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Palladium-Catalyzed C–O Cross-Coupling of Primary Alcohols

Hong ZhangID, Paula Ruiz-Castillo, and Stephen L. Buchwald*,ID
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Abstract

Two catalyst systems are described, which together provide mild and general conditions for the Pd-catalyzed C–O cross-coupling of primary alcohols. For activated substrates, such as electron-deficient aryl halides, the commercially available ligand L2 promotes efficient coupling for a variety of alcohol nucleophiles. In the case of unactivated electrophiles, such as electron-rich aryl halides, the new ligand L8 was developed to improve these challenging C–O bond-forming reactions.

Graphical abstract

Ethers are important structural components that are prevalent in many natural products,1 pharmaceuticals,2 and agrochemicals.3 In particular, alkyl aryl ethers are featured in approximately 20% of the top 200 pharmaceuticals in 2017 (Figure 1).2a

Significant efforts have been devoted to the development of mild and general syntheses of alkyl aryl ethers. Traditional approaches, such as the Williamson ether synthesis,4 the Mitsunobu reaction,5 and nucleophilic aromatic substitution,6 often provide limited functional group compatibilities and restricted substrate scope. In recent years, transition-metal-catalyzed7–9 or metal-free10 transformations have been invented to address these limitations. In particular, Pd-catalyzed O-arylation of aliphatic alcohols has become the subject of significant research activity.8 Unfortunately, the best results are often only realized with activated (i.e., electron-deficient) aryl halides, and in many instances, elevated

*Corresponding Author: sbuchwal@mit.edu.

ORCID
Hong Zhang: 0000-0002-4921-3395
Stephen L. Buchwald: 0000-0003-3875-4775

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temperatures are required. The most challenging Pd-catalyzed C–O cross-coupling reactions typically involve unactivated (i.e., electron-rich) aryl halides and alcohols bearing β-hydrogens, including primary alcohols. The generally accepted catalytic cycle for the Pd-catalyzed coupling reactions of aryl halides and alcohols is shown in Scheme 1. Reductive elimination from the intermediate [LₚPd(aryl)(alkoxide)] (IV) is slow in these reactions compared with the analogous process in Pd-catalyzed C–N cross-coupling reactions.11 Thus, competitive β-hydride elimination can occur, leading to the overall reduction of the aryl halide. Despite progress, new and more effective ligands for Pd-catalyzed C–O bond-forming processes are needed.

We previously reported RockPhos (L₁) (Figure 2) for the coupling of primary and secondary alcohols with aryl halides.8g It was proposed that the conformational rigidity of complex IV, afforded by the biaryl backbone, led to enhanced rates of reductive elimination, thus diminishing the amount of the undesired arene byproduct formed. The use of L₁ allowed the preparation of alkyl aryl ethers from an array of (hetero)aryl halides. However, electron-rich aryl chlorides remained challenging and more difficult than the corresponding aryl bromides for this catalyst system. This indicated that reductive elimination was not the only factor controlling the success of the transformation. More recently, our group reported the use of palladacycle precatalyst P₂ for the synthesis of short-chain alkyl aryl ethers.8d With the commercially available t-BuBrettPhos (L₂), a wide range of (hetero)aryl halides could be converted to the corresponding methyl ethers with 5 equiv of MeOH. Herein we report an expanded scope of compatible alcohol partners using L₂, without necessitating the use of a large excess of the alcohol, as well as the development of a new ligand L₈ to effect the more challenging coupling processes involving unactivated aryl chlorides.

Initially, electron-rich aryl halides containing a p-morpholino substituent (1, 2) and n-BuOH were chosen as model coupling partners. Under conditions similar to those employed in our previous report,8d we compared the reactivities of L₁ and L₂ in the form of their palladacycle precatalysts P₁ and P₂. For aryl bromide 1, P₂ provided a better ratio of product to reduction byproduct (Table 1, entries 1 and 2). However, neither ligand afforded more than 40% conversion in the case of aryl chloride 2 (Table 1, entries 3 and 4), consistent with previous observations of the lower reactivity of aryl chlorides compared with aryl bromides.

