

Copper Catalyzed Asymmetric Propargylation of Aldehydes

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Part A

I. General Information

Anhydrous solvents (THF and MTBE) were obtained from Aldrich or Fisher and utilized with a specification of < 50 ppm water determined by Karl Fisher analysis. Copper (II) isobutyrate was obtained from Strem (93-2909), and LiOtBu was obtained from Aldrich as a 1.0 M solution in THF. Diethyl zinc 1.1 M in toluene was obtained from Aldrich. All other reagents were utilized as received from commercial sources. Reactions were performed under an argon atmosphere unless otherwise indicated. Flash chromatography was performed on a Combi-Flash system with silica columns. HPLC analysis was performed with a TSK-gel SuperODS column (ID 4.6 mm, length 5.0 cm) at 220nm with a 10-90% MeCN gradient in water over 9 min, and hold at 90% MeCN for 1 min. NMR analysis was performed on a Bruker 400 MHz or 500 MHz instrument calibrated to TMS or residual solvent, CDCl₃ (Proton 7.26 ppm, Carbon 77.0 ppm), DMSO-d₆ (Proton 2.49 ppm, Carbon 39.5 ppm), or benzene-d₆ (Proton 7.16 ppm, Carbon 128.06 ppm). Borolane **1**¹ and BIBOP ligands² were prepared according to literature procedures. Standards of homopargylic alcohol **7** and allenylic alcohol **8** were prepared according to literature procedures.³

¹ Hoffmann, R.W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387-2394.

² Tang, W.; Qu, B.; Capacci, A.G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N.K.; Krishnamurthy, D.; Senanayake, C.H. *Org. Lett.* **2010**, *12*, 176-179.

II. Complete Optimization Studies

The reaction between the parent aldehyde and the propargyl borolane reagent **1** is slow at ambient temperature and favors the allene product³ (SI-Table 1). Addition of stoichiometric CuBr·SMe₂ or catalytic CuCl slightly accelerated the propargylation to favor the homopropargylic product.

Table SI-1: Background reactions^a

entry	conditions	temperature time	conversion ^b	7:8 ^c	yield ^d
1	Toluene	20 °C 3 d	86%	1 : 2	83%
2	THF	20 °C 20 h	31%	1 : 2	31%
3	5% CuCl	-10 °C, 18 h	51%	3 : 1	49%
4	1 equiv. CuBr·SMe ₂ , THF	20 °C 20 h	68%	2 : 1	68%

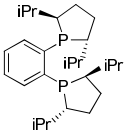
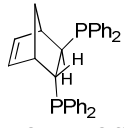
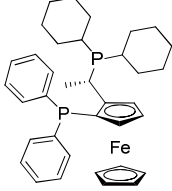
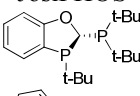
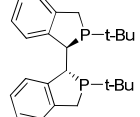
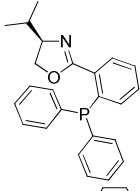
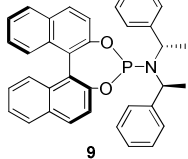
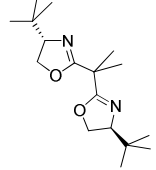
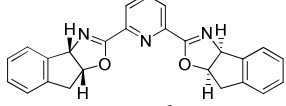
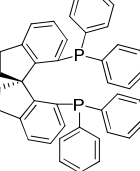
^a 1.5 equiv. borolane **1** to aldehyde. ^b Molar conversion based on recovered starting aldehyde **6**. ^c Site selectivity between alkyne **7** to allene **8**. ^d HPLC assay yield for both regioisomers.

The ligands examined for the Cu-OtBu catalyzed propargylation of p-anisaldehyde **6** are depicted in table **SI-2**.

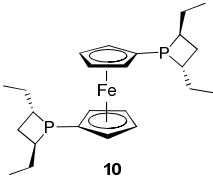
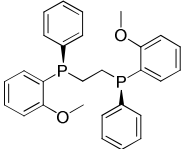
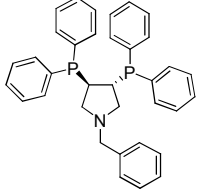
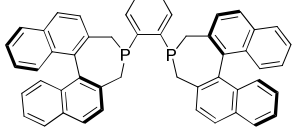
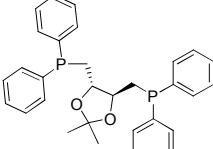
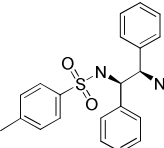
Table SI-2: Ligands examined for the Cu-OtBu catalyzed propargylation of aldehyde **6**^a

entry	ligand	temperature	time	conversion ^b	7:8 ^c	[ee] ^d
1 ^e	None	0 °C	18 h	100%	4 : 1	-
2 ^e		0 °C	18 h	100%	>100 : 1	-
3 ²		-20 °C	18 h	100%	93 : 1	82%
				100%	87 : 1	83%
4		-10 °C	18 h	100%	2 : 1	26%
4		-10 °C	18 h	100%	2 : 1	26%

³ Fandrick, D.R.; Fandrick, K.R.; Reeves, J.T.; Tan, Z.; Johnson, C.S.; Lee, H.; Song, J.J.; Yee, N.K.; Senanayake, C.H. *Org. Lett.* **2010**, *12*, 88-91.

