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METAL-FREE ACTIVATION OF C-H BONDS BY BORON TRIFLUORIDE

Vladimir Iashin

ACADEMIC DISSERTATION

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List of original publications

The thesis is based on following publications, which are cited in the text by Roman numbers:

I. Vladimir Iashin, Dr. Konstantin Chernichenko, Dr. Imre Pápai and Prof. Timo Repo; Atom-Efficient Synthesis of Alkynylfluoroborates Using BF_3-Based Frustrated Lewis Pairs, *Angew. Chem. Int. Ed.* **2016**, *55*, 14146–14150.

II. Vladimir Iashin, Dénes Berta, Dr. Konstantin Chernichenko, Dr. Martin Nieger, Karina Moslova, Prof. Imre Pápai and Prof. Timo Repo; Metal-Free C–H Borylation of N-Heteroarenes by Boron Trifluoride, *Chem. Eur. J.* **2020**, *26*, 1–8.

III. Vladimir Iashin, Dr. Konstantin Chernichenko and Prof. Timo Repo; BF_3 – Promoted Dismutation of Organic Trifluoroborates, *Manuscript under preparation*.

Author's contribution.

Paper I: V. Iashin performed the major experimental work: synthesis and analysis.

Paper II: V. Iashin performed the experimental work and wrote the manuscript.

Paper III: V. Iashin performed the experimental work and wrote the manuscript.

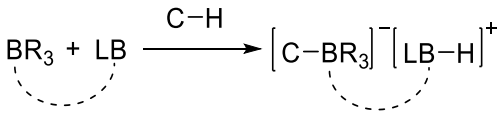
List of abbreviations

LA – Lewis acid
LB – Lewis base
FLP – Frustrated Lewis Pairs
PMP – 1,2,2,6,6-pentamethylpiperidine
Pr – n-propyl
Ph – phenyl
^{t}Bu – *tert*-butyl
TMS – trimethylsilyl
dba – dibenzylideneacetone
*o*Tol – *ortho*-tolyl
Me – methyl
THF - tetrahydrofuran
Bu – *n*-butyl
Mes – mesityl, 2,4,6-trimethylphenyl
Tipp – 2,4,6-triisopropylphenyl
TMP – 2,2,6,6-tetramethylpiperidine
Et – ethyl
BCF – tris(pentafluorophenyl)borane
Pin – pinacolyl
Cat – catecholyl
Thp – thiophene
Nmp – 1-methyl-1H-pyrrole
DFT – Density Functional Theory
ESI-MS – electrospray ionization mass-spectrometry
DIPEA – N,N-diisopropylethylamine
Bn – benzyl
NMR – nuclear magnetic resonance
BMP – 1-benzyl-2,2,6,6-tetramethylpiperidine
MMP – 2,2,6,6-tetramethyl-1-(2,4,6-trimethylbenzyl)piperidine
TMTU - tetramethylthiourea
TMAF – tetramethylammonium fluoride
DCE – 1,2-dichloroethane

Introduction

Scope of the thesis

C-H activation is a challenging problem in modern organic chemistry. Direct C–H borylation is one of the widely growing subclasses of C–H activation. As a rule, these reactions are performed by transition metal catalysis. However, recently a metal-free approach towards C-B boron bond formation has been growing intensively. Usually, metal-free borylations are performed with a boron compound as a Lewis acid (LA) component and a Lewis base (LB) as a proton acceptor, which may or may not be preorganized for this transformation (Scheme 1):



Scheme 1. General scheme of C-H activation by a Lewis acid (borane) and Lewis base.

Usually, such reactions require the use of boranes with high Lewis acidity such as $B(C_6F_5)_3$, BCl_3, BBr_3, etc. At the same time, the chemistry of the less acidic boron trifluoride, BF_3, as a borylating species is unprecedented. This work is aimed at uncovering the reactivity of BF_3 towards C-H borylation of C_{sp}–H and C_{sp2}–H bonds.

In this respect, the following factors were studied in the work:

- Formation of BF_3 adducts with various amines and their reactivity in C_{sp2}–H and C_{sp}–H borylation reactions
- Scope of borylation: influence of the substrates' electronic structure and various functional groups' compatibility
- Controlling the formation of mono-, bis-, tris-, and tetrakisorganoborates from BF_3, amine, and R_{sp}–H/R_{sp2}–H substrate.
- Reactivity difference between $BF_3{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, and BF3-1,2,2,6,6-pentamethylpiperidine ($BF_3{\cdot}$PMP) with respect to alkyne borylation

Because organoboranes are often unstable reactive species, they were converted to fluoroborates by tetramethylammonium fluoride. In this respect, competing reactions of protodeborylation and fluorination of organofluoroboranes were studied.

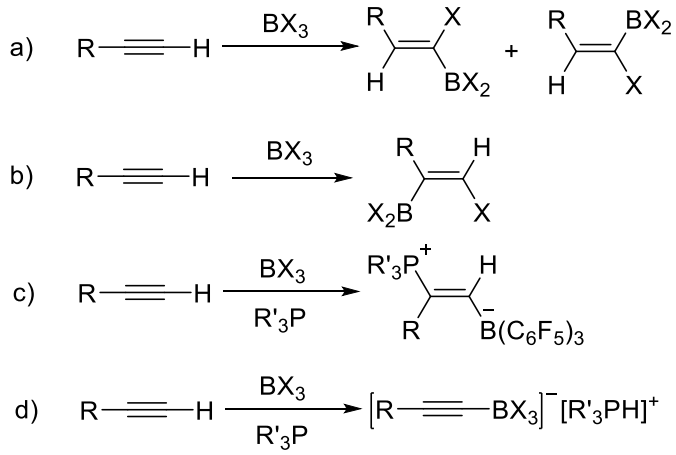
The literature review consists of two parts: metal-free borylation of triple bonds and double bonds. For triple bonds, the review is preferably limited to terminal acetylenes because internal alkynes cannot undergo C_{sp}–H activation. The influence of each component of a Lewis pair as well as its structure's selectivity for C–H borylation, 1,2-addition, and carboboration is discussed. The second part uncovers the topic of C-H borylation of C_{sp2}–H

bonds. It includes both concerted borylations and borylations by reactive borenium cations. There is a special accent on the chemistry of haloboranes. In order to limit the size of the review, the use of hydroboranes for C–H activation is reviewed least in this book.

Literature review

C_{sp}-H bonds activation

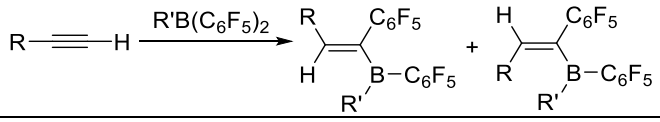
In general, reactions of terminal alkynes with borane and phosphine/amine can be divided into four types. Reaction of alkyne and borane in the absence of base gives either 1,1-carboboration (Scheme 2a)[1] or 1,2-carbo[2]- or haloboration[3] products (Scheme 2b). When a base (e.g., phosphine) is introduced into the system, the reaction outcome is usually either 1,2-addition (Scheme 2c)[4] or C-H activation (Scheme 2d)[4].



Scheme 2. Reactions of terminal alkynes with boranes and phosphines a) 1,1-carboboration; b) 1,2-carboboration; c) 1,2-addition; d) C-H activation.

1,1-carboboration

In the reactions of 1,1- and 1,2-carboboration, no Lewis base is formally present in the starting material nor in the product. Indeed, 1,1-carboboration can be performed by acidic borane derivatives which contain at least two C_6F_5 groups (Table 1). Substrate scope as well as the use of other C_6F_5 group containing boranes has been extensively studied by Erker et al.[5] (entry 3 in the Table 1). Aliphatic, aromatic, and propargylic alkynes undergo this reaction with 49-83% yields[5]. Interestingly, when a Lewis base and $B(C_6F_5)_3$ are present in the reaction, 1,1-carboboration also occurs if the Lewis base is not sufficiently basic to deprotonate the alkyne and the alkyne is too sterically crowded for the addition of the Lewis base as a nucleophile (Entry 2 in Table 1)[6].



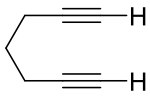
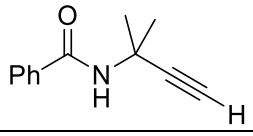
Entry	R	R’	REF
1	Pr, Ph	C_6F_5	[1]
2	^{t}Bu, $SiMe_3$	C_6F_5	[6]
3		C_6F_5	[7]
4	Pr, ^{t}Bu, $Ph(CH_2)_4$, $Cl(CH_2)_3$, $TMSOCH_2$, CH_3OCH_2	C_6F_5, CH_3, $(CH_2)_2Ph$	[5]
5		C_6F_5	[8]

Table 1. Typical examples of 1,1-carboboration of terminal alkynes by perfluoroaryl boranes.

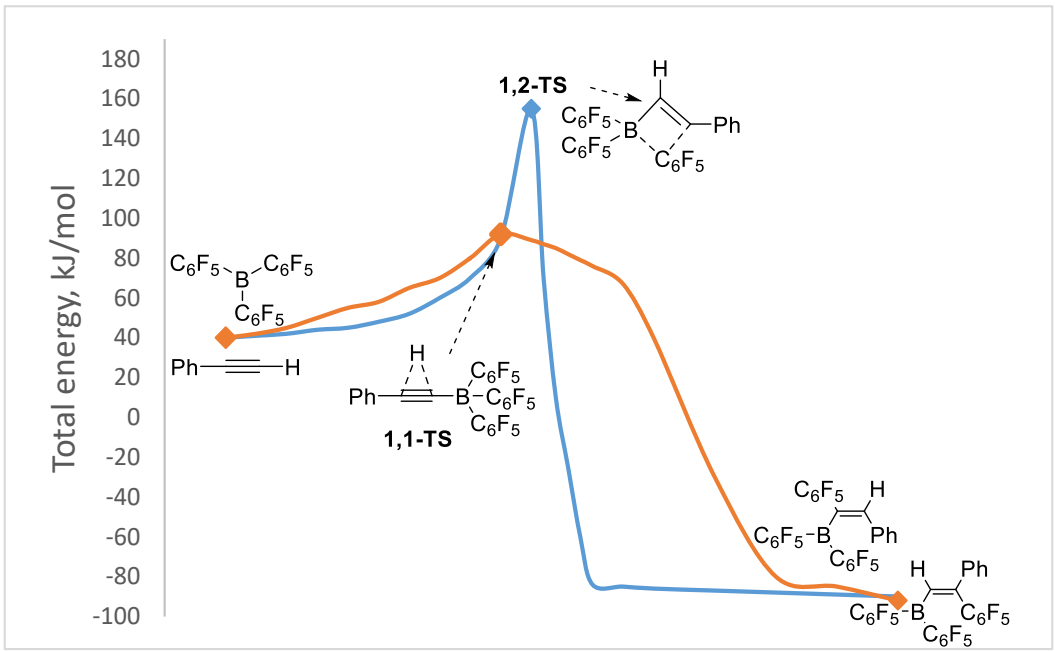


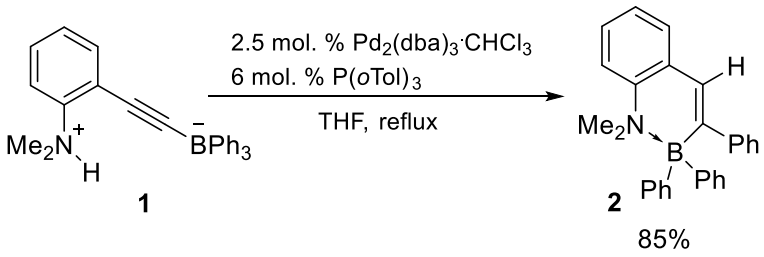
Figure 1. IRC (B3LYP/6-311++G(d,p)) energy profiles for 1,1-carboboration (red) and 1,2-carboboration (blue) of phenylacetylene by $B(C_6F_5)_3$ [9].

It has been shown that 1,1-carboboration is a two-step process [9]. It starts from slow 1,2-migration of a proton via the triple bond, and this is responsible for high energy barrier (92

kJ/mol). Furthermore, the C_6F_5 group migrates from boron to the adjacent alkynyl carbon thus forming the 1,1-carboboration product (Figure 1). In contrast, the corresponding hypothetic 1,2-carboboration proceeds as one step process through a four-membered cyclic transition state. However, the energetic barrier for this transformation is 152 kJ/mol, thus making 1,1-carboboration preferable over the 1,2-process. Ingleson et al. repute that the low migratory aptitude of C_6F_5 group is responsible for the preference of 1,1- over 1,2-carboboration [10].

The 1,1-carboboration reaction has also been expanded to internal alkynes. Examples of 1,1-carboboration of internal alkynes with 1,2-shift of $SiMe_3$[11-13], PR_2[14, 15], RTe[16], and aryl[17] groups are known. In case of alkynylsilicon, -germanium -tin, and –lead compounds, less acidic trialkylboranes can be utilized[18, 19].

Formal 1,1-carboboration products can also be obtained from triphenylalkynylborates **1** by a 1,2-shift of the phenyl ligand to the adjacent atom of the alkynyl moiety (Scheme 3). However, in this case, the presence of palladium is required and transfer of the phenyl group is done through the palladium atom, which is preceeded by hydropalladation of the triple bond[20, 21].

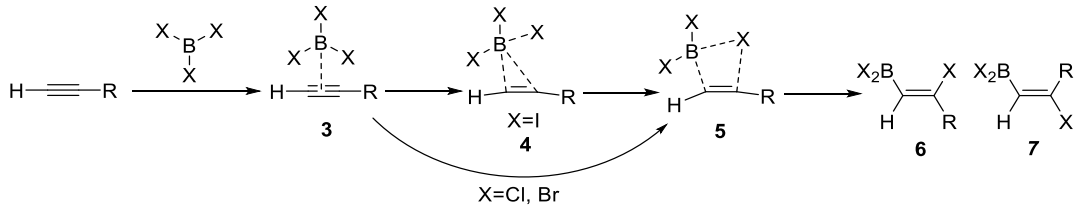


Scheme 3. Pd-catalyzed formal 1,1-carboboration of alkynylborate [20].

1,2-carboboration

Whereas 1,1-carboboration proceeds with acidic boranes $R_2B(C_6F_5)$, introduction of groups with higher migrating aptitude opens the pathway for 1,2-carboboration of triple bonds (Scheme 2b).

The mechanism of the haloboration involves formation of the van der Waals complex **3** from an alkyne and boron halide. This is then transformed to the transition state **5** either directly or via π-complex **4** when BI_3 is used (Scheme 4)[22].



Scheme 4. General mechanism of terminal alkynes haloboration [22].

