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Single-flask preparation of polyazatriaryl ligands by sequential borylation/Suzuki–Miyaura coupling

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ABSTRACT

We report a convenient single-flask methodology for the preparation of polyazatriaryl products with relevance to luminescence, catalysis, and pharmacology. The diborylation of 1,3-dibromobenzenes and double Suzuki–Miyaura coupling produces 1,3-diheteroarylbenzenes. Similarly, borylation of heteroaryl halides and double coupling to 2,6-dichloropyridine produces 2,6-diheteroarylpyridines. This methodology appears general in producing challenging polyheteroaryl targets as long as the boronic esters have no *ortho* heteroatoms and coupling avoids adjacent oxygens.

1. Introduction

Bisheteroarylbenzenes and bisheteroarylpyridines have attracted recent interest for their application in electroluminescent displays, catalysts, and pharmaceuticals. Ruthenium, iridium, and platinum complexes with 1,3-di(pyridin-2-yl)benzene ligands have been studied for their luminescent and electroluminescent properties particularly in conjunction with 2,2′:6′,2″-terpyridines (terpys).[1–5] Palladium, platinum, and mercury complexes with 1,3-di(pyridin-2-yl)benzene itself have been demonstrated as catalysts for the Heck reaction, and analogy of 1,3-diheteroarylbenzenes and 2,6-diheteroarylpyridines to terpy suggests an application to other catalytic systems.[6,7] Further, 1,3-di(benzo[*d*]thiazol-2-yl)benzene and 3,2′:6′,3″-terpyridine themselves have even been studied as pharmaceuticals for calcium transport control and antitumor activity, respectively.[8,9]

Several methodologies have been reported for preparing 1,3-diheteroarylbenzenes and 2,6-diheteroarylpyridines but each is somewhat limited in its scope. The older methods entail condensation of the end rings such as the reaction of 2-aminothiophenol with phthaldialdehyde to produce 1,3-di(benzo[*d*]thiazol-2-yl)benzene.[9] Substituted 1,3-di(pyridin-2-yl)benzenes have similarly been prepared by condensing pyridine rings through the reaction of 1,3-diacetylbenzene, the corresponding enones, and ammonium acetate.[6,10] The ring condensation method of preparing 1,3-di(pyridin-2-yl)benzene has been replaced by the more efficient reaction of 1,3-dicyanobenzene with excess acetylene catalyzed by organometallic cobalt complexes.[7,11,12] Stille coupling of 3-trimethylstannylpyridine or 2-tri-*n*-butylstannylpyridine to 1,3-dibromobenzenes represents a more modern and modular methodology for preparing 1,3-di(pyridinyl)benzenes.[3,5,13–16] The analogous Suzuki–Miyaura coupling of pyridin-3-ylboronic pinacol ester to 2-chloropyridine to form 2,3′-bipyridine as well as pyridin-3-ylboronic acid to 2,6-dichloropyridine to form 3,2′:6′,3″-terpyridine offers the advantage of lower toxicity than Stille coupling.[16–19]

Recently, the inconvenience of isolating boronic esters for Suzuki–Miyaura arene coupling reactions has been side-stepped by single-flask methodologies that produce these sensitive intermediates in situ. In one such strategy employed specifically toward pyridines, boronic ester intermediates are produced by the directed *ortho* metallation–borylation of chloro-, fluoro-, *O*-carbamoyl pyridines followed by coupling to aryl iodides and bromides. Unfortunately, this method requires the pyridine ring to bear electron withdrawing directing groups and has only been demonstrated for monoazabiaryl products.[20] A more generalized one-flask aryl–aryl coupling strategy entails the borylation of an aryl chloride and subsequent Suzuki–Miyaura coupling to a second aryl chloride.[21–24] This method typically utilizes a modest base such as KOAc to achieve the borylation of aryl chlorides with a palladium catalyst and subsequent coupling of the product arylboronic ester to another aryl halide with the addition of a stronger base such as K_2CO_3 or K_3PO_4. While this methodology is applicable to a wide range of aryl–aryl couplings, the borylation of pyridyl rings

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remains challenging and the coupling of arylboronic esters has been demonstrated to only 2-pyridine, 2 and 3-quinoline, and 3-thiophene heterocycles.[23,24] Overall, the scope of this methodology has not been widely explored or optimized for aryl–aryl coupling with heterocycles.

