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Amino Acids Catalyzed Asymmetric Synthesis of 4-(2-(diphenylphosphanyl) phenyl)-4-hydroxybutan-2-one

Muhammad Naseer Barak *[1], Darokhan Ulfat [1], Mohammad Amen Sabawon [1], Abdul Shakoor Karrimi [2]

A B S T R A C T

Purpose:
This study aims to investigate the catalytic efficiency of amino acids and their metal salts in promoting asymmetric aldol reactions. The focus is on identifying environmentally friendly and effective catalytic systems that can provide both high yield and enantioselectivity in direct aldol reactions.

Method:
The direct aldol reaction between 2-benzhydrylbenzaldehyde and acetone was studied using amino acids and their metal salts as catalysts. L-proline and its magnesium salt (L-pro-Mg) were employed under optimized conditions at a catalyst loading of 20 mol%. Reaction parameters such as solvent, temperature, and catalyst structure were systematically varied to evaluate their impact on product formation.

Results:
The catalytic systems tested successfully yielded 4-(2-(diphenylphosphanyl)phenyl)-4-hydroxybutan-2-one with high yield and moderate optical purity. Among the catalysts examined, L-proline and L-pro-Mg displayed the highest catalytic performance, providing significant enantioselectivity compared to other amino acid-based catalysts. Reaction outcomes were strongly influenced by catalyst type, reaction temperature, and solvent selection.

Practical Implications:
The findings demonstrate the potential of amino acid and amino acid–metal salt catalysts as sustainable alternatives in asymmetric synthesis. Their efficiency in producing enantioselective products highlights their value in green chemistry, where reduced reliance on toxic or expensive metal-based catalysts is desirable. These results may encourage broader adoption of bio-derived catalysts in synthetic organic chemistry.

Originality/Novelty:
This study contributes novelty by showcasing the superior catalytic performance of L-proline and its magnesium salt in asymmetric aldol reactions. It emphasizes the interplay between catalyst structure and reaction parameters in achieving enantioselectivity. The work highlights amino acid-derived catalysts as promising, eco-friendly options that bridge traditional organocatalysis and sustainable synthesis approaches.

Keywords: *Amino Acid Catalysis, Asymmetric Synthesis, Aldol Reaction, L-Proline, Enantioselectivity, Phosphorine Compounds, Metal Salt Catalysts, Chiral Building Blocks*

Author Affiliations:
[1]Department of Chemistry, Faculty of Education, Urozgan universe, Urozgan-Afghanistan.
[2]Department of Agronomy, Faculty of Agriculture, Urozgan universe, Urozgan-Afghanistan.
***Corresponding e-mail:** m.n.barak1990@gmail.com

1. Introduction

In the field of organic synthesis, aldol reactions are considered a foundational tool due to their central role in forming carbon-carbon bonds. These reactions are instrumental in generating hydroxy ketones and aldehydes, which serve as vital intermediates in the construction of complex organic compounds (*Afewerki & Cordova, 2016*). As such, aldol reactions are widely developed in the growth of diverse molecular architectures. This study focuses on the catalytic behavior of amino acid metal salts in direct aldol reactions, particularly examining their ability to enhance both catalytic efficiency and enantioselectivity (*Chen et al., 2019*). Asymmetric aldol reactions catalyzed by such systems are especially valuable for the synthesis of oxygen-containing organic molecules (*Mlynarski & Paradowska, 2008*). The first example of an enantioselective organocatalyzed aldol reaction was reported by Wiechert et al. in 1971, utilizing proline as a catalyst for the partial synthesis of steroid frameworks (*Wiechert et al., 1971*). This work was further advanced by Hajos and Parrish (*Hajos & Parrish, 1974*), and later by the research groups of List and Barbas, who successfully employed proline in direct aldol reactions. This supports the widely accepted role of proline as a versatile and highly effective organocatalyst in facilitating direct aldol transformations (*Turner et al., 2000*). Numerous studies have since demonstrated the reliability and effectiveness of proline in such transformations (*Okun, 2017*). More recently, metal salts derived from amino acids have emerged as promising alternative catalysts for asymmetric aldol reactions. Although the research in this area is still developing, reported studies-particularly those by Gati and Yamamoto *(Gati & Yamamoto, 2016).*These findings emphasize the emerging significance of amino acid-derived metal salts as viable catalysts that can deliver both stereochemical precision and high catalytic performance in aldol-type reactions.

