N₂Phos. An easily made, highly effective ligand designed for ppm level Pdcatalyzed Suzuki-Miyaura cross couplings in water

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General Information

Unless otherwise specified, all of the reactions were run under and inert atmosphere of argon. Silica gel TLC plates (UV 254 indicator, thickness 200 mm standard grade, glass backed and 230-400 mesh from Merck) or Aluminum Oxide 60 F254 polyester basked plates (Sigma-Aldrich, 0.2 mm thick) were used. The developed TLC plate was analyzed by a UV lamp (254 nm). The plates were further analyzed with the use of an aqueous potassium permanganate stain or butanolic vanillin and developed with a heat gun. All commercially available reagents were used without further purification. A 2 wt % TPGS-750-M/H₂O solution was prepared by dissolving TPGS-750-M in degassed HPLC grade water. TPGS-750-M was made as described previously¹ and is also commercially available. Tetrahydrofuran (THF) and toluene were all taken from an Innovative Technologies Solvent Purification System (SOS) and used immediately. N.N-Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were stored over activated 4Å molecular sieves and were purchased from Fisher Scientific. K₃PO₄ tribasic was purchased from Sigma-Aldrich and used without further purification. The source of Pd(OAc)₂ was either Spectrum Chemicals or Johnson Matthey. Reagents were purchased from Sigma-Aldrich, Combi-Blocks, Alfa Aesar, or Acros Organics. n-Butyllithium was purchased from Sigma-Aldrich and was titrated with diphenylacetic acid prior to use. Flash chromatography was performed using Silicycle Silicaflash® P60 unbonded grade silica. ¹H and ¹³C NMR were recorded at 25 °C on either a Varian Unity Inova 500 MHz or a Varian Unity Inova 600 MHz spectrometers in CDCI₃ with residual CHCI₃ (¹H = 7.26 ppm, ¹³C = 77.16 ppm) as the internal standard. Chemical shifts are reported in parts per million (ppm). The data presented will be reported as follows; chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constant (if applicable) and integration. HRMS data were recorded on a Waters Micromass LCT TOF ES+ Premier mass spectrometer using ESI ionization.

Synthesis and Analytical Data for N₂Phos



 N^2 , N^2 , N^7 , N^7 -TetrabenzyInaphthalene-2, 7-diamine (A)



In solution. To an oven dried 3-neck round bottom flask equipped with a stir bar under argon were added 2,7-dibromonaphthalene (1 equiv), potassium *t*-butoxide (3 equiv), and Pd-PEPPSI-iPent (0.02 equiv). The reaction flask was evacuated and backfilled three times with argon. The flask was sealed with a rubber septum after which *N*,*N*-dibenzylamine (2.05 equiv) was added via syringe followed by anhydrous toluene (0.5 M). The reaction flask was sealed with a rubber septum and a water jacketed condenser was attached. The reaction was set to stir at 80 °C for 16 h. Upon completion, the reaction was cooled to rt. The solvent was removed under reduced pressure. The crude reaction mixture was added to a beaker and distilled H₂O was added. The suspension was set to stir for 30 min. The beakers' contents were then vacuum filtered, and the filtered material was allowed to dry. The dried mixture was transferred to a flask and sonicated with several portions of hexanes. The material was vacuum filtered and washed with hexanes and allowed to dry. The product (86% yield) was obtained as a white solid and used without any further purification.

Using Mechanochemistry. The amination was run in a 30 mL stainless steel Form Tech Scientific grinding jar (https://www.FormTechScientific.com). To the jar was added 1.72 g (6.00 mmol, 1 equiv) of 2,7-dibromonaphthalene, 2.02 g (18.0 mmol, 3 equiv) potassium t-butoxide, and 95.0 mg (0.120 mmol, 0.02 equiv) Pd-PEPPSI-IPent, and a 1/2" stainless steel ball. The jar was closed, leaving a slight gap where the two halves join together. The middle of the jar was wrapped with Parafilm and flushed with argon for several min. After this, 2.48 mL (12.3 mmol, 2.05 equiv) N,N-dibenzylamine was added by syringe through the Parafilm. The Parafilm was removed and the jar was fully sealed. The reaction vessel was placed in a modified SPEX 8000M Mixer/mill and run for 10 h at 40 °C. Afterwards, the dry, yellow-orange reaction mixture was scraped out of the vial onto a watch glass using a metal spatula. The dry reaction mixture was finely divided up using the metal spatula. This was then added to a beaker and suspended with stirring in distilled H₂O for 30 min to remove salt. The beaker's contents were then vacuum filtered and allowed to dry. The dried mixture was transferred to a recovery flask. This was sonicated in several portions of hexanes and transferred to a Buchner funnel, washed a final time with hexanes, and allowed to dry. The product (2.806 g, 90% yield) was obtained as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 7.49 (d, J = 9.0 Hz, 2H), 7.33-7.29 (m, 8H), 7.25-7.22 (m, 12H), 6.85 (dd, J = 9.0, 2.4 Hz, 2H), 6.74 (d, J = 2.4 Hz, 2H), 4.68 (s, 8H). ¹³**C** NMR (126 MHz, CDCl₃) δ 147.87, 138.82, 136.69, 128.73, 126.99, 126.96, 120.69, 112.38, 104.70, 53.96. Chemical Formula: C38H34N2: El-MS [M⁺] calcd: 518.2722; found: 518.2720.

N^2 , N^2 , N^7 , N^7 -Tetrabenzyl-1-bromonaphthalene-2,7-diamine (B)



To an oven-dried round-bottom flask under a continuous flow of argon was added the substrate. The reaction vessel was evacuated and backfilled with argon two to three times. The substrate was dissolved in DMF (0.5 M) and cooled to 0 °C with an ice bath. A solution of *N*-bromosuccinimide (1 equiv) in DMF (0.5 M relative to substrate) was added dropwise slowly into the solution with the use of an addition funnel over a period of 10 min. The resulting mixture was removed from the ice bath and set to stir for an additional 3 h. Upon completion the reaction was diluted with ether and washed with

brine (4x the volume of organic solvent) to remove DMF. The resulting organic mixture was dried with anhydrous Na₂SO₄ and reduced under pressure. The compound was used without further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.42 (s, 1H) 7.43– 7.41 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.30 – 7.28 (m, 7H), 7.28 - 7.26 (m, 4H), 7.22 – 7.16 (m, 7H), 7.14 – 7.10 (m, 2H), 6.96 (dd, J = 9.0, 2.5 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 4.73 (s, 4H), 4.17 (s, 4H). ¹³C NMR (126 MHz, CDCl₃) δ 148.15, 147.62, 138.56, 138.44, 135.09, 129.32, 128.84, 128.83, 128.80, 128.28, 127.25, 127.21, 127.04, 127.02, 125.05, 119.09, 118.41, 115.21, 106.19, 57.03, 54.81. Yield: 96%, as a tan solid. Chemical Formula: C₃₈H₃₃BrN₂: EI-MS [M⁺] calcd: 596.1827; found: 596.1824

