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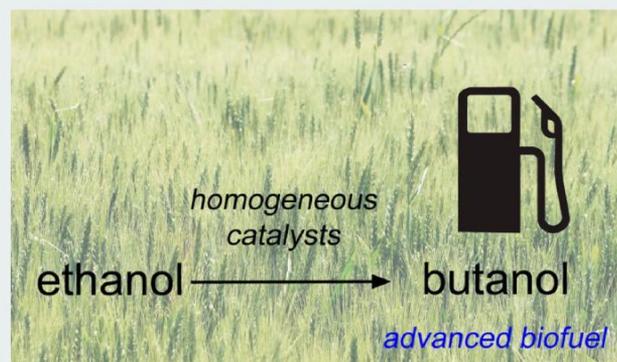
# Homogeneous Ethanol to Butanol Catalysis Guerbet Renewed

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**ABSTRACT:** The catalytic conversion of (bio)ethanol into butanol is an attractive route to upgrade the modest fuel characteristics of this widely available bioderived substrate into a molecule that has properties much closer to conventional gasoline. The Guerbet reaction, known for more than 100 years, provides an ideal mechanism for this transformation. However, despite the apparently simple nature of this reaction for ethanol, it provides formidable challenges, especially in terms of achieving high selectivity. There have been advances in both heterogeneous and homogeneous catalysis in this regard, and this Perspective focuses on the very recent reports of homogeneous catalysts that describe encouraging results in terms of achieving high selectivity, mechanistic understanding, and widening scope.

**KEYWORDS:** biofuels, ethanol upgrading, butanol, ruthenium, Guerbet catalysis



## 1. INTRODUCTION

The development of sustainable sources of energy is one of the most important objectives for the entire scientific community.<sup>1</sup> The issues regarding the use of fossil fuels are well-documented and complex, as are the economic, environmental, political, and technical issues related to the exploitation of nonconventional fossil fuels sources, especially shale gas.<sup>2</sup> Despite the complexity of these issues, the benefits of a move to a more sustainable energy portfolio are clear, even if again the specifics of this are multifaceted. Liquid fuels for transportation are a crucial part of our current energy portfolio, and they have long been reliant on catalytic processes from Fluidized Catalytic Cracking (FCC) to Fischer–Tropsch synthesis. Using renewable biomass as a source of liquid fuels also generates debate regarding wider factors, but there is little doubt that biofuels will be an important component of meeting energy demand in a more sustainable manner in the short and medium term.<sup>3</sup> It is also an area rich with possibilities for the catalytic chemist, from the acid-catalyzed transesterifications that are central to biodiesel manufacture to the biocatalysis of fermentation.

To date, bioethanol, obtained by the fermentation of sugar-containing crops, has dominated the biogasoline market, used on its own or as a blend with conventional fuels. However, ethanol has a number of significant drawbacks as compared to gasoline: it has a lower energy density (70% that of gasoline), it readily absorbs water, leading to separation and dilution problems in storage tanks, and it is corrosive to current engine technology and fuel infrastructure.

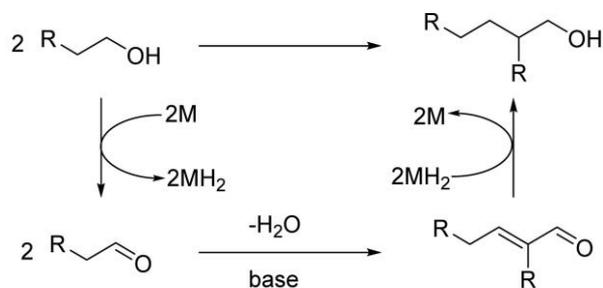
By contrast, butanol isomers have fuel properties that more closely resemble those of gasoline and can alleviate many of these problems associated with ethanol.<sup>4</sup> For example, n-butanol is essentially noncorrosive, immiscible with water, and has an energy density 90% that of gasoline. This improved performance has led to butanol being termed an “advanced

biofuel”, and the commercial availability of this material as a green drop-in alternative to gasoline is gathering pace.<sup>5</sup> However, the bulk synthesis of butanols from biosustainable feedstocks remains a challenge. Most recent interest focuses on revisiting the ABE fermentation process in which mixtures of acetone, butanol, and ethanol are produced by the use of strains of the bacterium *Clostridium acetobutylicum*. This is a difficult fermentation, limited by the toxicity of the butanol product, with low conversion and modest selectivity.<sup>6</sup>

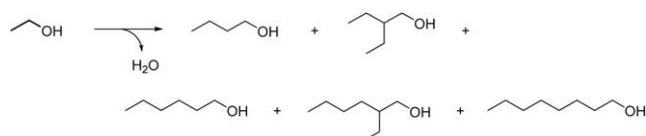
An attractive alternative approach is to catalytically convert or upgrade widely available (bio)ethanol into butanol. Catalytic reactions for the conversion of alcoholic substrates are surprisingly rare, but one ideal example exists in the Guerbet reaction, which enables facile C–C bond formation with normally unreactive alcohols.<sup>7</sup> This reaction has been known for more than 100 years, in which Guerbet’s original report describes the use of simple sodium alkoxide catalysts at elevated (200 °C) temperature.<sup>7a</sup> The widely accepted catalytic reaction scheme for this transformation was first proposed by Veibel and Neilsen;<sup>7c</sup> an alcohol is dehydrogenated to form an aldehyde, which then undergoes aldol coupling, with rehydrogenation of the product giving a longer-chain alcohol. Clearly, if the initial alcohol is ethanol then n-butanol will be the product (Scheme 1).

