Diastereodivergent chiral aldehyde catalysis for asymmetric 1,6-conjugated addition and Mannich reactions

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Chiral aldehyde catalysis is a burgeoning strategy for the catalytic asymmetric α-functionalization of aminomethyl compounds. However, the reaction types are limited and to date include no examples of stereodivergent catalysis. In this work, we disclose two chiral aldehyde-catalysed diastereodivergent reactions: a 1,6-conjugate addition of amino acids to para-quinone methides and a bio-inspired Mannich reaction of pyridinylmethanamines and imines. Both the syn- and anti-products of these two reactions can be obtained in moderate to high yields, diastereo- and enantioselectivities. Four potential reaction models produced by DFT calculations are proposed to explain the observed stereoselective control. Our work shows that chiral aldehyde catalysis based on a reversible imine formation principle is applicable for the α-functionalization of both amino acids and aryl methylamines, and holds potential to promote a range of asymmetric transformations diastereoselectively.

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Compounds containing multiple stereocentres can be found extensively in natural products, drugs and biology. Both the absolute and relative configuration of stereocentres can greatly affect biological activity. Selective access to all stereoisomers is important to chemists, biologists and pharmacologists alike. Over recent decades, great strides in asymmetric synthesis have been made with biocatalysis, transition metal catalysis and organocatalysis. Those achievements have led to numerous methods for the enantioselective synthesis of optically active molecules. Generally, the absolute configuration of the product can be controlled by choice of the enantiomer of the chiral catalyst. The selective generation of individual diastereomers is often more challenging; typically, one diastereomer is inherently preferred, and other diastereomers cannot be efficiently produced via the same strategy. Diastereodivergent catalysis is a wonderful concept which can overcome this diastereoselective bias in the chiral induction process. To date, several elegant catalytic asymmetric diastereodivergent strategies have been disclosed. Diastereodivergence in asymmetric catalysis has been achieved by changing reaction conditions and reaction procedures, or by employing an entirely different catalytic system. Many reports of diastereodivergence are serendipitous, but catalyst-induced diastereodivergence is more predictable and, as a result, more useful. Several elegant catalytic asymmetric diastereodivergent reactions controlled by either a single catalyst or two catalysts have been disclosed in recent years.

Chiral aldehyde catalysis is a burgeoning strategy for the creation of novel asymmetric reactions of amines, especially for the catalytic asymmetric α-functionalization of aminomethyl compounds. However, only four reactions have been successfully realised using this strategy, all of which employed amino acids as the sole type of nucleophiles. The chiral aldehyde-catalysed α-functionalization of aryl or alkyl-substituted aminomethyl compounds has not been reported, and no examples of diastereodivergence in chiral aldehyde catalysis have been disclosed. In 2014, we reported that chiral binaphthyl (BINOL)-derived 3-formyl aldehyde catalysed α-alkylation of 2-aminoalonates with 3-indolymethanols. In 2018, we reported another chiral aldehyde, 2-formyl BINOL aldehyde, catalysed nucleophilic addition of glycine derivatives to α,β-unsaturated ketones (Fig. 1). An investigation into the mechanism of these transformations indicated that both chiral aldehydes I and II use the formyl moiety to activate donors and the hydroxyl moiety to activate acceptors. Interestingly, the distribution of these two key moieties related to stereoselective control was conformationally distinct in chiral aldehydes I and II.

As shown in Fig. 1, by fixing the formyl plane and observing from the bottom, the Brønsted acid site (2′ hydroxyl) of chiral aldehyde I resides above the plane. Conversely, the steric hindrance group (R) is above in chiral aldehyde II. To navigate possible hydrogen bonding and steric effects, an acceptor would likely approach the formyl plane from different sides in chiral aldehydes I and II, and thereby expose a different face to react with the donor. Thus, we anticipated that I and II would be good candidates for the investigation of diastereodivergence in chiral aldehyde catalysis.

In this work, we first test a diastereodivergent 1,6-conjugate addition of amino acids to para-quinone methides catalysed by chiral BINOL aldehydes I and II, respectively. Both anti- and syn-conjugate additions can be achieved with high yields, diastereo- and enantioselectivities. We then seek to expand the scope of this catalytic system by investigating a bio-inspired Mannich reaction of pyridinylmethanamines and imines. The success of these two transformations suggests that it may be possible to achieve diastereodivergent chiral aldehyde catalysis for a whole series of asymmetric organic reactions using catalytic systems derived from BINOL aldehydes I and II.

