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Metallated dihydropyridinates: prospects in hydride transfer and (electro)catalysis

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Hydride transfer (HT) is a fundamental step in a wide range of reaction pathways, including those mediated by dihydropyridinates (DHP^-s). Coordination of ions directly to the pyridine ring or functional groups stemming therefrom, provides a powerful approach for influencing the electronic structure and in turn HT chemistry. Much of the work in this area is inspired by the chemistry of bioinorganic systems including NADH. Coordination of metal ions to pyridines lowers the electron density in the pyridine ring and lowers the reduction potential: lower-energy reactions and enhanced selectivity are two outcomes from these modifications. Herein, we discuss approaches for the preparation of DHP–metal complexes and selected examples of their reactivity. We suggest further areas in which these metallated DHP^-s could be developed and applied in synthesis and catalysis.

1. Introduction

Electron transfer (ET) and proton transfer (PT) reactions are fundamental processes in chemistry. Indeed, most chemical transformations of small molecules and functional groups familiar to the organic chemist, *e.g.* aldol reactions, esterifications, epoxidations, reductive amination, nitrile hydrolysis to name a few, involve one or both of ET and PT and often in combination with other bond-making or -breaking events.[1] For transformations limited to ET and PT only, these events commonly involve one electron and one proton (an H-atom transfer, $H^\bullet$) or two electrons and a proton (a hydride transfer, H^-). Hydrogenation reactions for reduction of ketones, imides

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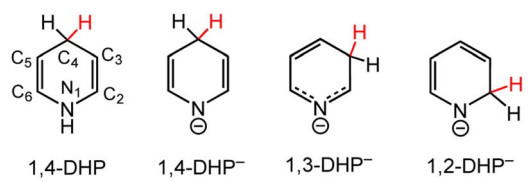
or alkenes, and dehydrogenative oxidation reactions involve a total of two ET and two PT events equivalent to a molecule of H_2; in most instances, this occurs with one proton (H^+) and one hydride (H^-) equivalent.[2,3] Multiple site proton coupled electron transfer (MS-PCET) is not covered in this perspective.[4]

Hydride transfer (HT) reagents in organic synthesis and catalysis will be discussed in this Perspective article with a focus on HT reactions mediated by functionalised dihydropyridinate (DHP^-) molecules. The IUPAC definitions for dihydropyridine (DHP) and for DHP^- are given in Scheme 1 and will be used throughout the remainder of this article. Following the Section 1: introduction, we discuss approaches to the synthesis of metallated DHP^-s in Section 2; and then selected reaction chemistry of metallated DHP^-s is addressed in Section 3. Open challenges and opportunities are mentioned throughout the text and discussed as an overview in Section 4.

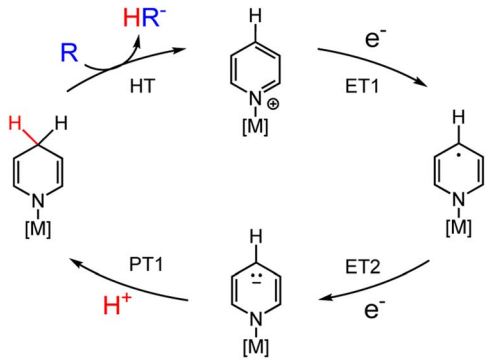
HT is a mechanism for many chemical transformations that afford X′–H bonds, where X′ could be C, N, or another atom. DHP^-s are already ubiquitous in organic synthesis.[5–7] We demonstrate in this Perspective that their synthetic tunability and redox activity should enable a far greater scope for applications of DHP^-s than is currently known for organic synthesis and catalysis.[8–17] Advances in reaction selectivity and energy efficiency are required to use DHP^-s in electrosynthesis, including the lowering of redox potentials for turnover of catalytic cycles. Theoretically, the formation of DHP^-s in a catalytic cycle can be readily achieved *via* two ET (ET1 and ET2) and one PT (PT1) step following the HT; and those ET steps can be driven electrochemically (Scheme 2). However, it is well-known that organohydride catalysts require ~1 V overpotentials to promote the turnover (or second) ET2 step in the cycle, and therefore, strategies for tuning the properties of DHP^-s *via* the incorporation of functional groups and particularly by incorporation of metal ions are needed.[18,19] Metal ions lower the reduction potential for ET but their effect on hydricity is largely unexplored although empirical plots of hydricity and E° suggest they are linearly correlated.[20,21]

1.1 Bioinspired DHP^- chemistry

The chemistry of DHP^-s cannot be discussed without acknowledging the significant chemistry performed by organohydride-containing biochemical cofactors, which have long served as inspiration for the development of synthetic systems. More knowledge of organohydride-containing cofactors is likewise needed to better understand their function in



Scheme 1 Dihydropyridine (DHP) and dihydropyridinate (DHP^-) regio-isomers are numbered according to the carbon atoms in the pyridyl ring.



Scheme 2 Possible catalytic cycle to enable electrochemical regeneration of DHP^- for hydride transfer (HT) reactions. ET = electron transfer; PT = proton transfer. In some cases, the ordering of the ET2 and PT1 elementary steps is reversed.

biological systems. Many enzymatic processes transfer hydride equivalents, and those transformations are most often facilitated by cofactors that contain the DHP^- functional group, including nicotinamide adenine dinucleotide (NAD)[22,23] and the nickel pincer nucleotide (NPN) found in lactate racemase (LarA) (Chart 1).[24,25] There are a handful of published structures in which the carbamoyl group (R–$CONH_2$) of NAD^+ is bound to a metal ion in a protein structure; example enzymes where this structure is found include isopropylmalate dehydrogenase,[26] and pyrrolysine synthase.[27] In isopropylmalate dehydrogenase, an activating potassium ion (K^+) coordinates to the carbamoyl nitrogen and a glutamate side chain. This structural positioning and activating effect of K^+ on the NAD^+ ring helps HT to the NAD^+ ring during substrate oxidation.[28] In pyrrolysine synthase, a magnesium ion (Mg^{2+}) is coordinated to the carbamoyl oxygen of NAD^+. The NPN cofactor promotes a more limited set of

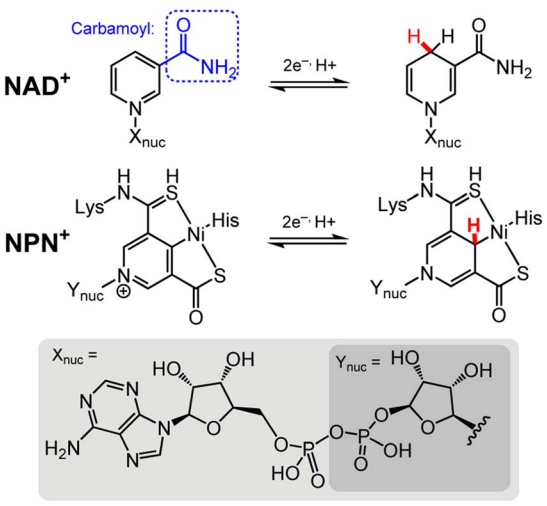


Chart 1 Structures of the NAD^+ and NPN^+ cofactors in their oxidised and reduced forms.[22,24], Lys = lysine; His = histidine; X_{nuc} = adenine dinucleotide (bottom, light grey shaded rectangle); Y_{nuc} = mononucleotide (bottom, dark grey shaded rectangle). The site for HT chemistry is indicated by a red H atom.

