



Preparation of a Chiral Cu(II)-Schiff Base Complex and Application for Asymmetric Catalysis

Kiral Cu(II)-Schiff Bazı Kompleksinin Hazırlanması ve Asimetrik Kataliz İçin Uygulaması

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Abstract

A chiral copper(II)-Schiff base complex was synthesized from L-Phenylalanine for the enantioselective Henry reaction. A variety of chiral β -nitroalcohols were obtained in good yield (up to 76%) with high enantioselectivities (up to 90% ee) under the optimized reaction conditions.

Keywords: Asymmetric Henry reaction, Schiff base, Chiral copper(II) catalyst, β -nitroalcohol

Öz

Kiral bakır(II)-Schiff bazı kompleksi L-Fenilalanin'den çıkılarak enantiyoseçimli Henry tepkimesi için sentezlendi. Çeşitli kiral β -nitroalkoller iyi verim (%76 ya kadar) ve yüksek enantiyoseçicilikle (%90 a kadar) optimize edilmiş tepkime koşulları altında elde edildi.

Anahtar Kelimeler: Asimetrik Henry tepkimesi, Schiff bazı, Kiral bakır(II) katalizörü, β -nitroalkol

1. Introduction

The Henry reaction (nitroaldol) is one of the most useful methods for the formation of C-C bonds in organic synthesis (Henry 1895). The resulting product of this reaction is optically active β -nitroalcohol in which hydroxyl and nitro groups have a vicinal relationship (Figure 1). This affords a template for acquiring valuable chemical entities including pharmaceuticals (Rosini et al. 1988).

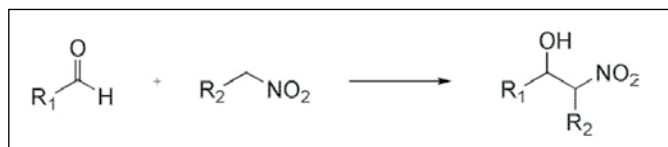


Figure 1. The Henry (nitroaldol) reaction.

For example, the asymmetric Henry reaction has been used for preparation of the vicinal amino alcohol motif which is contained in blocking agents of the β -adrenergic receptor (Figure 2). The active enantiomer of each of these drugs are

(S) configuration (Howe et al. 1968, Lunsford et al. 1960, Dukes et al. 1971).

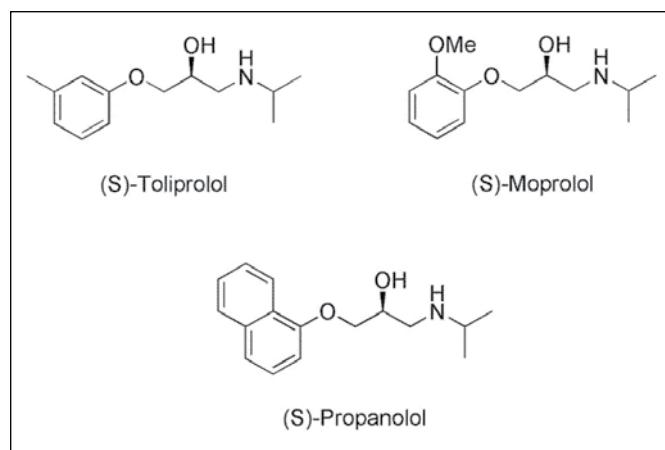


Figure 2. β -Adrenergic receptor blocking agents.

Since the Shibasaki group reported the first catalytic asymmetric Henry reaction (Sasai et al. 1992), a great deal of effort has been devoted to the development of various metal-containing catalysts (Trost et al. 2002, Palomo et al. 2004, Palomo et al. 2005, Dhakshinamoorthy et al. 2013, Kopylovich et al. 2011). However, the accomplishment of a

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good enantioselectivity is still a challenge, and the search for new catalysts that can be prepared easily and economically, is also important.

Herein, we report a copper(II)-Schiff base complex which can be readily synthesized from a natural amino acid and can be used as a catalyst in enantioselective Henry reactions under mild conditions giving high ee values and yields.