While this seems a simple reaction scheme, especially with ethanol as the substrate, there are inherent problems particularly with regard to selectivity. Because the n-butanol product itself can also undergo dehydrogenation higher alcohols often result as side products (Scheme 2). More generally, the base-catalyzed aldol coupling of acetaldehyde is

Scheme 1. Guerbet Reaction



Scheme 2. Main Products Obtained from the Guerbet Reaction of Ethanol



notoriously difficult to control and can lead to complex mixtures of oligomers and polymeric material. More recently, the Guerbet reaction has been reinvented and expanded as “borrowed hydrogen” chemistry, often using ruthenium or iridium catalysts.<sup>8</sup> There has been a realization that taking a more modern approach to catalyst design might unlock the potential of this chemistry in achieving good selectivity for a catalytic ethanol to butanol reaction, leading to a series of recent papers describing promising results in this regard.

This Perspective describes these recent results in homogeneous ethanol to butanol catalysis. It also attempts to put these results into context by contrasting selected recent advances with other approaches, specifically with heterogeneous catalysts. Reviews of borrowed hydrogen chemistry in its broader context are available and are complementary to this more focused article.<sup>8</sup> There are also many useful reviews on chemistries for the catalytic conversion of bioderived substrates in general.<sup>9</sup>

## 2. HETEROGENEOUS APPROACHES

While focusing on homogeneous catalysts here, it is useful to examine selected results with heterogeneous catalysts for ethanol to butanol chemistry an area that has seen similar and parallel recent advances. Several excellent recent reviews offer a more thorough discussion of heterogeneous systems. Davis reviewed heterogeneous catalysts for the Guerbet coupling of alcohols in 2014.<sup>10</sup> Muraza’s review from 2015 focuses on heterogeneous catalysts used specifically for the upgrading of bioethanol to fuel-grade biobutanol.<sup>11</sup> A review from Sels, Van Der Voort, and Verberckmoes, also published in 2015, offers an overview of the thermodynamics and proposed mechanisms for Guerbet condensation reactions as well as providing an in depth survey of heterogeneous, homogeneous, and mixed heterogeneous/homogeneous catalyst systems.<sup>12</sup>

Basic metal oxides have been extensively studied as catalysts for the Guerbet reaction of ethanol to higher alcohols in the vapor phase (>300 °C). MgO or mixtures of MgO with other basic metal oxides have been used to obtain selectivity to n-butanol of up to 70% at low conversion.<sup>13</sup> Ramasamy et al. have recently investigated the effect of calcination temperature on MgO–Al<sub>2</sub>O<sub>3</sub> mixed oxide catalysts derived from hydrotalcite (Mg<sub>6</sub>Al<sub>2</sub>(CO<sub>3</sub>)(OH)<sub>16</sub>·4H<sub>2</sub>O, HTC) for use in the ethanol to butanol reaction.<sup>14</sup> Untreated HTC itself displayed no activity

toward the Guerbet reaction of ethanol; however, on calcination to its MgO–Al<sub>2</sub>O<sub>3</sub> form, active catalysts were obtained. They investigated the effect of calcination temperatures between 450 and 800 °C. Catalytic reactions were performed at 300 °C, and they found that the highest conversion (44%) and selectivity (50%) was obtained for HTC calcined at 600 °C. Selectivity to n-butanol can often be increased when the ethanol to butanol reaction is performed in the condensed phase. Riittonen et al. studied γ-Al<sub>2</sub>O<sub>3</sub>-supported metal catalysts (Ru, Rh, Ni, Pd, Pt, Ag, Au) at 250 °C and autogenous pressures of up to 10 MPa. They found a Ni/Al<sub>2</sub>O<sub>3</sub> catalyst (20.7 wt % Ni) provided the best results giving good ethanol conversion (25%) with excellent selectivity to n-butanol (80%) after 72 h.<sup>15</sup> Recently, Jordison and co-workers found that yields of higher alcohols up to 38% with total higher alcohol selectivity of 85% can be obtained using a Ni/La<sub>2</sub>O<sub>3</sub>/γ-Al<sub>2</sub>O<sub>3</sub> (8 wt % Ni, 9 wt % La) mixed oxide system at 230 °C for 10 h. A maximum selectivity to n-butanol of 51% was achieved. They speculated that the increase in selectivity observed with the Ni/La<sub>2</sub>O<sub>3</sub>/γ-Al<sub>2</sub>O<sub>3</sub> system over the lanthanum free Ni/Al<sub>2</sub>O<sub>3</sub> system (higher alcohol yield 26%, n-butanol selectivity 45%) was due to the lanthanum-containing catalyst having the most appropriate balance of metal, acid, and base sites to facilitate the multistep Guerbet mechanism.<sup>16</sup> Dziugan and co-workers have also used a supported Ni catalyst (20% Ni/Al<sub>2</sub>O<sub>3</sub>) to convert raw and rectified bioethanol to n-butanol in a continuous process. A 13% yield of n-butanol (selectivity, 27%) could be obtained in a single pass using “rectified” bioethanol (~96% ethanol) as the feedstock at 330 °C and 12 MPa. Even raw bioethanol, obtained using very high gravity fermentation of thick sugar beet juice (~83% ethanol), gave 8% yield of n-butanol (selectivity, 35%) under milder conditions (310 °C and 8 MPa).<sup>17</sup> Earley et al. obtained high yields of ethanol (30%) using a mixed Cu/CeO<sub>2</sub> catalyst in a continuous flow supercritical CO<sub>2</sub> reactor at 250 °C, although n-butanol selectivity was modest at 45%. CO<sub>2</sub> was found to be beneficial and the authors suggested that its role might be to regenerate Ce<sup>4+</sup> species, which are active in the aldol step of the Guerbet cycle.<sup>18</sup>

