

Oxidation of Alkenes by Water with H₂ Liberation

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Supporting Information

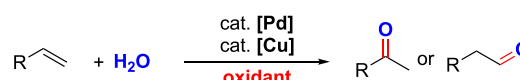
ABSTRACT: Oxidation by water with H₂ liberation is highly desirable, as it can serve as an environmentally friendly way for the oxidation of organic compounds. Herein, we report the oxidation of alkenes with water as the oxidant by using a catalyst combination of a dearomatized acridine-based PNP-Ru complex and indium(III) triflate. Compared to traditional Wacker-type oxidation, this transformation avoids the use of added chemical oxidants and liberates hydrogen gas as the only byproduct.

Catalytic oxidations of hydrocarbons are highly important transformations for the synthesis of fine and bulk chemicals.¹ Traditionally, stoichiometric amounts of chemical oxidants such as peroxides, metal salts, or oxygen are used in the oxidation of hydrocarbons. Under these conditions, oxidation-sensitive functional groups are not tolerated. Thus, there is a strong demand for catalytic oxidation of hydrocarbons with no added oxidants. Oxidation by water with H₂ liberation represents an ideal way for the oxidation of hydrocarbons.² However, only very few catalytic systems have been developed in utilizing water as a reagent in oxidative transformations of organic compounds.³ In 2013, our group reported the catalytic oxidation of alcohols to carboxylic acid salts in basic aqueous solution, with no oxidant added,⁴ with liberation of hydrogen gas, using a bipyridine-based PNN-Ru complex ([Ru]-1) as the catalyst. Later on, we reported an acridine-based PNP-Ru complex ([Ru]-2) catalyzed oxidation of cyclic amines to lactams using just water.⁵ Mechanistic studies indicated that the dearomatized acridine-based PNP-Ru complex ([Ru]-3) was the active catalyst.⁶ Herein, we report the unprecedented (nonphotochemical) oxidation of alkenes to ketones by water with H₂ liberation utilizing an acceptorless dehydrogenation reaction strategy.

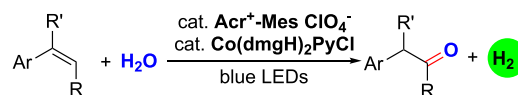
Wacker oxidation is a well-known organic transformation for the construction of carbonyl compounds from alkenes.⁷ By use of a dual Pd/Cu catalytic system, alkenes can usually be oxidized to ketones or aldehydes using oxygen or stoichiometric amounts of chemical oxidants (Scheme 1a). In 2016, Lei and co-workers reported a visible light promoted anti-Markovnikov oxidation of β -alkyl styrenes by water under external oxidant-free conditions (Scheme 1b).⁸ They used a combination of an acridinium photocatalyst and a cobaloxime catalyst. Up to now, there is no method available for the thermal oxidation of alkenes by water with H₂ liberation. It is known that acids can promote both the Markovnikov hydration of alkenes to secondary alcohols and dehydration of secondary alcohols to alkenes.⁹ Thus, an acid catalyst can help establish an equilibrium between an alkene and water. If an acceptorless dehydrogenation catalyst can be introduced, dehydrogenation of the secondary alcohol may help drive the equilibrium to promote the hydration of alkenes. Thus, we

Scheme 1. Wacker-Type Oxidation of Alkenes

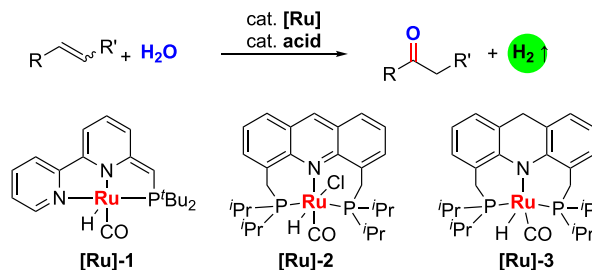
(a) Traditional Wacker-type oxidation of alkenes



(b) Photochemical anti-Markovnikov oxidation of β -alkyl styrenes by water



(c) Markovnikov oxidation of alkenes by water (*This work*)



envisioned that a combination of an acid catalyst and an acceptorless dehydrogenation catalyst might enable the Markovnikov oxidation of alkenes by water with H₂ liberation (Scheme 1c).

