

# Multi-component Heteroarene Couplings via Polarity-reversed Radical Cascades

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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<sub>2</sub>Cl<sub>2</sub> 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<sub>4</sub> stain. All yields are averages of at least two experimental runs.

Nuclear magnetic resonance (NMR) spectra (<sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F, <sup>31</sup>P) were recorded using either a Bruker AVIII 400, AVIII 600, or AVIII 850 MHz NMR spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are reported in parts per million and referenced to residual CHCl<sub>3</sub> signals in CDCl<sub>3</sub> (<sup>1</sup>H: δ 7.26; <sup>13</sup>C: δ 77.16) (unless otherwise noted). <sup>31</sup>P NMR chemical shifts are reported in parts per million and referenced to phosphoric acid as an external sample (δ 0.00). <sup>1</sup>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 <sup>13</sup>C, <sup>19</sup>F, and <sup>31</sup>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<sup>-1</sup>). Melting points were determined using an Electrotherman IA9000. Reagents were added to reactions with a Fischerbrand Single Syringe Pump (Model No: 78-01001).

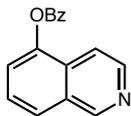
## II. General Procedures

**General Procedure 1 (GP1, azidation):** The heteroarene (0.1 mmol) and stir bar were combined in an oven-dried vial, then CH<sub>2</sub>Cl<sub>2</sub> (1ml) 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 CH<sub>2</sub>Cl<sub>2</sub> (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 (TMSN<sub>3</sub>) (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 NaHCO<sub>3</sub> (sat'd aq) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 12 ml), dried with Na<sub>2</sub>SO<sub>4</sub>, 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 CH<sub>2</sub>Cl<sub>2</sub> (1ml) 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 CH<sub>2</sub>Cl<sub>2</sub> (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 TMSN<sub>3</sub> (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 NaHCO<sub>3</sub> (sat'd aq) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 12 ml), dried with Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purified via flash chromatography (ethyl acetate/hexanes) to yield the target compound.

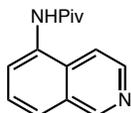
**General Procedure 3 (GP3, trifluoromethylation):** The heteroarene (0.1 mmol) and stir bar were combined in an oven-dried vial, then freshly distilled MeCN (1 ml) and trifluoroacetic acid (8 μL, 0.1 mmol, 1.0 eq) were added, and the solution was stirred at r.t. for 5 mins. To the solution was added 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 NaHCO<sub>3</sub> (sat'd aq), extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 12 ml), dried with Na<sub>2</sub>SO<sub>4</sub>, 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.<sup>1</sup>

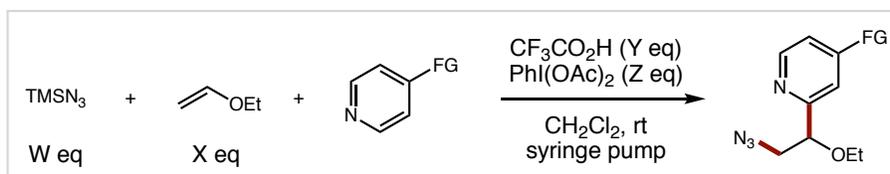


#### **N-(isoquinolin-5-yl)pivalamide**

Prepared according to Kanai's method (50%). Spectra matches literature values.<sup>2</sup>

## IV. Optimization of Reaction Conditions

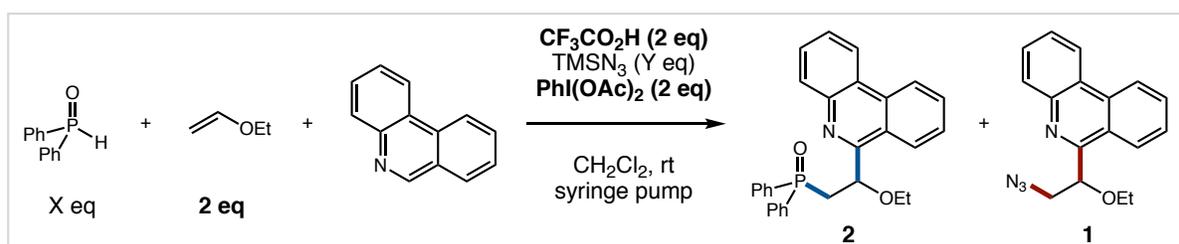
### A) Azidoalkylation of phenanthridine.



