

Cite this: *Chem. Sci.*, 2022, 13, 4313

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Water enables diastereodivergency in bispidine-based chiral amine-catalyzed asymmetric Mannich reaction of cyclic *N*-sulfonyl ketimines with ketones†

Gonglin Li, Yan Zhang, Hongkun Zeng, Xiaoming Feng, Zhishan Su* and Lili Lin*

Tuning diastereoselectivity is a great challenge in asymmetric catalysis for the inherent stereochemical bias of the substrates. Here, we report a diastereodivergent asymmetric Mannich reaction of cyclic *N*-sulfonyl ketimines with ketones catalyzed by a bispidine-based chiral amine catalyst, in which additional water switches the diastereoselectivity efficiently. Both chiral *anti*- and *syn*-benzosultams with potential *anti*-HIV-1 activity are obtained in excellent yields and good to excellent ee values. Control experiments and density functional theory (DFT) calculations were applied to study the diastereodivergent mechanism, which reveal that the diastereodivergent catalysis should be state-determined, and the water reverses the energies of states to realize the diastereodivergency. The findings are quite new and might inspire more diastereodivergent asymmetric synthesis.

Received 22nd January 2022
Accepted 20th March 2022

DOI: 10.1039/d2sc00446a

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Introduction

Multiple stereocenters are widely spread in natural products and drug molecules. Both the diastereomers and enantiomers of a molecule with multiple stereocenters might have distinct or even opposing biological activities because enzymes and receptors provide chiral environments in biological systems.^{1,2} So, all stereoisomers of pharmaceutical candidates need to be obtained for evaluating their bioactivities during the drug discovery and development process.² After rapid development of asymmetric catalysis, highly di- and enantioselective reactions or cascades have been developed to deliver one diastereoisomer of chiral products with two or more stereocenters in one step or in one pot, and the enantiomers can normally be achieved with equal ease by applying the quasi-enantiomeric catalyst. However, other diastereomers are often unavailable efficiently because of the inherent stereochemical bias of the substrates.

Diastereodivergent asymmetric catalysis³ is attractive and challenging because it aims to generate different chiral diastereomers starting from the same substrates just by small variation of reaction conditions, which is undoubtedly a starting

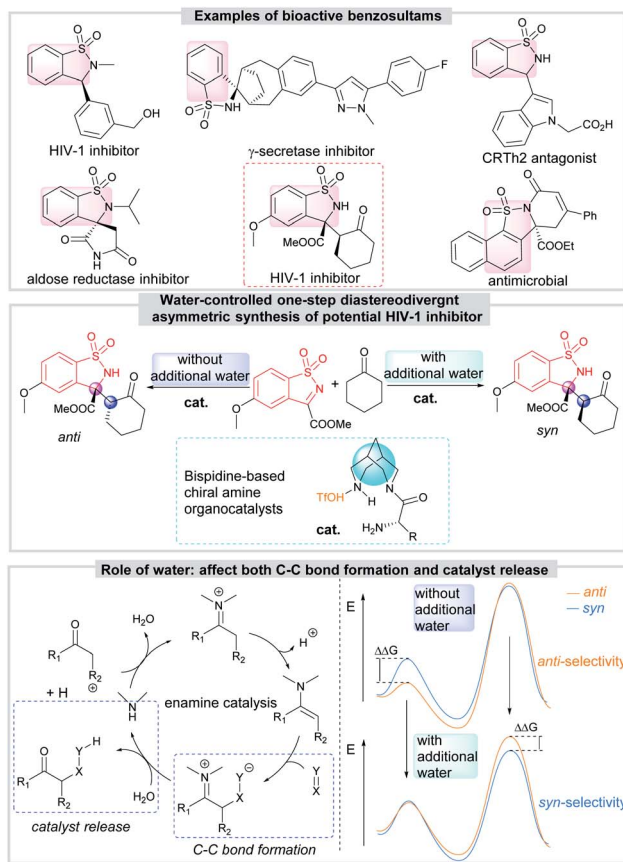
material-economy process with minimum possible expenditure. Diastereodivergent dual catalysis⁴ and cycle-specific catalysis,⁵ controlling different stereocenters in one step or in sequential steps with two different chiral catalysts, have developed as novel concepts. Diastereodivergency with a single catalyst is also developed. Besides elegant studies in metal-based diastereodivergent catalysis,⁶ organocatalysis can achieve diastereodivergency by modulating catalysts⁷ or additives.⁸ Barbas, III,^{7a} Shao,^{7b} Singh,^{7c} Kesavan^{7d} and Chen^{7e} realized the diastereodivergent asymmetric Mannich reactions of imines with aldehydes, hydroxyketones, benzofuran-3-ones and α,α -dicyanoolefins by varying organocatalysts based on amino acids, diamines and cinchona alkaloids. Though some progresses have been achieved, compared with the rapid development of asymmetric catalysis, diastereodivergent asymmetric catalysis is still in its infancy, and more diastereodivergent reactions need to be realized, more strategies need to be developed.

