Supporting Information

Rh-Catalyzed three-component reaction for the diastereoselective synthesis of pyrazolone derivatives with contiguous quaternary stereocenters

Chaoqun Ao, Jingjing Huang, Xinfang Xu, Shikun Jia, Zhenghui Kang* and Wenhao Hu*

Guangdong Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

E-mail: kangzhh3@mail.sysu.edu.cn.
       huwh9@mail.sysu.edu.cn

1. General information & materials ................................................................. 1
2. Experimental procedures ........................................................................... 2
3. General procedure for the scale up and product derivatizations .............. 3
4. Control experiments .................................................................................. 4
5. References .................................................................................................. 4
6. Single crystal X-ray diffraction data ......................................................... 5
7. Analytical data of products ....................................................................... 6
8. NMR spectra of products ......................................................................... 21
1. General information & materials

**General:** All $^1$H NMR (400 MHz, 500MHz) and $^{13}$C NMR (100 MHz, 125MHz) and $^{19}$F NMR (376 MHz, 471MHz) spectra were recorded on 400 or 500 MHz spectrometers in D$_6$-DMSO or CDCl$_3$; chemical shifts were reported in ppm with the solvent signal as reference, and coupling constants ($J$) were given in Hertz. The peak information was described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite signals. High-resolution mass spectrometry (HRMS) were recorded on a commercial apparatus (ESI or CI Source).

**Materials:** All reactions were carried out under nitrogen atmosphere in a well-dried glassware. Solvent CH$_2$Cl$_2$ was distilled over calcium hydride. Metal catalysts used in this reaction were purchased from commercial sources and used without further purification. Diazo compounds 2$^1$, Ketimine 3$^2$ were prepared according to literature procedures. 4 Å Molecular sieve was dried in a Muffle furnace at 250 °C over 5 h.
2. Experimental procedures

2.1 General procedure for optimization of conditions of the three-component reaction

To a 10-mL oven-dried vial containing a magnetic stirring bar, alcohol 1a (0.24 mmol, 1.2 equiv), ketimine 3a (0.2 mmol, 1.0 equiv), metal catalyst (x mol %), and activated 4Å molecular sieves (200 mg) in solvent (1 mL); 2 (0.24 mmol, 1.2 equiv) in solvent (1 mL) was added over 1 hour by syringe pump at room temperature. When the reaction was completed (monitored by TLC), then filtrated and evaporated in vacuo to give the crude product. The residue was subjected to proton NMR analysis in CDCl₃ without any additional treatment. Recycled residue of entry 4-5 were purified by flash column chromatography on silica gel without additional treatment (hexanes/ethyl acetate = 10:1 to 5:1) to afford the pure products.

<table>
<thead>
<tr>
<th>entry</th>
<th>[M]</th>
<th>x mol%</th>
<th>solvent</th>
<th>yield (4a/6a)ᵇ</th>
<th>drᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(CH₃CN)₄BF₄</td>
<td>5</td>
<td>DCM</td>
<td>&lt;10/ 90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[PdCl(Allyl)]₂</td>
<td>5</td>
<td>DCM</td>
<td>32/ 50</td>
<td>&gt; 95: 5</td>
</tr>
<tr>
<td>3</td>
<td>JohnphosAu(CH₃CN)SbF₆</td>
<td>5</td>
<td>DCM</td>
<td>&lt;10/ 40</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(OAc)₄</td>
<td>5</td>
<td>DCM</td>
<td>90/ &lt;10</td>
<td>&gt; 95: 5</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(OAc)₄</td>
<td>1</td>
<td>DCM</td>
<td>90/ &lt;10</td>
<td>&gt; 95: 5</td>
</tr>
<tr>
<td>6</td>
<td>Rh₂(OAc)₄</td>
<td>1</td>
<td>Toluene</td>
<td>89/ &lt;10</td>
<td>&gt; 95: 5</td>
</tr>
<tr>
<td>7</td>
<td>Rh₂(OAc)₄</td>
<td>1</td>
<td>THF</td>
<td>50/ &lt;10</td>
<td>&gt; 95: 5</td>
</tr>
<tr>
<td>8</td>
<td>Rh₂(OAc)₄</td>
<td>1</td>
<td>DCE</td>
<td>78/ &lt;10</td>
<td>&gt; 95: 5</td>
</tr>
</tbody>
</table>

2.2 General procedure for the three-component reaction

To a 10-mL oven-dried vial containing a magnetic stirring bar, alcohol 1 (0.24 mmol, 1.2 equiv), ketimine 3 (0.2 mmol, 1.0 equiv), Rh₂(OAc)₄ (0.88 mg, 1 mol %), and activated 4Å molecular sieves (200 mg) in dry DCM (1 mL); 2 (0.24 mmol, 1.2 equiv) in dry DCM (1 mL) was added over 1 hour by syringe pump at room temperature. When the reaction was completed (monitored by TLC), then the solvent was evaporated in vacuo and the residue was purified by flash column...
chromatography on silica gel without additional treatment (hexanes/ethyl acetate = 10:1 to 5:1) to afford the pure products 4 or 5 in good to high yields.

3. General procedure for the scale up and product derivatizations

**General procedure for the scale up**

![Chemical reaction diagram]

**General procedure for the scale up:** To a 25-mL oven-dried round-bottom flask containing a magnetic stirring bar, benzyl alcohol 1a (3 mmol, 0.32 g, 1.2 equiv), ketimine 3a (2.5 mmol, 0.72 g, 1.0 equiv), Rh$_2$(OAc)$_4$ (11 mg, 1 mol %), and activated 4Å molecular sieves (500 mg) in dry DCM (5 mL). Then 2a (3 mmol, 0.53 g, 1.2 equiv) in dry DCM (5 mL) was added over 1 hour by syringe pump at room temperature. When the reaction was completed (monitored by TLC), then the solvent was evaporated in vacuo and the residue was purified by flash column chromatography on silica gel without additional treatment (hexanes/ethyl acetate = 10:1 to 5:1) to afford 1.22 g pure 5a as white solid (90% yield).

**Product derivatization**

![Chemical reaction diagram]

**Synthesis of 7a:** To a 10-mL oven-dried round-bottom flask with a magnetic stirring bar, 5a (0.1 mmol, 54.3 mg, 1.0 equiv) in MeOH (1 mL). Then 2 M HCl in MeOH (0.06 mL, 1.2 equiv) was added into the flask. The mixture was stirred at room temperature about 24 hours. The mixture was evaporated in vacuo directly to give 46 mg pure product 7a in 96% yields.

**Synthesis of 8a:** To a 10-mL oven-dried round-bottom flask with a magnetic stirring bar, 5a (0.1
mmol, 54.3 mg, 1.0 equiv) in dry THF (1mL). The flask was sealed with a septum, evacuated and refilled with nitrogen (3 cycles). LiAlH₄ (2.5 mol/L in THF, 0.04 mL, 1.0 equiv) was dropped into the flask at 0 °C. The mixture was stirred at room temperature about 30 mins. MeOH (0.2 mL) was added slowly to quench the reaction. Then, water was added, and extracted with DCM. The organic extracts were combined and dried over Na₂SO₄. The solvent was evaporated in vacuo after filtration, and the residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 8:1- 4:1) to give 46.3 mg pure product 8a in 90% yields.

