The Hidden Role of Boranes and Borohydrides in Hydroboration Catalysis

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KEYWORDS. hydroboration, reduction, borane, borohydride, mechanism, catalysis, hidden catalysis

ABSTRACT The continued development of hydroboration catalysts typifies the importance of this transformation as a testbed for catalytic activity and as a fundamental reaction for organic synthesis. Catalytic hydroboration studies routinely investigated the decomposition of HBcat but in the case of HBpin, decomposition is not commonly investigated due to its perceived stability. Organoboranes catalyze the hydroboration of alkenes and alkynes; these species can be formed

from the facile decomposition of 1,3,2-dioxaborolanes (e.g. HBcat and HBpin) by nucleophiles and Lewis acids. Similarly, the nucleophilic decomposition of 1,3,2-dioxaborolanes to borohydride species can catalyze the reduction of carbonyl derivatives. These motifs are abundant in hydroboration catalysis; therefore, the potential for hidden boron catalysis is high and must be controlled for. This perspective discusses the current methods for probing 1,3,2-dioxaborolane decomposition, highlights the need to consider this hidden catalysis in the future development of hydroboration catalysis, and proposes a set of protocols for identification of hidden boron catalysis.

1. Introduction

Hydroboration catalysis is plagued by hidden boron catalysis; of the 412 publications of 'new' catalyzed hydroboration reactions using 1,3,2-dioxaborolanes reported between January 2010 and June 2020, only 20 (5%) made use of appropriate measures to identify hidden catalysis. Whilst the decomposition of 1,3,2-dioxaborolanes to active boron catalysts has been reported and is known by experts in the field, the wider synthetic community appears to be unaware.

Hidden catalysis has blighted the development of new synthetic methodologies, with notable examples including trace metal contamination,[1-3] hidden Brønsted[4] and complex acid catalysis,[5-11] and the failure of control reactions.[12] The nucleophile-mediated decomposition of catecholborane (HBcat) by several hydroboration 'catalysts' is well established, yet the development of pinacolborane (HBpin), and its perceived increase in stability, has led to these studies being overlooked.

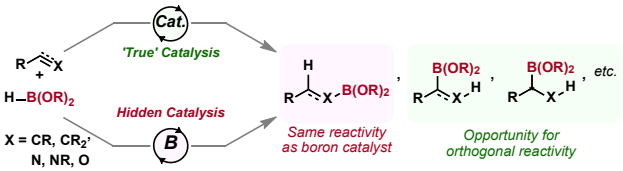
The hydroboration of unsaturated bonds, including alkenes, alkynes and carbonyl derivatives, with 1,3,2-dioxaborolanes can be achieved using catalysts from across the periodic table.[13-15] As nucleophilic groups are present throughout hydroboration catalysis (as ligands, pre-catalyst activators and inherently nucleophilic catalysts),[16] there is the potential for these nucleophiles to

mediate the decomposition of 1,3,2-dioxaborolanes to boranes and borohydride species.[16-19] BH_3,[20-22] and secondary-[23] and tertiary boranes[16, 24] have all been shown to catalyze the hydroboration of alkynes and alkenes with HBcat and HBpin. Similarly, trialkoxyborohydrides[16, 18-19] and triethylborohydride[25-26] catalyze the reduction of carbonyl derivatives. Therefore, careful control reactions are needed to determine whether 'true' or 'hidden' catalysis are operating.

It could be argued that it does not matter whether a 'catalyst' proceeds through 'true' or 'hidden' catalysis as both pathways lead to a hydroboration product (Scheme 1). However, the purpose of developing new catalysts is to find new reactivity (e.g. chemo-, regio-, stereoselectivity); catalysts that proceed only through hidden catalysis offer no greater understanding of chemical reactivity or improvement over commercially available boron catalysts and propagate misunderstanding in the wider community.

