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Valmet chiral-base ligands and their copper(II) complexes as organo, homogeneous and heterogeneous catalysts for Henry, cyanosilylation and aldol coupling reactions

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Supporting information for this article is given via a link at the end of the document.

Abstract: Cyanosilylation, aldol coupling and asymmetric Henry reactions were carried out with *L*- and *D*-valmet ligands in different configurations: *i*) coordinated to sodium ions, as organocatalysts, with weak base properties, *ii*) complexes with copper(II), as homogeneous catalysts, and *iii*) immobilized copper(II) complexes onto graphene oxide (GO) as heterogeneous catalysts. For the reaction of benzaldehyde and nitromethane in water these afforded an asymmetric Henry reaction, with a spectacular increase of the conversion and ee (92.5 and 95.8%, respectively) after the deposition on GO. Ligand complexed copper was also effective for cyanosilylation and Aldol coupling reaction.

Introduction

Copper coordinated by various ligands such as chelate and chelate-amine^[1], or N - heterocyclic carbenes^[2] have been largely investigated as homogeneous catalysts for various

reactions with the advantage of replacing expensive and scarce noble metals. More recently, organocatalysis elicited an additional interest by offering a green alternative to metal-complex catalysis through replacing the metal by organo-functionalities such as amine or thio- groups.^[3] Further immobilization of such structures enlarges the advantages of these catalytic systems affording an easier separation of the catalyst. Asymmetric catalytic reactions with such systems make even more appealing their utilization.

Based on this state of the art we pursued to investigate, from the catalytic point of view, three systems constructed from *i*) a chiral ligand obtained via the condensation reaction of *o*-vanillin and *D*-, respectively, *L*-methionine (*ie* the enantiomeric sodium complexes, [Na(*L*-valmetH)]·H₂O and [Na(*D*-valmetH)]·H₂O, (Figure 1, a-b, Figures S1 and S18), *ii*) the copper(II) complexes with these ligands (*ie* [Cu(*D*-valmet)(H₂O)]·H₂O and [Cu(*L*-valmet)(H₂O)]·H₂O, (Figure 1, c-d, Figures S2 and S18) and *iii*) the graphene oxide immobilized complexes. These structures

were investigated in three well-documented reactions: *i.e.* *i*) the copper-catalyzed asymmetric Henry reaction of benzaldehyde with nitro-methane, *ii*) cyanosilylation of carbonyl compounds with trimethylsilyl cyanide and *iii*) aldol-coupling of benzaldehyde with cyclohexanone.

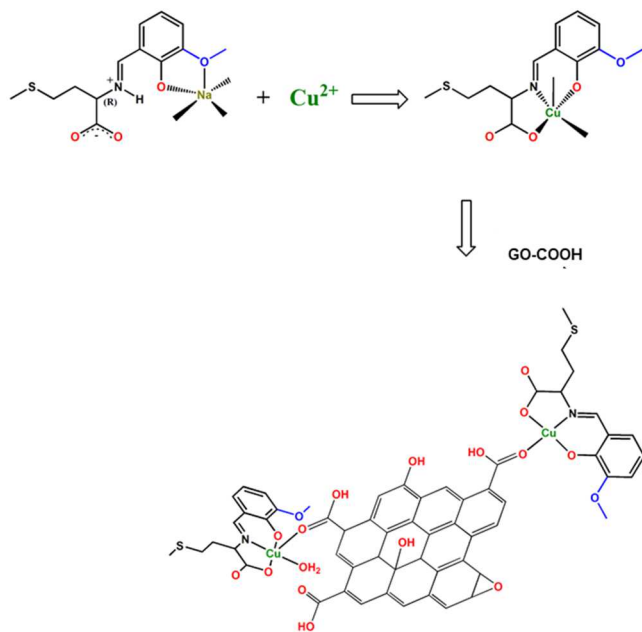
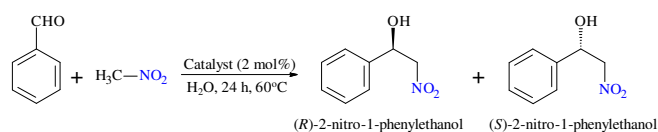


Figure 1. Details of the crystal structures of the investigated sodium (a and b) and copper (c and d) asymmetric complexes taking *D* (a and c) and *L* (b and d) ligand configurations.

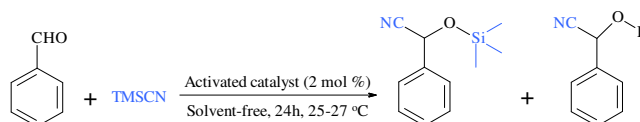
Henry reaction is nearly analogous to the aldol coupling. It produces β -nitro alcohols via coupling of a nitroalkane and an aldehyde or ketone and is typically catalyzed by a base.^[4] Asymmetric Henry reaction is also possible taking a transition metal complex containing a chiral ligand as catalyst.^[5]



Usually, based on constrained cyclic diamine scaffolds, the copper-catalyzed asymmetric Henry reaction is achieved with very high enantiomeric excesses using C2-symmetric ligands.^[6] Anyway, Zhou et al. reported a series of C1-symmetric chiral diamine ligands and found successful their application in highly enantioselective copper-catalyzed Henry reactions.^[7] Taking the above mentioned structures incorporating the two valmet ligands this study challenged an extension of the investigation of this reaction.

Cyanosilylation of carbonyl compounds with trimethylsilyl cyanide is another rapid, efficient and direct approach in organic synthesis for generating C–C bonds^[8] where inorganic

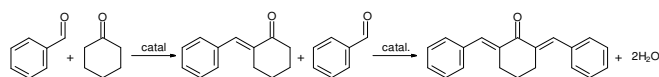
homogeneous/solid acids/bases as well as metallic Lewis acids/bases are able to catalyze this reaction. Practical application of organocatalysis, similar to homogeneous catalysis, is somehow limited due to above mentioned difficulty to separate and recycle the catalyst.^[9] However, it has been successfully applied for asymmetric reactions.^[10]



This study expands these investigations evaluating the role of copper in this reaction taking a comparison of the results collected from organocatalytic tests with both *D* and *L* ligand isomers as Na-valmet complexes and from homogeneous catalytic tests with Cu-*D*, *L*-Valmets.

Aldol-condensation also known as the Claisen-Schmidt condensation was firstly reported in 1881.^[11] However, it continue to elicit a practical importance in organic chemistry due to the simplicity and efficiency of the protocol allowing the synthesis of many compounds of strategic interest such as flavones, flavonoids, chalcones, dyes, food additives, flavors, antioxidants, anti-inflammatory, antimutagenic, antipyretic, antibacterial, pesticides, pigments, etc.^[12] This reaction is catalyzed by both homogenous base (NaOH ^[13]; KOH ^[14] or $\text{Ba}(\text{OH})_2$ ^[15]) and acid (HCl ^[16]; AlCl_3 ^[17], or $\text{SOCl}_2/\text{EtOH}$ ^[18]) catalysts. It is also catalyzed by heterogeneous base or acid catalysts that, in concordance to the principles of the green chemistry, are more attractive. Such catalysts included layered and cation-doped double hydroxides^[19], hydroxyapatite^[20], zirconium phosphate^[21] and chloride^[22], sulfated catalysts (AISBA-15- SO_3H ^[23]; sulfated TiO_2 -P25 (Degussa titania)^[24], etc.

