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This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:
Andrea Brunetti, A.P. (2023). Graphene-Oxide Mediated Chemodivergent Ring-Opening of Cyclobutanols. CHINESE JOURNAL OF CHEMISTRY, 41(11), 1333-1340 [10.1002/cjoc.202200757].

Availability:
This version is available at: https://hdl.handle.net/11585/950989 since: 2024-01-15

Published:

DOI: http://doi.org/10.1002/cjoc.202200757

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19 December 2024

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Graphene-Oxide Mediated Chemodivergent Ring-Opening of Cyclobutanols, A. Brunetti, A. Pintus, L. Lombardi, A. Kovtun, F. Mascietti, F. Bruno, E. Ravera, M. Melucci, G. Bertuzzi, M. Bandini, *Chin. J. Chem.* **2023**, *41*, 1333-1340.

The final published version is available online at: https://onlinelibrary.wiley.com/doi/full/10.1002/cjoc.202200757.

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Graphene-Oxide Mediated Chemodivergent Ring-Opening of Cyclobutanols

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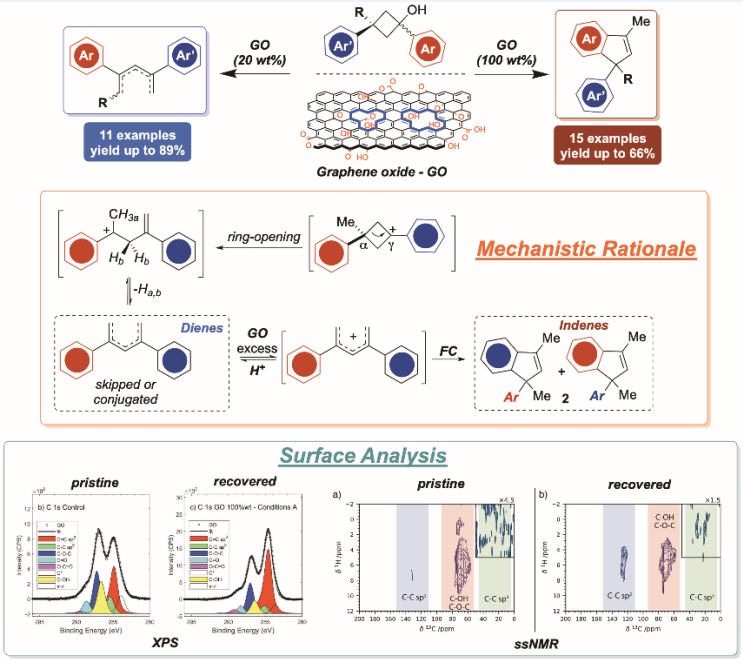
Comprehensive Summary

Abstract: The chemodivergent ring-opening of cyclobutanols is described under the carbocatalytic assistance of graphene oxide (**GO**). The protocol enables the synthesis of diversely functionalized dienes or indenes (26 examples) based on the amount of **GO** employed. Spectroscopic (XPS and ssNMR) as well as experimental investigations revealed a direct involvement of the π-domains of GO in tuning the stability of carbocationic intermediates during the reaction.



Keywords

Carbocatalysis | C-C activation | Graphene | Carbocations | Methodology and Reactions

Background and Originality Content

Sustainability, ***s***implicity and ***s***electivity (*i.e.* the "three-***s***-role") are main key factors to be simultaneously pursued in current organic synthesis, in order to match the increasingly stringent requisites for highly efficient green preparative methodologies. In this direction, the chemical catalysis is worldwide considered as an ultimate tool to reach this aim.

Very recently, the well-consolidated metal-, organo-, and biocatalytic strategies started being paralleled by the emerging "carbocatalysis" that build its foundations on the use of pre-designed nanostructured carbon materials as promoters of chemical transformations.[1] In this scenario, graphene oxide (**GO**) is playing a prominent role due to intrinsic and unique physical-chemical features such as robustness, high surface area, functional group density, ready availability (even on large scales), partial solubility in polar organic solvents.[2] These features enabled the use of **GO** as a greener synthetic tool for the replacement of harsh reaction conditions and toxic reagents with milder alternatives. In addition, the unique and multiple activation modes exerted by **GO** (Brønsted acid catalysis, single-electron transfer reaction mediation, and covalent catalysis) enabled new chemical reactivities to be discovered in redox protocols as well as C-C and C-X bond-forming processes (Figure 1a).[3]

