TUTORIAL REVIEW

How to make C-N bonds using boronic acids and their derivatives without transition metals

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This tutorial review describes recent developments in carbon-nitrogen bond-forming reactions (amination, amidation, nitration and nitrosation) that involve the use of boronic acids and some of their derivatives as carbon-nucleophiles in the absence of transition-metals. Issues pertaining to reagents and mechanisms are discussed.

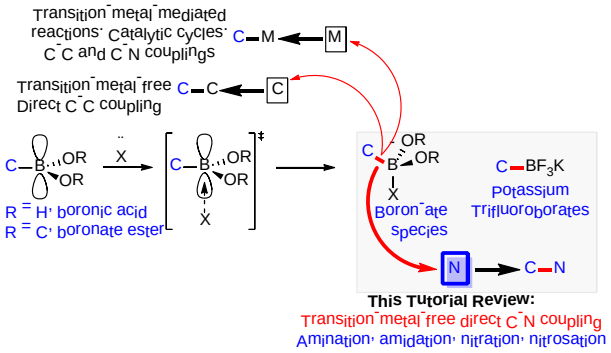
1. Introduction

C-N bond-formation is a hot topic in synthesis. Amines and amides are ubiquitous chemicals with broad practical application as pharmaceuticals, agrochemicals, polymers, and materials.[1,2] Besides, aromatic nitro[3] and nitroso[4] compounds constitute important building blocks for the synthesis of other nitrogen-containing molecules, including amines and amides. This has boosted the rapid development of multiple methods for the construction of C-N bonds.

Most of the modern C-N bond-forming procedures, such as the well-known Buchwald-Hartwig or Ullmann-Goldberg amination reactions, are based on the use of transition-metal catalysts.[5] These methods tend to overcome the serious limitations of classic C-N bond-formation such as S_N2 reactions (overalkylation and steric hindrance), S_NAr, S_EAr and aryne-mediated reactions (dependence on the electronics of the substituents on the aromatic moiety) or the N-acylation of acids or acid derivatives (stoichiometric amounts of activating reagents, use of water-labile and corrosive reagents including acid chlorides or anhydrides, incompatibility with unprotected OH and additional NH groups). Although with some limitations (*e.g.* aliphatic amines tend to coordinate strongly and easily inhibit the activity of metal complexes), these transformations are widely general. Their main shortcoming is that they frequently use toxic and expensive transition-metals whose removal from the final product can be cumbersome, and that many of them require complicated ancillary ligands and/or the presence of strong bases. In this realm, boronic acids and their derivatives have played a prominent role as C-nucleophiles in the Cu-catalyzed Evans-Chan-Lam C-N bond-forming reaction.[6]

Why use boronic acids in synthesis? Boronic acids, in particular, those with aryl moieties, are relatively bench-stable reagents that can be used as C-nucleophiles.[7] As opposed to conventional organometallics (*e.g.* organolithiums, Grignard reagents or cuprates), they can be handled with no special precautions against air or humidity. Also, they tolerate the presence of labile functional groups, like carbonyls or unprotected OH and NH. Their toxicity is low, they present no particular environmental issues, and upon consumption, they are finally converted into boric acid, so they can be considered as almost green reagents. Many of them are commercial, and there are lots of methods in the literature for their preparation. Replacement of the OH group of boronic acids by OR groups leads to boronate esters. Alkylboronic acids tend to be more sensitive to dehydration to anhydrides (formation of 1,3,5,2,4,6-trioxatriborinanes, known as boroxines) and to oxidation by air than their aryl counterparts. In these cases, the corresponding esters, which usually undergo the same reactions as boronic acids themselves, constitute a good alternative.

What is the drawback? Low C-nucleophilicity. According to the scale developed by Mayr,[8] in general lines the C-nucleophilicity of boronic acids and boronate esters lies in between that of organosilicons and organolithiums. However, this situation can be overcome by coordination (Scheme 1): From a structural standpoint, the boron atom in boronic acids and boronate esters has a trigonal planar sp^2-hybridization with the three substituents on the same plane and a low lying empty p atomic orbital perpendicular to it. This orbital has the correct energy to interact with n lone pairs (**X**) from heteronucleophiles (*e.g.* O, N) or with carbanionic species. This interaction gives rise to *ate* complexes (boron-ates), where the quaternized boron atom acquires sp^3-hybridization and a full electron octet. Al-



Scheme 1 Transition-metal-free C-N bond forming reaction using boronic acids and their derivatives.

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though boron-ates are depicted with a formal negative charge on boron, in fact this charge is spread out on the whole structure, and therefore, the carbon ligand (**C**) becomes anionically activated. This activation facilitates its transfer as a C-nucleophile to an electrophile in the vicinity. As a result, a new C-electrophile bond is formed, along with the boron going back to its original planar valence-unsaturated sp^2-shape. Potassium organotrifluoroborates are easy to handle crystalline derivatives of boronic acids that can be seen as stable *ate* complexes. In agreement with their anionic activation, the C-nucleophilicity of boron-ate complexes increases by factors > 10^5 in comparison with boronic acids or boronate esters.[8]

Traditionally, the most-used electrophiles for this type of C-electrophile bond-forming process have been high oxidation-state transition-metals (**M**, electron-poor) in organometallic compounds, which have vacant orbitals with the correct energy and symmetry to overlap with the electron-rich C-B bond. These newly generated organometallic templates may act as C-nucleophiles (*e.g.* in the Hayashi-Miyaura C-C bond formation) or can participate in reductive elimination processes that give rise to new C-C or C-N bonds (*e.g.* the Suzuki-Miyaura or the Evans-Chan-Lam reactions). In all these transformations, which take place in metal-based catalytic cycles, the starting boronic acid or boronate is only acting as a carbon feedstock, being the transient transition-metal complex (C-M) the actual reagent that participates in the key C-C[9] or C-N bond-forming process.

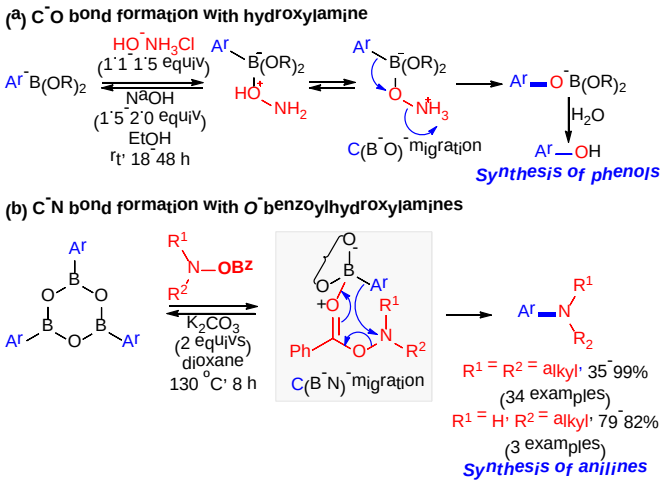
However, under certain circumstances, the C-B of boronic acids, boronate esters, or potassium organotrifluoroborates can be nucleophilic enough to engage directly in bond formation with carbon or nitrogen electrophiles. This Tutorial Review will show how to make amines, amides, nitroso and nitro compounds from boronic acids and their derivatives in a sustainable way, without the intermediacy of transition metals.

2. Amination reactions

2.1 Hydroxylamine derivatives

Hydroxylamine was originally reported as a reagent for the conversion of arylboronic acids and esters into phenols (Scheme 2a). However, Wang and co-workers have put forward (Scheme 2b) that conversion of the hydroxyl into a good leaving group still able to coordinate with B (OBz) can trigger the intramolecular nucleophilic attack on nitrogen instead of oxygen.[10] This strategy permits the synthesis of *N*,*N*-dialkylanilines using arylboroxines as reagents. The transformation is tolerant to aryl substituents such as halogens, ester, cyano, CF_3, and NHAc in *ortho*, *meta* or *para* positions, although it has only been reported for *N*,*N*-dialkylanilines with two equal alkyl substituents ($R^1 = R^2$), or embedded in a symmetric cycle (*N*-arylmorpholines, *N*-arylpiperidines). In addition to tertiary *N*,*N*-dialkylanilines, the reaction also permits the synthesis of bulky secondary *N*-alkylanilines (*e.g.* ^{i}Bu, ^{s}Bu, 2,4,4-trimethyl-pentan-2-yl) in good yields.

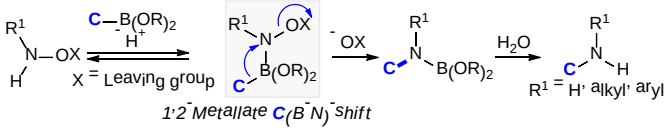
In contrast, some other hydroxylamine derivatives constitute useful reagents for the amination of boronic acids and their derivatives provided they have their OH group turned



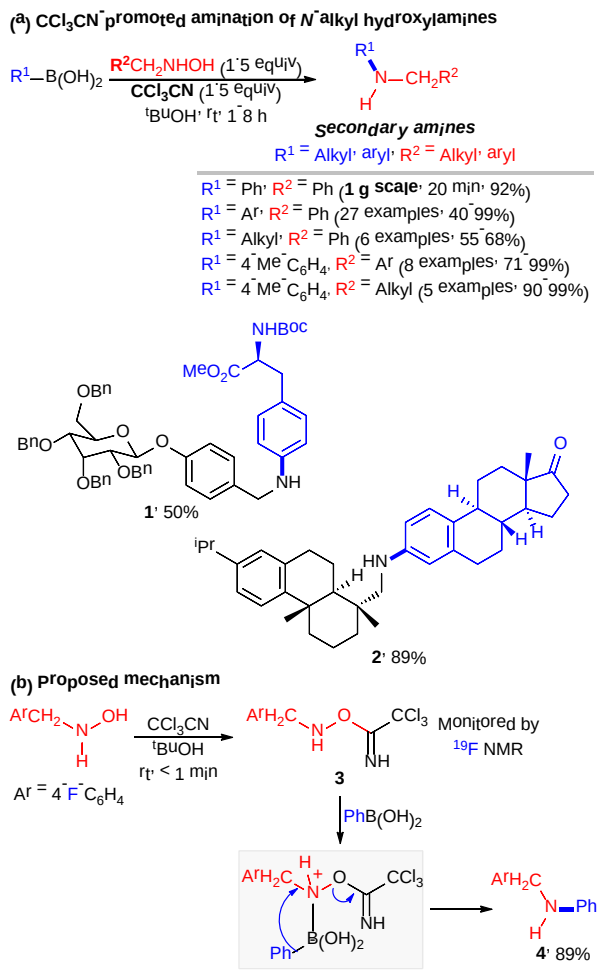
Scheme 2 C-O bond formation with hydroxylamine and C-N bond formation with *O*-benzoylhydroxylamines: Synthesis of phenols, and of tertiary and secondary anilines.

into a leaving group and are nucleophilic on nitrogen rather than on oxygen. The general mechanism for this kind of amination consists of the formation of an *ate* complex by the nucleophilic attack of nitrogen to boron, followed by an intramolecular substitution of the oxygen leaving group *via* a 1,2-C(B-N)-shift (Scheme 3). This strategy has proven of use for the synthesis of secondary and primary amines.

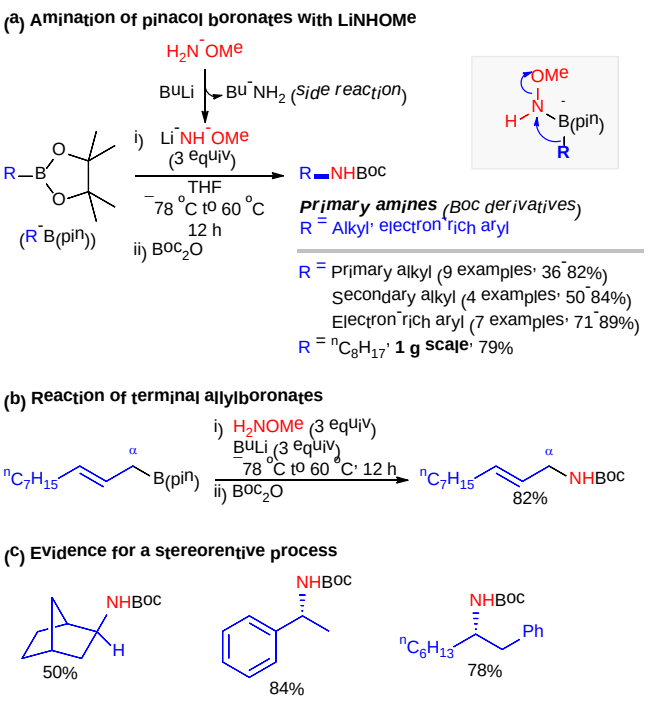
Thus, Niu and co-workers[11] managed to synthesize secondary amines by the reaction of boronic acids (alkyl and aryl) with *N*-alkyl hydroxylamines in the presence of CCl_3CN (Scheme 4a). The reaction is operationally simple, can be accomplished open to air, and does not require the presence of any base. In the case of (het)arylboronic acids, the method is tolerant of a wide range of functional groups, including halides, amides, ketones, esters, nitro, thiophene, furan and pyridine derivatives, and unprotected indole, alcohol or carboxylic acids, with substituents either at the *ortho*, *meta* or *para* positions. 2,4,6-Triphenylboroxine performs similarly to phenylboronic acid, but the corresponding pinacol ester or potassium trifluoroborate is unreactive. Alkylboronic acids (primary and secondary) are suitable reaction partners as well. Besides, both electron-rich and electron-poor (het)aryl groups are possible as substituents of the *N*-alkyl hydroxylamine moieties. With the exception of *N*-cycloheptylhydroxylamine (30% yield) the rest of *N*-alkyl hydroxylamines reported are primary. One of the main features of this methodology is the possibility of engaging sensitive substrates such as peptides, steroids or carbohydrates in the formation of secondary amines (*e.g.* **1**, **2**). ^{19}F NMR studies have put forward the rapid activation of a fluorinated *N*-benzyl hydroxylamine with CCl_3CN (rt, < 1 min) in the form of the *O*-imino hydroxylamine **3**. Upon exposure to $PhB(OH)_2$ followed by protonation, the *O*-imino hydroxylamine **3** furnishes the ex-



Scheme 3 N-B coordination of hydroxylamine derivatives followed by 1,2-C(B-N)-shift



Scheme 4 Trichloroacetonitrile-promoted amination of N-alkyl hydroxylamines: Synthesis of secondary amines.



