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Complete List of Authors:	Crawford, Sarah; Dalhousie University, Chemistry Wheaton, Craig; Dalhousie University, Chemistry Mishra, Vinayak; Dalhousie University, Chemistry Stradiotto, Mark; Dalhousie University, Chemistry
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Probing the Effect of Donor-Fragment Substitution in Mor-DalPhos on Palladium-Catalyzed C-N and C-C Cross-coupling Reactivity

Sarah M. Crawford,[‡] Craig A. Wheaton,[‡] Vinayak Mishra, and Mark Stradiotto*

[‡] these authors contributed equally to this work

Submitted to the special issue to honor Professor Neil Burford in recognition of his many outstanding contributions to the chemical community.

Department of Chemistry, Dalhousie University, 6274 Coburg Road, P.O. Box 15000, Halifax, NS, B3H 4R2, Canada.

Fax: 1-902-494-1310; Tel: 1-902-494-7190; E-mail: mark.stradiotto@dal.ca

ABSTRACT

The competitive catalytic screening of 18 known and newly prepared Mor-DalPhos ligand variants in the palladium-catalyzed cross-coupling of chlorobenzene with aniline, octylamine, morpholine, indole, ammonia, or acetone is presented, including ligands derived from the new secondary phosphine HP(^{Me2}Ad)$_2$ (^{Me2}Ad = 3,5-dimethyladamantyl). While triarylphosphine ancillary ligand variants performed poorly in these test reactions, ligands featuring either PAd$_2$ or P(^{Me2}Ad)$_2$ donors (Ad = 1-adamantyl) gave rise to superior catalytic performance. Multiple Mor-DalPhos variants proved effective in cross-couplings involving aniline, octylamine, or morpholine; conversely, only a smaller sub-set of ligands proved useful in related cross-couplings of indole, ammonia, or acetone. In the case of the *N*-arylation of indole, a Mor-DalPhos ligand variant featuring *ortho*-disposed PAd$_2$ and dimethylmorpholino donor fragments (**L13**) proved superior to all other ligands surveyed, including the parent ligand Mor-DalPhos (**L5**). Conversely, **L5** was found to be superior to all other ligands in the palladium-catalyzed monoarylation of ammonia. Ligand **L6** (i.e., the P(^{Me2}Ad)$_2$ variant of **L5**) proved superior to all other ligands in the monoarylation of acetone, and with the exception of indole *N*-arylation, was the most broadly useful of the Mor-DalPhos ligands surveyed herein.

Key Words: Amination, Cross-coupling, Ligand design, Palladium.

INTRODUCTION

Palladium-catalyzed cross-coupling of (hetero)aryl (pseudo)halides and NH substrates (i.e. Buchwald-Hartwig amination, BHA[1]) has emerged as a remarkably useful protocol for the synthesis of (hetero)anilines. The critical role that ancillary ligands play in promoting aryl-X oxidative addition, amine substrate binding, and/or aryl-N reductive elimination in the course of such transformations is well-established.[2] Optimal BHA catalyst systems have traditionally relied on: (a) monodentate phosphine or NHC ligands, with Buchwald's dialkylbiarylphosphines[1c, 3] and Organ's *N*-heterocyclic carbene (NHC)-based PEPPSI catalysts[4] representing noteworthy examples; or (b) strongly chelating bidentate bisphosphine ligands, including the JosiPhos[5] ligand variant CyPF-*t*Bu, as demonstrated by Hartwig and co-workers.[1b, 6] In 2010, we initiated the development of what can be considered as an electronically intermediate class of *ortho*-phenylene chelating ligands for use in addressing outstanding challenges in BHA and related cross-coupling chemistry, whereby a sterically demanding dialkylphosphino (or NHC) donor fragment is paired with a less Lewis-basic heteroatomic donor. While at the time *ortho*-phenylene P,N chelates such as phosphinooxazoline ligands (including Phox[7]) had proven useful in a variety of metal-catalyzed transformations, such ligand design concepts had not previously been employed successfully in the development of state-of-the-art ancillary ligands for use in BHA and related cross-coupling chemistry. In particular, we envisioned that a rigid chelating P,N-ligand structure might provide a means of attaining high levels of monoarylation selectivity with small nucleophilic coupling partners, thus providing an advantage over monodentate ligands. Moreover, we envisioned the possibility that P,N-ligand hemilability might provide access to both monodentate (e.g. κ^1-*P*,N) and bidentate (e.g. κ^2-*P*,*N*) binding modes, which in turn may facilitate both oxidative addition and reductive elimination steps, for which the electronic demands of the ancillary ligand are normally orthogonal.

Following our initial development of Me-DalPhos for use broadly in BHA,[8] a very brief ancillary ligand modification survey in the context of ammonia monoarylation enabled the development of Mor-DalPhos;[9] the structures of these DalPhos ligands are depicted in Figure 1.[10] Notably, Mor-DalPhos has since proven to be particularly useful in the selective monoarylation of a range of small, nucleophilic reaction partners such as ammonia,[9, 11] hydrazine,[12] and acetone,[13] as well as in challenging cross-couplings involving aryl mesylates,[13b] in some cases for the first time reported in the literature. While variants of Mor-DalPhos featuring pyrrole, pyridine, and benzophenone imine donor fragments in place of the morpholino group were examined in our initial study,[9] their vastly inferior catalytic behavior, as well as that of Me-DalPhos, in the challenging ammonia monoarylation test reaction employed suggests that the presence of a cyclic dialkylamino donor fragment *ortho* to the PAd_2 group (Ad = 1-adamantyl), as featured in Mor-DalPhos, may be particularly important in achieving optimal performance within this ligand class. Building on these observations, and in an effort to identify high-performing variants of Mor-DalPhos, we have subsequently explored the influence of backbone substitution,[14] as well as donor-fragment substitution, on palladium-catalyzed C-N and C-C cross-coupling reactivity employing Mor-DalPhos variants. Herein we report on our extensive examination of the latter structural variation, whereby 18 known or newly prepared Mor-DalPhos derivatives were systematically screened in test reactions involving the palladium-catalyzed cross-coupling of chlorobenzene with aniline, octylamine, morpholine, indole, ammonia, or acetone, with an emphasis on the examination of ligands featuring pairings of *ortho*-disposed PAd_2 (or the new dimethylated variant $P(^{Me2}Ad)_2$) and cyclic dialkylamino donor fragments (Figure 1).

EXPERIMENTAL

General Considerations. All reactions were set up inside a dinitrogen-filled, inert atmosphere glovebox (unless otherwise indicated) and isolated under standard benchtop conditions. Toluene and methylene chloride used in the glovebox were deoxygenated by purging with dinitrogen followed by passage through a double column solvent purification system equipped either with one alumina-packed column and one column packed with copper-Q5 reactant (toluene), or two alumina-packed columns (methylene chloride). 1,4-Dioxane and diethyl ether were dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. *tert*-Butanol was dried over CaH_2 followed by distillation under an atmosphere of dinitrogen. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Ligands **L1-L3**,[13a] **L5**,[9] **L7**,[8] **L10**,[9] and **L13**[15] were prepared according to literature procedures. All other reagents, solvents and materials were used as received from commercial sources. Flash column chromatography was performed on silica gel (SiliaFlash P60, Silicycle) or 150 mesh Brockmann III activated, neutral alumina oxide, as indicated. All ^{1}H NMR (500 MHz or 300 MHz) and ^{13}C NMR (125.8 MHz or 75.4 MHz) spectra were recorded at 300 K. Chemical shifts are expressed in parts per million (ppm) using the solvent signal as an internal reference. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). In some cases fewer than expected independent carbon resonances were observed despite prolonged acquisition times. Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode and GC data were obtained on an instrument equipped with a SGE BP-5, 30 m, 0.25 mm i.d. column. Crystallographic data for **L16** were obtained at 173(2) K on a Bruker D8/APEX II CCD diffractometer equipped with a CCD area detector, employing sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer. Unit cell parameters were determined and refined on all reflections. Data reduction, correction for Lorentz

polarization, and absorption correction were each performed. Structure solution and least-squares refinement on F^2 were used throughout. All non-hydrogen atoms were refined with anisotropic displacement parameters. Full crystallographic solution and refinement details are provided in the deposited CIF (CCDC-1824777).