4. Control experiments

![Chemical structure](image)

Control experiments starting from the O-H insertion product 9 and 3a was conducted under the standard condition, in which no three-component product was observed. These results exclude the possibility that the product is generated from the O-H insertion product.

![Chemical structure](image)

The by-product 6a derived from 1a and 3a, could not convert to product 5a under the reaction conditions, which indicate that 6a is not the intermediate for this transformation.

5. References


6. Single crystal X-ray diffraction data

Bond precision: C-C = 0.0061 Å, Wavelength=1.54184

Cell: a=8.3958(1) b=10.3211(2) c=33.5425(5)
alpha=90 beta=91.208(1) gamma=90
Temperature: 100 K

Calculated

Volume 2905.94(8) 2905.94(8)
Space group P 21/n  P 1 21/n 1
Hall group -P 2yn -P 2yn
Moisety formula C31 H32 Br N3 O6 C31 H32 Br N3 O6
Sum formula C31 H32 Br N3 O6 C31 H32 Br N3 O6
Mr 622.50 622.50
Dx,g cm−3 1.423 1.423
Z 4 4
Mu (mm−1) 2.333 2.333
F000 1288.0 1288.0
F000’ 1288.90
h,k,lmax 10,13,42 10,12,42
Nref 6135 5797
Tmin,Tmax 0.600,0.792 0.592,1.000
Tmin’ 0.473

Correction method= # Reported T Limits: Tmin=0.592 Tmax=1.000
AbsCorr = MULTI−SCAN

Data completeness= 0.945 Theta(max)= 76.990
R(reflection)= 0.0647( 5194) wR2(reflections)= 0.1546( 5797)
S = 1.073 Npar= 375
7. Analytical data of products

**Methyl-(S*)-2-(benzyloxy)-2-(4-bromophenyl)-2-(((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4a).**

White solid, mp 143.9-144.6 °C. 111.8 mg, 90% yield.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.51 (d, \(J = 7.0\) Hz, 2H), 7.48 – 7.42 (comp, 5H), 7.42 – 7.39 (m, 2H), 7.39 – 7.36 (m, 2H), 7.33 (d, \(J = 8.4\) Hz, 2H), 7.20 (t, \(J = 7.3\) Hz, 2H), 4.41 (q, \(J = 11.1\) Hz, 2H), 3.92 (s, 3H), 2.01 (s, 3H), t-Bu[1.36 (s, 6H)+1.13 (s, 2.5H)].

\(^13\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 169.2, 167.3, 157.8, 153.9, 137.4, 136.8, 130.9, 130.8, 130.5, 129.3, 129.1, 128.6, 127.9, 125.7, 123.2, 118.8, 85.8, 80.9, 71.5, 68.4, 53.9, 28.3, 15.6.

**HRMS (TOF MS ESI\(^+\))** calculated for C\(_{37}\)H\(_{32}\)N\(_3\)O\(_6\)BrNa\(^+\) [M + Na\(^+\)]: 644.1367, found 644.1367.

**Methyl-(S*)-2-(4-bromophenyl)-2-(((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(4-methoxybenzyl)oxy)acetate (4b).**

White solid, mp 155.5-156.3 °C. 80.0 mg, 63% yield.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.49 – 7.36 (comp, 8H), 7.32 (d, \(J = 8.3\) Hz, 2H), 7.25 (d, \(J = 7.6\) Hz, 2H), 7.19 (t, \(J = 7.2\) Hz, 1H), 7.13 (s, 1H), 4.34 (q, \(J = 10.8\) Hz, 2H), 3.92 (s, 3H), 2.34 (s, 3H), 1.98 (s, 3H), t-Bu[1.36 (s, 6H)+1.12 (s, 3H)].

\(^13\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 169.2, 167.3, 157.7, 153.8, 137.9, 137.4, 133.8, 130.9, 130.7, 130.6, 129.6, 129.3, 128.2, 125.7, 123.2, 118.8, 85.7, 80.9, 71.5, 68.4, 53.9, 28.3, 21.3, 15.6.

**HRMS (TOF MS ESI\(^+\))** calculated for C\(_{37}\)H\(_{34}\)N\(_3\)O\(_6\)BrNa\(^+\) [M + Na\(^+\)]: 658.1523, found 658.1526.

**Methyl-(S*)-2-(4-bromophenyl)-2-(((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((4 methoxybenzyl)oxy)acetate (4c).**

White solid, mp 163.8-164.1 °C. 102.1 mg, 78% yield.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.51 – 7.35 (comp, 8H), 7.33 (d, \(J = 8.4\) Hz, 2H), 7.19 (t, \(J = 7.2\) Hz, 1H), NH[7.14 (s, 0.75H)+6.76 (s, 0.25H)], 7.01 (d, \(J = 8.6\) Hz, 2H), 4.31 (q, \(J = 10.5\) Hz, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 1.97 (s, 3H), t-Bu[1.36 (s, 6H)+1.12 (s, 3H)].
Methyl-(S*)-2-((4-bromobenzyl)oxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4d).
White solid, mp 156.2 °C. 118.6 mg, 85% yield.

\( ^{1} \text{H NMR} \) (500 MHz, DMSO-\( d_{6} \)) \( \delta \) 7.66-7.63 (m, 2H), 7.52 – 7.44 (m, 4H), 7.43 – 7.36 (m, 4H), 7.30 (d, \( J = 8.3 \) Hz, 2H), NH[7.26 (s, 0.75H)+6.87(s, 0.25H)], 7.19 (t, \( J = 7.4 \) Hz, 1H), 4.39 (s, 2H), 3.91 (d, \( J = 2.0 \) Hz, 3H), 2.00 (s, 3H), t-Bu[1.36 (s, 6H)+1.13 (s, 3H)].

\( ^{13} \text{C NMR} \) (125 MHz, DMSO-\( d_{6} \)) \( \delta \) 169.2, 167.2, 157.7, 153.9, 137.4, 136.3, 132.0, 130.9, 130.76, 130.5, 130.2, 129.3, 125.6, 123.2, 121.7, 118.8, 85.8, 80.9, 71.4, 67.7, 53.9, 28.3, 15.6.

\( \text{HRMS (TOF MS ESI)}^{+} \) calculated for C\(_{32}\)H\(_{34}\)N\(_{5}\)O\(_{7}\)BrNa\(^{+} \): 672.0472, found 672.0471.

Methyl-(S*)-2-(4-bromophenyl)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4e).
White solid, mp 156.2-157.0 °C. 106.3 mg, 82% yield.

\( ^{1} \text{H NMR} \) (500 MHz, DMSO-\( d_{6} \)) \( \delta \) 7.92 (d, \( J = 8.1 \) Hz, 2H), 7.71 (d, \( J = 8.0 \) Hz, 2H), 7.46 (d, \( J = 7.5 \) Hz, 2H), 7.40 (m, 4H), 7.29 (d, \( J = 8.8 \) Hz, 2H), 7.20 (t, \( J = 7.3 \) Hz, 1H), 4.51 (m, 2H), 3.90 (s, 2H), 2.03 (s, 3H), t-Bu[1.36 (s, 6H), 1.14 (s, 3H)].

\( ^{13} \text{C NMR} \) (125 MHz, DMSO-\( d_{6} \)) \( \delta \) 169.2, 167.1, 157.7, 154.0, 142.6, 137.4, 132.9, 130.8, 130.4, 129.3, 128.4, 125.6, 123.3, 119.2, 118.8, 111.1, 85.9, 80.9, 71.5, 67.6, 53.9, 28.3, 15.6.