heteroarene	Method of Addition	CF <sub>3</sub> CO <sub>2</sub> H equiv	vinyl ether equiv	TMSN <sub>3</sub> equiv	PhI(OAc) <sub>2</sub> equiv	Prod <sup>b</sup>	SM <sup>b</sup>
lepidine	t = 0	1	4	2	2	20%	85%
lepidine	Syringe pump (2ml/hr)	1	4	2	2	41%	56%
lepidine	Syringe pump (2ml/hr)	1	4	4	4	75%	22%
lepidine	Syringe pump (2ml/hr)	1	4	6	6	73%	10%
lepidine	Syringe pump (2ml/hr)	1	6	6	6	73%	8%
<b>lepidine</b>	<b>Syringe pump (2ml/hr)</b>	<b>2</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>80% (56%)<sup>c</sup></b>	<b>13%</b>
isoquinoline	Syringe pump (2ml/hr)	0.5	4	2	2	70%	7%
<b>isoquinoline</b>	<b>Syringe pump (2ml/hr)</b>	<b>1</b>	<b>4</b>	<b>2</b>	<b>2</b>	<b>75% (58%)<sup>c</sup></b>	<b>0%</b>
isoquinoline	Syringe pump (2ml/hr)	2	4	2	2	63%	0%
isoquinoline	Syringe pump (2ml/hr)	5	4	2	2	9%	55%
phenanthridine	t = 0	1	4	2	2	30%	60%
<b>phenanthridine</b>	<b>Syringe pump (2ml/hr)</b>	<b>1</b>	<b>4</b>	<b>2</b>	<b>2</b>	<b>92% (88%)<sup>c</sup></b>	<b>0%</b>

- a) Conditions: heteroarene (0.1 mmol, 1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub> (1ml). b) <sup>1</sup>H NMR yield, dibromomethane standard. c) isolated yield.

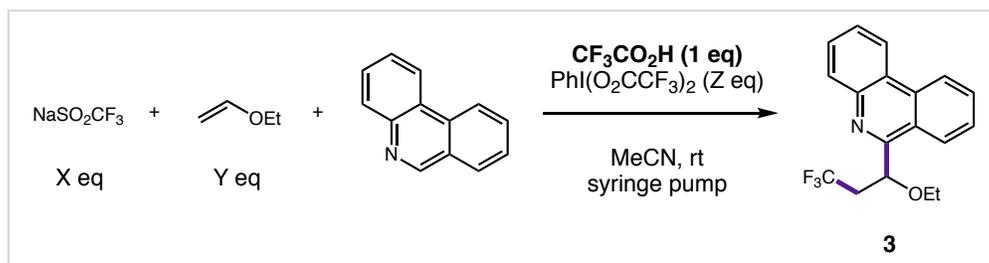
### B) Phosphylation of phenanthridine.



Method of Addition	Oxidant	Ph <sub>2</sub> P(O)H equiv	TMSN <sub>3</sub> equiv	Prod (2) <sup>d</sup>	Prod (1) <sup>d</sup>	SM <sup>d</sup>
t = 0	PhI(OAc) <sub>2</sub>	2	0	0%	0%	89%
t = 0	PhI(O <sub>2</sub> CCF <sub>3</sub> ) <sub>2</sub>	2	0	0%	0%	95%
<b>t = 0</b>	<b>PhI(OAc)<sub>2</sub></b>	<b>2</b>	<b>1</b>	<b>26%</b>	<b>54%</b>	<b>28%</b>
t = 0	PhI(OAc) <sub>2</sub>	4	1	66%	23%	0%
<b>t = 0<sup>b</sup></b>	<b>PhI(OAc)<sub>2</sub></b>	<b>6</b>	<b>1</b>	<b>92%</b>	<b>16%</b>	<b>0%</b>
t = 0	PhI(OAc) <sub>2</sub>	8	1	85%	trace	0%
Syringe pump (1ml/hr)	PhI(OAc) <sub>2</sub>	2	0	0%	0%	87%
Syringe pump (2ml/hr)	PhI(OAc) <sub>2</sub>	2	0	14%	0%	84%
<b>Syringe pump (2ml/hr)<sup>c</sup></b>	<b>PhI(OAc)<sub>2</sub></b>	<b>6</b>	<b>1</b>	<b>90%</b>	<b>0%</b>	<b>0%</b>

- a) Conditions: phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub> (1ml), trifluoroacetic acid (16 μL, 0.2 mmol, 2.0 equiv), ethyl vinyl ether (19 μL, 0.2 mmol, 2.0 equiv), and PhI(OR)<sub>2</sub> (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) <sup>1</sup>H NMR yield, dibromomethane standard.

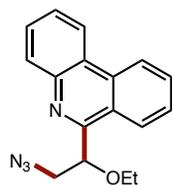
### C. Trifluoromethylalkylation of phenanthridine.



Method of Addition	vinyl ether equiv	$\text{CF}_3\text{SO}_2\text{Na}$ equiv	$\text{PhI(O}_2\text{CCF}_3)_2$ equiv	Prod ( <b>3</b> ) <sup>b</sup>	SM <sup>b</sup>
1	2	2	2	trace	-
2	2	2	2	trace	56%
3	2	2	2	35%	45%
6	2	2	2	51%	31%
6	4	4	4	51%	22%
<b>t = 0</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>60%</b>	<b>-</b>

- a) Conditions: phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), MeCN (1ml), trifluoroacetic acid (8  $\mu\text{L}$ , 0.1 mmol, 1.0 equiv). b) <sup>1</sup>H NMR yield, dibromomethane standard.

