ORGANIC LETTERS

2012
Vol. 14, No. 1
170–173

A New Biarylphosphine Ligand for the Pd-Catalyzed Synthesis of Diaryl Ethers under Mild Conditions

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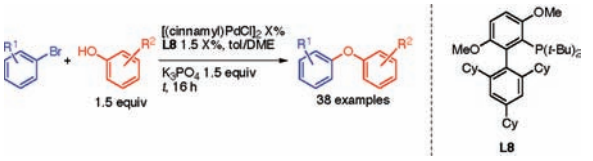
Received November 2, 2011

ABSTRACT



A new bulky biarylphosphine ligand (L8) has been developed that allows the Pd-catalyzed C−O cross-coupling of a wide range of aryl halides and phenols under milder conditions than previously possible. A direct correlation between the size of the ligand substituents in the 2′, 4′, and 6′ positions of the nonphosphine containing ring and the reactivity of the derived catalyst system was observed. Specifically, the rate of coupling increased with the size of these substituents.

Diaryl ethers are routinely found as structural elements in natural products and other biologically active compounds.[1] Traditionally, the synthesis of such ethers has been accomplished *via* Ullmann cross-couplings, which employ aryl halides and sodium or potassium aryloxides in the presence of a stoichiometric (or greater) amount of a copper species at elevated temperatures (125−220 °C).[2] Unfortunately, these relatively harsh conditions are not well tolerated for many synthetic applications. Consequently, several modifications to the original Ullmann conditions have been developed, allowing this reaction to be run with a catalytic amount of copper and under milder conditions.[3]

Alternatives to Cu-mediated or -catalyzed protocols are Pd-catalyzed C−O cross-coupling methods, several of which have been described employing a variety of phosphine-based ligands suitable for Pd.[4] In 2006 it was demonstrated that the use of sterically hindered, electron-rich biarylphosphine ligands, such as *t*-BuXPhos or Me$_4$*t*-BuXPhos (**L1** and **L2**, Table 1), afforded catalyst systems which could effectively promote the desired

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10.1021/ol202955h © 2011 American Chemical Society
Published on Web 12/19/2011

transformation under milder conditions and with a wider substrate scope than was previously possible.[5] However, the temperatures required were still > 100 °C, and most heteroaryl halides or heteroaromatic and electron-deficient phenols were not competent substrates with this system.

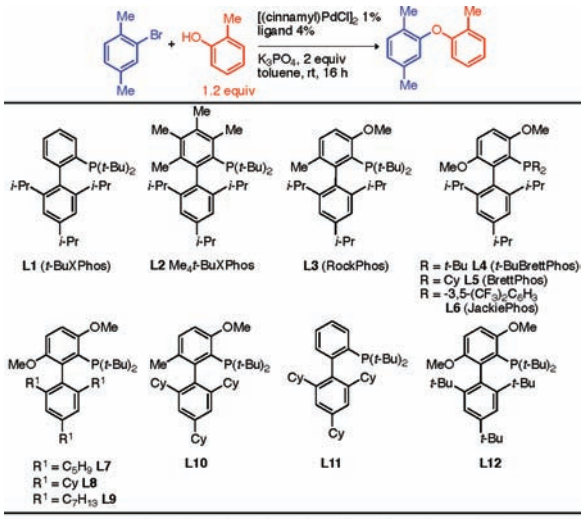
Prior to the current report, the only example of a Pd-catalyzed intermolecular C–O coupling at rt was that of the sodium salt of 4-methoxyphenol with 2-bromotoluene, a reaction that required 5 mol % Pd and required 70 h of reaction time using $Ph_5FcP(t\text{-}Bu)_2$ (QPhos) as the ligand.[4f] Thus, the development of a method that allows a general synthesis of diaryl ethers at rt and more generally under mild conditions, while increasing the scope of applicable substrates, would be of significant interest.

Previous studies regarding the mechanism of this transformation suggested reductive elimination as the probable rate-limiting step in the catalytic cycle.[6] Two commonly used strategies for facilitating reductive elimination from Pd(II) centers are (1) to decrease the electron-donating ability of the ligand[4d,6e] or (2) to increase the steric bulk of the ligand around the phosphorus center.[4e,6d,7] Based on these considerations, we prepared a new set of biarylphosphine ligands by modifying both the phosphine and the biaryl backbone substituents. Using these ligands, we sought to assess the effect of the substituents in each position on the activity of the derived catalyst in C–O bond-forming reactions.

