Tetrahedron: *Asymmetry* 24 (2013) 875–882

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# One-pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones catalyzed by amino acid-derived sulfonamides

Haixing Zheng, Qi Liu, Saishuai Wen, Hua Yang *, Yiming Luo *

*School of Chemistry and Chemical Engineering, Central South University, Changsha 410083, PR China*

ARTICLE INFO

*Article history:*
Received 18 April 2013
Accepted 28 May 2013
Available online 26 July 2013

ABSTRACT

An organocatalyzed approach to the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones using amino-acid derived sulfonamides as organocatalysts, which can be easily prepared starting from L-proline, L-alanine, and L-phenylalanine, has been developed in high yields (up to 92%) and with moderate to good enantioselectivities (up to 74% ee). Additionally, opposite enantioselectivities for primary and secondary amino acid sulfonamides have also been observed.



## 1. Introduction

The asymmetric Mannich reaction is one of the most important carbon–carbon bond and carbon–nitrogen bond forming reactions for the synthesis of optically active nitrogen-containing molecules.[1,2] The resulting chiral β-amino carbonyl compounds are valuable precursors in the preparation of many natural products and drugs. The products of the Mannich reaction can often be readily converted into various compounds with useful biological and pharmaceutical properties. Traditionally, asymmetric Mannich reactions are catalyzed by chiral transition-metal complexes.[3–5] In 2000, List et al. reported on the first direct asymmetric three-component Mannich reaction between an aldehyde, *p*-methoxyaniline (*p*-anisidine) and a ketone catalyzed by L-proline.[6,7] This landmark research stimulated the rapid development of many asymmetric organocatalytic Mannich reactions.[8–14] Typically, an organocatalytic approach to an asymmetric Mannich reaction is based on enamine activation of carbonyl compounds using secondary amine (pyrrolidine amide) organocatalysts.[15,16] Other types of organocatalysts such as chiral Brønsted acids,[17] cinchona alkaloids,[18] or phase-transfer catalysts[19] have also been successfully used for Mannich-type reactions.

2-Aryl-2,3-dihydro-4-quinolones, which can be considered as aza-analogues of flavanones, have demonstrated a wide range of biological activities and pharmaceutical properties as anticancer and antibiotic agents.[20,21] Since individual enantiomers of quinolones have different biological activities, it is highly desirable to develop enantioselective methods to access this class of important antibiotics. To the best of our knowledge, only five articles have so far been reported for the synthesis of enantioenriched 2-aryl-2,3-dihydro-4-quinolones. Hayashi[22a] and Hou[22b] made use of transition-metal-mediated catalytic processes and obtained high yields and enantioselectivities. Lu et al.[22c] obtained high yields and excellent enantioselectivities by using bifunctional thiourea catalysts instead of metal catalysts, while including multiple steps for the activation and removal of activating groups. Recently, Pitchumani et al.[22d] reported on a one-pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones catalyzed by per-6-amino-β-cyclodextrin in high yields and enantioselectivities. However, the cyclodextrins were biological macromolecules, which are unstable and difficult to modify to become catalytically active substances. Taking all of these reports into account, the employment of simple organic molecules as organocatalysts, which could not only produce less waste but also avoid complicated separation and purification protocols, is highly desirable.

In 2007, Chandrasekhar et al. reported on a proline-catalyzed one-pot synthesis of 2-aryl-2,3-dihydro-4-quinolones from the intramolecular Mannich reaction of aldehydes with 2-aminoacetophenone,[22e] with good yields being obtained. However, poor enantioselectivity (17% ee) was observed. Inspired by this finding, we designed and synthesized a series of new sulfonamide organocatalysts, which were expected to facilitate the reaction to prepare 2-aryl-2,3-dihydro-4-quinolones in high enantioselectivity and yield. Herein we report application of the amino acid-derived sulfonamides to catalyze the one-pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones.

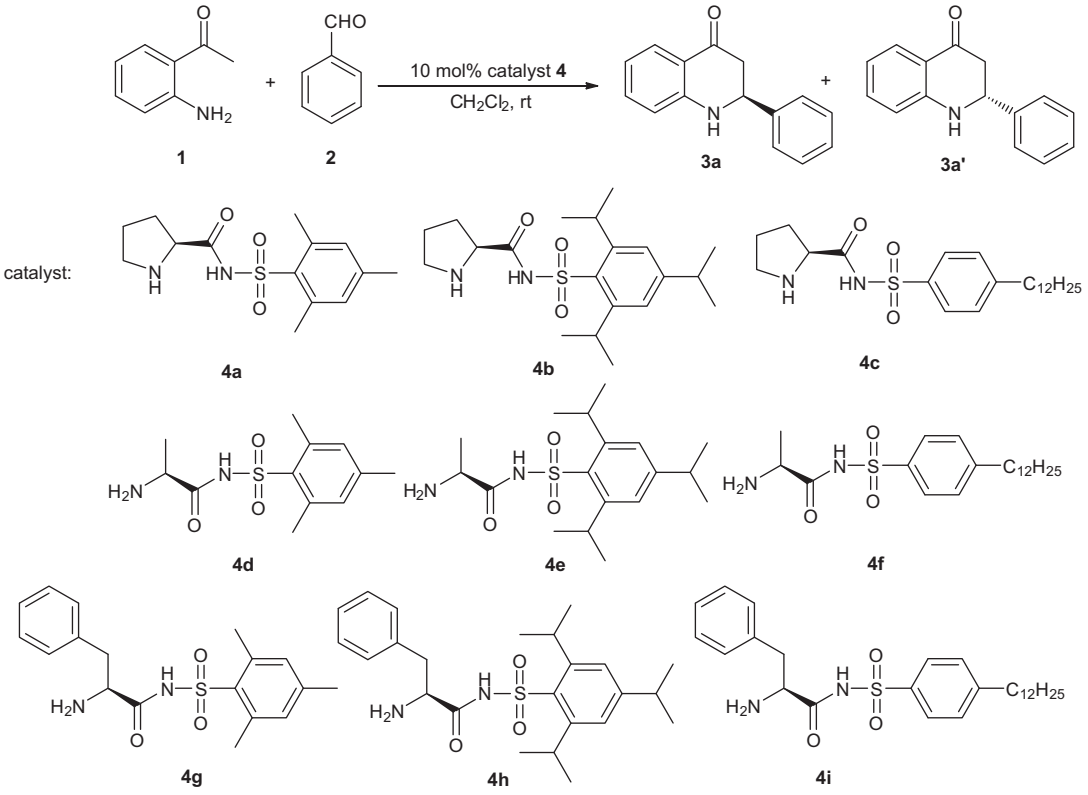
## 2. Results and discussion

Preliminary studies were conducted on 2-aminoacetophenone **1** and benzaldehyde **2** utilizing sulfonamide organocatalysts (Table 1). Catalysts **4a–i** used herein were easily prepared from the coupling reactions between the Boc-protected amino acids and the corresponding sulfonamides followed by deprotection.[23]

* Corresponding authors. Tel.: +86 731 88830833; tel.: +86 731 88864409.
*E-mail addresses:* hyangchem@csu.edu.cn (H. Yang), ymluo@csu.edu.cn (Y. Luo).

