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Graphene Oxide and Its Functionalized Derivatives as Carbocatalysts in the Multicomponent Strecker Reaction of Ketones

Ananya Sengupta, Chenliang Su, Chenlu Bao, Chang Tai Nai, and Kian Ping Loh*^[a]

Functionalized graphene oxide derivatives are found to be efficient and reusable carbocatalysts for the one-pot multicomponent Strecker reaction of aldehydes and ketones under neat and open-air conditions.

The development of synthetic methods that afford high yields of the target products with a minimal environmental footprint is a major goal in organic synthesis.^[1,2] The use of carbocatalysts is attractive owing to their low cost and high natural abundance.^[3–5] Carbocatalysts have been applied in the oxidative aromatization and preparation of heteroaromatic compounds such as pyridine, imidazole, and pyrimidine.^[6] Recently, graphene oxide (GO) has attracted interest as a new carbocatalyst in organic transformations.^[7] The capability of GO to catalyze organic transformations is due to the presence of oxygen-containing functional groups on its aromatic scaffold, which can act as soft acids or mild oxidants. For example, GO mediates the oxidation of various hydrocarbons, olefins, and sulfides and catalyzes Michael-type Friedel–Crafts reactions,^[8] azo-Michael additions,^[9] the hydration of alkynes,^[10] and ring-opening polymerization.^[11] Its amphiphilic character allows it to act as a phase-transfer reagent.^[12] Sulfonated graphene (S-graphene) has shown promise for the hydrolysis of esters.^[13]

One of the most important multicomponent reactions is the Strecker reaction to synthesize α -amino acids through the formation of α -amino nitriles. It is the key step in the preparation of various natural products such as saframycin A^[14,15] and ecteinascidin 743.^[16] Conventional homogeneous and heterogeneous catalysis is generally performed with the use of harsh Brønsted acids^[17,18] and toxic metal complexes.^[19,20]

The efficient, clean, three-component Strecker reaction of ketones is challenging. A few heterogeneous catalysts have been previously reported for the Strecker reaction of ketones. These included zeolite Al-MCM-41,^[21] solid-supported gallium triflate,^[22] tin-ion-exchanged montmorillonite,^[23] supported Co^{II}-SBA-15,^[24] and organometallic hollow spheres bearing bis(N-heterocyclic carbene)-palladium.^[19] These reactions typically require the use of toxic metals, long reaction times, and microwave irradiation. Herein, we evaluate various functional-

ized GOs in the Strecker reaction to correlate the efficiency of the catalysts to the acidity of the differently treated GOs. We show that S-graphene and GO, operating under solvent-free and near-room-temperature conditions, provide much better yields than conventional solid catalysts.

A wide range of functionalities can be introduced onto GO through covalent reactions. For example, sulfonate groups can be introduced to increase the acidity of GO. Herein, we abbreviate this as S-graphene (Figure 1). GO^[25] and S-graphene^[13] were synthesized by using reported procedures, and in the latter case, the sulfonate groups were covalently tethered onto reduced GO. The functionalities in the various GO derivatives were determined by FTIR spectroscopy (Figure 1b), X-ray photoelectron spectroscopy (XPS), and thermogravimetric analysis (TGA) (see the Supporting Information).

The amount of Brønsted acid groups in GO and S-graphene was confirmed by acid–base titration.^[26] The titration results revealed that the GO sample contained 0.0073 mmol mg⁻¹ carboxylic acid groups, whereas the S-graphene sample contained 1.5 mmol g⁻¹ acid groups. This value is considerably higher than that of commercially available solid acid Nafion NR 50 (0.80 mmol g⁻¹).^[13] The pH values of dispersions containing the same weight of S-graphene and GO were 2.6 and 4.2, respectively, at approximately 0.5 mg mL⁻¹, which is consistent with the expected trend that sulfonate is the most acidic group.

The various GO derivatives were examined for their catalytic activities in the Strecker reaction. In a typical experiment, a mixture of the aldehyde or ketone, the amine, and trimethylsilyl cyanide under neat conditions was allowed to react in the presence of the catalyst (Figure 2). A good yield was obtained within 1 h if the reaction was performed under neat conditions at room temperature, whereas a small amount of diethyl acetal was found if ethanol was used as the solvent. Upon completion of the reaction, the catalyst was recovered by simple filtration. The good catalytic yield with aldehydes motivated us to validate our protocol with ketones. Acetophenone, aniline, and TMSCN were used as the reactants in a model reaction to produce α -amino nitrile. Interestingly, phenyl-2-phenylaminopropanenitrile was obtained in 94% yield by using 40 wt% GO at 50 °C, and the yield was improved to 97% by using 12 wt% S-graphene at room temperature; all reactions were performed under neat conditions. The control experiments, which were performed in the absence of a catalyst, yielded no product other than 2% imine after 1 h.

