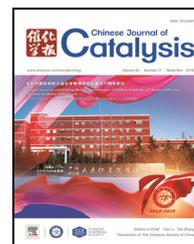


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Methanol as hydrogen source: Chemoselective transfer hydrogenation of α,β -unsaturated ketones with a rhodacycle

Ahmed H. Aboo^a, Robina Begum^{a,b}, Liangliang Zhao^a, Zahoor H. Farooqi^b, Jianliang Xiao^{a,*}^a Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD, United Kingdom^b Institute of Chemistry, University of the Punjab, New Campus, Lahore 54590, Pakistan

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ABSTRACT

Methanol is a safe, economic and easy-to-handle hydrogen source. It has rarely been used in transfer hydrogenation reactions, however. We herein report that a cyclometalated rhodium complex, rhodacycle, catalyzes highly chemoselective hydrogenation of α,β -unsaturated ketones with methanol as the hydrogen source. A wide variety of chalcones, styryl methyl ketones and vinyl methyl ketones, including sterically demanding ones, were reduced to the saturated ketones in refluxing methanol in a short reaction time, with no need for inter gas protection, and no reduction of the carbonyl moieties was observed. The catalysis described provides a practically easy and operationally safe method for the reduction of olefinic bonds in α,β -unsaturated ketone compounds.

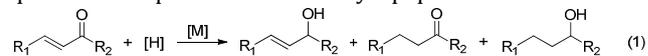
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1. Introduction

The selective hydrogenation of α,β -unsaturated ketones is of great importance with respect to both laboratory practice and production of various useful chemicals. The products of this selective hydrogenation, e.g. saturated ketones, have potential applications in the synthesis of food sweeteners, flavors, perfume products, pharmaceuticals and advanced functional materials [1–3]. However, mixtures of products are frequently obtained, because many catalysts reduce both the C=O and C=C bonds, rather than exclusively either the C=O or C=C bond (Eq. (1)) [4–9]. In particular, it has been difficult to achieve total chemoselective reduction of the carbon-carbon double bonds in the presence of other easily reducible groups like C=O, although the hydrogenation of a C=C double bond is generally thermodynamically more favorable as compared to that of a C=O bond [6–10]. Fully selective hydrogenation of carbonyl

groups of α,β -unsaturated ketones has been established with homogeneous catalysis [11,12]. The reduction of the olefinic group of unsaturated ketones is often carried out by heterogeneous catalysis using molecular hydrogen as reducing agent [13–15]. This is associated with such issues as low chemoselectivity and the hazard of hydrogen gas, in addition to the requirement of specialized laboratory equipment.



Transfer hydrogenation provides an alternative for the chemoselective reduction of alkenic double bond of α,β -unsaturated ketones, and has gained much attention in the last two decades due to its operational simplicity and high selectivity [12,16–18]. High molecular weight alcohols, formic acid and its salts have been reported as a good source of hydrogen in this methodology, with the reduction usually catalyzed by transition metal complexes [12,19–22]. In most cases,

* Corresponding author. E-mail: J.Xiao@liverpool.ac.uk

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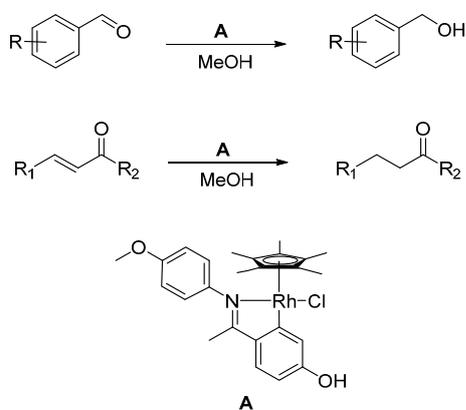
2-propanol is the choice of source of hydrogen. For example, Ishii and co-workers early reported chemoselective transfer hydrogenation of α,β -unsaturated compounds with 2-propanol in the presence of an iridium complex and a phosphine ligand [23]. Formate has also been used. An example is seen in the selective transfer hydrogenation of similar compounds catalyzed by a Rh-diamine complex in an aqueous medium, reported by Deng and coworkers [24]. Using an iridacycle catalyst, we recently reported the reduction of α,β -unsaturated ketones with formate in water. The chemoselectivity was poor, however, with both the C=C and C=O bonds being reduced [21,25].