N^2 , N^2 , N^7 , N^7 -Tetrabenzyl-1-(2,4-dimethoxyphenyl)naphthalene-2,7-diamine (C)



Aryl bromide (1 equiv), base (2 equiv), aryl boronic acid (1.5 equiv) and Pd(dppf)Cl₂ (2 mol %) were charged into a 3-neck round bottom flask under a continuous flow of argon. Upon addition of solids the flask was evacuated and then refilled with argon 3 times. Degassed toluene and water were then added to the reaction vessel in a 10:1 ratio of toluene to water. A reflux condenser was attached and the reaction was set to stir for 16 h at 80 °C. Upon completion, the reaction was diluted with EtOAc and the organic mixture was washed with water, and then brine. The resulting organic layer was dried over anhydrous Na₂SO₄ and the solvent was reduced under vacuum. The resulting crude mixture was purified via flash chromatography. ¹H NMR (500 MHz, CDCl₃) δ 7.55 (dd, *J* = 12.1, 8.8 Hz, 2H), 7.26 (d, *J* = 4.5 Hz, 2H), 7.24 (d, *J* = 0.8 Hz, 2H), 7.22 – 7.13 (m, 12H), 7.06 – 7.02 (m, 5H), 6.98 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.55 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 4.64 – 4.50 (m, 4H), 4.01 – 3.92 (m, 4H), 3.91 (s, 3H), 3.33 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 158.36, 139.27, 138.96, 135.72, 132.68, 129.05, 128.82, 128.64, 127.95, 127.34, 126.85, 126.80, 126.66, 118.53, 114.35, 105.45, 104.79, 98.57, 56.96, 55.62, 55.12, 55.10. **Yield:** 83%, as a yellow solid. **R**_f: 0.14 (10% EtOAc/hexanes) **Chemical Formula**: C₅₈H₆₃N₂O₂P EI-MS [M⁺] calcd: 859.4627; found: 850.4628.

 N^2 , N^2 , N^7 , N^7 -Tetrabenzyl-1-(3-(dicyclohexylphosphaneyl)-2,4-dimethoxyphenyl)naphthalene-2,7-diamine L1 (D; N₂Phos)



An oven dried round bottom flask was charged with substrate under a continuous flow of argon. The reaction vessel was evacuated and back-filled with argon three times. Anhydrous THF [0.2 M] was added to the reaction vessel and the reaction was cooled to 0 °C using an ice bath. n-Butyllithium ([2.3 M] in hexanes 1.2 equiv) was added to reaction dropwise via syringe over a period of 15 min. The resulting mixture was set to stir for an additional 30 min. Neat chlorodicyclohexylphosphine (1.05 equiv) was added dropwise via syringe over a period of 10 min. The reaction vessel was removed from the ice bath and set to stir for an additional 2 h. The solution was guenched with water and diluted with diethyl ether. The organic layer was washed with water and brine and dried over anhydrous Na₂SO₄. The resulting ether was concentrated under vacuum. The mixture was purified via flash chromatography utilizing basic alumina (5% EtOAc/hexanes) to afford a white solid; 75% yield; Rf = 0.28 (5% EtOAc/hexanes) on aluminum oxide plates. ¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.25 – 7.22 (m, 5H), 7.16 – 7.13 (m, 5H), 7.12 – 7.10 (m, 5H), 7.08 – 7.04 (m, 5H), 7.03 - 7.01 (m, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H),6.36 (d, J = 8.5 Hz, 1H), 4.56 – 4.48 (m, 4H), 3.99 (d, J = 14.2 Hz, 2H), 3.92 (d, J = 14.3 Hz, 2H), 3.81 (s, 3H), 3.19 (s, 3H), 2.44 (m, 1H), 1.96 (d, J = 8.4 Hz, 2H), 1.81 – 1.72 (m, 2H), 1.63 (g, J = 10.7, Hz, 3H), 1.37 – 1.27 (m, 5H), 1.24 – 1.19 (m, 2H), 1.07 – 0.95 (m, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 158.36, 139.27, 138.96, 135.72, 132.68, 129.05, 128.82, 128.64, 127.95, 127.34, 126.85, 126.80, 126.66, 118.53, 114.35, 105.45, 104.79, 98.57, 56.96, 55.62, 55.12, 55.10. ³¹P NMR (162 MHz, CDCl₃) δ -9.69. Chemical Formula: C₅₈H₆₃N₂O₂P. EI-MS [M⁺] calcd: 851.4705; found: 851.4692.

Reaction Optimization

Palladium Source Screening



¹Conversion based on ¹H NMR.

Conditions: Ligand L1:Pd (1.8:1) pre-complexed in toluene. Aryl halide (0.5 mmol), arylboronic acid or equivalent (0.75 mmol), $K_3PO_4 \cdot H_2O$ (0.75 mmol); 2 wt % TPGS-750-M/H₂O : toluene (9:1) at 45 °C.

Choice of Base



¹Conversion based on ¹H NMR.

Conditions: Ligand L1:Pd (1.8:1) pre-complexed in toluene. Aryl halide (0.5 mmol), arylboronic acid or equivalent (0.75 mmol), base (0.75 mmol); 2 wt % TPGS-750-M/H₂O : toluene (9:1) at 45 °C.

Ligand Screening



¹Conversion based on ¹H NMR.

Conditions: Ligand L1:Pd (1.8:1) pre-complexed in toluene. Aryl halide (0.5 mmol), aryl boronic acid or equivalent (0.75 mmol), base (0.75 mmol); 2 wt % TPGS-750-M/H₂O : toluene (9:1) at 45 °C.



¹Conversion based on ¹H NMR.

Conditions: Ligand L1:Pd (1.8:1) pre-complexed in toluene. Aryl halide (0.5 mmol), aryl boronic acid or equivalent (0.75 mmol), base (0.75 mmol); 2 wt % TPGS-750-M/H₂O : toluene (9:1) at 45 °C.

Pd:Ligand Optimization

(HO) ₂ B	Pd(OAc) ₂ 0. N₂Phos x	1 mol % mol %		
	2wt% TPGS-7 K ₃ PO ₄ [.] H ₂ O, 1 0.5 M, 45°	50-M/H ₂ O 0% toluene C, 6 h		
Entry	mol %	Conv (%) ¹		
1	0.1	69		
2	0.12	74		
3	0.15	84		
4	0.18	91		
5	0.2	90		
¹ Conve	ersion based on	¹ H NMR.		

Conditions: Ligand L1:Pd (X:1) pre-complexed in toluene. Aryl halide (0.5 mmol), arylboronic acid or equivalent (0.75 mmol), base (0.75 mmol); 2 wt % TPGS-750-M/H₂O : toluene (9:1) at 45 °C.

Recycle Study

The initial reaction was set up according to the general procedure. After 4 h, the reaction media was extracted three times with MTBE and the combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude reaction mixture was purified via flash chromatography.

