Magnesium-catalysed Hydroboration of Pyridines: Kinetic Analysis and Poly-pyridine Dearomatisation

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Abstract

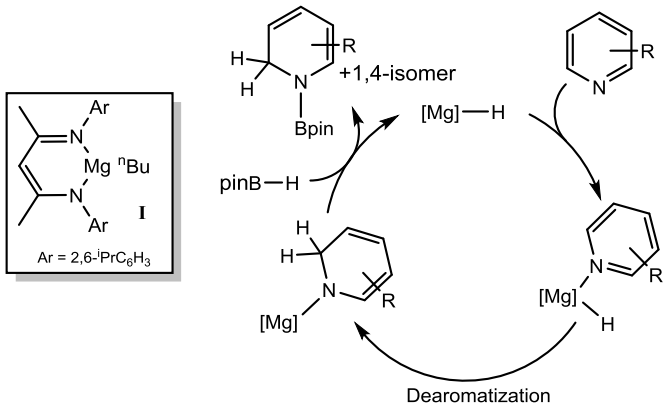
A kinetic analysis of the hydroboration of *iso*-quinoline with pinacol borane (HBpin) and catalysed by a β-diketiminato magnesium *n*-butyl pre-catalyst has provided evidence that the reaction proceeds via rate determining Mg-N/H-B metathesis of a dearomatised *iso*-quinolide anion. The reaction rate is suppressed by increasing [*iso*-quinoline] leading to the suggestion that catalytic turnover is also dependent on a pre-equilibrium involving dissociation of donor substrate molecules from the coordination sphere of the catalytic Mg centre. Stoichiometric reactions with a variety of poly-pyridine heterocycles have provided a range of magnesium derivatives of the dearomatised poly-pyridides either by alkyl or hydride transfer. The resistance of these latter species toward hydroboration is rationalised as a consequence of their additional coordinative stability providing corroborative evidence for the dissociative mechanism inferred from the kinetic analysis.

Keywords: magnesium; catalysis; hydroboration; pyridine ligands

Introduction

The dearomatisation of pyridine, along with its substituted and fused-ring derivatives, to yield dihydropyridines can provide access to a range of pharmaceutically relevant species.[1] Although synthetic routes to dihydropyridines have been developed from metal-based reduction reactions of pyridines to afford dearomatised metal-dihydropyridide complexes,[2] the harsh conditions employed and the relative instability of the dearomatized products do not necessarily lend themselves to extension to a more attractive catalytic regime. In the catalytic sphere Harrod reported the initial homogeneous catalytic titanocene-based hydrosilylation of pyridines,[3] and more recently Nikonov and co-workers have described a ruthenium-centred process.[4] Our own research efforts have centred upon the development of the β-diketiminate supported magnesium-*n*-butyl (**1**) pre-catalyst for the hydroboration of a variety of unsaturated substrates including pyridine (Scheme 1), the active species of which is a magnesium hydride formed by σ-bond metathesis with the pinacol borane (HBpin) substrate.[5] Since publication of this magnesium-catalysed process, several more examples of pyridine hydroboration have been noted in the literature. Suginome reported the first transition metal

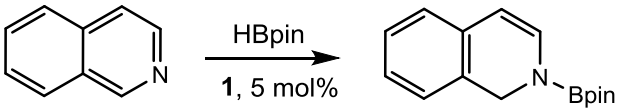
catalysed hydroboration of pyridines,[6] whilst Marks has recently described the use of the lanthanum catalyst ($\{Cp^*_2LaH\}_2$) both of which allowed the selective formation of *N*-boryl-1,2-dihydropyridines whilst showing tolerance towards a variety of functional groups.[7] Recent work by Harder has also shown a bis(magnesium) hydride supported by a bis(-*β*-diketiminate) ligand allows the efficient hydroboration of pyridines with a preference for 1,2-addition.[8] In this contribution we describe the extension of our catalytic studies to include a kinetic study and further observations on the application of this system to the deraromatisation of poly-pyridines.



Scheme 1: Magnesium-catalysed hydroboration of pyridines.