This perspective discusses select examples that have observed and investigated hidden catalysis in hydroboration reactions, exemplifies the effects of hidden catalysis on 'catalyzed' hydroboration reactions, and provides assistance to identify, control and avoid hidden boron catalysis.

Scheme 1. 'True' Catalysis versus Hidden Catalysis



2. Borane-catalyzed Hydroboration

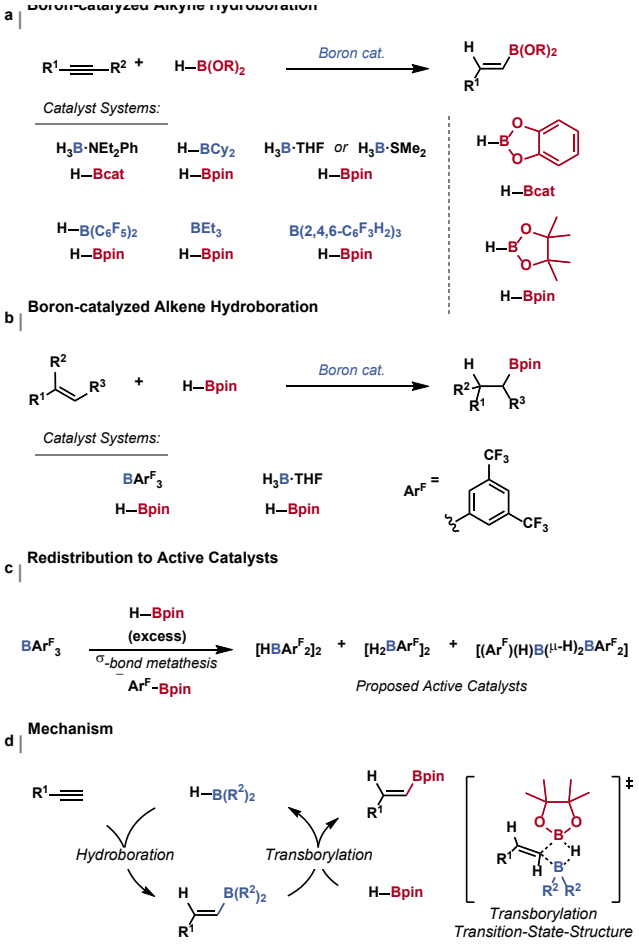
Prior to the development of HBpin, borane-catalyzed hydroboration was first shown by Periasamy using $H_3B{\cdot}N,N$-diethylaniline to catalyze the hydroboration of alkynes with HBcat (Scheme 2a).[20-21] Knochel's development of HBpin heralded a new era for hydroboration as the

products of alkyne and alkene hydroboration, alkenyl- and alkylboronic esters, were now air- and moisture-stable.[27] Although Knochel reported that the hydroboration of alkenes and alkynes with HBpin would proceed without a catalyst, numerous later studies have shown this to be irreproducible.[24, 28-29] This first instance of hydroboration using HBpin appears to proceed through hidden catalysis, where the HBpin was contaminated with $H_3B{\cdot}SMe_2$. Although it was stated that "for most applications this purification [distillation] is not necessary", purification of the HBpin would have prevented contamination and hidden catalysis. Boranes have been subsequently used as catalysts for the hydroboration of alkynes and alkenes with HBpin. Arase and Hoshi developed the dicyclohexylborane-catalyzed hydroboration of alkynes with HBpin (Scheme 2a),[23] Thomas showed that $H_3B{\cdot}THF$ or $H_3B{\cdot}SMe_2$ were active catalysts for the hydroboration of alkynes and alkenes with HBpin (Scheme 2, a and b),[22] and Stephan showed that the hydroboration of alkynes with HBpin can be initiated by Piers's borane [$HB(C_6F_5)_2$] (Scheme 2a).[30]

