Journal of Catalysis 406 (2022): 174-183

DOI: https://doi.org/10.1016/j.jcat.2022.01.009

Oxidized Multiwalled Nanotubes as Efficient Carbocatalyst for the General Synthesis of Azines

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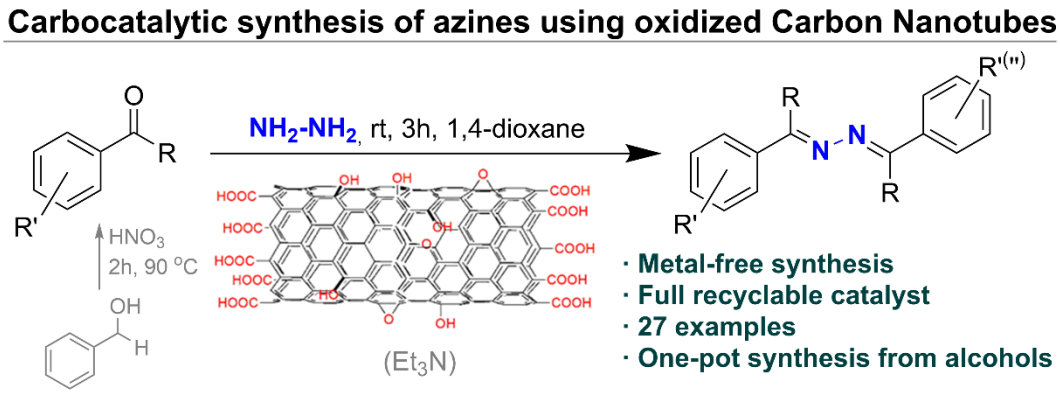
ABSTRACT: The carbocatalytic synthesis of azines (*N*-*N* linked diimines) by mild-oxidized multiwalled carbon nanotubes catalyst (**oxMWNT**) is presented. The material, just with a 5 %wt. loading, is able to carry out a smooth room-temperature metal-free condensation of aldehydes and hydrazine, without external additives, to obtain a wide library of symmetric and also asymmetric azines in excellent yields, even in gram scale, with an excellent selectivity for aromatic substrates. This methodology allows the synthesis of azines with application in nonlinear optics, and the organic materials and biological active compounds crafting. **oxMWNT** catalysed the reaction in just 3 hours with full recyclability upon the recovery of the catalyst. In addition, due to the inherent

oxMWNT oxidative capacity in the presence of nitric acid, we have also developed the one-pot synthesis of azines starting from alcohols.

Keywords: Azines, oxidized carbon nanotubes, carbocatalysis, biological relevant molecules, recyclability.

Graphical Abstract



Highlights

- Smooth azines carbocatalytic metal-free synthesis by oxidized carbon nanotubes
- General and easy procedure for the synthesis of symmetric and asymmetric azines
- Straightforward azines synthesis from alcohols under one-pot conditions
- Full recyclability of the heterogeneous catalyst over more than 8 reaction cycles
- Method able to generate relevant and biological active azines

1. INTRODUCTION

Azines are very interesting organic molecules that contain within their structure the conjugated C=N–N=C system, *i.e.*, *N–N* linked diimines.[1] Azines have gather increasing attention in the recent years since they have been widespread employed in several research and industrial fields.[2] Thus, azines constitute an important class of compounds applied in liquid crystals as twisted-nematic displays,[3],[4],[5] in nonlinear optics,[6] and as important scaffolds for drug designing due to their inherent modulating behaviour towards bioreceptors.[7],[8] Indeed, several azine-containing molecules have shown activity as antibacterial, anticancer or antifungal agents. In addition, these molecules have been recently employed in the synthesis of covalent organic frameworks (COFs) and as building blocks in supramolecular chemistry (Figure 1).[9],[10]

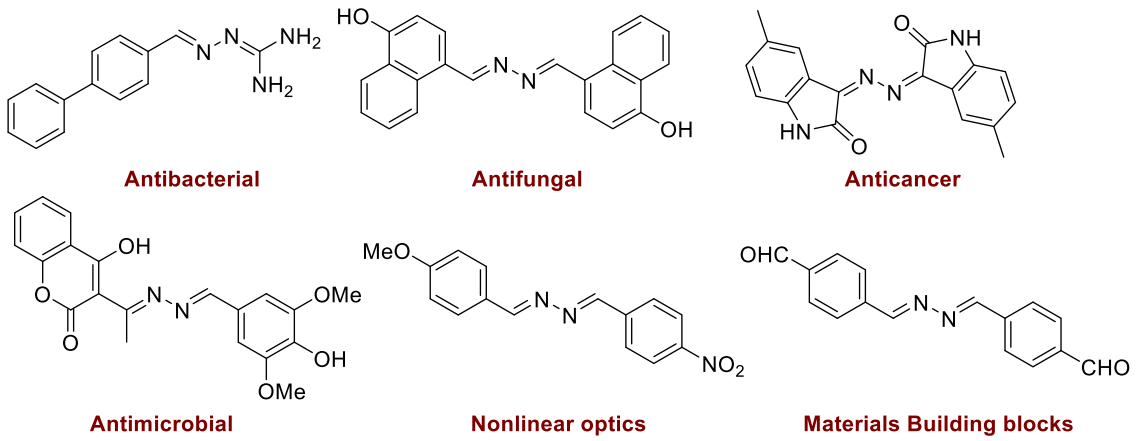


Figure 1. Relevant molecules containing the azine group to be applied in different fields.

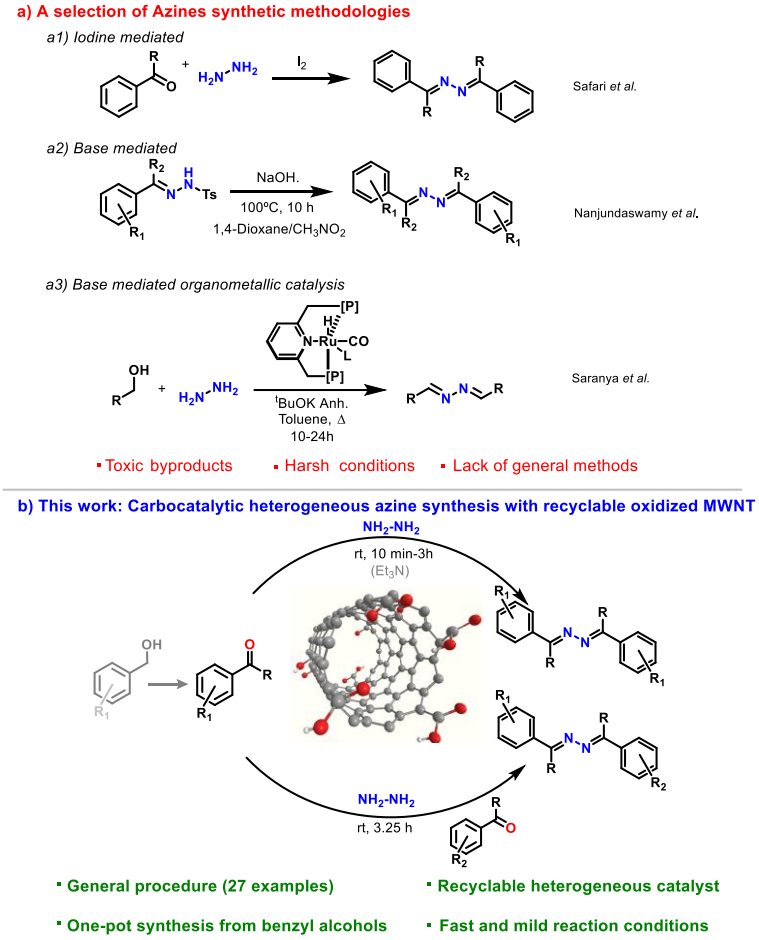
Although the ideal preparation of azines might seem simple since it should be carried out via direct condensation between hydrazine and a carbonyl group (aldehyde or ketone to yield aldazines and ketazines, respectively), this direct approach requires, in many cases, reflux conditions and/or the presence of promoters such as iodine, strong Brönsted or Lewis acids, or bases among other possibilities (see Scheme 1a).[11],[12],[13] In addition, these reactions often generate large amounts of unwanted and toxic by-products.

