The Hydrated Structure Factor in Additive Effect on Enantioselective Organocatalytic Transfer Hydrogenation Reactions with Hantzsch Esters

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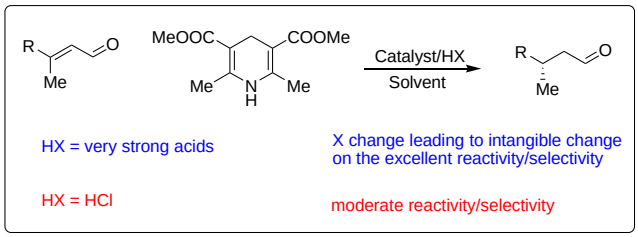
Abstract



Can the origin of the additive effect be elaborated with a bioinspired hydrated mechanism?

Would the selection of additive be designable?

Acid additives were frequently used in amine-catalyzed asymmetric catalysis as a practical strategy for the promotion of reaction activity/selectivity with a reduced amount of chiral catalyst. A fact is that the acid additives were discovered mostly by chance rather than by a logic prediction. Two bioinspired hydrated mechanisms for the organocatalytic transfer hydrogenation reactions were proposed in this work. And the proposed different acid-water-imine hydrated structures involved mechanism could well explain the additive effect supported by the reported experimental data. The new insight shows promise for assisting a logic acid additive screening in cationic imine-mediated asymmetric catalysis.

Keywords: acid-water-base complex; cation-π interaction; acid additive strategy; dual activation; anion hydration; hydrogen bonding.

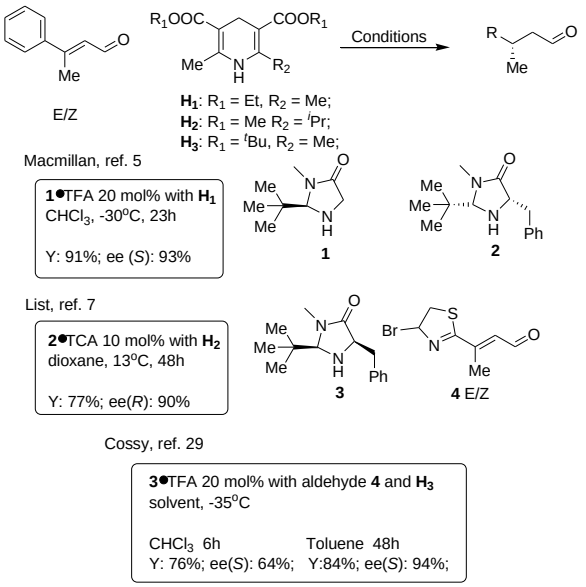
Introduction

Tremendous new efficient asymmetric transformations have been discovered in recent decades allowing direct access to various chiral compounds. Design of new chiral catalysts played a central role towards perfect asymmetric catalysis. On the other hand, the addition of achiral additives like acids proved to enhance the reactivity and thus enantioselectivity in many cases.[1,2] However, the screening of the additives was usually performed in the optimization stage rather than in the design stage, even though a dramatic change on enantioselectivity/reactivity was frequently observed[2-4]. A main reason is the unpredictive effect of additives, due to lack of the general theory on the additive effect[2]. New insights or models that are robust and general for additive selection in broad asymmetric catalysis are in great need[2], towards a predictive additive design strategy, benefiting potential applications of homogenous asymmetric catalysis in the industry.

An obvious acid additive effect was also observed in the bioinspired organocatalytic asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Hantzsch ester as a reductant (Scheme 1)[5-9]. This asymmetric catalytic reaction could proceed in a highly enantioselective manner either via a chiral imine cationic intermediate (along with an achiral anion)[5-7], or via a chiral counteranion directed achiral imine cationic intermediate (ACDC)[8,10]. Though the two distinct pathways were proposed respectively in the literatures, a more detailed analysis of the mechanisms is still needed for underpinning the future design of new catalysts and the complex related transformations.[11] A water

molecule (generated in the imine formation step) was not included in the two plausible mechanisms[5,7,8], meanwhile water-mediated salt bridges (acid-water-base structure) were often found in large biomolecules like enzymes[12] and proteins[13] as well as in supramolecular organic frameworks[14]. In this work, two hydrated imine cation model[15,16]-based mechanisms were proposed for both the pathways; and it is envisaged that a detailed study combining the hydration capability of both imine cationic moiety and the acid anion moiety might offer new insights on the origin of the acid additive effect. In addition, the smallest nucleophile hydrogen hydride used in this model reaction (Scheme 1) would minimize the potential impact of the steric factor from the nucleophile on yield and enantioselectivity, resulting into a control-like reaction for this study.

