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Asimetrik Michael Katılma Tepkimesi için Prolin bazlı β-Hidroksiamit Organokatalizörü

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Anahtar kelimeler
Michael katılması; Organokatalizör; Enantiyomerik aşırılık; *L*-Prolin.

Özet

Michael katılması gibi C-C bağı oluşturma yeteneğine sahip reaksiyon tiplerinde, kiral organokatalizör uygulamaları son yılların önemli araştırma alanlarındandır. Organik reaksiyon tiplerinden önemli çalışmalarından biri olan Michael katılmasına en iyi örneklerden biri de organokatalizörler varlığında nitroolefinlerin ketonlar ile reaksiyonudur. Bu çalışmada; *L*-prolin bazlı amit türevi, ılımlı bir verim ile sentezi gerçekleştirilmiş ve yapısı çeşitli teknikler ile aydınlatılmıştır. Sentezi gerçekleştirilen bu bileşiğin; organokatalizör olarak, Michael katılma çalışmalarında enantiyomerik aşırılık (e.e.) üzerine etkisi incelenmiş ve en iyi enantiyomerik aşırılık değerinin karbontetra klorür (CCl_4) içinde ve %65 olduğu tespit edilmiştir.

Prolines Based β-Hydroxyamide as Organocatalysts for Use in Asymmetric Michael Addition

Keywords
Michael addition; Organocatalyst; Enantiomeric excess; *L*-Proline.

Abstract

Applications of chiral organocatalysts in reaction types capable of forming C-C bonds, such as Michael addition, are one of the important research areas of recent years. One of the best examples of Michael addition, one of the important works of organic reaction types, is the reaction of nitroolefins with ketones in the presence of organocatalysts. In this study, *L*-proline-based amide derivative was synthesized with moderate yield and its structure was elucidated by various techniques. As an organocatalyst, its effect on enantiomeric excess (e.e.) was investigated in Michael addition studies and the best enantiomeric excess value was found to be 65% in carbontetra chloride (CCl_4).

1. Introduction

The use of stereoisomeric pure compounds in many industrial sectors such as pharmaceutical production is an issue that needs attention. (Bulger 2012) To obtain such compounds, scientists have studied many different methods. One of these studies is the use of organocatalysts in the production of pure stereoisomeric compounds. Organocatalysts, besides offering an effective and very useful way (Barrulas al 2014) both in industry and in research (Carlone al 2019), are among the most popular areas of recent interest with their low toxic effect (Susam al 2021). Organocatalysts are of interest because they are easy to obtain, inexpensive and environmentally friendly. (Dalko al. 2004, List 2006) As a matter of fact, the Nobel

Prize in chemistry in 2021 was given to two scientists who worked on asymmetric organocatalysts. Asymmetric organocatalysts have a valuable place in the synthesis of chiral organic molecules. (List 2004) The use of organocatalysts in reactions carried out to obtain chiral molecules with high enantiopurities makes the use of such catalysts important (Bozkurt 2008).

Organocatalysts consisting of enantiopure groups such as *L*-Proline are used in many reactions such as aldol condensation (Liu 2010), Michael addition (Jin 2016, Zhiwei 2022), Mannich reactions (Kumar 2019).

Michael addition, which is one of the useful reactions for the formation of C-C bonds, involves the addition of a nucleophile to the molecule with an electron withdrawing group (Castan 2018). In these reaction studies, obtaining an addition product with enantiopurity, thanks to the use of organocatalyst, is rather a young subject. An important example of these reactions is the addition of aldehyde (Durmaz 2013, Naziroglu 2012) or ketone (Vural 2016) to nitroolefins. The conversion of compounds containing nitro group to amine, nitrile oxide oxide, carbonyl with various synthetic steps increases the importance of these compounds even more (Shim 2020).

L-proline and its derivatives emerge as important chiral organocatalysts used in Michael addition reactions. In the literature, the use of different chiral organocatalysts has been encountered with the attachment of compounds such as diarylprolinol silylether (Zhu al 2010), proline lithium salt (Xu 2013), pyrrolidine-based triazole (Yan 2006) and pyrrolidine-based imidazole (Yumiko 2018) to the main skeleton of proline. As the formation of this reaction; It is predicted that first of all, an imine/enamine is formed between the ketone/aldehyde derivatives and the nitrogen atom of the prolidine, followed by the incorporation of nitroolefins into this imine (Michael 2015). The presence of various hydrogen donor and acceptor groups, as well as bulky groups with steric hindrance, in the structure of the enantiopure organocatalyst; causes nitroolefins to attack from a preferential direction (Hong 2021). In this case, the product to be formed allows the formation of an enantiomerically rich product. For the reasons mentioned above, we designed a new organocatalyst based on prolidine and containing bulky groups as well as hydrogen acceptor-donor groups in its structure.

