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Chemoselective Oxidation of Secondary Alcohols Using a Ruthenium Phenylindenyl Complex

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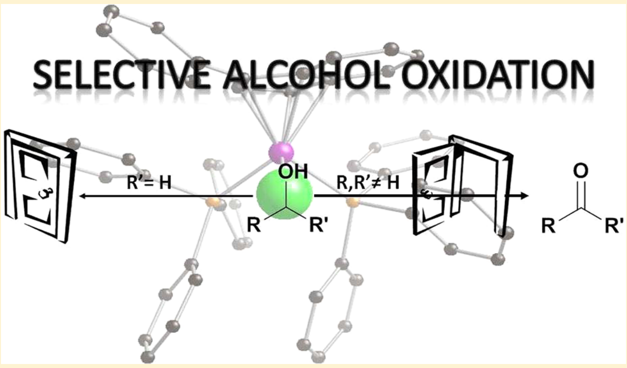
Supporting Information

ABSTRACT: A straightforward catalytic alcohol oxidation procedure using the recently reported complex [RuCl(PPh$_3$)$_2$(3-phenylindenyl)] (**1**) with KHMDS as cocatalyst, in acetone as the oxidant, is reported. Complex **1** shows remarkable chemoselectivity in oxidizing secondary alcohols to ketones.



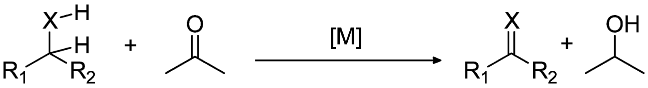
The oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones is a fundamental reaction in organic synthesis.[1] Traditionally, these transformations have been performed using stoichiometric amounts of oxidant, such as the Dess–Martin periodinane (DMP),[2] Jones's oxidant,[3] and Swern's methodology.[4] However, these methodologies often use toxic reagents or generate a significant amount of waste.[5]

In order to develop an efficient and greener alcohol oxidation protocol, numerous catalytic systems have been reported in the literature,[6−16] using a combination of organometallic complexes and mild oxidants to regenerate the active species. Although these procedures are a significant improvement, the co-oxidants used are usually expensive reagents (for example TEMPO and Ag_2O),[8,17] difficult to handle (such as using gaseous O_2),[18−21] or very reactive reagents, which are less compatible with sensitive substrates (for example, H_2O_2 and ^{t}BuOOH).[22−29] Moreover, most of the complexes used contain expensive metals, such as Pd or Ir, or costly ligands, making the systems less suitable for large-scale reactions and for industrial applications.[20,21,28,30−32]

One of the best alternatives among the existing methods is the Oppenauer oxidation, where the substrate is easily oxidized via transfer of two hydrogen atoms by a metal complex into a sacrificial ketone, such as acetone (Scheme 1).[33]

In order to achieve an efficient oxidation system using a relatively inexpensive metal complex, we focused on the use of ruthenium.[34] Indeed, the ruthenium-based complexes are usually a good compromise between activity and price, as already proven in a wide variety of reactions, such as olefin metathesis,[35,36] hydrogenation,[37,38] and oxidation,[25] among others.

Scheme 1. Oppenauer Oxidation



We proceeded to evaluate the catalytic activity of the recently reported complex [RuCl(PPh$_3$)$_2$(3-phenylindenyl)] (**1**). **1** can be easily and inexpensively synthesized, starting from a suitable propargylic alcohol and [RuCl$_2$(PPh$_3$)$_3$] (Scheme 2).[39]

Complex **1** is extremely active in alcohol racemization reactions, which are formally tandem hydrogenation/oxidation processes. Additionally, as previously reported, **1** is remarkably active in the hydrogenation of aldehydes, imines, and ketones, outperforming in activity the most commonly used ruthenium catalysts.[39,40] For these reasons, we hypothesized that **1** could be an efficient catalyst for alcohol oxidation (Scheme 3).

Using the oxidation of benzhydrol as a benchmark reaction, the reaction conditions were optimized (see Table 1). Complex **1** can catalyze alcohol oxidation at room temperature but requires long reaction times to achieve complete conversions. However, increasing the temperature significantly reduces the reaction time (Table 1, entries 1 and 2). Using toluene as a co-solvent has a beneficial effect on the reaction; in fact, conversion reached 86% in 1 h at 56 °C, a 10% increase in conversion in comparison to simply using acetone as solvent (Table 1, entries 2 and 3). Moreover, this solvent combination permits us to operate at higher temperatures, allowing quantitative conversions in shorter reaction times. Indeed at 110 °C, the optimized condition, benzhydrol (**2**) is fully oxidized to benzophenone (**3**) in just 0.5 h (Table 1, entry 6).

