Recent Progress in Reactivity Study and Synthetic Application of N-Heterocyclic Phosphorus Hydrides

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Abstract: N-heterocyclic phosphines (NHPs) have recently emerged as a new group of promising catalysts for metal-free reductions, owing to their unique hydridic reactivity. The excellent hydridicity of NHPs, which rivals or even exceeds those of many metal-based hydrides, is the result of hyperconjugative interactions between the lone-pair electrons on N atoms and the adjacent σ*(P–H) orbital. Compared with the conventional protic reactivity of phosphines, this umpolung P–H reactivity leads to hydridic selectivity in NHP-mediated reductions. This reactivity has therefore found many applications in the catalytic reduction of polar unsaturated bonds and in the hydroboration of pyridines. This review summarizes recent progress in studies of the reactivity and synthetic applications of these phosphorus-based hydrides, with the aim of providing practical information to enable exploitation of their synthetically useful chemistry.

Keywords: N-heterocyclic phosphate • diazaphospholene • hydride transfer • metal-free reduction • σ-bond metathesis

1. Introduction

The hydricity of an X–H bond is defined as its propensity to transfer a hydrogen atom along with an electron. This X–H bond cleavage can enable the reduction of various unsaturated substrates such as carbonyl compounds, CO2, imines, olefins and aromatics.[1-5] The corresponding hydride reagents are usually categorized as metal or organic hydrides, depending on whether the hydrogen atom is bound to a metal or a nonmetal. Metal hydrides, particularly those of noble metals, have a research history of over half a century.[1-3, 6, 7] They are versatile reductants and have been widely used in numerous reduction processes in both academia and industry.[8-11] However, because of concerns associated with their low abundance, high toxicity and harmful transition-metal residues, considerable research has recently focused on the use of organic counterparts as surrogates for conventional metal hydrides.

Inspired by enzymatic cofactors such as nicotine adenine dinucleotide (NADH) and flavin adenine dinucleotide, various organic hydrides have been developed and used in many reduction reactions.[12, 13] In this process, the design of novel structural frameworks with enhanced hydricities has attracted much attention. Generally, an X–H bond can be cleaved via three possible pathways: heterolysis to deliver a proton (H+), heterolysis to deliver a hydride (H−), and homolysis to yield a hydrogen atom (H•) (Scheme 1a). Choice of the reaction pathway is primarily dictated by the polarity of the particular X–H bond, i.e. the differences between the Pauling electronegativities (χ) of the hydrogen and attached element X.[12] Scheme 1b shows the electronegativities of some typical elements. The electronegativities of boron and silicon atoms (χB = 2.04 and 1.90, respectively) are lower than that of the hydrogen atom (χH = 2.20), therefore boron and silicon are good candidates for developing hydride reagents.[12, 14] Moreover, C–H bonds can be made less protic by introducing electron-rich or -resonant motifs to polarize the C–H bond or facilitate positive-charge delocalization in conjugated hydride acceptors. These beneficial effects help to explain why NADH and triphenylmethane analogs[15, 16] enable preferential release of a hydride over a proton under certain conditions. However, compared with the rapid progress made in the hydride chemistries of the elements mentioned above, exploration of P–H hydricity is lagging behind. Scheme 1b shows that the electronegativities of hydrogen and phosphorus atoms are similar. This suggests that the P–H bond is not highly polar. This paves the way for the use of P–H bonds in the construction of novel hydride donors. The described structure–hydricity relationship suggests that installing electron-donating or -resonant groups R into a P–H moiety (Scheme 1c) is an important method for improving P–H hydricity.
Scheme 1. Considerations in developing P–H hydrides. a) Three possible pathways for P–H bond cleavage. b) Pauling electronegativities ($\chi^p$) of elements used in organic hydrides. c) Cleavage of P–H to give a hydride ion. d) P–H hydride structures.

