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Synthesis of Trans-4-Hydroxyprolineamide and 3-Ketoproline Ethyl Ester for Green Asymmetric Organocatalysts

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ABSTRACT

Organocatalysts have become one of the three pillars in asymmetric reactions, along with metal catalysis and enzyme catalysis. Organocatalysis is widely acknowledged in both academia and industry as a practical and advantageous synthetic method owing to its operational ease, readily available catalyst, environmentally friendly, and minimal toxicity. Much attention has been focused on the organocatalyst for its superior properties as an efficient and clean catalyst. In this work, a series of green organocatalysts of *trans*-4-hydroxyprolineamide were efficiently obtained in a two-step reaction utilizing EDC.HCl and HOBT as coupling reagents via a condensation reaction. The yield furnished in 93% to 97% yields. These organocatalysts have big potential in asymmetric reactions such as aldol and Michael addition reactions.

1. Introduction

1.1 Proline

In modern organic synthesis, chiral pyrrolidines play a significant role as organocatalysts. The five-membered secondary amines structure of pyrrolidines has proven to provide powerful capacity in organocatalytic transformations via intermediate enamines and iminium ions. The concept of organocatalyst was introduced by Ostwald in the early 1900s. Many organocatalytic transformations may achieve remarkable efficiency and selectivity under moderate reaction conditions [1]. As a result, organocatalysis is commonly used in asymmetric reactions like Aldol, Mannich, Michael addition, and many more. In the 1970s, Hajos-Parrish-Eder-Sauer-Wiechert discovered a proline-based organocatalyst in the aldol reaction, yielding an important steroid precursor with high yield and enantiomeric excess [2]. Following that, in the 2000s, List, Barbas, and Lerner reintroduced proline as the organocatalyst in the aldol reaction between aldehyde and ketone[3,4]. Through these discoveries, chemists and researchers have extensively studied *L*-proline's ability as organocatalyst.

For many years, proline and proline derivatives have been the most efficient catalyst due to the presence of different bioisosteric groups [5]. Proline (Figure 1) is a naturally occurring α-amino acid

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with secondary amine functionality. This property raises the pKa value, placing proline ahead of other amino acids in terms of nucleophilicity [6]. The earliest discovery reported that proline is a "micro-aldolase", which is capable of activating the electrophile by its proton donor group, and also activating the nucleophile by its amine group [7]. This permits proline to take part in bifunctional asymmetric catalysis, which has been a successful laboratory strategy for enhancing chemical transformations [8]. *L*-Proline may therefore become stable under standard reaction conditions owing to the existence of its chiral structure.

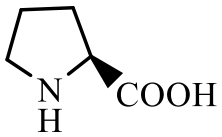

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Fig. 1. Structure of *L*-Proline

A starting material is manipulated by successive reactions using chiral reagents that maintain its chirality to achieve the desired target molecule. This is particularly appealing for target molecules with chirality comparable to affordable naturally occurring building blocks like sugars or amino acids. However, the number of potential reactions for the molecule is limited, and complicated synthetic routes may be needed [9]. The molecule that exists within the chiral pool is always in a chiral state. Lately, a wide variety of natural and non-natural products have been synthesized in a substrate-controlled manner using proline as the chiral pool substance [10]. Therefore, proline will assist the final product to be asymmetric.

Despite evidence that proline is an interesting organocatalyst for catalysing organic reactions, this tiny organic molecule has a number of limitations when it comes to promoting an efficient reaction with a high yield and high enantioselectivity. These include a longer reaction time [11], a large catalyst loading (20-30 mol%) to achieve adequate conversions, the utilization of non-environmentally friendly organic solvents [12], and poor performance and low reactivity in non-polar solvents [13]. Some organocatalysts generated from proline were inefficient in certain processes. As a result, a new focus has been shifted to prolineamide. Prolineamide derivatives with asymmetric pyrrolidine ring, an amide group, and a hydroxyl group are capable of hydrogen bonding to substrate molecules, thereby stabilizing the enamine in the activated intermediate complex. Additionally, these systems allow for the modification of the steric environment in order to standardize their catalytic properties [14].

1.2 Condensation Reaction

Condensation reaction is one of the powerful methods for the synthesis of desired products from the reaction between two reactants that yield one larger product and a byproduct of smaller molecules. There are various types of the condensation reaction. For example, Pungot and coworkers [15] utilized Claisen-Schmidt condensation via the reaction between acetophenone and benzaldehyde in the presence of alcoholic alkaline base. Acetophenone lost an α-hydrogen to generate an enol or enolate ion. Subsequently, the enol/enolate ion reacted with the carbonyl of benzaldehyde to form β-hydroxyketone, which was then dehydrated to provide the required chalcones.

Condensation is also a common approach towards the synthesis of β-carboline and its derivatives [16]. The main reaction includes the Pictet-Spengler condensation of tryptamine with different substituted aldehydes to form the β-carboline framework. This method is short and simple, and it is recommended since no heat is used to promote the reaction.