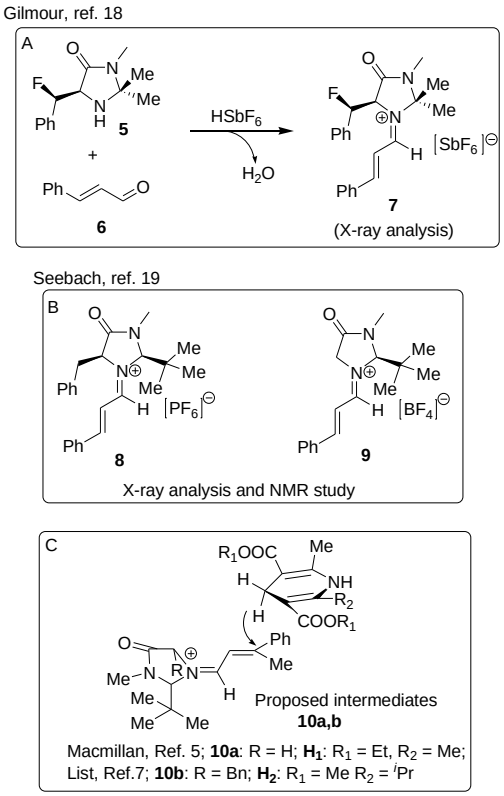
Scheme 1. Asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Hantzsch ester with Macmillan's catalyst.



Results and discussions

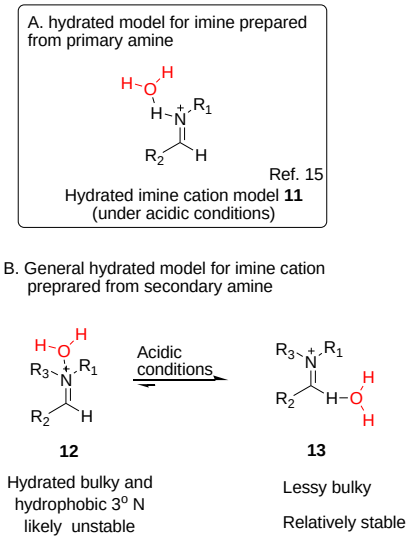
An imine model via a condensation of an aldehyde moiety with an amine losing a water molecule was usually proposed as a key intermediate for chiral amine-catalyzed transformations[17], including the organocatalytic asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Hantzsch ester (Scheme 2C)[7,9,11]. The X-ray crystal diffraction analysis of the iminium ion pair intermediate (base-acid complex) **7** generated from an α,β-unsaturated aldehyde and a fluoro-Macmillan's catalyst was reported by Gilmour (Scheme 2A).[18] An NMR study combining a X-ray crystal diffraction analysis of the similar iminium ion pair intermediates **8**,**9** via reactions of α,β-unsaturated aldehydes with Macmillan's catalyst or the diaryl prolinol ether was reported by Seebach (Scheme 2B).[19] Both studies provided important experimental evidences for the existence of the iminium ion pair intermediates **10a,b**. However, in both studies the imine ion pair intermediates **7**-**9** were prepared with a moisture-sensitive strong acid HBF_4, HPF_6 or $HSbF_6$, and either of the three strong acids could likely remove the generated water via an instant hydrolysis. The generated water molecule is necessary for regeneration of the aldehyde after a catalytic cycle and the iminium ion pair intermediates would tend to bind with a water molecule forming a hydrated form in order to avoid a potential energy penalty in a subsequent water addition to the imine cation step, based on the recent studies on the nucleophilicity of water molecule[20] and on the stability of water-organic complexes in organic solvents[21].

