# Improved Process for the Palladium-Catalyzed C–O Cross-Coupling of Secondary Alcohols

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**ABSTRACT:** An improved protocol for the Pd-catalyzed C–O cross-coupling of secondary alcohols is described. The use of biaryl phosphine L2 as the ligand was key to achieving efficient cross-coupling of (hetero)aryl chlorides with only a 20% molar excess of the alcohol. Additionally, we observed an unusual reactivity difference between an electron-rich aryl bromide and the analogous aryl chloride, and deuterium-labeling suggested that currently unidentified pathways for reduction play an important role in explaining this disparity.

T he synthesis of alkyl aryl ethers has seen significant advances in the past decade.<sup>1</sup> Traditional approaches, such as the Williamson ether synthesis,<sup>2</sup> the Mitsunobu reaction,<sup>3</sup> and nucleophilic aromatic substitution,<sup>4</sup> often require specific and limited classes of substrates to achieve efficient C–O bond formation. Transition-metal-catalyzed C– O cross-coupling reactions, including Pd,<sup>5</sup> Cu,<sup>6</sup> and Ni<sup>7</sup> catalysis, have also been improving to operate on an increasingly broad scope of (hetero)aryl halides and aliphatic alcohols. Alternative metal-free approaches involving sulfonate esters<sup>8a</sup> or diaryliodonium salts<sup>8b–d</sup> also show great promise.

The Pd-catalyzed O-arylation of aliphatic alcohols has been widely explored by our group and by others.<sup>5</sup> As depicted in Scheme 1, the slow rate of reductive elimination from intermediate  $[L_n Pd^{II}(Ar)(alkoxide)]$  (IV) is generally believed to account for the diminished efficiency of C-O bond formation, compared to the analogous C-N cross-coupling processes.<sup>9</sup> As a result, competitive  $\beta$ -hydride elimination can lead to the overall reduction of the aryl halide and the formation of undesired carbonyl side products. Between the two classes of aliphatic alcohols bearing  $\beta$ -hydrogens, secondary alcohols are typically considered more challenging coupling partners. Previously, the coupling reaction of primary alcohols has been shown to proceed with higher yields and less reduction of aryl halide, compared to that of the corresponding secondary alcohols under the same reaction conditions. 5c,g,i,n The most recent report from our group on the coupling reaction of secondary alcohols introduced the use of a bulky biaryl phosphine ligand RockPhos (L1, Figure 1) to facilitate C-O bond formation.<sup>51</sup> This method required the use of 2 equiv of alcohol substrate at somewhat elevated temperature





(90  $^{\circ}$ C) to provide moderate yields with a restricted scope of alcohol substrates (Scheme 2A).

Two recent reports from the groups of Ma<sup>6a</sup> and Stradiotto<sup>7a</sup> demonstrated great potential for utilizing Cuand Ni-catalyzed methods, respectively, to prepare secondary

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Figure 1. Ligands and precatalysts employed in Pd-, Cu-, and Nicatalyzed C-O cross-coupling of secondary alcohols.

# Scheme 2. Literature Precedents of Transition-Metal-Catalyzed C-O Cross-Coupling of Secondary Alcohols

A) Pd-catalyzed C–O cross-coupling of secondary alcohols (Buchwald, 2011)

(Het)ArX X = CI, Br	+	HO R R' 2 equiv	[(allyIPdCl) <sub>2</sub> ], L1 Cs <sub>2</sub> CO <sub>3</sub> toluene, 90 °C, 21 h	(Het)Ar ∕O						
B) Cu-catalyzed C–O cross-coupling of secondary alcohols (Ma, 2019)										
(Het)ArX X = CI, Br, I	+	HO R R' 2–3 equiv	[Cu]/L (K or) NaOt-Bu 1,4-dioxane or DMF 4 Å MS, 24 h 100 °C (X = Cl) 80 °C (X = Br) 60-80 °C (X = I)	(Het)Ar∽ <mark>O                                    </mark>						
C) Ni-catalyzed C–O cross-coupling of secondary alcohols (Stradiotto, 2018)										
(Het)ArX X = CI, Br, O	+ Ts	HO R' 1.5–3 equiv	C1 or C2 NaO <i>t</i> -Bu or Cs <sub>2</sub> CO <sub>3</sub> toluene, 110 °C, 18 h	(Het)Ar <sup>∕O</sup>						

alkyl aryl ethers. The use of two oxalic diamide ligands and sodium *tert*-butoxide enabled Cu-catalyzed C-O cross-coupling of secondary alcohols with aryl chlorides, bromides,

