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Direct aerobic oxidation of primary alcohols to methyl esters catalyzed by a heterogeneous gold catalyst

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Methyl esters can be produced in high yields by oxiding methanolic solutions of primary alcohols with dioxygen over a heterogeneous gold catalyst. The versatility of this new methodology is demonstrated by the fact that alkylic, benzylic and allylic alcohols, as well as alcohols containing an amine functionality are oxidized in good to excellent yields.

KEY WORDS: gold catalysis; catalytic oxidations; air; ester synthesis; methyl esters.

1. Introduction

One of the cornerstones of organic chemistry is the oxidation of alcohols to yield aldehydes, ketones, carboxylic acids and carboxylic acid derivatives. Today, these oxidations are most often carried out by the use of either stoichiometric amounts of heavy metal oxidants containing, e.g. chromium or manganese, or very expensive oxidants such as the Dess-Martin periodinane. Recently, more green approaches employing the ultimate oxidation agent, namely O_2, have been exploited [1–4].

Many methyl esters are industrially important chemicals, both as products in e.g. the perfume industry as solvents, extractants, diluents and as intermediates. An environmentally friendly route to such chemicals would be an important step towards a more green chemical industry. Here, we report that a range of primary alcohols in methanol can be selectively oxidized by dioxygen to the corresponding methyl esters using Au/TiO_2 as outlined in figure 1.

For the past two decades, the use of gold catalysts to facilitate simple aerobic oxidations has received considerable attention [5–8]. The field was pioneered by Haruta and co-workers who showed that CO can be oxidized into CO_2 by O_2 using Au/Fe_2O_3 [9, 10] and by Hutchings and co-workers who showed that acetylene can be hydrochlorinated using gold catalysts [11]. In recent years, the field has gained momentum following the observation that both aldehydes, ketones and carboxylic acids can be prepared by gold-mediated aerobic oxidations [12–17]. Currently, there is considerable interest in establishing a mechanistic understanding of the oxidations over heterogeneous gold catalysts. It is clear that special sites that only exist on gold nanoparticles are decisive for the unique catalytic activity [18, 19].

So far, the oxidation of carbon monoxide into carbon dioxide has most attracted interest in the rapidly growing area of heterogeneous gold catalysis. However, it has also become increasingly clear that the aerobic oxidation of various organic compounds, in particular compounds with C–O groups could provide "green" routes to a range of commodity chemicals and specialty chemicals. Obviously, selective oxidation with dioxygen is preferable to using any other oxidating agent, since oxygen is readily available and in ideal cases, the only byproduct is water. However, typically it has been a challenge to suppress the complete oxidation reaction that leads to the undesired formation of carbon dioxide. Recently, we showed that gold catalyst were efficient in oxidizing aqueous solutions of ethanol into acetic acid in high yields. This provides an alternative route to produce the key commodity chemical acetic acid by a sustainable and green approach in the sense that the feedstock is derived solely from renewable and no harmful byproducts are formed [17]. It has previously been shown by Hutchings and co-workers that oxidation of neat primary alcohols can lead to selective formation of the aldehydes [16]. Thus, it is clear that the solvent plays a significant role in the aerobic oxidation of primary alcohols. To further expand the range of products that are available by selective aerobic oxidation of alcohols with gold catalysts, we decided to explore the direct synthesis of esters by conducting the oxidation using methanol as the solvent. Methanol was chosen, since this would lead to formation of

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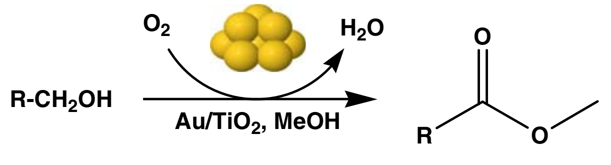

Figure 1. Schematic illustration of the selective aerobic oxidation of primary alcohols into esters using heterogeneous gold catalysts.

methyl esters that in many cases are important products or intermediates. Additionally, it appears that small primary alcohols are significantly more difficult to oxidize than larger, more substituted primary alcohols and this is obviously a prerequiste for achieving selective oxidations.