Chiral benzosultams are important compounds possessing interesting biological activities, such as γ -secretase inhibitors, HIV-1 inhibitors and aldose reductase inhibitors (Scheme 1).⁹ Among all the synthetic methods,¹⁰ the catalytic asymmetric reactions about cyclic *N*-sulfonyl ketimines are undoubtedly one of the most convenient and atom-economic one. Up to now, many asymmetric methodologies, including Mannich reaction,¹¹ aza-Friedel-Crafts reaction,¹² annulation,¹³ C(sp³)-H functionalization reaction,¹⁴ addition of organometallic reagents¹⁵ or unsaturated hydrocarbons¹⁶ to imines and so on,¹⁷ have been developed to synthesize various functionalized chiral

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: suzhishan@scu.edu.cn; lililin@scu.edu.cn; Web: http://www.scu.edu.cn/chem_asl/

† Electronic supplementary information (ESI) available: ¹H, ¹³C{¹H} and ¹⁹F{¹H} NMR, HPLC spectra, X-ray crystallographic data for 6. CCDC 2058446, 2002650, 2084361, 2097127 and 2090581. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d2sc00446a





Scheme 1 Diastereodivergent asymmetric Mannich reaction for synthesis of bioactive benzosultams.

benzosultams. However, there is still no diastereodivergent example in this area.

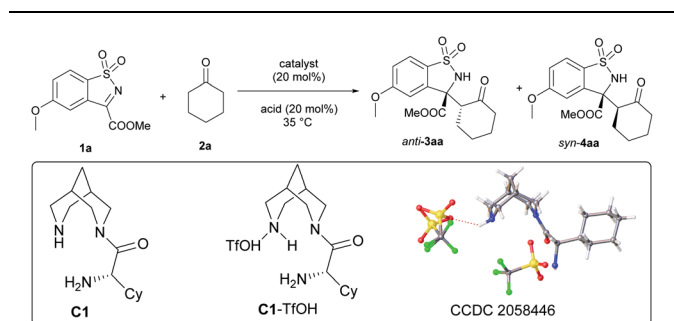
The asymmetric Mannich reaction of cyclic *N*-sulfonyl ketimines with cyclohexanone attracts our attention because it affords directly the chiral benzosultams containing vicinal tetrasubstituted and tertiary carbon stereocenters, more importantly, with *anti*-HIV-1 activity. Though *syn*-selective asymmetric reaction has been achieved by applying a bifunctional amino sulfonylhydrazide as catalyst,^{11a} the diastereodivergent asymmetric version is still not achieved. Developing efficient method to diversify the diastereochemical outcome of the reaction, obtaining both *syn*- and *anti*-products by small change of reaction conditions, is undoubtedly meaningful for further research on drug development. Bispidine-based chiral amines developed by our group show good ability in promoting asymmetric reactions through enamine catalysis.¹⁸ We envisaged such organocatalysts might have the potential to achieve the diastereodivergent goal since they possess unique core and multiple hydrogen-bonding donors and acceptors.

Herein, we report our finding that water can switch the enforced sense of diastereoselectivity when bispidine-based primary amine catalyzes the reaction of cyclic *N*-sulfonyl ketimines with ketones. DFT calculations reveal the diastereodivergent catalysis should be state-determined, and the water reverses the energies of states (Scheme 1).

Results and discussion

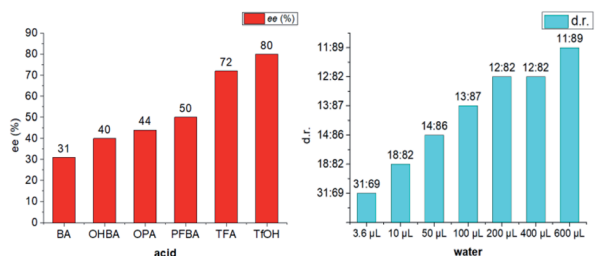
Initially, cyclic *N*-sulfonyl ketimine **1a** and cyclohexanone **2a** were selected as the model substrates to optimize the reaction conditions (Table 1). In our initial study, bispidine-based chiral amine catalysts derived from various amino acids could promote the reaction smoothly with *ortho*-phthalic acid (OPA) as cocatalyst at 35 °C. However, the di- and enantioselectivities were moderate (for details, see the ESI†). Representatively, **C1** derived from cyclohexyl substituted glycine could give **3aa** in near equivalent yield but only 76 : 24 dr and 67% ee (entry 1). Excitedly, when 4 Å molecular sieves (MS) were added to the system, only *anti*-selective Mannich reaction occurred (dr > 19 : 1, entry 2). When various acids as co-catalysts were detected, regularly, the enantioselectivity increased with the increase

