# ENANTIOSELECTIVE HENRY REACTION CATALYZED BY COPPER(II)–ARYLHYDRAZONE OF β-DIKETONE COMPLEX

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*Copper(II)–arylhydrazone of β-diketone complex, ([Cu(H₂O)₂]₂(μ-L)₂[Cu(H₂O)₄], H₃L = 3-(2-hydroxy-3-sulfo-5-nitrophenylhydrazone)pentane-2,4-dione), catalyzes the nitroaldol reaction between a variety of aromatic and aliphatic aldehydes and simple nitroalkanes such as nitromethane and nitroethane. The threo/erythro diastereoselectivity of the β-nitroalkanol products (total yields of ca. 97 %) was determined by $^{1}H$ NMR spectroscopy and was found to range from 5:1 to 1:8. The substituents of the aromatic aldehydes influenced the threo/erythro ratio.*
***Keywords:*** *Henri reaction, benzaldehyde , nitromethane,  nitroethane*

## I. INTRODUCTION

The addition reaction between nitroalkanes and carbonyl compounds to yield a nitroalcohol, namely the nitroaldol or Henry reaction (Scheme 1), has long been known [1]. It constitutes a powerful C–C bond-forming process in organic chemistry [2], providing efficient access to valuable functionalized structural motifs such as 1,2-amino alcohols and α-hydroxy carboxylic acids [3]. They are also useful intermediates in the synthesis of valuable pharmaceuticals and pharmaceutical intermediates such as (S)-propanolol [4], or (S)-(K)-pindolol [5], antibiotics (e.g., ezomycin [6], tunicamycin [7]), natural products such as the sex pheromone of the Douglas Fir Tussock moth [8] or cyclopeptide alkaloids [9]. Moreover, 2-nitroalkanol derivatives are important as fungicides [10]. Traditionally, like the aldol reaction, this reaction was mainly carried out in the presence of strong bases, leading to dehydration with concomitant formation of a nitroolefin [11].
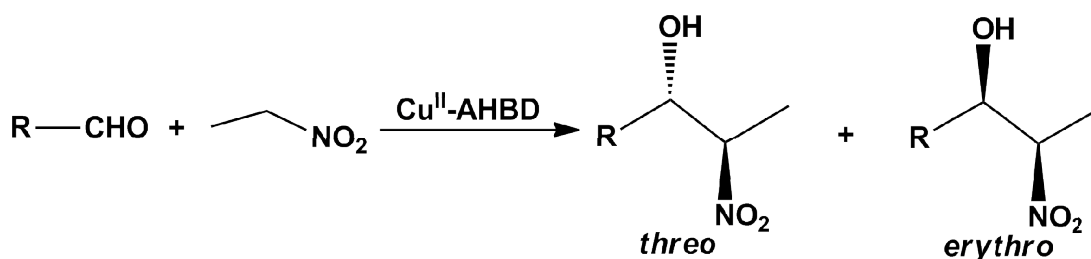


**Scheme 1.** Formation of nitroaldols by the Henry reaction.

The interest in asymmetric versions of this reaction started growing after the groundbreaking work of Shibasaki and co-workers on the use of chiral bimetallic lithium-lanthanum catalysts [12,13]. In the last two decades many other asymmetric metal catalysts have been developed: nowadays, aldehydes or α-keto esters can be converted to the corresponding nitroalcohols with mostly excellent diastereoselectivity [14]. Recently, we have tested complexes of zinc(II) with arylhydrazones of β-diketones (**AHBD**) in Henry reaction, and higher yields and diastereoselectivities were found. To our knowledge, the Cu[II]−AHBD complexes have not yet been reported as catalysts for the Henry reaction. Thus, we focused this work on the application of previously reported [15] copper(II) complex (Scheme 2), [Cu(H₂O)₂]₂(μ-L)₂[Cu(H₂O)₄] (**I**) (H₃L = 3-(2-hydroxy-3-sulfo-5-nitrophenylhydrazone) pentane-2,4-dione), in this field.
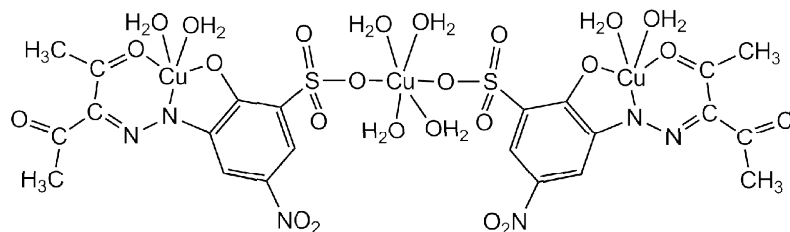
**Scheme 2.** Schematic representations of the [Cu(H$_2$O)$_2$]$_2$($\mu$-L)$_2$[Cu(H$_2$O)$_4$] (**I**).

