Supporting Information

Enantioselective Alkynylation of Unstabilized Cyclic Iminium Ions

Weiye Guan, Samantha O. Santana, Jennie Liao, Kelci Henninger, and Mary P. Watson*

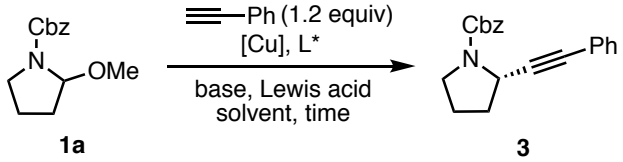
Department of Chemistry & Biochemistry, University of Delaware, Newark, Delaware 19716, United States
mpwatson@udel.edu

General Information

Reactions were performed either in a N_2-atmosphere glovebox in oven-dried 1-dram or 2-dram vials with Teflon-lined caps or in oven-dried round-bottomed flasks unless otherwise noted. Flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of N_2. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed on silica gel 60 (40-63 μm, 60Å). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with F254 indicator. Commercial reagents were purchased from Sigma Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: tetrahydrofuran, CH_2Cl_2, and Et_2O were dried by passing through drying columns.[1] DME and MeOH were purchased in sure-seal bottles, and used as such. $CDCl_3$ was stored over oven-dried potassium carbonate. Alkynes were degassed before use by either freeze-pump-thaw cycles or sparging with N_2. Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra, and fluorine nuclear magnetic resonance spectra (^{19}F NMR) were recorded on both 400 MHz and 600 MHz spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.16). Chemical shifts for fluorine were externally referenced to $CFCl_3$ in $CDCl_3$ ($CFCl_3$ = δ 0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using FTIR spectrophotometers with material loaded onto a KBr plate. The mass spectral data were obtained at the University of Delaware spectrometry facility. Melting points were taken on a Thomas-Hoover Uni-Melt Capillary Melting Point Apparatus. Optical rotations were measured using a 2.5 mL cell with a 0.1 dm path length.

Optimization Studies

Scheme S1. Model Reaction for Optimization



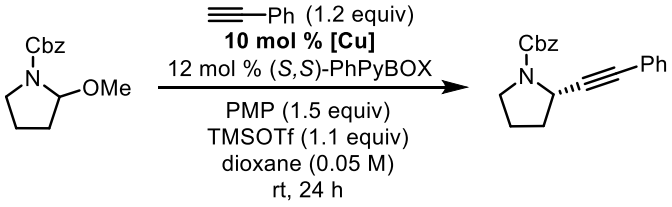
1a **3**

General Optimization Procedure

In a N_2-filled glovebox: To an oven-dried 1-dram vial was added copper salt (0.010 mmol, 10 mol %), ligand (0.012 mmol, 12 mol %), and solvent (0.5 mL). The vial was capped with a septum-lined pierceable cap. The mixture was stirred for 30 min at room temperature. Then phenylacetylene (13 μL, 0.12 mmol, 1.2 equiv), base (0.15 mmol, 1.5 equiv), aminal **1a** (23.5 mg, 0.10 mmol, 1.0 equiv), and solvent (1.5 mL, 0.05 M, unless noted otherwise) were added. The vial was again sealed with a septum-lined pierceable cap, removed from the glovebox, and cooled if indicated in the tables below. After 10 min, Lewis acid (0.11 mmol, 1.1 equiv) was slowly added via microsyringe, and the mixture was stirred for 24 h at the indicated temperature. The reaction mixture was then diluted with Et_2O (2 mL) and filtered through a plug of silica gel, which was then washed with more Et_2O (10 mL). The filtrate was concentrated. 1,3,5-Trimethoxybenzene (internal standard) and $CDCl_3$ were added, and the yield was determined by ^1H NMR analysis. An analytical sample of product was prepared via preparatory thin layer chromatography, and the ee of this sample was determined by HPLC using a chiral stationary phase. Changes to this general procedure are noted in the tables below.

Investigation of Copper Sources

Table S1. Investigation of Copper Sources

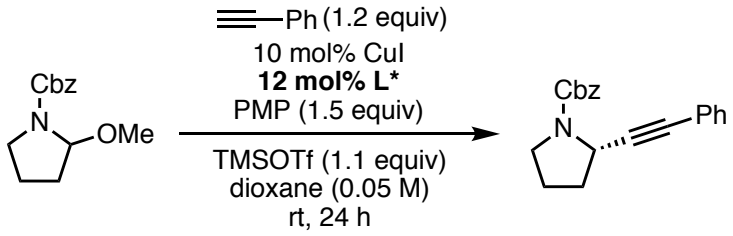


Entry	[Cu]	Yield(%)[a]	ee (%)[b]
1	CuI	61	47
2	CuCl	14	1
3	CuBr	10	7
4	$Cu(MeCN)_4PF_6$	4	0
5	$Cu(OTf)_2 \cdot C_6H_6$	7	2
6	CuSPh	0	1

[a]Determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard. [b]Determined by HPLC using a chiral stationary phase.

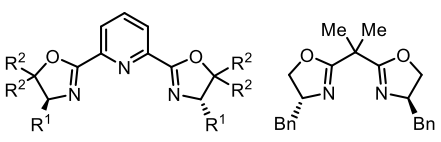
Investigation of Ligands

Table S2. Investigation of Ligands



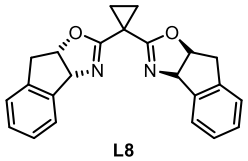
Entry	Ligand	Solvent	Temp (°C)	Yield (%)[a]	ee (%)[b]
1	**L1**	dioxane	rt	53	47
2	**L2**	dioxane	rt	31	37
3	**L3**	dioxane	rt	27	30
4	**L11**	dioxane	rt	< 5	23
5	**L7**	dioxane	rt	17	0
6	**L8**	dioxane	rt	0	nd[c]
7	**L1**	2-Me-THF	-30	54	52
8	**L9**	2-Me-THF	-30	37	21
9	**L10**	2-Me-THF	-30	79	18
10	**L4**	2-Me-THF	-30	80	82
11	**L5**	2-Me-THF	-30	80	85
12	**L6**	2-Me-THF	-30	74	55

[a]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.
[b]Determined by HPLC using a chiral stationary phase. [c]nd = not determined.

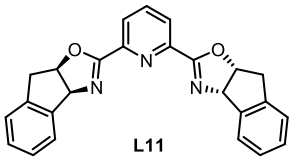


L1, R^1 = Ph, R^2 = H
L2, R^1 = *t*-Bu, R^2 = H
L3, R^1 = *i*-Pr, R^2 = H
L4, R^1 = Ph, R^2 = Me
L5, R^1 = Ph, R^2 = Et
L6, R^1 = Ph, R^2 = Ph
L9, R^1 = 4-MeO-C_6H_4, R^2 = H
L10, R^1 = 2-Cl-C_6H_4, R^2 = H

L7



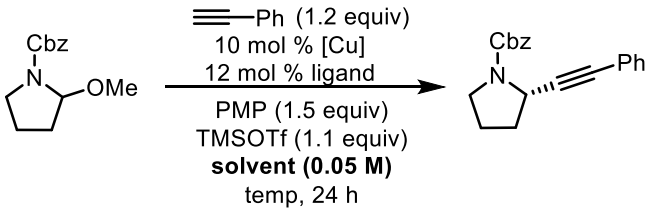
L8



L11

Investigation of Solvents

Table S3. Investigation of Solvents

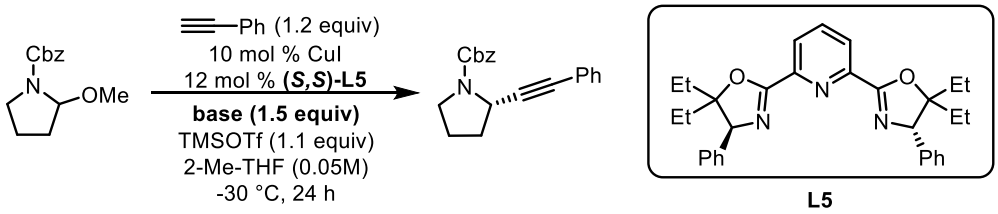


Entry	Solvent	Temp (°C)	Ligand	Yield(%)	ee (%)
1	dioxane	rt	**L1**	61	47
2	2-Me-THF	rt	**L1**	46	43
3	toluene	rt	**L1**	32	42
4	CH_2Cl_2	rt	**L1**	66	32
5	2-Me-THF	-30	**L5**	90	85
6	THF	-30	**L5**	74	85
7	Et_2O	-30	**L5**	18	73
8	MTBE	-30	**L5**	55	79
9	CPME	-30	**L5**	47	80
10	DME	-30	**L5**	50	91

[a]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.
[b]Determined by HPLC using a chiral stationary phase.

