On Rational Design of Stereodivergent Organocatalysis Controlled by Selective Hydration

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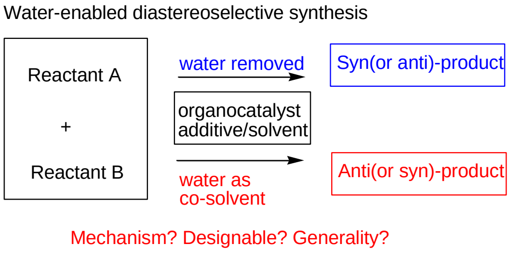
Abstract



Stereodivergent asymmetric synthesis via slightly tuning the catalytic conditions is very attractive for early-stage drug discovery, because it is a very time efficient and economical method for obtaining all potential biologically active diastereomers/enantiomers. However, the exploration is largely serendipity and no general strategy is available. A predictive hydrogen bonding rearrangement via selective hydration by water is proposed as a potential general strategy for rational design of stereodivergent organocatalysis. With the new concept and the proposed hydrated enamine/imine model, the origin of the divergent mechanism for the two recent successful water-modulated transformations could be very well elucidated.

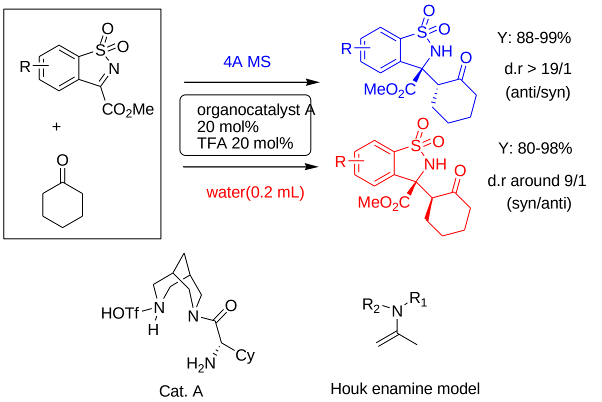
Key words: hydrated enamine/imine; “restricted” state; “relaxed” state; catalysis mechanism; hydrogen bonding; ^{1}H NMR shift.

Introduction

Thanks to the remarkable progress in asymmetric catalysis in the past three decades, construction of chiral molecules with two stereocenters is attainable mostly. Often, a single diastereomer or an enantiomer was produced in pursuit of the outstanding diastereoselectivity/enantioselectivity. However, all diastereomers or enantiomers would usually be required in early-stage drug discovery due to the uncertainty on initial screening for the most biologically active candidate. Stereodivergent catalysis[1-5] as a process accessible to any given distereomer/enantiomer of a product with several stereocenters from the same set of starting materials (ideally the catalysts would also be the same under slight tuning reaction conditions), is of paramount practical importance in term of time/cost. Significant progress has been achieved in this area. Many strategies including small changes of the organocatalysts or the organic ligands of metal catalysts, the dual catalysis, the cooperative catalysis, the addition of suitable additives, and the tuning of reaction temperatures proved to be crucial to achieve the reversal of the stereoselectivity.[1-5] But most of the results were treated as “unexpected” findings; to predict or to control a reversal of stereoselectivity is still a dream currently and it is highly desirable for a rational design currently.[1-5]

Very recently, water was employed as an additive in several organic transformations (Scheme 1)[6-8] and the excellent water enabled reverse of diastereoselectivity was achieved with the same set of starting materials and catalysts under almost the same reaction conditions. Though the water enabled mechanism was not clear yet as described in the literatures (Scheme 1)[6,7], such methods in the absence/presence of water leading to stereodivergent synthesis are ideal on minimizing the potential expenditures. The future advanced understanding of the hydration capability of the key functional groups (of both the substrates and the catalysts) and the relative stability in different organic solvents in the presence of water, is crucial to uncover the reaction mechanisms and to the future rational designs of more water-enabled stereodivergent systems.