Knoevegel condensation reaction, on the other hand, is a convenient method to facilitate the synthesis of 5-arylidine of Meldrum's acid derivatives [17]. Meldrum's acid includes unique ring-opening sequences based on nucleophile-sensitive carbonyl functional groups at C-4 and C-6, allowing for important synthetic transformations, as well as strong methylene hydrogen acidity at carbon position C-5. As a result, the molecule can function as a versatile reagent in subsequent reactions to produce various derivatives.

Prolineamide can be synthesized via condensation reaction utilizing coupling reagents. Figure 2 depicted a three-step reaction to synthesize a novel prolineamide 5 [18]. In this method N, N'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) were used as coupling reagents.

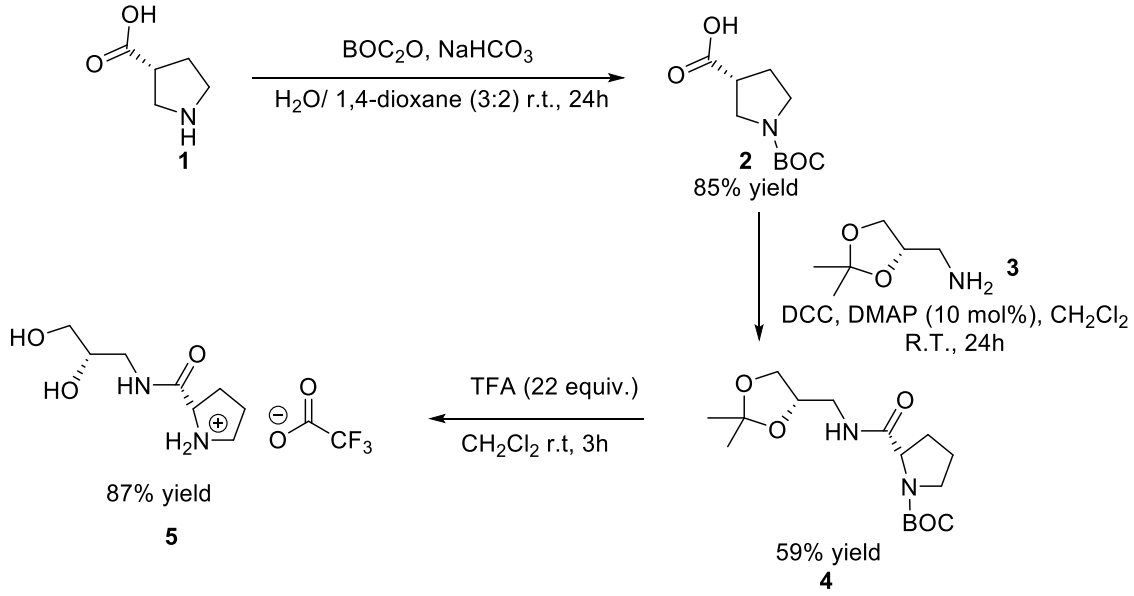


Fig. 2. Preparation Prolineamide Organocatalyst **5**

Reddy *et al.,* successfully synthesized organocatalyst **9** from 8-aminoquinoline **7** and *N*-BOC-*L*-proline **6** (Figure 3). The condensation reaction was carried out using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCl) and hydroxybenzotriazole (HOBt) in 0°C for five hours.

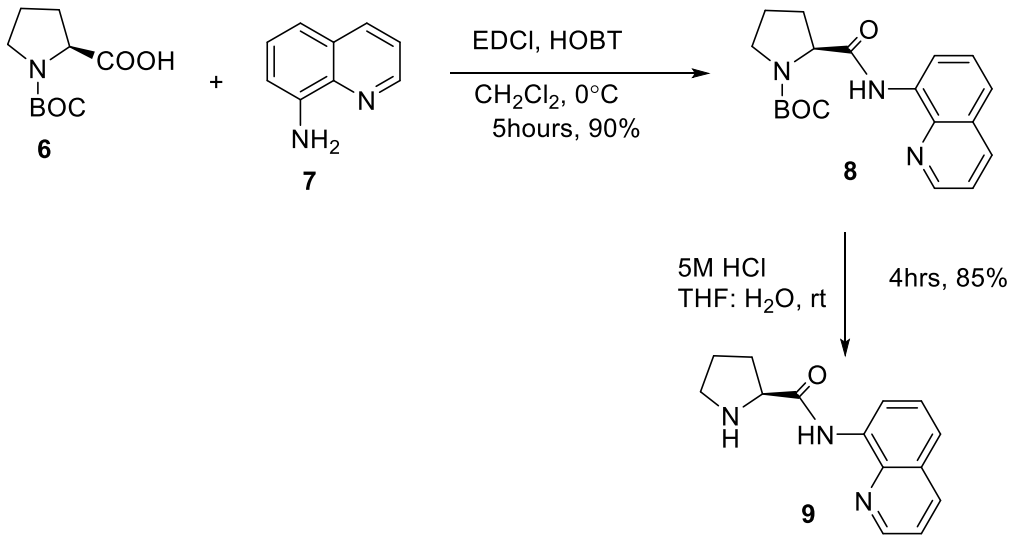


Fig. 3. Synthesis of (*S*)-*N*-(quinoline-8-yl) pyrrolidine-2-carboxamide, organocatalyst **9**

Both reactions were suitable for the condensation reaction to produce prolineamide-based organocatalysts. The essential feature of coupling methods was to give a high yield of products. In these reactions, the configurational integrity was not a problem since the starting material was in a fixed chiral molecule.

