Synlett J. P. Gillions et al. THIEME OPEN ACCESS Cluster Account

Recent Advances in Catalysis Using Organoborane-Mediated Hydride Abstraction

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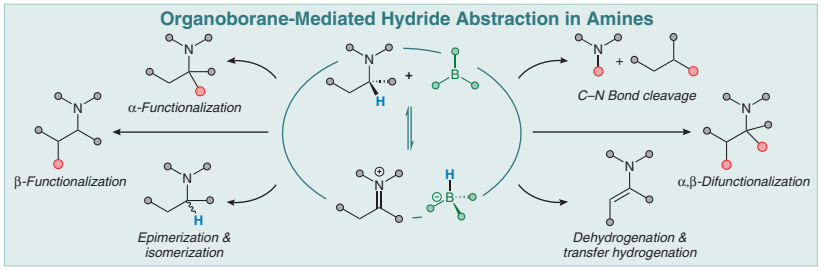


Dedicated to 60 years of Donald Matteson's boron homologation

Published as part of the Cluster
Modern Boron Chemistry: 60 Years of the Matteson Reaction

Received: 31.05.2023
Accepted after revision: 14.06.2023
Published online: 16.06.2023 (Accepted Manuscript), 04.09.2023 (Version of Record)
DOI: 10.1055/a-2111-9629; Art ID: ST-2023-05-0242-NT

Crowd-Reviewed

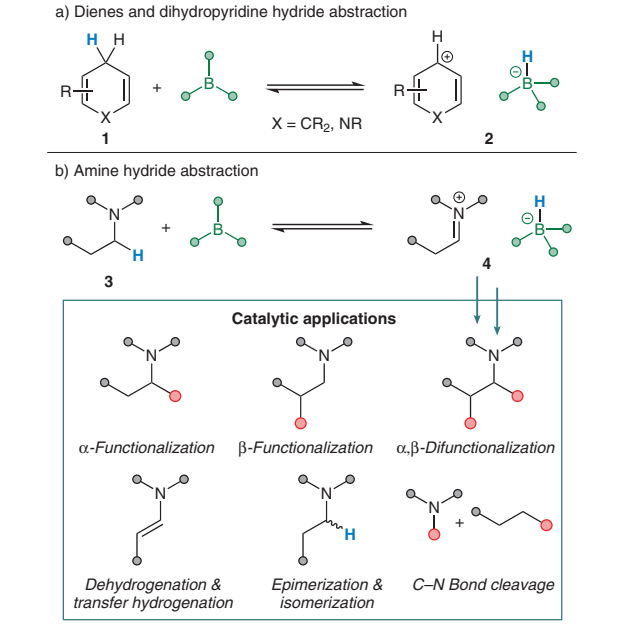
Abstract C–H functionalization is widely regarded as an important area in the development of synthetic methodology, enabling the design of more time- and atom-efficient syntheses. The ability of electron-deficient organoboranes to mediate hydride abstraction from α-amino C–H bonds is therefore of great interest, as the reactive iminium and hydridoborate moieties generated are able to participate in a range of synthetically useful transformations. In this review, we cover the recent advances made in organoborane-mediated hydride abstraction, and focus on the catalytic applications of electron-deficient boranes in α- or β-functionalization, α,β-difunctionalization, and the dehydrogenation of amines.

Key words boron, hydride abstraction, amines, iminium, functionalization

1 Introduction

Organoboranes are widely used as reagents and building blocks in synthetic chemistry. For example, hydroboranes and borohydrides are often used in reduction chemistry, whereas boronic acids are commonly employed in cross-coupling processes.[1,2] The use of organoboranes as catalysts has also received significant attention whereby the interaction of the Lewis acidic boron atom with a pair of non-bonding electrons or π-electron pairs is employed to activate the substrate.[3–5] Recent attention has focused on more electron-deficient organoboranes, such as $B(C_6F_5)_3$, in catalysis. These more Lewis acidic species can also interact with σ(C–H) bonds, resulting in hydride abstraction and the formation of a formal carbocation and a borohydride counterion.[6–8] When the C–H-bearing substrate is a cyclohexadiene, Wheland-type intermediates are formed,[9–12] and when dihydropyridines are used, pyridinium salts form (Scheme 1a).[13,14] The most explored reactions of this type are those that involve organoborane-mediated hydride abstraction from α-amino C–H bonds, during which iminium borohydride salts 4 are generated (Scheme 1b).

Organoborane-mediated hydride abstraction has been exploited in a variety of reactions that generate iminium salts in situ directly from the corresponding alkyl amines and include organoborane-catalyzed amine-based transfer hydrogenation and dehydrogenation, racemization and isomerization, α-functionalization, β-functionalization, dual α,β-functionalization, and C–N bond cleavage. In this review, we include new developments in organoborane-catalyzed processes involving organoborane-mediated hydride abstraction in amines that have been disclosed since our previous review.[6,15–17] New reactions herein include examples that generate complex amine products via cooperative organoborane-metal catalysis, incorporate hydride shuttles, lead to multifunctionalizations, and allow dehydrogenation of liquid organic hydrogen carriers. We will



Scheme 1 Borane-mediated hydride abstraction forms Wheland intermediates, pyridinium borohydrides, or iminium borohydrides

highlight key features of the reactions and discuss the mechanisms in the context of the fate of the iminium ion and how the borohydride reacts to allow catalyst turnover.

2 α-Functionalization of Amines

In our previous review[6] we reported studies whereby organoboranes catalyze the α-functionalization of amines. $B(C_6F_5)_3$-mediated α-amino $C(sp^3)$–hydride abstraction was shown to result in the formation of hydridoborate and iminium ions, which can be intercepted by various nucleophiles to result in formal α-*N* C–H functionalization processes with amines. In this review, we cover the reports since our prior review, which include α-alkynylation, α-furylation, and cyclization reactions.

In 2020, Wasa and co-workers reported the conversion of *N*-alkylamines **5** and alkynyl trimethylsilanes **6** into propargyl amines **7** via dual Lewis acid/organocopper catalysis (Scheme 2).[18] The catalyst system employed was composed of $B(C_6F_5)_3$ and $Cu(MeCN)_4PF_6$ in combination with various ligands such as (*S*)-Ph-PyBOX (**9a**), (*S*)-(3,5-Me_2-C_6H_3)-PyBOX (**9b**), or 1,2-bis(diphenylphosphino)ethane (**9c**). The

Biographical Sketches

from left to right

Joseph P. Gillions completed his MChem degree with a Year in Industry in 2020 at the University of York and GlaxoSmithKline. Joe is currently studying for his PhD at the University of Leicester with Dr Alex Pulis where he is working on new catalytic methodology for the functionalisation of amines.

Salma A. Elsherbeni received a Masters in Pharmaceutical Sciences at Tanta University (Egypt) and is now pursuing a PhD in Chemistry at Cardiff University.

