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Suzuki-Miyaura Cross-Coupling Reactions of Benzyl Halides with Potassium Aryltrifluoroborates

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Abstract

The palladium-catalyzed cross-coupling of potassium aryltrifluoroborates with benzylic halides occurs in good yield with high functional group tolerance. The increased stability of potassium aryltrifluoroborates compared to other boron coupling partners makes this an effective route to functionalized methylene-linked biaryl systems.

Introduction

Suzuki-Miyaura cross coupling has become a powerful synthetic tool for the synthesis of carbon-carbon bonds,¹ and recent advances have expanded the scope of this coupling to include alkyl halide cross-coupling.² High functional group tolerance, easily separable and non-toxic by-products, and increasing commercial availability of boron coupling partners have made the Suzuki-Miyaura coupling both a popular and effective tool.

Despite recent advances, coupling of traditional benzylic organoboron compounds has, in general, been difficult.³ Methods utilizing a Suzuki-Miyaura cross coupling to access methylene-linked biaryl systems, which are common structural elements of both biologically active compounds⁴ and pharmaceuticals,⁵ possess distinct drawbacks. For example, the synthesis of methylene-linked biaryl compounds using aryl halide coupling partners requires two equivalents of *B*-benzyl-9-BBN.⁶ Furthermore, the synthetic utility of the coupling of 9-BBN is less than ideal because of its poor atom economy, low functional group tolerance, and flammability.

Previous efforts to couple benzyl halides using arylmetallics to access methylene-linked biaryls engendered significant stoichiometric inefficiencies as well; reported procedures required either 1.5^{7,8} or 2.0⁹ equivalents of boronic acid or 1.5 equivalents of an arylstanane.¹⁰

Methylene-linked biaryl systems have also been accessed by the coupling of both benzyl carbonates¹¹ and benzyl phosphates¹² with boronic acids; however, coupling of benzylic electrophiles to heteroaryl boron coupling partners has not been demonstrated in either method. Furthermore, Cu(I)-catalyzed cross-coupling reactions between Grignard reagents and benzylic halides¹³ and phosphates¹⁴ have been reported, but Grignard reagents make the reaction incompatible with various functional groups including ketones, aldehydes, and substrates with acidic protons.

In addition to their air- and moisture stability,¹⁵ the greater nucleophilicity¹⁶ of the potassium trifluoroborates over the corresponding organoboranes and boronic acid derivatives makes the

organotrifluoroborates valuable starting materials for palladium-catalyzed cross coupling with sp^3 -hybridized benzylic electrophiles. Furthermore, the use of potassium aryltrifluoroborates expands the range of tolerated functionalized coupling partners while increasing atom economy.

Potassium aryltrifluoroborates for this procedure can be easily synthesized by various methods. However, aryltrifluoroborates are most commonly accessed by the addition of a Grignard reagent to trimethylborate¹⁷ followed by the addition of aqueous of KHF_2 .¹⁸ Addition of inexpensive, aqueous KHF_2 to either an aryl boronic acid or aryl boronate ester will also afford the potassium organotrifluoroborate directly.

Results and Discussion

Initial efforts focused on optimizing conditions under which benzyl bromide **1** couples to potassium phenyltrifluoroborate **2** (Table 1).

The screening indicated that there are numerous systems through which the desired cross coupling could occur, but $PdCl_2(dppf) \cdot CH_2Cl_2$ with Cs_2CO_3 afforded the optimum GC conversion to diphenylmethane **3** while requiring the lowest catalyst loading. With catalyst loading above the optimum, the starting material was consumed, but the percentage of homocoupled product was found to rise quickly.

Optimization revealed the requirement for three equivalents of base. Experiments attempting to reduce the amount of base prevented reactions from reaching completion. Additionally, there seems to be a requirement for Cs_2CO_3 . Reactions using 3 equivalents K_2CO_3 resulted in 3% each of the biphenyl and bibenzyl homocoupled product; however, when 1 equivalent Cs_2CO_3 was combined with 2 equivalents of K_2CO_3 , the reaction yielded full conversion to the desired product. Additionally, the reaction reached completion in comparable time with only 1% biphenyl homocoupled product when only 2 equivalents of Cs_2CO_3 were used. The use of $KHCO_3$ and K_3PO_4 resulted in lower assay yields, and reactions using these bases were not pursued.

