

Communication

Alcohol Dehydrogenation with a Dual Site Ruthenium, Boron Catalyst Occurs at Ruthenium

Zhiyao Lu, Brock Malinoski, Ana V. Flores, Brian L. Conley, Denver Guess and Travis J. Williams *

Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, CA 90089-1661, USA

* Author to whom correspondence should be addressed; E-Mail: travisw@usc.edu.

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Abstract: The complex $[(\kappa^3-(N,N,O\text{-py}_2\text{B}(\text{Me})\text{OH})\text{Ru}(\text{NCMe})_3)^+ \text{TfO}^-$ (**1**) is a catalyst for transfer dehydrogenation of alcohols, which was designed to function through a cooperative transition state in which reactivity was split between boron and ruthenium. We show here both stoichiometric and catalytic evidence to support that in the case of alcohol oxidation, the mechanism most likely involves reactivity only at the ruthenium center.

Keywords: bifunctional catalyst; oxidation; hydride abstraction; mechanism

1. Introduction

Dual site catalysts possess two active sites that cooperate to enable the formation and/or cleavage of functional groups that cannot be manipulated easily or selectively with single-site systems. Dual site catalysis involving ruthenium has been of high interest, particularly ligand-metal bifunctional catalysis wherein a proton in the ligand directs cleavage and formation of bonds to hydrogen [1–4]. Among other applications, such systems are of great research interest because of their potential for enabling formation and utilization of hydrogen [5–7].

Our group is developing bifunctional catalysts for manipulating hydride groups, e.g., C–H and other X–H bonds [8]. In our ongoing efforts we have recently reported a dual site ruthenium, boron complex (**1**) that has diverse oxidative reactivity [9], and in its synthesis uncovered a remarkable agostic interaction, which defines a very rare sample of an acetonitrile ligand being replaced by C–H bond [10,11]. This complex highlighted important potential synergy between the reactivity of the

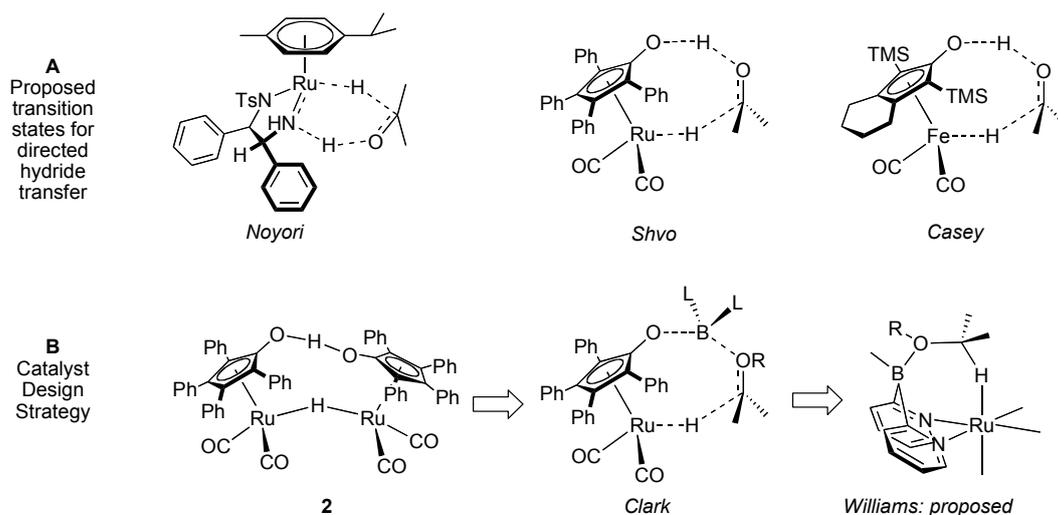
boron and ruthenium centers. More recently we have found that **1** is among the most robust and efficient homogeneous systems for ammonia borane dehydrogenation [12–14], which makes it a candidate for commercialization as a hydrogen storage system [15].

We report here on the mechanism of alcohol oxidation with **1**. Because mechanistic understanding is empowering for the development of new catalytic methods [16,17], we aim to understand **1** so that we and other might more effectively harness its remarkable reactivity. Here we will present evidence to show that, by contrast to the system's original design, this catalyst's oxidation of alcohols to ketones involves bond forming and breaking at only the ruthenium center.

