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A dual site catalyst for mild, selective nitrile reduction†

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We report a novel ruthenium bis(pyrazolyl)borate scaffold that enables cooperative reduction reactivity in which boron and ruthenium centers work in concert to effect selective nitrile reduction. The pre-catalyst compound [κ^3-(1-pz)$_2$HB(N = CHCH$_3$)]Ru(cymene)$^+$ TfO$^-$ (pz = pyrazolyl) was synthesized using readily-available materials through a straightforward route, thus making it an appealing catalyst for a number of reactions.

As part of our ongoing studies of dual site ruthenium and boron-containing catalysts for the manipulation of hydride groups, we have recently reported a series of [di(pyridyl)borate]ruthenium complexes (**1**, **2**)[1] that exhibit remarkable reactivity in a number of applications,[2] notably including dehydrogenation of ammonia borane.[3] Although they are successful catalysts, these di(pyridyl)dimethylborate-derived complexes are cumbersome to prepare, due largely to dependence on an expensive and reactive $BrBMe_2$ starting material and high water and oxygen sensitivity of intermediate complexes in their syntheses. Further, despite their catalytic utility, no direct evidence has been collected to give a mechanistic account of the cooperative role, if any, that boron and ruthenium play in the reactive mechanisms of **1** or **2**.[4] We suspect this is partially due to the robustness of the bridging μ-OH ligand between the boron and ruthenium centers in **2**, which inhibits access to a free borane in catalytic reactions (Fig. 1).

Here we show a conveniently prepared, borate-pendant ruthenium complex (**3**) that retains much of the reactivity of the original di(pyridyl)borate complexes (see ESI†), show that it is an efficient and selective catalyst for nitrile reduction, and provide evidence for the cooperative role that boron and ruthenium play in the reaction, as a hydride donor and an activating group, respectively.

The synthesis of **3** (Scheme 1) proceeds from potassium di(pyrazolyl)borohydride[5–7] and commercially-available (cymene)-ruthenium dichloride dimer to give intermediate chloride **4**.

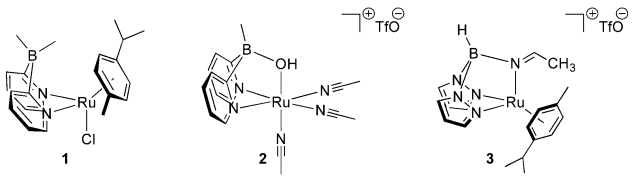
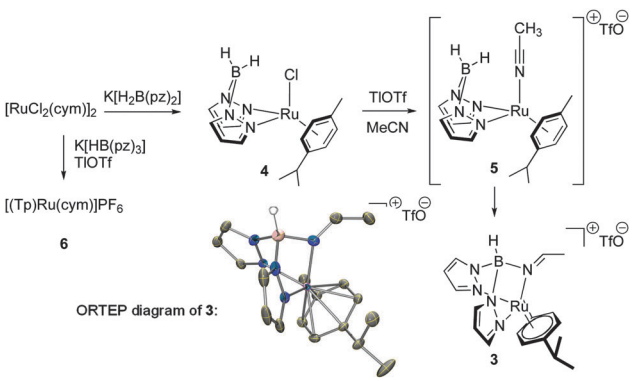


Fig. 1 Dual site catalysts for hydride manipulation.



Scheme 1 Synthesis of precursor **3** and complex **6**. Molecular structure of **3**.

Although **4** can be isolated, it is easily converted *in situ* to **3** by treatment with 1 equiv. of thallium (or silver) triflate in nitrile solution. The synthesis proceeds in two smooth steps without the need for materials that are cost-prohibitive or difficult to manipulate: all materials are amenable to handling using standard Schlenk techniques and/or a glove box. **3** can be crystallized using isopropanol and hexanes; its molecular structure was determined by single crystal X-ray diffraction (Scheme 1). The crystal structure of **3** shows the borate ligand bonded to boron in a tetrahedral geometry, which has analogy to the popular tris(pyrazolyl)borohydride (Tp) ligand series.[6–8]

The synthesis of **3** revealed an important insight into the mechanism of its catalytic reactivity. In the conversion of **4** to **3**, a hydride is transferred from a ligand B–H group to the coordinated nitrile of **5** in >90% NMR yield (Scheme 1). This reaction is the first example of our

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† Electronic supplementary information (ESI) available: Experimental details, graphical spectra, and kinetics data. CCDC 963291 contains supplementary crystallographic datafor **3**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47384h

envisioned cooperative reactivity of ruthenium and boron. Contrary to the design concept from which we originally prepared **2**,[2] boron in **3** does not behave as a Lewis acid. The structure of **3** shows that addition of the B–H group to the nitrile proceeds in a *cis* fashion, and NMR evidence reveals that the selectivity for this geometry is exclusive. Thus, we believe that the mechanism for this reaction involves intramolecular hydride transfer from boron to carbon, rapidly followed by (or concerted with) boron–nitrogen coordination.

