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Substituted potassium internal vinyltrifluoroborates: preparation and use in Suzuki–Miyaura cross-coupling reactions

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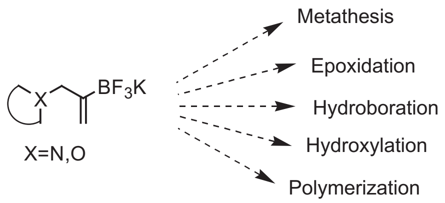
ABSTRACT

A collection of substituted potassium internal vinyltrifluoroborates was prepared and utilized in palladium-catalyzed cross-coupling reactions with aryl and heteroaryl halides. The cross-coupling reactions proceeded readily with $Pd(PPh_3)_4$ as a catalyst in toluene/H_2O under reflux in the presence of Cs_2CO_3. The process is regiospecific with regard to the internal vinyltrifluoroborate starting material and tolerates a variety of functional groups. This unique collection of substituted internal vinyltrifluoroborates can be readily utilized in research pharmaceutical applications.

Organoborons have long been used in synthetic organic chemistry to construct C–C, C–O, C–N, and C–S bonds via metal-mediated cross-coupling reactions.[1] Thus, organoborons are very valuable to synthetic chemists as key intermediates in the synthesis of more complex molecules. Substituted potassium internal vinyltrifluoroborates provide a systematic collection of a particular class of compounds that can carry a nitrogen or oxygen heteroatom at the allylic carbon center. These substituted internal vinyltrifluoroborates can be valuable in synthetic manipulations, as in olefin metathesis, to generate complex C=C bonds in molecules.[2] In general, the olefin moiety in a molecule is useful as a point of synthetic manipulation. One example is the functionalization of the olefin by hydroboration, reduction, epoxidation, cyclopropanation, dihydroxylation, ozonolysis, polymerization, and other reactions well known in the field (Scheme 1).[3]



Scheme 1. Applications of substituted potassium internal vinyltrifluoroborates.

Other organometallic reagents suffer from limitations that limit their utility. Organozinc reagents are prepared and immediately used as they cannot be stored for long periods of time.[4] Organotin reagents are toxic and also pose difficulty in removing the tin-containing byproducts.[5] On the other hand, organoboron byproducts are nontoxic and can be easily removed during standard reaction work up. Among the organoboron derivatives, trifluoroborates have several advantages over boronic acids and boronates.[6] Boronic acids can form cyclic trimers resulting in boroxines which are difficult to quantify. Organoboronates can potentially hydrolyze, making them difficult to purify and also afford byproducts in the cross-coupling reactions that need to be separated.

Organotrifluoroborates, however, are readily prepared from a variety of organoborons in situ with inexpensive KHF_2. They are monomeric, crystalline solids, air-stable, and can be stored for longer periods of time. It is known that vinylboronic acid and vinylboronates are unstable,[7] whereas internal vinyltrifluoroborates are quite stable and work well in cross-coupling reactions.[8]

Related materials have been reported, yet all suffer from significant limitations. Terminal olefin-boron derivatives (β-boroalkenes) have been easily obtained by established methods such as hydroboration.[9] However, the preparation of the internal vinylboron derivatives (α-boroalkenes) regiospecifically has been difficult, and particularly problematic when the allylic nitrogen atom exists as a free amine. The inherent ability to complex between the amine nitrogen and sp^2-boron makes them difficult to isolate. Markovnikov vinylboranes have been reported with simple alkyl substituents on the α-carbon, with all lacking a free amine at the

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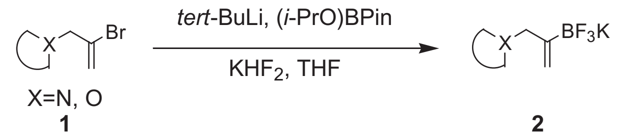
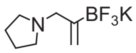
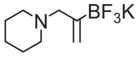
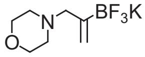
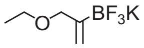
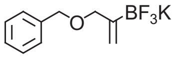
Table 1
Preparation of substituted potassium internal vinyltrifluoroborate[a]



Entry	Potassium internal vinyltrifluoroborates	Product	Isolated yield (%)
1		**2a**	43
2		**2b**	34
3		**2c**	41
4		**2d**	39
5		**2e**	45

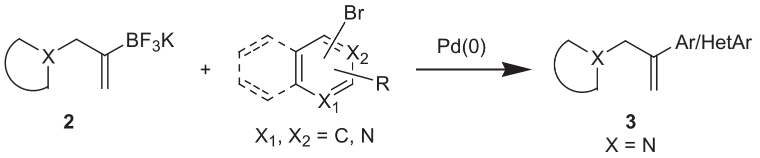
[a] Treated with 2 equiv of *tert*-BuLi, 1 equiv of (*i*-PrO)BPin and 3 equiv of KHF_2.

