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A Facile One-Pot Preparation of Organoselanyltrifluoroborates from Dihalobenzenes and Their Cross-Coupling Reaction

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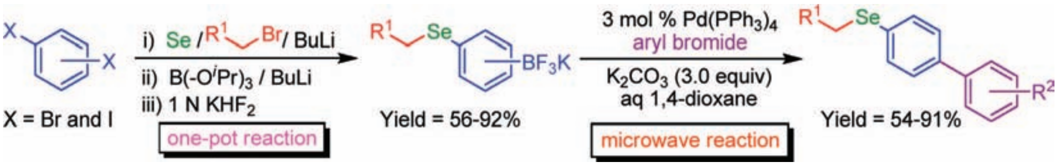
ABSTRACT



Potassium organoselanyltrifluoroborates have been prepared from the corresponding dihalobenzene compounds in 56−92% yields through a facile one-pot, multicomponent reaction. The microwave-promoted Suzuki−Miyaura cross-coupling reaction of these substrates with various aryl and alkenyl bromides in the presence of 3.0 mol % of $Pd(PPh_3)_4$ and 3.0 equiv of K_2CO_3 in aqueous 1,4-dioxane at 130 °C provided the desired compounds in 54−91% yields.

Organoselenium compounds have attracted considerable attention owing to their utility as synthetic intermediates[1] and their potential biological activities, serving as antioxidants, antimicrobials, antitumor, antiviral, and antihypertensive agents.[2] Generally, most organoselenium compounds have been prepared from the condensation of activated electrophiles with alkali metal selenolates as synthetic intermediates, which are generated from the corresponding organoselenol and diorganoyl diselenide compounds in the presence of strong base.[1] Alternatively, the metal selenolates may be prepared from aryl halides and BuLi in the presence of selenium. However, these synthetic methods have been limited by lengthy synthetic sequences and harsh reaction conditions. Thus, a facile and efficient protocol for the preparation of highly functionalized organoselenium compounds remains a high priority in various fields of chemistry.

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(1) (a) Patai, S.; Rappoport, Z. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley & Sons: New York, 1986 and 1987; Vols. 1 and 2. (b) Liotta, D.; Monahan, R., III *Science* **1986**, *231*, 356. (c) Krief, A.; Hevesi, L. In *Organoselenium Chemistry*; Springer-Verlag: Berlin, 1988; Vol. 1. (d) Back, T. G. In *Organoselenium Chemistry: A Practical Approach*; Oxford University Press: New York, 1999. (e) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3740, and references therein.

(2) (a) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (b) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255. (c) Grange, R. L.; Ziogas, J.; Angus, J. A.; Schiesser, C. H. *Tetrahedron Lett.* **2007**, *48*, 6301. (d) Garud, D. R.; Koketsu, M. *Org. Lett.* **2008**, *10*, 3319. (e) Okoronkwo, A. E.; Rosário, A. R.; Alves, D.; Savegnago, L.; Nogueira, C. W.; Zeni, G. *Tetrahedron Lett.* **2008**, *49*, 3252. (f) Sharma, A.; Schwab, R. S.; Braga, A.; Barcellos, T.; Paixão, M. W. *Tetrahedron Lett.* **2008**, *49*, 5172.

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Organotrifluoroborates[3] are becoming very useful reagents in the Suzuki−Miyaura cross-coupling reaction, which is among the most powerful yet mild protocols currently available for the formation of carbon−carbon bonds. The organotrifluoroborates provide numerous advantages over the corresponding boronic acids and boronate esters. For example, they are easily prepared by the addition of inexpensive KHF_2 to commercially available organoboron compounds and can be stored indefinitely without special precaution as a result of the air- and moisture-stable nature of the crystalline solids. Moreover, the organotrifluoroborates are inert to many nucleophilic reagents such as cyanide, azide, amines, enolates, alkoxides, and organometallic reagents because the boron atom in organotrifluoroborates does not have an empty p-orbital to interact with the incoming nucleophile. Therefore, direct functionalization of potassium organotrifluoroborates is successfully performed without loss of the valuable trifluoroborate group.

