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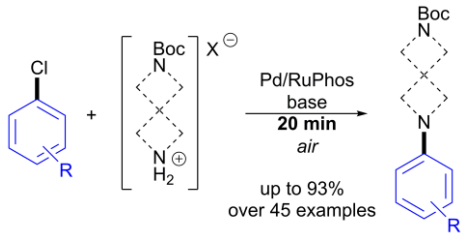

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Pd-catalyzed arylation of linear and angular spirodiamine salts under aerobic conditions

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ABSTRACT

Application of Buchwald-Hartwig catalysis for development of biologically relevant arylspirodiamine compounds is reported. This synthetic methodology requires no inert atmosphere and affords yields up to 93% in just 20 min. Linear and sterically hindered angular spirodiamines in salt and free-base form are coupled with electron-rich and -withdrawing aryl chlorides, demonstrating a broad scope and applicability of this protocol.

Introduction

Spirocylic scaffolds are structurally diverse compounds with broad applications throughout drug discovery,[1] chiral ligand development,[2] and organocatalysts for asymmetric synthesis.[3] Reports containing these privileged structures have grown exponentially in the past 10 years alone due to the advantageous structural and pharmacological properties of these motiffs.[4] The unique three-dimensional complexity of these compounds, measured by Fsp^3 (fraction of sp^3 carbon hybridization), correlates to increased physiochemical and biological properties, due to the enhanced selectivity of targeted proteins.[5] Thus, spirodiamine cores, most notably arylspiroalkanes (Figure 1), are present in many biologically active compounds[6] with reported antipsychotic,[7] anti-insomnia,[8] age-related macular degeneration (AMD),[9] and anti-viral[10] properties, among others.[1d, 9, 11]

Despite the many examples of biologically active compounds containing arylspirodiamine scaffolds, reports illustrating the synthesis thereof are exceedingly rare. One attractive approach is the Hartwig-Buchwald amination, a powerful synthetic tool in C–N bond formation, thereby providing a direct approach to aryl amines.[12] However, to our knowledge, the only report applying this catalysis to a broad scope of spirodiamine compounds was disclosed by Carreira and co-workers in 2008, which entailed anaerobic conditions and extended reaction times up to 46 h.[13] A protocol that does not necessitate prolonged reactions times or an inert atmosphere would undoubtedly assist in furthering the development of arylspirodiamine stuctures.

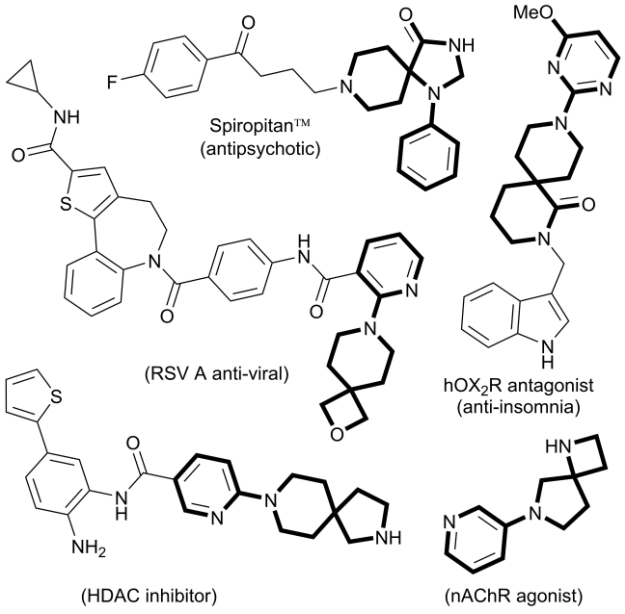

Figure 1. Arylspirodiamine scaffolds in compounds with pharmacological properties.

