2.4 EXPERIMENTAL SECTION

2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Unless otherwise stated, chemicals and reagents were used as received. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or CAM staining. Flash column chromatography was performed as described by Still et al.[29] using silica gel (particle size 0.032-0.063) purchased from Silicycle. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm). ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), and $CDCl_3$ (^{13}C, $\delta = 77.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent.

2.4.2. Starting Materials Synthesis

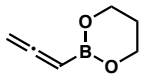
General Procedure for Synthesis of Boronates

According to the procedure of Schaus and coworkers,[22] $HgCl_2$ (0.17 mmol, 0.0017 equiv) and magnesium turnings (101 mmol, 1.01 equiv) were added to a 3-necked flask and flame dried under vacuum. To this were added dry Et_2O (15 mL) and 5% of the total propargyl bromide solution (80% wt in toluene, 5 mmol, 0.05 equiv). When the ether refluxed, the solution was cooled in an ice-salt bath. In a separate flame dried flask, the remainder of the propargyl bromide solution (95 mmol, 0.95 equiv) was dissolved in dry Et_2O (45 mL). The remainder of the propargyl bromide solution was added slowly to the flask with Mg^0. The ice bath was removed and the solution stirred 2 h at room temperature. The resulting allenyl Grignard reagent was titrated with 1,10-phenanthroline.

To a flame-dried flask were added $B(OMe)_3$ (100 mmol, 1.0 equiv) and Et_2O (100 mL). The solution was cooled to -78 ˚C and allenylmagnesium bromide solution added dropwise over 45 min. The reaction was allowed to warm to room temperature, then cooled to 0 ˚C, and 100 mL of 3M HCl were added slowly. The biphasic mixture was stirred until the solids dissolved, and then 20 min more. The mixture was poured into a separatory funnel and the organic layer removed. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the organic layers combined, dried over $MgSO_4$, and concentrated to 200 mL. To this solution was added $MgSO_4$ (100 g) and ethylene glycol (8.4 mL, 150 mmol). An overhead mechanical stirrer was added and the reaction stirred overnight at room temperature. The mixture was filtered and the $MgSO_4$ washed with Et_2O (2 x 75 mL). Per Schaus, “Solvent was removed by rotary evaporation and the crude product then

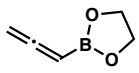
dissolved in 150 mL pentane and cooled to 0 ˚C. If necessary, excess diol is removed as the bottom layer. If a precipitate remains, the solution is filtered through a pad of oven-dried Celite®. The solvent was removed under reduced pressure and the resulting clear liquid was purified *via* Kugelrohr distillation".

_B_-(allenyl)-1,3,2-dioxaborinane (28)



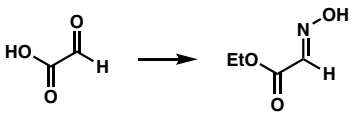
Prepared from 1,3-propanediol (10.8 mL, 150 mmol) following General Procedure for Synthesis of Boronates. The crude liquid was purified via Kugelrohr distillation to yield 3.228 g (17% yield) of **28** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (t, J = 7.0 Hz, 1H), 4.60 (d, J = 6.9 Hz, 2H), 4.06 (t, J = 4.5 Hz, 4H), 2.08 – 1.92 (m, 2H).

_B_-(allenyl)-1,3,2-dioxaborolane (29)



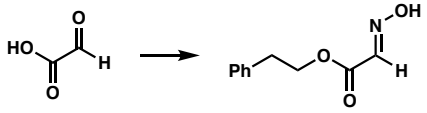
Prepared from ethylene glycol (8.4 mL, 150 mmol) following General Procedure for Synthesis of Boronates. The crude liquid was purified via fractional Kugelrohr distillation (40 ˚C, 10 mm Hg) to yield **29** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (t, J = 7.0 Hz, 1H), 4.68 (d, J = 7.1 Hz, 2H), 4.27 (d, J = 1.3 Hz, 4H); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.93.