Recycling of the surfactant solution involved first sparging the reaction vial with argon followed by addition of aryl bromide (0.5 mmol), aryl boronic acid (0.625 mmol), the base (0.5 mmol) and fresh catalyst solution (0.1 mL). The reaction vial was then flushed with argon, capped, and sealed with Teflon tape.



General procedure for catalyst solution preparation

Catalyst Preparation for SMC



To an oven dried 1-dram vile equipped with a stir bar was added Pd(OAc)₂ (2.25 mg, 0.01 mmol) and N₂Phos (14.8 mg, 0.018 mmol). The vial was capped with a 14/20 rubber septum sealed with Teflon tape. The vial was evacuated and backfilled with argon three times and left under a continuous flow of argon. Anhydrous toluene (1 mL) was added to the vile to achieve the desired Pd concentration (50 μ L of stock solution equates to 1000 ppm loading for a 0.5 mmol reaction). The mixture was set to stir for 15 min. The resulting mixture was stirred for additional 5 min. At this point the catalyst is ready and may be added to the reaction mixture.

General procedure for Suzuki-Miyaura couplings (SMC)

General Procedure for SMC reactions in aqueous TPGS-750-M



To an oven dried, 1-dram vial equipped with a magnetic stir bar was charged aryl bromide (0.5 mmol), organoboron (0.75 mmol), and potassium phosphate (0.75 mmol). The vial was fitted with a rubber septum and sealed with Teflon tape. The reaction vial was purged with argon with the use of a vent needle. At this point, a solution of 2 wt % TPGS-750-M in (0.9 mL) and toluene (50 μ L) were added, followed by the catalyst solution via syringe. The vial was placed in an aluminum heating block over a stir plate with a stir rate set to >1000 rpm with a thermocouple probe in the aluminum block set to 48 °C (this gives a temperature of 45 °C in the reaction vial). The reactions were monitored by either GC/MS or TLC analysis. Upon completion of the reaction, the vial was cooled to rt. The mixture was extracted with EtOAc and the organic layer was washed with brine three times. The layers were then

separated and the organic layer was dried over anhydrous Na₂SO₄. The mixture was concentrated under vacuum and the crude mixture was purified via flash chromatography.

General Procedure for SMC Reactions in Organic Solvent

To an oven dried 1-dram vial equipped with a magnetic stir bar was charged aryl bromide (0.5 mmol), organoboron (0.75 mmol), and potassium phosphate (0.75 mmol). The vial was fitted with a rubber septum and sealed with Teflon tape. The reaction vial was purged with argon with the use of a vent needle. Degassed organic solvent (either EtOAc or toluene) (0.8 mL), DI water (0.1 mL) and the catalyst solution were added via syringe. The vial was placed in an aluminum heating block over a stir plate with a stir rate set to >1000 rpm with a thermocouple probe in the aluminum block set to 48 °C (this gives a temperature of 45 °C in the reaction vial). The reactions were monitored by either GC/MS or TLC analysis. Upon completion of the reaction, the vial was cooled to rt. The mixture was extracted with EtOAc and the organic layer was washed with brine three times. The layers were then separated and the organic layer was dried over anhydrous Na₂SO₄. The mixture was concentrated under vacuum and the crude mixture was purified via flash chromatography.

Analytical data for products from Suzuki-Miyaura couplings



1-Methyl-5-(5-nitropyridin-2-yl)-1*H***-indole (1).** Prepared from 5-bromo-5-nitropyridine and 1methylindole-5-boronic acid according to the general procedure. ¹**H NMR** (500 MHz, CDCl₃) δ 9.48 (dd, J = 2.7, 0.7 Hz, 1H), 8.48 (dd, J = 8.8, 2.7 Hz, 1H), 8.41 (dd, J = 1.8, 0.6 Hz, 1H), 8.01 (dd, J = 8.7, 1.8Hz, 1H), 7.94 (dd, J = 8.8, 0.8 Hz, 1H), 7.44 (dt, J = 8.7, 0.8 Hz, 1H), 7.13 (d, J = 3.1 Hz, 1H), 6.61 (dd, J = 3.2, 0.9 Hz, 1H), 3.85 (s, 3H). ¹³**C NMR** (126 MHz, CDCl₃) δ 164.02, 145.40, 131.82, 130.49, 128.76, 121.53, 121.45, 119.54, 110.02, 102.66, 77.36, 33.22. **Yield**: 89%, 12 h; as a yellow solid. **R**_f: 0.31 (25% EtOAc/hexanes).



4-(2'-Fluoro-[1,1'-biphenyl]-4-yl)morpholine (2). Prepared from 4-bromophenylmorpholine and 2-fluorophenylboronic acid according to the general procedure. ¹**H NMR** (400 MHz, CDCl₃) δ 7.53 – 7.46 (m, 2H), 7.42 (td, *J* = 7.8, 1.9 Hz, 1H), 7.24 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.18 (td, *J* = 7.5, 1.4 Hz, 1H), 7.13 (ddd, *J* = 10.9, 8.0, 1.3 Hz, 1H), 7.02 – 6.95 (m, 2H), 3.91 – 3.86 (m, 4H), 3.24 – 3.20 (m, 4H). ¹³**C NMR** (101 MHz, CDCl₃) δ 150.76, 130.48, 129.95, 129.92, 128.37, 128.29, 124.43, 116.29, 116.06, 115.43, 67.03, 49.13. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -118.30 (dddt, *J* = 11.2, 8.3, 4.9, 1.7 Hz). **Yield**: 93%, as a white solid. **R**_f: 0.24 (15% EtOAc/hexanes).



2-(Benzofuran-2-yl)-6-methyl-3-nitropyridine (3). Synthesized with 2-bromo-3-nitro-6-methyl-pyridine and benzofuran-2-phenyl boronic acid according to the general procedure. ¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.3 Hz, 1H), 7.68 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.38 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 2.71 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 162.12, 155.82, 151.26, 141.09, 134.18, 132.24, 128.03, 126.27, 123.60, 122.71, 122.69, 122.15, 112.01, 109.33, 24.83, 24.50. **Yield:** 94%, as a yellow solid. **R**_f: 0.35 (25% EtOAc/hexanes).



6-(4-(Trifluoromethoxy)phenyl)benzo[*d***][1,3]dioxole-5-carbaldehyde (4).** Synthesized with 5-Bromopiperonal and 4-trifluoromethoxypehnyl boronic acid according to the general procedure. ¹**H NMR** (500 MHz, CDCl₃) δ 9.73 (s, 1H), 7.47 (s, 1H), 7.38 – 7.36 (m, 2H), 7.31 – 7.29 (m, 2H), 6.82 (s, 1H), 6.10 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 190.15, 152.35, 149.35, 148.27, 142.04, 136.37, 131.62, 129.04, 121.62, 120.96, 120.95, 110.33, 106.64, 102.39, ¹⁹F NMR (376 MHz, CDCl₃) δ -57.85; **Yield**: 92%, as a white solid. **R**_f**:** 0.30 (15% EtOAc/hexanes).



t-Butyl 2-(2-morpholinopyrimidin-5-yl)-1*H*-indole-1-carboxylate (5). Synthesized with 4-(5-bromopyrimidin-2-yl)morpholine and (1-(*t*-butoxycarbonyl)-1H-indol-2-yl) boronic acid according to the general procedure. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (s, 2H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.21 (m, 2H), 6.55 (s, 1H), 3.90 – 3.82 (m, 4H), 3.83 – 3.75 (m, 4H), 1.50 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 160.84, 157.27, 150.23, 137.27, 135.08, 129.25, 124.67, 123.27, 120.56, 117.87, 115.85, 110.63, 84.28, 66.96, 44.49, 28.11. **Yield:** 78%, 24 h as a white solid; **R**_f: 0.20 (15% EtOAc/hexanes).