Synthesis Method of Amino Acid Metal Salts:

Aligned with our continued interest in exploring amino acid salts as catalysts, we began by assessing their catalytic efficiency. A general synthetic procedure was applied: equimolar amounts of a selected amino acid and a metal hydroxide (MOH), or a 2:1 ratio in the case of divalent metal hydroxides ($M(OH)_2$), were dissolved in methanol using a round-bottom flask maintained at 0°C. The mixture was then stirred at room temperature until a transparent solution formed, indicating complete dissolution and initial salt formation. Methanol was then removed by evaporation, yielding solid amino acid metal salts. These products were used directly in catalytic tests without additional purification. This simple and reproducible method enabled the preparation of several proline-based metal salts. Utilizing these salts, we carried out direct aldol reactions between 2-(diphenylphosphanyl)benzaldehyde and acetone under gentle conditions, aiming to produce chiral products with good enantioselectivity.

Amino Acid (Salt) Catalyzed Direct Asymmetric Aldol Reaction of 2-(diphenylphosphanyl) Benzaldehyde and acetone

Previous studies on asymmetric aldol reactions and our research group's ongoing work on amino acid salt catalyzed asymmetric transformations have encouraged us to design a new aldol reaction to construct important chiral building blocks. Considering that chiral phosphorine compounds are wildly used as ligands in asymmetric catalysis, we selected commercially available 2-(diphenylphosphanyl)benzaldehyde as the electrophilic component. Our goal was to produce enantioenriched phosphorine derivatives through a direct asymmetric aldol reaction, as illustrated in Scheme 1. To achieve optimal results, we carefully studied and optimized key parameters including the influence of catalyst, solvent, loading and temperature. This methodical approach allowed for the development of an efficient and selective catalytic system for asymmetric synthesis.

Scheme1. catalytic asymmetric direct aldol of 2-(diphenylphosphanyl) benzaldehyde and acetone.

It was shown that the desired product (**3**) can be obtained when different salts of proline were employed as catalysts figure1.

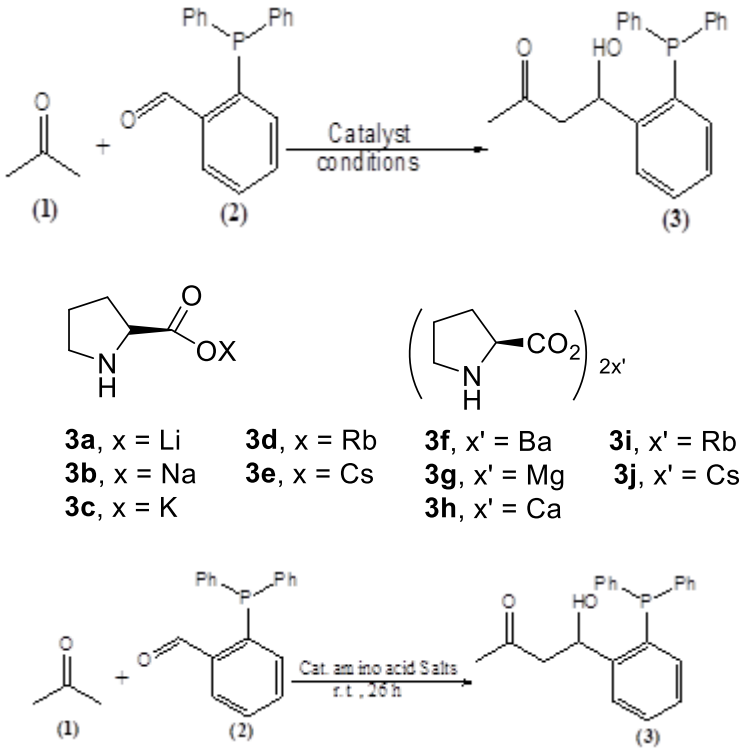


Fig1*. Amino Acid Salt Catalysts Used in This Work*

The cation of catalyst played important role on asymmetric conversion as well as enantiocontro table1. However, only moderate yield and enantioselectivity was obtained even under the promotion of the best catalyst-magnesium prolinate (table 1, entry 7, 65%, 70% ee).