In order to avoid these synthetic drawbacks, researchers have switched to alternative generation routes, typically employing transition-metal organometallic complexes coupled with reductants, strong bases and long reaction times.[14],[15],[16],[17],[18] Alternative synthetic methods have also been reported in the literature by means of unstable carbenes,[19] electrochemical [20] or supercritical techniques, and microwave or ultrasound protocols.[21] Consequently, the generation of azines is currently carried out through harsh and tedious synthetic conditions [2],[22] and therefore it is highly desirable to develop a general methodology for the obtainment of this class of compounds. On the other hand, while the synthesis of symmetric azines is driven via one specific procedure, the preparation of asymmetric azines (different substituents at each imine group) requires a completely diverse strategy.[2] To the best of our knowledge, a general and simple azines synthetic method that avoids the aforementioned disadvantages is still missing.

In this context, carbon (nano)materials have been presently employed as catalysts in a wide gamut of different organic transformations,[23] obtaining comparable or better results than the traditional procedures, and with the advantage that they can be recycled.[24] As metal-free materials, carbon (nano)materials are able to carbocatalyse, for instance, redox reactions such as the reduction of nitro compounds to anilines [25] or the oxidation of benzyl alcohols to aldehydes/acids,[26] Michael additions [27] and aldol or Knoevenagel condensations.[28] For this library of reactions, the flagship role corresponds to graphene oxide derivatives.[29] Nonetheless, several graphene oxide formulations can be found in the literature that show different sheet lateral size, degree of oxidation and exfoliation, C-sp^2 content, oxygen surface chemistry distribution, etc.,[30] which limits its employment in general synthetic protocols and its reproducibility. Conversely, carbon nanotubes (CNTs) represent a more controllable alternative regarding

the synthesis of the material, which can be even produced at the industrial scale.[31] Since CNTs are rolled graphene sheets over their axis forming a carbon-based cylinder, the properties of both pristine nanocarbons do not dramatically differ.[32] In addition, the CNTs' oxidation processes, which develop the surface oxygen chemistry, are well-known and stablished.[33] Thus, an appropriate oxidation treatment over the CNTs can generate the required oxygen chemistry to trigger the carbocatalytic character of the material. However, the use of oxidized or *N*-functionalized CNTs as carbocatalysts has only been employed for the aldol or the Knoevenagel condensation reactions.[34] Consequently, we envision that would be desirable to explore the catalytic activity of oxidized CNTs in other synthetic procedures, such as the synthesis of symmetric and asymmetric azines where CNTs could be used as a competitive catalyst.

Thus, in this work we describe a novel carbocatalytic, metal-free, general, and smooth synthesis of symmetric and asymmetric azines from aldehydes and hydrazine using just 5 % wt. of mild-oxidized multiwalled carbon nanotubes as catalyst (**oxMWNT**, see Scheme 1b). In addition, **oxMWNT** is also able to perform the same synthesis but starting from alcohols in one-pot conditions just employing nitric acid as additional reactant. The proposed methodology generates a large library of symmetric and asymmetric azines, even in the gram scale, using a fully recyclable material. The surface chemistry combined with the aromatic scaffold of the material is concluded to be responsible of the observed catalytic performance.



Scheme 1. a) Previous azines obtaining methods compared with b) this work.

2. EXPERIMENTAL SECTION

2.1 Materials and methods.

All chemicals and reagents, including Multi-Walled Carbon Nanotubes (MWNT) employed in this work (10 nm in average diameter, several μm in length, Merck), were purchased from commercial sources (reagent grade quality or better) and used without further purification. Purification of organic products was accomplished by flash chromatography using silica gel (Merck Geduran® Si 60). All the synthetic procedures performed to obtain the non-commercial substrates employed in the catalytic experiments are described at the supporting information, while the characterization data of known compounds matches previous reports.[2]

Nuclear Magnetic Resonance (NMR) spectra were acquired on a BRUKER AVANCE spectrometer running at 300 MHz for ^{1}H (75 MHz for ^{13}C; 471 MHz for ^{19}F) and are internally referenced to residual solvent signals ($CDCl_3$ referenced at δ 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, t = triplet, sept = septuplet, m = multiplet), coupling constant *J* (Hz) and integration. Data for ^{13}C NMR and ^{19}F NMR are reported on chemical shifts (δ ppm). Electrospray Ionization Mass Spectra (ESI-MS) were obtained on an Agilent Technologies 6120 Quadrupole LC/MS coupled with a Supercritical Fluid Chromatograph (SFC) Agilent Technologies 1260 Infinity Series instrument. Transmission Electron Microscopy (TEM) images were acquired with a JEOL-JEM 2100F instrument. Samples were dropcasted from nanotubes' methanol suspensions on holey-carbon copper grids. For the elemental analysis measurements, a LECO CHNS-932 Analyser (Model NO: 601-800-500) was used. Qualitative and quantitative Total

Reflected X-Ray Fluorescence analyses (TXRF) were performed with a benchtop S2 PicoFox TXRF spectrometer from Bruker Nano (Germany). TXRF system was equipped with a Mo X-ray source working at 50 kV and 600 μA, a multilayer monochromator with 80% of reflectivity at 17.5 keV (Mo Kα), a XFlash SDD detector with an effective area of 30 mm^2 and an energy resolution better than 150 eV for 5.9 keV (Mn Kα). For deconvolution and integration, commercial Spectra v. 7.5.3 software package from Bruker was used. Fourier Transformed IR (FTIR) were recorded on a FT-IR 4100 JASCO spectrometer, equipped with a Globar source, a DGTS detector and KBr optics with the ATR accessory. The IR spectra were recorded in the 4000–500 cm^{-1} range, with 200 scans and a resolution of 4 cm^{-1}. X-ray photoemission spectroscopy (XPS) data were acquired in a custom designed UHV system equipped with an Omicron EA125 electron analyzer and a non-monochromatized Al K source (DAR400) at room temperature. A suspension in methanol of the powder sample was drop-casted on a high purity copper support and left to outgas overnight in high vacuum prior to the measurements. Photoemission spectra were fitted with Voight functions after subtraction of a Shirley background. The atomic percentage of atoms in the investigated samples was obtained starting from photoemission intensity and using the cross section of Yeh and Lindau and the TTP2 algorithm to calculate electron inelastic mean free paths.