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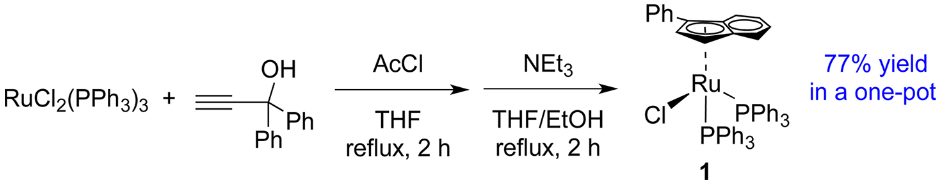
Scheme 2. Synthesis of Complex 1



Scheme 3. Reactions Catalyzed by Complex 1

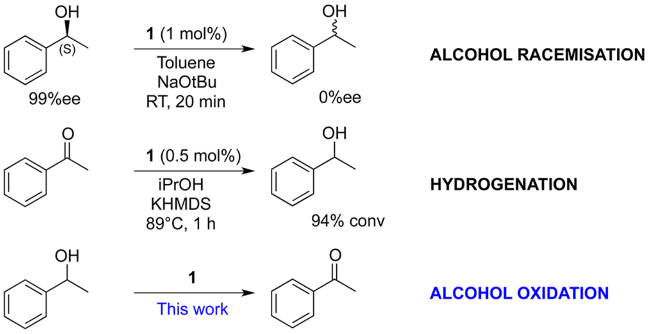
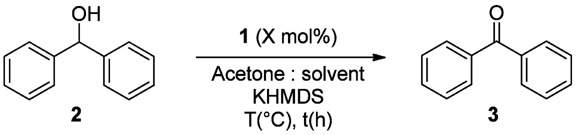


Table 1. Activity of Catalyst 1 under Various Conditions[a]



entry	solvent	T (°C)	t (h)	cat. loading (mol %)	conversn (%)[b]
1	toluene	room temp	16	0.5	45
2		56	1	0.5	72
3	toluene	56	1	0.5	86
4	toluene	56	0.5	0.5	79
5	toluene	89	0.5	0.5	90
6	toluene	110	0.5	0.5	>99
7	toluene	110	0.5	0	0
8	toluene	110	1	0.25	94
9	toluene	110	5	0.1	91
10	toluene	110	24	0.05	63

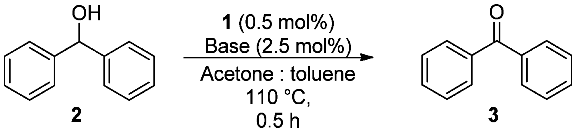
[a] Reaction conditions: benzhydrol (0.25 mmol), KHMDS (2.5 mol %), dissolved in 1/1 toluene/acetone (0.5 mL). [b] Conversion determined by ^{1}H NMR from an average of at least two runs.

To test the limits of **1**, a low catalyst loading screening was performed (Table 1, entries 8–10). **1** shows a maximum turnover number (TON) of 1250. This result demonstrates the high activity of the catalysts and showcases **1** as one of the best catalysts for the Oppenauer oxidation reaction.[13,31,41−45] Moreover, **1** also shows a remarkably high turnover frequency (TOF); for example, compound **2** is converted into the corresponding ketone with a TOF of 400 h^{-1}.

Although KHMDS is one of the best bases for the catalytic system used (as previously reported for the hydrogenation of ketones), different bases were also screened (Table 2).

As shown above, it is possible to perform the oxidation with a variety of bases, using cheaper bases such as KOH (Table 2, entry 3) or milder conditions using, for example, K$_2$CO$_3$ (Table 2, entry 4).

Table 2. Activity of Catalyst 1 with Different Bases[a]

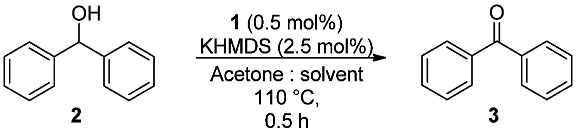


entry	base	conversn (%)[b]
1	KHMDS	>99
2	KO^{t}Bu	97
3	KOH	94
4	K$_2$CO$_3$	90

[a] Reaction conditions: benzhydrol (0.25 mmol), base (2.5 mol %), dissolved in 1/1 toluene/acetone (0.5 mL). [b] Conversion determined by ^{1}H NMR from an average of at least two runs.

A number of more industrially acceptable and “green” solvents were next evaluated with this system.[46] Complex **1** can perform alcohol oxidation in most “eco-friendly” solvents and also, very interestingly, in water (Table 3, entry 5).

