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The New Dimension of Graphene-oxide as a Mediator in Organic Synthesis: a mechanistic focus

Lorenzo Lombardi^[a] and Marco Bandini^{*[a]}

Dedicated to the memory of Prof. Kilian Muñiz

Abstract: Graphene oxide (GO) is experiencing a growing interest by synthetic organic chemists as a promoter of chemical transformations. The synergistic role of the multiple functionalities featuring the nanostructured carbon materials and their π -domains enables the interplay of specific activation modes towards organic compounds that can explore unprecedented chemical modifications. A detailed comprehension of the mechanistic dictates that governate the transformations guided by GO, is probably the still not fully solved task in the field. In this direction, always more sophisticated and diversified techniques are employed, providing insights towards intriguing activation modes exerted by the π -matrix and the oxygenated/sulfonate groups decorating the functionalized nano-carbon material. The present *Minireview Article* accounts for a critical survey of the most recent developments in the area of GO-mediated organic transformations with a specific focus on mechanistic aspects.

1. Introduction

The use of carbon-based nanostructured materials^[1] as promoters of organic transformations (commonly referred as carbocatalysis) is gaining growing credits within the chemical scenario.^[2] In this emerging and somehow controversial research area, graphene oxide (GO) is in the forefront of carbocatalysis due to its numerous peculiar properties.^[3] In particular, the partially disrupted and oxidized honeycomb graphene lattice imparts to GO crucial properties such as: the capability of generating stable dispersions in polar solvents (*i.e.* DMF, NMP, THF..) as well as aqueous media^[4] and chemical tunability via covalent and non-covalent derivatizations.^[5] In addition, availability on large scale,^[6] relatively high thermic stability and high surface area are contributing to propose GO as a valuable environmentally benign modulator for organic transformations.

Although a net dichotomy between the role of GO as a pure catalyst or co-reagent^[7] is still controversial, the use of this carbon nanomaterial in organic synthesis contributed substantially to the current popularity of “carbocatalysis”, that starts paralleling the most consolidated and widely diffused metal-, organo- and bio-catalytic tools.

Despite the young age (early and pioneering examples date back to 2010 with the oxidation of alcohols and unsaturated

hydrocarbons)^[8] the portfolio of chemical diversity accessible by means of this nanocarbon material has grown rapidly. In parallel, unpredictable activation modes exerted by GO on organic substrates are also discovered, serving as ongoing sources of inspiration for new developments.

In this context, the unique interplay and synergistic role of the π -matrix (*i.e.* aromatic or graphene domains, Csp^2 -atoms), oxygenated functional groups on the basal plane (epoxides and tertiary alcohols, Csp^3 -atoms) and dangling groups (carbonyls, enols, lactones, lactols, sulfonates) at the edges of the sheets/defects contributed in drawing the *Babel* of possible mechanistic scenario based on GO carbocatalysis.^[9]

In this respect, the most salient interactions/activation modes triggered by GO with reaction partners are as follows (Figure 1):

- i) Csp^2 -domains are believed to modulate the reactivity of unsaturated hydrocarbons via π - π -interactions;
- ii) Alcoholic, epoxydic and sulfonate groups can trigger temporary covalent linkages with the reaction partners;
- iii) Carboxylic, sulfonic and enolic units impart the Brønsted acidity characterizing the carbon material;
- iv) The combination of *zig-zag* sheets/vacancies edges, carrying unpaired electrons, holes and carboxylic acids can mediate single-electron transfer events;

As a result, graphene oxide is considered a collector of the most salient catalytic properties encountered in transition metal catalysis such redox-processes, π - and σ -acidity and charge transfer phenomena.

From a chemical architecture point of view, the widely accepted Lerf-Klinowski (LK) model^[10] describing the GO structure should also be implemented by the presence of several highly acidic sulfonate units (C:sulfonate group ca. 20:1) that have been documented being covalently bond to the carbon structure.^[11] These functionalities could likely emerge by the oxidative preparation of GO and relative uncomplete hydrolysis upon aqueous work-up (Hummers method).^[12] Intuitively, the sulfate content is deeply influenced by the aqueous washing and so it can change batch by batch. As a matter of fact, it has been determined that for deeply washed GO, the C:sulfate ratio can be as low as 90:1.^[13]

The acidity of GO will be frequently mentioned and accounted in the present *MiniReview* as a pillar chemical aspect affecting the catalytic performance of the nano-carbomaterial. In this context, it was recently demonstrated that, the Brønsted acidity of pristine GO (ca. one acidic site every 25 C atoms) cannot be entirely ascribed to the presence of native carboxylic groups.^[14] On the

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contrary, acidic enols as well as organic sulfonates should have a major role in accounting the overall acidic profile.

A careful assessment of the potential contribute of metal impurities on the overall catalytic performances of GO should also be taken into account.^[15] As a matter of fact, significant amounts of not innocent metallic impurities can persist from the natural and synthetic graphite contents or can be released to the carbon-nanomaterial during the oxidation treatments.

Additionally, the molecular structure of GO should not be considered immutable and immune to solvents as well (dynamic structure). As an example, the use of water or change of pH can trigger substantial structural reorganizations of the GO functional groups (*i.e.* carbonyl hydrolysis, epoxide ring-opening, disproportionation reaction with concomitant decarboxylation....).

Although the afore-cited Hummers' oxidative protocol ($\text{H}_2\text{SO}_4\text{conc}/\text{NaNO}_3/\text{KMnO}_4$) is widely employed for GO preparation, other valuable methodologies have been proposed during the time (namely: Staudenmaier, Brodie, Tour and Hofmann oxidations), delivering GO with dissimilar degrees of oxidation and chemical functionalization.^[16] Therefore, for sake of homogeneity/reproducibility, the structure of the pristine carbon-catalyst should be always taken into account.

In addition, the material science still features intrinsic limitations towards site-specific characterizations with respect to molecularly defined discrete compounds. *Therefore, it is not surprising to record the still ongoing degrees of uncertainty in the mechanistic elucidation beyond the chemical organic transformations promoted by graphene oxide.*

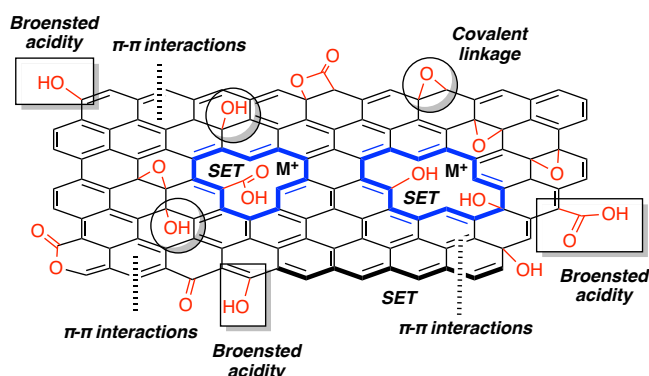
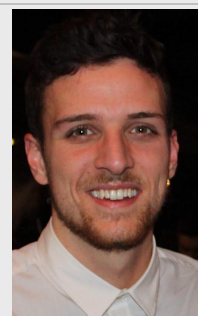


Figure 1. Pictorial representation of a monolayer of graphene oxide (LK-model). Defects are represented in blue and oxygenated functional groups in red. Some of the most salient and decrypted activation modes exerted by GO are highlighted.