Scheme 2. Isolated imine ion pair intermediates **7**-**9** and the proposed intermediates **10a**,**b**



A hydrated imine model **11** (Scheme 3A) was recently proposed for the rational design of stereodivergent organocatalysis controlled by selective hydration[15], and for elucidating the kinetic stereocontrol in Brønsted acid-catalyzed Pictet-Spengler reaction and the dynamic epimerization mechanism via crystallization-induced diastereomer transformations[16]. With the new hydrated model **11**, the stereochemistry could be better controlled theoretically. Two revised mechanisms via the two different pathways of the chiral amine-induced asymmetric control and the chiral anion-directed asymmetric control were proposed respectively based on a new hydrated secondary imine model **13** (Scheme 3B), with extensive discussions on the acid-water-base structure change during a catalytic cycle.

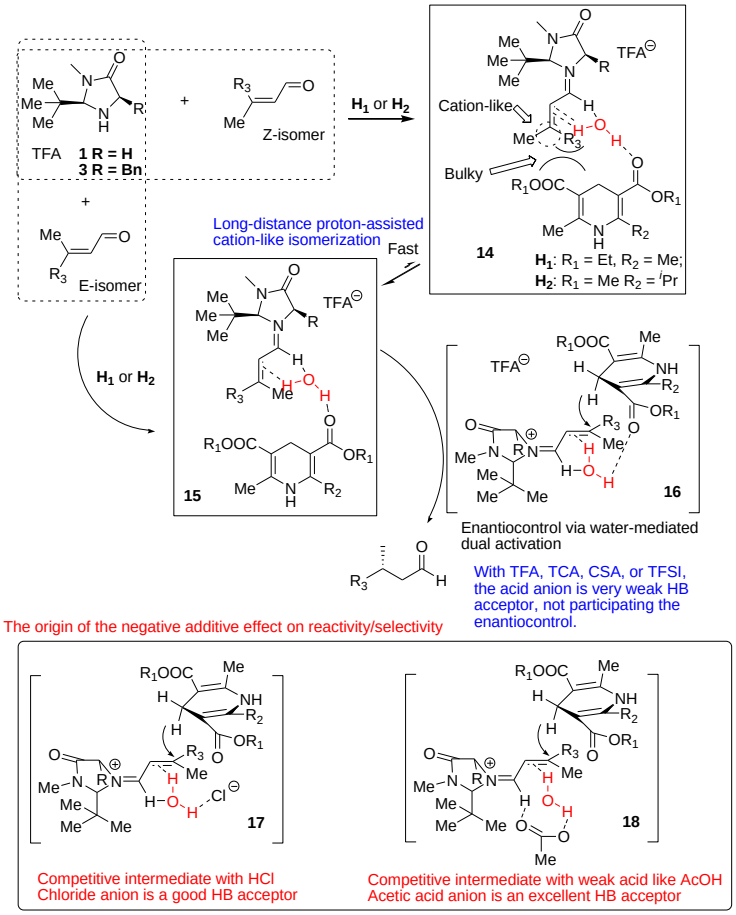
Scheme 3. Previous proposed hydrated primary imine model **11** and a new hydrated secondary imine model **12, 13** in this work



The revised chiral amine-induced mechanism and the hydrated imine ion pair intermediates

With the salt form of Macmillan's catalyst **1** or **2**, the Macmillan group[5,9] and the List group[6-7], both independently developed an organocatalytic asymmetric transfer hydrogenation of α, β-unsaturated aldehydes in dioxane or in chloroform with Hantzsch ester as a reductant. In both efficient catalytic systems, the trichloroacetic acid salt (or the trifluoracetic acid salt) form of the Macmillan's catalyst was superior than the hydrogen chloride salt form one in the reaction activity; and the better enantioselectivity in the reaction with the trichloroacetic acid salt form catalyst was also observed in both cases. The data suggested that the hydrated iminium ion pair intermediate with the trichloroacetic acid salt form catalyst might be slightly different with that with hydrogen chloride salt form catalyst.

Scheme 4. The water-involved mechanism for asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Macmillan's catalyst and the origin of additive effect