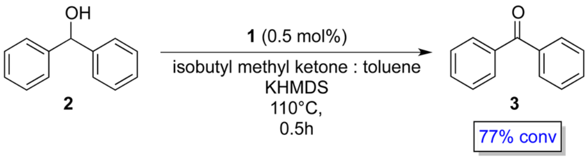
Table 3. Activity of Catalyst 1 under Different Conditions[a]



entry	solvent	conversn (%)[b]
1	toluene	>99
2	heptane	96
3	cyclopentyl methyl ether	80
4	acetone	79
5	2-Me-THF	96
6	water	77

[a] Reaction conditions: benzhydrol (0.25 mmol), KHMDS (2.5 mol %), dissolved in 1/1 solvent/acetone (0.5 mL). [b] Conversion determined by ^{1}H NMR from an average of at least two runs.

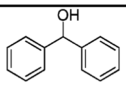
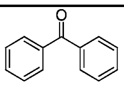
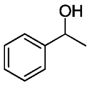
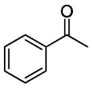
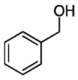
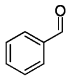
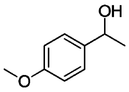
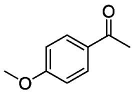
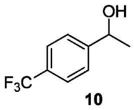
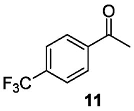
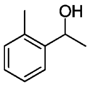
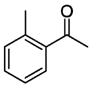
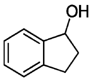
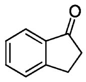
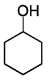
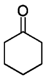
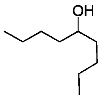
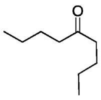
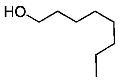
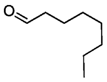
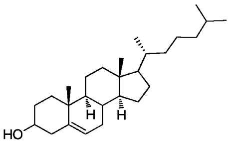
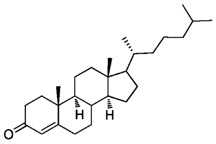
Taking further steps in the direction of a very green system, we modified the co-oxidant used, in our case acetone, to a more easily handled alternative. Indeed, the major issue with acetone is its low flash point (−20 °C) that makes it very flammable and less attractive for industrial-scale applications.[46] To highlight the utility of the system for industrial large-scale synthesis, isobutyl methyl ketone, which has a higher flash point (14 °C), was evaluated as the hydrogen acceptor (eq 1).



(1)

This ketone shows good compatibility with the system, although the conversion is lower than that with acetone (77% conversion). However, as shown, the system is very versatile

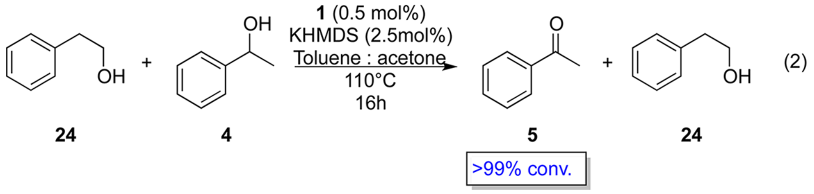
Table 4. Scope of the Oxidation Reaction[a]

Entry	Substrate	Product	t (h)	Conv.(%)[b]	Yield (%)[c]	TOF (h^{-1})
1	 2	 3	0.5	>99	97	400
2	 4	 5	0.5	97	96	388
3	 6	 7	16	5(6)[d,e]	-	-
4	 8	 9	0.5	>99	98	400
5	 10	 11	3	70	67	55
6	 12	 13	1	87	86	348
7	 14	 15	1	>99	97	200
8	 16	 17	0.5	>99	90	400
9	 18	 19	0.5	>99	87	400
10	 20	 21	16	-	-	-
11	 22	 23	1	85	84	340

[a] Reaction conditions: substrate (1 mmol), **1** (0.5 mol %), KHMDS (2.5 mol %), dissolved in 1/1 toluene/acetone (2 mL). [b] Conversion determined by ^{1}H NMR from an average of at least two runs. [c] Isolated yields are average of two runs. [d] Presence of dimerized product (7%). [e] Results in parentheses are referred to the conversion into the desired product under the following reaction conditions: 5 mol % of **1** and 5 mol % of KHMDS dissolved in 1/1 toluene/acetone (2 mL).

and leads to the possibility of using very mild conditions to carry out the oxidation.

