

Palladium-Catalyzed Cross-Coupling of *B*-Benzyl-9-borabicyclo[3.3.1]nonane To Furnish Methylene-Linked Biaryls

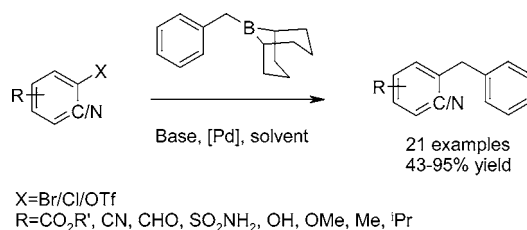
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ABSTRACT



Benzylboranes are noticeably uncommon partners within Suzuki–Miyaura coupling reactions. *B*-Benzyl-9-BBN was successfully coupled to a range of aryl/heteroaryl bromides, chlorides, and triflates to give pharmacologically important methylene-linked biaryl structures. Activated, deactivated, and sterically hindered substrates were successfully coupled in high yield using Pd(PPh₃)₄ or Pd(OAc)₂ with SPhos as the catalyst system.

During the final quarter of the 20th century, palladium-catalyzed reactions emerged as extremely powerful and general procedures for the construction of carbon–carbon and carbon–heteroatom bonds.¹ Among palladium-catalyzed cross-coupling processes, the Suzuki–Miyaura reaction of aryl and vinyl halides/triflates with organoboranes is emerging as a favorite.² These transformations offer the advantage of unrivalled functional group compatibility, they are environmentally benign, and a large number of organoboranes are commercially available.

Much of the recent effort on the Suzuki–Miyaura reaction has focused on developing new metal ligand systems that

facilitate the cross-coupling and expand the reaction scope.³ This has resulted in tremendous progress being achieved in the palladium-catalyzed cross-coupling of organometallic compounds even with unactivated aryl chlorides.⁴ However, only limited work has been directed toward expanding the range of organoboranes that can be used in the Suzuki–Miyaura reaction.⁵

Specifically, benzylboranes are noticeably uncommon coupling partners in Suzuki–Miyaura chemistry. Despite numerous publications on the preparation of benzylboronates via the borylation of benzyl halides with pinacolborane/diborane,⁶ subsequent use of these in a coupling reaction has not been described. This prompted our investigation into

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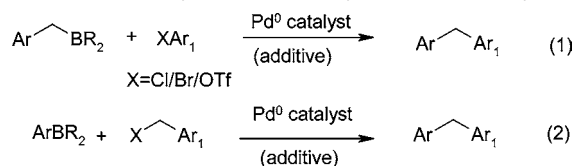
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the palladium-catalyzed reaction of *B*-benzyl-9-borabicyclo[3.3.1]nonane (*B*-benzyl-9-BBN) with aryl halides/triflates. Despite the commercial availability of *B*-benzyl-9-BBN, only two low-yielding examples of its use in a Suzuki–Miyaura reaction were found in the literature.⁷ Developing suitable coupling conditions for aryl halides/triflates to a benzylborane partner such as *B*-benzyl-9-BBN would allow formation of methylene-linked biaryls in one chemical step (Scheme 1, eq 1).

Scheme 1. Synthesis of Methylene-Linked Biaryls



Methylene-linked biaryls are ubiquitous structural constituents of pharmacologically interesting compounds,⁸ and the methylene bridge represents an important linkage that can result in molecules having unique conformational and binding properties. There is precedent for the coupling of phenylboronic acids with benzyl bromides⁹ or benzylic carbonates¹⁰ to give the diarylmethane product (Scheme 1, eq 2). Alternatively, Itami et al. described the coupling of (2-pyridyl)silylmethylstannanes with aryl iodides to generate methylene-linked diphenyls.¹¹ It was envisaged that the ability to couple benzylboranes to a wide range of aryl halides and triflates, and in particular aryl chlorides, which are available in abundance from commercial sources, would be a useful addition to the current methods.

Our initial efforts were directed toward finding suitable reaction conditions using ethyl 4-bromobenzoate **1a** as a model substrate (Table 1, entry 1). The cross-coupling of **1a** with *B*-benzyl-9-BBN in the presence of Pd(PPh₃)₄ in DMF was investigated using a range of different base activators. Briefly, use of K₃PO₄ (3 equiv) was found to be optimal. Cs₂CO₃ and KF were also found to be effective in the coupling reaction, but use of these bases resulted in significantly longer reaction times.¹² KO^tBu failed to promote the reaction.

