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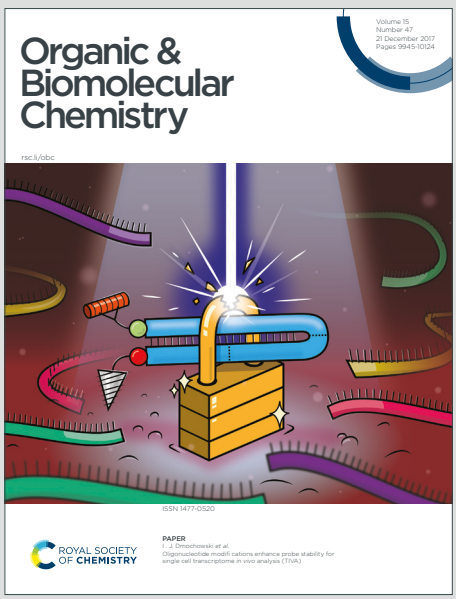

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ARTICLE

Ammonia borane as a reducing agent in organic synthesis

Faverio Chiara,[a] Boselli Monica Fiorenza,[a] Medici Fabrizio,[a] Benaglia Maurizio*[a]

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Ammonia borane $NH_3{\cdot}BH_3$ is considered a promising material for hydrogen storage and release, and is attracting an increasing attention as relatively inexpensive, atom economy-convenient and viable reagent for developing new green synthetic transformations. The present review offers a wide overview on the use of AB in the reduction of organic compounds, and highlights the versatility of this reagent, due to the possibility to modulate its activity employing different strategies, that include the use of transition metals, p-block species, organocatalysts and FLP systems.

1. Introduction

In the last decade Ammonia borane $NH_3{\cdot}BH_3$ (AB) has been receiving an increasing attention in the synthetic organic chemistry community, due to its many positive features. Due to its high dihydrogen percentage, AB is considered a convenient material for hydrogen storage and release.[1-3] But, considering the atom economy principles, it is also a convenient, relatively inexpensive reduction reagent for developing new green synthetic methodologies, used in combination with transition-metal catalysts[4-8] or, more recently, p-block species.[9] It is worth noting that much effort has been devoted also to study the regeneration of ammonia borane from the spent fuel reactants.[10]

Since some recent, excellent reviews have mainly discussed in details the dehydrogenation process of amine-boranes, either in the presence of metal catalysts[6-7] or p-block compounds[9], we have decided to focus our attention more on the synthetic application of ammonia borane in organic synthesis. The aim of the present review is to offer a wide overview on the use of AB in the reduction of organic compounds, and it is organized in five sections. After the presentation of the reactions where AB is employed without the use of any addictive, the ammonia borane-promoted reactions in the presence of organocatalysts will be presented, followed by AB-mediated reductions with FLP systems, use of AB in biocatalyzed transformations, and reductions in the presence of organometallic complexes.

2. Non-catalyzed ammonia borane-mediated reductions

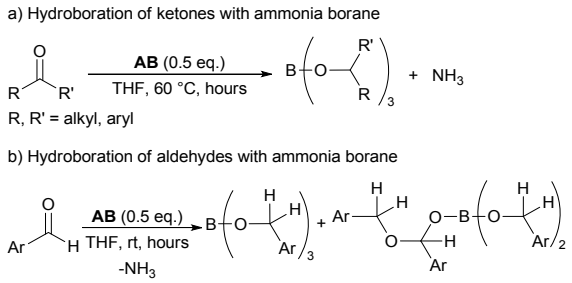
In the current section we report those publications where ammonia borane is employed as reducing agent alone, without the need of being activated by a catalyst. In some cases, AB is used in a stoichiometric amount, while elsewhere only a substoichiometric quantity is enough to carry out the reaction, since the ammonia borane dehydrogenated species are still able to reduce the substrate.

In particular, we focused on the reduction of C=O, C=N and C=C bond. In the first two cases ammonia borane could act as convenient replacement of the well-known hydrides (for example sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride), as safer and greener reagent. In the section devoted to the reactions with carbon-carbon multiple bonds, hydroboration-oxidation reactions are cited, even if they cannot be considered reductions, in order to provide a complete picture of the possible application of AB. At last, we describe the use of metal aminoboranes, which can be obtained by replacing one of the N-H hydrogen atoms of AB with an alkali or alkaline earth metal. These reagents proved to be efficient reducing agents toward aldehydes, ketones, imines and tertiary amides.

2.1 Reduction of aldehydes and ketones

One of the first works reporting the use of ammonia borane as reducing agent dates back to 1980.[11,12] Andrews demonstrated the ability of AB in reducing aldehydes and ketones under mild reaction conditions and in a short time. Moreover, an example of a chemoselective application of AB was implemented by reacting a 1:1 mixture of an aldehyde and a ketone with 0.33 equivalents of AB. It was possible to selectively isolate the reduced aldehyde, together with negligible traces of reduced ketone. More than thirty years later, Berke's group[13] investigated the reduction of ketones (Scheme 1a) and aldehydes (Scheme 1b) with half equivalent of AB in THF, trying to elucidate its mechanism.

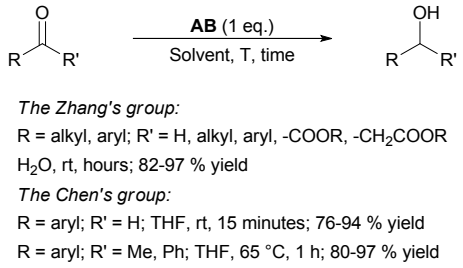
[a] Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy.



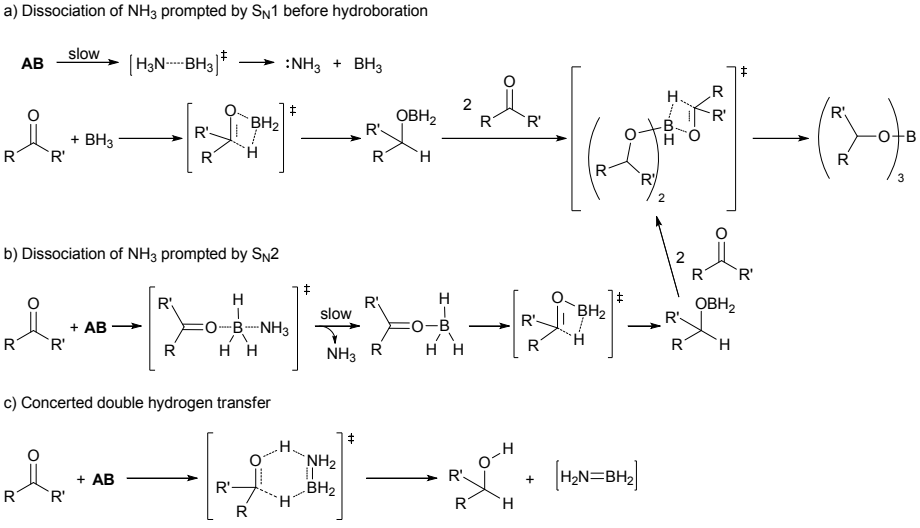
Scheme 1 Hydroboration of aldehydes and ketones

Unexpectedly, *in-situ* NMR studies evidenced the formation of trialkylborate, in the first case, and a mixture of the trialkylborate and the acetal derived borate ester, in the case of aldehydes along with ammonia evolution. The reaction was tested in CD_3OD and the expected alcohols were obtained, however the hydroxyl group resulted to be deuterated, indicating that the proton was transferred from the solvent to the substrate. The deuterium kinetic isotope effects (DKIE) were evaluated and the dissociation of NH_3 was assumed as the rate determining step of the process. Two pathways were proposed, the first one was S_N1-like, in which the slow dissociation of ammonia occurred first, thus leaving the free BH_3 capable of coordinating the O atom of the carbonyl moiety as shown in Scheme 3a. A four-membered ring structure was proposed for the insertion of the carbonyl into a B-H bond, followed by the hydroboration of other two equivalents of carbonyl species. The second route (Scheme 3b) was S_N2-type, involving a concerted coordination of the carbonyl while the dissociation of ammonia was taking place.

One year later, Zhang and co-workers[14] reported the reduction of aldehydes and ketones with one equivalent of AB in water. Under the conditions indicated in Scheme 2, various alcohols were obtained in high yields and the procedure was compatible with the presence of olefins, esters, nitro and cyano groups; moreover, neither base-labile protecting groups, (tosyl, acetyl and benzoyl groups) nor acid-labile ones (trityl and TBDMS groups) were removed. A comparison of AB and sodium borohydride was carried out in the reduction of α and β ketoester to α and β hydroxyl esters. Ammonia borane proved to reduce the substrates faster and more chemoselectively. At the same, Chen's group reported the reduction of aldehydes[15] and ketones[16] with a stoichiometric amount of ammonia borane in THF (Scheme 2). The reduction of aldehydes was achieved in short reaction time at room temperature, while the reduction of ketones required 65 °C and longer reaction time. Differently from Berke's work, when the reaction was followed by FT-IR and NMR, NH_3 was never detected. Experiments with deuterated AB showed that protic N-H was selectively transferred to the O atom of the carbonyl, while hydridic B-H ended up being bonded to the C atom of the carbonyl group. Based upon these observations, the authors suggested a concerted double hydrogen transfer (Scheme 3c).



Scheme 2 Reduction of aldehydes and ketones with AB



Scheme 3 Suggested mechanisms for the reduction of aldehydes and ketones with ammonia borane

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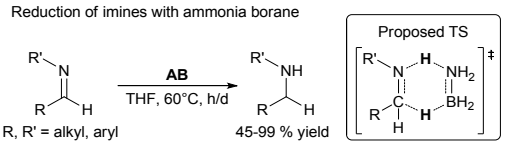
A depth investigation of the mechanism was carried out by Zhou and Fan[17] with theoretical studies. A comparison between the stepwise mechanism and the concerted double hydrogen transfer (DHT) mechanism for the formation of alcohols from aldehydes and ketones showed that the latter was more likely to take place, since the stepwise mechanism resulted to be higher in barrier by 3 to 10 kcal/mol. The formation of borate esters obtained experimentally by Berke was ascribed to the different AB/carbonyl stoichiometric ratio used in that case.

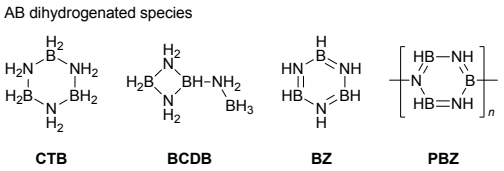
Recently, Ma and co-workers[18] performed theoretical calculations to study the aforementioned mechanisms, focusing the attention on the role of the solvent of the reaction. In particular, the mechanism of the dissociation of ammonia from AB resulted to be preferentially S_N1-like rather than S_N2, in both protic and aprotic solvents. Moreover, the concerted double hydrogen transfer was confirmed to be the more likely mechanism for the reduction of carbonyl by AB in protic or aprotic solvent, since its calculated free energy is lower than that of hydroboration by 4.7 kcal/mol.

2.2 Reduction of imines and reductive amination reactions

In 2010, Berke and co-workers studied the reduction of imines employing ammonia borane as reducing agent.[19]



Scheme 4 Reduction of imines

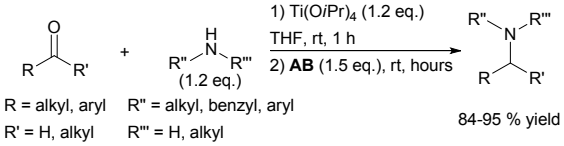


Scheme 5 AB dehydrogenated species

A series of aldimines was successfully reduced to the corresponding amines using an equivalent of AB at 60 °C in THF; the reaction time varied from a few hours to four days, depending on the substrate (Scheme 4). The authors investigated the reaction mechanism also by *in-situ* NMR analysis, deuterium labelling studies, Hammett correlations and DFT calculations using the Gaussian 03 program. It was noticed by NMR studies that several AB dehydrogenated species were present in solution, cyclotriborazane (CTB), *B*-(cyclodiborazanyl)aminoborohydride (BCDB), borazine (BZ) and poly(borazylene) (PBZ), which are reported in Scheme 5. After several days of reaction, it was found that only BZ and PBZ were present in solution, while both CTB and BCDB have been consumed. It was assumed that also CTB and BCDB are able to reduce imines and *N*-benzylidene aniline was reacted with 0.5 equivalents of AB to confirm this hypothesis; full-conversion to the corresponding amine was achieved. To further validate this assumption, *N*-benzylidene aniline was reduced in the presence of CTB and BCDB, while it was left untouched when it was mixed with BZ and PBZ.

Quantum mechanics calculations indicated that the reduction takes place with a double H transfer, where concerted hydrogenation and dehydrogenation reactions are merged into one elementary step. The proposed six-membered cyclic double-H-transfer transition state is reported in Scheme a: B-H···C and N-H···N transfers were found to be energetically favoured. Deuterated analogous of ammonia borane were employed to validate the calculations and deuterium kinetic isotope effects (DKIE) demonstrated that both H transfers participate in the rate-determining step. The reaction mechanism was later confirmed.[17]

Several protocols for reductive amination were developed since Berke's group disclosed the reduction of imines with ammonia borane. The first one was published by Ramachandran's group in 2010.[20] The reaction involved a two-step one pot procedure; at first, the formation of the imine, achieved by mixing an aldehyde or a ketone with 1.2 equivalents of amine, in the presence of 1.2 equivalents of Ti(*O*Pr)$_4$. was followed by the addition of 1.5 equivalents of ammonia borane to reduce the imine (Scheme 6).

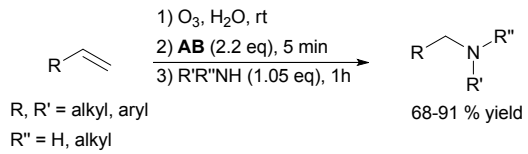


Scheme 6 Reductive amination of ketones

Secondary and tertiary amines were obtained in high yields and short reaction time. In order to synthetize primary amines, Ti(*O*Pr)$_4$ was added to the solution of the desired ketone, NH_4Cl, and triethylamine in ethanol to form the imine, which was further reduced by AB. The procedure was employed by Ramachandran to synthetize ring-substituted *N*-benzylated γ-phenyl GABA derivatives from ring-substituted 4-oxo-4-phenylbutyric acids with ring-substituted benzylamines.[21]

Another two-step one pot procedure involving a tandem olefin's ozonolysis, followed by a reductive amination, was developed by Tyagi and co-workers (Scheme 7).[22] The standard procedure involved a first oxidation step performed by bubbling a stream of O_3/O_2 through a solution of the alkene in water at room temperature; then AB was added, and the solution was stirred for 5 minutes before adding the amine. The reaction was performed under mild conditions and in short reaction times. The desired product was obtained in high

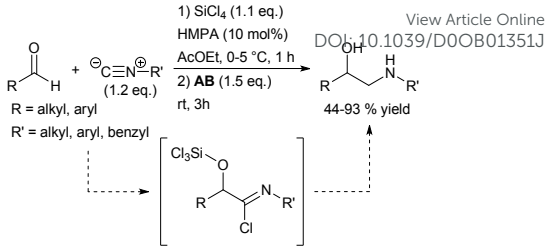
yield with both aliphatic and aromatic olefins, even if the scope is limited to monosubstituted alkenes.