We decided to study the oxidation of alkenes by water using a catalyst combination of a pincer ruthenium complex and an acid. Obviously, two side reaction pathways are required to be overcome for achieving the desired transformation: (1) homocoupling and polymerization of alkenes under acidic

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conditions;¹⁰ (2) transfer hydrogenation of alkenes.¹¹ We chose styrene (**1a**) as the model substrate and complex **[Ru]-3** as the acceptorless dehydrogenation catalyst to start the investigation. In a mixed solvent system of 1,4-dioxane and water (2:1), representative Brønsted acids and Lewis acids were tested upon external heating at 150 °C in a sealed tube at reflux (Table 1, entries 1–6). The hydrogen transfer product

Table 1. Optimization of the Catalytic System for the Oxidation of Styrene by Water^a

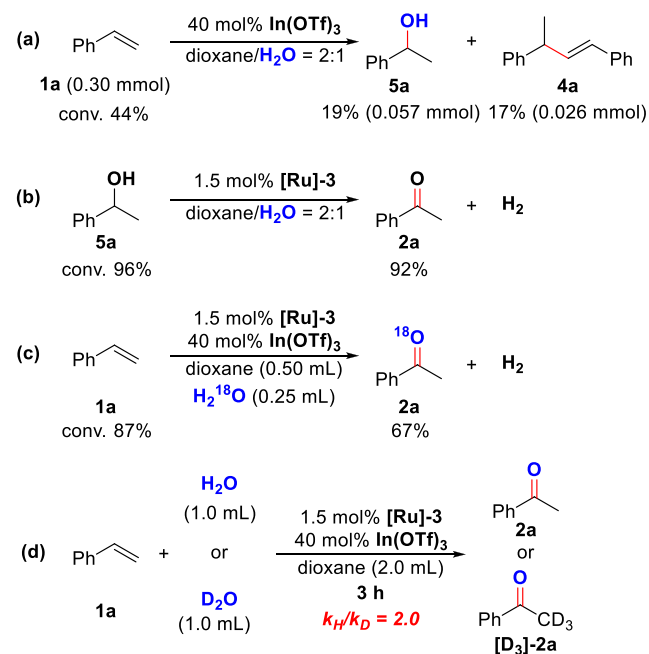
entry	[Ru]	acid (mol %)	conv (%)	yield (%)	
				2a	3a
1	[Ru]-3	HOTf (20)	62	39	11
2	[Ru]-3	HNTf ₂ (20)	74	44	13
3	[Ru]-3	TsOH·H ₂ O (20)	71	55	8
4	[Ru]-3	PhCOOH (20)	5	n.d.	1
5	[Ru]-3	Sc(OTf) ₃ (20)	73	50	8
6	[Ru]-3	In(OTf) ₃ (20)	82	63	7
7	[Ru]-3	none	9	n.d.	5
8	[Ru]-2	In(OTf) ₃ (20)	87	53	28
9	[Ru]-1	In(OTf) ₃ (20)	47	16	2
10	[Ru]-3	In(OTf) ₃ (40)	89	83	4

^aReaction conditions: **1a** (0.30 mmol), **[Ru]** (1.5 mol %), acid, 1,4-dioxane (2.0 mL), water (1.0 mL), heated in a sealed tube at 150 °C (silicon oil bath temperature) at reflux for 36 h. The reaction conversion and yields were determined by GC using mesitylene as the internal standard. n.d. = not detected.

ethylbenzene (**3a**) was observed in all the reaction systems. The cocatalyst indium(III) triflate gave the best result for Markovnikov oxidation of **1a** to **2a** by water (Table 1, entry 6). The Lewis acids FeCl₃ and AlCl₃ were also tested under the same conditions, but no desired product was observed. As expected, very low substrate conversion and no desired product were observed in the absence of acid catalysts (Table 1, entry 7). The catalytic efficiency of other pincer ruthenium(II) complexes was also investigated. Compared with complex **[Ru]-3**, the coordinatively saturated, aromatic acridine-based PNP-Ru complex (**[Ru]-2**) afforded a lower yield, along with a large amount of the hydrogen transfer product **3a**, which may be formed upon HCl elimination from **[Ru]-2** (Table 1, entry 8). In the case of the bipyridine-based PNN-Ru complex (**[Ru]-1**), much lower reaction selectivity and efficiency were observed, likely due to deactivation of this acid-sensitive dearomatized complex (Table 1, entry 9). Notably, quite good reaction selectivity and efficiency were obtained by using 1.5 mol % of **[Ru]-3** and 40 mol % of In(OTf)₃ (Table 1, entry 10). After cooling to room temperature, hydrogen gas was detected by GC analysis in 72% yield (see the Supporting Information, Figure S1, for details). The effect of changing the loading of **[Ru]-3** was also investigated (see the Supporting Information, Table S1, for details).

