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Communication

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Oxidation of Alkenes by Water with H_2 Liberation

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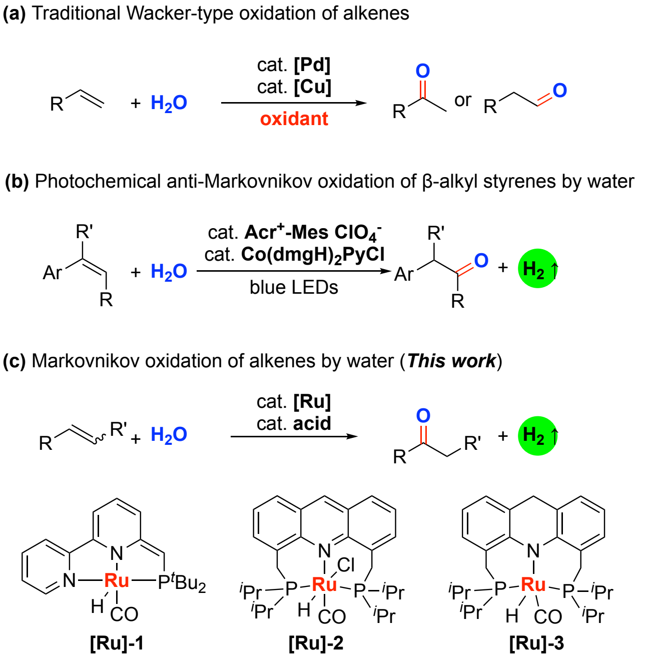
ABSTRACT: Oxidation by water with H_2 liberation is highly desirable, as it can serve as an environmentally friendly way for the oxidation of organic compounds. Herein, we report the oxidation of alkenes with water as the oxidant by using a catalyst combination of a dearomatized acridine-based PNP-Ru 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 H_2 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 (non photochemical) oxidation of alkenes to ketones by water with H_2 liberation utilizing an acceptorless dehydrogenation reaction strategy.

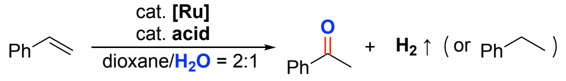
Scheme 1. Wacker-type Oxidation of Alkenes



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 H_2 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 envisioned that a combination of an acid catalyst and an acceptorless dehydrogenation catalyst might enable the Markovnikov oxidation of alkenes by water with H_2 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) homo-coupling and polymerization of alkenes under acidic 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 ethylbenzene (**3a**) was observed in all the reaction systems. The co-catalyst indium(III) triflate gave the best result for Markovnikov oxidation of **1a** to **2a** by water (Table 1, entry 6). The Lewis acids $FeCl_3$ and $AlCl_3$ 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).

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



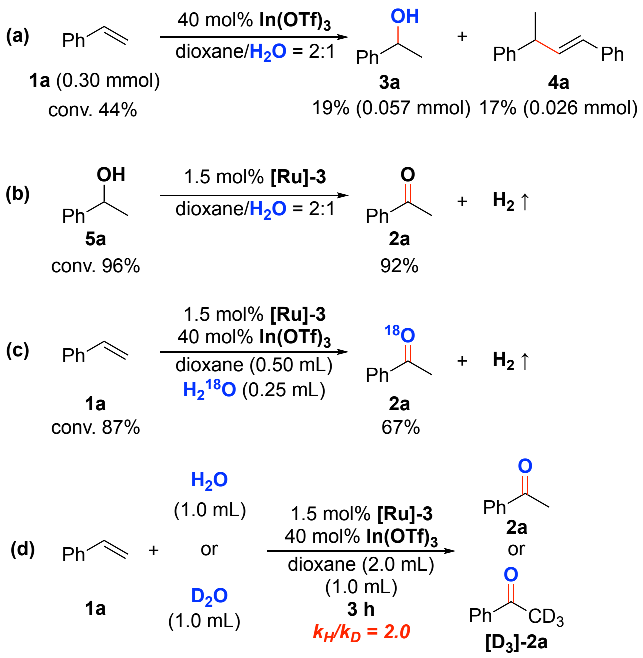
1a **2a** **3a**

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	$TsOH{\cdot}H_2O$ (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**

[a] Reaction 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 temperatur) at reflux for 36 h. The reaction conversion and yields were determined by GC using mesitylene as the internal standard. n.d. = not detected.