The oxidation of primary alcohols to carboxylic acids can be envisaged to proceed via an aldehyde intermediate followed by formation of the hydrate, which is subsequently oxidized to the carboxylic acid. A common by-product from the oxidation of primary alcohols is the corresponding ester. Indeed, in the absence of water, Corma and co-workers reported that the main product from oxidation of 3-phenyl-1-propanol was 3-phenylpropyl-3-phenylpropionate (in 88% yield) [15]. This can be easily explained since formation of the aldehyde hydrate is not possible, and the aldehyde will then form a hemiacetal with the alcohol. This hemiacetal can be further oxidized in the same manner as the aldehyde hydrate, leading to the corresponding ester as shown in figure 2.

The direct formation of methyl esters from the oxidation of primary alcohols in methanol is well known [20–24]. However, these methods all employ stoichiometric oxidants such as iodine [20], trichloroisocyanuric acid [21], (diacetoxy)iodobenzene [22] or hypochlorite reagents [23, 24]. The use of air as the oxidant in this transformation is still in its infancy. So far, only the oxidation of ethylene glycol to methyl glycolate has been described [25], and yet plans are already underway for industrializing the process [8].

The existing methodologies suggest that primary alcohols are oxidized more readily than methanol. Therefore, we decided to examine if primary alcohols can more generally be selectively oxidized to methyl esters by carrying out a gold catalyzed aerobic oxidation in methanol.

2. Experimental

2.1. Materials and equipment used

The supported gold catalyst used in this study, 1 wt% Au/TiO_2, was acquired from the World Gold Council (Gold reference catalyst #02-06, Sued-Chemie Catalysts Japan).

All chemicals were purchased from commercial sources and used without further purification: Methanol (99.9% pure, Sigma-Aldrich), 1-hexanol (98%, Riedel-de Haën), sodium methoxide solution (30 wt% in methanol, Sigma-Aldrich), cinnamyl alcohol (98%, Sigma-Aldrich), benzyl alcohol (>99%, Bie & Berntsen), 2-(hydroxymethyl) pyridine (98%, Aldrich), 1-adamantane methanol (99%, Aldrich) and dioxygen (>99.6%, Strandmøllen).

The autoclave used was a 325 mL titanium stabilized T316 autoclave, from the Parr Instrument Company.

The GC used for analyzing liquid reaction mixtures was an Agilent Technologies 6890N Network GC System equipped with a flame ionization detector (FID) and a DB-1 column (50 m × 0.320 mm, 5.00 micron, J&W Scientific, catalog 1231055). The GC program used was: 200 °C, hold 3 min; 250 °C, rate 20 °C/min, hold 20 min.

The GC used for analyzing gas mixtures was a Shimadzu GC-17A equipped with a thermal conductivity detector (TCD).

All NMR-spectra were recorded on a Varian Mercury 300 MHz instrument. Chemical shifts were correlated relative to chloroform. The data were processed with MestReC 4.7.4.0 software.

Transmission electron microscopy (TEM) was performed on a JEM 2000FX with an accelerating voltage of 300 kV. A few mg of the powdered samples was suspended in 2 mL ethanol, and the suspension was sonicated for 1 h. Then, the suspension was allowed to settle for 15 min, before a drop was taken and dispersed on a 300 mesh copper grid coated with holey carbon film.

2.2. Catalytic experiments

The autoclave was charged with Au/TiO_2 catalyst, methanol, substrate, and in some cases an additive

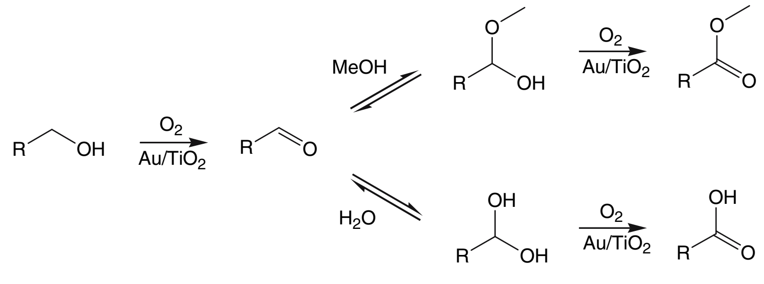

Figure 2. Proposed reaction pathway for the formation of methyl esters in methanol and carboxylic acids in water during aerobic oxidation of primary alcohols with heterogeneous gold catalysts.

