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Electron deficient borane-mediated hydride abstraction in amines: stoichiometric and catalytic processes

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The manipulation of amino C–H bonds has garnered significant interest from the synthetic community due to its inherently high atom, step and redox economy. This Tutorial Review summarises the ability of boranes to mediate hydride abstraction from α -amino and γ -amino conjugated C–H bonds. Borane-mediated hydride abstraction results in the generation of reactive iminium hydridoborate salts that participate in a variety of stoichiometric and catalytic processes. The reactions that have utilised this unusual reactivity include those that manipulate amino scaffolds (including dehydrogenation, racemisation, isomerisation, α - and β -functionalisation, and C–N bond cleavage) and those that use amine-based reagents (transfer hydrogenation, and alkylation).

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Key learning points

1. Amino C(sp³)–H functionalisation processes are a powerful strategy for the synthesis of complex amines.
2. Electron deficient boranes are capable of efficiently mediating hydride abstraction from a variety of amine substrates.
3. Borane-mediated hydride abstraction generates reactive intermediates that can be processed in a variety of chemical reactions.
4. Borane-mediated hydride abstraction is a versatile process that has been utilised in a variety of catalytic and stoichiometric processes, including sophisticated catalytic cycles and cascade reactions.
5. The current state of the borane-mediated hydride abstraction field and its exciting future prospects.

1 Introduction

Hydride transfer is a fundamental reactivity principle that has found numerous applications in synthesis.^{1,2} One of the archetypal examples of which is during the reduction of functional groups *via* hydride donation from a hydridoborate (a.k.a. borohydride) anion, such as in the conversion of carbonyls to alcohols or imines to amines.² The reverse process (hydride abstraction from a C–H bond by a borane, resulting in oxidation of the carbon atom) is far less studied and has found little utility in synthesis (Scheme 1a). However, given the great interest in C–H functionalisation strategies in synthesis due to high atom, step and redox economy, the use of borane-mediated hydride abstraction from an organic molecule is being recognised as an efficient route to generate reactive intermediates for downstream chemical processes.

There are two general classes of organic substrates that undergo hydride abstraction with an electron deficient borane (1): cyclohexa-1,4-dienes (2) and amines (4 and 6) (Scheme 1b and c). Hydride abstraction involving cyclohexa-1,4-dienes generates Wheland-type intermediates 3 and has been successfully utilised in various hydroelementation processes. This area, pioneered by Oestreich and co-workers, has been recently reviewed.^{3–5}

Iminium ions are valuable molecules that are widely applied in synthetic applications, for example in the Mannich reaction,⁶ and are usually formed *via* the condensation of an amine and a carbonyl derivative. Amines (*e.g.* 4 and 6) that bear α -amino and γ -amino conjugated C–H bonds respectively, undergo borane-mediated hydride abstraction to form iminium hydridoborate salts (5 and 7). This strategy is complementary to traditional approaches as the reactive iminium is formed directly from the parent amine *in situ*. In addition, there is great interest from the synthetic community, especially from the pharmaceutical industry,⁷ in efficient synthetic methods involving the C–H functionalisation of amines. Borane-mediated hydride abstraction in amines has provided an unusual but powerful method to mediate amine C–H

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functionalisation reactions and to activate amine-based reagents. This is reflected in the recent flurry of reports that utilise this reactivity.

This Tutorial Review will summarise processes involving borane-mediated hydride abstraction of amino C–H bonds. In both cases of α - and γ -amino conjugated hydride abstraction, the use of stoichiometric borane and then borane-catalysed processes are described. The use of tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, will be most frequently encountered in this context, but other boranes have also been explored more recently. We will also describe the proposed mechanistic steps and catalytic cycles that underpin these processes, focussing on the fate of both the iminium moiety and the hydridoborate counterion.

2 Borane-mediated α -amino hydride abstraction

2.1 Stoichiometric studies

This section will introduce the array of amines that undergo borane-mediated α -amino hydride abstraction with a stoichiometric

quantity of borane, including zirconium and zinc coordinated N -compounds, N -aryl amines, aliphatic tertiary amines, as well as intramolecular hydride transfer. The following sections are organised based on the fate of the resultant iminium hydridoborate salt (observation only, proton transfers, nucleophilic addition to the iminium moiety, and further hydride transfer), although there will be some overlap between these topics.

2.1.1 Observation of iminium hydridoborates. In 1995, Erker and co-workers reported a borane-mediated α -amino hydride abstraction during the reaction of alkyl(amido)zirconocene complexes **8** with $B(C_6F_5)_3$ (Scheme 2).⁸ Initially, the $B(C_6F_5)_3$ -mediated methyl abstraction from amidomethylzirconocene **8** formed amidozirconocene cation **9**. The ion pair **9** was found to be thermally labile and eliminated methane to form hydridoborate based ion pair **11**, which was proposed to be formed as a result of borane-mediated α -amino hydride abstraction from intermediate **10**.

The first example of borane-mediated α -amino hydride abstraction from simple amines was reported by Santini and co-workers in 2002 during NMR analysis of mixtures of dialkyl



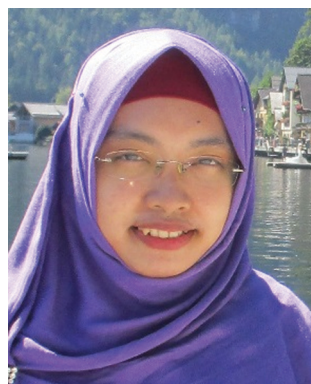
Shyam Basak

Dr Shyam Basak obtained his PhD from Indian Institute of Technology Kharagpur under the supervision of Prof. Dipakranjan Mal in 2017. Then he joined the group of Prof. Amit Basak as a research associate in the same institute for one year. In 2018, he moved to UK to pursue postdoctoral research at Cardiff University in the lab of Dr Louis Morrill to work in the field of FLP chemistry in collaboration with Dr Rebecca Melen. Currently, he is continuing as a postdoctoral researcher in the Morrill group to work on synthetic organic electrochemistry.



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Laura Winfrey completed her MChem degree with a year abroad in 2019 at the University of Leicester (UK) and Kent State University (USA). Laura is currently studying for her PhD at the University of Leicester with Dr Alex Pulis where she is discovering new catalytic methods for the sustainable synthesis of amines.



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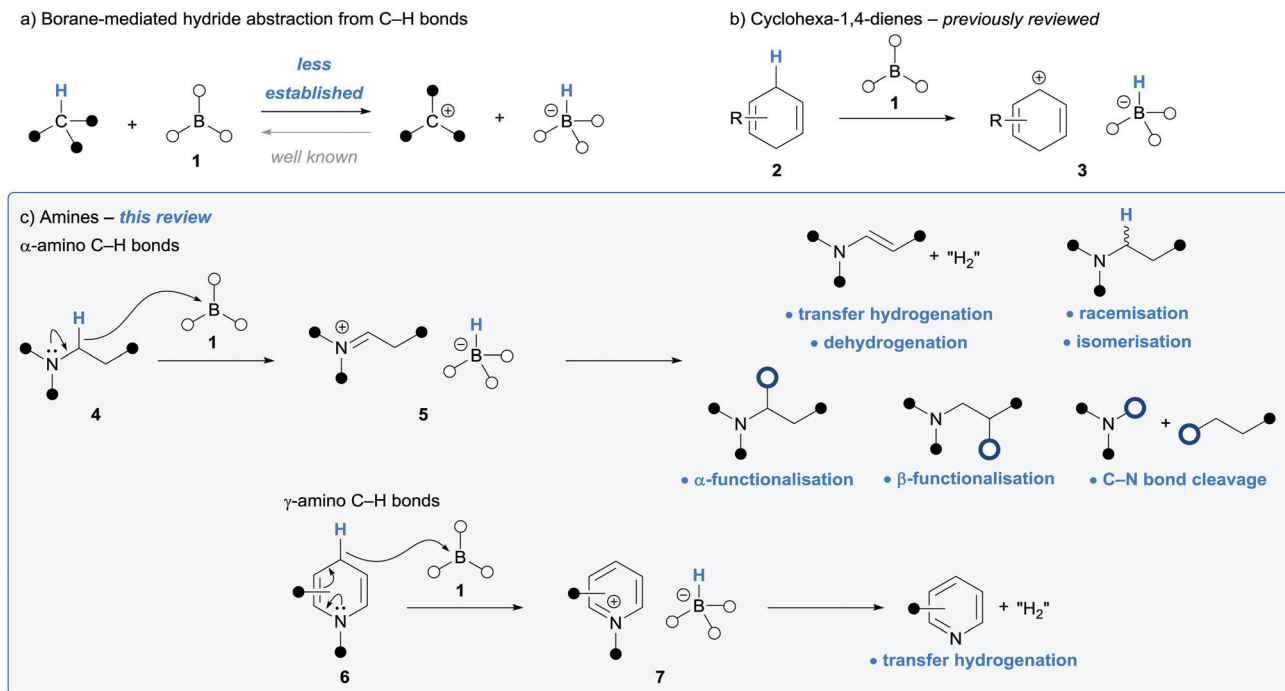
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Rebecca L. Melen

Dr Rebecca Melen studied for her PhD degree at the University of Cambridge (UK). Following Post-doctoral studies in Toronto (Canada) and Heidelberg (Germany), she took up a position at Cardiff University (UK) in 2014 where she is now a Reader in Inorganic Chemistry. In 2018, she was awarded an EPSRC early career fellowship and she was the 2019 recipient of the RSC Harrison Meldola Memorial Prize. Her research interests include diverse aspects of main group reactivity and catalysis, including the applications of main group chemistry in organic synthesis.





Scheme 1 Electron deficient borane-mediated hydride abstraction from C–H bonds.

anilines and $B(C_6F_5)_3$ (Scheme 3).⁹ In the case of dimethylaniline (**12a**), Lewis acid–base pairs **13a** were observed along with iminium hydridoborate ion pair **14a**, where the latter presumably forms as a result of borane-mediated hydride abstraction. On the other hand, diethyl aniline (**12b**) formed ammonium hydridoborate ion pair **15** and a mixture of *E*- and *Z*-iminium-borate zwitterions **17**. Zwitterions **17** are formed as a result of proton transfer from iminium **14b** to diethyl aniline (**12b**) and subsequent addition of enamine **16** to $B(C_6F_5)_3$. Further examples of the formation of iminium hydridoborates and subsequent proton transfers are given in Section 2.1.2.

In 2006, Chen and co-workers reported that binuclear zinc enolate complexes **18** in combination with $B(C_6F_5)_3$, form

cationic zinc enolates **19**, which were found to be highly active catalysts for acrylate polymerisation (Scheme 4).¹⁰

In 2012, as part of a study of amine/ $B(C_6F_5)_3$ frustrated Lewis pairs, Erker, Stephan and co-workers further expanded the range of amines that undergo borane-mediated hydride abstraction.¹¹ It was found that *N,N*-dimethylaniline (**12a**), used as supplied, reacted with $B(C_6F_5)_3$ to produce the iminium-borohydride ion pair **14a**, as in the study by Santini and co-workers.⁹ In contrast, hydride abstraction was not observed when *N,N*-dimethylaniline (**12a**) was carefully purified and the reaction was performed under rigorously dry conditions. The reaction of *N*-isopropyl aniline (**20**) with $B(C_6F_5)_3$ resulted in hydride abstraction, where iminium-hydridoborate **21** was a minor component of an equilibrium



Louis C. Morrill

Dr Louis Morrill received his PhD from the University of St Andrews in 2014 under the direction of Prof. Andrew Smith and undertook post-doctoral research at UC Berkeley with Prof. Richmond Sarpong. In June 2015, he initiated his independent research career at Cardiff University. Research in the group is focused on inventing new reactions in organic chemistry and developing sustainable catalytic methodologies for synthesis.

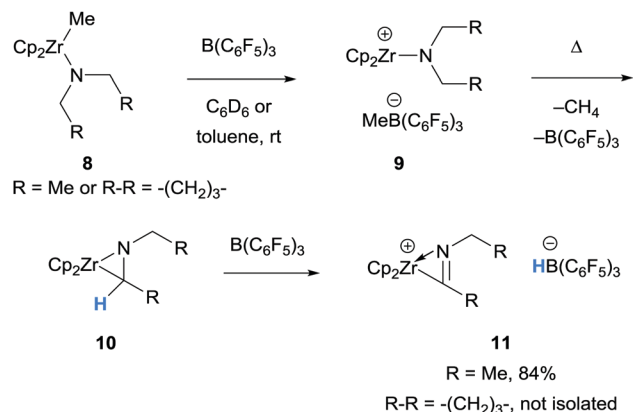


Alexander P. Pulis

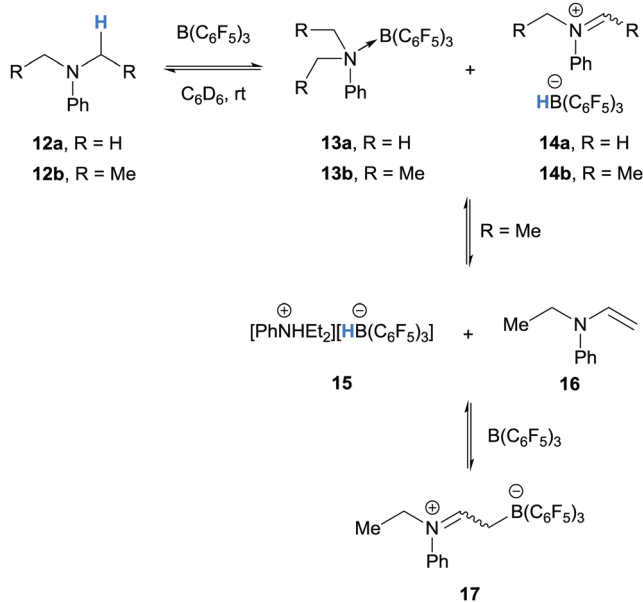
Dr Alex Pulis obtained his PhD from the University of Bristol (UK) under the guidance of Prof. Varinder K. Aggarwal. In 2014, he joined Prof. Douglas Stephan at the University of Toronto (Canada) for postdoctoral studies. He then moved to the University of Manchester (UK) as a fixed term Lecturer within the group of Prof. David J. Procter. Alex began his independent career at the University of Leicester (UK) in 2018 where he explores the reactivity of main group elements and applies these findings to challenges in chemical synthesis.



