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Rapid Pd-Catalyzed Synthesis of Piperazine Scaffolds Under Aerobic and Solvent-Free Conditions

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Abstract

A facile Pd-catalyzed methodology providing an efficient synthetic route to biologically relevant arylpiperazines under aerobic conditions is reported. Electron donating and sterically inducing aryl chlorides were aminated to afford yields up to 97%, with examples using piperazine as solvent, illustrating an eco-friendly, cost-effective synthesis of these privileged structures.

Graphical abstract

N-Arylpiperazine moieties are prevalent in a vast amount of biologically-active compounds¹ which display various pharmacological activities such as antiproliferative,² antidepressant,³ anti-retroviral therapy of HIV,⁴ antimalarial,⁵ anti-Parkinsons,⁶ anti-anxiety⁷ and dopamine selective properties,⁸ and represent a potential gateway in combating substance abuse and dementia (Figure 1).⁹ In 2001 alone, the MDDR (MDL Drug Data Report) contained 2271 phenyl-piperazines, with 16 accounting for marketed drugs, while 23 were in phase II/III clinical trials across 18 therapeutic areas.¹⁰ Furthermore, aripiprazole (AblifyTM) earned more than \$7.9 billion in 2015, making it the second highest selling medication after holding the top spot in 2014.¹¹ Therefore, synthesis and implementation of this privileged structure continues to play a vital role in drug development.

Traditional synthesis of *N*-arylpiperazines requires the appropriate aniline precursor and bis(2-chloroethyl)amine hydrochloride.¹² However, this synthetic method involves elevated temperatures, extended reaction times up to 24 hours, and is hampered by costly substituted anilines. Examples of microwave-assisted synthesis of *N*-arylpiperazines have been reported, but they too require substituted anilines¹³ and amine protecting groups.^{13b} The Buchwald-

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedure, NMR and mass spectral data of the isolated products (PDF)

Hartwig amination provides an attractive alternative via Pd-catalyzed C–N bond formation of aryl halides and amines.¹⁴ This catalysis has been applied to developing many bioactive compounds, and is currently the only reported methodology to facilitate a key step in the synthesis of Zykadia™, a drug for treating lung cancer.¹⁵ In 2008, Buchwald and co-workers reported 10 minute C–N cross coupling reactions with aryl chlorides using air- and moisture-stable Pd-precatalysts (Figure 2).¹⁶ To our knowledge, there have been no reports extending this 10 minute catalysis to a broad scope synthesis of *N*-arylpiperazines.

Compared to other examples of Pd-catalyzed *N*-arylpiperazine synthesis,¹⁷ this methodology would not require anhydrous solvents, an inert atmosphere, and would be applicable to notoriously unreactive, electron-rich and sterically-congested aryl chlorides. In this report, we provide a 10 minute, benchtop synthesis demonstrating a wide scope with readily available aryl and *N*-heterocyclic chlorides. We also include eco-friendly examples of using piperazine as solvent, affording modest to good yields. This methodology will assist in the development of structurally diverse and sterically demanding, *N*-arylpiperazine compounds having a wide range of biological activity.

Initial efforts to optimize piperazine *N*-arylation were conducted with **A** and **B** following previously reported conditions with 1.5 equiv of piperazine.¹⁸ Although minimal aryl chloride was detected by LCMS after 10 min, a significant amount of the undesirable bis-arylated piperazine was observed. After exhausting other solvents and catalyst loading options, a 2:1 ratio of RuPhos/Pd₂(dba)₃ consistently provided moderate to high yields of the mono-arylated piperazine in 10 min. With optimized conditions in hand, a broad range of electron rich and deficient aryl chlorides were investigated (Table 1). Screening was limited to chloride substrates due to the economic value of these commercially-available reagents, compared to bromides and iodides. It is worth noting, no additional product formation was observed beyond the 10 min reaction time, unless otherwise noted. Milder base (Cs₂CO₃) was examined throughout the aryl chloride scope (Table 1), however lower yields were obtained compared to trials conducted with NaO^tBu.

