Highly Selective Formation of *n*-Butanol from Ethanol through the Guerbet Process: A Tandem Catalytic Approach

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**S** *Supporting Information*

ABSTRACT: A highly selective (>99%) tandem catalytic system for the conversion of ethanol (up to 37%) to *n*-butanol, through the Guerbet process, has been developed using a bifunctional iridium catalyst coupled with bulky nickel or copper hydroxides. These sterically crowded nickel and copper hydroxides catalyze the key aldol coupling reaction of acetaldehyde to exclusively yield the C_4 coupling product, crotonaldehyde. Iridium-mediated dehydrogenation of ethanol to acetaldehyde has led to the development of an ethanol-to-butanol process operated at a lower temperature.

The efficient production of biofuels from renewable biomass sources as a greener alternative to conventional gasoline has recently been receiving increased attention.[1] Currently, ethanol is used as a sustainable fuel, made from the fermentation of sugar-containing crops such as corn.[2] Although ethanol is being explored as a renewable alternative to gasoline, it poses several disadvantages. Ethanol has only 70% of the energy density of gasoline, can be corrosive to current engine technology, and readily absorbs water, which causes problems in separation and transportation in existing fuel infrastructure. Alternatively, butanol offers a more viable option, as it has properties similar to that of gasoline.[3] Butanol has an energy density closer to gasoline (90%), is immiscible with water, is noncorrosive, and can be blended with gasoline at higher concentrations (16%) offering twice the renewable content than that of ethanol per gallon.[4] As a result, upgrading ethanol into an advanced biofuel, such as butanol, offers a more efficient alternative fuel from renewable biomass sources. Consequently, butanol is considered a "drop-in" replacement for gasoline.[4]

Despite these advantages, the incorporation of butanol into the energy economy remains underexplored. Common synthetic routes to produce butanol from ethanol, including bacterial fermentation (also known as the "A.B.E." process, which produces a mixture acetone, butanol, and ethanol)[5] and hydroformylation/hydrogenation of propylene,[6] and the Guerbet reaction[7] suffer from poor selectivity, separation issues, and low conversion and/or yield. Based on our recent reports on the reversible dehydrogenation–hydrogenation processes involving alcohols,[8] we became interested in converting ethanol into *n*-butanol via the Guerbet process. This industrial process is comprised of three steps: (a) dehydrogenation of a primary alcohol, (b) a base-catalyzed aldol coupling reaction, and (c)

hydrogenation of an α,β-unsaturated aldehyde (Scheme 1), allowing for the coupling of two primary alcohols into a longer-

Scheme 1. Guerbet Process
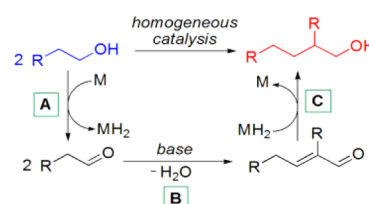
chained alcohol through "borrowed hydrogen" chemistry with no net loss of the hydrogen gas.[9] Homogeneous catalytic systems that utilize the Guerbet process typically feature precious metal catalysts for the de/hydrogenation steps (Scheme 1A,C) and an inorganic base to aid in the aldol coupling step (Scheme 1B).[10] Although most of these Guerbet processes have been performed with some longer-chain primary alcohols, the same reaction utilizing ethanol as a substrate remains a great challenge for several reasons.[11] These mainly include the uphill thermodynamic challenges associated with the dehydrogenation of ethanol (see Supporting Information (SI) for thermodynamic calculations) and the formation of side-products due to the uncontrolled aldol reaction involving highly reactive acetaldehyde.[11]

In 2009, Ishii et al. reported an iridium catalyst, Ir(COD)(acac) (COD: 1,5-cyclooctadiene, acac: acetylacetonate), in the conversion of ethanol to *n*-butanol with a moderate selectivity up to 67% at 12% conversion.[12] Catalytic reactions were carried out in the presence of a bidentate phosphine ligand, NaOEt, and 1,7-octadiene as a sacrificial hydrogen acceptor that likely assists in the ethanol dehydrogenation step. Longer-chain Guerbet alcohols were formed as side products because of the lack of selectivity in the aldol reaction for acetaldehyde.[11b,c] More recently, Wass et al. have reported ruthenium-based homogeneous catalysts that promote upgrading of ethanol to *n*-butanol with selectivity as high as >94% at 22% conversion.[13a] A bisphosphine ligand with a smaller bite-angle and its hemilabile nature in the related ruthenium complexes seemed critical for catalysis. According to a recent report by the same group, mixed donor phosphine-amine ligands are effective ligands with