To-date the aldol-condensation reactions mainly focused the synthesis of pharmaceutical compounds precursors^[25]; for the synthesis of epoxy resins and other polymers^[26]; raw material^[27], etc. However, the control of the selectivity of the condensation reactions affording the synthesis of both *mono*- or *two*-substituted aldol-products remains a key problem. It is mainly influenced by the relative ratios of the two reactant-molecules, the concentration of the catalytic active species, the solvent and the reaction temperature.^[28] Even more, a polar solvent may interact with the catalyst's acid/base sites blocking these.



Thus, as another important objective of this study, to facilitate the recoverability of the asymmetric complex catalysts, these have been as well supported onto graphene oxide and investigated in the aldol and Henry reactions. For comparison, reactions with reference solid catalysts such as base MgAlY and

MgO or acid H-ZSM-5 or graphene oxide (GO), have been also carried out. Not at the end, in order to further elucidate the relationship between the two aldol-coupling products, *i.e.* *mono*- and *di*- condensation, the effect of the cyclohexanone and benzaldehyde ratios has been also considered.

Results and Discussion

Catalysts characterization

Elemental analysis. Elemental analysis emphasized the presence of nitrogen (1.74 wt% N) and sulfur (3.81 wt% S). The calibration curve for nitrogen has $R^2=0.9994001$, -6,526 intercept and a slope of 5,137545E-04. Copper has been determined by ICP-OES (7.88 wt%) and like for N and S its loading corresponded to 0.12 atoms/g ie to a N:S:Cu ratio of 1:1:1.

Anchoring the Cu(L-valmet) complexes onto the support: The carboxyl groups of the modified GO served as linkers for the immobilization of the chiral complexes and FTIR and circular dichroism spectroscopy (CD) characterizations provided evidences for this. Figure 2 (a, b) depicts as well FTIR spectra of GO and GO-COOH. Besides the carboxyl group (band located at 1720 cm^{-1})^[33] these spectra confirmed the presence of additional oxygen functionalities such as the O-H (the strong broad-band centered at 3400 cm^{-1} and the band at 1225 cm^{-1})^[34] and C-O (epoxy) (identified as stretching vibrations from the band at 1070 cm^{-1}). In addition, the band at 1620 cm^{-1} , attributed to the C=C stretching vibrations represents a fingerprint of GO.^[35] Upon the treatment with NaOH and ClCH_2COOH , the increase of the intensity of the bands assigned to COOH (1722 cm^{-1}) and CH_2 (2949 cm^{-1}) groups confirms the anchorage of more carboxyl groups.^[36] After the treatment with NaOH and ClCH_2COOH the intensity of the C-O-C characteristic vibration bands (1070 cm^{-1}) decreased and a new band at 1300 cm^{-1} corresponding to the in-plane OH bending mode appeared.^[37]

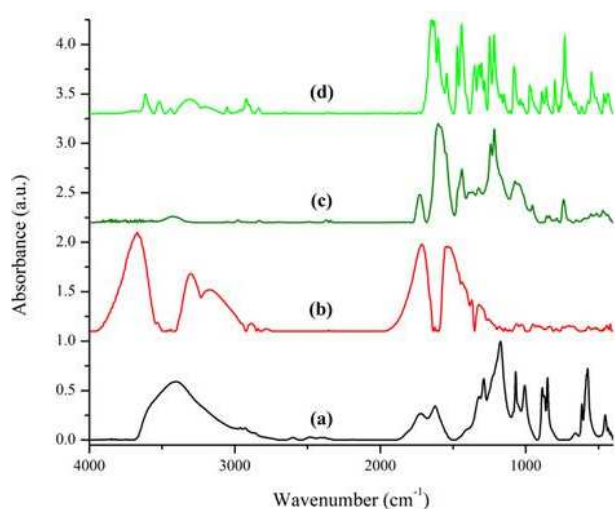


Figure 2. FTIR spectra of (a) GO, (b) GO-COOH, (c) GO-COOH/Cu(D-valmet) and (d) $[\text{Cu}(\text{D-valmet})(\text{H}_2\text{O})]\cdot\text{H}_2\text{O}$.

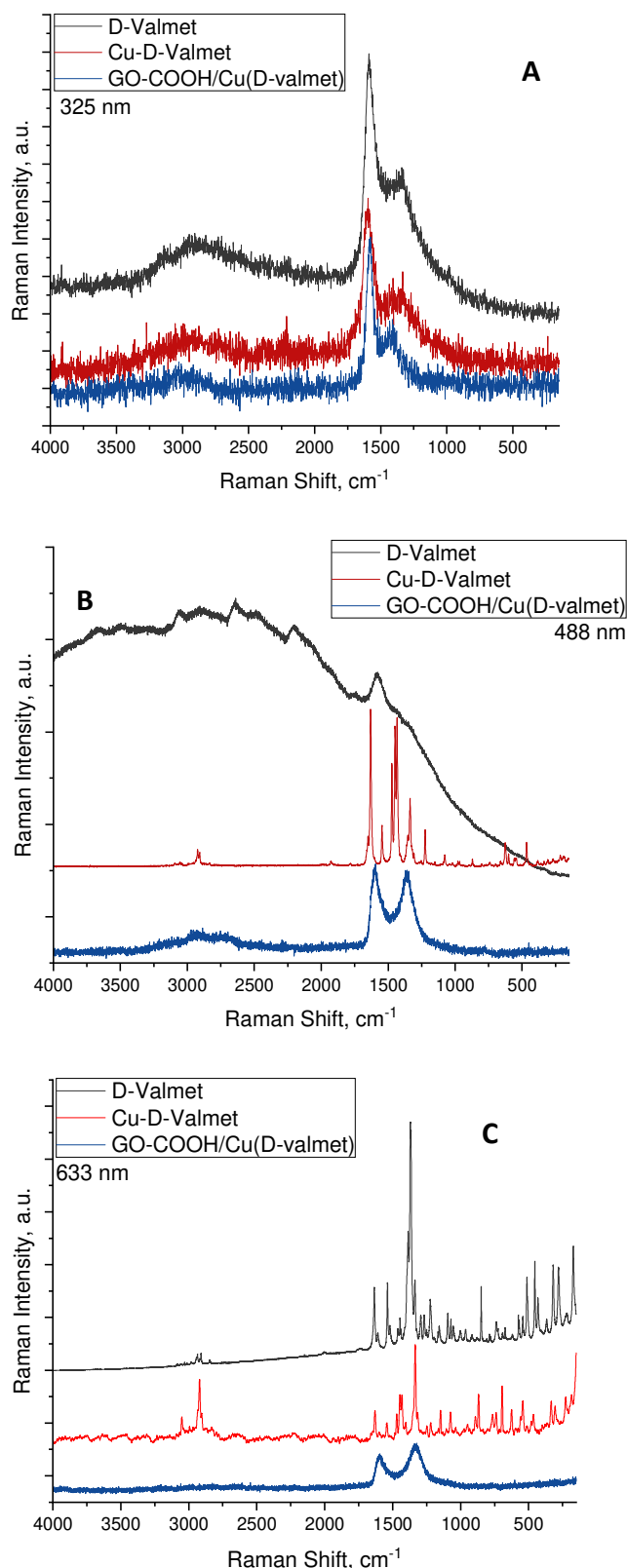


Figure 3. Raman spectra collected for the ligand (D-Valmet), copper complexated ligand (Cu-D-Valmet) and graphene oxide anchored copper complexated ligand (GO-COOH-Cu-valmet-D)

The FT-IR spectra of GO-COOH/Cu(*D*-valmet) and of the complex [Cu(*D*-valmet)(H₂O)]·H₂O itself are shown in Figures 2 (c, d) (also see Figures S1-S4). These reveal a decrease of the intensity of the band at 1727 cm⁻¹, indicating the immobilization of the complexes on GO-COOH through coordinate covalent bonds. The presence of the Schiff base in the final complex hybrid is revealed by the bands at 1630 cm⁻¹, 1217 cm⁻¹ and 1446 cm⁻¹ which are assigned to the stretching modes of the C=N and C-O (phenoxy) bonds and the deformation mode of the aromatic ring. Compared to the free complex, the bands in the spectrum collected for GO-COOH/Cu(*D*-valmet) are shifted to lower frequencies that is also a proof of the anchorage. The attachment of the complexes onto the surface can be also supported by π-π stacking interactions established between the phenyl rings of the ligands and the hexa-atomic carbon rings from the GO layer.