2.2 Nanotubes opening, oxidation and reduction.

In a typical opening-nanotubes experiment,[33] 50 mg of pristine and closed MWNT was added in an open flask with 50 mL of concentrated hydrochloric acid, and the mixture was magnetically stirred at 60 ºC for 2 h. After cooling down, the solid was isolated by centrifugation and washed with fresh Milli-Q water by centrifugation cycles till the supernatant reached neutral pH. Sample MWNT was dried under vacuum.

For the oxidation of the nanotubes,[35] 12 mg of opened MWNT were reacted with 6 mL of concentrated nitric acid under magnetic stirring at 80 ºC for 20 min. After cooling down, the solid was isolated and washed again by centrifugation cycles till the supernatant reached neutral pH. Samples were dried under vacuum for the yielding of **oxMWNT. oxMWNT*** sample was yielded identically by reaction with concentrated HNO_3 for 1h, while **oxMWNT-TR450** was obtained by thermal reduction at 450 ºC during 1h in a horizontal quartz furnace under an Ar flux of 200 mL min^{-1} (heating ramp: 5 ºC min^{-1}).[35]

2.3 Catalytic azine condensation

The typical symmetric azine condensation reaction was performed, if not otherwise stated, as follows. 0.25 mmol of the aldehyde was dissolved, in a 11 mL glass vial, in 0.5 mL of 1,4-dioxane. Then, the adequate amount of **oxMWNT** was added to reach a catalyst loading of 5 % wt. (for benzaldehyde is needed 1.3 mg of **oxMWNT**). To this suspension, 0.125 mmol of hydrazine hydrate was added, and the reaction was conducted at room temperature with magnetic stirring for the desired time, typically 3h. Once the reaction was finished, the black catalyst solid was filtered, solvent was removed under reduced pressure and the filtrated azine was analyzed by NMR and ESI methods, and purified by flash column chromatography when necessary (see supporting information). The reaction evolution tracking was performed withdrawing 0.05 mL aliquots at regular intervals and immediately analyzed by NMR methods. Then, gram-scale experiments were performed maintaining the same catalyst loading but increasing the amount of reagents (aldehyde, hydrazine, and solvent) by a 40 factor.

For the asymmetric azine yielding, 0.25 mmol of the first aldehyde, dissolved in 0.5 mL of 1.4-dioxane and in the presence of 5 % wt. **oxMWNT** catalyst loading, was

reacted with 0.25 mmol of hydrazine hydrate with magnetic stirring for 20 min at room temperature. After this time, 0.25 mmol of the second aldehyde was added, and the reaction was allowed to proceed at room temperature for an additional time, typically 3 h. Once the reaction was finished, the black catalyst solid was filtered, solvent was removed under reduced pressure and the filtrated azine was analyzed by NMR and ESI methods, and purified by flash column chromatography when necessary (see supporting information).

2.4 Catalytic benzyl alcohol oxidation

The standard benzyl alcohols oxidation was performed, if not otherwise stated, as follows. 0.25 mmol of the alcohol was dissolved, in a 4 mL Schlenck-type tube, in 0.5 mL of 1,4-dioxane. Then, the adequate amount of **oxMWNT** was added to reach a catalyst loading of 5 % wt., and finally, 0.5 mmol of HNO_3 was added to the mixture. The reactor was closed and the temperature raised to 90 ^{o}C, where reaction was maintained with magnetic stirring for a desired time, typically 2 h.[26] A 0.05 mL aliquot was withdrawn and analyzed by NMR methods to track the evolution of the oxidation.

2.5 One-pot azine synthesis

The synthesis of the azines performed by one-pot experiments was carried out following the general oxidation and condensation described above in a successive way. Indeed, once the oxidation was completed and the reactor was cooled down, 0.5 mmol of triethylamine was added to the reaction mixture under magnetic stirring for the quenching of HNO_3. After this neutralization, 0.125 mmol of hydrazine hydrate was added, and the reaction was allowed to proceed at room temperature for a desired time, typically 3 h. Once the reaction was finished, the black catalyst solid was filtered, solvent was removed under

reduced pressure and the azine was analyzed by NMR and ESI methods, and purified by flash chromatography (see supporting information).

2.6 Catalyst recovery

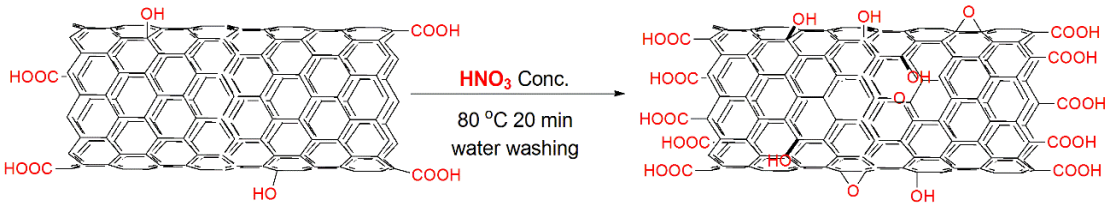
Once both the oxidation and the condensation (or even the one-pot synthesis) were finished, the black catalyst **oxMWNT** was filtered out from the reaction employing a 0.47 μm pore diameter polypropylene membrane. It was washed 3 times by filtration with a 1:1 mixture water-acetone, sonicating for 1 min between one washing cycle and another. Then, it was washed 3 additional times with a mixture of acetone-dichloromethane, repeating the sonication steps too. Finally, the solid was vacuum dried, and submitted to a new catalytic experiment without adding in any case new amounts of catalyst precursor. This procedure was constantly repeated throughout all this work.

3. RESULTS AND DISCUSSION

3.1 Catalysts' preparation and characterization.

Multiwalled carbon nanotubes (MWNT) of 10 nm in diameter and several μm in length were employed in all the experiments. Aiming for a carbocatalytic assessment of the carbon nanomaterials, the metals responsible of the nanotubes´ growth were removed by a mild acid treatment with HCl.[33] This procedure also opened the caps of the MWNT, dissolved the metallic impurities and wash them away. Preliminary HR-TEM observations showed tidy nanotubes opened on their terminations without electron dense regions, which could be assigned as metallic nanoparticles (see Figure S26 at supporting information). Upon this metal etch, the TXRF analysis found values of metals below 6 ppm ranging molybdenum or cobalt, while the other metals presented at least amounts 1

order of magnitude lower (see Table S1 and Figure S27 at supporting information). Elemental analysis of this material determined that the cap-opening cleaning treatment rises the oxygen content till a notably 16 % (see Table S2 at supporting information). In order to further increase the amount of oxygenated chemical groups at the MWNT surface, we employed a more powerful oxidizing agent as concentrated nitric acid. This methodology is able to develop a rich surface oxygen chemistry, in particular COOH groups.[33],[35] As schematically depicted in Scheme 2, the treatment of MWNT (12 mg) with 6 ml of HNO_3 at 80 ºC for 20 min yielded the target sample **oxMWNT**.



Scheme 2. MWNT oxidation to yield **oxMWNT** sample.