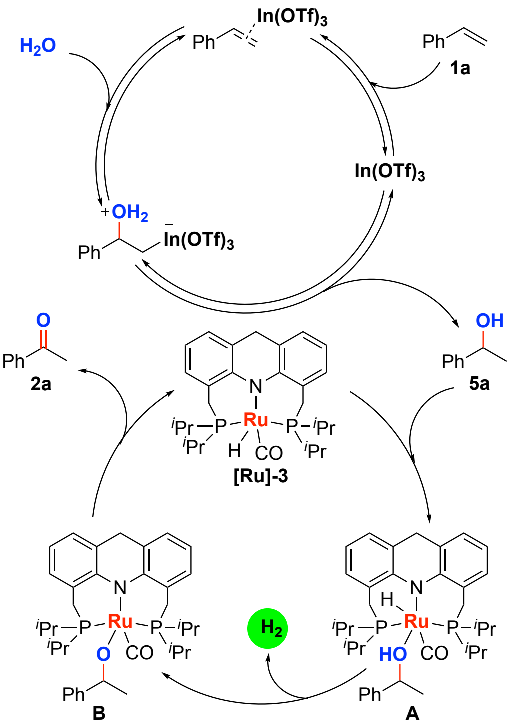
In order to understand the reaction mechanism, experiments were carried out to get an idea about the role of the two co-catalysts. The hydration reaction of styrene was first studied in the absence of dehydrogenation catalysts (Scheme 2a). It has been reported that $In(OTf)_3$ is a highly efficient catalyst for the homo-coupling of styrene in 1,4-dioxane.[12] However, only 44% conversion of **1a**, 19% to 1-phenylethanol (**5a**) and 17% to the homo-coupling 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 homo-coupling 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 $^{31}P\{^1H\}$ NMR analysis, the signal of complex **[Ru]-3** was the major peak in the reaction mixture of **[Ru]-3** and 10 eq. **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 Schemes 2a and 2b, complex **[Ru]-3** and $In(OT)_3$ are likely to work synergistically in the Markovnikov oxidation of styrene by water with H_2 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 $H_2{}^{18}O$ (0.25 mL, 97% ^{18}O-labelled) was used as solvents, 67% yield of **2a** was obtained and the product was detected by GC-MS to be 94% ^{18}O-labelled (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 H_2O and D_2O, 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).

Scheme 2. Mechanistic Studies



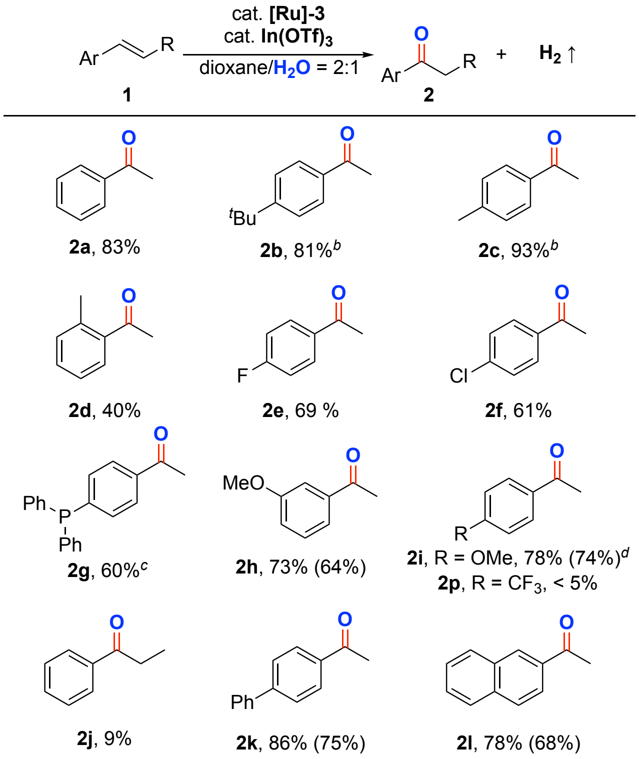
Based on the experimental results and literature reports,[6, 12] a plausible mechanism for the Markovnikov oxidation of **1a** by water with H_2 liberation is presented (Scheme 3). Coordination of **1a** to $In(OTf)_3$ can promote the hydration of **1a** to afford the secondary alcohol **5a**. This hydration process obeys 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).

