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Preparation of Potassium Alkynylaryltrifluoroborates from Haloaryltrifluoroborates via Sonogashira Coupling Reaction

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ABSTRACT

A novel series of alkyne-containing potassium organotrifluoroborates were prepared in good yields from the corresponding haloaryltrifluoroborates and various alkynes via Sonogashira coupling reaction. Also, the Suzuki−Miyaura cross-coupling reaction of alkynylaryltrifluoroborates with aryl and alkenyl bromides was achieved in the presence of 5 mol % of Pd(TPP)$_4$ and 3.0 equiv of Cs$_2$CO$_3$ in aqueous 1,4-dioxane at 150 °C by microwave irradiation.

Potassium organotrifluoroborates have become one of the most important coupling partners in Suzuki−Miyaura cross-coupling reactions as a result of their many advantages over the corresponding boronic acids or boronate esters such as easy preparation and purification, air- and moisture-stability, and convenient handling.[1] Moreover, the inert property of organotrifluoroborates to a number of reaction conditions has allowed the synthesis of more complicated molecules that may not be prepared from boronic acids or boronate esters. For example, the direct functionalization of organotrifluoroborates successfully performed include a variety of epoxidations,[2] *cis*-dihydroxylations,[3] oxidations,[4] olefinations (Wittig reactions),[5] nucleophilic substitution reactions,[6] metal−halogen exchange reactions,[7] 1,3-dipolar cycloadditions,[8] reductive aminations,[9] and condensation reactions.[10] Also, Molander and Sandrock reported the chemoselective transformation of boryl-substituted organotrifluoroborates via Pd-catalyzed cross-coupling to increase molecular complexity and diversity.[11] Recently, a copper-catalyzed C−N coupling reaction of organotrifluoroborates for the preparation of azidoaryltrifluoroborates has been demonstrated by our

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[1] (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (d) Darses, S.; Genet, J. -P. *Chem. Rev.* **2008**, *108*, 288. (e) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240. (f) Molander, G. A.; Sandrock, D. L. *Curr. Opin. Drug Discovery* **2009**, *12*, 811.

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[3] Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75.

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[5] (a) Molander, G. A.; Figueroa, R. *J. Org. Chem.* **2006**, *71*, 6135. (b) Molander, G. A.; Ham, J.; Canturk, B. *Org. Lett.* **2007**, *9*, 821. (c) Molander, G. A.; Oliveira, R. A. *Tetrahedron Lett.* **2008**, *49*, 1266.

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[7] Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2006**, *71*, 7491.

[8] Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2767.

[9] Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2008**, *73*, 3885.

[10] Molander, G. A.; Febo-Ayala, W.; Jean-Gérard, L. *Org. Lett.* **2009**, *11*, 3830.

[11] (a) Molander, G. A.; Sandrock, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 15792. (b) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2009**, *11*, 2369.

[12] Cho, Y. A.; Kim, D.-S.; Ahn, H. R.; Canturk, B.; Molander, G. A.; Ham, J. *Org. Lett.* **2009**, *11*, 4330.

10.1021/ol100081v

group.[12] Thus, these transformations using palladium or copper catalyst have proven to be very useful processes to prepare highly functionalized organotrifluoroborates without loss of the trifluoroborate group.

The Sonogashira reaction[13] has been used for the preparation of natural products, pharmaceuticals, agricultural chemicals, and industrial organic materials and is performed on terminal alkynes with aryl or alkenyl halides in the presence of palladium catalysts and a copper(I) halide as a co-catalyst. Therefore, the Sonogashira reaction would also provide a powerful method for constructing a C(sp)−C(sp^2) bond between terminal alkynes and haloaryltrifluoroborates as starting materials.

