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Review

Borane–Trimethylamine Complex: A Versatile Reagent in Organic Synthesis

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Abstract: Borane–trimethylamine complex ($Me_3N{\cdot}BH_3$; BTM) is the most stable of the amine–borane complexes that are commercially available, and it is cost-effective. It is a valuable reagent in organic chemistry with applications in the reduction of carbonyl groups and carbon–nitrogen double bond reduction, with considerable examples in the reduction of oximes, hydrazones and azines. The transfer hydrogenation of aromatic *N*-heterocycles and the selective *N*-monomethylation of primary anilines are further examples of recent applications, whereas the reduction of nitrobenzenes to anilines and the reductive deprotection of *N*-tritylamines are useful tools in the organic synthesis. Moreover, BTM is the main reagent in the regioselective cleavage of cyclic acetals, a reaction of great importance for carbohydrate chemistry. Recent innovative applications of BTM, such as CO_2 utilization as feedstock and radical chemistry by photocatalysis, have extended their usefulness in new reactions. The present review is focused on the applications of borane–trimethylamine complex as a reagent in organic synthesis and has not been covered in previous reviews regarding amine–borane complexes.

Keywords: borane; amine–borane complexes; reduction; ionic hydrogenation; radical reactions

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1. Introduction

Boron-based reagents play an important role in modern organic synthesis and especially borane carriers have reached a predominant position in the synthesis of pharmaceutics and natural products. Boranes form complexes with Lewis bases, such as amines and pyridines, that are stable, safer and easier to handle. There are few reviews in the literature concerning the use of amine–borane complexes in organic synthesis [1–8], but in some of them, the part describing the reactivity is quite limited. An early review [2] is the most representative in the description of the reactivity of several amine–borane complexes with examples of practical application in organic synthesis covering literature up to 1984; it is also the only one that describes some applications of borane–trimethylamine complex ($Me_3N{\cdot}BH_3$; BTM) while the subsequent reviews report either single reactions with this reagent or deal with different amine–boranes. A review on the chemistry of amine and phosphine–boranes was published [3] in 1999, whereas reductive amination was the topic of two reviews, one focused on amine–boranes [5] and the other with several boron reagents [4]. Amine–boranes forming frustrated Lewis pairs was the subject of a chapter in a book [6], whereas two recent reviews dealt with the reactivity of ammonia-borane complex [7,8]. This review aims to focus on the use of borane–trimethylamine complex as a reagent, mainly after 1984 and not covered in previous reviews regarding amine–borane complexes.

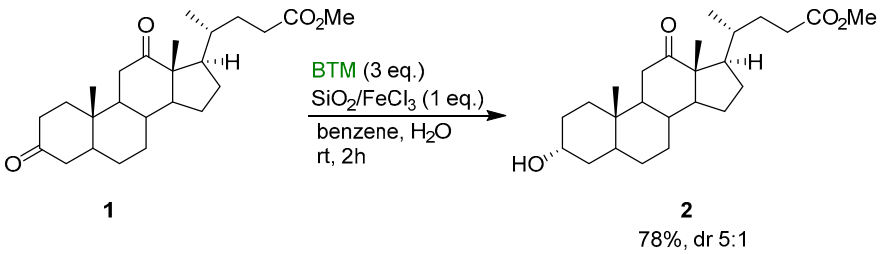
Of the various known complexes, BTM is the most stable [9], less sensitive to hydrolysis, even under acidic conditions [2], and does not require any special storage conditions. It is thermally stable up to 120 °C and can be purified by vacuum sublimation;

conversely, ammonia–borane complex explodes when heated, and an attempted distillation of borane–pyridine complex at reduced pressure resulted in violent decomposition [1]. BTM is very soluble in a wide variety of solvents [1], and its stability significantly increases with increasing solvent polarity [10]. It is relatively inexpensive compared with the other amine–borane complexes commercially available and considering the low molecular weight. Contrarily to borane complexes of ammonia, primary and secondary alkylamines, the inert nature of trimethylamine in BTM was a further advantage in avoiding the side reactions observed with the more reactive amines. Its reactivity can be opportunely activated in the reaction medium, and it is considered a valuable reagent in organic synthesis for laboratory as well as industrial scale. Since 1937, when it was synthesized for the first time, its applications have grown steadily, with some innovative ones in recent years.

2. Reductive Transformations with Carbon–Oxygen Double Bond

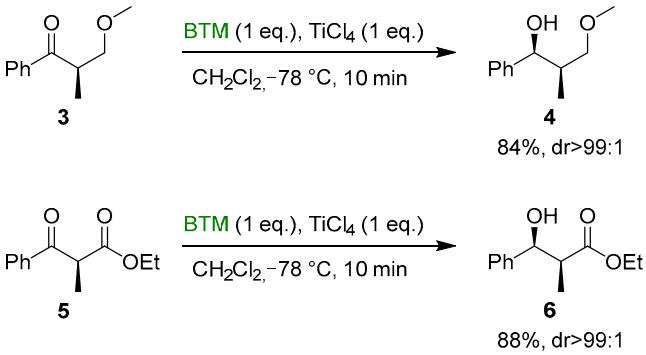
2.1. Reduction of Ketones

BTM is a weak hydride donor more reactive than trialkylsilanes and trialkylgermanes, comparable with that of trialkylstannanes [11]. The greater stability of BTM in the presence of Lewis or Brønsted acid allows the activation of the substrate by acid catalysis [2]; from kinetic studies, the rate of reduction of aldehydes and ketones increases with increasing acidity of the medium suggesting the formation of a protonated carbonyl species in rapid equilibrium, followed by the rate-determining step of the reduction. BTM was the reagent of choice for the selective reduction of steroidal diones, such as **1**, in the presence of wet silica gel impregnated with $FeCl_3$ (Scheme 1): C-3 carbonyl group was reduced preferentially to the alcohol **2** [12].



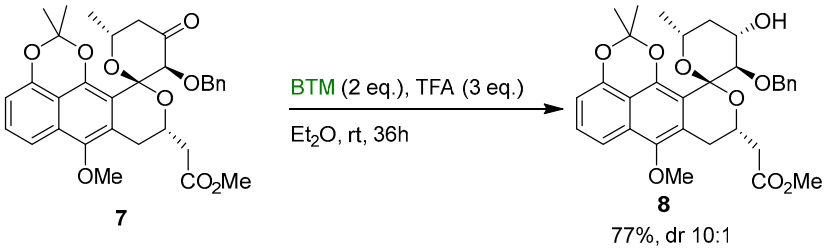
Scheme 1. Regioselective reduction of dione **1** on a silica gel surface.

The formation of a chelate between the Lewis acid and substrates **3** and **5** proved to be effective for the completely diastereoselective reduction to the corresponding alcohols **4** and **6** (Scheme 2) [13].



Scheme 2. Diastereoselective reduction of ketones **3** and **5**.

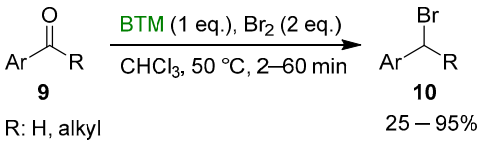
In a similar way, in the enantioselective total synthesis of analogs of griseusins [14], ketone **7** was reduced by BTM in good diastereoselectivity using TFA as acid (Scheme 3).



Scheme 3. Diastereoselective reduction of ketone **7**.

