °C; [α]$_D^{24}$ = +15.0 (c = 1.0, CH$_2$Cl$_2$); 97:3 er; HPLC: tR 3.14 min (major), 3.70 min (minor), 230 nm, n-heptane/i-PrOH, 8:2, 1.0 mL/min, Chiralpak IC column; IR (CHCl$_3$): 3330, 3006, 2313, 2105, 1739, 1600, 1485, 1368, 1219, 1075, 864, 746 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.52 – 7.49 (m, 1H, ArH), 7.39 – 7.32 (m, 3H, ArH), 7.24 – 7.20 (m, 2H, ArH), 7.00 – 6.98 (m, 1H, ArH), 6.79 – 6.77 (m, 2H, ArH), 4.68 (s, 1H, NH), 2.32 (s, 3H, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.5, 154.6, 141.9, 133.3, 132.0, 130.9, 130.8, 129.8 (2C), 128.6, 127.8, 122.9, 117.2 (2C), 112.3, 61.2, 14.4; MS (EI): m/z 323.9 M$^+$; Elemental Analysis (CHN): calculated for [C$_{17}$H$_{13}$N$_4$OCl]: C = 62.87%, H = 4.03%, N = 17.25%, found C = 62.87%, H = 3.96%, N = 17.29%.

(R)-1-(2-Chlorophenyl)-3-methyl-5-oxo-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3i). White solid (85 mg, 87%); 96:4 er; HPLC: tR 3.14 min (minor), 3.70 min (major), 230 nm, n-heptane/i-PrOH, 8:2, 1.0 mL/min, Chiralpak IC column.
(R)-3-Methyl-5-oxo-4-(phenylamino)-1-(p-tolyl)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3j). Reddish brown wax (72 mg, 79%); $[\alpha]_D^{24} = -18.0$ (c = 1.0, CH$_2$Cl$_2$); 97:3 er; HPLC: tR 11.86 min (minor), 43.87 min (major), 230 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, ChiralCel AD column; IR (CHCl$_3$): 3319, 2929, 2312, 2088, 1715, 1603, 1358, 1271, 1139, 749, 690 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.72 – 7.70 (m, 2H, ArH), 7.26 – 7.24 (m, 2H, ArH), 7.21 – 7.18 (m, 2H, ArH), 6.95 (t, $J = 7.5$ Hz, 1H, ArH), 6.69 – 6.67 (m, 2H, ArH), 4.78 (s, 1H, NH), 2.38 (s, 3H, CH$_3$), 2.34 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 164.6, 154.6, 142.0, 136.5, 134.5, 129.8 (2C), 129.7 (2C), 122.5, 119.3 (2C), 116.5 (2C), 112.4, 62.3, 21.1, 14.4; MS (ESI): m/z 303.9 M$^+$; HRMS Calcd for [C$_{18}$H$_{16}$N$_4$O + Na]$^+$: 327.1216, found: 327.1218.

(S)-3-Methyl-5-oxo-4-(phenylamino)-1-(p-tolyl)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3j). Reddish brown wax (68 mg, 75%); 96:4 er; HPLC: tR 11.84 min (major), 43.18 min (minor), 230 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.

(R)-1,3-Dimethyl-5-oxo-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3k). Brown wax (63 mg, 92%); $[\alpha]_D^{24} = -34.9$ (c = 0.6, CH$_2$Cl$_2$); 96.5:3.5 er; HPLC: tR 4.76 min (minor), 5.86 min (major), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column; IR (CHCl$_3$): 3369, 3013, 2277, 2088, 1725, 1601, 1493, 1375, 1221, 1034, 920, 746 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.22 – 7.20 (m, 2H, ArH), 6.99 – 6.92 (m, 1H, ArH), 6.65 – 6.63 (m, 2H), 4.59 (s, 1H, NH), 3.37 (s, 3H, N-CH$_3$), 2.22 (s, 3H, CH$_3$); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 166.5, 153.8, 142.0, 129.7 (2C), 122.3, 116.3 (2C), 112.3, 60.6, 32.3, 14.2; MS (EI): m/z 228.0 M$^+$; Elemental Analysis (CHN): calculated for [C$_{12}$H$_{12}$N$_2$O]: C = 63.15%, H = 5.30%, N = 24.55%, found C = 63.09%, H = 5.16%, N = 24.47%.
(S)-1,3-Dimethyl-5-oxo-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3k). Brown wax (63 mg, 92%); 97.5:2.5 er; HPLC: tR 4.77 min (major), 5.86 min (minor), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.

