ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2011, *56*(6), 675-679

CHIRAL BIS(OXAZOLINE)COPPER(II) COVALENTLY ANCHORED TO SINGLE WALL CARBON NANOTUBE AS RECOVERABLE CATALYST FOR ENANTIOSELECTIVE FRIEDEL-CRAFTS HYDROXYALKYLATION

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Received March 3, 2011

Preformed chiral bis(oxazoline)copper complex having a 4-aminobutyl linker in the *meso* carbon has been covalently attached to single wall carbon nanotubes (1 μm average length) through the carboxylic acid groups and the resulting material used as recoverable catalyst for the hydroxyalkylation of 1,3-dimethoxybenzene by ethyl trifluoropyruvate obtaining ee up to 97 %.

INTRODUCTION

Enantioselective reactions using chiral catalysts are the most powerful strategy in asymmetric synthesis.[1] Since the chiral ligands and catalysts are high valuable components, there is considerable interest in developing procedures for their recovery after the catalytic reaction and their reuse for consecutive runs. Anchoring successful homogeneous chiral catalysts in solid inorganic or polymeric supports has been one common methodology to obtain recoverable and reusable heterogeneous catalysts.[2] Heterogeneization of chiral catalysts may lead, however, to a decrease in activity due to the disturbance to the more favorable transition state producing the highest asymmetric induction.[3]

Complementary to heterogeneization, an alternative strategy consists in developing soluble, but recoverable catalytic systems by covalently anchoring a suitable derivative of the successful catalysts to a support soluble in a particular medium.[3-5] The approach for developing homogeneous, recoverable catalysts is based on the covalent modification of a given catalyst in such a way that the resulting derivative is highly soluble in a particular solvent, but insoluble in others.[5] Among the different approaches that have been reported, the most widely used are those in which derivatization renders the catalyst soluble in supercritical CO_2, perfluorinated solvents and ionic liquids.[4-10] Also covalent anchoring of the catalyst in low-molecular weight polymers such as polystyrenes and polyethylenglycols have been frequently employed.[11, 12]

In this context, herein, we illustrate a different approach to develop homogeneous, but recoverable catalysts by covalent anchoring of a

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chiral complex on single wall carbon nanotubes (SWCNTs). Suitably purified SWCNTs can form indefinitely persistent ink suspensions in different organic solvents such as DMF. In the purification process from the inorganic catalyst needed in the synthesis of the nanotubes by acid treatment, the nanotubes become shorter. This shortening is consequence of the creation of wall defects and subsequent rapid cutting of the tube through these defects with the formation of terminal carboxylic acid groups. Careful control of the conditions (temperature, time, sonication, etc.) and acid concentration can lead to SWCNTs of hundreds of nanometres in length.This shortening of the nanotubes increases their dispersability in water and organic solvents and makes them more suitable as support for homogeneous and recoverable catalysis.[13-15]

The long aspect ratio (hundreds of nanometers in length and about one nanometer in diameter) and high mass makes possible to fully recover the nanotubes from the suspension by filtration or centrifugation. This makes SWCNT suitable supports for their use in membrane reactors.[16] Precedents in which a carbapalladacycle complex and a chiral metal salen complex have been anchored to the carboxylic groups of the nanotube through peptide links have been previously reported.[17-19]

