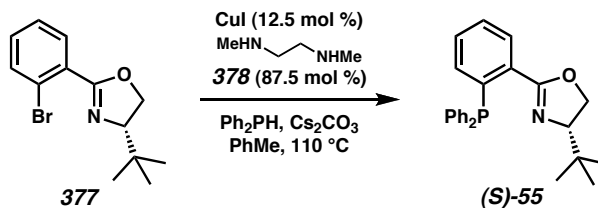


APPENDIX 6

*An Improved and Highly Efficient Copper(I)- Catalyzed Preparation of (*S*)-*t*-Bu-PHOX*

A6.1 INTRODUCTION AND BACKGROUND

Phosphinooxazoline (PHOX) ligands¹ have emerged as versatile chiral scaffolds for an array of transition-metal-catalyzed processes. As an important member of this class of P/N-chelates, (*S*)-*t*-Bu-PHOX (**55**)² has been critical to the development of palladium(0)-catalyzed decarboxylative alkylation³ and protonation⁴ technologies in our laboratory. Investigations of these methods prompted the synthesis of numerous PHOX derivatives.⁵ Ultimately, the efficacy of a copper(I) iodide-catalyzed diarylphosphine–aryl bromide coupling reported by Buchwald and co-workers⁶ enabled a mild and modular strategy toward the preparation of these useful ligands.^{3a,7} In this appendix, we detail our improvements to this coupling reaction that increase yields, reduce reagent quantities, and simplify purification.

Scheme A6.1.1. Original CuI-catalyzed coupling for the preparation of (*S*)-*t*-Bu-PHOX

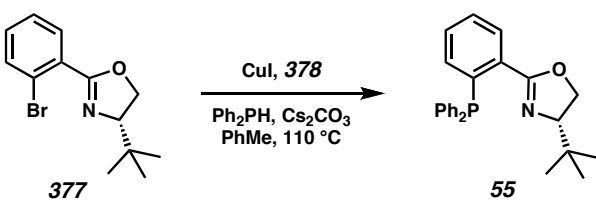
The Ullman-type coupling strategy has proven general for the preparation of a number of structurally and electronically diverse PHOX derivatives.^{7a} However, recent scale-up efforts of our optimal ligand, (*S*)-*t*-Bu-PHOX ((*S*)-**55**), to support applications in natural product total synthesis⁸ revealed a significant limitation to our standard Cu(I)-catalyzed coupling conditions. In particular, various coupling reactions failed to reach complete conversion (i.e., **377** → **55**), thus requiring tedious chromatographic purification. Upon consideration of our standard conditions, we identified several likely problematic factors for scale-up, including relatively high catalyst and ligand loadings, as well as excessive quantities of Cs₂CO₃ and diphenylphosphine. Due to the growing utility of this ligand in asymmetric catalysis,² and consequently, the synthesis of biologically relevant substances, we sought to improve these conditions to facilitate the large-scale preparation of **55**.

A6.2 REACTION OPTIMIZATION

Our efforts to maximize the reaction efficiency for the production of **55** first required a reliable coupling (Table A6.2.1, entry 1). We quickly recognized that it was essential to maintain vigorous stirring throughout the reaction,⁹ a straightforward task on smaller

scales but more difficult as quantities of heterogeneous solids increased. A successful coupling was observed as the CuI was reduced to 5 mol % (entries 2–4) to still provide complete conversions. Decreasing the equivalents of Ph₂PH and Cs₂CO₃ further improved conversion of **377** (entry 5). An increase in substrate concentration resulted in similar reactivity, enabling excellent results with 0.5 mol % CuI and a small excess of Ph₂PH in PhMe at 0.5 M (entries 6 and 7). Copper loadings can be further reduced to 0.1 mol %, although prolonged resulted in incomplete conversion (entry 8).

