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Regio- and Enantioselective Friedel–Crafts Reactions of Indoles to Epoxides Catalyzed by Graphene Oxide: A Green Approach

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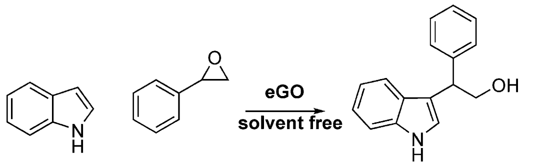
Graphene oxide efficiently promotes high regio- and enantioselective ring opening reactions of aromatic epoxides by indoles addition, in solvent- and metal-free conditions. The Friedel–Crafts products were obtained with enantioselectivity up to 99% *ee*. The complete inversion of stereochemistry indicates the occurrence of S_N2-type reaction, which assures high level of enantioselectivity.

Meeting the need for sustainable catalytic processes is an important task of modern synthetic chemistry, and has stimulated the development of new heterogeneous catalysts because they offer ease of handling, simple work-up, and, most importantly, reusability. Combining these benefits with the opportunity to avoid dangerous and expensive organic solvents, mainly by working in solvent-free conditions, realizes the possibility of green and economical procedures and the redesign of current organic chemistry processes by using environmentally benign alternatives.

Recently, carbon materials have emerged as cheap and metal-free catalysts and have attracted much attention,[1–3] mainly regarding the use of graphite oxide (GO) and exfoliated graphite oxide (eGO) in oxidation reactions,[4–7] Friedel–Crafts reactions,[8] aza-Michael additions,[9] Mukaiyama–Michael additions,[10] polymerizations,[11] and epoxide ring-opening reactions.[12] In particular, GO is an efficient catalyst for the Friedel–Crafts addition of indoles to α,β-unsaturated ketones,[8] giving 3-alkylindoles which are useful precursor structures for the synthesis of different drugs. Epoxides, however, are well-known carbon electrophiles and are susceptible, under appropriate conditions, to ring-opening reactions. Generally, high-pressure conditions[13] and SiO_2,[14] lanthanide triflate,[15] and some other Lewis acids[16,17] have been reported as mild catalysts to facilitate this reaction, while there are limited reports on ecofriendly conditions and heterogeneous catalysts. Only recently was an efficient procedure for room-temperature ring-opening of epoxides with methanol using GO reported, but a very large amount of nucleophile is required to obtain the product with high conversion.[12]

Although ring-opening of epoxides with nitrogen-, oxygen-, and sulfur-based nucleophiles has been extensively studied, the subject of regio- and stereoselective reactions with carbon nucleophiles to give new C–C bonds has been relatively unexplored.[18–21] Carbon-alkylated indoles are important synthetic intermediates owing to the presence of the indole core unit, which is characteristic of various natural products and biologically active molecules.[22,23] Much attention has been devoted to the study of regio- and stereoselective pathways, but very few procedures with ecofriendly conditions have been reported. Only in the last years, Friedel–Crafts alkylation of indole with epoxide was reported to occur in presence of nanocrystalline titanium(IV) oxide[24] and, more recently, catalyzed by magnetic Fe_3O_4 and $CuFe_2O_4$ nanomaterials.[25]

In this Communication, we report the first highly regio- and enantioselective ring-opening of aromatic epoxides by addition of indoles in the presence of catalytic amounts of eGO in solvent- and metal-free conditions (Scheme 1). To the best of our knowledge, ring-opening reactions of epoxides with indoles catalyzed by graphene oxide have not been reported before.



Scheme 1. Regioselective ring opening reaction of styrene oxide.

