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A Single Phosphine Ligand Allows for the Palladium-Catalyzed Intermolecular C–O Bond Formation with Secondary and Primary Alcohols**

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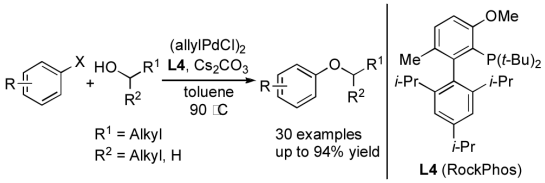
Abstract



An efficient, general palladium catalyst for C–O bond-forming reactions of secondary and primary alcohols with a range of aryl halides has been developed. Use of a catalyst based on a single bulky biarylphosphine ligand **L4** (RockPhos, soon to be commercially available) has expanded this chemistry to allow the transformation of a variety of heteroaryl halides, and for the first time, allows for the coupling of electron-rich aryl halides with secondary alcohols. Additionally, this new catalyst system provides the ability to effect these reactions with a diverse set of substrate combinations, while employing a single ligand. Thus the need to survey mutiple ligands, as was previously the case, is obviated.

Keywords

palladium; C–O cross-coupling; aryl alkyl ether; biarylphosphine ligand

Aryl alkyl ethers are present in many naturally occurring and medicinally-relevant compounds.[1] Copper[2]- and palladium-catalyzed C–O bond-forming reactions have become effective strategies for their preparation. Although reasonably efficient Pd catalysts for the coupling reactions of phenols[3] and tertiary alcohols,[4] which lack β-hydrogens, have been developed, much less progress in the realization of a practical and general system for the analogous coupling of primary and, especially, secondary alcohols[5] has, been realized. This is attributed to the competing β-hydride elimination pathway from the $L_nPd^{II}(Ar)(alkoxide)$ intermediates leading to significant amounts of arene formation.

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Our first report on Pd-catalyzed intermolecular cross-coupling reactions of primary alcohols with unactivated aryl bromides and chlorides[6a] necessitated the presence of an *ortho*-substituent or an electron-withdrawing substituent on the aryl halide, which increase the rate of reductive elimination, to achieve satisfactory results. In 2005, we disclosed an efficient protocol for cross-coupling of primary and secondary alcohols with aryl halides that utilized a collection of new (at the time) ligands.[6b] The ligands employed were carefully chosen to match the steric properties of the substrate combination. Additionally, the analogous reaction of electron-rich aryl halides with secondary alcohols remained a challenge due to the extensive formation of reduced arene.

Further, very few examples of Pd-catalyzed cross-coupling reactions of primary and secondary alcohols with heteroaryl halides have been reported to date.[7] Most recently, Beller disclosed that a single catalyst based on a modified version of Singer's Bippyphos ligand, **L2**,[8] was able to couple primary alcohols with a few types of heteroaryl halides. Examples carried out with this new system were restricted to reactions of primary alcohols with electron-neutral, - deficient, or *ortho*-substituted aryl halides, i.e., substrates that contain steric and electronic features that are known to facilitate reductive elimination.[6a] No examples with more challenging electron-rich aryl halides (e.g., *p*- or *o*-halo anisole) were described. Importantly, no examples of the successful coupling reactions of secondary alcohols were reported.

Herein, we report a catalyst based on a new ligand that provides a single general system for the coupling of both primary and secondary alcohols and is applicable to the reactions of formerly inaccessible substrates, such as a wider range of heteroaryl and electron-rich aryl halides.

In light of the aforementioned limitations for the Pd-catalyzed coupling reactions of secondary and primary alcohols with aryl halides, we felt that the development of a more general catalyst system for the preparation of (hetero)aryl alkyl ethers was highly desirable. On the basis of our recent observations that a catalyst based on the sterically demanding di-*tert*-butyl biarylphosphine ligand, **L3** (*t*BuBrettPhos), was able to promote the difficult reductive elimination to form the Ar-F,[9a] Ar-Br,[9b] and Ar-O[9c] bonds, we postulated that for reactions of secondary alcohols this catalyst may accelerate reductive elimination relative to the rate of β-hydride elimination. Use of a catalyst based on **L3** for the coupling of 2-butanol and 4-chloroanisole led to only a 20% yield of desired product (**2a**) and 63% of the reduced arene byproduct (**2a'**) (Table 1, entry 2).