ruthenium in the Guerbet reaction using ethanol in the presence of water.[13b] Remarkably, >90% selectivity was achieved with slightly higher ethanol conversion (31%). In addition to these homogeneous systems, heterogeneous catalysts have recently been reported for the same reaction with selectivity up to 80% at 25% ethanol conversion.[14] Recently, air-stable iridium catalysts are also reported that can work in aqueous medium.[15]
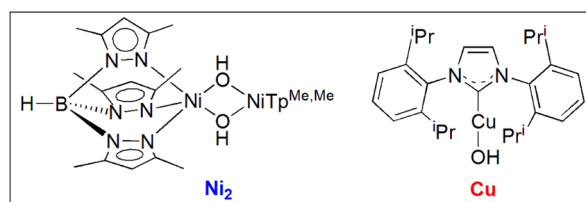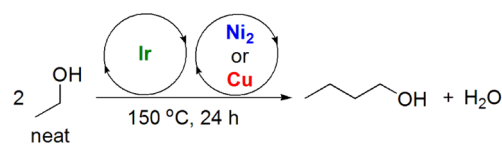
In order to develop an efficient process for upgrading ethanol, we first sought to identify a catalyst that can selectively dehydrogenate a primary alcohol, preferably in an acceptorless fashion, to produce an aldehyde under basic conditions. The Guerbet mechanism also requires the same catalyst to be active in the hydrogenation of α,β-unsaturated aldehydes. A thorough survey of the literature revealed that Fujita and Yamaguchi's Cp*Ir[(2-OH-6-phenyl)pyridine]Cl (**Ir**) catalyst, bearing a functional α-hydroxypyridine motif, is an excellent homogeneous catalyst for the acceptorless dehydrogenation of primary alcohols to produce aldehydes in the presence of bases such as NaOMe, NaO^{t}Bu, etc.[16] In general, Cp*Ir catalysts bearing α-hydroxypyridine derivatives have been reported to operate at high temperatures, which in turn demonstrates their thermal robustness.[17] The aldol coupling of acetaldehyde, on the other hand, is key to the selectivity of the formation of *n*-butanol and is often the primary reason for the production of longer-chain Guerbet products.[11b,c] In all of the previously studied Guerbet reactions, a simple inorganic base, such as NaOEt, was used to catalyze this critical step. However, Wass et al. have noted that the aldol coupling of acetaldehyde in the presence of NaOEt proceeded with a very poor selectivity toward the formation of the desired crotonaldehyde.[13]

As an alternative strategy to increase the selectivity of both the aldol coupling step and the net Guerbet reaction, we planned to replace the simple inorganic bases with highly basic transition-metal complexes containing sterically encumbered ligands (Scheme 2). We hypothesized that the selectivity of the key

Scheme 2. A Proposed Strategy to Improve the Selectivity of the Guerbet Process
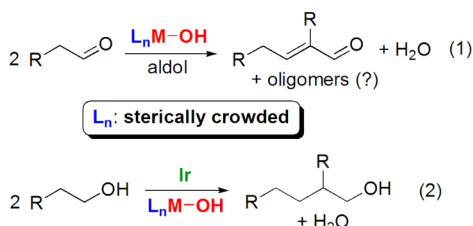
aldol condensation step could be controlled by fine-tuning the bulkiness of the ligands present in these transition-metal complexes. Transition-metal hydroxide complexes such as [Tp′Ni(μ−OH)]$_2$ (**Ni$_2$**)[18] and (IPr)CuOH (**Cu**)[19] [where Tp′: tris(3,5-dimethyl-pyrazolylborate) and IPr: 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene] have been shown to act as strong bases in simple stoichiometric reactions (chemical structures of these bases are shown in Figure 1). Therefore, we planned to explore their catalytic activity in related aldol coupling reactions (Scheme 2, eq 1) and viability for carrying out the Guerbet process using a combination of these metal hydroxides and **Ir** (Scheme 2, eq 2). Herein, we report a tandem catalytic process for the generation of *n*-butanol from ethanol with a remarkably high selectivity and good conversions.

