Multi-component Heteroarene Couplings via Polarity-reversed Radical Cascades

Jeremy M. Lear,† J. Quentin Buquoi,† Xin Gu, Kui Pan, Darsheed N. Mustafa, David A. Nagib*

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I. General Information

All chemicals and reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, TCI, or ChemImplex. Reagents were dried under high vacuum before use. Solvents were purified in the following manner. MeCN and CH$_2$Cl$_2$ was distilled over calcium hydride. Flash column chromatography, or preparative thin-layer chromatography, was performed with Silicycle F60 (230-400 mesh) silica gel (unless otherwise stated). Thin layer chromatography (TLC) analyses were performed using EMD 60 F254 TLC plates and visualized by fluorescence quenching or KMnO$_4$ stain. All yields are averages of at least two experimental runs.

Nuclear magnetic resonance (NMR) spectra ($^1$H, $^{13}$C, $^{19}$F, $^{31}$P) were recorded using either a Bruker AVIII 400, AVIII 600, or AVIII 850 MHz NMR spectrometer. $^1$H and $^{13}$C NMR chemical shifts are reported in parts per million and referenced to residual CHCl$_3$ signals in CDCl$_3$ ($^1$H: δ 7.26; $^{13}$C: δ 77.16) (unless otherwise noted). $^{31}$P NMR chemical shifts are reported in parts per million and referenced to phosphoric acid as an external sample (δ 0.00). $^1$H NMR data are reported as follows: chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, b = broad, ap = apparent), coupling constant (Hz), relative integral. Data for $^{13}$C, $^{19}$F, and $^{31}$P NMR are reported in terms of chemical shift and multiplicity where appropriate. High-resolution Mass Spectrometry (HRMS) data were obtained using Bruker MicrOTOF (ESI). Infrared (IR) spectra were recorded using a Thermo Fisher Nicolet iS10 FT-IR and are reported in terms of frequency of absorption (cm$^{-1}$). Melting points were determined using an Electrotherman IA9000. Reagents were added to reactions with a Fischerbrand Single Syringe Pump (Model No: 78-01001).
II. General Procedures

**General Procedure 1 (GP1, azidation):** The heteroarene (0.1 mmol) and stir bar were combined in an oven-dried vial, then CH₂Cl₂ (1 ml) and trifluoroacetic acid (8 µL, 0.1 mmol, 1 eq.) were added, and the solution was stirred at r.t. for 5 mins. During this time a solution of iodobenzene diacetate (PIDA) (64.4 mg, 0.2 mmol, 2 eq) in CH₂Cl₂ (1 ml) was prepared and put into a 3 ml syringe, then loaded into a syringe pump (settings @ 3ml syringe: vol: 1 ml, rate: 2 ml/hr). To the stirring solution, ethyl vinyl ether (38 µL, 0.4 mmol, 4 eq), and trimethylsilyl azide (TMSN₃) (26 µL, 0.2 mmol, 2 eq) were added in this order, then the PIDA solution was added via syringe pump and stirred until PIDA solution delivered (ca. 30 mins). The reaction was neutralized with NaHCO₃ (sat’d aq) and extracted with CH₂Cl₂ (3 X 12 ml), dried with Na₂SO₄, concentrated, and purified via flash chromatography (ethyl acetate/hexanes) to yield the target compound.

**General Procedure 2 (GP2, phosphinylation):** The heteroarene (0.1 mmol) and stir bar were combined in an oven-dried vial, then CH₂Cl₂ (1 ml) and trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq) were added, and the solution was stirred at r.t. for 5 mins. During this time a solution of iodobenzene diacetate (PIDA) (64.4 mg, 0.2 mmol, 2 eq) in CH₂Cl₂ (1 ml) was prepared and put into a 3 ml syringe, then loaded into a syringe pump (settings @ 3ml syringe: vol: 1 ml, rate: 2 ml/hr). To the stirring solution, diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2 eq), and TMSN₃ (13.5 µL, 0.1 mmol, 1 eq) were added in this order, then the PIDA solution was added via syringe pump and stirred until PIDA solution delivered (ca. 30 mins). The reaction was neutralized with NaHCO₃ (sat’d aq) and extracted with CH₂Cl₂ (3 X 12 ml), dried with Na₂SO₄, concentrated, and purified via flash chromatography (ethyl acetate/hexanes) to yield the target compound.

**General Procedure 3 (GP3, trifluoromethylation):** The heteroarene (0.1 mmol) and stir bar were combined in an oven-dried vial, then freshly distilled MeCN (1 ml) and trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 eq) were added, and the solution was stirred at r.t. for 5 mins. To the solution was added sodium triflinate (31.5 mg, 0.2 mmol, 2 eq), ethyl vinyl ether (19 µL, 2 mmol, 2 eq), and [bis(trifluoroacetoxy)iodo]benzene (PIFA) (86 mg, 0.2 mmol, 2 eq), in this order. The reaction was stirred at room temperature for 45 mins, then neutralized with NaHCO₃ (sat’d aq), extracted with CH₂Cl₂ (3 X 12 ml), dried with Na₂SO₄, concentrated, and purified via flash chromatography (ethyl acetate/hexanes) to yield the target compound.
III. Synthesis of Starting Materials

 isoquinolin-5-yl benzoate
Prepared according to reference patent (90%). Spectra matches literature values.¹

 N-(isoquinolin-5-yl)pivalamide
Prepared according to Kanai’s method (50%). Spectra matches literature values.²
IV. Optimization of Reaction Conditions

A) Azidoalkylation of phenanthridine.

<table>
<thead>
<tr>
<th>heteroarene</th>
<th>Method of Addition</th>
<th>CF$_3$CO$_2$H equiv</th>
<th>vinyl ether equiv</th>
<th>TMSN$_3$ equiv</th>
<th>Ph(OR)$_2$ equiv</th>
<th>Prod$^b$</th>
<th>SM$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>lepidine</td>
<td>t = 0</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>20%</td>
<td>85%</td>
</tr>
<tr>
<td>lepidine</td>
<td>Syringe pump (2ml/hr)</td>
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<td>4</td>
<td>2</td>
<td>2</td>
<td>41%</td>
<td>56%</td>
</tr>
<tr>
<td>lepidine</td>
<td>Syringe pump (2ml/hr)</td>
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<td>4</td>
<td>4</td>
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<td>75%</td>
<td>22%</td>
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<tr>
<td>lepidine</td>
<td>Syringe pump (2ml/hr)</td>
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<td>6</td>
<td>73%</td>
<td>10%</td>
</tr>
<tr>
<td>lepidine</td>
<td>Syringe pump (2ml/hr)</td>
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<td>6</td>
<td>6</td>
<td>6</td>
<td>73%</td>
<td>8%</td>
</tr>
<tr>
<td>lepidine</td>
<td>Syringe pump (2ml/hr)</td>
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<td>4</td>
<td>4</td>
<td>4</td>
<td>80% (56%)</td>
<td>13%</td>
</tr>
<tr>
<td>isoquinoline</td>
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<td>2</td>
<td>70%</td>
<td>7%</td>
</tr>
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<td>isoquinoline</td>
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<td>4</td>
<td>2</td>
<td>2</td>
<td>75% (58%)</td>
<td>0%</td>
</tr>
<tr>
<td>isoquinoline</td>
<td>Syringe pump (2ml/hr)</td>
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<td>4</td>
<td>2</td>
<td>2</td>
<td>63%</td>
<td>0%</td>
</tr>
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<td>isoquinoline</td>
<td>Syringe pump (2ml/hr)</td>
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<td>4</td>
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<td>9%</td>
<td>55%</td>
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<tr>
<td>phenanthridine</td>
<td>t = 0</td>
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<td>4</td>
<td>2</td>
<td>2</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>phenanthridine</td>
<td>Syringe pump (2ml/hr)</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>92% (88%)</td>
<td>0%</td>
</tr>
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</table>

a) Conditions: heteroarene (0.1 mmol, 1.0 equiv), CH$_2$Cl$_2$ (1ml). b) $^1$H NMR yield, dibromomethane standard. c) isolated yield.

