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Cross-Coupling

A Comparative Ancillary Ligand Survey in Palladium-Catalyzed C–O Cross-Coupling of Primary and Secondary Aliphatic Alcohols

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Abstract: The utility of RockPhos, Ad-BippyPhos, JosiPhos (CyPF-*t*Bu), and Mor-DalPhos in palladium-catalyzed C–O cross-coupling reactions involving aliphatic alcohols and (hetero)aryl halides under analogous conditions was examined, both at room temperature and at elevated temperature (90 °C). In general, the RockPhos-based catalyst system proved superior, especially at room temperature, but catalysts based on the other ligands examined also proved effective across a range of C–O cross-couplings, in some cases providing better catalytic performance than RockPhos. New reactivity was established in terms of the scope of room temperature reactions. Proof-of-principle examples of such cross-couplings involving aryl mesylates were also demonstrated.

Introduction

Aromatic ethers of primary and secondary aliphatic alcohols are common structural motifs in many naturally occurring and synthetic compounds with interesting biological activity;[1] a selection of top-selling pharmaceuticals featuring examples of this core structure are presented in Figure 1.

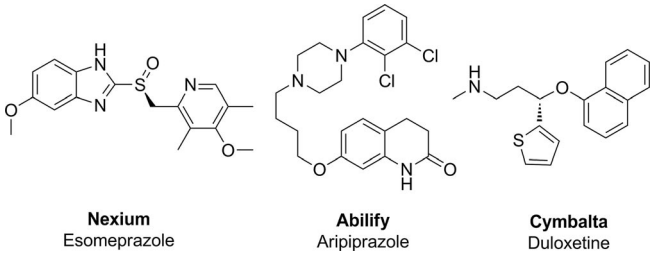

Figure 1. Selected pharmaceuticals featuring the aryl alkyl ether structural motif.

Aromatic ethers have traditionally been prepared by nucleophilic aromatic substitution or Ullmann coupling,[2] but the required forcing reaction conditions and for highly reactive aryl electrophiles in such protocols provide motivation for the development of alternative synthetic methods that could run under milder conditions and with a broader substrate scope. In this regard, late-transition-metal-catalyzed C–O cross-coupling reactions involving aliphatic alcohols and (hetero)aryl halides have emerged as effective and complementary methods for the synthesis of aryl alkyl ethers.[3] Palladium-based catalysts have proved to be particularly useful in such applications, although a judiciously chosen ancillary ligand set is required when using primary and secondary aliphatic alcohols in order to favor product-forming C–O bond reductive elimination over unwanted β-hydride elimination (Figure 2).

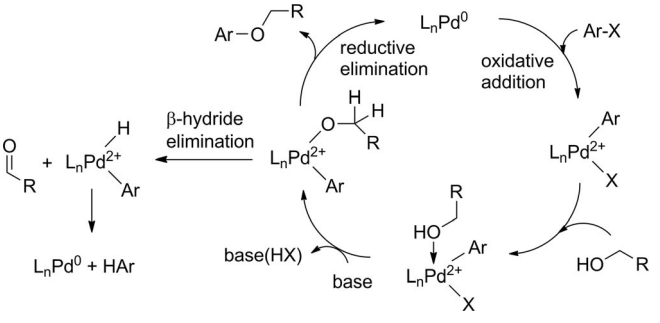

Figure 2. Generic catalytic cycle for the palladium-catalyzed cross-coupling of aliphatic alcohols and (hetero)aryl halides, showing unwanted β-hydride elimination.

The first reports of palladium-catalyzed C–O cross-coupling reactions using primary and secondary aliphatic alcohols as reaction partners were disclosed by Buchwald and coworkers in 2001 and 2005, respectively.[4] Since this time, the sterically demanding phosphines RockPhos (**L1**),[5] Ad-BippyPhos (**L2**),[6] and JosiPhos CyPF-*t*Bu (**L3**)[7] have emerged as some of the most effective ancillary ligands reported to date for such challenging palladium-catalyzed C–O cross-couplings (Figure 3).

