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# Graphene Oxide Catalyzed Ketone α-Alkylation with Alkenes: Enhancement of Graphene Oxide Activity by Hydrogen Bonding

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**Direct α-alkylation of carbonyl compounds represents a fundamental bond forming transformation in organic synthesis. We report the first ketone-alkylation using olefins and alcohols as simple alkylating agents catalyzed by graphene oxide. Extensive studies of the graphene surface suggest a pathway involving dual activation of both coupling partners. Notably, we show that polar functional groups have a stabilizing effect on the GO surface, which results in a net enhancement of the catalytic activity. The method represents the first alkylation of carbonyl compounds using graphenes, which opens the door for the development of an array of protocols for ketone functionalization employing common carbonyl building blocks and readily available graphenes.**

The direct α-alkylation of carbonyl compounds represents one of the most common transformations in organic synthesis (Fig. 1A).[1–3] Due to the versatility of the carbonyl function, the process has become the cornerstone of organic synthesis and has found essential applications for the synthesis of valuable chemical products within both industry and academia.[4,5] Traditionally, carbonyl alkylation requires the use of stoichiometric strong metal bases and alkyl halides as alkylating reagents.[1–5] This leads to problems associated with regioselectivity, operational-conditions, low atom economy, and generation of toxic halide waste.[6-8]

Recently, tremendous progress has been made in the development and application of new graphene-based materials as sustainable, metal-free, benign and readily available carbocatalysts for organic transformations.[9–11] The seminal studies by Bielawski[12] and Garcia[13] documented the advantage of carbocatalysis in metal-free aerobic oxidation and reduction reactions of prime significance to organic synthesis (Fig. 1B). In another direction, oxidative dimerization

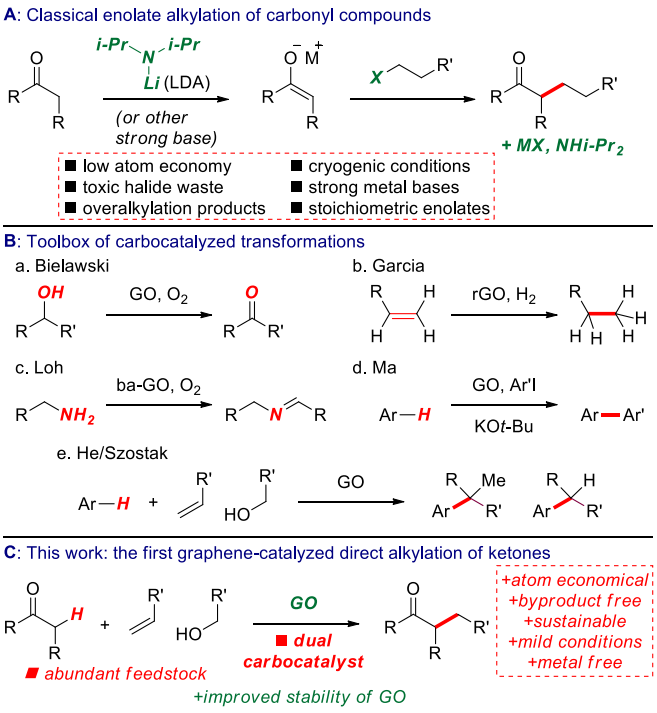


**Fig. 1** (A) Enolate Alkylation of Carbonyl Compounds. (B) Toolbox of Carbocatalyzed Transformations. (C) Graphene-catalyzed Alkylation of Ketones (this work).

of amines[14] and the activation of C–H bonds by graphene-based materials have emerged as highly promising approaches to generate N–C and C–C bonds of synthetic value.[15] From the practical standpoint, the use of graphenes as catalysts[16–18] is highly advantageous because these materials combine the benefits of the abundance of carbon[6,9–11] with heterogeneous reaction conditions[19] facilitating the work-up, while the modular nature of carbocatalysts offers distinct possibilities to introduce and fine-tune catalytically active sites, including surface modification[20] and heteroatom-doping.[21]

Our laboratory has deployed graphene carbocatalysis in the direct Friedel-Crafts alkylations with olefins and alcohols (Fig. 1B).[16a] Inspired by our interest in carbon-based materials[16]

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and realizing the importance of direct carbonyl α-alkylation methods,[1–7] herein, we report a general strategy for ketone-alkylation using olefins and alcohols as alkylating agents catalyzed by graphene-based materials (Fig. 1C).

