Abstract: Here, we report the tripeptide-catalyzed asymmetric aldol reaction between α-ketoesters and acetone under acidic cocatalysts-free conditions. H-Pro-Tle-Gly-OH 3g-catalyzed reactions between α-ketoesters and acetone resulted in up to 95% yield and 88% ee. Analysis of the transition state using density functional theory (DFT) calculations revealed that the tert-butyl group in 3g played an important role in enantioselectivity.

Keywords: organocatalyst; aldol reaction; peptide catalyst; α-ketoesters

1. Introduction

Optically active tertiary alcohols are partial structures present in various natural products and biologically active compounds [1–5]. Various synthetic methods for these compounds have been developed. Asymmetric nucleophile addition to functionalized ketones is one of the most useful synthetic methods, because highly functionalized optically active tertiary alcohols, which can undergo various transformations, can be obtained. For example, the direct asymmetric aldol reaction between α-ketoesters and acyclic ketones is a helpful asymmetric reaction, because it gives γ-keto-α-hydroxyesters, which can undergo various transformations [6–8]. Therefore, various asymmetric catalysts, such as bisprolinamide, primary amine, and diamine catalysts, have been developed for this reaction [9–17]. However, most catalysts require acidic cocatalysts for high enantioselectivity and high chemical yield. Thus, simpler catalytic systems that do not require acidic cocatalysts are needed. Nevertheless, the number of asymmetric catalysts that catalyze this reaction, under acidic cocatalyst-free conditions, is limited. Although Zhang et al. [18] reported a proline-catalyzed asymmetric aldol reaction between ethyl phenylglyoxylate and acetone under acidic cocatalyst-free conditions, this method was enantioselective to some degree [18]. To the best of our knowledge, for this reaction, an asymmetric catalyst displaying high enantioselectivity and chemical yield under acidic cocatalyst-free conditions has still not been reported.

Following the introduction of a proline-catalyzed asymmetric aldol reaction of aldehydes reported by List et al. [19], prolinamide catalysts for this reaction have been actively developed [20,21]. Synthetic peptides in prolinamide catalysts, are recognized as effective catalysts for the direct asymmetric aldol reaction using aldehydes as electrophiles [22–33]. However, peptide catalysts for the direct asymmetric aldol reaction using ketones as electrophiles are limited [29,33–36]. Previously, we developed tripeptide catalysts (Supplementary Materials) that catalyzed the direct asymmetric aldol reaction of isatins or...
trifluoromethyl ketones with acetone (Figure 1a) [37,38]. These catalysts, under acidic cocatalyst-free conditions, displayed good enantioselectivity and kinetics in these reactions. Herein, we will report the direct asymmetric aldol reaction between α-ketoesters and acetone catalyzed by tripeptide under acidic cocatalyst-free conditions (Figure 1b).

2. Results and Discussion

In this study, we investigated the effect of the catalyst structure on the rate and enantioselectivity of the reaction between methyl phenylglyoxylate (1a) and acetone (2) (Table 1, entries 1–9). H-Pro-Gly-Gly-OH 3a-catalyzed reaction progressed to give the corresponding aldol adduct 4a with 61% yield and 31% ee (Table 1, entry 1). To investigate the effect of introducing a methyl group to the C-terminal amino acid residue in 3a, H-Pro-Gly-Ala-OH 3b- and H-Pro-Gly-D-Ala-OH 3c-catalyzed reactions were carried out (Table 1, entries 2 and 3). Both reactions displayed higher reaction rates than the 3a-catalyzed reaction; however, enantioselectivities of both reactions were not improved, compared with that of the 3a-catalyzed reaction. H-Pro-Ala-Gly-OH 3d- and H-Pro-D-Ala-Gly-OH 3e-catalyzed reactions introduced a methyl group to the amino acid residue adjacent to the proline residue in 3a. The reaction between 1a and 2 gave 4a higher enantioselectivity than the 3a-catalyzed reaction (Table 1, entries 4 and 5). The 3d-catalyzed reaction displayed higher enantioselectivity than the 3e-catalyzed one. However, the reaction catalyzed by H-Pro-Val-Gly-OH 3f and H-Pro-Tle-Gly-OH 3g, containing bulkier isopropyl and tertiary butyl groups instead of methyl groups, displayed higher enantioselectivities than the 3d-catalyzed reaction (Table 1, entries 6–7). Above all, 3g-catalyzed reactions showed the highest enantioselectivity and reaction rates than any of the other catalyzed reactions. From these investigations, it was discovered that bulky substitution in L-amino acid adjacent to proline residue played an important role in determining enantioselectivity. From the results, we decided that the most efficient catalyst for this reaction was 3g, in terms of enantioselectivity and the reaction rate obtained.