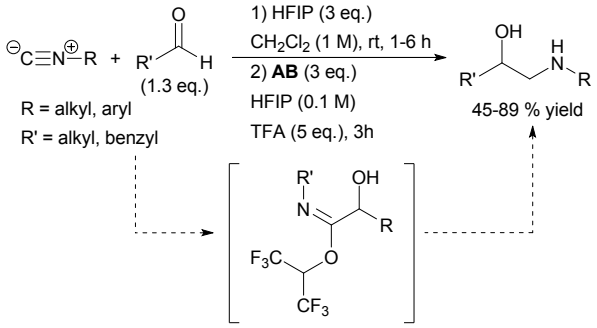
Scheme 7 Tandem olefin's ozonolysis and reductive amination

In the context of C=N bond reduction, two examples of the synthesis of *N*-substituted β-amino alcohols were reported by Orru, Ruijter and co-workers, which exploited a two-step one pot sequence, that involved a Passerini-type reaction followed by a reduction of the intermediate by ammonia borane. The first one[23] was published in 2015; in the first step 1.2 equivalents of isocyanide were added to a solution of the aldehyde in the presence of 1.1 equivalents of $SiCl_4$ and a catalytic amount of hexamethylphosphoramide (HMPA). Since silicon tetrachloride is a weak Lewis acid, a Lewis base, HMPA, was added to displace a chloride ion, in order to form a cationic silicon species capable of activating the aldehyde toward a nucleophilic attack. The intermediate α-trichlorosilyloxy imidoyl chloride, thus formed, was reduced by 1.5 equivalents of ammonia borane in the second step (Scheme 8). The substrate scope of the reaction is wide, various aromatic, heteroaromatic and aliphatic aldehydes were reacted with several aliphatic, benzylic and aromatic isocyanate. The reaction displayed an excellent functional groups tolerability, since the reaction conditions were compatible with halogens, nitro groups, (thio)ethers, nitriles, esters, amides, alkenes and alkynes.

In 2018, the same group studied the synthesis of *N*-substituted β-amino alcohols with a Passerini-type reaction, in which the acid was 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[24] As shown in Scheme 9, the optimized reaction conditions involved the addition of 1.3 equivalents of aldehyde and 3 equivalents of HFIP to a 1 M solution of isocyanate in dichloromethane. After a few hours, the solution was diluted with HFIP and 3 equivalents of AB were added. When aromatic isocyanates were involved in the reaction, it was necessary to add 5 equivalents of trifluoroacetic acid to achieve the reduction of the intermediate imidates. The reaction proceeded in short reaction time and under mild conditions, the product was isolated in moderate to high yield. Moreover, with this strategy, the synthesis of two APIs, Propranolol and (±)-Rivaroxaban, was successfully achieved.



Scheme 8 Synthesis of *N*-substituted β-amino alcohols



Scheme 9 Synthesis of *N*-substituted β-amino alcohols

The two methodologies have complementary scopes: in the first work, the preferential substrates were aromatic aldehydes and aliphatic isocyanates, while in the second publication aliphatic and benzylic aldehydes were reacted with aromatic isocyanides.

2.3 Reactions with alkenes and alkynes

The first example of a non-catalysed reduction of alkenes using ammonia borane as reducing agent was reported by Berke and co-workers.[25,26] Polarized olefins bearing two electron withdrawing groups (nitrile or ester groups) were chosen as substrates. Under the optimized reaction conditions, the activated olefins are reduced to the corresponding alkanes in excellent yields by 0.5 equivalents of $NH_3{\cdot}BH_3$ (Scheme 10a). Notably, the reaction is chemoselective, in fact neither the nitrile group nor the ester moiety were reduced by ammonia borane

Berke group carried out some experiments trying to elucidate the reaction mechanism. It was possible to point out that the hydric B_H hydrogen is transferred to the most nucleophilic carbon of the double bond by conducing the reaction in the presence of deuterated ammonia borane ($NH_3{\cdot}BD_3$ and $ND_3{\cdot}BH_3$). A stepwise process was suggested by the study of the primary deuterium kinetic isotope effect, Hammet correlation on *p*-aryl substituted olefins and by observing the reaction intermediate with *in-situ* NMR studies. The first step is the transfer of H_B, together with the hydroboration of the double bond. The intermediate is slowly converted into the product by intramolecular H_N transfer. A solvent stabilized $BH_2{=}NH_2$ species can reduce another

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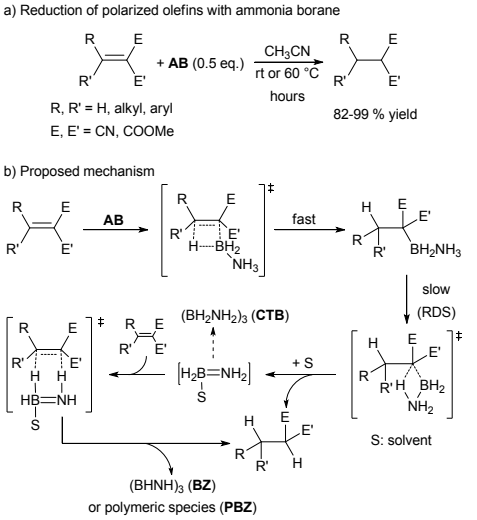
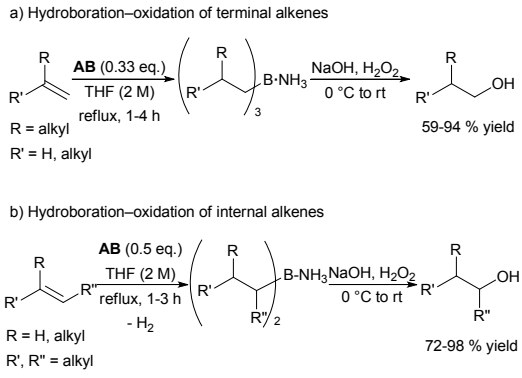
equivalent of olefin, obtaining borazine or polyborazylene as the dehydrocoupling products (Scheme 10b).



Scheme 10 Reduction of polarized olefins and suggested mechanism

Regarding the reduction of non-polarized olefins, a single example was published by Kinjo and co-workers in 2014.[27] The group studied the reaction of the central C=C bond of a C_4 cumulene derivative featuring 4-pyridylidene units with two equivalents of AB. Due to the limited reaction scope, we are not going to discuss it in details.

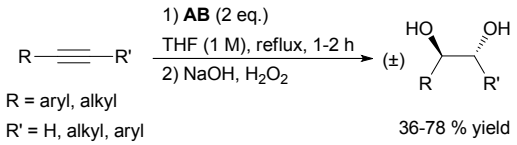
Two years later, the Ramachandran's group investigated the reaction between ammonia borane and poorly nucleophilic alkenes, reporting the first example of non-catalysed open-flask hydroboration of olefins in which the Lewis base (ammonia) remains linked to the boron center.[28]



Scheme 11 Hydroboration-oxidation of olefines

As shown in Scheme 11a, by reacting terminal olefins with 0.33 equivalents of AB, it was possible to obtain trialkylborane–ammonia complexes that were further converted by oxidation with hydrogen peroxide in alkaline medium to the terminal alcohols (ratio of the 1°/2° alcohol isomers: more than 93:7, with the exception of styrene). The reaction between internal alkenes and 0.5 equivalents of ammonia borane led to the formation of aminodialkylboranes in good yields, along with the evolution of an equivalent of hydrogen gas. In this case, it was possible to isolate either the aminodialkylborane or its corresponding alcohol (Scheme 11b). Using either internal or terminal alkenes, when a stereogenic center was present in the starting material, the enantiomeric excess of the olefin was retained in the product.

This method was employed by the same group to convert alkynes into the corresponding vicinal diols.[29] In order to achieve a full dihydroboration two equivalents of ammonia borane proved to be necessary. As shown in Scheme 12, the hydroborated intermediate is then oxidized to the geminal diol in which the two hydroxyl groups displayed an *anti*-arrangement. The reaction proceeded in a short reaction time and the product was recovered in moderate to good yields.

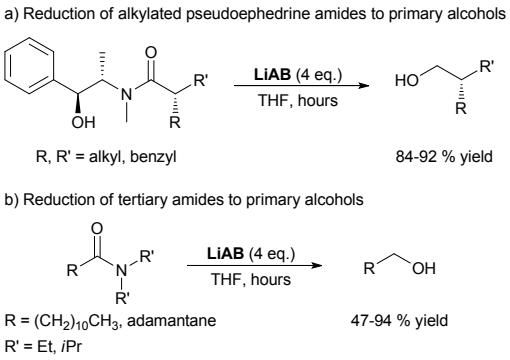


Scheme 12 Synthesis of vicinal diols from alkynes

2.4 Metal aminoboranes

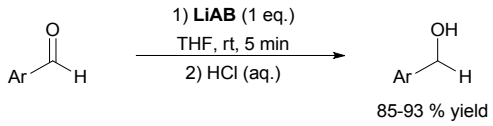
Before the interest in the use of ammonia borane started to rise, not only as hydrogen storage, but also as reducing agent in organic synthesis, Myers and co-workers synthetized LiAB, while they were evaluating different reductants for tertiary amide reduction. In more recent years, a variety of metal aminoboranes bearing an alkali (Group 1) or alkaline earth (Group 2) metal, was synthetized in order to study their hydrogen storage properties. In the current section we present the use of LiAB, NaAB and CaAB as reductants. These reagents are prepared from ammonia borane and *n*BuLi or LiH, NaH and $Ca(NH_2)_2$, respectively.

Myers and co-workers[30] studied the diastereoselective alkylation of pseudoephedrine amides and synthetized LiAB to remove the chiral auxiliary (Scheme 13a). The standard reaction conditions involved the use of 4 equivalents of reducing agent in THF, the reaction time and temperature varied depending on the different substrates. The primary alcohols were obtained in high yields with little or no epimerization of the α-stereocenter. As shown in Scheme 3b, the same method was employed to other tertiary amides, demonstrating that also adamantine-derived amides can be successfully converted to the desired product. The selectivity to primary alcohols with the respect to tertiary amines dropped when too hindered compounds were used.



Scheme 3 Reduction of tertiary amide with LiAB

In 2012, Chen's group worked extensively with metal aminoboranes achieving the reduction of aldehydes, ketones, aldimines and α,β-unsaturated carbonyls. Aromatic aldehydes[15] were reduced under the conditions reported in Scheme 14; the primary alcohols were obtained in high yields and short reaction time. The addition of HCl proved to be mandatory to hydrolyze the borate ester and to isolate the product, since LiAB transferred only hydric B-H to the carbon atom of the aldehyde. In order to elucidate the reaction mechanism, $LiNH_2BD_3$ was reacted with benzaldehyde and α-deuterobenzenemethanol (PhCHDOH) was obtained.

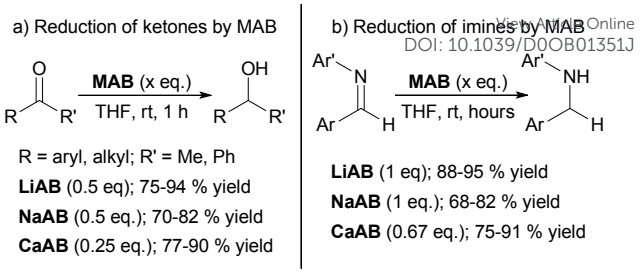


Scheme 14 Reduction of aldehydes with LiAB

In another work,[16] the group demonstrated the ability of the three aforementioned metal aminoboranes in the reduction of ketones and aldimines (Scheme 15). Secondary alcohols and secondary amines were obtained in high yields, under mild conditions. Comparing the results obtained with ammonia borane with those obtained with metal aminoboranes, the authors demonstrated the higher reactivity of the latter.

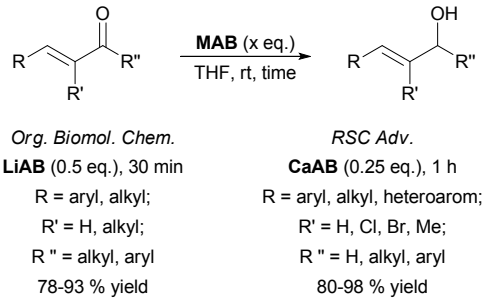
To clarify the reaction mechanism, *in-situ* FT-IR, NMR studies and reactions with deuterated LiAB were carried out; it resulted that both B-H and N-H were transferred to the substrate's carbonyl carbon and to the N atom, in the case of imines, or to the O atom, in the case of ketones, respectively. Based on DKIEs and theoretical studies, it was suggested that the reaction mechanism was not concerted as it was for AB.

The reduction of α,β-unsaturated carbonyls was studied in the presence of LiAB[31] and with CaAB.[32] As shown in Scheme 16, the reaction was chemoselective in both cases, leading to the 1,2 reduction product.



Scheme 15 Reduction of ketones and aldimines with metal aminoboranes

In both cases the reaction was performed in THF at room temperature; the allylic alcohol was isolated in high yields without the need of an acid hydrolysis step. Experiments with deuterated LiAB and CaAB demonstrated that both N-H and B-H were transferred to the α,β-unsaturated carbonyls O atom and C atom, respectively.



Scheme 16 Reduction of α,β-unsaturated carbonyls with metal aminoboranes

3 Reductions promoted by organocatalysts

In this section we discuss organocatalyzed reactions, with the exception of frustrated Lewis pair (FLP) catalysed reactions that are described in section 4. The first part is devoted to non-stereoselective reductions, where AB is often used in combination with different phosphorous-based species, whose activity was investigated in the last decade. Stereoselective reactions are reported in the second part, which is focused on the reduction of C=N and C=O bonds promoted by chiral phosphoric acids.