Results and Discussion

A series of earlier stoichiometric reactions have indicated that magnesium-centred dearomatisation occurs through initial hydride transfer to the pyridine 2-position, with subsequent rearrangement to the thermodynamically preferred 4-position to yield magnesium 1,4-dihydropyridides.[5,9] This process is, thus, competitive with borylation to form *N*-boryl-1,4-dihydropyridines under catalytic conditions. To further investigate the mechanism of the catalytic reaction a series of kinetic experiments were undertaken. The hydroboration of *iso*-quinoline (*i*-Quin) was selected for this study due opportune reaction times and mild conditions required to achieve catalytic turnover (>99% conversion is achieved in 4 hrs at room temperature, Scheme 2). This substrate is also restricted to the formation of the 1,2-dearomatised isomer limiting potential complications from secondary isomerisation reactions to form the 1,4-isomer. All reactions were carried out at 298 K unless stated otherwise and were monitored by ^{1}H NMR spectroscopy to three half-lives (80% product conversion). A small excess of pinacol borane (HBpin) was employed in order to generate the catalytic magnesium hydride species by *in situ* reaction of **1**. Activation of the precatalyst with concurrent formation of *n*-BuBpin was observed to occur rapidly indicating that the active catalyst is present at t = 0. Monitoring the standard reaction [5 mol% **1** (0.04 M) with 0.8 M *i*-Quin to 0.84 M of HBpin] at set time intervals, indicated that the reaction conformed to overall zero order kinetics (Figure S1).



Scheme 2: The hydroboration of *iso*-quinoline employed in the kinetic study.

The reaction order with respect to [Mg] was determined through a series of reactions carried out using variable catalyst loadings whilst keeping [*i*-Quin] and [HBpin] constant (Figure S2). The amount of active catalyst in solution was calculated from ^{1}H NMR integrals against an added standard of tetramethylsilane. As expected, increasing the catalyst concentration led to higher rates of reaction, while a plot of the observed rate constants indicated that this occurred with a first order variation with respect to [Mg] (Figure 1a).

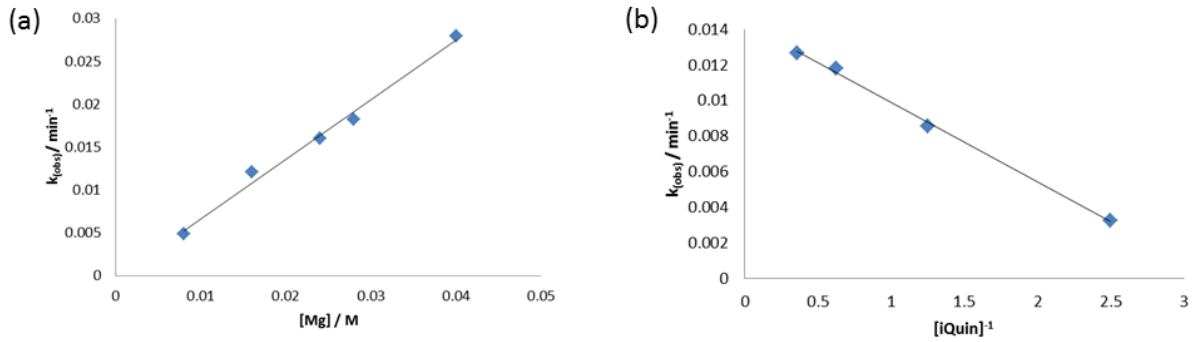


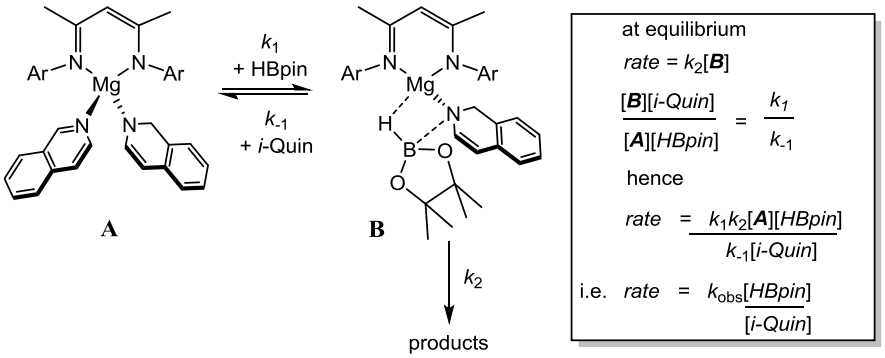
Figure 1: (a) Plot of observed rate constants $k_{(obs)}$ vs [Mg]; (b) Plot of $k_{(obs)}$ vs [*i*-Quin]$^{-1}$