(R)-3-Ethyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3l). Brown wax (74 mg, 81%); $[\alpha]_D^{24} = -4.0$ (c = 0.5, CH$_2$Cl$_2$); 96.5:3.5 er; HPLC: tR 8.03 min (minor), 21.64 min (major), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column; IR (CHCl$_3$): 3316, 2929, 2102, 1724, 1600, 1494, 1349, 1207, 1051, 933, 747, 686 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 – 7.85 (m, 2H, ArH), 7.46 – 7.42 (m, 2H, ArH), 7.29 – 2.27 m, 1H, ArH), 7.19 – 7.15 (m, 2H, ArH), 6.94 – 6.91 (m, 1H, ArH), 6.64 – 6.62 (m, 2H, ArH), 4.82 (s, 1H, NH), 2.75 – 2.60 (m, 2H, CH$_2$CH$_3$), 1.36 (t, $J = 7.3$ Hz, 3H, CH$_2$CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 165.0, 158.8, 142.1, 137.1, 129.8 (2C), 129.2 (2C), 126.5, 122.4, 119.2 (2C), 116.2 (2C), 112.6, 62.2, 22.2, 9.4; MS (EI): m/z 303.9 M$^+$; Elemental Analysis (CHN): calculated for [C$_{18}$H$_{16}$N$_4$O]: C = 71.04%, H = 5.30%, N = 18.41%, found C = 70.93%, H = 5.29%, N = 18.53%.

(S)-3-Ethyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3l). Brown wax (72 mg, 79%); 95.5:5.5 er; HPLC: tR 8.02 min (major), 21.65 min (minor), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.

(R)-3-n-Propyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3m). Brown wax (72 mg, 75%); $[\alpha]_D^{24} = -26.0$ (c = 0.5, CH$_2$Cl$_2$); 98:2 er; HPLC: tR 9.04 min (minor), 21.19 min (major), 230 nm, n-heptane/i-PrOH, 8:2, 1.0 mL/min, Chiralpak AD column; IR (CHCl$_3$): 3351, 2955, 2329, 2100, 1730, 1598, 1493, 1355, 1219, 1111, 885, 748 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.85 (d, $J = 8.1$ Hz, 2H, ArH), 7.46 – 7.42 (m, 2H, ArH), 7.28 – 7.24 (m, 1H, ArH), 7.20 – 7.15 (m, 2H, ArH), 6.92 (t, $J = 7.4$ Hz, 1H, ArH), 6.63 – 6.61 (m, 2H, ArH), 4.78 (s, 1H, NH), 2.69 – 2.51 (m, 2H, CH$_2$CH$_2$CH$_3$), 1.80 – 1.82
(m, 2H, CH₂CH₂CH₃), 1.05 (t, J = 7.3 Hz, 3H CH₂CH₂CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 164.9, 157.8, 142.1, 137.10, 129.8 (2C), 129.2 (2C), 126.5, 122.4, 119.2 (2C), 116.2 (2C), 112.6, 62.2, 30.5, 18.8, 13.8.; MS (EI): m/z 318.0 M⁺; HRMS Calcd for [C₁₉H₁₈N₄O + Na]⁺: 341.1373, found: 341.1372.

(S)-3-ₙ-Propyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3m). Brown wax (71 mg, 74%); 98.0:2.0 er; HPLC: tR 9.04 min (major), 21.15 min (minor), 234 nm, n-heptane/i-PrOH, 8:2, 1.0 mL/min, Diacel AD column.

(R)-3-iso-Propyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3n). Light brown wax (54 mg, 56%); mp = 73 – 75 °C; [α]D²⁴ = –16.7 (c = 0.6, CH₂Cl₂); 98.5:1.5 er; HPLC: tR 8.16 min (minor), tR 20.83 min (major), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, ChiralCel AD column; IR (CHCl₃): 3309, 2925, 2326, 2016, 1717, 1599, 1494, 1349, 1080, 911, 749 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 7.88 (dd, J = 9.0, 1.2 Hz, 2H, ArH), 7.47 – 7.44 (m, 2H, ArH), 7.23 – 7.27 (m, 1H, ArH), 7.16 – 7.18 (m, 2H, ArH), 6.91 (t, J = 7.2 Hz, 1H), 6.56 – 6.54 (m, 2H, ArH), 4.85 (s, 1H, NH), 2.95 (hept, J = 6.9 Hz, 1H, CH), 1.48 (d, J = 6.9 Hz, 3H, CH₃), 1.32 (d, J = 6.9 Hz, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃): δ 165.0, 162.0, 142.3, 137.2, 129.9 (2C), 129.3 (2C), 126.5, 122.1, 119.2 (2C), 115.6 (2C), 112.9, 61.7, 29.6, 21.3, 19.6; MS (EI): m/z 318.0 M⁺; HRMS Calcd for [C₁₉H₁₈N₄O + Na]⁺: 341.1373, found: 341.1388.