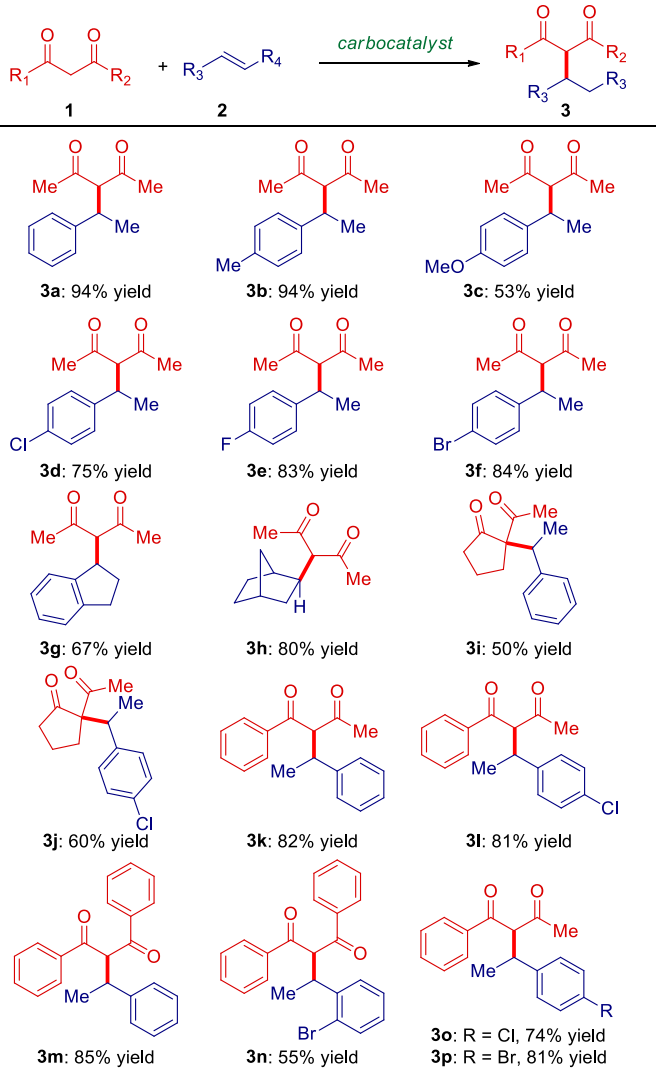
The following features are notable: (1) The method exploits dual activation mechanism of both coupling partners on the GO surface.[22] (2) The protocol is characterized by operationally-simplicity without the need for stoichiometric strong metal bases or cryogenic conditions.[1–3] (3) The reaction employs olefins and alcohols as abundant feedstock materials,[23] which is advantageous over toxic alkyl halides or equivalents as alkylating reagents.[24] (4) We demonstrate that polar functional groups have a stabilizing effect on the GO surface,[22,25] which results in a net enhancement of the catalytic activity.

Graphene oxide has emerged as a powerful material for developing metal-free carbocatalysts for a broad range of chemical reactions. However, the recyclability is always an issue because of the facile reduction by reactants and/or intermediates, resulting in a serious loss of catalytically-active sites, which typically consist of oxygen-containing groups on the GO surface. Specifically, at present, no strategy has been reported to regenerate these functional groups during catalytic reactions. Herein, we demonstrate that interactions between the reactants and GO surface by hydrogen bonding avoid reduction of GO, which (1) preserves the functional groups on the surface, and (2) may find future applications in carbocatalysis. Furthermore, we present applications to the streamlined synthesis of a repertoire of downstream products, illustrating the potential of carbocatalysis in chemoselective manipulation of functional groups in organic synthesis.[26,27]

