CHEMISTRY
AN ASIAN JOURNAL

## Accepted Article

**Title:** Positive Effect of Water in Asymmetric Direct Aldol Reactions with Primary-Amine Organocatalyst: Experimental and Computational Studies

**Authors:** Shin A. Moteki; Hiroki Maruyama; Keiji Nakayama; Hai-Bei Li; Galina Petrova; Satoshi Maeda; Keiji Morokuma; Keiji Maruoka



**To be cited as:** Chem. Asian J. 10.1002/asia.201500078

**Link to VoR:** http://dx.doi.org/10.1002/asia.201500078

An ACES journal

A sister journal of Angewandte Chemie and Chemistry – A European Journal

Supported by

GDCh Gesellschaft Deutscher Chemiker

ChemPubSoc Europe

Federation of Asian Chemical Societies

WILEY-VCH

CHEMISTRY AN ASIAN JOURNAL

COMMUNICATION

DOI: 10.1002/asia.200((will be filled in by the editorial staff))

# Positive Effect of Water in Asymmetric Direct Aldol Reactions with Primary-Amine Organocatalyst: Experimental and Computational Studies

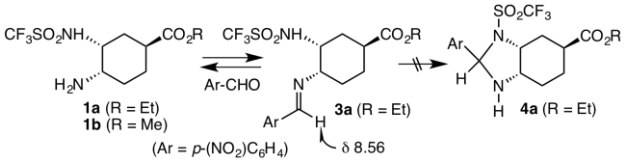
**Shin A. Moteki,[a] Hiroki Maruyama,[a] Keiji Nakayama,[a] Hai-Bei Li,[b,c] Galina Petrova,[b] Satoshi Maeda,[d] Keiji Morokuma,*[b] and Keiji Maruoka*[a]**

*Dedication ((optional))*

**Abstract:** The origin of higher reactivity in the water-accelerated asymmetric aldol reactions with our designed *primary*-amine organocatalyst was elucidated by both computational and experimental methods. As suggested by the calculated transition-state structures for water-promoted imine-enamine isomerization, anti-selective aldol reaction and hemiaminal formation, the rate of this aldol reaction was found experimentally to be even more accelerated by the addition of cis-2-butene-1,4-diol as additive.

The asymmetric aldol reaction is one of the most important and efficient carbon-carbon bond-forming reactions in organic synthesis for the construction of complex chiral polyol architectures.[1] In addition to aldolase enzymes and chiral metal catalysts, a variety of small organic molecules, including proline and various other chiral pyrrolidine derivatives, have been shown to be efficient organocatalysts for asymmetric aldol reactions.[2-3] These proline-based organocatalysts are believed to catalyze the direct aldol reaction via the enamine mechanism, which mimics the behavior of natural class I aldolase.[4] Such organocatalytic, asymmetric aldol reactions, if carried out in water solvent, are reported to exhibit high reactivity and selectivity,[5] although Armstrong and Blackmond clarified that the effect of water in the proline-catalyzed aldol reaction was not directly related to the catalytic cycle.[6] In contrast, acyclic *primary*-amino acids (alanine, threonine, tryptophan, etc.) and their derivatives have recently been found to be more effective in the asymmetric aldol reactions in aqueous solvents than polar aprotic solvents.[7] According to the mechanism of natural aldolase containing a primary amine site, the tautomerization of imine and enamine, and the subsequent aldol reaction are assisted by water-mediated proton rely system.[8] We assume that the role of water in *primary*-amine catalyzed aldol reaction is different from that of secondary amines such as proline. In this context, we are interested in the role of water[6,9] in the asymmetric aldol reactions with certain *primary*-amine organocatalysts. Here we wish to report our new findings on the origin of higher reactivity in the water-accelerated asymmetric aldol reactions with our designed *primary*-amine organocatalyst **1**[10] by both experimental and computational methods.