With a global production of ca. 110 million metric tonnes a year, methanol may be a cost-effective, easily available and eco-friendly source of hydrogen [26]. However, in comparison with 2-propanol, MeOH is thermodynamically more difficult to undergo dehydrogenation to afford H₂ or metal hydride for transfer hydrogenation [27]. Consequently, its use as a hydrogen source for hydrogenation has been much less documented. Examples are known of the transfer hydrogenation of C=C double bonds in α,β -unsaturated enones, alkenes and alkyne and ketones, with ruthenium, rhodium, iridium or nickel complexes as catalysts [19,28–33]. With these catalysts, high temperatures (120–180 °C) are generally necessary to drive the hydrogenation. For instance, using MeOH as the hydrogen donor, Garcia and coworkers reported the reduction of α,β -unsaturated dienones into the corresponding saturated ketones with a nickel catalyst [Ni(dippe)(μ -H)]₂ at 180 °C [31].

We recently showed that the rhodacycle **A** is an efficient catalyst for the transfer hydrogenation of aldehydes with MeOH as the sole hydrogen source (Scheme 1) [26]. Following this finding, we observed that **A** also catalyzes the highly chemoselective hydrogenation of the double bonds of various substituted conjugated ketones under mild, aerobic reaction conditions within a short reaction time. Herein we report the details of our finding.

2. Experimental

2.1. Preparation of the rhodium complex **A**



Scheme 1. Transfer hydrogenation with methanol catalyzed by the rhodacycle **A**.

The rhodium complex was prepared according to the previously reported procedures [26,34,35]. A representative preparation is as follows. The [Cp**Rh*Cl₂]₂ dimer (100 mg, 0.16 mmol) (Cp* = C₅Me₅), imine ligand (2.2 eq.) and NaOAc (10 eq.) were charged into a Radley tube equipped with a stir bar. DCM (10 mL) was then added and the reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The resulting mixture was filtered through Celite to remove insoluble materials and dried over MgSO₄. Following removal of the solvent, the product was washed with diethyl ether/hexane and vacuum-dried to afford an air and moisture stable pure compound of orange color.

2.2. Transfer hydrogenation of unsaturated ketones in methanol

A Radley tube was charged with an unsaturated ketone (0.3 mmol), catalyst (0.003 mmol) and K₂CO₃ (0.25 eq), to which was introduced MeOH (1.5 mL). The reaction mixture was heated to reflux at 90 °C for 1 h. The resulting mixture was then cooled to room temperature, followed by solvent evaporation under vacuum. The product was purified by flash column chromatography (hexane/ethyl acetate, 4:1).

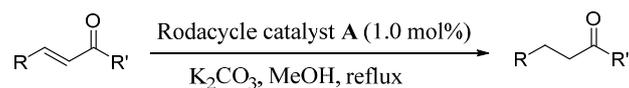
3. Results and discussion

3.1. Optimisation of reaction conditions

We set out to examine the transfer hydrogenation of 4,4'-dimethoxychalcone (**1**) to its corresponding saturated ketone (**2**), with the rhodacycle **A** as possible catalyst in methanol (Table S1). As mentioned, with the related iridacycles, the chemoselectivity of the reduction of α,β -unsaturated ketones with formate in water was poor [21]. Pleasingly, using the conditions established for the transfer hydrogenation of aldehydes [26], the chalcone **1** was fully reduced with MeOH in 1 h at 90 °C in the presence of 1 mol% of **A**, with no reduction of the carbonyl moiety being observed. That is, the transfer hydrogenation is totally chemoselective toward the reduction of the C=C double bond. Replacing the more expensive base Cs₂CO₃ with the cheaper K₂CO₃ and Na₂CO₃ brought about the same result under the conditions used. However, the reaction did not occur at all in the absence of a base. Our subsequent study of the scope of the reduction was therefore based on using **A** (1 mol%) as catalyst, K₂CO₃ (25 mol%) as base, and MeOH as both the reductant and solvent at 90 °C, with no inert gas protection.