Figure 1. Selective conversion of ethanol to *n*-butanol through tandem catalysis. [a][Ir] = 0.034 M. [b][Ni$_2$] = 0.85 M or [Cu] = 1.7 M. [c]Based on Ir.

entry	catalyst (mol %)[a]	base[b]	% conv. (% yield)	selectivity (%)	TON[c]
1	Ir (0.2)	Ni$_2$	37 (34)	>99	185
2	Ir (0.2)	Cu	32 (28)	>99	160

Through control experiments and mechanistic investigation we have uncovered the origin of high selectivity in this system.

We initially started our investigation employing **Ir** (0.2 mol %, 0.034 M) as the homogeneous catalyst for the Guerbet reaction of neat ethanol in the presence of common inorganic bases such as NaOEt, KO^{t}Bu, and KOH (Table 1, eq 3). Catalytic reactions were performed at 150 °C for 4−24 h in order to compare the catalytic activity of **Ir** with the previously reported ruthenium systems.[13] Although NaOEt was used in both Ishii's[12] and Wass's[13] systems, we observed only baseline catalytic activity

Table 1. Iridium-Catalyzed Conversion of Ethanol to *n*-Butanol using Common Inorganic Bases[a]
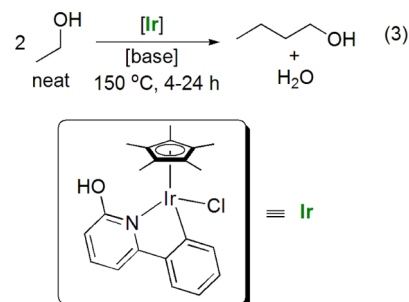
| entry	catalyst (mol %)	base	% conv. (% yield)[b]	selectivity (%)[c]	TON[d]
1	Ir (0.2)	NaOEt	6 (4)	91	30
2	Ir (0.2)	KO^{t}Bu	23 (12)	61	115
3	Ir (0.2)	KOH	31 (26)	83	155
4[e]	Ir (0.2)	KOH	40 (33)	77	200
5[e]	Ir (0.1)	KOH	34 (28)	80	340
6[e]	Ir (0.03)	KOH	21 (14)	78	700
7[e,f]	Ir (0.2)	–	21	–	105

[a]For a list of catalytic runs with other catalysts, please see the Table S1. [b]Conversion of ethanol to Guerbet products, with the yield of *n*-butanol in parentheses (determined by gas chromatography). [c]Selectivity of *n*-butanol in the liquid fraction (determined by gas chromatography). [d]Turnover number (TON) is calculated based on moles of ethanol converted to Guerbet products per mole of iridium. [e]Run for 24 h. [f]The only product is ethyl acetate.

with this base, (6% conversion, entry 1) affording a very small amount of desired *n*-butanol. When KO*t*Bu was substituted for NaOEt, the respective conversion of ethanol increased by a factor of 4 times (23% conversion, entry 2) the conversion with NaOEt, but the selectivity for the formation of *n*-butanol was only 61% due to the formation of other higher-order Guerbet products.[20] Replacing KO*t*Bu with KOH increased the conversion of ethanol to 31% with a decent selectivity up to 83% (entry 3).[21] Under standard catalytic conditions, running the reaction for longer time (24 h) converted ~40% ethanol with a slightly lower selectivity for *n*-butanol (entry 4). With KOH being the suitable base for this system, the catalyst loading could be further decreased to 0.03 mol % to convert ethanol into *n*-butanol with high turnovers and decent selectivity (entry 6). A control experiment in the absence of a base produced ethyl acetate as the sole product via dehydrogenative coupling of ethanol (entry 7).

Having established the protocol for the iridium-catalyzed ethanol-to-butanol conversion in the presence of KOH, we next planned to replace KOH with bulky transition-metal hydroxides as per our strategy to improve the selectivity of the net Guerbet reaction. For our initial investigation, we focused on the well-defined dimeric complex [Tp′Ni(μ-OH)]$_2$ (**Ni$_2$**)[18] and monomeric (IPr)CuOH (**Cu**)[19] complex reported in the literature. We hypothesized that the bulky Tp′ and IPr ligands present in these two complexes will only allow for small-molecule coupling in the critical aldol condensation step and hence increase the selectivity. Therefore, we explored the possibility of carrying out the Guerbet reaction of ethanol in a tandem catalytic fashion employing both **Ir** and **Ni$_2$** or **Cu** catalysts. Gratifyingly, when the Guerbet reaction of neat ethanol was performed at 150 °C for 24 h in the presence of both **Ir** and **Ni$_2$** (a relative ratio of 1:25), *n*-butanol was produced as the sole Guerbet product (Figure 1). Longer-chain Guerbet products, commonly observed in other cases, were not observed in this reaction which makes this tandem catalytic process unique (analyzed by gas chromatography, see the SI). We observed that 37% of ethanol was converted to *n*-butanol (34% GC yield) in this process with a selectivity as high as >99%.[22] Under the same conditions, the copper-containing base also produced *n*-butanol with a high yield and selectivity at 32% ethanol conversion. To the best of our knowledge, this tandem catalytic process represents the best activity observed to date in the Guerbet reaction of ethanol.