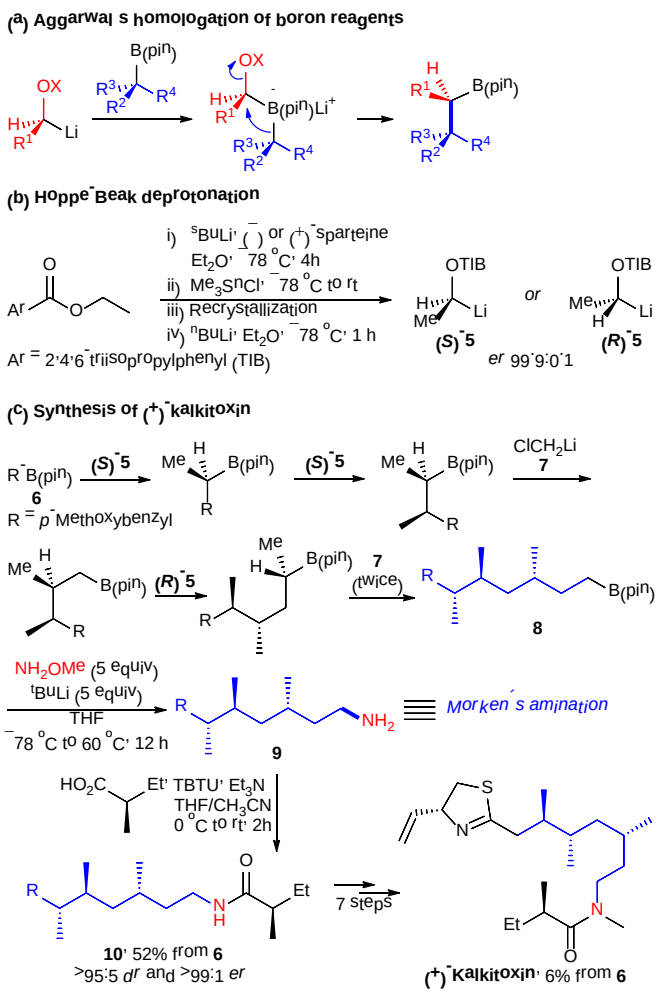
Scheme 5 Amination of pinacol boronates with LiNHOMe: Synthesis of primary anilines and C-primary and C-secondary primary alkyl amines (Boc derivatives).

pected product **4** (Scheme 4b). These observations suggest that the real aminating agent could be **3**. Hence, activation of the hydroxyl as a leaving group was achieved *in situ*, without the need for the independent synthesis of *O*-functionalized hydroxylamine derivatives. Using isotopic labelling, it was confirmed that the amination reaction was stereoretentive with respect to the C-B bond (Scheme 4c), in agreement with the proposed mechanism.

The preparation of primary amines was originally made possible by the almost simultaneous contributions of the groups of Morken[12] (boronate esters) and Kürti[13] (boronic acids).

Initial work by Morken[12] and co-workers enabled the stereospecific synthesis of aliphatic and aromatic primary amines from pinacol boronates (RB(pin)) using H_2NOMe/BuLi as the reagent (Scheme 5a). The reaction requires an excess of the aminating mixture to overcome the unavoidable competitive amination of BuLi (formation of butylamine, Bu^- acting as a nucleophile) in the deprotonation of $MeONH_2$. The reaction is effective for alkyl (primary and secondary) pinacol boronates with a variety of functional groups on their chains such as benzyl or TBS ethers, acetal, CN, and (*E*) or (*Z*) alkenes without isomerization, but fails for tertiary alkyl derivatives. The transformation is also possible in good yields using electron-rich aryl pinacol boronates substituted at the *ortho* and *para* positions of the Ar ring, but gives poor yields for electron-poor aryls and heteroaromatics (pyridine, furan and thiophene derivatives). Terminal allylboronates are also good substrates, which react at the boron-substituted carbon (Scheme 5b). The reaction with secondary alkyl boronates shows that the process is stereospecific, with complete retention of the configuration at the migrating carbon (Scheme 5c), in agreement with the general mechanism sketched in Scheme 3.

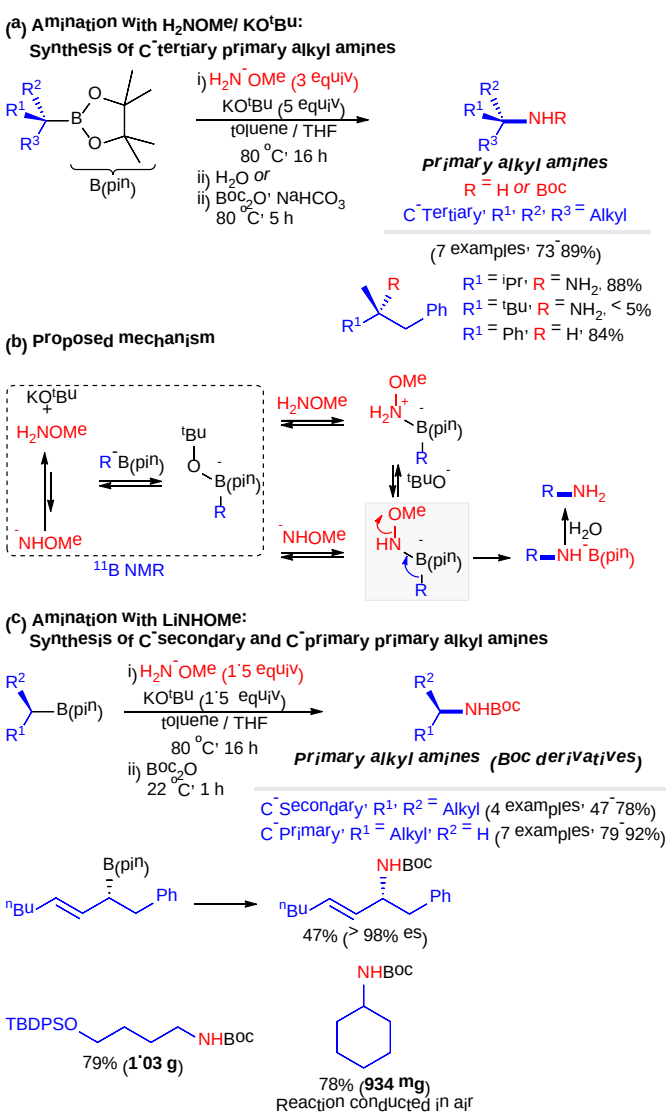
Aggarwal and co-workers have made use of this reaction for the synthesis of the natural product (+)-kalkitoxin, a neurotoxic lipopeptide isolated from the marine cyanobacterium *Lyngbya majuscule* (Scheme 6). The synthetic strategy is based on the lithiation-borylation methodology developed by Aggarwal´s group (Scheme 6a),[14] which constitutes a powerful means for the C-homologation of boron reagents. Thus, the lithiated benzoates (*S*)-**5** and (*R*)-**5** were prepared enantioselectively by the Hoppe–Beak deprotonation (Scheme 6b). Successive reaction of boronate **6** with (*S*)-**5** (twice), **7** (Matteson´s reagent) (*R*)-**5**, and **7** (twice) gives rise to pinacolboronate **8**, which is then subjected to Morken´s amination (LiNHOMe), to afford the key primary amine **9**. The whole sequence is executed with just simple benchtop filtrations of the reaction mixture between the homologation steps and without any other purification. Crude **9** is directly coupled to (*R*)-2-methylbutyric acid to afford amide



Scheme 6 Aggarwal´s lithiation-borylation methodology: Synthesis of (+)-kalkitoxin.

10. N-Methylation of the amide moiety followed by oxidative cleavage of the *p*-methoxyphenyl group (**R**) to carboxylic acid, coupling with (*R*)-1-(benzylthio)propan-2-amine, debenzylation of the thiol group, and final intramolecular cyclization to form the 4,5-dihydrothiazole ring completes the synthesis of (+)-kalkitoxin (Scheme 6c).

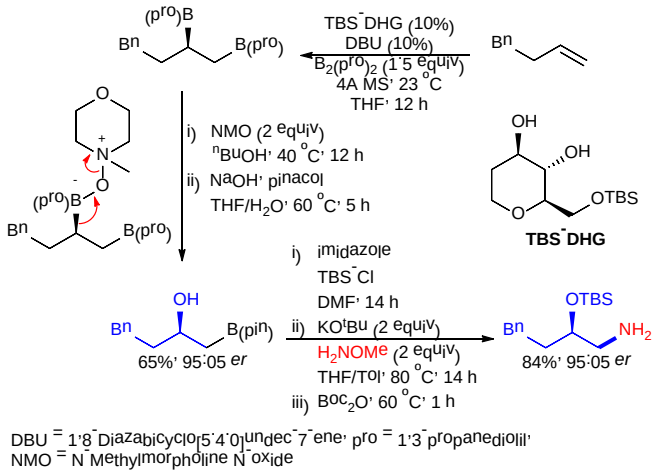
Later on, Morken and co-workers found that their amination reaction can be extended to the stereospecific synthesis of C-tertiary primary alkyl amines by using $MeONH_2$ together with the non-pyrophoric KO^{t}Bu in a one-pot procedure without preformation of an anionic nitrogen reagent (Scheme 7a).[15] The formation of the C-tertiary amines is stereospecific, with retention of the configuration at the reacting carbon center. Sterically encumbered tertiary centers such as those with an isopropyl substituent can successfully be converted into the amine, and the reaction tolerates functional groups like benzyl and silyl ethers. However, benzylic substrates are protodeborylated under the reaction conditions, and compounds with highly congested tertiary centers such as an adjacent ^{t}Bu substituent do not react. ^{11}B-NMR experiments are consistent with the reversible formation of an *ate* complex from the addition of ^{t}BuO$^-$ to the vacant orbital on boron and reaction either with a small equilibrium concentration of the deprotonated amine, or by the direct reaction of $MeONH_2$



Scheme 7 Amination of pinacol boronates with NH_2OMe/KO^{t}Bu: Synthesis of C-primary, C-secondary and C- tertiary primary alkyl amines.

followed by deprotonation (Scheme 7b). This change in the reaction pathway makes it possible to attain the high temperatures required for the reaction of a tertiary substrate (80 °C), preventing the otherwise unavoidable decomposition of a preformed anionic nitrogen reagent. This amination can also be applied to the synthesis of C-primary and C-secondary primary amines. In these cases, only 1.5 equiv of each reagent are required, and the reaction is compatible with a wider variety of substrates, including arene, pyridine, silane, and benzyl- and silyl-protected alcohols as functional groups. Again, benzylic boronates are not tolerated. The reactions of secondary substrates are stereoretentive, and secondary allylboronates react at the boron-substituted carbon. As a proof of concept for preparative scale synthesis, two of the examples have been performed at gram scale. The use of MeONHMe (synthesis of secondary methylamines) instead of $MeONH_2$ is not possible.

In a further example of application (Scheme 8), the $MeONH_2$ / KO^{t}Bu variant has also proven of use for the preparation of an



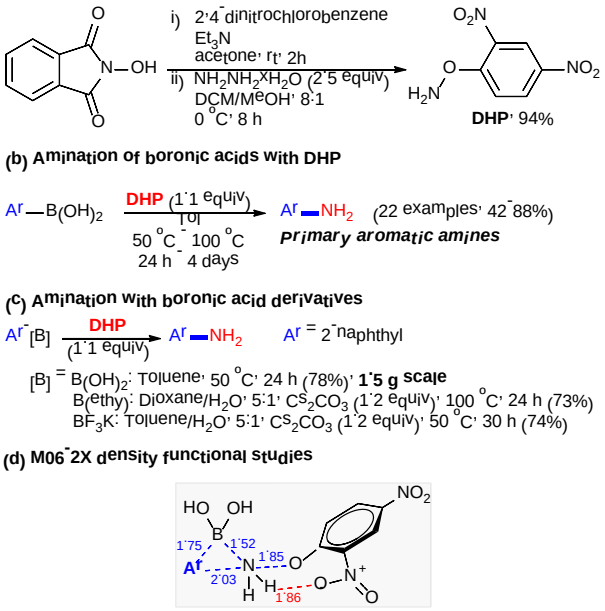
DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, pro = 1,3-propanediolil, NMO = N-Methylmorpholine N-oxide

Scheme 8 Synthesis of 1,2-aminoalcohols from terminal alkenes.

1,2-aminoalcohol from an *O*-protected primary α-hydroxyboronate.[16] The starting chromatographically-stable pinacol boronate was synthesized by the selective mono-oxidation of a 1,2-bis(boronate) derived from the enantioselective diboration of a terminal alkene with propanediol diboron.