Solvent optimization revealed that ethereal solvents tended to offer the highest isolated yields with minimal homocoupling (Table 2). Additionally, the rate of reaction was clearly accelerated by the use of solvents when heated at or above 90 °C. Reactions in cyclopentyl methyl ether (CPME) were the fastest, and occurred with the least homocoupled product as determined by gas chromatography. Even under optimized conditions, homocoupling of both coupling partners was seen in all reactions, each representing no more than 1.5% of the product mixture. This homocoupling was observed to occur progressively throughout the reaction.

Several general reactivity trends were observed (Table 3). Benzyl chloride is a viable partner when coupled to activated, electron rich potassium aryltrifluoroborates (entry 3); however, attempts to react benzyl chloride with electron poor potassium aryltrifluoroborates resulted in low yields of the coupled products. Although no detailed mechanistic studies have been performed, we speculate that the electron rich organotrifluoroborates facilitate the transmetalation step of the process. Because of the more favorable oxidative addition, benzyl bromides are coupled with better yields and higher functional group tolerance than the benzyl chlorides, although other factors could certainly play a role as well.

Because the SPhos ligand²⁶ is known to increase the rate of some cross-coupling reactions yielding diarylmethanes,¹⁶ catalytic amounts of $Pd(OAc)_2$ and SPhos were used in an attempt to increase the yield of reactions using benzyl chloride. Unfortunately, the $Pd(OAc)_2$ /SPhos system led to decomposition of the chloride starting material with only moderate conversion to the desired product **3** when using potassium phenyltrifluoroborate as a coupling partner.

Steric hindrance from aryltrifluoroborate **6** has no significant effect on the coupling. Furthermore, the coupling of benzyl bromide to potassium aryltrifluoroborates is tolerant of a broad range of functionality. Nitro groups seem to be the exception, as coupling of the nitro substituted trifluoroborate results in low yields (entry 10). Interestingly, although the use of CPME rather than THF typically results in an increase in reaction rate while achieving approximately the same yield, this higher-boiling solvent was required for the cross-coupling of compound **9** to occur. When THF was used to couple compound **9**, the reaction resulted in full conversion to the homocoupled bibenzyl product and decomposition of the trifluoroborate starting material.

Heterocycles examined participated effectively in the reactions (Table 4, entries 1, 2, and 5). The cross-coupling of potassium aryltrifluoroborates **13** and **14**, synthesized via Wittig reactions on the trifluoroborate benzaldehydes,¹⁹ highlights one advantage of aryltrifluoroborate coupling partners over boronic acids. No Wittig reactions on boronic acid aldehydes have been reported because of the incompatibility of the acidic protons of the boronic acids with the ylide,¹⁹ and there have been few reports of Wittig reactions on aromatic boronate esters, which suffer from poor atom economy.²⁰ Functionalized potassium aryltrifluoroborates, however, are readily synthesized using Wittig chemistry. Additionally, potassium organo-[1,2,3]-triazol-1-yl-trifluoroborates²¹ are easily accessed via a one-pot synthesis using haloalkyl starting materials, and the coupling of one of these reagents, **15**, occurs in high yield.

Several functionalized benzyl bromides were examined as substrates for the reaction (Table 5). The pattern of reactivity is consistent throughout the study as electron rich nucleophiles and electron poor electrophiles generally offer the best yields. Moreover, electron-poor trifluoroborates are more prone to homocoupling than are electron rich trifluoroborates, probably due to the slower rate of the desired coupling, which is similarly observed with boronic acid coupling partners.²²

Previous work¹¹ synthesizing diarylmethanes via a Suzuki–Miyaura cross-coupling of benzyl carbonates did not demonstrate examples of heteroaryl substrates as either coupling partner. Our attempts to use benzylic carbonate electrophiles (Table 6) showed limited success with potassium aryl trifluoroborates, and additionally the method did not tolerate the heteroaromatics tested. Carbonate starting material as well as deboronated trifluoroborates were isolated from these failed reactions.

While reactions were optimized with 2 mol % catalyst for 0.5 mmol reactions, catalyst loading can be successfully decreased on a 1 gram reaction scale without significantly affecting the yield or reaction times (eq 1).

