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1. Introduction

Organometallic reagents (R−M) are of increasing importance not only for organometallic chemists but also in organic chemistry and pharmaceutical synthesis and to access organic materials.[1] The usefulness of organomagnesium and organolithium compounds is taken for granted, but their high nucleophilicity and basicity sometimes preclude their use in many reactions with sensitive functional groups. Thus, for decades, chemists have looked for more selective organometallics, which tolerate a wider range of functionalities, such as Zn, Si, B, and Sn for carbon−carbon bond formation. The latter have been very useful in conjunction with transition-metal catalysts.[2] Among all the described organometallic reagents, organoboranes and organostannanes have emerged as reagents of choice in various transition-metal-catalyzed reactions. However, there are still drawbacks in the use of organostannanes because of their toxicity and their byproducts too.

On the other hand, since the discovery of the Suzuki−Miyaura reaction,[3] organoboranes have emerged as reagents of choice in transition-metal-catalyzed reactions, particularly in palladium-catalyzed reactions, allowing straightforward formation of carbon−carbon bonds. This reaction is now one of the most frequently used transition-metal-catalyzed reactions either in academic institutions or in industry. The increased number of applications of trivalent organoboranes, particularly boronic acids or esters, relies on the ready availability of these reagents via transmetalation or hydroboration reactions.[4] However, the most interesting features of organoboron reagents and their byproduct are their low toxicity, making these compounds environmentally sound compared to other organometallic reagents, particularly organostannanes.

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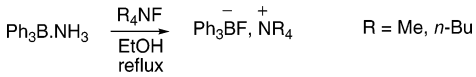
Sylvain Darses was born in Ussel, France, in 1969. He received his diploma degree in 1993 from the Ecole Nationale Supérieure de Chimie de Paris and his Ph.D. degree in 1997 from the University Pierre et Marie Curie in the group of Jean-Pierre Genet at ENSCP. After a 1 year postdoctoral stay with professor Anthony G. M. Barrett at Imperial College in London devoted to library synthesis on solid support, he was appointed Assistant Professor in 1999. In 2004 he obtained its Habilitation. His research interests involve the development of transition-metal-catalyzed reactions and their applications in organic synthesis, organoboron chemistry, and carbon–carbon bond formation via catalytic C–H bond activation.

Jean-Pierre Genet was born in Tulle, France, in 1942. He received his education in Paris (B.Sc.) and his Ph.D. degree from the University of Pierre and Marie Curie under the guidance of Professor Jacqueline Ficini in 1972. In 1975–1976 he did postdoctoral work with Professor B. M. Trost at the University of Wisconsin—Madison. He was appointed at the University Pierre and Marie Curie as Assistant Professor in 1966. He was promoted to Associate Professor with tenure in 1970, and then he became Full Professor at the same university in 1980. In 1988 he moved to the Ecole Nationale Supérieure de Chimie de Paris, where he holds the Chair of Organic Chemistry. He has received several awards including the French Academy of Science Award in 1988, a Japanese Society for the Promotion of Science Fellowship in 1998, Lady Davis Lecturer Technion, Haifa, Israel (1999), Innovation Award of University P. and M. Curie-ENSCP (2003), Novartis Lecturer (2003), and Le Bel Award of the French Chemical Society (2004). In 2007 he received the high recognition of "Chevalier de la Légion d'Honneur" (French Government). He has been a Visiting Professor at the University of Lausanne, Switzerland (1994), National University of Taiwan, Taiwan (1996), University of Lodz, Poland (1997), Technion, Haifa, Israel (1999), University of Potenza, Italy (2000), University of Las Algoas, Maceio, Brazil (2001), and University of Louvain, Belgium (2002). He has served as Chairman for OMCOS 10 in Versailles (1999). He was the President of the French Chemical Society of the Organic Division (1994–1998) and Vice-President of the French Chemical Society (1998–2000). His research interests cover organometallic chemistry in general with particular emphasis on homogeneous catalysis. Focal points are the design and application in organic synthesis of water-soluble organometallic complexes, synthesis of chiral phosphines, chemistry of organopotassium trifluroborates, asymmetric catalysis, and synthesis of biologically active compounds. The results of his research have been implemented in the pharmaceutical and perfumery industries.

Scheme 1. Preparation of Tetraalkylammonium Triphenylfluoroborates



However, many organoboranes are not stable under atmospheric conditions, particularly alkyl- and alkynylboranes. The lack of stability of organoboranes is due to the vacant orbital on boron, which can be attacked by oxygen[5] or water, resulting in decomposition of the reagent. One solution emerged in the 1960s with the discovery of potassium organotrifluoroborates, boron ate complex derivatives. In contrast to trivalent organoboranes, these reagents showed exceptional stabilities toward nucleophilic compounds as well as air and moisture. The vast majority can be stored indefinitely at room temperature without any precaution. However, this stability does not hamper their high reactivity in a large variety of reactions, particularly palladium-catalyzed cross-coupling reactions.

In 2003, in a short review we reported the principal application of potassium organotrifluoroborates in organic synthesis.[6] Since that date, numerous publications and patents on the topic have been reported in the literature. In recent papers, G. A. Molander[7] reviewed palladium-catalyzed cross-coupling reactions of potassium organotrifluoroborates, but examples reported were limited to journal articles and not patented applications. As this review was to be submitted, a review by H. A. Stefani and co-workers on potassium organotrifluoroborate chemistry was published,[8] but applications of organotrifluoroborates were still limited to journal articles and not patented applications. Moreover, the major part of the review was again dedicated to palladium-catalyzed cross-coupling reactions, particularly to tellurium substrates described by the authors.

The purpose of this article is to present an exhaustive review on these emerging reagents, potassium organotrifluoroborates, in organic synthesis. After reporting the various ways to prepare these boron ate complexes, their reactivity will be discussed, focusing on both academic and industrial applications. Outside the scope of this review are direct applications of organotrifluoroborate as counterions (mainly perfluorinated organotrifluoroborates of formula $C_nF_{2n+1}BF_3^-$) for electrolytes in lithium-ion cells[9,10] or for ionic liquids, which will not be described.[11,12]

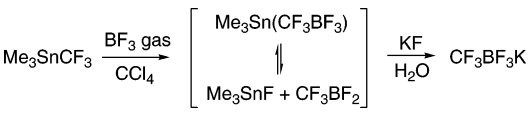
2. Preparation of Potassium Organotrifluoroborates

2.1. Historical Background—KHF_2 as Fluorinating Agent

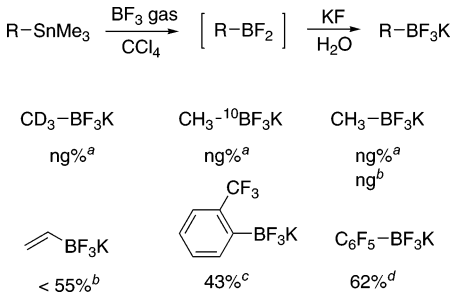
Organotrifluoroborate salts, or more generally compounds of formula $[R_nBF_{4-n}]^-$ ($n \leq 3$), were for a long time laboratory curiosities. Until very recently, few compounds of this type had been prepared. To our knowledge, the first report of the preparation of an organotrifluoroborate complex was described in 1940. The authors, Fowler and Krauss,[13] prepared tetramethylammonium and tetrabutylammonium triphenylfluoroborates by the reaction of a triphenylborane−ammonia complex with 1 equiv of tetraalkylammonium fluoride in unstated yield (Scheme 1).

Twenty years later, some publications appeared in the literature concerning the preparation of potassium organotrifluoroborates. Their preparation was motivated by forma-

Scheme 2. First Preparation of an Organotrifluoroborate Salt

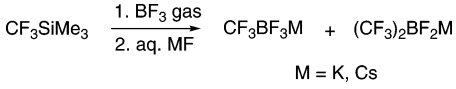


Scheme 3. Preparation of K[RBF$_3$] from Organostannanes



[a] From ref 19. ng: yield not given. [b] From ref 20, ng: yield not given. [c] From ref 21. [d] From ref 22.

Scheme 4. Preparation of Trifluoromethyltrifluoroborate Salts from Organosilanes



tion of stable perfluoroalkylated boron derivatives. Effectively, trivalent boron compounds bearing a fluorine atom in the α or β position are very unstable (migration of the fluorine from carbon to boron with formation of carbenes or alkenes), which is not the case of boron ate complexes. The first one, potassium trifluoromethyltrifluoroborate,[14] was prepared by Chambers et al. from trifluoromethyltrimethylstannane (Scheme 2).[15]

Treatment of trifluoromethyltrimethylstannane (prepared from hexamethylditin and trifluoroiodomethane)[16] with gaseous boron trifluoride afforded trimethyltin trifluoromethyltrifluoroborate in equilibrium with CF_3BF_2.[17,18] The former reacted with potassium fluoride in water to give potassium trifluoromethyltrifluoroborate in unstated yield. This compound was described as nonhygroscopic and highly thermally stable, not being decomposed below 300 °C. Other salts were prepared with different counterions but showed inferior stability.[15]

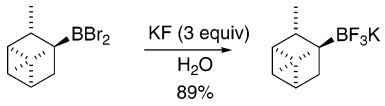
Under the same conditions, i.e., condensation of gaseous BF_3 followed by addition of potassium fluoride, other organostannanes were converted into potassium organotrifluoroborates (Scheme 3). The behavior of the other organostannanes was quite different from CF_3SnMe_3, and only organodifluoroboranes were intermediately isolated: no trimethyltin salts were formed.

Using this procedure K[CD_3BF_3],[19] K[$CH_3{}^{10}BF_3$],[19] and potassium methyl-,[19,20] vinyl-,[20] 2-trifluoromethylphenyl-,[21] and pentafluorophenyltrifluoroborate[22] were obtained. Starting with CF_3SiMe_3, $CF_3BF_3^-$ and $(CF_3)_2BF_2^-$ were isolated as their potassium or cesium salts (Scheme 4).[14,17,18]

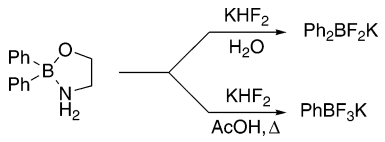
Treatment of dihalogenoorganoboranes with excess KF also allowed formation of trifluoroborate salts. Using this procedure, potassium (1*S*)-isopinocampheyltrifluoroborate was obtained in 89% yield from the corresponding dibromoborane derivative (Scheme 5).[23]

All those salts were described as highly stable and nonhygroscopic. However, these approaches to their preparation were not satisfactory since they implied the intermediate formation of the highly reactive and unstable organodihalogenoboranes. Moreover, transmetalation procedures from organostannanes were not desirable because of the high toxicity of organotin reagents.

Scheme 5. Preparation of K[RBF$_3$] from Dihalogenoboranes



Scheme 6. First Use of KHF_2 as Fluorinating Agent of Boron Derivatives



The development of potassium organotrifluoroborate chemistry in organic synthesis started with the improvement in their preparation procedures. It was only in 1995 that E. Vedejs described a highly efficient method using potassium hydrogen difluoride[24] (KHF_2) as fluorinating agent for trivalent boron reagents.[25] However, use of KHF_2 for the fluorination of boron compounds had been described earlier. In 1967, Thierig and Umland[26] reported the preparation of potassium diphenyldifluoroborate on treatment of the ethanolamine complex of Ph_2BOH with aqueous KHF_2 in unstated yield (Scheme 6). The same reaction conducted in refluxing acetic acid allowed formation of potassium phenyltrifluoroborate.

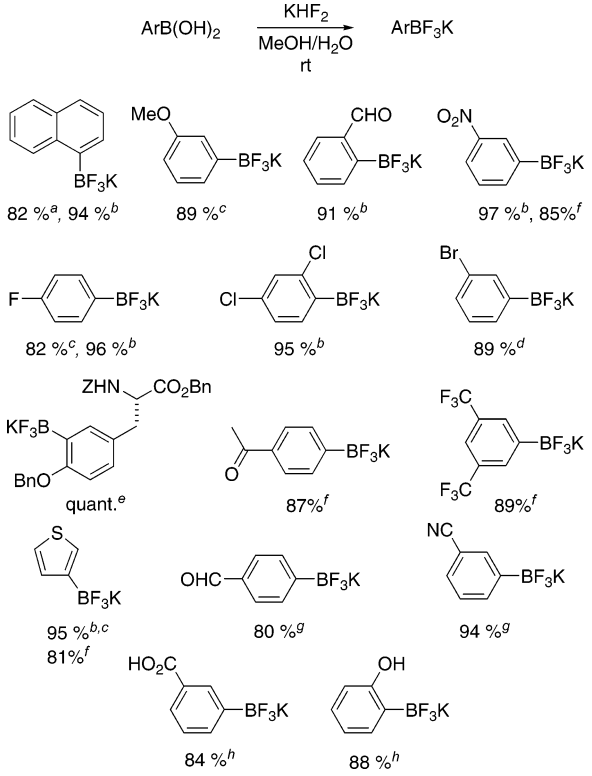
2.2. Potassium Organotrifluoroborates from Isolated Boronic Acids

In 1995, Vedejs et al.[25] reported that arylboronic acids were efficiently converted to potassium aryltrifluoroborates on treatment with KHF_2 in aqueous methanol (Scheme 7). Interestingly, KF was not able to displace the hydroxyl ligands of trivalent boronic acids. Using KHF_2, boroxines $(RBO)_3$ or boronic acid dimers $(RBO)_2$, which are usually present in isolated organoboronic acids, reacted equally well. Indeed, treatment of commercially available or readily accessible organoboronic acids or esters with aqueous KHF_2 furnishes quantitative yields of potassium organotrifluoroborate,[25,27−31] and will not be commented on further in this review. For example, potassium tyrosine-3-trifluoroborate was prepared in quantitative yield from the corresponding pinacolboronate derivative by treatment by KHF_2 (Scheme 7).[225] It is also important to note that many organotrifluoroborates are now commercially available.

2.3. Potassium Organotrifluoroborates via Transmetalation Reactions

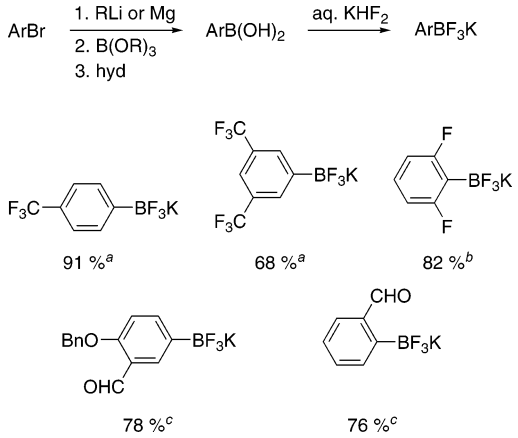
Preparation of potassium organotrifluoroborates does not require the use of purified organoboronic acids. Thus, generation of potassium organotrifluoroborates is straightforward using classical methods of organoboron synthesis.[4] For example, lithium−halogen exchange or magnesium insertion followed by boronation and hydrolysis furnished crude boronic acid, which, on treatment with KHF_2, gave aryltrifluoroborates in high yields (Scheme 8).[25,28,29] Using this procedure, electron-deficient potassium (fluoroaryl)-trifluoroborates were readily obtained from the corresponding aryl bromides.[32]

Scheme 7. Preparation of Potassium Aryltrifluoroborates from Boronic Acids



[a] From ref 27. [b] From ref 28. [c] From ref 30. [d] From ref 29. [e] Prepared from the corresponding pinacol ester: ref 225. [f] From ref 31. [g] From ref 170. [h] From ref 101.

Scheme 8. In Situ Formation of Potassium Aryltrifluoroborates

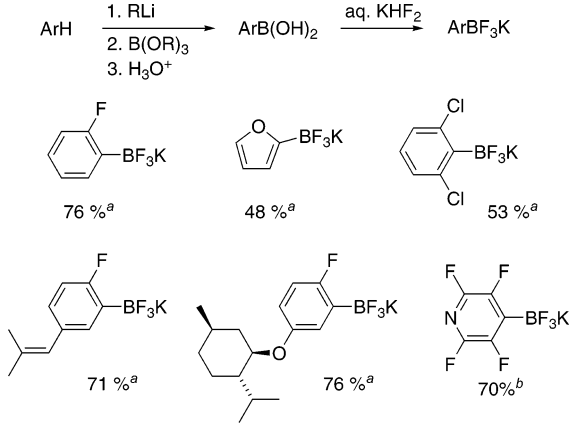


[a] From ref 25. [b] From ref 32. [c] From ref 29; the aldehyde moiety was protected with ethanediol and removed upon hydrolysis.

In the same way, highly efficient ortholithiation−boronation procedures[33] may be used for formation of potassium aryltrifluoroborates.[25] Using this approach, functionalized aryltrifluoroborates were obtained in fair yields (Scheme 9). More particularly, potassium 2,3,5,6-tetrafluoropyrid-4-yltrifluoroborate was prepared in 70% yield after recrystallization from water.[34]

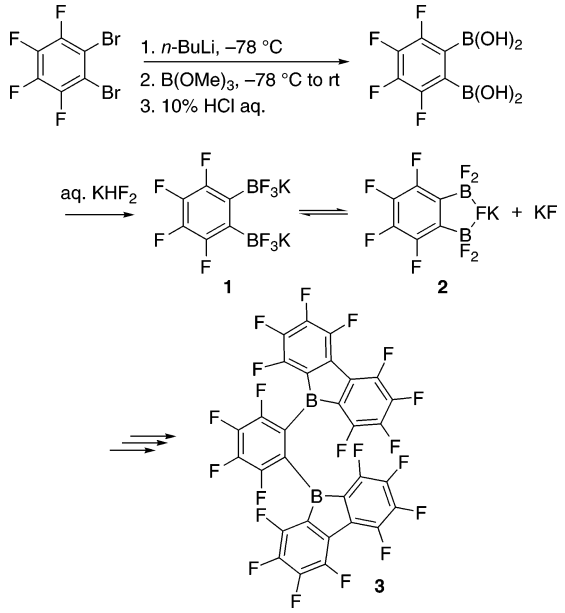
Synthesis of the bifunctional perfluoroarylborane **3**, used as cocatalyst in olefin polymerization, involved the intermediate formation of the bis-trifluoroborate salts **1** (Scheme 10).[35,36] The latter was obtained by dilithiation of 1,2-dibromotetrafluorobenzene using *n*-BuLi followed by boronation with $B(OMe)_3$. After hydrolytic workup, treatment of

Scheme 9. Orthometallation Procedures for the Preparation of Potassium Aryltrifluoroborates



[a] From ref 25. [b] From ref 34.

Scheme 10. Preparation of Bis-Trifluoroborate Salt 1

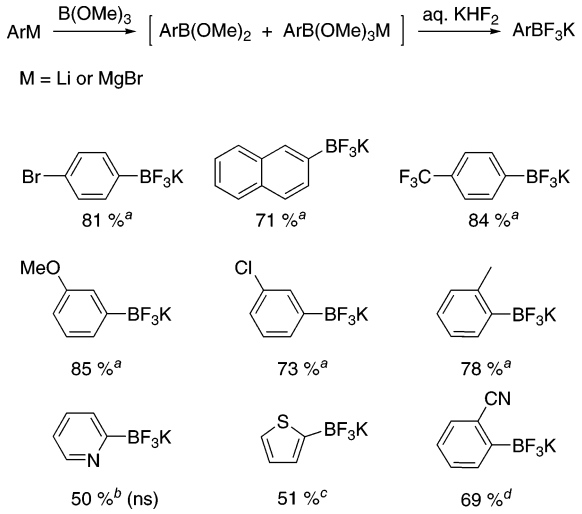


the bis-boronic acid with excess KHF_2 gave a solid comprised of a mixture of $[K^+]_2[C_6F_4\text{-}1,2\text{-}(BF_3)_2]^{2-}$ (**1**) and monoanionic $[K^+]\{C_6F_4\text{-}1,2\text{-}[(BF_2)_2(\mu\text{-}F)]\}^-$ (**2**) in 65% overall yield. Pure samples of **1** were obtained by crystallization from concentrated solutions of CH_3CN, while crystals of the μ-fluoride **2** were obtained from CH_3CN/H_2O solutions.

One-pot procedures have been developed, avoiding isolation of trivalent organoboron intermediates, which can be unstable. A combination of traditional procedures for the preparation of trivalent organoboron species followed by final treatment with KHF_2 allowed the preparation of a huge range of highly functionalized potassium organotrifluoroborates. Indeed, Darses and Genet have shown that KHF_2 is able to displace the alkoxo ligands of in situ generated mixtures of aryltrimethoxyborate and aryldimethoxyborane right after the boronation step (Scheme 11).[28,29]

Isolation and purification of potassium aryltrifluoroborates are straightforward as they often precipitate upon formation and can be simply filtered.[25] In our hands we found that higher yields were obtained by evaporation of the solvent after addition of KHF_2 and extraction (or continuous extraction) of the resulting solid with the appropriate solvent,

Scheme 11. One-Pot Formation of K[ArBF$_3$]



[a] From refs 28 and 29. [b] From ref 31. ns: not stable. [c] From ref 170. [d] From ref 109.

generally acetone.[28] This procedure proved to be quite general and was efficiently used with success by many other groups.[31,37,170] It is important to note that in all cases yields are comparable or generally higher than those reported for the synthesis of the corresponding boronic acid derivatives.

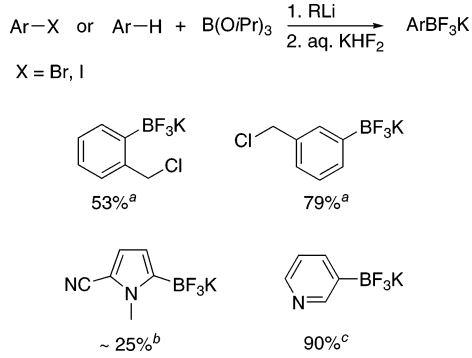
Moreover, purification by reprecipitation or recrystallization from acetonitrile or acetone/ether allowed the isolation of analytically pure compounds: in acetonitrile or acetone, inorganic salts such as KF, KHF_2, or KBF_4 are insoluble, allowing their separation from the product. Nevertheless, traces of KHF_2 have been observed as a contaminant using acetonitrile as the recrystallization solvent.[38]

Lithium−halogen exchange or magnesium insertion procedures to access organoboranes have some limitations in the case of substrates bearing incompatible functional groups or when the organolithium or organomagnesium intermediates are intrinsically unstable, as are many aromatic heterocycles. In such cases, organoboronic esters can be prepared from aryl halides or triflates via a palladium-catalyzed cross-coupling reaction with tetraalkoxydiboron or dialkoxyhydroborane.[39] Alternatively, organoboranes can be obtained via a protocol of lithium−halogen exchange and "in situ quench" with a tri(alkoxy)borane, particularly tri(isopropoxy)borane.[40] Using this "in situ quench", potassium 2- and 3-chloromethylphenyltrifluoroborates[92] or 3-pyridyltrifluoroborate[31] were obtained in moderate to good yields from the corresponding aryl bromides or iodides (Scheme 12). Potassium (5-cyano-1-methyl-1*H*-pyrrol-2-yl)trifluoroborate has been prepared from deprotonation of 1-methylpyrrole-2-carbonitrile with lithium diisopropylamide (LDA) in the presence of triisopropylborate.[41] This reagent underwent clean palladium-catalyzed cross-coupling reaction with some aryl bromides.

On treatment with potassium hydrogen difluoride, trivalent arylboranes bearing a proximal Brønsted base substituent did not afford the expected potassium salts but the HF salts. For example, reaction of 2-(*N*,*N*-diisopropylaminomethyl)phenylboronic acid with KHF_2 resulted in the exclusive formation of the HF salt **4** (Scheme 13).[42] In other instances, the presence of the amino substituent prevented formation of the trifluoroborate complex, the difluoroborane being obtained.[43]

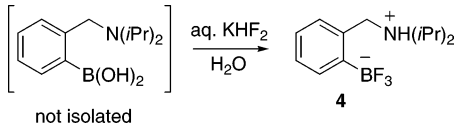
As in the case of arylboron compounds, it is also possible to form potassium alken-1-yltrifluoroborates from lithium

Scheme 12. K[ArBF$_3$] Prepared with "in Situ Quench" with Tri(alkoxy)boranes

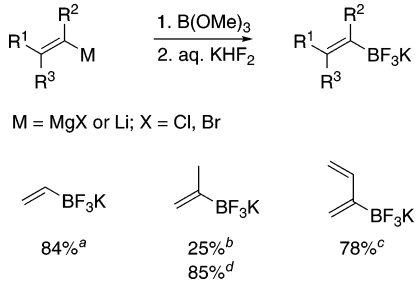


[a] From ref 92. [b] From ref 41. [c] From ref 31.

Scheme 13



Scheme 14. Potassium Alkenyltrifluoroborates from Organometallic Reagents

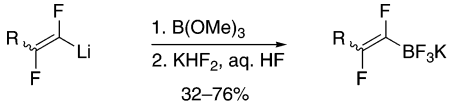


[a] From refs 28 and 44. [b] From refs 45 and 152. [c] From ref 47. [d] From ref 46.

or magnesium organometallic derivatives. A highly efficient preparation of potassium vinyltrifluoroborate was described by Darses and Genet et al.[28,44] This reagent was prepared on a large scale from vinylmagnesium chloride by treatment with trimethoxyborane followed by in situ addition of KHF_2 (Scheme 14). Molander et al. have shown that potassium isopropenyltrifluoroborate could be obtained from 2-bromopropene in a one-pot procedure involving lithium−bromine exchange, boronation with trimethylborate, followed by treatment by KHF_2.[45,152] These reagents have emerged as highly useful vinylating agents, particularly in palladium-catalyzed cross-coupling reactions (see section 5.1). Potassium 1,3-dienyl-2-trifluoroborate was prepared in good yield from the corresponding chloride via formation of the corresponding Grignard (Scheme 14).[46] This boron-substituted dienyl is a white, air-stable solid and showed no propensity to dimerize. The corresponding tetra-*n*-butyl ammonium (TBA) salt was also prepared. These reagents proved to be reactive in Diels−Alder reactions.[46]

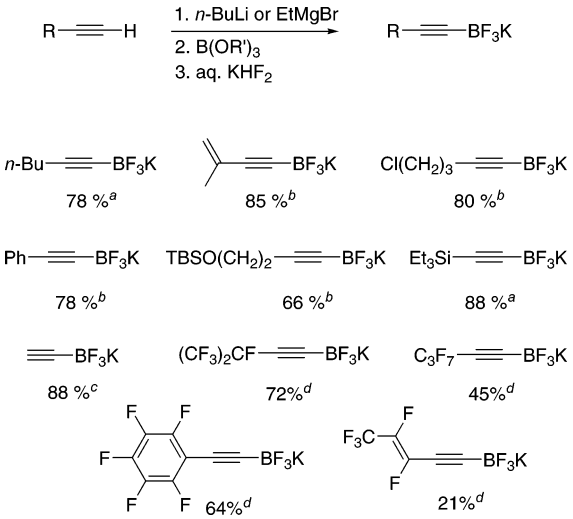
Of course, potassium alkenyltrifluoroborates can be prepared from commercial boronic acids or esters.[28,74] Purification and isolation of alkenyltrifluoroborate salts are conducted in the same fashion as their aromatic congeners. Once again, alkenyltrifluoroborate salts proved to be highly stable for several years at room temperature, which is not the case for the corresponding trivalent alkenylboron compounds.[4] For example, vinylboronic acid is highly unstable and cannot be isolated;[48] its ester, 4,4,6-trimethyl-2-vinyl-1,3,2-dioxabori-

Scheme 15. Preparation of Potassium Polyfluoroalken-1-yltrifluoroborates



R = F, Cl, *cis*-H, *trans*-C_4F_9, *cis*-C_2F_5,*cis*-C_6F_{13}, *trans*-C_4H_9, *trans*-C_6H_5, *trans*-Et_3Si, *cis*- and *trans*-CF_3, OC_3F_7

Scheme 16. Preparation of Potassium Alkyn-1-yltrifluoroborates



[a] From ref 28. [b] From ref 54. [c] Prepared from ethynylmagnesium bromide; ref 55. [d] From ref 56.

