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# Direct Palladium(II)-Catalyzed Synthesis of Arylamidines from Aryltrifluoroborates

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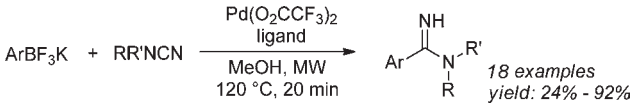
## ABSTRACT




**A fast and convenient synthesis of arylamidines starting from readily available potassium aryltrifluoroborates and cyanamides is reported. The coupling was achieved by Pd(II)-catalysis in a one step 20 min microwave protocol using $Pd(O_2CCF_3)$, 6-methyl-2,2′-bipyridyl, TFA, and MeOH, providing the corresponding arylamidines in moderate to excellent yields.**

Amidines[1] represent an important pharmacophore in drug discovery and can be found in DNA and RNA binding diamidine diminazene,[2] ASIC inhibitors,[3] muscarinic agonists for the treatment of Alzheimer's disease,[4] platelet aggregation inhibitors,[5] and, recently, serine protease inhibitors,[6] to give a few examples. Amidines are also useful precursors in the formation of various heterocyclic ring systems, e.g. quinazolines,[7] quinazolinones,[8] pyrimidines,[9] triazoles,[10] and benzimidazoles.[11] Typically, amidines are prepared from nitrile containing precursors via nucleophilic addition of a suitable amine. Similarly, amidines can also be accessed by nucleophilic amino substitution of thioamides or imidates.[12] There are also Pd(0)-catalyzed three-component methods,[13] and recently, a direct aryne insertion into thioureas was reported.[14]

We and others have previously developed Pd(II)-catalyzed protocols for the generation and insertion of an arylpalladium species into the polar nitrile bond.[15,16] This methodology has been used to generate arylketones, via a ketimine intermediate, from arylboronic acids, benzoic acids, arylsulfinates, and arenes. We hypothesized that a similar approach, starting from an appropriate arylpalladium(II) precursor and a cyanamide, could be used for facile preparation of arylamidines from readily available arylborons and

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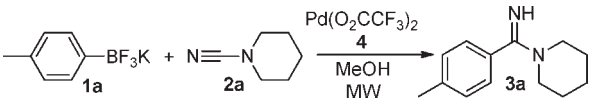
cyanamides. This would represent a powerful new and direct carbon−carbon bond forming method for the formation of this important functional group.

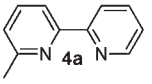
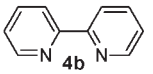
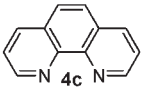
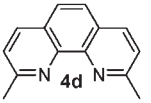
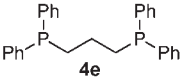
The investigation was initiated by evaluating potassium aryltrifluoroborates ($ArBF_3K$) as the aryl source.[17] These, readily prepared,[18] commercially available protected arylboronic acids are of interest due to a longer shelf life together with improved practical handling. In addition, they have been proven to undergo transmetalation with limited interference from competitive protodeboronation.[19]

We initiated our study employing the catalytic system previously reported for the 1,2-carbopalladation of nitriles[15i,h] but switched to methanol as the solvent to facilitate activation of the aryltrifluoroborates.[20] A test reaction was conducted with 4% $Pd(O_2CCF_3)$ and 6% 6-methyl-2,2′-bipyridyl as the catalytic system, potassium 4-methylphenyltrifluoroborate, 2 equiv of cyanamide, and 5 equiv TFA in methanol. The mixture was microwave (MW) irradiated[21] for 20 min in a sealed vial at 120 °C and to our delight furnished full conversion of the yield determining **1a** and concomitant formation of the arylamidine product **3y** according to $^1$H NMR analysis. A small optimization of the reaction conditions was then undertaken, revealing that the TFA excess could be reduced to 2 equiv without reducing the productivity. The outcome was monitored by $^1$H NMR analysis of the crude product mixture after MW processing. Furthermore, the cyanamide was replaced with 1-piperidinecarbonitrile to enable a more straightforward detection of aliphatic protons in the substrate. In order to simplify the purification,[22] the stoichiometry was reversed and the excess of $ArBF_3K$ was reduced to 1.1 equiv.

