Organocatalytic Asymmetric Aldol Reaction of Arylglyoxals and Hydroxyacetone: Enantioselective Synthesis of 2,3-Dihydroxy-1,4-diones

Yu-Hao Zhou, Yu-Zu Zhang, Zhu-Lian Wu, Tian Cai, Wei Wen * and Qi-Xiang Guo *

Key Laboratory of Applied Chemistry of Chongqing Municipality, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China; zyh8182868@email.swu.edu.cn (Y.-H.Z.); zhyzlongzhz@126.com (Y.-Z.Z.); wzl12@swu.edu.cn (Z.-L.W.); caitian@swu.edu.cn (T.C.)

* Correspondence: wenwei1989@swu.edu.cn (W.W.); qxguo@swu.edu.cn (Q.-X.G.)

Abstract: A highly efficient quinine-derived primary-amine-catalyzed asymmetric aldol addition of hydroxyacetone to arylglyoxals is described. Structurally diverse anti-2,3-dihydroxy-1,4-diones were generated in high yields, with good diastereoselectivities and enantioselectivities.

Keywords: organocatalysis; aldol reaction; asymmetric synthesis; 2,3-Dihydroxy-1,4-dione; arylglyoxal

1. Introduction

The enantioselective aldol reaction is among the most important synthetic tools for C–C bond formation in organic synthesis [1–3]. Arylglyoxals are endogenous α-oxoaldehydes that have been extensively used as electrophiles in related enantioselective aldol processes to afford synthetically important chiral 2-hydroxy-1,4-dicarbonyl compounds [4–19]. For example, in 2009, Feng and coworkers developed an asymmetric aldol-type reaction between arylglyoxal derivatives and 2-oxindoles catalyzed by an N,N′-dioxide-Sc(III) complex [4]. Various optically active 3-substituted oxindoles bearing α-hydroxyl ketone units were produced in excellent yields, with excellent diastereoselectivities and enantioselectivities. Subsequently, Hayashi and coworkers reported a chiral diarylprolinol-catalyzed direct aldol reaction of glyoxal derivatives with aldehydes, affording chiral 2-hydroxy-1,4-dicarbonyl compounds with good experimental outcomes [6]. Zhao and coworkers also reported an aldol reaction between cyclic ketones and arylglyoxals using a cinchona alkaloid-derived thiourea catalyst [10]. Most recently, Wang and coworkers disclosed an aldol reaction of 2-hydroxyacetophenone with ethyl glyoxylate catalyzed by a dinuclear zinc–azaphenol complex [11]. The desired aldol products were obtained with moderate diastereoselectivities. Several other research groups have also reported corresponding catalytic asymmetric aldol or aldol-type reactions, employing phenylglyoxal hydrate in a single example [12–19]. In general, reported examples have mainly focused on the catalytic asymmetric synthesis of α-hydroxyl ketones or 2,3-dihydroxyl esters (Scheme 1a,b), while the catalytic asymmetric construction of 2,3-dihydroxyl carbonyl compounds has yet to be explored. 2,3-Dihydroxyl-1,4-dicarbonyl compounds are known as excellent building blocks for the synthesis of multiple-hydroxyl-containing carbohydrates [20,21]. The direct catalytic asymmetric aldol addition of hydroxyacetone to arylglyoxals is an ideal transformation that can be anticipated to construct such 2,3-dihydroxyl-1,4-carbonyl units (Scheme 1c). Herein, we report a chiral primary amine-catalyzed direct organocatalytic asymmetric aldol reaction of arylglyoxals with hydroxyacetone, which afforded chiral 2,3-dihydroxy-1,4-diones in high yields with good to excellent diastereoselectivities and excellent enantioselectivities.
Previous works:

a) for α-hydroxy ketone and α-hydroxyl aldehyde synthesis

\[
\begin{align*}
R_1OH + R_2OH &\rightarrow RCH(OH)COOH \\
&\rightarrow RCH(OH)COOR
\end{align*}
\]

b) for 2,3-dihydroxy ester synthesis

\[
\text{ArOH} + \text{OEt} \rightarrow \text{ArH}_{\text{phen}}
\]

This work:

c) for 2,3-dihydroxy 1,4-diketone synthesis

\[
\text{ArOH} + \text{OEt} \rightarrow \text{Organocatalyst} \rightarrow \text{2,3-dihydroxy 1,4-diketones}
\]

Scheme 1. Catalytic asymmetric aldol reaction of glyoxal derivatives.

