Direct asymmetric aldol reactions between aldehydes and ketones catalyzed by L-tryptophan in the presence of water†

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Primary amino acids and their derivatives were investigated as catalysts for the direct asymmetric aldol reactions between ketones and aldehydes in the presence of water, and L-tryptophan was shown to be the best catalyst. Solvent effects, substrate scope and the influence of water on the reactions were investigated. Quantum chemical calculations were performed to understand the origin of the observed stereoselectivity.

Introduction

The aldol reaction has been recognized as one of the most important carbon–carbon bond-forming reactions, yielding β-hydroxy carbonyl compounds, which are valuable intermediates in organic synthesis.[1] In particular, asymmetric aldol reactions have drawn great attention from the synthetic community in the past few decades.[2] Following the seminal contributions from Masamune *et al.*,[3] Evans *et al.*,[4] and Iwasawa and Mukaiyama[5] in the early 1980s, transition metal complexes and Lewis bases were shown to be powerful catalysts in asymmetric aldol reactions, employing activated silyl enol ethers.[6] Catalytic enantioselective aldol reactions using unmodified ketones or aldehydes catalyzed by transition metal complexes certainly represent another important development.[7]

The past few years have witnessed astonishing progress in asymmetric organocatalysis,[8] which has now been established as one of the most promising and practical methods in asymmetric synthesis and catalysis. In particular, asymmetric organocatalytic aldol reactions have been intensively investigated ever since the renaissance of modern organic catalysis.[9] In this regard, proline and its various structural derivatives have been shown to be versatile organic catalysts for the intermolecular aldol reactions.[10] In contrast to the early studies on the use of proline and primary amino acids in intramolecular aldol reactions,[11] the employment of primary amino acids as catalysts in asymmetric reactions was virtually negligible in the early 2000s. It was not until 2004 when primary amino acids were carefully examined as potential effective catalysts for intermolecular aldol reactions, and impressive progress has been made in the past five years, establishing primary amino acids/amines as privileged organocatalysts.[12]

Water is an ideal solvent for chemical reactions, mainly due to its low cost and environmentally benign nature.[13] Developing organocatalytic reactions in a purely aqueous system is of great current interest.[14] Recently, the groups of Hayashi[15] and Barbas[16] reported asymmetric aldol reactions carried out in the presence of water, and hydrophobic proline derivatives were employed as efficient organocatalysts in their investigations.

We have keen interests in asymmetric organocatalytic reactions that can be promoted by chiral primary amines.[17] In one of our earlier communications,[17a] we reported that natural tryptophan could effectively catalyze the direct asymmetric aldol reactions between cyclic ketones and aromatic aldehydes in the presence of water. Herein, we present a full study and mechanistic understanding of the tryptophan-catalyzed direct asymmetric aldol reactions.

Results and discussion

Catalyst screening

The aldol reaction of *p*-nitrobenzaldehyde and cyclohexanone was selected as a model reaction to evaluate our organocatalysts. Since tryptophan was the best catalyst in our preliminary study, we intended to further test the catalytic effects of a few *N*-substituted tryptophan derivatives in direct aldol reactions, and the structures of the catalysts employed in our study are shown in Scheme 1. *N*-Methylated tryptophan **3a** is commercially available, and *N*-arylated tryptophan derivatives can be easily prepared. The copper-catalyzed *N*-arylation method developed by Buchwald *et al.*[18] was employed to install different aromatic moieties on the indole nitrogen of *N*-benzyloxycarbonyl-L-tryptophan benzyl ester **1**, yielding *N*-phenyl-, naphthyl- or biphenyl-substituted intermediates **2b**, **2c** or **2d**, respectively, and it was found that microwave irradiation could dramatically shorten the reaction time in the coupling step. After hydrogenolysis, *N*-arylated tryptophan derivatives **3b–d** were obtained.

The *N*-arylated tryptophan derivatives and a wide range of natural amino acids were evaluated in the model reaction under aqueous reaction conditions, which are summarized in Table 1. Amino acids with a small side chain (entry 1) or hydrophilic groups (entries 2–5) were ineffective, yielding the products either in low yields or with very poor enantioselectivity. With increasing size of the amino acid side chain, better enantioselectivities were observed (entries 6–11). Although Cbz-protected lysine was found to be effective in asymmetric induction (89% ee), the chemical yield was