Based upon these conditions a final ligand screen was performed (Table 1). Similar yields of 88% and 86%, respectively, were isolated from the related bipyridyl ligands **4a** and **4b** (entries 1 and 3). The more rigid ligand **4c** was found to reduce the isolated yield down to 69% (entry 4). Surprisingly the two additional 2,9-methyl substituents on **4d** totally suppressed the conversion of **1a**, furnishing only trace amounts of product **3a** (entry 5). A similar lack of reactivity was found with the phosphine based ligand **4e** (entry 6). Finally, three reference reactions were performed

**Table 1.** Ligand Screen




| entry | ligand | yield[a] |
|---|---|---|
| 1 |  **4a** | 88% |
| 2 | **4a** | traces[b] |
| 3 |  **4b** | 86% |
| 4 |  **4c** | 69% |
| 5 |  **4d** | traces |
| 6 |  **4e** | n.d. |
| 7 | no ligand | n.d. |
| 8 | **4a** | n.d.[c] |

[a] Isolated yield. Reaction conditions: $Pd(O_2CCF_3)_2$ (0.04 mmol), ligand **4** (0.06 mmol), TFA (2 mmol), $ArBF_3K$ **1a** (1.1 mmol), cyanamide **2a** (1 mmol), and MeOH (3 mL), heated by MW in a sealed vial at 120 °C for 20 min. [b] Without TFA. [c] Without $Pd(O_2CCF_3)_2$. n.d.: Product was not detected by LC-MS.

demonstrating the importance of TFA, ligand and Pd (entries 2, 7 and 8).

After the identification of highly productive reaction conditions (Table 1, entry 1), we next set about exploring the scope and limitations of the protocol. Thus, a set of various potassium aryltrifluoroborates was investigated, and the results are presented in Table 2. The electron-rich aryltrifluoroborates **1b** and **1c** performed well, producing the corresponding amidines **3b** and **3c** in 86% and 74% yield, respectively (Table 2, entries 1, 2).

Phenyltrifluoroborate also proved to be a productive substrate, giving benzamidine (**3d**) in 73% isolated yield (Table 2, entry 5). Pleasingly, full chemoselectivity was observed in the reaction of **1e** (Table 2, entry 6) furnishing 63% of **3e**, and no traces of byproduct resulting from Pd(0) mediated oxidative addition of the aryl bromide were detected.

Unfortunately, the electron-deficient aryltrifluoroborate **1f** (Table 2, entry 7) provided **3f** in only a moderate yield of 37% and only trace amounts of product were observed with the strongly electron-deficient substrate **1g** (entry 8). The lower yields of these electron-deficient arylating agents might be explained by a slower insertion

(17) (a) Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (c) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

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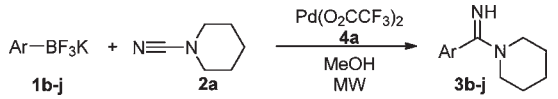
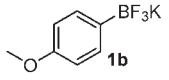
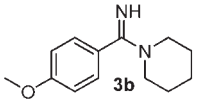
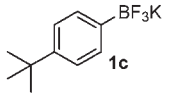
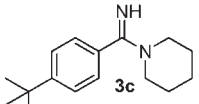
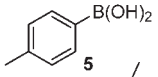
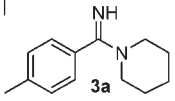
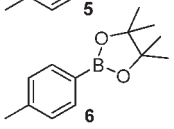
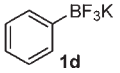
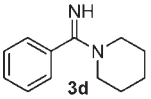
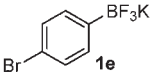
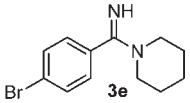
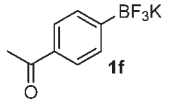
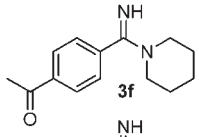
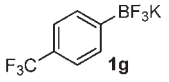
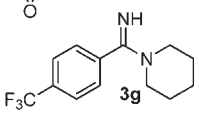
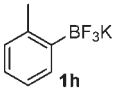
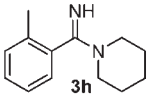
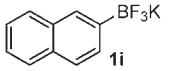
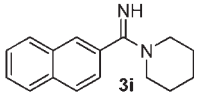
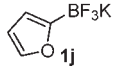
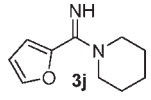
(21) Nilsson, P.; Olofsson, K.; Larhed, M. *Top. Curr. Chem.* **2006**, *266*, 103.