While each prolineamide exhibits distinct characteristics, the challenge lies in achieving high yields in condensation reactions, which is crucial for enabling successful future asymmetric reactions. The synthesis of prolineamide-based organocatalysts represents a significant advancement in catalyst development. These catalysts could potentially overcome the limitations of conventional proline-based catalysts and offer improved efficiency, reactivity, and selectivity. In this study, we focused on the synthesis of new prolineamide's organocatalysts and optimization of the reaction conditions to get a high yield.

2. Methodology

2.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used without further purification. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using silica gel 60 F254 aluminium precoated plates from Merck (0.25 mm), and compounds were visualized by irradiation with UV light. Column chromatography was performed on silica gel (MN Kieselgel 60 M, 0.063-0.200 mm, 70-230 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL 400 MHz spectrometer. Chemical shifts were reported in ppm (parts per million) according to residual solvent signals of $CDCl_3$ (^{1}H NMR; δ=7.26 ppm, ^{13}C NMR; δ=77.0 ppm), DMSO-d_6 (^{1}H NMR; δ=2.50 ppm, ^{13}C NMR; δ=39.43 ppm) and CD_3OD (^{1}H NMR; δ=3.30 ppm, ^{13}C NMR; δ=49.0 ppm). All spectra were acquired and processed using JEOL Delta 5.1.1.

Fourier transformed infrared absorption spectra were recorded on Varian 3100 Excalibur series instruments Spectrum 2000 or Spectrum One, both in the spectral range of 4000 to 400 cm^{-1}. Solid samples were run as nujol mulls on potassium bromide or sodium chloride discs or as thin films of their solution in dichloromethane. Oil or liquid samples were run neatly on potassium bromide or sodium chloride discs.

The molecular weight of synthesized compounds was recorded on GCMS Agilent Technologies 7890 A (GC System).

2.2 Synthesis of Organocatalyst

2.2.1 Method using DCC and DMAP as coupling reagent

To the stirred solution of (0.93 g, 2.2 mmol, 1.1 eq) *N,N*-dicyclohexylcarbodiimide, DCC in 10 ml dichloromethane was added (0.025 g, 0.2 mmol, 0.1 eq) 4-dimethylaminopyridine, DMAP and BOC-*trans*-4-hydroxy-*L*-proline **10** (0.25 g, 1.08 mmol, 1.1 eq), at ambient temperature. The mixture was stirred for 1 h, treated dropwise with the 5ml solution of 0.34 g aniline in dichloromethane and stirred for 24 hours. The afforded (2R,4S)-4-hydroxy-N-phenylpyrrolidine-2-carboxamide **12** was filtered off. The filtrate was washed sequentially with 1N HCl, 2% aqueous $NaHCO_3$ and water, dried (sodium sulfate) and concentrated in vacuum to give a residue.

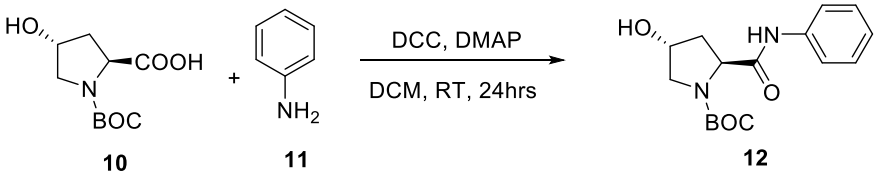


Fig. 4. Synthesis of compound **12**

2.2.2 Method using EDC.HCl and HOBT as coupling reagent

To a dry THF (10 ml) was added BOC-*trans*-4-hydroxy-*L*-proline **10** (0.25 g, 1.08 mmol, 1 eq), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, EDC.HCl (0.21 g, 1.08 mmol, 1 eq) and hydroxybenzotriazole, HOBT (0.03 g, 0.02 mmol, 0.19 eq) at 0°C under N_2 atmosphere. The reaction mixture was stirred for 30 min at 0°C, and then 2-aminoanthracene **13** was added and stirred at room temperature overnight. The reaction was quenched with saturated sodium hydrogen carbonate. The organic layer was separated, the aqueous layer was extracted with dichloromethane, and the combined organic layer was dried over anhydrous sodium sulphate, filtered, and evaporated. Further purification was through column (Hexane: Ethyl Acetate = 3:1) to give yellow powder of 97% yield BOC-(4*R*)-*N*-(anthracen-2-yl)-4-hydroxypyrrolidine-2-carboxamide **14**. The same procedure was used to prepare all the organocatalysts.