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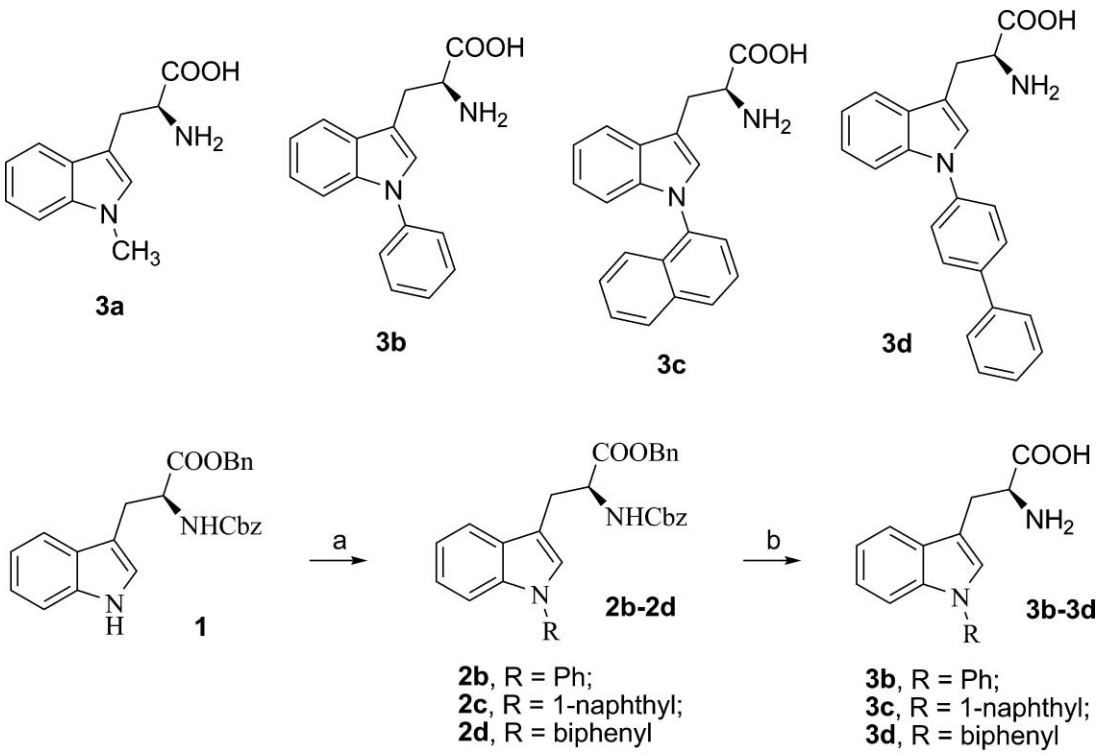
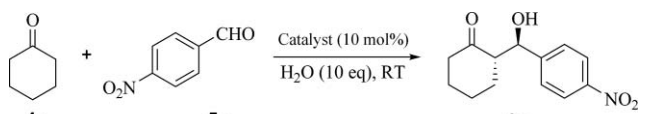
† Electronic supplementary information (ESI) available: Details of the preparation of tryptophan derivatives **3b–d**, analytical data and HPLC spectra of the aldol products, and quantum chemical calculations. See DOI: 10.1039/b921460g



Scheme 1 Prepared *N*-arylated tryptophan derivatives.

Table 1 Direct asymmetric aldol reactions catalyzed by primary amino acids and *N*-arylated tryptophan derivatives[a]



4a 5a 6a

Entry	Catalyst	Time/h	Yield (%)[b]	*Syn* : *anti*[c]	ee (%)[d]
1	L-Alanine	109	32	1 : 12	0
2	L-Tyrosine	28	<5	—	—
3	L-Serine	96	<10	—	—
4	L-Histidine	57	59	1 : 1.5	8
5	L-Arginine	18	83	1.4 : 1	14
6	L-Valine	144	84	1 : 4	65
7	L-Phenylalanine	48	75	1 : 4	70
8	L-Isoleucine	96	67	1 : 5	83
9	L-Leucine	96	81	1 : 3	79
10	L-Threonine	82	30	1 : 2	76
11	L-Cysteine	96	23	1 : 3	73
12	L-H-Lys-(*Z*)-OH	57	46	1 : 5.6	89
13	L-Tryptophan	23	85	1 : 4	86
14	**3a**	48	68	1 : 4	79
15	**3b**	19	85	1 : 4	25
16	**3c**	12	50	1 : 2	50
17	**3d**	19	88	1 : 4	70

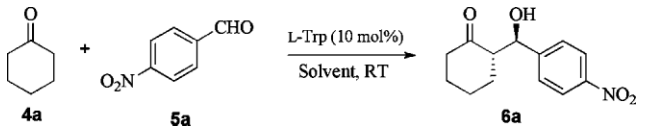
[a] The reaction was performed by employing *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (1.25 mmol), organocatalyst (0.025 mmol), and water (0.045 mL) at room temperature. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^{1}H NMR analysis of the crude aldol product. [d] The ee of the *anti* isomer was determined by HPLC analysis on a chiral phase.

low (entry 12). Overall, natural tryptophan was the best catalyst, yielding the desired product in a short reaction time, in high chemical yield, and with good diastereoselectivity and excellent enantioselectivity (entry 13). The results obtained by employing *N*-substituted tryptophan derivatives were disappointing. *N*-Methyl tryptophan showed a catalytic effect slightly inferior to that of natural tryptophan, affording the products in moderate yield and with good enantioselectivity (entry 14). The substitution of different aryl groups at the indole nitrogen led to catalysts that were less effective in promoting the direct aldol reactions, and the desired products were obtained with only poor to modest enantioselectivities (entries 15–17).

