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Synthesis of Vasorelaxaing 1,4-Disubstituted 1,2,3-Triazoles Catalyzed by a 4′-Phenyl-2,2′:6′,2″-Terpyridine Copper(II) Complex Immobilized on Activated Multiwalled Carbon Nanotubes

Hashem Sharghi,*[a] Sakineh Ebrahimpourmoghaddam,[a] Mohammad Mahdi Doroodmand,*[a] and Azar Purkhosrow[b]

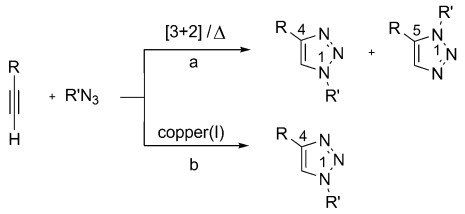
Abstract: A supported catalyst has been prepared by immobilization of a copper(II) complex of 4′-phenyl-2,2′:6′,2″-terpyridine on activated multiwalled carbon nanotubes [AMWCNTs-O-Cu^{II}-PhTPY]. This heterogeneous catalyst was characterized by scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), inductively coupled plasma (ICP) analysis, UV/vis and FT-IR techniques. To ensure the efficiency and fidelity of the copper species, the implementation of three-component strategies in click chemistry was tested. The catalyst enabled the development of one-pot, two-step, mild, and environmentally benign syntheses of diversely decorated 1,2,3-triazoles from alkynes, epoxides or benzyl/alkyl halides, and sodium azide in water. The complex has high catalytic activity, regioselectivity, and was recycled five successive times. In another experiment, the vasorelaxing effect of the triazole products was studied in isolated rat thoracic aorta. All of the selected compounds are vasorelaxants, based on the IC_{50} values obtained, and the vasorelaxing potency and maximal response for three of the compounds are comparable to acetylcholine.

Keywords: carbon nanotubes · click chemistry · terpyridines · triazoles · vasorelaxants

Introduction

Five-membered nitrogen heterocycles have a wide range of applications in biological systems.[1] Among these, 1,2,3-triazole scaffolds are potential targets for drug discovery because of their wide range of biological properties, such as anticancer, antituberculosis, antifungal, antibacterial, and anti-HIV properties.[1] Additionally, they are considered as useful building blocks in synthetic chemistry, agrochemicals, and for industrial applications, such as dyestuffs, corrosion inhibitors, light stabilizers, optical brighteners, and fluorescent whiteners.[2]

Because of their wide applications and potent usefulness, several synthetic methods for producing 1,2,3-triazoles have been developed recently. The traditional method for production of triazoles by cycloaddition requires prolonged reaction times, elevated temperature (typically at reflux), and also provides a mixture of 1,4- and 1,5-disubstituted triazoles (Scheme 1, path a).[3] The most common method for the synthesis of 1,2,3-triazoles is 1,3-dipolar cycloaddition reactions between alkynes and azide derivatives.[4] For this purpose, some reports have discussed the preparation of these structures on solid supports, whereas others include the reaction of sodium alkoxide or sodium phenyl acetylide with tosyl azides, or the addition of bromomagnesium acetylides to azides.[5]



Scheme 1. Traditional method for production of the triazoles (path a) and copper(I)-catalyzed "Huisgen" [2+3] dipolar cycloaddition reaction (path b).

Recently, click chemistry,[6] which describes chemistry tailored to generate substances quickly and reliably by joining small units together, has found many applications. One of the most popular reactions within the click chemistry concept is the azide alkyne "Huisgen" cycloaddition with a copper catalyst (copper-catalyzed azide–alkyne cycloaddi-

[a] Prof. H. Sharghi, S. Ebrahimpourmoghaddam, Dr. M. M. Doroodmand
Department of Chemistry, College of Sciences
Shiraz University, Shiraz 71454 (Iran)
Fax: (+98) 711-2280926
E-mail: shashem@chem.susc.ac.ir
doroodmand@shirazu.ac.ir

[b] A. Purkhosrow
Department of Pharmacology
School of Medicine, Shiraz University of Medical Sciences
Shiraz (Iran)

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tion, CuAAC, Scheme 1, path b).[6] Recent advances in copper(I)-[7a,b] or ruthenium(II)-catalyzed[7c–e] alkyne–azide cycloadditions have led to the evolution of the classical Huisgen reaction[6] into a highly efficient transformation that is able to deliver libraries of either 1,4- or 1,5-disubstituted 1,2,3-triazoles under mild conditions. Whereas copper(I) catalysis guarantees regiospecificity, wide substrate scope, and tremendous acceleration of the reaction rate, the inherent thermodynamic instability of copper(I) species causes easy oxidation[8a,b] to copper(II) species and/or disproportionation[8c] to copper(0) and copper(II) species. This instability generally imposes strict experimental conditions, such as inert atmospheres and anhydrous solvents, that usually require the use of ligands to accelerate the reaction,[9] thus minimizing the formation of undesired byproducts (probably due to shielding of the copper(I) species from interactions that lead to degradation). Most of these shortcomings have been elegantly surmounted by the generation of the copper(I) species in situ,[9] either by comproportionation of copper(0) and copper(II) species or by reduction of copper(II) salts (for example, copper(II) sulfate pentahydrate) by using a sacrificial reducing agent, typically sodium ascorbate. Whereas enriching the metal core with electrons can accelerate the investigated reaction, a stable copper(II) complex with an electron-donating ligand is a useful surrogate for copper(I) systems.[10b] Although some of these approaches are satisfactory and effective for alkyne-azide cycloadditions, the wide-ranging applications of CuAACs have stimulated the development of a plethora of new stable copper complexes, as well as catalytic systems that can preserve the reliability of the transformation during the assembly of diverse molecules.[9]

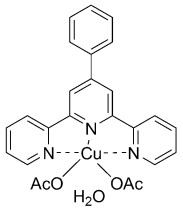
Oligopyridines, particularly the terpyridines (TPYs), are widely used in different research areas, such as organometallics,[11] medicinal chemistry,[12] photochemistry[13] and nanoscience.[14] As catalysts, TPY complexes of transition metals are especially interesting; the immobilization of TPYs onto a solid support could prove to be of importance in fields such as heterogeneous catalysis.[15] In the literature, to improve reuse and recovery, copper species have been immobilized onto various supports such as zeolites,[16] activated carbon,[10c] and amine-functionalized polymers.[17]

Herein, we report a one-pot, two-step, efficient, regioselective, and safe synthetic route to obtain 1,4-disubstituted 1,2,3-triazoles from epoxides or benzyl/alkyl halides, sodium azide, and alkynes in water, catalyzed by activated multiwalled carbon nanotubes (AMWCNTs) functionalized with copper(II)-4′-phenyl-2,2′:6′,2″-terpyridine [AMWCNTs-O-Cu^{II}-PhTPY] without any additives. The reactions proceeded smoothly to generate the 1,4-disubstituted 1,2,3-triazole derivatives in high yields.

Results and Discussion

Our ongoing interest in developing highly reliable reactions that are useful in both chemistry and biology[10] prompted us to revisit the Huisgen 1,3-dipolar cycloaddition of azides and alkynes. We have explored the viability of obtaining the desired compounds by a 1,3-dipolar cycloaddition from the reaction of 2-azidoalcohols, which are formed in situ from sodium azide and epoxides, with alkynes by means of click reactions with a catalytic amount of copper(II)-4′-phenyl-2,2′:6′,2″-terpyridine complex [Cu^{II}PhTPY].