Investigation of Bases

Table S4. Investigation of Bases



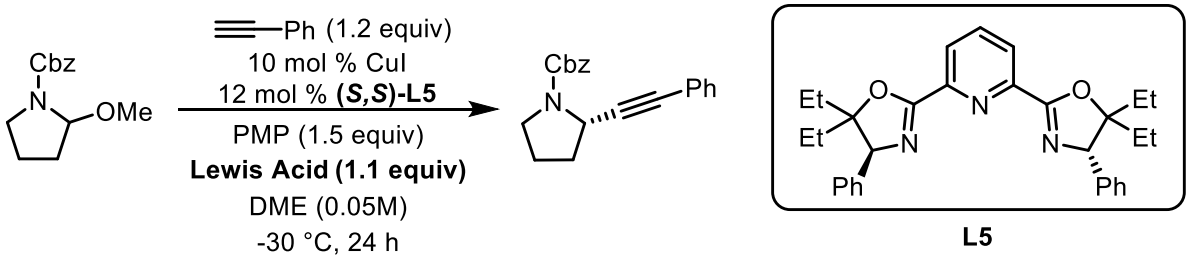
L5

Entry	Base	Yield(%)[a]	ee (%)[b]
1	PMP	84	86
2	*i*-Pr_2NEt	73	85
3	Cy_2NEt	72	85
4	Cy_2NMe	76	86
5	MTBD	< 5	nd[c]

[a]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.[b]Determined by HPLC using a chiral stationary phase. [c]nd = not determined.

Investigation of Lewis Acids

Table S5. Investigation of Lewis Acids

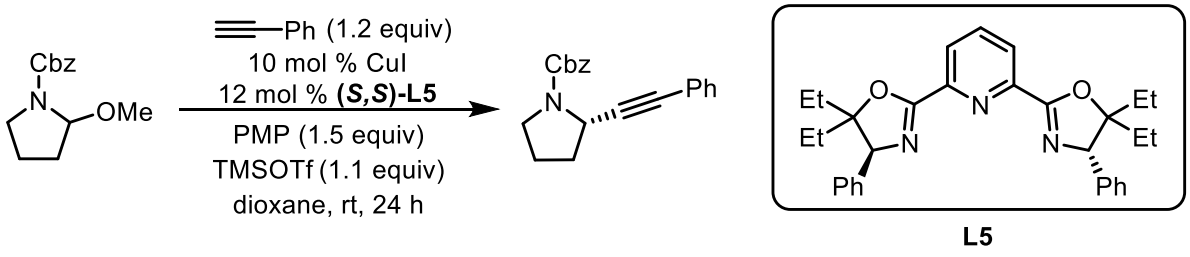


Entry	LA	Yield(%)[a]	ee (%)[b]
1	$TiCl_4$	59	88
2	$BF_3{\cdot}OEt_2$	85	90
3	$AlCl_3$	68	47
4	TMSOTf	50	91
5	$MgBr_2{\cdot}OEt_2$	< 5	nd[c]

[a]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.[b]Determined by HPLC using a chiral stationary phase. [c]nd = not determined.

Investigation of Concentration

Table S6. Investigation of Concentration



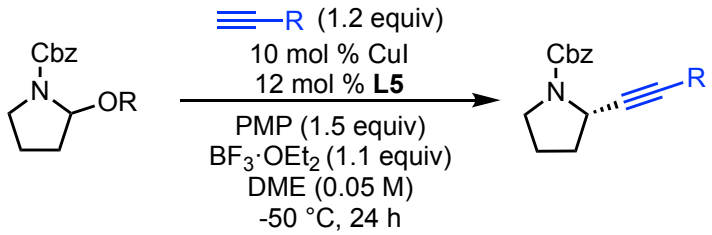
Entry	Concentration (M)	Yield(%)[a]	ee (%)[b]
1	0.13	32	39
2	0.08	51	43
3	0.06	55	45
4	0.05	46	47
5	0.04	44	47

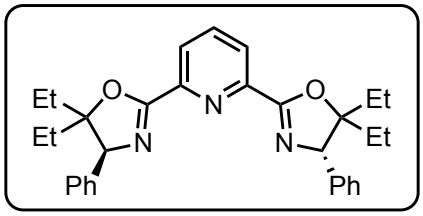
[a]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.[b]Determined by HPLC using a chiral stationary phase.

Investigation of Aminal Leaving Group

In addition to hemiaminal methyl ether **1**, we also investigated alternative leaving groups. Hemiaminal ethyl[2] and isopropyl ethers were prepared using the same procedure as for hemiaminal methyl ether **1**, but with the appropriate orthoformate and alcohol reagents. The acetate was prepared according to literature procedure.[3-4] The parent hemiaminal (entry 5) was prepared via the same reduction as for hemiaminal methyl ether **1** and was used without further purification.

Table S7. Investigation of Leaving Groups





L5

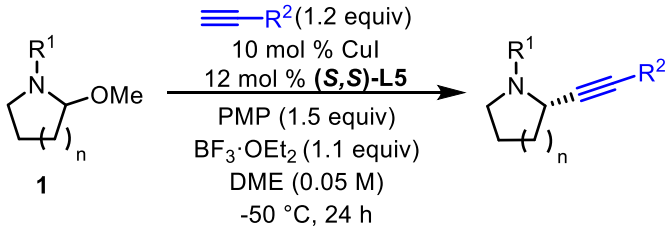
Entry	Aminal (OR)	Yield(%)[a]	ee (%)[b]
1	OMe	89	91
2	OEt	92	89
3	OiPr	83	86
4	OAc	27	93
5	OH	trace	nd[c]

[a]Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.[b]Determined by HPLC using a chiral stationary phase. [c]nd = not determined.

Enantioselective Alkynylation of Hemiaminal Ethers

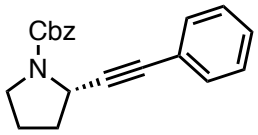
General Procedure A: Enantioselective Alkynylation

Scheme S2. General Conditions for the Enantioselective Alkynylation

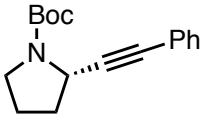


In a N_2-filled glovebox, CuI (5.7 mg, 0.030 mmol, 10 mol %), ligand (17.3 mg, 0.036 mmol, 12 mol %), and dimethoxyethane (DME, 1.5 mL) were added to a 2-dram vial. The vial was capped with a septum-lined pierceable cap. The mixture was stirred for 30 min at room temperature. Then alkyne (0.36 mmol, 1.2 equiv), 1,2,2,6,6-pentamethylpiperidine (PMP, 81.4 μL 0.45 mmol, 1.5 equiv), hemiaminal ether **1** (0.30 mmol, 1.0 equiv), and

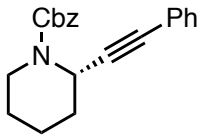
DME (4.5 mL, 0.05 M) were added. The vial was again sealed with a septum-lined pierceable cap, removed from the glovebox, and cooled to –50 °C. After 10 min, $BF_3 \cdot OEt_2$ (48% in Et_2O, 84.8 μL, 0.33 mmol, 1.1 equiv) was slowly added over 5 minutes via microsyringe, and the mixture was stirred for 24 h at –50 °C. The reaction mixture was then diluted with Et_2O (2 mL) and filtered through a plug of silica gel, which was then washed with more Et_2O (20 mL). The filtrate was concentrated and purified by silica gel chromatography.



Benzyl *(S)*-2-(phenylethynyl)pyrrolidine-1-carboxylate (3). Prepared via General Procedure A, except on a 1.0-mmol scale instead of 0.3-mmol scale. Crude material was purified by silica gel chromatography (8–16% ethyl acetate/hexanes) to give compound **3** (run 1: 271 mg, 89%; run 2: 280 mg, 92%) as light yellow oil. The enantiomeric excess was determined to be 92% (run 1: 92% ee; run 2: 91% ee) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 10% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 6.38 min, t_R(minor) = 5.55 min. $[\alpha]_D^{22}$ = –55.2 (c 1.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.43 – 7.26 (m, 10H), 5.34 – 5.11 (m, 2H), 4.84 – 4.77 (m, 1H), 3.62 – 3.44 (m, 2H), 2.18 – 2.14 (m, 3H), 1.98 – 1.95 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.7, 137.1, 132.0, 131.8, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 123.1, 89.6, 82.4, 67.0, 49.3, 48.9, 46.4, 46.0, 34.1, 33.4, 24.7, 23.9. The spectral data matches that reported in the literature.[5]

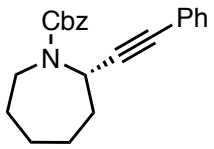


***tert*-Butyl *(S)*-2-(phenylethynyl)pyrrolidine-1-carboxylate (4).** Prepared via General Procedure A. Crude material was purified by silica gel chromatography (4–8% ethyl acetate/hexanes) to give compound **4** (run 1: 58.3 mg, 72%; run 2: 52.1 mg, 64%) as colorless oil. The enantiomeric excess was determined to be 91% (run 1: 91% ee; run 2: 90% ee) by chiral HPLC analysis (CHIRALPAK IC, 1 mL/min, 10% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 9.79 min, t_R(minor) = 7.27 min. $[\alpha]_D^{22}$ = –107.5 (c 1.75, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 4.77 – 4.63 (m, 1H), 3.54 – 3.36 (m, 2H), 2.11 – 1.92 (m, 4H), 1.50 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 131.7, 128.4, 128.1, 123.4, 90.1, 81.7, 79.8, 48.9, 45.8, 34.0, 28.7, 24.0. The spectral data matches that reported in the literature.[6] Comparison of the optical rotation to the literature value allows assignment of the absolute configuration as *S*.[7]

