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# Enantioselective Henry Reaction Catalyzed by $Cu^{II}$ Salt and Bipiperidine

Artur Noole, Kristin Lippur, Andrus Metsala, Margus Lopp, and Tõnis Kanger*

*Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia*

*kanger@chemnet.ee*

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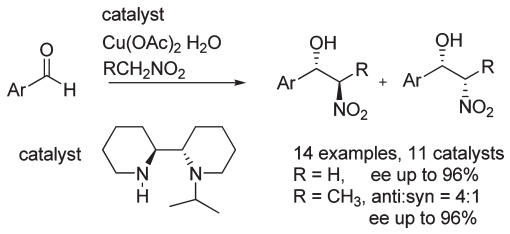


A complex derived from the enantiomeric bipiperidine and copper(II) acetate hydrate is an efficient catalyst for the enantioselective Henry reaction. The easy availability of both catalyst components, mild reaction conditions, high yield, and good to excellent enantioselectivity make the catalyst useful for everyday practice.

The Henry (nitro-aldol) reaction is a well-known tool for the building of a C−C bond.[1] Since the pioneering work of Shibasaki,[2] where the heterobimetallic catalyst was used, various versions of metal-catalyzed asymmetric Henry reactions have been described. Copper has a special place among the metals used as catalysts because it is a cheap, low toxicity metal and has been widely used in organic synthesis. The excellent chelating properties of that metal allow coordination of it with bidentate as well as with polydentate ligands. Copper complexes with various ligands, which include bisoxazolines,[3] bisoxazolidines,[4] boron-bridged bisoxazolines,[5] $C_2$-symmetric diamines,[6] pyridine derivatives,[7] chiral Schiff bases,[8] sparteine,[9] sulfonyldiamine,[10] and heteroorganic ligands[11] catalyze an asymmetric nitroaldol (Henry) reaction.[12] It is very difficult to find a common feature for the above-mentioned nitrogen-containing compounds. Thus, several very different diamines have been tested for the asymmetric induction ability.

We have investigated four types of enantiomeric ligands (compounds **1**−**4**) for the copper-catalyzed asymmetric Henry reaction (Figure 1).

Of these compounds, bimorpholines (**1** and **2**) and bipiperidines **4** are already known as efficient organocatalysts in aldol and Michael reactions, respectively.[13]

All these ligands are constructed similarly, by linking two heterocyclic rings, but they differ from each other in the number of coordinative sites in the molecule and the flexibility of the structure. Flexible $C_2$-symmetric (2*S*,2′*S*)-2,2′-bimorpholines **1** and (3*S*,3′*S*)-3,3′-bimorpholines **2** bear four donor atoms, but the electron-donating ability of the nitrogen atom is reduced by the close location of the electronegative oxygen atoms. A different position of the bridging bond between two heterocycles changes the accessibility of donor atoms by the metal. The replacement of oxygen atoms in rings by methylene groups leads to bipiperidine derivatives **4** which can be prepared much more easily than the corresponding morpholines. Racemic bipiperidine **4a** is straightforwardly derived from the commercially available dipyridyl in one chemical step.[14] Piperidinylpyridine **3** and bipiperidine **4** derivatives differ from the bimorpholines in terms of a reduced number of coordinative sites in the molecule. In addition, the nitrogen atoms in piperidinylpyridine **3** are chemically different, and furthermore, the two rings are structurally totally different: one is a flat aromatic pyridine ring and the other a flexible saturated piperidine ring. The steric hindrance surrounding the electron-donating center in all ligands can be easily modified by changing substituents $R_1$−$R_4$.

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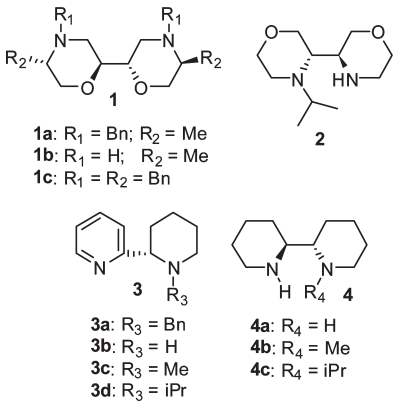



**FIGURE 1.** Bimorpholines **1** and **2**, piperidinylpyridine **3**, and bipiperidine **4**.

The synthesis of bimorpholine derivatives (**1** and **2**)[15,16] and (2*S*,2′*S*)-bipiperidine **4**[14] was described by us previously. Ligand **3a** was derived from bipyridyl, followed by its monoquaternization, selective reduction of one pyridine ring, and separation of enantiomers via crystallization with tartaric acid.[17] The synthesis of the new ligands **3c** and **3d** is described in the Supporting Information.