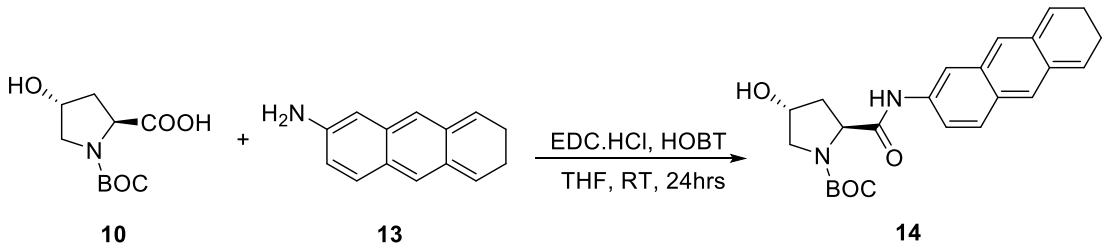


Fig. 5. Synthesis of compound **14**

2.2 BOC-Deprotection of the Organocatalyst

The starting BOC-(4*R)-N*-(anthracen-2-yl)-4-hydroxypyrrolidine-2-carboxamide **14** was dissolved in CH_2Cl_2. Trifluoroacetic acid (1 mmol sample: 5 ml) was added. The reaction mixture was stirred at room temperature for three hours. CH_2Cl_2 was evaporated and replaced by anhydrous toluene, which was then evaporated to azeotrope excess of trifluoroacetic acid. This operation was repeated three times to yield yellow powder which was dried in vacuo. The catalyst 1 was used without further purification.

Fig. 6. Synthesis of Catalyst 1

2.4 Experimental Data

Tert-butyl (2*S*,4*R*)-4-hydroxy-2-(pyrrolidine-1-carbonyl) pyrrolidine-1-carboxylate **12**; IR ν cm^{-1}: 3224 (NH), 1784 (C=O), 1736 (C=O). δ_H (MeOD, 400 MHz): 1.29 (6H, s, CH_3 x 2), 1.45 (3H, s, CH_3), 1.87 (4H, m, CH_2 x 4), 2.11-2.27 (2H, m, CH_2), 3.46-3.57 (4H, m, CH_2 x 2), 3.73-3.76 (2H, m, CH_2), 3.93 (1H, m, CH), 4.48 (1H, t, *J* = 7.10, 7.15, CH) ; ^{13}C (D_2O, 100 MHz): 25.54 (CH_2), 27.64 (CH_3), 35.89 (CH_2), 48.77 (CH_2), 58.26 (CH_2), 60.55 (CH), 67.65 (CHOH), 80.12 (quat. C), 155.48 (C=O), 172.63(C=O). MS (ESI) *m/z*: calculated for $C_{14}H_{24}N_2O_2$ (M^+) 284.17 found 283.98.

(2*R*,4*S*)-4-hydroxy-*N*-phenylpyrrolidine-2-carboxamide **15**; IR ν cm^{-1}: 3216 (NH), 1728 (C=O). δ_H (MeOD, 400 MHz): δ 1.34 (3H, s, CH_3 x 2), 1.44 (3H, s, CH_3), 2.02 -2.11 (1H, m, CH) , 2.21 - 2.29 (1H, m, CH), 3.28 (s, 1H), 3.48 (d, *J* = 11.5 Hz, 1H), 3.60 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.46 – 4.37 (2H, m, CH_2) and 7.08 – 7.56 (5H, m, aromatic H); ^{13}C (D_2O, 100 MHz): δ 38.72 (CH_2), 53.85 (CH_2), 59.27 (CH_2), 69.96 (CHOH), 124.54-128.67 (Ar-CH), 137.74 (Ar-C), 166.48 (C=O). MS (ESI) *m/z*: calculated for $C_{11}H_{14}N_2O_2$, (M^+) 206.11 found 206.13.

Tert-butyl (2*S*,4*R*) -4 - hydroxy-2-(isopropylcarbamoyl) pyrrolidine-1-carboxylate **17**; IR ν cm^{-1}: 3208 (NH), 1722 (C=O), 1659 (C=O). δ_H (MeOD, 400 MHz): δ 1.13 (6H, dd, *J* = 6.7 Hz, 11.3 Hz, CH_3 x 2), 1.42 (9H, d, *J* = 8 Hz, CH_3 x 3), 1.94-2.15 (2H, m, CH_2), 3.28-3.53 (2H, m, CH_2), 3.91-3.97 (1H, m, CH), 4.20-4.34 (1H, m, CH), 8.01 (NH); ^{13}C (MeOD, 100 MHz): 21.25 (CH_3), 27.33 (CH_3), 38.54 (CH_2), 41.25 (CH), 58.96 (CH_2), 69.36 (CH), 80.19 (quat. C), 154.87 (C=O), 173.23 (C=O). MS (ESI) *m/z*: calculated for $C_{13}H_{24}N_2O_4$, (M^+) 272.17 found 272.25.