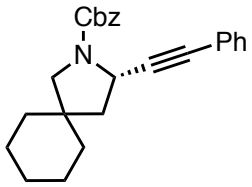


Benzyl *(S)*-2-(phenylethynyl)piperidine-1-carboxylate (5). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (5–10% ethyl acetate/hexane) to give compound **5** (run 1: 62.5 mg, 65%; run 2: 59.7 mg, 62%) as colorless oil. The enantiomeric excess was determined to be 94% (run 1: 94% ee; run 2: 93% ee) by chiral HPLC analysis (CHIRALPAK IE, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 14.47 min, t_R(minor) = 13.37 min. $[\alpha]_D^{22}$ = –108.3 (c 3.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 10H), 5.39 (s, br, 1H), 5.18 – 5.17 (m, 2H), 4.07 (d, J = 4.1 Hz, 1H), 3.24 – 3.17 (m, 1H), 1.90 – 1.67 (m, 5H), 1.50

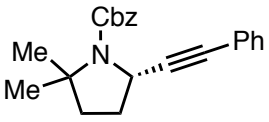
– 1.44 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 136.9, 131.9, 128.6, 128.4, 128.3, 128.1, 127.9, 123.0, 87.3, 84.6, 67.4, 45.1, 40.9, 30.9, 25.5, 20.2. The spectral data matches that reported in the literature.[6]



Benzyl *(S)*-2-(phenylethynyl)azepane-1-carboxylate (6). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (5–10% ethyl acetate/hexanes) to give compound **6** (run 1: 102.1 mg, 59%; run 2: 102.1 mg, 59%) as colorless oil. The enantiomeric excess was determined to be 59% (run 1: 60% ee; run 2: 58% ee) by chiral HPLC analysis (CHIRALPAK IB, 0.4 mL/min, 3% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 15.70 min, t_R(minor) = 17.70 min. $[\alpha]_D^{22}$ = –93.4 (c 2.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.42 – 7.26 (m, 10H, *overlaps with $CHCl_3$*), 5.28 – 5.06 (m, 3H), 3.98 – 3.85 (m, 1H), 3.22 – 3.14 (m, 1H), 2.30 – 2.20 (m, 1H), 1.83 – 1.37 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 156.2, 155.7, 137.1, 137.0, 131.9, 131.8, 128.6, 128.5, 128.4, 128.32, 128.30, 128.2, 128.1, 128.0, 127.9, 127.7, 123.2, 123.1, 89.2, 89.1, 83.0, 82.9, 67.4, 67.2, 48.1, 48.0, 43.1, 42.7, 35.9, 35.8, 29.0, 28.8, 28.6, 28.5, 25.0, 24.5; FTIR (neat) 2929, 1699, 1415, 1200, 756, 692 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{22}H_{24}NO_2$: 334.1807, found 334.1800.

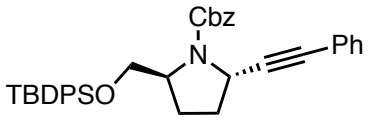


Benzyl *(S)*-3-(phenylethynyl)-2-azaspiro[4.5]decane-2-carboxylate (7). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (5–10% ethyl acetate/hexanes) to give compound **7** (run 1: 111.9 mg, 99%; run 2: 98.3 mg, 88%) as light yellow oil. The enantiomeric excess was determined to be 91% (run 1: 91% ee; run 2: 91% ee) by chiral HPLC analysis (CHIRALPAK IE, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 23.64 min, t_R(minor) = 20.20 min. $[\alpha]_D^{22}$ = –66.1 (c 2.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.44 – 7.25 (m, 10H, *overlaps with $CHCl_3$*), 5.35 – 5.08 (m, 2H), 4.77 – 4.72 (m, 1H), 3.45 – 3.36 (m, 2H), 2.16 – 2.00 (m, 2H), 1.70 – 1.39 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 155.0, 137.0, 131.7, 128.5, 128.3, 128.2, 127.8, 127.7, 123.3, 90.4, 82.9, 67.0, 56.9, 48.3, 47.8, 45.4, 36.1, 35.9, 26.1, 23.6, 23.5; FTIR (neat) 2925, 2854, 1706, 1450, 1411, 1354, 1116, 756, 693 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{25}H_{28}NO_2$: 374.2120, found 374.2111.



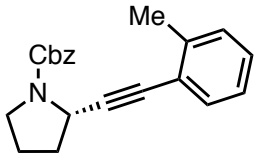
Benzyl *(S)*-2,2-dimethyl-5-(phenylethynyl)pyrrolidine-1-carboxylate (8). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (2–4% ethyl acetate/hexanes) to give compound **8** (run 1: 97.3 mg, 97%; run 2: 96.0 mg, 96%) as colorless oil. The enantiomeric excess was determined to be 92% (run

1: 93% ee; run 2: 90% ee) by chiral HPLC analysis (CHIRALPAK IE, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 10.93 min, t_R(minor) = 9.74 min. $[\alpha]_D^{22}$ = –134.9 (c 2.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.44 – 7.26 (m, 10H, *overlaps with $CHCl_3$*), 5.30 – 5.07 (m, 2H), 4.92 – 4.85 (m, 1H), 2.31 – 2.11 (m, 2H), 2.01 – 1.98 (m, 1H), 1.89 - 1.86 (m, 1H), 1.60 – 1.52 (m, 3H), 1.39 – 1.31 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 153.4, 137.4, 131.8, 128.5, 128.4, 128.2, 127.7, 127.5, 123.3, 90.3, 82.2, 67.2, 66.3, 61.7, 51.8, 50.9, 41.7, 40.5, 30.4, 30.1, 29.1, 28.0, 26.8, 25.6; FTIR (neat) 2965, 1703, 1399, 1347, 1071, 756, 692 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{22}H_{24}NO_2$: 334.1807, found 334.1798.



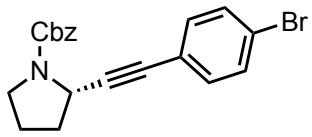
Benzyl *(2S,5S)*-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-(phenylethynyl)pyrrolidine-1-carboxylate (9). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (4–8% ethyl acetate/hexanes) to give compound **9** as a single diastereomer (run 1: 168.9 mg, 98%; run 2: 169.8 mg, 98%) and as light yellow oil. $[\alpha]_D^{22}$ = –115.1 (c 2.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.68 – 7.63 (m, 4H), 7.43 – 7.14 (m, 16H, *overlaps with $CHCl_3$*), 5.34 – 5.03 (m, 2H), 4.78 (dd, *J* = 16.3, 7.0 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.85 – 3.53 (m, 2H), 2.37 – 2.03 (m, 4H), 1.06 (d, *J* = 14.4 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 154.2, 137.1, 136.7, 135.7, 133.74, 133.70, 133.6, 133.5, 132.0, 131.8, 129.88, 129.85, 129.80, 129.77, 128.5, 128.3, 128.24, 128.21, 128.1, 128.0, 127.9, 127.83, 127.78, 127.7, 123.3, 123.2, 108.1, 90.1, 89.5, 82.2, 82.1, 67.0, 66.9, 64.5, 64.0, 59.0, 58.4, 50.4, 50.0, 32.2, 31.1, 27.6, 27.1, 27.0, 26.8, 19.4, 19.3; FTIR (neat) 2954, 2931, 2856, 1705, 1427, 1404, 1251, 1113, 701, 505 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{37}H_{40}NO_3Si$: 574.2777, found 574.2771.

Product **9** was also prepared by General Procedure A, except that (*R,R*)-**L5** was used and the reaction was performed on a 0.1-mmol scale, to give compound **9** as a single diastereomer in 66% as determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

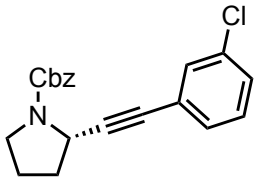


Benzyl *(S)*-2-(*o*-tolylethynyl)pyrrolidine-1-carboxylate (10). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (8–16% ethyl acetate/hexanes) to give compound **10** (run 1: 87.7 mg, 92%; run 2: 80.0 mg, 84%) as colorless oil. The enantiomeric excess was determined to be 94% (run 1: 94% ee; run 2: 93% ee) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 2% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 16.99 min, t_R(minor) = 14.85 min. $[\alpha]_D^{22}$ = –223.6 (c 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.64 – 6.86 (m, 9H), 5.33 – 5.09 (m, 2H), 4.90 – 4.78 (m, 1H), 3.61 (q, J = 10.4, 8.2 Hz, 1H), 3.45 (p, J = 7.8 Hz, 1H), 2.36 (d, J = 28.5 Hz, 3H), 2.26 – 1.88 (m, 4H).; ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.7, 154.6, 140.5, 140.3, 137.0, 132.1, 132.0, 129.5, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 125.6,

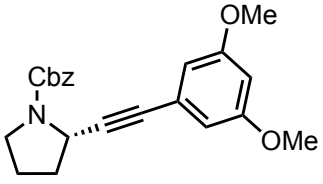
122.9, 122.8, 93.5, 93.3, 81.3, 67.0, 49.4, 49.0, 46.3, 45.9, 34.3, 33.5, 24.7, 23.9, 20.7; FTIR (neat) 3030, 2951, 1705, 1410, 1355, 1110, 1088, 757, 697 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{21}H_{22}NO_2$: 320.1651, found 320.1644.