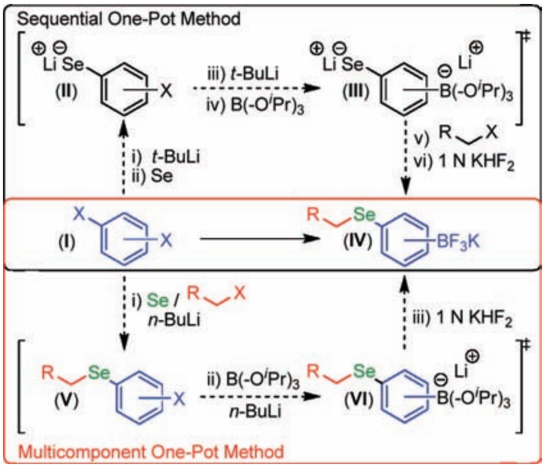
During the course of our synthetic studies on the development of potassium organotrifluoroborates as new coupling partners in the Suzuki−Miyaura cross-coupling reaction, we discovered a facile one-pot synthesis for the preparation of various potassium organoselanyltrifluoroborates from the corresponding dihalobenzenes. Although a selenium-containing organoboron compound, methylselenyl phenylboronic acid, was first reported in 1996 by Jones et al.,[4] its detailed method of preparation was not mentioned in this paper.

Herein we report initial results toward developing a convenient preparation of potassium organoselanyltrifluoroborates in good yields via a simple one-pot, multicomponent reaction involving dihalobenzenes, electrophiles, and selenium powder. Suzuki−Miyaura cross-coupling of the organotrifluoroborates thus obtained with various aryl and alkenyl bromides under microwave irradiation is also described.

In our initial studies, we attempted the one-pot, sequential preparation of organoselanyltrifluoroborates from the corresponding dihalobenzenes (**I** → **II** → **III** → **IV** in Scheme 1), in which the electrophile was added to a solution of intermediate **III** at the end of the reaction. The resulting organoboron intermediate was treated with 1 N KHF_2.

Although the desired organoselanyltrifluoroborates were obtained in good yields, reaction times were too long and the products were contaminated with potassium *tert*-butyltrifluoroborate as a side product during large-scale preparation. Thus, we developed a simple method for the preparation of organoselanyltrifluoroborates through a one-pot, multicomponent process (**I** → **V** → **VI** → **IV** in Scheme 1). In this reaction, intermediate **V** was generated in situ by addition of *n*-BuLi to a solution of equimolar amounts of dihalobenzene, selenium, and electrophile at −78 °C. After the reaction mixture became homogeneous, $B(\text{-O}^i\text{Pr})_3$ and *n*-BuLi were continuously added at −78 °C. Without isolation of the generated intermediate **VI**, the reaction mixture was quenched with 1 N KHF_2 and then purified according to the previous literature procedure.[3] These one-pot, multicomponent reactions proceeded readily to give the desired organoselanyltrifluoroborates in satisfactory yields without being contaminated with side products such as BuSeSeBu or $BuSeCH_2R$. The results are summarized in Table 1.

Scheme 1. One-Pot Syntheses of Potassium Organoselanyltrifluoroborate



In a test of reactivity between *o*-, *m*-, and *p*-dihalobenzenes (Table 1, entries 1 and 2), when using dibromobenzene as a starting material, similar yields of organoselanyltrifluoroborates were obtained. However, when using diiodobenzene, higher yields were achieved for the *para* isomers. 1,3-Disubstituted trifluoroborates could not be isolated from the corresponding *o*-dihalobenzenes (data not shown).

A wide range of functional groups could be tolerated, and the presence of an electron-donating or -withdrawing group on the benzyl bromide electrophiles did not affect the yields of products (Table 1, entries 3−8).