6-(Benzofuran-2-yl)benzo[*d*][1,3]dioxole-5-carbaldehyde (6). Synthesized from 5-bromopiperanal and benzofuran-2-phenylboronic acid according to the general procedure. ¹H NMR (500 MHz, CDCl₃) δ 10.27 (s, 1H), 7.64 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.54 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.50 (s, 1H), 7.36 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.29 (td, *J* = 7.5, 1.0 Hz, 1H), 7.23 (s, 1H), 6.87 (d, *J* = 1.0 Hz, 1H), 6.12 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 190.21, 155.47, 152.43, 152.36, 149.01, 130.65, 129.86, 128.69, 125.31, 123.53, 121.42, 111.54, 108.89, 108.13, 107.05, 102.55. **Yield**: 91%, 8 h, as a white solid. **R**_f: 0.31 (15% EtOAc/hexanes).



4-((2'-Methyl-[1,1'-biphenyl]-4-yl)sulfonyl)morpholine (7). Synthesized with 4-((4-bromophenyl)-sulfonyl)morpholine and methyl phenyboronic acid according to the general procedure. ¹H NMR (500 MHz, CDCl₃) δ 7.82 – 7.79 (d, 2H), 7.52 – 7.49 (d, 2H), 7.34 – 7.27 (m, 3H), 7.22 (dd, *J* = 7.2, 1.3 Hz, 1H), 3.80 – 3.76 (m, 4H), 3.10 – 3.04 (m, 4H), 2.27 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 147.22, 140.08, 135.28, 130.79, 130.07, 129.64, 128.39, 127.88, 126.21, 105.14, 66.30, 46.20, 20.51. Yield: 81%, 16 h, as a white solid. **R**_f: 0.55 (40% EtOAc/hexanes). **Chemical Formula:** C₁₇H₁₉NO₃S El-MS [M]⁺ calcd: 317.1086; found: 372.1253 [M+Na+MeOH]⁺.



2-(4-Methoxy-2-methylphenyl)-6-methyl-3-nitropyridine (8). Synthesized with 2-Bromo-6-methyl-3-nitropyridine and 2-methyl-4-methoxyphenyl boronic acid according to the general procedure. ¹H NMR

(500 MHz, CDCl₃) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.28 (dd, *J* = 8.3, 0.5 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.82 (dt, *J* = 2.8, 0.6 Hz, 1H), 6.79 (ddd, *J* = 8.3, 2.6, 0.6 Hz, 1H), 3.83 (s, 3H), 2.69 (s, 3H), 2.16 (s, 3H). ¹³**C NMR** (126 MHz, CDCl₃) δ 162.72, 160.17, 153.79, 137.51, 132.52, 129.69, 129.49, 122.13, 116.14, 111.47, 55.39, 24.95, 19.90. **Yield**: 91%, 8 h, as a yellow solid **R**_f: 0.20 (25% EtOAc/hexanes).



4-(5-(2-Fluorophenyl)pyrimidin-2-yl)morpholine (9). Synthesized with 4-(5-bromopyrimidin-2-yl)morpholine and 2-fluorophenyl boronic acid according to the general procedure. ¹**H NMR** (500 MHz, CDCl₃) δ 8.55 (d, J = 2.9 Hz, 2H), 8.54 (d, J = 1.6 Hz, 2H), 7.39 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 7.23 – 7.20 (m, 1H), 7.16 (m, 1H), 3.87 (dd, J = 5.7, 3.9 Hz, 4H), 3.79 (dd, J = 5.6, 3.9 Hz, 4H). ¹³**C NMR** (126 MHz, CDCl₃) δ 157.48, 157.45, 129.47, 129.44, 129.32, 129.25, 124.88, 124.85, 116.49, 116.31, 105.14, 66.98, 44.46. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -117.81 (dt, J = 7.7, 2.8 Hz). **Yield**: 83%, 22 h, as a white solid. **R**_f: 0.50 (25% EtOAc/hexanes). **Chemical Formula:** C₁₄H₁₄FN₃O El-MS [M]⁺ calcd: 259.1121; found: 260.1196.



4-Chloro-2',4'-difluoro-[1,1'-biphenyl]-3-carbaldehyde (10) Synthesized with 3-bromo-6chlorobenzalsehyde and 2,4-difluorophenyl boronic acid according to the general procedure. The pinacol ester of the boronic acid was also employed. ¹H NMR (500 MHz, CDCl₃) δ 9.84 (d, J = 3.0 Hz, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.63 (dd, J = 8.2, 2.3 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.03 (m, 1H), 6.98 – 6.94 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 190.02, 136.18, 135.47, 133.89, 132.96, 132.74, 132.71, 132.67, 132.63, 128.13, 112.24, 112.21, 112.07, 112.04, 104.74, 104.54, 104.33. ¹⁹F NMR (376 MHz, CDCl₃) δ -108.22 (qd, J = 8.3, 6.2 Hz), -110.85 (dd, J = 9.0, 2.9 Hz). **Yield:** 92% with the boronic acid. 94% as the pinacol ester as a white solid. **R**_f: 0.54 (15% EtOAc/hexanes).



Methyl 4-hydroxy-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-carboxylate (11). Synthesized with methyl 5-hydroxy-2-iodobenzoate and 4-trifluoromethoxyphenylboronic acid according to the general procedure. ¹H NMR (500 MHz, MeOH- d_4) δ 7.71 – 7.68 (m, 2H), 7.58 – 7.55 (m, 2H), 7.40 – 7.37 (m, 1H), 7.31 (dq, J = 7.8, 1.0 Hz, 2H), 3.90 (s, 3H). ¹³C NMR (126 MHz, MeOH- d_4) δ 166.90, 154.27, 136.93, 130.64, 130.33, 130.25, 120.55, 120.13, 116.34, 106.82, 51.20. ¹⁹F NMR (376 MHz, CDCl₃) δ -57.79. Yield: 83%, as a pale yellow solid. **R**_f: 0.45 (40% EtOAc/hexanes).