We first experimentally investigated the asymmetric aldol reaction of cyclohexanone with aldehydes catalyzed by *primary*-amine organocatalyst **1a** in polar aprotic solvents in the absence or presence of water, and selected results of forming *anti*- and *syn*-**2** are shown in Table 1. The reaction between cyclohexanone and aromatic aldehydes exhibited generally both higher reactivity and anti selectivity in aqueous solvents, particularly aqueous MeCN (entries 2 and 10 vs. 1 and 9, respectively). Furthermore, higher enantioselectivity was observed in aqueous THF (entries 6 and 12 vs. 5 and 11, respectively). In a $^1$H NMR study of the condensation of *p*-nitrobenzaldehyde and *primary*-amine catalyst **1a** in $CD_3OD$ under standard conditions, we observed a single peak of imine **3a** at δ 8.56. Although oxazolidinone formation is a major path in the case of proline catalyst, [6] we were not able to observe any formation of oxazolidinone **4a** by using *primary*-amine catalyst **1a**.




[a] Dr. S. A. Moteki, Mr. Hiroki Maruyama, Dr. Keiji Nakayama, Prof. Dr. K. Maruoka
Laboratory of Synthetic Organic Chemistry and Special Laboratory of Organocatalytic Chemistry, Department of Chemistry, Graduate School of Science
Kyoto University, Sakyo, Kyoto 606-8502, Japan
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

[b] Dr. H.-B. Li, Dr. G. Petrova, Prof. Dr. K. Morokuma
Fukui Institute for Fundamental Chemistry,
Kyoto University, Sakyo, Kyoto 606-8103, Japan
E-mail: morokuma@fukui.kyoto-u.ac.jp

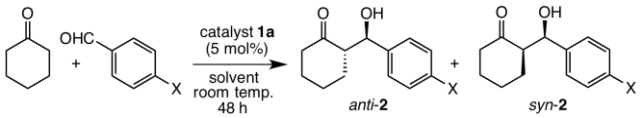
[c] Dr. H.-B. Li
School of Ocean, Shandong University, Weihai 264209, China

[d] Dr. S. Maeda
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200xxxxxx.((Please delete if not

10.1002/asia.201500078

Table 1. Effect of water in the asymmetric aldol reactions with *primary*-amine catalyst 1a.[a]




| Entry | Aldehyde (X) | Solvent | Yield [%][f] (*anti*/*syn*)[g] | *ee* [%][h] |
|---|---|---|---|---|
| 1 | *p*-$NO_2$ | MeCN | <5 (- : -) | 94 |
| 2 | | *aq.* MeCN[b] | 96 (92:8) | 98 |
| 3 | | neat | 54 (75:25) | 92 |
| 4 | | $H_2O$ | 51 (91:9) | 97 |
| 5 | | THF[c] | 43 (75:25) | 87 |
| 6 | | *aq.* THF[d] | 98 (94:6) | 98 |
| 7 | | *i*PrOH | 79 (90:10) | 97 |
| 8 | | MeOH | 83 (80:20) | 91 |
| 9 | *p*-CN | MeCN | <5 (- : -) | 95 |
| 10 | | *aq.* MeCN[e] | 93 (91:9) | 97 |
| 11 | | THF | 66 (74:26) | 92 |
| 12 | | *aq.* THF[d] | 98 (92:8) | 97 |

[a] Unless otherwise specified, asymmetric direct aldol reaction of cyclohexanone (30 equiv) and *p*-nitrobenzaldehyde (1 equiv) in the presence of 5 mol% of catalyst **1a** in solvents (1.8 mL) at room temperature. [b] MeCN/$H_2O$ = 17:1. [c] The change of the conversion with time was measured by NMR analysis with mesitylene as an internal standard in primary-amine-catalyzed asymmetric aldol reaction in THF-d8 at room temperature. See Supporting Information. [d] THF/$H_2O$ = 1:1. [e] MeCN/$H_2O$ = 1:1. [f] Isolated yield. [g] The *anti*/*syn* ratio of aldol products was determined by $^1$H NMR analysis. [h] Enantiopurity of aldol products was determined by HPLC analysis using a chiral column [DAICEL Chiralpak AD-H].

Based on the proposed mechanism on the proline-catalyzed asymmetric aldol reaction,[11] the asymmetric aldol reaction of cyclohexanone and substituted benzaldehydes catalyzed by *primary*-amine organocatalyst **1** has been assumed to proceed as shown in Figure 1. In order to explore the real detailed mechanism on the asymmetric aldol reaction of cyclohexanone and substituted benzaldehydes catalyzed by *primary*-amine organocatalyst **1**, we explored systematically and theoretically various plausible reaction pathways using the recently developed powerful reaction path search method, AFIR (artificial force induced reaction) method,[12] and performed density functional calculations for the *primary*-amine-catalyzed asymmetric aldol reaction. The AFIR method applies an artificial force between reacting molecules and efficiently explores many possible reaction pathways to determine the most preferred one without prior knowledge to transition states. The reaction has been found to proceed via the enamine mechanism as illustrated in Figure 1.[13-15]