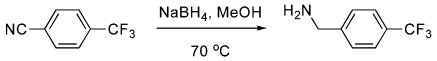
The stoichiometric reduction of acetonitrile observed in the synthesis of **3** can be made catalytic by treating **3** with nitrile and sodium borohydride,[9] thus enabling a mild and selective approach to the synthesis of primary amines from nitriles, which remains a contemporary topic in bifunctional catalysis.[10] Known methods for nitrile reduction, *e.g.* use of excess $LiAlH_4$, borohydride reduction of a nitrilium salt,[11] use of metal hydride reagents,[12] or high-pressure hydrogenation[13] can be incompatible with important synthetic handles, such as aryl bromide and nitro groups.[14] Milder conditions compatible with groups like these require a stoichiometric portion of a borane reagent,[15] which in some cases must be independently prepared. The new catalytic mechanism reported here enables high functional group tolerance while incorporating an inexpensive reducing agent.

Table 1 shows the discovery and optimization of our conditions for nitrile reduction. In the presence of 5 mol% **3**, 2.0 equiv. of $NaBH_4$ can reduce 4-trifluoromethylbenzonitrile (**7a**) to the corresponding benzylamine (**8a**) in 50% conversion by NMR in 5 hours (entry 1). When 1.0 equiv. of NaO^tBu was added, the analogous reaction reached >90% yield (>95% conversion) in the same time. With no catalyst, the reaction was much slower, reaching completion in 7 days with a 43% overall yield (entry 5). If the Tp-ligated homologue of **3** (**6**, Scheme 1) is used in this reaction, much of the starting material decomposes under the reaction conditions. This illustrates that the μ-acetimine ligand in **3** plays an essential role in nitrile reduction.

The substrate scope of nitriles that can be reduced under our optimized conditions is broad. As shown in Table 2, aromatic, aliphatic, and heterocyclic nitriles are smoothly reduced to amines under optimized conditions. Both electron-poor and electron-rich substrates can be reduced in high yield. For example, in the presence of 5 mol% **3**, 4.0 equiv. of $NaBH_4$ can reduce 4-trifluorobenzonitrile **7a** to the corresponding benzylamine **8a** in 82% isolated yield (entry 1). Electron-rich nitrile **7b** can be reduced with a similar facility in 87% yield (entry 2). Even more oxidative nitroarene **7c** can be reduced with exclusive selectivity for the nitrile over the nitro group (92%, entry 3). We believe that this startling result is attributable to selective binding and activation of the nitrile over the nitro group by the ruthenium center of the catalyst. Furthermore, we see this as additional evidence showing that nitrile binding to ruthenium is important to the catalytic mechanism.

Despite the highly reducing conditions, an aryl bromide group in nitrile **7d** is not derivatized in the course of amine synthesis. This is an important result because aryl bromides such as these are high value substrates for cross-coupling and amination reactions relevant to the synthesis of medicinally relevant compounds.[16] This example further illustrates high-yielding reduction of an alkyl nitrile. Whereas ketone groups are known to react with $NaBH_4$, the reduction of **7e** (entry 5)

Table 1 Optimization of nitrile reduction conditions

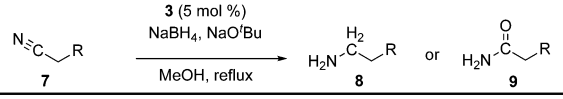


7a **8a**

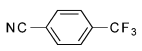
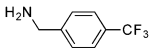
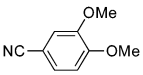
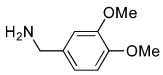
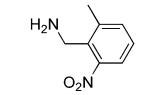
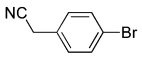
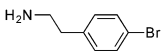
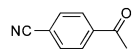
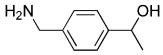
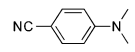
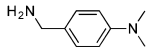
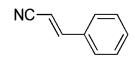
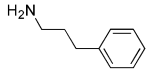
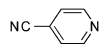
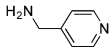
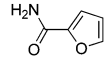
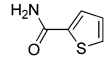
Entry	Catalyst	NaO^tBu	5 h conversion[a] (%)	NMR yield[b]
1	**3**	None	50	[c]
2	**3**	1 equiv.	>95	>90%, 5 h
3	**2**	1 equiv.	46	42%, 245 h
4	**6**	1 equiv.	41	Trace, 245 h
5	No catalyst	1 equiv.	38	43%, 245 h

[a] Starting material consumption by NMR in 5 hours. [b] Product formed upon consumption of nitrile and subsequent addition of water. [c] Not recorded.