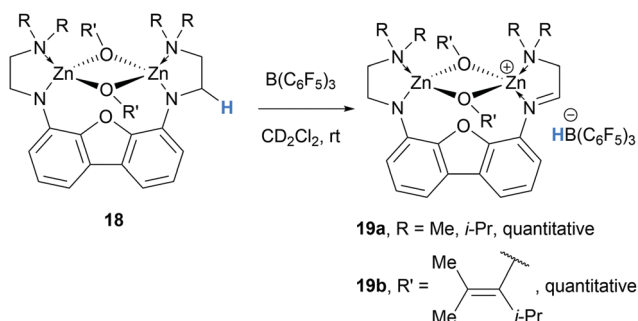
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Scheme 2 B(C₆F₅)₃-mediated α -amino hydride abstraction in the formation of (η^2 -iminoacyl)zirconocene cations. Cp = cyclopentadienyl.

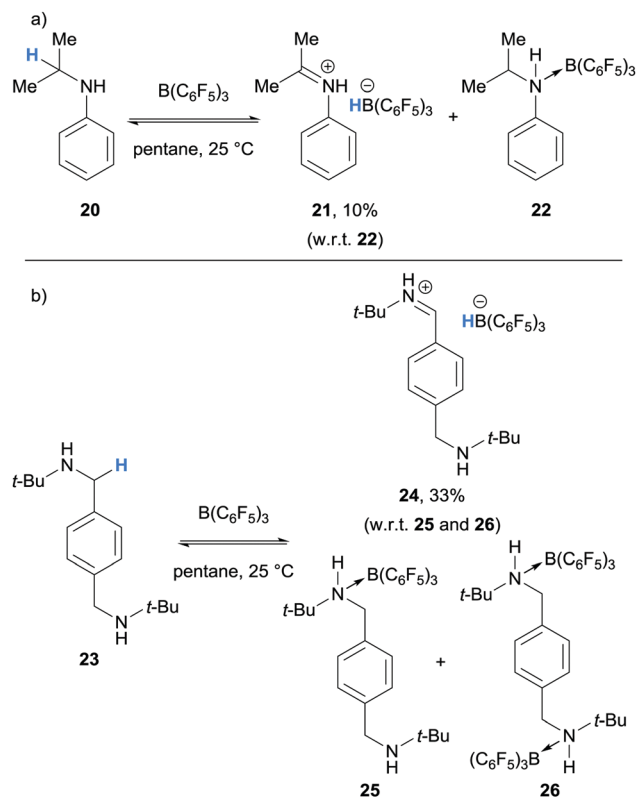


Scheme 3 B(C₆F₅)₃-mediated α -amino hydride abstraction from *N,N*-dialkylanilines.



Scheme 4 B(C₆F₅)₃-mediated α -amino hydride abstraction from cationic zinc enolates.

with adduct **22** (Scheme 5a). On treatment of B(C₆F₅)₃ with 1,4-C₆H₄(CH₂NH*t*-Bu)₂ (**23**), hydride abstraction was also observed in addition to mono- and bis-amine-borane adducts **25** and **26**



Scheme 5 B(C₆F₅)₃-mediated α -amino hydride abstraction from secondary amines.

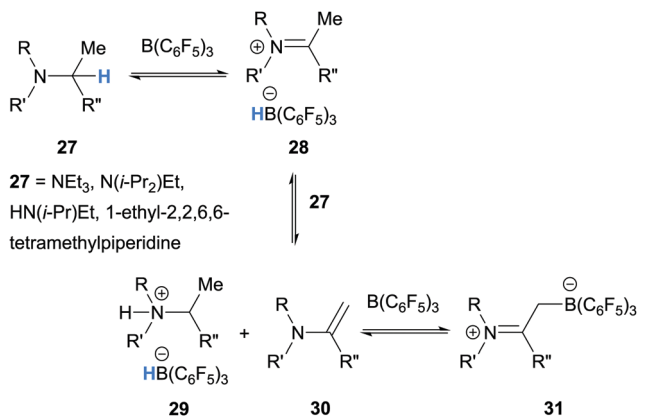
(Scheme 5b). On the other hand, hydride abstraction was not observed in the reaction of benzyldimethyl amine and B(C₆F₅)₃.

2.1.2 Formation of iminium hydridoborates and subsequent proton transfer. As demonstrated by Santini and co-workers (Scheme 3),⁹ when the iminium hydridoborate salts generated after hydride abstraction contain β -hydrogens, proton transfer is possible. Reports from Mercandelli, D'Alfonso, Resconi and co-workers,¹² Rieger, Repo and co-workers,¹³ and Berke and co-workers¹⁴ have shown that a variety of secondary and tertiary aliphatic amines **27** undergo borane-mediated hydride abstraction with B(C₆F₅)₃ to form the corresponding iminium hydridoborate salts **28** (Scheme 6). The salts **28** are deprotonated *in situ* by another equivalent of amine **27** to form enamines **30** and ammonium-hydridoborates **29**. The nucleophilic enamines **30** subsequently trap B(C₆F₅)₃ to form zwitterions **31**.

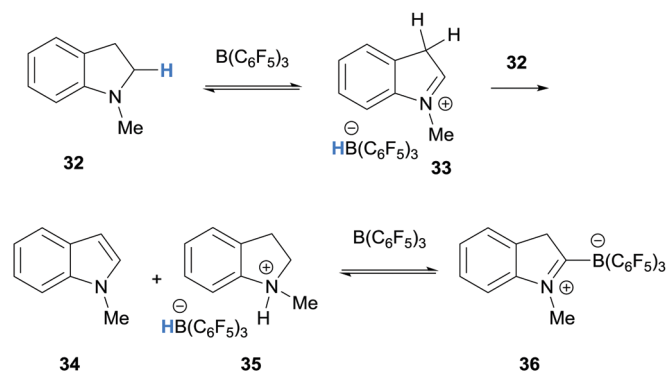
In a related process, Focante and co-workers, and Resconi and co-workers showed that the reaction of *N*-methylindoline (**32**) and B(C₆F₅)₃ forms ammonium-hydridoborate **35** and zwitterion **36** (Scheme 7).^{15,16} In this case, B(C₆F₅)₃-mediated hydride abstraction of indoline **32** and subsequent deprotonation of the iminium hydridoborate salt **33** forms a mixture of ammonium-hydridoborate **35** and indole **34**. The reaction of indole **34** and B(C₆F₅)₃ is known to form zwitterion **36**.¹⁷

2.1.3 Formation of iminium hydridoborates and subsequent intramolecular nucleophilic addition to the iminium ion. In addition to deprotonation events, the iminium hydridoborate salts can undergo addition processes with pendant nucleophiles.





Scheme 6 B(C₆F₅)₃-mediated α -amino hydride abstraction from aliphatic tertiary amines.



Scheme 7 B(C₆F₅)₃-mediated α -amino hydride abstraction from *N*-methylindoline.

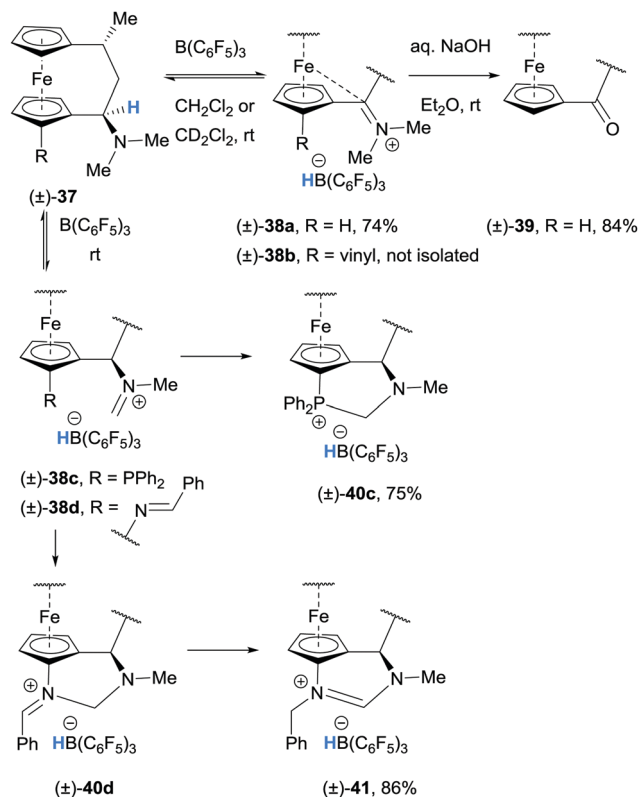
Grimme, Erker and co-workers performed a combined theoretical and experimental study on the generation and stability of α -ferrocenyl carbenium ions. Hydride abstraction was observed in the reaction of (\pm)-dimethylamino-[3]ferrocenophanes (\pm)-37a and (\pm)-37b with B(C₆F₅)₃ and the ferrocene stabilised iminium hydridoborate salts (\pm)-38a and (\pm)-38b were formed (Scheme 8).^{18–20} The iminium moiety in 38a was also hydrolysed to form (\pm)-ferrocenophane ketone (\pm)-39.¹⁹

Analogous ferrocenophanes (\pm)-37c and (\pm)-37d also underwent hydride abstraction with B(C₆F₅)₃. In both cases, (\pm)-37c and (\pm)-37d appeared to undergo hydride abstraction at the *N*-CH₃ substituent (rather than the C-secondary amino C–H bond as in (\pm)-37a and (\pm)-37b) resulting in formation of (\pm)-40c and (\pm)-41.²¹

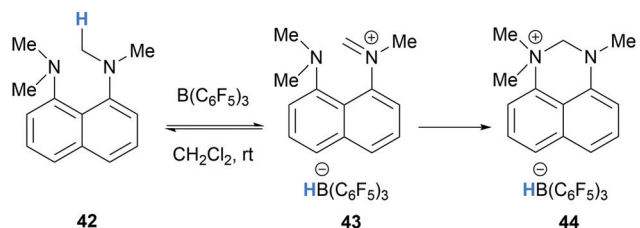
In iminium hydridoborate (\pm)-38c, the pendant phosphine moiety traps the electrophilic iminium carbon to form phosphonium salt (\pm)-40c. Similarly, (\pm)-38d, that bears a pendant imine, forms (\pm)-41 via intermediate (\pm)-40d (Scheme 8).

In a related process, Mercandelli, D'Alfonso, Resconi and co-workers reported the intramolecular trapping of iminium hydridoborate 43, generated via B(C₆F₅)₃-mediated hydride abstraction in 1,8-bis(dimethylamino)naphthalene (42), with a pendant amino group (Scheme 9).²²

2.1.4 Formation of iminium hydridoborates and subsequent hydride transfer to electron deficient π -bonds. The hydridoborate



Scheme 8 B(C₆F₅)₃-mediated α -amino hydride abstraction from dimethyl-amino-[3]ferrocenophanes (\pm)-37 and resultant reactivity.



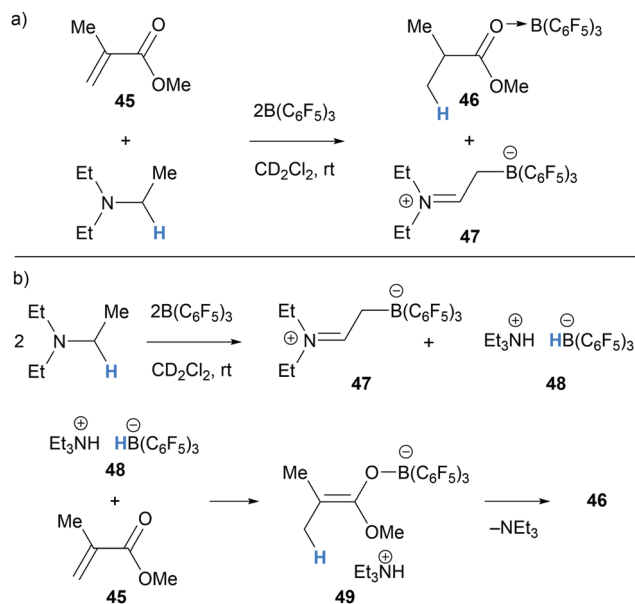
Scheme 9 B(C₆F₅)₃-mediated α -amino hydride abstraction from 1,8-bis(dimethylamino)naphthalene 42 and resultant intramolecular nucleophilic addition.

counterion, formed after borane-mediated hydride transfer, can also participate in downstream reactivity, such as hydride transfer to electron deficient alkenes. This process often triggers further reactivity, such as transfer hydrogenation and C–C bond forming reactions.