The combined use of interdisciplinary enabling techniques such as computational calculations,^[17] spectroscopic characterizations, use of model compounds and tailor-made experimental controls are routinely adopted to this aim. As a consequence, somehow unexpected and unprecedented mechanistic profiles with respect to *conventional* pathways, emerged.

It is not intention of the present *MiniReview* to furnish a comprehensive collection of GO mediated transformations but to provide guidelines for the mechanism-inspired design of chemical diversity/complexity in organic synthesis. Last but not least, the present collection of examples have been limited to native graphene oxide material and the parallel and highly promising fields related to heteroatom doped and co-doped GO and rGO catalyses^[18] should be considered out of the scope of the present *MiniReview* article. Last but not least, we believe that it could be useful for the readers to briefly address and clarify the somehow confusing nomenclature interchange between single-layer graphene oxide (GO) and multi-layer non-sonicated graphite oxide (GIO). As a matter of fact, although both GO and GIO are frequently and erroneously named as graphene oxides, these graphene-based materials feature numerous structural (*i.e.* number of layers) as well as physical-chemical properties (*i.e.* surface area, solubility)^[19] than can have important impacts also on their catalytic performances.^[20]

Lorenzo Lombardi was born in Jesi, Italy in 1994. He obtained his Bachelor's degree in 2016 from Camerino University under supervision of Professor Enrico Marcantoni. Then he moved to Bologna University where he got his Master's degree in Chemistry (2018) and entered the PhD programme under the supervision of Prof. Marco Bandini. His research interests deal with the development of new carbocatalytic methodologies in organic transformations.



Marco Bandini got the PhD in Chemistry at the University of Bologna in the 2000. After some research periods abroad (University of Chapel Hill, USA and University of York, UK) he got a permanent position at the Alma Mater Studiorum – Università di Bologna where he is currently holding the position of full Professor of organic chemistry. Authors of ca. 130 publications, his research interests deal with the development of catalytic systems to address challenges in synthetic organic chemistry.



2. Covalent activation modes

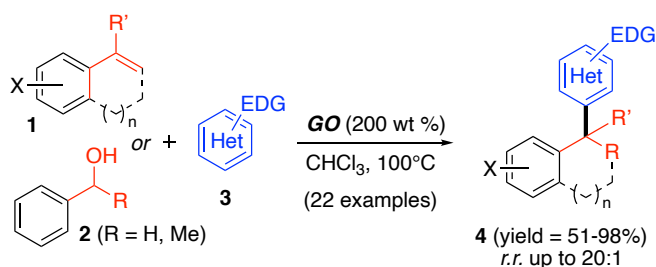
Covalent catalysis is well documented and exploited in organic transformations. In particular, bio-catalysis^[21] and organo-catalysis^[22] lay their efficiency on the engagement of covalent but reversible interactions between the catalyst and the reaction partners during the reaction course. Graphene oxide has been frequently proposed to endeavor similar activation modes in carbocatalyzed reactions, that can be clearly differentiated based

on the GO-functional groups actively involved in the interaction with the substrates.

2.1. Covalent activation modes via oxygenated functional groups

The oxygenated groups characterizing mainly the basal plane of the GO sheets (*i.e.* epoxide and alcoholic units) have been proposed as active sites in several chemical transformations. A univocal activation performed by these groups is far from being traced; however, the instauration of covalent *contacts* with the reaction partners as well as synergistic actions with the intrinsic Brønsted acidity of GO have been frequently invoked.

The segment was pioneered by He and Szostak (2015) that documented on the use of GO in the Friedel-Crafts (FC) alkylation of electron-activated arenes (**3**) with styrenes (**1**) and primary/secondary benzylic alcohols (**2**) as electrophiles.^[23] The reaction, (CHCl₃, 100 °C) required 200 wt % of GO and released the arylated products **4** in moderate to excellent yields (51-98%) and high benzylic alkylation selectivity (up to 20:1, Scheme 1).

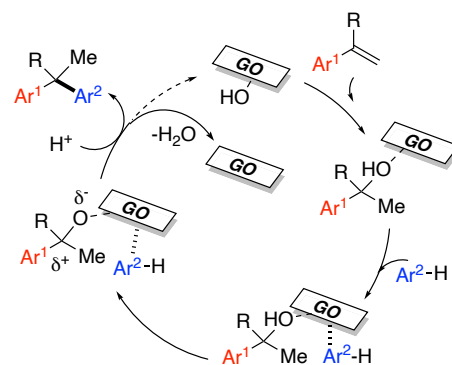


Scheme 1. GO promoted FC-alkylation of electron-rich arenes with styrenes and benzylic alcohols.

Analyses of the carbon material before and after the reaction (X-ray photoelectronic spectroscopy, (XPS) and atomic absorption spectroscopy, (AAS)) ruled out the possible contribution of metallic impurities that were determined below detection limit (< 20/50 ppb). Partial reduction of GO during the reaction course was also ascertained (XPS and FT-IR analysis), displaying a net decrease of C-O and C=O functional groups in the recovered GO. This evidence suggested their involvement in the process that was further corroborated by the inadequacy of rGO and graphite. Hammett studies supported a transition state (TS) in which a positive charge is generated at the benzylic carbon of the electrophilic partner and competition experiments highlighted the higher reactivity of benzylic alcohols with respect to styrenes. Last but not least, contrarily to classic LA-assisted FC protocols, primary benzylic alcohol was found more reactive than that the bulkier phenylethanol and the corresponding acetate.

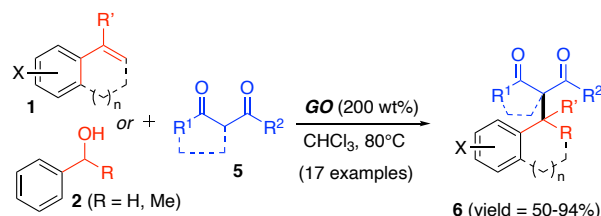
All at once, it was proposed a reaction mechanism occurring at the GO surface based on initial carbinol activation by the GO oxygenated groups. The key mechanistic step involves the pre-coordination of the olefin by the π -matrix and subsequent hydration promoted by the oxygenated groups on the surface. An

in situ covalent activation mode is therefore realized (Scheme 2). Upon pre-coordination of the nucleophile, a concerted C-C bond forming event yields the product with elimination of a water molecule, accounting for the observed reduction of GO after the process. Details on the reusability of the recovered GO were not reported in this work.