Results

1,6-Conjugated addition. para-Quinone methides are versatile building blocks in asymmetric catalysis, particularly as Michael acceptors reacting with various nucleophiles. The catalytic asymmetric nucleophilic α-addition of amino acids to para-quinone methides is an elegant strategy for the construction of optically active diarylmethanes and unnatural amino acid derivatives. However, current methods depend on the use of amino acid-derived Schiff bases or azlactones as nucleophiles. In light of the unique properties of chiral aldehyde catalysis that it can employ N-unprotected amino acids as reactants and the potential for a diastereodivergent catalytic system using 3- and 2-formyl BINOL aldehydes I and II, the 1,6-conjugate addition of amino acids to para-quinone methides was chosen for initial investigation.

We began by evaluating the reaction of para-quinone methide 1a with tert-butyl glycine ester 2a catalysed by chiral aldehyde 3a and 4a, respectively. Tetramethyl guanidine (TMG) was used as base, and toluene as solvent. As expected, when chiral aldehyde 3a was used as catalyst, anti-5a was generated in 49% yield, 81:19 dr (diastereomer ratio) and 33% ee (enantiomeric excess) (Table 1, entry 1); when catalyst 4a was employed, syn-5a was generated in 36% yield, 54:36 dr and 58% ee (Table 1, entry 2). Inspired by these preliminary results, we then optimised the reaction conditions of the anti- and syn-reactions independently. Reaction...
Table 1 Reaction condition optimisation for 1,6-conjugated addition.

| Entry | 3/4 | Time (h) | Yield (%) | dr (syn:anti) | ee (syn/anti) (%) |
|-------|-----|----------|-----------|--------------|-----------------|
| 1     | 3a  | 4        | 49        | 19:81        | -/33            |
| 2     | 3a  | 3        | 36        | 64:36        | 58/-            |
| 3     | 3b  | 2        | 39        | 7:93         | -/72            |
| 4     | 3c  | 2        | 54        | 13:87        | -/70            |
| 5     | 3d  | 3        | 36        | 14:86        | -/77            |
| 6     | 3e  | 2        | 54        | 15:85        | -/39            |
| 7     | 3f  | 3        | 44        | 18:82        | -/45            |
| 8     | 3g  | 5        | 58        | 11:89        | -/48            |
| 9     | 3h  | 6        | 64        | 10:90        | -/96            |
| 10d   | 3d  | 47       | 74        | 10:90        | -/97            |
| 11e   | 3d  | 33       | 33        | 80:20        | -/97            |
| 12    | 4b  | 10       | 57:43     | 34/-         | -/31/-          |
| 13    | 4c  | 3        | 37        | 62:38        | -/60/-          |
| 14    | 4d  | 7        | 40        | 63:37        | -/48/-          |
| 15    | 4e  | 3        | 48        | 73:27        | -/50/-          |
| 16    | 4f  | 10       | 36        | 76:24        | -/79/-          |
| 17    | 4g  | 5        | 37        | 79:21        | -/83/-          |
| 18g   | 4g  | 3        | 69        | 94:6         | -/86/-          |
| 19f   | 4g  | 7        | 95:5      | 90/-         | -/90/-          |
| 20f   | 4h  | 7        | 56        | 94:6         | -/84/-          |

*aReaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), 3 or 4 (0.02 mmol), TMG (0.1 mmol), PhCH3 (0.5 mL), at 25 °C.
*bIsolated yield.
*cDetermined by chiral HPLC.
*dUsing tBuOK as a base.
*eUsing 10 mol % 3d, 30 mol % tBuOK as base and 1 mL PhCH3 as solvent.
*fUsing mesitylene as a solvent.
*gUsing 30 mol % tBuOK as a base.
*hUsing 10 mol % 4g as a catalyst.
conditions of the anti-selective addition were investigated first (Table 1, entries 3–11). Catalyst screening indicated that chiral aldehyde 3d was optimal in terms of enantioselectivity (Table 1, entry 5). After we replaced the base TMG by potassium tert-butoxide (‘BuOK), the yield and stereoselectivities of product anti-5a were enhanced greatly (Table 1, entry 10). When the catalyst loading was decreased to 10 mol %; comparable results were maintained (Table 1, entry 11).