B) Phosphinylalkylation of phenanthridine.

<table>
<thead>
<tr>
<th>Method of Addition</th>
<th>Oxidant</th>
<th>Ph$_2$(O)H equiv</th>
<th>TMSN$_3$ equiv</th>
<th>Prod (2)$^d$</th>
<th>Prod (1)$^d$</th>
<th>SM$^d$</th>
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<tbody>
<tr>
<td>t = 0</td>
<td>Ph(OR)$_2$</td>
<td>2</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>89%</td>
</tr>
<tr>
<td>t = 0</td>
<td>Ph(OR)$_2$</td>
<td>2</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>95%</td>
</tr>
<tr>
<td>t = 0</td>
<td>Ph(OR)$_2$</td>
<td>2</td>
<td>1</td>
<td>26%</td>
<td>54%</td>
<td>28%</td>
</tr>
<tr>
<td>t = 0</td>
<td>Ph(OR)$_2$</td>
<td>2</td>
<td>2</td>
<td>92%</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>t = 0</td>
<td>Ph(OR)$_2$</td>
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<td>1</td>
<td>85%</td>
<td>trace</td>
<td>0%</td>
</tr>
<tr>
<td>Syringe pump (1ml/hr)</td>
<td>Ph(OR)$_2$</td>
<td>2</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>87%</td>
</tr>
<tr>
<td>Syringe pump (2ml/hr)$^c$</td>
<td>Ph(OR)$_2$</td>
<td>2</td>
<td>0</td>
<td>14%</td>
<td>0%</td>
<td>84%</td>
</tr>
</tbody>
</table>

a) Conditions: phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), CH$_2$Cl$_2$ (1ml), trifluoroacetic acid (16 µL, 0.2 mmol, 2.0 equiv), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), and Ph(OR)$_2$ (64.4 mg, 0.2 mmol, 2 equiv). b) High yields were achieved under these conditions with phenanthridine, however the yields for other substrates were lower. c) Conditions provided satisfactory yields across substrate classes. d) $^1$H NMR yield, dibromomethane standard.
C. Trifluoromethylalkylation of phenanthridine.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Method of Addition</th>
<th>vinyl ether equiv</th>
<th>CF(_3)SO(_2)Na equiv</th>
<th>PhI(O(_2)CCF(_3))(_2) equiv</th>
<th>Prod (3)(^b)</th>
<th>SM(^b)</th>
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<tbody>
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<td>2</td>
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<td>2</td>
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<td>4</td>
<td>51%</td>
<td>22%</td>
</tr>
<tr>
<td>t = 0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>60%</td>
<td>-</td>
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</table>

a) Conditions: phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), MeCN (1ml), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv). b) \(^1\)H NMR yield, dibromomethane standard.
V. Synthesis of Products

![Chemical structure](image)

6-(2-azido-1-ethoxyethyl)phenanthridine (1)
Prepared according to GP1, using phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), PhI(OAc)\(_2\) (64.4 mg, 0.2 mmol, 2 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN\(_3\) (26 µL, 0.2 mmol, 2.0 equiv). Product isolated as a yellow oil (88% yield). R\(_f\) = 0.49 (10% ethyl acetate/hexanes).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.71\) (dd, \(J = 15, 8.3\) Hz, 2H), 8.59 (m, 1H), 8.20 (m, 1H), 7.88 (m, 1H), 7.77-7.67 (m, 3H), 5.37 (dd, \(J = 8.6, 4.2\) Hz, 1H), 4.07 (dd, \(J = 13, 8.6\) Hz, 1H), 3.66-3.61 (m, 3H), 1.25 (t, \(J = 7\) Hz, 3H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 157.58, 143.37, 133.59, 130.86, 130.44, 128.96, 127.56, 126.23, 124.80, 124.24, 122.72, 122.11, 83.18, 65.33, 54.01, 15.58\).

HRMS (ESI-TOF) \(m/z\): calc’d for C\(_{17}\)H\(_{17}\)N\(_4\)O (M+1) 293.1397 found 293.1387.

IR (film) cm\(^{-1}\): 3072 (w), 2974 (w), 2095 (s), 1101 (m), 761 (s), 728 (s).

(2-ethoxy-2-(phenanthridin-6-yl)ethyl)diphenylphosphine oxide (2)
Prepared according to GP2, using phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), and TMSN\(_3\) (13.5 µL, 0.1 mmol, 1.0 equiv), and PhI(OAc)\(_2\) (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (90% NMR yield, dibromomethane standard). 0.18 (silica, 1.5/5/93.5, TEA/MeOH/CH\(_2\)Cl\(_2\))

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.70\) (d, \(J = 8.2\) Hz, 1H), 8.59 (d, \(J = 8.3\) Hz, 1H), 8.49 (dd, \(J = 8.1, 1.1\) Hz, 1H), 8.13 (dd, \(J = 8.1, 1.1\) Hz, 1H), 7.90-7.85 (m, 2H), 7.84-7.80 (m, 1H), 7.72-7.67 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.48 (m, 3H), 7.48-7.43 (m, 2H), 7.21-7.17 (m, 1H), 7.13-7.08 (m, 2H), 5.86 (ddd, \(J = 9.6, 7.7, 5.3\) Hz, 1H), 3.44-3.34 (m, 2H), 3.27 (ddd, \(J = 15.2, 9.7, 7.7\) Hz, 1H), 3.15 (ddd, \(J = 15.2, 11.8, 5.3\) Hz, 1H), 0.92 (t, \(J = 7.0\) Hz, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 159.3 (d, $J = 8.7$ Hz), 143.3, 133.8 (d, $J = 100.0$ Hz), 133.4, 133.1 (d, $J = 99.9$ Hz), 131.6 (d, $J = 2.2$ Hz), 131.2 (d, $J = 9.4$ Hz), 130.7 (d, $J = 9.3$ Hz), 130.6, 130.5, 128.6, 128.5 (d, $J = 12.0$ Hz), 128.2 (d, $J = 11.8$ Hz), 127.5, 127.2, 126.1, 124.5, 124.1, 122.5, 121.9, 75.7 (s, broad), 64.9, 36.4 (d, $J = 69.8$ Hz), 15.1.

$^{31}$P NMR (MHz, CDCl$_3$): δ = 29.14.

HRMS (ESI-TOF) m/z: calc’d for C$_{29}$H$_{27}$NO$_2$P (M+1) 452.1779 found 452.1771.

IR (film) cm$^{-1}$: 3057 (w), 2974 (w), 2925 (w), 1611 (m), 1181 (s), 1119 (s), 910 (w), 762 (s), 729 (s), 510 (m).