(either 30 wt% sodium methoxide in methanol or 37 wt% hydrochloric acid in water) was added with a pipette, see table 1 for specific details. A 3 cm magnetic stir bar was fitted in the autoclave which was then pressurized with dioxygen. The autoclave was placed in a 130 °C preheated oil bath, and the reaction mixture was stirred rapidly. The autoclave was removed from the oil bath after the specified reaction time and was allowed to cool to room temperature.

2.3. Analysis of reaction mixtures

Ca. 1 mL of the reaction mixture was transferred to a centrifuge vial and centrifuged. The clear liquid was analyzed by GC by injecting 0.2 μL into the GC. Retention times of the products were verified by comparison to authentic reference samples. Conversion and selectivity were calculated with respect to the substrate.

In order to determine the extent of methanol oxidation, a plastic balloon with a vent was flushed three times with dinitrogen and evacuated. The balloon was then filled with gas from the autoclave, and the gas was analyzed using GC and referenced to a gas sample containing 2 mol% CO_2.

2.4. Isolation of products

In order to verify the results of the GC analyses we isolated the reaction products after some of the experiments using standard procedures and confirmed their purity by ^1H NMR. Methyl hexanoate (table 1, Entry 11) and methyl benzoate (table 1, Entry 13) were isolated by extraction with pentane and subsequently purified by Kugel-rohr distillation. However, in order to isolate methyl cinnamate (table 1, Entry 14) it was necessary to remove the methyl benzoate byproduct by flash chromatography after the initial pentane extraction using a small amount of heptane as solvent (3 cm in diameter column; eluent: heptane:ethyl acetate 19:1; rf: 0.2). Methyl pyridine-2-carboxylate was isolated by distillation.

3. Results and discussion

To determine the size of the gold particles we recorded about 40 high-resolution TEM images of the 1 wt% Au/TiO_2 catalyst used in this study. Based on this TEM study, the gold nanoparticles have a quite narrow size distribution with more than 95% of the gold particles having a diameter of 2–5 nm. A representative TEM image of the Au/TiO_2 catalyst is shown in figure 3.

Initially, the effect of pH on the reaction was studied by addition of either acid (HCl) or base ($NaOCH_3$) to the reaction mixture, see figure 4. As seen in figure 4, the additive plays an important role, both in terms of conversion of 1-hexanol and in terms of selectivity towards methyl hexanoate. Under acidic conditions, conversion of 1-hexanol is very low, and the major product is the dimethyl acetal of hexanol. This result suggests that the hemiacetal intermediate is converted to the acetal under acidic conditions, and that this compound is relatively inert to further oxidation. Under neutral and basic conditions, conversion of hexanol is much higher, and methyl hexanoate is formed with a much better selectivity. However, conversion and selectivity increases only slightly when going from neutral to more basic conditions. This observation is in contrast to the oxidation of diols and glycerol to carboxylic acids, where the presence of base is essential to the oxidation reaction [12, 14], since it clearly shows that methyl hexanoate can

Table 1
Experimental details[a]

Entry	MeOH V (mL)	Substrate	Molar ratio[b]	V (mL)	Additive	Mol%	V (μL)	Reaction time (h)
1	12.20	1-hexanol	1:19	2.00	None	–	–	24
2	12.20	1-hexanol	1:19	2.00	HCl	2	26.2	24
3	12.15	1-hexanol	1:19	2.00	$NaOCH_3$	0.2	6.0	24
4	4.85	1-hexanol	1:19	0.80	$NaOCH_3$	2	24.2	24
5	12.20	1-hexanol	1:19	2.00	$NaOCH_3$	20	600	24
6	12.20	1-hexanol	1:19	2.00	$NaOCH_3$	0.2	6	1
7	12.15	1-hexanol	1:19	2.00	$NaOCH_3$	2	60	1
8	11.95	1-hexanol	1:19	2.00	$NaOCH_3$	10	302	1
9	5.80	1-hexanol	1:9	2.00	$NaOCH_3$	2	60	24
10	2.50	1-hexanol	1:4	2.00	$NaOCH_3$	2	60	24
11	12.15	1-hexanol	1:19	2.00	$NaOCH_3$	2	60	10
12	12.15	1-hexanol	1:19	2.00	$NaOCH_3$	2	60	6
13	12.15	benzyl alcohol	1:19	1.65	$NaOCH_3$	2	60	10
14	12.15	cinnamyl alcohol	1:19	2.05	$NaOCH_3$	2	60	10
15	12.15	2-(hydroxymethyl) pyridine	1:19	1.55	$NaOCH_3$	2	60	10

[a] The Au/substrate ratio was 1:625 in all experiments. The autoclave was pressurized to a total pressure of 10 bar (corresponding to a O_2 pressure of 9.2 bar) in all experiments except for the Entry 2 experiment where a total pressure of 4 bar was used (O_2 pressure 3.2 bar). The O_2/substrate ratio was 7:1 in all experiments.