Although collectively the performance of palladium catalysts featuring **L1**–**L3** in the C–O cross-coupling of primary and secondary aliphatic alcohols is impressive, each catalyst system shows some limitations. The reported catalyst system using **L1** is attractive in its ability to promote transformations involving both primary and secondary aliphatic alcohols in combination

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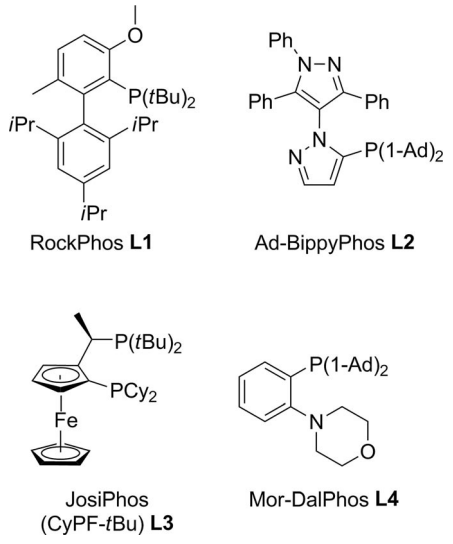

Figure 3. Ancillary ligands evaluated in this study.

with electron-rich electrophiles. However, the need to carefully preform the catalyst, and the requirement for 4 Å molecular sieves and/or trialkylamine additives make such protocols more complex than those reported involving **L2** or **L3**.[5] Conversely, the reported transformations involving an **L2**-based catalyst are more restricted in scope, and feature only a limited number of primary aliphatic alcohols.[6] The **L3**-based catalyst system shows an impressive scope with respect to the alcohol reaction partner, but some limitations were encountered in terms of the scope of the electrophile, even in reactions involving rather simple substrates such as bromo- or chlorobenzene, as well as 3-bromo- or 3-chloropyridine.[7] One challenge that exists in attempting to directly compare the reactivity profiles of **L1**–**L3** is that the catalytic reaction conditions differ significantly between these published reports,[5–7] most notably in terms of the palladium loadings (1–10 mol-%) and the reaction temperatures (80–140 °C).

In an effort to gain further insights into the relative catalytic abilities of **L1**–**L3** in palladium-catalyzed C–O cross-coupling reactions involving aliphatic alcohols and (hetero)aryl halides, we initiated a two-part comparative reactivity survey. We studied reactions carried out at 90 °C using relatively low catalyst loadings, as well as complementary room-temperature reactions using higher catalyst loadings. The latter set of experiments are of particular significance, given the operational advantages of room-temperature reactions, especially when using lower-boiling aliphatic alcohols, and also given the potential selectivity benefits that might be derived from carrying out C–O cross-couplings at room temperature. Although several methods for palladium-catalyzed room-temperature cross-coupling reac-