Scheme 2. Mechanistic sketch proposed for the GO promoted FC alkylation of arenes (the case for styrenes is presented).

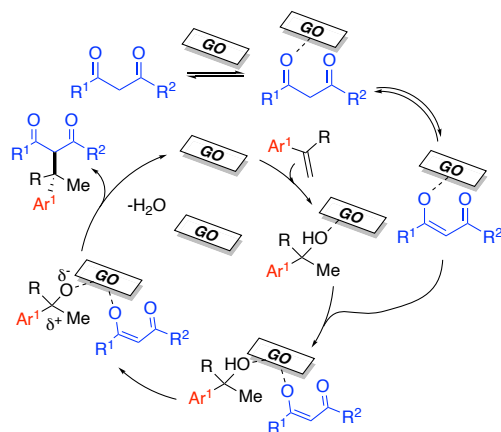
A similar approach was exploited by the same team (2019) in the alkylation of 1,3-dicarbonyl compounds **5** with styrenes and benzylic alcohols.^[24] Optimal conditions (GO 200 wt %, CHCl₃ at 80 °C) enabled the benzylation of a range of structurally diverse β -diketones under base-free and relatively mild conditions (**6**; yields up to 94%, Scheme 3).



Scheme 3. Benzylation of β -diketones assisted by GO.

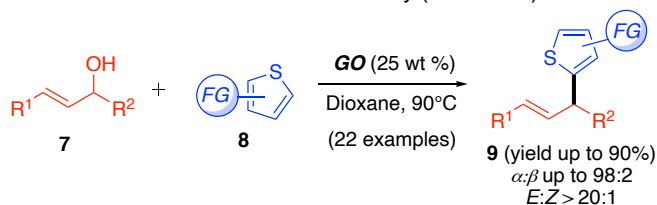
A detailed and extensive structural investigation on the carbon-material was also carried out. Firstly, the contribution of metallic impurities was excluded (XPS and AAS) and the inhibiting profile imprinted by base washing experiments highlighted the importance of acidic functionalities on GO. In contrast to the previous protocol, no reduction of GO was observed after the reaction (XPS and energy-dispersive X-ray spectroscopy (EDSX)) and also the acidity content was unchanged upon the catalytic transformation (pH = 4.19 vs 4.24 at 0.29 mg/mL concentration before and after catalysis). The ketones seem to protect the GO from an over-reduction that was recorded in absence of **5** (C/O increased to 3.2 from 2.1 in the parent GO). This intriguing phenomenon was ascribed to the instauration of a network of H-bond interactions between the enolizable carbonyls and the oxygenated GO moieties ("protecting action"). Mechanistically, the authors proposed a simplified pictorial sketch

of the reaction profile that parallels in several parts the one of the arylation protocol. A double activation role of the GO was proposed even if no detailed explanations on the preservation of the GO structure and reutilization of the carbon-material were provided.



Scheme 4. Mechanistic sketch of the GO promoted 1,3-dicarbonyl compounds alkylation with styrenes.

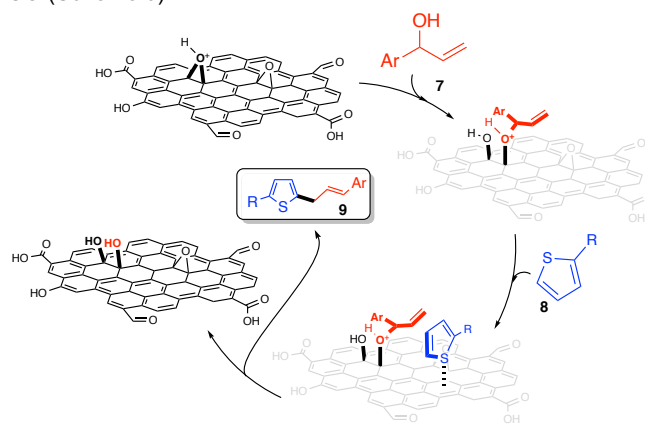
Our group (2018) contributed to the site-selective alkylation of arenes by exploiting the covalent activation mode exerted by GO. In particular, allylic alcohols **7** were tackled as alkylating agents^[25,26] for the Friedel-Crafts alkylation of mono and bi-thiophenes **8**.^[27] Optimal conditions (1,4-dioxane, 90 °C) involved an unprecedented low GO loading for C-C forming carbocatalytic protocols (25 wt %). The yields varied from modest to high (up to 90%) accompanied by a good α -regioselectivity and complete linear/branched as well as *E/Z* selectivity (Scheme 5).



Scheme 5. GO assisted allylic alkylation of mono- and bi-thiophenes with alcohols.

rGO and graphite proved inert as promoters, highlighting the importance of oxygenated functionalities. Control experiments using several organic acids under homogenous conditions excluded a simple acidic activation, while the combined use of benzoic acid and styrene oxide furnished the product in modest yield. These introductory findings suggested the synergic role of acidic functionalities and epoxide groups on the GO surface during the reaction course. C 1s XPS studies support this observation, showing a significant drop of epoxide content (40.3% \rightarrow 27.4% abundance) during the reaction. A detailed QM/MM computational analysis complemented the experimental data, leading to propose the covalent binding of the alcohol to the GO

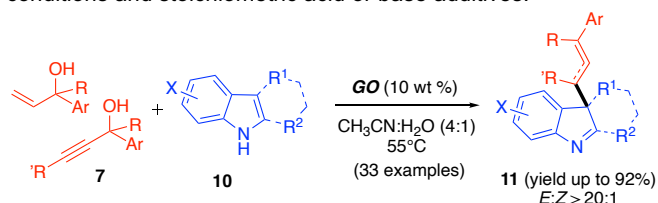
surface by means of an acid promoted epoxide ring-opening event. Notably, the intrinsic Brønsted acidity of GO is known to promote ring-opening of strained epoxides of the surface, releasing stabilized α -carbocations by the π -conjugate motif of GO (Scheme 6).^[28,29]



Scheme 6. Mechanistic profile for the thiophene allylic alkylation with alcohols.

Overall, the formation of the product is accompanied by the net loss of one epoxide unit on the material surface, which is converted into a 1,2-diol moiety. Additionally, calculations provided a convincing rationale for the observed regioselectivity with respect to the thiophene ring. Recovering and direct reuse of the GO revealed a progressive drop in catalytic performance (I run: 88% \rightarrow IV run: 29%), supporting the afore-described mechanism and suggesting that in this specific process the GO is behaving more likely as a co-reagent than that a genuine catalyst.

