Highly Enantioselective Phosphination and Hydrophosphonylation of Azomethine Imines: Using Chiral Squaramide as Hydrogen Bonding Organocatalyst

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1. General procedure for the preparation of catalysts................................. 2
2. Reference................................................................................................. 3
3. X-ray data of chiral 3g............................................................................ 3
4. $^1$H NMR, $^{13}$C NMR and $^{31}$P NMR spectra......................................... 6
5. HPLC spectra............................................................................................ 49
1. General procedure for the preparation of catalysts

Catalyst 1a-1k\(^1\) and 1l-1p\(^2\) which were described in this paper were prepared according to the similar reported procedures. 9-amino (9-deoxy) epi-quinine was obtained via the classic Mitsunobu and Staudinger reactions from quinine; subsequently transformed into isothiocyanate which was used as a common electrophile in the following reactions with corresponding primary amines to give those catalysts.

Procedure for the preparation of squaramide p derived from dihydroquinine

To a solution of 7 (2.12 g, 6 mmol) in MeOH (60 mL) was added a solution of DHQ-NH\(_2\)\(^3\) (1.63 g, 5 mmol) in MeOH (16 mL). After 24 h, the reaction mixture was filtered, and the precipitate was washed with cold MeOH (3 × 20 mL) to afford squaramide p (2.78 g, 86 %) as a pale yellow solid.\(^4\)

\[
\begin{align*}
\text{DHQ-NH}_2 \quad \xrightarrow{\text{Pd/C H}_2(3\text{atm})} \quad \text{DHQ-NH}_2 \\
\text{MeOH} \quad \text{3h} \\
95\% \text{ yield} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeOH} \quad \text{MeOH} \quad \text{r.t.} \quad \text{24h} \\
\text{86\% yield} \\
\end{align*}
\]

3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-(((1S)-((2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione Catalyst (p)

Pale yellow solid, mp 150-152 °C; \([\alpha]_D^{20} = -18.25\) (c 0.4, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.58 (d, \(J = 4.3\) Hz, 1H), 7.98 (d, \(J = 9.2\) Hz, 1H), 7.68 (d, \(J = 20.2\) Hz, 4H), 7.44 (d, \(J = 4.5\) Hz, 1H).
1H), 7.36 (dd, $J = 9.2$, 2.4 Hz, 1H), 6.14 (s, 1H), 4.67 (s, 2H), 3.87 (s, 3H), 3.57 – 3.27 (m, 2H), 3.13 (d, $J = 10.3$ Hz, 1H), 2.66 (s, 1H), 2.41 (d, $J = 11.5$ Hz, 1H), 1.65 (s, 2H), 1.55 – 1.34 (m, 3H), 1.32 – 1.08 (m, 3H), 0.75 (t, $J = 7.2$ Hz, 5H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 182.99, 182.62, 167.76, 167.31, 158.69, 147.62, 144.76, 140.53, 132.53, 132.19, 131.86, 131.53, 127.97, 127.21, 124.50, 122.11, 121.79, 119.08, 57.54, 55.88, 46.94, 40.93, 36.74, 27.90, 27.33, 25.49, 24.89, 11.93; IR: 3208.2, 2960.9, 2931.5, 2866.7, 1795.3, 1668.7, 1621.6, 1586.3, 1533.3, 1509.7, 1460.3, 1376.7, 1343.6, 1277.2, 1238.9, 1165.3, 1124.1, 1028.5, 972.8, 892.7, 838.7, 729.3, 703.7, 682.6 cm$^{-1}$; HRMS-ESI ($m/z$): calcd for C$_{33}$H$_{32}$F$_{6}$N$_{4}$O$_{3}$[M+H]$^{+}$: 647.2451; found: 647.2443, 1.3 ppm.

3. Reference


4. Single-Crystal X-ray Crystallography of 3g

Crystal data and structure refinement for 3g

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Wavelength                0.71073 Å
Crystal system, space group Monoclinic, P2(1)
Unit cell dimensions       a = 8.671(3) Å  alpha = 90 deg.
                          b = 15.948(6) Å  beta = 94.150(7) deg.
                          c = 15.692(6) Å  gamma = 90 deg.
Volume                     2164.3(14) Å³
Z, Calculated density      4, 1.528 Mg/m³
Absorption coefficient     2.119 mm⁻¹
F(000)                     1012
Crystal size               0.25 x 0.20 x 0.15 mm
Theta range for data collection 1.30 to 27.84 deg.
Limiting indices           -11<=h<=11, 0<=k<=20, 0<=l<=20
Reflections collected / unique 5219 / 5219 [R(int) = 0.0000]
Completeness to theta = 27.84 97.6 %
Absorption correction      Semi-empirical from equivalents
Max. and min. transmission 0.7417 and 0.6194
Refinement method          Full-matrix least-squares on F²
Data / restraints / parameters 5219 / 1 / 533
Goodness-of-fit on F²      1.074
Final R indices [I>2sigma (I)]
                          R1 = 0.0655, wR2 = 0.1762
R indices (all data)       R1 = 0.0812, wR2 = 0.1936
Absolute structure parameter 0.084(16)
Largest diff. peak and hole 1.910 and -1.126 e.A⁻³
The crystal was prepared from the solution of 3g in DCM and n-hexane. CCDC 941868 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

