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

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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 multiple 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 Copper2- 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 phenols3 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 alcohols5 has been realized. This is attributed to the competing β-hydride elimination pathway from the L₄Pd(III)(Ar)(alkoxide) intermediates leading to significant amounts of arene formation.

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.
Our first report on Pd-catalyzed intermolecular cross-coupling reactions of primary alcohols with unactivated aryl bromides and chlorides 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.

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. Most recently, Beller disclosed that a single catalyst based on a modified version of Singer’s Bippyphos ligand, L2, 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.

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 (BuBrettPhos), was able to promote the difficult reductive elimination to form the Ar-F, Ar-Br, and Ar-O 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). 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. 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. 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.\textsuperscript{12}

In an attempt to further probe the effect of the substituents in the 3- and 6-positions of the
ligand, catalysts based on \textit{L5–L10} were examined for this reaction (Table 1, entries 4 - 9).
When the 6- methyl group in \textit{L4} was removed (\textit{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 \textit{L7, L8, L9,} and \textit{L10,} which contain a
6-ethyl, 6-isopryl, 3-ethoxy, and 3-isopropoxy substituent, respectively, led to a slight
reduction in the production of \textit{2a} and a modest increase in that of \textit{2a'} formed (Table 1,
entries 6 - 9). This indicates that the 3-methoxy and 6-methyl in \textit{L4} are optimal for
promoting reductive elimination and suppressing \(\beta\)-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)\textsubscript{2}. In a few cases, Bu\textsubscript{3}N was chosen as the solvent due to its ability to suppress
the formation of the reduction byproduct.\textsuperscript{6b} A range of electron-rich aryl halides were found
unto undergo reactions with cyclic and acyclic secondary alcohols to afford aryl alkyl ethers in
moderate to good yields (\textit{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)\textsubscript{2} was required to give \textit{2e} in 86\% yield. In contrast a 63\% yield was obtained with
2 mol % Pd(OAc)\textsubscript{2} and 2.4 mol % \textit{L12}, which was previously the most efficient catalyst
system reported for this transformation.\textsuperscript{6b}

Furthermore, switching to toluene from Bu\textsubscript{3}N as solvent did not affect the efficiency of the coupling with basic nitrogen-containing heteroaryl halides as substrates, allowing simplified
isolation of the products (\textit{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 \textit{2h}). In this
case switching to Et\textsubscript{3}N 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)\textsubscript{2}, \textit{L4}, Cs\textsubscript{2}CO\textsubscript{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 \textit{2m}), and 5-chlorobenzothiazole (see
\textit{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 \textit{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)\textsubscript{2} and 1.5 mol
% \textit{L4}. The high efficiency displayed with \textit{L4} as the supporting ligand allowed the reactions
to be carried out in toluene, rather than in Bu\textsubscript{3}N as solvent as in our previous method.\textsuperscript{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 \textit{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.\textsuperscript{13} Thus, the reaction of trifluoroethanol with 4-chlorodiphenyl ether
afforded an 83% yield of the desired product (3e).\textsuperscript{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)\textsubscript{2} and the less bulky ligand L3 (BuBrettPhos) was optimal for the reaction of aryl bromides bearing ortho-alkyl substituents to give 3h and 3i in comparable yields.\textsuperscript{6b}

In contrast to a catalyst based on L2,\textsuperscript{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)\textsuperscript{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\textsuperscript{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.

**References**


*Angew Chem Int Ed Engl.* Author manuscript; available in PMC 2012 October 10.


Only three examples of Pd-catalyzed C–O coupling of alcohols with heteroaryl halides have been previously described (See footnote 6).


See supporting information for further studies on the effect of the substituent in the 6-position of the ligand.


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\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv. of 1a [%] (^{[b]})</th>
<th>Yield of 2a [%] (^{[b]})</th>
<th>Yield of 2a' [%] (^{[b]})</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>100%</td>
<td>26%</td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>L3</td>
<td>100%</td>
<td>20</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>L4</td>
<td>100%</td>
<td>70%</td>
<td>19%</td>
</tr>
<tr>
<td>4</td>
<td>L5</td>
<td>70%</td>
<td>trace</td>
<td>61%</td>
</tr>
<tr>
<td>5</td>
<td>L6</td>
<td>67%</td>
<td>3%</td>
<td>43%</td>
</tr>
<tr>
<td>6</td>
<td>L7</td>
<td>100%</td>
<td>66%</td>
<td>26%</td>
</tr>
<tr>
<td>7</td>
<td>L8</td>
<td>100%</td>
<td>64%</td>
<td>28%</td>
</tr>
<tr>
<td>8</td>
<td>L9</td>
<td>100%</td>
<td>57%</td>
<td>32%</td>
</tr>
<tr>
<td>9</td>
<td>L10</td>
<td>100%</td>
<td>54%</td>
<td>31%</td>
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</table>

\(^{[a]}\)Reaction conditions: 4-chloroanisole (1.0 mmol), 2-BuOH (2.0 mmol), (allylPdCl\(_2\)) (1 mol %), Ligand (3 mol %), Cs\(_2\)CO\(_3\) (1.5 mmol), 4Å molecular sieves (200 mg), Bu\(_3\)N (1 ml), 90 °C, 21 h.