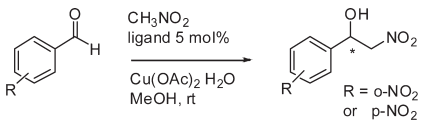
With the set of ligands in hand, we screened their selectivity and reactivity in the Henry reaction. The addition of nitromethane (10 equiv) to nitrobenzaldehyde (*ortho* or *para* isomer) in the presence of 5 mol % of $Cu(OAc)_2$ $H_2O$ and 5 mol % of ligand at room temperature was chosen as a model reaction. Our preliminary experiments revealed that alcohols are the best solvents for the reaction. The obtained results are presented in Table 1. We observed that the 2,2′-bimorpholine-derived catalysts **1a**−**c** were all nonselective (Table 1, entries 1−3). The piperidinylpyridine derivatives **3a**−**d** were found to be more selective and also more reactive, affording the product in high yield within ∼24 h (Table 1, entries 5−8). The highest selectivity at room temperature was obtained using *N*-isopropyl-3,3′-bimorpholine **2** (Table 1, entry 4). However, reactions with synthetically more easily available bipiperidine derivatives **4** also gave quite satisfactory enantioselectivities (for the screening), but the corresponding complexes were found to be much more reactive (Table 1, entries 9, 11, and 13). We assumed that the reaction using that ligand at a lower temperature should proceed at a reasonable rate and with increased enantioselectivity. The substituent at the nitrogen atom in **4** has a significant influence on the selectivity of the Henry reaction at lower temperature (−25 °C) (Table 1, entries 10, 12, and 14). The most selective ligand bipiperidine **4c** was selected as potential ligand for further studies.

The optimization of the reaction conditions was carried out with iPr-bipiperidine **4c**, copper(II) acetate hydrate (in 1:1 molar ratio), and *o*-nitrobenzaldehyde, in the presence or absence of the basic additive in MeOH (Table 2). The obtained results revealed a clear correlation between enantioselectivity and the temperature of the reaction (Table 2, entries 1−3). Although a considerably high enantiomeric purity of the product was obtained at −25 °C, the reaction was unreasonably slow at that temperature (Table 2, entry 3).

Basic additives are known to accelerate the Henry reaction.[18] Indeed, the use of 5 mol % of $Et_3N$ increased the rate of the reaction, and the product was formed in a 68% yield within 19 h at −25 °C. However, the additive caused lower stereoselectivity (Table 2, entry 4). A compromise between reactivity and selectivity was found by reducing the amount of nitromethane to 5 equiv and increasing the amount of the catalyst to 10 mol %. Thus, the reaction under those optimal conditions (5 equiv of nitromethane, 5 mol % of $Et_3N$, 10 mol % of catalyst at −25 °C in MeOH) afforded the product in a high yield and ee (79% and 81%, respectively) with a reasonable reaction time (Table 2, entry 6).

Next, the scope of the reaction was examined. Several aromatic aldehydes provided β-nitro alcohols in very high yields and ee in the reaction with nitromethane, catalyzed by (*S*,*S*)-bipiperidine **4c** or its enantiomer ***ent*-4c** complex with copper(II) acetate (Table 3). Comparing MeOH and EtOH as the reaction media, we observed that EtOH is clearly a preferable solvent, affording products in shorter reaction time and higher enantiomeric purity than running a reaction in

**TABLE 1. Screening of Catalysts for the Asymmetric Henry Reaction**




| entry | catalyst | aldehyde (R = ) | time (h) | yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | *p*-$NO_2$ | 18 | 46 | 0 |
| 2 | **1b** | *p*-$NO_2$ | 18 | 43 | 0 |
| 3 | **1c** | *p*-$NO_2$ | 90 | 91 | 11 |
| 4 | **2** | *o*-$NO_2$ | 21 | 92 | 69 |
| 5 | **3a** | *o*-$NO_2$ | 24 | 90 | 54 |
| 6 | **3b** | *p*-$NO_2$ | 22 | 93 | 20 |
| 7 | **3c** | *p*-$NO_2$ | 6 | 67 | 35 |
| 8 | **3d** | *p*-$NO_2$ | 18 | 83 | 13 |
| 9 | **4a** | *o*-$NO_2$ | 3 | 81 | 53[c] |
| 10 | **4a** | *o*-$NO_2$ | 111[d] | 28 | 63[c] |
| 11 | **4b** | *o*-$NO_2$ | 4 | 58 | 55 |
| 12 | **4b** | *o*-$NO_2$ | 93[d] | 91 | 55 |
| 13 | **4c** | *o*-$NO_2$ | 2 | 83 | 41 |
| 14 | **4c** | *o*-$NO_2$ | 70[d] | 17 | 85 |

