Cross-Coupling

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Design of New Ligands for the Palladium-Catalyzed Arylation of α-Branched Secondary Amines**

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Abstract: *In Pd-catalyzed C–N cross-coupling reactions, α-branched secondary amines are difficult coupling partners and the desired products are often produced in low yields. In order to provide a robust method for accessing N-aryl α-branched tertiary amines, new catalysts have been designed to suppress undesired side reactions often encountered when these amine nucleophiles are used. These advances enabled the arylation of a wide array of sterically encumbered amines, highlighting the importance of rational ligand design in facilitating challenging Pd-catalyzed cross-coupling reactions.*

Tertiary, *N*-aryl α-branched amines are frequently found as structural components of pharmaceutically relevant compounds and biologically active natural products (Figure 1).[1] Although Pd-catalyzed carbon–nitrogen (C–N) cross-coupling would provide an efficient means of accessing this valuable class of compounds, the use of α-branched secondary amine nucleophiles has seen only limited success, and in many instances low yields of the desired product are obtained.[2] Other methods for preparing tertiary *N*-aryl α-branched amines rely on the addition of an amine to an aryne[3] or nucleophilic aromatic substitution.[4] While effective, these methods typically have a narrow substrate scope or result in a mixture of regioisomeric products.[3] Copper-catalyzed electrophilic amination has also been utilized,[5] with a recent report by Lalic demonstrating its effectiveness for the arylation of sterically hindered secondary *O*-benzoyl hydroxylamine electrophiles.[5b] Despite these advances, there remains no general method for the direct arylation of α-branched secondary amines. Therefore, we sought to develop a catalyst system capable of cross-coupling sterically encumbered secondary amines.

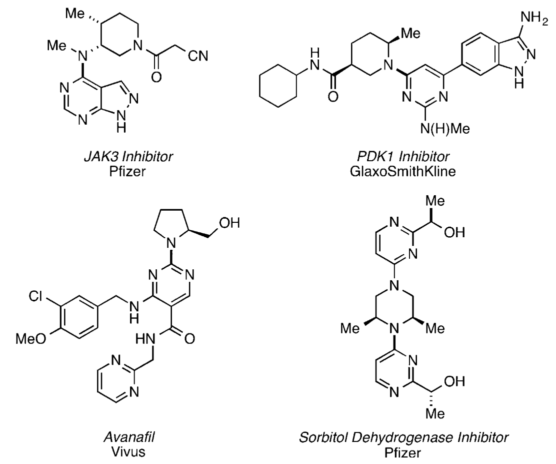

Figure 1. Selected examples of biologically active compounds containing tertiary *N*-aryl α-branched amines.[1]

The development of a highly effective catalyst system for the arylation of α-branched secondary amines must address the specific challenges presented by these coupling partners. Their poor nucleophilicity as a consequence of steric hindrance can lead to slower rates of amine transmetalation, resulting in the competitive reaction of the alkoxide base and the formation of the corresponding aryl *tert*-butyl ether (ArO*t*Bu, **V**, Figure 2). Additionally, β-hydride elimination may occur from the intermediate Pd^{II}-amido complex[6,7] (**IV**, Figure 2), leading to the formation of the reduced arene (**VI**,

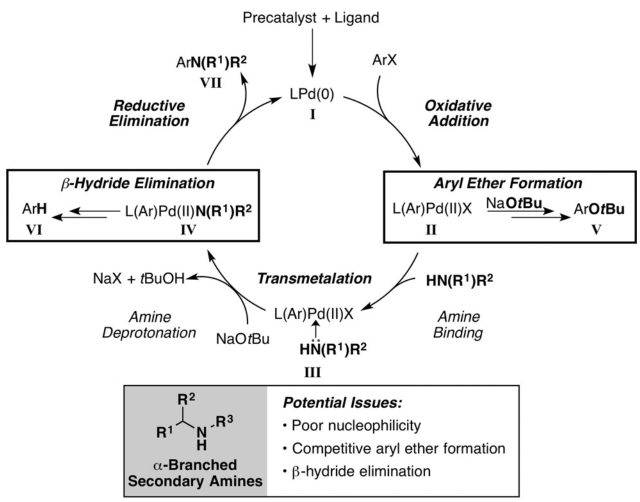

Figure 2. Proposed catalytic cycle and potential challenges presented by sterically hindered α-branched secondary amine nucleophiles.