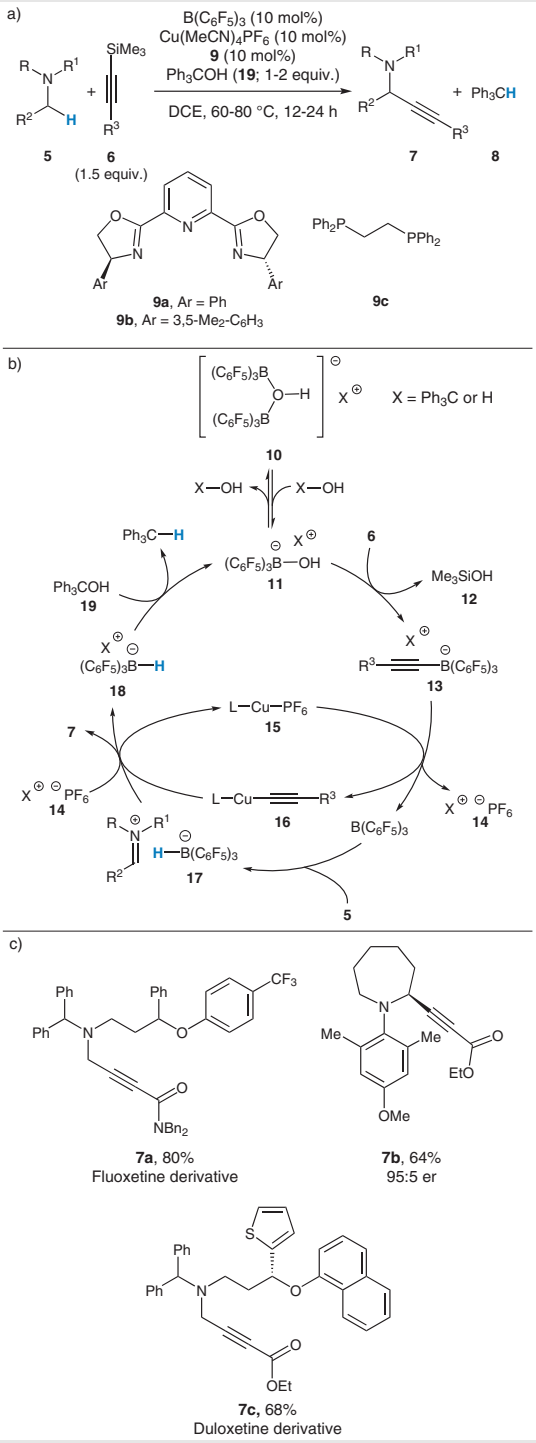
Laura Winfrey completed her MChem degree with a year abroad in 2019 at the University of Leicester (UK) and Kent State University (USA). Laura is currently studying for her PhD at the University of Leicester with Dr Alex Pulis focused on new catalytic methods for the synthesis of amines.

Lei Yun complete his Masters degree at the Dalian University of Technology (China) in 2021. Lei is now studying for his PhD in the Pulis Group at the University of Leicester funded by the China Scholarship Council. He is working on boron-catalyzed functionalisation of bioactive amines.

Prof. Rebecca Melen studied for her undergraduate and Ph.D. degrees at the University of Cambridge, completing her Ph.D. in 2012 with Prof. Wright. Following postdoctoral studies with Prof. Stephan in Toronto and with Prof. Gade in Heidelberg, she took up a position at Cardiff University in 2014, where she is now a Professor in inorganic chemistry. In 2018, she was awarded an EPSRC early career fellowship, and she is the recipient of the 2019 RSC Harrison Meldola Memorial Prize and a 2022 Philip Leverhulme Prize in Chemistry. Her research interests lie in main group chemistry and the applications of main group Lewis acids in synthesis and catalysis.

Louis Morrill received his PhD from the University of St Andrews in 2014 under the direction of Prof. Andrew Smith and undertook postdoctoral 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.

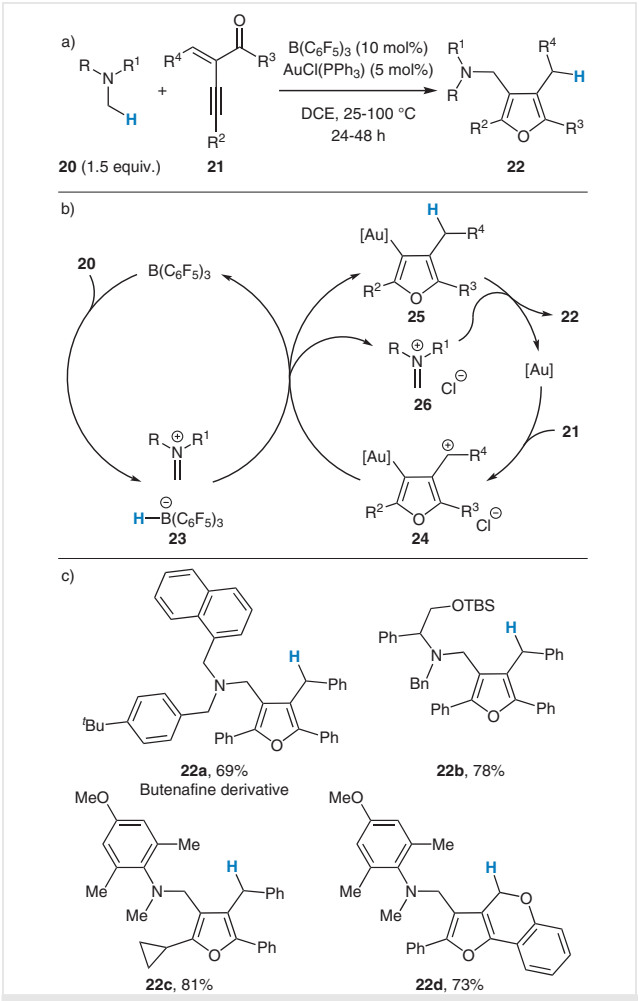
Dr Alex Pulis obtained his PhD from the University of Bristol (UK) under the guidance of Prof. Varinder K. Aggarwal. In 2014, he joined Prof. Douglas Stephan at the University of Toronto (Canada) for postdoctoral studies. He then moved to the University of Manchester (UK) as a fixed term Lecturer within 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 finding to challenges in chemical synthesis.



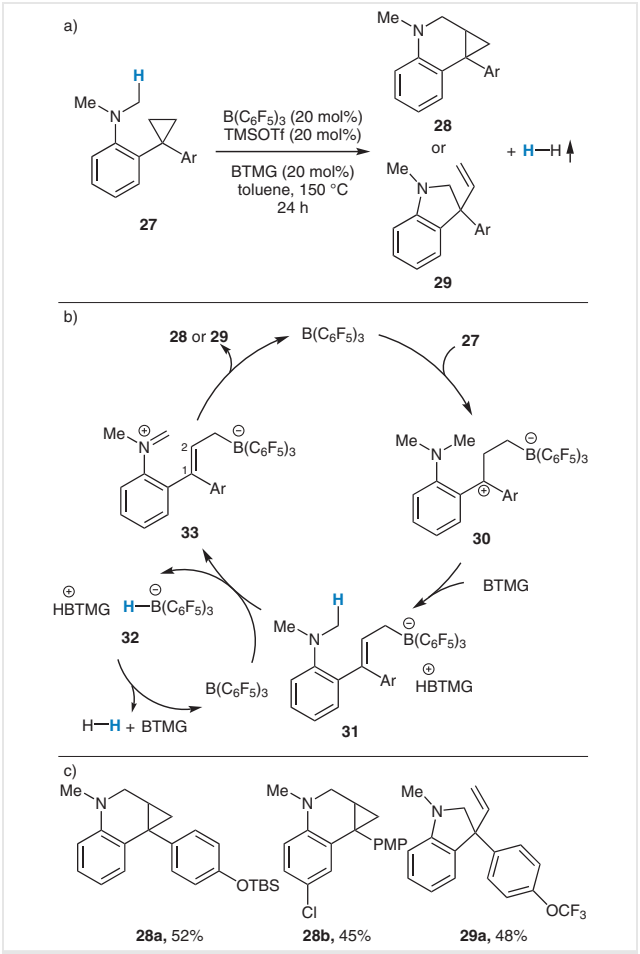
Scheme 2 Borane-mediated hydride abstraction for the direct conversion of *N*-alkylamines into *N*-propargylamines; DCE = 1,2-dichloroethane

proposed reaction mechanism is initiated by conversion of **10** into borate ion pair **11** in the presence of trityl alcohol or water. Ligand exchange in **11** with alkynyl silane **6** generates trimethylsilanol (**12**) and alkynyl borate **13**. Subsequent transmetalation generates an alkynyl copper intermediate **16** in addition to $B(C_6F_5)_3$, which abstracts a hydride from the α-*N* position within amine **5** to generate the iminium hydridoborate ion pair **17**. Addition of the alkynyl copper intermediate **16** to the iminium ion produces *N*-propargylamine **7**, while the hydridoborate ion reacts with trityl alcohol **19** to regenerate **11** and complete the catalytic cycle. Impressively, this approach enabled the derivatization of a wide range of *N*-protected bioactive molecules, such as the antidepressants fluoxetine (cf. **7a**) and duloxetine (cf. **7c**). The protocol tolerated a range of functional groups, such as protected alcohols, amides, esters, and halogens. For amine substrates with multiple sites of potential hydride abstraction, the regioselectivity of propargylation was attributed to the rapid consumption of short-lived CH_2 iminium ions (derived from $B(C_6F_5)_3$-mediated hydride abstraction at *N*-Me sites) before isomerization to lower energy iminium ions can occur. Furthermore, through employing chiral PyBOX ligand **9b**, a variety of *N*-propargylamines (e.g., **7b**) could be accessed with high levels of enantiocontrol (up to 94% ee).