In Figure 2, the catalytic activities of different GO derivatives are compared with those of some typical solid acid catalysts. It is clear that GO and S-graphene show the highest catalytic

[a] Dr. A. Sengupta, Dr. C. Su, Dr. C. Bao, C. T. Nai, Prof. K. P. Loh
Department of Chemistry and Graphene Research Centre
National University of Singapore
3 Science Drive 3, Singapore (Singapore)
E-mail: chmlhkp@nus.edu.sg

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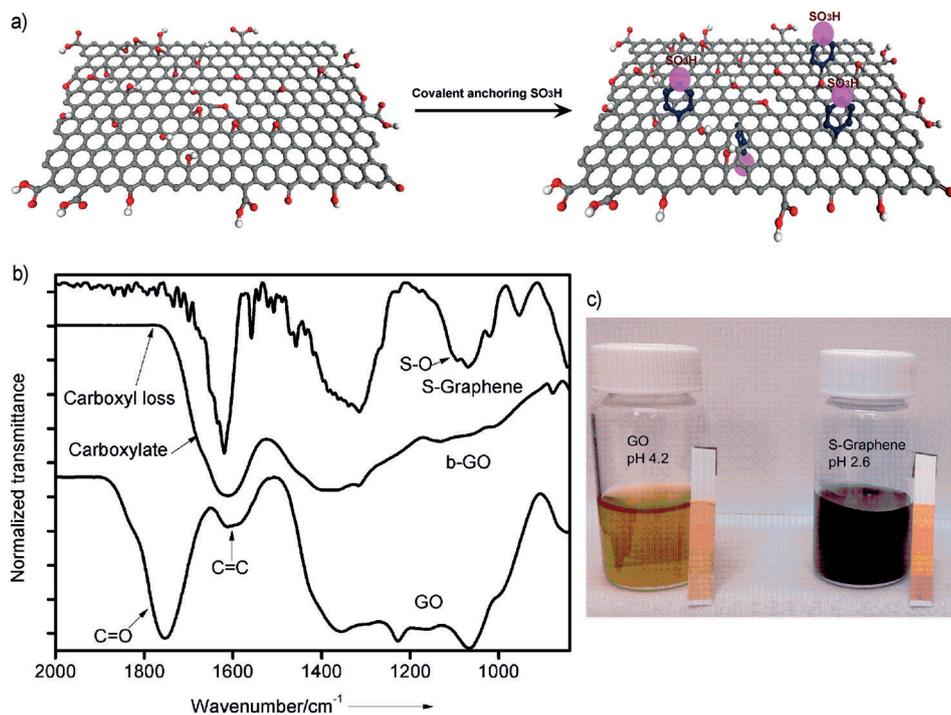


Figure 1. a) Schematic representation of GO and functionalized GO. b) Normalized transmission infrared spectra of GO, bGO, and S-graphene at room temperature. c) pH test of GO and S-graphene at approximately 0.5 mg mL⁻¹.

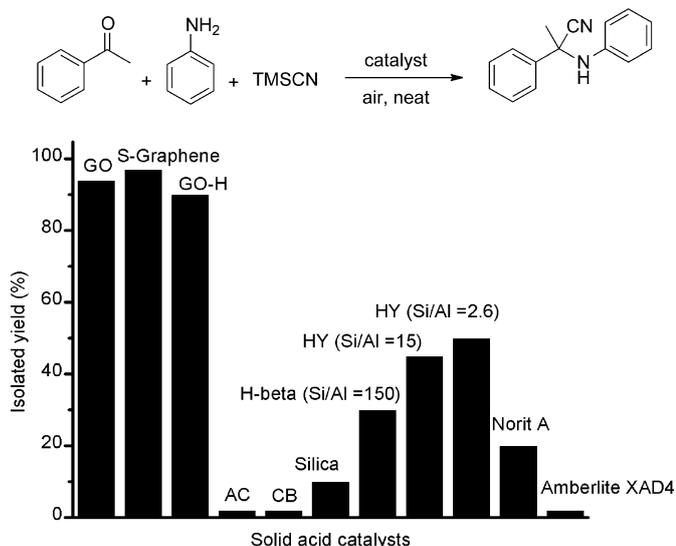


Figure 2. Screening of solid acids in the one-pot, three-component Strecker reaction. Reaction conditions: PhCOCH₃ (1 mmol), PhNH₂ (1 mmol), TMSCN (1.5 mmol), open to air, solvent-free conditions; catalyst 40 wt %, 50 °C, 1.5 h; catalyst 12 wt % for S-graphene at room temperature; GO-H = GO-Hummers method, AC = activated charcoal, and CB = carbon black.

yield for the Strecker reaction among all the catalysts tested. Commercially available carbon black and the ion-exchanger Amberlite did not show catalytic activity for the Strecker reaction. Industrially used porous H-beta and HY zeolites produced < 50% yield of the desired product. Good conversions

along with catalyst recyclability were observed for GO and S-graphene.