chemistries relative to NAD^+. As the name lactate racemase suggests, LarA mediates the racemisation of lactate, and that process proceeds following hydride abstraction from lactate by the NPN cofactor, to permit a C–C bond rotation before HT from NPN furnishes the racemised lactate molecule.[29] There are also cofactors that facilitate HT in biology *via* O–H and N–H bond chemistries; they are outside the scope of this Perspective and so those cofactors will not be discussed.[25,30–33]

This Perspective will primarily focus on the structure–reactivity relationships that govern control of HT chemistry (and the formation of hydride reagents) since it is the nuances of the chemical structure that guide selectivity in chemical reactions. Opportunities for functionalisation of DHP^-s are numerous and synthetically very accessible; they include N-coordination of metal ions, especially redox-inactive Lewis-acidic metal ions, and N-protonation. This viewpoint is provided through the lens of inorganic and coordination chemistry since metal-ion effects on DHP^- chemistry are significant for accessing lower reduction potentials. Our focus will be on chemistry reported within the last 10 years; however, older examples may be cited to give context or for completeness in some areas. We make no attempt to comprehensively review the literature on DHP^- chemistry and instead highlight only examples related to tuning the structures and function of DHP^- reagents to lower their redox potentials and access greater utility and selectivity in their chemistry. In Section 2, we discuss a few advances in the synthesis of metal-containing DHP^- reagents with a focus on achieving predictability in the regiochemistry of DHP^- formation from the pyridyl precursor. In Section 3, we discuss the reaction chemistry of (DHP^-)-based metal–ligand coordination complexes that have been employed in stoichiometric and catalytic HT chemistry. Throughout this Perspective article, the focus of our discussion will be on (1,4-DHP^-)-containing reagents, which are structurally far more diverse than the model and native cofactors such as NPN and NAD.

2. Synthesis of metallated DHP^- complexes (M-DHP^-s)

Elimination of unwanted side reactions in stoichiometrically, catalytically, and electrocatalytically driven HT reactions is an important ongoing effort,[34–36] with one approach being the development of milder conditions to achieve better regio- and chemo-selectivity as well as stereoselectivity.[37–39] In electrosynthesis applications, milder reaction conditions, especially through lowered redox potentials, would also correlate with a more energy-efficient process. In this section, we begin with a brief overview of common organohydride reagents and then explore the potential to incorporate metal ions into DHP and DHP^- structures; the resulting metallo-ligands may facilitate HT reaction chemistry. These synthetic approaches are relevant because HT reaction chemistry may be more widely employed if tuneable and regio-pure DHP^- structures were more synthetically accessible. We will provide selected example syntheses of coordination complexes where the pyridyl N or C atom are the donor ligands. We will not discuss the preparation of functionalised DHP^- ligand structures.[40,41]

In coordination chemistry, a ligand is a group or molecule that can form a dative bond with a metal ion. Based on the structure of the DHP^- core, which is common to (DHP^-)-containing ligands, there are a few possible binding modes for metal ions to DHP^-, and they may modulate the physical properties and reaction chemistry of DHP^-. In general, synthetic DHP^- ligands with variable N-coordination are either bi- or tridentate because the multi-dentate ligands form more stable metal complexes than a monodentate ligand due to the chelate effect.[42] The most common structure in the coordination chemistry of DHP^- comprises metal ions ligated by the pyridyl N or C atom (Chart 2 left). Functional groups on the DHP^- core can also potentially be ligands for the metal ion (Chart 2 right); this outer sphere approach can position substrates near the DHP^- hydride *via* docking to the metal and tune regioselectivity and reactivity as will be discussed in Section 3.4.

2.1 Background on organohydride reagents

Here we provide a brief survey of organohydride reagents since their chemistry can inform the design of next-generation metal-containing DHP^- reagents. Most commonly, the active C–H hydride in an organohydride reagent is found on a C atom of a N-containing heterocycle (Chart 3). The hydride-donor ability, often discussed in terms of the free energy for loss of hydride ion (hydricity, ΔG_{H^-}), of DHP^- reagents spans roughly 50–100 kcal mol^{-1} in MeCN.[18] NADH is often credited as inspiration for synthetic organohydrides that incorporate the pyridine ring; classic examples of this model NADH reagent class are 1-benzylnicotinamide (BNAH)[43] and the Hantzsch ester (HEH)[44] (Chart 3), which have enabled a great deal of HT reactivity and continue to be used in catalytic HT reactions.[45] New organohydrides have also been developed from HEH and BNAH by functionalisation of those scaffolds: examples of this strategy include N- or C-functionalisation of pyridines, as illustrated by the structures of 3,5-bis(2,6-dimethylphenyl)-1-mesityl-1,2-dihydropyridine (BDMH)[46] and 2,6-dimesityl-1-methyl-4-phenyl-1,4-dihydropyridine (DMPH) (Chart 3).[35] Both BDMH and DMPH contain bulky mesityl substituents (Mes), which likely prevent association of molecules in solution, increasing their stability toward H_2 evolution or other decomposition pathways. The mesityl substitution also changes the hydricity of

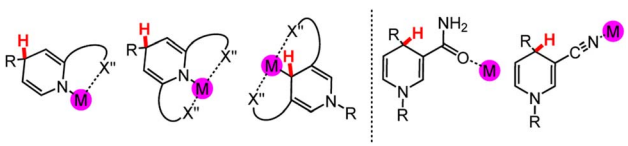


Chart 2 (Left) Possible N- and C-coordinated DHP^- ligands with typical examples of *C*- and *N*-alkylation patterns that support the coordination modes. (Right) Examples of functional groups on DHP^- ligand cores, including carbamoyl and nitrile[40] groups, that can bind metal ions or protons. M = a metal atom; X″ = coordinating heteroatom. Again, the site for HT chemistry is indicated by a red H atom.

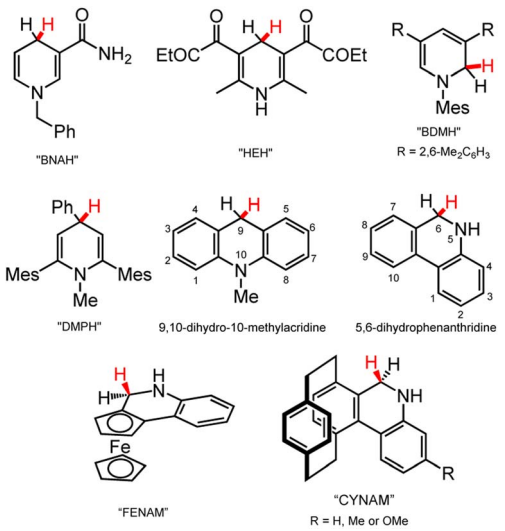
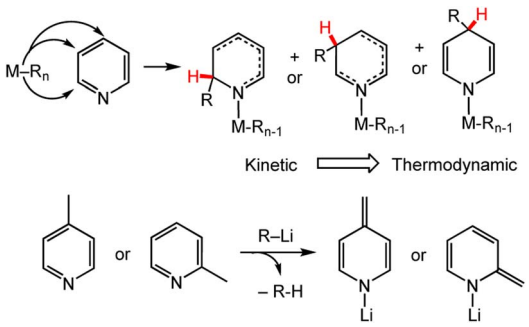


Chart 3 Selected organohydride reagents,[35,43–48] including NADH-inspired examples (BNAH, HEH), functionalised pyridines (BDMH, DMPH), and fused ring systems (acridine (Acr), phenanthridine (phen), FENAM, CYNAM). The site for HT chemistry is depicted with a red H atom. Mes = mesityl group.