In 2022, Wang and co-workers reported the α-furylation of *N*-methyl-substituted tertiary amines using a borane/gold(I) co-catalytic system (Scheme 3).[19] It was found that a range of tertiary *N*-methylamines **20** and α-alkynylenones **21** could be converted into substituted furans **22** in the presence of $B(C_6F_5)_3$ and $AuCl(PPh_3)$ catalysts. α-Furylation occurred regioselectively at *N*-methyl groups in the presence of *N*-benzyl groups. The mechanism was proposed to proceed via $B(C_6F_5)_3$-mediated α-amino hydride abstraction to form an iminium hydridoborate ion **23** with concurrent gold-promoted cycloisomerization of α-alkynylenone **21** to produce an [Au]-associated furyl 1,3-dipole **24**. Borohydride reduction of the furyl cation forms furyl species **25**, which then adds to the iminium ion **26** to produce the observed α-amino furylation product **22**, whilst regenerating the borane and gold catalysts. The procedure could be applied to a range of compounds, including bioactive compounds such as butenafine to yield derivative **22a**. The reaction showed good functional group tolerance, including protected alcohols **22b**, ethers **22c**, trifluoromethyl groups, and halogens. When the iminium ions contained β-protons, enamine intermediates were formed and engaged the aurated furans in [3+2] cycloadditions resulting in α- and β-functionalization (see Section 4).



Scheme 3 Borane-mediated hydride abstraction utilized in the α-furanylation of amines



Scheme 4 Borane-mediated hydride abstraction utilized in the cyclization of cyclopropyl anilines

In 2021, Wang and co-workers reported the synthesis of *N*-heterocycles **28** and **29** via the $B(C_6F_5)_3$-catalyzed dehydrogenative cyclization of 2-cyclopropyl-*N*,*N*-dimethylanilines **27** (Scheme 4).[20]

Their protocol combined $B(C_6F_5)_3$-mediated hydride abstraction with the $B(C_6F_5)_3$-catalyzed cyclopropane-ring opening previously reported by Wang's group in 2017.[21] Initially, $B(C_6F_5)_3$ opens the cyclopropane ring to form zwitterion **30**, before deprotonation by Barton's base (2-*tert*-butyl-1,1,3,3-tetramethylguanidine) (BTMG) yields alkene **31**. $B(C_6F_5)_3$-mediated abstraction of the α-*N* $C(sp^3)$–H hydride of the aniline then yields zwitterionic intermediate **33**. Finally, intramolecular attack of the alkene moiety on the iminium yields the cyclization products **28** or **29**. Electron-donating groups on the non-aniline aryl group promoted attack through the terminal alkenyl carbon (C2 of **33**) to yield 1,2,3,4-tetrahydroquinolines **28**. $B(C_6F_5)_3$ is regenerated via an acid–base reaction within guanidinium borohydride salt **32**, generating H_2. Electron-withdrawing groups gave mixtures of 1,2,3,4-tetrahydroquinolines **28** and indolines **29** (often the major product), formed by attack of the alkene through the benzylic carbon (C1) of the allylic borate. Functional group compatibility was demonstrated with, for example, protected phenol (**28a**), halide (**28b**), and trifluoromethyl ether (**29a**) substituents.

In 2022, Maulide and co-workers reported the stereoselective synthesis of a variety of azabicyclic structures **36** from enamines **34** (derived from *N*-heterocycles) and Michael acceptors **35** (Scheme 5).[22] Initially, the two substrates, enamine **34** and Michael acceptor **35**, react to form iminium **37**. A mixture of $B(2,6\text{-}F_2C_6H_3)_3$ and the corresponding tetrabutylammonium borohydride salt effectively isomerizes iminium ion **38** to form iminium **41** via a sequence of hydride donation to form **39** followed by hydride abstraction. A similar isomerization was also proposed by Oestreich in the β,β′-H silylation of tertiary amines described below (see Scheme 9). Interestingly, the Lewis acid $B(2,6\text{-}F_2C_6H_3)_3$ is significantly less electron-deficient than $B(C_6F_5)_3$, which is almost exclusively used in organoborane-

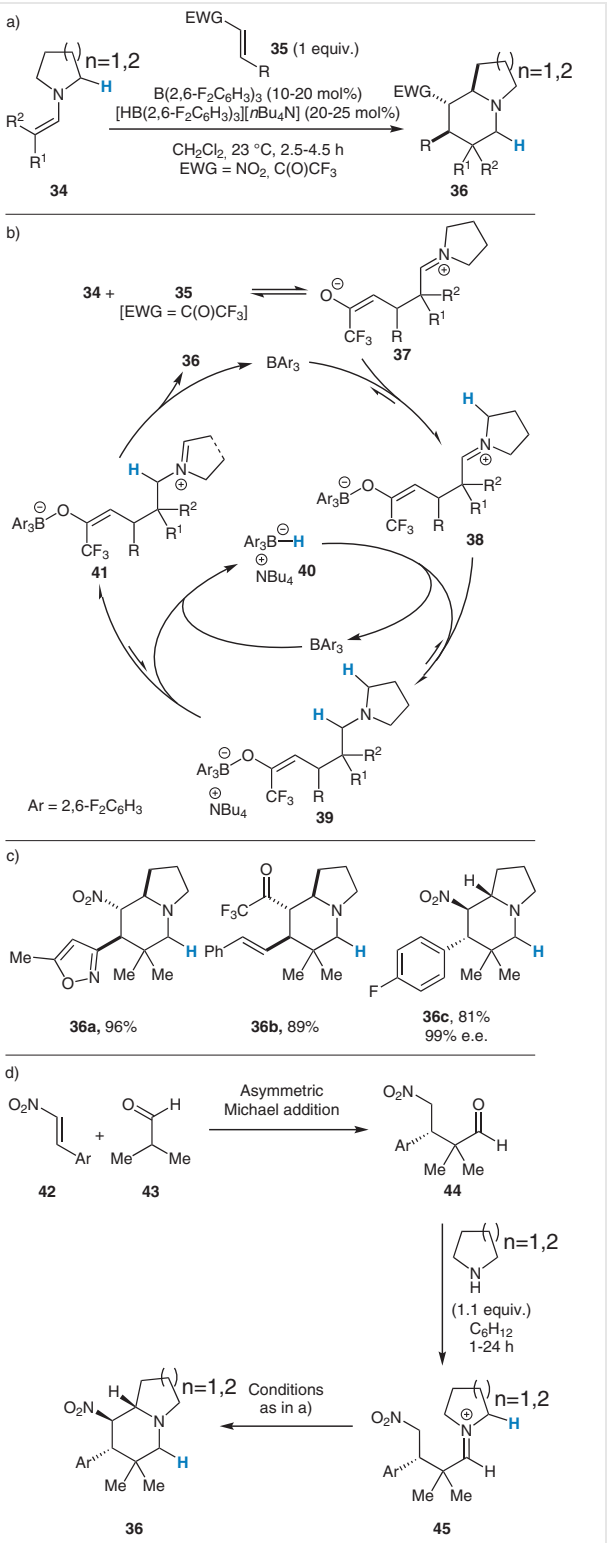
mediated hydride abstraction with amines. Other organoboranes, including $B(C_6F_5)_3$, $BMes(2,6\text{-}F_2C_6H_3)_2$ and BPh_3, failed to yield the desired products, whilst $B(2,4,6\text{-}F_3C_6H_2)_3$ gave yields of <10%. With the iminium in the correct position, cyclization occurs to give the desired aza-bicycles **36** as single diastereomers in most cases. The reaction tolerated a range of substituents on the Michael acceptor **35** and enamine **34**, including different heterocycles (e.g., **36a**), ethers, halides and protected alcohols. Nitro or trifluoromethyl ketones could also act as the electron-withdrawing group in **35**. Acyclic enamines were amenable to the method, forming highly substituted monocyclic piperidines. Additionally, it was shown that the process could be telescoped from the aldehyde and amine corresponding to the enamine. Impressively, an enantioselective variant was also reported, whereby an enantioselective organocatalyzed Michael addition yielded enantioenriched aldehyde **44** prior to formation of iminium **45**. Lewis acid/borohydride catalysis enabled the formation of azabicyclic products (e.g., **36c**) with very high enantioselectivity.