Recognizing the ability of graphene surface to mediate proton-transfer,[16a,28] we recently questioned whether carbon-based materials can be employed as metal-free catalysts to promote ketone-alkylation with olefins and alcohols by an isomerization mechanism. We started our investigations by examining α-alkylation of pentane-2,4-dione with styrene, a model reaction that is used to test performance of metal catalysts[7b] in the presence of graphene carbocatalysts.[28] Note that a 3:1 diketone/olefin ratio is typically used to minimize olefin by-products.[7a] We have employed 200 wt% of GO to benchmark the process against other isomerization reactions.[28] After extensive optimization, the desired product was obtained in 96% yield using GO (modified Hummers method,[16d] 200 wt%) in $CHCl_3$ at 80 °C. Importantly, the product was obtained with exquisite monoalkylation selectivity via a formal activation of the C($sp^3$) hybridized C–H bond.[24] To confirm the actual catalytic sites, the base-wash experiment was performed (pH = 8.6). As expected, this treatment resulted in a complete loss of catalytic activity.

XPS (X-ray photoelectron spectroscopy) and AAS (atomic absorption spectroscopy) measurements were performed to determine if trace quantities of transition metals were involved. XPS analysis indicated less than 50 ppm of trace metal contaminants (detection limit). AAS analysis indicated less than 1 ppm of trace metal contaminants for the following metals: Mn <0.20 ppm, Fe <0.60 ppm, Cu <0.30 ppm, Cd <0.20 ppm, Zn <0.10 ppm, Ni <1.0 ppm, Pb <1.0 ppm, Au <1.0 ppm)

**Table 2** GO-Catalyzed Ketone α-Alkylation with Olefins[a]




[a]Conditions: olefin (1.0 equiv), ketone (3.0 equiv), GO (200 wt%), $CHCl_3$ (0.20 M), 80 °C. See ESI for full details.

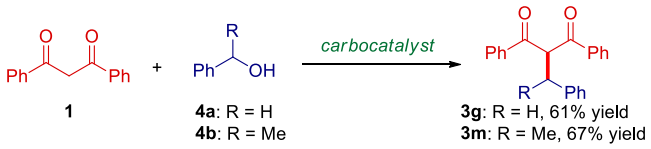



**Fig. 2** GO-catalyzed ketone α-alkylation with alcohols.

determined by comparison with standard metal ion solutions (detection limit). These results support metal-free carbocatalyzed process and indicate that our extensive purification excludes the presence of metallic impurities.[28]

We next explored the versatility of the protocol (Table 1). A broad range of ketones and olefins can be employed as effective coupling partners, including electronic variations (**3a-f**), sensitive halides (**3d-f**), unactivated aliphatic olefins (**3g-h**), cyclic ketones (**3i-j**), highly sterically-hindered mono- and diaryl-ketones (**3k-n**). Overall, the high reactivity, excellent regioselectivity and high atom economy compare very favorably with metal-mediated α-alkylation methods.

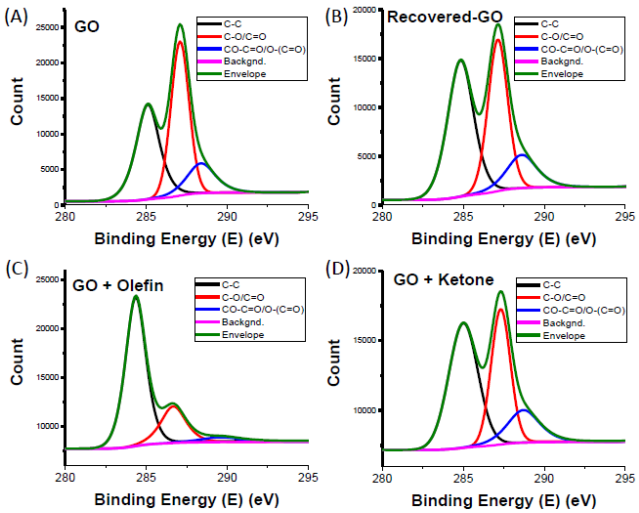



**Fig. 3** X-ray photoelectron spectroscopy C1s spectra: (A) GO. (B) Recovered GO after the alkylation reaction. (C) Recovered GO after the reaction with olefin substrate. (D) Recovered GO after the reaction with ketone substrate.

