

Control in Advanced Biofuels Synthesis via Alcohol Upgrading: Catalyst Selectivity to *n*-Butanol, *sec*-Butanol or Isobutanol

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Ruthenium complexes with tetradentate PNNP donor ligands demonstrate a marked change in selectivity compared to analogous bis bidentate PN complexes in Guerbet catalysis, producing mixtures of *n*-butanol (17%), *sec*-butanol (14%) and ethyl acetate (66%) rather than the usual 90%+ selectivity to *n*-butanol. Tridentate PNP ruthenium complexes such as [Ru(H)(Cl)(CO)(Ph₂PCH₂CH₂NHCH₂CH₂PPh₂)] also produce *sec*-buta-

anol and, in optimized conditions (120 °C, 10 mol% NaOEt base), achieve 71% selectivity to this butanol isomer. The same tri- and tetradentate complexes are efficient catalysts for the conversion of methanol/ethanol mixtures to isobutanol (up to 97% selectivity). In this way, judicious choice of ligand within this general catalyst family allows selectivity to three butanol isomers of interest as fuel molecules.

Introduction


Obtaining sustainable alternatives to liquid fossil fuels for transportation is a crucial objective, both from an environmental perspective as well as to ensure future energy security.^[1] The most widely used alternative to gasoline is bioethanol but this is by no means an ideal replacement; it is corrosive to engine technology, has a significantly lower energy density than gasoline and its hygroscopic nature can lead to storage problems.^[2] By contrast, butanol isomers have fuel characteristics much closer to that of conventional gasoline and are often considered 'advanced biofuels' because of this superior performance.^[3] Biosustainable routes to butanols, typically developed from Weizmann's ABE (acetone-butanol-ethanol) process, remain challenging because of poor conversion and mixed selectivity.^[4] We, and others, have been exploring an alternative route in which widely available bioethanol is upgraded to butanol using Guerbet chemistry.^[5] A key development in this field was our discovery of homogeneous ruthenium diphosphine catalysts that exhibit excellent selectivity to *n*-butanol.^[6] There have been several other recent examples of homogeneous ruthenium,^[7] iridium^[8] or manganese^[9] catalysts that demonstrate similar performance. A consequence of the


'borrowing hydrogen' mechanism by which all of these catalysts operate is that *n*-butanol is the sole C₄ alcohol product, this selectivity being set at the aldol condensation that leads to C–C bond formation during catalysis. Different butanol isomers have different fuel properties, with isobutanol (2-methylpropan-1-ol) typically being the most valuable due to factors such as a higher octane number and energy density (98% of that of gasoline) compared to the linear isomer.^[10] Obtaining isobutanol from ethanol alone is difficult to envisage using Guerbet chemistry but we have reported that our ruthenium catalysts are also capable of converting ethanol/methanol mixtures to isobutanol with high ethanol conversion (>75%) and excellent selectivity for isobutanol formation (>99%).^[11] In this case the "borrowing hydrogen" mechanism requires two cycles (ethanol/methanol to *n*-propanol, *n*-propanol/methanol to isobutanol) with two equivalents of water produced as the by-product. Building on these results, we have demonstrated the water tolerance of such catalysts using model substrates for industrial fuel fermentation broths.^[12] Other examples of homogeneous ruthenium,^[13] manganese^[14] and rhenium^[15] catalysts have also been reported.

Sec-Butanol (butan-2-ol) is another attractive isomer which already finds applications as a solvent and fuel additive^[16] and as a precursor for the solvent methylethylketone (MEK) via oxidation.^[17] *Sec*-Butanol production relies on glucose fermentation methods to date and its synthesis has not previously been reported directly via Guerbet catalysis. In this paper, we report homogeneous catalysts that, by judicious choice of ligand, can access all of the technologically-relevant butanol isomers including *sec*-butanol.

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Results and Discussion

Tetradentate vs bis bidentate ruthenium complexes

We have previously reported that ruthenium complexes of mixed donor P–N ligands (**1** and **2**, Figure 1) are effective catalysts for ethanol to *n*-butanol upgrading, showing advantages over diphosphine catalysts (**3** and **4**) in some aspects such as improved water tolerance.^[7a] In general, although the mono chelate cymene complexes are useful in that they allow rapid ligand screening by *in situ* reaction of ligand with the parent $[\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})_2]$, the bis bidentate complexes **2** and **4** are preferred since they tend to be more robust and long-lived over a typical catalytic run.