[b] Substrate: methanol molar ratio.

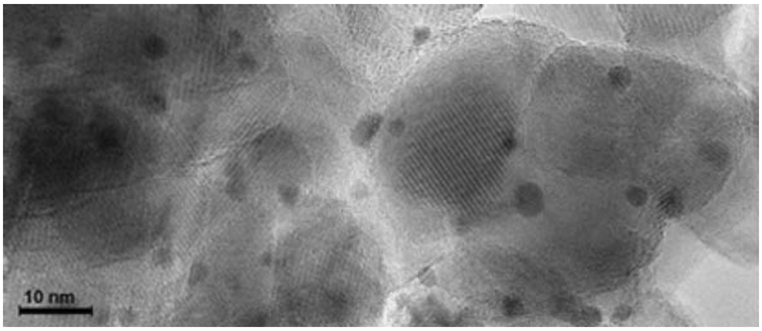

Figure 3. Representative transmission electron microscopy image of the Au/TiO_2 catalyst, showing mainly the presence of nanosized gold particles with a size of 2–5 nm.

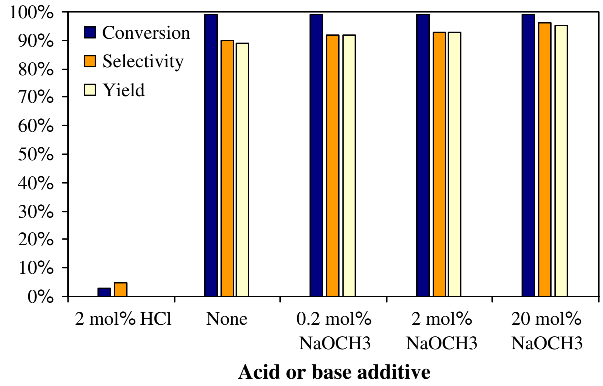

Figure 4. Effect of acid or base additives on the yield of methyl hexanoate at full conversion.

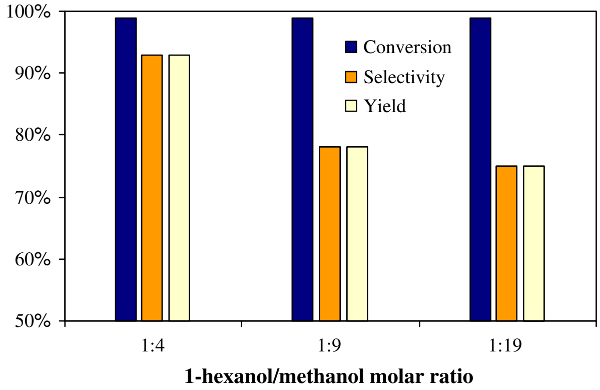

Figure 5. Effect of substrate/methanol ratio on the yield of methyl hexanoate.

be produced in excellent yield, even under neutral conditions. However, although presence of base is not essential for the reaction, it does have a pronounced influence on the reaction rate, as shown in table 2. Thus, to conduct the reaction at short reaction times, the desired amount of base can be added. This could be particularly important for alcohols that can isomerise or possibly even degrade under the reaction conditions. However, it might in many cases be desirable to avoid the use of base to ease purification and minimize waste.

GC-analysis of the reaction mixtures after neutralization with aqueous hydrochloric acid show that small amounts of formic acid, and very minute amounts of hexanoic acid are formed. For the Entry 4 experiment (see table 1), for instance, the neutralized reaction mixture contained *ca.* 2% of formic acid and less than 0.3% of hexanoic acid. Generally, the only major byproduct in these reactions result from the condensation of the oxidized alcohol with the substrate alcohol. No Claisen condensation products were observed in the reaction mixtures. GC analysis of the gas mixture after conducting the Entry 5 experiment (see table 1) showed that the gas mixture after reaction consisted of 78% CO_2, suggesting that some methanol is oxidized to CO_2 during the reaction. In all, the excess of O_2 present in the autoclave after the reaction corresponds to a maximum loss of 1–3 moles of methanol per mole of methyl ester formed, this methanol being oxidized to either formic acid, methyl formate or to CO_2.