## 2. EXPERIMENTAL

### 2.1. Materials and instrumentation

All the chemicals were obtained from commercial sources (Aldrich) and used as received. $^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance II + 300 and 400 MHz (UltraShield$^{TM}$ Magnet) spectrometers at ambient temperature. Chemical shifts ($\delta$) are relative to internal TMS. Electrospray mass spectra were run with an ion-trap instrument (Varian 500-MS LC Ion Trap Mass Spectrometer) equipped with an electrospray (ESI) ion source. For electrospray ionization, the drying gas and flow rate were optimized according to the particular sample with 35 p.s.i. nebulizer pressure. Scanning was performed from $m/z$ 10 to 1000 in methanol solution. The compounds were observed in the positive mode (capillary voltage = 80–105 V).

### 2.2. Catalytic activity studies

A typical reaction was carried out under air as follows: to 1.00–4.00 mol% of catalyst precursor (typically 4.00 mol%) contained in the reaction flask were added methanol (2 mL), nitroethane (4 mmol) and aldehyde (1 mmol), in that order. The reaction mixture was stirred for the required time at room temperature and air atmospheric pressure. After evaporation of the solvent, the residue was dissolved in DMSO-$d_6$ and analyzed by $^1$H NMR. The yield of $\beta$-nitroalkanol product (relatively to the aldehyde) was established typically by taking into consideration the relative amounts of these compounds, as given by $^1$H NMR and previously reported [1–14,16,17]. The adequacy of this procedure was verified by repeating a number of the $^1$H NMR analyses in the presence of 1,2-dimethoxyethane as internal standard, added to the DMSO-$d_6$ solution, what gave yields similar to those obtained by the above method. Moreover, the internal standard method also confirmed that no side products were formed. The ratio between the *threo* and *erythro* isomers was also determined by $^1$H NMR spectroscopy. In the $^1$H NMR spectra, the values of vicinal coupling constants (for the $\beta$-nitroalkanol products) between the $\alpha$-N–C–*H* and the $\alpha$-O–C–*H* protons identify the isomers, being $J$ = 7–9 or 3.2–4 Hz for the *threo* or *erythro* isomers, respectively [16,17]. Control experiments were performed under the same reaction conditions but in the absence of any of the **I** catalysts, in the presence of Cu(NO$_3$)$_2$·2.5H$_2$O or free ligand **H$_3$L** (metal free).

## 3. RESULTS AND DISCUSSION

### 3.1. Synthesis and spectroscopic study of [Cu(H$_2$O)$_2$]$_2$(µ-L)$_2$[Cu(H$_2$O)$_4$]

The synthesis and characterization of the 3-(2-hydroxy-3-sulfo-5-nitrophenylhydra-zone) pentane-2,4-dione (**H$_3$L**) and its copper complex [Cu(H$_2$O)$_2$]$_2$($\mu$-L)$_2$[Cu(H$_2$O)$_4$] (**I**) (Scheme 2) were reported earlier by us [15], and hence will not be discussed.

### 3.2. Catalytic activity of I in the Henry reaction

The optimization of the reaction conditions (amount of catalyst, reaction time, solvent, temperature) was carried out in a model nitroethane-benzaldehyde system with

complex **I** as the catalyst precursor (Scheme 1, Table 1). The best result was observed in the case of 4.00 mol% **I**, 20 h, in water and at 20ºC (entry 12, Table 1). Blank reactions were carried out in the absence of catalyst **I** but in the presence of $Cu(NO_3)_2·2.5H_2O$ or **H₃L** (Table 1, entries 17,18). Both cases lower yield is observed than that obtained in the presence of **I** (Table 1, entry 12). No nitroaldol reaction between benzaldehyde and nitroethane takes place in the absence of **I**

(Table 1, entry 19). Nitromethane is also a substrate, undergoing a high conversion into the nitroaldol (90 % yield after 20 h reaction catalyzed by **I**; entry 20, Table 1). When nitroethane reagent was used as solvent a lower but still considerable yield (63 %) was obtained (Table 1, entry 9). The systems exhibit (Table 1) diastereoselectivity towards the *threo* isomer, typically leading to *threo/erythro* molar ratios in the 80:20−52:48 range using nitroethane as substrate.

