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Discovery of a new palladacycle precatalyst and its applications to C–O coupling reactions between electron-deficient phenols and functionalized heteroaryl chlorides

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ABSTRACT

A new palladacycle precatalyst (**J009 PreCat**) was designed and synthesized. The precatalyst dramatically improved the yield of a class of extremely challenging cross-coupling reactions between functionalized heteroaryl chlorides and electron-deficient phenols. The reactions are easy to set up, are tolerant of various functional groups, and allow quick access to electron-deficient, highly functionalized diaryl ether compounds.

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Diaryl ethers are important structural motifs in natural products and other biologically active molecules.¹ Until recently, diaryl ethers are formed via S_NAr reaction from relatively expensive and less available aryl fluorides, or via Ullmann coupling reactions with aryl bromides or iodides in the presence of stoichiometric amount of copper reagents.² These reactions typically are performed under harsh reaction conditions, and thus have poor functional group tolerance. The recent advancement in Pd- and Cu-catalyzed methods has allowed this reaction to be run under much milder conditions. with greatly expanded substrate scope and improved functional group tolerance.^{3–5} Despite these improvements, the less reactive aryl and heteroaryl chlorides, and electron-deficient phenols are still generally not competent substrates in the Cu-catalyzed C-O coupling reaction.^{5b,5d} The use of bulky phosphine ligands has allowed Pd-catalyzed C-O coupling of aryl chlorides, 4e-g,6c and a wide range of phenols.^{4f-h} However, the direct coupling between aryl chlorides especially heteroaryl chlorides, which are much more readily available than heteroaryl bromides or iodides, and electron-deficient phenols has remained a vastly untackled challenge.

Electron-deficient diaryl ethers are highly desirable structural components in medicinal chemistry due to their superior

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http://dx.doi.org/10.1016/j.tetlet.2015.03.080 0040-4039/© 2015 Elsevier Ltd. All rights reserved. metabolic stability. In particular, for a discovery chemistry project, we were interested in the coupling reactions between aryl partners much like the ones shown in Eq. 1. Phenol **1a** is an extremely deactivated nucleophile, whereas the NHBoc-functionalized pyridyl chloride **2a** is also a very challenging electrophile. Not surprisingly, the S_N Ar reaction between **1a** and **2a** failed to take place under a variety of conditions.



Because of the known challenge of Cu methods for such deactivated substrates, we moved directly to investigate if a Pd catalyst system could promote this reaction. In 2012, using high throughput screening technology, the catalysis group at Merck process department discovered that the use of JosiPhos **J009** (R)-1-[(S_P)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-tert-butylphosphine⁶ allows C–O cross-couplings of activated aryl and heteroaryl halides with aliphatic alcohols.⁷ We attempted to take advantage of this reported condition and applied it to our specific C–O coupling reaction (Eq. 2). While we were finally able to observe the







formation of desired product, the conversion was extremely low (isolated yield = 3%) even at a high catalyst loading of 10 mol % Pd.



Nevertheless, at the time this result represented our best chance to obtain useful yield of compound **3a**. Therefore, we decided to use this condition as the starting point to optimize this reaction.

Recently, it has been demonstrated that palladacycle precatalysts of the types reported by Buchwald and coworkers allow for efficient catalyst activation under basic reaction conditions and can promote otherwise difficult coupling reactions.⁸ In addition, reactions with these precatalysts can often be run at lower temperature and thus improve functional group tolerability. While the earlier generations of the Buchwald precatalysts are not compatible with bulky di-*tert*-butyl substituted phosphine ligand, the most recent precatalyst system using mesylate as the counter ion enabled the incorporation of hindered ligands.⁹ Consequently, the Buchwald group has reported the use of di-*tert*-butyl-biaryl monophosphine ligands pre-ligated to the precatalysts for the coupling of alcohols and phenols.¹⁰

In light of the reported advantage of the precatalysts and our initial result of the reaction with **J009**, we decided to prepare palladacycle precatalyst of **J009**. Following literature protocol,⁹ **J009 PreCat** was formed readily in high yield from the μ -OMs Pd dimer with **J009** ligand in THF at RT (Eq. 3).