We report here a single-flask method optimized for the borylation and subsequent double Suzuki–Miyaura aryl–aryl coupling with heterocycles for the convenient and efficient preparation of a variety of 1,3-bisheteroarylbenzenes and 2,6-bisheteroarylpyridines with the potential as chelating or bridging ligands in transition metal complexes. This work explores the scope and limits of the borylation/coupling strategy to a range of heterocycles and demonstrates its applicability to challenging polyheteroaryl targets.

2. Results and discussion

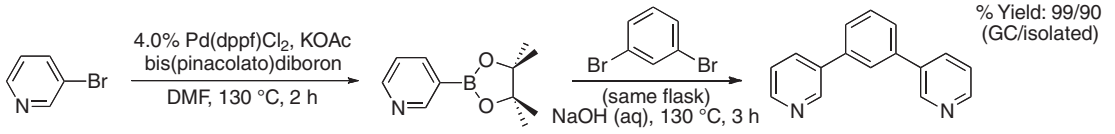
Our single-flask borylation/Suzuki coupling methodology was first optimized for the preparation of 1,3-di(pyridin-3-yl)benzene and required significant modification of the previously reported single-flask method for biarenes.[21] The borylation of 3-bromopyridine using Pd(dppf)Cl_2 catalyst and KOAc in dioxane required modest hydration of the solid KOAc for reactivity, but the absorbed water also resulted in a significant reduction of the 3-bromopyridine to pyridine. Even with an acceptable balance of KOAc hydration, the reaction in dioxane was slow requiring several hours at reflux to achieve 90% yield of the pyridine-3-ylboronic pinacol ester. However, the reaction of 3-bromopyridine with bis(pinacolato)diboron, KOAc, and 4 mol % Pd(dppf)Cl_2 catalyst in DMF resulted in greater than 95% borylation in 1–2 h (Scheme 1) with no sensitivity to KOAc hydration. The subsequent addition of 1,3-dibromobenzene and either aqueous K_2CO_3 or K_3PO_4 to the hot DMF reaction results in a slow double coupling to 1,3-di(pyridinyl-3-yl)benzene over 15 h without the need for an additional catalyst. However, the use of aqueous NaOH as the base dramatically achieved complete coupling within only 2–3 h (Scheme 1). Hydrolysis of DMF by the aqueous NaOH does not interfere in the aryl coupling or product isolation. In subsequent testing, the general conditions represented by Scheme 1 proved to be rapid and effective in producing 1,3-diheteroarylbenzenes as well as 2,6-diheteroarylpyridines.

The analogous single-flask borylation of 2,6-dibromobenzene and subsequent double Suzuki coupling to 3-bromopyridine is also very effective in producing 1,3-di(pyridin-3-yl)benzene (Scheme 2). 2,6-Dibromobenzene readily diboronates with bis(pinacolato)diboron, sodium acetate, and 4 mol % Pd(dppf)Cl_2 in DMF. The addition of 3-bromopyridine and aqueous sodium hydroxide to the reaction solution results in the rapid formation of the single coupling product that more slowly couples to a second equivalent of 3-bromopyridine. While the addition of excess 3-bromopyridine drives the reaction quicker and closer to completion, the addition of the additional catalyst does not improve the final yield. The best balance of reagent and yield calls for 3 equiv of 3-bromopyridine with respect to the diboronic ester resulting in a near complete conversion of diboronic ester into product.