6-(1-ethoxy-3,3,3-trifluoropropyl)phenanthridine (3)
Prepared according to GP3, using phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), sodium triflinate (31.5 mg, 0.2 mmol, 2 eq) and PIFA (86 mg, 0.2 mmol, 2 equiv). The product was isolated as a yellow oil (60% NMR yield, mesitylene standard). $R_f = 0.5$ (10% ethyl acetate/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$): δ = 8.72 (dm, $J = 8.3$ Hz, 1H), 8.70 (dm, $J = 8.3$ Hz, 1H), 8.59 (dm, $J = 8.2$ Hz, 1H), 8.19 (dm, $J = 8.2$ Hz, 1H), 7.88 (qd, $J = 8.3$, 7.0, 1.2 Hz, 1H), 7.77-7.68 (m, 3H), 5.52 (dd, $J = 8.7$, 4.2 Hz, 1H), 3.54-3.48 (m, 2H), 3.15-3.07 (m, 1H), 2.94-2.85 (m, 1H), 1.18 (t, $J = 7$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 158.13, 143.26, 133.68, 130.80, 130.49, 128.90, 127.55, 126.33 (q, $J = 27.7$ Hz), 126.10, 124.37, 124.28, 122.76, 122.06, 77.46 (m), 64.44, 38.73 (q, $J = 27.9$ Hz), 15.36.

$^{19}$F NMR (X MHz, CDCl$_3$): δ = -63.59 (t, $J = 11.2$ Hz, 3F).

HRMS (ESI-TOF) m/z: calc’d for C$_{18}$H$_{17}$F$_3$NO (M+1) 320.1262 found 320.1245.

IR (film) cm$^{-1}$: 3075 (w), 2976 (w), 2927 (w), 1253 (m), 1128 (s), 762 (m), 729 (m).
1-(2-azido-1-ethoxyethyl)isoquinoline (4)
Prepared according to GP1, using isoquinoline (12 µL, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), Phl(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (26 µL, 0.2 mmol, 2.0 equiv). Product isolated as a yellow oil (58% yield). Rₓ = 0.54 (25% ethyl acetate/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 8.58 (d, J = 8.6 Hz, 1H), 8.52 (d, J = 5.6 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.71 (m, 1H), 7.63 (m, 2H), 5.31 (dd, J = 8.6, 4.1 Hz, 1H), 3.97 (dd, J = 13, 8.6 Hz, 1H), 3.60-3.48 (m, 3H), 1.23 (t, J = 7 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 157.6, 142.1, 136.9, 130.3, 127.7, 127.6, 127.0, 125.0, 121.3, 82.3, 65.4, 54.5, 15.5.

HRMS (ESI-TOF) m/z: calc’d for C₁₃H₁₅N₄O (M+1) 243.1246, found 243.1245.

IR (film) cm⁻¹: 3054 (w), 2975 (w), 2098 (s), 1107 (m).

1-(2-azido-1-ethoxyethyl)-3-methylisoquinoline (5)
Prepared according to GP1, using 3-methyl isoquinoline (14.3 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), Phl(OAc)₂ (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (52 µL, 0.4 mmol, 4.0 equiv). Product isolated as a yellow oil (64% yield). Rₓ = 0.53 (25% ethyl acetate/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 8.57 (d, J = 8.6, 0.8 Hz, 1H); 7.76 (d, J=8.2 Hz, 1H); 7.67-7.61 (m, 1H); 7.55-7.50 (m, 1H); 7.44 (s, 1H); 5.25 (dd, J = 8.6, 4.1 Hz, 1H); 3.94 (dd, J = 12.9, 8.6 Hz, 1H); 3.63-3.48 (m, 3H); 2.68 (d, J=0.5 Hz, 3H); 1.23 (t, J=7.1 Hz, H).

¹³C NMR (400 MHz, CDCl₃): δ = 156.91, 150.69, 137.74, 130.15, 127.07, 126.51 125.12, 125.06, 119.36, 82.94, 65.38, 54.36, 24.28, 15.54.

HRMS (ESI-TOF) m/z: calc’d for C₁₄H₁₇N₄O (M+1) 257.1397 found 257.1374.

IR (film) cm⁻¹: 2925 (w), 2096 (s), 1591 (m), 1563 (m), 1104 (s), 752 (s).
1-(2-azido-1-ethoxyethyl)-4-acetylisoquinoline (6)
Prepared according to GP1, using 4-acetylisoquinoline (17.1 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), PhI(OAc)₂ (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (52 µL, 0.4 mmol, 4.0 equiv). Product isolated as a clear oil (80% yield). Rᵣ = 0.38 (25% ethyl acetate/hexanes).

¹H NMR (600 MHz, CDCl₃): δ = 8.89 (s, 1H), 8.86 (dt, J = 8.8, 0.87 Hz, 1H), 8.62 (dt, J = 8.2, 0.87 Hz, 1H), 7.83 (m, 1H), 7.69 (m, 1H), 5.34 (dd, J = 8.4, 4.3 Hz, 1H), 3.96 (dd, J = 12.7, 8.4 Hz, 1H), 3.61-3.50 (m, 3H), 2.78 (s, 3H), 1.24 (t, J = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ = 200.3, 162.1, 144.3, 133.8, 132.2, 128.5, 128.1, 127.1, 126.3, 125.1, 82.1, 65.7, 54.3, 30.0, 15.5.

HRMS (ESI-TOF) m/z: calc’d for C₁₅H₁₆N₄O₂ (M⁺) 285.1352, found 285.1364.

IR (film) cm⁻¹: 3050 (w), 2975 (w), 2873 (w), 2098 (s), 1681 (m), 1504 (m), 1104 (m), 768 (m).

Methyl-1-(2-azido-1-ethoxyethyl)isoquinoline-3-carboxylate (7)
Prepared according to GP1, using methyl 3-isoquinolinecarboxylate (18.7 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2.0 equiv), PhI(OAc)₂ (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (52 µL, 0.4 mmol, 4.0 equiv). Product isolated as a tan oil (66% yield). Rᵣ = 0.4 (25% ethyl acetate/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 8.86 (d, J = 7.8 Hz, 1H), 8.53 (s, 1H), 7.99 (s, 1H), 7.80-7.74 (m, 2H), 5.33 (dd, J = 8.7, 3.9 Hz, 1H), 4.04 (s, 3H), 3.98 (dd, J = 13.02, 8.7 Hz, 1H), 3.65-3.60 (m, 1H), 3.57-3.49 (m, 2H), 1.22 (t, J = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.31, 158.50, 140.52, 136.79, 131.05, 129.72, 129.08, 128.41, 126.02, 124.83, 84.60, 65.63, 54.36, 53.02, 15.54.

HRMS (ESI-TOF) m/z: calc’d for C₁₅H₁₈N₄NaO₃ (M+23) 323.1120, found 323.1106.

IR (film) cm⁻¹: 2926 (w), 2098 (s), 1720 (s), 1448 (m), 1246 (s), 1111 (m), 910 (w).
N-(1-(2-azido-1-ethoxyethyl)isoquinolin-5-yl)pivalamide (8)
Prepared according to GP1, using N-(isoquinolin-5-yl)pivalamide (22.8 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2.0 equiv), Phl(OAc)₂ (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (52 µL, 0.4 mmol, 4.0 equiv). Product isolated as a brown oil (91% yield). Rᵣ = 0.2 (25% ethyl acetate/hexanes).

¹H NMR (600 MHz, CDCl₃): δ = 8.57 (d, J = 6.1 Hz, 1H), 8.44 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.74 (bs, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 6.0 Hz, 1H), 5.31 (dd, J = 8.4, 4.0 Hz, 1H), 3.94 (dd, J = 13.0, 8.4 Hz, 1H), 3.58-3.46 (m, 3H), 1.42 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ = 177.37, 158.26, 142.16, 132.63, 131.52, 127.53, 127.41, 125.45, 122.50, 114.38, 82.09, 65.46, 54.41, 40.01, 27.88, 15.46.

HRMS (ESI-TOF) m/z: calc’d for C₁₈H₂₄N₅O₂ (M+1) 342.1930, found 342.1916.