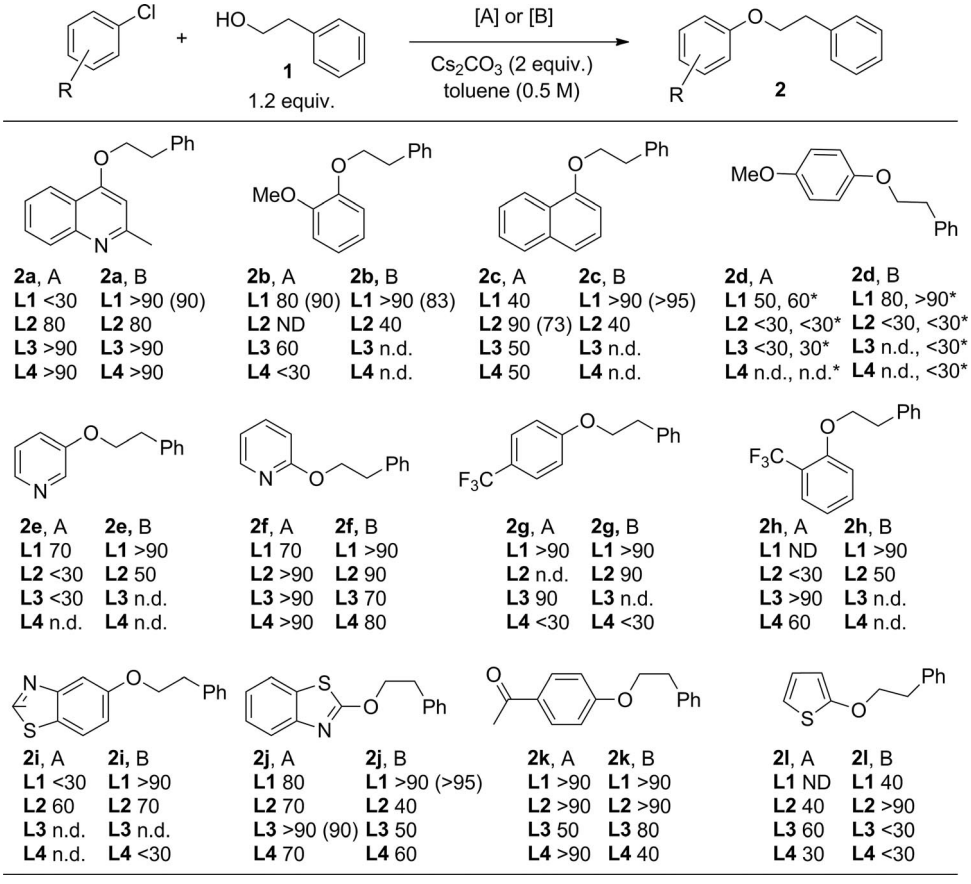

Figure 4. Cross-coupling of phenethyl alcohol (**1**) and (hetero)aryl chlorides. Estimated conversion to product **2** [%] after 16 h (unoptimized) on the basis of GC data, with selected isolated yields given in parentheses. Reaction conditions: [A] $[Pd(cinnamyl)Cl]_2$ (0.5 mol-%), ligand (1.5 mol-%), 90 °C. [B] $[Pd(cinnamyl)Cl]_2$ (3.5 mol-%), ligand (11.5 mol-%), 25 °C; n.d.: not detected. *Using the corresponding aryl bromide.

tions using relatively inexpensive and abundant (hetero)aryl chloride electrophiles have been developed,[8] to the best of our knowledge, examples of analogous C–O cross-couplings of aliphatic alcohols are limited to a single report by Cheung and Buchwald,[8n] in which an **L1**-containing palladium precatalyst was used in the arylation of methanol and ethanol (six examples).[9] As part of our reactivity survey of ancillary ligands, we opted to include Mor-DalPhos (**L4**).[8i] The application of **L4** in palladium-catalyzed C–O cross-coupling reactions has not been reported in the literature, but this ligand has proved to be particularly useful in related C–N cross-coupling chemistry.[8i,8k,10] In this paper, we report the results of this comparative reactivity survey of ancillary ligands.

Results and Discussion

We began our catalytic screening by examining the C–O cross-coupling of phenethyl alcohol (**1**) and with various (hetero)aryl chlorides, using a base and a solvent that had proved effective in previous studies involving **L1**–**L3** (Figure 4).[5–7] Our initial choice of 4-chloroquinaldine as the electrophilic reaction partner was made so as to allow a comparison with the extensive ligand screening conducted by Maligres et al.[7] In keeping with their results, **L1** performed poorly, whereas a high conversion to the target compound (i.e., **2a**) was achieved by using **L3**; under analogous conditions, we also observed that both **L2** and **L4** gave high conversion to **2a**. In moving to the previously unreported room temperature conditions outlined in Figure 4, each of **L1**–**L4** resulted in a high conversion to **2a**. The reason for the improved performance of **L1** in this test reaction at room temperature, relative to 90 °C, is unclear at present, but it is plausible that the use of milder reaction conditions discourages deleterious side reactions (e.g., β-hydride elimination; hydrodehalogenation) that may be more competitive at higher temperature. It is also worth mentioning that careful attention to the preformation of the catalyst in situ has been shown to be important when using **L1** in such C–O cross-couplings;[5,7,11] for operational simplicity, no special effort was made regarding precatalyst formation for the experiments described here.

Our continued exploration of the electrophile scope in combination with **1** revealed that, in contrast to **L2**–**L4**, the performance of **L1** at room temperature using higher catalyst loadings was invariably superior to that achieved by using lower catalyst loadings at 90 °C; our attempts to use lower catalyst loadings at room temperature with **L1** were unsuccessful. Although catalysts based on **L2**–**L4** each proved effective across a range of C–O cross-couplings involving **1** (Figure 4), the **L1**-based catalyst system in general proved superior, both in terms of enabling room-temperature transformations, and across each of the electrophiles examined when both sets of catalytic conditions are