2. Results and Discussion

2.1. Optimization of Reaction Conditions

Phenylglyoxal monohydrate (1a) and hydroxyacetone (2a) were selected as model reactants for initial tests, with various natural amino acids, including L-Proline, L-Serine, and L-Threonine, screened as catalysts [22,23] and N,N-dimethyl formamide (DMF) as solvent. Unfortunately, desired product 4a was not obtained (Table 1, entries 1–3). Chiral pyrrolidine derivatives 3a and 3b were also ineffective in this reaction (entries 4 and 5). Next, chiral trans-N,N-dialkyl dianinocyclohexanes 3c–3e were used as catalysts to promote this reaction [24], giving desired product 4a in good yields, with good diastereoselectivities and excellent enantioselectivities (entries 6–8). Catalyst 3f, derived from (15S,2S)-1,2-diphenylethane-1,2-diamine, was also tested, but generated product 4a with poor diastereoselectivity and moderate enantioselectivity (entry 9). The stereoselectivity of 4a was slightly enhanced when quinine-derived primary amine 3g was used as catalyst (84% yield, 94% ee, 89:11 dr; entry 10). Based on these results, chiral primary amine 3g was selected as the best catalyst for further optimization of the reaction conditions. Next, the effect of Brønsted acid additives was studied [25]. When additive 3,5-dinitrobenzoic acid (DNBA) was replaced by a weaker acid, p-nitrobenzoic acid, the reaction was slower and the yield, diastereoselectivity, and enantioselectivity of 4a were decreased slightly (entry 11). Similar results were observed when DNBA was replaced with tosic acid (entry 12). These results indicated that DNBA was the most suitable acid additive for this reaction. Decreasing the reaction temperature clearly enhanced the stereoselectivity. For example, when the reaction was conducted at 0 °C, 4a was obtained with 96% ee and 93:7 dr (entry 13). With the aim to further enhance the experimental outcome of 4a by introducing another hydrogen donor group, catalyst 3h was prepared. However, both the yield and stereoselectivity of 4a were decreased slightly in the reaction promoted by 3h (entry 14). An investigation of the catalyst loading indicated that 10 mol% of 3g was sufficiently effective for this reaction (entry 15). Further decreasing the catalyst loading greatly diminished the reaction outcome (entry 16). Various solvents were examined using catalyst 3g, with the results indicating that CHCl₃ was the best solvent in terms of yield, diastereoselectivity, and enantioselectivity. Based on these results, the reaction conditions depicted in entry 15 were selected as optimal for further substrate scope investigations.
The electronic properties and positions of substituents on the phenyl ring had almost no influence on the reactivity and stereoselectivity. For example, arylglyoxals bearing 3-Cl-, Br-, or MeO-substituted phenyl groups reacted with hydroxyacetone smoothly to give the corresponding 2,3-dihydroxy-1,4-diketone products in high yields (82–92%) with high enantioselectivities (86–93% ee). For arylglyoxals containing para-substituted phenyl groups, both electron-deficient and electron-rich phenyl-substituted substrates afforded products with excellent yields, diastereoselectivities, and enantioselectivities (Figure 1, 4e–4k). Arylglyoxals bearing disubstituted phenyls were also good reaction partners, Under the optimized reaction conditions, anti-selective aldol reactions of hydroxyacetone 2a with various phenylglyoxals 1b–1p were examined (Figure 1). In addition to phenylglyoxal monohydrate 1a, substituted arylglyoxal monohydrates were found to be good reaction partners in this transformation. The electronic properties and positions of substituents on the phenyl ring had almost no influence on the reactivity and stereoselectivity. For example, arylglyoxals bearing 3-Cl-, Br-, or MeO-substituted phenyl groups reacted with hydroxyacetone smoothly to give the corresponding 2,3-dihydroxy-1,4-diketone products 4b–4m in high yields (82–92%) with high enantioselectivities (86–93% ee). For arylglyoxals containing para-substituted phenyl groups, both electron-deficient and electron-rich phenyl-substituted substrates afforded products with excellent yields, diastereoselectivities, and enantioselectivities (Figure 1, 4e–4k). Arylglyoxals bearing disubstituted phenyls were also good reaction partners,

Table 1. Optimization of reaction conditions 

| Entry | Catalyst | Solvent | Time (h) | Yield (%) | dr<sup>c</sup>(anti:syn) | ee<sup>c</sup> (%) |
|-------|----------|---------|----------|-----------|-----------------|-----------------|
| 1<sup>d,e</sup> | L-Pro | DMF | 24 | n.r. | n.d. | n.d. |
| 2<sup>d,e</sup> | L-Ser | DMF | 60 | n.r. | n.d. | n.d. |
| 3<sup>d,e</sup> | L-Thr | DMF | 60 | n.r. | n.d. | n.d. |
| 4 | 3a | CHCl<sub>3</sub> | 143 | trace | n.d. | n.d. |
| 5 | 3b | CHCl<sub>3</sub> | 234 | trace | n.d. | n.d. |
| 6 | 3c | CHCl<sub>3</sub> | 16 | 49 | 80:20 | 94 |
| 7 | 3d | CHCl<sub>3</sub> | 13 | 85 | 80:20 | 94 |
| 8 | 3e | CHCl<sub>3</sub> | 12 | 82 | 86:14 | 92 |
| 9 | 3f | CHCl<sub>3</sub> | 80 | 62 | 57:43 | 57 |
| 10<sup>e</sup> | 3g | CHCl<sub>3</sub> | 13 | 84 | 89:11 | 94 |
| 11<sup>e</sup> | 3g | CHCl<sub>3</sub> | 84 | 74 | 75:25 | 92 |
| 12<sup>e</sup> | 3g | CHCl<sub>3</sub> | 15 | 75 | 86:14 | 90 |
| 13<sup>e</sup> | 3g | CHCl<sub>3</sub> | 46 | 89 | 93:7 | 96 |
| 14<sup>e</sup> | 3h | CHCl<sub>3</sub> | 60 | 85 | 87:13 | 89 |
| 15<sup>h</sup> | 3g | CHCl<sub>3</sub> | 60 | 83 | 93:7 | 96 |
| 16<sup>h</sup> | 3g | CHCl<sub>3</sub> | 108 | 59 | 93:7 | 96 |
| 17<sup>h</sup> | 3g | CH<sub>2</sub>Cl<sub>2</sub> | 60 | 17 | 87:13 | 95 |
| 18<sup>h</sup> | 3g | DCE | 60 | 30 | 87:13 | 94 |
| 19<sup>h</sup> | 3g | PhCH<sub>3</sub> | 60 | 48 | 87:13 | 88 |

<sup>a</sup> Unless otherwise noted, reactions were performed with 1a (0.2 mmol), 2a (1.0 mmol), DNBA (0.02 mmol), and catalyst (0.04 mmol) in the specified solvent (2.0 mL) at 30 °C. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC.