Figures 3 A-C present complementary structural information provided by the Raman spectra collected through the excitation of the ligand, the complex and the GO immobilized complex with wavelengths of 325, 488 and 633 nm, respectively. Moving from visible to UV the excitation energy affected the resulting Raman spectra. Thus, the samples adsorb weakly light at 325 nm so that the intensity of some Raman bands is only weakly enhanced due to pre-resonance effects and therefore only graphenic structures are observed in these spectra. Moving to higher wavelengths the structures of the ligand and metal-complexed ligand (Figure 3, c) become more visible (See Table S1) in the spectra of *D*-Valmet and copper complexed ligand (Cu-*D*-Valmet). However, for GO-COOH-Cu-valmet-*D* catalyst the spectrum is dominated only by the graphene structure with a evident difference in D/G intensity ratio compared to the spectra collected at lower excitation energies ((Figure 3, a and b).

The circular dichroism spectra of GO-COOH/Cu(*D*-valmet) and GO-COOH/Cu(*L*-valmet) recorded for the resulted solids confirmed the enantiomeric purity (Figure 4) as indicated by the broad band located at 620 nm (positive for GO-COOH/Cu(*L*-valmet) and negative for GO-COOH/Cu(*D*-valmet). The decrease in the intensity of this band after the immobilization of the complex is caused by the d-d transitions of the copper(II) ion.

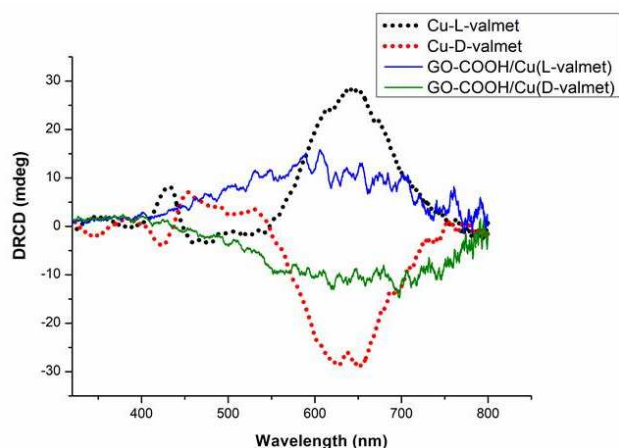


Figure 4. CD spectra of the copper complexes and of the hybrid chiral systems: GO-COOH/Cu(*L*-valmet) and GO-COOH/Cu(*D*-valmet)..

Acid-base properties of the investigated catalysts: *L*- and *D*-valmet ligands in the Na form showed base properties, as resulted from the CO₂-TPD measurements (0.11 mmoles CO₂/g). Further complexation of these ligands by copper decreased the CO₂ up-take (0.02 mmoles CO₂/g) while the deposition of these complexes onto GO afforded an additional increase of the basicity compared to the parent ligands (0.26 mmoles CO₂/g) that may also correspond to a partial decomplexation of copper (Figure 5.a and b). NH₃-TPD measurements on the same samples provided complementary information. *L*- and *D*-valmet ligands did not chemisorb NH₃ while for Cu(Valmet) predominate the acid sites (0.28 mmoles NH₃/g) that might be again correlated to a decomplexation of copper. Deposition of these complexes onto GO preserved the acidity but this was inferior to that of the complex (0.16 mmoles NH₃/g) (Figure 5.c and d).

CO₂- and NH₃-TPD analyses for the reference MgO, H-ZSM-5 and Mg/Al/Y mixed oxide indicated different properties. MgO exhibited dominant base properties (0.63 mmoles adsorbed CO₂ versus 0.26 mmoles adsorbed NH₃), H-ZSM-5 dominant acid properties (0.02 mmoles adsorbed CO₂ versus 1.31 mmoles adsorbed NH₃) while Mg/Al/Y mixed oxide mixed acid-base properties (0.51 mmoles adsorbed CO₂ versus 1.23 mmoles adsorbed NH₃).

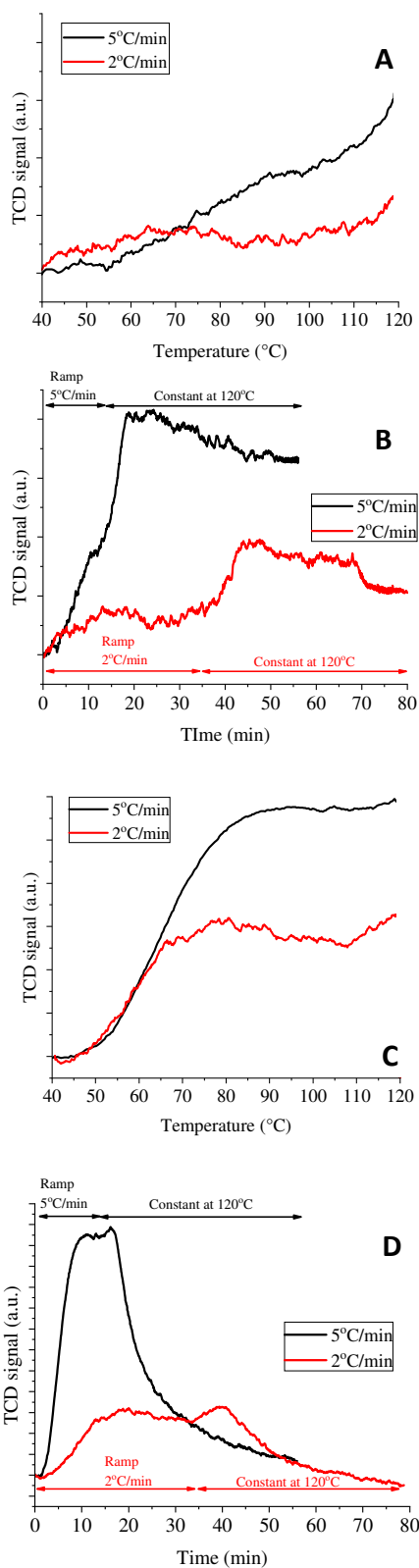


Figure 5. TPD measurements for GO-COOH/Cu(*D*-valmet): a) CO₂ desorption function of temperature; b) CO₂ desorption function of time; c) NH₃ desorption function of temperature; d) NH₃ desorption function of time. Differences in the intensity of the signals are due to the different amounts of the catalysts have been analyzed.

The TPD analyses occurred without any damage of the complexes. Except NH₃ and CO₂ no other adsorbed species were evolved during the TPD measurements coupled with MS analyses. Figure S5 presents the time evolution of the raw (as-measured) signals for $m/z=15$, 17 and 18. The $m/z=17$ molecular peak of ammonia is susceptible to water interference (the relative intensity of $m/z = 17$ is around 22 % from $m/z=18$ in the mass spectrum of water), therefore a corrected intensity of $m/z=17$ signal was calculated by subtracting $0.22 \times (\text{intensity of } m/z=18)$ from the intensity of the raw $m/z=17$ signal (Figure S6). The time-evolution of the corrected $m/z=17$ signal (containing solely the ammonia contribution) should yet coincide with the $m/z=15$, that is a weak signal ($\sim 7.5\%$ the intensity of $m/z=17$) present only in the NH₃ mass spectrum. The superposition between the time-evolution of the corrected $m/z=17$ signal and $m/z=15$ (amplified by multiplication with a constant) is very good, proving that water interference has been eliminated. The stability of the catalysts is as well demonstrated (see also figures S19-S21 for DTG measurements).