Unlike the primary amine based hydrated imine intermediate[16], the secondary amine based hydrated imine intermediate has no proton on the imine nitrogen atom and only has a hydrogen atom on the imine carbon atom (Scheme 3B). And this hydrogen atom is weakly acidic (δ = 8.9 – 9.3 ppm in $CDCl_3$)[19] based on the ^1H NMR data of the iminium ion pair intermediates via reactions of a cinnamaldehyde with one of Macmillan's catalysts reported by Seebach. This weakly acidic hydrogen atom may form a hydrogen bond as a donor with the oxygen atom of the generated water molecule, and one of hydrogen atom from the water would become acidic enough to coordinate with the conjugated alkene moiety (Scheme 4)[20]. Then, the positive charge would be concentrated on the carbon adjacent to the aromatic functional group, favouring the stereoconvergent isomerization from **14** to **15** and the subsequent hydride transfer from the Hantzsch ester. The other hydrogen atom from the water

molecule would like to activate Hantzsch ester via hydration of one carbonyl group, based on the recent water organic complex study[21]. Such dual activation might be responsible for the excellent reactivity as shown in the intermediate **16**. With the trichloroacetic acid salt (or the trifluoracetic acid salt) form of the Macmillan's catalyst, both the oxygen atoms are poor hydrogen acceptors[21], and would not be able to compete with the carbonyl oxygen atom from the Hantzsch ester, favouring the overall stereocontrol in the isomerization reaction. In another words, the trichloroacetic acid anion or the trifluoracetic acid anion would likely not be involved in the hydrogen bonding and would not participate the stereocontrol[15], instead, it might function simply as a relatively long-distance anion pair. With the hydrogen chloride acid salt form of the Macmillan's catalyst, the chloride anion would likely compete with the carbonyl oxygen atom from the Hantzsch ester in hydrogen bonding, though in an inferior manner (**17**, Scheme 4). The proposed β-carbon cationic-like intermediate **14** could be easily generated with both aliphatic and aromatic unsaturated aldehydes under the reaction conditions for the promotion of the observed stereoconvergent isomerization. Meanwhile, the methyl hydrogen at the β-carbon of aliphatic substrates examined by the Macmillan group[5,9] might not be acidic enough to follow the deprotonated pathway forming a diene-like intermediate proposed by the List group[7].

The observed much lower reactivity and poor enantioselectivity with a combination of proline (20 mol%) and a same loading (20 mol%) of trifluoracetic acid (TFA)[5] is also explainable, based on a hydrated model. The hydrogen atom from the carboxylate acid group of proline is more acidic than the hydrogen atom on the imine cation carbon, hence it would have a better chance to form a hydrogen bonding with the oxygen atom from the water molecule. However, the positive charge on the hydrogen atom from the carboxylate acid would be less than the hydrogen atom on the imine cation carbon, because of the neutrality effect from the carboxylate anion; and the relatively long-distance water-mediated stereocontrol would be weaker, leading to poor reactivity/enantioselectivity.

With the hydrated imine ion pair model, the acid additive effect in the organocatalytic asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Hantzsch ester, is generally predictable based on the structure of the acid additive used (**16**-**18**, Scheme 4). There are two important principles governing the structure factor: 1) the hydration capability of the acid anion, which will determine whether the anion would be involved in the hydrogen bonding for a stereocontrol; 2) the additional hydrogen donor group on the acid anion moiety, which might weaken the hydration capability of the anion via an intramolecular hydrogen bonding, or disturb the hydrogen bonding for a stereocontrol. Based on the two general principles, it is estimated that the reactivity/selectivity in the asymmetric transfer hydrogenation with the acetic acid form of the same Macmillan's catalyst would decrease dramatically due to the good hydration capability of the acetic anion (**18**, Scheme 4), though the data for this catalyst was not included in reported literatures. It should be noted that the hydration capability of the acid anion in specific organic solvent is half-quantitatively measurable[15] by measuring the ^{1}H NMR shift of the water peak by introducing one or two equivalent of water into a solution of the salt form catalyst in the organic solvent. A subsequent comparison with the reported water peak in different water organic complexes[21] would deliver the position information of the anion in the "hydration map".

The hydrated imine cation ion pair mediated mechanism clearly suggested several hints for future new catalyst design: 1) any change favouring donor capability of the imine cation hydrogen would be positive for the stereocontrol and enantioselective control; 2) any acid with poor hydrogen acceptor capability would be favoured; 3) single molecular water species might be beneficial to keep the hydrated intermediate at a higher concentration; too much water leading to water dimer/trimer might dramatically decrease the reactivity/enantioselectivity.

