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Development of the Suzuki−Miyaura Cross-Coupling Reaction: Use of Air-Stable Potassium Alkynyltrifluoroborates in Aryl Alkynylations

Gary A. Molander,* Bryson W. Katona, and Fouzia Machrouhi

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania,
Philadelphia, Pennsylvania 19104-6323

gmolandr@sas.upenn.edu

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The palladium-catalyzed cross-coupling reaction of potassium alkynyltrifluoroborates with aryl halides or triflates proceeds readily with moderate to excellent yields. The potassium alkynyltrifluoroborates are air- and moisture-stable crystalline solids that can be stored indefinitely, which will provide an advantage in applications to combinatorial chemistry. The alkynyl cross-coupling reaction can be effected using 9 mol % of $PdCl_2(dppf) \cdot CH_2Cl_2$ as catalyst in THF or $THF-H_2O$ in the presence of Cs_2CO_3 as the inorganic base. A variety of functional groups are tolerated in both partners.

Introduction

The Sonogashira coupling reaction of terminal alkynes with aryl or alkenyl halides has emerged as one of the most straightforward and powerful methods for the preparation of conjugated alkynes.[1] Many applications of this method in natural product synthesis and materials science have been reported.[2] However, few if any synthetic methods work well in every conceivable situation, and the Sonogashira coupling as it was initially conceived is no exception. In the quest for improvements of this palladium-catalyzed cross-coupling, several recent publications have illustrated the use of new ligand systems to accommodate a wider range of coupling partners under mild conditions.[3] As an example, P(*t*-Bu)$_3$ or phosphonium salts derived therefrom have recently proven effective for efficient coupling at room temperature.[4]

Even with these improvements, there will be instances where the Sonogoshira coupling fails to deliver product in acceptable yields. In anticipation of these inevitable shortcomings, complementary methods employing alkynylmetallic reagents have been developed. Although various organometallic acetylide intermediates have been explored [e.g., tin (Stille),[5] zinc (Negishi),[6] and others[7]], organoboron compounds (Suzuki−Miyaura) present several advantages.[8] Thus, organoboron compounds are less toxic than organostannane reagents,[9] and unlike alkynylzincs and -magnesiums many organoboron compounds possess remarkable oxidative and thermal stabilities.[10]

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Soderquist and co-workers reported Suzuki coupling reactions of *B*-alkynyl-9-BBN "ate" complexes (generated in situ by the addition of an alkynyllithium to *B*-methoxy-9-BBN) to a variety of aryl- and alkenyl bromides.[11] At the same time, Fürstner et al. developed a similar, high-yielding cross-coupling of alkynes with compatibility toward diverse functional groups.[12] However, this "ate" complex approach highlights some of the disadvantages of dealing with coupling agents incorporating the 9-BBN moiety. Thus, the difficulty in isolating the intermediate boron complexes and the lack of atom economy from the BBN residue make these methods less than ideal.[2a,8a,b,10]

Two reports on the use of alkynyltrialkoxyborate complexes have been communicated. In the first, an effective Suzuki–Miyaura coupling reaction between these alkynyl "ate" complexes generated in situ from acetylenic derivatives and unactivated aryl or alkenyl bromides was reported.[13] The influence of fluoride anions (CsF, KF, or TBAF) in the reaction was demonstrated on the ate complex obtained by treatment of octynyllithium with triisopropoxyborane. In this case a 30% excess of the alkynylboron "ate" complex generated in situ was required for the cross-coupling reaction. In the second report, lithium 1-alkynyl(triisopropoxy)borates were prepared quantitatively in diethyl ether from borination of the alkynyllithium species. These were isolated and proved to be quite stable for long periods of time at low temperature. They were subsequently used in the Suzuki cross-coupling reaction with aryl halide derivatives. Moderate to good yields were achieved in these reactions, but 2 equiv of the lithium 1-alkynyl(triisopropoxy)borates were required for effective cross-coupling.[14]

Given the overall desirability of using organoboron compounds for cross-coupling reactions, further modifications of these reagents to incorporate other attractive features seemed a worthy entreprise. It has been shown that potassium aryl- and alkenyltrifluoroborates, easily prepared from organoboronic acids or esters, undergo the palladium-catalyzed coupling reaction with arenediazonium tetrafluoroborates[15] or diaryliodonium salts.[16] Recently, our laboratory also demonstrated the feasibility of the cross-coupling reaction of potassium alkyl-,[17] alkenyl-,[18] and aryltrifluoroborates[19] with a variety of electrophiles in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ as a catalyst.

Herein we report a general procedure to access various air-stable and storable potassium alkynyltrifluoroborates, readily available from the corresponding 1-alkynyllithium reagents, and a novel palladium-catalyzed cross-coupling reaction that takes place with a variety of aryl and heteroaryl halides and triflates.

Results and Discussion

Vedejs et al. reported the reaction of arylboronic acids with inexpensive potassium hydrogen difluoride, providing crystalline $KArBF_3$ salts.[20] In a similar way, several groups have prepared various other potassium organotrifluoroborates.[16–21] In their original studies, Genêt et al. were the first to describe the preparation of potassium alkynyltrifluoroborates.[15] The deprotonation of 1-alkynes, followed by transmetalation with boronic esters and treatment in situ with KHF_2, provided an efficient and versatile procedure for the synthesis of potassium alkynyltrifluoroborates.