Substituent-induced P–H hydridic reactivity was first reported in 1997. It involved the reaction of a pincer-type phosphine A (Scheme 1d) with a trityl cation. The P–H hydricity of A stems from hypercoordination of the phosphorus atom with the electron-donating dimethylamino group.[17, 18] Significant progress was not made until the work of Gudat and co-workers in 2000. They synthesized a series of P-hydrido-1,3,2-diazaphospholenes B, which were the first reported examples of three-coordinated phosphines featuring hydridic reactivity (Scheme 1d).[19, 20] The N-heterocyclic skeleton endows the P–H bond with excellent hydricity via a hyperconjugative interaction between the nonbonding $\pi$-electrons in the C$_2$N$_2$ unit and the $\sigma^*(P–H)$ orbital, as reflected by the resonance structures of the diazaphospholene skeleton in Scheme 1d. The umpolung reactivities of phosphines derived in this way stimulated researchers to identify innovative structures with comparable or enhanced hydricities. Significant developments in the past decade have made P–H hydrides an attractive research area in main-group hydrides. Many N-heterocyclic phosphines (NHPs, Scheme 2) with diverse structures and reactivities have been developed and used as powerful stoichiometric or catalytic reductants in organic syntheses.
Several exhaustive reviews have previously discussed carbon- and borane-based hydrides in terms of their hydridic reactivities and applications in chemical transformations. However, there have been few summaries of up-to-date synthetic applications of NHPs, particularly with regard to recent progress in asymmetric chemistry. Here, we outline significant advances in this area. In the first section, we describe experimental methods for quantifying the thermodynamic and kinetic hydricities of NHPs, along with a brief introduction to the NHP catalytic mechanism. The synthetic uses of NHPs as hydridic catalysts, categorized by the identity of the terminal reductants, are summarized. Where applicable, the use of measured reactivity parameters to rationalize these catalytic reductions is attempted. A brief introduction to recent progress in radical reactions of NHPs is also provided. The final section discusses promising future applications of P–H hydrides in various fields.

2. Quantification of NHP hydricity and mechanistic analysis

Knowledge of the reactivity of reagents is important in designing new relevant transformations and understanding reaction mechanisms. The hydridic reactivity of NHPs was initially deduced empirically from their instability in protic and chlorinated solvents or from their fast hydride transfer to various electrophilic substrates at ambient temperature. A quantitative comparison of their hydridic reactivities was then made on the basis of thermodynamic and kinetic parameters. As shown in equation 1 (Scheme 3), the thermodynamic hydricity (\( \Delta G_{\text{hyd}} \)) is defined as the standard Gibbs free energy change for dissociation of a hydride donor RPH to generate its conjugated hydride acceptor RPH' and a hydride H'. The value of \( \Delta G_{\text{hyd}} \), i.e. the hydricity, can be obtained either by direct experimental measurements or density functional theory (DFT) calculations. A general method for hydricity determination involves establishing an equilibrium between an unknown RPH and a hydride acceptor A' of known hydricity (\( \Delta G_{\text{hyd}} \)) in certain media. The hydricity of RPH can then be deduced from equations 2 and 3. However, because three-coordinated phosphines are often air and moisture sensitive, an open-flask normal isothermal titration calorimetry may not be applicable. In such case, DFT calculations provide a practical alternative. The kinetic hydricity, which is described by the empirical nucleophilicity parameter N and nucleophile-specific sensitivity parameter \( s_{\text{nu}} \), is derived from the three-parameter relationship \( k_{\text{obs}} = s_{\text{nu}}(N + E) \) (equations 4 and 5), also known as the Mayr equation. It can be used as an alternative to the thermodynamic hydricity. Such nucleophilicity parameters are obtained from the second-order rate constants \( k_{\text{obs}} \) of hydride transfer between a nucleophile and reference acceptors A\( _i \), \( i = 1, 2, 3... \) with known electrophilicity parameters E. These parameters can be used to quantify the hydridic reactivity of an NHP and to guide rational selection of suitable NHPs for diverse substrates in reaction design.
Thermodynamic hydricity

\[ \Delta G_{\text{therm}} = \Delta G_{r-r} \Delta G_{r-r} \Delta G_{(\text{P-H})} \Delta G_{(\text{A-H})} \] (1)

Kinetic hydricity

\[ \log k_2 = s_N(N + E) \] (5)

Scheme 3. Thermodynamic and kinetic hydricities of R₂PH.