Conditions of the syn-selective reaction were then optimised through screening catalysts, solvents and bases, as well as tuning the reaction temperature and reactant concentrations (see Supplementary Tables 2–4). The best results were obtained when chiral aldehyde 4g was employed as a catalyst (Table 1, entry 17), mesitylene as solvent (Table 1, entry 18) and ‘BuOK as a base (Table 1, entry 19). Enantioselectivity was increased to 90% ee when the equivalency of ‘BuOK was decreased from 1 to 0.3 (Table 1, entry 20). When loading of chiral aldehyde 4g was decreased to 10 mol %, product syn-5a was generated in 56% yield, 94:6 dr and 84% ee (Table 1, entry 21). According to these results, the reaction conditions depicted in entries 11 and 20 were selected as optimal and applied for substrate-scope investigation.

We first examined the scope of para-quinoine methide and amino acid substrates for the anti-selective reaction. The scope of para-quinoine methide derivatives that can be used as a substrate is quite broad (Fig. 2). All of the para-quinoine methides bearing substituted phenyls, regardless of the degree of phenyl substitution, gave corresponding products in good-to-high yields (52–84%), high diastereoselectivities (88:12→99:1) and enantiomeric excesses (94–98% ee) (Fig. 2, anti-5b–5n). No obvious effects on stereoselectivity from substituent position or electronics were observed. When the 2-(methoxycarbonyl)phenyl-substituted para-quinoine methide was used as acceptor, an intramolecular amidation took place following the asymmetric conjugate addition, which gave product anti-5l in moderate yield and high diastereo- and enantioselectivity. Other aryl-substituted para-quinoine methides, including naphthyl, thienyl and indolyl, were also investigated. Although enantioselectivity of anti-5q and diastereoselectivity of anti-5r were moderate, experimental outcomes were acceptable overall (Fig. 2, anti-5o–5s). Amino acids other than glycine ester could participate in this reaction and give high stereoselectivities, but higher catalyst loading (20 mol%) and long reaction time were needed. The yields were greatly affected by the alkyl substituents (Fig. 2, anti-5t–5w).

The substrate scope of the syn-selective reaction was then investigated. All the para-quinoine methides investigated in the anti-selective reaction reacted smoothly with glycine ester 2a in the presence of chiral aldehyde catalyst 4g, giving the corresponding syn-5b–5s in good-to-high yields (50–83%), diastereoselectivities (70:30–98:2) and modest to high enantiomeric excesses (59–94% ee). However, no amino acids other than glycine esters reacted efficiently with para-quinoine methide 1a in this transformation, potentially as a result of the steric influence of the amino acids (Fig. 2, syn-5t–5w).

The absolute configurations of product anti-5g (RR, CCDC 1989580) was determined by X-ray single-crystal analysis, while that of syn-5g (SR) was assigned by comparing the specific rotation value with literature (see Supplementary Information). The stereoselective chemistries of other products 5 were assigned by analogy with those of anti-5g and syn-5g accordingly.

**Mannich reaction.** Use of the same diastereodivergent asymmetric catalytic strategy in multiple transformations provides a good indication of wider potential. To date, most of the reported diastereodivergent catalytic strategies are applicable to only one type of reaction. After successfully realising the diastereodivergent catalytic asymmetric 1,6-conjugate addition, we sought to illustrate a second example of diastereodivergence using the same approach.

Transamination is an important chemical process in biological systems. It involves the conversion of an α-keto acid into an α-amino acid from transaminase and co-enzyme pyridoxamine. One of the most important intermediates in transamination is the ketimine that is formed from the α-keto acid and pyridoxamine; this ketimine can then convert into an aldimine via proton exchange. The conversion between ketimine and aldimine illustrates how a carbonyl can activate the benzyl C–H bond of pyridoxamine via the formation of an imine and accelerate the subsequent deprotonation process. Inspired by this mode of reactivity, and deducing that pyridinylmethanamine can be viewed simply as the core unit of a pyridoxamine, we surmised that chiral aldehyde catalysis might be effective for the asymmetric α-functionalization of pyridinylmethanamines. The chiral pyridinylmethanamine unit is found frequently in biologically active compounds, chiral ligands and natural products, so the preparation of optically active pyridinylmethanamine derivatives is highly valuable work.