## V. Synthesis of Products



### 6-(2-azido-1-ethoxyethyl)phenanthridine (1)

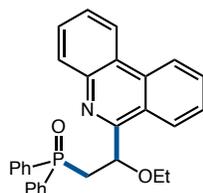
Prepared according to **GP1**, using phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv),  $\text{PhI}(\text{OAc})_2$  (64.4 mg, 0.2 mmol, 2 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (26  $\mu$ L, 0.2 mmol, 2.0 equiv). Product isolated as a yellow oil (88% yield).  $R_f = 0.49$  (10% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.71$  (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).

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

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

**IR (film)  $\text{cm}^{-1}$ :** 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  $\mu$ 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), and  $\text{TMSN}_3$  (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and  $\text{PhI}(\text{OAc})_2$  (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/ $\text{CH}_2\text{Cl}_2$ )

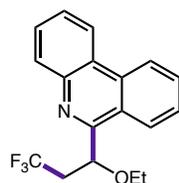
**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.70$  (d,  $J = 8.2$  Hz, 1H), 8.59 (d,  $J = 8.3$  Hz, 1H), 8.49 (dd,  $J = 8.1, 1.1$  Hz, 1H), 8.13 (dd,  $J = 8.1, 1.1$  Hz, 1H), 7.90-7.85 (m, 2H), 7.84-7.80 (m, 1H), 7.72-7.67 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.48 (m, 3H), 7.48-7.43 (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).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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.

**<sup>31</sup>P NMR (MHz, CDCl<sub>3</sub>):**  $\delta$  = 29.14.

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>29</sub>H<sub>27</sub>NO<sub>2</sub>P (M+1) 452.1779 found 452.1771.

**IR (film) cm<sup>-1</sup>:** 3057 (w), 2974 (w), 2925 (w), 1611 (w), 1574 (w), 1437 (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  $\mu$ L, 0.1 mmol, 1.0 equiv), ethyl vinyl ether (19  $\mu$ L, 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).

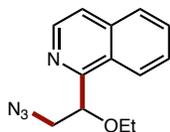
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  = 8.72 (dm,  $J$  = 8.3 Hz, 1H), 8.70 (dm,  $J$  = 8.3 Hz, 1H), 8.59 (dm,  $J$  = 8.2 Hz, 1H), 8.19 (dm,  $J$  = 8.2 Hz, 1H), 7.88 (qd,  $J$  = 8.3, 7.0, 1.2 Hz, 1H), 7.77-7.68 (m, 3H), 5.52 (dd,  $J$  = 8.7, 4.2 Hz, 1H), 3.54-3.48 (m, 2H),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

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 158.13, 143.26, 133.68, 130.80, 130.49, 128.90, 127.55, 126.33 (q,  $J$  = 277.3 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.

**<sup>19</sup>F NMR (X MHz, CDCl<sub>3</sub>):**  $\delta$  = -63.59 (t,  $J$  = 11.2 Hz, 3F).

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>18</sub>H<sub>17</sub>F<sub>3</sub>NO (M+1) 320.1262 found 320.1245.

**IR (film) cm<sup>-1</sup>:** 3075 (w), 2976 (w), 2927 (w), 1253 (m), 1128 (s), 762 (m), 729 (m).



#### 1-(2-azido-1-ethoxyethyl)isoquinoline (4)

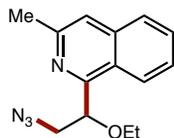
Prepared according to **GP1**, using isoquinoline (12  $\mu$ L, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv),  $\text{PhI}(\text{OAc})_2$  (64.4 mg, 0.2 mmol, 2 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (26  $\mu$ L, 0.2 mmol, 2.0 equiv). Product isolated as a yellow oil (58% yield).  $R_f = 0.54$  (25% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.58$  (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).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta = 157.6, 142.1, 136.9, 130.3, 127.7, 127.6, 127.0, 125.0, 121.3, 82.3, 65.4, 54.5, 15.5$ .

**HRMS (ESI-TOF)  $m/z$ :** calc'd for  $\text{C}_{13}\text{H}_{15}\text{N}_4\text{O}$  ( $M+1$ ) 243.1246, found 243.1245.

**IR (film)  $\text{cm}^{-1}$ :** 3054 (w), 2975 (w), 2098 (s), 1107 (m).



#### 1-(2-azido-1-ethoxyethyl)-3-methylisoquinoline (5)

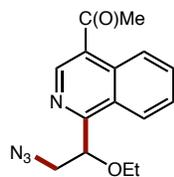
Prepared according to **GP1**, using 3-methyl isoquinoline (14.3 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv),  $\text{PhI}(\text{OAc})_2$  (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (52  $\mu$ L, 0.4 mmol, 4.0 equiv). Product isolated as a yellow oil (64% yield).  $R_f = 0.53$  (25% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.57$  (dd,  $J = 8.6, 0.8$  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, 3H).

**$^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 156.91, 150.69, 137.74, 130.15, 127.07, 126.51, 125.12, 125.06, 119.36, 82.94, 65.38, 54.36, 24.28, 15.54$ .

**HRMS (ESI-TOF)  $m/z$ :** calc'd for  $\text{C}_{14}\text{H}_{17}\text{N}_4\text{O}$  ( $M+1$ ) 257.1397 found 257.1374.