(22) All products were purified by a simple extraction of the crude mixture: 20 mL of DCM were extracted three times with 20 mL of sat. $NaHCO_3$ aq. The combined aqueous phases were basified to pH ~14 by the addition of NaOH and extracted three times with 60 mL of DCM. The combined organic phases were concentrated to provide the pure arylamidines.

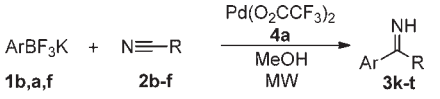
**Table 2.** Scope of the Aryltrifluoroborates in the Reaction with 1-Piperidinecarbonitrile

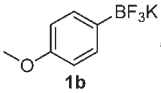
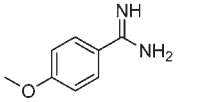
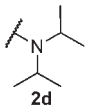
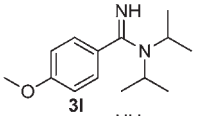
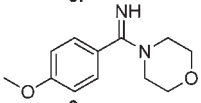
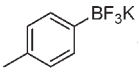
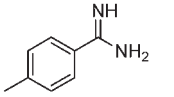
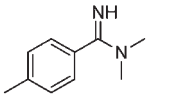
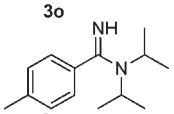
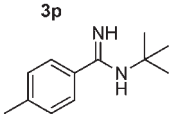



| entry | Ar-$BF_3K$ | product | yield[a] |
|---|---|---|---|
| 1 |  **1b** |  **3b** | 86% |
| 2 |  **1c** |  **3c** | 74% |
| 3 |  **5** |  **3a** | 33%[b] |
| 4 |  **6** | **3a** | 45%[c] |
| 5 |  **1d** |  **3d** | 73% |
| 6 |  **1e** |  **3e** | 63% |
| 7 |  **1f** |  **3f** | 37% |
| 8 |  **1g** |  **3g** | Trace |
| 9 |  **1h** |  **3h** | 66% |
| 10 |  **1i** |  **3i** | 40% |
| 11 |  **1j** |  **3j** | 66% |

[a] Isolated yield. Reaction conditions: $Pd(O_2CCF_3)_2$ (0.04 mmol), ligand **4a** (0.06 mmol), TFA (2 mmol), $ArBF_3K$ **1b**–**j** (1.1 mmol), cyanamide **2a** (1 mmol), and MeOH (3 mL), heated by MW in a sealed vial at 120 °C for 20 min. [b] 4-Methylphenylboronic acid was used instead of $ArBF_3K$. [c] 4-Methylphenylboronic acid pinacol ester was used instead of $ArBF_3K$.

**Table 3.** Scope of Cyanamides with Different Aryltrifluoroborates




| entry | $ArBF_3K$ | R | product | yield[a] |
|---|---|---|---|---|
| 1 |  **1b** |  **2b** |  **3k** | 70% |
| 2 | **1b** |  **2d** |  **3l** | 31% |
| 3 | **1b** |  **2f** |  **3m** | 92% |
| 4 |  **1a** |  **2b** |  **3n** | 73% |
| 5 | **1a** |  **2c** |  **3o** | 82% |
| 6 | **1a** |  **2d** |  **3p** | 24% |
| 7 | **1a** |  **2e** |  **3q** | 64% |
| 8 | **1a** |  **2f** |  **3r** | 58% |
| 9 |  **1f** |  **2b** |  **3s** | Trace |
| 10 | **1f** |  **2f** |  **3t** | 33% |

[a] Isolated yield. Reaction conditions: $Pd(O_2CCF_3)_2$ (0.04 mmol), ligand **4a** (0.06 mmol), TFA (2 mmol), $ArBF_3K$ **1a,b,f** (1.1 mmol), cyanamide **2b**–**f** (1 mmol), and MeOH (3 mL), heated by MW in a sealed vial at 120 °C for 20 min.

