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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  $\pi$ -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, simplicity and selectivity (*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.<sup>[1]</sup> 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.<sup>[2]</sup> 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  $\sigma$ -bond activation modes for the generation of chemical diversity.<sup>[4,5]</sup> 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.<sup>[6]</sup>



Figure 1. a) Schematic representation of GO and relative applications in carbocatalysis; b) Working-plan for the present C-C  $\sigma$ -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,<sup>[7]</sup> generating intrinsic limitations in terms of scalability and sustainability of the overall procedure.<sup>[8]</sup> 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,<sup>[9]</sup> we recently documented on the synergistic action of the **GO** functional groups for the covalent electrophilic activation of  $\pi$ -alcohols, towards chemo- and regioselective nucleophilic manipulations.<sup>[10,11]</sup>

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  $\sigma$ -bond cleavage (Figure 1b).<sup>[12]</sup> 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**,<sup>[13]</sup> 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  $\pi$ -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.<sup>[14]</sup>

#### **Results and Discussion**

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#### **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 carbonbased promoter, and loading of the catalyst) were assessed to identify the optimal conditions (see Table 1).

Table 1. Optimization of the reaction conditions.<sup>a</sup>

Me, <u>O</u> H			
Ne -		la l	Ph p-Tol
	Ph Me Cond. A	Cond. B	3a-mixture
р-Т	MaBF <sub>4</sub> , AcOEt 90 °C, 16 h 90 °C, 16 h <b>GO</b> (100 wt%)	AcOEt 90 °C, 16 h <b>GO</b> (20 wt%)	Ph Ph <b>Ph</b> <b>Ph</b> <b>P</b> -Tol <b>3a</b>
Run	Deviations from opti-	Yield <b>2a+2a'</b>	Yield <b>3</b> [%] <sup>c</sup> /
	mal	[%] <sup>b</sup>	3a/3a' <sup>d</sup>
1 <sup>e</sup>	Α	55	
2 <sup><i>f</i></sup>	Yb(OTf)₃ instead of <b>GO</b>	30	61/1:1
<b>3</b> <sup><i>f</i></sup>	FeCl₃ instead of <b>GO</b>	traces /	traces /
<b>4</b> <sup>f</sup>	AcOH instead of GO	NR	
5 <sup><i>f</i></sup>	<i>p</i> TSA instead of <b>GO</b>	/	89 / 1:20
6 <sup><i>f</i></sup>	<i>r</i> GO instead of <b>GO</b>	/	11 / 1:3
7	No NaBF4	43	
8	Toluene	39	57 / 1.3:1
9	PhCF₃	30	61/1:1
10	DCE	34	
11	<b>GO</b> 200 wt%	decomposi-	
		tion	
12	<b>GO</b> 75 wt%	50	29 / 1.5:1
13	<b>GO</b> 50 wt%	11	75 / 2.5:1
14	В		95 / 4.5:1
15	<b>GO</b> 10 wt%	-	56 <sup>g</sup> / 4.5:1
16	no <b>GO</b>	NR	
17	NaBF <sub>4</sub> as an additive	-	93 / 4.4:1

<sup>*a*</sup> All the reactions were carried out in reagent grade solvents and under air. *Cond. A*: **1a** (0.5 M) with **GO** 100 wt%, NaBF<sub>4</sub> (2.0 equiv). *Cond. B*: **1a** (0.015 M) with **GO** 20 wt%. <sup>*b*</sup> Isolated yield after flash chromatography and reported as a **2a+2a'** mixture (**2a** and **2a'** were formed in nearly 1:1 ratio). <sup>*c*</sup> Isolated yield after flash chromatography and reported as **3a+3a'** (**3a** was reported as a diene mixture). <sup>*d*</sup> Determined via <sup>1</sup>H-NMR analysis on the reaction crude. <sup>e</sup> The complete consumption of **1a** was recorded.<sup>[15] f</sup> 100 mol% of Lewis/Brønsted/carbon acid was utilized. <sup>g</sup> 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<sub>4</sub> (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<sub>3</sub>) led to a complete decomposition of the starting cyclobutanol (entry 3) and Yb(OTf)<sub>3</sub> 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 pTSA (entry 5). The beneficial role of NaBF<sub>4</sub> on the overall process was then verified through a blank reaction (43%, entry 7). Although the rationale of the NaBF<sub>4</sub> action is still unclear, we speculated that the presence of poorly coordinating anions such as BF<sub>4</sub>- 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.<sup>[16]</sup> 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<sub>3</sub>, 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<sub>4</sub> (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.<sup>a</sup>



<sup>*a*</sup> 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 <sup>1</sup>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,I). 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 **1**) 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%).<sup>[17]</sup>

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  $C_{\alpha}$ - $C_{\beta}$ 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  $\alpha$ -carbocationic intermediate upon  $C_{\alpha}$ - $C_{\beta}$  cleavage (see mechanistic rationale) can be hampered by the presence of electron-deficient arenes at the  $\alpha$ -position of the cyclobutane core.

