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Copper(II) arylhydrazone complexes as catalysts for C−H activation in the Henry reaction in water

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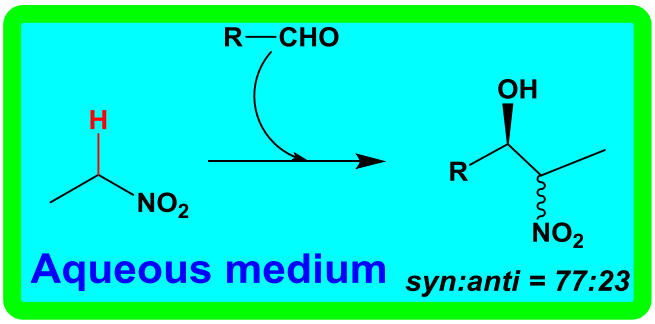
Dedicated to **Prof. Georgiy B. Shul'pin** on the occasion of his 70th birthday.

Graphical abstract



Highlights

► Stereoselective C−H functionalization in water
► Water-soluble mono- and dinuclear copper(II) complexes
► Sulfo-functionalized arylhydrazone of acetoacetanilide ligand
► Copper(II) complexes effectively catalyze the Henry reaction

Abstract

Three new water-soluble copper(II) complexes [Cu(HL)(H_2O){(CH_3)$_2$NCHO}] (**1**), [Cu(H_2L)$_2$(im)$_4$]·CH_3OH (**2**) and [Cu(HL)(CH_3OH)]$_2$(μ_2-py) (**3**) were synthesized from copper(II) nitrate and sodium (*Z*)-2-(2-(1,3-dioxo-1-(phenylamino)butan-2-ylidene)hydrazinyl)benzene-sulfonate (NaH_2L), in the absence (for **1**) and presence of imidazole (im) (for **2**) or pyrazine (py) (for **3**), and fully characterized. The complexes **1**−**3** have been tested as stereoselective C−H activating catalysts for the model nitroaldol (Henry) condensation of nitroethane with various aldehydes in water. **1** was the most active catalyst affording 64−87% yields with *syn/anti* diasteroselectivities up to 77:23.
Keywords: Arylhydrazone of acetoacetanilide, Copper(II) complexes, Henry reaction in aqueous medium, C−H activation.

1. Introduction

The C−H activation of alkanes in water with Pt complexes (the so-called Shilov reaction) remains a conceptual breakthrough which demonstrates the possibility to transform essentially inert and hydrophobic substrates into their water-soluble oxidation products of a much higher added value and reactivity [1]. In spite of the initial expectations, elaboration of new effective catalysts for such transformations is still far from perfection, and many efforts continue to be poured into the field [2].

One of the approaches is related to the preparation of suitable metal-organic catalytic species, which, on one hand, can provide (stereo)specific interaction with a hydrophobic substrate and a catalytic centre (*e.g.* a transition metal ion), while, on the other hand, facilitate interaction with reaction media, where water is the preferable case due to a number of reasons [1c,3].

Arylhydrazones of active methylene compounds (AHAMC) modified with $-SO_3H$ and/or –COOH substituents can be used as ligands for a number of copper(II) catalyzed C−H functionalizations in water [4]. Imidazole (im) and pyrazine (py) are also known to play an important role in the design of many C−H activating homogeneous catalysts, regulating their solubility, buffer capacity, stability and eventually the overall activity [4b,5]. Hence, the preparation of new heteroligand water-soluble copper homogeneous catalysts with the abovementioned ligands is of interest for the area of C−H (stereo)specific functionalization in aqueous media. The well studied and widely applied Henry coupling can be used as a model reaction to test the activity and stereoselectivity of the catalysts towards aliphatic nitroalkanes.

The Henry (nitroaldol) reaction concerns the interaction between the carbonyl carbon atom of an aldehyde and the α-carbon atom of an aliphatic nitro compound to give a new C−C bond. Using this simple transformation, one can construct a variety of biologically active polyfunctionalized compounds with several stereogenic centres from relatively cheap and available starting materials [6]. This reaction can be catalyzed by a base, transition *d* [7−11] or *f* [12] metal complexes as well as some organocatalysts [13]. Amongst these protocols, Cu-catalyzed Henry couplings have recently received much attention [7], but most of them are performed in harmful organic solvents. In order to avoid the organic solvents, one can prepare water-soluble copper complexes, *e.g*. by suitable functionalization of ligands, and study their catalytic performance towards the Henry reaction in water medium.