4′-Phenyl-2,2′:6′,2″-terpyridine was synthesized according to a published procedure.[18] The copper complex (Scheme 2) was obtained by adding 4′-phenyl-2,2′:6′,2″-terpyridine to an aqueous solution of copper(II) acetate monohydrate, and the mixture was stirred for 1 h, which resulted in a blue-green solution.



Scheme 2. Copper(II)-4′-phenyl-2,2′:6′,2″-terpyridine complex.

FT-IR spectrometry and UV/vis spectroscopy were used for characterization of copper complex, as shown in Figure 1. Figure 1a shows the FT-IR spectra of ligand PhTPY (I) and [Cu^{II}-PhTPY] (II). The sharp absorption bands at 1583.4 cm^{-1} and 1548.7 cm^{-1} in spectrum I (Figure 1a) are attributed to the C=C or C=N bond of PhTPY.[19] Also, the two absorption bands at 1465.8 cm^{-1} and 1390.6 cm^{-1} are correlated to the other C=C bonds in the PhTPY ligand. In spectrum II (Figure 1a), two absorption bands are detected for the C=C or C=N bond at 1610.4 cm^{-1} and 1575.7 cm^{-1}, respectively, in the copper complex. In comparison with FT-IR spectrum of PhTPY, these two sharp absorption bands are significantly shifted to higher frequencies, which is a result of the formation of the copper complex. Also, the broad peak at approximately 3444.6 cm^{-1} is attributed to the O–H bond of adsorbed water on the surface of the solid copper monohydrate complex. In Figure 1b, a sharp absorption band is detected at $\lambda_{max}=278$ nm. As is clearly shown, the formation of the copper complex leads to a significant red shift to $\lambda_{max}=291$ nm. The isobestic point at $\lambda=285$ nm clearly reveals the formation of the copper complex. Also, the inset in Figure 1b shows the diagram of absorbance versus different ratios of ligand/copper, which reveals a 1:1 ratio for the complex of copper with TPY. The complex-formation constant ($K_{Complex}$) was estimated to be 5.625×10^{6} M^{-1} by spectroscopic analysis of different ratios of Cu^{2+} ions (1×10^{-3} M) and PhTPY (5×10^{-5} M).

For our initial screening experiments, the 1,3-dipolar cycloaddition reaction between styrene oxide, sodium azide, and phenylacetylene in a 1:1.1:1 molar ratio at room temperature was chosen as the model reaction. In the next step, as the click azide-alkyne cycloaddition reaction was reported in a wide variety of organic solvents,[3] we checked the effect of various solvents (Table 1). It was found that the reaction is dependent on the nature of the solvent. The best results were obtained by using water as the solvent (Table 1, entry 3). Water is safe, nontoxic, economical and

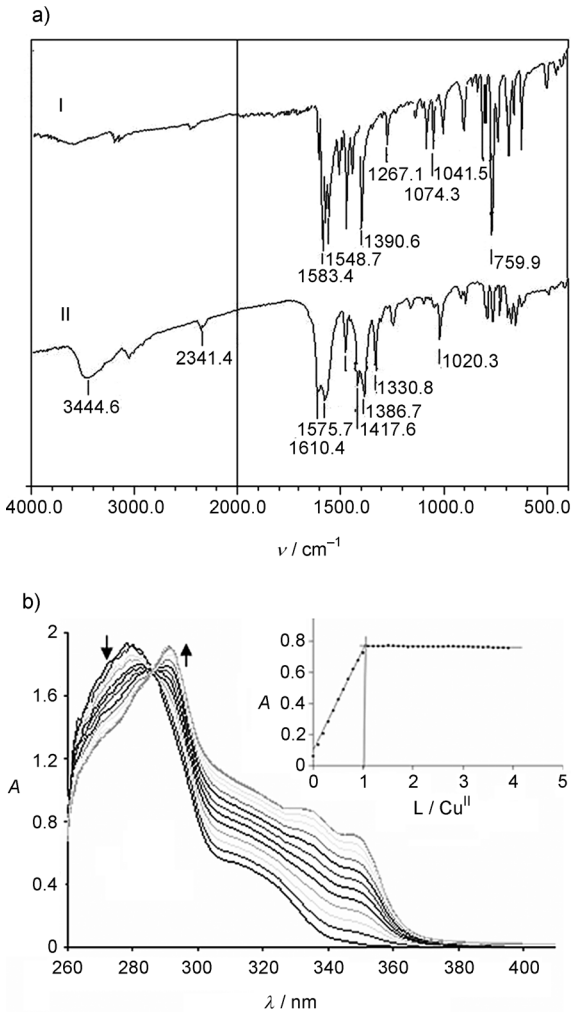
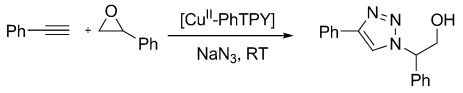


Figure 1. a) FT-IR: I) ligand PhTPY, II) [Cu^{II}-PhTPY]. b) UV/vis spectrum of the copper complex at different volume ratios of ligand (L) and Cu^{2+} ions. Inset: Diagram revealing the ratio of ligand coordinated with copper.

Table 1. Investigation of various solvents for the synthesis of **3a**.



1 **2** **3a**

Entry	Solvent	Yield of **3a**[a] [%]	*t* [h]
1	–[b]	0	4.0
2	ethanol	50	4.0
3	water	95	1.0
4	DMSO	10	4.0
5	DMF	5	4.0
6	toluene	5	4.0
7	1,4-dioxane	10	4.0
8	acetonitrile	45	4.0
9	ethanol/water(1:1)	90	1.0
10	1,4-dioxane/water(1:1)	85	1.0

[a] Yield of isolated product. [b] In the absence of solvent.

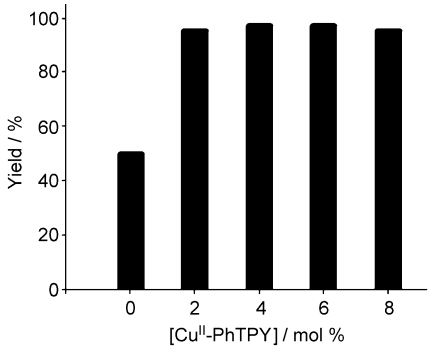


Figure 2. Plot of the yield of **3a** versus the amount of [Cu^{II}-PhTPY] used as catalyst in the reaction of styrene oxide, sodium azide, and phenylacetylene in a 1:1.1:1 molar ratio in water at room temperature.

recyclable.[20] Furthermore, deprotonation of the π-complex alkyne to form the copper acetylide can occur without the addition of a base in water, but in organic solvents, the formation of copper acetylide is unfavorable and a base is required for deprotonation[20d] (Table 1, entries 2, 4–8). When a mixure of water and other solvents, such as EtOH or 1,4-dioxane, were used the yields were comparable to water alone (Table 1, entries 9 and 10). The reaction conducted in the presence of 2.0 mol% of [Cu^{II}-PhTPY] in water furnished **3a** in 95% yield after stirring for 1 h at ambient temperature in an uncapped vial (Table 1, entry 3).