Previous studies from our group have shown that the substituent in the 3-position of our biarylphosphine ligands helps fix the Pd(II) center over the triisopropylphenyl ring, which in turn accelerates reductive elimination (Figure 2).[10] Further, we have disclosed, for both C–N and C–O cross-coupling reactions, that a ligand bearing a methoxy in the 3-position led to the most active catalyst systems.[9c,11] However, none of our previous studies have focused solely on the effect of the substituent in the 6-position of **L3**. We previously postulated that the 6-methyl in **L1** provided increased conformational rigidity in the ligated Pd(II) complexes, leading to accelerated rates of reductive elimination for cross-coupling reactions of phenols.[3d] Therefore, replacing the 6-methoxy in **L3** with a methyl group, as shown in **L4**, would provide a hybrid of **L1** and **L3**, which we hypothesized would accelerate the rate of reductive elimination and impede that of β-H elimination for reactions of secondary alcohols (Figure 2).

In support of this hypothesis, a catalyst based on **L4** was tested for the coupling of 2-butanol with 4-chloroanisole and gave 70% of the desired product (**2a**) and only 19% reduced arene (**2a'**) (Table 1, entry 3). This is the first example for the coupling of a secondary alcohol

with an electron-rich aryl halide. Moreover, this result reveals that the substituent in the 6-position of the ligand has a profound effect on the reactivity of the catalyst.[12]

In an attempt to further probe the effect of the substituents in the 3- and 6-positions of the ligand, catalysts based on **L5**–**L10** were examined for this reaction (Table 1, entries 4 - 9). When the 6- methyl group in **L4** was removed (**L6**), the activity of the derived catalyst dropped off substantially giving only 3% product (Table 1, entry 5). This result again demonstrates that subtle differences in ligand structure have a dramatic effect on these C–O cross-coupling reactions. Utilizing catalysts based on **L7**, **L8**, **L9**, and **L10**, which contain a 6-ethyl, 6-isopryl, 3-ethoxy, and 3-isopropoxy substituent, respectively, led to a slight reduction in the production of **2a** and a modest increase in that of **2a'** formed (Table 1, entries 6 - 9). This indicates that the 3-methoxy and 6-methyl in **L4** are optimal for promoting reductive elimination and suppressing β-H elimination.

We next explored the scope of the cross-coupling reactions of secondary alcohols with aryl halides (Table 2). Typically these reactions were carried out at 90 °C using 1 mol % $(allylPdCl)_2$. In a few cases, Bu_3N was chosen as the solvent due to its ability to suppress the formation of the reduction byproduct.[6b] A range of electron-rich aryl halides were found to undergo reactions with cyclic and acyclic secondary alcohols to afford aryl alkyl ethers in moderate to good yields (**2a-2d, 2f**, **2g**); these yields are the highest reported to date for this difficult process. For a slightly electron-deficient substrate, 3-chloroanisole, only 0.5 mol % $(allylPdCl)_2$ was required to give **2e** in 86% yield. In contrast a 63% yield was obtained with 2 mol % $Pd(OAc)_2$ and 2.4 mol % **L12**, which was previously the most efficient catalyst system reported for this transformation.[6b]