When 4-cyano- and 4-nitrobenzyl bromides were used (Table 1, entries 7 and 8), the corresponding organotrifluoroborates were not obtained by way of our one-pot, muticomponent procedure because the sensitive -CN and $-NO_2$ groups interfered in the reaction. Therefore, these substrates were utilized in the sequential one-pot method to obtain the desired products in 56% and 77% yields, respectively. By contrast, saturated alkyl halides gave good yields (Table 1, entries 11−15).

Next, we turned our attention to the Suzuki−Miyaura cross-coupling reaction of the organoselanyltrifluoroborates with aryl or alkenyl bromides using microwave irradiation (Table 2).

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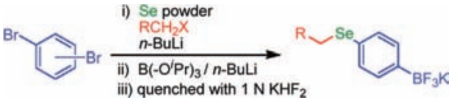
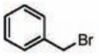
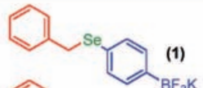
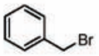
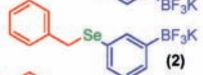
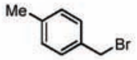
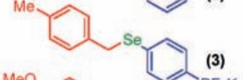
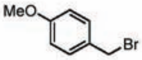
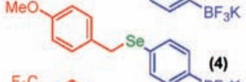
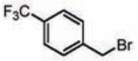
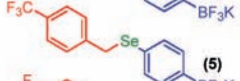
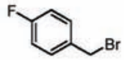
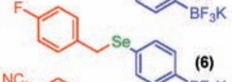
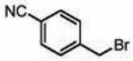
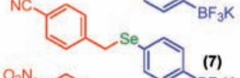
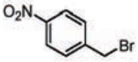
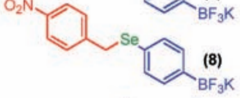
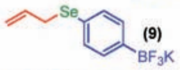
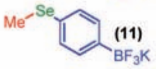
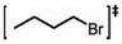
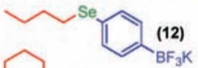
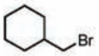
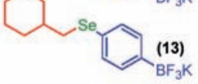
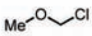
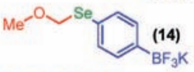
(3) (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (d) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (e) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (f) Park, Y. H.; Ahn, H. R.; Canturk, B.; Jeon, S. I.; Lee, S.; Kang, H.; Molander, G. A.; Ham, J. *Org. Lett.* **2008**, *10*, 1215. (g) Molander, G. A.; Febo-Ayala, W.; Ortega-Guerra, M. *J. Org. Chem.* **2008**, *73*, 6000. (h) Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2008**, *73*, 6841. (i) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708. (j) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257. (k) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135.

(4) Bahl, A.; Grahn, W.; Jones, P. G. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1996**, 2017.

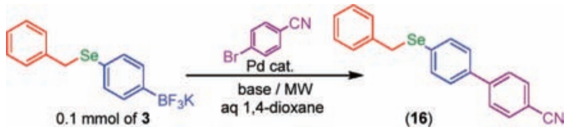
Table 1. One-Pot Preparation of Potassium Organoselanyltrifluoroborates from Dibromobenzene[a]



entry	RCH_2X	product	yield (%)[b]
1		 (1)	72 (82)[c]
2		 (2)	76 (53)[c]
3[d]		 (3)	77
4		 (4)	92
5		 (5)	87
6		 (6)	82
7[e]		 (7)	56
8[e]		 (8)	77
9		 (9)	78
10	Geranyl-Br	 (10)	80
11	CH_3-I	 (11)	91
12[f]		 (12)	84
13		 (13)	88
14		 (14)	76
15	$Ph(CH_2)_4$-Br	 (15)	74

[a] All reactions were performed on a 1.0 mmol scale. [b] Yields are given for isolated products. [c] Reactions were carried out with diiodobenzene (1.0 mmol). [d] Reaction was performed on a 3.5 mmol scale. [e] Reactions were carried out according to a sequential one-pot method. [f] 1-Bromobutane is produced as a byproduct of the halogen-lithium exchange step.