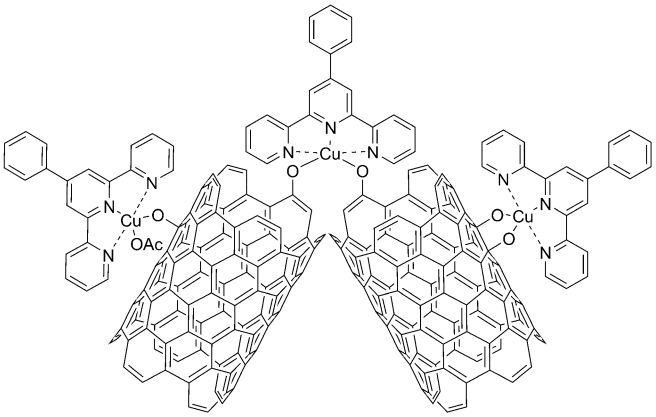
Having optimized the solvent, we applied different loadings of [Cu^{II}-PhTPY] as the catalyst in the synthesis of **3a**. As shown in Figure 2, the optimal catalyst loading is 2.0 mol%.

In the chemical and pharmaceutical industries, recycling of homogeneous catalysts has great economic and environmental importance. Immobilization of homogeneous catalysts on insoluble solid supports with high surface areas is usually the method of choice, as the immobilized catalysts can be easily recovered by a simple filtration process after reactions.[21]

Catalysis is currently recognized as a potential field of application for carbon nanotubes (CNTs), and throughout the past decade, the number of publications and patents on this subject has been increasing exponentially.[22] In most cases, the use of these nanomaterials as solid supports for catalysts results in better performance than conventional supports. Indeed, CNTs are an interesting alternative to conventional support structures because their high purity eliminates self-poisoning and results in high electrical conductivity, high thermal stability, impressive mechanical properties, and high accessibility of the active phase. The absence of microporosity also eliminates diffusion and intraparticle mass transfer in the reaction medium. The possibility of macroscopically shaping the support, as well as the opportunity to tune specific metal–support interactions, which can directly affect the catalytic activity and selectivity, are also attractive properties of CNTs, as is the possibility of confinement effects in their inner cavity. Furthermore, relative to conventional supports, CNTs have a high flexi-

bility for the dispersion of the active phase, as it is possible to modulate their specific surface area (50–500 $m^2 g^{-1}$ for multiwalled carbon nanotubes (MWCNTs)) or their internal diameter (5–100 nm for MWCNTs). It is also easy to chemically functionalization their surfaces, change their chemical composition (nitrogen- or boron-doped CNTs), and deposit lots of catalytic phase either on their external surface or in their inner cavity.[23]

As [Cu^{II}-PhTPY] proved to be the best homogeneous catalyst for the synthesis of 1,2,3-triazoles, we set out to prepare a reusable heterogeneous catalyst by simple immobilization of [Cu^{II}-PhTPY] onto CNTs. In our previous study, we found out that, MWCNTs had the largest surface area.[10b] Therefore, MWCNTs were selected as an appropriate support for the deposition of [Cu^{II}-PhTPY] (Scheme 3).



Scheme 3. [Cu^{II}-PhTPY] deposited on AMWCNTs.

Before direct use of the MWCNTs, their surface was activated by the introduction hydroxy groups by means of gas-phase oxidation under air. This modification increases the reactivity of CNTs and allows easier deposition of the metal precursors at the nucleating sites; thus, higher catalyst dispersions are to be expected.[23i]

Preparation of Heterogeneous Catalyst

For information on the immobilization of the 4′-phenyl-2,2′:6′,2″-terpyridine copper(II) complex onto AMWCNTs, see the Experimental Section.

Characterization of Heterogeneous Catalyst

In this study, scanning electron microscopy (SEM) and transmission electron microscopy (TEM), thermogravimetric analysis (TG), back-titration analysis, UV/vis and FT-IR spectrometry were used for characterization of the AMWCNTs. The morphology of the AMWCNTs, when doped with the copper complex also was evaluated by using SEM (Figure 3a), atomic force microscopy (AFM, Figure 3b) and a voltage profile (Figure 3c). The inductively coupled plasma (ICP) analysis results showed that the copper content of the supported complex was 4.895%.

The size distribution of the AMWCNTs doped with the copper(II) complex was evaluated by using the information obtained from SEM, TEM, and AFM images, and also according to the voltage profile of the copper catalyst (Figure 3). The band width at half the maximum height of the voltage profile peak reveals the size of the nanoparticles of copper(II) complex . The histogram in Figure 4 shows of the frequency percentages of the average size of the nanoparticles on the AMWCNTs obtained from the

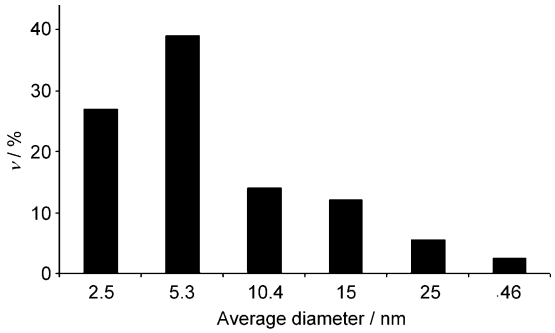


Figure 4. Histogram showing the average diameter of the copper complex doped on AMWCNTs.

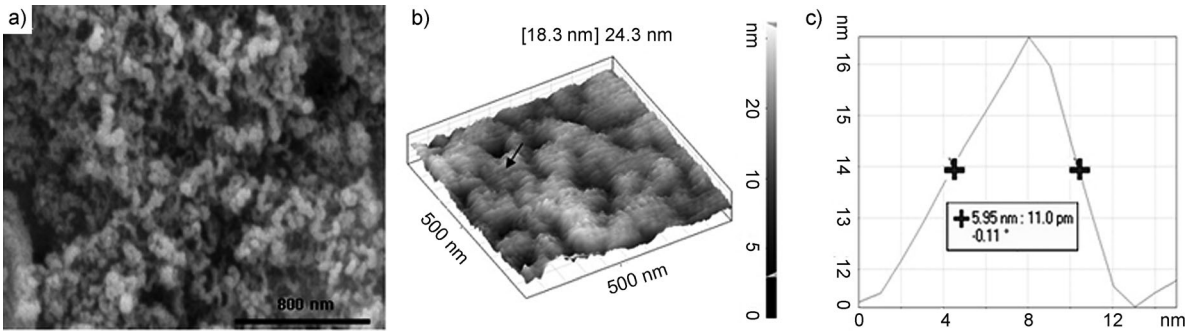


Figure 3. Characterization of [AMWCNTs-O-Cu^{II}-PhTPY] including: a) SEM, b) AFM, and c) voltage profile images of copper complex doped on AMWCNTs.

AFM images. According to this histogram, the diameter of the copper-complex nanoparticles is 2.5–40 nm. Also, the maximum average diameter of copper complex is estimated at approximately 5 nm.