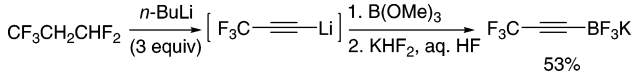
nane, is only slightly stable at −20 °C under nitrogen, whereas potassium vinyltrifluoroborate did not show any decomposition after several years.

Several polyfluoroalken-1-yltrifluoroborates were synthesized for the first time from the corresponding organolithium reagents (Scheme 15).[49−52,65] As in the case of perfluoroalkyltrifluoroborates (vide infra), final treatment with aqueous HF was generally required for the complete conversion to trifluoroborate salts. All of these salts are crystalline compounds that show exceptional stability toward air and water, the only exception being $K[C_3F_7OCF{=}CFBF_3]$, which slowly decomposed when stored in glass.[52] Aqueous treatment with KHF_2 even in the presence of HF does not remove the silane moiety.[50] Other salts of formula $K[(CF_2{=}CF)_3BF_{4-n}]$ (n = 2, 3) were prepared using this strategy.[53]

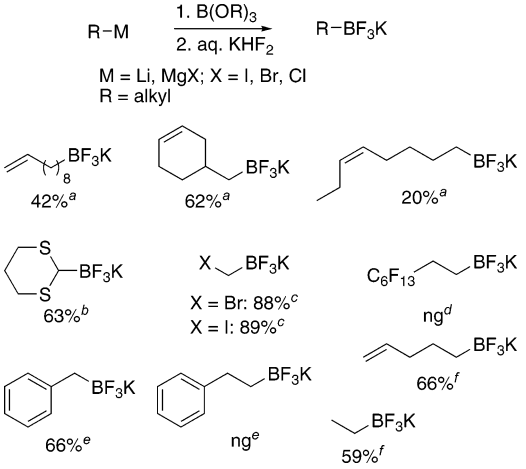
Efficient access to potassium alkyn-1-yltrifluoroborates from readily available alk-1-ynes was described by Darses and Genet et al. (Scheme 16).[28] These salts were easily obtained by deprotonation of alk-1-ynes, boronation, and in situ treatment with KHF_2. This three-step one-pot procedure provided an efficient and versatile method for the preparation of various potassium alkyn-1-yltrifluorobrate.[28,54] Interestingly, the triethylsilyl group attached to carbon and the TBS (*tert*-butyldimethylsilyl) attached to oxygen were not removed despite the use of a fluoride source.

Reaction of ethynylmagnesium bromide with trimethoxyborane followed by the usual one-pot fluorination procedure provided potassium ethynyltrifluoroborate in 88% yield (Scheme 16).[55] This procedure for the generation of alkynyltrifluoroborate derivatives proved to be general and was applied efficiently for the generation of [(perfluoroorgano)-ethynyl]trifluoroborates.[56] In the case of these electron-deficient trifluoroborates and similarly to the preparation of

Scheme 17. Preparation of Potassium (trifluoroprop-1-ynyl)trifluoroborate



Scheme 18. Potassium Alkyltrifluoroborates from Transmetalation Reactions



[a] From ref 79. [b] From ref 59. [c] From ref 60. [d] From ref 34. ng: yield not given. [e] From ref 37a. ng: yield not given. [f] From ref 172.

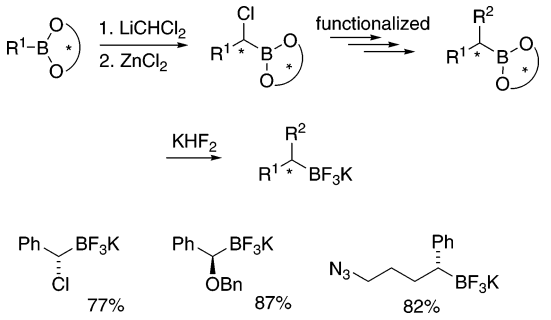
perfluoroalkenylborates, KHF_2 alone was not able to completely fluorinate the boron atom, and use of a solution of this reagent in aqueous HF was necessary. Other [(perfluoroorgano)ethynyl]trifluoroborates were prepared using other methods without direct metalation of the corresponding alkynes as more convenient paths to the organometallic reagent $R_fC{\equiv}CLi$ (R_f perfluoroalkyl) were available without the primary preparation of (perfluoroorgano)ethynes.[56] For example, trifluoromethylethynyllithium was generated from the reaction of 1,1,1,3,3-pentafluoropropane with 3 equiv of *n*-BuLi (Scheme 17) and then treated in a one-pot sequence by $B(OMe)_3$ followed by KHF_2 in aqueous HF, allowing formation of potassium (trifluoroprop-1-ynyl)trifluoroborate in 53% yield.

These compounds represent the first stable (toward oxygen and moisture) organoboron derivatives containing a $C_{sp}-B$ bond, although the chemistry of alkynylborates has been well documented.[57] Contrary to other alkynylboranes, which are not stable and are readily hydrolyzed in the presence of water or alcohol, these salts are once again indefinitely stable at room temperature.

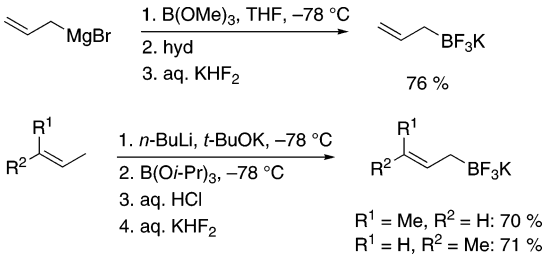
In the same way, potassium alkyltrifluoroborates were prepared by Molander et al. using conventional procedures[58] from organolithium or organomagnesium compounds, the last step of the preparation being in situ treatment with potassium hydrogen difluoride (Scheme 18).[37,79]

Formation of potassium trifluoro[1,3-dithiano]borate has been accomplished using this one-pot procedure.[59] Deprotonation of 1,3-dithiane with *n*-BuLi, boronation using trimethylborate, followed by treatment with aqueous KHF_2 afforded the expected compound as a white crystalline solid in 63% yield (Scheme 18). Potassium iodo- and bromomethyltrifluoroborates were prepared in high yields from dihalogenomethane by lithium−halogen exchange, boronation, and in situ treatment with aqueous KHF_2.[60] These compounds proved to be highly suitable starting materials for the elaboration of functionalized alkyltrifluoroborates by direct substitution reactions. Potassium iodomethyltrifluo-

Scheme 19. Synthesis of Optically Active Potassium Alkyltrifluoroborates



Scheme 20. Preparation of Potassium Allyltrifluoroborates



roborate could also be prepared from the bromo derivative by direct substitution using NaI as nucleophile.[60] Formation of potassium 1*H*,1*H*,2*H*,2*H*-perfluorooctyltrifluorborates was also reported and patented for the production of nonstick coatings.[34]

Optically active potassium trifluoro(alkyl)borates have been prepared by Matteson et al.[38] using their α-haloboronic ester chemistry[61] from pinanediol or 1,2-dicyclohexylethanediol (DICHED) boronic esters by treatment with KHF_2 (Scheme 19). This procedure allowed a quantitative and easy recovery of the chiral diol, which is not so easy using conventional cleavage of boronic esters.[38]

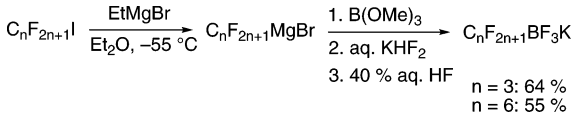
As we can see from those selected examples, use of KHF_2 tolerated various functional groups such as Cl, Br, N_3, etc. It is important to note that in their work, the authors observed that formation of alkyltrifluoroborates from hindered alkylboronic esters (DICHED or pinanediaol) is generally reversible and reaches equilibrium within 0.5−2 h at 22 °C, which explains the lower yields obtained from pinanediol esters.[38]

The preparation of potassium allyltrifluoroborates was achieved by Batey and co-workers in an analogous manner to that used for the synthesis of other organotrifluoroborate salts (Scheme 20).[62,63] The requisite allylboranes were formed by addition of allylmagnesium bromide or crotyl potassium to trialkylborates. Subsequent conversion to trifluoroborate salts was achieved by in situ treatment with aqueous KHF_2.[62,63] Once again, these salts are crystalline air- and water-stable solids that can be stored for extended periods of time at room temperature.

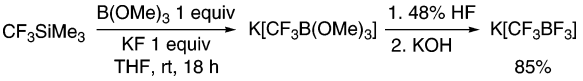
As already mentioned, one of the first potassium organotrifluoroborates was a perfluoroalkylated one: $K[CF_3BF_3]$,[15,16] which showed exceptional stability compared to other trivalent boron derivatives. With the exception of this compound, other perfluoroorganotrifluoroborates were not described until very recently. Synthesis of such compounds was studied by Frohn et al. in several papers (Scheme 21).[49,64,65] They first elaborated a convenient route to potassium perfluoroalkyltrifluoroborates starting from the easily available perfluoroalkyl iodides.[64]

Formation of the unstable perfluoroalkylmagnesium reagent was carried out at −55 °C by magnesium−halogen exchange using ethylmagnesium bromide. Treatment with trimethoxyborane followed by KHF_2 gave incomplete formation of trifluoroborate salts but mixtures of fluorinated borates of formula $K[R_fBF_n(OMe)_{3-n}]$. The remaining methoxy ligand was replaced by fluorine on treatment with aqueous HF.[64,65] The authors assumed[65] that replacement of the methoxy substituent by fluorine, a highly electron-withdrawing group, increases the Lewis acidity of the borane and prevents elimination of the MeO^- anion. However, protonation of the oxygen atom by acidification with aqueous HF facilitates elimination of the methoxy group.

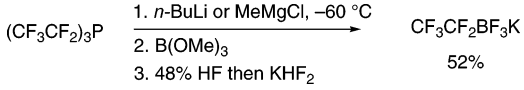
Scheme 21. Formation of Potassium Perfluoroalkyltrifluoroborates



Scheme 22. Potassium Trifluoromethyltrifluoroborate from Ruppert's Reagent



Scheme 23. Perfluoroorganoborate from Perfluoroorganophosphane



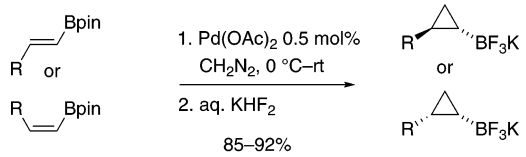
An improved preparation of potassium trifluoromethyltrifluoroborate[14,15] was described by Molander and coworkers starting from Ruppert's reagent.[66] Indeed, treatment of (trifluoromethyl)trimethylsilane with 1 equiv of potassium fluoride in the presence of 1 equiv of $B(OMe)_3$ produces (trifluoromethyl)trimethoxyborate, which upon treatment with 48% aqueous HF generated the trifluoroborate salt in a 85% overall yield after treatment with KOH (Scheme 22). In this reaction use of only 1 equiv KF is essential as excess KF upon treatment with HF generates KHF_2, deterring complete fluorination.[66] A similar approach was published concomitantly for generation of $Li[C_2F_5BF_3]$, $K[C_2F_5BF_3]$, and $K[CF_3BF_3]$ from the corresponding organosilanes.[67]

An alternative approach for the preparation of potassium perfluoroalkyltrifluoroborates was patented starting from tris(perfluoroalkyl)phosphanes. For example, treatment of tris(pentafluoroethyl)phosphane with 1 equiv of *n*-BuLi or MeMgCl, boronation with $B(OMe)_3$, followed by treatment with 48% aqueous HF and KHF_2 afforded a 52% yield of potassium pentafluoroethyltrifluoroborate (Scheme 23).[68] The corresponding lithium salt was also prepared on treatment of the potassium salt with $LiBF_4$.[68] An alternative procedure involves utilization of tris(perfluoroalkyl)phosphane oxide as starting material.[69]

Stereospecific preparation of potassium cyclopropyltrifluoroborates was achieved by cyclopropanation of the corresponding boronate pinacol esters. Indeed, palladium-catalyzed reaction of alkenylborane esters of pinacol with CH_2N_2, according to the Vaultier protocol,[70] followed by in situ treatment with KHF_2 afforded stereo-defined potassium cyclopropyltrifluoroborates in good to excellent yields (Scheme 24).[71] As expected, *trans*- and *cis*-cyclopropyltrifluoroborates were generated from (*E*)- and (*Z*)-alkenylboronic esters, respectively.[70]

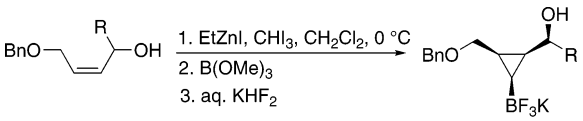
Preparation of highly functionalized 1,2,3-substituted potassium cyclopropyltrifluoroborates has been accomplished

Scheme 24. Preparation of Potassium Cyclopropyltrifluoroborates from Alkenylboranes



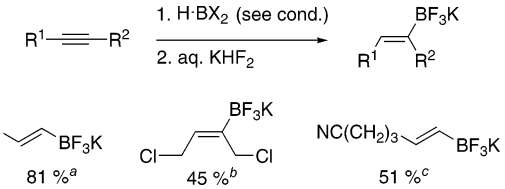
R = Ph, CH_2Ph, CH_2OCH_2Ph, C_5H_{11}

Scheme 25. Preparation of Potassium Cyclopropyltrifluoroborates from Allylic Alcohols



R = H, Me, Et, *i*-Pr

Scheme 26. Formation of Potassium Alkenyltrifluoroborates via Hydroboration



[a] From ref 74: cathecholborane (1 equiv). [b] From ref 28: (i) $HB(Ipc)_2$, rt; (ii) aq. formaldehyde, rt. [c] From ref 172: (i) $Br_2BH{\cdot}SMe_2$ (1 equiv), CH_2Cl_2, rt; (ii) H_2O, 0 °C.

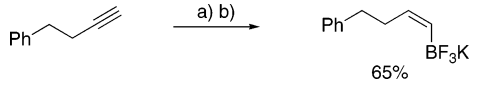
from allylic alcohols.[72] Reaction of allylic alcohols with *gem*-dizinc carbenoid, generated in situ from reaction of EtZnI with iodoform (CHI_3), furnishes an intermediate 1,2,3-substituted cyclopropylzinc species (Scheme 25). Boronation of the latter followed by in situ fluoration with aqueous KHF_2 afforded good yields of potassium cyclopropyltrifluoroborates. This reaction proved to be quite general for *Z*-alkenes, but lower yields were obtained with *E*-alkenes. It is important to note that the corresponding trivalent boronic acid species could not be cleanly isolated from the crude reaction mixture. By contrast, all the borate salts were indefinitely stable in air and able to undergo palladium-catalyzed Suzuki−Miyaura cross-coupling reactions.[72]

2.4. Potassium Organotrifluoroborates via Hydroboration

Generation of potassium organotrifluoroborates using KHF_2 as a reagent is very general and allowed formation of various potassium alken-1-yltrifluoroborates. Several procedures that are common to other organoboron preparation have been used to access these compounds.[4] One of the most important consists of the hydroboration of the corresponding alk-1-yne, catalyzed or not by transition metals.[73]

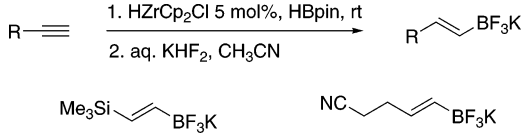
Using this procedure, potassium (*E*)-(2-phenylethenyl)-trifluoroborate and other alkenyl derivatives were obtained in high yield using a one-pot procedure,[74] avoiding isolation of the boronic acid (Scheme 26). Moreover, catechol is readily removed during the purification procedure because of the insolubility of $K[RBF_3]$ in nonpolar solvents. In another example, hydroboration of commercial 1,4-dichlorobut-2-yne with diisopinocampheylborane, followed by oxidation with acetaldehyde[75] and in situ treatment with aqueous KHF_2, afforded the corresponding alkenyltrifluoroborate in fair yield.[28] From these examples, KHF_2 proved to be sufficiently reactive to cleave the boron−oxygen bonds in boronic esters.

Scheme 27. $K[RBF_3]$ from Rhodium-Catalyzed *trans*-Hydroboration



[a] $[Rh(cod)Cl]_2$ 1.5 mol %, P(*i*-Pr)$_3$ 6 mol %, HBpin, Et_3N (1 equiv), rt. [b] aq. KHF_2, CH_3CN, rt.

Scheme 28. Zirconocene-Catalyzed Hydroboration of Alkynes



(*Z*)-Alken-1-yltrifluoroborates were also easily accessible using rhodium-catalyzed *trans*-hydroboration according to the procedure described by Miyaura.[73d] Indeed, potassium (*Z*)-phenyl-1-but-1-enyltrifluoroborates was prepared from the corresponding alkyne in a 65% yield using a two-step one-pot procedure (Scheme 27).[171]

Regioselective hydroboration of alkynes with pinacolborane (HBpin) catalyzed by $HZrCp_2Cl$[76] afforded the expected alkenyltrifluoroborates after treatment with KHF_2 (Scheme 28).[171]

In the same way, potassium alkyltrifluoroborates were prepared using conventional hydroboration procedures for formation of trivalent organoboron compounds, the last step of the preparation being in situ treatment with potassium hydrogen difluoride (Scheme 27).[37]

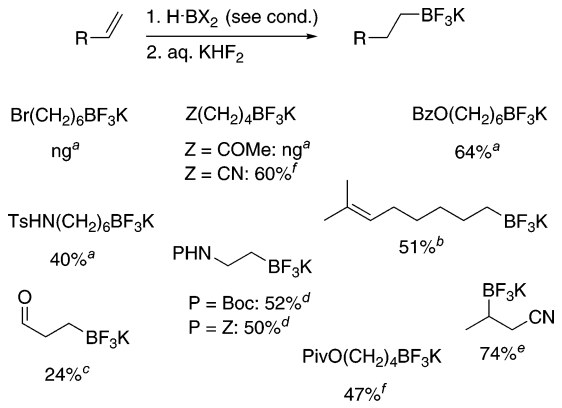
These literature protocols for formation of organoboron derivatives included hydroboration of alkenes either by dibromoborane−dimethylsulfide complex[78,172] or by catecholborane or pinacolborane in the presence of rhodium catalysts.[73] Potassium alkyltrifluoroborates bearing an alkene functional group were prepared in good yields[79] using di(isopropylprenyl)borane as hydroborating agent.[80] An alternative to these hydroboration reagents was described by Vedejs et al. using the pyridine borane $Py{\cdot}BH_2I$, which allowed high-yielding formation of potassium alkyltrifluoroborates from alkenes.[81]

2.5. Potassium Organotrifluoroborates via C−H Bond Activation

Direct borylation of unactivated carbon−hydrogen bonds offers a very attractive alternative to the boronation of organometallic reagents. Indeed, borylation of aromatic[82] or aliphatic[83] compounds via C−H bond activation has been achieved using rhodium or iridium complexes as catalyst and pinacolborane or bis(pinacolato)diboron as boronating agent. This reaction allowed straightforward access to potassium aryltrifluoroborates (Scheme 30).[84] Indeed, borylation of arenes catalyzed by the $[Ir(COD)(OMe)]_2$/dtbpy (dtbpy = di-*tert*-butylbipyridine) in the presence of bis(pinacolato)-diborane (B_2pin_2, 0.7 equiv) in THF at 80 °C followed by in situ treatment with aqueous KHF_2 afforded high yields of aryltrifluoroborates. More particularly, reaction of benzofuran and benzothiophene selectively formed the 2-substituted heteroaryl trifluoroborates in good to excellent yields.

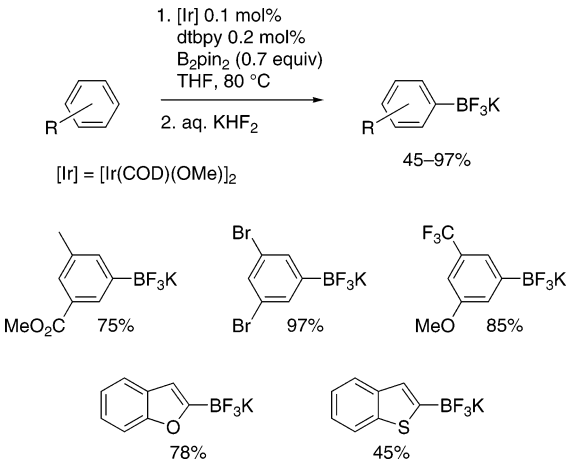
Hartwig et al. have also shown that aliphatic alkanes containing nitrogen, oxygen, or fluorine undergo rhodium-

Scheme 29. Preparation of Potassium Alkyltrifluoroborates

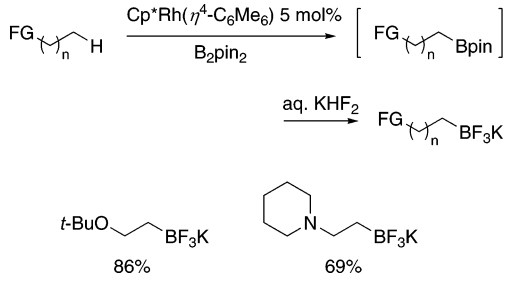


[a] From ref 37: (i) Rh(PPh3)Cl 1 mol %, pinacolborane (1 equiv), CH_2Cl_2, rt; ng, yield not given. [b] From ref 79: (i) di(isopropylprenyl)borane, rt; (ii) aq. formaldehyde, rt. [c] From ref 89: cond. ibid. [d] From ref 184: cond. ibid. [e] From refs 11a, 12b, and 77: (i) BCl_3, $HSiEt_3$, −78 °C; (ii) H_2O, 0 °C. [f] From ref 172: (i) $Br_2BH{\cdot}SMe_2$ (1 equiv), CH_2Cl_2, rt; (ii) H_2O, 0 °C.

Scheme 30. Potassium Aryltrifluoroborates from Arenes



Scheme 31. Potassium Alkyltrifluoroborates from Alkanes

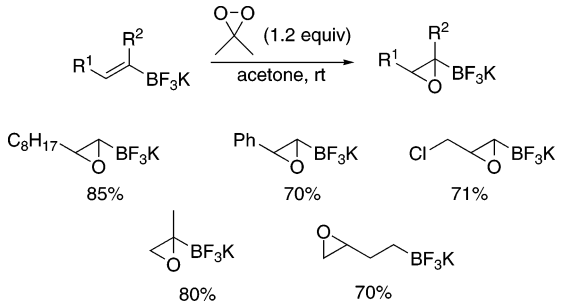


catalyzed C−H activation and borylation at the least hindered and least electron-rich methyl group, allowing direct access to aliphatic organoboranes (Scheme 31).[85] For example, reaction of bis(pinacolato)diborane (B_2pin_2) with an excess of functionalized aliphatic reagents, without solvent and in the presence of Cp*Rh(η^4-C_6Me_6), gave alkylboronate esters, which upon treatment with aqueous KHF_2 afforded alkyltrifluoroborates in high yields.

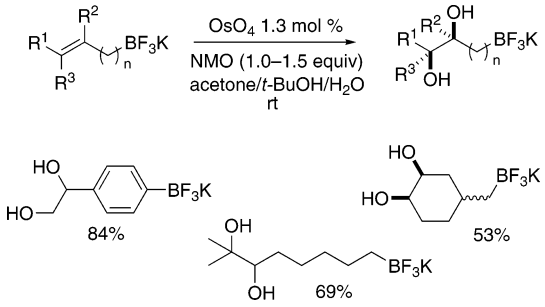
2.6. Functionalization of Potassium Organotrifluoroborates

The synthesis of functionalized organoboron compounds is often challenging because of the incompatibility of the methods employed (transmetalation or hydroboration) to introduce the organoboron moiety. Moreover, because of the Lewis acidity and sensitivity of the trivalent organoborane functionality to base, nucleophile, or oxidant, installation of further functionality and reactions with existing organoboranes, while attractive, are rarely feasible. On the other hand, boron ate complexes, like potassium organotrifluoroborates, are less sensitive to basic or nucleophilic conditions, allowing one to envision further reactions with these boron species. This goal was recently achieved in the literature.

Scheme 32. Epoxidation of Potassium Organotrifluoroborates



Scheme 33. Dihydroxylation of Potassium Organotrifluoroborates

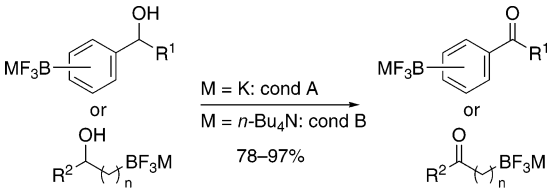


In 2003, G. A. Molander and co-workers reported an efficient procedure for the epoxidation of potassium organotrifluoroborates bearing alkene functionality using oxirane (Scheme 32).[86] For example, reaction of potassium *trans*-dec-1-en-1-yltrifluoroborate with 1.2 equiv of dimethyldioxirane in acetone at room temperature led to the clean generation of the expected epoxytrifluoroborate in 85% yield. All the epoxytrifluoroborates were found to be highly stable, which appears astonishing given their structural analogy with oxiranyl anions, which are known to be unstable. This stability is certainly due to the covalent nature of the C−B bond, preventing an α-elimination process. Potassium trifluoroborates were also resistant to *m*-CPBA oxidation as thioethers could be cleanly oxidized to sulfones.[86]

In the same way, *cis*-dihydroxylation of potassium alkyl- and aryltrifluoroborates in the presence of catalytic OsO_4 and *N*-methylmorpholine *N*-oxide furnished the expected diols in moderate to good yields (Scheme 33).[79] Reactions were best conducted in a mixture of acetone/*t*-BuOH/H_2O 18:1:1, from which the trifluoroborates precipitated, allowing easy and clean isolation. The dihydroxylation of potassium 7-methyl-6-octenyltrifluoroborate, containing a trisubstituted olefin, was achieved in 69% yield. The reaction conducted with potassium allyltrifluoroborate proceeded smoothly, but isolation of the trifluoroborate required the cation-exchange protocol described by Batey et al. (vide infra),[106] and the corresponding tetra-*n*-butylammonium (TBA) salt was isolated in a 70% yield.

Oxidation of primary or secondary alcohol functionality, present in organotrifluoroborates, to aldehydes or ketones

Scheme 34. Oxidation of Organotrifluoroborates

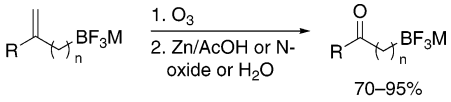


R^1 and R^2 = H or alkyl

cond A: IBX 3 equiv, acetone, reflux.

cond B: TPAP 1–2 mol%, NMO 1.1 equiv, MS 4Å, CH_2Cl_2.