We chose pyridin-2-ylmethanamine 6a and imine 7a as model reactants and chiral aldehydes 3a and 4a as catalysts. With 3a, syn-8a was generated with 89:11 dr (Table 2, entry 1). When catalyst by 4a, no diastereoselectivity was observed in the formation of product 8a, but the percentage of anti-isomer did increase to 48% (Table 2, entry 2). We then optimised the reaction conditions under the catalysis of chiral aldehydes 3 and 4, respectively. Initial catalyst screening indicated that chiral aldehyde 3d was the optimal catalyst for the syn-Mannich reaction in toluene (Table 2, entry 5), but subsequent solvent investigation showed that 3b gave better experimental results than 3d when dichloromethane (DCM) was used (Table 2, entries 13–14). Proceeding with catalyst 3b, further reaction conditions such as the type of base, the equivalency of base and the reaction temperature were investigated (see Supplementary Tables 5–10). The product syn-8a could be obtained in 83% yield, 97:3 dr and 90% ee when carried out in DCM at 0 °C with 0.7 equivalents DBU as a base (Table 2, entry 16).

We then optimised reaction conditions using chiral aldehydes 4. Catalyst screening showed that the steric effect of the R group had a great impact on both diastereoselectivity and enantioselectivity. Chiral aldehyde 4f, bearing a 4-tert-butyl-phenyl substituent at its 2′ position, yielded product anti-8a in 75:25 dr and 88% ee (Table 2, entry 21). Other reaction conditions including type of base, equivalency of base, reaction temperature and reactant concentration were then screened (see Supplementary Tables 11–16). Good yield (71%) and stereoselectivity (16:84 dr., 93% ee) of anti-8a were obtained when the reaction was carried out in o-xylene (0.1 M concentration) at −10 °C, with 0.3 equivalents DBU as a base (Table 2, entry 25). Based on these results, the reaction conditions depicted in entries 16 and 25 were selected for the investigation of substrate scope.

In the syn-Mannich reaction, phenyl imines bearing single substituent on the phenyl ring displayed favourable reactivity, giving products syn-8a–8g in good yields (59–83%), diastereoselectivities (95.5–>99:1) and enantioselectivities (82–90% ee). No obvious effects on stereoselectivity from substituent position or electronics were observed. Aldimines having two substituents at the 3,4-positions of phenyl ring were also suitable reactants, although dimethyl substitution provided for superior yield and selectivity compared to dichloro substitution (Fig. 3, syn-8h vs syn-8i). Other aryl imines, including naphthyl, thietyl and furyl aldimines, were then tested. Corresponding products 8j–8m were generated in good yields, high diastereoselectivities and good-to-
high enantioselectivities. Next, substituted pyridiniummethanamines were employed as donors. With respect to substituted pyridine-2-ylmethanamines, no matter the substituent installed at the C2, C5 or C4 position of the pyridine ring, products were obtained in good-to-high yields, enantioselectivities and diasteroselectivities (Fig. 3, syn-8n–8p). Pyridine-3-ylmethanamine gave product syn-8q in good yield, moderate diastereoselectivity and good enantioselectivity, while quinolin-2-ylmethanamine produced syn-8r in high yield, diastereoselectivity and moderate enantioselectivity.

Next, the substrate scope of the anti-selective Mannich reaction was investigated. All of the substituted imines and pyridiniummethanamines investigated in the syn-Mannich reaction displayed good reactivity in the anti-selective reaction. The yields of the anti-products were affected by substituent steric and electronic factors. Product yield decreased greatly when an imine
### Table 2 Reaction condition optimisation of the Mannich reaction

