

Room-Temperature Pd-Catalyzed Methoxycarbonylation of Terminal Alkynes with High Branched Selectivity Enabled by Bisphosphine-Picolinamide Ligand

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1. Supporting Tables and Figures.

Table S1. Effect of reaction temperature ^[a]

$\text{Ph-C}\equiv\text{C-H} + \text{CO} \xrightarrow[\text{MeOH, 50 min}]{\text{Pd(OAc)}_2 (2 \text{ mol}\%), \text{L1} (4 \text{ mol}\%), \text{TsOH} (8 \text{ mol}\%), (40 \text{ bar})}$			
entry	Temp (°C)	Conv. (%)	<i>b/l</i> ratio
1	60	>99	>99:1
2	40	>99	>99:1
3	25	>99	>99:1

$$\text{Ph-C}\equiv\text{C-H} \xrightarrow[\text{MeOH, 50 min}]{\text{Pd(OAc)}_2 (2 \text{ mol}\%), \text{L1} (4 \text{ mol}\%), \text{TsOH} (8 \text{ mol}\%), (40 \text{ bar})} \text{Ph-C}(\text{COOMe})=\text{CH}_2 + \text{Ph-CH}=\text{CH-COOMe}$$

1a (40 bar) **2a** (branched) + **2a'** (linear)

[a]. Reactions were performed with **1a** (0.5 mmol) in MeOH (2 mL). The conversions and *b/l* ratios were determined with ¹H-NMR and GC.

Table S2. Effect of palladium precursor. ^[a]

$\text{Ph-C}\equiv\text{C-H} + \text{CO} \xrightarrow[\text{MeOH, rt}]{[\text{Pd}] (2 \text{ mol}\%), \text{L1} (4 \text{ mol}\%), \text{TsOH} (8 \text{ mol}\%), (40 \text{ bar})}$				
entry	Pd salts	time	Conv. (%)	<i>b/l</i> ratio
1	Pd(OAc) ₂	50 min	>99	>99:1
2	Pd(dba) ₂	50 min	>99	>99:1
3	Pd(PPh ₃) ₄	50 min	>99	>99:1
4	Pd(PhCN) ₂ Cl ₂	3 h	>99	>99:1
5	PdCl ₂	3 h	>99	>99:1

$$\text{Ph-C}\equiv\text{C-H} \xrightarrow[\text{MeOH, rt}]{[\text{Pd}] (2 \text{ mol}\%), \text{L1} (4 \text{ mol}\%), \text{TsOH} (8 \text{ mol}\%), (40 \text{ bar})} \text{Ph-C}(\text{COOMe})=\text{CH}_2 + \text{Ph-CH}=\text{CH-COOMe}$$

1a (40 bar) **2a** (branched) + **2a'** (linear)

[a]. Reactions were performed with **1a** (0.5 mmol) in MeOH (2 mL). The conversions and *b/l* ratios were determined with ¹H-NMR and GC.

Table S3. Effect of catalyst loading. ^[a]

entry	x (mol%)	Temp (°C)	Time	Conv. (%)	b/l ratio
1	2	25 °C	50 min	>99	>99:1
2	1	25 °C	6 h	>99	>99:1
3	0.5	25 °C	18 h	55	>99:1
4	0.03	80 °C	24 h	97	98:2

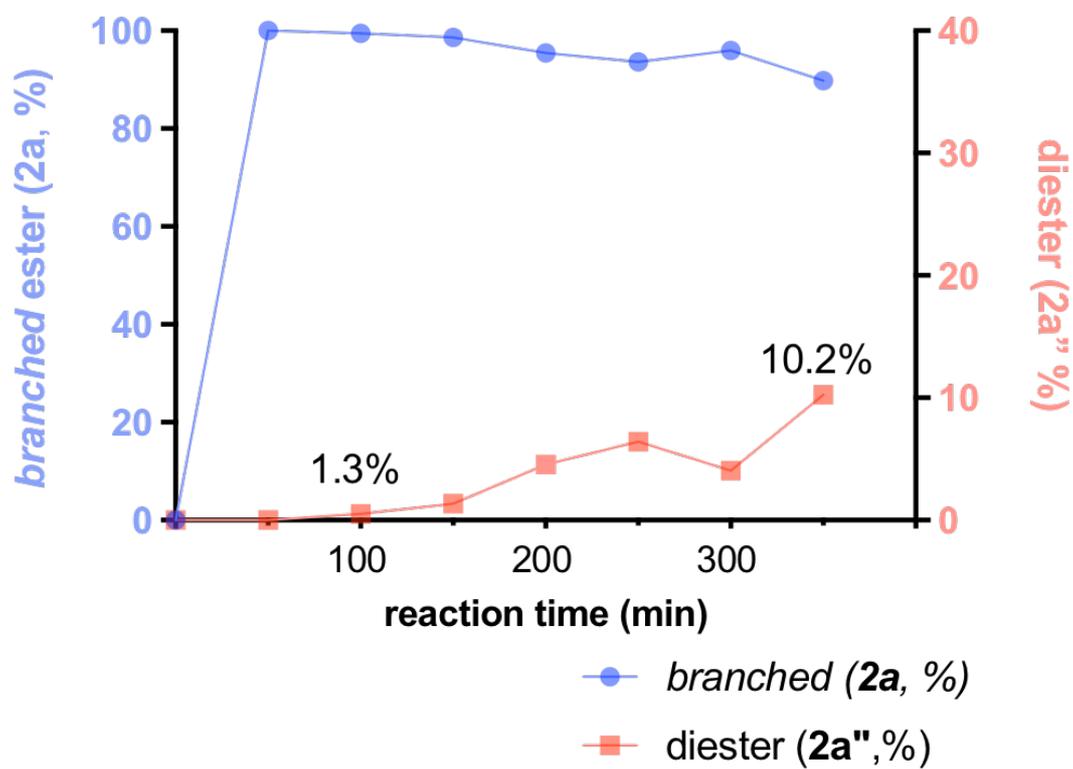
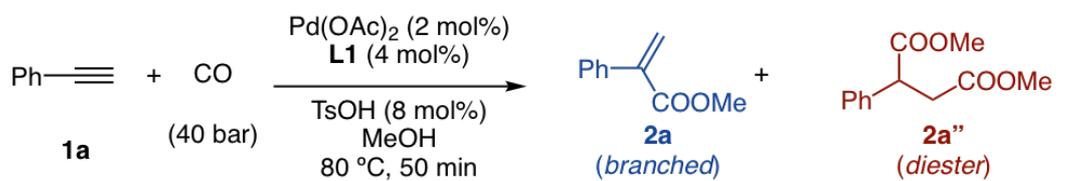
[a]. Reactions were performed with **1a** (0.5 mmol) in MeOH (2 mL). The conversions and *b/l* ratios were determined with ¹H-NMR and GC.

Table S4. Substrate competition experiments. ^[a]

entry	[1e] (M)	[1p] (M)	[Pd(OAc) ₂] ^[b]	Time (h)	Conv. (%)	
					1e	1p
1	0.25	0.25	2 mol%	16	>99	83
2	0.25	0.25	2 mol%	16	>99	98
3	0.125	0.125	4 mol%	16	>99	89
4	0.125	0.125	4 mol%	1	>99	85

[a]. Reactions were performed with **1e** (0.5 mmol) in different volumes of MeOH. *b/l* ratios were determined with ¹H NMR and GC analysis. [b]. Catalyst concentration relative to **1e**.

Figure S1. Reaction profile for **1a** at 80 °C.



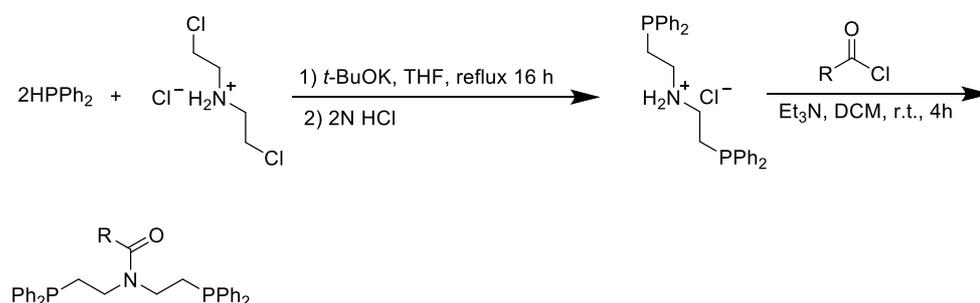
2. General information.

Commercial reagents and solvents were ordered from Aldrich, TCI and Bidepharm. Reagents and solvents were used as received unless otherwise stated. Where necessary, solvents were purified by passing through columns of alumina using a solvent purification system. Air- and moisture sensitive synthesis were performed under nitrogen atmosphere with oven-dried glassware. Column chromatography was performed on silica gel (100-200 mesh). Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates.

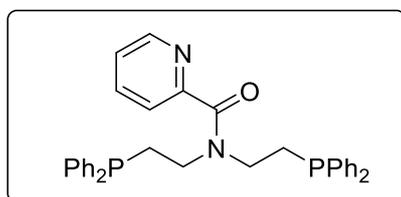
NMR spectra were recorded with a Bruker AVANCE III (400 MHz) spectrometer. Chemical shifts (δ , ppm) are given relative to solvent: references for CDCl_3 were 7.26 ppm (^1H NMR) and 77.16 ppm (^{13}C NMR). Data are reported as follows: chemical shift [multiplicity (br = broad, s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant(s) in Hertz, integration]. GC-MS analysis was carried out on Agilent 7820A GC system and Agilent 5977B MSD. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF spectrometer with electrospray ionization (ESI). Infrared data (IR) were obtained with a Thermo Fisher Scientific FT-IR. Combustion elemental analysis was performed with varioMicro elemental analyzer.