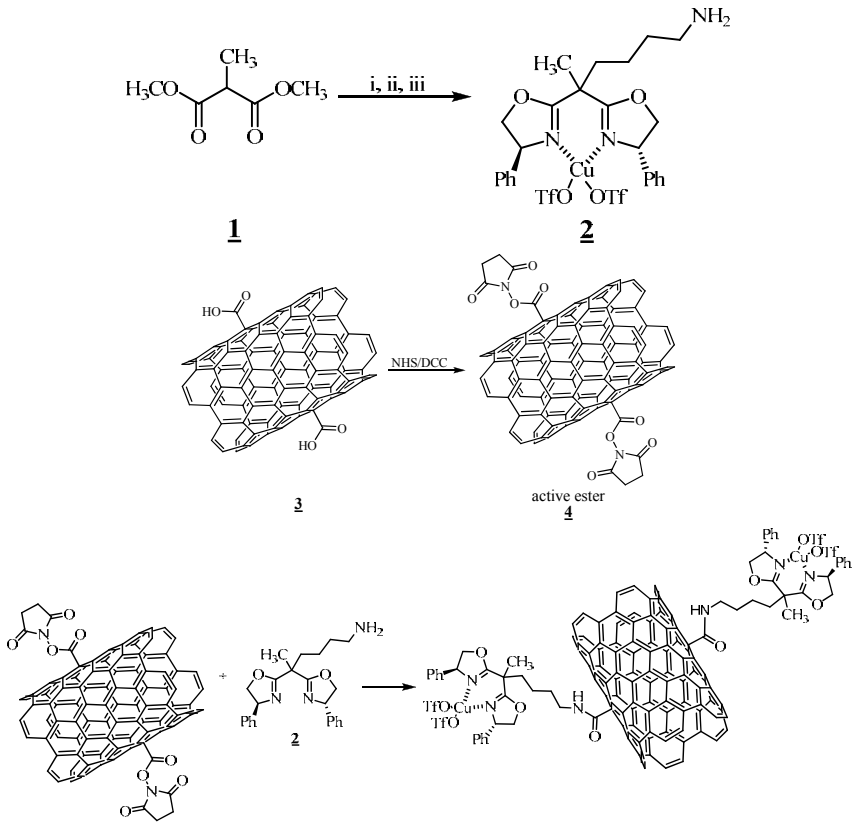
RESULTS AND DISCUSSION

In the present manuscript we describe the synthesis and catalytic activity of a chiral copper bisoxazolidine covalently anchored to the walls of SWNT. As it has been reported in homogeneous solution,[20-22] this metal complex anchored to SWNT exhibits a remarkable enantioselectivity towards the asymmetric Friedel-Crafts hydroxyalkylation of electron-rich aromatic compounds by reactive carbonylic compounds.

The route followed to anchor a bis(oxazoline)copper(II) complex to SWNT (CuL-SWNT) is indicated in Scheme 1. The key step is the formation of peptide bonds between the carboxylic groups present at the tips and wall defects of the SWNT and a ω-aminoalkyl bis(oxazoline) ligand. In order to form the amide bonds, the carboxylic groups of the SWNT were previously activated as N-hydroxysuccinimide esters using N,N`-dicyclohexylcarbodiimide as condensing agent. The chiral bisoxaline complex anchored to the SWNT was in turn prepared by metallation with copper(II) triflate of the corresponding pure bisoxazoline ligand. The bisoxazoline ligand was synthesized from dimethyl methylmalonate by alkylation with chlorhydrate of ω-chlorobutyronitrile and condensation with enantiomerically pure β-phenyl-β-aminoethanol, follow by a final hydrogenation of the nitrile group to amine. This bisoxazoline ligand synthesis parallels the route previously reported for analogous derivatives.[22] The length of the butylamine linker was selected to allow sufficient conformational freedom to the copper complex when bonded to SWNT. By having sufficient flexible and long linkers the chiral copper complex can have a spatial conformation similar to that found in solution far from the support surface. After formation of the copper(II) complex of bis(oxazoline), the complex was reacted with the N-hydoxysuccinimide ester of SWNT.

The resulting sample was characterized by TEM, Raman spectroscopy and chemical analyses. Fig. 1 shows TEM images of the resulting CuL-SWNT complex. As it can be seen there, the typical morphology of SWNT is still preserved upon functionalization. The average length of the SWNT scaffolds is around 1 μm. Notably, agglomeration and bundle formation, typically occurring in pristine SWNT samples, has been largely reduced as consequence of covalent functionalization.

Raman spectroscopy shows the expected bands due to the tangential vibration, wall defects and radial breathing mode appearing at 1600, 1350 and 180 cm^{-1}, respectively. The Raman spectra using the 730 nm diode laser is shown in Fig. 2. Compared to pristine SWNT, functionalization causes a decrease of the tangential vibration intensity and a concomitant increases in the broad band at 1350 cm^{1} associate to the wall defects. Importantly, the peak at 180 cm^{-1} specific of single walled carbon nanotubes is still present in the CuL-SWNT sample, proving again that the morphology of the nanotube is preserved in the functionalization steps. No peaks that can be attributed to the complex were observed in the Raman spectrum of CuL-SWNT. This fact is not totally unexpected in view of the literature precedents and the low percentage of CuL complex present in the sample.



Scheme 1 – Synthetic route for the preparation of CuL-SWNT:
i) reaction with $Br(CH_2)_3$ CN; ii) β-phenil-α-aminoethanol and hydrogenation; iii) $Cu(CF_3SO_3)_2$.

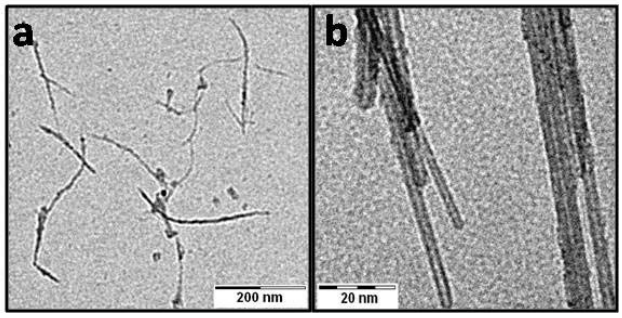


Fig. 1 – TEM images of CuL-SWNT complex.