(S)-3-iso-Propyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (ent-3n). Light brown wax (52 mg, 56%); 99:1.0 er; HPLC: tR 8.14 min (major), 21.01 min (minor), 254 nm, n-heptane/i-PrOH, 7:3, 1.0 mL/min, Chiralpak AD column.

(R)-5-Oxo-1,3-diphenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3p). Reddish brown wax (15 mg, 14%); [α]D²⁴ = –20.0 (c = 0.3, CH₂Cl₂); 92.8:7.2 er; HPLC: tR
28.49 min (minor), 32.03 min (major), 254 nm, n-heptane/i-PrOH, 97:3, 0.5 mL/min, Chiralpak OD column; IR (CHCl₃): 3347, 3050, 2918, 2638, 2453, 2299, 2078, 1988, 1718, 1598, 1493, 1376, 1296, 1114, 909, 751, 687 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 8.20 – 8.18 (m, 2H, ArH), 7.87 – 7.85 (m, 2H, ArH), 7.56 – 7.52 (m, 3H, ArH), 7.47 – 7.44 (m, 2H, ArH), 7.31 – 7.28 (m, 1H, ArH), 7.18 – 7.15 (m, 2H, ArH), 6.97 – 6.94 (m, 1H, ArH), 6.85 – 6.83 (m, 2H, ArH), 4.71 (s, 1H, NH); ¹³C NMR (151 MHz, CDCl₃): δ 165.1, 151.3, 141.6, 136.9, 132.2, 129.7 (2C), 129.4 (2C), 129.3 (2C), 127.9, 127.0 (2C), 126.8, 123.5, 119.5 (2C), 118.7 (2C), 113.1, 61.5; MS (ESI): m/z 351.9 M⁺; HRMS Calcd for [C₂₂H₁₆N₄O + H]⁺: 353.1397, found: 353.1390.

(S)-5-Oxo-1,3-diphenyl-4-(phenylamino)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3p). Reddish brown wax (14 mg, 13%); 92.0:8.0 er; HPLC: tR 28.27 min (major), 31.91 min (minor), 254 nm, n-heptane/i-PrOH, 97:3, 0.5 mL/min, Chiralcel OD column.

(S)-4-Amino-3-methyl-5-oxo-phenyl-4-5-dihydro-1H-pyrazole-4-carbonitrile (4). Brown wax (30 mg, 70%); [α]D²⁴ = -11.5 (c = 0.5, CHCl₃); 96.3:3.4 er; HPLC: tR 6.31 min (major), 7.61 min (minor), 254 nm, n-heptane/i-PrOH, 8:2, 1.0 mL/min, Chiralpak AD column; IR (CHCl₃): 3842, 2679, 2344, 2092, 1752, 1140 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.81 – 7.79 (m, 2H, ArH), 7.43 – 7.39 (m, 2H, ArH), 7.26 – 7.22 (m, 1H, ArH), 2.32 (s, 3H, CH₃), 2.30 – 2.20 (m, 2H, NH₂); ¹³C NMR (151 MHz, CDCl₃): δ 166.1, 154.9, 136.9, 129.2 (2C), 126.4, 119.1 (2C), 114.4, 58.8, 13.6; MS (EI): m/z 214.2; HRMS Calcd for [C₁₁H₁₀N₄O + H]⁺: 215.0927, found: 215.0929.
NMR Spectra:
3j
HPLC Data:

**AK Prof. Enders - Analytiklabor 4.04**

Sample name: SM 226 L  
Data file: C:\SNOOPY\SM226LIC.D  
Description: Mobile phase: n-Hexane/IPOH 97:3; The sample is solved in DCM/MeCN  
Injection date: 6/25/2016 3:30:41 PM  
Acq. Analysis method: CHIRALPAK IC-8LNP.M  
Column: Chiralpak IC, (150 x 4.6) mm, 5μ, SN: IC00CD-QF815

Pressure at start: 23 bar  
Start flow: 0.700 ml/min  
Column oven: 29.98 °C

**AK Prof. Enders - Analytiklabor 4.04**

Sample name: SM 227 L  
Data file: C:\SNOOPY\SM227LIC.D  
Description: Mobile phase: n-Hexane/IPOH 97:3; The sample is solved in DCM/MeCN  
Injection date: 8/25/2016 3:57:49 PM  
Acq. Analysis method: CHIRALPAK IC-8LNP.M  
Column: Chiralpak IC, (150 x 4.6) mm, 5μ, SN: IC00CD-QF015

Pressure at start: 23 bar  
Start flow: 0.700 ml/min  
Column oven: 29.98 °C

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Data file: D:\1ERN1\2M226J.D
Sample Info: Mobile phase: n-Heptane/IPrOH 7:3
The sample is solved in DCM/AM