Our group has recently embraced the fascinating and challenging profile of C-C σ-bond activation modes for the generation of chemical diversity.[4,5] In particular, the ring-opening of strained C4-cyclic scaffolds (*i.e.* cyclobutanones, cyclobutanols) has emerged as one of the most powerful strategy to build-up complex organic molecular architectures starting from readily available small organic compounds.[6]

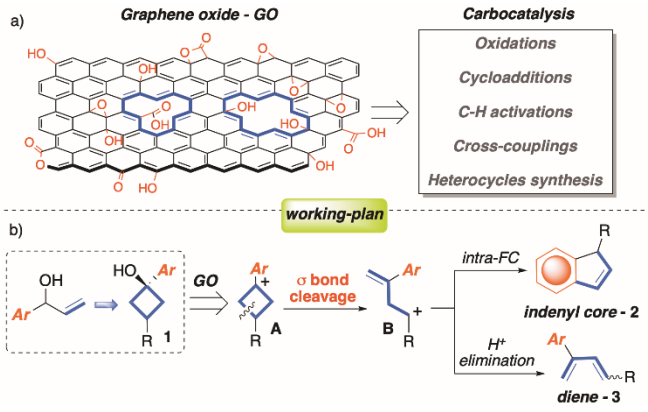


Figure 1. a) Schematic representation of **GO** and relative applications in carbocatalysis; b) Working-plan for the present C-C σ-bond activation-based synthesis of indenes **2** (FC: Friedel-Crafts) and dienes **3**.

However, the vast majority of the literature deals predominantly with noble-metal mediated processes,[7] generating intrinsic limitations in terms of scalability and sustainability of the overall procedure.[8] Additionally, the known protocols mostly converge to the preparation of aryl-ketones, providing a quite narrow scope in terms of chemical diversity. In line with our scientific interests in carbocatalytic procedures,[9] we recently documented on the synergistic action of the **GO** functional groups for the covalent electrophilic activation of π-alcohols, towards chemo- and regioselective nucleophilic manipulations.[10,11]

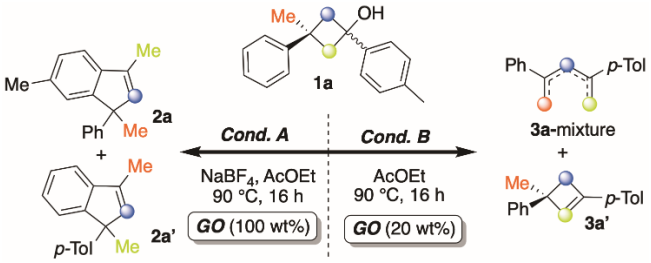
These findings led us to draw a working parallelism, in terms of reactivity, between allylic alcohols and cyclobutanols (**1**), envisioning graphene oxide as a valuable and sustainable promoter for the activation (**A**) and consequent ring-opening (**B**), of cyclobutanols via C-C σ-bond cleavage (Figure 1b).[12] Interestingly, the introduction of arene units at the carbinol atom of **1** would open a direct route towards the synthesis of synthetically valuable indenyl cores **2**,[13] via a cascade activation / C-C cleavage/ intramolecular Friedel-Crafts-type alkylation reaction. Alternatively, the diene scaffolds **3**i could be targeted when deprotonation would be predominant with respect to Friedel-Crafts alkylations. Stabilization effects exerted by the **GO** functional groups as well as π-domains, on the cationic reaction intermediates might be predicted as key elements for the success of the present working plan. Importantly, the employment of alcohols would result in the formation of water as the only stoichiometric co-product of the process.[14]

Results and Discussion

Optimization of reaction conditions

At the outset of the investigation, we elected cyclobutanol **1a** as the model substrate and an extensive range of reaction parameters (*i.e.* solvent, temperature, concentration, nature of carbon-based promoter, and loading of the catalyst) were assessed to identify the optimal conditions (see Table 1).