Previous work by Buchwald and co-workers illustrated highly active Pd catalysts bearing biarylphosphine ligands in C–N cross-coupling of aryl halides and secondary amines.[14] Inspired by these reports, we developed an aerobic piperazine arlyation protocol using precatalyst system $Pd_2(dba)_3$ and air- and

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moisture-stable biarylphosphine ligand RuPhos.[15] This bench-top method affords excellent yields of the mono-arylated product in just 10 min and eliminates the need for an inert atmosphere and anhydrous solvents. More impressively, we found this Pd-ligand system to be highly efficient in coupling notoriously unreactive electron-rich aryl chlorides in short reaction times as well. Described herein is an extension of this methodology to include arylation of commercially available linear and angular spirodiamine salt and free-base compounds **A**-**H** (Figure 2).

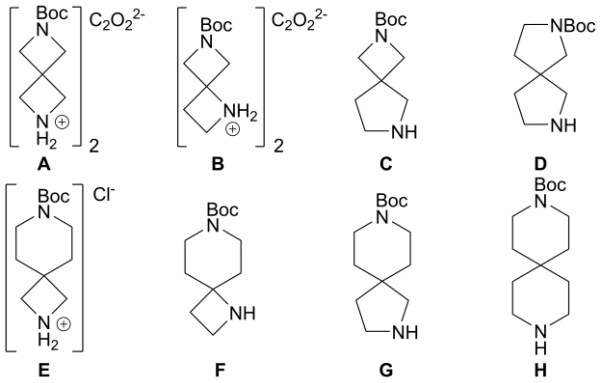


Figure 2. Spirodiamine compounds examined.

Currently, we have been examining **A** as a potential surrogate for piperazine due to the unique structural space the diamine can populate owing to the distinctive spirocyclic framework (Figure 3). Furthermore, pharmacokinetic properties, such as lipophilicity and metabolic stability of biologically relevant compounds can be advantageously modified by incorporation of **A**, along with analogous spiro[3.3]heptane structures, thus, providing an attractive alternative to piperazine, piperidines, and morpholine parent compounds.[16] In order to develop a library of arylated spirodiamine **A** compounds in an efficient and practical time-scale, we applied modified reaction conditions from our previous Pd-catalyzed C–N cross-coupling report outlined in Scheme 1.

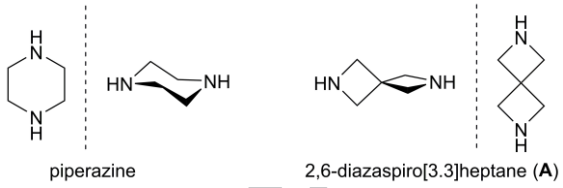
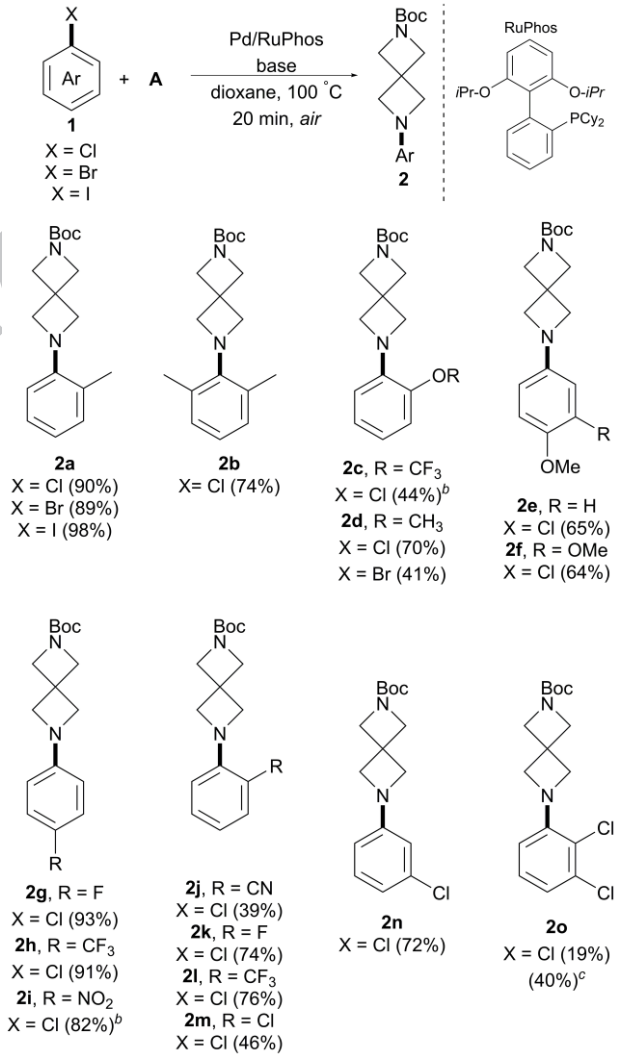


Figure 3 Structural comparison of piperazine and 2,6-diazaspiro[3.3]heptane (**A**).