Genêt was the first to attempt to utilize the alkynyltrifluoroborates in cross-coupling reactions, reporting that the cross-coupling reaction of potassium alkynyltrifluoroborate with aryl diazonium salts did not proceed satisfactorily because of electron transfer to the arenediazonium salts. Reduction was found to be the main reaction instead of the desired carbon–carbon bond formation.[15a] We sought to circumvent this problem by utilizing the more useful aryl halides and triflates as a starting point. For that purpose, we began by developing a general procedure based on the Genêt system for the synthesis of various alkynyltrifluoroborates as powders or crystalline solids in moderate to excellent yields (Table 1).

Thus, deprotonation of the corresponding terminal alkyne with 1 equiv of *n*-BuLi at −78 °C in THF was followed by reaction of the lithium salt with 1.5 equiv of $B(OMe)_3$. The transmetalation was performed at − 78 °C for 1 h and then 1 h at −20 °C. The resulting ate complex was reacted with KHF_2 and water at −20 °C for 1 h and then ambient temperature for 1 h to yield the desired potassium alkynyltrifluoroborate. The borates can easily be prepared on a preparative scale (1–2 g) and are indefinitely stable in air. This would appear to make them ideal for applications in combinatorial chemistry. This process avoids the use of any toxic reagents and is therefore also appropriate for pharmaceutical purposes. Furthermore, the alkynyltrifluoroborates prepared in this manner have been obtained in equal or higher yield than those reported in the literature.[15a] Despite the use of a fluoride source, trimethylsilyl (entry 8) and *tert*-butyldimethylsilyl (entry 7) protecting groups remain intact. This result has been previously observed by Genêt.[15a] We also carefully examined the scope of this method for functionalized alkynes bearing basic heteroatoms (e.g.,

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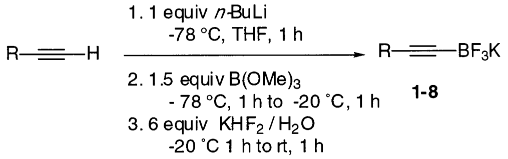
TABLE 1. Preparation of Potassium Alkynyltrifluoroborates



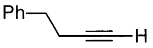
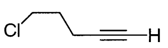
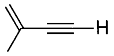
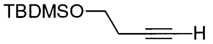
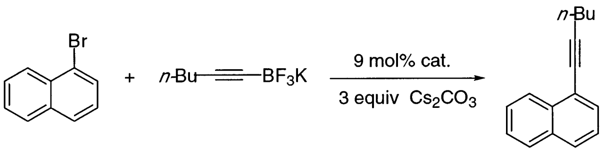
entry	R—≡—H	product	% isolated yield
1	n-Bu—≡—H	**1**	78
2	n-C_8H_{17}—≡—H	**2**	74
3	Ph—≡—H	**3**	78
4		**4**	70
5		**5**	80
6		**6**	85
7		**7**	66
8	TMS—≡—H	**8**	77

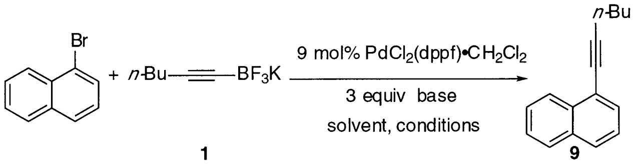
TABLE 2. Study of Catalyst Effect on Cross-Coupling Using Potassium (1-Hexyn-1-yl)trifluoroborate 1



1 **9**

entry	catalyst	solvent	conditions	% isolated yield **9**
1	$Pd(OAc)_2/PPh_3$	$THF-H_2O$ (10:1)	reflux, 12 h	34
2	$PdCl_2(PPh_3)_2$	$THF-H_2O$ (10:1)	reflux, 12 h	22
3	$PdCl_2$(cod)	$THF-H_2O$ (10:1)	reflux, 18 h	trace
4	$PdCl_2$(dppf)·CH_2Cl_2	$THF-H_2O$ (10:1)	reflux, 12 h	43
5	$PdCl_2$(dppf)·CH_2Cl_2	THF	reflux, 36 h	77
6	$PdCl_2$(dppf)·CH_2Cl_2	$THF-H_2O$ (20:1)	reflux, 12 h	87
7	$PdCl_2$(dppf)·CH_2Cl_2/ $P(t\text{-}Bu)_3$	THF	reflux, 12 h	66

TABLE 3. Study of Base Effect on Cross-Coupling Using Potassium (1-Hexyn-1-yl)trifluoroborate 1



1 **9**

entry	base	solvent	conditions	% isolated yield **9**
1	Cs_2CO_3	$THF-H_2O$ (10:1)	reflux, 12 h	43
2	K_2CO_3	$THF-H_2O$ (10:1)	reflux, 12 h	40
3	KF	$THF-H_2O$ (10:1)	reflux, 18 h	13
4	$Ba(OH)_2{\cdot}8H_2O$	$THF-H_2O$ (10:1)	reflux, 12 h	28
5	K_3PO_4	$THF-H_2O$ (10:1)	reflux, 12 h	42
6	NaO t-Bu	$THF-H_2O$ (10:1)	reflux, 12 h	trace
7	NEt_3	MeOH	reflux, 18 h	trace
8	NEt_3	EtOH	reflux, 48 h	trace

pyridyl, *N*,*N*-dimethylamino groups), cyano groups, and esters. Unfortunately, it failed to provide the corresponding potassium trifluoroborate salts in these cases.

