Mild Palladium-Catalyzed Cyanation of (Hetero)aryl Halides and Triflates in Aqueous Media

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Supporting Information

ABSTRACT: A mild, efficient, and low-temperature palladium-catalyzed cyanation of (hetero)aryl halides and triflates is reported. Previous palladium-catalyzed cyanations of (hetero)aryl halides have required higher temperatures to achieve good catalytic activity. This current reaction allows the cyanation of a general scope of (hetero)aryl halides and triflates at 2–5 mol % catalyst loadings with temperatures ranging from rt to 40 °C. This mild method was applied to the synthesis of lersivirine, a reverse transcriptase inhibitor.

The nitrile functional group is prevalent in organic materials, polymers, dyes, pesticides, natural products, and pharmaceuticals. The compact nature of the nitrile moiety, as well as its hydrogen bond accepting ability, metabolic stability in vivo studies, and use as a hydroxyl or carboxyl isostere has made it an important functional group in medicinal chemistry research.

Currently, there are over 30 approved drugs along with 20 additional leads in late-stage clinical trials that possess one or more nitrile substituents. These nitrile-containing bioactive molecules have been shown to treat a broad spectrum of ailments, such as depression, breast cancer, anti-HIV, and Parkinson’s disease. Nitriles are also an excellent synthetic handle to install a variety of functional groups such as amides, ketones, amines, and alcohols.

Palladium-catalyzed cross coupling of aryl halides and metallo-nucleophiles have seen tremendous advances over the last 30 years. In 1973, Takagi and co-workers reported the first palladium-catalyzed cyanation of aryl halides and KCN. This report included only a few substrates, and high temperatures (140 °C) were needed to achieve high conversion. Since this seminal report, there have been numerous advances by Beller, Grushin, our group, and others (Scheme 1, top). An interesting study by Grushin elucidated the challenges associated with the catalytic palladium cyanation of aryl halides. The high binding affinity and π-accepting nature of cyanide make it an excellent ligand for palladium. Therefore, complete solubilization of the nucleophilic cyanide source leads to rapid ligand displacement to form inactive off-cycle species, thus inhibiting product formation. Many have circumvented these undesired pathways by using biphasic solvent mixtures or solvents in which the cyanide source is sparingly soluble in the reaction mixture. These approaches have led to improvements in the palladium-catalyzed cyanation both in terms of substrate scope and reproducibility. However, these methods usually require grinding of the cyanide source to maintain a uniform particle size and high reaction temperatures (50–80 °C) to facilitate efficient and reproducible reactions for aryl and heteroaryl substrates. Previous stoichiometric studies in the palladium-catalyzed cyanation have shown that the oxidative addition, transmetalation, and reductive elimination steps occur at or below 40 °C. Despite these findings a substoichiometric method for a general room temperature palladium-catalyzed cyanation has not been reported. A mild palladium-catalyzed cyanation would allow safer reaction conditions, cleaner reaction profiles, and an expanded substrate scope. In this study, we disclose a general and efficient low temperature (rt to 40 °C) palladium-catalyzed cross coupling of (hetero)aryl halides and triflates with Zn(CN)₂ in aqueous media (Scheme 1, bottom).

This reaction does not require vigorous drying of the glassware or grinding of the Zn(CN)₂ and is amenable to a broad range of aryl halides/triflates, five- and six-membered heterocycles, and natural product derivatives. This method was directly utilized for the late-stage cyanation and synthesis of the non-nucleoside reverse transcriptase inhibitor, lersivirine. We began the examination of this room-temperature palladium-catalyzed cyanation by using our third-generation palladacycle precatalyst (P₁–P₃; Scheme 2) as the palladium source. Our initial experiments focused on the cyanation of

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ethyl 4-chlorobenzoate (2a) with Zn(CN)$_2$ (Table 1). We chose zinc cyanide as the nucleophile since it is commercially available, inexpensive, and significantly less toxic than the representative potassium and sodium salts. A preliminary solvent screen showed that only when conducting the reaction in THF was there any appreciable amount of product.