Table 1. Optimization of the reaction conditions.[a]



Run	Deviations from optimal	Yield **2a+2a'** [%][b]	Yield **3** [%][c] / **3a/3a'**[d]
1[e]	***A***	55	--
2[f]	$Yb(OTf)_3$ instead of **GO**	30	61 / 1:1
3[f]	$FeCl_3$ instead of **GO**	traces / --	traces / --
4[f]	AcOH instead of **GO**	NR	--
5[f]	*p*TSA instead of **GO**	-- / --	89 / 1:20
6[f]	*r*GO instead of **GO**	-- / --	11 / 1:3
7	No $NaBF_4$	43	--
8	Toluene	39	57 / 1.3:1
9	$PhCF_3$	30	61 / 1:1
10	DCE	34	--
11	**GO** 200 wt%	decomposition	--
12	**GO** 75 wt%	50	29 / 1.5:1
13	**GO** 50 wt%	11	75 / 2.5:1
14	***B***	--	95 / 4.5:1
15	**GO** 10 wt%	-	56[g] / 4.5:1
16	no **GO**	NR	--
17	$NaBF_4$ as an additive	-	93 / 4.4:1

[a] All the reactions were carried out in reagent grade solvents and under air. ***Cond. A***: **1a** (0.5 M) with **GO** 100 wt%, $NaBF_4$ (2.0 equiv). ***Cond. B***: **1a** (0.015 M) with **GO** 20 wt%. [b] Isolated yield after flash chromatography and reported as a **2a+2a'** mixture (**2a** and **2a'** were formed in nearly 1:1 ratio). [c] Isolated yield after flash chromatography and reported as **3a+3a'** (**3a** was reported as a diene mixture). [d] Determined via ^{1}H-NMR analysis on the

reaction crude. [e] The complete consumption of **1a** was recorded.[15] [f] 100 mol% of Lewis/Brønsted/carbon acid was utilized. [g] 40% of unreacted **1a** was recovered at the end of the process. *r*GO: reduced graphene oxide (O/C ratio of O/C = 0.16 ± 0.01). NR: no reaction.

Interestingly, by treating **1a** with commercially available **GO** (100 wt% loading) and $NaBF_4$ (2 equiv) in EtOAc at 90 °C for 16 h we isolated the desired indenes **2** (55% overall yield) as an equimolar mixture of isomers **2a** and **2a'** (entry 1). The 1:1 mixture of the two isomeric indenes accounts for a relative similar reactivity of the allylic carbocationic intermediates that undergo the final Friedel-Crafts (FC) alkylation (*vide infra* for a mechanistic interpretation). Interestingly, no cyclobutene **3a'** (dehydrative process) and diene mixture **3a** were detected in the reaction crude. Lewis acid catalysis (*i.e.* $FeCl_3$) led to a complete decomposition of the starting cyclobutanol (entry 3) and $Yb(OTf)_3$ provided **2a**/**2a'** as the minor products (entry 2). Analogously, a mere Brønsted acid assistance (100 mol%, entries 4,5) provided disappointing results, with complete **1a** recovery in case of AcOH (entry 4) and complete dehydration of **1a** with *p*TSA (entry 5). The beneficial role of $NaBF_4$ on the overall process was then verified through a blank reaction (43%, entry 7). Although the rationale of the $NaBF_4$ action is still unclear, we speculated that the presence of poorly coordinating anions such as BF_4^- could impact on the life-time of the intermediate carbocationic species favoring the final FC-type C-C bond forming event with respect to elimination reactions.[16] However, its presence does not interfere with the chemoselectivity of the process, with indenes **2a**/**2a'** being the sole products observed in entries 1 and 7. Due to the polar nature of the title reaction, it was not surprising to record the major role played by the solvent on the overall chemical outcome. In particular, AcOEt proved to be far superior to other media (*i.e.* Toluene, $PhCF_3$, DCE) in terms of indenes **2**/dienes **3** ratio (entries 8-10). Interestingly, we were pleased to discover the reaction chemoselectivity being markedly dependent on the **GO** loading (entries 11-14). In particular, as lower the loading of **GO** as higher the formation of dienes **3** with respect to indenes **2**, was observed. Here, when optimal 20 wt% of **GO** was employed, no traces of indenes were detected with the exclusive formation of a **3a**/**3a'** mixture (4.5:1, entry 14) in quantitative yield. Finally, we also proved that both lower **GO** loadings (*i.e.* 10 wt%, entry 15, 56% yield) and the addition of $NaBF_4$ (entry 17) were unfruitful in the synthesis of dienes. Interestingly, GO proved essential for the reaction as emerged from the blank reaction carried out in absence of graphene oxide (entry 16).