2. Experimental

2.1 General

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. IR spectra were obtained on a Perkin Elmer FTIR spectrum-100 FTIR spectrometer using ATR. Optical rotations were measured on an Atago AP-100 digital polarimeter. The HPLC measurements were carried out on Agilent 1100 equipment connected with chiral column. Elemental analyses were performed using a Leco CHNS-932 analyzer.

Analytical TLC was performed using Merck prepared plates (silica gel 60 F_{254} on aluminum). Flash chromatography separations were performed on a Merck Silica Gel 60 (230-400 Mesh). All reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. All starting materials and reagents used were of standard analytical grade from Fluka, Merck and Aldrich and used without further purification. Toluene was distilled from CaH_2 and stored over sodium wire. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$.

2.2 Syntheses

The synthesis of **Compound I** has been already described by us. (Bozkurt *al*. 2012)

2.2.1 Synthesis of benzyl (S)-2-(((S)-3-(dibenzylamino)-2-hydroxypropyl) carbamoyl) pyrrolidine-1-carboxylate (Compound II)

To a cooled solution of DCC (206 mg, 1 mmol) in CH_2Cl_2 (5 mL) was slowly added to a solution of N-Benzyloxycarbonyl-*L*-proline (260 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C. Stirred the reaction for an hour. Then, optically pure Amine **I** (1.15) in CH_2Cl_2 (5 mL) was added dropwise and the resulting solution was stirred for 24 h. Then, CH_2Cl_2 (10 mL)

was added and filtrated, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 20:1 as eluent) to afford **Compound II**. Viscous yellow oil, yield 79%; $\propto_D^{25}$= + 8.2 (c 0.74, $CHCl_3$); ^{1}H-NMR (400 MHz, *CDCl*$_3$): δ (ppm) 7.54–7.13 (m, 15H, Ar*H*), 6.59 (bs, 1H, N*H*), 5.26–4.97 (m, 2H, OCH_2Ar), 4.32–4.00 (m, 1H, NC*H*), 3.89–3.61 (m, 3H, C*H*OH and NCH_2), 3.57–3.32 (m, 5H, NCH_2, NCH_2, O*H*), 3.19–2.72 (m, 2H, NCH_2), 2.63–2.27 (m, 2H, NCH_2), 2.20–1.76 (m, 4H, C*H*CH_2, CH_2CH_2); 13C-NMR (100 MHz, *CDCl*$_3$) δ (ppm) 172.7, 154.3, 139.1, 136.1, 130.0, 128.4, 128.2, 127.9, 127.6, 127.3, 71.5, 67.2, 58.1, 56.8, 46.4, 41.2, 29.1, 20.5; Anal. Calcd for $C_{30}H_{35}N_3O_4$ (501.32): C, 71.83%; H, 7.03%; N, 8.38%; Found C, 71.79%; H, 7.04%; N, 8.39%.

Synthesis of (S)-N-((S)-3-(dibenzylamino)-2-hydroxypropyl)pyrrolidine-2-carboxamide (Compound III)

To a solution of **Compound II** (1.0 mmol) in ethanol (15 mL) was added Pd/C (156 g) and cyclohexene (0.5 mL). The mixture was refluxed for 3 h. After the completion of the reaction, the solution was cooled to rt, filtered on Celite to remove any solids, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column to obtain pure **Compound III**. Viscous yellow oil, yield 43%; $\propto_D^{25}$= + 10.2 (c 1.11, $CHCl_3$); ^{1}H-NMR (400 MHz, C*D*Cl_3): δ (ppm) 7.60 (t, *J* = 5.04 Hz, 1H, N*H*), 7.40–7.04 (m, 10H, Ar*H*), 3.86–3.66 (m, 3H, C*H*OH and NCH_2Ar), 3.49 (dd, *J* = 9.14, 5.46 Hz, 1H, NHCH_2), 3.41–3.23 (m, 3H, NHCH_2 and NCH_2Ar), 3.08 (ddd, *J* = 13.84, 6.54, 5.46 Hz, 1H, NHCH_2), 2.89–2.74 (m, 2H, NHC$H_2CH_2CH_2$), 2.41–2.27 (m, 3H, NCH_2CH and O*H*), 2.00 (tdd, *J* = 12.72, 9.10, 7.38, 7.38 Hz, 2H, CHCH_2CH_2), 1.72 (td, *J* = 19.27, 6.21, 6.21 Hz, 1H, CHCH_2CH_2), 1.66–1.54 (m, 2H, $CHCH_2CH_2$). ^{13}C-NMR (100 MHz, C*D*Cl_3) δ (ppm) 171.3, 138.6, 128.8, 128.2, 127.2, 68.7, 63.1, 61.4, 58.7, 46.3, 45.9, 30.7, 25.5; Anal. Calcd for $C_{22}H_{29}N_3O_2$ (367.28): C, 71.90%; H, 7.95%; N, 11.43%; Found C, 71.88%; H, 7.94%; N, 11.44%.

