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Potassium trifluoroborate salts as convenient, stable reagents for difficult alkyl transfers

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1. Introduction

The ability to incorporate alkyl groups selectively and conveniently into molecular substructures at a late stage is of critical strategic value in complex molecule synthesis. In the quest for a universal alkylating platform, various nucleophilic organometallic reagents have surfaced that are capable of facilitating such desired transformations [i]. However, the highly reactive nature of many of these reagents limits their use for polyfunctional molecules. The Suzuki-Miyaura cross-coupling reaction has emerged as one of the most powerful means to effect this type of transformation [ii]. The organoboron reagents employed in this reaction can be prepared readily using a variety of routes and have a high compatibility with a broad range of functional groups. The reaction is also particularly advantageous because, unlike the byproducts generated in other cross-coupling bond strategies, those generated via the Suzuki-Miyaura cross-coupling reaction are relatively benign inorganic salts that can be removed via an aqueous wash. As a testament to its effectiveness, strategies using the Suzuki-Miyaura cross-coupling reaction for the transfer of alkyl groups have been employed in the syntheses of various natural products and biologically significant analogues [iii].

The Suzuki-Miyaura reaction most often employs trialkylboranes as the nucleophilic partner because they are easily accessed via hydroboration reactions of the corresponding alkenes with dialkylboranes (i.e., 9-BBN, Chx_2BH, Sia_2BH). Many effective protocols have been established and optimized for the cross-coupling of trialkylboranes with various types of electrophilic partners. However, the reaction scope is limited by the incompatibility of these dialkylborane hydroborating agents with a variety of functional groups. The air- and

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The past decade has witnessed the emergence of potassium organotrifluoroborates as a new class of nucleophilic boron reagents for the Suzuki-Miyaura cross-coupling and Rh-catalyzed addition reactions. These substrates are easily prepared and most of them are indefinitely stable to air and moisture. Recent advances have focused on the utility of alkyltrifluoroborates in appending alkyl groups selectively and conveniently onto appropriate molecular substructures. Strategies employing these reagents are described herein.

moisture sensitivity of the resulting trialkylborane species requires them to be prepared and used *in situ*, making small-scale optimization an arduous task, in turn limiting their use in synthetic sequences.

Alkylboronic acids and alkylboronate esters can also be prepared and employed as the nucleophilic coupling partners. Reactions involving the cross-coupling of alkylboronic acids suffer from competitive protodeboronation, and as a result, significant excesses of the boronic acids are often employed to ensure complete consumption of the electrophilic coupling partner [iv]. One report details the preformation and isolation of an "activated borate" by treating an alkylboronic acid with sodium hydroxide. Once prepared, the alkyl trihydroxyborate salt is able to undergo a base-free cross-coupling with an aryl bromide, but only a moderate yield is obtained even with the use of an excess of the activated species [v].

Alkylboronate esters have a decreased propensity for protodeboronation and thus can also serve as suitable boron reagents. Their enhanced stability, however, comes at the cost of sluggish reactivity in many cases, as the use of these compounds generally leads to low yields unless highly toxic thallium bases (TlOH or Tl_2CO_3) are employed to facilitate the transmetalation step [vi]. A single report demonstrates a high yielding alkyl transfer reaction using a boronate ester without the use of a thallium base, but treatment *in situ* with *sec*-butyllithium was required to generate a lithium *n*-alkylborate reagent, the activated form required for transmetalation [vii].

Most notably, the aforementioned classes of organoboron compounds are all tricoordinate species, each possessing an empty p-orbital on boron, leaving them susceptible to reactions with important classes of reagents such as organic acids, oxidants, bases, and nucleophiles. As a result, these tricoordinate alkylborons are most often prepared and used directly, rather than carried though synthetic steps.

Since the discovery of the Suzuki-Miyaura cross-coupling reaction, much of the research has focused on optimization of the metal/ligand catalyst systems incorporating the classes of organoboron reagents outlined above [4,viii]. These studies have also incorporated the use of additives to facilitate product formation [ix]. Although important contributions have been made through these efforts, until recently little consideration had been given to modifying the organoboron reagent, which could lead to a more stable nucleophilic partner and potentially enhanced levels of reactivity.

Throughout the past decade, organotrifluoroborates have emerged as alternative nucleophilic partners in Suzuki-Miyaura cross-coupling [x,xi]. Their tetracoordinate nature masks the inherent reactivity of the C-B bond, making them protected forms of boronic acids that can endure a variety of synthetic transformations. Their reactivity can subsequently be unveiled under the same conditions required for cross-coupling.

Potassium alkyltrifluoroborates are easily prepared from commercially available, inexpensive starting materials {e.g., via hydroboration of the corresponding alkenes [xii,xiii,xiv,xv], transmetalation from other organometallics [xvi], or metalation reactions [xvii], followed by treatment with inexpensive potassium hydrogen fluoride (KHF_2) [xviii]}. Once prepared, most of them are indefinitely stable to air and moisture (Scheme 1).

These traits, partnered with their demonstrated ability to undergo transmetalation with limited interference from competitive protodeboronation, reinforce their value as appealing reagents for alkyl transfer reactions.

2. Cross-Coupling of Primary Alkyltrifluoroborates with Aryl- and Alkenyl Electrophiles

Various studies have focused on the incorporation of alkyl groups into aryl- or alkenyl compounds via the Suzuki-Miyaura cross-coupling reaction. The earliest reports used alkylboronic acids as the nucleophilic partner and commonly resulted in very low yields [xix]. Later studies by Falck and coworkers demonstrated vast improvements in the cross-coupling of alkylboronic acids, revealing high yields of the cross-coupled product. However, expensive silver oxide (2.5 equiv) was required as an additive to facilitate product formation [9]. More recently, the cross-coupling of alkylboronic acids with aryl halides and -triflates has been demonstrated using $PdCl_2(dppf)\cdot CH_2Cl_2$ and Cs_2CO_3 [xx], but the known instability of boronic acids prompted investigations into the use of the highly crystalline and indefinitely stable organotrifluoroborate salts as the nucleophilic partner.

2.1 Cross-Coupling of Primary Alkyltrifluoroborates with Aryl- and Alkenyl Electrophiles

Primary alkyltrifluoroborates can be accessed via the addition of alkyl Grignard reagents to trimethyl borate and by the hydroboration of alkenes employing several hydroborating protocols, followed in both cases by treatment with KHF_2.

Initial investigations focused on the cross-coupling of these alkyltrifluoroborates with aryl- and 1-alkenyl trifluoromethanesulfonates (Tf). This study illustrated that Cs_2CO_3 (3 equiv) was the most effective base to promote the transformation when used in combination with 9 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ and a THF/H_2O solvent system. These optimized conditions were also found to be suitable for the cross-coupling of alkylboronic acids and -esters with aryl electrophiles [xxi]. A subsequent study utilizing these same conditions expanded the scope of the cross-coupling reaction of alkyltrifluoroborates to include aryl bromides as the electrophilic partner [xxii] (Scheme 2).

These conditions were also employed in the cross-coupling of oxiranylethyltrifluoroborate with 4-bromobenzonitrile. However, in this case a base-catalyzed epoxide opening occurred, and the cross-coupled product was isolated as a diol [xxiii]. Simply reducing the amount of water in the solvent mixture to a 40:1 THF/H_2O mixture allowed the oxiranyl product to be obtained (Scheme 3).

A more recent account was published detailing the cross-coupling of potassium alkyltrifluoroborate substrates with aryl chlorides [xxiv]. Using a parallel microscale experimentation approach, optimal conditions of 2 mol % of $Pd(OAc)_2$ and 4 mol % of RuPhos (2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl) in combination with K_2CO_3 (3 equiv) and a toluene/H_2O solvent system were identified that were capable of cross-coupling a wide variety of aryl- and heteroaryl chloride substrates with alkyltrifluoroborates. This finding with chloride electrophiles represents an important extension of the alkyltrifluoroborate cross-coupling method because it allows the use of more stable and less expensive electrophilic partners to be employed. These newly optimized conditions were also found to be amenable to bromides, iodides, and triflates. Of particular note is the tolerance of a silyl ether derivative through not only the preparation of the trifluoroborate (with exposure to a fluoride source – KHF_2), but also the cross-coupling to 4-chloroanisole (Scheme 4).

The cross-coupling of potassium primary alkyltrifluoroborates has also been demonstrated with alkenyl bromides [xxv]. Using 10 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ and Cs_2CO_3 (3 equiv) and a toluene/H_2O solvent system, various alkenyl bromides underwent conversion to generate the cross-coupled products in good yields. Using these conditions, a dihydroxylated

potassium alkyltrifluoroborate was also found to be a suitable nucleophilic partner with alkenyl bromides [xxvi] (Scheme 5).