The formation of the nanoparticles was also evaluated by using FT-IR spectrometry. Figure 5 I and II show the FT-IR spectra of AMWCNTs and [AMWCNTs-O-Cu^{II}-PhTPY], respectively. Based on the FT-IR spectra (Figure 5 II), the

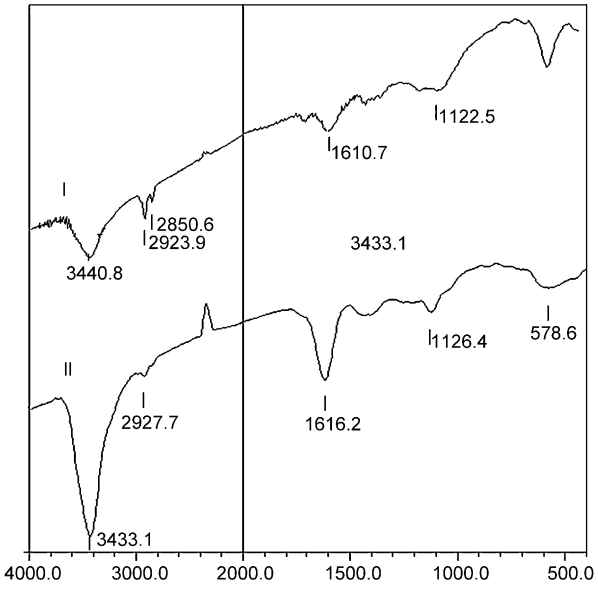


Figure 5. FT-IR spectra of I) AMWCNTs and II) [AMWCNTs-O-Cu^{II}-PhTPY].

sharp absorption band at 578.6 cm^{-1} is attributed to the Cu–O bond,[10b] and the broad absorption band at around 1616.2 cm^{-1} is correlated to the C=C bonds present in the CNT matrix overlapped with the functional groups in the copper complex.[19] It seems that low amounts of the copper complex on the CNT surface lead to broadening of the absorption bands in the [AMWCNTs-O-Cu^{II}-PhTPY] system. The percentage of free hydroxy groups was also estimated to 6.11 % based on the back-titration process.

In Figure 6 the absorption spectra of free [Cu^{II}-PhTPY], AMWCNTs, and [AMWCNTs-O-Cu^{II}-PhTPY] in ethanol are compared. [Cu^{II}-PhTPY] absorbs light at 288 nm and 320–350 nm and has sharp absorption bands with fine structures. The spectrum of AMWCNTs does not have any fine structure; however, a continuous absorption band is evident. According to Figure 6, the spectrum of [AMWCNTs-O-Cu^{II}-PhTPY] reveals that the characteristic absorption bands of [Cu^{II}-PhTPY] in [AMWCNTs-O-Cu^{II}-PhTPY] are broader relative to free [Cu^{II}-PhTPY], although the exact comparison at the same [Cu^{II}-PhTPY] concentration is impossible because of the masking effect from the AMWCNTs.[23j] These results verify efficient complex formation between [Cu^{II}-PhTPY] and the AMWCNTs.

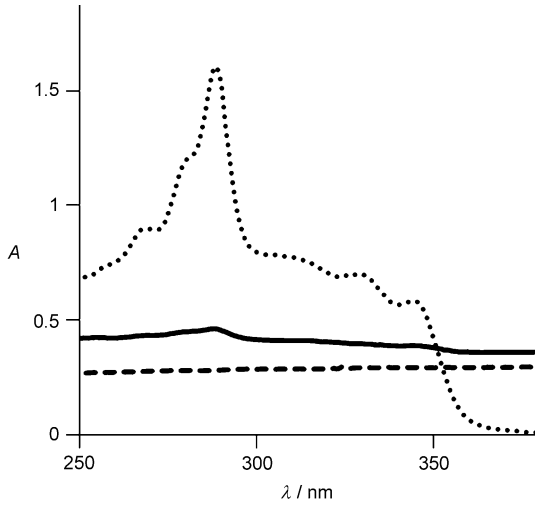


Figure 6. UV/Vis. spectra of AMWCNTs (-----), [AMWCNTs-O-Cu^{II}-PhTPY] (——), and [Cu^{II}-PhTPY] (•••••),obtained in ethanol.

Treatment of [AMWCNTs-O-Cu^{II}-PhTPY] with ethylenediaminetetraacetic acid (EDTA) solution resulted in the disappearance of the characteristic absorption bands from [Cu^{II}-PhTPY], which indicates that EDTA dissociates [Cu^{II}-PhTPY] by liberating the TPY ligands that absorb at 235–290 nm (Figure 7).

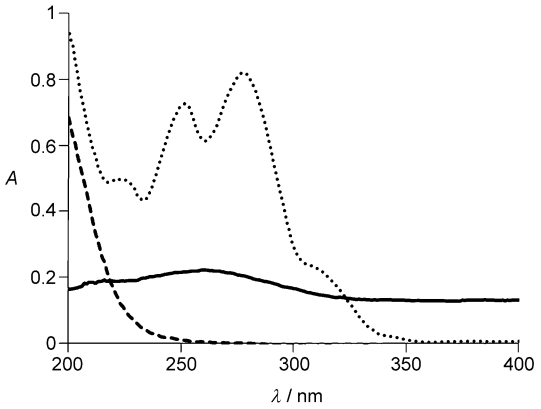


Figure 7. UV/Vis. spectra of EDTA (-----), EDTA treated [AMWCNTs-O-Cu^{II}-PhTPY] (——), and PhTPY (•••••) obtained in water/ethanol (1:1).

Activity and Reusability of the Heterogeneous Catalyst

The 1,3-dipolar cycloaddition in the model reaction (styrene oxide, sodium azide, and phenylacetylene in a 1:1.1:1 molar ratio in water at room temperature) was performed successfully within 0.8 h in the presence of 2.0 mol % of the heterogeneous catalyst. The recyclability of the heterogeneous catalyst was also examined for the model reactions at two different levels. Firstly, the [AMWCNTs-O-Cu^{II}-PhTPY] heterogeneous catalyst, which was recovered by filtration after each reaction, can be reused five successive times in cycloaddition experiments without dramatic loss of

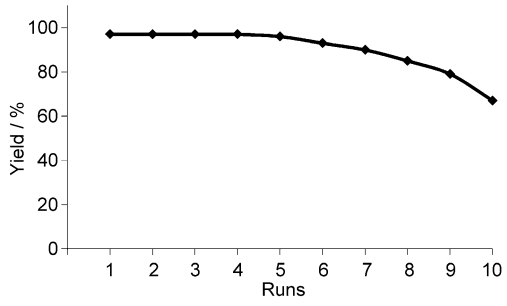


Figure 8. Recyclability of [AMWCNTs-O-Cu^{II}-PhTPY] heterogeneous catalyst for the synthesis of **3a**. All reactions were under the same conditions for 0.8 h.

yield and generates products with purities similar to those obtained in the first run (Figure 8). Secondly, the heterogeneous catalysts were stirred in water at room temperature for 5 h. The immobilized catalysts were removed and the filtrates were used for the model reaction to synthesize **3a** under the described reaction conditions. In this case, no product was obtained after 4 h.

To evaluate the copper content, the supported catalyst was treated with concentrated HCl and HNO_3 (3 M, 1:1) to digest the copper species and then analyzed by ICP analysis. After five consecutive reactions, the recovered catalyst was found to contain 4.832 % (w/w) of Cu complex based on ICP analysis, which is comparable to the initial value of 4.895 % (w/w). This result indicates that less than 1.29 % of the copper content was leached during the reaction cycles.

Catalytic Synthesis of β-Hydroxy 1,4-Disubstituted 1,2,3-Triazoles

After establishing the feasibility of the proposed method for the model compound, and also having recognized a set of optimal experimental conditions to perform the three-component click reaction with the prepared catalyst, the robustness and scope of the developed method was assessed by testing a set of assorted reactive precursors.