Very recently, our group has extended this methodology to the dearomative allylation/allenylation of 2,3-disubstituted indoles **10** with allylic alcohols and propargylic alcohols **7**.^[30] The reaction conditions appeared extremely interesting from a sustainable point of view since required only 10 wt % of GO, aqueous media and low temperatures (55 °C, Scheme 7). It is worth mentioning that the use of alcohols in dearomative protocols commonly requires expensive noble metal-catalysis, rigorous anhydrous conditions and stoichiometric acid or base additives.

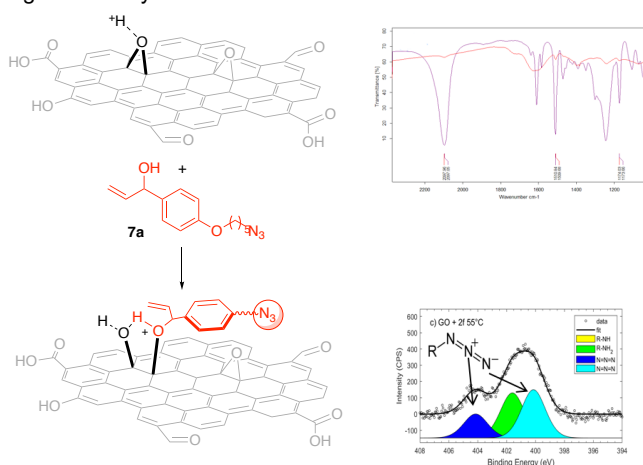


Scheme 7. GO-assisted dearomative allylation of indoles with alcohols.

A wide range of densely functionalized and stereochemically defined C(3)-allylated/allenylated indolenines **11** (33 examples) were isolated in yields up to 92% by using secondary, tertiary as well as heteroaromatic allylic/propargylic alcohols. Several control experiments were carried out in order to shed light on the reaction profile and in particular:

- 1) Conventional Brønsted acids promoted the process in lower and not-comparable extent;
- 2) rGO proved ineffective in the titled process;
- 3) Metal impurity contribution was excluded via dedicated experiments (*i.e.* $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ and EDTA);
- 4) XPS investigation provides insights towards the increase of diol content over epoxide one during the catalytic dearomatization reaction;

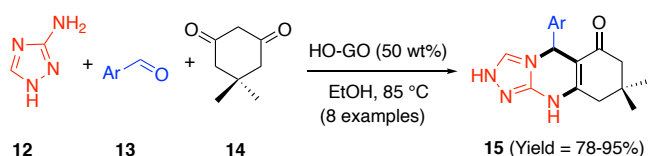
Furthermore, particular emphasis was devoted to verify the covalent anchoring of the alcohol to the GO surface during the FC-type dearomative process. Here, computational calculations supported the covalent grafting of the alcohol and identified a non-covalent interaction between the π -system of GO and the indole (*i.e.* N-H group of the indole) as the rational for the C(3)-regioselectivity.



Scheme 8. Experimental evidence (FT-IR and XPS, adapted from ref. 30) of the covalent anchoring of allylic alcohols on the GO surface.

Interestingly, further proofs towards the covalent grafting hypothesis were gained by tagging GO with the azido alcohol **7a** under optimal conditions. FT-IR and XPS analyses evidenced the presence of the N_3 -group in the recovered and chemically modified material (Scheme 8). Finally, regeneration of GO was easily obtained via simple acidic (aqueous HCl) treatment of the recovered material that led to a significant regeneration of the epoxide contents on the GO surface (XPS).

In 2019 Chen reported on the use of highly oxidized GO for the multi-component synthesis of triazoloquinazolinones **15** from 3-amino-1,2,4-triazole **12**, dimedone **14** and aromatic aldehydes **13**. Using ethanol as solvent at 85 °C, a small range of cyclic products was obtained in very good yields (up to 95%) by means of 50 wt % of over-oxidized GO (Scheme 9).^[28]



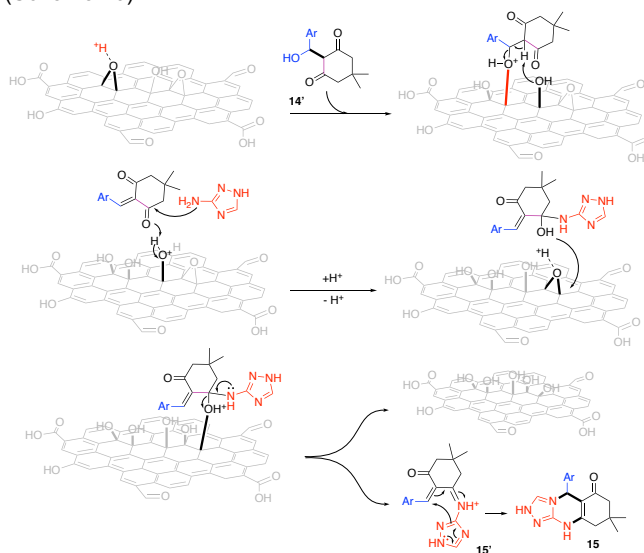
Scheme 9. GO-promoted synthesis of **15** via MC reaction (HO: highly-oxidized).

GOs featuring different oxidation degrees (C/O ratios from 1.257 to 1.494) were obtained via a slightly modified Hummers' procedure and were evaluated in the catalytic MCR. The results clearly showed an increase of activity along with the oxidation profile. As a matter of fact, the highest yield (95%, 35 min) was accessed with 3xGO (GO preparation involving threefold amount of KMnO_4).

Interestingly, while the epoxide and alcohol contents on the basal plane constantly increased with the preparative oxidation strength, the number of carboxylic units seem to reach a plateau during the 2xGO oxidative treatment. By combining these evidences, the authors extrapolated that the oxygenated groups on the basal plane must be pivotal to describe the overall catalytic attitude of GO.

XPS analysis of the carbon material before and after the reaction showed the decrease in epoxide content and the increase of hydroxyl groups, as well as deprotonation of carboxylic acids. Once again, it is the combination of carboxylic units and epoxides to play a key role in the activation of the organic substrates. Undirect proofs of that came by an experiment carried out through consecutive base (1M NaOH) and acid (1M HCl) treatments of the active GO. Interestingly, the ring-opening of epoxides/deprotonation of $-\text{CO}_2\text{H}$ and subsequent restoring of both epoxide and $-\text{CO}_2\text{H}$ contents caused the switch-on/off of the GO catalytic properties.

The proposed mechanism involves the initial covalent anchoring of the *in situ* formed benzylic alcohol **14'** with stabilized carbocations on the GO matrix formed by the acidic environment (Scheme 10).



