chemistry proceedings

MDPI

Proceeding Paper

Synthesis of Two Amphiphilic Organocatalysts Derived from L-Proline †

Erika Alarcón-Matus *, Cuauhtémoc Alvarado-Sanchéz *, Oswaldo I. Hernández-Abreu, Quirino Torres-Sauret, Erika M. Ramos-Rivera, Luis F. Roa, Ever A. Blé-González and Nancy Romero-Ceronio *

Centro de Investigación de Ciencia y Tecnología Aplicada de Tabasco, División Académica de Ciencias Básicas, Universidad Juárez Autónoma de Tabasco, Carretera Cunduacán-Jalpa km 1, Col. La Esperanza, Cunduacán 86690, Tabasco, Mexico; oswaldo.hernandez@ujat.mx (O.I.H.-A.); quirino.torres@ujat.mx (Q.T.-S.); erika.ramos@ujat.mx (E.M.R.-R.); fernando.roa@ujat.mx (L.F.R.); ever.ble@ujat.mx (E.A.B.-G.)

* Correspondence: erika.alarcon@ujat.mx (E.A.-M.); cuauhtemoc.alvarado@ujat.mx (C.A.-S.); nancy.romero@ujat.mx (N.R.-C.)

† Presented at the 29th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-29); Available online: https://sciforum.net/event/ecsoc-29.

Abstract

Organocatalysts synthesized from L-proline have demonstrated effectiveness in catalyzing various asymmetric reactions. Additionally, the choice of reaction medium plays a crucial role; using environmentally friendly solvents, such as water or brine solutions, can facilitate the formation of stable emulsions that enhance the interaction between the organocatalyst and the reactants. This work describes the synthesis of two organocatalysts derived from L-proline through a five-step process with overall yields of 37% and 5%, respectively. A significant advantage of these products is that they can be classified as amphiphilic catalysts due to the presence of both hydrophilic and hydrophobic components in their structures.

Keywords: amphiphilic organocatalysts; L-proline and azide

Academic Editor(s): Name

Published: date

Citation: Alarcón-Matus, E.; Alvarado-Sanchéz, C.; Hernández-Abreu, O.I.; Torres-Sauret, Q.; Ramos-Rivera, E.M.; Roa, L.F.; Blé-González, E.A.; Romero-Ceronio, N. Synthesis of Two Amphiphilic Organocatalysts Derived from L-Proline. *Chem. Proc.* **2025**, *volume number*, x. https://doi.org/10.3390/xxxxx

1. Introduction

In 2000, David W. C. MacMillan defined organocatalysis as the use of low-molecular-weight organic molecules as catalysts in organic reactions [1,2]. Since then, various groups have contributed to the development of new organocatalysts. Today, organocatalysts are regarded as essential tools in organic synthesis, particularly for asymmetric and sustainable transformations [3]. Additionally, the growing interest in using more environmentally friendly solvents has led many organic chemists to focus on reactions conducted in aqueous media [4,5]. As a result, there is an increasing demand for organocatalysts that exhibit better solubility or possess amphiphilic characteristics [6].

Amphiphilic organocatalysts possess both hydrophilic and hydrophobic components in their structure, which serve as a bridge to facilitate the interaction of organic reactants in an aqueous medium [6]. Interested in the field of organocatalysis, In this report, we present the synthesis of two amphiphilic organocatalysts derived from L-proline, (*S*)-7-(pyrrolidin-2-yl) tridecan-7-amine (**1**) and (*S*)-2-(7-azidotridecan-7-yl) pyrrolidine (**2**). Both were functionalized at C2 of the pyrrolidine ring with aliphatic chains of six carbon atoms (Figure 1).

The primary advantage of these compounds, given their characteristics, is that they can be classified as amphiphilic catalysts because they contain both hydrophilic and hydrophobic segments in their structures. This property allows the catalysts to form stable emulsions, facilitating organic reactions in aqueous media.