The synthesis of primary aromatic amines employing boronic acids themselves was pioneered by Kürti and co-workers using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) as the reagent (Scheme 9).[13] This compound can be prepared by Charette´s two-step procedure from *N*-hydroxyphthalimide (Scheme 9a), and is stable at 0 °C for several months. In most cases, the amination reaction with DPH can be achieved in toluene (50 °C, 24 h), although aromatics with electron-withdrawing groups require prolonged heating (up to 4 days), and polyhalogenated rings need an increase in temperature (100 °C). With the exception of *N*-acyl-substituted arylboronic acids, substrates with unprotected nitrogen (indole, pyrrole) or sulphur (thiophene) atoms, and ketone groups, the reaction is widely general, with good tolerance of a variety of functional groups (halogens, MeO, CF_3, CN, ester), as well as *ortho*-substituted compounds, and can be scaled up to 1 gram. The tolerance of mono- and polyhalogenated (I, Br, Cl) phenyl rings is especially noteworthy because the preparation of halogenated anilines under transition-metal catalysis is often prevented by competing cross-coupling processes. In some cases, the addition of a base (Cs_2CO_3, 1.2 equiv) is beneficial, giving rise to the products in increased yields and in shorter reaction times. In addition to arylboronic acids, the reaction can be accomplished with an ethyleneglycol boronate ester (B(ethy)) or with the corresponding potassium trifluoroborate. In these cases, the reaction requires the incorporation of water to the reaction mixture and the presence of Cs_2CO_3 (Scheme 9c).

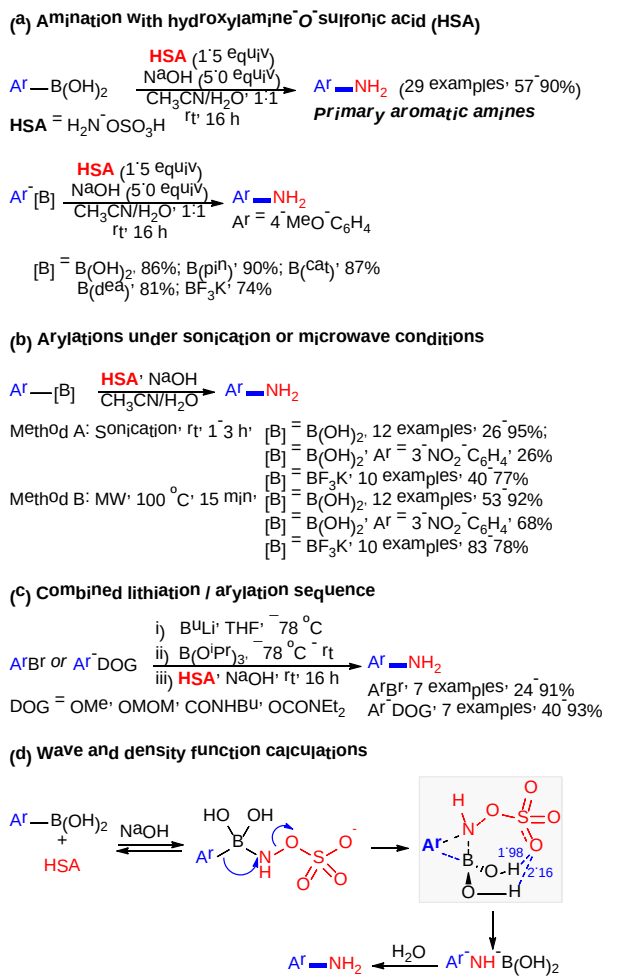
The M06-2X density functional method has been used to calculate possible transition states and reaction pathways. These calculations exclude a radical mechanism and support the 1,2-metallate rearrangement (1,2-aryl(B-N)-migration) alluded to above. In addition, the lowest energy concerted pathway (28 kcal/mol relative to separated starting materials) involves the participation of the *o*-NO_2 group on the reagent (DPH), which



Scheme 9 Amination of boronic acids with DPH: Synthesis of primary aromatic amines.

establishes a hydrogen bond with one of the N-H bonds (1.86 Å), and at the same time, stabilizes the developing leaving-group anion (Scheme 9d). These two combined effects contribute to lowering the barrier for the key 1,2-aryl(B-N)-migration step. The reaction leading to the product arising from this transition state is highly exergonic (ΔG_{rxn} = -72 kcal/mol).

McCubbin and co-workers found that the use of the common and inexpensive hydroxylamine-*O*-sulfonic acid (HSA) allows the synthesis of primary aromatic amines starting from aryl boronic acids under basic aqueous conditions in high yields (Scheme 10a).[17] The reaction is most effective for electron-rich aryls, and tolerates severe steric hindrance at the *ortho*-position (*e.g.* 2-^{i}Pr, 85% yield and 2,6-dimethoxy, 90% yield). The transformation of electron-poor substrates can also be achieved under forcing conditions (reflux, 5 h). Although functional groups including unprotected alcohol, phenol or amino, as well as ether, alkene and halogens are tolerated, nitro, keto, ester and cyano substituents are incompatible with the reaction conditions. The process can be applied to 8-quinolineboronic acid (90% yield), but it fails for the electron-poor heterocycles (*e.g.* 4-pyridineboronic acid) and for electron-rich heterocycles (*e.g.* 3-furylboronic acid). Aliphatic boronic acids and their derivatives are also incompatible. Using the synthesis of *p*-methoxyaniline as an example, it has been demonstrated that the method can also be applied to pinacol, catechol or diethanolamine boronates (B(pin), B(cat) and B(dea)), as well as to potassium organotrifluoroborates (in the presence of an excess of silica gel to facilitate hydrolysis). A further improvement of the method (Scheme 10b) using sonication or microwaves permits the amination of boronic acids and potassium organotrifluoroborates in shorter reaction times and better yields in general.[18] This variant allows the amination of aryls either with electron-rich or with strong



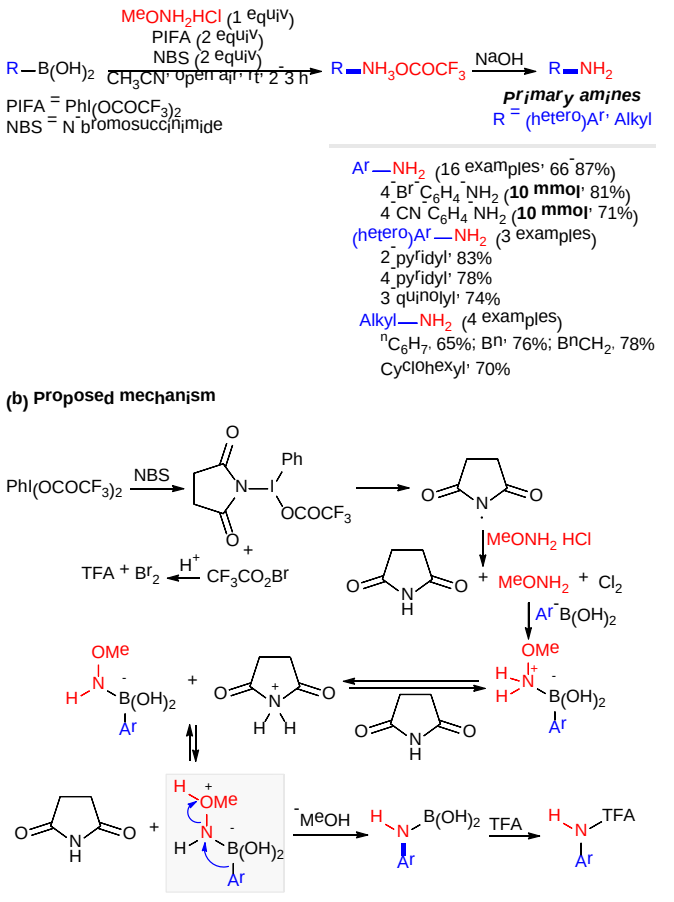
Scheme 10 Amination of boronic acids, boronate esters or potassium organotrifluoroborates with HSA: Synthesis of primary aromatic amines.

electron-withdrawing groups (microwave method), like *p*-nitrophenylboronic acid.

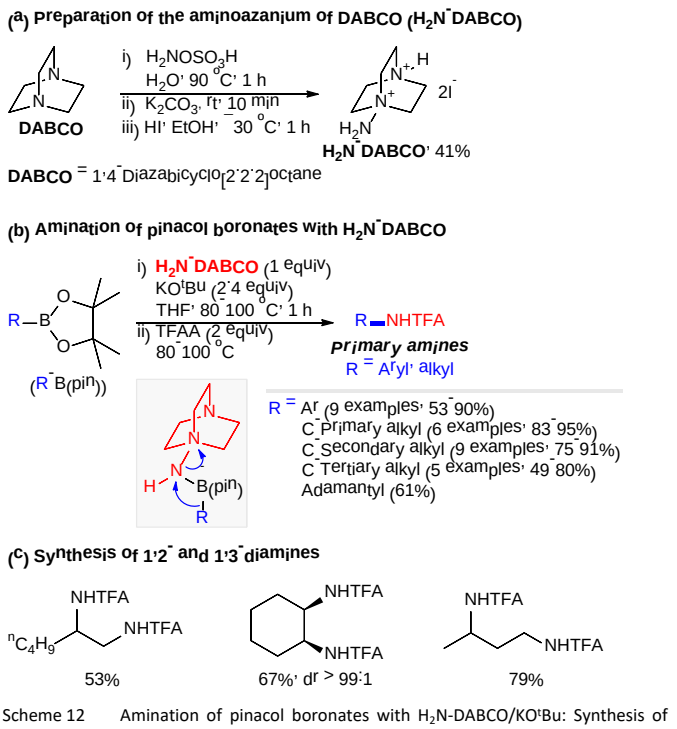
Together with the use of an inexpensive reagent (HSA) and the mild reaction conditions, an extra advantage of McCubbin´s amination method is the possibility of combining it with the lithiation of aryl rings, either by halogen-Li or by H-Li (directed *ortho*-metallation, DoM) exchange, when the reaction is performed in THF, in a one-pot procedure without isolation of intermediates (Scheme 10c).[17] This strategy permits the synthesis of anilines with a substitution pattern difficult to achieve by other methods.

Wave and density function calculations suggest that the reaction occurs via base-mediated activation of HSA, which is deprotonated twice (Scheme 10d). The resulting transition state shows a 2-fold hydrogen bonding arrangement between one of the sulfate oxygen atoms and the two OH hydrogens of the boron-ate moiety (1.98 and 2.16 Å). These observations help explain the need for an excess of base to drive the initial equilibrium between the reactants and the dianionic *ate* complex complex towards the latter, as well as the ease of the 1,2-aryl(B-N)-migration step at rt because of an increase in electron density on the boron atom upon hydrogen bonding. These calculations show that this type of transition state is 13 kJ/mol lower in energy than the lowest energy pathway using Kürti´s DPH as aminating reagent (Scheme 9d).[13]

Chatterjee and Goswami have reported the direct activation of $MeONH_2$ (used as the chlorohydrate) with PIFA and NBS for the synthesis of (hetero)aryl and alkyl primary amines from boronic acids under base-free conditions (Scheme 11a).[19] It is worth mentioning that other hypervalent iodine compounds like diacetoxyiodobenzene or Kosher´s acid cannot be used instead of PIFA. The method is of general use for the amination of arylboronic acids containing halogens, CF_3, MeO, CN, ester, ketone, and nitro groups at *ortho*, *meta* and *para* positions, as well as pyridine and quinoline derived boronic acids. (hetero)Aryl boronate esters are not successful substrates. Primary as well as a secondary alkylboronic acid (one example, cyclohexylboronic acid) can also be coupled successfully. Two of the examples have been achieved starting from 10 mmol of the corresponding boronic acid. The reaction occurs by a radical pathway (Scheme 11b), which is inhibited in the presence of TEMPO. The proposed reaction course is based on the reaction of PIFA with NBS to form a succinimidyl radical along with TFA and Br_2. The abstraction of a proton from $MeONH_2HCl$ produces the nitrogen nucleophile necessary for the generation of the key boron-ate complex, which evolves to the final product by 1,2-aryl(B-N)-migration, with MeOH as the leaving group.



Scheme 11 Base-free amination of (het)aryl and alkyl boronic acids with $MeONH_2HCl$/PIFA/NBS: Synthesis of primary (hetero)aryl amines, and of C-primary and C-secondary primary alkyl amines.



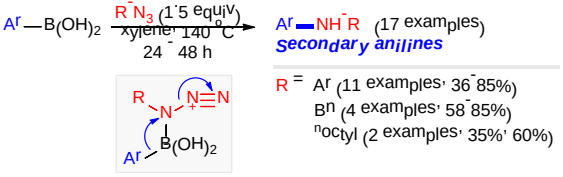
Scheme 12 Amination of pinacol boronates with H_2N-DABCO/KO^{t}Bu: Synthesis of primary anilines and C-primary, C-secondary and C-tertiary primary alkyl amines (TFA derivatives).