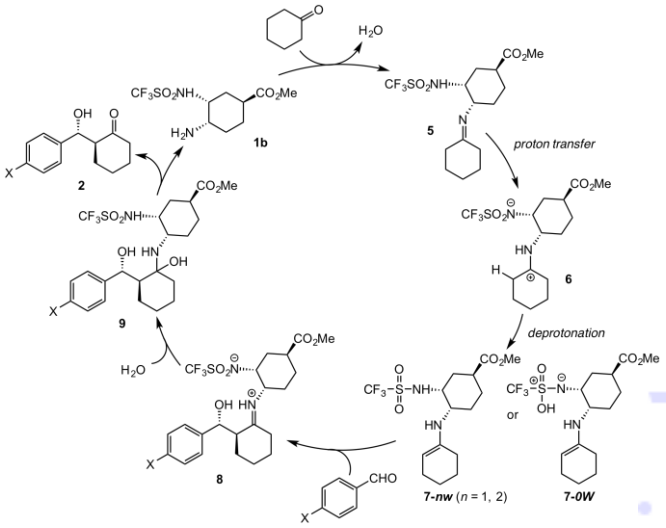



Figure 1. Theoretically proposed mechanism of the asymmetric aldol reaction with *primary*-amine organocatalyst **1b**.

In this mechanism, a *primary*-amine organocatalyst **1b** forms an imine intermediate **5** with cyclohexanone. Subsequently, conversion of **5** to the corresponding enamine **7**-*n*w is necessary for the following aldol reaction.[7b,12] This conversion has been found to occur by a stepwise proton transfer process via intermediate **6**. The sulfonamide proton in **5** is labile due to the strong electron-withdrawing effect of the Tf group and easily transfers to imine nitrogen with low free-energy barrier height (~7-10 kcal/mol), with or without water, to give **6**. The subsequent transfer of a proton from the β-carbon of the cyclohexyl group of **6** to the sulfonyl oxygen (without water) or the sulfonamide nitrogen (with water) gives rise to different enamine intermediates **7**-*n*w (Figure 1). Without water, the proton cannot reach the sulfonamide nitrogen, and the resultant intermediate is very unstable, thereby inducing the reverse reaction predominantly. At the transition state **TS6/7**-*nw* (*n* = 1, 2) one or two water molecules relay the proton to the desired sulfonamide nitrogen (See Figure 2), with free-energy barrier of ~22-24 kcal/mol, a possible rate-determining step for the entire reaction, to give stable intermediates **7**-*nw* (*n* = 1, 2). Thus, these intermediates are the starting points for the subsequent reactions.

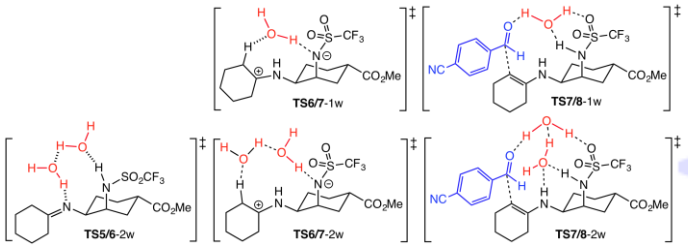



Figure 2. Transition state structures with one or two water molecules

The next step is the C-C bond formation reaction between **7** and *p*-substituted benzaldehyde to give the intermediate **8**. In this step, a proton is transferred from the sulfonamide NH to the carbonyl oxygen via hydrogen bonding network through one or two water molecules to activate the aldehyde by increasing its electrophilicity, and the C-C bond is formed between carbonyl carbon and enamine

β-carbon, via the **TS7/8**-*nw* (*n* = 1, 2) (See Figure 2) to give the intermediate **8**-*nw* (*n* = 1, 2) with a free energy barrier of ~4-7 kcal/mol, depending on the stereoselective transition states. This step is the stereoselectivity determining step, as in the case of proline-catalyzed aldol reaction.[11,16]

One notices in Figure 2 that proton transfers take place via two water molecules forming a hydrogen bond network. This finding suggests that some solvent molecule that can form a similar di-hydrogen-bonding structure may be able to play a role of two water molecules and accelerates the reaction, as illustrated in Figure 3.