Scheme 3. Proposed Mechanism



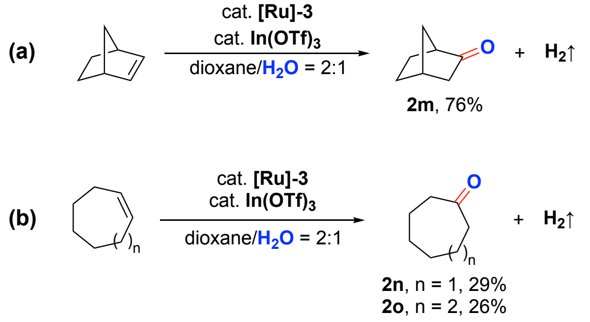
Following the successful establishment of the catalytic system for oxidation of styrene to acetophenone by water, the scope of this reaction protocol was studied (Scheme 4). Using 20 mol% of $In(OTf)_3$, styrene bearing a *tert*-butyl group at the para-position gave a similar reaction yield as styrene (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 64% isolated yield of the desired ketone with 40 mol% $In(OTf)_3$ (Scheme 4, **2h**) while 4-vinylanisole afforded 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 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 case of styrenes bearing strong electron withdrawing substituents is due to low concentration of secondary alcohols during the reaction process. Similarly, low reaction yield was observed for β-methyl styrene, 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.

Scheme 4. Oxidation of Styrene Derivatives by Water[a]



[a]Reaction 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. [b]20 mol% $In(OTf)_3$ was used. [c]3 mol% **[Ru]-1** and 60 mol% $In(OTf)_3$ were used. [d]1.0 mol% $In(OTf)_3$ was used.

Scheme 5. Oxidation of Cyclic Alkenes by Water



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, non-strained cyclic alkenes including cycloheptene and cyclooctene demonstrated lower reactivity even with higher catalyst loadings (Scheme 5b, **2n** and **2o**).

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 by-product in this new oxidative transformation.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. 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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REFERENCES

1. (a) Roduner, E.; Kaim, W.; Sarkar, B.; Urlacher, V. B.; Pleiss, J.; Gläser, R.; Einicke, W.-D.; Sprenger, G. A.; Beifuß, U.; Klemm, E.; Liebner, C.; Hieronymus, H.; Hsu, S.-F.; Plietker, B.; Laschat, S., Selective Catalytic Oxidation of C-H Bonds with Molecular Oxygen. *ChemCatChem* **2013,** *5*, 82; (b) Lu, W.; Zhou, L., *Oxidation of C-H bonds*. Wiley: Hoboken, New Jersey, **2017**.
2. (a) Tang, S.; Zeng, L.; Lei, A., Oxidative R^1–H/R^2–H Cross-Coupling with Hydrogen Evolution. *J. Am. Chem. Soc.* **2018,** *140*, 13128; (b) Gunanathan, C.; Milstein, D., Applications of

Acceptorless Dehydrogenation and Related Transformations in Chemical Synthesis. *Science* **2013,** *341*, 1229712; (c) Tang, S.; Liu, Y.; Lei, A., Electrochemical Oxidative Cross-coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation. *Chem* **2018,** *4*, 27; (d) Chen, B.; Wu, L.-Z.; Tung, C.-H., Photocatalytic Activation of Less Reactive Bonds and Their Functionalization via Hydrogen-Evolution Cross-Couplings. *Acc. Chem. Res.* **2018,** *51*, 2512.