3. Synthesis of ligands (L1, L2, L4-L8)

3.1 Synthesis of L1, L2, L4, L5.



N,N-bis(2-(diphenylphosphanyl)ethyl)picolinamide (L1):



Diphenylphosphine (14.0 mL, 80.0 mmol) was added via syringe to a suspension of potassium *tert*-butoxide (14.0 g, 128.0 mmol) in anhydrous THF (250 mL) under nitrogen. The resulting deep red solution was stirred for 10 min and bis(2-chloroethyl)amine hydrochloride (7.0 g, 40.0 mmol) was added as a coarse powder. The mixture was refluxed for 16 h, poured into 400 mL of hexane, and washed in succession with 150-mL portions of 10% aqueous NaOH and brine. The hexane layer was separated, filtered, and stirred vigorously with aqueous hydrochloric acid (2N, 400 mL) to give a dense white precipitate. The precipitate was recrystallized from hot acetonitrile (100 mL) to afford bis(2-(diphenylphosphanyl)ethyl)ammonium chloride as fine white needles (16.2 g, 85%).

Triethylamine (2.8 mL, 20.0 mmol) was added slowly to a solution of picolinoyl chloride (1.2 g, 10.0 mmol) in DCM (10 mL) under nitrogen at 0°C. After 5 min, bis(2-(diphenylphosphanyl)ethyl)ammonium chloride (5.3 g, 12.0 mmol) from the previous step was added to the mixture, and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. Saturated aqueous NaHCO₃ was added, and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The

residue was further purified by flash chromatography (eluent: 2% Methanol in dichloromethane) to afford L1 as a white solid (2.52 g, 46% yield).

Mp. 103.8-104.7 °C.

^1H NMR (400 MHz, CDCl_3) δ 8.35 (d, $J = 4.2$ Hz, 1H), 7.68 (td, $J = 7.7, 1.5$ Hz, 1H), 7.53 (d, $J = 7.8$ Hz, 1H), 7.51-7.42 (m, 4H), 7.38-7.29 (m, 6H), 7.29-7.19 (m, 11H), 3.69-3.52 (m, 2H), 3.55-3.34 (m, 2H), 2.58-2.43 (m, 2H), 2.44-2.25 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 168.4, 154.1, 148.1, 137.7 (d, $J = 12.2$ Hz), 137.2 (d, $J = 11.9$ Hz), 136.7, 132.6 (d, $J = 17.0$ Hz), 132.4 (d, $J = 17.2$ Hz), 128.6, 128.5, 128.43, 128.36, 124.2, 123.3, 46.7 (d, $J = 28.2$ Hz), 43.8 (d, $J = 25.6$ Hz), 27.6 (d, $J = 14.6$ Hz), 26.2 (d, $J = 14.2$ Hz).

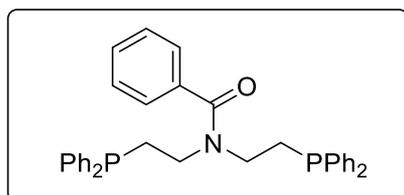
^{31}P NMR (162 MHz, CDCl_3) δ -20.73, -20.97.

IR (cm^{-1}): 3051.78, 1633.63, 1481.14, 1433.85, 1304.09, 1131.82, 738.01, 696.62.

HRMS(ESI): Calcd. for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{NaOP}_2$: $[\text{M}+\text{Na}]^+$ 569.1882; found: 569.1874.

Anal. Calcd. for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{OP}_2$: C, 74.71; H, 5.90; N, 5.13. Found: C, 74.57; H, 5.89; N, 5.13.

N,N-bis(2-(diphenylphosphaneyl)ethyl)benzamide (L2)



L2 was synthesized following the general procedure of **L1**.

Sticky colorless oil, 59% yield.

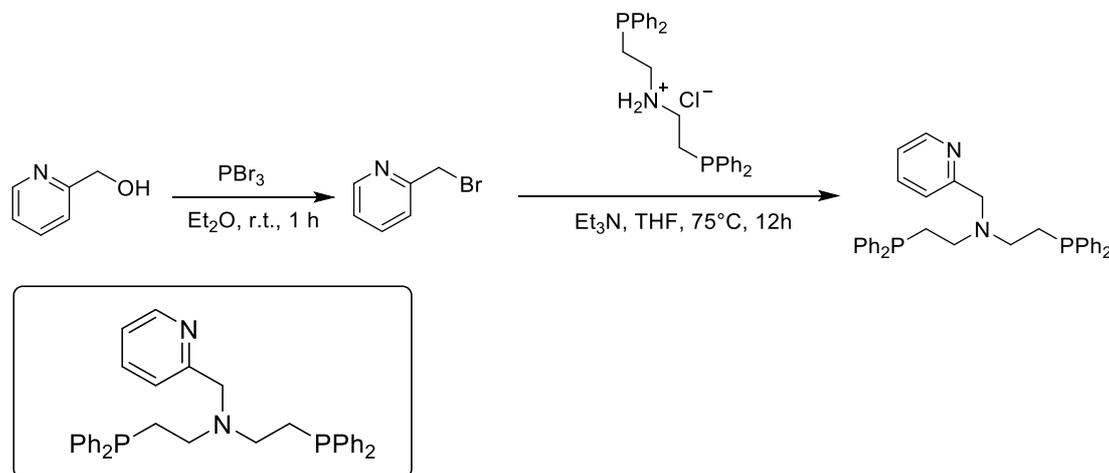
^1H NMR (400 MHz, CDCl_3) δ 7.47 (t, $J = 7.5$ Hz, 4H), 7.33-7.13 (m, 21H), 3.67-3.54 (m, 2H), 3.35-3.23 (m, 2H), 2.53-2.40 (m, 2H), 2.17-2.09 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 137.6 (d, $J = 12.5$ Hz), 136.7 (d, $J = 12.2$ Hz), 136.1, 132.3 (d, $J = 35.3$ Hz), 132.2 (d, $J = 35.6$ Hz), 129.0, 128.5, 128.4, 128.3, 128.2, 126.1, 46.7 (d, $J = 26.5$ Hz), 42.7 (d, $J = 23.6$ Hz), 27.4 (d, $J = 14.6$ Hz), 26.3 (d, $J = 14.2$ Hz).

^{31}P NMR (162 MHz, CDCl_3) δ -20.79, -21.62.

HRMS(ESI): Calcd. for $C_{35}H_{34}NOP_2$: $[M+H]^+$ 546.2110; found: 526.2091.

2-(diphenylphosphaneyl)-N-(2-(diphenylphosphaneyl)ethyl)-N-(pyridin-2-ylmethyl)ethan-1-amine (L4)^[1]

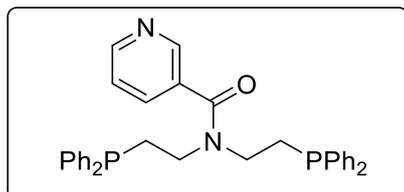


PBr_3 (0.52 mL, 5.5 mmol) was added to pyridin-2-ylmethanol (0.48 mL, 5.0 mmol) in Ethyl ether (10 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then quenched with methanol. After extraction with ethyl acetate, the combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure, leading to crude compound as yellow oil (839.8 mg, 99%). Triethylamine (0.8 mL, 5.7 mmol) was added slowly to a solution of 2-(bromomethyl)pyridine (0.45 g, 2.5 mmol) in THF (8.0 ml) under nitrogen at $0^\circ C$. After 5 min, bis(2-(diphenylphosphany)ethyl)ammonium chloride (1.10 g, 2.3 mmol) was added to the mixture, and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. Saturated aqueous $NaHCO_3$ was added, and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was further purified by flash chromatography (eluent: 2% Methanol in dichloromethane) to afford **L4** as a colourless oil (0.42 g, 34% yield) ^[1].

1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, $J = 4.2$ Hz, 1H), 7.57-7.50 (m, 1H), 7.36-7.30 (m, 9H), 7.29-7.25 (m, 12H), 7.12-7.06 (m, 1H), 3.74 (s, 2H), 2.69-2.57 (m, 4H), 2.18-2.10 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ 59.6, 148.8, 138.3 (d, $J = 12.8$ Hz), 136.3, 132.6 (d, $J = 18.7$ Hz), 128.5, 128.4 (d, $J = 6.8$ Hz), 122.9, 121.8, 59.8, 49.7 (d, $J = 22.1$ Hz), 25.2 (d, $J = 12.8$ Hz).

N,N-bis(2-(diphenylphosphaneyl)ethyl)nicotinamide (L5)



L5 was synthesized following the general procedure of **L1**.

Sticky colorless oil, 55% yield.

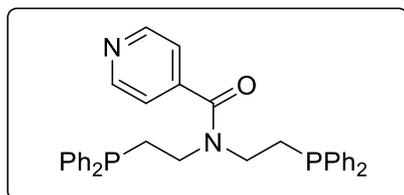
^1H NMR (400 MHz, CDCl_3) δ 8.57 (d, $J = 4.9$ Hz, 1H), 8.50 (s, 1H), 7.51-7.42 (m, 5H), 7.34-7.21 (m, 12H), 7.20-7.09 (m, 5H), 3.68-3.54 (m, 2H), 3.34-3.18 (m, 2H), 2.51-2.39 (m, 2H), 2.17-2.08 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 168.8, 150.2, 147.2, 137.5 (d, $J = 12.1$ Hz), 136.5 (d, $J = 11.9$ Hz), 133.9, 132.5 (d, $J = 18.8$ Hz), 132.2 (d, $J = 19.1$ Hz), 132.1, 128.8, 128.7, 128.5, 128.4, 123.0, 46.8 (d, $J = 26.4$ Hz), 43.0 (d, $J = 23.8$ Hz), 27.7 (d, $J = 16.4$ Hz), 26.3 (d, $J = 13.7$ Hz).

^{31}P NMR (162 MHz, CDCl_3) δ -20.91, -22.21.

HRMS(ESI): Calcd. for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{NaOP}_2$ $[\text{M}+\text{Na}]^+$: 569.1882; found: 569.1877.

N,N-bis(2-(diphenylphosphaneyl)ethyl)isonicotinamide (L6)



Sticky colorless oil, 62% yield.

