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# Mild and General Method for the α-Arylation of Heteroaromatic Ketones

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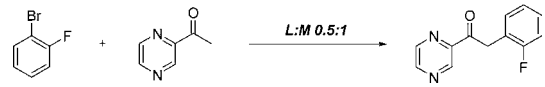
## ABSTRACT




**The development of a general and mild method for Pd-catalyzed α-arylation of a variety of ketones bearing multiple heteroatoms is described. The ligand to metal ratio and the position of the heteroatoms with respect to the carbonyl moiety significantly impact the efficiency of these transformations. In addition, these conditions were successfully applied to the α-arylation of cyclic imines. A detailed investigation of the scope of this methodology, including the effect of the ligand to metal ratio, is discussed.**

The α-aryl carbonyl functionality is an important component of many pharmaceuticals and bioactive molecules.[1] Hence, significant efforts have been devoted to the construction of this motif using transition metal catalysis. In particular, the palladium-catalyzed α-arylation reaction is an attractive method for the rapid construction of C−C bonds α to a carbonyl moiety.[2] Miura,[3] Buchwald,[4] Hartwig,[5] and others[2] have shown that this transformation is effective for the coupling of various aryl halides with esters, amides, unfunctionalized ketones, and aldehydes. Both electron-deficient and electron-rich aryl halides have been successfully employed, rendering the α-arylation reaction versatile and synthetically valuable. Furthermore, a recent report by Buchwald and co-workers expanded the scope toward arylation of heteroaromatic ketones.[6] Despite these advances, to the best of our knowledge, there have been no reported examples for α-arylation of multi-heteroaromatic ketones. This constitutes a limitation due to the ubiquitous presence of heteroaryl moieties in pharmaceuticals and agrochemicals. In addition, the strong bases typically employed for the arylation of simple methyl aryl ketones limits the functional group compatibility of these reactions. Hence, a general and mild method for the monoarylation of a wide array of methyl heteroaromatic ketones is desirable. Herein, we report the palladium-catalyzed α-arylation of substrates containing multiple heteroatoms using a mild base. Careful optimization of the ligand to metal ratio was critical in the development of these transformations.

Fluorinated arenes are widely prevalent in pharmaceuticals due to their enhanced metabolic stability, bioavailability, binding efficacy, selectivity, and solubility.[7] However, surveying the literature reveals that the use of fluorinated arenes, for example, 2-fluorobromobenzene (**A**), in α-arylation reactions is rare.[8] In addition, *β*-arylated pyrazine motifs are often found in biologically active molecules.[9] Therefore, our initial studies focused on α-arylation of 2-acetylpyrazine **1** with **A** (Table 1).

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(8) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209. The only reported example of arylation of 1-chloro-2-fluorobenzene with acetophenone used *n*BuPAd$_2$ as the ligand, 1 mol% of Pd(OAc)$_2$, and K$_3$PO$_4$ as the base in dioxane at 100 °C. The monoarylated product is formed in 57% yield, as a 2.5:1 mixture of mono and diarylated products.

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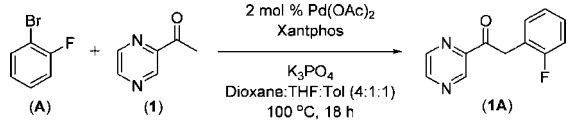
**Table 1.** Screening α-Arylation of 2-Acetylpyrazine (**1**)




| Entry | L:M | Ketone:ArBr | Solution yield[b] |
|---|---|---|---|
| 1 | 1:1 | 1:1 | 40% |
| 2 | 1:1 | 2:1 | 69% |
| 3 | 1.5:1 | 2:1 | 21% |
| 4 | 2:1 | 2:1 | 22% |
| 5 | 0.5:1 | 2:1 | 76% |
| 6 | 0.5:1 | 2:1 | 92%[a] |

[a] In-process yield obtained with 4 mol % of $Pd(OAc)_2$ and 2 mol % of Xantphos. Aryl bromide **A** as the limiting reagent. [b] Solution yield determined using an HPLC calibration, see SI for further information.