Scheme 3 (Top) The general reaction pathway for alkylation to make either 1,2-DHP$^-$, 1,3-DHP$^-$ or 1,4-DHP$^-$ metal complexes, including the relative stability of the alkylation products. M = metal centre; R_n = alkyl group. (Bottom) Deprotonation of acidic functional groups is a possible side reaction with metal–alkyl reagents;[60] avoiding this side reaction is a common challenge in the synthesis of M-DHP$^-$ compounds.

the reagents, so that they are stronger hydride donors relative to BNAH. Carbamoyl is more electron-withdrawing compared to mesityl, so carbamoyl-containing BNAH has lower hydride-donor ability and more positive hydricity, ΔG_{H-}, than Mes-containing BDMH and DMPH. Another class of organohydride based on the DHP$^-$ structure are fused ring systems, such as acridine (Acr)[47] and phenanthridine (phen).[48,49] The fused structures enable greater electron delocalisation across more atoms, so that the reduction potential for those structures is lowered, as is the hydride-donor strength relative to BNAH. In rough terms, fused-ring DHP$^-$ donors are roughly 5–20 kcal mol^{-1} weaker hydride donors than BNAH.[18,50] Functionalisation of fused ring scaffolds has also been pursued to afford asymmetric phenanthridine organohydrides, ferrocene-based FENAM[51,52] and [2.2]paracyclophane-based CYNAM[53] (Chart 3 bottom); both FENAM and CYNAM enable access to stereoselective reduction products.

2.2 Preparation of M-DHP$^-$s *via* reaction of pyridyl ligands with metal alkyls

A common synthetic route to DHP$^-$ coordination complexes is by reaction of the pyridyl form of the ligand with a metal–alkyl reagent, and this approach most often results in alkylation of the pyridine ring, which is activated by the N-coordination of the metal ion (Scheme 3 top).[54] To indicate that the ligand has been reduced to the dihydropyridinate form, the negative charge of DHP$^-$, and DHP$^-$ containing ligands, are explicitly shown; however, the positive charge of the M ion is understood and sometimes omitted. Groups 1 and 2 alkyl reagents have been explored most extensively and are very nucleophilic.[55,56] The drawback of this approach for synthesising DHP$^-$s is that it is not always selective for a product that is alkylated at the C_2, C_3 or C_4 pyridyl positions. Work by Campora and coworkers has provided a host of examples with chelating ligands that have pyridyl at their core, and their reactions with various metal–alkyl reagents.[39,57] Just one example is highlighted here; it is representative of the competition between thermodynamic and kinetic product outcomes and the challenges in achieving selectivity. Reaction of a diiminepyridine (**I_2P**) with dibenzylmagnesium (Bn_2Mg) results in isomers derived from unselective pyridine-ring substitution.[58] At low temperature, C_2 alkylation is favoured (−60 to 0 °C), while above 5 °C, a mixture of C_3 and C_4 alkylation products is present, but they ultimately converge to the C_4 alkylation product. These results suggest the relative thermodynamic preference of the alkylation product is of the order: $C_2 < C_3 < C_4$. The kinetic preference for 1,2- *vs.* 1,4-addition product has also been noted in other reactions producing M-DHP$^-$ complexes, such as the catalysed hydroboration of pyridines.[59] Another common challenge in achieving DHP$^-$ synthesis with metal alkyls is avoiding the deprotonation of acidic groups contained in functionalised pyridines. This is illustrated by reactions of 2-methyl- or 4-methyl pyridine with alkyl lithium reagents, RLi,[60] where dearomatization produces the enamide rather than alkylation of the pyridine ring (Scheme 3 bottom). Although undesirable for M-DHP$^-$ formation, this aromatization-dearomatization reactivity has been well documented in other reaction pathways.[61–64] Similarly, other basic groups such amines should be avoided in the ligand structure due to similar protonation/deprotonation reactivity.[65]

Recent efforts have been made to enhance the selectivity of metal–alkyl reagents using chelating ligands as co-reagents as well as metathesis reactions to substitute the metal ion. Ongoing efforts in synthetic chemistry seek to improve the selectivity of metal–alkyl reagents in the functionalisation of aryl and heterocyclic compounds by the addition of chelating co-reagents.[66–68] For example, using stoichiometric pyridine and *tert*-butyl lithium, *t*BuLi, followed by the addition of the chelating ligand Me_6TREN, [tris(*N*,*N*-dimethyl-2-aminoethyl) amine], in hexane solution, the first report on the solid-state structure of a monomeric Li-DHP$^-$ was presented.[69] Reactivity

of pyridine with other butyl lithium reagents, *n*-, iso-, *sec*-butyl lithium (*n*BuLi, iBuLi, *s*BuLi), as well as with cheaper ligands PMDETA (*N*,*N*,*N*′,*N*″,*N*″ = pentamethyldiethylenetriamine), Me_4AEE (bis-[2-(*N*,*N*-dimethylaminoethyl)]ether) and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), was later explored (Scheme 4).[70] In each case, 1,2-DHP$^-$ was obtained and bulky alkyl substituents increased the solubility of the M-DHP$^-$ in non-polar solvents. Metathesis reactions with 1-lithio-2-*t*Bu-1,2-DHP$^-$ (Li-2*t*-DHP$^-$) and sodium or potassium *tert*-butoxide (*t*BuONa or *t*BuOK) resulted in 1-sodium-2-*t*Bu-1,2-DHP$^-$ (Na-2*t*-DHP$^-$) or 1-potassium-2-*t*Bu-1,2-DHP$^-$ (K-2*t*-DHP$^-$) complexes, respectively (Scheme 4, M-2*t*-DHP$^-$ pathway).[71] The reactivity of these complexes including the influence of the metal ion will be discussed in greater detail in Section 3.

Given these factors, not all DHPs will be suitable for M-DHP$^-$ formation by metal alkyls. DHPs with acidic functional groups will have competing deprotonation pathways. However, with expanding efforts on selective metal–alkyl reagents and metathesis pathways, metal alkylation can serve as a good route to increase solubility of the M-DHP$^-$ and allow post-synthetic modifications by exchange of the metal ion.

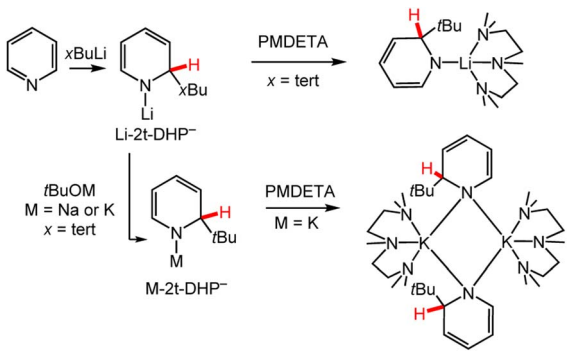
2.3 Hydride transfer (HT) to pyridyl ligand–metal complexes

Regioselective HT to pyridines has been approached *via* two primary routes: the metal-catalysed hydroboration or hydrosilylation of pyridines and the direct reaction of pyridines with metal–hydride reagents. Hydroboration and hydrosilylation and metal-free approaches will not be discussed in detail since they produce *N*-borylated and *N*-silylated DHP$^-$s and since boron and silicon are not metals, B-DHP$^-$s and Si-DHP$^-$s fall outside the scope of this Perspective.[59,72–83] An exception are select *N*-borylated compounds whose metalloid character is informative of metal ion effects on DHP$^-$s as discussed in Section 3.2.