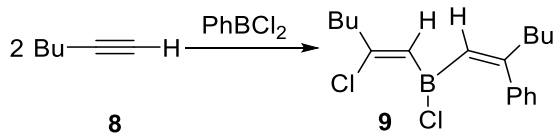
Transition state **5** is difficult to break due to the delocalized four centred six electron π-system in BX_3. Importantly, the electronegativity of the halide influences the stability of the transition state: the less electronegative the halide, the less polar and more stable is the intermediate **5** (Table 2). The energy required for propyne activation is significantly lower due to the effect of hyperconjugation from the methyl group[22].

Entry	R	X	G, kcal/mol				
			3	**4**	**5**	**6**	**7**
1	H	Cl	2.0	-	33.8	-4.4	-7.8
2	H	Br	2.0	-	25.9	-8.2	-12.2
3	H	I	1.9	15.4	19.7	-11.7	-17.4
4	Me	Cl	5.9	-	28.0	-1.5	-1.6
5	Me	Br	5.2	-	19.9	-5.8	-5.9
6	Me	I	5.1	11.4	13.6	-10.7	-10.0

Table 2. Gibbs energies (kcal/mol) of haloboration steps for acetylene and propyne [22].

Albeit the haloboration itself gives cis-products **6** (Scheme 4), isomerization to **7** is possible via further haloboration of the double bond, rotation of the single bond in the resulting boraalkane, and further retrohaloboration with elimination of BX_3[22].

The products of haloboration, alkenylboranes, can themselves serve as 1,2-boration agents, thus giving divinylboranes **9** (Scheme 5). An analogous reactions occurs when phenylacetylene is haloborated by BCl_3[3].

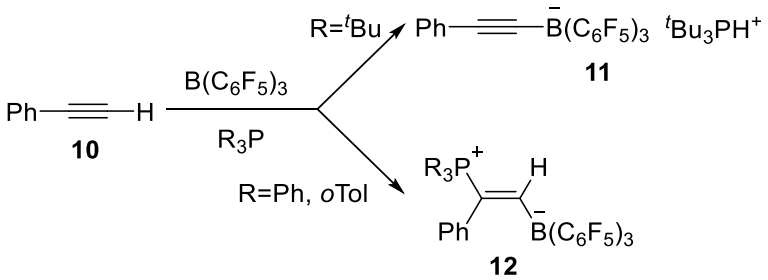


Scheme 5. Sequential carboboration-haloboration of hex-1-yne [3].

1,2-addition can also be performed by using haloborafluorenes[2, 23] and borane activation by borenium catalysis[10, 24, 25]. In special cases, haloboranes can facilitate 1,1-addition, if TMS-substituted internal alkynes are used[26].

1,2-addition vs C-H activation

In 2009, Stephan et al. showed that the combination of $B(C_6F_5)_3$ with various phosphines activates the phenylacetylene **10** giving either the product of C-H activation (**11**) or 1,2-addition (**12)** of phosphine and borane to the C-C bond[4] (Scheme 6):



Scheme 6. First metal-free activation of terminal acetylene by a Lewis base and Lewis acid [4].

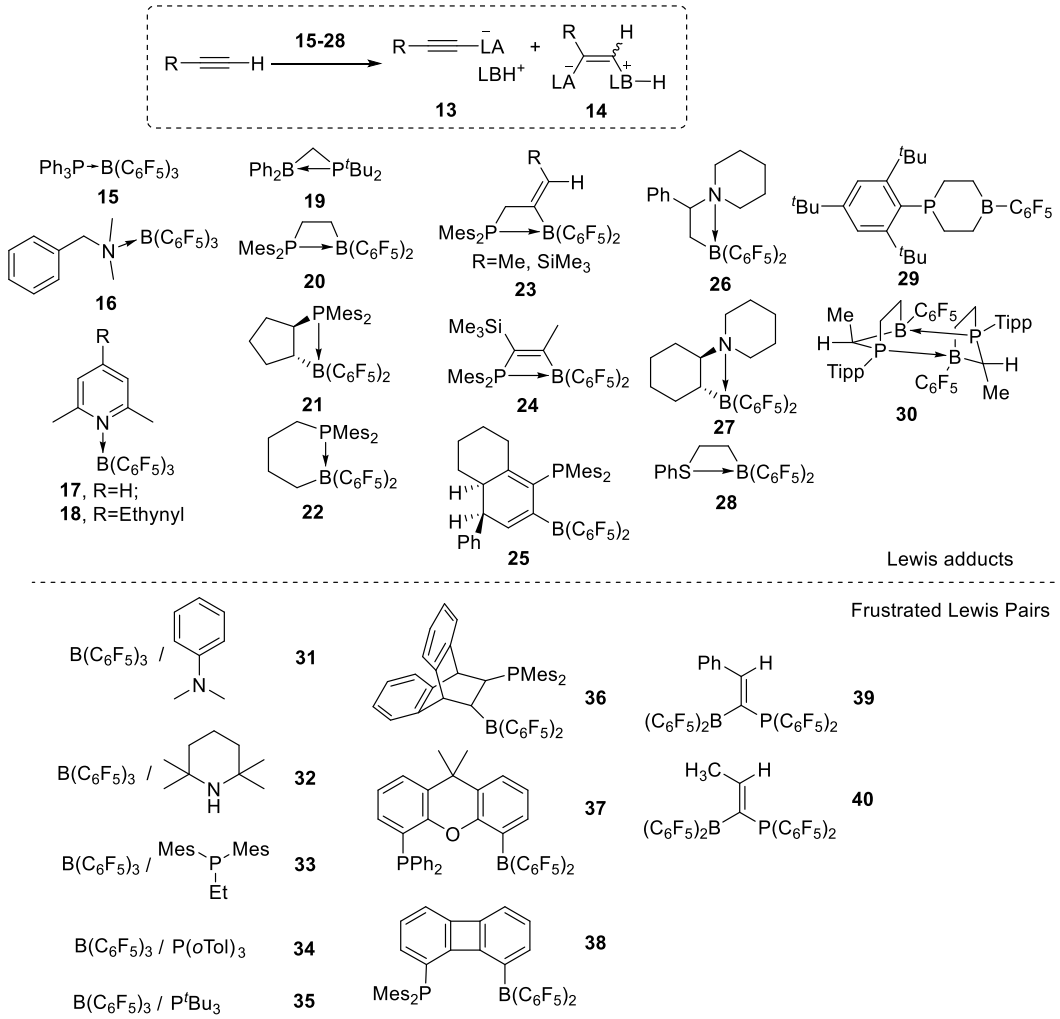
Interestingly, Ph_3P exists as an adduct with $B(C_6F_5)_3$, whereas oTol$_3$P was too bulky to form the adduct. Despite this, both aromatic phosphines acted as nucleophiles, whereas the more basic ^{t}Bu$_3$P led to alkyne deprotonation. Since then, a number of works about both 1,2-addition and C-H activation have been published. However, no systematic study of the preference of one or another reaction depending on the reagent's structure was found.

In most cases, C-H activation takes place when a Lewis acid and base form a classic Lewis adduct either in an intermolecular or intramolecular manner (Scheme 7):

Entry	Lewis pair	1,2-addition	C-H activation		Entry	Lewis pair	1,2-addition	C-H activation
1	**15**	Yes[4]	No		9	**23**	No	Yes[13]
2	**16**	No	Yes[6]		10	**24**	No	[e]Yes[27]
3	**17**	Yes[28]	Yes[28]		11	**25**	No	Yes[14]
4[a]	**18**	No	Yes[29]		12	**26**	No	Yes[30]
5	**19**	No	Yes[31]		13	**27**	No	Yes[30]
6	**20**	[b]Yes[32]	[c]Yes[11, 33]		14	**28**	Yes[34]	No
7	**21**	No	Yes[35]		15	**29**	No	Yes[36]
8	**22**	No	[d]Yes[37]		16	**30**	Yes[38]	No

Table 3. C-C addition vs C-H activation pathways in reactions of Lewis pairs with terminal alkynes. Phenylacetylene is used as a substrate except in special cases: [a]2,6-lutidylacetylene is used as terminal alkyne and a base simultaneously; [b]2-methyl-1,3-butenyne; [c]1-butyne; [d]p-tolylacetylene; [e]tert-butylacetylene.

As can be seen from Table 3, adducts of acidic aryl- and perfluoroarylboranes with sterically hindered phosphines and amines preferably give the C-H activation product (entries 2, 4-13). Herewith, the bulkier and more basic the base, the more preferable is the C-H activation pathway. Thus, the basic aminoboranes **26** and **27** promote the C-H activation pathway without significant steric hindrance.



*Scheme 7. General scheme of C-H activation and C-C addition by Lewis base-acid adducts (**15-30**) and Frustrated Lewis Pairs (**31-40**). Unless specified otherwise, the results are given for reactions with phenylacetylene.*

At the same time, system **17,** with less basic 2,6-lutidine, prefers the 1,2-addition pathway unless it is equipped with an ethynyl group (**18**). The 2,6-lutidyl group probably enhances the C-H acidity of the alkyne so that it is capable of deprotonating itself. From the list, the least basic but rather nucleophilic thioanisole-based Lewis pair undergoes 1,2-addition (**28**). Even though arylphosphines are weak bases unless they are equipped with electron donating groups (pK_a=1-3)[39], C-H activation dominates the addition pathway in most cases (**19**, **21-25**, **29**) unless steric hindrance is reduced (**15**, **20**, **30**).

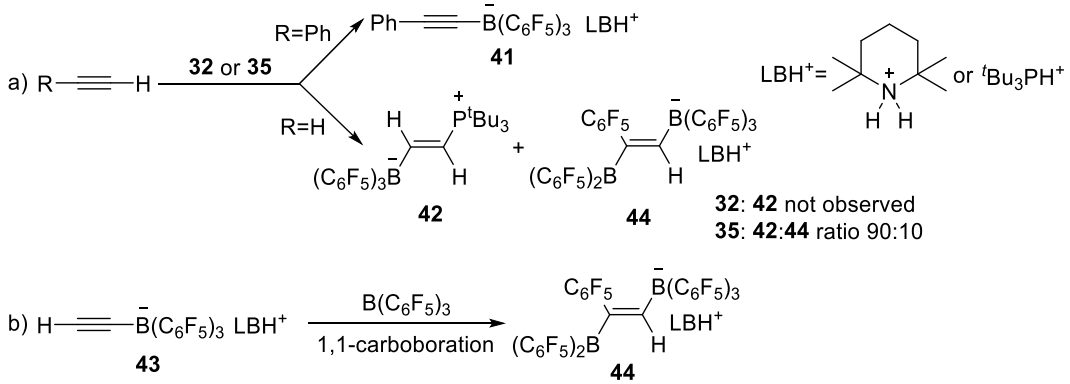
In contrast with Lewis adducts **15-30**, reactions of Frustrated Lewis Pairs, **31-40,** with terminal alkynes tend to give more 1,2-addition products and depend more on the alkyne's nature. Thus, the only FLP which was found to give selectively the C-H activation product

is **36** (Table 4). Probably, its structural and electronic parameters are close to various P/B adducts (**19**-**25**).

Entry	Lewis pair	1,2-addition	C-H activation		Entry	Lewis pair	1,2-addition	C-H activation
1	**31**	Yes[6]	No		9	**36**	No	Yes[40]
2	**32**	Yes[28]	Yes[28]		10	**37**	Yes[41]	Yes[41]
3	**33**	Yes[1]	Yes[1]		11	**38**	Yes[41]	Yes[41]
4	**34**	Yes[4]	No		12	**39**	Yes[42]	No
5	**35**	Yes[28]	Yes[4]		13	**40**	Yes[43]	No

*Table 4. Reactions of terminal alkynes with FLP **31**-**40**.*

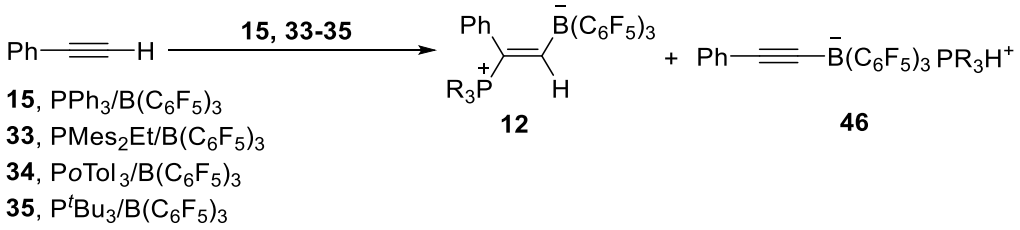
However, the prevailing tendency of the C-H activation pathway with increasing steric hindrance and basicity of the Lewis base still appears to be reasonable. Thus, phenylacetylene gives exclusively C-H activation products **41** with pairs **32** and **35**, which have strongly basic 2,2,6,6-tetramethylpiperidine (TMP) (**32**, pKa=11.07[28]) and tri-*tert*-butylphosphine (**35**, pKa=11.4[28]) (Scheme 8)[4, 28]. However, when the phenyl group is changed to a proton, the 1,2-addition pathway is preferred with **35** giving product **42**. Interestingly, the initial C-H activation product **43** is not isolated due to its further 1,1-carboboration by other molecule of $B(C_6F_5)_3$ giving **44**. This fact is in accordance with the 1,2-proton shift mechanism described in a previous chapter.



*Scheme 8. a) Reactivity of acetylene and phenylacetylene with FLP **32** and **35**. b) 1,1-carboboration of the C-H activation product of acetylene.*

In the case of **32**, the increased steric hindrance of TMP prevents the addition pathway, thus giving exclusively the C-H activation-carboboration product **44**.

The influence of phosphine basicity can be illustrated by comparing the reactivities of phenylacetylene with $B(C_6F_5)_3$ and PPh_3 (**15**), P*o*Tol_3 (**34**), $PMes_2Et$ (**33**), and P^tBu_3 (**35**) pairs (Scheme 9).



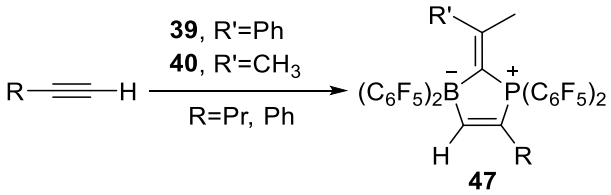
*Scheme 9. Reactivity of phenylacetylenes with FLP **15**, **33**, **34**, and **35**.*

C-H activation takes place exclusively with **35**; whereas the less sterically hindered and less basic **33** gives a 1:1 mixture of the 1,2-addition product **12** and the C-H activation product **46** (Table 5). In the case of the least basic and least sterically hindered phosphine pairs **15** and **33**, only the 1,2-addition product is observed. This is in accordance with the basicity and steric hindrance in the row P^tBu_3>$PMes_2Et$>$PoTol_3$>PPh_3.