2.1 Kinetic hydricities of NHPs

In our recent work, we used the Mayr equation to establish an NHP kinetic hydricity scale (Table 1).[26] The NHPs examined covered those frequently used in organic syntheses; B9 was included for comparison. The data in Table 1 show that the nucleophilicity parameters \( N \) of NHPs in MeCN span a broad range, namely 13.5–25.5. Among these, B1 \( (N = 25.5) \) is the most nucleophilic hydride donor ever quantified by the Mayr equation. It has a nucleophilicity far stronger than that of NaBH₄ \( (N = 14.74 \text{ in DMSO}) \). Therefore, B1 can be regarded as a super hydride donor, which can reduce inert CO₂ without activators (see the applications discussion). When the tertiary butyl groups in B1 are replaced with electronically different, bulkier aryl groups, such as in the 2,4,6-trimethylphenyl analog B3 and 2,6-diisopropylphenyl analog B5, the corresponding \( N \) values \( (N = 17.68 \text{ and } 19.85, \text{ respectively}) \) decrease to a level close to that of B6 \( (N = 18.74) \). This clearly shows that the kinetic hydricity is sensitive to variations in steric hindrance around the P–H bond. The benzannulated moiety in B7 attenuates the hydricity via delocalization of the lone-pair electrons on N atoms toward the phenyl ring. As expected, B9 and B10[27] show the weakest hydricities \( (N = 13.46 \text{ and } 8.64, \text{ respectively}) \) among the P–H reagents examined. However, they still have nucleophilicities stronger than, or similar to, those of many other commonly used organic hydrides[28] such as arylbenzimidazolines \( (N = 9.72–10.14 \text{ in MeCN})[29] \) and dihydropyridines \( (N = 7.53–9.00 \text{ in CH₂Cl₂})[30] \). The nucleophile-specific sensitivity parameters \( s_N \) are small (Table 1, \( s_N = 0.35–0.68 \)) and similar to those observed for other extremely reactive nucleophilic systems (e.g. N-heterocyclic carbenes). This reflects their low sensitivity to changes in electrophiles.[31-34] In combination with the electrophilic parameters of the hydride acceptors, these nucleophilicity parameters can be used to evaluate the feasibility of hydride transfer and to differentiate NHP reactivities toward different substrates. This will be further addressed in the synthesis part, if the necessary data are available.
concomitant process that compensates for the unfavorable thermodynamics is necessary. Considering the robustness of B–X and Si–X regeneration of a highly reactive P–H bond from a P–X bond is often thermodynamically unfavorable. For this step to proceed, a

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However, regeneration of the P–H bond to deliver product (step b).

Previous reactivity investigations have shown that NHPs have powerful hydride donicities, and this ensures smooth hydride release (step a). However, NHP regeneration (step b) may be problematic because regeneration of a highly reactive P–H bond from a P–X bond is often thermodynamically unfavorable. For this step to proceed, a concomitant process that compensates for the unfavorable thermodynamics is necessary. Considering the robustness of B–X and Si–X bonds, boranes and silanes are promising candidates for achieving the desired reactivity. This is because formation of a B–X or Si–X bond is highly exothermic, which can provide the required supplementary driving force for concurrent P–H bond formation.

2.3 Mechanism of NHP catalysis

In principle, the mechanism of a NHP–catalyzed reduction, even a simplified one, involves at least two basic steps (Figure 1), i.e. initial cleavage of the P–H bond to furnish intermediate 1B (bearing a newly formed P–X bond, X = OR or NR, step a), and subsequent regeneration of the P–H bond to deliver product 2 (step b). Previous reactivity investigations have shown that NHPs have powerful hydride donicities, and this ensures smooth hydride release (step a). However, NHP regeneration (step b) may be problematic because regeneration of a highly reactive P–H bond from a P–X bond is often thermodynamically unfavorable. For this step to proceed, a concomitant process that compensates for the unfavorable thermodynamics is necessary. Considering the robustness of B–X and Si–X bonds, boranes and silanes are promising candidates for achieving the desired reactivity. This is because formation of a B–X or Si–X bond is highly exothermic, which can provide the required supplementary driving force for concurrent P–H bond formation.