Scheme 10. Proposed mechanism for the GO promoted three-component synthesis of triazoloquinazolinones **15**.

Dehydration of the grafted intermediate leads to a Knoevenagel product that can undergo nucleophilic attack by **12**, leading to a hemiaminal intermediate which dehydrates once again via

covalent grafting to the GO surface. Therefore, final cyclization results in the tricyclic fused product **15**.

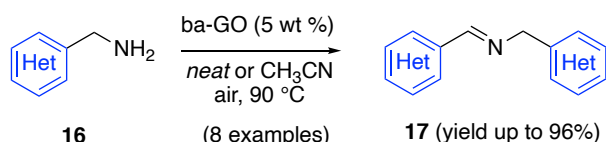
Through this pathway, the recovered GO shows a substantially different functional group composition. Interestingly, a slight loss of activity after two consecutive runs (95% yield vs 84% yield, respectively) was recorded, however proofs towards a full regeneration of catalytic activity (yield = 92%) were obtained via acid promoted (HCl treatment) ring-closing of epoxides.

2.2. Redox processes

Nano-dimensions of GO can origin unpaired spin states localized on the edges of the sheets, holes, defects and vacancies.^[31] These radical-like structures have been shown to promote redox processes generally involving the activation of molecular oxygen delivering superoxide radical $\bullet\text{O}_2^-$.

In this segment, Loh and coworkers reported the preparation of a highly porous GO material via consecutive base/neutralization/filtration treatments.^[32] The treatment removed the low molecular weight carbonaceous *debris* which remained on GO surface upon synthesis. The debris are acidic in nature and they occupy the holes and defect regions of the material, making them not accessible for the reaction partners. Their removal yielded the so-called ba-GO featured by a higher porosity (more holes available) and significantly lower oxygen content.

The authors applied ba-GO in promoting the aerobic oxidative coupling of primary benzylamines to *N*-benzylidene benzylamines with higher efficiency (yield up to 96%) with respect to untreated GO (*i.e.* 89% yield vs 65% yield under same conditions). The reaction was also performed under solvent-free conditions under air and with a ba-GO loading as low as 5 wt %. Aliphatic amines (*i.e.* *n*-pentylamine) proved inefficient under optimal conditions (Scheme 11). Extension of the protocol to the oxidative α -functionalization of tetrahydroisoquinolines with nitromethane and indoles was also documented.



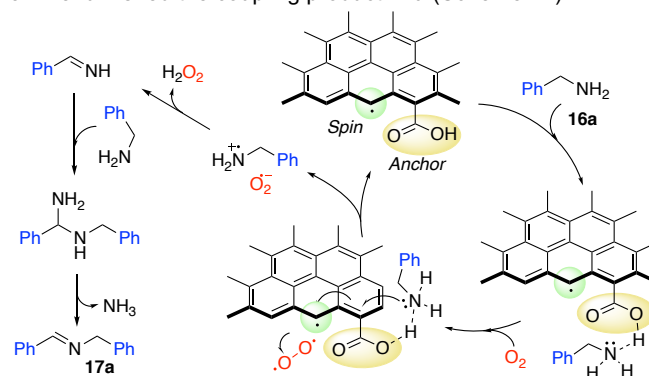
Scheme 11. ba-GO Promoted oxidative dimerization of benzylamines.

The study encompassed a large volume of experimental as well as spectroscopic investigations to elucidate the mechanism. The use of basic graphene oxides (b-GO) emphasized the crucial importance of the carboxylic sites, showing significantly lower catalytic activity with respect to ba-GO. Additionally, the use of 1-pyrene carboxylic acid as a promoter to mimic the acidic groups on the GO surface proved successful in the oxidative coupling of benzylamine **16a** (yield = 95%). Reusability of the recovered ba-GO was also ascertained (up to six cycles) simply via filtration and drying of the carbon material.

ESR (electron spin resonance) measurements showed the presence of unpaired spin states in ba-GO which were absent in

regular GO materials. Reducing the density of these states (by quenching the material via aryldiazonium coupling) caused the yield to drop significantly (from 89% to 30%). Additionally, the superoxide radical ($\bullet\text{O}_2^-$) and the expected production of H_2O_2 were identified. Given that carboxylic acids should be located on the edges of defects and holes, which are greatly increased by the base-acid treatment, the authors proposed the edges of holes and vacancies decorated with carboxylic acid groups as active sites for this transformation.

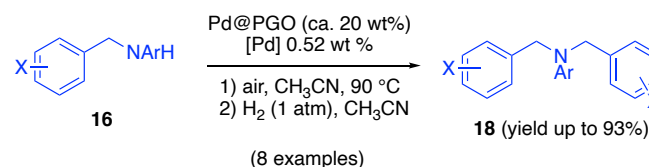
Mechanistically, upon initial coordination of the amine to the carboxylic groups via hydrogen bonding, molecular oxygen adsorbed on the edges is reduced to $\bullet\text{O}_2^-$, which is believed to stay at the surface to stabilize the positive vacancy generated in the material. The resulting positive vacancy is postulated to generate amine radical cation which undergoes α -H atom abstraction triggered by the superoxide radical. Condensation between the *in situ* formed imine and a molecule of unreacted amine furnished the coupling product **17a** (Scheme 12).



Scheme 12. Proposed mechanism for the oxidative dimerization of benzylamines promoted by ba-GO.

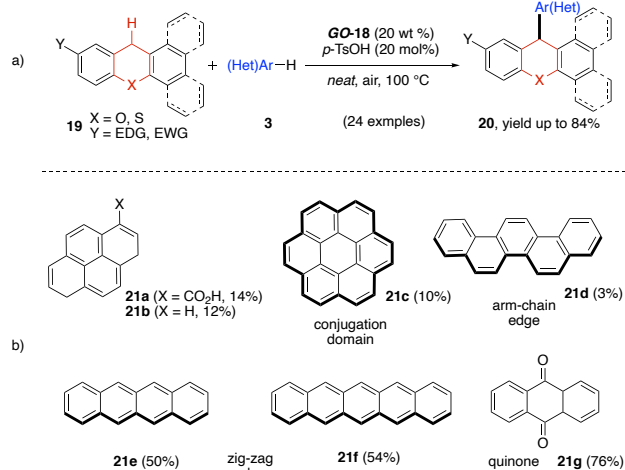
However, the efficiency in catalysis of 1-pyrene carboxylic acid (*vide infra*) poses some doubts on the veracity of the proposed activation of O_2 since unpaired spin states should not be present in the molecular mimic.

