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Magnesium-catalysed Hydroboration of Isonitriles

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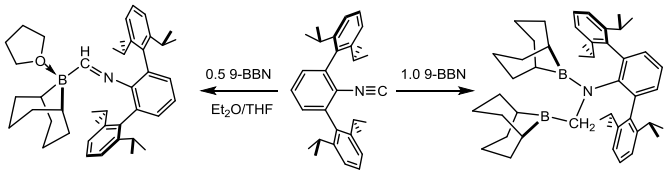
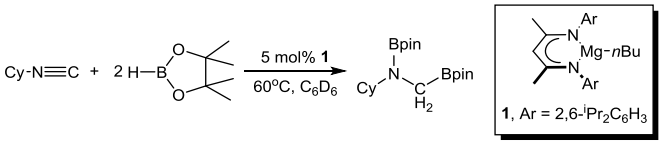
A β-diketiminato magnesium alkyl complex is shown to be an effective pre-catalyst for the first reported catalytic hydroboration of organic isonitriles, RNC, with HBpin. The reaction proceeds under mild conditions when R = alkyl and provides access to the corresponding 1,2-diborylated amine products.

The reactivity of organic isonitriles, RNC, is dictated by their ability to behave as both a nucleophile and an electrophile. A multiplicity of metal-catalysed multicomponent condensations, most notably variations of the Passerini and Ugi reactions, have been shown to yield a plethora of complex and medicinally-relevant nitrogenous structures.[1] In contrast, despite the relationship to Fischer-Tropsch reactivity arising from the isoelectronic relationship of the isonitrile functional group to carbon monoxide,[2] the reductive heterofunctionalisation of isonitriles appears to be solely represented by Figueroa's recent stoichiometric hydroboration of a *m*-terphenylisocyanide.[3] In this case an uncatalysed reaction with 0.5 equivalents of 9-borabicyclo[3.3.1]nonane (9-BBN) afforded the boryl(imino)methane 1,1-hydroboration product while use of a stoichiometric quantity of 9-BBN dimer provided the fully reduced 1,2-diborylated amine (Scheme 1). Notably, a similar reaction performed with a 10-fold excess of the less Lewis acidic pinacolborane (HBpin) yielded only the singly reduced 1,1-borylated product, even after prolonged heating at 100 °C.



Scheme 1: Uncatalysed hydroboration of *m*-terphenylisocyanide with 9-BBN

Our own interests have focussed on the use of reagents derived from the earth abundant and inexpensive alkaline earth elements to effect molecular catalysis.[4] We have recently reported that the well-defined β-diketiminato magnesium alkyl complex [CH{C(Me)NAr}$_2$Mg*n*Bu] (Ar = 2,6-i$Pr_2C_6H_3$) (**1**) is an effective pre-catalyst for the hydroboration of a variety of unsaturated substrates with pinacolborane.[5] In this contribution we describe a further extension of this reactivity to the reductive hydroboration of a range of commercially available isonitrile substrates.



Scheme 2: Hydroboration of CyNC with HBpin catalysed by 5 mol% **1**

An initial trial catalytic reaction using 10 mol% of **1** with cyclohexylisonitrile (CyNC) and 2 equivalents of HBpin proceeded with full consumption of the starting reagents within 30 minutes at 60°C (Scheme 2). Inspection of the resultant ^{11}B NMR spectrum confirmed the disappearance of the HBpin starting material and the emergence of a new species characterised by two signals in a 1:1 ratio at δ 37.5 ppm and δ 27.8 ppm. The corresponding ^{1}H NMR spectrum evidenced complete consumption of CyNC and the formation of the desired C-B and N-B functionalised amine product, CyN(Bpin)CH_2Bpin, which displayed a characteristic downfield shift from δ 2.96 ppm to δ 3.32 ppm arising from the nitrogen-bound methine of the Cy group and the appearance a new (2H) methylene singlet resonance at δ 2.81 ppm.

The success of this reaction encouraged us to expand the substrate scope to other commercially available isonitriles. Table 1 summarises the results of these catalytic isonitrile hydroboration reactions using 5 mol% of **1** in C_6D_6. Under these conditions, reactions with the cyclohexyl, 1-pentyl and *tert*-butyl isonitriles afforded the *N*-alkylated 1,2-bis(boryl)amines as the only products in less than 1 hour at 60°C (entries 1-3).