Table1. Effect of amino acid salt catalyzed asymmetric aldol reaction between (1) and (2) [a]

Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**3a**	26	45	7
2	**3b**	26	45	7
3	**3c**	26	9	46
4	**3d**	26	66	46
5	**3e**	26	57	36
6	**3f**	26	52	4
7	**3g**	26	65	70
8	**3h**	26	56	5
9	**3i**	26	45	7

[a] *Unless otherwise noted, the reactions were carried out with 1 mL acetone (**1**), 0.1 mmol 2-(diphenylphosphanyl) benzaldehyde (**2**) and catalyst (20 mol %) at r.t. for 26 h.* [b]*Isolated yield* [c]*Enantioselectivities were determined by chiral HPLC.*

Amino acid catalyzed direct asymmetric aldol reaction of 2-(diphenylphosphanyl) benzaldehyde and acetone

Inspired by above results, we hope to evaluate the catalytic ability of different amino acids. Subsequently, the aldol reaction of 2-(diphenylphosphanyl) benzaldehyde (**2**) was conducted in neat acetone. It was shown that the reaction results were largely dependent on the nature of amino acids, whereas number of them were employed herein Figure 2.

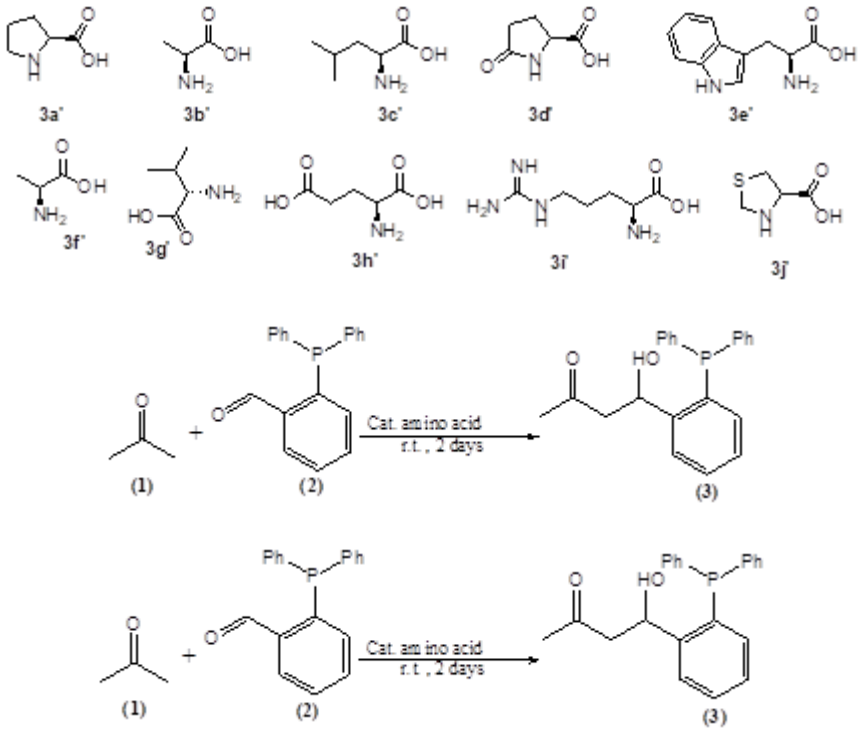


***Fig2**. Number of amino acid catalysts applied in this work.*

For example, we found that use of leucine catalyst afforded the desired product in excellent enantioselectivity but very low yield, while many other amino acids failed to promote reaction toward the desired product. Finally, the best catalyst was found to be L-proline, which afforded the desired product **(3)** in good yield 66% and 75%) ee) (table 2, entry 1).