and iodides with excellent efficiency.<sup>6a</sup> Compared to that of more reactive aryl bromides and iodides, the coupling reaction of aryl chlorides still required higher catalyst loading (10 mol % Cu) as well as elevated temperature (100 °C). Ni-catalyzed C-O cross-coupling of secondary alcohols with aryl halides was achieved with the use of (Cy)PAd-DalPhos-based precatalysts,<sup>7a</sup> proving the feasibility of such transformation in the absence of photoredox catalysts.<sup>7b</sup> Although the Nicatalyzed coupling of aryl chlorides with secondary alcohols was first achieved in this report, the method was limited to activated substrates and also required elevated temperature (110 °C). Additionally, all three metal-catalyzed methods necessitated the use of 100% or more molar excess of alcohols (i.e., more than 2 equiv of alcohol, with two exceptions<sup>7a</sup>) to ensure successful C-O bond formation. Therefore, the development of a method that operates under mild conditions, preferably at room temperature, and that utilizes a smaller excess of alcohol (i.e., less than 2 equiv of alcohol) for the coupling reactions of (hetero)aryl chlorides and secondary alcohols, remains a desirable goal.

We recently disclosed a catalyst system that employs one of two ligands for Pd-catalyzed C-O cross-coupling reactions of (hetero)aryl halides with primary alcohols.<sup>5b</sup> In particular, the use of a new (now commercially available, CAS no. 2197989-24-3) hybrid biaryl phosphine ligand L2 (Figure 1) allowed the effective coupling of challenging electrophiles, including unactivated aryl chlorides (e.g., electron-rich (hetero)aryl chlorides). Herein, we report the Pd-catalyzed C-O crosscoupling of secondary alcohols, facilitated by the use of L2, with a diverse range of (hetero)aryl chlorides under improved reaction conditions: more than half of the reactions proceeded at room temperature, while only requiring a 20% molar excess of alcohols. Additionally, we present examples of the Oarylation of secondary alcohols with aryl bromides and the observation of an unusual difference in reactivity between an electron-rich aryl bromide and the corresponding aryl chloride.<sup>5b,i,10</sup>

Following the conditions previously reported for the crosscoupling of primary alcohols,<sup>5b</sup> we employed palladacycle **P2** 



			+ s-BuOH 22.0 mol 9 NaOrBu (1) x equiv solvent (1) rt, 18 1: X = Cl 2: X = Br	$ \begin{array}{c} \frac{1}{6} \frac{P2}{2} \\ \frac{2}{2} \frac{equiv}{1}}{h} \\ h \\ 3 \\ \end{array} \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$		
entry	Х	solvent	equiv of sec-BuOH	conversion <sup>b</sup> (%)	yield of $3^{b}$ (%)	yield of $4^{b}$ (%)
1	Cl	dioxane	3	100	94	8
2	Cl	dioxane	2	78	62	14
3	Cl	dioxane	1.2	50	22	18
4	Cl	THF	3	100	98	3
5	Cl	THF	2	100	97	4
6	Cl	THF	1.2	100	90	9
7	Br	THF	3	100	67	31
8	Br	THF	2	100	72	27
9	Br	THF	1.2	100	63	33

<sup>*a*</sup>Reaction conditions: ArX (0.5 mmol), *s*-BuOH (*x* mmol), NaOt-Bu (0.6 mmol), P2 (2.0 mol %), solvent (0.5 mL, 1.0 M), rt, 18 h. dioxane = 1,4dioxane. THF = tetrahydrofuran. <sup>*b*</sup>Determined by GC analysis using an internal standard. All yields presented are not normalized. In certain cases, the sum of yields being over 100% is a result of the error in the analytical method used. (Figure 1) as the precatalyst and 1,4-dioxane as the solvent. Electron-rich aryl chloride 1, containing a *para*-morpholino substituent, and *sec*-butanol (*s*-BuOH) were chosen as model coupling partners. Lowering the number of equivalents of *s*-BuOH from 3 to 1.2 resulted in a decline in the efficiency of the reaction: the conversion of the starting aryl chloride 1 decreased by 50%, and the ratio of the reduction side product 4 to the coupling product 3 increased substantially (Table 1, entries 1–3). However, when the solvent was changed to THF, lowering the number of equivalents of *s*-BuOH to 1.2 had a negligible effect on the efficiency of the reaction (Table 1, entries 4–6). Therefore, THF was selected as an appropriate solvent for further exploration of the substrate scope.