General Catalytic Procedure for the C-N Cross-coupling of 2-Iodo-1-bromobenzene with Secondary Amines (GP1). In an atmosphere controlled glovebox $Pd_2(dba)_3$ (23 mg, 0.025 mmol, 0.01 equiv) and BINAP (46.5 mg, 0.075 mmol, 0.03 equiv) were added to a vial and dissolved in 5 mL THF. To the vial was added 18-crown-6 (1.58 g, 6.0 mmol, 1.3 equiv) and NaO^{t}Bu (580 mg, 6.0 mmol, 1.3 equiv), the vial was then capped with a PTFE lined septum cap and removed from the glovebox. 2-Bromoiodobenzene (650 μL, 5.0 mmol, 1.0 equiv) and amine (610 μL, 5.5 mmol, 1.2 equiv) when then added via syring and the reaction mixture was stirred at room temperature. Reaction progress was monitored by use of TLC or GC methods and after complete consumption of the aryl halide (24-48 h), the reaction was quenched with 75 mL of water extracted with 100 mL EtOAc two times. The organic layer was dried with $MgSO_4$, concentrated, and the product was purified by way of column chromatography. All reactions were conducted on 0.5 to 4.0 mmol scale

General Catalytic Procedure for P-C Cross-coupling of 2-Bromo-1-aminobenzenes with di(1-adamantyl)phosphine (GP2). To a vial containing $HP(Ad)_2$ (301 mg, 1.0 mmol), NaO^{t}Bu (115 mg, 1.2 mmol), and *N*-(2-bromophenyl)-*N*'-methylpiperazine (255 mg, 1.0 mmol) was added a solution of $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and DiPPF (15 mg, 0.036 mmol) in 2.5 mL toluene. The vial was capped with a PTFE lined screw cap and heated at 110 $^\circ$C for 18-48 h. The reaction mixture was then allowed to cool and filtered through a plug of silica washing with CH_2Cl_2 (3 x 15 mL). The filtrate was concentrated and the resulting solid was purified by washing with small solvent aliquots (Et_2O or pentane) or by column chromatography, as indicated.

Procedures for Ligand Screening. Estimated percent conversion to the target monoarylation products (average of at least two runs) were determined on the basis of response-factor corrected GC methods using a dodecane internal standard, based on calibrations generated from analytically pure samples of the products and starting materials. ***Toluene Catalyst Stock Solution:*** $[Pd(cinnamyl)Cl]_2$ (7.2 mg, 0.015 mmol), ligand (0.06 mmol) and 3 mL of toluene were added to a oven dried vial equipped with a stir bar and stirred until dissolution was complete. The resulting catalyst stock solution was used immediately. ***1,4-Dioxane Catalyst Stock Solution:*** $[Pd(cinnamyl)Cl]_2$ (4.8 mg, 0.010 mmol), ligand (0.04 mmol) and 2 mL of 1,4-dioxane were added to a oven dried vial equipped with a stir bar and stirred until dissolution was complete. The resulting catalyst stock solution was used immediately. ***Cross-Coupling of Chlorobenzene and Amines:*** A 0.5 mL aliquot of the toluene stock solution was added to a vial containing NaO*t*Bu (33.6 mg, 1.4 equiv) and stirred 5 min. Dodecane (40.9 mL, 0.18 mmol) was added followed by chlorobenzene (25.3 μL, 0.25 mmol, 1.0 equiv) and then 1˚ or 2˚ amine (0.30 mmol, 1.2 equiv, [aniline, 27.3 μL, *n*-octylamine, 49.5 μL; morpholine, 26.2 μL]) was added and the vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was heated to 110 ˚C with stirring for 18 h. An aliquot was sampled (0.1 to 0.25 mL), filtered through SiO_2 into a GC vial, diluted with methylene chloride to approximately 1 mL and analyzed by GC to quantify conversion to the target products (diphenylamine, *N*-octylaniline, and *N*-phenylmorpholine, respectively). ***Cross-Coupling of Chlorobenzene and Indole:*** A 0.5 mL aliquot of the toluene stock solution was added to a vial containing NaO*t*Bu (33.6 mg, 1.4 equiv) and indole (30.6 mg, 0.26 mmol, 1.05 equiv). Dodecane (40.9 μL, 0.18 mmol) was added followed by chlorobenzene (25.3 μL, 0.25 mmol, 1.0 equiv) and the vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was heated at 110 ˚C with stirring for 18 h. An aliquot was sampled (0.1 to 0.25 mL), filtered through SiO_2 into a GC vial, diluted with methylene chloride to approximately 1

mL and analyzed by GC to quantify conversion to the target product, *N*-phenylindole. ***Cross-Coupling of Chlorobenzene and Ammonia or Acetone:*** A 0.5 mL aliquot of the 1,4-dioxane stock solution was added to a vial containing NaO*t*Bu (48.1 mg, 2.0 equiv) and stirred 5 min. Dodecane (40.9 μL, 0.18 mmol) was added followed by chlorobenzene (25.3 μL, 0.25 mmol, 1.0 equiv) and then 1,4-dioxane (0.5 mL) and the vial was sealed with a cap containing a PTFE septum and removed from the glovebox. A 0.5 M solution of NH_3 in 1,4-dioxane (1.5 mL, 3 equiv) was added and the reaction mixture was heated to 90 ˚C with stirring for 18 h. An analogous protocol was used for the monoarylation of acetone, with the exception that Cs_2CO_3 (163 mg) was used in place of NaO*t*Bu, and acetone (0.5 mL) was used in place of the NH_3 in 1,4-dioxane. An aliquot was sampled (0.1 to 0.25 mL), filtered through SiO_2 into a GC vial, diluted with methylene chloride to approximately 1 mL and analyzed by GC to quantify conversion to the target products (aniline and phenylacetone).

***N*-(2-Bromophenyl)-azetidine (precursor to L8).** The title compound was synthesized using GP1 and was isolated as a clear, colorless oil in 53% yield (0.409 g, 1.93 mmol) after column chromatography (98:2 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, J = 1.5, 7.5 Hz, 1H), 7.18 (ddd, J = 1.5, 7.5, 8.5 Hz, 1H), 6.67 (ddd, J = 1.5, 7.5, 8.5 Hz, 1H), 6.55 (dd, J = 1.5, 8.5 Hz, 1H), 4.06 (t, J = 7.5 Hz, 4H), 2.27 (pentet, J = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 149.5, 134.2, 127.9, 120.3, 114.9, 108.8, 54.3, 17.0; *m/z* ESI$^+$ found 212.0068 $[M+H]^+$ calculated for $C_9H_{11}{}^{79}BrN$ 212.0069.

***N*-(2-Bromophenyl)-pyrrolidine (precursor to L9).** The title compound was synthesized using GP1 and was isolated as a clear, colorless oil in 81% yield (0.730 g, 3.22 mmol) after column chromatography (pure hexanes to 98:2 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, J = 1.5, 7.5 Hz, 1H), 7.19 (ddd, J = 1.5, 7.5, 8.5 Hz, 1H), 6.92 (dd, J = 1.5, 8.0 Hz, 1H), 6.74 (ddd, J = 1.5, 7.5, 8.0 Hz, 1H), 3.37-3.35 (m, 4H), 1.96-1.93 (m, 4H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 148.8,

134.7, 127.9, 121.4, 118.0, 113.9, 51.4, 25.8; *m/z* ESI$^+$ found 226.0237 $[M+H]^+$ calculated for $C_{10}H_{13}{}^{79}BrN$ 226.0226.

***N*-(2-Bromophenyl)-azepane (precursor to L11).** The title compound was synthesized using GP1 and was isolated as a clear, colorless oil in 84% yield (0.849 g, 3.34 mmol) after column chromatography (pure hexanes to 98:2 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.22 (ddd, *J* = 1.5, 7.5, 8.0 Hz, 1H), 7.11 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.83 (ddd, *J* = 1.5, 7.5, 8.0 Hz, 1H), 3.19-3.17 (m, 4H), 1.84-1.71 (m, 8H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 153.7, 133.9, 123.5, 123.0, 120.3, 55.8, 29.4, 27.3; *m/z* ESI$^+$ found 254.0549 $[M+H]^+$ calculated for $C_{12}H_{17}{}^{79}BrN$ 254.0539.

***N*-(2-Bromophenyl)-tetrahydroisoquinoline (precursor to L12).** The title compound was synthesized using GP1 and was isolated as a thick yellow oil in 83% yield (1.20 g, 0.41 mmol) after column chromatography (10:1 hexanes:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.61 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.30 (m, 1H), 7.20-7.15 (m, 4H), 7.11 (m, 1H), 6.95 (td, *J* = 1.6, 7.6 Hz, 1H), 4.28 (s, 2H), 3.41 (t, *J* = 5.8 Hz, 2H), 3.07 (t, *J* = 5.8 Hz, 2H). $^{13}C\{^1H\}$NMR ($CDCl_3$): δ 150.6, 134.9, 134.7, 134.1, 129.1, 128.3, 126.53, 126.46, 125.9, 124.4, 121.2, 119.9, 53.7, 50.6, 29.3. *m/z* ESI$^+$ found 288.0385 $[M+H]^+$ calculated for $C_{15}H_{15}{}^{79}BrN$ 288.0382.