FLP	Yield (**12**), %	Yield (**46**), %	Ref
15	84	0	[4]
34	75	0	[4]
33	[a]40	[a]40	[1]
35	0	82	[4]

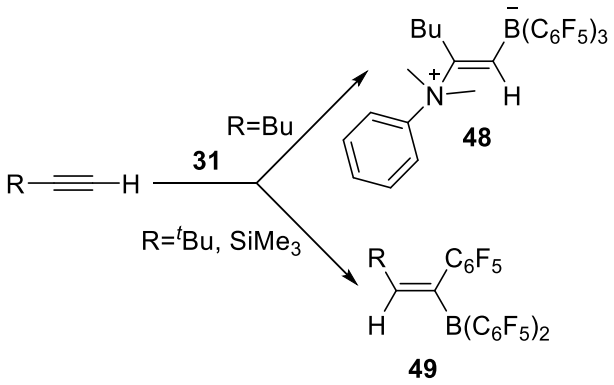
*Table 5. Competing reactions of C-C addition and C-H activation of phenylacetylene with FLP. [a]ca. 1:1 **12**:**46** mixture, 80% combined yield.*

The least basic site currently known is the $P(C_6F_5)_2$ moiety in the geminal FLPs **39** and **40**. They activate both alkyl- and arylalkynes selectively by the 1,2-addition pathway, giving the cyclic zwitterionic product **47** (Scheme 10)[42, 43].



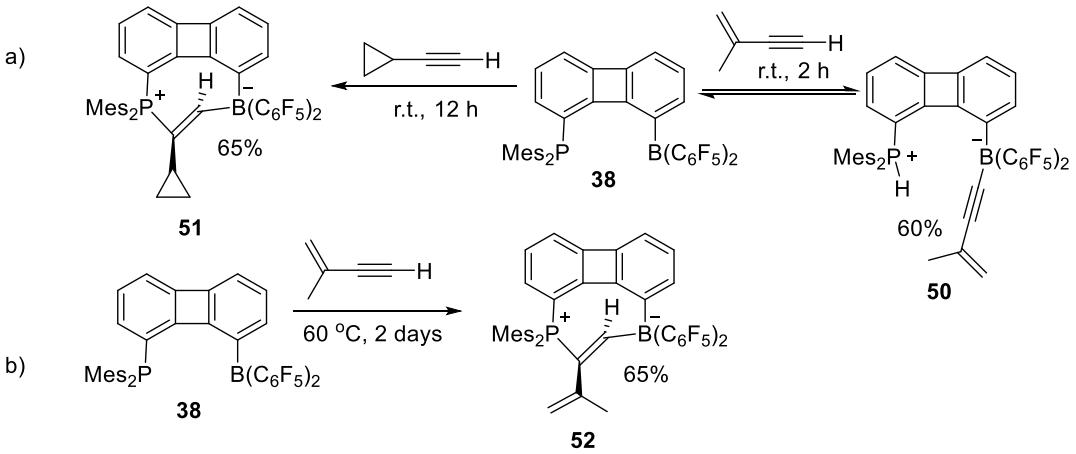
Scheme 10. Terminal alkynes activation by a geminal FLP with a weakly basic phosphine site.

When the basicity of the Lewis base is decreased so that C-H activation is unfavourable but the steric hindrance of the alkyne prevents the 1,2-addition pathway, the base is no longer involved in the reaction, and 1,1-carboboration takes place (Scheme 11)[6]. Thus, activation of butylacetylene with **31** gives the 1,2-addition product **48**, whereas *tert*-butylacetylene and trimethylsilylacetylene give 1,1-carboboration products **49**.



Scheme 11. The weakness of a Lewis base and the steric hindrance of an alkyne lead to the 1,1-carboboration product.

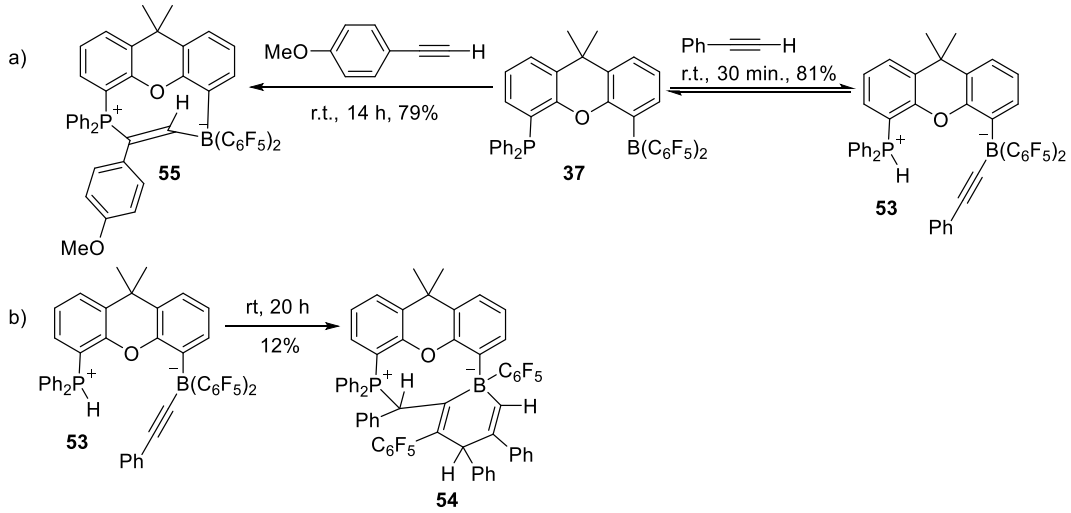
The importance of an alkyne's nature can also be shown in the examples of biphenylene- and xanthene based FLPs (**38** and **37**, respectively)[41, 44]. At room temperature, 2-methyl-1,3-butenyne forms the C-H activation product **50**, whereas cyclopropylacetylene undergoes the 1,2-addition pathway forming **51** (Scheme 12).



*Scheme 12. Reaction of terminal alkynes with the biphenylene based FLP **38**.*

However, when a mixture of **38** with 2-methyl-1,3-butenyne is heated at 60 °C for 48 h, signals of **50** gradually disappear and the 1,2-addition product **52** is formed[44]. Thus, the reversibility of the C-H activation reaction gives the possibility of choosing one or another pathway.

Dimethylxanthene based FLP **37** also reversibly activates phenylacetylene by the C-H activation pathway (Scheme 13). However, the C-H activation product **53** slowly reacts further with the initial phenylacetylene giving the cyclization product **54.** In contrast to this, 4-methoxyphenylacetylene gave the 1,2-addition product **55**.



*Scheme 13. Reaction of terminal alkynes with a dimethylxanthene based FLP **37** a) depending on the alkyne nature b) reaction time.*

The reactivity of terminal acetylenes with pairs **37** and **38** can be somewhat rationalized by their electronic nature. Thus, the propenylalkynyl anion is stabilized by resonance with the propenyl group, thus making C-H activation easier compared to cyclopropylacetylene (Scheme 12). On the other hand, the 4-methoxyphenylalkynyl anion is less stabilized due to the electron donating effect of the methoxy group, and therefore 1,2-addition is more favourable compared to phenylacetylene (Scheme 13).

In summary, reactions of terminal alkynes with boron-based Lewis acids can proceed by four main routes: C-H activation, 1,2-addition, and 1,1- and 1,2-carboboration. Examining the published studies gives several observations related to the reaction course:

- Boranes with high Lewis acidity are capable of activating terminal alkynes themselves by either 1,1-carboboration ($RB(C_6F_5)_2$) and 1,2-haloboration (BCl_3, BBr_3, BI_3); the migratory aptitude of the boron ligand dictates the direction of the reaction. Thus, ligands like C_6F_5 with low migratory aptitude promote 1,1-carboboration, whereas incorporation of ligands like Ph and Cl, Br, or I makes 1,2-addition preferable.

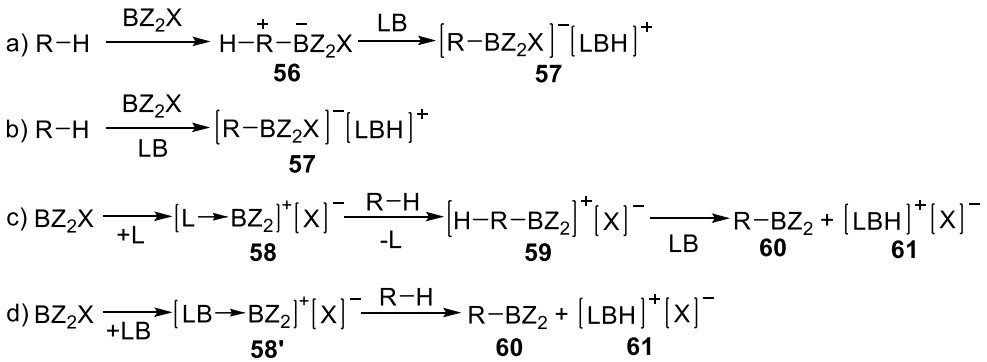
- Reactions of Lewis acid-base pairs with terminal alkynes give either 1,2-addition or C-H activation products. The C-H activation pathway prevails over C-C addition when the basicity and steric hindrance of the base is increased; at the same time, Lewis acid-base adducts favour C-H activation, when compared to FLP. More rare examples of alkyne activation by boroamidates[45], heterocycles[46, 47] and NHC-carbenes[48] also follow this observation.

- If the base is too weak to deprotonate an alkyne and the latter is sterically hindered enough to prevent 1,2-addition, then 1,1-carboboration by $B(C_6F_5)_3$ takes place.

- Increasing the alkyne C-H acidity makes the C-H pathway prevail over C-C addition.

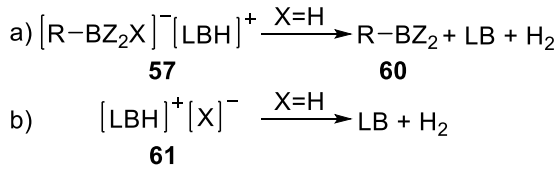
C_{sp2}-H bonds borylation

Probably the first published example of a C_{sp2}-H borylation study is the benzene activation by diborane at elevated (100 °C) temperatures[49]. Since then many works devoted to C-H borylation by hydroboranes have been published, including intramolecular aromatic[50, 51] and even aliphatic C-H bonds[52] borylation. However, borylation by other boranes is much less developed to date. Compared to terminal alkynes, C_{sp2}-H bonds are much less acidic (the pK_a for acetylene and ethylene are 25 and 44, respectively) and C-H borylation of the corresponding substrates is more challenging. Formally, the strategy of metal free borylation of C_{sp2}-H bonds can be divided into four major types. The first one consists of the stepwise addition of a neutral borane to a substrate with formation of the zwitterionic intermediate **56** and its further deprotonation by a Lewis base (Scheme 14a) to give the borylated product **57**. In another case, a Lewis acid and base can act simultaneously, thus allowing concerted borane addition and proton elimination from the substrate (Scheme 14b). Addition of certain ligands allows borane ionization thus forming the electrophilic borenium cation **58**, which attacks the substrate (Scheme 14c) with formation of the ionic product **59**. The latter is attacked by the Lewis base producing **60** and Lewis base salt **61**. Finally, if such a ligand can act as a Lewis base itself, a concerted borylation-deprotonation by a Lewis base-borenium complex can occur (Scheme 14d).



Scheme 14. Possible mechanisms for metal free borylation of a C_{sp2}-H bond a) neutral stepwise; b) neutral concerted; c) cationic stepwise borenium-assisted; d) cationic concerted borenium-assisted.

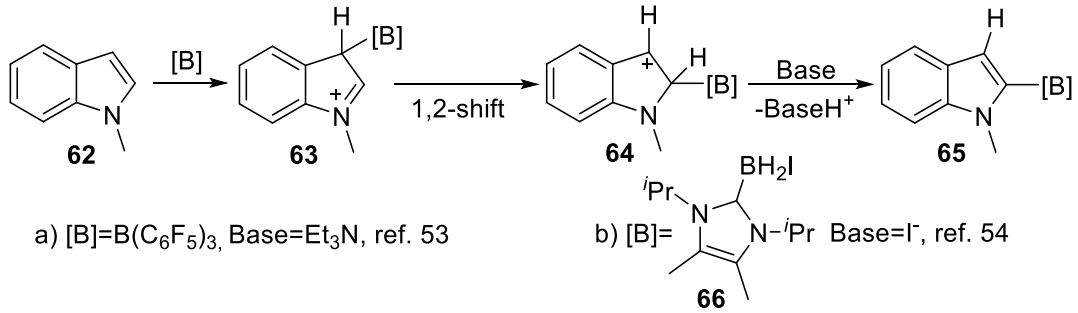
Whereas addition of borane to a substrate depends mainly on the substrate and the borane's nature and becomes more favourable on increasing the substrate nucleophilicity and borane Lewis acidity, deprotonation is favoured by the use of a strong base which has a high proton affinity. However, another option of proton elimination is utilization of hydroborane as a borylating agent. In this case, the charged intermediates **57** and **61** usually disproportionate with elimination of H_2. (Scheme 15a and 15b, respectively). This approach opens the pathway towards catalytic usage of the Lewis base.



Scheme 15. H_2 elimination is the thermodynamic driving force of the C-H borylation.

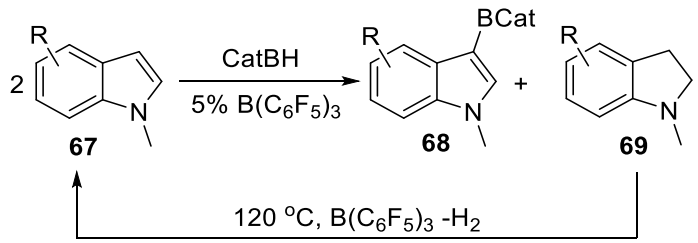
Neutral stepwise borylation

Direct electrophilic attack of uncharged boranes is relatively rare and occurs almost exclusively on indoles and pyrroles. Thus, 1-methylindole **62** is attacked by either BCF or NHC-carbene **66** giving the stabilized Wheland intermediate **63** (Scheme 16)[53, 54].



Scheme 16. Friedel-Crafts type C_2-selective borylation of N-methylindole by various boranes.