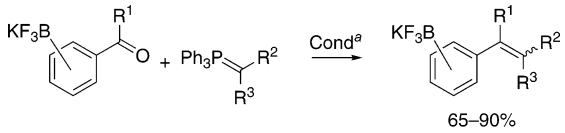
Scheme 35. Ozonolysis of Unsaturated Organotrifluoroborates



R = H or Me

M = K or n-Bu_4N

Scheme 36. Wittig Reaction with Potassium Organotrifluoroborates



R^1 = H or CH_3

R^3 = H and R^2 = CH_2CH_2CN, $CH_2N(CH_3)_2$, CN, $COCH_3$, CO_2Me, CON(OMe)Me

R^3 = R^2 = CH_3

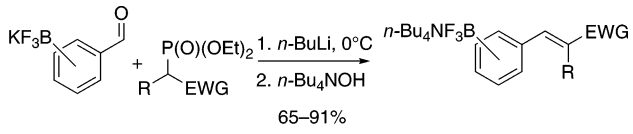
[a] For unstabilized ylides: THF/DMF/hexanes, −78 °C to rt, 3 h. For stabilized ylides: PhH/DMF, 90 °C, 2−2.5 h.

was readily achieved using common oxidation protocols.[87] As many oxidation procedures are conducted in chlorinated solvent, in which potassium salts are insoluble, the TBA organotrifluoroborates were first used. On such substrates TPAP/NMO, Swern and Dess−Martin periodinane oxidations were all successful. The former, because of its simplicity in execution, was selected for the study. Indeed, in the presence of 1−2 mol % TPAP (tetrapropylammonium perruthenate) and 1.1 equiv of NMO (*N*-methylmorpholine-*N*-oxide), TBA fluoroborates were readily oxidized in high yields, and no cleavage of the carbon−boron bond was observed. On the other hand, the potassium salts could be oxidized using 3 equiv of IBX (2-iodoxybenzoic acid) in refluxing acetone.[87] Simple filtration of the IBX byproducts gave a filtrate from which the oxidized products were isolated.

Ozonolysis of unsaturated organotrifluoroborates was also described, providing a new route to oxo-substituted organotrifluoroborates (Scheme 35).[88] Several conditions were evaluated to cleave the primary ozonides, generated upon ozonolysis, according to the substitution pattern of the substrates. Reactions were more efficiently conducted on the TBA (tetra-*n*-butylammonium) salts.

Potassium aryltrifluoroborates were also functionalized using Wittig or Horner−Wadsworth−Emmons reactions, allowing installation of further functionalities into these organoboron derivatives (Scheme 36).[89] The Wittig reaction of unstabilized ylides was best conducted in a THF/DMF/hexanes mixture for purification purposes, and the corresponding unsaturated aryltrifluoroborates were isolated in good yield with *Z*-selectivity. A reduction in selectivity was

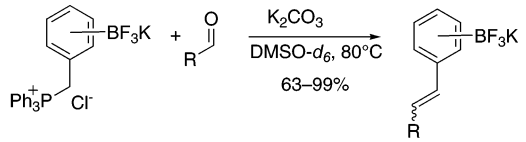
Scheme 37. HWE Olefination of Potassium Organotrifluoroborates



R = H or CH_3

EWG = CN, CO_2Et, CO_2Me, Ph

Scheme 38. Wittig Reaction with Potassium [(Trifluoroboratophenyl)methyl]triphenylphosphonium Chlorides



R = aryl, alkyl, alkenyl

E:*Z*: 1:2.1 to 7.6:1

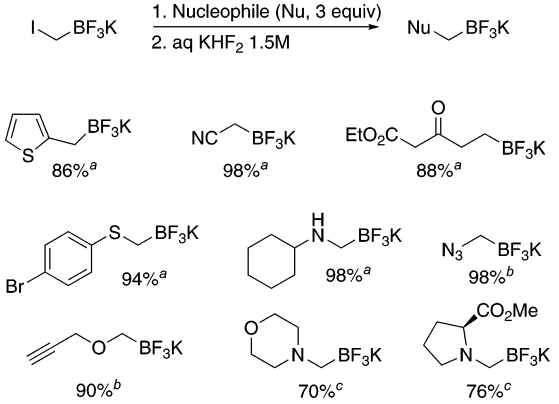
observed with ortho-substituted aryltrifluoroborates and certain functionalized ylides. The reaction works equally well with alkyl aldehydes, such as potassium 2-formylethyltrifluoroborate, and trisubstituted olefins could be prepared starting from potassium 4-acetylphenyltrifluoroborate.[89] Wittig reaction with stabilized ylides (benzene/DMF 1:1, 90 °C) allowed formation of α,β-unsaturated potassium aryltrifluoroborates bearing a nitrile, ketone, ester, or Weinreb amide functional group in good yields and *E*-selectivity.

Application of the Horner−Wadsworth−Emmons (HWE) olefination was also evaluated on appropriately functionalized organotrifluoroborates (Scheme 37).[89] The phosphonate carbanion was generated in situ by deprotonation with *n*-butyllithium followed by addition of the aldehyde. Isolation of the organotrifluoroborates was best achieved by conversion to the tetrabutylammonium salts (TBA) using the Batey cation-exchange reaction.[106] Using this procedure, the TBA salts migrated into the organic phase and the phosphonate byproduct remained in the aqueous phase, allowing isolation of the olefination product with good yields and *E*-selectivity.

The complementary process, i.e., generation and reaction of boron-functionalized phosphorus ylides with aldehydes, has also been described.[90] Potassium [(trifluoroboratophenyl)-methyl]triphenylphosphonium chlorides, prepared from the corresponding (chloromethyl)phenyltrifluoroborates, reacted with aromatic or aliphatic aldehydes in DMSO-d_6 at 80 °C in the presence of K_2CO_3 (Scheme 38). The stereoselectivity of the reaction was dependent on the aldehydes and increased according to the order of ortho- > meta- > para-positioned trifluoroborate unit in the aromatic ring.

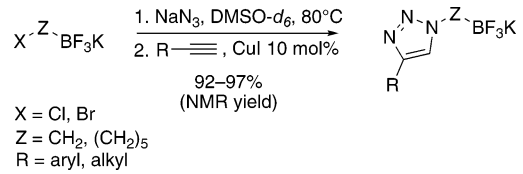
Preparation of functionalized potassium organotrifluoroborate could also be achieved via the direct nucleophilic substitution of potassium halomethyltrifluoroborates while leaving the trifluoroborate group intact. Indeed, treatment of potassium iodomethyltrifluoroborate with excess nucleophile (lithium or Grignard reagents, primary and secondary amines, alkoxides, stabilized carbanions, cyanide anion) all provided the expected product in good yield (Scheme 39).[60,91] In certain reactions, isolation of the products required treatment of the final reaction mixture with excess KHF_2, certainly because of the generation of trivalent boron species upon interaction with lithium or magnesium salts (see section 3).[25] The reaction is not limited to 1-halo-substituted substrates, and potassium 5-bromopentyltrifluoroborate, on reaction with 1 equiv of potassium cyanide, produced the

Scheme 39. Formation of Organotrifluoroborates from Nucleophilic Substitution

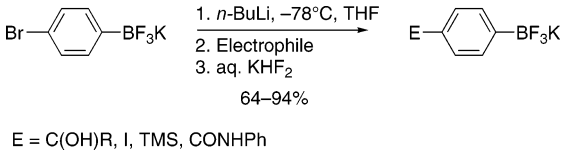


[a] From ref 60. [b] From ref 92. [c] From ref 91.

Scheme 40. Synthesis of Triazol-1-yltrifluoroborates via Nucleophilic Substitution



Scheme 41. Metalation of Aromatic Trifluoroborates

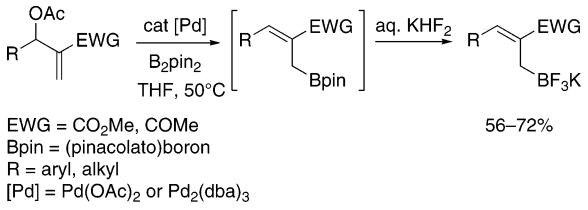


corresponding nitrile product. Using such a strategy, potassium azidoalkyltrifluoroborate was prepared from the corresponding halogen compounds.[92]

Indeed, the reactivity of the organotrifluoroborates is in sharp contrast with those observed with trivalent boron compounds where boronate esters are attacked by the nucleophile at the boron atom forming an ate complex followed by α-transfer of the nucleophile to the neighboring carbon.[61] Nucleophilic substitutions on organotrifluoroborates have also been used to develop a one-pot, multicomponent preparation of potassium organo-[1,2,3]triazol-1-yltrifluoroborates[92] via copper-catalyzed 1,3-dipolar cycloadditions of azides to alkynes (Scheme 40). Indeed, potassium haloalkyltrifluoroborates reacted efficiently when treated with NaN_3 in DMSO-d_6, and the resulting azido intermediates were smoothly transformed to the triazole products in the presence of an alkyne and 10 mol % CuI. Reverse procedures for the generation of triazole starting from potassium alkynyltrifluoroborates were also described.[92]

Further functionalization of potassium organotrifluoroborates was achieved by metalation of aryl bromides.[93] Indeed, G. A. Molander et al. have shown that on treatment with 1 equiv of *n*-butyllithium followed by addition to aliphatic or aromatic aldehydes, 4-bromophenyltrifluoroborate was converted to secondary alcohols, leaving the trifluoroborate moiety intact (Scheme 41).[94] Other electrophiles have been used, such as iodine, phenylisocyanate, or chlorotrimethylsilane (TMSCl). Less general were the reactions of meta-substituted bromophenyltrifluoroborates.[94] As in the case of nucleophilic substitution (vide supra), treatment of the crude reaction mixture with aqueous KHF_2 was necessary, certainly

Scheme 42. Potassium Allyltrifluoroborates from Baylis−Hillman Adducts



because of the generation of trivalent boron species upon interaction with lithium salts (see section 3).[25]

Indeed, the tetracoordinate nature of organotrifluoroborates shields them from reactions with Lewis bases and nucleophiles under normal reaction conditions. Retrosynthetic analyses could therefore be greatly expanded compared to trivalent boron derivatives.

2.7. Transition-Metal-Catalyzed Generation of Allytrifluoroborates

Among allylmetal reagents, allylboron compounds are very useful because of the high yield and excellent stereocontrol they provide in reactions with carbonyl compounds. However, availability of functionalized allylboron reagents remains limited, certainly because allylboronic acids or esters are not sufficiently stable, particularly under solvent-free conditions.[95]

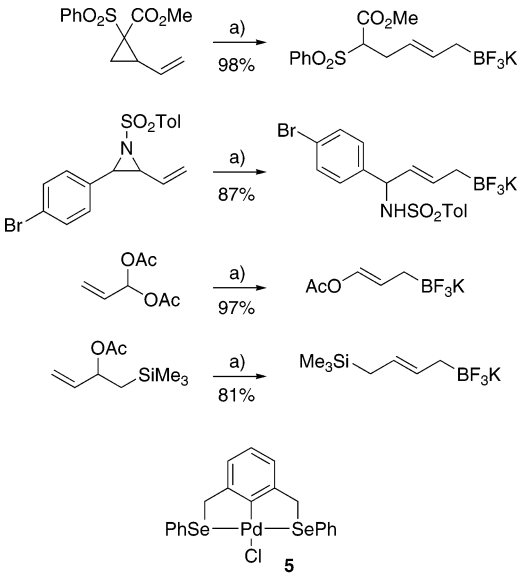
Potassium allyltrifluoroborates can be easily accessed using palladium-catalyzed cross-coupling reaction of Baylis−Hillman acetates with bis(pinacolato)diboron (B_2pin_2) and in situ fluoration using KHF_2 (Scheme 42).[96] Indeed, Baylis−Hillman acetates upon reaction with the diboron derivative, in the presence of 5 mol % $Pd(OAc)_2$ or 3 mol % $Pd_2(dba)_3$ in THF at 50 °C, furnished 2-alkoxycarbonyl-3-substituted allylboronates which, once treated with aqueous KHF_2, provided (*E*)-2-alkoxy-3-substituted allyltrifluoroborate potassium salts. Once again, all the allyltrifluoroborates were air- and water-stable solids and can be stored at room temperature.

Szabó and co-workers have shown that allyl vinyl cyclopropanes, vinyl aziridines, and allyl acetates can be converted to allylboronates using diboronic acid ($[B(OH)_2]_2$ or tetrahydroxyboron) in the presence of a catalytic amount of pincer complex **5** (Scheme 43).[97] Indeed, treatment of the various precursors in the presence of 5 mol % of palladium pincer **5** and diboronic acid afforded high yields of potassium allyltrifluoroborates after treatment with aqueous KHF_2. The mechanism of this palladium-catalyzed process was supposed to occur similarly to the trimethyltin transfer reactions with hexamethylditin.[98]

The same palladium pincer complex **5** was used in the conversion of allyl alcohols into allylboronates using diboronic acid.[99] The trivalent boron intermediates were directly converted to allyltrifluoroborates (Scheme 44). The boronation proceeded with excellent regioselectivity as branched allyl alcohols furnished exclusively linear allyltrifluoroborates. Moreover, it appeared that under these conditions, cinnamyl alcohol was converted significantly faster to allylborane than was cinnamyl acetate.

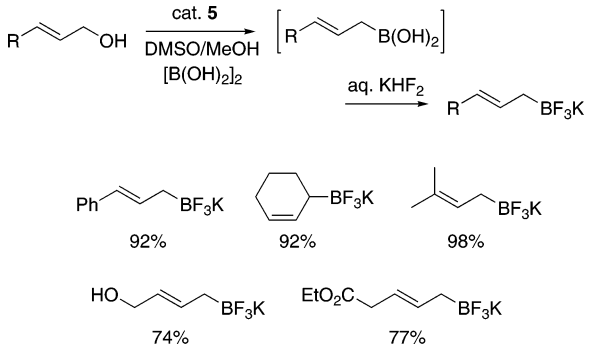
For some allyl alcohols, addition of catalytic amounts (3−5 mol %) of strong acids, such as *p*-toluenesulfonic acid (PTSA), considerably accelerated the reaction. Substitution of cyclic substrate **6** provided a single diastereomer **7** (Scheme 45), indicating that the boronation is both regio-

Scheme 43. Pincer Complex 5 Catalyzed Synthesis of Potassium Allyltrifluoroborates

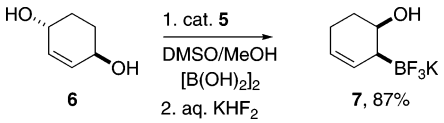


a) i) 5 mol % **5**, $[B(OH)_2]_2$, DMSO, 40 °C. ii) aq. KHF_2.

Scheme 44. Palladium-Catalyzed Direct Boronation of Allyl Alcohols



Scheme 45. Regio- and Stereoselectivity of the Palladium-Catalyzed Boronation of Allyl Alcohols



and stereoselective and that the reaction proceeded with allyl rearrangement and with trans stereoselectivity.

2.8. Properties of Potassium Organotrifluoroborates

From a practical viewpoint, preparation of potassium organotrifluoroborates, by in situ treatment with KHF_2, is straightforward and avoids isolation of trivalent organoboron species. Use of KHF_2 as a fluorinating agent is compatible with most functional groups; in particular, trialkylsilyl protecting groups are not removed despite the presence of fluorine anions.

2.8.1. Stability—Properties

With very few exceptions, all potassium organotrifluoroborates show high stability toward air and water, which is not the case of the vast majority of other organoboron compounds. For example, the widely known and used organoboronic acids show variable stability (vinyl-, alkyl-, and alkynylboronic are not very stable), and their purification is not straightforward. Moreover, isolated boronic acids generally contain large quantities of anhydrides or boroxines, which result in problems for determining their stoichiometry. On the other hand, boronic esters show higher stability but are generally less reactive than the free boronic acids. Moreover, diols used for their preparation are generally expensive and difficult to separate at the end of reactions. Finally, from an economical viewpoint, KHF_2 is less expensive than catechol and far less expensive than pinacol.

Potassium organotrifluoroborates are not hygroscopic and can be stored indefinitely at room temperature without any observed decomposition. It is important to note that contrary to trivalent boron substituents, trifluoroborate is an electron-donating substituent.[32]

In their early report,[15b] Chambers and co-workers noticed that "alkaline solutions of potassium trifluoromethyltrifluoroborate were stable to prolonged boiling, but the ion was destroyed by boiling with 50% sulfuric acid... fluoroform was not found". The relative instability of organotrifluoroborates toward acids (as all boron reagents) has been confirmed. Indeed, a study dealing with the stability of potassium organotrifluoroborates toward acids revealed some interesting features concerning the stability of these compounds toward hydrodeboration and gives an idea of the force of the carbon−boron bond.[100] In this work, several potassium organotrifluoroborates were reacted with different acids of different strength (CH_3CO_2H, CF_3CO_2H, and aqueous or anhydrous HF). From the results obtained, the following order of stability can be put forward concerning the different organic substituents: alkyl > aryl > alken-1-yl ≈ perfluoroalkyl > perfluoroaryl > perfluoroalken-1-yl. All the studied salts were stable in acetic acid at room temperature for prolonged periods.

In a report dealing with the noncovalent inhibition of the serine proteases, α-chymotrypsin and trypsin by organotrifluoroborates, the authors studied their stability to hydrolysis in an enzymatic study.[101] It was found that in D_2O or TRIS buffer, tris(hydroxymethyl)aminomethane, potassium aryltrifluoroborates were quite stable at 37 °C and pH = 7.0, depending on their structures, whereas potassium butyltrifluoroborate showed 30−50% hydrolysis to boronic acid after 24 h. Faster hydrolysis was observed in phosphate buffer.

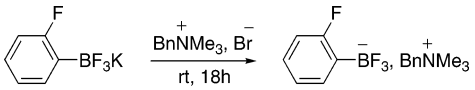
Organotrifluoroborates also proved not to be stable toward Lewis-acid reagents (see section 3.1), resulting in generation of trivalent compounds. Particularly, they proved to be sensitive to silica gel, regenerating boronic acids if stable![29,94] The slight sensitivity toward Lewis and Brønsted acids is largely compensated by their high stability toward Lewis or Brønsted bases and also nucleophiles, contrary to the vast majority of organoboranes.

The electrochemical behavior of some potassium aryltrifluoroborates has also been studied, and the potentials for the electrochemical oxidation of potassium polyphenyltrifluoroborates were measured by cyclic voltammetry in acetonitrile.[102]

2.8.2. Structures

Structure analysis of various potassium organotrifluoroborates have confirmed the ionic formulation of $K[RBF_3]$.[103] Since contacts between anions exceed the sums of the relevant van der Waals radii, the packing is apparently dictated by the cation−anion interactions.

Scheme 46. Counterion Exchange of K[RBF$_3$]



For example X-ray structure determination of K[CH_3BF_3] revealed that the cations form their closest contact with F atoms in five anions, the midpoint of which roughly describe a square pyramid.[19] These polyhedra are linked perpendicular to *a* into layer with CH_3 groups occupying the surfaces. Seven K−F contacts were found at 2.678(1)−2.965(1) Å. The symmetry of the $CH_3BF_3^-$ anion is approximately C_{3v} with the CH_3 group staggered with respect to the BF_3 fragment. The B−C bond length (1.575 Å) is one of the shortest reported for a borate complex.

2.8.3. Solubility

Potassium organotrifluoroborates generally show high solubility in polar solvents like methanol, acetonitrile, acetone, DMF, and DMSO. Some are slightly soluble in toluene, THF, and water but are insoluble, with some exceptions, in nonpolar solvents like dichloromethane, ether, and hydrocarbons.

2.8.4. Characterization

The purity of the salts can be easily checked by ^{19}F or ^{11}B NMR. The ^{11}B NMR spectra feature a reasonably well resolved 1:3:3:1 quartet, ranging from −2.5 to 7 ppm relative to $BF_3{\cdot}Et_2O$, corresponding to the coupling of ^{11}B with three equivalent fluorine atoms. This gives an indication of the substitution at the boron atom. In the ^{19}F NMR spectra, 1:1:1:1 quadruplets, ranging from −160 to −130 ppm relative to $CFCl_3$, were generally observed, as expected for the coupling of ^{19}F with ^{11}B of spin 3/2.

Exact mass measurements were obtained for a variety of potassium and tetra-*n*-butyl ammonium organotrifluoroborates using organic sulfate salts as internal reference standards.[104] Accuracies were determined within 5 ppm using a sector ESI mass spectrometer operating in the negative ionization mode.

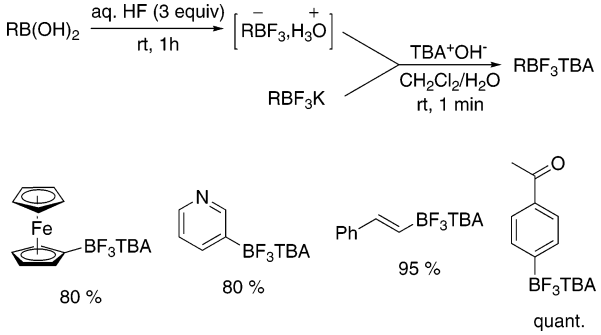
2.9. Other Organotrifluoroborates Salts

In their original publication Chambers et al.[15] described other salts of trifluoromethyltrifluoroborates. The ammonium salt $NH_4[CF_3BF_3]$ appeared to be less stable than the potassium one, and the barium salt proved to be highly hygroscopic.

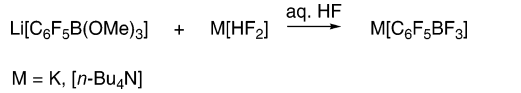
To increase the solubility of the fluoroborate salts in nonpolar solvents, some groups have prepared and used tetraalkylammonium salts. The first example concerned the preparation of tetra-*n*-butylammonium (TBA) phenyltrifluroborate from the condensation of phenyldifluoroborane with tetra-*n*-butylammonium fluoride.[105] Vedejs et al.[27] also reported formation of benzyltrimethylammonium salts from the potassium one on treatment with benzyltrimethylammonium bromide (Scheme 46).

This procedure was improved by R. A. Batey et al. by use of ammonium hydroxide instead of bromide.[106] Thus, counterion exchange of K[RBF_3] or [H_3O^+][RBF_3^-] was achieved by treating the salts with tetra-*n*-butylammonium (TBA) hydroxide (Scheme 47). All of the tetra-*n*-butylammonium compounds were found to be readily soluble in both

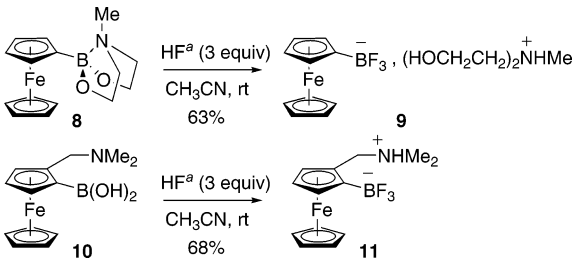
Scheme 47. Formation of Tetra-*n*-butylammonium Organotrifluoroborates



Scheme 48. [*n*-Bu$_4$N][HF$_2$] in the Generation of TBA Organotrifluoroborates

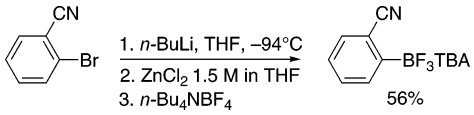


Scheme 49. Diethanolammonium Salts



[a] HF source: 2,4,6-trimethylpyridine·(HF)$_{1.5}$.

Scheme 50. Alternative Procedure for the Preparation of TBA Salts



polar and nonpolar solvents,[106] but no information concerning their stability compared to potassium salts was given.

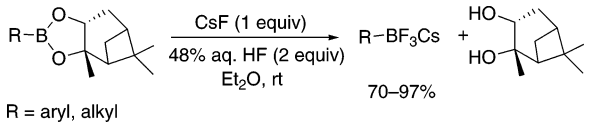
TBA salts could also be readily accessed by reacting trivalent or tetravalent organoboranes with [*n*-Bu$_4$N][HF$_2$].[107] Indeed, reaction of lithium pentafluorophenyltrimethoxyborate with [*n*-Bu$_4$N][HF$_2$] in aqueous HF furnished a 95% yield of the expected trifluoroborate salt (Scheme 48). The same reaction with the potassium salt occured in an analogous manner but lower yield.

Reaction of the ferrocenylborane compound **8** with 3 equiv of HF, provided in the form of the collidine complex 2,4,6-trimethylpyridine·(HF)$_{1.5}$, in acetonitrile at room temperature afforded the ferrocenyltrifluoroborate salts **9** as a crystalline solid in 63% yield (Scheme 49).[108] Similarly, treatment of the aminoboronic acid **10** leads to isolation of the zwitterionic species **11** in about 68% yield.

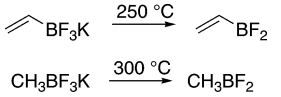
Another procedure can be employed for the preparation of TBA aryltrifluoroborates (Scheme 50).[109] Indeed, lithium−bromine exchange on 2-bromobenzonitrile followed by transmetalation with zinc chloride and addition of tetra-*n*-butylammonium tetrafluoroborate afforded directly the corresponding TBA cyanophenyltrifluoroborate.

Matteson and co-workers reported efficient preparation of cesium organotrifluoroborates using a combination of CsF/HF as reagents.[110] Cesium alkyltrifluoroborates were

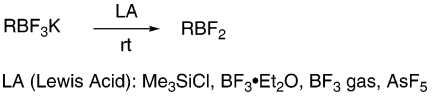
Scheme 51. Preparation of Cesium Organotrifluoroborates



Scheme 52. High-Temperature Generation of RBF_2



Scheme 53. Generation of Organodifluoroboranes from Potassium Organotrifluoroborates



precipitated in high yields by reaction of pinanediol (alkyl)-boronates in diethyl ether with equivalent amounts of a mixture of aqueous hydrofluoric acid and cesium fluoride (Scheme 51). Those salts were generally isolated by simple filtration but could be recrystallized from acetonitrile or acetonitrile/diethyl ether.

Lithium salts, with some minor exceptions, are generally not stable, and formation of organodifluoroborane and lithium fluoride is generally observed. Vedejs showed that the nature of the counterion of the trifluoroborate governed their stability.[25] Thus, in the presence of Mg^{2+} or Li^+ salts in water, organotrifluoroborates were rapidly decomposed to boronic acids via the intermediate formation of RBF_2.

3. In Situ Generation of RBF_2 and Applications

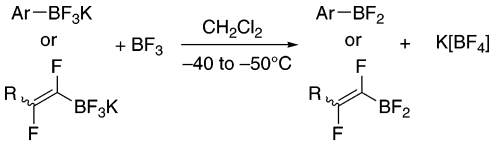
Very early, potassium organotrifluoroborates were regarded as potential precursors of organodifluoroboranes that are excellent Lewis acids. In the 1960s preparation of potassium vinyltrifluoroborate and methyltrifluoroborate and their use as precursors of the corresponding difluoroboranes were patented by Stafford et al.[20] They showed that heating these salts at high temperature allowed the generation of organodifluoroboranes of high purities (Scheme 52), which could be directly used for further applications (polymerization promoters, for example).