2. Materials and Methods

2.1. Materials

¹H-NMR spectra were carried out using a 600-MHz Agilent NMR spectrometer at ambient temperature. HPLC measurement were performed with Agilent 1200 instrument. The absolute configuration of β-nitroalcohols were determined by using a Chiralcel OD-H column and comparison with literature data (Evans et al. 2003, Saa et al. 2006, Boruwa et al. 2006). IR spectra were recorded using a Perkin Elmer 100 spectrometer.

2.2. Synthesis

Chiral amino acid ester (**1**) and amino alcohol (**2**) were prepared from L-Phenylalanine by standard esterification and Grignard addition procedures. The Schiff base ligand (**3**) was prepared by condensation of 3,5-di-tert-butylsalicylaldehyde with the amino alcohol (**2**) and was characterized by comparison with literature data (Hsieh et al. 2007).

2.2.1. Synthesis of L-Phenylalanine isopropyl ester hydrochloride (**1**)

Thionyl chloride (2.2 mL, 30 mmol) was added dropwise to L-phenylalanine (661 mg, 4 mmol) in 25 mL of isopropyl alcohol at 0 °C. After complete addition of thionyl chloride, the ice bath was removed and the solution was refluxed for 4 h. Excess thionyl chloride was evaporated in vacuo. The white solid compound was washed with ethyl acetate and hexane and dried with vacuo to give **1** which was used directly in the next step.

2.2.2. Synthesis of 2-amino-1,1,3-triphenylpropan-1-ol (**2**)

A Grignard reagent was prepared from bromobenzene (1.05 mL, 10 mmol) and magnesium turnings (486 mg, 20 mmol) in dry diethylether (20 mL). To the stirred solution was added dropwise an ethereal solution of L-Phenylalanine isopropyl ester hydrochloride (**1**) (487 mg, 2 mmol). The reaction mixture was stirred for 24 h at room temperature

and then quenched with saturated NH₄Cl. The solution was extracted with diethyl ether. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated to give crude product. The product **2** was purified with column chromatography using 1:5 ethyl acetate:hexane as an eluent. (61% yield). Mp: 141-142.2 °C. IR (CH₂Cl₂): 3855, 3818, 3804, 3649, 1596, 1493, 1447, 1171 cm⁻¹. ¹H-NMR (CDCl₃, δ ppm) 7.68-7.61 (m, 4H), 7.36-7.19 (m, 11H), 4.20 (dd, *J* = 10.8, 2.4 Hz, 1H), 2.67 (dd, *J* = 14.0, 2.0 Hz, 1H), 2.47 (dd, *J* = 14.0, 10.8 Hz, 1H). ¹³C-NMR (CDCl₃, δ ppm): 146.86, 144.38, 139.70, 129.11, 128.68, 128.51, 128.26, 126.78, 126.56, 126.46, 125.82, 125.44, 78.57, 58.24, 36.83.

2.2.3. Synthesis of 2-Hydroxy-3,5-di-tert-butylbenzaldehyde 2S-(1,1,3-triphenylpropan-1-ol) imine (**3**)

3,5-di-tert-butylsalicylaldehyde (200 mg, 0.85 mmol) was added to a solution of an amino alcohol (**2**) (258 mg, 0.85 mmol) in 20 mL methanol and stirred at room temperature for 3 hours. The solvent was evaporated and crude product was crystallized from CH₂Cl₂-hexane as yellow crystals (80% yield). Mp: 154.8-156 °C. IR (CH₂Cl₂): 3576, 3060, 2960, 2870, 1626, 1449, 1392, 1270, 1250, 1173, 1084 cm⁻¹. ¹H-NMR (CDCl₃): δ 7.67- 6.67 (m, 18H), 4.36 (dd, *J* = 1.2, 10.2 Hz, 1H), 3.03 (d, *J* = 13.2 Hz, 1H), 2.87 (dd, *J* = 10.2, 13.8 Hz, 1H), 1.41 (s, 9H), 1.23 (s, 9H) ppm. ¹³C-NMR (CDCl₃, δ ppm): 167.74, 157.49, 145.61, 144.21, 139.91, 139.15, 136.30, 128.39, 128.29, 128.24, 127.10, 126.94, 126.80, 126.20, 126.16, 126.10, 125.96, 79.83, 78.37, 37.51, 34.94, 34.01, 31.38, 29.38.