Effects of solvents

We also examined the influence of various organic solvents on the tryptophan-catalyzed direct aldol reactions, and the results are summarized in Table 2. In neat conditions, the reaction proceeded readily, with moderate diastereoselectivity and excellent enantioselectivity (entry 1). DMSO was found to be a good organic solvent, the reaction was completed in one day, and the desired products were obtained in good yield, with good diastereoselectivity and moderate enantioselectivity (entry 3). THF was less effective, and a slower reaction and decreased stereoselectivity were observed (entry 4). Common organic solvents, *e.g.* dichloromethane, chloroform, toluene, hexane and acetonitrile, were unsuitable for the tryptophan-promoted direct aldol reactions, and several days were required for the completion of the reactions, even though

Table 2 Tryptophan-catalyzed direct asymmetric aldol reactions in different solvents[a]



4a 5a 6a

Entry	Solvent	Time	Yield (%)[b]	*Syn* : *anti*[c]	ee (%)[d]
1	Neat	1 d	92	1 : 4	89
2	DMF	3 d	72	1 : 4	46
3	DMSO	1 d	93	1 : 4.6	73
4	THF	2 d	72	1 : 1	63
5	CH_2Cl_2	9 d	23	1 : 5	87
6	$CHCl_3$	9 d	41	1 : 4	89
7	Toluene	6 d	86	1 : 2.4	89
8	Hexane	6 d	88	1 : 2	87
9	CH_3CN	4 d	63	1 : 3	88
10	CH_3OH	9 d	42	1 : 3	45
11	EtOH	9 d	77	1 : 5	53
12	*i*-PrOH	9 d	51	1 : 4	60
13	*tert*-BuOH	41 h	97	1 : 2.3	83

[a] The reaction was performed by employing *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (1.25 mmol), L-tryptophan (0.025 mmol), and solvent (0.3 mL) at room temperature. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^{1}H NMR analysis of the crude aldol product. [d] The ee of the *anti* isomer was determined by HPLC analysis on a chiral phase.

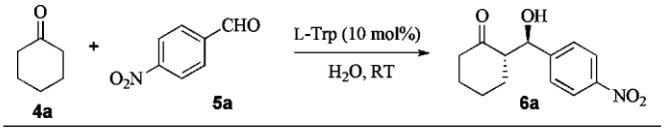
high enantioselectivity was attainable in certain cases (entries 5–9). Protic solvents, such as methanol, ethanol and isopropanol, were inappropriate solvents for the reactions (entries 10–12). *tert*-Butanol, however, was found to be an appropriate solvent (entry 13). The above results demonstrate that water is indispensable in the direct aldol reactions mediated by tryptophan. The presence of water led to shortened reaction time, higher chemical yield, and improved diastereo- and enantioselectivity, compared to the reactions performed in organic solvents.

Effects of water

The tryptophan-catalyzed direct aldol reaction using water as a solvent could be best described as a reaction proceeding "in the presence of water". The reaction mixture was a two phase system, with a solid tryptophan suspension, and this physical state was maintained throughout the reaction.

The influence of the amount of water on the tryptophan-promoted direct aldol reaction was further investigated, and the results are summarized in Table 3. In general, addition of various amounts of water favoured the reaction, leading to shortened reaction times and improved stereoselectivities. The results were similar when the molar amounts of water were below 10 (entries 1–5). The use of 15 and 20 molar amounts of water turned out to be optimal, affording the desired products in excellent yields, and with 5 : 1 dr and 96% ee (entries 6 and 7). Further increasing the amount of water was detrimental to the reaction, resulting in much slower reactions, lower chemical yields and decreased stereoselectivity (entries 8 and 9). When a large excess of water (300 equivalents) was used, the reaction proceeded extremely slowly, and the aldol products were obtained in low yield, with virtually no diastereoselectivity and much decreased enantioselectivity (entry 10). Moreover, the pH influence on the

Table 3 The influence of amounts of water on the tryptophan-catalyzed direct aldol reactions[a]



4a 5a 6a

Entry	H_2O (eq.)	Time/h	Yield (%)[b]	*Syn* : *anti*[c]	ee (%)[d]
1	1	26	90	1 : 4.5	92
2	2	26	86	1 : 5	85
3	3	26	83	1 : 5	87
4	5	19	86	1 : 5	86
5	10	23	84	1 : 5	86
6	15	19	85	1 : 5	96
7	20	19	91	1 : 5	96
8	56	38	79	1 : 6	91
9	111	38	66	1 : 5	89
10	300	160	40	1 : 1.4	83

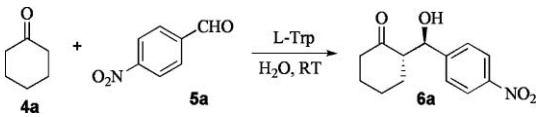
[a] The reaction was performed by employing *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (1.25 mmol), L-tryptophan (0.025 mmol) and water at room temperature. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^{1}H NMR analysis of the crude aldol product. [d] The ee of the *anti* isomer was determined by HPLC analysis on a chiral phase.

reaction was also examined. Buffer solutions with pH values at 6, 7 and 8 were used as the solvent, and similar results were obtained (pH 6, dr = 1 : 6, 85% ee; pH 7, dr = 1 : 5, 78% ee; pH 8, dr = 1 : 3, 81% ee).