We tested the condensation of a wide range of structurally different aldehydes and ketones with various types of amines and TMSCN to produce the corresponding α -amino nitriles in a one-pot reaction with GO and S-graphene. The results are summarized in Table 1. In the case of aldehydes, different types of amines including aromatic and heterocyclic units were readily coupled. In general, this protocol is effective regardless of the electronic nature of the substituted carbonyl, and different types of amines participated in the reaction. For example, acid-sensitive furfuraldehyde (Table 1, entry 25 and 26) gave the product in 93 and 95% yield in the presence of GO and S-graphene, respectively. In the case of aliphatic ketones (Table 1, entry 7–

12), cyclohexanone reacted with aniline and benzylamine to give excellent product yields of 90–95%. In addition, differently substituted aromatic ketones delivered moderate to excellent yields of the products within a few hours. However, in the presence of the electron-withdrawing nitro group in the *para* position of acetophenone, the yield of the desired product decreased to 35–52% (Table 1). Overall, the reactions were fast and no side products were found. We were not able to detect any cyanosilylated^[27] or oxidized product of the carbonyl group.^[10]

To investigate the role of the active sites in catalysis, we intentionally transformed the carboxylic acid groups in GO into carboxylate groups by treating GO with base. GO was stirred with aqueous 0.1 N sodium hydroxide overnight at room temperature. The FTIR spectrum (Figure 1a) of base-washed GO (b-GO) showed that the band corresponding to the carboxylic group was reduced, whereas the band assignable to the carboxylate group (COO⁻) increased in intensity. In addition, the hydroxyl region ($\tilde{\nu}$ = 3000–3600 cm⁻¹)^[28] became weaker, possibly as a result of base reduction. After base neutralization of GO, it was found that the catalytic activity of GO in the Strecker reaction was completely suppressed. This confirmed that the acidic groups in the GO derivatives are essential for catalytic action.

To test the recyclability of the catalyst, the GO catalyst was recovered after filtration and washed (Figure 3). The recovered catalyst was reused in consecutive reactions. S-graphene was found to have the highest recyclability, and no change in catalytic activity was observed after multiple cycles. However, a slight deactivation of the GO catalyst was noticed after a few

Table 1. One-pot, three-component Strecker reaction of carbonyl compounds by using GO-derived carbocatalysts.^[a]

$$\text{R}^1\text{-CO-R}^2 + \text{R}^3\text{-NH}_2 + \text{TMSCN} \xrightarrow[\text{air, neat}]{\text{graphene catalyst}} \begin{matrix} \text{CN} \\ | \\ \text{R}^1\text{-C} \\ | \\ \text{R}^2\text{-N} \\ | \\ \text{H} \\ | \\ \text{R}^3 \end{matrix}$$