We speculated that related tetradentate PNNP ligands would be interesting targets as a comparison to bis bidentate P–N ligand complexes. Such ligands are widely used in other areas of catalysis,^[18] have straightforward and modular syntheses, and offer the potential for precise control over the metal geometry and local electronic and steric environment. Four ligands (**5**–**8**) were obtained via literature methods or modifica-

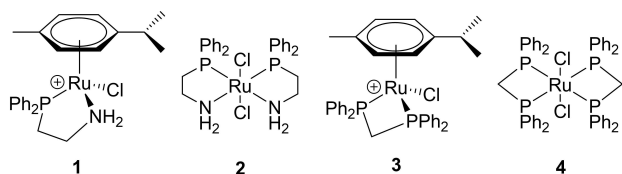
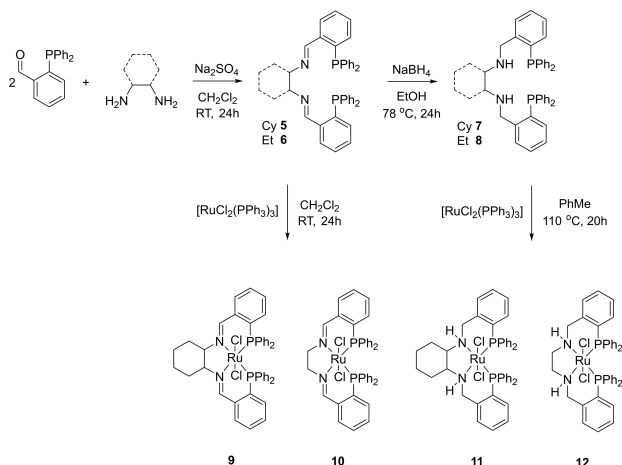
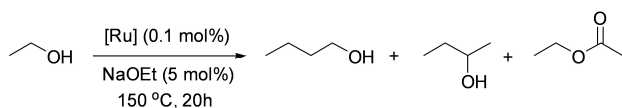


Figure 1. Selected ruthenium Guerbet catalysts. Chloride counterions omitted from **1** and **3** for clarity.



Scheme 1. Preparation of ligands **5**–**8** and complexes **9**–**12**.



Scheme 2. Ethanol upgrading catalysis with **1**–**4** and **9**–**12**.

tions thereof,^[19] and subsequently coordinated to ruthenium (Scheme 1).^[20]

Complexes **9**–**12** were screened for ethanol upgrading using our standard conditions (Scheme 2) as reported previously (150 °C, 20 hours, NaOEt base in sealed pressure vessel), alongside our previous best catalysts for this reaction **1**–**4**. Results are reported in Table 1.