Design of a Dual Site Ruthenium, Boron Catalyst

Our general design strategy to affect selective hydride manipulation is to devise catalysts that have two active sites that can work in concert to position and oxidize a particular substrate. Such a strategy is used prolifically in ligand, metal bifunctional catalysts, such as those pioneered by Noyori [18] and Shvo [19–22] (Figure 1). In these systems, a hydrogen bond is used to position a protic substrate with a C–H bond in the proximity of a ruthenium center, from which the hydrogen group is abstracted.

Figure 1. Coordination-directed hydride transfer.

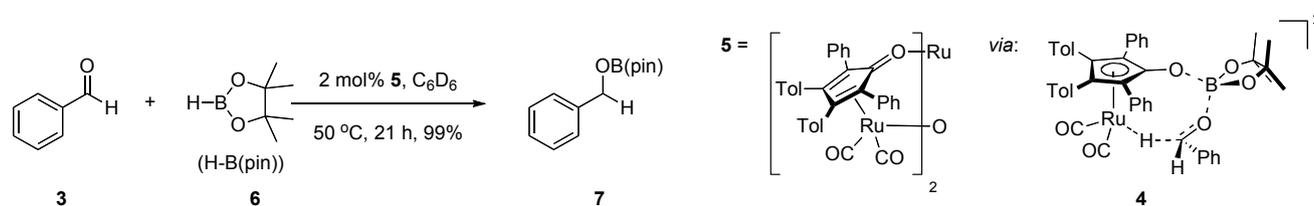


Our general strategy of devising a catalyst with a built-in Lewis acid to direct the metal to a particular substrate is analogous to these. Along these lines, the Shvo mechanism is similar to the Noyori systems and has been studied previously by Shvo [23], Casey [24,25], Bäckvall [6,26,27] us [28], and others. Alcohol oxidation with **1** has isotope effects on both C–H ($k_H/k_D = 2.6$) and O–H ($k_H/k_D = 1.8$), which indicates that both of these hydrogen atoms are transferred in (or possibly before) the rate-determining transition state (Figure 1A) [27]. Further, **1**-catalyzed oxidation of 1-phenylethanol has a Hammett ρ value of -0.9 , which is larger than expected for a transition state involving β -hydride elimination ($\rho = -0.43$) [29] or free-radical hydrogen atom transfer ($\rho = -0.3$) [30].

Our design is to replace the hydrogen atom in the Shvo transition state with a boron atom (Figure 1B) [31]. By replacing the proton in the transition state with a Lewis acid, we propose to enable abstraction of hydrides from groups other than alcohols [28]. Our first plan to prepare a dual site ruthenium, boron hydride transfer catalyst was to functionalize Shvo's catalyst with a boronic ester

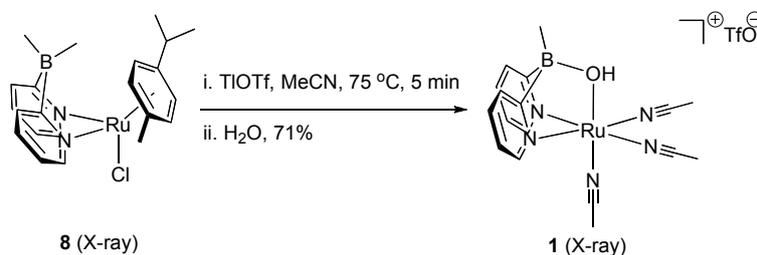
as sketched in **4** (Scheme 1) [32]. Along these lines, Tim Clark has realized such a transition state with the Shvo scaffold in reduction chemistry, and has reported that **5** will catalyze aldehyde and aldimine hydroboration with a transition state such as **4** [33]. By contrast, we have not been able to observe oxidative chemistry with the Shvo system in the presence of pinacol borane.

Scheme 1. A boron-functionalized homolog of the Shvo catalyst.



To overcome the apparent limitations of the Shvo system for catalytic, boron-directed oxidation, we prepared dual-site ruthenium, boron complexes **8** and **1** (Scheme 2) [9], which are characterized by X-ray crystallography [34]. Our mechanistic design for dual site oxidation chemistry with these is sketched in Scheme 3C. In this plan, **1** will substitute an alcohol substrate for its bridging hydroxyl group, which will be driven by the formation of water. The result will be a bridging alkoxide (**12**), which we proposed should rearrange to enable hydride abstraction from the pendant alkoxyborate through a transition state akin to **12** to give a ruthenium hydride and ketone product (**13**).