In that way, potassium organotrifluoroborates were regarded as an "excellent means of storing and handling organohaloboranes and regenerating these compounds in a highly pure form".[20] Some 25 years later, it was reported that treatment of potassium organotrifluoroborates with $BF_3{\cdot}Et_2O$ allowed a clean generation of the corresponding difluoroborane.[23] However, only one example was described, and general methods for generation of organodifluoroboranes needed to be reported.

3.1. Dihalogenoorganoborane Generation

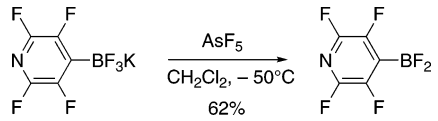
Vedejs et al. were the first to study the generation of trivalent boranes from organotrifluoroborates.[25] For their applications they found that the most efficient fluorophile was trimethylsilyl chloride (TMSCl). Indeed, on treatment with 1 equiv of trimethylsilyl chloride, potassium organotrifluoroborates decomposed cleanly, affording efficient access to difluoroboranes (Scheme 53). It is believed that RBF_2 is released from a silicon-activated intermediate containing B−F−Si linkage by simple B−F heterolysis.[25]

Scheme 54. Preparation of Polyfluoroorganodifluoroboranes

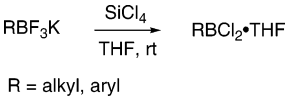


Ar = 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2,4,6-$F_3C_6H_2$, 2,3,4,5-F_4C_6H, C_6F_5,
R = F, Cl, *cis*-H, *trans*-C_4F_9, *cis*-C_2F_5,*cis*-C_6F_{13}, *trans*-C_4H_9, *trans*-C_6H_5, *trans*-Et_3Si, *cis*- and *trans*-CF_3

Scheme 55. AsF_5 as Lewis Acid for the Generation of RBF_2



Scheme 56. Organodichloroborane from $K[RBF_3]$



Other Lewis acids have been used for the in situ generation of organodifluoroboranes, including BF_3[32,34,62,63,111,112] and AsF_5,[34,64] but many other Lewis acids decompose organotrifluoroborates.[63]

For example, polyfluoroalken-1-yldifluoroboranes were prepared on reaction of the trifluoroborate with BF_3 gas at −40 °C (Scheme 54).[113] In the same way, (fluoroaryl)-difluoroboranes[32] and substituted 1,2-difluoroalk-1-enyldi-fluoroboranes[50,51] were obtained from a chlorocarbon solution (CH_2Cl_2, CCl_3F) of the corresponding trifluoroborate upon treatment with BF_3 gas. These solutions can be used directly, but the product can be also isolated by distillation.

On the other hand, perfluoroalkyldifluoroboranes were best generated upon treatment of the corresponding trifluoroborate with the stronger Lewis acid AsF_5 in CCl_3F or CH_2Cl_2 at −55 °C.[64] In that case, a stronger fluoride anion scavenger than BF_3 was necessary. Potassium 2,3,5,6-tetrafluoropyrid-4-yltrifluoroborate showed no reactivity when reacted with BF_3 gas in dichloromethane at −50 °C (Scheme 55), while clean generation of the corresponding difluoroborane was observed on treatment with AsF_5 under identical conditions (62% yield).[34]

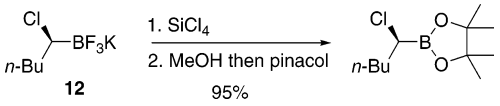
Contrary to the preceding fluorine scavengers, treatment of potassium organotrifluoroborates with tetrachlorosilane resulted in immediate evolution of gaseous tetrafluorosilane and formation of the corresponding solvated organodichloroborane, $RBCl_2$ (Scheme 56).[38,114] It was noted that in the presence of catalytic amounts of [18]crown-6 in dichloromethane the reaction stopped at the organodifluoroborane. Dichloroborane derivatives could also be generated on reaction with BCl_3.

In situ generated organodihalogenoboranes from potassium organotrifluoroborates have shown useful applications in organic synthesis.

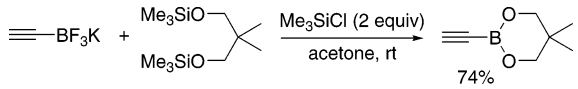
3.2. $K[RBF_3]$ as Stock Reagents for the Clean Formation of Boronate Esters

Potassium organotrifluoroborates can be useful precursors of boronic esters via the intermediate formation of dihalogenoborane. D. Matteson et al.[114] have shown that chiral [(*S*)-chloropentyl]trifluoroborate **12**, upon treatment with $SiCl_4$, provided the corresponding dichloroborane, which, on reac-

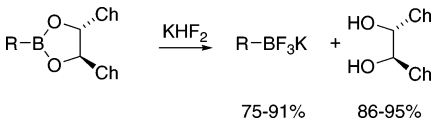
Scheme 57. Formation Pinacolyl Esters from K[RBF$_3$]



Scheme 58. Formation of Boronic Esters from Bis(trimethylsilyl) Ethers



Scheme 59. Deprotection of DICHED Boronic Esters



tion with methanol and pinacol, yielded the boronic ester in 95% yield (Scheme 57).

Another example is given by the preparation of ethynylboronate ester (Scheme 58). Generation of this boronate by condensation of ethynylmagnesium bromide to 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, using the standard procedure of Brown and co-workers,[57b] led to formation of the expected boronate in moderate yield and rather low purity.[55] Other procedures also met low success. On the other hand, treatment of readily available potassium ethynyltrifluoroborate with 2,2-dimethylpropane-1,3-diol bis(trimethylsilyl) ether in the presence of chlorotrimethylsilane in acetone at room temperature afforded ethynylborate in 74% yield and high purity (Scheme 58).[55] The latter reagent proved to be useful in transition-metal-catalyzed cycloadditions to provide direct access to functionalized arylboronates.[55,115]

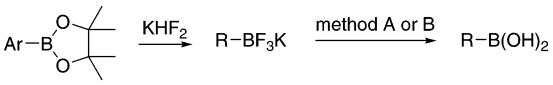
3.3. K[RBF$_3$] as Intermediates in the Mild Deprotection of Boronate Esters

Potassium organotrifluoroborates can be used as intermediates for removal of diol protecting group in boronic esters. Methods currently available for the deprotection of pinacolyl esters generally include destructive procedures such as use of periodate to cleave the protecting diol oxidatively or hydrolytic protocols. Transesterification has also been described but suffers from incomplete reactions or problems in separating the desired boronic acid from a large excess of transesterification partner.

E. Vedejs et al. observed that potassium phenyltrifluoroborate rapidly decomposed to phenylboronic acid in the presence of lithium or magnesium cations.[25] This observation furnished an entry for the mild deprotection of boronate esters as it was known that these esters could be readily converted to potassium organotrifluoroborates. Indeed, Matteson et al. have shown that pinanediol or DICHED (1,2-dicyclohexylethanediol) boronic esters, on treatment with KHF$_2$, allowed formation of the expected trifluoroborates and recovery of the diol in good yields (Scheme 59).[38] Separation of the products is facilitated by the insolubility or low solubility of K[RBF$_3$] in many organic solvents.

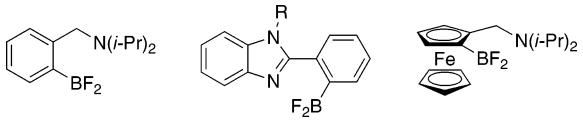
These observations resulted in an efficient two-step procedure for the deprotection of pinacolyl organoboronate esters and generation of free boronic acids (Scheme 60).[116] Conversion of arylpinacolylboronate to potassium aryltrifluoroborates was readily achieved by treatment with potassium hydrogen difluoride. Hydrolysis of the latter to boronic acid was performed using either lithium hydroxide or TMSCl in the presence of water. Indeed, formation of the boronic acids must occur via prior formation of the corresponding dihalogenoboranes as it has been shown that organotrifluoroborates are unstable toward fluorine scavengers like lithium cation or chlorosilane reagents.[25]

Scheme 60. Deprotection of Pinacolyl Organoboronate Esters

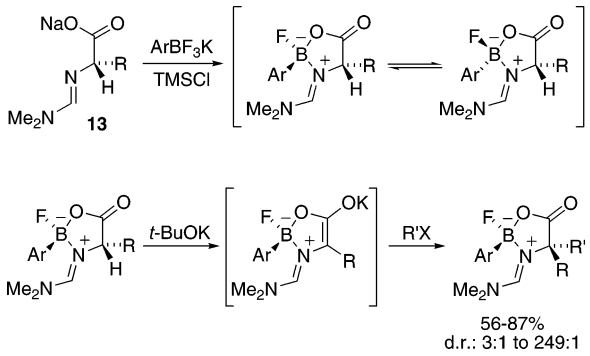


method: A: aq. LiOH (3.5 equiv), CH_3CN, rt. B: Me_3SiCl (3 equiv), CH_3CN/H_2O, rt.

Chart 1. Bifunctional Lewis-Acid–Lewis-Base Catalyst



Scheme 61. K[RBF$_3$] as Auxiliaries in Amino Acids Synthesis



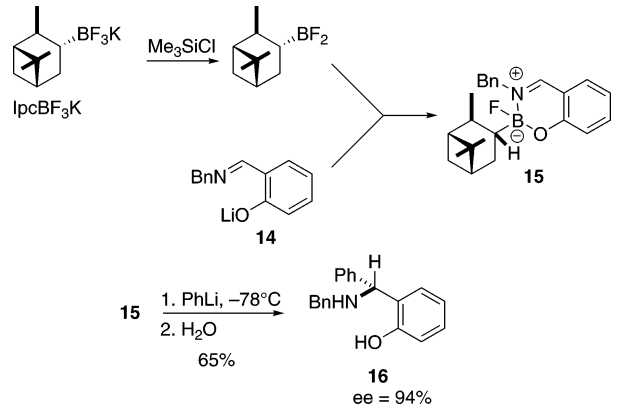
3.4. K[RBF$_3$] as Lewis Acid Catalyst Precursors

Potential bifunctional Lewis-acid–Lewis-base catalysts have been prepared and used in some reactions (Chart 1). Indeed, functionalized aminoaryldifluoroborane, generated in situ from the corresponding trifluoroborate, have shown some interesting catalytic activities in aldol or nitro–aldol reactions.[42,43]

3.5. K[ArBF$_3$] in Crystallization-Induced Asymmetric Transformations

The first application of the in situ generated aryldifluoroboranes from potassium organotrifluoroborates was described by E. Vedejs et al.[25,27,117] These boranes were used as Lewis acids in crystallization-induced asymmetric transformations for the generation of α,α′-disubstituted amino acids. Treatment of amidino carboxylates **13** with aryltrifluoroborates in the presence of trimethylsilyl chloride in THF afforded two diastereoisomeric boron ate complexes (Scheme 61). Under appropriate conditions, only one boron epimer was isolated in theoretical quantitative yield because interconversion between the two epimers occurred readily via dissociation of the ate complex. Thus, practically, the chiral information from the starting amino acid is stored at the boron atom. From the isolated major diastereomer, alkylation of the generated enolate occurs with good diastereoselectivity at the opposite face of the Ar substituent,

Scheme 62. K[RBF$_3$] as Auxiliaries in Chiral Amino Alcohol Synthesis



allowing, after hydrolysis, formation of amino acids containing quaternary enantioenriched carbon centers.[27] By varying the nature of the organotrifluoroborate, it was possible to increase the diastereoselectivity by facilitating the epimerization reaction.

A related process was described by the same authors using high-purity potassium isopinocampheyltrifluoroborate (K[IpcBF$_3$]),[23] whose preparation was improved from the original procedure via hydroboration of (+)-α-pinene using DMAP·BH$_3$ (DMAP = 4-dimethylaminopyridine).[118] Treatment of K[IpcBF$_3$] with 1 equiv of chlorotrimethylsilane furnished the corresponding difluoroborane, which on reaction with the lithium salt of salicaldimine **14** afforded the boron ate complex **15** as a single isomer after trituration with hexane (Scheme 62).

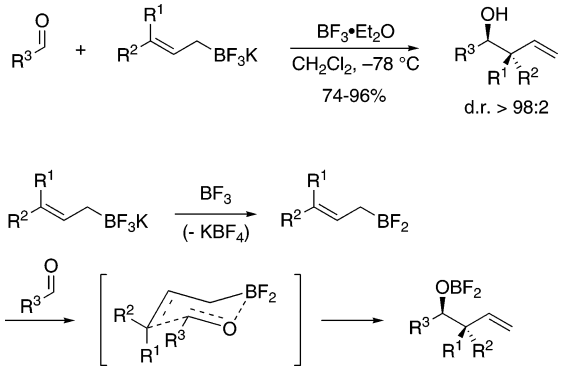
The relative configuration of the crystalline isomer obtained starting from (1*R*)-α-pinene was established by X-ray crystallography as (R_B)-2-fluoro-2-isopinocampheyl-3-benzyl-2*H*-benzo[*e*]-1,3,2-oxaza-boratane **15**. Addition of phenyllithium to **15** provided chiral amine **16** in 65% yield and 94% ee.

3.6. Diastereoselective Allylation Reactions of Aldehydes

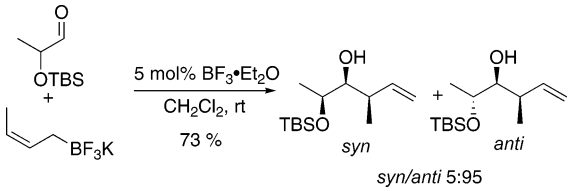
Aldehydes react with a variety of allylmetallic compounds to give homoallylic alcohols,[119] and among them, trivalent allyl- and crotylboron compounds are particularly useful because of the high yields and excellent levels of stereocontrol they provide.[120] However, a major disadvantage with these trivalent boranes is their sensitivity to air and/or moisture, so they are generally prepared immediately prior to use. To circumvent this problem, R. A. Batey et al. developed the use of potassium allyl- and crotyltrifluoroborates in allylation reactions (Scheme 63).[62,63] Allyldifluoroboranes were generated in situ by addition of BF$_3$·Et$_2$O and allowed to react with aldehydes at low temperatures. High yields were generally achieved with a variety of aldehydes. Crotylation using potassium (*Z*)- and (*E*)-crotyltrifluoroborates was found to provide excellent levels of stereocontrol, consistent with addition of tricoordinate boron species via a Zimmerman−Traxler-like transition state (Scheme 63), potassium (*Z*)- and (*E*)-crotyltrifluoroborates giving rise to the syn and anti product, respectively. The reaction could also be conducted using catalytic amounts of BF$_3$·Et$_2$O (5 mol %) at room temperature without affecting the yields.

This reaction was also applied to the allylation of aldehydes bearing α- or β-stereogenic centers (Scheme 64).[63]

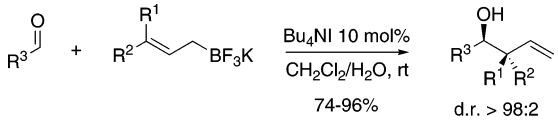
Scheme 63. Allylation of Aldehydes Using K[RBF$_3$]



Scheme 64. Crotylation of α-Substituted Aldehydes



Scheme 65. Phase-Transfer-Catalyzed Allylation of Aldehydes



For example, using (*Z*)-crotyl reagent, very good anti selectivity was observed in the addition to α-OTBS (TBS = *tert*-butyldimethylsilyl) substituted aldehydes. Use of other allylboron derivatives or β-substituted aldehydes generally resulted in lower diastereoselectivity.

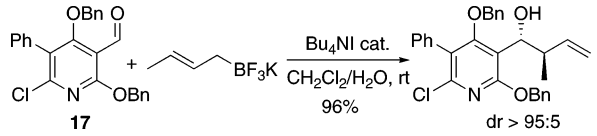
Improved conditions were developed by the same authors, conducting the reaction under aqueous biphasic medium using phase-transfer catalyst (PTC) in the absence of BF$_3$·Et$_2$O.[121] Among the different tested PTCs, tetra-*n*-butylammonium iodide proved to be the most efficient, affording allylation products in high yields at room temperature within 15 min in dichloromethane−water mixtures (Scheme 65). In the absence of PTC, the reaction was found to be rather sluggish. The presumed role of the PTC in this reaction is to transport the allyltrifluoroborate anion from the aqueous phase into the organic phase with reaction presumably occurring at the interface of the aqueous and organic phase.[121]

These conditions were found to be of general use for the allylation of aldehydes, and applications have appeared in the literature. Indeed, it was shown that allyltrifluoroborates, readily obtained from Baylis−Hillman acetates via palladium-catalyzed reactions, reacted with aldehydes to give the corresponding homoallylic alcohols in high yields and diastereoselectivities.[96] A strategy for the synthesis of phosphatase inhibitors TMC-69-6H and analogues involved diastereoselective crotylation under biphasic conditions (Scheme 66).[122] Indeed, reaction of potassium (*E*)-crotyltrifluoroborate with aldehyde **17** led to formation of the *anti*-homocrotyl alcohol product in 96% yield and dr > 95%.

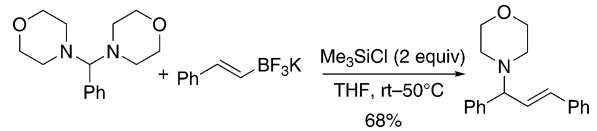
3.7. Lewis-Acid-Catalyzed Mannich-type Reactions

Thanks to their high Lewis acidity, in situ generated organodifluoroboranes have been shown to be very reactive

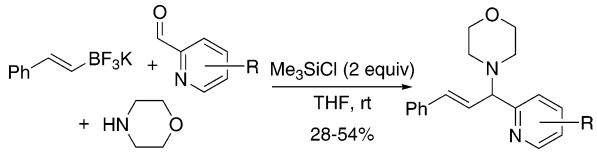
Scheme 66. Application of Phase-Transfer-Catalyzed Allylation



Scheme 67. Organotrifluoroborates in the Boronic Mannich Reaction

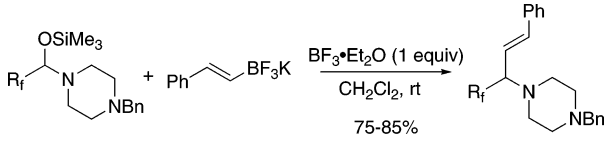


Scheme 68. Boronic Mannich Reaction with Potassium Alken-1-yltrifluoroborates



R = H, 2-Br, 2-MeO, 3-CO_2Me

Scheme 69. Vinylation of Fluorinated Iminiums with Potassium Alken-1-yltrifluoroborates



R_f = CF_3, $CClF_2$, CF_3CF_2

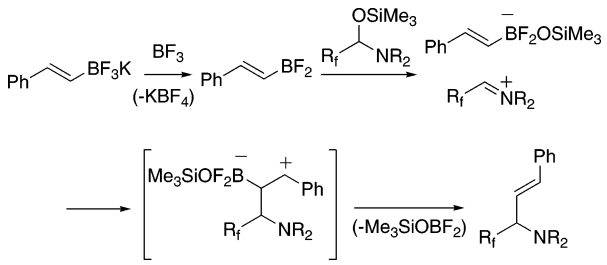
in addition reactions to iminiums and derivatives. The first example described concerned the use of potassium organotrifluoroborates in the boronic Mannich reaction (BMR), a three-component reaction between aldehydes, amines, and boronic acids.[123] As soon as he described the reaction, N. Petasis patented the use of organotrifluoroborates in the BMR (Scheme 67).[124] For example, reaction of 4,4′-benzylidenedimorpholine with potassium (*E*)-2-phenylethenyltrifluoroborate in the presence of 2 equiv of chlorotrimethylsilane furnished 1-morpholino-1,3-diphenyl-2-propene in 68% yield.

Heterocyclic aldehydes have also appeared to be suitable components in the BMR.[125] Potassium styryltrifluoroborate added efficiently to in situ generated iminium ions using chlorotrimethylsilane as a fluorophile (Scheme 68). Among the tested heterocyclic aldehydes, only aldehydes possessing a α-heteroatom to the aldehyde substituent gave the BMR product. Under these standard conditions, yields obtained using the corresponding boronic acid were always below 10%, demonstrating the higher electrophilicity of organodifluoroboranes compared to other trivalent organoboron derivatives. Moreover, reaction times were generally shorter.

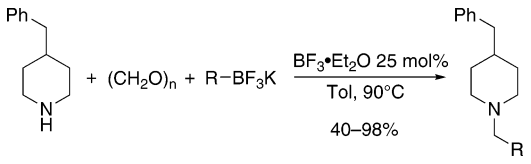
Potassium alken-1-yltrifluoroborates also proved to be good nucleophiles in the reaction with trifluoroacetaldehyde hemiacetals (Scheme 69).[112] In the presence of BF_3•Et_2O as the Lewis acid, the in situ generated alkenyldifluoroborane derivatives reacted with trifluoromethylated iminium ions in good yields in dichloromethane at room temperature, whereas alkenylsilanes failed to deliver α-fluoroalkylated amines.

Concerning the mechanism of such reactions, some general considerations were proposed. The in situ generated RBF_2 acts as a Lewis acid to activate the hemiaminal, generating an iminium and a nucleophilic species (Scheme 70).[112,126] The precise mechanism for the reaction between the iminium and the organoboron species is still unclear but should involve a nucleophilic attack of the double bond to the highly electrophilic iminium cation. In the BMR reaction, chelation of the organoboron compound to the electrophilic substrate seems to be necessary for the reaction to proceed.

Scheme 70. Proposed Mechanism for the Vinylation of Iminiums Cations

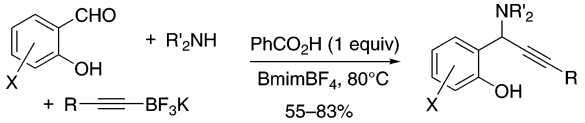


Scheme 71. Three-Component Petasis Reaction with Paraformaldehyde



R = aryl, alken-1-yl, allyl

Scheme 72. Potassium Alkynyltrifluoroborate in the Petasis Reaction



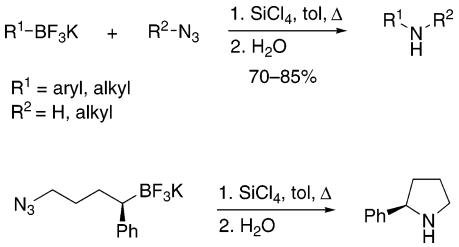
R = alkyl, aryl, trimethylsilyl
X = H, 5-NO_2, 3-Me, 5-Cl, 5-*t*-Bu
R′$_2$NH = morpholine, (PhCH$_2$)NH

The BMR using potassium organotrifluoroborates is not limited to introduction of alkenyl substituents, which is often the case with other boron reagents. It has been shown that in the presence of TiF_4 or BF_3.Et_2O as Lewis acids, potassium aryl-, alkenyl-, and allyltrifluroborates participated in the BMR (Scheme 71).[127] For example, the three-component reaction between 4-benzylpiperidine, paraformaldehyde, and organotrifluoroborate afforded functionalized amines in high yields. The reaction could also be conducted on other aldehydes but was still limited to aldehydes bearing an α or ortho activating group.

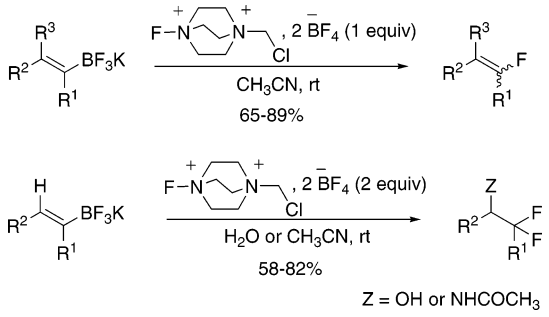
This three-component reaction was extended to potassium alkynyltrifluoroborates (Scheme 72).[128] Reaction of the latter with amines and salicylaldehydes or formaldehyde in the presence of 1 equiv of benzoic acid, using an ionic liquid as solvent, furnished the propargylamines in moderate to good yields. Addition of benzoic acid increased the reaction yields dramatically, presumably by favoring condensation of the aldehyde with the amine to generate the iminium ion. Once again, benzaldehyde derivatives lacking an *o*-hydroxy substituent were found to be unreactive.

Such Mannich-type reactions have also been described with α,α-dichloro aldimines.[129]

Scheme 73. Conversion of Organotrifluoroborates into Secondary Amines



Scheme 74. Fluorination of Potassium Alkenyltrifluoroborates



3.8. Organotrifluoroborates in Secondary Amine Synthesis

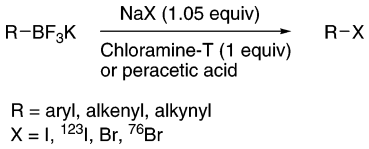
In situ generated alkyl- and aryl-dichloroboranes, from potassium alkyl- and aryltrifluoroborates, react with organic azides to give secondary amines (Scheme 73). As fluorine scavengers, D. S. Matteson et al. found that $SiCl_4$ allowed faster reactions than Me_3SiCl, presumably by generating organodichloroborane instead of difluoroborane.[38] Indeed, reaction of trifluoroborates with a slight excess of azide was efficiently promoted by tetrachlorosilane to afford secondary amines in good yields in refluxing toluene.

An example of an intramolecular reaction was also reported with the preparation of a chiral 2-phenylpyrrolidine starting from chiral potassium alkyltrifluoroborate (Scheme 73).[38] This reaction proved to be one of the most promising ones for formation of secondary amines from organoboron compounds. Moreover, use of in situ generated reactive organodihalogenoboranes appeared to be superior to previously described reactions using highly reactive and unstable alkyldichloroboranes or trialkylboranes, where only one of the three alkyl groups is transferred.[38]

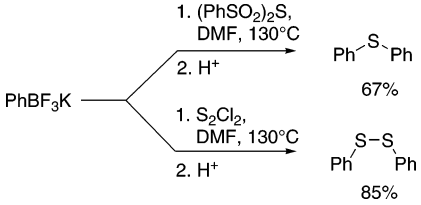
4. Reactions of Potassium Organotrifluoroborates with Electrophiles

One of the first applications of potassium organotrifluoroborates, other than for the in situ generation of organodifluoroboranes,[25] concerned their use in electrophilic fluorination (Scheme 74).[130] Indeed, N. A. Petasis et al. used potassium alkenyltrifluoroborates to produce alkenyl fluorides in good yields using Selectfluor as a fluorinating agent.[74] Reaction conditions (acetonitrile, room temperature) proved to be very mild, and it was found that the reaction was sluggish using the corresponding alkenylboronic acids. Concerning the mechanism, the reaction presumably involved an addition−elimination pathway via a carbocation intermediate.[74] Formation of a mixture of isomers and faster reaction with organotrifluoroborates compared to boronic acids are consistent with this mechanism. In the presence of a second equivalent of Selectfluor, the alkenyl fluorides underwent further reaction to produce a putative carbocationic intermediate, which was quenched with the solvent (Scheme 74).[74] This reaction only worked with compounds leading to benzylic carbocations (R^2 = Ar).