Table 1 Optimization of diastereodivergent reaction conditions^a



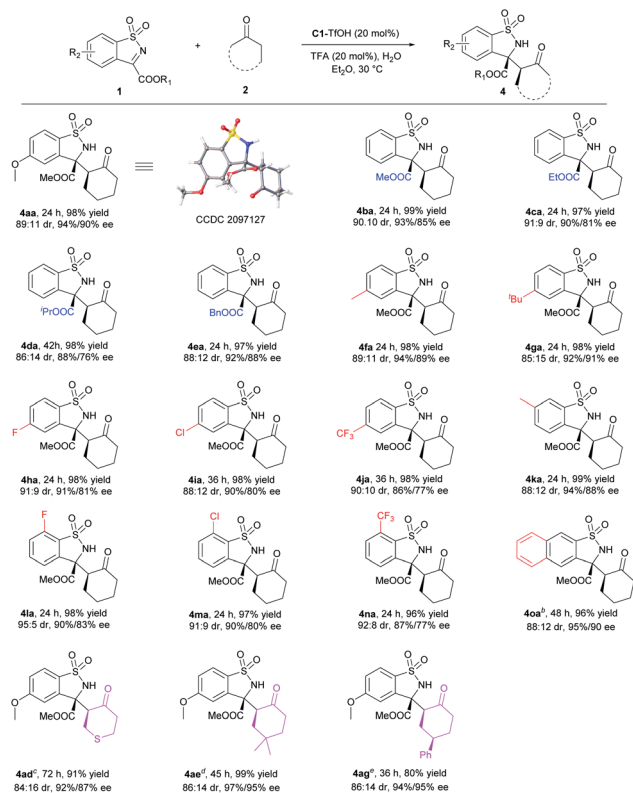
Entry	Catalyst/acid	Solvent	Additive	Yield ^b (%)	dr ^c (3/4)	ee ^c (%)
1	C1/OPA	—	—	99	76 : 24	67/—
2	C1/OPA	—	4 Å MS	95	>19 : 1	44/—
3	C1/TFA	—	4 Å MS	93	>19 : 1	72/—
4	C1/TfOH	—	4 Å MS	95	85 : 15	80/—
5	C1-TfOH/TFA	—	4 Å MS	99	>19 : 1	83/—
6	C1-TfOH/TFA	CH ₂ Cl ₂	4 Å MS	98	>19 : 1	92/—
7	C1-TfOH/TFA	CH ₂ Cl ₂	H ₂ O	99	21 : 79	—/93
8	C1-TfOH/TFA	Et ₂ O	H ₂ O	98	12 : 88	—/93
9	C1-TfOH/TFA	H ₂ O	H ₂ O	98	11 : 89	—/88
10 ^d	C1-TfOH/TFA	Et ₂ O	H ₂ O	98	10 : 90	—/94

left) Effect of acid on *anti*-selective reaction right) Effect of water on *syn*-selective reaction



^a Unless otherwise noted, all reactions were performed with catalyst/acid (1 : 1, 20 mol%), **1a** (0.20 mmol), **2a** (0.6 mL) at 35 °C for 20 h. If additive was added, the amount of 4 Å MS was 20 mg and H₂O was 0.2 mL. If solvent was added, **2a** (0.2 mL) in solvent (0.6 mL) for 12–16 h. ^b Isolated yields of two diastereomers. ^c Determined by SFC analysis on a chiral stationary phase. ^d The reaction was performed at 30 °C for 24 h. BA = benzoic acid; OHBA = *o*-hydroxybenzoic acid; OPA = *o*-phthalic acid; PFBA = pentafluorobenzoic acid; TfOH = trifluoromethanesulfonic acid; TFA = trifluoroacetic acid.

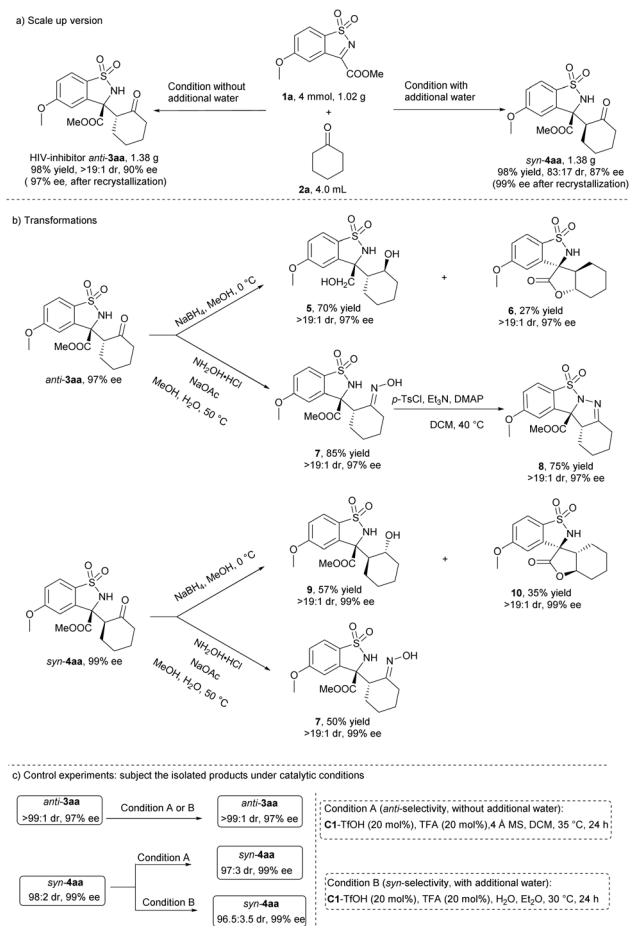


Scheme 3 Substrate scope of *syn*-selective Mannich reaction.

^a Unless otherwise noted, all reactions were performed with catalyst/acid (1 : 1, 20 mol%), **1** (0.20 mmol), **2** (0.2 mL) and H₂O (0.2 mL) in Et₂O (0.6 mL) at 30 °C. All yields were the isolated products of the two diastereomers. The ee values were detected by SFC analysis on a chiral stationary phase and dr values were determined by ¹H NMR analysis. ^b Et₂O (1.0 mL) as the solvent. ^c **2d** was 1.0 mmol, Et₂O (1.0 mL) as the solvent at 35 °C. ^d **2e** was 1.0 mmol, Et₂O (1.0 mL) as the solvent at 30 °C. ^e **2g** was 1.0 mmol, methyl tertiary butyl ether (MTBE, 0.6 mL) and H₂O (0.6 mL) as the solvent at 35 °C.

the more H acceptor or larger steric hindrance. The absolute configuration of **4aa** was determined to be (3*R*,2'*S*) by X-ray crystallography analysis.¹⁹ The newly generated chiral center of **4ag** was determined to be (*R*) by NMR analysis.

