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TUTORIAL REVIEW

Transition-metal-free C-C bond forming reactions of aryl, alkenyl and alkynylboronic acids and their derivatives

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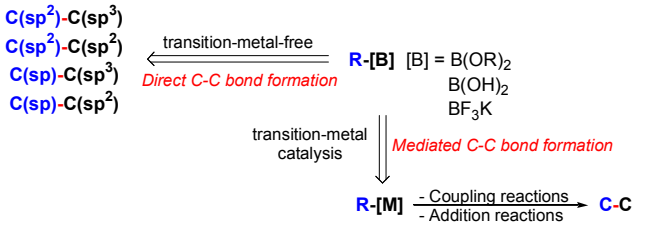
Investigations towards new methods for the synthesis of C-C bonds are fundamental for the development of new organic drugs and materials. Aryl-, alkenyl- and alkynylboronic acids and their derivatives constitute attractive reagents towards this end, due to their stability, low toxicity and ease in handling. However, these compounds are only moderately nucleophilic. Consequently, the most popular C-C bond forming reactions of these boronic acids, such as the Suzuki-Miyaura, Heck, and Hayashi-Miyaura reactions, or additions to C=O and C=N bonds, require catalysis by transition metals. However, due to the toxicity and cost of transition metals, some new methods for C-C bond formation using aryl-, alkenyl- and alkynylboronic acids under transition-metal-free conditions are beginning to emerge. In this tutorial review, the recent synthetic advances in this field are highlighted and discussed.

Key learning points
(1) Transition-metal-free catalysis
(2) C–C bond formation
(3) Boronic acids
(4) Stereochemisty

1. Introduction

The fundamental skeleton of organic molecules is constituted by hydrocarbon chains sprinkled with heteroatom-containing functional groups. The efficient building of such type of compounds requires the availability of two main types of synthetic methods: Those that make possible the construction of C–C bonds, and those that permit functional group transformations.

The development of new versatile procedures that enable the formation of C-C bonds with high selectivity, operational simplicity, functional-group tolerance, and environmental friendliness, using easily available starting materials, is a hot topic of active research highly valuable in the discovery of new drugs and materials. Among the different reagents useful for this purpose, boronic acids and their derivatives stand out due to their unique *green* characteristics, as they have low toxicity and are finally degraded to boric acid.[1] In addition, their manipulation does not require subambient temperatures, inert atmosphere, or anhydrous solvents, and they are widely compatible with sensitive functional groups which are readily attacked by other organometallics. The sum of these properties makes them highly attractive for large-scale synthesis. As an extra bonus, many of these compounds have become commercially available, and new methods for their preparation are being continuously reported in addition to the lots of already existing procedures.



Scheme 1 Methods for C-C bond formation with boronic acids

Aryl-, alkenyl- and alkynylboronic acids transmetallate easily to transition-metal complexes (Scheme 1). This makes possible a mediated C-C bond formation, the boronic acid acting as ultimate carrier of the carbon framework and the transition- metal being the true species responsible of the bond forming process. Thus, the most popular C-C forming reactions of these reagents such as couplings with aryl- and alkenylhalides and surrogates (the Suzuki-Miyaura reaction),

couplings to alkenes and alkynes (Heck-type reactions), conjugate additions (Hayashi-Miyaura reaction), and additions to C=O and C=N bonds are catalyzed by transition metals.[1]

Despite the amply recognized efficiency of these synthetic methods, the cost and toxicity of transition-metals has urged the development of new metal-free reactions. One of the handicaps of aryl-, alkenyl- and alkynylboronic acids and their derivatives is their low intrinsic nucleophilicity, which limits their participation in direct C-C bond forming processes with carbon-centered electrophiles. The benzhydrylium methodology has been recently applied by Mayr and Knochel for the evaluation of the nucleophilicity of organoboron compounds towards the design of transition-metal-free C-C bond forming reactions.[2] This methodology consists in the description of the rates (k) of C-C bonding reactions by using the equation $\log k = s(N+E)$, where s is a nucleophile-specific parameter, N is a nucleophilicity parameter, and E is an electrophilic parameter. Twenty-three diarylcarbenium ions have been defined as the electrophile basis set. Variation of the substituents alters their electrophilicities by 16 orders of magnitude. The application of Mayr´s equation has put forward a nucleophilicity of boronic acids in between that of organolithiums and organosilicons. Variations in nucleophilicity have also been observed among different derivatives of the same organoboronic acid. Thus for example, the potassium trifluoroborate salt of 5-methyl-2-furylboronic acid is more nucleophilic than the pinacol ester, which in turn is more nucleophilic than the MIDA-ester. The applicability of this scaling has been experimentally corroborated in the addition of the trifluoroborate reagent to several Michael acceptors and to an acridinium ion.

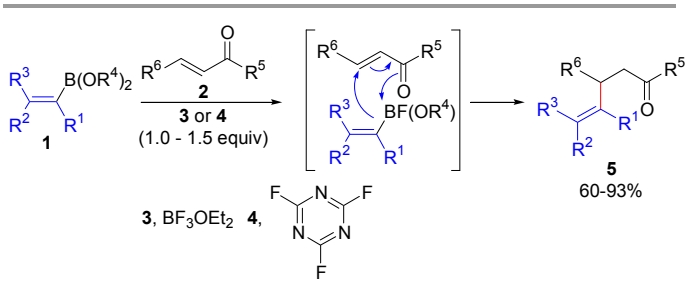
The uncatalyzed addition of boronic acids to imines and iminiums (the Petasis reactions and its variants) for the synthesis of substituted amines was disclosed in 1993 and has been extensively reviewed.[3] Comparatively, other synthetic transformations under metal-free conditions have remained scarce until recently. In this tutorial review, the recent synthetic advances in this field are highlighted and discussed.

2. Conjugate addition reactions

The addition of carbon-centered nucleophiles to electron-deficient alkenes constitutes one of the most relevant synthetic methods for C-C bond formation. In this regard, the transition-metal-catalyzed conjugate addition of aryl- and alkenylboronic acids and their derivatives to α,β-unsaturated carbonyl compounds has been amply developed (the Hayashi - Miyaura reaction), mainly using Rh(I), Ir(I) and Pd(II) catalysts.[1] The transition-metal-free variant of the conjugate addition reaction was the first of these types of transformations to be developed.