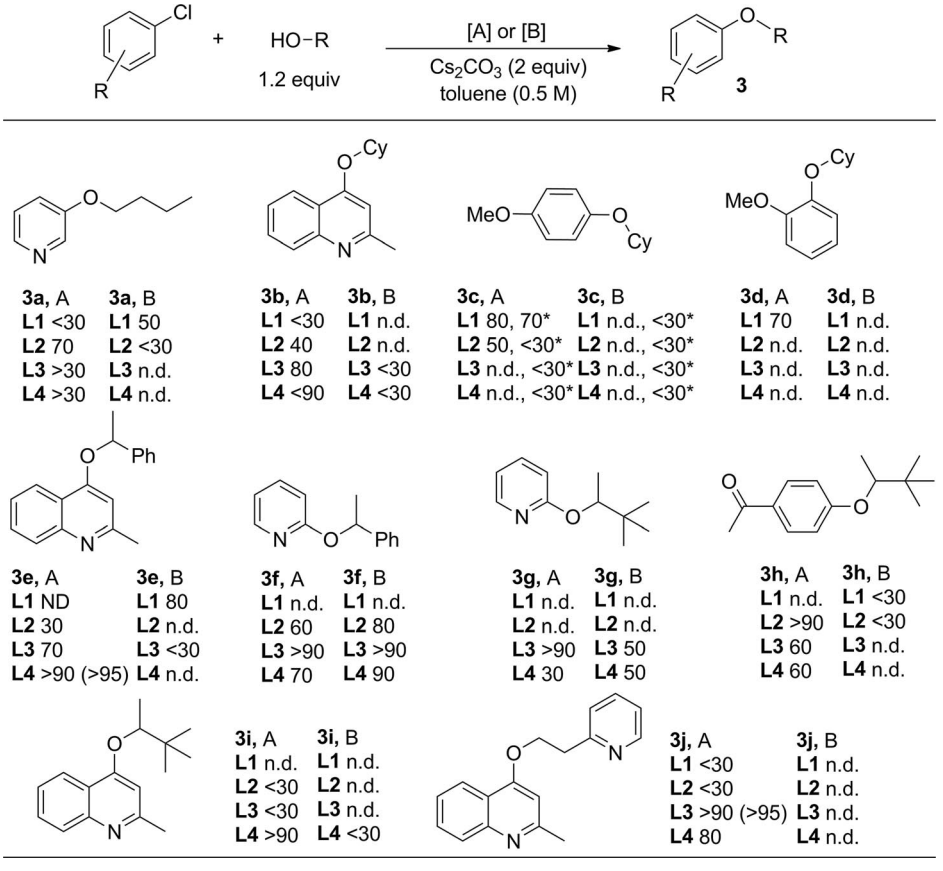

Figure 5. Cross-coupling of aliphatic alcohols and (hetero)aryl chlorides. Estimated conversion to product **3** [%] after 16 h (unoptimized) on the basis of GC data, with selected isolated yields given in parentheses. Reaction conditions: [A] $[Pd(cinnamyl)Cl]_2$ (0.5 mol-%), ligand (1.5 mol-%), 90 °C. [B] $[Pd(cinnamyl)Cl]_2$ (3.5 mol-%), ligand (11.5 mol-%), 25 °C; n.d.: not detected. *Using the corresponding aryl bromide.

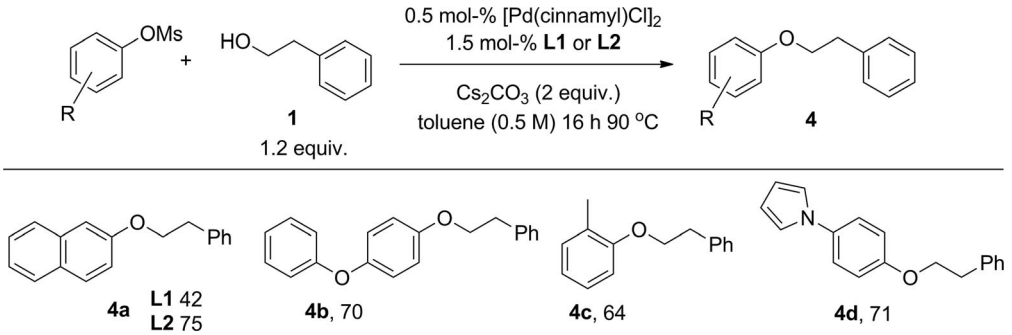

Figure 6. Cross-coupling of phenethyl alcohol (**1**) and selected aryl mesylates, with isolated yields of **4** [%] obtained using **L2** unless otherwise indicated.

considered. Indeed, only in the case of relatively activated substrates, for example leading to **2a**, **2f**, **2g**, and **2k**, did one or more of **L2**–**L4** prove competitive with **L1** at room temperature; the exception to this trend is found in the formation of **2l**, where **L2** proved optimal. A comparative reactivity survey involving the formation of **2d** revealed little difference in catalytic performance when using electron-rich aryl chlorides vs. bromides. Moreover, test reactions targeting product **2c**, but using NaO*t*Bu in place of Cs_2CO_3 resulted in complete consumption of the alcohol reagent, along with quantitative hydrodehalogenation of the aryl chloride, thus underscoring the importance of base selection with regard to achieving success in such C–O cross-couplings.