A one-pot synthesis of trisubstituted conjugated dienes was also demonstrated via sequential Suzuki-Miyaura cross-coupling reactions [xxvii]. A *gem*-dibromide could be partnered with an alkenyl trifluoroborate in the presence of 7 mol % of $Pd(PPh_3)_4$ and Cs_2CO_3 followed by reaction with a variety of alkyltrifluoroborates to furnish trisubstituted alkenes in excellent yields (Scheme 6).

2.2 Potassium Methyltrifluoroborate

In addition to the development of general methods to append primary alkyl groups onto organic molecules, strategies to incorporate specific organic moieties, particularly methyl groups, are of importance. Historically, methylation strategies using organometallics have proved to be less than ideal. One report details the cross-coupling of methylboronic acid, but necessitates the use of 40 mol % of triphenylarsine [xxviii]. In a more recent publication, a methylation procedure was described using methylboronic acid and aryl bromides with sodium dodecyl sulfate (SDS) [xxix]. Another means of introducing methyl groups into systems is through the use of trimethylboroxine (the cyclic trimer of methyl boronic acid). However, significant excesses of these reagents are often required (3 equiv of the boroxine) [xxx].

Molander and coworkers have reported the cross-coupling of potassium methyltrifluoroborate with bromide and triflate electrophiles using 9 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ or with chlorides using a combination of 2 mol % of $Pd(OAc)_2$ and 4 mol % of RuPhos to yield the methylated compounds in good yields [22,24]. Another recent publication outlined the cross-coupling of halopurines with potassium methyltrifluoroborate to generate substituted purines, which represent an important class of biologically active compounds [xxxi]. Notably, the use of $Pd(OAc)_2$ and trisodium triphenylphosphine-3,3′,3″-trisulfonate (TPPTS) under microwave conditions facilitated the cross-coupling of potassium methyltrifluoroborate with 6-chloropurine (Scheme 7).

3. Cross-Coupling of Secondary Alkyltrifluoroborates with Aryl Electrophiles

Beyond the exceptional reactivity of cyclopropylboron derivatives (which can be rationalized by the partial sp^2 character these compounds possess), there has been little precedent for the cross-coupling of secondary alkylboron derivatives [8,xxxii,xxxiii]. In the few published examples, there was no significant development toward identifying a general solution for this significant, unsolved problem. The difficulty in this cross-coupling reaction derives from two key steps of the mechanistic cycle – the transmetalation that is more difficult for secondary organoboron derivatives than other organic moieties, and the reductive elimination step, which competes with β-hydride elimination.

3.1 Cyclopropylation

Incorporating cyclopropyl groups into complex molecules is becoming increasingly important owing to the prevalence of cyclopropyl-substituted natural products and biologically active molecules. The ease of preparation of cyclopropylboron compounds makes the Suzuki-Miyaura cross-coupling reaction an attractive cyclopropylating platform. Much of the research in this area has focused on the cross-coupling of cyclopropylboronic acid. However, the propensity of this reagent to protodeboronate upon prolonged storage renders it unstable and unsafe. The trifluoroborate analogs serve as more suitable alternatives because they are more resistant to protodeboronation, and thus efforts in this

area focused on the preparation and cross-coupling of various cyclopropyltrifluoroborates with aryl halides.

Stereodefined substrates were first prepared from alkenylboronic acids through a sequence of reactions in which the pinacol boronates were generated in situ and treated with CH_2N_2 in the presence of $Pd(OAc)_2$. Subsequent treatment with KHF_2 afforded the cyclopropyltrifluoroborates[xxxiv]. These substrates were subsequently cross-coupled with aryl bromides using 2 mol % of $Pd(PPh_3)_4$ and $K_3PO_4{\cdot}3H_2O$ (3 equiv) in a toluene/H_2O solvent system, in each case retaining the configurations of the cyclopropane stereocenters during the cross-coupling event. A subsequent report detailed the synthesis of 1,2,3-*syn*-*cis*-substituted potassium cyclopropyltrifluoroborates from allylic alcohols, a readily prepared *gem*-dizinc carbenoid, and trimethyl borate with subsequent addition of KHF_2 [xxxv]. Using 3 mol % of $Pd(OAc)_2$ and 6 mol % of CyJohnPhos (2-biphenyldicyclohexylphosphine), K_3PO_4 (3.3 equiv) and a toluene/H_2O solvent system, these substrates could be cross-coupled with a variety of aryl bromides (Scheme 8).

A later report described the preparation potassium cyclopropyltrifluoroborate by treating the corresponding boronic acid with KHF_2 [xxxvi]. Using 3 mol % of $Pd(OAc)_2$ and 6 mol % of XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), K_2CO_3 (3 equiv) and a cyclopentyl methyl ether (CMPE)/H_2O solvent system, the organotrifluoroborate could be cross-coupled with both aryl- and heteroaryl chlorides.

Additionally, the use of $Pd(OAc)_2$ and di(1-adamantyl)-*n*-butyl-phosphine (*n*-$BuPAd_2$) facilitated the cross-coupling of potassium cyclopropyltrifluoroborate and 6-chloropurine to generate the cyclopropyl-substituted product in good yield [31] (Scheme 9).

3.2 Cross-Coupling of Other Secondary Alkyltrifluoroborate Substrates

The earliest development in this area using organotrifluoroborates is reported via a RuPhos-mediated cross-coupling of aryl- and heteroaryl bromides with potassium cyclopentyltrifluoroborate [xxxvii]. Although the yields were moderate, this clearly demonstrated the first example of a cross-coupling reaction with a secondary alkyltrifluoroborate. A few examples with *sec*-butyltrifluoroborate were also described, in each case generating the secondary alkylated derivatives in moderate yields (Scheme 10).

At the same time, another account was published describing the cross-coupling of potassium secondary alkyltrifluoroborates with a variety of aryl- and heteroaryl chlorides and -bromides. The optimized reaction conditions of $Pd(OAc)_2$ and *n*-$BuPAd_2$ were identified through a microscale parallel experimentation screen and found to be suitable for cyclic, symmetrical trifluoroborate derivatives [xxxviii]. Additionally, a strategy was identified using these conditions to incorporate cyclobutyl rings into molecules via the cross-coupling of cyclobutyltrifluoroborate [36]. These conditions proved to be somewhat substrate dependent when applied to this system. However, various aryl- and heteroaryl chlorides were shown to be suitable electrophiles, providing the aryl cyclobutane products (Scheme 11).

When these conditions were applied to secondary acyclic derivatives, such as potassium isopropyltrifluoroborate, a β-hydride elimination and subsequent isomerization occurred to generate a mixture of the desired branched product to an undesired straight chain product. Subsequent investigations showed that more sterically hindered ligands, *t*-Bu_2PPh and *t*-Bu_3P, were capable of inhibiting isomerization to generate higher ratios of secondary alkylated products to the undesired straight-chain products [38].

4. Cross-Coupling of Specialized Alkyltrifluoroborate Reagents with Aryl Electrophiles

In addition to the cross-couplings of primary and secondary alkyltrifluoroborates, the cross-couplings of several specialized alkyltrifluoroborates with aryl halides have also been described.

4.1 Aminoethyltrifluoroborates

Preliminary investigations in this area focused on the preparation of β-aminoethyltrifluoroborates via the Sniekus hydroboration with di(isopropylprenyl)borane [(*i*-PP)$_2$BH] [xxxix]. Once prepared, the cross-coupling of these substrates with a variety of aryl- and heteroaryl bromides was accomplished using $PdCl_2(dppf)\cdot CH_2Cl_2$. This method provided a convenient way to prepare a variety of phenethylamines.

A subsequent publication described advances in the scope of this aminoethylation reaction, now extending the preparation of the aminoethyltrifluoroborate partner to enecarbamate substrates, including Boc and Cbz protected derivatives [xl]. Investigations of substrate scope with the Cbz carbamate derivative and electron-poor aryl electrophiles demonstrated that the originally optimized conditions for aminoethylations were suitable for the cross-coupling. However, preliminary experiments with electron-rich electrophiles failed to provide the desired cross coupled products in satisfactory yields, demonstrating the need for further optimization. The utilization of a catalytic system of $Pd(OAc)_2$ and RuPhos offered significantly improved results, and also proved to be an appropriate catalyst component for the cross coupling with a variety of heteroaryl bromides as well. The Boc-protected aminoethyltrifluoroborate derivative also cross-coupled with equal facility. Once cross-coupled, these trifluoroborate substrates offer the potential for further functionalization and incorporation of the phenethylamine subunit into complex molecules (Scheme 12).