0957-4166/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2013.05.028

**Table 1**
Screening of catalysts for the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones[a]



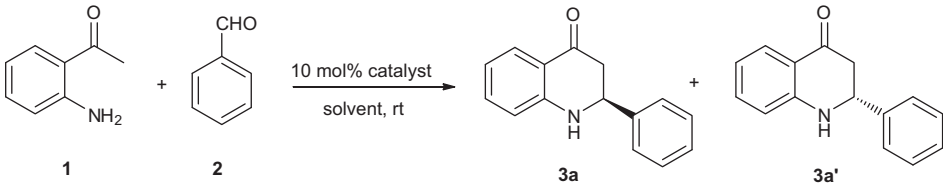

| Entry | Catalyst | Solvent | Yield[b] (%) | ee[c,d] (%) |
|---|---|---|---|---|
| 1 | **4a** | $CH_2Cl_2$ | 85 | 22 |
| 2 | **4b** | $CH_2Cl_2$ | 72 | 14 |
| 3 | **4c** | $CH_2Cl_2$ | 72 | 12 |
| 4 | **4d** | **$CH_2Cl_2$** | **84** | **−25** |
| 5 | **4e** | $CH_2Cl_2$ | 74 | −13 |
| 6 | **4f** | $CH_2Cl_2$ | 78 | −12 |
| 7 | **4g** | $CH_2Cl_2$ | 68 | −16 |
| 8 | **4h** | $CH_2Cl_2$ | 60 | −11 |
| 9 | **4i** | $CH_2Cl_2$ | 62 | −13 |

[a] Reaction conditions: 2-aminoacetophenone **1** (1.0 mmol), benzaldehyde **2** (1.5 mmol), catalyst **4a–i** (0.1 mmol), solvent ($CH_2Cl_2$, 1 mL), room temperature (25 °C), and reaction time (48 h).
[b] Yield of the isolated product after chromatography.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column).
[d] Absolute configurations were assigned through comparison of the specific rotations with literature data.[22a–d]

Initially, all of the reactions were performed under the conditions of 2-aminoacetophenone **1** (1.0 equiv) with benzaldehyde **2** (1.5 equiv) in the presence of 10 mol % catalyst **4a–i** in dichloromethane ($CH_2Cl_2$) at room temperature. Amongst the catalytic systems tested (Table 1), catalytic activities varied significantly. These organocatalysts **4a–i** exhibited good catalytic reactivity for this reaction (entries 1–9) in good yields (62–85%) within 48 h. The primary amine and secondary amine catalysts showed the opposite stereoselectivities for this transformation although these organocatalysts **4a–i** exhibited unsatisfactory enantioselectivities (11–25% ee). The proline sulfonamide catalyst **4a** and the primary amine sulfonamide catalyst **4d** provided superior catalytic activities in good yields (85% and 84%), and reasonable enantioselectivities (22% ee and −25% ee) respectively. It was observed that the introduction of a methyl group at the *ortho*-position of the sulfonamide in the catalyst structure provided the highest enantioselectivity. The existence of a more sterically demanding group such as an *iso*-propyl group, leads to a decrease in enantioselectivity. The proline sulfonamide derivative (2*S*)-*N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide, nicknamed as 'Hua Cat', showed inferior enantioselectivity. As for the primary amino acid derived sulfonamides, the alanine-derived sulfonamides gave comparatively higher chemical yields and enantioselectivities than the phenylalanine series. Presumably, the presence of a benzene ring in the phenylalanine interfered with the interaction between the catalyst and the substrate. Subsequently, catalyst **4a** and catalyst **4d** were selected for further optimization to improve the enantioselectivity of this transformation.

Next, several typical organic solvents (Table 2, entries 1–9) were screened in the presence of 10 mol % **4a** or **4d**. As shown in Table 2, the reaction yields and enantioselectivities were highly solvent dependent. Lower enantioselectivities were obtained when less polar aprotic solvents were used (entries 1–5). More polar solvents afforded the adduct **3** in significantly improved yields (entries 6 and 7). High yields (92%, 90%, entry 7) and moderate enantioselectivities (30% ee, −35% ee, entry 7) were achieved in

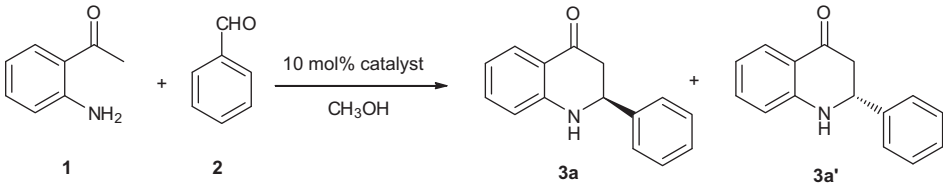
**Table 2**
Screening of solvents for the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones catalyzed by organocatalyst **4a** or **4d**[a]




| Entry | Solvent | Catalyst **4a** | | Catalyst **4d** | |
|---|---|---|---|---|---|
| | | Yield[b] (%) | ee[c,d] (%) | Yield[b] (%) | ee[c,d] (%) |
| 1 | $CH_2Cl_2$ | 85 | 22 | 84 | −25 |
| 2 | $CHCl_3$ | 80 | 25 | 82 | −20 |
| 3 | Toluene | 75 | 26 | 74 | −23 |
| 4 | THF | 77 | 32 | 72 | −35 |
| 5 | MeCN | 62 | 38 | 61 | −41 |
| 6 | DMF | 90 | 25 | 89 | −32 |
| 7 | DMSO | 92 | 30 | 90 | −35 |
| 8 | *i*-PrOH | 65 | 42 | 63 | −43 |
| **9** | **MeOH** | **79** | **45** | **79** | **−51** |
| 10 | $H_2O$ | 21 | 12 | 24 | −14 |
| 11 | Brine | 17 | 14 | 15 | −16 |