The stability of the complexes has also been demonstrated by the SEM and EDX analyses of the fresh and tested GO-COOH/Cu(*valmet*) catalysts (Figures 6-9). This no evidence of the catalysts decomposition, no agglomeration of copper and no change in the relative Cu/S ratio provided very good arguments in this sense.

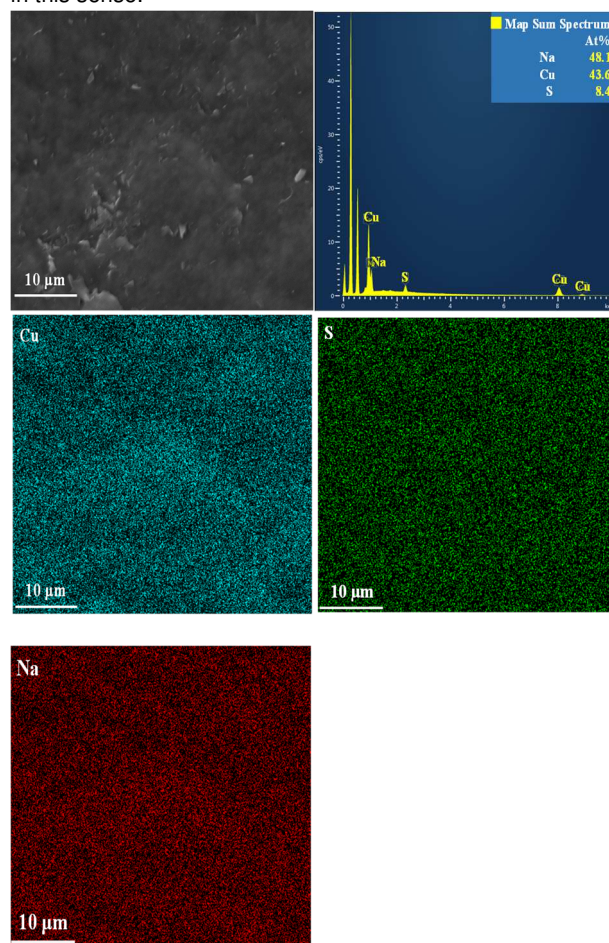


Figure 6. SEM and EDX spectra measurements for fresh Cu/GrO – L (10µm scale)

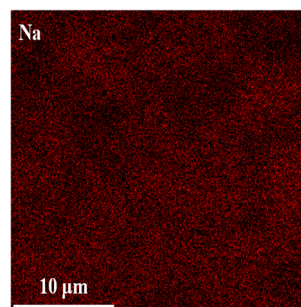
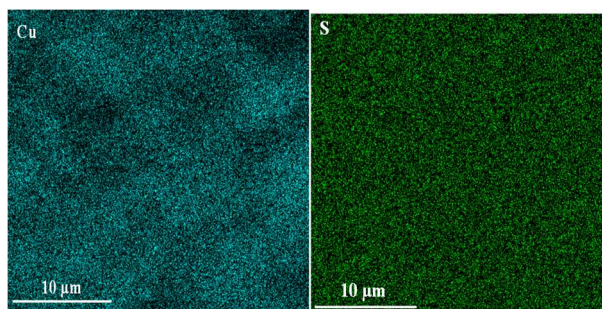
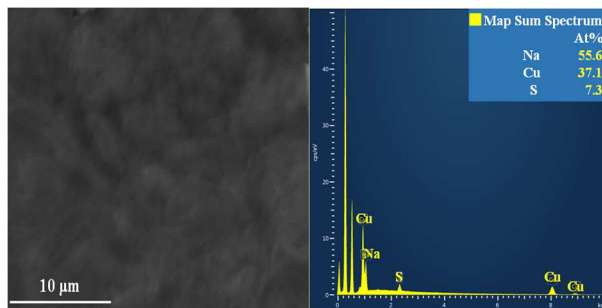
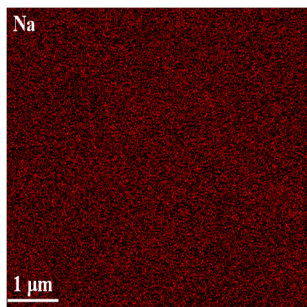
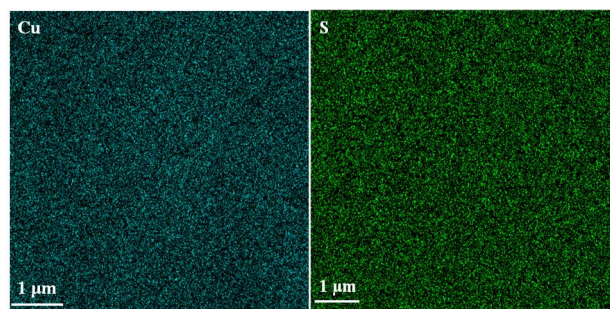
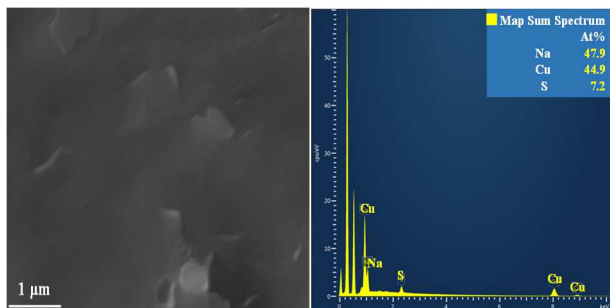


Figure 7. SEM and EDX spectra measurements for fresh GO-COOH-Cu-valmet-L (1 μm scale).

Figure 8. SEM and EDX spectra measurements for tested GO-COOH-Cu-valmet-D (10 μm scale).

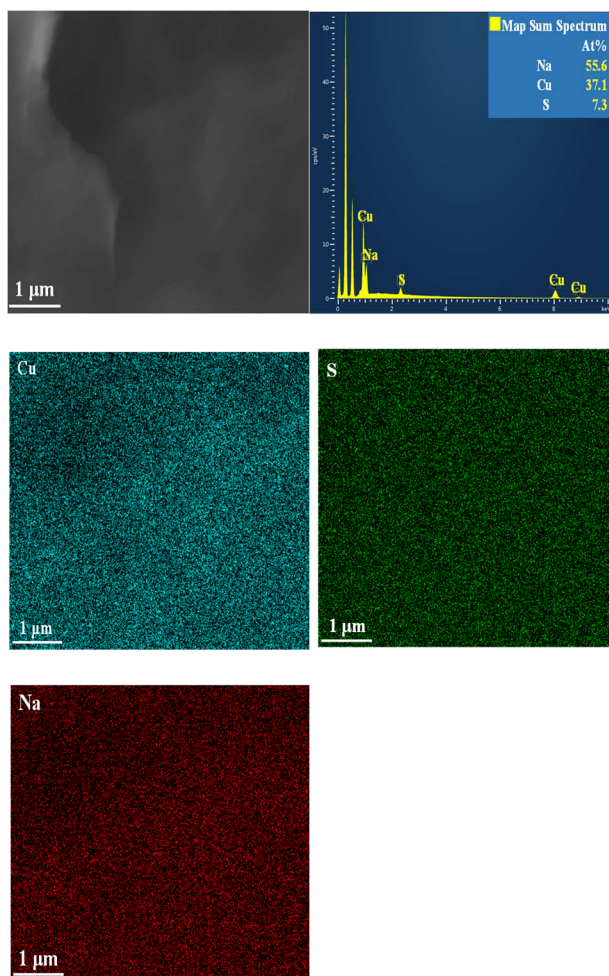


Figure 9. SEM and EDX spectra measurements for tested GO-COOH-Cu-valmet-D (1 μm scale).