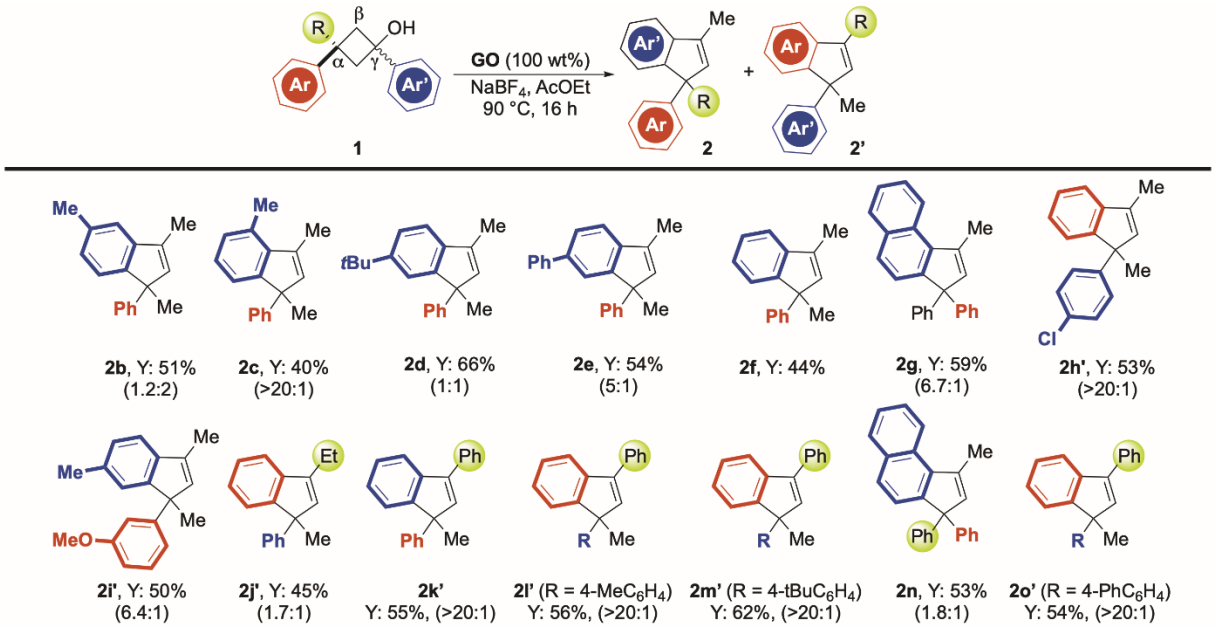
The unexpected chemoselectivity/**GO** loading trend, suggested the realization of a simple **GO**-controlled *formal chemodivergent* ring-opening of cyclobutanols.

Reaction Scope

Aiming to consolidate this formal divergency, a range of differently substituted carbinols **1b**-**o** were synthetized via a multi-step route (see SI for further details) and allowed to react under ***Conditions A*** (Table 1, entry 1). The resulting collected outcomes have been summarized in Scheme 1.

First, tolerance of the protocol toward carbinol decoration was ascertained by introducing differently substituted arenes at the tertiary alcohol framework (**2b**-**h**). Interestingly, in all cases moderate to good yields of indenes **2** (up to 66%) were obtained regardless the position of the substituent on the arene. In particular, *ortho*-tolyl substituted compound **1c** delivered **2c** in a regioselective manner (**2c**:**2c'** > 20:1) with the *o*-tolyl fragment being exclusively involved in the final FC alkylation process.

Scheme 1. Scope of the methodology: Synthesis of diversely functionalized indenes **2**.[a]



[a] All reactions were carried out in reagent grade AcOEt under air. Isolated yields after flash chromatography were reported. Between brackets the **2**:**2'** ratios, determined via ^{1}H-NMR analysis on the reaction crude.

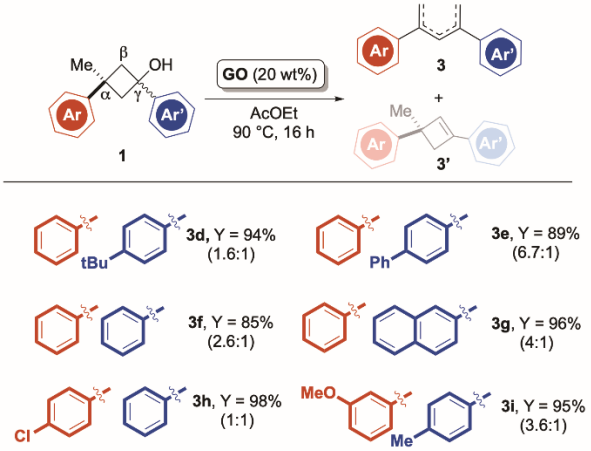
Both EWG (*i.e* 4-Cl) and EDG (*i.e.* 3-OMe) groups were effectively accommodated also at the aryl unit comprising the all-carbon quaternary stereocenter (**1h**,**l**). In both cases, indenes deriving from FC-type alkylation of the Ar' ring, were obtained predominantly or exclusively (yields up to 53%, **2**:**2'** up to 20:1).