2.2.4. Synthesis of di{[2-Hydroxy-3,5-di-tert-butylbenzaldehyde 2S-(1,1,3-triphenylpropan-1-ol) imino] copper(II)} (**4**)

The ligand (**3**) (172 mg, 0.33 mmol) was reacted with Cu(OAc)₂·nH₂O (60 mg, 0.33 mmol) in methanol (20 mL) for 24 h at room temperature. Evaporation of the solvent gave a residue, which was purified by column chromatography (5% hexane/ethyl acetate) to afford the title compound **4** as a green powder (83% yield). Mp: 160-162.3 °C (decomp.). IR (KBr): 3027, 2957, 2909, 1627, 1530, 1494, 1431, 1256, 1167 cm⁻¹. Elemental analysis, calculated for C₇₂H₇₈O₄N₂Cu₂: C, 74.39; H, 6.76; N, 2.41. Found: C, 73.65; H, 6.65; N, 2.16%. *R_f*(5% hexane/ethyl acetate) 0.39.

2.3. Application of complex **4** as a catalyst for the asymmetric Henry reaction

To a mixture of complex **4** (5 mmol %) and solvent (2 mL) at room temperature was added appropriate aldehyde (0.2

mmol). The mixture was allowed to stir and CH_3NO_2 (2 mmol) was added. The reaction mixture was stirred at room temperature until most of the aldehyde had been consumed. Evaporation of the solvent gave a residue which was purified by column chromatography (5:1 hexane/ethyl acetate). β -nitroalcohols were characterized by comparison with literature data (Evans et al. 2003, Saa et al. 2006, Boruwa et al. 2006, Lai et al. 2008).

2.3.1. (S)-1-(4-Nitrophenyl)-2-nitroethanol (5a)

White crystals, 71% yield. IR (CH_2Cl_2): 3522, 2924, 1556, 1519, 1380, 1349, 1083, 856 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): δ 8.26 (m, 2H), 7.63 (m, 2H), 5.61 (m, 1H), 4.60 (d, $J = 6$ Hz, 1H), 4.58 (d, $J = 2$ Hz, 1H), 3.17 (br, 1H) ppm.

3. Results and Discussion

Amino alcohol (**2**) derived from the chiral L-Phenylalanine isopropyl ester hydrochloride was obtained using a Grignard reaction. The amino alcohol was chosen to create a steric effect on the carbinol carbon. The reaction of 3,5-di-*tert*-butylsalicylaldehyde with the chiral amino alcohol (**2**) in methanol gave chiral Schiff base ligand (**3**). The chiral copper(II) complex (**4**) was prepared from the Schiff base

ligand (**3**) (Figure 3) was characterized by comparison with literature data (Gan et al. 2006, Lai et al. 2008).

Initial studies focused on the reaction of 4-nitrobenzaldehyde with nitromethane using complex **4** as a catalyst, as shown in Table 1. First of all, appropriate solvent was investigated for the reaction performed in the presence of 5 mmol % catalyst at room temperature. The reaction solvent was found to have a great influence on the enantioselectivity. When dichloromethane or *tert*-butyl methyl ether was used as the reaction solvent instead of alcoholic solvents, the reaction yield and enantiomeric excess (ee) values were reduced remarkably. The first experimental results show that the reaction yields and ee were higher when protic solvents are used as a solvent. The best result was obtained in *i*-propanol. After the selection of solvent, temperatures and the catalyst loading were tested in the asymmetric Henry reaction between 4-nitrobenzaldehyde and nitromethane. Surprisingly, ee value of the product at lower temperature decreased. Finally, different catalyst loadings were tested, and the results show that 5 mmol % catalyst loading was the optimum amount for this reaction.

With the optimized conditions in hand, different aromatic aldehydes were tested in order to extend the substrate