The redistribution of trialkyl- or triarylboranes with a 1,3,2-dioxaborolane results in the formation of a hydridoborane (e.g. a dialkyl- or monoalkylborane) (Scheme 2c). Therefore, systems which contain tertiary boranes will also catalyze hydroboration through hydridoborane catalysis (Scheme 2, a and b).[16, 24, 31] For highly Lewis acidic boranes, such as tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, in the presence of a Lewis base (LB), abstraction of the hydride from HBpin to form $[HB(C_6F_5)_3]^-$ and $[LB{\cdot}Bpin]^+$ occurs in place of redistribution.[32-33]

Mechanistic investigations by Lloyd-Jones and Thomas showed that dialkylborane-catalyzed alkyne hydroboration proceeded by hydroboration of the alkyne by the dialkylborane catalyst, followed by transborylation (B−C/B−H σ-bond metathesis) between the tertiary borane and HBpin to give the alkenyl boronic ester product and regenerate the dialkylborane catalyst (Scheme 2d).[28]

Scheme 2. Borane-catalyzed Hydroboration



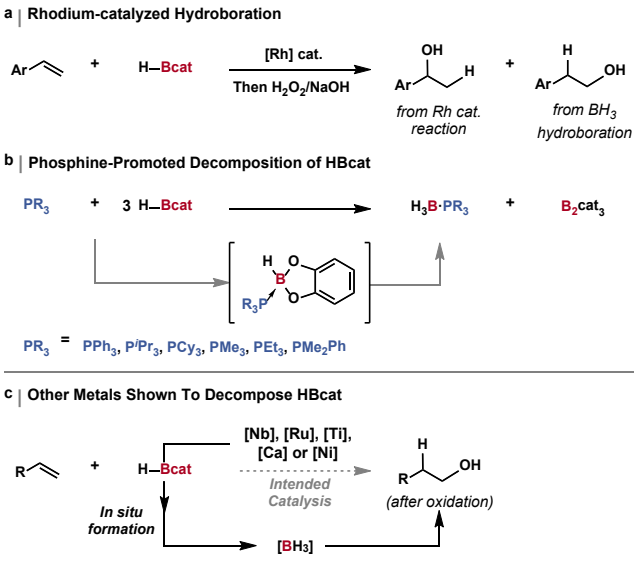
3. Nucleophile-Promoted Decomposition of 1,3,2-Dioxaborolanes

a. Alkyne and Alkene Hydroboration

Nöth's seminal report showed that a series of rhodium phosphine complexes would catalyze the hydroboration of aliphatic alkenes with HBcat, exhibiting anti-Markovnikov selectivity.[34] Subsequent work by Marder and Baker showed that rhodium complexes, including Wilkinson's catalyst [$RhCl(PPh_3)_3$], would catalyze the hydroboration of styrene derivatives with HBcat with Markovnikov regioselectivity (Scheme 3a).[35] In some cases, significant quantities of the anti-Markovnikov regioisomer were observed. Decomposition of HBcat to $H_3B{\cdot}THF$ was observed by ^{11}B NMR spectroscopy, which was used to rationalize the formation of the terminal alcohol by anti-Markovnikov alkene hydroboration with BH_3. When Burgess, Marder and Baker investigated

the reaction of HBcat with $RhCl(PPh_3)_3$, the formation of significant quantities of $H_3B{\cdot}PPh_3$ was observed; the labile PPh_3 ligand mediated the irreversible decomposition of HBcat.[36] Further examination showed a variety of alkyl and aryl tertiary phosphines promoted HBcat decomposition to $H_3B{\cdot}PR_3$ and B_2cat_3 (Scheme 3b).[17] Observations of HBcat decomposition are not limited to phosphine-containing systems. Nöth showed that B_2H_6 could be formed from the addition of $NaBH_4$ to HBcat.[37] Niobium,[38] ruthenium,[39] titanium,[40] calcium[41] and nickel complexes,[42] used in the hydroboration of alkenes, have all been shown to promote the decomposition of HBcat to BH_3 (Scheme 3c). All of these studies proposed that stoichiometric BH_3 hydroboration occurred and did not propose BH_3 catalysis.