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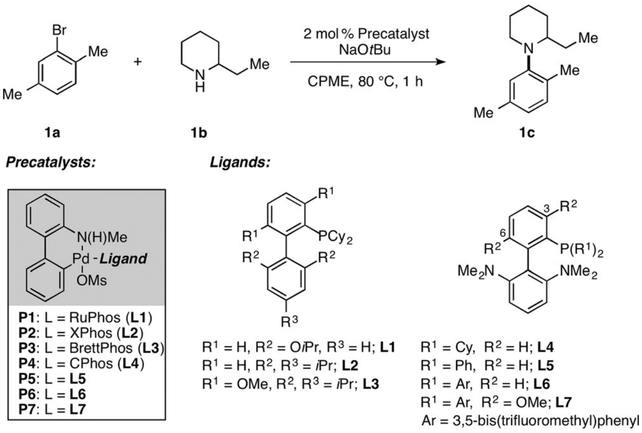
Figure 2). In this regard, the supporting ligand for the palladium catalyst must be carefully designed in order to facilitate the preferential formation of the desired aryl amine while suppressing side reactions.

We began our investigation by examining the effect of the supporting ligands on the efficiency of the catalyst system for the reaction shown in Table 1.[8] Catalyst systems based on

Table 1: Evaluation of supporting ligands.[a]



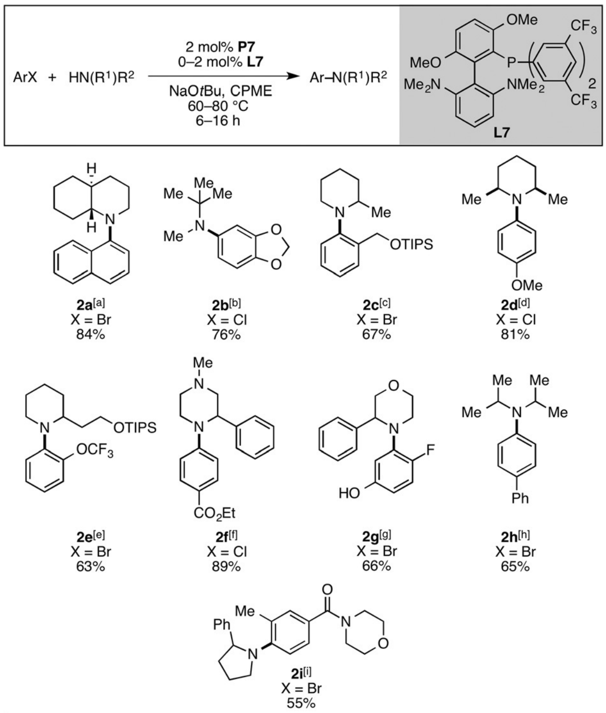
Entry	Precatalyst	Conversion	Reduction	Yield
1	**P1**	100%	68%	10%
2	**P2**	100%	85%	15%
3	**P3**	37%	15%	2%
4	**P4**	100%	53%	27%
5	**P5**	100%	18%	77%
6	**P6**	94%	trace	85%
7	**P7**	100%	trace	93%[b,c]

[a] Reaction conditions: **1a** (0.25 mmol), **1b** (0.30 mmol), NaO*t*Bu (0.35 mmol), 2 mol% precatalyst, CPME (0.5 mL), 80°C, 1 h. Conversion, C–N cross-coupling, and reduction product yields were measured by GC analysis of the crude reaction mixture using dodecane as the internal standard. [b] The reaction also produced 6% of the corresponding ArO*t*Bu. [c] Yield of isolated product: 89% (1 mmol scale, average of two runs). CPME = cyclopentyl methyl ether.

RuPhos (**L1**) have been demonstrated to be highly effective for the cross-coupling of secondary amines,[9] including some cases of reactions between sterically demanding coupling partners.[2a,c] However, when RuPhos precatalyst **P1** was used in the reaction of 2-bromo-*p*-xylene (**1a**) and 2-ethylpiperidine (**1b**), the desired product was obtained in only 10% yield (Table 1, entry 1). Other biaryl phosphine ligands such as XPhos (**L2**) and BrettPhos (**L3**) have also been used for promoting Pd-catalyzed C–N bond formation.[9] Nevertheless, these catalyst systems (**P2** and **P3**, respectively) proved to be inefficient in facilitating the desired transformation (Table 1, entries 2 and 3). In all cases, the major by-product was the reduced arene, which presumably arises as a result of β-hydride elimination.[10]

Given these results, we turned to CPhos (**L4**, Table 1), which has been demonstrated to suppress β-hydride elimination in Pd-catalyzed Negishi cross-coupling reactions.[11] Indeed, CPhos precatalyst **P4** produced aryl amine **1c** in an improved yield, although the reduced arene remained the major product (Table 1, entry 4).