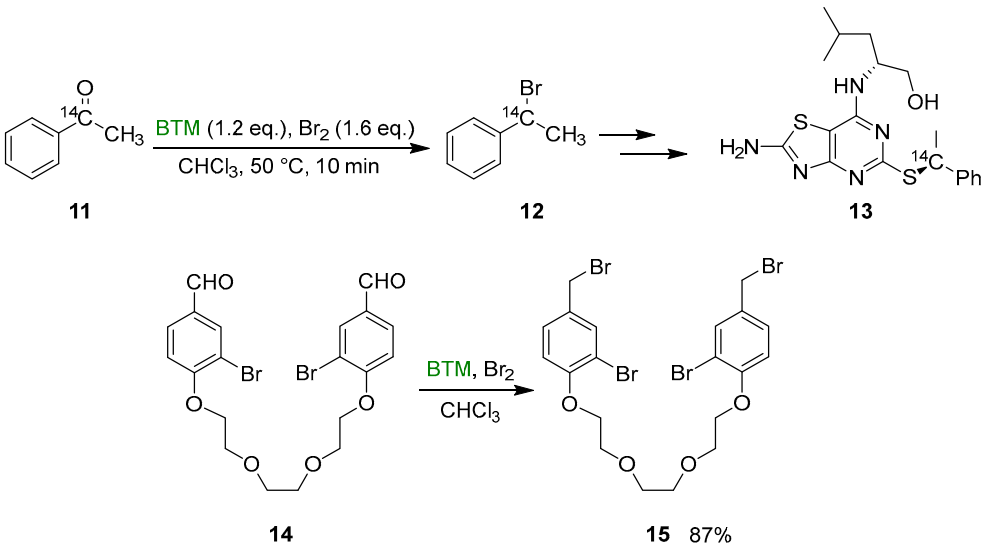
2.2. Reductive Bromation of Aromatic Carbonyl Compounds

Bromine was an effective activator in the reduction of both aldehydes and ketones by BTM [15], but in the case of aromatic compounds **9,** the reaction proceeded beyond the reduction to alcohol, leading to bromide derivative **10** in good yields (Scheme 4) with the exception of a product obtained in low yield after recrystallization.



Scheme 4. Reductive bromation of aromatic carbonyl compounds.

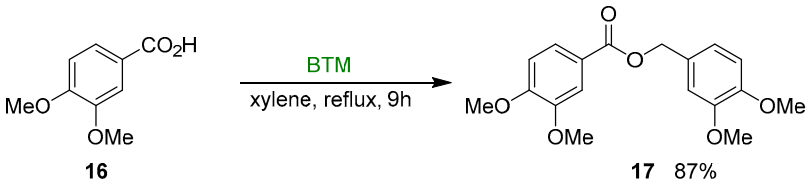
Some useful exploitations of the synthetic method were (Scheme 5) the synthesis of the ^{14}C labeled benzylbromide **12**, intermediate in the synthesis of CX_3CR1 antagonist **13** [16], and the synthesis of the dibromide derivative **15**, intermediate in the synthesis of crownophanes [17].



Scheme 5. Synthesis of the ^{14}C labeled benzylbromide **12** and the dibromide derivative **15**.

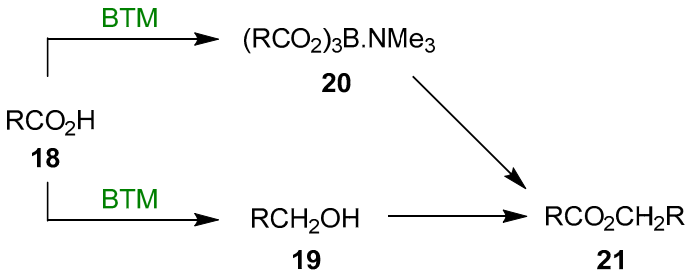
2.3. Reduction of Carboxylic Acids

At room temperature, carboxylic acids are inert in presence of BTM and can be used as solvent in the reduction reactions; on the other hand, refluxing a xylene solution of BTM and carboxylic acid **16** in molar ratio of 1.5:2, ester **17** was isolated in 87% yield [18] (Scheme 6); the reaction was suitable both to aliphatic and aromatic acids with moderate to good yields (28–87%).



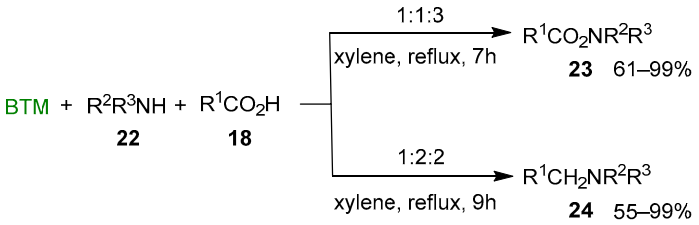
Scheme 6. Reduction of acid **16** to ester **17**.

A plausible reaction mechanism could be the presence of two concurrent reactions: the reduction of the acid **18** to alcohol **19**, isolated in every reaction, and the formation of the triacyloxyborane complex **20**, a known acylating compound; finally, the reaction of the two intermediates leads to the ester **21** (Scheme 7).



Scheme 7. Reaction mechanism of the acid reduction.

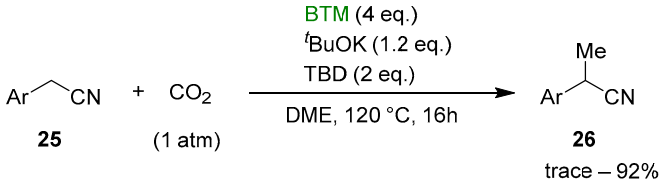
By adding either primary or secondary amine **22** to the previous reaction mixture and changing the ratio of the reagents, a different result was obtained (Scheme 8) [19]: with the molar ratio BTM:amine **22**:acid **18** = 1:1:3 led to amide **23**, seemingly by the action of acylating complex **20**; instead, the molar ratio 1:2:2 led to the tertiary amine **24**, likely by reduction of the acid **18** to an aldehyde equivalent (boryl acetal) followed by the reductive alkylation of amine **22**.



Scheme 8. Reaction of *N*-acylation or *N*-alkylation of amines **22** by carboxylic acids **18**.

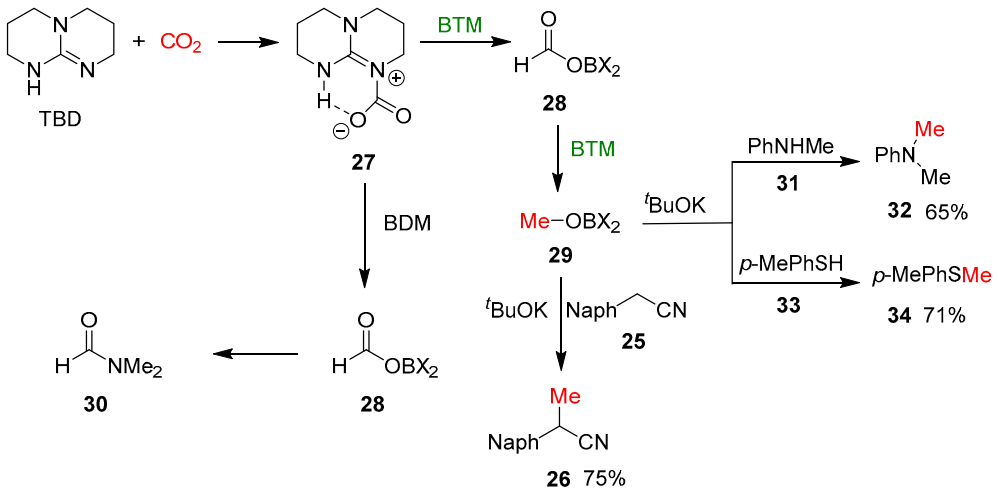
2.4. Reductive Methylation with CO_2

Recently, the reduction of CO_2 has emerged as a topic of great interest connected with global climate change and the urgent necessity to reduce the concentration of CO_2 in the atmosphere through sequestration and its utilization in the synthesis of useful compounds. An early study [20] reported the reduction of CO_2 to formate by BTM weakly bonded to the bulkier Lewis acid $Al(C_6F_5)_3$; then, the reaction mechanism was studied by quantum chemical calculations [21]. Subsequently, the reduction of CO_2 was exploited for the selective monomethylation of 2-arylacetonitriles **25** [22]; as shown in Scheme 9, the optimized reaction conditions involved the reaction, in a sealed tube, of a DME solution of nitrile **25**, ^{t}BuOK and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in an atmosphere of CO_2, obtaining selectively the monomethyl derivative **26**, with yields around 80% in almost all examples.