Scheme 3. Metal-catalyzed Hydroboration of Alkenes with HBcat



These decomposition studies instilled the need for control reactions when using HBcat in catalyzed hydroboration reactions. However, the introduction and easier handling of HBpin shifted the focus of hydroboration catalysis from HBcat to HBpin, and the HBcat decomposition studies are now largely overlooked. The decomposition of HBpin to BH_3 has been shown to be mediated by species from across the periodic table (Scheme 4a).[16] Significantly, ^{n}BuLi and ^{n}Bu$_2$Mg,

previously proposed to be active hydroboration catalysts,[43-45] were shown to promote the decomposition of HBpin and merely acted as nucleophilic mediators of hidden boron catalysis; BH_3, and secondary- and tertiary boranes all individually contributed to hydroboration catalysis.[16] Conversely, the $LiAlH_4$-promoted hydroboration of alkenes with HBpin[46] was shown to proceed by complementary aluminum-[47] and boron-catalyzed pathways.[16] This may also be the case for other catalyzed hydroboration reactions, where, instead of competing reactivity (as seen in the Rh-catalyzed hydroboration of alkenes through divergent regioselectivity),[17, 35-36] complementary reactivity is observed (both boron- and 'true'-catalyzed pathways give the same product). In cases where reactivity differs from the boron-catalyzed pathway, such as Markovnikov selectivity or enantioinduction, complementary reactivity can be ruled out. However, any contribution from hidden catalysis would lead to a deleterious effect on the regio- or stereoselectivity of the reaction. In these instances, selectivity could be improved further by inhibiting the hidden catalysis pathway.

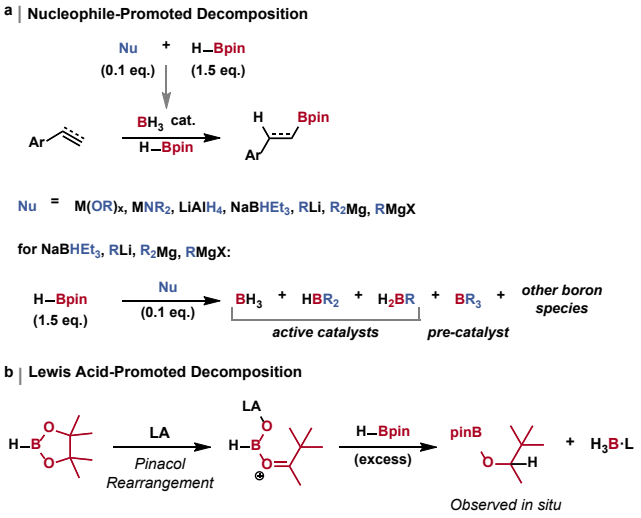
Thomas used three sets of reactions to determine the extent of hidden boron catalysis in the nucleophile-mediated hydroboration of alkynes and alkenes.[16] First, ^{11}B NMR spectroscopy was used to quantify the amounts of boron species formed when the nucleophilic catalyst was mixed with a large excess of HBpin. Addition of the catalyst to HBpin in a 1:1 ratio does not mirror reaction conditions and is therefore not a suitable control experiment. Singaram has shown that the stoichiometric addition of a Grignard to HBpin forms the alkyl or aryl boronic ester product without decomposition to BH_3,[48] providing evidence that it is crucial to match the stoichiometry of the reaction conditions when performing mechanistic investigations. It is likely that excess HBpin (relative to the catalyst) is required to act as the hydride acceptor to form a borohydride and initiate the decomposition process. Secondly, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was used to trap BH_3 under reaction conditions. The $H_3B{\cdot}$TMEDA and $(H_3B)_2{\cdot}$TMEDA adducts