Although further ligand development was clearly necessary to address the reactions of the most challenging unactivated aryl chlorides, we noted that the commercially available ligand L₂ was already highly effective in coupling reactions of activated aryl halides with a more diverse range of alcohols than previously reported (Scheme 2). Moreover, these couplings took place under mild conditions (rt–60 °C) and in many instances necessitated the use of only 1 mol % catalyst. Pharmaceutically relevant alcohols, such as fluorinated benzyl alcohol (to prepare 5), 3-methoxy-1-propanol (to prepare 6), and 1-adamantanemethanol (to prepare 9), readily underwent C–O bond formation. Further, efficient cross-coupling was achieved for a variety of (hetero)aryl halides. Heterocycles, such as pyridines (5, 6, 8, 12), quinolines (11, 15), an isoquinoline (14), a thiophene (15), a pyrazine (10), a quinoxaline (12), a dibenzothiophene (13) and a pyrazolopyrimidine (8), were tolerated either in the aryl halide or in the alcohol substrate. Compounds 8 and 14, which were previously prepared by

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Maligres and co-workers at Merck, can be obtained in similar yields under significantly improved conditions: the catalyst loading was reduced from 10 to 1 mol %, and the temperature was reduced from 80 to 40 °C.

Next, since efficient coupling of certain (hetero)aryl chlorides could not be achieved with L2 (see Scheme 3 for examples), we considered potential ligand modifications to achieve improvement in these cases.

As previously mentioned, successful Pd-catalyzed C–O cross-coupling reactions require that C–O reductive elimination be fast relative to competing β-hydride elimination. Our group and others have demonstrated that increasing the steric bulk around the palladium center facilitates reductive elimination processes. Thus, we envisioned that congeners of L2 bearing larger –P(R)R′ units might exhibit improved performance. In particular, the bulky ligand L3 containing two adamantyl groups is effective in Pd-catalyzed C–N cross-coupling of five-membered heterocyclic halides as well as in Pd-catalyzed C–F cross-coupling, two cases where reductive elimination is known to be difficult. However, employing L3 (in the form of its precatalyst) in our reaction resulted in only 24% conversion and 22% yield of the desired product (Table 1, entry 5). Likewise, with the smaller ligand BrettPhos (L4), poor conversion (5%) was observed (Table 1, entry 6). These results, combined with our recent work on the arylation of hindered, α-trisubstituted primary amines using a hybrid CPhos-based ligand, suggested to us that finer tuning of the steric and electronic environment near the palladium center may be necessary. Indeed, testing different combinations of R and R′ units with varying sizes and electronic properties (Table 1, entries 7–10) revealed that the use of L8 significantly improved the cross-coupling of 2 with n-BuOH (Table 1, entry 10). Increasing the loading of P8 to 1.2 mol % led to full conversion of the aryl halide and a 97% yield of the product in 15 h when the reaction was carried out at room temperature (Table 1, entry 11). These results further demonstrated that a successful ligand must be able to facilitate reductive elimination, as indicated by the poor performance of the small ligand L4. Meanwhile, the observation that the medium-sized ligand L8 provided the most efficient C–O bond formation suggested that reductive elimination should not be the sole consideration for ligand design.

The substrate scope of Pd-catalyzed C–O cross-coupling between unactivated aryl halides and alcohols was explored using L8, with a comparison to L2 under identical conditions (Scheme 3). In general, the use of L8 provided an improvement in both conversions and yields. Notably, coupling reactions of electron-rich aryl chlorides and challenging heterocyclic substrates all proceeded to full conversion with L8 and exhibited up to a 76% increase in the yield (by 1H NMR analysis) compared with the same reactions using L2. A small rate enhancement was also observed for the electron-rich aryl bromide (3). In addition, the use of L8 proved to be superior to L2 for ortho-substituted hindered substrates. Lastly, fluorinated primary alcohols, which have decreased nucleophilicity, were also arylated more efficiently with L8.