Scheme 2. Dual site ruthenium, boron complexes.



2. Results and Discussion

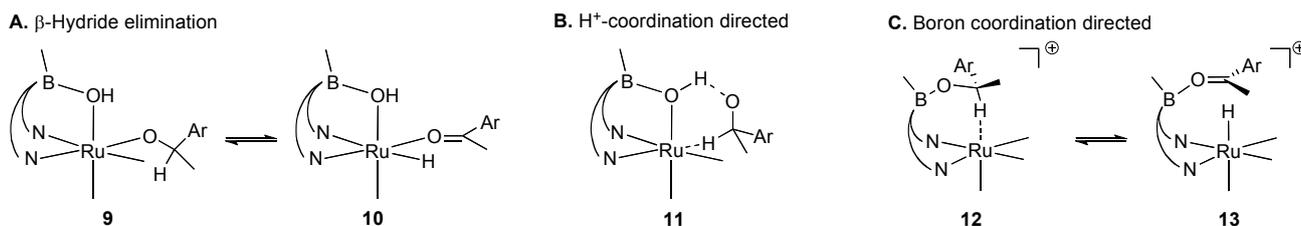
2.1. Stoichiometric Studies

C–H bond cleavage steps of three likely candidates for the mechanism of alcohol oxidation with **1** are sketched in Scheme 3. They include (A) a β -hydride elimination from a coordinated alkoxide. This type of mechanism is common for transfer dehydrogenation of alcohols with phosphine-ligated ruthenium(II) catalysts [29,35]. A second possibility (B) is a Shvo-like mechanism wherein the bridging hydroxyl directs the alkoxide to the metal center [24,36]. Our designed mechanism (C) is also possible.

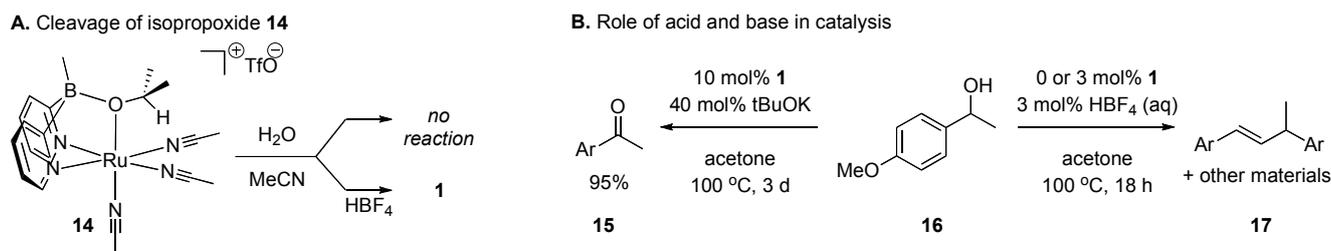
Our stoichiometric studies of this mechanism revealed key insights into the reactivity of the proposed intermediates (Scheme 4A). First we observed that substitution of the hydroxide bridge of **1** is slow: heating **1** in isopropanol did not result in hydroxide substitution at neutral pH. Conversely, the desired bridged isopropoxy complex **14** (independently prepared) is inert to reaction with neutral water in acetonitrile solution. This exchange is facile, however, in the presence of aqueous acid. Treatment

of alcohol **16** with **1** results in divergent outcomes depending on conditions (Scheme 4B): when the catalyst is activated with acid, no oxidative pathways are observed. In these conditions, we see elimination and apparent carbocation chemistry with or without **1**. In the presence of base, however, selective and high yielding oxidation of the alcohol to the corresponding ketone is possible (with concurrent formation of *i*PrOH-*d*₆). Taken together, these observations indicate that **1**'s μ -OH group is not labile under the conditions of alcohol oxidation catalysis.

Scheme 3. Mechanisms for base-mediated oxidation with **1**.



Scheme 4. Labiality of μ -OR groups in **1**: Roles of acid and base.