The synthesis of the ligands **L7**–**L12** commenced with the preparation of the precursor to the bottom (non-phosphine-containing) ring. Thus, 1,3,5-tricyclopentyl-, 1,3,5-tricyclohexyl-, and 1,3,5-tricycloheptyl-benzene were prepared from benzene under conventional Friedel–Crafts conditions.[8] These trisubstituted benzenes were then converted to the corresponding bromides by treatment with Br_2. The overall yields from benzene were 68%, 50%, and 38%, respectively. These, along with commercially available 1-bromo-2,4,6-tri-*tert*-butylbenzene, were subsequently converted to **L7**–**L12** *via* procedures analogous to those previously reported.[9]

The effectiveness of these new ligands in facilitating the desired transformations was assessed as shown in Table 1. As our starting point, we examined the coupling of 2-bromo-*p*-xylene and *o*-cresol at rt.[10] Under these conditions, none of our previously reported ligands bearing *i*-Pr substituents on the nonphosphine containing ring gave more than a 15% yield of the diaryl ether product (Table 1, **L1**–**L6**).[9b,11]

Table 1. Study of the Relationship of Ligand Substituents to the Activity of the Derived Catalyst



ligand	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12
yield[a] (%)	10	10	9	15	--	--	22	54	19	32	8	--

[a] Yields were calculated by GC using dodecane as an internal standard.

By employing ligand **L7** under identical conditions, the desired product could be obtained in 22% yield. Furthermore, catalyst systems derived from **L8** and **L10** (R^1 = Cy) furnished the diaryl ether product in 54% and 32% yields, respectively. In contrast, the desired product was obtained in only 19% yield when using **L9** as the ligand, suggesting that while a larger substituent is beneficial at these positions, one that is too large may inhibit the reaction. This effect was corroborated by the observation that by using **L12** as the ligand, which bears *tert*-butyl groups at these positions, no product formation was observed (Table 1, **L12**). The substitution pattern on the phosphine-containing ring was also crucial to the reactivity of the catalyst system. For example, a catalyst derived from **L11**, which lacks substituents on the upper ring, provided the product in a yield similar to that observed when **L1** was employed. Thus, **L8** was chosen as the optimal ligand and was used in further studies.

We next examined the role of the solvent in this transformation. We discovered that by employing 1,2-dimethoxyethane (DME) as a more polar cosolvent in addition to toluene, we were able to obtain the desired

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(10) (a) We chose $[(cinnamyl)PdCl]_2$ as our Pd source, since it has been demonstrated to generate the active Pd(0) species at lower temperatures than other commonly used precursors. (b) We were unable to employ palladium precatalysts of the type we have recently reported as we are unable to prepare them using *tert*-butylphosphino biaryls other than *t*-BuXPhos.

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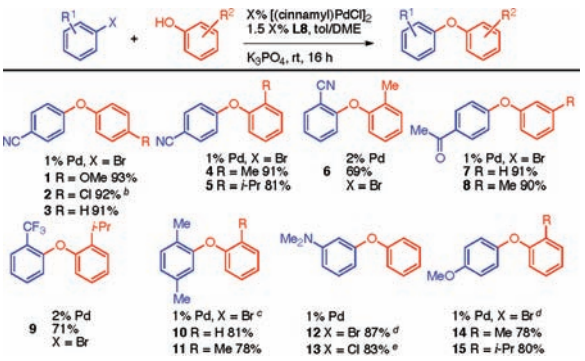
product in consistently higher yields as compared to reactions conducted in pure toluene.[12] The proper choice of base was also crucial for this transformation, and the use of 1 equiv of K_3PO_4 proved to be optimal.[12] Finally, we examined various Pd sources. Not surprisingly, a catalyst based on $Pd(OAc)_2$ was completely inactive at 40 °C, as reduction to Pd(0) likely does not occur under these conditions. We found $[(cinnamyl)PdCl]_2$ to be the most efficient Pd source, as it provided consistently superior yields to those obtained when Pd(0) sources such as Pd_2dba_3 were employed.[12,13]

Scheme 1. Pd-Catalyzed C−O Bond Formation with a Catalyst Based on **L8** under Mild Conditions[a]



[a] Reaction conditions: ArBr (1 mmol), phenol (1.5 mmol), K_3PO_4 (1.5 mmol), **L8**, $[(cinnamyl)PdCl]_2$, toluene/DME (0.6/0.3 mL), rt, 16 h; isolated yields, average of two runs. [b] **L8** (2.25 mol %), $[(cinnamyl)PdCl]_2$ (0.75 mol %). [c] 40 °C. [d] 80 °C. [e] 100 °C.

