EDGE ARTICLE

Check for updates

All publication charges for this article have been paid for by the Royal Society of Chemistry

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 [iD] * and Lili Lin [iD] *

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.

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 dia- 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.
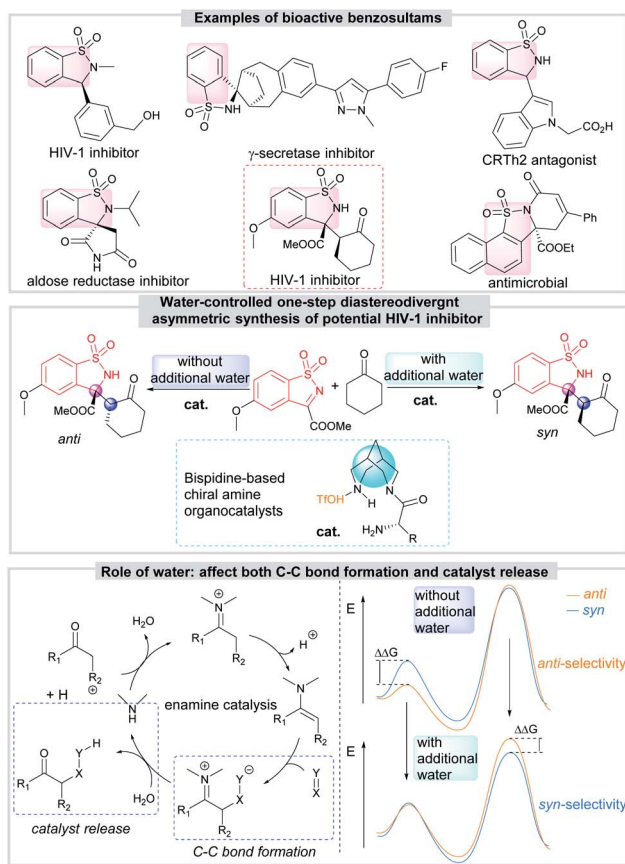
Diastereodivergent asymmetric catalysis[3] is attractive and challenging because it aims to generate different chiral diastereomers starting from the same substrates just by small variation of reaction conditions, which is undoubtedly a starting material-economy process with minimum possible expenditure. Diastereodivergent dual catalysis[4] 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 catalysts[7] 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 reagents[15] or unsaturated hydrocarbons[16] 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 sulfonohydrazide 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).
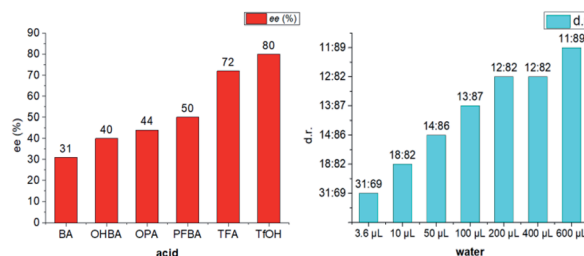
Results and discussion

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 dia- and enantioselectivities were moderate (for details, see the ESI†). Representatively, **C1** derived from cyclohexyl substituted glycine could gave **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	CH₂Cl₂	4 Å MS	98	>19 : 1	92/—
7	C1-TfOH/TFA	CH₂Cl₂	H₂O	99	21 : 79	—/93
8	C1-TfOH/TFA	Et₂O	H₂O	98	12 : 88	—/93
9	C1-TfOH/TFA	H₂O	H₂O	98	11 : 89	—/88
10[d]	C1-TfOH/TFA	Et₂O	H₂O	98	10 : 90	—/94