4. $^1$H NMR, $^{13}$C NMR and $^{31}$P NMR spectra

3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-(((1S)-((2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione Catalyst (p)
(R)-1-((diphenylphosphoryl)(phenyl)methyl)pyrazolidin-3-one (3a)
(R)-1-((diphenylphosphoryl)(2-fluorophenyl)methyl)pyrazolidin-3-one (3b)
(R)-1-((diphenylphosphoryl)(4-fluorophenyl)methyl)pyrazolidin-3-one (3c)
(R)-1-((2-chlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3d)
(R)-1-((3-chlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3e)
(R)-1-((4-chlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3f)
(R)-1-((2-bromophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3g)
(R)-1-((3-bromophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3h)
(R)-1-((4-bromophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3i)
(R)-1-((2,4-dichlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3j)
(R)-1-((diphenylphosphoryl)(4-(trifluoromethyl)phenyl)methyl)pyrazolidin-3-one (3k)
(R)-1-(((diphenylphosphoryl)(3-nitrophenyl)methyl)pyrazolidin-3-one (3l)
(R)-1-((diphenylphosphoryl)(m-tolyl)methyl)pyrazolidin-3-one (3m)
(R)-1-((diphenylphosphoryl)(4-isopropylphenyl)methyl)pyrazolidin-3-one (3n)
(R)-1-((diphenylphosphoryl)(2-methoxyphenyl)methyl)pyrazolidin-3-one (3p)
(R)-1-((diphenylphosphoryl)(4-methoxyphenyl)methyl)pyrazolidin-3-one (3q)
(R)-1-((3, 5-dimethoxyphenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3r)
(R)-1-((2, 4-dimethoxyphenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3s)
(R)-1-(benzo[dl][1,3]dioxol-5-yl(diphenylphosphoryl)methyl)pyrazolidin-3-one (3t)
(R)-1-(((diphenylphosphoryl)(naphthalen-1-yl)methyl)pyrazolidin-3-one (3u)
(R)-1-((diphenylphosphoryl)(naphthalen-2-yl)methyl)pyrazolidin-3-one (3v)
(R)-1-(((diphenylphosphoryl)(furan-3-yl)methyl)pyrazolidin-3-one (3w)
(R)-1-((diphenylphosphoryl)(thiophen-2-yl)methyl)pyrazolidin-3-one (3x)
(R)-1-(((diphenylphosphoryl)(pyridin-2-yl)methyl)pyrazolidin-3-one (3y)
\((R,E)-1-(1\text{-}(\text{diphenylphosphoryl})\text{-}3\text{-phenylallyl})\text{pyrazolidin-3-one}\ (3z)\)
(R)-1-(cyclohexyl(diphenylphosphoryl)methyl)pyrazolidin-3-one (3aa)
(R)-1-(((di-p-tolylphosphoryl)(phenyl)methyl)pyrazolidin-3-one (4b)
(R)-1-((bis(3,5-dimethylphenyl)phosphoryl)(phenyl)methyl)pyrazolidin-3-one (4c)
dimethyl (R)-((3-oxopyrazolidin-1-yl)(phenyl)methyl)phosphonate (6da)
dimethyl (R)-((3-chlorophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6de)
dimethyl (R)-((4-chlorophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6df)
dimethyl (R)-((2-bromophenyl)\(3\)-oxopyrazolidin-1-yl)methyl)phosphonate (6dg)
dimethyl (R)-((3-bromophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6dh)
dimethyl (R)-((4-bromophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6di)
dimethyl (R)-((3-oxopyrazolidin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phosphonate (6dk)
dimethyl (R)-((3-oxopyrazolidin-1-yl)(m-tolyl)methyl)phosphonate (6dm)
dimethyl (R)-((4-isopropylphenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6dn)
dimethyl (R)-(naphthalen-1-yl(3-oxopyrazolidin-1-yl)methyl)phosphonate (6du)
dimethyl (R)-(naphthalen-2-yl(3-oxopyrazolidin-1-yl)methyl)phosphonate (6dv)
dimethyl (R)-(cyclohexyl(3-oxopyrazolidin-1-yl)methyl)phosphonate (6daa)
5. HPLC spectra