3.1 Non-stereoselective reactions

Over the last decade, the reduction of *E*-azoarenes to 1,2-diarylhydrazine in the presence of AB and an organocatalyst was studied by several groups (Scheme 17). Different phosphorous-based catalysts have been developed to promote this reaction. In 2012, Radosevich and co-workers[33] demonstrated that catalyst **I**, a planar T-shaped, trivalent phosphorus compound developed by Arduengo's group in 1984,[34] can act as an organocatalyst in the reduction of azobenzene. Under the optimized reaction conditions, the

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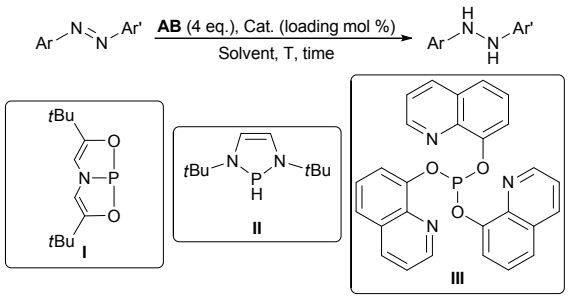
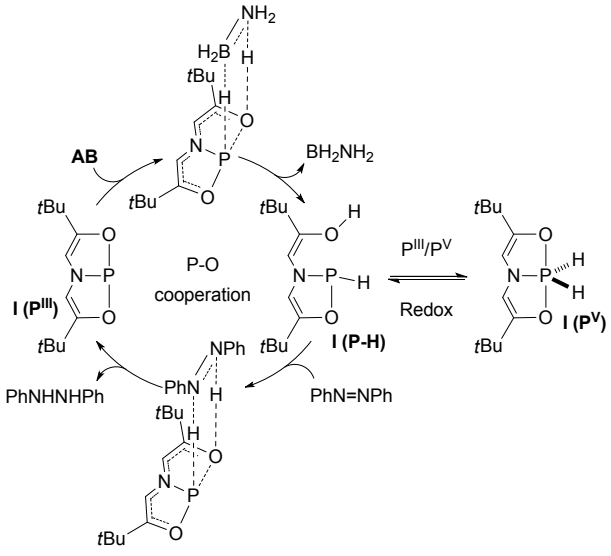
substrate was converted to diphenylhydrazine in high yield by 4 equivalents of AB, in the presence of catalyst **I**.



The Radosevich's group:
Cat. **I** (10 mol%), CH_3CN, 40 °C, 48 h, 94 % yield
The Kinjo's group:
Cat. **II** (5 mol%), CH_3CN, 50 °C, hours, 53-89 % yield
The Landaeta's group:
Cat. **III** (10 mol%), THF, 60 °C, 24 h, 35-95 % NMR conv.

Scheme 17 Reduction of *E*-azoarenes to 1,2-diarylhydrazine

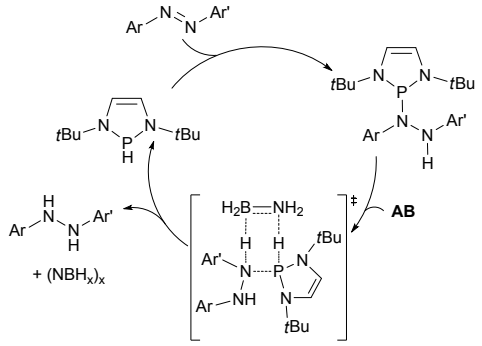
The mechanism of the reaction was theoretically studied by Sakaki and co-workers.[35,36] They demonstrated that the catalysis is based upon a phosphorous-ligand cooperation which resembles the mode of action of transition metal pincer complexes (Scheme 18). In fact, the catalyst **I** (**P^{III}**) interact with ammonia borane to form an intermediate in which P-O bond is broken along with the formation of P-H and O-H bonds; this implies a change in the geometry around the phosphorous atom that becomes tetrahedral-like.



Scheme 18 Proposed mechanism for *E*-azoarenes reduction with AB and catalyst **I**

The intermediate (**I (P-H)**) is capable of transfer the two hydrogen atoms to the azobenzene, thus regenerating the catalyst. The reduction of azobenzene resulted to be the rate determining step of the catalytic cycle. The mechanistic study highlighted also that the oxidized catalyst **I (P ^{V})**, that was experimentally isolated by Radosevich, was not involved in the reduction of azobenzene and it is obtained either by the reaction with NH_2=BH_2 or through an intermolecular hydrogen transfer between two molecules of **I (P-H)**.

Even if the reaction has a limited substrate scope and a long reaction time is needed to achieve complete conversion of the substrate, catalyst **I** paved the way to other phosphorous-based catalytic systems, such as the one reported by Kinjo's group in 2014.[37] The organocatalyst in this case was a diazaphospholene developed by Gudat and co-workers.[38] This catalyst was able to reduce azoarenes bearing both electron-donating and electron withdrawing substituents on the aromatic ring, as well as asymmetric azoarenes, in moderate to high yields. The substrate was reduced by 4 equivalents of AB, in the presence of catalyst **II** (5 mol%), in acetonitrile at 50 °C. The proposed mechanism is reported in Scheme 19; at first, the catalyst added to the substrate, thus forming an *N*-heterocyclic phosphinohydrazine. Then, the exocyclic P-N bond was broken by AB, forming the 1,2-diarylhydrazine and regenerating the catalyst. DFT calculations and deuterium kinetic isotope effects (DKIEs) confirmed the suggested mechanism, outlining a rate determining step in which concerted double hydrogen transfer is realized in a six-membered cyclic transition state.



Scheme 19 Proposed mechanism for *E*-azoarenes reduction with AB and catalyst **II**

The more recent example of the reduction of *E*-azoarenes was reported by Landaeta and co-workers in 2019.[39] The substrates were reduced by 4 equivalents of AB, in the presence of 10 mol % of **III** at 60 °C in 24 hours. The desired product was obtained in high yields when symmetrical azoarenes bearing electron-donating groups (EDG) were reduced by AB, being the only exception substrates with bulky *ortho*-substituents. Excellent results were obtained also with symmetrical and unsymmetrical azoarenes bearing electron-withdrawing groups (EWG) in the *para* position, except for substrates bearing -NH_2 and -COOH, this suggested that the reaction cannot be performed in the presence of acid protons.

Landaeta's group performed some studies to elucidate the mechanism of the reaction; thanks to kinetic studies, an induction time was detected, leading to the hypothesis that **III** is not the active form of the catalyst, but a pre-catalyst. This assumption was supported also by ^{31}P and ^{11}B NMR studies,

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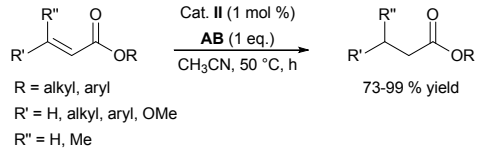
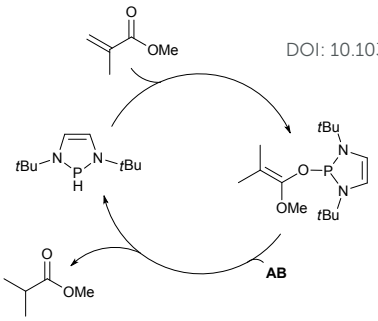
that indicated the formation of several phosphorus- and boron-containing species along with the dehydrogenation of AB. Eyring and Arrhenius analysis were performed and the sign and magnitude of the entropy of activation were compatible with a transition state of a bimolecular reaction with an associative mechanism. DIKEs were carried out and the outcome suggested that B–H and N-H bonds were simultaneously broken, probably in the rate-determining step. Further studies are needed to clarify the active catalytic species; however, it is worthy to notice that pre-catalyst **III** (Scheme 17) is prepared in a single reaction step from commercial reagents on a gram scale. This feature makes it more appealing for a possible application respect to **I** and **II**, which require a series of synthetic steps.

In 2017 Kinjo and co-workers[40] demonstrated that 1,3,2-diazaphospholene (catalyst **II**) is able to promote the reduction of α,β-unsaturated esters in the presence of ammonia borane. The substrate was chemoselectively reduced to ester in the presence of 1 equivalent of AB and catalyst **II**, in an extremely low amount, not common for organocatalysis (Scheme 20).



Scheme 20 Reduction of α,β-unsaturated esters

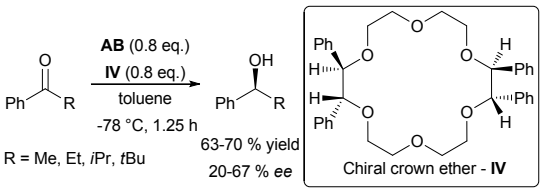
Different esters were obtained in high yields by reacting a variety of α,β-unsaturated ester substrates; both aliphatic and aromatic residues were tolerated. Moreover, the reaction was successfully tested in the presence of a substrate bearing an electron-donating methoxy group at β-position and also disubstituted methyl 3,3-dimethylacrylate was reduced with the optimized reaction conditions. To clarify the reaction mechanism, NMR studies were conducted. Reacting catalyst **II** with a stoichiometric amount of methyl methacrylate led to the 1,4-addition product, phosphinyl enol ether, quantitatively. When the catalytic reaction was performed with D_3NBH_3, the D-N atom was regioselectively transferred to the α-carbon of methyl methacrylate. Based upon these observations, the authors proposed the catalytic cycle reported in Scheme 21, claiming a transfer hydrogenation of the C=C bond using AB, via phosphinyl enol ether.



Scheme 21 Proposed catalytic cycle for the reduction of α,β-unsaturated esters

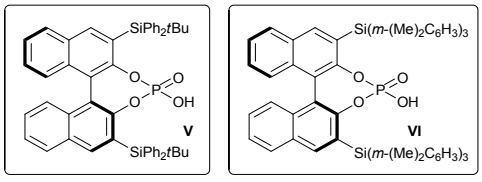
3.2 Stereoselective reactions

The first example of a stereoselective reduction employing ammonia borane as reducing agent dates back to 1984, when Williams and co-worker reported the asymmetric reduction of pro-chiral ketones in the presence of a substoichiometric amount of crown ether derivatives.[41] The optimized reaction conditions are reported in Scheme 22 and it involves the addition of the ketone to a solution of 0.8 equivalents AB and 0.8 equivalents of (*2S*,*3S*,*11S*,*12S*)-tetraphenyl-18-crown-6 derivative (**IV**), or its enantiomer, at -78 °C for one hour. The desired product was obtained in good yield, but with disappointingly low enantiomeric excess for non-sterically hindered R groups, while a good stereoselectivity was achieved with *i*Pr and *t*Bu residues. The recovery of the chiral crown ether was possible.



Scheme 22 Stereoselective reduction of ketones with AB

In 2018, Du and co-workers[42] reported the reduction of imines and β-enamino esters in the presence of a catalytic amount of a chiral phosphoric acid (Scheme 23).



Scheme 23 Two chiral phosphoric acid used in combination with AB

The reaction is reported in Scheme 24a; the substrates were reduced by 1 equivalent of AB in the presence of a catalytic amount of **V** (between 0.1 and 5 mol %), 1 equivalent

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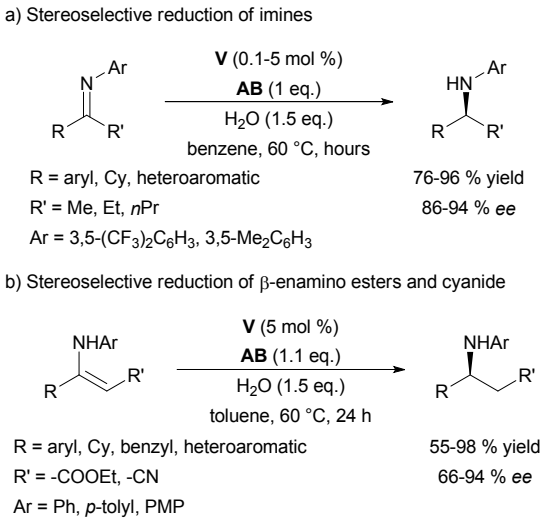
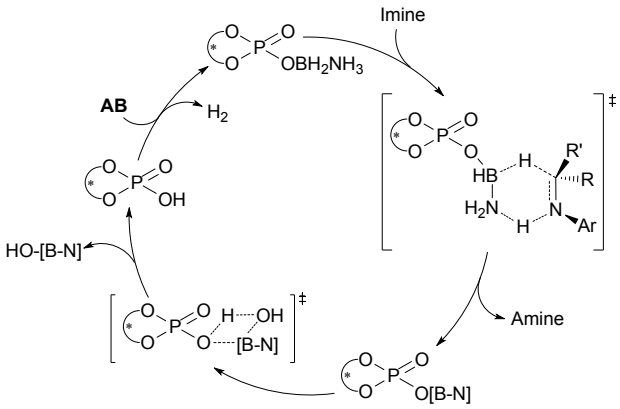
of water, in benzene at 60 °C. Various ketimines were reacted and the corresponding amines were obtained in high yields. Very bulky aromatic rings linked to the N atom of the imine, in combination to bulky silyl substituents at the 3,3' position on the binaphthyl scaffold of the chiral phosphoric acid (CPA) were both necessary to achieve good enantioselectivities.

The reduction of β-enamino esters and of a β-enamino cyanide was also reported by slightly modifying the reaction conditions (Scheme 24b); a higher catalyst loading, and longer reaction times were necessary to complete the reaction. The proposed reaction mechanism is reported in Scheme 25.



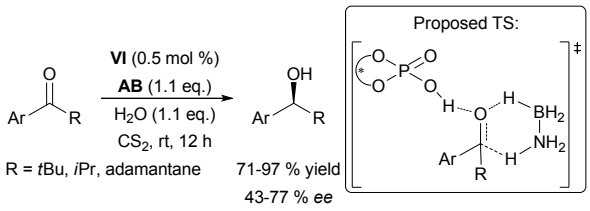
Scheme 24 Stereoselective reduction of imines and β-enamino esters

^{31}P NMR studies demonstrated that the addition of AB to a solution of **V** led to a shift of the peak corresponding to the catalyst, suggesting that **V** acts as a Brønsted acid to generate the reactive chiral ammonia borane. Using DFT calculations, a double hydrogen transfers via a concerted 6-membered ring transition state was predicted. After the imine reduction, several [N-B] species are formed; DFT calculation suggested that both water and AB are capable of breaking the O-B bond to regenerate **V**, however the experimental evidence indicated that water was the major responsible.



Scheme 25 Proposed mechanism of the stereoselective reduction of imines

In 2020, the same group proposed a stereoselective reduction of bulky ketones using the same method, as reported in Scheme 26.[43] In this case, a CPA bearing two extremely bulky substituents on the binaphthyl scaffold (**VI** in Scheme 26) was selected as organocatalyst. The optimized reaction condition, that was used for imines, was slightly modified, in particular, carbon disulfide was selected as solvent and the reaction was performed at room temperature. The secondary alcohols were obtained in excellent yields, however only with ketones bearing very hindered *ortho*-substituted aromatic rings, it was possible to reach good enantiomeric excess.

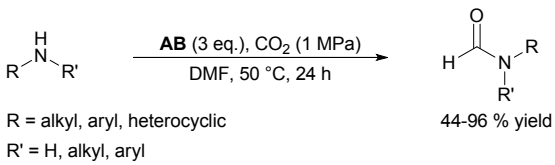


Scheme 26 Stereoselective reduction of ketones

The mechanism was studied; at first the chiral ammonia borane was synthetized by reacting **VI** and AB, then it was reacted with the ketone, but no secondary alcohol was detected after 10 hours in CS_2 at room temperature. This evidence suggests that, differently from the previous work regarding the imine reduction, CPA coordinates the ketone and promotes the double hydrogen transfer between the substrate and AB via six-membered transition state.