| E–H | N_H | E–H | N_H |
|-----|-----|-----|-----|
| B1  | 25.54 (0.20) | NaBH_4 | 14.74 (0.01) |
| B2  | 17.61 (0.25) | MeCN | 3.72 (0.22) |
| B3  | 19.55 (0.34) | MeCN | 9.00 (0.02) |
| B4  | 18.74 (0.47) | MeCN | 5.67 (0.02) |
| B5  | 20.90 (0.43) | MeCN | 4.97 (0.75) |
| B6  | 13.46 (0.55) | MeCN | 5.54 (0.90) |
| B7  | 8.64 (0.52) | MeCN | 3.56 (0.70) |
| B8  | 2.65 (0.71) | MeCN | 2.65 (0.71) |

Table 1. Nucleophilicity parameters for NHPs in MeCN and other commonly used hydride reagents for comparison (Mes = 2,4,6-trimethylphenyl and Dipp = 2,6-diisopropylphenyl).
Scheme 4.

In NHP-catalyzed reductions, HBpin, H$_3$N·BH$_3$, and sometimes Ph$_3$SiH$_2$ are preferentially used as terminal reductants. Several mechanistic studies of P–H bond regeneration have indicated that a concerted mechanism (σ-bond metathesis)[37] with a six-[38] or four-membered[39] cyclic transition state (TS, Figure 2) should be considered. We categorized these reactions into two primary types: non-asymmetric and asymmetric reductions. These are discussed in the following sections.

Figure 2. Four- (a) and six-membered (b) cyclic transition states (TS) for NHP regeneration.

3. Non-asymmetric reductions

3.1. Ammonia-borane (H$_3$N·BH$_3$) as reductant

In 2014, Kinjo and co-workers reported the first synthetic application of NHPs in catalytic hydrogenations.[38] They found that both B1 and B6 can reduce azobenzene smoothly at room temperature (Scheme 4a). Subsequent P–H regeneration with H$_3$N·BH$_3$ gave quantitative recovery of B1, whereas B6 was further reduced to PH$_3$. B1 was therefore selected as the catalyst. Hydrogenation of the N=N bond in 4 with H$_3$N·BH$_3$ was achieved in good to excellent yields (77%–95%) (Scheme 4b). Notably, for substrates 6 with 4-NH$_2$ or 4-MeO groups, subsequent cleavage of N=N bonds occurred, which gave further-reduced anilines 7 (Scheme 4c). This is presumably because electron-donating substituents at the para position increase the reactivity of the N=N bonds in the hydrazine intermediates, which favors further reduction. Kinetic and computational studies supported a concerted double-hydrogen-transfer mechanism with a six-membered TS for the regeneration of catalyst B1 (Figure 2). Notably, the calculated profiles show that reduction was initiated by nucleophilic attack of the B1 phosphorus atom on the N=N bond, rather than direct hydride transfer.

Scheme 4. NHP-catalyzed hydrogenation of N=N bonds with H$_3$N·BH$_3$. a) Stoichiometric reactions. b) and c) Catalyzed reductions.
Kinjo and co-workers later used a similar strategy for the catalytic reduction of \( \alpha, \beta \)-unsaturated esters on the basis of their preliminary results for stoichiometric reactions (Scheme 5a).[40] A combination of one equivalent of H\( \text{N-} \text{BH}_3 \) and 1 mol% \( \text{B1} \) efficiently converted \( \alpha, \beta \)-unsaturated esters 11 to saturated esters 12 (Scheme 5b). It is worth noting that the nucleophilicity \( N = 8 \) for H\( \text{N-} \text{BH}_3 \)[15] and electrophilicity \( E = −20 \) for unsaturated esters[41] suggest that the uncatalyzed reactions should not take place. Replacing H\( \text{N-} \text{BH}_3 \) with HBpin in the presence of nitriles at an elevated temperature (90°C) led to further C–C bond coupling between boryl enolate intermediates and nitrile 13. This afforded either single- (imine products 14, 71%–78% yields) or double-addition (15, 41%–85% yields) diester derivatives, depending on whether the steric congestion of the formed boryl enolate intermediates prevented the second addition to retain the imine moiety. The similar stoichiometric and catalytic conjugate reductions have been previously reported by Gudat[19, 20] and Speed[42] (see Scheme 8), respectively.