^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, $J = 5.9$ Hz, 2H), 7.59-7.41 (m, 4H), 7.39-7.21 (m, 12H), 7.20-7.10 (m, 4H), 7.07-6.98 (m, 2H), 3.69-3.49 (m, 2H), 3.35-3.04 (m, 2H), 2.59-2.35 (m, 2H), 2.23-2.05 (m, 2H).

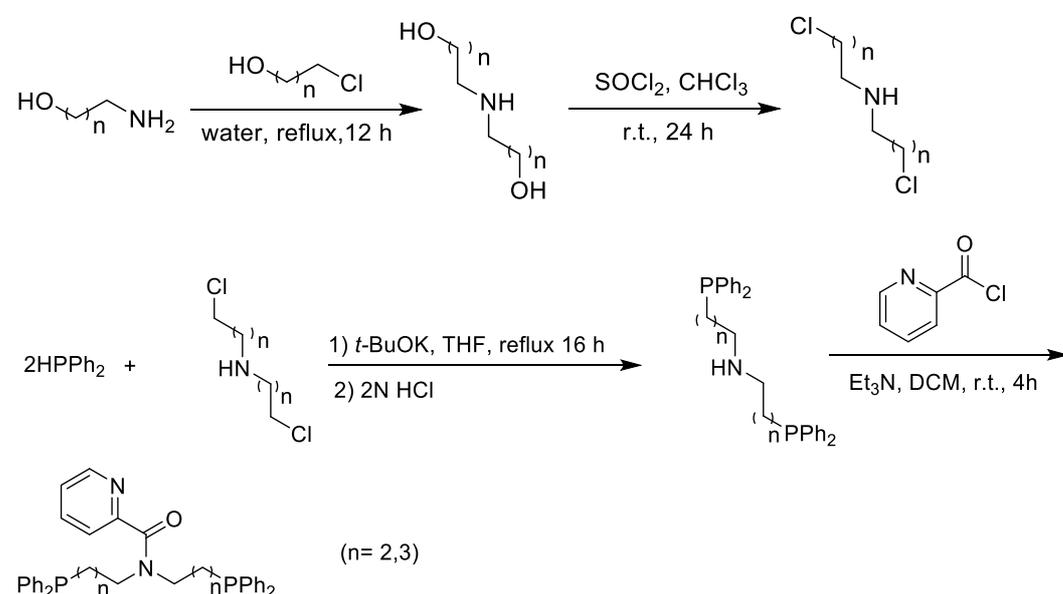
^{13}C NMR (101 MHz, CDCl_3) δ 168.7, 150.0, 143.7, 137.5 (d, $J = 12.1$ Hz), 136.4 (d, $J = 11.9$ Hz), 132.6 (d, $J = 18.8$ Hz), 132.2 (d, $J = 18.9$ Hz), 129.0, 128.8, 128.6 (d, $J = 2.5$ Hz), 128.5 (d, $J = 2.5$ Hz), 120.51, 46.5 (d, $J = 26.9$ Hz), 42.8 (d, $J = 23.7$ Hz), 27.7 (d, $J = 15.9$ Hz), 26.3 (d, $J = 14.4$ Hz).

^{31}P NMR (162 MHz, CDCl_3) δ -16.32, -17.17.

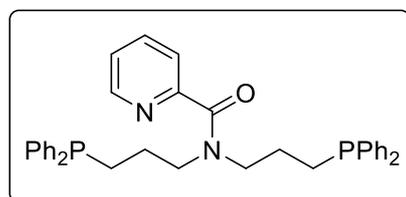
IR (cm^{-1}): 3069.23, 3052.66, 2936.38, 1634.13, 1481.43, 1433.74, 1307.38, 1281.79, 1131.40, 741.85, 697.98

HRMS(ESI): Calcd. for $\text{C}_{34}\text{H}_{32}\text{N}_2\text{NaOP}_2$ $[\text{M}+\text{Na}]^+$: 569.1882; found: 569.1880.

3.2 Synthesis of L7 and L8



N,N -bis(3-(diphenylphosphaneyl)propyl)picolinamide (L7)



Triethylamine (2.8 mL, 20.0 mmol) was added slowly to a solution of picolinoyl chloride (1.20 g, 10.0 mmol) in DCM (10 ml) under nitrogen at 0°C . After 5 min, bis(3-chloropropyl)amine (5.32 g, 12.0 mmol) was added to the mixture, and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. Saturated aqueous NaHCO_3 was added, and the aqueous layer was extracted with DCM. The

combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was further purified by flash chromatography (eluent: 2% Methanol in dichloromethane) to afford **L7** as colourless oil (1.66 g, 29% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.46 (d, $J = 5.5$ Hz, 1H), 7.70 (td, $J = 7.7, 1.8$ Hz, 1H), 7.48 (d, $J = 7.8$ Hz, 1H), 7.45-7.38 (m, 4H), 7.37-7.24 (m, 17H), 3.52 (t, $J = 7.5$ Hz, 2H), 3.40 (t, $J = 7.5$ Hz, 2H), 2.21-2.02 (m, 2H), 1.84-1.72 (m, 4H), 1.71-1.57 (m, 2H).

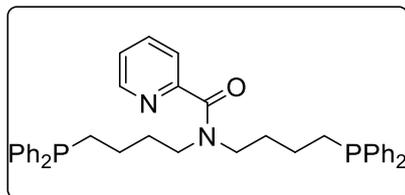
^{13}C NMR (100 MHz, CDCl_3) δ 168.8, 154.7, 148.1, 138.4 (d, $J = 12.8$ Hz), 138.2 (d, $J = 12.9$ Hz), 136.8, 132.7 (d, $J = 18.5$ Hz), 132.5 (d, $J = 18.6$ Hz), 128.62, 128.56, 128.44, 128.37, 124.1, 123.3, 49.5 (d, $J = 14.8$ Hz), 46.6 (d, $J = 14.4$ Hz), 25.2, 25.1, 24.9 (d, $J = 12.5$ Hz), 23.9 (d, $J = 16.5$ Hz).

^{31}P NMR (162 MHz, CDCl_3) δ -16.32, -17.17.

IR (cm^{-1}): 3069.23, 3052.66, 2936.38, 1634.13, 1481.43, 1433.74, 1307.38, 1281.79, 1131.40, 741.85, 697.98.

HRMS(ESI): Calcd. for $\text{C}_{36}\text{H}_{36}\text{N}_2\text{NaOP}_2$ $[\text{M}+\text{Na}]^+$: 597.2195; found: 597.2187.

N,N-bis(4-(diphenylphosphaneyl)butyl)picolinamide (L8)



A mixture of 4-aminobutan-1-ol (4.68 g, 50.0 mmol) and 4-chlorobutan-1-ol (3.40 g, 29.4 mmol) in water (25.0 mL) was refluxed for 12 h. Water was removed under reduced pressure and 4,4'-azanediylobis(butan-1-ol) was obtained as a yellow oil and used for the next step without further purification.

To a solution of 4,4'-azanediylobis(butan-1-ol) in chloroform at 0°C , a solution of thionyl chloride (15.0 mL, 20.8 mmol) in chloroform was added dropwise. The solution was stirred for 24 h at room temperature. The solvent was evaporated, and the crude product was purified by flash chromatography (eluent: 12.5% Methanol in dichloromethane) to afford bis(4-chlorobutyl)amine as a white solid (2.51 g, 43% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.36-7.29 (m, 8H), 7.28-7.22 (m, 12H), 2.83 (t, $J = 8.0$ Hz, 4H), 1.97 (t, $J = 8.0$ Hz, 4H), 1.87-1.69 (m, 4H), 1.45-1.32 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ 138.2 (d, $J = 12.0$ Hz), 132.6 (d, $J = 18.3$ Hz), 128.6, 128.4 (d, $J = 6.7$ Hz), 39.8, 29.4 (d, $J = 13.4$ Hz), 27.3 (d, $J = 11.4$ Hz), 23.0 (d, $J = 17.5$ Hz).

^{31}P NMR (162 MHz, CDCl_3) δ -16.8.

Triethylamine (2.8 mL, 20.0 mmol) was added slowly to a solution of picolinoyl chloride (1.20 g, 10.0 mmol) in DCM (10 ml) under nitrogen at 0°C . After 5 min, bis(4-chlorobutyl)amine (2.50 g, 5.0 mmol) was added to the mixture, and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. Saturated aqueous NaHCO_3 was added, and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was further purified by flash chromatography (eluent: 2% Methanol in dichloromethane) to afford **L8** as colorless oil (0.75 g, 25% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, $J = 4.9$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.51-7.37 (m, 6H), 7.36-7.25 (m, 15H), 7.22-7.16 (m, 1H), 3.43 (t, $J = 7.7$ Hz, 2H), 3.27 (t, $J = 7.6$ Hz, 2H), 2.21-2.02 (m, 2H), 1.91-1.84 (m, 2H), 1.83-1.73 (m, 2H), 1.70-1.60 (m, 2H), 1.57-1.45 (m, 2H), 1.30-1.11 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 168.4, 154.7, 147.9, 138.4 (d, $J = 17.9$ Hz), 138.3 (d, $J = 17.9$ Hz), 136.6, 132.44 (d, $J = 18.4$ Hz), 132.36 (d, $J = 18.4$ Hz), 128.33, 128.25, 128.2, 128.1, 123.8, 123.0, 48.1, 45.2, 30.0 (d, $J = 12.5$ Hz), 28.7 (d, $J = 12.8$ Hz), 27.5 (d, $J = 11.6$ Hz), 27.2 (d, $J = 11.8$ Hz), 23.2 (d, $J = 16.6$ Hz), 22.7 (d, $J = 16.6$ Hz).

^{31}P NMR (162 MHz, CDCl_3) δ -16.34, -16.72.

