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Facile preparation of highly-functionalized, nitrogen-bearing diarylmethanes

Jason R. Schmink [a], Matthew T. Tudge [b,*]

[a] UPenn/Merck HTE Center, Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania 231 S. 34th Street, Philadelphia, PA 19104-6323, USA
[b] Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, USA

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ABSTRACT

A palladium-catalyzed cross coupling of nitrogen bearing heterocyclic chloromethyl derivatives with aryl and heteroaryl boronic acids has been developed. In almost all cases, highly efficient cross-couplings were observed at ambient temperature, mitigating unwanted thermally induced side-reactions. The comprehensive substrate scope and respectable yields highlight the synthetic utility of this reaction.

Introduction

The diarylmethane structural motif is found in a range of biologically active compounds and has been incorporated into a number of promising pharmaceuticals. As shown in Figure 1, the diarylmethane substructure is present in Trimethoprim (TMP) **1** and piritrexim (PTX) **2** which are used to treat a wide range of bacterial infections[1] including treatment against opportunistic infections caused by *Pneumocystic carinii* and *Toxoplasma gondii* in patients with AIDS.[2] Additionally, the diarylmethane moiety plays a prominent role in a number of antiretroviral therapies targeting HIV1-Integrase, the enzyme mediating a crucial step in the replication of HIV.[3] Two such examples of small molecules having reached various stages of clinical development include Shionogi/GSK's S-1360 **3** and Gilead Science's GS-9137 (Elviltegravir) **4** which are currently in Phase III clinical trials for the treatment of HIV.[4]

Given the wide range of pertinent examples of diarylmethanes, it is of no surprise that there has been a recent emergence in developing methodologies to systematically effect the formation of the carbon–carbon bond linkage of the diarylmethane.[5] Since palladium-catalyzed C–C bond formation is one of the most powerful synthetic tools available to the organic chemist it is also of no surprise that the use of palladium has played a primary role in the development of new methodologies to afford diarylmethanes.

While there are numerous examples that utilize the robust and well-explored Suzuki–Miyaura reaction (SMR)[6] to generate all carbon diarylmethane scaffolds,[7] there are relatively few examples of basic *N*-heterocylic-halomethyl (*N*-Het-CH_2X) couplings.[8] Indeed, a detailed examination of the literature revealed only isolated examples[9] of this type of coupling highlighting the need for a more comprehensive study of this substrate class. Furthermore, these literature examples often require elevated temperatures and/or strongly basic conditions to achieve useful levels of reactivity thus resulting in low to moderate yields of the desired products.[8,9] To maximize the productivity of the SMR reaction in library-based diversity orientated syntheses,[10] we required reaction conditions that are: (i) tolerant of a wide array of functionality, (ii) generally robust, and (iii) operationally simple. With these guiding principles

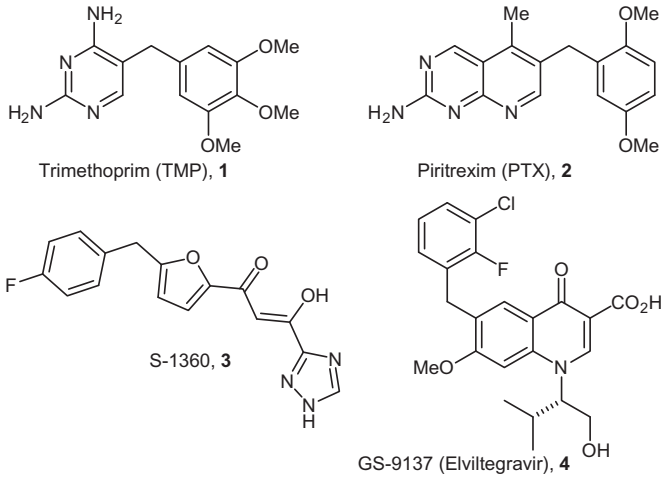

Figure 1. Examples of pharmaceutically-active small molecules containing a diarylmethane moiety.

* Corresponding author.
E-mail address: matthew_tudge@merck.com (M.T. Tudge).