In 2015, Chen and co-workers studied the application of a Et₃N/B(C₆F₅)₃ Lewis pair towards the polymerisation of acrylate monomers.²³ Instead of polymerisation taking place, a mixture of Et₃N/B(C₆F₅)₃/methyl methacrylate (45) (1 : 2 : 1) afforded methyl isobutyrate 46 in quantitative yield (Scheme 10a). NMR experiments revealed that upon mixing Et₃N, B(C₆F₅)₃ and methyl methacrylate in a 1 : 1 : 1 ratio, a mixture of zwitterion 47 and ammonium-hydridoborate salt 48 was formed. This observation was in line with previous reports of borane-mediated α -amino hydride abstraction followed by deprotonation of the



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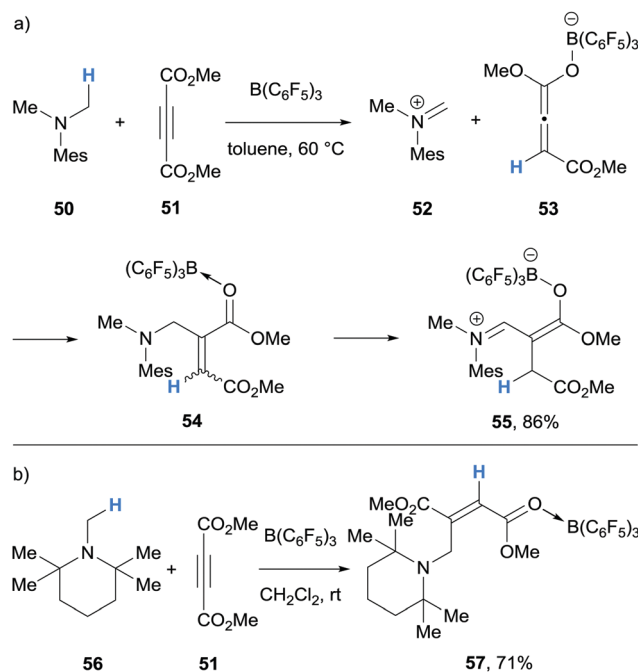


Scheme 10 $B(C_6F_5)_3$ -mediated α -amino hydride abstraction utilised in transfer hydrogenation of methyl methacrylate.

iminium hydridoborate salt as described above in Section 2.1.2. The addition of one further equivalent of $B(C_6F_5)_3$ presumably activates methyl methacrylate (**45**) for reduction by the hydridoborate counterion in **48** (Scheme 10b). Subsequent proton transfers in salt **49** results in the formation of the hydrogenated product **46**.

In 2017, Erker and co-workers undertook experimental and theoretical studies on the $B(C_6F_5)_3$ -mediated α -amino hydride abstraction from *N*-methyl amines in the presence of electron deficient alkynes and alkenes (Schemes 11 and 12).²⁴ In all cases, the generated hydridoborate counterions in the iminium salts (*cf.* **14a–14b**) reduced the electron deficient alkyne or alkene to form an enolate (*cf.* **53**, **59**, **64**). The nucleophilic enolates reacted with the iminium electrophile in a Mannich-type process to form new C–C bonds. In the case of the reaction of *N,N*-dimethylmesitylamine (**50**), dimethylacetylenedicarboxylate (**51**) and $B(C_6F_5)_3$, a nucleophilic allenolate **53** is formed. After C–C bond formation, the resulting product **54** isomerised to zwitterion **55** (Scheme 11a). An analogous process was reported in the reaction of 1,2,2,6,6-pentamethylpiperidine (**56**) and dimethylacetylenedicarboxylate (**51**) and $B(C_6F_5)_3$ (Scheme 11b).

Similar reactivity was also observed when α,β -unsaturated carbonyl compounds were used (Scheme 12). In the case of *N*-phenyl-maleimide (**58**), hydride abstraction and subsequent transfer generated enolate **59**, which then added to the iminium carbon in **52** to form succinamide **60**. The reaction of ethyl acrylate (**61**), amine **50** and $B(C_6F_5)_3$ initially followed a similar course and formed Mannich product **65**. However, **65** also underwent further $B(C_6F_5)_3$ -mediated hydride abstraction to form iminium hydridoborate **66**, which after proton transfer, resulted in the transfer hydrogenation of ethyl acrylate to form ethyl propionate (**63**).



Scheme 11 $B(C_6F_5)_3$ -mediated α -amino hydride abstraction and subsequent hydride transfer to electron deficient alkynes utilised in C–C bond forming reactions. Mes = 2,4,6-trimethylphenyl.

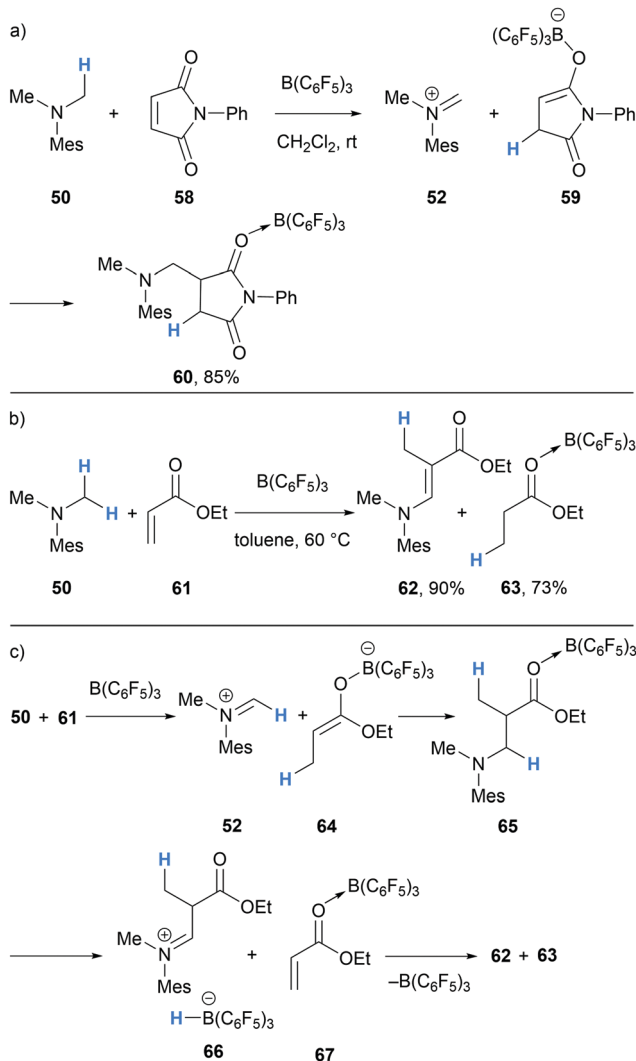
2.1.5 Intramolecular α -amino hydride abstraction. The majority of borane-mediated α -amino hydride abstraction has been reported with $B(C_6F_5)_3$. However, α -amino hydride abstraction can also be mediated with heteroleptic boranes that have fewer perfluoro aryl rings and are therefore weaker Lewis acids.

In 2011, Repo and co-workers observed racemisation during the synthesis of an ammonium hydridoborate **69** from enantio-enriched amine **68** (>99:1 e.r., Scheme 13a).²⁵ To explain this observation, it was proposed that the intermediate amino borane **70**, underwent reversible intramolecular hydride abstraction from the α -amino C–H bond to the $B(C_6F_5)_2$ moiety giving **71** (Scheme 13b).

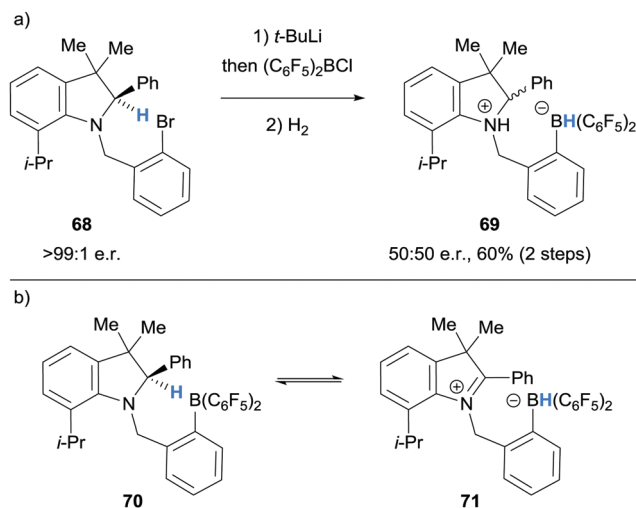
During a study of ethylene and hexylene bridged amino borane FLPs, Erker and co-workers reported the synthesis of zwitterions **74** from amino borane **72** (Scheme 14).²⁶ In this case, intramolecular hydride abstraction from the α -amino C–H bond to the $B(C_6F_5)_2$ moiety generated iminium hydridoborate **73** that reduced benzaldehyde or benzophenone yielding **74**.

In 2012, Mitzel and co-workers reported the formation of cyclic iminium borate **80** in the reaction between $HB(C_6F_5)_2$ and *N,N*-diisopropylallylamine (**75a**) (Scheme 15).²⁷ The formation of **80** was proposed to proceed *via* hydroboration of **75a** with $HB(C_6F_5)_2$ to form amino borane **76a**. Intramolecular borane-mediated hydride abstraction in **76a** formed iminium hydridoborate zwitterion **77**, which underwent proton transfer generating enaminium hydridoborate **78**. Dehydrogenation of **78** then allowed for intramolecular nucleophilic addition of the enamine moiety to the three-coordinate borane in **79** to form the cyclic product **80**. In contrast, less hindered allyl amines, such as diethylallylamine (**75b**), did not form the analogous

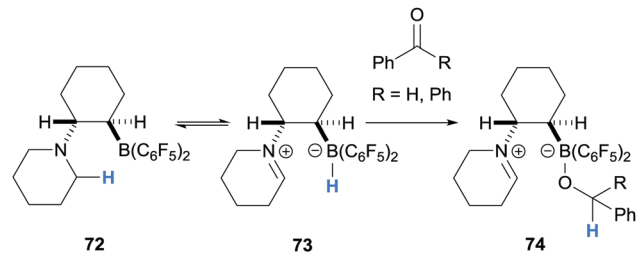




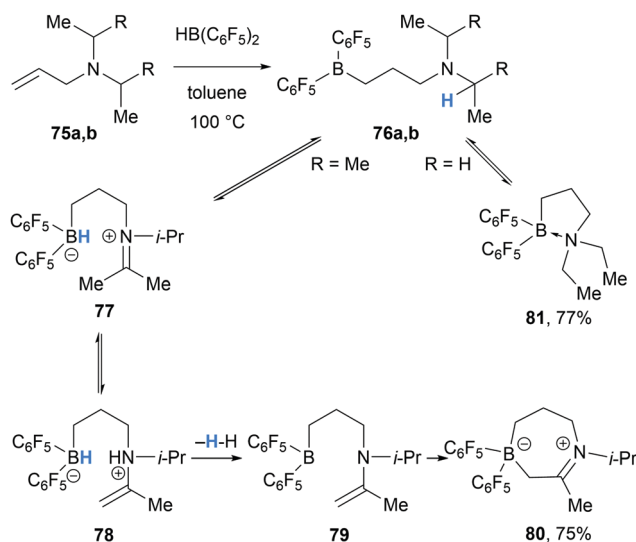
Scheme 12 $\text{B}(\text{C}_6\text{F}_5)_3$ -mediated α -amino hydride abstraction and subsequent hydride transfer to electron deficient alkenes utilised in C–C bond forming reactions.



Scheme 13 Borane-mediated intramolecular α -amino hydride abstraction and racemisation.



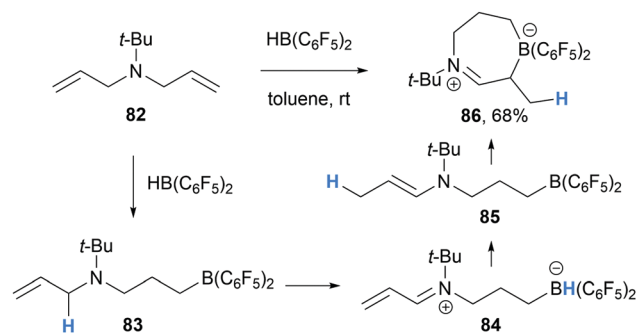
Scheme 14 Borane-mediated intramolecular α -amino hydride abstraction and subsequent carbonyl reduction.



Scheme 15 Borane-mediated intramolecular α -amino hydride abstraction and subsequent dehydrogenation and cyclisation.

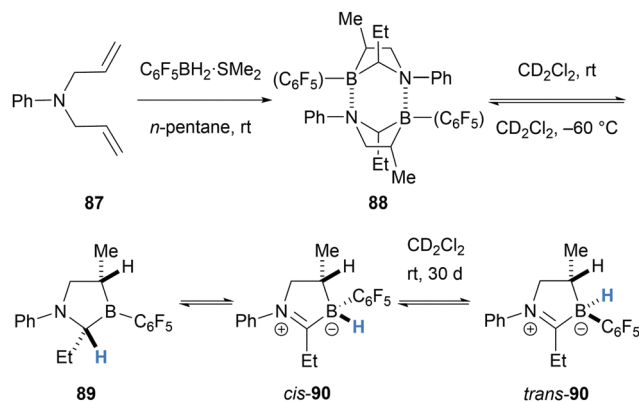
cyclic product, and instead formed intramolecular Lewis acid adduct **81**.