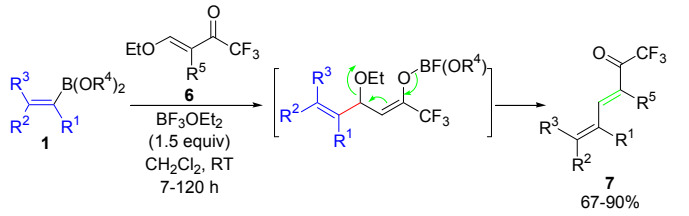
2.1. Early achievements and non-stereoselective syntheses

Transition-metal-free conjugate addition reactions of boronic acids and their derivatives were pioneered by the studies carried out in the 1990 decade by the group of Suzuki and Hara (Scheme 2).[4] They reported firstly that alkenylboronic esters and acids could add to acyclic α,β-unsaturated ketones under the action of BF_3. Subsequently they found that the reaction of alkenylboronic acids could be better promoted by cyanuric fluoride. This allowed the presence of acid-sensitive functionalities which were not tolerated by the initial method with BF_3. These reactions were of general scope but sensitive to steric hindrance at the β-position of the unsaturated ketone. This feature was used in advantage to functionalize α,β,α´,β´−diunsaturated ketones regioselectively. The transformations proceeded by the intermediacy of fluoroalkoxy- or fluorohydroxyboranes, generated either by disproportionation with boron trifluoride or by nucleophilic aromatic substitution on the triazine skeleton of cyanuric fluoride. The B-F bond increased the electron-deficiency of boron, and the conjugate addition reaction could take place by activation of the carbonyl group in a cyclic transition state.



Scheme 2 Conjugate addition of alkenylboronic esters and acids promoted by BF_3 or cyanuric fluoride. Reagents and conditions: a) **3** (1 equiv), CH_2Cl_2, Δ, 4 h - 2 days; b) **4** (1.5 equiv), Δ, 16 h - 6 days

More recently, it has been shown that this type of alkenylation can also be promoted by trifluoroacetic anhydride (TFAA, 0.3 equiv).[5] The experimental procedure is simple (CH_2Cl_2, 60 ºC, 18 h) and tolerant of β,β-disubstitution on the enone (65 - 90% yield). The use of BF_3 as promoter has been extended to the 1,4-alkynylation of acyclic enones, making use of diisopropoxyboronates (60 - 85% yield) or the bench-top stable potassium alkynyltrifluoroborates as reagents (40 - 87 % yield).[6-8]



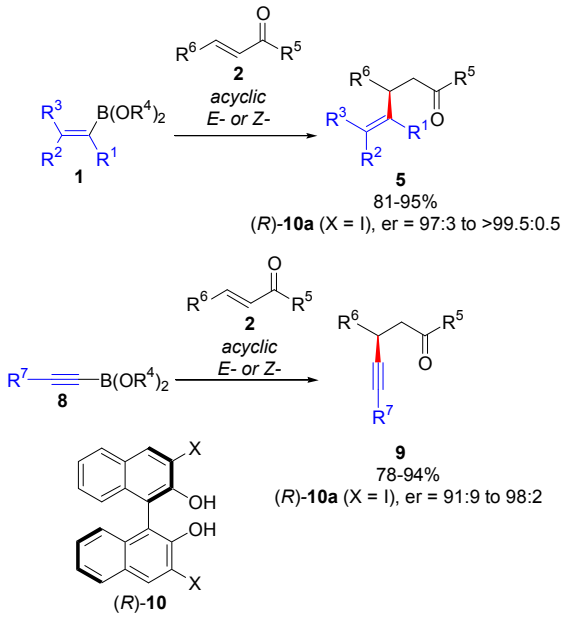
Scheme 3 Metal-free addition-elimination reaction.

In a related work,[9] Hara and Suzuki reported the synthesis of alkadienyl trifluoromethylketones by the reaction of alkenylboronic esters with 2-ethoxyvinyltrifluoromethylketones **6** under the action of BF_3 (Scheme 3). These transformations took place by an addition-elimination pathway, and from the standpoint of the end products, they are formally equivalent to the well-known metal-catalyzed Heck reaction. In these processes the stereochemistry of the starting alkenylboronic

ester was preserved, and the new C=C bond was formed selectively with the $COCF_3$ and incoming alkenyl group in *E* relative disposition.

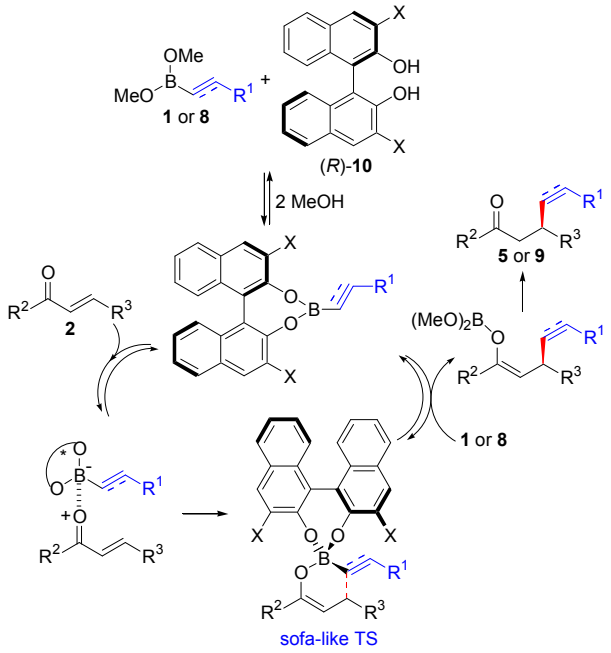
2.2. Stereoselective syntheses

Particularly noteworthy are the stereocontrolled variants of the conjugate addition reaction. Chong et al. reported the first catalytic enantioselective version of the conjugate addition of alkynylboronic esters using opticaly pure 3,3´-disubstituted-2,2´-binaphthols, which was subsequently applied to alkenyl groups (Scheme 4).[10-12] Alkenylboronic acids afforded lower yields and stereoselectivities. It was observed that simple diols such as ethyleneglycol, pinacol or diisopropyl tartrate gave no product in the reactions of alkenylboron reagents, albeit diisopropyl tartrate catalyzed the reaction of alkynylboronates but giving racemic product. It was also observed that rates of the reactions with methyl or isopropyl esters were negligible in comparison with the rate of the reaction with binaphthyl esters. Therefore, this transformation constitutes a rare example of ligand-accelerated catalytic asymmetric process. The reactions took place with high yields and enantiomeric ratios for a wide variety of enones and boronic acids. Best conversions and enantioselectivities were observed when using binaphthol (*R*)-**10a** (X = I) as catalyst.



Scheme 4 Catalytic enantioselective conjugate additions catalyzed by 3,3´-disubstituted-2,2´-binaphthols. Reaction conditions: **10a** (X = I, 10 - 20 mol%), CH_2Cl_2, MS 4A, 40 - 60 °C.