Catalytic behavior

Henry reaction: Experiments carried out at RT, irrespective of the structure/composition of the utilized catalyst and the solvent, occurred with no conversion. Further increase of the temperature at only 60 °C changed the catalytic behavior. In water, using the ligand itself as an organo-catalyst led to a rather small conversion but to an excellent enantioselectivity (~97%, Table 1, entries 1 and 2, Figures S7-S13). Complexation of copper by the ligand enhanced the conversion, however with an important depletion of the enantioselectivity (ee of 62%, Table 1, entry 3). Quite surprising, under similar conditions, the association of the same complex with GO led to a spectacular increase of the conversion (92.5%, with an ee of 95.8%, Table 1, entry 4). Replacing benzaldehyde with 4-hydroxy-benzaldehyde led to a much smaller conversion (7.8%) while the enantioselectivity increased to 98.6%. Under these conditions, blank experiments without catalysts showed no conversion. All these results are in concordance to the acid/base properties of these catalysts and may assign the catalytic behavior to the Lewis base/acid sites in a close proximity of a stereogenic center. Reference CuO-GO catalyst exhibited no catalytic activity in this reaction.

Literature already reported several examples of the increase of the catalyst enantioselectivity as an effect of the ligand immobilization. [38-40] Such an effect is associated either to a post-capping or non-covalent interaction affording more effective substrate-ligand interplay. In our case we expect that the immobilization affords a better availability to the asymmetric active site of the catalyst.

We have no evidence of leaching the copper ions or complex in the solution. Both the analytic results and catalytic tests on the recyclability of the catalysts demonstrated that the catalyst's reactivity has been preserved during five consecutive reactions with no measurable leaching of copper metal or loss in the reactivity. Thus, no cocktail-type catalysis has been identified.

Table 1. Catalytic results in the Henry reaction.

Entry	Catalyst	Temp. (°C)	Time (h)	Solvent	Conversion. (%)	ee (%)
1	L-Valmet	60	24	Water	8.0	97.6
2	D-Valmet	60	24	Water	8.5	96.7
3	Cu(L-Valmet)·xH ₂ O x<1	60	24	Water	39.0	62.0
4	GO/Cu(L-Valmet)·xH ₂ O x<1	60	24	Water	92.5	95.8
5	GO/Cu(L-Valmet)·xH ₂ O x<1	60	24	MeOH	76.2	94.8
6	GOCOOH	60	24	Water	0	0
7	GO/Cu(L-Valmet)(H ₂ O)	60	24	Water	27.3	38.6
8	CuO/GO	60	24	Water	0	0
9	Blank	70	36	Water	0	0
10	GO/Cu(L-Valmet)·xH ₂ O x<1	60	24	Water	7.8.	98.6

benzaldehyde (1 mmole, 100 μl) and nitromethane (10 mmoles, 535 μl), 2 mL solvent, 20 mg catalyst; *4-hydroxybenzaldehyde benzaldehyde (1 mmole, 100 μl) and nitromethane (10 mmoles, 535 μl), 2 mL solvent, 20 mg catalyst

Cyanosilylation reaction: Reactions carried out with GO occurred with no conversion. The two metal complexes, *ie* Cu(L-Valmet)(H₂O) and Cu(D-Valmet)(H₂O) afforded high conversions even at room temperature that is in a good accordance to their base properties. However, part of the coupling product was hydrolyzed to cyanohydrins as an effect of the presence of remnant water coordinated molecules after drying (Table 2, entries 1 and 2, Figures S14, S15). The participation of this water molecule in the hydrolysis of α-(trimethylsilyl)phenylacetone nitrile was confirmed at the increase of the temperature where the ratio between the two products

increases as an effect of the increase of the conversion, water hydrolyzing the same quantity compound (Table 2, entries 3 and 4). While the asymmetry of the ligand had no effect upon the stereoselectivity of the reaction, the collected results indicated the hydrolysis of α -(trimethylsilyl)phenylacetone nitrile was somehow limited working with *L* complex.

The formation of the racemic can also be explained by the fact that the activated catalyst possesses an unsaturated Cu center (Lewis acid active site) which makes this reaction feasible. Thus, an interesting aspect of this catalyst is that it can be used for both types of reactions, *ie* base catalyzed (taking N as active site) and, as well, as acid catalyzed reactions (taking Lewis Cu as active site).

Immobilization of these complexes on GO occurred with either no catalytic reaction (Table 2, entries 5 and 6), or with a small conversion (Table 2, entries 7 and 8) where α -(trimethylsilyl)phenylacetone nitrile was completely hydrolyzed to cyanohydrin.

Table 2. Catalytic performances with Cu(Valmet) complexes in the cyanosilylation reaction.

Entry	Catalyst	Temp. (°C)	Time (h)	Conv. (%)	Molar Ratio A/B
1	Cu(<i>L</i> -Valmet)·xH ₂ O; x<1	RT	24	97.0	11.9:1
2	Cu(<i>D</i> -Valmet)·xH ₂ O; x<1	RT	24	97.3	13.4:1
3	Cu(<i>L</i> -Valmet)·xH ₂ O; x<1	80	24	100	12.9:1
4	Cu(<i>D</i> -Valmet)·xH ₂ O; x<1	80	24	100	14.0:1
5	GO/Cu(<i>L</i> -Valmet)(H ₂ O)	RT	24	0	-
6	GO/Cu(<i>D</i> -Valmet)(H ₂ O)	RT	24	0	-
7	GO/Cu(<i>L</i> -Valmet)(H ₂ O)	80	24	24.4	0:100
8	GO/Cu(<i>D</i> -Valmet)(H ₂ O)	80	24	25.0	0:100

0.5 mmoles benzaldehyde, 1 mmol TMSCN, solvent-free conditions, 20 mg catalyst; A:: Phenyl-trimethyl-silyloxy-acetonitrile and B: Benzaldehyde cyanohydrin.

Aldol Reaction: The Aldol reaction occurred even in the absence of a catalyst but with much smaller reaction rates (Table 3, Entries 1-7). Very small conversions were measured in the blank experiments carried out at room temperature, after 7 days, irrespective of the cyclohexanone/benzaldehyde ratio (Table 3, Entries 1 and 4). The main reaction product was the mono-condensation compound. The increase of the temperature at 120 °C led to an increase of the reaction rate which remained however small (Table 3, Entries 2 and 3). Under these conditions, cyclohexanone has been especially converted to the *di*-condensation product (Figures S16, S17). Working in an inert atmosphere, and similar reaction conditions, did not produce any essential change in the conversion and selectivity (Table 3, Entries 5 and 6). However, the addition of H₂O₂ to the reaction mixture enhanced the conversion while the selectivity of the

reaction was mainly orientated to the *mono*-condensation product (Table 3, Entry 7).

Experiments taking the ligand as organo-catalyst led to higher reaction rates where the conversion increased with the temperature while the selectivity to the *di*-condensation product paralleled it (Table 3, Entries 9-17). The inhibitory effect of heptane has been preserved (Table 3, Entry 13). Also important to notice, the differences between the two stereoisomers (*D*-valmet and *L*-valmet) acting as organocatalysts were very small (Table 3, Entries 12 and 17).