To evaluate the synthetic potential of the diastereodivergent method, gram-scale synthesis of potential HIV-1 inhibitors *anti*-**3aa** and *syn*-**4aa** were carried out. As shown in Scheme 4, under respective optimized conditions, 4.0 mmol of cyclic *N*-sulfonyl ketimine **1a** reacted smoothly with 4.0 mL cyclohexanone **2a**, giving 1.38 g (98% yield) of *anti*-**3aa** with >19 : 1 dr and 90% ee (97% ee after single recrystallization), and 1.38 g (98% yield) of *syn*-**4aa** with 83 : 17 dr and 87% ee (99% ee after single recrystallization), separately. Reduction of *anti*-**3aa** in the presence of NaBH₄, both ketone and ester group were reduced, giving the compound **5** in 70% yield with maintained dr and ee value. Spirocyclic product **6** was also obtained in 27% yield, which might be formed through transesterification. The newly generated chiral center was determined to be (*S*) by NMR analysis. Reduction of *syn*-product **4aa** under the same condition gave the compound **9** with ester group in 57% yield and spirocyclic product **10** in 35% yield with maintained dr and ee value. The



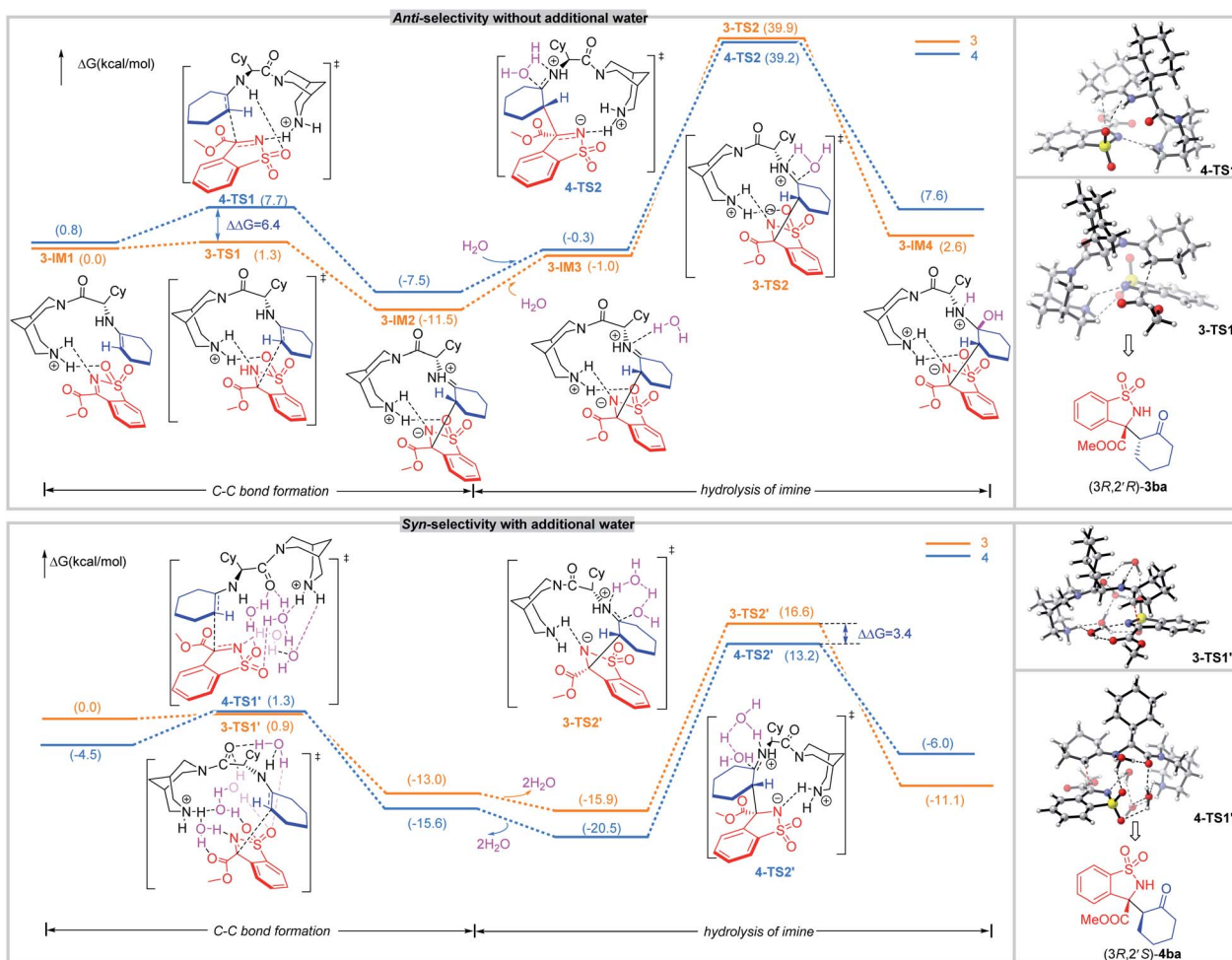
Scheme 4 Scale-up synthesis, further transformations and control experiments.

ester group was more difficult to be reduced, which might be due to the larger steric hindrance of *syn*-**4aa** compared with that *anti*-**3aa**. The product **3aa** could also be converted to oxime **7** in the presence of hydroxylammonium chloride and sodium acetate, and the configuration was determined to be *E* by X-ray crystallography analysis.¹⁹ The oxime **7** could be further converted to hydrazone **8** by tosyl chloride and 4-dimethylaminopyridine. When *syn*-**4aa** was converted in the same condition, *anti*-**7** was obtained, suggesting configuration reversal occurred in the reaction condition.