T*ert*-butyl-(2*S,*4*R*)-*N*-(anthracen-2-yl)-4-hydroxypyrrolidine-2-carboxamide **14**; IR ν cm^{-1}: 3214 (NH), 1682 (C=O), 1619 (C=O). ^1H NMR (400 MHz, MeOD) (ppm): δ 1.35 (6H, s, CH_3 x 2), 1.46 (3H, s, CH_3), 2.14 - 2.17 (1H, dd, *J* = 8 Hz, CH) 2.30 (1H, d, *J* = 8 Hz), 3.51 - 3.67 (2H, m CH_2), 4.46 – 4.59 (2H, m, CH_2), 7.37 - 7.42 (2H, Ar H), 7.51 - 7.54 (1H, dd, *J* = 8 Hz, Ar H), 7.92 - 7.98 (3H, m, aromatic H), 8.32 - 8.44 (3H, dd, *J* = 32, Ar H); ^{13}C NMR (400 MHz, MeOD) (ppm): δ 28.53 (CH_3), 28.56 (CH_3), 36.82 (CH_2), 58.42 (CH_2), 65.15 (CH), 68.23 (CH_2), 79.02(quat. C), 108.02 (Ar-CH), 117.10 (Ar-CH), 124.96 (Ar-CH), 125.34 (Ar-CH), 125.46 (Ar-CH), 125.84 (Ar-CH), 127.57 (Ar-CH), 127.90 (Ar-CH), 129.03 (Ar-CH), 129.42 (Ar-CH), 130.27 (Ar-CH), 131.51 (Ar-CH), 131.73 (Ar-CH), 132.39 (Ar-C), 154.28 (C=O), 171.23 (C=O). MS (ESI) *m/z*: calculated for $C_{24}H_{26}N_2O_4$, (M^+) 406.19 found 406.20.

(2*S*,4*R*)-*N*-(anthracen-2-yl)-4-hydroxypyrrolidine-2-carboxamide **Catalyst 1**; IR ν cm^{-1}: 3391 (NH), 1671 (C=O). ^{1}H NMR (400 MHz, MeOD) (ppm): δ 2.10-2.19 (3H, m, CH-CH_2), 2.53 - 2.58 (1H, m, CH), 3.38 -3.50 (2H, m, CH_2-N), 4.45-4.49 (1H, dd, *J* = 8.3, 6.9 Hz, CH-C=O), 7.39 - 7.45 (2H, m, aromatic H), 7.52 -7 .50 (1H, dd, *J* = 9.1 Hz, 1.9 Hz, Ar), 7.91 – 8.04 (3H, m, Ar), 8.34 - 8.44 (3H, m, Ar); ^{13}C NMR (400 MHz, MeOD) (ppm): δ 45.04 (CH_2), 55.04 (CH_2N) , 59.42 (CH), 70.02 (CHOH), 116.02 (Ar-CH), 120.10 (Ar-CH), 124.96 (Ar-CH), 125.34 (Ar-CH), 125.46 (Ar-CH), 125.84 (Ar-CH), 127.57 (Ar-CH), 127.90 (Ar-CH), 129.03 (Ar-CH), 129.42 (Ar-CH), 131.51 (Ar-CH), 131.73 (Ar-CH), 132.39 (Ar-CH), 134.54 (Ar-C), 166.89 (C=O). MS (ESI) *m/z*: calculated for $C_{19}H_{18}N_2O_2$, (M^+) 306.14 found 306.15.

(2*S*,4*R*)-4-hydroxy-*N*-(naphthalen-2-yl)pyrrolidine-2-carboxamide **Catalyst 2**; IR ν cm^{-1}: 3389 (NH), 1659 (C=O). ^{1}H NMR (400 MHz, MeOD) (ppm): δ 2.14 - 2.21 (H, tt, *J* = 6.6, 13.3 Hz, CH), 2.55 - 2.60 (1H, dd, *J* = 6.9, 13.2 Hz, CH), 3.28 - 3.29 (1H, m, CH), 3.34 - 3.46 (1H, dt, *J* = 12.6, 25.2 CH), 4.62 - 4.67 (2H, dd, *J* = 6.8, 10 Hz, CH_2), 7.39 - 7.44 (2H, m, Ar), 7.57 - 7.58 (1H, dd, *J = 1.9, 8.8 Hz,* Ar), 7.77 - 7.82 (3H, m, Ar), 8.22 - 8.233 (d, *J* = 1.1 Hz, Ar); ^{13}C NMR (400 MHz, MeOD) (ppm): δ 38.78 (CH_2), 53.96 (CH_2), 59.92 (CH), 69.97 (CHOH), 116.74 (Ar-CH), 119.50 (Ar-CH), 125.06 (Ar-CH), 126.37 (Ar-CH), 127.25 (Ar-CH), 127.32 (Ar-CH), 128.49 (Ar-CH), 131.02 (Ar-CH), 133.79 (Ar-CH), 135.21 (Ar-C), 166.70 (C=O). MS (ESI) *m/z*: calculated for $C_{15}H_{16}N_2O_2$, (M^+) 256.12 found 256.14.