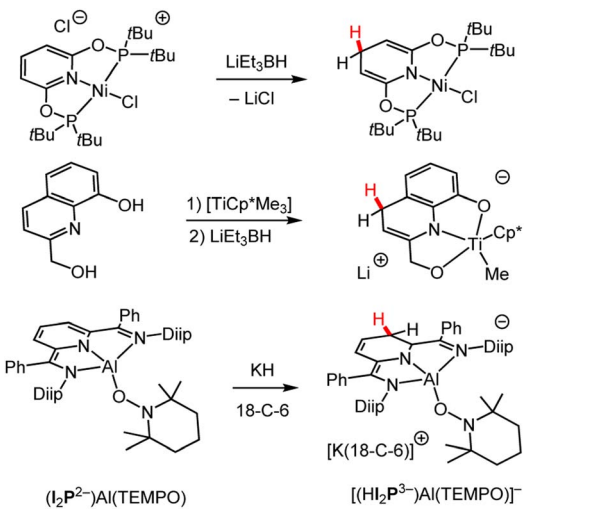
2.3.1 Reaction of metal pyridyls with metal hydrides. Strong hydride donors have been used extensively in the formation of (DHP$^-$)-containing ligand–metal complexes, although the regioselectivity can be unpredictable. Selected examples involving a variety of transition-metal and main-group centres are included here (Scheme 5).[84,85] With this approach, there are additional selectivity challenges including trans-metallation pathways[86,87] or HT to the metal rather than the pyridyl ring. Overreduction needs to be monitored and can usually be circumvented through the use of pure reagents, careful stoichiometric additions, and controlled low-temperature reactions.[88] Like the metal–alkyl approach, the direct HT approach is not compatible with molecules containing protic functional groups since H_2-evolution will be observed.

In some cases, the resonance pattern of the pyridine within a larger conjugated structure can be used to direct regioselective hydride formation. As an example, using the direct HT approach, selectivity for the 1,3-DHP$^-$ isomer of a tridentate diiminepyridine (**I_2P**) ligand was demonstrated (Scheme 5 bottom).[89] The identity of the metal in a metal hydride can also influence the regioselectivity of hydride addition. Comparison of Mg to calcium (Ca) reagents indicates that the larger ionic size of Ca favoured the formation of the M–(1,2-DHP$^-$) complex while the smaller Mg ion gave both 1,2- and 1,4-DHP$^-$ products.[90] This was explained in the primary literature where DFT calculations suggest high energy barriers required for Ca to form 1,4-DHP$^-$ products.

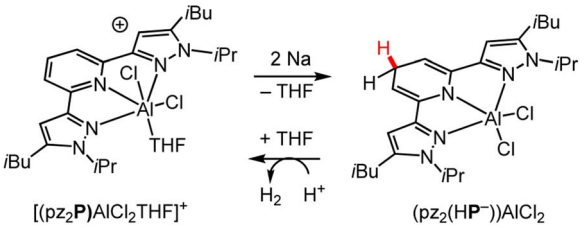
2.3.2 ET and PT reactions of M-DHP$^-$s. We have demonstrated that ET and PT routes can in some cases selectively produce a M–(1,4-DHP): the addition of two equivalents of Na metal to $[(pz_2\mathbf{P})AlCl_2THF]^+$ gives $(pz_2(H\mathbf{P}^-))AlCl_2$ in <50% yield, where pz is an imine—more specifically, a substituted pyrazolyl group—and **P** represents the pyridyl core of the ligand.[91] This suggests to us that sequential ET events from Na reduction and a PT event (likely from another equivalent of the ligand) occur, leading to the neutral $(pz_2(H\mathbf{P}^-))AlCl_2$ complex, as outlined in



Scheme 4 Use of chelating ligands to direct selective alkylation of pyridine for M-DHP$^-$ complex synthesis. Note that the Li-2*t*-DHP$^-$ and M-2*t*-DHP$^-$ products are formally neutral, with the "–" indicating the pyridinate form of the ligand. PMDETA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine; x = branching of butyl group, *n*-, iso-, *sec*-, and *tert*-.[60,69–71]



Scheme 5 Examples of syntheses of M-DHP$^-$ complexes by the addition of various metal hydrides.[84,85,89] Cp* = pentamethylcyclopentadienyl; Diip = 2,6-diisopropyphenyl; 18-C-6 = 18-crown-6 ether; **I_2P** = diiminepyridyl; TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.



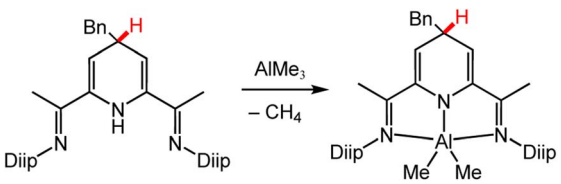
Scheme 6 Synthesis of $pz_2(HP^-)AlCl_2$,[91] where pz is the substituted pyrazolyl shown and P is the pyridyl ligand backbone. HP^- denotes the dihydropyridinate form, which is analogous to DHP^-. Protons are believed to be scavenged from ligand equivalents during reduction by Na.

Scheme 6; HP^- denotes the reduced dihydropyridinate ligand, which along with the Cl ligands formally compensate the Al^{III}). Reactivity of $(pz_2(HP^-))AlCl_2$ will be discussed in Section 3. Reduction of M-pyridines by metal reductants can result in pyridyl radicals which in the absence of protons have demonstrated C–C coupling to form dimerized M-DHP^-s,[87,92] but a survey of this reaction type is not included here.

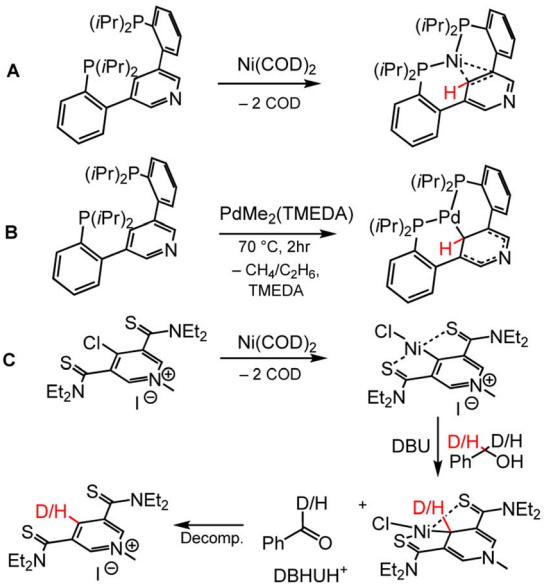
2.3.3 Deprotonation of DHP^-s. Although deprotonation is well established for forming anionic ligand–metal complexes,[93] it is a less well-established pathway for formation of metal–ligand complexes with (DHP^-)-based ligands. As an example, synthesis of aluminium $\mathbf{I_2P}$– complexes, Al–$\mathbf{I_2P}^-$, was achieved by the reaction of R_3Al with dihydro-$\mathbf{I_2P}$, where *R* is an alkyl group. The reaction liberates the alkane along with the ($\mathbf{I_2P}^-$) $Al(R)_2$ product; when $AlMe_3$ is used, the liberated alkane is methane (Scheme 7).[94] Once again, the negative refers to the form of diimine-pyridine ligand; the complex is neutral.