General Experimental Procedure for the Michael Addition of Cyclohexanone to Nitroolefins

To a mixture of catalyst (0.0025 mmol), nitroolefin (0.25 mmol) in carbontetrachloride (0.250 mL) was added the carbonyl compound (1.5 mmol). The reaction mixture was stirred at room temperature until the nitroolefin was completely consumed (monitored by TLC). After evaporation of the solvent under vacuum, the residue was separated by flash chromatography over silica gel (hexane/ethyl acetate = 10:1) to give the Michael adduct. The enantiomeric excess was determined by chiral HPLC with OD-H columns.

3. Result and Discussion

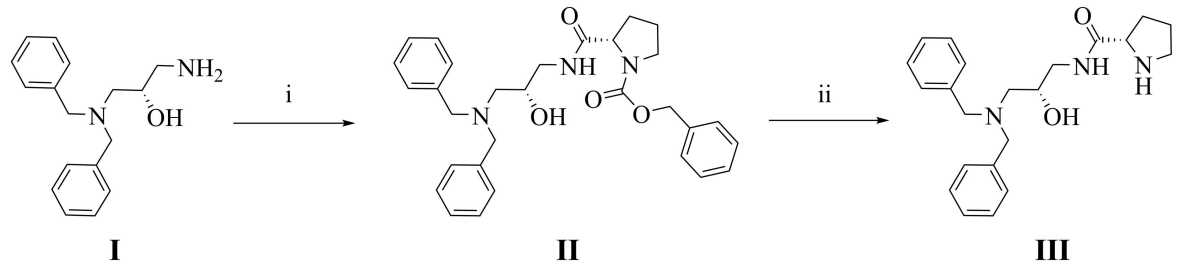
The synthesis of organocatalysts containing hydrogen donor-acceptor groups and bulky groups capable of pi-pi interaction is extremely important in obtaining enantiomerically rich compounds. In our previous studies, we obtained an amino alcohol derivative with two separate phenyl groups in its structure to contain it in bulky groups. To obtain an important derivative of these compounds; In this study, we synthesized a new proline amide as a result of the reaction of amine group protected *L*-proline with an amino alcohol derivative.

Compound I, prepared according to the procedures previously described by us, was treated with the enantiopure *L*-(-)-Cbz-protected proline in the presence of DCC (Dicyclohexylcarbodiimide) in dry CH_2Cl_2. Later on; Compound III is obtained as the final product by boiling it in a solution in ethanol in the presence of Pd/C (10%) and cyclohexane to remove the CBZ protecting group in the structure of Compound II in moderate yield as shown in *Scheme 1*. All products structures were determined by appropriate spectroscopic techniques such as ^{1}H-NMR, ^{13}C NMR.

When the ^{1}H NMR spectrum of Compound III was examined, it was observed that the amide proton resonated as a triplet at 7.60 ppm, while the NHCH_2 protons resonated as a doublet of a doublet of a doublet at 3.49 ppm. On the other hand, it was determined that CHOH protons formed multiplet-shaped peaks between 3.49–3.59 ppm. Moreover; It was observed that aromatic protons had multiplet resonance between 7.40–7.04 ppm.

To investigate the efficiency of the obtained proline amide derivative as a chiral organocatalyst; As a model reaction, on different solvents, the

reaction between cyclohexanone and β-nitrostyrene was studied. As can be seen in *Table 1*, first of all, the addition study in water was carried out. However, both the yield of the product formed and the yield of enantiopurity were not at the desired level.



Scheme 1. (i) DCC, Cbz-*L*-Proline, CH_2Cl_2, rt; (ii)Pd/C, cyclohexene, ethanol, reflux.

Then the same reaction; When repeated in different solvent environments, the product is obtained in both THF and chloroform with a yield of 75%; It was observed that the ee value reached 56% and 63% in these solvents, respectively.

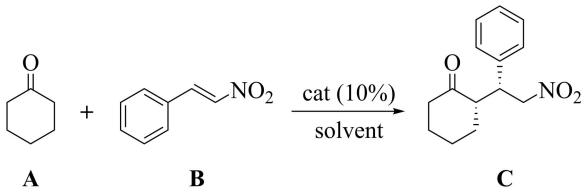


Table 1. Asymmetric Michael addition of cyclohexanone to trans-β-nitrostyrene

Entry	Solvent	Time (d)	Yield (%)[a]	d.r.[b]	e.e. (%)[c]
1	H_2O	3	38	99/1	13
2	H_2O+DMSO	3	40	99/1	18
3	THF	3	75	99/1	56
4	$CHCl_3$	3	75	99/1	63
5	CCl_4	3	80	99/1	64
6	Toluene	3	70	nd	nd

4. Conclusions

In conclusion, we synthesized a new chiral β-hydroxyamide-pyrrolidine-based catalysts for the Michael addition reaction of cyclohexanone with β-nitrostyrene. Moderate yields, high diastereoselectivities, and modarate enantioselectivities were achieved.

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