3 β-Functionalization of Amines

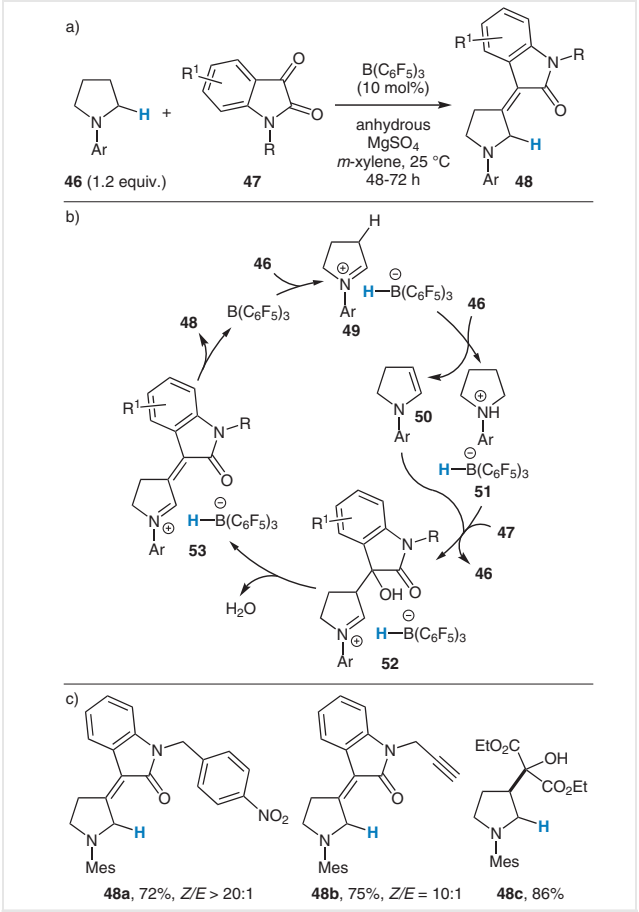
Our previous review covered organoborane-catalyzed β-functionalization of amines, describing reactions such as β-silylation, β-alkylation, and β-deuteration.[6] These reactions occur when the iminium species formed upon hydride abstraction undergoes deprotonation at the β-position, yielding reactive enamines. These enamines are capable of acting as nucleophiles, which, if an appropriate electrophile is available, can lead to β-functionalization. In this review, we cover new β-functionalizations with isatins and Michael acceptors, as well as β-silylation.

Yang, Ma and co-workers reported the β-functionalization of pyrrolidines **46** with isatins **47** to give substituted pyrrolidines **48** (Scheme 6).[23] The catalytic cycle proceeds via $B(C_6F_5)_3$-mediated abstraction of the α-*N* $C(sp^3)$–H hydride on pyrrolidine **46**. The β-proton of the resultant iminium **49** is then removed to form enamine **50** and ammonium borohydride salt **51**. Enamine **50** attacks the isatin **47** to form a new C–C bond in **52**. Elimination of water then forms unsaturated species **53**. Reduction of the iminium moiety in **53** with the hydride from the borohydride counterion forms β-functionalized product **48** and regenerates the $B(C_6F_5)_3$ catalyst. The reaction demonstrated good stereoselectivity and tolerated various functional groups such as halides, nitro groups (e.g., **48a**), *N*-branched alkenes and alkynes (e.g., **48b**). The use of diethyl ketomalonate rather than isatin **47** furnished product **48c**, where water was not eliminated. It was also possible to dehydrogenate the pyrrolidine products **48** to form pyrroles in situ (see Section 5).

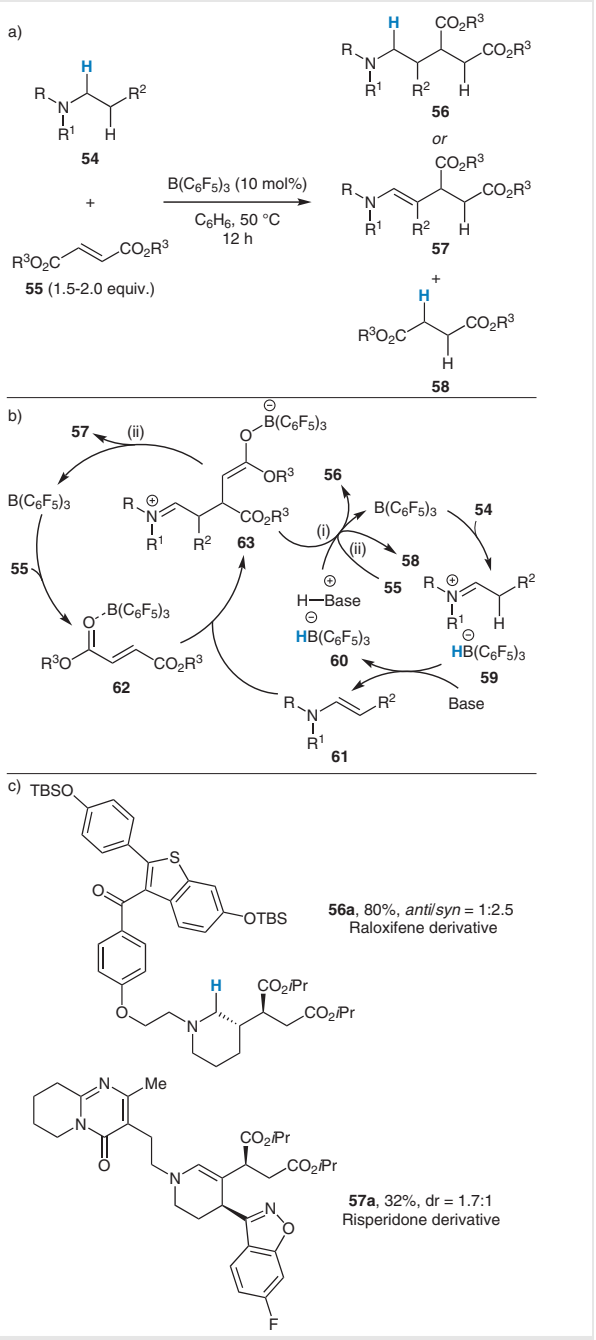
In 2021, Wasa and co-workers studied the application of $B(C_6F_5)_3$ in the β-amino C–H functionalization of amines **54** with Michael acceptors **55** to synthesize *N*-alkylamines **56**



Scheme 5 Borane-mediated hydride abstraction utilized in the diastereoselective construction of azabicycles from enamines and Michael acceptors. Asymmetric Michael addition conditions: (i) L-phenylalanine lithium salt (10 mol%), CH_2Cl_2, 48 h; or (ii) *O*-(*tert*-butyl)-L-threonine (5 mol%), 4-dimethylaminopyridine (5 mol%), sulfamide (5 mol%), toluene, 6–36 h.