2.4 Synthesis of C_4-coordinated M-DHP^-s

Metallation of the C_4 pyridyl carbon in a chelating ligand has been achieved using nickel (Ni) and palladium (Pd) chemistry; both of these metals have accessible two-electron chemistry that facilitates oxidative addition of the C_4–H pyridyl position. Both Ni and Pd complexes of bis(2-(diisopropylphosphaneyl)phenyl) pyridine (PCP) were synthesised by Agapie and coworkers, and bond metrics from single-crystal X-ray diffraction (XRD) reveal shortening of the C_2–C_3 and C_5–C_6 bonds in the pyridyl, indicative of DHP^- formation (Scheme 8A and 8B).[95] Inspired by the NCN cofactor in LarA, the Hu group has synthesised pincer ligands that are metallated at the C_4 position by Ni.[96,97] Metallation of the bis(diethylcarbamothioyl) methylpyridinium (SPS) ligand was achieved with bis(cyclooctadiene) nickel, $Ni(COD)_2$



Scheme 7 Deprotonation of DHP *via* metal–alkyl reaction to form an Al-DHP^- complex.[94] Diip = 2,6-diisopropyphenyl; Bn = benzyl group.



Scheme 8 Metallation of the C_4 position for the pincer ligands (A and B) PCP, bis(2-(diisopropyl-phosphane-yl)-phenyl)-pyridine, and (C) SPS, bis(diethyl-carbamo-thioyl) methyl-pyridinium.[95–97] COD = cyclooctadiene; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene. Location of HT is shown with red H or D atoms. Isotope experiments show C_4 of SPS ligand as hydride acceptor from benzyl alcohol, supporting proposed DHP^- intermediate.

(Scheme 8C). Oxidation of benzyl alcohol or benzyl-α,α,-D_2-alcohol to benzaldehyde or benzaldehyde-α-D_1 respectively by the (SPS)NiCl complex confirmed that the pyridinate form of the (SPS)NiCl (analogous to DHP^-, Scheme 8C, third complex) was accessible, as evidenced by H or D incorporation to the C_4 position of the SPS ligand, even though it could not be isolated. Metallation of the C_4 position can directly tune the electronics of the C_4 atom by the nature of bonding between metal and C_4, where strongly π-donating metals may increase the electron density relative to strongly π-accepting metals, offering another coordination mode for tuning DHP^- electronics.

3. Reactivity of M-DHP^-s

In this section, we will outline and discuss possible roles for metal ions in tuning HT that is mediated by (DHP^-)-based ligands. The potential for influences of metal ions on the properties and reactivity of DHP^- reagents can in some cases be rationalised and predicted by structure–function relationships. Other effects of metal ions on DHP^- chemistry arise from case-specific substrate interactions, or with ligand functional groups in the secondary coordination sphere. We will discuss both types of metal-ion effects.

As a starting point, we will consider the electronic effects and reactivity consequences of pyridyl N-coordination to a metal ion. Electron donation from the pyridyl N atom to a cationic metal ion should result in lowered electron density on the pyridyl ring, lowering the reduction potential for the pyridyl ring; it will also raise the free energy for loss of hydride from the

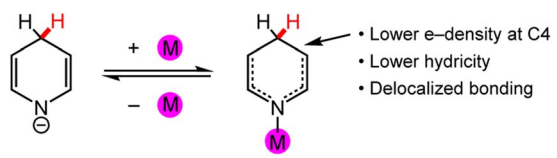
corresponding M-DHP$^-$, which means that the ligated DHP$^-$ is a weaker hydride donor relative to free DHP$^-$. In general, weaker hydride donors have the advantage of greater chemo- and regio-selectivity providing they have sufficient driving force for the reaction. Moreover, the hydricity of the DHP$^-$ should be tuneable by variation of the metal ion identity or oxidation state. In the context of a catalytic cycle for DHP$^-$ regeneration and HT to substrate, the lowered reduction potential of the bound DHP$^-$ will enable a lower applied reduction potential for catalytic turnover (Scheme 2). As an example from our research group, the reduction potential for **I$_2$P** ligands is about −2.1 V *vs.* SCE in THF whereas the **I$_2$P**$^{-/2-}$ couple for the Al-coordinated ligands in (**I$_2$P**$^-$)AlCl$_2$ lies at −0.90 V *vs.* SCE.[98,99] The advantages of a lower applied reduction potential include less chances for unwanted background reactions and a lower overall use of energy in the reaction. Tuneable hydride-donor abilities for the DHP$^-$s could be very helpful in designing chemo- and regioselective reactions (Scheme 9).[18]

3.1 Influence of protons on DHP$^-$ reaction chemistry

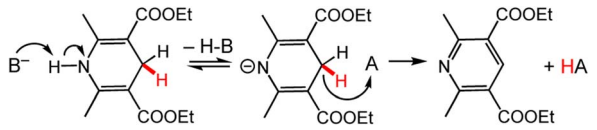
Known Bronsted-acid effects on DHP$^-$ reaction chemistry can be used to illustrate or predict possible metal-ion effects on DHP$^-$ chemistry, since protons and Lewis-acidic metal ions both bring the influence of a cationic group on DHP$^-$ properties. The interest in Bronsted-acid effects on DHP$^-$ stems largely from systems with chiral anions, which therefore direct stereoselectivity in reduction reactions of organic molecules. However, the influence of the (non-chiral) proton is also hugely important. Insights from the extensive literature using Bronsted-acid/base activation of DHP$^-$ can be used to think about how the driving force for HT chemistry from DHP$^-$ is modulated by the cation. As an illustrative example, the reaction between HEH and BNA$^+$ (Chart 3) has a free energy of Δ_rG = + 2.5 kcal mol^{-1}, and no reaction occurs in MeCN solution. In the presence of the strong base DBU (1,8-diazabicyclo(5.4.0)undec-7-ene), complete HT from HEH to BNA$^+$ occurs rapidly with a reported free energy change of Δ_rG = −16.6 kcal mol^{-1} (Scheme 10).[100] Isotope labelling studies suggested a pre-equilibrium deprotonation of HEH precedes a rate-limiting HT step. More generally, these results demonstrate the significant influence that coordination at the pyridyl ring N atom has on the kinetics and thermodynamics of HT from a DHP$^-$ reagent.

3.2 Reactivity of s- and p-block M-DHP$^-$s

In this section, we discuss the reaction chemistry for known N-metallated DHP$^-$ ligands with metal ions drawn from the s- and p-block elements. These examples include stoichiometric HT reactions and electrocatalytic reactions where DHP$^-$ regeneration is mediated *via* successive ET–ET–PT reaction steps.



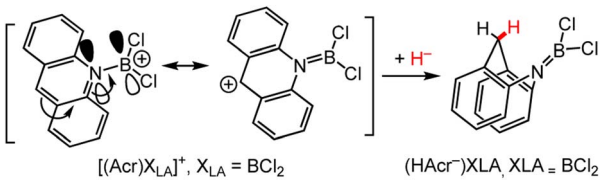
Scheme 9 Common changes to DHP$^-$ upon coordination of a metal atom, M, at the pyridyl N atom.



Scheme 10 (Top) The proposed mechanism for reaction of HEH with a hydride acceptor (A) in the presence of a base (B$^-$).[100] For the other example in the text, the acceptor A would be BNA$^+$; in both cases, the base B$^-$ is DBU.