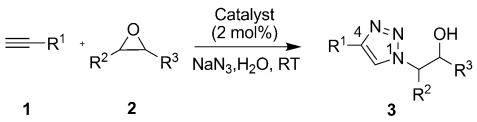
We were pleased to observe that simply mixing styrene oxide (**2a**), a range of acetylenes **1a–i**, and sodium azide with the homogeneous or heterogeneous copper catalyst under the conditions described in Table 2, led to smooth cycloaddition to afford the desired β-hydroxy 1,4-disubstituted 1,2,3-triazole derivatives **3** in good to excellent yields (Table 2, entries 1–9). In the cases where styrene oxide was used as the epoxide, product **3** was obtained as a result of the cleavage of the epoxide with sodium azide in a regioselective manner, with preferential attack at the more hindered position.[6j] A representative selection of the compounds obtained is depicted in Table 2. To purify the crude isolated adducts, simple preparative chromatography was used. The complete analytical and spectroscopic data for all of the described compounds are included in the Supporting Information. Encouraged by the results achieved with styrene oxide, our attention turned to various other epoxides (Table 2, entries 10–18). Cyclohexene oxide (**2b**) also reacted with sodium azide and acetylenes to produce cyclohexyl triazoles in excellent yield (Table 2, entries 10–15). The stereochemistry of the products was found to be trans from the coupling constants of the hydrogen atoms of the ring, as detected in most epoxide ring-opening reactions.[24] The product triazoles from other aliphatic epoxides 2-phenoxymethyl-oxirane (**2c**) and 2-allyloxymethyl-oxirane (**2d**) were obtained from the attack of the azide nucleophile at the less hindered position of epoxides[6j] (Table 2, entries 16–18).

As shown in Table 2, electronic and steric variation in the terminal aliphatic alkynes and epoxides, did not obviously affect the efficiency of the reactions, and the coupling tolerated different moieties, such as heteroaromatic and heteroatom-containing substituents (Table 2, entries 5–9, 15 and 17). We felt that this method could be extended to synthesize azacrown ether-containing triazoles. The reaction with azacrown ether propargylamine **1i** gave the corresponding triazole **3i** in good yield (Table 2, entry 9). Applying these conditions for the coumarin propargyl ether **1f** as starting material produced the corresponding target compound successfully (Table 2, entry 6). A terminal alkyne with a sulfonamide functional group also reacted without any problems to give the corresponding triazole **3g** in high yield (Table 2, entry 7). The reaction of simple aliphatic terminal alkynes **1b–1d** afforded the desired triazoles **3b–3d**, **3k**, and **3l** in good yields. In general, relative to with aromatic alkynes, aliphatic terminal alkynes required prolonged reaction times. In some cases, the reaction was performed at 40 °C to complete it in a shorter time and the alkynes were dissolved in 1.0 mL of 1, 4-dioxane for better mixing in aqueous media (Table 2, entries 6, 8 and, 15). As expected, internal alkynes gave no reaction.

A comparison of the effectiveness of the heterogeneous and homogeneous catalysts revealed that the use of the immobilized catalysts guaranteed quantitative consumption of reactants in shorter reaction times. In the case of product **3a** the yields of the reactions with the two different catalysts after 0.5 h was compared. The conversion of the starting material in the reaction with the homogeneous catalyst was around 50 %, whereas the heterogeneous catalyst gave the desired product in a better yield of 65 %. This difference could be attributed to the significant increase in the activity of the heterogeneous catalyst and this might be a result of the nanosized construction of the catalyst as well as the uniform dispersion of the copper complex on the high specific surface area of AMWCNTs. The regioselectivity of both heterogeneous and homogeneous catalysts remained unchanged and 1,4-substituted 1,2,3-triazole systems were the predominant products.

To assess the feasibility of applying this method on a preparative scale, the model reaction was performed on a 30 mmol scale in the presence of the homogeneous and heterogeneous catalysts. As expected, the reaction proceeded similarly to the smaller scale reaction (Table 2, entry 21), providing the desired **3a** in good yield.

Table 2. Regioelective synthesis of β-hydroxy-1,4-disubstituted 1,2,3-triazoles by way of a three-component reaction.[a]



1 2 3

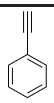
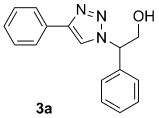
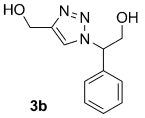
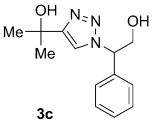
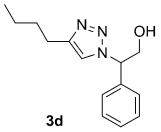
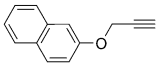
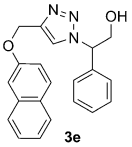
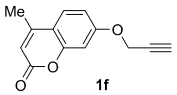
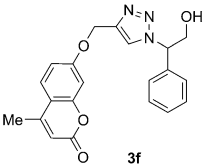
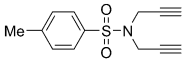
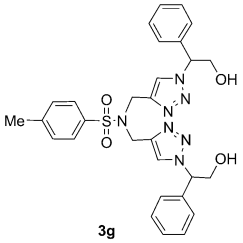
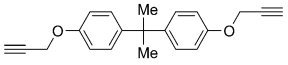
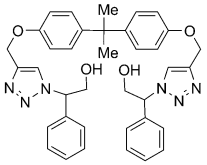
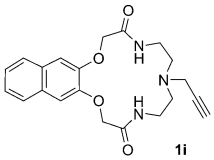
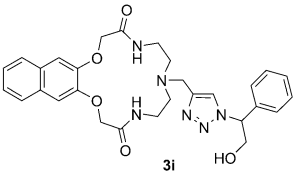
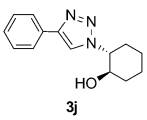
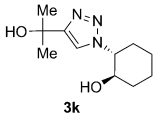
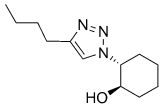
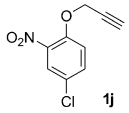
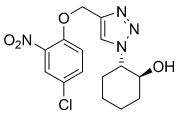
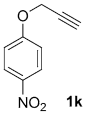
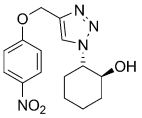
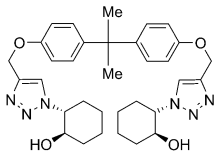
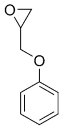
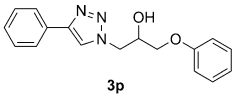
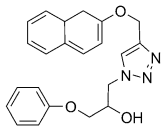
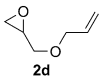
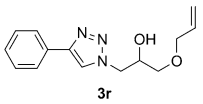
Entry	Alkyne	Epoxide	Product	Homogeneous[b]		Heterogeneous[c]	
				t [h]	Yield [%][d]	*t* [h]	Yield [%][d]
1	 1a	 2a	 3a	1.0	95	0.8	97
2	 1b	**2a**	 3b	5.5	85	3.0	89
3	 1c	**2a**	 3c	5.0	83	3.0	84
4	 1d	**2a**	 3d	5.8	75	4.0	88
5	 1e	**2a**	 3e	5.0	80	3.8	84
6[e]	 1f	**2a**	 3f	7.5	70	6.0	74
7	 1g	**2a**	 3g	4.5	80	4.0	82
8[e]	 1h	**2a**	 3h	4.0	78	3.8	83
9	 1i	**2a**	 3i	5.7	65	5.5	69
10	**1a**	 2b	 3j	1.5	87	1.0	91