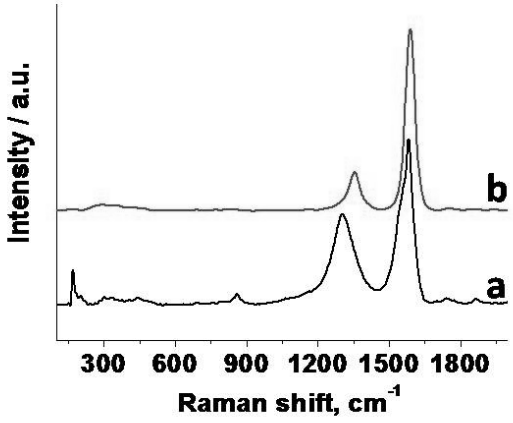


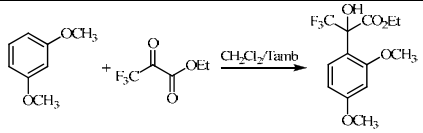
Fig. 2 – Raman spectra of SWNT (a) and CuL-SWNT (b).

The presence of the CuL complex attached to the SWNT was determined by elemental chemical analyses of N and Cu. Since the parent SWNT does not contain N, the percentage of N in CuL-SWNT can serve to quantify the ligand attached to the sample. Copper analysis matches the expected percentage based on the N content and the stoichiometry of the bis(oxazoline)complex. Thus, the amount of CuL corresponds to one complex every 385 carbons.

The catalytic activity of the CuL-SWNT sample was tested for the room temperature hydroxyalkylation of 1,3-dimethoxybenzene by ethyl trifluoropiruvate. The only product observed was the expected ethyl 2-(2,4-dimethoxyphenyl)-3,3,3-trifluoro-2-hydroxypropanoate with a very high enantiomeric excess and the same configuration at C-2 as that found for the analogous complex in homogeneous solution.Table 1 lists the catalytic results. Importantly, after the reaction, the catalyst was recovered by filtration through a standard 0.2 μm Nylon filter and reused in a subsequent run under the same conditions. As it can be seen in Table 1, the catalyst could be reused five times with minor decrease in the conversion and still exhibiting very high ee. The catalyst activity decay can be due to unavoidable losses during the recovery work-up.

Table 1

Results of the enantioselective hydroxyalkylation of 1, 3-dimethoxybenzene with ethyl trifluoropyruvate catalyzed by CuL-SWNT



6 7 8

Nr of uses	Yield (%)	ee (%)
1	43	97
2	45	96
3	39	92
4	40	90
5	38	90

[a] Reaction conditions: the reaction was carried out under an atmosphere of N_2 using anhydrous solvents and flame-dried glassware.

EXPERIMENTAL

Synthesis of 2-(4-cyanobutyl)-2-methylmalonic acid. A solution of 68.43 mmol of methyl malonate (Aldrich) and 82.11 mmol of NaH in 40 mL THF is added to 68.43 mmol of 4-bromobutanenitrile. The mixture was stirred at room temperature for 1.5 h. After this time the solvent was removed under vaccum and the residue was dissolved in 20 mL of chloroform and washed with 0.1 M aqueous HCl. The organic phase was dried using anhydrous $MgSO_4$ and concentrated in vacuo. Dimethyl 2-4-(cyanobutyl)-2-methylmalonate was recrystallized with ethanol. This ester was hydrolized at r.t. by treating with 25 wt% KOH in EtOH for 1.5 h. Then, EtOH was removed under vaccum and the residue dissolved in water and neutralized at pH 7. The aqueous solution was washed with CH_2Cl_2 to remove residual dimethyl ester, acidified to pH 3 and the malonic acid derivative extracted with ethyl acetate (4×30 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Synthesis of 2-(4-cyanobutyl)-2-methylmalonyl dichloride. 50 mmol of thionyl chloride were added dropwise at 0 ^oC to 25.9 mmol of 2-(4-cyanobutyl)-2-methylmalonic acid in 25 mL of dichloromethane. After completing the addition the mixture was gradually heated at 85 ^oC and then this temperature maintained for 6 h. At this time, the excess of $SOCl_2$ was removed under reduced pressure and the residue dissolved in CH_2Cl_2. The solution was washed with water and then dried over anhydrous $MgSO_4$.