Although it is widely accepted that aryl bromides exhibit higher reactivity in cross-coupling reactions than aryl chlorides, <sup>5b,i,10</sup> we observed an opposite trend between electron-rich aryl chloride 1 and aryl bromide 2. First, under the same set of reaction conditions (Table 1, entries 6 and 9), while the reaction of 1 provided a 90% yield of desired aryl ether 3, along with 9% reduction product 4, that of 2 only provided a 63% yield of 3, with a notable increase in the amount of 4 (33%) that was formed. Although this difference could be partially ameliorated by adjusting the quantity of *s*-BuOH to 2 equiv, a further increase of the amount of alcohol utilized did not lead to an additional improvement in the yield of 3 (Table 1, entries 7 and 8).

A variety of (hetero)aryl chlorides and secondary alcohols were surveyed to examine the generality of this method (Scheme 3). The C-O cross-coupling reactions took place under mild conditions, using only a 20% molar excess of alcohols. Many traditionally challenging substrates, including unactivated aryl chlorides (3, 5, 7) and five-membered heterocycles (9, 10, 11), readily underwent C-O bond formation at room temperature. Various heterocycles, such as a quinoline (7), a pyridazine (8), a pyrazole (8), a thiadiazole (9), a benzisothiazole (10), a benzimidazole (11), a pyrazine (12), a quinazoline (13), a pyrazolopyrimidine (14), and a pyridine (15), were tolerated as structural components in the electrophiles. Functional groups such as an unprotected tertiary hydroxyl group (6), a carbamate group (7), and a lactone (14) were also compatible with the reaction conditions. While sterically accessible alcohols proved to be good coupling partners at room temperature, secondary alcohols with moderate steric encumbrance at either the  $\alpha$ carbon (12, 13) or the  $\beta$ -carbon (14, 15) required moderate heating (40 °C) to react with activated heteroaryl chlorides and afford corresponding heteroaryl ethers in  $\geq$ 80% yields.

The coupling reactions between electron-rich aryl chlorides and more sterically demanding nucleophiles, however, remained challenging, as demonstrated in the reactions of aryl chloride 1 (Table 2). As the steric congestion around the  $\alpha$ -carbon of the alcohol increased (Table 2, entries 1 and 2). both the conversion and the yield of desired product decreased by approximately 40%, while a small increase in reduction product 4 was observed. We hypothesize that increasing the steric bulk around the  $\alpha$ -carbon could negatively impact the binding tendency of alcohol nucleophiles to the oxidativeaddition complex II (Scheme 1), thus accounting for the less efficient C-O bond formation. Although heteroaryl ethers 9, 12, and 13 were prepared and isolated in >80% yields, benzylic alcohols proved to be more difficult coupling partners for electron-rich aryl chloride 1 (Table 2, entries 3 and 4). The steric environment of the benzylic carbon also played an





<sup>a</sup>Reaction conditions: ArCl (1.0 mmol), alcohol (1.2 mmol), NaOt-Bu (1.2 mmol), P2 (2.0–4.0 mol %), THF (1.0 mL, 1.0 M), rt–40  $^{\circ}$ C, 18 h. Isolated yields represent the average result of two runs. <sup>b</sup>THF (7.0 mL) and higher temperature were used due to the poor solubility of the combination of aryl chloride, alcohol, and NaOt-Bu under standard reaction conditions.

important role in the coupling process, as a change from a methyl to an ethyl group led to a 60% decrease in conversion, and only a trace amount of desired product was detected (Table 2, entries 3 and 4).

As we continued to examine the scope of C–O crosscoupling reactions of aryl bromides, we noticed that the difference in reaction efficiency between the cross-coupling of aryl bromides and aryl chlorides was greatest for highly electron-rich substrates, such as 2 vs 1 (to prepare 3 in Schemes 4 and 3, respectively). In contrast, for weakly electron-rich, electron-neutral, and electron-deficient aryl bromides (to prepare 5, 16, and 17, respectively), the crosscoupling reactions proceeded with comparable levels of efficiency (>80% yield, Scheme 4).

To gain an understanding of the difference in reactivity between aryl halides 1 and 2, we performed experiments to examine the cause of increased reduction in the cross-coupling reaction of aryl bromide 2. In order to ascertain whether reduction product 4 resulted solely from  $\beta$ -hydride elimination, we prepared  $\alpha$ -deutero-alcohol 18-d (98%  $d_1$ , see the Supporting Information) and examined its reaction with aryl bromide 2. When 2 and protio-alcohol 18 were subjected to Table 2. Alcohol Evaluation for Pd-Catalyzed C–O Cross-Coupling of Electron-Rich Aryl Chloride  $1^a$ 



<sup>a</sup>Reaction conditions: ArCl (0.5 mmol), alcohol (0.6 mmol), NaOt-Bu (0.6 mmol), P2 (2.0 mol %), THF (0.5 mL, 1.0 M), rt, 18 h. <sup>b</sup>Determined by GC using an internal standard. <sup>c</sup>Determined by <sup>1</sup>H NMR using an internal standard.