Furthermore, switching to toluene from Bu_3N as solvent did not affect the efficiency of the coupling with basic nitrogen-containing heteroaryl halides as substrates, allowing simplified isolation of the products (**2g**, **2i**-**2m**). 6-Chloroquinoline, however, was found to be an exception to this trend. In toluene the reaction of 6-chloroquinoline and cyclopentanol resulted in the formation of a significant amount of reduced arene byproduct (see **2h**). In this case switching to Et_3N as solvent reduced the amount of quinoline formation and resulted in a 62% yield of the desired product. For the coupling of halo-pyridines and -pyrimidines we found it was necessary to premix the $(allylPdCl)_2$, **L4**, Cs_2CO_3, and 2-butanol in toluene at 90 °C for 3 minutes, followed by addition of the aryl halide (presumably due to the competitive binding of the substrate's nitrogen to the Pd center). In this way, 3-chloropyridine and 5- bromopyrimidine were coupled with 2-BuOH in 71% and 76% yields, respectively. Moreover, 5-chlorobenzoisoxazole (see **2m**), and 5-chlorobenzothiazole (see **2l**) proved to be proficient substrates in these reactions, giving the desired products in 61% and 63%, respectively. Thus, this suggests that the pyridine's (and related substrates) *N*-atom interferes with catalyst generation, more than with the catalyst itself.

We next decided to explore the application of **L4** for the cross-coupling of primary alcohols (Table 3). Excellent yields were obtained for the combination of primary alcohols with electron-rich, -neutral, and -deficient aryl halides using 0.5 mol % $(allylPdCl)_2$ and 1.5 mol % **L4**. The high efficiency displayed with **L4** as the supporting ligand allowed the reactions to be carried out in toluene, rather than in Bu_3N as solvent as in our previous method.[6b] For unactivated substrates, the coupling of aryl chlorides with primary alcohols was generally less efficient than that of aryl bromides and resulted in incomplete conversion of the starting material. For instance, the reaction of *n*-BuOH with 4-bromoanisole (see **3a**) proceeded within 21 hours using only 1 mol % of Pd. However, the analogous reaction with 4-chloroanisole using 2 mol % of Pd resulted in only ~85% conversion in the same time. Interestingly, the less nucleophilic fluorinated primary alcohol was a more efficient coupling partner than *n*-BuOH.[13] Thus, the reaction of trifluoroethanol with 4-chlorodiphenyl ether

afforded an 83% yield of the desired product (**3e**).[14] Further, the coupling of *N*-Boc-D-prolinol gave the desired product **3g** with no erosion of enantiopurity (86% yield, 98.5% ee). The catalyst combination of $Pd(OAc)_2$ and the less bulky ligand **L3** (^{t}BuBrettPhos) was optimal for the reaction of aryl bromides bearing *ortho*-alkyl substituents to give **3h** and **3i** in comparable yields.[6b]

In contrast to a catalyst based on **L2**,[8] whose application was limited to halo-pyridines and -quinolines, a variety of aryl alkyl ethers derived from five- and six-membered heteroaryl halides could be accessed under our new conditions (**3j**-**3o**). For example, 3- bromopyridine, 5-bromopyrimidine, and 4-bromoisoquinoline (see **3k**, **3m**, and **3o**) were all coupled with *n*-BuOH in good to excellent yields. The conversion of 4-bromoisoquinoline to **3o** proved more difficult, but could be efficiently accomplished by using 3 equivalents of *n*-BuOH and the premixing protocol described above for **3k** and **3l**.

In order to highlight the generality and efficiency of a catalyst based on **L4** we directly compared it to several of the previous reported systems. For the reaction of 4-bromoquinoline with a secondary alcohol our new catalyst system gave an 88% isolated yield, whereas a catalyst based on **L12** (previously the best reported system for reactions of secondary alcohols)[6b] gave no desired product (Scheme 1). Further, for the reaction of a primary alcohol with an electron-rich aryl halide a catalyst based on **L4** gave an 84% GC yield; for the same reaction a catalyst based on the recently reported **L2**[8] afforded no desired product and a catalyst based on **L1** gave a 73% GC yield (Table 4, **4a**). Switching to reactions of primary alcohols with heteroaryl bromides further displayed the superiority of a catalyst based on **L4** compared to previous catalyst systems (Table 4, **4b**-**4d**).

