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Ruthenium catalysed redox transformation of cinnamaldehyde to 3-phenylpropionic acid and methyl ester.

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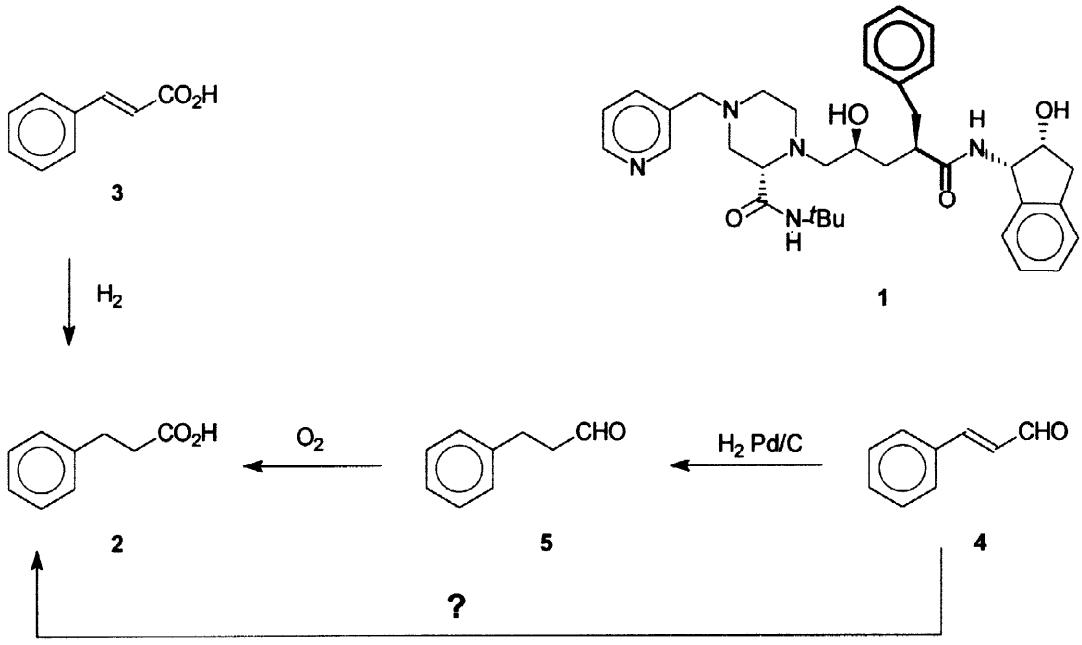
Abstract
3-Phenylpropionic acid (**2**) is an intermediate for the anti-aids drug Indinavir. The one step conversion of cinnamaldehyde (**4**) into **2** was attempted using homogeneous ruthenium catalysts. Use of $[H_2Ru(Ph_3P)_4]$ induced mainly decarbonylation of **4** to give styrene. Use of $RuCl_3/PCy_3$ gave a mixture of **2** and cinnamic acid (**3**). Performing the same reaction in methanol, instead of water/dimethoxyethane mixtures afforded methyl 3-phenylpropionate in 70% yield.

Indinavir (**1**) is a highly successful anti-aids agent which is currently used in combination therapy [1]. The compound and its building blocks have inspired many interesting synthetic efforts [2]. One of the less conspicuous constituents is 3-phenylpropionic acid (**2**). Though **2** can be easily produced by hydrogenation of cinnamic acid (**3**), cinnamaldehyde (**4**) is a much



Scheme 1. Preparation of 3-phenylpropionic acid, a building block for Indinavir.

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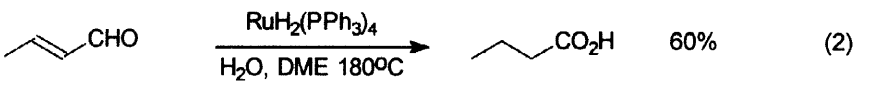
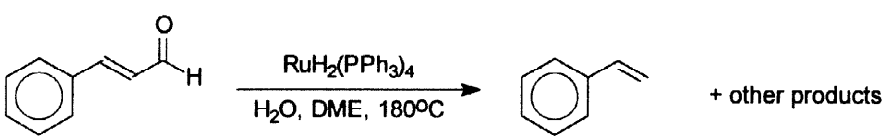
cheaper raw material than **3**. For this reason we have developed a simple and high yielding route to 3-phenylpropionic acid based upon the hydrogenation of **4** to 3-phenylpropionaldehyde (**5**), followed by air oxidation of **5** to **2** (Scheme 1.) [3]. Unfortunately, the higher number of reaction steps offsets the price advantage of cinnamaldehyde over cinnamic acid. Our aim was therefore to design a catalytic one step process for the conversion of cinnamaldehyde to 3-phenylpropionic acid. This would seem a viable venture as the net reaction works out thermodynamically advantageous and the hydrogen equivalents could be transferred via known transition metal catalysed steps. In fact, we could find one earlier reported instance of the desired transformation. In a paper by Murahashi *et al.* on the ruthenium catalysed oxidative transformation of alcohols and aldehydes to esters and lactones the transformation of crotonaldehyde to butyric acid catalysed by $[RuH_2(PPh_3)_4]$ [4] is described to take place in 68% yield (Scheme 2.) [5].



