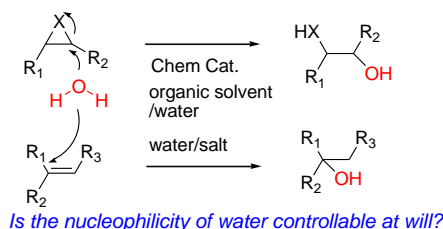


The Mechanism to Enhance the Nucleophilicity of Water in Hydroxylation of Alkenes, Epoxides, and Allylic Carbonates

Liuqun Gu

Abstract



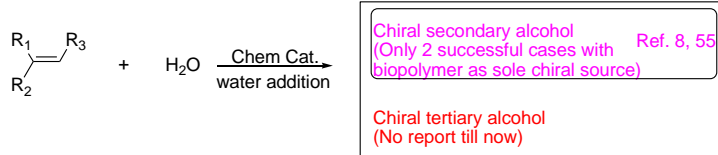
Direct asymmetric hydration of alkenes with water as a nucleophile toward chiral secondary/tertiary alcohols with chem catalysis is an unmet challenge in organic chemistry, though it is the most atom economic synthetic pathway. An obstacle was the lack of the general knowledge on how to improve the nucleophilicity of water, because water is a poor nucleophile tutorially. The mechanism to enhance the nucleophilicity of water is elucidated here and three general principles were proposed via a discussion on recent reported data.

Introduction

The Hydroxyl group is among the most important functional groups in biological active natural products, pharmaceutical intermediates, chemicals, and functional biopolymers tutorially. Efficient construction of chiral tertiary alcohols at quaternary carbon particularly is a challenging topic in asymmetric organic synthesis.¹⁻³ In comparison with the common strategy of preparing chiral tertiary alcohols through selective additions of various nucleophiles to ketones^{3,4} or the use of boron reagents⁵, water addition is the most atom economic and green method to produce tertiary alcohols theoretically. However, chemical catalysts⁶ to date are not very successful in the activation of water to enhance its nucleophilicity, unlike the enzyme catalysts⁷. Among the difficulties, the poor nucleophilicity of water is a key obstacle⁶ (Scheme 1A), since water or a water salt solution is commonly used to quench the organic transformation after the reaction was completed. In fact, there was only one successful non-enzymatic diastereospecific and enantioselective hydration of non-preactivated alkenes in water. Water *syn* addition to α , β -unsaturated ketones catalyzed by a Cu^{2+} based Artificial Metalloenzyme in the presence of DNA, resulted in chiral β -hydroxy ketones with up to 82% enantiomeric excess (ee).⁸ In order to meet the demanding task of efficient synthesis of chiral tertiary alcohols with water addition, the mechanism to enhance the nucleophilicity of water at the molecular level is highly desirable for the future rational design of the efficient catalytic systems.

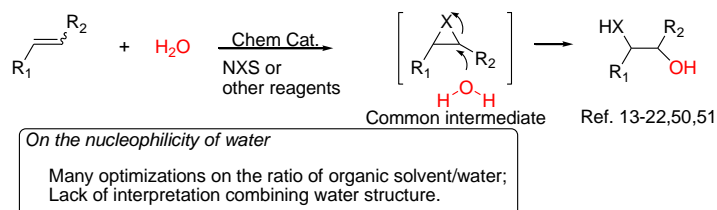
Scheme 1. The Direct Asymmetric Hydration

A. The direct asymmetric hydration of alkenes by the addition of water



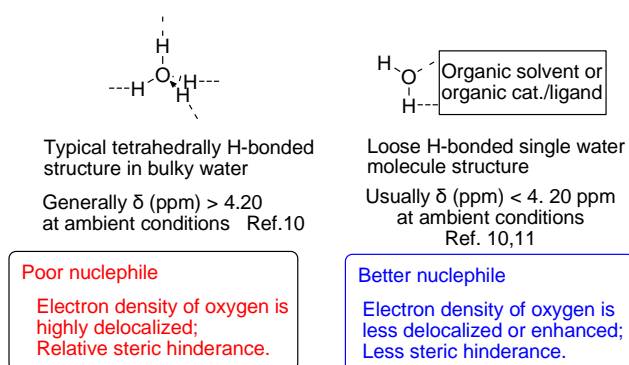
Key obstacle: the mechanism to enhance the nucleophilicity of water is still a mystery.

B. The regioselective/enantioselective hydroxylation of functionalized alkenes with water addition



At liquid state, water is tetrahedrally interconnected via hydrogen bonding networks at ambient conditions, allowing diversified water clusters to coexist simultaneously.⁹ Recently, we demonstrated that HDO was quantitatively sensitive to the NaCl concentration in a ¹H NMR investigation of NaCl-saccharide interaction.¹⁰ It is suggested that this NMR method with HDO as a “dynamic” reference could be able to measure the global salt effect in the aqueous solution resulted from the addition of various salts including the mixed salts. Such correlation indicated that the change of the hydrogen bonding networks affecting the nucleophilicity of water, could be monitored with a frequently used NMR spectroscopy. Very recently, with set chemical shift of the single molecular water, the water ligand interactions in various organic solvents were also investigated and the water organic complexes were proposed correlated to the reported chemical shifts of the water impurities.¹¹ This newly created knowledge would make the manipulation of the nucleophilicity of water through the use of a suitable organic solvent possible. Hence, a hypothesis (Figure 1) that loose H-bonded water is a good nucleophile was proposed; generally, the bigger upfield change in comparison with that of single molecular water, the better of the nucleophilicity of the water in the catalytic system, if not considering the steric effect of the water organic complex.

Figure 1. The Hypothesis in General



Combining the new knowledge^{10,11}, the water data parts from the recent two dozen successful water addition cases (reported mainly in non-asymmetric hydroxylation of alkenes, enantioselective hydroxylation of epoxides (Scheme 1B) and allylic carbonates) were interpreted and discussed carefully in order to gain insights on the mechanism to enhance the nucleophilicity of water at the molecular level. These literatures were not cherry-picked, but were selected randomly (only if the organic

transformations were performed at or below 70°C, to avoid a possible water vapor participation pathway).