4.2 Aminomethyltrifluoroborates

In addition to the importance of installing aminoethyl subunits into molecules, there are a variety of biologically active molecules that possess aminomethyl aryl linkages as well. There is ample precedent for the installation of this subunit via other bond-forming techniques (nucleophilic substitution, reductive amination, alkylation of iminium ions, etc.). However, a complementary cross-coupling strategy has been employed only to a limited extent to introduce this subunit. A singular example existed that demonstrated the cross-coupling of a highly specialized aminomethylorganostannane, but the perceived toxicity of tin reagents makes the use of the Stille reaction a less than ideal aminomethylating platform [xli].

A variety of *N*,*N*-dialkylaminomethyltrifluoroborates were prepared via reaction of secondary amines with bromomethyltrifluoroborate [xlii], and conditions involving 3 mol % of $Pd(OAc)_2$ and 6 mol % of XPhos were identified to be capable of facilitating the pairing of these substrates first with aryl- and heteroaryl bromides [xliii] and then further extended to include aryl chlorides [xliv]. In many cases, the results with aryl chlorides were actually superior to those obtained with bromides (Scheme 13).

The method was also extended to alkenyl electrophiles, albeit with limited success because the conditions optimized for this cross-coupling seemed to be substrate dependent. Nonetheless, these examples represent the possible utility of this reaction to incorporate an aminomethyl alkenyl subunit in complex molecule synthesis [44].

4.3 Alkoxymethyltrifluoroborates

A similar strategy was developed for the incorporation of an alkoxymethyl subunit into organic molecules [xlv]. Ethers are one of the most utilized protecting groups for alcohols and as a result, this strategy could provide a simplified synthesis of protected aryl- and heteroaryl alcohol derivatives, avoiding common multistep processes generally employed to access the compounds (i.e., carbonylation/carboxylation, reduction, and protection steps).

Alkoxymethylstannanes have been employed to a limited extent as hydroxymethylating agents, but the minimal use of this class of reagents is undoubtedly a result of the perceived toxicity of these reagents in combination with the known difficulty in purification after cross-coupling [xlvi]. The use of potassium alkoxymethyltrifluoroborates represents a more practical and convenient method of installing this moiety into organic molecules. Like their aminomethyl counterparts, these substrates were prepared via substitution reactions (in this case using nucleophilic alkoxides) with bromomethyltrifluoroborate as an electrophile. After an extensive optimization, $Pd(OAc)_2$ and RuPhos were identified as a capable catalytic system for the cross-coupling of these substrates with aryl- and heteroaryl chlorides, generating the desired cross-coupled products in good yields (Scheme 14).

4.4 3-Oxoalkyltrifluoroborates

Zinc ketohomoenolates have been used in palladium catalyzed reactions with acid chlorides. However, prior to the work Molander and coworkers performed in this area, there was no precedent of zinc, tin, or boro homoenolates having been employed in cross-coupling reactions with aryl electrophiles. Initial investigations in this area dealt with the preparation of potassium 3-oxoalkyltrifluoroborates via conjugate addition of bis(pinacolato)diboron to unsaturated carbonyl compounds [xlvii] or by alkylation of commercially available methyl ketones (via lithium enolates) with iodomethylpinacol boronate [xlviii] followed in both cases by treatment with KHF_2. Conditions were then identified allowing cross-coupling of the 3-oxoalkyltrifluoroborates with a variety of aryl bromides. Aryl chlorides and -triflates and an alkenyl bromide also served as suitable electrophilic partners in this reaction [xlix].

The scope and generality of this reaction was further investigated, and through the same procedures a family of trifluoroboratoketohomoenolates was prepared [l]. Although aliphatic ketohomoenolates were shown to cross-couple in good yields with a variety of aryl- and heteroaryl chlorides (Scheme 15), aromatic ketohomoenolates were significantly more challenging substrates to cross-couple.

A subsequent investigation extended the method to include the cross-coupling of potassium β-trifluoroborato amides with aryl- and heteroaryl chlorides (Scheme 16) [li].

This method could be applied to the synthesis of more highly functionalized molecules; in particular, functionalized dipeptides.

4.5 4-Oxoalkyltrifluoroborates

Another related class of compounds has recently emerged, prepared via the nickel-catalyzed borylation of aryl cyclopropyl ketones with bis(pinacolato)diboron [lii]. The resulting 4-oxoalkylboronates can be readily transformed into the corresponding trifluoroborate derivatives by treatment with KHF_2. This 4-oxoalkyltrifluoroborate can be cross-coupled with 4-bromoanisole using 5 mol % of $Pd(OAc)_2$, 10 mol % of RuPhos, and K_2CO_3 in a toluene/H_2O solvent system to provide the product in good yield (Scheme 17).

5. Rhodium-Catalyzed 1,2-Additions to Aldehydes

There is ample precedent for the Rh-catalyzed 1,2- and 1,4-additions of organoboron compounds to aldehydes and Michael acceptors; however, the difficulty in transmetalation and problems with β-hydride elimination associated with alkylboron compounds has restricted the method to the addition of sp^2-hybridized species. Recently, Aggarwal and coworkers have circumvented these limitations and described the first Rh-catalyzed 1,2-addition of chiral secondary and tertiary potassium alkyltrifluoroborates to aldehydes [liii]. Using 2.5 mol % $[RhCl(cod)]_2$ in a dioxane/H_2O solvent system, a variety of chiral trifluoroborates were found to add to aldehydes with complete stereoretention (Scheme 18).

6. Conclusions

Throughout the past decade, potassium alkyltrifluoroborates have emerged as exceptional reagents for difficult alkyl transfers. This class of organoboron reagents offers a superior shelf life and stability and in some cases enhanced reactivity compared to their tricoordinate organoboron analogs. Conditions have been identified for both primary (including trifluoroboratohomoenolates) and secondary trifluoroborate substrates for their cross-coupling with a variety of electrophilic species. Additionally, a number of specialized alkyltrifluoroborate substrates have been shown to cross-couple under various conditions to append aminomethyl-, aminoethyl-, and alkoxymethyl linkages to aryl electrophiles. The recent advances in Rh-catalyzed addition chemistry further strengthen the value of alkyltrifluoroborate reagents. The developments in this area represent an important progression in organometallic chemistry, because a number of alkyl groups can be readily transferred to increase structural complexity in highly functionalized molecules via C-C bond-forming reactions.

Abbreviationsp

KHF_2	potassium hydrogen fluoride
Tf	trifluoromethanesulfonate
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SDS	sodium dodecyl sulfate
TPPTS	trisodium triphenylphosphine-3,3′,3″-trisulfonate
CyJohnPhos	2-biphenyldicyclohexylphosphine
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
CPME	cyclopentyl methyl ether
Ad	adamantyl, **(*i*-PP)$_2$** di(isopropylprenyl)

References

•• of outstanding interest

• of special interest

i. Trost, BM.; Fleming, I., editors. Comprehensive Organic Synthesis. Vol. 3. Pergamon Press; Oxford: 1991. Tamao K. Coupling reactions; p. 435-480.

ii. Miyaura N, Suzuki A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. Chem Rev 1995;95(7):2457–2483.

iii. Nicolaou KC, Bulger PG, Sarlah D. Palladium-catalyzed cross-coupling reactions in total synthesis. Angew Chem Int Ed 2005;44(29):4442–4489.

iv. Walker SD, Barder TE, Martinelli JR, Buchwald SL. A rationally designed universal catalyst for Suzuki-Miyaura coupling processes. Angew Chem Int Ed 2004;43(14):1871–1876.

v. Cammidge AN, Goddard AHM, Gopee H, Harrison NL, Hughes DL, Schubert CJ, Sutton BM, Watts GL, Whitehead AJ. Aryl trihydroxyborates: easily isolated discrete species convenient for direct application in coupling reactions. Org Lett 2006;8(18):4071–4074. [PubMed: 16928076]

vi. Sato M, Miyaura N, Suzuki A. Cross-coupling reaction of alkyl- or arylboronic acid esters with organic halides induced by thallium(I) salts and palladium-catalyst. Chem Lett 1989;18(8):1405–1408.

vii. Zou G, Falck JR. Suzuki–Miyaura cross-coupling of lithium *n*-alkylborates. Tetrahedron Lett 2001;42(34):5817–5819.

viii. Littke AF, Dai C, Fu GC. Versatile catalysts for the Suzuki cross-coupling of arylboronic acids with aryl and vinyl halides and triflates under mild conditions. J Am Chem Soc 2000;122(17):4020–4028.

ix. Zou G, Reddy K, Falck JR. Ag(I)-promoted Suzuki–Miyaura cross-couplings of *n*-alkylboronic acids. Tetrahedron Lett 2001;42(41):7213–7215.