Complexating copper by these ligands (Table 3, Entries 18-19) led to a diminution of the conversion compared to the uncomplexated ligands that also corresponded to an increased selectivity to the *mono*-condensated product. Further, the immobilization of these complexes onto GO produced only a slight decrease in the conversion without any essential change in the selectivity (Table 3, Entries 20-21). GO support, due to the presence of the oxygenated functionalities exhibiting mixed acid and base properties also afforded a catalytic aldol reaction with a quit equilibrated ratio between the two products (Table 3, Entry 8). The comparison with the strongly acid H-ZSM-5 zeolite (Table 3, Entry 24) and acid Mg-Al-Y mixed oxide (Table 3, Entry 23) or base MgO (Table 3, Entry 22), which exhibit stronger acid or base properties, confirms the participation of the different functionalities of GO in this reaction. Pretty strong acid and base catalysts such as HZSM-5, mixed oxides or MgO orientate the reaction to the *di*-condensated product while weaker strengths such as GO to a mixture of these products.

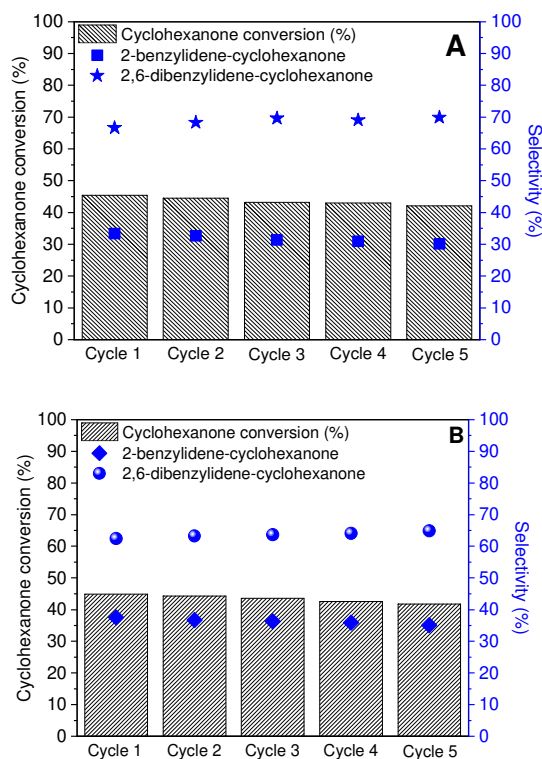


Figure 10. Recycling catalytic results for aldol condensation in the presence of: A. GO/(Cu-*D*-valmet); and B. GO/(Cu-*L*-valmet) catalysts. 20 mg catalyst

Results presented in Figure 10 confirm the recyclability of both the GO/(Cu-*D*-valmet) (A) and GO/(Cu-*L*-valmet) (B) catalysts. These are also in line with the electron microscopy analysis of the fresh and recovered catalyst.

Conclusion

L- and *D*-valmet ligands exhibit base properties and in consequence they may act as homogeneous organocatalysts. Further, Cu-complexed by valmet (*L* and *D*) behave as homogeneous catalysts for different reactions in which the active species are associated with either basic nitrogen in a close proximity of a stereogenic centre or to the free of nitrogen complexed copper. For the reaction of benzaldehyde and nitromethane the ligand plays the dominant role affording an asymmetric Henry reaction in water. The complexation of copper by these ligands enhanced the conversion, but with the price of an important depletion of the enantioselectivity. Rather surprising, the association of the same complex with GO led to a spectacular increase of the conversion (92.5%, with an ee of 95.8%).

For the case of cyanosilylation the active species is the free of nitrogen complexed copper. Thus, the formation of the racemic can be explained by the involvement of an unsaturated Cu center (Lewis active sites) which makes the reaction feasible but not stereoselective. The two metal complexes, *ie* Cu(*L*-Valmet)(H₂O) and Cu(*D*-Valmet)(H₂O) afforded high conversions even at room temperature, however, part of the coupling product being hydrolyzed to cyanohydrins as an effect of the presence of remnant water coordinated molecules, after drying. The participation of this water in the hydrolysis of α -(trimethylsilyl)-phenylacetonitrile was confirmed at the increase of the temperature where the ratio between the two products increases as an effect of the increase of the conversion. The immobilization of these complexes on GO occurred with either an inhibition of the activity or with a small conversion where α -(trimethylsilyl)-phenylacetonitrile was completely hydrolyzed to cyanohydrin.

Finally the base properties of these ligands were also demonstrated in the Aldol reaction. Complexating copper by these ligands led to a diminution of the conversion compared to the un-complexed ligands that also corresponded to an increased selectivity to the mono-condensated product. Further, the immobilization of these complexes onto GO produced only a slight decrease in the conversion without any essential change in the selectivity. GO support, due to the presence of the oxygenated functionalities exhibiting mixed acid and base properties, also afforded a catalytic aldol reaction with a quit equilibrated ratio between the two products.

In conclusion, valmet is a reliable ligand affording itself stereoselective organocatalytic reactions and, after complexation of copper, an effective cyanosilylation. The heterogeneization of such complexes generates effective heterogeneous catalysts for aldol coupling as well.

Table 3. Comparative Aldol coupling of cyclohexanone with benzaldehyde under non-catalytic and catalyzed reactions by *D*- and *L*-valmet ligands, Cu complexed by ligands and immobilized complexes also in comparison with inorganic base and acid catalysts.

Entry	Catalyst	Conversion of Cyclohexanone (%)	Selectivity (%)		Reaction conditions
			2-benzylidene-cyclohexanone	2,6-dibenzylidene-cyclohexanone	
1	No	5.4	78.0	22.0	7 days; RT; under air; CH/B=1/2
2	No	16.6	5.5	94.5	2 h; 120 °C; under air; CH/B=1/2
3	No	21.1	7.3	92.7	4 h; 120 °C; under air; CH/B=1/2
4	No	4.9	96.1	3.9	7 days; RT; under air; CH/B=2.5/1
5	No	13.5	9.8	90.2	2 h; 120 °C; under N ₂ ; CH/B=1/2
6	No	16.9	7.3	92.7	2 h; 120 °C; under He; CH/B=1/2
7	No	44.7	69.1	30.9	2 h; 120 °C; 1 mL H ₂ O ₂ ; CH/B=1/2
8	GO	39.1	48.4	51.6	2 h; 120 °C; under air; CH/B=1/2
9	<i>D</i> -valmet	37.1	0	100	7 days; RT; under air; CH/B=1/2
10	<i>D</i> -valmet	60.7	29.1	70.9	2 h; 80 °C; under air; CH/B=1/2
11	<i>D</i> -valmet	23.5	3.3	96.7	2 h; 80 °C; under air; CH/B=1/2; 0.5 mL heptane
12	<i>D</i> -valmet	70.2	17.6	82.4	2 h; 120 °C; under air; CH/B=1/2
13	<i>D</i> -valmet	28.1	0	100	2 h; 120 °C; under air; CH/B=1/2; 0.5 mL heptane
14	<i>D</i> -valmet	29.6	15.2	84.8	2 h; 120 °C; under air; CH/B=1/5
15	<i>D</i> -valmet	0.01	2.0	98.0	2 h; 80 °C; under air; CH/B=2.5/1
16	<i>D</i> -valmet	0.5	6.7	93.3	2 h; 120 °C; under air; CH/B=2.5/1
17	<i>L</i> -valmet	71.1	19.1	80.9	2 h; 120 °C; under air; CH/B=1/2
18	[Cu(<i>D</i> -valmet)(H ₂ O)]·H ₂ O	48.6	34.4	65.6	2 h; 120 °C; under air; CH/B=1/2
19	[Cu(<i>L</i> -valmet)(H ₂ O)]·H ₂ O	47.7	34.0	66.0	2 h; 120 °C; under air; CH/B=1/2
20	GO/(Cu- <i>D</i> -valmet)	45.5	33.3	66.7	2 h; 120 °C; under air; CH/B=1/2
21	GO/(Cu- <i>L</i> -valmet)	44.9	37.6	62.4	2 h; 120 °C; under air; CH/B=1/2
22	MgO	31.4	3.0	97.0	2 h; 120 °C; under air; CH/B=1/2
23	Mg/Al/Y mixed oxide	30.8	1.6	98.4	2 h; 120 °C; under air; CH/B=1/2; 1 mL H ₂ O ₂
24	H-ZSM-5	24.2	8.0	92.0	2 h; 120 °C; under air; CH/B=1/2