The HR-TEM analysis showed images where the **oxMWNT** presents somewhat irregular carbon walls with roughly amorphous carbon surrounding the tubular structure (Figure 2 and Figure S28 at supporting information). The procedure was not so harsh compared with other previous works,[33],[35] thus the tubular structure is firmly conserved, being difficult to find any disrupture along the carbon scaffold. Furthermore, the oxidation was confirmed efficient by elemental analysis, where the O content increased from 16 % in the metal-free MWNT sample to 25 % in the oxidized **oxMWNT** material (see Table S2 at supporting information for further details). The presence of oxygenated functional groups at the **oxMWNT** was determined employing FTIR (Figure 2 inset), which showed a prominent band at around 1100 cm^{-1} related to C-O bonds. In addition, the shoulder at ~ 1200 cm^{-1} could indicate the presence of epoxy moieties.[35] Interestingly, an important fraction of these surface oxygen groups belonged to COOH

functions, which were undoubtedly assigned by the detected band at 1720 cm^{-1} corresponding to the C=O vibrations of carboxylic acids.[36] Conversely, pristine MWNT, since it has not been strongly oxidized, only presented bands related to C-O and C=C bonds (~1100 cm^{-1} and 1550 cm^{-1}, see Figure S30).

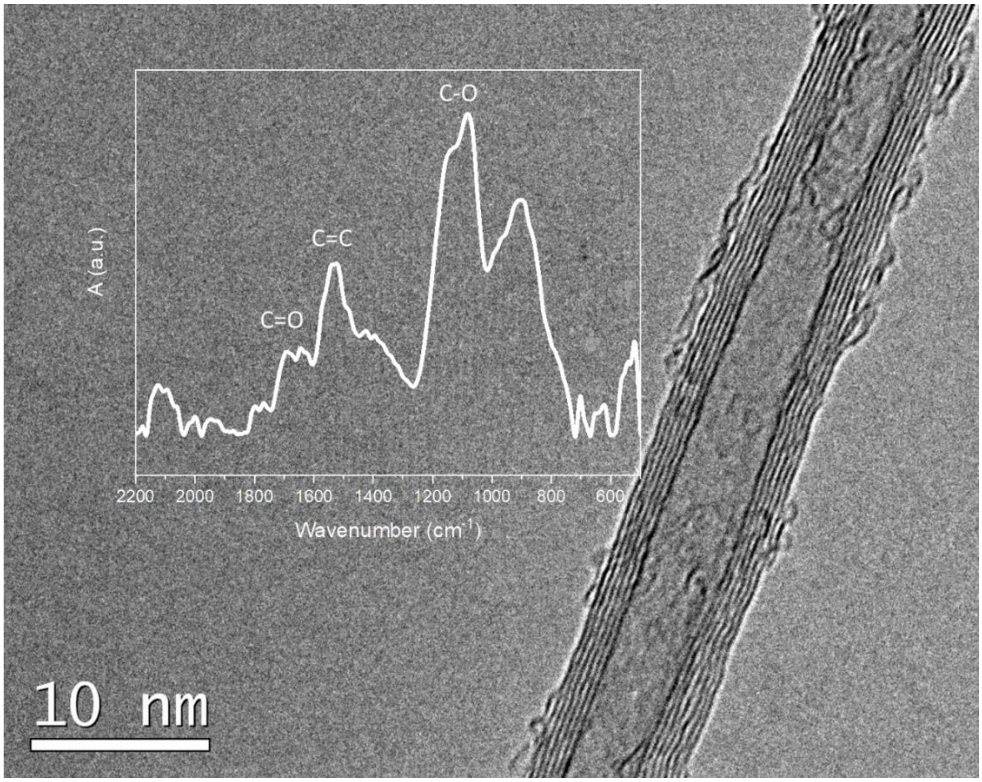


Figure 2. Representative TEM image of **oxMWNT**. Inset: FTIR spectrum of **oxMWNT.**

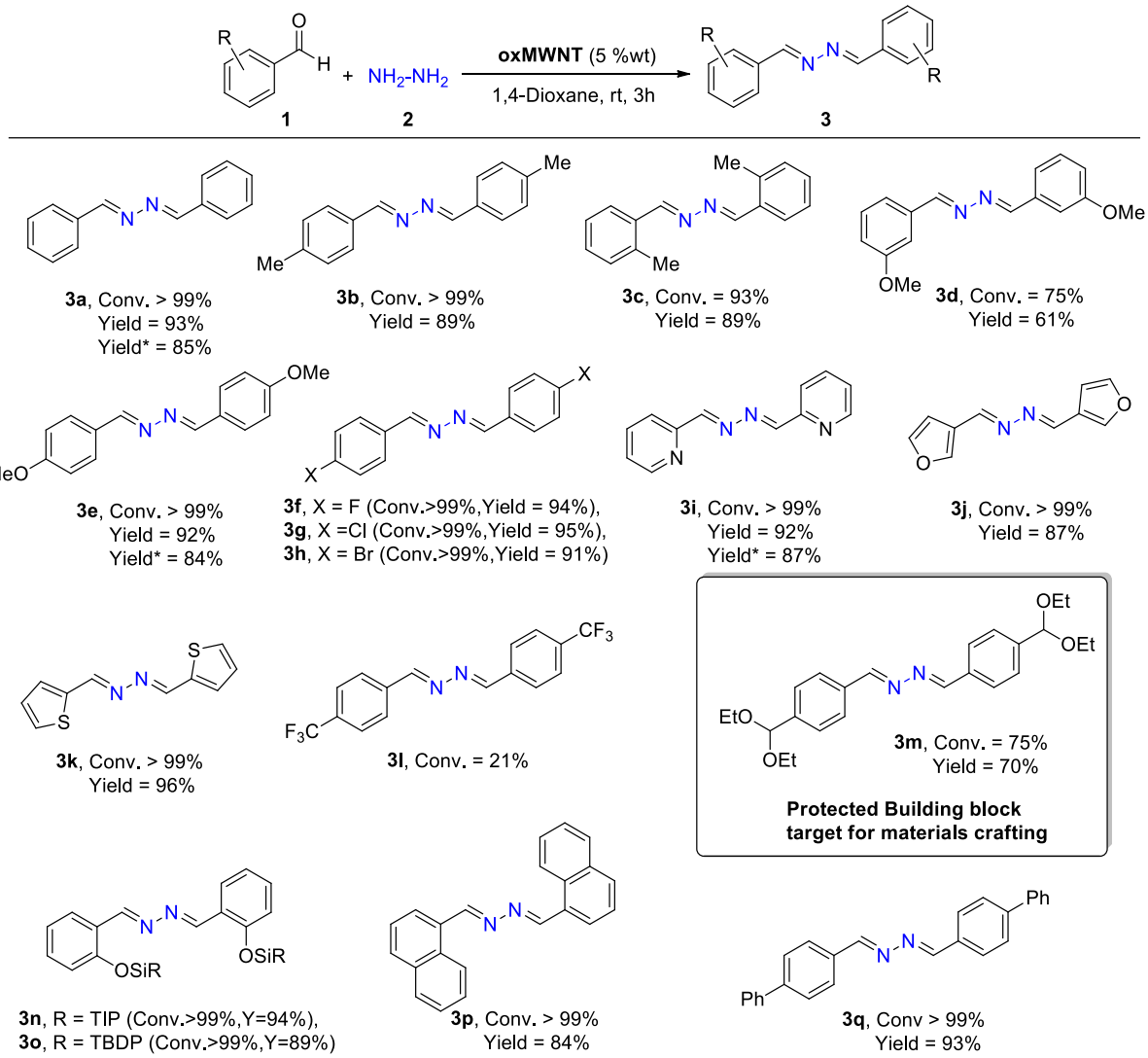
XPS cross-checked the FTIR and elemental analysis results (see Figure S31). Indeed, just a small amount (< 7.5%) of hydroxyl or epoxide groups (C-O, 286.5 eV of BE) was detected by the analysis of the C 1s XPS core level region of the pristine MWNT sample, in accordance with FTIR measurements. Highly oxidized species such as carbonyls (287.8 eV) or carboxylic acids (289.1 eV) were only barely detectable (< 2%).[35] On the other hand, after the HNO_3 treatment, the surface defects and oxygen chemistry were significantly increased and it was possible to clearly distinguish an almost doubled amount of oxygenated species in sample **oxMWNT** (22.1% *vs* 11.8 %); notably carboxyls and carbonyls chemically shifted components showed a relative intensity of 3.5% and