Methyl 6-(2,4-dimethylphenyl)-2-naphthoate (12). Synthesized with methyl 6-bromo-2-naphthoate and 2,4-methylphenylbornoc acid according to the general procedure. ¹**H NMR** (500 MHz, CDCl₃) δ 8.66 – 8.62 (m, 1H), 8.08 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.99 – 7.96 (m, 1H), 7.89 (dt, *J* = 8.6, 0.7 Hz, 1H), 7.79 (t, *J* = 1.1 Hz, 1H), 7.53 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.13 (m, 1H), 7.11 (m, 1H), 4.00 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H). ¹³**C NMR** (126 MHz, CDCl₃) δ 167.42, 142.21, 138.60, 137.56, 135.60, 135.39, 131.39, 130.99, 129.98, 129.04, 128.89, 128.32, 127.80, 127.39, 126.79, 125.66, 77.41, 77.16, 76.91, 52.37, 21.24, 20.57. **Yield:** 96%, 1.5 h as a white solid. **R**_f: 0.50 (25% EtOAc/hexanes).



1-(2-Fluoro-5-(1-methyl-1*H***-indol-6-yl)phenyl)pyrrolidin-2-one (13).** Synthesized from 1-(5-bromo-2-fluorophenyl)pyrrolidine-2-one and 1-methylindole-5-boronic acid according to the general

procedure. ¹**H NMR** (500 MHz, CDCl₃) δ 7.79 – 7.77 (m, 1H), 7.65 (dd, *J* = 7.3, 2.4 Hz, 1H), 7.50 (ddd, *J* = 8.4, 4.6, 2.3 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.37 – 7.35 (m, 1H), 7.20 (dd, *J* = 10.5, 8.6 Hz, 1H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 3.88 (t, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 2.61 (t, *J* = 8.0 Hz, 2H), 2.24 (p, *J* = 7.5 Hz, 2H). ¹³**C NMR** (126 MHz, CDCl₃) δ 174.91, 139.53, 132.69, 131.36, 129.76, 129.06, 127.20, 127.14, 126.73, 126.71, 121.36, 119.56, 116.90, 109.61, 101.48, 50.30, 33.09, 31.32, 19.22. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -124.22 (ddd, *J* = 11.1, 7.3, 4.7 Hz).

Yield: 80% 36 h as a tan solid. Rf: 0.24 (40% EtOAc/hexanes).



2-(4-(Trifluoromethyl)phenyl)benzo[*b***]thiophene (14)** Synthesized with benzothiophene-2-bornic acid and 4-trifluoromethylphenyl boronic acid according to the general procedure. ¹H NMR (500 MHz, CDCl₃) δ 7.87 – 7.84 (m, 1H), 7.82 (m, 3H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 0.7 Hz, 1H), 7.37 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 140.57, 126.75, 126.11, 126.08, 125.14, 124.96, 124.11, 123.80, 122.52, 121.41, 121.19. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.64. **Yield:** 87%, 16 h, as a white solid. **R**_f: 0.60 (25% EtOAc/hexanes).



5-Methyl-2-vinylpyridine (15). Prepared from 2-boromo-5-methylpyridine and potassium vinyltrifluoroborate according to the general procedure. ¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 7.41 (d, *J* = 9.0, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 6.78 (dd, *J* = 11.0, 17.5, 1H), 6.12 (dd, *J* = 17.5, 1H), 5.41 (d, *J* = 11.0 Hz, 1H) 2.31 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 153.51, 149.69, 138.03, 137.03, 132.38, 121.40, 117.15, 20.22. Yield: 89%, as a colorless oil. **R**_f: 0.20 (10% EtOAc/hexanes).



2,4-Dimethoxy-5-(5-methylpyridin-2-yl)pyrimidine (16). Prepared from 2-bromo-5-methylpyridine and (2,4-dimethoxypyrimidin-5-yl)boronic acid MIDA ester according to the general procedure. ¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1H), 8.52 – 8.48 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.1, Hz, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 2.37 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.96, 159.54, 150.18, 149.16, 136.94, 131.93, 123.56, 114.90, 110.16, 55.13, 54.32, 29.86. Yield: 87%, as a white solid. **R**_f: 0.30 (40% EtOAc/hexanes).



2,2'-(2,2'-bis(Methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(benzofuran) (17) Synthesized with 3,3'-diiodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene and benzofuran-2-boronic acid according to the general procedure. ¹H NMR (400 MHz, CDCl₃) δ 8.68 (s, 2H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.69 – 7.55 (m, 6H), 7.47 (t, *J* = 7.1 Hz, 2H), 7.29 (m, 8H), 4.81-4.53 (m, 4H), 2.56 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 154.6,152.3, 150.0, 134.0, 130.9, 129.2, 128.7, 128.1, 127.4, 126.7, 126.5, 125.9, 124.9, 124.2, 123.1, 121.6,111.1, 107.1, 98.7, 56.7. Yield: 79%, 24 h as a white solid. **R**_f: 0.40 (25% EtOAc/hexanes).



3-(2',4'-Difluoro-[1,1'-biphenyl]-4-yl)-5-isopropyl-1,2,4-oxadiazole (18). Prepared from 3-(4bromophenyl)-5-isopropyl-1,2,4-oxadiazole and 2,4-difluorophenylbornic acid according to the general procedure. ¹H NMR (400 MHz, CDCl₃) δ 8.21 – 8.13 (d, *J* = 8.4 2H), 7.64 (d, *J* = 1.7 Hz, 2H), 7.48 (td, *J* = 8.7, 6.4 Hz, 1H), 7.04 – 6.93 (m, 2H), 3.33 (hept, *J* = 7.0 Hz, 1H), 1.50 (d, *J* = 7.0 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 184.17, 168.00, 131.60, 129.45, 129.42, 127.73, 126.52, 112.03, 111.81, 104.71, 27.73, 20.39. ¹⁹F NMR (376 MHz, CDCl₃) δ -110.51 (p, *J* = 7.8 Hz), -113.12 (q, *J* = 9.1 Hz). **Yield**: 81%, as a white solid. **R**_f: 0.25 (5% EtOAc/hexanes).



4-Methoxy-4'-pentyl-1,1'-biphenyl (21). Synthesized from 4-chloroanisole and 4-pentylphenylboronic acid according to the general procedure (Pd(OAc)₂ 0.25 mol%). ¹**H NMR** (600 MHz, CDCl₃) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 2.65 – 2.62 (m, 2H), 1.67 – 1.63 (m, 2H), 1.38 – 1.34 (m, 4H), 0.93 – 0.90 (m, 3H). ¹³**C NMR** (151 MHz, CDCl₃) δ 141.60, 138.29, 133.92, 128.92, 128.11, 126.70, 114.28, 108.93, 77.37, 77.16, 76.95, 55.48, 35.70, 31.72, 31.37, 22.73, 14.20. **Yield**: 83%, as a white solid. **R**_f: 0.30 (5% EtOAc/hexanes).



4'-Methoxy-2'-methyl-[1,1'-biphenyl]-4-carbonitrile (22). Synthesied from 4-chlorobenzonitrole and 2-methyl-4-methoxyphenyl boronic acid according to the general procedure (Pd(OAc)₂ 0.25 mol%). ¹**H NMR** (600 MHz, CDCl₃) δ 7.68 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.84 – 6.81 (m, 2H), 3.84 (s, 3H), 2.26 (s, 3H). ¹³**C NMR** (151 MHz, CDCl₃) δ 159.63, 146.69, 136.70, 132.74, 132.04, 130.79, 130.29, 119.19, 116.20, 111.63, 110.42, 77.37, 77.16, 76.95, 55.44, 20.79. **Yield**: 94%, as a yellow solid. **R**_f: 0.25 (10% EtOAc/hexanes).