<sup>d</sup> Reaction performed in the absence of DNBA. <sup>e</sup> 20 mol% of catalyst used. <sup>f</sup> p-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H (0.02 mmol) used instead of DNBA. <sup>g</sup> Reaction performed at 0 °C. <sup>h</sup> 5 mol% of 3g used. DNBA = 3,5-dinitrobenzoic acid; DCE = 1,2-dichloroethene; n.r. = no reaction; n.d. = not determined.

2.2. Substrate Scope Study

Under the optimized reaction conditions, anti-selective aldol reactions of hydroxyacetone 2a with various phenylglyoxals 1b–1p were examined (Figure 1). In addition to phenylglyoxal monohydrate 1a, substituted arylglyoxal monohydrates were found to be good reaction partners in this transformation. The electronic properties and positions of substituents on the phenyl ring had almost no influence on the reactivity and stereoselectivity. For example, arylglyoxals bearing 3-Cl-, Br-, or MeO-substituted phenyl groups reacted with hydroxyacetone smoothly to give the corresponding 2,3-dihydroxy-1,4-diketone products 4b–4m in high yields (82–92%) with high enantioselectivities (86–93% ee). For arylglyoxals containing para-substituted phenyl groups, both electron-deficient and electron-rich phenyl-substituted substrates afforded products with excellent yields, diastereoselectivities, and enantioselectivities (Figure 1, 4e–4k). Arylglyoxals bearing disubstituted phenyls were also good reaction partners,
affording products 4l–4o with excellent experimental outcomes. 6-Methoxy-2-naphthyl-substituted arylyglyoxal reacted with 2a to giving product 4p in excellent yield (86%), with high diastereoselectivity (89:11 dr) and excellent enantioselectivity (95% ee). We also explored other hydroxy ketones, including α-hydroxyacetophenone, 1,3-dihydroxyacetone, and ketal-protected 1,3-dihydroxyacetone as donors, which reacted with 1a to obtain 4q–4s, but failed. Although all arylyglyoxals tested in this reaction gave excellent experimental outcomes, the substrate scope of this reaction could not be expanded further owing to the limited available of arylyglyoxal and α-hydroxyketone starting materials.

Figure 1. Substrate scope study. All reactions were performed with 1 (0.2 mmol), 2a (1.0 mmol), DNBA (0.04 mmol), and 3g (0.02 mmol) in CHCl₃ (2.0 mL) at 0 °C. Isolated yield. dr determined by ¹H-NMR. ee of anti-diastereomer determined by chiral HPLC. n.r. = no reaction.
2.3. Scale-Up Experiment and Crystal Structure of Compound 4j

Notably, this reaction was successfully conducted on a 2-mmol scale (Scheme 2), with product 4j obtained in 86% yield with 95% ee and 89:11 dr. The relative and absolute configurations of 4j (2S,3R) were determined by X-ray crystallography (see the Supplementary Materials) [26]. The stereochemistry of the other aldol products was assigned by comparison with 4j.

Scheme 2. Scaled-up 2-mmol reaction.

2.4. Plausible Reaction Mechanism and Transition States

A proposed catalytic cycle and transition state model [27] are shown in Scheme 3. The condensation of catalyst 3g with hydroxyacetone 2a affords imine intermediate I. Intermediate I then isomerizes to form a (Z)-enamine, with an intramolecular N–H–O hydrogen bond assumed to play a critical role in stabilizing the Z-enamine [23]. Meanwhile, the arylglyoxal is activated by hydrogen-bond formation with the protonated nitrogen atom of the quinuclidine. In the proposed transition state, the Re-face of the enamine attacks the Si-face of the arylglyoxal to give intermediate III. Finally, intermediate III undergoes hydrolysis to afford 4a with a 2S,3R-conformation. The Brønsted acid additive facilitates the enamine catalytic cycle.

Scheme 3. Plausible reaction mechanism.
3. Materials and Methods

3.1. General Information

Unless otherwise noted, commercial reagents were used as received. All reactions were monitored by TLC with silica gel coated plates. \(^1\)H-NMR (600 MHz) and \(^{13}\)C-NMR (150 MHz) spectra were recorded on Bruker Avance 600 MHz spectrometer. Chemical shifts (\(\delta\)) are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Proton gsignal multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of them. \(J\)-values are in Hz. HRMS (ESI-Q-TOF) spectra were recorded on Bruker Impact-II. Enantiomer ratios were determined by HPLC with chiral columns (Chiralpak AD-H, IC-H, IA-H, OD-H, OJ-H columns were purchased from Daicel Chemical Industries, LTD.). Optical rotations were determined at \(\lambda = 589 \text{ nm} \) (sodium D line) by using a Rudolph-API automatic polarimeter (Hackettstown, NJ, USA).

3.2. General Procedure for the Synthesis of 2,3-Dihydroxy-1,4-dione Diketone Products 4a-4p

A dry tube was charged with 1 (0.2 mmol), 2 (1 mmol) and DNBA (0.04 mmol). After addition of CHCl\(_3\) (2.0 mL), the mixture was effectively stirred at 0 °C and monitored by TLC. After the complete consumption of compound 1, the mixture was concentrated in vacuo and purified by flash chromatography on silica gel (PE:EtO\(_2\)O = 1:1.5) to afford diastereomeric mixtures of 4a-4p (yield: 82–92%), see Supplementary Materials.