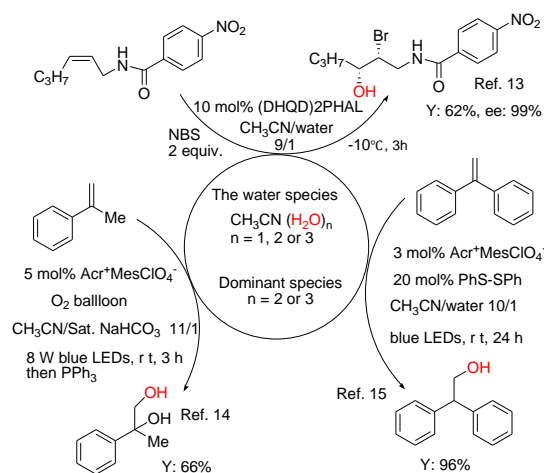
Results and discussions

Based on the above hypothesis (Figure 1), the most efficient strategy to break the hydrogen bonding networks of water is to use a suitable organic solvent in the presence of little water,¹¹ because water would be in its single molecular water form when it is an impurity in organic solvents^{11,12}. The second strategy is to create a confined space where the real active species could accumulate; it could be either via the design of the heterogeneous porous structure, or by the use of catalysts that could be able to confine/encapsulate/localize water via hydrogen bonding. The third possible strategy is to minimize water clusters by the addition of “antichaotropic” salts¹⁰. Strategies two and three are mostly applicable for reactions in aqueous media, in the absence of organic solvents or in the presence of a very small amount of organic solvents.

The use of a suitable organic solvent

According to the water organic solvent complexes correlated with the ¹H NMR chemical shifts of the water hydrogens, the higher electron density (the lower δ value of the water impurity peak) of the protons indicated the more electronegative oxygen of the water inside the complex.¹¹ Being more electronegative usually means being more nucleophilic if the organic solvent molecule is not so bulky in size. In fact, most of the hydroxylation reactions via water addition in organic solvents were carried out in the median polar organic solvents like acetonitrile (CH₃CN)¹³⁻¹⁵, acetone¹⁶⁻¹⁸, nitromethane (CH₃NO₂)¹⁹⁻²¹, and dichloromethane (DCM)²²; two of them were performed in the relatively polar solvent DMF (N, N -dimethylformamide)^{23,24}, and one was done in the non-polar solvent toluene²⁵. Chemical shifts of water impurities ranged from 0.43 to 2.84 (δ , ppm) in different deuterated organic solvents^{11,26,27} (0.43 in toluene-*d*₆, 1.52 in CD₂Cl₂, 1.90 in DMF-*d*₇,²⁸ 2.10 in CD₃NO₂,²⁹ 2.13 in CD₃CN, 2.84 in (CD₃)₂CO) at ambient conditions³⁰. The strong correlation between the chemical shift of water impurities in organic solvents and the reactivity/selectivity in hydroxylation reactions supports the proposed hypothesis in general. The screened data on the influences of the solvent to water ratio on the reactions in the literatures¹³⁻²⁵ would be discussed combing water ligand structures individually as shown below, in order to gain more clues on the mechanism to enhance the nucleophilicity of water.

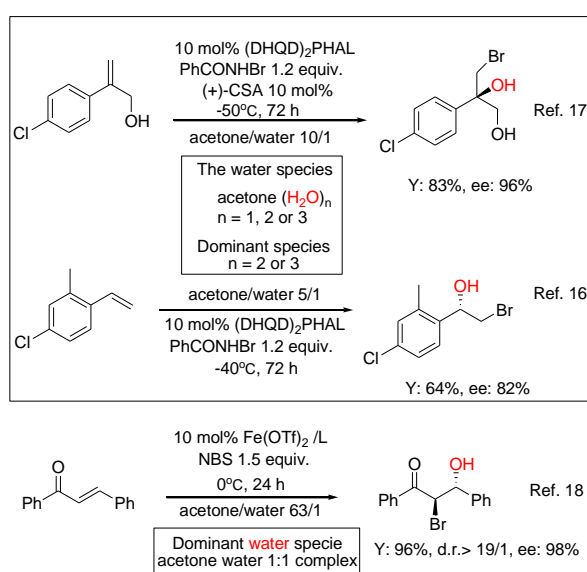
Scheme 2. The Three Hydroxylation Reactions in Acetonitrile/Water System



The three hydroxylation reactions in acetonitrile/water system via water addition were all catalyzed by the organic catalysts in the absence/presence of light under very mild conditions from -10°C to

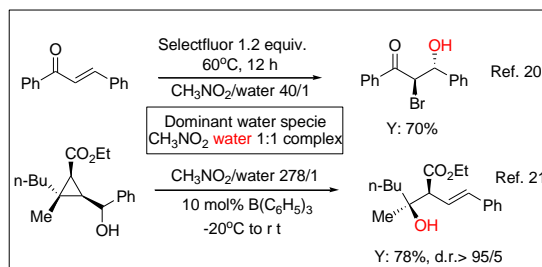
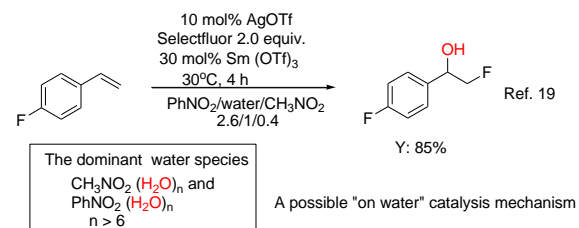
room temperature (Scheme 2).¹³⁻¹⁵ Interestingly, the optimized ratios of acetonitrile to water were 9:1,¹³ 10:1,¹⁵ and 11:1¹⁴ respectively; and it was well known that under these concentration zones, “low-order water aggregates”, like water dimers and trimers, would coexist with single molecular water (water acetonitrile 1:1 complex) species, evidenced by advanced IR^{12,31} and NMR methods^{12,32}. Hence, theoretically, the nucleophilicity of water under these conditions was not the strongest in each system. Though it is not proposed in the literature¹³, the amphiphilic catalyst might play a confining role in the further enhancement of the nucleophilicity of water in the halohydroxylation of allyl amides, which would be discussed later. In the dihydroxylation of styrenes¹⁴, the role of saturated NaHCO₃ solution, which enhances the nucleophilicity of water, would also be discussed later. A hydrogen-atom-transfer co-catalyst of 1,2-diphenyldisulfane was proposed to abstract a proton from water under visible light in a rate-determining manner, enhancing the nucleophilicity of water in anti-Markovnikov hydration of olefins.¹⁵

Scheme 3. The Three Asymmetric Bromohydroxylation Reactions in Acetonitrile/Water System



