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Homogeneous Catalysis

Towards a Green Process for Bulk-Scale Synthesis of Ethyl Acetate: Efficient Acceptorless Dehydrogenation of Ethanol**

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In 2008, the world market for ethyl acetate was estimated to be 2.5 million tons per annum.[1] This industrially, highly important intermediate is one of the major derivatives of acetic acid.[2] Apart from being used as solvent it is an important intermediate in the food industry, and for various customer applications such as glues, inks, and perfumes. Today, its manufacture mainly relies on three procedures: a) the Fischer esterification reaction of acetic acid,[3] b) the Tishchenko reaction by combination of two acetaldehyde molecules,[4] and c) the addition of acetic acid to ethylene.[5] All these processes use petrochemical feedstocks derived primarily from fossil fuels, a limited and intrinsically polluting supply.[6]

In contrast, ethanol—an inexpensive starting material for ethyl acetate—is easily accessed from biomass and represents an important renewable building block.[7] Obviously, the development of novel catalytic processes employing such renewable resources constitutes a key tool towards more sustainable production and the advancement of green chemistry. In fact, the valorization of bioethanol to a range of bulk intermediates including polymers is currently being intensively investigated.[7,8]

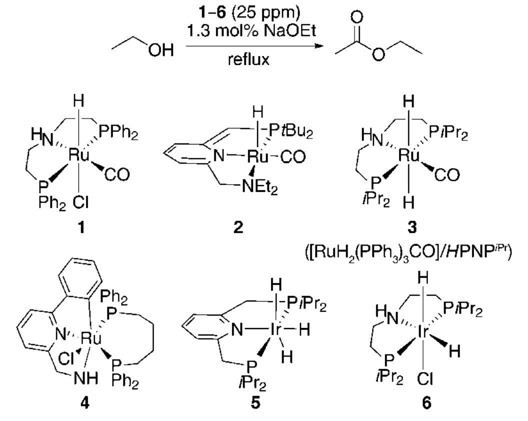
Based on our general interest in hydrogen production from alcohols,[9] and formic acid,[10] we were intrigued by the idea of synthesizing ethyl acetate by acceptorless dehydrogenative coupling directly from ethanol. To date, the acceptorless dehydrogenative synthesis of ethyl acetate from ethanol has been largely studied by using heterogeneous catalysts[11] with a special focus on copper-based catalysts.[11a–c] In general, this reaction requires high temperatures (>200 °C) and significant energy input, and it tends to lead to moderate selectivity. Hence, yields up to only 56 % have been achieved. In contrast, despite the recent advancements in homogeneously catalyzed dehydrogenation reactions of both primary and secondary alcohols,[9,12] limited progress has been observed with ethanol as a substrate.[9,12a,b] To the best of our knowledge, no reports on preparative acceptorless dehydrogenation of ethanol to form ethyl acetate exist. Obviously, applying known hydrogen acceptors to facilitate the reaction inherently results in low atom economy and waste formation. Thus, regarding cost and sustainability such procedures are not applicable on a larger scale. Therefore, developing a catalyst system capable of transforming ethanol into ethyl acetate under acceptorless and neat conditions is a major challenge.

Herein, we show that the ruthenium-based PNP pincer catalyst **1** (see Table 1 for structure) efficiently catalyzes the direct formation of ethyl acetate from ethanol. Notably, neither solvent nor additional hydrogen acceptors are employed in this green procedure.

Recently, pincer complexes have been proven to be highly efficient catalysts for acceptorless dehydrogenation of alcohols.[13,14] We therefore turned our attention to this type of complex. At the start of our investigations a selection of various ruthenium and iridium pincer complexes were tested for their activities in the target reaction (Table 1). Notably, in our system mild reaction conditions with refluxing ethanol in an open system are employed. This is a considerably lower reaction temperature compared to all known acceptorless dehydrogenations of other alcohols.

We were pleased to find that the *H*PNP^{Ph}/Ru complex **1**[9] showed high activity with a turnover frequency (TOF) of $1134\,h^{-1}$ (Table 1, entry 1). The catalyst **2**,[12m] reported by

Table 1: Acceptorless dehydrogenation of ethanol to give ethyl acetate.[a]



Entry	Catalyst	TOF [h^{-1}][b]
1	**1**	1134
2	**2**	<100
3	**3**	1107
4	**4**	898
5	**5**	<100
6	**6**	<100

[a] Performed with indicated catalyst (**1**–**6**; 25 ppm, 4.2 μmol) and NaOEt (1.3 mol %, 2.2 mmol) in refluxing EtOH (10 mL, 171.3 mmol), with an internal standard (1 mL hexadecane). [b] Determined by burette measurements after 2 h of reaction time.