We next probed the substrate scope using the optimal **L8**/$[(cinnamyl)PdCl]_2$ combination. We began our investigation by examing the rt coupling of electron-deficient aryl bromides with electron-rich and -neutral phenols. Both substrate combinations were efficient in this transformation, providing the desired products in high yields (Scheme 1, **1**−**9**). These rt processes could be conducted with moderate loadings of Pd (1−2%). It should be noted that the product from the coupling of 4-chlorophenol and *p*-cyanobromobenzene was obtained in 92% yield; there was no evidence of products resulting from oxidative addition of the C−Cl bond (Scheme 1, **2**).

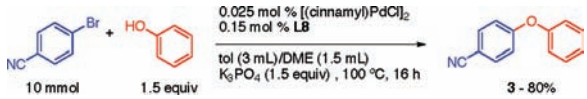
The increased activity of the catalyst based on **L8** enabled us to demonstrate the utility of this system on a large scale and with low catalyst loadings. By raising the temperature to 100 °C, the synthesis of **3** could be carried out on a 10 mmol scale employing 0.025 mol % of $[(cinnamyl)PdCl]_2$ and 0.075 mol % of **L8**. The isolated yield in this case was 80% (Scheme 2).

We next focused our investigation on reactions of electron-neutral and -rich aryl bromides. While these coupling processes were not efficient at rt, at 40 °C 2-Br-*p*-xylene could be coupled with phenol and *o*-cresol

(12) See the Supporting Information for detailed experimental information.

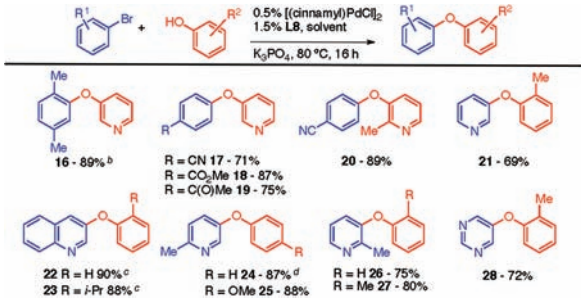
(13) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.

Scheme 2. Example of a Low Catalyst Loading Application



in high yields (Scheme 1, **10**−**11**). Both 3-Br- and 3-Cl-*N*,*N*-dimethylaniline could be coupled to afford the desired products in 87% and 83% yields, respectively (Scheme 1, **12**, **13**). Finally, an electron-rich aryl bromide, 4-Br-anisole, could be coupled at 80 °C with both *o*-cresol and 2-*i*-Pr-phenol in good yields (Scheme 1, **14**, **15**).

Scheme 3. Pd-Catalyzed C−O Bond Formation Employing Aryl or Heteroaryl Bromides and Aryl or Heteroaryl Phenols with a Catalyst Based on **L8**[a]



[a] Reaction conditions: aryl bromide (1 mmol), phenol (1.5 mmol), K_3PO_4 (1.5 mmol), **L8** (1.5 mol %), $[(cinnamyl)PdCl]_2$ (0.5 mol %), toluene/DME (0.6/0.3 mL), 80 °C, 16 h; isolated yields, average of two runs. [b] **L8** (4.5 mol %), $[(cinnamyl)PdCl]_2$ (1.5 mol %), 100 °C. [c] **L8** (2.25 mol %), $[(cinnamyl)PdCl]_2$ (0.75 mol %), 60 °C. [d] **L8** (3.0 mol %), $[(cinnamyl)PdCl]_2$ (1.0 mol %).

Our focus then turned to the synthesis of diaryl ether products derived from heteroaromatic substrates. Molecules containing 3-(aryloxy)pyridines have garnered significant interest within the medicinal chemistry community over the past 10 years.[14] However, methods for the synthesis of this molecular fragment are still limited to Cu-catalyzed processes, which require high temperatures and often result in low product yields under conditions with poor functional group tolerance.[15] To test the limits of our catalyst system based on **L8**, we thus chose to focus on 3-hydroxypyridine, since it is electron-deficient and possesses a heteroatom capable of coordinating to a Pd(II) center. Nonetheless, by using our catalyst system we found that it could be coupled effectively with an electron-neutral aryl bromide at 100 °C (Scheme 3, **16**) or with electron-deficient aryl bromides at even milder temperatures (Scheme 3, **17**−**20**).

(14) See the Supporting Information for a list of patents related to this class of compounds.