***N*-(2-Bromophenyl)-*N*'-methylpiperazine (precursor to L14).** The title compound was synthesized using GP1 and was isolated as a thick orange oil after column chromatography (CH_2Cl_2 to 200:20:1 CH_2Cl_2:MeOH:NH_4OH) in 64% yield (725 mg, 3.2 mmol). ^{1}H NMR ($CDCl_3$): δ 7.56 (dd, *J* = 1.6, 7.9 Hz, 1H), 7.28 (m, 1H), 7.08 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.93 (td, *J* = 1.6, 7.8 Hz, 1H), 3.12 (br s, 4H), 2.68 (br s, 4H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.7, 134.0, 128.5, 124.6, 121.2, 120.1, 55.4, 51.6, 46.3. *m/z* ESI$^+$ found 255.0485 $[M+H]^+$ calculated for $C_{11}H_{16}{}^{79}BrN_2$ 255.0491.

***N*-(2-Bromophenyl)-2-(piperazin-1-yl)pyrimidine (precursor to L15).** The title compound was synthesized using GP1 and was isolated as a clear, yellow oil in 92% yield (1.17 g, 3.67 mmol) after column chromatography (90:10 to 70:30 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, J = 4.5 Hz, 2H), 7.59 (dd, J = 1.5, 8.0 Hz, 1H), 7.28 (ddd, J = 1.5, 7.5, 8.0 Hz, 1H), 7.05 (dd, J = 1.5, 8.0 Hz, 1H), 6.94 (ddd, J = 1.5, 7.5, 8.0 Hz, 1H), 6.51 (t, J = 4.5 Hz, 1H), 4.01 (t, J = 5.0 Hz, 4H), 3.10 (t, J = 5.0 Hz, 4H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 161.9, 157.9, 150.7, 134.0, 128.4, 124.7, 121.1, 120.2, 110.1, 51.8, 44.2; *m/z* ESI^{+} found 319.0550 $[M+H]^{+}$ calculated for $C_{14}H_{16}{}^{79}BrN_4$ 319.0553.

Di-1-(3,5-dimethyladamantyl)phosphinic chloride. This was prepared following a modification of the literature procedure for the preparation of di(1-adamantyl)phosphinic chloride.[16] 1,3-Dimethyladamantane (5.0 g, 0.030 mol) and $AlCl_3$ (4.1 g, 0.031 mol) were combined in a Schlenk flask and purged with N_2. 15 mL of PCl_3 was added via cannula, and the reaction mixture was heated to reflux for 5 hours. Excess PCl_3 was removed by distillation, and the resulting orange slurry was taken up in chloroform and cooled to 0 °C. Water was added slowly with vigorous stirring, and subsequent steps were carried out under bench top conditions. The resulting mixture was Buchner filtered through a bed of Celite. The layers were separated and the organic phase was dried using Na_2SO_4 and filtered. Removal of solvent provided the title compound as a pale yellow solid in 99% yield (6.17 g, 0.015 mol). ^{1}H NMR (500 MHz; $CDCl_3$): δ 2.17-2.12 (m, 2H, C*H*), 1.98-1.92 (m, 4H, CH_2), 1.79-1.69 (m, 8H, CH_2), 1.41 (d, J = 12.5 Hz, 4H, CH_2), 1.34 (d, J = 12.6 Hz, 4H, CH_2), 1.18 (s, 4H, CH_2), 0.86 (s, 12H, CH_3). ^{31}P{^{1}H} NMR ($CDCl_3$, 202 MHz) δ 85.9 (s). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 50.5 (d, J = 1.9 Hz, *C*H_2), 47.5 (d, J = 59.1 Hz, P*C*), 43.0 (d, J = 2.5 Hz, *C*H_2), 42.9 (d, J = 2.2 Hz, *C*H_2), 42.7 (d, J = 1.8 Hz, *C*H_2), 42.7 (d, J = 1.8 Hz, *C*H_2), 35.8 (d, J = 1.9 Hz, *C*H_2), 31.1 (s, *C*CH_3), 31.0 (d, J = 1.6 Hz, *C*CH_3), 30.8 (s, *C*H_3), 29.2 (d, J = 11.9 Hz, *C*H). HRMS (ESI/$[M+Na]^{+}$) calcd. for $C_{24}H_{38}ClNaOP$: 431.2241. Found: 431.2224.

Di-1-(3,5-dimethyladamantyl)phosphine. This was prepared following a modification of the literature procedure for the preparation of di(1-adamantyl)phosphine.[16] 50 mL of dry THF was added to a Schelnk flask containing 5.76 g of **2**. The resulting suspension was cooled to –15 °C, and $LiAlH_4$ (1.28 g) was slowly added in small portions over 15 minutes, allowing evolution of gas to subside before each subsequent addition. The reaction was then warmed to ambient temperature and stirred for 1 hour. The reaction was cooled to –15 °C, and 1 mL of 1M HCl was added very slowly over approximately 10 minutes. An additional 30 mL of 1M HCl was slowly added, resulting in a two-phase system, with the aqueous phase being highly viscous. The THF layer was transferred via cannula to a Schlenk flask containing Na_2SO_4, stirred, and filtered through a sintered glass frit. Removal of solvent *in vacuo* gave the title compound in 87 % yield (4.72 g, 0.013 mol). ^{1}H NMR (500 MHz; C_6D_6): δ 3.01 (d, J = 201.9 Hz, 1H, P*H*), 1.98-1.93 (m, 2H, C*H*), 1.90-1.86 (m, 2H, CH_2), 1.80-1.76 (m, 2H, CH_2), 1.69-1.63 (m, 4H, CH_2), 1.61-1.51 (m, J = 4.7, 2.3 Hz, 4H, CH_2), 1.31 (app. d, J = 12.3 Hz, 4H, CH_2), 1.23 (app. d, J = 12.4 Hz, 4H, CH_2), 1.04 (s, 4H, CH_2), 0.80 (s, 12H, CH_3); ^{31}P{^{1}H} NMR (C_6D_6, 202 MHz) δ 14.8 (s); ^{13}C{^{1}H} NMR (C_6D_6, 126 MHz) δ 51.0 (s, *C*H_2), 50.4 (d, J = 9.7 Hz, *C*H_2), 50.0 (d, J = 12.3 Hz, *C*H_2), 43.2 (s, *C*H_2), 42.5 (d, J = 9.2 Hz, *C*H_2), 35.7 (d, J = 18.2 Hz, P*C*), 31.5 (d, J = 7.5 Hz, *C*CH_3), 31.4 (d, J = 8.5 Hz, *C*CH_3), 31.1 (s, *C*H_3), 30.5 (d, J = 7.3 Hz, *C*H). HRMS (ESI/$[M+H]^+$) calcd. for $C_{24}H_{40}P$: 359.2862. Found: 359.2858.

(L4) ***N*-(2-di-tert-butylphosphino)phenyl)-morpholine.** The title compound was synthesized using GP2, substituting di(tert-butyl)phosphine for di(1-adamantyl)phosphine, and was isolated as a white solid in 72% yield (0.220 g, 0.72 mmol) after column chromatography (90:10 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 7.07-7.03 (m, 2H), 3.83 (t, J = 4.5 Hz, 4H), 3.06 (t, J = 4.5 Hz, 4H), 1.19 (d, J = 12 Hz, 18H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 159.0 (d, J_{PC} = 20 Hz), 136.4, 134.0 (d, J_{PC} = 28 Hz), 129.7, 122.8, 120.0, 67.3, 53.6 (d, J_{PC} = 6 Hz), 32.3 (d, J_{PC}

= 26 Hz), 30.9 (d, J_{PC} = 16 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 18.6; *m/z* ESI^+ found 308.2128 $[M+H]^+$ calculated for $C_{18}H_{31}NOP$ 308.2138.