We began our investigation by examining **1a** halide derivatives to determine if the outlined one-pot reaction conditions could be expanded beyond aryl chlorides. Amination of **1a** substrates proceeded smoothly in each trial run, affording comparable **2a** yields to previous Pd-catalyzed arylation report in which a higher catalyst loading, along with 21 h reaction time, were required.[13] Sterically congested and electron-rich **1b** was efficiently coupled with **A** to afford **2b** at 74%. Reaction conditions were tolerable for trifluoromethoxy functional group, **1c**, providing a synthetically useful 44% yield. Substrates 2-chloro and 2-bromo anisole were both examined, with 2-chloroanisol providing a higher **2d** product yield. Impressive C–N cross-coupling activity was also observed with extremely electron-rich **1f**, yielding 64% in just 20 min.

As expected, *para*-substituted electron-deficient aryl chlorides provided excellent yields including NO_2 substituted **1i**. However, a noticeable decrease in C–N cross-coupling activity was observed with *ortho*-substituted electron-withdrawing functional groups. For example, only 39% of the desired product **2j** was afforded when compared to the higher yields obtained with substrates containing electron-donating substituents, traditionally less reactive substrates, in the *ortho* position (**1a-b** and **1d**). We then examined if **1k-l** would also result in a decrease in activity after affording excellent yields with analogous *para*-substituted aryl chlorides **1g-h**. Indeed, reaction yields dropped to 74% and 76% for **2k** and **2l**, respectively, demonstrating a consistent trend in diminished cross-coupling activity with aryl chlorides containing *ortho*-substituted electron-withdrawing groups. Nonetheless, this method provides a more efficient route to **2l**, compared to the 38% yield obtained in 24 h reaction time reported by Petrukhin and co-workers.[9] Arylspirodiamine chlorides **2m-o** accessed using reported conditions further demonstrates the synthetic versatility of this protocol with di- and tri-chloro aryl substrates. A higher yield of **2o** was achieved by increasing the Pd/Ruphos loading to 2 mol% and 4 mol%, respectively, and using **1o** in slight excess.

Scheme 1 Arylation of **A** with aryl chlorides[a]