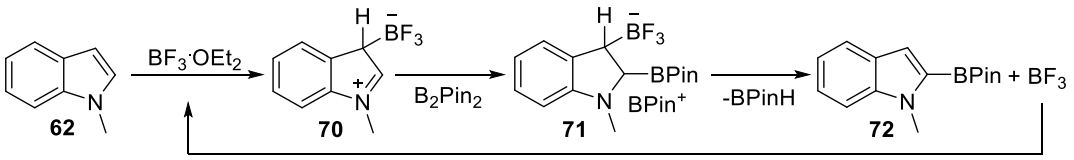
Importantly, the initial electrophilic attack occurs at an activated C_3-position, but **63** undergoes 1,2-migration of borane resulting in cationic intermediates, **64**. Further treatment of these by Brønsted bases leads to restoring aromaticity and C_2-borylated indole products, **65**. Importantly, indoles can themselves serve as proton acceptors. Thus, Zhang et al.[55] have utilized this property for capturing hydride from catecholborane (CatBH) and a proton from the initial indole **67** with formation of the borylated product **68** and the reduced indoline **69** (Scheme 17):



Scheme 17. Disproportionate borylation of indoles with $B(C_6F_5)_3$ and catecholborane.

The latter can be oxidized back to indole by heating with BCF at 120 °C, thus allowing indoles' catalytic borylation of the C_3-position.

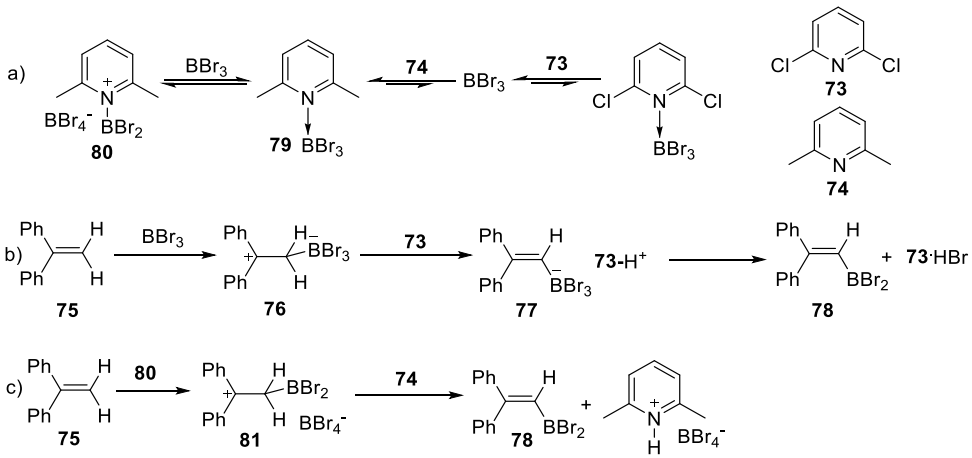
The C_3-position is more prone to protodeboronation compared to C_2[53, 56]. This property has been utilized for the synthesis of C_2-borylated indoles[56] catalyzed by $BF_3{\cdot}OEt_2$ (Scheme 18). Attack of $BF_3{\cdot}OEt_2$ on **62** gives the Wheland intermediate **70**, which further reacts with



Scheme 18. C_2-selective borylation of N-methylindole by B_2Pin_2 and $BF_3{\cdot}OEt_2$.

B_2Pin_2 as an ambiguous electrophilic and nucleophilic molecule giving intermediate **71**. The latter undergoes protodeboronation on the C_3-position giving the C_2-borylated indoles **72** with subsequent recovery of BF_3.

Another example of direct electrophilic borane attack is borylation by BBr_3 and 2,6-dichloropyridine, **73**. Compound **73** does not form a Lewis adduct with BBr_3 (Scheme 19a)[57]. Activation of the 1,1-diphenylethylene **75** thereby proceeds via direct electrophilic attack of BBr_3 with formation of carbocation **76**, which is deprotonated by **73** giving the borylation product **77** (Scheme 19b). Finally, the pyridinium salt **73**·HBr eliminates from **77** giving **78**.



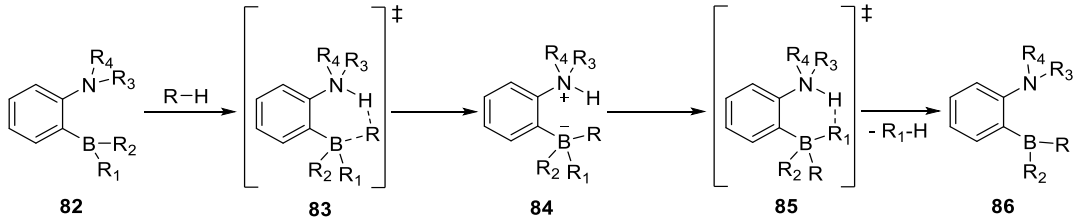
*Scheme 19. a) reactions of BBr_3 with 2,6-dichloropyridine (**73**) and 2,6-lutidine (**74**); borylation of a terminal alkene by BBr_3 through b) direct electrophilic attack of neutral borane or c) in situ formed borenium cation.*

Changing **73** to **74** dramatically changes the reaction mechanism. BBr_3 reacts with **74** to form adduct **79** which is ionized by another molecule of BBr_3 giving the borenium species **80**. The latter borylates **75** via a charged stepwise mechanism (Scheme 14c) forming the borylated carbocation **81** which undergoes deprotonation by **74** (Scheme 19b).

Neutral concerted borylation

Ortho-substitution of arylboranes by a Lewis base leads to geometrically preorganized *ansa*-amino- and phosphinoboranes. These systems are known to activate H_2[58], which leads to systems that are used for reduction of various substrates including imines[59] and alkynes[60].

In 2015, Fontaine et al. published the first metal free borylation of heteroarenes with this *ansa*-system[61]. Later, the system was improved by changing both the boryl and the amino site of the complex [62-64]. The general mechanism is depicted in Scheme 20. According to DFT data, C_{sp2}-H activation starts from the concerted borylation-deprotonation of the substrate giving the zwitterionic intermediate **84**. This aminium borate undergoes intramolecular protonolysis to give the C-H borylation product **86** and the protonated ligand R_1-H. The computed energies of this transformation are represented in Table 6. Analysis of the hydroboranes family, **87-90,** shows that they all exist in the form of dimers which need



Scheme 20. Mechanism of metal-free ansa-aminoboranes assisted C_{sp2}-H borylation.

to be broken prior to the C-H activation step. Thus, the upper level for dissociation of **87**, **88** and **90** was found to be 11-14[58], 20.7[62], and 23.3[62] kcal/mol, respectively. On the other hand, as can be seen on the example of both thiophene (Thp) and N-methylpyrrole (Nmp) borylation, the energy difference between **83** and **82** generally decreases with decreasing the steric hindrance of the amine. Therefore, for the aminoboranes **88** and **90,** dimer dissociation is the rate-limiting step; whereas C-H activation is slower for the bulky **87**. Even though overall C-H borylations for **87**-**91** are endergonic, H_2 elimination make these reactions favourable.

Whereas optimization of the Lewis base part gives a decrease in the energy barriers, the substrate scope of the systems **87**-**90** is generally limited to electron-rich thiophenes, indoles, and pyrroles[61-63]. Modification of the borane site to the more acidic aminoperfluoroarylborane **91** increases the Lewis pair reactivity and allows the borylation of various aromatic rings to give boranes **93**. Incorporation of the second C_6F_5 group (**92**) allows selective *trans*-C-H borylation of alkenes (Scheme 21)[64].

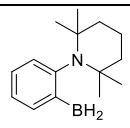
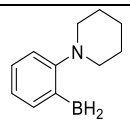
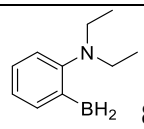
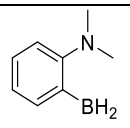
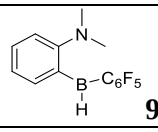
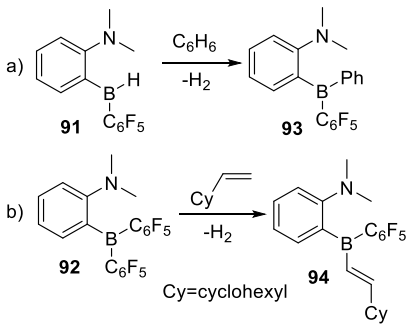
Entry	Aminoborane	Substrate	82	83	84	85	86	R_1-H	Ref.
1	 **87**	Thp Nmp	7.1 7.1	27.7 24.5	1.2 4.3	18.2 18.3	1.6 1.3	H_2	62[a]
2	 **88**	Thp Nmp	9.6 9.6	24.8 18.4	5.9 8.0	21.3 23.5	1.8 3.5	H_2	62[a]
3	 **89**	Thp Nmp	10.7 10.7	25.9 18.7	9.5 13.8	22.6 25.4	3.7 7.4	H_2	62[a]
4	 **90**	Thp Nmp	10.6 10.6	26.8 21.1	9.1 11.3	22.7 24.2	3.9 5.7	H_2	62[a]
5	 **91**	Thp C_6H_6	6.3 6.2	21.5 26.6	3.0 7.6	20.0 22.6	2.7 7.0	H_2	64[b]

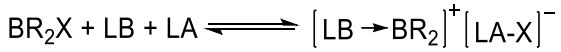
*Table 6. Computed energies for C_{sp2}-H borylation of N-methylpyrrole (NMP), thiophene (THP), and propene by various ansa-aminoboranes, kcal/mol. The following computational methods were used: [a] DFT/ωB97XD/6-31+G** (SMD, chloroform), [b] ωB97X-D/6-311++G(3df,3pd) (SMD, Substrate). For NMP and THP, energies for borylation of the α-position are given.*



Scheme 21. Borylation of a) arenes and b) alkenes by ansa-aminoperfluoroarylboranes.

Borenium cation borylations

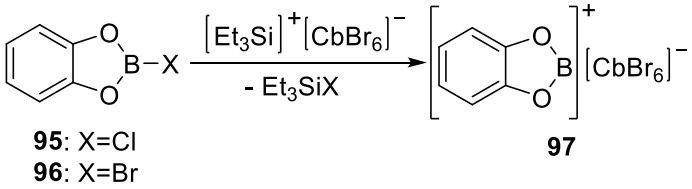
The general equation for the formation of borenium cations is depicted in Scheme 22:



Scheme 22. General equation of borenium cation formation from a neutral borane, a Lewis acid, and a Lewis base.

Usually, boranes exist in the neutral form and the equilibrium is shifted towards the left. However, when the cation is stabilized by a donating ligand, the equilibrium shifts to the

right side. Also, the driving force of borenium cation formation can be increased if the elimination of X from borane leads to a stabilized anion. To date, the only "ligand-free" borenium cation used for C-H borylation is the very strong Lewis acid catechol hexabromododecaborate salt **97,** which is formed from chloro- or bromo-catecholboranes **95** and **96** (Scheme 23)[65]:



Scheme 23. Generation of ligand free borenium cation from catecholchloroborane

Generally, non-nucleophilic anions are used for borenium cation stabilization. Among these are $AlCl_4^-$ [66-70], BBr_4^- [57, 71] and BF_4^- [72, 73] anions. On the other hand, an uncoordinated borenium cation is generally too reactive to be used for selective C-H borylation[65]. Besides, the donor ligand brings some stabilization to the cation itself. Therefore, nitrogen donors such as Et_3N[66, 69], N,N-dimethylaniline[66-69, 74, 75], and various pyridine[57, 64, 70, 71] derivatives are used for this purpose. Such borenium cations are usually produced from catecholborane [64, 66, 69, 75], haloboranes[57, 67, 68, 70, 71], and alkylboranes[74] derivatives. They allow C-H borylations of a wide scope of substrates, including aryls, hetaryls and olefins[76, 77].

Results and discussion

Experimental details

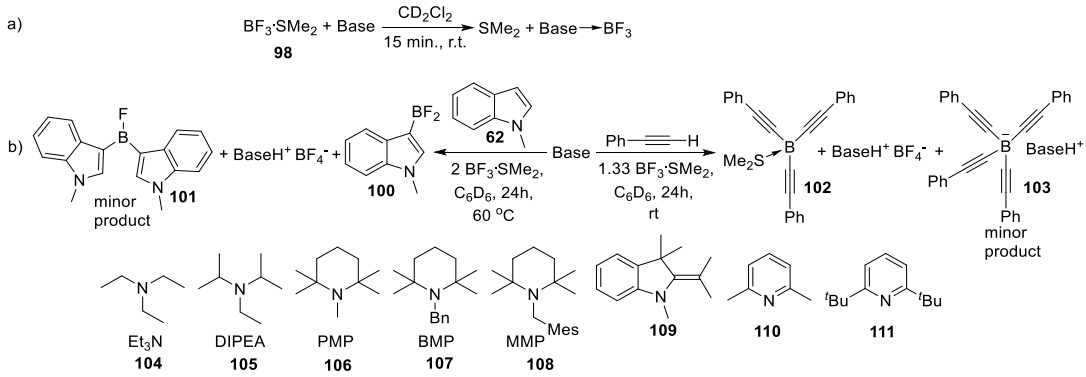
As BF_3 and its complexes are sensitive to hydrolysis, all of the manipulations were done in a dry argon atmosphere in a GloveBox. $BF_3{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, 1-methylindole, and PMP were distilled prior to use and stored in a GloveBox.

NMR measurements were conducted on a 300 MHz Varian Mercury Plus, a 500 MHz Varian Unity Inova, a 400 MHz Bruckner, and a 600 MHz Bruckner. Elemental analysis was performed on an Elementar Analyser system model Vario MICRO Cube. ESI-MS were recorded on a Bruker micrOTOF.

Other experimental details can be found in the experimental parts of the publications.

Adducts of BF_3 with Lewis bases

BF_3 is a typical Lewis acid which forms adducts with various Lewis bases. Considering that boron trifluoride is a gas at normal conditions, it is commonly used in the form of its SMe_2 (**98**) and OEt_2 (**99**) adducts. Their dissociation energies are estimated to be 0.7 and 4.2 kcal/mol, respectively, thus making **98** a convenient alternative for gaseous BF_3. We have investigated the interaction of $BF_3{\cdot}SMe_2$ (**98**) with amines that vary in their steric hindrance and basicity (Scheme 24, Table 7).



*Scheme 24. a) Reaction of $BF_3{\cdot}SMe_2$ with Lewis bases **104**-**111**. b) C-H activation of N-methylindole and phenylacetylene with $BF_3{\cdot}SMe_2$ and bases **104**-**111**.*

From the amines studied, we can see that the $BF_3{\cdot}SMe_2$/PMP system is the most promising. It borylates phenylacetylene in 2 hours in more than 90% yield and also gives the borylated N-methylindole **100** with 62% yield. In both cases, the reaction proceeds selectively to give the monoborylation product with N-methylindole **62** and trialkynylborane **102** from phenylacetylene, respectively. In addition to the major products, traces (1-3%) of products with other stoichiometry, **101** and **103,** were formed, which will be discussed in the chapter below. Evidently, borylation of phenylacetylene is more sensitive to the Lewis base used.

