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State-of-the-art advances in homogeneous molecular catalysis for the Guerbet upgrading of bio-ethanol to fuel-grade bio-butanol

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The upgrading of ethanol to *n*-butanol marks a major breakthrough in the field of biofuel technology, offering the advantages of compatibility with existing infrastructure while simultaneously offering potential benefits in terms of transport efficiency and energy density. With its lower vapour pressure and reduced corrosiveness compared to ethanol, *n*-butanol is easier not only to manage but also to transport, eliminating the need for costly infrastructure changes. This leads to improved fuel efficiency and reduced fuel consumption. These features position *n*-butanol as a promising alternative to ethanol in the future of biodiesel. This review article delves into the cutting-edge advancements in upgrading ethanol to butanol, highlighting the critical importance of this transformation in enhancing the value and practical application of biofuels. While traditional methods for making butanol rely heavily on fossil fuels, those that employ ethanol as a starting material are dominated by heterogeneous catalysis, which is limited by the requirement of high temperatures and a lack of selectivity. Homogeneous catalysts have been pivotal in enhancing the efficiency and selectivity of this conversion, owing to their unique mode of operation at the molecular level. A comprehensive review of the various homogeneous catalytic processes employed in the transformation of feedstock-agnostic bio-ethanol to fuel-grade bio-*n*-butanol is provided here, with a major focus on the key advancements in catalyst design, reaction conditions and mechanisms that have significantly improved the efficiency and selectivity of these Guerbet reactions.

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Introduction

Fossil fuels are the major source of energy, currently accounting for about 80% of the world's primary energy demand. Their exploration and utilization are associated with numerous challenges, including greenhouse gas emissions.[1–3] Their fast depletion, in combination with the ever-increasing energy demand, has become a major concern for energy imbalance (Fig. 1). Greenhouse gas emissions contribute to growing climate change and must be addressed through the implementation of new energy strategies.[4–7] The need for sustainable energy alternatives has triggered significant research attention in this direction. Consequently, there is a major shift in global emphasis towards alternative and renewable energy sources. The use of biofuels as an energy source has gained considerable attention from researchers, corporations and governments worldwide.[8–12] In fact, biofuels are expected to be a game changer, significantly contributing to the reduction in carbon emissions.

In this context, the upgrading of feedstock-agnostic ethanol into *n*-butanol and higher alcohols is advantageous not only because these higher alcohols have better fuel properties, including higher energy content and improved compatibility with existing fuel infrastructure, but also owing to the ready availability of ethanol from abundant biomass resources.[14] Thus, in comparison to conventional gasoline, *n*-butanol is emerging as a sustainable fuel, considering the ready access to its precursor ethanol through diverse biomass fermentation processes. Besides being a renewable energy source, *n*-butanol also results in lower greenhouse gas emissions. For example, the combustion of 1 kg of *n*-butanol emits less CO_2 while yielding equivalent amounts of energy in comparison to the CO_2 emissions from gasoline, as shown in Fig. 2.[15] On the other hand, a large amount of ethanol is required for an equivalent amount of energy, which again leads to higher CO_2 emissions (Fig. 2). Consequently, the global market for *n*-butanol is growing and is estimated to reach 2.8 million tons annually, worth around 5 billion USD.[16,17a]

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Sunil Dhole

Sunil Dhole is a serial entrepreneur with Master's and PhD degrees in Chemical Engineering from IIT Kanpur, earned in 2006, and completed his postdoctoral studies at UCL, Belgium, in 2008. His research focus areas range from polymers, membranes, nanotechnologies, and separation technologies to green technologies. Currently, his membrane-based drinking water purification products serve more than 7 million people per day in India. He is the founder and director of more than 5 companies.

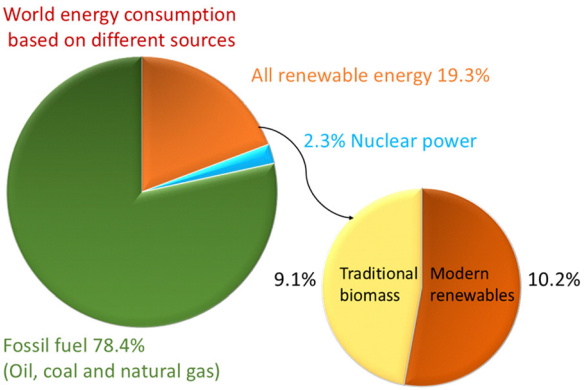


Fig. 1 World energy consumption in terms of energy obtained from different sources.[13]

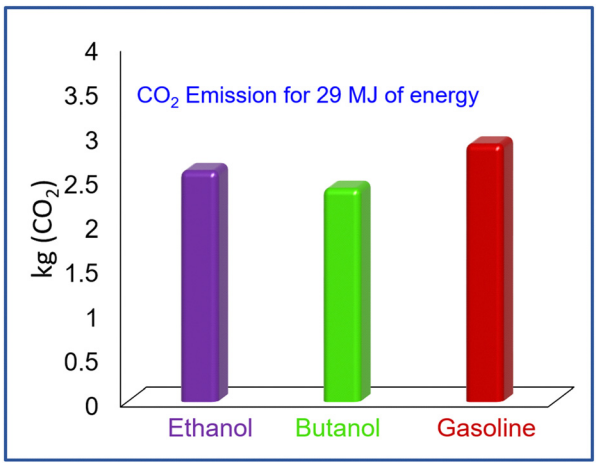


Fig. 2 Comparison of CO_2 emissions from gasoline, butanol, and ethanol while generating 29 MJ of energy.[13]

Apart from its potential use as a fuel, *n*-butanol, a four-carbon alcohol, plays a crucial role in a wide range of industries, including chemicals, pharmaceuticals, and energy.[17b–e] One of the primary uses of *n*-butanol is as a solvent for coatings (varnishes, resins and waxes), and in paints for providing smoother application and better finish.[17b] *n*-Butanol is also used in the manufacturing of various esters, such as butyl acetate and butyl acrylate, which is used in the production of co-polymers and homopolymers.[17c] Furthermore, *n*-butanol is a key ingredient in the production of plasticizers, which are chemical additives that are added to polymers to enhance mechanical properties, such as processability and ductility, especially in the manufacturing of PVC.[17d] The pharmaceutical industry also greatly benefits from *n*-butanol, as it is an effective solvent for extracting fairly water-soluble products.[17e] Another significant advantage of *n*-butanol is its relatively low toxicity and environmental impact when compared to other industrial solvents. Additionally, *n*-butanol is biodegradable, further reducing long-term environmental risks. As industries continue to prioritize green chemistry and sustainable practices, *n*-butanol's eco-friendly properties make it a popular choice as a cleaner alternative in various applications.[17]

Akshai Kumar

Akshai Kumar is from Mangalore, India, and completed his Bachelor's degree in 2002 from Mangalore University. He also obtained an MSc in 2004 with specialization in inorganic chemistry. He was awarded a PhD degree in 2009 for his research on organometallics under the supervision of Prof. Ashoka G. Samuelson at the Indian Institute of Science, Bangalore. After a postdoctoral position in the same laboratory, he joined the group of Prof. Andreas Terfort at Goethe University, Frankfurt, Germany, as a postdoctoral fellow in October 2010. In 2012, he extended his postdoctoral activities and worked in the Goldman group at Rutgers, The State University of New Jersey, New Brunswick. In 2015, he was appointed as an Assistant Professor in Chemistry at the Indian Institute of Technology Guwahati. Currently, he is an Associate Professor in the Department of Chemistry and the Head of the Centre for Nanotechnology at Indian Institute of Technology Guwahati. His research activities are broadly focused on organometallics, catalysis, organofluorine chemistry and mechanistic studies, with particular emphasis on pincer–metal-catalyzed C–H and C–F activation reactions for the synthesis of heteroatom-doped π-conjugated organic materials, hydrogen, fuel, and fine and specialty chemicals.

(Bio)ethanol and (bio)butanol as biofuels

The use of biofuel is an attractive alternative energy source. Back in 1912, Rudolf Diesel introduced peanut oil to an engine as a fuel.[17a,18,19] Henry Ford and Nikolaus August Otto proved that pure ethanol was able to run an engine with their respective motors. However, in 2005, David Ramey drove a car using butanol instead of gasoline across the United States.[20] A reduced emission of CO, hydrocarbons, and NOx was observed, although it consumed about 9% more butanol than gasoline, (**https://www.butanol.com/**, as of 22 August 2022).[17a] Recently, the Navigant research provided an approximate increase in demand of energy (biofuel) worldwide for *n*-butanol compared to other valuable alcohols (Fig. 3).

Biofuel can be produced from biomasses, which are biodegradable and are renewable. There are a large variety of available biofuels, such as ethanol, *n*-butanol, biodiesel and syngas.[21] Biofuels are present in different physical states, such as solid, liquid or gas. The primary fuels (*i.e.*, solid) are more often used for energy production (*e.g.*, wood and charcoal, Table 1),[22] while the secondary fuels (*i.e.*, liquid and gas) are used for transportation.[22] The four-carbon containing *n*-butanol, which up to recently was largely produced in the petrochemical industry, finds utility as a precursor to specialty

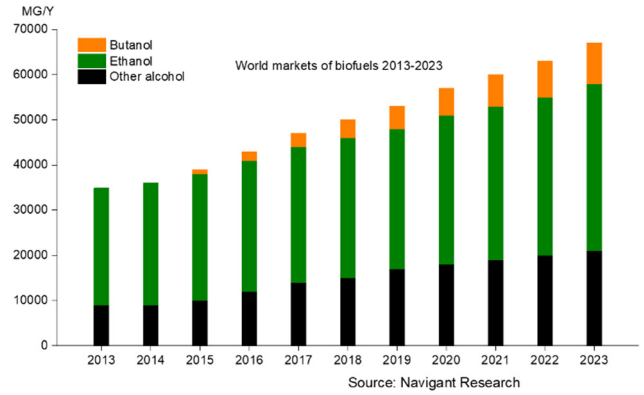


Fig. 3 Trend in annual global biofuel production by fuel type.[13] Image taken from an open-access article[13] licensed under Creative Commons Attribution 4.0, which permits unrestricted use, distribution and reproduction in any medium.

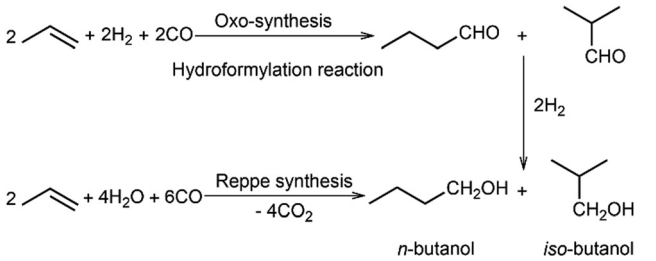
chemicals, solvents and supplements of biofuels.[23] Butanol has more advantages over other biofuels due to its higher energy density and high self-ignition temperature.[24] Another advantage of *n*-butanol is its low flammable nature, low volatility, and it also possesses low vapour pressure.[25] Interestingly, *n*-butanol can blend up to 85% for unmodified petrol engine compared to ethanol, which reaches up to only 10%.