N'-((2*S*,4*R*)-4-hydroxypyrrolidine-2-carbonyl)-3-methylbenzenesulfonohydrazide **Catalyst 3**; IR ν cm^{-1}: 3391 (NH), 1671 (C=O), 1659 (C=O). 1H NMR (400 MHz, MeOD) (ppm): δ 1.88 - 2.11 (2H, m, CH_2), 2.39 (3H, s, CH_3), 2.78 – 3.11 (2H, M, CH_2-N), 3.96 – 3.99 (2H, m, CHOH, CH-C=O), 7.39 – 7.41 (1H, m, Ar-H), 7.50 - 7.55 (1H, m, Ar-H), 7.70 – 7.73 (2H, m, Ar-H); (^{13}C NMR (400 MHz, MeOD) (ppm): δ 21.41 (CH_3), 40.14 (CH_2), 54.70 (CH_2), 58.27 (CH), 71.18 (CHOH), 124.05 (Ar-CH), 126.05 (Ar-CH), 127.56 (Ar-CH), 135.25 (Ar-C), 139.61 (Ar-C), 170.34 (C=O). MS (ESI) *m/z*: calculated for $C_{12}H_{17}N_3O_4S$, (M^+) 299.04 found 299.08.

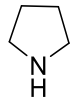
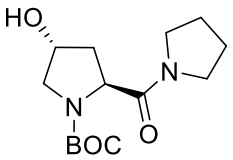
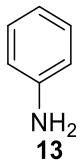
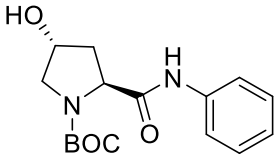
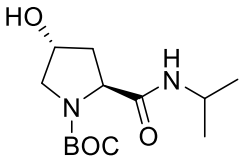
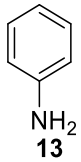
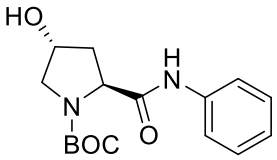
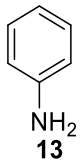
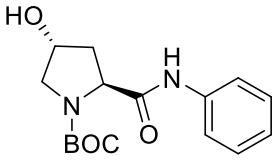
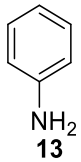
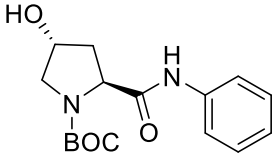
(2*S*,4*R*)-N'-(benzo[d]thiazol-2-yl)-4-hydroxypyrrolidine-2-carbohydrazide **Catalyst 4**; IR ν cm^{-1}: 3208 (NH), 1663 (C=O). ^{1}H NMR (400 MHz, MeOD) (ppm): δ 1.85- 2.14 (2H, m, CH_2), 2.81 – 3.02 (2H, m, CH_2), 3.70 – 3.75 (1H, m, CH), 7.50 - 7.52 (1H, m, Ar), 7.92 – 7.95 (1H, m, Ar–H), 7.99 - 8.03 (2H, m, Ar); ^{13}C NMR (400 MHz, MeOD) (ppm): 40.14 (CH_2), 54.24, (CH_2), 58.63 (CH), 71.80 (CHOH), 118.42 (Ar-CH), 120.32 (Ar-CH), 121.63 (Ar-CH), 124.90 (Ar-CH), 125.96 (Ar-CH), 130.56 (Ar-C), 153.71 (C=N), 174.66 (C=O), 175.44 (C=N). MS (ESI) *m/z*: calculated for $C_{12}H_{14}N_4O_2S$, (M^+) 278.08 found 278.10.

3. Results

3.1 Synthesis of Trans-4-Hydroxyprolineamide Organocatalyst

In an effort to obtain the highest yield of synthesized organocatalyst, a brief optimization involving several solvents and coupling reagents was conducted (Table 1). Amine selected in the reactions was readily available in our lab and is used to attempt the reaction for optimization purposes. Initially, the reaction was conducted in accordance with standard literature procedures. As the starting material, BOC-*Trans*-4-hydroxy-*L*-proline (1.0 eq) was coupled with pyrrolidine using 1.0 eq EDC.HCl, 0.19 eq HOBT, and TEA in DMF solvent at 0°C for 19 hours [20], yielding just 11% (entry 1). Using aniline as amine at the same condition marginally increased yield to 21% (entry 2). Changing the temperature from 0°C to room temperature boosted the yield to 33% (entry 3). Substituting dichloromethane for DMF as the solvent and lengthening the reaction period from 19 to 24 hours enhanced the yield by 46% (entry 4). By switching the coupling agent to DCC and DMAP [21], the yield of the organocatalyst was increased to 52% (entry 5). Changing the solvent to THF with 1.0 eq EDC.HCl and 0.19 eq HOBT produced a superb 91% yield (entry 6).