5		-10 °C	18 h	100%	3 : 1	2%
	iPr-DUPHOS					
6		-10 °C	18 h	100%	36 : 1	20%
	NORPHOS					
7		-10 °C	18 h	100%	3 : 1	14%
	JosiPHOS					
8 ⁴		-10 °C	18 h	100%	3 : 1	3%
9		-10 °C	18 h	100%	21 : 1	40%
	DUANPHOS					
10		-10 °C	18 h	100%	>100 : 1	13%
11		-10 °C	18 h	100%	55 : 1	34%
	9					
12		-10 °C	18 h	100%	19 : 1	3%
13		-10 °C	18 h	29 : 1	29 : 1	20%
14		-10 °C	18 h	100%	4 : 1	28%

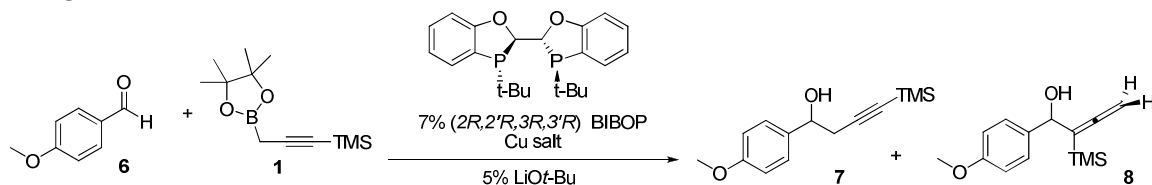
⁴ Tang, W.; Capacci, A.G.; White, A.; Ma, S.; Rodriguez, S.; Qu, B.; Savoie, J.; Patel, N.D. ; Wei, X. ; Haddad, N. ; Grinberg, N.; Yee, N.K.; Krishnamurthy, D.; Senanayake, C.H. *Org. Lett.* **2010**, 12, 1104-1107.

15		-10 °C	18 h	100%	12 : 1	63%
16		-10 °C	2 d	77%	19 : 1	10%
17		-10 °C	2 d	32%	9 : 1	5%
18		-10 °C	18 h	100%	47 : 1	57%
19		-10 °C	2 d	82%	17 : 1	17%
20		-10 °C	1 d	96%	40 : 1	4%

^a 1.5 equiv. borolane **1** to aldehyde. ^b Molar conversion based on recovered starting aldehyde **6**. ^c Site selectivity between alkyne **7** to allene **8**. ^d Absolute enantiomeric excess determined by Chiral HPLC (Chiralcel OJ-H).

The conditions for the copper catalyzed asymmetric propargylation of aldehyde **6** with the parent **BIBOP** ligand were further optimized as depicted in table **SI-3**.

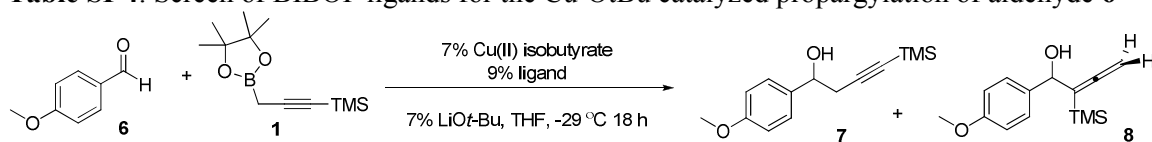
Table SI-3: Optimization of the Cu-OtBu catalyzed propargylation of aldehyde **6** with ligand **BIBOP**^a

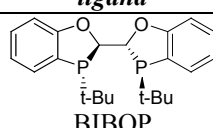
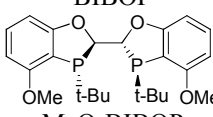


entry	solvent	Cu source ^b	temperature time	conversion ^c	7:8 ^d	ee ^e
1	THF	5% CuCl	-20 °C 18 h	100%	90 : 1	83%
2	Toluene	5% CuCl	-20 °C 2 d	100%	47 : 1	27%
3	DCM	5% CuCl	-20 °C 18 h	34%	23 : 1	84%
4	DMF	5% CuCl	-20 °C 18 h	71%	32 : 1	92%
5	EtOH	5% CuCl	-20 °C 18 h	84%	20 : 1	35%
6	MeCN	5% CuCl	-20 °C 18 h	32%	51 : 1	1%
7	p-Dioxane	5% CuCl	20 °C 18 h	100%	40 : 1	77%
8	DME	5% CuCl	-20 °C 18 h	76%	57 : 1	87%
9	EtOAc	5% CuCl	-20 °C 18 h	36%	27 : 1	62%
10	MTBE	5% CuCl	-20 °C 18 h	100%	73 : 1	76%
11	NMP	5% CuCl	-15 °C 2 d	97%	91 : 1	88%
12	THF	5% CuI	-20 °C 2 d	67%	30 : 1	60%
13	THF	2.5% (CuOTf) ₂ toluene	-20 °C 1 d	100%	87 : 1	89%
14	THF	5% Cu(OAc) ₂ H ₂ O	-20 °C 1 d	100%	87 : 1	88%
15	THF	5% CuCl ₂	-20 °C 2 d	64%	25 : 1	24%
16	THF	5% CuBr SMe ₂	-20 °C 1 d	99%	87 : 1	48%
17	THF	5% CuCl 5% AgSbF ₆	-20 °C 1 d	100%	90 : 1	70%
18	THF	5% Cu(BF ₄) ₂ H ₂ O	-20 °C 1 d	36%	29 : 1	68%
19	THF	5% Cu(OTf) ₂	-20 °C 1 d	81%	46 : 1	39%
20	THF	10% Cu(OAc) ₂ H ₂ O	-20 °C 1 d	100%	93 : 1	88%
21	THF	5% Cu(acac) ₂	-20 °C 1 d	43%	32 : 1	54%
22	THF	5% CuF ₂	-20 °C 1 d	99%	85 : 1	86%
23	THF	Cu(II) isobutyrate	-20 °C 1 d	100%	86 : 1	89%
24	THF	2.5% Cu(OAc) ₂ H ₂ O	-29 °C 3 d	98%	86 : 1	68%

^a 1.5 equiv. boronate **1** to aldehyde. ^b Molar percent to aldehyde. ^c Molar conversion based on recovered starting aldehyde **6**. ^d Site selectivity between alkyne **7** to allene **8**. ^e Enantiomeric excess determined by Chiral HPLC (Chiralcel OJ-H). DME = Dimethoxyethane, MTBE = Methyl *tert*-butylether, NMP = 1-methyl-2-pyrrolidinone.