3.2. Chemoselective reduction of α,β -unsaturated ketones

The general applicability of the rhodacycle catalyst **A** towards the reduction with MeOH of the C=C double bonds of α,β -unsaturated ketones was investigated under the optimized reaction conditions (Table 1). As can be seen, the catalyst is capable of highly chemoselective transfer hydrogenation of a variety of diversely substituted unsaturated ketones, affording the saturated ketones with excellent yields in general in a short reaction time of 1 h (Table 1, entries 1–36). For the chalcones,

Table 1Rhodcycle A-catalyzed transfer hydrogenation of α,β -unsaturated ketones with methanol ^a.

Entry	Substrate	Product	Yield (%) ^b	Entry	Substrate	Product	Yield (%) ^b
1			90	19			96
2			91	20			88
3			94	21			91
4			92	22			97
5			86	23			78
6			95	24			83
7			60	25			85
8			90	26			81
9			86	27			86
10			96	28			84
11			92	29			83
12			75	30			86
13			94	31			96 ^c
14			89	32			88 ^c
15			90	33			88 ^c
16			91	34			97 ^c
17			92	35			97 ^c
18			90	36			91 ^c

^a Reaction conditions: ketone (0.3 mmol), rhodcycle A (0.003 mmol), K₂CO₃ (0.075 mmol) and MeOH (1.5 mL), stirred at 90 °C for 1 h. ^b Yield of isolated product. ^c Yield determined by GC.

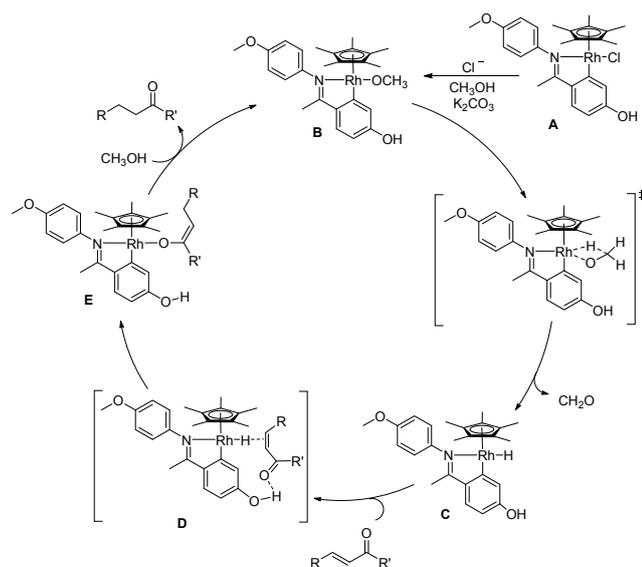
both electron-donating and withdrawing substituents on the styryl side are tolerated (Table 1, entries 1–22). Of particular note is that chalcones having 2-substituted or 2,6-disubstituted styryl units were all reduced with high yields (Table 1, entries 6, 9, 10, 16, 20), considering that the hydride addition would take place at the β position of the C=C double bond (see below).

The rhodacycle **A**-catalyzed reduction with MeOH also works for styryl methyl ketones (Table 1, entries 23–30). Again the transfer hydrogenation is highly chemoselective, only affording the saturated ketones. As in the case of chalcones, the reduction tolerates both electron-donating and withdrawing substituents on the styryl side (Table 1, entries 23, 24, 28, 29) and substrates bearing 2,6-disubstituted styryl units are equally viable (Table 1, entries 25–27).

We also examined the reduction of aliphatic methyl vinyl ketones with **A** in MeOH. As can be seen from Table 1, these ketones including examples of cyclohexenone and cycloheptenone were also reduced, affording the corresponding saturated ketones in high yields (Table 1, entries 31–36). Notably, a β -disubstituted methyl vinyl ketone was reduced with no difficulty (Table 1, entry 31).