While ethanol is regarded as a viable alternate fuel, it suffers from several limitations. These include a poor energy density (69% with respect to gasoline, Table 1),[26–29] corrosive nature[30] and higher water absorptivity[26,31,32] that poses challenges in its handling under advanced technologies. These limitations can be overcome by using butanol, which offers a higher energy density, *i.e.*, 86% of that of gasoline (see Table 1). Furthermore, butanol is both non-corrosive and water-insoluble.[19,30]

Among several methods known in the literature, *n*-butanol is efficiently produced by the simple hydrogenation of its common precursor, like crotonaldehyde.[33] It is noteworthy that the conversion of a C_2 or C_3-containing hydrocarbon to a higher C_4 hydrocarbon is an alternative and attractive methodology *via* hydroformylation or hydrocarbonylation reaction.[34,35] For instance, oxo synthesis of propylene gas in the presence of carbon monoxide and hydrogen by a cobalt or rhodium catalyst results in isobutyraldehyde and butyraldehyde production.[36]

Table 1 Comparison of the properties of various fuels[21]

Entry	Fuel	Specific energy (MJ kg^{-1})	Energy density (MJ L^{-1})
1	Methanol	−22.70	−17.80
2	Ethanol	−29.70	−23.30
3	1-Butanol	−36.10	−29.10
4	1-Hexanol	−39.00	−31.70
5	1-Octanol	−40.70	−33.50
6	Gasoline	−47.30	−33.80
7	Kerosene	−46.20	−38.30
8	Diesel	−44.80	−37.10
9	Coal (Anthracite)	−27.00	−36.40
10	Coal (Lignite)	−15.00	−12.00
11	Wood	−15.00	−9.00



Scheme 1 Classical routes to *n*-butanol.

Further hydrogenation of butyraldehyde affords *n*-butanol (oxo-synthesis; Scheme 1).[36] Similarly, in a single step, under low pressure and temperature, transition metals catalyze the reaction of propylene with carbon monoxide and water into *n*-butanol (Reppe synthesis; Scheme 1).[37]

On an industrial scale, *n*-butanol can be synthesized *via* two major pathways: (i) aldol self-condensation of acetaldehyde, followed by hydrogenation of the resulting crotonaldehyde to form *n*-butanol;[38] (ii) hydroformylation of propylene, followed by hydrogenation of butyraldehyde to butanol (Scheme 1).[39–42] Acetaldehyde can also be synthesized *via* Wacker process, which involves the oxidation of ethylene.[42] Thus, for the production of *n*-butanol, precursors like ethylene and propylene (produced from high-energy-intensive cracking of hydrocarbons) are required. Even the formation of CO involves the partial thermal oxidation of alkanes, which leads to an overall energy-intensive process.[43] Conventional *n*-butanol synthesis is currently expensive and not suitable for large-scale industrial applications. The surge in the use of *n*-butanol in blending with gasoline, owing to its better blending properties,[44] has been an attractive approach that has driven the implementation of numerous biomass valorization strategies to directly obtain *n*-butanol.[45–47] One such attractive strategy has been the upgrading of feedstock-agnostic ethanol to *n*-butanol, which is often referred to as the Guerbet reaction.

(Bio)butanol synthesis *via* the Guerbet reaction

The Guerbet reaction, which is usually catalysed by strong bases and metal catalysts, is a significant chemical transformation in which primary or secondary alcohols having a methylene group next to the hydroxylated carbon atom condenses and releases water to form higher chain alcohols.[48] Discovered by the French chemist Marcel Guerbet for the conversion of 1-butanol to 2-ethyl-1-hexanol at 200 °C in the presence of *in situ* formed sodium alkoxides in the early 20th century,[49] this reaction is particularly important for upgrading low-value alcohols, such as ethanol, into more valuable long-chain alcohols, which can serve as biofuels or intermediates in various chemical processes. Moreover, the Guerbet reaction is environmentally sustainable, as it can utilize renewable feedstocks and has the potential to decrease the global dependence on fossil fuels. Mechanistically, such process requires dehydrogenation of alcohols into its corresponding carbonyl compound, which will

undergo the aldol condensation reaction, leading to the formation of an α-β unsaturated aldehyde, followed by the elimination of water. A subsequent hydrogenation of the α-β unsaturated aldehyde will then give the desired higher alcohols.[48]

Over the years, heterogeneous catalysts have been extensively explored for the upgrading of ethanol to *n*-butanol.[50–52] Heterogeneous catalysis enables the reuse and recycling of the catalysts, significantly enhancing the practicality of the catalytic process.[53] For the Guerbet reaction, it is widely accepted that a catalyst is active only when the main active sites on the catalyst are basic sites.[54] The number of acidic and basic sites on the catalyst dictates the nature of the alcohol transformation. While the acidity of the catalyst is a very critical factor for the –OH group activation and the subsequent dehydration process, the basic sites play a crucial role in facilitating the dehydrogenation of the alcohol and its subsequent coupling.[55] Therefore, to obtain butanol in high yields, the composition of the catalyst and the density/strength of associated basic sites have become very important in generating an efficient catalyst. Various heterogeneous catalysts based on metal oxide systems,[56–64] hydroxyapatites,[65–67] and zeolites[68] are employed to accomplish the efficient transformation of ethanol to *n*-butanol. These catalysts not only aid in the conversion of ethanol, but also enable easier separation and recycling, making it an overall sustainable and economically viable process. Despite its huge success, heterogeneous catalysis is associated with several challenges, such as the requirement of a high temperature that is far beyond 250 °C, and the difficulty in attaining both high conversion and selectivity.[69] An effective reactor design is also essential in order to ensure optimal reaction conditions to maximize the overall efficiency of the process.[70a] This is particularly significant for facilitating the separation and purification of the products. Since water is produced during the reaction, which can have detrimental effect on the reaction's efficiency, implementing a reactor that can continuously separate water from the reaction can prove to be highly beneficial.

A few of these concerns could be efficiently mitigated by homogeneous molecular catalytic systems that operate with high selectivity under mild conditions.[70b–j] Opportunities that allow them to be immobilized on an inert support have been recently investigated, adding a new dimension to the field of molecular catalysts that can now potentially operate with good recyclability. Using heterogeneous catalysis in the Guerbet reaction for *n*-butanol synthesis has been reviewed extensively in several recent influential reports. From the context of the current review, an attempt is made here to provide a concise account on the current advancements in the development of homogeneous molecular catalytic systems for upgrading feedstock-agnostic ethanol to biofuel-grade butanol *via* the Guerbet reaction.

(Bio)butanol synthesis by homogeneous catalysis

Homogeneous catalysts have been extensively employed to accomplish not-otherwise possible organic transformations for several decades now.[70k–n] Until the 1960s, homogeneous catalysts primarily constituted simple acids, bases, or metal salts.[70o–q] In most cases then, the metals were not given any significant attention in terms of mechanistic considerations.[70r] The introduction of Wilkinson's hydrogenation[70b] and hydroformylation catalysts[70c] in the 1960s triggered a surge of interest in understanding the pivotal role that the metal plays in the mechanisms of these very selective reactions that are catalysed by organometallic complexes.[70d] The decades that followed have witnessed the design and development of several organometallic compounds to accomplish a plethora of industrially relevant transformations towards the synthesis of valuable chemicals.[70s–u] As researchers identified the limitation of anionic ligands (such as halides) and ancillary ligands (such as phosphines), special emphasis was focused on designing a wide range of new ligand types. The ability to tailor the functionalities and ligating atoms, along with the ease of ligand synthesis, have led to a plethora of complexes with a wide variety of metals.[70v–y] One can now pick complexes with desired steric and/or electronic parameters to suit the requirement of a particular transformation.[70v–y]

While the catalysis based on precious metals[71a–c] (such as Ru, Ir, Pt, and Pd) has enjoyed great success, recent global emphasis has shifted not only on the development of efficient catalytic systems derived from inexpensive and readily available base transition metals[71d,e] such as Mn, Cr, Cu, Fe, Co, and Ni, but also on the development of metal-free organo-catalytic systems.[71f,g] While organic acid and base catalysts have been used for many years, the recent development of organocatalysts designed for asymmetric reactions has significantly transformed the field of synthetic organic chemistry.[70e] Numerous influential reviews have thoroughly discussed the success and limitations of these homogeneous catalytic systems.[70f–j] In the context of the Guerbet reaction, which is a key method for the production of higher alcohols from lower alcohols, organometallic catalysts[71h] play a crucial role and hence have been discussed in-depth here.

Although numerous early patents[71i,72] issued by Guerbet typically involved precious metal-based homogeneous catalysts for the sequential hydrogenation/dehydration steps and an inorganic base to aid in the aldol coupling step, on a serious note, one of the first breakthroughs in the catalytic upgrading of ethanol based entirely on a homogeneous system was reported by Ishii and co-workers in 2009 using an iridium complex in the presence of a bidentate phosphine ligand.[72a] This approach not only improved the efficiency of the catalytic process, but also opened new avenues for development in biofuel production. Recent developments in homogeneous catalysis for Guerbet reactions are pushing the limits of conventional methods, enabling more efficient and sustainable processes.[71h–z] Transition metals such as ruthenium and iridium have been extensively studied for such transformation. To address the issues related with the noble metals, such as high costs, toxicity and relatively low abundance, researchers have been exploring molecular homogeneous catalytic systems based on non-noble metals, such as iron and manganese.

These alternatives not only offer a more sustainable approach, but have also demonstrated promising results in improving the overall efficiency.

Upgrading ethanol to butanol catalysed by iridium complexes containing bidentate ligands

In a pioneering work in 2009, Ishii and co-workers described a fully homogenous iridium catalytic system based on a bidentate phosphine ligand for the upgrading of ethanol to *n*-butanol. The complex **1** (0.01 mol%) in the presence of 1,7-octadiene (1 mol%) and NaOEt (5 mol%) at 120 °C could catalyse the transformation of ethanol selectively to *n*-butanol with up to 98 TON (Scheme 2). In the presence of other considered bases, such as KO^{t}Bu, KOEt, KOH and Na_2CO_3, **1** resulted in lower activity.[72a]

The authors also discussed the effect of various external ancillary ligands on the catalytic activity. The catalyst performed relatively poorly towards ethanol upgrading when it was employed in the absence of an external ligand (entry 1, Table 2). The catalyst **1** was then tested in combination with phosphine-based ligands towards the upgrading of ethanol (entries 2–5, Table 2). While the use of PPh_3 and dppe resulted in up to 7–8% conversion with exclusive formation of *n*-butanol with comparable TON (entries 2 and 3, Table 2), 0.01 mol% of the ligand **3** (dppp) in combination with 0.01 mol% of [Ir(COD)(acac)] (**1**) gave the highest ethanol conversion (*ca.* 41%) and *n*-butanol turnovers (21% yield with 1220 TON), albeit with lower selectivity (51%) (entry 4, Table 2).[72a] The function of 1,7-octadiene is anticipated as either a weak coordinating ligand or a sacrificial hydrogen acceptor. However, the Guerbet reaction is neutral in terms of hydrogen production or consumption.[72a]

Xu and Mu demonstrated the effective use of Ir–phenanthroline complexes (Fig. 4) in the selective conversion of ethanol to *n*-butanol, achieving high Guerbet selectivity without the need for hydrogen acceptors, even in the presence of water. They successfully heterogenised these molecular complexes by pyrolysis-induced immobilization of the *in situ* generated Ir–phenanthroline complexes on carbon, resulting in a highly active catalyst for the upgrading of ethanol to *n*-butanol. The prepared heterogeneous catalyst, containing 5 wt% Ir, exhibited remarkable stability, with neither loss of activity nor leaching of Ir even after two consecutive catalytic runs, yielding approximately 45% conversion and 25% yield of *n*-butanol after 16 hours.[73] In a parallel experiment, Xu and Mu explored the homogeneous Ir–phenanthroline systems as well for the conversion of ethanol to *n*-butanol in aqueous media. Notably, when combined with 10 equivalents of ligand **5**, the water-soluble homogeneous catalyst [Ir(OAc)$_3$] outperformed the heterogeneous counterpart (*vide supra*), achieving a 52% conversion and *n*-butanol yield of 26% with a selectivity of 50% under conditions devoid of additives, such as H_2 or alkenes, and under air.[73]