**Entry** | **3/4** | **Time (h)** | **Yield (%)**<sup>b</sup> | **dr (syn/anti)**<sup>c</sup> | **ee (syn/anti) (%)**<sup>c</sup>
--- | --- | --- | --- | --- | ---
1 | 3a | 24 | 74 | 89:11 | 12/-
2 | 4a | 12 | 70 | 52:48 | 23/70
3 | ent-3b | 12 | 95 | 93.7 | -66/-
4 | 3c | 12 | 95 | 92.8 | 65/-
5 | 3d | 12 | 92 | 94.6 | 74/-
6 | 3l | 12.5 | 86 | 94.6 | 61/-
7 | 3j | 9 | 86 | 96.4 | 59/-
8 | 3k | 12 | 74 | 91.9 | 8/-
9 | 3i | 12 | 52 | 89.11 | 16/-
10 | m | 12.5 | 71 | 87.13 | 0/-
11 | 3n | 12.5 | 69 | 91.9 | 24/-
12 | 3o | 12 | 73 | 91.9 | 26/-
13<sup>d</sup> | ent-3b | 12 | 87 | 95.5 | -76/-
14<sup>d</sup> | 3d | 17 | 87 | 94.6 | 75/-
15<sup>d,e</sup> | ent-3b | 12 | 85 | 94.6 | -81/-
16<sup>d,f</sup> | ent-3b | 66 | 83 | 97.3 | -90/-
17 | 4b | 12 | 90 | 78.22 | -/48
18 | 4c | 12 | 64 | 55.45 | -/59
19 | 4d | 12 | 64 | 48.52 | -/74
20 | 4e | 12 | 64 | 32.68 | -/85
21 | 4f | 12 | 64 | 25.75 | -/88
22 | 4g | 12 | 51 | 45.55 | -/30
23<sup>e</sup> | 4f | 12 | 72 | 21.79 | -/89
24<sup>f</sup> | 4f | 44 | 72 | 17.83 | -/93
25<sup>f</sup> | 4f | 44 | 71 | 16.84 | -/93

<sup>a</sup>Reaction conditions: 6a (0.1 mmol), 7a (0.13 mmol), 3 or 4 (0.01 mmol), DBU (0.03 mmol), PhCH₃ (0.5 mL), at 20°C.

<sup>b</sup>Isolated yield.

<sup>c</sup>Determined by chiral HPLC.

<sup>d</sup>0.5 mL DCM as a solvent.

<sup>e</sup>Using 0.07 mmol DBU.

<sup>f</sup>At 0°C.

<sup>g</sup>At -10°C.

<sup>h</sup>Using 0.5 mL of o-xylene as solvent.

<sup>i</sup>Using 1 mL of o-xylene as solvent.
bearing an electron-rich aryl substituent was introduced as acceptor (Fig. 3, anti-8i and anti-8m). Overall, moderate-to-high diastereoselectivities (37:63–99:1) and enantioselectivities (68–96% ee) were observed in the anti-selective Mannich reaction; only three products had enantioselectivities lower than 90% ee.

The absolute configurations of products anti-8a (RR, CCDC 1989581) and syn-8a (SR, CCDC 1989582) were determined by the X-ray single-crystal analysis of their derivatives (see Supplementary Information). The stereoselective chemistries of other products 8 were assigned by analogy with those of anti-8a and syn-8a accordingly.

**Steroselective control model investigation.** In order to clarify how the chiral aldehyde catalysts control stereoselectivity, we conducted comprehensive computational calculations to elucidate the possible reaction models of the 1,6-conjugate addition and Mannich reaction (see Supplementary Figs, 1–20 and Supplementary Data 1).

As our previous reported reaction process, the Schiff base intermediates formed by aminomethyl compounds and chiral aldehyde catalysts attacked para-quinone methide 1a and aldime 7a, then the produced intermediates were hydrolysed to form 5a and 8a. Since the chiral centre was formed with the formation of the C–C bond, transition states (TSS) for the nucleophilic attack were individually investigated as a critical process for stereoselectivity. Because both reactions could be catalysed by 3b and 4f, the transition states for the reactions using them as catalysts were calculated.

