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Use of 2-Bromophenylboronic Esters as Benzyne Precursors in the Pd-Catalyzed Synthesis of Triphenylenes

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ABSTRACT: ortho-Substituted aryl boronates are introduced as aryne precursors for transition-metal-catalyzed trans- formations. On treatment with ^tBuOK and Pd(0), metal- bound aryne intermediates are formed that undergo effective trimerization to form useful triphenylene compounds. For meta-substituted arynes, the 3:1 product ratio in favor of non- C₃ symmetric material is indicative of a benzyne mechanism.

Aryne chemistry has flourished in recent years, driven by the introduction of 2-trimethylsilylphenyl triflates, **1**, as precursors that function under mild reaction conditions.¹ Seminal observations from the groups of Pérez/Gutián² and Yamamoto³ established that these reagents were compatible with transition metal (TM) catalysis, a field that was entirely untapped in the classical era of benzyne chemistry. These reports exemplified the versatility of **1**, which has since being exploited in a tremendous variety of both metal-mediated and metal-free transformations.^{4,5}

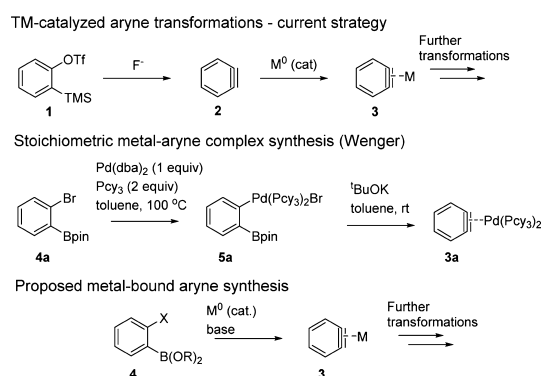
Our interest in transition-metal-catalyzed benzyne chemistry⁶ led us to speculate that an analogous ortho-substituted aryl boronate, **4**, could offer alternative reaction pathways in the TM catalysis arena, while retaining the benefits of usability conferred by silanes **1**. Verbit and co-workers reported the diazotization of *o*-amino boronic acid as a benzyne-generating method as early as 1966, but the method did not find wider application in synthesis.⁷ More recently, Hosoya and co-workers showed that (2-trifluoromethanesulfonyloxy)aryl- boronic esters (**4**, X = OTf) underwent activation with *t*-BuLi or *s*-BuLi at -78 °C, affording arynes on warming that could be trapped in a variety of σ -insertion and pericyclic reactions.⁸ The Akai group then demonstrated that fluoride could selectively activate the boron center of 2-boryl-6-(trimethylsilyl)phenyl triflates at room temperature, generating benzyne that were trapped with amines.⁹ Application of ortho- substituted arylboronic acid derivatives as benzyne precursors in transition metal catalysis, however, has yet to be reported.

We based our catalyst system on stoichiometric work from Wenger, Bennett, and co-workers, who synthesized a series of Pd(0) and Ni(0) benzyne complexes via ^tBuOK treatment of the organometallic prepared from (2-bromophenyl)boronic esters **4** (Scheme 1, shown for Pd(II) complex **5a**).¹⁰ The resulting complexes were characterized by X-ray crystallography in many cases, revealing the symmetrical η -2 coordination of the benzyne triple bond to the group 10 metal atom (**3a**).

If this approach could be adapted to a catalytic variant, it would have the interesting property of generating arynes as metal-bound intermediates immediately. This contrasts with existing approaches, whereby free benzyne (**2**) is slowly generated by fluoride treatment of **1** and then bound to a metal catalyst in a subsequent step.

We chose to explore the scope of compounds **4** using metal- catalyzed benzyne cyclotrimerization. Palladium-catalyzed aryne trimerization is one of the best-studied and most used TM- catalyzed aryne reactions, with the Peña and Gutián group having demonstrated extensive applications to the synthesis of extended aromatic arrays (e.g., nanographenes, cloverphenes, acenes, coronenes) for applications in organic materials science.^{11,12}

Scheme 1. Proposed Benzyne Generation from ortho- Substituted Arylboronic Acid Derivatives 4