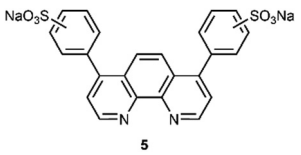


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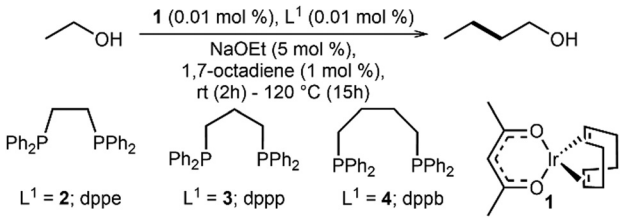
Fig. 4 Phenanthroline-based ligand used for ethanol upgrading by Xu and Mu.[73]

Li and co-workers have reported a series of Cp*Ir-based catalyst for the ethanol upgrading reaction.[74] Unlike previous reports that involved stronger bases such as NaOEt or a Ni or a Cu complex as a base, the current study utilized a relatively milder base Cs_2CO_3 (6 mol%), in the presence of 0.1 mol% of **6** at 150 °C. Under these conditions, 32% yield of *n*-butanol was obtained with 83% selectivity after 12 h. In contrast, other carbonate bases such as Na_2CO_3 and K_2CO_3 resulted in less than 1% and 20% yield of *n*-butanol, respectively, highlighting the impact of the strength of alkalinity in the reaction. Increasing the temperature to 180 °C resulted in an incremental increase in the yield from 32% to 37% with 80% selectivity. However, increasing the base loading from 6 mol% to 18 mol% did not significantly improve the *n*-butanol yield, possibly due to a reduced selectivity. Time-dependent analysis revealed that the yield of *n*-butanol increased gradually, and reached a plateau after 24 h. Despite the stable yield of *n*-butanol, the selectivity declined, which is likely due to the further conversion of *n*-butanol into higher alcohols.[74]

Based on several control experiments, a plausible mechanism was proposed (Fig. 5). The initial step involved the formation of coordinatively unsaturated species **6a** *via* elimination of HCl molecule. Subsequently, the ligand present on species **6a** will accept a proton from the ethanol molecule, leading to the formation of the alkoxy iridium species **6b,** which will undergo a β-hydride elimination to generate the iridium hydride species **6c**, along with the formation of acetaldehyde. The base-mediated aldol condensation of acetaldehyde produces crotonaldehyde as an intermediate. Two molecules of



Scheme 2 First example of the Guerbet reaction catalyzed by the homogeneous Ir-complex.[71a]

Table 2 Conversion and TON reported for the Guerbet reaction using Ir-catalyst **1** by Ishii[72a]

			TON				
Entry	L[13]	Conversion (%)	C_4	$^{Et}C_4$	C_6	$^{Et}C_8$	C_8
1	—	5	98	—	—	—	—
2	PPh_3	7	152		—	—	—
3	**2**	8	159		—	—	—
4	**3**	41	1220	464	464	261	87
5	**4**	18	594	132	132	75	—

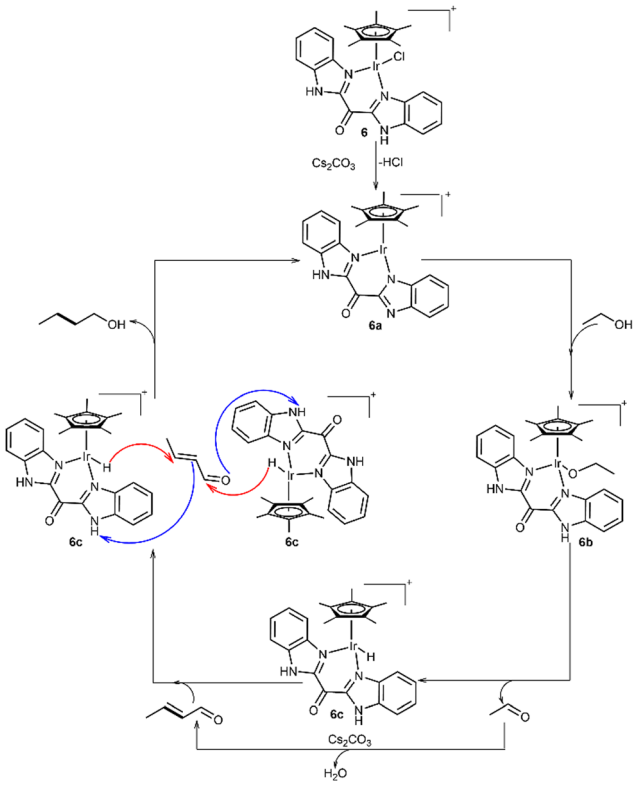
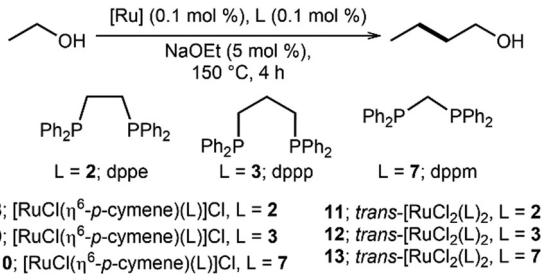


Fig. 5 Plausible mechanism proposed by Li and co-workers for ethanol upgrading using a Cp*Ir-based catalyst.[74]

6c each transfer one hydride and one NH proton from the ligand to give *n*-butanol, while regenerating **6a**.[74]

Ethanol upgradation to butanol catalysed by ruthenium complexes containing bidentate ligands

Similar to iridium-based complexes, ruthenium complexes have also been recognized as excellent catalysts for hydrogen-borrowing and dehydrogenation chemistry.[75–78] Wass and co-workers introduced ruthenium-based complexes for catalysing the ethanol upgradation reaction.[79] Initially, they reported $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.1 mol%) as a catalyst towards the upgrading of ethanol. The catalyst provided 7% ethanol conversion with 86% *n*-butanol selectivity at 150 °C. The authors then introduced ligands (**2**, **3** and **7**) with the $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ precursor, and employed them as a modified catalytic system (Scheme 3). Upon introducing one equivalent of diphosphine ligand **7** to the Ru centre to generate [RuCl(η^6-*p*-cymene)(**7**)]Cl (**10**), the ethanol conversion increased up to 22% (20% *n*-butanol yield) in the absence of any hydrogen acceptor within four hours of reaction. There was no increment in the conversion and yield even after the reaction was run for 20 h. Among all metal–ligand combinations, 1300 TON with 91% selectivity and 11% yield of *n*-butanol was obtained from the complex *trans*-$[RuCl_2(\mathbf{7})_2]$ (**13**) (0.01 mol%) in the presence of sodium ethoxide (5 mol%) after 20 h of reaction (Scheme 3).[79] Meanwhile, the highest selectivity (94%) towards *n*-butanol was achieved by employing a higher loading of [*trans*-$RuCl_2(\mathbf{7})_2$] (**13**)

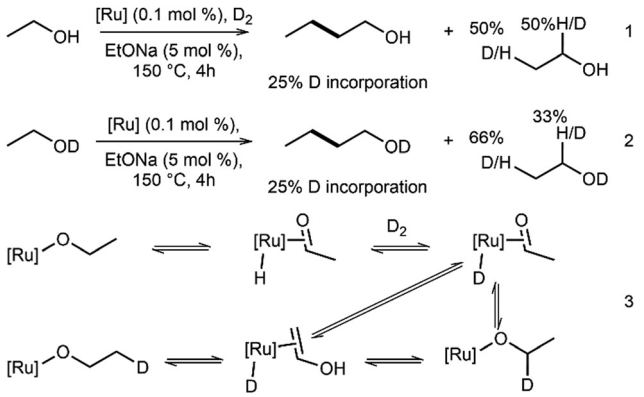


Scheme 3 Ruthenium-catalyzed Guerbet reaction reported by Wass and co-workers.[79]

(0.1 mol%) after 4 h of the reaction carried out at 150 °C in the presence of 5 mol% of sodium ethoxide.[79]

A detailed mechanistic investigation[79] revealed that the ruthenium catalyst plays a crucial role in the steps that precede and succeed the C–C bond formation step. In the absence of any Ru catalyst, the base mediates the transformation of acetaldehyde to crotonaldehyde. Hydrogenation experiments in the presence of 2.5 bar H_2 revealed that the aldol condensation of acetaldehyde is more favourable over the hydrogenation of butyraldehyde. This experiment suggests that the hydride remained coordinated to the metal centre, indicating a rapid exchange between the free and the bound hydrogen. The authors confirmed these observations when they performed deuterium labelling experiments using D_2 (2.5 bar), and observed a significant amount of D incorporation (25%) at all sites of *n*-butanol (eqn (1), Scheme 4). Interestingly, the reaction resulted in the loss of H at all sites of ethanol when they used deuterated ethanol (eqn (2), Scheme 4). They observed higher deuterium incorporation at the 2-position of the ethanol compared to the 1-position, which could be possible due to tautomerism during the catalysis, as shown in eqn (3) of Scheme 4.[79]

Wass also employed mixed ligand systems instead of the phosphine ligand (Fig. 6 and Table 3).[80] Among the mixed donor phosphine–amine ligand system, complex **20** with ligand **14** reaches 91% selectivity with 251 TON for the *n*-butanol formation (Fig. 6 and entry 1, Table 3).[80] However, in the



Scheme 4 Mechanistic insights into the ruthenium-catalysed Guerbet reaction, as proposed by Wass and co-workers.[79]

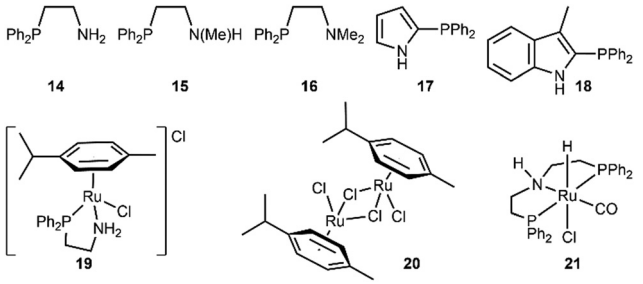


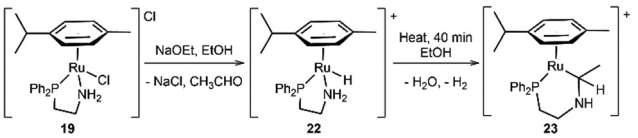
Fig. 6 Combination of mixed ligands and ruthenium complexes used by Wass and co-workers for the Guerbet reaction.[80]

Table 3 Conversion and TON reported for the Guerbet reaction catalysed by various ruthenium complexes using a combination of mixed ligands by Wass.[80]

Entry	L + [Ru] (0.1 mol%)	Conversion (%)	Selectivity	TON
1	**14** + **20**	25.1	91.1	251
2	**15** + **20**	23.8	84.9	238
3	**16** + **20**	16.7	79.6	167
4	**17** + **20**	19.7	92.4	197
5	**18** + **20**	31.4	92.7	314
6	**19**	23.6	90.8	236
7	Ru(**14**)$_2$Cl$_2$	18.8	93.5	188
8	**21**	13.3	12.4	133

presence of water, they showed that **20** in combination with **14** demonstrated 99% *n*-butanol selectivity with 98 TON. They also investigated the effect of the partial and fully methylated amine ligands **15** and **16**, respectively, with complex **20** for this reaction. The catalytic activity of the combination of ligand **15** and complex **20** was found to be very similar to that obtained when ligand **14** was complexed with **20** (entry 1 *vs.* entry 2, Table 3). In contrast, the result obtained from the combination of ligand **16** and complex **20** was relatively less significant in terms of yield, TON and selectivity (Fig. 6 and entry 3, Table 3).[80] Similarly, ligands **17** and **18** were also tested in combination with the metal precursor **20** towards the catalytic upgrading of ethanol. Interestingly, the combination of **20** with **18** provided 31% of ethanol conversion with 93% selectivity towards *n*-butanol (Fig. 6 and entry 5, Table 3). Under the reaction conditions, the PNP tridentate pincer complex **21** yielded ethyl acetate (5% yield with 40% selectivity) as a major product (Fig. 6).[80]