Table2. Effect of amino acids catalyzed asymmetric aldol reaction of (1) and (2) [a]

Entry	**Catalyst**	**Yield (%)*b***	**ee (%)*c***
1	**3a'**	66	75
2	**3b'**	5	88
3	**3c'**	9	90
4	**3d'**	39	0
5	**3e'**	trace	-

6	**3f'**	trace	-
7	**3g'**	trace	-
8	**3h'**	trace	-
9	**3i'**	trace	-
10	**3j'**	trace	-

[a] *Unless otherwise noted, the reactions were carried out with 1 mL acetone (**1**), 0.1 mmol 2-(diphenylphosphanyl) benzaldehyde (**2**) and catalyst (20 mol %) at r.t. for 2 days.* [b] *Isolated yield.* [c] *Enantioselectivities were determined by chiral HPLC.*

As illustrated in table 2, asymmetric aldol reaction of 2-(diphenylphosphanyl) benzaldehyde (**2**) and acetone (**1**), conducted under optimal conditions for 2 days. We noticed that other amino acid catalyst such as **3d`-3j`** failed to afford the target product **(3)**.

To improve the reaction results, the effect of catalyst loading was systematically studied. As described in table 3, the catalyst loading obviously influenced the enantiocontrol. When 5 mol % L-proline.was employed as catalyst, the desired product was obtained with best result of yield 68% and 87% ee (table 3 entry 1), while higher catalyst loading led to dramatically decreased enantioselectivity.

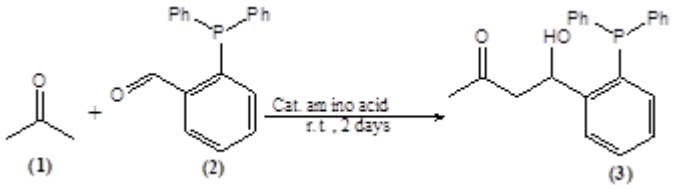
Table3. The effect of catalyst loading of L-proline on asymmetric aldol reaction [a]

Entry	**Catalyst loading**	**Yield (%)**[b]	**ee (%)**[c]
1	5 mol %	68	87
2	10 mol %	73	79
3	15 mol %	73	66
4	20mol %	66	75
5	25mol %	73	59
6	30 mol %	79	65

[a] *Unless otherwise noted, the reactions were carried out with 1 mL acetone (**1**), 0.1 mmol 2-(diphenylphosphanyl) benzaldehyde (**2**) and catalyst (6-30 mol %) at r.t. for 2 days.* [b] *Isolated yield.* [c] *Enantioselectivities were determined by chiral HPLC.*

Besides, the influence of solvent was also studied. As shown in table 4, the addition of THF in the reaction mixture dramatically lowered the reaction rate, which negatively affected on enantioselectivity (table 4, entries 1-3). Thus, caring out the reaction in neat acetone should be a good choice and the optimal condition for this reaction.

Table4*. The effect of THF solvent in asymmetric aldol reaction of **(1)** and **(2)*** [a]

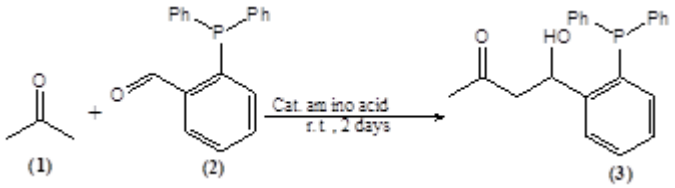


Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	THF/Acetone (1:1)	trace	-
2	THF/Acetone (1:2)	trace	-
3	THF/Acetone (1:5)	trace	-
4	THF/Acetone (1:10)	13	80
5	THF/Acetone (1:20)	17	80
6	THF/Acetone (1:30)	22	79
7	THF/Acetone (1:40)	35	73
8	THF/Acetone (1:50)	39	73

[a] *Unless otherwise noted, the reactions were carried out with 1 mL solvent, 0.1 mmol 2-(diphenylphosphanyl) benzaldehyde (**2**) and catalyst (20 mol %) at r.t. for 2 days.* [b] *Isolated yield.* [c] *Enantioselectivities were determined by chiral HPLC.*

Subsequently, the influence of temperature was also evaluated. According to the literature, lowing temperature is always found useful to the enantiocontrol. However, we found that decreasing the reaction temperature did little effect to the reaction enantiocontrol: the reaction carried out at either room temperature or as low as -40 ^{o}C resulted similar reaction outcomes (table 5). Thus, room temperature seems to be the best condition for our work.

