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Graphene oxide as catalyst for the diastereoselective transfer hydrogenation in the synthesis of prostaglandin derivatives

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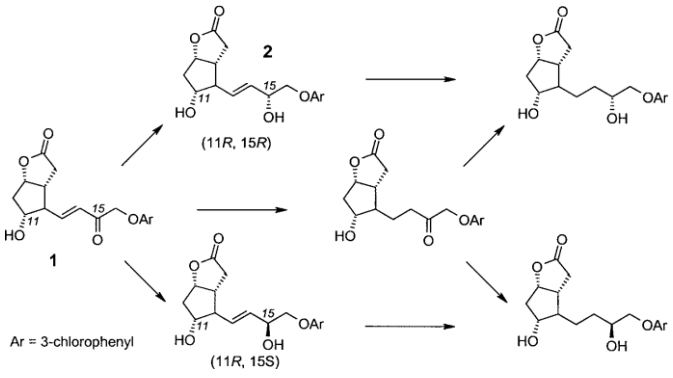
Modification of GO by organic molecules changes its catalytic activity in the hydrogen transfer from *i*-propanol to enones, affecting the selectivity to allyl alcohol and diastereoselectivity to the resulting stereoisomers. Noteworthy, the system does not contain metals and is recyclable.

The unprecedented development of pharmaceutical industries, currently based mostly on multi-step organic syntheses, came with the unwanted price of the huge amounts of harmful wastes produced with high environmental impact due to their biological activity. This situation entailed the need to apply green chemistry principles and, particularly, heterogeneous catalysis as alternative to stoichiometric reactions. Thus, many of the modern synthesis of the today pharmaceutical industry are based on catalytic reactions, but unfortunately many of them use precious metals as active components.[1] As a consequence, due to their limited abundance and low reserves, the use of noble or critical metals can become a bottleneck for the pharmaceutical industry, there being an interest in finding alternative sustainable catalysts.

Particularly, the high interest in the production of synthetic prostaglandins, with a wide range of medicinal applications, made us to develop not long ago noble metals (e.g., Ru, Ir, Pt) based catalysts for their synthesis. The hydrogenation of the lactonic enone intermediate used in the synthesis of the commercial drug Cloprostenol, a more stable structural analogue and with a more specific effect than natural $PGF_{2\alpha}$'s can be promoted efficiently and in a highly stereoselective manner in the presence of these metallic catalysts.[2]

In the context of the need of the identification and development of sustainable alternatives to precious or critical metal catalysts, application of carbon materials as metal-free catalysts is becoming increasingly attractive for a large variety of organic reactions[3, 4] such as hydration[5], Michael-type Friedel-Crafts[6] aza-Michael addition[7], polymerization[8], oxidation[5] and gas phase C-C multiple bond hydrogenations.[9]

With the aim to extend the applicability of such versatile materials also in the area of metal-free pharmaceutical syntheses, herein we report on the performance of graphene oxide (GO, 48.6 wt.% oxygen and 1.8 S content) in hydrogen transfer reduction of lactonic enone **1** ([3a*α*,4*α*(E),5*β*,6a*α*]-(±)-4-[4-(3-chlorophenoxy)-3-oxo-1-butenyl]-hexahydro-5-hydroxy-2H-cyclopenta[b]furan-2-one) (Scheme 1) used in the synthesis of the commercial drug Cloprostenol. The use of metal-free catalysts others than GO for hydrogen transfer reduction of carbonyl compounds by isopropanol has been reported in the literature.[10-12]



Scheme 1. The possible products of the prostaglandin intermediate **1** reduction

Among the two possible diastereomers shown in Scheme 1, only the 15*R* form of the allylic alcohol (compound **2**) exhibits biological activity and has practical importance (note that the atom numbers 11 and 15 are in agreement with the structure of $PGF_{2\alpha}$). Therefore, from practical considerations the synthesis should be chemoselective to the allylic alcohol and

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diastereoselective to its 15R form. However, as indicated in Scheme 1, other products besides the wanted 15*R* diasteromer can also be formed during the hydrogenation reaction.

Table 1 lists some results in the transfer hydrogenation of enone **1** using *i*-PrOH as transferring agent and GO as catalyst. Blank controls under the same conditions in the absence of catalyst did not allow to detect any enone **1** conversion.

In contrast to the blank experiment, Table 1 shows that for an enone/catalyst ratio of ca 1/1 wt. after 36 h (entry 4) more than 90% of the enone intermediate is converted. Even more important, for this high conversion, the selectivity to allylic alcohol (**2**) reached 50.4 %. Increasing the enone/catalyst ratio to 2/1 wt. the conversion decreased from 39.6 to 21.7% (Table 1, entries 1 and 5), while the selectivity to allylic alcohol **2** increased from 17.5 to 27.5%. Lower temperature (i.e., room temperature) improved the selectivity to 31.5% in detriment to the enone conversion (9.1%, entry 6). Lower reaction temperature had also a beneficial effect increasing d.e. selectivity value.