2.2 Hydrazine derivatives

Direct amination of DABCO with H_2NOSO_3H, followed by neutralization with K_2CO_3 and further treatment with HI, affords the aminoazanium of DABCO (H_2N-DABCO) (Scheme 12a). This stable solid, which can be considered as a hydrazine derivative, is also an efficient amination reagent for the transformation of aryl and alkyl pinacol boronates into primary amines (anilines and C-primary, C-secondary and C-tertiary alkyl amines).[20] Similarly to H_2N-OMe (Section 2.1) *in situ* deprotonation of H_2N-DABCO with KO^{t}Bu affords the N-nucleophile required for the formation of the key *ate* complex. 1,2-C(B-N)-shift explains the generation of the final amines, which are isolated as trifluoroacetyl derivatives (Scheme 12 b). The reaction is tolerant to CN, Cl, MeO, alkene, $PhSiMe_2$, and acetyl groups on the alkyl chains. In the aromatic series, the reaction is compatible with functional groups like F, CF_3, MeO, MeS, CN and methyl ketone. In the case of secondary alkyl-B(pin) compounds, the *dr* or *er* values of the starting materials are identical with their amination products, which confirms that the reaction is sterospecific. In the case of tertiary alkyl-B(pin) compounds, the reaction can be applied to severely hindered substrates (*e.g.* adamantylamine). It is also possible to apply this amination reaction to 1,2- and 1,3-diborylalkanes for the synthesis of 1,2- and 1,3-diamines (Scheme 12c).

2.3 Azides

The direct engagement of boronic acids in this class of amination reaction was reported by Zhang, Yu and co-workers



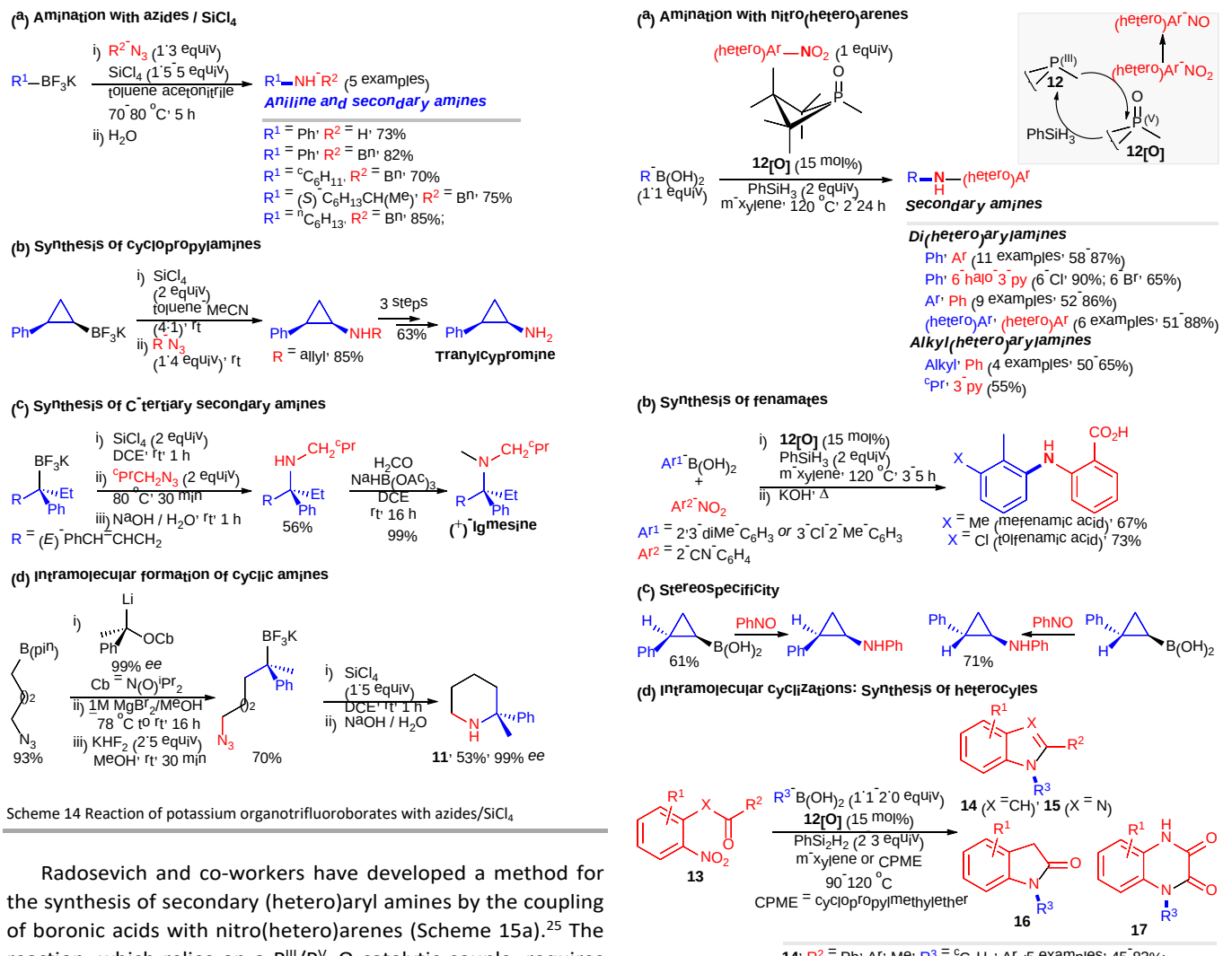
Scheme 13 Direct amination of boronic acids with azides: Synthesis of secondary anilines.

for the synthesis of secondary anilines (Scheme 13).[21] These reactions require prolonged heating at a relatively high temperature but do not require any extra additive. The transformation is fairly general and functional-group tolerant, compatible with the presence of Me, MeO, CHO, and F (mono- and trisubstituted phenyl rings) on the boronic acid moiety, as well as Me, MeO, halogens, and NO_2 in the case of aryl azides. 4-Pyridyl and 2-thienyl boronic acids do not react. Similarly to hydroxylamines, the general mechanism for this kind of amination consists of the formation of an *ate* complex through a nucleophilic attack of nitrogen to boron, followed by the intramolecular substitution of the leaving group via a 1,2-C(B-N)-rearrangement. In this case, the leaving group is a nitrogen molecule (Scheme 13).

Pioneered by Matteson and co-workers,[22] the use of azides together with potassium organotrifluoroborates (RBF_3K) has found more general use. Chlorotrimethylsilane is known to transform RBF_3K into organodifluoroboranes (RBF_2), while the addition of Cl_4Si to RBF_3K in THF or acetonitrile at 20–25 °C results in immediate evolution of gaseous SiF_4 and formation of the corresponding solvated reactive organodichloroborane ($RBCl_2$-Solv). Dihaloboranes are much prone to coordination with nucleophiles than boronic acids or boronate esters. On one hand, there is a significant orbital overlap between the n lone pairs on the hydroxy/alkoxy substituents and the empty p-orbital on B with contributes to the decreased reactivity of boronic acids/esters with respect to the haloboranes. On the other, halides are more electronegative than hydroxyl or alkoxy substituents. Both factors contribute to an increase of the electron deficiency on boron in the case of haloboranes. This strategy has been applied, for example, to the synthesis of aniline, N-benzylaniline and N-benzyl secondary alkyl amines (Scheme 14a),[22] the synthesis of cyclopropylamines (Scheme 14b),[23] and the synthesis of C-tertiary secondary amines like (+)-igmesine (Scheme 14c), a compound with activities in various therapeutic areas including depression, cancer, and diarrhea, permitting for the first time the establishment of the absolute configuration of (+)-igmesine, or to the intramolecular formation of cyclic amines such as **11** (Scheme 14d), a compound with potential neurokinin 1 (NK1) antagonist activity with antidepressant, anxiolytic, and antiemetic properties.[24]

2.4 Nitro and nitroso compounds

Nitro compounds,[3] in particular nitroarenes, are ubiquitous compounds. The deoxygenation of nitro compounds can turn them into useful electrophilic reagents for aminating purposes. Some of these transformations take place by the mediation of aromatic nitroso compounds[4] (*vide infra*).



Scheme 14 Reaction of potassium organotrifluoroborates with azides/$SiCl_4$

Radosevich and co-workers have developed a method for the synthesis of secondary (hetero)aryl amines by the coupling of boronic acids with nitro(hetero)arenes (Scheme 15a).[25] The reaction, which relies on a P^{III}/P^{V}=O catalytic couple, requires the presence of a small-ring organophosphorus-based precatalyst (**12[O]**) together with a stoichiometric hydrosilane reductant ($PhSiH_3$). Towards the synthesis of di(hetero)arylamines, the reaction is useful for the coupling of substituted aryl, 2-methoxy-4-pyridyl and 3-thienyl boronic acids with nitroarenes, 3-nitropyridine and 3-nitropyridines functionalized with F and ester groups. In addition, it presents good functional group compatibility on both the boronic acid and the nitroarene components (halogens, free NH_2 and OH groups, SMe, OMe, NO_2, BPin, CF_3, ester). In particular, the compatibility with halogens and amino groups makes the method orthogonal to other classic C-N bond-forming methods, like the Evans-Chan-Lam and the Buchwald-Hartwig reactions. Catecholboronate esters and boroxines can be used instead of boronic acids, although yields are lower. On the other hand, the reaction does not take place with a pinacolboronate. When synthesizing diarylamines in which both aryls have different electronic demands, the reaction is most productive for the union of electron-deficient nitroarenes with electron-rich arylboronic acids. The practical utility of this method for the synthesis of diarylamines has been demonstrated with the preparation of two members of the fenamate group of non-

Scheme 15 Reaction of boronic acids with nitro (hetero)arenes: Synthesis of secondary (hetero)arylamines and azaheterocycles.

steroidal anti-inflammatory drugs (NSAIDs), mefenamic and tolfenamic acids, on a 1 mmol scale (Scheme 15b).

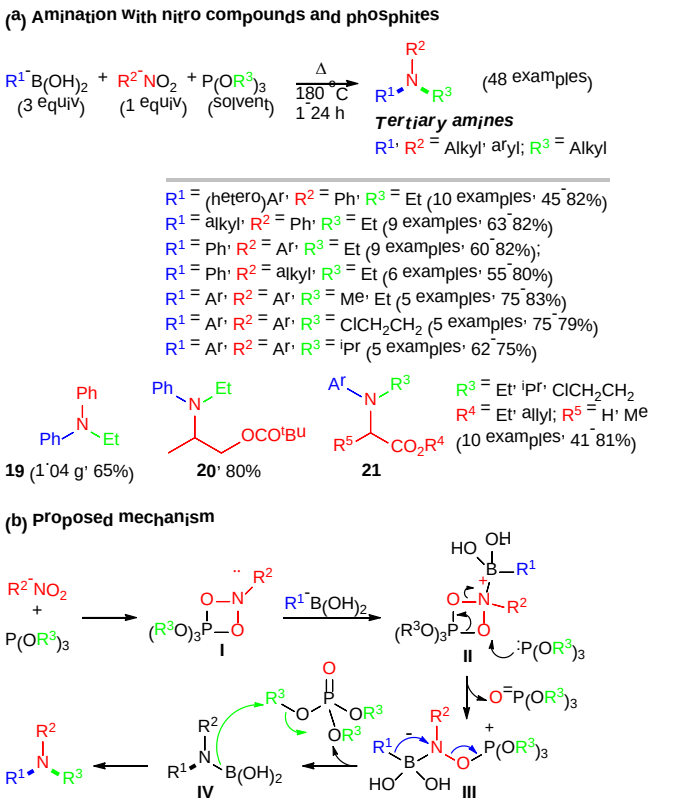
The reaction is also useful for the synthesis of alkyl(hetero)arylamines by the coupling of nitrobenzenes and 3-nitropyridine with methyl, benzyl, isopropyl, cyclopropyl and cyclobutyl boronic acids. The reaction between nitrobenzene and either *syn*- or *anti* 2-phenylcyclopropylboronic acids (Scheme 15c) reveals that the process is stereospecific with respect to the boronic acid component.

Starting from the *o*-functionalized nitroarene precursors **13** (Scheme 15d) and combined with intramolecular cyclizations, Radosevich´s methodology (Ph_2SiH_2 as reductant) has been extended to the synthesis of indoles (**14**) and benzimidazoles (**15**) (intramolecular carbonyl condensation) as well as oxindoles (**16**) and quinoxalinediones (**17**) (intramolecular acylation). In particular, the synthesis of imidazole **18** can be executed as a modular one-pot amidation/reductive *N*-arylative cyclization (Scheme 15e), and the synthesis of linopirdine, a KCNQ K^+ ion channel blocker, can be executed as a one-pot cyclization/alkylation procedure (Scheme 15f).

The combination of experimental, spectroscopic, and computational studies (Scheme 15g)[25] provides evidence that the deoxygenation of nitro compounds with trialkylphosphines takes place by a stepwise *O*-atom transfer via pentacoordinate azadioxaphosphetanes formed by a rate-limiting [3+1] cheletropic reaction. Subsequent decomposition of the azadioxaphosphetane by a retro-[2+2] fragmentation gives rise to the P^V=O species and a nitroso compound. In the case of R = Ar, the nitroso compound evolves to the final product via an oxazaphosphirane intermediate. Coordination with the boronic acid, antiperiplanar 1,2-migration of the organoboron residue to nitrogen and final hydrolysis affords the coupling product.

It has also been reported that this deoxygenative coupling of nitroarenes and boronic acids can be performed in an operationally simpler fashion by utilizing stoichiometric amounts of a commercially available phosphine alone (3 equiv of PEt_3, *m*-xylene, 120 °C), sparing the need for the synthesis of **12[O]** and the use of the reductant.

The synthesis of tertiary aromatic amines from nitro compounds has been realized by a three-component reaction that directly joins nitro compounds, boronic acids and trialkyl phosphites (Scheme 16a).[26] The reaction tolerates alkyl and aryl substituents on the nitro and boronic acid moieties, as well as functionalized phosphites (primary and secondary, including halogen functionalization). In the case of aryl rings, the reaction is compatible with functional groups such as halogens, OMe, free OH, CF_3 and CN either on the nitro or the boronic acid counterparts at the *ortho*, *meta* or *para* positions. The reaction is also successful with 3-thienylboronic acid and a variety of alkylboronic acids (linear primary and secondary, and cyclic secondary). The method is amenable to scaling, as shown by the 1 g scale synthesis of **19**. The possibility of coupling aliphatic nitro compounds (primary and secondary, including a 2-nitro-1-propanol derivative **20**) is noteworthy. The reaction is particularly useful for the assembly of the α-amino ester derivatives **21** when starting with nitroacetates.