6.4%, respectively, and the hydroxy/epoxy moieties were also incremented in a 12.2%, confirming the results of FTIR analysis. Therefore, both complementary techniques indicated an enrichment in oxygen moieties after treatment with the oxidizing agent.

3.2 Catalytic activity exploration.

Motivated by previous works where different carbon nanomaterials, especially oxidized graphene derivatives,[23],[29] were employed as carbocatalysts for different organic transformations, we thought it would be proper to check the ability of our *ad-hoc* **oxMWNT** to carry out condensation reactions. As starting point, we mixed, in the presence of 5 %wt. loading of **oxMWNT** (1.3 mg), pure benzaldehyde **1a** (0.25 mmol) with hydrazine **2** (0.5 equivalents) at room temperature in 1,4-dioxane aiming to yield a hydrazone.[37] For our surprise, the reaction afforded the azine **3a** in excellent yield (93%) after 3 h. It is worthy to point out that, even though the hydrazone formation does not need the presence of any type of catalyst, its additional condensation with another aldehyde to form the final azine is not trivial. This fact is due to the large delocalization of the free electron-pair at the hydrazone that produces a dramatic lower nucleophilicity of these species, making challenging its condensation to form the final azine.[38] Therefore, in many cases, a catalyst is needed for this second condensation process. Furthermore, the azine **3a** formation reaction catalysed by **oxMWNT** could be scaled up to 10 mmol of benzaldehyde (increased 40 times), achieving an impressive 85% yield in 24 h of room temperature stirring. Employing the general procedure depicted above, a large library of symmetric azines **3** could be yielded (see Table 1).

Table 1. Symmetric azine formation catalysed by **oxMWNT**[a]



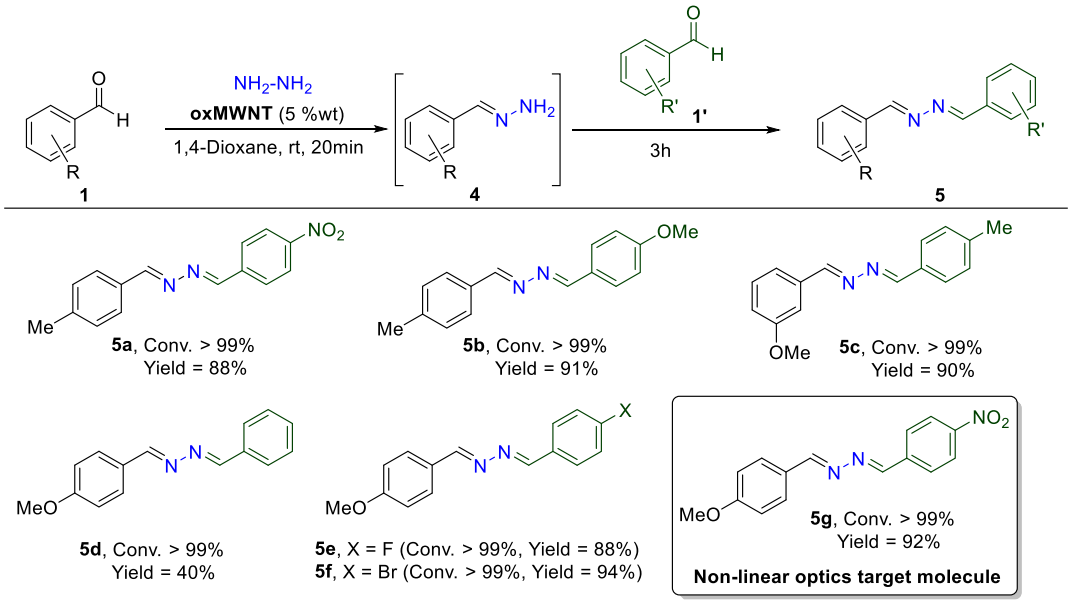
a) Reaction conditions: 0.25 mmol of aldehyde, 0.125 mmol of hydrazyne hydrate, 0.5 M 1,4-dioxane, 5 %wt. **oxMWNT**, for 3h at room temperature. Conv. stands for conversion (determined by ^{1}H-NMR). Yield* refers to a 10 mmol reaction

As can be seen in Table 1, the reaction tolerated electron-donating groups irrespectively their relative position at the phenyl ring (*ortho*, *metha* or *para*), obtaining the azines in excellent conversion and yield values. Hence, *o*-methyl and *p*-methyl aromatic azines could be generated with good yields (**3b** and **3c**, 89%). In addition, *m*-methoxy and *p*-methoxy symmetric azines (**3d** and **3e**) range from 61% to 92% yields, respectively. Interestingly, azine **3e** can be obtained in the gram scale with an 84% yield. Notably, a halogen atom (*p*-F, *p*-Cl or *p*-Br) in the aldehyde precursor is either tolerated in the azine formation reaction (**3f-h**) with very good performance (91-95% yield). Moreover, **oxMWNT** catalyst is also able to smoothly convert pyridine, furan and thiophene

aldehydes to the corresponding azines (**3i-k**) with yields ranging from 87 to 96%. The pyridine azine **3i** was also obtained in the gram scale (starting of 10 mmol) with a yield of 87%. However, the azine formation method owned some limitations, such as the presence of an electron-withdrawing group (EWG) at the aromatic ring. For example, the CF_3 azine **3l** was obtained in 21% conversion. Nevertheless, the protected aldehyde allowed the synthesis of azine **3m** in 75% of conversion, which have been used for organic materials crafting.[10] On the other hand, the method did not work with aldehydes with protic groups such as alcohols or amines. Conversely, this limitation can be overcome employing a simple protection pre-step with silanes as triisopropyl silane (TIPS) or *tert*-butyl diphenyl silane (TBDPS) (**3n** and **3o**), obtaining excellent yields (89% and 94%, respectively). Finally, other substrates such as a naphthyl aromatic ring (**3p**) could be tolerated in the formation of a more steric demanding azine in high yield (84%). In addition, a biphenyl derivative was also achieved with a very good isolated yield of 93% (**3q**). It should be noted that the presence of the **oxMWNT** causes a notable increase in the reaction performance since the reactions with *p*-bromobenzaldehyde or *o*-tolualdehyde without the **oxMWNT** gave rise to null or low conversions towards the intended azine, respectively (see Scheme S1 in SI). We also tried to synthesize alkyl azines but only the corresponding hydrazones were obtained in almost full conversion (see Table S3 in SI). Thus, the selectivity of the catalyst for aromatic substrates agrees with the performed scope discussed above and encloses a key factor concerning the adsorption of the substrate at the nanotube wall. Electron rich aldehydes π-π stick more efficiently than the electron poor substrates, which is reflected in the reactivity in strong contrast to the known electrophilicity of the non-converted electron poor aldehydes (see below), thus indicating that the reaction might be surface mediated.