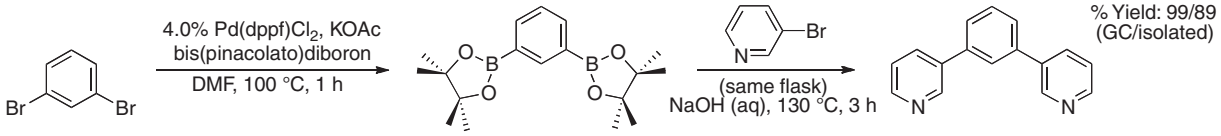
The single-flask borylation/double coupling methodology was easily extended to the preparation of symmetric 1,3-bisheteraryl-benzenes and 3,5-bisheteroarylpyridines. 2-Bromopyridines are readily converted into the boronic esters except that a significant amount of homocoupling occurs to form 2,2′-bipyridines. Surprisingly, the Pd(dppf)Cl_2 catalyst readily converts 2-chloropyridine into the boronic esters without significant homocoupling. Though this catalytic system does not boronate 3-chloropyridines, the 3-bromopyridines are readily boronated with little homocoupling. Unfortunately, pyridin-2-ylboronic pinacol esters were practically unreactive in the Suzuki coupling with bromoarenes using the Pd(dppf)Cl_2 catalyst. This is consistent with the literature reports of poor yields for Suzuki–Miyaura coupling of 2-heterocylic boronic esters attributed to slow transmetalation from boron to palladium versus competitive protodeboronation.[25] Strategies for facilitating 2-heterocycle transmetalation through organocopper intermediates or palladium phosphine oxide or chloride catalysts have resulted in modest coupling yields.[26–28] Efforts are underway to incorporate these strategies into our single-flask protocols. In spite of difficulties with pyridin-2-ylboronic pinacol esters, 2-chloropyridines readily couple with 1,3-phenylenediboronic pinacol esters (Table 1). The borylation/double coupling proceeds to 70–95% conversion with 50% excess of a range of 2-chloropyridine starting materials (entries 2–7). The borylation/double coupling methodology is tolerant of electron withdrawing and releasing substituents on the center and outer rings even in the potentially crowding 6 and 6″-positions. This method is also applicable to 5- or 6-member end rings with one or more nitrogens *ortho* to the coupling position (entries 8–11). The coupling reaction tolerates sulfur (entry 11) but not oxygen adjacent to the coupling carbon (entry 12). Substitution on the central 1,3-dibromopyridine is also tolerated (entry 13), and 3,5-dibromopyridine can be used in place of 1,3-dibromopyridines since the nitrogen is not *ortho* to either borylation site (entry 14).

In general, the tandem borylation/coupling strategy appears widely applicable as long as the boronic ester itself does not have a nitrogen *ortho* to the coupling position. As mentioned, 3,5-dibromopyridine serves well as the center ring to form 2,3′:5′,2″-terpyridine. 2,6-Heteroarylpyridine products can be analogously prepared by boronating the outer rings and coupling them to 2,6-dichloropyridines as long as the outer rings do not have *ortho* heteroatoms (Scheme 3). These reactions proceed to the disubstituted products in good yields and do not need an excess of either the end or center ring reactants.

Overall, this one-flask borylation/double coupling strategy is effective and should be applicable to many products beyond those illustrated in this communication. Further, the Supplementary data

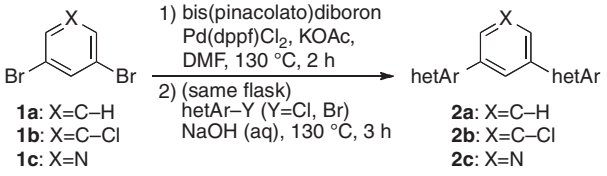


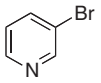
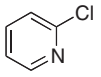
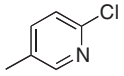
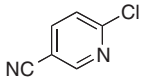
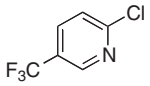
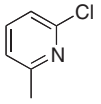
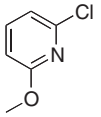
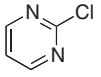
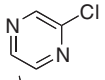
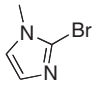
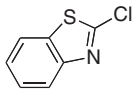
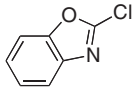
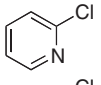
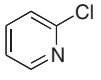
Scheme 1. Single-flask borylation of 3-bromopyridine and Suzuki–Miyaura coupling to 1,3-dibromobenzene.