[a]Isolated yield after column chromatography. [b]Determined by chiral HPLC. [c]The ee of the ligand was 90%. [d]The reaction was performed at −25 °C.

**TABLE 2. Optimization of the Reaction Conditions for the Asymmetric Henry Reaction in MeOH**

| entry | L/M (mol %) | additive (mol %) | temp (°C) | time (h) | yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 5 | | rt | 2 | 83 | 41 |
| 2 | 5 | | −10 | 25 | 52 | 77 |
| 3 | 5 | | −25 | 70 | 17 | 85 |
| 4 | 5 | $Et_3N$ (5) | −25 | 19 | 68 | 79 |
| 5 | 5 | $Et_3N$ (5) | −25 | 22 | 17 | 87[c] |
| 6 | 10 | $Et_3N$ (5) | −25 | 39 | 79 | 81[c] |

[a]Isolated yield after column chromatography. [b]Determined by chiral HPLC. [c]5 equiv of nitromethane was used.

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**TABLE 3. Henry Reaction of Aldehydes and Nitromethane Catalyzed by $Cu(OAc)_2\ H_2O$ and Ligand 2 or 4c Complex**

| entry | aldehyde[a] | ligand | nitromethane (equiv) | solvent | temp (°C) | time (h) | yield[b] (%) | ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | benzaldehyde | **4c** | 5 | MeOH | −25 | 40 | 93 | 94 (*R*) |
| 2 | benzaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 19 | 97 | 96 (*S*) |
| 3 | *o*-nitrobenzaldehyde | **4c** | 5 | MeOH | −25 | 39 | 79 | 81 (*R*) |
| 4 | *o*-nitrobenzaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 23 | 91 | 83 (*S*) |
| 5 | *p*-nitrobenzaldehyde | **4c** | 5 | MeOH | −25 | 47 | 60 | 71 (*R*) |
| 6 | *p*-nitrobenzaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 20 | 97 | 71 (*S*) |
| 7 | *p*-methoxybenzaldehyde | **4c** | 5 | MeOH | −25 | 72 | 26 | 81 (*R*) |
| 8 | *p*-methoxybenzaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 42 | 93 | 93 (*S*) |
| 9 | *p*-bromobenzaldehyde | **4c** | 5 | MeOH | −25 | 43 | 94 | 85 (*R*) |
| 10 | *p*-bromobenzaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 6 | 97 | 95 (*S*) |
| 11 | 2-naphthylaldehyde | **4c** | 5 | MeOH | −25 | 24 | 92 | 85 (*R*) |
| 12 | 2-naphthylaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 22 | 90 | 93 (*S*) |
| 13 | *trans*-cinnamaldehyde | **4c** | 5 | MeOH | −25 | 49 | 67 | 80 (*R*) |
| 14 | *trans*-cinnamaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 7 | 70 | 88 (*S*) |
| 15 | cyclohexanecarbaldehyde | **4c** | 5 | MeOH | −25 | 96 | 52 | 84 (*R*) |
| 16 | cyclohexanecarbaldehyde | ***ent*-4c** | 10 | EtOH | −25 | 70 | 43 | 92 (*S*) |
| 17 | *o*-nitrobenzaldehyde | **2** | 5 | MeOH | −25 | 48 | 80 | 83 (*S*) |
| 18 | *o*-nitrobenzaldehyde | **2** | 10 | EtOH | −25 | 24 | 94 | 76 (*S*) |

[a]Reaction conditions in MeOH: $Cu(OAc)_2\ H_2O$ (10 mol %), ligand (10 mol %), $Et_3N$ (5 mol %), $CH_3NO_2$ (5 equiv), −25 °C. In EtOH: $Cu(OAc)_2\ H_2O$ (10 mol %), ligand (10 mol %), $Et_3N$ (5 mol %), $CH_3NO_2$ (10 equiv), −25 °C. [b]Isolated yield after column chromatography.