We began by examining 2-bromo-phenylboronic acid as a substrate, as it is a commercially available, inexpensive crystalline solid. An initial experiment using 2 equiv of ^tBuOK, Pd(dba)₂ (5 mol %), and PPh₃ (10 mol %) in toluene at 100 °C afforded triphenylene 6a in a low 15% yield. Switching to the pinacol ester (4a), however, gave 6a in a far better 60% yield (Table 1, entry 1), so we chose to optimize the reaction around this substrate. Control experiments indicated that both metal and base were necessary to form triphenylene, and that the triphenylphosphine ligand enhanced the reaction yield. A full optimization study (see Supporting Information for details) established conditions of Pd(dba)₂ (5 mol %), bis[(2-diphenylphosphino)phenyl] ether (DPEphos, 5 mol %), ^tBuOK (1.1 equiv) in toluene at 100 °C, affording triphenylene in 78% yield (entry 2).

Table 1. Optimization of Pd-catalyzed Triphenylene Synthesis.^a

entry	X	conditions	yield ^b (%)
1	Br	Pd(dba) ₂ (5 mol %), PPh ₃ (10 mol %), ^t BuOK (2 equiv), toluene, 100 °C	60
2	Br	Pd(dba) ₂ (5 mol %), DPEphos (5 mol %), ^t BuOK (1.1 equiv), toluene, 100 °C	78
3	Cl	as entry 2 at 125 °C	25 ^c
4	OTf	as entry 2	80

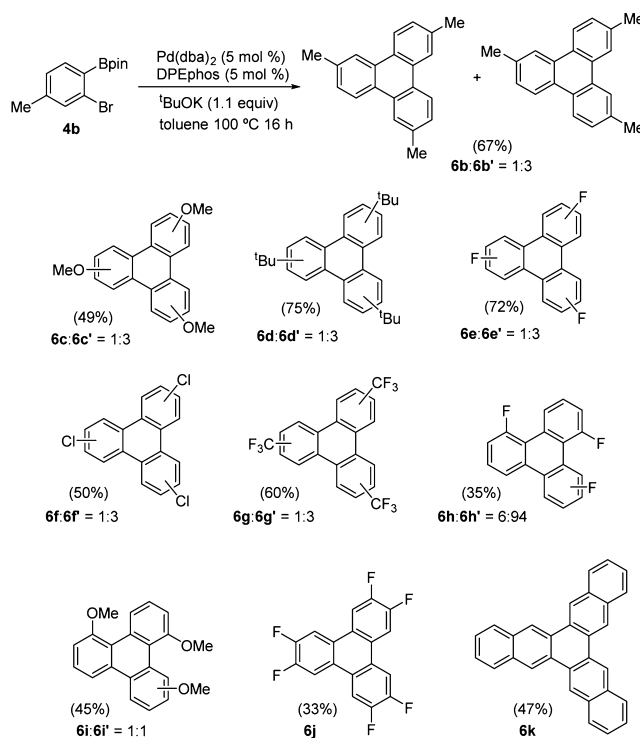
^aReactions carried out with 0.5 mmol of 4a in a Schlenk tube under a N₂ atmosphere at 100 °C. ^bIsolated yields. ^cNMR yield.

With an optimized procedure in hand, we examined alternatives to bromide in the ortho-position to the boronic ester. The 2-chloro substrate worked poorly, giving a 20% yield of 6a, increasing slightly to 25% at 125 °C (entry 3). The 2-triflate substrate, however, was highly effective, affording an 80% yield of triphenylene (entry 4). We elected, however, to focus on the bromo derivatives for further investigation, as their synthesis is easier and more economical. A range of 2-bromo-phenylboronic esters were accordingly synthesized from the corresponding 2-bromo-1-iodobenzenes using a simple two-step procedure: metal-iodine exchange and boronation, followed by esterification with pinacol. We focused initially on 4-substituted substrates such as 4b, as the substituent position in the product triphenylenes can provide insights into the reaction mechanism (Scheme 2).