Theoretical DFT studies carried out by Goodman and Pellegrinet[13,14] put forward a finally balanced catalytic cycle (Scheme 5) that is initiated by a reversible exchange of the methoxy ligands of the starting dimethylboronate (**1** or **8**) with the chiral binaphthol **10**. This generates an active binaphthylboronate ester, highly Lewis acidic and hence more reactive than the original dimethylboronate. Strong reversible coordination with the carbonyl oxygen of the enone lowers the energetic barrier of the subsequent fast and reversible intramolecular conjugate addition step, which goes through a sofa-like transition structure (five atoms of a six-membered ring in the same plane). In this transition state the boron atom is strongly bound to the carbonyl oxygen and lies in the plane of the enone moiety. The formation of this complex favours both the kinetics and the thermodynamics of the overall process. A boron binaphthylenolate is thus formed, which finally disproportionates with the starting dimethylboronate releasing the chiral binaphthylboronate to continue the catalytic cycle. Consistently with this mechanism, no reaction was found for enones unable to adopt an *s*-cis conformation.



Scheme 5 Catalytic cycle of the conjugate alkenylation catalyzed by binaphthols **10**.

FMO theory has been used to account for the greater reactivity of an alkenylbinaphthylboronate with respect to an alkenyldimethylboronate. Inspection of the optimized geometries of both reactants suggested that in the alkenylbinaphthylboronate the oxygens are less able to donate electron density to the boron atom, generating a higher electron deficiency on boron. This is further enhanced by delocalization of the oxygen lone pairs into de adjacent aromatic system, an effect reinforced by the presence of electron-withdrawing groups in the 3 and 3´ positions of the binaphthyl moiety. These effects lower considerably the LUMO of the alkenylbinaphthylboronate. The interaction between this LUMO and the HOMO of the enone gives rise to the formation of the coordination complex, which has a higher energy HOMO and a lower energy LUMO, and therefore experiences a very favorable HOMO/LUMO intramolecular interaction. On the other hand, the coordination complex between the alkenyldimethylboronate and the enone shows a weaker intramolecular HOMO/LUMO interaction, which is similar to that computed in the parent reagents.

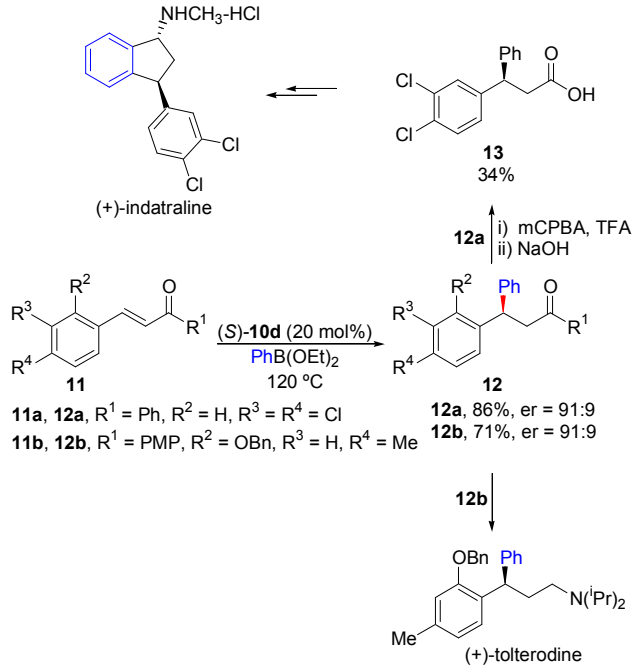
From the standpoint of the enantioselectivity, when using an (*R*)-configured binaphthol, the front face (*Re*) of the alkenyl or alkynyl moiety is shielded by one of the groups in position 3 of the chiral ligand, and the back face (*Si*) is the one that interacts with the front face of enone (*Re*) in an *ul* fashion.

The Chong reaction has been applied to the functionalization of heteroaryl-appended enones using alkenylboronic acids and alkynylboronic esters with high yields and enantiomeric ratios (75 - 93%, er = 80:20 to 99:1) for a wide variety of heterocycles, including furans, thiophenes, pyridines, quinolines, pyrazines, thiazoles, and either N-protected or N-unprotected pyrroles, imidazoles or indoles.[15,16] These constitute a challenging type of substrates due to the ease of epimerization of the final products and the propensity of the heterocyclic systems to deleterious side reactions in the presence of acid, base, oxygen and/or light. Successful reaction conditions (toluene, reflux, 4A MS, binaphthyl catalysts, 15 mol%) required an enhancement of the Lewis acidity of the chiral binaphthylalkenyl (or alkynyl) boronate. Best results were obtained with second-generation binaphthyls **10** endowed with highly electron-actractive substituents at their 3 and 3´positions (**10b**, X = perfluorophenyl, **10c**, X = *p*-CF_3-tetrafluorophenyl, 20 mol%). Also, the reactions were accelerated in the presence of substoichiometric amounts (0.1 equiv) of ^{t}BuOH or $Mg(O^tBu)_2$, which were postulated to facilitate the protonation of the chiral boron enolate intermediate.

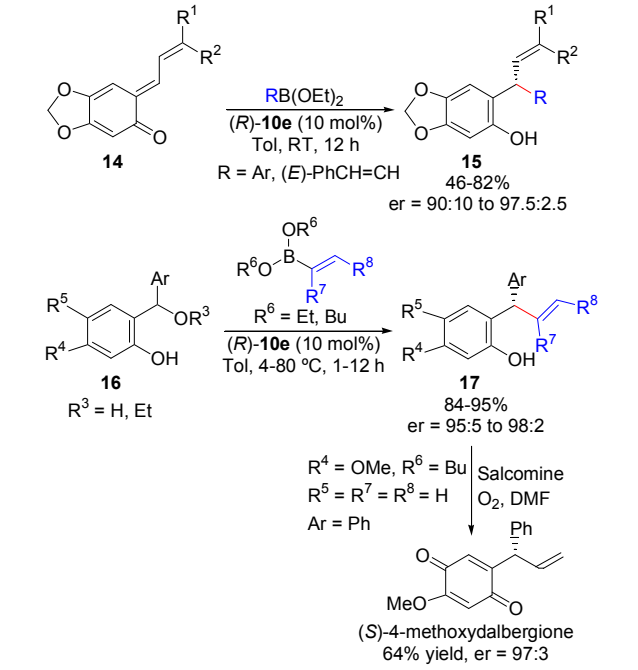
Arylations have proven elusive using conditions similar to those found to be effective for alkenylboronates. Chong et al. found that the asymmetric conjugate addition of arylboronate esters was possible using 3,3´-dichloro-2,2´-binaphthol as catalyst (**10d**, 20 mol %) under neat conditions (4 equiv of $ArB(OEt)_2$) after prolonged heating (120 ºC, 24 - 72 h).[12] Products were obtained with yields (70 - 90%) with high enantiomeric ratios (88:12 to 99:1). The utility of this reaction in drug synthesis was demonstrated with $PhB(OEt)_2$ in the preparation of advanced intermediates previous routes to (+)-indatraline and (+)-tolterodine (Scheme 6).