MeOH. Even deactivated anisaldehyde afforded, in EtOH, a complete conversion in a highly stereoselective manner, and the product was isolated in an almost quantitative yield and high ee (Table 3, entry 8). Stereoselectivities are not considerably influenced by the electronic and steric character of substituents in the aromatic ring, and enantiomeric purities were moderate to high (71−96%). A longer reaction time was needed for aliphatic aldehydes. Thus, cyclohexane carbaldehyde gave the corresponding nitro alcohol only approximately in 50% of the yield within ~90 h (Table 3, entries 15, 16). α,β-Unsaturation at formyl group does not hinder the reaction. Thus, cinnamaldehyde reacted smoothly in EtOH (Table 3, entry 14). Enantiomeric purities of aliphatic β-nitro alcohols were high (in the best case, 92%, Table 3, entry16).

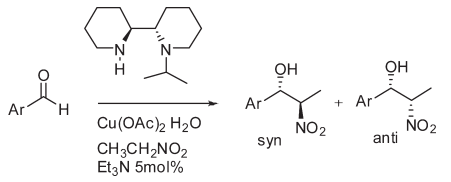
A comparison of bimorpholine **2** (Table 3, entries 17 and 18) and bipiperidine ligand **4c** (Table 3, entries 3 and 4) revealed that their catalytic properties are very similar. However, the easier synthetic availability of the latter ligand makes it more practical.

In the reaction of other nitroalkyl compounds besides nitromethane with aldehydes, two contiguous stereocenters are formed simultaneously. Although a copper-catalyzed enantioselective Henry reaction is well-documented, there are only a few instances where a high diastereoselectivity was achieved.[3c,10,19] We studied the reaction of nitroethane with aromatic aldehydes. The results are presented in Table 4.

The reaction of 2-naphthaldehyde with nitroethane was carried out in MeOH, EtOH, and iPrOH (Table 4, entries 1−3). EtOH was again the best solvent in terms of reactivity and stereoselectivity. In all of the evaluated cases, the ratio of the obtained *anti*/*syn* isomers was not very high (from 2:1 to 4:1). However, the isolated yield and the enantiomeric purity of the obtained *anti* and *syn* diastereoisomers were almost equally high (up to 96%).

To rationalize the stereochemical outcome of the reaction, first the complex was characterized by ESI HRMS. The main peak corresponds to a ligand **4c** copper monoacetate complex

**TABLE 4. Henry Reaction of Aldehydes and Nitroethane Catalyzed by $Cu(OAc)_2 \cdot H_2O$ and Ligand 4c Complex[a]**




| entry | Ar | solvent | time (h) | yield[b] (%) | *syn*/*anti*[c] | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 2-naphthyl | MeOH | 21 | 47 | 22:78 | 71/86 |
| 2 | 2-naphthyl | EtOH | 24 | 86 | 31:69 | 80/88 |
| 3 | 2-naphthyl | iPrOH | 19 | 89 | 23:77 | 75/82 |
| 4 | Phenyl | EtOH | 47 | 86 | 19:81 | 89/96 |
| 5 | *o*-$NO_2$-phenyl | EtOH | 19 | 88 | 25:75 | 74/89 |
| 6 | *p*-Br-phenyl | EtOH | 25 | 95 | 18:82 | 80/94 |
| 7 | *p*-MeO-phenyl | EtOH | 67 | 96 | 20:80 | 84/92 |
| 8 | 1-naphthyl | EtOH | 47 | 74 | 28:72 | 81/93 |

[a]Conditions: reaction was run at −25 °C in the presence of $Cu(OAc)_2 \cdot H_2O$ (10 mol %), ligand **4c** (10 mol %), $Et_3N$ (5 mol %), and nitroethane (10 equiv). [b]Isolated yield of the mixture of diastereoisomers. [c]Determined by chiral HPLC.