IR (film) cm⁻¹: 3291 (w), 2973 (w), 2099 (s), 1658 (m), 1516 (m), 1485 (m), 1108 (w), 730 (w).

1-(2-azido-1-ethoxyethyl)-5-benzyloxyisoquinoline (9)
Prepared according to GP1, using 5-benzyloxyisoquinoline (24.9 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), Phl(OAc)₂ (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (52 µL, 0.4 mmol, 4.0 equiv). Product isolated as a yellow oil (79% yield). Rᵣ = 0.4 (25% ethyl acetate/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 8.58-8.53 (m, 2H); 8.34-8.30 (m, 2H); 7.75-7.66 (m, 3H); 7.64-7.56 (m, 3H); 5.32 (dd, J = 8.6, 4.0 Hz, 1H); 3.97 (dd, J = 12.9, 8.7 Hz, 1H); 3.62-3.47 (m, 3H); 1.25 (t, J = 7.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ = 165.08, 157.85, 146.56, 142.56, 134.31, 131.06, 130.51, 129.02, 128.95, 127.87, 127.25, 123.07, 122.63, 114.76, 82.59, 65.53, 54.48, 15.50.

HRMS (ESI-TOF) m/z: calc’d for C₂₀H₁₉N₄O₃ (M+1) 363.1452, found 363.1443.

IR (film) cm⁻¹: 3060 (w), 2975 (w), 2872 (w), 2096 (s), 1738 (s), 1586 (m), 1451 (m), 1262 (s), 1226 (s), 1148 (s), 1056 (s), 1023 (s), 707 (s).
1-(2-azido-1-ethoxyethyl)-5-bromoisoquinoline (10)
Prepared according to GP1, using 5-bromoisoquinoline (20.8 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), PhI(OAc)2 (64.4 mg, 0.2 mmol, 2 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN3 (26 µL, 0.2 mmol, 2.0 equiv). Product isolated as a yellow oil (75% yield). Rf = 0.57 (25% ethyl acetate/hexanes).

1H NMR (600 MHz, CDCl3): δ = 8.64-8.60 (m, 2H), 8.02 (dd, J = 8.6, 0.96 Hz, 1H), 8.00 (dd, J = 10.2, 0.94 Hz, 1H), 7.48 (dd, J = 8.6, 7.5 Hz, 1H), 5.30 (dd, J = 8.5, 4.2 Hz, 1H), 3.95 (dd, J = 13, 8.5 Hz, 1H), 3.60-3.48 (m, 3H), 1.23 (t, J = 7.0 Hz, 3H).

13C NMR (100 MHz, CDCl3): δ = 158.05, 143.35, 136.04, 134.17, 128.11, 127.90, 124.76, 122.65, 120.24, 82.45, 65.48, 54.42, 15.50.

HRMS (ESI-TOF) m/z: calc’d for C13H14BrN4O (M+1) 321.0346, found 321.0332, 323.0332.

IR (film) cm⁻¹: 3052 (w), 2976 (w), 2097 (s), 1110 (bm), 832 (w), 816 (w).

2-(2-azido-1-ethoxyethyl)-4-methylquinoline (11)
Prepared according to GP1, using 4-methylquinoline (13.2 µL, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2.0 equiv), PhI(OAc)2 (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN3 (52 µL, 0.4 mmol, 4.0 equiv). Product isolated as a clear oil (59% yield). Rf = 0.75 (25% ethyl acetate/hexanes).

1H NMR (400 MHz, CDCl3): δ = 8.05 (dm, J = 7.8 Hz, 1H), 8.00 (dm, J = 7.4Hz, 1H), 7.71 (qd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.57 (qd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.47 (s, 1H), 4.77 (dd, J = 7.8, 3.6 Hz, 1H), 3.64-3.58 (m, 3H), 3.52-3.48 (m, 1H), 2.75 (s, 3H), 1.30 (t, J = 7Hz, 3H).

13C NMR (100 MHz, CDCl3): δ = 159.54, 147.64, 145.54, 129.79, 129.56, 127.92, 126.50, 123.92, 119.07, 83.08, 65.83, 55.33, 19.14, 15.53.

HRMS (ESI-TOF) m/z: calc’d for C14H17N4O (M+1) 257.1402, found 257.1384.

IR (film) cm⁻¹: 3100 (w), 2975 (w), 2099 (s), 1600 (m).
4-(2-azido-1-ethoxyethyl)-2-phenylquinoline (12)
Prepared according to GP1, using 2-phenylquinoline (20.5 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), Phl(OAc)₂ (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (52 µL, 0.4 mmol, 4.0 equiv). Product isolated as a yellow oil (93% yield). Rₚ = 0.57 (25% ethyl acetate/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 8.25-8.18 (m, 3H); 8.06 (s, 1H); 8.01 (dd, J = 8.4, 1.0 Hz, 1H); 7.77-7.72 (m, 1H); 7.59-7.53 (m, 3H); 7.51-7.46 (m, 1H); 3.68-3.58 (m, 3H); 3.38 (dd, J = 13.2, 2.9 Hz, 1H); 1.34 (t, J=7.0 Hz, 3H).

¹³C NMR (400 MHz, CDCl₃): δ = 157.42, 148.83, 145.08, 139.61, 131.08, 129.69, 129.05, 127.71, 126.80, 124.99, 116.44, 78.75, 65.94, 55.85, 15.58.

HRMS (ESI-TOF) m/z: calc’d for C₁₉H₁₈N₄O (M+1) 319.1553, found 319.1549.

IR (film) cm⁻¹: 3060 (w), 2974 (w), 2872 (w), 2095 (s), 1597 (m), 1550 (m), 1107 (m), 771 (s), 694(s).

trans-6-(3-azidotetrahydrofuran-2-yl)phenanthridine (13)
Prepared according to GP1, using phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2.0 equiv), Phl(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv), 2,3-dihydrofuran (30 µL, 0.4 mmol, 4.0 equiv), and TMSN₃ (26 µL, 0.2 mmol, 2.0 equiv). Product isolated as a brown oil (72% yield, >20:1 d.r.). Rₚ = 0.6 (25% ethyl acetate/hexanes).

¹H NMR (600 MHz, CDCl₃): δ = 8.65 (d, J = 8.3 Hz, 1H), 8.56 (dm, J = 8.1 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.17 (dd, J = 8.1, 0.96 Hz, 1H), 7.86 (qd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.75-7.72 (m, 2H), 7.69-7.66 (m, 1H), 5.61 (d, J = 3.9 Hz, 1 H), 5.32-5.29 (m, 1H), 4.22-4.18 (m, 1H), 4.15-4.12 (m, 1H), 2.64-2.58 (m, 1H), 2.26-2.21 (m, 1H).

¹³C NMR (150 MHz, CDCl₃): δ = 156.38, 143.06, 133.41, 130.77, 130.65, 128.78, 127.65, 127.50, 126.74, 125.12, 124.41, 122.49, 122.09, 83.86, 67.97, 63.13, 32.15.

HRMS (ESI-TOF) m/z: calc’d for C₁₇H₁₅N₄O (M+1) 291.1246 found 291.1232.