Benzyl *(S)*-2-((4-bromophenyl)ethynyl)pyrrolidine-1-carboxylate (11). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (10–20% ethyl acetate/hexanes) to give compound **11** (run 1: 103 mg, 89%; run 2: 99.5 mg, 86%) as light yellow oil. The enantiomeric excess was determined to be 92% (run 1: 93% ee; run 2: 91% ee) by chiral HPLC analysis (CHIRALPAK IA, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 10.97 min, t_R(minor) = 9.02 min. $[\alpha]_D^{22}$ = –194.7 (c 1.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.73 – 6.93 (m, 9H), 5.38 – 5.05 (m, 2H), 4.84 – 4.72 (m, 1H), 3.63 - 3.54 (m, 1H), 3.52 – 3.36 (m, 1H), 2.31 – 2.05 (m, 3H), 2.05 - 1.92 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 137.0, 133.4, 133.2, 131.6, 131.5, 128.6, 128.1, 127.9, 127.8, 122.5, 122.1, 122.0, 90.8, 90.4, 81.4, 67.0, 49.3, 48.8, 46.4, 46.0, 34.0, 33.3, 24.7, 23.9. The spectral data matches that reported in the literature.[5]

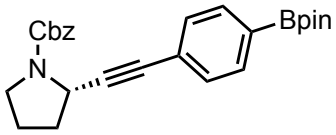


Benzyl *(S)-2*-((3-chlorophenyl)ethynyl)pyrrolidine-1-carboxylate (12). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (10–20% ethyl acetate/hexanes) to give compound **12** (run 1: 92.4 mg, 90%; run 2: 92.9 mg, 91%) as light yellow oil. The enantiomeric excess was determined to be 95% (run 1: 95% ee; run 2: 94% ee) by chiral HPLC analysis (CHIRALPAK IB, 0.6 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 16.60 min, t_R(minor) = 14.21 min. $[\alpha]_D^{22}$ = –188.2 (c 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.61 – 6.98 (m, 9H), 5.37 – 5.05 (m, 2H), 4.85 – 4.72 (m, 1H), 3.60 (m, 1H), 3.51 – 3.37 (m, 1H), 2.28 – 2.03 (m, 3H), 2.03 – 1.92 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 137.0, 134.2, 131.9, 131.7, 130.1, 129.9, 128.6, 128.1, 128.0, 127.8, 124.7, 90.9, 90.5, 81.0, 67.0, 49.2, 48.7, 46.4, 46.0, 34.0, 33.3, 24.7, 23.9; FTIR (neat) 2952, 2877, 1705, 1410, 1356, 1115, 1090, 767, 682 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{20}H_{19}ClNO_2$: 340.1104, found 340.1097.

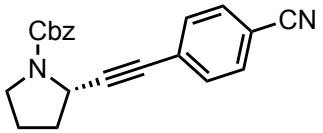


Benzyl *(S)-2*-((3,5-dimethoxyphenyl)ethynyl)pyrrolidine-1-carboxylate (13). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (30% ethyl acetate/hexanes) to give compound **13** (run 1: 69 mg, 63%; run 2: 89 mg, 82%) as colorless oil. The enantiomeric excess was determined to be 90% (run

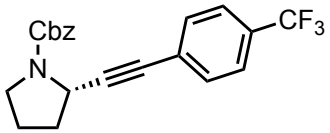
1: 91% ee; run 2: 88% ee) by chiral HPLC analysis (CHIRALPAK IB, 0.5 mL/min, 10% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 22.34 min, t_R(minor) = 17.54 min. $[\alpha]_D^{22}$ = –102.9 (c 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.53 – 7.18 (m, 5H), 6.65 – 6.38 (m, 3H), 5.36 – 5.08 (m, 2H), 4.88 - 4.71 (m, 1H), 3.75 (s, 6H), 3.66 – 3.52 (m, 1H), 3.51 – 3.36 (m, 1H), 2.27 – 2.06 (m, 3H), 2.03 – 1.90 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 160.5, 160.4, 154.6, 137.0, 136.9, 128.6, 128.5, 128.0, 127.8, 127.6, 127.5, 127.0, 124.4, 124.3, 109.6, 109.5, 101.8, 101.7, 89.1, 88.7, 82.3, 82.2, 66.9, 66.8, 55.5, 49.2, 48.7, 46.3, 45.9, 34.0, 33.3, 29.8, 24.6, 23.8; FTIR (neat) 2954, 1704, 1589, 1417, 1205, 1156 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{22}H_{24}NO_4$: 366.1705, found 366.1695.



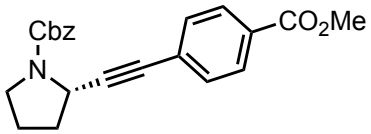
Benzyl *(S)-2-*((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethynyl)pyrrolidine-1-carboxylate (14). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (12–24% ethyl acetate/hexanes) to give compound **14** (run 1: 86.0 mg, 94%; run 2: 86.4 mg, 95%) as colorless oil. The enantiomeric excess was determined to be 92% (run 1: 92% ee; run 2: 92% ee) by chiral HPLC analysis (CHIRALPAK IE, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 23.64 min, t_R(minor) = 20.28 min. $[\alpha]_D^{22}$ = –92.0 (c 1.45, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.74 – 7.73 (m, 2H), 7.44 – 7.26 (m, 7H), 5.35 – 5.09 (m, 2H), 4.85 – 4.78 (m, 1H), 3.62 – 3.42 (m, 2H), 2.16 – 1.95 (m, 4H), 1.35 (s, 12 H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 137.0, 134.5, 131.1, 130.9, 128.5, 128.0, 127.8, 127.7, 125.9, 125.7, 90.9, 90.5, 84.0, 82.5, 66.9, 49.3, 48.8, 46.3, 45.9, 34.0, 33.3, 30.4, 25.0, 23.9; FTIR (neat) 2977, 1707, 1406, 1358, 1143, 1087 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{26}H_{31}BNO_4$: 432.2346, found 432.2349.



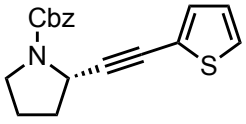
Benzyl *(S)-2-*((4-cyanophenyl)ethynyl)pyrrolidine-1-carboxylate (15). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (18–36% ethyl acetate/hexanes) to give compound **15** (run 1: 74.7 mg, 75%; run 2: 76.8 mg, 77%) as light yellow oil. The enantiomeric excess was determined to be 94% (run 1: 93% ee; run 2: 95% ee) by chiral HPLC analysis (CHIRALPAK IA, 0.5 mL/min, 10% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 17.92 min, t_R(minor) = 13.97 min. $[\alpha]_D^{22}$ = –118.6 (c 1.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.68 – 7.12 (m, 9H), 5.41 – 5.02 (m, 2H), 4.90 – 4.72 (m, 1H), 3.69 – 3.36 (m, 2H), 2.30 – 1.92 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 132.5, 132.3, 132.0, 128.6, 128.1, 128.0, 127.9, 118.6, 111.7, 94.3, 94.0, 81.0, 67.1, 49.3, 48.8, 46.4, 46.0, 33.9, 33.2, 24.8, 23.9; FTIR (neat) 2952, 2880, 2227, 1704, 1411, 1356, 1334, 1115, 1089, 840 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{21}H_{19}N_2O_2$: 331.1447, found 331.1442.



Benzyl *(S)*-2-((4-(trifluoromethyl)phenyl)ethynyl)pyrrolidine-1-carboxylate (16). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (10–20% ethyl acetate/hexanes) to give compound **16** (run 1: 81.9 mg, 73%; run 2: 89.2 mg, 80%) as colorless oil. The enantiomeric excess was determined to be 93% (run 1: 93% ee; run 2: 92% ee) by chiral HPLC analysis (CHIRALPAK IE, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 20.61 min, t_R(minor) = 13.63 min. $[\alpha]_D^{22}$ = –90.7 (c 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.67 – 7.11 (m, 9H), 5.37 – 5.06 (m, 2H), 4.87 – 4.73 (m, 1H), 3.54 (dd, J = 56.1, 10.9 Hz, 2H), 2.31 – 1.85 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 137.0, 136.9, 132.2, 132.0, 130.2, 129.9, 128.5, 128.1, 128.0, 127.8, 127.0, 125.2, 124.0 (q, *J* = 272.0 Hz), 120.0, 92.2, 91.8, 81.1, 67.0, 49.2, 48.8, 46.4, 46.0, 34.0, 33.2, 24.7, 23.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.8. The spectral data matches that reported in the literature.[5]

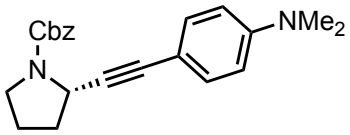


Benzyl *(S)*-2-((4-(methoxycarbonyl)phenyl)ethynyl)pyrrolidine-1-carboxylate (17). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (30% ethyl acetate/hexanes) to give compound **17** (run 1: 81 mg, 74%; run 2: 102 mg, 94%) as colorless oil. The enantiomeric excess was determined to be 93% (run 1: 92% ee; run 2: 94% ee) by chiral HPLC analysis (CHIRALPAK IA, 1 mL/min, 5% *i*PrOH/hexane, λ = 254 nm); t_R(major) = 16.10 min, t_R(minor) = 13.23 min. $[\alpha]_D^{22}$ = –110.8 (c 1.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.95 (d, J = 8.2 Hz, 2H), 7.55 – 7.18 (m, 7H), 5.42 – 5.00 (m, 2H), 4.90 – 4.69 (m, 1H), 3.90 (s, 3H), 3.69 – 3.53 (m, 1H), 3.53 – 3.34 (m, 1H), 2.25 – 1.91 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 166.6, 154.5, 137.0, 131.7, 129.6, 129.4, 128.5, 128.0, 127.9, 127.7, 92.7, 92.4, 81.7, 67.0, 52.2, 49.3, 48.8, 46.3, 45.9, 33.9, 33.2, 24.6, 23.9; FTIR (neat) 2951, 1706, 1409, 1356, 1276, 1111, 769 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{22}H_{22}NO_4$: 364.1549, found 364.1540.