The sample of GO used in this study was obtained by Hummers oxidation[26] of graphite followed by ball-milling exfoliation. Figure 1 A shows an X-ray diffraction (XRD) patterns of the high-surface-area graphite before oxidation. The XRD patterns of the oxidized samples, graphite oxide (GO) and exfoliated graphite oxide (eGO) (Figure 1 B and C, respectively), show that the 100 and 110 reflections are maintained while the periodicity perpendicular to the graphite layers (002 and 004 reflections) disappears. These reflections are mainly replaced by a broad reflection with spacing $d = 0.84$ nm and correlation length $D \approx 4.5$ nm (Figure 1 B), corresponding to the 001 reflection of a disordered GO.[27–30] The same reflections, for the milled graphite oxide sample of Figure 1 C, are mainly replaced by a very broad intense halo, centered at $d = 0.37$ nm with a correlation length of about 1 nm, indicating the presence of a large fraction of essentially exfoliated GO.[31] The

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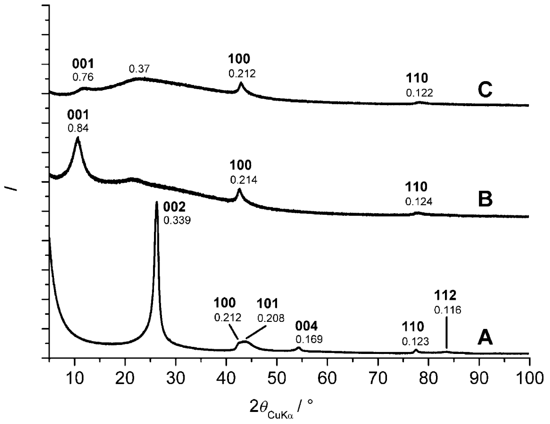
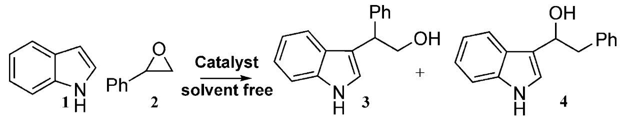


Figure 1. X-ray diffraction patterns (Cu Kα) of (A) the high-surface-area graphite, (B) the derived GO, and (C) eGO, obtained by ball-milling of GO. B) GO sample exhibiting a 001 reflection ($d_{001}=0.84$ nm) with half-height width larger than for the 100 reflection ($\beta_{001}=2^\circ$ and $\beta_{100}=0.5^\circ$), and hence higher correlation length parallel ($D_{100}=30$ nm) than perpendicular to the graphitic layers ($D_{001}=4.5$ nm). C) Exfoliated graphite oxide (eGO) maintaining essentially only the order parallel to the graphitic layers ($D_{100}=30$ nm).

weak reflection with $d=0.76$ nm and $D\approx2.5$ nm can be interpreted as 001 reflection of nonexfoliated GO, present in an amount lower than 10 wt%. Our GO and eGO samples present similar C/O ratios (nearly 1.7, according to elemental analysis) and largely different surface areas (according to Brunauer–Emmett–Teller (BET) measurements): 0.8 and 4.6 m^2g^{-1}, respectively. These surface area values agree well with those reported in the literature for GO samples,[32,33] while they are definitely lower than the value of the graphite starting material (308 m^2g^{-1}).

The activities of GO and eGO as acid catalysts were tested for the ring-opening reaction of styrene epoxide with indole, chosen as representative substrate, in solvent-free conditions. (Scheme 2). The possibility to perform the reaction with graphite oxide was explored by changing the catalyst loading and the temperature conditions. As reported in Table 1, the best results for yield and regioselectivity were obtained when using only 3 wt% of graphite oxide at room temperature in solvent-free conditions (entry 3). An attempt to reduce the reaction time by increasing the temperature failed as it led to a decreased control over regioselectivity (entry 2).



Scheme 2. Catalyst screening for the regioselective ring-opening reaction of styrene oxide with indole.

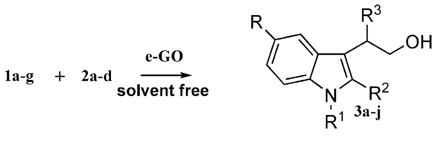
Notably, even in Friedel–Crafts reaction conditions, aromatic epoxides could rearrange to isomeric carbonyls as only the addition adducts **3** and **4** were observed and no side products were detected. In heterogeneous catalysis, the use of catalysts with smaller-size particles and higher surface areas can improve the catalytic performance, so we tested graphene oxide (eGO) to verify such improvements. The reaction was performed in the same conditions with 3 wt% of eGO and the product was obtained with the same efficiency and regioselectivity but in shorter time. (Table 1, entry 4 vs entry 3). The reaction was also explored in water, but a strong decrease of the yield was observed (entry 5).