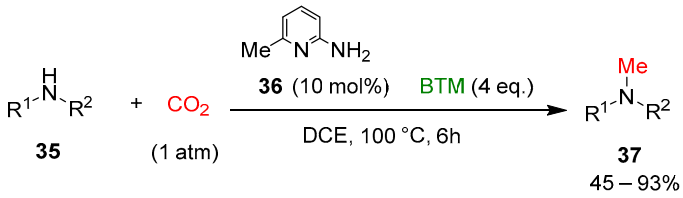
Scheme 9. Selective monomethylation of 2-arylacetonitriles **25**.

By using $^{13}CO_2$, the corresponding ^{13}C methyl derivative was obtained, confirming that the methyl group comes from CO_2. In the reaction, TBD has the role of activator of the CO_2 forming the adduct **27** (Scheme 10), and ^{t}BuOK of a strong base in deprotonation of 2-arylacetonitriles **25**. The reaction, shown in Scheme 9, performed without nitrile **25**, led to methyl borate **29** as the major product, which suggests that CO_2 undergoes a six-electron reduction with the formatoborohydride **28** as an intermediate. Differently from BTM, borane–ammonia complex reduced CO_2 to the formyl group; conversely, with the borane dimethylamine complex (BDM), the two-electron reduction product **28** reacted with dimethylamine, derived from BDM, leading to amide **30** and blocking further reduction (Scheme 10). In the presence of ^{t}BuOK, methyl borate **29** proved to be an effective methylating agent of nitrile **25,** obtaining the methylated product **26** in 75% yield; in a similar way, two different nucleophiles, such as aniline **31** and thiophenol **33,** were methylated in the same reaction condition.



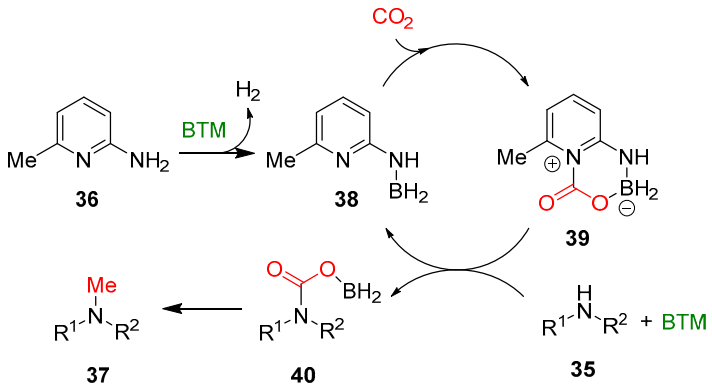
Scheme 10. The proposed mechanism of the reaction of monomethylation.

Recently, the selective methylation of amines with CO_2 was examined [23] by combining the organocatalyst 6-amino-2-picoline **36** and BTM (Scheme 11) to form a stable intramolecular frustrated Lewis pairs catalyst (Scheme 12), most of the secondary amines **35** used were *N*-alkyl or *N*-aryl anilines, with only two examples of alkyl heterocyclic amines, affording methylation products **37** in moderate to good yields.



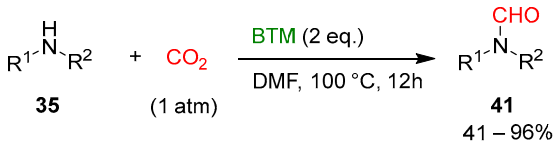
Scheme 11. Selective methylation of amines with CO_2.

On the basis of a series of control experiments, NMR and high-resolution mass spectrometry (HRMS) analyses, a possible reaction mechanism was proposed (Scheme 12). The first step is the reaction of 6-amino-2-picoline **36** and excess BTM leading to aminoborane **38**, with the quantitative evolution of H_2, followed by the CO_2 activation with zwitterionic intermediate **39**. The next steps are less evident, and the authors speculate the formation of intermediate **40** that is further reduced to product **37**.



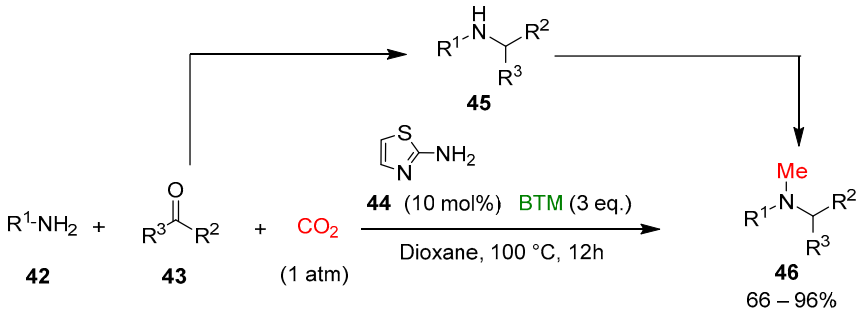
Scheme 12. Reaction mechanism of methylation of amines with CO_2.

Without a catalyst, halving the equivalents of BTM and with DMF as solvent (Scheme 13), the reduction afforded the corresponding monoformylation products **41**, an intermediate hypothesized in the reduction from **40** to product **37** (Scheme 12); most of the amines **35** used were primary anilines and yields were generally good.



Scheme 13. Formylation of amines with CO_2.

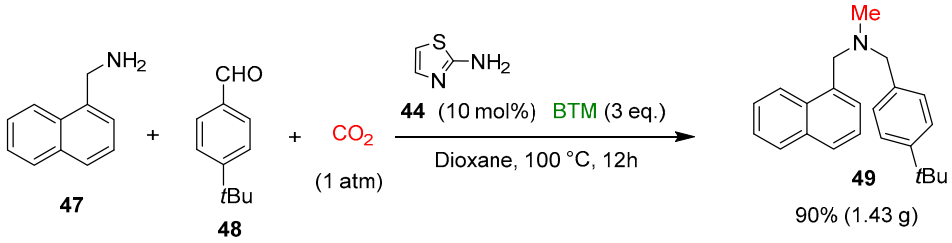
Finally, a tandem four-component reductive methylation of primary amines **42** was realized, coupling a reductive amination to secondary amines **45**, with the reduction of CO_2 to a methyl group, synthesizing tertiary *N*-methylamines **46** [24] (Scheme 14).



Scheme 14. Four-component reductive methylation of primary amines with CO_2.

On the contrary of catalyst **36**, 2-aminothiazole **44** catalyzed the reaction with higher efficiency, whereas BTM was the best choice in the screening of different types of boron-based reducing agents. The study of the scope of the reaction involved a large number of amines **42**, aldehydes and ketones **43,** leading to products in mostly good yields; the gram-

scale synthesis of the antifungal agent butenafine **49** was an example of the potentiality of the present synthetic method (Scheme 15).