\(^{[b]}\)Determined by GC.
Table 2

Coupling of Aryl Halides with Secondary Alcohols\textsuperscript{[a]}

\begin{center}
\begin{tabular}{c c c}
\hline
 & 2a, R\textsuperscript{'} = \textsuperscript{t}Bu (66\%) \quad & 2b, R\textsuperscript{'} = Cy (64\%) \\
\hline
 & 2e, 88\% (X = Cl)\textsuperscript{b,c} \quad & 2f, 72\% (X = Cl)\textsuperscript{b,c} \\
 & (1\% Pd, 1.5\% L\textsubscript{4}) \quad & (2\% Pd, 3\% L\textsubscript{4}) \\
\hline
 & 2g, 52\% (X = Br)\textsuperscript{b,d} \quad & 2h, 62\% (X = Cl)\textsuperscript{e} \\
 & (2\% Pd, 2.4\% L\textsubscript{4}) \quad & (2\% Pd, 3\% L\textsubscript{4}) \\
\hline
 & 2i, 82\% (X = Br) \quad & 2j, 71\% (X = Cl) \\
 & (2\% Pd, 3\% L\textsubscript{4}) \quad & (4\% Pd, 4.8\% L\textsubscript{4}) \\
\hline
 & 2k, 76\% (X = Br)\textsuperscript{e} \quad & 2l, 63\% (X = Cl) \\
 & (5\% Pd, 6\% L\textsubscript{4}) \quad & (2\% Pd, 2.4\% L\textsubscript{4}) \\
\hline
 & 2m, 61\% (X = Cl) \quad & \\
 & (4\% Pd, 4.8\% L\textsubscript{4}) & \\
\hline
\end{tabular}
\end{center}

\textsuperscript{[a]} Reaction conditions: ArX (1 mmol), alcohol (2 mmol), Cs\textsubscript{2}CO\textsubscript{3} (1.5 mmol), (allylPdCl\textsubscript{2})\textsubscript{2} (0.5 – 2.5 mol \%), L\textsubscript{4} (1.5 – 6 mol \%), toluene (1 mL), 90 °C, 21 h; isolated yields (average of two or more runs).

\textsuperscript{[b]} 200 mg of 4Å molecular sieves was added.

\textsuperscript{[c]} In Bu\textsubscript{3}N.

\textsuperscript{[d]} Cyclohexanol (1.5 mmol) was used.

\textsuperscript{[e]} In Et\textsubscript{3}N.

\textsuperscript{[f]} 24 h.
### Table 3

**Coupling of Aryl Halides with Primary Alcohols[^a]**

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Products</th>
<th>Isolated Yields (%)</th>
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</thead>
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<tr>
<td>ArX (1 mmol), alcohol (2 mmol), Cs₂CO₃ (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).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[^b]</td>
<td>200 mg of 4Å molecular sieves was added.</td>
<td></td>
</tr>
<tr>
<td>[^c]</td>
<td>(allylPdCl)₂ (2 mol %) and L₄ (4.8 mol %).</td>
<td></td>
</tr>
<tr>
<td>[^d]</td>
<td>alcohol (3 mmol).</td>
<td></td>
</tr>
<tr>
<td>[^e]</td>
<td>Pd(OAc)₂ (2 mol %) and L₃ (2.4 mol %).</td>
<td></td>
</tr>
<tr>
<td>[^f]</td>
<td>(allylPdCl)₂ (1 mol %) and L₄ (2.4 mol %).</td>
<td></td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: ArX (1 mmol), alcohol (2 mmol), Cs₂CO₃ (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).
### Table 4

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

<table>
<thead>
<tr>
<th></th>
<th>L4</th>
<th>L2</th>
<th>L11</th>
<th>L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>(previous best ligands for coupling primary alcohols)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[4a] MeO</td>
<td>84%</td>
<td>0%</td>
<td>NA(^{[d]})</td>
<td>73%</td>
</tr>
<tr>
<td>[4b] On-Bu</td>
<td>96%</td>
<td>0%(^{[b]})</td>
<td>26%</td>
<td>NA(^{[e]})</td>
</tr>
<tr>
<td>[4c] On-Bu</td>
<td>98%</td>
<td>57%(^{[c]})</td>
<td>12%</td>
<td>NA(^{[e]})</td>
</tr>
<tr>
<td>[4d] On-Bu</td>
<td>83%</td>
<td>29%</td>
<td>39%</td>
<td>NA(^{[e]})</td>
</tr>
</tbody>
</table>

\(^{[a]}\) 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.