(R)-1-(((diphenylphosphoryl)(phenyl)methyl)pyrazolidin-3-one (3a)

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 8.875 BB 0.2679 2787.76074 159.49817 50.5678
2 12.176 BB 0.4471 2725.15601 91.59124 49.4322

(R)-1-(((diphenylphosphoryl)(2-fluorophenyl)methyl)pyrazolidin-3-one (3b)

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 8.855 BB 0.2700 7231.14404 413.52521 99.6277
2 12.358 MM R 0.2969 27.02044 1.22473 0.3723
(R)-1-((diphenylphosphoryl)(4-fluorophenyl)methyl)pyrazolidin-3-one (3c)

(R)-1-((2-chlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3d)
(R)-1-((3-chlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3e)
(R)-1-((4-chlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3f)
(R)-1-((2-bromophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3g)

S53
(R)-1-((4-bromophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3i)

(R)-1-((2,4-dichlorophenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3j)

S54
(R)-1-((diphenylphosphoryl)(4-(trifluoromethyl)phenyl)methyl)pyrazolidin-3-one (3k)
(R)-1-((diphenylphosphoryl)(3-nitrophenyl)methyl)pyrazolidin-3-one (3l)

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S56
(R)-1-(((diphenylphosphoryl)(m-tolyl)methyl)pyrazolidin-3-one (3m)

(DAD1 C, Sig=210.8 Ref=360.100 (E:\WX\DATA\KLPSNAPSHOT.D))

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# [min] [min] [mAU*s] [mAU] %

| 1 | 7.991 | VB | 0.2486 | 1.15708e4 | 715.72253 | 50.1785 |
| 2 | 9.618 | MM | 0.4716 | 1.14885e4 | 405.96933 | 49.8215 |

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Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %

| 1 | 7.862 | BB | 0.2331 | 3154.88330 | 207.88969 | 98.9038 |
| 2 | 9.682 | MM | 0.3602 | 34.96645 | 1.61810 | 1.0962 |

(R)-1-(((diphenylphosphoryl)(4-isopropylphenyl)methyl)pyrazolidin-3-one (3n)

(DAD1 C, Sig=210.8 Ref=360.100 (E:\WX\DATA\KLPSNAPSHOT.D))

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %

| 1 | 6.269 | VB | 0.1883 | 5335.80029 | 431.50345 | 50.7728 |
| 2 | 11.087 | BB | 0.4993 | 5173.36914 | 155.02676 | 49.2272 |
(R)-1-((4-(dimethylamino)phenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3o)

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(S)58
(R)-1-((diphenylphosphoryl)(2-methoxyphenyl)methyl)pyrazolidin-3-one (3p)

(R)-1-((diphenylphosphoryl)(4-methoxyphenyl)methyl)pyrazolidin-3-one (3q)

S59
(R)-1-((3,5-dimethoxyphenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3r)

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
1 10.288 BB 0.3307 295.91208 13.76995 96.4869
2 19.747 MM R 0.7496 10.77427 2.39547e-1 3.5131

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1 11.484 BB 0.5195 7004.06738 195.70796 49.4268
2 14.001 BB 0.4780 7166.51270 230.96368 50.5732

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
1 12.113 MM R 0.5544 10.48377 3.15193e-1 0.3049
2 14.065 BB 0.4718 3427.93481 112.39103 99.6951
(R)-1-((2, 4-dimethoxyphenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3s)

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
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1 15.048 BB 0.4815 1067.99023 34.27734 50.2072
2 45.475 MM R 1.7479 1059.17639 10.09956 49.7928

(R)-1-(benzo[d][1,3]dioxol-5-yl(diphenylphosphoryl)methyl)pyrazolidin-3-one (3t)

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
--- | ------ | ------ | ------ | ------ |
1 15.070 BB 0.4633 209.68013 6.84697 100.0000

(R)-1-((2, 4-dimethoxyphenyl)(diphenylphosphoryl)methyl)pyrazolidin-3-one (3s)

Peak RetTime Type Width Area Height Area %
# [min] [min] [mAU*s] [mAU] %
--- | ------ | ------ | ------ | ------ |
1 13.587 BB 0.4550 371.22281 12.48024 50.3250
2 19.846 MM R 1.5882 366.42764 3.84533 49.6750
(R)-1-((diphenylphosphoryl)(naphthalen-1-yl)methyl)pyrazolidin-3-one (3u)

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(R)-1-((diphenylphosphoryl)(naphthalen-2-yl)methyl)pyrazolidin-3-one (3v)

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(R)-1-((diphenylphosphoryl)(furan-3-yl)methyl)pyrazolidin-3-one (3w)
((R)-1-((diphenylphosphoryl)(thiophen-2-yl)methyl)pyrazolidin-3-one (3x))
(R)-1-((diphenylphosphoryl)(pyridin-2-yl)methyl)pyrazolidin-3-one (3y)