\( \text{HRMS (TOF MS ESI)}^{+} \) calculated for C\(_{32}\)H\(_{34}\)N\(_{5}\)O\(_{7}\)BrNa\(^{+} \): 669.1319, found 669.1319.

Methyl-(S*)-2-(4-bromophenyl)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4f).
White solid, mp 147.9-148.5 °C. 94.4 mg, 74% yield.
\[ \text{Methyl-(S\textsuperscript{*})-2-(4-bromophenyl)-2-((R\textsuperscript{*})-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(2,6-dichlorobenzyl)oxy)acetate (4g).} \]

White solid, mp 157.9-158.7 °C. 115.7 mg, 84% yield.

\[ \text{\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6})} \delta 7.60 - 7.64 (m, 5H), 7.42 - 7.35 (m, 2H), 7.35 - 7.24 (m, 5H), 7.20 (t, J = 7.2 Hz, 1H), NH [7.03 (s, 0.75H)+6.66(s, 0.25H)], 4.40 (s, 2H), 3.93 (s, 3H), 2.32 (s, 3H), 1.98 (s, 3H), t- Bu[1.35 (s, 6H), 1.13 (s, 3H)]. \]

\[ \text{\textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6})} \delta 169.1, 169.7, 157.5, 153.8, 137.3, 136.5, 134.8, 130.8, 130.8, 130.4, 129.4, 128.7, 128.5, 126.6, 125.7, 123.3, 118.9, 85.7, 81.0, 71.5, 66.7, 53.9, 28.3, 19.0, 15.6. \]

HRMS (TOF MS ESI\textsuperscript{+}) calculated for C\textsubscript{32}H\textsubscript{34}N\textsubscript{3}O\textsubscript{8}BrNa\textsuperscript{+} [M+Na\textsuperscript{+}]: 658.1523, found 658.1519.

\[ \text{Methyl-(S\textsuperscript{*})-2-(4-bromophenyl)-2-((R\textsuperscript{*})-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(naphthalen-1-ylmethoxy)acetate (4h).} \]

White solid, mp 153.8-154.6 °C. 122.2 mg, 91% yield.

\[ \text{\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6})} \delta 8.17 (d, J = 8.0 Hz, 2H), 8.09 - 7.92 (m, 2H), 7.70 - 7.54 (m, 4H), 7.49 - 7.43 (m, 4H), 7.43 - 7.35 (m, 4H), 7.21 (t, J = 7.3 Hz, 1H), 7.01 (s, 1H), 4.91 (q, J = 11.4 Hz, 2H), 3.95 (s, 3H), 1.90 (s, 3H), t- Bu[1.34 (s, 6H)+1.13 (s, 3H)]. \]

\[ \text{\textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6})} \delta 169.0, 167.4, 157.7, 153.6, 137.3, 133.8, 132.4, 131.3, 130.9, 130.5, 129.4, 129.4, 129.2, 127.1, 126.7, 126.6, 126.0, 125.7, 124.0, 123.3, 118.9, 85.9, 80.8, 71.5, 67.0, 54.0, 28.3, 15.5. \]

HRMS (TOF MS ESI\textsuperscript{+}) calculated for C\textsubscript{35}H\textsubscript{36}N\textsubscript{3}O\textsubscript{8}BrNa\textsuperscript{+} [M+Na\textsuperscript{+}]: 694.1523, found 694.1519.
Methyl-\( \text{S*} \)\( -2\)-\((4\text{-bromophenyl})\)-2-\((5\text{-bromothiophen-2-yl)methoxy})\)-2-\((R*)\)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4i).

White solid, mp 145.2-146.2 °C. 125.7 mg, 89% yield.

\(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 7.45 (comp, 4H), 7.38 (t, \( J = 7.5 \) Hz, 2H), 7.33 (d, \( J = 8.1 \) Hz, 2H), 7.19 (d, \( J = 8.0 \) Hz, 2H), NH[\( 7.15 \) (s, 0.65H)+6.77(s, 0.27H)], 7.05 (s, 1H), 4.60 (d, \( J = 12.0 \) Hz, 1H), 4.51 (d, \( J = 11.8 \) Hz, 1H), 3.91 (s, 3H), 1.99 (s, 3H), \( t\text{-Bu} \)[1.36 (s, 6.5H)+ 1.13 (s, 2.5H)].

\(^13\)C NMR (125 MHz, DMSO) \( \delta \) 169.0, 166.9, 157.6, 153.7, 141.1, 137.3, 130.8, 130.7, 130.6, 130.4, 129.3, 128.7, 125.7, 123.4, 118.9, 112.6, 85.9, 80.9, 71.3, 64.1, 54.1, 28.3, 15.6.

HRMS (TOF MS ESI\(^+\)) calculated for \( C_{29}H_{30}N_3O_6Br_2Na^+ \) [M + Na]\(^+\): 728.0036, found 728.0036.

Methyl-\( \text{S*} \)\( -2\)-\((4\text{-bromophenyl})\)-2-\((R*)\)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4j).

White solid, mp 158.7-159.6 °C. 120.1 mg, 96% yield.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 7.47 – 7.32 (m, 6H), 7.27 (d, \( J = 8.3 \) Hz, 2H), 7.19 (t, \( J = 7.2 \) Hz, 1H), 6.94 (s, 1H), 3.88 (s, 3H), 3.28 – 3.15 (m, 1H), 2.97 (t, \( J = 7.3 \) Hz, 1H), 2.04 (s, 3H), 1.93 – 1.57 (m, 6H), 1.36 (s, 5H), 1.31 – 1.23 (m, 3H), 1.22 – 0.96 (m, 6H).

\(^13\)C NMR (125 MHz, DMSO-\(d_6\)) \( \delta \) 169.2, 167.4, 157.6, 153.8, 137.3, 130.9, 130.6, 130.5, 129.3, 125.6, 123.0, 118.8, 85.2, 80.9, 71.5, 71.5, 53.7, 37.8, 29.8, 28.3, 26.5, 25.7, 15.6.

HRMS (TOF MS ESI\(^+\)) calculated for \( C_{31}H_{38}N_3O_6BrNa^+ \) [M + Na]\(^+\): 650.1836, found 650.1835.

Methyl-\( \text{S*} \)\( -2\)-\((4\text{-bromophenyl})\)-2-\((R*)\)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4k).

White solid, mp 142.1-142.7 °C. 118.2 mg, 96% yield.

\(^1\)H NMR (400 MHz, CDCl\(_3\)-\(d_2\)) \( \delta \) 7.46 (s, 2H), 7.38 – 7.21 (comp, 6H), 7.15 (t, \( J = 7.0 \) Hz, 1H), 6.91 – 6.29 (m, 1H), 3.96 (s, 3H), 3.38 (t, \( J = 7.6 \) Hz, 1H), 3.19 – 2.98 (m, 1H), 2.46 – 2.27 (m, 1H), 2.12 (s, 3H), 1.88 (s, 2H), 1.64 (s, 4H), 1.51 – 1.11 (comp, 11H).
**13C NMR** (125 MHz, DMSO-<sup>d6</sup>) δ 169.2, 167.4, 157.9, 153.8, 137.3, 130.9, 130.6, 129.3, 125.6, 123.0, 118.8, 85.2, 80.8, 71.5, 70.4, 53.7, 29.4, 28.3, 25.4, 25.2, 15.5.