3.2.1 p-Block-supported M-DHP$^-$ HT reactivity. The chemistry of complexes with pyridyl N-coordination to p-block elements provides some examples of metal-ion and metalloid effects. Capitalising on the high Lewis acidity of the {BCl$_2$}$^+$ fragment,[101] coordination of Acr to {BCl$_2$}$^+$ yields carbon Lewis acids (Scheme 11).[102] The Lewis acidity of the C$_9$ position of Acr (see Chart 3 for numbering of acridine ring) was tuned over a range of 50 kcal mol^{-1} by coordinating different functional groups to the pyridyl N; these include BCl$_2^+$, BPin$^+$ (boronic pinacol ester), Me$^+$, and AlCl$_3$. As a specific example, (HAcr$^-$){BCl$_2^+$} is a much weaker hydride donor than (HAcr$^-$){Me$^+$} with enthalpies of HT of 75 and 53 kcal mol^{-1}, respectively, relative to triethylborohydride. This is believed to result, at least in part, from N$_{Acr}$–B double-bond character that reduces the electron density on the pyridyl ring in (HAcr$^-$){BCl$_2^+$}. Moreover, the nature of the B–Cl bonds determines the extent to which π-bonding contributes to the N$_{Acr}$–B bonding interaction. Competition between π-bonding of N$_{Acr}$–B bonds and that from B's other bonds was compared using bond lengths: the N$_{Acr}$–B bond in (HAcr$^-$){BCl$_2^+$} is shorter than in (HAcr$^-$){B(OR)$_2^+$}, which highlights the better π-donation ability of the alkoxo substituent relative to that of the chloro group. Additionally, computational studies were used to probe the hydride-donating ability of (HAcr$^-$){X$_{LA}$} compounds (where X$_{LA}$ = Me$^+$, Si(Me)$_3^+$ or BPin$^+$); the results suggest the following order for hydride-donating ability: (HAcr$^-$){BPin$^+$} < (HAcr$^-$){Si(Me)$_3^+$} < (HAcr$^-$){Me$^+$}.[102]

A handful of examples exist where a catalytic HT reaction is enabled by regeneration of a DHP$^-$ electrochemically; these have mostly been studied within the past decade and involve organic DHP$^-$s.[18,19,103] The applied potentials needed to drive these catalytic reactions vary greatly depending on the solvent



Scheme 11 Synthesis of (HAcr$^-$)X$_{LA}$, where X$_{LA}$ = BCl$_2^+$; X$_{LA}$ may also be other groups as indicated in the main text. (Left) Resonance forms of [(Acr)BCl$_2$]$^+$ and (right) (HAcr$^-$){BCl$_2^+$}, the HT product, which is stabilised by the N$_{Acr}$–B multiple bonding.[102]

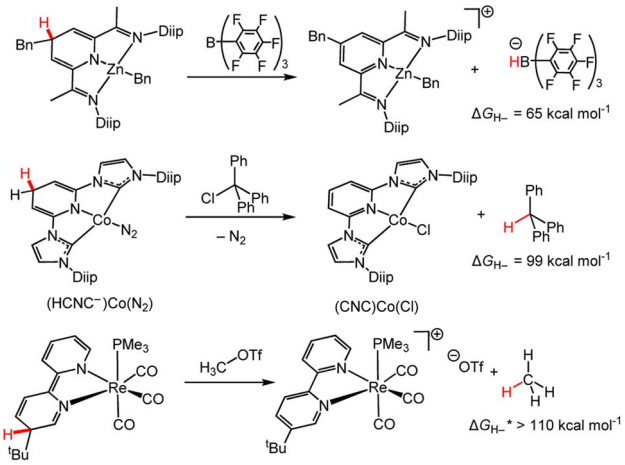
and choice of organohydride. Representative example ranges are 0.3 to −1.3 V *vs.* SCE in DMSO[19,104] and −0.6 to −1.15 in MeCN.[105,106] Metal-ion effects on electrocatalytic HT have been reported, and we highlight just one study here: the interconversion between $[(pz_2\mathbf{P})AlCl_2THF]^+$ and $(pz_2(H\mathbf{P}^-))AlCl_2$ that was described in Section 2.3.[91] The tridentate pyridyl-centred ligand, denoted as $pz_2\mathbf{P}$, is coordinated to an Al(III) centre. Electrochemical regeneration of $(pz_2(H\mathbf{P}^-))AlCl_2$ was demonstrated following its reaction with protons to liberate H_2 at −1.2 V *vs.* SCE (Scheme 6). No evidence for dimerisation *via* pyridyl C_4–C_4 coupling of the proposed radical intermediate $(pz_2\mathbf{P}^{\bullet})Al(THF)Cl_2$ formed following ET analogous to ET1 in Scheme 2, was reported in this work. This is consistent with the effects of the metal ion as discussed earlier in Section 3; *i.e.*, if N-coordination of a metal ion results in lowered electron density on the pyridyl ring and especially at C_4, then with metals such as Al, the C_4–C_4 coupling pathways should be disfavoured, which represents another advantage of N-metallation for organohydride reagents.

3.2.2 s-Block-supported M-DHP$^-$ HT reactivity. The synthesis of M-2*t*-DHP$^-$ was discussed in Section 2 where M = Li, Na or K (Scheme 4) The reaction chemistry of M-2*t*-DHP$^-$ spans stoichiometric HT reactions and dehydrogenative coupling of boranes although in these reactions, M-2*t*-DHP$^-$ is believed to dissociate to 2*t*-DHP and an active metal hydride species, M–H, which transfers hydride to substrate.[71] The reaction times for catalytic dehydrogenation of dimethylamine using Li-2*t*-DHP$^-$ (60 h), Na-2*t*-DHP$^-$ (72 h) or K-2*t*-DHP$^-$ (144 h) trend with their solubilities in non-polar solvents, implying that increasing solubility is an important factor in improving rate.[107,108] Future work with s-block DHPs can focus on ligand scaffolds that further improve solubility and avoid additional reaction steps such as formation of M–H intermediates.

3.3 Reactivity of d-block M-DHP$^-$s

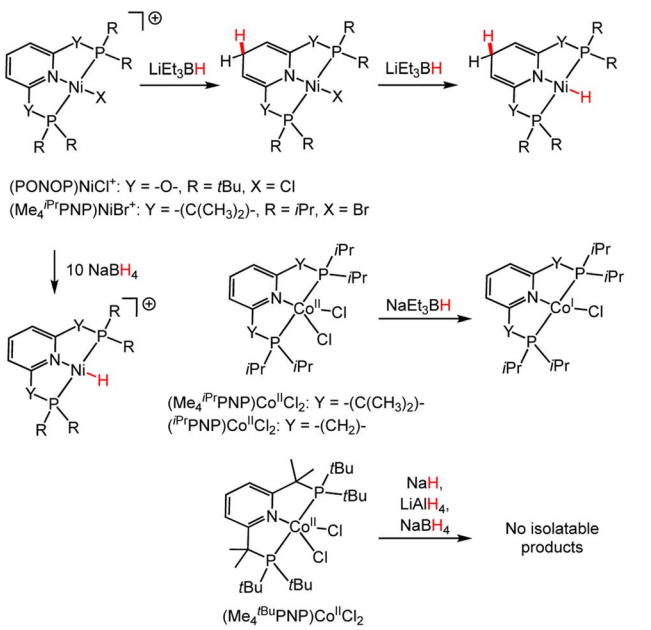
Here we explore selected reactions from the past decade where hydride is transferred from a M-DHP$^-$ to a non-pyridine acceptor and consider the insights we can obtain from this reaction chemistry. Typical stoichiometric HTs from d-block M-DHP$^-$ complexes involve moderate to strong hydride acceptors with hydride-donor abilities in the range of 65 to ∼110 kcal mol^{-1} (the hydricity of methane was approximated from the trend in ΔG_{H-} from substitution of phenyl groups on methane. ΔG_{H-} increases in the order H–C(Ph)$_3$ < H–CH(Ph)$_2$ < H–CH$_2$(Ph)).[18] As examples, the DHP$^-$ form of zinc–$\mathbf{I}_2\mathbf{P}$ complexes reacts with $B(C_6F_5)_3$,[86] the cobalt pincer bis(diisopropylphenyl) imidazole pyridinate ligand complex, (HCNC$^-$)CoN_2, reacts with trityl chloride to yield triphenyl methane,[109] and a rhenium-bipyridine-based DHP$^-$ reacts with methyl triflate to afford methane (Scheme 12).[110] Hydrogenation of alkenes with (CNC)CoCl was achieved under H_2, but no mechanistic studies were available to elucidate the hydride source; it was possible for both a Co–H or M-DHP$^-$ species to transfer hydride to the alkene.