(1)

Early studies¹³ demonstrated the inability to couple secondary benzylic halides to aryl boronic acids. Unfortunately, we also noted that in the presence of a Pd(II) species, β -hydride elimination of 1-bromoethylbenzene proceeded faster than the desired cross-coupling reaction, and styrene was isolated as the major by-product (eq 2).

(2)

Consequently, bromodiphenylmethane was selected as a model substrate to determine whether 2° benzylic coupling could transpire in the absence of a mechanistic pathway for β -elimination (eq 3). The yield for the secondary benzylic bromide cross-coupling was approximately 30%; however, the homocoupled product of bromodiphenylmethane and the desired coupling product could not be separated by either column chromatography or by recrystallization.

(3)

In conclusion, the palladium-catalyzed cross-coupling of benzyl halides with potassium aryltrifluoroborates occurs in high yield with good functional group tolerance. With low catalyst loading and broad reaction scope, this procedure is an effective method to access both highly functionalized natural products and pharmaceuticals with diarylmethane substructures.

Experimental Section

General Procedure for the Suzuki–Miyaura Cross-Coupling Reactions. Preparation of Diphenylmethane

A solution of potassium phenyltrifluoroborate (98.4 mg, 0.5 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (8 mg, 0.01 mmol), and benzyl bromide (90 mg, 0.5 mmol) in THF/ H_2O (10:1) (5 mL) was heated under a N_2 atmosphere in a sealed tube. The reaction mixture was stirred at 77 °C for 23 h, then cooled to rt and diluted with water (2 mL) followed by extraction with CH_2Cl_2 (10 mL $\times$ 3). The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (eluting with *n*-pentane/ether = 100:1) to yield diphenylmethane (70.56 mg, 84%): ^1H NMR (360 MHz, CDCl_3) δ 4.14 (s, 2H), 7.24–7.30 (m, 6H), 7.43 (t, J = 7.5 Hz, 4H); ^{13}C { ^1H } NMR (90 MHz, CDCl_3) δ 42.2, 126.3, 128.7, 129.2, 141.3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Screening Pd Catalyst Systems^a

entry	Pd source (mol %)	ligand (mol %)	solvent	conversion, ^{bc}
1	Pd(OAc) ₂ (5)	PPH ₃ (10)	toluene/H ₂ O	70 (20,3)
2	Pd(OAc) ₂ (2.5)	PPH ₃ (5)	toluene/H ₂ O	92 (6,2)
3	Pd(OAc) ₂ (1.5)	PPH ₃ (3)	toluene/H ₂ O	73 (3,11)
4	Pd(OAc) ₂ (2)	S Phos (4)	THF/H ₂ O	60 (0,0)
5	Pd(OAc) ₂ (2)	X Phos (4)	THF/H ₂ O	70 (10,10)
6	Pd(OAc) ₂ (2)	Ru Phos (4)	THF/H ₂ O	50 (8,12)
7	Pd(dppf)·CH ₂ Cl ₂ (9)	none	THF/H ₂ O	90 (6,1)
8	Pd(dppf)·CH ₂ Cl ₂ (3)	none	THF/H ₂ O	98 (3,1)
9	Pd(dppf)·CH ₂ Cl ₂ (2.5)	none	THF/H ₂ O	98 (0,2)
10	Pd(dppf)·CH ₂ Cl ₂ (1.5)	none	THF/H ₂ O	73 (0,5)

^a Reaction conditions: 0.5 mmol of **1**, 0.505 mmol of **2** and 1.5 mmol of base (K₃PO₄) for entries 1–3; Cs₂CO₃ for entries 4–7) in 5 mL of solvent. Solvent ratios are solvent:H₂O (10:1). dppf = 1,1'-bis(diphenylphosphino)ferrocene. S Phos = [2(dicyclohexylphosphino) dimethoxybiphenyl]. X Phos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. Ru Phos = 2-Dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl.

^b Reactions were monitored by gas chromatography after 24 hours.

^c The ratio of homocoupled products is given: (biphenyl, bibenzyl).