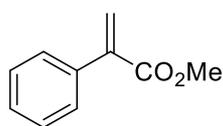
IR (cm^{-1}): 3049.12, 2928.64, 1629.15, 1432.12, 1418.24, 1305.52, 1128.02, 739.82, 695.12

HRMS(ESI): Calcd. for $\text{C}_{38}\text{H}_{40}\text{N}_2\text{NaOP}_2$ $[\text{M}+\text{Na}]^+$: 625.2508; found: 625.2505.

4. General procedure for Pd-catalyzed carbonylation of alkynes

A 10 mL reaction tube was charged with Pd(OAc)₂ (2.0 mol%), TsOH (8.0 mol%), and equipped with a stirring bar. MeOH (2.0 mL) was added to dissolve the catalyst, followed by the addition of substrate alkyne (0.5 mmol) and **L1** (4.0 mol%). The tube was placed in a WP-MSAR-250A autoclave. At room temperature, the autoclave was purged with nitrogen three times and carbon monoxide three times, then pressurized to 40 bar of carbon monoxide. The reaction was kept at room temperature for 12 h. Afterward, the pressure was carefully released. A sample of the mixture was analyzed by GC-MS and NMR. The pure product was obtained by column chromatography on silica gel (general eluent: petroleum ether /ethyl acetate = 30:1 to 15:1).

methyl 2-phenylacrylate (**2a**)^[2]



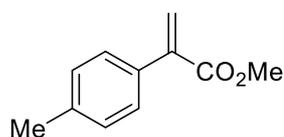
2a

68.8 mg, 85% yield, 0.5 mmol scale, colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.43-7.38 (m, 2H), 7.38-7.32 (m, 3H), 6.37 (d, *J* = 1.3 Hz, 1H), 5.89 (d, *J* = 1.3 Hz, 1H), 3.82 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 167.3, 141.2, 136.6, 128.3, 128.1, 128.1, 126.9, 52.2.

methyl 2-(*p*-tolyl)acrylate (**2b**)^[2]



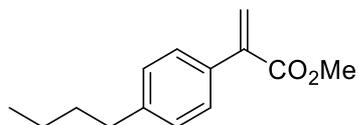
2b

68.1 mg, 77% yield, 0.5 mmol scale, colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.36 (d, *J* = 1.3 Hz, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 3.85 (s, 3H), 2.40 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 167.4, 141.1, 138.0, 133.7, 128.8, 128.1, 126.2, 52.1, 21.1.

methyl 2-(4-butylphenyl)acrylate (2c)



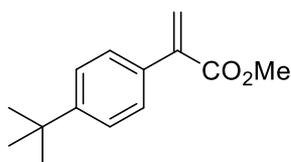
2c

83.8 mg, 77% yield, 0.5 mmol scale, colorless oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.32 (d, $J = 8.2$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 6.31 (d, $J = 1.3$ Hz, 1H), 5.86 (d, $J = 1.3$ Hz, 1H), 3.81 (s, 3H), 2.68-2.53 (m, 2H), 1.69-1.54 (m, 2H), 1.46-1.30 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.4, 143.0, 141.1, 133.9, 128.1, 128.1, 126.1, 52.1, 35.3, 33.5, 22.3, 13.9.

methyl 2-(4-(tert-butyl)phenyl)acrylate (2d)^[2]



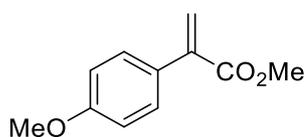
2d

83.8 mg, 77% yield, 0.5 mmol scale, colorless oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.47-7.33 (m, 4H), 6.35 (d, $J = 1.3$ Hz, 1H), 5.92 (d, $J = 1.3$ Hz, 1H), 3.85 (s, 3H), 1.36 (s, 9H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.5, 151.2, 141.0, 133.7, 127.9, 126.3, 125.1, 52.2, 34.6, 31.2.

methyl 2-(4-methoxyphenyl)acrylate (2e)^[2]



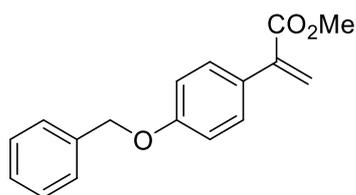
2e

2e. 81.1 mg, 84% yield, 0.5 mmol scale, colorless oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.47-7.31 (m, 2H), 6.98-6.79 (m, 2H), 6.28 (d, $J = 1.2$ Hz, 1H), 5.84 (d, $J = 1.2$ Hz, 1H), 3.82 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 159.6, 140.6, 129.5, 129.1, 125.5, 113.5, 55.3, 52.2.

methyl 2-(4-(benzyloxy)phenyl)acrylate (2f)^[3]



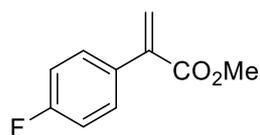
2f

2f. 83.4 mg, 62% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.56-7.27 (m, 7H), 7.06-6.87 (m, 2H), 6.27 (d, $J = 1.3$ Hz, 1H), 5.83 (d, $J = 1.2$ Hz, 1H), 5.07 (s, 2H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 158.8, 140.5, 136.8, 129.5, 129.3, 128.6, 128.0, 127.4, 125.5, 114.4, 69.9, 52.2.

methyl 2-(4-fluorophenyl)acrylate (2g)^[4]



2g

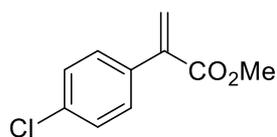
2g. 74.5 mg, 83% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.44-7.31 (m, 2H), 7.12-6.90 (m, 2H), 6.37 (d, $J = 1.1$ Hz, 1H), 5.88 (d, $J = 1.1$ Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 162.7 (d, $J = 247.5$ Hz), 140.1, 132.7 (d, $J = 3.5$ Hz), 130.1 (d, $J = 8.2$ Hz), 127.0, 115.0 (d, $J = 21.5$ Hz), 52.3.

^{19}F NMR (376 MHz, CDCl_3) δ -113.78.

methyl 2-(4-chlorophenyl)acrylate (2h)^[2]



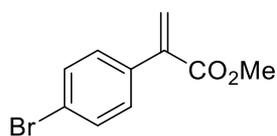
2h

2h. 73.4 mg, 75% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.38-7.28 (m, 4H), 6.39 (d, $J = 1.1$ Hz, 1H), 5.90 (d, $J = 1.1$ Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 140.1, 135.0, 134.2, 129.6, 128.3, 127.4, 52.3.

methyl 2-(4-bromophenyl)acrylate (2i)^[2]



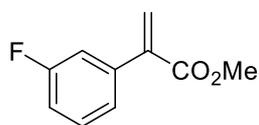
2i

2i. 87.9 mg, 73% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.53-7.44 (m, 2H), 7.33-7.27 (m, 2H), 6.40 (d, $J = 1.1$ Hz, 1H), 5.91 (d, $J = 1.1$ Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 140.1, 135.5, 131.2, 130.0, 127.5, 122.4, 52.3.

methyl 2-(3-fluorophenyl)acrylate (2j)^[5]



2j

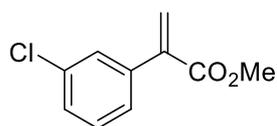
2j. 79.6 mg, 88% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.36-7.28 (m, 1H), 7.24-7.11 (m, 2H), 7.10-6.99 (m, 1H), 6.41 (d, $J = 1.0$ Hz, 1H), 5.93 (d, $J = 1.1$ Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.7 162.4 (d, $J = 245.4$ Hz), 140.1 (d, $J = 2.3$ Hz), 138.6 (d, $J = 8.1$ Hz), 129.6 (d, $J = 8.3$ Hz), 127.9, 124.0 (d, $J = 2.9$ Hz), 115.4 (d, $J = 22.4$ Hz), 115.1 (d, $J = 21.1$ Hz), 52.3.

^{19}F NMR (376 MHz, CDCl_3) δ -113.46.

methyl 2-(3-chlorophenyl)acrylate (2k)^[4]



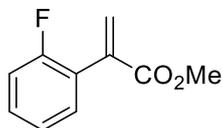
2k

2k. 51.7 mg, 53% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.45-7.37 (m, 1H), 7.34-7.25 (m, 3H), 6.41 (d, J = 1.1 Hz, 1H), 5.91 (d, J = 1.0 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 140.0, 138.3, 133.9, 129.3, 128.4, 128.2, 128.0, 126.5, 52.3.

methyl 2-(2-fluorophenyl)acrylate (2l)^[6].



2l

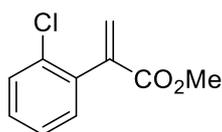
2l. 87.5 mg, 97% yield, 0.5 mmol scale, colorless oil

^1H NMR (400 MHz, CDCl_3) δ 7.40-7.21 (m, 2H), 7.20-6.89 (m, 2H), 6.51 (d, J = 1.2 Hz, 1H), 5.89 (d, J = 1.3 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 159.8 (d, J = 248.1 Hz), 136.4, 130.7 (d, J = 3.3 Hz), 130.1 (d, J = 8.3 Hz), 129.4 (d, J = 1.4 Hz), 125.0 (d, J = 14.9 Hz), 124.0 (d, J = 3.6 Hz), 115.5 (d, J = 21.8 Hz), 52.3.

^{19}F NMR (376 MHz, CDCl_3) δ -113.75.

methyl 2-(2-chlorophenyl)acrylate (2m)^[4].



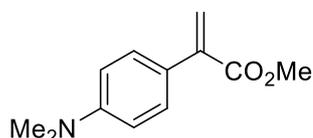
2m

2m. 83.7 mg, 85% yield, 0.5 mmol scale, colorless oil

^1H NMR (400 MHz, CDCl_3) δ 7.42-7.20 (m, 4H), 6.53 (d, $J = 1.3$ Hz, 1H), 5.79 (d, $J = 1.3$ Hz, 1H), 3.78 (s, 3H)

^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 140.1, 136.4, 133.3, 130.8, 129.5, 129.2, 129.2, 126.7, 52.3.

methyl 2-(4-(dimethylamino)phenyl)acrylate (**2n**)



2n

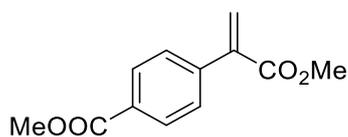
2n. 42.5 mg, 41% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.39-7.28 (m, 2H), 6.78-6.64 (m, 2H), 6.15 (d, $J = 1.3$ Hz, 1H), 5.78 (d, $J = 1.3$ Hz, 1H), 3.81 (s, 3H), 2.97 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 168.1, 150.3, 140.8, 129.0, 124.4, 123.3, 111.8, 52.1, 40.4.