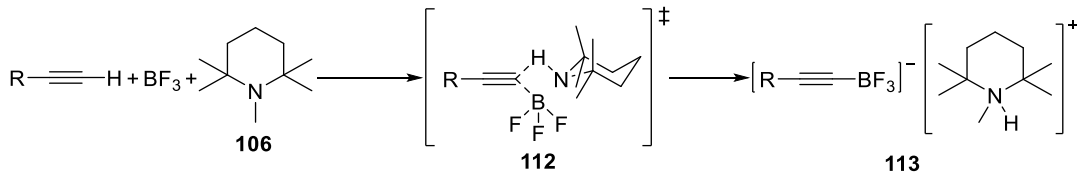
We found that PMP was the only base which assisted the C-H borylation of phenylacetylene. This is in accordance with the general trend of alkynes C-H borylation marked in the literature review. C-H borylation preferably happens with Lewis bases of high basicity which form an adduct with a boron Lewis acid. Probably, the reason for the inactivity of DIPEA·BF_3 and Et_3N·BF_3 adducts is their high binding strength (binding energies 7.8 and 16.7 kcal/mol, respectively). Increasing the steric hindrance near the piperidine ring

Base	ΔG_1[a]	ΔG_2[a]	Adduct	Reactivity with	
				Phenylacetylene	N-methylindole[c]
104	-16.7	1.4	Yes	No	No
105	-7.8	-0.3	Yes	Traces	22
106	**-1.9**	**0**	**Yes**	**90+**	**62[d]**
107	-	n.d.	No	Traces	35
108	-	n.d.	No	Traces	47
109	n.d.	n.d.	No	No	n.d.[b]
110	-	7.2	No	No	Traces
111	-8.0	8.0	Yes	No	n.d. [b]

*Table 7. Reactivities of BF_3·SMe_2 with Lewis bases and their BF_3 pairs with phenylacetylene and N-methylindole; [a] ΔG_1 and ΔG_2 refer to the energies of the reactions BF_3 + LB → BF_3·LB and $PMPH^+$ + LB → LBH^++ PMP, respectively, referring to CH_2Cl_2 solutions. [b] Bases **109** and **111** have not been tested for N-methylindole activation. [c] The NMR yields are referred to the signal of the internal standard, 1,3-difluoro-5-bromobenzene. [d] The yield is measured for monosubstituted $ArBF_2$. In addition to it, traces of Ar_2BF were observed in ^1H, ^{19}F and ^{11}B NMR; the probable mechanism of its formation is discussed in the next chapter.*

(**107**-**108**) leads to instability of the BF_3 adducts and precludes their approach to phenylacetylene. Bases with lower basicity (**109**-**111**) did not give the C-H borylation product either independently on their steric hindrance. Heating the mixture of phenylacetylene with **104**-**105**, **107**-**111** and BF_3·SMe_2 at 60 °C did not change the reaction outcome.

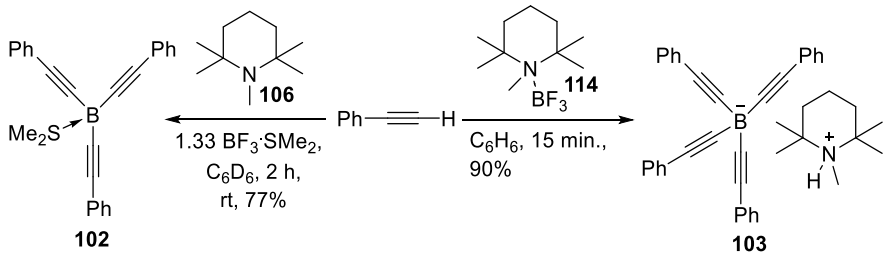
These observations allow us to make certain conclusions about the C-H borylation mechanism of phenylacetylene. Probably, C-H borylation of alkynes is a concerted process where boron and amine are in close proximity to activate the alkyne via the transition state **112** (Scheme 25).



Scheme 25. Concerted Lewis acid-base activation of terminal alkynes.

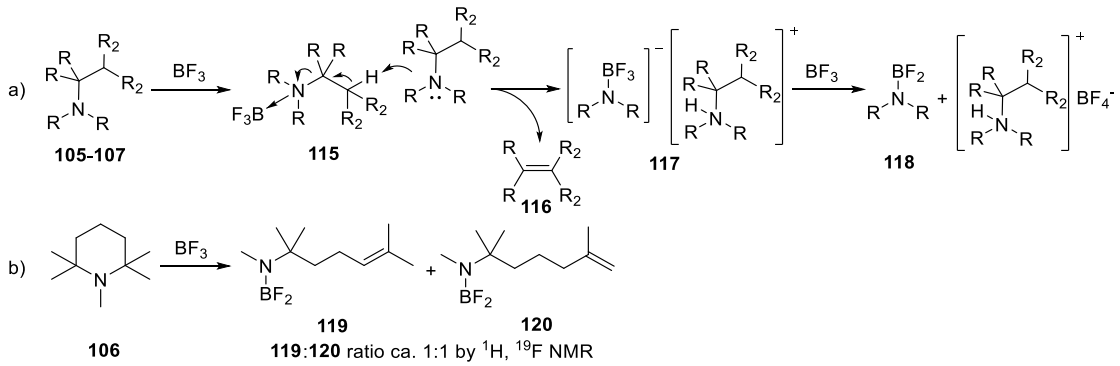
Formation of a π-complex by BF_3 is unlikely, even though its Van der Waals complex with acetylene has been reported at low temperatures [78, 79]. Also, the importance of adduct

formation was proven by the fact that whereas 2 h were needed to complete the phenylacetylene borylation by 1.33 BF_3·SMe_2 and PMP (**106**), borylation by the PMP·BF_3 complex **114** was completed in 15 minutes giving the tetraalkynylborate **103** (Scheme 26).



Scheme 26. Phenylacetylene borylation by BF_3·SMe_2/PMP and PMP·BF_3 complexes.

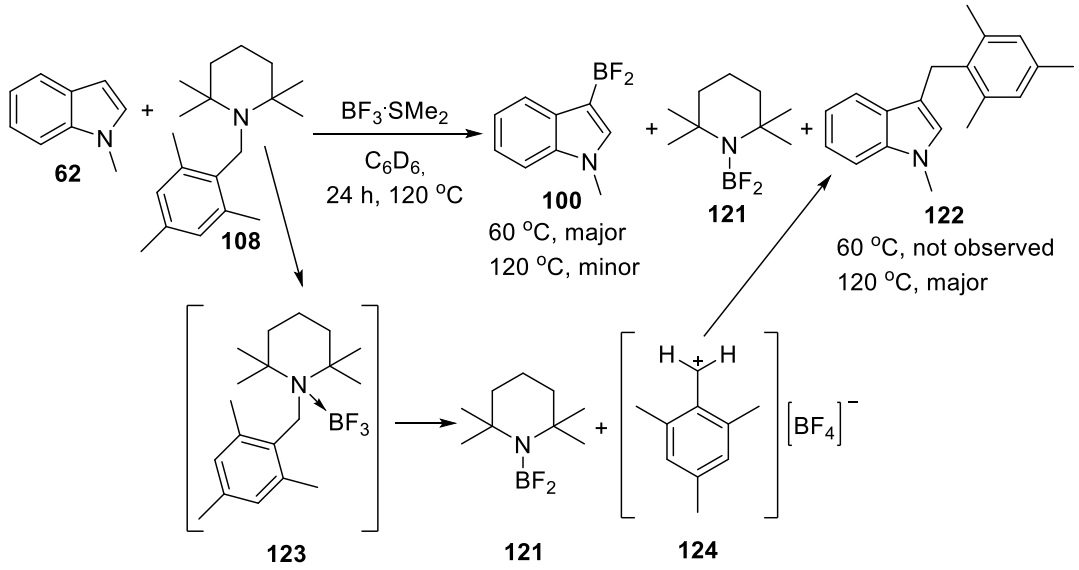
Compared with phenylacetylene, borylation of N-methylindole gave another trend. Except for Et_3N, all of the bases with a high pKa, similar to **106** (**105**, **107**-**108**), gave significant amounts of the borylation product. Importantly, C-H borylation at elevated temperatures (>40 °C) is complicated by the side reaction of amine·BF_3 adducts decomposition, which brings fluctuations when comparing the yields. Moreover, the outcome of such a decomposition varies depending on the base's structure. Thus, bases **105**-**107** undergo decomposition by a Hofmann-type elimination (Scheme 27a). After formation of the BF_3·Base complex **115**, a second molecule of the base attacks it with elimination of the alkene **116** and formation of the aminoboronium salt **117**. Another molecule of BF_3 defluorinates **117** with formation of the neutral aminoborane **118**. A typical example of such an elimination is depicted in Scheme 27b for PMP (**106**). The piperidine ring opening gives both possible products of elimination, **119** and **120,** in about a 1:1 ratio.



*Scheme 27. Hofmann-type decomposition of Amine·BF_3 adducts: a) General scheme b) Decomposition of PMP (**106**).*

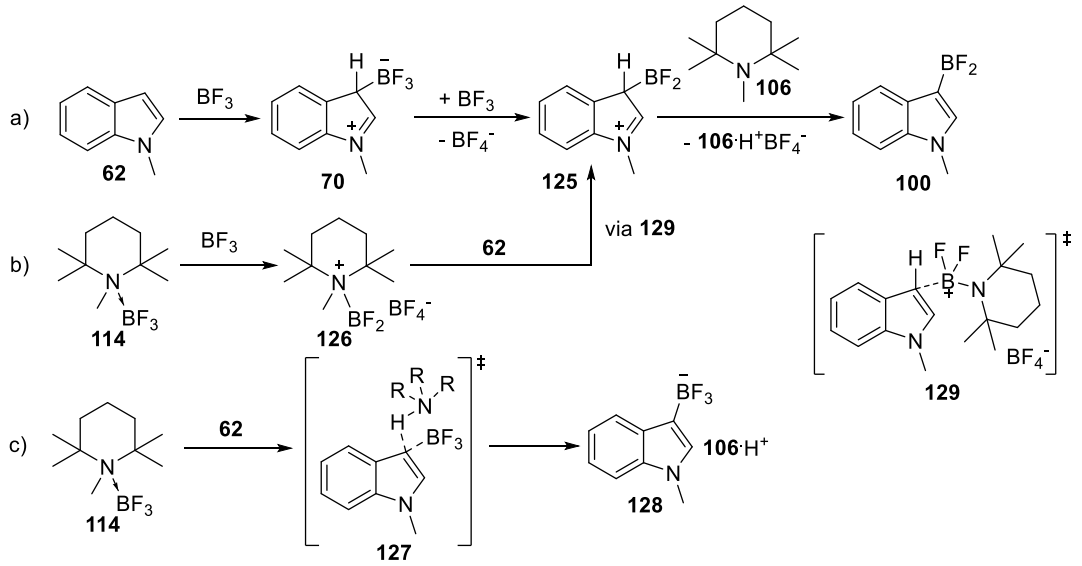
Base **107** doesn't form a stable adduct with BF_3. However, it undergoes decomposition to give products which are analogous to **119** and **120**. Apparently, the BF_3 adduct of **107** is an unstable intermediate which readily undergoes decomposition upon heating.

Among the screened bases **104-111**, base **108** is the most sterically hindered. It also undergoes decomposition upon heating with $BF_3 \cdot SMe_2$ but by a different mechanism. Thus, reaction of **108** with $BF_3 \cdot SMe_2$ (**98**) and N-methylindole **62** at 120 °C for 24 h gave only minor amount of the borylation product **100** (Scheme 28). Instead, we observed the aminoborane **121** along with a new indole pattern in the ^1H NMR. Purification of the reaction mixture by flash column chromatography gave the alkylated indole **122**. Considering that **62** is prone to electrophilic aromatic substitution, we assumed that the labile $Base \cdot BF_3$ intermediate forms and readily decomposes to the aminoborane **121** and the carbocation **124**. The latter reacts with **62** by an electrophilic aromatic substitution mechanism giving **122**.



*Scheme 28. Reaction of base **108**, N-methylindole **62**, and $BF_3 \cdot SMe_2$ at different temperatures; [**108**-H^+][BF_4^-] salt is omitted for clarity.*

Referring to possible C_{sp2}-H borylation pathways (Scheme 14), borylation of **62** can occur by three pathways (Scheme 29). The first one is a stepwise electrophilic aromatic substitution by boron trifluoride with the formation of the zwitterionic Weeland intermediate **70**. Further defluorination by an excess of BF_3 gives **125** and further deprotonation by **106** gives **100** (Scheme 29a). Another possibility is the formation of the borenium species **126**, which attacks **62** giving **125** (Scheme 29b). Indeed, some amines are capable of ionizing BF_3 and forming borenium cations which are additionally stabilized by formation of the stable BF_4^- anion[73]. The third possible mechanism involves the concerted action of a borane and an amine via transition state **127,** similar to the *ansa*-aminoboranes



Scheme 29. Possible mechanisms of BF_3-assisted borylation of N-methylindole: a) neutral stepwise b) cationic concerted c) neutral concerted.

(Scheme 29c). Considering that we didn't observe any signals of such intermediates by NMR spectroscopy studies, we decided to perform DFT analysis of the reaction. According to computations, the Wheland intermediate **70** is very prone to dissociation in benzene and could not be identified. Therefore, the neutral stepwise pathway (Scheme 29a) is unlikely to be operative. The barrier for formation of the borenium cation **127** was found to be 24.7 kcal/mol. However, its attack of **62** occurs via transition state **129**, which is too high in energy (34.7 kcal/mol); therefore the borenium pathway is likely ruled out as well. The neutral concerted pathway (Scheme 29c) gave more reasonable energies for the intermediates. Deeper insight into the mechanism showed that borylation proceeds via a concerted asynchronous mechanism (Figure 2). First, the PMP·BF_3 adduct **114** dissociates to initial borane and amine which then act in a concerted way similarly to classical *ansa*-systems via transition states **127** and **130** to give intermediate **131** which reacts with another molecule of BF_3 to form **132**. Finally, fluoride transfer from boron to boron via transition state **133** gives the borylated indole weak complex **134** which dissociates to **100** and the tetrafluoroborate salt of **106**·H^+. Interestingly, comparing the reactions of a similar substrate, N-methylpyrrole, with *ansa*-systems, the process is exergonic overall.

We observed that addition of a catalytic amount (5 mol%) of tetramethylthiourea (TMTU) **135** improves the yield of the borylation reaction. Although tetramethylthiourea (TMTU) is known to cause autoionization of BF_3 at low temperatures[80], we didn't observe any reaction intermediates other than the TMTU·BF_3 adduct **136** by monitoring the reaction by NMR spectroscopy. Therefore, we performed computational studies of this system as well.