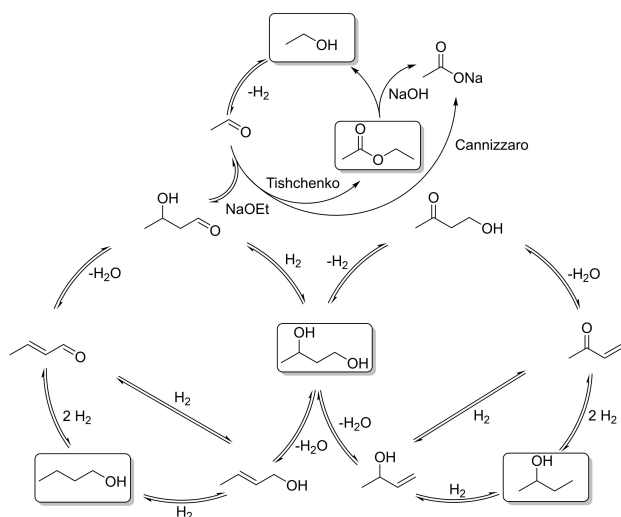
At first glance, the performance of these tetradentate complexes (runs **5**–**8**) is disappointing; conversion is low and selectivity to *n*-butanol is very poor compared to the related *bis* bidentate complexes (runs **1**–**4**). Such poor selectivity within the liquid fraction of products is typically due to a lack of control in limiting ethanol homologation to C_4 alcohols, higher alcohols undergoing further conversion to give higher Guerbet products such as hexanols and octanols. However, in this case, C_4 products still dominate and the results are consistent with a change in catalyst selectivity, implying a change in mechanism. Ethyl acetate is observed as the major liquid product with catalysts **9**–**12**, which implies a Tishchenko^[21] or Cannizzaro-type mechanism^[22] is operating, as has been previously observed for related catalysts.^[7] Ethyl acetate has very recently been reported to show some promise as a fuel blend additive, especially when co-produced with two molar equivalents of hydrogen.^[22c] More surprising is the production of *sec*-butanol alongside ethyl acetate; for example, catalyst **10** (run **6**) gives 8.8% ethyl acetate and 1.8% *sec*-butanol. To our knowledge, this has not previously been observed and, as well as being an intriguing mechanistic puzzle, it opens the possibility to tune catalyst selectivity to achieve yet higher yields of this potentially valuable product. A possible mechanism is illustrated in

Table 1. Ethanol upgrading catalysis with **1**–**4** and **9**–**12**.

Run ^[a]	[Ru]	Conversion [%] ^[b]	Selectivity (Yield) ^[c]			
			<i>n</i> -Butanol	<i>sec</i> -Butanol	Ethyl acetate	Other ^[d]
1 ^[e]	1	24	91 (21)	–	–	9.2 (3.1)
2 ^[e]	2	19	94 (17)	–	1.3 (0.2)	5.2 (1.5)
3 ^[f]	3	22	91 (20)	–	–	8.5 (2.8)
4 ^[f]	4	11	94 (9.6)	–	–	6.0 (1.9)
5	9	15	29 (4.3)	10 (1.5)	61 (8.9)	1.5 (0.3)
6	10	14	17 (2.3)	14 (1.8)	66 (8.8)	3.7 (0.7)
7	11	14	25 (3.5)	9.0 (1.3)	65 (9.3)	1.5 (0.3)
8	12	14	28 (3.7)	5.0 (0.7)	61 (8.1)	5.7 (1.2)

[a] Standard conditions: 10 mL EtOH (171 mmol), 0.1 mol% [Ru], 5 mol% NaOEt, 150 °C, 20 h. [b] Conversion of ethanol based on total amount of liquid products obtained as determined by GC analysis. [c] Total yield and selectivity of Guerbet products in the liquid fraction as determined by GC analysis. [d] Other products include 2-ethyl-1-butanol, 1-hexanol, 2-ethyl-1-hexanol and 1-octanol (see SI). [e] Result taken from reference [7a], conditions: 35 mL EtOH, 0.1 mol% [Ru], 5 mol% NaOEt, 150 °C, 4 h. [f] Result taken from reference [6], conditions: 35 mL EtOH, 0.1 [Ru], 5 mol% NaOEt, 150 °C, 4 h.

Scheme 3. After dehydrogenation of ethanol to acetaldehyde, two pathways are possible. Firstly, Tishchenko and/or Cannizzaro reactions leading to ethyl acetate and/or (in the presence of NaOH caused via hydrolysis of NaOEt base) saponification to sodium acetate. Since water is generated during the reaction, sodium acetate is very typically observed even in ethanol upgrading reactions that are selective to butanol in the liquid phase if all products (liquid and solid) are analyzed.^[7a] The second possibility is for aldol condensation to occur with the acetaldehyde. The aldol product is usually considered to rapidly dehydrate to yield crotonaldehyde that subsequently hydrogenates to give the desired *n*-butanol. Clearly, these two possibilities do not yet account for the formation of *sec*-butanol, and we speculated the aldol product might follow alternative pathways with these particular catalysts, isomerization of the aldol alcohol leading to 4-hydroxy-2-butanone, either directly or via a hydrogenation (to butane-1,3-diol) dehydrogenation



Scheme 3. Possible reaction pathways for the formation of ethyl acetate, *n*-butanol and *sec*-butanol.