The replacement of the methyl group at the quaternary stereocenter with other alkyl chains (*i.e.* Et **1j**) as well as aromatic units (**1k-o**) was then investigated. Interestingly, in all cases, the cascade process worked efficiently delivering the desired indenes in satisfying yields (up to 62%).[17]

Therefore, our attention moved towards the exploitation of the chemodivergency observed in Table 1 (entry 1 *vs* entry 14) for

the synthesis of diversely functionalized dienes. In this case, a selection of acetophenone-derived carbinols (**1b-i**) employed in the preparation of indenes **2** under ***Conditions A***, were subjected to ***Conditions B*** (**GO** = 20 wt%) and the results have been collected in Scheme 2. Interestingly, the ring-opening of the cyclobutane core was also effectively recorded through the cleavage of the C_α-C_β bond. The resulting formation of dienes **3** was obtained in high yields (85-98%) in combination with variable amounts of the dehydrated cyclobutene analogues **3'**. In particular, dienes **3** were always isolated as the major compounds (up to 87:13) except for chloro-containing carbinol **1h** that furnished a 1:1 **3h**:**3h'** mixture. This evidence suggests that the formation of the α-carbocationic intermediate upon C_α-C_β cleavage (see mechanistic rationale) can be hampered by the presence of electron-deficient arenes at the α-position of the cyclobutane core.

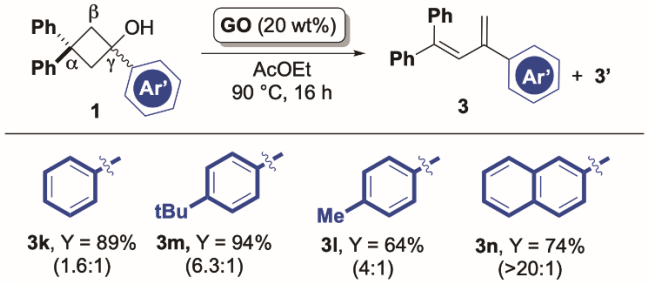
Scheme 2 GO-mediated synthesis of dienes **3** via ring-opening of cyclobutanol cores deriving from acetophenones.[a]



[a] Between brackets the **3**:**3'** ratios, determined via ^{1}H-NMR analysis on the reaction crude.

The generality of the protocol was further assessed by screening a range of benzophenone-derived cyclobutanols (**3k-n**, Scheme 3). In all cases, moderate to good conversions were observed (64-94%) with the formation of a single diene (**3**) as the major outcome. Interestingly, when an extended π-system (2-naphthyl moiety) was introduced on the initial cyclobutanol (**1n**), the ring-opening event was favored, precluding the formation of the cyclobutene **3n'**.

Scheme 3 GO-mediated synthesis of diene **3** via ring-opening of cyclobutanols deriving from benzophenones.[a]



[a] Between brackets the **3**:**3'** ratios, determined via ^{1}H-NMR analysis on the reaction crude.

Surface analysis

The recoverability and reusability of the graphene oxide were then investigated in the synthesis of the indenes **2a**/**2a'**. Here, regardless the use or absence of $NaBF_4$, the reused **GO** (100 wt%) guaranteed a complete conversion of **1a** although delivering a 5:1 mixture of **3a**/**3a'** and **2a**/**2a'**. In addition, high catalytic performance towards the ring-opening of the cyclobutane core were observed up to five reuses, however, the exclusive formation of dienes **3a** and cyclobutene **3a'** was recorded from the third run (see SI for details). Intrigued by this experimental evidence and with the aim of tracing a tentative reaction machinery, the surface of the **GO** material was investigated *via* XPS spectroscopy.[18]

Both **GO** powders - ***Conditions A*** and ***B*** - after the reactions, were analyzed by using XPS and solid-state NMR (ssNMR). All the structural modifications of **GO** after catalysis were evaluated with respect to a control experiment - **GO** control - that was obtained by exposing **GO** to the same reaction environment (AcOEt, 90 °C, 16 h), but in the absence of **1a**. XPS survey spectrum has mainly oxygen and carbon signals (O 1s and C 1s in figure 1), associated to C=C sp^2 aromatic carbon and C-O / C=O groups present in various forms on the **GO** surface: mainly epoxy and hydroxyl groups, with some minor contribution from carbonyl and carboxyl moieties were detected. We also monitored the overall oxidation degree after the first catalytic reaction and we observed a drastic decrease of the O/C ratio in the **GO** exposed to ***Conditions A***, from 0.36 in pristine **GO** to 0.27. While, after the reaction run under ***Conditions B*** the reduction was less intense, with a O/C ratio of 0.30 (see SI).

