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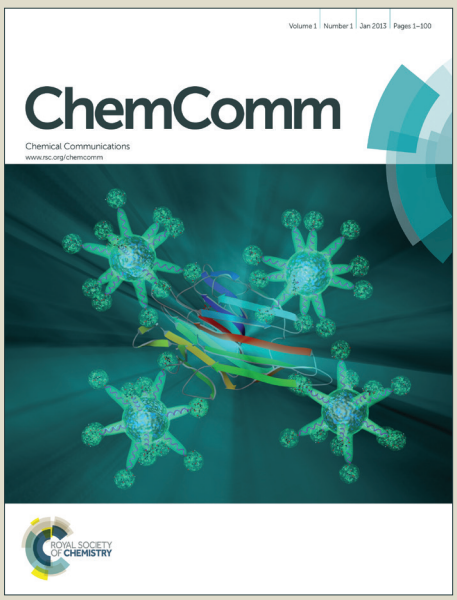

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A Dual Site Catalyst for Mild, Selective Nitrile Reduction

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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 from 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, 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 show a mechanistic account of the cooperative role, if any, that boron and ruthenium are playing 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, which inhibits access to a free borane in catalytic reactions.

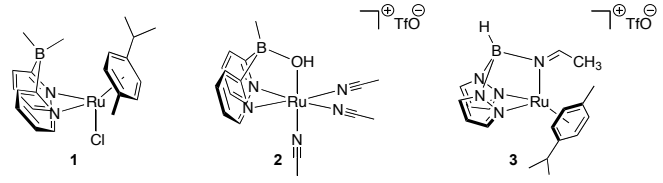
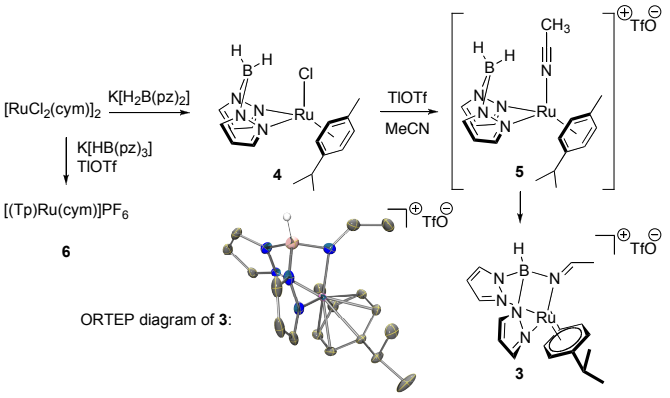


Fig. 1 Dual site catalysts for hydride manipulation.

We show here 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 hydride donor and activating group, respectively.

The synthesis of **3** (Scheme 1) proceeds from potassium di(pyrazolyl)borohydride[5, 6, 7] and commercially-available (cymene)ruthenium dichloride dimer to give intermediate chloride **4**. Although **4** can be isolated, it is easily converted in situ to **3** by treatment with 1 equiv. 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 from 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 in a tetrahedral geometry at boron, which has analogy to the popular tris(pyrazolyl)borohydride (Tp) ligand series.[6, 7, 8]



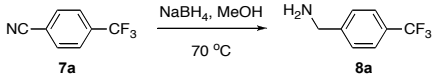
Scheme 1 Syntheses of precursor **3** and complex **6**. Molecular Structure of **3**.

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 **5**'s coordinated nitrile in >90% NMR yield (Scheme 1). This reaction is the first example of our envisioned cooperative reactivity of ruthenium and boron. Contrary to the design concept from which we originally prepared **2**,[2] boron in **3** is not behaving as a Lewis acid. The structure of **3** shows that B-H addition 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. excess $LiAlH_4$, borohydride reduction of a nitrilium salt,[11] metal hydride reagents,[12] or high-pressure hydrogenation[13] can be incompatible with important synthetic handles, such as aryl bromide and nitro.[14] More mild conditions compatible with groups like this require a stoichiometric portions 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 Optimization of Nitrile Reduction Conditions.



