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

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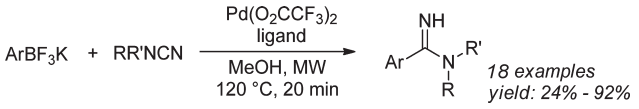
ABSTRACT



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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(2) Clement, B.; Immel, M.; Raether, W. *Arzneim.-Forsch.* **1992**, *42–2*, 1497.
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(16) For examples involving rhodium catalysis, see: (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (b) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339. (c) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, *3*, 217.

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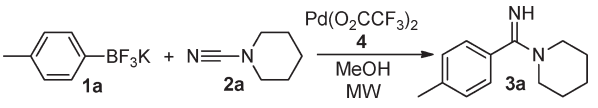
cyanamides. This would represent a powerful new and direct carbon−carbon bond forming method for the formation of this important functional group.

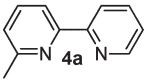
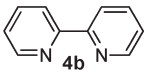
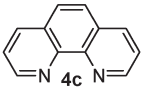
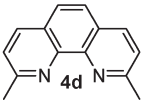
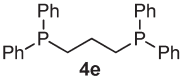
The investigation was initiated by evaluating potassium aryltrifluoroborates ($ArBF_3K$) as the aryl source.[17] These, readily prepared,[18] commercially available protected arylboronic acids are of interest due to a longer shelf life together with improved practical handling. In addition, they have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

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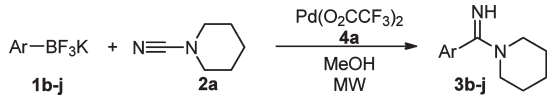
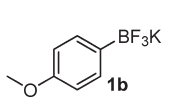
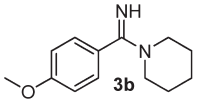
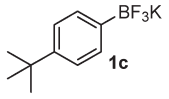
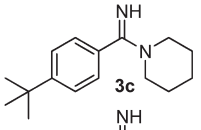
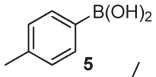
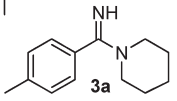
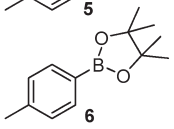
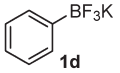
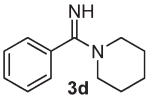
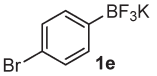
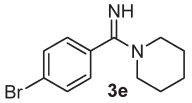
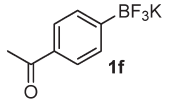
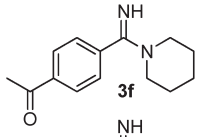
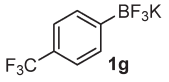
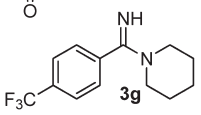
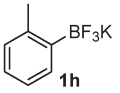
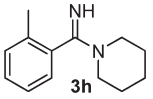
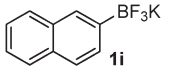
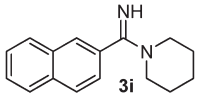
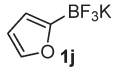
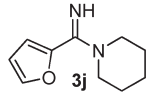
(21) Nilsson, P.; Olofsson, K.; Larhed, M. *Top. Curr. Chem.* **2006**, *266*, 103.

(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.

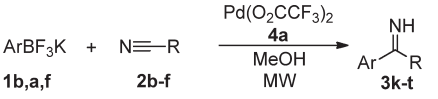
Table 2. Scope of the Aryltrifluoroborates in the Reaction with 1-Piperidinecarbonitrile

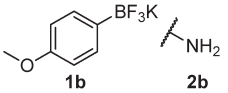
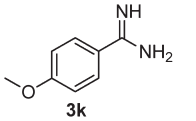
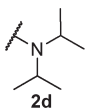
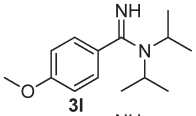
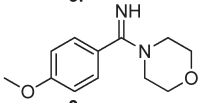
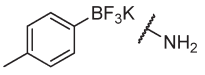
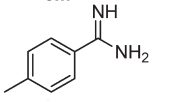
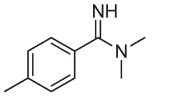
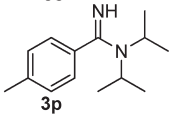
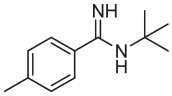


entry	Ar-BF_3K	product	yield[a]
1	 **1b**	 **3b**	86%
2	 **1c**	 **3c**	74%
3	 **5**	 **3a**	33%[b]
4	 **6**	**3a**	45%[c]
5	 **1d**	 **3d**	73%
6	 **1e**	 **3e**	63%
7	 **1f**	 **3f**	37%
8	 **1g**	 **3g**	Trace
9	 **1h**	 **3h**	66%
10	 **1i**	 **3i**	40%
11	 **1j**	 **3j**	66%

[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.

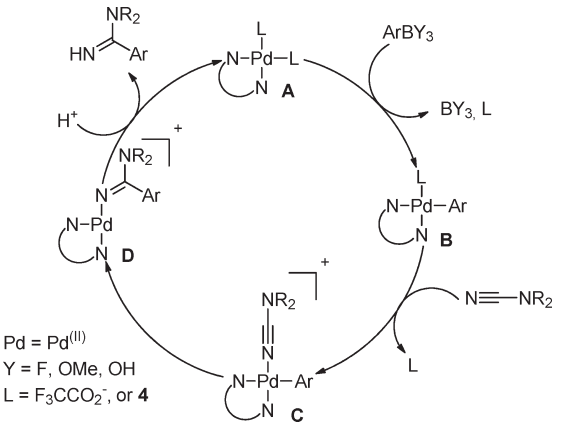


Figure 1. Proposed catalytic cycle.

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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.