ethyl 2-(hydroxyimino)acetate



A round bottom flask was charged with a stir bar, glyoxylic acid monohydrate (20.0 g, 217 mmol), NH_2OH•HCl (15.3 g, 220 mmol), *p*-TsOH•H_2O (3.12 g, 16 mmol), and EtOH (260 mL). It was then fitted with a Socklett extractor and condenser, and the reaction heated at 120 ˚C for 15 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The resulting oil was diluted in Et_2O (400 mL) and sat. $NaHCO_3$ (240 mL). The biphasic mixture was added to a separatory funnel and the aqueous layer removed. The organic layer was washed with sat. NH_4Cl (100 mL) and pH 7 buffer (100 mL). The aqueous layer was tested for product and re-extracted with Et_2O (150 mL) if necessary. Combined organic layers were washed with brine (100 mL), then dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the product (25.2 g, 99% yield) without need for further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 3H), 1.40 – 1.31 (t, *J* = 7.1 Hz, 2H).

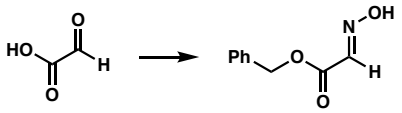
phenethyl 2-(hydroxyimino)acetate



A flask was charged with stir bar and the following reagents: glyoxylic acid monohydrate (1.50 g, 16.30 mmol), hydroxylamine hydrochloride (1.14 g, 16.46 mmol), 2-phenylethanol (5.87 mL, 48.9 mmol), *p*-TsOH•H_2O (0.233 g, 1.22 mmol). Toluene (50 mL) was added and a reflux condenser attached. The reaction was heated to 80 ˚C and stirred 15 min, then heated to 100 ˚C and stirred 1 h. Finally, the reaction was heated to 120 ˚C and stirred overnight. The reaction was then cooled to room temperature, diluted with 50 mL EtOAc, and added to a separatory funnel. The organic layer was washed with

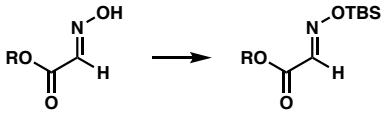
sat. $NaHCO_3$ (60 mL), sat. NH_4Cl (10 mL), pH 7 buffer (10 mL), and brine (20 mL). The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (20 → 30% EtOAc/Hexanes) to yield 1.053 g (33% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.55 (s, 1H), 4.47 (t, J = 7.2 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H).

benzyl 2-(hydroxyimino)acetate



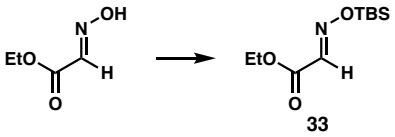
A flask was charged with stir bar and the following reagents: glyoxylic acid monohydrate (1.00 g, 10.9 mmol), hydroxylamine hydrochloride (0.764 g, 11.0 mmol), benzyl alcohol (3.39, 32.7 mmol), *p*-TsOH•H_2O (0.156 g, 0.818 mmol). Toluene (33 mL) was added and a reflux condenser attached. The reaction was heated to 80 ˚C and stirred 15 min, then heated to 100 ˚C and stirred 1 h. Finally, the reaction was heated to 120 ˚C and stirred overnight. The reaction was then cooled to room temperature, diluted with 33 mL EtOAc, and added to a separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (40 mL), sat. NH_4Cl (7 mL), pH 7 buffer (7 mL), and brine (15 mL). The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. BnOH was removed by vacuum distillation (265 mTorr, 68-70 ˚C). The product was subsequently purified by column chromatography (20 → 40% EtOAc/Hexanes). BnOH was still present so it was removed by a second vacuum distillation to furnish the product (0.443 g, 23% yield) with approximately 2% BnOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 7.59 (s, 1H), 7.47 – 7.30 (m, 5H), 5.29 (s, 2H).

General Procedure for Silylation of Oxime Esters



A flask was charged with a stir bar, the unprotected oxime (5.45 mmol, 1.0 equiv), TBSCl (8.18 mmol, 1.5 equiv), imidazole (16.9 mmol, 3.1 equiv), and DMF (10 mL) and stirred 48-72 h under a nitrogen atmosphere. The mixture was poured into 6:1 deionized water:brine (45 mL) and extracted with Et_2O (30 mL). The organic layer was washed with brine (6 mL) and dried over Na_2SO_4, then filtered and concentrated in vacuo. The crude product was purified via column chromatography (5% Et_2O/Hexanes).

