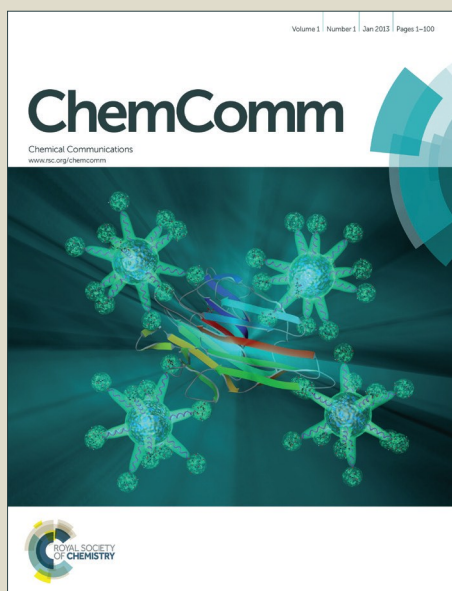


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COMMUNICATION

Upgrading Ethanol to 1-Butanol with a Homogeneous Air-Stable Ruthenium Catalyst

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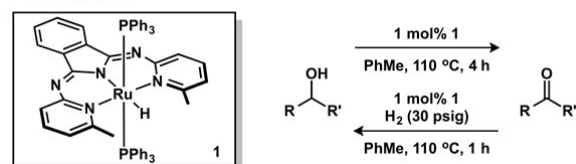
An amide-derived *N,N,N*-Ru(II) complex catalyzes the conversion of EtOH to 1-BuOH with high selectivity. Conversion to alcohol upgraded products exceeds 250 turnovers per hour (>50% conversion) with 0.1 mol% catalyst loading. In addition to high activity for ethanol upgrading, catalytic reactions can be set up under ambient conditions with no loss in activity.

Interest in alternative energy solutions for the transportation sector is driven largely by the finite supply of fossil fuels.¹ One potentially interim approach is to replace or blend gasoline with sustainable biofuels, such as alcohols.² Ethanol (EtOH), which is a direct product of biomass fermentation, has been widely used as a blend additive with gasoline.³ However, challenges associated with the widespread use of EtOH have limited broad implementation in the global transportation sector. Key roadblocks remaining are that EtOH: (1) has ~70% energy density of gasoline, (2) is corrosive to engine technology and fuel pipelines, and (3) forms an azeotrope with H₂O, and over extended timeframes, separates from gasoline blends; both leading to storage problems.⁴ These disadvantages are generally mitigated for higher order alcohols, including 1-butanol (1-BuOH), whose fuel properties more closely resemble those of gasoline (~90% energy density of gasoline). Furthermore 1-BuOH can be blended in higher 1-BuOH:gasoline ratios, and is immiscible with water.⁵ Although 1-BuOH is a highly desirable biofuel, the large-scale synthesis (fermentative production) from bio-feedstocks has been fraught with low conversion and poor selectivity.⁶

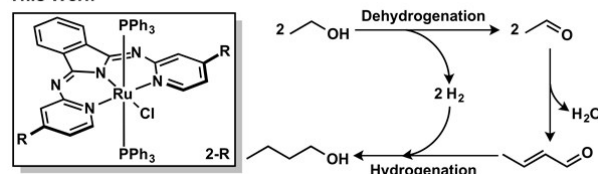
As an alternative to fermentation, an atom-economical approach for the bulk synthesis of 1-BuOH is the Guerbet reaction.⁷ This route applies a series of reactions related to "borrowed hydrogen" chemistry for the conversion of primary alcohols into higher order alcohol products.⁸ For

upgrading EtOH to 1-BuOH, EtOH dehydrogenation affords acetaldehyde, which undergoes aldol coupling to generate crotonaldehyde. Hydrogenation of crotonaldehyde produces 1-BuOH. Key parameters used to evaluate this reaction are the turnover number (TON), turnover frequency (TOF), and selectivity (yield of 1-BuOH divided by the total yield of Guerbet products). A few recent reports have demonstrated this reaction with heterogeneous^{9,10} and homogeneous¹¹ catalysts. To date, the best TONs reported with >30% conversion are 458,^{11d} 314,^{11b} 340,^{11a} and 304,^{11c} while the highest TOF reported was 79 h⁻¹ (314 TONs), using a Ru(II) complex with a bidentate P–N ligand.^{11b} A recent report demonstrated extremely high selectivity at the sacrifice of activity using a two-component Ir catalyst (99%, TON = 185, TOF = 8 h⁻¹). However, for large-scale applications required for the transportation sector, higher conversion and turnover are required.