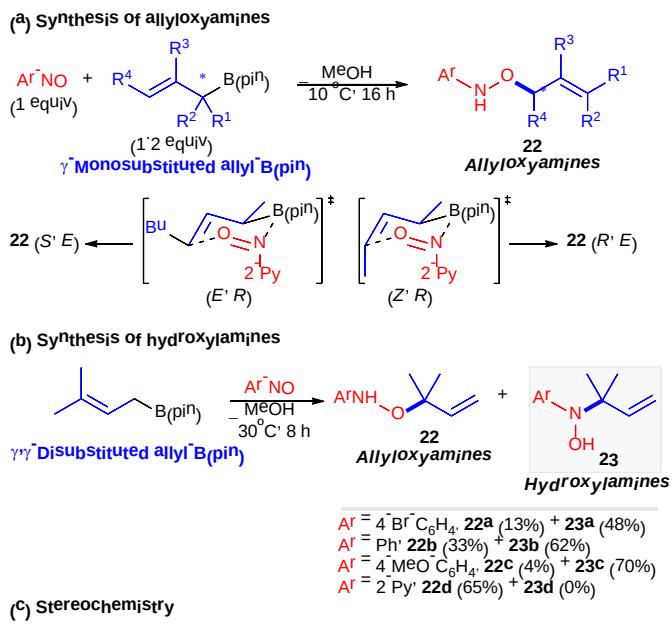


Scheme 16 Reaction of boronic acids with nitro compounds and trialkyl phosphites: Three-component synthesis of tertiary aromatic amines.

Regarding the reaction course (Scheme 16b), the possibility of using aliphatic nitro compounds in this three-component reaction is not consistent with the aforementioned generation of nitroso compounds as intermediates in the deoxygenation of nitro groups,[25] since aliphatic nitroso compounds would rapidly tautomerize to oximes. Therefore, the reaction must take place via the formation of an azadioxaphospetane **I**. Coordination of the nitrogen atom in **I** to boron gives rise to the boron-ate **II**. Ring-opening by an excess of the oxophilic phosphite gives rise to intermediate **III** together with a trialkyl phosphate. 1,2-Migration of the carbon ligand (R^1) produces the aminoborane **IV** together with an extra equivalent of phosphate. Last, alkylation of the aminoborane **IV** with the *in situ* generated phosphate explains the formation of the final product.

Nitroso compounds are far less ubiquitous than nitro compounds.[4] Whereas, as mentioned in the previous paragraph, aliphatic nitroso compounds are in tautomeric equilibrium with the more stable oximes, aromatic nitroso compounds are relatively stable materials that have found broad application as building blocks in synthesis (see Section 4.2). Depending on the mode of activation, nitrosoarenes can act as electrophiles either at the oxygen or the nitrogen atom. Similarly to nitro compounds, their deoxygenation can turn them into useful reagents for the synthesis of amines.

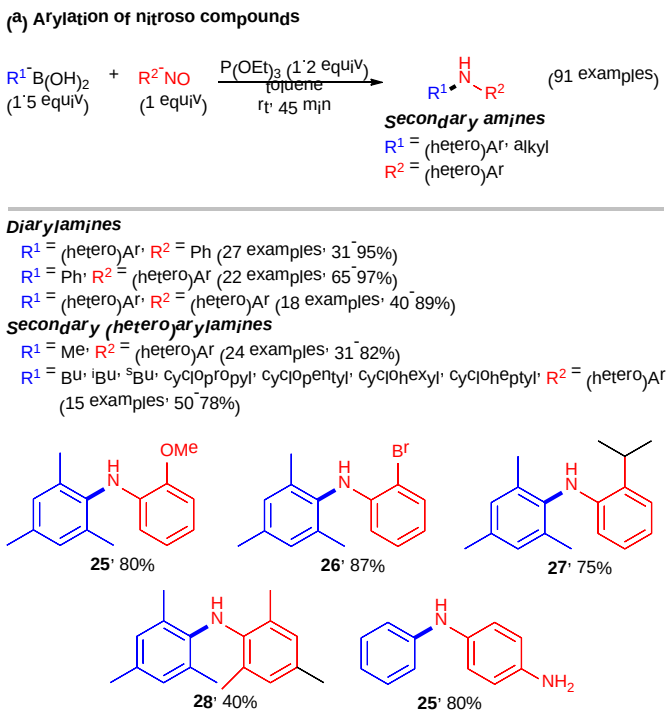
Nitroso (hetero)arenes have been mainly reported as reagents for the stereospecific *O*-allylation of chiral γ-mono substituted allyl pinacolboronates towards the synthesis of the chiral allyloxyamines **22** (Scheme 17a).[4] These *O*-functionalization reactions are presumed to take place via six-



Scheme 17 Reaction of allyl pinacolboronates with nitroso (hetero)arenes: Synthesis of allyloxyamines *vs N,N*-disubstituted hydroxylamines.

membered chair-type transition states. Instead, in the particular case of γ,γ-disubstituted allyl pinacol boronates, this reaction tends to favor *N*-allylation, especially when using electron-rich aryls, leading to the *N,N*-disubstituted hydroxylamines **23** (Scheme 17b). High enantiospecificity was reported for the synthesis of **24** (Scheme 17c). No explanation has been put forward for this change in reactivity when switching from γ-monosubstituted to γ,γ-disubstituted allyl bononates.

However, in the presence of trialkyl phosphites, nitroso (hetero)arenes have been used as reagents for the amination of boronic acids ((hetero)aryl and alkyl), affording secondary (hetero)arylamines (Scheme 18).[27,28] Thus, the reaction of nitroso (hetero)arenes with (hetero)arylboronic acids in the presence of $P(OEt)_3$ (Scheme 18a) gives rise to the formation of di(hetero)arylamines under mild conditions. The reactions can be accomplished in an open-flask, with no need to use specially dried solvents, reducing agents, bases, or other additives, and the products can be isolated by a simple filtration without the need for separation by chromatography. The method minimizes the generation of hazardous substances, since the subproducts of the reaction, triethyl phosphate and boric acid, are of low toxicity. This transformation is compatible with a variety of functional groups (aldehyde, ketone, ester, NO_2, halogens, free OH and NH groups) on the aryl moieties, and is successful for both electron-rich and electron-poor heterocycles (benzothiophene derivatives, NH-unprotected indoles, pyridines, pyrimidines). The synthesis of sterically hindered diarylamines that carry *ortho*-substituents on both aromatic



Scheme 18 Reaction of boronic acids with nitroso compounds: Synthesis of tertiary secondary (hetero)aromatic amines.

rings is often difficult by conventional transition-metal-catalyzed procedures. This $P(OEt)_3$-promoted reaction of nitrosobenzenes with arylboronic acids[27] is compatible with the presence of two and three *o*-substituents such as **25**-**28** in good yields. Even a compound with four *o*-Me substituents (**28**) can be synthesized in moderate yield. By this method, the syntheses of **29**, an important industrial antioxidant used in the manufacture of car tires, and phentolamine (Regitine, Vasomax), a reversible, nonselective α-adrenergic antagonist used clinically to control hypertensive emergencies, can be achieved at 10 g scale (Scheme 18b). Both transformations benefit from the tolerance of unprotected NH_2 and OH groups. Also, the method has been adapted as a laboratory experiment for upper-division undergraduate organic chemistry students towards the synthesis of flufenamic acid, another representative of the fenamate group of NSAIDs (Scheme 18c).[29]

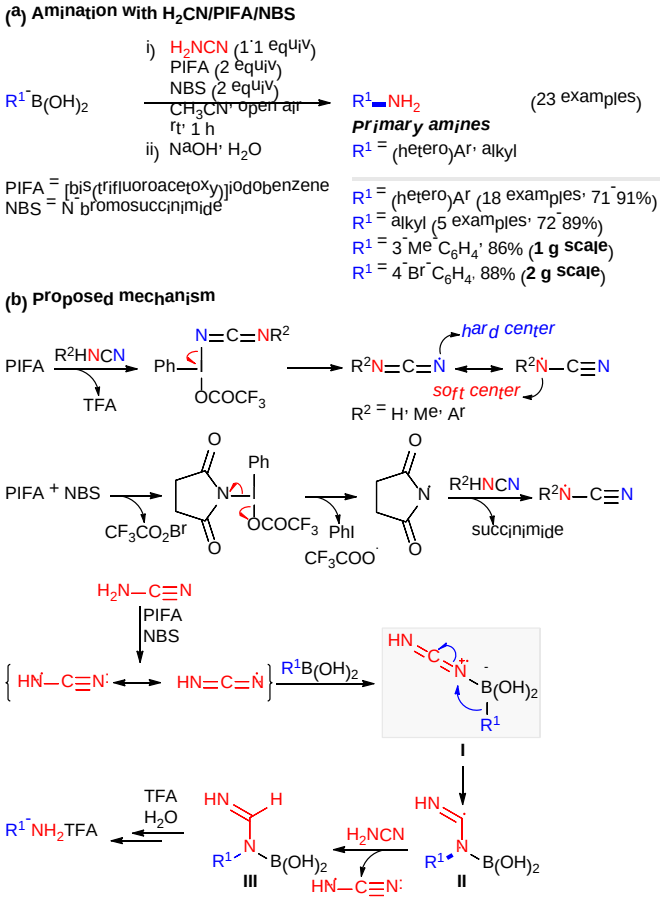
In addition to di(hetero)arylamines, this reaction has been extended to the synthesis of secondary anilines and secondary heterocyclic amines with C-primary and C-secondary N-substituents.[28] The method is particularly valuable for the preparation of mono-N-methyl derivatives (reactions with $MeB(OH)_2$), whose synthesis by the mono-N-methylation of anilines is often challenging due to the tendency of many of these transformations to overmethylation. This method has been applied to the 1 g-scale synthesis of Pittsburgh compound B (PiB), a well-known ligand for the cerebral amyloid-beta (Aβ) deposits that are characteristic of Alzheimer's disease (Scheme 18d).

These reactions can be understood starting by the interaction between the nitroso compound with $P(OEt)_3$ to give either an activated hydroxylamine derivative or a nitrene intermediate. Formation of a boron-ate species followed by 1,2-carbon B-N migration explains the formation of the secondary (hetero)arylamine product (Scheme 18e).

2.5 Cyanamides

Chatterjee and Goswami[19] have reported the use of cyanamide in combination with PIFA and NBS for the transformation of (hetero)aryl and alkylboronic acids into the corresponding primary amines (Scheme 19), initially obtained as their corresponding ammonium trifluoroacetate salts, and converted into the free amines by their treatment with NaOH. It is worth mentioning that the reaction can be promoted by PIFA itself in the absence of NBS, but yields are lower. The reaction is very general, shows tolerance to functional groups such as halogens, CN, ester, NO_2 and ketone in positions in *ortho*, *meta* and *para* of benzene rings, and is also possible for pyridine and quinoline derivatives. The reaction is not successful for the corresponding pinacol boronates.

This reaction is inhibited in the presence of TEMPO as a radical scavenger, which puts forward its radical nature. DFT calculations indicate that the formation of the key cyanamidyl radicals, the aminating species, can be promoted either starting from PIFA alone (slow ligand exchange with cyanamides followed by radical cleavage of the I-N bond) or from the



Scheme 19 Reaction of boronic acids with H_2NCN/PIFA/NBS: Synthesis of primary (hetero)aryl and alkyl amines.

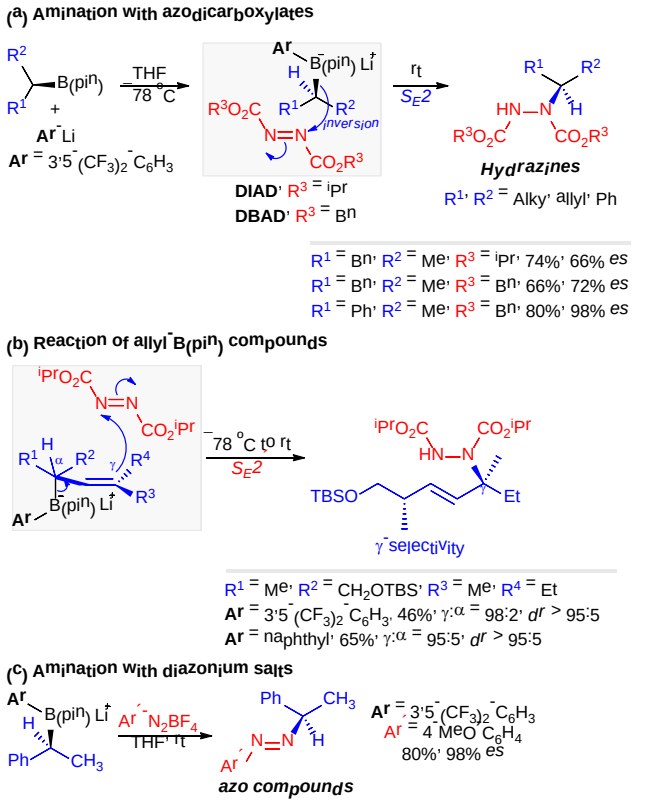
interaction of the cyanamides with a succinimidyl radical, itself generated by the reaction between PIFA and NBS. Although analysis of the ambident cyanamidyl radicals only shows a slight excess of spin density on the nitrile *N*-centre, the quantum chemical optimization can be performed from the intermediate of the attack of the harder nitrile *N*-center solely. This observation explains why experiments executed with ArNHCN reagents in the place of cyamide also lead to primary amination instead of the expected secondary amines. As exemplified for cyanamide (R^2 = H), the formation of **I** is the rate-limiting step of the whole process. The hydrogen abstraction from cyanamide by radical **II** after 1,2-C(B-N)-migration constitutes an exergonic process. Protonation of the aminoborane **III** followed by hydrolysis of the imine moiety explains the formation of the aniline product. Overall, this selective formation of anilines from cyanamidyl or substituted cyanamidyl radicals is a spontaneous highly exothermic process (~30–39 kcal/mol).