x•. Darses S, Genet JP. Potassium organotrifluoroborates: New perspectives in organic synthesis. Chem Rev 2008;108(1):288–325. Provides background on recent advances in the utility of organotrifluoroborates. [PubMed: 18095714]

xi. Darses S, Genet J-P. Cross-coupling reactions of arenediazonium tetrafluoroborates with potassium aryl- or alkenyltrifluoroborates catalyzed by palladium. Tetrahedron Lett 1997;38(25):4393–4396.

xii. Snieckus V, Kalinin AV, Scherer S. Di(isopropylprenyl)borane: A new hydroboration reagent for the synthesis of alkyl and alkenyl boronic acids. Angew Chem Int Ed 2003;42(29):3399–3404.

xiii. Vedejs E, Clay JM. Hydroboration with pyridine borane at room temperature. J Am Chem Soc 2005;127(16):5766–5767. [PubMed: 15839656]

xiv. Miyaura N, Ohmura T, Yamamoto Y. Rhodium- or iridium-catalyzed *trans*-hydroboration of terminal alkynes, giving (*Z*)-1-alkenylboron compounds. J Am Chem Soc 2000;122(20):4990–4991.

xv. Miyaura N, Yamamoto Y, Fujikawa R, Umemoto T. Iridium-catalyzed hydroboration of alkenes with pinacolborane. Tetrahedron 2004;60(47):10695–10700.

xvi. Matteson DS. Boronic Esters in Stereodirected Synthesis. Tetrahedron 1989;45(7):1859–1885.

xvii. Hartwig JF, Lawrence JD, Takahashi M, Bae C. Regiospecific functionalization of methyl C H bonds of alkyl groups in reagents with heteroatom functionality. J Am Chem Soc 2004;126(47):15334–15335. [PubMed: 15563132]

xviii. Vedejs E, Chapman RW, Fields SC, Lin S, Schrimpf MR. Conversion of arylboronic acids into potassium aryltrifluoroborates: Convenient precursors of arylboron difluoride Lewis acids. J Org Chem 1995;60(10):3020–3027.

xix. Wright SW, Hageman DL, McClure LD. Fluoride-mediated boronic acid coupling reactions. J Org Chem 1994;59(20):6095–6097.

xx. Molander GA, Yun C-S. Cross-coupling reactions of primary alkylboronic acids with aryl triflates and aryl halides. Tetrahedron 2002;58(8):1465–1470.

xxi. Molander GA, Ito T. Cross-coupling reactions of potassium alkyltrifluoroborates with aryl and 1-alkenyl trifluoromethanesulfonates. Org Lett 2001;3(3):393–396. [PubMed: 11428022]

xxii. Molander GA, Yun C-S, Ribagorda M, Biolatto B. *B*-Alkyl Suzuki-Miyaura cross-coupling reactions with air-stable potassium alkyltrifluoroborates. J Org Chem 2003;68(14):5534–5539. [PubMed: 12839444]

xxiii. Molander GA, Ribagorda M. Expanding organoboron chemistry: Epoxidation of potassium organotrifluoroborates. J Am Chem Soc 2003;125(37):11148–11149. [PubMed: 16220907]

xxiv••. Dreher SD, Lim S-E, Sandrock DL, Molander GA. Suzuki-Miyaura cross-coupling reactions of primary alkyltrifluoroborates with aryl chlorides. J Org Chem 2009;74(10):3626–3631. Studies providing a general method for alkylation reactions using alkyltrifluoroborates. [PubMed: 19271726]

xxv. Molander GA, Ham J, Seapy DG. Palladium-catalyzed cross-coupling reaction of alkenyl bromides with potassium alkyltrifluoroborates. Tetrahedron 2007;63:768–775. [PubMed: 18196177]

xxvi. Molander GA, Figueroa R. *cis*-Dihydroxylation of unsaturated potassium alkyl-and aryltrifluoroborates. Org Lett 2006;8(1):75–78. [PubMed: 16381571]

xxvii. Molander GA, Yokoyama Y. One-pot synthesis of trisubstituted conjugated dienes via sequential Suzuki-Miyaura cross-coupling with alkenyl- and alkyltrifluoroborates. J Org Chem 2006;71(6):2493–2498. [PubMed: 16526802]

xxviii. Mu Y, Gibbs RA. Coupling of isoprenoid triflates with organoboron nucleophiles: Synthesis of all-*trans*-geranylgeraniol. Tetrahedron Lett 1995;36(32):5669–5672.

xxix. Saha D, Chattopadhyay K, Ranu BC. Aerobic ligand-free Suzuki coupling catalyzed by in situ-generated palladium nanoparticles in water. Tetrahedron Lett 2009;50(9):1003–1006.

xxx. Perkins JR, Carter RG. Synthesis of programmable tetra-*ortho*-substituted biaryl compounds using Diels-Alder cycloadditions/cycloreversions of disubstituted alkynyl stannanes. J Am Chem Soc 2008;130(11):3290–3291. [PubMed: 18298122]

xxxi. Hasník Z, Pohl R, Hocek M. Cross-coupling reactions of halopurines with aryl-and alkyltrifluoroborates: The scope and limitation in the synthesis of modified purines. Synthesis 2009;8:1309–1317.

xxxii. Miyaura N, Ishiyama T, Sasaki H, Ishikawa M, Satoh M, Suzuki A. Palladium-catalyzed inter- and intramolecular cross-coupling reactions of B-alkyl-9-borabicyclo[3.3.1]nonane derivatives with 1-halo-1-alkenes or haloarenes. Syntheses of functionalized alkenes, arenes, and cycloalkenes via a hydroboration-coupling sequence. J Am Chem Soc 1989;111(1):314–321.

xxxiii. Kataoka N, Shelby Q, Stambuli JP, Hartwig JF. Air stable, sterically hindered ferrocenyl dialkylphosphines for palladium-catalyzed C C, C N, and C O bond-forming cross-couplings. J Org Chem 2002;67(16):5553–5566. [PubMed: 12153253]

xxxiv. Fang G-H, Yan Z-J, Deng M-Z. Palladium-catalyzed cross-coupling of stereospecific potassium cyclopropyl trifluoroborates with aryl bromides. Org Lett 2004;6(3):357–360. [PubMed: 14748592]

xxxv. Charette AB, Mathieu S, Fournier J-F. Diastereoselective synthesis of 1,2,3-substituted potassium cyclopropyl trifluoroborates via an unusual zinc-boron exchange. Synlett 2005;(11): 1779–1782.

xxxvi. Molander GA, Gormisky PE. Cross-coupling of cyclopropyl- and cyclobutyltrifluoroborates with aryl and heteroaryl chlorides. J Org Chem 2008;73(19):7481–7485. [PubMed: 18759480]

xxxvii. van den Hoogenband A, Lange JHM, Terpstra JW, Koch M, Visser GM, Visser M, Korstanje TJ, Jastrzebski JTBH. Ruphos-mediated Suzuki cross-coupling of secondary alkyl trifluoroborates. Tetrahedron Lett 2008;49(26):4122–4124.

xxxviii••. Dreher SD, Dormer PG, Sandrock DL, Molander GA. Efficient cross-coupling of secondary alkyltrifluoroborates with aryl chlorides: Reaction discovery using parallel microscale experimentation. J Am Chem Soc 2008;130(29):9257–9259. Provides development toward identifying a solution to append secondary alkyl groups into molecules. [PubMed: 18582050]

xxxix. Molander GA, Vargas F. β-Aminoethyltrifluoroborates: Efficient aminoethylations via Suzuki-Miyaura cross-coupling. Org Lett 9(2):203–206. [PubMed: 17217265]

xl. Molander GA, Jean-Gérard L. Scope of the Suzuki-Miyaura aminoethylation reaction using organotrifluoroborates. J Org Chem 2007;72(22):8422–8426. [PubMed: 17915931]

xli. Jensen MS, Yang C, Hsiao Y, Rivera N, Wells KM, Chung JYL, Yasuda N, Hughes DL, Reider PJ. Synthesis of an anti-methicillin-resistant Staphylococcus aureus (MRSA) carbapenem via stannatrane-mediated Stille coupling. Org Lett 2000;2(8):1081–1084. [PubMed: 10804559]

xlii•. Molander GA, Ham J. Synthesis of functionalized organotrifluoroborates via halomethyltrifluoroborates. Org Lett 2006;8(10):2031–2034. Demonstrates the utility of the halomethyltrifluoroborate building block in the preparation of compounds that cannot be prepared readily from transmetalation or hydroboration approaches. [PubMed: 16671774]