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 14.015 BB 0.4451 674.82007 22.94798 49.8520
2 17.968 BB 0.5906 678.82562 17.49825 50.1480

(R,E)-1-((diphenylphosphoryl)-3-phenylallyl)pyrazolidin-3-one (3z)

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 13.918 BB 0.4281 158.36691 5.53071 9.1024
2 17.646 BB 0.5822 1581.47595 41.53578 90.8976

S65
(R)-1-(cyclohexyl(diphenylphosphoryl)methyl)pyrazolidin-3-one (3aa)

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %

1 9.166 BB 0.2970 1287.45032 66.17896 92.6585
2 13.078 MM R 0.8450 102.00761 2.01194 7.3415

(R)-1-(cyclohexyl(diphenylphosphoryl)methyl)pyrazolidin-3-one (3aa)

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %

1 4.907 BB 0.3352 1147.37451 52.04100 50.4890
2 6.699 BB 0.5418 1125.14954 31.71932 49.5110

(R)-1-(cyclohexyl(diphenylphosphoryl)methyl)pyrazolidin-3-one (3aa)

Peak RetTime Type Width Area Height Area
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1 4.938 BB 0.3403 631.98218 28.32361 96.0626
2 6.767 MM R 0.4418 25.90326 9.77146e-1 3.9374
(R)-1-((di-p-tolyphosphoryl)(phenyl)methyl)pyrazolidin-3-one (4b)

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
1 42.794 MM R 3.6899 1424.09570 6.43242 50.8028
2 52.355 MM R 5.2843 1379.08801 4.34967 49.1972

(R)-1-((bis(3,5-dimethylphenyl)phosphoryl)(phenyl)methyl)pyrazolidin-3-one (4c)

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1 43.464 MM R 4.1395 766.63928 3.08665 97.8354
2 55.743 MM R 3.9727 16.96171 7.11589e-2 2.1646
dimethyl (R)-((3-oxopyrazolidin-1-yl)(phenyl)methyl)phosphonate (6da)
dimethyl (R)-(3-chlorophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6de)

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|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| # [min] [min] [mAU*s] [mAU] %                        |
| 1 11.583 BB 0.3211 2655.42480 125.39643 96.6054    |
| 2 12.938 BB 0.3459 93.30896 4.09400 3.3946        |

dimethyl (R)-(4-chlorophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6df)

| Peak RetTime Type Width Area Height Area % |
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| # [min] [min] [mAU*s] [mAU] %                        |
| 1 13.743 BV 0.6723 351.19781 7.58402 50.1071        |
| 2 15.428 VB 0.7854 349.69656 6.50227 49.8929        |

dimethyl (R)-(3-chlorophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6de)
dimethyl (R)-((2-bromophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6dg)
dimethyl (R)-((3-bromophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6dh)

dimethyl (R)-((4-bromophenyl)(3-oxopyrazolidin-1-yl)methyl)phosphonate (6di)

S71
### dimethyl (R)-((3-oxopyrazolidin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phosphonate (6dk)

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S72
**dimethyl (R)-((3-oxopyrazolidin-1-yl)(m-toly1)methyl)phosphonate (6dm)**

<table>
<thead>
<tr>
<th>Peak RetTime</th>
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<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
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<td>8.881</td>
<td>BB</td>
<td>0.2505</td>
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</tbody>
</table>

**dimethyl (R)-((3-oxopyrazolidin-1-yl)(m-toly1)methyl)phosphonate (6dm)**

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Width</th>
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<tbody>
<tr>
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<td>2240.28735</td>
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<td>10.419</td>
<td>BB</td>
<td>0.2750</td>
<td>2239.22412</td>
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</tbody>
</table>

**dimethyl (R)-((3-oxopyrazolidin-1-yl)(m-toly1)methyl)phosphonate (6dm)**

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Width</th>
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<th>Area</th>
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</thead>
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<tr>
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dimethyl \((R)-(4\text{-isopropylphenyl})(3\text{-oxopyrazolidin-1-yl})\text{methyl}\)phosphonate (6dn)

<table>
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<tr>
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<th>Area [mAU*s]</th>
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<td>90.90402</td>
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dimethyl \((R)-(naphthalen-1-yl)(3\text{-oxopyrazolidin-1-yl})\text{methyl}\)phosphonate (6du)

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S74
dimethyl (R)-(naphthalen-2-yl(3-oxopyrazolidin-1-yl)methyl)phosphonate (6dv)

dimethyl (R)-(cyclohexyl(3-oxopyrazolidin-1-yl)methyl)phosphonate (6daa)

S75
### Peak RetTime Type Width Area Height Area %

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### Peak RetTime Type Width Area Height Area %

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