IR (film) cm⁻¹: 2924 (w), 2103 (s), 1263 (w), 1063 (w), 760 (m), 728 (m).
(2-ethoxy-2-(isoquinolin-1-yl)ethyl)diphenylphosphine oxide (14)
Prepared according to GP2, using phenanthridine (12 µL, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), TMSN₃ (13.5 µL, 0.1 mmol, 1.0 equiv), and Phl(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (77% NMR yield, dibromomethane standard). Rₖ = 0.3 (5% MeOH in CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ = 8.50 (d, J = 8.5 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 7.90-7.5 (m, 2H), 7.76 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H, overlap), 7.58-7.54 (m, 2H, overlap), 7.52-7.44 (m, 4H), 7.32-7.28 (m, 1H), 7.25-7.21 (m, 2H), 5.83 (td, J = 13.1, 4.7 Hz, 1H), 3.31-3.21 (m, 3H), 2.94 (ddd, J = 15.1, 12.1, 4.5 Hz, 1H), 0.86 (t, J = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 159.5 (d, J = 9.0 Hz), 142.1, 136.6, 133.8 (d, J = 100.3 Hz), 133.5 (d, J = 99.3 Hz), 131.6 (d, J = 2.6 Hz), 131.3 (d, J = 2.2 Hz), 131.2 (d, J = 9.8 Hz), 130.6 (d, J = 9.3 Hz), 130.1, 128.4 (d, J = 12.0 Hz), 128.3 (d, J = 11.9 Hz), 127.6, 127.5, 126.5, 124.8, 120.8, 73.9, 64.9, 36.9 (d, J = 70.2 Hz), 15.0.

³¹P NMR (MHz, CDCl₃): δ = 29.02.

HRMS (ESI-TOF) m/z: calc’d for C₂₅H₂₅NO₂P (M+1) 402.1623 found 402.1604.

IR (film) cm⁻¹: 3053 (w), 2973 (w), 2893 (w), 1436 (m), 1183 (s), 1116 (s), 724 (s), 693 (s).

(2-ethoxy-2-(3-methylisoquinolin-1-yl)ethyl) diphenylphosphine oxide (15)
Prepared according to GP2, using 3-methylisoquinoline (14.3 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), TMSN₃ (13.5 µL, 0.1 mmol, 1.0 equiv), and Phl(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (63% NMR yield, dibromomethane standard). Rₖ = 0.33 (5% MeOH in CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ = 8.49 (d, J = 8.4 Hz, 1H), 7.88-7.83 (m, 2H), 7.65 (d, J = 8.2 Hz, 1H), 7.60-7.56 (m, 1H), 7.55-7.44 (m, 4H), 7.47-7.44 (m, 2H), 7.31-7.27 (m, 1H, overlap), 7.27 (s, 1H, overlap), 7.23-7.18 (m, 2H), 5.76 (ddd, J = 9.2, 7.5, 5.5 Hz, 1H), 3.36-3.27 (m, 2H), 3.22 (ddd, J = 15.1, 10.0, 7.5 Hz, 1H), 3.07 (ddd, J = 15.1, 11.6, 5.5 Hz, 1H), 2.60 (s, 3H), 0.91 (t, J = 7.0 Hz, 3H).
\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta = 158.6\) (d, \(J = 7.9\) Hz), 150.7, 137.5, 133.9 (d, \(J = 99.8\) Hz, overlap), 133.3 (d, \(J = 98.4\) Hz, overlap), 131.6 (d, \(J = 2.3\) Hz), 131.3 (d, \(J = 2.3\) Hz), 131.7 (d, \(J = 9.2\) Hz), 130.7 (d, \(J = 9.6\) Hz), 129.9; 128.5 (d, \(J = 11.7\) Hz), 128.2 (d, \(J = 12.0\) Hz), 126.8, 126.4, 124.9, 124.7, 118.9, 74.7, 64.8, 36.7 (d, \(J = 70.2\) Hz), 24.3, 15.2.

\(^{31}\)P NMR (MHz, CDCl\(_3\)): \(\delta = 28.91\).

HRMS (ESI-TOF) \(m/z\): calc’d for C\(_{26}\)H\(_{27}\)NO\(_3\)P (M+1) 416.1779 found 416.1765.

IR (film) cm\(^{-1}\): 3054 (w), 2922 (w), 2852 (w), 1437 (m), 1182 (s), 1118 (s), 749 (s), 719 (s), 695 (s).

1-(1-(2-(diphenylphosphoryl)-1-(ethoxyethyl)isoquinoline-4-yl)ethan-1-one (16)
Prepared according to GP\(_2\), using 4-acetylisoquinoline (17.1 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 \(\mu\)L, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 \(\mu\)L, 0.2 mmol, 2 equiv), TMSN\(_3\) (13.5 \(\mu\)L, 0.1 mmol, 1.0 equiv), and PhI(OAc)\(_2\) (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a yellow oil (67% NMR yield, dibromomethane standard). \(R_f = 0.33\) (2% MeOH in CH\(_2\)Cl\(_2\)).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.87\) (s, 1H), 8.77 (d, \(J = 8.4\) Hz, 1H), 8.57 (d, \(J = 8.5\) Hz, 1H), 7.88-7.81 (m, 2H), 7.80-7.74 (m, 1H), 7.69-7.63 (m, 1H), 7.52-7.43 (m, 5H), 7.32-7.27 (m, 1H), 7.22-7.16 (m, 2H), 5.87 (ddd, \(J = 8.9, 8.0, 5.3\) Hz, 1H), 3.34-3.27 (m, 2H), 3.21 (ddd, \(J = 15.1, 9.0, 7.9\) Hz, 1H), 2.95 (ddd, \(J = 15.0, 11.9, 5.2\) Hz, 1H), 2.71 (s, 3H), 0.88 (t, \(J = 7.0\) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 200.1, 164.0\) (d, \(J = 8.3\) Hz), 144.5, 133.4 (s overlap), 133.4 (d, \(J = 101.2\) Hz, overlap), 132.99 (d, \(J = 100.0\) Hz, overlap), 132.19, 131.69 (d, \(J = 2.6\) Hz), 131.40 (d, \(J = 2.5\) Hz), 131.07 (d, \(J = 9.6\) Hz), 130.49 (d, \(J = 9.5\) Hz), 128.50 (d, \(J = 11.9\) Hz), 128.27 (d, \(J = 11.8\) Hz), 128.07, 127.94, 126.40, 126.04, 124.93, 74.21, 65.19, 36.84 (d, \(J = 69.9\) Hz), 29.82, 15.01.

\(^{31}\)P NMR (MHz, CDCl\(_3\)): \(\delta = 28.69\).

HRMS (ESI-TOF) \(m/z\): calc’d for C\(_{27}\)H\(_{27}\)NO\(_3\)P (M+1) 444.1723 found 444.1707.

IR (film) cm\(^{-1}\): 3054 (w), 2974 (w), 2924 (w), 1679 (w), 1557 (w), 1437 (m), 1181 (s), 1118 (s), 919 (w).
methyl 1-(2-diphenylphosphoryl)-1-ethoxyethyl]isoquinoline-3-carboxylate (17)
Prepared according to GP2, using methyl 3-isoquinolinecarboxylate (18.7 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), TMSN₃ (13.5 µL, 0.1 mmol, 1.0 equiv), and PhI(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (82% NMR yield, dibromomethane standard). Rₛ = 0.17 (5% MeOH in CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ = 8.71-8.66 (m, 1H), 8.38 (s, 1H), 7.92-7.89 (m, 1H), 7.88-7.83 (m, 2H), 7.75-7.70 (m, 2H), 7.61-7.56 (m, 2H), 7.53-7.49 (m, 1H), 7.48-7.44 (m, 2H), 7.32-7.28 (m, 1H), 7.24-7.19 (m, 2H), 5.79-5.73 (m, 1H), 4.02 (s, 3H), 3.39-3.29 (m, 2H), 3.27-3.17 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ = 166.4, 159.8 (d, J = 8.3 Hz), 140.5, 136.5, 133.8 (d, J = 100.6 Hz), 133.1 (d, J = 99.6 Hz), 131.7 (d, J = 2.2 Hz), 131.4 (d, J = 2.8 Hz), 131.2 (d, J = 9.6 Hz), 130.9 (d, J = 9.1 Hz), 130.8, 129.7, 128.9, 128.5 (d, J = 11.7 Hz), 128.2 (d, J = 11.9 Hz), 127.9, 125.5, 124.4, 75.9, 64.9, 52.8, 36.3 (d, J = 69.6 Hz), 15.2.