2.6 Azodicarboxylates and diazonium salts

Azodicarboxylates contain an N=N bond in conjugation with two ester groups placed on each nitrogen. This feature makes the nitrogen atoms of the N=N bond sensitive to nucleophilic addition. At the same time, either the lone pairs on the N atoms

of the N=N group or the oxygen atoms of the ester moieties can act as Lewis bases. The reaction with boronic acid derivatives affords substituted hydrazines.

The addition of an aryllithium to a secondary pinacol boronic ester generates highly reactive lithium boron-ate complexes that can interact with a broad range of electrophiles by transferring their alkyl moiety as a C-nucleophile (Scheme 20a).[30] Opposite to their reactions with metal salts (MX), in which the aryl group acts as the nucleophile (formation of an Ar-M bond), this type of alkyl-aryl lithium boron-ate complex selectively transfers the secondary alkyl moiety as a chiral nucleophilic carbon ligand with high levels of sterocontrol when confronted with a non-metal electrophile. Although the polar S_E2 mechanism is the principal reaction course (inversion of the configuration at the reacting carbon nucleophile), the reaction with some electrophiles shows an eroded *er* due to competition with a SET pathway. This is the case when azodicarboxylates are used as electrophiles. Formation of the boron-ate complex using an electron-poor aryllithium (3,5-$(CF_3)_2C_6H_3Li$) favors the polar mechanism by preferentially slowing down the radical process. The use of dibenzyl (DBAD) instead of diisopropylazodicarboxylate (DIAD) affords better *er*. Allylboronic esters react with very high γ-selectivity and essentially complete stereospecificity, in agreement with an S_E2' mechanism (Scheme 20b).[31] Note that the site selectivity of the reactions of these allyl-aryl boron-ate complexes (γ-selectivity) is opposite to that observed when using amination methods for allylboronic substrates based on the use of hydroxylamine derivatives (Section 2.3, α-selectivity).



Scheme 20 Reaction of secondary pinacol boronates with azodicarboxylates and diazonium salts: Synthesis of chiral hydrazine derivatives and azo compounds.

The high reactivity of these lithium aryl/secondary-alkyl lithium boron-ates does also account for their direct reaction with diazonium salts to form azo compounds (Scheme 20c).

3. Amidation reactions

Firstly reported by Nozaki and co-workers in 2007, the synthesis of stable acylboron reagents is possible when decreasing the Lewis acidity of boron by using tetravalent ligands on boron. In particular, potassium trifluoroacyl borates (KATs), N-methyliminodiacetyl (MIDA) acylboronates and monofluoro acylboronates have become powerful reagents for amide formation, including protein ligation, under mild conditions.[32]

3.1 Azides

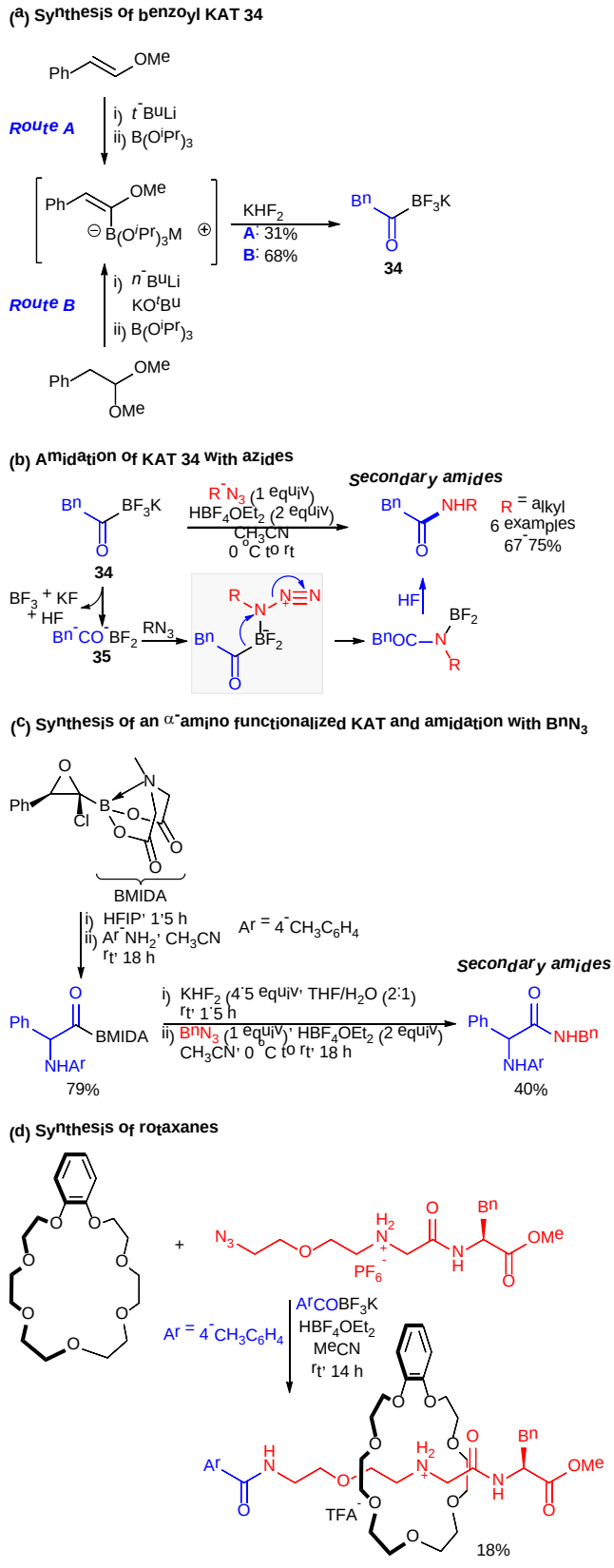
In 2010, Molander and co-workers synthesized benzoyl trifluoroborate **34**, the first isolated KAT whose reactivity was reported.[33] KAT **34** can be synthesized by two alternative routes: Direct deprotonation of (*E*)-(2-methoxyvinyl)benzene with *tert*-butyllithium (Route A), or metalation of dimethoxy acetal with *n*-butyllithium and potassium *tert*-butoxide as a base (Route B), both followed by quenching with triisopropyl borate and aqueous KHF_2 (Scheme 21a). Activation of **34** with HBF_4OEt_2 permits its reaction with azides to form secondary amides (Scheme 21b). Simple alkyl azides and azides bearing functional groups such as esters and nitriles are well tolerated, whereas other substrates such as aryl-, sulphonyl- or alkenyl-containing azides decompose under the reaction conditions. Similarly to the reactions of azides with other boronic acid reagents (Section 2.2), the reaction may proceed via the 1,2-acyl(B-N)-migration from the intermediate generated by coordination of the azide with an acyldifluroborane (**35**) formed from the interaction of **34** with HBF_4OEt_2, the latter acting as a fluoride scavenger.

Recently, a new approach for the divergent synthesis of α-functionalized acylborons by nucleophilic ring-opening of MIDA α-chloroepoxyboronates has been reported (Scheme 21c).[34] Ring-opening with *p*-anisidine followed by conversion of the resulting MIDA acylboronate into a KAT and *in situ* reaction with BnN_3 affords the amide ligation product. The KAT-azide coupling has also been used for the synthesis of rotaxanes (Scheme 21d).[35]

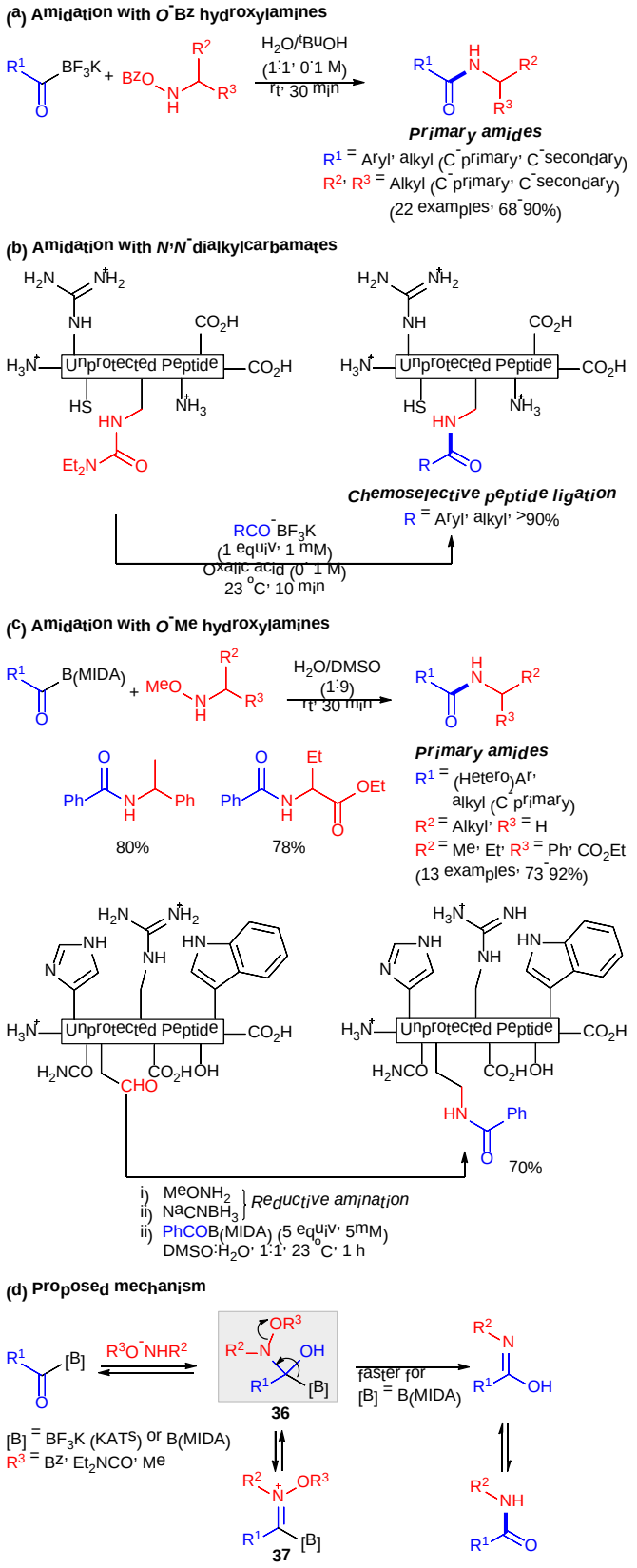
3.2 Hydroxylamine derivatives

In a series of papers from 2012 to 2016,[32] Molander,[36] Bode[37] and co-workers have disclosed that contrary to *O*-unsubstituted hydroxylamines, which react with KATs and MIDA boronates to give stable nitrones, the direct interaction between these boron reagents and *N*-alkyl substituted *O*-Bz, *O*-carbamoyl and *O*-Me hydroxylamines affords secondary amides (Scheme 22). Oppositely to the reactions of KATs with azides or amines (Sections 3.1 and 3.3), this reaction does not need any type of activation.

Using small molecules, it has been found that the reaction of KATs with *O*-Bz hydroxylamines is fast (5-60 min) in dilute



Scheme 21 Reaction of KATs with azides: Synthesis of secondary amides.