Table5. *The effect of temperature in asymmetric aldol reaction of (**1**) and (**2**)*



Entry	Catalyst	Temperature (^{o}C)	Yield (%)[b]	ee (%)[c]
1	L-proline	r.t.	66	75
2	L-proline`	-10	41	70
3	L-proline	-20	65	70
4	L-proline	-30	58	77
5	L-proline	-40	48	74

[a] *Unless otherwise noted, the reactions were carried out with 1 mL acetone (**1**), 0.1 mmol 2-(diphenylphosphanyl) benzaldehyde (**2**) and catalyst (20 mol %) at r.t. for 2 days.* [b]*Isolated yield.* [c] *Enantioselectivities were determined by chiral HPLC.*

2. Discussion

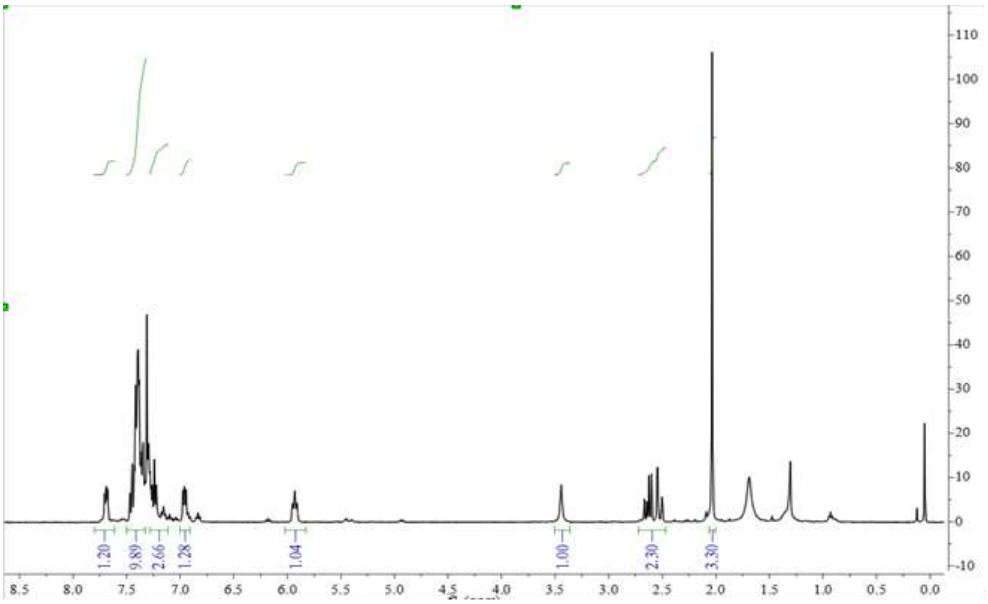
The current study demonstrates the effective catalytic performance of amino acids and their metal salts, particularly in promoting enantioselective direct aldol reactions. The successful synthesis **of 4-(2-(diphenylphosphanyl) phenyl)-4-hydroxybutan-2-one** through the reaction between 2-benzhydrylbenzaldehyde and acetone underscores the practical relevance of these catalysts in organic synthesis. Particularly, both **L-proline** and its magnesium salt (**L-pro-Mg**) displayed substantial catalytic activity and moderate to good enantiocontrol, highlighting their utility as organocatalysts in asymmetric synthesis. These findings align with previous studies that have recognized **L-proline** as a benchmark organocatalyst in asymmetric aldol reactions due to its ability to form stable enamine intermediates and activate both nucleophilic and electrophilic substrates simultaneously *(List & Barbas, 2000; Mukherjee et al., 2007; Seebach et al., 2007)*. The study emphasizes that the structural nature of the amino acid used as a catalyst plays a key role in determining both the yield and enantioselectivity of the aldol product. Among the tested catalysts, **L-proline and L-pro-Mg** stood out, providing optimal results at a catalyst loading of 20 mol%. This observation is consistent with earlier literature, which has reported high enantioselectivity in proline-catalyzed aldol reactions under similar conditions *(Tang et al., 2004; Notz & List, 2000*). Furthermore, this investigation confirms that reaction conditions such as **catalyst type, loading, solvent, and temperature** significantly influence both conversion and enantiomeric excess (ee) *(Hayashi, 2003); (Seebach, et al., 2007)* The moderate optical purity observed suggests that further tuning of conditions or exploration of modified amino acid structures could enhance stereoselectivity. For instance, studies have shown that structural modifications of proline or the use of bifunctional catalysts can lead to improved enantioselectivity and regioselectivity in aldol reactions (*Wang, 2009; Hayashi, 2003; Gruttadauria & Giacalone, 2012).*