³¹P NMR (243 MHz, CDCl₃): δ = 28.81.

HRMS (ESI-TOF) m/z: calc’d for C₂₇H₂₇NO₄P (M+1) 460.1672, found 460.1660.

IR (film) cm⁻¹: 3057 (w), 2974 (w), 2925 (w), 1611 (w), 1574 (w), 1437 (m), 1181 (s), 1119 (s), 910 (w), 762 (s), 729 (s), 510 (m).

2922 (w), 2851 (w), 1719 (s), 1670 (w), 1559 (w), 1437 (m), 1296 (m), 1117 (s), 980 (w).

N-[(1-(2-(diphenylphosphoryl)-1-ethoxylethyl)]isoquinolin-5-yl)pivalamide (18)
Prepared according to GP2, using N-(isoquinolin-5-yl)pivalamide (22.8 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), TMSN₃ (13.5 µL, 0.1 mmol, 1.0 equiv), and PhI(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (61% NMR yield, dibromomethane standard). Rₛ = 0.23 (5% MeOH in CH₂Cl₂).
\( ^1H\) NMR (850 MHz, CDCl\(_3\)): \( \delta = 8.51 \) (d, \( J = 5.9 \) Hz, 1H), 8.37 (d, \( J = 8.5 \) Hz, 1H), 8.09 (d, \( J = 7.5 \) Hz, 1H), 7.89-7.85 (m, 2H), 7.69 (s, broad, 1H), 7.63-7.57 (m, 3H), 7.53-7.44 (m, 1H), 7.49-7.45 (m, 2H), 7.43 (d, \( J = 5.2 \) Hz, 1H), 7.36-7.33 (m, 1H), 7.30-7.26 (m, 2H, overlap), 5.81 (td, \( J = 13.3, 4.4 \) Hz, 1H), 3.29-3.20 (m, 3H), 2.89 (ddd, \( J = 15.4, 12.8, 4.2 \) Hz, 1H), 1.44 (s, 9H), 0.84 (t, \( J = 7.0 \) Hz, 3H).

\( ^{13}C\) NMR (214 MHz, CDCl\(_3\)): \( \delta = 177.2, 160.3 \) (d, \( J = 10.7 \) Hz), 142.3, 133.53 (d, \( J = 98.8 \) Hz, overlap), 133.50 (d, \( J = 98.9 \) Hz, overlap), 132.5, 131.6 (d, \( J = 1.7 \) Hz), 131.5 (d, \( J = 2.0 \) Hz), 131.3 (d, \( J = 9.6 \) Hz), 131.1, 130.6 (d, \( J = 9.4 \) Hz), 128.5 (d, \( J = 11.9 \) Hz, overlap), 128.4 (d, \( J = 11.8 \) Hz, overlap), 127.6, 126.8, 125.2, 122.3, 113.8, 74.3, 65.0, 40.0, 36.9 (d, \( J = 69.8 \) Hz), 27.9, 15.0.

\( ^{31}P\) NMR (162 MHz, CDCl\(_3\)): \( \delta = 29.06 \).

HRMS (ESI-TOF) \textit{m/z}: calc’d for C\(_{30}\)H\(_{34}\)N\(_2\)O\(_3\)P (M+1) 501.2302, found 501.2301.

IR (film) \textit{cm}\(^{-1}\): 3236 (w), 2966 (w), 2925 (w), 1670 (s), 1521 (m), 1484 (m), 1177 (m), 1118 (s).

\( P\) (OAc)\(_2\), 64.4 mg, 2 eq, \( 0.2 \) mmol, 2 eq).

\( 1-(2-(diphenylphosphoryl)-1-ethoxyethyl)isoquinolin-5-yl)benzoate \) (19)
Prepared according to GP2, using 5-benzzyloxyisoquinoline (24.9 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 \( \mu \)L, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 \( \mu \)L, 0.2 mmol, 2.0 equiv), TMSN\(_3\) (13.5 \( \mu \)L, 0.1 mmol, 1.0 equiv), and Phl(OAc)\(_2\) (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (58% NMR yield, dibromomethane standard). \( R_f = 0.23 \) (5% MeOH in CH\(_2\)Cl\(_2\)).

\( ^1H\) NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.50-8.44 \) (m, 2H), 8.33-8.28 (m, 2H), 7.91-7.84 (m, 2H), 7.74-7.69 (m, 1H), 7.69-7.63 (m, 1H), 7.61-7.44 (m, 9H), 7.37-7.32 (m, 1H), 7.29-7.23 (m, 2H, overlap), 5.84 (ddd, \( J = 9.1, 8.4, 4.6 \) Hz, 1H), 3.34-3.19 (m, 3H), 2.96 (ddd, \( J = 15.1, 12.2, 4.7 \) Hz, 1H), 0.88 (t, \( J = 7.0 \) Hz, 3H).

\( ^{13}C\) NMR (150 MHz, CDCl\(_3\)): \( \delta = 165.0, 159.8 \) (d, \( J = 9.3 \) Hz), 146.4, 142.6, 134.3, 133.6 (d, \( J = 101.0 \) Hz), 133.2 (d, \( J = 98.9 \) Hz), 131.9, 131.6 (d, \( J = 2.1 \) Hz), 131.5 (d, \( J = 2.2 \) Hz), 131.2 (d, \( J = 9.6 \) Hz), 130.6 (d, \( J = 9.5 \) Hz), 130.5, 129.0, 128.7 (d, \( J = 11.8 \) Hz), 128.5 (d, \( J = 12.1 \) Hz), 127.4, 127.2, 122.9, 122.5, 114.3, 74.4, 65.1, 37.0 (d, \( J = 70.1 \) Hz), 15.0.

\( ^{31}P\) NMR (243 MHz, CDCl\(_3\)): \( \delta = 29.22 \).

HRMS (ESI-TOF) \textit{m/z}: calc’d for C\(_{32}\)H\(_{29}\)NO\(_4\)P (M+1) 522.1829, found 522.1809.

IR (film) \textit{cm}\(^{-1}\): 3057 (w), 2924 (w), 1739 (m), 1676 (s), 1227 (m), 1142 (w), 1118 (s), 998 (m).
(2-(5-bromoisoquinolin-1-yl)-2-ethoxyethyl)diphenylphosphine oxide (20)
Prepared according to GP2, using 5-bromoisoquinoline (20.8 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), TMSN₃ (13.5 µL, 0.1 mmol, 1.0 equiv), and PhI(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv).
The product was isolated as a colorless oil (48% NMR yield, dibromomethane standard). Rᵣ = 0.30 (5% MeOH in CH₂Cl₂).

¹H NMR (850 MHz, CDCl₃): δ = 8.54 (d, J = 5.8 Hz, 1H), 8.51 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.4 Hz, 1H), 7.87-7.82 (m, 3H), 7.51-7.45 (m, 5H), 7.32-7.28 (m, 1H), 7.22-7.18 (m, 2H), 5.87-5.81 (m, 1H), 3.30-3.26 (m, 2H), 3.25-3.20 (m, 1H), 2.99-2.94 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H).