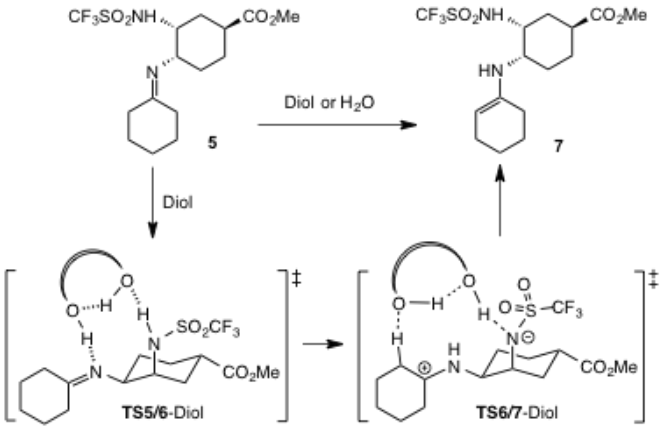
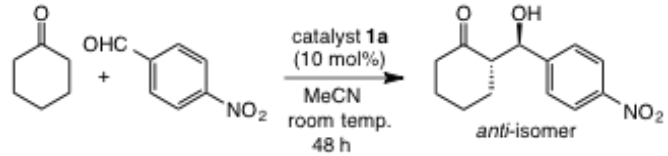
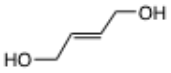
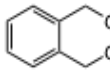



Figure 3. Effect of water and diol replacement in the transformation from imine to enamine by *primary*-amine **1b**.

Based on these computational findings, we further examined the effect of water by using replacements that may play a similar role of 2 equiv of water. Accordingly, some diol substrates were selected and screened as shown in Table 2.[17] Interestingly, the rate of this aldol reaction was even more accelerated by the addition of these diols in MeCN. Especially, cis-2-butene-1,4-diol afforded anti selective aldol adduct in excellent yield and enantioselectivity (entry 3 in Table 2). At the transition state **TS5/6**-diol and **TS6/7**-diol, two hydroxyl groups are found to play the role of two water molecules relaying the protons. The barrier heights in the process of enamine formation are very similar with two waters (**TS6/7**-2w, ~23.6 kcal/mol) and cis-2-butene-1,4-diol replacement (**TS6/7**-Diol, ~26.5 kcal/mol). Thus, these theoretical and experimental findings support each other on the role of water and water replacement.

Table 2. Effect of water and some diol replacements in asymmetric aldol reaction catalyzed by *primary*-amine **1a**.[a]




| Entry | Additive (equiv) | Yield [%][c] (*anti/syn*)[d] | *ee* [%][e] |
|---|---|---|---|
| 1 | none | <5 (- : -) | 94 |
| 2 | $H_2O$ (10)[b] | 67 (89:11) | 95 |
| 3 |  (5)[b] | 91 (90:10) | 97 |
| 4 |  (5) | 61 (76:24) | 92 |
| 5 |  (5) | 49 (93:7) | 98 |
| 6 |  (5) | 11 (75:25) | 91 |
| 7 | MeOH | 69 (78:22) | 92 |

[a] Unless otherwise specified, asymmetric direct aldol reaction of cycloalkanone (30 equiv) and *p*-substituted benzaldehyde (1 equiv) with 10 mol% of catalyst **1a** in the absence or presence of additive in MeCN (1.8 mL) at room temperature. [b] The change of the conversion with time was measured by NMR analysis with mesitylene as an internal standard in primary-amine-catalyzed asymmetric aldol reactions in the presence of cis-2-buten-1,4-diol or water in MeCN-d3. See Supporting Information. [c] Isolated yield. [d] The *anti/syn* ratio of aldol products was determined by $^1$H NMR analysis. [e] Enantiopurity of aldol products was determined by HPLC analysis using a chiral column [DAICEL Chiralpak AD-H].

Other selected examples are listed in Table 3, which indicates the superiority of cis-2-butene-1,4-diol as efficient water replacement in the asymmetric aldol reaction of cycloalkanone with aldehyde catalyzed by *primary*-amine organocatalyst **1a**.