3.2 HBpin as reductant

Among various hydrogen sources for NHP-catalyzed reductions, HBpin is the most common reagent because of its outstanding reaction performance, good solubility and low price. In 2015, Kinjo and co-workers reported the first metal-free catalytic hydroboration of carbonyl compounds by using 0.5–1 mol% \( \text{B1} \) and a stoichiometric amount of HBpin.[39] They synthesized intermediate 17 via the reaction of benzaldehyde 16 with \( \text{B1} \) (Scheme 6a).[20] \(^{11} \text{B}\) and \(^{31} \text{P}\) NMR spectroscopic investigations indicated that treatment of 17 with 1 eq of HBpin led to formation of \( \text{B1} \) and the hydroboration product 18. This confirms the feasibility of P–H regeneration from HBpin. DFT calculations supported a four-membered cyclic TS for P–H bond formation. High catalytic activity, at a catalyst loading as low as 0.5 mol%, was observed in the reaction with aldehydes 19 (Scheme 6b). Formyl groups can be selectively reduced in the presence of heterocycles and ketones, in contrast to previously reported results, i.e. dearomatization[43] or complete reduction.[44, 45] However, higher catalyst and reductant loadings (10 mol% and 1.3 eq) and temperature (90°C), and longer reaction times, were required to achieve reduction of ketones 21 (Scheme 6b) because of their lower electrophilicity[46] and larger steric hindrance. Under the optimized conditions, both acyclic and cyclic ketones were well tolerated and furnished the corresponding borate esters quantitatively.
To increase the moisture/oxygen tolerance of NHPs, Speed and co-workers developed alkoxydiazaphospholenes for catalytic reductions. The precatalysts 25, 26 and 27, which correspond to catalysts B1, B3 and B6, respectively, are sufficiently stable for open-air operation.[47] In the catalytic reduction of imines 23 with HBpin, they gave 98%, 25% and <2% yields, respectively (Scheme 7). Precatalyst 25 gave the best performance. The worst performance, i.e. by 27, partly resulted from failure to generate B6 from 27 in the presence of excess HBpin. Precatalyst 25 was then used to perform imine reductions with HBpin (Scheme 8). The reaction showed good functional group compatibility; and, various imines were reduced to amines in good yields. However, imines with sulfenyl or trifluoromethyl groups were not viable substrates. Perhaps these electron-withdrawing groups inhibit NHP regeneration from P–N intermediates. This system is also applicable to conjugated substrates; the corresponding products are obtained in moderate yields (Scheme 8).

Scheme 7. Condition optimization for alkoxydiazaphospholene-catalyzed imine reductions.

Scheme 6. NHP-catalyzed hydroboration of carbonyl compounds. a) Stoichiometric reactions. b) Catalyzed reductions.
The same group synthesized a series of triazaphospholenes 36 and 37, and investigated their reactivities in reductions of imines 32 and α,β-unsaturated aldehydes 34 (Scheme 9).[42] $^{31}$P NMR spectroscopy showed that P–H bonds were not formed from a mixture of 37 and HBpin in CD$_2$CN. This precludes a P–H hydride transfer mechanism. Presumably, catalyst 37 was ionized to the phosphonium cation, which can combine with the imine N atom to form a van der Waals prereaction intermediate Int1, which then interacted with HBpin to give the intermediate Int2. DFT calculations showed that Int2 was converted to the intermediate Int3 via a six-membered TS with an activation barrier of 23.0 kcal mol$^{-1}$. This cyclic TS may account for the high 1,2-chemoselectivity observed in unsaturated aldehyde reductions. Notably, the triazaphosphonium cations act as Lewis acids and activate the substrate imines rather than as precursors of P–H hydrides.