This observation is consistent with other magnesium- and calcium-catalysed reactions in which the alkaline earth centre is coordinated by a β-diketiminate ligand.[10] It is suggested that these data are, thus, indicative of the reaction proceeding through a mononuclear rate-determining step during the course of the catalysis. Variation of [*i*-Quin] under *pseudo*-first order conditions in [HBpin] again conformed to overall zero order kinetics. It was noted, however, that increasing the concentration of *i*=Quin seemingly had a negative impact on the rate of reaction. This observation was confirmed by plotting the deduced rate constants for the series of zero order plots against [*i*-Quin]$^{-1}$ (Figure 1b). Further examination of the reaction under *pseudo*-first order conditions in *i*-Quin with variation of the starting concentration of HBpin, indicated a first order rate dependence on [HBpin] and the combined rate law shown as Equation 1.

$$Rate = k_{obs}[iQuin]^{-1}[HBpin]^{1} \qquad (1)$$

We suggest that these kinetic data are predicated on the pre-equilibrium between the adduct species **A** and the formal borate intermediate **B** illustrated in Scheme 3. The basicity and resultant capability of

the *i*-Quin molecule to coordinate to the magnesium centre as a neutral donor, thus, impedes the interaction of the HBpin molecule with the coordination sphere of the magnesium and hinders B-H/N-Mg metathesis and hydroboration reactivity. This deduction is further supported by the first order dependence on [HBpin], wherein an increase of the concentration above the requisite 1:1 reaction stoichiometry favours the displacement of the neutral *i*-Quin molecule enabling subsequent catalytic turnover.



Scheme 3: Pre-equilibrium kinetics during the hydroboration of pyridines

Further insight into the nature of this mechanism was obtained through variable temperature kinetic studies used to deduce the activation parameters for the hydroboration of *iso*-quinoline. Reactions under the standard conditions of 5 mol% **1** (0.04 M) with a 1:1.05 ratio of *i*-Quin to HBpin (0.8 M and 0.84 M respectively) were carried out over a range of 5 different temperatures (288 K – 308 K). Temperatures above 308 K were not studied due to the rate of reaction becoming too fast to monitor. Extraction of the observed rate constants from plots of [*i*-Quin] vs time allowed the construction of Eyring (Figure 2a) and Arrhenius plots (Figure 2b). These analyses provided the reaction parameters shown in Table 1. Standard errors were calculated using the least squares method for linear regression.

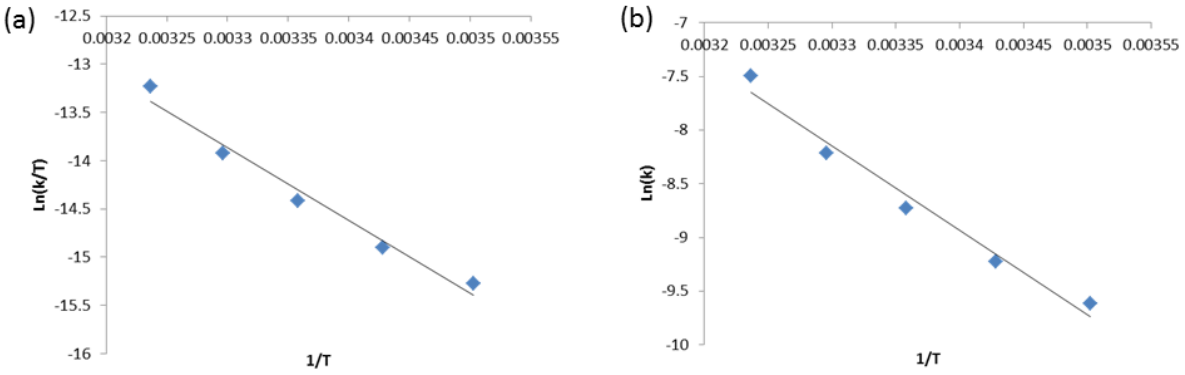


Figure 2: (a) Eyring and (b) Arrhenius plots from the variable temperature kinetic analysis of the hydroboration of *iso*-quinoline mediated by 5 mol% **1**.