The comparison between the parent BIBOP and MeO-BIBOP ligands on the copper catalyzed asymmetric propargylation of aldehyde **6** is depicted in table **SI-4**.

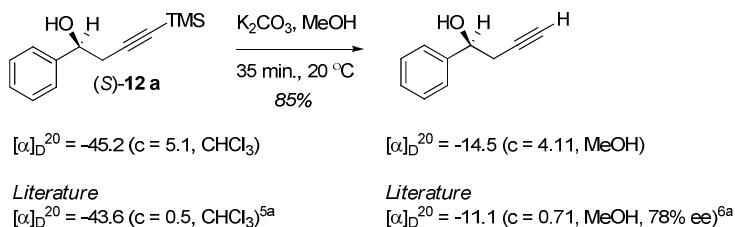
Table SI-4: Screen of BIBOP ligands for the Cu-OtBu catalyzed propargylation of aldehyde **6**^a


entry	Cu source	ligand	conversion ^b	7:8 ^c	ee ^d
1	Cu(II) isobutyrate	 BIBOP	100%	86 : 1	89%
2	Cu(II) isobutyrate	 MeO-BIBOP	100% ^e	49 : 1	98%

^a 1.5 equiv. borolane **1** to aldehyde. ^b Molar conversion based on recovered starting aldehyde **6**. ^c Site selectivity between alkyne **7** to allene **8**. ^d Enantiomeric excess determined by Chiral HPLC (Chiralcel OJ-H). ^e 97% Isolated yield.

III. Determination of Absolute Configuration

The absolute configuration of the homopropargylic alcohol **12 a** from the reaction with the (2*R*, 2'*R*, 3*R*, 3'*R*) MeO-BIBOP ligand was assigned as *S* by comparing the optical rotation of the protected homopropargylic alcohol **12a**⁵ and TMS deprotected adduct⁶ to literature precedents (Scheme SI-1). Homopropargylic alcohols **12b** through **12 j** were assigned by analogy.

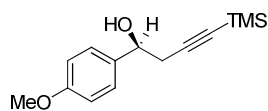
**Scheme SI-1:** Determination of Absolute Configuration for Homopropargylic alcohol **12 a**

⁵ a) Lee, K.-C.; Lin, M.-J.; Loh, T.-P. *Chem. Commun.* **2004**, 2456-2457. b) Compain, P.; Gore, J.; Vatele, J.-M. *Tetrahedron* **1996**, 52, 10405-10416.

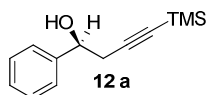
⁶ a) Inoue, M.; Nakada, M. *Org. Lett.* **2004**, 6, 2977-2980. b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, 104, 7667-7669. c) Denmark, S.E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, 123, 6199-6200.

IV. Experimental Procedures

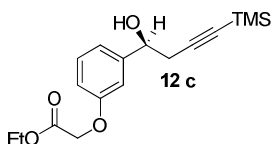
Representative Procedure for the Copper Catalyzed Asymmetric Propargylation of Aldehydes



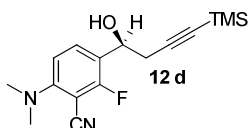
A dried r.b. flask was charged with copper (II) isobutyrate (137 mg, 0.575 mmol) and (2*R*, 2'*R*, 3*R*, 3'*R*) MeO-BIBOP (330 mg, 0.739 mmol). The vessel was flushed with argon. Anhydrous THF (<50 ppm water, 11 mL) was charged to above mixture at ambient temperature. The resulting cloudy blue – green solution was agitated at ambient temperature under argon for 45 minutes to afford a clear blue green solution. Lithium *tert*-butoxide (1.0 M in THF, 575 μ L, 0.575 mmol) was charged to above solution, and resulting dark green clear solution was agitated at ambient temperature for 30 minutes to afford the catalyst solution. A separate dried r.b. flask was charged with p-methoxybenzaldehyde (1.0 mL, 1.12 g, 8.22 mmol) and flushed with argon. The aldehyde was dissolved in anhydrous THF (<50 ppm water, 24 mL) and cooled to -30 °C. 3,3,4,4-tetramethyl-2-(3-trimethylsilyl-2-propynyl)-1,3,2-dioxaborolane **1** (94 wt%, 3.54 mL, 3.12 g, 12.3 mmol) was charged to the aldehyde solution. The catalyst solution was cooled to -10 to -20 °C and charged drop-wise to the above borolane and aldehyde solution at -30 °C under argon. The reaction solution was agitated at -30 °C for 18 h; at which point, HPLC (220nm) showed complete consumption of starting aldehyde. The reaction was warmed to ambient temperature and treated with diethanolamine (1.39 mL). After agitating the solution for 30 minutes, the solution was diluted with water (50 mL) and agitated for another 20 minutes. The mixture was diluted with IpAc (70 mL), and the lower blue aqueous layer was separated. The organic portion was washed with water (50 mL), and concentrated *in vacuo* to an oil. Purification by silica gel chromatography (10-15% EtOAc in hexanes) provided the homopropargylic alcohol (S) - **12b** as a clear and colorless oil (1.98 g, 97%). **Chiralcel OJ-H HPLC** (220nm, 10% isopropyl alcohol in heptane, 2 mL / min, 25 °C) showed 98% ee favoring the 3.69 min. over the 4.30 min. enantiomer. ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.27 (m, 2H), 6.90-6.86 (m, 2H), 4.80 (ddd, *J* = 2.3, 6.3, 6.3 Hz, 1H), 3.80 (s, 3H), 2.63 (d, *J* = 6.5 Hz, 2H), 2.43 (d, *J* = d, 3.0 Hz, 1H), 0.15 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 159.21, 134.74, 126.96, 113.70, 103.11, 87.76, 71.91, 55.25, 31.13, -0.02. **HRMS-EI** calcd for C₁₄H₂₀O₂Si [M]⁺ 248.1233 found 248.1232.