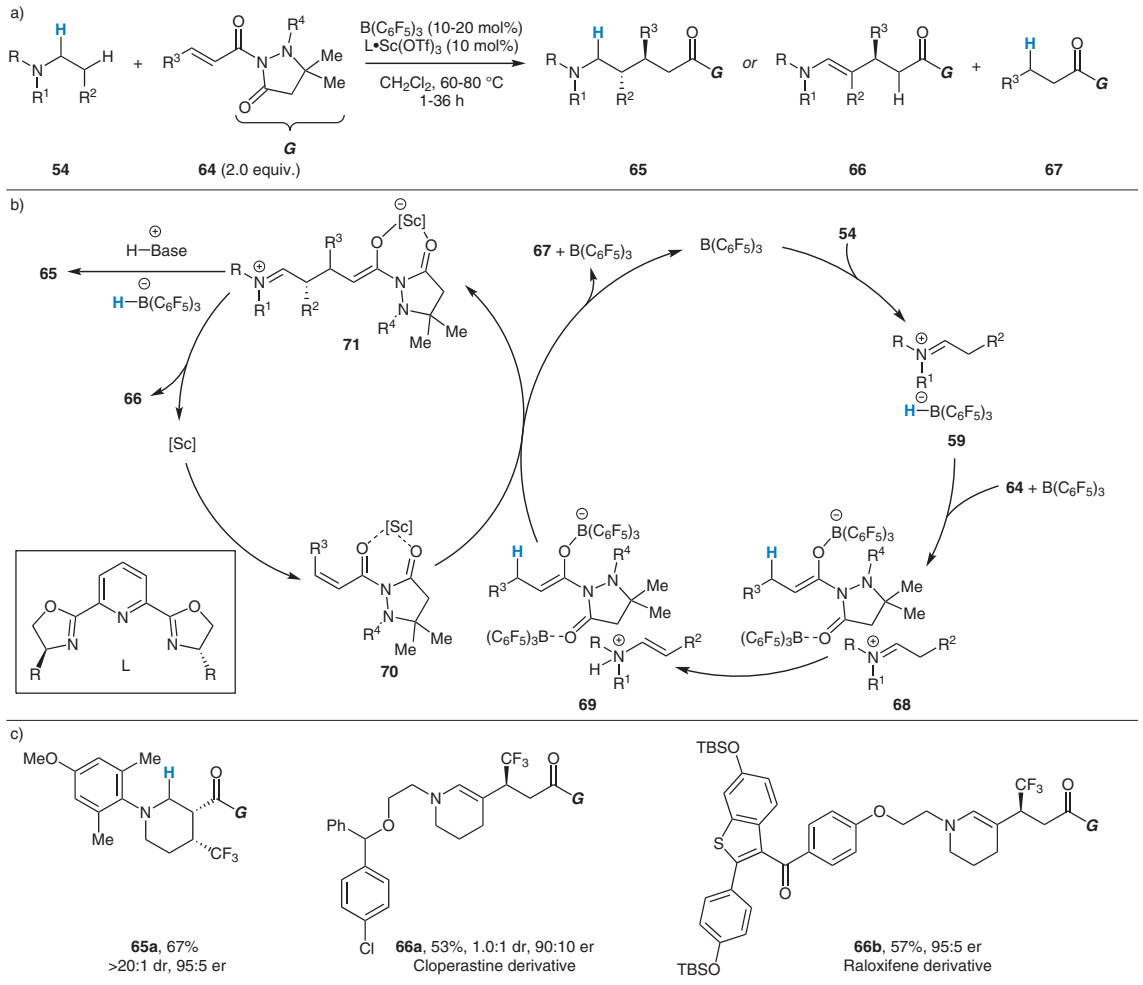
Scheme 6 Borane-mediated hydride abstraction for consecutive β-functionalization and acceptorless dehydrogenation



Scheme 7 Borane-mediated hydride abstraction for β-functionalization via a Michael-type reaction

or **57** (Scheme 7).[24] The reaction proceeds via $B(C_6F_5)_3$-mediated abstraction of the α-*N* C(sp^3)–H hydride yielding iminium borohydride **59**, before deprotonation by a base (e.g., **54** or **56**) to give enamine **61**. This then undergoes nucleophilic attack on the $B(C_6F_5)_3$-activated Michael acceptor **62** forming enolate **63**, before reduction by the protonated base and hydridoborate yields the product **56** (path i). Alternatively, enolate **63** can tautomerize to form alternative product **57**, with the protonated base/hydridoborate instead reducing the Michael acceptor **55** to yield alkane **58** (path ii). The method showed exceptional functional group tolerance, with examples including ethers, secondary amines, and protected alcohols. Excitingly, the method could also be used to derivatize bioactive compounds, including silyl-protected raloxifene and risperidone to give products **56a** and **57a**, respectively.

In the same paper,[24] the Wasa group also reported an enantioselective variation of the reaction, using a $B(C_6F_5)_3$/$Sc(OTf)_3$/PyBOX catalytic system to enable enantioselective C–C bond formation between *N*-alkylamines and Michael acceptors (Scheme 8). As with the racemic version, the reaction proceeds through $B(C_6F_5)_3$-mediated abstraction of the α-*N* C(sp^3)–H hydride to give iminium borohydride **59**. Mechanistic studies suggest that in the next step the borohydride reduces one equivalent of the Michael acceptor, yielding boron enolate **68**. Interestingly, kinetic and NMR spectroscopic studies suggest that the rate-limiting step is the proton transfer from the β-position to the *N*-position of the enamine, yielding intermediate **69**. This inter-



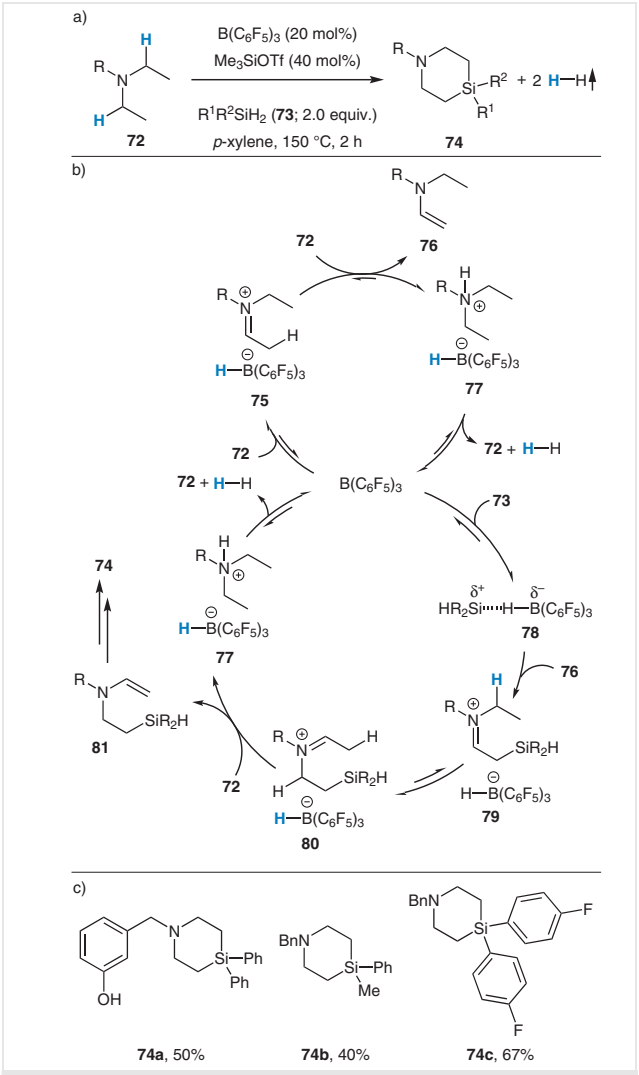
Scheme 8 Borane-mediated hydride abstraction for the enantioselective β-functionalization of amines through a Michael-type addition

mediate then protonates the boron enolate, giving **67** as a by-product, and freeing up the enamine to undergo nucleophilic attack on the Sc-bound Michael acceptor **70**, forming enolate **71**. Due to the chiral scandium complex, attack selectively occurs on the Michael acceptor. Product **66** can then form by intramolecular proton transfer, whilst product **65** forms upon reduction by a protonated base and the borohydride. As with the racemic version, the reaction showed exceptional functional group tolerance, with examples including trifluoromethyl groups (e.g., **65a**), ketones, and protected alcohols. Additionally, bioactive molecules were also derivatized (cf. **66a** and **66b**).