**HRMS (TOF MS ESI<sup>+</sup>)** calculated for C<sub>30</sub>H<sub>36</sub>N<sub>3</sub>O<sub>6</sub>BrNa<sup>+</sup> [M + Na]<sup>+</sup>: 636.1680, found 636.1681.

Methyl-(S*)-2-(4-bromophenyl)-2-(((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-p phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-methoxyacetate (4l).

White solid, 90 mg, 83 % yield.

**1H NMR** (500 MHz, DMSO-<sup>d6</sup>) δ 7.47 (d, J = 8.1 Hz, 2H), 7.44 – 7.36 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), NH[7.04 (s, 0.7H)+6.69 (s, 0.3H)], 3.89 (s, 3H), 3.28 (s, 3H), 2.01 (s, 3H), t-Bu[1.37 (s, 7H)+1.13 (s, 2H)].

**13C NMR** (125 MHz, DMSO-<sup>d6</sup>) δ 169.2, 167.2, 158.0, 153.8, 137.4, 130. 9, 130.6, 130.6, 130.6, 129.3, 125.7, 123.1, 118.9, 86.1, 80.8, 71.3, 54.9, 53.7, 28.3, 15.6.

**HRMS (TOF MS ESI<sup>+</sup>)** calculated for C<sub>25</sub>H<sub>28</sub>N<sub>3</sub>O<sub>6</sub>BrNa<sup>+</sup>[M + Na]<sup>+</sup>: 568.1054, found 568.1023.

Methyl-(S*)-2-(4-bromophenyl)-2-(((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-p phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-ethoxyacetate (4m).

White solid, 97 mg, 87 % yield.

**1H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.51 – 7.42 (m, 2H), 7.32 (comp, 4H), 7.24 (d, J = 7.2 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), NH[6.78 (s, 0.6H)+ 6.44 (s, 0.4H)], 3.95 (s, 3H), 3.54 – 3.29 (m, 2H), 2.10 (s, 3H), Boc[1.41 (d, J = 21.9 Hz, 9H)], 1.24 (d, J = 21.6 Hz, 3H).

**13C NMR** (125 MHz, DMSO-<sup>d6</sup>) δ 169.3, 167.4, 158.0, 153.8, 137.4, 130.9, 130.8, 130.6, 129.3, 125.6, 123.0, 118.9, 85.4, 80.8, 71.3, 62.4, 53.7, 28.4, 15.6, 15.1.

**HRMS (TOF MS ESI<sup>+</sup>)** calculated for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>6</sub>Br<sup>+</sup>[M + H]<sup>+</sup>: 560.1391, found 560.1345.
Methyl-(S*)-2-(4-bromophenyl)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(cinnamloyloxy)acetate (4n).

White solid, mp 137.1-137.9 °C. 122.8 mg, 95% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.53 (d, $J = 7.6$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.45 – 7.33 (comp, 8H), 7.31 (t, $J = 7.3$ Hz, 1H), 7.20 (t, $J = 7.4$ Hz, 1H), 7.10 (s, 1H), 6.74 (d, $J = 15.9$ Hz, 1H), 6.61 (dt, $J = 13.9$, 7.8 Hz, 1H), 4.04 (d, $J = 5.8$ Hz, 2H), 3.90 (s, 3H), 2.06 (s, 3H), t-Bu[1.37 (s, 6H)+1.13 (s, 3H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 169.2, 167.3, 157.9, 153.8, 137.4, 136.5, 133.3, 130.9, 130.7, 129.3, 129.1, 128.5, 127.1, 125.7, 124.8, 123.2, 118.8, 85.5, 80.9, 71.4, 67.7, 53.8, 28.3, 15.7.

HRMS (TOF MS ESI$^+$) calculated for C$_{33}$H$_{34}$N$_3$O$_6$BrNa$^+$ [M + Na$^+$]: 670.1523, found 670.1523.

Methyl-(S*)-2-(allyloxy)-2-(4-bromophenyl)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (4o).

White solid, mp 125.5-126.1 °C. 108.0 mg, 95% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.46 (d, $J = 8.0$ Hz, 2H), 7.40 (comp, 4H), 7.28 (d, $J = 8.2$ Hz, 2H), 7.20 (t, $J = 7.3$ Hz, 1H), NH[7.05 (s, 0.7H)+ 6.69 (s, 0.3H)], 6.15 – 6.00 (m, 1H), 5.43 (d, $J = 17.3$ Hz, 1H), 5.31 (d, $J = 11.8$ Hz, 1H), 3.88 (comp, 5H), 2.03 (s, 3H), t-Bu[1.36 (s, 6.5H)+1.13 (s, 2.5H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 169.1, 167.2, 157.8, 153.8, 137.3, 133.7, 130.7, 130.7, 129.3, 125.7, 123.2, 118.9, 118.1, 85.5, 80.9, 71.3, 67.6, 53.8, 28.3, 15.6.

HRMS (TOF MS ESI$^+$) calculated for C$_{27}$H$_{34}$N$_3$O$_6$BrNa$^+$ [M + Na$^+$]: 594.1210, found 594.1215.

Methyl-(S*)-2-(4-bromophenyl)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(prop-2-yn-1-yloxy)acetate (4p).

White solid, mp 143.7-144.6 °C. 101.0 mg, 89% yield.
$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.44 (comp, 4H), 7.42 – 7.36 (m, 2H), 7.34 (d, $J$ = 8.3 Hz, 2H), 7.19 (t, $J$ = 7.4 Hz, 1H), 7.08 (s, 1H), 4.18 (d, $J$ = 15.1 Hz, 1H), 4.08 (d, $J$ = 15.2 Hz, 1H), 3.87 (d, $J$ = 2.0 Hz, 3H), 3.73 (d, $J$ = 2.5 Hz, 1H), 2.03 (s, 3H), t-Bu[1.37 (s, 7H) + 1.14 (s, 2H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 168.9, 166.6, 157.6, 153.8, 137.3, 130.8, 130.6, 130.4, 129.3, 125.7, 123.4, 118.9, 85.8, 80.9, 79.2, 79.0, 71.2, 55.8, 53.9, 28.3, 15.6.

HRMS (TOF MS ESI$^+$) calculated for $C_{27}H_{38}N_2O_6BrNa^+$ [M + Na]$^+$: 592.1054, found 592.1051.

Methyl-($S^*$)-2-(benzyloxy)-2-((R$^*$)-4-((tert-butoxycarbonylamino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-phenylacetate (5a).

White solid, mp 120.8-121.5 °C. 105.6 mg, 97% yield.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.51 (d, $J$ = 7.1 Hz, 2H), 7.49 – 7.42 (comp, 4H), 7.42 – 7.33 (comp, 5H), 7.29 (t, $J$ = 7.1 Hz, 1H), 7.24 – 6.76 (comp, 4H). 4.48 (d, $J$ = 11.1 Hz, 1H), 4.39 (d, $J$ = 11.1 Hz, 1H), 3.91 (s, 3H), 2.00 (s, 3H), t-Bu[1.36 (s, 6H) + 1.12 (s, 3H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.3, 167.7, 157.6, 153.8, 137.5, 137.0, 131.0, 129.5, 129.3, 129.1, 128.5, 128.5, 127.8, 127.8, 125.5, 118.7, 86.0, 80.8, 71.6, 68.3, 53.7, 28.3, 15.6.