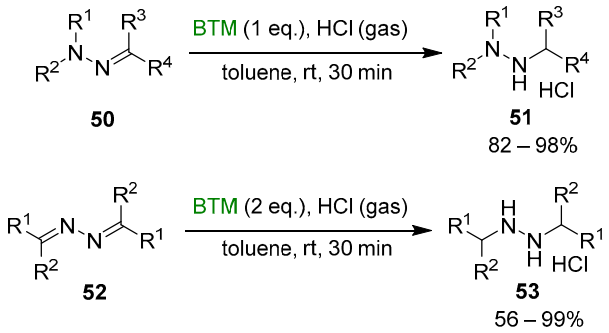


Scheme 15. Synthesis of the antifungal agent butenafine **49**.

3. Carbon–Nitrogen Double Bond Reduction

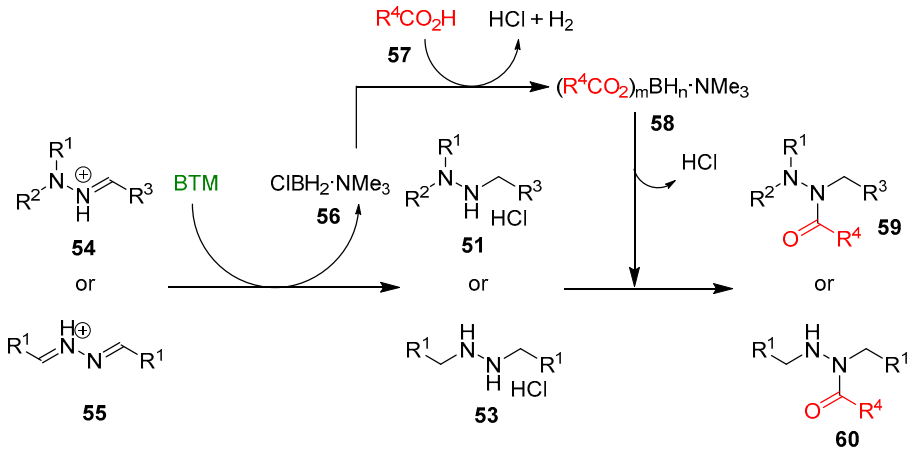
3.1. Reduction of Hydrazones and Azines

Although the reduction of hydrazones and azines is hampered by opposite conjugation effects, the presence of an acid in the reaction medium can activate the C=N bond to the attack of nucleophiles [25,26]. The improved stability of BTM in a strong acidic medium enabled the efficient reduction of both hydrazones **50** and azines **52** (Scheme 16), affording a wide range of highly functionalized mono-, di- and trialkyl hydrazines as stable and safe hydrochlorides and in excellent yields for most of the compounds.



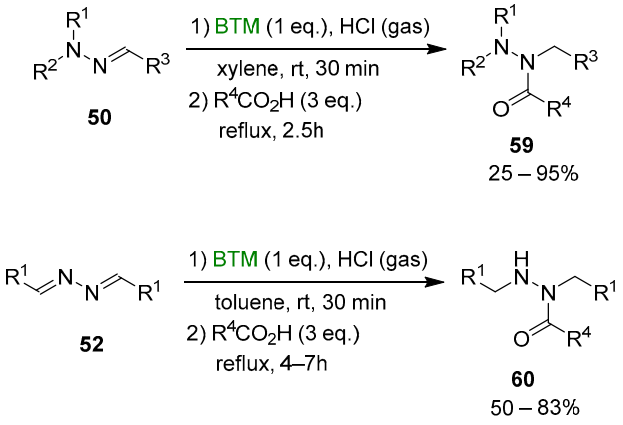
Scheme 16. Reduction of hydrazones and azines.

The work-up operationally simple was another credit of the method, as the byproduct of reduction **56** (Scheme 17) was soluble in toluene, contrary to products **51** or **53,** which are completely insoluble (except for two compounds) and easily separated by filtration.



Scheme 17. The proposed mechanism of the synthesis of hydrazides.

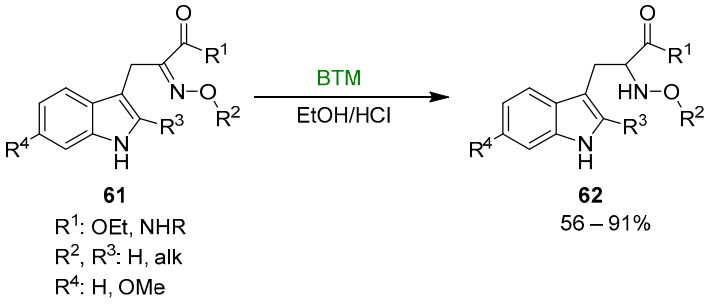
Byproduct **56** was exploited in the "one pot" synthesis of hydrazides by adding carboxylic acid **57** at the end of the reduction step and producing, in situ, a mixture of acyloxyboranes **58** (Scheme 17) that proved to be an effective acylating agent of both alkylhydrazine hydrochloride **51** and **53** (Scheme 18); the yields were susceptible to the bulkiness of both carboxylic acids and alkylhydrazines limiting the reaction to less hindered hydrazones and azines derived from aldehydes. The tight steric requirement for the acylation by the acyloxyboranes made the synthesis of hydrazides **60** completely selective without the formation of the related diacyl hydrazines side-product, generally observed with common acylating agents.



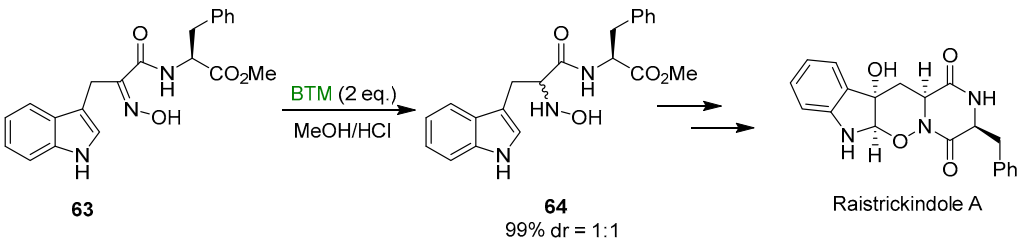
Scheme 18. Synthesis of hydrazides.

3.2. Reduction of Oximes

Early studies on the reduction of oximes by BTM and HCl were directed to the synthesis of *N*-hydroxy derivatives of tryptophan **62** (Scheme 19), useful intermediates for the synthesis of β-Carbolines [27–30], fungal metabolites Neoechinulins [31,32] and recently the marine fungal metabolite raistrickindole A [33] (Scheme 20); with some oximes the reduction of indole to indoline (see Section 3.3) was observed [32].

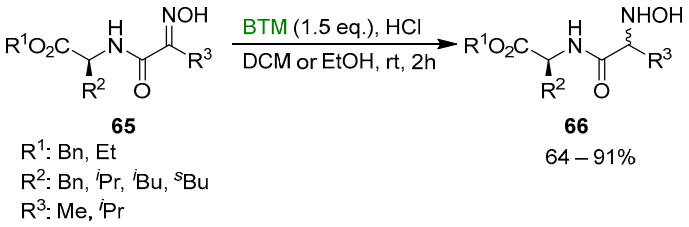


Scheme 19. Synthesis of *N*-hydroxy derivatives of tryptophan **62**.



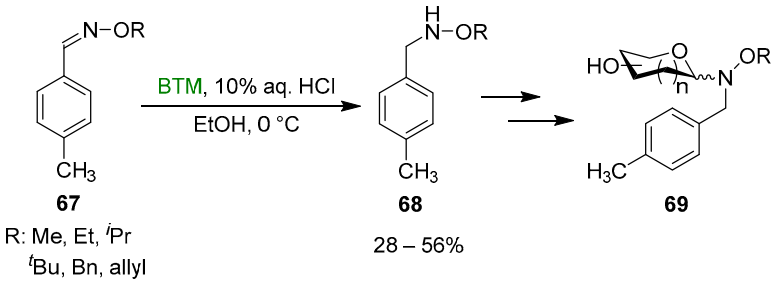
Scheme 20. Synthesis of raistrickindole A.