2-Fluoro-3'-methyl-1,1'-biphenyl (23). Synthesized from 3-chlorotoluene and 2-fluorophenyl boronic acid according to the general procedure (Pd(OAc)₂ 0.25 mol%). ¹**H NMR** (500 MHz, CDCl₃) δ 7.44 (m, *J* = 7.8, 1.8 Hz, 1H), 7.39 – 7.34 (m, 3H), 7.33 – 7.29 (m, 1H), 7.21 (m, *J* = 7.5, 1.4 Hz, 2H), 7.15 (m, *J* = 11.0, 8.2, 1.5 Hz, 1H), 2.43 (s, 3H). ¹³**C NMR** (126 MHz, CDCl₃) δ 138.16, 135.90, 130.96, 129.91, 129.00, 128.46, 126.28, 124.42, 116.27, 116.09, 21.65. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -117.96 (m). **Yield**: 87%, as a colorless oil. **R**_f: 0.35 (5% Et₂O/hexanes).



(*E*)-5-Nitro-2-styrylpyridine (24). Synthesized with 2-chloro-5-nitropyridine and (*E*)-phenethylboronic acid according to the general procedure. ¹H NMR (500 MHz, CDCl₃) δ 9.43 – 9.40 (m, 1H), 8.44 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.87 (d, *J* = 16.0 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.50 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.24 (d, *J* = 15.9 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 161.09, 145.59, 138.26, 131.92, 129.78, 129.10, 127.89, 125.92, 121.78, 105.15. Yield: 93%, 16 h, as a yellow solid. **R**_f: 0.40 (25% EtOAc/hexanes).



3-(3-((2-Fluorobenzyl)oxy)phenyl)-2-methylpyridine (25). Synthesized from 3-chloro-2-methylpyridine and 3-((2-fluorobenzyl)oxy)phenyl boronic acid according to the general procedure (Pd(OAc)₂ 0.25 mol%). ¹**H NMR** (400 MHz, CDCl₃) δ 8.50 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.39 – 7.29 (m, 2H), 7.20 – 7.15 (m, 2H), 7.09 (ddd, *J* = 9.6, 8.2, 1.1 Hz, 1H), 7.04 – 7.00 (m, 1H), 6.95 – 6.91 (m, 2H), 5.17 (s, 2H), 2.49 (s, 3H). ¹³C **NMR** (101 MHz, CDCl₃) δ 161.81, 158.58, 155.96, 148.16, 141.55, 137.20, 136.87, 129.97, 124.45, 124.41, 122.06, 121.09, 115.83, 113.94, 110.15, 63.94, 23.51. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -118.53 (ddd, *J* = 10.3, 7.4, 5.5 Hz). **Yield**: 91%, 16 h, as a yellow oil. **R**_f: 0.21 (25% EtOAc/hexanes).

2-Methoxy-3-(pyren-1-yl)pyridine (26). Synthesized from and pyrene boronic acid according to the general procedure (Pd(OAc)₂ 0.25 mol%). ¹**H NMR** (600 MHz, CDCl₃) δ 8.34 (dd, *J* = 5.1, 1.9 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 8.19 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.16 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.09 (s, 2H), 8.02 – 7.98 (m, 2H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.71 (dd, *J* = 7.1, 1.9 Hz, 1H), 7.10 (dd, *J* = 7.1, 5.1 Hz, 1H), 3.89 (s, 3H). ¹³**C NMR** (151 MHz, CDCl₃) δ 161.91, 146.59, 140.74, 132.31, 131.51, 131.17, 131.07, 129.24, 127.99, 127.72, 127.59, 127.54, 126.13, 125.36, 125.33, 125.18, 124.93, 124.70, 124.13, 116.94, 53.74. **Yield:** 91%, as a white solid. **R**_f: 0.25 (10% EtOAc/hexanes) **Chemical Formula**: C₂₂H₁₅NO El-MS [M]⁺ calcd: 310.1232; found: 310.1227.



5-Chloro-2-(2,4-dimethoxyphenyl)-*N*-(1-(3-methoxyphenyl)ethyl)pyrimidin-4-amine (27). Synthesized from 2,5-dichloro-*N*-(1-(3-methoxyphenyl)ethyl)pyrimidin-4-amine and 2,4-dimethoxyphenylboronic acid according to the general procedure (Pd(OAc)₂ 0.25 mol %). ¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 7.67 – 7.62 (m, 1H), 7.36 – 7.30 (m, 2H), 6.92 – 6.87 (m, 2H), 6.54 (m, 2H), 5.43 (dt, J = 13.6, 7.3 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 1.62 (d, J = 6.5 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 163.00, 162.09, 159.29, 158.96, 156.66, 152.59, 135.82, 133.12, 127.61, 121.32, 114.11, 111.79, 104.72, 99.40, 77.36, 56.14, 55.56, 55.45, 49.59, 22.09. Yield: 76%, as a tan solid. **R**_f: 0.25 (30% Et₂O in hexanes) **Chemical Formula:** C₂₁H₂₂ClN₃O₃ El-MS [M]⁺ calcd: 399.1350; found: 401.1360 [M+2H].



Isopropyl-2-(4-(2',4'-dimethyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)-2-methylpropanoate (28). Synthesized from isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate and 2,4-dimethylphenylboronic acid according to the general procedure (Pd(OAc)₂ 0.25 mol%). ¹H NMR (500 MHz, CDCl₃) δ 7.83 – 7.78 (m, 4H), 7.42 – 7.39 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 2.6 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.7 Hz, 1H), 5.10 (h, *J* = 6.2 Hz, 1H), 3.85 (s, 3H), 2.30 (s, 3H), 1.67 (s, 6H), 1.21 (d, *J* = 6.3 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 195.42, 173.33, 159.63, 159.31, 145.80, 136.86, 136.33, 133.69, 132.15, 130.93, 130.89, 129.84, 129.40, 117.35, 116.07, 111.45, 105.14, 79.52, 69.45, 55.43, 25.54, 21.68, 20.93. Yield: 92%, 12 h, as a white solid. **R**_f: 0.45 (25% EtOAc/hexanes). **Chemical Formula:** C₂₈H₃₀O₄ EI-MS [M⁺ calcd: 430.2144. found: 430.2143.