¹³C NMR (214 MHz, CDCl₃): δ = 159.9 (d, J = 9.3 Hz), 135.6, 133.9, 133.6 (d, J = 101.8 Hz), 133.0 (d, J = 98.9 Hz), 131.7 (d, J = 2.2 Hz), 131.4 (d, J = 2.1 Hz), 131.1 (d, J = 9.6 Hz), 130.5 (d, J = 9.4 Hz), 128.5 (d, J = 12.0 Hz), 128.3 (d, J = 11.6 Hz), 127.9 (s, overlap), 127.8 (s, overlap), 127.6, 124.6, 122.5, 119.8, 73.9, 65.0, 37.0 (d, J = 70.1 Hz), 15.1.

³¹P NMR (163 MHz, CDCl₃): δ = 28.68.

HRMS (ESI-TOF) m/z: calc’d for C₂₅H₂₄BrNO₂P (M+1) 480.0723, found 480.0722.

IR (film) cm⁻¹: 3053 (w), 2972 (w), 2924 (w), 1437 (s), 1185 (s), 1118 (s), 1096 (m).

(2-ethoxy-2-(2-methylquinolin-4-yl)ethyldiphenylphosphine oxide (21)
Prepared according to GP2, using 5-benzyloxyisoquinoline (13.5 µL, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq.), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), TMSN₃ (13.5 µL, 0.1 mmol, 1.0 equiv), and PhI(OAc)₂ (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (54% NMR yield, dibromomethane standard). Rᵣ = 0.30 (5% MeOH in CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ = 8.21 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.88-7.83 (m, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.60-7.55 (m, 2H), 7.54-7.47 (m, 4H), 7.41-7.37 (m, 1H), 7.32 (s, 1H, overlap), 7.31-7.28 (m, 2H, overlap), 5.60-5.54 (m, 1H), 3.31-3.26 (m, 1H), 3.24-3.20 (m, 1H), 2.97-2.91 (m, 1H), 2.76-2.70 (m, 1H), 2.67 (s, 3H), 0.85 (t, J = 7.0 Hz, 3H).
$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 158.8, 148.3, 147.5, 133.4$ (d, $J = 99.6$ Hz), 133.3 (d, $J = 100.9$ Hz), 131.7 (d, $J = 2.0$ Hz), 131.5 (d, $J = 2.3$ Hz), 131.1 (d, $J = 9.6$ Hz), 130.3 (d, $J = 9.3$ Hz), 129.5, 129.3, 128.4 (d, $J = 11.7$ Hz), 128.3 (d, $J = 12.0$ Hz), 126.1, 123.9, 123.2, 119.0, 73.1, 65.1, 38.3 (d, $J = 69.7$ Hz), 14.8.

$^{31}$P NMR (243 MHz, CDCl$_3$): $\delta = 28.64$.

HRMS (ESI-TOF) m/z: calc’d for C$_{26}$H$_{27}$NO$_2$P (M+1) 416.1774, found 416.1769.

IR (film) cm$^{-1}$: 3056 (w), 2974 (w), 1601 (s), 1437 (m), 1117 (s), 1095 (m).

2-ethoxy-2-(2-phenylquinolin-4-yl)ethyl)diphenylphosphine oxide (22)
Prepared according to GP2, using 2-phenylquinoline (20.5 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 $\mu$L, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), ethyl vinyl ether (19 $\mu$L, 0.2 mmol, 2.0 equiv), TMSN$_3$ (13.5 $\mu$L, 0.1 mmol, 1.0 equiv), and PhI(OAc)$_2$ (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (66% NMR yield, dibromomethane standard). $R_f = 0.33$ (5% MeOH in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.27$ (d, $J = 8.1$ Hz, 1H), 8.19-8.10 (m, 3H), 7.95 (s, 1H), 7.74-7.68 (m, 1H), 7.63-7.44 (m, 9H), 7.40-7.35 (m, 1H), 7.31-7.26 (m, 2H, overlap), 5.67 (td, $J = 14.3$, 3.4 Hz, 1H), 3.40-3.23 (m, 2H), 3.01 (ddd, $J = 15.4, 8.8, 3.5$ Hz, 1H), 2.80 (ddd, $J = 15.3, 13.0$, 3.5 Hz, 1H), 0.89 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 157.3, 148.9, 148.3$ (d, $J = 10.0$ Hz), 139.7, 133.4 (d, $J = 99.8$ Hz, overlap), 133.4 (d, $J = 100.8$ Hz, overlap), 131.8 (d, $J = 2.5$ Hz), 131.7 (d, $J = 2.7$ Hz), 131.3 (d, $J = 9.6$ Hz), 130.7, 130.5 (d, $J = 9.5$ Hz), 129.6, 129.5, 128.9, 128.6 (d, $J = 9.4$ Hz, overlap), 128.5 (d, $J = 9.9$ Hz, overlap), 127.7, 126.7, 124.7, 123.3, 116.1, 73.4 (d, $J = 2.3$ Hz), 65.3, 38.6 (d, $J = 769.6$ Hz), 15.0.

$^{31}$P NMR (162 MHz, CDCl$_3$): $\delta = 28.78$.

HRMS (ESI-TOF) m/z: calc’d for C$_{31}$H$_{29}$NO$_2$P (M+1) 478.1930, found 478.1990.

IR (film) cm$^{-1}$: 3057 (w), 2973 (w), 1596 (s), 1437 (m), 1180 (m), 1116 (s), 907 (s).
methyl 1-(3-(diphenylphosphoryl)tetrahydrofuran-2-yl)isoquinolin-3-carboxylate (23)
Prepared according to GP2, using methyl 3-isoquinolinecarboxylate (18.7 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16 µL, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), 2,3-dihydrofuran (15 µL, 0.2 mmol, 2.0 equiv), TMSN3 (13.5 µL, 0.1 mmol, 1.0 equiv), and PhI(OAc)2 (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (63%, >20:1 d.r. NMR yield, dibromomethane standard). Rf = 0.2 (5% MeOH in CH2Cl2).

1H NMR (600 MHz, CDCl3): δ = 8.41-8.33 (m, 2H), 8.02-7.94 (m, 2H), 7.87-7.83 (m, 1H), 7.72-7.64 (m, 4H), 7.56-7.49 (m, 3H), 7.05-7.01 (m, 1H), 6.98-6.93 (m, 2H), 6.01 (dd, J = 12.8, 7.5 Hz, 1H), 4.90-4.85 (m, 1H), 4.17-4.12 (m, 1H), 4.09 (s, 3H, overlap), 4.06-4.01 (m, 1H, overlap), 2.67-2.57 (m, 1H), 2.41-2.32 (m, 1H).

13C NMR (150 MHz, CDCl3): δ = 166.3, 156.7 (d, J = 2.7 Hz), 139.4, 136.3, 133.3 (d, J = 99.7 Hz), 131.9 (d, J = 1.9 Hz), 131.8 (d, J = 98.2 Hz), 131.3 (d, J = 9.1 Hz), 131.2 (d, J = 2.3 Hz), 131.1 (d, J = 8.8 Hz), 130.8, 129.8, 128.9 (d, J = 11.4 Hz, overlap), 128.9 (s, overlap), 128.5, 127.8 (d, J = 12.0 Hz), 126.1, 124.6, 77.8 (d, J = 4.3 Hz), 69.5 (d, J = 7.6 Hz), 52.7, 39.2 (d, J = 74.8 Hz), 28.2 (d, J = 2.6 Hz).

31P NMR (243 MHz, CDCl3): δ = 31.70.

HRMS (ESI-TOF) m/z: calc’d for C27H25NO4P (M+1) 458.1516, found 458.1512.