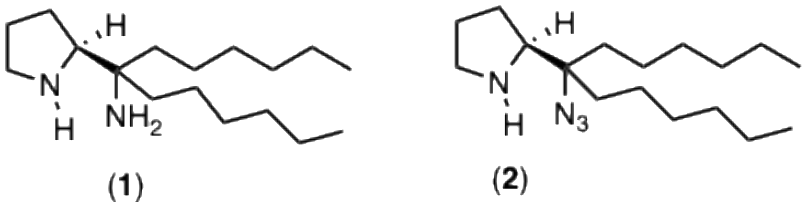

Figure 1. The synthesized amphiphilic organocatalysts: (*S*)-7-(pyrrolidin-2-yl) tridecan-7-amine (**1**) and (*S*)-2-(7-azidotridecan-7-yl) pyrrolidine (**2**).

To synthesize this compound, we adapted part of the synthesis sequence reported by Palomo and Reyes-Rangel [7–11]. Organocatalysts (**1**) and (**2**) were obtained through a five-step process, yielding 37% and 5%, respectively (Figure 2).

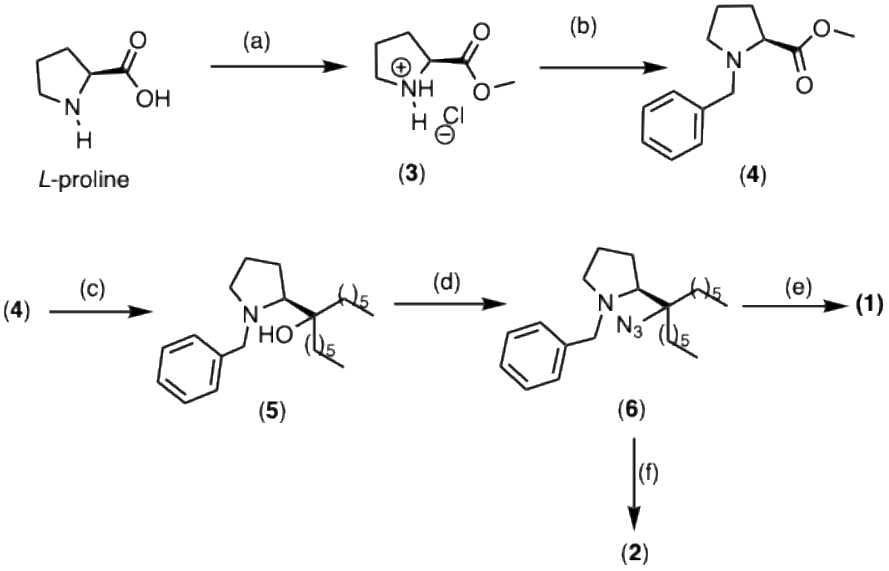

Figure 2. Reagents and conditions: (a) $SOCl_2$, MeOH, relux, 1 h, 100%; (b) BnBr, Et_3N, CH_2Cl_2, r. t., 4 h, 76%; (c) *n*-$C_6H_{13}Br$, Mg; THF, 0 °C, 18 h, 98%; (d) NaN_3, CF_3CO_2H, H_2SO_4, $CHCl_3$-H_2O, reflux, 6 h, 88% (e) Pd-C (10% mo), AcOH-H_2O (3:1), H_2, 48 h, 57%; (f) H_2/Pd–C, AcOEt, r. t., 7.9% [7–11].

The products were characterized using ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY, HSQC, and HMBC techniques, and the signals corresponded to their proposed structures.

2. Materials and Methods

General Information

Starting materials for the preparation of compounds **1** and **2** were obtained from Sigma-Aldrich in reagent-grade quality. Commercially available reagents and solvents were used as received. Tetrahydrofuran (THF) was distilled from sodium and benzophenone before use. Flash column chromatography was performed on silica gel (230–400 mesh) Thin-layer chromatography (TLC) was performed on precoated silica gel F_{254} plates (Merck). Detection was performed with iodine vapor staining and UV light irradiation (UV lamp, model UV-IIB). Infrared spectra (IR) were recorded on a Perkin-Elmer Spectrum One FTMS spectrometer. NMR spectra were recorded on a Varian VX-400

spectrometer with tetramethylsilane (TMS) as an internal standard, and chemical shifts are reported in δ (ppm).