Table 2. Optimization of Cross-Coupling Reaction Conditions by Microwave Irradiation[a]

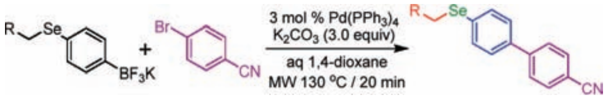


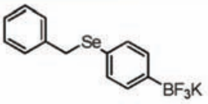
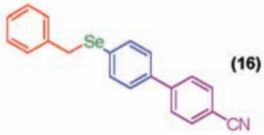
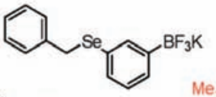
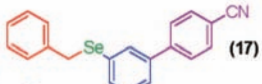
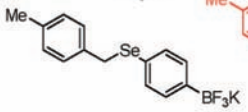
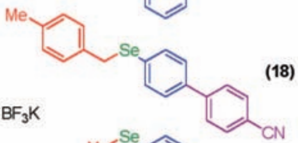
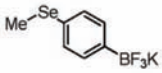
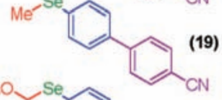
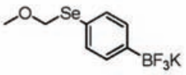
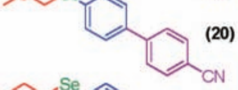
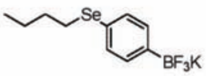
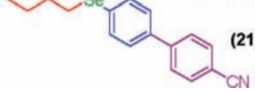
entry	Pd catalyst (3 mol %)	base (3 equiv)	MW (°C)[b]	reaction time	yield (%)[c]
1[d]	$Pd(OAc)_2$	K_2CO_3	80[e]	12 h	21
2	$Pd(PPh_3)_4$	K_2CO_3	80[e]	12 h	47
3	$Pd(PPh_3)_4$	K_2CO_3	100	1 h	42
4	$Pd(OAc)_2$	K_2CO_3	130	20 min	45
5	$Pd(PPh_3)_4$	K_2CO_3	130	20 min	87
6[f]	$Pd(OAc)_2$	Cs_2CO_3	130	30 min	76
7[g]	$PdCl_2(dppf)$	Cs_2CO_3	130	30 min	81

[a] All reactions were performed on a 0.05 mmol scale. [b] Initial microwave irradiation of 80 W was used. [c] Yields are given for isolated products. [d] Reaction solvent was MeOH. [e] Reactions were performed in an oil bath. [f] 6 mol % of RuPhos was used as a ligand. [g] 10 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ was used.

Optimization studies were carried out to access **16**, which was formed in yields of 21% and 47% when reactions were performed at 80 °C in an oil bath for 12 h with the use of $Pd(OAc)_2$ and $Pd(PPh_3)_4$, respectively (Table 2, entries 1 and 2). Changes in reaction temperature with microwave-heating conditions had a much greater impact on reaction rates and product yields. When the reaction temperature was increased from 80 to 130 °C, not only did the reaction time dramatically decrease from 12 h to 20 min, but the yield of **16** also increased from 47% to 87% with use of $Pd(PPh_3)_4$ (Table 2,

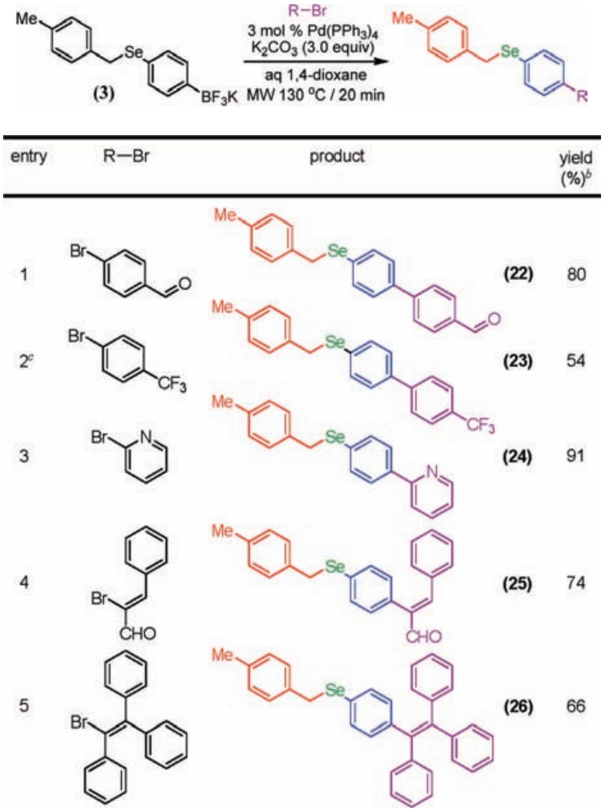
Table 3. Cross-Coupling Reaction of Various Potassium Organoselanyltrifluoroborates with 4-Bromobenzonitrile[a]