Table 2. Catalysis with addition of butane-1,3-diol and in open system.

Run [a]	[Ru]	Conditions	Selectivity (Yield) ^[b]		
			<i>n</i> -Butanol	<i>sec</i> -Butanol	Ethyl acetate
9	4	[c]	80 (24)	1.0 (0.3)	-
10	4	[d]	82 (17)	2.1 (0.4)	-
11	9	[c]	15 (2.6)	30 (5.3)	55 (9.7)
12	9	[d]	21 (3.0)	61 (8.7)	16 (2.2)
13	4	[e]	94 (1.5)	-	-
14	4	[f]	84 (15)	1.1 (0.2)	-
15	9	[e]	0.4 (0.3)	0.6 (0.6)	99 (93)
16	9	[f]	29 (4.3)	18 (2.7)	53 (7.9)

[a] Standard conditions: 10 mL EtOH (171 mmol – butane-1,3-diol mmol as stated), 0.1 mol% [Ru], 5 mol% NaOEt, 150 °C, 20 h. [b] Total yield and selectivity of Guerbet products in the liquid fraction as determined by GC analysis. [c] 5.0 mol% butane-1,3-diol added. [d] 12.5 mol% butane-1,3-diol added. [e] Performed in an open vessel at reflux temperature: 10 mL EtOH (171 mmol), 0.1 mol% catalyst, 5 mol% NaOEt, samples were removed periodically for analysis (see SI) [f] no butane-1,3-diol added.

sequence; either way, dehydration followed by hydrogenation (analogous to the usual pathway) now yields *sec*-butanol.

To understand the formation of the experimentally observed products, we performed a series of experiments in which the possible catalytic intermediate butane-1,3-diol was added at the start of catalysis and any changes to performance recorded (Table 2).

Catalyst 4 was examined as an exemplar *n*-butanol-selective catalyst, and catalyst 9 as an example producing *sec*-butanol. Butane-1,3-diol was identified as a potentially revealing intermediate; from this common species, routes to *n*-butanol (via dehydrogenation of the primary alcohol or dehydration of the secondary alcohol) or *sec*-butanol (via dehydrogenation of the secondary alcohol or dehydration of the primary alcohol) are possible. When varying amounts of this intermediate are added, catalyst 4 continues to give the same selectivity to *n*-butanol within error (compare runs 9 and 10 to run 14); however, catalyst 9 now gives significantly more *sec*-butanol relative to ethyl acetate (compare runs 11 and 12 to run 16). This suggests a catalyst-structure-dependent change in selectivity with regard to the conversion of this intermediate may be responsible for the observed changes in selectivity. Catalysts selective for the conversion of ethanol to ethyl acetate are well-known; this reaction co-generates two equivalents of hydrogen, and catalysts are therefore typically run in an open system in which hydrogen is released.^[23] Employing such conditions for catalyst 4 did not lead to a switch to ethyl acetate formation, rather a simple reduction in the amount of *n*-butanol produced (compare runs 13 and 14). By contrast, catalyst 9 produces ethyl acetate in 99% selectivity in an open system compared with the mixture of ethyl acetate and butanol isomers in a closed system (compare runs 15 and 16). This again implies ligand structure as being key to controlling selectivity.

Tridentate PNP Ru complexes

Complexes with tridentate PNP donor sets are well established in the catalytic conversion of ethanol to ethyl acetate and related chemistries.^[23] For example, Beller and co-workers have previously reported that 13 readily converts ethanol to ethyl acetate by acceptorless dehydrogenative coupling under mild reaction conditions.^[23a–b] The conditions for such reactions are in open vessels to vent the hydrogen produced, i.e. analogous to Table 2, runs 13 and 15); under normal Guerbet conditions such catalysts are poor for ethanol-ethanol homocoupling.^[23e] We were intrigued as to whether these catalysts in the closed conditions for which we observe *sec*-butanol with tetradentate species would also produce this alcohol isomer. A range of complexes (Figure 2) were accessed by a slightly modified literature procedure (see SI). Complex 13 is commercially available, whilst complexes 14–16 were prepared following the literature procedure developed by Ding and co-workers,^[24] the PNP ligands readily displacing the triphenylphosphine ligands of [Ru(H)(Cl)(CO)(PPh₃)₃] to give the desired complexes in good yield (72–82%). These systems were screened in sealed autoclave conditions, see Table 3.