Table 3. Superiority of cis-2-butene-1,4-diol as additive in asymmetric aldol reaction catalyzed by *primary*-amine **1a**.[a]


| Entry | Substrate | Additive (equiv) | Yield [%][b] (*anti/syn*)[c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | n = 1; Z = CN | $H_2O$ (10) | 73 (91:9) | 94 |
| 2 | | cis-2-butene-1,4-diol (5) | 89 (92:8) | 97 |
| 3 | n = 1; Z = $CO_2Me$ | $H_2O$ (10) | 77 (90:10) | 91 |
| 4 | | cis-2-butene-1,4-diol (5) | 98 (91:9) | 94 |
| 5 | n = 0; Z = $NO_2$ | $H_2O$ (10) | 64 (98:2) | 90 |
| 6 | | cis-2-butene-1,4-diol (5) | 88 (98:2) | 95 |

[a] Unless otherwise specified, asymmetric direct aldol reaction of cycloalkanone (30 equiv) and *p*-substituted benzaldehyde (1 equiv) with 10 mol% of catalyst **1a** in the absence or presence of additive in MeCN (1.8 mL) at room temperature. [b] Isolated yield. [c] The *anti/syn* ratio of aldol products was determined by $^1$H NMR analysis. [d] Enantiopurity of aldol products was determined by HPLC analysis using a chiral column [DAICEL Chiralpak AD-H].

## Conclusions

In summary, we have succeeded in elucidating the origin of higher reactivity in the water-accelerated asymmetric aldol reactions with our designed *primary*-amino organocatalyst **1** by both experimental

and computational methods. Some diols have been found to work as replacement of two water molecules and accelerate the rate of the Aldol reaction. Our interpretation is in principle applicable to other asymmetric aldol reaction with acyclic *primary*-amino acids (alanine, threonine, tryptophan, etc.) and their derivatives as organocatalysts, and further effort to this end is currently underway in our laboratories.

## Experimental Section

General procedure for asymmetric aldol reaction with primary-amine catalyst **1a**: To a mixture of catalyst **1a** (9.6 mg, 10 mol%) in MeCN (1.8 ml) was added aldehyde (0.3 mmol), *cis*-2-butene-1,4-diol (130 mg, 5 equiv), and cyclohexanone (0.9 ml, 9.0 mmol). The mixture was stirred at room temperature for 48 hours. Then, saturated $NH_4Cl$ solution and ethyl acetate were added with vigorous stirring, the organic layer was separated and washed with brine. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was then purified by column chromatography on silica gel (mixture of ethyl acetate/hexane) to give the 2-(hydroxy-*p*-nitrophenylmethyl)cyclohexan-1-one as colorless solid (68 mg, 91% yield).

## Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the MEXT, Japan. The computer resources at the Academic Center for Computing and Media Studies (ACCMS) at Kyoto University and Research Center of Computer Science (RCCS) at the Institute for Molecular Science are acknowledged.

**Keywords:** aldol • amine • organocatalysis • water • computation

[1] Reviews: (a) T. Mukaiyama, *Org. React*. **1982**, *28*, 203. (b) C. H. Heathcock in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, B. M., I. Fleming C. H. Heathcock), Pergamon Press: Oxford, **1991**, pp. 99-319. (c) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1999**, *4*, 1137. (d) Modern Aldol Reactions, *Vols. 1, 2*; R. Mahrwald, Ed.; Wiely-VCH: Weinheim, **2004**. (e) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Soc. Rev.* **2004**, *33*, 65. (f) L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* **2009**, *20*, 131. (g) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600. (h) S. Matsunaga, T. Yoshino, *Chem. Rec*. **2011**, *11*, 260.

[2] Recent reviews of proline or chiral pyrrolidine derivatives catalyzed direct asymmetric aldol reactions: (a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev*. **2007**, *107*, 5471. (b) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* **2008**, *37*, 1502. (c) M. M. Heravi, S. Asadi, *Tetrahedron: Asymmetry* **2012**, *23*, 1431. (d) V. Bisai, A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 4541. (e) Modern Methods in Stereoselective Aldol Reactions, R. Mahrwald, Ed.; Wiley-VCH: Weinheim, **2013**.