We next turned our attention to palladium-catalyzed C–O cross-couplings involving potentially more challenging linear and branched aliphatic alcohols (Figure 5). In such transformations, no single ligand dominated; the observed catalytic performance was substrate dependent. In most cases, poor conversion (≤50 %) to the target product was achieved at room temperature, with synthetically useful conversions limited to relatively activated substrates leading to **3e** and **3f**. Absent from Buchwald's[5,11] reports regarding the use of **L1** in palladium-catalyzed C–O cross-couplings are examples where both the alcohol and the electrophile feature nitrogen-based heterocyclic motifs. The challenge of such combinations when using **L1** is evident in transformations leading to **3j**, especially when compared to the successful formation of analogous phenethyl-based product **2a** at room temperature when using **L1** (Figure 4). The ability of both P,P ligand **L3** and P,N ligand **L4** to provide high conversion to **3j** may be attributable to the strongly chelating nature of such ligands, compared to **L1** and **L2**.

Notwithstanding the utility of the Williamson ether synthesis in the preparation of unsymmetrical ethers from alcohols and alkyl (pseudo)halides, we sought to test the feasibility of using aryl mesylates in palladium-catalyzed C–O cross-couplings of aliphatic alcohols. In addition to being complementary to existing protocols, the use of aryl mesylates as coupling partners is attractive as they are derived from abundant phenols,[12] and the cross-coupling by-product formed upon hydrolysis (i.e., methanesulfonic acid) is naturally occurring, and can undergo biodegradation under conventional waste-water processing.[13] In a brief catalytic screening involving **L1** and **L2** in the palladium-catalyzed cross-coupling of **1** with selected aryl mesylates, **L2** proved superior; selected transformations are presented in Figure 6.

Conclusions

The competitive reactivity survey disclosed in this paper allows a direct comparison to be made between commercially available ligands **L1**–**L4** in palladium-catalyzed C–O cross-coupling reactions involving aliphatic alcohols and (hetero)aryl halides under analogous conditions. New reactivity was established in terms of the scope of room temperature reactions; proof-of-principle examples of such cross-couplings involving aryl mesylates were also demonstrated. In general, the **L1**-based catalyst system proved superior, both in terms of enabling room-temperature transformations, and in terms of the (hetero)aryl chlorides accommodated. But catalysts based on **L2**–**L4** also proved effective across a range of C–O cross-couplings, in some cases providing superior catalytic performance relative to **L1**. Future work in our laboratory will be directed toward the development of new ancillary ligands in the quest to identify increasingly effective catalysts for such transformations.

Experimental Section

General Remarks: All reactions were set up in a glovebox under a nitrogen atmosphere, and products were isolated under standard benchtop conditions. Toluene used in the glovebox was purified by sparging with nitrogen followed by passing through a double column purification system equipped with one alumina-packed column and one copper-Q5-packed column. Solvents used in the glovebox were stored over 4 Å molecular sieves. Aryl mesylates were prepared using literature procedures.[14] All other reagents, solvents, and materials were used as received from commercial suppliers. Products were purified by column chromatography over Brockmann I activated neutral alumina. All ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded with a Bruker AV-500 spectrometer at 300 K. In some cases, fewer carbon resonances than anticipated were observed, despite prolonged acquisition times. Chemical shifts are expressed in parts per million (ppm), and the residual $CHCl_3$ solvent peak (^1H δ = 7.26 ppm, ^{13}C δ = 77.0 ppm) was used as an internal reference. Coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are described as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained with ion-trap instruments using electrospray ionization in positive-ion mode. GC data were obtained using an instrument equipped with a SGE BP-5, 30 m, 0.25 mm internal diameter column.