Hydroxyapatite (Ca<sub>10</sub>(PO<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub>, HAP) catalysts have also been studied for Guerbet chemistry.<sup>10–12</sup> HAP catalysts exhibit both acidic and basic sites within their structures, and the ratio of these sites can be varied by modifying the Ca/P ratio. Increasing this ratio reduces the number of acidic sites, and this has been found to increase n-butanol selectivity by favoring dehydrogenation over the competing dehydration pathway to ethylene. For example, Tsuchida studied the Guerbet reaction of ethanol at 400 °C using HAP catalysts with different Ca/P ratios.<sup>19</sup> An optimum Ca/P ratio of 1.64 gave n-butanol in up to 70% selectivity at 23% ethanol conversion. Ogo and co-workers found that n-butanol selectivity could be increased by modifying HAP by replacing Ca ions with Sr ions leading to more basic catalysts.<sup>20</sup> Using strontium HAP increased the n-butanol selectivity to 81% (from 74% for the unmodified HAP) albeit at low ethanol conversion (<8%). Further gains were made by increasing the Sr/P ratio to 1.70 with n-butanol selectivity increasing to 86% at 11% ethanol conversion. The authors found that replacing phosphate ions for vanadate ions was detrimental to n-butanol selectivity.<sup>21</sup>

Xu et al. explored the use of homogeneous (vide infra) and heterogenized Ir-phenanthroline systems for the self-condensation of alcohols in the aqueous phase.<sup>22</sup> Several phenanthroline

ligands were tested with the best results achieved when using the water-soluble ligand **1** (Figure 1). Although the primary

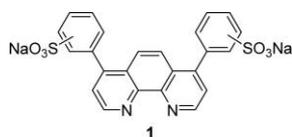


Figure 1. Phenanthroline-based ligand **1** used by Xu et al.

focus of the paper was on the conversion of n-butanol to 2-ethylhexanol, the catalysts were also investigated for activity in the ethanol to n-butanol reaction. The heterogeneous catalyst was prepared by immobilization of in situ-generated Ir-phenanthroline complexes on activated carbon (5 wt % Ir) followed by pyrolysis. Using this catalyst in the aqueous phase with potassium hydroxide base (1 equiv wrt ethanol) at 160 °C for 16 h, n-butanol yields of up to 25% could be obtained (selectivity, 56%). The catalyst was reused without loss of activity, and Ir leaching was not observed.

Zhang and co-workers have reported a hydrothermal synthesis of n-butanol from ethanol over commercial cobalt powder with NaHCO<sub>3</sub> in water. Selectivity of up to 74% could be obtained, but conversions were very low (<3%), only rising to 10%, with a concurrent drop in selectivity to 62%, after 20 days of reaction.<sup>23</sup>

While recent years have undoubtedly seen an explosion of interest in heterogeneous ethanol to n-butanol Guerbet chemistry and significant advances in terms of selectivity, and despite the general technological advantages of heterogeneous systems in terms of catalyst stability, separation, cost, and applicability to continuous processes, they are still challenged by low conversion and/or selectivity. It is difficult to envisage surmounting this impasse without better understanding of the catalysts at a molecular level. In this regard, homogeneous catalysts could offer useful model systems, as well as presenting commercially realistic technology in their own right.

### 3. HOMOGENEOUS APPROACHES

There are several early reports of transition-metal catalysts for Guerbet reactions with higher alcohols (C<sub>4</sub>+), with the first homogeneous examples discovered in 1972 by Ugo. The authors reported a series of tertiary phosphine Group VIII complexes, which proved successful as butanol condensation catalysts under relatively mild conditions (110–140 °C, ambient pressure).<sup>24</sup> Over a decade later, Burk extended this work in an effort to identify a homogeneous Guerbet catalytic system.<sup>25</sup> These studies resulted in the employment of the well documented rhodium-based precatalyst di-μ-chlorotetrakis-(cyclooctene)dirhodium(I), [Rh(COE)<sub>2</sub>Cl]<sub>2</sub>. The authors found that in situ catalysis with a range of phosphine, phosphite, arsine and heterocyclic nitrogen based ligands promoted dimerization of n-butanol and n-pentanol to higher alcohols. Preliminary mechanistic studies however revealed that Guerbet activity operated via a heterogeneous rather than homogeneous route.

The first well-documented, truly homogeneous catalytic system for ethanol coupling to yield n-butanol was reported by Ishii and co-workers in 2009, utilizing a series of Ir-based catalysts.<sup>26</sup> The family of catalysts selected for screening were based on work previously published by the same group which focused on coupling primary alcohols to β-alkylated primary alcohols.<sup>27</sup> The most effective precursor complexes to emerge

from these studies were [IrCl(COD)]<sub>2</sub> (COD: 1,5-cyclo-octadiene) and [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (Cp\*: 1,2,3,4,5-pentamethylcyclo-pentadiene).