3. Zheng, Y.-W.; Chen, B.; Ye, P.; Feng, K.; Wang, W.; Meng, Q.-Y.; Wu, L.-Z.; Tung, C.-H., Photocatalytic Hydrogen-Evolution Cross-Couplings: Benzene C–H Amination and Hydroxylation. *J. Am. Chem. Soc.* **2016,** *138*, 10080.
4. Balaraman, E.; Khaskin, E.; Leitus, G.; Milstein, D., Catalytic transformation of alcohols to carboxylic acid salts and H_2 using water as the oxygen atom source. *Nat. Chem.* **2013,** *5*, 122.
5. Khusnutdinova, J. R.; Ben-David, Y.; Milstein, D., Oxidant-Free Conversion of Cyclic Amines to Lactams and H_2 Using Water As the Oxygen Atom Source. *J. Am. Chem. Soc.* **2014,** *136*, 2998.
6. Gellrich, U.; Khusnutdinova, J. R.; Leitus, G. M.; Milstein, D., Mechanistic Investigations of the Catalytic Formation of Lactams from Amines and Water with Liberation of H_2. *J. Am. Chem. Soc.* **2015,** *137*, 4851.
7. (a) Michel, B. W.; Steffens, L. D.; Sigman, M. S., The Wacker Oxidation. In *Organic Reactions*, Denmark, S. E., Ed. John Wiley & Sons, Inc., Hoboken, New Jersey: **2014**; Vol. 84, pp 75; (b) Tsuji, J., Synthetic Applications of the Palladium-Catalyzed Oxidation of Olefins to Ketones. *Synthesis* **1984,** *1984*, 369; (c) Keith, J. A.; Henry, P. M., The Mechanism of the Wacker Reaction: A Tale of Two Hydroxypalladations. *Angew. Chem. Int. Ed.* **2009,** *48*, 9038; (d) Takacs, J. M.; Jiang, X-t. The Wacker Reaction and Related Alkene Oxidation Reactions. *Curr. Org. Chem.* **2003**, *7,* 369 (e) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Paladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev*. **2018,** *118*, 2636.
8. Zhang, G.; Hu, X.; Chiang, C.-W.; Yi, H.; Pei, P.; Singh, A. K.; Lei, A., Anti-Markovnikov Oxidation of β-Alkyl Styrenes with H_2O as the Terminal Oxidant. *J. Am. Chem. Soc.* **2016,** *138*, 12037.
9. (a) Schubert, W. M.; Lamm, B.; Keefee, J. R., The Hydration of Styrenes. *J. Am. Chem. Soc.* **1964,** *86*, 4727; (b) Nowlan, V. J.; Tidwell, T. T., Structural effects on the acid-catalyzed hydration of alkenes. *Acc. Chem. Res.* **1977,** *10*, 252; (c) Liu, C.; Pan, B.; Gu, Y., Lewis base-assisted Lewis acid-catalyzed selective alkene formation via alcohol dehydration and synthesis of 2-cinnamyl-1,3-dicarbonyl compounds from 2-aryl-3,4-dihydropyrans. *Chin. J. Catal.* **2016,** *37*, 979.
10. Bianchini, E.; Pietrobon, L.; Ronchin, L.; Tortato, C.; Vavasori, A., Trifluoroacetic acid promoted hydration of styrene catalyzed by sulfonic resins: Comparison of the reactivity of styrene, n-hexene and cyclohexene. *App. Catal. A: Gen.* **2019,** *570*, 130.
11. (a) Horn, S.; Albrecht, M., Transfer hydrogenation of unfunctionalised alkenes using N-heterocyclic carbeneruthenium catalyst precursors. *Chem. Commun.* **2011,** *47*, 8802; (b) Wang, Y.; Huang, Z.; Leng, X.; Zhu, H.; Liu, G.; Huang, Z., Transfer Hydrogenation of Alkenes Using Ethanol Catalyzed by a NCP Pincer Iridium Complex: Scope and Mechanism. *J. Am. Chem. Soc.* **2018,** *140*, 4417.
12. Dai, J.; Wu, J.; Zhao, G.; Dai, W.-M., In(OTf)3-Catalyzed Highly Chemo- and Regioselective Head-to-Tail Heterodimerization of Vinylarenes with 1,1-Diarylethenes. *Chem. Eur. J.* **2011,** *17*, 8290.
13. Dehydrogenation steps are rate limiting in ethylene glycol dehydrogenration catalyzed by **[Ru]-3**: Zou, Y.-Q.; von Wolff, N.; Anaby, A.; Xie, Y.; Milstein, D., Ethylene glycol as an efficient and reversible liquid-organic hydrogen carrier. *Nat. Catal.* **2019,** *2*, 415.
14. Liu, B.; Jin, F.; Wang, T.; Yuan, X.; Han, W., Wacker-Type Oxidation Using an Iron Catalyst and Ambient Air: Application to Late-Stage Oxidation of Complex Molecules. *Angew. Chem. Int. Ed.* **2017,** *56*, 12712.
15. (a) McGrath, D. V.; Grubbs, R. H., The mechanism of aqueous ruthenium(II)-catalyzed olefin isomerization. *Organometallics* **1994,** *13*, 224; (b) Liniger, M.; Liu, Y.; Stoltz, B. M., Sequential Ruthenium Catalysis for Olefin Isomerization and Oxidation: Application to the Synthesis of Unusual Amino Acids. *J. Am. Chem. Soc.* **2017,** *139*, 13944.

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