General Screening Procedure for Reactions Conducted at Room Temperature (GPA): [Pd(cinnamyl)Cl]$_2$ (5.8 mg, 3.75 mol-%), ligand (11.25 mol-%), Cs_2CO_3 (196 mg, 0.6 mmol), and toluene (0.6 mL) were added to a glass vial equipped with a magnetic stirrer bar. The vial was sealed with a screw cap fitted with a PTFE/silicone septum and removed from the glovebox. Aryl halide (0.30 mmol) and alcohol (0.36 mmol) were then added by microsyringe. The vial was then placed on a stirrer plate, and the solution was stirred magnetically for 16 h. After 16 h, an aliquot was filtered through a small plug of silica, which was then washed with dichloromethane, and the eluent was subjected to GC analysis.

General Screening Procedure for Reactions Conducted at 90 °C (GPB): [Pd(cinnamyl)Cl]$_2$ (1.6 mg, 0.5 mol-%), ligand (1.5 mol-%), Cs_2CO_3 (391 mg, 1.2 mmol), and toluene (1.2 mL) were added to a glass vial equipped with a magnetic stirrer bar. The vial was sealed with a screw cap fitted with a PTFE/silicone septum and removed from the glovebox. Aryl halide (0.60 mmol) and alcohol (0.72 mmol) were then added by microsyringe. The vial was then placed on a temperature-controlled aluminum plate set to 90 °C, and the solution was stirred magnetically for 16 h. After 16 h, the vial was removed from the heating block, and was cooled to room temperature. An aliquot was filtered through a small plug of silica, which was then washed with dichloromethane, and the eluent was subjected to GC analysis.

General Procedure for the Formation and Isolation of Products at Room Temperature (GPC): [Pd(cinnamyl)Cl]$_2$ (11.6 mg, 3.75 mol-%), ligand (11.25 mol-%), Cs_2CO_3 (196 mg, 1.2 mmol), and toluene (1.2 mL) were added to a glass vial equipped with a magnetic stirrer bar. The vial was sealed with a screw cap fitted with a PTFE/silicone septum, and was then removed from the glovebox. Aryl halide (0.60 mmol) and alcohol (0.72 mmol) were then added by microsyringe. The vial was then placed on a stirrer plate, and the solution was stirred magnetically for 16 h. After 16 h, the reaction mixture was filtered through an alumina and Celite filter with dichloromethane. The eluent containing the crude product was concentrated by rotary evaporation, and the residue was purified by column chromatography.

General Procedure for the Formation and Isolation of Products at 90 °C (GPD): [Pd(cinnamyl)Cl]$_2$ (1.6 mg, 0.5 mol-%), ligand (1.5 mol-%), Cs_2CO_3 (391 mg, 1.2 mmol), and toluene (1.2 mL) were added to a glass vial equipped with a magnetic stirrer bar. The vial was sealed with a screw cap fitted with a PTFE/silicone septum, and was then removed from the glovebox. Aryl halide (0.60 mmol) and alcohol (0.72 mmol) were then added by microsyringe. The vial was then placed on a temperature-controlled aluminum plate set to 90 °C, and the solution was stirred magnetically for 16 h. After 16 h, the vial was removed from the heating block, and was cooled to room temperature. The reaction mixture was then filtered through an alumina and Celite filter with dichloromethane. The eluent containing the crude product was concentrated by rotary evaporation, and the residue was purified by column chromatography.

General Procedure for the Formation and Isolation of Products Derived from Aryl Mesylates (GPE): [Pd(cinnamyl)Cl]$_2$ (2.6 mg, 0.5 mol-%), ligand (1.5 mol-%), Cs_2CO_3 (652 mg, 2.0 mmol), and toluene (2.0 mL) were added to a glass vial equipped with a magnetic stirrer bar. The vial was sealed with a screw cap fitted with a PTFE/silicone septum, and was then removed from the glovebox. Aryl halide (1.0 mmol) and alcohol (1.2 mmol) were then added by microsyringe. The vial was then placed on a temperature-controlled aluminum plate set to 90 °C, and the solution was stirred magnetically for 16 h. After 16 h, the vial was removed from the heating block, and was cooled to room temperature. The reaction mixture was then filtered through an alumina and Celite filter with dichloromethane. The eluent containing the crude product was concentrated by rotary evaporation, and the residue was purified by column chromatography.