Subsequently, the synthetic method was extended to the synthesis of a new type of pseudopeptides, the *N*-hydroxy dipeptides **66** [34], as a diastereoisomeric mixture (Scheme 21).



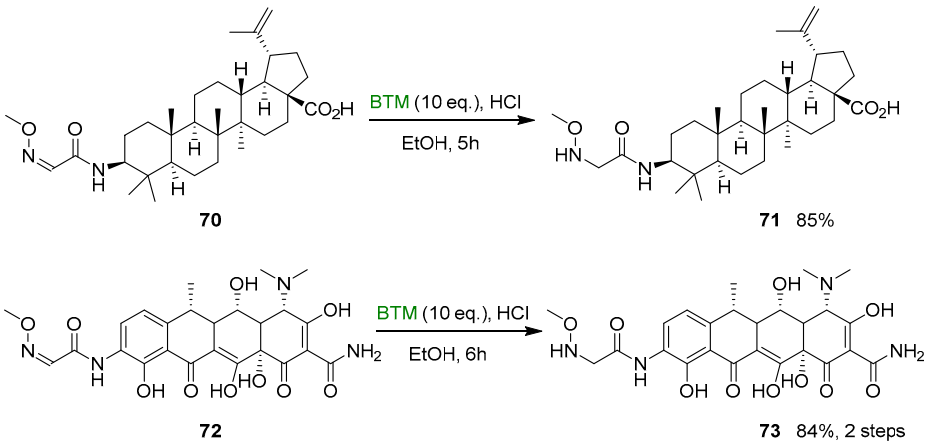
Scheme 21. Synthesis of *N*-hydroxy dipeptides.

Reduction of oximes was the easiest method of synthesis of the *N*-alkyl-hydroxylamines **68** [35], requisite for the neoglycosylation reaction optimization in the synthesis of glycosylated **69** (Scheme 22); the yields were mediocre to moderate, likely due to the use of diluted HCl aqueous solution.



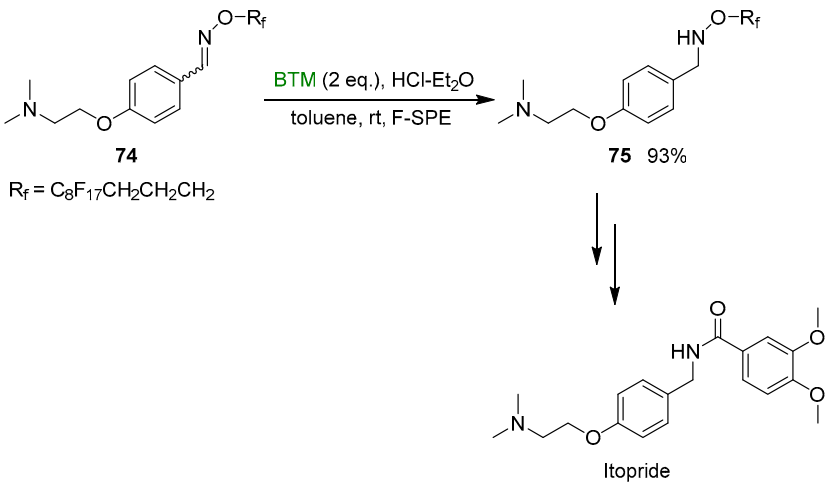
Scheme 22. Synthesis of *N*-alkyl-hydroxylamines **68**.

Similarly, the betulinic derivative **71** [36] and 9-amino doxycycline derivative **73** [37], suitable substrates for the neoglycosylation reaction, were synthesized from the corresponding oximes in good yields, making use of HCl in ethanol and large excess of BTM (Scheme 23).



Scheme 23. Synthesis of *N*-alkyl-hydroxylamines **71** and **73**.

Finally, a new fluorous-tagged hydroxylamine [38], as an ammonia equivalent, was successfully exploited in the synthesis of itopride, a drug used for the treatment of functional dyspepsia; the work-up step was simplified by fluorous solid-phase extraction (F-SPE), relative with this strategy (Scheme 24).

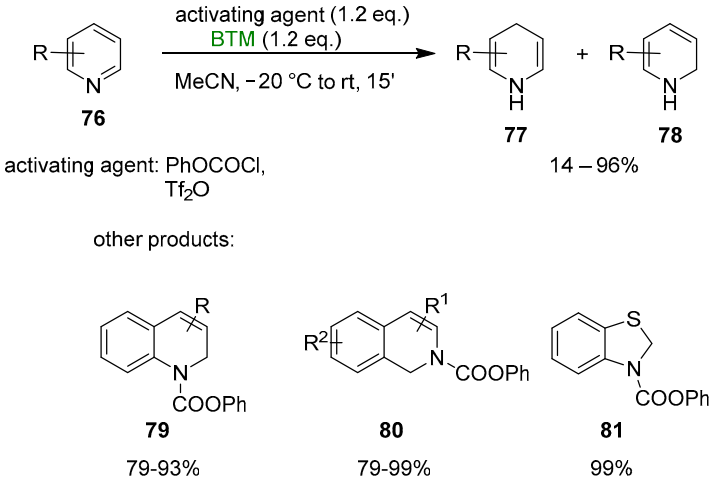


Scheme 24. Synthesis of itopride.

3.3. Transfer Hydrogenation of Aromatic N-Heterocycles

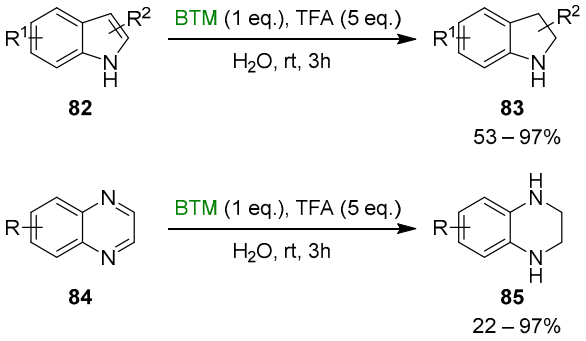
Several aromatic *N*-heterocycles can react with protic acid or acylating agents, leading to salts with an immonium substructure that can be reduced by BTM similarly to the reduction of imines activated with protic acid [2]; reduction of indoles to indolines was reported in a previous review [2].

BTM reduced pyridines **76** (Scheme 25), activated by reaction with phenyl chloroformate, to 1,4 dihydropyridine **77** (majority product) and 1,2 dihydropyridine **78** (minority product) [39]; the use of triflic anhydride improved the regioselectivity toward dihydropyridine **77** reaching, in the best case, the 99:1 regioselectivity and 76:24 for the worst case. Substituents in the 4-position completely inverted the selectivity in favor of regioisomer **78**. The reaction could also be applied for the synthesis of other N-heterocycles, such as dihydroquinolines **79**, dihydroisoquinolines **80** and benzothiazoline **81**, among others.



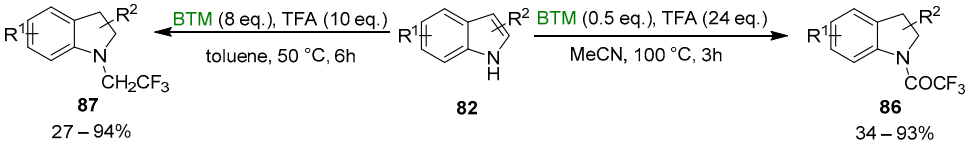
Scheme 25. Dearomatization of *N*-heterocycles.

Trifluoroacetic acid (TFA), as an acidic activator, offered several opportunities; both indoles **82** and quinoxalines **84** [40] were reduced to indolines **83** and tetrahydroquinoxalines **85,** respectively, in water as solvent (Scheme 26).