Scheme 8. Alkoxymidazaphospholene-catalyzed imine and conjugate reductions.

All the reductions mentioned above focused on polar double bonds, e.g. polar olefin, imine and carbonyl substrates. Reduction of aromatic compounds under metal-free conditions is challenging because dearomatization is thermodynamically unfavorable. In 2018, Kinjo and co-workers reported the hydroboration of pyridines catalyzed by 1,3,2-diazaphosphenium triflates.[48] Condition optimization indicated that diazaphosphenium 44 gave the best performance (Scheme 10a). A variety of pyridines can be reduced with 5 mol% 44 to 1,4-hydroboration products, some of which are otherwise unavailable. This reaction has excellent reactivity, good selectivity and a broad substrate scope, except for pyridines with 2-Cl, 2-CN, 2,6-Me$_2$ and 4-Me$_2$N groups. Mechanistic studies ruled out the possibility of pyridine
activation by phosphonium cations. A borane–pyridine complex was therefore considered as the active intermediate. The proposed mechanism is shown in Scheme 10b. First, Int4 and B1 were formed via activation of HBpin by pyridine 38 and a triflate anion. Another pyridine coordinated with Int4 to produce Int5, which was isolated and spectroscopically characterized. One of the activated pyridines in Int5 then abstracted a hydride from B1 to complete the reduction. Speed and co-workers later reported a similar strategy for pyridine hydroboration with catalyst 25. Unlike the broad substrate scope with 44, Speed’s system only worked for electron-deficient pyridines.[49]

Scheme 10. Pyridine hydroboration catalyzed by diazaphosphenium triflates. a) Yields and chemoselectivities with different diazaphosphenium triflates as catalysts. [a] Reaction temperature: 70°C. b) Proposed reaction mechanism.

Hydride transfer from NHPs can also initiate Claisen rearrangement[50, 51]. Cramer and co-workers developed a NHP-catalyzed reductive Claisen rearrangement for effectively constructing C–C bonds, particularly those bearing quaternary carbon centers. The reaction, which was performed at ambient temperature with 1 mol% precatalyst 46, was compatible with a variety of functional groups (Scheme 11).[52] Mechanistic studies suggested two possible pathways: B-[3,3] and P-[3,3] rearrangements. The initial hydride transfer between 45 and B1 (generated in situ from 46 and HBpin) gave either a P–C or P–O intermediate (Int6 or Int7), depending on the substrate. Both intermediates can be converted to intermediate Int8 via a σ-bond metathesis with HBpin. The B-[3,3] Claisen rearrangement then directly converted Int8 to 49. The P-[3,3] pathway yielded the same product 49 via a two-step process: the Claisen rearrangement of Int7 to 48, and subsequent metathesis with HBpin.
Examples of productive endocyclic P–N bond cleavage are rare. Recently, Radosevich and co-workers reported a geometrically deformed tricoordinated phosphorus triamide 50.\(^\text{[53]}\) This triamide reacted with HBpin to give B8 via scission of an endocyclic P–N bond (Scheme 12). This reactivity stems from cooperation between an electrophilic phosphorus center and a proximal basic N-methylanilide nitrogen, i.e., a behavior similar to that of a frustrated Lewis pair. B8 showed good hydridic reactivity and reduced imine 51 to intermediate Int9. Rapid intramolecular boryl transfer eliminated the N-borylamine 52 and catalyst 50. This P–N ligand cooperation provides a platform for designing new constrained main-group catalysts.

Recently, Speed and co-workers discovered that the air-stable secondary phosphine oxide (SPO) 53 was transformed into B1 in the presence of HBpin (Scheme 13a).\(^\text{[54]}\) This bench-purifiable SPO could replace highly air-sensitive NHPs as reduction catalysts. This possibility was confirmed by performing SPO-catalyzed imine and conjugate reductions, and pyridine hydroboration, with HBpin (Scheme 13b). These results will help to overcome the limitations associated with reagent sensitivity to help popularize NHP chemistry.
3.3 \( \text{Ph}_2\text{SiH}_2 \) as reductant