With the trifluoroborates in hand, the conditions for carrying out the coupling reaction were optimized by using potassium (1-hexyn-1-yl)trifluoroborate **1** and bromonaphthalene as the electrophilic partner (Table 2).

We determined that in $THF-H_2O$ (10:1), $Pd(PPh_3)_4$ [prepared in situ through the mixing of $Pd(OAc)_2$ and PPh_3 in THF (entry 1)][2a,b] and $PdCl_2(PPh_3)_2$ (entry 2) gave low yields of the desired product 1-(1-hexyn-1-yl)naphthalene **9**. The use of $PdCl_2$(dppf)·CH_2Cl_2 (entry 4) afforded 43% of the aryl alkyne **9**. It is noteworthy that the use of anhydrous conditions (entry 5) led to 77% yield of **9** in 36 h. Indeed, the potassium alkynyltrifluoroborates are generally not stable to a variety of proton donors and water at higher temperatures over long periods of time because they suffer protiodeborination.[8] The ligand system $PdCl_2$(dppf)·CH_2Cl_2/$P(t\text{-}Bu)_3$ in THF did improve the coupling significantly (entry 7; compare with entry 4).[3] However, through careful optimization of the catalyst, we found that the cross-coupling reaction with bromonaphthalene as a partner could be realized in the presence of 9 mol % of palladium catalyst with no additional ligand additive and 3 equiv of Cs_2CO_3 in $THF-H_2O$ (20:1) (entry 6).

Next we turned our attention to the study of the base in the presence of $PdCl_2$(dppf)·CH_2Cl_2, the most efficient catalyst, to improve the yield of the product **9**. Table 3 summarizes the reaction conditions we utilized for potassium (1-hexyn-1-yl)trifluoroborate **1**.

The cross-coupling in each case was performed in the presence of 3 equiv of base. The use of Cs_2CO_3 in $THF-H_2O$ (10:1) heated at reflux provided a 43% yield of aryl alkyne **9** after 12 h (entry 1). Inorganic bases such as K_2CO_3 (entry 2) and K_3PO_4 (entry 5) led to similar yields (40–42%). It is known that strong bases such as $Ba(OH)_2{\cdot}8H_2O$ can improve the cross-coupling.[22] However, in the present case it only furnished a 28% yield of product (entry 4). Recently we have found that amine bases such as NEt_3 in MeOH provide satisfactory results in the cross-coupling between potassium alkenytrifluoroborates and alkenyl and aryl halides.[18,23] However, with potassium alkynyltrifluoroborates under these conditions the coupling was not successful (entries 7 and 8). It is possible that these amine bases might deactivate the catalyst by their potential to bind to the palladium.[24] On using KF (entry 3) or NaO*t*-Bu (entry 6), the palladium-catalyzed reaction proceeded in only very low yield (≤13%).

Subsequently, we performed several experiments using various solvents (THF, DME, dioxane, toluene) and inorganic bases such as Cs_2CO_3, K_2CO_3, and K_3PO_4 in

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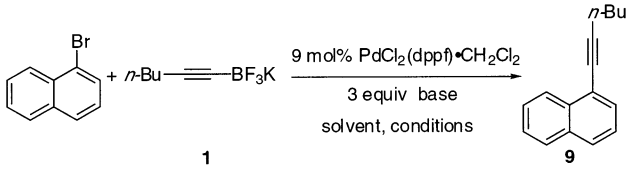
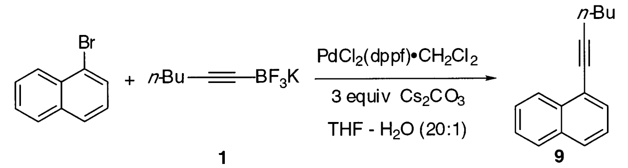
TABLE 4. Study of Effect of Different Solvents on Cross-Coupling Reaction of Aryl Bromides



entry	base	solvent	conditions	% isolated yield **9**
1	Cs_2CO_3	THF	reflux, 36 h	77
2	Cs_2CO_3	THF−H_2O (10:1)	rt, 12 h	23
3	Cs_2CO_3	THF−H_2O (10:1)	reflux, 12 h	43
4	Cs_2CO_3	THF−H_2O (20:1)	reflux, 12 h	87
5	Cs_2CO_3	DME-H_2O (10:1)	reflux, 12 h	trace
6	Cs_2CO_3	dioxane-H_2O (10:1)	reflux, 12 h	16
7	Cs_2CO_3	toluene-H_2O (10:1)	reflux, 12 h	trace
8	K_2CO_3	THF−H_2O (20:1)	reflux, 12 h	87
9	K_3PO_4	THF−H_2O (20:1)	reflux, 12 h	63

TABLE 5. Catalyst Loading in the Reaction with Aryl Bromides



entry	mol % cat.	time (h)	% isolated yield **9**
1	9	12	87
2	5	20	80
3	2	20	48

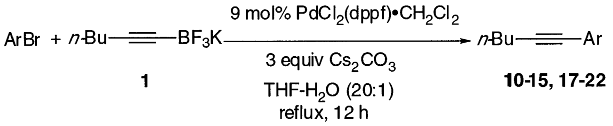
order to evaluate the effects of both solvents and inorganic bases on the coupling reaction (Table 4).