3.3. Mechanistic considerations

On the basis of our previous study [26], a plausible reaction mechanism for the **A**-catalyzed chemoselective reduction of unsaturated ketones with methanol is proposed in Scheme 2. Under the basic reaction conditions employed, the alkoxide complex **B** is formed from the rhodacycle **A** in MeOH. Then the complex **B** undergoes β hydrogen elimination, giving rise to the hydride complex **C** while releasing formaldehyde, support for which was provided in our study of reduction of aldehydes with methanol [26]. The next step sees the hydride in complex **C** being transferred to the β position of the C=C double bond, affording the species **E**. The hydride transfer may proceed via an intermediate **D**, in which the ligand hydroxyl group hydro-



Scheme 2. A possible catalytic cycle for the rhodacycle **A**-catalyzed selective transfer hydrogenation of unsaturated ketones with MeOH.

gen-bonds with the ketone oxygen, rendering the C=C bond more electrophilic and thereby facilitating the hydride transfer. Such ligand-facilitated reduction has been well documented; however, the ligand-substrate interaction is usually confined to a smaller ring [11,12,36]. Finally, protonation of **E** with MeOH affords the saturated ketone while regenerating **B**.

4. Conclusions

This report shows that under the catalysis of the rhodacycle **A**, methanol can be used as an effective hydrogen source for the highly chemoselective transfer hydrogenation of α,β -unsaturated ketones under mild conditions. Catalyzed by **A**, a wider variety of chalcones, styryl methyl ketones and vinyl methyl ketones, including sterically demanding ones, were reduced to the saturated ketones in refluxing methanol in a short reaction time. Using safe, cheap and easily available methanol as both reductant and solvent, the protocol has the potential to be practically useful.

Acknowledgments

We thank the Higher Committee for Education Development in Iraq for financial support (AHB) and the Commonwealth Scholarships Commission in the UK for a Split-Site PhD Scholarship (RB).

Conflict of interest

The authors declare no conflict of interest.

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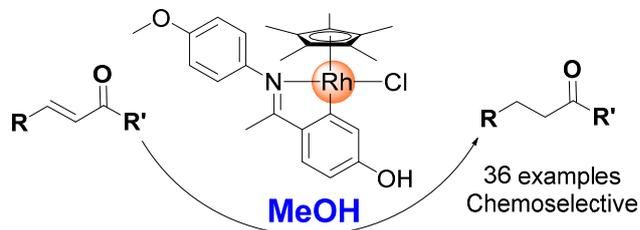
Graphical Abstract

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Methanol as hydrogen source: Chemoselective transfer hydrogenation of α,β -unsaturated ketones with a rhodacycle

Ahmed H. Aboo, Robina Begum, Liangliang Zhao, Zahoor H. Farooqi, Jianliang Xiao^{a,*}
University of Liverpool, United Kingdom;
University of the Punjab, Pakistan

A rhodacycle catalyzes highly selective transfer hydrogenation of α,β -unsaturated ketones with MeOH as the source of hydrogen, affording saturated ketones exclusively.



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甲醇为氢源: Rhodacycle催化 α,β -不饱和酮化学选择性转移加氢反应

Ahmed H. Aboo^a, Robina Begum^{a,b}, Liangliang Zhao^a, Zahoor H. Farooqi^b, Jianliang Xiao^{a,*}

^a利物浦大学化学系, 利物浦, L69 7ZD, 英国

^b旁遮普大学化学所, 新校区, 拉合尔54590, 巴基斯坦

摘要: 甲醇是一种安全、经济、易处理的氢源, 然而它很少用于转移加氢反应中. 本文以甲醇为氢源, 报道了一种环金属化铑配合物, Rhodacycle, 催化 α,β -不饱和酮的高度化学选择性加氢反应. 在回流甲醇中反应很短的时间, 将各种查尔酮、苯乙烯基甲基酮和乙烯基甲基酮(包括空间要求大的酮)还原为饱和酮, 无需惰性气体保护, 也未观察到羰基部分的还原. 该催化反应为 α,β -不饱和酮化合物中烯键的还原提供了一种简便、操作安全的方法.

关键词: α,β -不饱和酮; 转移加氢; 甲醇; 铑络合物; 化学选择性

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*通讯联系人. 电子信箱: J.Xiao@liverpool.ac.uk

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