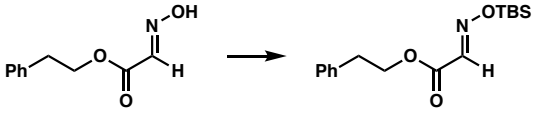
ethyl 2-(((*tert*-butyldimethylsilyl)oxy)imino)acetate (33)



33

Prepared from ethyl 2-(hydroxyimino)acetate (25.2 g, 215 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography (3.5 → 4.5% Et_2O/Hexanes) to yield **33** as a clear oil (28.787 g, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.23 (s, 6H).

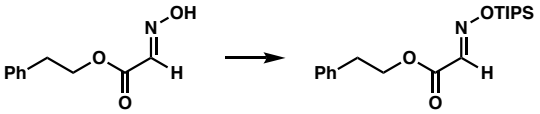
phenethyl 2-(((*tert*-butyldimethylsilyl)oxy)imino)acetate (35)



35

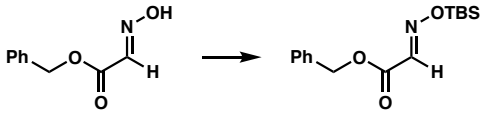
Prepared from phenethyl 2-(hydroxyimino)acetate (1.053 g, 5.45 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography (5% Et_2O/Hexanes) to yield **35** as a clear oil (1.032 g, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.35 – 7.20 (m, 5H), 4.44 (t, *J* = 6.9 Hz, 2H), 3.01 (t, *J* = 6.9 Hz, 2H), 0.96 (s, 9H), 0.25 (s, 6H).

phenethyl 2-(((triisopropylsilyl)oxy)imino)acetate



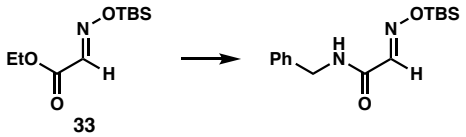
Prepared from phenethyl 2-(hydroxyimino)acetate (1.40 g, 7.2 mmol) and TIPSCl (2.31 mL, 10.8 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography to yield the product (1.647 g, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.32 – 7.21 (m, 5H), 4.44 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 1.33 – 1.22 (m, 3H), 1.10 (d, *J* = 7.4 Hz, 18H).

benzyl 2-(((*tert*-butyldimethylsilyl)oxy)imino)acetate



Prepared from benzyl 2-(hydroxyimino)acetate (0.440 g, 2.46 mmol) following the General Procedure for Silylation of Oxime Esters. The crude product was purified via column chromatography (5% Et_2O/Hexanes) to yield the product (0.504 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.42 – 7.32 (m, 5H), 5.28 (s, 2H), 0.94 (s, 9H), 0.23 (s, 6H).

_N_-benzyl-2-(((*tert*-butyldimethylsilyl)oxy)imino)acetamide



Oxime **33** (0.440 g, 1.90 mmol) was dissolved in $BnNH_2$ (4.0 mL, 36.6 mmol) in a microwave vial with a stir bar. The mixture was irradiated for 15 min at 100 ˚C. It was then tested for product via TLC (20% EtOAc/Hexanes). Since some starting material remained, the mixture was irradiated 5 min more at 100 ˚C. The reaction mixture was then dissolved in 4 mL CH_2Cl_2 and washed with 1 M HCl (3 x 12 mL). The organic layer was concentrated in vacuo. The crude product was purified by column chromatography (10 → 15 → 20 % EtOAc/Hexanes) to give 0.211 g (38% yield) of the desired amide product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.41 – 7.27 (m, 5H), 6.78 (br s, 1H), 4.55 (d, J = 6.1 Hz, 3H), 0.93 (s, 9H), 0.20 (s, 6H).