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Milstein and co-workers, unfortunately showed no activity for this transformation under the given reaction conditions (entry 2). To the contrary, the in situ system **3**,[9] comprising an *H*PNP^{iPr} ligand coordinated to a RuH_2-type structure, showed an activity similar to that of **1**. Baratta's catalyst[15] **4** also showed decent activity, however at a lower level than that of **1** and **3** (entry 4 versus entries 1 and 3). In addition, we tested two iridium complexes in the target reaction. However, both the Nozaki catalyst[16] **5** and the *H*PNP^{iPr}-based Gusev–Abdur–Rashid complex[17] **6** unfortunately led to very little conversion (entries 5 and 6, respectively). These results suggest that utilizing aliphatic PNP pincer ligands on a ruthenium-based system is required to achieve significant catalytic activity in this reaction. Having two equally active catalysts, **1** and **3**, in hand, we continued our investigations with the commercially available complex **1**.

After testing a series of different base additives (see Table SI3 in the Supporting Information), NaOEt was identified to be the optimal choice, thus leading to the highest turnover frequency. Within the range of 0.3–3.2 mol% NaOEt, similar activity is observed (see Table SI4). From a practical point of view it is important to note that the catalyst activity proved to be steady over at least a 10 hour reaction period and with up to approximately 90% conversion (see Tables and Figures SI5-6).

Next, we turned out attention to improving the yield for ethyl acetate and the catalyst turnover numbers (TON). Table 2 summarizes the results collected by varying the catalyst loading and temperature, and conducting the reaction until gas evolution had ceased. Increasing the catalyst loading from 25 to 500 ppm, and conducting the reaction until gas evolution ceased led to 81% yield of ethyl acetate with a TON of 1620 and a TOF, after 2 h, of 498 h^{-1}. An attempt to lower the reaction temperature resulted in a slightly lower yield and TON (70% and 1400, respectively). Nevertheless, this example demonstrates that the reaction can be performed even at temperatures below that of reflux, and the catalyst is active even at 60°C, albeit at a lower rate (see the Supporting Information). To the best of our knowledge, this is the first example of acceptorless dehydrogenation of ethanol.

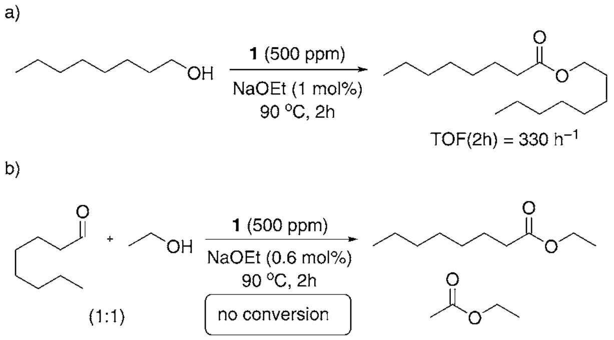
Table 2: Acceptorless dehydrogenation of ethanol catalyzed by **1** to give ethyl acetate.[a]

Entry	**1** (ppm)	NaOEt (mol%)	*T* [°C][b]	Yield [%][c]	TON
1	500	1.3	90	81	1620
2	500	1.3	70	70	1400
3	50	0.6	90	77	15400

[a] Performed with catalyst **1** (amount given in Table 2) and NaOEt (amount given in Table 2) in EtOH (10 mL, 171.3 mmol) with an internal standard (1 mL hexadecane). An oil trap was employed immediately after the condenser. All reactions were conducted until gas evolution had ceased (6 h in entry 1, 24 h in entry 2, 46 h in entry 3). [b] Applied temperature. [c] Determined by GC.

Finally, employing only 50 ppm of **1** led to a high yield of ethyl acetate with a TON of 15400. The TOF of the active catalyst species is almost constant for the first 10 hours of the reaction with an overall TOF(2 h) of 934 h^{-1} and overall TOF(10 h) of 730 h^{-1} (see the Supporting Information). This diminished activity is probably due to the exhaustion of ethanol during the reaction course. Apparently, ethyl acetate formation does not impede the reaction nor does the catalyst seem to be considerably deactivated over time.