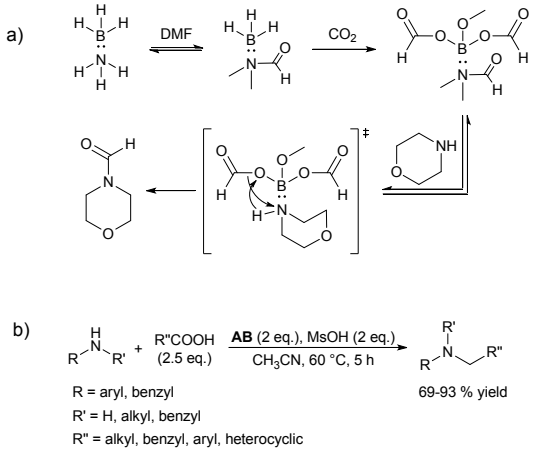
3.3 Miscellaneous

In 2017, Hu, Wu and co-workers[44] developed a synthesis of formamides by *N*-formylation of amines, employing carbon dioxide as the C_1 source and AB as the reducing agent. The optimized reaction conditions are shown in Scheme 27. A primary or secondary amine, either aliphatic or aromatic, was reacted in the presence of three equivalents of ammonia borane, in DMF at 50 °C under CO_2 atmosphere (1 MPa) for one day. The desired formamides were obtained in moderate to high yields and, notably, the formation of the *N*-methylated amine was not observed. The reaction was carried out without a catalyst and the separation of the product was easy as the dehydrogenated AB species are water soluble, however a high pressure of CO_2 was needed to achieve good results.



Scheme 27 Catalyst-free *N*-formylation of amines

Some control experiments were carried out to elucidate the reaction mechanism, it was demonstrated that transformylation of amine to formamide with DMF was not possible under the standard reaction conditions. Knowing that there is an equilibrium between CO_2 and the amine–CO_2 adduct, it was suggested that this could be the intermediate and the reaction was tested on the morpholine–CO_2 adduct. However, the hypothesis proved to be wrong, since the product was detected in traces. The reaction was, then, studied by NMR; an equilibrium between AB and DMF-borane adduct was detected by ^{11}B analysis. After the system was pressurized with CO_2 at 1 MPa, it was possible to isolate the adduct boron-formate and B–OCH_3 by adding ethyl acetate to the mixture. The reaction of this adduct with morpholine gave the product in high yields. The proposed mechanism is reported in Scheme 28.

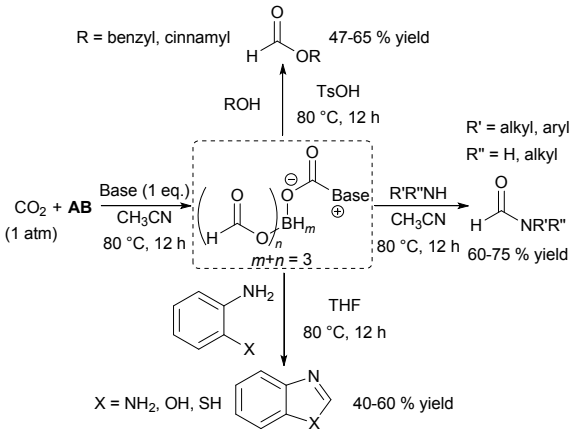


Scheme 28 Proposed mechanism for *N*-formylation of amines

A reductive *N*-alkylation of primary and secondary amines with carboxylic acids as alkylating agents was developed by Zhou, Song and co-workers.[45] The reaction is an alternative to reductive aminations and *N*-alkylations with toxic alkyl halides. Both primary and secondary amines were reacted with 2.5 equivalents of acid in the presence of 2 equivalents of AB and 2 equivalents of methanesulfonic acid (MsOH). The reaction was conducted under inert atmosphere in acetonitrile at 60 °C for 5 hours (see Scheme 28b).

Only aromatic or benzylic amines were alkylated, while the substrate scope of acids was wider, aliphatic and aromatic acids were successfully reacted. Moreover, when unsaturated aliphatic acids were employed, the C=C bond was left untouched. In the presence of primary amine, both the mono and the bis-alkylated product was obtained, by simply tuning the amount of the reagents. Notably, the alkylation was *N*-selective, no traces of *O*-alkylated products were obtained when a hydroxyl group was present in the molecule scaffold. The more likely reaction pathway seemed to involve a transient formation of the amide, which was then reduced by ammonia borane. The methanesulfonic acid seemed to be involved in both the amide synthesis and the reduction step.

An example of carbon dioxide reduction with AB promoted by a base was published by Xi and co-workers.[46] One equivalent of AB was reacted with one equivalent of base under CO_2 atmosphere (1 atm) using acetonitrile as solvent, at 80 °C for 12 hours. Using either triethylamine (Et_3N) or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as base, it was possible to form boryl formates (species in the box in Scheme 29), which were studied by ^1H and ^{11}B NMR.



Scheme 29 Use of boryl formate as formyl transfer agent

Using TBD as base, the reaction was quenched with diluted deuterated hydrochloric acid solution to afford deuterated formic acid or with ammonium hydroxide, thus obtaining formamide. Adding primary or secondary amines to boryl formates, followed by the heating of the mixture at 80 °C for 12 hours, led to a two-step one pot *N*-formylation of amines in good yields. When the amine added to the mixture was 2-substituted aminobenzene (being the substituent another nucleophile), the amide formed was trapped by the nucleophile in a cascade reaction to form a benzoheterocyclic ring in moderate to good yields. In order to obtain esters, it was necessary to use Et_3N as base, followed by the addition of *p*-toluenesulfonic acid (TsOH) and an alcohol. Only benzyl and cinnamyl alcohols were investigated and the esters were isolated in moderate to good yields.

4. FLP (Frustrated Lewis Pairs) catalyzed reductions

In the last fifteen years, the frustrated Lewis pairs (FLPs) have been investigated as innovative, metal-free catalysts for hydrogenation. The seminal discovery in 2006 of H_2 splitting with FLPs by Stephan and co-workers represents a landmark in the field and opened the way to many other studies and applications.[47] The heterolytic cleavage of bonds involves synergistic interactions of the vacant orbital of the Lewis acid and the lone-pair electron orbital of the Lewis base with the σ bonding and σ* antibonding orbitals of H_2, thus generating a

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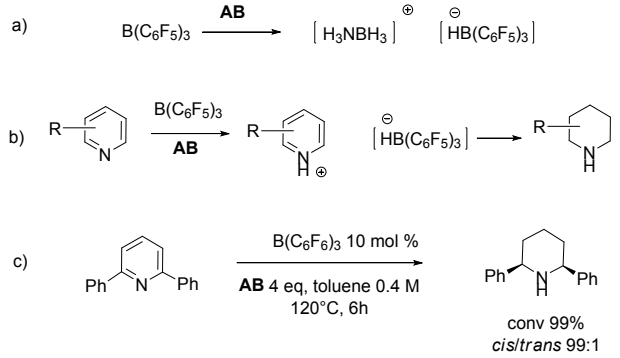
proton and a hydride, which could be transferred to an unsaturated compound.[48-49] In addition to the cleavage of H_2, the FLPs could split other bonds like Si-H[50-51] and B-H, from ammonia borane (AB) complex. The generation of a hydride without the high pressure required for the H_2 splitting is a valid methodology to hydrogenate different unsaturated compounds. Due to its atom economy, high hydrogen storage capabilities and a good stability against air and moisture, AB is a very attractive reagent that has found an increasing use in this type of activation. In this paragraph, we will illustrate the most interesting reductions through FLPs catalyst with AB as the hydrogen source, discussing both non-stereoselective and stereoselective reactions.

4.1- Non-stereoselective reductions

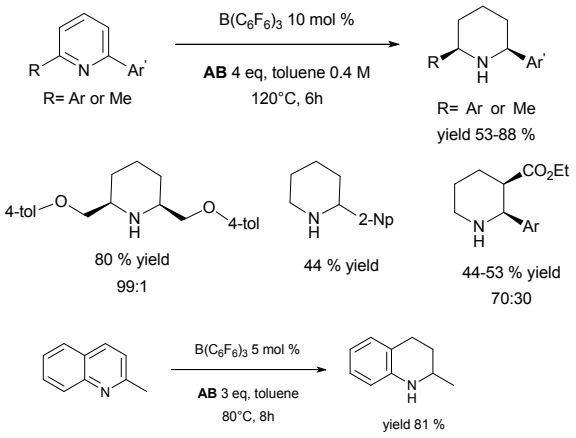
The first examples where AB was used to reduce a zwitterion intermediate generated from a FLP were reported in 2010 by Stephan and co-workers[52] and by Miller and Bercaw.[53] From this findings and based on the previous work by Dixon and Baker on the formation of a zwitterion species for the treatment of $B(C_6F_6)_3$ with AB (Scheme 30a),[54] in 2016 Du and co-workers decided to exploit the FLP strategy to activate AB, in the presence of $B(C_6F_6)_3$ to realize the reduction of the pyridine ring (Scheme 30b).[55] The FLP adduct was able to split the N-H and B-H bonds of the AB complex and the generated zwitterion specie converted completely the pyridines into the corresponding piperidines.



Scheme 30. FLP adduct formation from ammonia borane and pyridines

After having established $B(C_6F_6)_3$ as the best borane to synthetize the more reactive FLP, the authors optimized the experimental conditions for the metal-free reduction and found that best results could be obtained by operating in a 0.4 M toluene solution (Scheme 30c).

The methodology was extended to the reduction of a variety of 2,6-diarylpyridines under the optimal reaction conditions. Electron-withdrawing and electron-releasing functional groups in *ortho*, *meta*, *para* positions on phenyl or aromatic heterocyclic rings were well tolerated and the piperidines were obtain in 63-88% yields with high *cis* selectivities. 2-Aryl-6-methylpyridines and 2,6-dialkylpyridine were also effective substrates for this transfer hydrogenation, and *cis*-piperidines as predominate isomers were obtained in 56–88% yields. Instead, monosubstituted and 2,3-disubstituted pyridines were less reactive substrates and gave the corresponding piperidines in a moderate yield. (Scheme 31)



Scheme 31 Transfer Hydrogenation of 2,6-Diarylpyridines, 2-Aryl-6-methylpyridines, monosubstituted and 2,3-disubstituted pyridines

In 2017, Shi and co-workers studied the hydrogenations of N-heterocycles complex with $B(C_6F_6)_3$ and AB as a hydrogen source.[56] Initially the hydrogenation of quinaldine was studied as model reaction (Scheme 32); from the optimization studies it emerged that the reaction temperature had a fundamental role, and only working at temperature higher than 80 °C good yields could be reached.

Scheme 32 Optimization of the Transfer Hydrogenation conditions of quinaldine

After having established the optimal procedure, the authors have investigated how the transfer hydrogenation proceeded both with six-membered N-heterocycles rings such as quinolines and quinoxalines substituted in different positions, and with five-membered N-heterocycles rings as 2- or 7-substituted indoles. The reaction worked smoothly with electron-withdrawing, electron-donating and hindered functional groups, and was not influenced by the the substituents' position (Scheme 33).

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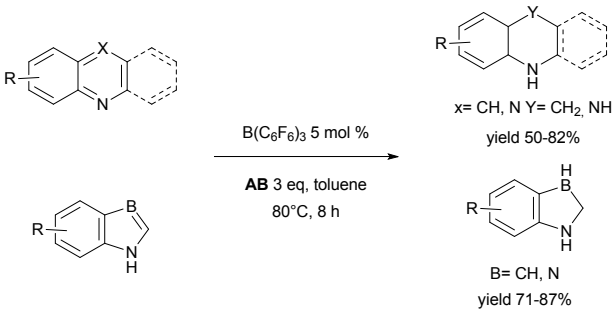
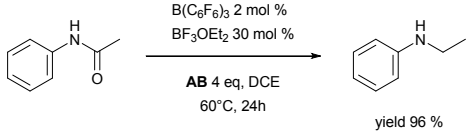


Scheme 33 Transfer Hydrogenations of various N-heterocycles

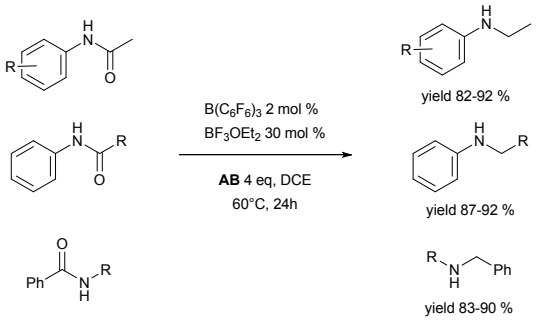
More recently, in 2019, Xiao and co-workers have applied to the deoxygenative reduction of amides into the corresponding amines.[57] The reduction of phenylacetamide into the N-ethylaniline was been studied as the model reaction (Scheme 34).



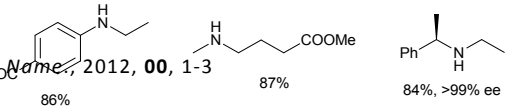
Scheme 34 Optimization of the Transfer Hydrogenation conditions of phenylacetamide

In the first tests, the authors observed the formation of aniline as byproduct in a significant amount, but using the 1,2-dichloroethane (DCE) only the desired product was obtaned. Moreover, it was necessary to add a catalytic amount of an acidic additive to have a better perform of the C-O bond cleavage which brought to the reduced product. From this optimization studies it emerged that $BF_3{\cdot}OEt_2$ was the best acidic additive and $B(C_6F_6)_3$ the best boron catalyst

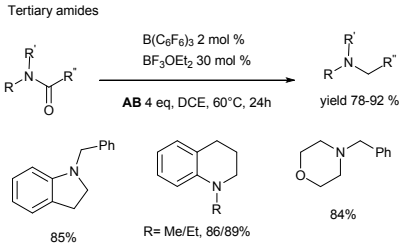
Having optimised the reaction conditions, the authors, firstly, have tested a series of secondary amides, tweaking the substituents' tolerance on the aryl and on the amidic portions. Both *N*-arylacetamides substituted with functional groups different in electronic nature and position and *N*-phenyl amides with aliphatic and aryl acyl groups have afforded good and excellent yields (Scheme 35).