**Scheme 2** GO-mediated synthesis of dienes **3** via ring-opening of cyclobutanol cores deriving from acetophenones.<sup>*a*</sup>



<sup>*a*</sup> Between brackets the **3:3'** ratios, determined via <sup>1</sup>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  $\pi$ -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.<sup>a</sup>



<sup>a</sup> Between brackets the **3:3'** ratios, determined via <sup>1</sup>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<sub>4</sub>, 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.<sup>[18]</sup>

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<sup>2</sup> 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<sup>2</sup> 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.<sup>[19]</sup> 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 {1H}-13C HETCOR experiments<sup>[20]</sup> (Figure 3, co-processed for denoising)<sup>[21]</sup> we observed, in both cases (Conditions A and **B**), the emergence of correlation peaks between the <sup>13</sup>C signals at 20-30 ppm and the <sup>1</sup>H signals in the 0-2 ppm region, commonly associated with the presence of aliphatic carbon units (C-C sp<sup>3</sup>).<sup>[22]</sup> The massive change after the reaction of the aromatic region intensity - 13C at 130 ppm - is strongly suggestive of the presence of protons near the aromatic C=C-(sp<sup>2</sup>) domains of GO and, again, the 2D {<sup>1</sup>H}-<sup>13</sup>C HETCOR experiment can be used to clarify this aspect: in the bottom panel of Figure 3 we reported the 2D {<sup>1</sup>H}-<sup>13</sup>C signals of GO after subjection to Conditions B acquired with a longer crosspolarization contact time, which allowed us to observe couplings at longer range. Here the correlation between aromatic carbons (13C at 130 ppm) and aliphatic protons (1H 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 {<sup>1</sup>H}-<sup>13</sup>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 {<sup>1</sup>H}-<sup>13</sup>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  $C_{\alpha}$ - $C_{\beta}$  bond cleavage, based on ringstrain 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  $H^+/\pi$ -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 Csp<sup>3</sup>-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  $\pi$ - $\pi$  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-capvial was charged with reagent grade EtOAc (3.5 ml), the desired cyclobutanol 1 (0.1 mmol), NaBF<sub>4</sub> (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  $\mathbf{1}$  (0.1 mmol) and  $\mathbf{GO}$  (20 wt% with respect to  $\mathbf{1}$ ). The reaction mixture was warmed at 90 °C and stirred at the same temperature overnight. Removal of the  $\mathbf{GO}$  by filtration (Celite pad) and subsequent purification via flash chromatography led to the isolation of compounds  $\mathbf{3}$  (generally as a mixture of isomers).





#### **Supporting Information**

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

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### References

[1] General reviews on carbocatalysis: a) Dreyer, D. R.; Bielawski, C. W., Carbocatalysis: Heterogeneous carbons finding utility in synthetic chemistry, Chem. Sci. 2011, 2, 1233-1240; b) Chua, C. K.; Pumera, M., Carbocatalysis: The State of "Metal-Free" Catalysis, Chem. Eur. J. 2015, 21, 12550-12562; c) Su, D. S.; Wen, G.; Wu, S.; Peng, F.; Schløgl, R., Carbocatalysis in Liquid-Phase Reactions, Angew. Chem. Int. Ed. 2017, 56, 936-964; d) Duan, X.; Sun, H.; Wang, S., Metal-Free Carbocatalysis in Advanced Oxidation Reactions, Acc. Chem. Res. 2018, 51, 678-687; e) Veerakumar, P.; Thanasekaran, P.; Subburj, T.; Lin, K.-C., A Metal-Free Carbon-Based Catalyst: An Overview and Directions for Future Research, C, 2018, 4, 54; f) Antonietti, M.; Lopez-Salas, N.; Primo, A., Adjusting the Structure and Electronic Properties of Carbons for Metal-Free Carbocatalysis of Organic Transformations, Adv. Mater. 2019. 31. 1805719: g) Campisciano. C.: Gruttadauria. M.: Giacalone, F., Modified Nanocarbons for Catalysis, ChemCatChem. 2019, 11, 90-113; h) Lenarda, A.; Witanen, T.; Helaja, J., Carbon Materials as Catalytic Tools for Oxidative Dehydrogenations and Couplings in Liquid Phase. Synthesis. 2022. 55. 45-61: i) Singha. R.: Basak. P.: Ghosh. P., Catalytic applications of graphene oxide towards the synthesis of bioactive scaffolds through the formation of carbon-carbon and carbon-heteroatom bonds, *Phys. Sci. Rev.* **2021**, doi.org/10.1515/psr-2021-0096; j) Dandia, A.; Parihar, S.; Kumar, K.; Sini, S.; Parewa, V., Carbocatalysis: a metal free green avenue towards carbon-carbon/heteroatom bond construction, *Phys. Sci. Rev.* **2022**, doi.org/10.1515/psr-2022-0004.