In a related reaction, Mitzel and co-workers reported the formation of seven-membered iminium-borate **86** during the hydroboration of *N,N*-diallyl-*N*-*tert*-butylamine (**82**) with $\text{HB}(\text{C}_6\text{F}_5)_2$ (Scheme 16).²⁸ In line with previous reports, mono-hydroboration of **82** generated the amino borane **83** which undergoes intramolecular α -amino hydride abstraction to form α,β -unsaturated iminium hydridoborate **84**. We propose that iminium-borate **84**



Scheme 16 Borane-mediated intramolecular α -amino hydride abstraction and subsequent hydride transfer and cyclisation.





Scheme 17 1,2-Hydride migration from an α -amino C–H bond to a borane atom.

then undergoes intramolecular conjugate reduction from the hydridoborate moiety to the β -position of the α,β -unsaturated iminium **84**. The generated enamine **85** intramolecularly traps the electrophilic borane moiety to form the cyclic zwitterion **86**.

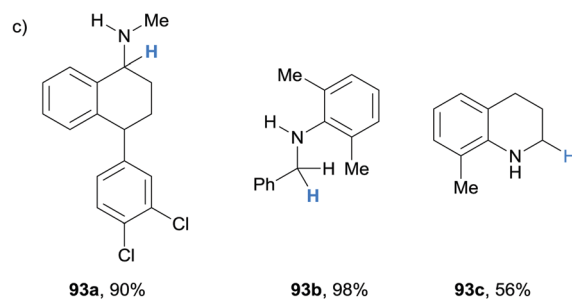
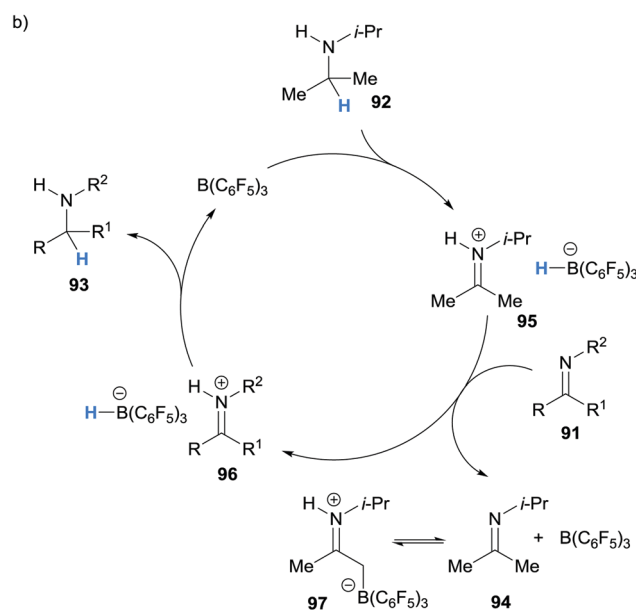
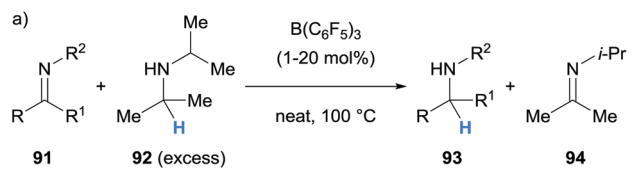
In 2016, Erker and co-workers reported an interesting 1,2-hydride migration from an α -amino C–H bond to a borane atom (Scheme 17).²⁹ The dimer **88** was formed after double hydroboration of *N,N*-diallylaniline (**87**) with $C_6F_5BH_2$. Under dilute conditions, dimer **88** dissociates to form monomer **89** which can undergo the stereospecific 1,2-hydride migration to form *cis*-iminium-hydridoborate zwitterion **90**. The *cis*-isomer **90** slowly equilibrates to a 1 : 1 mixture with the *trans*-isomer, presumably *via* intermolecular hydride transfer.

2.2 Catalytic applications

Borane-mediated α -amino hydride abstraction has been successfully utilised in a variety of catalytic manifolds by virtue of the range of processes by which the hydridoborate counterion can react in downstream processes. In this section we will discuss borane-catalysed transfer hydrogenation, dehydrogenation, racemisation, isomerisation, α - and β -functionalisation of amines, and processes that involve C–N bond cleavage. All of these transformations are made possible by the unique hydride acceptor and donation abilities of the boron Lewis acids used.

2.2.1 Transfer hydrogenation. In 2011, Stephan and co-workers reported the $B(C_6F_5)_3$ -catalysed transfer hydrogenation of aldimines and ketimines **91** using diisopropylamine (**92**) as a H_2 surrogate (Scheme 18a).³⁰ The catalytic cycle (Scheme 18b) proceeds *via* $B(C_6F_5)_3$ -mediated hydride abstraction in diisopropylamine (**92**) to generate iminium **95**. Proton transfer from **95** to the substrate imines **91** and subsequent hydride transfer from the hydridoborate counterion gave amines **93**. In agreement with the work reported by Santini and co-workers,⁹ the zwitterion **97** was identified to exist in equilibrium with the ketimine **94** and $B(C_6F_5)_3$. In addition to imines **91**, other classes of molecules such as enamines, a quinoline (*cf.* **93c**) and an aziridine were hydrogenated (Scheme 18c). Stephan's catalytic transfer hydrogenation was applied to the synthesis of the antidepressant sertraline (**93a**).

2.2.2 Dehydrogenation. In the same issue, both Grimme and Paradies,³¹ and Kanai³² reported the $B(C_6F_5)_3$ -catalysed

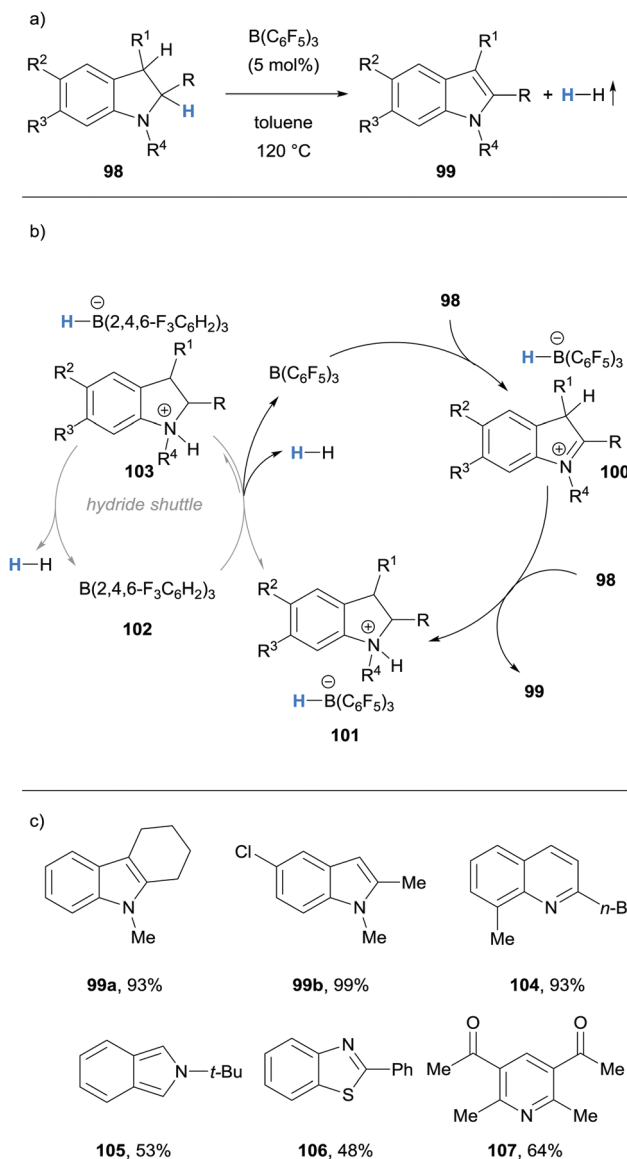


Scheme 18 Borane-mediated hydride abstraction utilised in $B(C_6F_5)_3$ -catalysed transfer hydrogenation.

acceptorless dehydrogenation of N-heterocycles (Scheme 19 and 20, respectively).

Grimme, Paradies and co-workers described the dehydrogenation of a variety of indolines **98** to the corresponding indoles **99**, as well as examples of the dehydrogenation of 1,2-dihydroquinolines (*cf.* **104**), an isoindoline (*cf.* **105**), a benzothiazoline (*cf.* **106**) and dihydropyridines (*cf.* **107**) in a process mediated by hydride abstraction (Scheme 19a and c).³¹ Using indoles as an example, $B(C_6F_5)_3$ -mediated hydride abstraction occurred at the C2 position of indoline **98** to form iminium **100** (Scheme 19b). The indole product **99** was formed through subsequent deprotonation at the C3 position by a second equivalent of **98**. Hydrogen gas and the $B(C_6F_5)_3$ catalyst were then liberated from the ammonium hydridoborate salt **101** in what was calculated to be the rate limiting step. Interestingly, a rate enhancement was observed upon addition of the weaker Lewis acid $B(2,4,6-F_3C_6H_2)_3$ (**102**). Whilst **102** did not



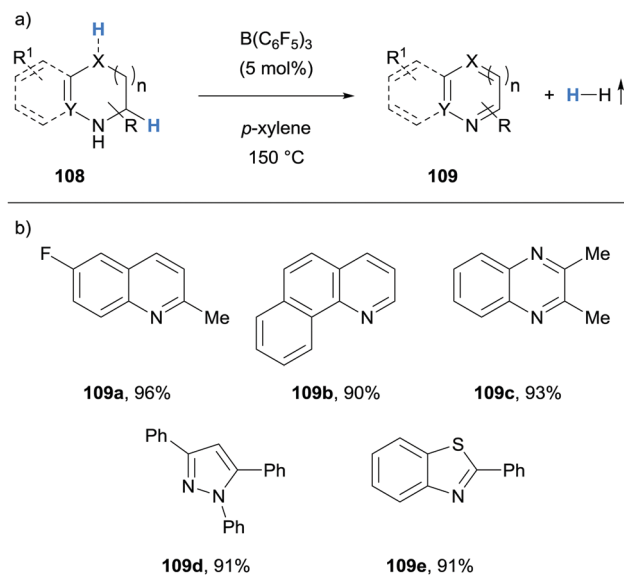


Scheme 19 Borane-mediated hydride abstraction utilised in B(C₆F₅)₃-catalysed acceptorless dehydrogenation.

mediate hydride abstraction, it served as a hydride shuttle whereby the hydridoborate counterion in **103** was more basic than in **101**, so that the formation of H₂ was more favourable. The hydride shuttle strategy enabled the dehydrogenation of a 1,2-dihydroquinoline (*cf.* **104**), an isoindoline (*cf.* **105**), a benzothiazoline (*cf.* **106**) and dihydropyridines (*cf.* **107**).

Kanai and co-workers reported the B(C₆F₅)₃-catalysed acceptorless dehydrogenation of N-heterocycles (Scheme 20).³² The substrate scope included the dehydrogenation of indolines, tetrahydroquinolines (*cf.* **109a**), tetrahydroquinoxalines (*cf.* **109c**), pyrazolines (*cf.* **109d**) and benzothiazolines (*cf.* **109e**). Notably, coordinating functional groups and atoms, such as thioether and methoxy groups, were tolerated.

Acknowledging the ability of B(C₆F₅)₃ to catalyse the dehydrogenation of indolines, Zhang and co-workers made use of this in their direct C3 C–H silylation and borylation approach to



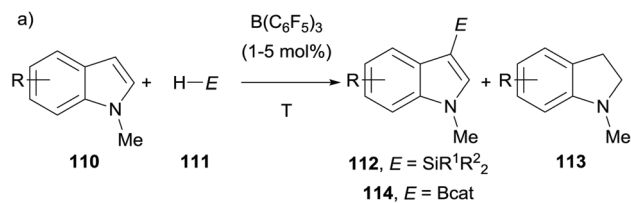
Scheme 20 Borane-mediated hydride abstraction utilised in B(C₆F₅)₃-catalysed acceptorless dehydrogenation.

substituted indoles **112** and **114** (Scheme 21).^{33,34} The initial role of B(C₆F₅)₃ was to activate the silane or catecholborane to form the weak adduct **115**. Adduct **115** then underwent nucleophilic attack by indoles **110**, forming the iminium hydridoborate salts **116**. Another equivalent of **110** deprotonated **116** to form the desired C3-functionalised product **112** or **114**. Hydride transfer within **117** resulted in regeneration of B(C₆F₅)₃ and formed indolines **113**. The disproportionation reaction yields C3-functionalised indole **112** or **114** and indoline **113** at room temperature. In a bid to improve the atom economy, the temperature was increased which promoted the B(C₆F₅)₃-mediated hydride abstraction and subsequent dehydrogenation of indoline **113** to form indole **110**. The dehydrogenation presumably occurred in a related catalytic cycle to that described by Grimme and Paradies (*cf.* Scheme 19). The catalytic performance of B(C₆F₅)₃ was investigated by sequentially adding batches of indole and hydrosilane or catecholborane to the same reaction mixture and analysing the yield of desired product each time. The B(C₆F₅)₃ remained catalytically competent over 10 sequential reactions.