In a detailed mechanistic study, Wass demonstrated that the complex **23** was generated as an active form of the catalyst, as confirmed by ^{1}H and ^{31}P NMR spectroscopy, as well as by mass spectrometry.[80] During the early stages of the reaction, the ruthenium hydride species **22** was observed, which is further converted to the unusual, unexpected complex **23** (Scheme 5). The presence of metalated alkyl amine species **23** indicates an initial dehydrogenation from **22**, followed by an insertion of the ethyl group (presumably obtained from dehydration) into the Ru–N bond of the resulting amido bis-chelate complex. The authors believe that the formation of **23** is one of the steps involved in the catalytic cycle after acetaldehyde is formed *via* the dehydrogenation of ethanol. Similarly, another complex has



Scheme 5 An unusually active catalyst **23** for the Guerbet reaction reported by Wass.[80]

been detected by mass spectrometry, which is consistent with a bis-chelate complex containing a bound C_4 dioxygenated fragment, pointing to a remote possibility of a metal-templated aldol condensation. Such ligand-assisted $H/C_2/C_4$ transfer pathways in Guerbet reactions offer new possibilities.[80]

Ethanol upgrading to butanol catalysed by ruthenium complexes containing pincer ligands

The use of tris-chelate pincers as ancillary ligands enhances the stability and reactivity of the metal centre. As a first example, the utility of NNN pincer complexes **24** and **25** for the ethanol upgrading process was reported by Szymczak and co-workers.[81] Encouraged by their success with catalyst **24**, which was capable of mediating reversible transformations between alcohols and ketones *via* sequential hydrogenation – acceptorless dehydrogenation reaction in a previous report, they employed **24** for the ethanol upgrading reaction as well (Fig. 7).[81] Upon using 0.1 mol% of **24** in combination with 5 mol% of NaOEt at 150 °C, only 10% yield of *n*-butanol was observed with 10% ethanol conversion, but with 100% selectivity.[81]

Catalysts **25a–c** that were derivatives of **24**, but lacked a methyl group on the *o*-position of the flanking pyridyl nitrogen, were also tested for the upgrading of ethanol to *n*-butanol. The absence of the *o*-methyl group on catalyst **25a–c** reduced the steric hindrance during the key β-hydride elimination step, thereby resulting in higher catalytic activity when compared to the corresponding activity of **24**. However, among the considered catalysts **25a–c** that differed from each other by subtle electronic modifications, almost comparable activity was observed. This indicates that the electronic modifications on the pincer scaffold hardly had any influence on the activity and selectivity towards the Guerbet reaction.[81]

Among all three catalysts, 0.1 mol% of **25a** resulted in higher ethanol conversion (30%) with 25% yield of *n*-butanol, but with a lower selectivity (91%) when compared with catalyst **24**.

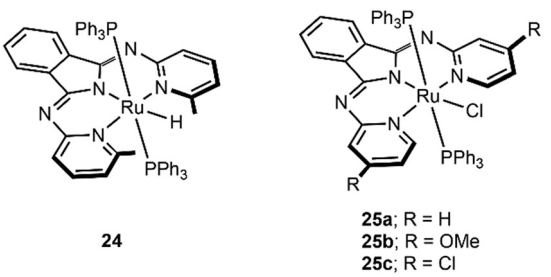


Fig. 7 Pincer–ruthenium catalysts reported for ethanol upgrading by Szymczak.[81]

Interestingly, the complex **25a** at 0.1 mol% loading demonstrated similar catalytic activity (27% *n*-butanol yield with 83% selectivity) when the reaction was performed under air, highlighting the air stability of the catalyst, which could offer significant practical advantages. However, when the reaction was performed at a lower loading of 0.001 mol% of **25a**, only 1.4% yield of *n*-butanol was observed with TONs reaching up to 1400. Furthermore, on performing the reaction using 20% of 1-BuOH by volume, a similar conversion (35%) and yield (23%) were observed, but with an increase in the yield of higher alcohols (4% to 12%). This is consistent with their hypothesis that at higher concentration, *n*-butanol can compete with EtOH as a substrate by competitive Guerbet pathways, which can lead to the generation of higher alcohols, simultaneously obstructing the yield of *n*-butanol. They also demonstrated that the reaction proceeded through a deactivation pathway *via* decarbonylation reaction, which can be minimized by using the excess PPh_3 ligand. In order to enhance the activity of the catalyst by suppressing the PPh_3 dissociation, excess PPh_3 was added. This showed a positive impact by mitigating the limitation of phosphine dissociation in catalysis (49% and 53% conversion of ethanol at 38% and 37% yield of *n*-butanol upon the addition of 0.1 mol% PPh_3 and 0.4 mol% PPh_3, respectively).[81]

Milstein and co-workers investigated a series of PNP and PNN-pincer ruthenium complexes for the Guerbet reaction with the objective of enhancing the selectivity and maximizing the yield of *n*-butanol.[82] These systems serves as efficient catalysts, facilitating the conversion of ethanol into *n*-butanol under relatively milder conditions (Fig. 8).[82] Among the complexes listed in Fig. 8, the pincer–ruthenium complexes **26–30** at 0.02 mol% loading in the presence of 4 mol% of NaOEt have demonstrated lower activity towards the Guerbet reaction. Furthermore, among the catalysts **26–30**, the catalyst **28** exhibited the highest conversion (8.4%) with 1.3% *n*-butanol yield and 420 TON at 110 °C after 16 h of reaction.[82]

On the other hand, 20.9% yield of *n*-butanol with 23.4% ethanol conversion (92.5% selectivity, *ca.* 1171 TON) was observed when the acridine-based complex **31** was used as a catalyst under similar reaction conditions. This complex **31** resulted in 35.9% yield of *n*-butanol and 62.4% conversion of ethanol (68.1% selectivity, *ca.* 3122 TON) when the reaction was carried out at 150 °C. Furthermore, reducing the time from 16 h to 4 h resulted in a similar yield of *n*-butanol (34.2%), and at a higher selectivity (79.4%). Under these conditions, notably, the de-aromatized acridine-based complex **32** effectively produced 38.4% of *n*-butanol (*ca.* 3345 TON) (Fig. 8). The comparable *n*-butanol yields obtained with **31** and **32** are suggestive of the fact that **32** is plausibly the actual active catalyst involved in the Guerbet reactions catalysed by **31**. A highest TON of 18209 was achieved with 86.1% of *n*-butanol selectivity when the reaction was performed at 0.001 mol% of **31** for 7 days.[82]

A detailed investigation was carried out to find out the relationship between the reaction time, ethanol conversion, yield and selectivity of *n*-butanol. It was revealed that after 4 hours of the reaction time, the yield of *n*-butanol (34.2%) did not significantly increase. However, an increase in the ethanol conversion was observed from 48% to 65% (Fig. 9).[82] This result suggests that with increasing time, the rate of formation of *n*-butanol became similar to its rate of consumption, giving rise to higher alcohols *via* homo-coupling and cross-coupling, eventually leading to decreased *n*-butanol selectivity, as observed by Szymczak and co-workers.[81] The mechanistic studies established by the authors show that the central acridine heterocycle in complex **31** gets dearomatized during the catalytic cycle.[82] This was the first time that authors have highlighted the significance of alcohols beyond butanol, *i.e.*, C6 and C8 linear and branched chain alcohols for biofuel production, which was earlier viewed as merely side products.

Recently, Kumar and co-workers[83] reported a series of air- and moisture-stable bis(imino)pyridine pincer–ruthenium complexes (**33–34**) and 2,6-bis(benzimidazole-2-yl) pincer–ruthenium complexes (**35–36**), which exhibited very high catalytic activity towards alcohol dehydrogenation[84] or dehydrogenative coupling[85] reactions (Fig. 10). When these complexes were tested for the Guerbet reaction, **35a** demonstrated satisfactory activity towards ethanol upgradation under neat conditions.[83] High *n*-butanol turnovers (2100 TON) and selectivity (up to 70%) were obtained after 72 h of reaction carried out at 140 °C in a closed vessel system at a very low catalyst loading of 0.025 mol% in the presence of 10 mol% NaOEt.

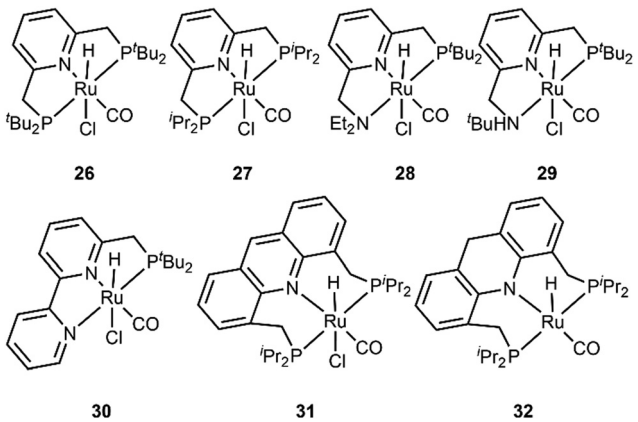


Fig. 8 Pincer ruthenium catalyst reported for ethanol upgrading by Milstein and co-workers.[82]

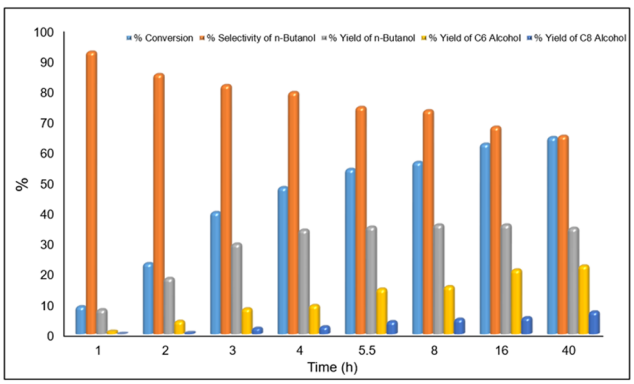


Fig. 9 Reaction profile for the **31**-catalysed ethanol upgrading reaction reported by Milstein and co-workers.[82]

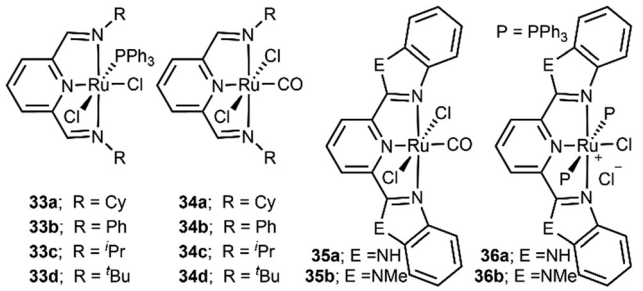


Fig. 10 Pincer–Ru catalysts reported for the upgrading of ethanol to *n*-butanol by Kumar.[83]

Kumar reported a TON of 710 h^{-1} using 0.05 mol% of the catalyst **35a**. In detailed kinetic studies, Kumar and co-workers demonstrated a linear relationship of rate not only with the concentration of the catalyst but also with the ethanol concentration. These results indicate that the reaction has a first order dependence of the rate relative to both the catalyst and ethanol concentration.[83]

Soon after, Kumar reported that the upgrading of ethanol to *n*-butanol using pincer–ruthenium complexes **33–36** under microwave (mw) irradiation (75 W at 110 °C) was highly efficient in the presence of 10 mol% NaOEt within 2 h of reaction.[86] Notably, their findings demonstrate that the microwave irradiation enhances the reactivity of these catalysts, leading to better ethanol conversion at lower temperatures compared to traditional Guerbet reactions. Among the considered carbonyl and phosphine-based pincer–ruthenium complexes (**33–36**), the bis(imino) pyridine pincer–ruthenium complexes demonstrated poor activity towards ethanol upgrading under microwave irradiation.[86] On the other hand, the pincer–ruthenium complexes **35a** and **36a** based on the 2,6-bis(benzimidazole-2-yl)pyridine ligand showed higher activity towards the Guerbet reaction. For instance, in the **36a** catalysed (0.00225 mol%) ethanol upgradation in the presence of 10 mol% NaOEt, the highest rate (8534 TOs per h, *ca.* 18% yield of *n*-butanol at 90% selectivity) was obtained at 110 °C under microwave irradiation at 75 W.[86] While the best productivity (72% ethanol conversion and 42% yield of *n*-butanol at 57% selectivity) was obtained using 1 mol% **35a**, the highest turnovers (*ca.* 13022 TON with 23% yield of *n*-butanol at 78% selectivity) were obtained in the presence of 0.00225 mol% **35a** (Table 4).[86] Immobilization of **35** and its derivatives onto solid supports was also attempted.