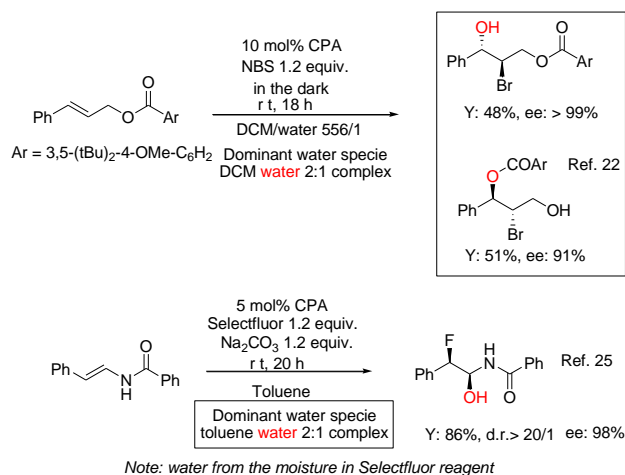
The three enantioselective hydroxylation reactions in “acetone to water” system via water addition were catalyzed by the organic catalysts or the liganded Fe(OTf)₂ catalyst at from -50°C to 0°C (Scheme 3).¹⁶⁻¹⁸ The optimized ratios of acetone:water were 5:1,¹⁶ 10:1,¹⁷ and 63:1,¹⁸ respectively. It should be noted that the chemical shift of water was still well below 4.00 ppm under the concentration zone (acetone:water, 5:1 or 10:1)³³, as that under the optimized ratios of acetonitrile:water system³². The organic catalyst (DHQD)₂PHAL showed a better tolerance than the organometallic catalyst to a relatively large amount of water^{13,16,17}. Its potential role via the hydration and encapsulation of water would be discussed later in the next section. Another interesting phenomenon was that the enantioselectivity was generally better for all cases when the water content was lower.^{13,16,17} The evidences suggested that maximising the content of the single molecular water species via lowering the water content to the impurity level to enhance the nucleophilicity of water was crucial to enantioselective excellence.

Scheme 4. The Fluorohydroxylation Reactions and the Nucleophilic Substitution of Cyclopropyl Carbinol Derivative in Nitromethane/Water System



A rare high content of water (25%) was used in the optimized solvent mixture ($\text{PhNO}_2/\text{water} = 2.6/1/0.4$) in the hydroxylation of styrene with the AgOTf catalyst, in the presence of 2 equivalent Selectfluor at 40°C (Scheme 4).¹⁹ A possible reason is that the reaction is an "on water" catalysis and only a significant amount of water under vigorous stirring could be able to generate the remarkably more acidic/polar water cluster in the oil phase as a weak acid promoter³². And under the acid catalyzed mechanism, the nucleophilicity threshold of water is relatively low because of the concerted mechanism.^{34,35} A low yield (12%) was observed with water only as a media; the evidence showed that both water in the bulky media and the water molecules in the hydrated shell of silver cation in the absence of any organic ligand were not good nucleophiles. A later study²⁰ found that a ratio of $\text{MeNO}_2/\text{water}$ 40:1 was the best in the regioselective hydroxylfluorination of chalcone at 60°C under a catalyst-free condition. A very low water content in MeNO_2 (0.36%, V/V) was the optimized condition for an efficient $\text{B}(\text{C}_6\text{H}_5)_3$ catalyzed construction of the homoallyl tertiary alcohol from a cyclopropyl raw material from -20°C to the room temperature (Scheme 4).²¹ In both cases, the water content is an impurity level ($< 0.75\%$, V/V)^{26,27} and a nitromethane water 1:1 symmetric complex was expected to be the dominant single molecular water species³⁶. The strong donating effect from both oxygen atoms of the nitro group increase the proton electron density remarkably, leading to a similar upfield effect on the chemical shift of single molecular water (δ 2.10 ppm)²⁹ in comparison with that of the water acetonitrile complex¹¹. And it also proved/showed the high reactivity of the single molecular water species under both conditions.

Scheme 5. The Fluorohydroxylation Reactions and the Nucleophilic Substitution of Cyclopropyl Carbinol Derivative in Nitromethane/Water System

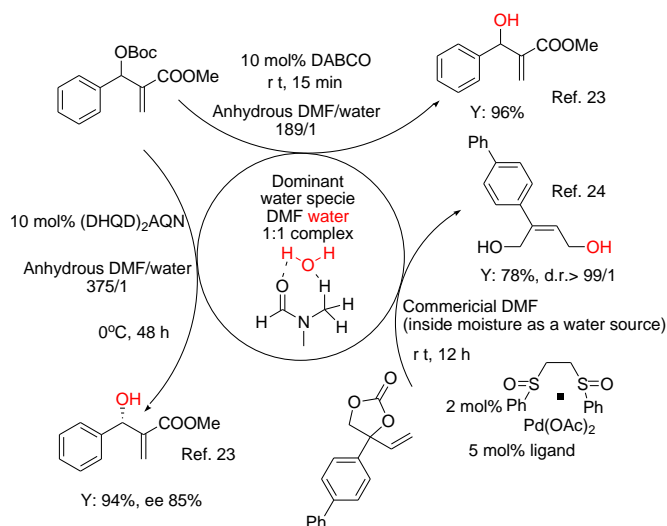


Water addition to NBS (N-Bromosuccinimide) activated alkenes with chiral phosphoric acid (CPA) as a catalyst under very low water content (0.18%, V/V) in dichloromethane solution was also reported (Scheme 5).²² The single molecular water impurity in the water dichloromethane complex¹¹ was proved to be a good nucleophile in “addition reactions” to broad substrates benefiting to the outstanding enantioselectivity. In another work (Scheme 5)²⁵, the intrinsic moisture in the Selectfluor reagent was used as a water source in the presence of 1.2 equiv. Na₂CO₃ for the enantioselective hydroxylfluorination of amide functionalized alkenes with the CPA as a catalyst. The presence of Na₂CO₃ or its hydrate form is crucial for the successful transformation. It is likely that Na₂CO₃ or its hydrate form played a water buffer role in the transportation of water moisture from the Selectfluor reagent (hydrate form) to the toluene, forming the active single molecular toluene complex¹¹ as a good nucleophile. In fact, salt hydrate as a water buffer was a known effective strategy in controlling the water content for manipulating the activity of enzyme catalysts.³⁷