2.2.3 Racemisation and isomerisation. Due to the often-reversible nature of borane-mediated α -amino hydride abstraction, racemisation and isomerisation processes have been found to occur in several cases. In 2011, Repo and co-workers showed that the borane-mediated α -hydride abstraction can be used in the racemisation of amines **119** and **120** (Scheme 22).²⁵ The racemisation process proceeds *via* the formation of iminium hydridoborate intermediates after hydride abstraction, followed by a non-face selective hydride transfer to reform the amine. Complete racemisation was observed when enantiomerically enriched amines **119** and **120** were subjected to the B(C₆F₅)₃ catalyst under an argon atmosphere. Interestingly, in the case of amine **119**, racemisation could be fully suppressed when the reaction was performed under a H₂ atmosphere.



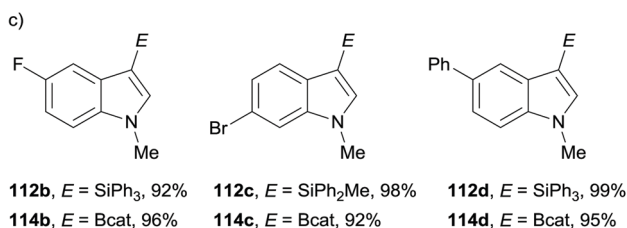
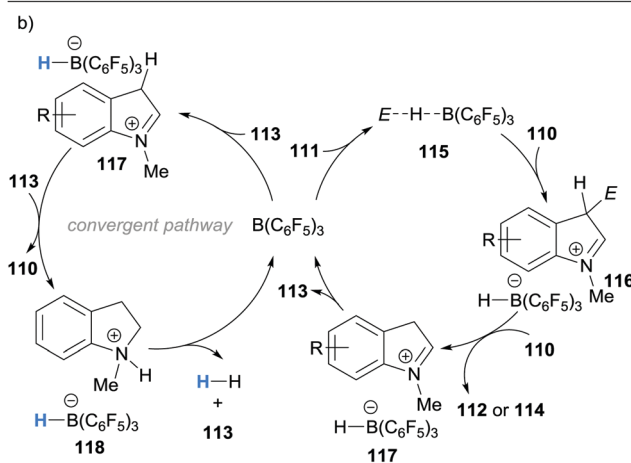
Tutorial Review



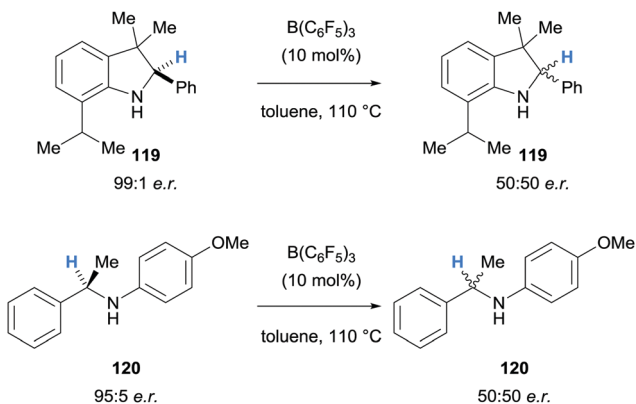
For example:

R = 5-Ph, E = SiPh₂Me

T	112a	113a
rt	45%	47%
120 °C	99%	0%

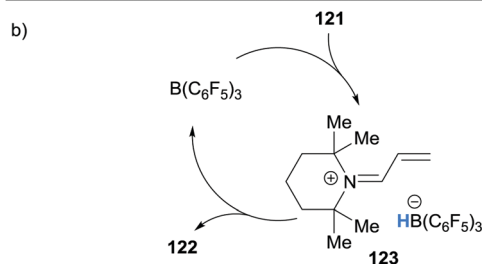
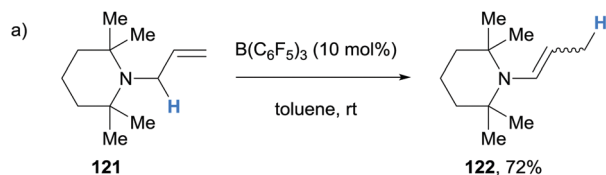


Scheme 21 Borane-mediated hydride abstraction utilised in B(C₆F₅)₃-catalysed convergent C3-silylation and borylation of indoles.



Scheme 22 Borane-mediated hydride abstraction utilised in the racemisation of amines.

In 2017, Erker and co-workers reported an example of B(C₆F₅)₃-catalysed isomerisation of *N*-allyltetramethylpiperidine (**121**) to the



Scheme 23 Borane-mediated hydride abstraction utilised in the isomerisation of an alkene.

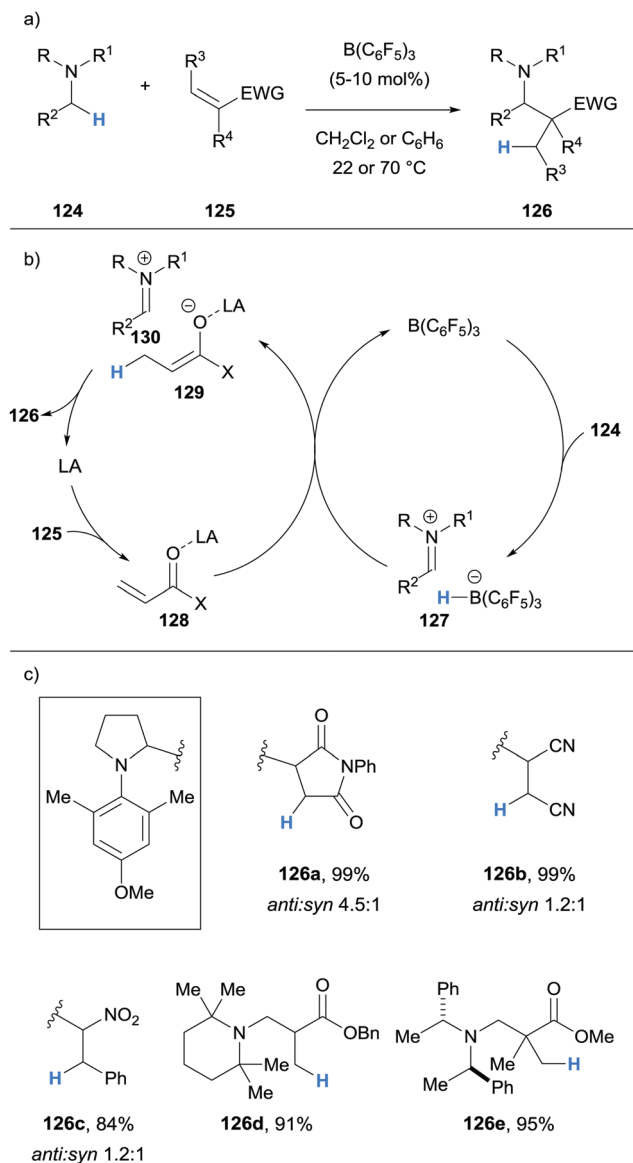
corresponding enamine **122** (Scheme 23a).³⁵ The authors proposed that isomerisation of **121** occurred *via* a B(C₆F₅)₃-mediated hydride abstraction to form α,β-unsaturated iminium hydridoborate **123** (Scheme 23b). Hydride transfer from the counterion then occurred in a conjugate fashion to form enamine **122** as a mixture of *cis*-/*trans*-isomers.

2.2.4 α-Functionalisation of amines. In 2018, Wasa reported the redox neutral, B(C₆F₅)₃-catalysed α-functionalisation of *N*-alkylamines in a Mannich-type reaction (Schemes 24 and 25).³⁶ In this process, amines **124**, such as *N*-aryl cyclic amines and tertiary alkyl amines, were coupled to variety of α,β-unsaturated compounds **125**, including α,β-unsaturated esters, α,β-unsaturated nitriles, α,β-unsaturated thioesters, an acetylenedicarboxylate and a maleimide (Schemes 24a and 25a). The mechanism was proposed to proceed *via* B(C₆F₅)₃-mediated α-amino hydride abstraction in amine **124**, forming the iminium hydridoborate **127**. The hydride was transferred from the hydridoborate counterion in **127** to the α,β-unsaturated compound **125**, that is itself activated by a Lewis acid catalyst (see below), thus regenerating the B(C₆F₅)₃ catalyst. Using an α,β-unsaturated carbonyl as an example, the resultant enolate **129** (or related stabilised carbanions) attacked the iminium **130**, affording Mannich product **126**. In this strategy, B(C₆F₅)₃ had a dual role involving hydride abstraction as well as activating the α,β-unsaturated substrate (Scheme 24b, LA = B(C₆F₅)₃).

Impressively, Wasa also reported an enantioselective version of the reaction, where a variety of *N*-aryl pyrrolidines **124** and acryloyloxazolidinones **131** were coupled to form Mannich type products **132** with good diastereoselectivity and excellent enantioselectivity (Scheme 25). In this case, the Lewis acid co-catalyst (LA) was derived from Mg(OTf)₂ and chiral ligand **133**. The selective activation of the acryloyloxazolidinone Michael acceptors **131** by the chiral co-catalyst was crucial to enantioselectivity, and it was suggested that the high steric hindrance of B(C₆F₅)₃ limited its ability to coordinate to **131**.

Wasa and co-workers have also reported Mannich-type reactions involving silyl enol ethers **134** and iminium ions generated *via* borane-mediated hydride abstraction from *N*-alkylamines **124**

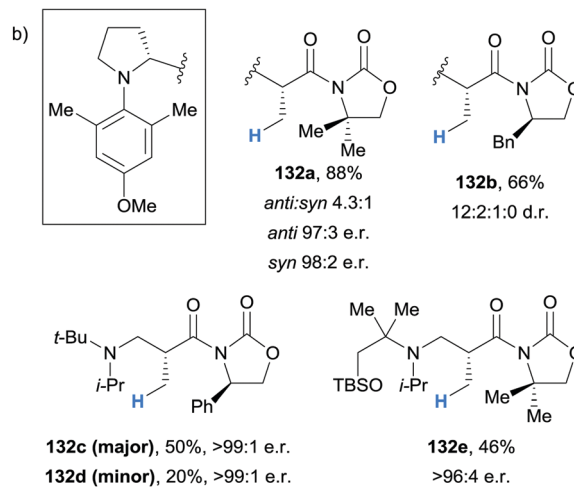
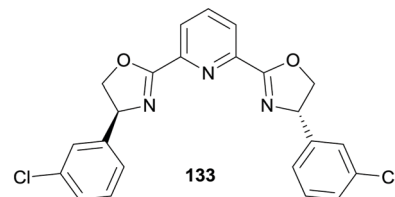
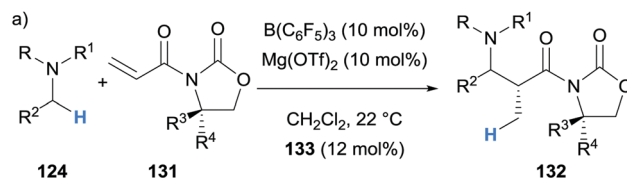




Scheme 24 Borane-mediated α -amino hydride abstraction utilised in a redox neutral, $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed α -functionalisation of *N*-alkylamines. LA = Lewis acid.

(Scheme 26a).³⁷ After generation of the iminium hydrido-borates **136**, nucleophilic silyl enol ethers **134** react to form a new C–C bond and form salt **137**. The hydrido-borate counterion in **137** was proposed to react with the silyl moiety, thus releasing the β -amino carbonyl product **135**, trimethylsilane and the $\text{B}(\text{C}_6\text{F}_5)_3$ catalyst (Scheme 26b). Various amines **124**, such as pyrrolidines, *N,N*-dialkylanilines and trialkylamines, were amenable to the process (Scheme 26c). The researchers applied this method to the synthesis of biologically important molecules such as the fluoxetine derivative **135c**, a known antidepressant.

Borane-mediated hydride abstraction has also been used in the synthesis of tetrahydroquinolines by the research groups of Grimme and Paradies,³⁸ and Wang³⁹ (Schemes 27 and 28, respectively). In both cases, $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed the efficient conversion of 2-amino styrenes **138** and **145** into tetrahydroquinolines

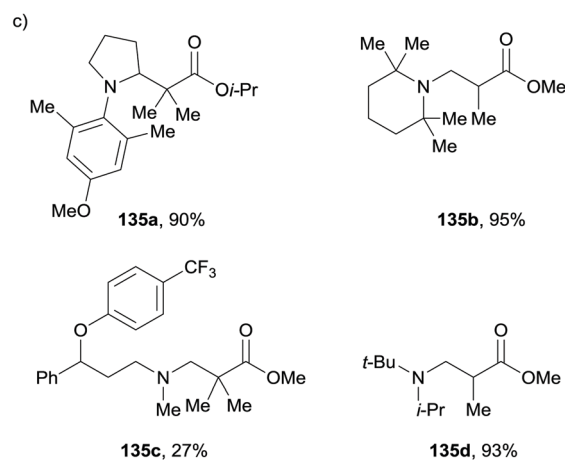
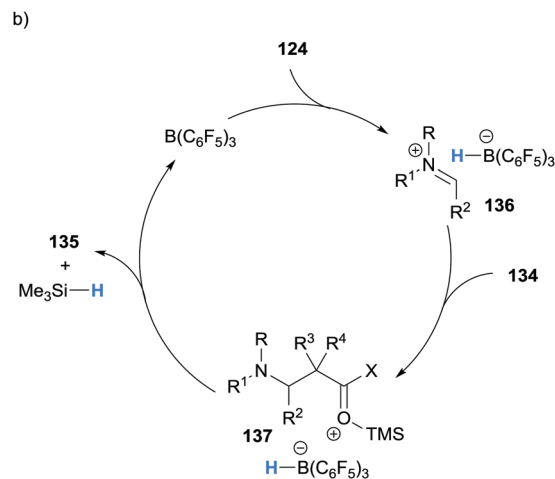
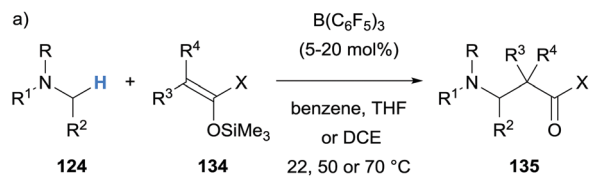


Scheme 25 Borane-mediated hydride abstraction utilised in a redox neutral, $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed asymmetric α -functionalisation of *N*-alkylamines.