Table 2. (Continued)

Entry	Alkyne	Epoxide	Product	Homogeneous[b]		Heterogeneous[c]	
				t [h]	Yield [%][d]	*t* [h]	Yield [%][d]
11	**1c**	**2b**	 **3k**	6.5	88	4.5	92
12	**1d**	**2b**	 **3l**	6.8	82	4.0	85
13	 **1j**	**2b**	 **3m**	7.5	77	5.0	82
14	 **1k**	**2b**	 **3n**	4.0	74	2.5	80
15[e]	**1h**	**2b**	 **3o**	4.5	80	4.0	84
16	**1a**	 **2c**	 **3p**	5.5	71	3.8	75
17	**1e**	**2c**	 **3q**	5.3	67	3.5	75
18	**1a**	 **2d**	 **3r**	3.5	70	2.5	87
19	**1a**	**2a**	**3a**	1.8	88[f]	1.2	92[f]

[a] Reagents and conditions: epoxide (1.0 mmol), terminal alkyne (1.0 mmol), sodium azide (1.1 mmol), homogeneous or heterogeneous copper(II)-4′-phenyl-2,2′:6′,2″-terpyridine (2.0 mol%), water, RT. [b] Reactions performed in the presence of homogeneous catalyst [Cu^{II}-PhTPY]. [c] Reactions performed in the presence of heterogeneous catalyst [AMWCNTs-O-Cu^{II}-PhTPY]. [d] Yield of isolated product. [e] The reaction was performed at 40 °C and the alkynes were dissolved in 1.0 mL of 1,4-dioxane for better mixing. [f] The reaction was performed on a 30 mmol scale.

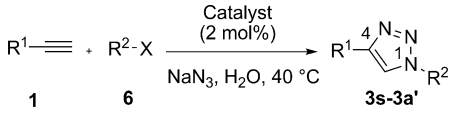
Three-component Catalytic Synthesis of 1,2,3-Triazole Derivatives from Benzyl or Alkyl Halides

Recently, we reported Cu^{I}/C as an apropriate catalyst for the generation of organic azides in situ by using a one-pot procedure as a direct route to 1,2,3-triazoles. The reaction proceeds by capturing the dipolarophile with an organic azide that is generated in situ from the appropriate halide and sodium azide.[10c] Encouraged by the results described above, it was anticipated that the exploitation of the dual role exhibited by the copper(II) catalyst described here would facilitate the development of a general, simple, and mild three-component procedure to prepare libraries of 1,2,3-triazoles from terminal alkynes, benzyl or alkyl halides, and sodium azide.

Only slight modifications to the previously optimized experimental protocol were required to verify that, in the presence of [Cu^{II}-PhTPY] (2 mol%), phenylacetylene (**1a**), sodium azide, and benzyl bromide (**4a**) in a 1:1.1:1 molar ratio are smoothly converted to 1-benzyl-4-phenyl-1,2,3-triazole (**3s**) in satisfactory yield. Here again, the best solvent was water, and it should be noted that, in a clear contrast with the results obtained for the synthesis of β-hydroxy 1,4-

disubstituted 1,2,3-triazoles, a higher temperature (40 °C) was required to achieve complete conversion in this three-component version of the Huisgen reaction in the reasonable reaction times. As the optimal conditions for the efficient catalysis of the Huisgen reaction had been determined, to investigate the generality and versatility of this method, the reaction was extended to different terminal alkynes and benzyl or alkyl halides. A representative selection of compounds obtained is depicted in Table 3. As previously demonstrated, the heterogeneous catalyst is recyclable and its activity is retained after five reaction cycles. The yield of the reactions was generally greater than 97%, as judged by GC analysis or ^{1}H NMR spectroscopy, so the crude products only needed recrystallization to purify them. Compounds that did not reach this level of conversion were purified by simple preparative chromatography. The complete analytical and spectroscopic data for all compounds described are included in the Supporting Information.

Table 3. Regioelective synthesis of 1,4-disubstituted 1,2,3-triazoles by way of a click reaction.[a]



6a : R^2 = benzyl, X = Br
6b : R^2 = benzyl, X = Cl
6c : R^2 = 4-Br-benzyl, X = Br
6d : R^2 = 4-NO_2-benzyl, X = Cl
6e : R^2 = 4-CH_3-benzyl, X = Cl
6f : R^2 = allyl, X = Br
6g: R^2 = CH_2CO_2Et, X = Br

Entry	Alkyne	Halide	Product	Homogeneous[b]		Heterogeneous[c]	
				t [h]	Yield [%][d]	*t* [h]	Yield [%][d]
1	**1a**	**4a**	**3s**	2.0	90	1.5	92
2	**1a**	**4b**	**3s**	4.0	88	2.8	90
3	**1a**	**4c**	**3t**	2.8	85	2.5	86
4	**1a**	**4d**	**3u**	5.5	80	3.2	83
5	**1a**	**4e**	**3v**	2.8	88	2.0	92
6	**1a**	**4f**	**3w**	12.0	79	9.0	84
7	**1a**	**4g**	**3x**	15.0	74	12.5	80
8	**1d**	**4b**	**3y**	10.0	81	8.0	82
9	**1e**	**4a**	**3z**	8.0	87	5.8	88
10	**1f**	**4a**	**3a'**	10.0	73	8.0	75
11	**1a**	**4a**	**3s**[e]	2.8	85	2.0	87

[a] Reagents and conditions: halide (1.0 mmol), terminal alkyne (1.0 mmol), sodium azide (1.1 mmol), homogeneous or heterogeneous copper(II)-4'-phenyl-2,2':6',2''-terpyridine (2.0 mol%), water, 40 °C. [b] Reactions performed in the presence of homogeneous catalyst [Cu^{II}-PhTPY]. [c] Reactions performed in the presence of heterogeneous catalyst [AMWCNTs-O-Cu^{II}-PhTPY]. [d] Yield of isolated product. [e] The reaction was performed on a 30 mmol scale.

It can be seen that the reaction allows the preparation of not only 1,4-substituted 1,2,3-triazoles derived from phenylacetylene (Table 3, entries 1–7), but also those derived from aliphatic alkynes (Table 3, entries 8–10). We were pleased to find that the reaction with an alkyl halide instead of a benzyl halide also led to smooth cycloaddition to afford the desired 1,2,3-triazoles, although longer reaction times were required (Table 3, entries 6 and 7).

The use of this method in the reaction of sodium azide and alkyl or benzyl halides with different terminal alkynes produced only one of the possible regioisomers. Various benzyl halides with electron-donating and electron-withdrawing substituents were subjected to the same reaction conditions to furnish the corresponding 1,2,3-triazole derivatives. However, the rate of reaction drops as electron-withdrawing substituents are added (Table 3, entries 3 and 4). Here again, the model reaction was performed on a 30 mmol scale in the presence of the homogeneous or heterogeneous catalysts. As expected, the reaction proceeded similarly to the smaller scale reaction (Table 3, entry 11), to provide the desired **3s** in good yield.

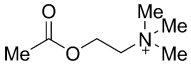
Pharmacological Evaluation: Vasorelaxing Activity of 1,4-Disubstituted 1,2,3-Triazole Derivatives.