Table 2

Solvent Optimization^a

entry	solvent (10:1)	temp (°C)	assay yield % ^b
1	Toluene/H ₂ O	95	88
2	DMF/H ₂ O	95	0
3	Dioxane/H ₂ O	95	93
4	CPME/H ₂ O	95	97
5	THF/H ₂ O	77	74
6	MTBE/H ₂ O	53	0
7	Acetone/H ₂ O	rt	30

^aReaction conditions: 0.5 mmol of benzyl bromide, 0.505 mmol of potassium phenyltrifluoroborate and 1.5 mmol Cs₂CO₃ with 2 mol % of PdCl₂(dppf)·CH₂Cl₂. All reaction concentrations were 0.1 M.

^bGC yields based on *n*-dodecane as an internal standard.

Table 3
Coupling of Potassium Trifluoroborates with Benzyl Bromide^a

entry	aryltrifluoroborate	time (h)	cond. ^b	yield % ^b
1		23	A	84
2		16	B	85
3 ^d		20	A	91
4		20	B	86
5		12	A	81
6		21	A	82
7		18	B	87
8		15	B	80
9		15	B	87
10		15	B	69

^aReaction Conditions: 0.5 mmol of benzyl bromide, 0.505 mmol of aryltrifluoroborate and 1.5 mmol of Cs₂CO₃ with 2 mol % of PdCl₂(dppf)·CH₂Cl₂. All reaction concentrations were 0.1 M.

^bCondition A: THF/H₂O (10:1) at 77 °C. Condition B: CPME/H₂O (10:1) at 90 °C.

^cThe yield refers to isolated material.

^dBenzyl chloride was used.

Table 4Coupling of Functionalized Potassium Trifluoroborates with Benzyl Bromide^a

entry	trifluoroborate	time	cond. (h) ^b	yield % ^c
1		14	B	72
2		22	B	67
3 ^d		19	B	74
4 ^d		16	A	70
5 ^e		16	A	86

^aReaction Conditions: 0.25 mmol of benzyl bromide, 0.25 mmol of trifluoroborate and 0.75 mmol of Cs₂CO₃ with 2 mol % of PdCl₂(dppf)·CH₂Cl₂. All reaction concentrations were 0.1 M.

^bCondition A: THF/H₂O (10:1) at 77 °C. Condition B: CPME/H₂O (10:1) at 90 °C.

^cThe yield refers to isolated material.

^dReaction scale was 0.35 mmol with the same ratio of all other reagents.

^eReaction scale was 0.055 mmol with the same ratio of all other reagents.

Table 5Coupling of Potassium Aryltrifluoroborates with Functionalized Benzyl Halides^a

$\text{Ar}^1\text{CH}_2\text{X} + \text{Ar}^2\text{BF}_3\text{K} \xrightarrow[\text{Cs}_2\text{CO}_3, \text{ solvent}]{2 \text{ mol } \% \text{ PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2} \text{Ar}^1\text{CH}_2\text{Ar}^2$				
entry	electrophile	trifluoroborate	time/cond. (h) ^b	product % ^c
1		2	16/B	80
2		2	12/A	91
3		4	14/B	72
4		2	14/B	78

^a Reaction Conditions: 0.5 mmol of benzyl bromide, 0.505 mmol of aryltrifluoroborate and 1.5 mmol of Cs₂CO₃ with 2 mol % of PdCl₂(dppf)·CH₂Cl₂. All reaction concentrations were 0.1 M.

^b Condition A: THF/H₂O (10:1) at 77 °C. Condition B: CPME/H₂O (10:1) at 90 °C.

^c The yield refers to isolated material.

Table 6Coupling of Benzyl Carbonates with Potassium 4-Methoxyphenyl Trifluoroborate^a

$\text{Ar-CH}_2\text{-O-CO-OEt} + 4 \xrightarrow[\text{Cs}_2\text{CO}_3, \text{ THF/H}_2\text{O (10:1), 77 }^\circ\text{C}]{\text{2 mol \% PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2} \text{Ar-CH}_2\text{-C}_6\text{H}_4\text{-OMe}$			
entry	carbonate	time (h)	yield % ^b
1		18	91
2	20 	24	71
3	21 	24	trace
4	22 	24	trace
	23 		

^aReaction Conditions: 0.25 mmol of benzyl carbonate, 0.25 mmol of trifluoroborate and 0.75 mmol of Cs₂CO₃ with 2 mol % of PdCl₂(dppf)·CH₂Cl₂. All reaction concentrations were 0.1 M.

^bThe yield refers to isolated material.