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Oxidant-free oxidation: ruthenium catalysed dehydrogenation of alcohols

Gareth R. A. Adair and Jonathan M. J. Williams*

Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

Abstract—The oxidation of alcohols has been achieved using Grubbs' catalyst or a ruthenium *p*-cymene complex without the presence of an added oxidant.

We have recently demonstrated that alcohols can be used as substrates for C–C and C–N bond formation, using both ruthenium and iridium catalysts.[1,2] In these reactions, the alcohol undergoes dehydrogenation to give a carbonyl compound, which undergoes in situ conversion into the corresponding alkene or imine, followed by return of the 'borrowed hydrogen' to provide the product alkane or amine. In some cases, we have observed a net oxidation, with product remaining at the alkene/imine oxidation level, suggesting a competing hydrogen loss process.

Herein, we report the development of conditions, which exploit this oxidation process, involving the catalysed dehydrogenation of an alcohol into a ketone with the concomitant loss of hydrogen gas. There is some literature precedent for ruthenium catalysed dehydrogenation, with a very recent example being reported by Junge and Beller.[3] Ruthenium hydride complexes have also been used by Morton and Cole-Hamilton[4] in the generation of hydrogen and other workers have used the Shvo and Robinson catalysts.[5,6] Our focus was on the development of a process using commercially available catalysts that would lead to alcohol oxidation reactions, potentially allowing for further in situ conversion into alkenes, imines or asymmetric reduction back into alcohols.

Preliminary studies investigated the oxidation of phenethyl alcohol **1** into acetophenone **2** using a variety of

Table 1. Study of ruthenium catalysts for oxidation of alcohol **1**

Ruthenium complex[a]	Conversion (%)[c]
CpRuCl(PPh$_3$)$_2$	16
(Indenyl)RuCl(PPh$_3$)$_2$	22
[(Benzene)RuCl$_2$]$_2$	24
[(*p*-Cymene)RuCl$_2$]$_2$	58
PhCH = Ru(PCy$_3$)$_2$Cl$_2$	71
Ru(IMes)(PPh$_3$)$_2$CO(H)$_2$[b]	17

[a] 5 mol % Ru, 5 mol % KOH, PhMe, 110 °C, 24 h, flow of Ar.
[b] No base added for this catalyst.
[c] Conversion was determined from analysis of the ^{1}H NMR spectra.

ruthenium catalysts. As shown in Table 1, this survey identified Grubbs' catalyst, PhCH = Ru(PCy$_3$)$_2$Cl$_2$, and the ruthenium precursor to Noyori's transfer hydrogenation catalyst, [(*p*-cymene)RuCl$_2$]$_2$/PPh$_3$, as promising systems under the conditions that we employed— 5 mol % (in Ru) catalyst, 5 mol % KOH, toluene, 110 °C, 24 h. It is clear that many ruthenium complexes have the ability to oxidise alcohols in the absence of an oxidant. Reactions were performed under a gentle flow of argon, in order to remove hydrogen gas formed. We assume that in each case a ruthenium hydride species is formed.[7]

Optimisation experiments of the reaction shown in Scheme 1 were then performed for each of these
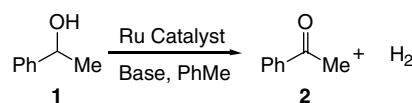
Scheme 1. Ruthenium catalysed dehydrogenation of alcohol **1**.

Table 2. Optimisation of the Grubbs catalyst oxidation reaction

Base used[a]	Conversion (%)[d]
No base	6
K_2CO_3	23
Cs_2CO_3	75
DBU	72
LiOH	85
LiOH[b]	100
LiOH[c]	100

[a] 15 mol % base, 5 mol % Grubbs' catalyst, PhMe, 110 °C, 24 h.
[b] Reaction performed over 48 h.
[c] Reaction performed using second generation Grubbs' catalyst.
[d] Conversion was determined from analysis of the ^1H NMR spectra.

Table 3. Optimisation of [(p-cymene)RuCl$_2$]$_2$/PPh$_3$ for oxidation

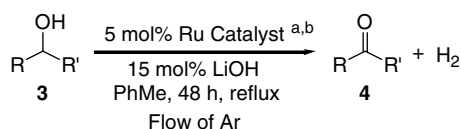| PPh$_3$ equivalents[a]	Conversion (%)[b]
0	24
1	45
2	62
3	81
4	83
5	85
6	90

[a] 2.5 mol % dimer (5 mol % in Ru), 15 mol % LiOH, PhMe, 110 °C, 24 h.
[b] Conversion was determined from analysis of the ^1H NMR spectra.