(2S,3R)-2,3-dihydroxy-1-phenylpentane-1,4-dione. Product 4a was obtained as a white solid in 83% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 80/20, flow rate 1.0 mL/min, \(T = 30 ^\circ\)C, \(t_R\) (major) 9.298 min, \(t_R\) (minor) 10.169 min, m.p. 53.3–55.3 °C; [\(\alpha\)]\(_D\)\(^{25}\) = −31.03 (c = 0.145, CH\(_2\)Cl\(_2\)). The diastereomeric ratio was determined to be 92: 8 by \(^1\)H-NMR on Bruker Avance 600 spectrometer; \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.97 (d, \(J = 7.6 \text{ Hz}, 2\text{H}\)), 7.84 (d, \(J = 7.4 \text{ Hz}, 1\text{H}\)), 7.52 (t, \(J = 7.7 \text{ Hz}, 2\text{H}\)), 5.28 (s, 1H), 4.47 (s, 1H), 4.05 (d, \(J = 5.7 \text{ Hz}, 1\text{H}\)), 3.94 (d, \(J = 5.8 \text{ Hz}, 1\text{H}\)), 2.13 (s, 3H); HRMS(ESI): calcd. for C\(_{11}\)H\(_{12}\)NaO\(_4\) (M\(^+\)): 231.0628, found 231.0628.

(2S,3R)-1-(3-chlorophenyl)-2,3-dihydroxypentane-1,4-dione. Product 4b was obtained as a white solid in 82% yield after flash chromatography and the enantiomeric excess was determined to be 90% by HPLC analysis on Daicel Chirapak IC-H column (hexane/isopropanol = 85/15, flow rate 1.0 mL/min, \(T = 30 ^\circ\)C, \(t_R\) (major) 9.905 min, \(t_R\) (minor) 10.732 min, m.p. 59.1–61.9 °C; [\(\alpha\)]\(_D\)\(^{25}\) = −22.78 (c = 0.237, CH\(_2\)Cl\(_2\)). The diastereomeric ratio was determined to be 78: 22 by \(^1\)H-NMR on Bruker Avance 600 spectrometer; \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.85 (s, 1H), 7.84 (d, \(J = 7.8 \text{ Hz}, 1\text{H}\)), 7.64–7.55 (m, 1H), 7.45 (t, \(J = 7.9 \text{ Hz}, 1\text{H}\)), 5.17 (d, \(J = 4.1 \text{ Hz}, 1\text{H}\)), 4.41 (d, \(J = 4.1 \text{ Hz}, 1\text{H}\)), 3.91 (d, \(J = 58.8 \text{ Hz}, 2\text{H}\)), 2.21 (s, 3H); \(^{13}\)C-NMR (151 MHz, CDCl\(_3\)) \(\delta\) 207.51, 197.96, 197.94, 136.07, 135.29, 134.07, 131.16, 128.90, 127.01, 79.19, 75.53, 27.31. HRMS(ESI): calcd. for C\(_{11}\)H\(_{12}\)ClNaO\(_4\) (M\(^+\) + Na): 231.0628, found 231.0628.

(2S,3R)-1-(3-bromophenyl)-2,3-dihydroxypentane-1,4-dione. Product 4c was obtained as a white solid in 86% yield after flash chromatography and the enantiomeric excess was determined to be 95% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 70/30, flow rate 1.0 mL/min, \(T = 30 ^\circ\)C, \(t_R\) (major) 6.140 min, \(t_R\) (minor) 4.920 min, m.p. 66.5–68.1 °C; [\(\alpha\)]\(_D\)\(^{25}\) = −14.91 (c = 0.248, CH\(_2\)Cl\(_2\)). The diastereomeric ratio was determined to be 81: 19 by \(^1\)H-NMR on Bruker Avance 600 spectrometer; \(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.11 (s, 1H), 7.89 (d, \(J = 7.7 \text{ Hz}, 1\text{H}\)), 7.76 (d, \(J = 7.8 \text{ Hz}, 1\text{H}\)), 7.40 (t, \(J = 7.9 \text{ Hz}, 1\text{H}\)), 5.16 (s, 1H), 4.41 (s, 1H), 3.86 (d, \(J = 61.5 \text{ Hz}, 2\text{H}\)), 2.21 (s, 3H); \(^{13}\)C-NMR (151 MHz, CDCl\(_3\)) \(\delta\) 207.43, 197.88, 137.05, 136.22, 131.83, 130.40, 127.47, 123.22, 79.18, 75.42, 27.36. HRMS(ESI): calcd. For C\(_{11}\)H\(_{12}\)BrNaO\(_4\) (M\(^+\) + Na): 308.9733, found 308.9735.
(2S,3R)-2,3-dihydroxy-1-(3-methoxyphenyl)pentane-1,4-dione. Product 4d was obtained as an oil in 90% yield after flash chromatography and the enantiomeric excess was determined to be 93% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, tR (major) 7.784 min, tR (minor) 9.664 min), [α]25D = −4.73 (c = 0.169, CH2Cl2). The diastereomeric ratio was determined to be 89: 11 by 1H-NMR on Bruker Avance 600 spectrometer; 1H-NMR (600 MHz, CDCl3) δ 7.54 (d, J = 7.6 Hz, 1H), 7.49 (s, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.18 (dd, J = 8.2, 2.3 Hz, 1H), 5.25 (d, J = 2.6 Hz, 1H), 4.49 (d, J = 3.0 Hz, 1H), 3.87 (s, 3H), 2.13 (s, 3H); 13C-NMR (151 MHz, CDCl3) δ 207.26, 198.68, 133.29, 132.39, 130.53, 129.78, 79.43, 75.86, 55.53, 27.31. HRMS(ESI): calcd. for C12H14NaO5 (M+ + Na): 261.0733, found 261.0730.

(2S,3R)-1-(4-fluorophenyl)-2,3-dihydroxypentane-1,4-dione. Product 4e was obtained as a white solid in 87% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, tR (major) 8.384 min, tR (minor) 9.897 min, m. p. 67.2–69.3 °C; [α]25D = −31.62 (c = 0.117, CH2Cl2). The diastereomeric ratio was determined to be 90: 10 by 1H-NMR on Bruker Avance 600 spectrometer; 1H-NMR (600 MHz, CDCl3) δ 8.03 (dd, J = 7.9, 5.7 Hz, 2H), 7.19 (t, J = 8.4 Hz, 2H), 5.19 (s, 1H), 4.41 (s, 1H), 3.99 (d, J = 6.6 Hz, 1H), 3.88 (d, J = 6.6 Hz, 1H), 2.19 (s, 3H); 13C-NMR (151 MHz, CDCl3) δ 207.61, 198.27, 133.29, 132.39, 130.53, 129.78, 79.43, 75.86, 55.53, 27.31. HRMS(ESI): calcd. for C11H11ClNaO4 (M+ + Na): 249.0534, found 249.0534.