HRMS (TOF MS ESI$^+$) calculated for $C_{31}H_{33}N_3O_6Na^+$ [M + Na]$^+$: 566.2262, found 566.2258.

Methyl-($S^*$)-2-(benzyloxy)-2-((R$^*$)-4-((tert-butoxycarbonylamino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(p-tolyl)acetate (5b).

White solid, mp 134.6-135.4 °C. 108.1 mg, 97% yield.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.52 – 7.42 (comp, 6H), 7.38 (m, 3H), 7.26 (d, $J$ = 8.1 Hz, 2H), 7.18 (t, $J$ = 7.3 Hz, 1H), NH[7.11 (s, 0.7H) + 6.75 (s, 0.3H)], 7.01 (d, $J$ = 8.0 Hz, 2H), 4.46 (d, $J$ = 11.2 Hz, 1H), 4.38 (d, $J$ = 11.2 Hz, 1H), 3.90 (s, 3H), 2.21 (s, 3H), 2.00 (s, 3H), t-Bu[1.36 (s, 6H) + 1.14 (s, 3H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.4, 167.8, 157.6, 153.8, 138.9, 137.5, 137.1, 129.2, 129.1, 128.5, 128.3, 128.0, 127.8, 125.5, 118.8, 86.0, 80.8, 71.6, 68.2, 53.6, 28.3, 21.0, 15.6.

HRMS (TOF MS ESI$^+$) calculated for $C_{32}H_{35}N_3O_6Na^+$ [M + Na]$^+$: 580.2418, found 580.2416.
Methyl-\((S^*)\)-2-(benzyloxy)-2-\(((R^*)\)-4-\(((\text{tert-butoxycarbonyl})\text{amino})\)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl\)-2-(4-chlorophenyl)acetate (5c).
White solid, mp 122.8-123.8 °C. 109.6 mg, 95% yield.

\[^1\text{H}\]NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.51 (d, \(J = 7.2\) Hz, 2H), 7.48 – 7.43 (comp, 4H), 7.39 (comp, 5H), 7.29 (d, \(J = 8.4\) Hz, 2H), 7.20 (t, \(J = 7.2\) Hz, 2H), 4.42 (q, \(J = 11.1\) Hz, 2H), 3.93 (s, 3H), 2.02 (s, 3H), \(\tau\)-Bu[1.36 (s, 6H)+1.15 (s, 3H)]

\[^1\text{C}\]NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 169.2, 167.3, 157.7, 153.9, 137.4, 136.8, 134.5, 130.6, 130.1, 129.3, 129.1, 128.6, 127.9, 127.8, 125.6, 118.8, 85.7, 80.9, 71.6, 68.4, 53.9, 28.3, 15.6.

HRMS (TOF MS ESI\(^+\)) calculated for C\(_{33}\)H\(_{32}\)N\(_3\)O\(_5\)ClNa\(^+\) [M + Na\(^+\)]: 600.1872, found 600.1868.

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{Boc}
\end{array}
\]

Methyl-\((S^*)\)-2-(benzyloxy)-2-\(((R^*)\)-4-\(((\text{tert-butoxycarbonyl})\text{amino})\)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl\)-2-(4-iodophenyl)acetate (5d).
White solid, mp 153.6-154.5 °C. 122.1 mg, 91% yield.

\[^1\text{H}\]NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.50 (d, \(J = 7.1\) Hz, 2H), 7.48 – 7.42 (comp, 4H), 7.39 (t, \(J = 7.0\) Hz, 3H), 7.23 – 7.13 (m, 4H), 4.43 (d, \(J = 10.9\) Hz, 1H), 4.37 (d, \(J = 11.0\) Hz, 1H), 3.91 (s, 3H), 2.00 (s, 3H), \(\tau\)-Bu[1.36 (s, 7H)+1.13 (s, 2H)].

\[^1\text{C}\]NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 169.2, 167.3, 157.7, 153.8, 137.4, 136.9, 136.6, 130.9, 130.8, 129.3, 129.1, 128.6, 127.9, 125.7, 118.9, 96.7, 85.8, 80.9, 71.5, 68.4, 53.9, 28.3, 15.6.

HRMS (TOF MS ESI\(^+\)) calculated for C\(_{33}\)H\(_{32}\)N\(_3\)O\(_5\)I\(_2\)Na\(^+\) [M + Na\(^+\)]: 692.1228, found 692.1231.

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{Boc}
\end{array}
\]

Methyl-\((S^*)\)-2-(benzyloxy)-2-\(((R^*)\)-4-\(((\text{tert-butoxycarbonyl})\text{amino})\)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl\)-2-(3,4-dichlorophenyl)acetate (5e).
White solid, mp 141.5-141.8 °C. 102.6 mg, 84% yield.

\[^1\text{H}\]NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.51 (d, \(J = 7.5\) Hz, 2H), 7.49 – 7.44 (m, 5H), 7.40 (d, \(J = 8.5\) Hz, 4H), 7.27 (s, 1H), 7.20 (t, \(J = 7.5\) Hz, 1H), 4.46 (d, \(J = 11.3\) Hz, 1H), 4.40 (d, \(J = 11.3\) Hz, 1H), 3.94 (d, \(J = 2.4\) Hz, 3H), 2.00 (s, 3H), \(\tau\)-Bu[1.37 (s, 7H)+1.13 (s, 2H)].

\[^1\text{C}\]NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 169.1, 166.8, 157.9, 154.0, 137.2, 136.7, 132.6, 132.3, 131.2, 130.8, 130.1, 129.4, 129.1, 128.7, 128.0, 125.7, 118.7, 85.5, 81.0, 71.6, 68.7, 54.1, 28.3, 15.5.

HRMS (TOF MS ESI\(^+\)) calculated for C\(_{33}\)H\(_{33}\)N\(_3\)O\(_5\)Cl\(_2\)Na\(^+\) [M + Na\(^+\)]: 634.1482, found 634.1476.
Methyl-(S*)-2-(benzylxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(napthalen-2-yl)acetate (5f).

White solid, mp 130.5-131.2 °C. 112.8 mg, 95% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (s, 1H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.71 (d, $J = 8.7$ Hz, 1H), 7.66 (d, $J = 7.9$ Hz, 1H), 7.57 (d, $J = 7.3$ Hz, 2H), 7.49 (t, $J = 7.5$ Hz, 3H), 7.47 – 7.40 (m, 3H), 7.38 (d, $J = 7.8$ Hz, 2H), 7.30 (t, $J = 7.9$ Hz, 2H), NH[7.21 (s, 0.65H)+6.83(s, 0.25H)], 7.14 (t, $J = 7.3$ Hz, 1H), 4.58 (d, $J = 11.1$ Hz, 1H), 4.46 (s, 1H), 3.95 (s, 3H), 2.02 (s, 3H), t-Bu[1.37 (s, 6.5H)+1.12 (s, 2.5H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 169.4, 167.7, 157.8, 153.9, 137.4, 137.1, 133.1, 132.2, 129.2, 129.1, 128.8, 128.8, 128.6, 128.6, 128.0, 127.6, 126.8, 126.8, 126.7, 125.7, 125.5, 118.7, 86.3, 80.8, 71.7, 68.6, 28.3, 15.6.

HRMS (TOF MS ESI$^+$) calculated for C$_{35}$H$_{35}$N$_3$O$_6$Na$^+$ [M + Na]$^+$: 616.2418, found 616.2420.