2.4.3. Ligand Synthesis

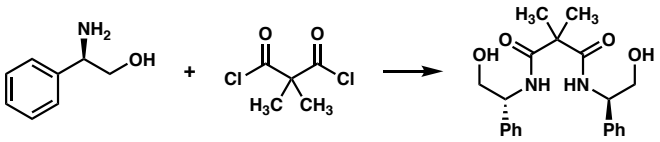
2,2-dimethylmalonyl chloride

2,2-dimethylmalonic acid (4.00 g, 30.3 mmol) and DMF (0.304 mL, 3.94 mmol) were dissolved in CH_2Cl_2 (30 mL) and the solution cooled to 0 ˚C. Oxalyl chloride (7.80 mL, 90.9 mmol) was added to the solution dropwise over 1 hour. The mixture was then warmed to room temperature, stirred 18 h, and concentrated in vacuo. The crude product was purified by distillation (77 ˚C, 60 Torr) to give 3.90 g (76% yield) of 2,2-dimethylmalonyl chloride as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 6H).

(*R*)-(–)- 2-phenylglycinol [(*R*)-2-amino-2-phenylethanol]

To a flame-dried flask were added R-phenylglycine (4.00 g, 26.4 mmol), $NaBH_4$ (2.50 g, 66 mmol), and THF (110 mL). In a separate flame-dried flask, I_2 (8.05 g, 31.7 mmol) was dissolved in THF (40 mL). The phenylglycine solution was cooled to 0 ˚C and the I_2 solution added slowly via cannula over 1 h, trying to maintain a white slurry. The reaction mixture was then heated to reflux (66 ˚C) under N_2 for 66 h. The mixture was then cooled to room temperature and MeOH was added until the solution became clear. The solvent was removed via rotary evaporation, leaving a thick white oil. To this oil was added 20% aq KOH (75 mL), and the resulting solution was stirred 4 h at room temperature. The solution was extracted with CH_2Cl_2 (4 x 75 mL) and the organic layers dried over Na_2SO_4 and concentrated in vacuo to give R-phenylglycinol as a white solid (3.00 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 5H), 4.05 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.75 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.55 (dd, *J* = 10.7, 8.3 Hz, 1H), 2.08 (br s, 3H).

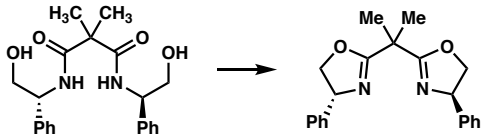
N^1,N^3-bis((*R*)-2-hydroxy-1-phenylethyl)-2,2-dimethylmalonamide



To a flame-dried flask were added phenylglycinol (2.508 g, 18.3 mmol) and CH_2Cl_2 (73.2 mL). The solution was cooled to 0 ˚C and freshly distilled Et_3N (5.8 mL, 41.6 mmol) was added dropwise, followed by dimethylmalonyl chloride (1.10 mL, 8.32

mmol) dropwise. The reaction was allowed to warm to room temperature and stirred 3 h under a nitrogen atmosphere. The reaction was then quenched with 1 M HCl to pH 0. (If precipitate is present, filter with several portions of water and concentrate in vacuo.) No precipitate was present, so the solution was extracted with CH_2Cl_2 and the organic layers concentrated in vacuo to give 2.866 g (93% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.19 (m, 10H), 7.10 (d, *J* = 7.6 Hz, 2H), 5.12 (td, *J* = 7.0, 3.9 Hz, 2H), 3.94 (dd, *J* = 11.5, 4.0 Hz, 2H), 3.81 (dd, *J* = 11.4, 6.6 Hz, 2H), 1.53 (s, 6H), 1.41 (t, *J* = 7.3 Hz, 2H).

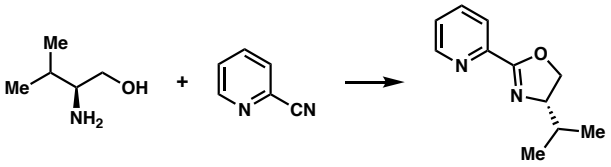
(4*R*,4'*R*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) (PhBOX, L19)



PhBox (**L19**)

To a flame-dried flask were added amide (2.428 g, 6.55 mmol), DMAP (0.120 g, 0.98 mmol), and CH_2Cl_2 (65 mL). The flask was placed in a water bath and freshly distilled Et_3N (4.01 mL, 28.8 mmol) added dropwise. TsCl (2.745 g, 14.4 mmol) was added in one portion and the reaction stirred at room temperature under a nitrogen atmosphere for 36 h. The reaction was quenched with NH_4Cl and water. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (15% acetone/hexanes) to give **L19** (1.113 g, 51% yield) as a viscous, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 10H), 5.24 (dd, *J* = 10.1, 7.6 Hz, 2H), 4.68 (dd, *J* = 10.1, 8.3 Hz, 2H), 4.17 (dd, *J* = 8.3, 7.6 Hz, 2H), 1.69 (s, 6H).