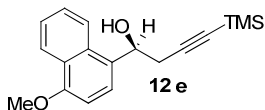
Homopropargylic alcohol (S)-**12a** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (27.4 mg, 0.115 mmol), (2*R*, 2'*R*, 3*R*, 3'*R*) MeOBIBOP (66.2 mg, 0.148 mmol), LiOtBu (1.0 M in THF, 115 μ L, 0.115 mmol), benzaldehyde (167 μ L, 175 mg, 1.64 mmol), and borolane **1** (94 wt%, 802 μ L, 707 mg, 2.79 mmol). Homopropargylic alcohol (S)-**12a** was isolated after silica gel chromatography (EtOAc in hexanes) as a clear and colorless oil (365 mg, 99%). **Chiralcel OJ-H HPLC** (210 nm, 5% isopropyl alcohol in heptane, 2 mL / min, 25 °C) showed 97% ee favoring the 3.26 min. over the 3.62 min. enantiomer. $[\alpha]_D^{20} = -45.2^\circ$ (*c* = 5.1, CHCl₃). Literature $[\alpha]_D^{20} = -43.6^\circ$ (*c* = 0.5, CHCl₃).⁵ ¹H and ¹³C NMR spectra also correspond to literature.^{5b}



Homopropargylic alcohol (*S*)-**12c** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (27.4 mg, 0.115 mmol), (*2R*, *2'R*, *3R*, *3'R*) MeOBIBOP (66.2 mg, 0.148 mmol), LiOtBu (1.0 M in THF, 115 μ L, 0.115 mmol), ethyl 2-(3-formylphenoxy)acetate (342 mg, 1.64 mmol), and borolane **1** (94 wt%, 802 μ L, 707 mg, 2.79 mmol). Homopropargylic alcohol (*S*)-**12c** was isolated after silica gel chromatography (EtOAc in hexanes) as a clear and colorless oil (502 mg, 95%). **Chiralcel OD-H HPLC** (220nm, 35 % isopropyl alcohol in heptane, 2 mL / min, 25 $^{\circ}$ C) showed 99% ee favoring the 5.61 min. over the 7.03 min. enantiomer. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.25 (t, J = 7.9 Hz, 1H), 7.02-6.95 (m, 2H), 6.82 (dd, J = 2.2, 8.2 Hz, 1H), 4.84 – 4.78 (m, 1H), 4.61 (s, 2H), 4.26 (q, J = 7.10 Hz, 2H), 2.65 (dd, J = 5.6, 16.8 Hz, 1H), 2.60 (dd, J = 7.3, 16.7 Hz, 1H), 2.57 (d, J = 3.0 Hz, 1H), 1.29 (t, J = 7.20 Hz, 3H), 0.15 (s, 9H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 168.83, 157.88, 144.40, 129.41, 119.11, 113.83, 112.11, 102.80, 87.80, 71.96, 65.37, 61.30, 31.05, 14.10, -0.06. **HRMS-ESI** calcd for $\text{C}_{17}\text{H}_{24}\text{O}_4\text{Si}+\text{H}$ $[\text{M}+\text{H}]^+$ 321.1516 found 321.1510.

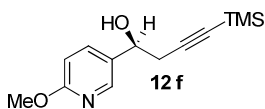


Homopropargylic alcohol (*S*)-**12d** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (9.77 mg, 0.041 mmol), (*2R*, *2'R*, *3R*, *3'R*) MeOBIBOP (22 mg, 0.049 mmol), LiOtBu (1.0 M in THF, 041 μ L, 0.041 mmol), 6-(dimethylamino)-2-fluoro-3-formylbenzonitrile (158 mg, 0.822 mmol), and borolane **1** (94 wt%, 350 μ L, 313 mg, 1.23 mmol). Homopropargylic alcohol (*S*)-**12d** was isolated after silica gel chromatography (EtOAc in hexanes) as a clear and yellow oil (235 mg, 94%). **Chiralpak AD-H** (254nm, 20 % isopropyl alcohol in heptane, 2 mL / min, 25 $^{\circ}$ C) showed 96% ee favoring the 2.389 min. over the 2.880 min. enantiomer. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.51 (t, J = 8.5 Hz, 1H), 6.62 (d, J = 9.0 Hz, 1H), 5.08 (dd, J = 5.5, 6.9 Hz, 1H), 3.10 (s, 6H), 2.69 (dd, J = 5.3, 16.9 Hz, 1H), 2.61 (dd, J = 7.3, 16.9 Hz, 1H), 2.50 (bs, 1H), 0.14 (s, 9H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) coupling due to fluoride δ 161.6 (d, J = 255 Hz), 155.46 (d, J = 3.3 Hz), 131.95 (d, J = 7.1 Hz), 118.80 (d, J = 12.9 Hz), 114.62 (d, J = 3.2 Hz), 111.56 (d, J = 3.1 Hz), 101.80 (s), 89.07 (d, J = 19.4 Hz), 88.47 (s), 65.33 (s), 65.31 (s), 42.72 (s), 29.81 (s), -0.09 (s). **HRMS-ESI** calcd for $\text{C}_{16}\text{H}_{21}\text{FN}_2\text{Osi}+\text{H}$ $[\text{M}+\text{H}]^+$ 305.1479 found 305.1473.