Table A6.2.1. Optimization of the coupling conditions



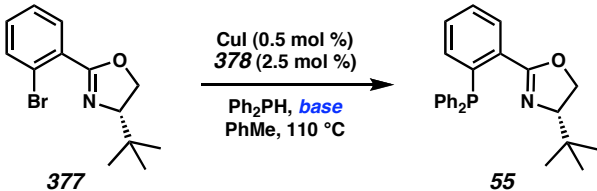
entry	CuI (mol%)	378 (mol%)	Ph ₂ PH (equiv)	Cs ₂ CO ₃ (equiv)	[PhMe] (M)	conversion ^a (%)
1	12.5	87.5	1.88	3.25	0.12	40–97
2	5	35	1.88	3.75	0.12	97
3	1	7	1.88	3.75	0.12	>99
4	0.5	3.5	1.88	3.75	0.12	>99
5	1	5	1.5	1.88	0.12	98
6	1	5	1.25	1.5	0.25	97
7	0.5	2.5	1.25	1.5	0.50	>99
8	0.1	0.5	1.25	1.5	0.50	98

^a Conversion measured by ¹H NMR analysis of crude reaction filtrates after 6–16 h.

With our optimized conditions in hand, we examined several common inorganic bases to determine their utility for this coupling.¹⁰ Standard use of Cs₂CO₃ produced excellent conversions and high yields of **55** on a variety of reaction scales (Table A6.2.2, entries 1 and 2). Surprisingly, other carbonates such as Li₂CO₃ and Na₂CO₃ were

ineffective (entries 3 and 4). Good reactivities were observed for both K_2CO_3 (entries 5 and 6) and K_3PO_4 (entry 7), however lower conversions were achieved.

Table A6.2.2. Inorganic base screen



entry ^a	base	time (h)	conversion (%)	yield (%) ^b
1	Cs_2CO_3	21	>99	94
2 ^c	Cs_2CO_3	21	>99	91
3	Li_2CO_3	24	0	—
4	Na_2CO_3	24	0	—
5	K_2CO_3	24	94	68
6 ^d	K_2CO_3	24	97	72
7	K_3PO_4	24	71	55

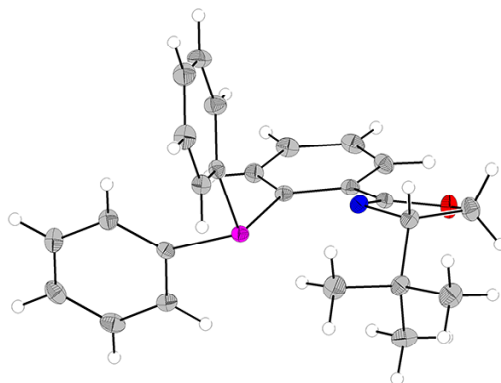
^a Reactions performed at 2.5 mmol of **378** using 1.25 equiv of Ph_2PH and 1.5 equiv of base in PhMe (0.5 M). ^b Isolated yield. ^c Performed on 20 mmol. ^d With 3 equiv of base.

A6.3 CRYSTALLIZATION AND IMPROVED PURIFICATION

During the course of our investigations, we have obtained numerous reaction filtrates composed of varying mixtures of **55** and **377** (e.g., entries 5–7, Table A6.2.2). The previous combination of these two chromatographically similar compounds necessitated difficult column purification. In our search for an alternative purification method, we fortuitously discovered that acetonitrile promotes the rapid and selective crystallization of **55** as large blocks. Application of this procedure to impure samples enabled facile recovery of **55** (yields obtained for entries 5–7, Table A6.2.2) and produced high quality crystals for X-ray analysis (Figure A6.3.1).¹¹ In addition to the new purification

procedure, our newly optimized conditions employing 0.5 mol % catalyst facilitate complete conversion of **377** (entries 1 and 2, Table A6.2.2), thus simplifying the isolation of **55**. A straightforward silica gel plug to remove copper salts and excess diphenylphosphine, followed by concentration of the remaining filtrate, layering with acetonitrile, and final removal of volatiles under vacuum provided ligand **55** as a white crystalline solid in excellent yield and >99% purity as determined by various analytical methods.