In order to understand the reaction mechanism, experiments were carried out to get an idea about the role of the two cocatalysts. The hydration reaction of styrene was first studied in the absence of dehydrogenation catalysts (Scheme 2a). It has been reported that In(OTf)₃ is a highly efficient catalyst for

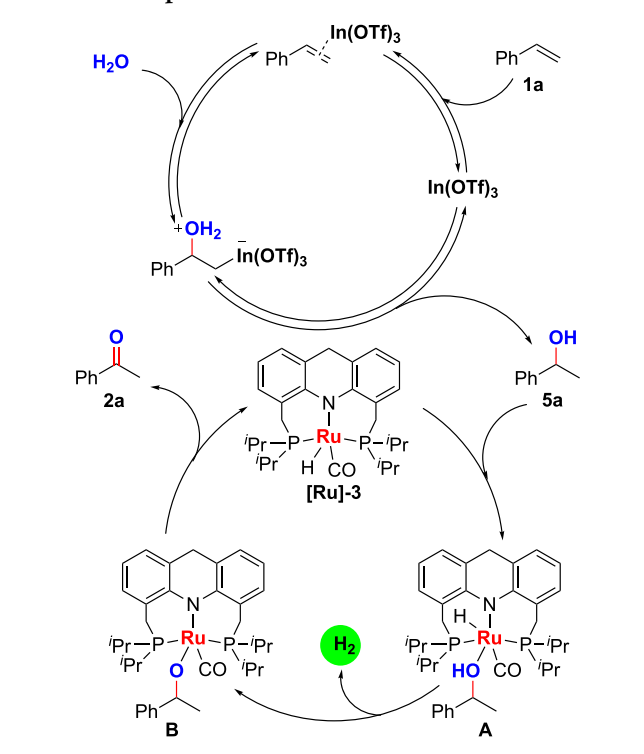
Scheme 2. Mechanistic Studies



the homocoupling of styrene in 1,4-dioxane.¹² However, only 44% conversion of **1a**, 19% to 1-phenylethanol (**5a**), and 17% to the homocoupling product **4a** (the rest likely being polymerized styrene) were observed when 40 mol % of In(OTf)₃ was used in the mixed solvent system of 1,4-dioxane and water (2:1). This result indicated that water suppressed the homocoupling of styrene. In the next step, dehydrogenation of the secondary alcohol **5a** by complex **[Ru]-3** was studied in the absence of acids (Scheme 2b). An excellent reaction yield (92%) of the ketone product **2a** was obtained along with the observation of hydrogen gas liberation. Efforts have also been made to identify the complex intermediates during the dehydrogenation process. According to ³¹P{¹H} NMR analysis, the signal of complex **[Ru]-3** was the major peak in the reaction mixture of **[Ru]-3** and 10 equiv of **5a** at room temperature or after heating (see the Supporting Information, Figure S2 for details). It indicates that complex **[Ru]-3** is the resting state during the dehydrogenation of **5a**. Combining the reaction results in Scheme 2a and b, complex **[Ru]-3** and In(OT)₃ are likely to work synergistically in the Markovnikov oxidation of styrene by water with H₂ liberation. Additionally, an isotopic labeling experiment was carried out to confirm that the oxygen atom of **2a** originates from water. When a mixture of dioxane (0.50 mL) and H₂¹⁸O (0.25 mL, 97% ¹⁸O-labeled) was used as solvents, 67% yield of **2a** was obtained, and the product was detected by GC-MS to be 94% ¹⁸O-labeled (Scheme 2c; see the Supporting Information, Figure S3 for details). The kinetic isotope effect (KIE) of O–H bond cleavage was studied by performing in two parallel reactions using H₂O and D₂O, resulting in about *k_H/k_D* = 2.0, indicating that O–H bond cleavage is likely involved in the rate-determining step (Scheme 2d; see the Supporting Information, Scheme S1 for details).