One of the most serious health problems nowadays is hypertension. As hypertension increases the risk for cardiovascular diseases, such as congestive heart failure, stroke, and myocardial infarction, it is major goal in medicinal chemistry to search for new antihypertensive agents.[25] A survey of literature revealed that substituted triazoles have received much attention during recent years on account of their prominent potential as anticancer, antituberculosis, antifungal, antibacterial, and anti-HIV properties.[1] In this study, we tested our synthesized triazole derivatives as potential compounds for the treatment of hypertension. The vasorelaxing activity of compounds **3a**, **3e–3i**, **3k–3m**, **3o**, **3q**, and **3z** was compared with acetylcholine (ACh) in rat aortic rings.

Thoracic aortic rings from six normal Sprague-Dawley rats were suspended for isometric tension recording. They were precontracted with phenylephrine (Phe, 10^{-6} M). Dose-relaxation response to the test compounds (10^{-9}–10^{-4} M) was performed at the plateau of contractile response to Phe. The IC_{50} value (the concentration necessary for 50% reduction of maximal Phe-induced contracture) and maximal response (E_{max}) achieved for each compound were compared with that of acetylcholine. All compounds were dissolved in dimethylsulfoxide (DMSO) as stock solution (10^{-9}–10^{-4} M), as was ACh (reference standard).

The findings of our study revealed that all of the compounds have vasorelaxing activity on the isolated thoracic rat aorta. The comparison of the groups based on the IC_{50} values obtained shows the vasorelaxing activity of compounds 7-{[1-(2-hydroxy-2-phenylethyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-4-methyl-4a,8a-dihydro-2*H*-chromen-2-one (**3f**), *N*,*N*-bis{[1-(2-hydroxy-2-phenylethyl)-1*H*-1,2,3-triazol-4-yl]methyl}-4-methyl benzene sulfonamide (**3g**), and (1*R*)-2-(4-butyl-1*H*-1,2,3-triazol-1-yl)cyclohexanol (**3l**) had the highest vasorelaxing potency. The vasodilatation activity data are reported in Table 4 and Figure 9.

Table 4. Necessary concentration of compounds **3f**, **3g**, **3l** to reduce the maximal phenylephrine induced contracture by 50% (IC_{50}) in thoracic rat aortic rings.

Entry	Compound	$IC_{50\%}$ [log concentration]
1		−6.18±0.19
2	**3f**	−6.72±0.64
3	**3g**	−6.94±0.76
4	**3l**	−7.28±0.52

3f (92.66±7.33) and **3l** (96.57±3.42) did have comparable maximal response (E_{max}) to ACh (90.66±4.17, Figure 9).

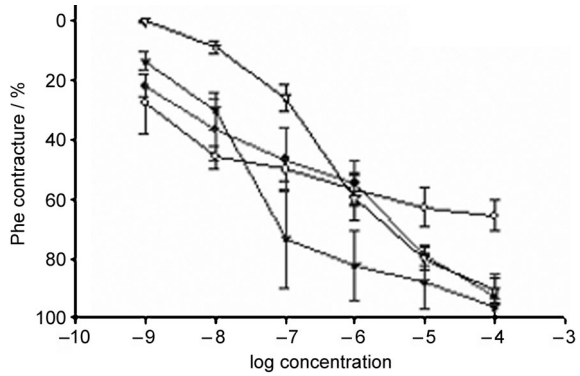


Figure 9. Effect of **3f** (●), **3g** (○), **3l** (▼), and ACh (▽) in the concentration range 10^{-9}–10^{-4} M on contracture induced by phenylephrine (10^{-9}–10^{-4} M) in thoracic rat aortic rings.

Conclusions

In conclusion, we have reported a robust and recyclable heterogeneous catalysts that contributes to expanding the reliability and scope of the Huisgen 1,3-dipolar cycloaddition. The use of these catalysts facilitates the implementation of high-throughput synthetic methods, and the exceptional efficacy of the TPY framework as a copper scavenger guarantees negligible copper leaching. The exploitation of the dual role of the new catalytic systems enabled the development of regioselective, operationally simple, and efficient three-component transformations that allow the rapid assembly of complex 1,4-disubstituted 1,2,3-triazoles. Pharmacological evaluation of some synthesized 1,4-disubstituted 1,2,3-triazole derivatives was also performed. Among those tested, compounds **3f**, **3g**, and **3l** have the highest antihypertensive activity. Therefore, it was concluded that triazole derivatives may be further modified to have better potency than the standard antihypertensive drugs. The 1,4-disubstituted 1,2,3-triazoles derivatives obtained in this study may provide valuable therapeutic intervention for the treatment of hypertension. Further work is in progress in our laboratory to develop new multicomponent transformations based on the reactivity profile of [AMWCNTs-O-Cu^{II}-PhTPY].

Experimental Section

Instrumentation, Analysis, Materials and General Experimental Details

NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR 250 MHz and ^{13}C NMR 62.9 MHz) in pure deuterated solvents with tetramethylsilane (TMS) as internal standards. Scanning electron micrographs were obtained on a Philips XL-30 FEG SEM at 20 kV. Transition electron micrographs were obtained on Philips CM-10 TEM at 130 KV. AFM images were obtained on a Danish Micro Engineering scanning probe microscope (DME-SPM) and processed on DME-SPM software, version 2.0.0.9. FT-IR spectroscopy was performed on a Shimadzu FT-IR 8300 spectrophotometer and was used for characterization of the heterogeneous catalyst. The TG analysis of the samples was carried out on a labmade TG analyzer. The metal content of the catalysts was analyzed on a Varian Vista-pro ICP analyzer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX instrument at 70 or 20 eV. Melting points determined in open capillary tubes in a Buchi-535 circulating oil melting point apparatus. UV/vis spectra were obtained on an Ultrospec 3000 UV/visible spectrometer. Elemental analyses were performed on a Thermo Finnigan CHNS-O 1112 series analyzer. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV254 plates or on a Shimadzu Gas Chromatograph (GC-10A) instrument with a flame-ionization detector with a column of 15% carbowax 20 M chromosorb-W acid washed 60–80 mesh. Column chromatography was carried out on short columns of silica gel 60 (70–230 mesh) in glass columns (2–3 cm diameter) with 15–30 grams of silica gel per one gram of crude mixture. Reagents were either prepared in our laboratories or were purchased from Fluka, Sigma–Aldrich, or Merck.

Preparation of 4′-Phenyl-2,2′:6′,2″-terpyridine

4′-Phenyl-2,2′:6′,2″-terpyridine was synthesized according to the literature method and characterized by NMR spectroscopy, IR and mass spectrometry, and elemental analysis.[18] Pale yellow crystals; 0.15 g, 47% yield; m.p. 122–125 °C. IR (KBr): $\tilde{\nu}$=682(m), 893(m), 1041(m), 1267(m), 1465(s), 1583 cm^{-1}(s). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.07–7.42(m, 5H), 7.71–7.81(m, 4H), 8.53–8.67(d, J=7.5 Hz, 2H), 8.59–8.62(d, J=7.5 Hz, 2H), 8.63 ppm (s, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ=118, 121, 123, 127, 128, 129, 136, 138, 149, 150, 155, 156 ppm. MS: m/z (%): 310(66.5) $[M+1]^+$, 309(98.8) $[M]^+$, 231(61.3), 209(41.0), 176(12.1), 106-(38.7), 78(97.1). Elemental analysis calcd (%) for $C_{21}H_{15}N_3$ (309.360): C 81.53, H 4.89; found: C 81.37, H 4.74.