Figure A6.3.1. X-ray crystal analysis of (*S*)-*t*-Bu-PHOX ((*S*)-**55**). The molecular structure is drawn with 50% probability ellipsoids.



A6.4 CONCLUSION

In summary, we have described a significant improvement to our original copper(I) iodide catalyzed diarylphosphine–aryl bromide coupling reaction that enables reliable and efficient access to (*S*)-*t*-Bu-PHOX (**55**). Our optimized conditions employ 0.5 mol % of the copper(I) iodide catalyst and feature reduced quantities of Cs₂CO₃ and diphenylphosphine with increased substrate concentrations convenient for large-scale

preparation. Coupling reactions typically proceed to complete conversion, facilitating a simplified purification procedure consisting of a silica gel plug, and our discovery of a selective acetonitrile crystallization provides **55** as a stable, crystalline solid in high yields and >99% purity. We believe our findings can be extended to a general synthesis of PHOX ligands and provide opportunities for future discoveries in asymmetric catalysis.

A6.5 EXPERIMENTAL SECTION

A6.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. CuI (98%) was purchased from Strem and used as received. Ph₂PH (99%) was purchased from Strem and cannula transferred to a dry Schlenk storage tube under nitrogen to prolong reagent life. Cs₂CO₃ (ReagentPlus, 99%) and diamine **378** were purchased from Sigma Aldrich and used as received. Bromooxazoline **377** was prepared according to ref 7b. The reaction stirring rate was set at ca. 700 setting on an IKAmag RET basic stir/hot plate (a range between 500–800 rpm is sufficient). Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliCycle SiliaFlash P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to Me₄Si (δ 0.0 ppm).¹² Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). ³¹P NMR spectra were recorded on a Varian Mercury 300 (at 121 MHz) and are reported relative to an H₃PO₄ external standard (δ 0.0 ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm⁻¹). Melting points were acquired using a

Buchi Melting Point B-545 instrument and the values are uncorrected. High-resolution mass spectra were acquired from the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

A6.5.2 PREPARATIVE PROCEDURES

(*S*)-*t*-Bu-PHOX ((*S*)-55). To a 250 mL Schlenk flask equipped with a Teflon valve, a 14/20 glass joint, and a large stir bar was added copper(I) iodide (19.0 mg, 0.10 mmol, 0.005 equiv), diphenylphosphine (4.35 mL, 25.0 mmol, 1.25 equiv), diamine **378** (53.3 μ L, 0.50 mmol, 0.025 equiv) and toluene (20 mL). The colorless contents were stirred at ambient temperature for 20 min, and the flask was charged with bromooxazoline **377** (5.642 g, 20.0 mmol, 1.0 equiv), Cs₂CO₃ (9.775 g, 30.0 mmol, 1.5 equiv), and toluene (20 mL, 0.50 M total) to wash the neck and walls of the flask. The Teflon valve was closed and the yellow heterogeneous reaction was placed in a 110 °C oil bath and vigorously stirred. Following consumption of starting material by TLC analysis, the reaction was allowed to cool to ambient temperature, filtered through a pad of Celite, and the filter cake washed with CH₂Cl₂ (2 x 40 mL). The filtrate was concentrated under reduced pressure to a pale yellow semi-solid, dissolved in a minimal amount of dichloromethane (ca. 40 mL) and ethyl ether (ca. 50 mL), and dry-loaded onto 10 g of silica gel. This material was flushed through a silica gel plug eluting with 24:1 hexanes/Et₂O until excess Ph₂PH elutes, then with a 9:1 CH₂Cl₂/Et₂O mixture until the desired product elutes. The combined fractions are concentrated to a viscous pale yellow oil and layered with ca. 5 mL acetonitrile to facilitate crystallization. The flask was swirled while crystals form within seconds, and after ca. 15 minutes, the flask is placed under high vacuum to remove volatiles to afford (*S*)-**55** (7.033 g, 18.15 mmol, 90.8% yield) as white blocks. R_f = 0.64 (4:1 hexanes/Et₂O, developed twice); mp = 114–115 °C (MeCN); ³¹P NMR (121 MHz, CDCl₃) δ -5.33 (s); ¹H NMR (300 MHz, CDCl₃) δ 7.94