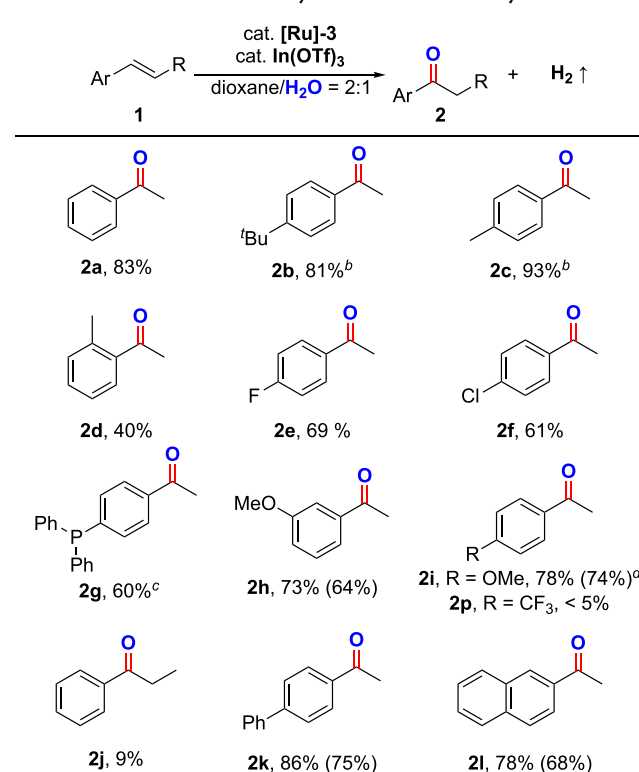
Based on the experimental results and literature reports,^{6,12} a plausible mechanism for the Markovnikov oxidation of **1a** by water with H₂ liberation is presented (Scheme 3). Coordination of **1a** to In(OTf)₃ can promote the hydration of **1a** to afford the secondary alcohol **5a**. This hydration process obeys

Scheme 3. Proposed Mechanism



the Markovnikov selectivity and is reversible. The secondary alcohol **5a** generated in the hydration process will then coordinate complex **[Ru]-3** to afford complex **A**. At the reaction temperature, complex **A** can liberate H_2 to furnish complex **B**. This O–H cleavage step is likely rate limiting, in line with the observed KIE.¹³ At last, β -hydride elimination from the pentacoordinated complex **B** gives the ketone product **2a** and regenerates complex **[Ru]-3**. Ethylbenzene (**3a**) is likely to be formed by hydrogenation of **1a** by the generated hydrogen gas catalyzed by **[Ru]-3**. Hydrogenation of styrene under the reaction conditions was confirmed in separate experiments (see the Supporting Information, [Scheme S2](#)).

Following the successful establishment of the catalytic system for oxidation of styrene to acetophenone by water, the scope of this reaction protocol was studied ([Scheme 4](#)). Using 20 mol % of $In(OTf)_3$, styrene bearing a *tert*-butyl group at the para-position gave a similar reaction yield to that of styrene ([Scheme 4](#), **2b**). Under similar reaction conditions, 4-methylstyrene furnished the desired ketone in an excellent yield ([Scheme 4](#), **2c**, 93%). However, styrene bearing a methyl group at the ortho-position afforded only 40% yield, which might be due to the steric effect in the alcohol dehydrogenation process ([Scheme 4](#), **2d**). Halide substituents including fluoride and chloride were well tolerated under the standard reaction conditions ([Scheme 4](#), **2e** and **2f**). Significantly, a diphenylphosphine substituent, which can be easily oxidized under metal-catalyzed aerobic conditions,¹⁴ was tolerated in this transformation ([Scheme 4](#), **2g**). Electron-rich and electron-deficient styrenes were then tested. 3-Vinylanisole gave a 64% isolated yield of the desired ketone with 40 mol % $In(OTf)_3$ ([Scheme 4](#), **2h**), while 4-vinylanisole afforded a 74% isolated yield using, quite remarkably, only 1.0 mol % of $In(OTf)_3$ ([Scheme 4](#), **2i**). However, only a trace amount of the desired product was observed in the presence of the strong