7a **8a**

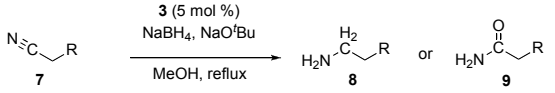
Entry	Catalyst	NaO^{t}Bu	5 h conversion [a]	NMR Yield [b]
1	**3**	None	50%	[c]
2	**3**	1 equiv.	> 95%	> 90%, 5 hr
3	**2**	1 equiv.	46%	42%, 245 hr
4	**6**	1 equiv.	41%	trace, 245 hr
5	no catalyst	1 equiv.	38%	43%, 245 hr

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

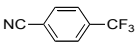
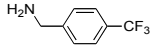
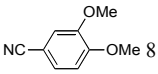
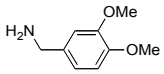
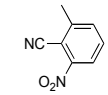
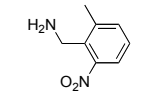
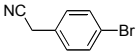
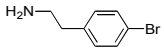
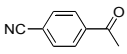
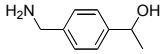
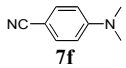
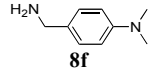
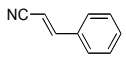
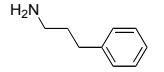
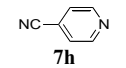
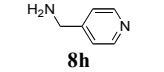
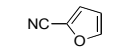
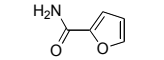
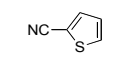
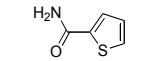
Table 1 shows the discovery and optimization of our conditions for nitrile reduction. In presence of 5 mol% **3**, 2.0 equiv. $NaBH_4$ can reduce 4-trifluoromethylbenzonitrile (**7a**) to the corresponding benzylamine (**8a**) in 50% conversion by NMR in 5 hours (entry 1). When 1.0 equiv. of NaO^{t}Bu 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 **3**'s Tp-ligated homologue (**6**, Scheme 1) is used in this reaction, much of the starting material decomposed 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 using 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 presence of 5 mol% **3**, 4.0 equiv. $NaBH_4$ can reduce 4-trifluorobenzonitrile **7a** to the corresponding benzylamine **8a** in 82% isolated yield (entry 1). Electron rich nitrile **7b** can be reduced with 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 by the catalyst's ruthenium center. Furthermore, we see this as additional evidence that nitrile binding to ruthenium is important to the catalytic mechanism.

Table 2 Scope of **3**-Catalyzed Nitrile Reduction.



7 **8** **9**

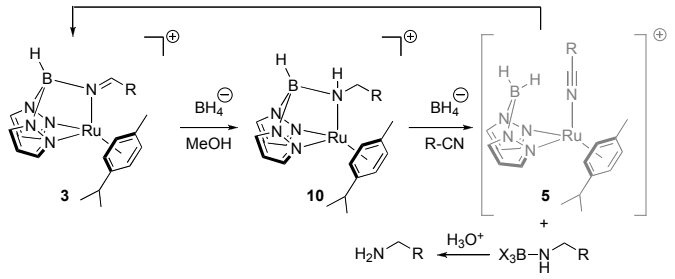
Entry	Nitrile	Conditions	Product	Yield [a]
1	 **7a**	5 mol% **3** 4 eq $NaBH_4$, 1 eq NaO^{t}Bu MeOH, reflux,12 h	 **8a**	82%
2	 **7b**	5 mol% **3** 8 eq $NaBH_4$, 1 eq NaO^{t}Bu MeOH, reflux, 12 h	 **8b**	87%
3	 **7c**	5 mol% **3** 4 eq $NaBH_4$, 1 eq NaO^{t}Bu MeOH, reflux, 4 h	 **8c**	92%
4	 **7d**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

[a] Reported yields are isolated yields.

Despite the presence of highly reducing conditions, an aryl bromide group in nitrile **7d** is not derivitized in the course of amine synthesis. This is an important result because aryl bromides such as this 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) illustrates high-yielding double reduction for the synthesis of aminoachohol **8e**. 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 reduced. Thus, amides **9ij** 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 **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 desymmeteriation of the catalyst's cymene and pyrazole C—H groups, consistent with the formation of diastereotopic protons, as expected with the pyramidalization of the bridging nitrogen ligand (see ESI for graphical spectra). Still, the intermediacy of **10** remains a proposal because we have not established the kinetic role of this transient material.



Scheme 2 Mechanistic Template for Nitrile Reductions.

We propose that the bridging amine ligand is replaced by 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 do observe 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, by ^{1}H-coupled ^{11}B NMR, which indicates 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 of the nitrile substrate to the ruthenium center. 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 has comparable reactivity to the old in several key reactions and introduces 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 activating group (ruthenium) and 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.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details, graphical spectra, and kinetics data. CCDC 963291 contains supplementary crystallographic data for **3**. See DOI: 10.1039/c000000x/

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