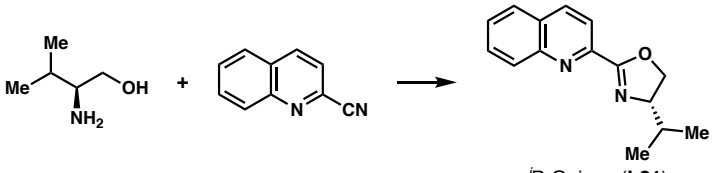
(*S*)-4-isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole (^{i}PrPyOx, L20)



^{i}PrPyOx (**L20**)

According to the procedure of Hassine and coworkers,[30] 2-cyano-pyridine (0.050 g, 0.48 mmol) and L-valinol (0.06 mL, 0.53 mmol) were mixed and sealed in a microwave vial. The vial was irradiated at 150 ˚C for 90 min, then allowed to come to room temperature. The reaction was quenched with EtOAc, then filtered through silica, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (2% MeOH/CH_2Cl_2) to give **L20** (25 mg, 27% yield). ^{1}H NMR (500 MHz, $CDCL_3$) δ 8.70 (ddt, *J* = 4.8, 1.7, 0.8 Hz, 1H), 8.06 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.80 – 7.73 (m, 1H), 7.42 – 7.35 (m, 1H), 4.55 – 4.48 (m, 1H), 4.27 – 4.13 (m, 2H), 1.97 – 1.83 (m, *J* = 6.7 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

(*S*)-4-isopropyl-2-(quinolin-2-yl)-4,5-dihydrooxazole (^{i}PrQuinox, L21)

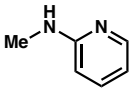


^{i}PrQuinox (**L21**)

According to the procedure of Hassine and coworkers,[30] L-valinol (0.04 mL, 0.35 mmol) and 2-quinolinecarbonitrile (50 mg, 0.32 mmol) were mixed and sealed in a microwave vial. The vial was irradiated at 150 ˚C for 60 min, then allowed to come to room temperature. The reaction was quenched with EtOAc, then filtered through silica, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column

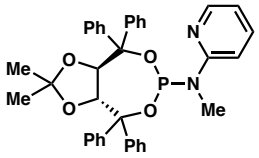
chromatography (35% EtOAc/Hexanes) to give **L21** (17.1 mg, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 – 8.24 (m, 1H), 8.23 (s, 2H), 7.85 (ddd, *J* = 8.2, 1.6, 0.7 Hz, 1H), 7.75 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.66 – 4.54 (m, 1H), 4.35 – 4.17 (m, 2H), 2.01 – 1.87 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

_N_-methylpyridin-2-amine



According to the procedure of Singh and coworkers,[31] in a flame-dried flask, 2-aminopyridine (1.000 g, 10.6 mmol) was dissolved in dry THF (8.50 mL). The solution was cooled to 0 ˚C and ^{n}BuLi (4.24 mL, 10.6 mmol) was added dropwise. The reaction was allowed to come to room temperature and stirred 30 min. CH_3I (0.66 mL, 10.6 mmol) was added dropwise with cooling in an ice bath to prevent refluxing. The reaction was stirred 1 h at room temperature, then poured into 3 mL water. NH_4Cl (0.567 g, 10.6 mmol) was added and the organic layer separated. The aqueous layer was extracted with $CHCl_3$ (4 x 10 mL) and 10% ^{i}PrOH in $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (5%/1%/94% → 25%/2%/73% EtOAC/Et_3N/Hexanes) to give the product as a yellow oil (0.346 g, 30% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.5, 7.1, 1.9 Hz, 1H), 6.57 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.38 (dt, *J* = 8.3, 1.0 Hz, 1H), 4.55 (br s, 1H), 2.92 (d, *J* = 4.9 Hz, 3H).