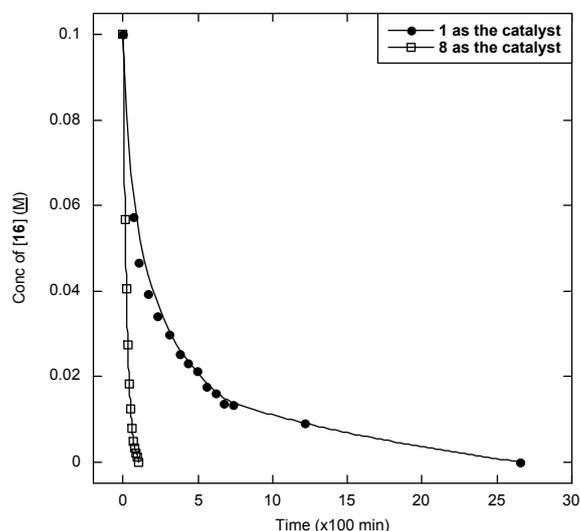


2.2. Catalytic Studies

In catalytic experiments, we have shown that cymene adduct **8** is a more reactive catalyst for alcohol oxidation than **1** (Figure 2). This provides further data refuting a (B) or (C) class mechanism: a class (B) mechanism would require the presence of the μ -OH group of **1**, and a class (C) mechanism would necessitate a free Lewis acid site on boron. Neither of these is available in catalyst precursor **8**, yet alcohol oxidation with **8** is far faster than alcohol oxidation with **1** under analogous conditions.

In analyzing the above data, one must consider a scenario in which a methylborate group in **8** is cleaved in the course of the reaction to reveal a boron hydroxide or a free Lewis acid. To test this hypothesis, we compared the ¹¹B NMR chemical shifts of the materials formed in situ at the conclusion of the reaction of **8** with **16** with the ¹¹B chemical shifts of **8** and **1**. The catalytic species in this reaction appear to speciate into three boron-containing moieties, which appear at ¹¹B $\delta = -14.1$, -14.7 , and -15.4 ppm. By comparison, the corresponding ¹¹B NMR chemical shifts for **8** and **1** are -12.0 and -8.1 ppm in acetone, respectively. Thus, because the ¹¹B species of this reaction are upfield of **8** and **1** is downfield, we surmise that if a methylborate group is cleaved in **8** in the course of this reaction, it is not converted to a boron hydroxide.

Figure 2. Oxidation of **16** (10 μ L, 71 μ mol) by **1** (4.1 mg, 8.7 μ mol, 12 mol%) and **8** (4.6 mg, 8.7 μ mol, 12 mol%) in acetone- d_6 (0.7 mL) in the presence of potassium *tert*-butoxide (1.6 mg, 14 μ mol, 20 mol%) at 100 °C in a sealed J-Young tube. Points are plotted for the concentration of **16** vs. time, where circles and squares respectively represent reactions catalyzed by **8** and **1**.



3. Experimental

3.1. General Procedures

All air and water sensitive procedures were carried out either in a Vacuum Atmosphere glove box under nitrogen (0.5–10 ppm O₂ for all manipulations) or using standard Schlenk techniques under nitrogen. Deuterated NMR solvents were purchased from Cambridge Isotopes Laboratories. Benzene- d_6 and acetonitrile- d_3 were dried over sodium benzophenone ketyl and calcium hydride, respectively, and distilled prior to use. Anhydrous *i*PrOH was distilled from NaOiPr, stirred over molecular sieves and silica gel for 20 h, then filtered through a Millipore filter prior to use. Shvo's catalyst was purchased from Strem Chemicals. ¹H and ¹¹B NMR spectra were obtained on a Varian 600 spectrometer (600 MHz in ¹H, 192 MHz in ¹¹B) with chemical shifts reported in units of ppm. All ¹H chemical shifts are referenced to the residual ¹H solvent (relative to TMS). All ¹¹B chemical shifts are referenced to a BF₃-OEt₂ in diglyme in a co-axial external standard (0 ppm). NMR spectra were taken in 8" J-Young tubes (Wilmad) with Teflon valve plugs. The NMR tubes were shaken vigorously for several minutes with chlorotrimethylsilane then dried in vacuo on a Schlenk line prior to use. Compound **1** and **8** were synthesized according to our published procedure [4].

3.2. Trisacetonitrile μ -Isopropoxy Ruthenium Triflate **14**

14 was generated *in situ* according to the following procedure. In a glove box, **1** (10.0 mg, 11 μ mol) was dissolved in dichloromethane (0.6 mL) in a 8 inch J-Young tube that had been pre-treated with chlorotrimethylsilane. Silane residue had been removed under reduced pressure before use. Trifluoroacetic anhydride (5.0 μ L, 38 μ mol, 2.0 eq.(molar equivalents)) was added to the tube. The

mixture was then heated to 60 °C for 20 h and cooled to room temperature, then anhydrous iPrOH (7.3 μ L, 96 μ mol, 5 eq) was added to the J-Young tube in the glove box. The reaction mixture was heated at 60 °C for 20 h. All volatiles were removed under reduced pressure on the Schlenk line. Recrystallization from dichloromethane/hexane yielded a pale yellow solid 2.3 mg (21%) (see Figures 3 and 4 for NMR spectra).