(2S,3R)-1-(4-chlorophenyl)-2,3-dihydroxypentane-1,4-dione. Product 4f was obtained as a white solid in 83% yield after flash chromatography and the enantiomeric excess was determined to be 90% by HPLC analysis on Daicel Chirapak IA-H column (hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, tR (major) 9.256 min, tR (minor) 9.740 min), m. p. 81.0–83.1 °C; [α]25D = −10.97 (c = 0.164, CH2Cl2). The diastereomeric ratio was determined to be 91: 9 by 1H-NMR on Bruker Avance 600 spectrometer; 1H-NMR (600 MHz, CDCl3) δ 7.93 (dd, J = 5.4, 3.1 Hz, 2H), 7.49 (dd, J = 5.4, 3.1 Hz, 2H), 5.16 (s, 1H), 4.38 (s, 1H), 3.98–3.71 (m, 2H), 2.20 (s, 3H); 13C-NMR (151 MHz, CDCl3) δ 207.40, 197.92, 140.94, 132.73, 130.37, 129.28, 79.22, 75.31, 27.37. HRMS(ESI): calcd. for C11H11ClNaO4 (M+ + Na): 265.0238, found 265.0232.

(2S,3R)-1-(4-fluorophenyl)-2,3-dihydroxypentane-1,4-dione. Product 4g was obtained as a white solid in 92% yield after flash chromatography and the enantiomeric excess was determined to be 86% by HPLC analysis on Daicel Chirapak IA-H column (hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, tR (major) 18.602 min, tR (minor) 20.004 min, m. p. 110.2–112.3 °C; [α]25D = −28.62 (c = 0.205, CH2Cl2). The diastereomeric ratio was determined to be 87: 13 by 1H-NMR on Bruker Avance 600 spectrometer; 1H-NMR (600 MHz, CDCl3) δ 7.84 (dd, J = 8.4, 2.1 Hz, 2H), 7.65 (dd, J = 8.1, 2.8 Hz, 2H), 5.18 (s, 1H), 4.40 (s, 1H), 4.03 (d, J = 26.9 Hz, 1H), 3.93 (d, J = 33.1 Hz, 1H), 2.18 (s, 3H); 13C-NMR (151 MHz, CDCl3) δ 207.66, 198.27, 133.29, 132.39, 130.53, 129.78, 79.37, 75.53, 27.48. HRMS(ESI): calcd. for C11H11BrNaO4 (M+ + Na): 308.9733, found 308.9732.

(2S,3R)-2,3-dihydroxy-1-p-tolylpentane-1,4-dione. Product 4h was obtained as a white solid in 89% yield after flash chromatography and the enantiomeric excess was determined to be 97% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, tR (major) 7.000 min, tR (minor) 7.893 min, m. p. 86.1–89.7 °C; [α]25D = −2.49 (c = 0.281, CH2Cl2). The diastereomeric ratio was determined to be 93: 7 by 1H-NMR on Bruker Avance 600 spectrometer; 1H-NMR (600 MHz, CDCl3) δ 7.89 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 5.24 (d, J = 3.5 Hz, 1H), 4.46 (d, J = 3.5 Hz, 1H), 3.89 (ddd, J = 95.5, 59.2, 31.9 Hz, 2H), 2.44 (s, 3H), 2.13 (d, J = 11.8 Hz, 3H); 13C-NMR (151 MHz, CDCl3) δ 207.03, 198.36, 145.63, 131.62, 129.69, 129.02, 79.64, 75.60, 27.35, 21.78. HRMS(ESI): calcd. for C12H14NaO4 (M+ + Na): 245.0784, found 245.0787.
(2S,3R)-1-(4-cyclohexylphenyl)-2,3-dihydroxypentane-1,4-dione. Product 4i was obtained as a white solid in 85% yield after flash chromatography and the enantiomeric excess was determined to be 95% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 7.562 min, t_R (minor) 9.270 min), m.p. 66.1-68.1 °C; [α]_D^{25} = -11.46 (c = 0.218, CH₂Cl₂). The diastereomeric ratio was determined to be 92: 8 by ¹H-NMR on Bruker Avance 600 spectrometer; ¹H-NMR (600 MHz, CDCl₃) δ 7.92 (J, d = 8.0 Hz, 2H), 7.35 (J, d = 8.1 Hz, 2H), 5.24 (d, J = 2.8 Hz, 1H), 4.47 (s, 1H), 3.85 (d, J = 7.29 Hz, 2H), 2.6 (d, J = 8.4 Hz, 1H), 2.12 (s, 3H), 1.88 (s, 4H), 1.78 (d, J = 12.8 Hz, 1H), 1.43 (d, J = 9.1 Hz, 3H); ¹³C-NMR (151 MHz, CDCl₃) δ 206.89, 198.39, 155.49, 131.83, 129.17, 127.57, 79.67, 75.68, 44.86. 34.03, 27.39, 26.69, 26.01. HRMS(ESI): calcd. for C₁₁H₁₂NaO₄(M⁺ + Na): 313.1410, found 313.1413.