To improve enantioselectivity, we optimized the reaction conditions for a 3g-catalyzed reaction between 1a and 2 (Table 1, entries 8–21). This reaction was carried out in various solvents (Table 1, entries 8–13). In THF and diethyl ether, the reaction displayed higher enantioselectivity than in any other solvent (Table 1, entries 12 and 13). The reaction in THF and diethyl ether at 0 °C produced 4a with higher enantioselectivity than that at 20 °C. However, the reaction rate at 0 °C in diethyl ether was lower than that in THF at 0 °C. Therefore, we determined that the best solvent for this reaction was THF, in terms of enantioselectivity and reaction rate (Table 1, entries 14 and 15). The reaction in THF at −15 °C did not progress (Table 1, entry 16). The reaction in THF at 0 °C was also slow when the catalytic amount was reduced from 20 mol% to 10 mol% (Table 1, entry 17). The increase and decrease in the amounts of 2 and THF, respectively, caused a reduction in reaction rate (Table 1, entries...
From all the reaction conditions tested, it was revealed that the optimum reaction was 3g (20 mol%)-catalyzed reaction using 2 (100 eq.) in THF (1 mL) at 0 °C, because this reaction gave 4a with 76% chemical yield and 88% ee under less acidic conditions (Table 1, entry 16).

### Table 1. Optimization of catalysts and reaction conditions.

| Entry | Catalyst | Solvent | Yield (%) | ee (%) |
|-------|----------|---------|-----------|--------|
| 1     | H-Pro-Gly-Gly-OH 3a | neat | 61 | 31 |
| 2     | H-Pro-Gly-Ala-OH 3b | neat | 81 | 30 |
| 3     | H-Pro-Gly-D-Ala-OH 3c | neat | 70 | 26 |
| 4     | H-Pro-Ala-Gly-OH 3d | neat | 50 | 38 |
| 5     | H-Pro-D-Ala-Gly-OH 3e | neat | 49 | 34 |
| 6     | H-Pro-Val-Gly-OH 3f | neat | 49 | 50 |
| 7     | H-Pro-Tle-Gly-OH 3g | neat | 90 | 65 |
| 8     | 3g | MeOH | 40 | 30 |
| 9     | 3g | MeCN | 62 | 54 |
| 10    | 3g | CHCl₃ | 81 | 68 |
| 11    | 3g | PhMe | 44 | 70 |
| 12    | 3g | THF | 82 | 79 |
| 13    | 3g | Et₂O | 74 | 82 |
| 14    | 3g | THF | 76 | 88 |
| 15    | 3g | Et₂O | 45 | 88 |
| 16    | 3g | THF | — | — |
| 17    | 3g | THF | 39 | 89 |
| 18    | 3g | THF | 56 | 87 |
| 19    | 3g | THF | 57 | 89 |
| 20    | 3g | THF | 34 | 89 |
| 21    | 3g | THF | 56 | 83 |

a Isolated yield after preparative thin layer chromatography. b Determined by HPLC. Absolute configuration of 4a was determined by comparing optical rotation between 4a and previous report [14]. c Reaction was carried out at 0 °C. d Reaction was carried out at −15 °C. e 3g (10 mol%) was used. f 2 (150 eq.) was used. g 2 (50 eq.) was used. h Reaction was carried out in THF (2 mL). i Reaction was carried out in THF (0.5 mL).