(L6) *N*-(2-di-(3,5-dimethyladamantyl)phosphino-1-phenyl)-morpholine. The title compound was synthesized using GP2, substituting di-1-(3,5-dimethyladamantyl)phosphine for di(1-adamantyl)phosphine, and was isolated as a beige solid in 89% yield (0.922 g, 1.77 mmol) after washing with cold hexanes. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.66 (d, *J* = 7.6 Hz, 1H, 3-Ph), 7.30 (td, *J* = 7.6, 1.3 Hz, 1H, 5-Ph), 7.07-7.03 (m, 2H, 4-Ph + 6-Ph), 3.82 (t, *J* = 4.5 Hz, 4H, OCH_2), 3.03 (t, *J* = 4.4 Hz, 4H, NCH_2), 1.99 (m, 2H, Ad C*H*), 1.75 (m, 4H), 1.62 (d, *J* = 12.4 Hz, 2H), 1.51-1.42 (m, 6H), 1.34-1.23 (m, 8H), 1.10-1.04 (m, 4H), 0.77 (s, 6H, CH_3), 0.74 (s, 6H, CH_3). $^{13}C(^{1}H)$ NMR ($CDCl_3$, 126 MHz): δ 159.4 (d, *J* = 20.9 Hz), 137.5 (d, *J* = 3.0 Hz, 3-Ph), 131.6 (d, *J* = 27.4 Hz), 129.6 (s, 5-Ph), 122.4 (s, 4-Ph), 120.2 (d, *J* = 3.7 Hz, 6-Ph), 67.3 (s, OCH_2), 53.5 (d, *J* = 5.8 Hz, NCH_2), 51.1 (s, Ad CH_2), 48.7 (d, *J* = 14.7 Hz, Ad CH_2), 48.2 (d, *J* = 12.5 Hz, Ad CH_2), 43.3 (s, Ad CH_2), 40.3 (d, *J* = 11.3 Hz, Ad CH_2), 38.1 (d, *J* = 27.5 Hz, Ad *C*P), 31.4 (d, *J* = 6.1 Hz, Ad CCH_3), 31.4 (d, *J* = 5.1 Hz, Ad CCH_3), 31.1 (s, CH_3), 30.1 (d, *J* = 8.0 Hz, Ad *C*H). $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 202 MHz): δ 18.8 (s). HRMS (ESI/$[M+H]^+$) calcd. for $C_{34}H_{51}NOP$: 520.3703. Found: 520.3687.

(L8) *N*-(2-diadamantylphosphino)phenyl)-azetidine. The title compound was synthesized using GP2 and was isolated as a white solid in 61% yield (0.700 g, 2.59 mmol) after column chromatography (95:5 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (dt, *J* = 2.0, 7.5 Hz, 1H), 7.22-7.19 (m, 1H), 6.71 (td, *J* = 1.0, 7.5), 6.46 (ddd, *J* = 1.0, 5.0, 8.5 Hz, 1H), 4.09 (t, *J* = 7.2 Hz, 4H), 2.20 (pentet, *J* = 7.2 Hz, 2H), 1.99-1.96 (m, 6H), 1.89-1.87 (m, 12H), 1.67 (bs, 12H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 158.2 (d, J_{PC} = 24 Hz), 138.5, 129.3, 118.1 (d, J_{PC} = 32 Hz), 116.3, 113.1 (d, J_{PC} = 6.1 Hz), 56.2 (d, J_{PC} = 14 Hz), 42.3 (d, J_{PC} = 13 Hz), 37.4 (d, J_{PC} = 25 Hz), 37.2, 29.1 (d, J_{PC} = 9.0 Hz), 17.3 (d, J_{PC} = 8.1

Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 18.4; *m/z* ESI^+ found 434.2954 $[M+H]^+$ calculated for $C_{29}H_{41}NP$ 434.2971.

(L9) *N*-(2-diadamantylphosphino)phenyl)-pyrrolidine. The title compound was synthesized using GP2 and was isolated as a light brown solid in 28% yield (0.250 g, 0.56 mmol) after washing with pentane (3 x 3 mL). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.25-7.22 (m, 1H), 6.97 (ddd, *J* = 1.5, 4.5, 8.5 Hz, 1H), 6.85 (td, *J* = 1.5, 7.0 Hz, 1H), 3.36-3.34 (m, 4H), 1.98-1.86 (m, 24H), 1.67 (bs, 12H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 157.5 (d, J_{PC} = 23 Hz), 138.5 (d, J_{PC} = 11 Hz), 129.4, 125.6 (d, J_{PC} = 29 Hz), 118.8, 117.3 (d, J_{PC} = 5.3 Hz), 53.2 (d, J_{PC} = 12 Hz), 42.1 (d, J_{PC} = 13 Hz), 37.3 (d, J_{PC} = 26 Hz), 37.2, 29.1 (d, J_{PC} = 8.5 Hz), 25.4; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 24.5; *m/z* ESI^+ found 448.3140 $[M+H]^+$ calculated for $C_{30}H_{43}NP$ 448.3128.

(L11) *N*-(2-diadamantylphosphino)phenyl)-azepane. The title compound was synthesized using GP2 and was isolated as a light brown solid in 62% yield (0.236 g, 0.50 mmol) after washing with pentane (3 x 3 mL). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.27-7.24 (m, 1H), 7.12 (ddd, *J* = 1.0, 4.5, 8.0 Hz, 1H), 6.97 (td, *J* =1.0, 7.0 Hz, 1H), 3.16 (t, *J* = 6.0 Hz, 4H), 1.98-1.88 (m, 18H), 1.77-1.64 (m, 24H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 161.5 (d, J_{PC} = 20 Hz), 137.4 (d, J_{PC} = 3.0 Hz), 131.7 (d, J_{PC} = 27 Hz), 129.3, 121.5, 120.4 (d, J_{PC} = 3.5 Hz), 54.8 (d, J_{PC} = 5.5 Hz), 42.0 (d, J_{PC} = 13 Hz), 37.3, 36.8 (d, J_{PC} = 28 Hz), 29.2 (d, J_{PC} = 8.3 Hz), 26.2, 24.5; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 21.1; *m/z* ESI^+ found 476.3440 $[M+H]^+$ calculated for $C_{32}H_{47}NP$ 476.3441.

(L12) *N*-(2-(diadamantylphosphino)phenyl)-tetrahydroisoquinoline. The title compound was synthesized using GP2 and was isolated as a light yellow solid in 56% yield (340 mg, 0.67 mmol) after washing with Et_2O (2 x 5 mL). The ^{13}C spectra showed two signals for each of the tetrahydroisoquinoline carbons ortho to nitrogen, possibly due to restricted rotation about the C_{aryl}-N

bond. ^{1}H NMR ($CDCl_3$): δ 7.75 (dt, J = 1.4, 7.6 Hz, 1H), 7.31 (m, 1H), 7.18-7.13 (m, 4H), 7.10-7.05 (m, 2H), 4.25 (s, 2H), 3.41 (t, J = 5.6 Hz, 2H), 3.00 (t, J = 5.5 Hz, 2H), 2.00-1.86 (m, 18H), 1.67 (br s, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.9 (d, J_{PC} = 21 Hz), 137.8, 136.1, 135.7 (d, J_{PC} = 2 Hz), 131.3 (d, J_{PC} = 27 Hz), 129.6, 129.1, 126.5, 125.9, 125.6, 122.1, 120.8 (d, J_{PC} = 3 Hz), 54.9 (2), 51.7 (2), 42.0 (d, J_{PC} = 13 Hz), 37.2, 36.9 (d, J = 27 Hz), 29.1 (2 unique signals). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 20.8. *m/z* ESI$^+$ found 510.3273 $[M+H]^+$ calculated for $C_{35}H_{45}NP$ 510.3284.

(L14) *N*-(2-(diadamantylphosphino)phenyl)-*N*'-methylpiperazine. The title compound was synthesized using GP2 and was isolated as a beige solid in 61% yield (290 mg, 0.61 mmol) after washing with Et_2O (2 x 5 mL). ^{1}H NMR ($CDCl_3$): δ 7.70 (dt, J = 1.4, 7.6 Hz, 1H), 7.29 (m, 1H), 7.09 (ddd, J = 1.1, 4.4, 8.0 Hz, 1H), 7.03 (td, J = 1.2, 7.4 Hz, 1H), 3.10 (br s, 4H), 2.62 (br s, 4H), 2.40 (s, 3H), 1.97-1.89 (m, 18H), 1.71-1.67 (m, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.9 (d, J_{PC} = 21 Hz), 137.6, 131.4 (d, J_{PC} = 27 Hz), 129.5, 122.2, 120.3 (d, J_{PC} = 3 Hz), 55.4, 52.9 (d, J_{PC} = 6 Hz), 46.2, 42.1 (d, J_{PC} = 13 Hz), 37.2, 36.9 (d, J_{PC} = 27 Hz), 29.1 (d, J_{PC} = 18 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 20.7. *m/z* ESI$^+$ found 477.3392 $[M+H]^+$ calculated for $C_{31}H_{46}N_2P$ 477.3393.

