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Synthesis of benzannulated heterocycles by twofold Suzuki–Miyaura couplings of cyclic diarylborinic acids†

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Two-fold Suzuki–Miyaura cross-couplings of cyclic diarylborinic acids are described. This novel annulation method enables the synthesis of benzo-fused heterocycles from dihaloarenes or *gem*-dibromoolefins.

The Suzuki-Miyaura cross-coupling reaction is a powerful tool for C-C bond construction, and extensive effort has been dedicated to broadening its substrate scope. Advances in this direction include couplings of aryl chlorides,¹ substrates having C-O bonds (e.g., aryl ethers, esters, carbamates and sulfamates),² and unactivated primary or secondary alkyl halides.³ Likewise, the range of organoboron compounds that can be employed has been expanded to encompass such species as alkylboronic acid derivatives,⁴ organotrifluoroborates,⁵ organotrialkoxyborates⁶ and N-methyliminodiacetic acid (MIDA) boronates.7 Given that the functional group compatibility and air/ moisture tolerance of organoboron compounds are key advantages of the Suzuki-Miyaura reaction, it is not surprising that relatively few attempts at cross-couplings of borinic acid derivatives (R₂BOH), which are generally more oxidation-prone than boronic acids, have been made.8,9 Nonetheless, reactions of this type have been reported in cases where the borinic acid was obtained more conveniently¹⁰ or provided a higher yield¹¹ than the corresponding boronic acid. In addition, systematic studies of the cross-couplings of potassium diaryldifluoroborates,¹² magnesium diorganoboronates¹³ and borinic acids¹⁴ have been described recently.

Herein, we describe two-fold Suzuki–Miyaura cross-couplings of cyclic diarylborinic acids, generating benzannulated heterocyclic products. This work builds on our studies of 9-hetero-10-boraanthracene-derived borinic acids (*e.g.*, **1a** and **1b**, Scheme 1) as catalysts for monosulfonylation, alkylation and glycosylation of di- and triols.¹⁵ Unlike most diarylborinic



Scheme 1 Preparation and envisioned twofold Suzuki-Miyaura crosscoupling of cyclic diarylborinic acids.

acids, which undergo oxidation quite readily under ambient conditions, these heterocyclic variants are air-stable, crystalline solids.^{16,17} The attenuated Lewis acidity at boron arising from incorporation into a 6π electron system, and/or geometric constraints of the heterocyclic system that kinetically disfavor the oxidation pathway, may contribute to this property. The prospect that such cyclic diarylborinic acids could represent convenient (and hitherto unexplored) bis-boron reagents for annulation reactions motivated us to study their Pd-catalyzed couplings with dihaloarenes (Scheme 1).¹⁸

Given that 9-hetero-10-boraanthracene-derived borinic acids are poorly Lewis acidic, and considering current mechanistic proposals for transmetallation of boronic acids to Pd(II),¹⁹ we anticipated that this step could be problematic. Therefore, our initial efforts were aimed at identifying conditions for reaction of 1a with bromobenzene by coupling of both C-B bonds, generating the 2:1 adduct 2a (Table 1). Relatively high reaction temperatures were required for activation of 1a, and protodeboronated 2b was obtained as a side product. The 2a:2b ratio was found to depend on the ligand (entries 3-5), Pd precatalyst (entries 6, 7), base and solvent (entries 8, 9). Optimal results were achieved using tri-tert-butylphosphine as ligand, dibenzylideneacetone (dba) complex $Pd_2(dba)_3$, and Cs_2CO_3 as base in toluene at 100 °C. These conditions were effective for coupling of 4-bromoanisole, but not for electron-deficient 4-bromonitrobenzene (Scheme 2). A marginal improvement

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 Table 1
 Dependence of the outcome of cross-couplings of 1a and bromobenzene on the reaction conditions employed



^{*a*} Yields determined by ¹H NMR with 1,3,5-trimethoxybenzene as a quantitative internal standard. ^{*b*} Isolated yields. ^{*c*} dppf = 1,1'-bis-(diphenylphosphino)ferrocene. ^{*d*} S-Phos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl. ^{*e*} IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride.