Interestingly, the porosity of the GO (p-GO or PGO) was employed to support Pd nanoparticles (initial Pd-loading = 4.4 wt%, ICP, size range 4-8 nm).^[32b] The innovative bifunctional catalyst was adopted in the unprecedented and simultaneous activation of O_2 and H_2 by the same chemical entity and employed in the “redox-neutral” synthesis of dibenzyl amines **18**, starting from primary and secondary benzyl amines **16** (yields up to 93%, Scheme 13).



Scheme 13. Bifunctional Pd/GO promoted simultaneous activation of H_2 and O_2 in the synthesis of dibenzylamines **18**.

An elegant example of genuine catalytic activity of GO in C-C bond forming reactions was documented by Su and Loh very recently (2018).^[33] The protocol involves the cross-dehydrogenative C-H/C-H cross-coupling of xanthenes and thioxanthenes **19** with electron-rich arenes **3**. The protocol resulted operationally accessible (air, solvent-free conditions), low loading of GO was utilized (20 wt %) and the carbocatalyst could be recovered and reused without any regeneration step. The additional use of *p*-TsOH (20 mol%) enabled excellent yields (up to 89%) to be obtained with a fairly large variety of coupling partners (24 examples, Scheme 14a).

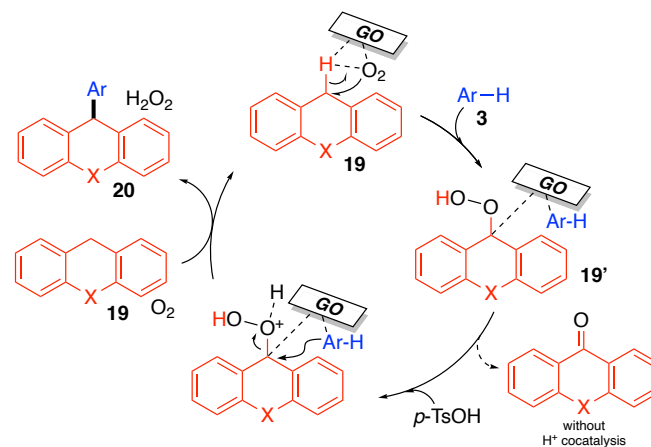


Scheme 14. a) GO (GO-18 was utilized) catalysed cross-dehydrogenative coupling of electron-rich arenes and (thio)xanthene derivatives. b) Polyarenes tested as molecular carbocatalysts.

Graphite demonstrated inert while r-GO and ba-GO, possessing much less oxygen functionalities than GO, could promote the reaction to a similar extent. These findings clearly emphasized that not all the oxygenated functional groups seemed crucial for the reaction course. In this direction, the authors synthesized and tested a series of GOs (GO-1/-3/-6/-10/-18) featuring different oxidation degrees. XPS demonstrated that from G-10 on (G-18 showed the higher catalytic properties), the signal of the C=O (quinone-type) started increasing with respect to C-O (hydroxyl and epoxydic units), proposing the more oxidized functional groups directly being involved in the dehydrogenative C-H activation process. Additional insights into the reaction mechanisms came from some dedicated experiments in which GO-18 was replaced by polyaromatic molecular compounds (**21**) mimicking the functional groups present in the GO material (Scheme 14b).

Polyarenes presenting “armchair” edges (**21d**) could only promote the reaction to little extent. Differently, better results were obtained by using molecules featuring “zig-zag” edges (**21g**, yield = 76%). The pivotal role of these “zig-zag” edges was ascertained by subjecting the material to thermal annealing (> 800-1000 °C) in order to remove the oxygen functionalities (**21e,f**). The so obtained reduced GO (FT-IR and XPS) did promote the reaction in similar extent (50-54%), supporting the zig-zag edges (radical-

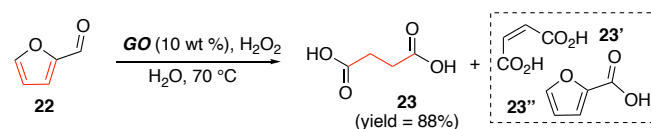
like, STM and DFT) as the most likely active site. Finally, the detection of superoxide radicals (EPR) leads to a mechanism proposal similar to the one proposed for the coupling of benzylamines (Scheme 15).



Scheme 15. Proposed mechanism for the GO-18 catalyzed dehydrogenative C-H/C-H cross-coupling.

After adsorption of xanthene and molecular oxygen on GO, xanthene peroxide **19'** is postulated via interaction with superoxide radical generated by the unpaired spin states of the zig-zag edges. Upon protonation (*p*-TsOH) the activated xanthene peroxide can undergo FC-type alkylation with an electron-rich arene (**3**) yielding the product **20** and H₂O₂. This work highlights for the first time the importance of the morphology of the material for its catalytic activity, although a detailed rationale for the peroxide formation and for the alkylation step was not documented.

An interesting covalent-mode catalysis played by GO was proposed by Yang and Lv (2019) in the selective oxidation of furfural **22** to succinic acid **23** with H₂O₂.^[34] Interestingly, GO (10 wt %) demonstrated more efficient than other commonly used acidic promoters in this reaction, delivering the product in 88% yield (water, 70 °C). As a matter of fact, *p*-TsOH and Amberlyst15 provided **23** only in 70% and 68% yield, respectively, along with lower selectivity (maleic acid **23'** and furoic acid **23''**) are the common byproducts for this process, Scheme 16).

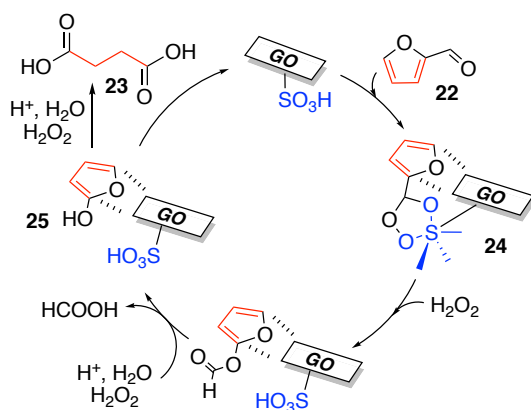


Scheme 16. GO promoted oxidation of furfural to succinic acid with H₂O₂.

To investigate the nature of the active sites, GO was subjected to tailored structural modifications. While high temperature annealing of GO (removal of SO₃H functionalities as well as oxygenated groups) generated an inactive carbon-material, the selective restoring of the -SO₃H or carboxylic contents (H₂SO₄ or

HNO₃ oxidation, respectively) provided interesting outcomes regarding the preferential role of the organic sulfonate groups over to the classic carbo-oxygenated ones. These results together with the competence of *p*-TSA and Amberlyst15 in the reaction, suggested sulfonic groups as the key active sites. The high surface area of GO and the acidity tuning exerted by the carbonaceous matrix are finally accounted to rationalize the higher performance of GO with respect to different solid acids.