The reduction of **GO** was also monitored by using the XPS C 1s signal, that was fitted as described in the SI. From this it was possible to determine the structural composition of carbon functional groups on the **GO** surface: the relative intensity of the epoxy and hydroxyl groups (binding energies at 286.8 eV and 286.2 eV, respectively) decrease with respect to the aromatic sp^2 carbon (284.4 eV) after subjection to ***Conditions A*** (Figure 2). The magnitude of reduction was in agreement with the O/C ratio changes discussed above; in particular, epoxy/hydroxyl signal show a decrease from 23%/18% in **GO** control sample to 18%/10% after ***Conditions A***, while only small changes were observed in **GO** (***Conditions B***): 24%/13% (see supporting information).

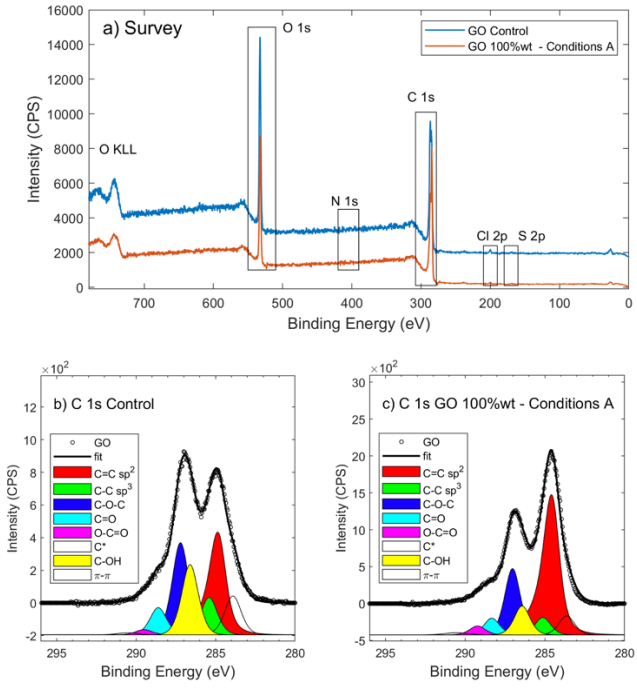


Figure 2. (a) XPS Survey of and control GO (AcOEt 90 °C 16 h) and XPS C1s of control GO. (b) and GO ***Conditions A***.

The accuracy of the ratio between epoxy and hydroxyl groups obtained by XPS C 1s fit was relatively low, since the two peaks

have a narrow energy separation. Besides XPS, ssNMR has proven to be a reliable and useful tool for the characterization of the functional groups in graphene oxide.[19] Thus, the relative amount of epoxy and hydroxyl groups was refined by measuring the direct excitation solid state Nuclear Magnetic Resonance (DE ssNMR spectra in SI), where two well-resolved peaks at 58 and 69 ppm were present, for epoxy and hydroxyl moieties respectively. ssNMR confirmed the overall decrease in oxidation degree, on **GO** samples used under ***Conditions A***. In both cases the epoxy/hydroxyl ratio was substantially unchanged, within the expected range for **GO** (between 1.5 and 2), suggesting that the epoxy ring opening can be excluded as possible intermediate reaction step under both reaction conditions.

From 2D {^{1}H}-^{13}C HETCOR experiments[20] (Figure 3, co-processed for denoising)[21] we observed, in both cases (***Conditions A*** and ***B***), the emergence of correlation peaks between the ^{13}C signals at 20-30 ppm and the ^{1}H signals in the 0-2 ppm region, commonly associated with the presence of aliphatic carbon units (C-C sp^3).[22] The massive change after the reaction of the aromatic region intensity - ^{13}C at 130 ppm - is strongly suggestive of the presence of protons near the aromatic C=C-(sp^2) domains of **GO** and, again, the 2D {^{1}H}-^{13}C HETCOR experiment can be used to clarify this aspect: in the bottom panel of Figure 3 we reported the 2D {^{1}H}-^{13}C signals of **GO** after subjection to ***Conditions B*** acquired with a longer cross-polarization contact time, which allowed us to observe couplings at longer range. Here the correlation between aromatic carbons (^{13}C at 130 ppm) and aliphatic protons (^{1}H at 0 ppm) becomes apparent. Collectively, the XPS and ssNMR data can indicate the presence of aliphatic molecules adsorbed on **GO** after the reactions. This evidence could explain the loss of mass balance recorded when increasing amounts of GO were utilized.