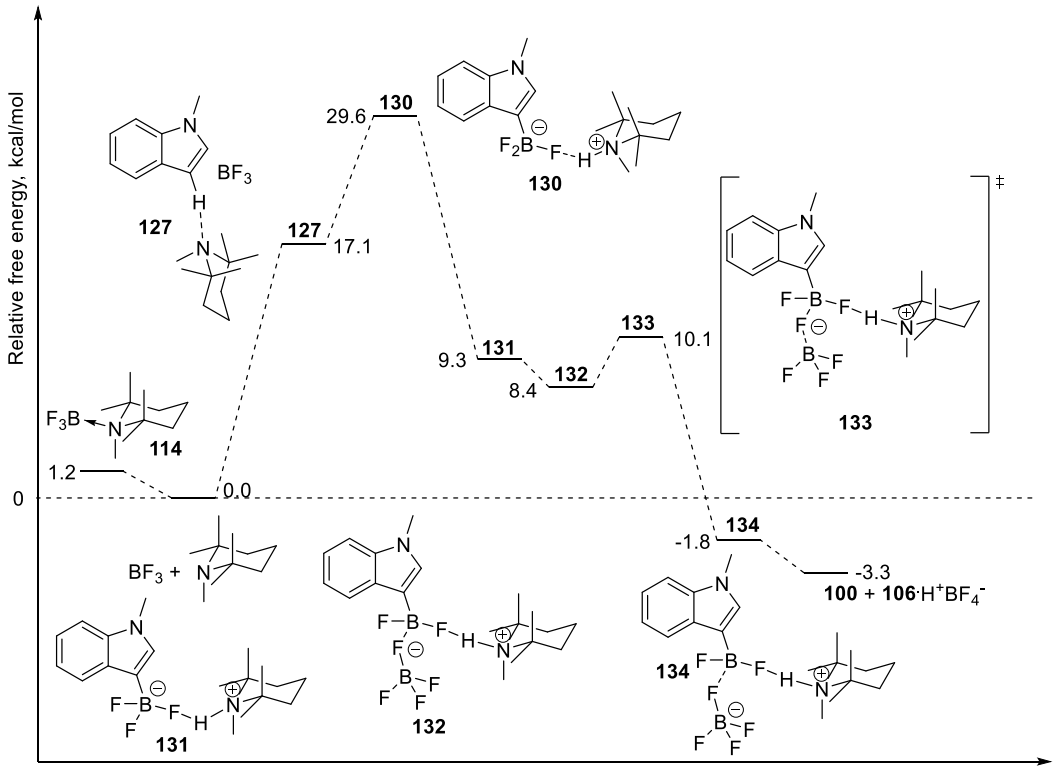
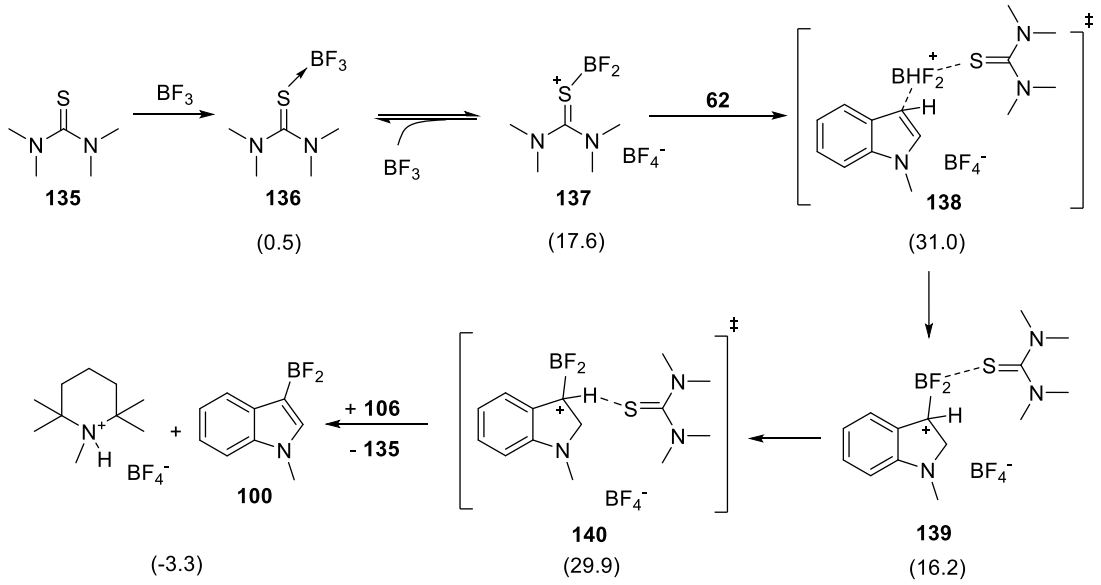


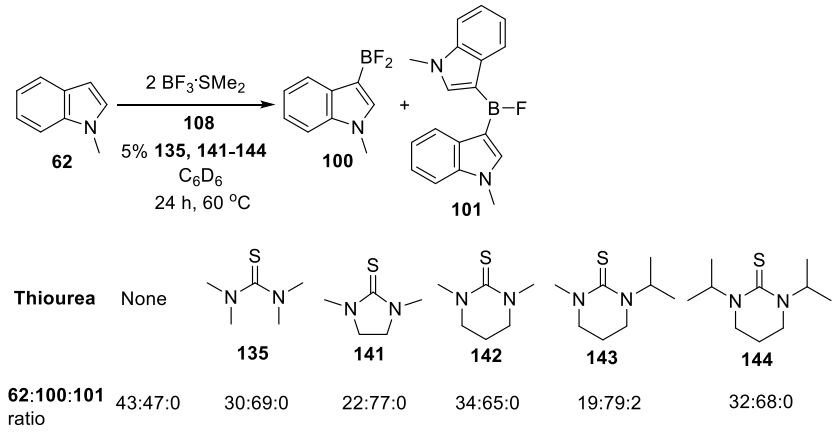
*Figure 2. Computational aspects of N-methylindole borylation by BF_3 and PMP (from ref. **II**).*

DFT studies show that the reaction is switched to the borenium cation pathway in the presence of **135** (Scheme 30). Compound **135** assists in BF_3 ionization to give the borenium cation **137**. The barrier of formation of the borylation product **139** was found to be 31.0 kcal/mol (transition state **138**), which is comparable to that of the concerted mechanism (29.6 kcal/mol for **130**, Figure 2). Interestingly, according to this mechanism, thiourea can also act as a base (**140**, Scheme 30) which then delivers the proton to the more basic **106**. Attempts to perform the reaction in the absence of an amine Lewis base with stoichiometric amounts of **135** were unsuccessful and no borylation product was found, although the computed barrier of FLP pathway with **135** as a base (31.7 kcal/mol) is comparable with that of borenium. Considering that **135** still acts simultaneously as a stabilizing ligand for the borenium cation and as a primary base, the mechanism can be classified as cationic concerted (Scheme 14d).



Scheme 30. Computation study of thiourea-assisted borylation of 1-methylindole via borenium pathway.

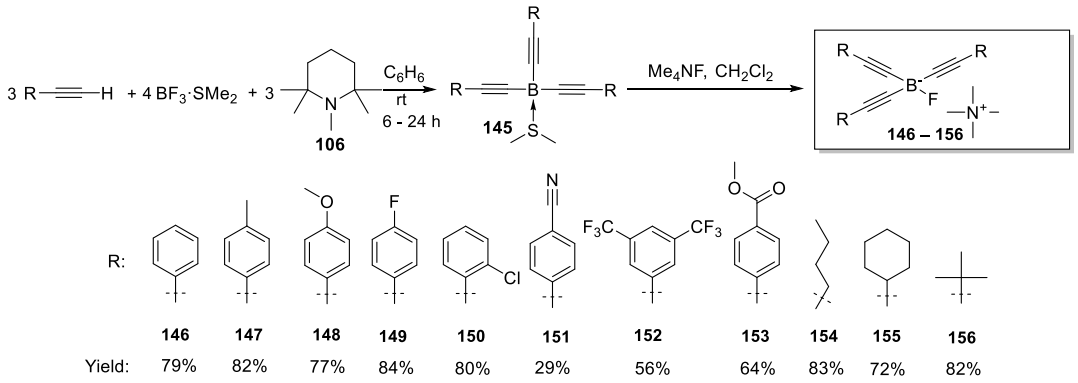
Thus, an amine Lewis base is not directly involved in the borylation step. Therefore, we changed **106** to the more stable but more sterically hindered **108** without significant loses in the reactivity. Structural modification of thioureas leads to different yields of **100.** The performance of thioureas in the C-H borylation reaction is in accordance with their electron donating properties (Scheme 31). Thus, activities of cyclic thioureas **141**-**143** are higher compared to **135**. Compound **143** provides the best activity and has one of highest electron donating abilities. Unfortunately, the even more electron donating thiourea **144** had less activity. This was probably due to too high steric hindrance. Also, ring strain probably affects the activity. Thus, **141** was found to be more active compared with **142**.



Scheme 31. Influence of thioureas nature on the yield of 3-borylated N-methylindole.

Substrate scope of borylation

$BF_3{\cdot}SMe_2$ with **106** borylates a wide scope of alkynes. We didn't isolate most of the dimethylsulfide adducts **145**, but rather converted them *in situ* into trialkynylfluoroborates by treating them with tetramethylammonium fluoride (TMAF) (see the last chapter about boranes fluorination). The resulting yields are displayed in Scheme 32. The system is capable of borylating both aliphatic and aromatic alkynes with a reasonable yield. The only trend

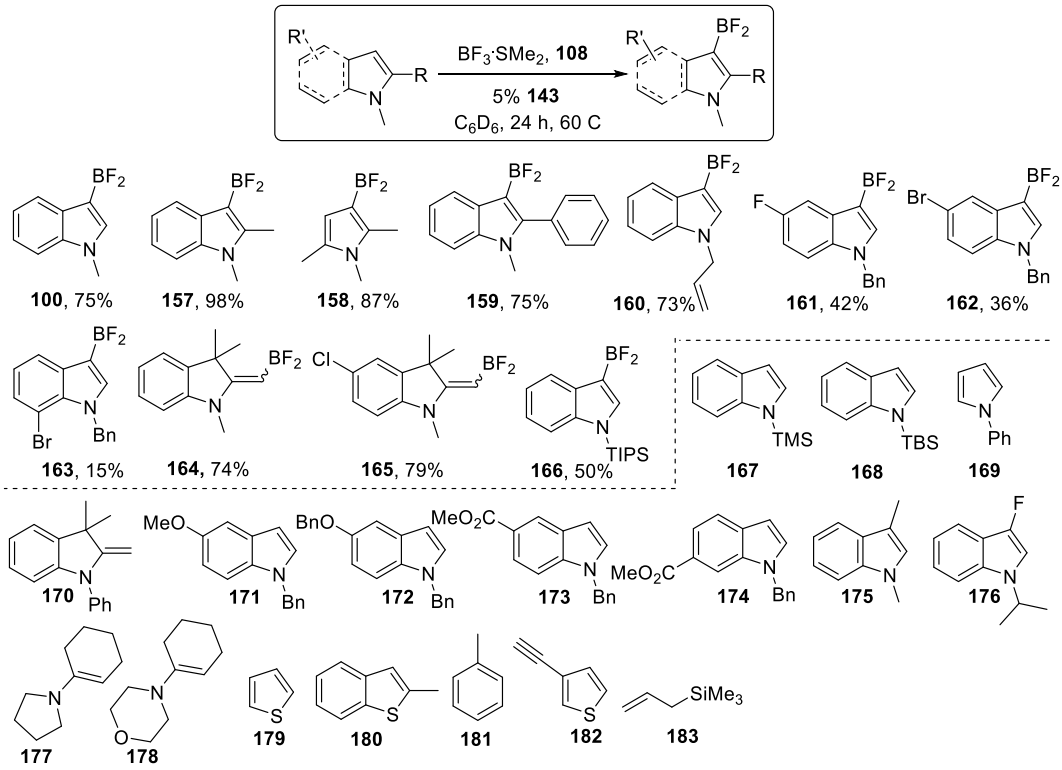


Scheme 32. Substrate scope of terminal alkynes C-H borylation by $BF_3{\cdot}SMe_2$/PMP pair.

of decreased yields was observed in case of electron deficient acetylenes **150-153**, where significant amounts of pentamethylpiperidinium tetraalkynylborates were formed and precipitated from the reaction mixture.

Unlike terminal alkynes, borylation of C_{sp2}-H bonds was very sensitive to the nature of the substrate and was limited mainly to electron rich indoles and pyrroles (**100, 157-160**, Scheme 33). Importantly, the reactive N-allyl group remained intact during borylation of the indole ring (**160**). Incorporation of electron withdrawing groups significantly decreased the yields. Thus, the haloindoles **161-163** gave only modest conversions (Scheme 33). Interestingly, the presence of halogen in the aromatic ring had only a minor influence when the indolenines **164-165** were tried as substrates. Both gave reasonable yields, 74% and 79%, respectively. Interestingly, the N-TIPS protected indole **166** gave 50% conversion with only traces of TIPS group cleavage in the reaction conditions. The less sterically hindered TBS and TMS groups were instantly cleaved in BF_3 media with no borylation observed by ^{1}H, ^{11}B and ^{19}F NMR (examples **167-168**). The N-phenylpyrrole **169** gave only traces of borylated product. Apparently, the presence of a phenyl ring on the nitrogen significantly slowed down the reaction. Thus, N-phenylindolenine **170** remained intact in the reaction conditions.

Examples **157** and **158** show that introduction of an electron donating group into the aromatic ring increases the reaction yield. Unfortunately, benzyloxy and methoxy groups were instantly cleaved by BF_3 with no traces of a borylation product detected (**171-172**).