Scheme 4. Oxidation of Styrene Derivatives by Water^a

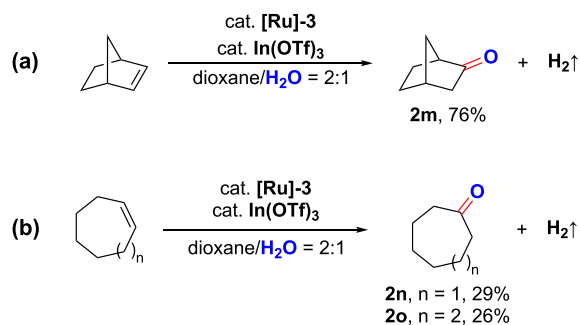
^aReaction conditions: **1** (0.30 mmol), **[Ru]-1** (1.5 mol %), $In(OTf)_3$ (40 mol %), 1,4-dioxane (2.0 mL), water (1.0 mL), heated in a sealed tube at 150 °C (silicon oil bath temperature) at reflux for 36 h. The reaction yield was determined by GC using mesitylene as the internal standard. Isolated yields are shown in parentheses. ^b20 mol % $In(OTf)_3$ was used. ^c3 mol % **[Ru]-1** and 60 mol % $In(OTf)_3$ were used. ^d1.0 mol % $In(OTf)_3$ was used.

electron-withdrawing CF_3 substituent, using 40 mol % of $In(OTf)_3$ ([Scheme 4](#), **2p**). It has been reported that the electron density and substitution mode of alkenes have a strong effect on the concentration of secondary alcohols in the acid-catalyzed alkene-hydration/alcohol-dehydration equilibrium.^{9a} Since catalyst deactivation could be observed during the reaction process, we believe that the low yield in the case of styrenes bearing strong electron-withdrawing substituents is due to low concentration of secondary alcohols during the reaction process. Similarly, a low reaction yield was observed for β -methylstyrene, which might also be due to the low concentration of secondary alcohols in the hydration/dehydration equilibrium of internal alkenes ([Scheme 4](#), **2j**). Other aromatic alkenes such as 4-vinylbiphenyl and 2-vinyl naphthalene were also suitable in this transformation, affording the desired ketone in good yields ([Scheme 4](#), **2k** and **2l**). Hydrogen gas was detected in all the reactions.

Besides aromatic alkenes, oxidation of aliphatic alkenes by water was also explored. Linear aliphatic alkenes were first tried in this transformation. Aliphatic alkenes are known to undergo isomerization by ruthenium catalysts.¹⁵ When 1-octene was used as the substrate, isomerization of 1-octene was observed, resulting in a mixture of three ketones as observed by GC-MS (see the Supporting Information, [Figure S4](#) for details). Cyclic alkenes were then tried as substrates. A strained cyclic alkene, norbornene, afforded the desired ketone in 76% yield under the standard reaction conditions ([Scheme 5a](#), **2m**). However,

nonstrained cyclic alkenes including cycloheptene and cyclooctene demonstrated lower reactivity even with higher catalyst loadings (Scheme Sb, 2n and 2o).

Scheme 5. Oxidation of Cyclic Alkenes by Water



In conclusion, we have demonstrated that synergistic cooperation of acid-catalyzed hydration and pincer-Ru-catalyzed acceptorless dehydrogenation enabled the oxidation of alkenes by water in the absence of added oxidant. A dearomatized acridine-based PNP-Ru complex and In(OTf)_3 were found to be the optimized catalyst combination. Both functionalized styrenes and cyclic aliphatic alkenes can be oxidized with a good functional group tolerance through this reaction protocol. Quite remarkably, water is the only oxidant in this reaction, and hydrogen gas is generated as the only byproduct in this new oxidative transformation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c01592>.

Experimental details and NMR spectra of isolated products (PDF)

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Notes

The authors declare no competing financial interest.

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