[a] Reaction conditions: 2-aminoacetophenone **1** (1.0 mmol), benzaldehyde **2** (1.5 mmol), catalyst **4a** or **4d** (0.1 mmol), solvent (1 mL), room temperature (25 °C), and reaction time (48 h).
[b] Yield of the isolated product after chromatography.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column).
[d] Absolute configurations were assigned by comparison of the specific rotations and chiral chromatography with literature data.[22a–d]

**Table 3**
Screening of the reaction temperature for the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones catalyzed by organocatalyst **4a** or **4d**[a]




| Entry | Catalyst[a] | *T* (°C) | Time (h) | Yield[b] (%) | ee[c,d] (%) |
|---|---|---|---|---|---|
| 1 | **4a** | 25 | 24 | 79 | 45 |
| 2 | **4a** | 0 | 48 | 76 | 52 |
| **3** | **4a** | **−20** | **72** | **68** | **65** |
| 4 | **4a** | −40 | 72 | 45 | 68 |
| 5 | **4d** | 25 | 24 | 76 | −51 |
| 6 | **4d** | 0 | 48 | 70 | −56 |
| **7** | **4d** | **−20** | **72** | **63** | **−70** |
| 8 | **4d** | −40 | 72 | 38 | −72 |

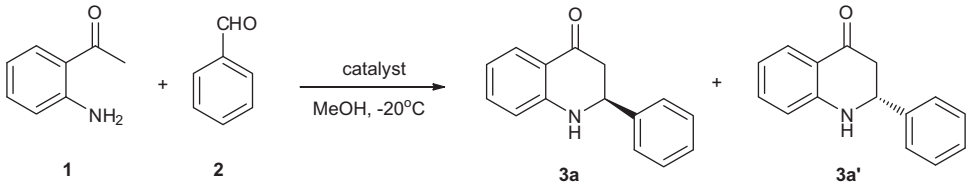
[a] Reaction conditions: 2-aminoacetophenone **1** (1.0 mmol), benzaldehyde **2** (1.5 mmol), catalyst **4a** or **4d** (0.1 mmol), and solvent (MeOH, 1 mL).
[b] Yield of the isolated product after chromatography.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column).
[d] Absolute configurations were assigned by comparison of the specific rotations and chiral chromatography with the literature data.[22a–d]

DMSO (analytic grade). Protic organic solvents such as *i*-PrOH and MeOH seemed to have a beneficial effect on the enantioselectivity (entries 8 and 9). We found that MeOH was the most suitable organic solvent (entry 9). The corresponding product **3** was obtained in moderate yields with the highest enantioselectivity (45% ee, −51% ee) in MeOH. The water compatible behavior of catalysts **4a** and **4d** was also tested. However, only a small amount of the desired product was obtained in water or brine and the enantioselectivities were poor (entries 10 and 11, Table 2). Therefore, MeOH was chosen as the solvent for subsequent tests.

The reaction temperature was also screened for this transformation in order to improve the enantioselectivity further. By decreasing the reaction temperature from room temperature to −20 °C, the enantioselectivity increased from 45% to 65% for **4a** and −51% to −70% for **4d** without a loss of chemical yield (Table 3, entries 3 and 7). Lowering the reaction temperature further (−40 °C) led to sluggish reaction but improved the enantioselectivities slightly. Taking into account the reactivity and enantioselectivity, −20 °C was considered to be the optimal reaction temperature.

Catalyst loading is usually an important issue in organocatalytic reactions. For instance, L-proline is typically used at approximately 20 mol %. As shown in Table 4, when the catalyst loading was less than 20 mol % of **4a** or **4d**, it led to prolonged reaction times and reduced chemical yields (entries 3–4 and 7–8). On the other hand, a higher catalyst loading (30 mol %) provided similar results compared to 20 mol % of catalyst loading for catalyst **4a** or **4d** (entries

**Table 4**
Screening of the catalyst loading for the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones catalyzed by organocatalyst **4a** or **4d**[a]




| Entry | Catalyst | Catalyst loading (mol %) | Time (h) | Yield[b] (%) | ee[c,d] (%) |
|---|---|---|---|---|---|
| 1 | **4a** | 30 | 14 | 83 | 65 |
| **2** | **4a** | **20** | **20** | **82** | **65** |
| 3 | **4a** | 10 | 48 | 65 | 65 |
| 4 | **4a** | 5 | 72 | 53 | 63 |
| 5 | **4d** | 30 | 16 | 79 | −70 |
| **6** | **4d** | **20** | **22** | **72** | **−70** |
| 7 | **4d** | 10 | 48 | 60 | −70 |
| 8 | **4d** | 5 | 72 | 50 | −69 |

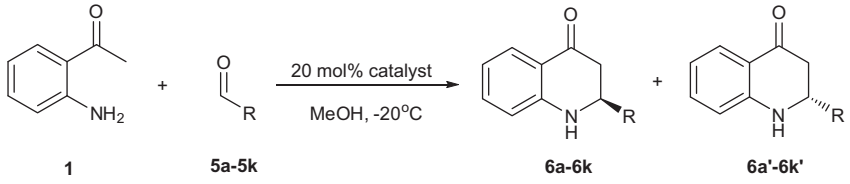
[a] Reaction conditions: 2-aminoacetophenone **1** (1.0 mmol), benzaldehyde **2** (1.5 mmol), solvent (MeOH, 1 mL), and reaction temperature (−20 °C).
[b] Yield of the isolated product after chromatography.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column).
[d] Absolute configurations were assigned by comparison of the specific rotations and chiral chromatography with the literature data.[22a–d]

1–2 and 5–6). Therefore, 20 mol % catalyst loading for **4a** and **4d** was applied in our continued investigation of this transformation.

The reaction scope was explored under the optimized conditions (20 mol % of catalyst in MeOH at −20 °C) for catalysts **4a** and **4d**. The results are summarized in Table 5. The substrate tolerance seems particularly broad. Both aromatic (with various substitution patterns) and aliphatic aldehydes were well suited to this transformation. Good chemical yields and moderate to good enantioselectivities were obtained uniformly, regardless of electronics and substitution pattern. Catalysts **4a** and **4d** consistently afforded the opposite stereoselectivities with all of the substrates tested. Typically, catalyst **4a** afforded the (*S*)-enantiomers while the corresponding (*R*)-enantiomers of the products were obtained by using catalyst **4d**. This observation might open up the pathway to enantioselectively prepare both enantiomers of this type of compounds only using natural amino acid derivatives. The electronic nature of the substituents only had a minor effect on this transformation (Table 5, entries 1–11). For both catalysts, relatively high enantiomeric excesses were observed for the aromatic aldehyde bearing a hydroxyl group in the *ortho*-position, which might be involved in hydrogen-bonding with the catalyst (entry 2, 69%, −74%). The aliphatic aldehyde provided the corresponding adduct with slightly lower enantioselectivity (Table 5, entry 9) than the aromatic aldehydes. The heteroaromatic aldehyde pyridinyl-2-carbaldehyde also gave the corresponding products with 63% and −67% ee, respectively (Table 5, entry 10).