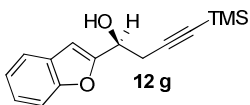


Homopropargylic alcohol (*S*)-**12e** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (27.4 mg, 0.115 mmol), (*2R*, *2'R*, *3R*, *3'R*) MeOBIBOP (66.2 mg, 0.148 mmol), LiOtBu (1.0 M in THF, 115 μ L, 0.115 mmol), 4-methoxy-1-naphthaldehyde (306 mg, 1.64 mmol), and borolane **1** (94 wt%, 802 μ L, 707 mg, 2.79 mmol). Homopropargylic alcohol (*S*)-**12e** was isolated after silica gel chromatography (EtOAc in hexanes) as a clear and colorless oil (510 mg, 98%). **Chiralcel OJ-H HPLC** (220nm, 10 % isopropyl alcohol in heptane, 2 mL / min, 25 $^{\circ}$ C) showed 97 % ee favoring the 4.93 min. over the 6.44 min. enantiomer. $^1\text{H NMR}$ (500 MHz, $\text{DMSO}-d_6$) δ 8.19 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.53 (t, J = 8.3 Hz, 1h), 7.48 (t, J = 7.1 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 5.56 (d, J = 4.2 Hz, 1H), 5.39 (q, J = 5.5 Hz, 1H), 3.95 (s, 3H), 2.70 (d, J

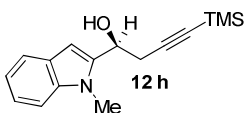
= 6.0 Hz, 2h), -0.01 (s, 9H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 154.07, 131.73, 131.06, 126.17, 124.73, 124.65, 123.98, 123.47, 121.88, 105.37, 103.50, 85.88, 67.80, 55.52, 29.89, -0.03. **HRMS-ESI** calcd for $2(\text{C}_{18}\text{H}_{22}\text{O}_2\text{Si})+\text{Na}$ $[2\text{M}+\text{Na}]^+$ 619.2670 found 619.2685.



Homopropargylic alcohol (*S*)-**12f** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (27.4 mg, 0.115 mmol), (2*R*, 2'*R*, 3*R*, 3'*R*) MeOBIBOP (66.2 mg, 0.148 mmol), LiOtBu (1.0 M in THF, 115 μL , 0.115 mmol), 6-methoxynicotinaldehyde (225 mg, 1.64 mmol), and borolane **1** (94 wt%, 802 μL , 707 mg, 2.79 mmol). Homopropargylic alcohol (*S*)-**12f** was isolated after silica gel chromatography (EtOAc in hexanes) as a yellow oil (380 mg, 93%). **Chiralcel OD-H HPLC** (220nm, 10 % isopropyl alcohol in heptane, 2 mL / min, 25 $^{\circ}\text{C}$) showed 97 % ee favoring the 3.13 min. over the 2.80 min. enantiomer. ^1H NMR (500 MHz, CDCl_3) δ 8.12 (s, 1H), 7.63 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 4.82 (bs, 1H), 3.92 (s, 3H), 2.65 (d, J = 6.2 Hz, 2H), 2.52 (bd, J = 2.2 Hz, 1H), -0.14 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.01, 144.65, 136.45, 130.69, 110.68, 102.30, 88.44, 69.94, 53.47, 30.94, -0.07. **HRMS-ESI** calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2\text{Si}+\text{H}$ $[\text{M}+\text{H}]^+$ 250.1258 found 240.1249.

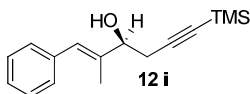


Homopropargylic alcohol (*S*)-**12g** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (27.4 mg, 0.115 mmol), (2*R*, 2'*R*, 3*R*, 3'*R*) MeOBIBOP (66.2 mg, 0.148 mmol), LiOtBu (1.0 M in THF, 115 μL , 0.115 mmol), benzofuran-2-carbaldehyde (240 mg, 1.64 mmol), and borolane **1** (94 wt%, 802 μL , 707 mg, 2.79 mmol). Homopropargylic alcohol (*S*)-**12g** was isolated after silica gel chromatography (EtOAc in hexanes) as a yellow oil (326 mg, 77%). **Chiralcel OJ-H HPLC** (220nm, 10 % isopropyl alcohol in heptane, 2 mL / min, 25 $^{\circ}\text{C}$) showed 93 % ee favoring the 3.36 min. over the 3.81 min. enantiomer. ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, J = 7.4 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.27 (dt, J = 1.4, 7.1 Hz, 1H), 7.21 (dt, J = 1.2, 7.6 Hz, 1H), 6.70 (s, 1H), 4.99 (q, J = 6.0 Hz, 1H), 2.92 (dd, J = 5.7, 16.9 Hz, 1H), 2.87 (dd, J = 6.7, 16.9 Hz, 1H), 2.59 (d, J = 5.9 Hz, 1H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 157.31, 154.77, 127.98, 124.25, 122.80, 121.10, 111.24, 103.20, 101.53, 88.65, 66.54, 27.78, -0.06. **HRMS-ESI** calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2\text{Si}+\text{NH}_4$ $[\text{M}+\text{NH}_4]^+$ 276.1414 found 276.1406. calcd for $2(\text{C}_{15}\text{H}_{18}\text{O}_2\text{Si})+\text{Na}$ $[2\text{M}+\text{Na}]^+$ 539.2044 found 539.2036.