Methyl-(S*)-2-(benz[d][1,3]dioxol-5-yl)-2-(benzylxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)acetate (5g). White solid, mp 135.0-136.3 °C. 110.3 mg, 94% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.51 – 7.42 (comp, 6H), 7.39 (m, 3H), 7.19 (t, $J = 7.5$ Hz, 1H), 7.11 (s, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 6.83 – 6.75 (m, 2H), 5.98 (s, 1H), 5.82 (s, 1H), 4.47 (d, $J = 11.3$ Hz, 1H), 4.39 (d, $J = 11.2$ Hz, 1H), 3.90 (s, 3H), 2.00 (s, 3H), t-Bu[1.36 (s, 6.5H)+1.14(s, 2.5H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 169.4, 167.7, 157.9, 153.8, 148.1, 147.1, 137.5, 137.1, 129.3, 129.1, 128.5, 127.7, 125.5, 124.4, 122.5, 118.8, 109.2, 107.6, 101.8, 86.0, 80.8, 71.7, 68.3, 28.3, 15.6.

HRMS (TOF MS ESI$^+$) calculated for C$_{32}$H$_{31}$N$_3$O$_6$Na$^+$ [M + Na]$^+$: 610.2160, found 610.2163.

Ethyl-(S*)-2-(benzyloxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(4-chlorophenyl)acetate (5h).

White solid, mp 101.5-102.2 °C. 111.0 mg, 94% yield.
$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.50 (d, $J = 7.1$ Hz, 2H), 7.46 (m, 4H), 7.43 (s, 1H), 7.42 – 7.35 (m, 4H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.11 (s, 1H), 4.55 – 4.29 (comp, 4H), 2.03 (s, 3H), 1.43 – 1.29 (comp, 9H), 1.12 (s, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.2, 166.5, 157.7, 153.8, 137.4, 136.9, 134.4, 130.7, 130.1, 129.3, 129.1, 128.5, 127.9, 127.8, 125.6, 118.9, 85.6, 80.7, 71.4, 68.3, 63.2, 28.3, 15.6, 14.2.

HRMS (TOF MS ESI$^+$) calculated for C$_{32}$H$_{34}$N$_3$O$_6$ClNa$^+$ [M + Na]$^+$: 614.2028, found 614.2028.

Benzyl-($S^*$)-2-(benzyloxy)-2-((R$^*$)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(4-chlorophenyl)acetate (5i).

White solid, mp 107.2-108.0 °C. 117.7 mg, 90% yield.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.52 (d, $J = 5.4$ Hz, 2H), 7.42 (comp, 14H), 7.29 (d, $J = 7.8$ Hz, 2H), 7.20 (t, $J = 7.3$ Hz, 1H), 7.00 (s, 1H), 5.49 (d, $J = 12.2$ Hz, 1H), 5.35 (s, 1H), 4.46 (d, $J = 11.0$ Hz, 1H), 4.36 (d, $J = 10.5$ Hz, 1H), 2.01 (s, 3H), t-Bu[1.30 (s, 7H) + 1.13 (s, 2H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.2, 166.5, 157.7, 153.6, 137.4, 136.7, 135.2, 134.5, 130.6, 130.0, 129.3, 129.1, 129.0, 128.9, 128.6, 128.0, 127.8, 125.7, 118.9, 85.8, 80.7, 71.4, 68.8, 68.4, 28.2, 15.6.

HRMS (TOF MS ESI$^+$) calculated for C$_{37}$H$_{36}$N$_3$O$_6$ClNa$^+$ [M + Na]$^+$: 676.2185, found 676.2180.

$t$-Butyl-($S^*$)-2-(benzyloxy)-2-((R$^*$)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(4-chlorophenyl)acetate (5j).

White solid, mp 119.6-120.5 °C. 81.6 mg, 66% yield.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.53 – 7.51 (m, 2H), 7.49 – 7.45 (comp, 3H), 7.43 (s, 2H), 7.42 – 7.35 (comp, 4H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.19 (t, $J = 7.2$ Hz, 1H), 7.04 (s, 1H), 4.53 (d, $J = 11.2$ Hz, 1H), 4.37 (d, $J = 11.2$ Hz, 1H), 2.04 (s, 3H), 1.58 (s, 9H), t-Bu[1.36 (s, 7H) + 1.13 (s, 2H)].

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.3, 165.0, 157.7, 153.7, 137.4, 137.1, 134.3, 130.8, 130.2, 129.3, 129.1, 128.5, 127.7, 127.7, 125.6, 118.9, 85.9, 85.6, 80.6, 71.3, 68.1, 28.3, 28.0, 15.7.

HRMS (TOF MS ESI$^+$) calculated for C$_{34}$H$_{38}$N$_3$O$_6$ClNa$^+$ [M + Na]$^+$: 642.2341, found 642.2344.
Ethyl-(S*)-2-(benzyloxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl)acetate (5k).

White solid, mp 157.1–157.9 °C. 91.4 mg, 95% yield.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.93 (s, 1H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.49 – 7.34 (comp, 6H), 7.34 – 7.26 (m, 1H), 7.18 (t, $J = 7.3$ Hz, 1H), 4.62 (d, $J = 10.7$ Hz, 1H), 4.47 (d, $J = 10.8$ Hz, 1H), 4.35 (s, 1H), 4.04 – 3.95 (m, 1H), 3.95 – 3.86 (m, 1H), 2.04 (s, 3H), $t$-Bu[1.35 (s, 6.5H)+1.15 (s, 2.5H)], 0.94 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.9, 167.7, 159.4, 154.4, 138.3, 137.6, 129.4, 128.8, 128.7, 128.2, 128.1, 125.1, 118.1, 80.3, 79.4, 72.7, 68.0, 62.0, 28.4, 15.2, 14.0.

HRMS (TOF MS ESI$^+$) calculated for C$_{26}$H$_{31}$N$_3$O$_5$Na$^+ [M + Na]$+: 504.2105, found 504.2106.

![Ethyl-(S*)-2-(benzyloxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl)acetate](image)

Ethyl-(S*)-2-(benzyloxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl)propanoate (syn-5l).

White solid, mp 100.6–101.5 °C. 43.6 mg, 44% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.77 (d, $J = 6.6$ Hz, 2H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.38 – 7.27 (comp, 5H), 7.21 (t, $J = 7.3$ Hz, 1H), 6.62 (s, 1H), 4.58 (d, $J = 10.9$ Hz, 1H), 4.28 (comp, 3H), 2.03 (s, 3H), 1.51 (s, 3H), $t$-Bu[1.33 (s, 6H)+1.13 (s, 3H)], 1.28 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.5, 158.4, 153.8, 138.1, 137.7, 129.5, 128.8, 128.2, 128.1, 125.4, 118.5, 80.8, 80.5, 70.4, 67.0, 62.5, 28.3, 15.6, 15.2, 14.3.

HRMS (TOF MS ESI$^+$) calculated for C$_{27}$H$_{33}$N$_3$O$_5$Na$^+ [M + Na]$+: 518.2262, found 518.2264.

![Ethyl-(S*)-2-(benzyloxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl)propanoate](image)

Ethyl-(R*)-2-(benzyloxy)-2-((R*)-4-((tert-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4, 5-dihydro-1H-pyrazol-4-yl)propanoate (anti-5l).