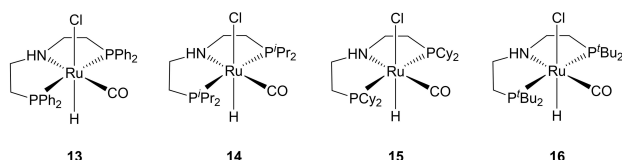


Figure 2. Tridentate PNP catalysts 13–16.

Table 3. Ethanol upgrading catalysis with 13–16.						
Run ^[a]	[Ru]	Conv. [%] ^[b]	Selectivity (Yield) ^[c]			
			<i>n</i> -Butanol	<i>sec</i> -Butanol	Ethyl acetate	Other ^[d]
17	13	21	8.2 (1.7)	32 (6.6)	60 (13)	0.2 (0.1)
18 ^[e]	13	18	9.6 (1.7)	37 (6.6)	54 (9.5)	–
19	14	24	21 (4.8)	15 (3.4)	63 (16)	0.6 (0.2)
20	15	23	21 (4.5)	18 (3.8)	61 (14)	0.7 (0.3)
21	16	15	88 (12)	0.7 (0.1)	0.5 (0.1)	11 (2.4)
22 ^[f]	13	13	10 (1.3)	54 (6.6)	36 (4.5)	0.4 (0.1)
23 ^[g]	13	29	6.3 (1.8)	23 (6.6)	71 (20)	0.2 (0.2)
24 ^[h]	13	16	17 (2.6)	71 (11)	11 (1.8)	1.3 (0.3)
25 ^[i]	13	19	28 (5.1)	68 (13)	1.2 (0.2)	3.4 (1.0)
26 ^[j]	13	15	33 (4.6)	57 (8.2)	8.5 (1.3)	1.9 (0.5)
27 ^[k]	13	27	2.6 (0.7)	34 (9.2)	63 (17)	–
28 ^[l]	13	22	4.2 (0.9)	73 (16)	21 (4.6)	–
29 ^[m]	13	4.2	1.4 (0.1)	78 (3.2)	18 (0.8)	1.9 (0.1)

[a] Standard conditions: 10 mL EtOH (171 mmol), 0.1 mol% [Ru], 5 mol% NaOEt, 150 °C, 20 h. [b] Conversion of ethanol based on total amount of liquid products obtained as determined by GC analysis. [c] Total yield and selectivity (%) of Guerbet products in the liquid fraction as determined by GC analysis. [d] Other products include 2-ethyl-1-butanol, 1-hexanol, 2-ethyl-1-hexanol and 1-octanol (see SI). [e] Reaction run for 4 h. [f] 120 °C. [g] 180 °C. [h] 120 °C, 10 mol% NaOEt. [i] 120 °C, 20 mol% NaOEt. [j] 120 °C, 10 mol% NaOEt, 0.01 mol% [Ru]. [k] 5.0 mol% butane-1,3-diol added [l] 12.5 mol% butane-1,3-diol added. [m] 120 °C, 10 bar H₂.

Under these conditions, catalyst **13** gives appreciable amounts of *sec*-butanol (up to 37% of total liquid products) alongside *n*-butanol and the more usual ethyl acetate (runs 17 and 18). Catalyst **14**, whilst still favoring ethyl acetate, now gives a mixture of *n*- and *sec*-butanol as alcoholic products (run 19). Increasing the bulk of the phosphine substituents in this family of catalyst leads to increasing selectivity towards *n*-butanol until **16** gives 88% *n*-butanol at 15% conversion (run 21), similar figures of merit to other ethanol to *n*-butanol catalysts. Clearly, changes to structure within this single family of tridentate PNP ligands can influence selectivity towards the main butanol isomer produced. Initial experiments to optimize *sec*-butanol yield and selectivity reveal that temperature and base loading are crucial factors. Decreasing temperature to 120 °C increases selectivity to *sec*-butanol to 54% (run 22); increasing temperature to 180 °C decreases selectivity (run 23). This is not surprising given the endergonic nature of the ethyl