Scheme 2 Preparation of substituted biaryl ethers by two-fold Suzuki couplings of 1a.

over the latter result was obtained by using 4-iodonitrobenzene as the coupling partner.

Having developed conditions that enabled transmetallation of both the starting borinic acid and the boronic acid-type intermediate, we turned our attention to the preparation of heterocyclic compounds by sequential inter- and intramolecular couplings. Specifically, the synthesis of tribenzo [b,d,f]oxe- and azepines by coupling of ortho-dihaloarenes with 1a/1b was targeted. Known methods for the synthesis of tris-benzannulated heterocycles of this type make use of linear, multi-step sequences, often involving Pschorr-type or photochemical cyclizations.²⁰ Using 1a and 4,5-dibromoveratrole as test substrates, the desired oxepine 5a was obtained in 38% yield under the optimal conditions from Table 1 (Scheme 3). The yield was improved to 90% by using tert-butanol (t-BuOH) as the solvent. Under these conditions, the preparation of azepine 5b from 9-aza-10-boraanthracene 1b was more challenging, and resulted in a 22% yield. Transmetallation may be particularly slow for 1b, which is less Lewis acidic than 1a and possesses shorter C-B bond distances.15 Nonetheless, the preparation of 5b was improved to 89% by using tert-amyl alcohol (t-AmOH) as solvent at a higher temperature. The presence of water has a beneficial effect on the yield of the



Scheme 3 Synthesis of tribenzo[*b*,*d*,*f*]oxe- and azepines by Suzuki couplings of **1a**/**1b** with dibromoveratrole: solvent/temperature effects.

annulation process: acceptable yields were obtained using a batch of Cs_2CO_3 that contained a significant quantity of the hydrate. When anhydrous Cs_2CO_3 was used, deliberate addition of water (up to 10 equiv.) was needed to restore the yield of benzannulated product (see the ESI† for details).²¹

Scheme 4 illustrates the range of benzo-fused heteroaromatic compounds that can be prepared by this annulation method. Although the depicted products were prepared on 0.1 mmol scale, the process is reasonably efficient for the synthesis of larger quantities: for example, 5c was obtained in 73% yield (0.9 g) from a reaction conducted on 5.0 mmol scale. Sterically hindered oxaboraanthracenes displayed sluggish reactivity, generating methoxy-substituted 5d and naphtho-fused 5e in relatively low yields. In the case of 5e, side products resulting from cross-coupling followed by protodebromination and/or protodeboronation were identified. A heteroaryl-fused oxepine (5f) was generated from N-methyl-2,3dibromoindole: as was the case for 5e, the product of crosscoupling/protodeboronation was obtained as a side product. It should be noted that the preparation of non-benzo-fused oxepines by couplings of 1a with 1,2-dibromoalkenes was not



Scheme 4 Synthesis of fused heterocycles by Suzuki–Miyaura crosscouplings of cyclic borinic acids. ^a t-BuOH solvent, 80 °C. ^b t-AmOH solvent, 100 °C.



Fig. 1 Solid-state structure of tetrabenzooxonine 5i.

successful. However, 9-methylenexanthenes **5g** and **5h** were accessed by couplings of the corresponding β , β -dibromostyrenes. The coupling of **1a** with 2,2'-dibromobiphenyl generated tetrabenzooxonine **5i** in 61% yield. The solid-state structure of this previously unreported ring system was determined by X-ray crystallography, revealing a nonplanar structure with an alternating up/down arrangement of phenylene groups (Fig. 1).

Conclusions

Despite the relatively poor Lewis acidity of heteroboraanthracene-derived borinic acids that appears to hinder transmetallation, these species can be employed productively in Suzuki-Miyaura cross-couplings to generate two carbon–carbon bonds. These reactions enable the one-step synthesis of benzofused heterocycles from readily available, bench-stable organoboron reagents and dihalogenated coupling partners. Although the yields are modest in some instances, the modular and convergent nature of this synthesis may provide a useful complement to other methods for the preparation of these types of heterocycles.

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