We also investigated the reaction between various \(\alpha\)-ketoesters 1a–1h and 2 under optimized conditions (Table 2). To reveal the effect of ester substituents, reactions of 1a–1c having various ester groups were carried out (Table 2, entries 1–3). In reactions using 1a–1c as substrates with alkyl esters, the bulkier the alkyls esters were, the slower the reactions progressed. The substrates 1a–1c generated the corresponding aldol adducts 4a–4c with good enantioselectivities. To estimate the contribution of the methoxycarbonyl group of 1a, the reaction between acetophenone and acetone was carried out. This reaction was not progressed. To investigate the effect of substituents on phenyl groups, reactions of 4-substituted \(\alpha\)-ketoesters 1d–1g were carried out (Table 2, entries 4–7). Reactions of 4-Cl 1d and 4-CF₃ 1e were faster than that of 1a, and especially that of 1e, which was completed after three days. However, enantioselectivities of reactions 1d and 1e were lower than that of the reaction of 1a (Table 2, entries 4 and 5, respectively). In the reactions of 4-Me 1f and 4-MeO 1g, the reaction rates and enantioselectivities were also lower than that of the reaction of 1a (Table 2, entries 6 and 7, respectively). The reactions of methyl pyruvate (1h) and methyl trimethylpyruvate as aliphatic \(\alpha\)-ketoesters were investigated. The reaction between 1h and 2 gave corresponding aldol adduct 4h, with good chemical yield and medium enantioselectivity (Table 2, entry 8). Additionally, the reaction of more bulky genusmethyl trimethylpyruvate (R¹ = 'Bu) with 2 did not give corresponding aldol adduct. Cyclohexanone, 2-butanone, and acetophenone were applied as nucleophiles. These nucleophiles were not reacted.
was determined by comparing optical rotation between 4a and previous report [14].

\[ \text{Absolute configuration of aldol adduct 4 was determined at the C–C bond formation step.} \]

It was assumed that the catalytic cycle of this reaction was similar to that of the proline-catalyzed asymmetric aldol reaction (Figure 2a) [9]. Therefore, 2 was activated by enamine formation by reacting with the amino group of 3g. The C–C bond was then formed by nucleophilic addition to the 1 of enamine as a nucleophile to generate the iminium cation. Finally, the aldol adduct was produced by the hydrolysis of the iminium cation. In this reaction, the absolute configuration of the aldol adduct 4 was determined at the C–C bond formation step.

To understand the effect of tert-leucine residue in H-Pro-Tle-Gly-OH 3g on enantioselectivity, origins of enantioselectivity of 3g and H-Pro-Gly-Gly-OH 3a were investigated. Specifically, transition states of the stereo-determining C–C bond forming step of 3g- and 3a-catalyzed reactions between 1a and 2 were investigated via density functional theory (DFT) calculations (Figures 2b and 3) [39,40].

\[ \text{Absolute configuration of aldol adduct 4 was determined by HPLC.} \]

Investigation of transition states of the stereo-determining C–C bond forming step of 3a-catalyzed reactions between 1a and 2 via DFT calculations revealed that the major (R)-aldol adduct was produced through 3a-TS-(R), and the minor (S)-aldol adduct was produced through 3a-TS-(S) in the 3a-catalyzed reaction (Figure 2b). Like the experimental result where (R)-aldol adduct was preferentially obtained via DFT calculations revealed that the major (R)-aldol adduct was preferentially obtained.