[2] a) Dai, L. in Carbon-Based Metal-Free Catalysts: Design and Applications, Wiley-VCH, Weinheim, **2019**; b) Pyun, J., Graphene Oxide as Catalyst: Application of Carbon Materials beyond Nanotechnology, *Angew. Chem. Int. Ed.* **2011**, *50*, 46-48; c) Haag, D.; Kung, H. H., Metal Free Graphene Based Catalysts: A Review, *Top. Catal.* **2014**, *57*, 762-773; d) Deng, D.; Novoselov, K. S.; Fu, Q.; Zheng, N.; Tian, Z.; Bao, X., Catalysis with two-dimensional materials and their heterostructures, *Nat. Nanontechnol.* **2016**, *11*, 218-230; e) Veerakumar, P.; Thanasekaran, V.; Subburj, T.; Lin, K.-C., A Metal-Free Carbon-Based Catalyst: An Overview and Directions for Future Research, *J. Carbon Res.* **2018**, *4*, 54; f) Huang, J.; Xi, J.; Chen, W.; Bai, Z., Graphene-derived Materials for Metal-free Carbocatalysis of Organic Reactions, *Acta Chim. Sinica*, **2021**, *79*, 1360-1371.

[3] Lombardi, L.; Bandini, M., Graphene Oxide as a Mediator in Organic Synthesis: a Mechanistic Focus, *Angew. Chem. Int. Ed.*, **2020**, *59*, 20767-20778.

[4] Lombardi, L.; Cerveri, A.; Ceccon, L.; Pedrazzani, R.; Monari, M.; Bertuzzi, G.; Bandini, M., Merging C–C  $\sigma$ -bond activation of cyclobutanones with CO2 fixation via Ni-catalysis, *Chem. Commun.* **2022**, *58*, 4071-4074.

For general reviews, see: a) Jun. C.-H., Transition metal-cata-[5] lyzed carbon-carbon bond activation, Chem. Soc. Rev. 2004, 33, 610-618; b) To, C. T.; Chan, K. S., Carbon–Carbon Bond Activation by Group 9 Metal Complexes, Eur. J. Org. Chem. 2019, 6581-6591; c) Deng, L.; Dong, L., Carbon-Carbon Bond Activation of Ketones. Trends Chem. 2020, 2, 183-198; d) McDonald, T. R.; Mills, L. R.; West, M. S.; Rousseaux, S. A. L., Selective Carbon-Carbon Bond Cleavage of Cyclopropanols, Chem. Rev. 2021, 121, 3-79; e) Sokolova, O. O.; Bower, J. F., Selective Carbon–Carbon Bond Cleavage of Cyclopropylamine Derivatives, Chem. Rev. 2021, 121, 80-10; f) Wang, J.; Blaszczyk, S. A.; Li, X.; Tang, W., Transition Metal-Catalyzed Selective Carbon-Carbon Bond Cleavage of Vinylcyclopropanes in Cycloaddition Reactions, Chem. Rev. 2021. 121. 110-139: g) Cohen. Y.: Cohen. A.: Marek. I., Creating Stereocenters within Acyclic Systems by C-C Bond Cleavage of Cyclopropanes, Chem. Rev. 2021, 121, 140-161; h) Pirenne, V.; Muriel, B.; Waser, J., Catalytic Enantioselective Ring-Opening Reactions of Cyclopropanes, Chem. Rev. 2021, 121, 227-263; i) Lutz, M. D. R.; Morandi, B., Metal-Catalyzed Carbon-Carbon Bond Cleavage of Unstrained Alcohols, Chem. Rev. 2021, 121, 300-326.