Isobutyl 2-(5-methoxy-1-(4'-methoxy-2'-methyl-[1,1'-biphenyl]-4-carbonyl)-2-methyl-1*H***-indol-3yl)acetate (29a). Synthesized from isobutyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1***H***-indol-3yl)acetate and 2-methyl-4-methoxyphenyl boronic acid (Pd(OAc)₂ 0.25 mol %). ¹H NMR (500 MHz, CDCl₃) \delta 7.76 – 7.72 (m, 2H), 7.44 – 7.40 (m, 2H), 7.21 (d,** *J* **= 8.2 Hz, 1H), 7.00 (d,** *J* **= 6.0 Hz, 1H), 6.99 (s, 1H), 6.86 – 6.82 (m, 2H), 6.69 (dd,** *J* **= 9.1, 2.5 Hz, 1H), 3.89 (d,** *J* **= 6.6 Hz, 2H), 3.85 (d,** *J* **= 2.1 Hz, 6H), 3.69 (s, 2H), 2.42 (s, 3H), 2.30 (s, 3H), 1.92 (dp,** *J* **= 13.4, 6.7 Hz, 1H), 0.90 (d,** *J* **= 6.7 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 171.17, 169.52, 159.46, 156.06, 146.68, 136.79, 136.04, 133.71, 133.32, 131.20, 130.88, 130.70, 129.89, 129.80, 116.14, 115.18, 112.51, 111.81, 111.54, 101.23, 71.20, 55.85, 55.44, 30.64, 27.87, 20.92, 19.18, 13.49. Yield: 88%, 12 h, as a yellow solid. R**_f: 0.43 (25% EtOAc/hexanes). **Chemical Formula**: C₃₁H₃₃NO₅ EI-MS [M]⁺ calcd: 499.2359, found: 499.2351.



Isobutyl 2-(5-methoxy-2-methyl-1-(4-(1-methyl-1*H*-indol-5-yl)benzoyl)-1*H*-indol-3-yl)acetate (29b). Synthesized from isobutyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate and 1-methylindole-5-boronic acid (Pd(OAc)₂ 0.25 mol%). ¹H NMR (600 MHz, CDCl₃) δ 7.92 (s, 1H), 7.78 – 7.73 (m, 4H), 7.53 (dt, *J* = 8.5, 1.6 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.11 – 7.08 (m, 1H), 7.01 – 6.97 (m, 2H), 6.67 (dt, *J* = 9.0, 1.9 Hz, 1H), 6.57 – 6.54 (m, 1H), 3.88 (dd, *J* = 6.6, 1.5 Hz, 2H), 3.83 (d, *J* = 1.5 Hz, 6H), 3.68 (s, 2H), 2.43 (d, *J* = 1.5 Hz, 3H), 1.91 (hept, *J* = 13.4, 6.7, 1.4 Hz, 1H), 0.89 (d, *J* = 6.7, 1.4 Hz, 6H). ¹³C NMR (151 MHz, CDCl₃) δ 171.24, 169.58, 155.97, 147.36, 136.15, 133.10, 131.24, 130.61, 130.03, 129.19, 127.43, 121.32, 119.99, 115.20, 112.27, 111.75, 109.88, 108.92, 101.77, 101.17, 71.19, 55.85, 33.15, 30.67, 27.88, 19.19, 13.45. Yield: 80%, 16 h, as a yellow solid. **R**r: 0.40 (20% EtOAc/hexanes). **Chemical Formula:** C₃₂H₃₂N₂O₄ El-MS [M]+ calcd: 508.2362; found: 509.2369 [M+H].



5-(2,4-Dimethylphenyl)-N-((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5-

yl)methyl)thiophene-2-carboxamide (30). Synthesized from rivaroxaban and 2,4-dimethylphenylboronic acid. DMSO 10% v/v used as a co-solvent at 60 °C with 0.5 mol % loading of palladium. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.86 (t, *J* = 5.9 Hz, 1H), 7.76 (d, *J* = 3.8 Hz, 1H), 7.55 - 7.52 (m, 2H), 7.39 – 7.36 (m, 2H), 7.26 (d, J = 7.8 Hz, 1H), 7.15 (d, J = 3.8 Hz, 1H), 7.11 (s, 1H), 7.04 (dd, J = 8.0, 1.7 Hz, 1H), 4.83 (dd, J = 8.9, 5.5 Hz, 1H), 4.16 (s, 2H), 3.94 – 3.91 (m, 2H), 3.68 – 3.65 (m, 2H), 3.60 (t, J = 5.6 Hz, 2H), 2.32 (s, 3H), 2.26 (s, 3H). ¹³**C NMR** (101 MHz, DMSO-*d*₆) δ 165.95, 161.73, 154.14, 147.14, 138.31, 137.95, 137.04, 136.51, 135.10, 131.66, 130.00, 129.72, 128.75, 127.20, 126.92, 125.93, 118.32, 71.41, 67.72, 63.46, 49.00, 47.46, 42.18, 20.77, 20.63. **Yield**: 68%, as a white solid. **R**_f: 0.20 (5% methanol in DCM). **Chemical Formula:** C₂₇H₂₇N₃O₅S EI-MS [M]⁺ calcd: 505.1671; found: 538.2104 [M+MeOH+H].



N-(4-(*N*-(Cyclohexylcarbamoyl)sulfamoyl)phenethyl)-3'-((2-fluorobenzyl)oxy)-4-methoxy-[1,1'biphenyl]-3-carboxamide (31). Prepared from glibenclamide and (3-((2-fluorobenzyl)oxy)phenyl) boronic acid. DMSO was used as a co-solvent at 55 °C with 0.5 mol % loading of palladium. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.30 (bs, 3H), 8.23 (t, J = 5.7 Hz, 1H), 8.03 (s, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 2.8 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.45 (m, 3H), 7.42 – 7.34 (m, 2H), 7.22 (m, 2H), 7.11 (d, J = 8.9 Hz, 1H), 6.34 (d, J = 7.8 Hz, 1H), 5.09 (s, 1H), 3.76 (s, 3H), 3.51 (q, J = 6.7 Hz, 2H), 2.89 (t, J = 7.0 Hz, 2H), 1.56 (m, 4H), 1.46 – 1.41 (m, 1H), 1.23 – 0.99 (m, 6H). ¹³C NMR (101 MHz, DMSO*d*₆) δ 163.67, 157.58, 155.70, 150.52, 145.20, 138.24, 131.53, 130.59, 130.33, 130.24, 129.52, 129.30, 128.66, 127.32, 126.86, 124.82, 124.55, 124.34, 124.00, 119.87, 116.54, 115.48, 115.28, 114.15, 109.59, 63.27, 56.23, 48.08, 40.20, 34.68, 32.30, 25.01, 24.20. ¹⁹F NMR (376 MHz, DMSO*d*₆) δ -118.53 (ddd, J = 10.3, 7.4, 5.5 Hz). **Yield:** 61%, as a white solid. **R**_f**:** 0.15 (10% methanol in DCM). **Chemical Formula**: C₃₆H₃₈FN₃O₆S EI-MS [M]+ calcd: 659.2465; found: 692.3128 [M+H+MeOH].