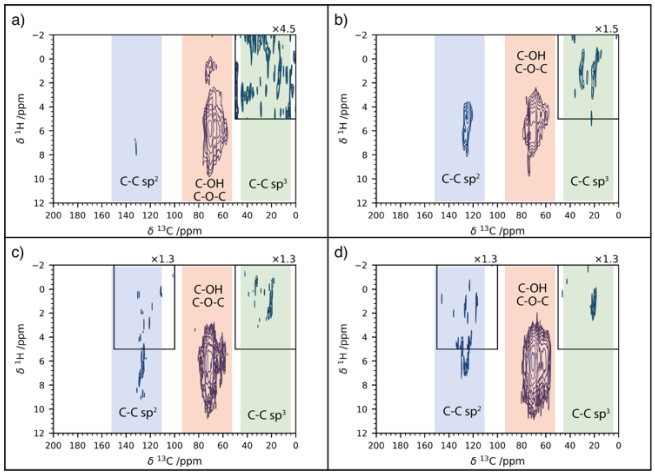


Figure 3. 2D {^{1}H}-^{13}C HETCOR spectra of **GO** after reaction in ***Conditions A*** (b) and ***B*** (c) compared to the control (a), acquired with 1 ms of cross-polarization contact time. Insets show magnifications to appreciate the presence or absence of the correlations to aliphatic protons. The bottom panel (d) shows the 2D {^{1}H}-^{13}C HETCOR spectra of **GO** in ***Conditions B*** acquired with 4 ms of cross-polarization contact time.

Mechanistic proposal

Based on spectroscopic evidence, as well as chemical outcomes, the following reaction mechanisms can be envisioned (Scheme 4). The initial formation of the tertiary carbocation **A** (**GO**-promoted dehydration of **1a**) could result in two different reaction channels. In particular, cyclobutene **3'** can be formed *via* direct deprotonation; alternatively, **A** can undergo the desired ring-opening of the cyclobutane ring via C_α-C_β bond cleavage, based on ring-strain release as a main driving force. The resulting benzylic carbocation **B** will be finally quenched *via* deprotonation reaction to give skipped as well as conjugated dienes **3**. Subsequently, the employment of larger quantities of graphene oxide (*i.e.* 100 wt%) could promote further protonation of **3** to the corresponding allylic cationic intermediate **C** that could be ultimately stabilized by p-stacking contacts with the p-domains of **GO** (Scheme 4 - inset). Extending the lifetime of intermediates **C** could then favor the intramolecular trapping of the carbocationic site by one of the arene rings generating the corresponding indenes **2**. To support the latter part of the proposed mechanistic scheme, we treated dienes **3a** under ***Conditions A***. Interestingly, indenes **2a**/**2a'** was isolated in nearly 1:1 isomeric mixture and 33% overall yield, demonstrating that the dienes **3** represent key intermediates for the obtainment of the indenes **2**. Overall, the proposed H$^+$/π-electron-based activation mode agrees with both XPS and ssNMR investigation. As a matter of fact, while the reduction of **GO** upon catalysis could be ascribed to a partial absorption on the **GO** surface of carbonous fragments/compounds, the inertness of C*sp*^{3}-O based functional groups (alcohol, epoxide) ruled out any possible covalent activation modes exerted by the carbon nano-material.

Conclusions

We have documented on the chemodivergent synthesis of densely functionalized indenes as well as dienes by means of graphene-oxide mediated site-selective ring-opening of cyclobutanols. The chemical outcomes could be conveniently controlled by dosing the loading of **GO** in the reaction mixture. This aspect, combined with the intriguing scaffold and mild reaction conditions confers to the protocol high degree of simplicity and practicability. Dedicated spectroscopic (*i.e.* XPS and ssNMR) investigations revealed unambiguously the pivotal role of the nanostructured carbon nano-form in assisting the sequences of the chemical machinery via both Brønsted acid catalysis and π-π stacking stabilization of the highly delocalized carbocationic intermediates.