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Table 1. Palladium-Catalyzed Coupling of Activated Aryl/Heteroaryl Halides with *B*-Benzyl-9-borabicyclo[3.3.1]nonane*

entry	X	aryl halide	time (h)	cond.	product, % ^a
1	Br		1	A	2a , 70%
2	Br		2	B ^b	2a , 83%
3	Br		1	A	2b , 74%
4	Cl		1	B ^c	2b , 63%
5	Cl		2.5	B ^b	2b , 89%
6	Br		1	A	2c , 55%
7	Br		2	B ^b	2c , 76%
8	Br		1	B	2d , 94%
9	Cl		16	B ^c	2d , 70%
10	Br		1	A	2e , 62%
11	Cl		1	B ^c	2e , 72%
12	Br		2.5	B ^b	2f , 93%
13	Cl		11	B ^c	2g , 62%
14	Cl		1	B ^b	2h , 76%

*Reaction conditions: (A) 1.0 equiv of aryl halide, 2.0 equiv of *B*-benzyl-9-BBN, 3.0 equiv of K₃PO₄, 4 mol % of Pd(PPh₃)₄, DMF, 1 mL of water, 60 °C; (B) as in A but 2 mol % of Pd(OAc)₂ and 4 mol % of SPhos used, anhydrous conditions. ^a Isolated yield. ^b 3 mol % of Pd(OAc)₂ and 6 mol % of SPhos used. ^c THF was used as solvent.

Pleasingly, using K₃PO₄ as base, and 2 equiv of *B*-benzyl-9-BBN, the coupling of **1a** was found to go to completion in 2 h after heating at 60 °C in either DMF or THF. The reaction was markedly slower when toluene was used as the solvent. Aqueous conditions were also considered, and addition of water aided the reaction (shorter coupling time), possibly due to better dissolution of the base. Complete conversion of the starting material to the desired methylene-linked biphenyl **2a** in 70% yield was now achieved¹³ in 1 h (Table 1, entry 1).

(12) The reaction was monitored by LC/MS for disappearance of starting aryl bromide.

$\text{Pd}(\text{PPh}_3)_4$ was found to be an efficient catalyst in the coupling of a number of electron deficient aryl bromides. Ester (**1a**), cyano (**1b**), sulfonamide (**1d**), and formyl (**1g**) substituted aryl bromides were all coupled in 1 h to give the corresponding methylene-linked compounds in respectable yields (Table 1, entries 1, 3, 6, and 10 respectively). Applying the same reaction conditions to 4-chlorobenzonitrile **1c**, however, failed to give any product even after heating at 60 °C for 16 h. This prompted us to screen a range of palladium sources. Briefly, combining $\text{Pd}(\text{OAc})_2$ with the recently described SPhos (2-(dicyclohexylphosphino) dimethoxybiphenyl) ligand⁴ proved to be a superior system for Suzuki–Miyaura coupling of *B*-benzyl-9-BBN to a wide range of aryl halides. The latter were readily varied in terms of their electronic and steric properties without detriment to the coupling reaction. Anhydrous conditions were found to be best with this $\text{Pd}(\text{OAc})_2/\text{SPhos}$ system.

Pleasingly, 4-chlorobenzonitrile **1c** was now coupled in 1 h to give the methylene-linked biphenyl using SPhos (4 mol %) and $\text{Pd}(\text{OAc})_2$ (2 mol %) as the catalyst system. An improved yield of the product **2c** (89%) was obtained when the catalyst loading was slightly increased (Table 1, entry 5). In general, the reactions were cleaner and yields improved on using the more activated ligand system (Table 1, cf. entries 1 and 2 and also entries 6 and 7).

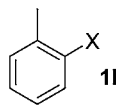
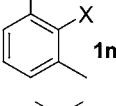
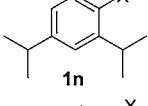
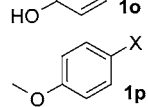
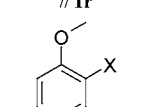
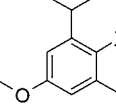
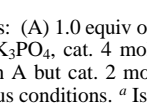
In some cases, longer reaction times were required for complete conversion of the aryl chloride compared to the corresponding bromide (Table 1, entries 8 and 9). As can be seen a range of functional groups (ester, formyl, sulfonamide, cyano) are well tolerated in the aryl halide coupling partner. A number of heterocyclic halides were also successfully derivatized to their benzyl-substituted analogues (Table 1, entries 13 and 14).

The coupling reaction could also be carried out on ortho-substituted sterically hindered substrates (Table 2, entries 1 and 2). Although reaction times were longer (16–18 h at 60 °C), this could be reduced by increasing the reaction temperature as for the triisopropyl substituted aryl bromide **1n** (Table 2, entry 3).