entry	organoselanyl-trifluoroborate	product	yield (%)[b]
1		 **(16)**	87
2		 **(17)**	84
3		 **(18)**	87
4		 **(19)**	61
5		 **(20)**	77
6		 **(21)**	64

[a] All reactions were carried out on 0.1 mmol scale using the optimized conditions of **16** for 20 min and an initial microwave irradiation of 80 W. [b] Yields are given for isolated products.

Table 4. Cross-Coupling Reaction of Potassium 4-(4-Methylbenzylselanyl)phenyltrifluoroborate (**3**) with Various Aryl and Alkenyl Bromides[a]



entry	R−Br	product		yield (%)[b]
1			**(22)**	80
2[c]			**(23)**	54
3			**(24)**	91
4			**(25)**	74
5			**(26)**	66

[a] All reactions were carried out on 0.1 mmol scale using the optimized conditions of **16** for 20 min and an initial microwave irradiation of 80 W. [b] Yields are given for isolated products. [c] Reaction was performed with 6 mol % of Pd(PPh$_3$)$_4$.

entries 2, 3, and 5). In the study of different palladium catalysts (Table 2, entries 5−7), although the desired compound **16** was obtained in good yields, Pd(OAc)$_2$ required 6 mol % of RuPhos as a ligand, and PdCl$_2$(dppf)•CH$_2$Cl$_2$ required at least 10 mol % of the catalyst to achieve consistent results.

Using the optimized conditions, the cross-coupling reaction of various organoselanyltrifluoroborates was performed with 4-bromobenzonitrile in the presence of 3 mol % of Pd(PPh$_3$)$_4$ and 3.0 equiv of K$_2$CO$_3$ in aqueous 1,4-dioxane at 130 °C with microwave heating (Table 3).

As shown in Table 3, all organoselanyltrifluoroborates gave rise to the corresponding products in satisfactory yields within a short reaction time. The coupling reaction of potassium 4- and 3-(benzylselany)phenyltrifluoroborates led to the corresponding compounds in 87% and 84% yields, respectively (Table 3, entries 1 and 2). Interestingly, the cross-coupling yields of alkylselanylphenyltrifluoroborates (Table 3, entries 4 and 6) were slightly lower than those of benzylselanylphenyltrifluoroborates.

Finally, we examined the Suzuki−Miyaura cross-coupling reaction of various aryl and alkenyl bromides with potassium 4-(4-methylbenzylselanyl)phenyltrifluoroborate (**3**) under the same conditions, the results of which are summarized in Table 4. The coupling reaction with aryl and alkenyl bromides containing an aldehyde functional group gave the desired products in 80% and 74% yields, respectively (Table 4, entries 1 and 4). Also, a high yield (91%) was obtained for the coupling reaction with 2-bromopyridine (Table 4, entry 3). However, when 4-trifluoromethylphenyl bromide was used, product **22** was obtained in only 54% yield even in the presence of 6 mol % of catalyst (Table 4, entry 2).

In summary, we have successfully prepared potassium organoselanyltrifluoroborates from dihalobenzenes through a one-pot, multicomponent reaction and performed the cross-coupling reaction with various aryl and alkenyl bromides with microwave irradiation. The potassium organoselanyltrifluoroborates should prove useful for the preparation of a variety of organoselenium compounds.

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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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