Very recently, Szymczak and co-workers have demonstrated a tandem Guerbet alkylation technique for the ruthenium-catalyzed upgrading of ethanol to higher-order alcohols.[87] These higher-order alcohols then undergo additional C–C bond-formation *via* hydrogen borrowing strategies. Studies into catalyst design has resulted in the development of **37a** (Fig. 11), an extremely efficient catalyst for producing biofuels and valuable chemicals from ethanol through Guerbet and tandem Guerbet reactions.

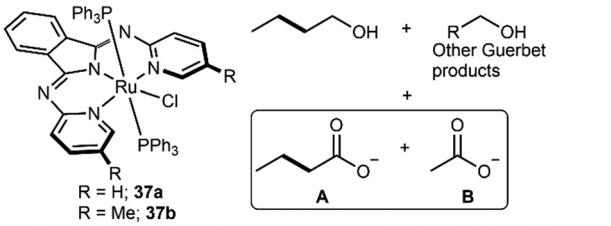
Catalytic Guerbet processes with ethanol are often carried out neat at temperature above 150 °C. At these high temperatures,

Table 4 Yield and TON reported for the Guerbet reaction catalysed by pincer–ruthenium complex **35a** reported by Kumar and co-workers.[86]

Entry	**35a** (mol%)	Temperature (°C)	% Ethanol conversion	*n*-BuOH yield (%)	TON
1	0.025	140 °C	33	26	1320
2	0.025	110 °C	3.8	3.7	152
3	0.025	110 °C (mw)	50	28	2000
4	0.1	110 °C (mw)	69	41	690
5	1.0	110 °C (mw)	72	42	72
6	0.00225	110 °C (mw)	29.3	22.8	13 022

competitive reactions with an aldehyde intermediate can produce carboxylate salt from hydroxide (Cannizzaro)[88,89] or alkoxide species (Tishchenko),[90–92] which can lower the yield and hinder the reactivity (Fig. 11).

Initial optimization using 0.1 mol% of **37a**, 0.1 mol% of PPh_3 and 10 mol% of NaOEt at 150 °C for 2 h resulted in 51% yield of Guerbet alcohols.[87] Further addition of mesitylene as a solvent resulted in comparable yield (53%) of Guerbet alcohols. On increasing the catalyst loading to 0.2 mol% and base loading to 40 mol% in the presence of 0.2 mol% of PPh_3, the total yield of alcohols increased to 58% (Fig. 11). Out of several bases screened, NaO^{t}Bu was found to give the highest reproducible mass balance. Szymczak observed an association between the identity of the alkali metal and the high prevalence of the undesirable Cannizzaro reaction pathway during base optimization with KO^{t}Bu. Specifically, when 20 mol% KO^{t}Bu was employed, the yield of the carboxylate salt increased, accompanied by a higher conversion of ethanol. Further increasing the loading of KO^{t}Bu to 40 mol% resulted in lower yields of Guerbet alcohols, while simultaneously producing a notable 38% yield of carboxylate (Fig. 11). These observations suggest that the excessive amount of KO^{t}Bu favour side reactions, particularly the Cannizzaro reaction and deteriorating the overall efficiency. Interestingly, the inclusion of 40 mol% of 18-crown-6 as an additive with KO^{t}Bu improved the economy of the reaction by reducing the loss of ethanol *via* undesired pathway to 5%. This highlights that the additive not only mitigates side reaction but also enhances the overall efficiency, making it a valuable strategy in optimizing reaction conditions. They also extended this work to the alkylation of fluorene and



R = H; **37a**
R = Me; **37b**

All reactions below were done in the presence of 0.2 mol% PPh_3	**A** (%)	**B** (%)	Total Guerbet Product (%)	Mass Balance(%)
37a(0.2 mol%) NaO^{t}Bu (40 mol%)	6	11	58	95
37a(0.2 mol%) KO^{t}Bu (40 mol%)	8	38	42	94
37b(0.2 mol%) NaO^{t}Bu (40 mol%)	1	9	65	94

Fig. 11 Pincer–Ru complexes used for ethanol upgrading by Szymczak and co-workers.[87]

its various derivatives, such as nitriles and ketones, which have the potential to experience competitive side reactions. These studies established the generality of the sequential functionalization technique *via* the Guerbet reaction, while showcasing an intriguing advancement in combining multiple reactions in just one step.[87]

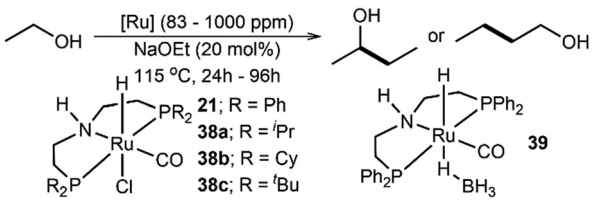
After ensuring the effectiveness of the sequential functionalization process, Szymczak sought to enhance the reactivity of the ethanol upgrading reaction by making a simple modification on the ligand scaffold, where methyl substituents were introduced at the 6-, 5- and 4-positions of pyridyl rings on the bpi (1,3-bis(2,2′-pyridylimino)isoindolate) system.[87] It was found that catalyst **37b**, having methyl group at 5-position (Fig. 11), resulted in a significant increase in the yield of Guerbet alcohols to 65% with suppressed carboxylate products (10% *vs.* 17%). In contrast, the other two variations (methyl at 6-, and 4-positions) were found to be less effective than **37a.** The initial catalytic rate of the reaction showed that catalyst **37a** performed better in the beginning, but catalyst **37b** demonstrated prolonged catalytic activity, resulting in a higher yield of Guerbet alcohols. The catalyst **37b** showed the highest TOF (12 690 h^{-1} based on 2 h data, entry 1, Table 5) and TON (155 890) for the ethanol upgrading reaction at 0.0001 mol% loading after 7 days of the reaction (Table 5).[87]

Nielsen and co-workers have reported the direct conversion of ethanol to primary and secondary alcohols using pincer–Ru MACHO (**21**, **38a–c**) and pincer–Ru MACHO-BH (**39**), along with the formation of a low amount of butene and butane (Scheme 6).[93] Initial optimization with 1000 ppm of **21** with 20 mol% of NaO^{t}Bu at 115 °C resulted in only 3% yield of *n*-butanol after 96 h of the reaction (Scheme 6), along with 12% yield of 2-butanol and a total of 22% yield of secondary alcohols (220 TON).[93] Decreasing the catalyst concentration from 1000 to 250 ppm resulted in comparable yields of 2-butanol (10%). Similarly, 250 ppm of catalyst **39** achieved a 12% yield of 2-butanol and 18% yield of total secondary alcohols (720 TON).[93] While complexes **38a** and **38b** resulted in the unselective production of primary and secondary alcohols, complex **38c** featuring bulky phosphine substituents demonstrated >99% selectivity towards primary alcohols with 13% yield of *n*-butanol at 115 °C with no formation of secondary alcohols even after 96 h. The selectivity between primary and secondary alcohols is greatly influenced by the nature of the substituents present on the phosphine. Less bulky substituents tend to favour the formation of secondary alcohols, whereas bulky substituents favour primary alcohol formation.

In a typical Guerbet reaction, acetaldol is first formed from two acetaldehyde molecules, which then dehydrate to form crotanaldehyde, followed by subsequent hydrogenation to form *n*-butanol. However, an alternative hydrogenation/dehydrogenation pathway can lead to the formation of a novel key intermediate 4-hydroxy-2-butanone. This intermediate undergoes dehydration to form methyl vinyl ketone (MVK), which, upon hydrogenation, results in the formation of 2-butanol.[93]

Table 5 Guerbet reaction catalysed by the pincer–Ru catalyst **37b** reported by Szymczak[87]

Entry	**37b** (mol%)	Time (h)	Guerbet yield (%)	TON	TOF (h^{-1})
1	0.0001	2	2.5	25 380	12 690
2	0.0001	48	14.3	143 160	2983
3	0.0001	168	15.6	155 890	928

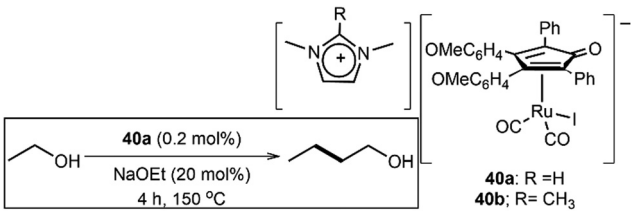


Scheme 6 Pincer–Ru MACHO catalysts reported for ethanol upgrading by Nielsen.[93]

Upgrading of ethanol to butanol catalysed by ruthenium complexes based on phosphine-free systems

In 2019, Mazzoni introduced the first phosphine free ruthenium system, featuring an ionic carbonyl cyclopentadienone complex in the presence of a dimethylimidazolium salt for the upgrading of pure ethanol, as well as ethanol obtained from wine waste, into *n*-butanol and higher alcohols in the presence of an inorganic base as a cocatalyst (Scheme 7).[94] When the reaction was conducted with 0.2 mol% of catalyst **40a** and 20 mol% of NaOEt, it resulted in 32% yield of *n*-butanol with 70% selectivity at 150 °C after 4 h with minimal carbon loss. A slight decrease in the yield was observed when the reaction was performed using different bases, such as NaOH or NaOMe. However, when the reaction was performed with an acid as a cocatalyst to address the problems associated with Cannizzaro reaction, no activity was observed. Recyclability of the catalyst **40a** was examined under optimized condition by removing the alcohol mixture under vacuum, and by adding fresh EtOH and NaOEt. The result showed that the catalyst retained its efficiency. Scaling up the reaction by tenfold has resulted in a comparable yield of *n*-butanol and an increase in the yield of higher alcohols.[94]

Building on their previous work, the same group has reported on several other ionic ruthenium-based complexes for the ethanol upgrading reaction, and they have found that the catalytic activity is largely influenced by the imidazolium counterion.[95] Catalyst **40b**, having a methyl group present on the NCN carbon atom of the imidazolium counterion, exhibited



Scheme 7 A phosphine-free Ru catalyst reported for the ethanol upgrading reaction by Mazzoni and co-workers.[94]

a reduced *n*-butanol yield compared to catalyst **40a** (15% *vs.* 32%). A further decline in the *n*-butanol yield was observed when the catalyst (having bulky substituents on the heteroatom) was employed, dropping from 32% to 9%. A similar decrease in the yield to 10% was observed when the imidazolium salt was replaced with the non-protic triethylammonium counterion (TEA). From the electronics perspective, catalyst **40a** exhibited the strongest hydrogen bond and highest hydride donor ability. This likely enhances the reduction step, while slowing down the dehydrogenation step, thus favouring the Guerbet reaction. Moreover, the addition of 1.5 mol% of 2,6-dimethoxy-1,4-benzoquinone (BQ-OMe) as a cocatalyst led to 6% increase in the *n*-butanol yield (38%) and 19% increase in the total alcohol yield (61%) compared to catalyst **40a**, which resulted in 32% yield of *n*-butanol and 42% yield of total alcohol. The addition of benzoquinone (BQ) as a co-catalyst has remarkably boosted the conversion and selectivity of the reaction. Furthermore, it has avoided hydrogen evolution as a side reaction, making the system more resilient to water. The selectivity towards *n*-butanol decreases after using BQ-OMe (76% *vs.* 62%). On the other hand, the selectivity was found to improve (24% *vs.* 38%) in the case of higher alcohols. This observation suggests that the co-catalysts preferentially favour the formation of higher alcohols over *n*-butanol.[95]