Table 1. Ring-opening reaction of styrene oxide with indole.

Entry	Catalyst (%wt)	Amount [wt%]	*t* [h]	*T* [°C]	Yield **3**[a] [%]	Regioselectivity[b] (**3**/**4**)
1	GO	10	48	RT	20	96:4
2	GO	3	72	100	55	70:30
3	GO	3	120	RT	80	98:2
4	eGO	3	96	RT	80	98:2
5	eGO in H_2O	3	96	RT	30	67:33
6	HSAG[c]	3	96	RT	25	97:3
7	carbon black	3	96	RT	–	–

[a] All the yields refer to the pure isolated product. [b] The regioselectivity was determined by ^{1}H NMR analysis (400 MHz) on the crude products. [c] High-surface-area graphite.

We also investigated the possible catalytic activity of high-surface-area graphite as well as carbon black (with C/O ratios nearly equal to 30) towards the reaction. Both catalysts are active diastereoselective catalysts for Mukaiyama–Michael additions,[10] possibly because of π-stacking of the aromatic substrate with graphite. The notably reduced and negligible yields observed for the high-surface-graphite of Figure 1 A (Table 1, entry 6) and carbon black (entry 7), respectively, suggest that the catalytic activity of GO samples is due to their carboxylic and hydroxyl groups. To assess the scope of the reaction, a range of indoles variously substituted was reacted with styrene oxide under the conditions previously reported (Scheme 3).

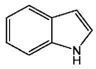
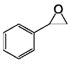
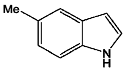
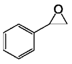
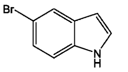
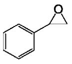
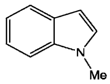
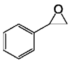
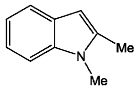
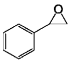
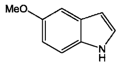
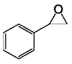
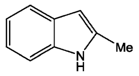
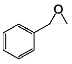
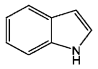
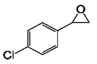
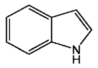
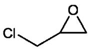
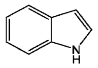
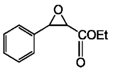


Scheme 3. General scope of the reaction.

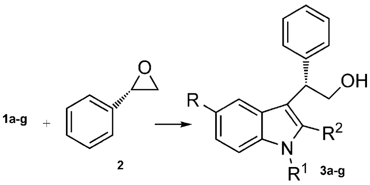
Table 2 shows that the corresponding alcohols can be obtained in moderate to good yields from the tested indoles with aromatic epoxy electrophiles. The decreased yield observed for substituted indoles is not strictly dependent on the electron-donating or -withdrawing nature of the substituents, while according to the expected trend, ethyl 3-phenylglycidate (mixture of *trans* and *cis*) afforded the product **3 j** in 35% yield. Furthermore, the reaction of indole with epicholoroidrine did not proceed at all because of the (commonly observed) lower reactivity of aliphatic epoxides compared to aryl epoxides.

The reusability of eGO was investigated by using the addition of indole **1 a** to styrene oxide **2 a** as model reaction. The solid eGO, recovered after extraction from the aqueous solution and dried at 60 °C overnight, was used without any further

Table 2. General scope of the ring-opening reaction of styrene oxide with indoles variously substituted.

Entry	1		2		*t* [days]	Product	Yield[a] [%]
1		**1a**		**2a**	4	**3a**	80
2		**1b**		**2a**	4	**3b**	78
3		**1c**		**2a**	5	**3c**	61
4		**1d**		**2a**	4	**3d**	54
5		**1e**		**2a**	4	**3e**	69
6		**1f**		**2a**	4	**3f**	25
7		**1g**		**2a**	4	**3g**	68
8		**1a**		**2b**	4	**3h**	75
9		**1a**		**2c**	5	**3i**	–
10		**1a**		**2d**	5	**3j**	35

[a] All the yields refer to pure, isolated product.



Scheme 4. Regio- and enantioselective ring opening reaction.

treatment. The reaction conditions (RT and 96 h) were kept the same in all cycles. As shown in Table 3, both the yield of the reaction (a reduction from 80 to 75 %) as well as the regioselectivity remained almost unchanged after five recycling steps (Scheme 4).