As with (CNC)CoCl, ambiguity in the reactive site for HT—metal hydride (M–H) *vs.* M-DHP$^-$—has been illustrated in other catalytic systems. Terpyridine DHP$^-$s studied by Dub and



Scheme 12 HTs from M-DHP$^-$ complexes. ΔG_{H-} are the reported for the hydride acceptors.[18,86,109,110] Bn = benzyl; Diip = 2,6-diisopropylphenyl; CNC = tridentate pincer ligand coordinating at 2 C and 1 N, as shown; OTf = triflate.

coworkers are active catalysts for the hydroboration of ketones,[111] reduction of C=O, C=C and C=N bonds,[112] and hydroboration of alkynes to vinyl borates.[113] In each system, the active catalytic species bears both a M–H and a DHP$^-$ ligand. Furthermore, it is unclear from reactivity studies of bis((dialkylphosphaneyl)oxy)pyridine Ni complexes, (PONOP)NiCl$^+$ (Scheme 13),[114] whether a M-DHP$^-$ hydride or M–H hydride is involved in the HT. In reactions of (PONOP)NiCl$^+$ and (Me_4-^{iPr}PNP)NiBr$^+$,[87] where PONOP and Me_4^{iPr}PNP are both planar tridentate ligands (Scheme 13), stronger hydride-donating



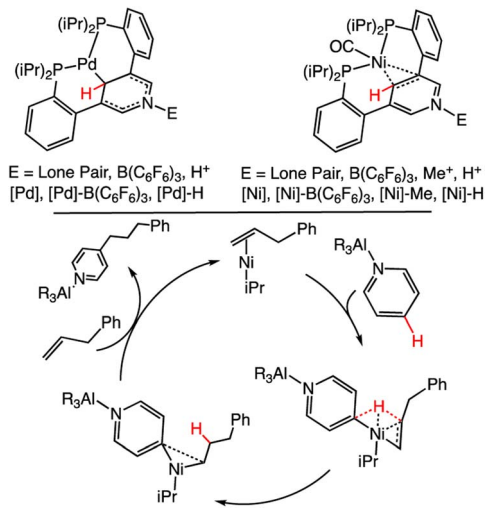
Scheme 13 Reactions highlighting the influence of the ligands and metal ion on the HT selectivity: Ni complexes, (PONOP)NiCl$^+$,[114] and (Me_4^{iPr}PNP)NiBr$^+$,[87] and Co complexes (Me_4^{iPr}PNP)Co^{II}Cl$_2$,[115] (^{iPr}PNP)Co^{II}Cl$_2$ (ref. 116) and (Me_4^{tBu}PNP)Co^{II}Cl$_2$.[117]

reagents tend to favour DHP^- formation, while weaker hydride donors tend to favor M–H formation after multiple equivalents are added. In the case of $(Me_4{}^{iPr}PNP)Co^{II}Cl_2$ (ref. 115) or $(^{iPr}PNP)Co^{II}Cl_2$,[116] addition of one equivalent of sodium triethylborohydride, $NaEt_3BH$, gives $(Me_4{}^{iPr}PNP)Co^{I}Cl$ or $(^{iPr}PNP)Co^{I}Cl$ (Scheme 13). For $(Me_4{}^{tBu}PNP)Co^{II}Cl_2$ various hydride donors do not afford isolable M-DHP^- or metal–hydride products, and this may reflect low selectivity or another result (Scheme 13).[117] All of the work in the foregoing paragraph is consistent with a trend where square planar d^8 transition metal complexes favour DHP^- formation when strong hydride donors are used.

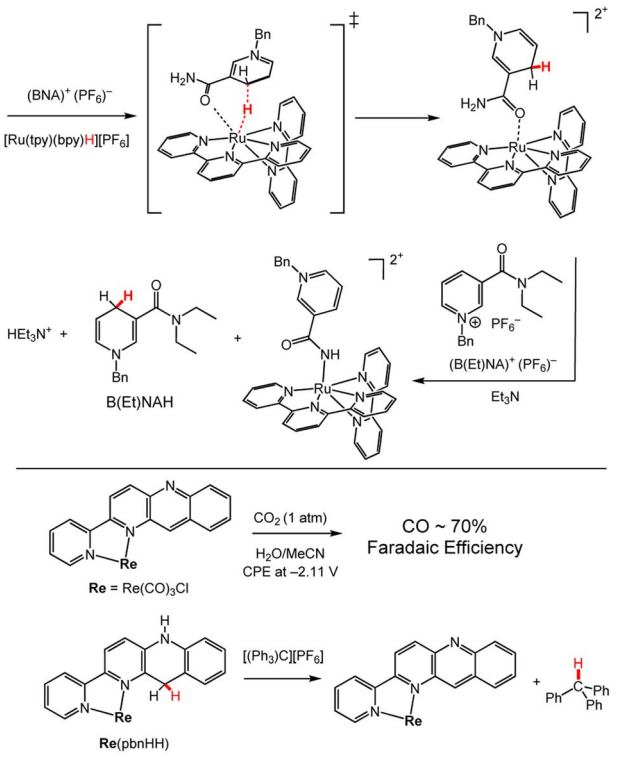
Effects of bimetallic activation on (DHP^-)-containing ligands has also been studied but with only a few examples. A pincer ligand, 3,5-bis(2-phosphinophenyl)-pyridine, coordinates *via* two phosphorus (P) donors and the pyridyl C atom to a Ni or Pd centre; the pyridyl N atom can coordinate to a variety of Lewis acids, including metals, and alkyl substituents, which we denote as E.[95] We abbreviate the complexes as [Ni], [Ni]–$B(C_6F_5)_3$, [Ni]–Me and [Ni]–H, when E = lone pair, $B(C_6F_5)_3$, Me^+ and H^+ (Scheme 14). Shifts in the ^1H NMR spectra for the pyridyl C_4 and $C_{2/6}$ suggest stronger Ni-py π-bonding when E = Me^+ than for E = $B(C_6F_5)_3$ or E = lone pair. This is consistent with Me^+ being more electron-withdrawing than the $B(C_6F_5)_3$ group. CO was used to probe the electronic effects of the pyridine/metal centre, and wavenumber values for ν(CO) involving the Ni centre are 1930, 1976, 1966 and 1975 cm^{-1} for [Ni], [Ni]–$B(C_6F_5)_3$, [Ni]–Me and [Ni]–H, respectively (Scheme 14, top). These data suggest that the electron-withdrawing substituents (E) can influence the electron density at the C_4 carbon. Furthermore $B(C_6F_5)_3$, Me^+ and H^+ all have a similar effect on electronic structure. Catalytic alkylation of pyridine was reported using AlR_3 as Lewis acid to activate the pyridine ring;[118] in this process, E = AlR_3. Proposed mechanisms for the pyridine alkylation reaction have included Ni(0) insertion into the py C_4 bond or a Ni-supported, direct HT from the py C_4 to the alkene (Scheme 14, bottom).[119] Recent computational and experimental work support the latter pathway. These results suggest that bimetallic pyridine systems as shown in Scheme 14, can support new HT reaction pathways, which incorporate reaction processes supported by transition metals.