139 and **146**. In the Grimme and Paradies study, the mechanism was investigated computationally, and it was proposed that after borane-mediated hydride abstraction to form iminium hydrido-borates **140**, a disrotatory 6π -electrocyclisation occurred to form cationic intermediates **141**. Hydride transfer from the hydrido-borate anions of **141** formed the desired heterocyclic products **139** and regenerated the $\text{B}(\text{C}_6\text{F}_5)_3$ catalyst (Scheme 27b). Products that bear β -amino C–H bonds, such as in **139a** and **139b**, were involved in an off-cycle equilibrium where further $\text{B}(\text{C}_6\text{F}_5)_3$ -mediated hydride abstraction formed enamines **143** and zwitterions **144** in a related process, as observed in other cases (*cf.* Scheme 6 above). However, NEt_3 was used in the work up which converted zwitterion **144** to product **139**. It was also shown that stabilisation of the benzylic carbocation in **141** was essential, as only substrates that formed tertiary carbocations were successful in the formation of tetrahydroquinolines **139**. Some substrates were prone to autoxidation during the workup (*cf.* **139b**).

In the Wang and co-workers $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed synthesis of tetrahydroquinolines, Me_3SiOTf (20 mol%) was used as an additive, and its role was to accept the hydride from the hydrido-borate counterion (Scheme 28). The weaker Lewis acidity of Me_3SiOTf facilitated subsequent donation of the hydride to the benzylic cation, which was determined to be the rate-limiting step.

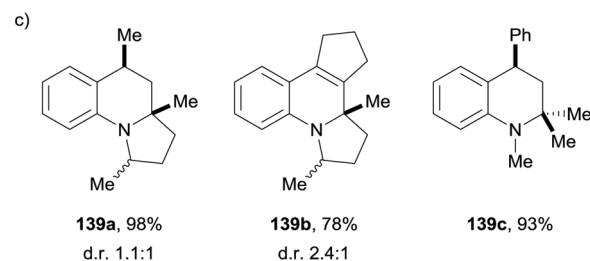
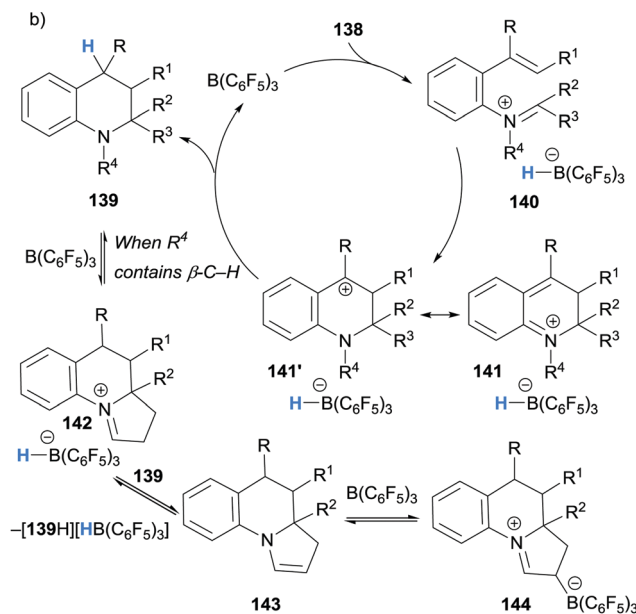
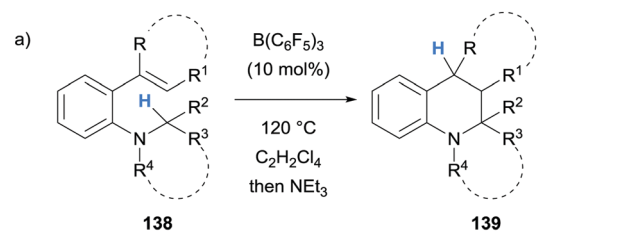




Scheme 26 Borane-mediated hydride abstraction utilised in an α -functionalisation of *N*-alkylamines using silyl enol ethers.

2.2.5 β -Functionalisation of amines. As described above, the resulting iminium hydridoborate salts generated after borane-mediated α -amino hydride abstraction often undergo deprotonation to form enamines (see above). The process is often reversible and does not interfere with the desired downstream reactivity. However, several reports have shown that the enamine can be utilised in borane-catalysed β -functionalisation of amines.

Chang and Park have described the $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed formation of polycyclic bridged sila-*N*-heterocycles **149** from *N*-aryl piperidines **147** and methyl phenyl silane (**148**) (Scheme 29).⁴⁰ Experimental⁴⁰ and theoretical⁴¹ studies have revealed a triple role for the $\text{B}(\text{C}_6\text{F}_5)_3$ catalyst. Firstly, $\text{B}(\text{C}_6\text{F}_5)_3$ mediates the hydride abstraction step that enables the formation of iminium hydridoborate **150** and subsequent formation of enamine **151**

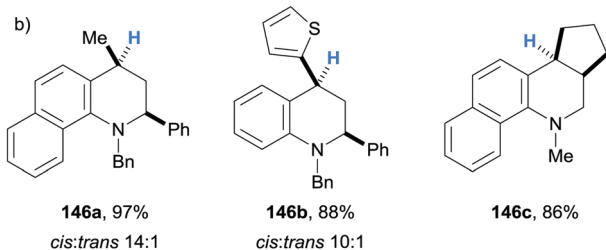
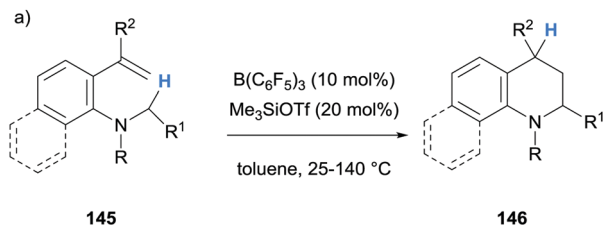


Scheme 27 Borane-mediated hydride abstraction utilised in the $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed synthesis of tetrahydroquinolines.

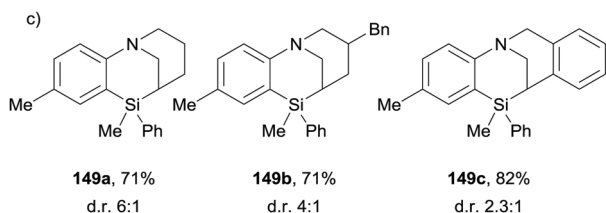
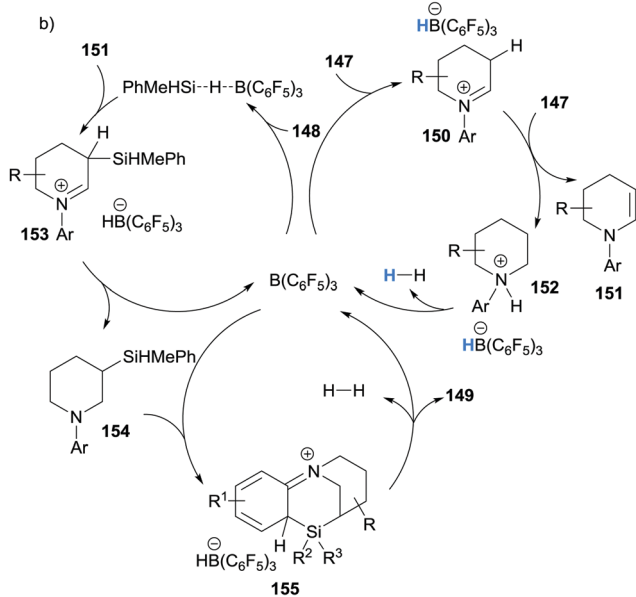
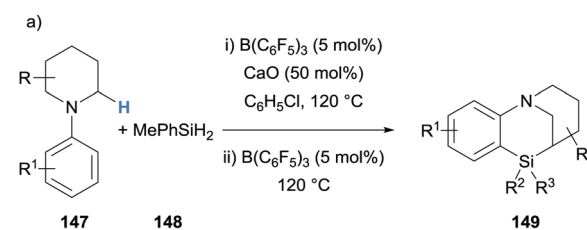
in a related process to that previously described (*cf.* Scheme 6). Piperidinium borohydride **152** then releases hydrogen to regenerate $\text{B}(\text{C}_6\text{F}_5)_3$. The second role of $\text{B}(\text{C}_6\text{F}_5)_3$ is to activate methyl phenyl silane (**148**) for nucleophilic addition by enamine **151**. Hydride transfer from the hydridoborate counterion to the iminium moiety in **153** provides amine **154**. Finally, $\text{B}(\text{C}_6\text{F}_5)_3$ activates the Si-H bond for electrophilic silylation of the aromatic ring in **154**, which subsequently releases hydrogen to form polycyclic bridged sila-*N*-heterocycles **149**. The additive CaO was used and proposed to assist with the proton transfer steps of the ionic cascade mechanism.

Ma and co-workers reported the β -alkylation of acyclic tertiary amines **156** with *para*-quinone methides **157** (Scheme 30).⁴² The $\text{B}(\text{C}_6\text{F}_5)_3$ -mediated hydride abstraction of amines **156** allowed for the formation of ammonium hydridoborate **160** and enamine **161**. Conjugate addition between the nucleophilic enamine **161**

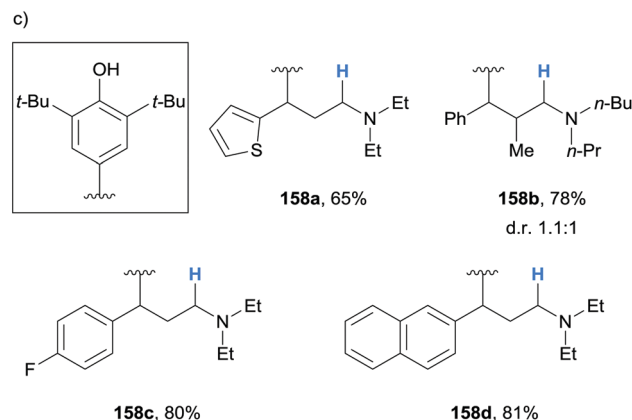
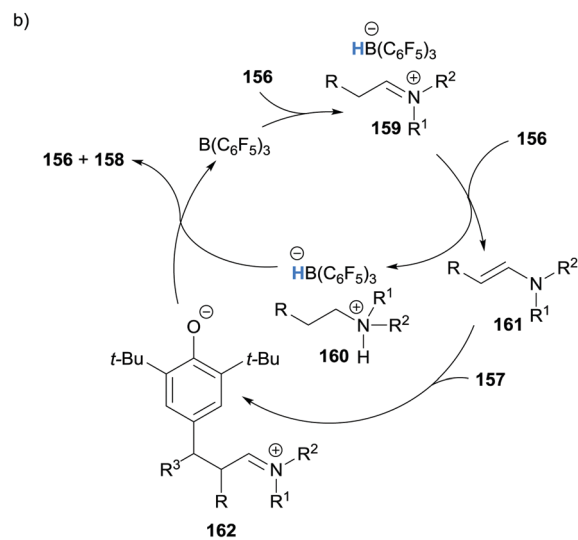
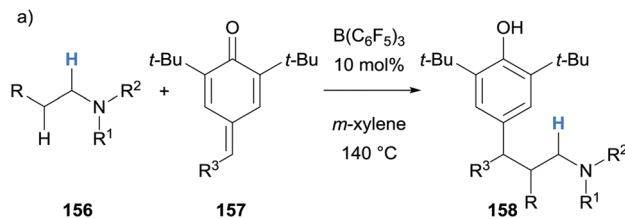




Scheme 28 Borane-mediated hydride abstraction utilised in the $\text{B(C}_6\text{F}_5)_3$ -catalysed synthesis of tetrahydroquinolines.



Scheme 29 Borane-mediated hydride abstraction utilised in a $\text{B(C}_6\text{F}_5)_3$ -catalysed silylative cascade.