The authors proposed the formation of 5-membered ring covalent intermediate **24** between **22** and SO₃H groups favored by the π - π interactions between the furyl ring and the aromatic regions that ensure the correct spatial arrangement of the reagents (Scheme 17). This intermediate undergoes a Bayer-Villiger-type rearrangement in the presence of H₂O₂, that upon hydrolysis can originate 2-hydroxyfuran **25**. Tautomeric equilibrium and subsequent acidic ring-opening of the lactone core (2-(3H)-furanone) will deliver succinic acid **23**.



Scheme 17. Proposed mechanism for the GO promoted oxidation of furfural to succinic acid with H₂O₂.

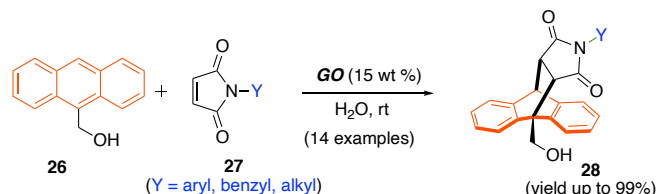
2.3. Non-covalent activation by π - π and other dispersive interactions with the carbon matrix

The capability of the conjugated π -matrix of carbon materials to establish non-covalent interactions with different chemical species (*i.e.* π -systems, radicals and cations) is well documented.^[35] Although this kind of dispersive forces can be considered a somewhat secondary phenomena with respect to the main activation pathways, π - π interactions between unsaturated organic systems and the carbon domain of GO can impact deeply the stereochemistry, selectivity and activation energy of the processes.

A few reports have shown indeed that the aromatic “patches” of GO can be themselves, a “primary” active site in various organic transformations.

In this direction, De (2017) reported on the use of GO as a promoter for the Diels-Alder cycloaddition of 9-hydroxymethylanthracene **26** and variously substituted *N*-arylmaleimides **27** in water.^[36] The reaction proceeds at room temperature using 15 wt % of GO, yielding the [4+2]-adducts **28** in moderate to quantitative yields (Scheme 18). Concerning the

dienophile, EWG-substituents at the *N*-atom were elected as the most efficient ones.

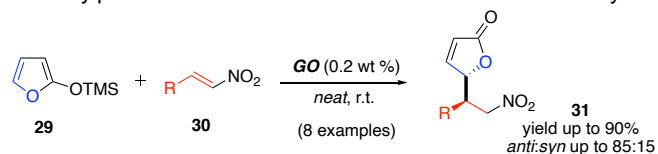


Scheme 18. GO promoted Diels-Alder reaction. Activation mode based on π - π interactions.

Interestingly, anthracene did not take part to the cycloaddition, suggesting the presence of hydrogen bonding contacts between the diene and the polar groups of the GO surface. Structural analysis of GO before and after the reaction shows no major changes with a proved reusability of the GO up to 6 times with no significant loss of activity.

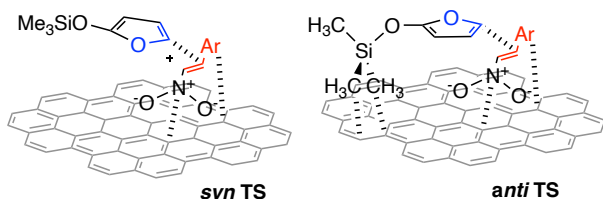
The Diels-Alder reaction commonly features an intrinsic high activation entropy due to its ordered transition state. The authors proposed that the π -surface of GO can orient the substrates in a fruitful spatial arrangement via non-covalent binding interactions.

Few years earlier (2014) Guerra and colleagues also exploited this activation mode in the GO assisted Mukayama-Michael addition of 2-(trimethylsilyloxy)furan (**29**) and aromatic β -nitrostyrenes (**30**).^[37] The reaction proceeded in the absence of solvent, at room temperature, and by using GO with a loading as low as 0.2 wt % (8 examples, Scheme 19). Interestingly, the resulting butenolides **31** were isolated with an *anti* stereoselectivity (up to 85:15) that is in contrast to the *cis* product normally predominant with other Lewis or Brønsted acid catalysts.



Scheme 19. *Anti*-diastereoselective Mukayama-Michael addition catalysed by GO.

Control experiments indicated that high surface area of the material is crucial to obtain high yields and selectivity. Additionally, DFT calculations (performed on graphite-type sheets) could perfectly reproduce the observed selectivity. In the proposed model the nitrostyrene engaged a strong non-covalent π - π interaction with the GO surface. As a result, nucleophilic attack can only proceed from the side opposite to the GO surface. The selective formation of the *anti*-isomer is driven by dispersive interactions between the OTMS group and the π -matrix, which are only possible for one of the two nucleophilic approaches over the nitrostyrene.



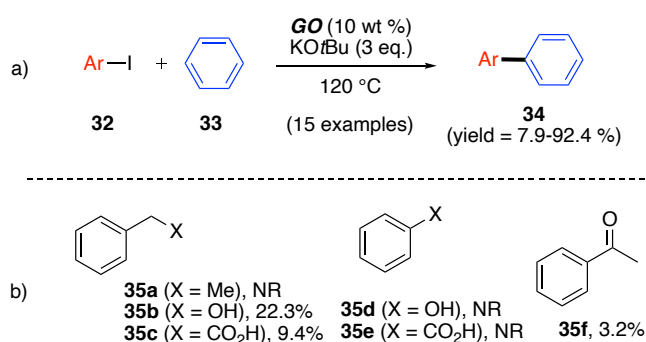
Scheme 20. Computed TS leading to *syn* and *anti*-product. The dispersive interactions are highlighted with dashed lines.

Subsequent reaction of the silylated intermediate with OH groups present in the reaction system yields the product. The scarce reactivity of aliphatic nitroalkenes also supports the importance of π interactions for this kind of activation.

2.4. GO as additive or active species stabilizer

In parallel to the development of exclusive GO-promoted transformations, graphene oxide has been also adopted in conjunction with other catalytic systems or as an additive to optimize reaction profiles.^[38]

A very elegant example was recently documented by Ma, in which GO was used in conjunction with KO^tBu for the direct C-H arylation of benzene (**33**) with aryl iodides **32**.^[39] The reaction proceeds at 120 °C using benzene as solvent with a GO loading of 10 wt % and 3 equivalents of KO^tBu. A wide range of biphenyls **34** were obtained in yields up to 92.4% (Scheme 21a).



Scheme 21. a) C-H benzene arylation promoted by GO and KO^tBu; b) model substrates employed as promoters (used in stoichiometric amount) for mechanistic investigations (NR = no reaction).