With the precatalyst in hand, we subjected it to the test reaction in Eq. 2. To our delight, the reaction resulted in full conversion and an 82% isolated yield with 2 mol % catalyst loading, (Table 1, entry 1). The NHBoc group was tolerated under reaction conditions. Given the excellent result of this reaction, we decided to quickly investigate the generality of this catalyst system for coupling with electron-poor phenols. As shown in Table 1, a wide range of electron-deficient phenols can be coupled effectively using **J009 PreCat**. Not only mono-nitrile substitution on the phenol was tolerated, the more electron-poor 5-hydroxyisophthalonitrile (**1b**) also reacted smoothly to give a 76% isolated yield (Table 1, entry 2).

Notably, 3-chloro-5-hydroxybenzonitrile (**1c**) also gave a reasonably high yield of 62% (Table 1, entry 3). It should be noted that the chloride on **1c** had been posing chemoselectivity challenges in various cross-coupling reactions in our hands. Therefore, we were very pleased to see that in this **J009 PreCat** catalyzed C–O coupling reaction with **1c** a moderately high yield of the chemoselective coupling product **3c** was obtained.

Table 1

C-O couplings using J009 PreCat^a



 a Reaction conditions: 2 mol % J009 PreCat, 2 equiv $Cs_2CO_3,$ toluene, 0.44 M substrate, 100 °C, 24 h.

^b 5 mol % J009 PreCat was used.

^c 10 mol % J009 PreCat was used.

The effect of substitution positions of the nitrile group on the reaction conversion was also investigated. While *para*- and *meta*-cyanophenols gave good conversions to products (Table 1, entry

1 and 2), the reaction with 2-nitrile phenol (**1d**) gave a moderate 61% yield (Table 1, entry 4). In all cases, the nitrile group on the phenol remained intact.

Next, we investigated the tolerability of more labile electronwithdrawing functional groups. Methyl 4-hydroxybenzoate (**1e**) was tolerated under the reaction conditions, giving an isolated yield of 82% of the desired coupling product (Table 1, entry 5). Methyl 2-hydroxybenzoate (**1f**), on the other hand, resulted in a much messier reaction, presumably due to self-reaction of **1f** between the hydroxyl and the neighboring ester functionality (Table 1, entry 6).

In addition to phenols bearing electron-withdrawing groups, we were also interested in the reactivity of hydroxyl heterocycles, particularly the nitrogen bearing heterocycles, which also have reduced electron density on the ring. To our delight, 2-(methylthio)pyrimidin-5-ol (**1g**) reacted under the reaction conditions very smoothly, giving 79% isolated yield (Table 1, entry 7). In addition, the much more challenging nucleophile 3-hydroxyl pyridyine^{4g} (**1h**) still provided a useful yield of 21% (Table 1, entry 8).

Finally, we investigated the scope of electron-deficient heterocyclic chlorides. Simple 2-chloropyridine (2b) reacted very well with phenol **1a**, giving a quantitative yield (Table 1, entry 9). More complex substrate 4-chloro-5-methyl-2-(methylthio)-6-(2-(trimethylsilyl)ethoxy)pyrimidine (2c) also reacted nicely to give around 71% isolated yield, with good tolerance of the TMS alkyl ether functionality and the sterical hindrance of the ortho methyl group (Table 1, entry 10). The good conversion on such advanced intermediate provides proof-of-concept of using this C-O coupling reaction at a late stage of a synthetic sequence thus allowing facile analog syntheses. Lastly, the much less activated aryl halide substrate tert-butyl (6-chloro-5-methylpyridazin-3-yl)carbamate (2d) still gave 10% isolated yield, which again is significant for medicinal chemistry SAR study purposes considering other coupling approaches failed to provide any desired product for this substrate in our hands.

In conclusion, we have successfully designed and synthesized a novel Pd precatalyst **J009 PreCat**, and applied this precatalyst toward the challenging synthesis of diaryl ethers from functionalized electron-deficient heteroaryl chlorides and electrondeficient phenols. The catalyst system provided significantly improved reaction yield. Additional advantages of this system include low catalyst loading, good functional group tolerance, and convenient reaction setup. Highly challenging substrates in C–O coupling reactions have shown to provide useful yields for medicinal chemistry SAR purposes. Thanks to its functional group tolerability and relatively mild reaction conditions, this reaction has the potential for late stage modifications of advanced intermediates and thus enables rapid analog syntheses in drug discovery.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.03. 080.

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