



Sterically Demanding Aryl-Alkyl Suzuki-Miyaura Coupling

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Sterically Demanding Aryl-Alkyl Suzuki-Miyaura Coupling

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Efficient sterically demanding aryl-alkyl Suzuki-Miyaura coupling between di-ortho-substituted aryl halides and secondary alkylboronic acids has been achieved with a Pd-AntPhos catalyst that have shown high reactivity and a broad substrate scope with unprecedented steric hindrance. The methodology has facilitated the synthesis of molecular gears such as by cross-couplings.

Despite the recent advances in the area of aryl-aryl Suzuki-Miyaura coupling reactions,^{1,2} the development of efficient aryl-alkyl cross-couplings is more challenging and relatively unexplored.³ In contrast to the *sp*²-hybridized arylboronic acids, the *sp*³-hybridized alkylboronic acids are relatively bulkier and slower for transmetalation. Moreover, the presence of β -hydrogen in alkylboronic acid allows β -hydride elimination pathway and facilitates the reduction of aryl halides during cross-coupling (Figure 1). The formation of β -hydride elimination-reduction side-product increases significantly with the growing steric bulk on the substrates. It thus remains a significant challenge for the development of sterically demanding aryl-alkyl Suzuki-Miyaura coupling particularly of di-ortho-substituted aryl halide substrates. Herein we report an

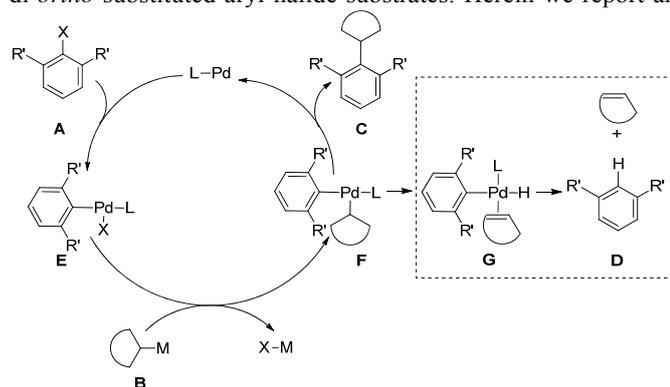


Figure 1. Pd-catalyzed sterically demanding aryl-alkyl coupling and β -hydride elimination-reduction side pathway

efficient method for Suzuki-Miyaura coupling between di-ortho-substituted aryl halides and secondary alkylboronic acids, and cross-coupling product was formed for the first time between di-ortho-secondary-alkyl aryl bromide and cyclic alkylboronic acids. The methodology has facilitated the synthesis of molecular gears such as hexaalkylbenzenes by cross-couplings.

The steric and electronic properties of the phosphorus ligands significantly impact the reactivity and outcome of palladium-catalyzed cross-coupling reactions.⁴ During our study in sterically hindered aryl-aryl Suzuki-Miyaura coupling,⁵ we observed the excellent reactivity of ligand **1** (BI-DIME) and ligand **2** (AntPhos)⁶ for tetra-ortho-substituted biaryl coupling. In particular, an interesting coordination between the Pd center and the anthracenyl moiety of AntPhos was revealed in the X-ray structure of the Pd(0)-AntPhos complex. Although there is no information whether such coordination still exists during the catalytic cycle of cross-coupling, the coordination ability of the rigid anthracenyl moiety should make the formation of G unfavorable (Figure 1) during the aryl-alkyl cross-coupling and thus inhibit the β -hydride elimination-reduction pathway. We thus envisioned that AntPhos would be advantageous for sterically demanding aryl-alkyl Suzuki-Miyaura coupling and further broaden the synthetic utility of Suzuki-Miyaura coupling.

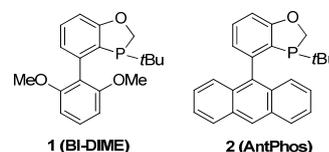
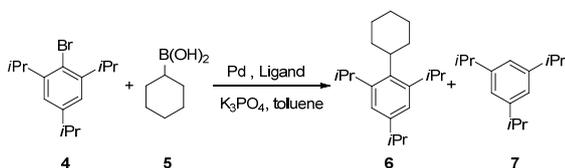