Table 2. Substrate scope.

| Entry | R¹ | R² | 1 | 4  | Yield (%) ¹ | ee (%) ² |
|-------|----|----|---|----|-------------|---------|
| 1     | Ph | Me | 1a| 4a | 76          | 88(R)   |
| 2     | Ph | Et | 1b| 4b | 63          | 82      |
| 3     | Ph | iPr| 1c| 4c | 33          | 86      |
| 4     | 4-ClPh | Me | 1d| 4d | 84          | 75      |
| 5     | 4-CF₂Ph | Me | 1e| 4e | 95          | 50      |
| 6     | 4-MePh | Me | 1f| 4f | 25          | 75      |
| 7     | 4-MeOPh | Me | 1g| 4g | 10          | 65      |
| 8     | Me | Me | 1h| 4h | 92          | 39      |

⁻ Isolated yield after preparative thin layer chromatography. ² Determined by HPLC. ³ Absolute configuration of 4a was determined by comparing optical rotation between 4a and previous report [14]. ⁴ Reaction was demonstrated for 3d.

Figure 2. (a) A plausible catalytic cycle; (b) transition states of C–C bond forming step of 3a-catalyzed reaction between 1a and 2. All calculations were carried out via CPCM(acetone)/B3LYP/6-31G(d',p')//B3LYP/6-31G(d',p') level of theory.
(Table 1, entry 1), 3a-TS-(R) was the more stable transition state. To understand the origin of enantioselectivity of 3a, we focused on hydrogen bonds in transition states of the stereo-determining C–C bond forming step. Hydrogen bonds a, b, and c were formed in both transition states. However, hydrogen bonds d and e were present in only 3a-TS-(R), and hydrogen bond f was present in only 3a-TS-(S). Namely, 3a-TS-(R) had more hydrogen bonds than 3a-TS-(S). This was the reason why 3a-TS-(R) was the more stable transition state. The investigation of transition states of the C–C bond forming step of the 3g-catalyzed reaction via DFT calculation found four transition states, such as 3g-TS-(R)-1, 3g-TS-(R)-2, 3g-TS-(S)-1, and 3g-TS-(S)-2 (Figure 3). When this 3g-catalyzed reaction passed through 3g-TS-(R)-1 and 3g-TS-(R)-2, the major (R)-aldol adduct was obtained. Similarly, when this 3g-catalyzed reaction passed through 3g-TS-(S)-1 and 3g-TS-(S)-2, the minor (S)-aldol adduct was obtained. Focusing on conformations of these transition states, 3g in 3g-TS-(R)-1 and 3g-TS-(S)-1 had a similar conformation to 3a in the transition state of the C–C bond forming step of the 3a-catalyzed reaction. However, the presence of 3g in these transition states introduced steric repulsion between the 1 Bu of tert-leucine residue and the carbonyl group of proline residue, causing destabilization of these transition states. In contrast, this steric repulsion was mitigated in 3g-TS-(R)-2 and 3g-TS-(S)-2, due to the change in conformation influenced by the 1 Bu group. Due to this change of steric environment in these transition states, 3g-TS-(R)-2 and 3g-TS-(S)-2 were more stable than 3g-TS-(R)-1 and 3g-TS-(S)-1. For that reason, it was concluded that (S)- and (R)-aldol adducts were formed through 3g-TS-(S)-2 and 3g-TS-(R)-2 in the 3g-catalyzed reaction, respectively.

Finally, 3g-TS-(R)-2 and 3g-TS-(S)-2 were analyzed and a comparison of their Gibbs free energy revealed that 3g-TS-(R)-2 was 2.2 kcal/mol more stable than 3g-TS-(S)-2. This difference in Gibbs free energy was larger than that between 3a-TS-(R) and 3a-TS-(S). Moreover, DFT calculations reproduced the experimental results such that 3g displayed higher enantioselectivity than 3a, mainly because of the difference in stabilization caused by hydrogen bonds. In both 3g-TS-(R)-2 and 3g-TS-(S)-2, multiple hydrogen bonds a, b, and c formed. Hydrogen bonds g and h formed only in 3g-TS-(R)-2. The conformational change of 3g by the introduction of 1 Bu group to 3a created a larger difference in the number of hydrogen bonds formed between 3g-TS-(R)-2 and 3g-TS-(S)-2 than that between 3a-TS-(R) and 3a-TS-(S). Hence, difference of stabilization by hydrogen bonds between 3g-TS-(R)-2 and 3g-TS-(S)-2 was larger than that between 3a-TS-(R) and 3a-TS-(S). From the above results, we concluded that the control of 3g conformation by 1 Bu groups played an important role in the production of enantioselectivity.