To understand the mechanism of the reaction, control experiments were conducted (Scheme 4c). Highly pure *anti*-**3aa** (>19 : 1 dr and 97% ee) and *syn*-**4aa** (47 : 1 dr and 99%), which were obtained through recrystallization of the corresponding products isolated from the catalytic system, were subjected under both catalytic conditions. After 24 hours, there was not any or very little change about the dr and ee values of both *anti*- and *syn*-products, which indicated that the diverse diastereochemical outcomes of the reaction came from the catalytic process rather than isomerization of the products in the catalytic conditions.

In addition, density functional theory (DFT) calculations were performed at the M062X-D3/6-31G(d,p) (SMD, CH₂Cl₂)





Scheme 5 DFT calculations for diastereodivergent and enantioselective mechanism.

level of theory (Scheme 5). In the catalytic system without additional water, **1b** interacts with the enamine species generated by condensation between the primary amine of catalyst and cyclohexanone **2a**. Then, the C–C bond is constructed *via* transition state **3-TS1** and **4-TS1**. For **3-TS1**, the H-bonds between protonated hydrogen on piperidine of catalyst and the nitrogen atom on the imine as well as the oxygen atom on a sulfonyl group, fix the *N*-sulfonyl ketimine so that the bispidine **C1** can interact with two substrates at the same time. The regeneration of catalyst is predicted to be the rate-determining step (RDS). So, the pre-steps should be fully equilibrated, and the diastereoselectivity should be determined by more stable states. By calculation, the states to form *anti*-products are more stable, typically, the ΔG of **3-TS1** is lower than that of **4-TS1** by $6.4 \text{ kcal mol}^{-1}$. In **3-TS1**, the enamine and the *N*-sulfonyl ketimine react both with *Si*-faces, leading to **(3*R*,2'*R*)-3ba**.

To get insight into the effect of water on the diastereoselectivity, the reaction mechanism in the presence of additional water was studied. In the chiral controlling C–C bond formation step, the optimized geometries of key intermediates and transition states with one to four water molecules in the structures were located (for details, see the ESI[†]). The relative

energy difference of the two competing transition states **3-TS1'** and **4-TS1'** decreased, especially for those with four waters. In addition, waters can also accelerate the re-generation of catalyst by decreasing the activation barrier in the hydrolysis of imine step. The states to form *syn*-product are more stable, for example, the ΔG of **4-TS2'** is lower than that of **3-TS2'** by $3.4 \text{ kcal mol}^{-1}$, so *syn*-**4** is predominantly formed in the presence of water. In **4-TS1'**, the enamine reacts with the *N*-sulfonyl ketimine with its *Re*-face from the *Si*-face of the latter, leading to **(3*R*,2'*S*)-4ba**.

Conclusions

We realize a bispidine-based amine-catalyzed diastereodivergent asymmetric Mannich reaction of cyclic *N*-sulfonyl ketimines with ketones through additional water switching the enforced sense of diastereoselectivity. Both *syn*- and *anti*-benzosultams with potential *anti*-HIV-1 activity are obtained in good to excellent yields, good to excellent dr and ee. DFT calculations support that the additional water is more likely through reversing the energies of states in the C–C bond formation and hydrolysis of imine steps to switch the



diastereoselectivity. The methodology offers a new idea for diastereoselective modulation, which is valuable for organic synthesis and drug research. Further efforts will be devoted to realizing more diastereodivergent catalytic asymmetric reactions.

Data availability

Further details of experimental procedure, ^1H , $^{13}\text{C}\{^1\text{H}\}$ and $^{19}\text{F}\{^1\text{H}\}$ NMR, SFC spectra, CD spectra, computational methods and X-ray crystallographic data are available in the ESI.†

Author contributions

G. L. L. performed the experiments. H. K. Z. repeated data. Y. Z. and Z. S. S. conducted the DFT calculations. X. M. F. and L. L. L. supervised the project. G. L. L. and L. L. L. co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We appreciate the National Natural Science Foundation of China (No. 22171189, 21871188 and 21973066) for financial support. We are grateful to Dr Yuqiao Zhou from College of Chemistry, Sichuan University for the X-ray single crystal diffraction analysis.