[6] a) Fumagalli, G.; Stanton, S.; Bower, J. F., Recent Methodologies That Exploit C–C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes, *Chem. Rev.* **2017**, *117*, 9404-9432; b) Wu, X.; Zhu, C., Recent Advances in Ring-Opening Functionalization of Cycloalkanols by C-C  $\sigma$ -Bond Cleavage, *Chem. Rec.* **2018**, *18*, 587-598; c) Murakami, M.; Ishida, N., Cleavage of Carbon–Carbon  $\sigma$ -Bonds of Four-Membered Rings, *Chem. Rev.* **2021**, *121*, 264-299; d) Yan, H.; Smith, G. S.; Chen, F.-E., Recent advances using cyclopropanols and cyclobutanols in ring-opening asymmetric synthesis, *Green Synth. Catal.* **2022**, *3*, 219-226.

For representative examples of metal-catalyzed C-C  $\sigma$ -bond [7] activation of cyclobutanols see: a) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S., Palladium-Catalyzed Asymmetric Arylation, Vinylation, and Allenylation of tert-Cyclobutanols via Enantioselective C-C Bond Cleavage, J. Am. Chem. Soc. 2003, 125, 8862-8869; b) Seiser. T.; Roth, O. A.; Cramer, N., Enantioselective Synthesis of Indanols from tert-Cyclobutanols Using a Rhodium-Catalyzed C C/C H Activation Sequence, Angew. Chem. Int. Ed. 2009, 48, 6320-6323; c) Seiser, T.; Cathomen, G.: Cramer, N., Enantioselective Construction of Indanones from Cyclobutanols Using a Rhodium-Catalyzed C-C/C-H/C-C Bond Activation Process, Synlett, 2010, 1699-1703; d) Ziadi, A.; Martin, R., Ligand-Accelerated Pd-Catalyzed Ketone y-Arylation via C-C Cleavage with Aryl Chlorides, Org. Lett. 2012, 14, 1266-1269; e) Ziadi, A.; Correa, A.; Martin R., Formal y-alkynylation of ketones via Pd-catalyzed C-C cleavage, Chem. Commun. 2013, 49, 4286-4288; f) Ren, R.; Zhao, H.; Huan, L.; Zhu, C., Manganese-Catalyzed Oxidative Azidation of Cyclobutanols: Regiospecific Synthesis of Alkyl Azides by C C Bond Cleavage, Angew. Chem. Int. Ed. 2015, 54, 12692-12696; g) Huang, F.-Q.; Xie, J.; Sun, J.-G.; Wang, Y.-W.; Dong, X.; Qi, L. W.; Zhang, B., Regioselective Synthesis of Carbonyl-Containing Alkyl Chlorides via Silver-Catalyzed Ring-Opening Chlorination of Cycloalkanols, Org. Lett. 2016, 18, 684-687; h) Wang, Q.; Chen, R.; Lou, J.; Zhang, D. H.; Zhou, Y.-G.; Yu, Z., Highly Regioselective C–H Alkylation of Alkenes Through an Aryl to Vinyl 1,4-Palladium Migration/C-C Cleavage Cascade, ACS Catal. 2019, 9, 11669-11675; i) Allen, B. D. W.; Hareram, M. D.; Seastram, A. C.; McBride, T.; Wirth, T.; Browne, D. L.; Morrill, L. C., Manganese-Catalyzed Electrochemical Deconstructive Chlorination of Cycloalkanols via Alkoxy Radicals, Org. Lett. 2019, 21, 9241-9246; k) Yu, J.; Yang, S.; Wu, Z.; Zhu, C., Annulation of Benzylic Alcohols with Alkynes for Rapid and Efficient Synthesis of Indenes and Spiroindenes, Chin. J. Org. Chem. 2019, 39, 223-231; j) Zhang, Z.-M.; Zhang, J.; Chen, F., Palladium-Catalyzed Asymmetric Cross-Coupling Reactions of Cyclobutanols and Unactivated Olefins, Org. Lett. 2021, 23, 9520-9525; I) Li, X.-S.; Kong, X.; Wang, C.-T.; Niu, Z.-J.; Wie, W.-X.; Liu, H.-C.; Zhang, Z.; Li, Y.; Liang, Y.-M., Lewis-Acid-Catalyzed Tandem Cyclization by Ring Expansion of Tertiary Cycloalkanols with Propargyl Alcohols, Org. Lett. 2021, 23, 9457-9462; m) Lu, Y.-C.; West, J. G., C-C Bond Fluorination via Manganese Catalysis, ACS Catal. 2021, 11, 12721-12728; n) Hu, Y.; Luo, H.; Tu, X.; Xue, H.; Jin, H.; Liu, Y.; Zhou, B., Selective cine-arylation of tertcyclobutanols with indoles enabled by nickel catalysis. Chem. Commun. 2021, 57, 4686-4689; o) Wang, Z.; Hu, Y.; Jin, H.; Liu, Y.; Zhou, B., Nickel-Catalyzed Arylation/Alkenylation of tert-Cyclobutanols with Aryl/Alkenyl Triflates via a C-C Bond Cleavage, J. Org. Chem. 2021, 86, 466-474