Taking into consideration the excellent catalytic performance of **oxMWNT** in the synthesis of symmetric azines, we decided to move our efforts for the synthesis of asymmetric azines, which are more challenging products to obtain.[39] Thus, symmetric azines **5** could be easily synthetized when the general azine formation reaction, but using 1 equivalent of hydrazine **2,** was stopped after 20 minutes. At this point, the formation of the hydrazone **4** was observed, and immediately a second aldehyde was added to this mixture, allowed them to react for 3 hours (see Table 2).

Table 2. Asymmetric azine formation catalysed by **oxMWNT.**



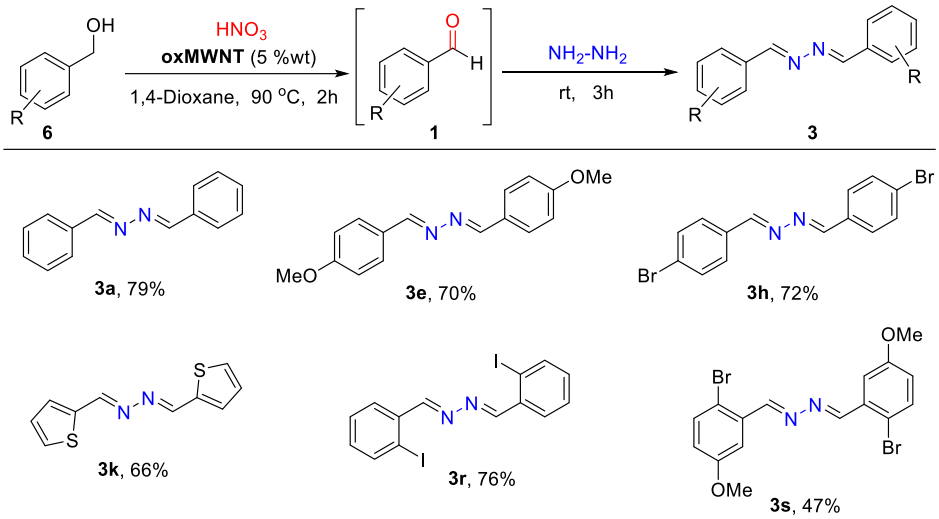
Reaction conditions: 0.25 mmol of aldehyde, 0.25 mmol of hydrazyne hydrate, 0.5 M 1,4-dioxane, 5 %wt. **oxMWNT**, for 20 min at room temperature. Then, 0.25 mmol of second aldehyde for 3 h. Conv. stands for conversion (determined by ^{1}H-NMR).

Using this slightly modified methodology, the limitations from the symmetric azine synthesis method, such as the use of EWGs, could be overcome. Operating in such way, this reactivity was expanded to different substituents in both phenyl units. For instance, the azine (**5a**), with a *p*-methyl and a *p*-nitro at each aromatic ring, can be synthesized with full conversion and selectivity, and with a yield of 88%. It is worthy to mention that the relative position of the substituents (*metha* or *para*) does not change the result of the reaction. Hence, an azine where one phenyl ring contained a methoxy group, while the

other phenyl ring with a *p*-methyl unit was synthetized in an excellent 91-90% yield (**5b** and **5c,** respectively). However, the azine **5d** was achieved in only 40% yield. This low yield can be explained by the fact that symmetric azines **3a** and **3e** were also obtained in this reaction. The presence of halogens atoms at an aromatic ring also afforded derivatives **5e** and **5f** in good yields. In addition, the electron-rich hydrazone bearing a *p*-methoxy group reacted with the electron-poor aldehyde (*p*-nitrobenzaldehyde) to give the azine **5g** with a 92% yield, which can be applied for nonlinear optics.[6] It should be noted that, using our conditions and without the presence of the **oxMWNT** (or not waiting 20 min, Scheme S2), azine **5b** could not be obtained with good results.

We also challenged the **oxMWNT** catalyst to perform an azine one-pot synthesis starting from benzylic alcohols. To carry out this task, we previously studied the oxidation of benzyl alcohols to aldehydes carbocatalyzed by **oxMWNT** in the presence of nitric acid as co-oxidant, as previously has been reported for similar transformations.[26] For our delight, and upon optimization (see Figure S32 and Table S4 at supporting information), **oxMWNT** was able to accomplish this particular transformation in just 2h oxidation at 90 ^{o}C with an 80% of conversion and selectivity (comparison of performance is shown in Table S5 and Table S6 at supporting information). After formation of corresponding aldehydes **1**, and acid neutralization, the mixture was treated with hydrazine for 3h, obtaining the final azines in moderate to good overall yields from 48 to 80% (see Table 3). Using this method, we were able to synthetize symmetric azines, in one-pot manner, with a phenyl (**3a**) (79% yield), a *p*-bromo (**3h**) and an *o*-iodophenyl (**3r**) group (72% and 76 % yield, respectively), a *p*-methoxy-C_6H_4 (**3e**) (70% yield), an thienyl group (**3k**) (66%) and a more substituted azine bearing a bromo and a methoxy moieties at the aryl ring (**3s**) (47% yield).