Table 1. Catalytic performance of GO as hydrogen transfer catalyst in the transfer hydrogenation of enone **1**[a]

Entry	Reaction time, h	Conv. %	$S_{allylic\ alhohol\ 2}$, %	D.e., % / conf.
1	6	39.6	17.5	13.4/(11R, 15R)
2	12	51.0	29.3	Racemic
3	24	62.1	48.0	Racemic
4	36	94.2	50.4	Racemic
5[b]	6	21.7	27.5	Racemic
6[c]	24	9.1	31.5	77.8/(11R, 15S)

[a] Reaction conditions: 30 mg GO, 28 mg enone, 5 mL *i*-PrOH, 80 °C; [b] 7 mg GO, 14 mg enone, 2.5 mL *i*-propanol 80°C; [c] 7 mg GO, 14 mg enone, 2.5 mL i-PrOH, r. t..

The chemoselectivity to product **2** increases in time (Table 1, entries 1-4), a fact that might be related to alternation of the proportion of active sites in GO during the course of the reaction due to the reductive conditions during the hydrogenation reaction. This phenomenon, also known as "*reaction-induced selectivity improvement*", has previously been described in literature[13] and also observed and reported by some of us[14] in the Meerwein-Ponndorf-Verley reaction using PtSnx alloys as catalysts. A lower reaction temperature has also as effect an increased diastereoselectivity from racemic to 77.8 % (epi-like diastereomer).

There exist on the surface of GO‡ different functional groups, including epoxide, hydroxyl and ether groups on the basal plane and carboxylic acids, quinones, at the edges or defect sites, all these groups summing 42.1 wt% of oxygen.[9] Besides these, aromatic C-H at the edges or defect sites and small aromatic domains (2-3 nm) isolated within the sp^3 C-O matrix (Figure 1)[15] are also present. While carboxylic and hydroxylic groups display acidic properties, ethers and carbonyls are neutral or may form basic structures the nature of which is still open to debate, such as quinone groups.[16] In addition, the π-electron system of the basal planes contributes to the carbon basicity.[17] The GO surface picture is completed by taking also into consideration the possible existence of metal impurities in trace amounts levels, particularly of Mn (150±23 ppm) and Fe (8±2 ppm), as determined by quantitative chemical analysis.[9]

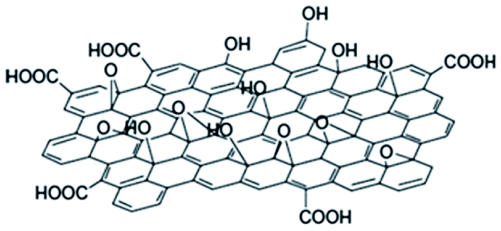
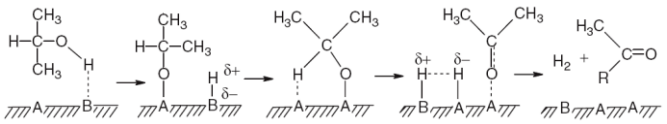


Figure 1. Functional groups on the surface of GO[12]

The conversion of alcohols on carbon catalysts has been studied most extensively.[18] Clearly, *i*-propanol suffers simultaneous dehydration and dehydrogenation processes, due to the presence of carboxylic groups and Lewis acid-base pairs on the GO surface, the catalytic activity being controlled by the number and strength of the functional groups. On the basis of this known activity of Lewis acid–base pairs acting as metal-free hydrogenation/dehydrogenation catalysts, a reasonable proposal to rationalize the catalytic activity of the GO as hydrogen transfer catalysts would be the existence on the GO layer of similar type of frustrated Lewis acid–base pairs located on the sheet at an adequate distance to promote the *i*-propanol dehydrogenation with the simultaneous formation of H^+-like and H^--like sites (Scheme 2). NH_3-TPD measurements of GO catalyst confirmed the presence of the strong acid sites (Figure SI1). Based on prior studies showing the catalytic activity of hydrogensulfate and sulfonic groups introduced in the GO sheet due to the use of strong sulfuric acid in the formation of graphite oxide from graphite,[19-20] it is proposed also that these S containing groups are the ones contributing to the observed catalytic activity.



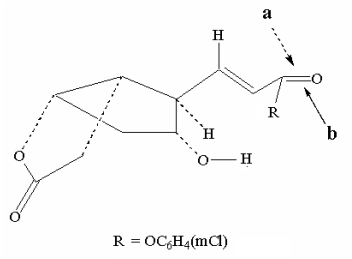
Scheme 2. Proposed dehydrogenation mechanism of secondary alcohols due to the presence of frustrated Lewis acid-base pairs.