As can be seen from Table 2, electron-rich, and as such deactivated, aryl halides can also be converted to the methylene-linked diphenyls using this protocol. For example, 4-bromophenol (**1o**) was found to undergo the coupling reaction in 2.5 h and gave the desired product (**2l**) in 83% yield. Similarly, a methoxy substituent, on the aryl halide, is well tolerated when it is para (Table 2, entry 5). A lower yield results when the aryl bromide is ortho-substituted with this group (Table 2, entry 8). Comparing the corresponding bromide, chloride and triflate anisole (**1p**, **1q**, **1r**, respectively), it was noted that the triflate has a much shorter

(13) **General Procedure.** K_3PO_4 (3 equiv) was added to the catalyst $\text{Pd}(\text{PPh}_3)_4$ or $\text{Pd}(\text{OAc})_2$ and SPhos in THF or DMF (3 mL/mmol). When $\text{Pd}(\text{PPh}_3)_4$ was used, H_2O (1 mL/mmol) was added. The aryl halide/triflate (1 equiv) was subsequently added along with the *B*-benzyl-9-BBN (2 equiv of a 0.5 M solution in THF). The resulting mixture was heated with stirring in a sealed tube until the reaction had reached completion, as judged by LC/MS. The crude mixture was diluted with EtOAc, the organics washed with 2 M NaOH, brine, dried (MgSO_4) and concentrated in vacuo to yield the crude product. Purification was carried out on silica gel using pentane/ethyl acetate to give the desired methylene-linked biaryl product.

Table 2. Palladium-Catalyzed Coupling of Deactivated/Sterically Hindered Aryl Halides/Triflates with *B*-Benzyl-9-borabicyclo[3.3.1]nonane*

1		2	
entry	X	aryl halide/triflate	time (h) cond product, % ^a
1	Br		16 B 2i , 77%
2	Br		16 B 2j , 80%
3	Br		1.5 B ^b 2k , 52%
4	Br		2.5 B ^c 2l , 83%
5	Br		16 B 2m , 95%
6	Cl	// 1q	16 B ^d 2m , 53%
7	OTf	// 1r	1 B ^d 2m , 84%
8	Br		16 B ^d 2n , 43%
9	Br		4.5 B ^b 2o , 80%

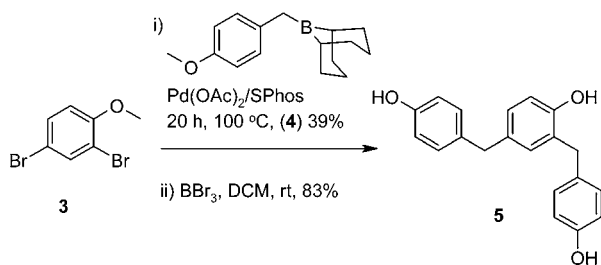
*Reaction conditions: (A) 1.0 equiv of aryl halide, 2.0 equiv of *B*-benzyl-9-BBN, 3.0 equiv of K_3PO_4 , cat. 4 mol % of $\text{Pd}(\text{PPh}_3)_4$, DMF, 1 mL of water, 60 °C; (B) as in A but cat. 2 mol % of $\text{Pd}(\text{OAc})_2$ and 4 mol % of SPhos ligand, anhydrous conditions. ^a Isolated yield. ^b Reaction carried out at 100 °C. ^c 3 mol % of $\text{Pd}(\text{OAc})_2$ and 6 mol % of SPhos ligand used. ^d THF was used as solvent.

coupling time (1 h vs 16 h for the bromide/chloride) and gives a comparable yield to the bromide. As before, increasing the temperature, to 100 °C, gave shorter reaction times even for the sterically hindered, electron-rich aryl bromide **1t** which was coupled in excellent yield (80%, Table 2, entry 9).

As outlined below (Scheme 2), the benzylation reaction was used to synthesize naturally occurring 2,4-bis(4-hydroxybenzyl)phenol¹⁴ (**5**) in two steps from commercially available 2,4-dibromoanisole. Thus, dibenylation of the unactivated bisbromide (**3**) was achieved in a reasonable yield

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Scheme 2. Synthesis of 2,4-Bis(4-hydroxybenzyl)phenol



using *B*-(4-methoxybenzyl)-9-BBN as the benzylating agent. The latter was prepared from *B*-methoxy-9-BBN using standard chemistry.¹⁵ Global demethylation was carried out on the product from the coupling reaction (4) using boron tribromide to furnish the natural product (5) in a reasonable overall yield (32%).

In summary, benzylboranes are noticeably uncommon partners in palladium-catalyzed cross-coupling reactions. We

have successfully explored the coupling of such a benzylborane, namely *B*-benzyl-9-BBN, with a range of aryl/heteroaryl halides and a triflate. Catalytic amounts of palladium [Pd(PPh₃)₄ or Pd(OAc)₂ with SPhos] were employed to transfer a benzyl group to a range of electron rich, poor and sterically hindered aryl partners, furnishing high yields of functionalized methylene-linked biphenyls.

Furthermore, aryl chlorides which are available in abundance from commercial sources, were shown to be suitable substrates in this palladium-catalyzed process. We feel this increases the scope of the method, which may offer a useful addition to the repertoire of coupling reactions that are currently catalyzed by palladium.

Acknowledgment. We thank Dr. Chris Hayes, Dr. Simon Woodward, and Dr. Garry Pairaudeau for helpful discussions.

Supporting Information Available: ¹H and ¹³C NMR data and literature references for the products illustrated in Tables 1 and 2 and Scheme 2. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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