Scheme 35 Reduction of Secondary Amides with AB

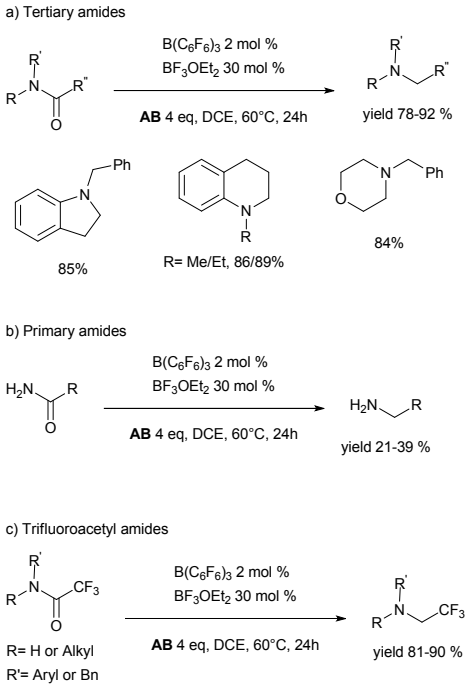


The reaction proofed to be chemoselective, as ester groups were not reduced, and respectful of the stereogenic centers: enantiopure amides could be converted into *N*-alkyl chiral amines in good yields and with no erosion of enantiomeric excess (Scheme 35).



Scheme 36 Reduction of Tertiary Amides with AB

The tertiary amides behaved similarly to the secondary amides: electron-withdrawing and electron-realising substituents on the nitrogen and on the carbonyl moiety were well tolerated; it is possible to reduce lactams thus synthesizing *N*-substituted heterocycles (Scheme 36).



Scheme 37 Reduction of Tertiary, Primary and Trifluoroacetyl Amides with AB

Primary amides did not afford good results; the target products were isolated in low yields, along with the recovery of starting materials. Finally, the trifluoracetamides, which are useful buildings blocks for the pharmaceutical industry, have been reduced in good yields, either with *N,N*-dialkyl or diaryl substituted substrates (Scheme 37).

After the successful deoxygenative reduction of amides, the authors extended the protocol to the synthesis of cyclic amines from lactams. As expected, the reduction of 3,4-dihydroquinolin-2(1H)-one proceeded well and the yield didn't

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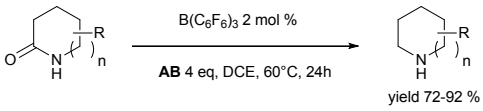
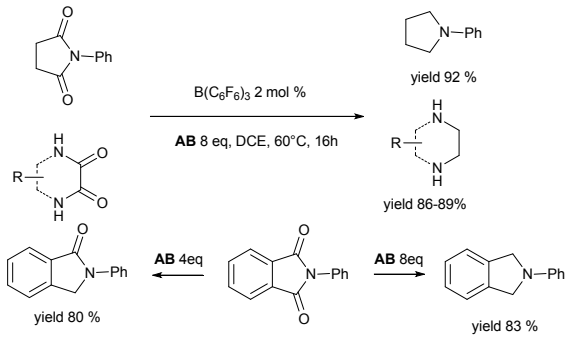
undergo variations in the absence of any co-catalyst, highlighting that it wasn't necessary the addition of $BF_3{\cdot}OEt_2$ to get an easier lactams reduction. A series of benzo-fused and aliphatic lactams were investigated; the ring size and the presence of amine group didn't have any impact on the reaction efficiency (Scheme 38).



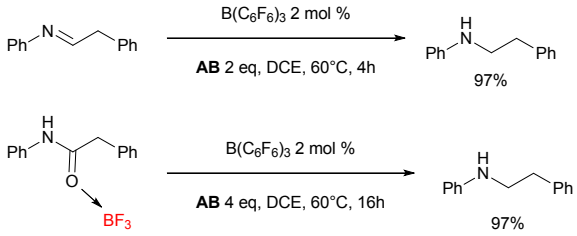
Scheme 38 Reduction of Lactams with AB

Also, cyclic imides and oxalamides gave excellent results under the transfer hydrogenation catalysed by $B(C_6F_6)_3$ and AB as reductant. Moreover, modifying the AB equivalents it was possible to obtain a mono or double reduction (Scheme 39).



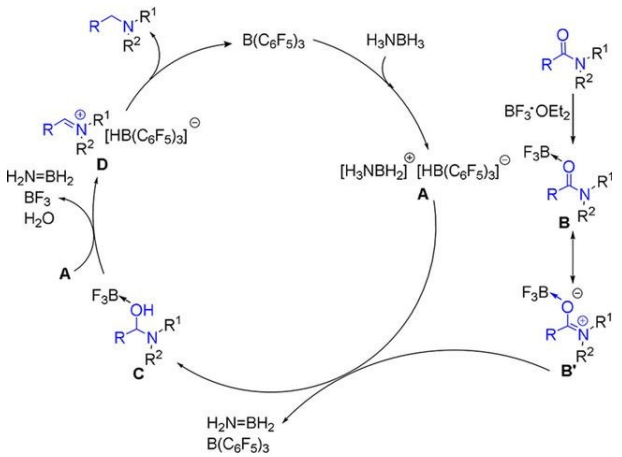
Scheme 39 Reduction of Cyclic Imides and Oxalamides with AB

After having established the extraordinary versatile and strength of this methodology, and based on Milstein studies,[58] Xiao and co-workers have studied the reaction's mechanism. Comparing the reduction of imine *N*-phenyl imine of phenylacetaldehyde, with that of *N*-phenyl amide of phenylacetic acid, the role of co-catalyst $BF_3{\cdot}OEt_2$ was highlighted as *in situ* activator of the carboxyamide group (Scheme 40).



Scheme 40 Control Experiments for mechanistic studies

From that observations, the authors have proposed the mechanism reported in scheme 41, where the generation of the zwitterionic species **A** from $B(C_6F_6)_3$ and AB reacted with the activated $BF_3{\cdot}OEt_2$-amide complex **B** to afford the intermediate **C**. Next, **C** was hydrated by the zwitterionic species leading to the formation of an imine intermediate **D** that was reduced to the desired amine product with the release of $B(C_6F5)_3$ catalyst.



Scheme 41 Proposed mechanism for the amide reduction

4.2 Stereoselective reductions

The development of catalytic, enantioselective reactions with ammonia borane would represent a significant step forward the establishment of AB-mediated reductions as powerful and viable synthetic tool, but the topic is still underdeveloped. The first asymmetric reduction with complexes of AB was documented in 1984, when Williams and co-workers have described the asymmetric reduction of imines with chiral 18-crown-6 derivatives, to give the products in up to 67% ee.[59]

More than twenty years later Du and co-workers in 2016 investigated a new methodology for an asymmetric metal-free reduction of imine.[60] They have chosen (*S*)-*tert*-butylsulfinamide (**(*S*)-1**) as chiral auxiliary and as Lewis base in the proposed FLP the for its coordinating properties, appropriate steric hindrance, and weak N-H acidity. Piers' borane $HB(C_6F_5)_2$ was selected as suitable Lewis acid, due to its strong Lewis acidity, good hydride nucleophilicity, and correct steric requirements. Firstly, a stoichiometric asymmetric transfer hydrogenation was developed, using 1.1 eq. of Piers' borane and 1.1 eq. of **(*S*)-1** in CH_2Cl_2 at rt for 14h. The desired product was obtained in quantitative conversion with 90 % ee. Next, a series of imines were tested into the transfer hydrogenation. As shown in scheme 42, the reaction tolerates electron-poor and electron-rich groups on the aromatic ring, in *ortho*, *meta* and *para* position, producing the target products in 78-96% yields with 73-96% ee. Then imines with different protecting groups on the nitrogen atom were analysed.

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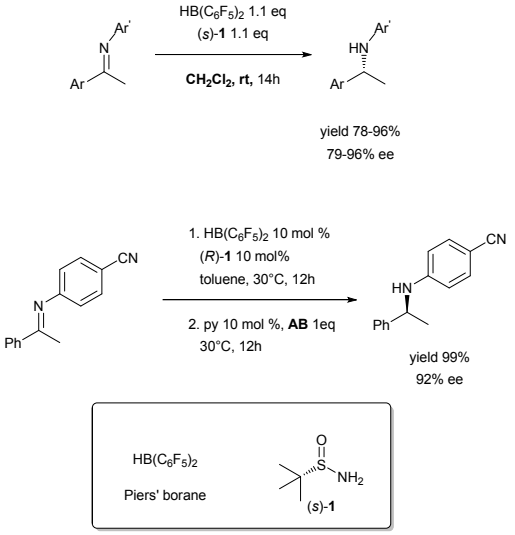


Scheme 42 Stoichiometric Asymmetric Transfer Hydrogenation of Imines

In order to make catalytic the reduction, the crucial step was to find the appropriate hydrogen source to close the catalytic cycle and reform the reducing agent Piers' borane. The transfer hydrogenation of *N*-(1-phenylethylidene)aniline was re-examined using Piers' borane (10 mol %) and (*R*)-*tert*butylsulfinamide (***R*)-1** (10 mol %) in toluene with H_2 (20 bar) and AB respectively. Although the use of H_2 afforded the product with promising enantiomeric excess, the conversion was very low (10%); on the other hand, the AB-mediated reduction suffered from a low ee (35%), although an almost total conversion was observed. This loss of ee was due to other competitive pathways which do not involve the chiral catalyst.

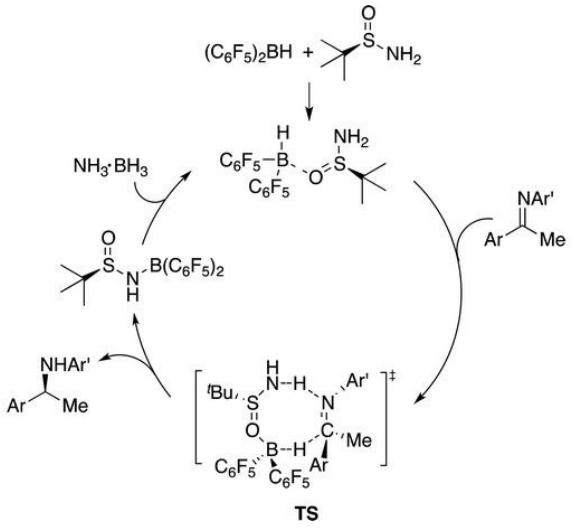
The better strategy to improve the enantioselectivity involves the addition of AB in a second step, after a 12 h stirring of the chiral catalyst and the borane, and the presence of pyridine as an additive. With these precautions, it was possible to reach, a 99% conversion and 92% ee.

Under optimal conditions, the substrate scope was studied for the catalytic asymmetric transfer hydrogenations and a quite wide range of functionalised substrates were successfully reduced in 78-99% yields with 84-95% enantioselectivities.

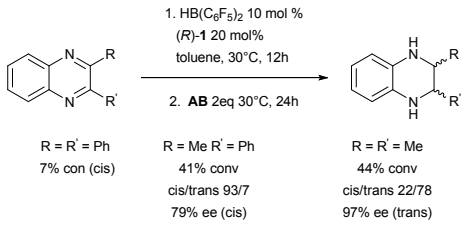
Finally, Du and co-workers have proposed a catalytic pathway, described in scheme 43, based on experimental and theoretical studies. In these studies, they have identified the more stable isomer, the B-O complex formed by the interaction of Piers' borane and **(*R*)-1**. Then, ^{11}B NMR studies have highlighted the gradually decreased of the B-O complex and the increase of the signal of the B-N complex, while DFT calculations have suggested that the reaction proceeded through an 8-menbered ring transition state TS. Other ^{11}B NMR studies on the B-N complex have underlined the regeneration of the complex B-O, while DFT calculations have confirmed that it has occurred through a 6-menberd ring transition state.

Scheme 43 Proposed catalytic pathway of the catalytic asymmetric reduction of imines

After these findings, in 2017 Du and co-workers investigated the catalytic asymmetric reduction of



quinoxalines, to afford optically active tethahydroquinoxalines, products of interest in medicinal chemistry, for their biologically activity.[61-62] It was found that 2,3-diphenylquinoxaline reacted sluggishly and gave only a small amount of product with cis selectivity; however, 2-methyl-3-phenylquinoxaline and 2,3-dimethylquinoxaline afforded the corresponding tethahydroquinoxalines in 41% and 44% yields with the 79% ee for the *cis* and the 97% ee for the *trans* isomer, respectively (Scheme 44).



Scheme 44 Asymmetric Transfer Hydrogenation of 2,3-Disubstituted Quinoxalines

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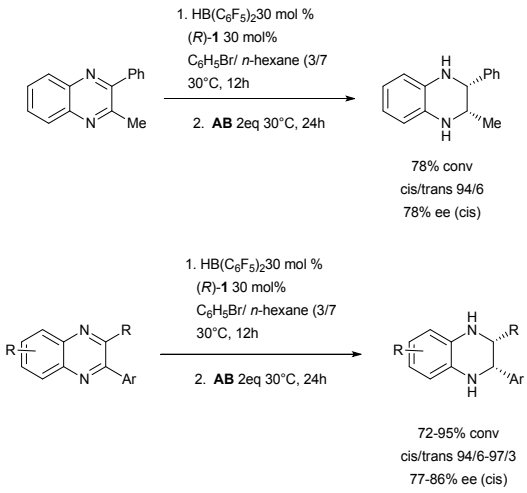
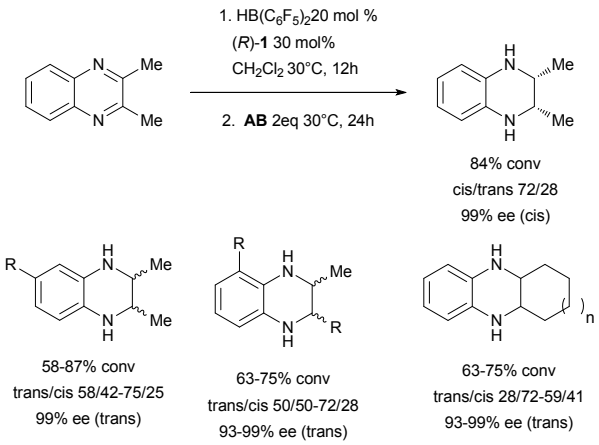


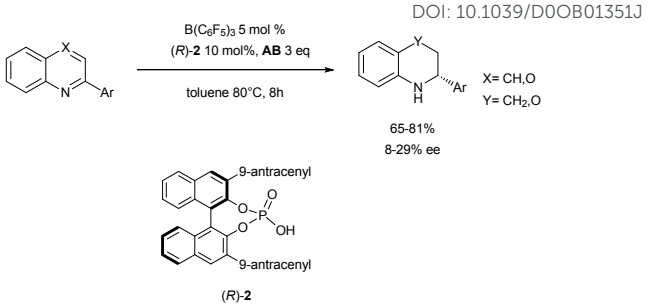
Scheme 45 Asymmetric Transfer Hydrogenation of 2-Alkyl-3-arylquinoxalines

Under the optimal reaction conditions (30 mol % of catalyst and 3/7 mixture of bromobenzene/*n*-hexane as solvent) a variety of 2-alkyl-3-arylquinoxalines were successfully reduced in 72−95% yield, high *cis* selectivity and 77−86% ee.
Also he asymmetric reduction of 2,3-dimethylquinoxaline was optimized using CH_2Cl_2 as solvent and the combination of Piers' borane (20 mol %) and (*R*)-*tert*butylsulfinamide **(*R*)-1** (30 mol %) as catalysts. Under these conditions, a series of 2,3-dimethylquinoxaline were reduced in 58−86% yield with 50:50−75:25 dr and 89−99% ee for the *trans* isomers.