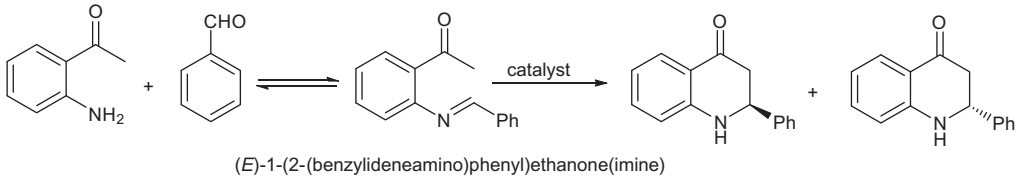
The pathway of this transformation is proposed in Scheme 1. Presumably, an unstable imine is formed via a dehydration

**Table 5**
Asymmetric one-pot synthesis of 2-aryl-2,3-dihydro-4-quinolones catalyzed by **4a** or **4d** with various substituted aldehydes[a]




| Entry | Aldehyde | Product **6** | Catalyst **4a** | | Catalyst **4d** | |
|---|---|---|---|---|---|---|
| | R | | Yield[b] (%) | ee[c,d] (%) | Yield[b] (%) | ee[c,d] (%) |
| 1 | $C_6H_5$– | **6a** | 82 | 65 | 72 | −70 |
| 2 | *o*-$OHC_6H_4$– | **6b** | 85 | 69 | 77 | −74 |
| 3 | *p*-$OHC_6H_4$– | **6c** | 90 | 67 | 79 | −69 |
| 4 | *p*-$BrC_6H_4$– | **6d** | 80 | 61 | 65 | −63 |
| 5 | *m*-$OCH_3C_6H_4$– | **6e** | 88 | 63 | 80 | −66 |
| 6 | *m*-$ClC_6H_4$– | **6f** | 78 | 59 | 66 | −64 |
| 7 | *p*-$NMe_2C_6H_4$– | **6g** | 92 | 68 | 80 | −72 |
| 8 | *p*-$NO_2C_6H_4$– | **6h** | 80 | 60 | 67 | −62 |
| 9 | $(CH_3)_2CH_2CH$– | **6i** | 69 | 59 | 58 | −60 |
| 10 | 2-Pyridinyl– | **6j** | 86 | 63 | 75 | −67 |
| 11 | 3-Indolyl– | **6k** | 88 | 66 | 78 | −68 |

[a] Reaction conditions: 2-aminoacetophenone **1** (1.0 mmol), aldehyde **6a–6k** (1.5 mmol), catalyst (**4a** or **4d**, 0.2 mmol), solvent (MeOH, 1 mL), reaction temperature (−20 °C), and reaction time (24 h).
[b] Yield of the isolated product after chromatography.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H column).
[d] Absolute configurations were assigned by comparison of the specific rotations and chiral chromatography with the literature data.[22a–d]




**Scheme 1.**

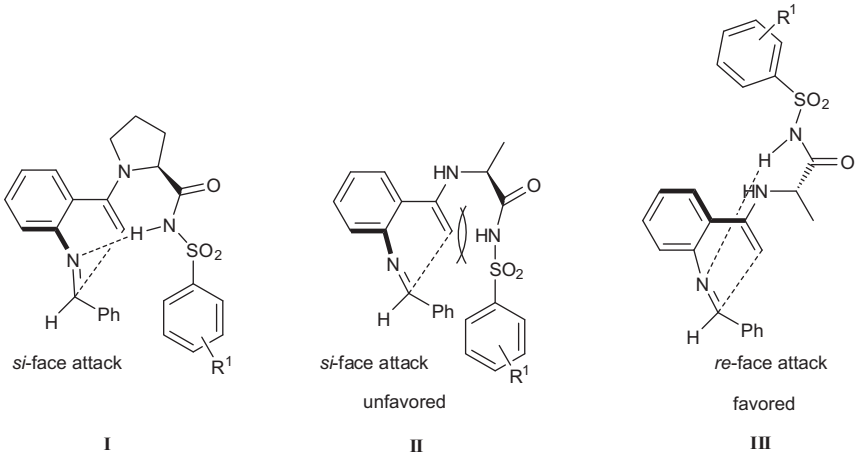



**Figure 1.** Proposed transition state models for the intramolecular Mannich reaction catalyzed by amino acid-derived sulfonamides.

reaction at first. Then, the amino acid-derived sulfonamides catalyze the intramolecular Mannich reaction to provide 2-phenyl-2,3-dihydroquinolin-4(1*H*)-ones. In order to account for the stereochemical outcome, several plausible transition state models are proposed and shown in Figure 1. The transition state model **I**, which is attributed to the reaction catalyzed by proline-derived sulfonamides **4a–c**, is similar to the *one*-proline enamine mechanism proposed by List and Houk.[24] Here the carbonyl group of the imine is activated to form an enamine by the N–H of the pyrrolidine moiety, while the C=N of the imine is also activated by the forming hydrogen-bond between the nitrogen-atom and the sulfonamide N–H. The enamine attacks the carbon atom of the C=N on one face and leads to the formation of the favored (*S*)-enantiomer as the major product. However, the (*R*)-enantiomer is favored as the major product when using primary amine sulfonamides **4d–i** to catalyze the aforementioned reaction. Two plausible transition state models **II** and **III** are proposed to elaborate upon this stereoselectivity. As shown in transition state model **II** (*si*-face attack), a severe steric repulsion is involved from the interaction between sulfonamide unit and the enamine part. However, this steric effect could be relieved by simply rotating the sulfonamide unit away from the enamine in the transition state model **III** (*re*-face attack), leading to formation of the corresponding (*R*)-enantiomer.

## 3. Conclusion

In conclusion, an efficient organocatalytic approach for the asymmetric preparation of biologically important 2-aryl-2,3-dihydro-quinolin-4(1*H*)-ones has been developed by utilizing the readily prepared amino acid-derived sulfonamides. Good yields (up to 92%) and moderate to good enantiomeric excesses (up to 74%) were achieved. The primary and secondary amine sulfonamides provided the opposite enantioselective outcomes respectively, which may facilitate the preparation of both enantiomers for 2-aryl-2,3-dihydro-quinolin-4(1*H*)-ones using only natural amino acid derivatives. Moreover, this protocol may find wide applications in the synthesis of other bioactive nitrogen containing cyclic structures in future research.