**IR (film)  $\text{cm}^{-1}$ :** 2925 (w), 2096 (s), 1591 (m), 1563 (m), 1104 (s), 752 (s).



### 1-(2-azido-1-ethoxyethyl)-4-acetylisquinoline (6)

Prepared according to **GPI**, using 4-acetylisquinoline (17.1 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv),  $\text{PhI}(\text{OAc})_2$  (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (52  $\mu$ L, 0.4 mmol, 4.0 equiv). Product isolated as a clear oil (80% yield).  $R_f = 0.38$  (25% ethyl acetate/hexanes).

$^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.99$  (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).

$^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ ):  $\delta = 200.3, 162.1, 144.3, 133.8, 132.2, 128.5, 128.1, 127.1, 126.3, 125.1, 82.1, 65.7, 54.3, 30.0, 15.5$ .

**HRMS (ESI-TOF)  $m/z$** : calc'd for  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}_2$  ( $M+1$ ) 285.1352, found 285.1364.

**IR (film)  $\text{cm}^{-1}$** : 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)

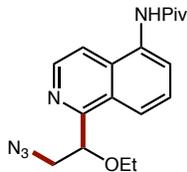
Prepared according to **GPI**, using methyl 3-isoquinolinecarboxylate (18.7 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16  $\mu$ L, 0.2 mmol, 2.0 equiv),  $\text{PhI}(\text{OAc})_2$  (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (52  $\mu$ L, 0.4 mmol, 4.0 equiv). Product isolated as a tan oil (66% yield).  $R_f = 0.4$  (25% ethyl acetate/hexanes).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.86$  (d,  $J = 7.8$  Hz, 1H), 8.53 (s, 1H), 7.99 (d,  $J = 7.5$  Hz, 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).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 166.31, 158.50, 140.52, 136.79, 131.05, 129.72, 129.08, 128.41, 126.02, 124.83, 84.60, 65.63, 54.36, 53.02, 15.54$ .

**HRMS (ESI-TOF)  $m/z$** : calc'd for  $\text{C}_{15}\text{H}_{16}\text{N}_4\text{NaO}_3$  ( $M+23$ ) 323.1120, found 323.1106.

**IR (film)  $\text{cm}^{-1}$** : 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)

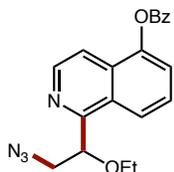
Prepared according to **GPI**, using *N*-(isoquinolin-5-yl)pivalamide (22.8 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16  $\mu$ L, 0.2 mmol, 2.0 equiv),  $\text{PhI}(\text{OAc})_2$  (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (52  $\mu$ L, 0.4 mmol, 4.0 equiv). Product isolated as a brown oil (91% yield).  $R_f = 0.2$  (25% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.57$  (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).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta = 177.37$ , 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  $\text{C}_{18}\text{H}_{24}\text{N}_5\text{O}_2$  ( $M+1$ ) 342.1930, found 342.1916.

**IR (film)  $\text{cm}^{-1}$ :** 3291 (w), 2973 (w), 2099 (s), 1658 (m), 1516 (m), 1485 (m), 1108 (w), 730 (w).



### 1-(2-azido-1-ethoxyethyl)-5-benzyloxyisoquinoline (9)

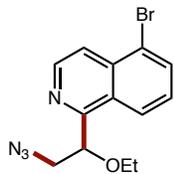
Prepared according to **GPI**, using 5-benzyloxyisoquinoline (24.9 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv),  $\text{PhI}(\text{OAc})_2$  (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (52  $\mu$ L, 0.4 mmol, 4.0 equiv). Product isolated as a yellow oil (79% yield).  $R_f = 0.4$  (25% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.58$ -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).

**$^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 165.08$ , 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  $\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_3$  ( $M+1$ ) 363.1452, found 363.1443.

**IR (film)  $\text{cm}^{-1}$ :** 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-bromoquinoline (10)

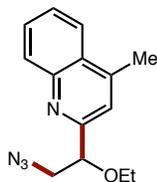
Prepared according to **GPI**, using 5-bromoquinoline (20.8 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv),  $\text{PhI}(\text{OAc})_2$  (64.4 mg, 0.2 mmol, 2 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (26  $\mu$ L, 0.2 mmol, 2.0 equiv). Product isolated as a yellow oil (75% yield).  $R_f = 0.57$  (25% ethyl acetate/hexanes).

$^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.64\text{--}8.60$  (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).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 158.05, 143.35, 136.04, 134.17, 128.11, 127.90, 124.76, 122.65, 120.24, 82.45, 65.48, 54.42, 15.50$ .

**HRMS (ESI-TOF)  $m/z$** : calc'd for  $\text{C}_{13}\text{H}_{14}\text{BrN}_4\text{O}$  ( $M+1$ ) 321.0346, found 321.0332, 323.0332.