Trimerization of 4b gave a 1:3 mixture of triphenylenes 6b (C₃ symmetric) and 6b' (no rotational symmetry) in 67% overall yield (ratio determined by ¹H and ¹³C NMR and GC-MS). Compound 6b' has previously been prepared via Pd-catalyzed aryne trimerization using benzoic acid (34% yield)^{6a} and phthalic anhydride (31% yield) precursors,^{12a} whereas 6b has been prepared through cyclohexanone cyclo-condensation and subsequent oxidation (53% yield).¹³ The cyclotrimerization

reaction proved tolerant of both electron-withdrawing and -donating groups at the 4-position of 4, affording moderate yields for the methoxy- and chloro-substituted triphenylenes **6c** and **6f** and good yields of the tert-butyl-, fluoro-, and trifluoromethyl-substituted **6d**, **6e**, and **6g**. In all cases a 1:3 mixture of regioisomers was observed in favor of the non- C_3 symmetric product. Substitution at the 6-position, ortho to the developing triple bond, gave a selective reaction for the fluoro derivative in favor of the novel triphenylene **6h'** (35% total yield, 6:94 of a separable mixture). The ^{19}F NMR spectrum of the major nonsymmetric isomer **6h'** showed a singlet and an AB quartet ($^5J_{\text{F-F}} = 142$ Hz), the latter signal an example of the very large “through-space” coupling experienced by the two crowded fluorine atoms in the bay region of the triphenylene structure.¹⁴ Methoxy substitution at this position, however, led to a 1:1 mixture of products **6i** and **6i'** in 45% yield. This lack of regioselectivity contrasts with the highly selective Pd-catalyzed cyclotrimerization of 3-methoxybenzyne from 2- (trimethylsilyl)phenyl triflate precursors (in favor of the nonsymmetrical **6i'**) reported by Guitián et al.² and suggests this substrate undergoes cyclization through a hybrid mechanism (vide infra). The symmetrical triphenylene **6j** and trinaphthylene **6k** were then prepared from the appropriate 2- bromoaryl boronic esters in moderate yield. Both compounds have previously been synthesized from the analogous 2- trimethylsilylphenyl triflates, in yields of 55% for **6j** and 41% for **6k**.^{2,15}

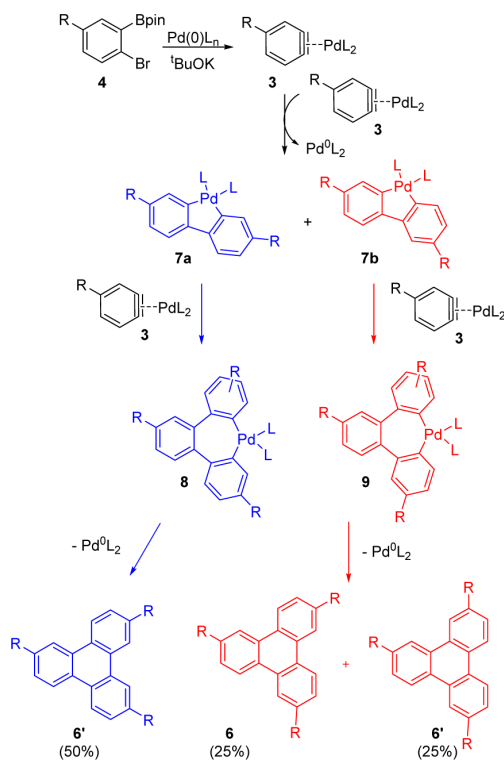
Scheme 2. Triphenylene Substrate Scope



While the precursors and reaction were designed in the context of Pd-catalyzed aryne chemistry, it is conceivable that a stepwise Suzuki–Miyaura mechanism may be in operation. The consistent 1:3 ratio of triphenylene regioisomers from 4- substituted starting materials, however, strongly supports an aryne pathway. The Suzuki–Miyaura mechanism cannot be operating via three successive intermolecular couplings (see Supporting Information for a discussion on this mechanism), as that would yield the C_3 -symmetric regioisomer **6** as the exclusive product. The alternative aryne mechanism, however, fits nicely with the observed product ratio via the pathway shown in Scheme 3. Initial oxidative addition of Pd(0) is followed by base-activated aryne formation to form complex **3**, in line with observations from Wenger and co-workers (Scheme 1).¹⁰ Ligand exchange between two molecules of **3** sets up a cyclopalladation reaction to give the two isomeric palladacycles **7a** and **7b**. We assume a 1:1 ratio of these two intermediates, as meta-substitution typically exerts no regiocontrol in benzyne chemistry.