Table 1
Optimization of the catalyst using *N*-BOC-*trans*-4-hydroxy-*L*-proline as starting material

No.	Amine	Reagent	Solvent	Temp/Time	Product	Yield
1.	 **11**	EDC.HCl, HOBT, TEA	DMF	0°C/ 19hrs	 **12**	11%
2.	 **13**	EDC.HCl, HOBT, TEA	DMF	0°C/ 19hrs	 **15**	21
3.	 **16**	EDC.HCl, HOBT, TEA	DMF	25°C/ 19 hrs	 **17**	33
4.	 **13**	EDC.HCl, HOBT, TEA	$CHCl_3$	25°C/ 24 hrs	 **15**	46
5.	 **13**	DCC, DMAP	DCM	25°C/ 24 hrs	 **15**	52
6.	 **13**	EDC.HCl, HOBT, TEA	THF	25°C/ 24 hrs	 **15**	91

The reaction with DCC and DMAP (entry 5) obtained a similar yield as reported in the literature review. Through the process of optimizing conditions, we gained insights indicating that EDC.HCl and HOBT, as utilized in entry 6, stand out as superior coupling reagents for the synthesis of prolineamide-based organocatalysts. Our outcomes were notably favourable, with the product achieving an outstanding yield while being amenable to reaction at room temperature.

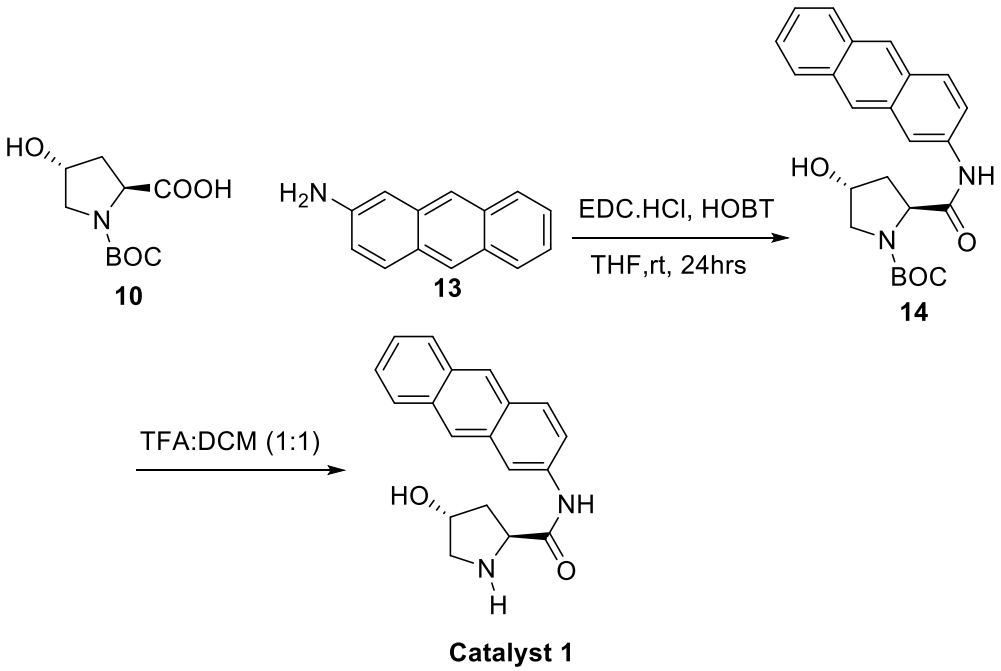


Fig. 7. Two steps reaction to synthesis **Catalyst 1**

With the optimum reaction conditions in hand, the target organocatalyst was synthesized by combining *N*-BOC-trans-4-hydroxy-L-proline with 2-aminoanthracene. Similarly, various prolineamide derivatives were synthesized from *N*-BOC-*trans*-4-hydroxy-*L*-proline, and the corresponding amino compounds using the synthetic approach indicated in Figure 4. Catalysts 1,2,3,4 and 6 produced high yields of 97%, 93%, 94% and 95%, respectively. The BOC-protecting group was removed from these compounds using a 1:1 (TFA: DCM) ratio, yielding high quantitative yields. Figure 8 shows a newly synthesized prolineamide-based organocatalyst.

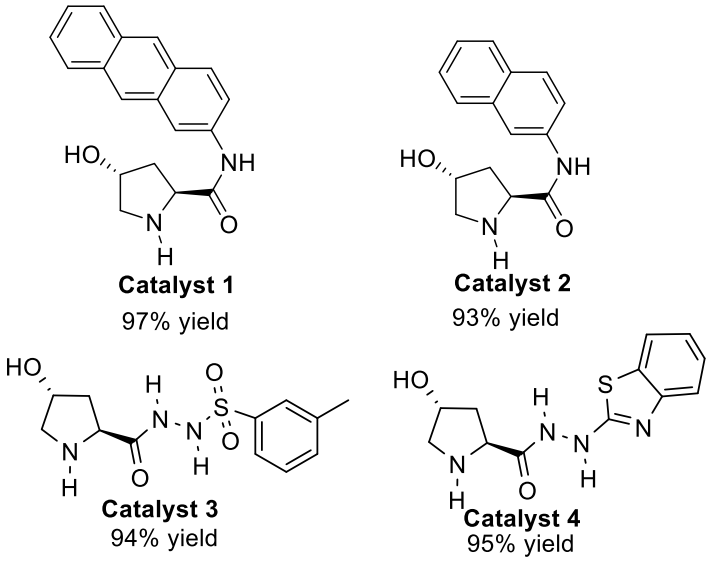


Fig. 8. Newly synthesized *trans*-4-hydroxyprolineamide-based organocatalyst

The mechanism for HOBt mediated prolineamide organocatalyst formation using EDC.HCl is depicted in Figure 9. In the initial step, the carboxylic acid of BOC-*trans*-hydroxy-*L*-proline **10** was reacted with carbodiimide **18**. The nucleophilic carboxylate **20** then attacks the activated

carbodiimide **19**, yielding an *O*-acylisourea intermediate **21**. The production of the very stable, water-soluble urea product **23** forced the activated ester to be extremely sensitive to nucleophilic substitution. Interception of **21** by HOBt **22** results in the formation of the activated ester **25**, which is nucleophilically attacked by aniline **13** to yield the desired prolineamide organocatalyst **15**.