Methyl (*S*)-pyrrolidine-2-carboxylate hydrochloride (3)

(S)-pyrrolidine-2-carboxylate methyl hydrochloride (3) was prepared following established procedures [7–11]. In a 20 mL round-bottom flask fitted with a magnetic stirrer and a condenser, 200 mg of L-proline (1.73 mmol) was dissolved in 1.5 mL of anhydrous methanol at 0 °C. Thionyl chloride (SOCl2) (0.138 mL, 1.91 mmol) was then added slowly, and the reaction mixture was refluxed for 1 h. After the reflux period, methanol and thionyl chloride were removed under reduced pressure using a rotary evaporator, yielding a yellow oily liquid. This product was utilized in the subsequent reaction without further purification and was obtained in quantitative yield.

(*S*)-*N*-benzylpyrrolidine-2-carboxylate methyl ester (4)

To prepare the protected compound (**4**), a solution of (*S*)-pyrrolidine-2-carboxylate methyl ester (**3**, 0.225 g, 1.36 mmol) hydrochloride was created in 7 mL of dichloromethane (CH_2Cl_2) at 0 °C. Triethylamine (0.38 mL, 2.72 mmol) was added, followed by benzyl bromide (0.117 mL, 1.50 mmol). The reaction mixture was stirred continuously for 4 h at room temperature. After the reaction was complete, the mixture was treated with a saturated sodium bicarbonate solution and then extracted with dichloromethane (2 × 20 mL). The organic phase was dried over anhydrous magnesium sulfate and concentrated using a rotary evaporator under reduced pressure. The residue was purified by flash chromatography (Hex:AcOEt, 9:1). The *N*-benzylated L-proline ester (**4**) was obtained as a yellow oil with a yield of 76%. ^{1}H-NMR spectrum ($CDCl_3$, 600 MHz) δ(ppm): 1.71 (m, 1H); 1.86 (m, 2H); 2.06 (m, 1H); 2.32 (c, 1H, *J* = 8.4 Hz); 2.97 (td, 1H); 3.18 (dd, 1H); 3.50 (d, 1H, *J* = 12.8 Hz); 3.57 (s, 3H); 3.81 (d, 1H, *J* = 12.8); 7.17 (c, 1H); 7.24 (m, 4H). ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) δ (ppm): 23.1, 29.5, 51.8, 53.4, 58.9, 65.4, 127.2, 128.3, 129.4, 138.4, 174.7.

(*S*)-7-(1-benzylpyrrolidin-2-yl)tridecan-7-ol (5)

To prepare the protected amino alcohol (**5**), the in-situ formation of the Grignard reagent was necessary. In a 20 mL two-necked round-bottom flask equipped with a magnetic stirrer, septum, and reflux system, 0.144 g of magnesium turnings (5.95 mmol) was added to 3 mL of anhydrous THF. The flask was sealed, cooled to 0 °C, and purged with nitrogen. Subsequently, 0.416 mL of bromohexane (0.490 g, 2.97 mmol) was added. After stirring the mixture for two hours at 0 °C, the color changed from dark gray to light gray, indicating the formation of the Grignard reagent. Next, a solution of (**4**) (0.163 g, 0.743 mmol) in 2 mL of THF was added to the Grignard reagent. The cooling system was turned off, and the mixture was stirred continuously at room temperature for 16 h. Upon completion of the reaction, the mixture was treated with 2 mL of saturated ammonium chloride solution (NH_4Cl) and stirred for 30 min. The mixture was then filtered and concentrated using a rotary evaporator under reduced pressure. The resulting suspension was extracted with dichloromethane (CH_2Cl_2) (3 × 5 mL). The organic phase was washed with a 9% saline solution and dried over magnesium sulfate. After filtration, the mixture was again concentrated with a rotary evaporator. The residue was purified by flash chromatography (Hex:AcOEt, 95:5), yielding a light-yellow oil in 98% yield. ^{1}H-NMR spectrum ($CDCl_3$, 600 MHz) δ(ppm): 0.80 (dt, 6H, *J* = 17.94 Hz); 1.22 (m, 18H); 1.40 (m, 3H); 1.60 (m, 2H); 1.76 (m, 2H); 2.40 (m, 1H, *J* = 6.24, 8.52 Hz); 2.75 (m, 1H, *J* = 6.42, 8.52 Hz); 2.80 (t, 1H, *J* = 7.38 Hz), 3.51 (d, 1H, *J* = 13.7 Hz); 3.94 (d, 1H, *J* = 13.7 Hz); 7.16 (tt, 1H, *J* = 1.62, 7.20 Hz); 7.24 (td, 2H, *J* = 1.74, 6.69 Hz); 7.28 (dd, 2H, *J* = 1.68, 8.19 Hz) ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) δ (ppm): 14.0, 14.0, 22.6, 22.6, 23.4, 23.7, 24.9, 27.3, 30.1, 30.2, 31.8, 31.8, 34.4, 37.8, 55.0, 63.1, 70.5, 75.7, 126.9, 128.2, 128.3, 140.4.