Although a number of methods have been reported in the literature for the synthesis of alkynylarylboronate esters from various terminal alkynes and haloarylboronate ester through the Sonogashira reaction, these previous methods still leave the problem of protecting the boronic acid moiety with a relatively expensive diol reagent such as pinacol or neopentyl glycol prior to the Sonogashira reaction, and extant methods require long reaction times or high reaction temperatures to obtain satisfactory results.[14] Moreover, the coupling of terminal alkynes using potassium haloaryltrifluoroborates has not been reported so far to the best of our knowledge.

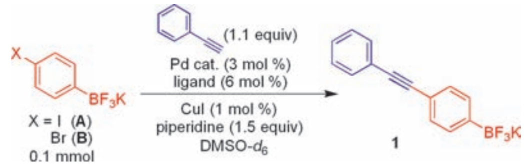
During the course of our synthetic studies on the development of novel organotrifluoroborates, we discovered a facile and highly efficient method for the preparation of potassium alkynylaryltrifluoroborates from the corresponding haloaryltrifluoroborates and various alkynes via the Sonogashira reaction. The resulting organotrifluoroborates could then be utilized as coupling partners in cross coupling reactions.

Herein, we report our results on the development of such a transformation and the Suzuki−Miyaura cross-coupling reaction of these alkynylaryltrifluoroborates by microwave irradiation.

First, we investigated Pd-catalyzed Sonogashira reaction of 4-iodo- and 4-bromophenyltrifluoroborate[15] with phenylacetylene under various conditions. The reactions were performed in the presence of several palladium catalysts, CuI as a co-catalyst, and piperidine as a base in an NMR tube using DMSO-d_6 (0.5 mL) as a solvent. The reaction conditions explored are summarized in Table 1.

A number of different palladium catalysts were screened for their effectiveness in promoting the Sonogashira reaction with 4-iodophenyltrifluoroborate (Table 1, entries 1−5). Among them, when PdCl$_2$(TPP)$_2$, Pd(TPP)$_4$, and Pd(OAc)$_2$/TPP were used, the desired compound **1** was readily prepared at room temperature within 30 min, and their isolated yields were 98%, 91%, and 88%, respectively (Table 1, entries 1, 2, and 4). However, when Pd(OAc)$_2$ and Pd(OAc)$_2$/XPhos were used, the reactions did not go to completion because 1,4-diphenylbutadiyne was rapidly produced as a byproduct (Table 1, entries 3 and 5).

Table 1. Optimization of Sonogashira Reaction for the Preparation of Potassium 4-(Phenylethynyl)phenyltrifluoroborate (**1**)[a]



entry	X	Pd catalyst	ligand	time (h)/ temp (°C)	conversion yield (%)[b]
1	I	PdCl$_2$(TPP)$_2$	none	0.5/rt	100 (98)[c]
2	I	Pd(TPP)$_4$	none	0.5/rt	100 (91)[c]
3	I	Pd(OAc)$_2$	none	0.5/rt	48
4	I	Pd(OAc)$_2$	TPP[d]	0.5/rt	100 (88)[c]
5	I	Pd(OAc)$_2$	XPhos[e]	0.5/rt	54
6	Br	PdCl$_2$(TPP)$_2$	none	1/rt	trace
7	Br	PdCl$_2$(TPP)$_2$	none	1/80	22
8	Br	Pd(TPP)$_4$	none	1/80	30
9	Br	Pd(OAc)$_2$	none	1/80	trace
10	Br	Pd(OAc)$_2$	TPP	1/80	22
11	Br	Pd(OAc)$_2$	XPhos	1/80	74
12[f]	Br	Pd(OAc)$_2$	XPhos	1/80	92
13[f,g]	Br	Pd(OAc)$_2$	XPhos	1/80	100 (93)[c]

[a] All reactions were performed on a 0.1 mmol scale in 0.5 mL of DMSO-d_6 in an NMR tube. [b] The conversion yield was based on the integration of peaks at 7.14 (**A**), 7.24 (**B**), and 7.28 (**1**) ppm, respectively. [c] Isolated yield of **1**. [d] Triphenylphosphine. [e] 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [f] 1.5 equiv of phenylacetylene was used. [g] Reaction was performed without CuI.