left) Effect of acid on *anti*-selective reaction   right) Effect of water on *syn*-selective reaction
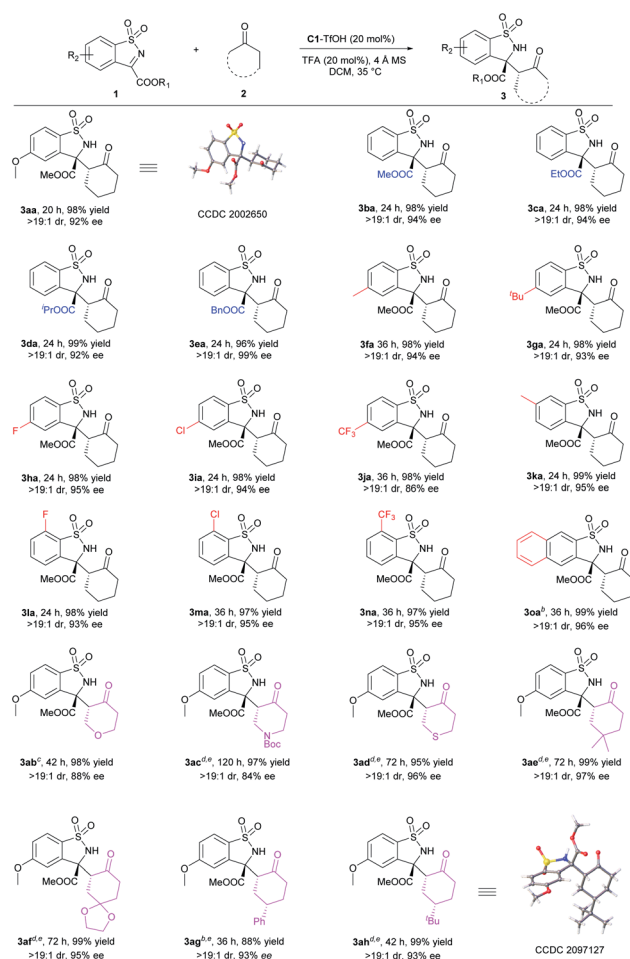
[a] Unless otherwise noted, all reactions were performed with catalyst/acid (1 : 1, 20 mol%), **1a** (0.20 mmol), **2a** (0.6 mL) at 35 °C for 20 h. If additive was added, the amount of 4 Å MS was 20 mg and H₂O was 0.2 mL. If solvent was added, **2a** (0.2 mL) in solvent (0.6 mL) for 12–16 h. [b] Isolated 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.

of acidity (bottom, left histogram). When trifluoroacetic acid (TFA) was applied as co-catalyst, the ee value of major product was improved to 72% (entry 3). Exceptionally, trifluoromethanesulfonic acid (TfOH) gave 85 : 15 dr although it could further improve ee value (entry 4). With *in situ* prepared **C1**-TfOH as catalyst and trifluoroacetic acid as cocatalyst, the ee value was improved to 83% (entry 5). Undergoing in dichloromethane, the reaction afforded *anti*-**3aa** in 98% yield with >19 : 1 dr and 92% ee (entry 6). Analyzing the experimental data, we guess the influence of 4 Å MS and TfOH on dr might be caused by their water-absorbing quality. The 4 Å MS decreased the effect of water on diastereoselectivity, differently, TfOH increased the effect of water on diastereoselectivity.

Realizing trace amount of water might greatly affect the diastereoselectivity, we wondered whether *syn*-selective Mannich reaction could be achieved if additional water was added to the system. Exhilaratingly, reversion of diastereoselectivity really happened. When 0.2 mL water was added, *syn*-**4aa** was obtained as the major product with 79 : 21 dr and 93% ee (entry 7). The diastereoselectivity could be improved to 88 : 12 when the solvent changed from dichloromethane to ether (entry 8). Regularly, the diastereoselectivity increased with the increase of the amount of water (bottom, right histogram). It is worth mentioning that this reaction could take place even in aqueous phase though the ee value of **4aa** was slightly decreased (entry 9). Finally, the diastereoselectivity further increased to 90 : 10 when the temperature was adjusted to 30 °C (entry 10).