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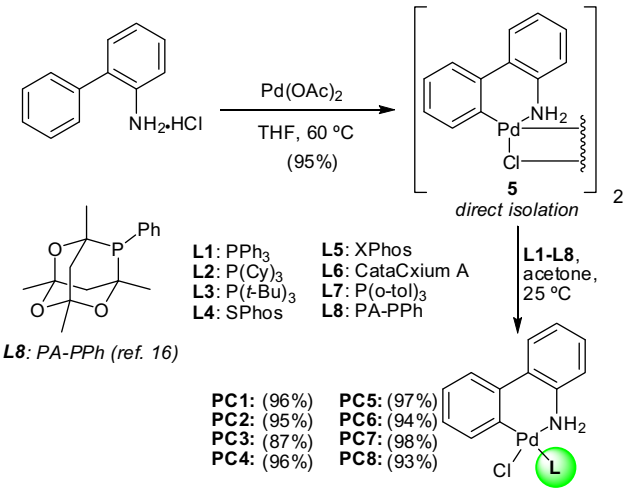


Scheme 1. Preparation of palladium aminobiphenyl precatalysts. SPhos = 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, CataCXium A = di(1-adamantyl)-*n*-butylphosphine. PA-PPh = 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenylphosphadamantyl.

in mind, we sought to develop a general SMR based synthesis of *N*-heterocyclic diarylmethanes containing basic nitrogen motifs. Herein, we report the results of our investigations toward this important goal.

Results & discussion

Since pre-defined catalysts reproducibly generated under mild conditions may offer enhanced levels of robustness and activity, our initial investigations focused on assessing the reactivity of a novel class of air-stable precatalysts **PC1-PC8** developed within our laboratories, and independently by Buchwald and co-workers (Scheme 1).[11] Complexes such as **PC6**, when treated with mild bases at ambient temperature undergo reductive elimination of carbazole to form active $L_1Pd(0)$ catalysts in a highly reproducible manner.[12] This predictable reactivity was successfully exploited by Buchwald and co-workers in the room-temperature Csp^2–Csp^2 SMR of sensitive poly-fluorinated aryl boronic acids and aryl-chlorides.[13] An array of biaryl-palladacycle precatalysts bearing sterically and electronically diverse ligands[14] that are known to facilitate Csp^2–Csp^3 and/or Csp^2–Csp^2 bond formation were prepared using the chemistry outlined in Scheme 1. Formation of the μ-chloro-dimer **5**[15] was readily achieved by heating 2-aminobiphenyl hydrochloride with palladium acetate in THF to afford **5** in 85% yield after direct isolation from the reaction mixture. Finally, treatment of μ-chloro-dimer **5** with phosphines **L1-L8**[16] in acetone, at room temperature, afforded precatalysts **PC1-PC8**.

Utilizing high-throughput experimentation techniques (HTE) developed within our laboratories,[17] we examined the cross coupling between 3-picolyl chloride·HCl **5** and the hindered 2, 6-dimethylphenylboronic acid **6a** against a range of solvents and aqueous bases (8 precatalysts × 4 aqueous bases × 6 co-solvents × 2 temperatures = 384 discrete reaction conditions; Fig. 2). The choice of **6** was based on the propensity of this compound to undergo base promoted polymerization through quaternization of the pyridine nitrogen, especially at the elevated temperatures routinely employed for Csp^2–Csp^3 SMR reactions.[7–9] Finally, while significant excess of the boronic acid is commonly utilized in cross-coupling reactions, we opted to limit the excess boronic acid to 1.1 equiv to increase the practicality of the transformation.

In an effort to select the most generalized set of conditions from the 384 reactions shown in Figure 2, we focused our analysis on