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† Electronic Supplementary Information (ESI) available: Full experimental details including NMR spectra and X-ray crystallography. CCDC 1411822 See DOI: 10.1039/x0xx00000x

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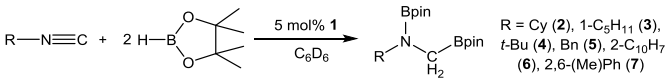
Table 1. Magnesium-catalysed hydroboration of commercially available isonitriles



Entry	Isonitrile, R-NC (R)	Time (hrs)	Temp (°C)	NMR conv. (%)
1	cyclohexyl	1	60	>99
2	1-pentyl	1	60	>99
3	*tert*-butyl	1	60	>99
4	benzyl	0.5	60	>99
5	2-napthyl	48	100	55
6	2,6-dimethylphenyl	48	100	53

Whereas benzylisonitrile provided even more rapid conversion to the amine product (entry 4), reactions with the *N*-aryl substrates, 2-napthyl and 2,6-dimethylphenyl isonitrile, required an increase in temperature to 100°C to induce any significant reaction and had only reached 50% conversion after 48 hrs. Although undoubtedly a consequence of the change in the electronic nature of the aryl substituent, this reduced conversion is also attributed to the apparent degradation of HBpin at such elevated temperatures and increased reaction times. Notably, attempts to isolate the boryl(imino)methane product, CyNCHBpin, through a catalytic reaction performed with 1 equivalent of HBpin, failed to yield the desired boryl(imino)methane species. Rather, all attempts to carry out this reaction led to the isolation of the fully reduced product, **2**, with half the isonitrile reagent remaining unreacted.

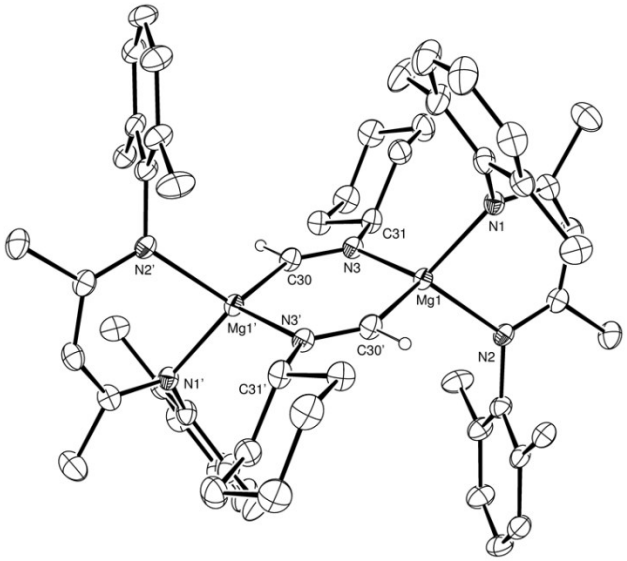


Figure 1. ORTEP representation of compound **9**. Thermal ellipsoids set to 30% probablity. Hydrogen atoms, except H(30) and H(30)', and the methyl groups of the β-diketiminate 2,6-di-*iso*-propylphenyl substituents are removed for clarity. Selected bond lengths (Å) and angles (°): Mg(1)-N(1) 2.083(3), Mg(1)-N(2) 2.100(3), Mg(1)-N(3) 2.109(3), Mg(1)-C(30)' 2.179(3), C(30)-N(3) 1.284(4), N(3)-C(31) 1.495(4), N(3)-Mg(1)-C(30)' 112.90(12), C(30)-N(3)-Mg(1) 111.4(2), N(3)-C(30)-Mg(1)' 135.7(2). Symmetry transformations used to generate equivalent atoms: -x,-y+1,-z+1.

A series of stoichiometric reactions were undertaken to shed light on the initial course of the catalytic reactions. We have reported previously that reaction of compound **1** with HBpin produces a kinetically competent magnesium hydride equivalent.[5] A reaction was, thus, performed between the isolated dimeric β-diketiminato magnesium hydride, $[CH\{C(Me)NAr\}_2MgH]_2$ (Ar = 2,6-*i*-$Pr_2C_6H_3$) (**8**)[6] and 2 molar equivalents of CyNC. This process was found to provide a new species (**9**), the formation of which was characterised by the appearance of a downfield singlet at δ 9.99 ppm in the resultant ^{1}H NMR spectrum. This signal was revealed by a subsequent HSQC analysis to correlate with a ^{13}C resonance at δ 217 ppm consistent with the formation of a new formimidoyl Mg-CH=NCy moiety. Crystallisation of compound **9** from the reaction mixture at room temperature provided single crystals suitable for X-ray diffraction analysis.‡ The results of this analysis (Figure 1) revealed that **9** crystallises as a centrosymmetric 6-membered heterocyclic dimer as a result of intermolecular interactions between the Mg centres and the nitrogen atoms of the *N*-cyclohexyl formimidoyl units. The C=N bond length of 1.284(4) Å is also consistent with its assignment as a C=N double bond and is similar to those reported in closely related, and similarly dimeric, calcium and aluminium species reported by Harder and Uhl.[7-9]

