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Oxidation of alcohols by transfer hydrogenation: driving the equilibrium with an intramolecular trap

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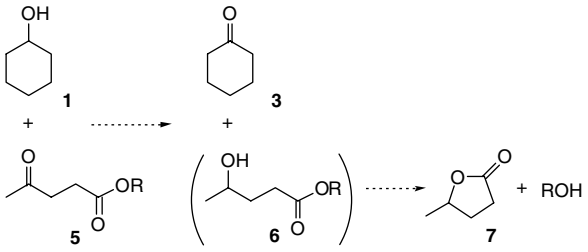
Abstract—Levulinic acid and its esters participate in transfer hydrogenation with a range of secondary alcohols. Reduction of the levulinate leads to cyclisation into a γ-lactone, thereby acting as an oxidant for alcohols without the need for a large excess of reagents.

Transfer hydrogenation reactions between alcohols and ketones have been catalysed by a variety of metal complexes.[1] The equilibrium position of such reactions depends on the relative stabilities of the ketones with respect to their corresponding alcohols, and can be calculated from the oxidation potentials of the ketones involved.[2,3] For example, the oxidation of cyclohexanol **1** with 1 equiv of acetone **2** is expected to give a 22% conversion into cyclohexanone **3** and isopropanol **4** at equilibrium at 25 °C (Scheme 1).[4,5]

In order to achieve a greater conversion of cyclohexanol into cyclohexanone, a large excess of acetone could be employed. However, we wanted to achieve the oxidation of alcohols without the need for a large excess of the acceptor ketone,[6] and considered the possibility of an intramolecular trap in order to drive the equilibrium. A ketone with a pendant leaving group, such as a levulinate ester **5**, would be expected to participate in transfer hydrogenation to give alcohol **6**, which would then cyclise to lactone **7**, driving the equilibrium to the right hand side (Scheme 2). Ideally, the alcohol ROH released upon cyclisation should be completely inert to oxidation

Scheme 1. Equilibration in transfer hydrogenation.



Scheme 2. Lactonisation as an intramolecular trap.

(e.g., *t*-BuOH or PhOH). However, we chose to use commercially available methyl levulinate as the hydrogen acceptor, reasoning that the liberated methanol would be difficult to oxidise.[3] We have recently been using $Ru(PPh_3)_3(CO)H_2$ and related complexes for transfer hydrogenation reactions,[7] and herein we report the use of this catalyst to demonstrate the viability of using levulinates as oxidants in transfer hydrogenation reactions.

In a preliminary experiment, 1-phenylethanol **8** was reacted with 1.2 equiv of methyl levulinate **10** using $Ru(PPh_3)_3(CO)H_2$/diphosphine as the catalyst. We were pleased to find that all of the alcohol had been completely converted into acetophenone **9**, as judged by analysis of the crude ^1H NMR spectrum and GC trace (Scheme 3).

Either DPE-phos[8] or Xantphos[9] were effective ligands, affording a slightly faster reaction (80% conversion in 24 h in the absence of either ligand). After 3 h, the

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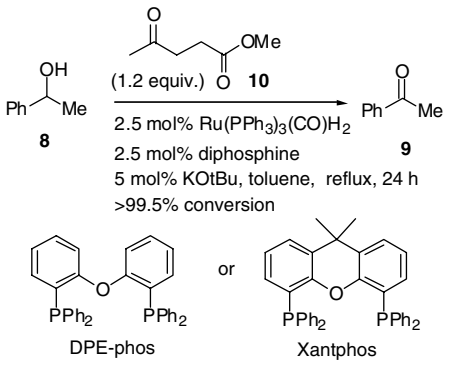


Scheme 3. Complete oxidation of 1-phenylethanol.

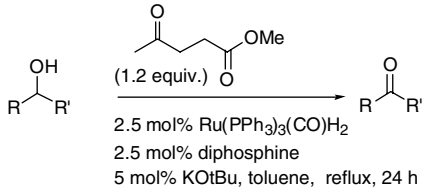
reaction with DPE-phos had reached 98% conversion, whereas the reaction with Xantphos had only reached 64% conversion.

Since the ruthenium complex was already in the activated dihydride form, the addition of base (KO*t*-Bu) was not essential, although reactions proceeded slightly more quickly in its presence.[10]

Methyl levulinate was then used for the oxidation of other alcohols, providing high conversions under these reaction conditions (see Table 1). Separation of the product ketones from lactone **7** was achieved by column chromatography with reasonable isolated yields. In the case of the oxidation of the primary alcohol (entry 8), the main product was the ester, with minor impurities visible in the crude NMR spectrum. Even cyclohexanol could be oxidised with almost complete conversion, despite the relatively high reduction potential of this ketone (entry 9). The use of ethyl levulinate as the oxidant was less satisfactory, affording 88% conversion for the oxidation of alcohol **8** into ketone **9**. This may be due to the easier oxidation of ethanol in comparison with methanol.[3]

Levulinic acid itself could also be used as the oxidant, and was applied to the oxidation of the secondary alcohols identified in Table 2.

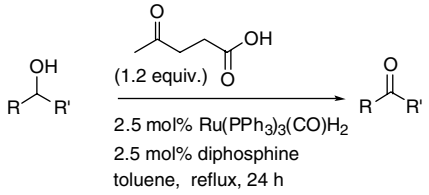
Table 1. Oxidation of other alcohols



Entry	Ligand	R	R′	Conv. (%)[a]
1	DPE-phos	Ph	Me	100 (81)
2	Xantphos	Ph	Me	100
3	DPE-phos	Ph	Et	100 (88)
4	DPE-phos	$Ph(CH_2)_2$	Me	99.5 (68)
5	DPE-phos	3-(F_3C)Ph	Me	99.4
6	DPE-phos	2-Furyl	Me	100 (83)
7	Xantphos	$PhOCH_2$	Me	95.6[b]
8	DPE-phos	$Ph(CH_2)_3$	H	(60)[c]
9	DPE-phos	Cyclohexanol		98.6

[a] Isolated yields in parentheses.
[b] 48 h.
[c] The isolated product was the ester $Ph(CH_2)_3O_2C(CH_2)_2Ph$.

Table 2. Oxidation of alcohols with levulinic acid



Entry	Ligand	R	R′	Conv. (%)
1	Xantphos[a]	Ph	Me	100
2	DPE-phos	Ph	Et	98
3	Xantphos[a]	3-(F_3C)Ph	Me	100
4	DPE-phos	$Ph(CH_2)_2$	Me	100

[a] Reaction performed with 1.25 mol % catalyst.

In summary, levulinic acid and its methyl ester can be used as oxidants in a transfer hydrogenation reaction. An excess of this reagent is not required due to the subsequent cyclisation, which drives the equilibrium.

Acknowledgement

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References and notes

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2. Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71*, 3622.
3. Representative oxidation potentials, E_0, include: acetophenone (118 mV); 2-acetylfuran (122 mV); acetone (129 mV); cyclohexanone (162 mV); acetaldehyde (226 mV); formaldehyde (270 mV). Ref. 2 provides a list of the oxidation potentials of over 90 carbonyl compounds.
4. The equilibrium constant K for two carbonyl compounds A and B can be calculated from $E_0(\mathrm{A}) - E_0(\mathrm{B}) = (RT/NF)\ln K$. The ratio of ketones at equilibrium is given by $\sqrt{K}$:1. The ketone with the lower oxidation potential will be the major component.
5. The equilibrium position at 110 °C is predicted to be 27% cyclohexanone.
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