Thus, in this work we combine the abovementioned approaches towards the following aims: *i*) to synthesize a new water-soluble AHAMC ligand bearing a $-SO_3H$ group, namely (*Z*)-2-(2-(1,3-dioxo-1-(phenylamino)butan-2-ylidene)hydrazinyl)benzenesulfonate (NaH_2L); *ii*) to prepare new aquasoluble Cu^{II}-AHAMC complexes, bearing imidazole and pyrazine ligands; *iii*) to test the obtained complexes as catalysts or catalyst precursors for the Henry reaction in water medium, as well as in other solvents or under solvent-free conditions, for comparative purposes.

2. Experimental

2.1. Materials and instrumentation

All the chemicals were obtained from commercial sources (Aldrich) and used as received. The infrared spectra (4000–400 cm^{-1}) were recorded on a BIO-RAD FTS 3000MX instrument in KBr pellets. Carbon, hydrogen, and nitrogen elemental analyses were done using a "2400 CHN Elemental Analyzer" by Perkin Elmer. The ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker Avance II + 300 (UltraShield^{TM} Magnet) spectrometer operating at 300.130 and 75.468 MHz for proton and carbon-13, respectively. The chemical shifts are reported in ppm using tetramethylsilane as the internal reference. Electrospray mass spectra (ESI-MS) were run with an ion-trap instrument (Varian 500-MS LC Ion Trap Mass Spectrometer) equipped with an electrospray 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* 0 to 1200 in methanol solution. The compounds were observed in the negative or positive mode (capillary voltage = 80–105 V).

2.2. Synthesis of NaH_2L

NaH_2L was synthesized similarly to a well-established procedure [4], by azocoupling of 2-sulfobenzenediazonium chloride with acetoacetanilide in the presence of sodium hydroxide.
Diazotization: A 10 mmol (1.73 g) portion of 2-aminobenzenesulfonic acid was dissolved in 50 mL of water upon addition of 0.6 g of solid NaOH. The solution was cooled in an ice bath to 0 °C and 10 mmol (0.69 g) of $NaNO_2$ were added with subsequent addition of 2 mL 33 % HCl in portions of 0.4 mL for 1 h, under vigorous stirring. During the reaction, the temperature of the mixture must not exceed +5 °C. The obtained diazonium salt was used for the next stage (see below).
Azacoupling: 10 mmol (0.40 g) of NaOH were added to a mixture of 10 mmol (1.77 g) of acetoacetanilide with 30 mL of water-ethanol (1/30, v/v). The solution was cooled in an ice bath, and a suspension of the diazonium salt (prepared according to the procedure described above) was added in two equal portions under rigorous stirring for 1 h. The formed yellow precipitate of NaH_2L was filtered off, recrystallized from methanol and dried in air.
NaH_2L: Yield 77 % (based on acetoacetanilide), yellow powder, soluble in water, DMSO, methanol, ethanol and dimethylformamide and insoluble in non-polar solvents. Anal. Calcd. for $C_{16}H_{14}N_3NaO_5S$ (*Mr* = 383.35): C, 50.13; H, 3.68; N, 10.96. Found: C, 50.03; H, 3.72; N, 10.88 %. IR (KBr): 3532 (br.) $\nu(H_2O)$, 3098 and 2925 ν(NH), 1669 ν(C=O), 1601 ν(C=O···H), 1563 ν(C=N) cm^{-1}. MS (ESI) (negative ion mode): m/z: 360.3 $[Mr–Na]^-$. ^{1}H NMR (DMSO-d_6): δ 2.55 (3H,

CH_3), 7.14−7.80 (9H, Ar−H), 11.11 (s, 1H, NH), 14.37 (s, 1H, NH). $^{13}C\{^1H\}$ (DMSO-d_6): δ 26.6 (CH_3), 116.0, 120.7, 124.3, 124.8, 128.0, 129.5 (Ar−H), 131.3 (Ar−SO_3Na), 135.5 (C=N), 138.0 (C−NH), 139.0 (Ar−NH−N), 161.2 and 199.4(C=O).

2.3. Synthesis of [Cu(HL)(H_2O){(CH_3)$_2$NCHO}] (**1**)

0.1 mmol (38 mg) of NaH_2L were dissolved in 5 mL of methanol, then 0.1 mL DMF, 2 drops of Et_3N and 0.1 mmol (23 mg) of $Cu(NO_3)_2{\cdot}2.5H_2O$ were added. The mixture was stirred for 5 min and left for slow evaporation. The greenish crystals of the product started to form after *ca*. 1 d at room temperature; they were filtered off and dried in air.