A further reaction performed between isolated crystals of compound **9** and a stoichiometric equivalent of HBpin per magnesium centre in C_6D_6, resulted in no observable reaction at room temperature. After heating at 60°C for an hour the emergence of the C-B and N-B environments of compound **2** was apparent in the ^{11}B spectrum in a 1:1 ratio. This procedure, however, provided only a low conversion to this product (<20%) and the dimeric molecule **9** was otherwise observed to persist throughout the reaction and to crystallise from solution on cooling to room temperature.

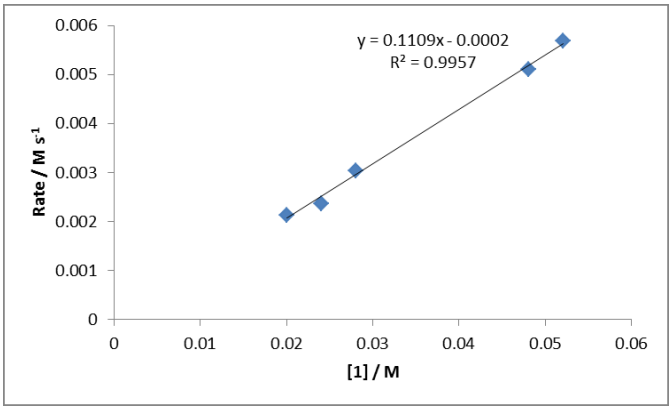


Figure 2: Plot of the observed rate constant ($k_{(obs)}$) vs [Mg] for the reaction of a 0.82 M solution of HBpin and a 0.4 M solution of CyNC in C_6D_6 catalysed by **1** at 323 K

The mechanism of this magnesium-based isonitrile hydroboration catalysis was investigated through a kinetic study undertaken of the reaction between CyNC and HBpin. An initial series of reactions carried out at 323 K with a 0.82 M solution of HBpin and a 0.4 M solution of CyNC in C_6D_6 were monitored by ^{1}H NMR spectroscopy. Experiments undertaken with variation of [**1**] between 0.02 and 0.052 M were found to conform to zero order kinetics up to a

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period of three half-lives and provided a resultant linear plot of the observed rate constants, k_{obs}, against [**1**] shown in Figure 2. This latter observation highlights a clear first order dependence on the pre-catalyst concentration and, in contrast to the dimeric constitution of compound **9**, we suggest that this deduction implicates the involvement of a mononuclear magnesium centre during catalytic turnover. Additional kinetic experiments under *pseudo* first order conditions employing an excess of HBpin (8.0 M) and 0.02 M [**1**] with variation of the starting concentration of CyNC between 0.4 M and 3.2 M provided a further series of zero order rate plots. Under these conditions analysis of the variation across the resultant k_{obs} values indicated a first order dependence upon the starting concentration of [CyNC] (Figure S7).