A relatively big range of water usage was optimized in a Lewis base catalyzed enantioselective allylic hydroxylation of Morita-Baylis-Hillman carbonates in DMF with water as a nucleophile (Scheme 6).²³ The highest yield (96%) was obtained in the presence of a very low content of water (0.5% (V/V), water/DMF = 1/189 (V/V)). A slight increase of the water content to 1.32% and 2.64% (V/V) led to obvious drop of yield to 78%, and 66% respectively; and reaction could not proceed in water/DMF 1/1 solution (V/V). This data clearly showed that the nucleophilicity of water was the best when the water content is very low, at impurity level (typically water content is below < 1% and the well-known water impurity data²⁷ for ¹H NMR was performed in the presence of 0.75% water in organic solvents), and the excellent enantioselectivity could be achieved with the same low water content if a chiral catalyst (DHQD)₂AQN was used. And a water DMF 1:1 complex is proposed here as the most active single molecular water species based on the NMR study³⁸ and the study by Raman spectroscopy³⁹. In the complex (Scheme 6), two hydrogen bondings were involved, one hydrogen atom of the water molecule binds to oxygen (CO), and the oxygen of the water binds to a hydrogen atom from the CH₃ group (NMe₂). Key evidence³⁸ was that the ¹H NMR chemical shift of protons on the methyl group of DMF showed a clear upfield change when the use of water decreased to the near zero. The proposed structure well matches the remarkable upfield change (δ 1.90 ppm)²⁸ of the water protons in comparison with that of the water DMSO complex (δ 3.33 ppm) or water acetone complex (δ 2.84 ppm)¹¹. Such O (water) – H (N(CH₃)₂) bond would be weakened when more water is present, decreasing the electron density of oxygen (water) and lowering the nucleophilicity in the hydroxylation reaction. Under weak base-catalysed condition, the nucleophilic attack step with water could be a rate-determining step⁴⁰, and hence the threshold of the nucleophilicity is relatively high. However, in anhydrous DMF in which water content was ultra-low, the reaction proceeded at a very slow rate and

a modest yield was obtained; this data indicated that both controlling the nucleophilicity via the decrease of the water content and maintaining a general reactivity determined by the concentration via keeping relatively more water should be considered with a good balance. The use of commercial DMF (for an ACS grade reagent, water content < 0.15% V/V) with the inside water impurity as a water source, excellent reactivity was achieved in a Pd-catalyzed hydroxylation of allylic carbonates for 1,4-diols (Scheme 6).²⁴

Scheme 6. The Nucleophilic Substitution of Allylic Carbonates in DMF/Water System

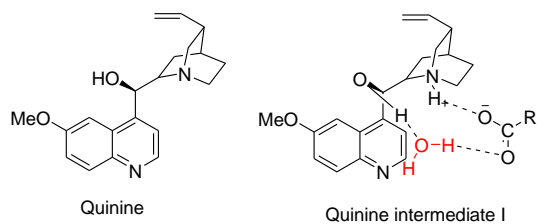


With those clues in hand, it is concluded that the ¹H NMR chemical shift of water impurities in the proposed water organic structures in the previous work¹¹ and this work could be a good indicator for future reaction optimization to enhance the nucleophilicity of the water. However, the organic solvent of choice would be difficult to be determined because of the uncertainty of the solvent effect on the catalyst and the other reactants in the catalytic system. A water impurity below 1% (V/V) in the organic solvent is recommended for maximising the content of the single molecular water species with the strongest nucleophilicity. A strategy of the use of commercial organic solvents with water impurities as a water source in the presence of a suitable salt hydrate is highly recommended to be adopted, in order to keep the water impurity at a constant optimized concentration in the reaction system during the reaction time.

The creation of a confined reaction place at the molecule level

The general mechanism to enhance the nucleophilicity of water via the creation of a confined reaction place at molecular level is to block the entrance of water clusters via size control for the solid-state inert material, meanwhile to encapsulate the single molecular water inside hydrated monomer/dimer/oligomers via loose hydrogen bonding. A recent report⁴¹ indicated that nucleophilicity of water inside lipid nanochannels could be enhanced via detecting the pH increase of the water. Here the focus would be the recent successful design of organic catalysts or organic ligands which could confine water via hydration.

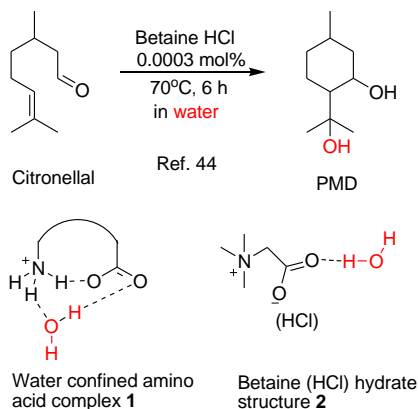
Figure 2. The Proposed Eleven-membered Ring Quinine-based Intermediate with a Loose H-bonded Single Molecular Water



The quinine-based organic catalyst (DHQD)₂PHAL was proved to be better water-tolerated for bromohydroxylation via water addition in the acetone/water system¹⁷ or CH₃CN/water system¹³ as discussed earlier. An additive of a Brønsted acid led to an obvious improvement on both the reactivity and the enantioselectivity.¹⁷ The hypothesis that the combination of the quinine-based organic catalyst (DHQD)₂PHAL and a Brønsted acid might form an active complex involved a water molecule via the hydrogen bonding, is rationally proposed here (Figure 2). The crystal evidences were reported that a single molecular water was loosely bonded to the asymmetric unit of a quininium salicylate monohydrate⁴², and the two quininium salts of phenylacetic acid and 4-hydroxyphenylacetic acid⁴³. In the quinine intermediate I (Figure 2), the water involved a hydrogen bonding eleven-membered ring, which included three bondings⁴²: a protonated quaternary amine cation bonding with an oxygen of the carboxylate (or sulfonate anion) anion from the acid, a hydroxyl hydrogen atom from quinine bonding with the oxygen atom of single molecular water, and one of the hydrogen atoms from the water bonding to the other oxygen of carboxylate (or the sulfonate anion) anion from the acid.

Amino acid salts containing a zwitterionic structure (complex **1**, Scheme 7) would have similar water confining capabilities like the quininium acid salts.⁴⁴ Very recently, the biosourced ammonium salts was applied as a catalyst to the cyclization-hydration of citronellal to p-Menthane-3,8-diols (PMD) in water; particularly, the betaine hydrochloride (cat. loading: 0.0003%, 83% conv., 95% selectivity) outperformed HCl (cat. Loading: 0.006 mol%, 90% conv., 71% selectivity) at 20°C for 6 hours.⁴⁴ The relatively mild improvement on reactivity is consistent with the proton assisted concerted mechanism under acid conditions, as discussed earlier.^{34,35} The data showed that the betaine structure might play a role in confining a water molecule to enhance its nucleophilicity via breaking the hydrogen bonding networks of the bulky water (complex **2**, Scheme 7), contributing the excellent chemoselectivity of the cyclization-hydration. This possibility was evidenced by the reported crystal structure betaine HCl monohydrate involved a single molecular water⁴⁵ and the recent aggregation study that the two betaine molecules were proposed to be linked through their carboxylate groups, bridged by one water molecule⁴⁶.