(2S,3R)-2,3-dihydroxy-1-(4-methoxyphenyl)pentane-1,4-dione. Product 4j was obtained as an oil in 85% yield after flash chromatography and the enantiomeric excess was determined to be 95% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 8.752 min, t_R (minor) 9.923 min). [α]_D^{25} = -16.04 (c = 0.187, CH₂Cl₂). The diastereomeric ratio was determined to be 92: 8 by ¹H-NMR on Bruker Avance 600 spectrometer; ¹H-NMR (600 MHz, CDCl₃) δ 7.99 (J, d = 8.8 Hz, 2H), 6.99 (J, d = 8.8 Hz, 2H), 5.22 (dd, J = 5.7, 4.2 Hz, 1H), 4.45 (dd, J = 6.1, 4.1 Hz, 1H), 4.05 (d, J = 6.0 Hz, 1H), 3.95 (d, J = 6.8 Hz, 1H), 3.89 (s, 3H), 2.13 (s, 3H); ¹³C-NMR (151 MHz, CDCl₃) δ 207.37, 197.17, 164.74, 131.64, 127.06, 114.58, 79.82, 75.48, 55.72, 27.52. HRMS(ESI): calcd. for C₁₂H₁₄O₃Na₂(M⁺ + Na): 261.0736, found 261.0736.

(2S,3R)-2,3-dihydroxy-1-(4-phenoxycyphenyl)pentane-1,4-dione. Product 4k was obtained as an oil in 85% yield after flash chromatography and the enantiomeric excess was determined to be 94% by HPLC analysis on Daicel Chirapak IC-H column (hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 7.932 min, t_R (minor) 8.424 min), [α]_D^{25} = -2.08 (c = 0.048, CH₂Cl₂). The diastereomeric ratio was determined to be 92: 8 by ¹H-NMR on Bruker Avance 600 spectrometer; ¹H-NMR (600 MHz, CDCl₃) δ 7.97 (J, d = 8.8 Hz, 2H), 7.41 (t, J = 7.9 Hz, 2H), 7.22 (s, 1H), 7.08 (J, d = 7.7 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 5.19 (d, J = 3.4 Hz, 1H), 4.44 (d, J = 3.7 Hz, 1H), 2.16 (s, 3H); ¹³C-NMR (151 MHz, CDCl₃) δ 207.38, 197.23, 163.22, 154.95, 131.42, 130.17, 128.51, 125.07, 120.47, 114.73, 79.55, 75.38, 27.41. HRMS(ESI): calcd. for C₁₃H₁₄O₃Na₂(M⁺ + Na): 323.0890, found 323.0886.

(2S,3R)-1-(2,4-difluorophenyl)-2,3-dihydroxypentane-1,4-dione. Product 4l was obtained as an oil in 87% yield after flash chromatography and the enantiomeric excess was determined to be 97% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 8.257 min, t_R (minor) 9.181 min), [α]_D^{25} = -16.08 (c = 0.143, CH₂Cl₂). The diastereomeric ratio was determined to be 87: 13 by ¹H-NMR on Bruker Avance 600 spectrometer; ¹H-NMR (600 MHz, CDCl₃) δ 7.98 (dd, J = 15.0, 8.3 Hz, 1H), 7.10 – 7.00 (m, 1H), 6.95–6.87 (m, 1H), 5.10 (s, 1H), 4.35 (s, 1H), 4.01 (d, J = 5.5 Hz, 1H), 3.67 (d, J = 5.8 Hz, 1H), 2.42 (s, 3H); ¹³C-NMR (151 MHz, CDCl₃) δ 207.97, 195.81, 195.79, 167.56, 167.48, 165.85, 165.76, 163.40, 163.32, 161.69, 161.61, 133.31, 133.28, 133.24, 133.21, 113.13, 113.11, 112.98, 112.96, 105.25, 105.08, 104.90, 79.43, 78.08, 78.03, 27.27. HRMS(ESI): calcd. for C₁₁H₁₀F₂NaO₄(M⁺ + Na): 267.0439, found 267.0446.

(2S,3R)-1-(3,4-difluorophenyl)-2,3-dihydroxypentane-1,4-dione. Product 4m was obtained as a white solid in 82% yield after flash chromatography and the enantiomeric excess was determined to be 93% by HPLC analysis on Daicel Chirapak OJ-H column (hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 8.205 min, t_R (minor) 8.988 min), m.p. 68.6-70.4 °C; [α]_D^{25} = -13.79 (c = 0.087, CH₂Cl₂). The diastereomeric ratio was determined to be 86: 14 by ¹H-NMR on Bruker Avance 600 spectrometer; ¹H-NMR (600 MHz, CDCl₃) δ 7.86 (t, J = 8.3 Hz, 1H), 7.82–7.75 (m, 1H), 7.30 (dd, J = 17.1, 8.6 Hz, 1H), 5.11 (s, 1H), 4.37 (s, 1H), 3.91 (s, 1H), 3.83 (s, 1H), 2.25 (s, 3H); ¹³C-NMR (151 MHz, CDCl₃) δ 207.73, 196.96, 155.33, 155.25, 153.61, 153.53, 151.54, 151.45, 149.87, 149.78, 131.70, 126.50, 126.47, 126.45, 126.42, 118.72, 118.60, 118.05, 117.93, 79.15, 75.31, 27.50. HRMS(ESI): calcd. for C₁₁H₁₀F₂NaO₄(M⁺ + Na): 267.0439, found: 267.0441.
(2S,3R)-1-(3,4-dimethoxyphenyl)-2,3-dihydroxypentane-1,4-dione. Product 4n was obtained as a white solid in 88% yield after flash chromatography and the enantiomeric excess was determined to be 97% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 80/20 min, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 14.002, t_R (minor) 15.915 min), m.p. 73.0–74.6 °C; [α]_D^{25} = −14.41 (c = 0.215, CH_2Cl_2). The diastereomeric ratio was determined to be 92: 8 by 1H-NMR on Bruker Avance 600 spectrometer; 1H-NMR (600 MHz, CDCl_3) δ 7.64 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 5.23 (dd, J = 5.6, 4.3 Hz, 1H), 4.50–4.44 (m, 1H), 4.03 (dd, J = 10.9, 6.0 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.94–3.89 (m, 1H), 2.15 (s, 3H); 13C-NMR (151 MHz, CDCl_3) δ 207.43, 197.19, 154.69, 149.60, 127.17, 124.17, 111.06, 110.48, 79.95, 75.40, 56.30, 56.21, 27.56. HRMS(ESI): calcd for C_{12}H_{16}NaO_6(M^+ + Na): 291.0839, found 291.0844.