Synthesis of 1-(4-cyanobutyl)-N,N`-bis(2-hydroxyl-1-phenhylethyl)-2-methylmalonamide. 56 mmol of triethylamine were dropwise added during 20 min into a solution of 40 mmol of D(-)-α-phenylglycinol in 50 mL of CH_2Cl_2 cooled in a ice bath. Then, a solution of 18.24 mmol of 2-(4-cyanobutyl)-2-methylmalonyl dichloride in 10 ml of CH_2Cl_2 was dropwise added for 20 min. The reaction was stirred at room temperature for 2 h. Then the solution was washed with 2 M aqueous HCl and with a saturated aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum.

Synthesis of 4,4-bis[(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)-1-butanamine. A solution of methanesulfonyl chloride (8,7 mmol) in 2 ml of dichloromethane was dropped during 20 min to a solution of the 1-(4-cyanobutyl)-N,N`-bis(2-hydroxy-1-phenylethyl)-2-methylmalonamide (2 mmol) and triethylamine (10 mmol) in 10 mL of CH_2Cl_2 at -5ºC. The reaction was followed by thin layer chromathography and after completion the mixture was washed with a saturated aqueous NH_4Cl solution (10 mL). The organic phase was

separated and the aqueous phase extracted with CH_2Cl_2 (2×10 mL). The organic extracts were combined, washed with water and dried over $MgSO_4$. After filtration the mixture was concentrated in vaccuo and submited to catalytic reduction by H_2 over Pd/C (5%) to obtain the target bisoxazoline ligand (L).

L (bisoxazoline): yield 74 %. Yellow oil. IR: 3062; 2931; 28665; 2852; 2840; 1463; 1352 cm^{-1} ^{1}HNMR: δ 9,58 (t, J= 14,02 Hz, 2H), 7,23–7,32 (m, 10 H), 5,22 (dd, J=11; 9 Hz, 2H), 5,01 (dd, J= 11; 9 Hz, 2H), 4,65 (t, 8,2 Hz, 1H), 4,13 (t, 8,0 Hz, 1H), 2,19 (m, 2H), 2,10 (m,2H), 1,53 (m, 2H), 1,51 (t, J=8,1 Hz, 2H), 1,56 (s, 3H), elemental analysis $C_{24}H_{29}N_3O_2$ calculed: C 73,56 %, H 7,41.%, N 10,73 %, O 8,17 % Found : C 73,60 %, H 7,50.%, N 11,01 %, O 7,89 %.

Catalyst preparation. *N*-hydroxysuccinimide (3.3 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (3.3mmol) were added over a suspension of carbon nanotubes in 10 mL of CH_2Cl_2. After vigorous stirring for 3 hours, a solution of the bisoxazoline in dichloromethane was added and left under agitation overnight. After filtration of the solid the black material was submitted to backward flow of chloroform in the soxhlet for 3 h and dried in vacuo. The heterogeneous catalyst was characterized by elemental analysis: C 85,10 %, H 4,95 %, N 5,90%, O 4,05%, calculed C : 82,97%; H: 5.19%; N:3,61%; O: 8,23% . Then, the solid (100 mg) was added to a solution of 36,2 mg of $Cu(OTf)_2$ in 10 mL of methanol. The mixture was left ovrnight under vigorous stirring and then filtered and then extracted in continuous with Sohlet using first methanol and then chloroform as solvents. The determination of Cu was carried out by atomic absorption.

Catalytic tests. The reactions were carried out under nitrogen atmosphere using anhydrous solvents. CuL-SWCNT (18,1 mg) was added in a "flame dried" Schlenk tube and vacuum was performed during 1 h. Then a solution of ethyl trifluoropyruvate (85 mg, 0,5 mmol) and 1,3-dimethoxybenzene (76 mg, 0,55 mmol) in 1 mL of dry dichloromethane was added under stirring during 24 h and the reaction mixture was allowed to reach room pressure. The crude reaction was filtered and the product purified by column chromatography using silica as stationary phase (eluent: Et_2O/hexane; 40/60 v/v). The enantioselectivity (ee) was determined by HPLC using a chiral column: ChromTech Ltd, CHIRAL-AGP TM (100-4 mm), 5 μm, chain HPLC PERKIN ELMER 200 SERIES.

CONCLUSION

In summary, covalent functionalization of SWCNTs is a topic of much current interest mostly in the field of optoelectronic materials and nanotechnology. In the present report, we show that due to the remarkable stability of their colloidal suspensions and the possibility to recover the suspended material by centrifugation or filtration. These materials are also very useful in catalysis to develop soluble and recoverable catalysts. This concept has been herein demonstrated by attaching a chiral bis(oxazoline)copper complex and showing that the resulting material exhibits a very high enantioselectivity for the hydroxyalkylation of electron rich aromatics.

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