## 4. Experimental

### 4.1. General

All reagents were used without purification as commercially available. The reactions were monitored by TLC (thin layer chromatography). Purification of the reaction products was carried out by flash chromatography on silica gel (200–300 mesh). Chemical yields refer to pure isolated substances. Melting points were measured on a XR-4 apparatus (thermometer uncorrected). Optical rotations were recorded with a Jasco-P-2000 digital polarimeter. Nuclear Magnetic Resonance (NMR) spectra were measured using a Bruker Avance 400 spectrometer operating at 100 MHz for $^{1}$H NMR and 100 MHz. Chemical shift values ($\delta$) are reported in ppm relative to either TMS at 0.0 ppm or the NMR solvent peak. NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Infrared spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrophotometer using KBr disks in the 400–4000 cm$^{-1}$ region. Enantiomeric excesses were determined by HPLC using Chiralcel OD-H (Daicel Chemical Industries) column using *n*-Hexane/*i*-PrOH as a mobile phase and detected by UV at 365 nm. The absolute configurations of products **3a** and **6a–k** were assigned by comparison of the sign of optical rotation with literature data.[22a–d] Compounds **4b** and **4c** (Hua Cat) were prepared according to the reported procedures.[25,26]

### 4.2. General method for the synthesis of catalysts 4a–4f

Under a dry nitrogen atmosphere, to a stirred solution of substituted benzenesulfonamide (10.0 mmol) in dichloromethane (40 mL) were added Boc-amino acid (11.0 mmol), DMAP (1.21 g,

11.0 mmol), and EDCI (2.12 g, 11.0 mmol). The resulting mixture was stirred at room temperature for 72 h before being partitioned between EtOAc (150 mL) and aq. HCl (1 M, 100 mL). The organic layer was washed with half-saturated brine (2 × 40 mL). The dried ($Na_2SO_4$) extract was concentrated in vacuo and the crude product was used for the next step without further purification. The deprotection of Boc-protected sulfonamides was carried out according to the general method.[27] A solution of crude Boc-protected sulfonamides in dichloromethane (20 mL) was cooled to 0 °C. Trifluoroacetic acid (5 mL) was added dropwise to this chilled solution and the reaction mixture was stirred at room temperature for 2 h. Next, the solvent and excess TFA were removed in vacuo. The residue was redissolved in dichloromethane (10 mL), neutralized with 28% ammonia and the aqueous layer extracted with dichloromethane (5 × 15 mL). The combined extracts were washed with saturated NaCl aqueous solution, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Next, the resulting mixture was purified via flash chromatography ($CH_2Cl_2$/MeOH = 19:1) to provide the corresponding sulfonamides **4a–4i**.[23]

### 4.3. Characterization of sulfonamides 4a, 4d–4i

#### 4.3.1. *N*-2,4,6-Tris-(methylbenzene)sulfonyl-L-proline amide 4a

White solid, yield: 1.56 g, 48%; $[\alpha]_D^{25} = +67.7$ (*c* 1, $CHCl_3$); mp: 130–132 °C; IR (KBr disk) *v*: 3495, 2979, 2774, 1603, 1454, 1381, 1264, 1126, 935, 822, 658 $cm^{-1}$; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 6.88 (s, 2H), 4.35 (t, *J* = 7.4 Hz, 1H), 3.31–3.37 (m, 2H), 2.66 (s, 6H), 2.30–2.40 (m, 2H), 2.26 (s, 3H), 1.92–2.01 (m, 2H), 1.82–1.84 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 173.8, 141.2, 138.8, 137.7, 61.6, 46.3, 30.1, 24.8, 22.7, 21.1.

#### 4.3.2. *N*-2,4,6-Tris-(methylbenzene)sulfonyl-L-alanine amide 4d

White powder, yield: 1.54 g, 52%; $[\alpha]_D^{25} = -34.5$ (*c* 1, MeOH); mp: 222–223 °C; IR (KBr disk) *v*: 3155, 3102, 2932, 1630, 1568, 1397, 1280, 1056, 969, 878, 680, 588 $cm^{-1}$; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 7.71 (br s, 1H), 6.78 (s, 2H), 3.37–3.45 (m, 3H), 2.58 (s, 6H), 2.18 (s, 3H), 1.25 (d, *J* = 4.0 Hz, 3H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 173.6, 140.3, 138.7, 138.4, 130.6, 79.6, 50.9, 23.0, 20.7, 17.7.

#### 4.3.3. *N*-2,4,6-Tris-(isopropylbenzene)sulfonyl-L-alanine amide 4e

White powder, yield: 1.64 g, 42%; $[\alpha]_D^{25} = -25.2$ (*c* 1, MeOH); mp: 207–210 °C; IR (KBr disk) *v*: 3181, 2956, 2868, 1704, 1596, 1397, 1364, 1137, 967, 878, 684, 567 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.00 (s, 2H), 4.61 (t, *J* = 4.0 Hz, 2H), 3.37–338 (m, 1H), 2.80–2.83 (m, 2H), 1.86–1.87 (m, 3H), 1.28 (d, *J* = 4.0 Hz, 3H), 1.13 (br s, 18H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 173.8, 149.5, 140.3, 123.4, 51.7, 39.4, 28.4, 26.5, 24.2, 23.7,17.8.

#### 4.3.4. *N*-4-Dodecylbenzenesulfonyl-L-alanine amide 4f

White solid, yield: 2.35 g, 54%; $[\alpha]_D^{25} = -77.4$ (*c* 1, $CHCl_3$); mp: 198–200 °C; IR (KBr disk) *v*: 3498, 3098, 2946, 2846, 1627, 1587, 1468, 1367, 1280, 1135, 869, 672, 587 $cm^{-1}$; $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 7.56–7.67 (m, 2H), 7.17–7.20 (m, 2H), 3.76–3.81 (m, 1H), 0.68–1.91 (m, 30H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 173.4, 140.6, 136.5, 128.8, 127.4, 55.7, 45.6, 45.1, 36.9, 36.1, 31.8, 29.8, 29.5, 29.2, 27.6, 27.3, 22.7, 22.4, 14.6, 14.3, 12.3.