Characterization of Isolated Materials

2-Methyl-4-phenethoxyquinoline (2a): Following GPC [**L1** (31.6 mg), aryl halide (121 μL), alcohol (86.2 μL)], compound **2a** was isolated (90 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.5 Hz, 1 H), 7.97 (d, J = 8.5 Hz, 1 H), 7.68 (t, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.5 Hz, 1 H), 7.38–7.39 (m, 4 H), 7.28–7.33 (m, 1 H), 6.63 (s, 1 H), 4.41 (t, J = 7 Hz, 2 H), 3.29 (t, J = 7 Hz, 2 H), 2.70 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 161.6, 160.2, 149.0, 138.0, 129.9, 129.2, 128.8, 128.2, 126.9, 124.9, 121.8, 120.0, 101.3, 69.1, 35.7, 26.1 ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{18}NO$ [M + H]$^+$ 264.1344; found 264.1383.

1-Methoxy-2-phenethoxybenzene (2b): Following GPC [**L1** (31.6 mg), aryl halide (76.2 μL), alcohol (86.2 μL)], compound **2b** was isolated (83 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.40 (m, 4 H), 7.27–7.32 (m, 1 H), 6.94–7.00 (m, 4 H), 4.28 (t, J = 7.6 Hz, 2 H), 3.92 (s, 3 H), 3.28 (t, J = 7.6 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 150.0, 148.7, 138.5, 129.5, 128.9, 126.9, 121.6, 121.3, 113.9, 122.5, 70.3, 56.4, 36.2 ppm. HRMS (ESI$^+$): calcd. for $C_{15}H_{17}O_2$ [M + H]$^+$ 229.1184; found 229.1223.

Following GPD [**L1** (6.0 mg), aryl halide (76.2 μL), alcohol (86.2 μL)], compound **2b** was isolated (90 %) as a colorless oil.

1-Phenethoxynaphthalene (2c): Following GPC [**L1** (31.6 mg), aryl halide (81.7 μL), alcohol (86.2 μL)], compound **2c** was isolated (>95 %) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.48–7.54 (m, 2 H), 7.46 (d, J = 8.5 Hz, 1 H), 7.36–7.43 (m, 5 H), 7.27–7.31 (m, 1 H), 6.85 (d, J = 7.6 Hz, 1 H), 4.41 (t, J = 6.9 Hz, 2 H), 3.30 (t, J = 6.9 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 154.8, 138.7, 134.7, 129.3, 128.7, 127.6, 126.7, 126.5, 126.0, 125.9, 125.3, 122.3, 120.4, 104.9, 69.1, 36.2 ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{17}O$ [M + H]$^+$ 249.1235; found 249.1274.

Following GPD [**L2** (6 mg), aryl halide (81.7 μL), alcohol (86.2 μL)], compound **2c** was isolated (73 %) as a pale brown solid.

2-Phenethoxybenzo[*d*]thiazole (2j): Following GPC [**L1** (31.6 mg), aryl halide (78.1 μL), alcohol (86.2 μL)], compound **2j** was isolated (>95 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.1 Hz, 1 H), 7.67 (d, J = 7.9 Hz, 1 H), 7.32–7.42 (m, 5 H), 7.24–7.31 (m, 2 H), 4.82 (t, J = 7.1 Hz, 2 H), 3.22 (t, J = 7.0 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 172.9, 149.6, 137.6, 132.1, 129.2, 128.7, 126.9, 126.1, 123.6, 121.4, 121.0, 72.3, 35.4 ppm. HRMS (ESI$^+$): calcd. for $C_{15}H_{14}NOS$ [M + H]$^+$ 256.0751; found 256.0791.

Following GPD [**L3** (47.2 mg), aryl halide (78.1 μL), alcohol (86.2 μL)], compound **2j** was isolated (90 %) as a white solid.

2-Methyl-4-(1-phenethoxy)quinoline (3e): Following GPD [**L4** (4.2 mg), aryl halide (121 μL), alcohol (86.9 μL)], compound **3e** was isolated (>95 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, J = 8.3 Hz, 1 H), 7.97 (d, J = 8.5 Hz, 1 H), 7.70 (t, J = 7.1 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.37–7.41 (m, 2 H), 7.43–7.47 (m, 2 H), 7.30–7.35 (m, 1 H), 6.51 (s, 1 H), 5.61 (q, J = 6.5 Hz, 1 H), 2.60 (s, 3 H), 1.82 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 160.6, 160.0, 149.1, 142.1, 129.8, 129.0, 128.3, 128.1, 125.5, 124.9, 122.0, 120.4, 103.1, 76.5, 26.1, 24.4 ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{18}NO$ [M + H]$^+$ 264.1344; found 264.1383.