were observed by ^{11}B NMR spectroscopy after work-up, providing confirmation of BH_3 formation. However, this qualitative assessment did not determine whether hydroboration proceeded through 'true' or hidden catalysis, or the rates of each pathway. The third set of reactions used a comparison of initial rates of reaction to determine the route of hydroboration. The concentration of BH_3 formed by a given nucleophile under catalytic reaction conditions was measured and that concentration was used to determine the initial rate of (the BH_3-catalyzed) reaction. This was then compared to the initial rate of reaction for the nucleophile-mediated hydroboration. If the initial rates of reaction were the same, the reaction proceeded by hidden catalysis only. For 'catalysts' that contained nucleophilic alkyl groups, a more complex situation presented where BH_3, and primary, secondary- and tertiary boranes were all formed. These other boranes also contributed to hidden catalysis and should be considered when exploring catalyzed hydroboration reactions.

As observed by Ingleson in the zinc-catalyzed triboration of terminal alkynes,[49] the decomposition of HBpin can also be mediated by strong Lewis acids, through the promotion of a pinacol rearrangement (Scheme 4b). Borane and borohydride species were observed by ^{11}B NMR spectroscopy under reaction conditions. Furthermore, the hydroboration product of pinacolone with HBpin was observed in situ by ^{1}H NMR spectroscopy.

Decomposition is not limited to HBcat and HBpin. Takacs observed BH_3 formation from the decomposition of new 1,3,2-dioxaborolanes and 1,3,2-dioxaborinanes developed for the rhodium-catalyzed asymmetric hydroboration of β,γ-unsaturated Weinreb amides.[50]

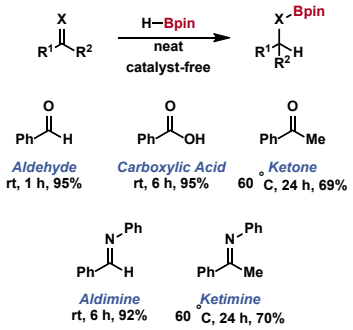
Scheme 4. Decomposition of HBpin



b. Hydroboration of Carbonyl Derivatives

There has been a sudden surge in catalyzed hydroboration reactions of carbonyl derivatives with 1,3,2-dioxaborolanes, with 125 publications reported between January 2019 and June 2020.[51] Contrary to the negligible hydroboration of alkynes and alkenes by HBpin, direct hydroboration of carbonyl derivatives in solvent-free conditions is facile (e.g. aldehyde, 1 h, rt)[52] and should be taken into account when devising new catalysts for these transformations (Scheme 5).[52-57] Dilution of the reaction mixture reduces the yield of hydroboration.[55] Borohydrides are active catalysts for carbonyl hydroboration (e.g. aldehyde, 5 min, rt);[25] therefore, hidden boron catalysis existing in 'catalyzed' carbonyl hydroboration reactions is possible. As this field continues to proliferate, the need for new, elaborate catalysts should be questioned as direct hydroboration with HBpin occurs readily and with good regio- and chemoselectivity.