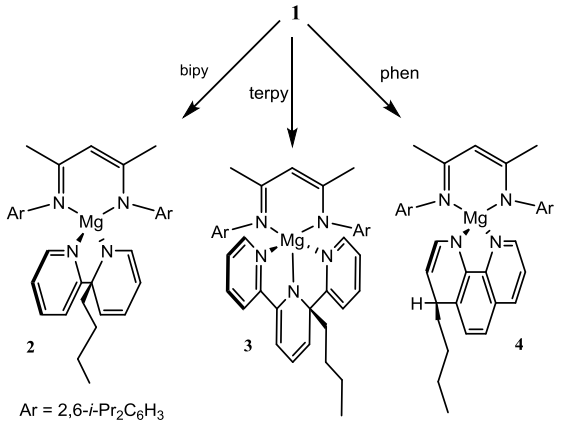
Table 1. Kinetic activation parameters for the magnesium-catalysed hydroboration of *iso*-quinoline with HBpin.

	Value	**Error**
***E*a**	65.3 kJ mol^{-1}	± 7.4
$\Delta H^{\neq}$	62.8 kJ mol^{-1}	± 7.4
$\Delta S^{\neq}$	-105.5 J k^{-1} mol^{-1}	± 24.7
$\Delta G^{\neq}_{298}$	94.3 kJ mol^{-1}	n/a

The value for $\Delta H^{\neq}$ closely resembles that of the activation energy and provides values which suggest the assembly of a rate determining transition state with significant bond making to compensate for bond breaking (B-N vs B-H respectively). The large negative $\Delta S^{\neq}$ indicates a significant entropic influence over the observed reaction kinetics and supports the assembly of a highly organised rate determining transition state in which the neutral pyridine molecule must be displaced as the HBpin substrate enters the coordination sphere of the magnesium centre. In such circumstances, the driving force of the reaction is, thus, provided by the formation of the B-N bond. Previous studies group 2 catalysed processes have highlighted a pronounced entropic influence on both intra- and intermolecular heterofunctionalisation reactions.[11] A similar course of reaction has also been identified in a recent DFT study on the lanthanum-catalysed hydroboration of pyridines reported by Marks.[7] In this case, however, the experimentally derived rate law was also indicative of inhibition by HBpin. Nonetheless, it was reasoned that the overall driving force of the reaction was again the σ-bond metathesis step with resultant B-N bond formation. In mitigation of the deductions in the current work, the lanthanide-based catalysis also provided very similar experimental activation parameters [$\Delta H^{\neq}$ = 65.7 (± 2.1) kJ mol^{-1}, $\Delta S^{\neq}$ = –113.8 (±1.3) J K^{-1} mol^{-1} and *E*a = 68.2 (±1.7) kJ mol^{-1}] which were again indicative of a significantly organised rate determining transition state.

Dearomatisation of poly-pyridine heterocycles

As noted during our initial report of the magnesium-catalysed hydroboration of pyridines, attempted extension of this hydroboration reactivity to the poly-pyridine derivative 2,2-bipyridine (bipy) failed to yield any catalytic turnover.[5] Rather, an instant colour to purple was noted upon addition of bipy to the reaction mixture, which persisted even with heating in the presence of excess HBpin. Further investigation indicated that reaction of equimolar quantities of the magnesium *n*-butyl derivative **1** with bipy also provided an instantaneous change to a similar dark purple colour. Analysis of this reaction by NMR spectroscopy, most notably a diagnostic resonance at δ 64.5 ppm in the ^{13}C NMR spectrum attributed to the newly formed N-*C* quaternary carbon, indicated that dearomatisation had occurred through transfer of the *n*-butyl chain to the 2,2′-position of the bipyridine ring with the unambiguous formation of compound **2** (Scheme 4).



Scheme 4: The synthesis of compounds **2** – **4** by dearomatisation of bipy, terpy and phen by **1**.

This observation of dearomatisation by alkyl transfer is reminiscent of an earlier report by Kiplinger of the reaction between [Lu(CH_2SiMe_3)$_3$(THF)$_2$] and 2,2';6',2"-terpyridine (terpy).[12] A further reaction was, thus, performed between compound **1** and a single equivalent of terpy (Scheme 4). This reaction also provided an instant colour change to dark green to yield the corresponding alkyl dearomatised product, compound **3**. Although the main features of the collated NMR data for this compound were similar to those described by Kiplinger and, thus, indicative of dearomatisation at the 2′ position of the central terpy pyridine ring, the nature of the dearomatisation was confirmed through the isolation of single crystals suitable for X-ray crystallographic analysis. The results of this analysis are shown in Figure 3 while selected bond lengths and angles are provided in the figure caption.