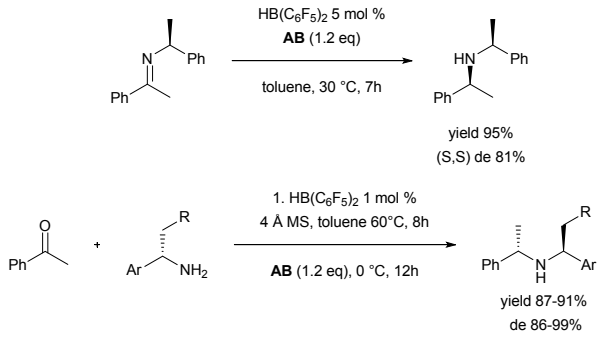
Scheme 46 Asymmetric Transfer Hydrogenation of 2,3-Dialkylquinoxaline

In the same year, Shi and co-workers[56] have published an asymmetric transfer hydrogenation of quinolines and 1,4-benzoxazine derivatives with $B(C_6F_5)_3$ and **(*R*)-2** as FLP catalysts and AB as hydrogen source. Unfortunately, all the reactions have given the desired products in 65-81% yields and very low ee (8-29%) (Scheme 47).



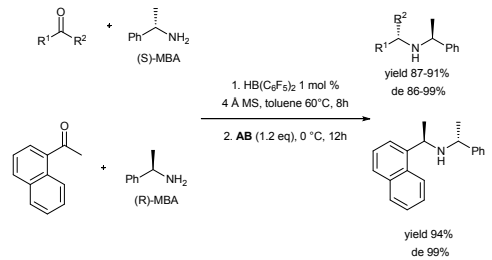
Scheme 47 Asymmetric transfer hydrogenations of quinolines and 1,4-benzoxazine derivatives

Inspired by the Stephan' 2011 work in which they have reported a $B(C_6F_5)_3$-catalyzed diastereoselective catalytic hydrogenation of imines,[63] in 2018 Zhong and co-workers have focused on the reductive amination of ketones with a $B(C_6F_5)_3$-catalyzed and silanes as hydrogen source.[64] The first tests highlighted how a less hindered silane brought a better diastereoselectivity, though still moderate. So, the authors selected AB as a better hydrogen source; the authors developed an optimized one pot reductive amination of ketones, where improved yields were achieved by the addition of 4Å molecular sieves, which reduced the *in-situ* generation of H_2O, indicating that the drying of the reaction mixture was crucial. The decrease of the temperature to 0 °C in the second step of the reaction allowed to increase the diastereoselectivity up to 91% (Scheme 48).



Scheme 48 $B(C_6F_5)_3$-Distereoselective Catalyzed Hydrogenation of Imine

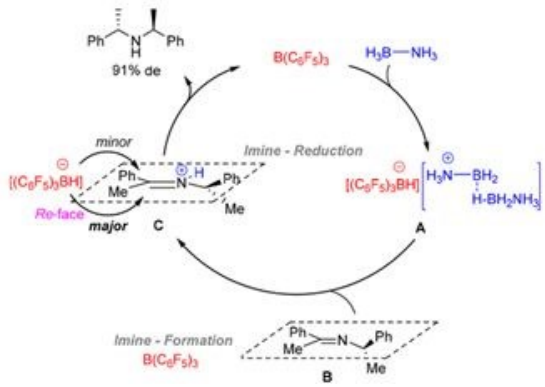
Next, Zhong and co-workers have analysed the effect of the chiral auxiliary on the diastereoselectivity of the product. It was found that electronic effect had less relevance, on the contrary the steric effect of the chiral auxiliary has bought a remarkably improvement of the diastereoselectivity.



Scheme 49 Effect of Chiral Auxiliary on the Diastereoselectivity of Product

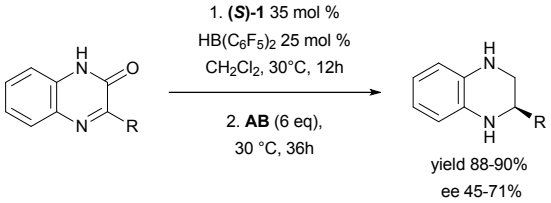
Although the 1-(naphthalen-1-yl)ethanamine has given the best result, in consideration of the atom economy and the easy removal of the chiral auxiliary, the α-MBA remains the best choice. Hindered ketones led to an increase of the diastereoselectivity. Replacing the (*S*)-α-MBA with the corresponding (*R*) enantiomer in the reductive amination of the 1-acetonaphthone, it afforded desired product in 94% yield with 99% de (Scheme 49).

The authors have also proposed a catalytic pathway for this asymmetric reductive amination, where $B(C_6F_5)_3$ promoted the ketone-amine condensation, resulting in the formation of trans- imine **B** via a B···O interaction. $B(C_6F_5)_3$ activated ammonia borane to generate species **A** with an ion pair, followed by the protonation of the imine to give intermediate **C**. Owing to the low reduction temperature, the *trans-to-cis* imine isomerization of **C** rarely takes place, which is the key requirement for the high diastereoselectivity of product. Finally, the borohydride attacks at the iminium carbon from the less encumbered *Re*-face to afford the (*S,S*)-product in 91% de along with the release of $B(C_6F_5)_3$ (Scheme 50).



Scheme 50 Proposed mechanism for diastereoselective AB-mediated reductions.

In 2019, Xiao and co-workers, inspired by the Du's findings on the asymmetric transfer hydrogenation using Piers' borane and (S)-1 as FLP catalyst, have synthetized chiral 1,2,3,4-tetrahydroquinoxalines via sequential reduction of imine and amide moieties.[57] They have obtained the desired products in 88-90% yields with 45-71% ee. While molecules featuring aromatic rings in position 3 were reduced in high yields, although with moderate enantioselectivity, methyl and benzyl substituents showed to be poorly reactive (Scheme 51).



Scheme 51 Synthesis of Chiral 1,2,3,4-Tetrahydro-quinoxalines.

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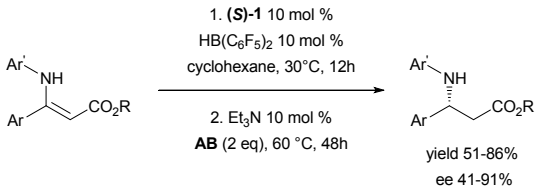
Very recently Du and co-workers have developed a catalytic asymmetric reduction of β-enamino esters, interesting building blocks in the synthetic and medicinal chemistry.[65] The best chiral catalyst was the known combination of the (S)-*tert*-butylsulfinamide (**(*S*)-1**) and Piers' borane $HB(C_6F_5)_2$. The authors have used ethyl (Z)-3-(4-methoxyphenyl)amino)-3-phenylacrylate as model substrat. It was found that the solvent had a large impact on the reaction's enantioselectivity and those alkanes, like cyclohexane, have given the better results. A Lewis base is necessary as additive to avoid the possible racemic pathway catalysed by the free Piers' borane.



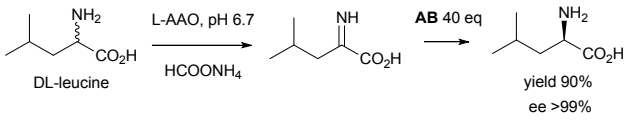
Scheme 52 Asymmetric transfer hydrogenations of β-enamino esters

Next a variety of ethyl (Z)-3-amino-3-phenylacrylates with diverse *N*-substituents were subjected to the asymmetric transfer hydrogenation under the optimal reaction conditions, to give the desired products in moderate yields 51-79% with 41-85% ee's. Substituents in *ortho* position led to lower yields and ees. When the effect of the ester group was investigated, the *tert*-butyl group gave the best result (Scheme 52).

5. Biocatalyzed reactions. Amine borane in deracemization processes

The deracemization process is a clever strategy for the synthesis of enantiomerically pure chiral compounds. It consists in a cyclic oxidation/reduction cascade where an enantiomer of a racemic mixture has been oxidized by an enzyme to an achiral intermediate. The achiral intermediate was subsequently reduced by a non-selective reductant. The repetition of this process leads to the accumulation of a single enantiomer. Commonly used non-selective reductants are sodium borohydride and sodium cyanoborohydride. AB may represent a valuable alternative in the deracemization process, in fact it is stable in water and at neutral and basic pH and a soluble in a wide range of protic and aprotic solvents. Turner and co-workers in 2002[66] have examined the deracemization process of DL-mixture of amino acids with L-amino acid oxidase (L-AAO) from *Proteus myxofaciens*. The authors first have studied the process of DL-leucine, the reaction was performed at pH 6.7 in 50 mM ammonium formate solution (Scheme 28). It was necessary to use 40 equivalents of AB to obtain an immediate reduction of the intermediate α-imino acid and avoid the hydrolysis to the keto acid. Next several racemic mixtures of natural and unnatural amino acids were then subjected to the deracemization process using AB and L-amino acid oxidase: all of them have given excellent yields and

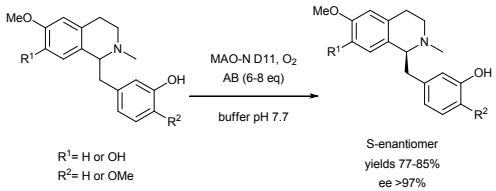
ee's.



Scheme 53 Deracemisation of DL-leucine with L-amino acid oxidase and AB

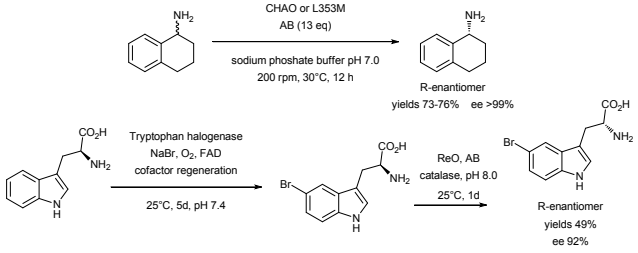
Kroutil and co-workers in 2014[67] have described the deracemization process of benzylisoquinoline alkaloids using AB as reducing agent and monoamine oxidases (MAO-N), which have derived from *Aspergillus niger* and it was been engineered for selected amines. The first step was a screening to find the more active MAO-N for benzylisoquinolines; the authors have demonstrated with a colorimetric assay based on hydrogen peroxide formation that MAO-N D11 had the best activity with preference for the (R)-enantiomer. A variety of benzylisoquinolines were tested being incubated with the enzyme for 24 h in the absence of a reducing agent.

Once chosen the best active substrates, it was established that the loading of the biocatalyst had to be high. Also, it was demonstrated the stability of the biocatalyst under the process conditions: 37 °C, 10 % v/v DMSO and 40 mM AB. In the end, using these conditions it was possible to scale up the process converting 0.5 mmol of the racemic benzylisoquinolines into the optical pure S enantiomer with high yields.



Scheme 54 Deracemisation of benzylisoquinolones.

In the same year, Zhu and co-workers have studied the use of cyclohexylamine oxidase (CHAO)[68] of bacterial origin and five engineered mutants, which derive from it, into the deracemization process of primary amines. After having obtained the recombined enzymes (wild-type CHAO and mutants), the authors have verified them pH and temperature stability. These enzymes have exhibited the maximum activity at pH 6.5, but they have maintained an acceptable activity over a broad range of pH 6.0-9.0 pH, while wt CHAO was been stable at 40 °C for at least 30 min, but decreased rapidly above 40 °C.A series of primary amines, with diverse structural features, were selected to characterize the substrate profiles of the wt CHAO and its mutants. In addition, for those racemic substrates that have given positive results, it was found that the enzymes had a preferential activity for the (R)-enantiomers. The wt CHAO and the mutants was found to be active towards most of the amines with aliphatic, cycloaliphatic, or aromatic moieties. The position (*ortho*, *meta*, *para*) of the substituent and their size have influenced the specific activity of wt CHAO; in fact, the more hindered substituents the less specific activity of the enzymes was observed. Also, the nature of the substituents has played a significant role, suggesting that electron-withdrawing substituents have enhanced the rate of a-C–H bond cleavage.



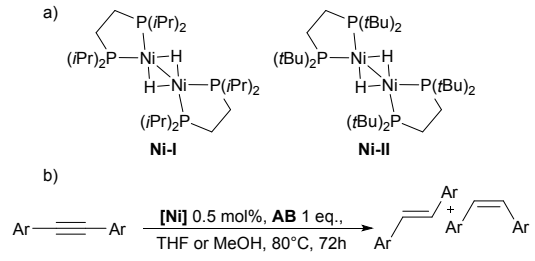
Scheme 55 Deracemisation of primary amines.

A significantly example of the deracemization process was that of 1-aminotetraline: it was carried out by combining wt CHAO or mutant L353M with borane–ammonia complex as achiral reducing agent. The mixture was shaken at 200 rpm and 30 °C on an orbital shaker for 12 h, the pH of the reaction was then carefully adjusted to pH 9 with NaOH solution. The racemic 1-aminotetraline was inverted to (R)-1-aminotetraline (ee>99), which was obtained in 76 % yield for L353M and 73 % for wild-type CHAO, respectively.

Very recently, in 2019 Sewald and co-workers have studied a dynamic stereoinversion using an amino acid oxidase (AAO) from *L.aerocolonigenes* (RebO) with AB as a concomitant reducing agent, to give access to substituted D-tryptophans derivatives with excellent ee.[69] In a one-pot strategy, enzymatic halogenation and stereoinversion were combined to afford the D- tryptophan derivative starting from natural L-tryptophan. From HPLC purification, it was obtained D-5-Br-Trp in 49% yield over three steps and 92.0% ee.

6. Reductions promoted by organometallic complexes

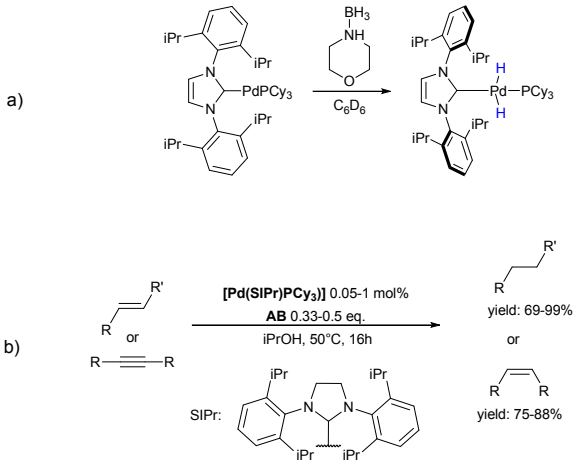
As aforementioned in the previous paragraphs, AB fulfils a preminent role in indirect hydrogenations. It was only a matter of time before the transition metal started to be paired with this reagent, the role of the metal being to mediate the hydrogen release from AB to a chosen substrate.