**IR (film)  $\text{cm}^{-1}$** : 3052 (w), 2976 (w), 2097 (s), 1110 (bm), 832 (w), 816 (w).



### 2-(2-azido-1-ethoxyethyl)-4-methylquinoline (11)

Prepared according to **GPI**, using 4-methylquinoline (13.2  $\mu$ L, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16  $\mu$ L, 0.2 mmol, 2.0 equiv),  $\text{PhI}(\text{OAc})_2$  (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (52  $\mu$ L, 0.4 mmol, 4.0 equiv). Product isolated as a clear oil (59% yield).  $R_f = 0.75$  (25% ethyl acetate/hexanes).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.05$  (dm,  $J = 7.8$  Hz, 1H), 8.00 (dm,  $J = 7.4$  Hz, 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,  $J = 7$  Hz, 3H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 159.54, 147.64, 145.54, 129.79, 129.56, 127.92, 126.50, 123.92, 119.07, 83.08, 65.83, 55.33, 19.14, 15.53$ .

**HRMS (ESI-TOF)  $m/z$** : calc'd for  $\text{C}_{14}\text{H}_{17}\text{N}_4\text{O}$  ( $M+1$ ) 257.1402, found 257.1384.

**IR (film)  $\text{cm}^{-1}$** : 3100 (w), 2975 (w), 2099 (s), 1600 (m).



#### 4-(2-azido-1-ethoxyethyl)-2-phenylquinoline (12)

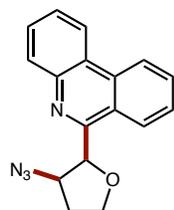
Prepared according to **GPI**, using 2-phenylquinoline (20.5 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv),  $\text{PhI}(\text{OAc})_2$  (128.8 mg, 0.4 mmol, 4 equiv), ethyl vinyl ether (38  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (52  $\mu$ L, 0.4 mmol, 4.0 equiv). Product isolated as a yellow oil (93% yield).  $R_f = 0.57$  (25% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.25$ -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); 5.30 (dd,  $J = 8.6, 2.8$  Hz, 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).

**$^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 157.42, 148.83, 145.08, 139.61, 131.08, 129.69, 129.05, 127.71, 126.80, 124.99, 122.30, 116.44, 78.75, 65.94, 55.85, 15.58$ .

**HRMS (ESI-TOF)  $m/z$ :** calc'd for  $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}$  ( $M+1$ ) 319.1553, found 319.1549.

**IR (film)  $\text{cm}^{-1}$ :** 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)

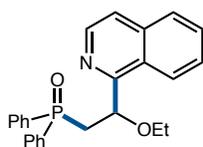
Prepared according to **GPI**, using phenanthridine (18 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (16  $\mu$ L, 0.2 mmol, 2.0 equiv),  $\text{PhI}(\text{OAc})_2$  (64.4 mg, 0.2 mmol, 2 equiv), 2,3-dihydrofuran (30  $\mu$ L, 0.4 mmol, 4.0 equiv), and  $\text{TMSN}_3$  (26  $\mu$ L, 0.2 mmol, 2.0 equiv). Product isolated as a brown oil (72% yield, >20:1 d.r.).  $R_f = 0.6$  (25% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.65$  (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, 1H), 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).

**$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):**  $\delta = 156.38, 143.06, 133.41, 130.77, 130.65, 128.78, 127.65, 127.50, 126.74, 125.12, 124.41, 122.49, 122.09, 83.86, 67.97, 63.13, 32.15$ .

**HRMS (ESI-TOF)  $m/z$ :** calc'd for  $\text{C}_{17}\text{H}_{15}\text{N}_4\text{O}$  ( $M+1$ ) 291.1246 found 291.1232.

**IR (film)  $\text{cm}^{-1}$ :** 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  $\mu$ L, 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<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (77% NMR yield, dibromomethane standard).  $R_f$  = 0.3 (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

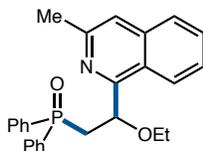
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  = 8.50 (d,  $J$  = 8.5 Hz, 1H), 8.45 (d,  $J$  = 5.6 Hz, 1H), 7.90-7.5 (m, 2H), 7.76 (d,  $J$  = 8.1 Hz, 1H), 7.65 (t,  $J$  = 7.5 Hz, 1H), 7.60 (t,  $J$  = 7.6 Hz, 1H, overlap), 7.58-7.54 (m, 2H, overlap), 7.52-7.44 (m, 4H), 7.32-7.28 (m, 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).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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.

**<sup>31</sup>P NMR (MHz, CDCl<sub>3</sub>):**  $\delta$  = 29.02.

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>25</sub>H<sub>25</sub>NO<sub>2</sub>P (M+1) 402.1623 found 402.1604.

**IR (film) cm<sup>-1</sup>:** 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  $\mu$ 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<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (63% NMR yield, dibromomethane standard).  $R_f$  = 0.33 (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

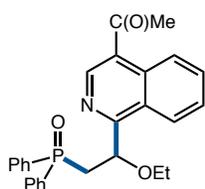
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  = 8.49 (d,  $J$  = 8.4 Hz, 1H), 7.88-7.83 (m, 2H), 7.65 (d,  $J$  = 8.2 Hz, 1H), 7.60-7.56 (m, 1H), 7.55-7.44 (m, 4H), 7.47-7.44 (m, 2H), 7.31-7.27 (m, 1H, overlap), 7.27 (s, 1H, overlap), 7.23-7.18 (m, 2H), 5.76 (ddd,  $J$  = 9.2, 7.5, 5.5 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).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ = 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.