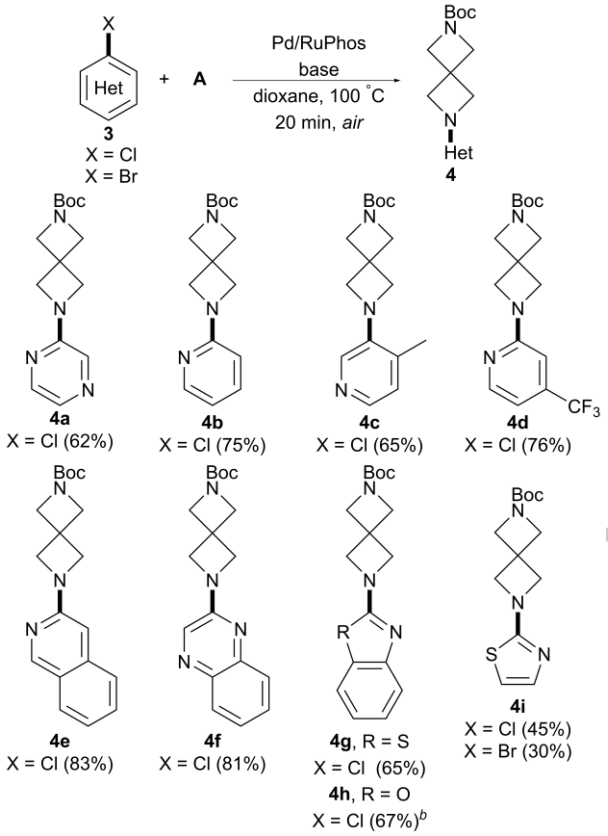


[a]Conditions: $Pd_2(dba)_3$ (1 mol %), RuPhos (2 mol %), aryl chloride (0.5 mmol), **A** (0.55 mmol), NaO*t*-Bu (3.0 equiv), and dioxane (1.5 mL), 20 min. Isolated yields. Reaction monitored by LCMS. [b]2.5 equiv of NaO*t*-Bu was used. [c]$Pd_2(dba)_3$ (2 mol %), RuPhos (4 mol %), **1o** (1.1 mmol), **A** (1.0 mmol), NaO*t*-Bu (3.0 equiv), and dioxane (3.0 mL), 20 min.

We next investigated if conditions would be tolerable with *N*-aryl chlorides due to the prevalence of nitrogen heterocycles biologically active compounds (Scheme 2). The coupling of 2-chloropyrazine was met with modest activity, yielding 62% of the desired product **4a**. A comparable yield of **4b** was obtained at a faster rate and lower catalyst loading than those previously

reported by Carreira under anaerobic conditions.[13] Electron-rich and –poor pyridine chlorides were also well tolerated, as good yields were afforded for both products, **4c**-**d**. Screening continued with bicyclic *N*-aryl chlorides quinolone and quinoxaline, obtaining **4e**-**f** in excellent yields. Efficient coupling continued with benzothiazole and benzooxazxole substrates, **3g**-**h**, compounds with known anti-cancer[17] and antipsychotic properties[18], respectively. We briefly examined 5-membered heterocycle rings with the chloro and bromo variants of **3i**, affording respectable yields for the aminated thiazole product.

Scheme 2 Arylation of **A** with *N*-aryl chlorides[a]

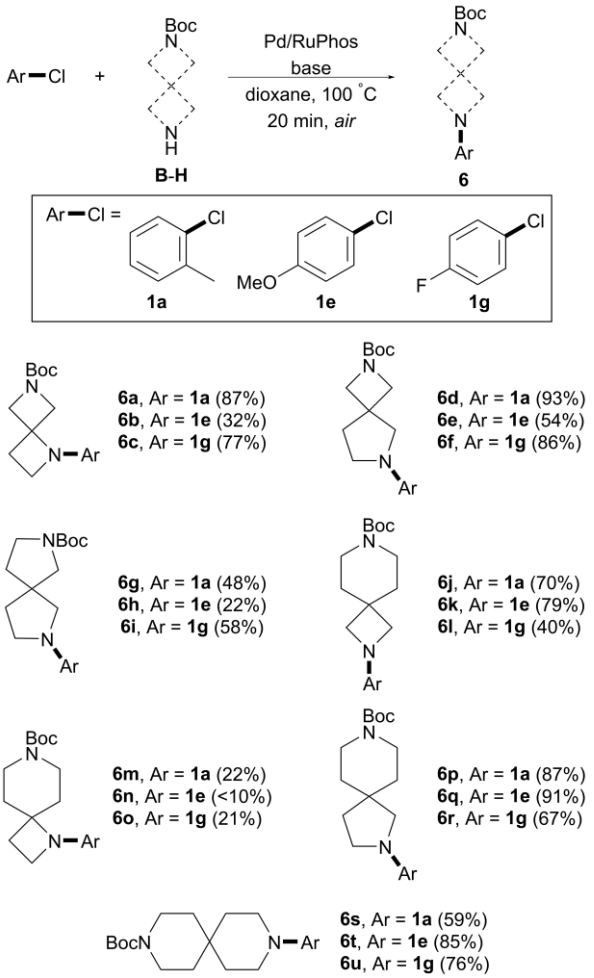


[a]Conditions: $Pd_2(dba)_3$ (1 mol %), RuPhos (2 mol %), aryl chloride (0.5 mmol), **A** (0.55 mmol), NaO*t*-Bu (3.0 equiv), and dioxane (1.5 mL), 20 min. Isolated yields. Reaction monitored by LCMS. [b]3.0 equiv of Cs_2CO_3 used instead of NaO*t*-Bu