Schaus et al. have found that chiral binaphthols are able to catalyze the enantioselective addition of (hetero)aryl and alkenylboronates to *o*-quinone methides with high yields and enantiomeric ratios when using 3,3´-dibromo-2,2´-binaphthol (*R*)-**10e** (Scheme 7).[17] These systems are more reactive than classical enones, as the conjugate addition process is thermodynamically driven by aromatization. They have also shown that the chiral boronate intermediates are acidic enough to generate *in situ* labile *o*-quinone methides from *o*-hydroxy-substituted benzyl alcohols or ethers. The method has been applied to the two-step synthesis of (*S*)-4-methoxydalbergione.

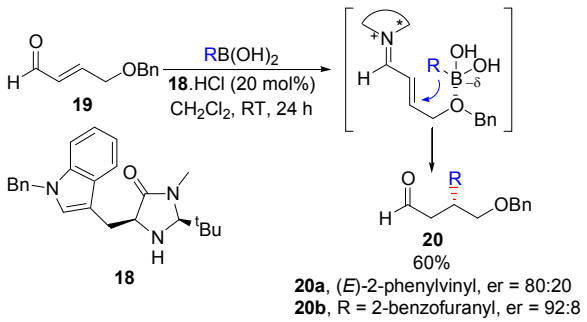
Enals and enones bearing an oxy substituent at the γ-position have attracted particular interest as substrates for conjugate additions, as the products of these reactions may lead to unique cyclic compounds. MacMillan et al. pioneered the extension of the three-component 1,2-iminium addition of aryl- and vinylboronic acids to α-hydroxyaldehydes devised by Petasis to the functionalization of the β-carbon by means of a two-component condensation in which the amine acted as catalyst.[18] Thus, under the influence of the imidazolidinone catalyst **18**, LUMO lowering together with boron activation led to the conjugate addition products of 2-phenylvinyl and 2-benzofuranyl boronic acids to 4-benzyloxybutenal (Scheme 8).



Scheme 6 Conjugate arylations catalyzed by 3,3´-dichloro-2,2´-binaphthol **10d**.

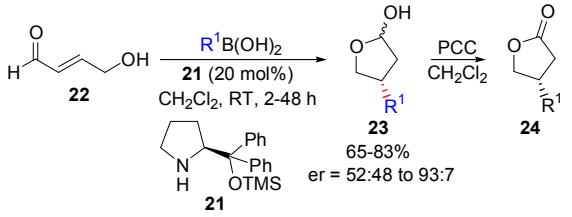


Scheme 7 Enantioselective conjugate additions to *o*-quinone methides.

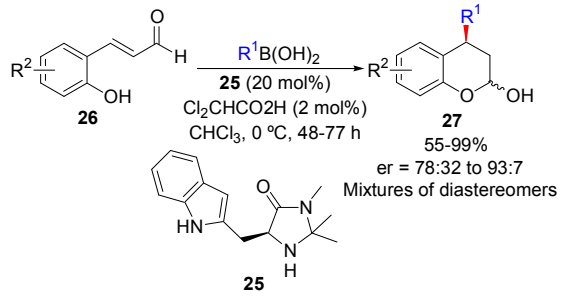


Scheme 8 Iminium catalysis in the conjugate addition to γ-oxy-substituted aldehydes.

Using γ-hydroxybutenal as substrate, Kim et al. were able to catalyze the conjugate addition of vinylboronic acids with good yields and high enantioselectivities (Scheme 9).[19] The addition of (hetero)arylboronic acids was possible only for electron-rich substrates, but required the presence of NaOH as activator and took place with low enantiomeric ratios (52:48 to 61:39). The products were transformed into the β-substituted γ-lactones **24**. These findings were extended to *o*-hydroxycinnamaldehyde to generate the chiral chromanols **27** (Scheme 10).[20,21]



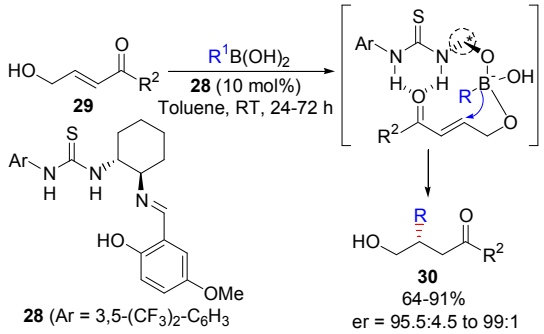
Scheme 9 Synthesis of the β-substituted γ-lactones **24**. Additional reaction conditions: H_2O (2 equiv, R^1 = alkenyl); 0.5 M NaOH (10 equiv, R^1 = Ar).



Scheme 10 Synthesis of the chiral chromanols **27**.

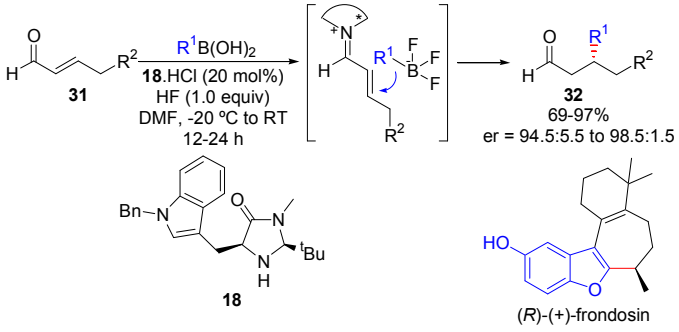
More recently a resin-supported peptide catalyst has been used for the conjugate addition to γ-hydroxybutenal.[22] Again, good results (yields and enantiomeric ratios) were found for alkenylboronic acids, but lower enatiomeric ratios were reported for (hetero)arylboronic acids.

An iminophenol-type thiourea catalyst has been reported to promote the conjugate addition reaction of alkenylboronic acids to γ-hydroxyenones with high enantiomeric ratios (Scheme 11).[23] The combination of carbonyl activation together with boron activation by formation of a boron-tethered nucleophile through coordination with the γ-hydroxy group of the substrate was postulated as responsible of the reaction in an intramolecular fashion.



Scheme 11 Thiourea-catalyzed conjugate addition to γ-hydroxyenones.