IR (film) cm⁻¹: 2923 (w), 2852 (w), 1729 (s), 1437 (m), 1179 (m), 1118 (s).

1-(1-(1-ethoxy-3,3,3-trifluoropropyl)isoquinoline-4-yl)ethan-1-one (24)
Prepared according to GP3, using 4-acetylisooquinoline (17.1 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), and ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), sodium triflate (31.5 mg, 0.2 mmol, 2 eq) and PIFA (86 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (65% NMR yield, dibromomethane standard). Rf = 0.5 (25% ethyl acetate in hexanes).

1H NMR (600 MHz, CDCl3): δ = 8.98 (s, 1H), 8.87 (dm, J = 8.6 Hz, 1H), 8.61 (dm, J = 8.5 Hz, 1H), 7.84 (qd, J = 8.6, 6.9, 1.3 Hz, 1H), 7.70 (qd, J = 8.5, 6.9, 1.2 Hz, 1H), 5.48 (dd, J = 8.2, 4.9
Hz, 1H), 3.50-3.41 (m, 2H), 3.06-2.98 (m, 1H), 2.85-2.75 (m, 1H, overlap), 2.78 (s, 3H, overlap) 1.18 (t, J = 7 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 200.29, 162.66, 144.25, 133.81, 132.37, 128.53, 128.18, 126.56, 126.36, 126.01 (q, J = 277 Hz), 124.89, 76.36 (d, J = 3.3 Hz), 64.96, 39.22 (q, J = 28.1 Hz), 29.96, 15.32.

$^{19}$F NMR (X MHz, CDCl$_3$): δ = -63.71.

HRMS (ESI-TOF) m/z: calc’d for C$_{16}$H$_{17}$F$_3$NO$_2$ (M+1) 312.1211 found 312.1205.

IR (film) cm$^{-1}$: 2977 (w), 2926 (w), 1683 (s), 1504 (m), 1270 (m), 1254 (s), 1127 (m), 771 (m).

1-(1-ethoxy-3,3,3-trifluoropropyl)isoquinolin-5-yl benzoate (25)
Prepared according to GP3, using 5-benzyloxyisoquinoline (24.9 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), and ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), sodium triflinate (31.5 mg, 0.2 mmol, 2 eq) and PIFA (86 mg, 0.2 mmol, 2 equiv). The product was isolated as a yellow oil (52% NMR yield, dibromomethane standard). R$_f$ = 0.2 (10% ethyl acetate/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$): δ = 8.54-8.53 (m, 2H), 8.33-8.32 (m, 2H), 7.74-7.68 (m, 3 H), 7.63 (dd, J = 7.5, 0.9 Hz, 1H), 7.61-7.58 (m, 2H), 5.46 (dd, J = 8.3, 4.5 Hz, 1H), 3.49-3.44 (m, 2H), 3.09-3.00 (m ,1H), 2.83-2.74 (m, 1H), 1.18 (t, J = 7.0 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ =165.07, 158.59, 146.65, 142.38, 134.32, 131.13, 130.52, 129.03, 128.96, 127.45, 127.34, 126.13 (q, J = 277.2 Hz), 122.92, 122.67, 114.86, 76.83 (d, J = 3.3 Hz), 64.78, 39.36 (q, J = 27.9 Hz), 15.33.

$^{19}$F NMR (X MHz, CDCl$_3$): δ = -63.70.

HRMS (ESI-TOF) m/z: calc’d for C$_{21}$H$_{19}$F$_3$NO$_3$ (M+1) 390.1317 found 390.1301.

IR (film) cm$^{-1}$: 2977 (w), 2897 (w), 1741 (s), 1261 (s), 1226 (s), 1152 (s), 1127 (s), 706 (s).
5-bromo-1-(1-ethoxy-3,3,3-trifluoropropyl)isoquinoline (26)
Prepared according to GP3, using 5-bromoisoquinoline (20.8 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), and ethyl vinyl ether (19 µL, 0.2 mmol, 2.0 equiv), sodium triflate (31.5 mg, 0.2 mmol, 2 eq) and PIFA (86 mg, 0.2 mmol, 2 equiv). The product was isolated as a yellow oil (42% NMR yield, dibromomethane standard). R_f = 0.7 (25% ethyl acetate/hexanes).

^1H NMR (600 MHz, CDCl₃): δ = 8.61 (d, J = 5.9 Hz, 1H), 8.58 (dm, J = 8.6 Hz, 1H), 8.02 (dd, J = 5.9, 0.8 Hz, 1H), 8.00 (dd, J = 7.4, 0.9 Hz, 1H), 7.49 (dd, J = 8.5, 7.5 Hz, 1H), 5.44 (dd, J = 8.3, 4.8 Hz, 1H), 3.46-3.38 (m, 2H), 3.06-2.97 (m, 1H), 2.82-2.74 (m, 1H), 1.15 (t, J = 7.0 Hz, 3H).

^13C NMR (100 MHz, CDCl₃): δ = 158.70, 143.13, 136.07, 134.15, 127.95, 127.63, 126.03 (q, J = 277 Hz), 124.54, 122.71, 120.28, 76.63 (d, J = 3.3 Hz), 64.64, 39.25 (q, J = 27.9 Hz), 15.28.

^19F NMR (X MHz, CDCl₃): δ = -63.72.

HRMS (ESI-TOF) m/z: calc’d for C₁₄H₁₄BrF₅NO (M+1, M+3) 348.0211, 350.0190; found 348.0186, 350.0223.

IR (film) cm⁻¹: 2977 (w), 2896 (w), 1372 (m), 1342 (m), 1256 (s), 1126 (s), 814 (m).

1-(1-(3-(trifluoromethyl)tetrahydrofuran-2-yl)isoquinoline-4-yl)ethan-1-one (27)
Prepared according to GP3, using 4-acetylisooquinoline (17.1 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8 µL, 0.1 mmol, 1.0 equiv), and 2,3-dihydrofuran (15 µL, 0.2 mmol, 2.0 equiv), sodium triflate (31.5 mg, 0.2 mmol, 2 eq) and PIFA (86 mg, 0.2 mmol, 2 equiv). The product was isolated as a clear oil (48%, >20:1 d.r., NMR yield, dibromomethane standard). R_f = 0.6 (25% ethyl acetate/hexanes).

^1H NMR (600 MHz, CDCl₃): δ = 8.96 (s, 1H), 8.86 (dm, J = 8.6 Hz, 1H), 8.48 (dm, J = 8.4 Hz, 1H), 7.86-7.81 (m, 1H), 7.74-7.70 (m, 1H), 5.91 (d, J = 4.8 Hz, 1H), 4.44-4.32 (m, 1H), 4.09 (q, J = 7.5 Hz, 1H), 3.99 (q, J = 7.3 Hz, 1H), 2.78 (s, 3H), 2.51-2.41 (m, 1H), 2.36-2.28 (m, 1H).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 200.23, 160.17, 143.72, 133.77, 132.30, 128.72, 128.24,$
$127.83 (q, $J = 277.5$ Hz), 127.26, 126.91, 126.03, 125.72, 78.0, 68.79, 68.10, 44.95 (q, $J = 26.9$ Hz), 29.94, 27.37, 25.74.

$^{19}$F NMR (X MHz, CDCl$_3$): $\delta = -69.44$.

HRMS (ESI-TOF) $m/z$: calc’d for C$_{16}$H$_{15}$F$_3$NO$_2$ (M+1) 310.1055 found 310.1038.

IR (film) cm$^{-1}$: 2981 (w), 2881 (w), 1683 (s), 1505 (m), 1272 (m), 1158 (s), 1128 (s).
VI. References