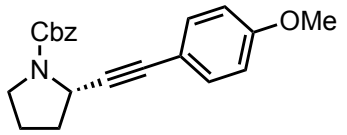


Benzyl *(S)*-2-(thiophen-2-ylethynyl)pyrrolidine-1-carboxylate (18). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (10–20% ethyl acetate/hexanes) to give compound **18** (run 1: 75.6 mg, 81%; run 2: 74.5 mg, 80%) as light yellow oil. The enantiomeric excess was determined to be 91% (run 1: 90% ee; run 2: 91% ee) by chiral HPLC analysis (CHIRALPAK IE, 1 mL/min, 8% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 17.48 min, t_R(minor) = 16.15 min. $[\alpha]_D^{22}$ = –132.1 (c 1.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.63 – 6.82 (m, 8H), 5.36 – 5.07 (m, 2H), 4.88 – 4.73 (m, 1H), 3.67 – 3.35 (m, 2H), 2.31 – 1.87 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 137.0, 136.9, 132.2, 132.0, 128.6, 128.1,

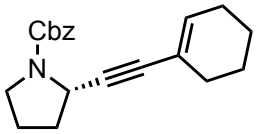
127.9, 127.7, 127.0, 126.9, 123.1, 123.0, 93.4, 93.1, 75.7, 75.6, 67.0, 49.4, 49.0, 46.4, 46.0, 34.0, 33.2, 24.7, 23.9; FTIR (neat) 3479, 3032, 2978, 2951, 2878, 2222, 1704, 1446, 1411, 1356, 1196, 1113, 769, 698 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{18}H_{18}NO_2S$: 312.1058, found 312.1052.



Benzyl *(S)*-2-((4-(dimethylamino)phenyl)ethynyl)pyrrolidine-1-carboxylate (19). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (12–24% ethyl acetate/hexanes) to give compound **19** (run 1: 74.7 mg, 70%; run 2: 74.5 mg, 78%) as yellow oil. The enantiomeric excess was determined to be 70% (run 1: 72% ee; run 2: 68% ee) by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 19.04 min, t_R(minor) = 12.88 min. $[\alpha]_D^{22}$ = –101.2 (c 1.75, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.59 – 7.11 (m, 7H), 6.60 (d, J = 8.2 Hz, 2H), 5.37 – 5.07 (m, 2H), 4.87 – 4.72 (m, 1H), 3.67 – 3.34 (m, 2H), 2.97 (s, 6H), 2.28 – 1.87 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 154.8, 150.2, 137.3, 132.9, 128.5, 128.0, 127.8, 127.7, 111.9, 87.2, 83.2, 66.9, 49.5, 49.1, 46.3, 45.9, 40.4, 34.3, 33.6, 24.6, 23.9; FTIR (neat) 2949, 2222, 1703, 1608, 1521, 1411, 1355 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{22}H_{25}N_2O_2$: 349.1916, found 349.1910.

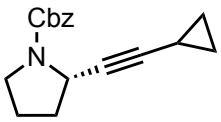


Benzyl *(S)*-2-((4-methoxyphenyl)ethynyl)pyrrolidine-1-carboxylate (20). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (10–20% ethyl acetate/hexanes) to give compound **20** (89.7 mg, 89%) as colorless oil. The enantiomeric excess was determined to be 77% by chiral HPLC analysis (CHIRALPAK IB, 0.5 mL/min, 10% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 24.98 min, t_R(minor) = 15.29 min. $[\alpha]_D^{22}$ = –134.6 (c 1.85, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.56 – 7.16 (m, 7H), 6.81 (d, J = 8.2 Hz, 2H), 5.36 – 5.07 (m, 2H), 4.86 – 4.73 (m, 1H), 3.81 (s, 3H), 3.69 - 3.33 (m, 2H), 2.26 – 1.89 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 159.4, 154.5, 137.0, 133.2, 133.0, 128.4, 127.9, 127.6, 127.5, 115.0, 113.8, 113.7, 88.0, 87.6, 82.1, 66.7, 55.2, 49.2, 48.7, 46.2, 45.8, 34.0, 33.3, 24.5, 23.7; FTIR (neat) 2952, 1704, 1606, 1509, 1411, 1356, 1248, 1172, 1113, 1088, 833 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{21}H_{22}NO_3$: 336.1600, found 336.1593.

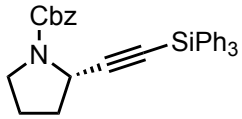


Benzyl *(S)*-2-(cyclohex-1-en-1-ylethynyl)pyrrolidine-1-carboxylate (21). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (5–10% ethyl acetate/hexanes) to give compound **21** (59.7 mg, 64%) as colorless oil. The enantiomeric excess was determined to be 58% by chiral HPLC analysis

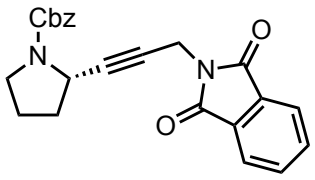
(CHIRALPAK IA, 0.8 mL/min, 1% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 26.84 min, t_R(minor) = 30.69 min. $[\alpha]_D^{22}$ = –80.9 (c 1.35, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.53 – 7.24 (m, 5H), 6.04 (d, J = 29.9 Hz, 1H), 5.33 – 5.05 (m, 2H), 4.76 - 4.62 (m, 1H), 3.63 – 3.28 (m, 2H), 2.24 – 1.81 (m, 8H), 1.66 – 1.50 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 154.7, 137.3, 134.9, 128.5, 128.0, 127.8, 127.7, 120.5, 84.2, 66.8, 49.3, 48.8, 46.3, 45.9, 34.3, 33.5, 29.4, 25.7, 24.6, 23.8, 22.5, 21.7; FTIR (neat) 3456, 2929, 1705, 1411, 1356, 1113, 697 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{20}H_{24}NO_2$: 310.1807, found 310.1797.



Benzyl *(S)*-2-(cyclopropylethynyl)pyrrolidine-1-carboxylate (22). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (7–14% ethyl acetate/hexanes) to give compound **22** (33.0 mg, 41%) as colorless oil. The enantiomeric excess was determined to be 50% by chiral HPLC analysis (CHIRALPAK IB, 1 mL/min, 3% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 8.57 min, t_R(minor) = 9.40 min. $[\alpha]_D^{22}$ = –34.3 (c 1.15, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.51 – 7.27 (m, 5H), 5.33 – 5.04 (m, 2H), 4.61 – 4.45 (m, 1H), 3.58 – 3.28 (m, 2H), 2.15 – 1.82 (m, 4H), 1.25 - 1.11 (m, 1H), 0.78 – 0.47 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 137.2, 128.5, 128.0, 127.8, 127.6, 85.6, 75.6, 75.2, 66.7, 48.9, 48.5, 46.2, 45.8, 34.3, 33.5, 29.8, 24.5, 23.7, 8.2, -0.4; FTIR (neat) 2951, 2877, 2239, 1705, 1446, 1412, 1357, 1181, 1112, 1088, 769, 697 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{17}H_{20}NO_2$: 270.1494, found 270.1488.