#### 4.3.5. *N*-2,4,6-Tris-(methylbenzene)sulfonyl-L-phenylalanine amide 4g

Light yellow powder, yield: 1.86 g, 49%; $[\alpha]_D^{25} = -64.4$ (*c* 1, MeOH); mp: 230–232 °C; IR (KBr disk) *v*: 3461, 3029, 2924, 1629, 1603, 1491, 1359, 1227, 1057, 957, 826, 698, 588 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.08–7.15 (m, 3H), 7.01 (d, *J* = 12.0 Hz, 2H), 6.91 (s, 2H), 4.09 (br s, 1H), 3.20–3.24 (m, 2H), 2.99–3.05 (m, 2H), 2.58 (s, 6H), 2.29 (s, 3H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 173.6, 140.5, 138.6, 138.4, 136.6, 131.0, 130.2, 128.2, 127.1, 56.6, 37.8, 23.3, 21.4.

#### 4.3.6. *N*-2,4,6-Tris-(isopropylbenzene)sulfonyl-L-phenylalanine amide 4h

Light yellow powder, yield: 2.03 g, 43%; $[\alpha]_D^{25} = -46.2$ (*c* 1, MeOH); mp: 150–152 °C; IR (KBr disk) *v*: 3426, 2959, 2868, 1740, 1601, 1496, 1362, 1239, 1060, 977, 880, 672, 566 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.05–7.30 (m, 7H), 4.33 (t, *J* = 4.8 Hz, 1H), 3.43 (d, *J* = 4.0 Hz, 1H), 2.85–2.92 (m, 2H), 2.39–2.41 (m, 1H), 1.15–1.26 (m, 18H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 172.1, 149.5, 149.2, 139.9, 137.1, 129.9, 128.9, 127.1, 122.6, 56.5, 37.9, 33.8, 28.6, 25.3, 25.1, 24.2.

#### 4.3.7. *N*-4-Dodecylbenzenesulfonyl-L-phenylalanine amide 4i

White powder, yield: 2.60 g, 50%; $[\alpha]_D^{25} = -98.2$ (*c* 1, MeOH); mp: 206–207 °C; IR (KBr disk) *v*: 3085, 2956, 2926, 1658, 1622, 1494, 1294, 1137, 979, 898, 699, 585 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.83–7.89 (m, 4H), 6.93–6.99 (m, 5H), 4.58 (br s, 1H), 3.22 (d, *J* = 3.0 Hz, 2H), 2.58–2.63 (m, 1H); 0.79–1.63 (m, 25H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 170.1, 135.3, 130.0, 128.7, 127.9, 127.7, 127.2, 55.3, 45.5, 45.2, 36.8, 36.3, 31.7, 29.7, 29.4, 29.1, 27.5, 27.1, 22.6, 22.4, 14.4, 14.3, 12.4.

### 4.4. General procedure for the synthesis of 2,3-dihydro-4-quinolone derivatives and characterization for compounds 6a–6k

To a stirred solution of 2-aminoacetophenone **1** (135 mg, 1.0 mmol) and aldehydes **5** (1.5 mmol) in MeOH (1 mL), catalyst **4a** or **4d** (0.2 mmol) was added at −20 °C. The reaction mixture was stirred at the same temperature for the required time. After the 2-aminoacetophenone was consumed as determined by TLC analysis, the mixture was treated with saturated ammonium chloride solution (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via silica gel column chromatography (ethyl acetate/petroleum ether = 1:5) to give compounds **6a–6k**.[22e]

#### 4.4.1. 2-Phenyl-2,3-dihydroquinolin-4(1*H*)-one 6a

Pale yellow solid, mp: 150–151 °C (lit.[22d] mp: 149–150 °C); Catalyzed by **4a**: 183 mg, 82% yield; 65% ee, $[\alpha]_D^{25} = +17.9$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 161 mg, 72% yield; −70% ee; $[\alpha]_D^{25} = -19.4$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 8.2 min (major) and 9.9 min (minor); Catalyzed by **4d**: retention time: 8.4 min (minor) and 10.1 min (major); IR (KBr disk) *v*: 3324, 3079, 1641, 1607, 1505, 1397, 1252, 1121, 740 $cm^{-1}$:$^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.87–7.90 (m, 1H), 7.46–7.49, (m, 2H), 7.33–7.43 (m, 4H), 6.78–6.82 (m, 1H), 6.70–6.73 (m, 1H), 4.75–4.79 (m, 1H), 4.50 (br s, 1H), 2.81–2.90 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.8, 151.3, 140.7, 135.0, 128.7, 128.2, 127.2, 126.3, 118.6, 117.8, 115.4, 57.8, 45.8.

#### 4.4.2. 2-(2-Hydroxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 6b

Yellow solid, mp: 165–167 °C (lit.[22d] mp: 164–168 °C); Catalyzed by **4a**: 203 mg, 85% yield; 69% ee, $[\alpha]_D^{25} = +29.6$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 184 mg, 77% yield; −74% ee, $[\alpha]_D^{25} = -31.8$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 5.3 min (major) and 8.5 min (minor); Catalyzed by **4d**: retention time: 5.4 min (minor) and 8.8 min (major); IR (KBr disk) *v*: 3539, 3310, 1606, 1538, 1389, 1243, 1095, 768 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.93–7.95 (m, 1H), 7.76

(s, 1H), 7.40–7.44 (m, 1H), 7.16–7.24 (m, 1H), 6.90–6.95 (m, 1H), 6.83–6.88 (m, 4H), 4.87–4.92 (m, 1H), 4.72 (s, 1H), 3.06–3.13 (m, 1H), 2.82–2.86 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 193.6, 155.3, 150.6, 135.5, 129.9, 128.0, 127.8, 124.8, 120.7, 120.6, 120.5, 117.4, 117.3, 57.6, 43.6.

#### 4.4.3. 2-(4-Hydroxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 6c

Pale yellow solid, mp: 156–159 °C (lit.[22d] mp: 158–161 °C); Catalyzed by **4a**: 215 mg, 90% yield; 67% ee, $[\alpha]_D^{25} = +22.4$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 189 mg, 79% yield; −69% ee, $[\alpha]_D^{25} = -23.1$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 10.5 min (major) and 16.0 min (minor); Catalyzed by **4d**: retention time: 10.4 min (minor) and 15.7 min (major); IR (KBr disk) *v*: 3548, 3067, 1653, 1527, 1498, 1267, 1103, 957, 898, 768 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.94–7.96 (m, 1H), 7.22–7.26 (m, 3H), 6.77–6.80 (m, 4H), 5.16–5.21 (m, 1H), 4.64 (br s, 2H), 3.03 (dd, *J* = 15.4, 5.6 Hz, 1H), 2.81–2.84 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.4, 156.5, 149.6, 135.6, 131.0, 127.9, 127.1, 123.3, 117.9, 117.1, 116.1, 55.5, 42.6.