Scheme 5. Background Hydroboration of Carbonyl Derivatives with HBpin

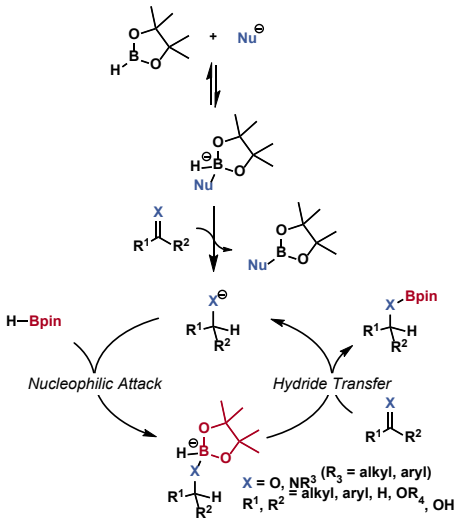


Metal alkoxides can be used to promote the hydroboration of carbonyl derivatives by HBcat[18] and HBpin.[19] The mechanism of alkoxide-mediated hydroboration of ketones was proposed by Clark (Scheme 6).[19] The formation of a trialkoxyborohydride from the reaction of NaO^{t}Bu with HBpin was confirmed by ^{11}B NMR spectroscopy. The trialkoxyborohydride mediated the first reduction of the ketone, forming an alkoxide. This reacted with HBpin to generate a new trialkoxyborohydride which acted as a new hydride donor to reduce another ketone molecule and propagate the reaction. The trialkoxyborohydride formed from the reaction between the product (1-phenylethoxide) and HBpin was independently prepared and was subsequently shown to be an active catalyst for the hydroboration of acetophenone.[16] Whilst Clark used NaO^{t}Bu to form the trialkoxyborohydride catalyst, it is conceivable that this mechanism can be applied more generally to nucleophile-mediated hydroboration of carbonyl derivatives. Cowley proposed an analogous mechanism for the silyl anion-mediated hydroboration of ketones and aldehydes with HBpin, observing the corresponding silyl-borohydride.[58] Hreczycho reported the triethylborohydride-catalyzed hydroboration of aldehydes and ketones with HBpin, proposing a different mechanism to Clark.[25] Triethylborohydride reduced the carbonyl group to give the formal hydroboration product, an alkoxytriethylborate. σ-Bond metathesis between this and HBpin was proposed to reform the catalyst with concomitant formation of the alkoxyboronic ester product. As the alkoxytriethylborate is coordinatively-saturated, σ-bond metathesis is likely to be a high energy process and a mechanism analogous to that proposed by Clark may be operating. Findlater has

subsequently shown that triethylborohydride will catalyze the reduction of nitriles with HBpin,[26] proposing an analogous mechanism to that proposed by Hrecyzcho.

Applying the Clark mechanism more generally, borohydride species have been proposed in the sodium hydride-catalyzed hydroboration of aldimines,[59] the calcium-catalyzed hydroboration of ketones,[60] and observed in the magnesium-catalyzed hydroboration of esters,[61] the lanthanum-catalyzed hydroboration of epoxides,[62] the organolithium-catalyzed hydroboration of aldehydes and ketones,[63] and the lithium amide-catalyzed hydroboration of nitriles to amines.[64] This final case may also have implications on the veracity of other metal amide-catalyzed hydroboration reactions.[65-69] The hydroboration of imines with HBpin can be mediated by the addition of alcohol or water.[70] Whilst the exact mechanism is as yet unclear, protic impurities should also be considered when devising new carbonyl hydroboration reactions.

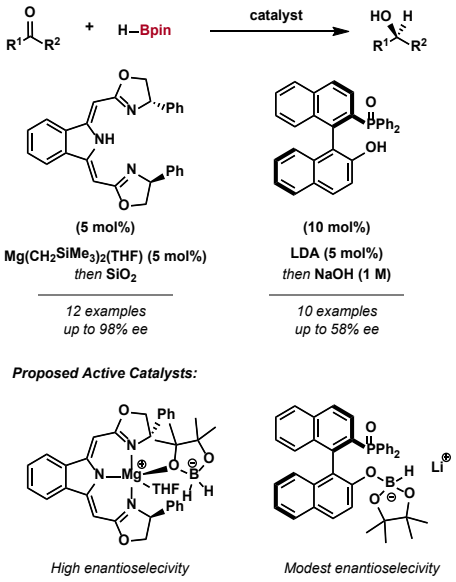
Scheme 6. Nucleophile-promoted Carbonyl Hydroboration