1: Yield, 45 % (based on Cu). Calcd. for $C_{19}H_{22}CuN_4O_7S$ (*Mr* = 514.01): C 44.40, H 4.31, N 10.90; found C 44.13, H 4.22, N 10.83. MS (ESI, positive ion mode), *m/z*: 423.8 [*Mr*−H_2O−DMF+H]$^+$. IR (KBr): 3616 and 3530 (s, br) ν(OH), 1694 (s) *ν*(C=O), 1561 (s) *ν*(C=N) cm^{-1}.

2.4. Synthesis of [Cu(H_2L)$_2$(im)$_4$]·CH_3OH (**2**)

0.2 mmol (74 mg) of NaH_2L were dissolved in 7 mL of methanol, then 0.1 mmol (23 mg) of $Cu(NO_3)_2{\cdot}2.5H_2O$ and 0.4 mmol (27 mg) of imidazole (im) were added, and the system was stirred for 5 min. After *ca*. 2 d at room temperature, greenish crystals precipitated, which were then filtered off and dried in air.

2: Yield, 40 % (based on Cu). Calcd. for $C_{45}H_{48}CuN_{14}O_{11}S_2$ (*Mr* = 1088.63): C 49.65, H 4.44, N 18.01; found C 49.54, H 4.32, N 17.94. MS (ESI, positive and negative ion modes), *m/z*: 423.8 [*Mr*−H_2O−DMF+H]$^+$, 168.7 $[Cu(im)_4]^{2+}$ and 360.3 $[H_2L]^-$. IR (KBr): 3173 (s, br) ν(OH), 2951 and 2846 ν(NH), 1681 and 1601 (s) *ν*(C=O), 1521 (s) *ν*(C=N) cm^{-1}.

2.5. Synthesis of [Cu(HL)(CH_3OH)]$_2$(μ_2-py) (**3**)

0.1 mmol (38 mg) of NaH_2L were dissolved in 6 mL of methanol, then 0.1 mmol (23 mg) of $Cu(NO_3)_2{\cdot}2.5H_2O$ and 0.1 mmol (8 mg) of pyrazine (py) were added, and the system was stirred for 5 min. After *ca*. 2 d at room temperature, greenish crystals precipitated, which were then filtered off and dried in air.

3: Yield, 49 % (based on Cu). Calcd. for $C_{38}H_{38}Cu_2N_8O_{12}S_2$ (*Mr* = 989.98): C 46.10, H 3.87, N 11.32; found C 45.98, H 3.78, N 11.34. MS (ESI, positive ion mode), *m/z*: 926.8 [*Mr*−2CH_3OH+H]$^+$. IR (KBr): 3436 (s, br) ν(OH), 3103 and 3058 ν(NH), 1685 and 1593 (s) *ν*(C=O), 1549 (s) *ν*(C=N) cm^{-1}.

2.6. Crystal structure determination

X-ray diffraction intensities of **1**−**3** were collected using a Bruker SMART APEX-II CCD area detector equipped with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) at 298(2) K. Absorption correction was applied by SADABS [14a,b]. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares using Bruker's SHELXTL-97 [14c]. All non-hydrogen atoms were refined anisotropically. The details of the crystallographic data, selected bond distances and angles for **1**−**3** are summarized in Tables S1 and S2 (Electronic supplementary information). Crystallographic data for the structural analysis has been deposited to the Cambridge Crystallographic Data Center (CCDC 1476160 for **1**, 1476161 for **2** and 1476163 for **3**). Copy of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (+44) 1223-336033; E-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk/data_request/cif).

2.7. Catalytic activity studies

The catalyst (1.0−5.0 mol%), 2 mL solvent (MeCN, MeOH or H_2O), aldehyde (1 mmol) and nitroethane (4 mmol) were added, in this order, to a 10 mL flask and the resulting mixture was stirred for a specified period of time at room temperature. After evaporation of the solvent, the residue was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR to evaluate the yield of the β-nitroalkanol product as reported previously [15]. The adequacy of the procedure was verified by blank ^{1}H NMR analyses with 1,2-dimethoxyethane as an internal reference. The internal standard method [8e,15] confirmed that no side products were formed. The ratio between the *syn* and *anti* isomers was also determined by ^{1}H NMR spectroscopy, since the values of vicinal coupling constants for the β-nitroalkanol products between the α-N–C–H and the α-O–C–H protons are different (J = 7–9 and 3.2–4 Hz for the *syn* and *anti* isomers, respectively) [15].