Figure 5 shows the effect of the hexanol/methanol ratio on the yield of methyl hexanoate. These experiments were all conducted using 2% $NaOCH_3$ with a reaction time of 24 h. As is evident, the selectivity towards the methyl ester increases when increasing the

Table 2
Effect of base on reaction rate

Entry in Table 1	Substrate	Reaction time (h)	$NaOCH_3$ additive (mol%)	Product	Conv. (%)	Yield (%)
6	1-hexanol	1	0.2	methyl hexanoate	56	52
7	1-hexanol	1	2	methyl hexanoate	60	57
8	1-hexanol	1	10	methyl hexanoate	85	81

Table 3
Results obtained for the experiments with lowering of the reaction time in the oxidation of 1-hexanol

Entry in Table 1	Substrate	Reaction time (h)	$NaOCH_3$ additive (mol%)	Product	Conv. (%)	Yield[a](%)
4	1-hexanol	24	2	methyl hexanoate	> 99	93
11	1-hexanol	10	2	methyl hexanoate	97	93 (79)
12	1-hexanol	6	2	methyl hexanoate	96	91

[a] The yield in parenthesis is the isolated yield.

Table 4
Results obtained for the experiments with oxidizing various primary alcohols to yield methyl esters

Entry in Table 1	Substrate	Reaction time (h)	$NaOCH_3$ additive (mol%)	Product	Conv. (%)	Yield[a](%)
13	benzyl alcohol	10	2	methyl benzoate	> 99	> 99 (79)
14	cinnamyl alcohol	10	2	methyl cinnamate	> 99	88 (76)
15	2-(hydroxymethyl) pyridine	10	2	methyl pyridine- 2-carboxylate	95	95 (85)

[a] The yields in parenthesis are the isolated yield.

excess of methanol. This trend is most likely caused by the more favored formation of the methyl hemiacetal compared to the hexyl hemiacetal. However, good yields of methyl hexanoate (75%) can still be obtained by using a substrate/methanol ratio of just 1:4. Thus, the selection of substrate alcohol/methanol ratio obviously represents a compromise between maximizing the yield and making the separation as easy as possible since at high methanol concentrations the separation of the product is more energy and time-consuming. Furthermore, the reaction is obviously slower when it is conducted at high dilution. However the separation is generally very simple since the methyl esters are usually recovered in high yields by a straightforward distillation.

Then we investigated the importance of the reaction time. The results of these experiments are listed in table 3. It is seen, that the reaction time can easily be reduced from 24 to 10 h or even to 6 h since nearly full conversion and an excellent selectivity towards the methyl ester is achieved after only 6 h. However, the yield is still slightly higher when the longer reaction times are used. This is because no loss of selectivity is observed at full conversion.

We also investigated the versatility of this new methodology by carrying out oxidations of other substrates than 1-hexanol. These results are shown in table 4, and it is seen that the method is quite versatile since both benzyl alcohol, cinnamyl alcohol, and 2-(hydroxymethyl)pyridine can be oxidized to the corresponding methyl esters in good to excellent yields. Thus, an amine functionality does not deactivate the gold catalyst. However, the highly sterically demanding 1-adamantane methanol fails to undergo oxidation. Also for these substrate, GC-analysis of the reaction mixtures after neutralization with aqueous hydrochloric acid show that small amounts of formic acid, and very minute amounts of carboxylic acid are formed. However, in the oxidation of cinnamyl alcohol, *ca*. 10% of methyl benzoate was formed as a by-product.

4. Conclusions

In conclusion, we have presented here a new application in the field of gold catalysis with the direct formation of methyl esters from various primary alcohols, using O_2 as oxidant. Importantly, the primary alcohols are evidently oxidized much more readily than methanol. It must be noted, however, that no attempts have so far been made to optimize the reaction conditions and thereby reduce the methanol loss during reaction, although this work is underway.

Acknowledgments

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