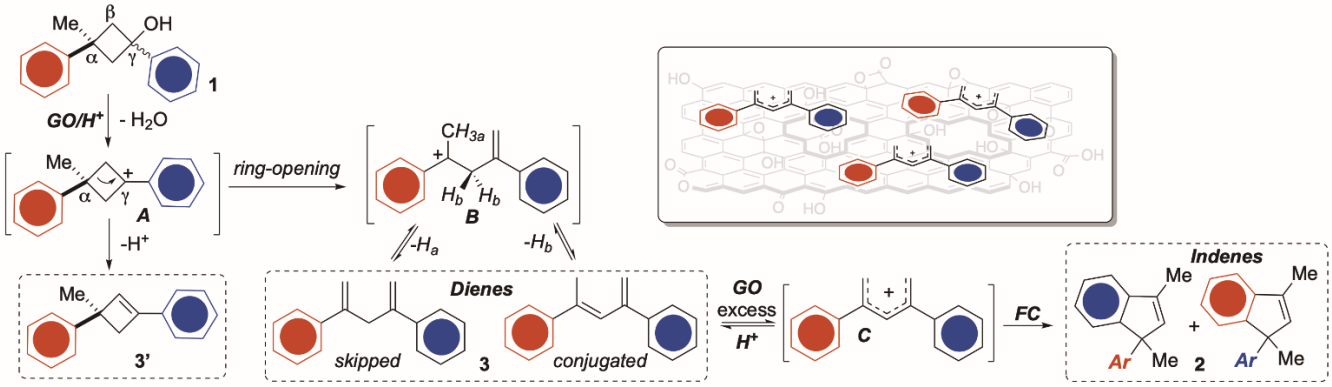
Attempts to extend the present protocols to readily available alcohols are underway in our laboratories and will be communicated in due course.

Experimental

General procedure for the synthesis of indenes. A screw-cap-vial was charged with reagent grade EtOAc (3.5 ml), the desired cyclobutanol **1** (0.1 mmol), $NaBF_4$ (0.2 mmol, 21.8 mg) and **GO** (100 wt% with respect to **1**). The reaction mixture was warmed at 90 °C and stirred at the same temperature overnight. Removal of the **GO** by filtration and subsequent purification via flash chromatography (100% *n*-Hex) led to the isolation of **2**, generally as a mixture of isomers.

General procedure for the synthesis of dienes. A screw-cap-vial was charged with reagent grade EtOAc (3.5 ml), the desired cyclobutanol **1** (0.1 mmol) and **GO** (20 wt% with respect to **1**). The reaction mixture was warmed at 90 °C and stirred at the same temperature overnight. Removal of the **GO** by filtration (Celite pad) and subsequent purification via flash chromatography led to the isolation of compounds **3** (generally as a mixture of isomers).

Scheme 4. Mechanistic proposal for the GO mediated synthesis of indenes and dienes via ring-opening of cyclobutanols **1**.



Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement

We are grateful to the University of Bologna for financial support and to the Italian Ministry of Education, University and Research (MIUR) PRIN-2017 project 2017W8KNZW. The research leading to these results has received funding from the European Union's Horizon 2020 research and innovation programme under GrapheneCore3 881603-Graphene Flagship. F.B. and E.R. acknowledge the MIUR, and European Social Fund (ESF) for the PON R&I 2014-2020 program, action IV.4 "Doctorates and research contracts on Innovation topics" This work benefited from access (ITA017) to CERM/CIRMMP, Italy centre of Instruct-ERIC, a Landmak ESFRI project, for the ssNMR measurements and support.

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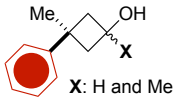

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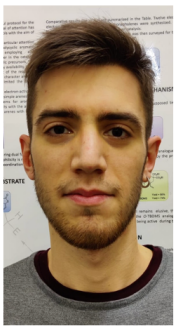

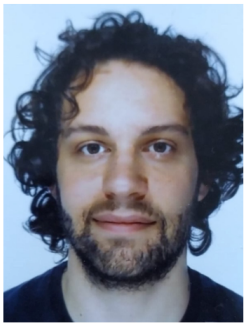

Left to Right (top): Andrea Brunetti, Angela Pintus, Lorenzo Lombardi, Alessandro Kovtun, Federico Mascetti

Left to Right (bottom): Francesco Bruno, Enrico Ravera, Manuela Melucci, Giulio Bertuzzi, Marco Bandini