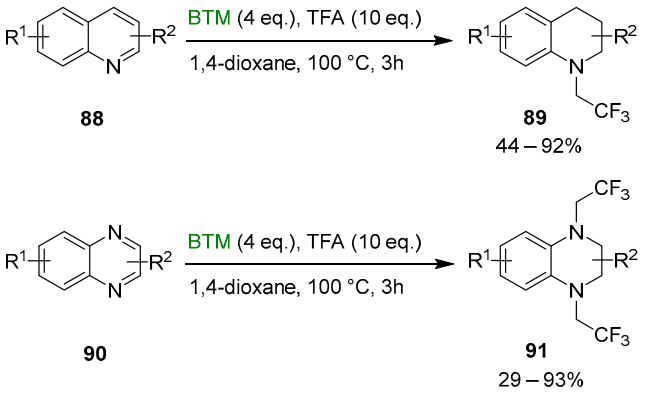
Scheme 26. Reduction of indoles **82** and quinoxalines **84**.

Tuning the reaction condition and the equivalents of BTM and TFA, as shown in Scheme 27, to go beyond the reduction, obtaining a different product [41]. A reduced amount of BTM, increased equivalents of TFA and the use of an aprotic solvent brought to the *N*-trifluoroacetylated indolines **86**, while the increase of BTM brought to the *N*-trifluoroethylated indolines **87**, similarly to the reduction, by BTM, of carboxylic acid in the presence of amines (Section 2.3, Scheme 8).



Scheme 27. Synthesis of *N*-trifluoroacetylated indolines **86** and *N*-trifluoroethylated indolines **87**.

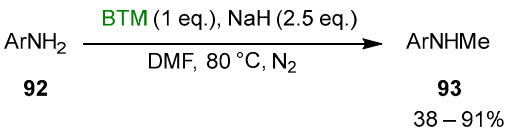
The synthetic method was successfully extended to the synthesis of *N*-trifluoroethylated tetrahydroquinoline **89** and *N*-trifluoroethylated tetrahydroquinoxalines **91** (Scheme 28) [42].



Scheme 28. Synthesis of *N*-trifluoroethylated tetrahydroquinoline **89** and *N*-trifluoroethylated tetrahydroquinoxalines **91**.

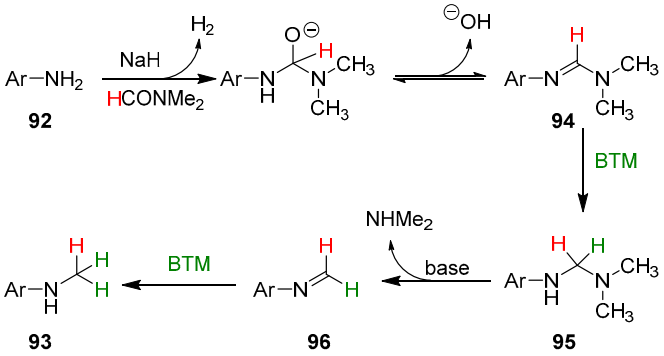
3.4. Selective N-Monomethylation of Primary Anilines

Primary anilines **92** were selectively monomethylated [43] by reaction with BTM and NaH in DMF (Scheme 29).



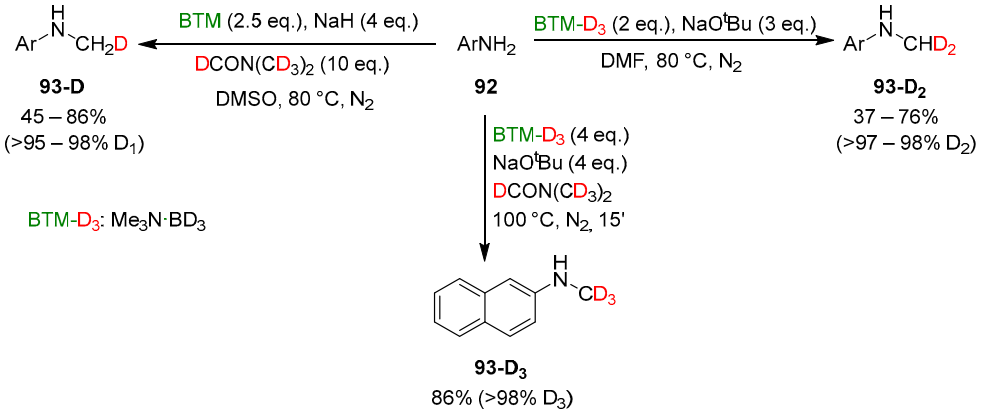
Scheme 29. Monomethylation of anilines.

In the proposed reaction mechanism (Scheme 30), the first step is the reaction of aniline **92** with NaH and DMF obtaining amidine **94** that, likewise, the reduction of imines by BTM [2], is reduced to aminal **95**; subsequent elimination of dimethylamine generated an imine that is easily reduced to the final product.



Scheme 30. Proposed reaction mechanism of the monomethylation of anilines.

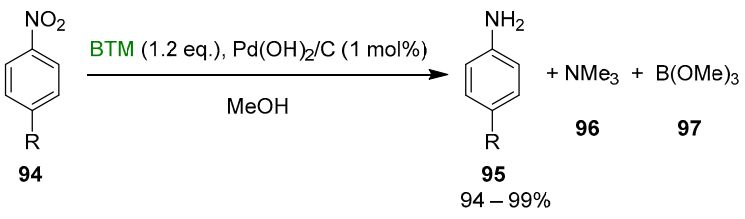
The sources of the hydrogens of the methyl group in monomethyl anilines **93** (in red and green in Scheme 30) and the easy synthesis of BTM-D_3 ($Me_3N{\cdot}BD_3$) by deuterium exchange in acidic D_2O [2] were exploited in the synthesis of products with specific numbers of deuterium atoms into the methyl groups (Scheme 31) and excellent deuterium incorporation ratio, based on which deuterated reagent was used for the reaction.



Scheme 31. Synthesis of **93-D**, **93-D**$_2$ and **93-D**$_3$ anilines.

4. Reduction of Nitrobenzenes to Anilines

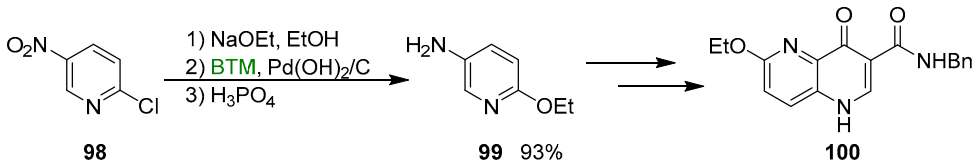
BTM is hydrolytically stable in alcohols, but it can be activated in situ through palladium catalysis [44], and the reaction can be coupled with the reduction of nitroaryls **94** to anilines **95** (Scheme 32). Measuring the kinetic of the reaction pointed out that the reduction was faster than hydrogen liberation: BTM acted as hydrogen-transfer reagent and palladium hydride likely as the transient species; indeed, the reaction was an open vessel reduction, even performed at reflux, without concomitant loss of hydrogen.



Scheme 32. Reduction of nitroaryls **94** to anilines **95**.

Credits of the reaction were excellent yield and operationally simple work-up procedure as both byproducts **96** and **97** were removed by simple concentration, and BTM surplus was completely consumed by methanolysis.

A practical use of this procedure was the "one pot" multigram synthesis of pyridine **99** (Scheme 33), a key intermediate in the synthesis of quinolone **100**, a subtype-selective GABA-A receptor inverse agonist [45].