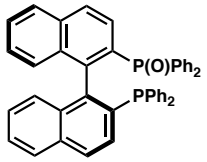
_N_-((3a_R_,8a_R_)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-_e_][1,3,2]dioxaphosphepin-6-yl)-_N_-methylpyridin-2-amine (L38)



(_R_,_R_)-TADDOL-P-N(Me)(2-py) (L38)

According to the procedure of Kitamura and coworkers,[32] PCl_3 (0.08 mL, 0.925 mmol) was dissolved in THF (2.8 mL). To this solution was added *N*-methylpyridin-2-amine (0.100 g, 0.925 mmol) and the reaction was stirred 1.5 h at room temp. In a separate flask, Et_3N (0.41 mL, 2.94 mmol) and (-)-TADDOL (0.392 g, 0.841 mmol) were dissolved in THF (5.6 mL). The PCl_3 solution was cooled to 0 ˚C and the TADDOL solution added. The reaction was allowed to warm to room temperature and stirred 24 h. The solution was then filtered through Celite and washed with THF (15 mL), then concentrated in vacuo. The crude product was purified via column chromatography (5% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.19 (m, 1H), 7.86 – 7.77 (m, 2H), 7.59 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.49 – 7.18 (m, 17H), 6.87 – 6.82 (m, 1H), 6.75 (ddd, *J* = 7.2, 5.0, 0.9 Hz, 1H), 5.31 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.89 (d, *J* = 8.5 Hz, 1H), 3.38 (d, *J* = 2.6 Hz, 3H), 1.35 (s, 3H), 0.33 – 0.27 (s, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 135.68.

(_S_)-(2'-(diphenylphosphaneyl)-[1,1'-binaphthalen]-2-yl)diphenylphosphine oxide ((_S_)-BINAP(O); L39)

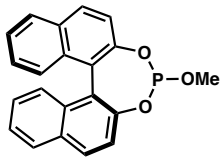


(S)-BINAP(O) was synthesized according to the procedure of Grushin.[33] (*S*)-BINAP (0.250 g, 0.40 mmol) and PdI_2 (0.0032 g, 0.009 mmol) were dissolved in CH_2Cl_2 (2.5 mL) in a flame-dried flask under nitrogen atmosphere. The solution was stirred 3 h at room temperature. NaOH (0.226 g, 5.64 mmol) was dissolved in water (1.5 mL) and added to the BINAP solution, followed by 1,2-dibromoethane (0.23 mL, 2.65 mmol). The biphasic solution was heated to 50 ˚C for 18 h. The reaction was cooled to room temperature and acidified to pH 3 using 20% aq H_3PO_4. Ethylenebis(diphenylphosphine) (dppe, 10 mg, 0.025 mmol) was added and the solids rinsed with CH_2Cl_2. The reaction was stirred 5 min, then the organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified via column chromatography (100% CH_2Cl_2 → 10% EtOAc/CH_2Cl_2) to give the product (0.109 g , 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.77 – 7.54 (m, 6H), 7.45 – 6.58 (m, 24H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.15, -15.33.

Dichloro(methoxy)phosphane

According to the procedure of Turhanen and coworkers,[34] PCl_3 (0.31 mL, 3.50 mmol) was dissolved in dry Et_2O (2.9 mL) and cooled to 0 ˚C under a nitrogen atmosphere. Methanol (0.16 mL, 3.85 mmol) was added dropwise with stirring. The reaction was allowed to warm to room temperature and stirred 4 h with monitoring by ^{31}P NMR. The product was used in solution without further purification. ^{31}P NMR (121 MHz, $CDCl_3$) δ 180.80.

(11b*S*)-4-methoxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (BINOL-P-OMe, L41)



According to the procedure of Tanaka and coworkers,[35] (*S*)-BINOL (0.836 g, 2.92 mmol) and DIPEA (1.67 mL, 9.64 mmol) were dissolved in dry CH_2Cl_2 and cooled to 0 ˚C for 15 min. Dichloro(methoxy)phosphane solution was added via cannula and the reaction stirred 1 h at room temperature. The solvent was removed via rotary evaporation and the crude product purified by column chromatography (5% EtOAc/hexanes → 100 % EtOAc). The resulting residue was further purified by column chromatography using Florisil® (5% → 25% EtOAc/hexanes) to obtain the product phosphite (63 mg, 6% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.84 (m, 5H), 7.57 – 7.29 (m, 7H), 3.55 (d, J = 9.9 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 139.98.