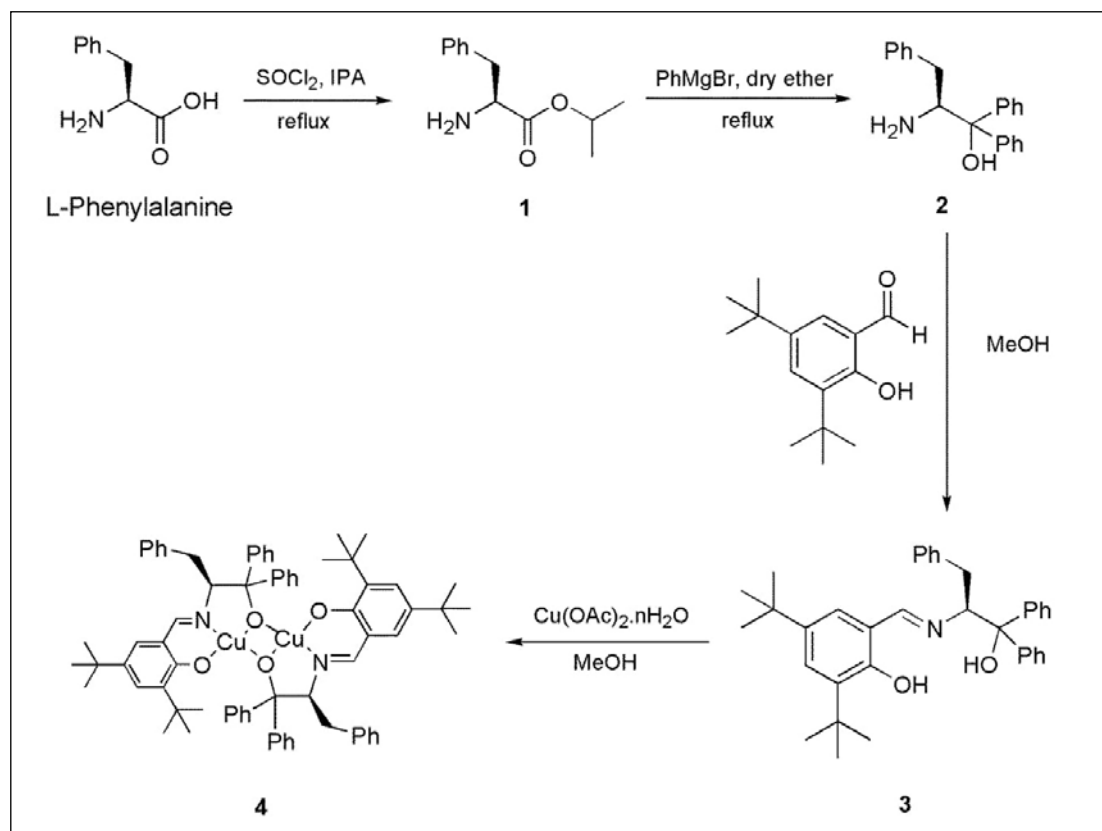
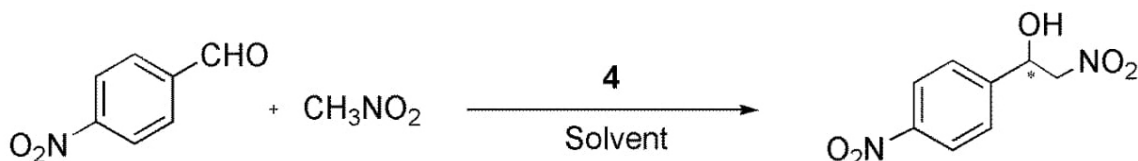
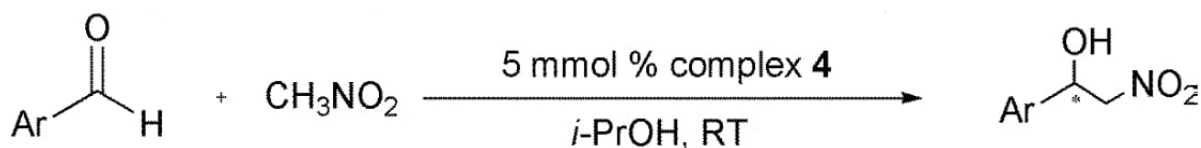


Figure 3. Synthesis of the chiral Schiff base ligand and the copper(II) complex.

Table 1. Optimization of the asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane using complex 4 as a catalyst.