In summary, we have developed a general system for the palladium-catalyzed C–O cross-coupling reactions of aryl halides with secondary and primary alcohols. We found that the substituent in the 6-position of the biarylphosphine ligand scaffold has a profound effect on the catalytic activity of these systems and that a catalyst based on **L4** (RockPhos, soon to be commercially available), which contains a methyl group in the 6-position, displays the highest reactivity reported to date for these reactions. We postulate that the introduction of 6-methyl, rather than a 6-methoxy, in the ligand provides increased conformational rigidity in the LPd(Ar)(alkoxide) complexes and, therefore, accelerates the rate of reductive elimination while preventing β-hydride elimination. Thus, the utilization of catalyst based on **L4** allows for the synthesis of an array of aryl alkyl ethers with unprecedented substrate scope of both the aryl halide and alcohol coupling partners.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[14]. The conversion of 4-chlorodiphenyl ether, which coupled with n-BuOH using 2 mol% Pd in 24 h, was less than 80% (determined by GC) using variety of bases or at elevated temperature.

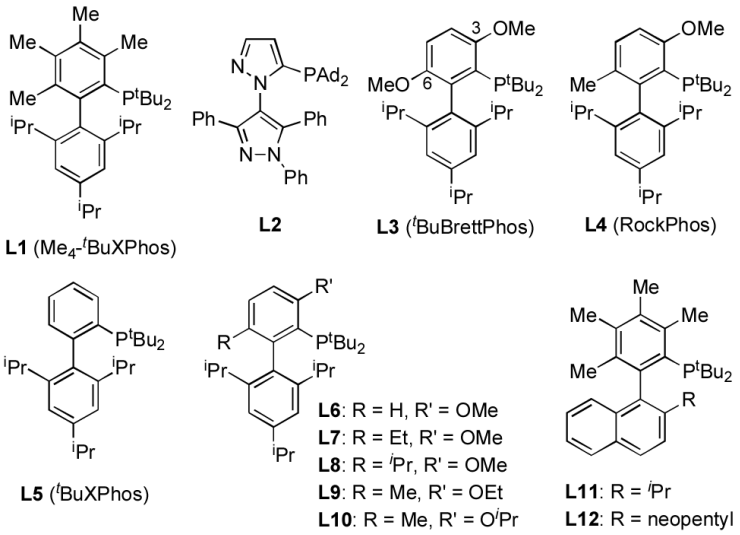


Figure 1.
Ligands for Pd-catalyzed C–O cross-coupling reactions.

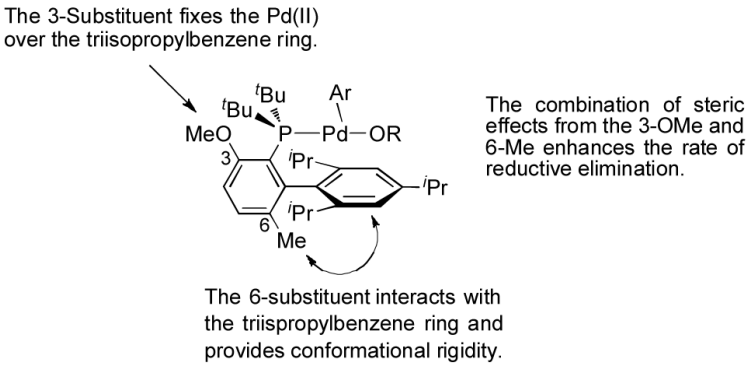
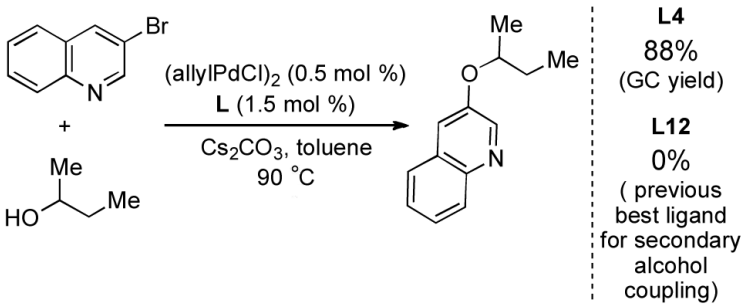


Figure 2.
Rationalizing the Substituent Effect on Reductive Elimination.