Figure 2. Ligands for sterically demanding aryl-alkyl cross-couplings

While most known palladium catalysts only apply for couplings between mono-ortho-substituted aryl halides and secondary alkylboronic acids or coupling between di-ortho-substituted aryl halides and primary alkylboronic acids, only two examples⁷ are available for the coupling between di-ortho-substituted aryl halides and secondary alkylboronic acids or

zinc reagents with limited substrate scope. We applied ligands **1** and **2** for the Suzuki-Miyaura coupling between 2,4,6-triisopropylphenyl bromide and cyclohexylboronic acid, an extremely sterically demanding and unexplored cross-coupling system. The reactions were performed under nitrogen at 110 °C in toluene for 12 h at 1 mol % palladium loading. To our delight, the desired coupling product was isolated in 31% yield with BI-DIME (**1**) as the ligand along with the reduction side-product **7** (Table 1, entry 1). The yield increased significantly when AntPhos (**2**) was applied as the ligand (entries 2). Elevation of the reaction temperature by using xylenes as the solvent provided **6** in 63% isolate yield. To the best of our knowledge, this is the most sterically demanding aryl-alkyl cross-coupling product to date. To investigate whether other commercially available ligands are applicable, a series of mono- or bis-phosphorus ligands were also employed for comparison (entries 4-12). Except that S-Phos provided a low yield (3%, entry 8) of **6**, no other ligands were applicable for this system, indicating the uniqueness and power of AntPhos for the success of this reaction.

Table 1. Cross-coupling between 2-bromo-1,3,5-trimethylbenzene and cyclohexylboronic acid



Entries ^[a]	Ligand	Conv.(%) ^[b]	Yield of 6 (%) ^[c]	7 (%)
1	1 (BI-DIME)	100	31	69
2	2 (AntPhos)	100	58	42
3 ^[d]	2	100	63	37
4	DPPF	54	0	54
5	DPPE	100	0	98
6	DPPP	100	0	97
7	DPPB	100	0	98
8	S-Phos	100	3	97
9	X-Phos	46	0	46
10	Ru-Phos	52	0	52
11	PCy ₃	100	0	97
12	PPh ₃	83	0	83

[a] The reactions were performed in toluene under nitrogen at 110 °C for 24 h in the presence of 1 mol % Pd(OAc)₂ and 2 mol % ligand with K₃PO₄ as the base unless otherwise specified. [b] Conversions were analyzed by reversed phase HPLC on a C-18 column. [c] Isolated yields. [d] The reaction was run in xylenes at 140 °C for 12 h.

We then looked into the substrate scope of this sterically hindered cross-coupling reaction. As can be seen in Table 2, a series of di-*ortho*-substituted aryl bromides were successfully coupled with 3-,4-,5-, and 6-membered cyclic alkyl boronic acids with a Pd-AntPhos catalyst to form the corresponding coupling products in good to excellent yields (70-99%). In general, the yields followed the trend of the ring size of the cyclic alkyl boronic acids: 3>4>5>6 (entries 12, 14, 16 vs table 1, entry 3). High yields were achieved on reactions with cyclopropyl boronic acids (entries 15-16) due to its

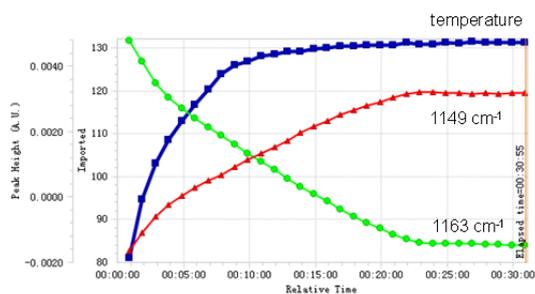
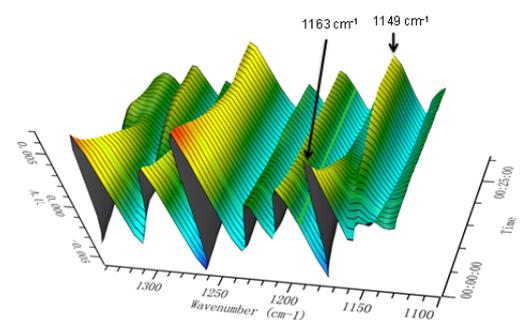
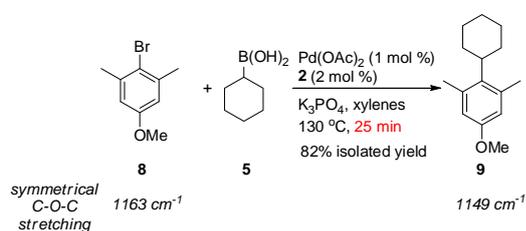
Table 2. Sterically hindered aryl-alkyl cross-couplings

Entry ^[a]	Aryl halide	Boronic Acid	Product	Yield ^[b] (%)
1				92
2 ^[c]				74
3				82
4				70
5 ^[c]				80
6				93
7				80
8				87
9				75
10				79
11 ^[c]				79
12				81
13				92
14				90
15				99
16				99
17 ^[d]				6/82