Scheme 75. Organic Halides from Potassium Organotrifluoroborates



Scheme 76. Sulfuration of Potassium Phenyltrifluoroborate



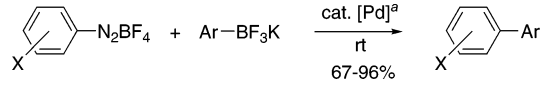
Kabalka et al. found that organic halides can be readily prepared from potassium organotrifluoroborates. In the presence of sodium iodide and chloramine-T, potassium aryl-, alkenyl-, and alkynyltrifluoroborates were rapidly converted to iodides under mild conditions (Scheme 75).[131] Potassium aryltrifluoroborates containing electron-withdrawing groups generally required slightly higher reaction temperature, and the reaction with potassium alkyltrifluoroborates was found to be less efficient. In the same way, organic bromides were obtained in good yields using sodium bromide.[132] In these reactions, alkenyltrifluoroborates were rapidly converted to alkenyl halides with retention of stereochemistry, providing access to either (*E*)- or (*Z*)-alkenyl halides. These procedures were also applied to the preparation of iodine-123[133] or bromine-76[134] labeled compounds. In these reactions peracetic acid was preferred as oxidant over chloramine-T.[135]

Electrophilic sulfuration of organotrifluoroborates was described by M. Gingras et al., allowing formation of sulfides or disulfides (Scheme 76).[136] Indeed, reaction of potassium phenyltrifluoroborate with bis(phenylsulfonyl)sulfide in DMF at 130 °C afforded, after acidic treatment, diphenyl sulfide in 67% yield. On the other hand, reaction with sulfur monochloride (S_2Cl_2) under identical conditions gave diphenyl disulfide in 85% yield. Among the tested organoborate salts, potassium organotrifluoroborates proved to be the most reactive. The reaction is believed to operate via an ionic mechanism.[136]

5. Potassium Organotrifluoroborates in Transition-Metal-Catalyzed Reactions

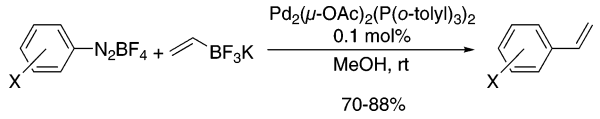
Very early it had been shown that potassium organotrifluoroborates participated in transition-metal-catalyzed reactions;[137] in other words, transmetalation of organotrifluoroborates to transition metals was feasible. Since this pioneering work, potassium organotrifluoroborates have been used in several transition-metal-catalyzed reactions such as Suzuki−Miyaura cross-coupling reactions,[3] addition to α,β-unsaturated substrates or aldehydes (Miyaura−Hayashi-type reactions),[138] and formation of ethers or amines. There has been an exponential growth of publications and patents in this area.

Scheme 77. Cross-Coupling of Arenediazonium with Aryltrifluoroborates



[a] Cond A: $Pd(OAc)_2$, dioxane. Cond B: $Pd_2(\mu\text{-}OAc)_2(P(o\text{-tolyl})_3)_2$, methanol.

Scheme 78. Vinylation of Arenediazonium Tetrafluoroborates



5.1. Palladium-Catalyzed Cross-Coupling Reactions

Palladium-catalyzed cross-coupling reactions (Miyaura−Suzuki-type reactions)[3] with potassium organotrifluoroborates constitute the major advance in organotrifluoroborate chemistry and have known increased applications, particularly in the pharmaceutical industry. After a survey of the various conditions developed and the compatible substrates, application of these reactions to the synthesis of organic materials and more particularly of biologically active compounds will be detailed.

5.1.1. Cross-Coupling with Arenediazonium Salts

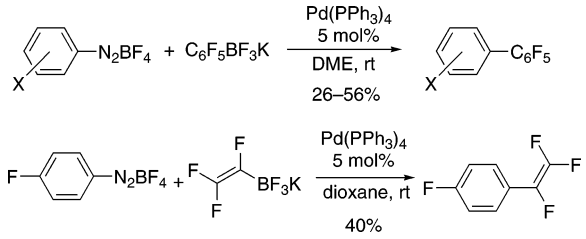
In 1997, Darses and Genet were the first to show that potassium aryltrifluoroborates were suitable substrates in palladium-catalyzed reactions (Scheme 77).[137] As coupling partners, the highly stable and nonexplosive arenediazonium tetrafluoroborates[139] were chosen because of their ready availability from inexpensive aromatic amines.[140] It was shown that in the presence of a catalytic amount of palladium and in the absence of any base, cross-coupling of arenediazonium with potassium aryltrifluoroborates occurred at room temperature to afford biaryls in high yields within 1−4 h.[28,44,137]

Two sets of catalyst/solvent systems worked efficiently: $Pd(OAc)_2$ in 1,4-dioxane and the palladacycle $Pd_2(\mu\text{-}OAc)_2(P(o\text{-tolyl})_3)_2$[141] in methanol. The reactivity of aryltrifluoroborates was far superior to that of the corresponding boronic acids,[139] giving higher yields of biaryls,[28,137] particularly when hindered substrates were involved.

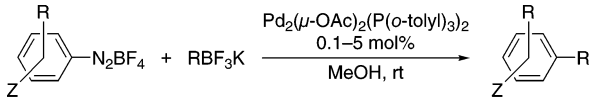
These conditions were also suitable for introduction of a alken-1-yl substituent on diazonium salts using potassium alkenyltrifluoroborates.[28,44] More particularly, potassium vinyltrifluoroborate proved to be a highly efficient vinylating agent of diazonium salts (Scheme 78). Indeed, palladium-catalyzed cross-coupling reactions of arenediazonium tetrafluoroborates with potassium vinyltrifluoroborate afforded styrene derivatives as the sole products in good yields at room temperature.[44] It is important to note that the cross-coupling reaction with vinylboronate esters was not selective, giving mixtures of compounds arising from Suzuki−Miyaura and Heck reactions in all cases.[142] The reactions were generally very fast (less than a few minutes), even in the presence of low catalyst loading at room temperature (TOF $> 3000\ h^{-1}$).

Cross-coupling of arenediazonium tetrafluoroborates and potassium aryltrifluoroborates could also be achieved in ionic liquid as reaction media.[143] High turnover frequency (TOF $= 6000\ h^{-1}$) was obtained using an azapalladacycle as the palladium source. Extension of this coupling to potassium polyfluorophenyltrifluoroborates was reported (Scheme 79).[144] Reaction conditions were optimized for that particular type of substrate, and the authors showed that moderate yields of biaryls could be obtained using $Pd(PPh_3)_4$ as catalyst in DME at room temperature.[144]

Scheme 79. Cross-Coupling with Polyfluorinated Organotrifluoroborates



Scheme 80. Chemoselectivity of the Coupling with Arenediazonium Salts



These lower yields of biaryls compared with those obtained with non-fluorinated aryltrifluoroborates may be attributed to the lower reactivity of $K[C_6F_5BF_3]$ and to its sensitivity to hydrodeboration. In another example,[144] the authors showed that (trifluoroethenyl)trifluoroborate, the fluorous analogue of vinyltrifluoroborate, could also couple with diazonium salts, even in lower yields (Scheme 79). This later example represents the first coupling of a perfluoroalken-1-yl organometallic reagent catalyzed by a transition metal.

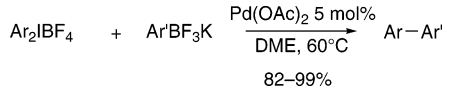
One interesting feature of these cross-coupling reactions is their high chemoselectivity toward diazonium in the presence of triflate, bromo, or iodo substituents (Scheme 80).[28,44,137] Indeed, it was possible to couple the diazonium group selectively with potassium organotrifluoroborates in the presence of triflate, bromo, and, in many cases, iodo substituents, allowing formation of products that can be further functionalized by iterative cross-coupling reactions. From these results it appeared that the diazonium group was clearly far more reactive, and the order of reactivity of the different electrophiles is as follows: $N_2^+ > I > Br, OTf$.

It has also been reported that palladium-catalyzed carbonylative amidation of arenediazonium salts with potassium aryltrifluoroborates, carbon monoxide, and ammonia gave aryl amides in good yields in the presence of *N*-heterocyclic carbene ligand.[145] However, the generality of this reaction using potassium organotrifluoroborates was not demonstrated (only one example given). A recoverable homogeneous palladium(0) catalyst for cross-coupling reactions of arenediazonium salts with potassium organotrifluoroborate has been described.[146] Use of electrospray ionization mass spectrometry (ESI-MS) allowed the direct detection and identification of several palladium intermediates involved in the reaction.

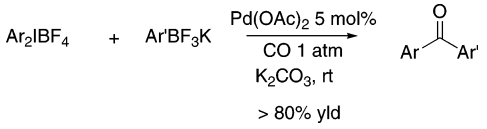
5.1.2. Cross-Coupling with Hypervalent Iodonium Compounds

Hypervalent iodonium salts were used efficiently as partners in palladium-catalyzed cross-coupling reactions. Z.-C.

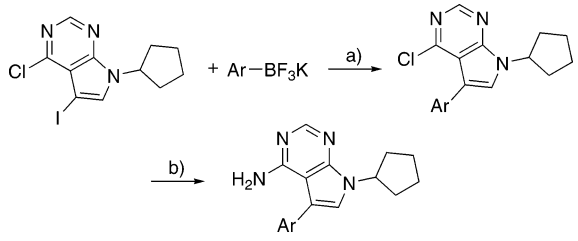
Scheme 81. Cross-Coupling with Aryliodonium Salts



Scheme 82. Carbonylative Cross-Coupling Reactions



Scheme 83. Preparation of Pyrrolo[2,3-d]pyrimidine via Palladium-Catalyzed Cross-Coupling with K[RBF$_3$]



Ar = 2-PhOC$_6$H$_4$, 3-PhOC$_6$H$_4$

a) cat. $PdCl_2(PPh_3)_2$, Na_2CO_3, Tol/EtOH/H_2O, 105°C. b) aq. NH_3, 120°C.

Chen et al.[147] have shown that in the presence of 5 mol % of palladium acetate in DME at 60 °C coupling of diaryliodonium tetrafluoroborates with potassium aryltrifluoroborates afforded high yields of biaryls (Scheme 81). As in the case of diazonium salts, addition of a base was not necessary for the cross-coupling, and as coupling partners, hydroxy(tosyloxy)iodoarene ArI(OH)OTs also participated in this reaction.[147]

Diaryliodonium salts could also serve as substrates for carbonylative cross-coupling reactions with potassium aryltrifluoroborates (Scheme 82).[148] Optimization of the reaction revealed that, in the palladium carbonylative process, the presence of a base was necessary to suppress direct formation of biaryl compounds.

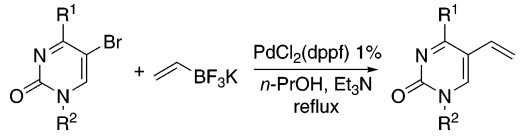
The tetrafluoroborate counterion proved to be superior to chloride or tosylate anions, and hydroxy(tosyloxy)iodoarenes were not suitable as they afforded only direct cross-coupling products.

5.1.3. Cross-Coupling with Organic Halides and Sulfonates

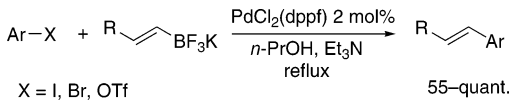
Efficient cross-coupling reactions with arenediazonium or aryliodonium could be accomplished at low temperature and in the absence of any added base. Unfortunately, the cross-coupling of potassium organotrifluoroborates with aryl halides or triflates (with one exception, vide infra) required addition of a base for the reaction to proceed. In its absence, no cross-coupling products were obtained.[28,149] Thus, under basic conditions, aryl-, alken-1-yl-, alkyl-, allyl-, and alkyn-1-yltrifluoroborates have been shown to participate efficiently in palladium-catalyzed cross-coupling reactions.[7]

5.1.3.1. Coupling with Potassium Alkenyl- and Aryltrifluoroborates. The first cross-coupling reaction of potassium organotrifluoroborates with organic halides was reported in the patent literature. In 1998, an international patent by Knoll A.-G. Chemische Fabriken (BASF) reported the cross-coupling of an aryl halide with potassium aryltrifluoroborates in the presence of a base (Scheme 83).[150] Indeed, reaction of 5-iodopyrrolo[2,3-d]pyrimidine with potassium

Scheme 84. Vinylation of Bromopyrimidines



Scheme 85. Cross-Coupling of Alkenyltrifluoroborates with Aryl Halides



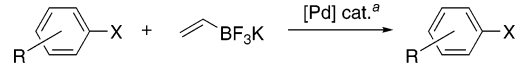
aryltrifluoroborates was efficiently catalyzed by $PdCl_2(PPh_3)_2$ in the presence of Na_2CO_3 as a base. The pyrrolo[2,3-d]-pyrimidine thus prepared was a tyrosine kinase inhibitor, useful in treating proliferative diseases and disorders of the immune systems in mammals.

In 2000, Scalone and co-workers, at Hofmann-La Roche, described the introduction of a vinyl substituent on pyrimidine derivatives using potassium trifluoro(vinyl)borate (Scheme 84).[151] Reaction conditions were optimized, and it was found that $PdCl_2$(dppf) (dppf = bis(diphenylphosphino)ferrocene) showed the best activity; the highest conversions and purities were achieved in high boiling alcoholic solvents like propanol or butanol. The influence of the base was less pronounced, but aliphatic amines (*i*-Pr_2NEt, *t*-$BuNH_2$, or Et_3N) were the most effective.

These conditions (association of an alcoholic solvent and an amine as a base) proved to be quite general for introduction of an alkenyl moiety on aryl halides or pseudo-halides. Indeed, G. A. Molander et al. showed that under these conditions ($PdCl_2$(dppf), isopropanol/H_2O, and *t*-$BuNH_2$), potassium alken-1-yltrifluoroborates effected the cross-coupling reaction with aryl iodides, bromides, and triflates, allowing efficient access to alken-1-yl-substituted aromatic compounds (Scheme 85).[45,152] Use of Et_3N as base in association with anhydrous *n*-PrOH also provided good results, and a variety of diverse heteroaryl halides reacted efficiently with potassium alken-1-yltrifluoroborates. High yields were achieved with aryl iodides and non-electron-rich aryl bromides and triflates, but no reaction occurred with aryl chlorides. It is important to note that, as in the case of palladium-catalyzed cross-coupling of alken-1-ylboronic acids,[3] the reaction is stereospecific as coupling of (*Z*)-styryltrifluroborate afforded only cross-coupling adduct with (*Z*) stereochemistry.[152] Alkenylation of aryl iodides could also be achieved under microwave irradiation using otherwise identical conditions.[153]

As in the case of arenediazonium salts,[44] potassium trifluoro(vinyl)borate proved to be an efficient vinylating agent of aryl halides and triflates.[45] Indeed, in the presence of 2 mol % of $PdCl_2$(dppf) in *n*-propanol and using triethylamine as a base, various functionalized styrenes were obtained in moderate to good yields (Scheme 86). These conditions were further improved, and a more general procedure for the vinylation of aryl halides and pseudo-halides was described by G. A. Molander et al.[154] It was found that higher yields of styrenes were obtained using $PdCl_2$ in association with PPh_3 in the presence of Cs_2CO_3 as a base in THF/H_2O at 85 °C. Vinylation of hindered aryl bromides was best performed using cesium carbonate as a base in THF/H_2O as solvent, but moderate yields were generally observed.[155] On the other hand, using Buchwald's RuPhos ligand,[156] good yields of styrenes were observed on

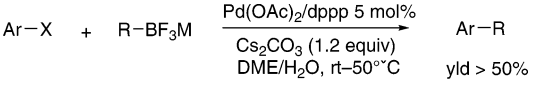
Scheme 86. Vinylation of Aryl Halides and Triflate



X = I, Br, OTf

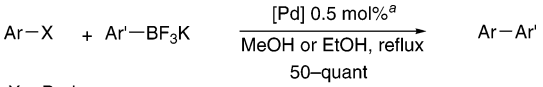
[a] From ref 45: $PdCl_2$(dppf) 2 mol %, Et_3N (1 equiv), *n*-PrOH, reflux. From refs 45 and 155: $PdCl_2$(dppf)·CH_2Cl_2 9 mol %, Cs_2CO_3 (3 equiv), THF/H_2O (10:1), reflux. From ref 154: $PdCl_2$ 2 mol %, PPh_3 6 mol %, Cs_2CO_3 (3 equiv), THF/H_2O (9:1), 85 °C.

Scheme 87. Coupling of Aryl- and Alken-1-yltrifluoroborates



X = Br, I
R = aryl, alken-1-yl
M = K, *n*-Bu_4N

Scheme 88. Biaryl Synthesis via Use of Potassium Aryltrifluoroborates



X = Br, I
Ar, Ar' = aryl or heteroaryl

[a] From refs 30 and 31: cond A, $Pd(OAc)_2$, K_2CO_3 (3 equiv); cond B, $Pd(OAc)_2$/PPh_3, K_2CO_3 (3 equiv); cond C, $PdCl_2$(dppf).CH_2Cl_2, Et_3N (3 equiv).

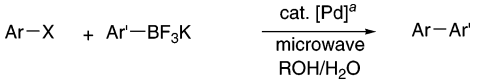
those hindered substrates.[154] This ligand also proved to be adapted for the vinylation of 4-chloroacetophenone.[154]

Concomitant to the work of Molander and co-workers, Batey et al.[106] described another catalytic system for the cross-coupling of alkenyl- and aryltrifluoroborates with aryl halides (Scheme 87). Indeed, in the presence of Cs_2CO_3 as a base and $Pd(OAc)_2$/dppp (dppp = 1,2-bis(diphenylphosphino)propane) as catalyst, aryl bromides and triflates were cross-coupled in a DME/H_2O solvent mixture.

Higher yields (25−50%) were generally achieved using tetrabutylammonium salts instead of potassium, but interestingly, the reactivity of the latter was restored using tetrabutylammonium iodide as phase-transfer agent.[106] It was also found that use of water as a cosolvent was essential for the reaction to proceed. Reactions performed in the absence of water showed low conversion in the case of the TBA salts and no reaction with potassium salts. In the case of aryl halides bearing electron-withdrawing substituents, cross-coupling reactions were conducted at room temperature.

Use of expensive cesium carbonate could be avoided in cross-coupling reactions with aryltrifluoroborates. In a detailed study, G. A. Molander et al.[31] have shown that several conditions may be used for the cross-coupling reaction of potassium aryltrifluoroborates with aryl halides (bromide and iodides) using only 0.5 mol % palladium catalyst (Scheme 88). In general, optimal conditions were found to involve use of alcohols as solvents. Ligandless conditions (condition A) were found to be the most suitable in the vast majority of the studied reactions with either aryl or heteroaryl bromides.[30,31] In the case of ortho-substituted substrates or electron-rich aryl bromides, the presence of a phosphane ligand (condition B or C) was necessary to obtain high yields of the cross-coupling product and minimize the homocoupling of the aryl bromide.[31] It is also important to note that under both ligand and ligandless conditions, the reactions could be performed in air without a reduction in the yield. Treatment of the reaction mixture was generally

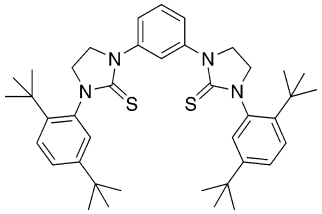
Scheme 89. Biaryl Synthesis under Microwave Irradiation



X = Br, I
Ar, Ar' = aryl or heteroaryl
50–quant

[a] From ref 157 (X = I): $PdCl_2(dppf)_2$·CH_2Cl_2 2 mol %, *i*-Pr_2NEt (3 equiv), *i*-PrOH/H_2O 2:1, 100 °C, 10 min. From ref 158 (X = Br): 2.5 ppm Pd, Na_2CO_3 (3.7 equiv), *n*-BuN_4Br (1 equiv), EtOH/H_2O 1:1, 150 °C, 5 min. From ref 159 (X = Br): $PdCl_2$ (1.2 mol %), K_2CO_3 (3 equiv), MeOH/H_2O 1:1, 125 °C, 20 min.

Chart 2. *N,N′*-Disubstituted Bis-Thiourea Ligand[160]



straightforward, as in many cases the products precipitated upon addition of water to the cooled reaction medium.

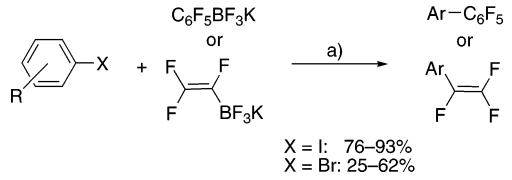
G. W. Kabalka et al. have also shown that under microwave irradiation aryl iodides coupled rapidly and efficiently with aryltrifluoroborates using $PdCl_2$(dppf) as catalyst, 3 equiv of *i*-Pr_2NEt in isopropanol−water mixture at 100 °C for 10 min (Scheme 89).[157] Under these microwave conditions, it was also reported that ultralow catalyst loading (up to 2.5 ppm) could be used in the cross-coupling reaction with aryl bromide or iodide.[158] At these ultralow palladium concentrations, lowering either the amount of base (from 3.7 to 3 equiv) or the temperature (from 150 to 135 °C) has a deleterious effect on product yield. However, these conditions were not suitable for sterically demanding aryl bromide or potassium alkyltrifluoroborates. Cross-coupling of bromoarenes with aryltrifluoroborates has also been reported under ligand-free conditions and in the absence of tetraalkylammonium salts using catalytic $PdCl_2$ (Scheme 89).[159] Higher yields were generally observed using water as cosolvent.

Low catalytic loading in palladium (0.1 mol %) were also achieved using a *N,N′*-disubstituted bis-thiourea (Chart 2) as ligand in the cross-coupling of potassium aryltrifluoroborates with electron-deficient aryl bromides.[160] Once again, it was found that under identical conditions trifluoroborate salts were more reactive than the corresponding boronic acids. Cross-coupling of potassium aryltrifluoroborates with aryl iodides or electron-deficient aryl bromides have been reported using palladium metal colloids supported on poly(vinylpyrrolidone).[161] Good yields of biaryls were obtained in pure water as solvent and potassium carbonate as a base at 100 °C. The palladium metal could be recovered and recycled for eight consecutive trials without significant loss of activity.

Cross-coupling of pentafluorophenyltrifluoroborate and (trifluoroethenyl)trifluoroborate with aryl iodides or bromides occurred only under modified conditions: addition of Ag_2O was necessary (Scheme 90).[162] The presence of K_2CO_3 is not essential using Ag_2O, but it seems to prevent hydrodeboronation of the trifluoroborate salt.[162] Cross-coupling with potassium pentafluorophenyltrifluoroborate was applied to the preparation of molecular tweezers.[163]

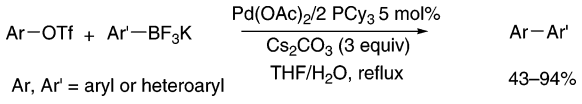
Cross-coupling with aryltrifluoroborates was extended to aryl triflates as electrophiles by G. A. Molander in the synthesis or biaryl and heterobiaryl compounds (Scheme

Scheme 90. Cross-Coupling with Polyfluorinated Organotrifluoroborates

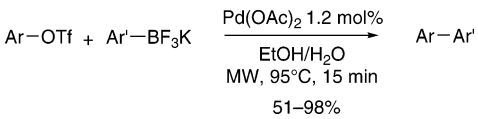


[a] $Pd(OAc)_2$ 10 mol %, PPh_3 20 mol %, Ag_2O (1.2 equiv), K_2CO_3 (2 equiv), toluene, 100 °C.

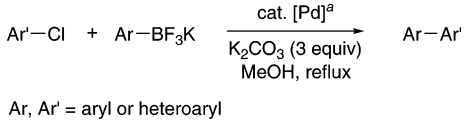
Scheme 91. Biaryl Synthesis from Aryl Triflates



Scheme 92. Base-Free Biaryl Synthesis under Microwave Irradiation

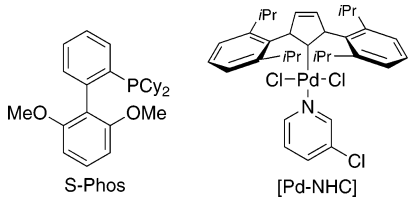


Scheme 93. Palladium-Catalyzed Cross-Coupling Reaction of K[RBF_3] with Aryl Chlorides



[a] From ref 166: $Pd(OAc)_2$ 1 mol %, S-Phos 2 mol %, 73−98%. From ref 169: [Pd−NHC] 2 mol % (3 examples).

Chart 3. Ligands for the Cross-Coupling Reaction with Aryl Chlorides

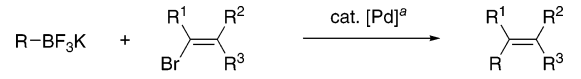


91).[164] Under ligandless conditions, only electron-poor aryl triflates underwent the coupling. Optimization of the catalytic system has shown that the association of $Pd(OAc)_2$ with tricyclohexylphosphane (PCy_3) as ligand in the presence of Cs_2CO_3 allowed formation of cross-coupled products with good yields. Interestingly, when 4-bromophenyl triflate was used as the electrophile, coupling occurred at the bromide rather than the triflate.

G. W. Kabalka et al. have also shown that aryl triflate could be cross-coupled, in the absence of base, under microwave irradiation (Scheme 92).[165] Indeed, under ligandless conditions, the palladium-catalyzed reaction of aryl triflates with potassium aryltrifluoroborates furnished high yields of biaryls within 15 min. These conditions should be very useful as aryl triflates are base sensitive and thermally liable so that long reaction times and basic conditions lead to their destruction. However, it is not clear at present if aryl triflates cross-couple under thermal conditions and in the absence of base.

Palladium-catalyzed cross-coupling with aryl chlorides was readily achieved by Buchwald and co-workers using S-Phos ligand (Scheme 93, Chart 3).[166] Indeed, in the presence of $Pd(OAc)_2$ and 2 equiv S-Phos, using K_2CO_3 as base and

Scheme 94. Palladium-Catalyzed Cross-Coupling Reactions with Alkenyl Bromides



[a] Cond A (R = aryl): $Pd(PPh_3)_4$ 2 mol %, K_2CO_3 or Cs_2CO_3 (3 equiv), toluene−H_2O, 90 °C. Cond B (R = alken-1-yl): $Pd(OAc)_2$/2 PPh_3 5 mol %, Cs_2CO_3 (3 equiv), THF−H_2O, 70 °C.

methanol or ethanol as solvent, high yields of biaryls were obtained, even with electron-rich or hindered aryl chlorides. For example, 2,2′,6-trimethylbiphenyl could be prepared in 92% yield via the coupling of potassium *o*-tolyltrifluoroborate with 2-chloro-*m*-xylene at 50 °C. Potassium 3-pyridyltrifluoroborate also participated in the coupling, whereas the corresponding boronic acid was inert.