xliii. Molander GA, Sandrock DL. Aminomethylations via cross-coupling of potassium organotrifluoroborates with aryl bromides. Org Lett 2007;9(8):1597–1600. [PubMed: 17367156]

xliv•. Molander GA, Gormisky PG, Sandrock DL. Scope of the aminomethylations via Suzuki-Miyaura cross-coupling of organotrifluoroborates. J Org Chem 2008;73(6):2052–2057. Provides a convenient aminomethylating platform for the inclusion of the subunit with a variety of electrophilic species. [PubMed: 18284257]

xlv•. Molander GA, Canturk B. Preparation of potassium alkoxymethyltrifluoroborates and their cross-coupling with aryl chlorides. Org Lett 2008;10(11):2135–2138. Describes a convenient procedure to implement alkoxymethyl linkages into molecules. [PubMed: 18439019]

xlvi. Falck JR, Patel PK, Bandyopadhyay A. Stereospecific cross-coupling of α-(thiocarbamoyl)organostannanes with alkenyl, aryl, and heteroaryl iodides. J Am Chem Soc 2007;129(4):790–793. [PubMed: 17243814]

xlvii. Mun S, Lee J-E, Yun J. Copper-catalyzed β-boration of α,β-unsaturated carbonyl compounds: Rate acceleration by alcohol additives. Org Lett 2006;8(21):4887–4889. [PubMed: 17020328]

xlviii. Whiting A. A convenient preparation of β-boronate carbonyl derivatives. Evidence for the intervention of boronate “ate”-complexes in enolate alkylations. Tetrahedron Lett 1991;32(11): 1503–1506.

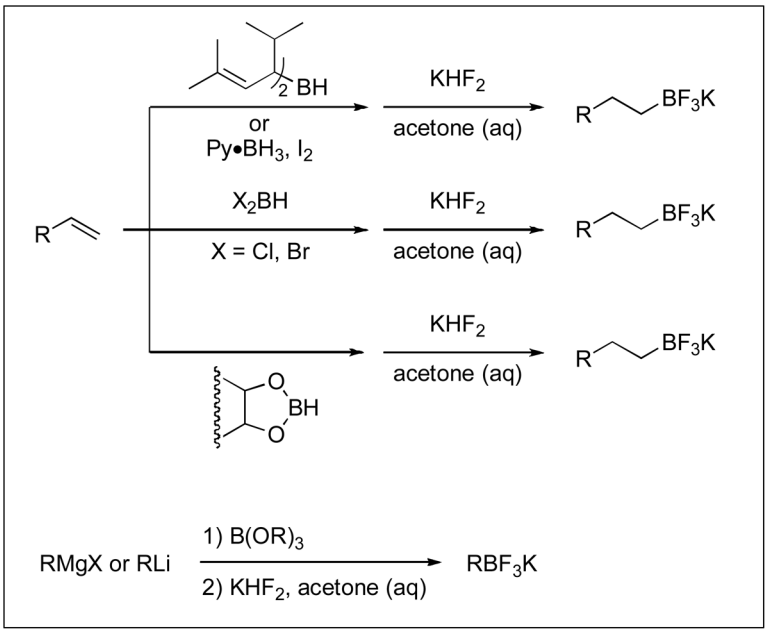
xlix. Molander GA, Petrillo DE. Suzuki-Miyaura cross-coupling of potassium trifluoroboratohomoenolates. Org Lett 2008;10(9):1795–1798. [PubMed: 18393522]

l. Molander GA, Jean-Gérard L. Scope of the Suzuki-Miyaura cross-coupling reaction of potassium trifluoroboratoketohomoenolates. J Org Chem 2009;74(3):1297–1303. [PubMed: 19133770]

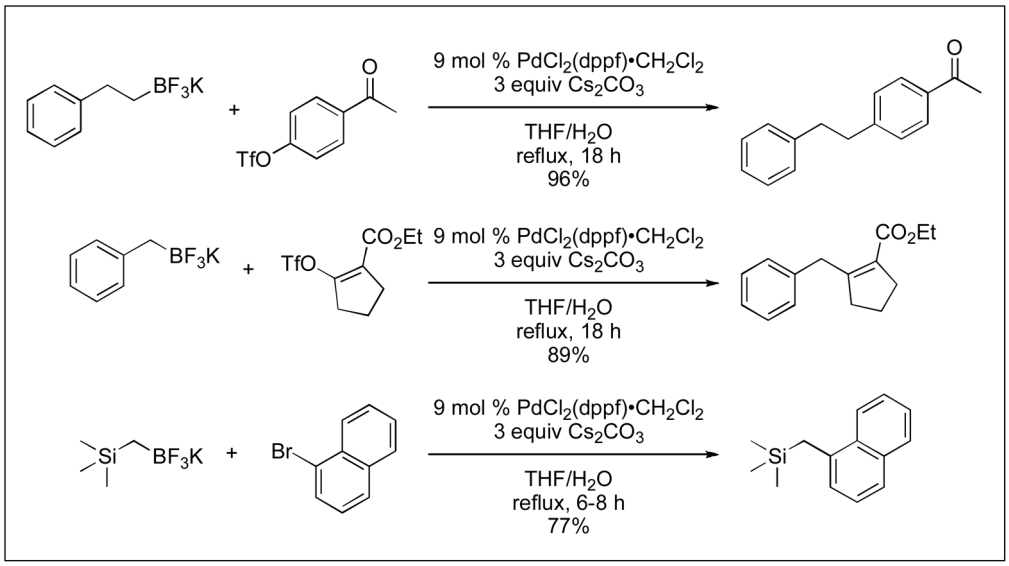
li•. Molander GA, Jean-Gérard L. Use of potassium β-trifluoroborato amides in Suzuki-Miyaura cross-coupling reactions. J Org Chem 2009;74(15):5446–5450. Demonstrates a procedure that could be applied to the preparation of valuable functionalized dipeptide compounds. [PubMed: 19572522]

lii. Sumida Y, Yorimitsu H, Oshima K. Nickel-catalyzed borylation of aryl cyclopropyl ketones with bis(pinacolato)diboron to synthesize 4-oxoalkylboronates. J Org Chem 2009;74(8):3196–3198. [PubMed: 19278207]

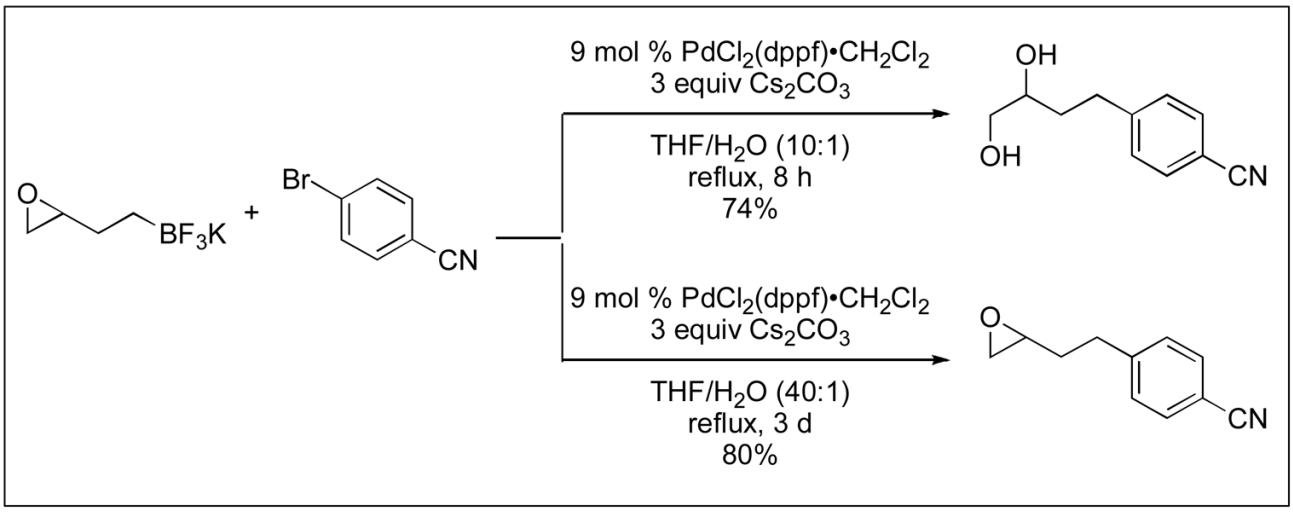
liii••. Ros A, Aggarwal VK. Complete stereoretention in the rhodium-catalyzed 1,2-addition of chiral secondary and tertiary alkyl potassium trifluoroborate salts to aldehydes. Angew Chem Int Ed 2009;48(34):6289–6292. Provides significant development in the area of stereoretention through a metal-catalyzed event.