HRMS(ESI): Calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}_2$: $[\text{M}+\text{H}]^+$ 206.1176; found: 206.1178.

methyl 4-(3-methoxy-3-oxoprop-1-en-2-yl)benzoate (**2o**)^[4]



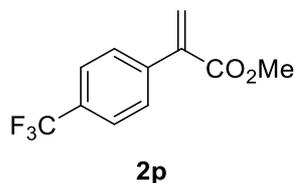
2o

2o. 79.0 mg, 72% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 8.09-7.96 (m, 2H), 7.55-7.43 (m, 2H), 6.46 (d, $J = 1.0$ Hz, 1H), 5.98 (d, $J = 1.0$ Hz, 1H), 3.92 (s, 3H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 166.5, 141.0, 140.4, 129.6, 129.3, 128.3, 128.3, 52.3, 52.1.

methyl 2-(4-(trifluoromethyl)phenyl)acrylate (2p)^[7]



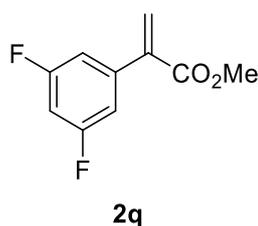
2p. 75.9 mg, 66% yield, 0.5 mmol scale, colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.72-7.40 (m, 4H), 6.48 (d, *J* = 1.0 Hz, 1H), 5.96 (d, *J* = 1.0 Hz, 1H), 3.83 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 166.5, 140.2 (q, *J* = 1.6 Hz), 140.1, 128.7, 128.6, 125.0 (q, *J* = 3.8 Hz), 125.0 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 271.9 Hz), 52.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -62.7.

methyl 2-(3,5-difluorophenyl)acrylate (2q)



2q. 46.6 mg, 47% yield, 0.5 mmol scale, light yellow oil.

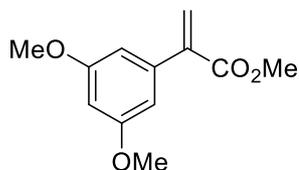
¹H NMR (400 MHz, CDCl₃) δ 7.03-6.94 (m, 2H), 6.86-6.76 (m, 1H), 6.47 (s, 1H), 5.97 (s, 1H), 3.86 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 166.1, 163.8 (d, *J* = 13.1 Hz), 161.3 (d, *J* = 12.9 Hz), 139.4 (d, *J* = 29.1 Hz), 128.7, 111.4 (dd, *J* = 26.3, 12.1 Hz), 103.6 (t, *J* = 25.3 Hz), 52.4.

¹⁹F NMR (376 MHz, CDCl₃) δ -110.17.

HRMS(ESI): Calcd. for C₁₀H₉F₂O₂: [M+H]⁺ 199.0565; found: 199.0563.

methyl 2-(3,5-dimethoxyphenyl)acrylate (2r)^[8]



2r

2r. 82.3 mg, 74 yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 6.56 (d, $J = 2.3$ Hz, 2H), 6.45 (t, $J = 2.3$ Hz, 1H), 6.34 (d, $J = 1.3$ Hz, 1H), 5.89 (d, $J = 1.3$ Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 160.3, 141.1, 138.5, 127.1, 106.5, 100.2, 55.3, 52.2.

methyl 2-(2,4-difluorophenyl)acrylate (2s)



2s

2s. 61.8 mg, 62% yield, 0.5 mmol scale, light yellow oil.

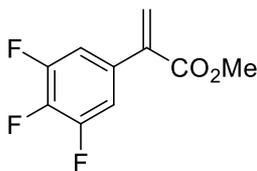
^1H NMR (400 MHz, CDCl_3) δ 7.30-7.20 (m, 1H), 6.95-6.78 (m, 2H), 6.52 (d, $J = 1.1$ Hz, 1H), 5.88 (d, $J = 1.2$ Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 162.9 (dd, $J = 249.1, 11.1$ Hz), 160.0 (dd, $J = 251.4, 12.5$ Hz), 135.5, 131.5 (dd, $J = 9.6, 4.7$ Hz), 129.7, 121.2 (dd, $J = 15.1, 3.9$ Hz), 111.1 (dd, $J = 21.3, 3.7$ Hz), 103.9 (t, $J = 25.7$ Hz), 52.4.

^{19}F NMR (376 MHz, CDCl_3) δ -109.35 (d, $J = 8.2$ Hz), -109.68 (d, $J = 8.2$ Hz).

HRMS(ESI): Calcd. for $\text{C}_{10}\text{H}_9\text{F}_2\text{O}_2$: $[\text{M}+\text{H}]^+$ 199.0565; found: 199.0566.

methyl 2-(3,4,5-trifluorophenyl)acrylate (2t)



2t

2t. 83.5 mg, 77% yield, 0.5 mmol scale, light yellow oil.

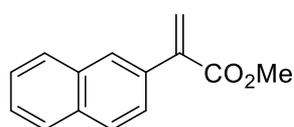
^1H NMR (400 MHz, CDCl_3) δ 7.15-7.06 (m, 2H), 6.47 (s, 1H), 5.96 (s, 1H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 165.9, 150.70 (ddd, $J = 249.3, 10.1, 4.3$ Hz), 139.66 (dt, $J = 253.0, 15.3$ Hz), 138.50-138.42 (m), 132.39 (td, $J = 8.3, 5.0$ Hz), 128.7, 112.94-112.52 (m), 52.5.

^{19}F NMR (376 MHz, CDCl_3) δ -134.74 (dd, $J = 20.4, 3.5$ Hz), -160.64--161.06 (m).

HRMS(ESI): Calcd. for $\text{C}_{10}\text{H}_8\text{F}_3\text{O}_2$: $[\text{M}+\text{H}]^+$ 217.0471; found: 217.0478.

methyl 2-(naphthalen-2-yl)acrylate (**2u**)^[2]



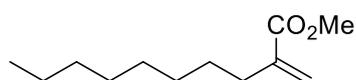
2u

2u. 58.3 mg, 55% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.92-7.88 (m, 1H), 7.87-7.75 (m, 3H), 7.54-7.43 (m, 3H), 6.44 (d, $J = 1.1$ Hz, 1H), 6.01 (d, $J = 1.1$ Hz, 1H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 141.2, 134.1, 133.0, 132.9, 128.2, 127.6, 127.5, 127.4, 127.2, 126.3, 126.2, 126.1, 52.3.

methyl 2-methylenedecanoate (**4a**)



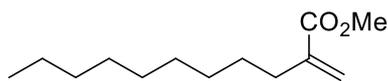
4a

4a. 87.0 mg, 88% yield, 0.5 mmol scale, colorless oil^[9].

^1H NMR (400 MHz, CDCl_3) δ 6.13 (d, $J = 1.3$ Hz, 1H), 5.52 (d, $J = 1.5$ Hz, 1H), 3.75 (s, 3H), 2.29 (t, $J = 7.5$ Hz, 2H), 1.51-1.40 (m, 2H), 1.31-1.22 (m, 10H), 0.87 (t, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 140.8, 124.4, 53.4, 51.7, 31.8, 29.4, 29.2, 29.2, 28.3, 22.6, 14.1.

methyl 2-methyleneundecanoate (**4b**)^[10]



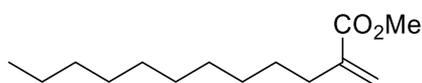
4b

4b. 91.2 mg, 86% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 6.13 (d, $J = 1.5$ Hz, 1H), 5.54-5.49 (m, 1H), 3.75 (s, 3H), 2.29 (t, 2H), 1.51-1.40 (m, 2H), 1.31-1.24 (m, 12H), 0.87 (t, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.8, 140.8, 124.4, 51.7, 31.9, 31.8, 29.5, 29.4, 29.3, 29.2, 28.3, 22.6, 14.1.

methyl 2-methylenedodecanoate (4c)^[11]



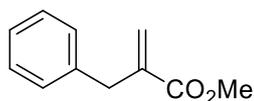
4c

4c. 100.4 mg, 89% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 6.13 (d, $J = 1.5$ Hz, 1H), 5.56-5.48 (m, 1H), 3.75 (s, 3H), 2.29 (t, $J = 7.6$ Hz, 2H), 1.50-1.40 (m, 2H), 1.31-1.24 (m, 14H), 0.87 (t, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 140.8, 124.4, 51.7, 31.9, 31.8, 29.6, 29.6, 29.4, 29.3, 29.2, 28.3, 22.7, 14.1.

methyl 2-benzylacrylate (4d)^[12]



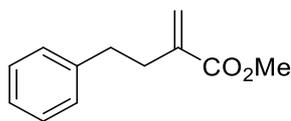
4d

4d. 68.8 mg, 78% yield, 0.5 mmol scale, light yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.36-7.24 (m, 2H), 7.23-7.10 (m, 3H), 6.23 (s, 1H), 5.45 (s, 1H), 3.72 (s, 3H), 3.63 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 140.1, 138.7, 129.1, 128.5, 126.4, 126.3, 51.9, 38.1.

methyl 2-methylene-4-phenylbutanoate (4e)^[13]



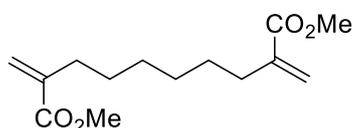
4e

4e. 84.5 mg, 89% yield, 0.5 mmol scale, light yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.32-7.25 (m, 2H), 7.22-7.15 (m, 3H), 6.15 (d, $J = 1.4$ Hz, 1H), 5.50 (d, $J = 1.5$ Hz, 1H), 3.76 (s, 3H), 2.79 (t, 2H), 2.62 (t, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 141.3, 139.7, 128.4, 128.3, 125.9, 125.4, 51.8, 34.8, 33.8.

dimethyl 2,9-dimethylenedecanedioate (4f)



4f

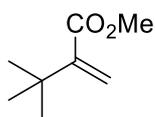
4f. 98.9 mg, 78% yield, 0.5 mmol scale, light yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 6.13 (d, $J = 1.5$ Hz, 2H), 5.52 (d, $J = 1.5$ Hz, 2H), 3.75 (s, 6H), 2.29 (t, $J = 7.6$ Hz, 4H), 1.52-1.42 (m, 4H), 1.37-1.30 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 140.6, 124.4, 51.7, 31.8, 28.9, 28.2.