[a] Unless otherwise specified, the reactions were carried in toluene under nitrogen at 110 °C for 24 h in the presence of 1 mol % Pd(OAc)₂

and 2 mol % AntPhos with K_3PO_4 as the base. [b] Isolated yields. [c] The reactions were run in xylenes at 140 °C for 12 h. [d] The major coupling product is *n*-propyl arene (82%), along with isopropyl arene (6%) and the reduction side-product (12%).

relative small size as well as its inability to undergo β -hydride elimination pathway. The β -hydride elimination-reduction side-product became more severe with the increase of the ring size, as indicated by diminished coupling yields. The reactions proceeded well with di-*ortho*-methyl, ethyl, or isopropyl substituents (entries 1, 5, 6, 13-16). 9-Anthracenyl, 2-methylnaphthyl bromide, 2-methoxynaphthyl bromide was also applicable (entries 2-4, 7-9). Functionalities such as methoxy, nitro, and cyano groups were well tolerable (entries 9-11). When isopropylboronic acid was employed to couple with 2-bromo-1,3,5-trimethylbenzene, the major product was unfortunately the *n*-propyl substituted arene (entry 17) derived from isomerization-coupling. No formation of *tert*-butyl substituted arene was observed when *tert*-butylboronic acid was used as the starting material.

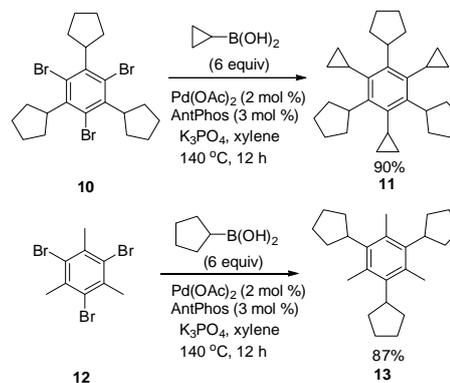


Scheme 1. Reaction profile of the cross-coupling between 2-bromo-5-methoxy-1,3-dimethylbenzene (**8**) and cyclohexylboronic acid (**5**) by ReactIR: a) 3D-FTIR profiles. b) Component profiles.

In order to gain kinetic insight of this cross-coupling methodology, the coupling of 2-bromo-5-methoxy-1,3-dimethylbenzene (**8**) and cyclohexylboronic acid (**5**) was performed in xylenes in the presence of 1 mol % Pd(OAc)₂ and

2 mol % AntPhos, monitored by ReactIR. As shown in Scheme 1, the amount of bromide **8** and the coupling product **9** was easily traced by their IR absorbance at 1163 cm⁻¹ and 1149 cm⁻¹ (symmetrical C-O-C bondstretching), respectively. The reaction proceeded rapidly when the reaction temperature elevated over 80 °C and bromide **8** was completely consumed in only 25 min at 130 °C, demonstrating the high reactivity of the Pd-AntPhos catalyst for this reaction. The desired product **9** was isolated in 82% yield, along with 15% reduction side-product.

Hexaalkylbenzenes are molecular gears⁸ that have unique static and dynamic behaviors due to restricted rotation of each substituent on benzene ring. These compounds are traditionally accessed by trimerization of disubstituted alkynes,⁹ and few reports are available on their syntheses by metal-catalyzed cross-coupling.¹⁰ We believe this methodology provides a facile and versatile method to these interesting molecules. Thus, the coupling of 1,3,5-tribromo-2,4,6-tricyclopentylbenzene (**10**) with cyclopropylboronic acid provided the coupling product **11** in 90% yield (Scheme 2). In a similar fashion, 1,3,5-tricyclopentyl-2,4,6-trimethylbenzene (**12**) can be synthesized from 1,3,5-tribromo-2,4,6-trimethylbenzene (**12**) and cyclopentaneboronic acid in 87% yield by using this methodology. Such structures, which are difficult to access by cyclotrimerization of alkynes, could provide interesting physical organic properties.



Scheme 2. Synthesis of "molecular gears" by Suzuki-Miyaura Coupling

In summary, efficient sterically demanding aryl-alkyl Suzuki-Miyaura couplings between di-*ortho*-substituted aryl halides and secondary alkylboronic acids has been achieved with a Pd-AntPhos catalyst that have shown high reactivity and a broad substrate scope with unprecedented steric hindrance. The unique structure of AntPhos plays a major role for its reactivity and allows overcoming β -hydride elimination-reduction side pathway. The methodology has been applied successfully for efficient synthesis of molecular gears such as hexaalkylbenzenes by cross-coupling. Further study on sterically demanding aryl-alkyl Suzuki-Miyaura coupling and application of the Pd-AntPhos catalyst in broadening the scope of metal-catalyzed cross-coupling is currently ongoing in our laboratory.

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