[8] Sporadic examples of metal-free Brønsted acid mediated ringopening of cyclobutanols were documented: a) An, Z.; Liu, Y.; Sun, Y.; Yan, R., TFA-Catalyzed [3+2] Spiroannulation of Cyclobutanols: A Route to Spiro[cyclobuta[a]indene-7,1'-cyclobutane] Skeletons, *Chem. Asian J.* **2020**, *15*, 3812-3815; b) Fei, C.; Liu, J.; Peng, H.; Jiang, D.; Yin, B., BINOL-phosphoric acids-catalyzed furylogous pinacol rearrangement of 1-[5-(hydroxy-diaryl-methyl)-furan-2-yl]-cyclobutanols into spiro cyclopentanones, *Tetrahedron*, **2018**, *74*, 6939-6945. For electrochemically induced and indirect ring-opening of cyclobutanes see: c) Petti, A.; Natho, P.; Lam, K.; Parsons, P. J., Regioselective Electrochemical Cyclobutanol Ring Expansion to 1-Tetralones, *Eur. J. Org. Chem.* **2021**, 854-858; d) Liu, X.-F.; Zhang, K.; Wang, L.-L.; Wang, H.; Huang, J.; Zhang, X.-T.; Lu, X.-B.; Zhang, W.-Z., Electroreductive Ring-Opening Carboxylation of Cycloketone Oxime Esters with Carbon Dioxide, J. Org. Chem. **2022**, doi.org/10.1021/acs.joc.2c01816; e) Zhao, L.; Zhong, Q.; Tian, J.; Luo, M.; Yang, C.; Guo, L.; Xia, W., Electrochemical Synthesis of  $\beta$ -Functionalized Ketones via Ring-Opening of Cycloalkanols, Org. Lett. **2022**, 24, 4421-4426.

[9] Pintus, A.; Mantovani, S.; Kovtun, A.; Bertuzzi, G.; Melucci, M.; Bandini, M., Recyclable GO-Arginine Hybrids for CO2 Fixation into Cyclic Carbonates, *Chem. Eur. J.* doi.org/10.1002/chem.202202440.

[10] a) Favaretto, L.; An, J.; Sambo, M.; De Nisi, A.; Bettini, v; Melucci, M.; Kovtun, A.; Liscio, A.; Palermo, V.; Bottoni, A.; Zerbetto, F.; Calvaresi, M.; Bandini, M., Graphene Oxide Promotes Site-Selective Allylic Alkylation of Thiophenes with Alcohols, *Org. Lett.* **2018**, *20*, 3705-3709; b) Lombardi, L.; Bellini, D.; Bottoni, A.; Calvaresi, M.; Monari, M.; Kovtun, A.; Palermo, V.; Melucci, M.; Bandini, M., Allylic and Allenylic Dearomatization of Indoles Promoted by Graphene Oxide by Covalent Grafting Activation Mode, *Chem. Eur. J.* **2020**, *26*, 10427-10432.