Jones has shown that β-diketiminato magnesium(I) dimers decompose HBpin to form Mg complexes with ligated boron species, including a pinacol borohydride $[H_2Bpin]^-$ and BH_3. These observations led Jones to question hydroboration studies that proposed the magnesium(I) dimer to be the active catalyst.[71] Subsequent work by Gade showed that borohydride intermediates were

integral to catalysis in the magnesium-catalyzed enantioselective hydroboration of ketones (Scheme 7).[72] Treating the magnesium pre-catalyst with excess HBpin led to the formation of a complex containing $[H_2Bpin]^-$ ligated to the magnesium cation through an oxygen atom of the pinacol group. Comparable enantioselectivity was observed with this isolated complex when it was used in place of the catalyst generated in situ. The reaction was proposed to proceed in a similar manner to the Clark mechanism, with an added role of the magnesium center to coordinate the borohydride and ketone, producing an alcohol of high enantiopurity.[72] Melen used an enantioenriched alkoxide to promote the hydroboration of ketones with modest enantioselectivity (Scheme 7) and it was suggested that the reaction also proceeded by the Clark mechanism.[73] The modest enantioselectivity observed by Melen suggests that free ligand reacting with a 1,3,2-dioxaborolane to form a borohydride cannot induce high enantioselectivity alone; to achieve high enantioinduction the ligand needs to be coordinated to a metal borohydride. Therefore, the possibility that borohydrides work in combination with a metal catalyst to induce high enantioinduction should be considered and that enantioselective hydroboration reactions of carbonyl derivatives do not necessarily proceed through a metal-hydride species.

Scheme 7. Borohydrides in Asymmetric Carbonyl Hydroboration Reactions



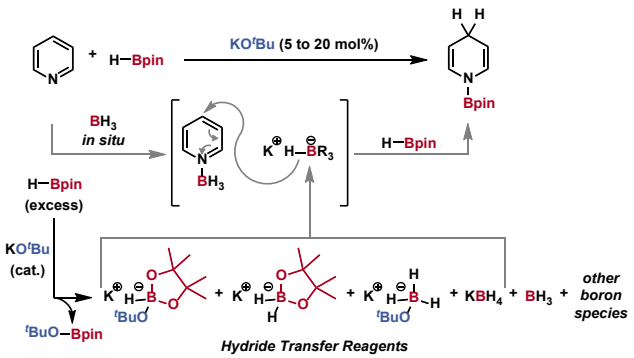
c. Hydroboration of Other Substrate Classes

For other substrate classes that undergo hydroboration, there is limited to no information regarding hidden boron catalysis. As the formation of boranes and borohydrides from 1,3,2-dioxaborolanes occurs readily, the possible existence of hidden catalysis remains for any substrate class that undergoes stoichiometric hydroboration or reduction by boranes or borohydrides, respectively.[74]

The 1,4-hydroboration of N-heteroarenes was shown by Chang to be promoted by KO^{t}Bu in the presence of HBpin. The reaction between KO^{t}Bu and HBpin formed borohydride species and BH_3, which co-catalyzed the hydroboration reaction (Scheme 8). Borohydride species were detected by ^{11}B NMR spectroscopy and promoted the hydroboration of N-heteroarenes through hydride transfer.[75] BH_3 accelerated the rate of reaction by activating the arene with the key step in the reaction being hydride transfer from the borohydride species to the BH_3-activated arene. Chang has subsequently shown that an N-heterocyclic carbene (NHC) will catalyze the 1,2-hydroboration of quinolines with HBpin.[76] A similar mechanism to the 1,4-hydroboration of N-heteroarenes was proposed, based on the observation of a borohydride by ^{11}B NMR spectroscopy from the reaction

between the NHC and HBpin. Evidently, hidden boron catalysis can operate in the hydroboration of N-heteroarenes and should be reflected upon accordingly.

Scheme 8. KO^{t}Bu-promoted Hydroboration of Pyridine



4. Protocols for the Identification of Hidden Boron Catalysis

To confirm that a given hydroboration catalyst does not decompose the 1,3,2-dioxaborolane to catalytically active boron species, the catalyst should be reacted with the 1,3,2-dioxaborolane using the same stoichiometries, concentration and temperature as those used for the hydroboration reaction. It is possible to observe any decomposition by ^{11}B NMR spectroscopy.[16] Similarly, commercial samples of 1,3,2-dioxaborolanes should be checked for impurities by ^{11}B NMR spectroscopy. If catalytically active boron species are observed in the samples of 1,3,2-dioxaborolanes, they should be distilled prior to use.