HRMS(ESI): Calcd. for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_4$: $[\text{M}+\text{H}]^+$ 255.1591; found: 255.1590.

methyl 3,3-dimethyl-2-methylenebutanoate (4g)^[14]

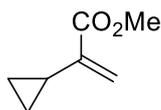


4g

4g. 66% GC yield, 0.5 mmol scale, light yellow oil. Volatile. ^1H NMR spectrum was obtained from the crude reaction mixture.

^1H NMR (400 MHz, CDCl_3) δ 5.93 (d, $J = 0.9$ Hz, 1H), 5.53 (d, $J = 0.9$ Hz, 1H), 3.74 (s, 3H), 1.21 (s, 9H).

methyl 2-cyclopropylacrylate (4h)^[15]



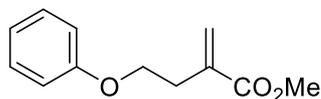
4h

4h. 71% GC yield, 0.5 mmol scale, colorless oil. Volatile

^1H NMR (400 MHz, CDCl_3) δ 6.03 (d, $J = 1.1$ Hz, 1H), 5.31 (t, $J = 1.1$ Hz, 1H), 3.78 (s, 3H), 1.80-1.68 (m, 1H), 0.83-0.76 (m, 2H), 0.53-0.47 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 142.2, 120.7, 51.8, 11.8, 7.1.

methyl 2-methylene-4-phenoxybutanoate (4i)



4i

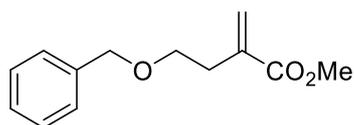
4i. 41.2 mg, 40% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.31-7.24 (m, 2H), 6.96-6.86 (m, 3H), 6.29 (d, $J = 1.3$ Hz, 1H), 5.73 (d, $J = 1.3$ Hz, 1H), 4.11 (t, $J = 6.6$ Hz, 2H), 3.77 (s, 3H), 2.80 (td, $J = 6.6, 1.2$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 158.6, 136.5, 129.4, 127.5, 120.7, 114.5, 66.0, 51.9, 31.9.

HRMS(ESI): Calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_3$: $[\text{M}+\text{H}]^+$ 207.1016; found: 207.1020.

methyl 4-(benzyloxy)-2-methylenebutanoate (4j)^[16]



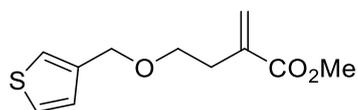
4j

4j. 74.8 mg, 68% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.36-7.29 (m, 4H), 7.29-7.23 (m, 1H), 6.22 (d, $J = 1.3$ Hz, 1H), 5.65 (d, $J = 1.4$ Hz, 1H), 4.50 (s, 2H), 3.73 (s, 3H), 3.61 (t, $J = 6.6$ Hz, 2H), 2.64 (td, $J = 6.6, 1.2$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 138.2, 137.2, 128.2, 127.5, 127.4, 126.6, 72.7, 68.5, 51.7, 32.2.

methyl 2-methylene-4-(thiophen-3-ylmethoxy)butanoate (4k)



4k

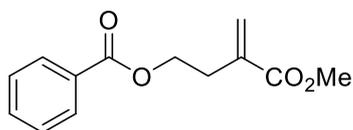
4k. 79.1 mg, 70% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.35-7.24 (m, 1H), 7.22-7.14 (m, 1H), 7.09-6.96 (m, 1H), 6.22 (d, $J = 1.4$ Hz, 1H), 5.64 (q, $J = 1.3$ Hz, 1H), 4.51 (s, 2H), 3.73 (s, 3H), 3.60 (t, $J = 6.6$ Hz, 2H), 2.62 (td, $J = 6.6, 1.3$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 139.4, 137.1, 127.1, 126.6, 125.8, 122.5, 68.4, 67.9, 51.7, 32.2.

HRMS(ESI): Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_3\text{S}$: $[\text{M}+\text{H}]^+$ 227.0736; found: 227.0735.

3-(methoxycarbonyl)but-3-en-1-yl benzoate (4l)



4l

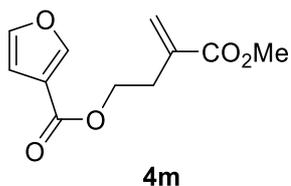
4l. 77.4 mg, 66% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 8.09-7.97 (m, 2H), 7.62-7.51 (m, 1H), 7.43 (t, $J = 7.6$ Hz, 2H), 6.29 (s, 1H), 5.79-5.62 (m, 1H), 4.47 (t, $J = 6.5$ Hz, 2H), 3.76 (s, 3H), 2.80 (t, $J = 8.0$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 166.3, 136.5, 132.9, 130.1, 129.4, 128.3, 127.4, 63.1, 51.9, 31.4.

HRMS(ESI): Calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_4$: $[\text{M}+\text{H}]^+$ 234.0965; found: 234.0963.

3-(methoxycarbonyl)but-3-en-1-yl furan-3-carboxylate (4m)



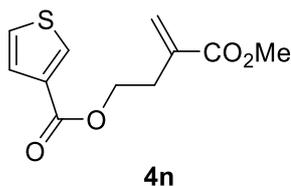
4m. 74.6 mg, 67% yield, 0.5 mmol scale, light yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 8.03-7.95 (m, 1H), 7.42 (t, $J = 1.7$ Hz, 1H), 6.72 (d, $J = 1.2$ Hz, 1H), 6.27 (d, $J = 1.3$ Hz, 1H), 5.68 (q, $J = 1.3$ Hz, 1H), 4.39 (t, $J = 6.6$ Hz, 2H), 3.77 (s, 3H), 2.75 (td, $J = 6.5, 1.2$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 162.8, 147.6, 143.6, 136.4, 127.3, 119.2, 109.6, 62.6, 51.9, 31.4.

HRMS(ESI): Calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_5$: $[\text{M}+\text{H}]^+$ 225.0767; found: 225.0763.

3-(methoxycarbonyl)but-3-en-1-yl thiophene-3-carboxylate (4n)



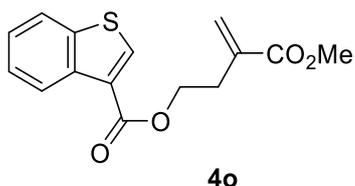
4n. 87.7 mg, 73% yield, 0.5 mmol scale, light yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 8.15-8.02 (m, 1H), 7.56-7.43 (m, 1H), 7.34-7.20 (m, 1H), 6.27 (s, 1H), 5.69 (s, 1H), 4.42 (t, $J = 6.5$ Hz, 2H), 3.77 (s, 3H), 2.77 (t, $J = 6.4$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 162.4, 136.4, 133.4, 132.6, 127.7, 127.3, 125.9, 62.8, 51.9, 31.4.

HRMS(ESI): Calcd. for $\text{C}_{11}\text{H}_{13}\text{O}_4\text{S}$: $[\text{M}+\text{H}]^+$ 241.0529; found: 241.0524.

3-(methoxycarbonyl)but-3-en-1-yl benzo[b]thiophene-3-carboxylate (4o)



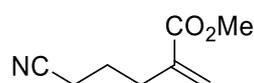
4o. 110.0 mg, 76% yield, 0.5 mmol scale, light yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 8.66-8.48 (m, 1H), 8.43-8.24 (m, 1H), 7.95-7.78 (m, 1H), 7.58-7.34 (m, 2H), 6.30 (s, 1H), 5.73 (s, 1H), 4.61-4.42 (m, 2H), 3.78 (s, 3H), 2.94-2.73 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 162.5, 139.9, 136.6, 136.6, 136.6, 127.5, 127.0, 125.3, 125.0, 124.6, 122.4, 62.9, 52.0, 31.6.

HRMS(ESI): Calcd. for $\text{C}_{15}\text{H}_{15}\text{O}_4\text{S}$: $[\text{M}+\text{H}]^+$ 291.0686; found: 291.0684.

methyl 5-cyano-2-methylenepentanoate (4p)^[17]



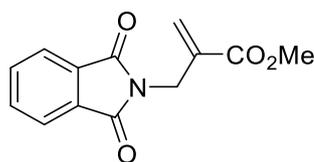
4p

4p. 136.0 mg, 89% yield, 1 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 6.24 (s, 1H), 5.70-5.59 (m, 1H), 3.77 (s, 3H), 2.47 (t, $J = 7.5$ Hz, 2H), 2.38 (t, $J = 7.2$ Hz, 2H), 1.87 (p, $J = 7.3$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 138.1, 126.3, 119.1, 51.7, 30.7, 23.9, 16.2.

methyl 2-((1,3-dioxisoindolin-2-yl)methyl)acrylate (4q)^[18]



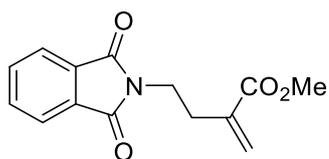
4q

4q. 97.2 mg, 79% yield, 0.5 mmol scale, white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.96-7.83 (m, 2H), 7.81-7.71 (m, 2H), 6.33 (s, 1H), 5.65-5.55 (m, 1H), 4.56 (s, 2H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 165.6, 134.2, 134.1, 131.8, 125.9, 123.3, 52.0, 38.1.

methyl 4-(1,3-dioxisoindolin-2-yl)-2-methylenebutanoate (4r)



4r

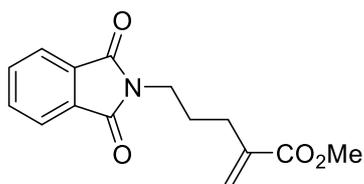
4r. 114.4 mg, 88% yield, 0.5 mmol scale, white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.89-7.80 (m, 2H), 7.77-7.67 (m, 2H), 6.15 (d, $J = 1.3$ Hz, 1H), 5.54 (d, $J = 1.3$ Hz, 1H), 3.91 (t, $J = 6.7$ Hz, 2H), 3.79 (s, 3H), 2.78-2.67 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 166.6, 136.9, 133.8, 131.8, 127.2, 123.0, 51.8, 36.6, 31.3.