The substrate ratio and catalyst loading

Having established water as the best solvent for the reaction, and optimized the equivalents of water required in the reaction system, we then investigated the influence of substrate ratios on the reaction, and the results are summarized in Table 4. By

Table 4 The effects of substrate ratio and catalyst loading[a]



4a 5a 6a

Entry	Catalyst (mol%)	Aldehyde : ketone	Time/h	Yield (%)[b]	*Syn* : *anti*[c]	ee (%)[d]
1	10	1 : 1	36	82	1 : 4	74
2	10	1 : 2	36	85	1 : 5	84
3	10	1 : 3	24	87	1 : 6	80
4	10	1 : 4	24	89	1 : 6	80
5	10	1 : 5	19	91	1 : 5	96
6	1	1 : 5	128	41	1 : 1	84
7	2	1 : 5	73	79	1 : 4	71
8	3	1 : 5	73	88	1 : 4	81
9	4	1 : 5	43	92	1 : 3	89
10	5	1 : 5	36	85	1 : 5	92
11	15	1 : 5	22	88	1 : 4	92
12	20	1 : 5	22	86	1 : 5	93

[a] The reaction was performed by employing *p*-nitrobenzaldehyde (0.25 mmol), cyclohexanone (1.25 mmol), L-tryptophan (0.025 mmol), and water (5 mmol) at room temperature. [b] The combined isolated yield of the diastereomers. [c] The diastereoselectivity was determined by ^{1}H NMR analysis of the crude aldol product. [d] The ee of the *anti* isomer was determined by HPLC analysis on a chiral phase.

utilizing an equal molar ratio of aldehyde and ketone, moderate enantioselectivity was attainable (entry 1). With further increases in the amount of cyclohexanone, the reaction times were shortened and good enantioselectivities were obtained (entries 2–4). Five equivalents of cyclohexanone were found to be optimal, and under such conditions short reaction time, very high chemical yield, good diastereoselectivity and excellent enantioselectivity were observed (entry 5). Compared to the results obtained with 10 mol% catalyst, lowering the catalyst loading resulted in reduced reaction rates, and slightly decreased stereoselectivity (entries 6–10). When the catalyst loading was increased to 15 and 20 mol%, no improvement in the reaction was observed (entries 11 and 12). Taken together, 10 mol% catalyst loading and a 1 : 5 aldehyde : ketone ratio are the optimal reaction conditions, yielding the desired product with high enantioselectivity within 1 d.

Substrate scope

The substrate scope was next investigated, as illustrated in Table 5. Various acyclic ketones, including a number of α-oxygenated ketones, proved to be unsuitable substrates for the tryptophan-promoted direct aldol reaction, and no desired product was observed (entries 1–9). In the case of 3-pentanone, the aldol products could be obtained, although in low yield and with low enantioselectivity (entry 10). The observed non/low reactivity of acyclic ketones in the tryptophan-catalyzed aldol reaction could be attributed to inefficient formation of the active enamine intermediates from acyclic ketones. In a stark contrast to the acyclic ketones, cyclic ketones, including cyclopentanone, cyclohexanone and cycloheptanone, have been demonstrated to be excellent substrates. In addition, substituted cyclohexanone could also be employed, yielding the aldol products with three stereogenic centers (entries 29 and 30).

The scope of aldehyde acceptors was evaluated. Electron-poor aromatic aldehydes offered the best reactivity, and the desired aldol products were obtained in good chemical yields, and with *anti*-diastereoselectivity and generally high enantioselectivity (entries 11–18). For instance, when *o*-nitrobenzaldehyde was used, the *anti*-aldol adduct **6e** was obtained in 77% chemical yield, with 1 : 52 dr and 90% ee (entry 14). However, the reaction with *o*-trifluoromethyl-substituted aldehyde turned out to be ineffective, likely due to the large amount of steric hindrance induced by the CF_3 group (entry 19). Electron-rich or electron-neutral aromatic aldehydes could be tolerated for the reaction (entries 20–22), and heteroaromatic aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde were also found to be suitable (entries 23–25). Moreover, halogenated aromatic aldehydes could be employed, even though longer reaction times were generally required (entries 26–28).

Mechanistic investigation: computational studies to understand the observed stereoselectivities

To shed light on the mechanism and stereoselectivity of the L-tryptophan-catalyzed aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde, quantum chemical calculations were performed.[19] It is well established that amino acid-catalyzed aldol reactions involve enamine intermediates.[20–22] For the catalytic aldol reaction examined here, the formation of an enamine from cyclohexanone and tryptophan is calculated to be a slightly endothermic process, by 9.4 kJ mol^{-1}. It is instructive to first examine the structures and energies of this enamine intermediate involved. Conformational analysis was carried out initially to determine various possible low-lying conformations. The optimized geometries and calculated relative energies of the 8 lowest-energy conformations of the enamine intermediate are given in the ESI.† There are two important lowest-energy conformations of the enamine intermediate: **enam1** and **enam2**. The amine N–H proton is on the same side as the cyclohexenyl double bond in **enam1** and the opposite side in **enam2** (Fig. 1). These two conformers lie close in energy, with a slight preference for the **enam2** form (by 3.8 kJ mol^{-1}).