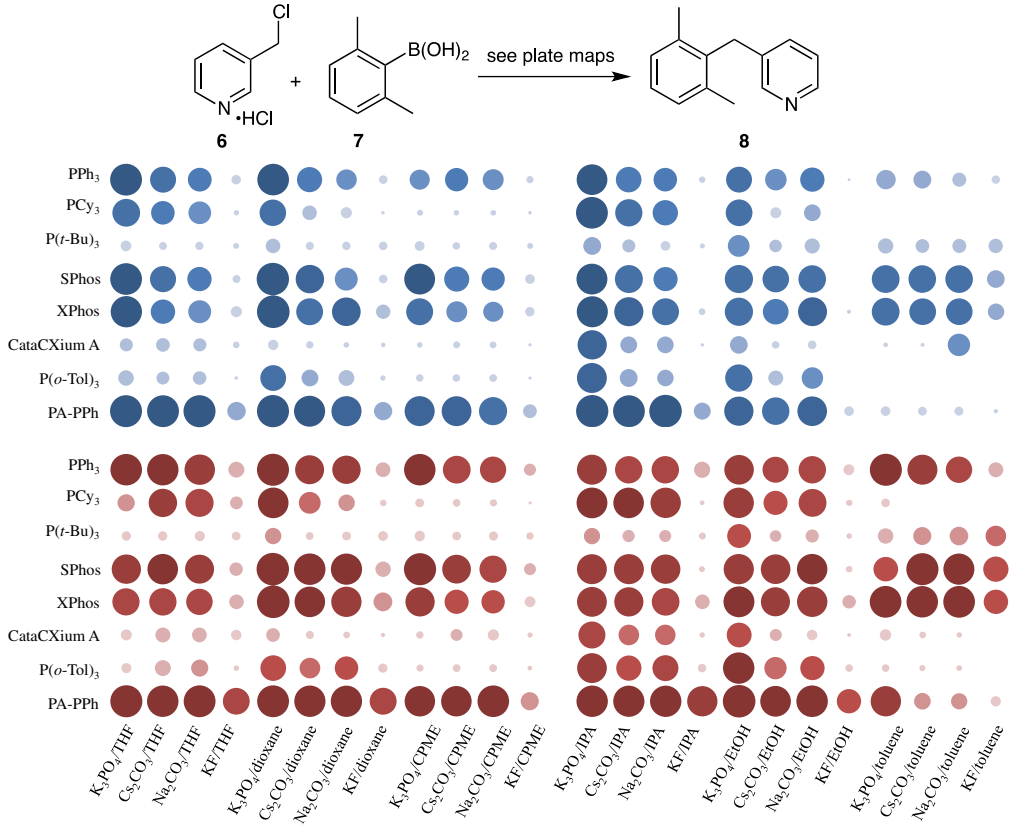
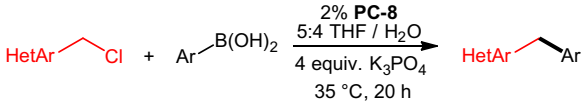


Figure 2. Initial screen and graphical representation of percentage yield across 384 reactions. Conditions: 0.1 M (10.0 μmol **6**, 11.0 μmol **7**), 4 equiv aqueous base, 2 mol % **PC1-PC8**. Results in blue run at 35 °C; red at 50 °C. For comprehensive quantitative data, see the Supporting Information.

Table 1
Cross-coupling of arylboronic acids with various heterobenzyl chlorides



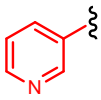
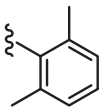
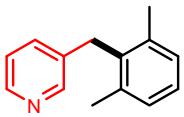
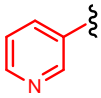
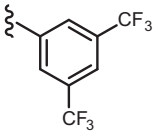
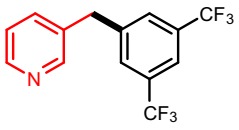
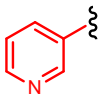
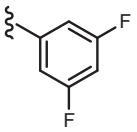
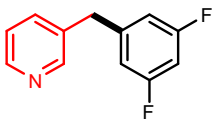
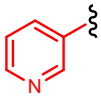
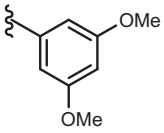
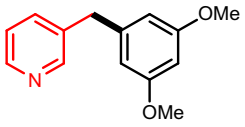
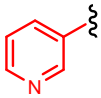
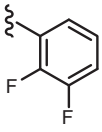
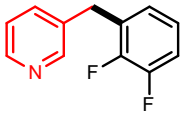
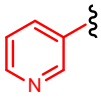
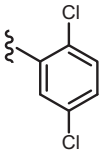
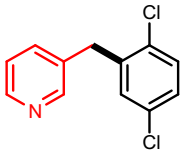
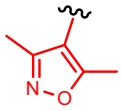
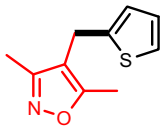
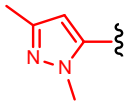
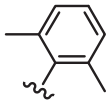
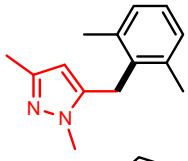
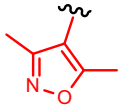
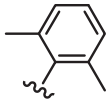
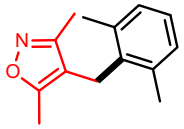
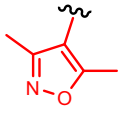
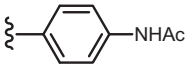
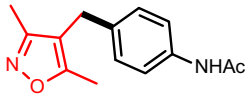
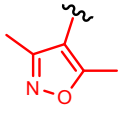
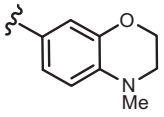
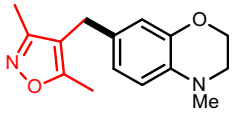
Entry	HetAr	Aryl (Ar)	Product	Yield (%)
1				86[a] (85)
2				72[a] (75)
3				77[a] (82)
4				83[a]
5				89[a]
6				81[a]
7				94[b]
8				71[b]
9				86[b]
10				94[b]
11				90[b]