The tolerance of the catalytic system to different substrates bearing various structural motifs was next examined, and the



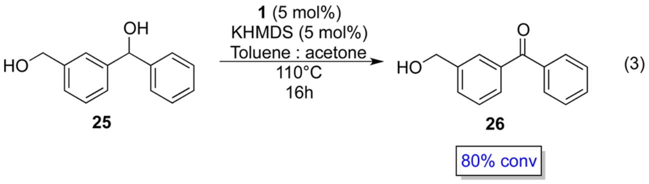
results are presented in Table 4. Complex **1** exhibits high activity in the oxidation of secondary alcohols, typically achieving full conversions in 1 h. It is highly active with aliphatic and aromatic substrates (Table 4). Alcohols bearing electron-withdrawing substituents are less prone to be oxidized than electron-rich analogues (Table 4, entries 4 and 5). Substrates that are sterically hindered at the aromatic positions are more difficult to oxidize; however, electronic effects appear to have more impact than steric effects (Table 4, entries 5 and 6). Moreover, this methodology is suitable for biologically active molecules. In fact, catalyst **1** oxidizes cholesterol (**22**) in 1 h, surpassing the catalytic activity of the very efficient and versatile Shvo catalyst under its optimized conditions (Table 4, entry 11).[41,47] Interestingly, the oxidized product of **22** is not the 7*β*-cholest-5-en-3-one; instead, isomer **23**, where the double bond is rearranged to bring it into conjugation, is obtained.

Complex **1** shows no activity in the oxidation of primary alcohols to aldehydes (Table 4, entries 3 and 10). With aromatic primary alcohols, there is formation of traces of the corresponding ester, resulting from dimerization of the starting material. Even when the catalyst loading was increased to 5 mol %, the conversion remained the same, suggesting that primary alcohols can be dehydrogenated, but the mechanism is thermodynamically not favored, as hydrogenation of the produced aldehyde is favored over hydrogenation of acetone.[48]

In order to showcase the high selectivity of catalyst **1**, a competition experiment was performed (eq 2).

In a 1/1 mixture of phenylethanol isomers, complex **1** oxidizes 1-phenylethanol (**4**) to acetophenone (**5**), without oxidizing the other isomer. However, the presence of primary alcohols in the reaction mixtures leads to longer reaction times to reach complete conversion.

To further evaluate this selectivity, a molecule containing primary and secondary alcohols was tested with our system (eq 3). Although the reaction required slightly higher loading and longer reaction times, complex **1** is capable of oxidizing selectively the secondary alcohol moiety in **25**. In fact, as shown in the previous experiments, primary alcohols have a detrimental effect on the activity of **1**. *However, only the secondary alcohol has been oxidized, proving the high selectivity of 1!* Considering this result, **1** could be a useful catalyst for densely functionalized molecules or for mixtures of alcohols.



In conclusion, a novel application of $RuCl(PPh_3)_2$(3-phenylindenyl)] (**1**) has been disclosed. This catalyst can be used in the oxidation of mixtures of alcohols but proves to be completely selective for secondary alcohols. Work is currently underway to explore further applications of this easily accessible complex.[49]

EXPERIMENTAL SECTION

General Procedure for Oxidation Reactions. In a vial fitted with a screw septum cap, benzhydrol (**2**; 0.25 mmol), **1** (0.00125 mmol), and base (0.005 mmol) were charged inside the glovebox and dissolved in organic solvent (0.25 mL). To this mixture was added acetone (or isobutyl methyl ketone) (0.25 mL). The solution was stirred at a given temperature for 1 h (in the case of Table 1 the reactions were analyzed at 0.5 and 1 h). The solvent was removed under vacuum, and the crude reaction mixture was analyzed by ^1H NMR spectroscopy.

General Procedure for Oxidation Reactions in Table 4. In a 10 mL J. Young type Schlenk flask, the substrate considered (1 mmol), **1** (0.005 mmol), and KHMDS (0.02 mmol) were charged inside the glovebox and dissolved in toluene (1 mL). To this mixture was added acetone (1 mL). The solution was stirred at 110 °C for the time reported in Table 4. The solvent was removed under vacuum, and the crude reaction mixture was purified by column chromatography using as eluent a 95/5 mixture of pentane and ethyl acetate (with the exception of entry 11, Table 4, where dichloromethane was used as eluent).

Low Catalyst Loading Procedure. In a 10 mL J. Young type Schlenk flask, inside the glovebox, an aliquot of **1** from a stock solution of catalyst **1** in toluene (2.6 mg in 5 mL) was added and diluted with toluene to a total volume of 0.25 mL. Benzhydrol (**2**; 0.25 mmol), KHMDS (0.0625 mmol, 1.2 mg) and acetone (0.25 mL) were added. The solution was stirred at 110 °C for a period of time indicated in Table 1. The solvent was removed under vacuum, and the crude reaction mixture was analyzed by ^1H NMR spectroscopy.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving synthetic procedures and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(49) [RuCl(PPh$_3$)$_2$(3-phenylindenyl)] (**1**) is now commercially available from Strem Chemicals, Inc. with catalog number 44-0138.