**Table 1.** Optimization of the parameters of the Henry nitroaldol reaction between benzaldehyde and nitroethane with **I** as the catalyst precursor.[a]
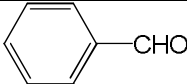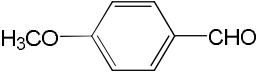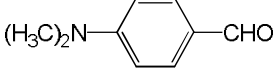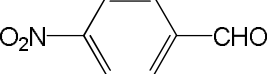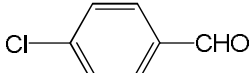
| Entry | Catalyst | Time (h) | Amount of **I** (mol%) | Temp (ºC) | Solvent | Yield (%)[b] | Selectivity *threo/ erythro*[c] |
|---|---|---|---|---|---|---|---|
| 1 | **I** | 20 | 1.00 | 20 | MeOH | 33 | 57:43 |
| 2 | **I** | 20 | 2.00 | 20 | MeOH | 57 | 64:36 |
| 3 | **I** | 20 | 3.00 | 20 | MeOH | 86 | 74:26 |
| 4 | **I** | 20 | 4.00 | 20 | MeOH | 88 | 77:23 |
| 5 | **I** | 5 | 4.00 | 20 | MeOH | 49 | 70:30 |
| 6 | **I** | 10 | 4.00 | 20 | MeOH | 71 | 76:24 |
| 7 | **I** | 20 | 4.00 | 20 | MeOH | 88 | 77:23 |
| 8 | **I** | 40 | 4.00 | 20 | MeOH | 87 | 77:23 |
| 9[d] | **I** | 20 | 4.00 | 20 | − | 63 | 70:30 |
| 10 | **I** | 20 | 4.00 | 20 | $CH_3CN$ | 44 | 65:35 |
| 11 | **I** | 20 | 4.00 | 20 | DMF | 58 | 77:33 |
| 12 | **I** | 20 | 4.00 | 20 | $H_2O$ | 93 | 80:20 |
| 13 | **I** | 20 | 4.00 | 20 | $H_2O$ | 93 | 80:20 |
| 14 | **I** | 20 | 4.00 | 40 | $H_2O$ | 88 | 79:21 |
| 15 | **I** | 20 | 4.00 | 60 | $H_2O$ | 61 | 65:35 |
| 16 | **I** | 20 | 4.00 | 80 | $H_2O$ | 52 | 60:40 |
| 17[e] | **H₃L** | 48 | 4.00 | 20 | $H_2O$ | 24 | 57:43 |
| 18[e] | $Cu(NO_3)_2·2.5H_2O$ | 48 | 4.00 | 20 | $H_2O$ | 12 | 52:48 |
| 19[e] | Blank | 48 | – | 20 | $H_2O$ | − | − |
| 20[f] | **I** | 48 | 4.00 | 20 | $H_2O$ | 90 | − |

[a]*Reaction conditions: 1.00–4.00 mol% of catalyst precursor (typically 4.00 mol%), solvent (2 mL), nitroethane (4 mmol) and aldehyde (1 mmol).* [b]*Determined by* [1]*H NMR analysis.* [c]*Calculated by* [1]*H NMR.* [d]*Solvent-free conditions, using nitroethane as solvent (2 mL).* [e]*For comparatives purposes.* [f]*Nitromethane was used as substrate.*

The reactions of a variety of *para*-aromatic and aliphatic aldehydes with nitroethane were also studied (Table 2). For aryl aldehydes, those bearing electron-withdrawing groups exhibit higher reactivities compared to those having electron-donating

moieties (Table 2, entries 1−5), what relates with the increased electrophilicity of the substrate with the former substituents. Aliphatic aldehydes lead to higher selectivities for the *erythro* diastereoisomer (Table 2, entries 6–8).