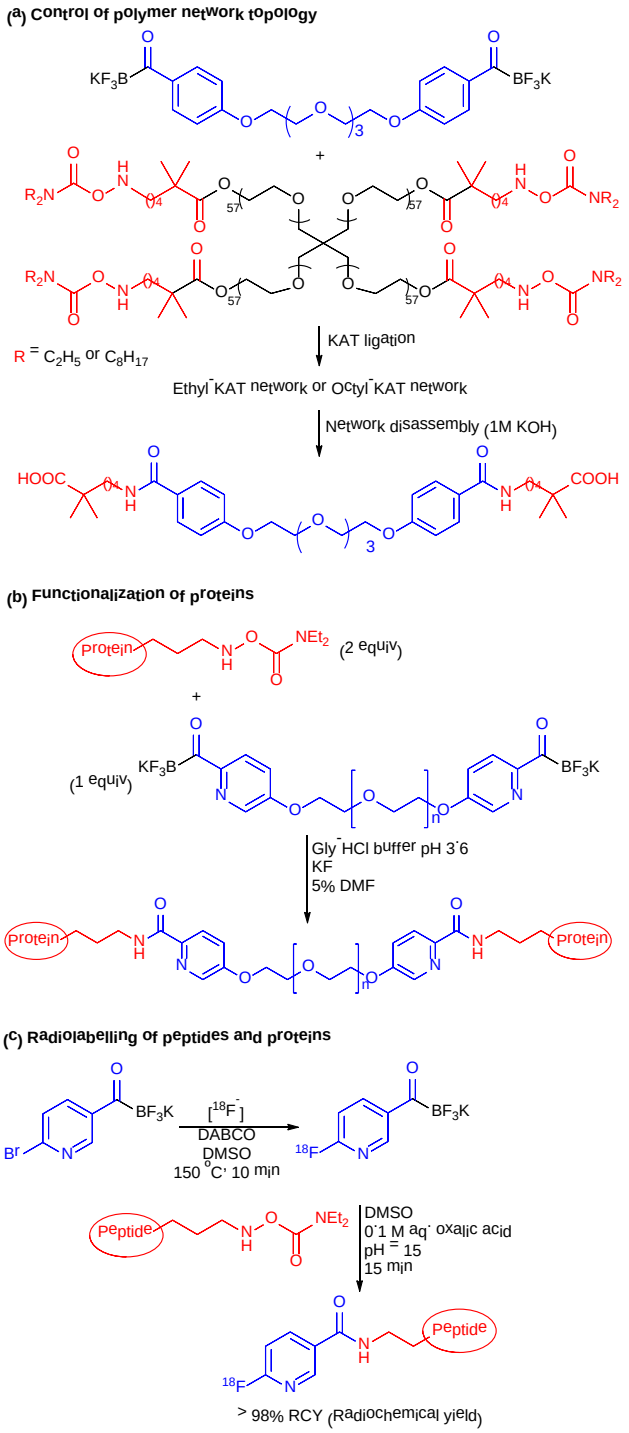
Scheme 22 Reaction of KATs and MIDA boronates with *O*-functionalized hydroxylamines: Synthesis of secondary amides.

aqueous solvents without the addition of any other reagents or catalysts (Scheme 22a). This amidation is remarkably general with regard to both the acyl donors (C-primary and C-secondary alkyl and aryl) and the hydroxylamines (C-primary and C-secondary alkyl), and tolerates substituents such as alkenes, trialkylsilylacetylene, halogen, aldehyde, ester, unprotected

alcohol groups or carbamate-protected amines. In addition to *O*-benzoyl hydroxylamines, isoxazolidines are also adequate substrates for the synthesis of secondary amides by reaction with KATs. These initial findings have rapidly been developed into a method for the chemical ligation of biomolecules. The *O*-Bz hydroxylamines are not stable enough towards the standard synthetic protocols required for their incorporation into peptides or other biological targets. In search of efficient reagents that could permit chemoselective conjugation reactions under aqueous conditions, Bode and co-workers introduced the use of *N,N*-dialkylcarbamates.[32] These are almost as reactive as the *O*-Bz substrates (second-order rate constant of around 20 M^{-1} s^{-1}, reactions accelerated in the presence of acid) but stable toward the ligation conditions and unprotected primary amines, and tolerate Boc-deprotection (TFA) and Fmoc-cleavage (N-Boc-piperidine). The utility of the method has been demonstrated by PEGylation, palmitoylation, biotinylation, and introduction of an azobenzene dye onto a 31-amino acid residue analogue of the antidiabetic peptide GLP-1 in the presence of unprotected common functional groups on the lateral side-chains of the peptide (Scheme 22b). In addition, *O*-alkyl hydroxylamines are smaller and more chemically stable than the *O*-acyl variants, which makes them good candidates for their incorporation into expressed biological materials. Albeit the ionic nature of KATs prevent their reaction with *O*-alkylhydroxylamines, neutral MIDA acylboronates are reactive enough to undergo chemoselective amide bond-forming ligations in water with *O*-Me hydroxylamines, including unprotected peptide substrates. Prior to peptide ligation, the reaction has been tested with small molecules (Scheme 22c) using primary aliphatic, halogen-bearing aromatics and heteroaryl MIDA acylboronates, which smoothly provides the secondary amides in good to excellent yields in their couplings with linear and α-branched *O*-Me hydroxylamines, which even tolerate functional groups on the lateral chains. The reaction only fails for sterically hindered substrates like *O*-Me-*N*-^{t}butylhydroxylamine or a tertiary hydroxylamine. With regard to peptides, this reaction has been applied, for example, to the ligation with peptides containing the *O*-Me-hydroxylamine tag (introduced from aldehyde) and unprotected OH, NH_2, CO_2H, $CONH_2$, guanididino, imidazole and indole groups (Scheme 22c).[38] However, these peptide ligations require an excess of the acylating reagent due to the instability of MIDA acylboronates under aqueous conditions. It has been proposed[37] that in the absence of a fluorophore, these ligation reactions take place via the attack of the hydroxylamine to the electrophilic carbonyl group of the starting acyl boron species to form hemiaminals **36** (Scheme 22d) rather by than via an acyldifluoroborane species (see **35** Scheme 21). Due to the neutral nature of **37** in the case of KATs, the concentration of **36** is diminished with respect to the case of B(MIDA) derivatives, which explains the increased amination reactivity of the latter.

Some recent advances include the control of polymer network topology,[39] the application of KAT-ligation to large functionalized proteins,[40] and the radiolabelling of peptides and proteins.[41]

Thus, Bode, Johnson, and co-workers have been able to synthesize topologically isomeric polymer networks by a traceless KAT ligation with *O*-carbamoyl hydroxylamines (Scheme 23a).[39] The control of the polymer network topology can be achieved using self-assembled structures as templates that are not themselves incorporated into the network and are expelled during the gelation process. Addition of a bis-KAT reagent to two network-precursor four-arm PEG-based star polymers prepared either with *O*-ethyl or *O*-octyl carbamoyl hydroxylamine chain ends, which are used as network precur-



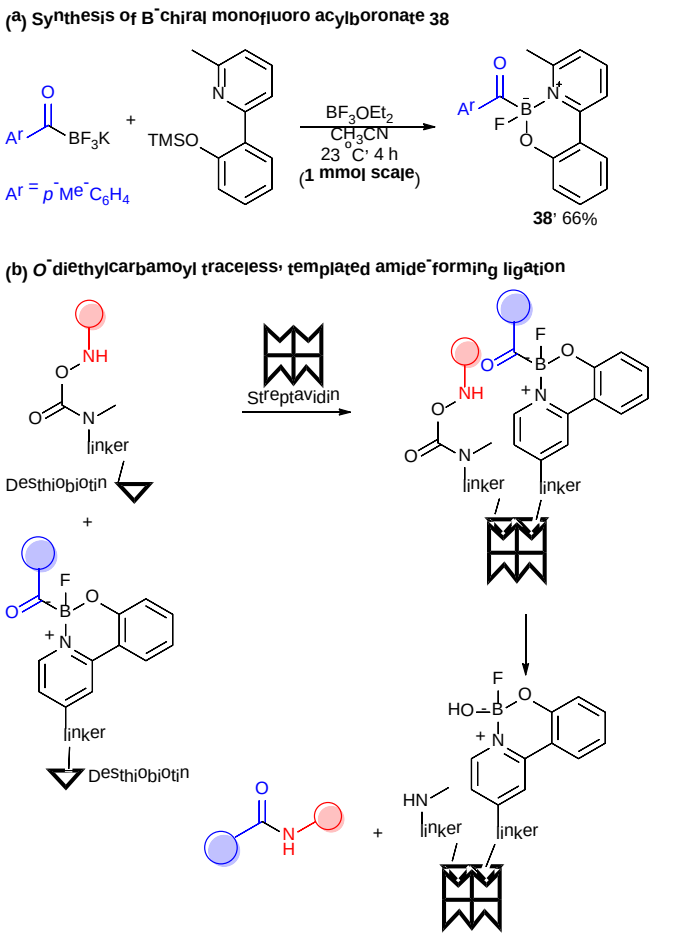
Scheme 23 Ligation reactions of KATs: Recent examples.

sors, induce amide bond formation and concomitant expulsion of the ethyl or octyl traceless topological modifiers.This gives rise to topologically isomeric PEG gels with identical chemical compositions but vastly different physical properties, due to the differences in chain-end hydrophobicity of both carbamoyl chains, which produces different self-assembly states in solution prior to amide formation.

Besides, pyridyl KATs have been shown to display significantly enhanced ligation kinetics over their aryl counterparts (Scheme 23b). This may be accounted for by protonation of the pyridine group, which facilitates the activation of the leaving group and allows the adoption of the correct conformation for a concerted elimination. While keeping the aqueous, acidic and equimolar conditions disclosed in previous work, the use of 2-pyridyl KATs permits the ligation of folded proteins at micromolar concentrations. This had not been achieved previously, in part as a consequence of the difficulty in obtaining concentrated solutions of larger molecules because of their high molecular mass and limited solubility. The method has been applied to the PEGylation and the covalent homodimerization of proteins with a good conversion.[40]

Moreover, the synthesis of radiolabelled materials towards the development of radiotracers for positron emission tomography (PET) is hampered by short half-lives of common positron-emitting radionuclides (*e.g.* ^{11}C = 20 min, ^{18}F, 109.8 min). This requires the development of synthetic methods rapid enough to overcome the natural decay of the probe so as to furnish the targets in high radiochemical yields. Bode, Ametamey, and co-workers have shown that pyridyl KATs can be functionalized with ^{18}[F]fluoride by S_NAr and the resulting radiolabelled KATs can be used as prosthetic groups for the fast radiolabelling of peptides and proteins at room temperature (Scheme 23c).[41] The S_NAr proceeded without any detectable $^{18}F/^{19}F$ isotopic exchange.

Besides MIDA boronates and KATs, Bode and co-workers have reported the gram-scale synthesis of B-chiral monofluoro acylboronates, a new class of acylboronates stable under air, in water, and on silica gel, yet exceptionally reactive (Scheme 24a).[37] Subtle changes of the substituents can modulate the properties and reactivities of these acylboronates in amide-forming ligation. In particular, **38** is more than three times as reactive as the corresponding KAT and about 1.6 times more reactive than the corresponding MIDA boronate in amide formation with an *O*-diethylcarbamoyl traceless, templated amide-forming ligation that proceeds at a low micromolar concentration (Scheme 24b).[42]

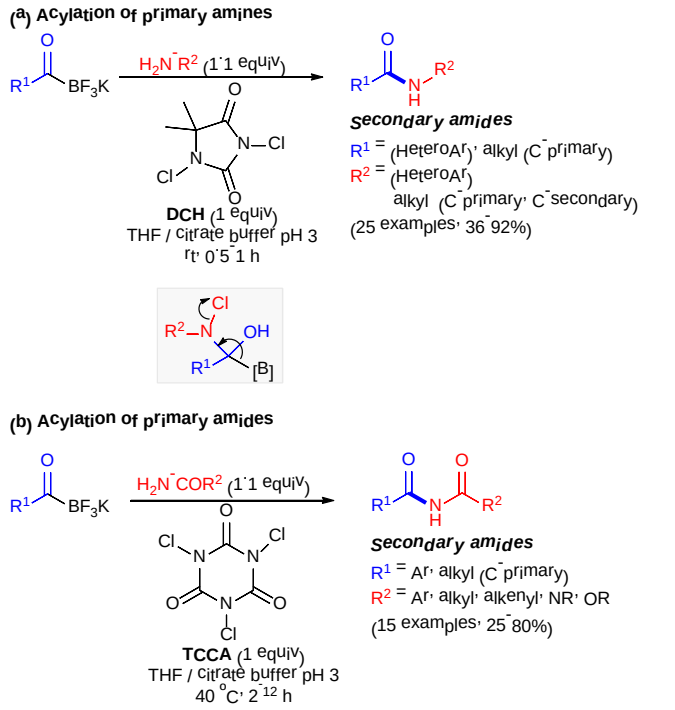


Scheme 24 Ligation reactions with monofluro acylboronates.

3.3 Amines and amides

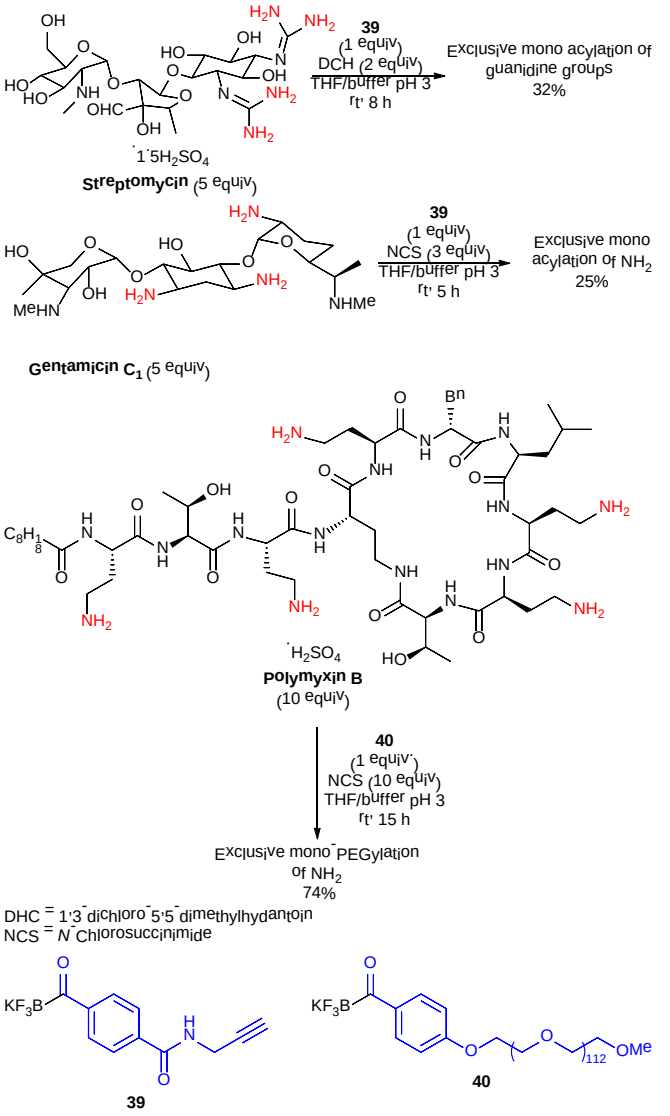
In situ activation of the *N*-atom of primary amines with N-chlorinating agents permits their fast coupling with KATs in an aqueous solvent (Scheme 25a).[2] The reaction is favoured at acidic pH, presumably because of a lack of protonation of the N-chloroamines under these conditions. Best results for amide formation are obtained in 1:1 THF/pH 3 citrate buffer (second-order rate constant ~10 M^{-1} s^{-1}) using 1,3-dichloro-5,5-dimethylhydantoin (DCH) as the chlorinating agent. Free amines or their salts can be used directly in the reaction. This transformation tolerates lateral chain functionalization at the amines with alkenes, unprotected alcohols, phenols, carbonyls, or carboxylic acids, including examples derived from carbohydrates and nucleosides, as well as KATs having different aryl, heteroaryl, and alkyl residues bearing coumarin, sulforhodamine, azide, silyl, and terminal alkyne groups. The acylation of primary amines occurs selectively in the presence of unprotected secondary or tertiary amines. Epimerization of the α-carbon is not observed when optically active *L*-phenylalanine methyl ester is used as a substrate. Electron-rich anilines often give complex mixtures derived from ring chlorination or oxidation, but electron-poor aryl and heteroarylamines can be acylated using 1,3,5-trichloroisocyanuric acid (TCCA) as the chlorinating agent. This is a notable contrast to classical amide formations using coupling reagents, which often fail with electron-deficient amines. Similarly to other KAT reactions with nitrogen nucleophiles (Section 3.2) in the absence of fluorophores, the reaction can be understood starting from the direct interaction of the N-chloroamine with the carbonyl group of the KAT.