Previous Work



This Work



Scheme 1 Previous work demonstrated reversible transformations between ketones and alcohols via sequential hydrogenation-acceptorless dehydrogenation reactions mediated by **1**. This work presents the catalytic conversion of EtOH to 1-BuOH using the same family of Ru(II) complexes.

We recently reported an *N,N,N*-bMepi (bMepi = 1,3-bis(6'-methyl-2'-pyridylimino)isoindolate) Ru(II) hydride complex (**1**, HRu(bMepi)(PPh₃)₂) capable of mediating

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization, and reaction details. See DOI: 10.1039/x0xx00000x

Table 1 Catalytic Conversion of EtOH to 1-BuOH^a

Entry	Catalyst	Base	Modifications/Additives	Conversion (%) ^b	Yield (%)	Selectivity (%) ^c	TON ^d	Final TOF ^e
1	1	NaOEt	—	10	10	100	100	50
2	2-H	NaOEt	—	30	25	91	300	150
3	2-OMe	NaOEt	—	28	24	89	280	140
4	2-Cl	NaOEt	—	25	21	89	250	125
5	2-H	LiOEt	—	3.9	3.9	100	39	18
6	2-H	KOEt	—	23	19	89	230	115
7	2-H	NaOH	—	30	26	90	300	150
8	2-H	NaOEt	0.3 mol% 2-H	27	23	89	92	46
9	2-H	NaOEt	180 °C	41	28	78	410	205
10	2-H	NaOEt	10 mol% NaOEt	42	31	82	420	210
11	2-H	NaOEt	0.05 mol% 2-H	25	20	81	500	250
12	2-H	NaOEt	0.01 mol% 2-H	6.3	5.4	86	630	315
13	2-H	NaOEt	0.001 mol% 2-H	1.4	1.4	100	1400	700
14	2-H	NaOEt	Set up under air	34	27	83	340	170
15	2-H	NaOEt	10 mol% NaOEt under air	39	29	89	390	195
16 ^f	2-H	NaOEt	20% 1-BuOH by volume	35	23	85	350	175
17	2-H	NaOEt	0.1 mol% PPh ₃	49	38	84	490	245
18	2-H	NaOEt	0.4 mol% PPh ₃	53	37	78	530	265

^a All reactions were performed on a 17.1 mmol scale in neat EtOH under an inert atmosphere and were stopped after 2 h. The conversion, yield, and selectivity were determined by GC-FID integration of the reaction mixture using naphthalene as an internal standard. ^b Total conversion of EtOH to Guerbet products. ^c Total selectivity to 1-BuOH determined by mmol of 1-BuOH per mmol of all Guerbet products. ^d TON based on mmol of substrate converted to products per mmol of Ru. ^e Final TOF based on mmol of substrate converted to products per mmol of Ru after proceeding for 2 h. ^f With 0.2 mL of 1-BuOH added (20% by volume).

reversible transformations between ketones and alcohols via sequential hydrogenation-acceptorless dehydrogenation reactions (Scheme 1).¹² Mechanistic analysis of the acceptorless alcohol dehydrogenation (AAD)¹³ revealed that **1** operated via an inner-sphere β -H elimination pathway where β -H elimination is the turnover-limiting step at high alcohol concentration. Because of the steric hindrance of the methyl groups on the β -H elimination process, higher catalytic AAD activity was observed when Ru-b4Rpi complexes (**2-R**) were used. As a result of the ability of **1** to promote successive hydrogenation-dehydrogenation reactions, we hypothesized that, if using our family of bis(pyridylimino)isoindolate (bpi) Ru(II) complexes, similar “borrowed hydrogen” chemistry might be adapted for alcohol upgrading reactions. Herein, we report the application of **2-R** as homogeneous catalysts that promote the conversion of EtOH to 1-BuOH with unprecedented activity and high selectivity.