Scheme 2. Alternative single-flask diborylation of 1,3-dibromobenzene and Suzuki–Miyaura coupling to 3-bromopyridine.

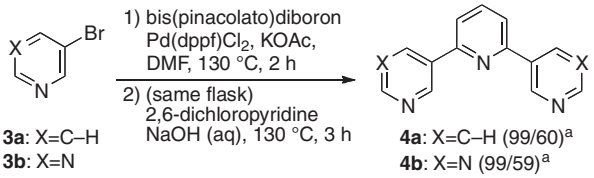
Table 1
Products of single-flask diborylation of 1,3-dibromobenzenes and subsequent Suzuki–Miyaura coupling to halogenated heterocyles



Entry	1	hetAr-Y	2	Yield[a]
1	**1a**		**2a**	99/89
2	**1a**		**2a**	73/64
3	**1a**		**2a**	67/59
4	**1a**		**2a**	91/28
5	**1a**		**2a**	86/82
6	**1a**		**2a**	94/37
7	**1a**		**2a**	93/80
8	**1a**		**2a**	62/56
9	**1a**		**2a**	96/75
10	**1a**		**2a**	36/32
11	**1a**		**2a**	36/33
12	**1a**		**2a**	None
13	**1b**		**2b**	89/78
14	**1c**		**2c**	43/12

[a] Yields (percent measured by GC/isolation). Slow, irreversible binding of products to preparative TLC gels are responsible for large yield differences.

of this report detail the preparation and characterization of the new compounds from entries 4–9 and 13 in Table 1. All of the products described herein are of particular interest for their potential as transition metal ligands and as analogs of 2,2′:6′,2″-terpyridine. Efforts are underway to prepare and study complexes incorporating these new ligands. Attempts are also underway to develop an analogous one-flask protocol to couple multiple heterocyclic rings with *ortho* nitrogens on both sides of the C–C couplings.



Scheme 3. Products of single-flask borylation of bromoheterocycles and subsequent Suzuki–Miyaura coupling to 2,6-dichloropyridine. Percent yields measured by GC/isolation. Slow, irreversible binding of products to preparative TLC gels responsible for large yield differences.

3. General procedure for one-flask borylation/Suzuki–Miyaura coupling illustrated with borylation of 1,3-dibromobenzene and coupling to 3-bromopyridine to prepare 2a (hetAr = 3-pyridine) (Table 1, entry 1)

To degassed DMF (8.0 mL) was added Pd(dppf)Cl_2 (73 mg, 0.10 mmol), bis(pinacolato)diboron (508 mg, 2.0 mmol), potassium acetate (589 mg, 6.0 mmol), and 2,6-dibromobenzene (0.121 mL, 236 mg, 1.0 mmol) in order at room temperature. The mixture was heated to 130 °C for 1 h to complete formation of the boronic ester. Then 3-bromopyridine (0.289 mL, 474 mg, 3.0 mmol) and degassed aqueous sodium hydroxide (2.00 mL, 3.0 M, 6.0 mmol) were sequentially added to the hot reaction, and heating at 130 °C was continued for another 3 h when the reaction was complete (by GC–MS). The reaction was cooled and evaporated to a residue in vacuo. The residue was extracted with chloroform, and the combined extracts were concentrated and applied to preparative silica TLC plates. After development by 1:1 THF/EtOAc the product bands were removed and extracted with DME. Evaporation of extract solutions resulted in the yield. The product could be further purified by sublimation at 180 °C and 10 mm Hg if needed.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.136.

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