HRMS(ESI): Calcd. for $\text{C}_{14}\text{H}_{14}\text{NO}_4$: $[\text{M}+\text{H}]^+$ 260.0917; found: 260.0916.

methyl 5-(1,3-dioxisoindolin-2-yl)-2-methylenepentanoate (4s)



4s

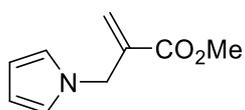
4s. 90.5 mg, 67% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.92-7.80 (m, 2H), 7.79-7.68 (m, 2H), 6.19 (d, $J = 1.1$ Hz, 1H), 5.62 (q, $J = 1.4$ Hz, 1H), 3.76-3.69 (m, 5H), 2.37 (t, $J = 7.6$ Hz, 2H), 1.99-1.80 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 167.3, 139.2, 133.9, 132.0, 125.4, 123.1, 51.8, 37.4, 29.0, 27.1.

HRMS(ESI): Calcd. for $\text{C}_{15}\text{H}_{16}\text{NO}_4$: $[\text{M}+\text{H}]^+$ 274.1074; found: 274.1077.

methyl 2-((1H-pyrrol-1-yl)methyl)acrylate (4t)



4t

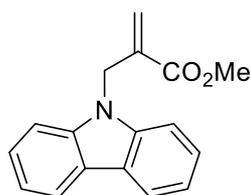
4t. 49.6 mg, 30% yield, 0.5 mmol scale, colorless oil. Volatile.

^1H NMR (400 MHz, CDCl_3) δ 6.65 (t, $J = 2.1$ Hz, 2H), 6.33-6.24 (m, 1H), 6.17 (t, $J = 2.1$ Hz, 2H), 5.34-5.24 (m, 1H), 4.81-4.69 (m, 2H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 137.9, 126.3, 121.2, 108.5, 52.1, 49.9.

HRMS(ESI): Calcd. for $\text{C}_9\text{H}_{12}\text{NO}_2$: $[\text{M}+\text{H}]^+$ 166.0863; found: 166.0865.

methyl 2-((9H-carbazol-9-yl)methyl)acrylate (**4u**)



4u

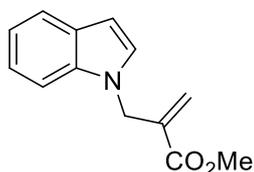
4u. 86.1 mg, 65% yield, 0.5 mmol scale, colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, $J = 7.8$ Hz, 2H), 7.52-7.38 (m, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.24 (t, $J = 7.4$ Hz, 2H), 6.17 (s, 1H), 5.15 (s, 2H), 5.02 (s, 1H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 140.3, 134.6, 125.9, 125.6, 123.0, 120.4, 119.3, 108.7, 52.1, 43.3.

HRMS(ESI): Calcd. for $\text{C}_{17}\text{H}_{16}\text{NO}_2$: $[\text{M}+\text{H}]^+$ 266.1176; found: 266.1174.

methyl 2-((1H-indol-1-yl)methyl)acrylate (**4v**)



4v

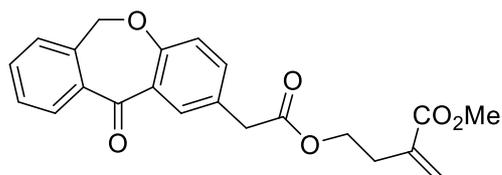
4v. 75.0 mg, 70% yield, 0.5 mmol scale, light yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.63 (dt, $J = 7.8, 1.0$ Hz, 1H), 7.27-7.22 (m, 1H), 7.21-7.16 (m, 1H), 7.14-7.06 (m, 2H), 6.52 (dd, $J = 3.2, 0.9$ Hz, 1H), 6.26-6.16 (m, 1H), 5.13 (td, $J = 1.8, 0.7$ Hz, 1H), 4.97 (t, $J = 1.6$ Hz, 2H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 136.2, 135.9, 128.5, 128.3, 126.1, 121.7, 120.9, 119.5, 109.5, 101.8, 52.0, 46.7.

HRMS(ESI): Calcd. for $\text{C}_{13}\text{H}_{14}\text{NO}_2$: $[\text{M}+\text{H}]^+$ 216.1019; found: 216.1017.

methyl 2-methylene-4-(2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetoxy)butanoate (4w)



4w

4w. 95.6 mg, 50% yield, 0.5 mmol scale, colorless oil.

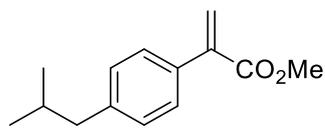
^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, $J = 2.4$ Hz, 1H), 7.88 (d, $J = 7.9$ Hz, 1H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.40 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.35 (d, $J = 7.4$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.20 (s, 1H), 5.56 (s, 1H), 5.17 (s, 2H), 4.25 (t, $J = 6.5$ Hz, 2H), 3.75 (s, 3H), 3.62 (s, 2H), 2.64 (t, $J = 6.5$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 190.6, 171.1, 166.8, 160.3, 140.3, 136.2, 136.0, 135.4, 132.6, 132.3, 129.3, 129.1, 127.7, 127.6, 127.4, 124.9, 120.9, 73.4, 62.9, 51.8, 40.0, 31.3.

HRMS(ESI): Calcd. for $\text{C}_{22}\text{H}_{21}\text{O}_6$: $[\text{M}+\text{H}]^+$ 381.1333; found: 381.1333.

5. Synthesis of Ibuprofen and Venlafaxine

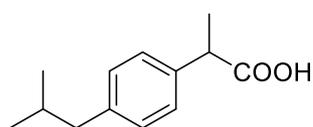
Synthesis of Ibuprofen (9a)^[5]



8

8.^[5] ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 1.3 Hz, 1H), 5.91 (d, *J* = 1.3 Hz, 1H), 3.86 (s, 3H), 2.52 (d, *J* = 7.2 Hz, 2H), 1.99-1.85 (m, 1H), 0.97 (s, 3H), 0.95 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 167.4, 141.8, 141.1, 134.0, 128.8, 127.9, 126.0, 52.1, 45.1, 30.1, 22.3.



9

A 10 mL reaction tube was charged with methyl 2-(4-isobutylphenyl)acrylate (220.8 mg, 1.0 mmol), [Rh(COD)Cl]₂ (5.3 mg, 1 mol%), BINAP (12.6 mg, 2 mol%) and equipped with a stirring bar before MeOH (2.0 mL) and triethylamine (52.1 mg, 0.5 mmol) was added. The tube was placed in a WP-MSAR-250A autoclave. At room temperature, the autoclave was purged with nitrogen three times and hydrogen three times, then pressurized to 40 *bar* of hydrogen, and the reaction mixture was stirred at room temperature for 12 h before releasing the hydrogen. The reaction mixture was extracted with ethyl acetate. Evaporation of solvent afforded the crude product methyl 2-(4-isobutylphenyl)propanoate.

To a 10 mL round-bottom flask, methyl 2-(4-isobutylphenyl)propanoate, THF/H₂O (1:1, 4 mL) and LiOH (174 mg, 4.0 mmol) were added sequentially at room temperature. The reaction mixture was heated to 80 °C for 4 h, and the resulting mixture was cooled to room temperature, acidified with 2N HCl and extracted with ethyl acetate. The combined organic layer was dried over NaSO₄, filtered and concentrated

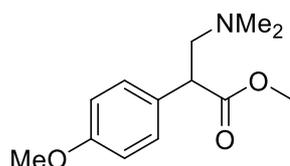
under reduced pressure to afford 2-(4-isobutylphenyl)propanoic acid **9** (155.3 mg, 75% yield) as a white solid.

9. ^1H NMR (400 MHz, CDCl_3) δ 7.21 (d, $J = 8.1$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 3.69 (q, $J = 7.1$ Hz, 1H), 2.44 (d, $J = 7.2$ Hz, 2H), 1.91-1.71 (m, 1H), 1.48 (d, $J = 7.1$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 181.2, 140.8, 136.9, 129.4, 127.3, 45.0, 45.0, 30.2, 22.4, 18.1.

Synthesis of Venlafaxine (**6**)

methyl 3-(dimethylamino)-2-(4-methoxyphenyl)propanoate (**5**)

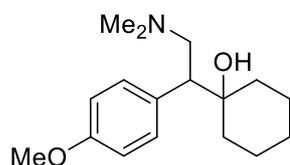


5

A 50 mL reaction tube was charged with $\text{Pd}(\text{OAc})_2$ (22.4 mg, 2.0 mol%), TsOH (69.5 mg, 8.0 mol%), and equipped with a stirring bar. MeOH (2.0 mL) was added to dissolve the catalyst, followed by the addition of **1e** (1.32 g, 10.0 mmol) and **L1** (110.8 mg, 4.0 mol%). The tube was placed in a WP-MSAR-250A autoclave. At room temperature, the autoclave was purged with nitrogen three times and carbon monoxide three times, then pressurized to 40 bar of carbon monoxide. The reaction was kept at room temperature for 12 h. Afterward, the pressure was carefully released. A solution of dimethylamine in H_2O (0.33 M, 2.76 g, 2.0 equiv) was added, and the mixture was reacted at room temperature for 2 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel (eluent: petroleum ether /ethyl acetate = 3:1) to afford **5** as a colorless oil (2.07 g, 87% yield)^[19].