Ethanol upgrading to butanol catalysed by ruthenium complexes in aqueous medium

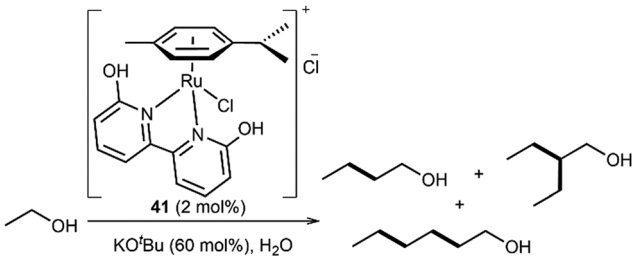
It is important to note that water is a by-product of the aldol condensation reaction. Szymczak and other groups have demonstrated that the presence of water significantly inhibits the efficiency of the Guerbet reaction. This finding highlights the necessity for improving water tolerance in catalytic processes. In fact, the ultimate goal is to directly use the fermentation broth, which typically contains about 10% ethanol, for a more efficient and sustainable approach. Jones and co-workers used the 6,6′-dihydroxybypyridine-based ruthenium complex **41**, along with a sterically bulky base (potassium *tert*-butoxide) towards the upgrading of ethanol (Scheme 8 and Table 6).[96] The reaction was carried out at 80–85 °C in water. The high solubility of this ruthenium complex in basic aqueous media poses significant difficulties in its removal from the reaction mixture after completion. Various attempts were made, including acidification and organic solvent extraction, to remove the catalyst. However, the high solubility of ethanol in water made it difficult for the authors to quantify the ethanol conversion. Additionally, vacuum transfer was used, but these approaches were unsuccessful due to the loss of some alcohols.

Table 6 Yield of *n*-butanol reported for the Guerbet reaction using ruthenium catalyst **41**, which was reported to be performed in aqueous medium by Jones and co-workers[96]

Entry	**41** (mol%)	KO^{t}Bu (mol%)	Temperature (°C)	H_2O : EtOH (v/v)	Yield (%)
1	1.5	50	80	84 : 16	24
2	1.5	50	85	84 : 16	23
3	2.0	60	85	84 : 16	29
4	2.5	70	80	91 : 9	20

Ultimately, a sequential filtration method through neutral alumina, followed by reverse phase silica (C^{18}), lead to the successful separation of the complex and ethanol. The reaction resulted in 24% *n*-butanol yield with 57% selectivity using 1.5 mol% of **41** and 50 mol% of KO^{t}Bu at 80 °C for 18 h in the presence of 0.3 mL of water. Increasing the water content from 0.3 mL to 0.58 mL resulted in a drastic decrease in the *n*-butanol yield, dropping from 24% to 13%. The low yield of *n*-butanol under dilute conditions is attributed to the low ethanol concentration. On further optimization, the yield of *n*-butanol could be increased to 29% with 51% selectivity by using 2 mol% of the catalyst and 60 mol% of the base under the optimized reaction condition at an elevated temperature (85 °C) (Table 6). Fermentation broth is also tolerated under the optimized reaction conditions, albeit with a decreased yield (20%) and selectivity (48%). The authors claimed that the selectivity of the product could be improved by using water-soluble bases derived from Ni and Cu. It is noteworthy that the Guerbet reaction was performed at an unprecedented low temperature of 80 °C in this work. This method marks a significant advancement; as a much higher temperature is typically required to facilitate the reaction effectively.

Very recently, Jones reported a series of *in situ* prepared Ru(III) complexes supported by readily available N-donor organic pincer ligands (**42–45**) for the ethanol upgrading reaction under aerobic conditions (Fig. 12).[97a] The initial optimization involved performing the reaction with 0.1 mol% of $RuCl_3 \cdot 3H_2O$ and 0.1 mol% of ligand **42** in the presence of 10 mol% of KO^{t}Bu under inert condition for 24 h at 150 °C, and 28% yield



Scheme 8 A water-soluble ruthenium catalyst **41** used for the upgrading of ethanol.[96]

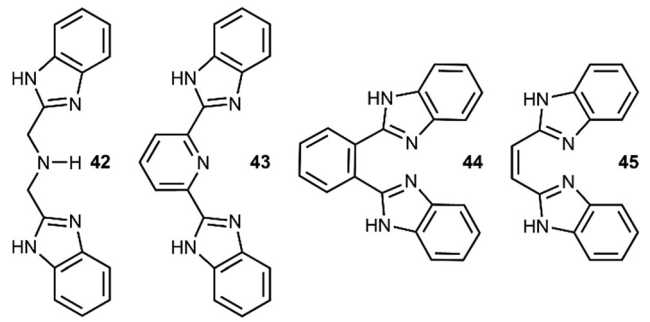


Fig. 12 Ligands used in combination with $RuCl_3 \cdot 3H_2O$ for the catalytic ethanol upgradation studied by Jones and co-workers.[97a]

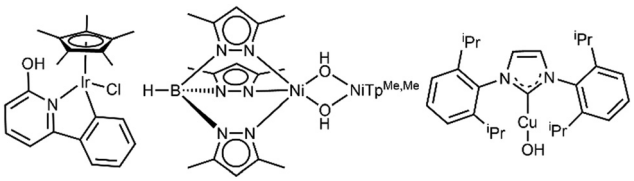
of *n*-butanol was observed with 70% selectivity. Interestingly, when the same reaction was performed under air, similar activity was observed with 27% yield of *n*-butanol and 71% selectivity. This observation suggests that the active species generated in the reaction mixture remains unaffected under air. Increasing the base loading to 25 mol% resulted in only a slight increment in the yield of *n*-butanol (33%), albeit with lower selectivity. Increasing the catalyst loading from 0.1 mol% to 0.5 mol% at 10 mol% base loading resulted in a slight increment in the yield from 27% to 32%. However, on further increasing the catalyst loading to 1 mol%, a decline in the yield was observed, dropping from 27% to 20%.

Given the crucial role of steric and electronic factors in catalysis, various ligand systems with different ligation patterns and dissimilar backbones were included in the study by Jones in order to enhance the reactivity.[97a] Notably, ligand **43** featuring a pyridine backbone (Fig. 12) exhibited slightly better performance, giving 29% yield of *n*-butanol, with the selectivity (70%) comparable to that of **42**. A mercury poisoning test ruled out the possibility of any contribution from nanoparticles. In order to study the influence of water, which is a main by-product of the Guerbet reaction, several reactions were performed in presence of additional water. The addition of 100 mol% of water resulted in the sharp decline in the *n*-butanol yield (11%), highlighting the detrimental effect of water. However, increasing the base loading to 25 mol% resulted in a slight increment in the *n*-butanol yield (16%), suggesting that it is the base that is undergoing decomposition in the presence of water. Further increasing the water content (200 mol%) led to decline in the reactivity (7% *n*-butanol). Inclusion of molecular sieves was anticipated to enhance the reactivity, but it gave almost comparable performance with 28% yield of *n*-butanol.[97a]

Ethanol upgradation to butanol catalysed by base-metal complexes

Nearly a decade ago, a majority of the homogeneous alcohol dehydrogenation catalytic systems relied on noble metals,[97b] specifically ruthenium[97b] and iridium.[97c] However, the reliance on noble metals, though effective, posed significant challenges due to their high costs, limited availability, toxicity and their tedious extraction process. As a result, the exploration of alternative catalyst became a growing area of research.[97d] Researchers are now actively investigating the potential of first row transition metals to serve as alcohol dehydrogenation catalysts,[97d–j] as they are more abundant and less expensive.

For the first time in 2015, Jones and Baker used first-row transition metals for the Guerbet reaction.[98] Their approach did not solely rely on base metals; instead, they developed a hybrid system that incorporated both base metal catalysts and iridium. In this work, the base metal catalysts act a substitute for traditional inorganic bases. This work marks a pivotal shift towards more sustainable catalytic processes. They reported a tandem catalytic process using bi-functional iridium-based complex **46** coupled with bulky Ni and Cu hydroxides to selectively catalyze the Guerbet reaction (Fig. 13).[98] Fujita and Yamaguchi have demonstrated that the complex **46** bearing the



46 **47** **48**

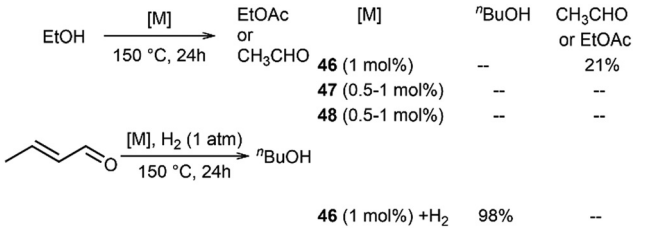
Fig. 13 Bi-functional iridium/Ni catalytic system used for the upgrading of ethanol by Jones and Baker.[98]

α-hydroxypyridine group is an outstanding catalyst for the acceptorless dehydrogenation of alcohols to produce aldehydes in the presence of various inorganic bases.[99] On the other hand, aldol condensation of acetaldehyde plays a key role in determining the selectivity towards the formation of *n*-butanol and often ends up with the production of longer-chain alcohols. Therefore, in order to increase the selectivity of *n*-butanol, simple inorganic bases were replaced with highly basic transition metal complexes exhibiting sterically encumbered ligands that can be fine-tuned. The bulky base-metal hydroxide complexes such as $[Tp'Ni(\mu\text{-}OH)]_2$, (Tp′ = tris(3,5-dimethyl-pyrazolylborate), **47** and [(IPr)CuOH], (IPr = 1,3-bis(2,6-diisopropyl-phenyl)-1,3-dihydro-2*H*-imida-zol-2-ylidene), **48** act as strong bases in sub-stoichiometric amounts (Fig. 13). The complex **46** (0.2 mol%) in the presence of **47** (relative ratio of 1 : 25) resulted in 37% of ethanol conversion with *n*-butanol as the sole by-product (34%) at 150 °C after 24 h of reaction. Similarly, 32% of ethanol conversion was observed with 28% *n*-butanol yield in the presence of **48** under similar reaction conditions.[98]

Jones and Baker studied the Guerbet reaction in detail in order to determine the reactivity of these synthesized Ni and Cu complexes towards the aldol coupling step. In a detailed study, it was observed that complexes **47** and **48** were involved in the aldol condensation reaction to selectively produce the crotonaldehyde product, *i.e.*, **C4** aldol, and only a trace amount of **C8** aldol was detected.

On the other hand, the reaction yielded crotonaldehyde with relatively lower selectivity (23%) when the reaction was performed in the presence of KOH. These results clearly indicate that the complexes **47** and **48** predominantly determined the product distribution on the aldol coupling step under the Guerbet reaction conditions. Interestingly, they also observed that complexes **47** and **48** had no role in the dehydrogenation of ethanol or hydrogenation of crotonaldehyde in the presence of H_2 (Scheme 9).