Another hydridic reductant, i.e. \( \text{Ph}_2\text{SiH}_2 \), can also regenerate NHPs through a \( \sigma \)-metathesis mechanism. An example was reported by Kinjo’s group.\[55\] Building on the success of catalytic reduction of carbonyl groups by \( \text{B1} \), the authors investigated NHP-catalyzed \( \text{CO}_2 \) reduction. They found that exposure of \( \text{B1} \) to 1 atm of \( \text{CO}_2 \) gave a hydrophosphination product, namely the phosphorus(III) formate \( \text{54} \). Regeneration of catalyst \( \text{B1} \) was achieved by adding a half-equivalent of \( \text{Ph}_2\text{SiH}_2 \) to the reaction mixture. This furnished \( \text{B1} \) and electrophilic \( \text{Ph}_2\text{Si(OCHO)}_2 \) \( \text{55} \), along with siloxane \( \text{56} \) as a minor product (Scheme 14a). Primary and secondary amines were then examined as nucleophiles for N-formylation at a 5 mol% catalyst loading. The reaction had a broad substrate scope, which included alkyl and aryl amines (Scheme 14b). Note that sterically hindered and highly basic amines such as disisopropylamine and 2,2,4,4-tetramethylpiperidine afforded N-methylated products because of over-reduction of the corresponding N-formylamines.\[56, \text{57}\]

DFT calculations performed by Ye and co-workers showed competition between formylation and methylation of amines.\[58\]

a) Activation of \( \text{CO}_2 \) by \( \text{B1} \):

\[
\begin{align*}
\text{51} + \text{CO}_2 & \rightarrow \text{54} \\
\text{51} + \text{CO}_2 & \rightarrow \text{55} \\
\text{51} + \text{CO}_2 & \rightarrow \text{56} \\
\end{align*}
\]

b) \( \text{B1} \)-catalyzed N-formylation of amines with \( \text{CO}_2 \):

\[
\begin{align*}
\text{51} + \text{R}-\text{N}^\text{H} & \rightarrow \text{57} \\
\text{51} + \text{R}-\text{N}^\text{H} & \rightarrow \text{58} \\
\end{align*}
\]

3.4 Mg powder as electron donor

In addition to single-component reductants, a combination of Mg powder as an electron donor and a Bronsted acid can also serve as a
formal hydrogen donor in NHP recovery from diphosphines. Gudat and co-workers found that during NHP syntheses some of the formed NHPs were converted to diphosphine $B_2$ under ultraviolet irradiation (Scheme 15).[59] Unlike $P_3H_4$,[60, 61] these diphosphines are photostable, and can therefore be recycled in photocatalytic reactions. Based on this, Gudat explored the photocatalytic generation of $H_2$ from catalyst $B$ with $Et_3NH^+Cl^-$ and Mg as the formal hydrogen source. DFT calculations showed that prior to $H_2$ evolution, the key dimer $B'$ was formed. Its subsequent photochemical excitation yielded $H_2$ and the diphosphine $B_2$ (Scheme 15). $B_2$ was then reduced to NHPs by the reductant pair $Et_3NH^+Cl^-$ and Mg. This process can be regarded as a NHP-catalyzed photochemical reduction of a proton to $H_2$ by Mg.

Scheme 15. NHP-catalyzed photochemical $H_2$ evolution.

4. Asymmetric reductions

The unusual reactivities of NHPs in non-asymmetric reductions have stimulated interest in the development of asymmetric variants by using chiral diamine motifs, which are versatile building blocks in the synthesis of chiral N-heterocyclic carbenes.[62] dianimophosphine oxides[63] and phosphordiamidite ligands.[64] Representative structures are shown in Scheme 2 ($B12$–15). All of these retain the diazaphosphole skeleton, which is crucial for achieving excellent hydricity.

In 2017, Speed and co-workers reported the first use of NHPs as chiral catalysts for asymmetric reductions (Scheme 16).[65] They reported that use of 2 mol% $62$ (the precatalyst of $B12$) enabled imine reduction by HBpin, with moderate enantioselectivities (er 55:45 to 88:12). This was the best reported enantioselectivity for alkylimine hydroboration with HBpin at that time. Changing the catalyst from $B12$ to $B13$ or $B14$ decreased the enantioselectivity. Control experiments suggested a similar mechanism to that for the non-asymmetric version.