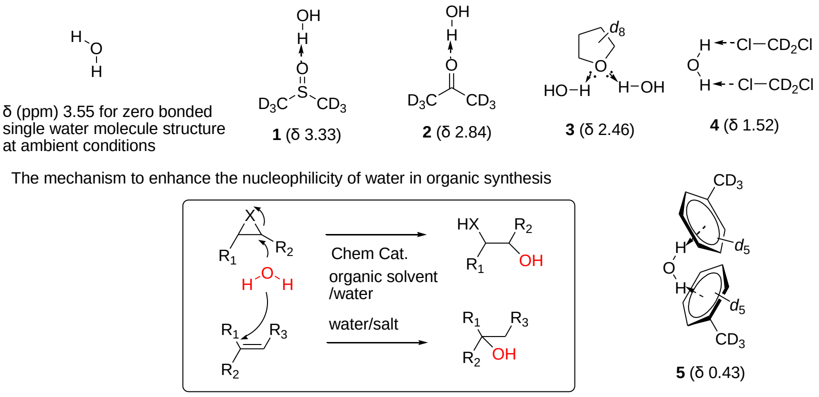
Scheme 1. The reported[7] water-enabled diastereodivergent organocatalysis and the enamine model



With Houk enamine model, there is a difficulty in explaining the efficient catalyst recovery step via water addition in the reaction with 4A MS.

The “hydrogen bridge”, proposed decades ago summarizing of the three major types of hydrogen bridged interactions[9,10] (strong hydrogen bonds and weak hydrogen bonds via electrostatic interactions, very weak interaction via van der Waals interactions), based on the composite nature of the interaction, could be an important quantitative knowledge basis in the understanding of the hydrogen bridged interactions within the key intermediates in organocatalysis systems. The commonly used organic solvents could complex the hydrogen bridged interactions via the increase/elimination of some weak hydrogen bonds. On the other hand, in aqueous media some of the very weak van der Waals interactions could also be possibly enhanced via enhanced hydrophobic interactions.[11,12] The organocatalysts might also interface the hydrogen bridged interactions by creating new hydrogen bonds in the catalystic systems. All these possibilities inevitably increase the difficulty to precisely predict the real hydrogen bridged interactions that potentially determine the stereoselectivity of the product during the bond formation step in each reaction system.

Scheme 2. The selected water organic complexes and the mechanism to enhance the nucleophilicity of water



The nucleophilicity of single molecular water species is strongest among all water species

Very recently, a new ^{1}H NMR tool with HDO water peak in the bulky water as a dynamic reference, was developed for measuring the interaction between monosaccharides and NaCl in NaCl aqueous solution quantitatively, decoupling from the global salt effect.[13] The method shows promise as a convenient tool in tackling the hydrogen bonding interactions of biomolecules with other inorganic salts or mixed salts. Further expansion of this method to quantify the water ligand interactions in organic solvents was also explored, in comparison with the newly rationally set single molecular water with zero bonds. (Scheme 2);[14] the identified/proposed water organic complexes associated with the

^{1}H NMR shift of water impurity provide a better quantitative knowledge on the stability of common hydrogen bridged interactions in organic solvents. The newly created knowledge in the both studies are expected to be useful in advancing the understanding of the real hydrogen bridged interactions in the absence/presence of water in organocatalyzed stereodivergent systems. Meanwhile, another investigation[15] on the mechanism to enhance the nucleophilicity of water (Scheme 2), might also offer new insights in mechanistic study of organocatalysis. Particularly, in primary amines/secondary amines-catalyzed transformations in organic solvents, an elimination of water in the imine formation step and a water addition to the imine in the catalyst recovery step were frequently proposed in the mechanism studies[5,16]. Based on this new knowledge and advanced understanding on hydrogen bonding interaction in both organic solvents and in bulky water, a new concept of stereodivergent organocatalysis is tentatively proposed here. With the concept and knowledge, the mechanism of the recently discovered stereodivergent catalysis enabled by water could also be better elucidated.