Preparation of 4′-Phenyl-2,2′:6′,2″-terpyridine Copper(II) Complex

4′-Phenyl-2,2′:6′,2″-terpyridine (6.18 mg, 0.02 mmol) was added to solution of $Cu(CH_3COO)_2.H_2O$ (4 mg, 0.02 mmol) in water (2 mL). Stirring for 0.5 h at room temperature resulted in a clear blue-green solution. This solution was used as the homogenous catalyst.

Synthesis of Multiwalled Carbon Nanotubes

MWCNTs were synthesized by the chemical vapor deposition (CVD) process with acetylene as the source of carbon and ferrocene as the source of iron nanoparticles at a temperature of approximately 1300 °C in an inert atmosphere of argon. A trace flow of oxygen in argon was introduced to the CVD production line for purification of MWCNTs from any amorphous carbon or bulky nanomaterials, such as fullerene, opening the CNT bundles, and activation of the carbon nanostructures to form hydroxy functional groups. Briefly, ferrocene solution in benzene (5 mol%) was used for the production of iron nanoparticles (diameter = 2–10 nm), then decomposition of acetylene, generation of carbon vapors, and finally deposition onto the metal nanoparticles completed the synthetic sequence. The synthesized MWCNT bundles were then directly purified by purging with oxygen and nitric acid vapors. In accordance with the TG analysis and Raman spectroscopy, the purity of the MWCNT bundles was estimated to be approximately 99%.

Activation of Multiwalled Carbon Nanotubes

To develop hydroxy groups on the surface for better anchoring of the metal complex, a high temperature air activation method was used. A tubing resistance furnace with a 150 mm diameter and 1.0 m length, with the two ports open, was initially set to 700 °C. The purification step was achieved in an in-line process, after the synthesis of MWCNTs by the CVD method. The quartz tube carrying the MWCNTs by the flow of argon was placed in the center of the furnace tube. The temperature was maintained at 700 °C and the argon was pumped in at a flow rate of approximately 200 mL min^{-1} so that MWCNTs were mixed with air to produce the desired AMWCNTs.

Preparation of AMWCNTs-ONa

A suspension of AMWCNTs (1 g) in an alkaline solution of NaOH (10 N, 30 mL) was refluxed for 2 h. The resulting black precipitate was filtered through a celite pad, washed with water until pH 8–9 was reached. The black solid was dried in vacuo to afford AMWCNTs-ONa (1 g).

Immobilization of 4′-Phenyl-2,2′:6′,2″-Terpyridine Copper(II) Complex onto AMWCNTs

AMWCNTs-ONa (0.5 g) was added to a freshly prepared solution of aqueous [Cu^{II}-PhTPY] (0.5 mmol, 20 mL), then the mixture was sonicated for 1 h and stirred at room temperature for 24 h. The resulting black precipitate was filtered through a celite pad, washed with water (25 mL), MeOH (25 mL), and ether (25 mL), dried in vacuo to afford [AMWCNTs-O-Cu^{II}-PhTPY] as a black solid.

General Procedure for the Synthesis of β-Hydroxy 1,4-Disubstituted-1,2,3-Triazole Derivatives Catalyzed by Homogeneous [Cu^{II}-PhTPY]

For each reaction, epoxide (1 mmol), alkyne (1 mmol) and sodium azide (1.1 mmol) were stirred in an aqueous solution of the [Cu^{II}-PhTPY] catalyst (2 mL, 2 mol% of catalyst) at room temperature in an uncapped vial. Alkynes **1g** and **1i** were dissolved in 1,4- dioxane (1 mL) for better mixing in aqueous media and the reactions were performed at 40 °C. After the completion of the reaction, as monitored by TLC (*n*-hexane/ethyl acetate), the mixture was diluted with H_2O (5 mL), the product was extracted with ethyl acetate (3×10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo, then a simple short chromatography a on silica gel column (*n*-hexane/ethyl acetate) afforded the pure β-hydroxy-1,4-disubstituted-1,2,3-triazole derivatives.

General Procedure for the Synthesis of β-Hydroxy 1,4-Disubstituted 1,2,3-Triazole Derivatives Catalyzed by Heterogeneous [AMWCNTs-O-Cu^{II}-PhTPY] and Recycling of the Catalyst

The [AMWCNTs-O-Cu^{II}-PhTPY] heterogeneous catalyst was subjected to five successive reuses under the reaction conditions. For each reaction, epoxide (1 mmol) and alkyne (1 mmol) and sodium azide (1.1 mmol) were stirred in water (2 mL) in the presence of [AMWCNTs-O-Cu^{II}-PhTPY] (2 mol%) at room temprature in an uncapped vial. After the completion of the reaction, as monitored by TLC (*n*-hexane/ethyl acetate), the mixture was diluted with H_2O (5 mL), then the mixture was vacuum filtered through a sintered glass funnel, and the residue was consecutively washed with ethyl acetate (30 mL) then water (5 mL). The heterogeneous catalyst was recharged with epoxide, alkyne, sodium azide, and water for another reaction run. The combined supernatant and organic washings were extracted with ethyl acetate (3× 10 mL), then the combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo, then purification by chromatography a on silica gel column (*n*-hexane/ethyl acetate) afforded the pure β-hydroxy 1,4-disubstituted-1,2,3-triazole derivatives. All the triazoles produced were characterized in detail by IR, ^1H and ^{13}C NMR, mass spectroscopy, and elemental analysis.

General Procedure for the Synthesis of 1,4-Disubstituted 1,2,3-Triazole Derivatives from Benzyl or Alkyl Halides Catalyzed by the Homogeneous or Heterogeneous Catalyst

For each reaction, halide (1.0 mmol), alkyne (1.0 mmol), and sodium azide (1.1 mmol) were stirred in water (2 mL) in the presence of the homogenous or heterogeneous catalyst (2.0 mol%) at 40 °C in an uncapped vial. After the completion of the reaction, as monitored by TLC or GC, the mixture was diluted with H_2O (5 mL), and the product was extracted with ethyl acetate (3×10 mL). In the case of heterogeneous catalyst the mixture was vacuum filtered through a sintered glass funnel and the residue was consecutively washed with ethyl acetate (20 mL) then water (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was recrystallized from H_2O/EtOH or hexane/ethyl acetate. Compounds that could not be purified by recrystallization were purified by simple preparative chromatography on a silica gel column (hexane/ethyl acetate) to afford the pure 1,4-disubstituted 1,2,3-triazole derivatives.

Preparation of the Rat Aorta.

Experiments were performed on Male rats Sprague-Dawely (250–300 g), after light ether anesthesia, the rats were sacrificed by cervical dislocation and bleeding. Thoracic aorta was rapidly removed, gently cleaned taking care not to damage the endothelium and cut into four rings of about 3 mm each. Aortic rings were placed in a 20 mL organ bath containing Krebs solution composed of (mmol L^{-1}): NaCl 118, KCl 4.7, KH_2PO_4 1.2, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 25, D-glucose 10; warmed at 37 °C and bubbled continuously with 95% O_2 and 5% CO_2 mixture. The rings were mounted between two triangular stainless steel hooks that were passed through the lumen, stretched to an optimal passive tension of approximately 1.0 gram, and maintained at this tension for 1 h. Changes in tension were measured by isometric force transducers and recorded on a physiographic recording system.

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