In the reactivity test of 4-bromophenyltrifluoroborate, although the optimized Sonogashira reaction conditions of 4-iodophenyltrifluoroborate were used, the reaction rate was very slow (Table 1, entry 6). Also, we could not completely obtain the desired compound **1** despite an increase of the reaction temperature to 80 °C (Table 1, entries 7−10). By contrast, when using Pd(OAc)$_2$/XPhos as a catalytic system and increasing the equivalents of phenylacetylene, the conversion yields of the cross-coupling reaction remarkably increased (Table 1, entries 11 and 12). Fortunately, a 93% isolated yield of product **1** was successfully obtained in the absence of CuI as a co-catalyst (Table 1, entry 13).

With the optimized conditions for the formation of **1** from 4-iodophenyltrifluoroborate in hand (Table 1, entry 1), we examined the scope of the Sonogashira reaction for the

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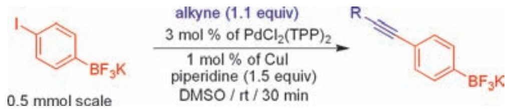
(13) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (d) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (e) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (f) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

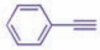
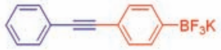
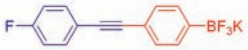
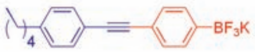
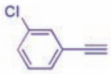
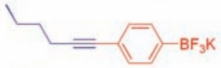
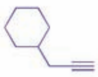
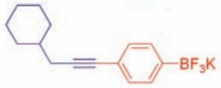
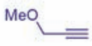
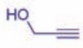
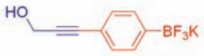
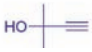
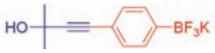
(14) (a) Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1999. (b) Perttu, E. K.; Arnold, M.; Iovine, P. M. *Tetrahedron Lett.* **2005**, *46*, 8753. (c) Zheng, S.-L.; Reid, S.; Lin, N.; Wang, B. *Tetrahedron Lett.* **2006**, *47*, 2331. (d) Nakamura, H.; Kuroda, H.; Saito, H.; Suzuki, R.; Yamori, T.; Maruyama, K.; Haga, T. *ChemMedChem* **2006**, *1*, 729. (e) Yamamoto, Y.; Hattori, K. *Tetrahedron* **2008**, *64*, 847. (f) Matsuda, T.; Kadowaki, S.; Yamaguchi, Y.; Murakami, M. *Chem. Commun.* **2008**, 2744.

(15) For the preparation of these potassium haloaryltrifluoroborates, see the Supporting Information of ref 12.

synthesis of alkyne-functionalized organotrifluoroborates using various terminal alkynes. The results are summarized in Table 2.

Table 2. Preparation of Potassium Alkynylaryltrifluoroborates with Various Alkynes via the Sonogashira Reaction[a]



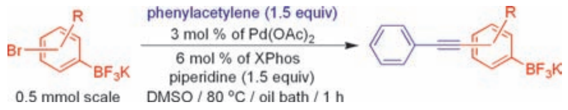
entry	alkyne	product		yield (%)[b]
1			1	96
2			2	95
3			3	94
4			4	95
5			5	93
6			6	74
7[c]			7	89
8[c]			8	95
9			9	94
10			10	96
11			11	79
12			12	94

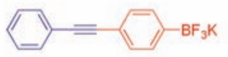
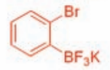
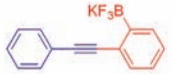
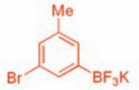
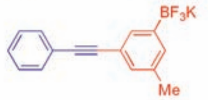
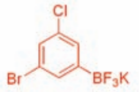
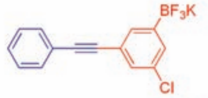
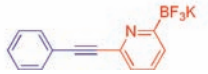
[a] All reactions were carried out on a 0.5 mmol scale in 2.0 mL of DMSO according to the optimized conditions of entry 1 in Table 1. [b] Isolated yields. [c] Reaction time was 2 h.