Notes and references

- (a) E. M. Carreira and L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley, Weinheim, 2009; (b) E. N. Jacobsen, A. Pfaltz and H. Yamamoto, *Comprehensive Asymmetric Catalysis, Supplements I and II*, Springer, New York, 1999, vol. I-III; (c) E. M. Carreira and H. Yamamoto, *Comprehensive Chirality*, Elsevier Science, Amsterdam, 2012, vol. 1-9.
- (a) K. Jozwiak, W. J. Lough and I. W. Wainer, *Drug Stereochemistry: Analytical Methods and Pharmacology*, Informa, New York, 2012; (b) K. M. Rentsch, *J. Biochem. Biophys. Methods*, 2002, **54**, 1; (c) B. M. Trost, *Science*, 1983, **219**, 245.
- For selected reviews of diastereodivergent synthesis, see: (a) L. L. Lin and X. M. Feng, *Chem.-Eur. J.*, 2017, **23**, 6464; (b) S. Krautwald and E. M. Carreira, *J. Am. Chem. Soc.*, 2017, **139**, 5627; (c) M. Bihani and J. C.-G. Zhao, *Adv. Synth. Catal.*, 2017, **359**, 534; (d) G. Zhan, W. Du and Y.-C. Chen, *Chem. Soc. Rev.*, 2017, **46**, 1675; (e) I. P. Beletskaya, C. Nájera and M. Yus, *Chem. Rev.*, 2018, **118**, 5080.
- For selected examples of stereodivergent dual catalysis, see: (a) S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science*, 2013, **340**, 1065; (b) S. Krautwald, M. A. Schafroth, D. Sarlah and E. M. Carreira, *J. Am. Chem. Soc.*, 2014, **136**, 3020; (c) X. Huo, R. He, X. Zhang and W. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 11093; (d) F. A. Cruz and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 1029; (e) X. Jiang, J. J. Beiger and J. F. Hartwig, *J. Am. Chem. Soc.*, 2017, **139**, 87; (f) L. Wei, Q. Zhu, S.-M. Xu, X. Chang and C.-J. Wang, *J. Am. Chem. Soc.*, 2018, **140**, 1508; (g) Q. Zhang, H. Yu, L. Shen, T. Tang, D. Dong, W. Chai and W. Zi, *J. Am. Chem. Soc.*, 2019, **141**, 14554; (h) M.-M. Zhang, Y.-N. Wang, B.-C. Wang, X.-W. Chen, L.-Q. Lu and W.-J. Xiao, *Nat. Commun.*, 2019, **10**, 2716; (i) S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc and F. Glorius, *Nat. Catal.*, 2020, **3**, 48; (j) B. Kim, Y. Kim and S. Y. Lee, *J. Am. Chem. Soc.*, 2021, **143**, 73; (k) S.-Q. Yang, Y.-F. Wang, W.-C. Zhao, G.-Q. Lin and Z.-T. He, *J. Am. Chem. Soc.*, 2021, **143**, 7285.
- For selected examples of cycle-specific catalysis, see: (a) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051; (b) B. Wang, F. Wu, Y. Wang, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2007, **129**, 768; (c) Y. Chi, S. T. Scroggins and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2008, **130**, 6322; (d) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2009, **48**, 9834; (e) J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang and W.-H. Hu, *J. Am. Chem. Soc.*, 2011, **133**, 8428; (f) N. K. Rana, H. Huang and J. C.-G. Zhao, *Angew. Chem., Int. Ed.*, 2014, **53**, 7619; (g) S.-L. Shi, Z. L. Wong and S. L. Buchwald, *Nature*, 2016, **532**, 353; (h) D. Lotter, A. Castrogiovanni, M. Neuburger and C. Sparr, *ACS Cent. Sci.*, 2018, **4**, 656; (i) Y. Kwon, A. J. Chinn, B. Kim and S. J. Miller, *Angew. Chem., Int. Ed.*, 2018, **57**, 6251; (j) B. M. Trost, C.-I. (Joey) Hung, T. Saget and E. Gnanamani, *Nat. Catal.*, 2018, **1**, 523; (k) X.-J. Liu, S. Jin, W.-Y. Zhang, Q.-Q. Liu, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2020, **59**, 2039; (l) D.-X. Zhu, J.-G. Liu and M.-H. Xu, *J. Am. Chem. Soc.*, 2021, **143**, 8583.
- For selected examples of metal-based diastereodivergent catalysis, see: (a) X.-X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X.-L. Hou and Y. D. Wu, *J. Am. Chem. Soc.*, 2008, **130**, 14362; (b) A. Nojiri, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 3779; (c) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2011, **50**, 4382.
- For selected examples of diastereodivergent synthesis by modulating catalysts, see: (a) S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2006, **128**, 1040; (b) J. Dai, D. Xiong, T. Yuan, J. Liu, T. Chen and Z. Shao, *Angew. Chem., Int. Ed.*, 2017, **56**, 12697; (c) V. Bisai, R. A. Unhale, A. Suneja, S. Dhanasekaran and V. K. Singh, *Org. Lett.*, 2015, **17**, 2102; (d) K. Sivamuthuraman and V. Kesavan, *J. Org. Chem.*, 2018, **83**, 8936; (e) X.-F. Xiong, Z.-J. Jia, W. Du, K. Jiang, T.-Y. Liu and Y.-C. Chen, *Chem. Commun.*, 2009, 6994; (f) Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman and L. Deng, *J. Am. Chem. Soc.*, 2007, **129**, 6364; (g) X. Feng, Z. Zhou, R. Zhou, Q.-Q. Zhou, L. Dong and Y.-C. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 19942; (h) C. Verrier and P. Melchiorre, *Chem. Sci.*, 2015, **6**, 4242; (i) Y. Wei, S. Wen,