Results and discussions

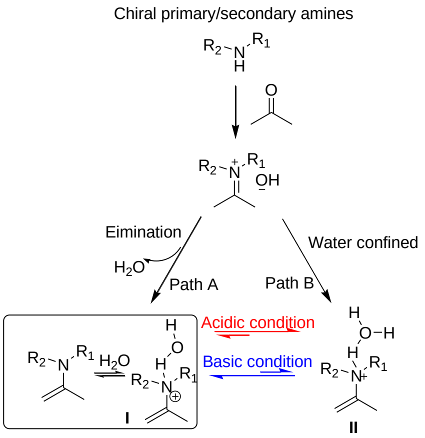
Electrostatic interactions and/or electrostatics-dominated non-covalent interactions are often decisive in determining reactivity and stereoselectivity in organocatalytic systems.[17-20] To design catalysts with transient electrostatic directing groups or even to tune the electrostatic environments distant from the catalytic center was recently explored focusing on radical chemistry, for a rational design of more selective catalysts.[20] Such theoretical and experimental exploration showed that manipulation of the electrostatic interactions and/or weak non-covalent interactions of the reaction intermediates could be possible in combining the well-evidenced mechanistic studies.[17-19] The chiral amine-catalyzed or simple organic acids-catalyzed organocatalytic systems are chosen here for initial design, because the catalytic pathways were well studied[5,16], and the key intermediates were well characterized[21]. Moreover, unlike the possible variation on the number of ligands coordinating the metal center due to the valence change of the metal, interactions between the chiral amines or the organic acids and the reaction substrates are predictable.

To design water-enabled stereodivergent catalysis, the understanding of the potential influence of water on the catalytic system, including the catalysts, the substrates and solvents is crucial for controlling the electrostatic interactions and hydrogen bonding interactions. Water was proved to be essential and might be necessary for asymmetric organocatalysis, particularly for chiral amine-catalyzed systems[5,16], because a molecule of water would be generated in the imine/enamine intermediate formation and water addition would be necessary for the catalyst recovery step[21]. The water effect on reactivity and stereoselectivity in organocatalyzed asymmetric reactions was reviewed and discussed in recent reviews/perspective articles[22-24]. In general, water could promote reaction activity and generate excellent stereoselectivity in some cases, and the reversal was also true in other cases. The exact mechanism on the role of water at the molecular level is far from clear.[22-24] Though it is essential for the control of the stereoselectivity, the hydration of the intermediate involved with both the catalyst and the substrates at various stages by water and the relevant water structures under the condition are not yet investigated, to my best knowledge.

The hydration of chiral amine intermediates

For chiral primary/secondary amine catalysis, the generated imine intermediates are electron-positive charged due to the nitrogen atom sharing its lone electron pair with the adjacent carbon from the substrate[5,16,21]. Theoretically, the positively charged imine intermediates would have much bigger chance in forming the hydrated intermediate with the “eliminated” hydroxyl anion via a strong electrostatic bond[9,10], than the bulky organic solvent molecules. The water ligand interactions in organic solvents are very weak in general[14] and the single molecular water complexes significantly enhances the nucleophilicity of water in addition reactions to charged unsaturated bonds[15]. Hence, the hydrated imine or enamine intermediate with a water molecule close to the double bond is proposed to be dominant at the imine/enamine formation step in chiral primary amine catalysis, particularly under acidic conditions (Scheme 3). For secondary amine catalysis, when the imine intermediates changes to an enamine intermediate via an equilibrium, a hydrated enamine intermediate **I** (Scheme 3) with a proton shifting from a carbon to the nitrogen atom is still theoretically preferred for forming a strong electrostatic hydrogen bond[9,10]. In other words, the water molecule might not be eliminated from the enamine intermediates, rather the covalent bond between the hydroxyl group and the carbon weakens, forming a non-covalent bond. The better catalytic reactivity of proline compared to pyrrolidine (without carboxylic acid moiety) in most cases, via the imine/enamine pathway, is an indirect evidence on acid assistance. However, the hydrated secondary enamine intermediates would likely be less stable in comparison with the primary ones, and subsequently a small portion of the hydrated secondary enamine intermediates might lose the competition with the organic solvent, forming the well-known Houk enamine model (Scheme 3). This possibility could also explain why a very small amount of water actually favor the reactivity for many secondary amine catalysis via an enamine intermediates.[22-24] The presence of a catalytic amount of acid as an additive could add positive charge to the enamine intermediate **II** (Scheme 3) via the protonation of the nitrogen atom, enabling a stronger electrostatic bond[9,10] with the "eliminated" water molecule. The hydrated forms of the enamine/imine could also explain the fast rate of water addition to enamine intermediates regenerating the amine catalysts in organic solvent because of the intramolecular manner, since the intermolecular water addition to alkenes under basic or neutral condition was proved to be challenging in the recent mechanistic study[15]. The water in the intermediates **I** and **II** could be able to be exchanged with the water in the organic solvent via a possible concerted mechanism; which is compatible with the mechanistic evidence of the ^{18}O incorporation experiments[21] with ^{18}O-enriched water (3 vol%) in the Hajos-Parrish-Eder-Sauer-Wiechert cyclization of ketones. These newly proposed hydrated forms of enamine intermediates **I** and **II** is crucial to the new concept because more hydrogen donors (two hydrogen atoms of a water molecule) could be able to be concentrated to the enamine or the imine center of the reaction intermediate, leading to potentially better control the stereoselectivity via multiple hydrogen bondings and the single molecular water mediated distance bonding.