(*S*)-2-(3-Azidopentan-3-yl)-1-benzylpyrrolidine (6)

In a two-necked round-bottom flask equipped with a magnetic stirrer, septum, condensation system, and a $NaHCO_3$ trap, 0.1 g of compound (**5**) (0.27 mmol) was added to 3

mL of chloroform. The mixture was stirred vigorously at 0 °C under a nitrogen atmosphere. Following this, 106 μL of trifluoroacetic acid (1.39 mmol) was added, quickly followed by the addition of 72 mg of sodium azide (NaN_3) (1.11 mmol). Next, 0.46 mL of water and 1 mL of concentrated sulfuric acid (H_2SO4) were added. The reaction mixture was then refluxed for 6 h, with progress monitored by TLC. After refluxing, the mixture was cooled to room temperature, and the organic layer was extracted with dichloromethane (CH_2Cl_2) (3 × 15 mL). The organic phase was washed with a 5% sodium bicarbonate solution followed by a 9% saline solution and and dried over anhydrous sodium sulfate, filtered, and concentrated using a rotary evaporator. The resulting mixture was purified by column chromatography (Hex:AcOEt,98.5:1.5). The pure product was obtained in 88% yield. $[\alpha]_D^{25} = -33.3$ (c = 1.0, CH_2Cl_2). ^{1}H-NMR spectrum ($CDCl_3$, 600 MHz) δ(ppm): 0.88 (t, 6H); 1.31 (m, 14 H); 1.47 (m,2H); 1.71 (m, 4H); 1.97 (c, 1H, J = 8.82, 17.4 Hz); 2.12 (m, 4H); 2.90 (d, 1H, J = 13.1Hz); 2.95 (t, 1H, J = 8.31 Hz); 3.26 (t, 1H, J = 8.28); 3.92 (d, 1H, J = 13.14 Hz); 7.20 (s, 1H); 7.28 (m, 4H). ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) δ (ppm): 14.1, 14.1, 22.6, 22.6, 22.7, 27.3, 29.2, 29.3, 29.6, 29.7, 30.1, 30.7, 31.6, 31.9, 53.5, 58.5, 64.8, 126.6, 128.1, 128.6, 140.3.

(*S*)-7-(pyrrolidin-2-yl) tridecan-7-amine (1)

In a round-bottom flask, 100 mg (0.260 mmol) of compound (**6**) was dissolved in 0.5 mL of a 3:1 acetic acid-water solution. A 10% palladium on carbon (Pd-C) catalyst, weighing 31 mg (0.0291 mmol), was added to the mixture, which was then subjected to hydrogenolysis for 48 h. The progress of the reaction was monitored using thin-layer chromatography (TLC). Upon completion, the mixture was filtered through Celite and evaporated to dryness. Next, 10 mL of water was added to the residue, and the pH was adjusted to 1 using hydrochloric acid (HCl). A liquid-liquid extraction was then performed using ethyl acetate (2 × 15 mL). The aqueous phase was treated with 2N sodium hydroxide (NaOH) and ethyl acetate (2 × 15 mL). The organic phase was dried with anhydrous sodium sulfate, filtered, and then evaporated to dryness using a rotary evaporator under reduced pressure. The resulting crude product was purified by column chromatography with a solvent system of dichloromethane (CH2Cl2) and methanol (MeOH) in a 9:1 ratio. The pure product was obtained as a clear oil with a yield of 57%. ^{1}H-NMR spectrum ($CDCl_3$, 600 MHz) δ(ppm): 0.89 (t, 6H); 1.28 (m, 24 H); 1.73 (q, 2H, J = 7.62 Hz); 2.95 (t, 2H, J = 8.01 Hz); 7.01 (2H). ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) δ (ppm): 14.1, 22.7, 23.9, 26.6, 28.4, 29.8, 31.9, 33.2, 33.5, 37.4, 39.9.