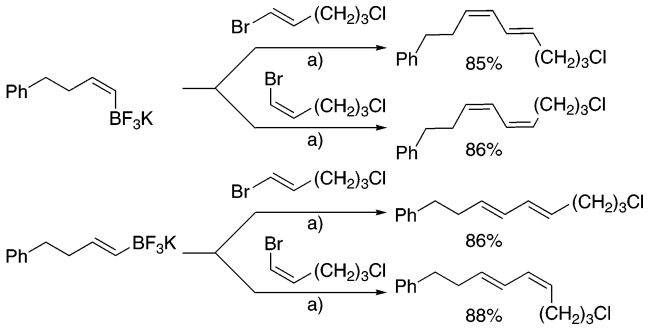
Fu et al. have also shown that palladium-catalyzed cross-coupling reaction of 3-pyridyltrifluoroborate with an aryl chloride could be achieved using $P(Cy)_3$ as ligand.[167] However, only one example was given, and in that case, K_3PO_4 was found to be the most suitable base. With electron-deficient heterocyclic chlorides, the reaction could be conducted in the absence of added ligand. Indeed, the cross-coupling of 3,5-dichloroisothiazole-4-carbonitrile with potassium phenyltrifluoroborate was efficiently catalyzed by palladium acetate in the presence of K_2CO_3 (1−1.5 equiv) and 18-crown-6 (0.5 equiv) in refluxing anhydrous toluene.[168]

Air- and moisture-stable palladium *N*-heterocyclic carbene (Pd−NHC, Chart 3) has shown promising catalytic activity in the coupling of aryl chlorides with boronic acids and also with potassium aryltrifluoroborates (Scheme 93).[169] Indeed, using the conditions described by Buchwald,[166] i.e., K_2CO_3 as a base in methanol as solvent, good yields of biaryls and heterobiaryls were obtained using diisopropylphenylimidazolium ligand for the palladium.

Efficient palladium-catalyzed cross-coupling reactions with alkenyl bromides have also been described. Arylation of alkenyl bromide was best achieved using $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as a base in a toluene−H_2O mixture at 90 °C (Scheme 94).[170] These conditions were suitable for electron-rich or neutral boron derivatives. However, electron-poor aryltrifluoroborates were best coupled using $P(t\text{-}Bu)_3$ as ligand or $PdCl_2$(dppf) as catalyst precursor. Noteworthy, the reactions could be carried out rapidly using as little as 0.5 mol % of catalyst loading. When (*Z*)-bromoalkenes were employed, the (*Z*)-styryl moiety was formed stereospecifically.

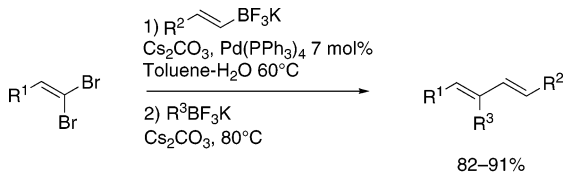
The stereoselective synthesis of conjugated dienes was reported using air-stable potassium alken-1-yltrifluoroborates as coupling partners (Scheme 95).[171] Indeed, the palladium-catalyzed cross-coupling reaction of potassium (*E*)- and (*Z*)-alken-1-yltrifluoroborates with either (*E*)- or (*Z*)-alkenyl bromides proceeded readily with moderate to excellent yields to give the corresponding (*E*,*E*)-, (*E*,*Z*)-, (*Z*,*E*)-, or (*Z*,*Z*)-conjugated dienes stereospecifically. Best conditions employed a combination of $Pd(OAc)_2$ and PPh_3 as catalyst precursors in a THF−H_2O mixture as solvent in the presence of Cs_2CO_3 as a base at 70 °C, and conditions using $PdCl_2$(dppf) in alcoholic solvents led to only moderate yields and low stereoselectivity. As observed in other palladium-catalyzed cross-coupling reactions with potassium organotrifluoroborates, the silyl ether groups survived the reaction conditions, even though a fluoride counterion and a base is present during the course of the reaction

Scheme 95. Stereoselective Synthesis of Conjugated Dienes



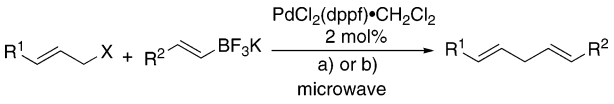
a) $Pd(OAc)_2/_2$ PPh_3 5 mol%, Cs_2CO_3 (3 equiv), THF-H_2O 10:1, 70 °C.

Scheme 96. Sequential Suzuki−Miyaura Cross-Coupling Reactions



R^1, R^2, R^3 = alkyl

Scheme 97. Cross-Coupling Reaction of Allyl Acetates and Chlorides



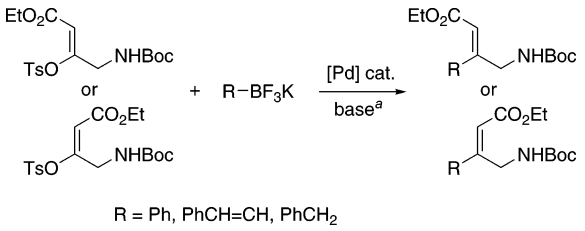
R^1 = Ph, H; R^2 = Ph, alkyl.
X = Cl, OAc.

a) X = OAc: *i*-Pr_2NEt/*i*-PrOH (2:1), 80°C, 10 min. b) X = Cl: *i*-PrOH/H_2O (2:1), *i*-Pr_2NEt (3 equiv), 100°C, 20 min.

One-pot syntheses of trisubstituted conjugated dienes via sequential Suzuki−Miyaura cross-coupling with alkenyl- and alkyltrifluoroborates were achieved by G. A. Molander et al. (Scheme 96).[172] Indeed, the sequential and stereoselective palladium-catalyzed cross-coupling of 1,1-dibromoalkenes with potassium alken-1-yltrifluoroborates followed by alkyltrifluoroborates in the presence of $Pd(PPh_3)_4$ as catalyst and Cs_2CO_3 as a base in toluene−H_2O at 60−80 °C afforded the trisubstituted conjugated dienes in excellent yields. In each reaction an undesired byproduct was formed that originated from coupling of 1,1-dibromoalkene with 2 equiv of alkenyltrifluoroborates in about 10% yield. This amount could be lowered to <5% using only 1 equiv of alkenylborate. The second cross-coupling had to be conducted at higher temperature (80 °C) for the reaction to proceed. For the reaction of unfunctionalized potassium alkyltrifluoroborate, increasing the temperature to 90 °C, further addition of $PdCl_2$(dppf), and use of anhydrous conditions were necessary to achieve the cross-coupling.

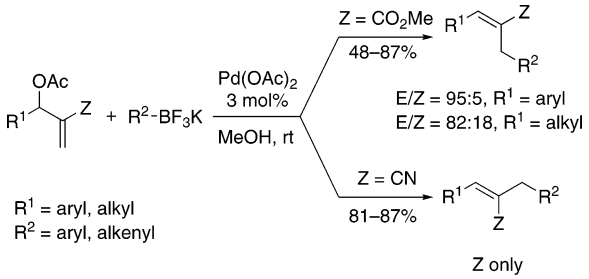
Formation of the 1,4-diene framework was readily achieved via cross-coupling reaction of allyl acetates[173] or chlorides[174] with potassium alken-1-yltrifluoroborates (Scheme 97). Reaction of these allylic substrates was best conducted using $PdCl_2$(dppf)·CH_2Cl_2 as catalyst and Hünig's base (*i*-Pr_2NEt) under microwave heating. The coupling reactions were stereoselective in that the *E* isomers were the only observed product and regioselective, although traces of the isomeric products were formed in the product derived from cinnamyl acetate.

Scheme 98. Palladium-Catalyzed Cross-Coupling with Enol Tosylates



[a] For conditions, see ref 175.

Scheme 99. Cross-Coupling Reaction with Acetates of Baylis−Hillman



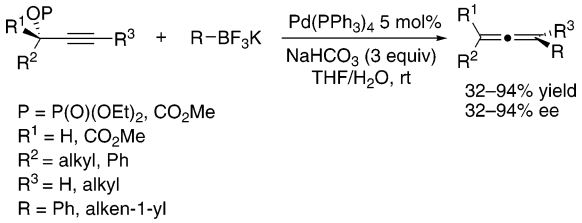
Enol tosylates were also shown to be viable partners in palladium-catalyzed cross-coupling reactions with potassium organotrifluoroborates (Scheme 98).[175] Employing conditions optimized by G. A. Molander et al.,[31,152] coupling of potassium phenyltrifluoroborate with both (*E*)- and (*Z*)-enol tosylates provided the desired ester product in good yield, which was shown to be comparable to that of the cross-coupling reaction with phenylboronic acid. Introduction of an alken-1-yl or benzyl moiety on enol tosylates was also achieved using the appropriate trifluoroborate reagent.

4-Tosyloxycoumarins and 4-tosyloxyquinolin-2(1*H*)-one were also arylated using potassium aryltrifluoroborates.[176] Indeed, in the presence of $Pd(PPh_3)_4$ and KF as a base, the palladium-catalyzed cross-coupling afforded good yields of 4-substituted coumarins and quinolin-2(1*H*)-one.

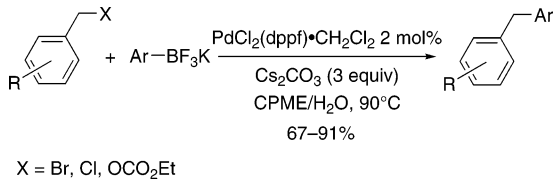
Kabalka et al. found that cross-coupling of potassium organotrifluoroborates with acetates of Baylis−Hillman adducts proceeded readily in moderate to excellent yields to afford trisubstituted alkenes (Scheme 99).[177] Indeed, in the presence of 3 mol % $Pd(OAc)_2$ in methanol at room temperature, 3-acetoxy-2-methylenealkanoates reacted with a variety of potassium aryl- and alken-1-yltrifluoroborates to provide (*E*)-2-substituted 2-alkenoates as the major product. Lower stereoselectivities were generally observed with aliphatic substituted Baylis−Hillman adducts. On the other hand, reaction of 3-acetoxy-2-methylenealkanenitriles provided (*Z*)-2-substituted alk-2-enenitriles.

G. A. Molander et al. described an elegant synthesis of chiral ene-allenes via palladium-catalyzed cross-coupling reaction with potassium alken-1-yltrifluoroborates (Scheme 100).[178] In the presence of $Pd(PPh_3)_4$ as catalyst, $NaHCO_3$ as a base in a THF/water mixture, reaction of propargylic carbonates and phosphates furnished allenes in moderate to good yield. Using chiral propargylic phosphates, enantioenriched allenes were formed, while with carbonates nearly racemic products were obtained. Under these conditions, allenes possessing high ee were initially formed, followed by racemization of the formed allene. These conditions also proved to be suitable for the coupling of potassium phenyltrifluoroborate, while potassium alkyl- and alkynyltrifluoroborates failed to coupled.

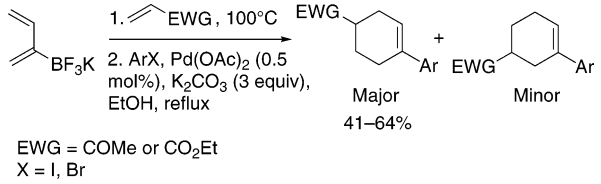
Scheme 100. Synthesis of Chiral Ene−Allenes via Palladium-Catalyzed Cross-Coupling Reaction



Scheme 101. Palladium-Catalyzed Cross-Coupling Reaction of Benzyl Halides



Scheme 102. Tandem Diels−Alder Reactions and Subsequent Palladium-Catalyzed Reaction

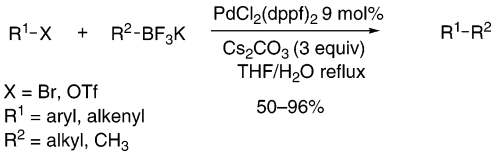


Palladium-catalyzed cross-coupling reactions of benzyl halides with potassium aryltrifluoroborates afforded straightforward access to methylene-linked biaryl compounds (Scheme 101).[179] The best conditions for this reaction involved use of $PdCl_2(dppf)\cdot CH_2Cl_2$ as catalyst and cesium carbonate as base, ethereal solvent (particularly CPME, cyclopentyl methyl ether) tending to offer the highest isolated yields with minimal homocoupling. Benzyl bromides were found to be the most suitable, benzyl chloride being limited to the coupling of electron-rich potassium aryltrifluoroborates. Benzyl carbonates used as coupling partners showed limited success: carbonate starting material as well as protodeboronated product were isolated from failed reactions. It is important to note that previously reported conditions using trivalent organobonanes generally required using excess reagent.

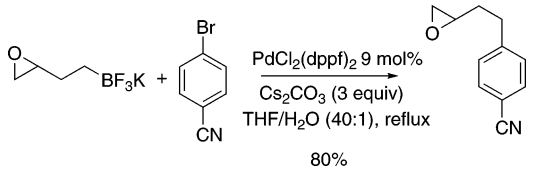
Tandem Diels−Alder reactions of potassium 1,3-dienyl-2-trifluoroborate and subsequent palladium-catalyzed reaction have been described (Scheme 102).[46] Heating the dienyltrifluoroborate and a dienophile (mainly ethyl acrylate and methyl vinyl ketone) afforded the intermediate cyclohex-en-1-yltrifluoroborates which, on addition of $Pd(OAc)_2$ (0.5 mol %), K_2CO_3 (3 equiv), and an aryl halide in refluxing ethanol, provided the expected cross-coupled product in moderate yield. The yields were generally slightly higher for acrylate rather than methyl vinyl ketone adducts. Moreover, the preference for the para over the meta regioisomer ranged from 3 to 5:1. In this tandem process, tetra-*n*-butylammonium organotrifluoroborates afforded identical results.[46]

Other isolated examples of palladium-catalyzed coupling reaction with potassium organotrifluoroborate have been reported, such as a regio- and stereoselective route to tetrasubstituted olefins using three-component coupling,[180] access to 3-substituted-1,2,4-triazines,[181] and arylation of bromophenols.[182]

Scheme 103. Cross-Coupling with Potassium Alkyltrifluoroborates



Scheme 104. Cross-Coupling of Potassium Epoxytrifluoroborates



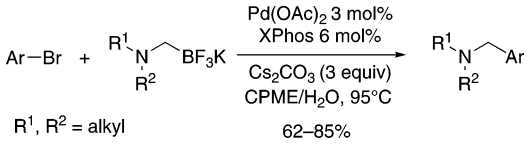
5.1.3.2. Coupling with Potassium Alkyltrifluoroborates. Introduction of an alkyl substituent via palladium-catalyzed cross-coupling reaction is not generally a straightforward reaction because of the undesirable β-elimination side reaction. Trivalent alkylboron derivatives have shown to be good candidates in these reactions but still suffer from sensitivity toward air and moisture.[3] Indeed, the highly stable potassium alkyltrifluoroborates would be more desirable in such processes. G. A. Molander et al.[37a] have shown that the palladium-catalyzed reaction of potassium alkyltrifluoroborates with aryl- and alkenyltriflates could be readily achieved using 9−10 mol % of $PdCl_2(dppf)$ and 3 equiv of Cs_2CO_3 as a base in a THF/water mixture (Scheme 103).

The presence of water in the reaction was found to be essential, and under these conditions alkylboronic acids and esters also participated in the cross-coupling. Aryl bromides proved to be more reactive than triflates as the coupling of 4-bromophenyltrifluoroborate only afforded products bearing triflate substituent.[37] Thus, in this system, the reactivity of the electrophiles decreases in the order I > Br > OTf ≫ Cl. Finally, secondary alkylborates were found to be reluctant partners in this coupling, β-elimination and dehydroboration products being the major reaction pathways. Methylation of aryl bromides was efficiently achieved using highly stable potassium methyltrifluoroborate (Scheme 103).[37b] Reactions with electron-rich electrophiles generally proved more difficult. Methylation of alkenyl bromide was best achieved in a toluene/water mixture.

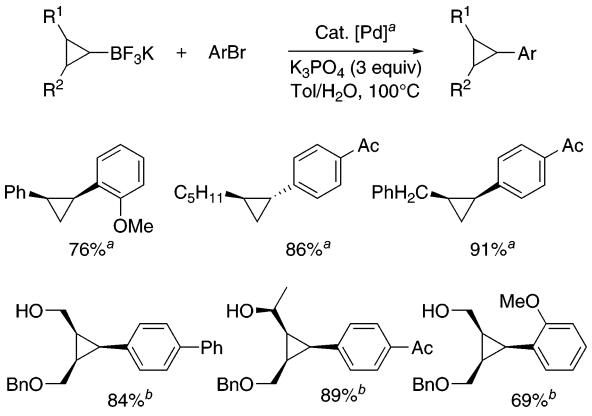
These conditions were employed for coupling of potassium (cyclopentylmethyl)trifluoroborate, readily obtained via organolanthanide-catalyzed cyclization/boration of 1,5-dienes,[183] or coupling of β-aminoethyltrifluoroborates.[184] These conditions proved to be suited for coupling of potassium epoxytrifluoroborates,[86] giving the Suzuki cross-coupled product in good yield, simply decreasing the amount of water to prevent ring opening of the epoxide (Scheme 104). Potassium 4-(1′,2′-dihydroxyethyl)phenyltrifluorobororate, readily obtained via dihydroxylation procedure, also underwent clean palladium-catalyzed cross-coupling reaction.[87]

The Suzuki−Miyaura cross-coupling reaction of *N*,*N*-dialkylaminomethyltrifluoroborates with aryl or heteroaryl bromides has been accomplished (Scheme 105).[91] Best conditions for this cross-coupling reaction employed $Pd(OAc)_2$ and XPhos ligand[156] in the presence of 3 equiv of Cs_2CO_3, allowing construction of an aminomethyl aryl linkage with good yields. Yields were generally improved

Scheme 105. Aminomethylation of Aryl Bromides

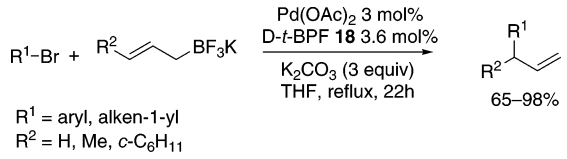


Scheme 106. Cross-Coupling of Potassium Cyclopropyltrifluoroborates with Aryl Bromides



[a] From ref 71: $Pd(PPh_3)_4$ 2 mol %. From ref 72: $Pd(OAc)_2$ 3 mol %, 2-biphenyldicyclohexylphosphane 6 mol %.

Scheme 107. Cross-Coupling Reaction of Potassium Allyltrifluoroborates



using cyclopentyl methyl ether (CPME) at 95 °C instead of THF.

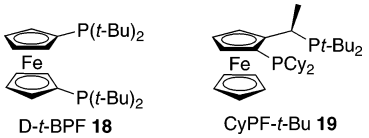
Conditions for the palladium-catalyzed cross-coupling reaction of potassium cyclopropyltrifluoroborates were also described. Deng et al. have shown that in the presence of $Pd(PPh_3)_4$ and using K_3PO_4 as a base, good yields of cyclopropyl-substituted arenes were obtained from the reaction of aryl bromides with potassium cyclopropyltrifluoroborates (Scheme 106).[71] K_3PO_4 was chosen as an alternative base to the expensive Cs_2CO_3, which worked equally well. Other palladium catalysts could be used in this coupling, such as $PdCl_2$(dppf) and $Pd(OAc)_2$ in conjunction with 2-biphenyldicyclohexylphosphane.[71] The latter was also chosen for the coupling of 1,2,3-trisubstituted cyclopropyltrifluoroborates (Scheme 106).[72] In that case, some competitive reduction of the trifluoroborate moiety was also observed.

5.1.3.3. Coupling with Potassium Allyltrifluoroborates. Miyaura and Yamamoto described an efficient protocol for the allylation of organic halides.[185] Indeed the cross-coupling reaction of potassium allyltrifluoroborates with aryl or alken-1-yl bromides occurred at the γ carbon of the allylborane moiety with perfect regioselectivities (>99%) in the presence of a palladium/D-*t*-BPF **18** (D-*t*-BPF = 1,1′-bis(di-*tert*-butylphosphino)ferrocene) complex and K_2CO_3 in refluxing THF (Scheme 107, Chart 4).

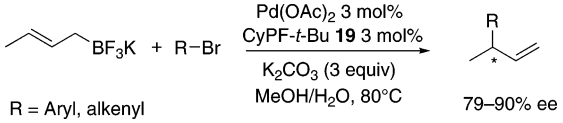
It was noted that steric hindrance of ortho substituents did not affect the yields and selectivities. Moreover, coupling with bromoalkenes resulted in lower yields, but the regioselectivity in favor of the γ-adduct was nearly perfect.

Asymmetric reactions of potassium (*E*)-crotyltrifluoroborate with aryl and 1-alken-1-yl bromides has also been

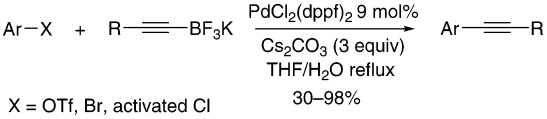
Chart 4. Ligands for the Cross-Coupling of Allyltrifluoroborates



Scheme 108. Asymmetric Crotylation of Aryl and Alkenyl Bromides



Scheme 109. Cross-Coupling with Potassium Alkynyltrifluoroborates



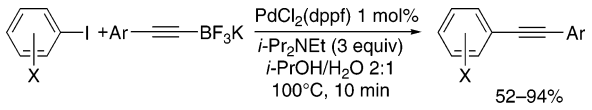
described by the same authors (Scheme 108)[186] in the presence of $Pd(OAc)_2$ and Josiphos-type ligand CyPF-*t*-Bu **19** (Chart 4), K_2CO_3 (3 equiv) as a base, in methanol/water (9:1). Reaction of $K[CH_3CH{=}CHCH_2BF_3]$ occurred once again regioselectively at the γ carbon of the 2-butenylborane moiety with regioselectivities in a range of 84−99%. Moreover, enantioselectivities in a range of 77−90% ee were attained for various substrates using the Josiphos-type ligand, lower ee's being observed for ortho-substituted aryl bromides

5.1.3.4. Coupling with Potassium Alkynyltrifluoroborates. Palladium-catalyzed reactions of terminal alkynes with organic halides, known as the Sonogashira reaction,[187] have proved to be a powerful method for preparation of substituted alkynes. Nevertheless, in cases where the Sonogashira reaction fails to provide products, alternative approaches using alkynylmetal reagents have been developed, including zinc, tin, and boron. Molander et al.[54] have shown that the crystalline potassium alkyn-1-yltrifluoroborates[28] participated in palladium-catalyzed cross-coupling reactions with aryl halides and triflates (Scheme 109). Under the conditions described for the coupling of alkyltrifluoroborates, that is $PdCl_2$(dppf) as catalyst and Cs_2CO_3 as a base, moderate to good yields of substituted alkynes were obtained.

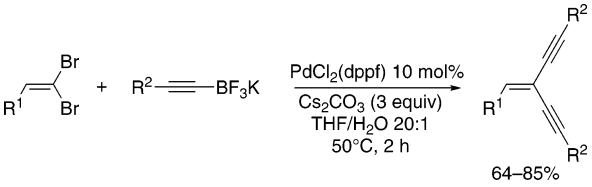
Once again, the presence of water was found to have a beneficial effect by increasing the reaction rates. Cross-coupling with aryl triflates was best conducted under anhydrous conditions to prevent their hydrolysis. Catalyst loading could be reduced to 0.005 mol % in the case of triflate derivatives, while with aryl bromides, a decrease in the catalyst loading resulted in a proportional decrease in the yield. Under these conditions activated heterocyclic aryl chlorides were alkynylated in good yields. This time, the order of reactivity was found to be OTf > Br > I, which is different from that observed for the cross-coupling of alkyltrifluoroborates.[37]

Kabalka and co-workers have shown that under microwave irradiation aryl iodides were alkynylated in the presence of $PdCl_2$(dppf) (1 mol %) and *i*-Pr_2NEt as base in a mixture of isopropanol/water as solvent at 100 °C for 10 min (Scheme 110).[188] Under these conditions, the product yields were generally similar to those obtained in the thermal conditions.

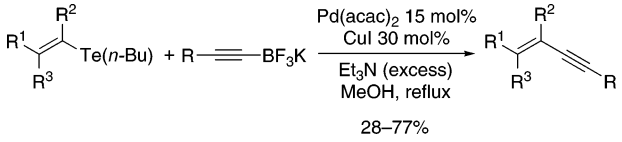
Scheme 110. Cross-Coupling of Potassium Alkynyltrifluoroborates under Microwave Irradiation



Scheme 111. Synthesis of Cross-Conjugated Enediynes



Scheme 112. Synthesis of 1,3-Enynes from Vinylic Tellurides



An efficient synthesis of cross-conjugated enediynes has been developed using the palladium-catalyzed cross-coupling reaction of 1,1-dibromo-1-alkenes with potassium alkynyltrifluoroborates (Scheme 111).[189] It was found that under the standard conditions described by G. A. Molander et al.,[54] good yields of enediynes were achieved using 10 mol % $PdCl_2$(dppf) and cesium carbonate as base at 50 °C in a THF/water mixture as solvent. Such compounds have received attention due to their applications in nonlinear optics, macrocyclic ligands, optical switches, and synthesis of polycyclic aromatic compounds.

4-(1-Alkynyl)-2(5*H*)-furanones and coumarins have been prepared via palladium-catalyzed cross-coupling with potassium alkynyltrifluoroborates.[190] It is important to note that the reaction with bromofuranones could be achieved in the absence of added base.

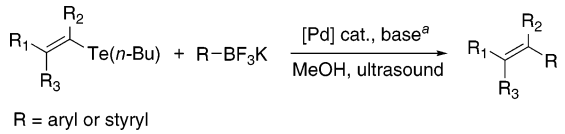
5.1.4. Cross-Coupling with Organotellurides

As an alternative to the widely used organic halides and pseudo-halides in palladium-catalyzed reactions, H. A. Stefani et al. have shown that organotellurides participated in cross-coupling reactions with potassium organotrifluoroborates. Indeed, a protocol for the synthesis of 1,3-enynes from potassium alkynyltrifluoroborates and vinylic tellurides was described (Scheme 112).[191] The best conditions involved use of 15 mol % $Pd(acac)_2$ as catalyst and 30 mol % CuI in the presence of triethylamine in dry methanol under reflux. Enynes were generally obtained in moderate to good yields, and the (*Z*) stereochemistry of the double bond was retained during the cross-coupling, allowing selective formation of (*Z*)-enynes.

Vinylic tellurides were also cross-coupled with potassium (*E*)-styryl-[192] and aryltrifluoroborates,[193] allowing the synthesis of 1,3-dienes or styrene derivatives (Scheme 113). These palladium-catalyzed reactions with sp^2-hybridized organotrifluoroborates were best achieved using $Pd(PPh_3)_4$ (from 8 to 20 mol %) and AgOAc or Ag_2O (2 equiv) in methanol under ultrasound-assisted conditions.

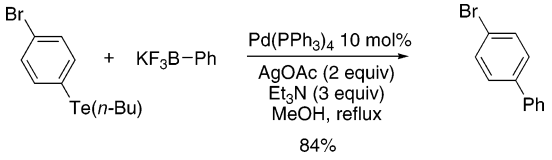
Biaryl formation using aryl tellurides and potassium aryltrifluoroborates was also achieved (Scheme 114).[194] Conditions for the cross-coupling reaction were very similar to those employed previously:[192] 10 mol % $Pd(PPh_3)_4$, Ag_2O (2 equiv), and Et_3N (3 equiv) in refluxing methanol. Using

Scheme 113. Arylation and Vinylation of Vinylic Tellurides

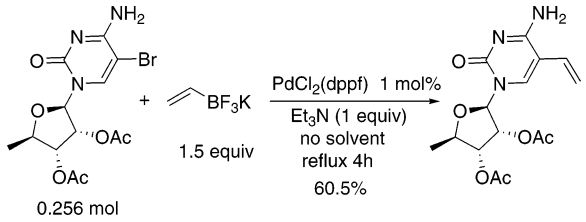


[a] R = styryl: $Pd(PPh_3)_4$ 20 mol %, AgOAc (2 equiv), Et_3N (2 equiv). R = aryl: $Pd(PPh_3)_4$ 8 mol %, Ag_2O (2 equiv).