On the basis of proposed isomerization mechanism,[16a,29] we hypothesized that the protocol could be expanded to alcohols as alkylating reagents (Fig. 2). Notably, benzyl alcohols undergo addition under carbocatalyzed conditions, indicating that direct C–O bond cleavage without preactivation can be utilized as a bond-forming strategy in this protocol.

Extensive characterization studies delineate the key role of graphene-materials before and after the reactions (referred to as 'GO' and 'recovered GO') in this novel α-alkylation platform.

(1) Surface area analysis indicated a surface area of 873.6 $m^2\ g^{-1}$, suggesting a slight increase of π-stacking interactions as compared to the parent GO material (SA of 1008.6 $m^2\ g^{-1}$ ).

(2) pH of GO (pH = 4.19 at 0.29 mg $mL^{-1}$) and the recovered GO (pH = 4.14 at 0.29 mg $mL^{-1}$) indicated a slightly acidic nature of GO, and no changes in the acidity after the reaction.

(3) EDXS analysis showed C/O atomic ratio of 1.9, which slightly increased to C/O atomic ratio of 2.1 after the reaction, indicating that the majority of the oxygen functionalities have been maintained on the GO surface during the reaction.

(4) Detailed XPS analysis showed C/O of 2.2 (Fig. 3, Tables SI-1 and SI-4), which increased to C/O of 2.4 after the reaction. C1s spectrum of the GO catalyst before and after the reaction indicated a decrease of C–O/C=O functional groups (from 30.9% to 27.0%, 1st run; 21.1%, 6th run) with a concomitant increase of C-C bonds (from 26.2% to 32.5%, 1st run; 50.2%, 6th run). These changes include slight loss of C=O and C–O functions from the GO surface (epoxide, hydroxyl) and reduction of anhydride and carboxylic acid functional groups on the surface (from 10.0% to 9.7%, 1st run; 5.5%, 6th run).

(5) FTIR measurements demonstrated no change in the intensity of signals at 1222, 1712, 1408, 1813 $cm^{-1}$, attributed to C–O (C–OH/C–O–C, hydroxyl/ epoxide), C=O (carbonyl groups), carboxylic acid RCOO-H bending vibrations and anhydride C=O stretching vibrations respectively in the recovered GO. The FTIR spectrum also revealed that the signal at 1610 $cm^{-1}$, attributed to the presence of $sp^2$ C=C bonds in GO, has separated into 1576 and 1610 $cm^{-1}$, indicative of

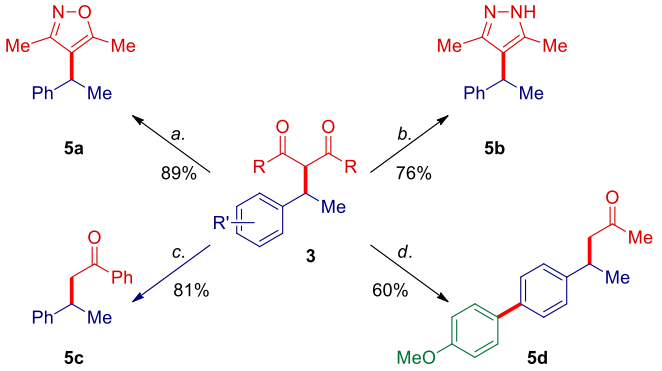



**Fig. 4** Transformations of ketone α-alkylation products. Conditions: a. $NH_2OH$; b. $NH_2NH_2$ c. $K_2CO_3$; d. $Pd(OAc)_2$, 4-MeO-$C_6H_4$-$B(OH)_2$, $Na_2CO_3$. See ESI for full details. Note that all reactions have been performed in one-pot.