#### 4.4.4. 2-(4-Bromophenyl)-2,3-dihydroquinolin-4(1*H*)-one 6d

Yellow solid, mp: 160–162 °C (lit.[28] mp: 160 °C); Catalyzed by **4a**: 241 mg, 80% yield; 61% ee, $[\alpha]_D^{25} = +16.8$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 196 mg, 65% yield; −63% ee, $[\alpha]_D^{25} = -17.4$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 8.8 min (major) and 17.9 min (minor); Catalyzed by **4d**: retention time: 8.9 min (minor) and 18.0 min (major); IR (KBr disk) *v*: 3343, 2901, 1623, 1345, 1112, 1023, 821, 713 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.47–7.54 (m, 2H), 7.27–7.36 (m, 3H), 6.76–6.78 (m, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 4.72 (dd, *J* = 12.7, 4.7 Hz, 1H), 4.43 (br s, 1H), 2.79–2.85 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 192.8, 151.4, 140.2, 135.4, 132.6, 128.3, 127.6, 122.3, 119.1, 118.7, 116.5, 57.8, 46.5.

#### 4.4.5. 2-(3-Methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one 6e

Brownish yellow solid, mp: 128–130 °C (lit.[22d] mp: 129–131 °C); Catalyzed by **4a**: 223 mg, 88% yield; 63% ee, $[\alpha]_D^{25} = +22.1$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 202 mg, 80% yield; −66% ee, $[\alpha]_D^{25} = -23.2$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 9.2 min (major) and 11.8 min (minor); Catalyzed by **4d**: retention time: 9.4 min (minor) and 12.0 min (major); IR(KBr disk) *v*: 3348, 2923, 1659, 1375, 1234, 1191, 1073, 847 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95–7.97 (m, 1H), 7.21–7.28 (m, 2H), 6.98–7.05 (m, 2H), 6.77–6.82 (m, 3H), 5.71 (br s, 1H), 5.14–5.17 (m, 1H), 3.76 (s, 3H), 2.95–3.06 (m, 1H), 2.73–2.84 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 191.5, 159.7, 149.6, 143.6, 130.8, 129.4, 127.0, 123.2, 121.3, 117.8, 116.7, 114.4, 112.8, 55.9, 55.6,42.3.

#### 4.4.6. 2-(3-Chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one 6f

Pale yellow solid, mp: 144–146 °C (lit.[22d]mp: 143–145 °C); Catalyzed by **4a**: 200 mg, 78% yield; 59% ee, $[\alpha]_D^{25} = +14.2$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 170 mg, 66% yield; −64% ee, $[\alpha]_D^{25} = -15.4$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$= 365 nm, Catalyzed by **4a**: retention time: 11.3 min (major) and 15.6 min (minor); Catalyzed by **4d**: retention time: 11.2 min (minor) and 15.7 min (major); IR(KBr disk) *v*: 3314, 2919, 1656, 1608, 1438, 1284, 1105, 758 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93–7.96 (m, 1H), 7.48 (s, 1H), 7.25–7.32 (m, 4H), 6.78–6.80 (m, 2H), 5.76 (br s, 1H), 5.14–5.20 (m, 1H), 3.04 (dd, *J* = 15.0, 3.3 Hz, 1H), 2.84–2.86 (m,1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.5, 151.4, 143.1, 135.5, 134.8, 130.1, 128.6, 127.4, 126.7, 124.6, 119.0, 118.7, 116.0, 57.8, 46.2.

#### 4.4.7. 2-(4-(Dimethylamino)phenyl)-2,3-dihydroquinolin-4(1*H*)-one 6g

Yellow solid, mp: 182–185 °C (lit.[22d] mp: 182–184 °C); Catalyzed by **4a**: 245 mg, 92% yield; 68% ee, $[\alpha]_D^{25} = +18.2$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 213 mg, 80% yield; −72% ee, $[\alpha]_D^{25} = -19.3$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 10.4 min (major) and 14.3 min (minor); Catalyzed by **4d**: retention time: 10.2 min (minor) and 14.0 min (major); IR (KBr disk) *v*: 3357, 2898, 1649, 1478, 1328, 1198, 1056, 890, 756 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96–7.98 (m, 1H), 7.24–7.27 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.77–6.80 (m, 2H), 6.59–6.62 (m, 2H), 5.79 (br s, 1H), 5.16 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.53 (s, 6H), 3.02–3.05 (m, 1H), 2.82 (dd, *J* = 15.4, 3.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 193.9, 151.8, 150.6, 135.3, 128.4, 127.5, 127.2, 118.8, 118.1, 115.9, 112.4, 57.9, 46.3, 40.5.

#### 4.4.8. 2-(4-Nitrophenyl)-2,3-dihydroquinolin-4(1*H*)-one 6h

Orange solid, mp: 201–202 °C (lit.[22d] mp: 200–202 °C); Catalyzed by **4a**: 214 mg, 80% yield; 60% ee, $[\alpha]_D^{25} = +17.9$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 180 mg, 67% yield; −62% ee,$[\alpha]_D^{25} = -19.4$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 13.6 min (major) and 18.5 min (minor); Catalyzed by **4d**: retention time: 13.5 min (minor) and 18.4 min (major); IR (KBr disk) *v*: 3358, 2910, 1670, 1467, 1368, 1188, 1073, 868, 762 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16–8.19 (m, 2H), 7.94–7.97 (m, 1H), 7.82–7.85 (m, 2H), 7.24–7.27 (m, 1H), 6.79–6.82 (m, 2H), 5.80 (br s, 1H), 5.22–5.24 (m, 1H), 2.97 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.79 (dd, *J* = 15.6, 5.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 190.6, 151.3, 141.5, 139.7, 134.8, 128.6, 124.3, 123.8, 118.6, 117.4, 115.8, 57.3, 47.1.

#### 4.4.9. 2-Isobutyl-2,3-dihydroquinolin-4(1*H*)-one 6i

Brownish yellow sticky oil; Catalyzed by **4a**: 140 mg, 69% yield; 59% ee, $[\alpha]_D^{25} = +24.8$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 118 mg, 58% yield; −60% ee, $[\alpha]_D^{25} = -25.2$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 9.7 min (major) and 11.5 min (minor); Catalyzed by **4d**: retention time: 9.5 min (minor) and 11.1 min (major); IR (neat) *v*: 3360, 2945, 1664, 1345, 1278, 1130, 898, 749 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.92–7.94 (m, 1H), 7.24–7.27 (m, 1H), 6.75–6.81 (m, 2H), 5.48 (br s, 1H), 3.96–4.04 (m, 1H), 2.23–2.28 (m, 1H), 2.11–2.18 (m, 1H), 1.36–1.56 (m, 3H), 0.88 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.5, 150.8, 131.6, 127.2, 121.9, 116.8, 116.4, 46.5, 43.9, 43.1, 24.9, 22.2.