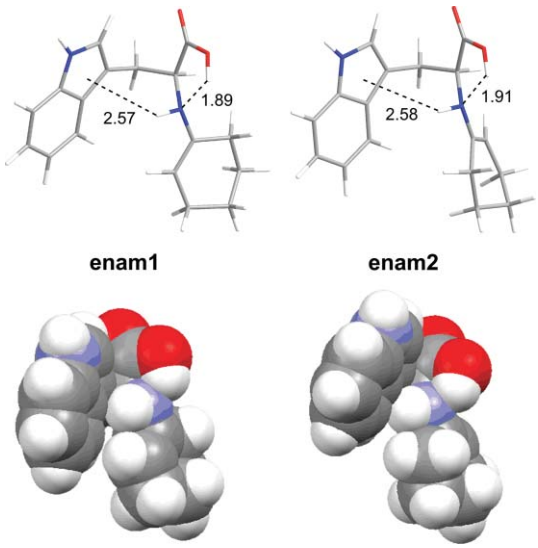
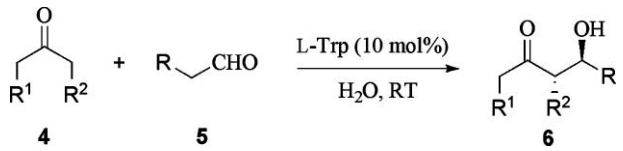


Fig. 1 Optimized (B3LYP/6-31G**) geometries of the two lowest-energy conformations of enamine (**enam1** and **enam2**). Bond distances are given in Å.

Both enamine conformations are characterized by two key structural features: (1) a hydrogen bond between the amine nitrogen and the carboxyl O–H proton and (2) N–H/π interaction between the amine N–H and the indole moiety. For comparison, a similar **enam1** conformation with the indole group away from the N–H has a significantly higher relative energy of 11.4 kJ mol^{-1}. The stabilizing energetic effect of the N–H/π interaction is further supported by NBO second-order perturbation theory energy analysis. A donor–acceptor interaction energy of ~5 kJ mol^{-1} between an indole C=C π-bonding orbital and the N–H antibonding orbital is estimated for both conformers. The existence of the N–H/π interaction is further confirmed by topological analysis based on Bader's theory of atoms in molecules (AIM). Previous theoretical studies have shown that an X–H/π (X = C, N or O) interaction is characterized by a bond path and its associated bond critical point.[23] For the N–H/π contact examined here, there exists a bond path linking the hydrogen atom with both carbon atoms of the indole C=C bond. The calculated topological properties at the bond critical points, namely electron density (ρ), Laplacian of electron density ($\nabla_2 \rho$) and ellipticity (ε), are similar to the characteristic topological properties of a weak hydrogen bond, such as CH···O[24] and C–H···π[23] interactions. Due to these

Table 5 L-Tryptophan-catalyzed direct aldol reactions between various ketones and aldehydes[a]



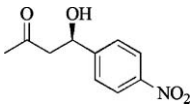
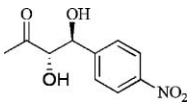
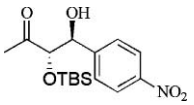
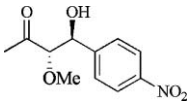
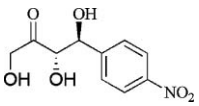
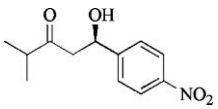
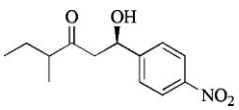
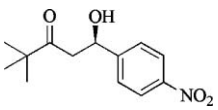
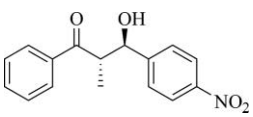
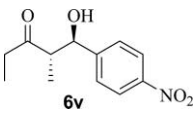
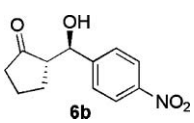
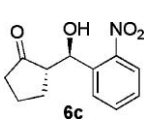
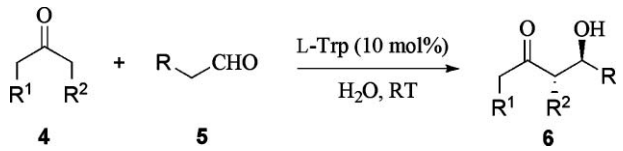
Entry	Product	Time/h	Yield (%)[b]	*Syn* : *anti*[c]	ee (%)[d]
1		196	—[e]	—	—
2		96	—[e]	—	—
3		53	—[e]	—	—
4		72	—[e]	—	—
5		72	—[e]	—	—
6		170	—[e]	—	—
7		170	—[e]	—	—
8		170	—[e]	—	—
9		96	—[e]	—	—
10	 **6v**	216	38	1 : 1	54
11	 **6b**	12	74	1 : 1	78
12	 **6c**	48	99	4 : 1	82