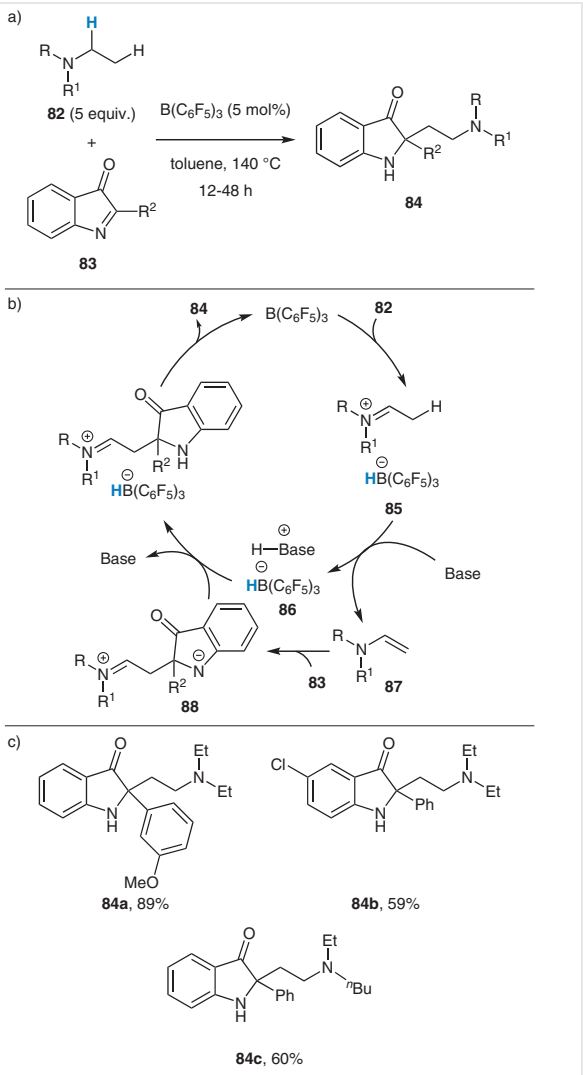
In 2021, Oestreich and co-workers reported a $B(C_6F_5)_3$-catalyzed β,β′-H silylation of tertiary amines **72**, yielding sila analogues of piperidines **74** (Scheme 9).[25]

The mechanism proceeds through $B(C_6F_5)_3$-mediated abstraction of the α-*N* C(sp^3)–H hydride in **72**, to give iminium borohydride **75**, before deprotonation by another equivalent of the amine **72** yields enamine **76** and ammonium borohydride **77**. The ammonium borohydride then eliminates H_2 to reform the active $B(C_6F_5)_3$ catalyst and amine **72**. The $B(C_6F_5)_3$ catalysis can also activate the Si–H bond (cf. **78**), creating an Si electrophile that can be attacked by enamine **76** to form a C–Si bond. The resulting iminium **79** can then undergo borohydride-induced tautomerization to give iminium **80**, which can be deprotonated by another equivalent of **72** to yield enamine **81** and ammonium borohydride **77**. The enamine **81** then proceeds through further $B(C_6F_5)_3$-mediated C–Si bond formation, as before, to yield the desired product **74**, with the ammonium borohydride **77** evolving H_2 to reform the active catalyst $B(C_6F_5)_3$. The reaction tolerated functional groups on the amine starting material such as unprotected phenols (e.g., **74a**), halogens, and trifluoromethyl groups, and the silane could also be varied to give unsymmetric silanes (e.g., **74b**) and substituted diarylsilanes (e.g., **74c**).

In 2023, He, Zhao and co-workers reported the $B(C_6F_5)_3$-catalyzed β-alkylation of tertiary amines **82** with 3*H*-indol-3-ones **83** to yield 2-alkylindolin-3-ones **84** (Scheme 10).[26]



Scheme 9 Borane-mediated hydride abstraction leads to the β,β′-H silylation of tertiary amines for the synthesis of sila-piperidines



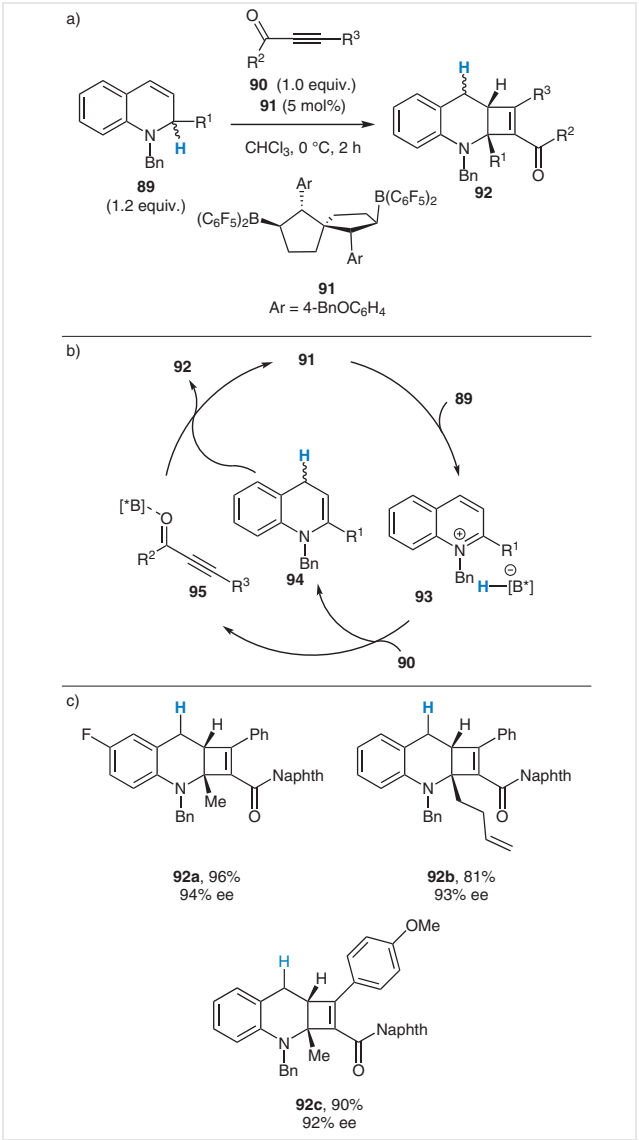
Scheme 10 Borane-mediated hydride abstraction facilitates the β-functionalization of amines with 3*H*-indol-3-ones

The reaction is proposed to proceed through $B(C_6F_5)_3$-mediated abstraction of the α-*N* C(sp^3)–H hydride to yield iminium borohydride **85**. This can then be deprotonated by a base (e.g., amines **82** or **88**) to yield enamine **87**, which undergoes nucleophilic addition to the 3*H*-indol-3-one **83** to give zwitterionic intermediate **88**. This can then accept a proton from **86**, before borohydride reduction to yield the desired product **84**, as well as reforming $B(C_6F_5)_3$. Functional group tolerance was demonstrated with ethers (e.g., **84a**) and halogens (e.g., **84b**), as was various substitution patterns around the aromatic rings. Additionally, the reaction was demonstrated to work with *N*-butyl-*N*,*N*-diethylamine to give amine **84c**.