Investigation began with a series of anisoles, affording the desired products **2a-b** in good yield; however, only a 66% yield was obtained with strongly deactivated **1c**. The base sensitivity of the trifluoromethyl ether substituent on **1d** required reducing the NaO^tBu to 1.1 equiv to obtain a good yield of **2d**. The reaction conditions were also applied to synthesize **2e**, a key intermediate in the development of fluorinated D₃ dopamine receptor ligands for positron emission tomography (PET) imaging studies,¹⁹ currently ongoing in our lab. Catalytic activity was impeded with sterically crowded **1g**; however, a modest 62% isolated yield was still obtained in 10 min (**2g**).

Functional group compatibility was further explored to determine the tolerance of these substituents in the current reaction conditions. No product formation was observed with **1h**, potentially due to coordination of the thiol substituent to the Pd-center, thus inhibiting catalytic activity. When using 1.1 equiv of the alkoxide base, nitro arene **2i** was isolated in 86% yield, while other electron-poor aryl chlorides **1j-l** provided excellent yields as well. The reaction conditions also provided access to chloro-containing *N*-arylpiperazines, motifs found in many antipsychotics,²⁰ in good yield (**2m-n**). However, only a 37% yield of **2o** was

obtained due to side-product formation with the tri-chloro substrate **1o**. Lastly, substrate **1p** was investigated using 1.5 equiv of milder base Cs₂CO₃ to determine if non-aryl substrates were compatible to the illustrated reaction conditions. Indeed, the desired piperazine motif, present in Ciladopa, was afforded at a 75% yield (**2p**).

Nitrogen heterocycles were then investigated as these N-arylpiperazine scaffolds are commonly found in many medically-relevant compounds (Table 2).²¹ The high yields obtained with N-aryl chlorides matched previously reported trends of faster reductive elimination rates to form carbon–nitrogen bonds from Pd-complexes containing a heteroaromatic ring.²² For example, a yield of 94% was obtained with **3a** and excellent yields of **4c–e** were afforded with milder base Cs₂CO₃. The scope was expanded beyond six-membered heteroaromatic rings (**3g–h**), to include 2-chloroquinoline, affording the serotonin receptor agonist,³ Quipazine, in 93% yield (**4h**). Excellent yields were also obtained with benzothiazole and benzoxazole chlorides (**3i–j**), compounds with anti-cancer²³ and antipsychotic²⁴ properties, respectively. However, sluggish reactivity was observed with the five-membered heterocycle 2-chlorooxazole (**3k**), despite extending the reaction time beyond 10 min. Lower reactivity of five-membered heterocyclic electrophiles has previously been reported due to the electronic properties of certain ring positions which can be unfavorable for Pd-catalyzed coupling.²⁵

Lastly, we wanted to investigate a solvent-free arylation of piperazine to demonstrate a “green” amination procedure (Table 3). While the Buchwald-Hartwig remains a dominant tool in C–N bond formation, reports illustrating solvent-free conditions are rare.²⁶ Of those reports, only one example of unprotected piperazine has been examined, resulting in a high yield of the bis-arylated product.^{26g} After optimizing piperazine equivalents with **2b**, we were able to obtain modest yields of the desired mono-arylated products with selected chloride substrates. Although the afforded isolated yields are lower than those listed in Table 1 and 2, mainly due to bis-arylation, this method provides a more eco-friendly alternative by eliminating the need for potentially hazardous solvents.

In conclusion, excellent yields of arylpiperazines were obtained in a one-pot, 10 min Buchwald-Hartwig amination, under aerobic conditions. Moderate to good yields were also obtained when conducting the reactions neat in piperazine, demonstrating an eco-friendly application to this catalysis. Finally, this procedure eliminates reaction times of many hours, and provides an efficient and vastly synthetically useful methodology in developing complex piperazine scaffolds of biological and pharmaceutical interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Bioactive compounds containing cyclic and arylpiperazine scaffolds

Figure 2.
Pd-precatalyst (**A**) and RuPhos (**B**)

Table 1

Piperazine Arylation Scope with Aryl Chlorides^a

Table 2

Piperazine Arylation Scope with *N*-Aryl Chlorides^a

Table 3

Piperazine Arylation Conducted Neat^a

^aConditions: Pd₂(dba)₃ (1 mol %), **B** (2 mol %), substrate (1 mmol), piperazine (2.5 equiv), NaO^tBu (1.5 equiv), 10 min. Isolated yields. Reaction monitored by LCMS. ^b1.2 equiv of NaO^tBu used as base. ^c1.5 equiv of Cs₂CO₃ used as base. ^dReaction time extended to 30 min.