Table 5 *(Contd.)*



4 5 6

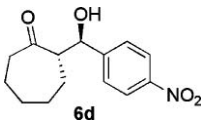
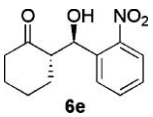
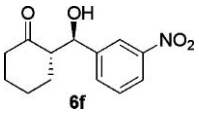
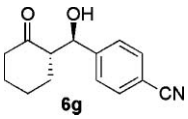
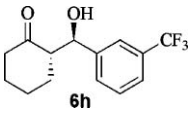
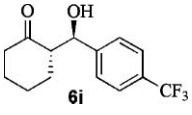
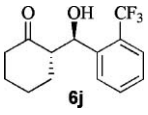
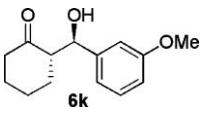
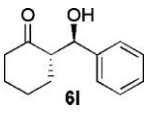
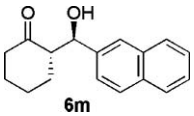
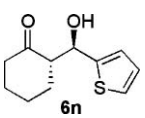
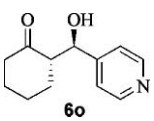
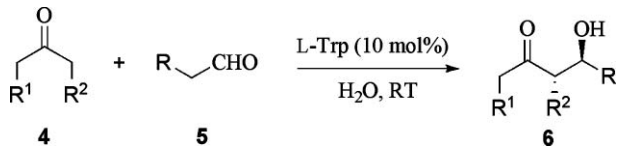
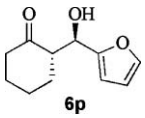
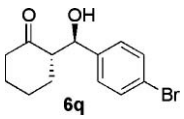
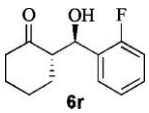
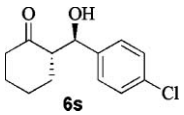
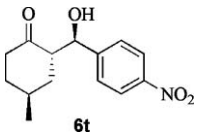
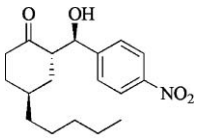
Entry	Product	Time/h	Yield (%)[b]	*Syn* : *anti*[c]	ee (%)[d]
13	 **6d**	24	73	2 : 3	84
14	 **6e**	24	77	1 : 52	90
15	 **6f**	24	79	1 : 20	89
16	 **6g**	24	78	1 : 3	88
17	 **6h**	48	73	1 : 2	75
18	 **6i**	39	65	1 : 19	76
19	 **6j**	48	24	5 : 1	66
20	 **6k**	42	42	1 : 10	87
21	 **6l**	92	47	1 : 78	89
22	 **6m**	24	57	1 : 16	92
23	 **6n**	72	49	1 : 5	85
24	 **6o**	24	76	10 : 1	59

Table 5 *(Contd.)*



Entry	Product	Time/h	Yield (%)[b]	*Syn* : *anti*[c]	ee (%)[d]
25	 **6p**	24	40	1 : 2	60
26	 **6q**	96	66	1 : 17	82
27	 **6r**	25	51	1 : 88	86
28	 **6s**	96	74	1 : 4	79
29	 **6t**	36	97	1 : 4	73
30	 **6u**	41	90	1 : 2	86

[a] The reactions were performed with aldehyde (0.5 mmol), cyclohexanone (2.5 mmol) and tryptophan (0.05 mmol) in water (10 mmol) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the products. [d] ee of *anti* isomer. [e] No product was observed.

two key stabilizing intramolecular interactions, both enamine forms have a rather rigid geometry. Most importantly, the indole moiety partially shields one face of the π-bond of the cyclohexene moiety in the enamine. For instance, the *si*-face of **enam1** is partially shielded by the indole unit leaving the *re*-face exposed for enantioselective C–C bond formation with benzaldehyde (see the space filling model in Fig. 1).

A previous theoretical study on a related alanine-catalyzed aldol reaction by Himo *et al.* showed that the most accessible pathway corresponds to C–C bond formation coupled with proton transfer from the carboxylic group of the alanine moiety in the transition state.[22] For the tryptophan-catalyzed aldol reaction examined here, we have established a similar mechanistic preference through calculations on the competitive pathways, namely amino-, enamine- and enaminium-catalyzed mechanisms. Indeed, this theoretical result strongly supports the experimental finding that the tryptophan carboxylic acid function is important for the asymmetric induction, as the tryptophan methyl ester afforded a virtually racemic product.[17a]

Next, we consider various plausible transition states of the carboxylic acid-catalyzed enamine pathway leading to the four different stereoisomers. Based on the fact that there are (1) two low-lying conformations of the enamine intermediate, (2) two possible modes of approach (*re* and *si*) of the prochiral carbon of enamine on benzaldehyde, and (3) two orientations of benzaldehyde (with respect to enamine), there are 8 conceivable transition states to be examined. This C–C bond forming step is the rate-determining step[25] and governs the stereochemistry of the final product. Fig. 2 shows the four transition state structures (**TS1–TS4**) that produce the four different stereoisomers with the lowest energy barriers. The calculated activation barriers ($\Delta G^{\ddagger}_{298}$), with respect to enamine and *p*-nitrobenzaldehyde, of the four transition states leading to the formation of the (*S*,*R*), (*S*,*S*), (*R*,*S*) and (*R*,*R*) products are 32.4, 47.4, 58.2 and 62.9 kJ mol^{-1}, respectively. Overall,