Table 2 Scope of **3**-catalyzed nitrile reduction



7 **8** **9**

Entry	Nitrile	Conditions	Product	Yield[a] (%)
1	 **7a**	5 mol% **3** 4 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 12 h	 **8a**	82
2	 **7b**	5 mol% **3** 8 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 12 h	 **8b**	87
3	 **7c**	5 mol% **3** 4 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 4 h	 **8c**	92
4	 **7d**	5 mol% **3** 8 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 14 h	 **8d**	85
5	 **7e**	5 mol% **3** 4 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 8 h	 **8e**	80
6	 **7f**	5 mol% **3** 4 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 12 h	 **8f**	84
7	 **7g**	5 mol% **3** 8 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 12 h	 **8g**	60
8	 **7h**	5 mol% **3** 4 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 8 h	 **8h**	64
9	 **7i**	5 mol% **3** 4 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 8 h	 **9i**	56
10	 **7j**	5 mol% **3** 4 eq. $NaBH_4$, 1 eq. NaO^tBu MeOH, reflux, 8 h	 **9j**	87

[a] Reported yields are isolated yields.

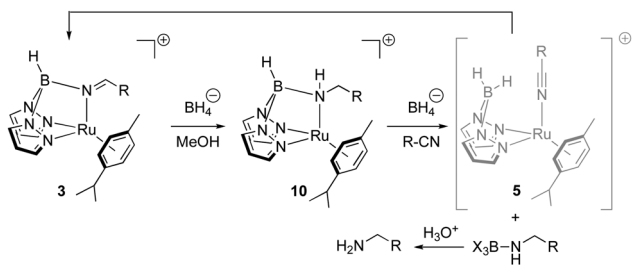
illustrates high-yielding double reduction for the synthesis of aminoachohol **8e**. A similar double reduction is observed in the reaction of cinnamonitrile (**7g**, entry 7) to give alkyl amine **8g** in 60% yield.

Reactions of nitriles appended to aromatic heterocycles afforded complicated results. For example, pyridine **7h** is compatible with the conditions and resulted in the formation of aminomethylpyridine **8h** in 64% yield (entry 7). By remarkable contrast, more electron-rich heterocycle systems are not reduced. For example, 2-cyanofuran **7i** and 2-cyanothiophene **7j** are selectively monohydrated as opposed to being reduced. Thus, amides **9i** and **9j** were isolated as the main products (entries 9 and 10). We suspect that the mechanism for these reactions involves the addition of methanol (solvent) to a ruthenium-coordinated nitrile, and that the amide products are formed upon aqueous work-up. We do not currently have a proposal to account for the selectivity of hydration *versus* reduction.

According to the insight gained from the stoichiometric synthesis of **3** from **4**, we propose the following template mechanism for catalysis (Scheme 2). We suspect that the bridging imine of **3** is reduced by borohydride to produce the amine product. We do not have direct evidence for the intermediacy of **10**; however, treatment of **3** with a stoichiometric portion of $NaBH_4$ in methanol-d_4 results in clean desymmetrization of cymene and pyrazole C–H groups of the catalyst, consistent with the formation of diastereotopic protons, as expected with the pyramidalization of the bridging nitrogen ligand (see the ESI† for graphical spectra). Still, the intermediacy of **10** remains a proposal because we have not established the kinetic role of this transient material.

We propose that the bridging amine ligand is replaced by an incoming substrate, and the borohydride group of **5** is regenerated by a hydride from $NaBH_4$, although we do not know the details of these steps. We observed by ^{1}H-coupled ^{11}B NMR spectroscopy that treatment of **3** with a stoichiometric portion of $NaBH_4$ in methanol-d_4 results in the formation of $(MeO)_4B^-$, unreacted BH_4^- and a catalyst doublet, which indicates that a $(pz)_2BH_2$ intermediate, if formed, is transient. Thus, we suspect that X in Scheme 2 is methoxide. ^{1}H NMR studies of the working catalyst reveal that once ligated, the reductions of the nitrile groups and imine groups are very facile. Thus, the rate-determining step could be amine for nitrile substitution in the conversion of **10**. This mechanism is a subject of ongoing work in our laboratory.