Independent experiments demonstrated that the complex **46** catalyzed the dehydrogenation of ethanol to 21% ethyl acetate (Scheme 9). On the other hand, the complex Cp*Ir[(2-OH-6-phenyl)-pyridine](H) **46** also catalysed the hydrogenation of crotonaldehyde to *n*-butanol quantitatively in the presence of hydrogen (H_2) (Scheme 9). These control experiments imply that the catalyst **46** was involved in the dehydrogenation and hydrogenation in the catalytic cycle, while complexes **47** and **48** were involved in the aldol condensation reaction. This bi-functional catalytic system comprising iridium complex **46** in



Scheme 9 Bi-functional iridium/Ni-catalysed upgrading of ethanol reported by Jones and Baker.[98]

combination with sterically crowded hydroxide complexes **47** or **48** was able to selectively convert ethanol to *n*-butanol under the Guerbet reaction conditions with high selectivity (>99%) and good conversions, even at 100 °C.[98]

In 2017, Q. Liu reported on the first homogeneous system that was exclusively based on first-row transition metals. They employed a PNP-manganese pincer complex **49** (0.000098 mol%) to upgrade ethanol to higher alcohol, and reached up to 114 120 TON with 11.2% ethanol conversion after 7 days of reaction in the presence of NaOEt (12 mol%).[100] Notably, **49** is a mixture with **49′**. The highest yield obtained for *n*-butanol is 22.7% (TON 286) using 0.1 mol% of **49**, while the highest selectivity reached around 100% (TON 170) at 1.7% conversion of ethanol to *n*-butanol (Fig. 14).[100]

The mechanistic path of their reaction is likely to be similar as that reported by Jones and Baker.[98] Regardless of the presence or absence of a catalyst, the EtONa-catalyzed aldol condensation of acetaldehyde afforded crotonaldehyde and **C4+** higher oligomers, with comparable yield and selectivity in both cases. This observation suggests that the catalyst does not have a substantial impact on the reaction's selectivity. A similar trend was observed for the conversion of crotonaldehyde to **C4+** higher oligomers (Scheme 10). These results contrast with those obtained by Wass and co-workers using ruthenium catalyst, in which they were able to inhibit the aldol reaction of **C4** aldehyde and thereby achieve higher selectivity towards *n*-butanol.[79] Consequently, the hydrogenation of acetaldehyde or crotonaldehyde using 1 mol% of **49** in the presence of hydrogen resulted in the formation of *n*-BuOH, crotyl alcohol and higher **C4** oligomers. These results demonstrate that

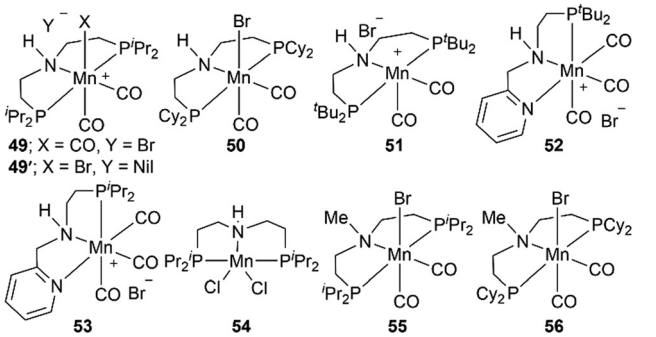
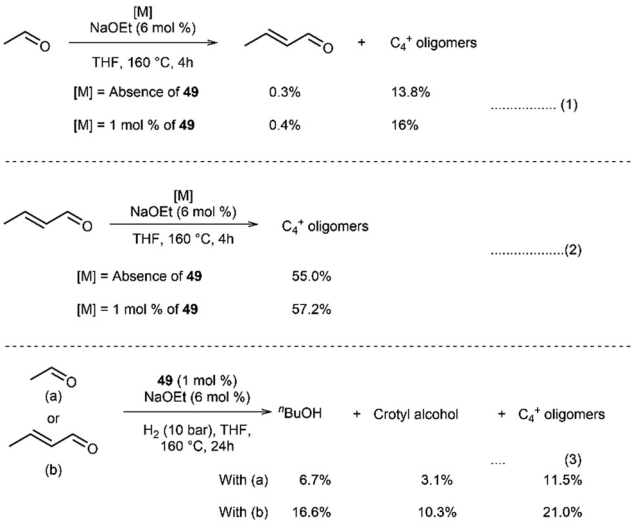


Fig. 14 Pincer–Mn catalysts used for the upgrading of ethanol by Liu and co-workers.[100]



Scheme 10 Mechanistic studies performed by Q. Liu during the **49**-catalysed upgrading of ethanol to higher alcohols.[100]

acetaldehyde takes part as an intermediate during the ethanol upgrading reaction in the presence of H_2 and complex **49** (Scheme 10). Moreover, when the reaction was performed using complex **49** and **55**, the selectivity towards C4 alcohol was found to be lower for **55** than **49**, which suggests that the catalyst bearing the N–H moiety plays an essential role in the hydrogenation step in the catalytic cycle. The water tolerance was also tested, and it was found that the addition of 10 mmol of water decreases the overall efficiency of the reaction (7.5% ethanol conversion with 4.8% butanol yield and 79% selectivity) using 0.01 mol% loading of **49** when compared with the one without water at 0.01 mol% catalyst loading (9.7% ethanol conversion with 6.8% butanol yield and 83% selectivity).[100,101]

In a similar parallel investigation, Jones used the PNP pincer-manganese complex **49′** at a 0.5 mol% loading and 25 mol% of NaOEt, achieving a 30% yield of *n*-butanol and 10% yield of higher alcohols (Fig. 14).[102] The reactivity of the catalyst was observed to decrease after 24 h of the reaction, which was likely due to the formation of water as the primary by-product of the Guerbet reaction. In order to determine the role of water, two independent experiments were conducted with 10 mol% and 30 mol% of added water. The result showed a decrease in the *n*-butanol yield, dropping from 30% to 24% and 15%, respectively. To investigate whether the effect of water occurs *via* deactivation of the catalyst or base, additional experiments were conducted. These experiments revealed that the water produced during the reaction reacts with base NaOEt to form NaOH, which then facilitates the Cannizzaro reaction and results in the formation of NaOAc. The loss of base due to this side reaction contributes to the decreased activity observed after 24 h. Consequently, higher base loading is required in order to enhance the reactivity.[98,102] To study the ethanol upgrading *via* Guerbet reaction into various products, the reaction progress was monitored by carrying out the reaction using 0.5 mol% of **49′** and 25 mol% of NaOEt (Fig. 14). The results obtained showed that the amount of *n*-butanol and *n*-hexanol

increased slowly over the course of the reaction. As the reaction progressed, the amount of gas (ethanol vapors) formed remained constant even after 4 h of the reaction.[102]

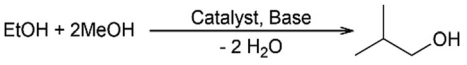
Miscellaneous applications of the Guerbet reaction

For many years, research groups have attempted to upgrade ethanol to butanol, since the latter has better energy density and fuel properties than its precursor. This century-old reaction has been modified by some scientists to produce other value-added products. This upgrading reaction can be modified, and a synthesis pathway for a selective, branched higher alcohol from ethanol can be devised. For instance, this reaction protocol can be utilized to couple two methanol molecules (which is also obtained from bio-sustainable sources) and one ethanol molecule to generate iso-butanol (Scheme 11), which is a more advantageous fuel than *n*-butanol (having a higher-octane number and 98% energy density, as compared to that of gasoline).[103] Ethanol and methanol are initially dehydrogenated to form acetaldehyde and formaldehyde, respectively. These aldehydes then undergo aldol condensation to form acrylaldehyde, which is subsequently hydrogenated to yield propanol. Propanol and methanol then go through the same series of reactions to produce iso-butanol.[104]

The first example of this reaction was reported by Ueda, who used a variety of metal–oxide systems. Among them, MgO was found to be the most favorable, giving 60% conversion of ethanol, with 46% selectivity towards iso-butanol.[105] This initial study was followed by another work from the same group, which provided insights on the mechanistic aspects, indicating that hydrogen transfer takes place rapidly from methanol to the C=C and C=O bonds of the intermediates, which are adsorbed on the catalytic surface.[106]

Carbon-based, MgO-doped catalysts were used by Olson *et al.* for the iso-butanol production using a flow-through reactor with N_2 as carrier gas. This gave 100% ethanol conversion with 85% iso-butanol yield.[107] Introduction of 0.6% Ni impurity into a similar catalyst resulted in 90% yield of iso-butanol. An Ir-based catalyst anchored on N-functionalized carbon support was used by Mu for the selective formation of iso-butanol (91% selectivity).[108] The catalyst was effectively recyclable up to 5 times and also could be applied towards the upgrading of fermentation broth with 49% conversion and 90% selectivity towards iso-butanol.

Apart from these initial developments on heterogeneous catalysts, there have been a few notable examples with homogenous complexes. The first homogeneous catalyst for iso-butanol synthesis *via* Guerbet-type coupling was reported by Wass and co-workers in 2016 using ruthenium diphosphine complexes based on dppm and dppe ligands (Fig. 15).[109] Among the considered complexes, the catalyst **57**, as a consequence of having smaller bite angle, gave ethanol conversions



Scheme 11 Guerbet-type reaction for the synthesis of isobutanol.

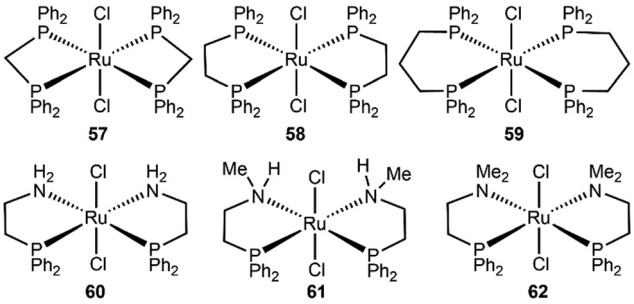


Fig. 15 Ru complexes reported by Wass for the synthesis of iso-butanol *via* Guerbet-type coupling.[109]

(up to 75%).[109] Promising results were also shown by using mixed P–N ligands (like the ones depicted in Fig. 15), and **57** exhibited high ethanol conversion (>75%) and excellent selectivity towards iso-butanol (>99%). Following this first report based on the homogenous catalyst, Wass used the same set of catalysts to further their previous understanding by establishing the *trans*-[$RuCl_2(dppm)_2$] (**57**) to be the most stable in the presence of water and other biogenic impurities, rendering it to be highly active (*ca.* 36% yield) towards selective (*ca.* 78% yield) iso-butanol formation.[110]

Soon after, Mansell reported a series of ruthenium complexes based on bis(phosphinophosphinine) ligands for the conversion of a methanol/ethanol mixture to iso-butanol in 38% yield with 88% selectivity after 2 h of the reaction. Further continuing the reaction until 20 h led to 50% yield of iso-butanol with 96% selectivity.[111]

The Wass group then used first-row transition metal Mn complexes based on dppm and dppe ligands towards the selective iso-butanol formation (82% selectivity with 27% yield) (Fig. 16).[112a] Notably, in a previous report, the Jones[102] and Liu[100] groups had independently reported PNP based pincer–Mn complexes (Fig. 14) to be active for Guerbet-type reactions. Liu further applied the catalyst for obtaining iso-butanol in 40% yield with 96% selectivity using a very high base loading (350 mol%

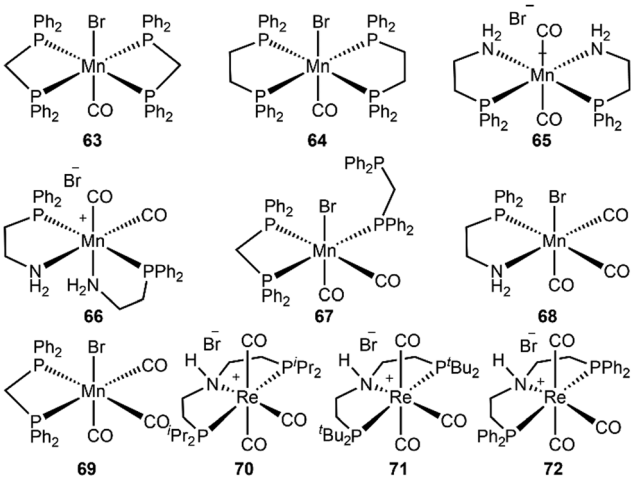


Fig. 16 Mn[112a] and Re[112b] complexes reported for the synthesis of iso-butanol.

relative to ethanol).[101] In their recent report, Wass thus demonstrated that pincer-type backbone for metal complexes is not a necessary prerequisite for such Guerbet-type reactions, although most of the previous reports has been focused on the pincer-type complexes.[112a]

The Carlini group has been carrying out investigations towards applying the Guerbet reaction to selectively produce other alcohols, typically branched alcohols, other than *n*-butanol. In 2002 and 2003, the group published a three-part series[113–115] of their work regarding the selective synthesis of iso-butanol. The first part reported that they had screened a variety of heterogeneous catalyst systems, in combination with sodium methoxide as a base to convert propanol and methanol to selectively produce iso-butanol.[113] The two catalysts used for this experiment, Cu/RANEY®-Ni and Cu 1995-P (a copper chromite catalyst), exhibited much higher activity for the conversion as compared to various homogenous catalysts. High iso-butanol yield of up to 68.8% and 77.5% was achieved while using Cu/Ni and Cu chromite, respectively, with almost 100% selectivity. Incidentally, it was found that replacing the reaction atmosphere from H_2 to N_2 significantly increased the catalyst activity, while the CO/H_2 atmosphere proved to be similar to that of H_2 and the optimum temperature, giving the maximum yield at about 200–220 °C.