(2S,3R)-1-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydroxypentane-1,4-dione. Product 4o was obtained as a white solid in 84% yield after flash chromatography and the enantiomeric excess was determined to be 96% by HPLC analysis on Daicel Chirapak AD-H column (hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 21.336 min, t_R (minor) 16.964 min), m.p. 73.9–75.2 °C; [α]_D^{25} = −9.55 (c = 0.314, CH_2Cl_2). The diastereomeric ratio was determined to be 93: 7 by 1H-NMR on Bruker Avance 600 spectrometer; 1H-NMR (600 MHz, CDCl_3) δ 7.61 (d, J = 8.2 Hz, 1H), 7.47 (s, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.08 (s, 2H), 5.16 (dd, J = 6.0, 4.3 Hz, 1H), 4.44 (dd, J = 6.7, 4.2 Hz, 1H), 4.00 (d, J = 6.2 Hz, 1H), 3.92 (d, J = 6.6 Hz, 1H), 2.15 (s, 3H); 13C-NMR (151 MHz, CDCl_3) δ 207.41, 196.86, 153.12, 148.65, 128.85, 125.88, 108.66, 108.42, 102.33, 79.77, 75.46, 27.55. HRMS(ESI): calcd for C_{12}H_{12}NaO_6(M^+ + Na): 275.0526, found 275.0528.

(2S,3R)-2,3-dihydroxy-1-(6-methoxynaphthalen-2-yl)pentane-1,4-dione. Product 4p was obtained as a white solid in 89% yield after flash chromatography and the enantiomeric excess was determined to be 97% by HPLC analysis on Daicel Chirapak IA-H column (hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, t_R (major) 15.424 min, t_R (minor) 18.251 min), m.p. 131.2–132.3 °C; [α]_D^{25} = 8.9, 2.2 Hz, 1H), 7.16 (s, 1H), 5.48–5.33 (m, 1H), 4.55 (dd, J = 8.9, 2.2 Hz, 1H), 7.16 (s, 1H), 5.48–5.33 (m, 1H), 4.55 (dd, J = 6.4, 4.0 Hz, 1H), 4.06 (d, J = 6.2 Hz, 1H), 4.01–3.86 (m, 4H), 2.13 (s, 3H); 13C-NMR (151 MHz, CDCl_3) δ 207.23, 198.41, 160.63, 138.17, 131.56, 131.11, 129.45, 127.85, 124.87, 120.35, 106.08, 79.93, 75.80, 55.63, 27.56. HRMS(ESI): calcd for C_{16}H_{16}NaO_3(M^+ + Na): 311.0890, found 311.0877.

4. Conclusions

In summary, we have developed a highly stereoselective anti-aldol reaction of arylyglyoxal monohydrates with hydroxyacetone catalyzed by quinine-derived primary amine 3g. The desired 2,3-dihydroxy-1,4-dione products were obtained in high yields (up to 92%), with excellent enantioselectivities (up to 97% ee) and diastereoselectivities (up to 93.7 dr).

Supplementary Materials: Supporting information including the spectrums of 1H, 13C-NMR and HPLC are available online.

Author Contributions: Q.-X.G. and W.W. directed this project Y.-H.Z. and Y.-Z.Z. carried out all of the experiments; Z.-L.W. and T.C. finished all of the HRMS analysis. All authors have read and agreed to the published version of the manuscript.

Funding: National Natural Science Foundation of China (NSFC, 21871223), the Fundamental Research Funds for the Central Universities (XDJK2019AA003) and the Chongqing Science Technology Commission (cstc2018jcyjAX0548).

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Mukaiyama, T. Directed aldol reaction. Org. React. 1982, 28, 203–331.
2. Mahrwald, R. (Ed.) Modern Aldol Reactions; Wiley-VCH: Weinheim, Germany, 2004; Volume 1–2.
3. Palomo, C.; Olarbide, M.; García, J.M. Current progress in the asymmetric aldol addition reaction. *Chem. Soc. Rev.* **2004**, *33*, 65–75. [CrossRef] [PubMed]

4. Shen, K.; Liu, X.; Zheng, K.; Li, W.; Hu, X.; Lin, L.; Feng, X. Catalytic asymmetric synthesis of 3-(α-Hydroxy-β-carbonyl) oxindoles by a Sc(III)-catalyzed direct aldol-type reaction. *Chem. Eur. J.* **2010**, *16*, 3736–3742. [CrossRef] [PubMed]

5. Zhao, J.; Zheng, K.; Yang, Y.; Shi, J.; Lin, L.; Liu, X.; Feng, X. Asymmetric mukaiyama aldol reaction catalyzed by C2-symmetric N,N'-dioxide-Ni(II) complex. *Synlett* **2011**, *7*, 903–906. [CrossRef]

6. Hayashi, Y.; Yasui, Y.; Kojima, M.; Kawamura, T.; Ishikawa, H. Diarylprolinol in an asymmetric aldol reaction of an α-alkyl-α-oxo aldehyde as an electrophile. *Chem. Commun.* **2012**, *48*, 4570. [CrossRef]