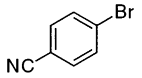
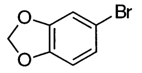
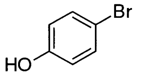
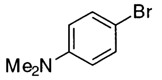
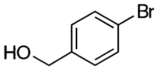
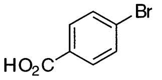
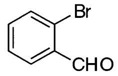
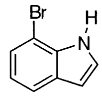
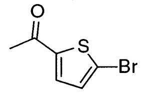
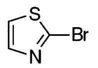
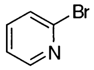
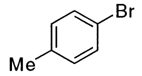
When DME (entry 5) or a nonpolar solvent (entry 7) was employed, the alkynylation of bromonaphthalene was ineffective. Toluene was problematic because of the low solubility of the various components of the reaction, whereas catalyst decomposition appeared to occur in DME. THF proved to be the best solvent to complete the cross-coupling reaction of potassium alkynyltrifluoroborates.[1,2,5−8] The crucial role of water has also been previously noted (Table 2, entry 5). In fact water facilitates the solubilization of the components of the coupling reaction. However, solubilization is accomplished at the expense of promoting the protiodeborination of the potassium salt,[8a] as confirmed by experiment (entry 4). Thus, a delicate balance must be reached, and we found that the reaction of potassium alkynyltrifluoroborate **1** with bromonaphthalene and 9 mol % of $PdCl_2(dppf) \cdot CH_2Cl_2$ in the presence of a lower ratio of water in THF (20:1 THF−H_2O instead of 10:1) provided the cross-coupled product **9** in an optimum yield of 87%. Under anhydrous conditions the reaction required a longer time to reach completion (entry 1). However, product **9** was obtained in 77% yield in that case.

The use of $PdCl_2(dppf) \cdot CH_2Cl_2$ with 3 equiv of Cs_2CO_3 in 20:1 THF−H_2O mixture was employed to study the catalyst loading (Table 5).

These results indicate that the use of 9 mol % of $PdCl_2(dppf) \cdot CH_2Cl_2$ (entry 1) produces the best yield. However, 5 mol % of catalyst proved to be comparably effective (entry 2), yielding 80% of **9** in 20 h rather than the 87% obtained with 9 mol % in 12 h. However, when the loading was dropped to 2 mol % the yield decreased dramatically to 48% after 20 h (entry 3), thus illustrating the minimum amount of catalyst needed for this reaction to be efficient.

TABLE 6. Cross-Coupling Reaction of Aryl Bromides



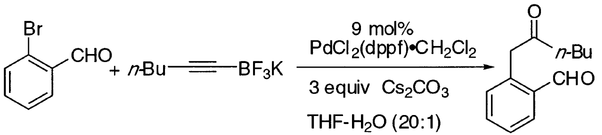
entry	ArBr	product	% isolated yield
1		**10**	98
2		**11**	44 (75)^a
3		**12**	48 (trace)^a
4		**13**	61 (33)^a
5		**14**	76
6		**15**	73
7		**16 (17)**^{a}	53^b (89)^a
8		**18**	46 (97)^a
9		**19**	47 (88)^a
10		**20**	78
11		**21**	30
12		**22**	trace (36)^a

[a] Anhydrous THF used as solvent. [b] Yield of keto aldehyde. See eq 1.

To demonstrate the limits of the new procedure, these conditions were applied to various aryl bromides (Table 6). Most importantly, the coupling turned out to be general with respect to a diverse array of functionality. Compatibility was demonstrated with cyano, aldehyde, ketone, and hydroxy groups as well as carboxylic acids.[2,5−6] The latter two are surprising in view of the susceptibility of the alkynyltrifluoroborates to protiodeborination. Activated bromides, for instance, 4-bromobenzonitrile (entry 1), *p*-bromobenzoic acid (entry 6), and 2-bromobenzaldehyde (entry 7), offer high yields of the corresponding cross-coupled product, as did the unprotected 7-bromoindole (entry 8).

2-Bromothiazole gave the interesting 2-(1-hexyn-1-yl)-thiazole in good yield (entry 10). This structural motif is broadly used in materials science and in biologically important molecules.[25] With less reactive bromides (entry 12) no significant coupling was observed.

We found it necessary to vary the reaction conditions for 4-bromo-1,3-benzodioxole (entry 2), 7-bromoindole (entry 8), and 2-acetyl-5-methylthiophene (entry 9). We were pleased to see that the coupling in THF instead of THF$-$H$_2$O as solvent gave 97%, 88%, and 75% yields, respectively, of the desired coupled product. Under anhydrous conditions, *p*-bromotoluene still proved problematic (entry 12). The choice of anhydrous reaction conditions is important in those cases and also for 2-bromobenzaldehyde (entry 7). In fact, in the presence of water the alkyne of the cross-coupled product in the latter case was completely hydrated through a combination of palladium catalysis and intramolecular assistance of the aldehyde on the ortho position (eq 1). The regioselective hydration of alkynones under mild conditions by PdCl$_2$(MeCN)$_2$ has been reported previously,[26] with the orientation of the alkyne hydration being controlled by neighboring group participation.



