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Synthesis of hindered biphenyls by sequential non-transition metal-catalyzed reaction/palladium-catalyzed cross-couplings

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Abstract

The sequential reaction of 1,2-dihalobenzenes with aryl lithiums followed by palladium-catalyzed cross-coupling reactions with Grignard reagents and arylboronic acids is described. This sequential reaction provides a convenient and expeditious access to tri-*ortho* substituted biaryl derivatives.

Over the past decades, palladium-catalyzed cross-coupling reactions, e. g., the Suzuki coupling, the Kumada coupling, the Stille coupling, the Heck coupling, the Sonogashira coupling, and the amination of aryl halides with amines, etc., have become some of most powerful transformations in organic synthesis.^{1,2} They have been extensively employed for the synthesis of a wide variety of organic compounds ranging from small organic molecules to macromolecules.^{1,2} In our laboratory, we are interested in developing highly active transition metal catalysts and new reactions/processes that could further heighten the efficiency of transition metal catalysis.³ We are particularly interested in developing new reactions/processes by combining two or more transition metal-catalyzed cross-coupling reactions into one synthetic operation through sequential or tandem/domino fashions. We have recently documented Pd-catalyzed Suzuki cross-coupling of dihaloarenes with arylboronic acids, a process that combines two Pd-catalyzed cross-coupling reactions.^{3f} We have also reported the indole formation from 1,2-dihaloobenzenes, terminal alkynes and amines, which involve Pd-catalyzed sequential C-C and C-N bond formations.^{3e} More recently, we have also reported annulative tandem/domino reactions of 1,2-dihaloarenes and 2-haloaryl tosylates with hindered Grignard reagents to form substituted fluorenes,^{3c} a process that combines the cross-coupling strategy with sp³ C-H activation strategy. As many bond forming reactions do not involve transition metal catalysis, we reasoned that if non-transition metal-catalyzed bond forming reactions could be combined with transition metal catalysis in a sequential or tandem fashion, new, efficient reaction processes could be developed. Herein, we report our preliminary results in this field, specifically, on the synthesis of tri-*ortho* substituted biaryls via sequential anionic - Pd-catalyzed cross-coupling strategy.

Biaryls are found in important biologically active molecules such as the naturally occurring terpenin⁴ or in synthetic anti-HIV derivatives⁵ and are used as core structures for molecular recognition devices,⁶ organic semiconductors, material for nonlinear optics, and metal ligands for catalysts.⁷ Many catalysts/methods have been developed for the synthesis of such biaryl structures.^{8,9} However, catalysts/methods that can effectively lead to the formation of tri- or

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Supporting Information Available: General procedures and characterizations of the sequential reactions.

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tetra-*ortho* substituted biphenyls are still very limited.^{10,11} For the formation of tri-*ortho* substituted biphenyls, there are three general routes: (a) cross-coupling of *ortho*-substituted aryl halides with 2,6-disubstituted arylorganometallic reagents, (b) cross-coupling of *ortho*-substituted arylorganometallic reagents with 2,6-disubstituted aryl halides, and (c) cross-coupling of 2-halo-2',6'-disubstituted biphenyls with an organometallic reagents (Scheme 1). While routes **a** and **b** involve highly sterically hindered 2,6-disubstituted substrates or reagents and often required expensive catalyst systems, route **c** involves much less sterically hindered mono-*ortho* substituted halobenzenes as substrates. As mono-*ortho* substituted halobenzenes in route **c** could be readily available through the reaction of 1,2-dihaloarenes with lithium reagents or Grignard reagents (Scheme 2),^{11a,12} we thus envisioned that combining the anionic tri-*ortho* substituted 2-bromobiphenyl formation process with cross-coupling catalysis (Scheme 1, route **d**) could be an efficient reaction sequence for the preparation of tri-*ortho* substituted biphenyls from readily available 1,2-dihaloarenes and catalyst systems.

We began our study by identifying palladium catalysts that could effect the cross-coupling of tri-*ortho* 2-bromobiphenyls with organometallic reagents. Bulky 2-mesitylmagnesium bromide was chosen as the model reagent as we reasoned that catalysts that can effect the cross-coupling with 2-mesitylmagnesium bromide as reagent should catalyze cross-coupling reactions with less sterically hindered organometallic reagents. Several combinations of readily available palladium reagents and phosphines were tested and the results are summarized in Table 1. We found that both Cy₃P and *t*-Bu₃P were highly efficient ligands (Table 1, entries 5-7). Since Pd(OAc)₂ and Cy₃P are cheaper and easier to handle than Pd(dba)₂ and *t*-Bu₃P, Pd(OAc)₂/Cy₃P was chosen for further study.