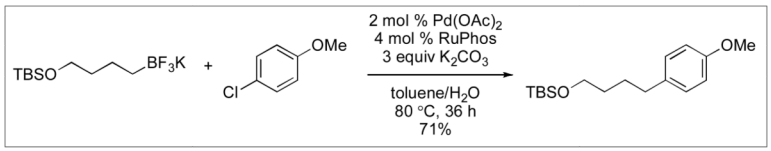
Scheme 1.
Synthetic Routes to Alkyltrifluoroborates



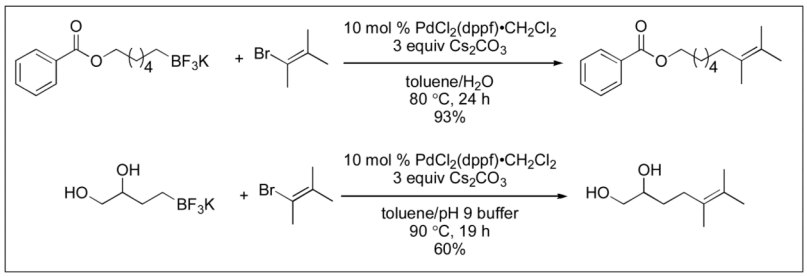
Scheme 2.
Cross-Coupling of Primary Alkyltrifluoroborates with Triflate and Bromide Electrophiles



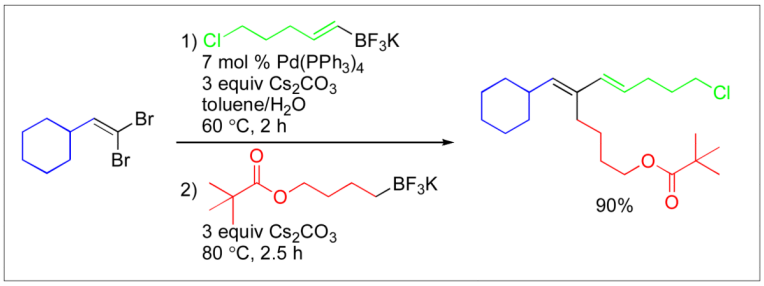
Scheme 3.
Cross-Coupling of Epoxytrifluoroborates



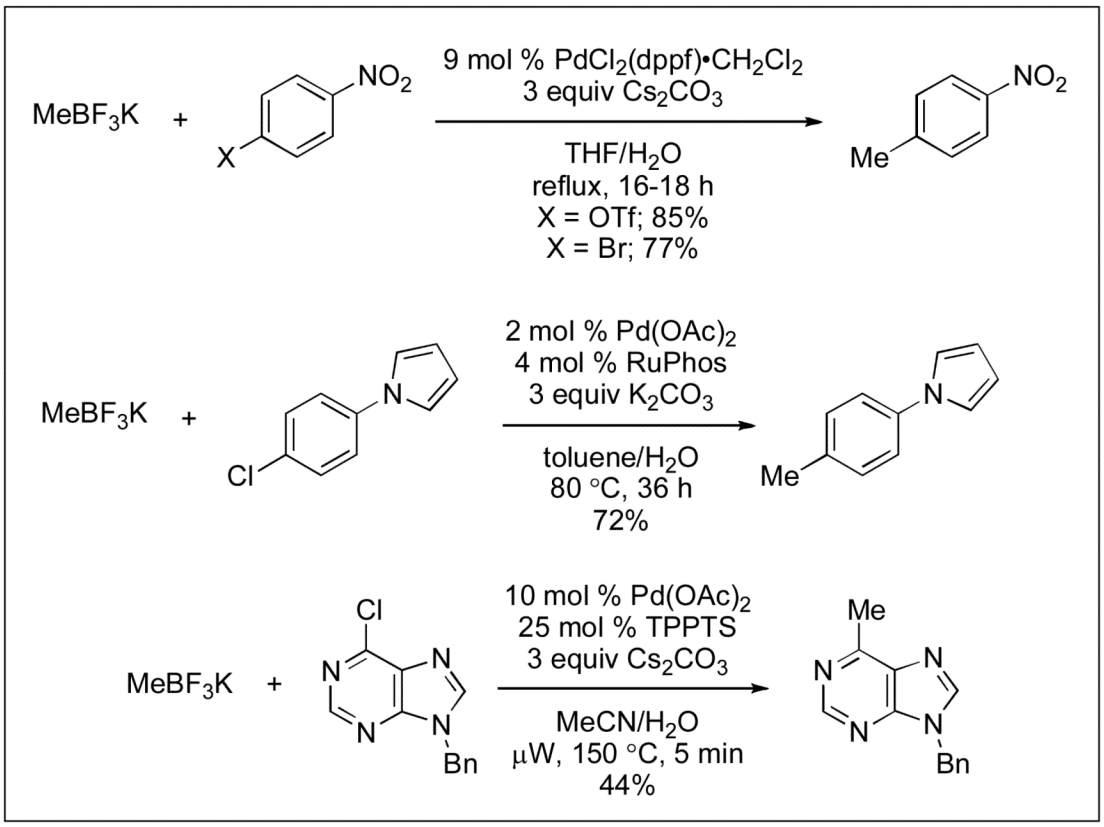
Scheme 4.
Cross-Coupling of Primary Alkyltrifluoroborates with Aryl Chlorides



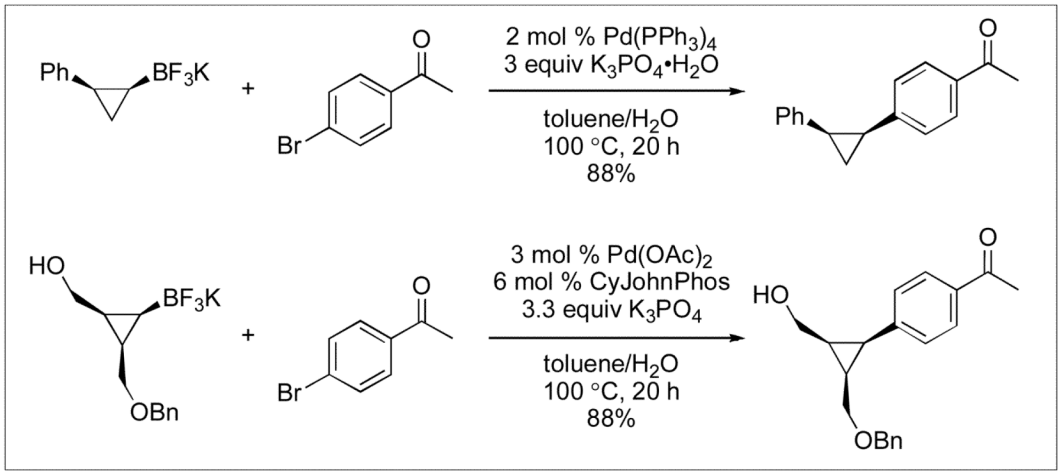
Scheme 5.
Cross-Coupling of Alkyltrifluoroborates with Alkenyl and Aryl Bromides



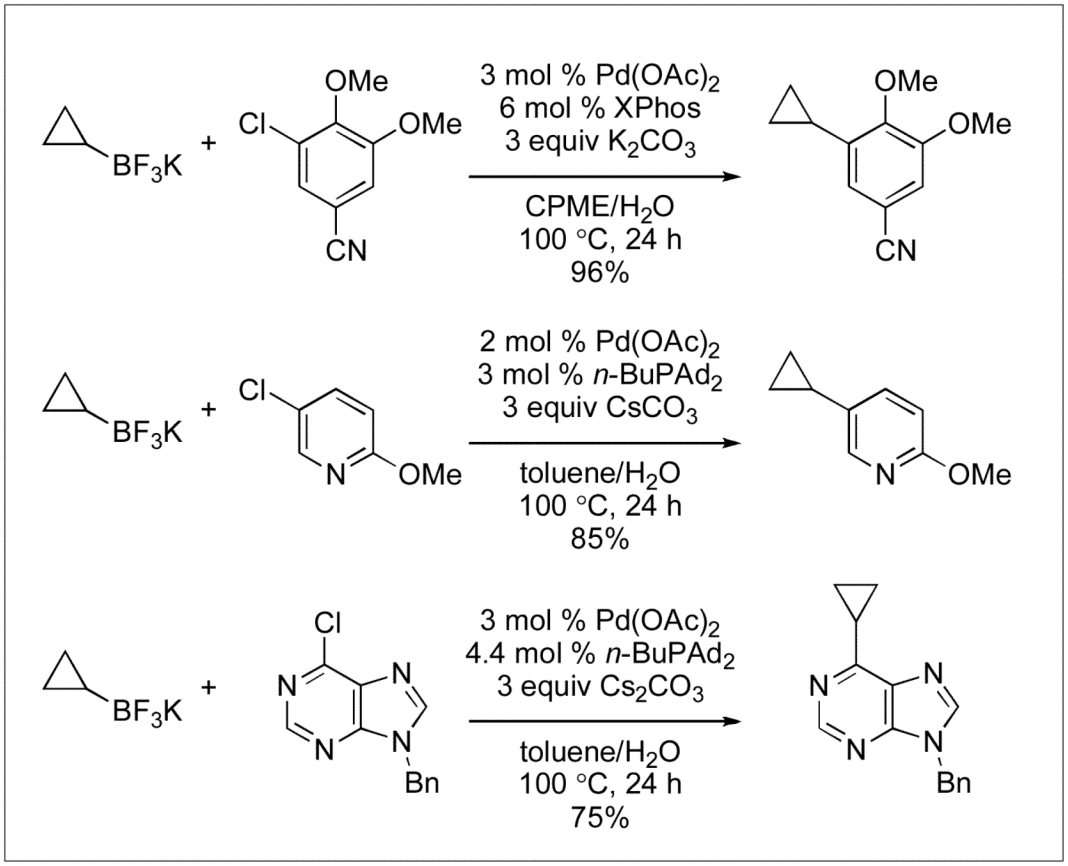
Scheme 6.
One-Pot Synthesis of Trisubstituted Conjugated Dienes