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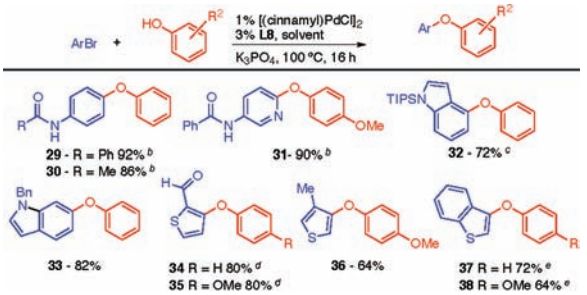
A wide range of bromopyridine electrophiles were also suitable substrates using lower catalytst loadings than previously reported. For example, using our previous best ligand the coupling of 3-bromopyridine with *o*-cresol required 8 mol % Pd at 115 °C, while the coupling of 3-bromoquinoline required 4 mol % Pd at the same temperature.[5] Employing the current protocol, 1 mol % Pd at 80 °C was sufficient to provide the product in 69% yield in the case of 3-bromopyridine (Scheme 3, **21**), while 1.5 mol % Pd and 60 °C were sufficient for the cross-coupling of 3-bromoquinoline (Scheme 3, **22**–**23**). All other 3-bromopyridine substrates were coupled with phenol, *o*-cresol, and 4-OH-anisole at 80 °C to provide products in yields ranging from 75 to 88% (Scheme 3, **24**–**27**). Finally, the coupling of 5-bromopyrimidine with *o*-cresol provided the desired product in 72% yield (Scheme 3, **28**).

To test the limits of our new catalyst system further, we applied it to traditionally recalcitrant substrates such as five-membered-ring heteroaryl halides, as well as aryl halides containing functional groups with acidic protons. Those containing free carboxylic acids were not suitable substrates; however, secondary amide-containing substrates could be effectively coupled simply by including an extra equivalent of base (Scheme 4, **29**–**31**). Heteroaromatic amides were also suitable coupling partners (Scheme 4, **31**). Significantly, compounds similar to **31** have been studied extensively in both industry and academia as potential antidepressant/anxiolytic agents (SB-243213).[16] We also found N-protected 4- and 6-bromoindoles to be suitable substrates (Scheme 4, **32, 33**). Finally, a variety of thiophenes could also be readily combined with phenols. For example, 3-bromo-2-thiophenecarbaldehyde reacted readily at 40 °C, and while 3-bromo-4-methylthiophene required 100 °C, the corresponding products were obtained in good yields (Scheme 4, **34**–**36**). Additionally, 3-bromo-1-benzothiophene was coupled effectively with phenol and 4-OH-anisole, though a higher Pd loading (3 mol %) was required (Scheme 4, **37**, **38**).[17]

In summary, we have developed a new catalytic system which employs a more reactive Pd source, [(cinnamyl)PdCl]$_2$, in combination with new ligand **L8** that facilitates the synthesis of diaryl ethers under mild conditions. The increased reactivity of the catalyst based on **L8** allows C–O cross-coupling to occur at rt in several cases and further allows coupling to occur between previously unreactive coupling partners. Interestingly, the ligands synthesized for this study demonstrate how a seemingly small difference in the size of the substituents of the lower (nonphosphine-containing) ring of biarylphosphine ligands can significantly affect the reactivity of the resulting catalysts. The structural features of the catalysts derived from **L7**–**L12** and their mechanistic implications are the object of ongoing study in our laboratory.

Scheme 4. Pd-Catalyzed C–O Bond Formation Using Amides and Heteroaromatic Aryl Bromides with a Catalyst Based on **L8**[a]



[a] Reaction conditions: aryl halide (1 mmol), phenol (1.5 mmol), K_3PO_4 (1.5 mmol), **L8** (3.0 mol %), [(cinnamyl)PdCl]$_2$ (1.0 mol %), toluene/DME (0.6/0.3 mL), 100 °C, 16 h; isolated yields, average of two runs. [b] K_3PO_4 (3.0 mmol). [c] **L8** (1.5 mol %), [(cinnamyl)PdCl]$_2$ (0.5 mol %). [d] **L8** (1.5 mol %), [(cinnamyl)PdCl]$_2$ (0.5 mol %), 40 °C. [e] **L8** (4.5 mol %), [(cinnamyl)PdCl]$_2$ (1.5 mol %).

Acknowledgment. We thank the National Institutes of Health for financial support of this work (Grant GM58160). This activity was also partially supported by an educational donation provided by Amgen. We thank FMC Lithium for a generous gift of *tert*-Bu_2PCl. We also thank Jorge García Fortanet (Novartis – Cambrige MA) for first synthesizing **L7** and **L8**.

Supporting Information Available. Experimental procedures and characterization data for all new and known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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