^1H NMR (600 MHz in dichloromethane- d_2 at 25 °C): δ = 8.57 (d, pyridyl 2H, J = 5.6 Hz), 7.59 (dt, pyridyl 2H, J = 1.6, 7.6 Hz), 7.39 (d, pyridyl 2H, J = 7.8 Hz), 7.07 (dt, pyridyl 2H, J = 1.6, 6.6 Hz), 3.82 (m, $(\text{CH}_3)_2\text{CH-O}$, 1H), 2.66 (s, CH_3CN axial, 3H), 2.55 (s, CH_3CN equatorial, 6H), 0.80 (d, $(\text{CH}_3)_2\text{CH-O}$ 6H, J = 6.4 Hz), 0.43 (s, $\text{CH}_3\text{-B}$ 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (150.84 MHz in dichloromethane- d_2 at 25 °C) δ = 184.33 (broad s, ipso pyridyl-B), 152.87 (pyridyl), 134.81 (pyridyl), 125.73 (axial CH_3CN), 125.53 (equatorial CH_3CN), 125.39 (pyridyl), 121.48 (pyridyl), 70.49 ($(\text{CH}_3)_2\text{CH-O}$), 23.42 ($(\text{CH}_3)_2\text{CH-O}$), 5.27 (axial CH_3CN), 4.70 (equatorial CH_3CN), 1.33 (broad s, $\text{CH}_3\text{-B}$). $^{11}\text{B}\{^1\text{H}\}$ (192 MHz in dichloromethane- d_2 at 50 °C): δ = 2.17.

Figure 3. Graphical spectra for **14**. A, B and C are ^1H , ^{13}C and ^{11}B NMR spectral data, respectively. The bigger peak in ^{11}B spectrum corresponds to a BF_3 etherate standard.