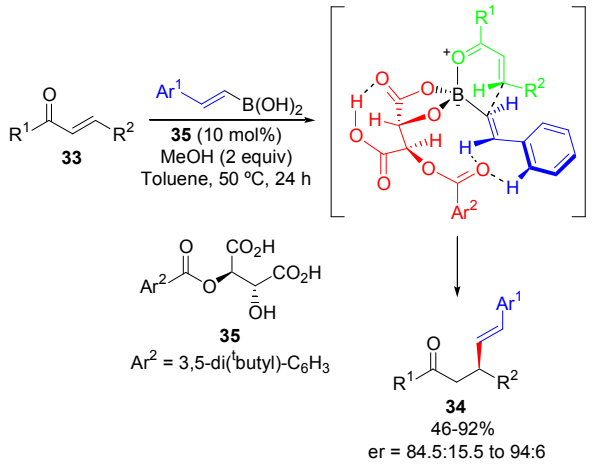
Conjugated carbonyls devoid of an anchoring group able for boron activation have been found more reluctant to the organocatalyzed asymmetric conjugate addition of (hetero)aryl- and vinylboronic acids. The iminium activation of MacMillan was successful when using potassium trifluoroborates instead of boronic acids (Scheme 12).[18] The use of trifluoroborates avoids the requirement of pre-association to an alkoxy group pendant from the substrate. Both vinyl and heteroaryltrifluroborates, but not phenyl derivatives, reacted with good yields and enantiomeric ratios. The presence of HF was required to sequester the BF_3 byproduct in the form of a KBF_4 precipitate. This protocol has been used as key step (94%, er = 94:06) for the synthesis of (+)-(R)-frondosin B (4 steps, 61%) by reaction between potassium 5-methoxy-2-benzofuranyltrifluoroborate and crotonaldehyde.[24]



Scheme 12 Iminium catalysis in the conjugate addition of potassium trifluoroborates.

Diisopropyl tartrate had been reported not to catalyze the conjugate addition of alkenylboronic acids to enones, and to give racemic products in the additions of alkynylboronates. Also, tartaric acid derived catalysts afforded very low enantiomeric ratios in the additions of arylboronates to *o*-quinone methides. However, Sugiura et al. found that *O*-monoacyltartaric acids were useful for the addition of alkenylboronic acids to enones (Scheme 13). Among the different substrates assayed to test the influence of the electronic effect and the bulkiness of the substitution in the

performance of the catalyst, the 3,5-di-^{t}butylbenzoate group gave the best results.[25] Theoretical DFT calculations[26] suggest transition structures that are stabilized by strong H-bonding between the free carboxy group derived from the catalyst and the carbonyl group of the cyclic acyloxyborane, together with weak nonclassical H-bonds with the carbonyl group of the 3,5-di-^{t}butylbenzoate moiety. Also 2-furyl (55% yield, er = 84:16) and 2-benzofuranylboronic acids (79% yield, er = 90.5:9.5) showed moderate enantioselectivities.[25]

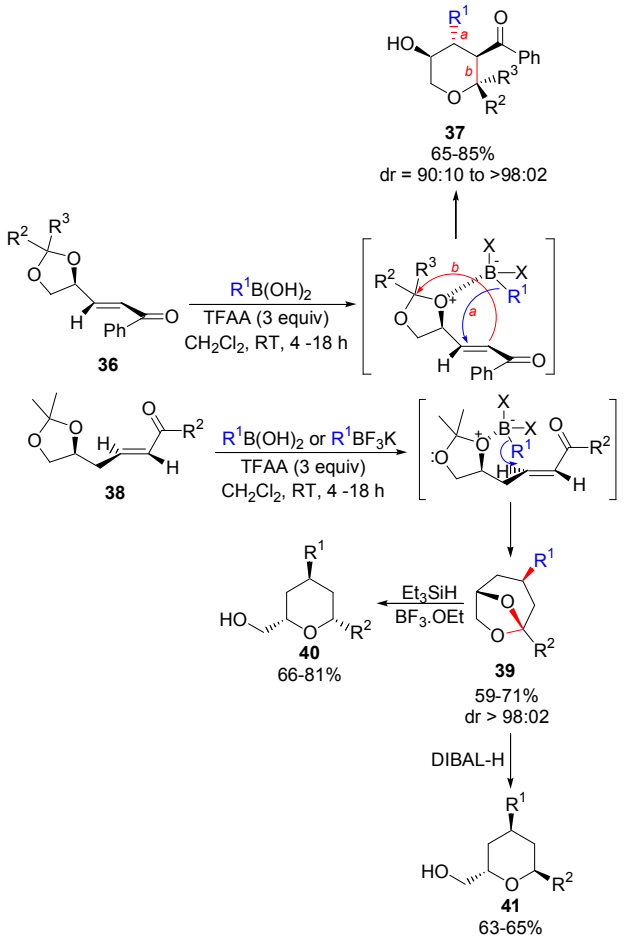


Scheme 13 Catalytic enantioselective conjugate additions catalyzed by *O*-3,5-di(^{t}butyl)benzoyltartaric acid **35**.

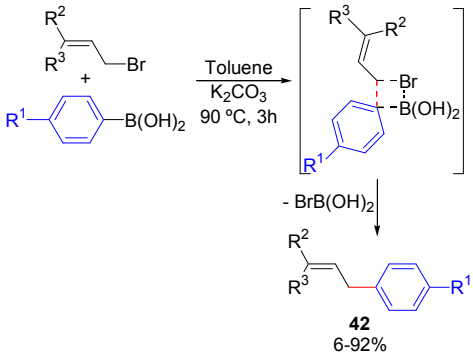
Diastereoselective versions of the conjugate addition of alkenylboronic acids activated by trifluoroacetic anhydride (TFAA) have been developed towards the synthesis of densely functionalized tetrahydropyrans (Scheme 14). When starting from the glyceraldehyde-derived acetals **36**,[27] a tandem process initiated by the diastereoselective conjugate addition of an alkenylboronic acid and followed by the intramolecular ring-opening of the cyclic acetal led to optically pure polysubstituted tetrahydropyrans. Two new C-C bonds and up to three stereocentres were formed in a single step. The reaction allows the generation of quaternary sterocentres. On the other hand, when starting from compounds **38**,[28] the substrate-controlled 1,3-diastereoselective conjugate addition of alkenylboronic acids or potassium alkenyltrifluoroborates was followed by transacetalization to the bicylic acetals **39**, which were used as key intermediates in the stereodivergent synthesis of optically pure polysubstituted tetrahydropyrans.

3. Transition-metal-free Suzuki reactions

In 2003, Leadbeater and Marco reported the transition-metal-free Suzuki reaction of aryl bromides with a limited set of arylboronic acids for the synthesis of biphenyls.[29] The reaction was carried out in water under MW irradiation at 150ºC in the presence of sodium carbonate. Although no traces of metals were detected by inductively coupled plasma atomic absorption spectroscopy down to 1 ppm, they found later that in fact the process was an ultra-low metal-catalyzed Suzuki coupling,[30] as minute amounts of only 50 ppb of palladium present as contaminant of the commercial base (Na_2CO_3) were able to catalyze the reaction. Much more recently, Scrivanti et al. have reported the coupling of arylboronic acids with electron-rich allylic bromides through conventional heating in toluene in the presence of K_2CO_3 (Scheme 15).[31] The reaction was found to be completely regioselective, affording only the α-coupled products **42**, in sharp contrast to the Pd-catalyzed reaction, which gave rise to mixtures of regioisomeric alkenes.