[11] For other examples of GO assisted manipulation of alcohols, see a) Hu, F.; Patel, M.; Luo, F.; Flach, C.; Mendelsohn, R.; Garfunkel, E.; He, H.; Szostak, M., Graphene-Catalyzed Direct Friedel–Crafts Al-kylation Reactions: Mechanism, Selectivity, and Synthetic Utility, *J. Am. Chem. Soc.* **2015**, *137*, 14473-14480; b) Meng, G.; Patel, M.; Luo, F.; Li, Q.; Flach, C.; Mendelsohn, R.; Garfunkel, E.; He, H.; Szostak, M., Graphene oxide catalyzed ketone  $\alpha$ -alkylation with alkenes: enhancement of graphene oxide activity by hydrogen bonding, *Chem. Commun.* **2019**, *55*, 5379-5382; c) Li, J.; Li, F.; Yang, Q.; Wang, S.; Sun, H.; Yang, Q.; Tang, J.; Liu, S., Tailoring collaborative N–O functionalities of graphene oxide for enhanced selective oxidation of benzyl alcohol, *Carbon*, **2021**, *182*, 715-724.

[12] Kausar, N.; Roy, I.; Chattopadhyay, D.; Das, A. R., Synthesis of 2,3-dihydroquinazolinones and quinazolin-4(3H)-ones catalyzed by graphene oxide nanosheets in an aqueous medium: "on-water" synthesis accompanied by carbocatalysis and selective C–C bond cleavage, *RSC Adv.* **2016**, *6*, 22320-22330.

[13] Rinaldi, A.; Scarpi, D.; Occhiato, E. G., Recent Advances in the Synthesis of Indenes, *Eur. J. Org. Chem.* **2019**, 7401-7419.

[14] a) Bandini, M.; Tragni, M.,  $\pi$ -Activated alcohols: an emerging class of alkylating agents for catalytic Friedel–Crafts reactions, Org. Biomol. Chem. 2009, 7, 1501-1507; b) Bandini, M., Allylic Alcohols: Sustainable Sources for Catalytic Enantioselective Alkylation Reactions, Angew. Chem. Int. Ed. 2011. 50. 994-995; c) Bandini. M.: Cera. G.: Chiarucci, M., Catalytic Enantioselective Alkylations with Allylic Alcohols, Synthesis 2012, 4, 504-512; d) Sundararaju, B.; Achard, M.; Bruneau, C., Transition metal catalyzed nucleophilic allylic substitution: activation of allylic alcohols via  $\pi$ -allylic species, Chem. Soc. Rev. 2012, 41, 4467-4483; e) Li, H.; Mazet, C., Iridium-Catalyzed Selective Isomerization of Primary Allylic Alcohols, Acc. Chem. Res. 2016, 49, 1232-1241; f) Zhang, J.; Liao, J.; Wei, Y.-F.; Cheng, G.; Luo, R., Recent Advance of Allylic Alcohol Reagents in Organic Synthesis, Mini-Rev. Org. Chem. 2018, 15, 476-487; g) Qian, H.; Huang, D.; Bi, Y.; Yan, G., 2-Propargyl Alcohols in Organic Synthesis, Adv. Synth. Catal. 2019, 361, 3240-3280; h) Akkarasamiyo, S.; Ruchirawat, S.; Ploypradith, P.; Samec, J. S. M., Transition-Metal-Catalyzed Suzuki-Miyaura-Type Cross-Coupling Reactions of π-Activated Alcohols, Synthesis **2020**, *52*, 645-659; i) Wu, G.; Wu, J.-R.; Huang, Y. Yang, Y.-W., Enantioselective Synthesis of Quaternary Carbon Stereocenters by Asymmetric Allylic Alkylation: A Review, Chem. Asian J. 2021, 18, 1864-1877.

[15] Partial decomposition of the carbocation intermediates (see mechanistic interpretation for details) can be account for the lack in mass balance during the reaction.

[16] a) Achilonu, M. C.; Umesiobi, D. O., The formation of carbon– carbon and carbon–heteroatom bonds using silver tetrafluoroborate as a promoter, *Arab. J. Chem.* **2016**, *9*, S1984-S2003; b) De Rosa, M.; Gambaro, S.; Soriente, A.; Della Sala, P.; Iuliano, V.; Talotta, C.; Gaeta, C.; Rescifina, A.; Neri, P., Carbocation catalysis in confined space: activation of trityl chloride inside the hexameric resorcinarene capsule, *Chem. Sci.* **2022**, *13*, 8618-8625 [17] Secondary alcohols or tertiary fully aliphatic carbinols were tested but proved inertness under *Conditions A*.