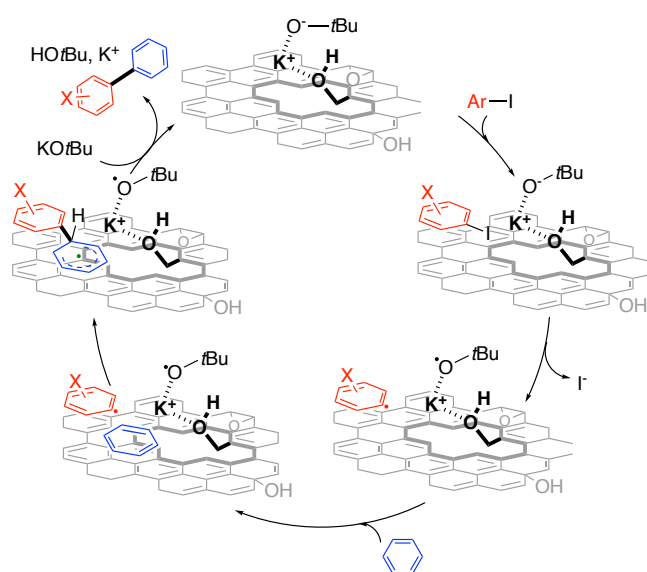
In order to address the active mechanistic pathway a number of dedicated experiments were carried out.

- 1) The use of radical scavengers (TEMPO) confirmed that the process is radical in nature;
- 2) Contributions from metal impurities (in both GO and KO^tBu) were extensively ruled out;
- 3) The absence of GO caused a complete inhibition of the reaction.

Experiments carried out with GOs having different amounts of oxygen showed a linear dependence of the yield by the oxygen content (XPS O 1s), suggesting the active role of oxygenated

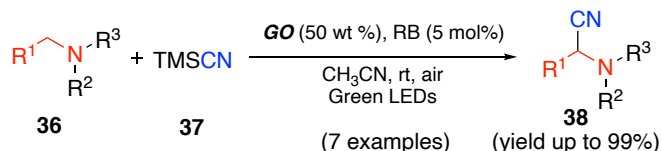
functional groups. In addition, to determine the nature of the active groups, a series of model compounds (**35**, Scheme 21b) mimicking the oxygen group present on GO were tested as promoters. The best yield (22.3%) was obtained using benzyl alcohol, electing C-OH as the most likely active species.

In details, upon adsorption of iodobenzene, the GO-KO^tBu adduct (DFT calculations supported strong interactions between K⁺ ions and the benzyl OH located at the edges and pores of the surface) could promote the formation of a benzene radical via SET reduction. This radical (tentatively stabilized by the π system as well as positively charged benzylic hydrogens adjacent to the active OH groups) would react with adsorbed benzene giving a biphenyl radical that evolves to the product via H⁺ and e⁻ loss (Scheme 22). Interestingly, the catalyst could be reused up to 6 cycles with little loss of activity.



Scheme 22. Proposed mechanistic pathway for the arylation of benzene promoted by GO-KO^tBu adduct.

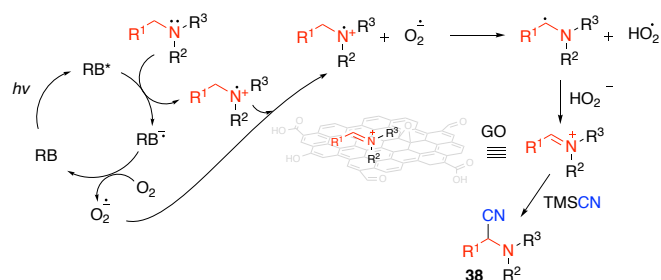
In the context of GO-accelerated reactions based on additional catalytic systems, the study reported by Tan and co-workers (2011) on the photocatalytic aerobic α -cyanation of tertiary amines is worth mentioning.^[40] The protocol involved Rose Bengal (RB) as the photosensitizer (5 mol%), TMSCN as nucleophile and did not require any moisture restriction (green LED irradiation). Under optimal conditions, the cyanation of densely functionalized *N*-aryltetrahydroisoquinolines **36** was performed in up to 99% yield. For all substrates, the addition of GO (50 wt %) dramatically improved the yield from ca. 60% to over 90%. Various acyclic trialkyl amines were also found to be competent in the protocol, showing benefit from the presence of GO in both yield and regioselectivity (mono vs bis-cyanation, Scheme 23).



Scheme 23. GO-assisted photocatalyzed α -cyanation of amines.

Firstly, the synergistic role of both light and GO was demonstrated. While no product was obtained in the absence of light, GO alone led to the formation of product only in traces.

Mechanistically, in accordance with previously reported photocatalyzed α -functionalization of amines, a SET oxidation of the amine was proposed via excited state of RB. In particular, the reduced RB molecule (ground state) can produce superoxide anion $\cdot\text{O}_2^-$ that is accounted for generating an iminium intermediate via proton and electron transfer. The iminium intermediate then reacts with TMSCN to yield the final product **38** (Scheme 24). The beneficial role of GO in the transformation is still not clear. The facts that it can be reused in a second run with no loss of activity and that it cannot promote the reaction alone, suggested that it has no significant oxidative activity. The authors proposed that its high surface area and the slight acidic nature could stabilize the iminium intermediate and enhance the rate of the reaction since GO/RB supramolecular architectures were ruled out by UV/Vis studies.



Scheme 24. Proposed mechanism for the photocatalytic α -cyanation of amines.

3. Conclusion

The use of GO as a mediator in organic transformations is gaining credits within the chemical community also because of the growing comprehension of mechanistic aspects. The combined use of enabling techniques allowed complex and unexpected interplays between GO and reaction partners, leading to activation modes being operating in challenging tasks such as C-H activations, dearomatization protocols and redox-active condensations.

Currently, the common statement diffused among the synthetic organic chemistry community, referring to GO as a simple solid Brønsted acid for heterogeneous catalysis is no longer acceptable and subscribed. As a matter of fact, its unique chemical properties are inspiring a growing number of scientists in creating chemical diversity through this tool.

However, several key questions still suffer for the lack of conclusive answers and should inspire chemists to build-up innovative research themes. Some of them are as follows:

1) Is GO providing a catalysis in a homogeneous environment or do the chemical events occur at the surface of insoluble GO aggregates in solution?

2) Is the predetermined GO-structure the real catalytic active morphology or should it be better considered as a pre-catalytic form due to potential modifications during the catalytic process itself?

3) Would it be feasible to create intrinsically chiral GO to be adopted in asymmetric transformations?

In conclusion, in the present *MiniReview* article, we wished to outline the pivotal role of the mechanism comprehension in drafting the new dimension of graphene oxide in organic synthesis with perspective applications both in academia and industry. Undoubtedly, new developments in the field are predictable in the near future.

Acknowledgements

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Keywords: Graphene oxide • Reaction mechanism • Organic Synthesis • Catalysis • Selectivity

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