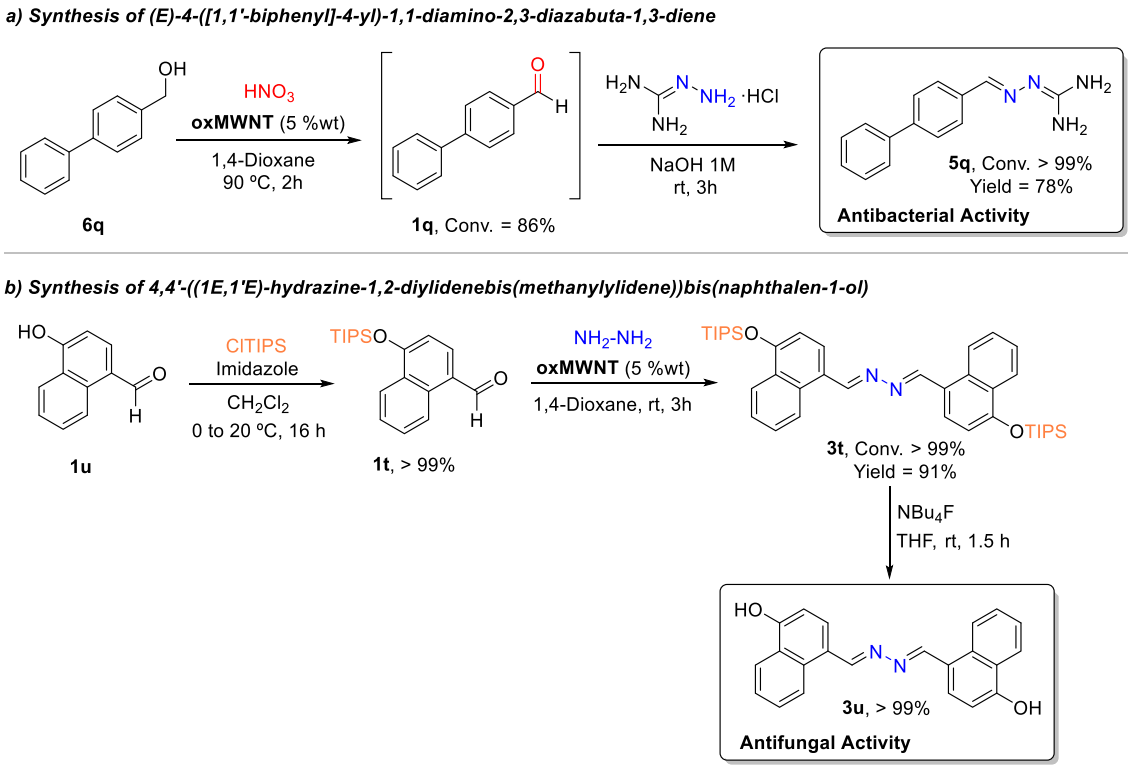
Table 3. One-pot formation of azines from benzyl alcohols catalysed by **oxMWNT**



Reaction conditions: Step 1: 0.25 mmol of alcohol, 0.5 mmol of HNO_3, 0.5 M 1,4-dioxane, 5 %wt. **oxMWNT**, for 2h at 90 °C. Step 2: Reactor cooled to room temperature, 0.5 mmol of Et_3N and 0.125 mmol of hydrazine hydrate, for 3 h at room temperature. Values stand for total isolated yield

In order to add value to our methodology, we thought it would be suitable to apply our **oxMWNT** at the synthesis of azines with biological interest. Notably, azines, as introduced previously, are important compounds that present interesting pharmacological properties. [40],[41] Remarkably, an asymmetric biphenyl-based azine combined with a guanidine is described to present strong antibacterial activity.[40] Therefore, starting from the alcohol **6q,** we set the oxidation in the presence of **oxMWNT** and nitric acid as mentioned previously (see Scheme 3 upper panel). This oxidation generated the biphenyl aldehyde derivative **1q** with 86% conversion, which was reacted with aminoguadinine hydrochloride in the presence of 1.0 equiv. of NaOH for the neutralization of the hydrochloride salt at room temperature for 3h. For our delight, **oxMWNT** was able to yield the antibacterial azine **5q** with an excellent 78% of global yield for this one-pot process. On the other hand, since symmetric azine **3u** possesses antifungal activity (see Scheme 3 lower panel),[41] we thought that would be very interesting to synthesize it using our methodology. Thus, the 4-hydroxynaphtaldehyde protected as TIPS (**1t**) was submitted to the condensation with hydrazine catalysed by **oxMWNT** under the standard

conditions depicted above. Upon deprotection, the antifungal azine **3u** was obtained in almost quantitative yield (91% global yield, 3 steps).



Scheme 3. Biological active molecules synthetized with the proposed methodology.

Then, we studied the recyclability of the carbocatalyst. Indeed, nanotubes were collected by filtration methods after finishing each experiment, washed with water and organic solvents and set for a new oxidation-condensation reaction. Any loss of activity was detected when performing a cycling study on benzyl alcohol (**6a**) oxidation-condensation runs (see Figure 3). Moreover, the HRTEM, FTIR and elemental analysis characterizations carried after the catalytic study indicated that the material seems to not be modified. Indeed, only a very small shoulder was observed in the spectrum of the recovered sample at around 1200 cm^{-1} which is still related with hydroxy and/or epoxy bonds (see Table S2 and Figures S29 and S30 at supporting information).

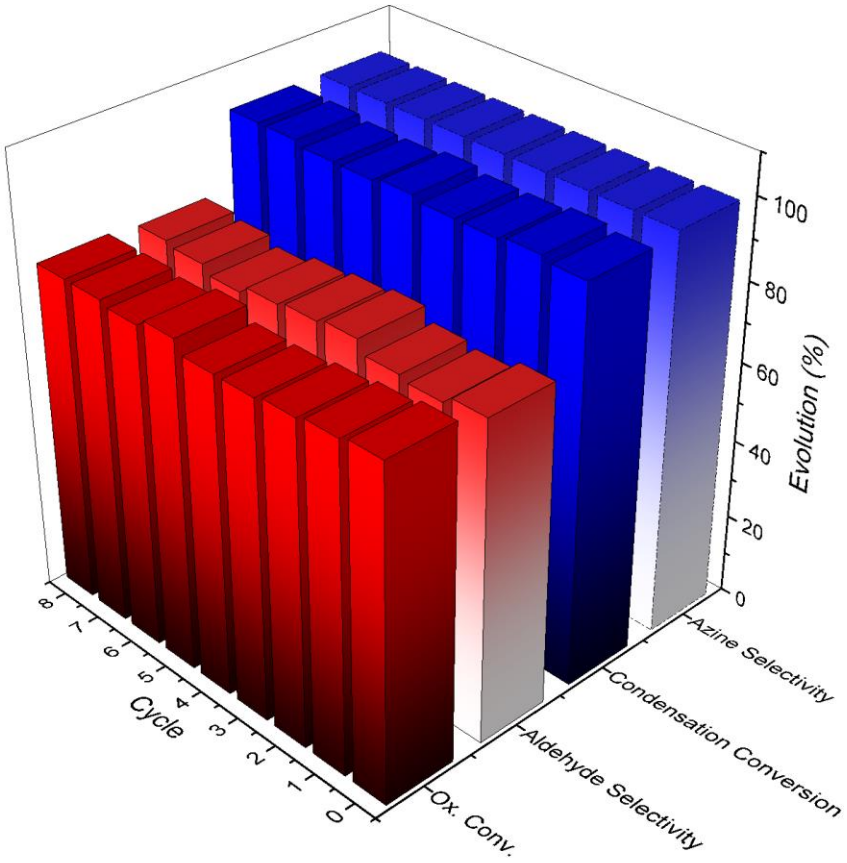


Figure 3. Cycling study for the oxidation of benzyl alcohol (red bars) and further azine **3a** condensation (blue bars), including conversion (dark lightning) and selectivity (clear lightning), catalysed both by **oxMWNT.**

3.3 Mechanism elucidation.

Once, we have carried out the reaction scope, we wanted to get insights in the reigning mechanism that rules the formation of azines in the presence of carbon nanotubes. Thus, we initially monitored the condensation reaction withdrawing aliquots at regular intervals. The NMR tracking of the reaction showed a *pseudo*-first order kinetic evolution in the azine formation (see Figure 4).