(L15) *N*-(2-diadamantylphosphino)phenyl)-2-(piperazin-1-yl)pyrimidine. The title compound was synthesized using GP2 and was isolated as a light brown solid in 88% yield (0.478 g, 0.88 mmol) after after column chromatography (90:10 hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, J = 5.0 Hz, 2H), 7.71 (apparent d, J = 7.5 Hz, 1H), 7.29 (td, J = 1.5 Hz, 1H), 7.05-7.02 (m, 2H), 6.48 (t, J = 4.5 Hz, 1H), 3.95 (bs, 4H), 3.11 (t, J = 5.0 Hz, 4H), 1.99-1.89 (m, 18H), 1.67 (bs, 12H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 162.4, 159.8 (d, J_{PC} = 21 Hz), 157.8, 137.6 (d, J_{PC} = 3.0 Hz), 131.5 (d, J_{PC} = 28 Hz), 129.5, 122.2, 120.1, 109.8, 53.1 (d, J_{PC} = 5.8 Hz), 44.2, 42.1 (d, J_{PC} =13 Hz), 37.2, 37.0 (d, J_{PC} = 27 Hz), 29.1 (d, J_{PC} = 9.3 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$): δ 20.6; *m/z* ESI$^+$ found 541.3451 $[M+H]^+$ calculated for $C_{34}H_{46}N_4P$ 541.3455.

(L16) ***N*-(2-di-(3,5-dimethyladamantyl)phosphino-1-phenyl)-3,5-dimethylmorpholine.** The title compound was synthesized using GP2 from *N*-(2-bromophenyl)-2,6-dimethylmorpholine[15] and di-1-(3,5-dimethyladamantyl)phosphine, affording a light yellow powder in 65% yield (715 mg, 1.30 mmol) after washing with cold hexanes. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.66 (d, *J* = 7.7 Hz, 1H, 3-Ph), 7.29 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05-7.01 (ov m, 2H, 4-Ph + 6-Ph), 3.92-3.86 (m, 2H, OC*H*), 3.14 (d, *J* = 11.8 Hz, 2H, NC*H*H), 2.45 (t, *J* = 10.5 Hz, 2H, NCH*H*), 1.99 (m, 2H, Ad), 1.77-1.71 (m, 4H, Ad), 1.62 (d, *J* = 12.4 Hz, 2H, Ad), 1.46 (m, 6H, Ad), 1.28 (m, 8H, Ad), 1.19 (s, 3H, CH_3 Morph), 1.18 (s, 3H, CH_3 Morph), 1.07 (q, *J* = 11.8 Hz, 4H, Ad), 0.77 (s, 6H, CH_3 Ad), 0.74 (s, 6H, CH_3 Ad). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 159.1 (d, *J* = 20.5 Hz), 137.5 (d, *J* = 2.9 Hz, 3-Ph), 131.6 (d, *J* = 27.2 Hz), 129.5 (s, 5-Ph), 122.3 (s, 4-Ph), 120.4 (d, *J* = 3.7 Hz, 6-Ph), 71.9 (s, O*C*H), 59.2 (d, *J* = 5.5 Hz, N*C*H$_2$), 51.1 (s, *C*H$_2$), 48.7 (d, *J* = 14.7 Hz, *C*H$_2$), 48.3 (d, *J* = 13.0 Hz, *C*H$_2$), 43.3 (s, *C*H$_2$), 40.3 (d, *J* = 11.3 Hz, *C*H$_2$), 38.1 (d, *J* = 27.5 Hz, *C*P Ad), 31.4 (d, *J* = 5.5 Hz, *C*CH$_3$ Ad), 31.3 (d, *J* = 4.9 Hz, *C*CH$_3$ Ad), 31.1 (s, C*C*H$_3$ Ad), 30.1 (d, *J* = 7.8 Hz, *C*H Ad), 19.2 (s, *C*H$_3$ Morph). ^{31}P{^{1}H} NMR ($CDCl_3$, 202 MHz) δ 19.0 (s). HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{36}H_{55}NOP$: 548.4016. Found: 548.4017.

(L17) ***N*-(3-di-(3,5-dimethyladamantyl)phosphino-2-pyridyl)-morpholine.** The title compound was synthesized using GP2 from *N*-(3-bromopyridin-2-yl)morpholine[14b] and di-1-(3,5-dimethyladamantyl)phosphine, affording light yellow crystals in 56% yield (293 mg, 0.56 mmol) after recrystallization from hexanes. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.27 (d, *J* = 4.7 Hz, 1H, Py), 7.89 (d, *J* = 7.4 Hz, 1H, Py), 6.92 (dd, *J* = 7.4, 4.8 Hz, 1H, Py), 3.82 (t, *J* = 4.5 Hz, 4H, OCH_2), 3.34 (t, *J* = 4.1 Hz, 4H, NCH_2), 2.00 (m, 2H, Ad), 1.72 (m, 4H, Ad), 1.57 (m, 2H, Ad), 1.44 (m, 6H, Ad), 1.33-1.28 (m, 10H, Ad), 1.07 (m, 4H, Ad), 0.77 (s, 6H, CH_3), 0.75 (s, 6H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 168.4 (d, *J* = 19.8 Hz, Py), 148.2 (s, Py CH), 146.4 (s, Py CH), 123.5 (d, *J* = 34.5 Hz, Py), 117.1 (s, Py CH), 67.1 (s, OCH_2), 51.9 (d, *J* = 9.1 Hz, NCH_2), 51.0 (s, *C*H$_2$ Ad), 48.7 (d, *J* = 14.7 Hz, *C*H$_2$ Ad), 48.2

(d, J = 12.1 Hz, CH$_2$ Ad), 43.2 (s, CH$_2$ Ad), 40.3 (d, J = 11.3 Hz, CH$_2$ Ad), 38.6 (d, J = 27.5 Hz, CP Ad), 31.5 (d, J = 5.4 Hz, CCH$_3$ Ad), 31.4 (d, J = 4.2 Hz, CCH$_3$ Ad), 31.1 (s, CH$_3$ Ad), 30.0 (d, J = 8.0 Hz, CH Ad). ^{31}P{^{1}H} NMR (CDCl$_3$, 202 MHz): δ 19.0 (s). HRMS (ESI/[M+H]$^+$) calcd. for $C_{33}H_{50}N_2OP$: 521.3655. Found: 521.3676.

(L18) *N*-(3-di-(3,5-dimethyladamantyl)phosphino-2-thienyl)-morpholine. The title compound was synthesized using GP2 from *N*-(3-bromothiophen-2-yl)morpholine[14a] and di-1-(3,5-dimethyladamantyl)phosphine, affording a white powder in 57% yield (170 mg, 0.32 mmol) after purification by column chromatography (10:1 hexanes:EtOAc). ^{1}H NMR (500 MHz; CDCl$_3$): δ 7.13 (d, J = 5.6 Hz, 1H, thiophene), 6.93 (d, J = 5.6 Hz, 1H, thiophene), 3.82 (t, J = 4.6 Hz, 4H, OCH_2), 3.05 (t, J = 4.5 Hz, 4H, NCH_2), 1.99 (m, 2H, Ad), 1.68 (m, 4H, Ad), 1.56 (d, 2H, Ad), 1.45 (m, 6H, Ad), 1.28 (m, 8H, Ad), 1.07 (m, 4H, Ad), 0.77 (s, 6H, CH_3), 0.75 (s, 6H, CH_3). ^{13}C{^{1}H} NMR (CDCl$_3$, 126 MHz) δ 166.5 (d, J = 25.1 Hz), 131.6 (d, J = 4.1 Hz, thio CH), 121.9 (d, J = 27.5 Hz), 116.9 (s, thio CH), 67.1 (s, OCH$_2$), 55.3 (d, J = 3.3 Hz, NCH$_2$), 51.0 (s, CH$_2$ Ad), 48.3 (d, J = 13.3 Hz, CH$_2$ Ad), 48.2 (d, J = 12.5 Hz, CH$_2$ Ad), 43.2 (s, CH$_2$ Ad), 40.2 (d, J = 11.0 Hz, CH$_2$ Ad), 38.2 (d, J = 23.0 Hz, Ad CP), 31.4 (d, J = 5.8 Hz, CCH$_3$ Ad), 31.3 (d, J = 5.2 Hz, CCH$_3$ Ad), 30.1 (s, CH Ad). ^{31}P{^{1}H} NMR (CDCl$_3$, 202 MHz) δ 9.9 (s). HRMS (ESI/[M+H]$^+$) calcd. for $C_{32}H_{49}NOPS$: 526.3267. Found: 526.3260.