Subsequently, a successful catalytic system for ethanol homocoupling based on this earlier work was established.<sup>26</sup> Ishii used a combination of an iridium precursor complex with 1,3-bis(diphenylphosphino)propane (dppp) as a supporting ligand, 1,7-octadiene and sodium ethoxide as a base cocatalyst (Figure 2). [IrCl(COD)]<sub>2</sub> achieved butanol yields of 22%

0.01 mol% [Ir(acac)(COD)] 0.01 mol% diphosphine 1 mol% 1,7-octadiene 5 mol% NaOEt rt (2h) - 120 °C (15h)				
diphosphine =	con. %	yield %	sel. %	TON
dppp	41	21	51	1220
dppb	18	12	67	594
dppe	8	3	38	159
PPh <sub>3</sub>	7	3	43	152

Figure 2. Selected results reported by Ishii et al. using [Ir(acac)(COD)]/diphosphine system.

(selectivity, 58%), while [Ir(acac)(COD)] (acac: acetylacetonate) exhibited impressive turnover numbers (1220) with similar yields obtained (21%) but with a slight drop in selectivity (51%). After further catalyst and base screening, it was shown that the system was sensitive to the supporting ligand used (Figure 2). Significant improvements in selectivity were achieved, with 67% observed for n-butanol, albeit at a reduced conversion of 18%, using the wider bite angle bidentate phosphine ligand 1,4-bis(diphenylphosphino)butane (dppb). The smaller bite angle bidentate ligand 1,2-bis(diphenylphosphino)ethane (dppe) and monodentate triphenylphosphine, gave poor conversions and lower selectivity. Interestingly, 1,7-octadiene, proposed to have a role as a sacrificial hydrogen acceptor, was crucial to achieve turnover. Because the Guerbet reaction is stoichiometrically neutral in terms of hydrogen production and consumption, presumably this acceptor is only actually needed for catalyst initiation, or significant quantities of non-Guerbet products (for example, ethyl acetate or metal acetates via Tishchenko/Cannizzaro-type pathways)<sup>28</sup> should be observed. The need for this 1,7-octadiene additive adds experimental complexity and limits industrial viability. The selectivity of the catalyst is also modest, with the expected higher alcohol products (2-ethyl-1-butanol, n-hexanol, 2-ethyl-1-hexanol, and n-octanol) accounting for over 30% of the products even with the best performing catalysts.

Ruthenium has previously demonstrated excellent performance in both dehydrogenation and borrowed hydrogen chemistry,<sup>8</sup> and it would seem to be an ideal candidate for homogeneous ethanol to butanol catalysis. In 2010, a patent from the Mitsubishi Chemical Corporation described the use of Group VIII-X metal complexes with supporting phosphine ligands for the conversion of ethanol to n-butanol.<sup>29</sup> In the examples provided, the transition-metal precursors [Ru(acac)<sub>3</sub>], [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>], and [RhCl<sub>3</sub>].3H<sub>2</sub>O were tested with an excess of triphenylphosphine and potassium tert-butoxide base cocatalyst under various pressures of hydrogen. n-Butanol yields of up to 21% were achieved with selectivity as high as 93% when using 0.5 mol % [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>], 3.5 mol % PPh<sub>3</sub>,

and 3.5 mol %  $\text{KO}^t\text{Bu}$  base (180 °C, 2 MPa hydrogen, 3 h reaction time). The reaction proceeded with *o*-xylene added as a solvent or with neat substrate. Performing the catalysis without a hydrogen atmosphere was detrimental to *n*-butanol yield (18%) and selectivity (59%). The Rh system performed similarly with *n*-butanol obtained in 20% yield with 93% selectivity.

In 2011, we reported ruthenium complexes containing small bite angle diphosphine ligands that, at the time, exhibited unprecedented performance.<sup>30</sup> During initial catalyst screenings, the dimeric  $[\text{RuCl}_2(\eta^6\text{-p-cymene})]_2$  species was selected as a catalytic precursor, with a variety of bidentate phosphine ligands (Figure 3). Initial experiments gave highly promising

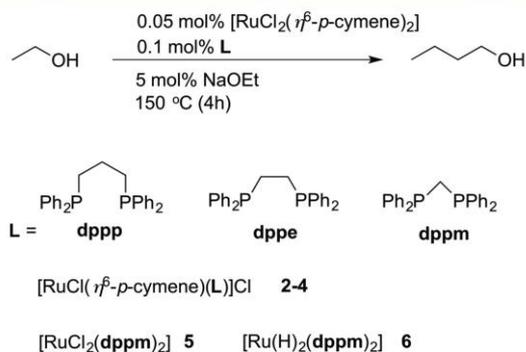


Figure 3. Reaction conditions, ligands, and complexes tested by Wass and co-workers.

results of 90% *n*-butanol selectivity (17% yield) within the liquid product fraction when 1,1-bis(diphenylphosphino)methane (dppm) was used, wider bite angle ligands (dppe, dppp) being less successful (up to 11% yield). Preformed complexes 2–4 gave similar results to catalysts formed in situ with a slight improvement in yield (21%) and selectivity (94%) observed for complex 4. Neither hydrogen or hydrogen acceptors such as 1,7-octadiene were needed for good performance. Adding two equivalents of diphosphine per Ru, or preforming catalyst precursors of the type  $[\text{RuX}_2(\text{dppm})_2]$ , 5–6 (X = Cl, H), in general gave a less active catalyst but one that was longer lived, so that conversions over 40% could be achieved, still at good (>85%) selectivity. Preliminary mechanistic studies indicated the crucial role of the ruthenium catalyst in controlling the formation of the C–C bond in the aldol coupling step; when acetaldehyde was exposed to base in typical reaction conditions in the absence of ruthenium, a mixture of higher-molecular-weight materials was obtained with little C<sub>4</sub> product. By contrast, adding the ruthenium catalyst, even with neat acetaldehyde, favored the formation of C<sub>4</sub> product. The precise role of the catalyst in this regard is still to be elucidated, but it is tempting to suggest an on-metal condensation reaction.