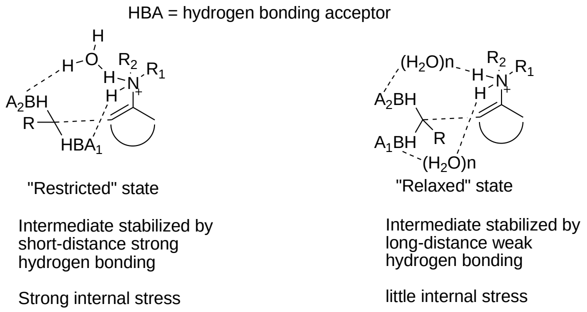
Scheme 3. The formation of Houk enamine model and the hydrated enamine model **I/II**



The concept of a "restricted" state and a water enabled "relaxed" state

The new concept for the general approach of water enabled diastereodivergent reactions, with chiral amines as organocatalysts in organic solvents, was proposed as shown in Scheme 4. In the absence of water additive, two “active” electron-donating functional groups from the stereocenter carbon of the electrophile reactant would be interconnected to the hydrated imine center (or the hydrated enamine center) via hydrogen bondings; both the hydrogen atoms from the water molecule stabilized by the imine/enamine nitrogen and the hydrogen atoms on the nitrogen would be the single source center of the hydrogen donors. Under the hydrogen donor scarce condition, both the hydrogen acceptors and the nitrogen atom from the imine/enamine center would be pulled together to the same direction almost at the same surface via hydrogen bonding, resulting into the product with a dominant stereoselectivity. The absence of additional water is crucial to the excellent stereoselectivity, because the single water mediated hydrogen bonding should be relatively short. The binding force would be stronger than the electrostatic dispersion force between the hydrogen acceptors, maintaining a “restricted” state of the reaction intermediates if the intermediate has a balance of rigidity and flexibility on its structure. When significant water is introduced into the catalytic system, hydration of the hydrogen acceptors by water would likely occur and the long-distance hydrogen bonding mediated by the two or more water molecules would be dominant. The binding force would decrease and it would be less than the dispersion force, naturally releasing the internal stress to a “relaxed” state of the intermediate (Scheme 4), eventually leading to the reversal of stereoselectivity.

Scheme 4. The concept of a “restricted” state under water scarce conditions and a “relaxed” state under water-rich conditions