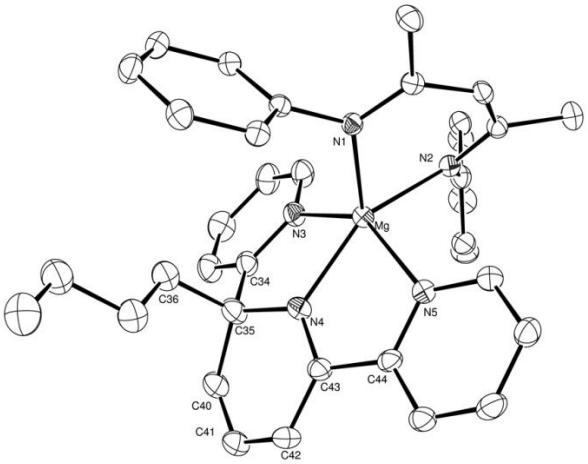
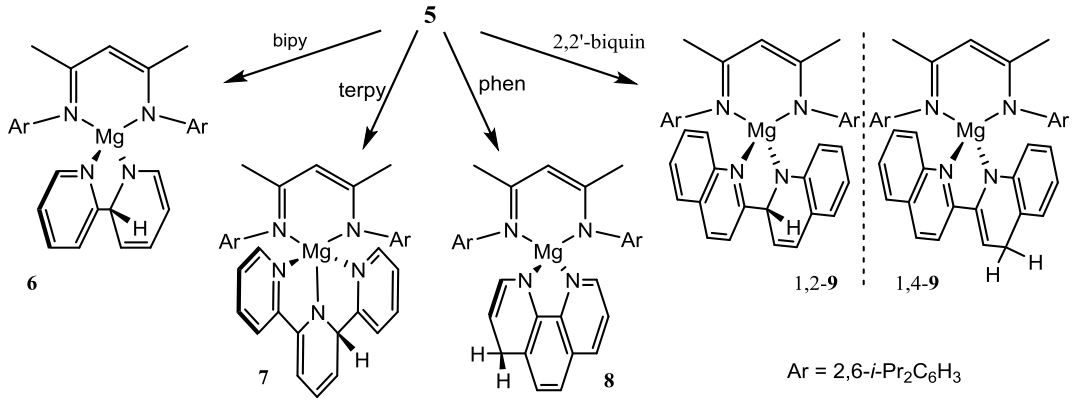


Figure 3: ORTEP representation (25% probability ellipsoids) of compound **3**. Hydrogen atoms and *iso*-propyl groups are removed for clarity. Selected bond lengths (Å) and angles (°): Mg-N(4) 2.062(3); Mg-N(1) 2.092(3), Mg-N(2) 2.131(3), Mg-N(3) 2.228(3), Mg-N(5) 2.249(3), N(4)-C(43) 1.343(4), N(4)-C(35) 1.471(4), C(35)-C(40) 1.503(5), C(40)-C(41) 1.345(6), C(41)-C(42) 1.411(5), C(42)-C(43) 1.381(4), N(4)-Mg-N(1) 123.07(11), N(4)-Mg-N(2) 147.73(11), N(1)-Mg-N(2) 89.09(10), N(4)-Mg-N(3) 74.73(11), N(1)-Mg-N(3) 114.42(10), N(2)-Mg-N(3) 95.62(10), N(4)-Mg-N(5) 75.05(10), N(1)-Mg-N(5) 96.32(10), N(2)-Mg-N(5) 100.86(10), N(3)-Mg-N(5) 145.27(11).

Compound **3** comprises a 5-coordinate magnesium centre with an N_5-coordination sphere provided by the β-diketiminate ligand and the three nitrogen donors of the dearomatised terpy anion. The formal anionic charge of the amide moiety is evidenced by the Mg-N(4) bond distance of 2.062(3) Å which is marginally shorter than even both of the Mg-N distances to the β-diketiminate ligand. Inspection of the bond distances within the central pyridine ring of this newly formed anionic ligand highlight the loss of aromaticity though the elongation of the bond lengths to the quaternary C(35) centre and the alternation of the short C(40)-C(41) [1.345(6) Å] and long C(41)-C(42) [1.411(5) Å] bonds.

A further reaction performed between compound **1** and the fused ring 1,10-phenanthroline (phen), also provided an instantaneous colour change to purple symptomatic of the formation of a new species (**4**, Scheme 4). In this case analysis by NMR spectroscopy was indicative of dearomatisation of the pyridine ring through contrasting 1,4-alkyl transfer. We suggest that this process most likely occurs through initial *n*-butyl transfer to the external 2-position with rapid rearrangement to the thermodynamically preferred 1,4-position.