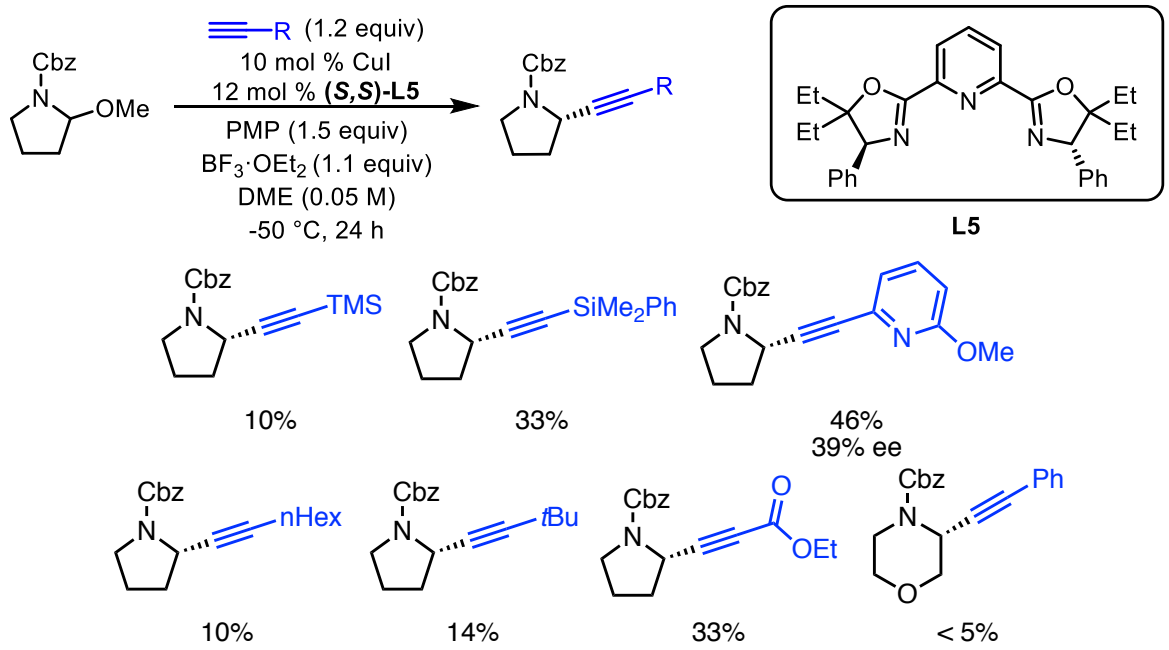
Benzyl *(S)*-2-((triphenylsilyl)ethynyl)pyrrolidine-1-carboxylate (23). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (7–14% ethyl acetate/hexanes) to give compound **23** (102.7 mg, 70%) as colorless oil. The enantiomeric excess was determined to be 43% by chiral HPLC analysis (CHIRALPAK IA, 1 mL/min, 5% *i*-PrOH/hexane, λ = 254 nm); t_R(major) = 10.10 min, t_R(minor) = 6.81 min. $[\alpha]_D^{22}$ = –44.6 (c 2.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.82 – 6.79 (m, 20H), 5.23 – 5.08 (m, 2H), 4.81 - 4.67 (m 1H), 3.68 - 3.53 (m, 1H), 3.52 - 3.36 (m, 1H), 2.27 - 12.04 (m, 3H), 2.04 - 1.90 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 154.7, 135.7, 133.8, 133.6, 130.0, 128.5, 128.1, 127.8, 110.8, 82.0, 81.8, 67.2, 67.0, 60.5, 49.6, 49.1, 46.4, 45.9, 34.2, 33.3, 24.7, 24.0; FTIR (neat) 3067, 2951, 2172, 1706, 1428, 1410, 1355, 1113, 709, 698, 509 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{32}H_{30}NO_2Si$: 488.2046, found 488.2036.



Benzyl *(S)*-2-(3-(1,3-dioxoisoindolin-2-yl)prop-1-yn-1-yl)pyrrolidine-1-carboxylate (24). Prepared via General Procedure A. Crude material was purified by silica gel chromatography (7–14% ethyl acetate/hexanes) to give compound **24** (80.1 mg, 68%) as yellow solid. The enantiomeric excess was determined to be 34% by chiral HPLC analysis (CHIRALPAK IA, 1 mL/min, 15% *i*PrOH/hexane, λ = 254 nm); t_R(major) = 24.48 min, t_R(minor) = 33.86 min. $[\alpha]_D^{22}$ = –25.0 (c 2.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.84 (dd, J = 5.5, 3.1 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.47 – 7.07 (m, 5H), 5.19 – 5.04 (m, 2H), 4.65 – 4.26 (m, 3H), 3.54 – 3.27 (m, 2H), 2.10 – 1.80 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 167.0, 154.4, 136.9, 134.2, 132.1, 128.4, 127.9, 127.7, 127.6, 123.5, 83.2, 83.0, 75.6, 66.9, 48.6, 48.1, 46.2, 45.8, 33.7, 33.0, 27.5, 27.3, 24.4, 23.6; FTIR (neat) 2954, 1772, 1720, 1418, 1392, 1348, 1117, 942, 721 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{23}H_{21}N_2O_4$: 389.1501, found 389.1489.

Limitations in Substrate Scope[a]

Scheme S3. Limitations in Substrate Scope

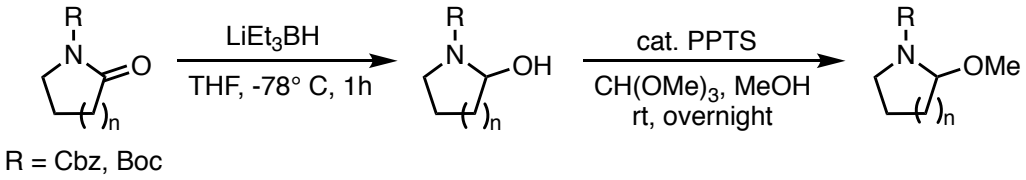


[a] Yields are determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. ee determined by HPLC using a chiral stationary phase.

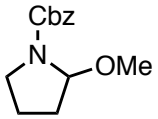
Preparation of Aminal Substrates

General Procedure B: Conversion of Carbamates to Hemiaminal Ethers

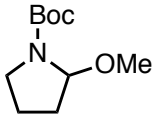
Scheme S4. Synthesis of Hemiaminal Ethers



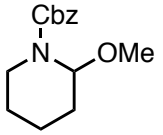
This procedure is adapted from a literature procedure.[8] A solution of lithium triethylborohydride in THF (1.0 M, 1.2 equiv) was added dropwise to a solution of carbamate (1.0 equiv) in anhydrous THF (0.18 M) at –78 °C under N_2. After stirring at –78 °C for 1 h, the reaction mixture was allowed to warm to 0 °C and treated with saturated aqueous $NaHCO_3$ (10 mL), and 1 drop of H_2O_2. The mixture was stired for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with H_2O (20 mL) and sat. NaCl (20 mL), dried ($MgSO_4$), filtered, and concentrated to provide the hemiaminal as an oil. It was then dissolved in anhydrous MeOH (0.77 M) and treated with trimethyl orthoformate (5.0 equiv) and PPTS (pyridinium *p*-toluenesulfonate, 15 mol %). After stirring at room temperature overnight, Et_3N (0.40 equiv) was added. The solvent was evaporated and the crude methoxyaminal was purified by silica gel chromatography.



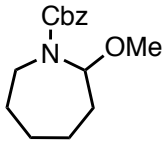
Benzyl 2-methoxypyrrolidine-1-carboxylate (1a). Prepared via General Procedure B on a 10-mmol scale with benzyl 2-oxopyrrolidine-1-carboxylate. Crude material was purified by silica gel chromatography (8–16% ethyl acetate/hexanes) to give **1a** (1.83 g, 78%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.44 – 7.27 (m, 5H), 5.27 – 5.09 (m, 3H), 3.57 – 3.48 (m, 1H), 3.47 - 3.23 (m, 4H), 2.14 – 1.99 (m, 1H), 1.99 – 1.84 (m, 2H), 1.83 – 1.69 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 155.9, 155.1, 136.8, 128.6, 128.2, 128.0, 89.3, 88.7, 67.3, 67.0, 56.1, 55.5, 46.1, 45.9, 32.7, 32.1, 22.8, 21.9. The spectral data matches that reported in the literature.[9]



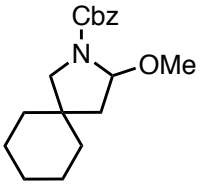
***tert*-Butyl 2-methoxypyrrolidine-1-carboxylate (1b).** Prepared via General Procedure B on a 5-mmol scale with commercially available *tert*-butyl 2-oxopyrrolidine-1-carboxylate. Crude material was purified by silica gel chromatography (10% ethyl acetate/hexanes) to give **1b** (0.84 g, 84%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 5.26 – 5.02 (m, 1H), 3.42 (m, 1H), 3.38 – 3.24 (m, 4H), 2.10 – 1.95 (m, 1H), 1.92 – 1.85 (m, 2H), 1.81 – 1.69 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 154.6, 88.8, 80.1, 79.8, 56.0, 55.6, 46.1, 45.5, 32.9, 32.1, 28.6, 22.8, 21.9. The spectral data matches that reported in the literature.[9]



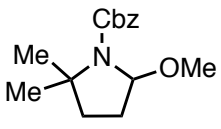
Benzyl 2-methoxypiperidine-1-carboxylate (1c). Prepared via General Procedure B on a 10-mmol scale with benzyl 2-oxopiperidine-1-carboxylate. Crude material was purified by silica gel chromatography (10% ethyl acetate/hexanes) to give **1c** (2.07 g, 89%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.44 – 7.22 (m, 5H, *overlaps with $CHCl_3$*), 5.48 – 5.30 (m, 1H), 5.27 – 5.03 (m, 2H), 4.06 – 3.89 (m, 1H), 3.33 – 3.09 (m, 3H), 3.07 – 2.88 (m, 1H), 1.96 – 1.30 (m, 6H). The spectral data matches that reported in the literature.[9]