Performing the reaction with 1-octanol instead of ethanol shows that other alcohols are applicable in this dehydrogenative esterification as well (Scheme 1a). Thus, the catalyst TOF is only lower by a factor of 1.5 for 1-octanol compared to that of ethanol under the same reaction conditions. This is expected because of a lower hydroxy/carbon chain ratio in 1-octanol.



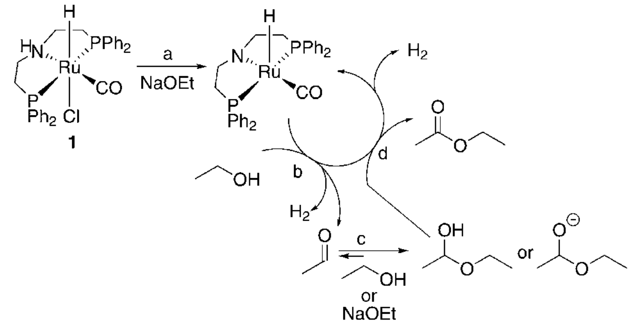
Scheme 1. a) Acceptorless dehydrogenation of 1-octanol to give the corresponding ester. b) Coupling of octanal and ethanol.

From a mechanistic point of view it is important to note that applying the same reaction conditions on equivalent amounts of octanal and ethanol led to no formation of either ethyl octanate or ethyl acetate (Scheme 1b). In agreement with this observation no hydrogen evolution is obtained. In fact, only products arising from the aldol condensation of octanal were observed by in situ ^{1}H NMR spectroscopy. Apparently, the presence of large amounts of aldehyde inhibits the catalyst. These experiments suggest that the concentration of "free" aldehyde should be kept at a minimum during the reaction course of acetate formation. This is also in agreement with the data of the ^{1}H NMR spectra of the crude reaction mixture for the ethanol to ethyl acetate reaction (see ^{1}H NMR spectra SI7-9 in the Supporting Information). During the entire reaction course, neither acetaldehyde nor its aldol condensation product (croton aldehyde) was observed. Therefore, the formation of ethyl acetate by a Tishchenko-type reaction can be clearly ruled out. Furthermore, this observation suggests that the rate-determining step of the process is the initial dehydrogenation step.

Notably, during their studies on the synthesis of amides from alcohols and amines, Madsen and co-workers suggested that the initially formed aldehyde stays coordinated to the metal complex.[12d,17] However, in their system dehydrogenation of the alcohol is still observed even in the presence of large amounts of aldehyde, albeit at a lower rate.

As the presence of aldehyde completely blocks any dehydrogenation activity in our system, the Madsen mechanistic proposal may not be applied here. The fact that the amount of NaOEt is crucial for maintaining a steady catalyst activity suggests a more subtle role besides activation of the catalyst. Furthermore, it might be involved in a fast trapping of the aldehyde intermediate to give the hemiacetal or its anionic equivalent.

Based on these observations, we propose the reaction mechanism shown in Scheme 2: First, the catalyst **1** is activated by the base (step a). Then, ethanol is oxidized to acetaldehyde through an outer-sphere dehydrogenation and hydrogen is released from the ruthenium center (step b). The formed acetaldehyde likely stays in the vicinity of the catalyst, or is even coordinated to the metal center, when another molecule of ethanol attacks the aldehyde to form a hemiacetal (step c). Probably, an ethoxide anion is responsible for this attack, thus leading to an anionic hemiacetal. Finally, a second β-hydride elimination step leads to ethyl acetate (step d) and the catalyst is regenerated after hydrogen release.



Scheme 2. Proposed mechanism for the acceptorless dehydrogenation of ethanol to give ethyl acetate.

In conclusion, we have developed the first catalytic acceptorless dehydrogenation of ethanol to ethyl acetate. This industrially important reaction allows a cost-efficient synthesis of ethyl acetate which produces hydrogen as an additional value-generating product. Applying catalyst loadings in the ppm range led to a high yield of ethyl acetate with a TONs exceeding 15000. In addition, we show that other primary alcohols are converted into their corresponding esters as well. This report constitutes an important example of using renewable feedstocks for more benign production of bulk chemicals.

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