RESULTS AND DISCUSSION

The Mor-DalPhos ancillary ligand variants (**L1-L18**) examined herein were prepared in synthetically useful yields as outlined in Scheme 1, using a methodology analogous to that employed for the parent Mor-DalPhos ligand.[9] Starting from 2-bromoiodobenzene, the nitrogen donor fragment was introduced at the iodide position by use of a BHA protocol using Pd$_2$dba$_3$/BINAP; subsequent palladium-catalyzed C-P cross-coupling of the derived aniline in the presence of Pd(OAc)$_2$/D*i*PPF afforded the target P,N-ligands **L1-L18**. Ligands **L1-L3**,[13a] **L5**,[9] **L7**,[8] and **L10**[9] were reported by our

group previously, whereas ligand **L13**[15] was reported for use in oxidative gold catalysis by Zhang and co-workers during the course of our investigations herein; otherwise, **L4**, **L6**, **L8-L12**, and **L14-L18** represent new compounds that are disclosed for the first time herein. In all cases the new Mor-DalPhos ligand variants were found to be air-stable, and were characterized by use of NMR spectroscopic and high-resolution mass spectrometric techniques, as well as X-ray crystallographic methods in the case of **L16** (Figure 2). Notably, ligands **L6** and **L16-L18** are derived from the new secondary phosphine $HP(^{Me2}Ad)_2$, which was prepared by using a synthetic method directly analogous to that reported for the synthesis of $HPAd_2$.[16] Combination of 1,3-dimethyladamantane and PCl_3 in the presence of $AlCl_3$ afforded after aqueous workup $Cl(O)P(^{Me2}Ad)_2$, which in was be transformed into $HP(^{Me2}Ad)_2$ (86% overall isolated yield across both steps) upon reduction with $LiAlH_4$.

With a series of systematically modified Mor-DalPhos ancillary ligand variants in hand (**L1-L18**), we conducted an initial competitive screen of these ligands focused on the palladium-catalyzed cross-coupling of chlorobenzene with aniline, octylamine, or morpholine (Figure 3; 2 mol% Pd, 4 mol% **L**). Chlorobenzene was chosen specifically given the difficulty associated with the cross-coupling of aryl chlorides,[17] and as a representative substrate lacking electronic or steric activation. Furthermore, the nucleophiles selected represent relatively easy substrates in BHA chemistry,[1a] which we viewed as being an appropriate starting point in our reactivity survey.

The poor performance of the triarylphosphines **L1** and **L2** in the *N*-arylation of aniline, octylamine, or morpholine with chlorobenzene was readily apparent, whereby ≤ 40% conversion to the target product was noted in all cases. These observations are consistent with the established trend that strongly electron-releasing ancillary ligands are needed in order to achieve effective catalytic turnover in palladium-catalyzed cross-couplings of aryl chlorides.[1a, 18] By contrast, a number of dialkylphosphine Mor-DalPhos variants proved effective for such transformations. In the *N*-arylation of aniline, each of

L3-**L18** afforded >90% conversion to diphenylamine under the test conditions employed. Whereas analogous cross-couplings of octylamine to give *N*-octylaniline also proved to be facile, poor conversion to product was noted when using **L3** and **L12**. The poor performance of **L3** (featuring a PCy_2 moiety) relative to that of **L4** or **L5** (featuring comparatively larger $P(tBu)_2$ or PAd_2 moieties, respectively) in the *N*-arylation of octylamine underscores the need for a particularly sterically demanding dialkylphosphino donor group within the Mor-DalPhos framework for such cross-couplings. The inferior behavior of **L12** (a benzannulated derivative of **L10**) in this context may arise from differing ligation properties of this less-flexible ancillary ligand versus other variants featuring a strictly saturated six-membered nitrogen heterocyclic donor group. More variation in the catalytic behavior of **L3**-**L18** was noted in the *N*-arylation of morpholine, with **L4**-**L7**, **L17**, and **L18** affording ≥ 85% conversion to the target *N*-phenylmorpholine, and conversely ≤ 70% conversion to product achieved by use of **L10**, **L12**-**L15**. The apparently divergent performance of the piperidine ligand **L10**, relative to the morpholine-derived Mor-DalPhos **L5**, in the *N*-arylation of morpholine may arise from the differing basicity of these fragments (pK_a(ammonium) in water: piperidine 11.22; morpholine 8.36). While the established potential for κ^3-*P*,*N*,*O* coordination[19] involving **L5** that is not feasible with **L10** may also contribute to the desirable performance of **L5**, such reactivity benefits are not apparent when using the structurally related piperazine ligands **L14** and **L15**. At first glance it is tempting to attribute the inferior behavior of the dimethylmorpholino ligand **L13** versus the parent **L5** in the formation of *N*-phenylmorpholine as arising due to the greater steric demand of **L13**; however, the efficacy of **L16** featuring *both* methylated morpholino and adamantyl fragments would appear to contradict this hypothesis. In fact, each of the ancillary ligand variants featuring the $P(^{Me2}Ad)_2$ donor fragment, including **L6**, **L16**, and the heterocyclic variants **L17** and **L18**, were observed to perform well in the *N*-arylation of morpholine.

We subsequently turned our attention to what are typically more challenging palladium-catalyzed cross-couplings, including the *N*-arylation of indole,[20] as well as the monoarylation of ammonia or acetone,[21] with chlorobenzene (Figure 4). The first of these transformations proved to be particularly problematic, with no observed conversion to *N*-phenylindole noted for nine of the 18 Mor-DalPhos variants examined. This observation notwithstanding, the dimethylmorpholino ancillary ligand **L13** afforded quantitative conversion to the target product. While high conversion to product was also realized by use of the P(^{Me2}Ad)$_2$ variants **L6** and **L16**, the related heterocyclic variants **L17** and **L18** proved significantly less effective.

The selective monoarylation of ammonia or acetone share the common challenge that the derived products (i.e., in the case of phenyl electrophiles, aniline or phenylacetone) are often superior substrates relative to ammonia or acetone, thereby leading to uncontrolled polyarylation even in the presence of excess nucleophile.[21] In this context, Mor-DalPhos **L5** has proven to be one of the most effective ancillary ligands known for such difficult palladium-catalyzed cross-couplings.[9, 13a] In keeping with this theme, **L5** afforded high conversion and selectivity for the monoarylation of ammonia with chlorobenzene under the test conditions employed herein. While none of the ligands surveyed were found to out-perform **L5** in this regard, comparable catalytic behavior was noted when using the P(^{Me2}Ad)$_2$ analogue **L6**; ligands **L10** (as observed previously[9]), **L13**, **L16**, and **L17** also performed reasonably well in this transformation. In quantifying the formation of diphenylamine as part of this ancillary ligand screening process, significant competing diarylation (> 20%) was noted in the case of **L3**, **L7**, **L9**, **L14**, and **L18**.

The palladium-catalyzed selective monoarylation of acetone with chlorobenzene was found to be a transformation for which a larger number of the Mor-DalPhos ancillary ligand variants proved capable (Figure 4). Ligands **L6** and **L12** proved to be particularly effective in this transformation, affording

>90% conversion to phenylacetone, with **L14** following very close behind. Unlike **L3** and **L14** (each affording ≥80 % conversion to phenylacetone), which generated significant quantities of diphenylamine in cross-couplings of ammonia (*vide supra*), the excellent performance of **L12** in the monoarylation of acetone is somewhat surprising, considering that this ligand afforded *no conversion* to aniline in our analogous ammonia monoarylation survey.