Application of these conditions to **4** led to quite different results, however. Only minor amounts of **2** were formed, and styrene (**6**) was found to be the main product. At later stages in the reaction the amount of **6** diminished, presumably due to polymerisation (Fig. 1).



4 **6**

Conditions: 3 mmol $[RuH_2(PPh_3)_4]$, 50 mmol cinnamaldehyde, 2ml H_2O and 18ml DME, 180°C, 2h

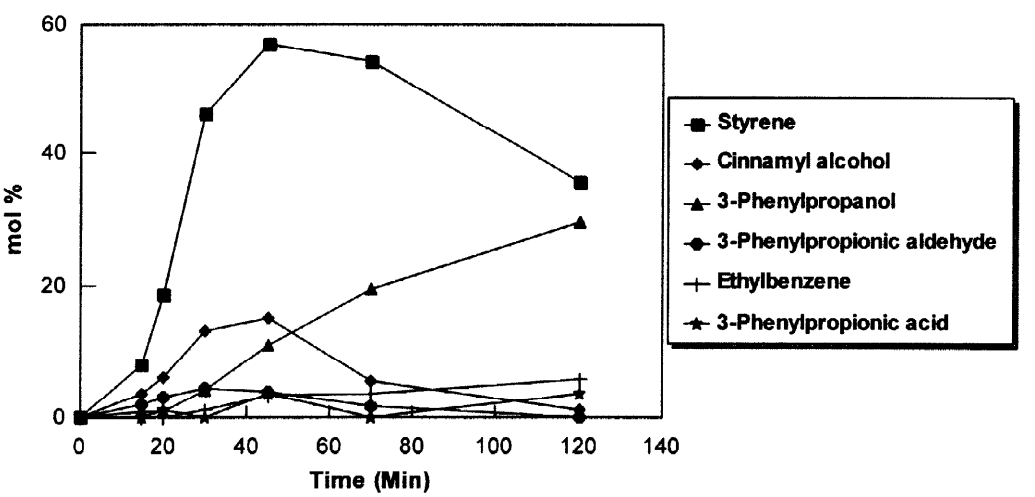
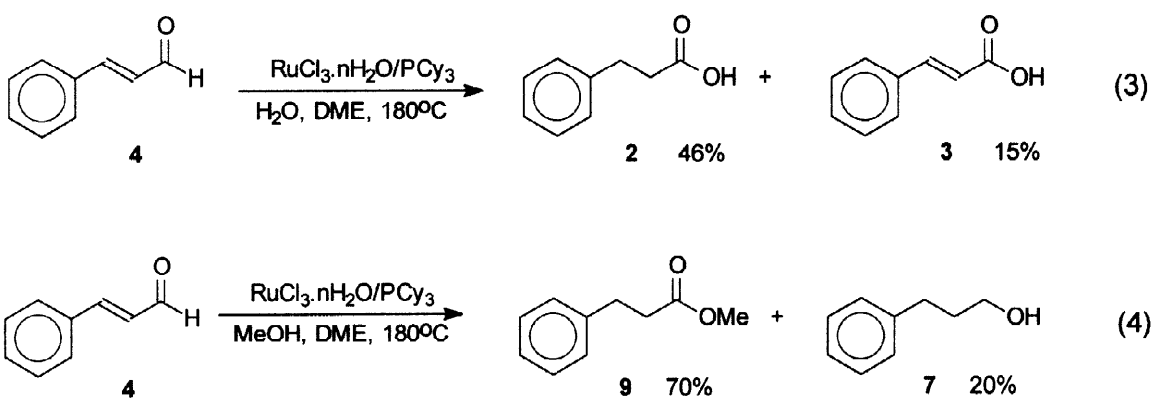


Figure 1. Decarbonylation of cinnamaldehyde.