**<sup>31</sup>P NMR (MHz, CDCl<sub>3</sub>):** δ = 28.91.

**HRMS (ESI-TOF) *m/z*:** calc'd for C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub>P (M+1) 416.1779 found 416.1765.

**IR (film) cm<sup>-1</sup>:** 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 **GP2**, using 4-acetylisquinoline (17.1 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), TMSN<sub>3</sub> (13.5 μL, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a yellow oil (67% NMR yield, dibromomethane standard). R<sub>f</sub> = 0.33 (2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

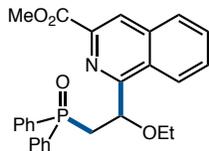
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ = 8.87 (s, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.57 (d, *J* = 8.5 Hz, 1H), 7.88-7.81 (m, 2H), 7.80-7.74 (m, 1H), 7.69-7.63 (m, 1H), 7.52-7.43 (m, 5H), 7.32-7.27 (m, 1H), 7.22-7.16 (m, 2H), 5.87 (ddd, *J* = 8.9, 8.0, 5.3 Hz, 1H), 3.34-3.27 (m, 2H), 3.21 (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).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ = 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.

**<sup>31</sup>P NMR (MHz, CDCl<sub>3</sub>):** δ = 28.69.

**HRMS (ESI-TOF) *m/z*:** calc'd for C<sub>27</sub>H<sub>27</sub>NO<sub>3</sub>P (M+1) 444.1723 found 444.1707.

**IR (film) cm<sup>-1</sup>:** 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  $\mu$ 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<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (82% NMR yield, dibromomethane standard).  $R_f = 0.17$  (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta = 8.71$ -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).

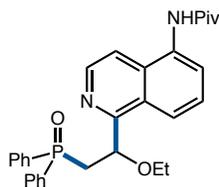
**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta = 166.4$ , 159.8 (d,  $J = 8.3$  Hz), 140.5, 136.5, 133.8 (d,  $J = 100.6$  Hz), 133.1 (d,  $J = 99.6$  Hz), 131.7 (d,  $J = 2.2$  Hz), 131.4 (d,  $J = 2.8$  Hz), 131.2 (d,  $J = 9.6$  Hz), 130.9 (d,  $J = 9.1$  Hz), 130.8, 129.7, 128.9, 128.5 (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.

**<sup>31</sup>P NMR (243 MHz, CDCl<sub>3</sub>):**  $\delta = 28.81$ .

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>27</sub>H<sub>27</sub>NO<sub>4</sub>P (M+1) 460.1672, found 460.1660.

**IR (film) cm<sup>-1</sup>:** 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-ethoxyethyl)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  $\mu$ 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<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (61% NMR yield, dibromomethane standard).  $R_f = 0.23$  (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

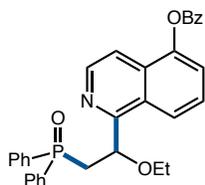
**<sup>1</sup>H NMR (850 MHz, CDCl<sub>3</sub>):** δ = 8.51 (d, *J* = 5.9 Hz, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.89-7.85 (m, 2H), 7.69 (s, broad, 1H), 7.63-7.57 (m, 3H), 7.53-7.44 (m, 1H), 7.49-7.45 (m, 2H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.36-7.33 (m, 1H), 7.30-7.26 (m, 2H, 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).

**<sup>13</sup>C NMR (214 MHz, CDCl<sub>3</sub>):** δ = 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.

**<sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>):** δ = 29.06.

**HRMS (ESI-TOF) *m/z*:** calc'd for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>P (M+1) 501.2302, found 501.2301.

**IR (film) cm<sup>-1</sup>:** 3236 (w), 2966 (w), 2925 (w), 1670 (s), 1521 (m), 1484 (m), 1177 (m), 1118 (s).



### 1-(2-(diphenylphosphoryl)-1-ethoxyethyl)isoquinolin-5-yl)benzoate (19)

Prepared according to **GP2**, using 5-benzyloxyisoquinoline (24.9 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), TMSN<sub>3</sub> (13.5 μL, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (58% NMR yield, dibromomethane standard). *R<sub>f</sub>* = 0.23 (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

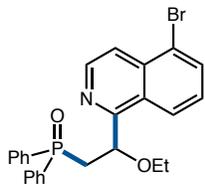
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):** δ = 8.50-8.44 (m, 2H), 8.33-8.28 (m, 2H), 7.91-7.84 (m, 2H), 7.74-7.69 (m, 1H), 7.69-7.63 (m, 1H), 7.61-7.44 (m, 9H), 7.37-7.32 (m, 1H), 7.29-7.23 (m, 2H, overlap), 5.84 (ddd, *J* = 9.1, 8.4, 4.6 Hz, 1H), 3.34-3.19 (m, 3H), 2.96 (ddd, *J* = 15.1, 12.2,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

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):** δ = 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.