Building on these results, mixed donor chelating phosphine-amine ligands have also exhibited good performance (Figure 4).<sup>31</sup> High selectivity (>90%) and good conversion (up to 31%) was achieved, and this family of ruthenium catalysts also exhibited enhanced activity at higher water concentrations than can be tolerated by the  $[\text{RuCl}_2(\eta^6\text{-p-cymene})]_2/\text{dppm}$  system. Surprisingly, the related PNP complex 14, which is a very active catalyst for converting ethanol to ethyl acetate<sup>32</sup> gave very low yields of *n*-butanol (yield, 2%, selectivity, 12%) with a higher proportion of ethyl acetate formed (yield, 5%, selectivity, 41%)

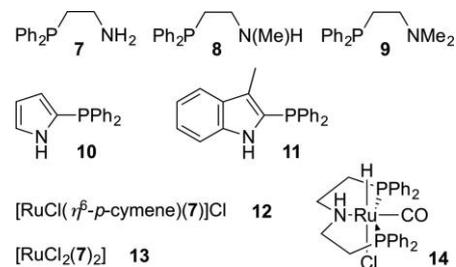


Figure 4. Phosphine-amine ligands and complexes tested by Wass and co-workers.

under our reaction conditions, thus implying a genuine ligand effect on selectivity. Mechanistic investigations with complex 12, utilizing in situ electrospray ionization mass spectrometry (ESI-MS) and  $^1\text{H}$  and  $^{31}\text{P}\{^1\text{H}\}$  NMR spectroscopy allowed for examination of some of the organometallic species formed during a typical catalytic reaction. The ruthenium hydride species 15 was observed in the early stages of the experiment, as well as an unusual complex, 16, resulting from the insertion of an acetaldehyde fragment into the metal–ligand structure (Figure 5). This complex implies the expected presence of

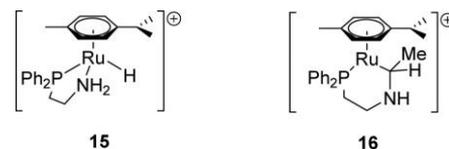


Figure 5. Intermediates observed during ESI-MS reaction monitoring under Guerbet-type conditions.

acetaldehyde formed by ethanol dehydrogenation. Another species of interest was a complex formulated to have a bound C<sub>4</sub> aldol product, giving indirect evidence for an on-metal cycle for this step of catalysis.

As highlighted earlier, Xu and co-workers reported the use of a heterogenized supported Ir phenanthroline system for the conversion of ethanol to *n*-butanol in water. They also investigated various homogeneous versions in the same paper.<sup>22</sup> The best catalyst tested was  $[\text{Ir}(\text{OAc})_3]$  with 10 equiv (wrt Ir) of ligand 1 (Figure 1), potassium hydroxide (1.5 equiv wrt ethanol), and sodium acetate (1 equiv wrt ethanol) at 150 °C for 16 h to obtain 26% yield of *n*-butanol (selectivity, 50%). The performance was very similar to that obtained with the heterogenized analogue.

Jones and Baker have reported very selective catalysts based on iridium complexes and a series of unusual transition-metal bases (Figure 6).<sup>33</sup> The Ir catalyst, 17, itself is based on previous dehydrogenation studies performed by Fujita and Yamaguchi, and bears a functional  $\alpha$ -hydroxypyridine motif.<sup>34</sup> Basic transition-metal hydroxide complexes  $[\text{Tp}'\text{Ni}(\mu\text{-OH})_2]$ , 18 (Tp': tris(3,5-dimethyl-pyrazolyl)borate), and  $[\text{IPr}\text{CuOH}]$ , 19 (IPr: 1,3-bis(2,6-diisopropyl-phenyl)-1,3-dihydro-2H-imidazo-2-ylidene), both of which have been shown to act as strong bases in stoichiometric reactions, were investigated. The system this group utilized does not require a hydrogen acceptor and gave excellent results for the homocoupling of ethanol to *n*-butanol. Using iridium catalyst 17 and the two sterically encumbered nickel or copper basic catalysts, under optimized conditions, conversions of up to 37% (using 18) and unprecedented selectivity of >99% were achieved. In order to determine the origin of the superior selectivity, focus was given

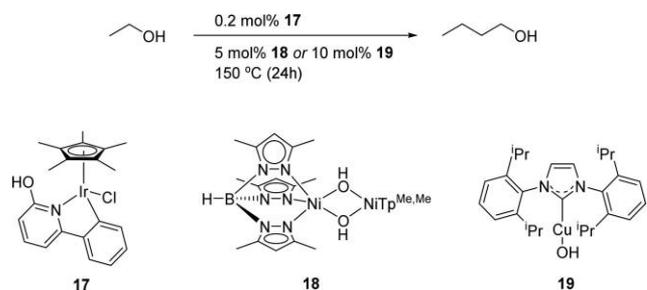


Figure 6. Catalytic system employed by Jones, Baker, and co-workers using Ir catalyst 17 and highly basic transition-metal complexes 18 and 19 with sterically encumbered ligands.

to the basic transition-metal-catalyzed aldol coupling step. Remarkably, the authors observed that the Ni or Cu catalyzed condensation step gave exclusively crotonaldehyde, whereas analogous runs using KOH gave crotonaldehyde at only 23% selectivity. This selectivity to crotonaldehyde under Guerbet conditions is unprecedented in the literature, and it was confirmed by attempting to couple 1-butanol and observing, at most, only trace amounts of the resultant  $\alpha$ - $\beta$ -unsaturated C<sub>8</sub> aldehyde. These results indicate that steric crowding at the metal centers of the two transition metals, Ni and Cu, may be fundamental in determining the level of aldol coupling and product distribution. Additional studies confirmed that the basic Ni<sub>2</sub> and Cu complexes, 18 and 19, were not involved in the dehydrogenation step, yet it remains possible that the Ir catalyst assists in the aldol coupling step.