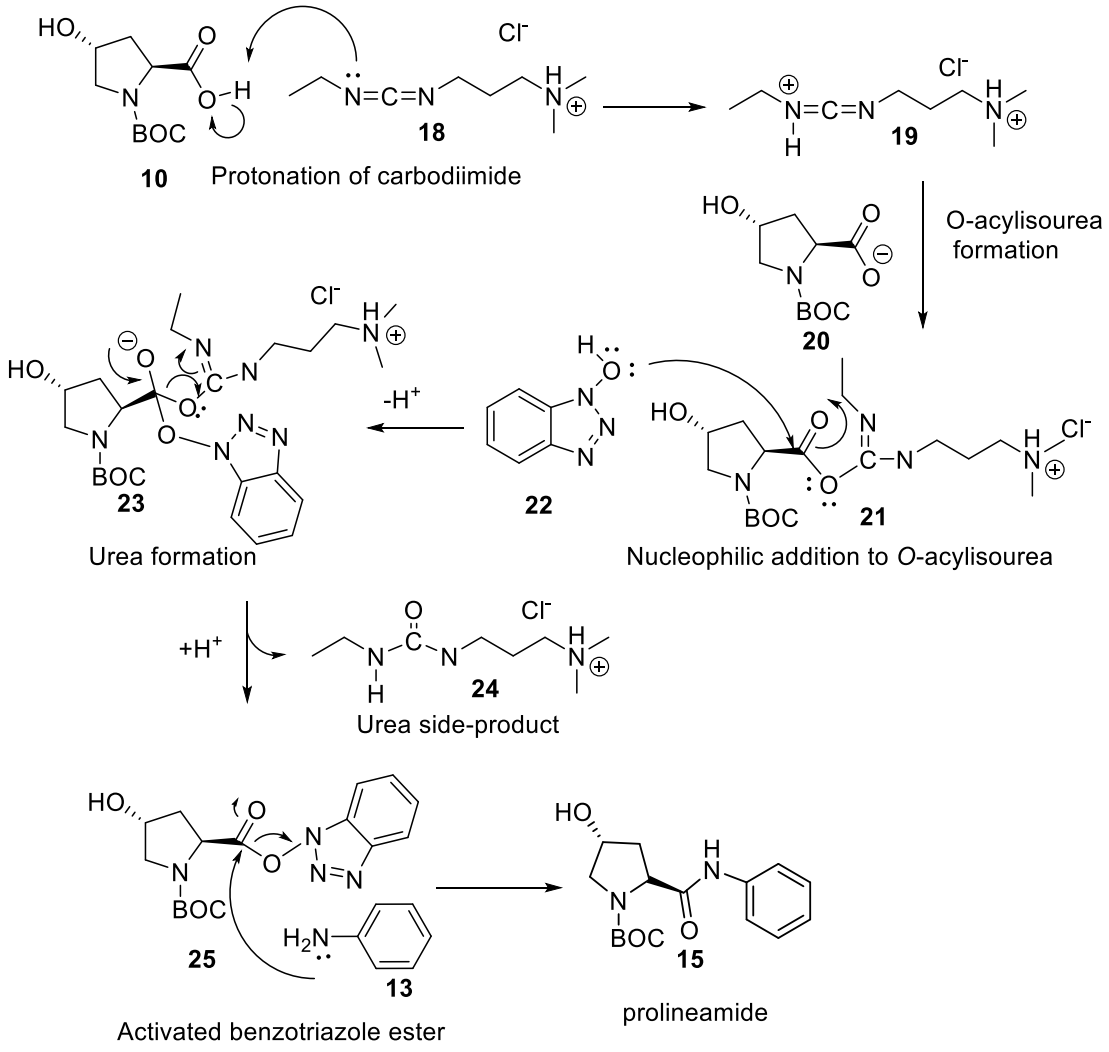


Fig. 9. Mechanism of synthesis of prolineamide organocatalyst mediated by EDC.HCl and HOBt as coupling reagent

4. Conclusions

In conclusion, four new prolineamide-based organocatalysts were successfully synthesized using EDC.HCl and HOBT as coupling reagents. The optimal reaction conditions are at room temperature and with THF as the solvent. Removal of BOC protecting group using 1:1 (TFA: DCM) furnished highly quantitively yield. This work has further used in asymmetric aldol and Michael addition reaction.

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