Table 4. Oxidation of other alcohols

Entry	R	R′	Grubbs' catalyst[a] Conversion (%)[c]	[(p-Cymene)RuCl$_2$]$_2$[b] Conversion (%)[c]
1	Ph	Me	100	100
2	p-FC$_6$H$_4$	Me	100	100
3	p-MeOC$_6$H$_4$	Me	100	100
4	Ph	H	2	3
5	Ph	Ph	54	100
6	Ph(CH$_2$)$_2$	Me	58	91
7	Tetralol		100	100

[a] PhCH = Ru(PCy$_3$)$_2$Cl$_2$.
[b] With PPh$_3$ (20 mol %).
[c] Conversion was determined from analysis of the ^1H NMR spectra.

catalysts, as shown in Table 2 for Grubbs' catalyst and Table 3 for the ruthenium *p*-cymene complex. Caesium carbonate, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and lithium hydroxide were all found to be suitable bases using the Grubbs catalyst.

In the case of the ruthenium *p*-cymene complex, the addition of triphenylphosphine was found to be beneficial, as shown in Table 3. In subsequent reactions, we employed four equivalents of phosphine as a compromise between reactivity and the requirement for excess phosphine.

The oxidation of a range of alcohols was then performed using both the Grubbs catalyst and the [(*p*-cymene)RuCl$_2$]$_2$/PPh$_3$ system using the optimised conditions (Scheme 2). The alcohols were successfully oxidised to the corresponding ketones in moderate to quantitative conversion as shown in Table 4.

In a typical experiment, alcohol (3 mmol), ruthenium catalyst (0.15 mmol in Ru) and LiOH·H$_2$O (0.45 mmol, 18.9 mg) were heated at reflux in toluene (3 mL) for
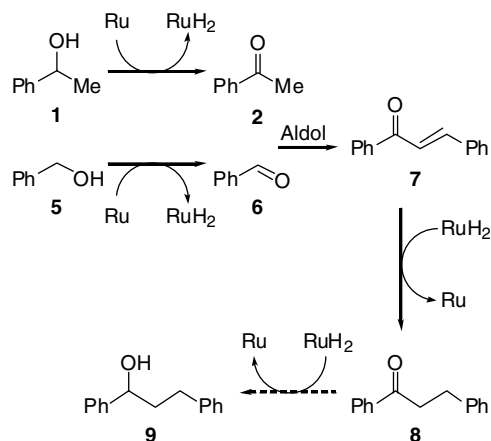
48 h, whilst maintaining a gentle flow of argon in order to remove hydrogen gas.

Both catalytic systems were effective for the oxidation of secondary alcohols, although the more hindered alcohol, benzhydrol (entry 5), was oxidised more slowly by Grubbs' catalyst. The alcohol remote from the phenyl ring, 4-phenyl-2-butanol (entry 6), also underwent a slower oxidation, as expected.[8] A representative sample of ketones was isolated by column chromatography showing isolated yields to be broadly comparable to the conversion attained. For example, *p*-methoxyphen-ethyl alcohol (entry 3) was isolated in 84% and 97% yields using the Grubbs and ruthenium *p*-cymene catalyst systems, respectively. In the presence of excess base, small amounts (typically 5–10%) of reduced aldol condensation products were observed, presumably formed by self aldol condensation of the ketone, followed by alkene hydrogenation.

The attempted oxidation of the primary alcohol, benzyl alcohol **5** is noteworthy, since both catalysts essentially fail in this case. We thought that the initially formed benzaldehyde might de-activate the catalyst via the formation of a ruthenium carbonyl complex.[9] We therefore performed an experiment where both benzyl alcohol **5** and phenethyl alcohol **1** were present, anticipating the benzyl alcohol or benzaldehyde formed to deactivate the catalyst, thus preventing the oxidation of the phenethyl alcohol. Interestingly, all of the benzyl alcohol and phenethyl alcohol were consumed during the course of the reaction, however, no benzaldehyde or acetophenone was detected. Instead, the products formed were ketone **8** and alcohol **9** (Scheme 3).

Using the catalyst PhCH = Ru(PCy$_3$)$_2$Cl$_2$, ketone **8** and alcohol **9** were formed in 26% and 74% yield, whilst for the catalyst [(*p*-cymene)RuCl$_2$]$_2$ the ratio was 52% to 48%.

We assume that during the oxidation reaction, the benz-aldehyde and acetophenone formed react together via an aldol condensation, a process which serves to remove the aldehyde thus discouraging the catalyst deactivation. The aldol condensation product is then reduced as outlined in Scheme 3. Cho, Shim and co-workers have reported a related reaction involving the coupling of primary and secondary alcohols, which required the

Scheme 2. Oxidation of other alcohols with ruthenium catalysts. [a] 5 mol% in Ru. [b] 20 mol % PPh$_3$ employed with [(*p*-cymene)RuCl$_2$]$_2$.

Scheme 3. Oxidation of phenethyl alcohol in the presence of benzyl alcohol.

use of an alkene to act as a hydrogen acceptor, and the solvent used, dioxane, as a hydrogen source.[10]

In summary, ruthenium complexes can be employed for the oxidation of alcohols in the absence of an oxidant. In some cases, oxidation is coupled with C–C bond formation, and the development of this and related processes provides an opportunity for additional domino reactions to be addressed. This use of the Grubbs catalyst adds to the number of reactions that this complex catalyses which do not involve alkene metathesis.[11]

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