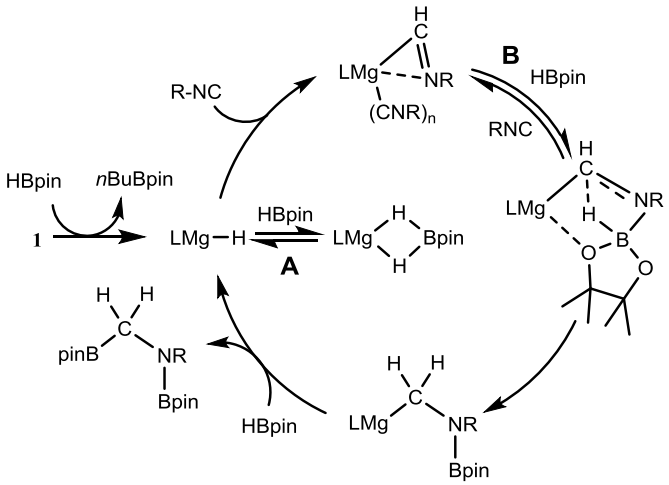
Application of a similar *pseudo* first order methodology with an excess of CyNC was complicated by the production of a previously unobserved compound, which was clearly apparent through the appearance of an additional resonance δ 5.95 ppm in the ^{1}H NMR spectrum. This new signal, tentatively assigned to the formation of pinB(Cy)NC(H)=C=NCy, which was observed to increase in intensity over time concurrent with the formation of the desired (CyN(Bpin)CH_2Bpin), was rationalised to be the result of multiple isonitrile insertion and competitive C-C coupling reactions as a consequence of the large excess of CyNC present in solution. Harder has made similar observations in his studies of the stoichiometric reactivity of β-diketiminato calcium hydrides.[7] This complication notwithstanding, the formation of compound **2** under these conditions also conformed to zero order kinetic behaviour across a range of borane concentrations, with k_{obs} values that increased linearly with increasing [HBpin] (Figure S9).

Variable temperature kinetic experiments carried out using the standard reaction of 5 mol% [**1**] (0.02 M), HBpin (0.82 M) and CyNC (0.4 M) over a range of 4 different temperatures (308 K to 325 K) allowed the construction of Arrhenius and Eyring plots and the extraction of the kinetic parameters shown in Table 2. Although little can be deduced from the macro- and microscopic activation energetics, the effective zero activation entropy, $\Delta S^{\neq}$, suggests that the components of the reaction are pre-assembled prior to a rate determining C-H formation and/or B-H bond breaking process.

Table 2: Kinetic activation parameters for the magnesium-catalysed hydroboration of CyNC with HBpin.

	Value	Error
E_a	104.5 kJ mol-1	± 3.5
$\Delta H^{\neq}$	101.8 kJ mol^{-1}	± 3.5
$\Delta S^{\neq}$	-12.7 J k^{-1} mol^{-1}	± 11.0
$\Delta G^{\neq}_{298}$	105.6 kJ mol^{-1}	n/a

On the basis of these observations, we propose the provisional mechanism shown in Scheme 3 for the magnesium-catalysed hydroboration of isonitriles. While pre-catalyst initiation requires conversion of the **1** to a magnesium hydride, given the facile formation of compound **9**, this species is likely to be very short lived and to undergo rapid insertion by the polarised isonitrile C≡N group. The observed zero order behaviour at catalytically relevant reagent concentrations is a reflection of saturation kinetics with the rate of reaction governed solely by the starting concentration of **1**. The apparent first order dependences with respect to both the isonitrile and borane reagents under *pseudo* first order conditions are consistent with a consequent perturbation of the respective pre-equilibria depicted as **A** and **B** in Scheme 3. The position of both equilibriation processes regulates the assembly of a magnesium formimidoylhydridoborate whereupon, and in line with a negligible deduced entropy of activation, the likely turnover limiting process of the catalysis is provided by an intramolecular hydride transfer from boron to carbon. Although subsequent borane metathesis, shown as a discrete process in Scheme 3, will provide the 1,2-diborylated amine product without the necessary intermediacy of a boryl(imino)methane, we do not discount the possibility that the formidoyl reduction and borane metathesis steps may take place in a concerted fashion.



Scheme 3: Proposed catalytic cycle for the magnesium-catalysed hydroboration of isonitriles

In conclusion, a β-diketiminato magnesium alkyl complex is shown to be an effective pre-catalyst for the first reported catalytic hydroboration of organic isonitriles with HBpin. We are continuing to study this and related reactivity.

We thank the EPSRC for the provision of a project studentship (CEW).

Notes and References

‡X-ray diffraction data for **9**. $C_{74.10}H_{109.20}Mg_2N_6$, M = 1132.69, monoclinic, $P2_1/c$, a = 18.9579(8) Å, b = 19.7413(9) Å, c = 18.7107(8) Å, β = 99.765(4)°, V = 6901.1(5) Å^3, Z = 4, ρ = 1.090 g cm^{-3}, R_1 [$I > 2\sigma(I)$] = 0.0810, wR_2 [$I > 2\sigma(I)$] = 0.2100, R_1 [all data] = 0.1157, wR_2 [all data] = 0.2414, measured reflections = 50997, unique reflections = 12177, R_{int} = 0.0901.

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