3. Results and discussion

*3.1. Synthesis and characterization of NaH_2L and **1**−**3***

The highly water soluble sodium salt NaH_2L was synthesized via C−N coupling reaction between 2-sulfobenzenediazonium chloride and acetoacetanilide in a sodium hydroxide water-ethanol solution, and characterized by IR, ESI-MS, NMR spectroscopies and elemental analysis. The hydrazone =N−N<u>H</u>− signal is observed at δ 14.37 in the ^{1}H-NMR spectrum. The IR spectrum shows ν(OH), $\nu(NH)_{hydrazone}$ and $\nu(NH)_{amide}$ vibrations at 3532, 3098 and 2925 cm^{-1}, respectively,

while ν(C=O), ν(C=O···H) and ν(C=N) are observed at 1669, 1601 and 1563 cm^{-1}, correspondingly, supporting the existence of the H-bonded hydrazone structure in the solid state.

Treatment of $Cu(NO_3)_2 \cdot 2.5H_2O$ with NaH_2L in methanol in the absence or presence of imidazole or pyrazine led to the Cu^{II} complexes $[Cu(HL)(H_2O)\{(CH_3)_2NCHO\}]$ (**1**), $[Cu(H_2L)_2(im)_4] \cdot CH_3OH$ (**2**) and $[Cu(HL)(CH_3OH)]_2(\mu_2\text{-py})$ (**3**), respectively (Scheme 1). All complexes are characterized by elemental analysis, ESI-MS, IR spectroscopy and single crystal X-ray diffraction (see below). In the IR spectra of **1**−**3**, the ν(C=O) and ν(C=N) signals appear at 1694 and 1561, 1681 and 1521, 1685 and 1549 cm^{-1}, respectively, values that are significantly shifted in relation to the corresponding signals of NaH_2L (see above). Mass spectrometry of a methanol solution of **1**−**3** shows relevant peaks at m/z = 423.8 $[Mr-H_2O-DMF+H]^+$ (for **1**), 168.7 $[Cu(im)_4]^{2+}$ and 360.3 $[H_2L]^-$ (for **2**), and 926.8 $[Mr-2CH_3OH+H]^+$ (for **3**). Elemental analyses and X-ray crystallography are also in agreement with the proposed formulations.

The structure of complex **1** shows the Cu atom in a square pyramidal environment formed, in the basal plane, by two O and one N atoms from HL^{2-} [O2, O6 and N1] and the formamide O7 atom; the apical position is taken by O1 of a water molecule (Scheme 1, Fig.). In compound **2**, the Cu atom is within a distorted octahedral coordination environment, where the positions are occupied by four im ligands (4 equatorial N atoms) and two H_2L^- ligands (the 2 apical O atoms, Scheme 1, Fig.). The copper cations adopt a square pyramid geometry in the dinuclear compound **3** (Fig.). All compounds present intra- and intermolecular hydrogen bond interactions that lead to intricate supramolecular frameworks (Fig. S1).

*3.2. Catalytic activity of **1**−**3** in the Henry reaction*

A series of reactions of nitroethane and benzaldehyde (representative model substrates) in various solvents (MeCN, MeOH and H_2O) were studied in order to evaluate the catalytic efficacy of **1**−**3** in different solvents (Scheme 2, Table 1). For comparative purposes, blank reactions in the absence of **1**−**3** were also performed in such solvents or in added solvent-free conditions and in the presence of $Cu(NO_3)_2 \cdot 2.5H_2O$, and in all the blank experiments no β-nitroalkanol was detected (entries 1−7, Table 1).

When catalyst **1** was tested in water, the obtained yield (Table 1, entry 10) was better than in acetonitrile or methanol media (entries 8 and 9, respectively), and much higher than those achieved in the presence of **2** and **3** (entries 11−16). The higher catalytic activity of **1** is possibly stipulated by

the two adjacent labile sites, coordinated water and DMF molecules, which can be easily replaced along the reaction. Thus, **1** and water were chosen as catalyst and green solvent, respectively, for the following studies.

On the next step, for the reaction with catalyst **1** in water media, we optimized the reaction temperature within the interval of 10−75 ºC (Table 2, entries 4, 14−17). To this end, 20 ºC was found to be a suitable compromise for the following studies, since the yield increase until 75 ºC (from 79 to 84 %) is not marked, whereas the diasteroselectivity decreases. The increase of reaction time from 0.5 h to 24 h (entries 1−6) led to higher conversions, but 5 h is the best compromise since extending the reaction beyond this period does not result in a significance yield increase (*e.g.*, from 79 to 80 % for 5 h to 24 h). The same can be concluded about the catalyst loading of 3 mol% (entries 8−12). Possibly due to the poor solubility of **1** in the reaction mixture (nitroethane + benzaldehyde), a lower yield (51 %) was achieved under added solvent-free conditions (entry 13).