(*S*)-2-(7-azidotridecan-7-yl) pyrrolidine (2)

In a round-bottom flask equipped with magnetic stirring, 100 mg of compound (**6**) (0.260 mmol) was dissolved in 1 mL of AcOEt. Next, 28 mg of 10% Pd-C (0.0260 mmol) was added as a catalyst, and the mixture was subjected to hydrogenolysis for 24 h. Upon completion of the reaction, the mixture was filtered through Celite, washed with methanol, and then evaporated to dryness. The resulting product was purified by column chromatography, SiO2, methanol/triethylamine (98:2). The compound (**2**) was obtained with a yield of 7.9%. ^{1}H-NMR spectrum ($CDCl_3$, 600 MHz) δ(ppm): 0.88 (t, 6H, J = 7.11 Hz); 1.25 (m, 23H); 1.44 (q, 2H, J = 7.29 Hz); 2.70 (t, 2H, J = 7.14 Hz); 4.12 (c, 1H, J = 7.14 Hz,-NH) ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) δ (ppm): 14.1, 22.7, 24.0,26.7, 29.7, 29.8, 31.9, 33.6, 33.7, 37.5, 41.9.

3. Results and Discussion

The synthesis of compounds (**1**) and (**2**) was initiated using L-proline, where aliphatic chains (-C_6H_{13}) were added to the carbonyl group to form alcohol (**5**). This was followed by the substitution of the -OH group with an azido group, and then catalytic hydrogenation was performed. In both synthetic pathways, azide (**6**) serves as the key intermediate, and depending on the hydrogenation conditions, either compound (**1**) or compound (**2**)

can be obtained. The choice of solvent for the hydrogenolysis of (**6**) was crucial. When a methanol and acetic acid mixture was used, free aminoazide (**2**) could not be detected. AcOEt proved to be the appropriate solvent.

When analyzing the 1H-NMR spectrum of compounds (**6**) and (**2**), we can clearly see the influence of the azido group. As an electron-withdrawing group, it causes a deprotecting effect. The protons in the pyrrolidine ring of compound (**6**) exhibited greater shifts compared to the corresponding protons in the aminoalcohol (**5**). A similar trend was observed in the diamine (**1**) and aminoazide (**2**); specifically, the chemical shift of the N-H proton in the pyrrolidine ring was greater in the aminoazide than in the diamine.

The resulting organocatalysts are anticipated to exhibit potential in semi-aqueous reactions, particularly in Michael-type reactions. The effectiveness of some intermediates obtained in these processes has already been demonstrated, as shown with compound (5), which successfully functioned as an organocatalyst in Michael addition reactions as reported by Palomo in 2006 and Lu in 2008 [7,8]. Similarly, independent research groups led by Hosoda, Olivares-Romero, and Reyes-Rangel synthesized organocatalysts derived from pyrrolidine with aryl substituents at the C-2 position, with reported encouraging results in Mannich and Michael-type reactions [9–11].

4. Conclusions

The synthesis of (*S*)-7-(pyrrolidin-2-yl) tridecan-7-amine (**1**) and (S)-2-(7-azidotridecan-7-yl) pyrrolidine (**2**) was successfully completed, yielding moderate results overall. This process involved a five-step sequence, with the compound (**6**) serving as a common intermediate in the final step of the synthesis. Both organocatalysts (**1**) and (**2**) are functionalized at C2 of the pyrrolidine ring with two aliphatic chains, each containing six carbon atoms. As a result, these organocatalysts can be classified as amphiphilic and are expected to be effective in reactions conducted in aqueous media.