With the optimal conditions in hand, the substrate scope was then investigated. For the *anti*-selective Mannich reaction, all *anti*-**3** were obtained with dr > 19 : 1 (Scheme 2). The steric hindrance of ester group in cyclic *N*-sulfonyl ketimine displayed a limited influence on either the reactivity or the stereoselectivity (**3ba**–**3ea**). Next, various substituents on aromatic ring of *N*-sulfonyl ketimines were tested. Regardless of the steric or electronic effect of the substituents at C5 position, all the corresponding *anti*-benzosultams could be obtained smoothly with good results (**3fa**–**3ja**, 98% yields, >19 : 1 dr, and 86–95% ee). Limited by the synthesis method, *N*-sulfonyl ketimines with electron-donating substituent at C6 position and with electron-withdrawing substituent at C7 position could be obtained. They transformed to the corresponding **3ka**–**3na** in excellent yields and excellent ee values. Naphthyl **3o** could also transform to the corresponding product in 99% yield, >19 : 1 dr and 96% ee. Varation of ketones showed that six-membered cyclic ketones **2b**–**2d** containing heteroatom and **2e**–**2h** with substituents at C4 position were all suitable substrates. By reacting with *N*-sulfonyl ketimine **1a**, the corresponding **3ab**–**3ah** were delivered in good to excellent yields with good dr and ee. When **2g** and **2h** were applied, desymmetrization occurred and three stereocenters formed in excellent stereoselectivity. Regretfully, other ketones, such as cyclobutanone, cyclopentanone, cycloheptanone and acyclic ketones, were not suitable. Low stereoselectivities or trace amounts of products were given (for details, see ESI†). The absolute configuration of **3aa** was determined to be (3*R*,2′*R*) by X-ray crystallography analysis,[19] and the configurations of other products were assigned to be (3*R*,2′*R*) by comparison with the CD spectrum of compound **3aa**. The newly generated chiral
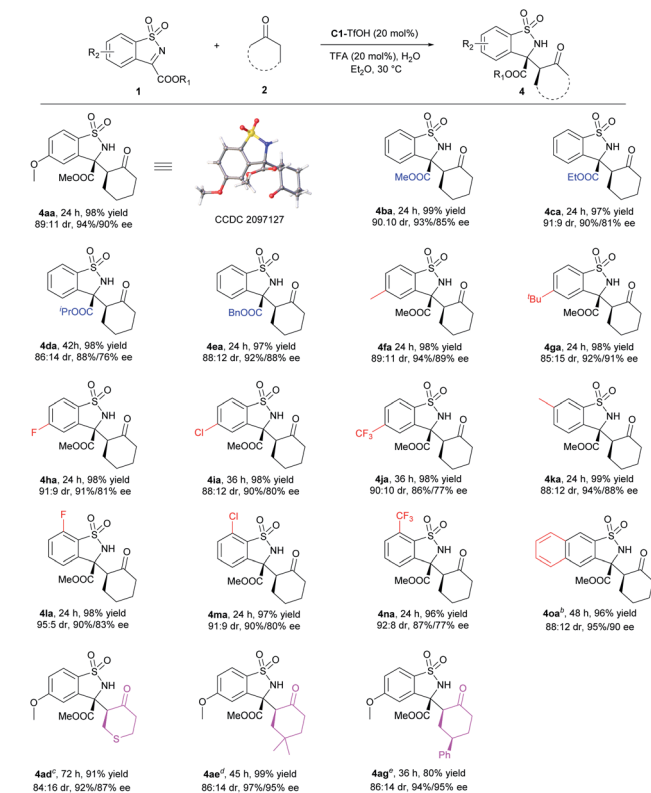

Scheme 2 Substrate scope of *anti*-selective Mannich reaction. *a* Unless otherwise noted, all reactions were performed with catalyst/acid (1 : 1, 20 mol%), **1** (0.20 mmol), **2** (0.2 mL) and 4 Å MS (20 mg) in CH₂Cl₂ (0.6 mL) at 35 °C. All yields were the isolated products of the two diastereomers. The ee values were detected by SFC analysis on a chiral stationary phase and dr values were determined by ¹H NMR analysis. *b* CH₂Cl₂ (1.0 mL) as the solvent. *c* CH₂ClCH₂Cl (0.6 mL) as the solvent at 40 °C. *d* CH₂ClCH₂Cl (1.0 mL) as the solvent at 40 °C. *e* Solid ketones were 1.0 mmol.