General Procedure for Hydration of Alkynes

Precatalyst N₂Phos-gold(I) chloride synthesis was performed as previously described.¹

Gold pre-catalyst synthesis. N₂Phos-gold(I) chloride (0.9 mg, 0.001 mmol) and silver(I)hexafluoroantimonate (0.7 mg, 0.002 mmol) were charged under an inert atmosphere (glovebox) into a 1-dram vial containing a Teflon-coated magnetic stir bar and a rubber septum. The vial was covered with aluminum foil to protect it from light. Anhydrous DCM (1 mL) was added and the solution was stirred for 15 min.

1-Pot reaction set-up. To a dried 1-dram vial was added, under an argon atmosphere, 0.2 mL of the gold pre-catalyst solution (1000 ppm or 0.1 mol %). DCM was evaporated under argon. Alkyne (0.2 mmol, 1.0 equiv) was added to the vial, followed by toluene (20 μ L), a 3 wt % TPGS-750-M/H₂O solution (0.2 mL, 1.0 M), and trifluoroacetic acid (46 mg, 0.4 mmol, 2.0 equiv). The resulting mixture was stirred at rt for 24 h. The reaction was then extracted with EtOAc. The organic layer was washed with H₂O, dried over anhydrous MgSO₄ and concentrated under vacuum. The products were purified by flash chromatography (100:0 → 80:20 hexanes/EtOAc).



¹ Klumphu, P. *et al.* Micellar catalysis-enabled sustainable ppm Au-catalyzed reactions in water at room temperature. *Chem. Sci.* **8**, 6354–6358 (2017).

Analytical Data for Products from Hydration of Alkynes



Benzylacetone. Synthesized according to general procedure B. ¹H NMR (600 MHz, CDCl₃) δ 7.30 (dd, J = 8.6, 6.6 Hz, 2H), 7.23 – 7.18 (m, 3H), 2.91 (t, J = 7.7 Hz, 2H), 2.78 (dd, J = 8.3, 7.0 Hz, 2H), 2.15 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 208.1, 141.1, 128.6, 128.4, 126.2, 45.3, 30.2, 29.9, 6.6. **Yield:** 95%, as a colorless oil. **R**_f: 0.65 (20% EtOAc/hexanes) – UV + CAM stain.



N,*N*-Dimethylaminoacetophenone. Synthesized according to general procedure B. ¹H NMR (600 MHz, CDCl₃) δ 7.90 – 7.84 (m, 2H), 6.69 – 6.62 (m, 2H), 3.08 – 3.04 (m, 6H), 2.51 (t, *J* = 0.9 Hz, 3H).¹³C NMR (151 MHz, CDCl₃) δ 196.4, 153.5, 130.6, 125.4, 110.7, 40.1, 26.1. Yield: 97%, as a white powder. **R**_f: 0.35 (8:2 hexanes/EtOAc) – UV + CAM stain.



1-(6-Methoxynaphthalen-2-yl)ethan-1-one. Synthesized according to general procedure B. ¹H NMR (600 MHz, CDCl₃) δ 8.40 (s, 1H), 8.01 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.21 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 3.95 (s, 3H), 2.70 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 198.0, 159.9, 137.4, 132.8, 131.2, 130.2, 128.0, 127.2, 124.8, 119.9, 105.9, 55.6, 26.7. **Yield:** 53%, as a beige solid. **R**f: 0.46 (20% EtOAc/hexanes) – UV + CAM stain.



1-Acetyl-1-cyclohexene. Synthesized according to general procedure B. ¹**H NMR** (600 MHz, CDCl₃) δ 6.93 – 6.87 (m, 1H), 2.27 (t, *J* = 1.1 Hz, 3H), 2.27 – 2.18 (m, 4H), 1.68 – 1.55 (m, 4H). ¹³**C NMR** (151 MHz, CDCl₃) δ 199.6, 141.1, 139.8, 26.2, 25.3, 23.1, 22.0, 21.6. **Yield:** 90%, as a colorless oil. **R**_f: 0.33 (15% EtOAc/hexanes) CAM stain.

Procedure for the 1-pot process



ADH-101¹⁻³ is commercially available within the enzyme kit EZK-001 from Johnson Matthey. NAD⁺ was purchased from Bioworld and NADP⁺ was purchased from Chem-Impes. Isopropanol was purchased from VWR. All other commercially available reagents were used without further purification. To a 2-dram vial equipped with a stir bar was added the ketone (0.2 mmol, 1 equiv), MgSO₄ (0.8 mg), NAD⁺ (2.6 mg) and NADP⁺ (2.4 mg). *i*-PrOH (0.1 mL) and a [0.2 M] phosphate buffer solution at pH = 7 (0.7 mL) and 2 wt % aqueous TPGS-750-M were added. ADH-101 (20 mg) was then added. The reaction was set to stir at 37 °C for 16 h. The reaction was monitored by HPLC. Upon completion, the reaction was charged with the arylboronic acid (0.3 mmol, 1.5 equiv) and potassium phosphate (0.3 mmol, 1.5 equiv). The reaction vial was fitted with a rubber septum and sealed with Teflon tape. The reaction vial was purged with argon with the use of a vent needle. At this point a solution of Pd(OAc)₂ and N₂Phos in toluene (0.05 mL) was added via syringe. The reaction was set to stir at 45 °C and monitored by

either GC/MS or TLC analysis. Upon completion of the reaction, carbonyl Fe powder (CIP, 5 equiv) and HCI (3 equiv) was added to the reaction vial. The reaction was set to stir at rt and monitored by TLC analysis. Upon completion, the reaction was extracted with EtOAc and the organic layer was washed with brine three times. The layers were then separated and the organic layer was dried over anhydrous Na₂SO₄. The mixture was concentrated under vacuum and then purified via flash chromatography (40% EtOAc in hexanes). **1H NMR** (400 MHz, CDCl₃) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.90 (t, *J* = 2.0 Hz, 1H), 6.68 (dd, *J* = 7.9, 1.4 Hz, 1H), 4.95 (q, *J* = 6.5 Hz, 1H), 3.74 (s, 2H), 1.54 (d, *J* = 6.5 Hz, 3H). ¹³**C NMR** (101 MHz, CDCl₃) δ 146.84, 144.88, 142.20, 140.77, 129.83, 127.35, 125.87, 117.75, 114.24, 113.94, 70.35, 25.27. **Yield**: 81%, as a yellow solid. **R**_f: 0.33 (40% EtOAc in hexanes). **Chemical Formula**: C14H15NO EI-MS [M]⁺ calcd: 213.1154; found: 213.1147.

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¹H, ¹³C, ³¹P and ¹⁹F NMR of synthesized products



























































































11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 fl (ppm)





Fig. 2: ¹³C NMR spectra of benzylacetone



Fig. 3: ¹H NMR spectra of N-dimethylaminoacetophenone



Fig. 4: ¹³C NMR spectra of N-dimethylaminoacetophenone



... 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 fl (ppm)





Fig. 6: ¹³C NMR spectra of 1-(6-methoxynaphthalen-2-yl)ethan-1-one



... 0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 f1 (ppm)

Fig. 7 :¹H NMR spectra of 1-acetyl-1-cyclohexene



Fig. 8: ¹³C NMR spectra of 1-acetyl-1-cyclohexene