Under the established optimal conditions, the scope of the system (with catalyst **1**) was also investigated for a variety of aldehydes, in water at room temperature (Table 3). The electronic properties of the substituent in the aromatic aldehydes have a pronounced effect on the yield and diastereoselectivity. In general, the aromatic aldehydes with an electron-withdrawing group (nitro or chloro) in *para* position provide the nitroaldol products in higher yields (85 or 82 %, respectively) and stereoselectivities (Table 3, entries 5 and 6). This is consistent with the higher electrophilicity of the aldehyde CHO carbon and eventually can also be related to a possible strengthening of the π-π stacking interactions in reaction intermediates (see below), which can increase if an electron-withdrawing group is introduced into an aryl ring [16]. When aliphatic aldehydes, such as propionaldehyde, butyraldehyde and pentanal, are applied as substrates, also high yields and diastereoselectivities are achieved (Table 3, entries 10−12).

The nitroaldol yields obtained in this work, diastereoselectivities, used solvents and reaction times and temperatures were compared with those reported for other copper complexes with: *i*) Schiff base ligands derived from *Cinchona* alkaloids [17a]; *ii*) N^1,N^2-*bis*((*Z*)-pyridin-2-ylmethylene)oxalohydrazide [17b]; *iii*) (*S*)-2-((2-(hydroxydiphenylmethyl)pyrrolidin-1-yl)methyl)-6-(trifluoromethyl)phenol [17c] (Table 4). Our catalytic system, besides its simplicity, has also the advantage of operating in water and at the convenient room temperature, leading usually to comparable yields and stereoselectivities.

A proposed mechanism for the nitroaldol reaction of nitroethane with benzaldehyde in the presence of **1** (Scheme 3) could involve the substitution of solvent (DMF or water) for aldehyde to form an intermediate **I** (observed at the positive ion mode in methanol) with an increased electrophilicity of the carbonyl group. In fact, the liberated DMF molecule was detected by ESI-MS

analysis in the positive ion mode (*m/z* =74, DMF+H^+, Fig. S2). The π-π interactions between aromatic moieties of the substrate and ligand, known [16,18−20] to occur in some catalytic intermediates, can provide additional stabilization and orient the aldehyde in a specific way to facilitate the following stereoselective transformation. Intermediates related to **I** are known [19,20] and its formation is supported by ESI-MS data (Fig. S2). Displacement of the solvent ligand in **I** by nitroethane forms a nitronate type intermediate **II** (also supported by ESI-MS analysis at the positive ion mode in methanol, Fig. S3), which, in its turn, can be additionally stabilized by a charge-assisted hydrogen bonding (CAHB, Scheme 3). The formation of such non-covalent interactions is well documented [21−23] and was proposed to play crucial role in some catalytic intermediates [24]. Within **II**, the nucleophilic attack of the nitronate ligand to the activated aldehyde gives the nitroaldol product (see Fig. S4, ESI-MS data after 5 hours) which, upon replacement by solvent, completes the catalytic cycle.

3. Conclusions

Three new water soluble copper(II) molecular catalysts bearing a sulfo-functionalized arylhydrazone of acetoacetanilide have been synthesized, characterized and applied for an effective activation of nitroethane towards its addition to various aldehydes (Henry or nitroaldol reaction) to give the corresponding β-nitroalkanols in aqueous media. Complex **1** was found to be the most active one, providing β-nitroalcohols in good yields (up to 87 %) and diastereoselectivities (*syn/anti* up to 77:23). Compared to other related catalytic systems, that studied in this work appears to be among the best ones for the nitroalkane CH activation, having also the advantage of operating in aqueous media at room temperature.

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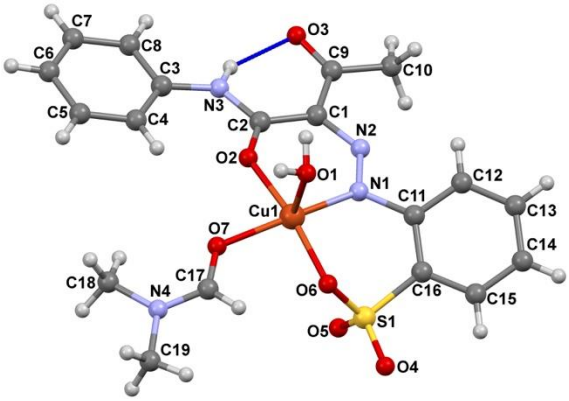