Table 3. Recycling test of eGO catalyst.

Run[a]	Yield **3**[a] [%]	Regioselectivity (**3**/**4**)[b]
1	80	98:2
2	78	98:2
3	75	97:3
4	79	96:4
5	76	97:3

[a] Conditions as mentioned in the text. [b] All the yields refer to pure, isolated product. [c] The regioselectivity was determined by ^{1}H NMR analysis (400 MHz) on the crude products.

The procedure described is simple, metal-, and solvent-free and represents the first carbocatalyzed ring-opening reaction with indole compounds. Moreover, the catalyst loading is only 3 wt % with respect to the styrene epoxide, and the catalyst can be recycled and reused without losing efficiency or regioselectivity. Indole is a key motif in many pharmacologically[34] and biologically active compounds[35] as well as in many natural products, and a direct synthesis of optically active indolyl derivatives is desired. Because enantioenriched epoxides are readily available, an enantioselective version of our approach could be realized and become a new and very attractive as tool in the synthesis of optically active aromatic compounds.

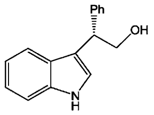
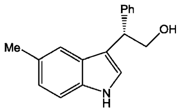
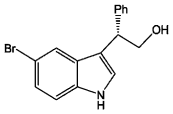
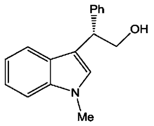
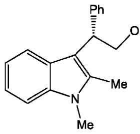
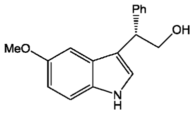
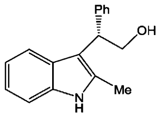
In Friedel–Crafts reaction conditions, aromatic optically active epoxides can not only rearrange to isomeric carbonyl compounds but also racemize. Herein, we report the first example of enantioselective Friedel–Crafts reaction catalyzed by graphene oxide in solvent-free conditions, proceeding in good yield and high enantioselectivity without side products and with high regioselectivity.

The absolute configuration of the products obtained by the attack of indole to (*S*)-styrene oxide were assigned by comparison by chiral HPLC analysis, previously reported in literature for compounds **3a–g**.[36] The generality of the procedure with a chiral epoxide in the presence of graphene oxide is summarized by the data reported in Table 4. The reaction proceeded efficiently with various substituted indoles with high enantioselectivities. In agreement with the nucleophilicity scale reported by Mayr,[36] the competitive racemization gave a slight reduction of enantioselectivity only for indole, 5-Br-indole, and *N*-Me-indole (entries 1, 3, and 4).

In fact, the presence of different acidic functionalities on the carbocatalyst surface activates the epoxide ring-opening and forms an incipient carbocation ready to react with the nucleophilic carbon of the indole before the occurrence of fast racemization usually associated to carbocation intermediates. So, as reported in literature,[16,36] partial racemization, coming from a competitive S_N1 pathway, possibly occurs in presence of a reduced nucleophilicity. In every case the high stereoselectivities observed, with complete inversion of stereochemistry, indicate the occurrence of S_N2-type reaction even if the nucleophilic attack takes place regioselectively at the benzylic position, usually favored in S_N1- type processes

In conclusion, we show that graphene oxide is an effective catalyst for epoxide ring-opening reactions by indole addition, giving synthetic intermediates that are important for many pharmacologically and biologically active compounds. The eGO catalyst can operate in solvent-free conditions at a loading of 3 wt % with high regioselectivity and, for the first time, high stereoselectivity, ensuring that products are obtained in high enantioselectivity. Being a heterogeneous catalyst, the catalyst can be recycled and reused without loss of efficiency or regioselectivity. The metal- and solvent-free procedure is effective and more economically and environmentally convenient than catalysts presently described in the literature.

Table 4. Enantioselective ring opening reactions of (*S*)-styrene oxide with indoles variously substituted.

