**Methanol as Hydrogen Source: Chemoselective Transfer Hydrogenation of α,β-Unsaturated Ketones with a Rhodacycle**

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**A B S T R A C T**

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.

**Keywords:** α,β-Unsaturated ketones, transfer hydrogenation, methanol, rhodium complex, chemoselectivity

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, because the hydrogenation of a C=C double bond is generally thermodynamically more favorable as compared to that of a C=O bond [6-10], although 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, 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 chemoselectiviy 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)(-H)]2 at 180 oC [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.



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

# Experimental section

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

The rhodium complex was prepared according to the previously reported procedures [26, 34-35]. A representative preparation is as follows. The [Cp\*RhCl2]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.

* 1. *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).

1. **Results and discussion** 
   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, Supporting Information). 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.

* 1. *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 (Entries 1-36). For the chalcones, both electron-donating and withdrawing substituents on the styryl side are tolerated (Entries 1-22). Of particular note is that chalcones having 2-sustituted or 2,6-disubstituted styryl units were all reduced with high yields (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 (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 (Entire 23, 24, 28, 29) and substrates bearing 2,6-disubstituted styryl units are equally viable (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 (Entries 31-36). Notably, a -disubstituted methyl vinyl ketone was reduced with no difficulty (Entry 31).

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| **Table 1:** Rhodcycle **A**-catalyzed transfer hydrogenation of -unsaturated ketones with methanol a | | | |
|  | | | |
| Entry | Substrate | Product | Yield (%) b |
| 1 |  |  | 90 |
| 2 |  |  | 91 |
| 3 |  |  | 94 |
| 4 |  |  | 92 |
| 5 |  |  | 86 |
| 6 |  |  | 95 |
| 7 |  |  | 60 |
| 8 |  |  | 90 |
| 9 |  |  | 86 |
| 10 |  |  | 96 |
| 11 |  |  | 92 |
| 12 |  |  | 75 |
| 13 |  |  | 94 |
| 14 |  |  | 89 |
| 15 |  |  | 90 |
| 16 |  |  | 91 |
| 17 |  |  | 92 |
| 18 |  |  | 90 |
| 19 |  |  | 96 |
| 20 |  |  | 88 |
| 21 |  |  | 91 |
| 22 |  |  | 97 |
| 23 |  |  | 78 |
| 24 |  |  | 83 |
| 25 |  |  | 85 |
| 26 |  |  | 81 |
|  |  |  |  |
| 27 |  |  | 86 |
| 28 |  |  | 84 |
| 29 |  |  | 83 |
| 30 |  |  | 86 |
| 31 |  |  | 96 c |
| 32 |  |  | 88 c |
| 33 |  |  | 88 c |
| 34 |  |  | 97 c |
| 35 |  |  | 97 c |
| 36 |  |  | 91 c |
| a Reaction conditions: ketone (0.3 mmol), rhodacycle **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. | | | |

* 1. *Mechanistic considerations*



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

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  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 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 hydrogen-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**.

1. **Conclusion**

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.

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**Conflict of interest**

The authors declare no conflict of interest.

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