(ddd, $J = 7.4, 3.5, 1.3$ Hz, 1H), 7.36 (app dt, $J = 7.4, 1.3$ Hz, 1H), 7.33–7.21 (comp m, 11H), 6.86 (ddd, $J = 7.4, 4.0, 1.3$ Hz, 1H), 4.08 (dd, $J = 10.1, 8.2$ Hz, 1H), 4.01 (dd, $J = 8.0, 8.0$ Hz, 1H), 3.88 (dd, $J = 10.1, 8.0$ Hz, 1H), 0.73 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.8 (d, $J_{\text{CP}} = 2.8$ Hz), 138.9 (d, $J_{\text{CP}} = 25.3$ Hz), 138.7 (d, $J_{\text{CP}} = 12.4$ Hz), 138.4 (d, $J_{\text{CP}} = 9.7$ Hz), 134.5 (d, $J_{\text{CP}} = 21.2$ Hz), 134.2, 133.7 (d, $J_{\text{CP}} = 20.3$ Hz), 132.1 (d, $J_{\text{CP}} = 19.8$ Hz), 130.5, 130.0 (d, $J_{\text{CP}} = 3.2$ Hz), 128.6 (d, $J_{\text{CP}} = 20.2$ Hz), 128.5, 128.4 (2 lines), 128.2, 76.8, 68.4, 33.7, 25.9; IR (Neat Film NaCl) 3053, 2954, 2902, 2867, 1652, 1477, 1434, 1353, 1336, 1091, 1025, 966, 743, 696, 503 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{25}\text{H}_{27}\text{NOP}$ $[\text{M} + \text{H}]^+$: 388.1830, found 388.1831; $[\alpha]_{\text{D}}^{23} -61.5^\circ$ (c 0.925, CHCl_3 , >99% ee); Anal. calc'd. for $\text{C}_{25}\text{H}_{27}\text{NOP}$: C, 77.50; H, 6.76; N, 3.62. Found: C, 77.10; H, 6.62; N, 3.71.

A6.6 NOTES AND REFERENCES

- (1) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566–568. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772. (c) Dawson, G. J.; Frost, C. G.; Coote, S. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149–3150. (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.
- (2) For representative examples of **1** in stereoselective transformations, see: (a) von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573–584. (b) Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2687–2689. (c) Baldwin, I. C.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1995**, *6*, 1515–1518. (d) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200–202. (e) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602. (f) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 7944–7952. (g) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437–1447. (h) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966–8977. (i) Schulz, S. R.; Blechert, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3966–3970. (j) Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302–9303. (k) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wroblewski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377. (l) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162–16163.
- (3) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927. (c) Seto, M.; Roizen, J. L.; Stolz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876.

- (4) (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042.
- (5) For a recently developed *t*-Bu-PHOX practical equivalent, see: Bélanger, E.; Pouliot, M.-F.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 2201–2204.
- (6) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315–2318.
- (7) (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.
- (8) (a) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739. (b) Behenna, D. C.; Stockdill, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4077–2080. (c) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811. (d) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (e) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292. (f) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295.
- (9) See subsection A6.5.2 for details.
- (10) For reports utilizing various inorganic bases for copper-catalyzed C–P bond formation, see: (a) Van Allen, D.; Venkataraman, D. *J. Org. Chem.* **2003**, *68*, 4590–4593. (b) Thielges, S.; Bisseret, P.; Eustache, J. *Org. Lett.* **2005**, *7*, 681–684. (c) Huang, C.; Tang, X.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 5020–5022.

- (11) For a detailed X-ray crystallography report of (S)-**55**, see Appendix 8.
- (12) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.