With a slight modification of the reaction conditions (Scheme 25b), this procedure can also be applied to the acylation of primary aromatic, aliphatic, and α,β-unsaturated



Scheme 25 Reaction of KATs with amines and amides.

amides, ureas, and carbamates. Other *N*-functional groups typically resistant to classical acylations under mild conditions, such as guanidines and sulphonamides are also suitable partners for this class of coupling. This protocol is suitable for the late-stage functionalization of natural products such as Streptomycin, Gentamicin C_1 and Polymyxin B (Scheme 26),[2] as well as to the preparation of chemically cross-linked hydrogels based on a multi-arm PEG-bearing bearing KAT functional groups with multi-dentate amines.[43]



Scheme 26 Late-stage amidation of natural products. Products isolated as a mixture of isomers acylated on any of the nitrogen atoms marked in red.

4. Nitration and nitrosation reactions

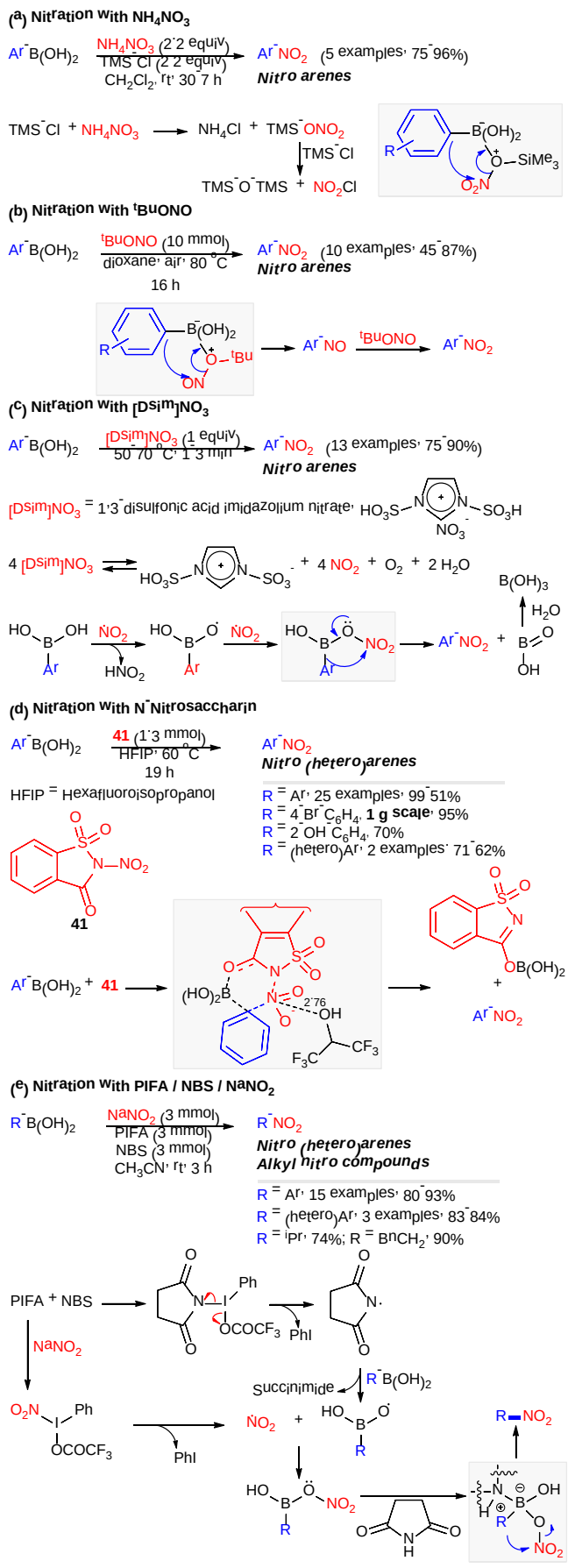
4.1 Nitrations

Traditional methods for the synthesis of nitroaromatics based on S_EAr using nitric and sulfuric acid or N_2O_5 are hampered by poor regioselectivity, oxidation, and functional group compatibility.[3] Significant achievements have been made by the use of metal-catalyzed procedures and with the use of several nitrite metal salts. Some of them are limited by the need to use large amounts of metal salts and/or harsh reaction conditions. On the other hand, resorting to boronic acids as starting materials permits the control of the regioselectivity and the use of metal-free conditions.

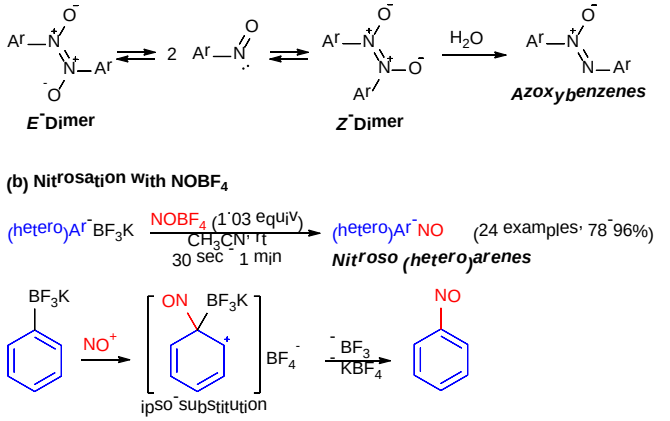
Prakash and co-workers were the first to report the *ipso*-nitration of arylboronic acids with the combination of NH_4NO_3 and trifluroacetic anhydride (TFAA) or TMSCl under mild conditions (Scheme 27a).[44] Although the use of TFAA tends to give mono- and dinitro products (arising from *ipso*-nitration together with S_EAr), the use of TMSCl affords better yields of the mononitro products both for electron-rich and electron-poor arenes. However, some contamination (2-10%) with monochlorinated products is observed in certain cases due to the possibility of the mixture TMS-Cl and NH_4NO_3 to act as a chlorinating agent.

By using inexpensive ^{t}BuONO, the mononitration of various arylboronic acids can be achieved directly without the need of any other catalyst (Scheme 27b).[45] The reaction is tolerant of functional groups such as methyl, phenyl, ether, halogen or aldehyde, and is presumed to take place by the initial formation of a nitrosoarene and subsequent oxidation to the nitro compound with an excess of the nitrite reagent.

The use of 1,3-disulfonic acid imidazolium nitrate ([Dsim]NO_3) under solvent-free conditions at rt permits the fast mononitration (1-3 min) of several arylboronic acids with electron-releasing and electron-withdrawing substituents, including free OH, ether, ketone, aldehyde, nitro and halogen substituents on the aromatic ring (Scheme 27c).[46] The reaction follows a radical pathway. The reagent [Dsim]NO_3 can produce NO_2 in equilibrium with N_2O_4. The interaction of NO_2 with $PhB(OH)_2$ gives rise nitrous acid together with an oxo radical, which evolves to nitrobenzene and oxoborinic acid.



Scheme 27 *ipso*-Nitration of boronic acids under metal-free conditions.



Scheme 28 *ipso*-Nitrosation of boronic acids under metal-free conditions.

Using N-nitrosaccharin (**41**) in hexafluoroisopropanol (HFIP) as the solvent, Katayev and co-workers[47] have carried out the nitration of aryl and heteroaryl (furan and thiophene derivatives) boronic acids. This transformation is tolerant of functional groups such as ester, ether, thioether, amide, nitro and halogens. The tolerance to OH is noteworthy. Theoretical calculations have put forward that the reaction takes place by a concerted and asynchronous mechanism with C–N bond formation as the rate-determining step. The elimination of $B(OH)_2$ is assisted by by the carbonyl group of the saccharin scaffold. The solvent (HFIP) assists the cleavage of the N–N bond and concomitant addition of the nitronium species to the aromatic ring by interacting through is O atom with the N atom of NO_2 (2.76 Å).

In addition to (hetero)arylboronic acids, the nitration of alkylboronic acids has been achieved by the use of the combination of PIFA with NBS and $NaNO_2$ (Scheme 27d).[20] The reaction of arylboronic acids is tolerant of functional groups such as halide, ether, nitro, aldehyde, keto or nitrile, including *ortho*-functionalized substrates. It can also be applied to pyridine, quinoline, and thianthrene. The reaction may take place by the coupling of the nitro radical, generated from PIFA and $NaNO_2$, with an oxo radical generated from PIFA and NBS.

4.2 Nitrosations

Although less common than nitro compounds, arylnitroso compounds are useful as radical scavengers, antioxidants, metal coordinating agents or pharmaceuticals.[4] The nitroso group is strongly electron-withdrawing, which combined with the presence of a lone pair on nitrogen, makes that aromatic compounds of this type (blue/green) tend to be in equilibrium with dimers (colorless) in solution. Besides, protonation on one of the oxygen atoms of any the dimers followed by dehydroxylation gives rise to stable azoxybenzenes (Scheme 28a). Despite these features, nitrosoarenes can be used as reactants in a variety of synthetically useful transformations such as Grignard, ene, nitroso aldol or cycloaddition reactions, as well as couplings with alkynes or amines.[4] Together with oxidation of amines or reduction of nitro compounds, the most frequent method for the synthesis of nitroso compounds by C-

N bond-formation is S_EAr. As stated previously in the case of nitration reactions, the utility of this reaction is diminished by regioselectivity and functional group tolerance.

Molander and Cavalcanti[48] have developed a mild, selective, fast (30 seconds to 1 min) and scalable (up to 1 g) *ipso*-nitrosation of electron-rich and electron-poor (hetero)aryl potassium trifluoroborates with $NOBF_4$ (Scheme 28b). The reaction is very much general and tolerant of functional groups such as alkyl, ether, ester, ketone, aldehyde, amide, halogens, nitro and carboxylic acid on the aryl rings, and is also successful for heterocyclic rings such as pyridine, isoquinoline, pyrimidine, dibenzothiophene, dibenzofuran, and indole. However, the reaction with the boron moiety as a substituent of a 5-membered heterocycle led to protodeborylation. These nitrosation reactions can be followed visually: The slurry formed by the trifluoroborate in CH_3CN becomes a bright green, homogeneous solution, which is immediately worked up by the addition of water followed by extraction and filtration. Prolonged reaction times lead to oxidation of the nitroso products, affording mixtures with the corresponding nitroaromatics. Using *p*-MeO-C_6H_4 derivatives, it has been demonstrated that arylboronic acids afford the nitroso product in nearly the same yield as the trifluoroborates, while boronate esters provide the nitroso product in moderate yields after 1 h, with starting material being recovered.

The combination of TMSCl with $NaNO_2$ has also been used for the *ipso*-nitrosation of electron-rich arylboronic acids. However, electron-poor substrates lead to nitration products instead.[49]

Conclusions

Boronic acids and their derivatives are familiar to the chemistry community for their use in popular transition-metal-catalyzed reactions such as the Suzuki, the Hayashi-Miyaura (C-C bond-formation) or the Evans-Chan-Lam reactions (C-N bond-formation). However, their ability to behave as C-nucleophiles in the absence of transition-metals is much less well-known to users. Investigations towards new methods for the synthesis of C-N bonds have an exceptional impact on the development of new organic drugs and materials. The cost and toxicity of transition-metals have urged the development of new metal-free reactions. This Tutorial Review shows how alkyl-, (het)aryl- and acylboronic acids can be used for the synthesis of amines, amides, nitro, and nitroso compounds, as well as some other related functional groups, without using transition-metals. These C-N bond-forming reactions are highly important in the construction of pharmaceuticals, polymers, and materials, and for the functionalization of biomolecules under highly sustainable conditions. Future challenges and developments will have to address the encompassing of more types of boronic acid derivatives, such as alkenyl and alkenyl derivatives, and new nitrogen reagents suitable to widen the scope of amination, amidation, nitration, and nitrosation reactions, including the direct synthesis of primary and tertiary amides derived from natural products and acylboronates.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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