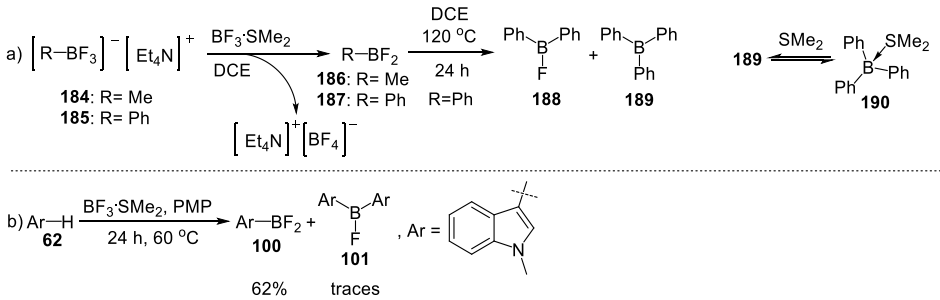


*Scheme 33. Substrate scope of C_{sp2}-H bonds borylation by BF_3·SMe_2 and base **108** in presence of thiourea **143**.*

Furthermore, we didn't observe any traces of borylation of indoles equipped with carboxylic esters (**173-174**). Instead, we observed a quartet around 0 ppm in the ^{11}B spectrum of the reaction media, which can be likely attributed to the BF_3 adduct of the carboxylic ester. In order to try electrophilic substitution to a position other than the C_3-position of indole, we performed borylation of the 1,3-dimethylindole **175** and the 3-fluoro-1-isopropylindole **176**. Unfortunately, no traces of borylation were found with **175,** and **176** gave an intractable mixture with no signal in the ^{11}B NMR which might correspond to any borylated product. Enamines **177-178** led only to their BF_3 adducts with no borylated product in the NMR spectra, whereas the other aromatic cycles (thiophene **179**, 2-methylbenzo[b]thiophene **180,** and toluene **181**) remained completely untouched. Surprisingly, 3-ethynylthiophene **182** gave traces of a borylation product according to ^{11}B and ^{19}F spectra. Although the solution contained a complex mixture, no product of C_{sp}-H activation was found, which is in accordance with observations made about the C-H activation of terminal alkynes with FLPs. Interestingly, the allyltrimethylsilane **183** gave traces of a borylated product. The presence of a trimethylsilylfluoride signal in the ^{19}F NMR spectrum is likely a sign of TMS group cleavage. Thus, the mechanism of borylation of **183** is unclear and will be investigated elsewhere.

Ligands dismutation

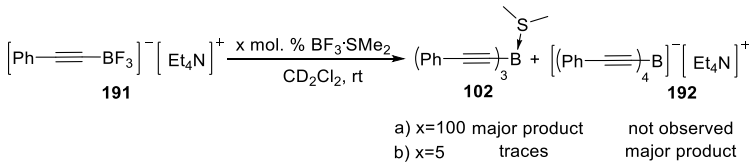
Although the PMP/BF_3·SMe_2 system was able to borylate both terminal alkynes and electron rich N-heteroarenes, the variation of stoichiometry of borylation of both $C_{sp}H$ and C_{sp2}-H bonds (trialkynylboranes **102** vs tetraalkynylborates **103** and monoaryl- (**100**) vs diarylfluoroboranes (**101**), respectively) forced us to investigate these reactions in more detail. Assuming that the first step of C-H borylation by BF_3 is the formation of an aminium trifluoroborate intermediate, we studied the reaction of various trifluoroborates with BF_3·SMe_2. We performed cation exchange to Et_4N in potassium trifluoroborates to increase their solubility in organic solvents. The reaction of methyl- and phenyltrifluoroborates **184-185** with an equimolar amount of BF_3·SMe_2 at room temperature gave the expected organodifluoroboranes **186-187** with no evidence of boranes with different stoichiometry by NMR spectroscopy (Scheme 34a). Whereas methyldifluoroborane remained unchanged upon heating at 120 °C for 24 h, heating of **185** with BF_3·SMe_2 in DCE gave traces of the



Scheme 34. Aromatic ligands dismutation in fluoroboranes a) RBF_3 salts; b) In the course of C-H borylation by BF_3·SMe_2.

dismutation products, diphenylfluoro- and triphenylborane **188** and **189**. In addition to **189**, its SMe_2 complex **190** was detected. Attempts to increase the amounts of **188-190** by prolonging the reaction time were unsuccessful. The possibility of aromatic ligands dismutation on the boron atom was also seen during studies of the C-H borylation of **62** by BF_3·SMe_2 described in the previous chapter. In addition to the standard borylation product **100**, trace amounts of diindolylfluoroborane **101** were also detected by NMR.

The alkynyltrifluoroborate **191** behaved differently in its reaction with an equimolar amount of BF_3·SMe_2. The addition of **98** to **191** in CD_2Cl_2 at room temperature gave the trialkynylborane complex **102** instantaneously (Scheme 35a). Attempts to observe any intermediates of this rearrangement at 0 °C or -10 °C were unsuccessful.



Scheme 35. Acetylenic ligands exchange in RBF_3 salts with a) stoichiometric and b) catalytic amounts of $BF_3{\cdot}SMe_2$.

Whereas exchange of alkynyl ligands between boranes and borates with organolithum reagents has been known since the 1970s[81], dismutation of organofluoroboranes has been only recently discovered[82-84]. Computations show that exchange between two alkynyldifluoroboranes takes place through a four-membered transition state with further expulsion of boron trifluoride and the corresponding dialkynylfluoroborane (Figure 3)[83].

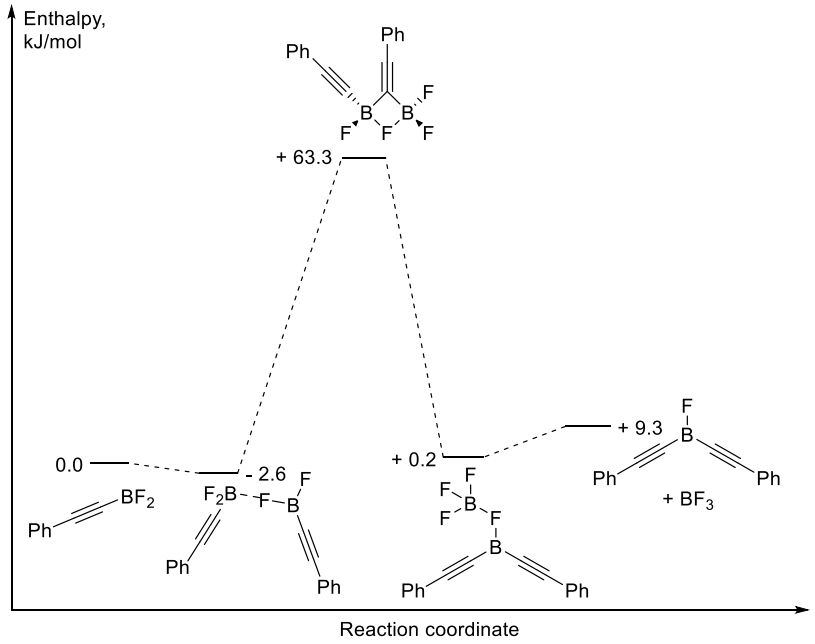
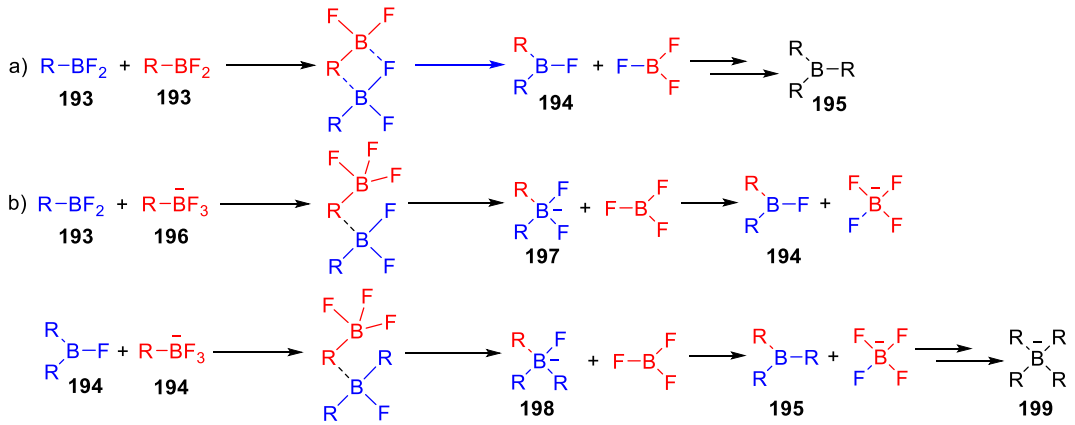


Figure 3. Enthalpy profile for phenylethynyl exchange between two molecules of phenylethynyldifluoroborane (from ref. 83).

The resulting dialkynylfluoroborane undergoes the same exchange with the initial difluoroborane, thus giving trialkynylborane. The same mechanism has similar energies (65.2 kJ/mol for the transition state), and it is exergonic overall[83].

Although this mechanism could explain the rearrangement of **191** with an equimolar amount of $BF_3{\cdot}SMe_2$, it won't explain the significant change in the reaction outcome when catalytic amounts (5 mol %) of $BF_3{\cdot}SMe_2$ were added to **191** (Scheme 35b). Compound **191** gave only traces of the trialkynylborane **102** along with the major product tetraethylammonium tetraphenylethynylborate, **192**. This transformation worked with sub-stoichometric amounts

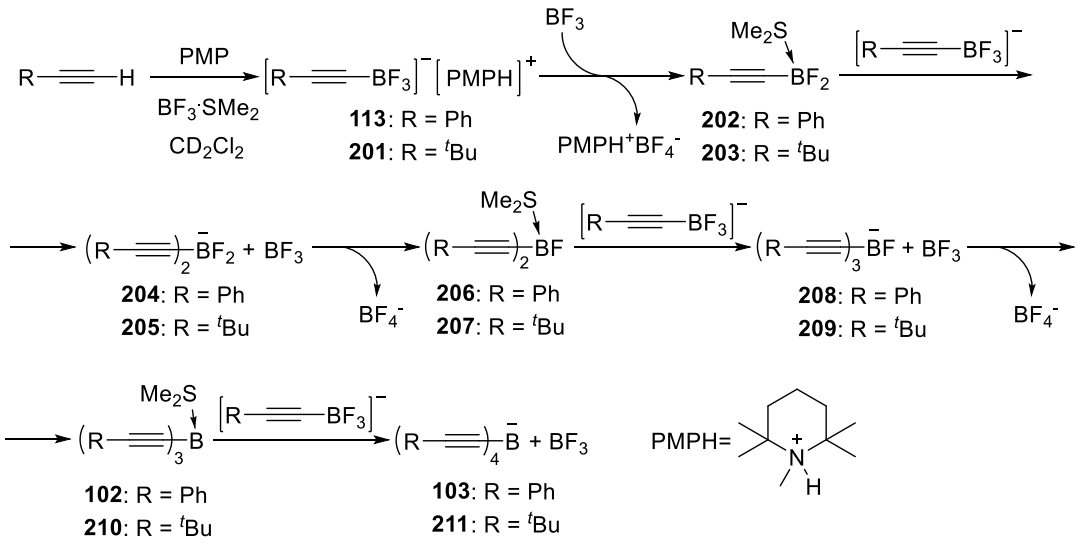
of $BF_3 \cdot SMe_2$. Therefore, we suggest an alternative mechanism for this transformation. Instead of ligand exchange between two neutral boranes **193** (Scheme 36a), **193** reacts with the charged trifluoroborate **196** (Scheme 36b). Whereas exchange between two neutral boranes **193** can lead only to the trisubstituted borane **195** (Scheme 36a), the reaction between **193** and **196** gives expulsion of BF_3 along with formation of borate **197** which is instantly attacked by BF_3 to form the disubstituted fluoroborane **194**. The latter interacts with RBF_3^- in the similar way, and after three cycles, the reaction leads to tetrasubstituted borate **199**. We suppose that the exchange is preferably taking place between the neutral boranes **193**-**195** and **196** as the latter is present in excess in the reaction, although we cannot exclude exchange between other charged and neutral species.



Scheme 36. Ligand exchange mechanisms in organofluoroboranes between a) two neutral boranes b) a neutral borane and a charged borate.

Importantly, rearrangement of phenyltrifluoroborate **185** (Scheme 34) didn't give any traces of the Ph_4B^- product. Moreover, when the reaction was performed with 5% of $BF_3 \cdot SMe_2$, no traces of the rearrangement were detected even at 120 °C after 24 h. Supposedly, rearrangement of **185** can proceed via both mechanisms (Scheme 36a-b).

Having this mechanism in our hands, we rationalized the mechanism of borylation of terminal acetylenes by $BF_3 \cdot SMe_2$ and **106** (Scheme 37). The first step is formation of the $BF_3 \cdot$PMP adduct **114** which then borylates acetylenes by a concerted mechanism, described in the previous chapter, forming trifluoroborates **113** and **201**. Both are instantly defluorinated by another molecule of BF_3 forming **202**-**203**, which undergoes the dismutation described in Scheme 36b to give trialkynylboranes **102**, **210** and tetraalkynylborates **103**, **211**. Such a mechanism explains the presence of various amounts of tetraalkynylborates in the one pot borylation-fluorination (Scheme 32). This is probably responsible for the decreased yields with electron deficient terminal acetylenes.

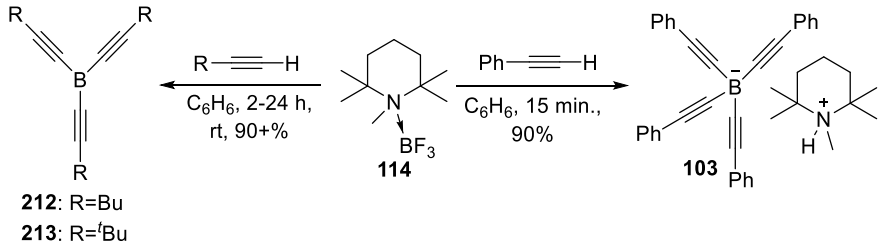


Scheme 37. Terminal acetylenes C-H borylation mechanism by BF_3·SMe_2 and PMP.

Interestingly, unlike the $[RBF_3]^-[Et_4N]^+$ rearrangements discussed above (Scheme 35), kinetic studies of C-H borylation of phenylacetylene by means of ^{11}B NMR spectroscopy at -9 °C made it possible to also observe the intermediates **202-203** and **206-207** (^{11}B δ 5.6 and -8.7 ppm, respectively) under low temperature kinetic studies (-9 °C). Their concentration decreased during the course of the reaction along with the simultaneous growth in the concentration of **102** or **210**.