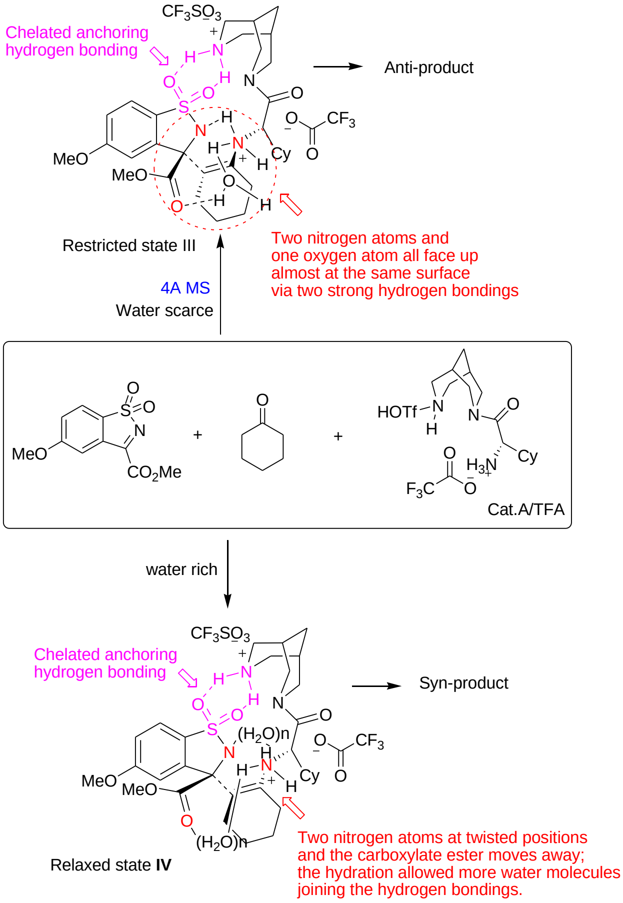


With this concept, new mechanisms are proposed here, focusing on the diastereoselectivity, for the two recent reported samples[6,7] of water enabled diastereodivergent organocatalysis. It would demonstrate the existence of both the “restricted” state and “relaxed” state in the absence/presence of water additives. The scope of the electron-donating functional groups for eligible electrophile/nucleophile reactants and the generality of this new approach would be discussed later subsequently.

The new mechanism for the diastereodivergent asymmetric Mannich reaction elucidated with the concept

In the diastereodivergent asymmetric Mannich reaction of cyclic N-sulfonyl, ketimines with ketones catalyzed by a bispidine-based chiral amine catalyst, a chiral enamine intermediate was proposed in the literature to determine the diastereoselectivity during the bond formation step evidenced by the control reactions[7]. A hydrated enamine intermediate is proposed here in the new mechanism with the bulky amine cation “anchoring” to both oxygen atoms of the sulfonyl moiety of the intermediate with two protons individually as shown in the Scheme 5. The very polar trifluoromethane group on TfOH (trifluoromethane sulfonic acid) likely weakens the capability of the sulfonic acid anion as a hydrogen acceptor, unparticipating the hydrogen bonding in the intermediate. Trifluoroacetic acid (TFA) anion likely would also not be involved in the hydrogen bonding due to the same reason as well. However, in the presence of 4Å MS removing any free water in the organic solvent, TFA is expected to play an important role in stabilizing the generated water molecule onto the enamine moiety and in improving the strength of the hydrogen bonding connected with the nitrogen atom of sulfonyl ketimine, via the protonation of the nitrogen atom as mentioned earlier, since the lone electron pair of the nitrogen atom is eager to abstract a proton from the enamine nitrogen cation. Meanwhile, one of the hydrogen atoms from the water molecule would form a bond with the carbonyl oxygen from the carboxylate ester functional group. Both key hydrogen bonds along with the "anchored" hydrogen bondings (between sulfonyl oxygens and the two hydrogen atoms on the bulky amine cation moiety), contribute to stabilizing the "restricted' state of the hydrate enamine intermediate, and resulting the dominant *anti*-product. In the crystal structures of the two *anti*-products and one *anti*-product derivative, the carbonyl oxygen (from the carboxylate ester), the oxygen of the ketone group (the nitrogen from C=NOH group for the derivative) and the nitrogen from the sulfonyl amide all face the same direction within a short distance. And that crystal data in the literature[7] is consistent with the proposed "restricted" state of the intermediate **III** (Scheme 5).

Scheme 5. New mechanism for the reported water-enabled diastereodivergent Mannich reaction