**<sup>31</sup>P NMR (243 MHz, CDCl<sub>3</sub>):** δ = 29.22.

**HRMS (ESI-TOF) *m/z*:** calc'd for C<sub>32</sub>H<sub>29</sub>NO<sub>4</sub>P (M+1) 522.1829, found 522.1809.

**IR (film) cm<sup>-1</sup>:** 3057 (w), 2924 (w), 1739 (m), 1676 (s), 1227 (m), 1142 (w), 1118 (s), 998 (m).



**(2-(5-bromoquinolin-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  $\mu$ 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<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv).

The product was isolated as a colorless oil (48% NMR yield, dibromomethane standard).  $R_f$  = 0.30 (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

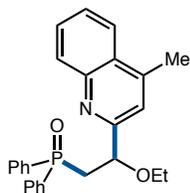
**<sup>1</sup>H NMR (850 MHz, CDCl<sub>3</sub>):**  $\delta$  = 8.54 (d,  $J$  = 5.8 Hz, 1H), 8.51 (d,  $J$  = 8.5 Hz, 1H), 7.94 (d,  $J$  = 7.4 Hz, 1H), 7.87-7.82 (m, 3H), 7.51-7.45 (m, 5H), 7.32-7.28 (m, 1H), 7.22-7.18 (m, 2H), 5.87-5.81 (m, 1H), 3.30-3.26 (m, 2H), 3.25-3.20 (m, 1H), 2.99-2.94 (m, 1H), 0.88 (t,  $J$  = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (214 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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.

**<sup>31</sup>P NMR (163 MHz, CDCl<sub>3</sub>):**  $\delta$  = 28.68.

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>25</sub>H<sub>24</sub>BrNO<sub>2</sub>P (M+1) 480.0723, found 480.0722.

**IR (film) cm<sup>-1</sup>:** 3053 (w), 2972 (w), 2924 (w), 1437 (s), 1185 (s), 1118 (s), 1096 (m).



**(2-ethoxy-2-(2-methylquinolin-4-yl)ethyl)diphenylphosphine oxide (21)**

Prepared according to **GP2**, using 5-benzyloxyisoquinoline (13.5  $\mu$ L, 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<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (64.4 mg, 0.2 mmol, 2 equiv). The product was isolated as a colorless oil (54% NMR yield, dibromomethane standard).  $R_f$  = 0.30 (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

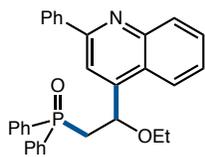
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  = 8.21 (d,  $J$  = 8.3 Hz, 1H), 8.00 (d,  $J$  = 8.4 Hz, 1H), 7.88-7.83 (m, 2H), 7.66 (t,  $J$  = 7.6 Hz, 1H), 7.60-7.55 (m, 2H), 7.54-7.47 (m, 4H), 7.41-7.37 (m, 1H), 7.32 (s, 1H, overlap), 7.31-7.28 (m, 2H, overlap), 5.60-5.54 (m, 1H), 3.31-3.26 (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).

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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.

**<sup>31</sup>P NMR (243 MHz, CDCl<sub>3</sub>):**  $\delta$  = 28.64.

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub>P (M+1) 416.1774, found 416.1769.

**IR (film) cm<sup>-1</sup>:** 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<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub>).

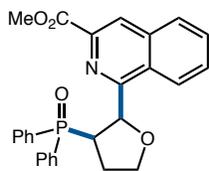
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 8.27 (d,  $J$  = 8.1 Hz, 1H), 8.19-8.10 (m, 3H), 7.95 (s, 1H), 7.74-7.68 (m, 1H), 7.63-7.44 (m, 9H), 7.40-7.35 (m, 1H), 7.31-7.26 (m, 2H, overlap), 5.67 (td,  $J$  = 14.3, 3.4 Hz, 1H), 3.40-3.23 (m, 2H), 3.01 (ddd,  $J$  = 15.4, 8.8, 6.8 Hz, 1H), 2.80 (ddd,  $J$  = 15.3, 13.0, 3.5 Hz, 1H), 0.89 (t,  $J$  = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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.

**<sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>):**  $\delta$  = 28.78.

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>31</sub>H<sub>29</sub>NO<sub>2</sub>P (M+1) 478.1930, found 478.1990.

**IR (film) cm<sup>-1</sup>:** 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  $\mu$ L, 0.2 mmol, 2 eq), diphenylphosphine oxide (121 mg, 0.6 mmol, 6 eq), 2,3-dihydrofuran (15  $\mu$ L, 0.2 mmol, 2.0 equiv), TMSN<sub>3</sub> (13.5  $\mu$ L, 0.1 mmol, 1.0 equiv), and PhI(OAc)<sub>2</sub> (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).  $R_f$  = 0.2 (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>).