**Table 2.** Henry reaction of various aldehydes and nitroethane with catalyst **I**.[a]

| Entry | Substrate | Yield (%)[b] | Selectivity *threo/ erythro*[c] |
|---|---|---|---|
| 1 | (benzaldehyde) —CHO | 93 | 80:20 |
| 2 | H$_3$CO— —CHO | 73 | 76:24 |
| 3 | (H$_3$C)$_2$N— —CHO | 69 | 72:28 |
| 4 | O$_2$N— —CHO | 95 | 83:17 |
| 5 | Cl— —CHO | 91 | 81:19 |
| 6 | CH$_3$CH$_2$CHO | 86 | 11:89 |
| 7 | CH$_3$(CH$_2$)$_2$CHO | 83 | 15:85 |
| 8 | CH$_3$(CH$_2$)$_3$CHO | 77 | 19:81 |

[a] *Reaction conditions: 4.00 mol% of catalyst **I**, water (2 mL), nitroethane (4 mmol) and aldehyde (1 mmol), reaction time: 20h.* [b] *Determined by* $^1$H *NMR analysis.* [c] *Calculated by* $^1$H *NMR.*

In general, **I** is highly effective, what is an excellent result if compared with other copper catalysts described in the literature (Table 3) [18,19]. Moreover, selectivity is usually higher than that reported system (Table 3) [19].

**Table 3.** Comparison of activities of catalysts towards the Henry reaction using aldehyde and nitroethane.

| Catalyst | Solvent | Aldehyde | Yield (%) | Selectivity *threo/ erythro* | Reference |
|---|---|---|---|---|---|
| **I** | Water | Benzaldehyde | 93 | 80:20 | this work |
| Copper(II) Schiff base[a] | CH$_2$Cl$_2$ | Benzaldehyde | 92 | 60:40 | [18] |
| Phenoxide substituted Cu complexes[i] | THF | Benzaldehyde | 75 | nd[b] | [19] |

[a] Chiral binuclear Cu(II) Schiff base complexes. [b] nd: not determined, because nitromethane was used as substrate.

For to study the mechanism of reaction we have used ESI-MS$^+$ method, and on the base collected data we can conclude that the **I** Lewis acid centre activates both nitroethane (increasing its acidity) and aldehyde (increasing its electrophilic character), as reported by us [20].

## 4. CONCLUSIONS

In summary, we have shown Cu-AHBD complex effective catalyst the Henry reaction. Isolated yields of the final products were very dependent on structural limitations, obtaining most of them with good to excellent isolated yields (69–95 %). The *threo/erythro* diastereoselectivity of the nitroaldol products can be controlled over a considerably wide range, depending on the catalyst, the substrates and experimental conditions.

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## *MİS(II)-İN β-DİKETONUN ARİLHİDRAZONU İLƏ ƏMƏLƏ GƏTİRDİYİ KOMPLEKS ENANTİOSELEKTİV HENRİ REAKSİYASINDA KATALİZATOR KİMİ*

### *K.T.Mahmudov*

*Mis(II)-in β-diketonun arilhidrazonu ilə əmələ gətirdiyi kompleks ([Cu(H₂O)₂]₂(μ-L)₂[Cu(H₂O)₄], H₃L = 3-(2-hidroksi-3-sulfo-5-nitrofenilhidrazon)pentan-2,4-dion) aromatik və alifatik aldehidlərin nitroalkanlarla (nitrometan, nitroetan) reaksiyasında (nitroaldol reaksiyası) katalitik aktivlik göstərir. β-Nitroalkanol məhsulların (ümuni çıxım təqribən 97 %-dir) threo/erythro diasteroselektivliyi ¹H NMR spektroskopiyası metodu ilə təyin edilmişdir (5:1-dən 1:8-ə kimi dəyişir). Aromatik aldehidlərdə əvəzedicilər threo/erythro nisbətinə təsir göstərir.*

***Açar sözlər:*** *Henri reaksiyası, benzaldehid, nitrometan, nitroetan*

## *КОМПЛЕКС МЕДИ С АРИЛГИДРАЗОНОМ β-ДИКЕТОНА КАК КАТАЛИЗАТОР ЭНАНТИОСЕЛЕКТИВНОЙ РЕАКЦИИ ГЕНРИ*

### *К.Т.Махмудов*

*Установлено, что комплекс меди с арилгидразоном β-дикетона ([Cu(H₂O)₂]₂(μ-L)₂[Cu(H₂O)₄], H₃L =3-(2-гидрокси-3-сульфо-5-нитрофенилгидразон)пентан-2,4-дион) проявляет каталитическую активность в реакции ароматических и алифатических альдегидов с нитроалканами (нитрометан, нитроэтан). Трео/эритро диастереселективность продуктов (общий выход β-нитроалканолов 97%) определена методом ¹H NMR спектроскопии.*

***Ключевые слова:*** *реакция Генри, бензальдегид, нитрометан, нитроэтан*