In the proposed catalytic cycle, the β-hydride elimination pathway competes with reductive elimination from the Pd^{II}–amido intermediate (**IV**, Figure 2). We thus envisioned that using a less electron-rich biaryl phosphine ligand would increase the rate of C–N reductive elimination.[12] A less electron-rich biaryl phosphine ligand could also increase the rate of transmetalation (amine binding and deprotonation, Figure 2) by rendering the Pd^{II} intermediates **II** and **III** more electrophilic (Figure 2).[13] Based on this hypothesis, we examined a catalyst system based on the ligand **L5** (**P5**, Table 1).[14,15] The use of precatalyst **P5** dramatically increased the yield of **1c**, while the amount of reduced arene decreased (Table 1, entry 5). Following these results, we changed the phosphorus substituents from phenyl to 3,5-bis(trifluoromethyl)phenyl groups to provide ligand **L6** (**P6**, Table 1). The use of precatalyst **P6** led to an additional improvement in the yield and further diminished the formation of the reduced arene (Table 1, entry 6). To achieve additional improvements in catalyst performance, we incorporated methoxy groups at positions 3 and 6 of the biaryl framework (Table 1), as these groups are known to increase the rate of reductive elimination from Pd^{II} complexes.[16] This modification led to **L7** (**P7**),



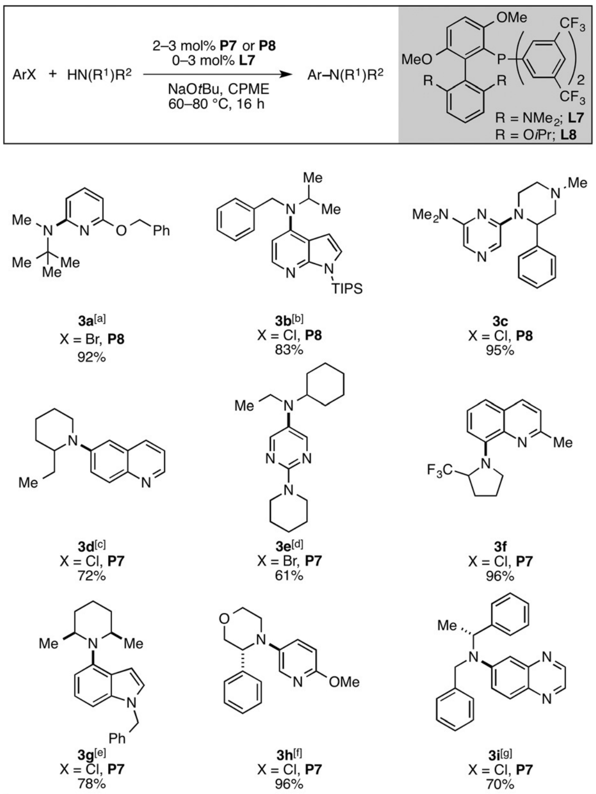
Scheme 1. Scope of C–N cross-coupling reactions using **P7**. Reaction conditions: aryl halide (1.0 mmol), amine (1.2 mmol), NaO*t*Bu (1.4 mmol), 2 mol% **P7**, 0–2 mol% **L7**, CPME (2 mL), 60–80°C, 6–16 h. Yields are of isolated products, average of two runs. [a] 1:49 *cis*:*trans* isomers of the arylated amine. Determined by GC analysis of the crude reaction mixture. 2% reduction, 4% ArO*t*Bu. [b] 9% ArO*t*Bu. [c] 27% reduction, 6% ArO*t*Bu [d] 22:1 *cis*:*trans* isomers of the arylated amine. Determined by GC analysis of the crude reaction mixture. [e] 28% reduction. [f] K_3PO_4 (6.0 mmol) used as base. [g] 34% reduction. [h] Amine (9.6 mmol), NaO*t*Bu (10.8 mmol), 7% reduction, 9% ArO*t*Bu. [i] 37% reduction.

which provided the most efficient catalyst system for the desired transformation (Table 1, entry 7).[17]

Precatalyst **P7** enabled a wide variety of C–N cross-coupling reactions with α-branched secondary amines (Scheme 1). Hindered cyclic secondary amines were well-tolerated, including in reactions with aryl halides containing *ortho* substituents (**2a**, **2c**, **2e**, **2g**, and **2i**, Scheme 1). Lower yields were obtained in the more sterically encumbered cases,[18,19] where the formation of the reduced arene by-product was observed. Acyclic α-branched amines could also be efficiently arylated (**2b** and **2h**, Scheme 1). Previously, the arylation of diisopropylamine through Pd-catalyzed C–N cross-coupling has resulted in very low yields,[2f,20] presumably as a result of its steric hindrance. By using **P7**, however, diisopropylamine was successfully arylated in 65% yield (**2h**, Scheme 1), although additional equivalents of amine and base were necessary to favor the formation of the desired product.[21,22]