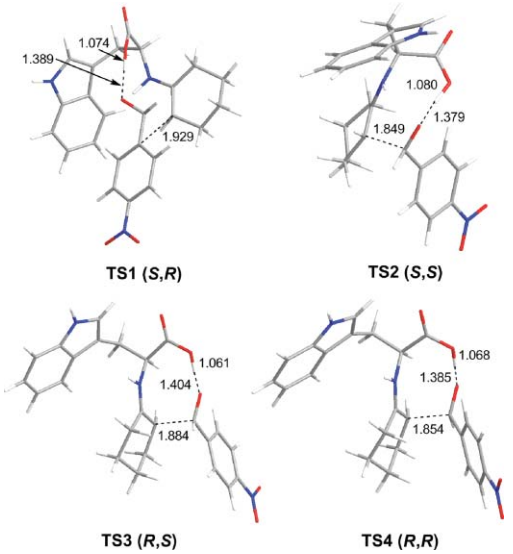


Fig. 2 Optimized (B3LYP/6-31G**) geometries of the four transition states (**TS1–TS4**) leading to the formation of (*S*,*R*), (*S*,*S*), (*R*,*S*) and (*R*,*R*) enantiomeric products. Bond distances are given in Å.

the lowest activation barrier corresponds to the formation of the (*S*,*R*) enantiomer (*via* **TS1**), which is indeed the product observed experimentally. In **TS1**, the *re*-face of the acceptor benzaldehyde is approached by the *re*-face of the catalytically generated chiral enamine (Fig. 2). The calculated relative energies of these four transition states are consistent with the observed high enantioselectivity (96% ee) and *anti* diastereoselectivity (*anti* : *syn* = 5 : 1).[17a] In particular, the (*R*,*S*) enantiomer is formed through **TS3**, which lies 25.8 kJ mol^{-1} higher in energy than **TS1**. Fig. 3 provides a schematic diagram summarizing the structures and relative energies of species involved in the formation of the (*S*,*R*) enantiomeric product.

Closer examination of the optimized geometries of these four low-lying transition-state structures reveals a few important structural effects that contribute to the stereoselectivity of the catalytic aldol reaction. All four transition states (**TS1–TS4**) are characterized by a strong O–H···O hydrogen bond. The O–H and O···H distances are in the ranges 1.06–1.08 Å and 1.38–1.40 Å, respectively (Fig. 2). Close contact between the amino proton and carboxyl oxygen is found in **TS1** and **TS2** (the N–H···O distances are 2.19 and 2.11 Å, respectively). This suggests that a weak N–H···O hydrogen bond is present. Similar findings were reported in the alanine-catalyzed aldol reaction.[22] As in the case of the enamine intermediates (**enam1** and **enam2**), the N–H/π interaction has a stabilizing effect on several transition states. This is readily supported by the NBO second-order perturbation theory energy analysis. Transition states without this stabilizing interaction are significantly higher in energy. In other words, the indole functional group of tryptophan provides a stabilizing effect on the transition states. This result indicates that the indole structural motif of the amino acid is essential to catalyze the direct asymmetric aldol reaction with high stereoselectivity, and provides a possible explanation for the better stereoselectivity of tryptophan over other amino acids. Finally, the higher activation barrier of **TS2** compared to **TS1** is likely to be attributed to the non-bonding repulsion between enamine ring protons and benzaldehyde protons, as reflected in the close H···H contact distance (2.03 Å) in **TS2**. This differential steric effect is confirmed by NBO steric analysis.

It is important to note that the quantum chemical calculations carried out here correspond to gas phase conditions. Several recent studies have demonstrated that the enamine-based organocatalysis "in the presence of water" is best described as a "concentrated organic phase".[14] In other words, the catalytic aldol reaction takes place in a biphasic reaction mixture. To provide a more realistic description of an organic-phase environment, reaction field calculations based on the polarizable continuum model (PCM)