2-Methyl-4-[2-(pyridin-2-yl)ethoxy]quinoline (3j): Following GPD [**L3** (4.7 mg), aryl halide (121 μL), alcohol (81.1 μL)], compound **3j**

was isolated (>95 %) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60–8.62 (m, 1 H), 8.09 (d, J = 8.3 Hz, 1 H), 7.96 (d, J = 8.5 Hz, 1 H), 7.64–7.70 (m, 2 H), 7.43 (t, J = 7.4 Hz, 1 H), 7.36 (d, J = 7.8 Hz, 1 H), 7.18–7.22 (m, 1 H), 6.51 (s, 1 H), 4.63 (t, J = 7.4 Hz, 2 H), 3.45 (t, J = 7.4 Hz, 2 H), 2.71 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 161.6, 160.3, 158.2, 149.7, 148.9, 136.7, 129.9, 128.1, 124.9, 123.9, 122.0, 121.8, 120.0, 101.4, 67.6, 37.9, 26.0 ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{17}N_2O$ [M]$^+$ 265.1344; found 265.1335.

2-Phenethoxynaphthalene (4a): Following GPE [**L2** (10.0 mg), aryl mesylate (222.3 mg), alcohol (144 μL)], compound **4a** was isolated (75 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74–7.83 (m, 3 H), 7.48 (t, J = 7.3 Hz, 1 H), 7.36–7.42 (m, 5 H), 7.29–7.34 (m, 1 H), 7.18–7.23 (m, 2 H), 4.36 (t, J = 7.1 Hz, 2 H), 3.23 (t, J = 7.1 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 157.0, 138.4, 134.7, 129.5, 129.2, 128.7, 127.8, 126.9, 126.7, 126.5, 123.8, 119.1, 106.9, 68.9, 36.0 ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{17}O$ [M + H]$^+$ 249.1235; found 249.1274.

Following GPE [**L1** (31.6 mg), aryl mesylate (133.4 mg), alcohol (86.2 μL)], compound **4a** was isolated (42 %) as a white solid.

1-Phenethoxy-4-phenoxybenzene (4b): Following GPE [**L2** (10.0 mg), aryl mesylate (264.3 mg), alcohol (144 μL)], compound **4b** was isolated (70 %) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.46 (m, 7 H), 7.14 (apparent t, J = 7.4 Hz, 1 H), 7.04–7.09 (m, 4 H), 6.96–7.00 (m, 2 H), 4.26 (t, J = 7.1 Hz, 2 H), 3.21 (t, J = 7.1 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 158.6, 155.2, 150.3, 138.3, 129.7, 129.1, 128.6, 126.6, 122.5, 120.9, 117.7, 115.7, 69.3, 36.0 ppm. HRMS (ESI$^+$): calcd. for $C_{20}H_{19}O_2$ [M + H]$^+$ 291.1340; found 291.1380.

1-Methyl-2-phenethoxybenezne (4c): Following GPE [**L2** (10.0 mg), aryl mesylate (200.3 mg), alcohol (144 μL)], compound **4c** was isolated (64 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.45 (m, 4 H), 7.33–7.37 (m, 1 H), 7.22–7.26 (m, 2 H), 6.96 (t, J = 7.4 Hz, 1 H), 6.89–6.92 (m, 1 H), 4.28 (t, J = 6.9 Hz, 2 H), 3.22 (t, J = 6.9 Hz, 2 H), 2.33 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 157.0, 138.7, 130.7, 129.2, 128.4, 126.9, 126.8, 126.5, 120.4, 111.0, 68.7, 36.1, 16.3 ppm. HRMS (ESI$^+$): calcd. for $C_{15}H_{16}NaO$ [M + Na]$^+$ 235.1099; found 235.1093.

1-(4-Phenethoxyphenyl)-1*H*-pyrrole (4d): Following GPE [**L2** (10.0 mg), aryl mesylate (237.3 mg), alcohol (144 μL)], compound **4d** was isolated (71 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.39 (m, 7 H), 7.02–7.04 (m, 2 H), 6.96–7.00 (m, 2 H), 6.35–6.37 (m, 2 H), 4.24 (t, J = 7.1 Hz, 2 H), 3.16 (t, J = 7.1 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 156.9, 138.1, 134.6, 129.0, 128.5, 126.5, 122.1, 119.7, 115.3, 109.8, 69.1, 35.8 ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{18}NO$ [M + H]$^+$ 364.1344; found 264.1383.

Supporting information (see footnote on first page of this article): Copies of the ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compounds.

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