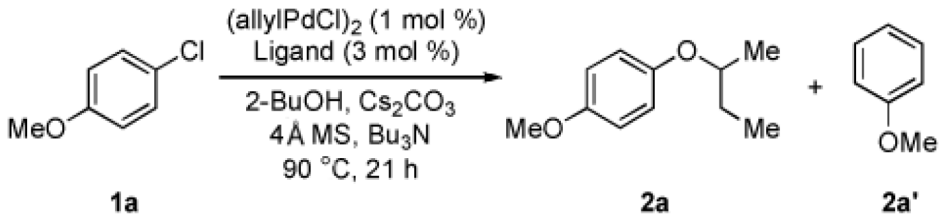


Scheme 1.

Comparison of Catalysts Based on **L4** and **L12** for the Coupling of a Secondary Alcohol.

Table 1

Ligand Evaluation[a]



1a **2a** **2a'**

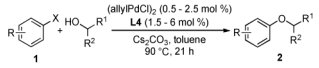
Entry	Ligand	Conv. of 1a [%][b]	Yield of 2a [%][b]	Yield of 2a' [%][b]
1	**L1**	100%	26%	54%
2	**L3**	100%	20	63%
3	**L4**	100%	70%	19%
4	**L5**	70%	trace	61%
5	**L6**	67%	3%	43%
6	**L7**	100%	66%	26%
7	**L8**	100%	64%	28%
8	**L9**	100%	57%	32%
9	**L10**	100%	54%	31%

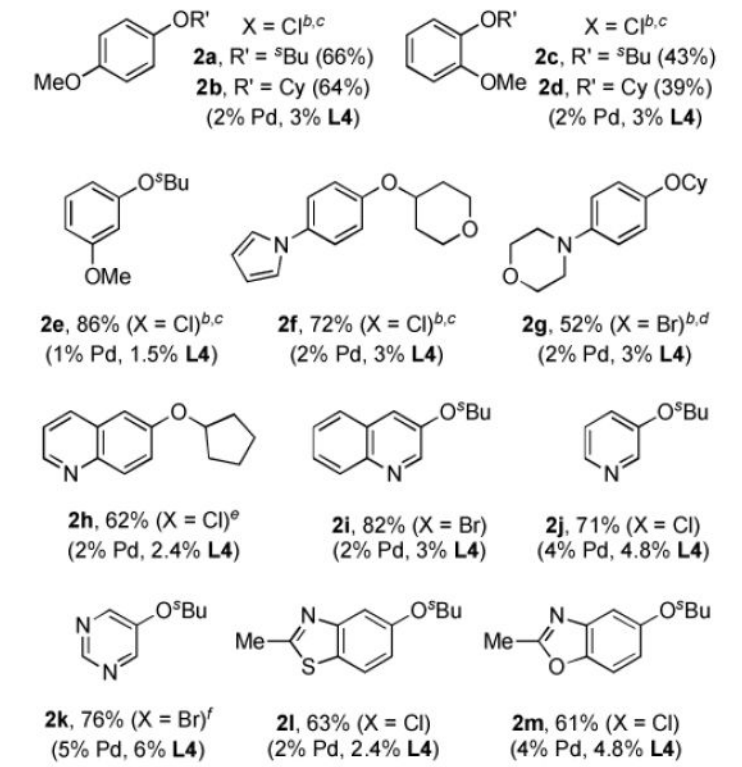
[a]Reaction conditions: 4-chloroanisole (1.0 mmol), 2-BuOH (2.0 mmol), (allylIpdcI)$_2$ (1 mol %), Ligand (3 mol %), Cs_2CO_3 (1.5 mmol), 4Å molecular sieves (200 mg), Bu_3N (1 ml), 90 °C, 21 h.

[b]Determined by GC.