CONCLUSION

In conclusion, our competitive catalytic screening of a family of Mor-DalPhos ligand variants in the palladium-catalyzed cross-coupling of chlorobenzene with aniline, octylamine, morpholine, indole, ammonia, or acetone revealed some informative ancillary ligand design trends. Notably, triarylphosphine variants **L1** and **L2** performed poorly in these test reactions, likely owing in part to the challenging nature of the C(sp^2)-Cl oxidative addition; conversely, ligands featuring either PAd_2 or $P(^{Me2}Ad)_2$ donors in general gave rise to superior catalytic performance. While multiple Mor-DalPhos variants proved highly effective for palladium-catalyzed C-N cross-couplings involving aniline, octylamine, or morpholine, only selected ligands of this type proved useful in the more challenging cross-couplings of indole, ammonia, or acetone. In the case of the *N*-arylation of indole, a Mor-DalPhos ligand variant featuring *ortho*-disposed PAd_2 and dimethylmorpholino donor fragments (**L13**) proved superior to all other ligands surveyed, including the closely related parent Mor-DalPhos (**L5**) and the $P(^{Me2}Ad)_2$ analogue of **L13** (i.e., **L16**); evidently the steric and electronic profile of **L13** (versus **L5** and **L16**) is exquisitely optimized for this indole *N*-arylation reaction. Conversely, the parent Mor-DalPhos (**L5**) was found to be superior to all other ligands in the palladium-catalyzed monoarylation of ammonia with chlorobenzene – an apparent example of "Bercaw's Law of Initial Optimization[22]". Finally, the

monoarylation of acetone provided some intriguing results. Ligand **L6** (i.e., the P(^{Me2}Ad)$_2$ variant of parent Mor-DalPhos **L5**) proved superior to all other ligands in this transformation. In fact, it can be argued that with the exception of indole *N*-arylation, **L6** (followed closely by **L13** and **L16**) is the most broadly useful of the Mor-DalPhos ligands surveyed herein, thereby highlighting the reactivity benefits that can be derived from substitution of the adamantyl and morpholino groups of parent Mor-DalPhos. While it is our view that the beneficial effect of methylation in this context is associated with increased ancillary ligand steric demand, perhaps resulting in reduced bi-molecular decomposition, more subtle electronic effects including rendering the donor fragments more electron-rich cannot be discounted. This is not to say that we completely understand all of the observed structure-reactivity phenomena; the efficacy of **L12** in the palladium-catalyzed monoarylation of acetone was particularly surprising, given that this ligand variant proved inactive in the conceptually related monoarylation of ammonia. Collectively, the results presented herein serve to underscore the benefits of systematically examining, through structural modification, an effective ancillary ligand structure, as a means of better understanding structure-reactivity properties and also as an entry-point to more effective catalytic systems.

SUPPLEMENTARY MATERIAL

NMR Spectra of the newly prepared ligands and their precursors reported herein.

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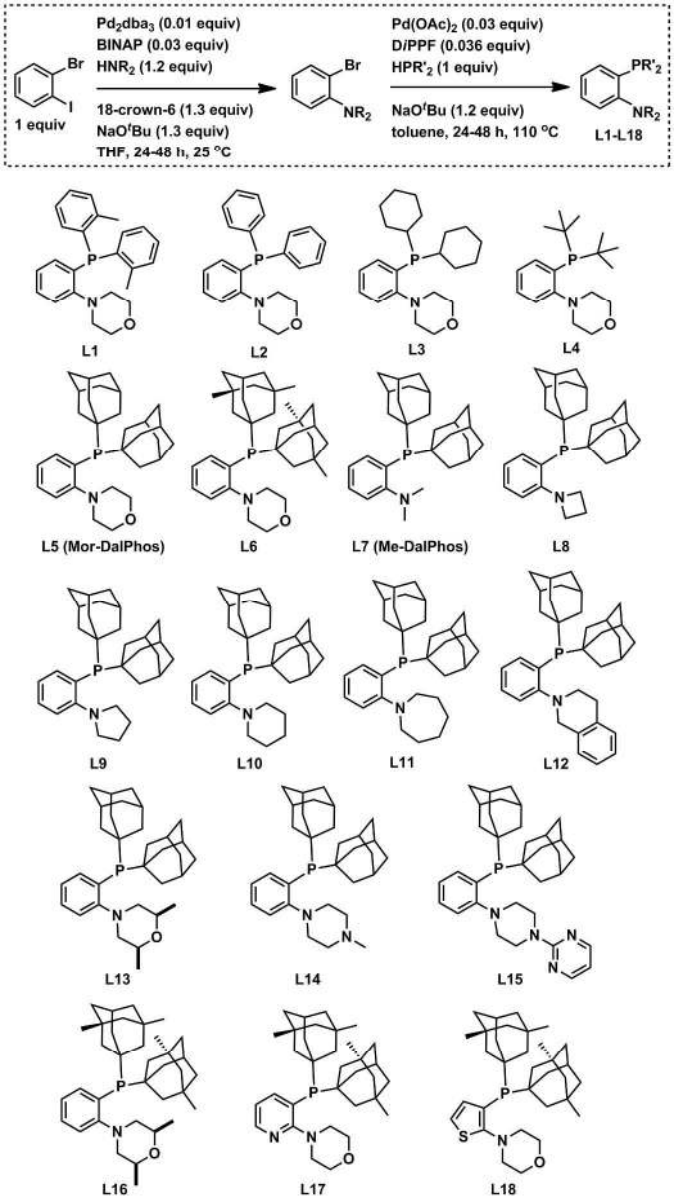
Scheme 1. Synthesis of the Mor-DalPhos ligand variants examined herein.

Figure 1. Structures of Me-DalPhos and Mor-DalPhos, with sites of structural variation within the latter as examined herein indicated.

Figure 2. Crystallographically determined structure of **L16**. Selected interatomic distances (Å): P-aryl 1.8549(12), N-aryl 1.4305(15).

Figure 3. Competitive screening of **L1**-**L18** in palladium-catalyzed cross-coupling of chlorobenzene with aniline, octylamine, or morpholine, employing $[Pd(cinnamyl)Cl]_2$ (0.0025 mmol), ligand (0.01 mmol), NaO*t*Bu (0.35 mmol), dodecane (0.18 mmol), chlorobenzene (0.25 mmol), and amine (0.30 mmol) at 110 ˚C for 18 h. Estimated percent conversion to the target monoarylation complex (Y-axis) determined on the basis of calibrated GC data. See the Experimental Section for full details.

Figure 4. Competitive screening of **L1**-**L18** in palladium-catalyzed cross-coupling of chlorobenzene with indole, ammonia, or acetone, employing $[Pd(cinnamyl)Cl]_2$ (0.0025 mmol), ligand (0.01 mmol), base (NaO*t*Bu or Cs_2CO_3), dodecane (0.18 mmol), chlorobenzene (0.25 mmol), and indole (0.26 mmol), ammonia (0.75 mmol), or acetone (0.5 mL) at 110 ˚C (for indole) or 90 ˚C (for ammonia or acetone) for 18 h. Estimated percent conversion to the target monoarylation complex (Y-axis) determined on the basis of calibrated GC data. See the Experimental Section for full details.



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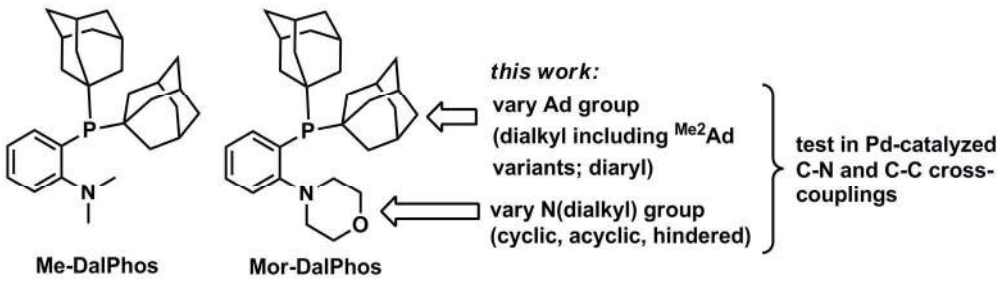