Scheme 14 Tandem conjugate addition - cyclizations towards the synthesis of polysubstituted tetrahydropyrans.

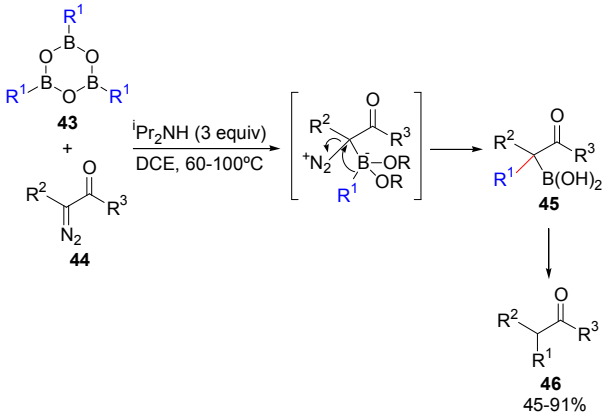


Scheme 15 Metal-free Suzuki alkenylation of arylboronic acids.

Analyses carried out by inductively coupled plasma mass spectroscopy were able to detect transition-metals only below 4.1 ppb, a concentration which seems too low to promote a metal-catalyzed reaction. The transformation may take place *via* the formation of an adduct between the boronic acid and the allylic bromide, followed by migration of the aryl from the boron to the α-carbon of the allyl in a concerted fashion. Using Cs_2CO_3 (CH_2Cl_2:H_2O 10:1, 60ºC, 18 h), Ryu *et al* have been able to extend the scope and generality of the reaction including the possibility of coupling allylic bromides with alkenylboronic acids (56-95% yields).[32] The change of CH_2Cl_2 for $CHBr_3$ together with an increase in the reaction temperature to 90ºC has permitted the reaction of electron-rich arylboronic acids with arylpropargylic bromides (13-84% yields).[32]

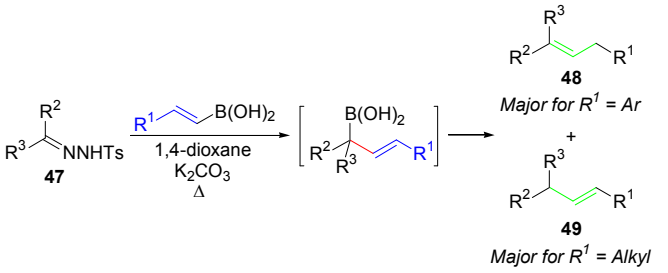
4. Reactions with α-diazocarbonyl compounds and tosylhydrazones

In a useful alternative to the Pd-catalyzed Buchwald-Hartwig arylation of carbonyl compounds, Wang et al. reported the transition-metal free reductive arylation and alkenylation of α-diazoketones, esters and amides with boroxines under mild conditions (Scheme 16).[34] The reaction was thought to proceed by an initial attack of the nucleophilic diazo carbon to the boron atom of the boroxine, followed by 1,2-migration of the aryl or alkenyl backbone with concomitant elimination of N_2. Final protodeborylation of the resulting alkylboronate would account for the final product. Diisopropylamine was required presumably to prevent the diazo substrate from decomposition in the presence of acidic subproducts.



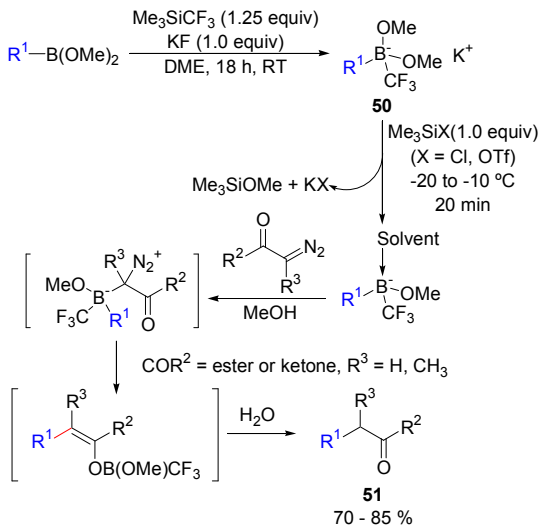
Scheme 16 Arylation and vinylation of α-diazocarbonyl compounds with boroxines.

The scope of this type of reaction has been considerably broadened by the group of Barluenga and Valdés et al. by using tosylhydrazones derived from ketones and aldehydes as precursors of unstable diazocompounds and boronic acids instead of boroxines (51-99% yields).[35] The reaction required a relative high temperature (dioxane, 110ºC) in the presence of a base (K_2CO_3, 1.5 equiv) in order to generate the diazocompounds. This transformation, which is tolerant of a wide variety of sensitive functional groups either in the tosylhydrazone or the boronic acid counterparts, could be carried out as a one-pot procedure by mixing tosylhydrazide with the corresponding aldehyde or ketone prior to the addition of an arylboronic acid without isolation of the resulting tosylhydrazone, and was amenable to multigram scaling. The overall transformation can be considered a direct reductive coupling of a carbonyl compound, an unprecedented reaction. This reductive coupling was demonstrated to take place also with alkylboronic acids. Initial results with alkenylboronic acids or unsaturated ketones gave rise to a mixture of alkenes that differ in the position of the double bond. Further refinement of the reaction[36] (Scheme 17) turned out a new method of olefination of ketones in a predictable manner depending on the nature of the substituents. Different behaviour was observed between alkenylboronic acids R^1-CH=CH-$B(OH)_2$ with R^1 = aryl or R^1 = alkyl. The former gave rise to the formation of the alkene **48**, with the only exception of pyruvate-like hydrazones, which gave mixtures of **48** and **49** (49-96 % yield). When dealing with non-symmetrical ketones, good E/Z ratios were obtained depending on the structure. On the other hand, 2-alkyl-substituted boronic acids afforded as major compound the alkene regioisomer **49**, with the exception of aryl-alkyl hydrazones, which gave mixtures of **48** and **49**. It was also noted that reactions with R^1 = alkyl took place with lower yields (35-69%), requiring MW heating at 150 ºC. The formation of two regioisomers was attributed to the possibility of different rates for α- or γ-protonation of the allylboronic intermediate depending on the substitution pattern, although the intervention of [1,3]-borotropic rearrangement followed by protonation was not discarded.



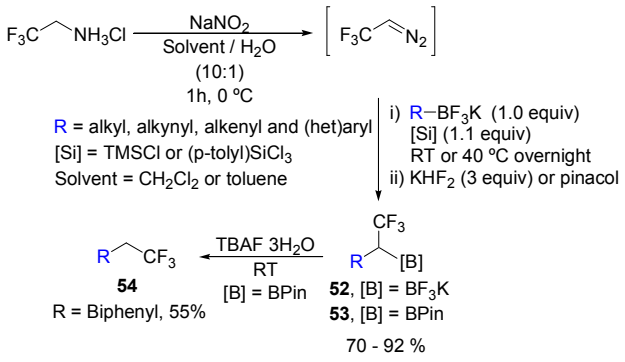
Scheme 17 Reductive alkenylation of tosylhydrazones with boronic acids.