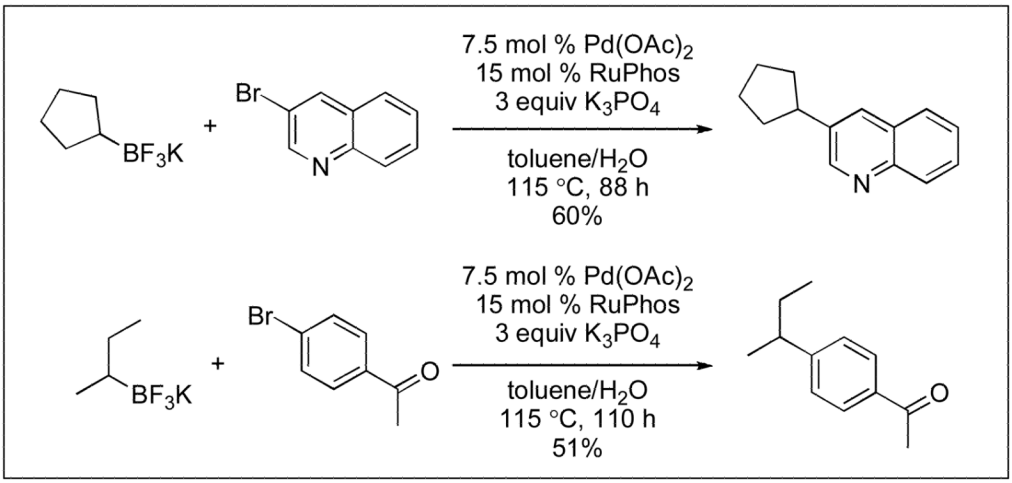
Scheme 7.
Methylation via Cross-Coupling of Potassium Methyltrifluoroborate



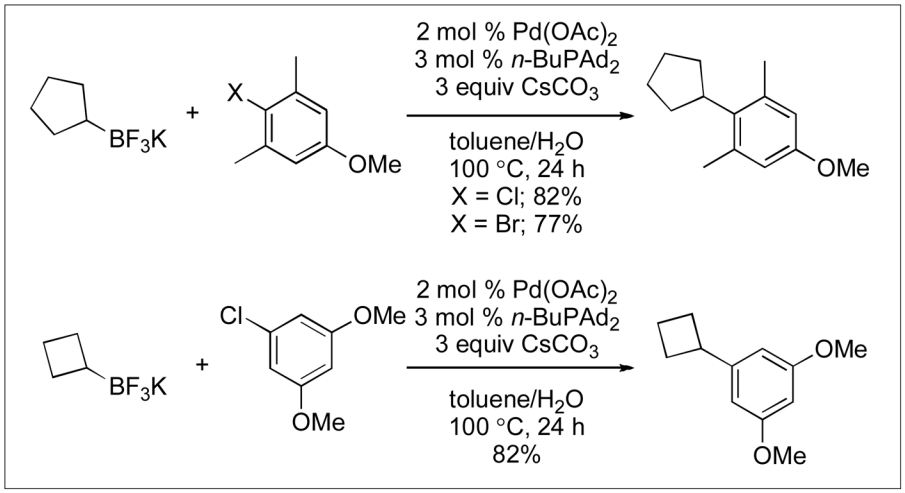
Scheme 8.
Cyclopropylation via Cross-Coupling with Retention of Configuration



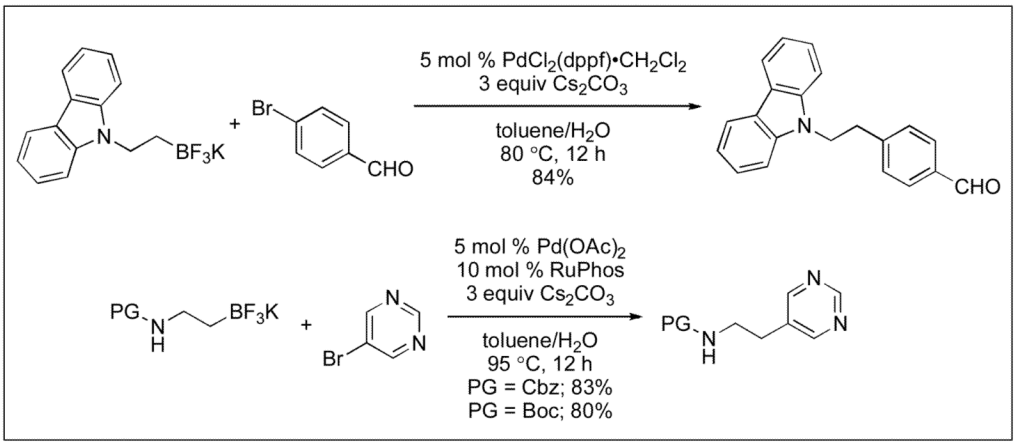
Scheme 9.
Cross-Coupling of Cyclopropyltrifluoroborate



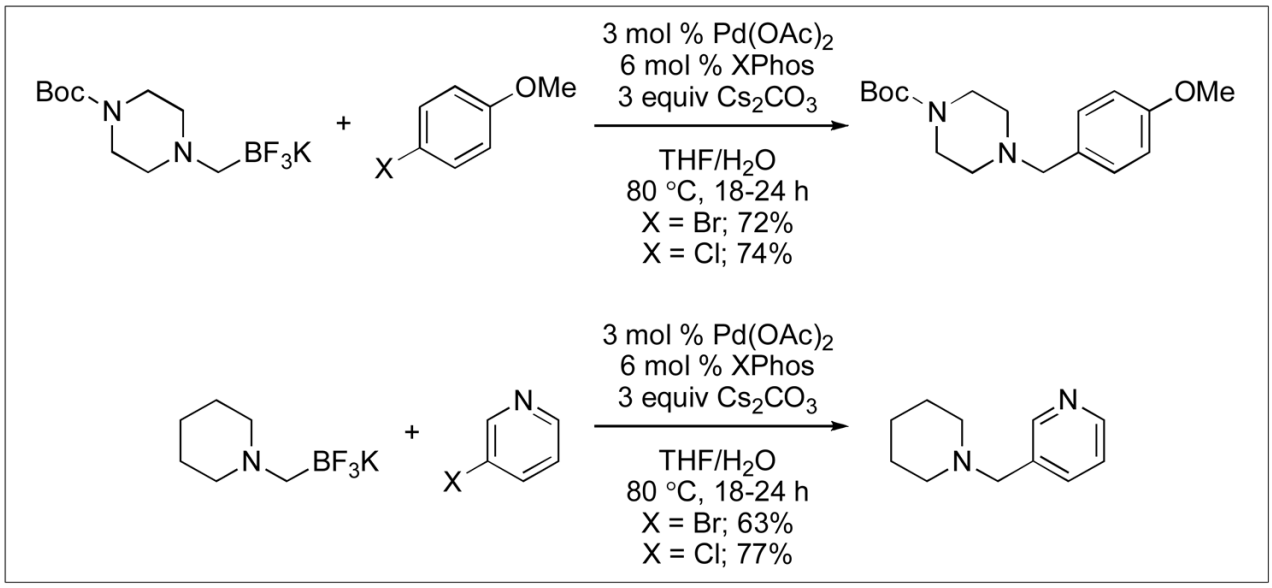
Scheme 10.
RuPhos-Mediated Cross-Coupling of Secondary Alkyltrifluoroborates