centers of **3ag** and **3ah** were determined to be (*S*) by X-ray crystallography analysis or NMR analysis.[19]
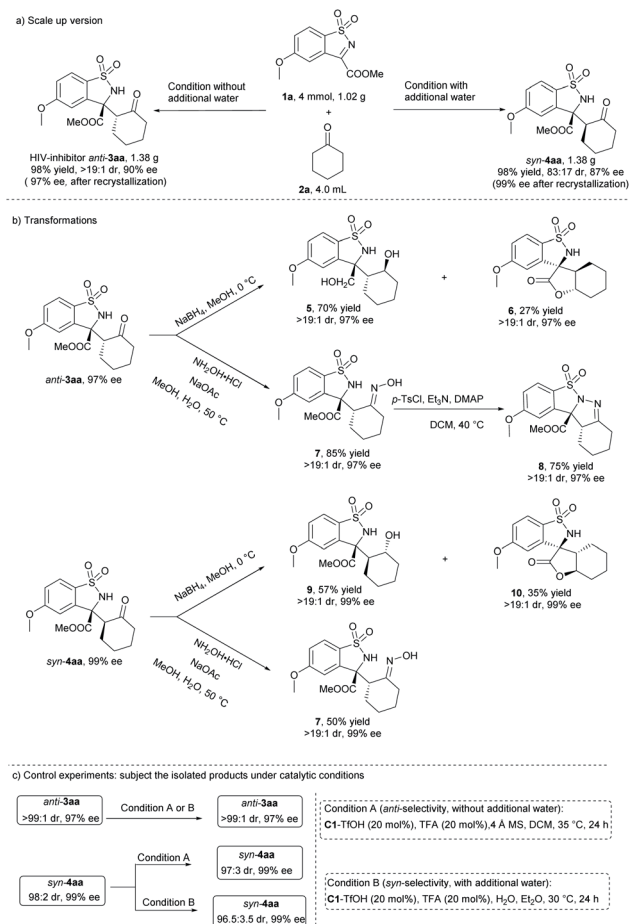
Subsequently, the substrate scope of *syn*-selective Mannich reaction was investigated (Scheme 3). Similarly, ester groups and both electron-donating and electron-withdrawing substituents on phenyl ring of ketimines had no significant effect on the reactivity and stereoselectivity. Various *syn*-benzosultams **4aa**–**4oa** were obtained in excellent yields with good to excellent dr and ee values (96–99% yields, 85 : 15–95 : 5 dr, and 86–95% ee). When cyclic ketones were examined, the heterocyclic tetrahydrothiopyran-4-one **2d**, 4-dimethyl cyclohexanone **2e** and 4-phenyl cyclohexanone **2g** could smoothly form *syn*-**4ad**–**4ag** in good to excellent yields, good dr and excellent ee. Ketones **2b**, **2c**, **2f** with O or N hetero atom and **2h** with bulky *t*Bu group proceeded mainly *anti*-selective Mannich reaction under this condition (for details, see the ESI†), which might be caused by

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 H_2O (0.2 mL) in Et_2O (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] Et_2O (1.0 mL) as the solvent. [c] **2d** was 1.0 mmol, Et_2O (1.0 mL) as the solvent at 35 °C. [d] **2e** was 1.0 mmol, Et_2O (1.0 mL) as the solvent at 30 °C. [e] **2g** was 1.0 mmol, methyl tertiary butyl ether (MTBE, 0.6 mL) and H_2O (0.6 mL) as the solvent at 35 °C.