Table 2

Coupling of Aryl Halides with Secondary Alcohols[a]





[a]Reaction conditions: ArX (1 mmol), alcohol (2 mmol), Cs_2CO_3 (1.5 mmol), (allylPdCl)2 (0.5 – 2.5 mol %), **L4** (1.5 – 6 mol %), toluene (1 mL), 90 °C, 21 h; isolated yields (average of two or more runs).

[b]200 mg of 4Å molecular sieves was added.

[c]in Bu_3N.

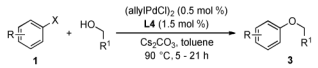
[d]cyclohexanol (1.5 mmol) was used.

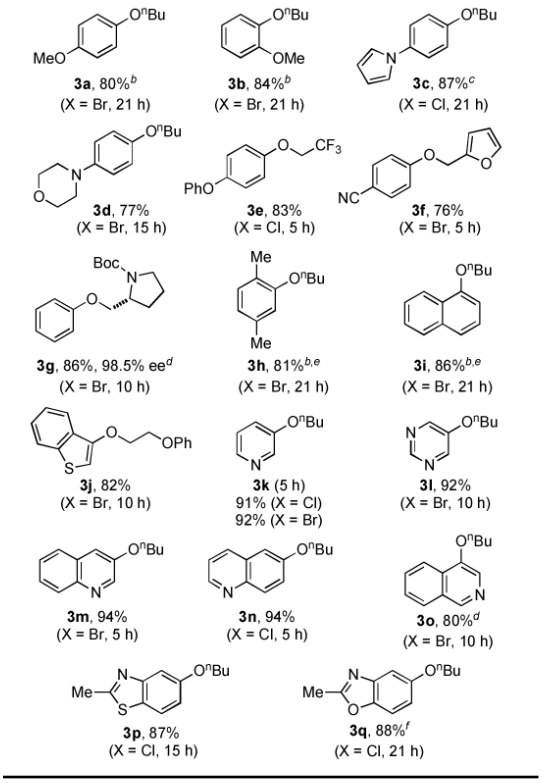
[e]In Et_3N.

[f]24 h.

Table 3

Coupling of Aryl Halides with Primary Alcohols[a]





[a]Reaction conditions: ArX (1 mmol), alcohol (2 mmol), Cs_2CO_3 (1.5 mmol), $(allylPdCl)_2$ (0.5 mol %), **L4** (1.5 mol %), toluene (1 mL), 90 °C, 5 - 21 h; isolated yields (average of two or more runs).

[b]200 mg of 4Å molecular sieves was added.

[c]$(allylPdCl)_2$ (2 mol %) and **L4** (4.8 mol %).

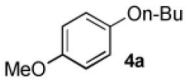
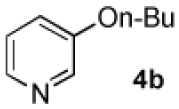
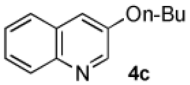
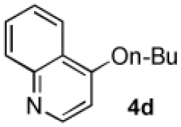
[d]alcohol (3 mmol).

[e]$Pd(OAc)_2$ (2 mol %) and **L3** (2.4 mol %).

[f]$(allylPdCl)_2$ (1 mol %) and **L4** (2.4 mol %).

Table 4

Comparison of Catalysts Based on L4 and the Previously Reported Ligands for the C–O Cross-Coupling Reactions of Primary Alcohols.[a]

	L4	L2 (previous best ligands for coupling primary alcohols)	L11	L1 (primary alcohols with electron-rich arylhalides)
 4a	84%	0%	NA[d]	73%
 4b	96%	0%[b]	26%	NA[e]
 4c	98%	57%[c]	12%	NA[e]
 4d	83%	29%	39%	NA[e]

[a] Corrected GC yields.

[b] No desired product was obtained under our conditions or the conditions reported by Beller.[8]

[c] Using the conditions reported by Beller. [8]

[d] A catalyst based on this ligand was reported to not be efficient for coupling electron-rich aryl halides.

[e] A catalyst based on this ligand was reported to only be efficient for reactions of electron-rich aryl halides.