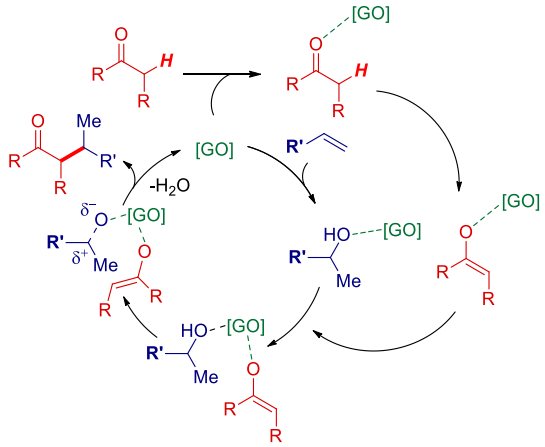



**Fig. 5** Proposed mechanism for sustainable ketone α-alkylation.

repositioning of electron withdrawing groups (e.g., hydroxyl, carboxylic acid, anhydride, epoxide) on the GO surface.

Thus, the surface area, EDXS, XPS and FTIR measurements indicate that polar functional groups are not removed from the GO surface,[30-32] which is in sharp contrast to the related isomerization processes not involving carbonyl substrates.

To determine the effect of reaction components, we exposed GO to established alkylation conditions (1) in the presence of olefin substrate, (2) in the presence of ketone substrate, and (3) in the absence of both substrates, meaning only the solvent, $CHCl_3$ is present (see ESI).

XPS analysis indicated that GO was slightly reduced in (1) (C/O ratio increases to 3.2 from 2.1 in parent GO), while in (2) GO oxidation level is slightly changed (C/O ratio remains at 2.0) (Figure 3), in (3) GO is slightly more oxidized compared to the initial GO (C/O ratio decreases to 1.8).

FTIR analysis indicated that in (1) the intensity of signals corresponding to polar functional groups become weaker or disappear (1046 $cm^{-1}$ (C-O), 1082 $cm^{-1}$ (C-O), 1222 $cm^{-1}$ (C-O), 1355 $cm^{-1}$ (C-O/COOH), 1408 $cm^{-1}$ (COOH)), and the signal at 1610 $cm^{-1}$ has shifted to 1576 $cm^{-1}$ (C=C). In (2) no visible changes are detected except at 1576 $cm^{-1}$, which now appears along with the peak at 1610 $cm^{-1}$ (C=C), indicative of repositioning of the graphene domains. In (3) additional C–O (alcohols, ethers) and C=O (carbonyls) groups are present in the recovered GO; the peaks at 1046 $cm^{-1}$, assigned to C–O, and at 1712 $cm^{-1}$, assigned to C=O, become stronger.

Thus, these observations are consistent with (1) reduction of GO to rGO in the presence of olefin substrate,[25] (2) oxidation of GO in the absence of both substrates[33] and, most crucially, (3) stabilization of the GO surface in the presence of carbonyl substrate. Carbonyl groups are capable of binding to surface via hydrogen bonding, thus preserving the integrity of GO from reduction.[34] While heating affects repositioning of functional groups, carbonyl substrates maintain a steady-state on the surface, wherein the oxygen content remains constant. The net result is that carbonyl substrates maintain the integrity of polar functional groups within the surface.

To illustrate the synthetic potential, we have performed a series of diversifications directly after $\alpha$-ketone alkylation in one-pot (Fig. 4). Additional kinetic, Hammett and competition studies were conducted (see ESI). We propose a mechanism for ketone $\alpha$-alkylation shown in Fig. 5. The key step involves dual activation of both coupling partners by transient coordination to the graphene surface.[22,28]

In summary, we have reported the first general method for $\alpha$-alkylation of carbonyl compounds catalyzed by graphene-based materials. Since graphene deactivation by reduction is a major side process in carbocatalysis,[9,10] this study offers an effective way to enhance the catalytic activity of graphene-based materials in organic synthesis.