1 16 (1)

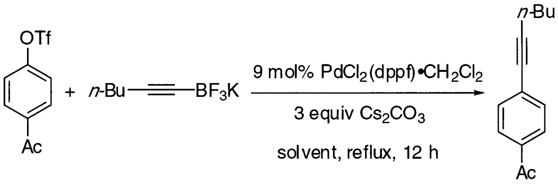
For the 4-bromophenol (entry 3) and 4-bromo-*N*,*N*-dimethylaniline (entry 4), the coupling could not be improved under anhydrous conditions.

Aryl triflates are an important family of electrophiles in palladium-catalyzed cross-coupling reactions because of their ease of preparation from readily available phenols. Aryl triflates are susceptible to base hydrolysis,[27] and thus a separate set of conditions were developed for these substrates. In an attempt to optimize this cross-coupling, we employed 4-acetylphenyltriflate as the electrophile (Table 7). Our results suggested an increase of reactivity when the coupling was performed under anhydrous conditions (entry 3). The desired product was formed with excellent yield (87% versus 68% yield in the 10:1 THF$-$H$_2$O mixture) after 12 h in THF heated at reflux.

The other variable investigated for triflates was the catalyst loading. Similar to the case with the bromides, values of 9, 5, and 2 mol % of PdCl$_2$(dppf)·CH$_2$Cl$_2$were used with Cs$_2$CO$_3$ as the base in THF (Table 8).

Unlike the aryl bromide case, however, 2 mol % (entry 3) produced yields comparable to those obtained with 9 and 5 mol %, although it required a reaction time of 12 h as opposed to 8 h. Thus, the loading was decreased even further to 0.5 mol % (entry 4) and 0.05 mol % (entry 5).

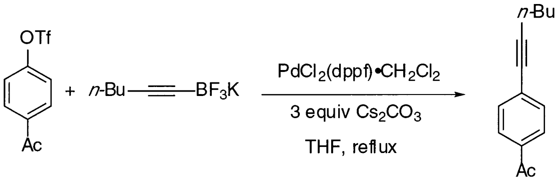
TABLE 7. Study of Effect of Different Solvents on Cross-Coupling Reaction of Aryl Triflates



1 23

entry	solvent	% isolated yield **23**
1	THF$-$H$_2$O (10:1)	68
2	THF$-$H$_2$O (20:1)	73
3	THF	87

TABLE 8. Catalyst Loading in Reaction with Aryl Triflates



1 23

entry	mol % cat.	time (h)	% isolated yield **23**
1	9	8	87
2	5	8	84
3	2	12	85
4	0.5	12	88
5	0.05	16	87

In both cases, similar yields were obtained with respect to entries 1$-$3. These results illustrate that the catalyst loading in the reaction of aryl triflates can be much lower than the loading required in the couplings of aryl bromides.

To enlarge the scope of aryl alkynylation, we examined the cross-coupling of various aromatic triflates (Table 9).

In the presence of 9 mol % of PdCl$_2$(dppf)·CH$_2$Cl$_2$ (unfortunately, these studies were carried out before we realized that extremely low catalysts loading could be used) and 3 equiv of Cs$_2$CO$_3$ under anhydrous conditions, activated aryl triflates (entries 1, 3, and 4), as well as an electron-rich triflate (entry 5), led to the corresponding coupled product in good to excellent yield. Heteroaryl triflates gave modest alkynylation, perhaps as a result of the deactivation of the catalyst by complexation to the pyridine (Table 9, entry 1 and Table 6, entry 11). Interestingly, the *p*-methylphenyltrifluoromethanesulfonate offered 55% yield of the desired product (entry 2). This result confirms the fact that the triflates are much more reactive than the aryl bromide in the palladium-catalyzed alkynylation reaction. Indeed, *p*-bromotoluene provided substantially less cross-coupling product with alkynyltrifluoroborate **1** (cf. Table 6, entry 12).

In a further study, we established the order of reactivity of the electrophilic partner in our reaction system using 9 mol % PdCl$_2$(dppf)·CH$_2$Cl$_2$, 3 equiv of Cs$_2$CO$_3$, and THF$-$H$_2$O (20:1) or THF as the solvent (Table 10).

These results illustrate that under anhydrous conditions, the aryl triflate (entry 1) was the most reactive electrophile for the formation of **23** (87% yield after only 8 h). This was followed by the aryl bromide (entry 3) and

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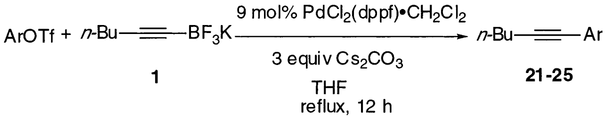
[25] (a) Dondoni A. *Phosphorus Sulfur Relat. Elem.* **1985**, *24*, 381. (b) Sinha, R. R.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Wash C. T. *Nat. Prod. Rep.* **1999**, *16*, 249. (c) Dondoni A. *Bull. Soc. Chim. Belg.* **1992**, *101*, 433.

[26] Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127.