We were interested in applying the developed conditions to the amination of heteroaryl halides because of their presence in many pharmaceutically relevant compounds.[2] However, our initial attempts to utilize activated heteroaryl electrophiles (**3a**, **3b**, and **3c**, Scheme 2) resulted in low yields and the formation of significant amounts of the corresponding ArO*t*Bu.[23,24] Through systematic ligand modification,[25] we found that ligand **L8** (**P8**, Scheme 2) provided higher yields in these cases. With all other substrates, **P7** was again very effective in producing high yields of the desired product. In certain instances, the use of additional equivalents of the amine was necessary to further deter the formation of ArO*t*Bu (**3a**, **3g**, and **3i**, Scheme 2). Additionally, a trace of the epimerized product was observed when *cis*-2,6-dimethylpiperidine (**3g**, Scheme 2) or an enantiomerically enriched amine was used (**3h** and **3i**, Scheme 2). Despite these considerations, the combined substrate scope using precatalysts **P7** and **P8** allows efficient cross-coupling of a wide variety of challenging α-branched secondary amines with different heteroaryl halides (Scheme 2).

In summary, we have developed two new catalyst systems for the arylation of sterically demanding α-branched secondary amines. Notably, the unprecedented levels of reactivity in C–N cross-coupling reactions with these amines were achieved because of the ability of the new precatalysts to suppress both the β-hydride elimination pathway and arylation of the alkoxide base. Overall, this work highlights the potential of rational ligand design to modulate catalyst behavior and ultimately facilitate the cross-coupling of sterically demanding amine coupling partners.



Scheme 2. Scope of C–N cross-coupling reactions with heteroaryl halides and hindered secondary amines. Reaction conditions: aryl halide (1.0 mmol), amine (1.2 mmol), NaO*t*Bu (1.4 mmol), 2–3 mol% **P7** or **P8**, 0–2 mol% **L7** (used only with **P7**), CPME (2 mL), 60–80°C, 16 h. Yields are of isolated products, average of two runs. [a] Amine (2.4 mmol), NaO*t*Bu (2.8 mmol). [b] 9% reduction, 8% ArO*t*Bu. [c] 2% reduction, 3% ArO*t*Bu. [d] 13% reduction. [e] Amine (3.6 mmol), NaO*t*Bu (4.2 mmol); 20:1 *cis*:*trans* isomers of the arylated amine product. Determined by GC analysis of the crude reaction mixture. [f] Starting amine: 99% *ee*; product: 98% *ee*. [g] Amine (2.4 mmol), NaO*t*Bu (2.8 mmol), dioxane (2 mL); 24% ArO*t*Bu, 6% reduction; starting amine: ≥97% *ee*; product: 83% *ee*.

Keywords: amination · cross-coupling · ligand design · palladium · synthetic methods

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[17] In this case, the difference in performance between ligands **L6** and **L7** was not significant. However, **L7** performed considerably better than **L6** in the reaction with other substrates, particularly aryl chlorides, see the Supporting Information.

[18] The length of the C–F bond is more similar to the length of the C–O bond than to that of the C–H bond, making the steric effects of an *ortho*-fluoro substituent slightly more significant than those of an *ortho*-hydrogen substituent. See: K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881.

[19] The amounts of the corresponding reduced arene and ArO*t*Bu by-products that were observed have been indicated in the table footnotes. In most cases, these by-products could be readily separated from the desired aryl amine product. Only in the case of **2c** was the separation difficult and the isolated material contained less than 5% of the corresponding ArO*t*Bu.

[20] The cross-coupling of diisopropylamine with 4-bromoanisole was reported by Herrmann to provide the aryl amine product in 78% yield. In our hands, the products under these conditions resulted from the arylation of the corresponding *N*-isopropyl-propan-2-imine see: W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23 and the Supporting Information.

[21] A control experiment produced none of the arylated diisopropylamine or the corresponding ArO*t*Bu, see the Supporting Information.

[22] An excess of amine relative to NaO*t*Bu led to the incomplete conversion of the aryl electrophile. As such, the same amine-to-base ratio was maintained for all reactions, see the Supporting Information.

[23] Control experiments for substrates **3a**, **3b**, and **3c** showed no formation of the product or the corresponding ArO*t*Bu, see the Supporting Information.

[24] When **P7** was used, the yields of **3a**, **3b** and **3c** were 5%, 60%, and 70% respectively, see the Supporting Information.

[25] See the Supporting Information.

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