Author Contributions: Conceptualization, methodology, and writing—original draft: E.A.-M.; methodology, supervision, and resources: C.A.-S. and N.R.-C.; validation, formal analysis, and investigation: Q.T.-S.; data curation and writing—original draft preparation: E.M.R.-R.; writing—review and editing and visualization: C.A.-S. and L.F.R.; project administration and funding acquisition: O.I.H.-A. and E.A.B.-G.; methodology: C.A.-S. All authors have read and agreed to the published version of the manuscript.

Funding: We are grateful for financial support PFI-UJAT (Project 2013-IB-13). E.A.-M. thanks CONACyT for a doctoral Scholarship No. 447166.

Institutional Review Board Statement: Not applicable**.**

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Acknowledgments: The authors sincerely thank to the Chemistry Center (BUAP).

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

References

1. MacMillan, D.W.C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304–308. https://doi.org/10.1038/nature07367.
2. Jen, W.S.; Wiener, J.J.M.; MacMillan, D.W.C. New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition. *J. Am. Chem. Soc*. **2000**, *122*, 9874–9875. https://doi.org/10.1021/ja005517p.
3. Xiang, S.-H.; Tan, B. Advances in Asymmetric Organocatalysis over the Last 10 Years. *Nat. Commun.* **2020**, *11*, 3786. https://doi.org/10.1038/s41467-020-17580-z.

4. Chatgilialoglu, C.; Barata-Vallejo, S.; Gimisis, T. Radical Reactions in Organic Synthesis: Exploring in-, on-, and with-Water Methods. *Molecules* **2024**, *29*, 569. https://doi.org/10.3390/molecules29030569.
5. Torres-Sauret, Q.; Vilchis-Reyes, M.A.; Martínez, R.; Romero-Ceronio, N.; Alarcon-Matus, E.; Hernández-Abreu, O.; Vázquez Cancino, R.; Alvarado Sánchez., C. Crossing Borders: On-Water Synthesis of Flavanones. *ChemistrySelect* **2022**, *7*, e202202567. https://doi.org/10.1002/slct.202202567.
6. Alarcón-Matus, E.; Alvarado, C.; Romero-Ceronio, N.; Ramos-Rivera, E.M.; Lobato-García, C.E. Proline-derived Long-aliphatic-chain Amphiphilic Organocatalysts (PDLACAOs) for Asymmetric Reactions in Aqueous Media. *Asian J. Org. Chem*. **2020**, *9*, 1667–1687. https://doi.org/10.1002/ajoc.202000419.
7. Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, Á.; Vera, S. Water-Compatible Iminium Activation: Organocatalytic Michael Reactions of Carbon-Centered Nucleophiles with Enals *Angew. Chem. Int. Ed*. **2007**, *46*, 8431–8435. https://doi.org/10.1002/ange.200703261.
8. Lu, J.; Lui, F.; Loh, T.-P. Enantioselective Michael Addition of Dicyanoolefins to α,β-Unsaturated Aldehydes in Aqueous Medium. *Adv. Synth. Catal.* **2008**, *350*, 1781–1784. https://doi.org/10.1002/adsc.200800145.
9. Hosoda, N.; Kamito, H.; Takano, M.; Takebe, Y.; Yamaguchi, Y.; Asami, M. Synthesis of chiral 2-(anilinophenylmethyl)pyrrolidines and 2-(anilinodiphenylmethyl)pyrrolidine and their application to enantioselective borane reduction of prochiral ketones as chiral catalysts. *Tetrahedron* **2013**, *69*, 1739–1746. https://doi.org/10.1016/j.tet.2012.12.024.
10. Olivares-Romero, J.L.; Juaristi, E. Synthesis of three novel chiral diamines derived from (S)-proline and their evaluation as precursors of diazaborolidines for the catalytic borane-mediated enantioselective reduction of prochiral ketones. *Tetrahedron* **2008**, *64*, 9992–9998. https://doi.org/10.1016/j.tet.2008.07.080.
11. Reyes-Rangel, G.; Vargas-Caporali, J.; Juaristi, E. In search of diamine analogs of the α, α-diphenyl prolinol privileged chiral organocatalyst. Synthesis of diamine derivatives of α, α-diphenyl-(S)-prolinol and their application as organocatalysts in the asymmetric Michael and Mannich reactions. *Tetrahedron* **2013**, *72*, 379–391. https://doi.org/10.1016/j.tet.2015.11.032.