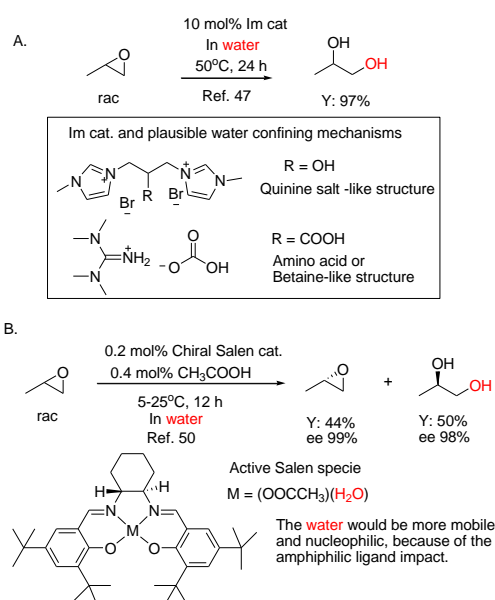
Scheme 7. The Nucleophilic Cyclization in Water and the Proposed Confined Water Complexes



Imidazolium salts were found to be the efficient catalysts in the hydration of epoxides forming diols at 50°C for 24 hours in the absence of any organic solvent (Scheme 8A).⁴⁷ The addition of the guanidine

carbonate under 1 atm CO₂ gas had a synergy effect on the promotion of the hydration and a remarkable improvement of the yield was observed. The supramolecular gelation of imidazolium salts in water via confining water was well studied⁴⁸, and the promotion of the small molecules was also known via hydrogen bonding interactions⁴⁹. The water in the gel network would likely be a better nucleophile towards a possible epoxide or a carbonate intermediate than that of the bulky water, which could be a reasonable molecular mechanism for the catalysis (Scheme 8A). Terminal epoxides readily reacted with water alone under a solvent free condition in the presence of the chiral salen cobalt catalyst with the acetic acid as an additive, producing hydrolytic kinetic resolution product selectively (Scheme 8B).⁵⁰ A following systematic study⁵¹ of the three types of catalysts including the salen cobalt catalysts for the catalytic hydration of ethylene oxide (EO) to monoethylene glycol (MEG) indicated that a good balance of acidity and basicity was crucial for selective hydration (the addition of the acetic acid was proposed for decreasing the basicity of the salen catalyst). However, the isolated water containing active species salen cobalt (O₂CCH₃) (H₂O) and the zwitterionic form of the catalyst (the organic ligand) suggested that the single molecular water confining capability of the active catalyst might play an important role in enhancing the nucleophilicity of water (Scheme 8B).

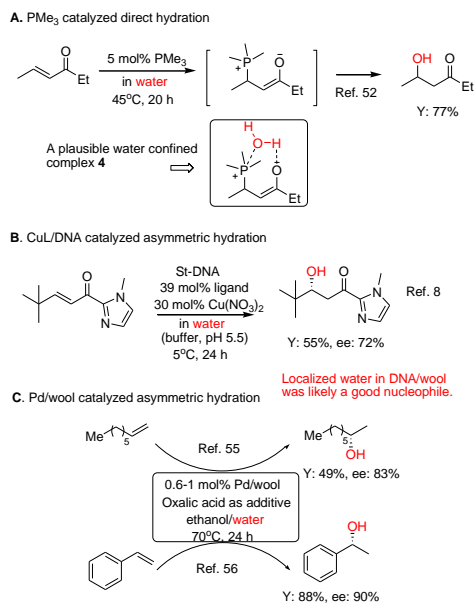
Scheme 8. The Hydration of Epoxide in Water and the Proposed Water Confined Mechanisms



A recent trimethylphosphine-catalyzed hydration (Scheme 9A) in water by the addition of water to an enone, represented a highly selective direct preparation of β -hydroxyl ketones;⁵² and it was a rare case that the base-catalyzed side reaction products⁴⁰ were not observed. In the proposed catalytic cycle, initial conjugate addition by the phosphine catalyst to the unsaturated ketone resulted in the formation of a phosphonium enolate intermediate.⁵² The intermediate is composed of a trimethylphosphine cation and an enolate anion, which is a typical zwitterionic form like betaine; and it would be very likely that a single molecular water could be stabilized into the intermediate, forming a new cyclic structure. The single molecular water loosely bonded inside the structure would be expected to be more nucleophilic (complex **4**, Scheme 8A). As it was mentioned in the introduction, an enantioselective hydration of α , β -unsaturated ketones by addition of water with DNA as the only chiral source in water could proceed in the presence of a copper catalyst and a ligand (Scheme 9B).⁸ Initially, the highly localized water by DNA was proposed as the water nucleophile, although water from the bulky media was not excluded.⁸ Later theoretical studies⁵³ combined Quantum Mechanics (QM) and Force Field approaches, the phenanthroline (phen) or the bipyridine ligand copper complex (phen-Cu(II)-(H₂O)₂ complexes) was proposed to be able to embed 6 or 2 explicit water molecules via

loose Hydrogen bonding in water or a protein solution, respectively. The stabilized single molecular water was a better nucleophile than the water in bulky media. In fact, a reported experimental data⁵⁴ showed that an enzyme–inhibitor–water complex was sufficiently stable to exist in the gas phase, and the nucleophilic water was successfully identified by Mass Spectrometry.

Scheme 9. The Role of Confined Water Complexes in the Direct Hydration of Alkenes/Styrene



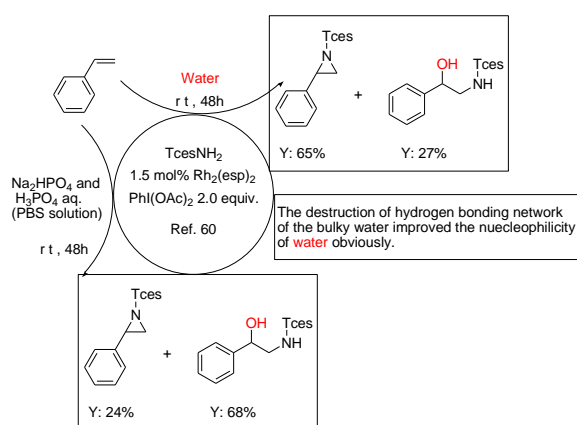
Another successful asymmetric hydration of two alkenes⁵⁵ and various styrenes⁵⁶ in the ethanol/water system was catalyzed by Pd-wool catalysts at 70°C for 24 hrs (Scheme 9C). The catalytic system shared a similar composition with that of those in enantioselective hydration of α , β -unsaturated ketones catalyzed by Cu/phen/DNA in water⁸. The insoluble wool (most are amino acids in the chemical structure with the rich bonds of amides, SO_3H , NH_2 and $-\text{S}-\text{S}-$) was the sole chiral source^{55,56} like the DNA, albeit with a requirement of thermal conditions (50 - 70°C) for activation via a partial hydration; and a ligand of oxalic acid was also proved to be crucial to the reactivity and the enantioselectivity of the asymmetric hydration just like the phenanthroline/bipyridine ligand in the previous system. The localized water in the wool might play the same role as a nucleophile, though it was not proposed in the literatures^{55,56}.