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

the more H acceptor or larger steric hindrance. The absolute configuration of **4aa** was determined to be (3R,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 $NaBH_4$, both ketone and ester group were reduced, gaving 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
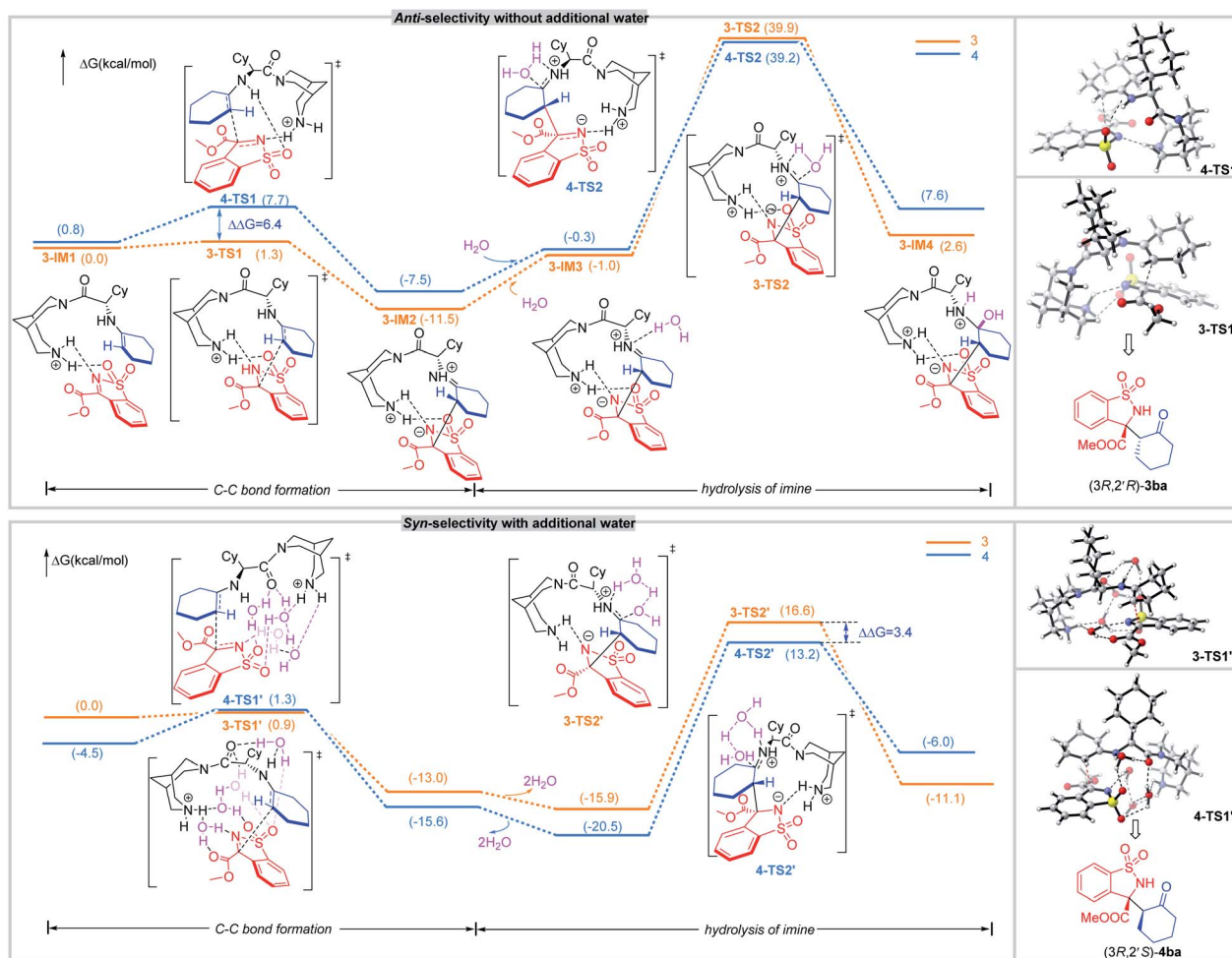
ester group was more difficult to be reduced, which might be due to the larger steric hindrance of *syn*-**4aa** compared with that *anti*-**3aa**. The product **3aa** could also be converted to oxime **7** in the presence of hydroxylammonium chloride and sodium acetate, and the configuration was determined to be *E* by X-ray crystallography analysis.[19] The oxime **7** could be further converted to hydrazone **8** by tosyl chloride and 4-dimethylamino-pyridine. 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 recrystalization 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, CH_2Cl_2)

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 kcal mol^{-1}. In **3-TS1**, the enamine and the *N*-sulfonyl ketimine react both with *Si*-faces, leading to $(3R,2'R)$-**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 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 $(3R,2'S)$-**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, ^{1}H, ^{13}C$\{^1$H$\}$ and ^{19}F $\{^1$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

Notes and references

1 (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.

2 (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.

3 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.

4 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.

5 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.

6 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.

7 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.