3.4 Secondary coordination sphere (SCS) effects on HT chemistry

In coordination chemistry, synthetic pyridyl ligands incorporating a carbamoyl functional group or other C_3 substituent, have been studied as models for NADH since coordination of the carbamoyl group influences the HT reactivity of nicotinamide derivatives in biological systems.[26,28] An illustrative synthetic example is HT from BNAH to $B(Et)NA^+$, which does not spontaneously occur in solution.[120] However, when a solution of BNA^+ and $[Ru(tpy)(bpy)H]^+$ was added to a solution of $B(Et)NA^+$ and Et_3N, HT was observed from the BNAH–Ru complex, $[(BNAH)Ru(tpy)(bpy)]^{2+}$, to $B(Et)NA^+$ (Scheme 15, top; tpy = terpyridine, bpy = bipyridine, BNAH (see Chart 3)). It is believed that coordination of the carbamoyl group of the *in situ*-formed BNAH–Ru complex increases the acidity of the $-NH_2$ protons so that deprotonation by triethylamine occurs. This in turn enhances the hydride-donor ability of coordinated BNAH



Scheme 14 (Top): Structures of [Pd]–E and [Ni]–E.[95] For the CO vibrational studies to probe the electronic effects on the [Ni]–E complex, the CO was bound directly to the Ni as shown. (Bottom): Proposed mechanism for C_4 alkylation, which is believed to pass through a ligand-to-ligand HT rather than an oxidative insertion step.[118]



Scheme 15 Examples of SCS effects on HT chemistry. (Top) Reaction between BNA^+ and $[Ru(tpy)(bpy)H]^+$ to form the $[(BNAH)Ru(tpy)(bpy)]^{2+}$ complex, and its HT reaction with $B(Et)NA^+$.[119,120] Bn = benzyl; tpy = terpyridine; bpy = bipyridine. (Bottom) Reactions of Re(pbn) and Re(pbnHH).[121] pbn = 2-(2-pyridyl)benzo[*b*]-1,5-naphthyridine; pbnHH denotes the ligand in its DHP^- form.

relative to free BNAH. It is also known that this reaction selectively produces the 1,4-DHP$^-$ regio-isomer of B(Et)NAH and no formation of the 1,2- or 1,6-DHP$^-$ regio-isomers was observed.[121]

Other ligand modifications have shown promise for expanding HT reactivity by taking advantage of metal coordination to substrate. We highlight modification of Acr to 2-(2-pyridyl)benzo[*b*]-1,5-naphthyridine (pbn) providing a bidentate ligand where the metal centre is positioned in close proximity to the DHP/DHP$^-$ functional group.[122] This positioning proves advantageous for HT reactions where the substrate can bind to a metal centre, rhenium (Re) in this case, and accept a hydride from pbn. This reactivity has been demonstrated for CO_2, which had a binding constant of 40 M^{-1} to Re(pbn); controlled potential electrolysis experiments (CPE) at −2.11 V *vs.* Fc^+/Fc, furnish CO with 70% faradaic efficiency, where Fc = ferrocene. More work has been done by the group of Tanaka with Rh(pbn) complexes, which can also facilitate catalytic HT to CO_2 under electrocatalytic conditions.[123] Hydricity of the of Re(pbnHH) was bracketed by reaction with trityl cation thermodynamic cycles, giving $\Delta G_{H^-} = \sim 84$ to ~ 99 kcal mol^{-1}. Analogous 9,10-dihydro-10-methylacridine is a stronger hydride donor with $\Delta G_{H^-} = \sim 70$ kcal mol^{-1} (Chart 3). The electron-withdrawing effects of the nitrogen and the coordination of the metal centre in Ru(pbnHH) likely led to the more positive hydricity values and lower hydride-donor ability.

We have provided two examples of SCS effects: first, metals coordination can modify the electronic properties of DHP functional groups; and second, molecular design allows for substrate coordination near the dihydroxy functional group of DHP$^-$. Future systems can employ SCS effects to tune the electronics of the DHP$^-$ and or substrate.

4. Conclusions and outlook

We have described the influence of the metal ions on hydride formation and HT from M-DHP$^-$s. Broadly speaking, metals lower the electron density on the pyridine ring, which in turn, lowers the reduction potential for electrochemical hydride formation and raises the free energy loss for HT of the M-DHP$^-$ relative to the non-metallated DHP$^-$ species. In Section 2, we described multiple avenues for synthesis and isolation of M-DHP$^-$s. Alkylation with metal–alkyl reagents can provide access to M-DHP$^-$s in a single step, provided the ligand does not have acidic protons. HT from a hydride donor can selectively provide the metallated 1,2-, 1,3- or 1,4-DHP$^-$ species through judicious choice of catalyst, hydride donor or ligand design. Additionally, deprotonation of a DHP to form a M-DHP$^-$ uses established deprotonation pathways to form anionic coordination compounds. By having multiple routes to M-DHP$^-$ formation, access to a developing library of these complexes becomes easier and will propel future studies, expanding HT chemistry in organic synthesis.

Proof-of-principle reactions where HT is achieved from M-DHP$^-$ complexes were described in Section 3. A more accurate report for hydride-donating ability of M-DHP$^-$s is warranted along with greater exploration of substrate scope. Based on prior work, it is likely that M-DHP$^-$s can carry out the HT chemistry currently performed by organohydrides in synthetically relevant transformations; and this may lower the reduction potentials and make catalytic cycles such as those for electrocatalysis attainable (Scheme 2). The chemistry of M-DHP$^-$s that are metallated at the C_4 pyridyl position is underexplored at this time.

Current challenges in understanding reaction pathways of M-DHP$^-$s often stem from the presence of a metal–hydride species and M-DHP$^-$ complex. This creates ambiguity in identifying the active HT species in solution, and therefore, difficulties in redesigning next-generation HT reagents. Post-synthetic modifications also offer an attractive way to further tune HT chemistry. For example, metal coordination to the pyridyl N of main-group-coordinated pbn systems tunes the metal centre. The resulting bimetallic systems can marry established transition-metal chemistry with metal-ion influences on DHP chemistry. Less electron-rich rings are more prone to metallation, and this metallation then can bring HT pathways facilitated by through-bond polarisation effects on the substrate or by the positioning of reactive groups.

Taken together, the history of metallated DHP$^-$ reagents offer a broad scope for further development of reaction chemistry particularly in the context of current interest in electrochemically driven organic transformations. Along with lowered energy demands, lower reduction potentials for ET provide benefits such as chemo- and regio-selectivity and the suppression of background H_2 evolution. To expand the scope of M-DHP$^-$ chemistry, chemists can capitalise on the wealth of existing pyridine-centred organic scaffolds and ligands and develop metallation routes to produce tuneable HT reaction chemistry.

Author contributions

All authors contributed to the writing and editing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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