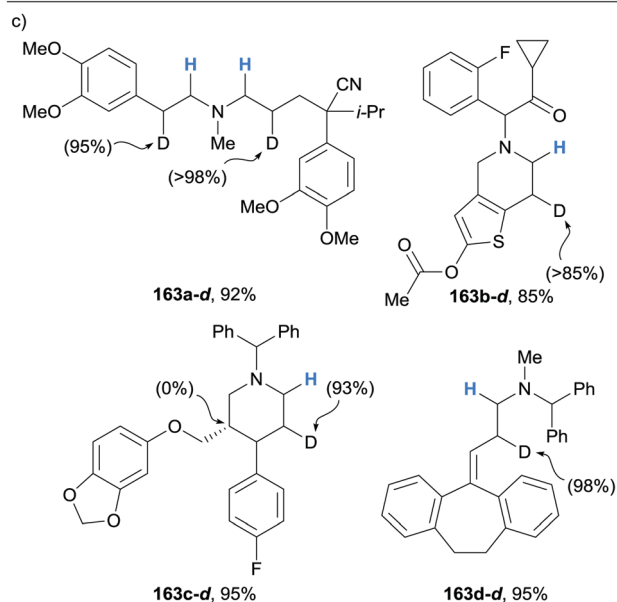
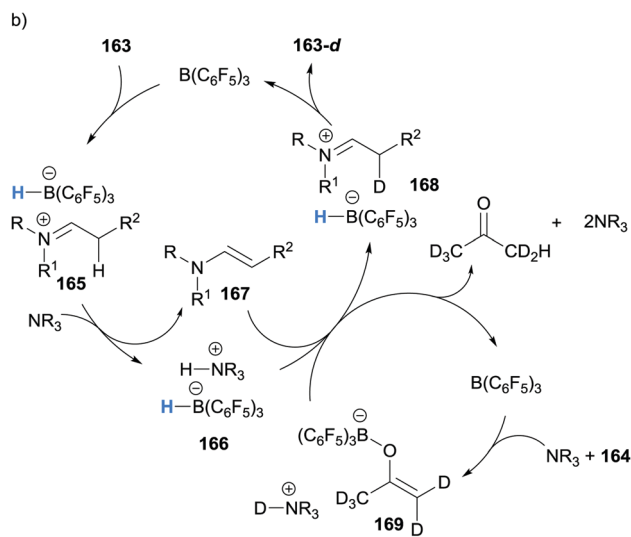
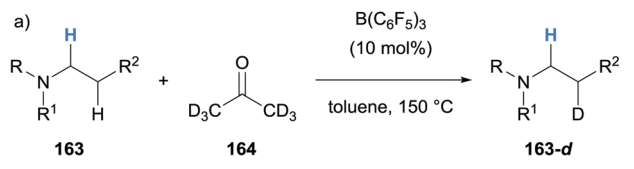


Scheme 30 Borane-mediated hydride abstraction utilised in a $\text{B(C}_6\text{F}_5)_3$ -catalysed β -amino alkylation.

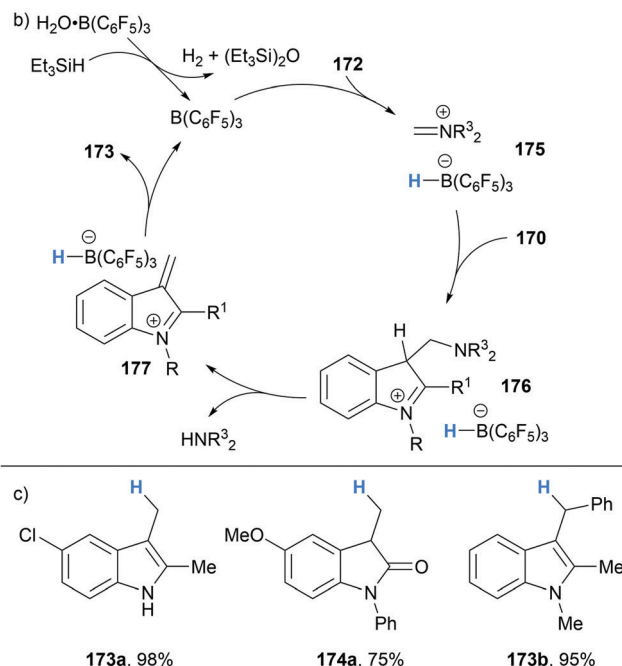
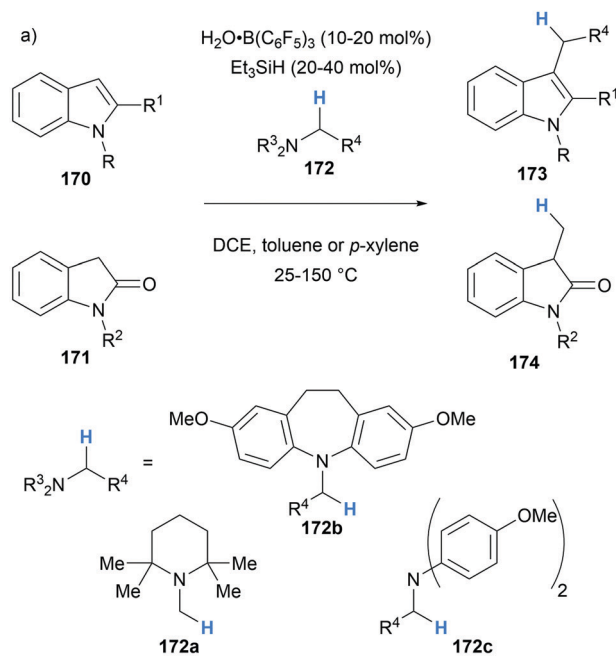
and *para*-quinone methide **157** occurred to produce iminium **162**. Protonation of **162** and hydride transfer from the ammonium hydridoborate **160** yielded β -functionalised product **158**. An unsymmetrical tertiary amine was reacted where β -functionalisation occurred preferentially on ethyl instead of the *n*-butyl chain.

In 2019, Wasa showed that borane-mediated α -amino hydride abstraction could be used to efficiently deuterate β -amino C-H bonds of *N*-alkylamines **163**, including pharmaceutical compounds (Scheme 31).⁴³ As seen before, $\text{B(C}_6\text{F}_5)_3$ mediated the formation of ammonium hydridoborate **166** and enamine **167**. It was proposed that $\text{B(C}_6\text{F}_5)_3$ also has the role of mediating FLP-like deprotonation of deuterated acetone (**164**) to form ammonium borate **169**, which serves as the deuterium source for the deuteration of enamine **167**. Impressively, pharmaceutically





Scheme 31 Borane-mediated hydride abstraction utilised in a $\text{B(C}_6\text{F}_5\text{)}_3$ -catalysed β -amino deuteration. Parenthesis refer to %D incorporation.



Scheme 32 Borane-mediated hydride abstraction utilised in a $\text{B(C}_6\text{F}_5\text{)}_3$ -catalysed alkylation of indoles and oxindoles.

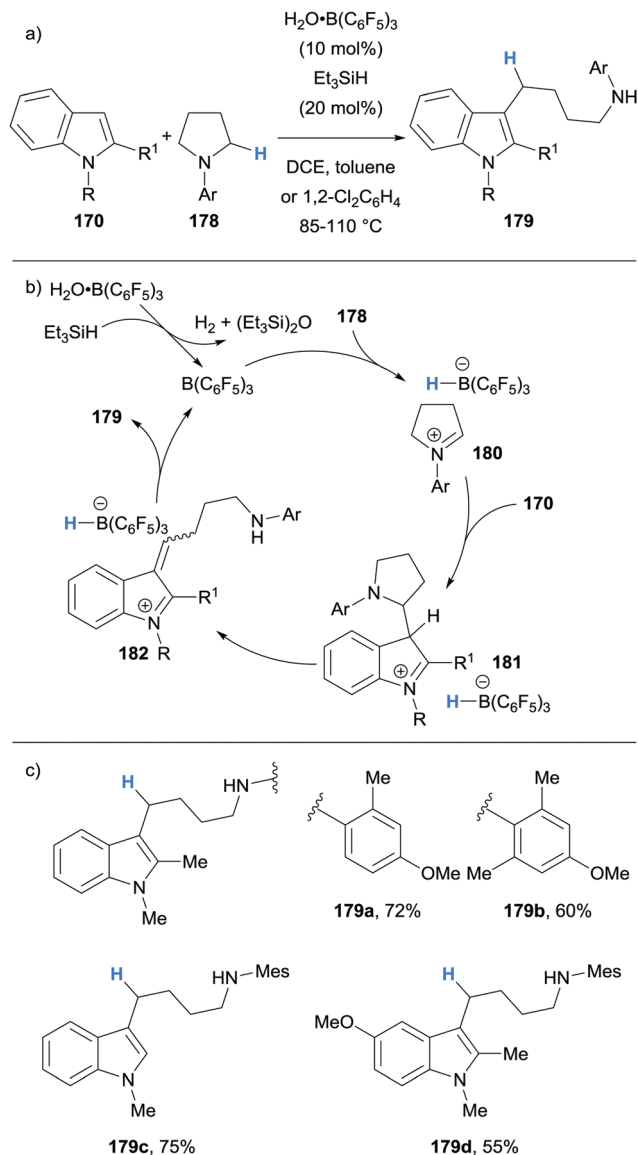
active compounds, with some containing Lewis acid-sensitive functional groups such as cyano, ester, amide and ketones, were successfully deuterated.

2.2.6 C–N bond cleavage. Borane-mediated hydride abstraction has also been used in challenging catalytic C–N bond breaking processes, such as in the use of amines as novel alkylating agents, and in the dealkylation of amines (including ring deconstruction).

In 2020, we reported the application of borane-mediated α -amino hydride abstraction in a $\text{B(C}_6\text{F}_5\text{)}_3$ -catalysed C3 alkylation

of indoles and oxindoles that utilised amine based alkylating agents (Scheme 32).⁴⁴ The mechanism was proposed to begin with the generation of iminium hydridoborate 175 after $\text{B(C}_6\text{F}_5\text{)}_3$ -mediated hydride abstraction of the alkylating agent 172. The iminium 175 underwent nucleophilic attack by the indole 170 (or oxindole 171) to form a new C–C bond. Subsequent proton transfers resulted in the formation of α,β -unsaturated iminium 177, presumably *via* an E1cB-like elimination. Hydride transfer from the hydridoborate counterion to 177 allowed the formation of alkylated indoles 173 (and oxindoles 174).

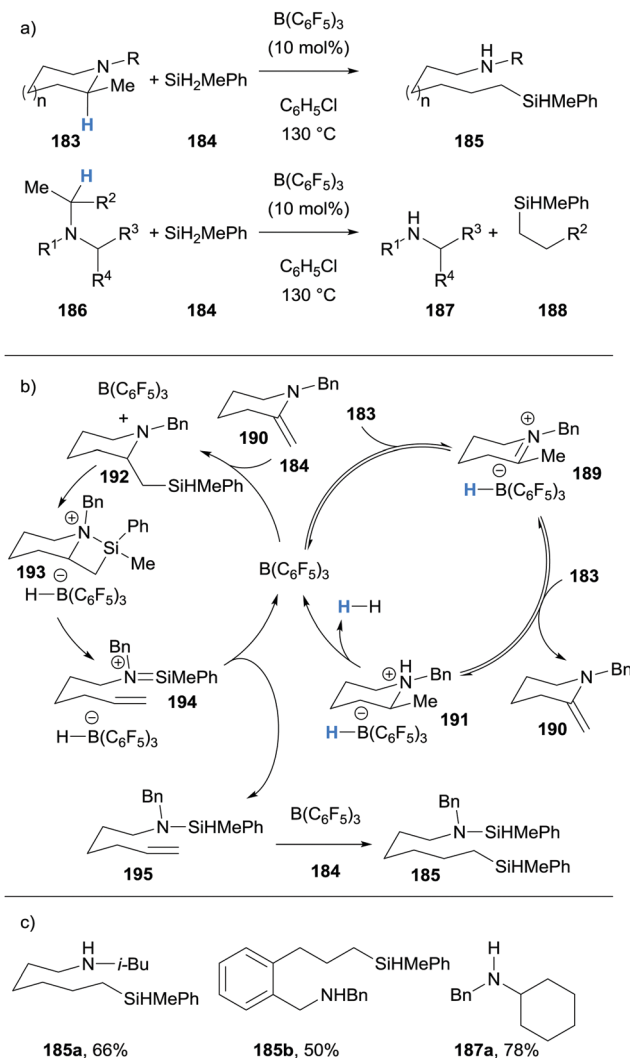




Scheme 33 Borane-mediated hydride abstraction utilised in a $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed alkylation-ring opening cascade.

In the same report, we also reported the use of borane-mediated hydride abstraction in a ring-opening cascade process between indoles **170** and pyrrolidines **178** to form 4-(3-indolyl)butylamines **179**, a privileged motif found in several serotonergic/dopaminergic drug molecules (Scheme 33).⁴⁴ The mechanism was proposed to proceed in a similar fashion to the previously described alkylation process (*cf.* Scheme 32), except the cyclic nature of amine **178** allowed for the amine portion to be retained in product **179** after elimination (Scheme 33). The use of Et_3SiH (20 mol%) serves to free the $\text{B}(\text{C}_6\text{F}_5)_3$ catalyst from its water adduct *in situ*. This modification allowed the authors to directly use $\text{B}(\text{C}_6\text{F}_5)_3$ as received from the supplier and weigh it in air on the open bench, thus negating the use of a glove box and additional catalyst purification.