[27] (a) Nelson, P. H.; Carr, S. F.; Devens, B. H.; Eugui, E. M.; Franco, F. *J. Med. Chem.* **1996**, *39*, 4181. (b) Cabri, W.; Candiani, I.; Zarini, F.; Sergio, P.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 9197. (c) Murakami, Y.; Yasuoki, H.; Nakazawa, Y.; Koshimizu, M.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1989**, *30*, 2099.

TABLE 9. Cross-Coupling Reaction of Various Aryl Triflates with 1



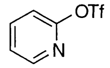
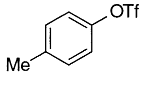
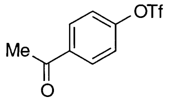
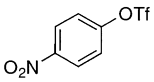
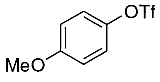
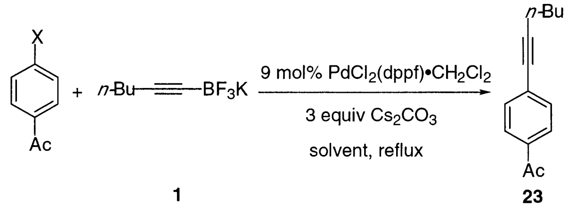
entry	ArOTf	product	% isolated yield
1		21	31
2		22	55
3		23	87
4		24	98
5		25	78

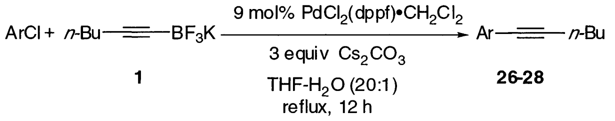
TABLE 10. Study of Reactivity of Various Electrophiles with 1

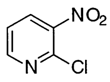
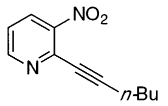
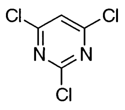
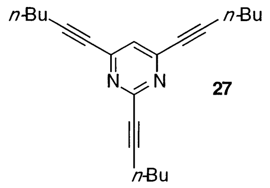
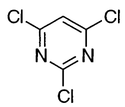
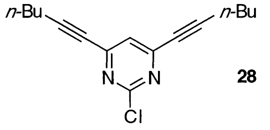


entry	X	solvent	time (h)	% isolated yield **23**
1	OTf	THF	8	87
2	OTf	THF$-$H$_2$O (20:1)	12	68
3	Br	THF	60	59[a]
4	Br	THF$-$H$_2$O (20:1)	12	80
5	I	THF	60	30[a]
6	I	THF$-$H$_2$O (20:1)	12	48[a]
7	OTs	THF	60	
8	OMs	THF	60	
9	Cl	THF	60	40[a]
10	Cl	THF$-$H$_2$O (20:1)	12	29[a]

[a] Reaction was not complete and starting material was recovered.

TABLE 11. Cross-Coupling Reaction of Aryl Chlorides with 1



entry	ArCl	product		% isolated yield
1			26	85
2			27	70[a]
3			28	62[b]

[a] Nine equivalents of base used. [b] Six equivalents of base used.

aryl iodide (entry 5), which were still not complete after 60 h. However, when water was added to the reaction, the aryl bromide (entry 4) was complete after 12 h, offering **23** in 80% yield, whereas the aryl iodide (entry 6) was still not complete after 12 h. The tosylate derivative of *p*-hydroxy acetophenone (entry 7) and the corresponding mesylate (entry 8) were unreactive under these conditions. The chloride derivative provided only a modest yield of **23** in anhydrous THF (entry 9) as well as in THF$-$H$_2$O (20:1) (entry 10). These results lead to the establishment of the following reactivity order: OTf > Br > I ≈ Cl under anhydrous conditions. This observed reactivity is quite different from the one reported by our group for the cross-coupling of potassium alkyltrifluoroborates (Br > OTf ≫ Cl),[17] for the Stille coupling,[5] and for *B*-alkyl-9-BBN cross-coupling reactions.[8i]

The Suzuki cross-coupling reactions of some activated aryl chlorides[28] in the presence of 9 mol % of PdCl$_2$(dppf)·CH$_2$Cl$_2$ and 3 equiv of Cs$_2$CO$_3$ in THF$-$H$_2$O (20:1) have also been investigated as outlined in Table 11. For example, 2-chloro-3-nitropyridine reacts with the trifluoroborate salt **1** to provide the functionalized heteroarylalkyne in excellent yield (entry 1). Heteroaryl chlorides such as 2,4,6-trichloropyrimidine derivatives were also suitable substrates as the electrophilic partner. The trisubstituted product was obtained in high yield in the presence of 9 equiv of Cs$_2$CO$_3$ (entry 2). When 6 equiv of base was used, the Suzuki cross-coupling using 2,4,6-trichloropyrimidine occurred selectively at positions 2 and 4 of the pyrimidine ring (entry 3). The arylation of halogenated (I, Br, Cl) pyrimidines via a Suzuki coupling reaction has been used for the synthesis of a variety of unsymmetrical biaryl compounds. The fact that the reactivity of chlorides at the C-4 and C-6 positions could be differentiated from that of the C-2 chloride provides an interesting pathway to prepare derivatives of pyrimidines in which substituents emplaced at those positions are different.[29]

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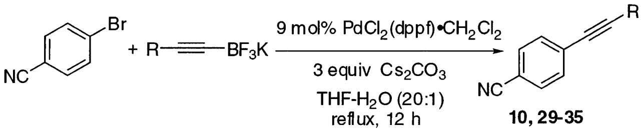
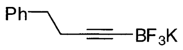
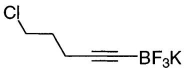
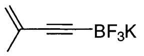
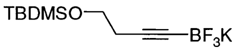
(28) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. (b) Stürmer, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3307. (c) Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Thies, J. E. *J. Org. Chem.* **1988**, *53*, 2052. (d) Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273. (e) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743. (f) Janietz, D.; Bauer, M. *Synthesis* **1993**, 33. (g) Uemura, M.; Nishimura, H.; Kamikawa, K.; Nakayama, K.; Hayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 1909. (h) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575.