Scheme 56 a) Nickel catalyst used in the test b) General reaction conditions

To the best of our knowledge, Garcia *et al.* were the first to use a transition metal as a catalyst for this scope, performing the semìhydrogenation of alkyne.[70] By GC analysis of the

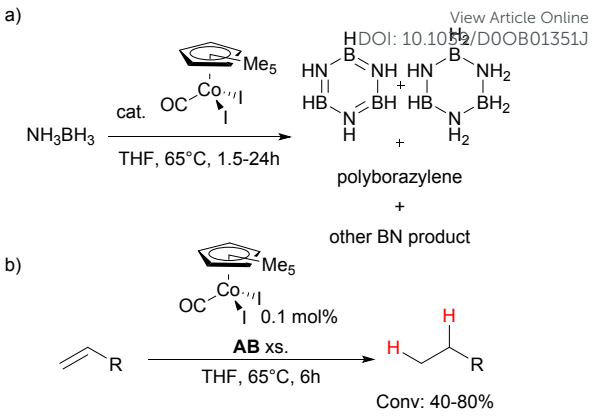
reaction crude, it was observed that the *E/Z* ratio was particularly dependent from the solvent: while THF promoted preferentially the *Z*-product, MeOH led to the *E* stereoisomer. Some years later, Cazin used a Pd(0) complex for the hydrogenation of alkene and the semihydrogenation of alkyne.[71] Based on a previous work, describing the activation of H_2 by a [Pd(NHC)$(PR)_3$] complex,[72] they decided to combine the same catalyst class with NH_3BH_3. Before even starting with catalysis tests, it was necessary to verify if the palladium complexes could release hydrogen from AB. ^{1}HNMR studies of a mixture of [Pd(IPr)$(PCy)_3$] (IPr=*N-N'*-bis-(2,6-di-iso-propylphenyl)imidazole-2-ylidene) and morpholine-borane in C_6D_6 resulted in the immediate gas release, H_2, and when the experiment was repeated in a sealed NMR tube, the dihydride complex was obtained, as depicted in Scheme 57a. After optimisation, the best conditions were identified to perform the reduction in good yields (Scheme 57b).



Scheme 57 Dihydride complex formation and Pd-catalysed reduction

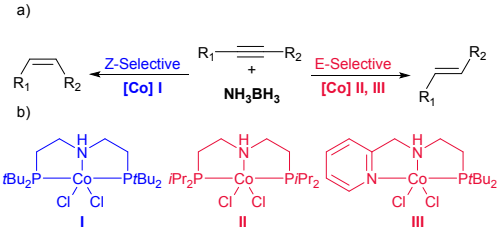
The semihydrogenation of alkyne worked well, obtaining from good to excellent yield, the Z-isomer, with a very low [Pd] catalytic loading (below 1 mol%). The reduction of alkene also proceeds smoothly, with good to excellent yield.

Up to now, the simple dehydrocoupling reaction of AB, without further application, was obtained only with noble metals like Rh[73] and Ir.[74] With the heavier elements of the group 9 displaying such behaviour with ammonia-borane, it wouldn't be wrong to assume that, also cobalt, will display a similar nature, with the further advantage to be an earth-abundant metal, compared to Rh and Ir. Wateman *et al.* in 2015 reported a Co complex able to perform a tandem reaction. Indeed, Cp*Co(CO)I_2 was able to dehydrogenate AB (Scheme 58a), and then perform hydrogen transfer (Scheme 58b).[75] At RT the reaction gave really low conversion (<10%); it was also demonstrated that a sealed environment inhibited the dehydrocoupling rate due to the accumulation of hydrogen. However, the catalyst is robust enough to resist to aerobic condition and operating at 65°C good yields were obtained.



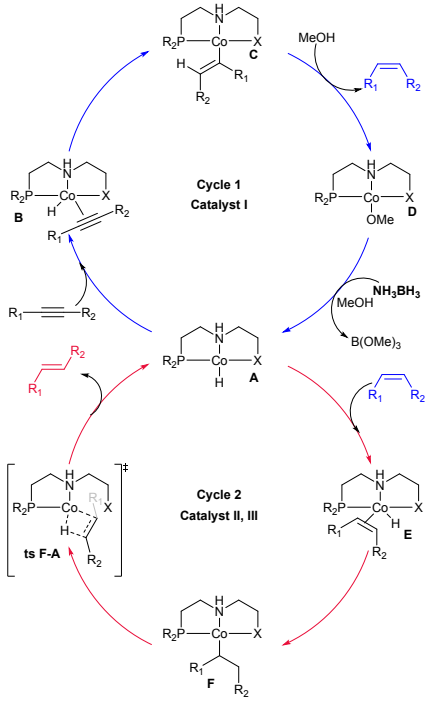
Scheme 58 a) Dehydrocoupling reaction of AB; b) Hydrogenation of alkene

A further step was made by Liu, who published a stereodivergent alkyne semihydrogenation with a cobalt complex in the presence of AB as hydrogens source (Scheme 59).[76] The selective control of the reaction was possible thanks to a rational catalyst design, in particular, by a careful tuning of the steric properties of the ligand.



Scheme 59 a)Stereodivergent synthesis of alkene b) Structure of [Co] catalysts

To retrieve the *E* product, a catalyst with a low steric hindrance is required, like **II**, or better with a hemilabile ligand as **III**.

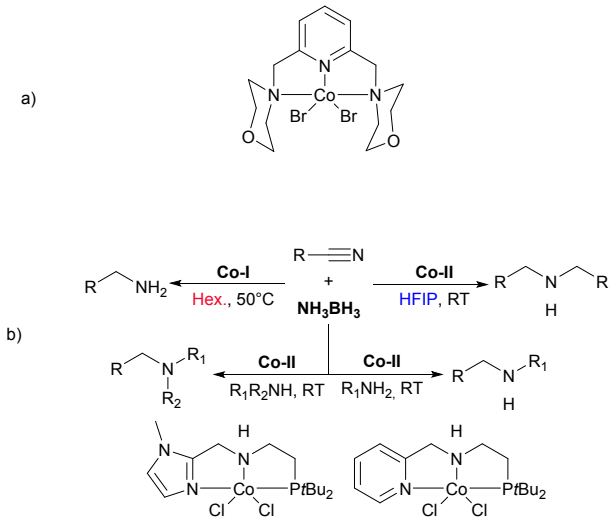


Scheme 60 Proposed catalytic cycle

View Article Online DOI: 10.1039/D0OB01751J

The proposed mechanism started with the formation of the hydrido complex from the dichloride cobalt complex by reaction with AB. π-coordination to the alkyne and consequent insertion in the Co-H bond are the following steps, that gave the alkenyl-cobalt intermediate **C** (Scheme 60). At this point, the protonation of the substrate by methanol, as confirmed by deuterium labelling experiment, leads to the Z-product; on the other side, if the catalyst used was **II** or **III**, the reaction proceeds through cycle 2. Here, the hydrido complex can easily interact with the Z-alkene just obtained, giving, after insertion on the Co-H bond, the alkyl-cobalt intermediate **F**. The isomerisation step can be now accomplished; indeed, with a low steric hindrance or with a hemilabile ligand, the β-elimination results to be faster than the protonation mediated by methanol, thus diverting the reaction through the *E*-product. A kinetic study on reaction mediated by catalyst **III** showed that when the concentration of alkyne drops down, the *Z*-alkene, that can be always formed, was immediately converted in the *E*-alkene.

In 2018, Balaraman and co-workers developed a transfer semi-hydrogenation of unbiased internal alkynes to Z-alkenes, employing a novel, air-stable NNN-cobalt (II) pincer complex (Scheme 61, a), together with ammonia borane as the transfer hydrogenating source. Remarkably, the reaction proceeded under mild conditions and no additive was needed. Both symmetrical and unsymmetrical biaryl substituted alkynes and acyclic aliphatic alkynes were subjected to the optimized reaction conditions, that involved the use of 1.1 equivalents of AB, in the presence of 4 mol% of the catalyst in methanol at 80 °C. The present method was compatible with the presence of trifluoromethyl, cyano, nitro, O-silyl protected alcohols and ester moieties. Moreover, terminal alkynes were reduced to the alkenes in high yields when the reaction was conduced at 50 °C; the corresponding alkanes were selectively obtained when the reaction mixture was heated at 80 °C.

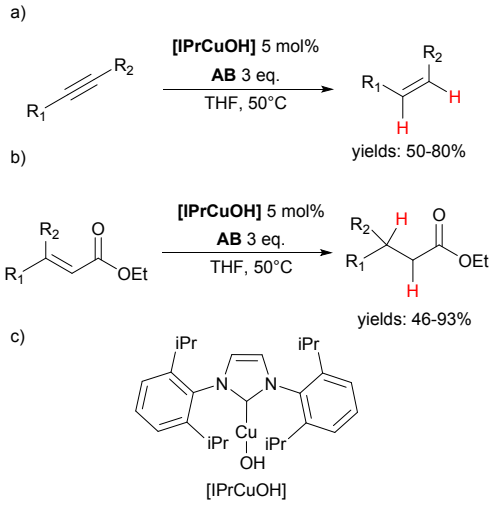


Scheme 61 a) NNN-Co Complex for alkyne reductions; b) controlled reduction of nitriles

Liu group, applying the same class of NNP pincer Co(II) complexes, was able to reduce nitrile to primary, secondary and tertiary amine in a controlled manner (Scheme 61, b).[79]

Looking at the best conditions found for the nitrile reduction, the solvent has a prominent role; indeed in the optimisation test, hexane and HFIP gave opposite results with the same catalyst.

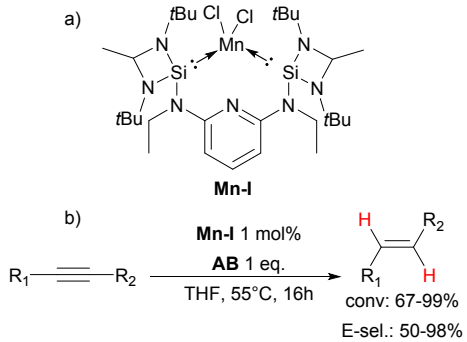
Other transition metals were also used; in one example, reported by Teichert's group, NHCCuOH complexes became the catalyst for the hydrogenation transfer from AB to alkyne.[80]



Scheme 62 a) Semihydrogenation of alkyne b) Conjugate transfer hydrogenation c) Structure of [IPrCuOH]

The inspiration came from their previous work, where NHCCu(I) complexes resulted excellent promoters of hydrogenation reaction.[81] The hydroxyl-Cu(I) compound is a bench stable precatalyst that doesn't require the typical *in situ* preactivation to generate the active copper(I) alkoxide complex; moreover, as for the previous case with Co(II), the active species is the Cu-hydrido derivatives. However, in this case, no stereocontrolled reaction was achieved, Z-alkene being the principal product (Scheme 62a). Noteworthy, with propiolate the corresponding Z-alkene was not obtained, but the corresponding conjugate transfer hydrogenation product was achieved (Scheme 62b).

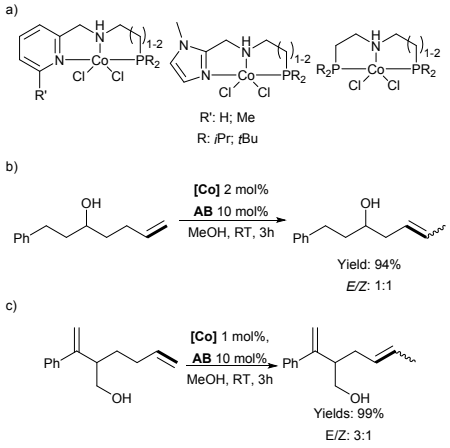
Driess *et al.* demonstrated that manganese(II) complexes, that are funding an increasing use in chemistry,[82] can be also a suitable catalyst for a benchmark reaction as the alkyne semihydrogenation.[83] The class of ligands under consideration was the N-Heterocycle Silylenes (NHSis), a powerful tool that in the last decades have gained significant relevance.[84]



Scheme 63 a) Mn(II) catalyst used by Driess et al. b) general reaction condition for the alkyne hydrogenation

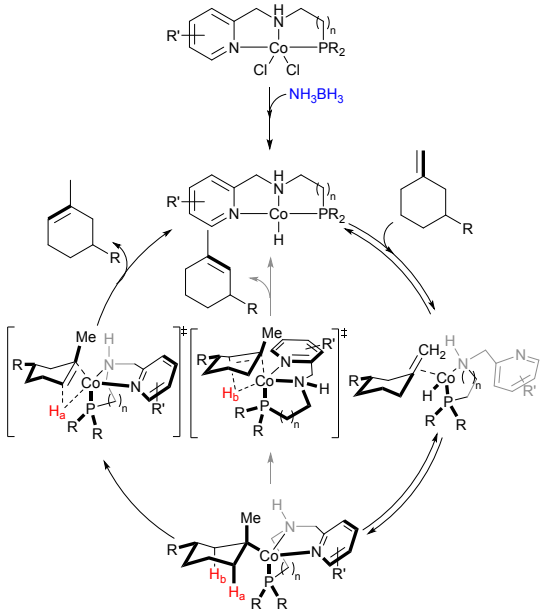
1 mol% of catalyst in presence of 1 equivalent of AB resulted to be sufficient for the hydrogenation, that normally proceeds with an excellent conversion and *E/Z* ratio between 50-99% in favour of *E*. The system demonstrated to have also a good tolerance of functional groups, although, CN/NH_2/NO_2/OH groups reduced the conversion due to the possible coordination of these groups to the catalyst. The Driess's group during this study decided to investigate also the influence of the oxidation state of manganese on the reaction. Mn(I) allows to achieve high conversion but a low *E*-selection, while, Mn(0) gave conversion <5%. As for the mechanism, tests with different NHSis complex prove to be unable to activate H_2, meaning that also in this case a direct hydrogen transfer mechanism is preferred; indeed, FT-IR studies reveal the presence of an Mn-Hydride species in solution.

In 2018 Liu's group employed cobalt complexes and AB in a olefin monoisomerisation (Scheme 64).[85] Taking advantage of the fine-tunability of NNP pincer ligands, they were able to develop a kinetically-controlled reaction. Normally, this type of isomerisation is dictated by thermodynamic control. In this study, 1,1-di and γ-substituted olefin were taken into consideration, due to a solid literature base with other catalytic systems to make a comparison.