rate and a subsequent increase in the amount of byproduct resulting from protodeboronation and homocoupling. Surprisingly, 2-naphthyltrifluoroborate **1i** afforded a somewhat lower yield of **3i** (40%), mainly due to the competing protodeboronation. Finally, the *ortho*-substituted **1h** (Table 2, entry 9) and the heterocyclic **1j** both gave reasonable yields of **3h** and **3j** (66% each), indicating that the protocol has a tolerance for steric hindrance, as well as a heteroatom. The 4-methylphenylboronic acid **5** and the corresponding pinacol ester derivative **6** (Table 2, entries 3 and 4) were both evaluated under these conditions, providing a significantly lower yield (33% and 45%, respectively) of **3a** compared with the corresponding $ArBF_3K$, **1a** (88%).

Next, we extended the scope of the cyanamide substrate to include unsubstituted cyanamide **2b**, the disubstituted **2c**–**d**, and cyclic **2f**. Cyanamide (**2b**) was a productive substrate, producing the unsubstituted amidines **3k** (70%) and **3n** (73%) in good isolated yields (entries 1, 4) but only trace amounts of the electron-poor **3s** (entry 9). The bulky diisopropylcyanamide **2d** furnished only moderate yields of product **3l** (31%) and **3p** (24%), presumably due to unfavorable steric effects. The cyclic cyanamide **2f** (Table 3, entries 3, 8, and 10) performed well, giving excellent to moderate yields of the desired amidine products **3m** (92%), **3r** (58%), and **3t** (33%). The dimethylcyanamide **2c** (entry 5) was also well tolerated affording an excellent 82% isolated yield of the desired product **3o**. Interestingly, the presence of one bulky *tert*-butyl substituent as in **2e** had only a minor influence on the reaction outcome, yielding 64% of **3q** (Table 3, entry 7). Once again, the reaction was found to be dependent upon the electronic nature of the aryltrifluoroborate, with the electron-rich substrates **1a**–**b** affording consistently higher yields than the electron-poor substrate **1f**.

A plausible catalytic cycle, as adapted from the mechanistic studies performed on the Pd(II)-catalyzed alkylnitrile insertion reactions,[15h,i] is depicted in Figure 1. Starting with the ligand coordinated Pd(II)-complex **A**, transmetalation occurs with an arylboronate to generate the arylpalladium intermediate **B**. Next, ligand exchange to furnish the cyanamide coordinated complex **C**, followed by a 1,2 carbopalladation into the nitrile bond, affords complex **D**. Finally, the protonation of the charged amidine by TFA liberates the free amidine and Pd(II) species **A**.

In conclusion, we have developed a novel and convenient approach for the direct formation of arylamidines, furnishing both substituted and unsubstituted amidines in excellent to acceptable yields. However, the electron-deficient aryltrifluoroborates afforded low productivity under these conditions, and further developments to improve the scope of this methodology are ongoing in our laboratory.

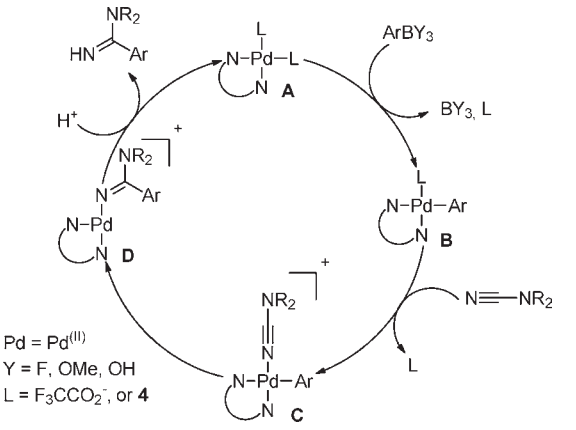



**Figure 1.** Proposed catalytic cycle.

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**Supporting Information Available.** General experimental procedures, characterization data and copies of $^{1}H$ and $^{13}C$ NMR spectra of all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.