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A Dual Site Catalyst for Mild, Selective Nitrile Reduction

Zhiyao Lu and Travis J. Williams*

The synthesis of 3 (Scheme 1) proceeds from potassium di(pyrazolyl)borohydride 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,b 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 nitrium 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 portion of borane,\(^15\) 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 presence of 5 mol\% 3, 2.0 equiv. NaBH\(_4\) can reduce 4-trifluoromethylnitrite (7a) to the corresponding benzylamine (8a) in 50% conversion by NMR in 5 hours (entry 1). When 1.0 equiv. of NaO\(_{Bu}\) 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 \(\mu\)-acetilimine 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-trifluoromethylnitrite 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 nitro over the nitro group (92%, entry 3). We believe that this starting 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 nitrite binding to ruthenium is important to the catalytic mechanism.

Table 2 Scope of 3-Catalyzed Nitrile Reduction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>4 eq NaBH(<em>4), 1 eq NaO(</em>{Bu}), MeOH, reflux, 12 h</td>
<td>8a</td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>8 eq NaBH(<em>4), 1 eq NaO(</em>{Bu}), MeOH, reflux, 12 h</td>
<td>8b</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>7c</td>
<td>4 eq NaBH(<em>4), 1 eq NaO(</em>{Bu}), MeOH, reflux, 4 h</td>
<td>8c</td>
<td>92%</td>
</tr>
<tr>
<td>4</td>
<td>7d</td>
<td>8 eq NaBH(<em>4), 1 eq NaO(</em>{Bu}), MeOH, reflux, 14 h</td>
<td>8d</td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td>7e</td>
<td>4 eq NaBH(<em>4), 1 eq NaO(</em>{Bu}), MeOH, reflux, 8 h</td>
<td>8e</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>7f</td>
<td>5 mol% 3, MeOH, reflux, 12 h</td>
<td>8f</td>
<td>84%</td>
</tr>
<tr>
<td>7</td>
<td>7g</td>
<td>8 eq NaBH(<em>4), 1 eq NaO(</em>{Bu}), MeOH, reflux, 12 h</td>
<td>8g</td>
<td>60%</td>
</tr>
<tr>
<td>8</td>
<td>7h</td>
<td>5 mol% 3, MeOH, reflux, 8 h</td>
<td>8h</td>
<td>64%</td>
</tr>
<tr>
<td>9</td>
<td>7i</td>
<td>5 mol% 3, MeOH, reflux, 8 h</td>
<td>8i</td>
<td>56%</td>
</tr>
<tr>
<td>10</td>
<td>7j</td>
<td>5 mol% 3, MeOH, reflux, 8 h</td>
<td>8j</td>
<td>87%</td>
</tr>
</tbody>
</table>

\(^a\) Starting material consumption by NMR in 5 hours. \(^b\) Product formed upon consumption of nitrile and subsequent addition of water. \(^c\) Not recorded.

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 aminoachol 8e. Similar double reduction is observed in the reaction of cinnamionitrile 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 amine 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 NaBH₄ in methanol-d₄ results in clean desymmetrization 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](image)

We propose that the bridging amine ligand is replaced by incoming substrate, and the borohydride group of 5 is regenerated by a hydride from NaBH₄, although we do not know the details of these steps. We do observe that treatment of 3 with a stoichiometric portion of NaBH₄ in methanol-d₄ results in the formation of (MeO)₂B₂, unreacted BH₄⁻ and a catalyst doublet, by ¹H-coupled ⁱ¹B NMR, which indicates a (pz₂)BH₂ intermediate, if formed, is transient. Thus, we suspect that X in Scheme 2 is methoxide. ¹H NMR studies of the working catalyst reveal that once ligated, the reductions of the nitride groups and imine groups are very facile. Thus, the rate-determining step can be amine for nitrite substitution of the nitrite 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(pyrindyl)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 nitride 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 π 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/c0000000x/

12. For example, stoichiometric portions of Niii, Coii, Osiv, Iriii, Pvi, are known to mediate nitrite and nitro group reduction in the presence of excess NaBH₄. Y. Suzuki, Y. Miyaji, Z. Imai, Tetrahedron Lett., 1969, 52, 4555-4558.