The ruthenium and rhodium catalysed decarbonylation of saturated aldehydes has been reported by Prince and Raspin [6]. The catalytic decarbonylation of cinnamaldehyde has been reported using Pd/C [7], Pt/C, Ra-Ni [8] and $[RhCl(PPh_3)_3]$ [9]. However, we also considered the possibility that styrene is formed by decarboxylation of **2** [6, 10]. Treatment of **2** with the catalyst under the same reaction conditions afforded no styrene. Finally, the possibility that **6** is formed via a radical pathway was investigated by the addition of 2,6-di-*t*-butylphenol as radical inhibitor. This did not stop the decarbonylation reaction but had the surprising side effect of inducing the reduction of styrene to ethylbenzene (25% yield). Ruthenium catalysed decarbonylation of cinnamaldehyde therefore seems the most likely mechanism for this synthetically useful transformation.

A number of other ruthenium catalysts were tested for the desired conversion under the same conditions [11]. From this search the catalyst obtained by stirring a solution of $RuCl_3$ and 3 equivalents of tri-cyclohexylphosphine (PCy_3) in CH_3OH under N_2 for 1 hr, followed by evaporation of CH_3OH to leave a dark green solid, gave the best results [12]. With 0.5 mol% of catalyst the aldehyde **4** was fully converted after 28 hr at 180°C in a water dimethoxyethane (DME) mixture (Scheme 3). In addition to the desired **2** (46%) some **3** (15%) was also obtained. Analysis of the reaction mixtures over time using ^1H NMR and GC showed that the formation of **2** and **3** continues even after all **4** has been converted. This can be explained by the formation of a stable intermediate product. As it is known that ruthenium complexes can catalyse the Tishchenko reaction [13] we independently synthesised cinnamyl cinnamate. However, this compound was not found in any quantities, nor did we find **5**, 3-phenylpropanol (**7**) or cinnamyl alcohol (**8**).

The poor mass balance can be a result of retro-condensation of cinnamaldehyde to give acetaldehyde and benzaldehyde, which both react to a multitude of other products. To suppress this reaction we next decided to investigate the formation of methyl 3-phenyl-propionate (**9**) by carrying out the transformation of **4** in CH_3OH instead of water (Scheme 4.).



This reaction proceeds much faster than the one in water, resulting in a much higher selectivity. The main side product was **7** (20%). From this mixture **2** can be obtained in pure form by basic hydrolysis ($NaOH/CH_3OH$), work-up by evaporation, partitioning between ether and water, followed by acidification of the aqueous layer.

In conclusion, direct redox transformation of cinnamaldehyde in DME/H_2O at 180°C catalysed by a catalyst made *in situ* from $RuCl_3/PCy_3$ gave an inseparable mixture of 3-phenylpropionic acid and cinnamic acid. Performing the same reaction in CH_3OH gave a useful 70% yield of methyl 3-phenylpropionate, from which 3-phenylpropionic acid can be isolated in pure form. Treatment of cinnamaldehyde with $RuH_2(PPh_3)_4$ in DME/water induced decarbonylation to styrene.

Experimental Section

Preparation of methyl 3-phenylpropionate: To $RuCl_3.nH_2O$ (0.1g, 0.4 mmol) and PCy_3 (0.3 g, 1.2 mmol) in a Schlenk tube degassed CH_3OH (15 ml) was added under N_2 and the solution was stirred for 1h at ambient temperature. The green solution was transferred to an autoclave (Parr Hastelloy C) and **4** (9.0g, 68 mmol) and CH_3OH (10 ml) were added. The autoclave was brought to 180°C and the mixture was stirred at this temperature till completion of the reaction (5h). Samples were taken for GC analysis after 0.5, 1, 2, 3 and 5 h. GC was performed on a Chrompac wcot fused silica column, using the following temperature program: T_{init} 70°C 1 min, 10°/min, T_{final} 220°C. 1,2,4 trichlorobenzene was added to the samples as internal standard.

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[11]The following catalysts were tested but gave lower yields of the desired product: $[RuCl_2(DMSO)_4]$, $[CpRuCl(PPh_3)_2]$, $[Ru_3O(OAc)_6(H_2O)_3]^+OAc^-$, $[Ru(CO)_2(Ph_4CpOH)]_2$, $[RuCl_2(p\text{-Cymene})]_2$, $RuCl_3$ with 3 eq. of PPh_3, P*i*-Pr_3, or Pn-Bu_3.

[12] ^{31}P NMR analysis of the catalyst showed several species. The most abundant (50%) was $[RuHCl(CO)(PCy_3)_2]$. See: James BR, Preece M, Robinson SD. Adv. Chem. Ser. 1982;196:145-161.

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