After considering various conformations, the conformation with the lowest energy to form a different configuration of 5a by...
the 1,6-conjugate addition catalysed by 3b was calculated and shown in Fig. 4. We found the energy difference of C-3b-RS-TS1 and C-3b-SR-TS1 with the value of 1.41 kcal/mol. According to Van’t Hoff equation, we predicted that the ee value was 83%, which is similar to the experimental value of 72%. As the energies of C-3b-RR-TS1 and C-3b-SS-TS1 were 1.52 kcal/mol and 2.31 kcal/mol higher than C-3b-RS-TS1, we predicted that the dr value was 92:8, which is compared with experimental data (93:7) in good agreement. By looking into the structures, there is an intermolecular hydrogen bond between the oxygen atom of 1a and 2’ hydroxyl of 3b in C-3b-RS-TS1, which may play an important role in selectivity control. This inference was also supported by our experimental results: using the catalysts 3e, 3f, 3g and 3h with a big R group, that may affect the intermolecular hydrogen bond, resulting in worse ee values (see Table 1, entries 6–9). Additionally, these results indicate that the mechanism involving TS (transition state) C-3b-RS-TS1 and leading to the final product with (RS)-configuration had the most favourable transition state structure.

On the other side, using 4f as a catalyst led to the product with (SS)-configuration. Similarly, various conformations were calculated, and the conformation with the lowest energy for each configuration is shown in Fig. 4. It is likely that steric hindrance from 4-tert-butylyphenyl would result in attack at Si face being more favourable. It is consistent with our experimental results: 4g with a bigger steric hindrance group as 3,5-diter-butylyphenyl resulted in a better selectivity, while 4c with a steric hindrance group as phenyl led to a wore one. In addition to steric effect, π–π interaction between the aryl ring of 1a and binaphthyl also promotes the stereoselective formation of the SS configuration. Moreover, the predicted ee value based on the energy difference of C-4f-SS-TS1 and C-4f-RR-TS1 (0.59 kcal/mol) was 46% was slightly lower than the experimental result (50%). Also, the predicted dr value (77:23) is agreed with the experimental result (73:27).

Interestingly, the stereoselectivity for the Mannich reaction was different from the 1,6-conjugate addition when using the same catalyst ent-3b and 4f. For Mannich reaction of 6a and 7a catalysed by ent-3b, the syn-8a was the main product, which anti-5a was the main product for the reaction of the 1,6-conjugate addition of 1a and 2a. To explain the stereoselectivity, the TS structures and energies for the additional step were calculated and were shown in Fig. 5. As the energy barrier of M-ent-3b-RR-TS1 was 1.93 kcal/mol lower than M-ent-3b-SS-TS1, we predicted the ee value was 96%, which was slightly higher than the experimental results (90%). On the other hand, the predicted dr value (88:12) was lower than the experimental results (97:3). By looking into the structure, the intermolecular hydrogen bond between P = O group of 7a and 2’ hydroxyl of ent-3b with a distance of 1.62 Å may play an important role for the selectivity, because we also found that using catalysts 3k–3o with a big R group at the 3’ position that may affect the intermolecular hydrogen bond, resulted in worse ee values (Table 2, entries 8–12). In addition, reduction of steric repulsion and the π–π interaction between the C-phenyl of 7a and the pyridinyl of 6a in M-ent-3b-RR-TS1 may also contribute to its lower energy. Compared to the TSs for 1,6-conjugate addition involving similar hydrogen bond (C-3b-RS-TS1 and M-ent-3b-RR-TS1), this π–π interaction might be the might main difference and the possible reason for the different stereoselectivity.

Considering the nucleophilic addition of the Schiff base formed from catalyst 4f and 6a to aldimine 7a, it is logical to think that steric hindrance from 4-tert-butylyphenyl at the Re-face would again result in attack at Si face being more favourable. However, in this case, the experimental results showed that anti-8a (RS) was formed by Re-face attack. Therefore, we calculated various TS structures for both Re-face and Si-face attack and discovered that the energy barrier of M-4f-RS-TS1 was the lowest. The energy of M-4f-SR-TS1 was 1.64 kcal/mol higher than M-4f-RS-TS1. Based on it, the ee value for this reaction was predicted as 94%, which is
agreeing with the experimental results (93%). Additionally, the predicted ee value (77:23) was slightly lower than experimental results (84:16) as the energies of M-4f-RR-TS1 and M-4f-SS-TS1 were 0.88 kcal/mol and 0.87 kcal/mol higher than M-4f-RS-TS1, respectively. By looking to the structure, the angle between the tert-butyl and the conjugated pyridine plane was small and coincided with the C-phenyl ring of 7a. Additionally, the distance between the H atom of tert-butyl group and C-phenyl ring of 7a was just 2.53 Å, which suggests a potential favourable interaction between C–H and π in M-4f-RS-TS1. These results were also consistent with our catalyst screening results. Not only 4g with a bigger steric hindrance group as 3,5-ditet-butylphenyl but also 4c with a smaller group as phenyl, resulted into worse selectivities, suggesting the C–H and π interaction play an important role in the selectivity.