The Barluenga boronic coupling has been implemented in a continuous flow system,[37] and has also been tuned for the preparation of small drug-like and drug fragment-like compounds containing heterocyclic moieties.[38,39] Borinic acids have been used as alternative to boronic acids in the synthesis of diarylmethanes.[40] Stable potassium alkyl, aryl, alkenyl and alkynyltrifluoromethyldimethoxy boronates **50** react with TMSCl and α-diazocarbonyl compounds to give similar products **51** (Scheme 18).[41]



Scheme 18 Reactions of CF_3-substituted boranes with α-diazocarbonyl compounds.

Using 2,2,2-trifluorodiazoethane, Molander *et al* have been able to isolate the bench-stable α-trifluoromethylated potassium trifluoroborates **52** or pinacolboronates **53** which result from the addition of RBF_3K reagents (R = alkyl, alkynyl, alkenyl and (het)aryl) in the presence of TMSCl or (*p*-tolyl)$SiCl_3$ (Scheme 19).[42] These compounds were amenable to classical C-B fuctionalization reactions such as protodeboronation, thus providing a good method for trifluoroethylation (*eg.*, **54**).



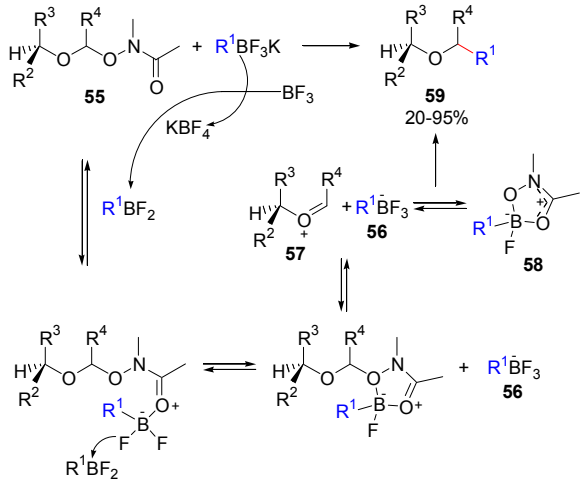
Scheme 19 Synthesis and applications of α-trifluoromethylated alkylboron compounds

5. Reactions with persistent carbenium ions

5.1. Functionalization of acetals

In a general approach to the synthesis of non-symmetically substituted dialkyl ethers under mild conditions, Bode et al. reported the reaction of (hetero)aryl-, alkenyl- and alkynyltrifluoroborates with mixed acetals (Scheme 20).[43,44] Treatment of *O*-methoxymethyl (MOM) acetals with potassium alkynyl and alkenyltrifluoroborates in the presence of $BF_3.OEt_2$ afforded the corresponding ethers with good yields. The reaction also tolerated aryltrifluoroborates, but poor results were observed for electron-deficient substrates. Further improvement of the reaction parameters led to the use of a hydroxamate leaving group that improved the regioselectivity of challenging substrates, reduced the requirement of a large excess of organotrifluoroborate and Lewis acid as well as their precomplexation, and improved the yields, permitting the use of electron-withdrawing aryls as well as heteroaryls.

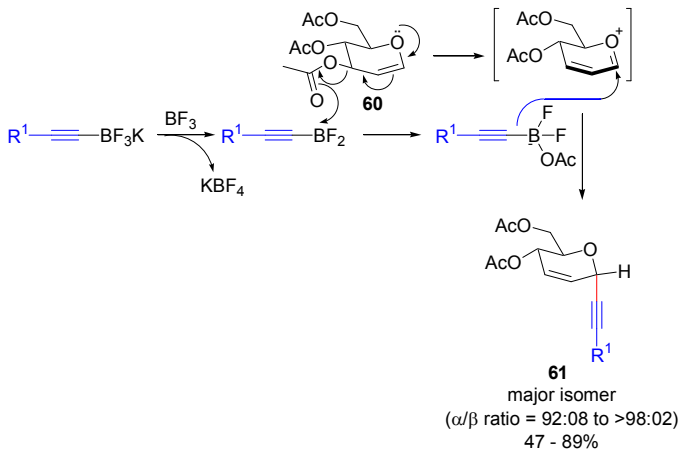
The isolation of a putative intermediate, crossover and control experiments, and careful study of the reaction by ^{1}H-NMR allowed for the proposal of a revised mechanism.[44] The reaction is initiated by the *in situ* generation of an organodifluoroborane from the interaction of the starting potassium organotrifluoroborate and BF_3. The enhanced Lewis acidity of the boron atom in this species facilitates coordination to the hydroxamate leaving group. Fluoride abstraction with RBF_2 leads to the formation of a five-membered ring complex, which reversible dissociates to the organotrifluoroborate **56** and the oxocarbenium ion **57**, in equilibrium with complex **58**. Either **56** or **58** may act as nucleophiles to transfer the organic moiety R^1 to the oxocarbenium ion **57**, irreversibly forming the final ether product **59**.



Scheme 20 Synthesis of dialkyl ethers from organotrifluoroborates and acetals.

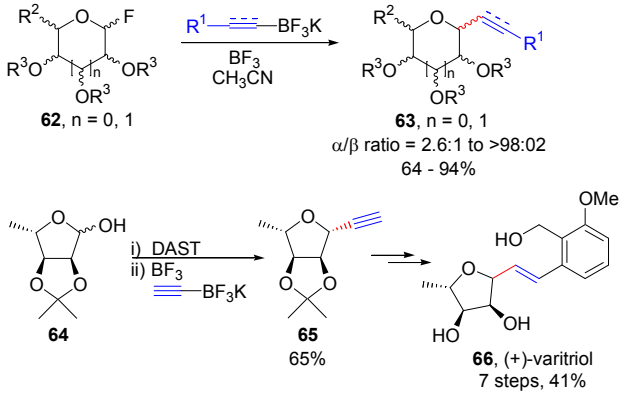
5.2. Reactions with other oxocarbenium Ions

C-glycosides constitute a particular type of ethers which have attracted considerable attention recently due to their pharmacological properties and their usefulness as building blocks. Stefani et al. devised a mild and highly stereoselective method for α-*C*-alkynylation by the interaction of D-glucal **60** with potassium alkynyltrifluoroborates under BF_3 activation (Scheme 21).[45] The reaction is presumed to take place by a Ferrier rearrangement that starts from the acetate scavenging of an allylic acetoxy group with the alkynyldifluoroborane which is generated from the alkynyltrifluoroborate and BF_3. Delivery of the alkynyl moiety from the acetoxydifluoroborate intermediate to the α-face of the oxonium cation at C-1 to give **61** as major isomer can be understood by electronic effects on the electrophile.