To determine the origin of high selectivity in these reactions, we focused our attention to the base-catalyzed aldol coupling step (Scheme 1B) that primarily governs the selectivity of the Guerbet reaction. We first investigated the nickel and copper-catalyzed reaction of acetaldehyde and compared the results of the same reaction catalyzed by KOH. Consistent with Wass's result with NaOEt,[13] we found that KOH-catalyzed aldol condensation of acetaldehyde produced the desired C$_4$ coupling product, crotonaldehyde, with only 23% selectivity after 1 day at 150 °C.[23] In marked contrast, the same reaction catalyzed by either **Ni$_2$** or **Cu** generated crotonaldehyde as the exclusive coupling product under the same conditions (Scheme 3). The remarkable selectivity observed in the aldol reaction of acetaldehyde with these bulky transition-metal hydroxide complexes is unprecedented in the literature and provides a strategy to chemically discriminate for coupling between two small (C$_2$) aldehyde molecules. To further test this hypothesis, catalytic aldol coupling of 1-butanal (C$_4$) was performed in the presence of **Ni$_2$** (1 mol %), and only traces of C$_8$ product were detected by gas chromatography (Scheme 3). Furthermore, nickel-catalyzed aldol reaction of crotonaldehyde did not
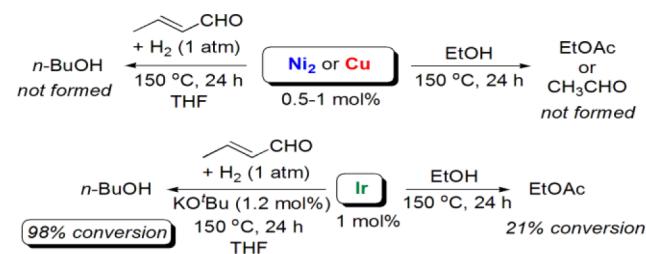
Scheme 3. Nickel and Copper-Catalyzed Aldol Reactions

Scheme 4. Control Experiments
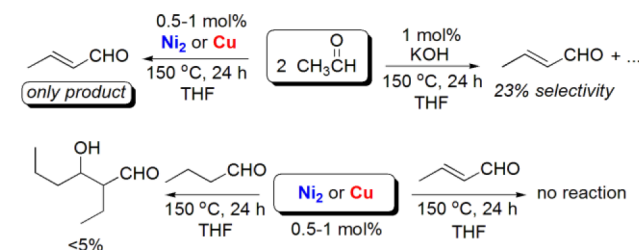
generate any C$_8$ or longer-chain products. A similar trend in reactivity was observed with **Cu**, however products were formed with slightly lower yields as the thermal stability of **Cu** was found to be lower than the **Ni$_2$** complex. Nonetheless, these results indicate that the steric crowding at the metal center plays a key role in determining the aldol-product distribution, and this feature can be fine-tuned to dictate the outcome of the reaction.

In order to determine if **Ni$_2$** or **Cu** is involved in the dehydrogenation and hydrogenation steps of the Guerbet process (steps A and C, Scheme 1), dehydrogenation of ethanol and hydrogenation (with 1 atm H$_2$) of crotonaldehyde were carried out using either **Ni$_2$** or **Cu** as catalysts (Scheme 4). None of these reactions resulted in butanol formation, suggesting that these metal hydroxides only assist in the aldol condensation step in the Guerbet reaction sequence. On the other hand, **Ir**-catalyzed dehydrogenation of ethanol produced ethyl acetate as the only product (21%, entry 7, Table 1). Catalytic hydrogenation (1 atm H$_2$) of crotonaldehyde with either a mixture **Ir** and KO*t*Bu (1:1.2) or the related Cp*Ir[(2-OH-6-phenyl)-pyridine](H)[16] complex produced the fully hydrogenated product *n*-butanol quantitatively (Scheme 4). These control studies imply that while **Ir** catalyst participates in the dehydrogenation and hydrogenation steps, **Ni$_2$** or **Cu** aids in the aldol condensation step involved in the Guerbet reaction. However, these control experiments do not rule out the mechanism in which the iridium catalyst also assists in the aldol step during the Guerbet catalysis.