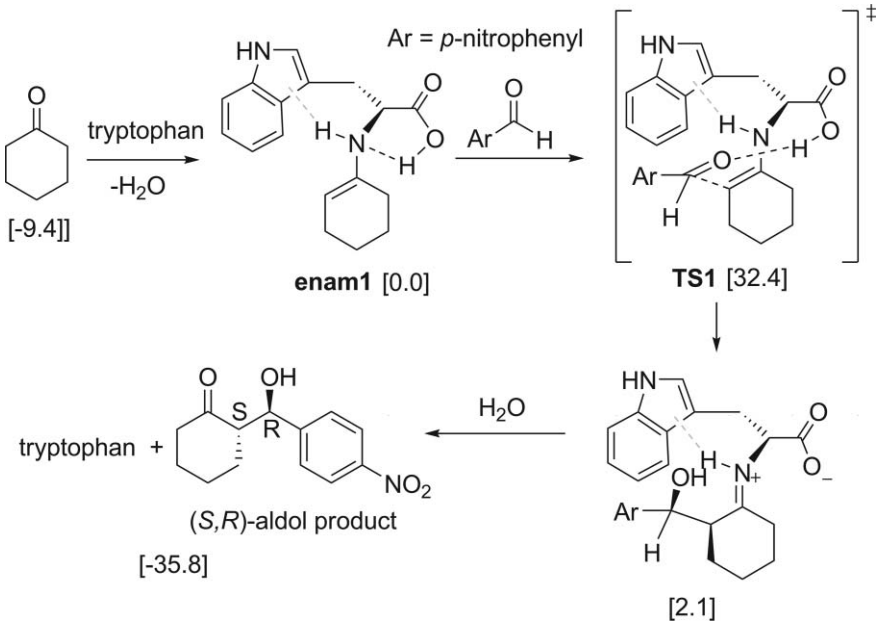


Fig. 3 Schematic diagram of the structures and energies of species involved in the formation of the (*S*,*R*) enantiomeric product. Calculated relative free energies (ΔG_{298}, kJ mol^{-1}) MP2/6-311+G**//B3LYP/6-31G** level, are given in square brackets.

were also performed in cyclohexane solvent. Not surprisingly, the solvent effect on energetics is very small. The calculated activation barriers for the formation of (*S*,*R*), (*S*,*S*), (*R*,*S*) and (*R*,*R*) products are 28.1, 38.6, 52.0 and 55.1 kJ mol^{-1}, respectively. The predicted stereoselectivity in cyclohexane is very close to that calculated in the isolated state.

Conclusions

We have developed highly efficient organocatalytic aldol reactions between cyclic ketones and aromatic aldehydes that can be catalyzed by natural tryptophan in the presence of water. Solvent studies demonstrated that water is the best reaction medium for the described direct asymmetric aldol reactions, and the desired products can be obtained with excellent *anti* selectivity and good enantioselectivity. The reaction mechanism was investigated by performing quantum chemical calculations. We showed that a carboxylic acid-catalyzed enamine mechanism was involved. Moreover, our computational studies provide key insights into the origin of the stereoselectivity, and correctly predict the stereochemistry of the observed product. In particular, the indole moiety of tryptophan is found to play an essential role in stabilising the transition state.

Experimental

General methods

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), br s (broad singlet). Coupling constants (*J*) are reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin-layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatography separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral phase HPLC analysis.

Representative procedure for the tryptophan-catalyzed direct aldol reaction

L-Tryptophan (0.0102 g, 0.05 mmol) was added to a suspension of *p*-nitrobenzaldehyde (0.0755 g, 0.5 mmol), cyclohexanone (0.25 mL, 2.5 mmol) and water (0.18 mL, 10 mmol) at room temperature. The reaction mixture was stirred for 19 h, quenched by adding saturated aqueous ammonium chloride solution, and extracted with dichloromethane several times. The combined organic layers were concentrated, and the residue was purified by flash chromatography on silica gel (EtOAc–hexane = 1 : 3) to give 2-(hydroxy(4-nitrophenyl)methyl)cyclohexanone as a yellow solid (0.1137 g, 91%). Reactions employing other catalysts or substrates were performed in a similar manner.

Computational details

Geometry optimizations were performed with the hybrid B3LYP[26] functional in conjunction with the split-valence polarized 6-31G** basis set. Higher-level relative energies were obtained through single-point energy calculations at MP2 level using a larger 6-311+G** basis set. The MP2 theory is important for reliable prediction of the energies of the transition states and enamine intermediates which are stabilized by N–H$\cdots\pi$ interactions since dispersion is a major source of this weak intermolecular interaction.[23b,27] Frequency calculations based on the B3LYP/6-31G** optimized geometries were performed to verify the nature of stationary points as equilibrium structures or transition states and to evaluate zero-point energies (ZPE). Equilibrium structures are characterized by all real frequencies while transition states have one and only one imaginary frequency. The identities of several key transition states were confirmed by intrinsic reaction coordinate (IRC) calculations. The effect of solvent was investigated by the polarizable continuum model (PCM).[28] PCM-B3LYP/6-311+G** single-point energy calculations in cyclohexane (ε = 2.02) were performed on the gas-phase optimized geometries. Unless otherwise noted, the relative free energies (ΔG_{298}) in the text correspond to the MP2/6-311+G**//B3LYP/6-31G** level. The directly calculated ZPE's were scaled by a factor of 0.9804.[29] All calculations were performed using the *Gaussian 03* suite of programs.[30] Natural bond orbital (NBO)[31] analysis was carried out for all transition states. The donor–acceptor interaction energies of various types of weak molecular interaction in the transition states were estimated using the second-order perturbation theory energy analysis.[31] Charge density analysis, based on Bader's theory of atoms in molecules (AIM)[32] was performed to examine the N–H/π interaction.

Acknowledgements

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