In conclusion, a mild and general procedure for the Pd-catalyzed C–O cross-coupling of primary alcohols has been developed. The commercial ligand L2 was effective in the O-arylation of several pharmaceutically relevant and heterocycle-containing alcohols with...
activated (hetero)aryl halides. Additionally, a new hybrid biaryl phosphine ligand, L8, was effective for the more challenging coupling of unactivated (hetero)aryl halides, including many instances where employing L2 failed to deliver synthetically useful conversions and yields. We are undertaking mechanistic studies to rationalize more precisely the better performance of L8 and gain general insight into the mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Examples of pharmaceutical molecules containing alkyl aryl ethers.
Figure 2.
Biaryl phosphine ligands and their palladacycle precatalysts.
Scheme 1.
General Catalytic Cycle for Pd-Catalyzed C–O Cross-Coupling of Aryl Halides and Primary Alcohols
Scheme 2.
Pd-Catalyzed C–O Cross-Coupling of Activated Aryl Halides with Primary Alcohols\textsuperscript{a,b}\n\textsuperscript{a}Reaction conditions: ArX (1.0 mmol), \textit{n}-BuOH (2.0 mmol), NaOt-Bu (1.2 mmol), P2 (1.0–2.0 mol %), 1,4-dioxane (1.0 mL, 1.0 M), rt–60 °C, 6–15 h. \textsuperscript{b}The reported isolated yields are average results of two runs.
Scheme 3.
Pd-Catalyzed C–O Cross-Coupling of Unactivated Substrates$^{a,b,c,d}$

$^a$Reaction conditions: ArX (1.0 mmol), $n$-BuOH (2.0 mmol), NaOt-Bu (1.2 mmol), P$_2$/P$_8$ (1.0–2.5 mol %), 1,4-dioxane (1.0 mL, 1.0 M), rt–80 °C, 2.5–18 h. $^b$Y: yields determined by $^1$H NMR spectroscopy using an internal standard. $^c$C: conversions determined by GC using an internal standard. $^d$IY: average isolated yields from two runs.
Table 1

Ligand Evaluation for Pd-Catalyzed C–O Cross-Coupling of Electron-Rich Aryl Halides with n-BuOH

| entry | X   | ligand | conversion (%)<sup>b</sup> | yield of 3 (%)<sup>c</sup> | yield of 4 (%)<sup>c</sup> |
|-------|-----|--------|---------------------------|---------------------------|---------------------------|
| 1     | Br  | L1     | 100                       | 84                        | 13                        |
| 2     | Br  | L2     | 100                       | 96                        | 3                         |
| 3     | Cl  | L1     | 36                        | 29                        | 7                         |
| 4     | Cl  | L2     | 33                        | 25                        | 3                         |
| 5     | Cl  | L3     | 24                        | 22                        | 3                         |
| 6     | Cl  | L4     | 5                         | –                         | 4                         |
| 7     | Cl  | L5     | 20                        | –                         | 9                         |
| 8     | Cl  | L6     | 27                        | 19                        | 7                         |
| 9     | Cl  | L7     | 56                        | 38                        | 12                        |
| 10    | Cl  | L8     | 88                        | 80                        | 3                         |
| 11<sup>d</sup> | Cl | L8     | 100                       | 97                        | –                         |

<sup>a</sup>Reaction conditions: ArX (0.5 mmol), n-BuOH (1.0 mmol), NaOt-Bu (0.6 mmol), P1–P8 (1.0 mol %), 1,4-dioxane (0.5 mL, 1.0 M), rt, 15 h.

<sup>b</sup>Determined by GC using an internal standard.

<sup>c</sup>Determined by <sup>1</sup>H NMR spectroscopy using an internal standard.

<sup>d</sup>P8 (1.2 mol %).