Chang and co-workers described the use of borane-mediated hydride abstraction in a dehydrogenation/ β -silylation/C–N bond



Scheme 34 Borane-mediated hydride abstraction utilised in a $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed *cis*-silylative ring opening and tertiary amines deconstruction processes.

cleavage cascade process (Scheme 34).⁴⁵ Cyclic tertiary amines (**183**) underwent *cis*-silylative ring opening to form amines **185**, and tertiary amines (**186**) underwent deconstruction to form secondary amines **187** and alkyl silanes **188**. Impressively, $\text{B}(\text{C}_6\text{F}_5)_3$ has multiple roles in these processes. Using the *cis*-silylative ring opening to illustrate the mechanism, cyclic amines **183** undergo $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed dehydrogenation to form enamines **190** and ammonium hydridoborate **191** in the rate limiting step. $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed β -silylation of enamines **190** with silanes **184** then gave silylated amine **192**. Amine **192** is predisposed to form silazetidinium intermediate **193** *via* $\text{B}(\text{C}_6\text{F}_5)_3$ -mediated activation of the Si–H bond. Cycloreversion cleaved the C–N bond in **193** and gave **194**, which after hydride transfer from the hydridoborate counterion, gave amino alkene **195**. $\text{B}(\text{C}_6\text{F}_5)_3$ -catalysed hydrosilylation of the alkene moiety in **195** allowed the formation of product **185**. Interestingly, theoretical and experimental investigations revealed that borane-mediated hydride abstraction preferentially occurred at the more substituted carbon of the



ring (*cf.* formation of **189**) and that *exo*-enamine **190** formation was more favoured than the corresponding *endo*-enamine.

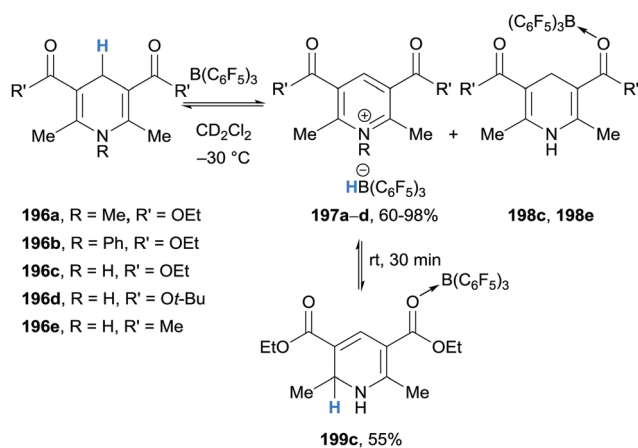
3 Borane-mediated γ -amino hydride abstraction

In contrast to α -amino hydride donors, donation from a γ -amino conjugated C–H bond will be more familiar. 1,4-Dihydropyridines are well studied hydride donors in both a biological (*e.g.* NADH) and chemical (*e.g.* Hantzsch esters) setting.¹ However, γ -hydride abstraction of conjugated amines with boranes has received relatively little attention. In this section, stoichiometric investigations of hydride abstraction from 1,4-dihydropyridines and 2-alkylideneimidazolines will be discussed. An application of this reactivity in transfer hydrogenation will also be included.

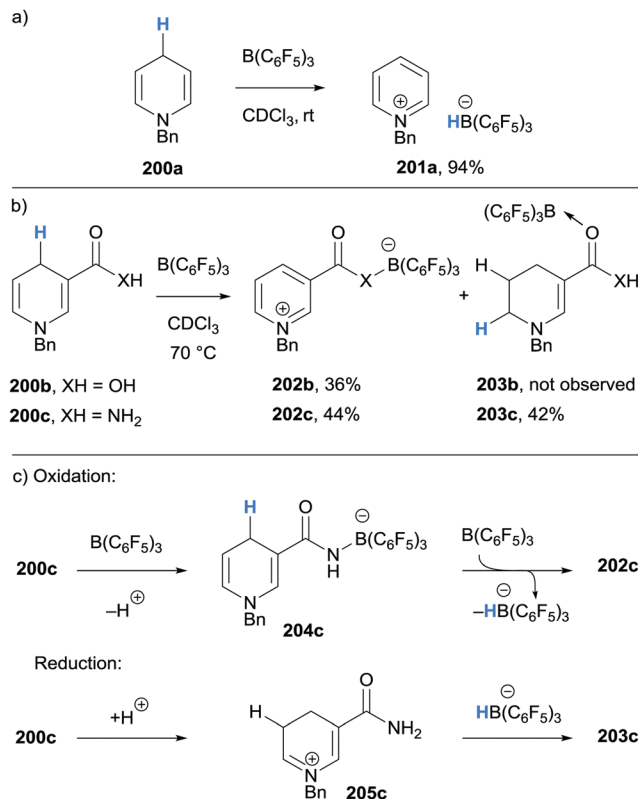
3.1 Stoichiometric studies

3.1.1 1,4-Dihydropyridines. In 2010, Crudden, Stephan and co-workers studied the $B(C_6F_5)_3$ -mediated hydride abstraction in a series of Hantzsch ester analogues **196a–196e** (Scheme 35).⁴⁶ Hantzsch esters **196a–196d** underwent γ -amino hydride abstraction to form pyridinium hydridoborates **197a–197d** in good yields at low temperatures. The $B(C_6F_5)_3$ adduct **198c** of the Hantzsch ester **196c** was also observed. In the case of the keto derivative **196e**, only the $B(C_6F_5)_3$ adduct **198e** was observed. Upon warming the pyridinium hydridoborates **197a–197d**, the $B(C_6F_5)_3$ adduct of 1,2-dihydropyridines **199** were formed, presumably *via* hydride transfer from the hydridoborate counterion to the pyridinium cation *via* 1,2-addition.

Inspired by the naturally occurring organic hydride donor NAD(P)H, Melen and co-workers studied the $B(C_6F_5)_3$ -mediated hydride abstraction of *N*-benzyl-1,4-dihydropyridine derivatives (**200a–200c**).⁴⁷ The reaction between *N*-benzyl-1,4-dihydropyridine **200a** and $B(C_6F_5)_3$ afforded pyridinium borohydride **201a** in excellent yield *via* γ -amino hydride abstraction (Scheme 36a). A similar outcome was observed when carboxylic acid substituted 1,4-dihydropyridine **200b** was treated with $B(C_6F_5)_3$ (Scheme 36b).



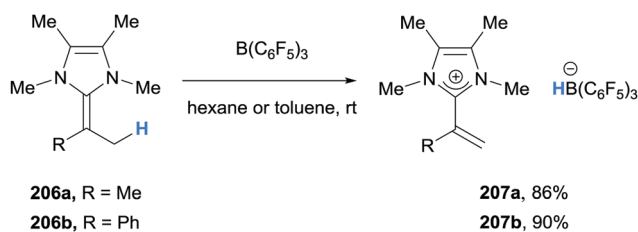
Scheme 35 Borane-mediated γ -amino hydride abstraction from Hantzsch ester derivatives.



Scheme 36 Borane-mediated γ -amino hydride abstraction from 1,4-dihydropyridine derivatives.

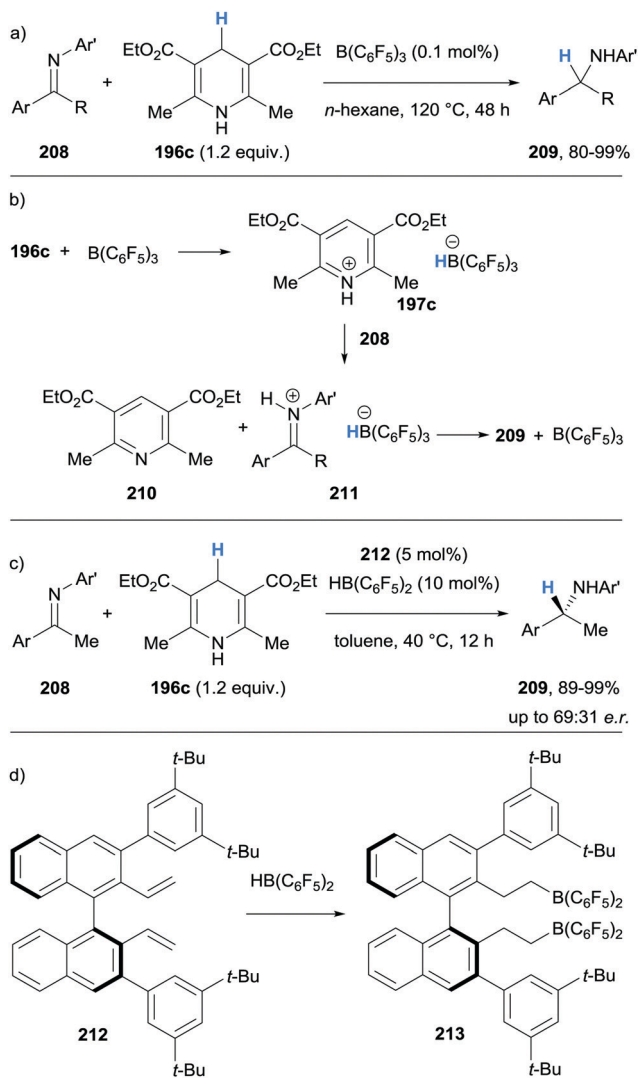
Interestingly, when nicotinamide derivative **200c** was reacted with $B(C_6F_5)_3$, a disproportionation was observed and pyridinium borate zwitterion **202c** and $B(C_6F_5)_3$ coordinated 1,2-dihydropyridine **203c** were formed. The mechanism, supported by deuterium labelling experiments, was proposed to involve initial coordination of $B(C_6F_5)_3$ to nicotinamide derivative **200c** to acidify the N–H bond and allow protonation of another molecule of **200c** (Scheme 36c). Borane-mediated hydride abstraction then formed a hydridoborate counterion that transfers a hydride to the iminium moiety in **205c**.

3.1.2 2-Alkylideneimidazoline. In 2013, Tamm and co-workers widened the scope of borane-mediated γ -amino hydride abstraction to include acyclic enamines. When 2-alkylideneimidazoline derivatives **206a–206b** that possess γ -amino $C(sp^3)$ -H bonds were reacted with $B(C_6F_5)_3$, 2-vinylimidazolium hydridoborates **207a–207b** were formed (Scheme 37).⁴⁸



Scheme 37 Borane-mediated γ -amino hydride abstraction from 2-alkylideneimidazolines.





Scheme 38 Borane-mediated γ -amino hydride abstraction from Hantzsch esters utilised in the $B(C_6F_5)_3$ -catalysed transfer hydrogenation of imines.

3.2 Catalytic applications

3.2.1 Transfer hydrogenation. Related to Crudden, Stephan and co-workers' study of borane-mediated γ -amino hydride abstraction involving Hantzsch esters, Du and co-workers reported the $B(C_6F_5)_3$ -catalysed transfer hydrogenation of imines (Scheme 38).⁴⁹ Remarkably, as little as 0.1 mol% loading of $B(C_6F_5)_3$ was effective. The key iminium hydridoborate salt **211**, formed after borane-mediated hydride abstraction and proton transfer, was proposed to be the key intermediate where hydride transfer occurs from the hydridoborate counterion to the electrophilic iminium.⁵⁰ Furthermore, work towards an enantioselective transfer hydrogenation of imines **208** was also reported, whereby an enantiomerically enriched borane **213** was used as a catalyst. Borane **213** was formed *in situ* hydroboration of divinyl BINAP derivative **212** with $HB(C_6F_5)_2$.

4 Summary and outlook

Borane-mediated hydride abstraction has been observed in a variety of amino substrates. The most common substrate class reported are amines that bear α -amino C–H bonds where, in stoichiometric studies, iminium hydridoborates have been observed. There are a variety of chemical reactions that the iminium hydridoborate generated can undergo, which include proton transfers to form enamines, nucleophilic addition to the electrophilic iminium, and further hydride transfers.

Due to the array of reactions that both the iminium and hydridoborate ions can undergo, borane-mediated hydride abstraction has been employed as a key event in many powerful borane-catalysed processes. These include novel strategies for reagent activation, such as the use of amines as H_2 surrogates in transfer hydrogenation, and as alkylating agents. In addition, new methods for the manipulation of amines, including dehydrogenation, racemisation, isomerisation, α - and β -functionalisation, and C–N bond cleavage have all been reported. The application of these methods in synthesis has demonstrated the high functional group tolerance possible in processes involving borane-mediated hydride abstraction. Borane-mediated hydride abstraction involving γ -amino conjugated C–H bonds has also been reported.

Borane-mediated hydride abstraction is a relatively young field and there is no doubt that advances will continue to be made. By far the most commonly used borane has been $B(C_6F_5)_3$, likely because it is commercially available, robust and well-established use in the borane catalysis arena. However, we expect that optimisation of the borane structure will be a fruitful endeavour with respect to tuning regio- and chemo-selectivity. In addition, asymmetric processes are poorly represented with respect to borane-mediated hydride abstraction and we anticipate growth in this area. Furthermore, expansion of the amine scope with respect to other classes of conjugated amines may lead to valuable methods involving remote functionalisation. Given the great interest, especially from the pharmaceutical industry,^{6,7} in efficient synthetic methods that manipulate C–H bonds of amines, borane-mediated hydride abstraction will continue to be exploited in novel processes.

Conflicts of interest

There are no conflicts to declare.

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