Extensive screening using $Pd(OAc)_2$ as the metal precursor and $K_3PO_4$ as the base demonstrated Xantphos to be the most competent ligand in implementing the α-arylation, albeit affording the product **1A** in only 40% solution yield (entry 1). Increasing the concentration of **1** relative to **A** (entry 2) enhanced the yield of the desired product.[10] We reasoned that the presence of multiple heteroatoms might be impacting the effective ligand to metal ratio by binding to the metal. In order to test this hypothesis, we conducted a systematic screening of the ligand to metal ratio (L:M) required for this transformation (entries 3−5) and were gratified to observe increased yields when the L:M was reduced to 0.5 (entry 5). The highest in-process yield (92%) of **1A** was obtained with an increased catalyst loading of 4 mol % of $Pd(OAc)_2$, 2 mol % of Xantphos, and 2.8 equiv of $K_3PO_4$ in 4:1:1 1,4-dioxane/THF/toluene at 100 °C for 18 h (entry 6). Interestingly, under these conditions, none of the diarylated product was observed. The results in Table 1 suggest that under our conditions the reactivity of multi-heteroaromatic ketones greatly depends on the ligand to metal ratio. In order to determine the generality of this effect, we studied the impact of varying ligand and metal stoichiometries on the α-arylation reaction of various heteroaromatic ketones (acetylpyridine **2**, acetylpyrazine **1**, 5-acetyl pyrimidine **3**, and 4-acetylpyrimidine **4**).

As depicted in Figure 1, an interesting correlation was observed between the L:M and the number and position of heteroatoms in the substrate. The optimal L:M range (2.5−2) for **2**,[11] containing only one heteroatom, is analogous to that of acetophenone **5**. This is in sharp contrast to the 1:1 L:M reported for Xantphos for α-arylation reactions in the literature.[4b] On the other hand, a lower L:M is required to obtain good yields for the arylation of substrates containing

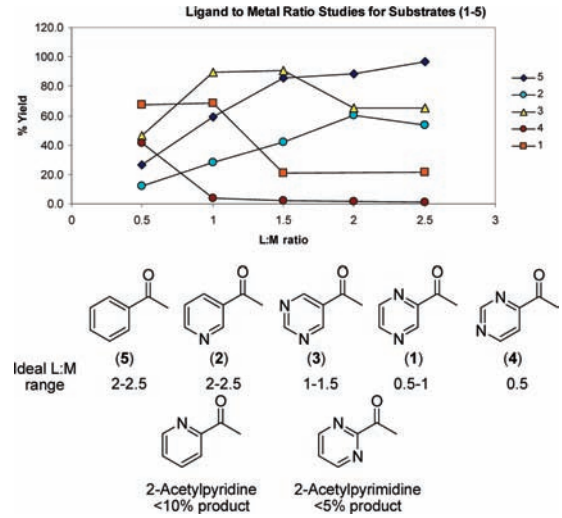
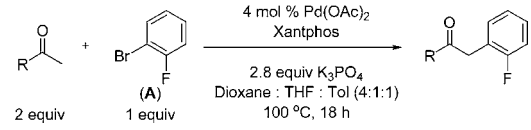



**Figure 1.** Ligand to metal ratio studies for substrates **1**−**5**.

multiple heteroatoms (**1**, **3**, and **4**). The application of these studies toward obtaining optimum yields for the arylation of substrates **1**−**7** is summarized in Table 2.