![Diagram](image-url)

**Figure 3.** Transition states of C–C bond forming step of 3g-catalyzed reaction between 1a and 2. All calculations were carried out via CPCM(acetone)/B3LYP/6-31G(d,p')//B3LYP/6-31G(d,p') level of theory.
3. Materials and Methods

3.1. General Methods

Column chromatography was carried out on a column packed with spherical silica gel 60N of neutral size, 40–50 µm. Thin layer chromatography was prepared using PLC Silica gel (60 F254, 1 mm, Merck). NMR spectra were recorded on a JEOL JNM-ECA600 spectrometer (1H, 600 MHz; 13C, 150 MHz). Chemical shifts of 1H NMR and 13C NMR signals, reported as δ ppm, were referenced to an internal standard SiMe4 or sodium 3-(trimethylsilyl)-1-propanesulfonate. HRMS were obtained at an ionization potential of 70 eV with a JEOL JMS-T100GCV spectrometer. Melting points were measured on an AS ONE ATM-01 melting-point apparatus. Optical rotations were measured by a JASCO P-1010 Polarimeter. HPLC analysis was performed with a Daicel Chiralpak AD-H column (25 cm × 4.6 mm × 5 µm) and Chiralpak OD-H column (25 cm × 4.6 mm × 5 µm). All reagents and solvents were purchased from commercial sources and used without purification. Compounds 1a–1g were synthesized by the previously reported method [41,42]. Tripeptide catalysts were synthesized by the literature methods [37,38].

3.2. General Procedure for the Asymmetric Aldol Reaction between α-Ketoesters and Acetone

A mixture of H-Pro-Tle-Gly-OH 3g (20 µmol, 5.7 mg), acetone (10 mmol, 0.74 mL), and THF (1.0 mL) was stirred at 0 °C for 10 min. To the resulting mixture, α-ketoester (0.1 mmol) was added. The mixture was stirred at 0 °C for six days and then filtered to remove the catalyst. The resulting mixture was concentrated under reduced pressure. Preparative thin layer chromatography on silica gel using hexane/ethyl acetate as the eluent gave the aldol adduct. The enantiomeric excess of aldol adduct was determined by chiral HPLC.

4. Conclusions

We have developed a direct asymmetric aldol reaction between α-ketoesters and acetone, catalyzed by a tripeptide under acidic cocatalyst-free conditions. The 3g-catalyzed reaction gave various aldol adducts with up to 95% yield and 88% ee. Investigation of the transition state via the C–C bond forming step by DFT calculations has revealed the role of the tBu group in 3g in determining enantioselectivity.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/6/514/s1, 1. General; 2. Materials; 3. Preparation of the tripeptide catalysts; 4. General procedure for tripeptide-catalyzed asymmetric aldol reaction; 5. Computational Details; 6. Reference; 7. Copy of NMR spectra; 8. Copy of HPLC spectra; 9. Geometries and Cartesian Coordinates. Figure S1: Synthesis of tripeptide catalysts.