Scheme 114. Biaryls Formation Using Aryl Tellurides



Scheme 115. Vinylation of 5′-Deoxy-5-bromocytidine



lower catalytic loading generally resulted in a notable decrease in yield. Regioselective cross-coupling reactions could be achieved as the telluride moiety showed higher reactivity than chloride or bromide substituents.

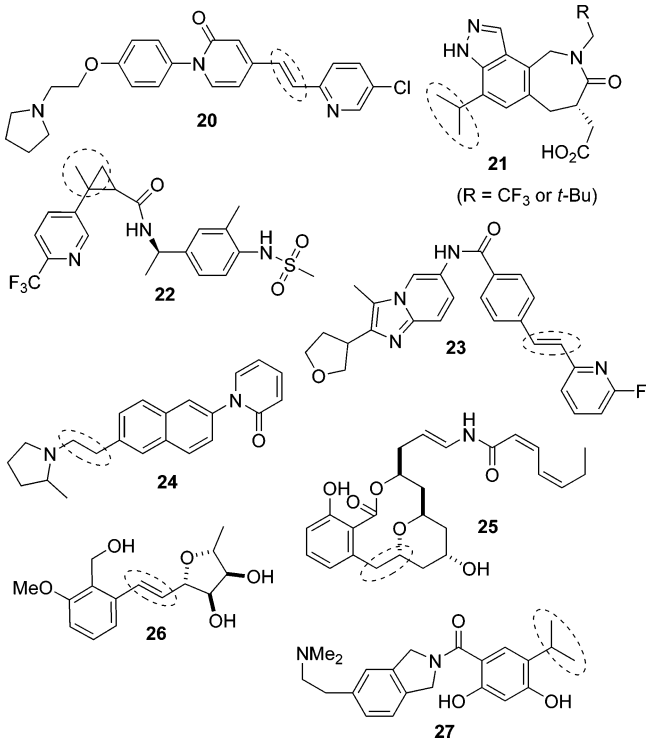
5.1.5. Applications

5.1.5.1. Potassium Vinyltrifluoroborate as Vinylating Agent. Potassium vinyltrifluoroborate has emerged as an efficient and nontoxic vinylating agent compared with tributyl(vinyl)stannane. In this section we will present some selected industrial and academic applications of this trifluoroborate salt in the synthesis of biologically active compounds or useful functionalized compounds as well as use of potassium isoprenyltrifluoroborate.

As mentioned earlier, one of the first cross-coupling reactions involving organic halides and organotrifluoroborates was described by Hoffmann-La-Roche in 2000 for the preparation of vinylpyrimidine derivatives (Scheme 115).[151] After optimization of the reaction conditions, they found that 5′-deoxy-5-bromocytidine was efficiently vinylated with potassium vinyltrifluoroborate in the presence of 1 mol % $PdCl_2$(dppf) using 1 equiv of triethylamine without added solvent. Of importance is that this reaction could be conducted on kilogram scale.[195] These vinylpyrimidinones, which were originally obtained using tributyl(vinyl)stannane, were of great interest in the therapy of cancer.

Pyridone derivative **20** (Chart 5), acting as an antagonist to melanin concentrating hormone receptor, was obtained by two subsequent palladium-catalyzed reactions: vinylation of 1,4-dichloropyridine with vinyltrifluoroborate followed by Heck reaction with a 4-iodopyridine derivative.[196] Novel CGRP-receptors (calcitonin gene-related peptide) antagonist **21**, effective for the treatment of neurogenic inflammation, migraine, and other disorders were synthesized.[197] The isopropyl substituent was introduced by cross-coupling reaction of the aryl bromide with potassium isoprenyltrifluoroborate followed by catalytic hydrogenation. Cyclopropanecarboxamide compounds like **22** are useful as antagonists of the VR1 (type I vanilloid) receptor for the treatment

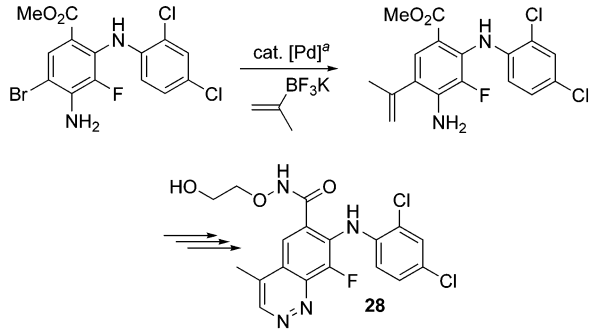
Chart 5. Synthesis of Bioactive Compounds Involving Vinylation with Potassium Trifluoro(vinyl)borate and Isoprenyltrifluoroborate



of pain, neuralgia, nerve injury, or migraine.[198] The cyclopropane unit of **22** was introduced via palladium-catalyzed cross-coupling of isoprenyltrifluoroborate with 5-bromo-2-trifluoromethyl-pyridine followed by cyclopropanation. Imidazopyridine compound **23** has been shown to be a melanin concentrating hormone receptor antagonist and is useful in preventing or treating agents for various circular system diseases, nervous system diseases, metabolic diseases, genital diseases, respiratory diseases, digestive diseases, etc.[199] Its preparation involves two palladium-catalyzed subsequent steps: cross-coupling of 2-bromopyridine with vinyltrifluoroborate followed by Heck reaction. Pyridazinone derivative **24**, active in histamine-3-mediated conditions and diseases, was prepared via introduction of the vinyl substituent in the naphthalene ring followed by lithium-mediated hydroamination.[200] Formal synthesis of (−)-Apicularen A (**25**) involved a palladium-catalyzed cross-coupling with vinyltrifluoroborate.[201] The absolute and relative stereochemistries of the stereogenic centers were introduced by a Sharpless asymmetric dihydroxylation, a π-allyl-catalyzed reduction, a stereoselective reduction, and a base-promoted transannulation. Using this vinylating agent, the first total synthesis and absolute configuration determination of varitriol (**26**) was described starting from an aryl triflate precursor.[202] Hydroxybenzamide compounds of type **27**, which inhibit or modulate the activity of the heat shock protein Hsp90, have shown some activity in the treatment or prophylaxis of disease states or conditions mediated by Hsp90.[203] The isopropyl moiety of **27** was introduced via sequential introduction of isoprenyl substituent followed by catalytic hydrogenation.

Synthesis of compounds of type **28** (Scheme 116), which are MEK (mitogen-activated/extracellular signal regulated kinase, MAP kinase) inhibitors and appear to be useful in the treatment of hyperproliferative diseases, such as cancer and inflammations, have been prepared by cross-coupling reaction of potassium isoprenyltrifluoroborate.[204]

Scheme 116. Preparation of MEK Inhibitor 28



[a] Catalyst: $PdCl_2(dppf)$, *t*-$BuNH_2$, PrOH/H_2O, 70 °C.

Heteroarylphenylurea derivative **29** (Scheme 117) has been shown to be a Raf inhibitor and an angiogenesis inhibitor and, indeed, is useful for treating growth diseases such as cancer, psoriasis, or atherosclerosis.[205] The aromatic lateral chain bearing a diol functionality was introduced via palladium-catalyzed cross-coupling of the corresponding aryl bromide with potassium vinyltrifluoroborate followed by dihydroxylation.

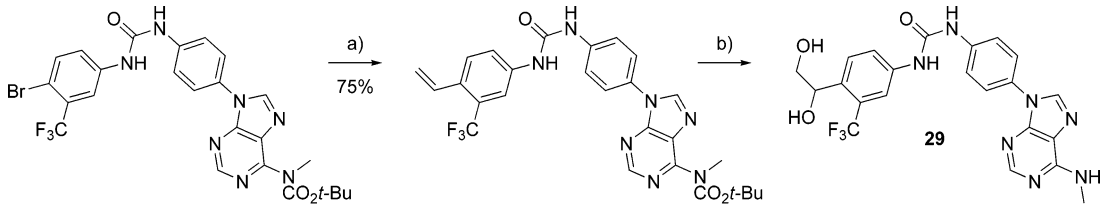
There has been a major effort in recent years to find compounds that modulate the immune system. Examples of such compounds, which have demonstrated cytokine inducing and immunomodulating activity, include certain 1-amino-1*H*-imidazoquinoline **30** compounds that modulate cytokine biosynthesis (Scheme 118).[206] The ethylene unit between the 1-pyridyl fragment and the imidazoquinoline was introduced via three sequential steps involving palladium-catalyzed reactions: cross-coupling with potassium trifluoro(vinyl)-borate followed by Heck reaction with 3-bromopyridine and finally hydrogenation of the double bond.

Novel macrocyclic lactam **31** has been shown to be useful for treatment of neurological or vascular disorders to beta-amyloid generation and/or aggregation (Scheme 119).[207] Its preparation involved initial introduction of the vinyl substituent using potassium vinyltrifluoroborate. Subsequent amide formation, ring-closing metathesis using Grubbs II catalyst, followed by opening of the lactam afforded the expected compound **31**.

Synthesis of many other compounds, which involve a palladium-catalyzed cross-coupling step with trifluoro(vinyl)-borate, have appeared in the literature. Formation of nitrogen-containing heterocyclic compounds were achieved via introduction of a vinyl substituent on an aromatic ring.[208] Indolone derivatives, capable of modulating tyrosine kinase signal transduction in order to regulate, modulate, and/or inhibit abnormal cell proliferation, were achieved in the same way.[209] Vinyl-substituted pyrrolidones and piperidinones[210] or constrained indazoloazepinones[211] also involved introduction of vinyl or isoprenyl substituent.

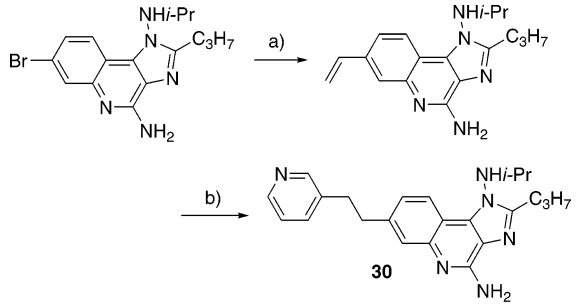
Conjugated polymers such as poly(fluorenylenevinylene)s,[212] poly(phenanthrylene-vinylene),[213] or poly(2,7-fluorenylene-vinylene-*co*-carbazolylenevinylene)[214] have been prepared via a cascade Suzuki−Heck reaction (Scheme 120). For example, reaction of 2,7-dibromofluorenes with potassium vinyltrifluoroborate in the presence of $Pd(PPh_3)_4$ (5 mol %) and potassium carbonate as a base afforded the expected polymers in good yields with low percentages of structural 1,1-diarylenevinylene defects. Rigid-rod push−pull naphthalenediimide photosystems[215] or pyridocarbazole pharmaco-

Scheme 117. Synthesis of Heteroarylphenylurea Derivative



a) $PdCl_2(PPh_3)_2$ 6 mol %, $(CH_2CH)BF_3K$, *n*-PrOH, *i*-Pr_2NH, 80 °C. b) i) OsO_4, H_2O_2. ii) CF_3SO_3H

Scheme 118. Synthesis of 1-Amino-1*H*-imidazoquinoline



a) $K[CH_2CHBF_3]$, $PdCl_2$(dppf) cat., Et_3N, *n*-PrOH, 100 °C. b) i) 3-bromopyridine, $Pd(OAc)_2/P(o\text{-tolyl})_3$ cat., Et_3N, CH_3CN, 120 °C. ii) Pd/C cat., H_2.

phore[216] were readily synthesized through use of potassium aryltrifluoroborates.

Preparation of some macrocyclic peptides, which are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, has been described (Scheme 121).[217] The macrocycle was cyclized via ring-closing metathesis thanks to the vinyl moiety, which was introduced using palladium cross-coupling with potassium vinyltrifluoroborate.

These constitute some representative examples, but many other applications have been described using potassium vinyl-[218] or isoprenyltrifluoroborates.[47]

5.1.5.2. Other Potassium Organotrifluoroborates and Their Applications. Even if potassium vinyltrifluoroborate constitutes the main use of organotrifluoroborates in palladium-catalyzed cross-coupling reactions, many other synthetic approaches involve the use of various trifluoroborate derivatives. Indeed, the cross-coupling reaction with arenediazonium tetrafluoroborates has been used industrially in the preparation of compounds **32**, active in the treatment of Alzheimer's disease (Scheme 122).[219] The 3-thienyl substituent was introduced via the trifluoroborate derivative using base-free conditions as described before.[28] Saponification of the intermediate, followed by coupling with a β-amino alcohol, afforded the amide **32**.

The intermediate stilbene **34** in the synthesis of bis-(oligophenyleneethynylenes), a novel potential nonlinear optical material,[220] was obtained from reaction of the arenediazonium **33** with potassium (*E*)-styryltrifluoroborate in 58% yield (Scheme 123). Under standard Heck reaction conditions using the triflate derivative, e.g., under basic conditions, a lower yield was achieved because of unwanted silyl deprotection of the arylalkyne building block.

4-Cycloalkylaminopyrazolo pyrimidine compounds have been shown to be NMDA/NR2B antagonists useful for the treatment of neurological conditions such as pain, Parkinson's disease, Alzheimer's disease, epilepsy, and other conditions (Scheme 124).[221] The 2,6-difluorophenyl moiety was introduced via palladium-catalyzed cross-coupling using a bromostyrene precursor in 60% yield under standard conditions, e.g., using $PdCl_2$(dppf) as catalyst and Et_3N as a base.

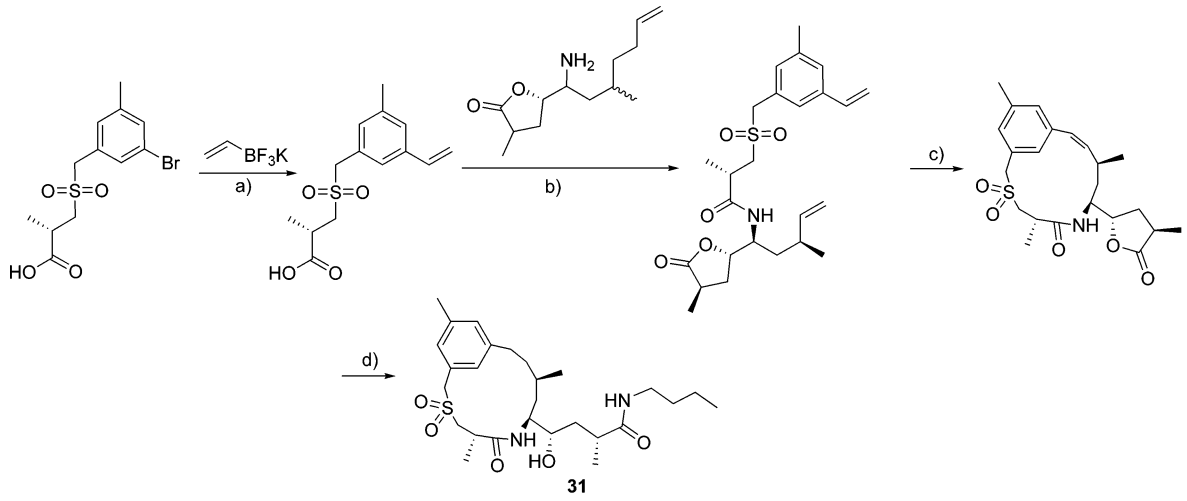
A formal total synthesis of Oximide II (**37**) was achieved employing a Suzuki-type coupling approach to construct the highly strained, polyunsaturated 12-membered macrolatone (Scheme 125).[222] Hydroboration of the terminal alkyne in **35** followed by aqueous KHF_2 treatment allowed formation of the trifluoroborate **36** in virtually quantitative yield. Intramolecular Miyaura−Suzuki cross-coupling reaction gave the desired cyclized product **37** in 42% overall yield from alkyne **35**.

1-Alkyl-2-aryl-4-(1-naphthoyl)pyrroles such as **38** (Chart 6), which show high affinity for the cannabinoid CB_1 and CB_2 receptors, were synthesized via palladium-catalyzed cross-coupling reactions with potassium aryltrifluoroborates.[223] Coupling of potassium phenylcyclopropyltrifluoroborate with bromoindoles afforded mPGES-1 inhibitors **39**, active for treatment of inflammation (Chart 6).[224] The tyrosine trimer **40** was prepared via a double cross-coupling reaction of potassium tyrosine-3-trifluoroborate with 3,5-diiodotyrosine.[225] In this reaction the corresponding pinacol esters also afforded the title compound **40** but in low yield. The lateral chain of orcinol-type depsides **41** was introduced using potassium alken-1-yltrifluoroborate, allowing the first total synthesis of gustastatin in 10 steps from commercially available trihydroxybenzoic acid.[226] A variety of substituted cationic porphyrins **42**[227] and sulfophtalocyanines[228] were prepared via cross-coupling with potassium aryl- or vinyltrifluoroborate. Coupling of potassium styryltrifluoroborate with 2-chloropyridine derivatives afforded aryloxyethylamines **43**, which show binding affinity at α7 nicotinic acetylcholine receptors.[229] Benzyl substituents on piperidinyl-substituted isoquinoline derivatives **44** were introduced via a cross-coupling reaction with benzyltrifluoroborate.[230] This family of compounds was evaluated as inhibitors of Rho-kinase.

Losartan **45** and derivatives (Chart 6), angiotensin II receptors agonists, were prepared via palladium-catalyzed cross-coupling using 2-cyanophenyltrifluoroborate.[109] Arylcyclopropylalkylamines **46**, which show 5-HT2C agonist activity, were readily obtained via the cross-coupling reaction of cyclopropyltrifluoroborates derivative with aryl bromides.[231] Total synthesis of Amphidinolide V involved a palladium-catalyzed cross-coupling step with potassium alkenyltrifluoroborate.[232]

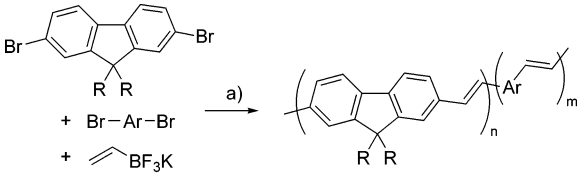
Functionalized azobenzenes, useful as photoswitch tools to influence protein activity, were obtained through the cross-coupling reaction with organotrifluoroborates (Scheme 126).[233] It was found that the corresponding pinacol ester did not couple at all, while low yields were observed with the boronic acid. On the other hand, moderate to good yields were achieved using the potassium trifluoroborate in the cross-coupling reaction with various aryl iodides.

Scheme 119. Synthesis of Macrocyclic Lactams 31 Using Potassium Vinyltrifluoroborate



a) $PdCl_2(dppf)$, Et_3N, *n*-PrOH, reflux. b) i) HOBt, EDC.HCl, Et_3N, rt. ii) Separation. c) Grubbs II catalyst. d) i) *n*-$BuNH_2$, 65°C. ii) H_2, Pd/C, MeOH.

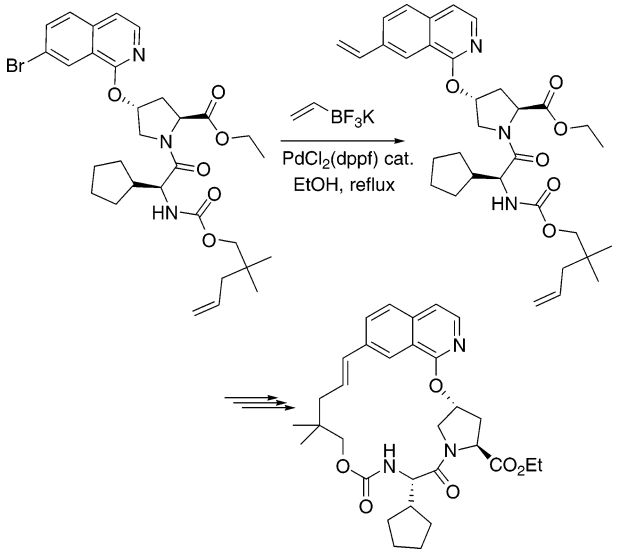
Scheme 120. Preparation of Poly(fluorenylenevinylene)s



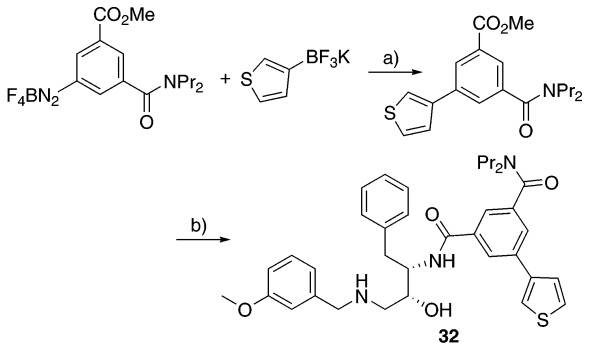
R = alkyl chain

a) $Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (3 equiv), dioxane, reflux

Scheme 121. Preparation of Macrocyclic Peptides

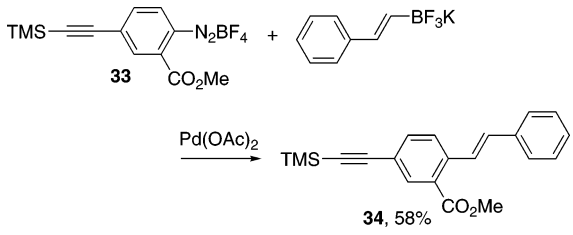


Scheme 122. Amino Alcohol 32 Synthesis via Cross-Coupling with Arenediazonium Salt



a) $Pd(OAc)_2$ 5 mol%, dioxane, rt. b) i) NaOH, THF/MeOH. ii) (2*R*,3*S*)-3-amino-1-(3-methoxybenzylamino)-4-phenylbutan-2-ol dihydrochloride, EDC, HOBt.

Scheme 123. Stilbene Derivatives for the Synthesis of Bis(oligophenyleneethynylenes)

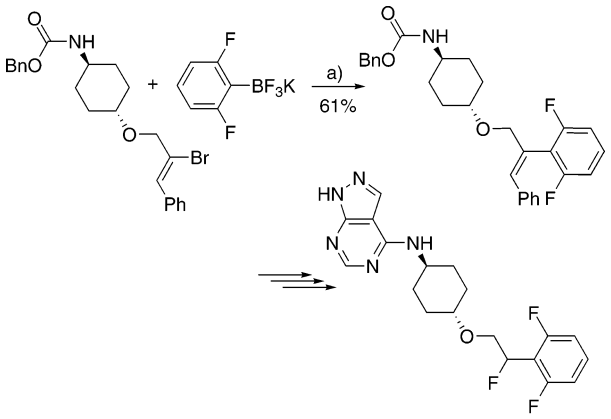


5.2. Palladium-Catalyzed Allylation of Imines

Allylpalladium species, generated via transmetalation between an allylstannane and a palladium complex, have been shown to react with electrophiles.[234] Because of the toxicity of organotin reagents, it has been shown that allylstannanes could be advantageously replaced by potassium allyltrifluoroborates in such reactions. Indeed, Szabó et al.[235] have shown that the pincer complex **47** catalyzes the reaction of potassium allyltrifluoroborates with a wide range of tosylimines under mild and neutral reaction conditions (Scheme 127).

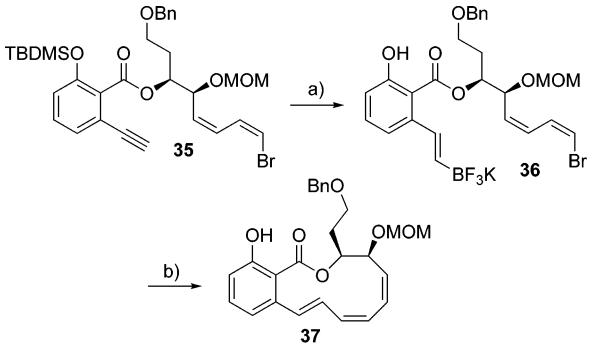
This catalytic transformation affords homoallylic branched amines in good to excellent yields and with high regioselectivity. The stereoselectivity of this process was very high when cinnamyltrifluoroborate was employed. However, reaction with crotyltrifluoroborate resulted in poor stereoselectivity. Mechanistic studies have clearly shown that potassium allyltrifluoroborates undergo transmetalation with the palladium pincer complex **47**, affording an η^1-allylpalladium−pincer complex. An asymmetric version of this palladium-catalyzed allylation reaction has recently been described by the same authors using a chiral 1,1′-bi-2-naphthol-based pincer complex.[236] However, moderate enantioselectivities were generally obtained (48−85%)

Scheme 124. Preparation of 4-Cycloalkylaminopyrazolo Pyrimidine



a) $PdCl_2(dppf)•CH_2Cl_2$ cat., Et_3N, EtOH, reflux.

Scheme 125. Synthesis of Oximide II (37)



a) i) 2,5-dimethylhexa-2,4-diene, BH_3•DMS, THF, 0 °C, then H_2O, then CH_2O. ii) KHF_2, CH_3CN, acetone, H_2O, rt, ~99 %. b) $Pd(PPh_3)_4$ 10 mol %, Cs_2CO_3 (5 equiv), THF/H_2O (10:1) 1 mM, 42 %.

5.3. Copper-Catalyzed Ether and Amine Synthesis

Formation of carbon−heteroatom bonds catalyzed by transition metals has rapidly emerged as a powerful tool in organic synthesis.[237] It has been shown simultaneously by Chan and Evans that cross-coupling of arylboronic acids with phenols was efficiently mediated by copper salts.[238] In this reaction, stoichiometric amounts of base and $Cu(OAc)_2$ were necessary to achieve high yields of biaryl ethers. Batey et al. described a protocol for the copper(II)-catalyzed etherification using potassium organotrifluoroborates as coupling partners (Scheme 128).[239] Indeed, reaction of 2 equiv of potassium aryl- and alken-1-yltrifluoroborate with 1 equiv of aliphatic alcohol in the presence of 10 mol % $Cu(OAc)_2$•H_2O, 20 mol % DMAP, and 4 Å MS in CH_2Cl_2 at room temperature under an atmosphere of O_2 furnishes good yields of ethers.

The presence of 4 Å MS was required as in its absence only traces of ether were observed. Moreover, the reaction seems to be sensitive to steric effects around the hydroxyl group, and lower yields were obtained with secondary alcohols. Under these conditions, boronic acids also undergo cross-coupling reactions, although yields were lower than with potassium organotrifluoroborates.