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Table 1 (*continued*)

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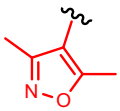
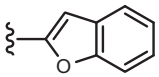
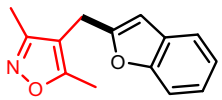
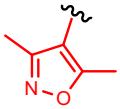
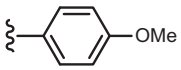
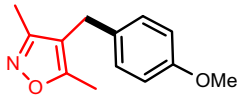
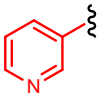
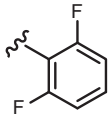
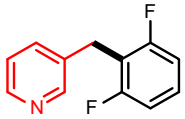
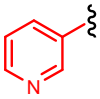
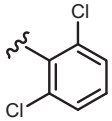
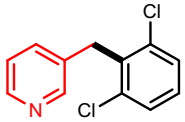
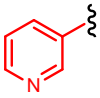
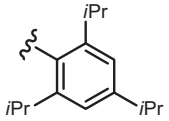
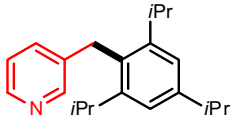
12				66[b] (91)
13				97[b]
14				0
15				0
16				0

All yields refer to isolated yields. (IPA as cosolvent). [1.5 Equiv boronic acid].

[a] Isolated as the HCl salt.

[b] Isolated after column chromatography.

reactions generating coupled product **8** in >90% assay yield.[18] At both 35 °C and 50 °C **PC-8** provided **8** >90% yield across the widest range of base/solvent combinations (8/24 and 17/24 respectively), clearly making it the precatalyst of choice.

Potassium phosphate proved to be the most general base affording >90% assay yield of coupled product **8** in 32/96 precatalyst/solvent/temperature combinations. In contrast, Cs_2CO_3, Na_2CO_3, and KF only gave >90% assay yield of **7** in 15/96, 14/96, and 1/96 precatalyst/solvent/temperature combinations respectively. THF, dioxane, and IPA all proved to be effective solvents affording **8** in >90% yield 12/64, 15/64, and 12/64 precatalyst, base, and temperature combinations. Ultimately, THF was selected as the reaction solvent due to the lower toxicity relative to dioxane and its enhanced solvation properties relative to IPA.

With a generalized set of conditions in hand (2 mol % **PC-L8**, 1.1 equiv boronic acid, 5:4 THF:H_2O, 4 equiv K_3PO_4), we turned our attention to evaluating the substrate scope of the reaction (Table 1). Special attention was paid to potentially problematic boronic acid coupling partners, especially electron-poor, sterically demanding, or those particularly prone to deboronation. A variety of arylboronic acids were coupled with **6** to provide the corresponding SMR adducts in good yields (Table 1, entries 1–6). In addition, the optimized conditions smoothly coupled pyrazole and isoxazole chloromethyl derivatives with a range or boronic acids to afford the resultant products in excellent yields (Table 1, entries 7–13).