3. Conclusion

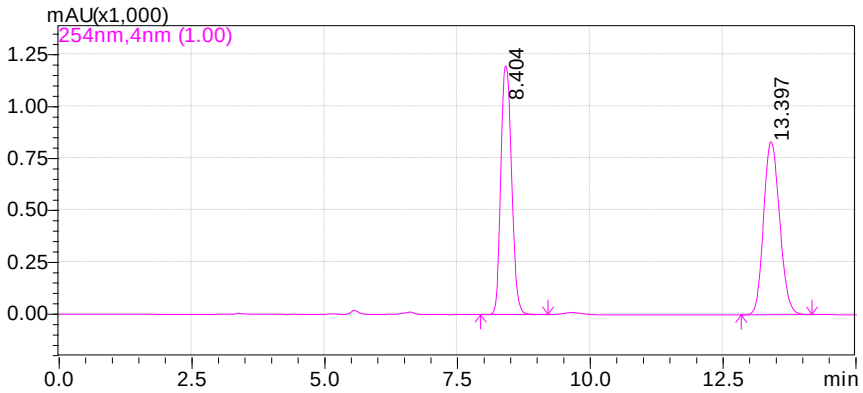
In this research, we have successfully developed a catalytic asymmetric aldol reaction between acetone and 2-(diphenylphosphanyl)benzaldehyde, using L-proline as a natural amino acid catalyst. This transformation led to the formation of the desired aldol product bearing a phosphorine moiety, with both good yield and enantioselectivity. The investigation included a comprehensive evaluation of the structural impact of various amino acids and their corresponding metal salts on catalytic performance. Moreover, various critical factors including the amount of catalyst used, the selected solvent, and the reaction temperature were carefully fine-tuned to enhance the efficiency and selectivity of the reaction. Overall, this method demonstrates an efficient and practical strategy for synthesizing enantioenriched phosphorine-containing compounds using readily available starting materials and environmentally benign catalysts.

NMR spectra of 4-(2-(diphenylphosphanyl) phenyl)-4-hydroxybutan-2-one

^{1}H NMR (500 MHz, DMSO) δ 7.65 (m, 1H), 7.22-7.49 (m, 12H), 6.88- 6.96 (m,1H), 5.82- 5.95 (m, 1H), 3.48 (s, 1H), 2.48-2.69 (m, 2H), 2.02 (s, 3H).

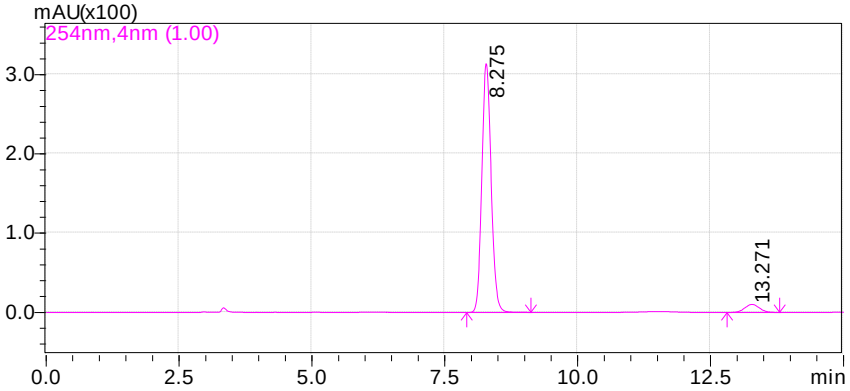


HPLC spectra of 4-(2-(diphenylphosphanyl) phenyl)-4-hydroxybutan-2-one



Ret. Time Peak Start Peak End Area% 8.404 7.936 9.205 49.1777

13.397 12.843 14.176 50.8223



Ret. Time Peak Start Peak End Area% 8.275 7.915 9.120 95.0014

13.271 12.811 13.803 4.9986

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