Entry	Solvent	Temp.(°C)	Time (h)	Yield ^a (%)	ee (%)	Config.
1	<i>i</i> -propanol	RT	48	71	74	<i>S</i>
2	Ethanol	RT	48	61	62	<i>S</i>
3	Methanol	RT	48	51	51	<i>S</i>
4	1-Butanol	RT	48	-	-	-
5	CH ₂ Cl ₂	RT	48	59	6	<i>S</i>
6	THF	RT	48	48	51	<i>S</i>
7	TBME	RT	48	20	9	<i>S</i>
8	<i>i</i> -propanol ^b	RT	48	76	74	<i>S</i>
9	<i>i</i> -propanol	0	48	40	69	<i>S</i>

^aIsolated yields after column chromatography.^bWith 10 mmol % catalyst loading.**Table 2.** The asymmetric Henry reaction of various aromatic aldehydes with CH₃NO₂

Entry	Product	ArCHO	Temp.(°C)	Time (h)	Yield ^a (%)	ee (%)	Config.
1	5a	4-Nitrobenzaldehyde	RT	48	71	74 ^c	<i>S</i>
2	5b	2-Chlorobenzaldehyde	RT	48	62	90 ^d	<i>S</i>
3	5c	2-Chlorobenzaldehyde ^b	RT	48	60	85 ^d	<i>S</i>
4	5d	2-Nitrobenzaldehyde	RT	24	75	88 ^e	<i>S</i>
5	5e	3-Nitrobenzaldehyde	RT	24	60	76 ^f	<i>S</i>
6	5f	Benzaldehyde	RT	96	60	81 ^g	<i>S</i>
7	5g	4-Methylbenzaldehyde	RT	96	40	75 ^h	<i>S</i>
8	5h	4-Methoxybenzaldehyde	RT	96	45	67 ⁱ	<i>S</i>

^aIsolated yields after column chromatography.^bReactions were performed with 0.2 mmol 2-Chlorobenzaldehyde, 5% mmol Schiff base (3) and Cu(OAc)₂·nH₂O, and 2 mmol nitromethane in 2 mL of *i*-PrOH at room temperature.^cHPLC conditions: 90:10 hexane:*i*-PrOH, flow rate 1.0 mL/min, λ 267 nm, *t*_{minor} = 31.1 min (R), *t*_{major} = 38.7 min (S)^dHPLC conditions: 93:7 hexane:*i*-PrOH, flow rate 0.8 mL/min, λ 267 nm, *t*_{minor} = 14.7 min (R), *t*_{major} = 15.5 min (S)^eHPLC conditions: 90:10 hexane:*i*-PrOH, flow rate 1.0 mL/min, λ 267 nm, *t*_{minor} = 16.9 min (R), *t*_{major} = 19.2 min (S)^fHPLC conditions: 90:10 hexane:*i*-PrOH, flow rate 1.0 mL/min, λ 267 nm, *t*_{minor} = 29.3 min (R), *t*_{major} = 32.9 min (S)^gHPLC conditions: 90:10 hexane:*i*-PrOH, flow rate 1.0 mL/min, λ 267 nm, *t*_{minor} = 14.6 min (R), *t*_{major} = 16.7 min (S)^hHPLC conditions: 85:15 hexane:*i*-PrOH, flow rate 0.5 mL/min, λ 267 nm, *t*_{minor} = 20.3 min (R), *t*_{major} = 24.7 min (S)ⁱHPLC conditions: 90:10 hexane:*i*-PrOH, flow rate 1.0 mL/min, λ 267 nm, *t*_{minor} = 21.5 min (R), *t*_{major} = 26.9 min (S)

scope, as shown in Table 2. A variety of aldehydes were successfully used in the Henry reaction to provide the β -nitroalcohol in good yields and high selectivities. Generally, electron-deficient aldehydes gave better results than the electron-rich aldehydes. For instance, electron-deficient *para*-nitrobenzaldehyde gave the Henry product **5a** in 71% yield with 74% ee, whereas the electron-rich *para*-methoxybenzaldehyde gave the corresponding product **5h** in only 45% yield with 67% ee. To examine the electronic and steric effects of the substrate on the reaction, aromatic aldehydes with different substituents at the *ortho*, *meta* and *para* positions were employed. These results indicate that the substrates with *ortho*-substituents give higher ee values than other ones. The absolute configuration of β -nitroalcohols were determined by comparison with the literature values (Evans et al. 2003, Saa et al. 2006, Boruwa et al. 2006, Lai et al. 2008).

4. Conclusions

A novel chiral copper(II)-Schiff base complex has been synthesized easily and can be used in enantioselective metal-catalyzed reactions. The enantioselective Henry reaction was performed under mild conditions and various β -nitroalcohols were obtained with good yields and ee values.

5. Acknowledgments

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6. References

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