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## Notes and references


1 M. Braun, *Modern Enolate Chemistry: From Preparation to Applications in Asymmetric Synthesis*, Wiley, 2016.
2 D. Seebach, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 1624.
3 B. M. Trost and I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, 1991.
4 E. M. Carreira and L. Kvaerno, *Classics in Steroselective Synthesis*, Wiley, 2009.
5 (*a*) B. Pearson, *Speciality Chemicals: Innovations in Industrial Synthesis and Applications*, Elsevier, 1991; (*b*) D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443.
6 (*a*) C. J. Li and B. M. Trost, *Proc. Natl. Acad. Sci.*, 2008, **105**, 13197; (*b*) R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437.
7 (*a*) F. Mo and G. Dong, *Science*, 2014, **345**, 68; (*b*) X. Yao and C. J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 6884.
8 (*a*) R. Kumar and E. V. van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 1121; (*b*) U. Kazmaier, *Org. Chem. Front.*, 2016, **3**, 1541.
9 (*a*) S. Navalon, A. Dhakshinamoorthy, M. Alvaro and H. Garcia, *Chem. Rev.*, 2014, **114**, 6179; (*b*) D. R. Dreyer, A. D. Todd and C. W. Bielawski, *Chem. Soc. Rev.*, 2014, **43**, 5288; (*c*) C. K. Chua and M. Pumera, *Chem. Eur. J.*, 2015, **21**, 12550; (*d*) P. Tang, G. Hu, M. Li and D. Ma, *ACS Catal.*, 2016, **6**, 6948; (*e*) S. Navalon, A. Dhakshinamoorthy, M. Alvaro, M. Antonietti and H. Garcia, *Chem. Soc. Rev.*, 2017, **46**, 4501.
10 L. Dai, *Carbon-Based Metal-Free Catalysts: Design and Applications*, Wiley, 2018.
11 (*a*) D. R. Dreyer, R. S. Ruoff and C. W. Bielawski, *Angew. Chem. Int. Ed.*, 2010, **49**, 9336; (*b*) J. Pyun, *Angew. Chem. Int. Ed.*, 2011, **50**, 46.
12 (*a*) D. R. Dreyer, H. P. Jia and C. W. Bielawski, *Angew. Chem. Int. Ed.*, 2010, **49**, 6813; (*b*) H. P. Jia, D. R. Dreyer and C. W. Bielawski, *Tetrahedron*, 2011, **67**, 4431; (*c*) H. P. Jia, D. R. Dreyer and C. W. Bielawski, *Adv. Synth. Catal.*, 2011, **353**, 528.
13 A. Primo, F. Neatu, M. Florea, V. Parvulescu and H. Garcia, *Nat. Commun.*, 2014, **5**, 5291.
14 C. Su, R. Tandiana, J. Balapanuru, W. Tang, K. Pareek, C. T. Nai, T. Hayashi and K. P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 685.
15 Y. Gao, P. Tang, H. Zhou, W. Zhang, H. Yang, N. Yan, G. Hu, D. Mei, J. Wang and D. Ma, *Angew. Chem. Int. Ed.*, 2016, **55**, 3124.
16 For selected studies from our laboratory, see: (*a*) F. Hu, M. Patel, F. Luo, C. Flach, R. Mendelsohn, E. Garfunkel, H. He and M. Szostak, *J. Am. Chem. Soc.*, 2015, **137**, 14473; (*b*) M. Patel, F. Luo, M. R. Khoshi, E. Rabie, Q. Zhang, C. R. Flach, R. Mendelsohn, E. Garfunkel, M. Szostak and H. He, *ACS Nano*, 2016, **9**, 2305; (*c*) M. Patel, W. Feng, K. Savaram, M. R. Khosi, R. Huang, J. Sun, E. Rabie, C. Flach, R. Mendelsohn, E. Garfunkel and H. He, *Small*, 2015, **11**, 3358; (*d*) P. L. Chiu, D. D. T. Mastrogiovanni, D. Wei, C. Louis, M. Jeong, G. Yu, P. Saad, C. R. Flach, R. Mendelsohn, E. Garfunkel and H. He, *J. Am. Chem. Soc.*, 2012, **134**, 5850.