We next turned our attention to combine the formation reaction of 2-bromo-2',6'-dimethoxybiphenyl from 1,2-dibromobenzene (**1a**) and 2-lithio-1,3-dimethoxybenzene (**2**) with palladium-catalyzed cross-coupling with 2-mesitylmagnesium bromide to test the new sequential reaction process. 2-Lithio-1,3-dimethoxybenzene (**2**) was *in situ* generated by following reported method of treating 1,3-dimethoxybenzene with *n*-BuLi.^{12a} After several trials, we were pleased to find that with the use of 1.25 equiv. of **2** relative to **1a**, the sequential reaction product **4a** was obtained in high yield (Table 2, entry 1).

By using 1.25 equiv. of **2** relative to **1a** and Pd(OAc)₂/PCy₃ as catalyst, a series of sequential reactions based on anionic coupling of 1,2-dibromobenzene and 1-bromo-2-chlorobenzene with aryllithiums followed by palladium-catalyzed cross-coupling with Grignard reagents were studied and the results are summarized in Table 2.

The sequential reactions were found to be general and efficient. The reactions proceeded smoothly and the hindered biaryl derivatives were obtained in good to excellent yields. Variation of R and R' substituents in 1,3-dimethoxybenzene and Grignard reagents did not have a great effect on the yields of biphenyls; both arylmagnesium bromide and arylmagnesium chloride could generate the corresponding biaryl derivatives in high yields (Table 2, entries 3 and 6). In the case of with 1-bromo-2-chlorobenzene as the substrate (entries 8 and 9), with the lithiation process being carried out at 0° C and Pd-catalyzed cross-coupling step at 60 °C, the sequential reaction products were obtained in good yields.

To further demonstrate the utility of this method and broaden the reagent scope, we also investigated the sequential reaction of anionic reaction/Pd-catalyzed cross-coupling with arylboronic acids as coupling partners. Under the reaction condition similar to the sequential reaction with Grignard reagent as coupling partners, the sequential reaction of aryl lithium, 1,2-dibromobenzene and arylboronic acids give excellent yields of tri-*ortho* substituted biphenyls (up to 96%) (Scheme 3).

In summary, we have demonstrated that non transition metal-catalyzed reaction of 1,2-dihalobenzenes with aryl lithiums to form 2-bromo-2',6'-dimethoxybiphenyls can be combined with palladium-catalyzed cross-coupling reactions. With Grignard reagents and arylboronic acids as coupling partners, tri-*ortho*-substituted biaryls could be efficiently obtained in good to excellent yields from this new sequential reaction. We are currently exploring sequential/tandem reactions that involve other non transition metal-catalyzed reactions with transition metal catalysis and our results will be reported in due course.

Supplementary Material

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Scheme 1.
Reported methods **a-c** to access tri-*ortho* substituted biphenyls

Scheme 2.

Reported synthesis of 2-bromo-2',6'-dimethoxybiphenyls from 1,2-dihalobenzenes

Scheme 3.
Sequential reactions with arylboronic acids as coupling partners

Table 1

Catalyst screening ^a

Entry	Catalyst	Conversion(%) ^b
1	3% Pd(OAc) ₂	32
2	3% Pd(PPh ₃) ₄ + 6% Cy ₃ P	39
3	3% Pd(PPh ₃) ₄ + 6% Ph ₃ P	92
4	3% Pd(PPh ₃) ₄ + 6% <i>o</i> -Tol ₃ P	94
5	3% Pd(PPh ₃) ₄ + 6% Cy ₃ P	100(94) ^c
6	3% Pd(PPh ₃) ₄ + 6% <i>t</i> -Bu ₃ P	100
7	3% Pd(dba) ₂ + 6% Cy ₃ P	100

^a Reaction conditions: bromide (1.0 equiv.), 2-mesitylmagnesium bromide (2.5 equiv.), 3% catalyst, THF, 60 °C, 5h.^b Based on ¹H NMR.^c Isolated yields

Table 2

One-pot, sequential reaction to access tri-*ortho* substituted biaryls with Grignard reagents as coupling partners
^a

Entry	R	Dihalobenzene	ArMgX	Yields (%) ^b
1	H			89
2	H			71
3	H			92
4	H			77
5	CH ₃ O			80
6	CH ₃ O			86
7	CH ₃ O			95
8	R= H			77 ^c
9	R= H			86 ^c

^a Reaction conditions: 1,2-dihalobenzene (1.0 equiv.), aryllithium (1.25 equiv.), 3% Pd(OAc)₂/6% Cy₃P, Grignard reagents (2.5 equiv.)

^b Isolated yields based on 1,2-dihalobenzene after recrystallization.

^c Reaction carried out at 0°C for the first step.