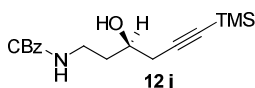


Homopropargylic alcohol (*S*)-**12h** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (27.4 mg, 0.115 mmol), (2*R*, 2'*R*, 3*R*, 3'*R*) MeOBIBOP (66.2 mg, 0.148 mmol), LiOtBu (1.0 M in THF, 115 μL , 0.115 mmol), 1-methyl-indole-2-carbaldehyde (262 mg, 1.64 mmol), and borolane **1** (94 wt%, 802 μL , 707 mg, 2.79 mmol). Homopropargylic alcohol (*S*)-**12h** was isolated after silica gel chromatography (EtOAc in hexanes) as a yellow solid (382 mg, 86%). **Chiralcel OJ-H HPLC** (220nm, 25 % isopropyl alcohol in heptane, 2 mL / min, 25 $^{\circ}\text{C}$) showed 97 % ee favoring the 3.46 min. over the 3.89 min. enantiomer. **mp** = 73 – 75 $^{\circ}\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 7.58 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 6.51 (s, 1H), 5.02 (bq, J = 5.3 Hz, 1H), 3.81 (s, 3H), 2.97 (dd, J = 7.5, 16.9 Hz, 1H), 2.92 (dd, J = 5.1, 16.9 Hz, 1H),

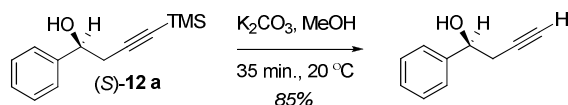
2.35 (bd, $J = 4.6$ Hz, 1H), 0.17 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 139.77, 137.89, 127.04, 121.96, 120.83, 119.57, 109.09, 102.36, 99.33, 88.57, 65.17, 30.15, 28.13, -0.01. HRMS-ESI calcd for $\text{C}_{16}\text{H}_{21}\text{NOSi} + \text{H}$ $[\text{M} + \text{H}]^+$ 272.1465 found 272.1457.



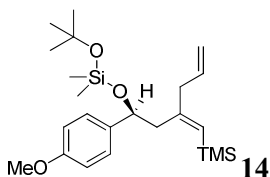
Homopropargylic alcohol (*S*)-**12i** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (27.4 mg, 0.115 mmol), (2*R*, 2'*R*, 3*R*, 3'*R*) MeOBIBOP (66.2 mg, 0.148 mmol), LiOtBu (1.0 M in THF, 115 μL , 0.115 mmol), α -methyl-*trans*-cinnamaldehyde (241 mg, 1.64 mmol), and borolane **1** (94 wt%, 802 μL , 707 mg, 2.79 mmol). Homopropargylic alcohol (*S*)-**12i** was isolated after silica gel chromatography (EtOAc in hexanes) as a yellow oil (409 mg, 96%). Chiralcel OJ-H HPLC (220nm, 25 % isopropyl alcohol in heptane, 2 mL / min, 25 $^\circ\text{C}$) showed 97 % ee favoring the 2.29 min. over the 2.69 min. enantiomer. ^1H NMR (500 MHz, CDCl_3) δ 7.33 (t, $J = 7.6$ Hz, 2H), 7.27 (d, $J = 7.2$ Hz, 2H), 7.22 (t, $J = 7.3$ Hz, 1H), 6.58 (s, 1H), 4.34 (bt, $J = 5.3$ Hz, 1H), 2.62 (dd, $J = 5.8, 17.0$ Hz, 1H), 2.59 (dd, $J = 6.9, 16.9$ Hz, 1H), 2.21 (bs, 1H), 1.87 (d, $J = 1.0$ Hz, 3H), 0.15 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 138.18, 137.36, 128.97, 128.07, 126.51, 126.35, 102.85, 87.90, 75.34, 27.71, 13.51, 0.02. HRMS-ESI calcd for $\text{C}_{16}\text{H}_{22}\text{OSi} + \text{NH}_4$ $[\text{M} + \text{NH}_4]^+$ 276.1778 found 276.1781.



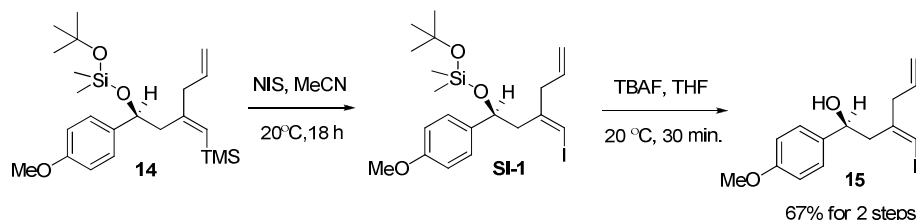
Homopropargylic alcohol (*S*)-**12j** was prepared by the representative copper catalyzed asymmetric propargylation procedure with copper (II) isobutyrate (9.77 mg, 0.041 mmol), (2*R*, 2'*R*, 3*R*, 3'*R*) MeOBIBOP (22 mg, 0.049 mmol), LiOtBu (1.0 M in THF, 41 μL , 0.041 mmol), benzyl 3-oxopropylcarbamate (170 mg, 0.822 mmol), and borolane **1** (94 wt%, 350 μL , 313 mg, 1.23 mmol). Homopropargylic alcohol (*S*)-**12j** was isolated after silica gel chromatography (EtOAc in hexanes) as a yellow oil (249 mg, 95%). Chiralcel OD-H HPLC (220nm, 1 % isopropyl alcohol in heptane, 2 mL / min, 25 $^\circ\text{C}$) showed 90 % ee favoring the 11.83 min. over the 10.82 min. enantiomer. ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.25 (m, 5 H), 5.19 (bs, 1 H), 5.10 (s, 2 H), 3.86 – 3.77 (m, 1 H), 3.56 – 3.44 (m, 1 H), 3.32 – 3.21 (m, 1 H), 2.81 (bs, 1 H), 2.43 (d, $J = 5.7$ Hz, 2 H), 1.85 – 1.73 (m, 1 H), 1.68 – 1.55 (m, 1 H), 0.15 (s, 9 H). ^{13}C NMR (100 MHz, CDCl_3) δ 156.96, 136.45, 128.50, 128.11, 128.09, 102.83, 87.68, 67.91, 66.77, 38.03, 36.06, 28.82, 0.02. HRMS-ESI calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_3\text{Si} + \text{H}$ $[\text{M} + \text{H}]^+$ 320.1676 found 320.1663.