The second report consisted of their study regarding the catalytic activity of the two previously used catalyst systems[113] to a ternary mixture of methanol/ethanol/*n*-propanol.[114] It was observed that the higher ethanol conversion, when used in combination with methanol, was achieved with copper chromite (61.2%) with 98.4% iso-butanol selectivity and a minor amount of propanol. A comparison with the results of the previous report yielded the conclusion that ethanol was less reactive in combination with methanol, as compared to propanol. A significant drawback of the process is the excessive use of the base MeONa, due to its continual hydrolysis to NaOH. Increased catalyst concentration and an optimum temperature of 200 °C gave the best iso-butanol yields when MeOH/EtOH/PrOH ternary mixtures were used.[114]

The third report further explored the methanol/*n*-propanol combination while using Ni, Ru and Rh-based heterogeneous catalysts, all of which proved to be active in the selective formation of iso-butanol when combined with MeONa.[115] Among the Ni heterogeneous catalysts, Ni/k (nickel supported on keiselguhr) was found to be most effective, in presence of MeONa as base, at 200 °C in N_2 atmosphere, yielding up to 55% of iso-butanol. The homogenous $Ni(OAc)_2$ and $NiCl_2(P^iPr_3)_2$ were found to be moderately active with turnovers up to 65 h^{-1}; the active catalytic species could be attributed to both homogenous and heterogeneous counterparts as black precipitates were found after each reaction. The use of Ru/Al_2O_3, Ru5/C and Rh/C yielded respectable yields. Almost complete selectivity of iso-butanol and catalytic activity was found to increase if they were not pre-activated.

Carlini also investigated the reaction using Pd catalysts, among which heterogeneous Pd/C in combination with MeONa gave excellent iso-butanol yields up to 93.2%, while homogenous ones like $Pd(PPh_3)_4$, $Pd(dba)_2$ and $Pd(dppe)Cl_2$ yielded high propanol conversion (up to 84%) which progressively increased with increasing reaction time.[116] In 2004, they reported that a mixture of two heterogeneous catalysts, copper chromite and Mg/Al mixed oxides catalysed the conversion of propanol/methanol selectively to iso-butanol with yields up to 29%.[117] A significant advantage was that the co-produced water did not inhibit the reaction by hydrolysing the base MeONa. A 2005 report by the same group showed that M/Mg/Al mixed metal oxides (M = Pd, Rh, Ni, Cu) exhibited very little catalytic activity towards iso-butanol formation with the exception of $Pd(dba)_2$ when used together with MgO and MeONa as bases (50% yield) and a few Cu/Mg/Al based catalysts (yield up to 79%), albeit at a higher reaction temperature of 280 °C.[118]

Carlini and co-workers also extended their work on the applications of Guerbet reaction to selectively produce 2-ethyl-1-hexanol from *n*-butanol using homogenous and heterogeneous Pd catalysts and copper chromite. $Pd(ddpe)Cl_2$ showed *n*-butanol conversion up to 42% and 51 turnovers, whereas Pd2/C gave up to 80 turnovers. Copper chromite catalysts showed significantly better *n*-butanol conversion up to 61%, but both catalytic systems showed a detrimental effect of the co-produced water on the reactivity.[119]

In 2021, Wass and co-workers reported a series of rhenium-based complexes utilizing bidentate and tridentate phosphinoamine ligands, designed for the selective production of iso-butanol from methanol and ethanol, which is an important advanced biofuel. Among the rhenium pincer complexes investigated, complexes **70–72** were identified as effective catalysts for this transformation. Notably, complex **72** demonstrated a remarkable catalytic performance, achieving iso-butanol formation with a yield of 35% and 97% selectivity over a 16-hour reaction period, even at extremely low catalyst loadings of 0.07 mol%. Despite these promising catalytic metrics, the study highlighted a significant limitation regarding the overall selectivity of these catalysts. Alongside the desired iso-butanol, the formation of a considerable amount of carboxylate salt solid by-product was observed, suggesting that the rhenium complexes, although efficient in the primary reaction, also facilitated undesirable side reactions leading to by-product formation.[112b]

Very recently, Wass and co-workers utilized diphosphine 1,1-bis(diphenylphosphino)ethylene (dppen)-based ruthenium complexes for the catalytic upgrading of ethanol and methanol to iso-butanol with 50% yield and 90% selectivity within 2 h of reaction.[112c] Table 7 provides a succinct summary of a few efficient catalysts that have been reported for the Guerbet upgradation of ethanol to *n*-butanol.

Summary and outlook

The Guerbet reaction involves a series of alcohol dehydrogenation to aldehyde, aldol condensation of the aldehyde, and hydrogenation of the resulting α,β-unsaturated aldehyde. Overall, two catalytic (de)hydrogenation fragments are coupled by an uncatalyzed, base-mediated aldol condensation segment to

Table 7 Efficient catalysts reported for the Guerbet upgrading reaction of ethanol

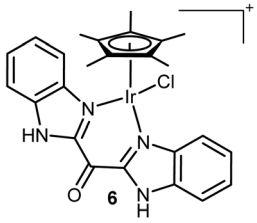
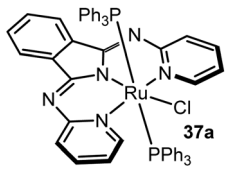
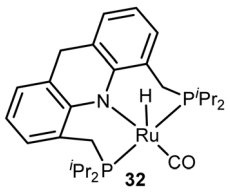
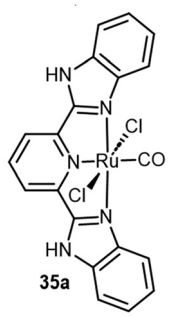
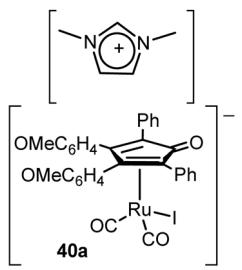
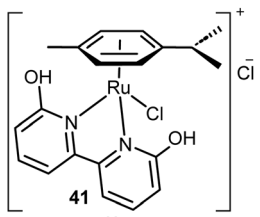
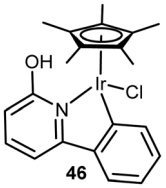
Catalyst	Reaction conditions	Reaction outcome
 6 Li, **2024**[74]	Catalyst 0.1 mol% Cs_2CO_3 (6 mol%) 180 °C, 12 h	Conversion = 47% Butanol yield = 37% Selectivity = 80% TON = 470 TOF = 39 h^{-1}
 37a Szymczak, **2016**[81]	Catalyst (0.1 mol%) NaOEt (5 mol%) 150 °C, 2 h	Conversion = 30% Butanol yield = 25% Selectivity = 91% TON = 300 TOF = 150 h^{-1}
 32 Milstein, **2016**[82]	Catalyst (0.02 mol%) NaOEt (4 mol%) 110 °C, 16 h	Conversion = 66.9% Butanol yield = 38% Selectivity = 68% TON = 3345 TOF = 209 h^{-1}
 35a Kumar, **2023**[86]	Catalyst (1 mol%) NaOEt (10 mol%) 110 °C (mw), 2 h	Conversion = 72% Butanol yield = 42% Selectivity = 57% TON = 72 TOF = 36 h^{-1}
 40a Mazzoni, **2022**[95]	Catalyst (0.2 mol%) NaOEt (20 mol%) 150 °C, 4 h 1.5 mol% of BQ	Conversion = 79% Butanol yield = 39% Selectivity = 62% TON = 195 TOF = 75 h^{-1}
 41 Jones, **2016**[96]	Catalyst (2 mol%) KO^{t}Bu (60 mol%) 85 °C, 24 h	Conversion = n.d. Butanol yield = 29% Selectivity = 51% TON = 29 TOF = n.d.

Table 7 (*continued*)

Catalyst	Reaction conditions	Reaction outcome
 46 Jones and Baker, **2015**[98]	Catalyst (0.2 mol%) $[Tp'Ni(\mu\text{-}OH)]_2$ (5 mol%) 150 °C, 24 h	Conversion = 37% Butanol yield = 34% Selectivity ≥ 99% TON = 185 TOF = n.d.

transform low-molecular weight alcohols to high-molecular weight alcohols. Notably from the context of the Guerbet reaction, the current pursuit worldwide is to formulate a powerful catalytic system comprising of a single catalyst capable of accomplishing the catalytic (de)hydrogenation fragments in the presence of an efficient base capable of driving the aldol coupling segment for the upgradation of feed-agnostic ethanol to fuel-grade *n*-butanol.

One of the major challenges associated with this reaction is the formation of water as a by-product. Water can not only potentially deactivate the (de)hydrogenation catalyst but also can reduce the rate of aldol condensation. While the former is detrimental for catalyst productivity, the latter potentially diminishes the selectivity of the C–C coupled product. The choice and the amount of the base is very crucial, as these factors dictate the extent of side reactions such as Cannizzaro and Tishchenko. These lead to the generation of unwanted side products while consuming the base and significantly affecting the overall efficiency of the reaction.

A long-term goal on a global front is to utilize the fermentation broth, which normally consists of 90% water and 10% ethanol, directly in a practical application. In addition to being effective, this strategy supports the idea of sustainability. However, in order to apply this methodology, it is essential to lessen the negative impact of water on the catalyst's deactivation, which compromises the efficiency of the reaction. The water formed in the reaction medium can be eliminated in numerous ways, including distillation, filtration and extraction. Apart from this, employing water scavengers which can bind with water molecules and lower its concentration, is a further strategy for dealing with water removal. On a parallel approach, emphasis may also be laid to the design and development of stable molecular catalytic systems that only tolerate water to operate efficiently in the fermentation broth, but also to selectively produce *n*-butanol, which can be easily separated from the broth owing to its immiscible nature with water.

Towards this end, the development of stable molecular homogeneous catalytic systems is associated with the challenge of their separation from reaction mixtures that makes them difficult to recycle and hence very expensive for the industrial applications. Additionally, molecular catalysts tend to be sensitive to air, moisture and temperature which ultimately leads to degradation and loss of activity. Developing methods that enable their immobilization on inert solid supports not only

aids the design of efficient catalysts that retain the selectivity signature of molecular catalysts, but also enables their efficient separation and recycling much like a heterogeneous catalyst.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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