Szymczak and co-workers reported an amide-derived N,N,N'-ruthenium complex that also shows excellent activity for the conversion of ethanol to n-butanol (Figure 7). This originated

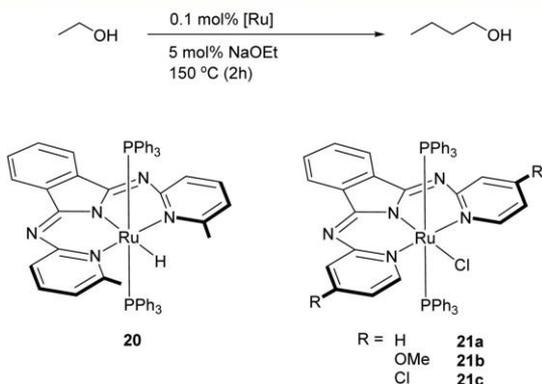


Figure 7. Ru(II) catalysts tested by Szymczak et al.

from earlier work by the same group, which involved utilizing an N,N,N'-bMepi ruthenium(II) hydride catalyst, 20, in transfer hydrogenation reactions (bMepi: 1,3-bis(6'-methyl-2'-pyridyl-imino)isoindolate), specifically for reversible transformations between ketones and alcohols.<sup>35</sup>

Subsequent to mechanistic studies of catalyst 20 and the evidence gained that transfer hydrogenation occurred via an inner-sphere  $\beta$ -H elimination pathway, it was postulated that a structurally similar family of bis(pyridylimino)-isoindolate (bpi) ruthenium(II) complexes, 21a-c, would therefore be suitable for alcohol upgrading catalysis (Figure 7).<sup>36</sup> Most notably, the Ru(II) catalyst 21a carried forward for optimization experiments demonstrates catalytic performance that is unaffected in the presence of oxygen (n-butanol yield, 27%, selectivity, 83%).

Unlike the high selectivity reported by Jones and Baker, and ourselves, this catalyst appeared to allow higher alcohols to compete for substrate coordination/activation and hence give higher alcohols. This was confirmed by experiments that used 20% n-butanol by volume, and observing an increase in yield from 4% to 12% of the higher alcohol Guerbet products in the liquid fraction. Finally, in order to minimize a decarbonylation deactivation pathway, excess phosphine ligand, PPh<sub>3</sub>, was added to the reaction to limit phosphine dissociation. Addition of one equivalent proved sufficient in raising the activity of the catalyst to 49% conversion (selectivity, 84%), whereas 4 equiv did not seem to make as much of an impact, with a conversion of 53% (selectivity, 78%).

Pincer complexes of ruthenium with P-N-P donor sets are reported by Milstein and co-workers to also be very effective catalysts for this transformation under similar conditions.<sup>37</sup> A range of complexes were investigated, the best results coming from an acridine-based ligand system 22 (Figure 8) which gave

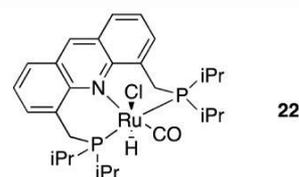


Figure 8. Pincer-type complexes reported by Milstein and co-workers.

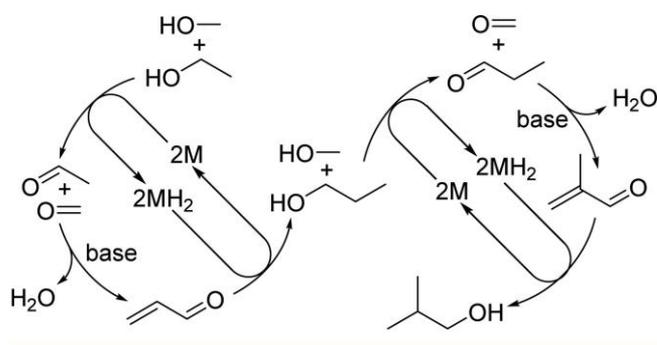
very high turnover numbers (in excess of 18 000) at low (0.001 mol %) catalyst loading and good ethanol conversion (73%) at 0.02 mol % catalyst. Similarly to the Szymczak system, these catalysts more readily react with the higher alcohols produced, so that this high conversion is balanced by more modest selectivity to butanol (36% yield to C<sub>4</sub> at 73% ethanol conversion) with significant amounts of C<sub>6</sub> and C<sub>8</sub> alcohol side products. Preliminary mechanistic studies suggest an active complex in which the central acridine heterocycle is dearomatized; a hydrido dicarbonyl ruthenium complex of such a ligand was structurally characterized from a post reaction solution.