[3] Other type *secondary*-amine organocatalysts: (a) I. K. Mangion, A. B. Northup, D. W. C. MacMillan, *Angew. Chem., Int. Ed*. **2004**, *43*, 6722. (b) T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem. Int. Ed*. **2005**, *44*, 3055. (c) T. Kano, O. Tokuda, J. Takai, K. Maruoka, *Chem. Asian. J.* **2006,** *1-2*, 210. (d) T. Kano, Y. Yamaguchi, Y. Tanaka, K. Maruoka, *Angew. Chem., Int. Ed*. **2007**, *46*, 1738. See also: (e) T. Kano, O. Tokuda, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 7423. (f) J. Liu, Z. Yang, Z. Wang, F. Wang, X. Chen, X. Liu, X. Feng, Z. Su, C. Hu, *J. Am. Chem. Soc*. **2008**, *130*, 5654. (g) L. -Q. Lu, X. -L. An, J. -R. Chen, W. -J. Xiao, *Synlett* **2012**, *23*, 490. (h) L. Zhang, S. Luo, *Synlett* **2012**, *23*, 1575. (i) T. Kano, S. Song, K. Maruoka, *Chem. Commun.* **2012**, *48*, 7037.

[4] (a) T. D. Machajewski, C.-H. Wong, *Angew. Chem., Int. Ed*. **2000**, *39*, 1352. (b) F. Tanaka, R. Fullerand, C. F. Barbas III, *Biochemistry* **2005**, *44*, 7583. (c) P. Clapes, X. Garrabou, *Adv. Synth. Catal*. **2011**, *353*, 2263.

[5] Certain proline-derived catalysts are reported to show high reactivity and selectivity in water. See: a) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734; b) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urashima, M. Shoji, *Angew. Chem., Int. Ed*. **2006**, *45*, 958. For reviews on organocatalysis in water and its effect, see: (c) U. M. Lindstrom, *Chem. Rev*. **2002**, *102*, 2751. (d) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33. (e) M. Raj, V. K. Singh, *Chem. Commun.* **2009**, 6687. (f) L.-W. Xu, J. Juo, Y. Lu, *Chem. Commun.* **2009**, 1807. (g) R. N. Butler, A. G. Coyne, *Chem. Rev*. **2010**, *110*, 6302. (h) J. Mlynarski, S. Bas, *Chem. Soc. Rev.* **2014**, *43*, 577.

[6] The role of water in proline-mediated aldol reaction was recently reported: N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc*. **2007**, *129*, 15100.

[7] Representative examples on direct asymmetric aldol reactions mediated by *prim*-amino acid-based organocatalysts in aqueous solvent: Reviews: (a) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047. (b) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807. See also: (c) A. Córdova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun*. **2005**, 3586. (d) M. Amedjkouh, *Tetrahedron Asymmetry* **2005**, *16*, 1411. (e) Z. Jiang, Z. Liang, X. Wu, Y. Lu, *Chem. Commun*. **2006**, 2801. (f) A. Córdova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem.–Eur. J*. **2006**, *12*, 5383. (g) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.*, **2007**, *349*, 812. (h) F.-Z. Peng, Z.-H. Ahao, X.-W. Pu, H.-B. Zhang, *Adv. Synth. Catal*. **2008**, *350*, 2199. (i) Y. Hayashi, T. Itoh, N. Nagase, M. Ohkubo, H. Ishikawa, *Synlett* **2008**, *10*, 1565. (j) X. Ma, C-S. Da, L. Yi, Y-N. Jia, Q-P. Guo, L-P. Che, F-C. Wu, J-R. Wang, W-P. Li, *Tetrahedron: Asymmetry* **2009**, *20*, 1419. (k) T. Miura, Y. Yasaku, N. Koyata, Y. Murakami, N. Imiai, *Tetrahedron Lett.* **2009**, *50*, 2632. (l) M. Markert, U. Scheffler, R. Mahrwald, *J. Am. Chem. Soc*. **2009**, *131*, 16642. (m) Z. Jiang, H. Yang, X. Han, J. Luo, M. W. Wong, Y. Lu, *Org. Biomol. Chem.* **2010**, *8*, 1368. (n) X. Zhang, Y. Xiong, S. Zhang, X. Ling, J. Wang, C. Chen, *Asian J. Chem.* **2012**, *24*, 751.

[8] A. Heine, G. DeSantis, J. G. Luz, M. Mitchell, C,-H. Wong, I. A. Wilson, *Science* **2001**, *294*, 369.

