

Oxidation of primary alcohols to methyl esters by hydrogen transfer†

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The oxidation of alcohols in the presence of methanol has been achieved using a ruthenium catalyst with crotononitrile as the hydrogen acceptor.

The oxidative dimerisation of primary alcohols to give esters has been reported using hydrogen transfer reactions¹ and with acceptorless dehydrogenation.² In this chemistry, an alcohol is initially oxidised to an aldehyde which reacts reversibly with more alcohol to form a hemiacetal and further oxidation leads to the formation of the ester. Related to this process is the conversion of diols into lactones.³ The metal-catalysed Tishchenko dimerisation reaction of aldehydes to give esters is also well-known.⁴

However, the reaction of two alcohols to give an ester by oxidative coupling is more problematic due to the potential formation of a mixture of products. The conversion of activated alcohols, such as cinnamyl alcohol, into methyl esters has been reported using manganese dioxide with cyanide,^{5,6} which is capable of oxidising the cinnamyl alcohol and intermediate cyanohydrin, but not methanol. A similar strategy has been employed using iodosobenzene as the oxidant.⁷

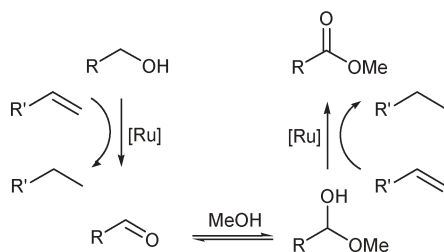
We were interested in the possibility of using metal catalysed hydrogen transfer processes to effect the oxidation of alcohols to methyl esters according to Scheme 1. Methanol is harder to oxidise than most primary alcohols due to the high oxidation potential of methanol,⁸ and by using methanol as solvent, we hoped to be able to form methyl esters selectively. We chose to use an alkene as the hydrogen acceptor, although the use of a ketone as the hydrogen acceptor or acceptorless dehydrogenation are also potentially viable approaches. We have recently reported the use of Ru(PPh₃)₃(CO)H₂ with the bidentate ligand Xantphos for

processes which involve the transfer of hydrogen from an alcohol to an alkene⁹ or alkyne.¹⁰

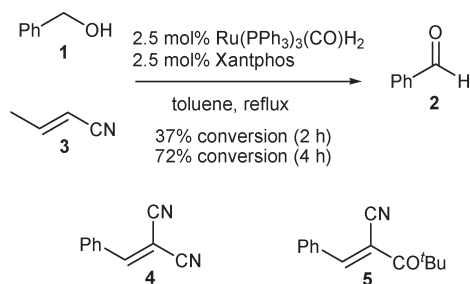
In preliminary experiments, we wished to identify a suitable alkene as the hydrogen acceptor, and chose to examine the oxidation of benzyl alcohol to benzaldehyde using 2.5 mol% Ru(PPh₃)₃(CO)H₂ with 2.5 mol% Xantphos¹¹ as shown in Scheme 2. α,β -Unsaturated nitriles were found to be effective for this transformation, while simple alkenes and alkynes including 1-hexene, styrene, trimethylvinylsilane, methyl acrylate, 1-hexyne and phenylacetylene all gave less than 5% conversion under these conditions. Whilst the more electron deficient alkenes **4** and **5** gave a greater conversion within 2 h (95% and 67% respectively), crotononitrile **3** was chosen as the most suitable alkene due to the volatility of this alkene and its reduced product.

Using methanol as a cosolvent led to the formation of methyl esters from a range of alcohols (Scheme 3, Table 1). After some optimisation, it was found that allowing complexation between 5 mol% Ru(PPh₃)₃(CO)H₂ and 5 mol% Xantphos for 1 h, followed by 24 h at 110 °C in a methanol–toluene (1 : 1) solution in the presence of 3 equivalents of crotononitrile **3** was suitable for the oxidation of most alcohols. The addition of a small amount of water was also found to be beneficial.

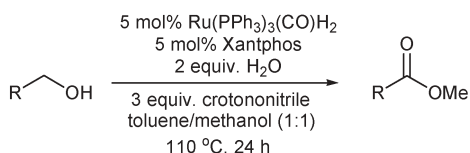
The majority of alcohols underwent clean transformation into the corresponding esters with essentially complete conversion, and were isolated in good yields. There were three alcohols where incomplete conversion was observed under these conditions; these were the sterically most hindered substrates: benzyl alcohol, *p*-nitrobenzyl alcohol and cyclohexylmethanol. Benzylic alcohols would normally be expected to undergo oxidation more readily



Scheme 1 Oxidation of primary alcohols to methyl esters.



Scheme 2 Alkenes as hydrogen acceptors for alcohol oxidation.



Scheme 3 Reaction conditions for methyl ester formation.

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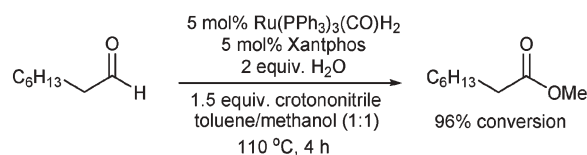
Table 1 Conversion of alcohols into methyl esters

| Alcohol | Methyl ester | Yield (%) ^d |
|----------------|----------------|------------------------|
| | | 83 ^b |
| | | 79 |
| Ar = 3-indenyl | Ar = 3-indenyl | |
| | | 84 |
| | | 87 |
| | | (70) ^c |
| | | 74 |
| | | 76 |
| | | 86 |
| | | 84 ^d |
| | | (76) ^c |
| | | (>95) ^c |

^a Isolated yield after purification by column chromatography, except where indicated. ^b 48 h. ^c Conversion. ^d 36 h.

than aliphatic alcohols, and we wondered whether a disfavoured hemiacetal formation from the intermediate aldehyde was responsible for the lower conversion. However, both unreacted benzyl alcohol and benzaldehyde (~1 : 1) were present in the crude product, suggesting that both initial oxidation and hemiacetal formation were disfavoured relative to the aliphatic examples. In the cases of *p*-nitrobenzyl alcohol and cyclohexylmethanol, conversions of 84% and 76% were observed, with no intermediate aldehyde detected in the ¹H NMR spectrum of the crude product.

We were pleased to note that the alkene-containing alcohols cinnamyl alcohol and citronellol underwent oxidation without reduction or isomerisation of the alkene.

**Scheme 4** Oxidation of octanal to the methyl ester.

In all cases, small quantities of the product arising from conjugate addition of methanol to crotononitrile, MeCH(OMe)CH₂CN, were observed. This byproduct was readily removed by column chromatography or by evaporation under high vacuum.

The reaction was also applied to the conversion of octanal into its methyl ester (Scheme 4). Murahashi has previously reported the reaction of octanal with methanol in the presence of mesityl oxide as the hydrogen acceptor, which gave 66% methyl octanoate after 4 days at 140 °C using 10 mol% Ru(PPh₃)₄H₂.¹

In summary, primary alcohols have been oxidised to the corresponding methyl esters in good isolated yields using a ruthenium catalysed hydrogen transfer process.

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