#### 4. FROM n-BUTANOL TO ISOBUTANOL

Although n-butanol is a superior fuel to ethanol, the branched isomer isobutanol has even more desirable characteristics,<sup>38</sup> making it an interesting target for catalysis. It is not obvious how Guerbet chemistry could be adapted for the direct conversion of ethanol alone to isobutanol; however, the co-condensation of methanol (which could also be obtained via biosustainable sources) and ethanol is an attractive potential route. Using these substrates, methanol and ethanol are dehydrogenated to formaldehyde and acetaldehyde, which undergo aldol coupling to yield, after rehydrogenation, n-propanol. A further dehydrogenation, aldol coupling, rehydrogenation cycle with a second equivalent of methanol yields isobutanol (Scheme 3). Achieving high selectivity to isobutanol rather than the various other possible alcohol coupling products (for example, ethanol-ethanol to n-butanol) is crucial to a viable process.

Ueda reported the first example of methanol/ethanol co-condensation via the Guerbet reaction.<sup>39</sup> They studied different metal oxide catalysts (MgO, ZnO, CaO, ZrO<sub>2</sub>) at atmospheric pressure in a continuous-flow reaction system. MgO gave the best results at 360 °C, converting 60% ethanol to mixtures of n-

Scheme 3. Co-Condensation of Methanol and Ethanol via Guerbet Chemistry



propanol (selectivity, 29%) and isobutanol (selectivity, 46%). Small amounts of other products, including n-butanol, acetaldehyde, and 2-methylpropan-1-ol, were also obtained. CaO proved to be a poor catalyst providing very low conversions (0.8%), ZnO produced mainly acetaldehyde, and ZrO<sub>2</sub>, being more acidic, gave ethers via dehydration. Incorporating metal ions such as Mn, Cr, and Zn (3 wt %) reduced conversion (32–35%) and showed stronger preference for dehydrogenation with a marked increase in selectivity toward acetaldehyde (32–47%) and a concurrent decrease in selectivity to isobutanol (4–10%) and n-propanol (12–24%). In a later paper, they proved that rapid hydrogen transfer occurred between adsorbed species by utilizing isotope exchange reactions. From these results, they proposed that hydrogen transfer from methanol takes place to hydrogenate C–C and C–O bonds of adsorbed unsaturated species before desorption, facilitating the formation of saturated alcohols, and resulting in high selectivity toward n-propanol and isobutanol.<sup>40</sup>

In 2002, Carlini and co-workers investigated heterogeneous copper-containing catalysts for the co-condensation of methanol with ethanol.<sup>41</sup> Three catalysts, Cu-Raney, a commercial Cu-chromite catalyst (wt % Cu, 36.0, Cr, 33.0, Mn, 3.0), and a zinc-modified Cu-chromite catalyst (wt % Cu, 32.6, Cr, 21.9, Zn, 8.4%), were tested on the basis of previous work from the same group on co-condensation of n-propanol and methanol.<sup>42</sup> All three catalysts were active at 180 °C in batch experiments with sodium methoxide as a cocatalyst giving ethanol conversions of 11–32% and high selectivity to isobutanol (79–83%). After optimizing the reaction conditions (200 °C, 6 h, 5 mol % catalyst, 3.15 equiv NaOMe wrt ethanol,

30 MPa N<sub>2</sub>) the most productive catalyst, Cu-chromite, exhibited an ethanol conversion of 61% with very high selectivity to isobutanol (98%, isobutanol yield, 60%). A large excess of NaOMe was used in order to counteract the deactivation of the basic catalyst by hydrolysis to inactive sodium hydroxide. Two moles of water are formed for every mole of isobutanol generated during the condensation reaction, and reduced activity occurred when the amount of base was lowered. The catalyst displayed exclusively heterogeneous activity as Cu leaching was not detected. Carlini et al. have also widely investigated the related co-condensation of methanol and n-propanol with both heterogeneous Ru, Rh, Ni and Pd supported catalysts (isobutanol yields up to 49, 59, 55, and 93%, respectively) and homogeneous Ni and Pd catalysts (isobutanol yields up to 39 and 84%, respectively). However, decomposition to metal precipitates was noted with the homogeneous systems, suggesting dual heterogeneous/homogeneous activity.<sup>43</sup>

Olsen reported very high ethanol conversions and isobutanol yields using MgO impregnated carbon based catalysts (10–20 wt % MgO). The reactions were performed in a tubular-flow-through reactor at 360 °C for 1 h. A methanol/ethanol ratio of 7.2 was used at a flow rate of 0.1 mL min<sup>-1</sup> with a N<sub>2</sub> carrier flow rate of 66 mL min<sup>-1</sup>. Several carbon-based catalysts were evaluated and the highest yield of isobutanol obtained was 85% using a proprietary catalytic carbon support. This was achieved at 100% ethanol conversion, with the other products being mainly 2-methylpropanol (6% yield), n-propanol (2%), and 2-methylbutanol (5%). Incorporating Ni (0.6 wt %) into another MgO-carbon based catalyst (based on Calgon 400) led to an even higher isobutanol yield of 90%.<sup>44</sup>

Liu and co-workers have used an immobilized Ir catalyst for the upgrading of ethanol and methanol mixtures to isobutanol in air using water as a solvent.<sup>45</sup> The authors used an N-functionalized carbon support synthesized by mixing a protic salt of phenanthroline with an activated carbon in water and ethanol, followed by removal of the solvents and calcining at 900 °C. Ir was incorporated by mixing IrCl<sub>3</sub>·xH<sub>2</sub>O with the support in water and reducing with NaBH<sub>4</sub>. An oxidation treatment at 250 °C in air for 8 h afforded the supported Ir catalyst (5 wt % Ir). Co-condensation of methanol and ethanol was performed in an autoclave in air at 160 °C using water as a solvent and a catalyst loading of 0.48 mol %. After optimizing conditions K<sub>3</sub>PO<sub>4</sub> (1 equiv, wrt ethanol) was found to be the most suitable base with isobutanol produced in 91% selectivity at 52% conversion after 32 h. The catalyst was amenable to recycling and was used five times with only a small reduction in activity and selectivity. Interestingly, the catalyst was also able to convert a fermentation broth (after treatment with activated carbon, ~ 95% ethanol) to give comparable results to pure ethanol runs under similar conditions (conversion, 49%, selectivity to isobutanol, 90%).