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References
1. Trost, B.M.; Dirat, O.; Gunzner, J.L. Callipeltoside A: Assignment of Absolute and Relative Configuration by Total Synthesis. Angew. Chem. Int. Ed. 2002, 41, 841–843. [CrossRef]
2. Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. Catalyst-Controlled Asymmetric Synthesis of Fostriecin and 8-epi-Fostriecin. J. Am. Chem. Soc. 2005, 127, 17111–17117. [CrossRef] [PubMed]
3. Lei, X.; Porco, J.A. Total Synthesis of the Diazobenzofluorene Antibiotic (−)-Kinamycin C1. J. Am. Chem. Soc. 2006, 128, 14790–14791. [CrossRef] [PubMed]
4. Nicolau, K.C.; Li, H.; Nold, A.L.; Pappo, D.; Lenzen, A. Total Synthesis of Kinamycins C, F, and J. J. Am. Chem. Soc. 2007, 129, 10356–10357. [CrossRef]
5. Carpenter, J.; Northrup, A.B.; Chung, D.; Wiener, J.J.M.; Kim, S.-G.; MacMillan, D.W.C. Total Synthesis and Structural Revision of Callipeltoside C. Angew. Chem. Int. Ed. 2008, 47, 3568–3572. [CrossRef] [PubMed]
6. Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T.; Maruoka, K. A Practical Synthesis of (S)-2-Cyclohexyl-2-phenylglycolic Acid via Organocatalytic Asymmetric Construction of a Tetrasubstituted Carbon Center. Org. Lett. 2005, 7, 5103–5105. [CrossRef] [PubMed]

7. Xu, X.-Y.; Tang, Z.; Wang, Y.-Z.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. Asymmetric Organocatalytic Direct Aldol Reactions of Ketones with α-Keto Acids and Their Application to the Synthesis of 2-Hydroxy-γ-butyrolactones. J. Org. Chem. 2007, 72, 9905–9913. [CrossRef]

8. Zheng, C.; Wu, Y.; Wang, X.; Zhao, G. Highly Enantioselective Organocatalyzed Construction of Quaternary Carbon Centers via Cross-Aldol Reaction of Ketones in Water. Adv. Synth. Catal. 2008, 350, 2690–2694. [CrossRef]

9. Wang, F.; Xiong, Y.; Liu, X.; Feng, X. Asymmetric Direct Aldol Reaction of α-Keto Esters and Acetone Catalyzed by Bifunctional Organocatalysts. Adv. Synth. Catal. 2007, 349, 2665–2668. [CrossRef]

10. Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. Asymmetric Direct Aldol Reaction of Functionalized Ketones Catalyzed by Amine Organocatalysts Based on Bispidine. J. Am. Chem. Soc. 2008, 130, 5654–5655. [CrossRef]

11. Liu, Q.-Z.; Wang, X.-L.; Luo, S.-W.; Zheng, B.-L.; Qiu, D.-B. Facile Preparation of Optically Pure Diamines and Their Applications in Asymmetric Aldol Reactions. Tetrahedron Lett. 2008, 49, 7434–7437. [CrossRef]

12. Raj, M.; Parashari, G.S.; Singh, V.K. Highly Enantioselective Organocatalytic syn- and anti-Aldol Reactions in Aqueous Medium. Adv. Synth. Catal. 2009, 351, 1284–1288. [CrossRef]

13. Jiang, Z.; Lu, Y. Direct asymmetric aldol reaction of acetone with α-ketoesters catalyzed by primary–tertiary diaminocatalysts. Tetrahedron Lett. 2010, 51, 1884–1886. [CrossRef]

14. Zhu, X.; Liu, A.; Fang, L.; Li, W.; Zhu, C.; Cheng, Y. In Situ Formed Bifunctional Primary Amine–Imine Catalyst for Asymmetric Aldol Reactions of α-Keto Esters. Chem. Eur. J. 2011, 17, 8281–8284. [CrossRef] [PubMed]

15. Viózcz, S.F.; Bañón-Caballero, A.; Guillena, G.; Nájera, C.; Gómez-Bengoa, E. Enantioselective Direct Aldol Reaction of α-keto esters Catalyzed by (S)-binam-D-prolinamide under Quasi Solvent-Free Conditions. Org. Biomol. Chem. 2012, 10, 4029–4035.