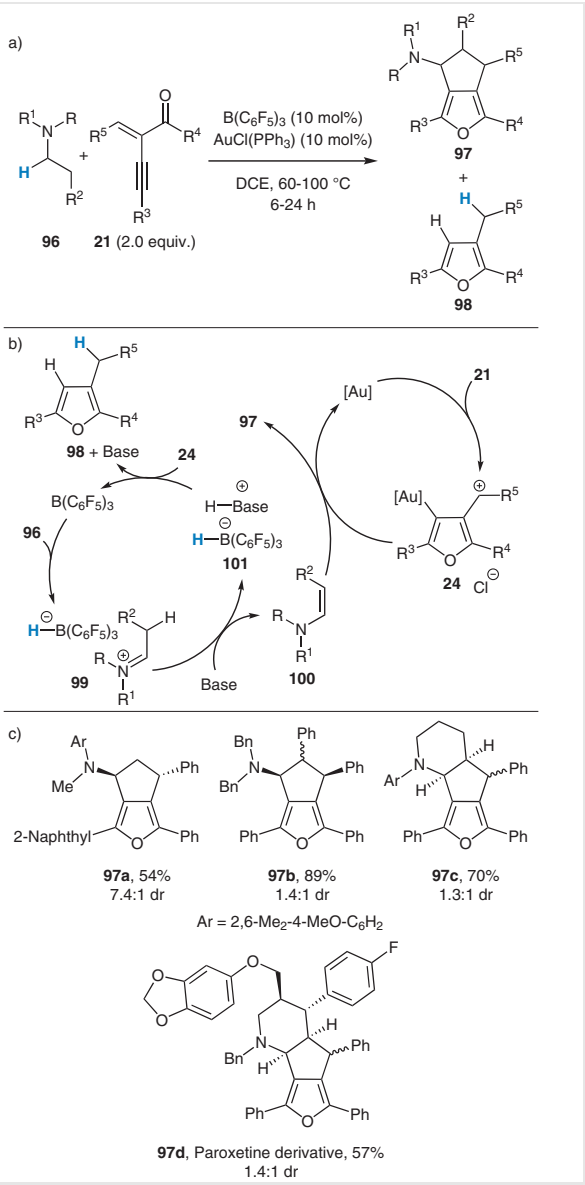
4 α,β-Difunctionalization of Amines

α,β-Difunctionalization of amines facilitated by organoborane-mediated hydride abstraction had not been reported at the time of our previous review,[6] and represents a new reaction class. Here the enamine can participate in cycloaddition reactions resulting in α,β-difunctionalization. In this section we will look at how this is leveraged to form cyclobutenes, furan-fused cyclopentenes, and alkyl-amino-functionalized quinolines.

In 2021, Wang and Zhang reported the enantioselective organoborane-catalyzed coupling of 1,2-dihydroquinolines **89** with alkynes **90** to deliver cyclobutene-fused 1,2,3,4-tetrahydroquinolines **92** (Scheme 11).[27] The catalytic cycle is proposed to occur via hydride abstraction mediated by or-



Scheme 11 Borane-mediated hydride abstraction leads to a [2+2] cycloaddition reaction between the α- and β-positions of amines and alkynes



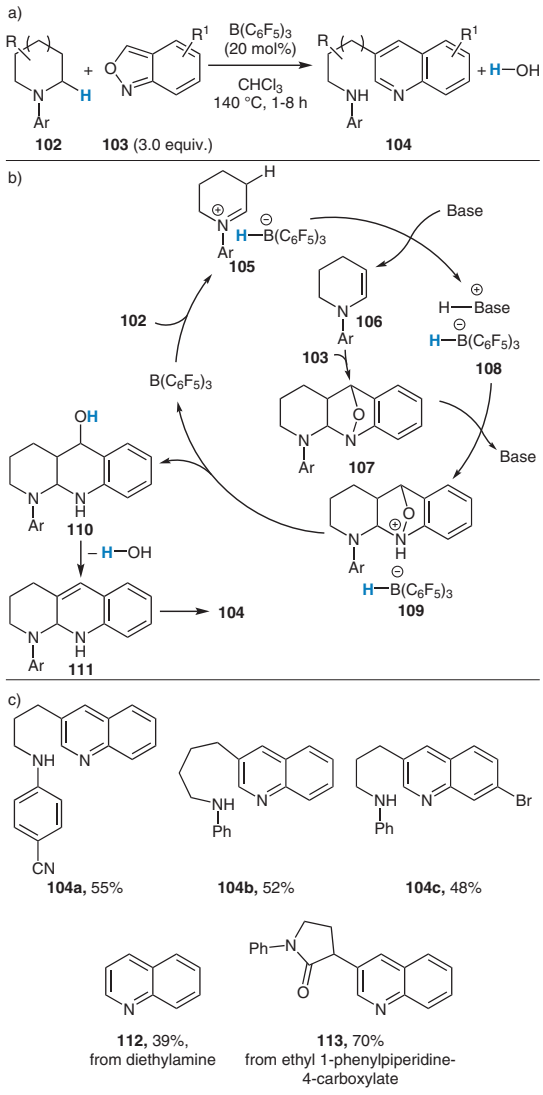
Scheme 12 Borane-mediated hydride abstraction in conjunction with gold(I)-catalysis leads to the formal [3+2] cycloaddition of amines and α-alkynylenones

ganoborane **91** that converts 1,2-dihydroquinoline **89** into quinolinium **93**. Transfer of the hydride in **93** to the quinolinium fragment forms 1,4-dihydroquinoline **94**. Effectively, organoborane **91** mediates isomerization of the dihydroquinoline via hydride abstraction. Organoborane **91** then plays the role of a conventional Lewis acid, activating alkyne **90** to allow the [2+2] cycloaddition with **94** to occur.

As part of their study into the borane/gold(I)-co-catalyzed α-furylation of tertiary *N*-methylamines **20** (c.f. Scheme 3), Wang and co-workers discovered that formal [3+2] cycloaddition products were observed when utilizing *N*-alkyl-substituted tertiary amines **96** containing β-hydrogens (Scheme 12).[19] It was found that a broad range of cycloadducts **97** could be accessed from tertiary *N*-alkylamines **96** and α-alkynylenones **21**. In this case, $B(C_6F_5)_3$-mediated hydride abstraction generates an iminium borohydride **99**, which is deprotonated by a base (e.g., amines **96** or **97**) to generate enamine intermediate **100**. A subsequent [3+2] cycloaddition involving the enamine **100** and the aurated furan 1,3-dipole **24** gives the cycloaddition adduct **97** and regenerates the gold catalyst, whilst $B(C_6F_5)_3$ can be reformed by transfer hydrogenation of another molecule of **24**. The reaction was shown to tolerate substituents at the β-position of the amine (e.g., **97b**), as well as ethers (e.g., **97a**), halogens, and protected phenols. The reaction condi-

tions could also be applied to the derivatization of bioactive compounds, such as in the formation of paroxetine derivative **97d**.

In 2022, He, Fan and co-workers reported an α,β-functionalization strategy involving anilines **102** and benzo[*c*]isoxazoles **103** followed by a C–N bond cleavage to furnish functionalized quinoline derivatives **104** (Scheme 13).[28] The catalytic cycle proceeds via $B(C_6F_5)_3$-mediated abstraction of the α-*N* C(sp^3)–H on *N*-aryl *N*,*N*-dialkyl amine **102**. Deprotonation of the resultant iminium **105** (e.g., with **102** or **104**) forms enamine **106** and ammonium borohydride salt **108**. A [4+2] cycloaddition of enamine **106** with isoxazole **103** forms α,β-functionalized piperidine **107**, which is then protonated by the ammonium salt **108** to form intermediate borohydride salt **109**. Hydride from the borohydride counterion cleaves the N–O bond in **109** to form alcohol **110** and regenerate the catalyst. Elimination of water gives **111** before a tautomerization and subsequent C–N bond cleavage furnishes functionalized quinoline **104**. The reaction tolerated a broad range of functional groups on the aniline **102** ring including cyano (e.g., **104a**), trifluoromethyl, nitro, ether and thioether groups. The saturated heterocycle in **102** was varied to allow for pyrrolidines, piperidines, azepanes (e.g., **104b**), and even azocanes and azonanes to all be used in the protocol. Acyclic examples such as diethylaniline and dipropylaniline were used to furnish quinoline **112** and 3-methylquinoline respectively. When ethyl 1-phenylpiperidine-4-carboxylate was used, a further intermolecular condensation of the secondary amine and ester group delivered product **113** with a lactam moiety.