Benzyl 2-methoxyazepane-1-carboxylate (1d). Prepared via General Procedure B on a 7.4-mmol scale with 2-oxoazepane-1-carboxylate. Crude material was purified by silica gel chromatography (10% ethyl acetate/hexanes) to give **1d** (0.58 g, 30%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.42 – 7.27 (m, 5H), 5.43 – 5.25 (m, 1H), 5.24 – 5.11 (m, 2H), 3.81 – 3.63 (m, 1H), 3.33 – 3.14 (m, 3H), 3.04 – 2.93 (m, 1H), 2.32 – 2.18 (m, 1H), 1.87 – 1.74 (m, 1H), 1.71 – 1.61 (m, 2H), 1.59 – 1.44 (m, 2H), 1.37 – 1.25 (m, 1H), 1.23 – 1.10 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 157.3, 156.1, 137.9, 136.8, 128.7, 128.2, 128.13, 128.09, 127.8, 86.3, 86.1, 67.4, 67.2, 55.3, 55.0, 41.1, 40.8, 34.9, 34.7, 30.1, 30.0, 28.5, 27.6, 22.7, 22.6. The spectral data matches that reported in the literature.[9]

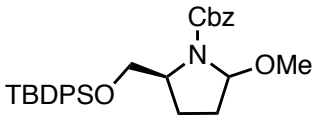


Benzyl 3-methoxy-2-azaspiro[4.5]decane-2-carboxylate (1e). Prepared via General Procedure B on a 5.0-mmol scale with benzyl 3-oxo-2-azaspiro[4.5]decane-2-carboxylate. Crude material was purified by silica gel chromatography (5% ethyl acetate/hexanes) to give **1e** (0.18 g, 12%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.43 – 7.28 (m, 5H), 5.25 – 5.09 (m, 3H), 3.47 – 3.18 (m, 5H), 1.87 – 1.73 (m, 2H), 1.72 – 1.27 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 156.1, 155.1, 136.8, 136.6, 128.6, 128.2, 128.0, 90.1, 89.4, 67.3, 67.1, 56.7, 56.4, 55.7, 44.9, 44.1, 41.9, 41.0, 37.9, 37.7, 36.9, 36.7, 25.9, 23.8, 23.7, 23.5; FTIR (neat) 2926, 2853, 1708, 1406, 1078, 697 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{18}H_{26}NO_3$: 304.1913, found 304.1903.



Benzyl 5-methoxy-2,2-dimethylpyrrolidine-1-carboxylate (1f). Prepared via General Procedure B on a 2.64-mmol scale with benzyl 2,2-dimethyl-5-oxopyrrolidine-1-carboxylate. Crude material was purified by silica gel chromatography (5% ethyl acetate/hexanes) to give **1f** (0.60 g, 86%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$,

mixture of rotamers) δ 7.46 – 7.26 (m, 5H), 5.28 – 5.08 (m, 3H), 3.43 – 3.15 (m, 3H), 2.21 – 2.00 (m, 1H), 1.85 – 1.70 (m, 3H), 1.58 – 1.41 (m, 3H), 1.39 – 1.22 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 156.0, 153.6, 136.7, 136.5, 129.49, 128.45, 128.1, 127.9, 91.1, 90.1, 67.1, 66.5, 61.6, 61.1, 55.8, 55.3, 39.8, 38.5, 29.1, 28.8, 28.1, 26.0, 24.7; FTIR (neat) 2966, 2945, 1705, 1455, 1399, 1351, 1300, 1092, 1070, 697 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{15}H_{22}NO_3$: 264.1600, found 264.1592.



Benzyl (2S)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-methoxypyrrolidine-1-carboxylate (1g). Prepared via General Procedure B on a 3.22-mmol scale with benzyl (S)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-5-oxopyrrolidine-1-carboxylate. Crude material was purified by silica gel chromatography (6–12% ethyl acetate/hexanes) to give **1g** (1.05 g, 65%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.92 – 6.83 (m, 15H), 5.35 – 4.90 (m, 3H), 3.99 (d, J = 8.3 Hz, 2H), 3.71 - 3.50 (m, 1H), 3.38 – 3.10 (m, 3H), 2.26 - 2.05 (m, 2H), 1.97 – 1.69 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ 156.1, 155.3, 136.5, 135.7, 133.9, 129.7, 128.6, 128.1, 128.05, 127.7, 90.4, 89.7, 67.2, 66.7, 65.8, 59.8, 59.2, 55.6, 55.2, 32.2, 31.6, 27.4, 27.0, 19.4. The spectral data matches that reported in the literature.[10]

Preparation of Carbamates

The Cbz-protected lactams **1aa, 1cc, 1ff** were all synthesized as described previously,[10] as was **1dd**,[11] **1ee**,[11] and **1gg** (Figure 1).[12]

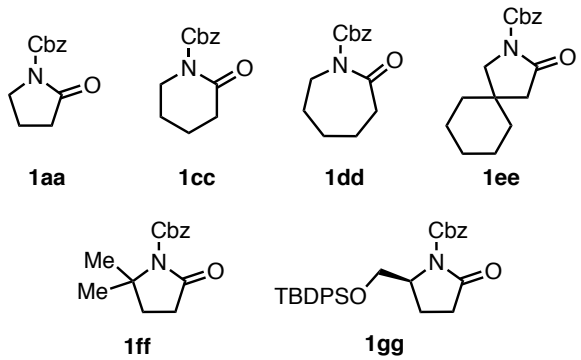
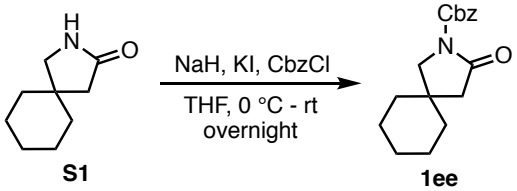
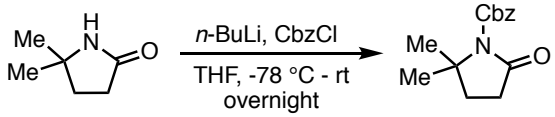


Figure S1. Cbz-protected lactams.



Benzyl 3-oxo-2-azaspiro[4.5]decane-2-carboxylate (1ee). Prepared according to a procedure adapted from the literature.[11] A solution of commercially available lactam **S1** (3.06 g, 20 mmol) in anhydrous THF (22 mL) was added under N_2 to a mixture of NaH (60%, 0.96 g 24 mmol), KI (4.18 g, 25 mmol), and anhydrous THF (20 mL).

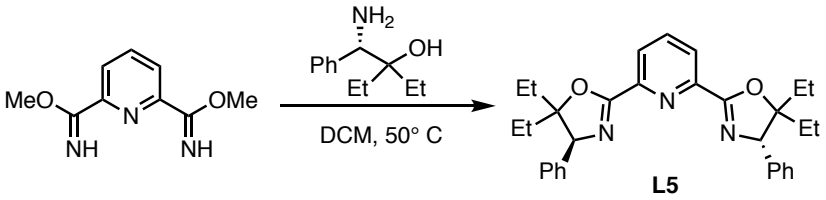
The mixture was stirred at 0 °C for 15 min. The mixture was then stirred at rt for 1 h, and cooled again to 0 °C before the addition of benzyl chloroformate (2.84 mL, 20 mmol). After being stirred for 1 h at 0 °C, the mixture was warmed to rt and stirred overnight. A saturated aqueous solution of NH_4Cl (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with H_2O (30 mL × 2) and sat. NaCl (30 mL × 1), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel chromatography to give **1ee** (2.45 g, 43%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 5H), 5.27 (s, 2H), 3.56 (s, 2H), 2.39 (s, 2H), 1.55 – 1.35 (m, 10H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 151.8, 135.5, 128.7, 128.6, 128.4, 128.3, 127.8, 127.1, 77.4, 77.2, 77.0, 68.1, 65.5, 57.3, 45.5, 36.3, 35.3, 25.6, 22.7, 14.3; FTIR (neat) 3503, 3032, 2926, 2853, 1789, 1752, 1718, 1452, 1382, 1311, 1218, 1173, 1047, 774, 736, 697 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{17}H_{22}NO_3$: 288.1600, found 288.1591.



S2 **1ff**

Benzyl 2,2-dimethyl-5-oxopyrrolidine-1-carboxylate (1ff). Prepared according to a procedure adapted from the literature.[13] A solution of *n*-BuLi in hexanes (2.5 M, 1.1 equiv) was added dropwise to a solution of commercially available lactam **S2** (4.4 mmol, 1.0 equiv) in anhydrous THF (0.27 M) at –78 °C under N_2. After stirring at –78 °C for 30 minutes, CbzCl (1.1 equiv) was added, and the reaction mixture was stirred at –78 °C for 1 h. Then the reaction was allowed to warm to room temperature and stirred overnight. Water was added, and the mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with H_2O (30 mL × 2) and sat. NaCl (30 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel chromatography to give **1ff** (0.65 g, 60%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 5H), 5.29 (s, 2H), 2.51 (t, J = 8.1 Hz, 2H), 1.88 (t, J = 8.1 Hz, 2H), 1.47 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 151.9, 135.5, 128.7, 128.4, 128.1, 77.4, 77.2, 77.0, 68.0, 62.7, 34.5, 30.9, 26.8; FTIR (neat) 3490, 2959, 2891, 1791, 1752, 1717, 1383, 1361, 1313, 1268, 1188, 1049, 774, 738, 698 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{14}H_{18}NO_3$: 248.1287, found 248.1278.