With reports outlining synthetic methods of spirodiamine cores increasing over the past few years,[1a, 4, 16, 19] we sought to apply this protocol to other structurally diverse spirodiamine compounds. We expanded the scope to include examples of C–N cross-coupling with **B**-**H** (outlined in Figure 2) and aryl chlorides **1a**, **1e**, and **1g** (Scheme 3). These aryl substrates were selected to examine how sterics and electronics affect catalytic C–N coupling with linear and angular spirodiamine compounds **B**-**H**.

Excellent cross-coupling activity was observed with **B** and **1a** yielding **6a** at 87%. Electron-rich **1e** proved to be an unfavorable coupling partner, affording **6b** at 32% yield. Reaction conditions were more tolerable with **1g**, as product yield of **6i** occurred at 77%. High yields were obtained with **1a** and **1g** when coupled with **B**, however only modest reactivity was again observed with **1e** yielding **6e** at 54%. Sluggish reactivity was observed with **D** and aryl substrates **1a** and **1e** resulting in modest yields, although product yield improved slightly with **1g**. Compound **E**, a common core in molecular scaffolds with applications in type 2 diabetes mellitus (T2DM) and obesity,[20] was coupled with **1a** and **1e** affording good yields of **6j**-**k**. Decreased activity, however, resulted with substrate **1e**, yielding only 40% of desired product **6l**.

Scheme 3 Arylation of **B**-**H**[a]



[a]Conditions: $Pd_2(dba)_3$ (1 mol %), RuPhos (2 mol %), aryl chloride (1.0 mmol), **B**-**H** (1.1 mmol), NaO*t*-Bu (3.0 equiv), and dioxane (3.0 mL), 20 min. Isolated yields. Reaction monitored by LCMS.

Catalytic activity was considerably lower with sterically hindered **F,** affording low yields for **6m**-**o**. We postulated the reduced product formation of **6m**-**o**, compared to higher yields afforded with angular spirodiamine **B**, could be a result of increased steric congestion illustrated in Figure 4. A decrease in bond distance is observed when comparing the bond distance between carbon (C_1) in **F** and aryl carbon (C_2) in the coupled arene ring, compared to the analogous atoms of angular spirodiamine **B**. This increase in steric crowding could provide an unfavorable environment for the active catalyst, resulting in the poor yields observed for **6m**-**o**.

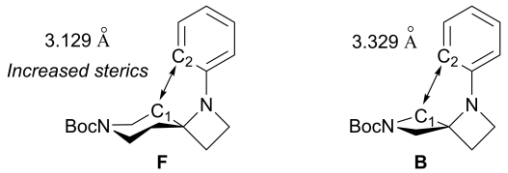


Figure 4 Comparison of C–C bond distances of sipirodiamine **F** and **B**.[21]

Excellent reactivity was observed with **G**, yielding >80% for both **6p** and **6q**, and a respectable 67% for **6r**. Reaction conditions were also tolerable for **H,** a common core found in biologically active compounds with application in thrombotic disease, pain and inflammation, and inhibition of GPIIb-IIIa.[21]

Conclusion

In summary, Pd/Ruphos catalyst system has been shown to be highly active in arylation of linear and angular spirodiamines in salt and free-base form. This extension of our previous work is a rare example of C–N bond formation that does not require an inert atmosphere or extended reaction times. Finally, reactions with activated and deactivated aryl chlorides were afforded at moderate to excellent yield at a constant catalyst loading in just 20 min.

Acknowledgments

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Supplementary Material

Electronic Supplementary Information (ESI) available: Experimental procedure, NMR and mass spectral data of the isolated product (PDF). See DOI: 10.1039/x0xx00000x.

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Highlights

- Efficient arylation of sterically congested spirodiamine compounds is demonstrated.
- Protocol does not require anhydrous solvents or inert atmosphere.
- Good to modest yields obtained with electron rich aryl halides in just 20 minutes.