We initiated studies on Guerbet catalysis with EtOH using our previously reported Ru-bpi complexes (**1** and **2-R**). Standard reaction conditions employed a 10 mL vial containing 17.1 mmol EtOH, 5 mol% NaOEt base, and 0.1 mol% Ru(II) precatalyst.¹⁴ After the reaction mixture was heated to 150 °C for 2 h, the product distribution was determined by GC-FID using naphthalene as an internal standard. Higher activity (>3 $\times$) was found when **2-H** (Table 1, entry 2) was used instead of **1** (Table 1, entry 1). Analysis of the reaction products (Table 1, entry 2) showed high selectivity (91%) for the production of 1-BuOH and 4% yield

of C₆ alcohols (2-ethylbutanol and 1-hexanol, see Table S1) as side products, consistent with Guerbet coupling of 1-BuOH with EtOH. Control experiments showed that **2-H** and NaOEt were both required for catalysis (see Table S1). In addition, electronic modifications of the pincer scaffold had no effect on the activity and selectivity. For instance, the conversion and selectivity were within the experimental error (3%)¹⁵ when **2-OMe** (Table 1, entry 3) or **2-Cl** (Table 1, entry 4) was used instead of **2-H**.

Guided by the high selectivity for 1-BuOH exhibited by **2-H**, we investigated conditions to improve the activity. The identity of the alkali metal had a significant effect. For example, lower activities were observed when LiOEt (Table 1, entry 5) or KOEt (Table 1, entry 6) was used instead of NaOEt, while NaOH (Table 1, entry 7) produced the same results as NaOEt (consistent with solvent leveling effects). Unfortunately, a higher catalyst loading (0.3 mol%, Table 1, entry 8) did not improve activity and selectivity. However, at high temperature (180 °C, Table 1, entry 9) or higher NaOEt base loading (10 mol%, Table 1, entry 10), the conversion increased, with concomitant decrease in selectivity for 1-BuOH. For instance, when 10 mol% NaOEt was used, 42% conversion of EtOH to Guerbet alcohols was noted with 82% selectivity for 1-BuOH. Analysis of the reaction products showed higher yield of side products, which included C₆ alcohols (10%) and C₈ alcohols (2% yield of 2-ethylhexanol and 1-octanol, see Table S1).

Air-stable catalysts provide significant practical advantages, and are more easily deployed on an industrial-scale. We found that the activity of **2-H** was retained when

set up under ambient conditions. For example, when weighing all reagents in the air and adding air saturated solvents followed by heating the sealed vessel containing 17.1 mmol EtOH, 0.1 mol% **2-H**, and 5 or 10 mol% NaOEt to 150 °C for 2 h (Table 1, entries 14 and 15) resulted in 34% and 39% conversion (30% under N₂) respectively. These results clearly demonstrate that catalytic performance is unaffected in the presence of O₂, which suggests that the active species is neither decomposed nor oxidized to a higher-valent ruthenium complex. Based on known reports of upgrading EtOH to 1-BuOH, our system **2-H** is the first ruthenium catalyst to mediate this reaction under air.

To assess the overall reaction efficiency, a time dependence study was conducted by varying the reaction time at 150 °C (Fig. 1). When evaluated over 24 h, the reaction profile displayed a linear region and reached culmination after approximately 4 h. Analysis of the reaction profile and the reaction products revealed an increase in production of higher order alcohols (10% to 14% C₆ and C₈ Guerbet products from 4 to 6 h) while the yield of 1-BuOH remained constant. We hypothesized that high concentration (ca. 2.1 M or 25% yield) of 1-BuOH could compete with EtOH as a substrate, and thus impede production of 1-BuOH by competitive Guerbet pathways to generate longer chain alcohols. In support, a control experiment using 20% of 1-BuOH by volume (Table 1, entry 16) afforded similar conversion and yield. However, the yield of longer chain alcohols increased from 4% to 12% and the yield of 1-BuOH remained 23% (25% without the addition of 1-BuOH), which is consistent with competitive 1-BuOH binding/reactivity at high concentration.