allylic position.[10] Transition metal catalyzed hydroboration approaches utilizing terminal alkynes also have limitations of isolation and regioselectivity. There is currently no general method to prepare internal vinylboron derivatives with a nitrogen atom from free amine at the allylic position. To the best of our knowledge there are no methods or suppliers of such vinylboron derivatives that are regiospecifically pure with a diverse selection of systematic substituents at the allylic center. The substituted potassium internal vinyltrifluoroborates described in this report represent new reagents to address many of the limitations of previous reported reagents.

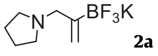
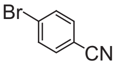
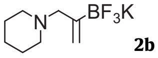
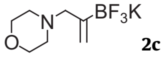
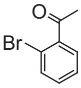
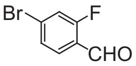
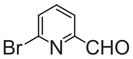
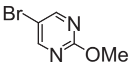
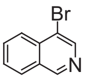
A key distinction of the work described in this letter when compared to previously reported related chemistry describes the use of free amines of internal vinyl boronates in cross-coupling reactions. To address this unmet need, we developed a method to generate a regiospecific collection of functionally complex internal vinyltrifluoroborates as potassium salts, featuring amine and ether functionalities in the allylic position, as air-stable crystalline products (Table 1). These substituted potassium internal vinyltrifluoroborates are prepared from corresponding vinyl bromides that are either known in the literature or commercially available, and the reactions can be performed from gram to multigram scale.[11] This approach enables chemists to generate a collection of systematically substituted potassium internal vinyltrifluoroborates which are expected to be valuable additions for research and pharmaceutical applications.

To establish their absolute structures, stability, and reactivity, these internal vinyltrifluoroborates were used in Suzuki–Miyaura

Table 2
Reactions of substituted potassium internal vinyltrifluoroborates with aryl and heteroaryl bromides[a]



R= F, OMe, CN, CHO, -C(=O)CH3

Entry	Vinyltrifluoroborates	Ar/HetArBr	Product	Yield[b] (%)
1	 **2a**		**3a**	80
2	 **2b**		**3b**	88
3	 **2c**		**3c**	67
4	**2a**		**3d**	80[c]
5	**2b**		**3e**	87[d]
6	**2c**		**3f**	72
7	**2a**		**3g**	71
8	**2b**		**3h**	80[c]
9	**2c**		**3i**	73
10	**2a**		**3j**	64
11	**2b**		**3k**	88
12	**2c**		**3l**	70
13	**2a**		**3m**	85
14	**2b**		**3n**	71
15	**2c**		**3o**	88
16	**2a**		**3p**	72
17	**2b**		**3q**	73[d]
18	**2c**		**3r**	77[e]

[a] Heated to reflux with 9 mol% $Pd(PPh_3)_4$, Cs_2CO_3, toluene/H_2O (10:1), for 16 h.
[b] Isolated yield.
[c] Reaction time 24 h.
[d] Reaction time 36 h.
[e] Reaction time 56 h.

cross-coupling reactions as shown in Table 2. A variety of aryl and heteroaryl bromides bearing electron-rich and electron-poor functional groups were employed to determine their applicability in Suzuki–Miyaura cross-coupling reactions.

The application of metal-mediated arylation with the aryl and heteroaryl bromide substrates requires careful optimization of catalyst, ligand, base, solvent, and reaction temperature. Several palladium catalysts including $PdCl_2(dppf)$, $Pd(PPh_3)_4$, and $Pd(OAc)_2$ were used with methanol, THF, H_2O, and toluene as solvents with Cs_2CO_3, *tert*-butylamine, and PPh_3 as bases and ligands. The best coupling results were achieved with $Pd(PPh_3)_4$ as catalyst in toluene-H_2O (10:1) under reflux in the presence of Cs_2CO_3, and the reactions proceeded regiospecifically.

In summary, the substituted potassium internal vinyltrifluoroborates were most conveniently prepared in one pot by in situ lithiation of commercially available, inexpensive substituted vinyl bromides, quenched with isopropoxy-pinacol-borate, and treated with KHF_2. Palladium catalyzed cross-coupling reactions of substituted potassium internal vinyltrifluoroborates with aryl and heteroaryl halides proceed with clean retention of configuration with respect to both coupling partners and were achieved in good yields tolerating a variety of functional groups. The substituted potassium internal vinyltrifluoroborates generated are air-stable monomeric solids that are easily isolated and purified, thus making them highly attractive intermediates for numerous synthetic applications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.119.

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