(29) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125.

TABLE 12. Cross-Coupling Reaction of Various Potassium Alkynyltrifluoroborates



entry	R—≡—BF_3K	product	% isolated yield
1	n-Bu—≡—BF_3K	**10**	98
2	n-C_8H_{17}—≡—BF_3K	**29**	91
3	Ph—≡—BF_3K	**30**	69
4		**31**	92
5		**32**	85
6		**33**	87
7		**34**	88
8	TMS—≡—BF_3K	**35**	60

Under the conditions established for the aryl bromides, we applied the palladium-catalyzed cross-coupling reaction with different potassium alkynyltrifluoroborate partners as outlined in Table 12.

On using 4-bromobenzonitrile as the electrophile, all of the coupling reactions proceeded with satisfactory to excellent yields (60−98%). Once again, the reaction was tolerant of a variety of sensitive functional groups despite the aqueous basic conditions, as represented by potassium (4-*tert*-butyldimethylsiloxy-1-butyn-1-yl)trifluoroborate and potassium (trimethylsilylethynyl)trifluoroborate, which afforded 88% and 60% yields of the desired products **34** and **35**, respectively. Interestingly, the TBDMS and TMS groups survive during the cross-coupling, although a fluoride source is present.[15]

The mechanism of the reaction has not been studied in detail, but boronic acids generated in situ could very well be the reactive species under aqueous conditions.[19b] Fluorinated boron species such as alkynylBF_3^-, alkynyl-$BF_2(OH)^-$, and/or alkynyl$BF(OH)_2^-$ might also be involved.[17,30] Under anhydrous conditions, boronic acid derivatives cannot be implicated. It is possible that, under both aqueous and anhydrous conditions, the reaction is somehow accelerated by fluoride ions. The positive influence of fluoride ions has been previously reported in the palladium cross-coupling reaction with alkynylboronic esters in DME.[13] We believe that in the latter case the boronic esters could be converted to fluoroborate species in situ.

Conclusion

In summary, palladium-catalyzed cross-coupling reactions of potassium alkynyltrifluoroborates with aryl halides and triflates have been achieved. As demonstrated, $PdCl_2(dppf)\cdot CH_2Cl_2/Cs_2CO_3/THF-H_2O$ or $PdCl_2(dppf)\cdot CH_2Cl_2/Cs_2CO_3/THF$ have emerged to be the most effective systems, providing the desired coupling products in good yields. This procedure possesses several advantages, one of which is that functionalized potassium alkynyltrifluoroborates are readily synthesized in one pot. Thus, deprotonation of the alkyne with RLi and transmetalation to boron, followed by in situ treatment with KHF_2, provides high yields of the desired organoborons. Second, the alkynyltrifluoroborates are crystalline solids possessing complete air stability. Therefore, they are easy to handle. As a consequence, highly functionalized alkynyltrifluoroborates can be simply prepared and stored indefinitely, which allows a convenient entry to combinatorial synthesis. Furthermore, the use of alkynyltrifluoroborates offers the advantage of atom economy when compared to the alkynylborons bearing the BBN moiety. Finally, the inorganic byproducts of the trifluoroborate reactions are environmentally friendly and are easily removed by simple workup. These novel features make the potassium alkynyltrifluoroborates useful alternatives to other organometallics used in palladium-catalyzed cross-coupling reactions and promising reagents for organic synthesis.

Experimental Section

General Methods and Materials. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were measured on spectrometers at 500.13, 125.75, and 470.55 MHz, respectively. ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). ^{11}B NMR spectra at 64.2 MHz were obtained on a spectrometer equipped with the appropriate decoupling accessories. All ^{11}B chemical shifts were referenced to external $BF_3\cdot OEt_2$ (0.0 ppm), with a negative sign indicating an upfield shift. The melting points were uncorrected. Standard flash chromatography procedures were followed using 32−63 mm silica gel. CI mass spectra were obtained at 70 ev with direct inlet. THF was distilled from sodium/benzophenone, and all water used was degassed with argon. All of the following experiments were carried out under an argon atmosphere.