- Z. Liu, X. Wu, B. Zeng and J. Ye, *Org. Lett.*, 2015, **17**, 2732; (j) D. Uraguchi, K. Yoshioka and T. Ooi, *Nat. Commun.*, 2017, **8**, 14793; (k) S. B. J. Kan, H. Maruyama, M. Akakura, T. Kano and K. Maruoka, *Angew. Chem., Int. Ed.*, 2017, **56**, 9487; (l) P.-G. Ding, F. Zhou, X. Wang, Q.-H. Zhao, J.-S. Yu and J. Zhou, *Chem. Sci.*, 2020, **11**, 3852.
- 8 For selected examples of diastereodivergent synthesis by modulating additives, see:(a) J. Gao, S. Bai, Q. Gao, Y. Liu and Q. Yang, *Chem. Commun.*, 2011, **47**, 6716; (b) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo and P. Melchiorre, *J. Am. Chem. Soc.*, 2011, **133**, 17934; (c) A. Martinez-Castaneda, H. Rodriguez-Solla, C. Concellon and V. del Amo, *J. Org. Chem.*, 2012, **77**, 10375.
- 9 For selected examples of various bioactive molecules and natural products, see:(a) J. Wrobel, A. Dietrich, S. A. Woolson, J. Millen, M. McCaleb, M. C. Harrison, T. C. Hohman, J. Sredy and D. Sullivan, *J. Med. Chem.*, 1992, **35**, 4613; (b) R. J. Cherney, R. Mo, D. T. Meyer, K. D. Hardman, R.-Q. Liu, M. B. Covington, M. Qian, Z. R. Wasserman, D. D. Christ, J. M. Trzaskos, R. C. Newton and C. P. Decicco, *J. Med. Chem.*, 2004, **47**, 2981; (c) J. De Vicente, R. T. Hendricks, D. B. Smith, J. B. Fell, J. Fischer, S. R. Spencer, P. J. Stengel, P. Mohr, J. E. Robinson, J. F. Blake, R. K. Hilgenkamp, C. Yee, G. Adjabeng, T. R. Elworthy, J. Li, B. H. Wang, J. T. Bamberg, S. F. Harris, A. Wong, V. J. Leveque, I. Najera, S. Le Pogam, S. Rajyaguru, G. Ao-Ieong, L. Alexandrova, S. Larrabee, M. Brandl, A. Briggs, S. Sukhtankar and R. Farrell, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5652; (d) G. J. Wells, M. Tao, K. A. Josef and R. Bihovsky, *J. Med. Chem.*, 2001, **44**, 3488; (e) Y. Takeuchi and Z. Liu, *Heterocycles*, 2002, **56**, 693; (f) A. Jirgensons, G. Leitis, I. Kalvinsh, D. Robinson, P. Finn, N. Khan, Patent Appl. WO2008142376 A1, 2008; (g) J. Mao and D. C. Baker, *US pat.*, 6458962B1, 2003.
- 10 For selected review of synthesis of benzosultams, see: Q.-Q. Zhao and X.-Q. Hu, *Molecules*, 2020, **25**, 4367.
- 11 For selected examples of Mannich reaction, see:(a) S. Zhang, L. J. Li, Y. B. Hu, Z. G. Zha, Z. Y. Wang and T.-P. Loh, *Org. Lett.*, 2015, **17**, 1050; (b) B. K. Qiao, Y.-J. Huang, J. Nie and J.-A. Ma, *Org. Lett.*, 2015, **17**, 4608; (c) H.-X. Duan, Y. Zhang, Z.-Z. Zhang and Y.-Q. Wang, *J. Org. Chem.*, 2020, **85**, 11331; (d) J. Lv, J. Xu, X. Pan, Z. Jin and Y. R. Chi, *Sci. China: Chem.*, 2021, **64**, 985; (e) L. Xie, H. Ma, J. Li, Y. Yu, Z. Qin and B. Fu, *Org. Chem. Front.*, 2017, **4**, 1858; (f) Q. Shao, L. Wu, J. Chen, I. D. Gridnev, G. Yang, F. Xie and W. Zhang, *Adv. Synth. Catal.*, 2018, **360**, 4625; (g) M. Zhou, Q. Su, Y. Addepalli, Y. He and Z. Wang, *Org. Biomol. Chem.*, 2018, **16**, 2923; (h) S. Nakamura, M. Sano, A. Toda, D. Nakane and H. Masuda, *Chem.-Eur. J.*, 2015, **21**, 1; (i) H. Zhang, C. Jiang, J.-P. Tan, H.-L. Hu, Y. Chen, X. Ren, H.-S. Shang and T. Wang, *ACS Catal.*, 2020, **10**, 5698; (j) S. Zhang, L. Li, L. Xin, W. Liu and K. Xu, *J. Org. Chem.*, 2017, **82**, 2399.
- 12 For selected examples of the aza-Friedel-Crafts reaction, see:(a) L. Wu, R. R. Liu, G. Zhang, D. J. Wang, H. Wu, J. Gao and Y. X. Jia, *Adv. Synth. Catal.*, 2015, **357**, 709; (b) L. Wang, A. Rahman and X. Lin, *Org. Biomol. Chem.*, 2017, **15**, 6033; (c) B. B. Huang, L. Wu, R. R. Liu, L. L. Xing, R. X. Liang and Y. X. Jia, *Org. Chem. Front.*, 2018, **5**, 929.