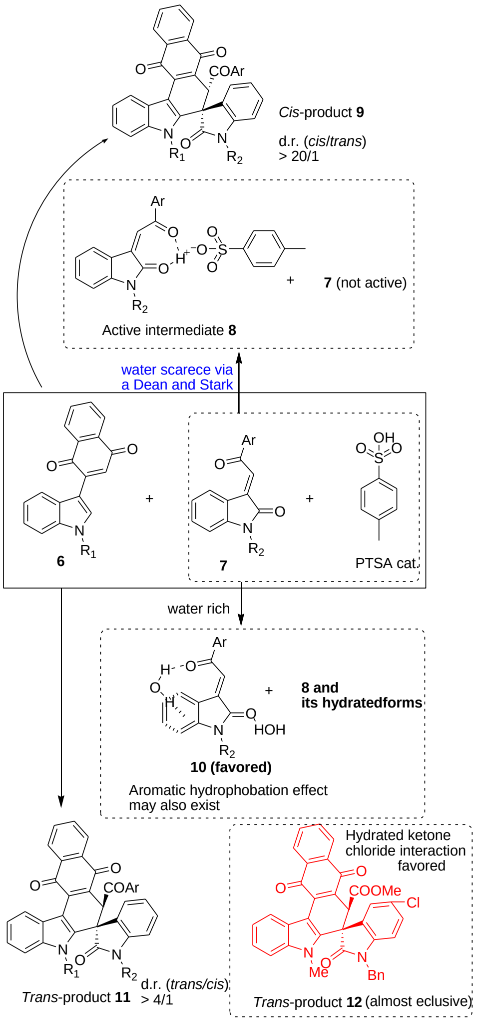


In the presence of a significant amount of water, the chelated strong hydrogen bondings between the sulfonyl oxygen and the two hydrogen atoms on the bulky amine cation moiety, would likely keep unchanged (Scheme 5). However, the hydration of carbonyl oxygen (from the carboxylate ester) and the sulfonyl ketimine by water would form the relatively long-distance hydrogen bonding, involving more water molecules, because the C=O-H bonding and the N-H bonding belongs to strong hydrogen bondings and they tend to form quickly under water-rich conditions via hydration[9,10,14]. The long-distance hydrogen bondings allow the enamine nitrogen, the carbonyl oxygen (from the carboxylate ester functional group) and the sulfonyl nitrogen to move away from each other, releasing the dispersion force among these anions in the intermediate **IV** (Scheme 5). The crystal data of the *syn*-product resulted from the "relaxed" state also showed that both the oxygen atoms from the cyclic ketone and the carbonyl group (from the carboxylate ester) shifted away from the face, facing different direction in a twisted manner. Because water dimers or water oligomers can only exist when a significant amount of water is mixed with organic solvents in the recent study[14], the diastereoselectivity increase correlated with the volume increase of the water additive in the literature[7] could be rationally explained.

The new mechanism for the water modulated diastereoselective Diels–Alder reaction based on the concept

In the water modulated diastereoselective synthesis of *cis*/*trans*-spiro[indoline-3,6′-naphtho[2,3-*c*]carbazoles, it was suggested that the Diels-Alder reactions proceeded in a concerted manner with a retention of the configuration determining the disastereoselectivity of the products from the data of the control experiments.[6] Though remarkable conversion of (*E*)-3-phenacylideneoxindole to (*Z*)-3-phenacylideneoxindole was observed via ^{1}H NMR spectroscopy when the mixture solution of the normal prepared (*E*)-3-phenacylideneoxindole and *p*-TsOH (*p*-toluenesulfonic acid) was refluxed under a Dean and Stark apparatus for 4 hours, the mechanism for the formation of exclusive *trans*-products under the competitive reaction conditions of both indole isomers is not yet clear.[6] Meanwhile, the role of the additional water for the reversal of the diastereoselectivity, producing the major *cis*-products was also not demonstrated. With the new concept, the diastereoselective controls under both conditions are explainable (Scheme 6).

Scheme 6. New mechanism for water-modulated disastereodivergent Diels-Alder reaction



Under a Dean and Stark apparatus, any water from the catalytic system including the generated water via oxidation/elimination after the cycloaddition, would be removed continuously. And the system would be scarce of hydrogen donors, resulting in strong bridged hydrogen bonding complex **8** between *p*-TsOH and (*E*)-3-phenacylideneoxindole (Scheme 6). The new complex in "restricted" state would likely be the "active" species in cycloaddition to the other dione reactant, producing the *trans*-product **9** almost exclusively, because the (*Z*)-3-phenacylideneoxindole **7** could not form the similar complex with between *p*-TsOH due to the long distance of the two carbonyl groups.

With *p*-TsOH monohydrate in toluene/water, the hydration of both the carbonyl groups of (*Z*)-isomer **7** resulted in the more favored complex **10** via new interactions involved with one or more water molecules, in competition with the "restricted" complex **8** (Scheme 6). The possible water enabled interactions[14] including the aromatic π- π interaction with a water molecule inside, the ketone-water-π interaction, and the carbonyl-water-chloride interaction (3-chloroindole as shown in the product **12**). All these new interactions in the "relaxation" state evidenced by the close positions in the crystal data of the products in the literature[6] would be favored with sterically less hindered (*Z*)-3-phenacylideneoxindole **7**, resulting in the formation of *cis*-product **11** as the major one. Because the small amount of complex **8** could still be generated under water-rich conditions, around 20% *trans*-product **9** could still be observed. It is worthy to be mentioned that the carbonyl-water-chloride hydrogen bonding could be strong enough to be the dominant interaction, producing almost exclusively *cis*-product **12** when the methyl carboxylate ester replaced the phenylketone functional group.