In conclusion, we report here a conveniently prepared homologue of our successful di(pyridyl)borate-ligated ruthenium complexes. The new catalytic scaffold shows comparable reactivity to the old one in several key reactions and confers new reactivity to the cooperative ruthenium–boron catalytic motif by enabling selective and high yielding nitrile reduction under mild conditions. Furthermore, this platform has yielded new insight into the cooperative reactivity of ruthenium and boron by showing a plausible scenario of how these two centers can work together, respectively, as an activating group (ruthenium) and a hydride donor (boron). Ongoing work in our laboratory regards the application of this system to the reduction of other high-value pi systems and the elucidation of the mechanistic details of these reactions.



Scheme 2 Mechanistic template for nitrile reductions.

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Notes and references

1 B. L. Conley and T. J. Williams, *J. Am. Chem. Soc.*, 2010, **132**, 1764–1765.
2 B. L. Conley and T. J. Williams, *Comments Inorg. Chem.*, 2011, **32**, 195–218.
3 B. L. Conley, D. Guess and T. J. Williams, *J. Am. Chem. Soc.*, 2011, **133**, 14212–14215.
4 Z. Lu, B. Malinoski, A. V. Flores, D. Guess, B. L. Conley and T. J. Williams, *Catalysts*, 2012, **2**, 412–421.
5 *Scorpionates: The Coordination of Polypyrazolylborate Ligands*, ed. S. Trofimenko, Imperial College Press, London, 1999.
6 For recent reviews of organometallic chemistry of poly(pyzalolyl)borate ligated complexes, see: (*a*) L. M. Caldwell, *Adv. Organomet. Chem.*, 2008, **56**, 1–94; (*b*) M. Lail, K. A. Pittard and T. B. Gunnoe, *Adv. Organomet. Chem.*, 2008, **56**, 95–153; (*c*) E. Becker, S. Pavli and K. Kirchner, *Adv. Organomet. Chem.*, 2008, **56**, 155–197; (*d*) I. R. Crossly, *Adv. Organomet. Chem.*, 2008, **56**, 199–321.
7 R. J. Abernethy, A. F. Hill, M. K. Smith and A. C. Willis, *Organometallics*, 2009, **28**, 6152–6159.
8 S. Bhambri and D. A. Tocher, *J. Chem. Soc., Dalton Trans.*, 1997, 3367–3372.
9 A ruthenium-ligated acetonitrile was reduced by $NaBH_4$, however the system produced unidentified products.13: L. F. Rhodes and L. M. Venanzi, *Inorg. Chem.*, 1987, **26**, 2692–2695.
10 M. Vogt, A. Nerush, M. A. Iron, G. Leitus, Y. Diskin-Posner, L. J. W. Shimon, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.*, 2013, **135**, 17004–17018.
11 R. F. Borch, *Chem. Commun.*, 1968, 442–443.
12 For example, stoichiometric portions of Ni^{II}, Co^{II}, Os^{IV}, Ir^{III}, Pt^{II}, are known to mediate nitrile and nitro group reduction in the presence of excess $NaBH_4$. Y. Suzuki, Y. Miyaji and Z. Imai, *Tetrahedron Lett.*, 1969, **52**, 4555–4558.
13 For selected examples, see: H. Paul, S. Bhaduri and G. K. Lahiri, *Organometallics*, 2003, **22**, 3019–3021; P. A. Chase, T. Jurca and D. W. Stephan, *Chem. Commun.*, 2008, 1701–1703; R. Reguillo, M. Grellier, N. Vautravers, L. Vendier and S. Sabo-Etienne, *J. Am. Chem. Soc.*, 2010, **132**, 7854–7855; X. Miao, C. Fischmeister, C. Bruneau, J.-L. Dubois and J.-L. Couturier, *ChemSusChem*, 2012, **5**, 1410–1414.
14 P. Magnus, N. Sane, B. P. Fauber and V. Lynch, *J. Am. Chem. Soc.*, 2009, **131**, 16045–16047.
15 D. Haddenham, L. Pasumansky, J. DeSoto, S. Eagon and B. Singaram, *J. Org. Chem.*, 2009, **74**, 1964–1970.
16 For selected reviews of utilization of aryl bromides in medicinal synthesis, see: J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359–1470; D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644–4680; J.-P. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651–2710; F.-S. Han, *Chem. Soc. Rev.*, 2013, **42**, 5270–5298; Y. Aubin, C. Fischmeister, C. M. Thomas and J.-L. Renaud, *Chem. Soc. Rev.*, 2010, **39**, 694–711; G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447–2464; T. R. M. Rauws and B. U. W. Maes, *Chem. Soc. Rev.*, 2012, **41**, 2463–2497.