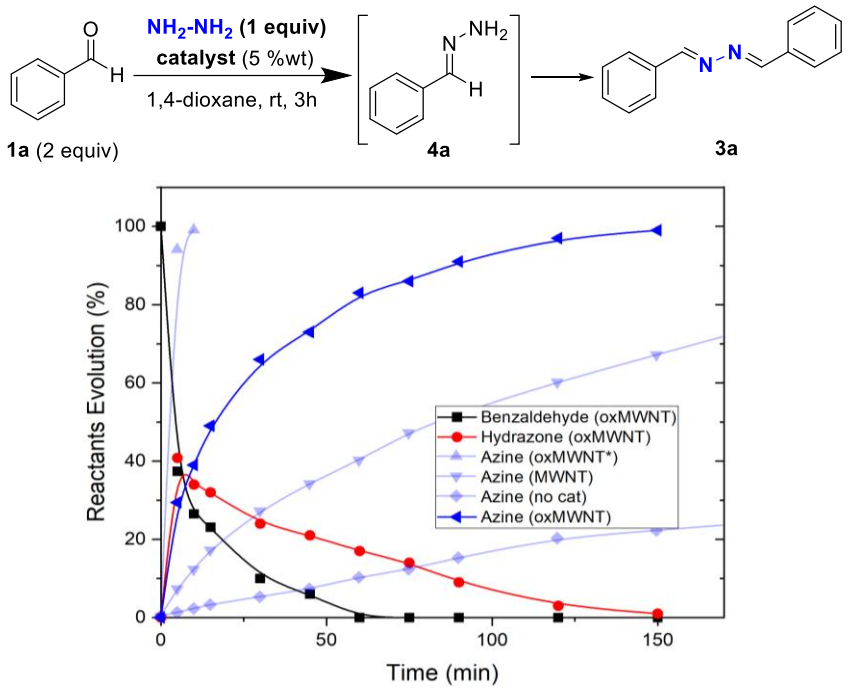


Figure 4. Temporal evolution of diphenyl azine formation catalysed by the different CNTs (lines are guide for the eyes).

The evolution shown in Figure 4 suggests that the azine seems to be formed by reaction of the immediately generated hydrazone in the presence of **oxMWNT**. On the other hand, the aldehyde was consumed after the first hour of reaction, while the hydrazone was progressively transformed in the final product until reaching almost full conversion in the last 100 min of reaction. This particular evolution made us think that the nanotubes may play a key role in the formation of the azine. The employment of the "non-oxidized" MWNT sample showed just 60 % conversion of azine after 150 min of reaction. Finally, the amount of condensed azine obtained decreased to 20 % in a reaction performed without the carbon material. Hence, the presence of **oxMWNT** material is essential to catalyse the azine formation. Furthermore, a more oxidized MWNT sample, prepared by oxidation with HNO_3 for 1h at 80 ºC (**oxMWNT*,** see supporting information for further characterization details), was able to finish the condensation in just 10 min of reaction. Conversely, a sample treated at 450 ºC for 1h under inert atmosphere in order to thermally

remove the labile oxygen groups (**oxMWNT-TR450**, see supporting information for further characterization details on the dramatic decrease of oxygen moeities) just achieved 75 % conversion in the standard **3a** azine formation reaction (Scheme S3). As a result of these tests, we believe that the surface oxygen groups present at the nanotube walls and generated during the oxidation procedures interact with the reactants by non-covalent interactions (typical Lewis acid behaviour [42]), which drives the reactivity towards the generation of the intended symmetric and asymmetric products. It is also important to point out that the reactants used are aromatic, and this kind of substrates are able to be physisorbed at the surface of the material in a very efficient manner by π-stacking interactions, and then find the active centre to be transformed to the condensed product.[25],[43] Conversely, aliphatic substrates as propanal, butanal or pentanal (see Table S3 at supporting information) do not show enough affinity for the nanotube wall, as previously mentioned. As a result, aliphatic aldehydes are mainly converted to the corresponding hydrazones (>98% conversion) but not to azines (<2%). The absence of interactions with the nanotube wall may explain the observed behaviour, and therefore aliphatic substrates experience an uncatalyzed reactivity that stops in the hydrazone.

The reaction seems to proceed via surface adsorption to further evolve through the classic condensation mechanism that is activated via the surface oxygen chemistry. Nevertheless, other possible mechanisms could also take place, such as radical pathways. Taking into account that carbon nanotubes can drive radical reactions in the presence of light,[44] we performed the standard azine **3a** condensation in the presence of 3.6 equivalents of TEMPO (the archetypical radical scavenger [45]). We obtained the azine **3a** with a very similar performance to that obtained during the reaction scope. This experiment discarded a radical mechanism as responsible of the *N*-containing molecule formation (see Figure S33 at supporting information). On the other hand, the water molecules released in the

azine formation reaction could also influence the outcome of the transformation. Thus, we carried out the condensation in absence of water using $MgSO_4$ as desiccant to dismiss that the water molecule generated during the hydrazone formation was the responsible to the azine generation. This test afforded the azine **3a** with the same performance to the standard run (see Figure S34 at supporting information). In addition, starting from the corresponding hydrazone **4a** in absence or in the presence of the stoichiometric amount of water resulted in the same full conversion reaction to the azine **3a** formation. These tests showed that the presence of water has no effect in the formation of azines catalyzed by **oxMWNT** because the aromatic azine formation reaction mainly takes place at the surface of the nanotubes.

In summary, the reigning mechanism might be a surface version of a classic condensation, where the substrate is strongly adsorbed at the carbonaceous scaffold by π interactions. Once adsorbed, the access to the active sites becomes simplified, and the oxidized nanotube with its Lewis acid character catalyzed the azine formation reaction.

4 CONCLUSIONS

This work describes a carbocatalytic method able to generate a wide library of azines using as catalyst mild acid oxidized multiwalled carbon nanotubes. The azine synthesis was carried out by direct mixing of an aldehyde with hydrazine hydrate using as catalyst loading just 5 %wt. of **oxMWNT**. Moreover, the reaction can be scaled up to the gram scale. **oxMWNT** is able to yield symmetric and asymmetric azines in very good conversions, selectivity and yields within reaction times typically of 3h but depending on the amount of oxygen groups developed in the oxidation of the nanotube. In addition, these azines can be synthetized carrying out one-pot procedures using as substrate the

corresponding alcohol thanks to the state-of-the-art **oxMWNT** oxidizing capability, achieving the final condensed product with total yields as high as 80%. Thus, aromatic aldehydes strongly stack to the nanotube wall could be condensed while aliphatic substrates were not physisorbed and therefore not converted. The gathered data suggest that the substrates, once fixed at the **oxMWNT** oxygen surface chemistry, are able to react following this surface version of the general condensation.

Acknowledgments

Financial support was provided by the European Research Council (ERC-CoG, Contract Number: 647550, ERC-PoC, Contract No. 861930), the Spanish Government (RTI2018-095038-B-I00), the 'Comunidad de Madrid' and European Structural Funds (S2018/NMT-4367) and proyectos sinérgicos I+D (Y2020/NMT-6469). M.B. wishes to thank the Spanish Government for a Juan de la Cierva contract (IJC2019-042157-I). We also acknowledge the electron microscopy analysis from CNME and J. R. Avilés-Moreno for his support with FTIR analysis.

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