#### 4.4.10. 2-(Pyridin-2-yl)-2,3-dihydroquinolin-4(1*H*)-one 6j

Brownish yellow solid, mp: 127–129 °C (lit.[22d] mp: 128–130 °C); Catalyzed by **4a**: 193 mg, 86% yield; 63% ee, $[\alpha]_D^{25} = +18.4$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 168 mg, 75% yield; −67% ee, $[\alpha]_D^{25} = -19.6$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$= 365 nm, Catalyzed by **4a**: retention time: 7.8 min (major) and 11.2 min (minor); Catalyzed by **4d**: retention time: 7.6 min (minor) and 11.0 min (major); IR (KBr disk) *v*: 3365, 2952, 1668, 1607, 1323, 1247, 1154, 1067, 983, 750 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.58 (d, *J* = 7.8 Hz, 1H), 7.86–7.88 (m, 1H), 7.63 (m, 1H), 7.15–7.34 (m, 3H), 6.77–6.87 (m, 2H), 5.15 (dd, *J* = 9.0, 3.4 Hz, 1H), 4.48 (br s, 1H), 3.13–3.16 (m, 1H), 2.77 (dd, *J* = 15.6, 3.9 Hz,

1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 191.7, 153.5, 150.1, 140.9, 136.7, 134.5, 131.4, 126.8, 125.0, 124.1, 117.1, 115.7, 52.1, 46.3.

#### 4.4.11. 2-(4-(1*H*-Indol-3-yl)phenyl)-2,3-dihydroquinolin-4(1*H*)-one 6k

Yellow solid, mp: 170–172 °C (lit.[28] mp: 172 °C); Catalyzed by **4a**: 231 mg, 88% yield; 66% ee, $[\alpha]_D^{25} = +10.9$ (*c* 0.5, $CHCl_3$); Catalyzed by **4d**: 204 mg, 78% yield; -68% ee, $[\alpha]_D^{25} = -11.2$ (*c* 0.5, $CHCl_3$); HPLC analysis: Diacel Chiralcel OD-H, *n*-Hexane/*i*-PrOH = 70/30, flow rate = 1 mL/min, $\lambda$ = 365 nm, Catalyzed by **4a**: retention time: 8.8 min (major) and 18.0 min (minor); Catalyzed by **4d**: retention time: 8.5 min (minor) and 17.6 min (major); IR (KBr disk) $\nu$ :3335, 2922, 1648, 1602, 1328, 1267, 1134, 1027, 973, 740 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.30 (br s, 1H), 7.90–7.92 (m, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.31–7.42 (m, 2H), 7.14–7.25 (m, 3H), 6.76–6.80 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.08 (dd, *J* = 12.6, 3.4 Hz, 1H), 4.66 (br s, 1H), 3.12–3.20 (m, 1H), 2.86–2.91 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 194.4, 151.7, 136.4, 135.5, 127.7, 125.5, 122.7, 122.2, 119.9, 119.3, 119.0, 118.3, 115.8, 111.5, 51.1, 45.2.

## Acknowledgments

We gratefully acknowledge the financial support from the Central South University, National Natural Science Foundation of China (21276282) and Hunan Provincial Science & Technology Department (2012WK2007).

## References

1. For recent reviews, see (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartolim, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171; (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4338–4360; (c) Longbottom, D. A.; Franckevicius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichim. Acta* **2008**, *41*, 3–11.
2. For reviews of enantioselective Mannich reactions, see: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–107; (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797–5803; (c) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348–352.
3. Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089–2100.
4. Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569.
5. Charette, A. B.; Boezio, A. A.; Cote, A.; Moreau, E.; Pytkowicz, J.; Desrosiers, J. N.; Legault, C. *Pure Appl. Chem.* **2005**, *77*, 1259–1267.
6. List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.
7. List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.
8. Tanaka, F.; Barbas, C. F. In *Aldol and Mannich-Type Reactions*; Dalko, P., Ed.; Wiley-VCH: Weinheim, 2007; pp 19–55.
9. Verkade, J. M. M.; Hemert, L. J. C. V.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41.
10. Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.
11. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
12. Xu, L.-W.; Lu, Y.-X. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053.
13. Davie, E. A. C.; Miler, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.
14. Xu, L.-W.; Luo, J.; Lu, Y.-X. *Chem. Commun.* **2009**, 1807–1821.
15. Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212.
16. Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 2246–2249.
17. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.
18. Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257.
19. Ooi, T.; Kameda, M.; Fujii, J.-I.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397–2399.
20. (a) Hradil, P.; Hlavac, J.; Soural, M.; Hajduch, M.; Kolar, M.; Vecerova, R. *Mini-Rev. Med. Chem.* **2009**, *9*, 696–708; (b) Larsen, R. D. In *Science of Synthesis*; Black, D. S., Ed.; Thieme: Stuttgart, 2005; Vol. 15, p 551; (c) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155–1163.
21. Zhang, S.-X.; Feng, J.; Kuo, S.-C.; Brossi, A.; Hamel, E.; Tropsha, A.; Lee, K.-H. *J. Med. Chem.* **2000**, *43*, 167–177.
22. (a) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5317–5319; (b) Lei, B.-L.; Ding, C.-H.; Hou, X.-L. *J. Am. Chem. Soc.* **2009**, *131*, 18250–18251; (c) Liu, X.-Q.; Lu, Y.-X. *Org. Lett.* **2010**, *12*, 5592–5595; (d) Kanagaraj, K.; Pitchumani, K. *J. Org. Chem.* **2013**, *78*, 744–751; (e) Chandrasekhar, S.; Vijeender, K.; Sridhar, C. *Tetrahedron Lett.* **2007**, *48*, 4935–4937.
23. Wu, Y.-Y.; Zhang, Y.-Z.; Yu, M.-L.; Zhao, G.; Wang, S.-W. *Org. Lett.* **2006**, *8*, 4417–4420.
24. (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283; (b) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16–17; (c) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479; (d) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839–5842; (e) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557.
25. Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141–1146.
26. Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649–4652.
27. Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96.
28. Chandrasekhar, S.; Chatla, S.; Mukhopadhyay, D.; Ganganna, B.; Vijeender, S.; Srihari, P.; Bhadra, U. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 645–648.