Various BF_3 adducts as borylating agents

Adduct **114** allows selective formation of either trialkynylboranes or tetraalkynylborates. The reaction outcome depends on the nature of the alkyne. Thus, whereas phenylacetylene borylation by **114** in benzene gives exclusively tetraalkynylborate **103**, trialkynylboranes **212-213** are obtained from the same reaction with hex-1-yne and *tert*-butylacetylene (Scheme 38). This difference can be rationalized by significant resonance stabilization of

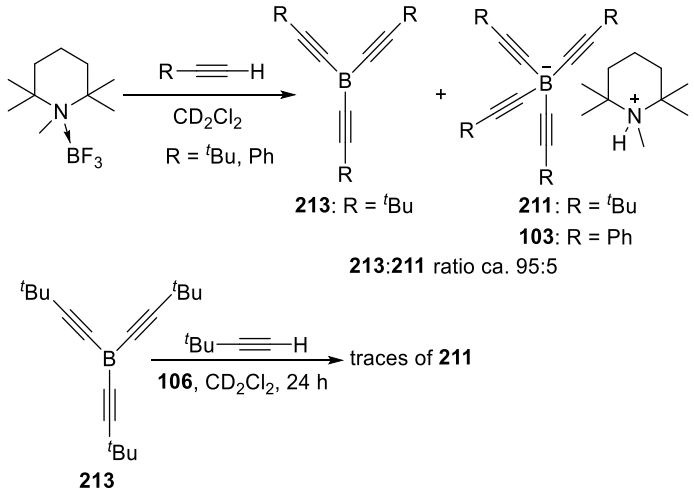


*Scheme 38. C-H borylation of terminal alkynes by PMP·BF_3 complex **114**.*

tetraphenylalkynylborates compared to the corresponding alkyl derivatives. Importantly, the use of benzene as a solvent doesn't stabilize charged structures. Thus, keeping the reaction

of phenylacetylene with **114** for longer reaction times leads to decomposition of **103**, which can be seen by an increase in the broad intractable signal in the aromatic region of the ^{1}H NMR spectrum as well as by formation of a dark insoluble solid.

When benzene was changed to dichloromethane, **211** didn't undergo decomposition even after keeping the solution for 48 h under Ar. Interestingly, borylation of *tert*-butylacetylene in CD_2Cl_2 also gives minor amounts of the tetraalkynylborate **211**. This can be explained by the better stabilization of charged ions in CD_2Cl_2 compared to C_6D_6 (Scheme 39). Attempts to achieve full conversion of *tert*-butylacetylene to **211** were not successful, which is a sign of equilibrium between its borane and borate form. This was



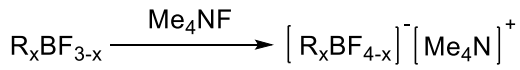
Scheme 39. Borylation of terminal alkynes by PMP·BF_3 in CD_2Cl_2.

also proved by mixing **106**, **213**, and *tert*-butylacetylene in CD_2Cl_2 (Scheme 39). After 24 h, traces of **211** were observed. The same reaction with phenylacetylene couldn't be performed due to instability of uncoordinated triphenylethynylborane.

The reactivity of the $BF_3{\cdot}OEt_2$/PMP system is somewhat similar to that of the $BF_3{\cdot}$PMP pair. Trialkynylboranes don't generally coordinate OEt_2, and the reaction gives either **103** with phenylacetylene or **213** with *tert*-butylacetylene. $BF_3{\cdot}OEt_2$ is a stronger adduct compared with $BF_3{\cdot}SMe_2$, and its reaction with *tert*-butylacetylene gives high yields (90%) only at elevated temperatures and rather long reaction times (60 °C, 24 h).

Fluorination of boranes with Me_4NF towards organofluoroborates

Commonly, organoboranes are strong Lewis acids and can serve as precursors for charged organofluoroborates (Scheme 40). The latter ones are widely used, bench-stable reagents in modern organic synthesis[85, 86]. Whereas unstabilized haloboranes often do not tolerate moisture, the corresponding organofluroborates are crystalline salts, and some of these can even be stored in an air atmosphere.

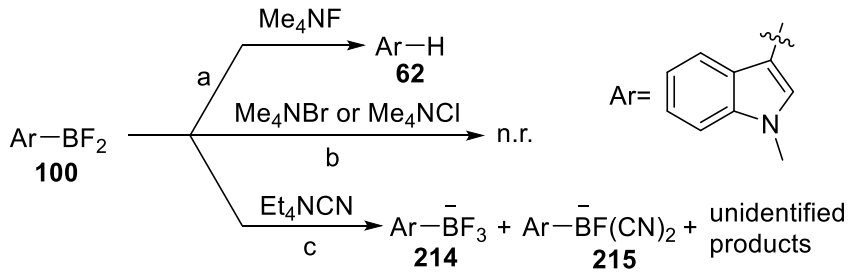


Scheme 40. Straightforward fluorination of organofluoroborates by tetramethylammonium fluoride.

Organofluoroborates are usually synthesized either by fluorination of derivatives of boronic acids[87, 88] or from related organohaloboranes[89, 90]. At the same time, direct fluorination of the corresponding boranes is least developed (Scheme 40). In the papers I-II, we developed direct fluorination of organoboranes by tetramethylammonium fluoride.

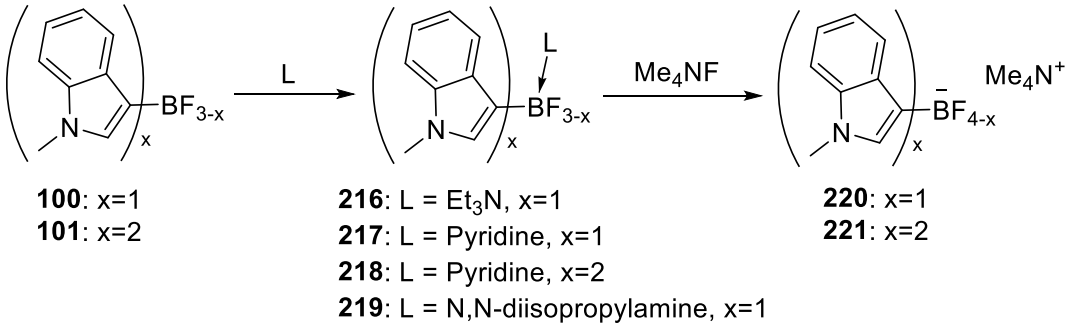
Products of terminal alkyne borylation, trialkynylboranes dimethylsulfide adducts **145**, are solid compounds which are stable on air. Their treatment with an equimolar amount of tetramethylammonium fluoride gives tetramethylammonium trialkynylfluoroborates **146-156** (Scheme 32).

However, the same straightforward conversion of the borylated indole **100** to the corresponding trifluoroborate did not succeed. Instead, treatment of **100** with TMAF gave complete protodeborylation of borane to **62** with trace amounts of the target trifluoroborate (Scheme 41a). Attempts of aryldifluoroborane fixation by other nucleophiles were unsuccessful. Thus, tetramethylammonium bromide and chloride did not react with **100** (Scheme 41b); whereas the reaction of **100** with tetraethylammonium cyanide gave mixed arylfluorocyanides which dismutated into a complex set of products (Scheme 41*c*).



*Scheme 41. Reaction of indolyldifluoroborane with nucleophiles: a) TMAF gives protodeboronation of the indolylfluoroborane; b) No reaction is observed with Me_4NX (X=Cl, Br); c) CN^- reacts with **100**, giving various aromatic cyanofluoroborates and other unidentified products; Et_4N^+ counter-cation was omitted for clarity.*

Trying to stabilize the reactive indolylfluoroboranes **100**-**101**, we studied their reactions with various Lewis bases (Scheme 42; Table 8). No changes in ^1H, ^{11}B and ^{19}F spectra were observed when equimolar amounts of DIPEA (**105**) and tribenzylamine (**220**) were added to the reaction mixture (entries 3-4), which indicates the absence of a reaction between them and **100**-**101**. In contrast, triethylamine (**104**), pyridine (**223**), and N,N-dimethylaniline (**224**) formed adducts with **100** (Table 8, entries 2, 5, 6). Among the screened ligands, only pyridine formed an adduct with **101** (Table 8, entry 5).

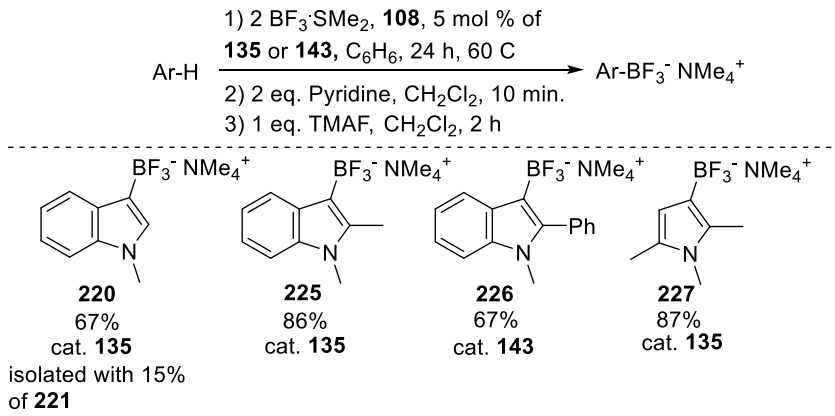


Scheme 42. Indolylfluoroboranes form adducts with nitrogen ligands, some of which are fluorinated to indolylfluoroborates.

The outcome of reactions of the adducts **216**-**219** with TMAF depended on the ligands. No reaction was observed with the triethylamine adduct **216**, whereas both pyridine adducts, **217** and **218**, were successfully fluorinated, giving the corresponding tri- and difluoroborates **220**-**221** without significant protodeboronation. Reaction of the N,N-dimethylaniline adduct **219** with TMAF gave a complex mixture.

Entry	L	Reaction with **100**	Reaction with **101**	Reactions of adducts **216**-**219** with TMAF
1	-	-	-	Protodeboronation
2	Et_3N (**104**)	**216**	-	No reaction
3	DIPEA (**105**)	-	-	-
4	Bn_3N (**222**)	-	-	-
5	Pyridine (**223**)	**217**	**218**	**220** and **221**
6	N,N-dimethylaniline (**224**)	**219**	-	Complex mixture

*Table 8. Reaction of **100** and **101** with Lewis bases. *Complexes - $L{\cdot}R_xBF_{3-x}$ are reported.*



Scheme 43. One-pot synthesis of aryltrifluoroborates by C-H borylation-fluorination of aromatic compounds.

Overcoming the problem of protodeboronation of arylfluoroboranes allowed us to perform a one-pot metal free synthesis of several aryltrifluoroborates from the corresponding aromatic compounds (Scheme 43). The parent indolyltrifluoroborate **220** was isolated along with 15% of the diindolylfluoroborate **221**. Importantly, we found that commercially available tetramethylthiourea (TMTU, **135**) gave nearly the same yields with electron rich indoles and pyrroles, when compared to **145**. Therefore, we used **135** as a cheaper catalyst for the synthesis of **220**, **225** and **227**, whereas the most active compound **145** was used for synthesis of the less electron rich **226**.

Conclusions

Frustrated Lewis Pair (FLP) chemistry of boron has been intensively studied during the last decade. In most of these studies, the boron side is either a part of preorganized *ansa*- or *peri*-aminoboranes or contains strongly electron withdrawing perfluoroaryl substituents such as C_6F_5. Their synthesis is a multistep time-consuming and expensive process. This work shows that inexpensive boron trifluoride forms both Lewis acid-base adducts and Frustrated Lewis Pairs with various amines. The strength of the adduct can be easily tuned by steric hindrance and the basicity of the amine. At the same time, whereas usage of the gaseous BF_3 is inconvenient in the research laboratory, it can be avoided by utilizing the commercially available inexpensive adducts $BF_3{\cdot}SMe_2$ and $BF_3{\cdot}OEt_2$.

According to our knowledge, C-H borylation of terminal acetylenes is almost exclusively done by using weak Lewis base-acid adducts. In this respect, the combination of BF_3 and 1,2,2,6,6-pentamethylpiperidine (PMP) gives a weak but stable adduct which performs C-H borylation of terminal alkynes with a wide substrate scope and functional group tolerance[I]. C-H borylation didn't work when the steric hindrance of the amine was changed towards the formation of the stronger adduct or FLP. Such a trend is also observed with previously known FLP systems when it leads to FLP addition across the triple bond or its carboboration.

Unlike Csp-H, Csp_2-H bonds activation appears to be dictated by the nature of boron ligands and the substrate. Thus, $BF_3{\cdot}SMe_2$ is able to borylate N-methylindole with bases over a wide range of basicity and steric hindrance[II]. As the reaction works in non-polar solvents, it is likely to occur via a concerted asynchronous pathway rather than by forming the electrophilic borenium cations, which usually happens with other boron halides, BCl_3 and BBr_3. Unfortunately, currently electron rich indoles, pyrroles, and indolenines are found to be the only substrates which undergo C-H borylation by BF_3. Introduction of even weakly electron withdrawing substituents such as phenyl or halogens significantly decreases the reaction rate. Elevation of the reaction time or temperature didn't change the borylation yield due to the unwanted process of BF_3-R_3N adduct decomposition by a Hofmann-type mechanism with the formation of aminodifluoroboranes[I]. Interestingly, addition of small amounts of thiourea derivatives increased the yield. Computational studies reveal that the reaction likely proceeds via an electrophilic borenium cation, $TMTU{\cdot}BF_2^+$, although stabilization of ionic compounds is quite low in non-polar solvents such as benzene.

C-H borylation of terminal alkynes by BF_3 gives trialkynylboranes and tetraalkynylborates, depending on the BF_3 adduct, the solvent and the nature of the alkyne[III]. Generally, formation of tetrasubstituted derivatives is preferable when the arylalkyne is used together with a more polar solvent. The former leads to greater resonance stabilization inside the molecule, whereas the use of more polar solvents is preferable with charged species. The same dismutation is observed in organotrifluoroborates when they are treated with boron trifluoride adducts. The detailed step by step mechanism of dismutation is unclear, but the two main processes are ligand exchange between borane and borate or the already known interaction between the two neutral boranes. The former is the only one which can explain

the formation of a charged tetraalkynylborate, whereas dismutation of $ArBF_3$ salts can be rationalized by the latter known process. These studies towards the reaction between RBF_3 salts and BF_3 adducts give additional information about the mechanism of trifluoroborates' action in modern metal-free and transition metal catalysed C-C couplings.

Finally, this work sheds light on protodeboronation, which as a rule is an unwanted side reaction in organoboron chemistry. Whereas trialkynylboranes SMe_2 adducts are directly fluorinated by TMAF to give stable trialkynylfluoroborate salts, the arylfluoroboranes instantly undergo protodeborylation under the same conditions. Their stabilization by forming their pyridine complexes prior to TMAF addition leads to selective fluorination without significant formation of the protodeboronation product[II].

Overall, this work expands the known chemistry of one of the most common Lewis acids, boron trifluoride, towards its utilization in metal-free C-H borylation reactions. Therefore, it can serve as an alternative to typical organolithium or transition metal catalyzed C-B bond formation procedures. Besides, this work expands knowledge about the synthesis and stability of organofluoroborates, which are widely used salts in modern organic synthesis. Main group element chemistry in general and Frustrated Lewis Pairs of boron halides in particular will certainly continue developing in the future.

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