The benefits of the very clean reaction profile were exploited in many cases by simply isolating the HCl salt of the products after a standard aqueous-organic workup, eliminating the need for chromatographic purification of substrates that contained a basic nitrogen and lacking acid sensitive functionality, (entries 1–6). Interestingly, Csp^2–Cl bonds were well tolerated (entry 6) with no evidence of the orthogonal cross-coupling product. In instances where competitive protodeboronation proved to be problematic (entry 12), an improvement in yield could be realized by simply increasing the 2-benzofuranboronic acid loading to 1.5 equiv.

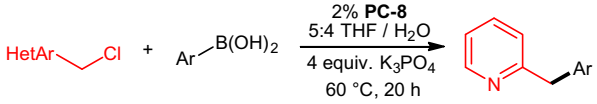
The limitations of this methodology were met in the attempted cross-coupling of 2,6-difluoro- or 2,6-dichlorophenylboronic acid with **6** (Table 1, entries 14 and 15). In these instances, protodeboronation proved far more facile than the desired cross-coupling. In addition, the highly sterically-hindered boronic acid 2,4,6-triisopropylphenylboronic acid also proved problematic yielding <1% of the desired product (Table 1, entry 16).

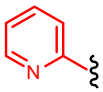
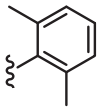
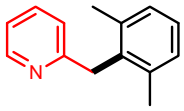
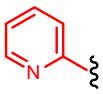
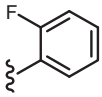
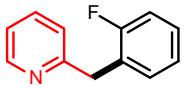
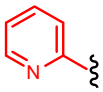
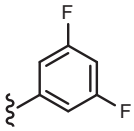
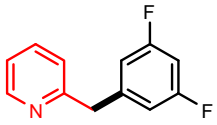
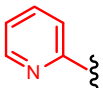
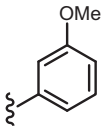
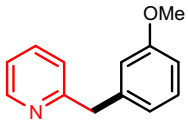
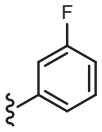
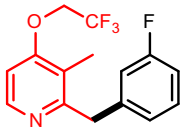
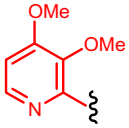
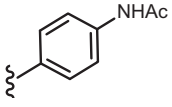
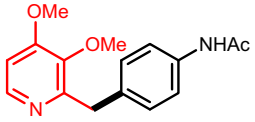
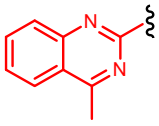
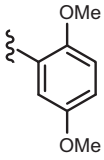
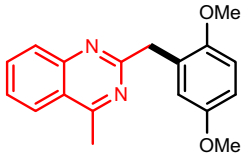
In the case of 2-chloromethyl substituted heterocycles, we observed a sluggish conversion into the desired product when the reactions were carried out at 35 °C. By increasing the reaction temperature to 60 °C, the desired coupling products could be furnished in synthetically useful yields (Table 2, entries 1–6). Indeed, under our optimized reaction conditions even electron rich pyridines provided the corresponding products in good yield without polymerization of the starting materials (Table 2, entries 5 and 6). We speculate that after the oxidative insertion of palladium into the C–Cl bond, the lone pair of the pyridine nitrogen atom may coordinate with the palladium-(II) center thereby attenuating the electrophilic character of the metal center necessitating higher reaction temperatures to facilitate reductive elimination.[19] This problem appears to be exacerbated when using a 2-chloromethyl pyrimidine derivative (entry 7) where two opportunities for coordination exist.

Summary & conclusions

In summary, we have developed a generalized set of conditions for the Suzuki coupling of a diverse array of heterocyclic-chloromethyl derivatives. Notably, the mild conditions and the use of a novel palladium precatalyst lend themselves perfectly to diversity-orientated synthesis by simplifying parallel operations and imparting a greater overall robustness. Studies in order to understand better the nature of the active catalysts and the attenuated reactivity of the 2-picolyl derivatives are underway and will be reported in due course.

Table 2
Top: cross-coupling of arylboronic acids with 2-picolyl chloride derivatives required an elevated reaction temperature and/or extended reaction times



Entry	HetAr	Aryl (Ar)	Product	Yield (%)
1				77
2				72
3				66
4				61
5				70
6				74
7				24

(a) Boronic acid; (b) pinacol ester; (c) isolated as the HCl salt; (d) isolated by column chromatography.

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