As mentioned earlier, acceptorless dehydrogenation of ethanol is one of the most challenging steps involved in the Guerbet process. Often high temperatures are required to favor the equilibrium toward the product, acetaldehyde.[11] If this step could be performed effectively at a lower temperature, the overall Guerbet process could be carried out under much milder conditions. To explore this possibility, we investigated this key step separately by NMR spectroscopy. As **Ni$_2$** is a paramagnetic complex and it causes NMR signal-broadening, we used the diamagnetic **Cu** complex for these NMR studies. The iridium complex is known to operate in a cooperative fashion.[16,24] Thus, we first treated **Ir** with 1 equiv of basic **Cu** (Scheme 5) which caused an instantaneous reaction to generate a new iridium

Scheme 5. Dehydrogenation of Ethanol and the Guerbet Reaction at 100 °C
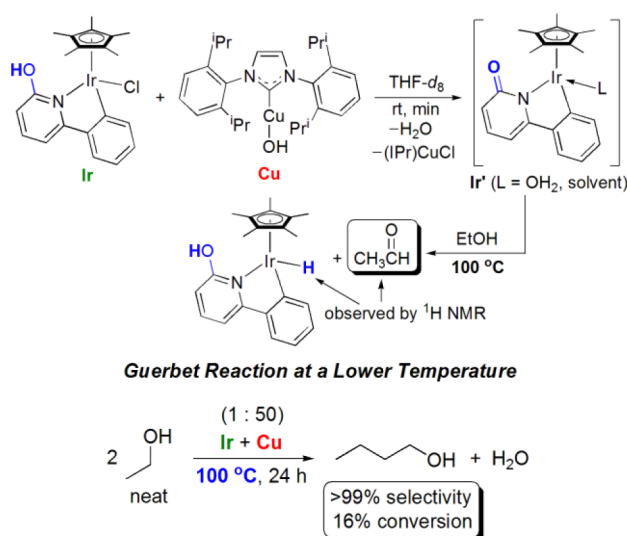
species observable by the ^{1}H NMR spectroscopy. The characteristic OH resonance of **Ir** at δ 8.07 disappeared, suggesting formation of the pyridone form of the catalyst (**Ir′**). When 1 equiv of ethanol was added to the *in situ* formed **Ir′** at room temperature, no significant difference was noticed. However, when the same reaction mixture was heated to 100 °C, the release of acetaldehyde was observed (δ 9.66, CH$_3$CHO) by ^{1}H NMR spectroscopy with the simultaneous formation of the corresponding iridium hydride (δ −15.27, IrH) (Scheme 5). The results of these ^{1}H NMR studies indicate that it is possible to perform the dehydrogenation of ethanol, and therefore the Guerbet process, at temperatures as low as 100 °C. We observed that ethanol could be successfully converted to *n*-butanol even at 100 °C with >99% selectivity.

In summary, a tandem catalytic process, employing a bifunctional iridium catalyst and sterically crowded nickel or copper-based catalysts, has been developed to convert ethanol to *n*-butanol through the Guerbet process. This process produces *n*-butanol with a remarkably high selectivity (>99%) at good conversions. It has been independently demonstrated that the bulky nickel or copper hydroxide complexes catalyze the aldol coupling of acetaldehyde to only produce the C$_4$ coupling product, crotonaldehyde, which is in fact the origin of the high selectivity observed in the Guerbet process. We have been able to selectively convert ethanol to *n*-butanol at even 100 °C, albeit with a lower conversion.

ASSOCIATED CONTENT

ⓈSupporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10257.

Experimental procedures and product characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(23) Note that the initial concentration of acetaldehyde in these reactions is likely to be much higher than the actual concentration during catalysis.

(24) Catalytic Guerbet reaction with Cp*Ir(phenylpyridine)Cl (no OH functionality) did not produce *n*-butanol.