**Table 2.** Screening α-Arylation for Heteroaromatic Ketones




| Entry | Substrate | Product | L:M | Yield[a] |
|---|---|---|---|---|
| 1 | (1) | (1A) | 0.5:1 | 80% |
| 2 | (2) | (2A) | 2.0:1 | 81% |
| 3 | (3) | (3A) | 1.0:1 | 76% |
| 4 | (4) | (4A) | 0.5:1 | 40% |
| 5 | (5) | (5A) | 2:1 | 85% |
| 6 | (6) | (6A) | 0.5:1 | 77% |
| 7 | (7) | (7A) | 1:1 | 68% |

[a] Isolated yields and average of two runs.

As shown in Table 2, the position of the heteroatom in the substrate appears to dictate the optimal L:M.[12] For

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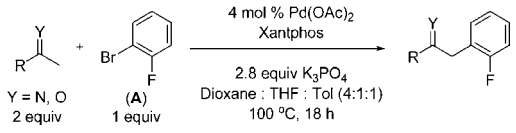
example, ketones **1**, **3**, and **4** differing only in the relative positions of the two nitrogens, require L:M ranging between 0.5−1, 1.0−1.5, and 0.5, respectively, to obtain the optimum yield of the arylated product. In addition, the bidentate chelation of the substrate to the metal appears to impact both the L:M and the efficiency of these transformations. This is exemplified by the arylation of substrates bearing a nitrogen atom ortho to the carbonyl moiety. For example, substrates **1** and **4** require lower L:M relative to other ketones while 2-acetylpyridine and 2-acetylpyrimidine exhibit extremely poor reactivity. The difference in reactivity between **1** (and **4**) and 2-acetylpyridine (and 2-acetylpyrimidine) suggests that the presence of multiple heteroatoms facilitates the arylation of substrates capable of bidendate chelation to the metal. In all, these studies suggest that a complex interplay of the number, position, and chelating ability of heteroatoms dictates the optimal L:M required for the arylation of multi-heteroaromatic ketones.

With these results in hand, we next studied the versatility of these mild conditions for the arylation of other ketones. A variety of heteroaromatic substrates were successfully α-arylated with **A** (Table 3). Besides methyl ketones,

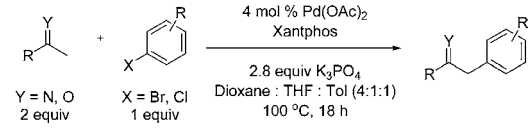
**Table 3.** Substrate Scope for α-Arylation




| Entry | Substrate | Product | L:M | Yield[a] |
|---|---|---|---|---|
| 1 | (8) | (8A) | 2:1 | 72% |
| 2 | (9) | (9A) | 2:1 | 82% |
| 3 | (10) | (10A) | 2:1 | 45% |
| 4 | (11) | (11A) | 2:1 | 79% |
| 5 | (12) | (12A) | 2:1 | 75% |
| 6 | (13) | (13A) | 2:1 | 75% |
| 7 | (14) | (14A) | 2:1 | 69% |

[a] Isolated yields and average of two runs.

**Table 4.** Scope of Aryl Halides




| Entry | Substrate | Product | L:M | Yield[a] |
|---|---|---|---|---|
| 1 | (B) | (1B) | 0.5:1 | 70% (10:1)[b] |
| 2 | (C) | (1C) | 0.5:1 | 55% (2:1)[b] |
| 3 | (D) | (1A) | 0.5:1 | 69% |
| 4 | (E) | (1E) | 0.5:1 | 69% |
| 5 | (F) | (1E) | 0.5:1 | 62% |
| 6 | (G) | (1G) | 0.5:1 | 57% (3:1)[b] |
| 7 | (H) | (1H) | 0.5:1 | 62% (6:1)[b] |
| 8 | (I) | (13I) | 2:1 | 72% |
| 9 | (J) | (3J) | 1:1 | 42% |
| 10 | (J) | (2J) | 2:1 | 43% |

[a] Isolated yields and average of two runs. [b] Ratio of monoarylated: diarylated product.

arylation of ethyl ketone **8**, having increased substitution at the α-carbon, is also feasible. Substrates such as acetylthiophene **9** and acetylfuran **11** were compatible under our conditions. Regardless of the heteroatom, the optimal L:M range for ketones containing a single heteroatom such as **9** and **11** was 2.0−2.5, consistent with the trend observed in Figure 1. In addition, these reaction conditions were compatible with electron-rich arenes (entry 7, Table 3) and benzylic

(10) Refs 4 and 5 illustrate that excess ketone is generally used for α-arylation reactions.