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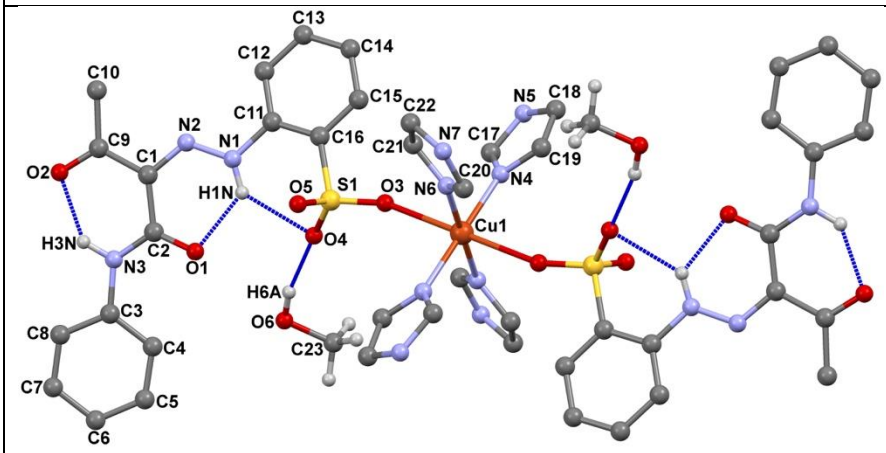

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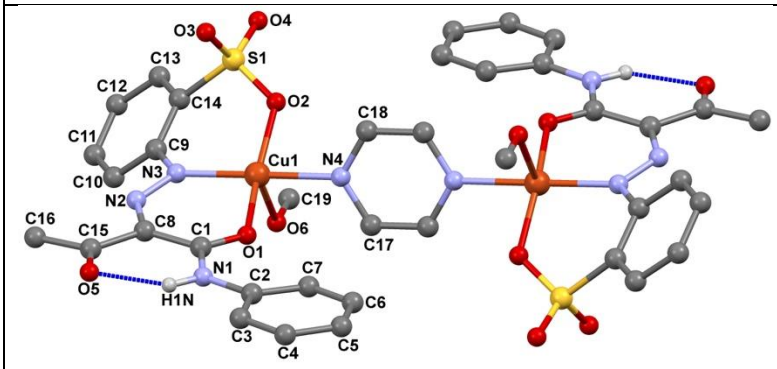
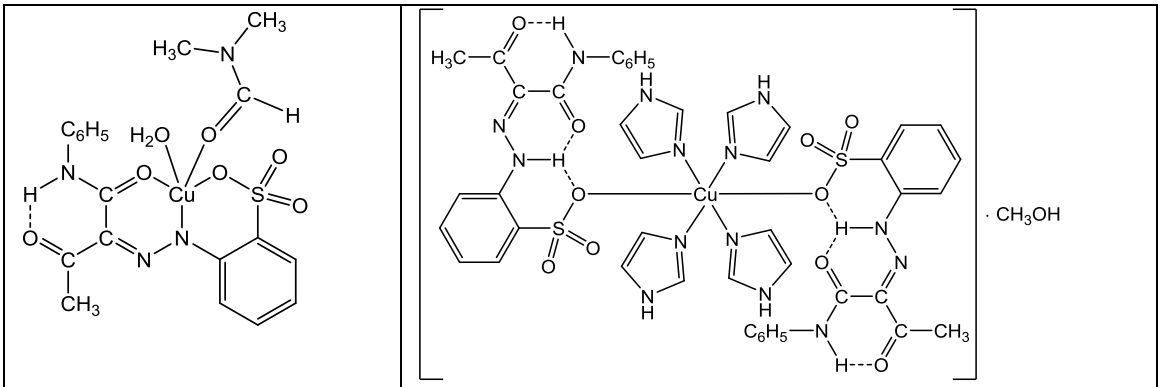
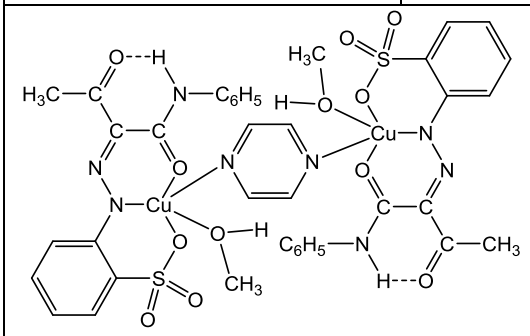


3

Figure. Crystal structures of **1**−**3** with partial atom numbering scheme. H-bond interactions are shown as dashed blue lines.