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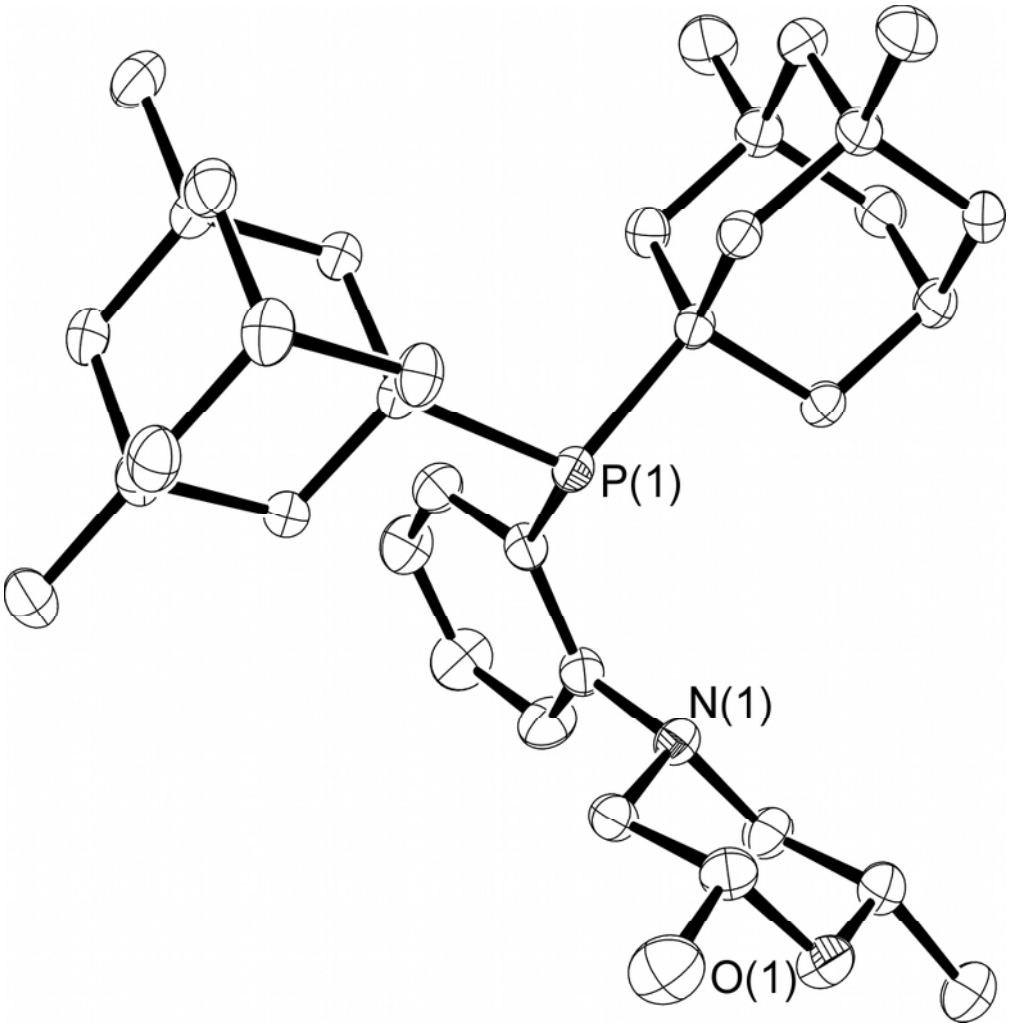

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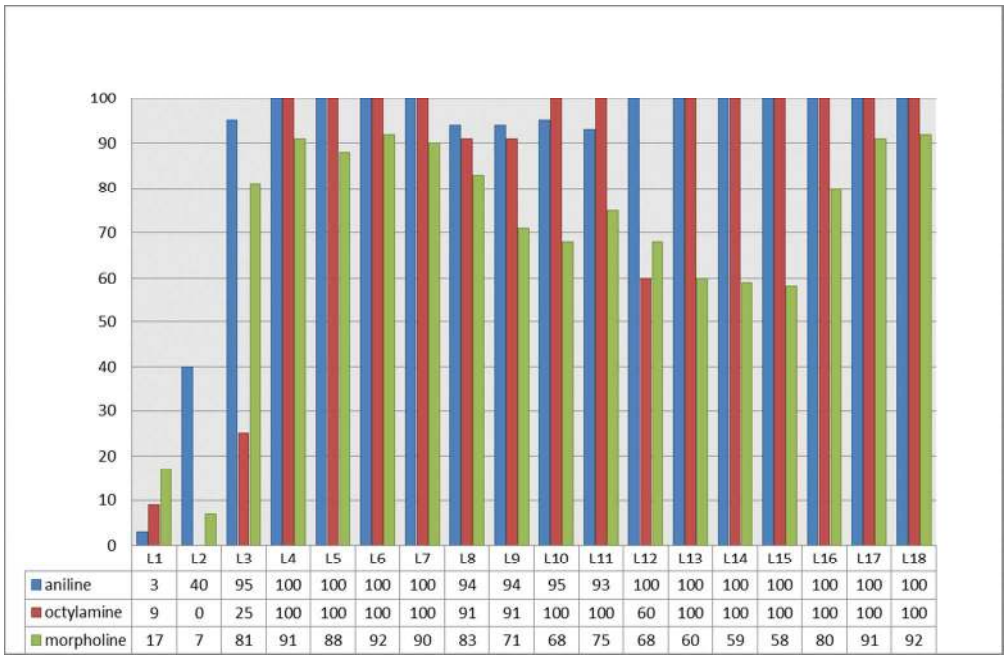
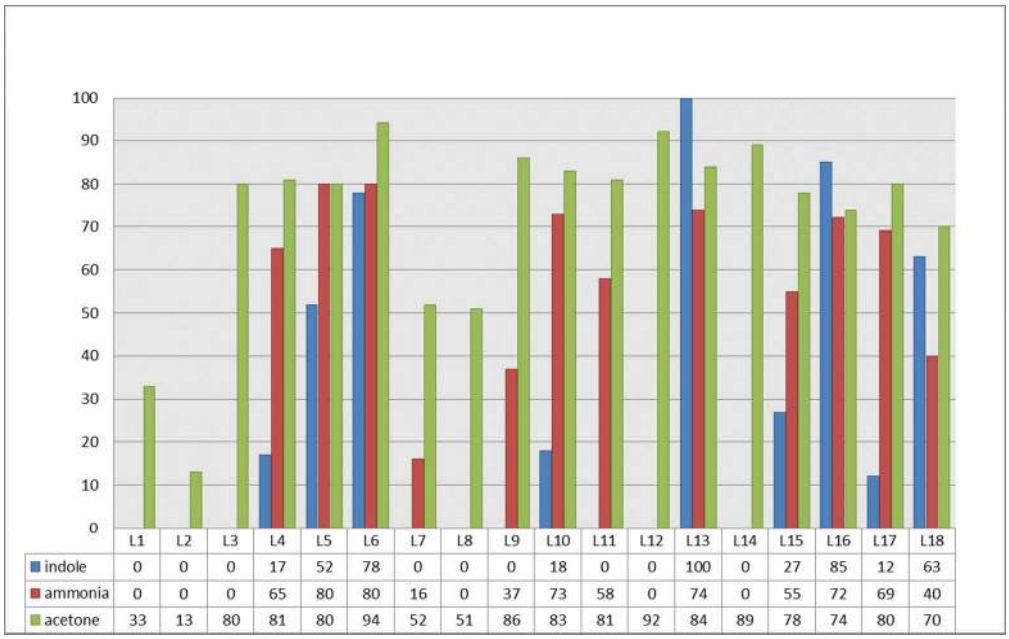
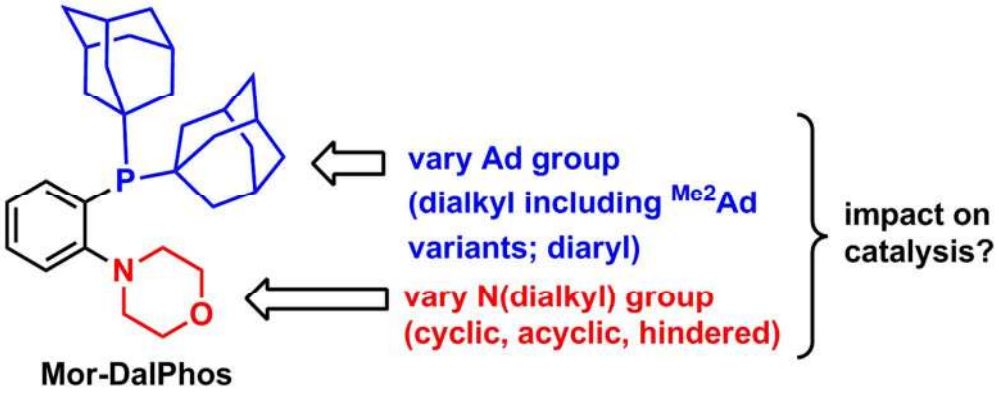


	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18
aniline	3	40	95	100	100	100	100	94	94	95	93	100	100	100	100	100	100	100
octylamine	9	0	25	100	100	100	100	91	91	100	100	60	100	100	100	100	100	100
morpholine	17	7	81	91	88	92	90	83	71	68	75	68	60	59	58	80	91	92



	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18
indole	0	0	0	17	52	78	0	0	0	18	0	0	100	0	27	85	12	63
ammonia	0	0	0	65	80	80	16	0	37	73	58	0	74	0	55	72	69	40
acetone	33	13	80	81	80	94	52	51	86	83	81	92	84	89	78	74	80	70



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