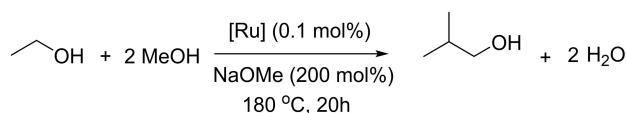
acetate forming reaction; the increase in ethanol conversion observed at this temperature is balanced by the increase in ethyl acetate rather than other products. Increasing base loading also improves selectivity to *sec*-butanol with a modest increase in overall conversion (runs 24 and 25); the figure of 71% for run 24 represents the highest selectivity we have observed (without hydrogen addition). Catalyst loading can be decreased with little loss in conversion and run 26 at 0.01 mol% catalyst equates to a turnover number of 820 to *sec*-butanol.

Experiments in which butane-1,3-diol was added were performed. As before, this led to an increase in the amount of *sec*-butanol with catalysts favoring this alcohol isomer (**13**, runs 27 and 28). Finally, hydrogen (10 bar) was added in an attempt to suppress ethyl acetate formation (run 29). A significant drop in overall conversion was observed but *sec*-butanol can now be obtained in 78% selectivity within liquid products.

Conversion of methanol/ethanol to isobutanol

Isobutanol is a preferred isomer of butanol in terms of fuel properties, requiring a mixture of methanol and ethanol for its synthesis via two Guerbet borrowed hydrogen cycles (methanol/ethanol to *n*-propanol, methanol/*n*-propanol to isobutanol). The tri- and tetradentate ligands explored here were screened in this reaction using our standard conditions for this reaction (Scheme 4, Table 4).^[11]

In contrast to ethanol homocoupling, in which *sec*-butanol and/or ethyl acetate are the main products in the liquid fraction with these catalysts, the expected Guerbet product of isobutanol is observed in all cases. Clearly, the sequence of hydrogen transfer and aldol condensation reactions leading to this



Scheme 4. Methanol/ethanol upgrading catalysis with 9–16.

Table 4. Methanol/Ethanol upgrading catalysis with 9–16.					
Run ^[a]	[Ru]	Conversion [%] ^[b]	Selectivity (Yield) ^[c]		
			isobutanol	Propanol	Other ^[d]
30	9	50	97 (47)	2.8 (1.4)	1.9 (1.9)
31	10	59	97 (56)	2.0 (1.2)	1.0 (1.7)
32	11	53	96 (50)	2.1 (1.1)	2.1 (2.2)
33	12	58	96 (55)	1.7 (1.0)	1.9 (2.2)
34	13	53	89 (44)	4.8 (2.4)	6.7 (6.7)
35	14	21	82 (15)	4.1 (0.8)	14 (5.0)
36	15	19	86 (15)	4.9 (0.8)	14 (3.8)
37	16	19	89 (16)	8.1 (1.4)	3.1 (1.1)

[a] Standard conditions: 1 mL ethanol (17.13 mmol), 10 mL methanol (247.13 mmol), 0.1 mol% [Ru], NaOMe (200 mol%) (mol% based on ethanol substrate), 180 °C, 20 h. [b] Conversion of ethanol based on total amount of liquid products obtained as determined by GC analysis. [c] Total yield and selectivity of Guerbet products in the liquid fraction as determined by GC analysis. [d] See SI.

product is preferred with methanol as a substrate. In general, the tetradentate ligand complexes **9–12** outperform the tridentate complexes **13–16** in terms of both conversion and selectivity.