Investigation of a qualified catalytic base to activate the precatalysts showed that as the pK$_a$ of the base increased, the corresponding conversion to the aryl nitrile decreased (entries 1–5), with potassium tert-butoxide resulting in no conversion (entry 6). Examination of this reaction in the absence of base resulted in the highest level of conversion (entry 7). Presumably, cyanide acts as the ideal base to activate the precatalyst to form the Pd(0)-L species. Exploration of other precatalysts with different ligands did not provide any higher levels of conversion. To improve the rate of transmetalation of cyanide we examined a H$_2$O/THF solvent mixture. The assumption was that the Zn(CN)$_2$ would be solubilized in the aqueous phase and a slow diffusion of the cyanide to the organic phase would allow a moderate rate of transmetalation without deactivation of the palladium catalyst. Ranges of different ratios of H$_2$O/THF mixtures were surveyed (entry 8–14). Higher levels of conversion were observed when the percentage of water in the THF/H$_2$O mixture was increased. It was eventually determined that 5:1 H$_2$O/THF solvent allowed full conversion of aryl chloride 2a and an 89% isolated yield of nitrile 3a (entry 12). Further exploration of the reaction revealed that running this reaction with just precatalyst P1 and no additional ligand furnished nitrile 3a in 93% isolated yield (entry 15). It is interesting to point out that the substitution on the phosphine environment of the tert-butyl phosphine prevents displacement of the ligand by cyanide during the course of the reaction, thus allowing efficient cross-coupling without poisoning of the palladium catalyst.

With the optimized reaction conditions in hand, we explored the substrate scope for this palladium-catalyzed cyanation (Scheme 3). Aryl bromides with electron-withdrawing substitution were first examined. Aldehyde (3b), ketone (3c), and nitrile (3d) functional groups were readily tolerated on the aryl halide. No benzoquin products were observed with the p-aldehyde substrate (3b), even though cyanide is known to catalyze the benzoquin reaction. Use of 2-fluoro-4-nitromobenzene furnished only the mononitrile compound (3e), implying that nucleophilic aromatic substitution is not a dominant pathway in this protocol at 40 °C.

We next surveyed aryl bromides with electron-donating functional groups. Methoxy (3f and 3h) and dioxolane (3i) substitution was accommodated, providing the corresponding nitriles in excellent yields (>95% yield). Dioxolane 3i is an aromatic nitrile that has reported micromolar ED$_{50}$ values for treatment against Ermatophagoides farinae, Dermatophagoides pteronyssinus, and Tyrophagus putrescentiae. Ordo-substitution (3g) was tolerated, although the reaction needed to be heated at 40 °C for optimal efficiency. Additionally, this method exhibits a high compatibility for substrates bearing free N–H and O–H functional groups, such as benzyl alcohol (3j), phenol (3k), and aniline (3l) moieties. Lastly, this protocol was compatible with a boronate ester (3m), with homocoupling not observed.

We then turned our attention toward the cyanation of heteroaromatics. Our method was found to be applicable toward a wide range of five- and six-membered heterocycles. The cyanation of five-membered heterocycles such as indoles (4a + 4b), benzothiophene (4c), benzo[4d], thiophene (4e), unprotected thiazole (4f), pyrazole (4g), and pyrrole (4h) proceeded in excellent efficiency. Additionally, benzoazole (4i), and unprotected benzothiazole (4j) furnished the corresponding aryl nitrile in excellent yield. Six-membered heterocycles, such as quinoline (4k), pyridine (4l), and pyrimidine (4m), also furnished the corresponding nitrile in excellent yield.

To demonstrate the robustness and generality of this method we then explored the cyanation of natural product derivatives. Cyanation of estrone, coumarin, and δ-tocopherol trimethylsilyl esters furnished the corresponding cyanaryl natural products in high yield (5a, 5b, and 5c respectively). The cross-coupling of Boc-protected 4-bromophenylalanine provided the nitrile derivative (5d) without removal of the protecting group or epimerization of the stereocenter.