1 **2**



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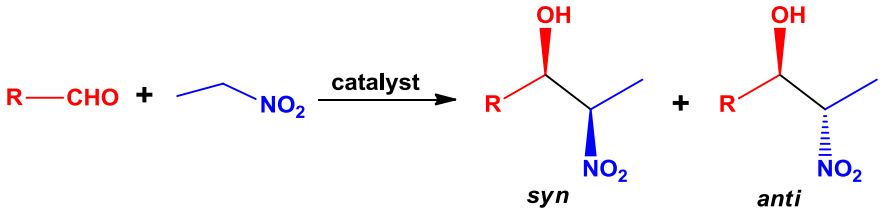
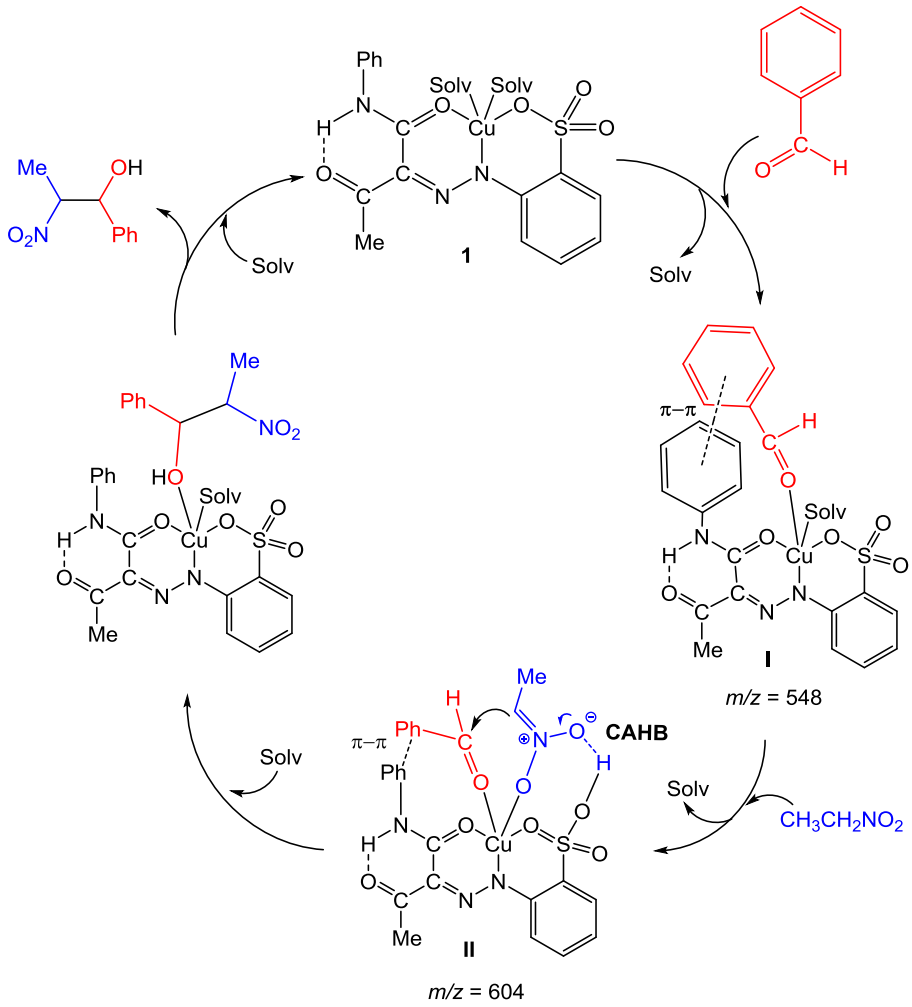
Scheme 1. Schematic representation of **1**−**3**.



Scheme 2. Nitroaldol reaction of aldehydes with nitroethane.



Scheme 3. Possible mechanistic pathway for the nitroaldol formation catalyzed by **1**.

Table 1. Catalyst screening and solvent optimization for the Henry reaction of benzaldehyde with nitroethane.[a]

Entry	Catalyst	Solvent	Yield, %[c]	Selectivity, *syn*/*anti*[d]
1[b]	Blank	No solvent	–	–
2		MeCN	–	–
3		MeOH	–	–
4		H_2O	–	–
5	$Cu(NO_3)_2 \cdot 2.5H_2O$	MeCN	–	–
6		MeOH	–	–
7		H_2O	–	–
8	**1**	MeCN	46	63:37
9		MeOH	54	69:31
10		H_2O	60	76:24
11	**2**	MeCN	30	50:50
12		MeOH	41	58:42
13		H_2O	46	68:32
14	**3**	MeCN	35	58:42
15		MeOH	46	63:37
16		H_2O	49	70:30

[a] Reaction conditions: catalyst precursor: $Cu(NO_3)_2 \cdot 2.5H_2O$, **1**–**3** (1.0 mol%), acetonitrile, methanol or H_2O (2 mL), nitroethane (4 mmol) and benzaldehyde (1 mmol), reaction time: 24 h, reaction temperature: 20 °C. [b] Added solvent-free conditions, using the substrate nitroethane as solvent (2 mL), [c] Determined by ^{1}H NMR, based on the starting benzaldehyde. [d] Calculated by ^{1}H NMR.