20 mg catalyst, CH=cyclohexanone/B=benzaldehyde is molar ratio. All reactions were carried out in batch conditions.

Experimental Section

Synthesis of the catalysts

Synthesis of ligands and complexes: The chiral compounds [Cu(*D*-valmet)(H₂O)]·H₂O, [Cu(*L*-valmet)(H₂O)]·H₂O and their precursors, [Na(*L*-valmetH)]·H₂O and [Na(*D*-valmetH)]·H₂O, were synthesized according to a reported procedure.^[29] The Schiff base ligands were prepared by adding 0.15 mmoles of *o*-vanillin to a methanolic solution consisting of 0.5 mmoles of *L*-methionine, respectively *D*-methionine and 0.5 mmoles NaOH. The yellow solution was stirred one hour and left to crystallize at room temperature. After few days, yellow crystals were isolated by filtration and dried in air. The copper complexes were then synthesized by pouring a methanolic solution of Cu(CH₃COO)₂·H₂O over a mixture of water and methanol (1/5, v/v) in which the corresponding precursor was dissolved and the solution was stirred for one hour. After several days, blue greenish crystals were obtained from slowly evaporation of the green solution at room temperature. The compounds were isolated by filtration and then dried in air.

Synthesis of GO and GO-COOH: Graphene oxide (GO) was prepared using the modified Hummers' method as previously reported in the literature.^[30] Thereby, 0.5 g graphite were added to a solution prepared by mixing 60 mL H₂SO₄, 98% with 7 mL H₃PO₄, under continuous stirring conditions. Then, 2.933 g KMnO₄ were slowly added to this solution and after another 6 hours of stirring the colour of the mixture turned to dark green when 1.5 mL of hydrogen peroxide were dropwise added. Finally, a solution of 25 mL HCl and 70 mL H₂O was added to this mixture after 10 minutes stirring. The supernatant was separated by centrifugation and washed three times with water and hydrochloric acid. The resulted graphene oxide was dried in an oven at 50 °C for 12 h. The functionalization of the graphene oxide surface was achieved taking a derivatization method with chloroacetic acid (GO-COOH).^[31]

Synthesis of GO-COOH/Cu(*D*-valmet) and GO-COOH/Cu(*L*-valmet) ligands: Carboxylated graphene oxide was utilized as a support to immobilize [Cu(*D*-valmet)(H₂O)]·H₂O and [Cu(*L*-valmet)(H₂O)]·H₂O complexes. Accordingly, a methanolic solution of the copper complex (0.15 g [Cu(*D*-valmet)(H₂O)]·H₂O or [Cu(*L*-valmet)(H₂O)]·H₂O) was dropwise added to the support suspension (0.1 g/50 mL methanol) and the mixture was stirred for 24 hours at room temperature. The final products (GO-COOH/Cu(*D*-valmet) and GO-COOH/Cu(*L*-valmet)) were separated by centrifugation and washed several times with methanol, then dried in an oven at 40 °C for 12 hours.

Synthesis of Mg/Al/Y mixed oxide: Mg_{0.75}Al_{0.125}Y_{0.125}-LDH precursor was prepared by a mechano-chemical method^[32] using established amounts of Mg(NO₃)₂·6H₂O, Al(NO₃)₃·9H₂O and Y(NO₃)₃·6H₂O (at a molar ratio Mg/Al+Y=3) dispersed in 100 mL tetra-methyl ammonium hydroxide (25 wt. % in H₂O). The mixture was directly milled in a RM 200 Mortar Grinder for 1h at 100 rpm at a constant pH of 10. After that, the whole content was filtered and washed with distilled water (~250 mL) until the pH 7. The cake was dried at 90 °C for 24 h in air atmosphere and further calcinated in air atmosphere, at 460 °C for 18 h.

MgO was purchased from Sigma-Aldrich having >99.99%. Before being used in the reaction, it underwent a similar heat treatment as for the MgAlY-mixed oxides. H-ZSM-5 also purchased from Sigma-Aldrich has been activated by calcination in air under similar conditions to Mg/Al/Y and MgO.

Characterization of the catalysts

Elemental analysis: The nitrogen and sulfur elemental analysis was performed on an Eurovector Elemental Analyzer using sulphanimide B2131-2 as reference (0.4-1.44 mg). The sample was placed in a tin capsule and weighed using a microbalance (1.0420 mg sample). Helium 5.0 was used as carrier gas. Set-up conditions of the method were: carrier- 110 kPa, purge-80 mL/min, oxygen-15 mL, ΔpO₂=35 kPa, oxidation time-6.6 sec, sample delay- 5 sec, front furnace-980 °C. The temperature in the GC oven was set to 100 °C. Gas chromatography coupled with a thermal conductivity detector (TCD) was used to separate and identify the resulted gases, respectively. The results were interpreted using the 5.1 Callidus software. Copper has been analyzed using Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) on an Agilent 5110 SVDV ICP-OES. The sample introduction system consisted of a seaspray glass concentric nebulizer, double-pass glass cyclonic spray chamber, and a standard single piece 1.8 mm internal diameter injector torch. The instrument operated at a max rinse time of 30 s, pump speed 12 rpm., RF power of 1.3 kW, auxiliary flow of 1 L min⁻¹, plasma flow of 12 L min⁻¹ and a nebulizer flow of 0.7 L min⁻¹.

Measurements of the acid-base properties: Acid-base properties of the investigated catalysts were measured by CO₂- and NH₃-TPD analyses. CO₂-TPD and NH₃-TPD experiments were carried out in an AutoChem II 2920 station from Micromeritics. The samples, placed in a U-shaped quartz reactor with an inner diameter of 0.5 cm, were pretreated under He (Purity 5.0, from Linde) at 120 °C (for organic samples) or 450 °C (for inorganic samples) for 1 h and then exposed to a flow of CO₂ or NH₃ (from SIAD) for 1 h. After that, the samples were purged with a flow of He (50 mL·min⁻¹) for 20 min at 25 °C in order to remove the weakly adsorbed species. TPD was then started, with a heating rate of 2 or 5 °C·min⁻¹ till 120 or 450 °C, respectively. The desorbed products were analysed with a TC detector. The desorbed NH₃ or CO₂, expressed as mmols per gram of catalyst, was determined using a calibration curve.