A mixture of homopropargylic alcohol (*S*)-**12 a** (270 mg, 1.24 mmol) and potassium carbonate (532 mg, 3.85 mmol) was agitated in methanol (4 mL) under nitrogen for 35 minutes; at which point, HPLC showed complete conversion. The reaction was diluted with water (30 mL) and isopropyl acetate (30 mL). The mixture was agitated for 30 minutes until all solids dissolved. The layers were separated, and the organic portion was washed with water (2 x 20 mL). The organic portion was concentrated to the desired (*S*)-1-phenylbut-3-yn-1-ol (154 mg, 85%) as a clear and colorless oil. $[\alpha]_D^{20} = -14.5^\circ$ ($c = 4.11$, MeOH). Literature $[\alpha]_D^{20} = -11.1^\circ$ ($c = 0.71$, MeOH).^{6a} ^1H and ^{13}C NMR spectra correspond to literature.^{6c}

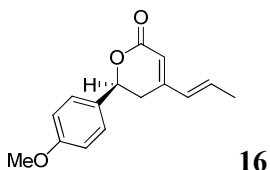


A neat solution of the homopropargylic alcohol (**S**) – **12b** (3.00 g, 12.08 mmol) and 1,1,3,3 tetramethyldisilazane (6.00 mL, 4.51 g, 33.8 mmol) was agitated under argon in a dried flask at 60 °C for 18 h; at which point, ¹H NMR showed complete consumption of starting homopropargylic alcohol. The reaction was concentrated under vacuum to an oil at 60 °C. It was found to be important for the subsequent transformation to remove all excess 1,1,3,3 tetramethyldisilazane. The oil was purged with argon and diluted with anhydrous THF (20 mL). At ambient temperature, platinum (0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex xylene solution (0.05 M, 0.483 mL, 0.024 mmol) was charged to the reaction. The reaction was heated to 50 °C for 2 h; at which point, HPLC (220nm) showed complete consumption of starting material to afford a THF solution of the hydrosilylated homopropargylic alcohol. The solution was cooled to ambient temperature. In a separate dried r.b. flask, LiOtBu (1.0 M in THF, 18.1 mL, 18.1 mmol) was charged to a suspension of CuI (3.45 g, 18.1 mmol) in anhydrous THF (20 mL) under argon. The resulting dark mixture was agitated for 1 h at ambient temperature to dissolve most of the solids to afford a Cu-OtBu solution. The Cu-OtBu solution was charged to the hydrosilylated homopropargylic alcohol solution at ambient temperature followed by allyl bromide (1.57 mL, 2.19 g, 18.1 mmol). The reaction was agitated under argon at 40 °C for 2 days. HPLC (220nm) showed only trace amounts (< 4%) of the hydrosilylated intermediate remaining. The reaction was cooled to ambient temperature and diluted with water (20 mL) and isopropyl acetate (20 mL). The mixture was agitated for 10 minutes; at which point, the lower aqueous layer was separated. The organic portion was passed through a silica plug eluting with isopropyl acetate. The organic filtrate was concentrated to an oil and purified by silica gel chromatography (1-3 % EtOAc in hexanes) to provide the vinyl silane **14** as a slightly yellow oil (3.43 g, 68%). [α]_D²⁰ = -22.1° (c = 1.58, Dichloroethane). ¹H NMR (400 MHz, C₆D₆) δ 7.35 (dt, *J* = 8.5, 1.7 Hz, 2 H), 6.81 (dt, *J* = 8.7, 2.0 Hz, 2 H), 5.91 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1 H), 5.55 (s, 1 H), 5.17 – 5.07 (m, 3 H), 3.31 (s, 3 H), 3.02 (d, *J* = 6.8 Hz, 2 H), 2.92 (dd, *J* = 13.5, 8.7 Hz, 1 H), 2.59 (dd, *J* = 13.3, 4.9 Hz, 1 H), 1.24 (s, 9 H), 0.24 (s, 9 H), 0.18 (s, 3 H), 0.12 (s, 3 H). ¹³C NMR (100 MHz, C₆D₆) δ 159.47, 154.47, 137.77, 137.14, 127.65, 127.59, 116.53, 113.93, 74.25, 72.38, 54.72, 47.01, 44.95, 32.02, 1.01, 0.81, 0.75. HRMS-ESI calcd for C₂₃H₄₀O₃Si₂+Na [M+Na]⁺ 443.2408 found 443.2375.