Table 2. Optimization of the Henry reaction conditions catalyzed by **1**.[a]

Entry	Time, h	Amount of catalyst, mol%	Temp., ºC	Yield, %[b]	Selectivity, *syn*/*anti*[c]
1	0.5	3.0	20	49	76:24
2	1	3.0	20	66	77:23
3	3	3.0	20	73	76:24
4	5	3.0	20	79	76:24
5	10	3.0	20	79	77:23
6	24	3.0	20	80	77:23
8	5	1.0	20	60	76:24
9	5	2.0	20	72	77:23
10	5	3.0	20	78	76:24
11	5	4.0	20	79	77:23
12	5	5.0	20	80	76:24
13[d]	5	3.0	20	51	71:29
14	5	3.0	10	35	75:25
15	5	3.0	35	82	75:25
16	5	3.0	55	83	71:29
17	5	3.0	75	84	66:34

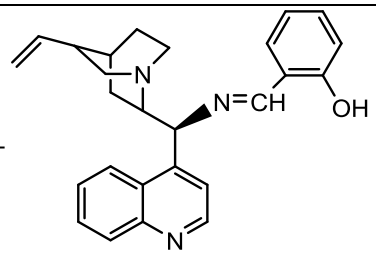
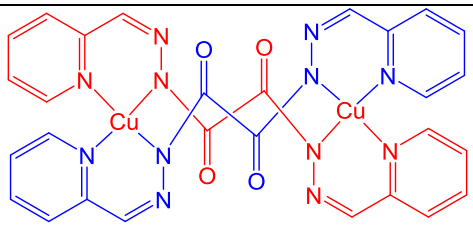
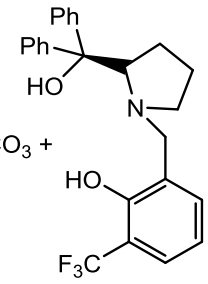
[a] Reaction conditions: 1.0−5.0 mol% of catalyst **1**, H_2O (2 mL), nitroethane (4 mmol) and benzaldehyde (1 mmol), 20 ºC. [b] Determined by ^{1}H NMR analysis (see Experimental section). [c] Calculated by ^{1}H NMR. [d] Solvent-free conditions, using nitroethane as solvent (2 mL).

Table 3. Henry reaction of nitroethane with various aldehydes catalyzed by **1**.[a]

Entry	Substrate	Yield, %[b]	Selectivity, *syn*/*anti*[c]
1	4-(Dimethylamino)benzaldehyde	64	75:25
2	4-Methoxybenzaldehyde	70	75:25
3	4-Methylbenzaldehyde	75	76:24
4	Benzaldehyde	78	76:24
5	4-Chlorobenzaldehyde	82	77:23
6	4-Nitrobenzaldehyde	85	77:23
7	2-Nitrobenzaldehyde	72	70:30
8	2-Methylbenzaldehyde	68	68:32
9	2,4,6-trimethylbenzaldehyde	60	61:39
10	Propionaldehyde	87	77:23
11	Butyraldehyde	86	76:24
12	Pentanal	86	76:24

[a] Reaction conditions: 3.0 mol% of catalyst **1**, H_2O (2 mL), nitroethane (4 mmol) and aldehyde (1 mmol), reaction time: 5 h, 20 ^oC. [b] Determined by ^1H NMR analysis (see Experimental part). [c] Calculated by ^1H NMR.

Table 4. Comparison of catalytic activity in the Henry reaction of benzaldehyde with nitroethane catalyzed by homogeneous copper complexes.

Catalyst	Time, h	Temp. ^{0}C	Solvent	Yield, %	*syn*/*anti* selectivity[c]	Ref.
1	5	20	Water	78	76:24	this work
Cu(II) + 	20	−20	THF	72	76:24	[17a]
	8	45	Water+ MeOH	83	82:18	[17b]
$CuBr_2$ + Cs_2CO_3 + 	24	−15	THF	81	1:20	[17c]