Scheme 16. Asymmetric imine hydroboration catalyzed by chiral diazaphosphole $62$.

Cramer and co-workers developed a series of new chiral NHPs for performing asymmetric conjugate reductions with HBpin (Scheme 17).[66] Initially, they used $B12$ and $B13$ (generated in situ from their corresponding precatalysts) as catalysts, but obtained moderate e.r. values. To improve the enantioselectivity, they synthesized $65$, a precatalyst of $B15$, which has more rigid moieties around the P–H bond. Condition optimization showed that 5 mol% $65$ in toluene at 2°C gave the best result. Based on this, various conjugated substrates were
reduced with high enantioselectivity (e.r. values up to 95.5:4.5).

Scheme 17. Asymmetric conjugate hydroboration catalyzed by chiral diazaphospholene 65.

In the above examples, 62 and 65 are both neutral alkoxydiazaphospholenes. Recently, Speed and co-workers used the phosphonium cation 68 to achieve asymmetric reduction. Cyclic imines can be reduced by HBpin with good e.r. values (around 90:10) at a catalyst loading of 1 mol% (Scheme 18).[67] This reaction has good compatibility with imines bearing reducible aromatic heterocycles. A plausible mechanism was proposed for phosphenium-catalyzed pyridine reductions, in which 68 abstracts a hydride from the pinacolborane–imine adduct Int10 and then redelivers the hydride to the resultant imineborenium 70. HBpin acts as a Lewis acid in imine activation, therefore relatively basic imines are preferred. This reactivity complements borane-based frustrated Lewis pair catalysis, in which electron-deficient substrates are needed to avoid product inhibition of electrophilic borane catalysts.

Scheme 18. Enantioselective imine reduction catalyzed by chiral phosphenium ion 68. [a] Enantiomer of 68 was used as the catalyst.

5. Radical reactions of NHPs
The reactions discussed above mainly depend on the hydridic reduction ability of NHPs. On the basis of our recent findings that NHPs can serve as good hydrogen-atom donors and their corresponding phosphinyl radicals are excellent electron donors,[27] we envisioned that the hydride ion of NHPs could be transferred in a multi-step mechanism (Scheme 19a), i.e. the hydrogen-atom and electron transfer.
alternative pathway might provide a route to previously inaccessible reactivity in the hydric reduction of substrates. Our group verified this assumption by using azodiisobutyronitrile (AIBN) as a radical initiator to trigger the initial hydrogen-atom transfer. As expected, the produced phosphinyl radicals showed high electron donor activity and enabled hydrodebromination/dechlorination reactions of aryl and alkyl halides[68], and chemoselective cleavage of the α-C–O bonds in α-carboxy ketones[69]. Similar radical reactivity was reported by Speed and co-workers in their bis(diazaphospholene) system.[70]

Scheme 19. (a) Two pathways for hydride transfer of NHPs and (b) radical reactions of NHPs initiated by azodiisobutyronitrile.

6. Conclusions and Outlook

In summary, we have outlined recent progress in NHP chemistry, with special attention to reactivity studies and synthetic applications. The recently disclosed NHP hydricity, as a surrogate for metal-based hydricity, has opened up a new avenue to main-group hydrides, and complements conventional P–H protonic reactivity. Exploitation of new NHPs with greater structural diversity and expansion of their application scope to more challenging substrates will be mainstream in the future. A systematic investigation of the structure–reactivity relationships of NHPs is needed to lay the foundation for this chemistry. Our recent thermodynamic and kinetic studies have shown the ability of NHPs to act as hydrogen-atom donors and of their corresponding phosphinyl radicals to act as potent electron donors. Based on this, we investigated some preliminary applications in electron-transfer-initiated radical reductions. This is a potentially promising area for exploring NHP radical chemistry, particularly in combination with contemporary photocatalytic and electrocatalytic techniques.

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Conflict of interest statement.

None declared.

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