Column: DAICELAD.M
Column info: (250 x 4)mm 5µ non-chiral column
Operator: Analytical Lab AMEN

Injektion Time: 09:07:35
Injektion Date: 29.08.2016
Instrument Conditions: At Start At Stop
Temperature in °C: 30.0 30.0
Pressure in bar: 40.2 40.7
Flow in ml/min: 1.0 1.0

[Graph of chromatogram for (R)-3g]

Sample Name: SM2273
Data file: D:\1ERN1\SM227JAD.D
Sample Info: Mobile phase: n-Heptane/IPrOH 7:3
The sample is solved in DCM/AM

Column: DAICELAD.M
Column info: (250 x 4)mm 5µ non-chiral column
Operator: Analytical Lab AMEN

Injektion Time: 09:22:12
Injektion Date: 29.08.2016
Instrument Conditions: At Start At Stop
Temperature in °C: 30.0 30.0
Pressure in bar: 41.8 41.0
Flow in ml/min: 1.0 1.0

[Graph of chromatogram for (S)-3g]
Sample Name: SM226m
Data file: D:\CHTHK\SM226MAD.D
Sample Info: Mobile phase: n-Heptane/IPyOH 8:2
The sample is solved in DCM/DM

Column: DAICELAD.M
Column info: Chiralpak AD (250 x 4.6)mm 10µ
Operator: Analytical Lab ASEN

Injection Time: 14:25:36
Injection Date: 29.08.2016

Instrument Conditions: At Start At Stop
Temperature in °C: 30.0 30.0
Pressure in bar: 36.4 35.7
Flow in ml/min: 1.0 1.0

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Sample Name: SM227m
Data file: D:\CHTHK\SM227MAD.D
Sample Info: Mobile phase: n-Heptane/IPyOH 8:2
The sample is solved in DCM/DM

Column: DAICELAD.M
Column info: Chiralpak AD (250 x 4.6)mm 10µ
Operator: Analytical Lab ASEN

Injection Time: 15:00:29
Injection Date: 29.08.2016

Instrument Conditions: At Start At Stop
Temperature in °C: 30.0 30.0
Pressure in bar: 36.4 35.7
Flow in ml/min: 1.0 1.0

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### Table 1

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Sample Info: Mobile phase: n-Heptane/EtOH 97:3;
The sample is solved in DCM/MP

Säule: DAICELOD.M
Säuleninfo: Chiralpak AD (250x4,6)mm
Operator: Analytik Labor AKEN

Injektion Time: 13:11:45
Injektion Date: 25.11.2016

Instrument Conditions: At Start At Stop
Temperature in °C: 30.0 °C 30.0°
Pressure in bar: 19.1 19.9
Flow in ml/min: 0.50 0.50

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Sample Name: SM-227B
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Sample Info: Mobile phase: n-Heptane/EtOH 97:3;
The sample is solved in DCM/MP

Säule: DAICELOD.M
Säuleninfo: Chiralpak AD (250x4,6)mm
Operator: Analytik Labor AKEN

Injektion Time: 14:02:58
Injektion Date: 25.11.2016

Instrument Conditions: At Start At Stop
Temperature in °C: 30.0 °C 30.0°
Pressure in bar: 19.2 19.3
Flow in ml/min: 0.50 0.50

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Total: 4291.30 100.00
Sample Name: PC11108AC
Data file: Dr\GONZO\PC\PC11108AC.D
Sample Info: Chiralpak AD, 0.2 (Hex:EtOH), 1 ml min⁻¹
The sample is solved in DCN/MeOH

Sample: DAICELAD-M
Säuleninfo: Chiralpak AD (250x4,6) mm
Technik: Analytik Labor AKN

Injection Time: 15:49:55
Injection Date: 05.03.2017

Instrument Conditions:  

- Temperature in °C: 30, 30
- Pressure in bar: 35.6, 35.8
- Flow in ml/min: 1.00, 1.00

\[ \text{DAD1A, Sig=254.16 Ret=360.100 (PC/PC11108AC.D)} \]

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Total 1291.31 100.00

Sample Name: PC1112
Data file: Dr\GONZO\PC\PC1112.D
Sample Info: n-Hexane/EtOH at 2 S Flow 1.0 ml min⁻¹, Chiralpak AD
The sample is solved in DCN/MeOH

Sample: DAICELAD-M
Säuleninfo: Chiralpak AD (250x4,6) mm
Technik: Analytik Labor AKN

Injection Time: 10:17:46
Injection Date: 03.04.2017

Instrument Conditions:  

- Temperature in °C: 30, 30
- Pressure in bar: 33.3, 33
- Flow in ml/min: 1.00, 1.1

\[ \text{DAD1A, Sig=254.16 Ret=360.100 (PC/PC1112.D)} \]

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Total 1023.13 100.00