As expected, all of the alkynylaryltrifluoroborates were readily generated from the corresponding terminal alkynes and obtained in good yields without being contaminated with byproducts such as alkyne-dimer or piperidine HI salt. Interestingly, the presence of functional groups at the *para* position of phenylacetylene did not affect the yields of products (Table 2, entries 2−5). However, when using 3-chlorophenylacetylene as a starting material, the isolated yield of desired trifluoroborate **6** was slightly lower than those of *p*-alkyne-substituted trifluoroborates under the same reaction conditions (Table 2, entry 6). In the reactivity test of various alkyl alkynes, although using saturated alkyl alkynes resulted in prolonged reaction (Table 2, entries 7 and 8), there was no significant influence by the functional group unit in the alkyl chain (Table 1, entries 9−12).

Next, the Sonogashira reactions of various bromoaryltrifluoroborates with phenylacetylene were explored under optimized condition (Table 1, entry 13). The results are collected in Table 3.

Table 3. Preparation of Potassium Alkynylaryltrifluoroborates with Various Potassium Bromoaryltrifluoroborates[a]



entry	BrRBF$_3$K	product		yield (%)[b]
1			1	94
2			13	68 84[c]
3			14	(11)[d]
4			15	76
5			16	68
6			17	dec. 97[e]

[a] All reactions were carried out on a 0.5 mmol scale in 1.0 mL of DMSO according to the optimized conditions of entry 13 in Table 1. [b] Isolated yields. [c] Reaction was performed with potassium 3-iodophenyltrifluoroborate as a starting material and the optimized conditions of entry 1 in Table 1. [d] Conversion yield. [e] Reaction was performed with 3.0 equiv of phenylacetylene and 1.5 equiv of Cs_2CO_3 instead of piperidine for 2 h.

In a test of reactivity between *o*-, *m*-, and *p*-bromophenyltrifluoroborates, the yields of the corresponding organotrifluoroborates increased in the order *para* > *meta* ≫ *ortho* (Table 3, entries 1−3). Indeed, *ortho*-substituted trifluoroborate could not be isolated from the reaction mixture (data not shown). 3-Bromophenyltrifluoroborates bearing a substituent at the 5-position of the aromatic ring (Table 3, entries 4 and 5) were converted into the corresponding alkynylaryltrifluoroborates in moderate yields. When 6-bromo-2-pyridyltrifluoroborate as a starting material was used, by increasing the equivalents of phenylacetylene and using Cs_2CO_3 as a base instead of piperidine, the desired product was isolated in excellent yield (Table 3, entry 6).

Finally, we turned our attention to the Suzuki−Miyaura cross-coupling reaction of these alkynylaryltrifluoroborates.

As optimization studies revealed (Table 4), the cross-coupling compound **18** was formed in a low yield of 21% when the reaction was carried out at 100 °C in an oil bath for 7 h with use of $Pd_2(dba)_3$ and K_2CO_3 (Table 4, entry 1). However, using $Pd(OAc)_2$ and $Pd(TPP)_4$ under the same conditions, isolated yields of **18** increased to 60% and 62%, respectively (Table 4, entries 2 and 5). When Cs_2CO_3 was used as a base instead of K_2CO_3, the product yield increased slightly (Table 4, entries 5 and 7).