Conclusion

Ruthenium complexes with tetradentate PNNP donor ligands (**9–12**) demonstrate a marked change in selectivity compared to analogous bis bidentate complexes, e.g. **2**, in Guerbet catalysis, producing mixtures of *n*-butanol, *sec*-butanol and ethyl acetate rather than high selectivity to *n*-butanol alone. A full rationale for this change in selectivity requires further study but ligand-induced changes in preferred reaction pathway from aldol-type intermediates seems likely. Tridentate PNP ruthenium complexes (**13–16**) can also control selectivity with bulkier ligands (**16**) favoring *n*-butanol and less bulky ligands (**13**) favoring *sec*-butanol and ethyl acetate. In optimized conditions, 70% selectivity to *sec*-butanol can be achieved. The same complexes are also efficient catalysts for the conversion of methanol/ethanol mixtures to isobutanol. Butanol isomers are of current and growing interest as fuel molecules; being able to produce *n*-, *sec*-, or isobutanol on demand could lead to important applications for catalyst technology in meeting sustainability targets.

Experimental Section

More details of modified ligand and complex synthesis, procedures for performing the catalytic experiments and characterizing data can be found in the Supporting Information.

General: All procedures were carried out under an inert atmosphere (N_2) using standard Schlenk line techniques or in an inert atmosphere glovebox (Ar). Chemicals were purchased from the usual suppliers and used without further purification.

Ligand and complex synthesis: Complex **4**^[25a] and 2-(diphenylphosphino)benzaldehyde^[25b] were synthesised by literature methods. Ligands **5–8**, and complexes **9–12** and **14–16** were synthesised using modified literature procedures; ligands **5** and **7** were synthesised using Gao's method.^[19] Ligands **6** and **8** were synthesised using a modification of the same method.^[20a] Complexes **10** and **12** were synthesised using Wong's method.^[20a] Complexes **9** and **11** were synthesised using a modification of the same method. Complexes **14–16** were prepared according to a modified literature procedure.^[24] Other ligands and catalysts were obtained commercially (Sigma-Aldrich or Alfa Aesar).

Catalytic runs: These were carried out in a sealed 100 cm³ Parr stainless steel autoclave with an aluminium heating mantle and using magnetic stirring. A typical procedure using catalyst **9** is given below.

Complex **9** (0.142 g, 0.171 mmol, 0.1 mol%), NaOEt (0.583 g, 8.57 mmol, 5 mol%) and a stirrer bar were added to a clean oven-dried fitted PTFE insert inside a glove box. The insert was sealed within a 100 cm³ Parr stainless steel autoclave which was then transferred to a nitrogen/vacuum manifold. Ethanol (10 cm³, 171.3 mmol) was injected into the autoclave through an inlet

against a flow of nitrogen. The autoclave was sealed and placed into a pre-heated (150 °C) aluminium heating mantle and stirred at 500 rpm. After the reaction run time (20 h), the autoclave was cooled to room temperature in an ice-water bath. The autoclave was carefully vented to remove any gas generated during the reaction. A liquid sample was removed, filtered through a short plug of alumina (acidic) and analysed by GC (100 μm³ of sample, 25 μm³ of hexadecane standard, 1.7 cm³ diethyl ether – sample filtered through a glass filter paper to remove insoluble salts).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

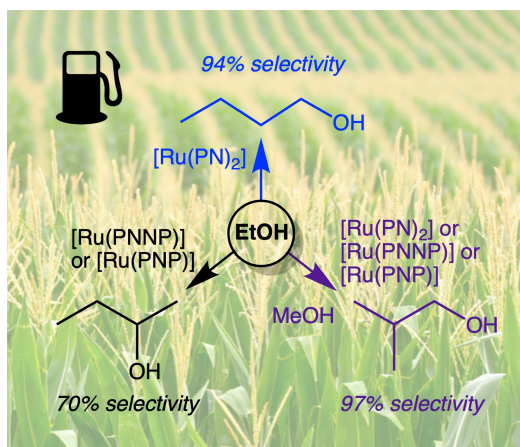
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Biofuel · Butanol · Guerbet · Catalysis · Ruthenium

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**Control in Advanced Biofuels
Synthesis via Alcohol Upgrading:
Catalyst Selectivity to *n*-Butanol,
sec-Butanol or Isobutanol**



**Catalyst Technology for Biofuel
Synthesis:** Renewing Guerbet
chemistry – changes in ligand
structure and reaction conditions in

ruthenium-catalyzed alcohol
upgrading chemistry switches selec-
tivity between butanol isomers
relevant as sustainable fuels.