Scheme 64 a) General structure of Co pincer complex b) Isomerisation of γ-substituted alkene c) Isomerisation of diene

The library of synthesised catalysts was successfully used in a variety of olefin isomerisation tests. Remarkable points in the reaction conditions are: the low catalyst loading, the presence of a catalytic amount of AB and the absence of by-products like overisomerisation, more common in thermodynamic controlled reactions. We decided to focus our attention on two particular examples. The first (Scheme 8b) is an isomerisation from 1-alkene to a 2-alkene in which a hydroxy group is present in γ-position. Usually, the expected product from this reaction is the corresponding, more stable, isomerised ketone, since the hydroxyl is an efficient directing group for chain walking reaction. However, thanks to the kinetic control achieved by the catalyst, the hindrance also played an important role in this case and the 2-alkene is the only obtained product. Generally, *E*-selectivity is achieved. The second example is particularly interesting because the substrates is a diene; the two carbon-carbon double bonds are characterised from the presence of a substituent in α and γ respectively, and gladly, Liu's catalysts were able to selectively isomerise the double bond featuring the γ-substitution. Besides, in both examples, the 2-alkenes are protected by further chain walking reaction, due to the presence of a substituent in β-position. In this work, a in deep investigation of the mechanism was also pursued A scrambling deuterium labelling experiment, where a mixture of D_4-substrates and nondeuterated ones, treated under standard isomerisation condition, gave partial deuteration of the allylic position. This excluded an intramolecular 1,3-hydrogen shift. They also verified the possibility of a radical mechanism, simply by adding a radical scavenger to the reaction. As expected, no influence on the result was observed. Assisted by DFT calculation, they proposed the following mechanism. The cycle started with the formation of the Co-hydride; after insertion of the substrate in the Co-H bond, the β-elimination gave the product. Due to the catalyst ability to discern between H_a and H_b the kinetic product is obtained.



Scheme 65 Proposed mechanism for the isomerisation process

More recently, in 2020, Findlater and co-workers[86] developed a stereoselective synthesis of trisubstituted alkenes by isomerization of geminal disubstituted olefins. The catalyst of the reaction was a novel Co-hydride species, generated in situ by cobalt (II) bromide, the ligand (**I** or **II**) and AB. Sodium *tert*-butoxide was added as activator under inert atmosphere in toluene at 60 °C for 12 hours (Scheme 66). Various substrates reacted under these optimized reaction conditions and afforded the isomerized products in moderate to excellent yields and *E/Z* ratios. Substrates with reactive functional groups (bromine, heteroarenes, amines, and ester) were tested and the reaction proceeded with a lower yield and selectivity. Dienes were also examined, and good results were obtained with both conjugated and nonconjugated dienes.

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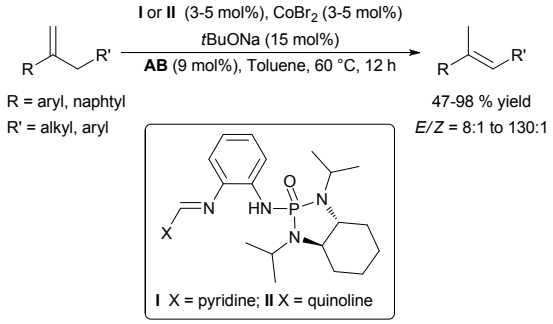
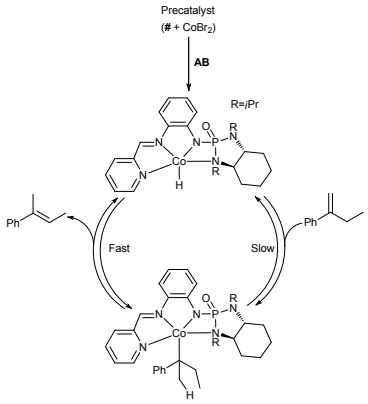


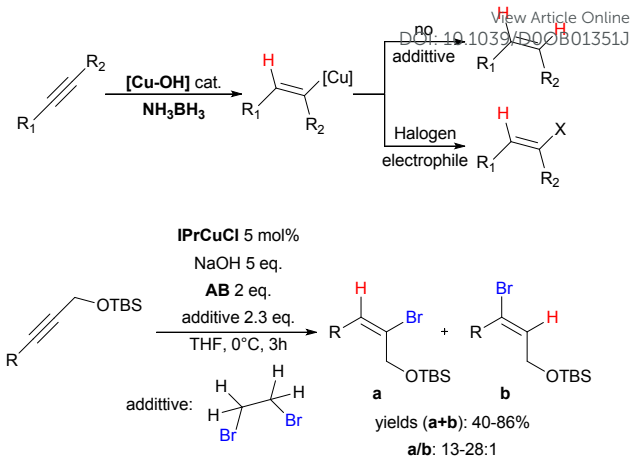
Scheme 66 Stereoselective olefins isomerization

Based on mechanistic studies the authors suggested the metal-hydride pathway as the most likely reaction mechanism. Running the reaction on mixed isomers of product led to a slightly increase in the ratio of E isomer, suggesting that the stereoselectivity of the reaction could be ascribed to the isomerization reaction of terminal to internal alkenes and not to the *E/Z* isomerization of the product. When R group was aliphatic, a dramatic loss of efficiency and selectivity was observed, suggesting the presence of crucial π–π stacking interactions between the substrate and the catalyst. As shown in Scheme 67, AB was not employed as a stoichiometric reducing agent, but it served to generate the active catalyst.



Scheme 67 Proposed catalytic cycle

Lately, Teichert proposed a new application of the Cu-AB system.[87] The reaction is a stereoselective hydrohalogenation of internal alkyne, using AB as substrate "activator". Inspired by a recent paper on hydrobromination of terminal alkyne with Cu(I)[88] and by their previous work on the Cu-catalysed hydrogen transfer from AB**,** they have attempted to trap the transfer hydrogenation intermediate with a halogen electrophile in two-step one-pot reaction.

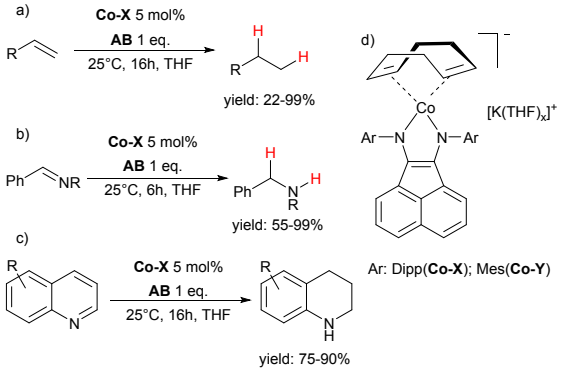


Scheme 68 Hydrobromination of propargylic s,ilylk ethers

The first step is characterised by the formation of the Cu-Hydrido catalyst, followed by the substrate insertion in the Cu-H bond. At this point, the alkenyl-cuprate obtained can undergo two different paths: if no additive is present, then, as aforementioned, the semyhydrogenation compound is formed; on the other end, if an electrophilic halogen source is added, the organo-cuprate intermediate will be easily trapped by it, giving the corresponding vinyl halide. Even though the reaction proceeds smoothly once optimised, the problem of the regiocontrol remains. Indeed, simple internal alkyne, like phenylpropyne, gave both the possible regioisomers.

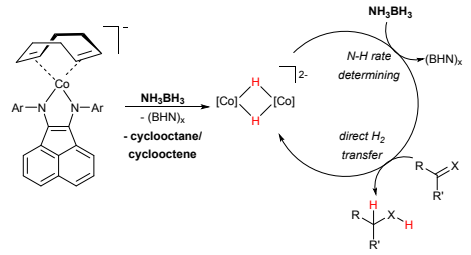
To control the regioselectivity, propargyl silyl ethers were employed.[89] As expected the use of silyl ethers as the directing group was the right choice, boosting the regiocontrol of the overall reaction. These conditions can be applied also for hydrochlorination and hydroiodination, by using NCS or NIS as additive. This behaviour is in contrast with the use of NBS that was ineffective, probably due to the presence of Br_2 in the reagent. In summary, the reaction showed by the group of Teichert is a valid simple and powerful alternative to obtain vinyl halide that can be further functionalised, for example by cross-coupling reactions.

In 2019 Wolf and von Wangelin synthesised a new class of cobalt complexes and applied them in transfer hydrogenation reaction from AB to alkene, imine and quinoline. The complexes took into consideration were two derivatives of a diamino cobaltate that can release more than 1 eq. of H_2 from ammonia-borane under mild conditions.[90] The catalyst resulted to be efficient, by being able to transfer hydrogen from AB at low temperature and to a different type of substrates. Mechanistic studies showed that the rate determining step was the transfer of H from ammonia-borane to the cobalt atom. In addition, kinetics studies suggested that more than one atom of Co is involved (Scheme 70).



Scheme 69 a) Alkene reduction b) Imine reduction c) Quinoline reaction d) Structure of Wolf's catalyst

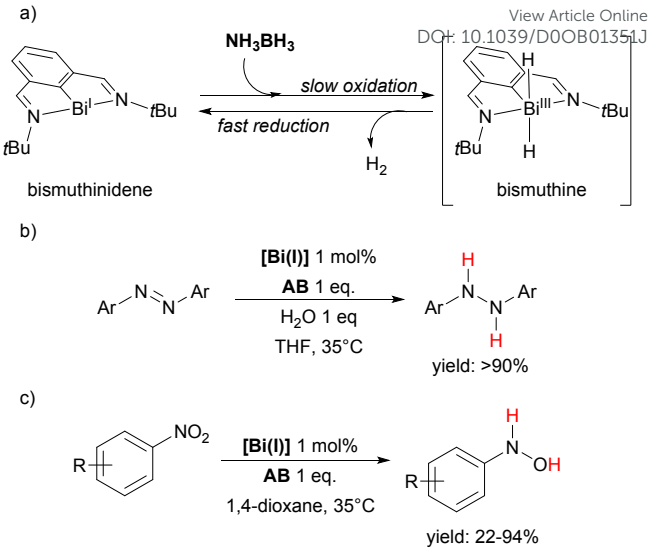
This system was less effective in the hydrogenation of highly substitutes olefin. However, it was found that when the reaction is conducted at 60°C and with the addition of 10 bar of H_2 the reaction yield increased up to 90%. The presence of AB is still necessary, thus demonstrating that the catalyst is not able to activate H_2 and that the mechanism remains a hydrogen atom transfer.



Scheme 70 Proposed mechanism of the Cobalt-catalysed reaction

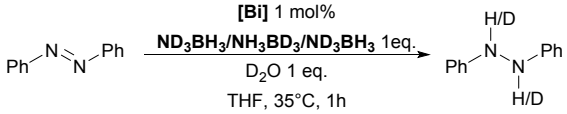
The same year Cornella introduced bismuth(I) catalyst as a new partner in the dehydrogenation of ammonia-borane.[91] The heaviest element of the pnictogens group possess low toxicity, it is more abundant compared to the noble metals and with properties at the border between metal and metalloid. Bi(I) up to 2019 was not very present in organic chemistry, also because its synthesis requires to start from the unstable Bi(III)dihydride that rapidly eliminates H_2.[90] Inspired by this behaviour, they synthesised a well-defined NCN-Bi(I) complex and employed it as the catalyst for hydrogen transfer from AB to azoarene and nitroarenes.

The NCN-Bi(I) pincer complex in presence of ammonia-borane will form the dihydride Bi(III) complex. The oxidation resulted to be slow, but as expected, once formed the bismuthine, it easily release H_2 returning to is initial state. The bismuth(III) complex is the key intermediate in the reaction being able to transfer hydrogens to the substrates. Interesting to note is the addition of 1 equivalent of water in the reduction of azoarene. During the optimisation screening, the same reaction, 99% yield in 3h, without water, gave 53% yield after 16h. Cornella and coworkers hypothesised that H_2O promoted the oxidation of Bi(I) to Bi(III) by H-bond stabilisation.



Scheme 71 a) Catalyst structure and reactivity toward AB b) Azoarene reduction c) Nitroarene reduction

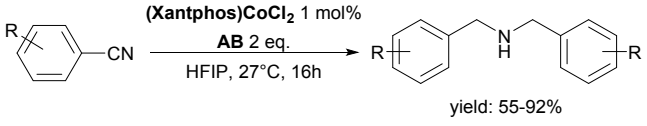
The reaction scope pointed out that the substituents on the aromatic ring on azarene didn't affect the final yield. As for nitroarene, orto-substitution lowered the yield and hydroxylamine is the only product obtained in all the case. To gain insight into the mechanism, the KIE experiment with deuterium labelling was effectuated (Scheme 72).



Scheme 72 KIE experiment with deuterium labelling

Confronting the yield with the three different deuteriums labelled AB with the same reaction performed with normal ammonia-borane, they calculated the following KIE: 1,63, 3,94, 7,05. These values indicate that the breaking of N-H and B-H bonds are the rate-determining step.

Up to now, we have discussed how cobalt is the most used element for the hydrogen transfer from ammonia-borane; however, it has always required particular ligands to modulate its activity. Punji and Sharma introduced what they call a "user-friendly cobalt catalyst" for the synthesis of secondary amine starting from nitrile.[92]



Scheme 73 Reductive amination of nitriles

(Xantphos)$CoCl_2$ is an efficient catalyst, able to reduce the nitrile to symmetric amine in high yields and with good tolerance to different functional groups. The authors tried also to synthesise asymmetric product, using a mixture of nitrile and a primary amine. Unfortunately, AB as hydrogen source gave a low selectivity

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between the asymmetric/symmetric products. The reaction worked far better when Me_2NH-BH_3 is used instead.

7. Conclusions

In conclusion, ammonia-borane has proven to be a very useful alternative hydrogen source, and in the years, different groups have demonstrated to be able to modulate the activity of AB employing different strategies, that include the use of transition metals, p-block species, organocatalysts and FLP systems. Due to its versatility, and the possibility to fine tuning its reactivity, AB is gaining an increasing attention as sustainable and atom-economy winning reagent for the reduction of several substrates.

Future studies are needed to address the present issues and to open new horizons in its applications.[93] For example, the development of continuous processes, either by taking advantage of flow reactors or other technologies available for realizing *in continuo* productions, such as CSTRs (continuous stirring tank reactors), may be easily predicted. The use of ammonia borane in alternative, environmentally benign solvents, is another topic for future investigation.

However, at the moment, the major issue is probably represented by the need to design and realize more chemo-, regio- and stereoselective processes. The discovery of new, efficient selective reduction methods, where AB could be used to specifically reduce only selected functional groups is highly desirable. But the greatest challenge is the development of truly efficient and reliable enantioselective reactions with ammonia borane. At the present, very few examples of efficient stereoselective transformations are known, and it can be envisaged that other efficient chiral systems, able to promote enantioselective AB-mediated reactions will be reported in the next future.

There are no conflicts to declare.

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