White solid, mp 133.8–134.6 °C. 45.5 mg, 46% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.84 – 7.72 (m, 3H), 7.48 (d, $J = 7.3$ Hz, 2H), 7.45 – 7.34 (comp, 4H), 7.32 (t, $J = 7.0$ Hz, 1H), 7.17 (t, $J = 6.8$ Hz, 1H), 4.57 (d, $J = 10.0$ Hz, 1H), 4.35 (d, $J = 9.9$ Hz, 1H), 4.13 – 3.93 (m, 1H), 3.92 – 3.71 (m, 1H), 2.01 (s, 3H), 1.80 (s, 3H), $t$-Bu[1.34 (s, 6H)+1.12 (s, 3H)], 1.04 – 0.83 (m, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 170.0, 169.5, 160.3, 154.7, 138.4, 138.3, 129.3, 128.6, 128.5, 128.1, 124.9, 118.2, 83.7, 80.2, 69.8, 67.1, 62.3, 28.5, 16.2, 13.9, 13.8.

HRMS (TOF MS ESI$^+$) calculated for C$_{27}$H$_{33}$N$_3$O$_5$Na$^+ [M + Na]$+: 518.2262, found 518.2264.
tert-Butyl-((R*)-4-((S*)-3-(benzyl oxy)-1-methyl-2-oxoindolin-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)carbamate (5m).

White solid, mp 194.9-195.9 °C, 80.0 mg, 74% yield.

^1H NMR (400 MHz, DMSO-d6) δ 7.40 – 7.31 (comp, 5H), 7.31 – 7.19 (comp, 7H), 7.15 – 7.07 (m, 2H), 7.02 (t, J = 7.5 Hz, 1H), 4.09 (d, J = 10.6 Hz, 1H), 4.00 (d, J = 10.6 Hz, 1H), 3.20 (s, 3H), 2.28 (s, 3H), t-Bu[1.35 (s, 6.5H)+ 1.14 (s, 2.5H)].

^13C NMR (125 MHz, DMSO-d6) δ 171.5, 168.7, 156.9, 154.1, 144.6, 137.2, 136.8, 132.4, 129.1, 128.9, 128.5, 128.3, 125.6, 125.2, 123.3, 119.9, 119.0, 110.2, 81.0, 80.2, 71.1, 68.0, 28.3, 26.8, 16.3.

HRMS (TOF MS ESI+) calculated for C_{31}H_{32}N_{4}O_{3}Na [M + Na]^+: 563.2265, found 563.2260.

Methyl-((S*)-2-(benzyl oxy)-2-((R*)-4-((tert-butoxycarbonylamino)-1-(4-chlorophenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-2-phenylacetate (5n).

White solid, mp 152.9-153.6 °C, 102.6 mg, 89% yield.

^1H NMR (400 MHz, DMSO-d6) δ 7.54 – 7.43 (m, 7H), 7.43 – 7.34 (m, 4H), 7.29 (t, J = 7.3 Hz, 1H), 7.21 (comp, 3H), 4.48 (d, J = 11.1 Hz, 1H), 4.40 (d, J = 11.1 Hz, 1H), 3.91 (s, 3H), 2.00 (s, 3H), t-Bu[1.35 (s, 6H)+1.13 (s, 3H)].

^13C NMR (125 MHz, DMSO-d6) δ 169.4, 167.6, 158.1, 153.9, 137.0, 136.3, 131.0, 129.6, 129.3, 129.1, 128.5, 127.8, 127.8, 120.1, 86.0, 80.9, 71.7, 68.3, 53.7, 28.3, 15.6.

HRMS (TOF MS ESI+) calculated for C_{31}H_{32}N_{4}O_{6}ClNa [M + Na]^+: 600.1872, found 600.1868.

Methyl-((S*)-2-(benzyl oxy)-2-((R*)-4-((tert-butoxycarbonylamino)-3-ethyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-phenylacetate (5o).

White solid, mp 121.4-122.2 °C, 96.1 mg, 86% yield.

^1H NMR (400 MHz, DMSO-d6) δ 7.53 – 7.44 (comp, 6H), 7.43 – 7.34 (comp, 5H), 7.30 (t, J = 7.3 Hz, 1H), 7.19 (q, J = 7.3 Hz, 3H), NH[7.12 (s, 0.75H)+6.76(s, 0.25H)], 4.49 (d, J = 11.1 Hz, 1H), 4.39 (d, J = 11.1 Hz, 1H), 3.91 (s, 3H), 2.60 – 2.52 (m, 1H), 2.44 – 2.29 (m, 1H), 1.36 (s, 6H), 1.13 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H).

^13C NMR (125 MHz, DMSO-d6) δ 169.5, 167.7, 161.2, 153.8, 137.6, 137.0, 131.0, 129.5, 129.2, 129.1, 128.6, 128.5, 127.8, 127.7, 125.5, 118.8, 86.1, 80.7, 71.7, 68.3, 53.7, 28.3, 22.7, 9.7.
HRMS (TOF MS ESI) calculated for $\text{C}_{32}\text{H}_{35}\text{N}_{3}\text{O}_{6}\text{Na}^+$: 580.2418, found 580.2418.

Methyl-$(S^*)$-2-(benzylxy)-2-{$(R^*)$}-4-{$(\text{tert-butoxycarbonyl})$}amino)-3-isopropyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-phenylacetate (5p).

White solid, mp 118.0-118.8 °C. 95.8 mg, 84% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.55 - 7.44 (comp, 6H), 7.39 (m, 3H), 7.31 (m, 3H), 7.24 - 7.13 (comp, 4H), 4.57 - 4.31 (m, 2H), 3.89 (s, 3H), 3.04 (m, 1H), 1.35 (s, 6H), 1.19 - 1.00 (m, 6H), 0.88 (m, 6.8 Hz, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.3, 167.6, 163.2, 153.7, 137.7, 137.2, 131.1, 129.5, 129.3, 129.2, 128.6, 127.7, 127.5, 125.5, 118.9, 86.4, 80.5, 71.8, 68.3, 53.6, 30.1, 28.4, 21.9, 19.5.

HRMS (TOF MS ESI) calculated for $\text{C}_{33}\text{H}_{37}\text{N}_{3}\text{O}_{6}\text{Na}^+$ [M + Na]$^+$: 594.2575, found 594.2580.

Methyl-$(S^*)$-2-(benzylxy)-2-{$(R^*)$}-4-{$(\text{tert-butoxycarbonyl})$}amino)-3-{$(\text{tert-butyl})$}-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-phenylacetate (5q).

White solid, mp 125.5-126.5 °C. 75.1 mg, 64% yield.

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.54 - 7.53 (m, 6H), 7.50 - 7.45 (m, 2H), 7.45 - 7.34 (comp, 4H), 7.28 (t, $J = 7.0$ Hz, 1H), 7.16 - 6.79 (comp, 4H), 4.51 - 4.30 (m, 2H), 3.88 (s, 3H), 1.38 (s, 6H), 1.12 (s, 6H), 1.09 (s, 6H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.7, 168.1, 165.6, 153.7, 137.6, 136.6, 131.4, 129.5, 129.4, 129.3, 129.0, 128.9, 128.7, 127.2, 125.5, 118.8, 87.8, 80.5, 74.3, 69.2, 53.4, 36.4, 30.7, 28.5.

HRMS (TOF MS ESI) calculated for $\text{C}_{34}\text{H}_{39}\text{N}_{3}\text{O}_{6}\text{Na}^+$ [M + Na]$^+$: 608.2731, found 608.2735.