16. Lisnyak, V.G.; Kucherenko, A.S.; Valeev, E.F.; Zlotin, S.G. (1,2-Diaminoethane-1,2-diyl)bis(N-methylpyridinium) Salts as a Prospective Platform for Designing Recyclable Prolinamide-Based Organocatalysts. J. Org. Chem. 2015, 80, 9570–9577. [CrossRef] [PubMed]

17. Kochetkov, S.V.; Kucherenko, A.S.; Zlotin, S.G. Asymmetric Aldol Reactions in Ketone/ketone Systems Catalyzed by Ionic Liquid-Supported C2-symmetrical Organocatalyst. Mendeleev Commun. 2015, 25, 168–170. [CrossRef]

18. Wang, Y.-J.; Shen, Z.-X.; Li, B.; Zhang, Y.-W. Proline Catalyzed Asymmetric Aldol Reaction between Methyl Ketones and α-Ketoesters. Chin. J. Chem. 2006, 24, 1196–1199. [CrossRef]

19. List, B.; Lerner, A.R.; Barbas, C.F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. J. Am. Chem. Soc. 2000, 122, 2395–2396. [CrossRef]

20. Bisai, V.; Bisai, A.; Singh, V.K. Enantioselective Organocatalytic Aldol Reaction Using Small Organic Molecules. Tetrahedron 2012, 68, 4541–4580. [CrossRef]

21. Heravi, M.M.; Zadsirjan, V.; Dehghani, M.; Hosseintash, N. Current Applications of Organocatalysts in Asymmetric Aldol Reactions: An Update. Tetrahedron: Asymmetry 2017, 28, 587–707. [CrossRef]

22. Shi, L.-X.; Sun, Q.; Ge, Z.-M.; Zhu, Y.-Q.; Cheng, T.-M.; Li, R.-T. Dipeptide-Catalyzed Direct Asymmetric Aldol Reaction. Synlett 2004, 12, 2215–2217. [CrossRef]

23. Krattiger, P.; Kovács, R.; Revell, J.D.; Wennemers, H. Using Catalyst–Substrate Coimmobilization for the Discovery of Catalysts for Asymmetric Aldol Reactions in Split-and-Mix Libraries. QSAR Comb. Sci. 2005, 24, 1158–1163. [CrossRef]

24. Krattiger, P.; Kovács, R.; Revell, J.D.; Ivan, S.; Wennemers, H. Increased Structural Complexity Leads to Higher Activity: Peptides as Efficient and Versatile Catalysts for Asymmetric Aldol Reactions. Org. Lett. 2005, 7, 1101–1103. [CrossRef] [PubMed]

25. Revell, J.D.; Gantenbein, D.; Krattiger, P.; Wennemers, H. Solid-Supported and Pegylated H-Pro–Pro–Asp–NHR as Catalysts for Asymmetric Aldol Reactions. Biopolymers (Pept. Sci.) 2006, 84, 105–113. [CrossRef] [PubMed]