Table 4. Optimization of Cross-Coupling Reaction Conditions[a]

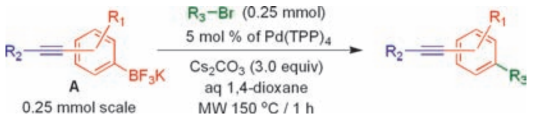
entry	Pd catalyst/ligand	base	time (h)	yield (%)[b]
1	$Pd_2(dba)_3$	K_2CO_3	7	21
2	$Pd(OAc)_2$	K_2CO_3	7	60
3	$Pd(OAc)_2$/TPP	K_2CO_3	7	46
4	$Pd(OAc)_2$/XPhos	K_2CO_3	7	58
5	$Pd(TPP)_4$	K_2CO_3	7	62
6	$PdCl_2(dppf)\bullet CH_2Cl_2$	K_2CO_3	7	54
7	$Pd(TPP)_4$	Cs_2CO_3	7	65
8[c]	$Pd(TPP)_4$	Cs_2CO_3	7	30
9[d]	$Pd(TPP)_4$	Cs_2CO_3	7	42
10[e]	$Pd(TPP)_4$	Cs_2CO_3	1	72
11[f]	$Pd(TPP)_4$	Cs_2CO_3	1	78

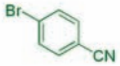
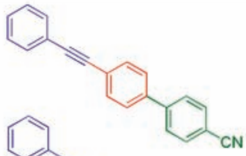
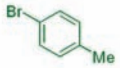
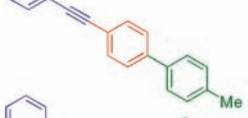
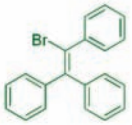
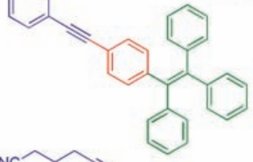
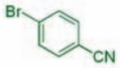
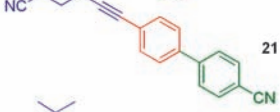
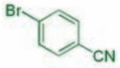
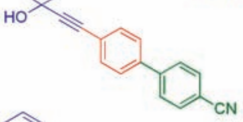
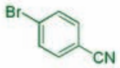
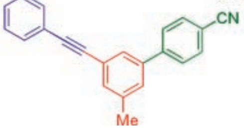
[a] All reactions were performed on a 0.1 mmol scale in 1.0 mL of 20% aqueous 1,4-dioxane at 100 °C in an oil bath. [b] Isolated yields. [c] MeOH was used as a solvent at 80 °C. [d] Reaction solvent was 20% aqueous toluene. [e] Initial microwave irradiation of 80 W was used at 100 °C. [f] Microwave temperature was 150 °C.

In the survey of solvent effects, 20% aqueous 1,4-dioxane was the best solvent, since the reactions in other solvents (methanol or 20% aqueous toluene) gave lower yields of **18** (Table 4, entries 8 and 9). Interestingly, we found that changing the heating source from an oil bath to microwave led to not only increased yield of cross-coupling product but also decreased reaction time from 7 to 1 h (Table 4, entry 10). Especially, the yield of **18** increased to 78% when the reaction was performed at 150 °C for 1 h with microwave irradiation (Table 4 entry 11).

According to the optimized cross-coupling reaction conditions, we examined the Suzuki−Miyaura reaction of various alkynylaryltrifluoroborates with aryl and alkenyl bromides by microwave irradiation. The results are shown in Table 5. As expected, the coupling reactions were completed in 1 h at 150 °C and provided the corresponding products in good yields.

Table 5. Cross-Coupling Reactions by Microwave Irradiation[a]



entry	A	R_3−Br	product		yield (%)[b]
1	1			18	80
2	1			19	66
3	1			20	71
4	9			21	79
5	11			22	64
6	15			23	62

[a] All reactions were carried out on a 0.25 mmol scale using the optimized conditions of entry 11 in Table 4 and an initial microwave irradiation of 80 W. [b] Isolated yields.

In summary, we have successfully prepared novel potassium alkynylaryltrifluoroborates from the corresponding haloaryltrifluoroborates with various terminal alkynes through the Sonogashira reaction and performed the cross-coupling reaction with microwave irradiation. Further applications using these trifluoroborates are currently in progress.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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