5. ^[19] ^1H NMR (400 MHz, CDCl_3) δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 3.79-3.70 (m, 4H), 3.67 (s, 3H), 3.15-3.04 (m, 1H), 2.45-2.36 (m, 1H), 2.26 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 158.8, 129.4, 128.8, 114.0, 62.9, 55.1, 51.9, 49.3, 45.6.



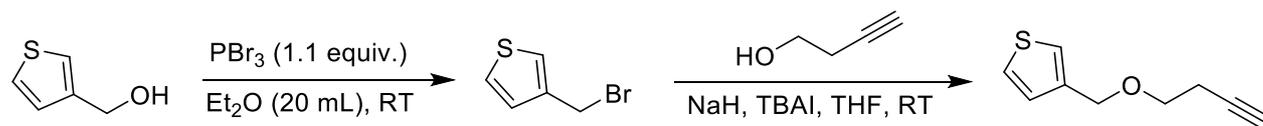
6

To a 25 mL round-bottom flask magnesium turnings (267.1 mg, 11.0 mmol) and a granular of iodine were added, followed by dropwise addition of a solution of dibromopentane (1.15 g, 5.0 mmol) in THF (10 mL) at room temperature. After addition, the reaction mixture was stirred for 1 h until most of the magnesium was consumed. The formed Grignard reagent (4.6 mL, 1.3 equiv.) was transferred to a 25 ml round-bottom flask and cooled to 0 °C. A solution of amino ester **5** (450.6 mg, 1.8 mmol) in THF (5 mL) was added dropwise. After the addition, the reaction mixture was allowed to warm to room temperature for 30 min and then heated to reflux for 3.5 h. The reaction mixture was cooled to room temperature, and 50% aq. NaOH solution was added to the reaction mixture (pH = 12). The mixture was extracted with ethyl acetate and washed with water and brine. The combined organic phase was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluent: 5% MeOH in CHCl_3) to furnish venlafaxine **6** as a white solid (209.4 mg, 42% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.05 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 3.79 (s, 3H), 3.29 (t, $J = 12.6$ Hz, 1H), 2.95 (dd, $J = 12.4, 3.4$ Hz, 1H), 2.32 (s, 6H), 2.28 (d, $J = 3.4$ Hz, 1H), 1.75-1.65 (m, 2H), 1.60-1.47 (m, 3H), 1.41-1.18 (m, 3H), 1.01-0.82 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ 158.2, 132.6, 130.0, 113.2, 74.2, 61.1, 55.1, 51.5, 45.4, 38.0, 31.0, 25.9, 21.5, 21.2.

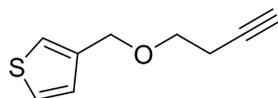
6. Synthesis of substrates



To a flask were added thiophen-3-ylmethanol (1.14 g, 10.0 mmol) and Et_2O (20 mL) under air atmosphere. Followed by the addition of PBr_3 , the mixture was then stirred at room temperature for 12 hours. After completion, the reaction was carefully quenched with CH_3OH (3 mL). The solution was poured into water (40 mL), and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over Na_2SO_4 . After concentration in vacuo, crude product 3-(bromomethyl)thiophene (1.74 g, 98% yield) was obtained as a yellow oil and used for the next step without purification^[20].

To a flask were added but-3-yn-1-ol (0.91 mL, 12.0 mmol) and THF (20 mL). Followed by the addition of NaH (60% in mineral oil, 0.48 g, 12.0 mmol), TBAI (0.37 g, 1.0 mmol) and crude 3-(bromomethyl)thiophene (1.74 g, 9.8 mmol) under nitrogen at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h until the reaction was completed. The reaction was quenched with saturated NH_4Cl solution, and the mixture was extracted with ethyl ether. The organic layers were combined, washed with brine and dried over Na_2SO_4 . The mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (eluent: petroleum ether) to give **3k** as a yellow oil liquid (1.02 g, 63% yield).

3-((but-3-yn-1-yloxy)methyl)thiophene (3k)

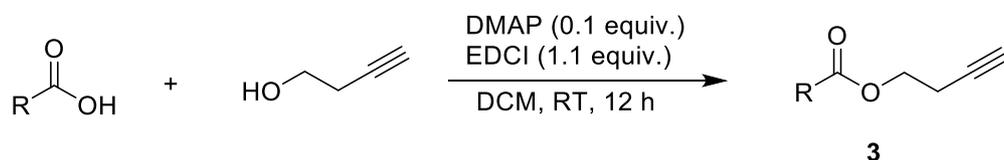


3k

^1H NMR (400 MHz, CDCl_3) δ 7.32-7.26 (m, 1H), 7.23-7.18 (m, 1H), 7.07 (d, $J = 4.9$ Hz, 1H), 4.55 (s, 2H), 3.58 (t, $J = 6.9$ Hz, 2H), 2.53-2.41 (m, 2H), 1.99 (t, $J = 2.7$ Hz, 1H).

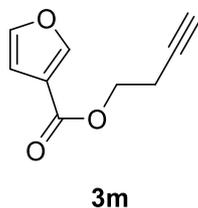
^{13}C NMR (100 MHz, CDCl_3) δ 139.1, 127.2, 126.0, 122.8, 81.2, 69.3, 68.1, 67.9, 19.8.

HRMS(ESI): Calcd. for $\text{C}_9\text{H}_{11}\text{OS}$: $[\text{M}+\text{H}]^+$ 167.0525; found: 167.0528.



A Schlenk tube was charged with carboxylic acid, EDCI (1.1 equiv.), DMAP (0.1 equiv.) and anhydrous DCM under nitrogen, followed by the addition of but-3-yn-1-ol (1.2 equiv.). The reaction mixture was stirred at room temperature for 12 h. Upon completion, the solvent was removed under reduced pressure, and the crude material was purified by silica gel column chromatography to afford the corresponding product^[21].

but-3-yn-1-yl furan-3-carboxylate (3m)

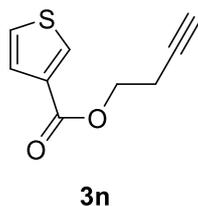


^1H NMR (400 MHz, CDCl_3) δ 8.07-8.02 (m, 1H), 7.47-7.40 (m, 1H), 6.82-6.69 (m, 1H), 4.42-4.29 (m, 2H), 2.68-2.56 (m, 2H), 2.06-2.02 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 162.7, 147.9, 143.7, 119.0, 109.7, 79.9, 69.9, 62.0, 19.0.

HRMS(ESI): Calcd. for $\text{C}_9\text{H}_9\text{O}_3$: $[\text{M}+\text{H}]^+$ 165.0548; found: 165.0546.

but-3-yn-1-yl thiophene-3-carboxylate (3n)

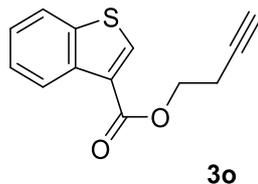


^1H NMR (400 MHz, CDCl_3) δ 8.18-8.06 (m, 1H), 7.58-7.48 (m, 1H), 7.35-7.26 (m, 1H), 4.43-4.28 (m, 2H), 2.70-2.51 (m, 2H), 2.08-1.98 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 162.3, 133.2, 132.9, 127.8, 126.0, 79.9, 70.0, 62.2, 19.0.

HRMS(ESI): Calcd. for $\text{C}_9\text{H}_9\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$ 181.0316; found: 181.0318.

but-3-yn-1-yl benzo[b]thiophene-3-carboxylate (3o)

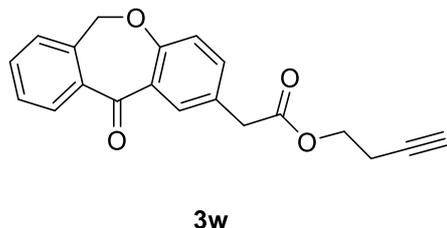


^1H NMR (400 MHz, CDCl_3) δ 8.63-8.57 (m, 1H), 8.41 (s, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.52-7.45 (m, 1H), 7.44-7.37 (m, 1H), 4.47 (t, $J = 6.7$ Hz, 2H), 2.70 (td, $J = 6.7, 2.6$ Hz, 2H), 2.06 (t, $J = 2.7$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 162.3, 139.9, 137.0, 136.6, 126.8, 125.4, 125.0, 124.7, 122.4, 80.1, 70.1, 62.2, 19.1.

HRMS(ESI): Calcd. for $\text{C}_{13}\text{H}_{11}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$ 231.0474; found: 231.0477

but-3-yn-1-yl 2-(11-oxo-6,11-dihydrodibenzo[b,e]loxepin-2-yl)acetate (3w)



^1H NMR (400 MHz, CDCl_3) δ 8.1 (d, $J = 2.4$ Hz, 1H), 7.9-7.8 (m, 1H), 7.6-7.5 (m, 1H), 7.5-7.4 (m, 2H), 7.3 (d, $J = 7.5$ Hz, 1H), 7.0 (d, $J = 8.4$ Hz, 1H), 5.2 (s, 2H), 4.2 (t, $J = 6.8$ Hz, 2H), 3.7 (s, 2H), 2.5 (td, $J = 6.8, 2.7$ Hz, 2H), 2.0 (t, $J = 2.7$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 190.7, 171.0, 160.4, 140.3, 136.3, 135.4, 132.7, 132.4, 129.3, 129.1, 127.7, 127.4, 125.0, 120.9, 79.8, 73.4, 70.0, 62.4, 39.9, 18.8.

HRMS(ESI): Calcd. for $\text{C}_{20}\text{H}_{17}\text{O}_4$: $[\text{M}+\text{H}]^+$ 321.1121; found: 321.1118.

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7. NMR Spectra