General Procedure for Potassium Alkynyltrifluoroborate Synthesis. Preparation of Potassium(1-hexyn-1-yl)-trifluoroborate (1). A solution of 1-hexyne (0.82 g, 10 mmol, 1 equiv) in 20 mL of dry THF was cooled to −78 °C under argon. *n*-BuLi (6.25 mL, 1.6 M in hexane, 10 mmol, 1 equiv) was added dropwise, and the solution was stirred for 1 h at this temperature. Trimethylborate (1.56 g, 15 mmol, 1.5 equiv) was then added dropwise at −78 °C. The solution was stirred at this temperature for 1 h after which it was allowed to warm to −20 °C for 1 h. A saturated aqueous solution of potassium hydrogen difluoride (4.7 g, 60 mmol, 6.0 equiv) was added to the vigorously stirred solution. The resulting mixture was allowed to stir for 1 h at −20 °C after which it was allowed to warm to room temperature for 1 h. The solvent was removed under reduced pressure, and the resulting white solid was dried under high vacuum for 2 h to remove all water. The solid was then washed with acetone and with hot acetone. The resulting organic solution was filtered, and the solvent was removed to afford a fluffy white solid. This solid was then dissolved in hot acetone and precipitated with diethyl ether, after which the solution was cooled to −20 °C to complete precipitation of the solid. The product was collected as a white crystalline solid (1.66 g, 78%). The spectra obtained are in agreement with previously reported data:[15a] mp = 256 °C

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(30) Wright, S. M.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

(decomp); ^{1}H NMR (500 MHz, acetone-d_6) δ 2.06−2.01 (m, 2H), 1.40−1.37 (m, 4H), 0.88−0.85 (m, 3H); ^{13}C NMR (126 MHz, acetone-d_6) δ 32.5, 22.7, 19.7, 14.1; ^{11}B NMR (64.2 MHz, acetone-d_6) δ −1.1 (d, J = 37.8 Hz); ^{19}F NMR (471 MHz, acetone-d_6) δ −134.7 (q, J = 36.9 Hz). IR (KBr plate) 2190 cm^{-1}. Anal. Calcd for $C_6H_9BF_3K$: C, 38.32; H, 4.82. Found: C, 38.12; H, 4.96.

Sample Procedure for Suzuki Coupling Reactions of Potassium Alkynyltrifluoroborates under Aqueous Conditions. Preparation of 1-(1-Hexyn-1-yl)naphthalene (9).[31] Potassium (1-hexyn-1-yl)trifluoroborate (94 mg, 0.5 mmol, 1 equiv), 1-bromonaphthalene (104 mg, 0.5 mmol, 1 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (36 mg, 0.045 mmol, 9 mol %), and Cs_2CO_3 (489 mg, 1.5 mmol, 3 equiv) were mixed with THF (5 mL) and degassed water (0.25 mL) under argon (20:1 THF to water ratio). The solution was heated at reflux for 12 h. After this time the mixture was cooled, and 10 mL of water was added to the flask. The resulting solution was then extracted with diethyl ether. The combined organic extracts were washed with 1 M HCl and brine and then dried over $MgSO_4$. After filtering off the solid the solvent was removed under reduced pressure to afford a brown oil. This oil was purified by flash chromatography silica gel (elution with hexane) to provide the product **9** as a clear oil (90.3 mg, 87%): $R_f = 0.40$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 7.1 Hz, 1H), 7.57 (t, J = 7.0 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 2.59 (t, J = 7.1 Hz, 2H), 1.75−1.69 (m, 2H), 1.62−1.55 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHZ, $CDCl_3$) δ 133.5, 133.2, 130.0, 128.2, 127.8, 126.4, 126.3, 126.2, 125.2, 121.8, 95.5, 78.5, 31.0, 22.1, 19.4, 13.7; exact mass calculated for $C_{16}H_{16}$ 208.2982, found 208.2986 (M^+).

Sample Procedure for Suzuki Coupling Reactions of Potassium Alkynyltrifluoroborates under Anhydrous Conditions. Preparation of 4-(1-Hexyn-1-yl)acetophenone (23). Potassium (1-hexyn-1-yl)trifluoroborate (94 mg, 0.5 mmol, 1 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (36 mg, 0.045 mmol, 9 mol %), and Cs_2CO_3 (489 mg, 1.5 mmol, 3 equiv) were added to a flame-dried flask and dried under high vacuum for 2 h after which they were placed under argon. To this flask was added 4-acetylphenyl trifluoromethanesulfonate (134 mg, 0.5 mmol, 1 equiv) and dry THF (5 mL). The solution was heated at reflux for 12 h. After this time the mixture was cooled, and 10 mL of water was added to the flask. The resulting solution was then extracted with diethyl ether. The combined organic extracts were washed with 1 M HCl and brine and then dried over $MgSO_4$. After the solid was filtered off, the solvent was removed under reduced pressure to afford a brown oil. This oil was purified by flash chromatography silica gel (elution with hexane) to afford the product **23** as a clear oil (90.3 mg, 87%), $R_f = 0.50$. The spectra obtained are in agreement with previously reported data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 6.7, 2.0 Hz, 2H), 7.47 (dd, J = 6.7, 1.9 Hz, 2H), 2.58 (s, 3H), 2.44 (t, J = 7.1 Hz, 2H), 1.62−1.59 (m, 2H), 1.50−1.47 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4, 135.6, 131.6, 129.2, 128.1, 94.4, 80.1, 30.6, 26.6, 22.0, 19.2, 13.6.

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Supporting Information Available: Experimental details and structural data (^{1}H and ^{13}C NMR spectra) for all compounds described within the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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[31] Takahashi, T.; Shen, B.; Nakajima, K.; Xi, Z. *J. Org. Chem.* **1999**, *64*, 8706.