- 13 For selected examples of addition of annulation, see:(a) R. R. Liu, J.-P. Hu, J.-J. Hong, C.-J. Lu, J.-R. Gao and Y.-X. Jia, *Chem. Sci.*, 2017, **8**, 2811; (b) P. Wonneberger, N. König, F. B. Kraft, M. B. Sárosi and E. Hey-Hawkins, *Angew. Chem., Int. Ed.*, 2019, **58**, 3208; (c) B. S. Li, Y. Wang, Z. Jin, P. Zheng, R. Ganguly and Y. R. Chi, *Nat. Commun.*, 2015, **6**, 6207; (d) X. Wang, M. Lu, Q. Su, M. Zhou, Y. Addepalli, W. Yao, Z. Wang and Y. Lu, *Chem.-Asian J.*, 2019, **14**, 3409; (e) M. Rommel, T. Fukuzumi and J. W. Bode, *J. Am. Chem. Soc.*, 2008, **130**, 17266; (f) A. G. Kravina, J. Mahatthananchai and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 9433; (g) X. Y. Chen, Z. H. Gao, C. Y. Song, C. L. Zhang, Z. X. Wang and S. Ye, *Angew. Chem., Int. Ed.*, 2014, **53**, 11611; (h) P. Zheng, S. Wu, C. Mou, W. Xue, Z. Jin and Y. R. Chi, *Org. Lett.*, 2019, **21**, 5026; (i) Y.-H. Chen, X.-J. Lv, Z.-H. You and Y.-K. Liu, *Org. Lett.*, 2019, **21**, 5556.
- 14 For selected examples of C(sp³)-H functionalization reaction, see:(a) Y. Li, M. Lei and L. Gong, *Nat. Catal.*, 2019, **2**, 1016; (b) W. K. Weigel, H. T. Dang, H.-B. Yang and D. B. C. Martin, *Chem. Commun.*, 2020, **56**, 9699.
- 15 For selected examples of addition of organometallic reagents to imines, see:(a) T. Nishimura, A. Noishiki, G. C. Tsui and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 5056; (b) H. Wang, T. Jiang and M. H. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 971; (c) C. Jiang, Y. Lu and T. Hayashi, *Angew. Chem., Int. Ed.*, 2014, **53**, 9936; (d) Y. Álvarez-Casao, D. Monge, E. Álvarez and R. Fernández, *Org. Lett.*, 2015, **17**, 5104; (e) M. Quan, X. Wang, L. Wu, I. D. Gridnev, G. Yang and W. Zhang, *Nat. Commun.*, 2018, **9**, 2258; (f) Z. Qiu, Y. Li, Z. Zhang and D. Teng, *Transition Met. Chem.*, 2019, **44**, 649; (g) M. F. Li, A.-Q. Miao, H.-Y. Zhu, R. Wang, W.-J. Hao, S.-J. Tu and B. Jiang, *J. Org. Chem.*, 2020, **85**, 13602.
- 16 For selected examples of addition of unsaturated hydrocarbons to imines, see:(a) R.-R. Liu, D.-J. Wang, L. Wu, B. Xiang, G.-Q. Zhang, J.-R. Gao and Y.-X. Jia, *ACS Catal.*, 2015, **5**, 6524; (b) K. Morisak, M. Sawa, R. Yonesaki, H. Morimoto, K. Mashima and T. Ohshima, *J. Am. Chem. Soc.*, 2016, **138**, 6194; (c) Z. Liang, S. Singh, F. Xie, L. Wu and W. Zhang, *Chem. Commun.*, 2017, **53**, 5364.
- 17 For selected examples, see:(a) J. Pan, J.-H. Wu, H. Zhang, X. Ren, J. P. Tan, L. Zhu, H. S. Zhang, C. Jiang and T. Wang, *Angew. Chem., Int. Ed.*, 2019, **58**, 7425; (b) Y. Yao, J.-L. Li, Q.-Q. Zhou, L. Dong and Y.-C. Chen, *Chem.-Eur. J.*, 2013, **19**, 9447; (c) Y. Li, K. Zhou, Z. Wen, S. Cao, X. Shen, M. Lei and L. Gong, *J. Am. Chem. Soc.*, 2018, **140**, 15850; (d) L. Z. Hou, T. F. Kang, L. K. Yang, W. D. Cao and X. M. Feng, *Org. Lett.*, 2020, **22**, 1390; (e) H. B. Hepburn and H. W. Lam, *Angew. Chem., Int. Ed.*, 2014, **53**, 11605; (f) C. A. Osborne, T. B. D. Endean and E. R. Jarvo, *Org. Lett.*, 2015, **17**, 5340; (g) J. Kim, M. Shin and S. H. Cho, *ACS Catal.*, 2019, **9**, 8503; (h) J. Wang, Q. Zhang, B. Zhou, C. Yang, X. Li and J.-P. Cheng, *iScience*, 2019, **16**, 511.



- 18 For selected examples of bispidine-based chiral amines, see: (a) J. Liu, Z. G. Yang, Z. Wang, F. Wang, X. H. Chen, X. H. Liu, X. M. Feng, Z. S. Su and C. W. Hu, *J. Am. Chem. Soc.*, 2008, **130**, 5654; (b) Z. G. Yang, J. Liu, X. H. Liu, Z. Wang, X. M. Feng, Z. S. Su and C. W. Hu, *Adv. Synth. Catal.*, 2008, **350**, 2001; (c) J. Liu, Z. G. Yang, X. H. Liu, Z. Wang, Y. L. Liu, S. Bai, L. L. Lin and X. M. Feng, *Org. Biomol. Chem.*, 2009, **7**, 4120; (d) G. L. Li, M. H. Z. Liu, S. J. Zou, X. M. Feng and L. L. Lin, *Org. Lett.*, 2020, **22**, 8708.
- 19 CCDC number 2058446 (**C1-2TfOH**); CCDC 2002650 (**3aa**); CCDC 2084361 (**4aa**); CCDC 2097127 (**3ah**); CCDC 2090581 (**7**) contain the supplementary crystallographic data for this paper.