Methyl-$(S^*)$-2-(benzylxy)-2-{$(R^*)$}-4-{$(\text{ethoxycarbonyl})$}amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-phenylacetate (5r).

White solid, 88 mg, 86% yield.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.50 (d, $J = 8.2$ Hz, 2H), 7.48 - 7.41 (comp, 6H), 7.41 - 7.36 (m, 1H), 7.30 (comp, $J = 7.1$ Hz, 3H), 7.20 (t, $J = 7.6$ Hz, 2H), 7.14 (d, $J = 7.4$ Hz, 1H), 7.04 (s, 1H), 4.56 (d, $J = 11.1$ Hz, 1H), 4.45 (d, $J = 11.0$ Hz, 1H), 4.10 (t, $J = 7.1$ Hz, 2H), 3.98 (s, 3H), 2.09 (s,
3H), 1.26 (t, J = 7.3 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 169.1, 167.7, 157.3, 154.6, 137.3, 136.4, 130.5, 129.6, 128.6, 128.3, 127.6, 127.1, 125.4, 119.7, 86.2, 71.7, 68.2, 61.8, 53.3, 15.5.

HRMS (TOF MS ESI$^+$) calculated for C$_{29}$H$_{29}$N$_3$O$_6$Na$^+$ [M + Na]$^+$: 538.1949, found 538.1913.

Methyl-(S*)-2-((R*)-4-amino-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-(benzyl)oxy)-2-phenylacetate (7a)
White solid. mp 110.5-112.1 °C, 46.3 mg, 96% yield

$^1$H NMR (500 MHz, CDCl$_3$-d) δ 10.15 (s, 2H), 7.64 (s, 2H), 7.43 (s, 2H), 7.26 (comp, 6H), 7.21 – 7.14 (comp, 4H), 7.11 (s, 1H), 4.57 (d, J = 10.5 Hz, 1H), 4.38 (d, J = 10.3 Hz, 1H), 3.98 (s, 3H), 2.22 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$-d) δ 166.6, 165.6, 155.0, 136.4, 135.6, 130.2, 129.6, 128.6, 128.5, 128.1, 128.0, 127.9, 126.1, 120.3, 85.2, 69.0, 68.2, 54.4, 16.7.

HRMS (TOF MS ESI$^+$) calculated for C$_{26}$H$_{25}$N$_3$O$_4$Na$^+$ [M + Na]$^+$: 466.1737, found 466.1732.

tert-Butyl-((R*)-4-((S*)-1-(benzyl)oxy)-2-hydroxy-1-phenylethyl)-3-methyl-5-oxo-1-phenyl-4,5 -dihydro-1H-pyrazol-4-yl)carbamate (8a)
White solid, mp 125.5-126.3 °C, 46.3 mg, 90% yield

$^1$H NMR (500 MHz, DMSO-d$_6$) δ NH8.25 (s, 1H), 7.47 (d, J = 7.0 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.31 – 7.12 (m, 9H), 7.07 (t, J = 7.0 Hz, 1H), 6.21 (t, J = 3.8 Hz, 1H), 5.13 (dd, J = 12.1, 4.8 Hz, 1H), 4.74 (t, J = 11.1 Hz, 1H), 4.22 (d, J = 10.7 Hz, 1H), 4.14 (dd, J = 12.2, 3.4 Hz, 1H), 2.14 (s, 3H), t-Bu[1.35 (s, 6.5H)+1.12 (s, 2.5H)].

$^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 171.0, 159.3, 154.4, 138.4, 137.5, 134.8, 128.9, 128.9, 128.2, 128.1, 128.1, 127.0, 125.1, 118.8, 81.9, 80.1, 73.3, 65.2, 59.1, 28.4, 16.9.

HRMS (TOF MS ESI$^+$) calculated for C$_{30}$H$_{33}$N$_3$O$_5$Na$^+$ [M + Na]$^+$: 538.2312, found 538.2311.
tert-Butyl-(4-(benzyloxy)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)carbamate (6a).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, $J = 8.0$ Hz, 2H), 7.41 (t, $J = 7.9$ Hz, 2H), 7.36 – 7.27 (m, 5H), 7.20 (t, $J = 7.6$ Hz, 1H), 5.35 (s, 1H), 4.66 (d, $J = 10.9$ Hz, 1H), 4.55 (d, $J = 10.9$ Hz, 1H), 2.19 (s, 3H), 1.36 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 167.1, 157.3, 152.5, 137.6, 136.0, 128.9, 128.5, 128.3, 128.0, 125.3, 118.6, 85.7, 66.4, 28.1, 13.0.
8. NMR spectra of products

$^1$H NMR and $^{13}$C NMR spectrum for 4a
$^1$H NMR and $^{13}$C NMR spectrum for 4b
$^{1}$H NMR and $^{13}$C NMR spectrum for 4c
$^1$H NMR and $^{13}$C NMR spectrum for 4d
$^1$H NMR and $^{13}$C NMR spectrum for 4e
$^1$H NMR and $^{13}$C NMR spectrum for 4f
$^1$H NMR and $^{13}$C NMR spectrum for 4g
$^1$H NMR and $^{13}$C NMR spectrum for 4h
$^1$H NMR and $^{13}$C NMR spectrum for 4i
$^1$H NMR and $^{13}$C NMR spectrum for 4j
$^1$H NMR and $^{13}$C NMR spectrum for 4k
$^1$H NMR and $^{13}$C NMR spectrum for 4I
$^1$H NMR and $^{13}$C NMR spectrum for 4m
$^1$H NMR and $^{13}$C NMR spectrum for 4n

![Chemical structure of 4n with NMR spectra]
$^1$H NMR and $^{13}$C NMR spectrum for 4o
$^1$H NMR and $^{13}$C NMR spectrum for 4p
$^{1}$H NMR and $^{13}$C NMR spectrum for 5a
$^1$H NMR and $^{13}$C NMR spectrum for 5b
$^1$H NMR and $^{13}$C NMR spectrum for 5c
$^1$H NMR and $^{13}$C NMR spectrum for 5d

![NMR spectrum image]
$^1$H NMR and $^{13}$C NMR spectrum for $5e$
$^1$H NMR and $^{13}$C NMR spectrum for 5f
$^1$H NMR and $^{13}$C NMR spectrum for 5g
$^1$H NMR and $^{13}$C NMR spectrum for 5h
$^1$H NMR and $^{13}$C NMR spectrum for 5i
$^1$H NMR and $^{13}$C NMR spectrum for 5j
$^{1}$H NMR and $^{13}$C NMR spectrum for 5k
$^1$H NMR and $^{13}$C NMR spectrum for syn-5I

$^{13}$C NMR spectrum for syn-5I
$^1$H NMR and $^{13}$C NMR spectrum for anti-5l
**1H NMR and 13C NMR spectrum for 5m**
H NMR and C NMR spectrum for 5n
$^1$H NMR and $^{13}$C NMR spectrum for 5o

$^{13}$C NMR spectrum for 5o
$^1$H NMR and $^{13}$C NMR spectrum for 5p
$^1$H NMR and $^{13}$C NMR spectrum for 5q
$^1$H NMR and $^{13}$C NMR spectrum for 5r
$^1$H NMR and $^{13}$C NMR spectrum for 6a
$^1$H NMR and $^{13}$C NMR spectrum for 7a

$^1$H NMR and $^{13}$C NMR spectrum for 8a