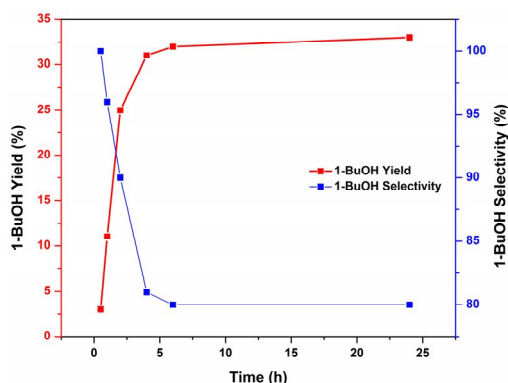


Fig. 1 Reaction profile of conversion of EtOH to 1-BuOH catalyzed by **2-H**. The conditions were identical to Table 1, entry 2 except the reaction time. Each data point represents an average of two runs with a maximum experimental error of 3%.

To complement the time dependence study that demonstrated minimal catalyst activity after 6 h, we targeted Ru-bpi compounds with CO ligands that likely bear similarity to the catalyst deactivation product (ν_{CO} band at 1923 cm⁻¹ observed by IR spectroscopy).¹⁶⁻¹⁸ Three different types of CO complexes were prepared from bpi variants to aid in the assignment of the decomposition products. The addition of CO (30 psig) to a solution of Ru(bMepi)(PPh₃)Cl

resulted in the clean conversion to Ru(bMepi)(PPh₃)(Cl)CO (**3**). The ³¹P{¹H} NMR spectrum exhibited a singlet at 43.5 ppm, and the IR spectrum displayed a ν_{CO} band at 1929 cm⁻¹. The solid-state structure revealed CO ligand *trans* to the isoidolate nitrogen atom (Fig. 2).

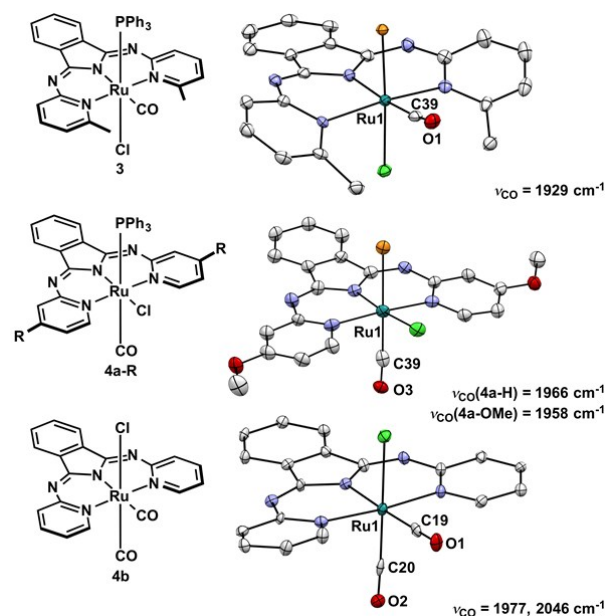


Fig. 2 Crystal structures of **3** and **4** with thermal ellipsoids depicted at 50% probability (30% probability for **4a-OMe**). The hydrogen atoms and PPh₃ phenyl groups are omitted for clarity. Selected bond distances (angstroms) for **3**: Ru1—C39, 1.867(3); and O1—C39, 1.155(3). Selected bond distances (angstroms) for **4**: Ru1—C39, 1.859(9); and O3—C39, 1.096(9). Selected bond distances (angstroms) for **4b**: Ru1—C19, 1.910(7); Ru1—C20, 1.903(9); O1—C19, 1.146(9); and O2—C20, 1.12(1).