For this protocol to have direct application in pharmaceutical research, we need to demonstrate that these high yields can be reproduced at larger scale. With this aspect in mind, we examined the 10 mmol reaction for the cyanation of 4-bromobenzaldehyde, 4-bromonaphtalene, and unprotected 5-bromoindole. The corre-
sponding nitriles (3b, 3f, and 4a respectively) were isolated in comparable yields without significant modification to the reaction conditions. To demonstrate the practicality and robustness of this method we applied this developed method toward the late-stage cyanation of a non-nucleoside reverse transcriptase inhibitor, lersivirine (Scheme 4). Reverse transcriptase inhibitors are an important class of antiretroviral drugs used in the treatment of HIV and other retroviruses. Previous approaches to the synthesis of lersivirine involved the installation of the nitriles before the formation of the pyrazole. By using our procedure we were able to achieve the double cyanation of pyrazole 9 and formation of lersivirine in 88% yield at 40 °C.

The relative rate for this room-temperature palladium-catalyzed cyanation was shown to follow the general trend reported by Hartwig, in which aryl bromides with para electron-withdrawing substituents reacted at a slower rate than aryl rings with electron-donating substitution. This is consistent with the notion that the rate-determining step for this cyanation is the reductive elimination.

In conclusion, we have developed a mild and practical palladium-catalyzed cyanation of (hetero)aryl halides and triflates. Previous reports have required higher temperatures and harsher conditions to achieve good catalytic activity for (hetero)aryl halides and triflates. To date, this method requires the lowest reported temperature to achieve a general catalytic palladium cyanation for hetero(aryl) bromides and triflates,
including five-membered heterocycles. This reaction does not require grinding of the cyanide source, is run under aqueous conditions, and is easily set up. Finally, the utility of this cyanation was demonstrated by late-stage cyanation and synthesis of lersivirine. We anticipate that this palladium-catalyzed cyanation will be readily integrated into the fields of pharmaceutical and academic research.

**ASSOCIATED CONTENT**

 Supporting Information

Experimental procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): MIT holds or has filed patents on some of the ligands and precatalysts used in this work, for which S.L.B. receives royalty payments.

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**REFERENCES**

(1) Höller, C. J.; Müller-Buschbaum, K. *Inorg. Chem.* 2008, 47, 10141−10149.

(2) Goujon, L. J.; Khalidi, A.; Maziz, A.; Plesse, C.; Nguyen, G. T. M.; Aubert, P.-H.; Vidal, F.; Chevrot, C.; Teyssie, D. *Macromolecules* 2011, 44, 9685−9691.

(3) An, M.; Sarker, A. K.; Jung, D. C.; Hong, J. D. *B. Korean Chem. Soc.* 2011, 32, 2083−2086.

(4) Song, H. Y.; Yang, J. Y.; Suh, J. W.; Lee, H. S. J. *Agric. Food Chem.* 2011, 59, 7759−7764.

(5) F. Fleming, F. Nat. Prod. Rep. 1999, 16, 597−606.

(6) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. J. *Med. Chem.* 2010, 53, 7902−7917.

(7) (a) Patterson, A. W.; Wood, W. J. L.; Hornsby, M.; Lesley, S.; Spaggon, G.; Ellman, J. A. *J. Med. Chem.* 2006, 49, 6298−6307. (b) Boyd, M. J.; Crang, S. N.; Robichaud, J.; Scheigeta, J.; Black, W. C.; Chauret, N.; Wang, Q.; Massé, F.; Oballa, R. M. *Bioorg. Med. Chem. Lett.* 2009, 19, 675−679.

(8) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* 1995, 95, 2457−2483. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* 2004, 2419−2440.

(9) Negishi, E.; Hu, Q.; Huang, Z. H.; Qian, M. X.; Wang, G. W. *Aldrichimica Acta* 2005, 38, 71−88. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* 2008, 41, 1461−1473. (e) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem.* Int. Ed. 2012, 51, 5062−5085.

(10) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Oka, S. *Chem. Lett.* 1973, 2, 471−474.