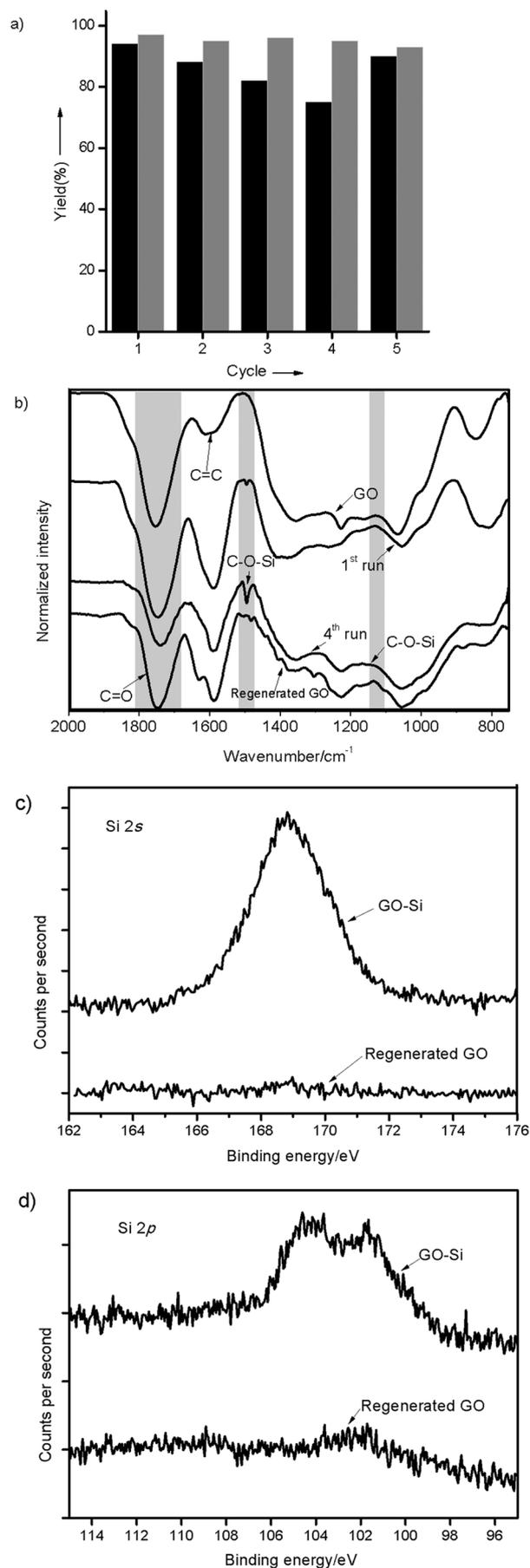
Entry	R ¹	R ²	R ³	Cat. ^[b]	t [h]	Yield [%] ^[c]
1 ^[d]	Ph	Me	Ph	A	2	94
2				B	1.5	97
3 ^[e]	4-ClC ₆ H ₄	Me	Ph	A	24	80
4 ^[f]				B	24	85
5 ^[e]	4-FC ₆ H ₄	Me	Ph	A	24	56
6 ^[f]				B	24	90
7	-(CH ₂) ₅ -		Ph	A	2	92
8				B	1	95
9	Me	Me	Ph	A	10	84
10				B	4	88
11	-(CH ₂) ₅ -		PhCH ₂	A	2	90
12				B	1	95
13	Ph	Me	4-ClC ₆ H ₄	A	12	88
14				B	12	93
15 ^[e]	4-NO ₂ C ₆ H ₄	Me	Ph	A	24	35
16 ^[f]				B	24	50
17	2-furyl	Me	Ph	A	24	78
18				B	24	84
19	-(CH ₂) ₅ -		1-phenylethyl	A	5	82
20				B	4	92
21	Ph	H	Ph	A	1	95
22				B	1	97
23	4-FC ₆ H ₄	H	Ph	A	24	82
24				B	24	92
25	2-furyl	H	Ph	A	6	93
26				B	6	95
27	Ph	H	4-ClC ₆ H ₄	A	2	90
28				B	2	92
29	Ph	H	PhCH ₂	A	5	88
30				B	5	92

[a] Reaction conditions: PhCOCH₃ (1 mmol), PhNH₂ (1 mmol), TMSCN (1.5 mmol), catalyst, neat conditions. [b] Cat. A: GO 40 wt%, Cat. B: S-graphene 12 wt%. [c] Yield of isolated product. [d] Determined by ¹H NMR spectroscopy. [e] 100 wt% GO. [f] 25 wt% S-graphene.

runs. This is due to the gradual silylation of the hydroxyl and carboxylic groups by the trimethylsilyl group. Evidence for silylation can be seen in the XPS and FTIR spectrum of the recovered catalyst, for which a band at $\tilde{\nu} = 1495 \text{ cm}^{-1}$ attributable to the presence of the OSiMe₃ group could be seen. To reactivate the catalyst after the fourth run, the GO catalyst was stirred for 24 h at room temperature with tetra-*n*-butylammonium fluoride (TBAF). XPS analysis confirmed that the amount of silicon (from the trimethylsilyl group) became negligible after washing with TBAF. To our delight, it was found that the catalytic activity of TBAF-washed GO was recovered to the same level as that of pristine GO in the first cycle.