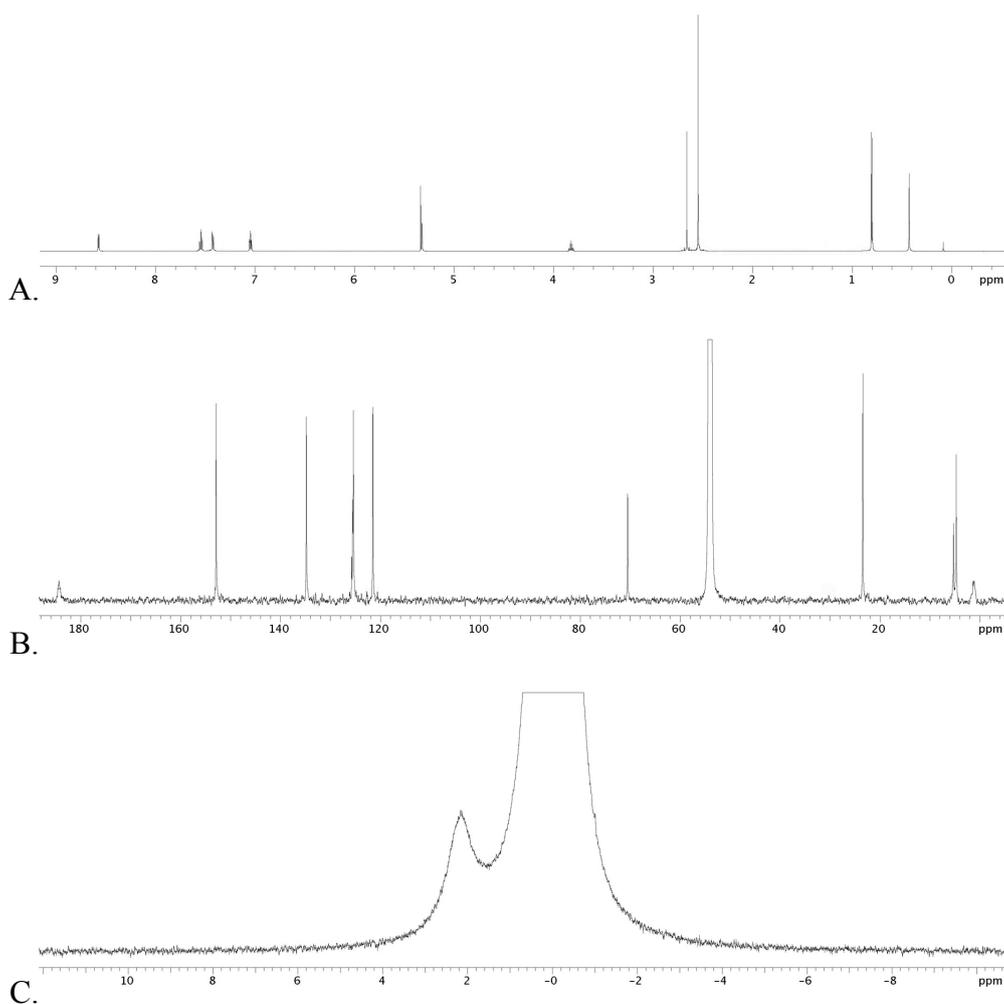
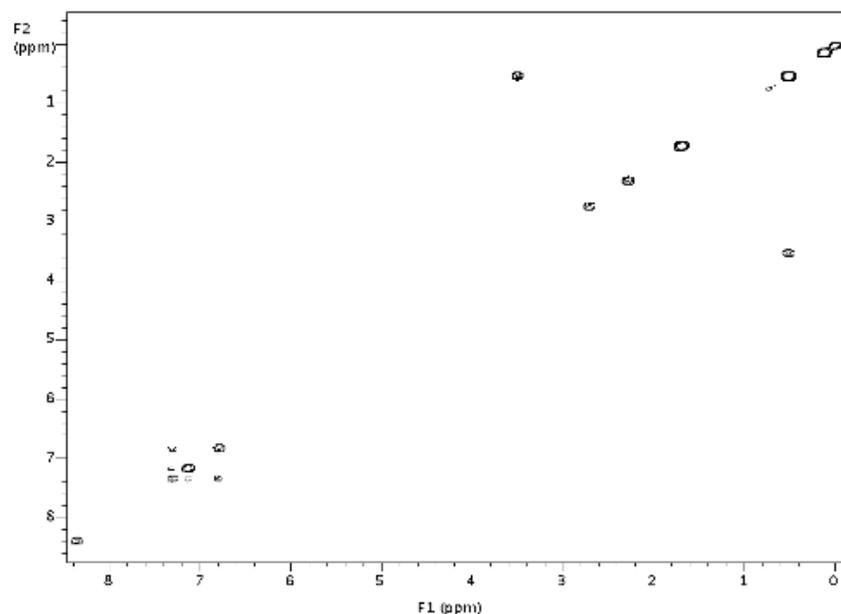


Figure 4. Graphical ^1H - ^1H COSY spectrum for **14**.

3.3. Diarylbutene **17**

A mixture of 1.8 μL **16** (13 μmol), 0.6 μL HBF_4 (4.2 μmol) and 2.4 mg **1** (4.2 μmol) was dissolved in 0.6 mL acetonitrile- d_3 in a sealed J-Young tube. The tube was then heated in a regulated oil bath at 100 $^\circ\text{C}$ for 18 h. The structure of **17** was determined based on NMR data and previously reported reference [37].

4. Conclusions

In sum, we present here evidence that **1**-catalyzed oxidation of secondary alcohols is most likely to be happening through a mechanism that does not involve simultaneous participation of both boron and ruthenium in the way we originally proposed. This is supported by two key observations: (1) In a stoichiometric experiment wherein the requisite intermediate for a class (C) mechanism is prepared in isolation, it cannot be converted to the necessary product at an appreciable rate; (2) In a catalytic experiment, we see that the synthetic precursor to the proposed dual site catalyst is far more reactive in alcohol oxidation than the proposed catalyst itself. This reactivity shows that a pathway such as those shown in classes (B) and (C) are probably high energy relative to one that involves only the ruthenium active site.

Ongoing work in our lab involves mechanistic elucidation of reactions in which both a late metal and acidic site on the catalyst are involved, such as ammonia borane dehydrogenation with **1** [15] and the Shvo system [38,39], and new reaction development around a dual site catalyst motif.

Acknowledgments

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