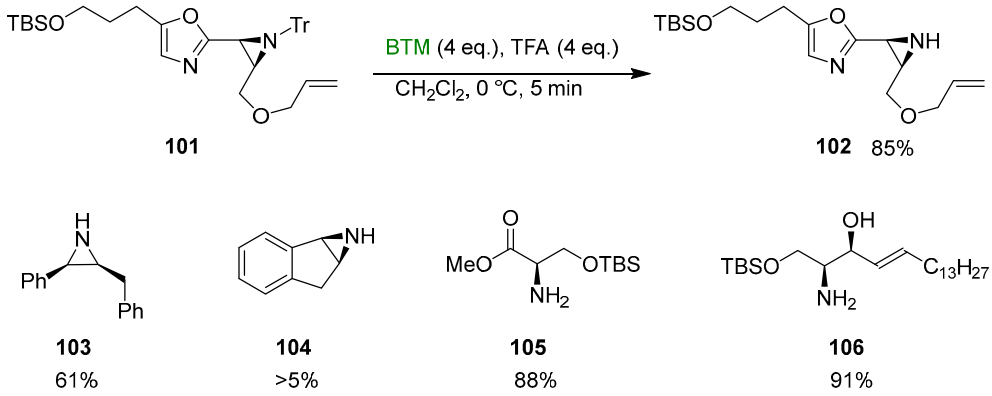


98 **99** 93% **100**

Scheme 33. Synthesis of the pyridine **99**.

5. Reductive Deprotection of *N*-Tritylamines

BTM reacts with some carbenium ions [11] by hydride abstraction; this reaction was exploited for the trapping of trityl cation in the deprotection of N-tritylamines, especially for sensitive substrates such as *N*-tritylaziridine **101** (Scheme 34) [46,47], an intermediate in the synthesis of aziridinomitosenes.



101 **102** 85%

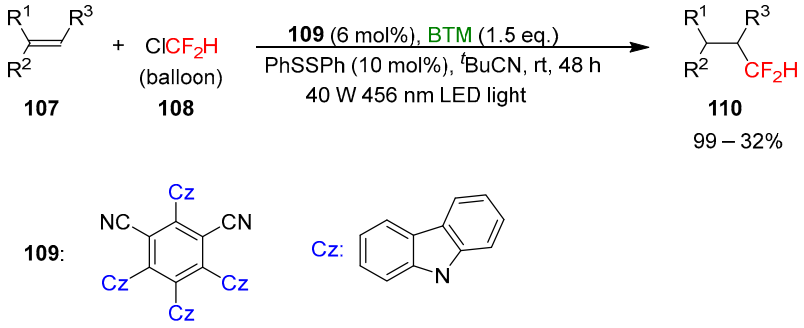
103 61% **104** >5% **105** 88% **106** 91%

Scheme 34. Reductive deprotection of *N*-tritylamines.

In addition, the method was tested for the deprotection of the aziridines **103** and **104** [48] with a low yield in the latter case due to problems with aziridine ring opening; in the absence of potential complications, the yields were excellent as for the protected serine **105** [48] and intermediate **106** in the synthesis of phytosphingosines [**49**].

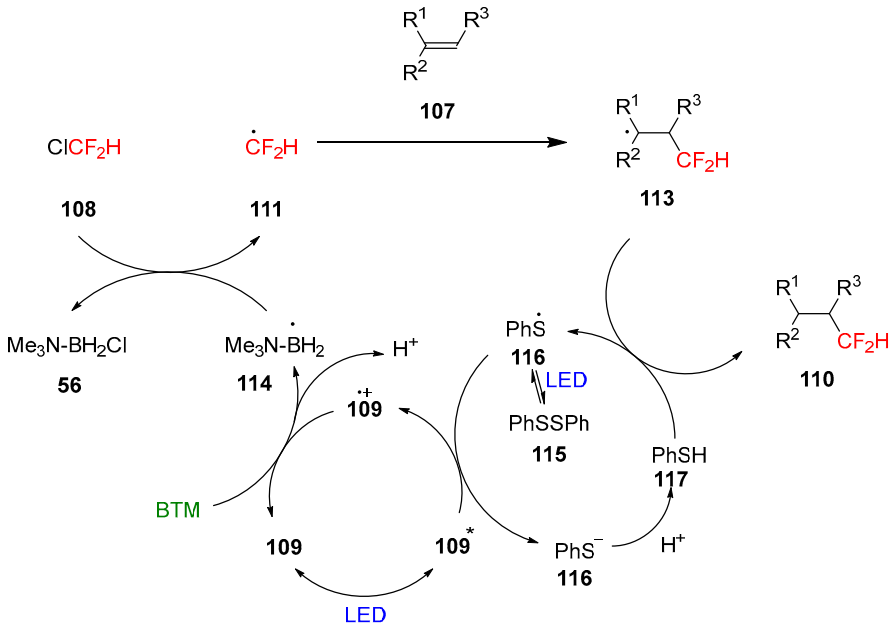
6. Photocatalytic Difluoromethylation of Unactivated Alkenes

Ligated boryl radicals, with the general formula $L_B{}^{+}$-$R_2B^{\bullet -}$, are intermediates in the activation of halogenated compounds by a reaction of halogen atom transfer (XAT) owing to the nucleophilic character of boryl radicals. Exploiting this process, BTM was utilized for the photocatalytic trifluoromethylation [50] of unactivated alkenes **107** by activation of Freon-22 **108**, an inexpensive feedstock, under 456 nm blue LED light irradiation (Scheme 35).



Scheme 35. Photocatalytic difluoromethylation of unactivated alkenes.

Difluoromethylated product **110** is of enormous interest in pharmaceutical and agrochemical science owing to the properties of the group CF_2H, bioisostere of hydroxyl, thiol, and amine groups. Alkenes suitable for the reaction protocol were extremely broad with the limitation of sterically encumbered tetra-substituted alkenes, unreactive, styrenes and electron-deficient alkenes where the reduction was a competitive reaction. The tolerance of various functional groups was also proved in the late-stage functionalization of complex pharmaceutical molecules and natural products; the yields were generally good, with limited examples with low yields. Supported by experimental and calculation results, the proposed mechanism of the reaction is shown in Scheme 36.



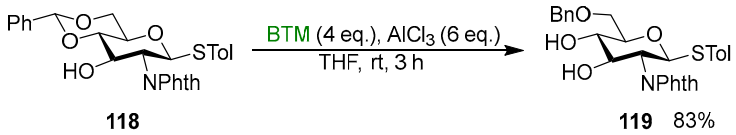
Scheme 36. Proposed mechanism of the reaction.

Aryl thiyl radical **116** is generated from disulfide homolysis under blue light irradiation and subsequently reduced to thiolate **116** by the excited state of **109**; the produced oxidized form **109**$^{\cdot+}$ is reduced back by BTM generating the amine-boryl radical **114** that undergoes a XAT reaction with Freon-22 **108** to generate the transient radical **111**. Subsequently, the intermolecular radical addition with the alkene substrate **107** and the quench of the radical adduct **113** by thiol **117** completed the reaction.

7. Reductive Cleavage of Acetals

Regioselective cleavage of cyclic acetals in the presence of a Lewis acid is the main application of BTM in the field of organic synthesis, and it is almost completely related to

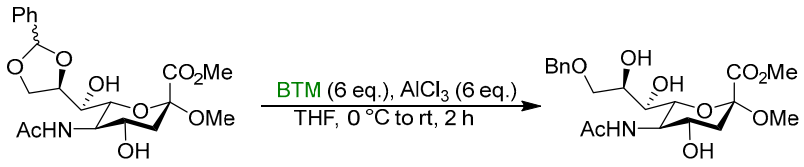
carbohydrate chemistry. Carbohydrates protected as 4,6-*O*-benzylidene acetals were regioselectively reduced by BTM in the presence of $AlCl_3$ [51–102], forming a free alcohol at one position and a benzyl ether protection at the other, useful for further modifications; Scheme 37 shows an example [93].