26. Dodda, R.; Zhao, C.-G. Organocatalytic Enantioselective Synthesis of Secondary α-Hydroxycarboxylates. Synlett 2007, 10, 1605–1609. [CrossRef]
27. D’Elia, V.; Zwicknagl, H.; Reiser, O. Short α/β-Peptides as Catalysts for Intra- and Intermolecular Aldol Reactions. J. Org. Chem. 2008, 73, 3262–3265. [CrossRef] [PubMed]
28. Wu, F.-C.; Da, C.-S.; Du, Z.-X.; Guo, Q.-P.; Li, W.-P.; Yi, L.; Jia, Y.-N.; Ma, X. N-Primary-Amine-Terminal β-Turn Tetrapeptides as Organocatalysts for Highly Enantioselective Aldol Reaction. J. Org. Chem. 2009, 74, 4812–4818. [CrossRef] [PubMed]
29. Pearson, A.J.; Panda, S. N-Prolinylanthranilamide Pseudopeptides as Bifunctional Organocatalysts for Asymmetric Aldol Reactions. Org. Lett. 2011, 13, 5548–5551. [CrossRef] [PubMed]
30. Barrulas, P.; Benaglia, M.; Burke, A.J. Synthesis of Novel Cinchona-Amino Acid Hybrid Organocatalysts for Asymmetric Catalysis. Tetrahedron: Asymmetry 2014, 25, 923–935. [CrossRef]
31. Szöllösi, G.; Csámpai, A.; Somlai, C.; Fekete, M.; Bartók, M. Unusual enantioselectivities in heterogeneous organocatalyzed reactions: Reversal of direction using proline di- versus tri-peptides in the aldol addition. J. Mol. Catal. A: Chem. 2014, 382, 86–92. [CrossRef]
32. Milbeo, P.; Maurent, K.; Moulat, L.; Lebrun, A.; Didierjean, C.; Aubert, E.; Martinez, J.; Calmès, M. N-Pyrrolidine-Based α/β-peptides Incorporating ABOC, A Constrained Bicyclic β-Amino Acid, for Asymmetric Aldol Reaction Catalysis. Tetrahedron 2016, 72, 1706–1715. [CrossRef]
33. Vlasserou, I.; Sfetsa, M.; Gerokonstantis, D.-T.; Kokotos, C.G.; Moutevelis-Minakakis, P. Combining Prolinamides with 2-pyrrolidinone: Novel Organocatalysts for The Asymmetric Aldol Reaction. Tetrahedron 2018, 74, 2338–2349. [CrossRef]
34. Luppi, G.; Cozzi, P.G.; Monari, M.; Kaptein, B.; Broxterman, Q.B.; Tomasini, C. Dipeptide-Catalyzed Asymmetric Aldol Condensation of Acetone with (N-Alkylated) Isatins. J. Org. Chem. 2005, 70, 7418–7421. [CrossRef]
35. Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahim, I.; Reyes, E.; Xu, Y. Direct Asymmetric Intermolecular Aldol Reactions Catalyzed by Amino Acids and Small Peptides. Chem. Eur. J. 2006, 12, 5383–5397. [CrossRef]
36. Luppi, G.; Monari, M.; Corrêa, R.J.; Violante, F.A.; Pinto, A.C.; Kaptein, B.; Broxterman, Q.B.; Garden, S.J.; Tomasini, C. The First Total Synthesis of (R)-convolutamydine A. Tetrahedron 2006, 62, 12017–12024. [CrossRef]
37. Kon, K.; Kohari, Y.; Murata, M. Unnatural Tripeptide as Highly Enantioselective Organocatalyst for Asymmetric Aldol Reaction of Isatins. Tetrahedron Lett. 2019, 60, 415–418. [CrossRef]
38. Kon, K.; Kohari, Y.; Murata, M. Tripeptide-Catalyzed Asymmetric Aldol Condensation of Acetone with (N-Alkylated) Isatins. J. Org. Chem. 2005, 70, 7418–7421. [CrossRef]
39. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A., Jr.; Vreven, T.; Kudin, K.N.; Burant, J.C.; et al. Gaussian 03, Revision C.02. Gaussian, Inc.: Wallingford, CT, USA, 2004. Available online: https://gaussian.com/g03citation/ (accessed on 8 June 2019).
40. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; et al. Gaussian 09, Revision E.01. Gaussian, Inc.: Wallingford, CT, USA, 2009. Available online: https://gaussian.com/g09citation/ (accessed on 8 June 2019).
41. Szőri, K.; Balázsi, K.; Felföldi, K.; Bartók, M. Study of Enantioselective Hydrogenation of Bulky Esters of Phenylglyoxylic Acid on Pt-CD and Pt-β-ICN Chiral Catalysts: Steric Effect of Ester Groups and Inversion of Enantioselectivity. J. Catal. 2006, 241, 149–154. [CrossRef]
42. Creary, X. Reaction of Organometallic Reagents with Ethyl Trifluoroacetate and Diethyl Oxalate. Formation of Trifluoromethyl Ketones and α-Keto Esters via Stable Tetrahedral Adducts. J. Org. Chem. 1987, 52, 5026–5030. [CrossRef]