Entry	Indole	*t* [days]	Product		Yield [%][a]	*ee*[b] [%]
1	**1 a**	4		**3 a**	80	91
2	**1 b**	4		**3 b**	78	98.5
3	**1 c**	5		**3 c**	61	87
4	**1 d**	4		**3 d**	54	94
5	**1 e**	4		**3 e**	69	97
6	**1 f**	4		**3 f**	25	99
7	**1 g**	4		**3 g**	68	99

[a] All the yields refer to pure, isolated product.[b] Enantiomeric excess was evaluated by HPLC analysis with chiral column. The absolute configurations match those reported in literature.

Experimental Section

Materials

High surface area graphite, with Synthetic Graphite 8427 as trademark, was purchased from Asbury Graphite Mills Inc., with a minimum carbon wt% of 99.8. Nitrostyrene, trimethylsiloxyfuran, sulfuric acid, sodium nitrate, potassium permanganate were purchased from Sigma–Aldrich and used without any further purification. TLC was performed on silica gel 60 F254 0.25 mm on glass plates Merck and non-flash chromatography was performed on silica gel (0.063–0.200 mm) (Merck). All ^{1}H NMR and ^{13}C NMR spectra were recorded with a DRX 400 MHz instrument, by using $CDCl_3$ (δ = 7.26 ppm in ^{1}H NMR spectra and δ = 77.0 ppm in ^{13}C NMR spectra) as solvent (400.135 MHz for ^{1}H and 100.03 MHz for ^{13}C).

For the products **3 a–g** the ^{1}H NMR and ^{13}C NMR match with those reported in literature.[36]

Synthetic procedures

Preparation of graphite oxide: Graphite oxide samples were prepared by Hummers' method (see Supporting Information), from graphite samples. 120 mL of sulfuric acid and 2.5 g of sodium nitrate were introduced into a 2000 mL three-neck round bottomed flask immersed into an ice bath and 5 g of graphite were added, under nitrogen, with a magnetic stirring. After obtaining an uniform dispersion of graphite powders, 15 g of potassium permanganate were added very slowly to minimize the risk of explosion. The reaction mixture was thus heated to 35 °C and stirred for 24 h. The resulting dark green slurry was firstly poured into a copious amount of deionized water, and then centrifuged at 10 000 rpm for 15 min with a Hermle Z 323 K centrifuge. The isolated GO powder was washed twice with 100 mL of a 5 wt% HCl aqueous solution and subsequently with deionized water. Finally, it was dried at 60 °C for 12 h.

Exfoliation of graphite oxide by ball-milling: Graphite oxide powders were introduced in 125 mL ceramic jars (inner diameter of 75 mm) together with stainless steel balls (10 mm in diameter) and were dry-milled in a planetary ball mill (Retsch GmbH 5657 Haan) for 2 h with a milling speed of 500 rpm and a ball-to-powder mass ratio of 10 to 1.

General procedure for Friedel–Crafts addition of indole to epoxide: The reaction was carried out in a vial. Styrene oxide (120.2 mg, 1.0 mmol) and indole (140.6 mg, 1.2 mmol) were added to the GO catalyst (3 wt%) at room temperature. The reaction mixture was stirred at the same temperature for the time indicated The reaction mixture was extracted with AcOEt and the combined organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel in gradient elution with Petroleum Ether/AcOEt to obtain the pure product.

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Keywords: carbocatalysis · enantioselectivity · epoxides · graphene oxide · indoles

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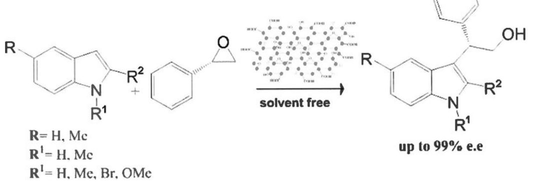
Regio- and Enantioselective Friedel–Crafts Reactions of Indoles to Epoxides Catalyzed by Graphene Oxide: A Green Approach



Do not pass GO: Graphene oxide efficiently promotes highly regio- and enantioselective ring opening reactions of aromatic epoxides by addition of indoles, in solvent- and metal-free conditions. The Friedel–Crafts products were obtained with enantioselectivity up to 99 % *ee*. The complete inversion of stereochemistry indicates the occurrence of S_N2-type reactions, which assures high level of enantioselectivity.