(11) Along with Xantphos, high yield of the arylated product **2A** was obtained with cataCXiumPOMeCy as ligand (L:M 2:1) and $K_3PO_4$ as base in toluene at 100 °C. To the best of our knowledge, this is the first report of using cataCXiumPOMeCy as a ligand for an α-arylation reaction, making it a valuable alternative.

hydrogens (entry 7, Table 2 and entries 3−5 and 7, Table 3). Notably, the selective arylation of methyl ketone versus the amide in substrate **12** exemplifies the chemoselectivity for these reactions (entry 5, Table 3).

We were also interested in studying the arylation of imines such as **13** and **14**, which would allow access to motifs prevalent in many biologically active molecules.[13] Importantly, our conditions were mild, selective, and general enough to successfully α-arylate these challenging heterocyclic substrates (entries 6 and 7, Table 3).

Surveying the imine arylation literature reveals that only NaO*t*Bu, LiO*t*Bu, and a few examples with $Cs_2CO_3$ have been reported to promote α-arylation of imines, albeit in low selectivity for mono- versus diarylation.[14] Hence, the success of our mild basic conditions for affording monoarylated products **13A** and **14A** in high selectivity is an important addition to the previously reported imine arylations. We are currently expanding the boundaries of this process.

The scope of the ketone arylation reaction with respect to the aryl halide was investigated next. As shown in Table 4, electron-rich (**G**), electron-deficient (**B**−**E**), and heteroaryl halides (**I**,**J**) were effective substrates. In general, better selectivity for monoarylation versus diarylation was observed for electron-deficient or heteroaryl halides.[15] Interestingly, while diarylation was not observed with 1-bromo-2-fluorobenzene,[8] 27% diarylated product is formed with 1-bromo-4-fluorobenzene. This difference in selectivity can be attributed to the more electron-deficient character of 1-bromo-2-fluorobenzene over 1-bromo-4-fluorobenzene. Such electronic effects with *ortho*- and *para*-fluorinated arenes have been previously documented.[16] Notably, aryl chlorides such as **D** and **F** are also effective coupling partners for the α-arylation reaction (entries 3 and 5, Table 4). However, given the option, preferential oxidative addition into the C−Br bond is observed (entry 7, Table 4). An important feature of these α-arylation reactions is that the required L:M is dictated by only the ketone coupling partner. As illustrated in Figure 1, the range of L:M preference was 1−1.5 for 5-acetylpyrimidine **3** and 0.5−1 for 2-acetylpyrazine **1**. Unexpectedly, the α-arylation of **3** or **2** with **J** proceeded similarly at L:M ranging from 0.5 to 2.0. These preliminary results indicate that heteroaryl halides do not significantly impact the ligand to metal ratio.[17]

In summary, we have reported α-arylation reactions of an unexplored class of multi-heteroaromatic ketones, namely, pyrazines, pyrimidines, and quinoxaline. The reactivity of these substrates was dictated by the ligand to metal ratio. In addition, we have developed a mild, chemoselective, and general method to effectively α-arylate a variety of substrates such as imines, acetylthiophenes, acetylfurans, and acetylpyridines. We are currently conducting mechanistic studies to elucidate the intriguing effect of the ligand to metal ratio on the reactivity of these substrates.

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

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(15) Ref 5a discusses that the selectivity between mono- and diarylation is base-dependent. Arylations of electron-rich or electron-neutral aryl bromides were more selective for monoarylation with KHMDS as the base, while electron-deficient aryl bromides were more selective with NaO*t*BU as the base.

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