NH₃-TPD experiments monitored by MS were performed using a Thermo Scientific (Trace 1300 ISQ) GC-MS setup using He carrier gas, by packing ~50 mg GO-COOH-Cu-valmet-L catalyst sample inside the liner. The chromatographic column was replaced by a short (~30 cm) silica capillary connecting the inlet to the MS transfer line. An initial degassing step was performed by heating and maintaining the sample at 120 °C for 30 min. under He flow, followed by free cooling at room temperature. A mixture of 10% (vol.) NH₃ in He was then passed for one hour through the GO-COOH-Cu-valmet-L catalyst sample by connecting the gas source to the glass body of a 10 μL syringe whose needle pierces the inlet septum, reaching thus the middle of the packed catalyst bed inside the GC liner. The elimination of excess ammonia gas was performed by overnight He flushing of the inlet assembly. The desorption curves were recorded while heating with 5 °C/min from room temperature to an isothermal dwell of 120 °C, under a He flow. MS spectra were acquired for an m/z range from 10 to 50 with 0.8 seconds scanning time. The amount of the analyzed catalyst was in the range 0.02-0.06 g.

IR Spectra: DRIFT spectra were collected using a Bruker Tensor II spectrometer fitted with a Harrick Praying Mantis Diffuse Reflection Accessory. The spectra were a collection of 32 scans with a resolution 4 cm⁻¹ and atmospheric compensation was automatically applied. KBr was used as reference. Raman spectra were acquired in the spectral region from 150 to 4000 cm⁻¹. Raman analysis was carried out with a Horiba JobinYvon-Labram HR UV-Visible-NIR Raman Microscope using the excitation wavelengths of 325, 488, and 633 nm, respectively.

Scanning Electron Microscopy (SEM) images were recorded on a Hitachi S-4700 Cold Field Emission Gun Scanning Electron Microscope with a resolution of 1.5 nm. Elemental analysis and chemical mapping were carried out by Energy-dispersive X-ray Spectroscopy (EDS). An Oxford EDS system was employed to analyze elemental composition of the sample analyzed.

Powder X-ray diffraction: Powder X-ray diffraction (XRD) patterns were recorded on a Shimadzu XRD-7000 diffractometer using Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$, 40 kV, 40 mA) at a scanning speed of 0.10 degrees/min in the 10°–90° 2 θ range.

Catalytic tests

Henry reaction: Henry reaction was carried out in batch reactor conditions by placing a mixture of benzaldehyde (1 mmole, 100 μ l) and nitromethane (10 mmoles, 535 μ l) in 2 mL solvent in the presence of a specified amount of catalyst in a capped glass vial. The mixture has been stirred at 60 °C for 24 h. Upon removing the catalyst by centrifugation and filtration from the reaction mixture, the filtrate was evaporated under a vacuum to give the crude product.

Aldol condensation: Aldol condensation was carried out for 2 h at 120 °C by reacting a mixture of benzaldehyde (2 mmoles, ReagentPlus >99%, Sigma-Aldrich) and cyclohexanone (1 mmol >99%, Sigma-Aldrich) under batch and solvent-free conditions with a specified amount of catalyst (20 mg of catalyst, benzaldehyde/catalyst ratio of 10/1). At the end of reaction the catalyst was removed from the mixture by filtration.

Cynosilylation Reaction: Cynosilylation reaction was carried out in batch conditions by placing a mixture of benzaldehyde (0.5 mmoles) and TMSCN (1 mmol) under solvent-free condition with a specified amount of catalyst at room temperature for 24 h. For this reaction both the complexes were used as it is without the immobilization onto GO. Complexes were first activated under vacuum oven for 8 h at 80 °C in order to make the unsaturated Cu centre (Lewis active sites). Catalyst was removed with silica. Pale yellow oily product was obtained.

Analysis of the reactants and reaction products

Henry reaction: The conversion and enantioselectivity of the product in each run was determined by ¹H NMR spectroscopy and HPLC. For the HPLC analysis, the sample was mixed with an equal volume of the mobile phase for adjusting the polarity of the sample comparing to mobile phase. HPLC-DAD analysis was performed with a modular system (Agilent 1260) equipped with a chiralcel OD-H column and DAD detector. The HPLC-DAD system was set up for injecting 10 μ L sample and the analysis was performed at 25 °C with a flow rate of 0.8 mL·min⁻¹ in a mobile phase (85% n-hexane and 15% 2-propanol). The detection was performed at 254 nm. NMR spectra were recorded taking CDCl₃ as solvent on a Bruker Advance III Ultrashield Plus 500 MHz spectrometer, operating at 11.74 T, corresponding to the resonance frequency of 500.13 MHz for the ¹H nucleus, equipped with a direct detection four nuclei probe head and field gradients on z axis. Samples were analysed in 5 mm NMR tubes (Wilmad). The chemical shifts are reported in ppm. Typical parameters for ¹H NMR spectra were: 45° pulse, 8.3 s acquisition times, 8.01 kHz spectral window, 16 scans, 20 K data points, delay time 1 s. The average acquisition time of the ¹H NMR spectra was approximately 3 minutes. The resonance frequency for the ¹³C nucleus is 125.77 MHz, 45° pulse, 1.67 s acquisition times, 39.68 kHz spectral window, 1024 scans, 64 K data points, delay time 1 s. The average acquisition time of the ¹³C NMR spectra was approximately 50 minutes.

Aldol Condensation: The filtrate was analyzed using a GC K072320 Thermo Quest Chromatograph equipped with a FID detector and a capillary column of 30 m length with DB5 stationary phase. The reaction products were identified by mass spectrometer coupled chromatography, using a GC/MS/MS Varian Saturn 2100 T equipped with a CP-SIL 8 CB Low Bleed/MS column of 30 m length and 0.25 mm diameter. The reactions in the presence of hydrogen peroxide were carried out by

adding to the reaction mixture 1 mL of a H₂O₂ solution (30 % (w/w)), while with heptane 0.5 mL (anhydrous 99%, from Sigma-Aldrich). Nitrogen and helium (both of 99.999% purity) were from Linde. Tests with the inorganic catalysts utilized 40 mg of catalysts.

Cynosilylation Reaction: The conversion of benzaldehyde substrate and selectivity to products A and B were determined by ¹H-NMR analysis on the same Bruker Advance III Ultrashield Plus 500 MHz spectrometer considering typical signals of the compound A (¹H-NMR (500 MHz, CDCl₃, δ ppm): 7.47-7.36 (m, 5H, H-4, H-5, H-6, H-7 and H-8), 5.50 (s, 1H, H-2), 0.24 (s, 9H, -Si(CH₃)₃) and B (¹H-NMR (500 MHz, CDCl₃, δ ppm): 7.47-7.36 (m, 5H, H-4, H-5, H-6, H-7 and H-8), 5.53 (s, 1H, H-2).

Acknowledgements

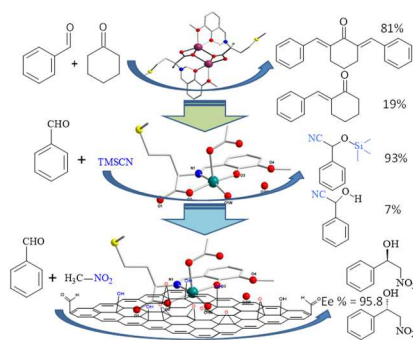
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Keywords: L- and D-valmet ligands as organocatalysts • Cu-complexed by valmet as homogeneous catalysts • heterogeneous GO immobilized Cu-complex catalysts • Henry, cyanosilylation and aldol reactions

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Entry for the Table of Contents



L- and *D*-valmet ligands prepared from the condensation of *o*-vanillin and *L*-, respectively, *D*-methionine exhibit a different catalytic behavior affording asymmetric Henry condensation, cyanosilylation reaction after complexation with copper or the Aldol reaction after the immobilization of these complexes onto GO.