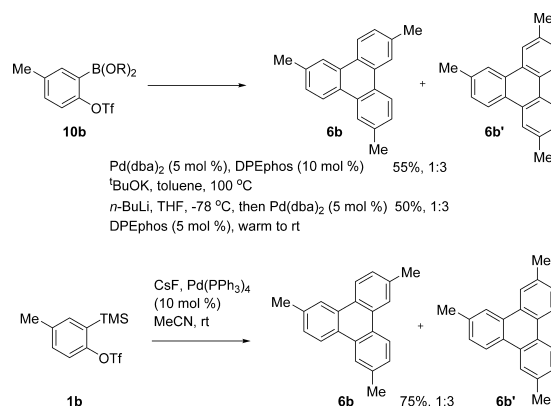
The C_2 -symmetric palladacycle **7a** can lead only to the unsymmetrical triphenylene isomer **6'**, regardless of the orientation of subsequent aryne insertion, thus accounting for 50% of the material (pathway shown in blue). Palladacycle **7b**, on the other hand, can give an equal amount of either the C_3 -symmetric triphenylene **6** or the nonsymmetric product **6'**, again making the assumption that there will be no regioselectivity in the orientation of meta-substituted aryne insertion into the Pd-C bond (pathway shown in red).¹⁶ Hence, the total product ratio of **6**:**6'** is a statistical 1:3 mixture.¹⁷

Scheme 3. Mechanistic Pathway for Cyclotrimerization



To probe the possibility of free benzyne in the reaction, we added 2,5-dimethylfuran (2 equiv) to the trimerization of **4a** and isolated triphenylene **6a** in 40% yield. There was no trace of any aryne Diels–Alder adduct, suggesting that free benzyne is not present in the reaction in appreciable quantities. Next, we used (2-triflate-5-methyl-phenyl)boronic ester **10b** as a substrate, obtaining a 55% yield of **6b** and **6b'** in the same 1:3 regioisomeric mixture, using the same reaction conditions as Scheme 2 ($t\text{BuOK}$ and catalytic $\text{Pd}(\text{dba})_2$, toluene, 100 °C). In a second experiment, we treated **10b** with $n\text{-BuLi}$ in THF at -78 °C, conditions demonstrated by Hosoya to produce benzyne on warming. Addition of $\text{Pd}(\text{dba})_2$ (5 mol %) and DPEphos (5 mol %) and warming to room temperature gave a 50% yield of **6b** and **6b'** as a 1:3 mixture. Finally, we compared our results with *o*-bromophenyl boronic ester **4b** to the established aryne-generation route of fluoride activation of 2-trimethylsilyl aryl triflates. Treating (4-methyl-2-(trimethylsilyl))benzene triflate (**1b**) with Guitián's conditions of CsF and $\text{Pd}(\text{PPh}_3)_4$ (10 mol %) in dry CH_3CN , a reaction not previously reported for this substrate, gave a 75% yield of triphenylenes **6b**:**6b'** in the familiar 1:3 ratio. Collectively, these results underline the involvement of Pd-bound benzyne intermediates in the reaction mechanism.

Scheme 4. Triphenylene Synthesis Using Alternative Precursors



In conclusion, we have introduced a new class of precursor to transition-metal-catalyzed aryne chemistry. The 2-bromo-phenylboronic esters are readily accessed in just two steps from inexpensive haloarene starting materials. In contrast to conventional 2-(trimethylsilyl)phenyl triflate precursors, where fluoride is used to trigger benzyne formation, the Pd catalyst itself initiates both benzyne formation and subsequent C–C bond forming transformations. Further studies of these precursors in aryne chemistry are underway in our group.

ASSOCIATED CONTENT

* Supporting Information

Synthetic procedures for all new compounds and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>

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Notes

The authors declare no competing financial interest. Synthetic procedures for all new compounds and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) Some selectivity would be expected in the relative rates of insertion into the two C–Pd bonds in 7b, given the differing orientations of the R-groups in each case. However, this has no bearing on the overall selectivity, as the two separate insertion events lead to an identical 1:1 mixture of 6 and 6' in each case.
- (17) A hybrid mechanism involving Suzuki–Miyaura coupling plus aryne formation cannot definitively be ruled out (see Supporting Information), for example, through the reaction of an aryne–Pd complex (3) with the starting material (4) to give 7. However, the consistent 1:3 product ratio across different 4-substituted precursors argues against such a pathway for these isomers.