The mechanism of the Strecker reaction involves attack of the amino group of **2** at the carbonyl group of **1** by nucleo-

Figure 3. a) Recyclability of GO (black) and S-graphene (gray) in the Strecker reaction. b) FTIR spectrum of GO after the first and fourth runs of GO and regenerated GO (after washing with TBAF). c) XPS of the Si2s spectra of GO-Si after reaction and regenerated GO after washing with TBAF. d) XPS of the Si2p spectra of GO-Si and regenerated GO.



philic addition to form an amino alcohol.^[18] In the presence of an acid catalyst, the amino alcohol undergoes dehydration to produce an imine or an iminium intermediate, and this is followed by nucleophilic attack of cyanide from TMS-CN to form an α -amino nitrile. To elucidate the mechanistic pathway, we first studied the model reaction by only adding GO without the use of TMS-CN. After quenching the reaction with H₂O, we identified an imine intermediate (by ¹H NMR spectroscopy: δ = 2.20 ppm; see Figure S5 in the Supporting Information). However, no amino alcohol was isolated from the reaction mixture. This could be due to the very fast dehydration step of the amino alcohol in the presence of a high concentration of the free hydroxyl and carboxylic acid groups in GO. Subsequently, upon adding TMS-CN to the reaction mixture, the cyanide nucleophile attacks the activated iminium intermediate (nucleophilic addition) in a concerted manner to produce the α -amino nitrile (Figure 4). GO (as well as its derivatives) plays the role of the acid catalyst and helps with the protonation of the carbonyl group to favor nucleophilic addition by the amine, as well as the subsequent dehydration of the amino alcohol to facilitate the formation of the imine.

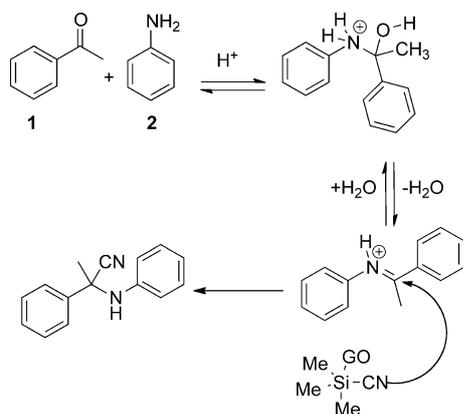


Figure 4. Proposed mechanism for the GO-catalyzed three-component Strecker reaction.

In summary, we demonstrated that functionalized GO derivatives were able to catalyze the one-pot Strecker reaction of carbonyls, amines, and trimethylsilyl cyanide efficiently to produce α -amino nitriles. The catalytic activities are due to acidic groups in the GO derivatives. The catalyst showed good recyclability under solvent-free conditions in open air without the formation of side products.

Experimental Section

Preparation of S-graphene

A suspension of GO (1 mg mL⁻¹) was reduced with hydrazine hydrate at 100 °C for 24 h followed by washing several times with deionized water to afford reduced graphene oxide. 4-Benzenediazonium sulfonate was prepared by diazotization of sulfanilic acid. Sulfanilic acid (0.01 mol) was dispersed in 1 M HCl (100 mL). The temperature was 2–3 °C. Then, a 10% excess amount of 1 M NaNO₂ was

added dropwise. The white precipitate was filtered off after 1 h and was washed with a small amount of deionized water. Then, the diazonium salt (see Figure S4) was added to reduced graphene (60 mg) in a water/ethanol mixture (1:1, 40 mL). Subsequently, H₃PO₂ (50 wt%, 20 mL) was added, and the temperature was 0–2 °C. After 30 min, again more H₃PO₂ (50 wt%, 20 mL) was added, and the mixture was stirred for another 2 h. It was then washed and dried.

Preparation of base-washed graphene oxide (b-GO)

GO (100 mg) was dispersed in deionized water (1 mg mL⁻¹, 100 mL) by sonication. 0.3 N NaOH (50 mL) was added to the GO solution. The mixture was stirred overnight. Subsequently, base-treated GO was filtered and washed with deionized water and acetone.

Three-component Strecker reaction

Representative procedure: Functionalized graphene catalyst (12 wt% S-graphene or 40 wt% GO) was added to a mixture of the carbonyl compound (0.25 mmol), amine (0.25 mmol), and TMS-CN (0.375 mmol), and the resulting mixture was stirred at room temperature (S-graphene) or at 50 °C (GO) in open air for the required time under solvent-free conditions. The catalyst was recovered by filtration and washed with dichloromethane. The solvent was removed under reduced pressure to obtain the α -amino nitrile.

Regeneration of the catalyst by using TBAF

Tetra-*n*-butylammonium fluoride (250 mg) was added to a solution of recovered GO (100 mg) in water (5 mL), and the mixture was stirred for 24 h at room temperature. After washing with water, the GO was stirred in 3 N HCl for 2 h. The final regenerated GO was washed with water and acetone.

Keywords: carbocatalyst · graphene · heterogeneous catalysis · multicomponent reactions · solid acid

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