Scheme 5: The synthesis of compounds **6** – **9** by dearomatisation of bipy, terpy, phen and 2,2′-biquin by **5**.

Compounds **2** – **4** did not provide any evidence of onward borylation reactivity, even when heated for extended periods with an excess of HBpin. We, thus, carried out additional reactions between the same series of poly-pyridine heterocycles and the isolable β-diketiminate-supported magnesium hydride [HC{(Me)CN-2,6-*i*-$Pr_2C_6H_3$}$_2$MgH]$_2$ (**5**).[13] These reactions again provided instantaneous colour changes upon reaction with poly-pyridines to provided colours reminiscent of the alkyl transfer reactions and indicative of the formation of the new compounds **6** – **8** (Scheme 5). In these cases, analysis by ^{1}H and ^{13}C NMR provided spectroscopic signatures analogous to those observed for compounds **2** - **4** indicative of hydride transfer to the same positions of the poly-pyridide ligands. Although none of these compounds provided crystals suitable for analysis by X-ray diffraction, a further reaction performed between compound **5** and 2,2′-biquinoline (2,2′-biquin) resulted in the instantaneous precipitation of bottle green crystals of compound **9**. Although attempts to dissolve the

crystals for NMR analysis were unsuccessful, the results of a consequent X-ray diffraction analysis, shown in Figure 4, were consistent with dearomatisation of one of the quinolide rings. In this case, however, a smearing of electron density across the both of the 2- and 4-positions was consistent with the presence of both the 1,2- and 1,4-isomeric forms of the dearomatised biquinolide anion. A 50:50 disorder was modelled for C14 and for the carbon atoms C40-C46 and the hydrogen atoms attached to C(40)-C(46) were included as aromatic C-H bonds, as it is not possible to resolve ¼ occupancy CH_2 hydrogens using X-ray data. The concomitant lengthening and shorting of bond distances is, thus, averaged across the heterocyclic motif precluding any meaningful discussion of the bond lengths and angles within the structure.

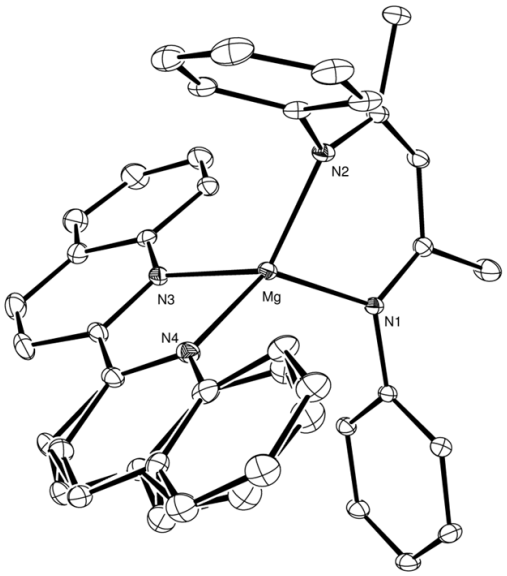


Figure 4: ORTEP representation (25% probability ellipsoids) of compound **9** highlighting the 50:50 disorder for C14 and for the carbon atoms C40-C46 indicative of the presence of both 1,2- and 1,4-hydride transfer prodcuts. Hydrogen atoms and *iso*-propyl groups are removed for clarity.

Attempted reactions of compounds **6** – **9** with HBpin were also unsuccessful. We suggest that the inability of these substrates and compounds **2** – **4** to undergo hydroboration is consistent with the dissociative mechanism outlined in Scheme 3 and the increased stability toward onward B-N metathesis provided by the chelation of the poly-pyridide anions.

Conclusions

Kinetic analysis of the magnesium-catalysed hydroboration of *iso*-quinoline with HBpin is consistent with rate determining B-N/H-B metathesis dependent on a dissociative pre-equilibrium of neutral *iso*-quinoline donors. A consequent inability to extend this catalytic reactivity to poly-pyridine substrates is, thus, attributed to the coordinative stability of the chelated poly-pyridide anions.

Acknowledgements

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Appendix A. Supplementary data

The supplementary information for this paper includes full experimental and characterisation data, corroborative NMR spectra and details of the kinetic analysis. CCDC 1415766 and 1415767 contain the supplementary crystallographic data for compounds **3** and **9** respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at http:/…

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