17 For additional examples, see: (*a*) X. H. Li, J. S. Chen, X. Wang, J. Sun and M. Antonietti, *J. Am. Chem. Soc.*, 2011, **133**, 8074; (*b*) J. Long, X. Xie, J. Xu, Q. Gu, L. Chen and X. Wang, *ACS Catal.*, 2012, **2**, 622; (*c*) Y. Gao, G. Hu, J. Zhong, Z. Shi, Y. Zhu, D. S. Su, J. Wang, X. Bao and D. Ma, *Angew. Chem. Int. Ed.*, 2013, **52**, 2109; (*d*) X. H. Li and M. Antonietti, *Angew. Chem. Int. Ed.*, 2013, **52**, 4572; (*e*) A. Dhakshinamoorthy, A. Primo, P. Concepcion, M. Alvaro and H. Garcia, *Chem. Eur. J.*, 2013, **19**, 7547; (*f*) M. Latorre-Sanchez, A. Primo and H. Garcia, *Angew. Chem. Int. Ed.*, 2013, **52**, 11813; (*g*) G. Wen, S. Wu, B. Li, C. Dai and D. S. Su, *Angew. Chem. Int. Ed.*, 2015, **54**, 4105; (*h*) S. Yang, L. Peng, P. Huang, X. Wang, Y. Sun, C. Cao and W. Song, *Angew. Chem. Int. Ed.*, 2016, **55**, 4016.
18 For further studies, see: (*a*) A. Dhakshinamoorthy, M. Alvaro, P. Concepcion, V. Fornes and H. Garcia, *Chem. Commun.*, 2012, **48**, 5443; (*b*) Y. Kim, S. Some and H. Lee, *Chem. Commun.*, 2013, **49**, 5702; (*c*) H. Yang, X. Cui, X. Dai, Y. Deng and F. Shi, *Nat. Commun.*, 2015, **6**, 6478.
19 D. S. Su, S. Perathoner and G. Centi, *Chem. Rev.*, 2013, **113**, 5782.
20 V. Georgakilas, M. Otyepka, A. B. Bourlinos, V. Chandra, N. Kim, K. C. Kemp, P. Hobza, R. Zboril and K. S. Kim, *Chem. Rev.*, 2012, **112**, 6156.
21 X. K. Kong, C. L. Chen and Q. W. Chen, *Chem. Soc. Rev.*, 2014, **43**, 2841.
22 For an excellent review on catalytic mechanisms in graphene-catalyzed reactions, see Ref. 9e.
23 Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333.
24 W. F. von Oettingen, *The Halogenated Hydrocarbons of Industrial and Toxicological Importance*, Elsevier, 1964.
25 P. V. Kumar, N. M. Bardhan, S. Tongay, J. Wu, A. M. Belcher and J. C. Grossman, *Nat. Chem.*, 2014, **6**, 151.
26 N. A. Afagh and A. K. Yudin, *Angew. Chem. Int. Ed.*, 2010, **49**, 262.
27 R. C. Larock, *Comprehensive Organic Transformations*, Wiley, 1999.
28 For an excellent study on the effect of metallic impurities, see: A. Ambrosi, C. K. Chua, B. Khezri, Z. Sofer, R. D. Webster and M. Pumera, *Proc. Natl. Acad. Sci. USA*, 2012, **109**, 12899.
29 M. R. Karim, K. Hatakeyama, T. Matsui, H. Takehira, T. Taniguchi, M. Koinuma, Y. Matsumoto, T. Akutagawa, T. Nakamura, S. Noro, T. Yamada, H. Kitagawwa and S. Hayami, *J. Am. Chem. Soc.*, 2013, **135**, 8097.
30 Y. Zhu, M. D. Stoller, W. Cai, A. Velamakanni, R. D. Piner, D. Chen and R. S. Ruoff, *ACS Nano*, 2010, **4**, 1227.
31 T. Szabo, E. Tombacz, E. Illes and I. Dekany, *Carbon*, 2006, **44**, 537.
32 M. Acik, G. Lee, C. Mattevi, A. Pirkle, R. M. Wallace, M. Chhowalla, K. Cho and Y. Chabal, *J. Phys. Chem. C*, 2011, **115**, 19761.
33 B. Konkena, S. Vasudevan, *J. Phys. Chem. Lett.*, 2012, **3**, 867.
34 S. Pei and H. M. Cheng, *Carbon*, 2012, **50**, 3210.


 