118 **119** 83%

Scheme 37. Regioselective cleavage of benzylidene acetal **118.**

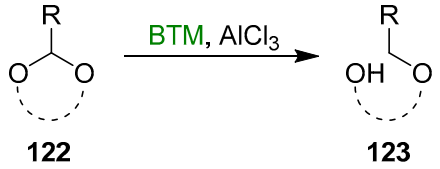
Alternative acidic activators were $BF_3{\cdot}Et_2O$ [103–118], Me_2BBr [119] and methanesulfonic acid [120]. Five-membered cyclic benzylidene acetals were suitable reactants for the synthetic protocol as well [121–134]; Scheme 38 shows a recent example [134]



120 **121** quant.

Scheme 38. Regioselective cleavage of benzylidene acetal **121.**

Acetals **122** (Scheme 39) with R different from the phenyl group allowed us to obtain the reduced product **123** with a hydroxyl protected with a different protecting group instead of the benzyl group, allowing more flexibility in the synthesis. Several examples were reported in the literature for R = *p*MeOPh (for six [135–138] and five [139] membered cyclic acetals), 2-naphthyl (for six- [140–145] and five- [146–148] membered cyclic acetals) and vinyl (five-membered cyclic acetals [149]).



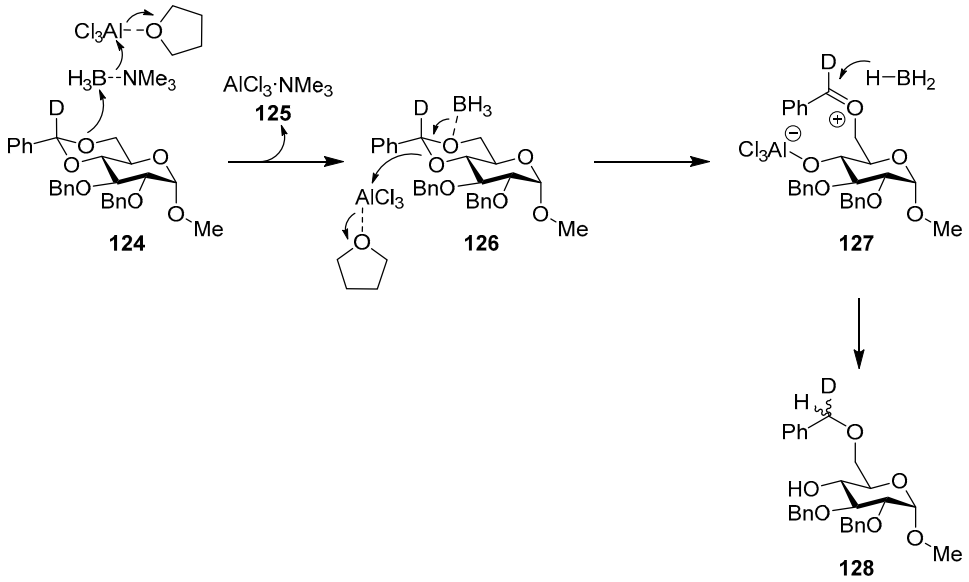
122 **123**

R: *p*MeOPh, 2-naphthyl, $CH{=}CH_2$

Scheme 39. Cleavage of cyclic acetals **122**.

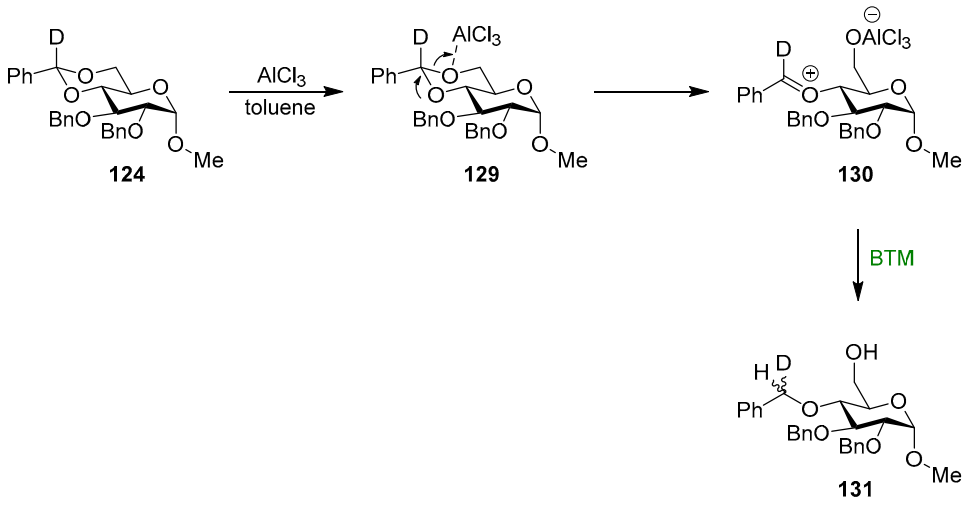
The reaction was extensively investigated, and an early study [150] showed that the addition of two equivalents of water to the reaction mixture (four equivalents of BTM and six equivalents of $AlCl_3$) improved the efficiency of benzylidene reductive cleavage without the observation of products of benzylidene acetal hydrolysis and rate enhancement of approximately four times. In order to decipher the mechanistic details of the reaction, several model compounds, kinetic experiments, ^{11}B NMR spectroscopy, computational calculations, deuterium labeling, alternative reducing reagents and solvents were used [151–154], bringing to the proposed mechanism for the reaction in THF, where the Lewis acid is complexed to the solvent (Scheme 40). In the first step, BTM is activated by $AlCl_3$, making the borane the most electrophilic species and leading to the interaction with the most electron-rich oxygen in intermediate **126**, whilst the driving force is the formation of the highly stabilized $AlCl_3{\cdot}NMe_3$ **125**; the opening of the acetal is obtained by the action of a second Lewis acid molecule with the formation of an oxocarbenium ion **127** as the rate-

controlling step; finally, oxocarbenium ion is then reduced with low stereoselectivity to give product **128**.



Scheme 40. Proposed mechanism for the reaction in THF.

The reaction in toluene had different regioselectivity and usually gave low yields due to degradation. In this case, in the proposed mechanism (Scheme 41), the strongest Lewis acid is $AlCl_3$, which reacts very fast to give the oxocarbenium ion **130** that is then reduced by BTM, with low stereoselectivity to give product **131**.



Scheme 41. Proposed mechanism for the reaction in toluene.

8. Conclusions

In conclusion, BTM has several credits as a reagent in modern organic synthesis. It is relatively inexpensive, and considering its low molecular weight, it has a low price per mole. It is a stable solid with a good safety profile linked with its relative inertness. Its reactivity can be opportunely activated in the reaction medium, generally in the presence of Lewis or Brønsted acids. BTM undergoes rapid deuterium exchange in acidic D_2O, allowing easy conversion to BTM-D_3, an effective reagent for the synthesis of deuterium-labeled compounds. BTM is very soluble in a wide variety of solvents, offering more ver-

satility in the reaction options. The tolerance of various functional groups was a well-substantiated feature of this reagent. The main application of BTM is the regioselective cleavage of cyclic acetals, a reaction of great importance for carbohydrate chemistry. Carbon–nitrogen double bond reduction is another class of reactions where the activation by acids plays an important role in the BTM reactivity. Finally, recent findings in organocatalysis have contributed to develop some innovative applications of BTM, such as the CO_2 utilization as feedstock and the radical chemistry by photocatalysis.

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Conflicts of Interest: The author declares no conflicts of interest.

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