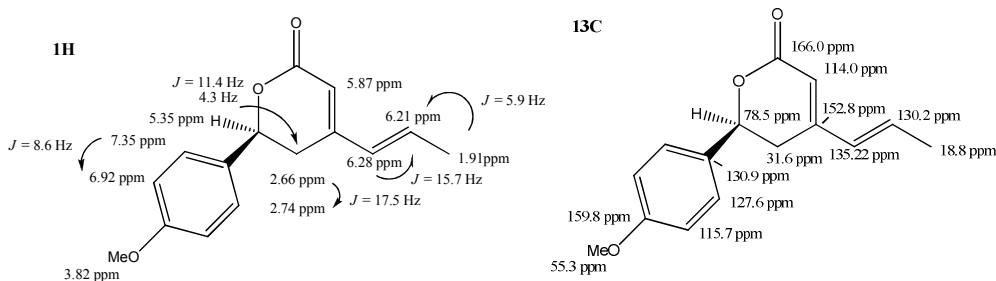


A suspension of *N*-iodosuccinimide (1.16 g, 5.13 mmol) in acetonitrile (15 mL) was charged drop wise to a solution of the vinyl silane **14** (2.16 g, 5.13 mmol) in acetonitrile (5 mL) at ambient temperature protected from light. HPLC showed complete consumption of the starting vinyl silane **14** in 30 minutes. The resulting red solution was concentrate to ~5 mL. The oil was dissolved in isopropyl acetate (40 mL) and treated with water (20 mL) and saturated NaHSO₃ (2 mL). The mixture was agitated for 5 minutes; at which point, the red – purple color dissipated into a yellow color. The layers were separated. The organic portion was washed with water (2 x 15 mL) and concentrated to the silyl protected vinyl silane **SI-1** as a yellow oil. The intermediate **SI-1** was used in the subsequent deprotection without further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.28 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 6.00 (s, 1 H), 5.67 (ddt, *J* = 16.9,

9.8, 6.9 Hz, 1 H), 5.07 – 4.95 (m, 3 H), 3.80 (s, 3 H), 2.82 – 2.63 (m, 3 H), 2.47 (dd, $J = 13.1$, 6.0 Hz, 1 H), 1.22 (s, 9 H), 0.004 (s, 3 H), -0.01 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.82, 147.51, 136.72, 134.92, 127.26, 117.22, 113.37, 78.07, 72.43, 72.37, 55.23, 47.44, 43.25, 31.87, 0.54, 0.42. All the intermediate vinyl iodide **SI-1** above was subjected to deprotection by tetrabutyl-ammonium fluoride (1.0 M in THF, 7.61 mL, 7.61 mmol) in THF (20 mL) at ambient temperature under argon protected from light. After 30 minutes, HPLC showed complete consumption of the intermediate silyl alcohol **SI-1**. The reaction was diluted with isopropyl acetate (60 mL) and washed with water (2 x 40 mL). The organic portion was concentrated to an oil and purified by silica gel chromatography (15% EtOAc in hexanes) to provide the vinyl iodide **15** as a yellow oil (1.19 g, 67%). $[\alpha]_{\text{D}}^{20} = +4.0^\circ$ ($c = 3.7$, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ 7.32 (dt, $J = 8.6$, 2.6 Hz, 2 H), 6.89 (dt, $J = 8.7$, 2.1 Hz, 2 H), 6.10 (s, 1 H), 5.72 (ddt, $J = 17.0$, 10.1, 6.9 Hz, 1 H), 5.08 (d, $J = 10.0$ Hz, 1 H), 5.04 (dd, $J = 17.0$, 1.2 Hz, 1 H), 4.91 (dd, $J = 8.1$, 6.0 Hz, 1 H), 3.80 (s, 3 H), 2.90 (ddd, $J = 15.5$, 6.7, 0.5 Hz, 1 H), 2.84 (dd, $J = 15.5$, 6.9 Hz, 1 H), 2.74 (dd, $J = 13.6$, 8.8 Hz, 1 H), 2.53 (dd, $J = 13.6$, 5.2 Hz, 1 H), 1.85 (s, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.25, 146.89, 136.12, 134.76, 127.01, 117.51, 113.86, 78.94, 72.35, 55.30, 46.32, 42.51. HRMS-ESI calcd for $2(\text{C}_{14}\text{H}_{17}\text{IO}_2) + \text{Na}$ $[2\text{M} + \text{Na}]^+$ 711.0439 found 711.0408.



A mixture of the vinyl iodide **15** (400 mg, 1.16 mmol), triethylamine (486 μL , 353 mg, 3.49 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (47.5 mg, 0.058 mmol) in toluene (6 mL) and methanol (2 mL) was agitated at 50°C under 400 psi CO for 4 h. TLC (silica gel, 25 % EtOAc in hexanes) showed complete consumption of starting iodide. The reaction was cooled to ambient temperature and purged with nitrogen. The reaction was concentrated to a red oil. The oil was directly purified by silica gel chromatography (18-20% EtOAc in hexanes, 330 g silica) to provide the intended product **16** as a white solid (259 mg, 91%). Chiralpak AD-H HPLC (270 nm, 25 % isopropyl alcohol in heptane, 2 mL / min, 25°C) showed 97 % ee favoring the 7.99 min. over the 5.67 min. enantiomer. $[\alpha]_{\text{D}}^{20} = -160.0^\circ$ ($c = 2.08$, CHCl_3 , 97% ee). $\text{mp} = 124 - 126^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dt, $J = 8.6$, 1.8 Hz, 2 H), 6.92 (dt, $J = 8.7$, 1.9 Hz, 2 H), 6.28 (d, $J = 16.0$ Hz, 1 H), 6.21 (dq, $J = 15.7$, 6.2 Hz, 1 H), 5.87 (s, 1 H), 5.35 (dd, $J = 11.4$, 4.3 Hz, 1 H), 3.82 (s, 3 H), 2.74 (dd, $J = 17.5$, 4.5 Hz, 1 H), 2.66 (dd, $J = 17.5$, 11.5, 2.1 Hz, 1 H), 1.91 (d, $J = 5.9$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.95, 159.77, 152.79, 135.22, 130.85, 130.18, 127.57, 115.65, 113.97, 78.45, 55.31, 31.63, 18.79. HRMS-ESI calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3 + \text{H}$ $[\text{M} + \text{H}]^+$ 245.1172 found 245.1161.



Key NMR Spectral Observations for Structural Determination of (S)-16