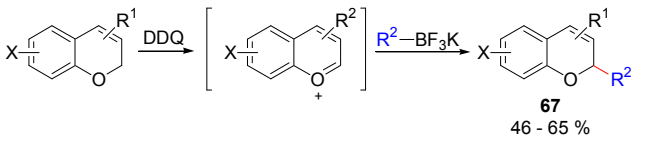
Scheme 21 Stereoselective synthesis of α-C-glycosides from a D-glucal. Reaction conditions: CH_3CN, BF_3OEt_2 (2 - 4 equiv), -45 to 0 °C, 10 - 20 min.

Glycopyranosyl and glycofuranosyl fluorides **62** can also be converted into *C*-glycosides **63** by reaction with alkynyl and alkenyltrifluoroborates under BF_3 promotion (Scheme 22).[46] The α-diastereoselectivity exhibited by most of the examples depends on the conformation of the oxonium intermediates. This methodology was applied to an efficient synthesis of the cytotoxic compound (+)-varitriol **66** using as key step the addition of potassiumethynyltrifluoroborate to glycosyl fluoride **64** (7 steps, 41% overall yield).



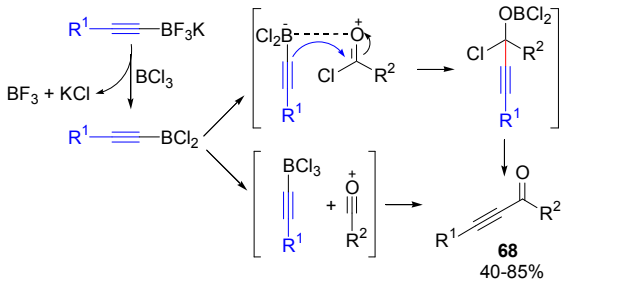
Scheme 22 Stereoselective C-glycosidation of glycosyl fluorides.

In a related work, Floreancig et al. have demonstrated the possibility of forming persistent aromatic oxocarbenium ions from the reaction of 2*H*-chromenes with DDQ through an oxidative C-H cleavage. Reaction of these oxocarbenium intermediates with alkynyl, alkenyl or phenylpotassium trifluoroborates afforded the corresponding 2-substituted-2*H*-chromenes **67** (Scheme 23).[47]



Scheme 23 Synthesis of the 2-substituted-2*H*-chromenes **67**. Reaction conditions: DDQ (1.3 equiv), $LiClO_4$ (1.0 equiv), 4A MS, CH_3CN, 0 °C

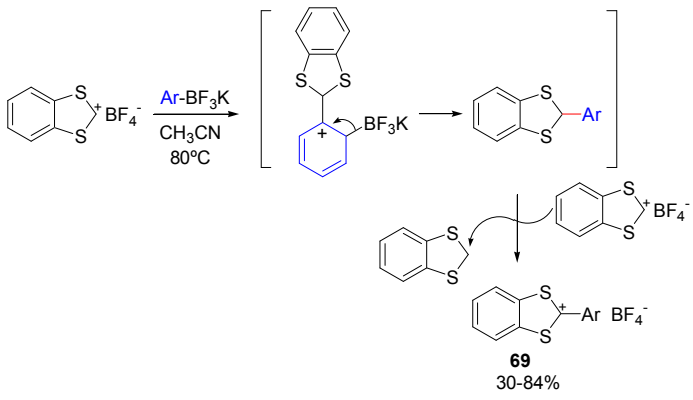
Bolshan *et al* have carried out the metal-free synthesis of ynones **68** from acyl chlorides and potassium alkynyltrifluoroborate salts in the presence of BCl_3 (Scheme 24).[48] The reaction takes place via the corresponding dichloroboranes either by direct complexation to the oxygen atom of the acyl chloride or by chlorine scavenging followed by reaction of an alkynyltrichloroborate with an oxocarbenium ion.



Scheme 24 Synthesis of ynones from acid chlorides and potassium alkynyltrifluoroborates. Reaction conditions: CH_2Cl_2, RT, 30 min.

5.3. Reactions with other carbenium ions

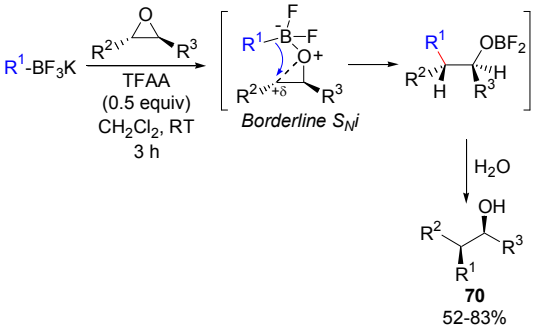
Other systems able to form relatively stable carbocations have also been successfully coupled with boronic acids. As stated in the Introduction, the reaction with benzhydrylium cations has been used to correlate the nucleophilicity of orgaboron compounds.[2] Taking advantage of this information, Cozzi *et al* have reported the reaction of potassium (hetero)aryltrifluoroborates with benzodithiolylium tetrafluoroborate (Scheme 25).[49] The transformation gives rise to the arylcarbenium ions **69** by a hydride shift with excess of the reagent. Salts **69** are stable in air, and can subjected to further reactions typical of 1,3-dithianes. The key C-C bond forming process is presumed to take place by an *ipso* Friedel-Crafts electrophilic aromatic substitution.



Scheme 25 Reaction of potassium aryltrifluoroborates with benzodithiolylium tetrafluoroborate.

6. Ring-opening of epoxides

We have recently reported the ring-opening reaction of epoxides with aryl and alkenyltrifluoroborates using trifluoroacetic anhydride (TFAA) as promoter (Scheme 26).[50] The reactions were completely regioselective, giving rise to the formation of a single diastereomer of alcohols **70** with retention of the configuration at the reacting centre of the epoxide. The reaction may take place by generation of a difluoroborane which can coordinate the oxygen of the epoxide thus enabling the operation of a borderline S_Ni mechanism. Lithium alkynyltetrafluoroborates react with terminal epoxides to afford the corresponding homopropargylic alcohols.[51]



Scheme 26 Stereospecific ring-opening of epoxides with potassium trifluoroborates.

7. Concluding remarks

The transition-metal-free C-C bond-forming reactions of aryl and alkenylboronic acids and their derivatives summarized in this Tutorial Review represent an important progress in the chemistry of this important type of reagents. Although a handful of reactions have been already been put forward, further developments are required both to emulate known reactions previously carried out in the presence of transition-metals, and more challenging, to devise new yet unknown transformations that may facilitate the synthesis of complex molecules.

Acknowledgements

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Notes and references

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