Recently, we reported that bis-chelate diphosphine and mixed donor P–N ruthenium systems, previously having shown promise in ethanol homocoupling (Figure 9), were also active

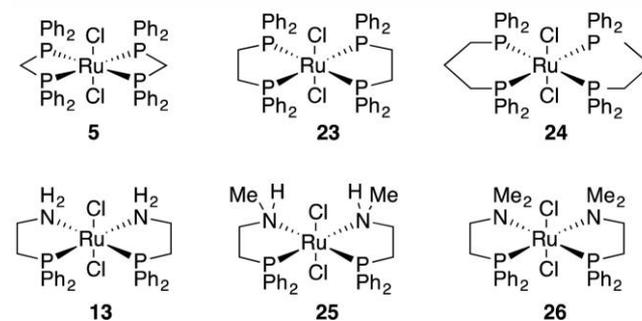


Figure 9. Ruthenium(II) complexes tested for co-condensation of methanol/ethanol by Wass and co-workers.

catalysts for the cross condensation of methanol with ethanol.<sup>46</sup> Complex 5 featuring the small bite angle ligand dppm was again the most successful with isobutanol yields of up to 75% obtained in 99.8% selectivity (180 °C, 20 h). An excess of methanol (molar methanol/methoxide: ethanol 16.4:1) was chosen to minimize possible ethanol homocoupling. As with previous studies for isobutanol synthesis, a high concentration of sodium methoxide base was used (up to 2 equiv wrt ethanol) with a reduction in base found to be detrimental to the system. Catalyst 5 was also active when cheaper hydroxide base was used and when using wet ethanol (2 equiv added at start of run

wrt ethanol) to give essentially the same result as when anhydrous conditions were used. Additionally, over shorter reaction times (2 h), catalyst 5 was still very active (yield, 65%, selectivity, 98%).

Unlike the homogeneous catalysts tested by Carlini for the condensation of methanol and n-propanol,<sup>43</sup> catalyst 5 appeared to be stable with no metal precipitation observed. Extremely low activity (<5% ethanol conversion) was observed for complexes 23 and 24 with wider bite angle diphosphines. The P–N ligand complexes (13, 25–26) were also less successful, but with longer reaction times (20 h), reasonable conversion (29–55%) and good selectivity (90–95%) were achieved. Some loss in activity was observed as the amine group was methylated, but moderate activity was still observed with the fully methylated ligand, seemingly ruling out an outer-sphere type mechanism. A Guerbet-type mechanism was supported by the observation of the intermediate propanol as a minor product in reactions. This was further corroborated by a labeling study in which <sup>13</sup>CH<sub>3</sub>OH was used under standard conditions with unlabeled ethanol. The <sup>13</sup>C label was observed by NMR spectroscopy to be exclusively in the methyl positions of the isobutanol product, as expected from the proposed series of aldol condensations.

## 5. CONCLUSION AND OUTLOOK

In many ways, the main aim of this Perspective article is to alert the homogeneous catalysis community to the importance of ethanol to butanol catalysis as an objective. There have been a series of very recent advances in this regard, suggesting the area is on the cusp of rapid expansion.

It seems remarkable that a reaction first reported more than 100 years ago still has so many facets that are unexplored. Clearly, there are many opportunities for ligand and complex development; a variety of donor groups have shown promise but an understanding of ligand structure property relationships is, as yet, underdeveloped. There would also seem to be possibilities away from ruthenium and iridium, the metals that have been the focus of developments to date. More fundamentally, there are unanswered questions regarding mechanism that could unlock possibilities for rational catalyst design. The Guerbet reaction has many cousins in other types of dehydrogenative catalysis, such as Tishchenko and Cannizzaro chemistry,<sup>28</sup> which lead to other (still valuable) products such as organic and inorganic acetates. At higher temperatures for heterogeneous catalysts, many of the products for Guerbet chemistry are intermediates en route to butadiene via Lebedev chemistry.<sup>47</sup> The subtle changes to ligand structure and reaction conditions, which can lead to these different pathways being followed, are not understood.

Homogeneous catalysts also clearly have a role to play as model systems for heterogeneous systems, which have seen a similar and parallel increase in interest. The well-known advantages of heterogeneous catalysis in terms of process development certainly place them in pole position for commercial operation. However, it would be wrong to rule out the industrial adoption of homogeneous catalysts for this application if they continue to offer the best performance in terms of selectivity; it is not too great a leap of imagination to move from the highest volume commodity petrochemical processes using homogeneous catalysis, for example, hydroformylation, to processes at the fuel scale. One certainty is that this renewed interest in ethanol to butanol chemistry make

Guerbet chemistry increasingly important as it enters its second century.

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Notes

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