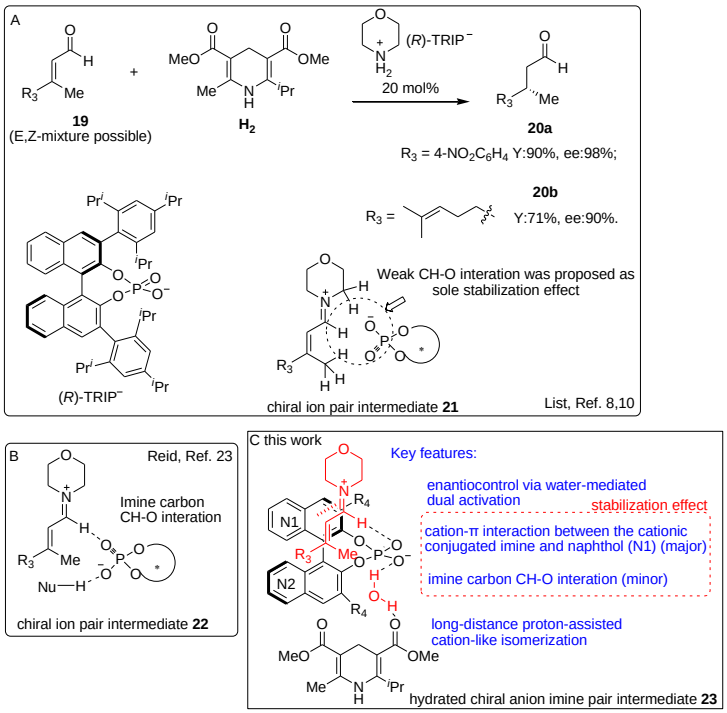
The hydrated model also underpinned that broad nucleophiles with a good hydrogen bonding acceptor group like carboxylate ester group might be activated for a conjugated addition to the unsaturated aldehydes under the similar catalytic systems.

A general hydrated model including a water molecule in the key intermediates (**11**,**13** Scheme 3) could also explain the acid additive effect in other amine/acid systems like chiral diamine/acid for asymmetric aldol reaction[4,22], and the detail analysis would be reported separately later.

The revised chiral anion-directed mechanism and the hydrated imine ion pair intermediates

By mixing commercially available secondary achiral amines with known chiral binaphthol-derived phosphoric acids, another type of amine-acid salt form catalyst was designed by the List group[8,10] for the asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Hantzsch ester (Scheme 5). In the catalytic system, achiral amine was an additive and the chiral anion (TRIP anion) was the sole chiral source. However, the reaction proceeded via a similar imine ion pair intermediate according to the proof-of principle of the asymmetric counteranion-directed catalysis (ACDC)[10]. And a weak hydrogen (from the adjacent carbon of the achiral amine moiety)-oxygen (from TRIP anion) bonding was initially proposed to play a key role in the stabilization of the imine cation-acid anion complex in the organic solution (**21**, Scheme 5).[10] A very recent work by the Reid group[23] and the Goodman group[24] on reaction mechanisms for chiral phosphoric acid-catalyzed transformations involved cationic intermediates and protic nucleophiles proposed a dual activation pathway; an imine cationic carbon hydrogen-oxygen (from TRIP anion) bonding and a hydrogen (protic nucleophile)-oxygen (from another oxygen of TRIP anion) bonding were found to be the most probable non-covalent interactions governing the stereochemistry and reactivity via a computational method (**22**, Scheme 5). Still the generated water molecule via an imine condensation was not included in the proposed non-covalent interactions.

Scheme 5. The reported key intermediates **21**, **22** and the water-involved key intermediate **23** proposed in this work



A hydrated acid anion imine ion pair is proposed as a key intermediate **23** in the new mechanism as shown in Scheme 5C. The oxygen atom (P=O) would likely form a hydrogen bond with the hydrogen atom from imine carbon (N=CH), since the hydrogen atom was showed to be the most acidic in the imine ion pair characterized by ^{1}H NMR spectroscopy[19]. A key difference is a direct hydrogen bonding between the TRIP anion and the achiral imine cation (P=O-HC=N), meanwhile, a water-mediated hydrogen bonding was proposed in the hydrated chiral imine cation ion pair intermediate for Macmillan's catalyst system (**16**, Scheme 4). There are two main reasons: 1) the hydrogen bonding capability of oxygen from phosphoric acid is among the strongest[25,26]; 2) the positive charged proton will increase in magnitude for a hydrogen bonding[25,26]; 3) the significant hydrophobicity of the aromatic moiety (TRIP). Another oxygen anion (TRIP) would be free to form a hydration bonding with a hydrogen atom of water molecule (**23**, Scheme 5C). The free hydrogen atom from water would be much weaker in positive charge in comparison that from hydrated chiral imine cation ion pair intermediate for Macmillan's catalyst system, because of the bonded TRIP anion with a negative charge. Hence, its activation of Hantzsch ester via hydration of the carbonyl group would also be weaker. It is estimated that a cationic imine-π interaction between the cationic conjugated imine and one of the binaphthols might likely play an important role on enantioselective control, as well as on the stereoconvergent isomerization of the alkene with assistance of the hydrogen atom from water (**23**, Scheme 5C). Though such cationic imine-π interaction was never proposed as a dominant stabilization force for chiral phosphoric acid-catalyzed transformations in the literatures to my best of knowledge[27], it is quite likely theoretically because both tyrosine with a phenolic group and tryptophan with an indole moiety[16] showed marked preference to interact with cationic side chains in structure biology[28].