# Scheme 4. Pd-Catalyzed C–O Cross-Coupling of Aryl Bromides with Secondary Alcohols<sup>a</sup>



<sup>*a*</sup>Reaction conditions: ArBr (1.0 mmol), alcohol (2.0 mmol), NaOt-Bu (1.2 mmol), P2 (2.0–2.5 mol %), THF (1.0 mL, 1.0 M), rt, 18 h. Isolated yields represent the average result of two runs. <sup>*b*</sup>1.5 equiv of alcohol. <sup>*c*</sup>THF (5.0 mL) and higher temperature were used due to the poor solubility of the combination of aryl chloride, alcohol, and NaOt-Bu under standard reaction conditions.

the standard cross-coupling conditions, the desired product 19 and the reduction product 4 were observed in 47% and 54% yield, respectively, as determined by <sup>1</sup>H NMR analysis, while ketone 20 was formed in 31% yield, as judged by GC analysis (Scheme 5A). Ketone 20 is believed to result from  $\beta$ -hydride elimination from the intermediate  $[L_{,}Pd^{II}(Ar)(alkoxide)]$  (IV, Scheme 1) and should theoretically be formed in a 1:1 ratio with 4. Therefore, these results indicate that  $\beta$ -hydride elimination only accounts for a fraction of the formation of 4. When 2 and 18-d were subjected to the cross-coupling conditions, the desired product 19-d was formed in 65% yield and contained the same amount of deuterium (98%) as in 18-d (estimated by <sup>1</sup>H NMR analysis, Scheme 5B). Reduction product 4-d was formed in 36% yield (by <sup>1</sup>H NMR analysis) and was 80%  $d_1$  (by HRMS analysis). Ketone 20 was detected in 20% yield by GC analysis. Taken together, these experiments demonstrate that not all reduction side product

Scheme 5. Pd-Catalyzed C–O Cross-Coupling of Aryl Bromide 2 with (A) Cyclohexanol 18 and (B) Deutero-cyclohexanol 18-d<sup>a</sup>



<sup>a</sup>Reaction conditions: 2 (0.5 mmol), 18 or 18-d (0.6 mmol), NaOt-Bu (0.6 mmol), P2 (2.0 mol %), THF (0.5 mL, 1.0 M), rt, 18 h. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis using an internal standard. <sup>c</sup>Determined by GC analysis using an internal standard. <sup>d</sup>Determined by HRMS analysis.

arises from  $\beta$ -hydride (deuteride) elimination, and some stems from (as yet) unidentified processes. It is conceivable that the reduction byproduct may arise from protodemetalation of the oxidative addition complex  $[L_nPd^{II}(Ar)X]$  (II, Scheme 1). Similar findings have been reported by Hartwig, in his studies of the Pd-catalyzed amination of aryl bromides in the presence of bidentate ligands.<sup>11</sup>

In conclusion, we have developed a significantly improved procedure for the Pd-catalyzed C-O cross-coupling of secondary alcohols. This protocol employs a previously disclosed hybrid biaryl phosphine ligand L2, while using THF as the reaction solvent in lieu of 1,4-dioxane as in our previous report. A variety of (hetero)aryl ethers were obtained in higher yields from the corresponding (hetero)aryl halides under more user-friendly reaction conditions than in our earlier method. For instance, a 20% molar excess of alcohols sufficed to allow the cross-coupling reaction of (hetero)aryl chlorides at room temperature or 40 °C. An interesting but unconventional reactivity difference between an electron-rich aryl bromide 2 and chloride 1 was discovered. A deuteriumlabeling study suggested the possibility of as yet unidentified pathways responsible for the greater reduction of aryl bromide 2, indicating the need for further studies to establish a better detailed understanding of the mechanism of the Pd-catalyzed C-O coupling under these conditions.

# ASSOCIATED CONTENT

#### Supporting Information

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Experimental procedures and characterization data for new compounds (PDF)

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#### Notes

The authors declare the following competing financial interest(s): MIT has or has filed patents on ligands/ precatalysts that are described in the paper from which S.L.B. and former coworkers receive royalty payments.

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