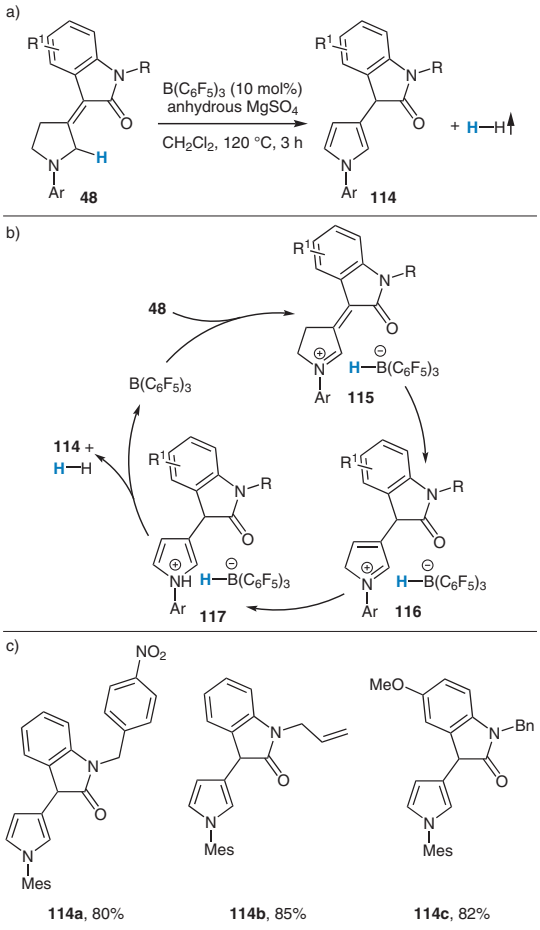
Scheme 13 Borane-mediated hydride abstraction for the conversion of benzo[*c*]isoxazoles into functionalized quinolines

5 Dehydrogenation of Amines

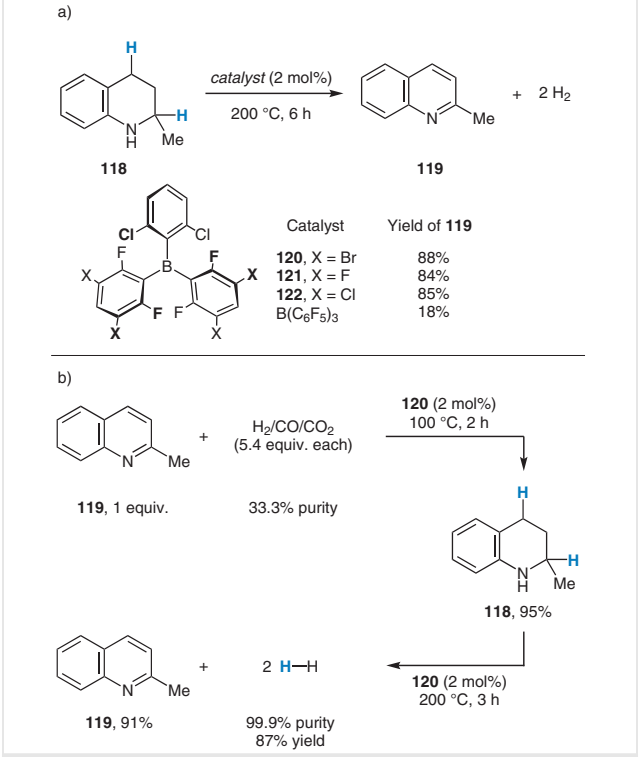
In our previous review,[6] we observed how hydride abstraction had been utilized in the dehydrogenation of a variety of benzofused *N*-heterocycles,[29] as well as the dehydrogenative coupling of indoles with silanes and boranes. These reactions are believed to proceed via an acceptorless dehydrogenation pathway, where an ammonium borohydride intermediate (generated after hydride abstraction and iminium tautomerization) undergoes an acid–base reaction to evolve H_2. We have also seen a few examples of H_2 evolution in several of the examples described above. Here, we look at the dehydrogenation of β-functionalized pyrrolidines, and how the dehydrogenation of tetrahydroquinolines has been utilized for hydrogen storage and purification.

In the report from Yang, Ma and co-workers described in Section 3 on the β-functionalization of pyrrolidines **46** with isatins **47**, a pyrrolidine acceptorless dehydrogenation process was also reported.[23] The products of the aforementioned β-functionalization of pyrrolidines **48** were converted into pyrroles **114** (Scheme 14). Simply increasing the temperature of the standard β-functionalization conditions led to the formation of pyrroles. The authors proposed that the mechanism proceeds through $B(C_6F_5)_3$-mediated hydride abstraction on product **48** (as formed above in Scheme 6) to form iminium species **115**. Isomerization of **115** into **117** (or **116**) creates an acidic proton that reacts with the borohydride counterion, causing aromatization, loss of H_2 and reformation of $B(C_6F_5)_3$. Functional group tolerance was demonstrated for the two-step procedure with nitro groups (e.g., **114a**), halogens, alkenes (e.g., **114b**), and ethers (e.g., **114c**).

Ogoshi, Hoshimoto and co-workers have reported an organoborane-catalyzed dehydrogenation applied to the purification of molecular hydrogen (Scheme 15).[30]



Scheme 14 Borane-mediated hydride abstraction for the acceptorless dehydrogenation of isatin-functionalized pyrrolidines



Scheme 15 Borane-mediated hydride abstraction for the interconversion of liquid organic hydrogen carriers.

A selection of organoboranes was shown to mediate the dehydrogenation of tetrahydroquinoline **118** to form quinoline **119** in high yield. Organoborane derivatives based on (2,6-dichlorophenyl)bis(2,6-difluorophenyl)borane (e.g., **120**–**122**), were shown to be optimal for the dehydrogenation of **118**, with the brominated derivative **120** performing across both dehydrogenation and hydrogenation steps (see below). Whilst no mechanism for the dehydrogenation was proposed, it is likely that the reaction proceeds in a manner analogous to the acceptorless dehydrogenations encountered above (e.g., Scheme 13, conversion of **102** into **106**) and in our previous review.[6] The ability of organoboranes to mediate dehydrogenation via hydride abstraction was applied to the purification of hydrogen from gaseous mixtures via a hydrogenation–dehydrogenation sequence. Hydrogen was removed from a mixture of H_2, CO and CO_2 and incorporated into tetrahydroquinoline **118** via frustrated Lewis pair hydrogenation of quinoline **119**.[31] Tetrahydroquinoline **118** was easily removed from the gas mixture, and separately dehydrogenated with borane **120**, concurrently forming high purity H_2 gas. Interestingly, the ubiquitous $B(C_6F_5)_3$ borane performed significantly worse in the initial hydrogenation step due to competing reactions with the $H_2/CO/CO_2$ mixture, as well as in the dehydrogenation step (88% vs 18% of **119**).

6 Summary and Future Prospects

In this review update, we have covered the recent advances made in organoborane-mediated hydride abstraction. We have shown that various Lewis acidic borane catalysts are able to mediate hydride abstraction from α-amino C–H bonds to yield a reactive iminium cation and a hydridoborate anion. These have been demonstrated to participate in a range of synthetically useful transformations, including α- or β-functionalization, α,β-difunctionalization, and the dehydrogenation of amines. It has become clear that further investigations are needed around the structure and electronic properties of the organoborane catalyst, as subtle changes play an important role in catalyst performance, as underscored by the work of Maulide,[22] Wang,[27] and Ogoshi and Hoshimoto[30] described above. The repurposing of common amine starting materials for novel transformations is an important area in synthetic chemistry and we envision that further development in the area of orga-

noborane-mediated hydride abstraction will advance synthetic methodology, and lead to more time- and atom-efficient syntheses in the future.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

A.P.P. thanks the Engineering and Physical Sciences Research Council (EPSRC) for funding (EP/W02151X/1 and EP/Y00146X/1). R.L.M. would like to thank the EPSRC for a research fellowship (EP/R026912/1). J.P.G., L.W., L.Y. and A.P.P. thank the University of Leicester for generous support. L.Y. thanks the China Scholarship Council for funding. S.A.E., R.L.M. and L.C.M. gratefully acknowledge the School of Chemistry, Cardiff University for generous support. S.A.E. thanks the British Council and the Egyptian Cultural Affairs and Missions Sector for a Ph.D. studentship through the Newton-Mosharafa Fund.

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