Overall, following enzymes' approach to control water activity⁵⁷ via confining/localizing water into the active catalytic species proved to be an effective strategy for hydration, particularly for the asymmetric hydration of unactivated alkenes with the biopolymers like DNA or wool as a sole chiral source^{8,55}. Design of new chiral organic catalysts or chiral organic ligands along with metal catalysts that compose of amphiphilic structures like betaine to enhance the nucleophilicity of water would be highly desirable for direct asymmetric hydration of various unactivated alkenes by addition of water, in the absence of organic solvent or in the presence of a low amount of organic solvents mixed with more water. It should be noted that neutral or weak acidic or weak basic catalysts/ligands are preferred towards good chemoselectivity/enantioselectivity since the strong acids or the strong bases usually lead to poor selectivity⁵¹. The water confining/localizing capability in water could potentially be identified ($\delta < 4.20$ ppm typically) and be quantified with the newly developed ^1H NMR method with an external standard of D_2O^{10} , in comparison with the recent set chemical shift of the single molecular water¹¹.

The addition of "antichaotropic" salts

It was well studied that the hydrogen bonding networks could be partially disrupted, and the average H-bonded number would become less by the addition of alkali halides⁵⁸ and other inorganic salts⁵⁹. However, to quantify the change was very specialized and challenging, and the barrier led to low adoption by organic chemists in the catalysis development in/on salt solution. Recently, using HDO as a dynamic reference, the global salt effect could be able to be measured quantitatively even in the mixed salt solution with ¹H NMR spectroscopy¹⁰, frequently used by organic chemists. This method¹⁰ shows a barrier-free solution to be adopted by organic chemists for the future rational optimization of a suitable salt solution to enhance the mobility to the confined spaces, or to enhance the nucleophilicity of water by addition to alkenes.

Scheme 10. The Salt Effect in hydroxylation



In the dihydroxylation of styrenes¹⁴, the use of the saturated NaHCO₃ solution instead of pure water increased the reactivity of the reaction significantly, likely via an efficient destruction of the hydrogen bonding network, enhancing the mobility and the nucleophilicity of water. The salt solution (PBS solution) effect had obvious influence on the reactivity of the aminohydroxylation reaction with water addition under acid-catalyzed mechanisms as well.⁶⁰ Particularly, 4 equivalent MgO was quite necessary for the aminohydroxylation of the less reactive substrate 3,4,6-tri-O-acetyl-D-glucal⁶⁰; it is proposed here that MgO could likely change to the Mg²⁺ form as the acid inside the reaction system, and the bivalent cations like Mg²⁺ were known to have a strong effect on destruction of the hydrogen bonding network^{10,59} of the bulky water, enhancing the mobility and the nucleophilicity of water. In fact, such specific ion effects were also observed in moderate acid-catalysed hydroxylation and uncatalyzed hydroxylation in aqueous solution in a very early study⁶¹, though the mechanism at the molecular level was not elucidated.

Conclusions

The mechanism at the molecular level to enhance the nucleophilicity of water in recent progress on the hydroxylation of alkenes, epoxides, and allylic carbonates was elucidated via an extensive discussion combining water structure knowledge. Three common strategies including the use of a suitable organic solvent, the creation of a confined reaction places at the molecular level, and the addition of the “antichaotropic” salts in water, were summarised. Loose H-bonded water was demonstrated to be a good nucleophile in all cases, particularly, the nucleophilicity of the single molecular water species (water organic complexes) in organic solvents, or being confined/localized by organic catalysts/ligands/biopolymers, are the most enhanced ones. A new strategy of the use of commercial organic solvents with water impurities as a water source in the presence of a suitable salt hydrate (as water buffer) is highly recommended, in order to keep the water impurity (in water organic complex form) at a constant optimized concentration in the reaction system during the reaction time.

Design of small molecular chiral organic catalysts or chiral organic ligands, along with metal catalysts that compose of amphiphilic structures like betaine to better enhance the nucleophilicity of water would be highly desirable in addressing the unmet challenge of chem catalysis for the direct asymmetric hydration of various unactivated alkenes by the addition of water towards the most economic construction of second/tertiary alcohols. The newly developed ^1H NMR method via the measurement of the water molecules confined in the organic catalysts/ligands in water, or the water impurities in organic solvents shows promise to be a valuable tool in identifying and quantifying the effort of the future catalysts/ligands/solvent optimization.

Author Information

Liuqun Gu --- currently unaffiliated, Singapore, ORCID: 0000-0002-42546824.

Acknowledgments

This work is done by personal interest and no funding is available.