(11) For a nickel-catalyzed cyanation, see: (a) Cassar, L. J. *Organomet. Chem.* 1973, 54, C57−C58. For copper-catalyzed cyanations, see: (b) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* 2003, 125, 2890−2891. (c) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* 2005, 11, 2483−2492. (d) Schareina, T.; Zapf, A.; Magerlein, W.; Müller, N.; Beller, M. *Chem.—Eur. J.* 2007, 13, 6249−6254.

(12) (a) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. J. *Organomet. Chem.* 2003, 684, 50−55. (b) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* 2003, 42, 1661−1664. (c) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* 2004, 1388−1389.

(13) (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* 2011, 40, 5049−5067. (b) Shim, Y. J.; Lee, H. J.; Park, S. *J. Organomet. Chem.* 2012, 696, 4173−4178. (c) Zhang, D.; Sun, H.; Zhang, L.; Zhou, Y.; Li, C.; Jiang, H.; Chen, K.; Liu, H. *Chem. Commun.* 2012, 48, 2909−2911. (d) Zou, T.; Feng, X.; Liu, H.; Yu, X.; Yamamoto, Y.; Bao, M. *RSC Adv.* 2013, 3, 20373−20384.

(14) For the use of benzyl cyanide as the cyanide source, see: Wen, Q.; Jin, J.; Hu, B.; Lu, P.; Wang, Y. *RSC Adv.* 2012, 2, 6167−6169.

(15) For a palladium-catalyzed cyanation of aryl halides at 65 °C and heteroarylhalides at 80 °C, see: (a) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wespieke, J. P. *J. Org. Chem.* 1998, 63, 8224−8228. For a palladium-catalyzed cyanation of aryl halides at 56 °C, see: (b) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C. Y. *Org. Lett.* 2004, 6, 3723−3725. For palladium-catalyzed cyanation at 50 °C for aromatic bromides, see: (c) Yeung, P. Y.; Tsang, C. P.; Kwong, F. Y. *Tetrahedron Lett.* 2011, 52, 7038−7041.

(16) Klinkenberg, J. L.; Hartwig, J. F. *J. Am. Chem. Soc.* 2012, 134, 5758−5761.

(17) For the palladium-catalyzed cyanation of aryl halides at 50−80 °C, see ref 14. These examples include mainly aryl halides. Six-membered heterocycles needed to be heated to 80 °C to achieve a large substrate scope (ref 14a). Additionally, these reports do not contain any examples of five-membered heterocycles.

(18) For a room-temperature cyanation of aryl bromides and aryl iodides with Zn(CN)2 in the presence of Pd2(dba)2/PhBu3, see: Ramnauth, J.; Bhandraj, N.; Renton, P.; Rakhit, S.; Maddaford, S. P. *Synlett* 2003, 2237−2239. This reaction uses an air-sensitive P-Bu3 ligand, higher catalyst loadings (5 mol %), an excess of Zn(CN)2 (1.8 equiv), and additional zinc. The substrate scope only includes aryl bromides and iodides, and there are no examples of five- or six-membered heterocycles.

(19) (a) Abel-Malak, M.; Gallati, C.; Moussa, S. A. *Drug Future* 2008, 33, 691−699. (b) Fäktenheuer, G.; Stasewski, S.; Flottenburg, A.; Hackman, F.; Layton, G.; McFadyen, L.; Davis, J.; Jenkins, T. M. *AIDS* 2009, 23, 2115−2122.

(20) (a) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* 2013, 15, 2876−2879. (b) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* 2013, 4, 916−920.

(21) See the Supporting Information for more details.

(22) Although ary1 chlorides can be utilized for the cyanation of aryl rings with electron-withdrawing substitution, electron-donating substituents gave poor conversion (∼10%) after 18 h. Full conversion was observed with the corresponding aryl bromide. For consistency, we examined the complete substrate scope with hetero(aryl) bromides.

(23) See Scheme 3 parenthesis yields. Decreasing the reaction molarity from 0.33 to 0.2 M was necessary to achieve full conversion for 3b and 4a.

(24) (a) Waters, L.; John, L.; Nelson, M. *Int. J. Clin. Pract.* 2007, 61, 105−118. (b) Nurtudinova, D.; Overton, E. T. *Expert Opin. Drug Safety* 2009, 8, 683−694.