To confirm that BH_3 does not form under reaction conditions, TMEDA can be added to the hydroboration reaction.[16] The presence of BH_3 can be confirmed after work-up by ^{11}B NMR spectroscopy by diagnostic peaks corresponding to $H_3B{\cdot}$TMEDA and $(H_3B)_2{\cdot}$TMEDA adducts,[77] providing a qualitative assessment of BH_3 formation.

To discern true catalysis from hidden boron catalysis quantitatively, a combination of kinetic analysis and ^{11}B NMR spectroscopy can be used.[16] Measurement of the BH_3 concentration formed when the catalyst is reacted with the 1,3,2-dioxaborolane by ^{11}B NMR spectroscopy can give an

active BH_3 catalyst concentration. Subsequently, the initial rate of reaction for the hydroboration reaction should be measured, followed by using $H_3B{\cdot}SMe_2$ at the observed BH_3 concentration in place of the catalyst. All other conditions must be kept the same. If the initial rates of reaction for the standard catalyst reaction match that of the BH_3-catalyzed reaction, the system only proceeds through hidden catalysis. If the rates are different, hidden catalysis cannot necessarily be excluded; complementary 'true'- and hidden-catalyzed pathways could be operating, and in cases where trialkyl-, dialkyl- and monoalkylboranes are formed, extra care should be taken as all can catalyze hydroboration but are not necessarily easy to prepare or quantify in situ.

To exclude the possibility of the reaction proceeding by the Clark mechanism,[19] the nucleophile-HBpin borohydride should be prepared[16, 19] and tested as a catalyst in the reaction, comparing the initial rate to the standard reaction. The modest enantioselectivity observed in Melen's hydroboration of ketones[73] suggests that free ligand cannot alone induce high enantioinduction through the formation of a borohydride. However, this does not exclude hidden borohydride catalysis from enantioselective hydroboration, as Gade has shown.[72]

5. Conclusion

Many catalysts have been developed for hydroboration reactions of alkenes, alkynes and carbonyl derivatives with 1,3,2-dioxaborolanes, with 412 papers published between January 2010 and June 2020. The decomposition of 1,3,2-dioxaborolanes by nucleophiles or Lewis acids to borane and borohydride species occurs readily, all of which are active hydroboration catalysts. However, only 5% of these publications account and control for this decomposition. Any species added to the reaction that has these properties has the potential to form active hydroboration catalysts. Therefore, care must be taken to ensure that any newly-proposed hydroboration 'catalyst' does not merely mediate the formation of borane- or borohydride species under reaction

conditions. Reactions that only proceed through hidden catalysis do not offer orthogonal reactivity and therefore do not advance the field of catalyzed hydroboration. Guidelines for the detection and prevention of hidden boron catalysis have been provided and must be considered in the future. NMR spectroscopy offers a convenient probe for boron catalyst formation quantitatively, provided appropriate stoichiometries and concentrations that match the reaction conditions are used. Kinetic analysis can be used to identify contributions from the boron- and the 'true'-catalyzed pathways. For the hydroboration of carbonyl derivatives, the background reactions with the 1,3,2-dioxaborolane in the absence of catalyst should be performed. Future hydroboration catalysis must consider both the background reactions of 1,3,2-dioxaborolanes and the in situ formation of boron-based catalysts. 'True' hydroboration catalysis publications cannot continue to be diluted by systems that only proceed through hidden catalysis, as this will only lead to the detriment of the field of hydroboration.

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Author Contributions

All authors drafted the manuscript and have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

SPT thanks the Royal Society for a University Research Fellowship. SPT, ADB and KN thank AstraZeneca and the EPSRC for iCASE awards.

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SYNOPSIS TOC