References

1. Christoffers, J.; Baro, A. (eds) Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis (Wiley-VCH, 2005).
2. Corey, E. J.; Guzman-Perez, A. The catalytic enantioselective construction of molecules with quaternary carbon stereocentres. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401.
3. Shibasaki, M.; Kanai, M. Asymmetric synthesis of tertiary alcohols and α -tertiary amines via Cu-catalysed C-C bond formation to ketones and ketimines. *Chem. Rev.* **2008**, *108*, 2853-2873.
4. Betancort, J. M.; Garcia, C.; Walsh, P. J. Development of the first practical catalyst for the asymmetric addition of alkyl- and arylzinc reagents to ketones. *Synlett* **2004**, 749-760, and therein references.
5. Stymiest, J.; Bagutski, V.; French, R. M.; Aggarwal, V. K. Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols. *Nature* **2008**, *456*, 778-782.
6. Resch, V.; Hanefeld, U. The selective addition of water. *Catal. Sci. Technol.* **2015**, *5*, 1385-1399.
7. Jin, J.; Hanefeld, U. The selective addition of water to CQC bonds; enzymes are the best chemists. *Chem. Commun.* **2011**, *47*, 2502-2510.
8. Boersma, A. J.; Coquière, D.; Geerdink, D.; Rosati, F.; Feringa, B. L.; Roelfes, G. Catalytic enantioselective syn hydration of enones in water using a DNA-based catalyst. *Nat. Chem.* **2010**, *2*, 991-995.
9. Clark, G. N. I.; Cappa, C. D.; Smith, J. D.; Saykally, R. J.; Head-Gordon, T. The structure of ambient water. *Mol. Phys.* **2010**, *108*, 1415-1433.
10. Zhu, G.; Li, H.; Li, Y.; Gu, L. ^1H NMR Elucidation of observed stable sugar-NaCl-water complexes in aqueous solution. *Chemistry-Methods* **2023**, *3*, e202200063.
11. Gu, L. ^1H NMR shift of single molecular water and its water ligand interactions in organic solvents. Preprint deposited at *ChemRxiv* **2023**, DOI: 10.26434/chemrxiv-2023-s1.
12. Kovacs, H.; Laaksonen, A. Molecular dynamics simulation and NMR study of water-acetonitrile mixtures. *J. Am. Chem. Soc.* **1991**, *113*, 5596-5605, and therein referenes.
13. Soltanzadah, B.; Jaganathan, A.; Staples, R. J.; Borhan, B. Highly stereoselective intermolecular haloetherification and haloesterification of allyl amides. *Angew. Chem. Int. Ed.* **2015**, *54*, 9517-9522.
14. Yang, B.; Lu, Z. Visible light-promoted dihydroxylation of styrenes with water and dioxygen. *Chem. Commun.* **2017**, *53*, 12634-12637.
15. Hu, X.; Zhang, G.; Bu, F.; Lei, A. Visible-light-mediated anti-Markovnikov hydration of olefins. *ACS Catal.* **2017**, *7*, 1432-1437.
16. Zhang, X.; Li, J.; Tian, H.; Shi, Y. Catalytic asymmetric bromination of unfunctionalized olefins with H_2O as a nucleophile. *Chem. Eur. J.* **2015**, *21*, 11658-11663.
17. Li, J.; Li, Z. Q.; Zhang, X.; Xu, B.; Shi, Y. Catalytic enantioselective bromohydroxylation of aryl olefins with flexible functionalities. *Org. Chem. Front.* **2017**, *4*, 1084-1090.
18. Li, W.; Zhou, P.; Li, G.; Lin, L. Catalytic asymmetric halohydroxylation of α , β -unsaturated ketones with water as the nucleophile. *Adv. Synth. Catal.* **2020**, *362*, 1982-1987.
19. Li, Y.; Jiang, X.; Zhao, C.; Fu, X.; Xu, X.; Tang, P. Silver-catalyzed anti-Markovnikov hydroxyfluorination of styrenes. *ACS Catal.* **2017**, *7*, 1606-1609.
20. Zhou, J. D.; Fang, Y.; Wang, F.; Li, J. J. Catalyst-free regioselective hydroxyfluorination and aminofluorination of α , β -unsaturated ketones. *Biomol. Chem.* **2019**, *17*, 4470-4474.
21. Chen, X.; Patel, K.; Marek, I. Stereoselective construction of tertiary homoallyl alcohols and ethers by nucleophilic substitution at quaternary carbon stereocenters. *Angew. Chem. Int. Ed.* **2023**, *62*, e202212425.
22. Cao, Y.-M.; Lentz, D.; Christmann, M. Synthesis of enantioenriched bromohydrins via divergent reactions of Racemic intermediates from anchimeric oxygen borrowing. *J. Am. Chem. Soc.* **2018**, *140*, 10677-10681.
23. Zhu, B.; Yan, L.; Pan, Y.; Lee, R.; Liu, H.; Han, Z.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. Lewis base catalyzed enantioselective allylic hydroxylation of Morita-Baylis-Hillman carbonates with water. *J. Org. Chem.* **2011**, *76*, 6894-6900.