Based on these DFT calculation results, possible catalytic cycles for the four optimal model reactions were proposed. As shown in Fig. 6, all of these four reactions underwent via Schiff base formation, deprotonation, nucleophilic addition and hydrolysis process. In the 1,6-conjugated addition, chiral aldehyde 3 gave syn-selective products due to the formation of a hydrogen bond between the catalyst and para-quinone methide; while chiral aldehyde 4 was favoured to giving anti-selective products because of the steric effect and π–π interaction (Fig. 6a). With respect to the Mannich reaction, the hydrogen bond and π–π interaction formed between catalyst and imine induced the syn-selective products; while the steric effect and C–H–π interaction of catalyst 4 and imine promoted to form corresponding anti-Mannich products (Fig. 6b).

A 1,6-conjugate addition of amino acids to para-quinone methides and a Mannich reaction of pyridinylmethamines and aldimines were realised stereodivergently by chiral aldehyde catalysis. Chiral 3-formyl BINOL aldehyde catalysts were used to efficiently achieve the anti-1,6-conjugate addition and syn-Mannich reaction, while chiral 2-formyl BINOL aldehyde catalysts gave the syn-selective conjugate addition and anti-Mannich products. Generally, products of all transformations were obtained in good yield with high diastereoe- and enantioselectivity. DFT calculations indicate that the orientation of formyl, hydroxyl and steric hindrance groups in chiral aldehydes I and II is the key factor in achieving diastereoselectivity. It is promising for chemists to develop new stereodivergent reactions by chiral aldehyde catalysis under the guidance of these computational study results. The development of further stereodivergent reactions by chiral aldehyde catalysis is ongoing in our lab.

**Methods**

**Methods for the catalytic asymmetric 1,6-conjugated addition.** A dried 10 mL Schlenk tube was charged with para-quinone methides 1 (0.01 mmol), catalyst 3d (0.01 mmol) or 4 g (0.02 mmol), BuOK (0.03 mmol) and α-amino acid derivatives 2 (0.2 mmol). Then dry solvent toluene (1.0 mL) or mesitylene (0.5 mL) was added to the tube, and the resulted solution was effectively stirred at 25 °C for a suitable time. After the complete consumption of para-quinone methides 1 by TLC (Thin Layer Chromatograph), the solvent was removed by rotary evaporation. The crude mixture was subjected to 1H NMR analysis to determine the diastereoselective ratio. Subsequently, a flash silica column chromatography separation was performed for further purification. The details of the full experiments and compound characterisations are provided in the Supplementary Information.

**Methods for the catalytic asymmetric Mannich addition.** A dried Schlenk tube was charged with imine 7 (0.13 mmol), catalyst R-3b (0.01 mmol) or 4f (0.01 mmol). Dry solvent CH2Cl2 (0.5 mL) or o-xylene (1 mL) was added, and the resulted solution was stirred at the indicated reaction temperature for 10 min. Then aminomethylpyridine 6 (0.1 mmol) and DBU (0.07 or 0.03 mmol) were added, and the resulted mixture was effectively stirred at the indicated temperature for a suitable time. After the complete consumption of aminomethylpyridines 6, the solvent was removed by rotary evaporation. The crude mixture was subjected to 1H NMR analysis to determine the diastereoselective ratio. Subsequently, a flash silica column-chromatography separation was performed for further purification. The details of the full experiments and compound characterisations are provided in the Supplementary Information.
Fig. 6 Proposed catalytic cycles. **a** The proposed catalytic cycles for the anti-selective 1,6-conjugated addition reaction (left) and syn-selective one (right). **b** The proposed catalytic cycles for the syn-selective Mannich reaction (left) and anti-selective one (right).

**Data availability**

The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif. The authors declare that all other data supporting the findings of this study are available within the article and its Supplementary Information file.

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