The generally lower reactivity in the asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Hantzsch ester via ADDC catalysis[8] in comparison that with Macmillan's catalyst[5,7] is consistent with the prediction based on the proposed two hydrated mechanisms.

The acid anion dependant hydrated imine cation ion pair structure

Two different acid-water-base structures were proposed in the two new mechanisms for better explaining the stereocontrol/enantiocontrol, particularly for the additive effect. The hydration capability of the acid anion plays an important role in determining the hydrated structure as shown the above discussions. An counterion screening including trifluoroacetate, trichloroacetate, trifluoromethanesulfonimidate or a chiral counterion such as (+)- or (-)- camphorsulfonate by the Cossy group[29], showed little influence on reactivity/selectivity in the enantioselective organocatalytic conjugate reduction of β-azole-containing α,β-unsaturated aldehydes with Macmillan's catalyst (Scheme 1). The experimental data supported the hydrated intermediate-based mechanism, in which a poor hydrogen acceptor would not be involved in the stereocontrol and would not participate in the dual activation (**16**, Scheme 4). The presence of oxazole group and thiazole group in α,β-unsaturated aldehydes had a strong influence on both reactivity and enantioselectivity, and the electron-withdrawing character of the azole ring was proposed by the authors. The much better enantioselectivity in toluene over that in chloroform, combining the difference of water solubility in both solvents[21] suggested that the hydration of azole might play a role. In toluene, water impurity is very low and the hydration of the azole group could be minimized since the relatively hydrophobic amine/oxygen in the azole group is a poor hydrogen acceptor and they would likely not be able to compete with imine cation. The hydration of heterocylic group from the aldehyde reactant might also play an important role in the unclear mechanism of tunable and cooperative catalysis for enantioselective Pictet-Spengler reaction with varied nitrogen-containing heterocyclic carboxaldehydes reported by the Miller group[30], because hydration is expected to affect the hydrogen

bonding controlled catalysis supported by the fact that the careful selection of the carboxylic acid additive/co-catalyst was proved to be essential for the reaction enantioselectivity in the report.

Conclusions

The bioinspired organocatalytic asymmetric transfer hydrogenation of α, β-unsaturated aldehydes with Hantzsch ester was revisited by integration of the very recent progress in water-involved interactions/hydration of alkenes in organic synthesis, in order to gain some general insights on the origin of the additive effect. Via a detailed analysis, two new mechanisms with a hydrated imine cation ion pair intermediate **16** or a hydrated anion imine ion pair intermediate **23** were proposed for asymmetric transfer hydrogenation with Macmillan's catalyst or via ADDC catalysis. A conjugated imine cation-π interaction between the cationic conjugated imine and one of the binaphthols was proposed to play a key role in the stabilization of the chiral complex for enantioselective control via ADDC catalysis, for the first time to our best knowledge.

Based on the hydrated mechanism, the reported additive effect on reactivity/selectivity could be well elucidated and the stereoconvergent control of the E/Z-unsaturated aliphatic aldehydes could also be well explained. It was found that hydration capability of acid anion plays an important role to determine the structure of the key hydrated intermediate (acid-water-based complex) and a practical method to half-quantify the hydration capability of specific acid anions was described. The new hydrated intermediates show promise as general models for the molecular understanding of imine catalysis with an acid additive. And it is demonstrated that an acid additive strategy is possible and that the selection is designable, towards "perfect asymmetric catalysis" with reduced use of relatively expensive organic catalysts, compared with the additive.

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