The generality of this new approach and the scope of the functional groups for eligible electrophile/nucleophile reactants

Generally, the catalytic systems should be workable under both the anhydrous conditions and the organic solvents/water conditions. Another key requirement is the scarcity of the hydrogen donor on the substrates and in the system under water scarce conditions; substrates with at least one aliphatic/aromatic cyclic structure are preferred to keep the two states at a good balance of rigidity and flexibility. And the existence of only one "active" hydrogen donor center in the "restricted" state of the intermediates is a must. The explored asymmetric and diastereoselective synthetic methodologies, with chiral secondary/primary amine acid salt as an organocatalyst, would likely be suitable systems for the future design of new water-enabled diastereodivergent catalysis, if the enamines/imines are the active intermediates. This is because the charged enamines have the strong capability to keep the generated water molecule maintaining an "active" hydrogen donor center, to stabilize the "restricted" state under the hydrogen donor scarce condition. The systems following a neutral enamine intermediate pathway with chiral secondary amine catalysts might not be stable enough to hold the water molecule, theoretically. Subsequently the electrostatic force might not be able to pull all the hydrogen acceptors together in the "restricted" state. The neutral or weak acidic enamine catalysis, like the proline catalysis, were known to be more efficient in the presence of some water[22], in order to avoid the catalyst deactivation via suppressing the side reactions[25].

For eligible functional groups as hydrogen acceptors, carbonyl groups like ketones and carboxylate esters as well as halogen atoms on aromatic moieties are highly favored, located at the stereocenter carbon because they could easily form relatively strong hydrogen bondings with the protonated enamine/imine under anhydrous conditions, and they also have strong hydration capability to reorganize the bonds in the presence of more water. Sulfinyl group (RS=O) might also be a suitable functional group due to the same reasons; however, the sulfonyl groups including the sulfonyl amides and sulfonic acids are likely not suitable functional groups for interconnected with the imine/enamine center due to their strongly chelated strong hydrogen bonding potential with the hydrogen donor center, leading to an unremovable bonding in the presence of water. But they could be ideal functional groups to anchor the bulky amine moiety of the diamine catalysts. In fact, the choice of the suitable functional groups could potentially be identified by checking the reported ^{1}H NMR data of the water impurity peak in the most functional-similar solvent. Based on the set ^{1}H NMR shift of the single molecular water with zero bond (δ 3.55 ppm)[14], the key functional group of the solvent is likely the suitable hydrogen acceptor group, if the water impurity peak in the solvent lies in the range of δ 2.5 to 3.5 ppm.

For the choice of the acid additives, strong acids with anions that lack of nucleophilicity, would be ideal for organocatalysis with stereo-control at the bond formation step. It is quite necessary in order to minimize the potential interruption of the acid anions in the key hydrogen bonding, determining the diastereoselectivity. For organic acid catalysis with retention of the configuration of one reactant, the choice of the acid can be broader.

Following these general guidelines, it is demonstrated that the water-enabled diastereodivergent organocatalysis is designable with the concept of “restricted” state under anhydrous conditions and “relaxed” state under water-rich conditions. Slight changes on the functional groups of the reactants (for example by adding a carboxylate ester functional group at a stereocenter) from the established diastereoselective and enantioselective organocatalytic systems in order to enable both a “restricted” state and a “relaxed” state under the specific condition, could be envisaged as an efficient way for the design.

Conclusions

A hydrated enamine/imine intermediate model was proposed, based on the recent progress in water ligand interactions in organic solvents, and in the new understanding to enhance the nucleophilicity of water at the molecular level in several types of organic transformations. With the new model, the diastereoselective control for organocatalysis with the chiral amines could be better elucidated. And subsequently a concept of “restricted” state under the hydrogen donor scarce conditions and the “relaxed” state under water-rich conditions, was proposed as a general approach for future design of water-enabled diastereodivergent organocatalysis. Based on the concept, new mechanisms were proposed for the recent two successful samples, and they could be able to better explain the diastereocontrol under both conditions. The generality of this approach and the potential scope of the eligible functional groups were also included, for inspiring the future rational design of more water-enabled diastereodivergent organocatalysis.

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