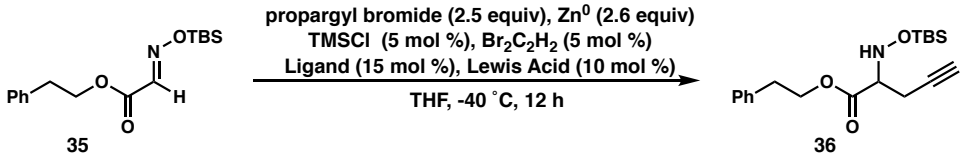
2.4.4. Propargylation Reactions

(±)-ethyl 2-(((*tert*-butyldimethylsilyl)oxy)amino)pent-4-ynoate (34)

Zn^0 (147.1 mg, 2.25 mmol) was added to a round bottom flask and flame dried under vacuum. Dry THF (8 mL) was added, followed by 1,2-dibromoethane (3 μL, 0.04 mmol) and TMSCl (5 μL, 0.04 mmol). The suspension was stirred 5 min and propargyl bromide (80% wt in toluene, 0.24 mL, 2.16 mmol) added. The mixture was heated gently until

reaction was observed, then stirred vigorously at room temperature until zinc was no longer consumed (10 min). In a separate flask, oxime **33** (0.200 g, 0.864 mmol) was dissolved in THF (8 mL). Organozinc solution was added to the solution of **33**, and the reaction stirred 1.5 h in a room temperature water bath. Upon disappearance of starting material, the reaction was quenched with sat. $NaHCO_3$ (4 mL). The salts were filtered off through a pad of Celite, and washed with Et_2O (2 x 12 mL). The organic layers were washed with brine (2 x 8 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via column chromatography (3.5 → 5% EtOAc/Hexanes) to give **34** (0.121 g, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (q, *J* = 7.1 Hz, 2H), 3.63 (td, *J* = 6.4, 0.6 Hz, 1H), 2.67 – 2.48 (m, 2H), 2.02 (td, *J* = 2.7, 0.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 6H).

General Procedure for Organozinc Propargylation Screens



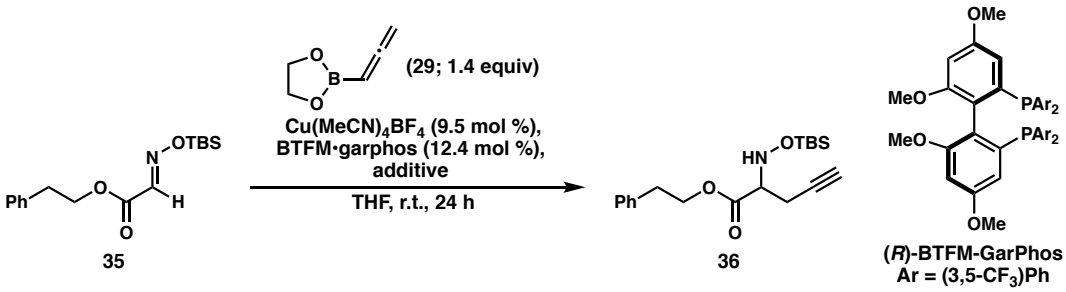
The Lewis acids (0.10 equiv, 5 μmol per reaction) were weighed into vials. The ligand (0.15 equiv, 7.5 μmol per reaction) was dissolved in THF (0.1 mL per reaction). Oxime **35** (1.0 equiv, 0.05 mmol per reaction) was dissolved in THF (0.5 mL per reaction). The ligand and oxime solutions were combined and stirred 20 min at room temperature, then added to the vials with the Lewis acids.