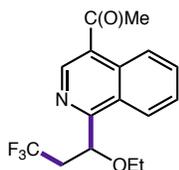
**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  = 8.41-8.33 (m, 2H), 8.02-7.94 (m, 2H), 7.87-7.83 (m, 1H), 7.72-7.64 (m, 4H), 7.56-7.49 (m, 3H), 7.05-7.01 (m, 1H), 6.98-6.93 (m, 2H), 6.01 (dd,  $J$  = 12.8, 7.5 Hz, 1H), 4.90-4.85 (m, 1H), 4.17-4.12 (m, 1H), 4.09 (s, 3H, overlap), 4.06-4.01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

**<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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),

**<sup>31</sup>P NMR (243 MHz, CDCl<sub>3</sub>):**  $\delta$  = 31.70.

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>27</sub>H<sub>25</sub>NO<sub>4</sub>P (M+1) 458.1516, found 458.1512.

**IR (film) cm<sup>-1</sup>:** 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-acetyloquinoline (17.1 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv), and ethyl vinyl ether (19  $\mu$ L, 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 colorless oil (65% NMR yield, dibromomethane standard).  $R_f$  = 0.5 (25% ethyl acetate in hexanes).

**<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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

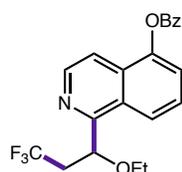
Hz, 1H), 3.50-3.41 (m, 2H), 3.06-2.98 (m, 1H), 2.85-2.75 (m, 1H, overlap), 2.78 (s, 3H, overlap) 1.18 (t,  $J = 7$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 200.29, 162.66, 144.25, 133.81, 132.37, 128.53, 128.18, 126.56, 126.36, 126.01$  (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.

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

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

IR (film)  $\text{cm}^{-1}$ : 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  $\mu\text{L}$ , 0.1 mmol, 1.0 equiv), and ethyl vinyl ether (19  $\mu\text{L}$ , 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).

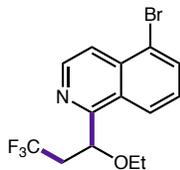
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.54$ -8.53 (m, 2H), 8.33-8.32 (m, 2H), 7.74-7.68 (m, 3 H), 7.63 (dd,  $J = 7.5, 0.9$  Hz, 1H), 7.61-7.58 (m, 2H), 5.46 (dd,  $J = 8.3, 4.5$  Hz, 1H), 3.49-3.44 (m, 2H), 3.09-3.00 (m, 1H), 2.83-2.74 (m, 1H), 1.18 (t,  $J = 7.0$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 165.07, 158.59, 146.65, 142.38, 134.32, 131.13, 130.52, 129.03, 128.96, 127.45, 127.34, 126.13$  (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.

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

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

IR (film)  $\text{cm}^{-1}$ : 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  $\mu$ L, 0.1 mmol, 1.0 equiv), and ethyl vinyl ether (19  $\mu$ L, 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 (42% NMR yield, dibromomethane standard).  $R_f = 0.7$  (25% ethyl acetate/hexanes).

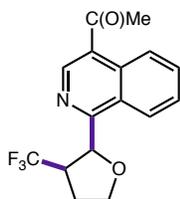
**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.61$  (d,  $J = 5.9$  Hz, 1H), 8.58 (dm,  $J = 8.6$  Hz, 1H), 8.02 (dd,  $J = 5.9, 0.8$  Hz, 1H), 8.00 (dd,  $J = 7.4, 0.9$  Hz, 1H), 7.49 (dd,  $J = 8.5, 7.5$  Hz, 1H), 5.44 (dd,  $J = 8.3, 4.8$  Hz, 1H), 3.46-3.38 (m, 2H), 3.06-2.97 (m, 1H), 2.82-2.74 (m, 1H), 1.15 (t,  $J = 7.0$  Hz, 3H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta = 158.70, 143.13, 136.07, 134.15, 127.95, 127.63, 126.03$  (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.

**$^{19}\text{F}$  NMR (X MHz,  $\text{CDCl}_3$ ):**  $\delta = -63.72$ .

**HRMS (ESI-TOF)  $m/z$ :** calc'd for  $\text{C}_{14}\text{H}_{14}\text{BrF}_3\text{NO}$  ( $M+1, M+3$ ) 348.0211, 350.0190; found 348.0186, 350.0223.

**IR (film)  $\text{cm}^{-1}$ :** 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-acetylisquinoline (17.1 mg, 0.1 mmol, 1.0 equiv), trifluoroacetic acid (8  $\mu$ L, 0.1 mmol, 1.0 equiv), and 2,3-dihydrofuran (15  $\mu$ L, 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 clear oil (48%, >20:1 d.r., NMR yield, dibromomethane standard).  $R_f = 0.6$  (25% ethyl acetate/hexanes).

**$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):**  $\delta = 8.96$  (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).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 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.

**<sup>19</sup>F NMR (X MHz, CDCl<sub>3</sub>):**  $\delta$  = -69.44.

**HRMS (ESI-TOF)  $m/z$ :** calc'd for C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub> (M+1) 310.1055 found 310.1038.

**IR (film) cm<sup>-1</sup>:** 2981 (w), 2881 (w), 1683 (s), 1505 (m), 1272 (m), 1158 (s), 1128 (s).

## VI. References

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2. L. Zhu; R. Qiu; X. Cao; S. Xiao; X. Xu; C.-T. Au; S.-F. Yin, *Org. Lett.*, **2015**, *17*, 5528-5531.