7. Alberg, D.G.; Poulsen, T.B.; Bertelsen, S.; Christensen, K.L.; Birkler, R.D.; Johannsen, M.; Jørgensen, K.A. Organocatalysis with endogenous compounds: Towards novel non-enzymatic reactions. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3888. [CrossRef]

8. Hayashi, Y.; Kojima, M. Asymmetric aldol reaction of glyoxal catalyzed by diarylprolinol. *ChemCatChem* **2013**, *5*, 2883. [CrossRef]

9. Moles, F.J.N.; Guillena, G.; Nájera, C. Aqueous enantioselective aldol reaction of methyl- and phenylglyoxal organocatalyzed by N-Tosyl-(S)-β-bim-t-prolinamide. *Synlett* **2015**, *26*, 656–660. [CrossRef]

10. Konda, S.; Guo, Q.-S.; Abe, M.; Huang, H.; Arman, H.; Zhao, J.C.-G. Organocatalyzed Asymmetric Aldol Reactions of Ketones and β,γ-Unsaturated α-Ketoesters and Phenylglyoxal Hydrates. *J. Org. Chem.* **2015**, *80*, 806–815. [CrossRef]

11. Zhang, Z.-F.; Yang, X.-C.; Lu, H.-J.; Wang, M.-C. Enantioselective direct synthesis of syn- and anti-α,β-dihydroxy γ-keto esters using a dinuclear zinc-AzePhenol complex. *Eur. J. Org. Chem.* **2018**, *785–793*. [CrossRef]

12. Ren, L.; Lian, X.-L.; Geng, L.-Z. Brensted acid/Rhodium(II) cooperative catalytic asymmetric three-component aldol-type reaction for the synthesis of 3-amino oxindoles. *Chem. Eur. J.* **2013**, *19*, 3315–3318. [CrossRef] [PubMed]

13. Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. syn-Selective and enantioselective direct cross-aldol reactions between aldehydes catalyzed by an axially chiral amino sulfonamide. *Angew. Chem. Int. Ed.* **2007**, *46*, 1738–1740. [CrossRef] [PubMed]

14. Kano, T.; Yamaguchi, Y.; Maruoka, K. A designer axially chiral amino sulfonamide as an efficient organocatalyst for direct asymmetric anti-selective mannich reactions and syn-selective cross-aldol reactions. *Chem. Eur. J.* **2009**, *15*, 6678–6687. [CrossRef] [PubMed]

15. Xiong, Y.; Wang, F.; Dong, S.; Liu, X.; Feng, X. Asymmetric bisprolinamide-catalyzed cross-aldol reaction of aldehydes. *Synlett.* **2008**, *1*, 73.

16. Guo, Q.; Bhanushali, M.; Zhao, C.-G. Quinidine thiourea-catalyzed aldol reaction of unactivated ketones: Highly enantioselective synthesis of 3-alkyl-3-hydroxyindolin-2-ones. *Angew. Chem. Int. Ed.* **2010**, *49*, 9460–9464. [CrossRef]

17. Guan, J.; Guo, Q.; Zhao, J.C.-G. Acetylphosphonate as a surrogate of acetate or acetamide in organocatalyzed enantioselective aldol reactions. *Org. Lett.* **2012**, *14*, 3174–3177. [CrossRef]

18. Gioia, C.; Ricci, A.; Bernardi, L.; Bourahla, K.; Tanchoux, N.; Robitzer, M.; Quignon, F. Chitosan aerogel beads as a heterogeneous organocatalyst for the asymmetric aldol reaction in the presence of water: An assessment of the effect of additives. *Eur. J. Org. Chem.* **2013**, *588–594*. [CrossRef]

19. Quintard, A.; Rodrigue, J. Didecarboxylative Iron-catalyzed bidirectional aldolization towards diversity-oriented ketodiol synthesis. *Chem. Eur. J.* **2015**, *21*, 14171–14172. [CrossRef]

20. Gijssen, H.J.M.; Qiao, L.; Fitz, W.; Wong, C.-H. Recent advances in the chemoenzymatic synthesis of carbohydrates and carbohydrate mimetics. *Chem. Rev.* **1996**, *96*, 443–473. [CrossRef]

21. Enders, D.; Voith, M.; Lenz, A. The dihydroxyacetone unit—A versatile C3 building block in organic synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 1304–1325. [CrossRef]

22. List, B.; Lerner, R.A.; Barbas, C.F., III. Proline-catalyzed direct asymmetric aldol reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. [CrossRef]

23. Ramasastry, S.S.V.; Zhang, H.; Tanaka, F.; Barbas, C.F., III. Direct catalytic asymmetric synthesis of anti-1,2-Amino alcohols and syn-1,2-diols through organocatalytic anti-mannich and syn-aldol reactions. *J. Am. Chem. Soc.* **2007**, *129*, 288–289. [CrossRef] [PubMed]
24. Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. A simple primary-tertiary diamine-Brønsted acid catalyst for asymmetric direct aldol reactions of linear aliphatic ketones. *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075. [CrossRef]

25. Crotti, S.; Iorio, N.D.; Artusi, C.; Mazzanti, A.; Righi, P.; Bencivenni, G. Direct access to alkylideneoxindoles via axially enantioselective knoevenagel condensation. *Org. Lett.* **2019**, *21*, 3013–3017. [CrossRef]

26. CCDC 1974588 (4j) Contains the Supplementary Crystallographic Data for This Paper. Available online: www.ccdc.cam.ac.uk/data_request/cif (accessed on 29 December 2019).

27. Czarnecki, P.; Plutecka, A.; Gawroński, J.; Kacprzak, K. Simple and practical direct asymmetric aldol reaction of hydroxyacetone catalyzed by 9-amino *Cinchona* alkaloid tartrates. *Green Chem.* **2011**, *13*, 1280–1287. [CrossRef]

**Sample Availability:** Samples of the compounds are available from the authors.