Carbonyl complexes with the bpi ligand were prepared using a similar method. The addition of 30 psig CO to a solution of **2-H** resulted in a mixture of **4a-H** and **4b** in a 37:1 ratio. The ³¹P{¹H} NMR spectrum displayed one major resonance at 10.7 ppm with concomitant formation of free PPh₃, and the IR spectrum showed one major ν_{CO} band at 1966 cm⁻¹. After 24 h, the mixture fully converted to the bis-CO complex (**4b**), and the IR spectrum exhibited new ν_{CO} bands at 2046 and 1977 cm⁻¹, while the solid state structure revealed a Ru(II) center coordinated to two *cis* CO ligands and a chloride (Fig. 2). Although a crystal structure of **4a** could not be obtained, a substituted variant (**4a-OMe**)¹⁹ that featured a very similar ν_{CO} band (1958 cm⁻¹) was structurally characterized by X-ray (Fig. 2). Because of the close proximity of the ν_{CO} bands between **3** and the decomposition product from Guerbet reactions (1929 vs. 1923 cm⁻¹), we propose that the deactivated catalyst contains a CO ligand (resulting from decarbonylation) *trans* to the isoidolate nitrogen atom.

To optimize activity by preventing a competitive EtOH decarbonylation pathway, excess PPh₃ was added to suppress phosphine dissociation. Addition of 1 equiv of PPh₃ (with respect to catalyst) to the standard reaction

conditions (0.1 mol% **2-H**, 5 mol% NaOEt, 150 °C; Table 1, entry 17) enhanced the catalyst activity to 49% conversion (an increase of 76% based on conversion and 72% based on TOF). Increasing the PPh₃ loading to 4 equiv had a minimal increase on the catalyst activity (53%; Table 1, entry 18).²⁰ Prior state-of-the-art catalysts afforded a TON of 458 (46% conversion; TOF = 19 h⁻¹)^{11d} or 314 (31% conversion; TOF = 79 h⁻¹).^{11b} Thus, our system surpassed the activity of the previous premier systems by exhibiting a higher TON of 530, with a TOF of 265 h⁻¹ at 53% conversion for catalytically upgrading EtOH.

In conclusion, we have developed Ru-bpi complexes (**2-R**) capable of converting EtOH to 1-BuOH with up to 91% selectivity. Higher activity (>50% conversion) was obtained at the sacrifice of selectivity (~10%) when using 1-4 additional equiv PPh₃. Note that currently used liquid fuels such as gasoline, are blends of hydrocarbons rather than single components. Thus, mixtures of higher order alcohols can likely serve a similar role as drop-in gasoline additives. Although prior studies have demonstrated homogeneous catalysts for EtOH upgrading, to our knowledge, our system is the most active, with a TOF of 265 h⁻¹ at over 50% conversion. Of particular note, complex **2-H** upgrades EtOH to 1-BuOH when set up in air with minimal loss of catalytic activity. This improvement in catalyst performance represents a substantial step forward toward processes that use a bio-derived feedstock for one-step fuel-forming reactions with minimal intervention required to the existing transportation infrastructure. Ongoing efforts are focused on mechanistic analyses as well as other sustainable energy applications derived from renewable biomass feedstocks.

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- The experimental error was determined by >3 runs of the standard reaction (Table 1, entry 2).
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- To further characterize the ruthenium species during catalysis, allowing **2-H** to react with NaOEt resulted in multiple species (65.9 ppm, 55.1 ppm, and free PPh₃) as observed by ³¹P NMR spectroscopy.
- Single crystals of **4a-OMe** were obtained from vapor diffusion of pentane into a C₆H₆ solution (see cif file), which confirmed the structure of **4a**. Complex **4a-OMe** shared similar ¹H and ³¹P NMR features, which included a ³¹P NMR resonance at 10.8 ppm (10.7 ppm for **4a-H**).
- The active catalyst was probed using mercury and substoichiometric ligand poisoning experiments; the results were consistent with a homogeneous system (see Table S2).