[9] For the theoretical investigation on the enhanced activity of organocatalysis on water, see: (a) Y. Jung, R. A. Marcus, *J. Am. Chem. Soc*. **2007**, *129*, 5492. (b) Q. Zhao, Y.-h. L., M. K., C. Xu, K. N. Houk, C. E. Schafmeister, *J. Org. Chem*. **2012**, *77*, 4784.

[10] K. Nakayama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 17666.

[11] (a) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc*. **2003**, *125*, 2475. (b) C. Allemann, R. Gordillo, F. R. Clemente, P. H. Cheong, K. N. Houk, *Acc. Chem. Res*. **2004**, *37*, 558. (c) B. List, L. Hoang, H. J. Martin, *Proc. Nat. Acad. Sci*. **2004**, *101*, 5839. (d) F. R. Clemente, K. N. Houk, *Angew. Chem. Intl Ed*. **2004**, *43*, 5765. (e) T. J. Dickerson, T. Lovell, M. M. Meijler, L. Noodleman, K. D. Janda, *J. Org. Chem*. **2004**, *69*, 6603. (f) F. R. Clemente, P. H. Cheong, K. N. Houk, *J. Am.Chem. Soc*. **2005**, *127*, 11294. (g) A. Fu, B. List, W. Thiel, *J. Org. Chem*. **2006**, *71*, 320. (h) X. Zhu, F. Tanaka, R. A. Lerner, C. F. Barbas III, I. A. Wilson, *J. Am. Chem. Soc.* **2009**, *131*, 18206.

[12] S. Maeda, K. Ohno, K. Morokuma, *Phys. Chem. Chem. Phys.* **2013**, *15*, 3683 and references cited therein.

[13] All stationary points (reactants, transition states, intermediates and products) were optimized and characterized by frequency and IRC analysis using B3LYP-D/6-31+G(d) method as implemented in Gaussian 09, with the IEFPCM solvation model for THF solvent. Single-point calculations were performed at the level of B3LYP-D/6-311++(2d,p)/IEFPCM//B3LYP-D/6-31+(d)/IEFPCM. The free energies were calculated at 298.15 K and 1 atm.

[14] Gaussian 09, Revision A.1, M. J. Frisch, et. al. Gaussian, Inc., Wallingford CT, **2009**.

[15] (a) V. Brone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995. (b) M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comput. Chem.* **2003**, *24*, 669.

[16] We will discuss the diastereo- and enantioselective C-C bond formation in more details in a future publication.

[17] Other diols such as ethylene glycol and catechol gave less satisfactory results (<5% yields).

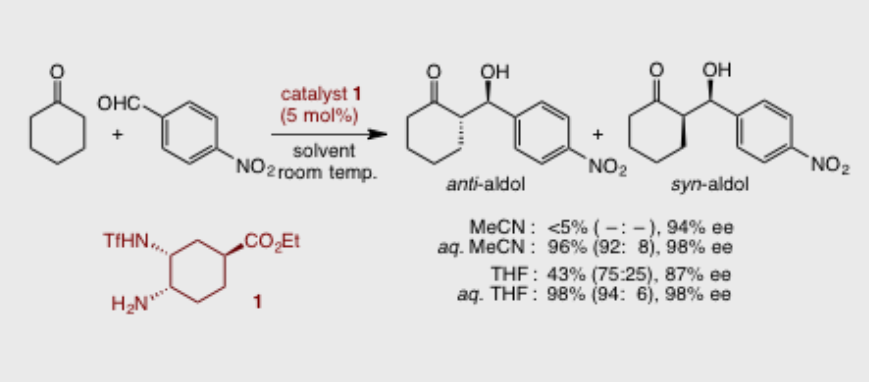
Received: ((will be filled in by the editorial staff))
Revised: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

10.1002/asia.201500078

**Entry for the Table of Contents** (Please choose one layout only)

Layout 2:

**COMMUNICATION**




The origin of higher reactivity in the water-accelerated asymmetric aldol reactions with our designed *primary*-amine organocatalyst was elucidated by both computational and experimental methods.

*Shin A. Moteki, Hiroki Maruyama, Keiji Nakayama, Hai-Bei Li, Galina Petrova, Satoshi Maeda, Keiji Morokuma,* and Keiji Maruoka**
…….…… Page – Page

**Positive Effect of Water in Asymmetric Direct Aldol Reactions with Primary-Amine Organocatalyst: Experimental and Computational Studies**