(found 332.1527; theoretical 332.1525; see the Supporting Information for details). Calculations of the geometry of the complex and energetic parameters were performed at the B3LYP/6-31+G* highest level,[20] using the Gaussian03 program.[21] The optimal geometry is represented in Figure 2. One can see that

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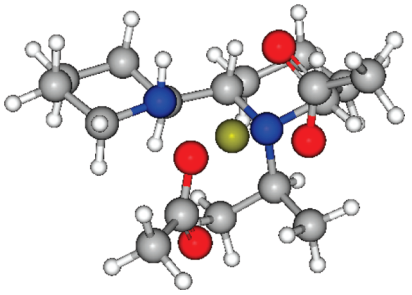


**FIGURE 2.** Calculated conformation of (*S,S*)-*N*-iPr-bipiperidine and $Cu(OAc)_2$ complex in ethanol.

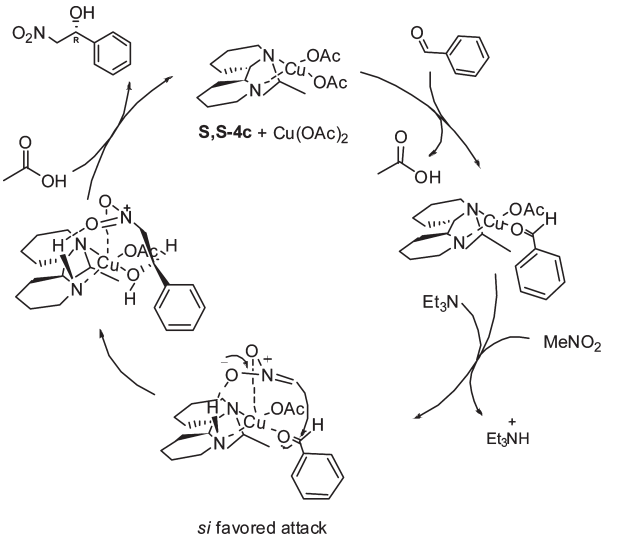
the *N*-iPr group of the piperidine ring is perpendicular to the almost planar structure of the tetra-coordinated copper complex. According to the model proposed by Evans,[3d] in the most reactive intermediate nitromethane is also in the perpendicular position and aldehyde is in the same plane with the ligand. In our case, catalyst **4** in the (*S*,*S*) configuration afforded the product with an *R* configuration. Thus, nitronate attacked the *si*-face of the aldehyde. It is assumed that the nitronate in the axial position (opposite the iPr group) was fixed with the hydrogen bonding with the N−H group and the electrophile in the equatorial position was oriented in the most appropriate way, leading to the *si* attack (Scheme 1).

In conclusion, we have shown that an easily available bipiperidine **4c** and commercially available $Cu(OAc)_2 \cdot H_2O$ formed a new practical catalytic system that afforded a highly stereoselective Henry reaction between aromatic aldehydes and aliphatic nitro compounds. Henry adducts were formed in good yields and high enantioselectivities, under mild conditions.

## Experimental Section

**General Procedure for the Asymmetric Henry Reaction. (*S*)-2-Nitro-1-phenylethanol (Table 3, Entry 2).** A solution of ligand **4c** (0.05 mmol, 10.5 mg, 10 mol %) and $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol, 10 mg, 10 mol %) in EtOH (0.9 mL) was stirred for 10 min at an ambient temperature to generate the catalyst. Benzaldehyde (0.5 mmol, 53 mg, 1 equiv) was added, and the reaction mixture was cooled to −25 °C. Nitromethane (5 mmol, 270 $\mu$L, 10 equiv) and a solution of $Et_3N$ (0.025 mmol, 3.5 $\mu$L, 5 mol %) in 100 $\mu$L of EtOH were added after 5 min of stirring. After the completion of the reaction, 200 $\mu$L of 1 N HCl was added, and the mixture was concentrated and directly purified by column chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate to yield 81 mg (97%) of product as clear oil. Enantiomeric purity (96%) was determined by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 15% iPrOH in hexane, 230 nm), (*R*) $t_R$ = 9.31 min (minor) and (*S*) $t_R$ = 11.02 min (major); $[\alpha]^{25}_D$ = +12.5 (*c* = 2.04 in EtOH), absolute stereochemistry assigned by comparison of the retention times in HPLC and optical rotation signs with literature data: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 − 7.33 (m, 5H), 5.47 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.61 (dd, *J* = 13.4, 9.6 Hz, 1H), 4.52 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.85 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 138.2, 129.2, 129.1, 126.1, 81.4, 71.1.

**SCHEME 1. Proposed Catalytic Cycle of the Henry Reaction**

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**Supporting Information Available:** Experimental procedures and characterizations, NMR and chiral-phase HPLC data, computational aspects, and optimized structures for calculated species. This material is available free of charge via the Internet at http://pubs.acs.org.