24. Guo, W.; Martinez-Rodriguez, L.; Martin, E.; Escudero-Adan, E. C.; Kleij, A. W. Highly efficient catalytic formation of (Z)-1,4-But-2-ene diols using water as a nucleophile. *Angew. Chem. Int. Ed.* **2016**, *55*, 11037-11040.
25. Honjo, T.; Phipps, R. J.; Rauniyar, V.; Toste, F. D. A doubly axially chiral phosphoric acid catalyst for the asymmetric tandem oxyfluorination of enamides. *Angew. Chem. Int. Ed.* **2012**, *51*, 9684–9688.
26. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. NMR chemical shifts of common laboratory solvents as trace impurities. *J. Org. Chem.* **1997**, *62*, 7512-7515.
27. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR chemical shifts of trace impurities: common laboratory solvents, organics, and gases in deuterated solvents relevant to the organometallic chemist. *Organometallics* **2010**, *29*, 2176-2179.
28. The data is from description of N, N -dimethyl-formamide-D7 (D, 99.5%; DLM-25), official website of Bruker.
29. Mammoli, D.; Salvi, N.; Milani, J.; Buratto, R.; Borney, A.; Sehgal, A. A.; Canet, E.; Pelulessy, P.; Carnevale, D.; Jannin, S.; Bodenhausen, G. Challenges in preparing, preserving and detecting para-water in bulk: overcoming proton exchange and other hurdles. *Phys. Chem. Chem. Phys.* **2015**, *17*, 26819-26827.
30. Though the chemical shift of water impurity in nitrobenzene-*d*₅, was not found in any reported literature, it is estimated that the value should lie in the range of 0.43 to 2.84 (δ , ppm) at the ambient conditions based on the data in both benzene-*d*₆ and CD₃NO₂.
31. Cringus, D.; Yeremenko, S.; Pshenichnikov, M. S.; Wiersma, D. A. Hydrogen bonding and vibrational energy relaxation in water-acetonitrile mixtures. *J. Phys. Chem. B* **2004**, *108*, 10376–10387, and therein references.
32. Oka, K.; Shibue, T.; Sugimura, N.; Watabe, Y.; Winther-Jensen, B.; Nishide, H. Long-lived water clusters in hydrophobic solvents investigated by standard NMR techniques. *Sci. Rep.* **2019**, *9*:223.
33. Mizuno, K.; Ochi, T.; Shindo, Y. Hydrophobic hydration of acetone probed by nuclear magnetic resonance and infrared: Evidence for the interaction C–HOH₂. *J. Chem. Phys.* **1998**, *109*, 9502-9507, and therein references.
34. Jensen, J. L.; Carre, D. J. Kinetics and mechanisms of reactions of 3-buten-2-one and related compounds in aqueous perchloric acid. *J. Org. Chem.* **1974**, *39*, 2103-2107.
35. Erp, T. S.; Meijer, E. J. Proton-assisted ethylene hydration in aqueous solution. *Angew. Chem. Int. Ed.* **2004**, *43*, 1660–1662.
36. Myshakin, E. M.; Jordan, K. D.; Sibert III, E. L.; Johnson, M. A. Large anharmonic effects in the infrared spectra of the symmetrical CH₃NO₂·(H₂O) and CH₃CO₂·(H₂O) complexes. *J. Chem. Phys.* **2003**, *119*, 10138-10145.
37. Kuhl, P.; Halling, P. J. Salt hydrates buffer water activity during chymotrypsin-catalysed peptide synthesis. *Biochim Biophys Acta.* **1991**, *1078*, 326-328 and therein references.
38. Lei, Y.; Li, H.; Pan, H.; Han, S. Structures and hydrogen bonding analysis of N, N-dimethylformamide and N, N-dimethylformamide-water mixtures by molecular dynamics simulations. *J. Phys. Chem. A* **2003**, *107*, 1574-1583.
39. Yang, B.; Lang, H.; Liu, Z.; Wang, S.; Men, Z.; Sun, C. Three stages of hydrogen bonding network in DMF-water binary solution, *J. Mol. Liq.* **2021**, *324*: 114996.
40. Jensen, J. L.; Hashtroudi, H. Base-catalyzed hydration of α , β -unsaturated ketones. *J. Org. Chem.* **1976**, *41*, 3299-3302.
41. Roy, B.; Hazra, P. Nucleophilicity and pH of water inside lipidic nano-channels of lyotropic liquid crystalline phases. *J. Mol. Liq.* **2019**, *285*, 178-184, and therein references.
42. Oleksyn, B. J. Salt-bridge formation by cinchona alkaloids: quinium salicylate monohydrate. *Acta Cryst.* **1993**, *B49*, 530-535.
43. Noa, F. M. A.; Jacobs, A. Salts of phenylacetic acid and 4-hydroxyphenylacetic acid with Cinchona alkaloids: crystal structures, thermal analysis and FTIR spectroscopy. *J. Mol. Struct.* **2016**, *1114*, 30-37.
44. Stanovych, A.; Pelissier, F.; Grison, C. M.; Grison, C. Efficient and greener process for the production of p-menthane-3,8-diols Using biosourced ammonium salts as catalysts. *ACS Sustainable Chem. Eng.* **2023**, *11*, 6427-6434.
45. Chen, X.-M.; Mak, T. C. W. Crystal structure of the bis(betaine) hydrochloride monohydrate. *J. Mol. Struct.* **1990**, *240*, 69-75.
46. Gioacchino, M. D.; Bruni, F.; Ricci, M. A. Aqueous solution of betaine: Hydration and aggregation. *J. Mol. Liq.* **2020**, *318*: 114253.
47. Zhao, Z.; Zhang, W.; Jiang, L.; Tao, H.; Wang, S.; Wang, J.; Lin, W.; Shi, G.; Li, H.; Wang, C. Computer-assisted design of metal-free catalysts for highly efficient hydration of epoxides at mild temperatures and atmospheric pressure via multiple hydrogen bonding interactions. *Green Chem.* **2023**, *25*, 3437-3442.
48. D'Anna, F.; Vitale, P.; Marullo, S.; Noto, R. Geminal imidazolium salts: a new class of gelators. *Langmuir* **2012**, *28*, 10849-10859, and therein references.
49. Singh, W. P.; Koch, U.; Singh, R. S. Gelation of ionic liquids by small-molecule gelators and their applications. *Soft Mater.* **2020**, *18*, 386-410.
50. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric catalysis with water: efficient kinetic resolution of terminal epoxides by means of catalytic hydrolysis. *Science* **1997**, *277*, 936-938.
51. Hal, J. W.; Ledford, J. S.; Zhang, X. Investigation of three types of catalysts for the hydration of ethylene oxide (EO) to monoethylene glycol (MEG). *Catal. Today* **2007**, *123*, 310–315.
52. Stewart, I. C.; Bergman, R. G.; Toste, F. D. Phosphine-catalyzed hydration and hydroalkoxylation of activated olefins: use of a strong nucleophile to generate a strong base. *J. Am. Chem. Soc.* **2003**, *125*, 8696-8697.
53. Alonso-Cotichico, L.; Sciortino, G.; Vidossich, P.; Pedregal, J. R.-G.; Drienovská, I.; Roelfes, G.; Lledós, A.; Maréchal, J.-D. Integrated computational study of the Cu-catalyzed hydration of alkenes in water solvent and into the context of an artificial metallohydratase. *ACS Catal.* **2019**, *9*, 4616-4626.
54. Wang, S.; Lim, J.; Thomas, K.; Yan, F.; Angeletti, R. H.; Schramm, V. L. A complex of methylthioadenosine/S-adenosylhomocysteine nucleosidase, transition state analogue, and nucleophilic water. *J. Am. Chem. Soc.* **2012**, *134*, 1468-1470.
55. Xue, L.; Jia, B.; Tang, L.; Ji, X. F.; Huang, M. Y.; Jiang, Y. Y. Asymmetric hydration of alkenes catalyzed by wool-palladium complex. *Polym. Adv. Technol.* **2004**, *15*, 346-349.
56. Wang, S.; Zhang, Z.; Chi, C.; Wu, G.; Ren, J.; Wang, Z.; Huang, M. Y.; Jiang, Y. Y. Asymmetric hydration of ortho- or para-substituted styrenes catalyzed by biopolymer-metal complex wool-Pd. *React. Funct. Polym.* **2008**, *68*, 424-430.
57. Wehtje, E.; Adlercreutz, P. Water activity and substrate concentration effects on lipase activity. *Biotechnol. Bioeng.* **1997**, *55*, 798-806.

58. Cappa, C. D.; Smith, J. D.; Wilson, K. R.; Messer, B. M.; Gilles, M. K.; Cohen, R. C.; Saykally, R. J. Effects of alkali metal halide salts on the hydrogen bond network of liquid water. *J. Phys. Chem. B* **2005**, *109*, 7046-7052.
59. Tielrooij, K. J.; Garcia-Araez, N.; Bonn, M.; Bakker, H. J. Cooperativity in ion hydration. *Science* **2010**, *328*, 1006-1009.
60. Shi, Y.; Wang, Y.; Lu, X.; Zhang, Y.; Wu, Y.; Zhong, F. Rhodium-catalyzed aminohydroxylation of unactivated alkenes in aqueous media for the benign synthesis of 1,2-amino alcohols. *Green Chem.* **2019**, *21*, 780-784.
61. Berndt, D. C.; Ward, I. E. Kinetics and mechanism of acidic and alkaline hydrolysis of hindered N-methylarylhydroxamic acids. *J. Org. Chem.* **1976**, *41*, 3297-3299.
- 62.