In a separate flask, Zn^0 (2.6 equiv, 0.125 mmol per reaction) was suspended in dry THF (0.5 mL per reaction) and 1,2-dibromoethane (0.05 equiv, 2.5 μmol per reaction) and TMSCl (0.05 equiv, 2.5 μmol per reaction) were added. Propargyl bromide (2.5

equiv, 0.125 mmol per reaction) was added and the solution stirred 30 min at room temperature.

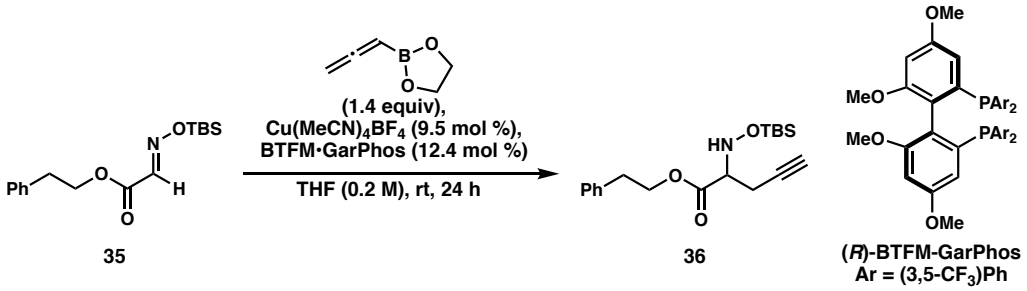
The oxime solutions were cooled to -40 ˚C. The organozinc solution was added and the reactions stirred at -40 ˚C overnight. The reactions were allowed to come to room temperature and quenched with sat. $NaHCO_3$ (0.2 mL per vial). Each reaction was filtered through $MgSO_4$ and Celite and washed with Et_2O (2 x 2 mL), then concentrated in vacuo. ^{1}H NMR and SFC analyses were done on the crude mixtures.

General Procedure for Copper-Catalyzed Asymmetric Addition Reaction Screens



In the glove box, oven-dried vials were charged with stir bars, $[Cu(MeCN)_4]BF_4$ (0.095 equiv, 0.0038 mmol per reaction), and any additives. Oxime **35** (1.0 equiv, 0.040 mmol per reaction) and borolane **29** (1.4 equiv, 0.056 mmol per reaction) were dissolved in THF (0.05 mL per reaction) to make a stock solution. BTFM-GarPhos (**L37**, 0.124 equiv, 0.0050 mmol per reaction) was dissolved in THF (0.15 mL per reaction). The BTFM-Garphos solution was added (0.15 mL to each vial) and the vials stirred 5 min. The oxime/borolane stock was then added (0.05 mL to each vial) and the reactions stirred 24 h at room temperature. The reactions were quenched with 20% EtOAc/Hexanes and filtered through a small silica plug. ^{1}H NMR and SFC analyses were done on the crude mixtures.

Copper-Catalyzed Asymmetric Addition Scale-Up



To an oven-dried 1-dram vial charged with a stir bar were added $[Cu(MeCN)_4]BF_4$ (0.0185 mmol, 0.0058 g) and BTFM-GarPhos (0.0242 mmol, 0.0287 g). Oxime **35** (0.195 mmol, 0.060 g) and borolane **29** (0.273 mmol, 0.040 g) were dissolved in THF (0.25 mL) in a separate vial. THF (0.75 mL) was added to the Cu and GarPhos, and both vials were pre-stirred 5 min at room temperature. The oxime/borolane solution was added to the Cu/GarPhos solution and the reaction stirred 24 h at room temperature. The reaction was quenched with 0.5 M EDTA in pH 8 NH_3/NH_4Cl buffer (1 mL). EtOAc (2 mL) was added and the layers separated. The aqueous layer was extracted with EtOAc (1 mL) and the combined organic layers washed with brine (4 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via column chromatography (3% → 50 % EtOAc/Hexanes) to give **36** (26.5 mg, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.17 (m, 5H), 5.59 (s, 1H), 4.40 (td, J = 7.1, 1.3 Hz, 2H), 3.63 (t, J = 6.4 Hz, 1H), 2.98 (t, J = 7.0 Hz, 2H), 2.65 – 2.43 (m, 2H), 1.99 (t, J = 2.7 Hz, 1H), 0.89 (s, 10H), 0.10 (d, J = 2.2 Hz, 6H).