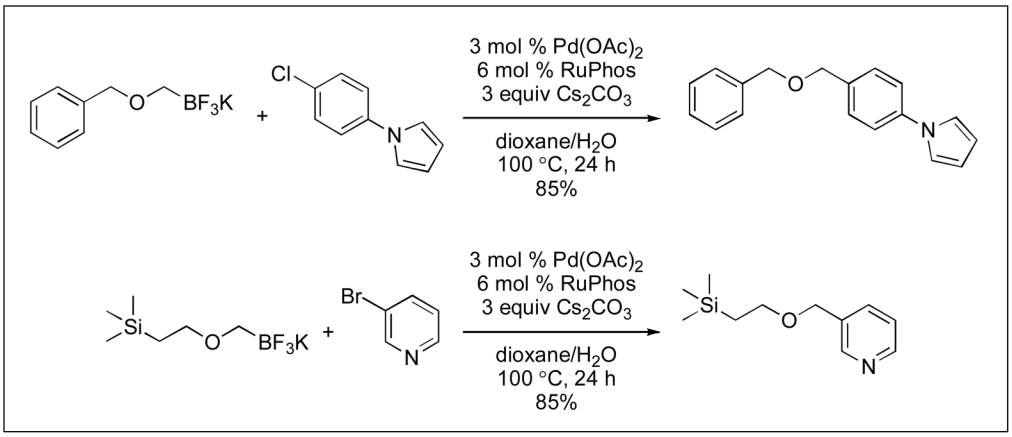
Scheme 11.
Cross-Coupling of Secondary Trifluoroborates with Aryl Chlorides



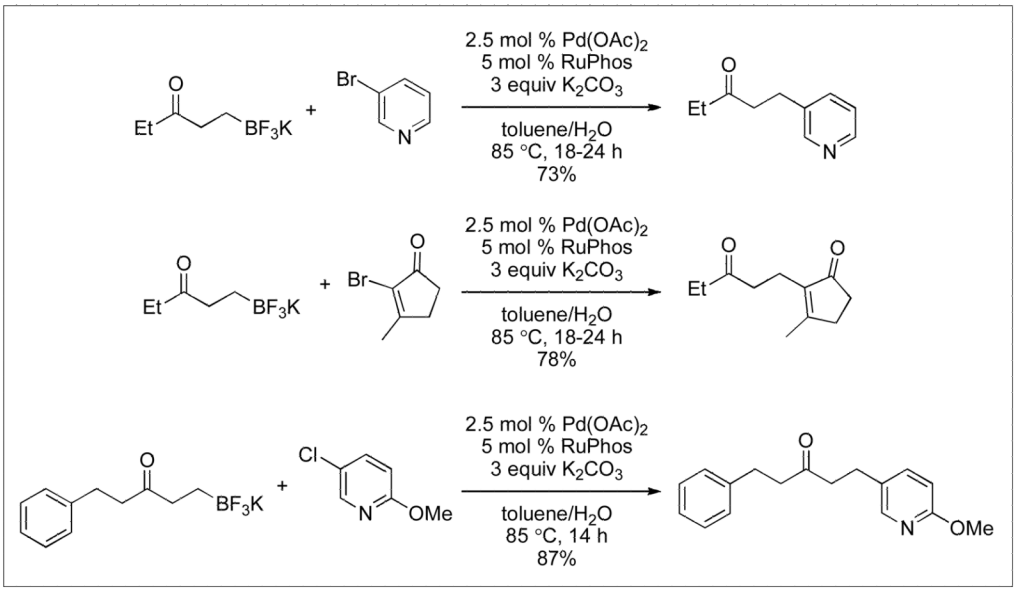
Scheme 12.
Cross-Coupling of Aminoethyltrifluoroborates with Aryl- and Heteroaryl Electrophiles



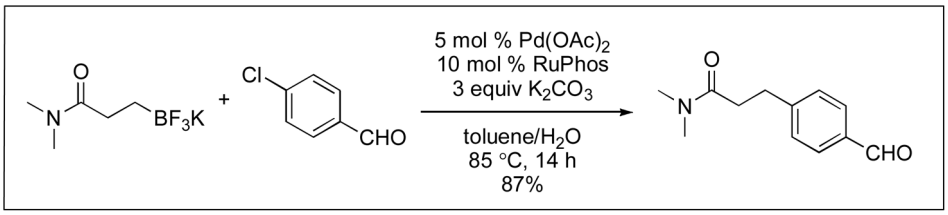
Scheme 13.
Aminomethylations via Cross-Coupling Reactions



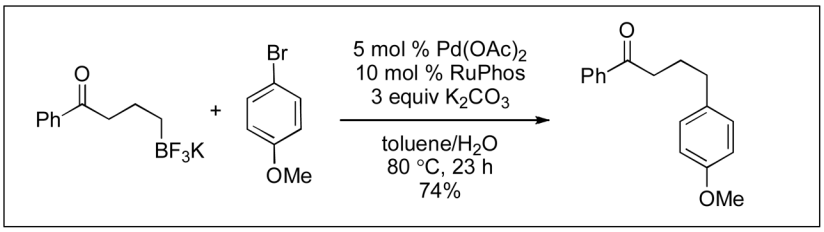
Scheme 14.
Cross-Coupling of Alkoxymethyltrifluoroborates with Aryl and Heteroaryl Electrophiles



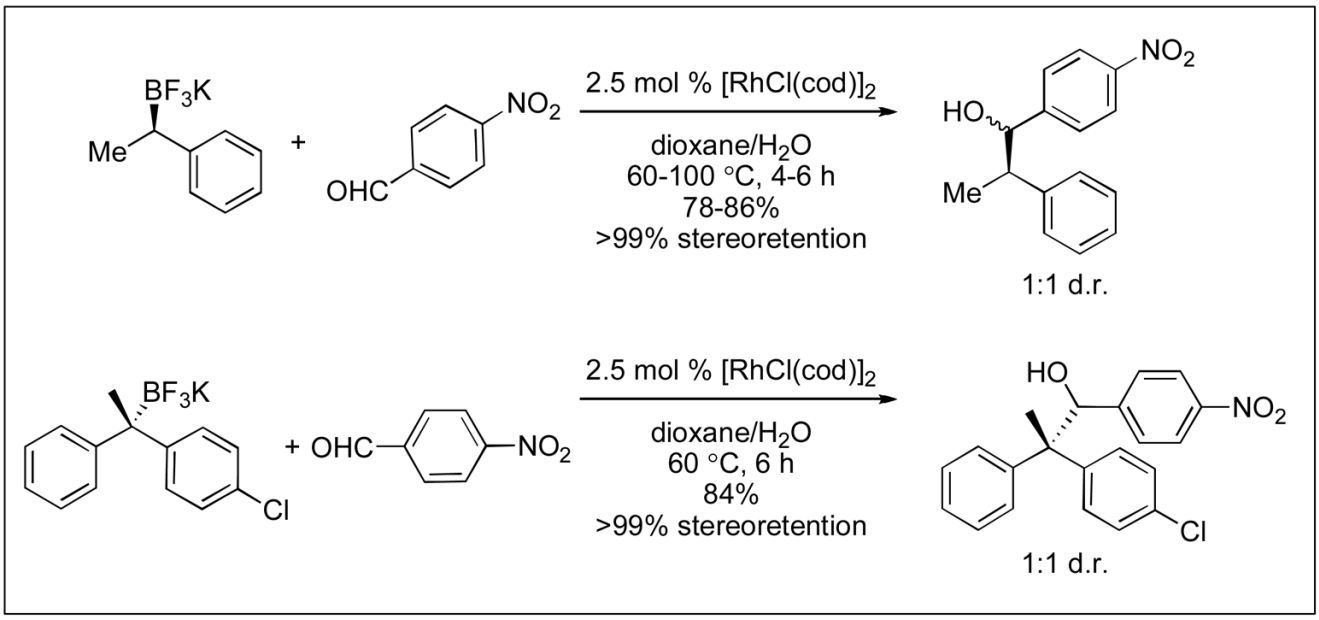
Scheme 15.
Cross-Coupling of Trifluoroboratoketohomoenolates with Various Electrophiles



Scheme 16.
Cross-Coupling of β-Trifluoroborato Amides with Aryl Chlorides



Scheme 17.
Cross-Coupling of 4-Oxoalkyltrilfuoroborate with 4-Bromoanisole



Scheme 18.
Rh-Catalyzed 1,2-Addition of Secondary- and Tertiary Alkyltrifluoroborates to Aldehydes