Preparation of Ph-PyBox ligand L5



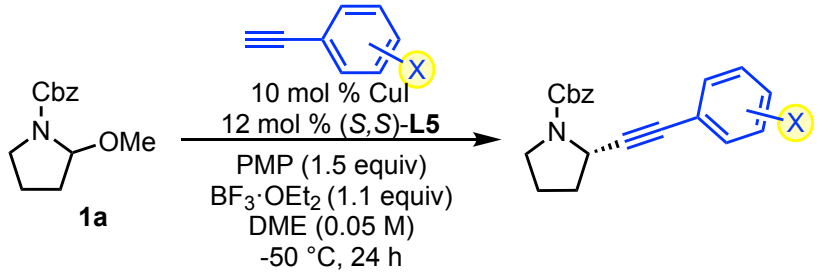
L5

2,6-bis((S)-5,5-diethyl-4-phenyl-4,5-dihydrooxazol-2-yl)pyridine (L5). Prepared according to a procedure adapted from the literature using the corresponding amino alcohol.[14] To an oven-dried, 15-mL pressure tube was added bisimidate (0.259 g, 1.34 mmol, 1.0 equiv), chiral amino alcohol (2.68 mmol, 2.0 equiv), and anhydrous CH_2Cl_2 (5 mL, 0.27 M). The tube was sealed, and the mixture was heated in an oil bath at 50 °C for 2 days. The

reaction was then allowed to cool to rt. The crude mixture was diluted with CH_2Cl_2 (10 mL), and washed with H_2O (10 mL × 3). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified via silica gel chromatography to give **L5** (0.45 g, 48%) as a yellow solid (mp 52–56 °C): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, J = 7.9 Hz, 2H), 7.90 (t, J = 7.9 Hz, 1H), 7.33 - 7.31 (m, 4H), 7.28 – 7.24 (m, 6H, *overlaps with CHCl₃*), 5.23 (s, 2H), 2.00 - 1.95 (m, 4H), 1.42 (dq, J = 14.8, 7.4 Hz, 2H), 1.17 (dq, J = 14.6, 7.3 Hz, 2H), 1.08 (t, J = 7.4 Hz, 6H), 0.80 (t, J = 7.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 147.4, 138.3, 137.5, 128.2, 128.1, 127.6, 126.0, 93.4, 76.2, 30.1, 27.5, 8.3, 7.8; FTIR (neat) 3430, 3061, 3029, 2971, 2941, 2881, 1639, 1573, 1453, 1382, 1264, 1102, 935, 735, 701 cm^{-1}; HRMS (ESI+) $[M+H]^+$ calculated for $C_{31}H_{36}N_3O_2$: 482.2808, found 482.2814.

Hammett Correlation

Table S8. Hammett Correlation



entry	X	σ	ee	er	log er
1	*p*-OMe	-0.27	77	7.7	0.89
2	*m*-OMe	0.12	90	19	1.28
3	*p*-NMe_2	-0.83	70	5.67	0.75
4	*p*-CF_3	0.54	93	27.57	1.44
5	*p*-CN	0.66	94	32.33	1.51
6	*p*-CO_2Me	0.45	93	27.57	1.44
7	*m*-Cl	0.37	95	39	1.59
8	*p*-Br	0.23	92	24	1.38

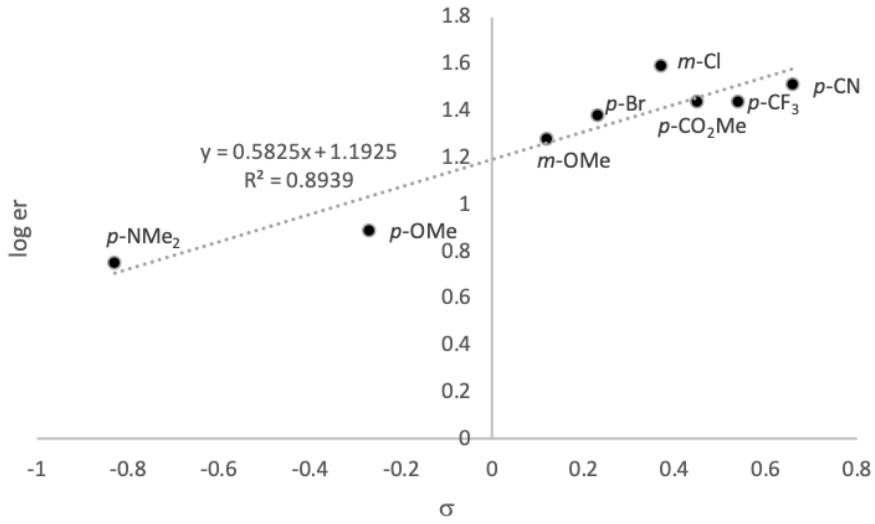


Figure S2. Hammett Correlation

References

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15* (5), 1518–1520. https://doi.org/10.1021/om9503712.

(2) Steffan, T.; Renukappa-Gutke, T.; Höfner, G.; Wanner, K. T. Design, Synthesis and SAR Studies of GABA Uptake Inhibitors Derived from 2-Substituted Pyrrolidine-2-Yl-Acetic Acids. *Bioorganic Med. Chem.* **2015**, *23* (6), 1284–1306. https://doi.org/10.1016/j.bmc.2015.01.035.

(3) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. Total Synthesis of Swinholide a, Preswinholide a, and Hemiswinholide A. *Chem. - A Eur. J.* **1996**, *2* (7), 847–868. https://doi.org/10.1002/chem.19960020718.

(4) De Mattos, M. C.; De Fonseca, T. S.; Da Silva, M. R.; De Oliveira, M. D. C. F.; De Lemos, T. L. G.; De

Marques, R. A. Chemoenzymatic Synthesis of Rasagiline Mesylate Using Lipases. *Appl. Catal. A Gen.* **2015**, *492* (1), 76–82. https://doi.org/10.1016/j.apcata.2014.12.015.

(5) Le Vaillant, F.; Courant, T.; Waser, J. Room-Temperature Decarboxylative Alkynylation of Carboxylic Acids Using Photoredox Catalysis and EBX Reagents. *Angew. Chemie - Int. Ed.* **2015**, *54* (38), 11200–11204. https://doi.org/10.1002/anie.201505111.

(6) Yang, C.; Yang, J. D.; Li, Y. H.; Li, X.; Cheng, J. P. 9,10-Dicyanoanthracene Catalyzed Decarboxylative Alkynylation of Carboxylic Acids under Visible-Light Irradiation. *J. Org. Chem.* **2016**, *81* (24), 12357–12363. https://doi.org/10.1021/acs.joc.6b02385.

(7) Wang, Y.; Wen, X.; Cui, X.; Zhang, X. P. Enantioselective Radical Cyclization for Construction of 5-Membered Ring Structures by Metalloradical C-H Alkylation. *J. Am. Chem. Soc.* **2018**, *140* (14), 4792–4796. https://doi.org/10.1021/jacs.8b01662.

(8) Louwrier, S.; Tuynman, A.; Hiemstra, H. Synthesis of Bicyclic Guanidines from Pyrrolidin-2-One. *Tetrahedron* **1996**, *52* (7), 2629–2646.

(9) Kabeshov, M. A.; Musio, B.; Murray, P. R. D.; Browne, D. L.; Ley, S. V. Expedient Preparation of Nazlinine and a Small Library of Indole Alkaloids Using Flow Electrochemistry as an Enabling Technology. *Org. Lett.* **2014**, *16* (17), 4618–4621. https://doi.org/10.1021/ol502201d.

(10) Liu, X. K.; Ye, J. L.; Ruan, Y. P.; Li, Y. X.; Huang, P. Q. Total Synthesis of (-)-Sessilifoliamide J. *J. Org. Chem.* **2013**, *78* (1), 35–41. https://doi.org/10.1021/jo3014484.

(11) Sureshbabu, P.; Azeez, S.; Muniyappan, N.; Sabiah, S.; Kandasamy, J. Chemoselective Synthesis of Aryl Ketones from Amides and Grignard Reagents via C(O)-N Bond Cleavage under Catalyst-Free Conditions. *J. Org. Chem.* **2019**, *84* (18), 11823–11838. https://doi.org/10.1021/acs.joc.9b01699.

(12) Martin, S. F.; Bur, S. K. Vinylogous Mannich Reactions. Stereoselective Formal Synthesis of Pumiliotoxin 251D. *Tetrahedron* **1999**, *55* (29), 8905–8914. https://doi.org/10.1016/S0040-4020(99)00452-4.

(13) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. Organometallic Ring-Opening Reactions of N-Acyl and N-Alkoxycarbonyl Lactams. Synthesis of Cyclic Imines. *J. Org. Chem.* **1989**, *54* (1), 228–234. https://doi.org/10.1021/jo00262a048.

(14) Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Magerlein, W.; Hugl, H.; Beller, M. Ruthenium-Catalyzed Asymmetric Epoxidation of Olefins Using H 2O2, Part I: Synthesis of New Chiral N,N,N,-Tridentate Pybox and Pyboxazine Ligands and Their Ruthenium Complexes. *Chem. - A Eur. J.* **2006**, *12* (7), 1855–1874. https://doi.org/10.1002/chem.200501261.

NMR Spectra

HPLC and SFC Traces