[18] a) Larciprete, R.; Fabris, S.; Sun, T.; Lacovig, P.; Baraldi, A.; Lizzit, S. Dual path mechanism in the thermal reduction of graphene oxide, J. Am. Chem. Soc. 2011, 133, 17315-17321; b) Mattevi, C.; Eda, G.; Agnoli, S.; Miller, S.; Mkhoyan, K. A.; Celik, O.; Mastrogiovanni, D.; Granozzi, G.; Garfunkel, E.; Chhowalla, M., Evolution of electrical, chemical, and structural properties of transparent and conducting chemically derived graphene thin films, Adv. Funct. Mat. 2009, 19, 2577-2583; c) Guo, S.; Garaj, S.; Bianco, A.; Ménard-Moyon, C. Controlling covalent chemistry on graphene oxide, Nat. Rev. Phys. 2022, 4, 247-262.

[19] a) He, H.; Riedl, T.; Lerf, A.; Klinowski, Solid-state NMR studies of the structure of graphite oxide, J. J. Phys. Chem. 1996, 100, 19954-19958; b) Cai, W.; Piner, R. D.; Stadermann, F. J.; Park, S.; Shaibat, M. A.; Ishii, Y.; Yang, D.; Velamakanni, A.; An, S. J.; Stoller, M.; An, J.; Chen, D.; Ruoff, R. S., Synthesis and Solid-State NMR Structural Characterization of <sup>13</sup>C-Labeled Graphite Oxide, Science, 2008, 321, 1815-1817; c) Casabianca, L. B.; Shaibat, M. A.; Cai, W. W.; Park, S.; Piner, R.; Ruoff, R. S.; Ishii, Y., NMR-Based Structural Modeling of Graphite Oxide Using Multidimensional <sup>13</sup>C Solid-State NMR and ab Initio Chemical Shift Calculations, J. Am. Chem. Soc. 2010, 132, 5672-5676; d) Vacchi, I. A.; Spinato, C.; Raya, J.; Bianco, A.; Ménard-Moyon, C., Chemical reactivity of graphene oxide towards amines elucidated by solid-state NMR, Nanoscale, 2016, 8, 13714-13712; e) Nacken, T. J.; Halbig, C. E.; Wawra, S. E.; Damm, C.; Romies, S.; Walter, J.; Tehrani, M. J.; Hu, Y.; Ishii, Y.; Eigler, S.; Peukert, W., Structural factors controlling size reduction of graphene oxide in liquid processing, Carbon, 2017, 125, 360-369; f) Tricomi, J.; Cacaci, M.; Biagiotti, G.; Caselli, L.; Niccoli, L.; Torelli, R.; Gabbani, A.; Di Vito, M.; Pineider, F.; Severi, M.; Sanguinetti, M.; Menna, E.; Lelli, M.; Berti, D.; Cicchi, S.; Bugli, F.; Richichi, B., Ball milled glyco-graphene oxide conjugates markedly disrupted Pseudomonas aeruginosa biofilms, Nanoscale, 2022, 14, 10190-10199.

a) Vinogradov, E.; Madhu, P. K.; Vega, S., High-resolution proton solid-state NMR spectroscopy by phase-modulated Lee–Goldburg experiment, *Chem. Phys. Lett.* **1999**, *314*, 443-450; b) Vinogradov, E.; P. K. Madhu, Vega S., Proton spectroscopy in solid state nuclear magnetic resonance with windowed phase modulated Lee–Goldburg decoupling sequences, *Chem. Phys. Lett.* **2002**, *354*, 193-202; c) Leskes, M.; Thakur, R. S.; Madhu, P. K.; Kurur, N. D.; Vega, S., Imodal Floquet description of heteronuclear dipolar decoupling in solid-state nuclear magnetic resonance, *J. Chem. Phys.* **2007**, *127*, 024501.

[21] Bruno, F.; Francischello, R.; Bellomo, G.; Gigli, L.; Flori, A.; Menichetti, L.; Tenori, L.; Luchinat, C. Ravera, E., Multivariate Curve Resolution for 2D Solid-State NMR spectra, *Anal. Chem.* **2020**, *92*, 4451-4458.

[22] Caputo, S.; Kovtun, A.; Bruno, F.; Ravera, E.; Lambruschini, C.; Melucci, M.; Moni, L., Study and application of graphene oxide in the synthesis of 2,3-disubstituted quinolines *via* a Povarov multicomponent reaction and subsequent oxidation, *RSC Adv.* **2022**, *12*, 15834-15847.

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