Preparation of some sulfonylamino-based peptidomimetics, having affinity and selectivity for the somatostatin receptor subtypes sst1 and sst4, involved copper-catalyzed coupling of ornithinol derivatives with potassium aryltrifluoroborates (Scheme 129).[240] Chiral amines, which have been used in enantioselective addition of organolithium reagents to aldehydes, were obtained via copper-catalyzed ether synthesis.[241]

These conditions were extended to amine synthesis. Indeed, under ligandless and base-free conditions the copper-catalyzed cross-coupling of potassium aryltrifluoroborates (or boronic acids) with primary and secondary amines and anilines occurred under mild conditions and in good yields (Scheme 130).[242] In this reaction, the presence of the DMAP ligand (required for *O*-arylations) was unnecessary, probably because the amine nucleophile is a much better ligand for copper. When compared to their alcohol analogues, aliphatic amines gave greater yields and, whereas tertiary alcohols do not undergo cross-coupling, tertiary alkyl-substituted amines do undergo arylation. Anilines proved to be poorer cross-coupling partners under these conditions, affording only low to moderate yields of unsymmetrical diarylamine products.[242] Heteroaromatic amines, such as imidazole or benzimidazole, also failed to give good yields of cross-coupled product under these conditions.[243] A microwave-assisted amination procedure was also developed under solvent-free conditions.[244] This reaction was applied to the preparation of novel octahydro-1*H*-pyrido[1,2-a]pyrazines, μ-opioid receptor antagonists.[245]

It has also been shown that in the presence of a catalytic amount of copper salts, reaction of aryltrifluoroborates with diphenyl diselenide and ditelluride afforded the corresponding unsymmetrical diarylselenides and tellurides in good yields.[246] Reactions were best conducted in DMSO at 100 °C in the presence of 10 mol % CuI.

5.4. Transition-Metal-Catalyzed Additions to Unsaturated Substrates

The 1,2- and 1,4-addition of organometallic reagents to unsaturated compounds are among the most versatile reactions in organic synthesis.[247] In that context, it has been shown that organoboronic acids can efficiently add to unsaturated substrates in the presence of catalytic amounts of rhodium catalysts.[138,248]

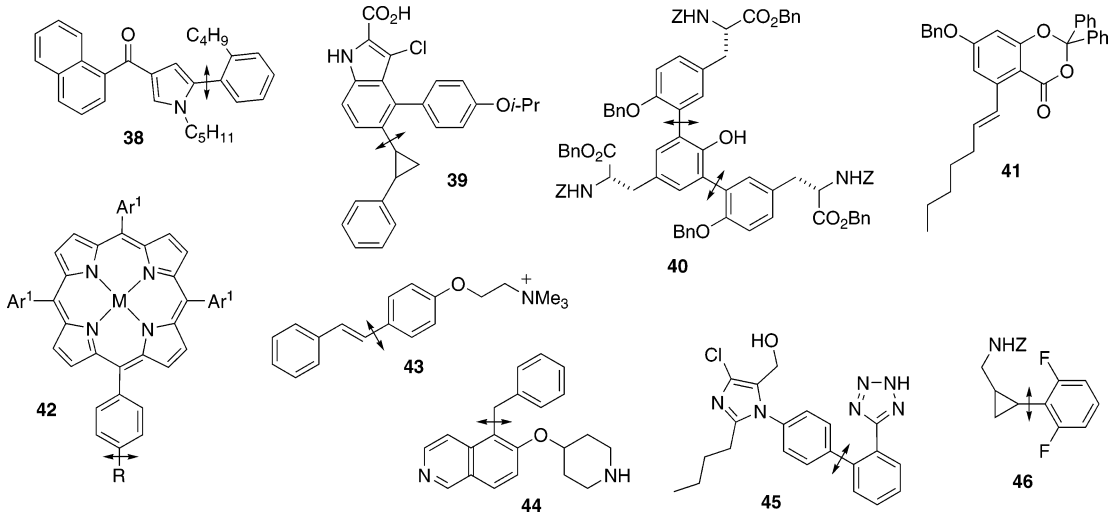
5.4.1. 1,4-Additions to Michael Acceptors

Very early, Batey et al.[249] showed that potassium organotrifluoroborates also participated in rhodium-catalyzed 1,2- and 1,4-additions to aldehydes and enones (Scheme 131). Indeed, in the presence of catalytic amounts of Rh(acac)-$(CO)_2$ and a bidentate ligand (dppp = diphenylphosphinopropane), good yields of 1,4-addition adducts were obtained. Moreover, it is important to note that under identical conditions the reaction proceeded more rapidly using organotrifluoroborates than the corresponding boronic acids.[249] This greater reactivity of organotrifluoroborates in this rhodium-catalyzed reaction was supposed to reflect the more facile transmetalation to form the active Rh−R species. Another significant advantage in using potassium organotrifluoroborates instead of organoboronic acids is that generally higher yields were obtained, and certain boronic acids proved to be unreactive. In this reaction, addition of water has an accelerating effect.

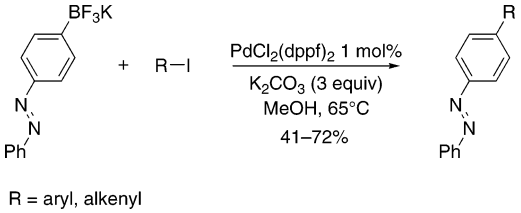
An asymmetric version of this 1,4-addition of potassium organotrifluoroborates to enones has been described by Darses and Genet.[250] Optimization of the conditions revealed that high yields and enantiomeric excesses could be achieved using cationic $Rh(cod)_2PF_6$ complexed with atropoisomeric binap ligand (**48**, Chart 7) in a toluene/water mixture as solvent, conducting the reaction above 100 °C (Scheme 132).

Among the tested rhodium complexes, only cationic precursors allowed quantitative conversion and high ee.

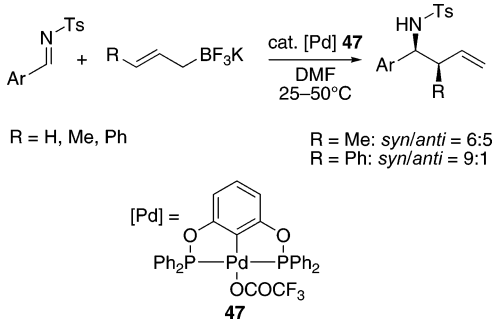
Chart 6. Some Applications of Palladium-Catalyzed Cross-Coupling Reactions



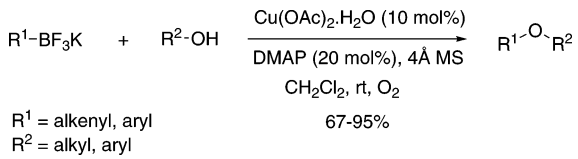
Scheme 126. Functionalized Azobenzenes through Cross-Coupling



Scheme 127. Pd-Catalyzed Allylation of Imines

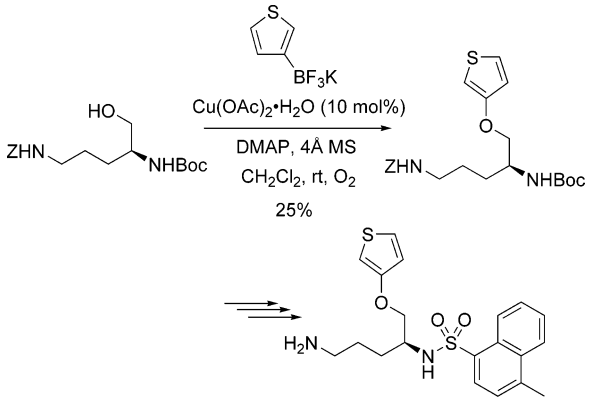


Scheme 128. Copper-Catalyzed Ether Synthesis

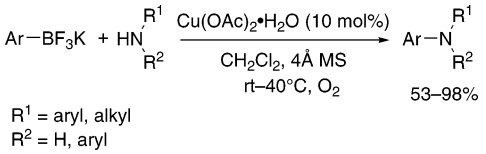


Solvent has a major influence on the enantioselectivities, with higher ee being obtained in aprotic and nonpolar solvents (toluene, heptane). The presence of water is also crucial for this reaction: in its absence, the reaction is very slow as well as the asymmetric induction. On the other hand, a large excess of water slows the reaction down, and in pure water no asymmetric induction is observed. Indeed, for practical purposes, one should use a slight excess of water compared to boron reagent (typically a 10:1 mixture of toluene/water). Under these conditions, organoboronic acids react slower, although similar yields and enantiomeric excesses are obtained,[250] proving once again the higher reactivity of potassium organotrifluoroborates. Moreover, compared to Miyaura−Hayashi conditions using organoboronic acids derivatives,[248] this reaction generally requires lower amounts

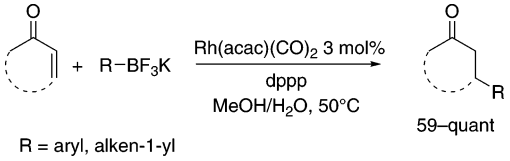
Scheme 129. Sulfonylamino-Based Peptidomimetics via Copper-Catalyzed Ether Formation



Scheme 130. Copper-Catalyzed Amine Synthesis

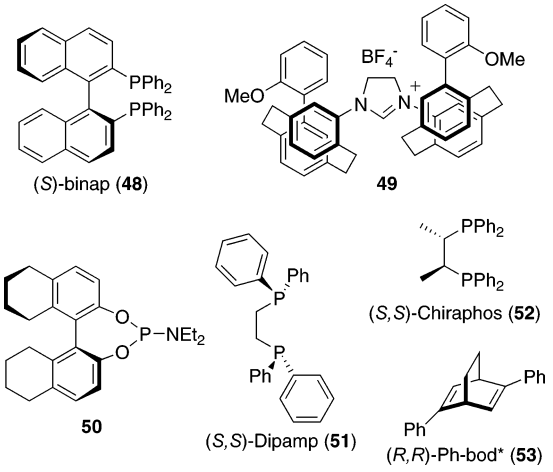


Scheme 131. Rh-Catalyzed 1,4-Addition of K[RBF$_3$] to Enones

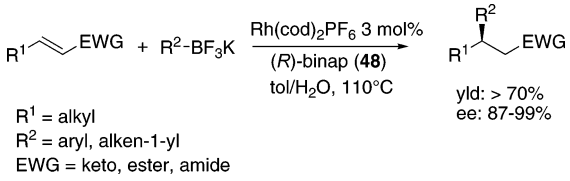


of the organometallic reagent. Using potassium vinyltrifluoroborate, high yields of vinylated Michael adducts are obtained. These conditions proved to be general for the functionalization of other Michael acceptors such as α,β-unsaturated amides[251] and esters.[252] Particularly, addition to α,β-unsaturated amides occurred without addition of base, whereas for the reaction with boronic acids, addition of a base was necessary to allow the reaction to go to completion.[253] Moreover, under these conditions higher amounts of boronic acids compared to potassium organotrifluoroborate are needed to achieve quantitative conversion. Efficient access to alanine derivatives has also been described via the rhodium-catalyzed 1,4-addition to dehydroamino esters.[254]

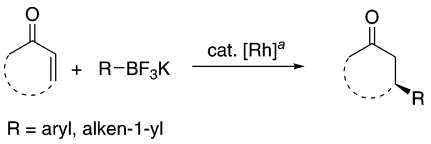
Chart 7. Chiral Ligands in the Rh- and Pd-Catalyzed 1,4-Addition of K[RBF$_3$]



Scheme 132. Asymmetric Rh-Catalyzed 1,4-Addition of K[RBF$_3$]



Scheme 133. Rh-Catalyzed 1,4-Additions to Enones



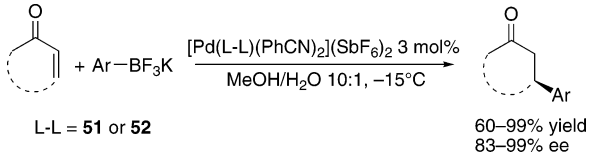
[a] From ref 256: Rh(acac)(C_2H_4)$_2$ 2 mol %, **49** 3 mol %, THF/H_2O, 60 °C, >90% yield, 73−96% ee. From ref 257: Rh(acac)(C_2H_4)$_2$ 4 mol %, **50** 10 mol %, EtOH, reflux, 70−100% conv, 71−99% ee.

A process for the stereoselective preparation of tolterodine was patented using asymmetric 1,4-addition of potassium phenyltrifluoroborate to 9-methylcoumarin.[255]

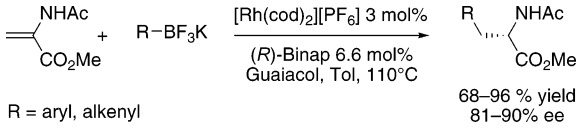
New C_2-symmetric dicyclophane imidazolium ligands, in particular **49** (Chart 7), have been shown to be useful in the rhodium-catalyzed asymmetric 1,4-addition of potassium aryltrifluoroborates to enones.[256] High yields of 1,4-addition adducts were achieved in the presence of 2 mol % Rh(acac)(C_2H_4) in association with 3 mol % **49** in a mixture of THF/water at 60 °C (Scheme 133). Under these conditions trifluoroborate reagents reacted at a faster rate than boronic acids, but selectivities were generally lower (ee from 73% to 96%). Reactions with acyclic enones were also efficient but the selectivities were significantly lower.

Monodentate phosphoramidite ligands have also been utilized in the rhodium-catalyzed asymmetric 1,4-addition of potassium aryltrifluoroborates to enones (Scheme 133).[257] A systematic search for effective catalysts has been performed by use of high-throughput screening methods. Among the library of phosphoramidites, ligand **50** (Chart 7) has been shown to be the most useful, and vinylation of cyclohexenone and 4-phenyl-3-buten-2-one has been achieved with 88% and 42% ee, respectively. As in the case of the binap ligand,[250] phenylation of cyclohexenone gave 3-phenylcyclohexanone with 99% ee. In the presence of chiral diene (*R*,*R*)-Ph-bod* **53** (Chart 7) and rhodium complex, potassium vinyltrifluoroborate added to quinone monoketal with high yield and enantiomeric excess.[258]

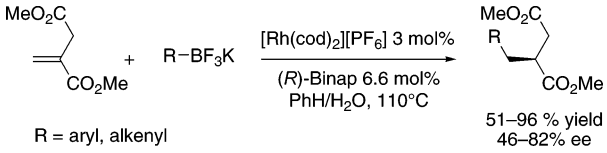
Scheme 134. Asymmetric Pd-Catalyzed 1,4-Addition of K[RBF$_3$] to Enones



Scheme 135. Rhodium-Catalyzed 1,4-Addition/ Enantioselective Protonation



Scheme 136. Synthesis of Enantioenriched 2-Substituted Succinic Esters

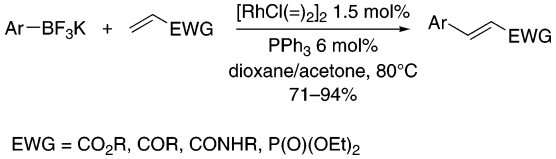


These 1,4-addition reactions of organometallic reagents to Michael acceptors could also be realized using dicationic palladium catalysts.[259] Indeed, the asymmetric Michael addition of potassium aryltrifluoroborates to enones was efficiently catalyzed by the chiral palladium complexes [Pd(**51**)(PhCN)$_2$](SbF$_6$)$_2$ and [Pd(**52**)(PhCN)$_2$](SbF$_6$)$_2$ (Chart 7 and Scheme 134).[260] Reaction occurred at −15 °C in aqueous methanol to afford the 1,4-addition adducts in high yields. The highest enantioselectivities, giving β-aryl ketones in up to 99% ee, were obtained using (*S*,*S*)-chiraphos (**52**) as the chiral ligand for 2-cyclopentenone and acyclic (*E*)-enones, whereas (*S*,*S*)-dipamp (**51**) resulted in the best selectivities for 2-cyclohexenone and 2-cycloheptenone (89−96% ee). High enantioselectivities were also obtained with β-arylenones, whereas rhodium complexes were generally less efficient on these substrates.

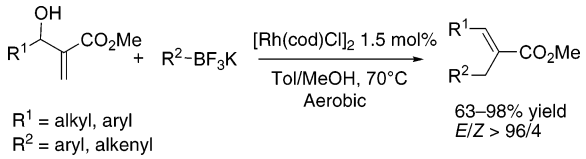
High-yielding protocols have been described using either rhodium or palladium catalysis for the enantioselective introduction of a chiral center in the β position of activated alkenes. Darses and Genet have shown that the α chiral center could also be controlled by choosing a suitable proton source instead of water (Scheme 135).[261] Indeed, the conjugate addition of potassium aryl- and alkenyltrifluoroborates to *N*-acylamidoacrylate mediated by a chiral rhodium complex in the presence of achiral phenol derivatives furnishes a variety of α-amino acid derivatives with good enantioselectivities. The best proton source was found to be inexpensive and nontoxic 2-methoxyphenol or guaiacol. Under these conditions, boronic acids gave low conversion and modest enantiomeric excesses (40%).

This reaction, involving 1,4-addition/enantioselective protonation using potassium organotrifluoroborate, has also been applied by C. G. Frost and co-workers in the synthesis of 2-substituted succinic esters (Scheme 136).[262] The rhodium-catalyzed addition of aryl- and alkenyltrifluoroborates to dimethyl itaconate was best achieved using 2 equiv of binap as chiral ligand compared to rhodium and using water as a proton source. It was found that use of benzene as solvent resulted in a significant enhancement of enantioselectivity compared to toluene or dioxane.

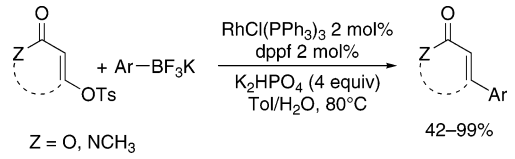
Scheme 137. Base-Free Rhodium-Catalyzed Heck-Type Reactions



Scheme 138. Access to Stereodefined Trisubstituted Alkenes via Rhodium-Catalyzed 1,4-Addition



Scheme 139. Rhodium-Catalyzed Reactions with Alkenyl Tosylates



In the absence of external proton source, the reaction course of these rhodium-catalyzed processes is totally changed. Indeed, Darses and Genet have shown[263] that in the absence of water, a Heck-type product was selectively obtained, and they developed a base-free rhodium-catalyzed Mizoroki−Heck reaction using potassium aryltrifluoroborates as the arylating agent of alkenes and acetone as a green "oxidant".

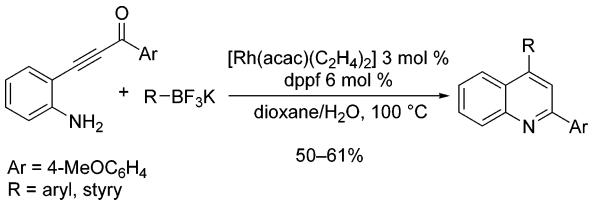
Access to stereodefined trisubstituted alkenes via rhodium-catalyzed 1,4-addition of potassium organotrifluoroborates to Baylis−Hillman (BH) adduct has been reported (Scheme 138).[264] Indeed, in the presence of 1.5 mol % $[Rh(cod)Cl]_2$, reaction of potassium alkenyl- and aryltrifluoroborates to BH substrates furnished high yields of alkenes, resulting formally from 1,4-addition to the activated alkene followed by β-hydroxy elimination.[265] The reaction was best conducted in toluene/methanol at 70 °C in the absence of added phosphane ligand and under aerobic conditions. The stereoselectivities, in favor of the (*E*)-alkene, were higher than 96%.

Alkenyl tosylates have also been shown to be used in rhodium-catalyzed reactions with potassium aryltrifluoroborates (Scheme 139).[266] In the presence of Wilkinson complex $RhCl(PPh_3)_3$ and additional bis(diphenylphosphano)ferrocene ligand (dppf), reaction of potassium aryltrifluoroborates with various enol tosylates occurred in moderate to good yields to afford formal Suzuki−Miyaura cross-coupling products. K_2HPO_4 was found to be the base of choice; however, the reaction was not run in its absence. It was also noted that lower yields were generally observed with 4-tosyloxy-2(5*H*)-furanone and 4-tosyloxyquinolin-2(1*H*)-one.

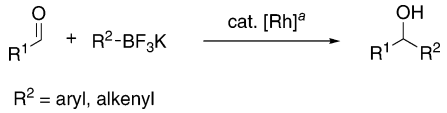
4-Aryl and 4-vinyl quinolines were prepared via a sequential procedure involving regioselective $[Rh(acac)(C_2H_4)_2]$/dppf-catalyzed hydroarylation/hydrovinylation of β-(2-aminophenyl)-α,β-ynones with potassium aryl and vinyl trifluoroborates followed by nucleophilic attack of the amino group onto the carbonyl (Scheme 140).[267]

Indeed, from these preliminary results in 1,4-addition reactions catalyzed by rhodium complexes, potassium organotrifluoroborates compared favorably and very often even surpassed the use of boronic acids because of their higher reactivity and exceptional stabilities.

Scheme 140. Rhodium-Catalyzed Synthesis of Quinolines



Scheme 141. Rhodium-Catalyzed Addition of $K[RBF_3]$ to Aldehydes



[a] From ref 249: $Rh(acac)(CO)_2$ 3 mol %, dppf 3 mol %, DME/H_2O, 80 °C, 71−88% (R^1 = aryl, cyclohexyl). From ref 272: $[RhCl(C_2H_4)]_2$ 3 mol %, P(*t*Bu)$_3$ 3 mol %, Toluene/H_2O, rt to 60 °C, 63−99% (R^1 = aryl, alkyl).

5.4.2. Additions to Aldehydes

Rhodium-catalyzed addition of organometallic reagents to aldehydes has been developed to a lesser extent, whereas diarylmethanols are important intermediates for the synthesis of biologically active compounds. Even if the addition of strong organometallics (RLi, RMgX) to aldehydes constitutes one of the most versatile methods to generate secondary alcohols, limitations to their use arise from their high reactivity as nucleophiles or bases, which often give rise to undesired side reactions in the synthesis of multifunctional compounds. Addition of organozinc reagents to aldehydes in racemic and asymmetric versions is now well documented,[268] but examples of aryl transfer are often limited to introduction of a phenyl group. Indeed, the rhodium-catalyzed addition of arylstannanes,[269] arylsilanes,[270] and arylboronic acids[271] to aldehydes has emerged as a promising alternative. Moreover, they afford the opportunity to conduct reactions under aqueous conditions.

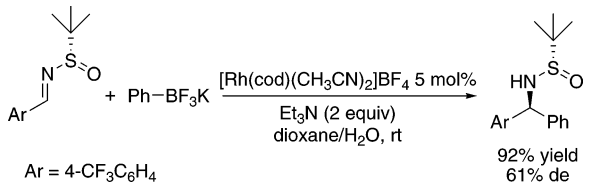
Batey et al. were the first to describe the feasibility of the addition of potassium aryltrifluoroborates to aryl aldehydes (Scheme 141).[249] Indeed, in the presence of catalytic amounts of $Rh(acac)(CO)_2$ and a bidentate ligand (dppf, bis(diphenylphosphino)ferrocene), good yields of carbinols were obtained. Moreover, it is important to note that under identical conditions the reaction proceeds more rapidly using organotrifluoroborates than the corresponding boronic acids. However, the reaction was generally limited to electron-deficient aryl aldehydes.

More efficient conditions were developed using tri-*tert*-butylphosphane[271b] as ligand in this rhodium-catalyzed process (Scheme 141).[272] Highly hindered diarylmethanols could be formed under these conditions, and electron-deficient aryl aldehydes were also tolerated. Moreover, aliphatic aldehydes were also reactive, and the reaction could be run at room temperature for many substrates.

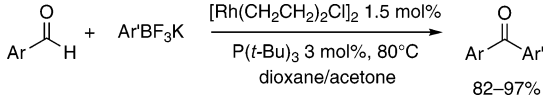
It has also been shown that addition of phenyltrifluoroborate to a chiral sulfinimine proceeded under mild conditions at room temperature using a rhodium catalyst in the absence of external phosphane ligand (Scheme 142).[273] The sulfinamide adduct was formed with high diastereoselectivity.

Direct access to ketones from aldehydes via a rhodium-catalyzed cross-coupling reaction with potassium organotrifluoroborates was readily achieved (Scheme 143).[274]

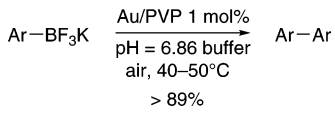
Scheme 142. Diastereoselective Addition to Chiral Sulfinimine



Scheme 143. Direct Access to Ketones from Aldehydes and K[RBF$_3$]



Scheme 144. Au-Catalyzed Homocoupling of K[RBF$_3$]



Indeed, reaction of aryl aldehydes and potassium aryltrifluoroborates, in the presence of $[Rh(C_2H_4)_2Cl]_2$ in conjunction with P(*t*-Bu)$_3$ ligand at 80 °C in a binary mixture of 1,4-dioxane/acetone at 80 °C, afforded high yields of diaryl ketones. Particularly, acidic hydroxyl substituents on the aromatic aldehyde were tolerated, preventing tedious protection/deprotection sequences.

Deuterium-labeling studies suggested that this reaction occurred via a Heck-type mechanism followed by unusual hydride transfer thanks to inexpensive acetone playing the part of hydride acceptor.

5.5. Miscellaneous

Gold(0) nanoclusters, stabilized by poly(*N*-vinyl-2-pyrrolidone) (PVP), have been shown to catalyze the oxidative homocoupling reaction of potassium aryltrifluoroborates in water and air (Scheme 144).[275] Catalytic activity was dependent on the size of the cluster and pH of the reaction medium: in weakly basic to neutral solutions (pH 9.18−6.86), biaryls were obtained as the sole products. Potassium stryryltrifluoroborate also underwent homocoupling under these conditions, giving 1,4-(*E*,*E*)-diphenylbutadiene in 67% yield. The catalyst was reusable (up to three times).

6. Conclusion

Discovered in the 1960s, potassium organotrifluoroborates are emerging as promising alternatives to the use of organoboronic acids. In fact, the number of publications dedicated to potassium organotrifluoroborates chemistry has experienced an exponential growth for the last 6 years, demonstrating the increased interest of the chemical community to such organoboron derivatives (Figure 1).

This interest is certainly due to the exceptional stability of these boron ate complexes toward oxygen and moisture as compared to all other described organoboron derivatives. Another interesting aspect of organotrifluoroborate is their ease of preparation and purification compared to boronic acids, and higher yields are generally achieved in their preparation. It has also been demonstrated that contrary to trivalent organoboranes, these reagents can easily be functionalized using a great variety of reactions. Moreover, in many organic transformations as well as in transition-metal-catalyzed reaction, potassium organotrifluoroborates have shown comparable and very often superior reactivity compared to organoboronic acids. We hope the readers will be convinced to the usefulness of these reagents in organic synthesis.

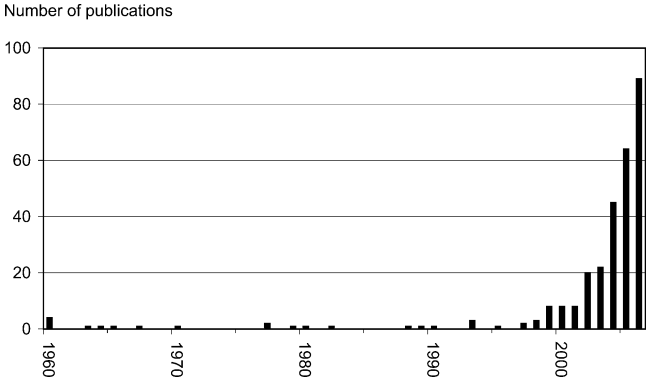


Figure 1. Number of publications per year dedicated to organotrifluoroborate chemistry.

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