Accordingly, it seems that the reaction mechanism should involve the uptake of H_2 from *i*-propanol on the GO sheet, probably as hydride and proton that subsequently would transfer to the enone **1**. Evidences for the existence of such sites are detailed in ref.[9]

The stereospecificity of the reduction of the carbonyl group would require a preferential direction of attack of the nucleophilic hydrogen (axis a or b) present on the catalyst surface and the existence of a single conformation in the

enone (Scheme 3)[2] Corey et al.[21] demonstrated that in order to observe a preferential direction of the attack of hydride to the carbonyl group, leadig to the formation of (11R, 15R)–natural type configuration a large steric hindrance to avoid the hydrogen attack on "b" direction is not sufficient and that a preferential *cis* enone conformation is also necessary.

To gain some information about the possible role of acid and bases, a series of control experiments were carried out. By adding acetic acid or pivalic acid (trimethylacetic acid) into the liquid phase the enone conversion was highly improved while the selectivity to **2** highly decreased. However, while acetic acid lead to a racemic mixture of the two stereoisomers, the steric hindrance generated by the pivalic acid-enone interaction controls the stereoselectivity in the favor of the natural-like configuration (d.e. = 100 %, Table 2, entries 3 and 4). However, the increase of the reaction time from 6 to 24 h led to a depletion of the selectivity to allylic alcohol from 29% to only 3.5%, due to the subsequent hydrogenation of the C=C double bond.



Scheme 3. Possible directions "a" or "b" of the hydrogen attack to prostaglandin precursor.

Contrarily, the butylamine-enone interactions do not influence significantly the interaction of substrate **1** with the GO surface, the catalytic efficiency being more or less similar with that in the absence of butylamine (Table 2, entries 1 and 5). However, replacing butylamine by pyridine produced remarkable results both in terms of activity and selectivity to allylic alcohols and also in terms of diastereoselectivity (Table 2, entry 9). Accordingly, the chemoselectivity to allylic alcohol **2** increased to 79.2% for an enone conversion of 89 %, while the d.e. to natural-like configuration (*ie*, (11R, 15R)) was 91.1%. Then, replacing GO catalyst by *p*-toluenesulfonic acid (TsOH), a typical Brønsted acid, afforded an increase of both enone conversion and selectivity to allylic alcohol from 9.1 % (Table 2, entry 10) to 96.1 % and from 31.5 % (Table 1, entry 1) to 93.6% (7 mg p-toluenesulfonic acid, 14 mg enone, 2.5 mL *i*-propanol, room temperature, 24 h). However the d.e. with p-toluensulfonic acid was of only 73.6%.

Since TsOH is insoluble in *i*-propanol, the enhancement of the catalytic performance is exclusively due to the presence of Brønsted acid sites onto the catalytic system. The addition of pyridine to *p*-toluenesulfonic acid led to a decrease of the selectivity to allylic alcohol **2** to 58.8% for a conversion of enone of 96.1% (Table 2, entry 10) while the d.e. increased to 90.0% in the favors of *epi*-like configuration (*ie*, (11R, 15S)). Noteworthy, the presence of pyridine in the TsOH based system provokes its solubilization, and the catalytic system becomes in this case homogeneous.

An explanation of the activity data could be that an excess of carboxylic acid groups and acid groups favors the dehydration against the dehydrogenation of *i*-propanol providing in this way a too low concentration of $H^{\delta-}$ nucleophiles for the transfer hydrogenation. Contrarily, the interaction of butylamine and even more of pyridine with the acid groups creates a balance of acid and basic sites necessary for the generation on the catalyst surface $H^{+\delta}$ and $H^{-\delta}$ pairs. The IR spectra shown in Figure 2 evidenced the differences between the functional groups in GO and the modification introduced by the addition of organic acid and bases.

Table 2. Influence of different organic acids and bases molecules added in liquid phase on the catalytic performance of GO in the transfer hydrogenation of enone **1**[a]

	Organic molecule	Conv., %	$S_{allylic\ alhohol\ 2}$, %	D.e., % / conf.
1	-	9.1	31.5	77.8/(11R, 15S)-epi
2	Acetic acid	64.0	1.0	racemic
3[b]	Pivalic acid	83.2	28.9	100/(11R, 15R)-nat.
4	Pivalic acid	88.0	3.5	100/(11R, 15R)-nat.
5	Butylamine	2.2	46.0	64.4/(11R, 15S)-epi
6[c]	Acetic acid	2.1	95.6	49.5/(11R, 15S)-epi
7[c]	Butylamine	78.8	2.0	racemic
8[c]	Pivalic acid	2.0	81.3	86.7/(11R,15R)-nat
9	Pyridine	89.1	79.2	91.1 /(11R, 15R)-nat.
10[d]	Pyridine and p-toluensulfonic acid	96.1	58.8	90.0/(11R, 15S)-epi
11[e]	p-toluensulfonic acid	1.7	23.4	100/(11R, 15S)-epi

[a] Reaction conditions: 7 mg GO, 14 mg enone, 0.5 mL organic compound, 2.5 mL *i*-propanol, room temperature, 24 h; [b] 6 h; [c] pre-modified catalyst with 0.5 mL of organic molecule, room temperature; [d] 7 mg p-toluenesulfonic acid, 14 mg enone, 0.5 mL pyridine, 2.5 mL i-propanol, room temperature, 24 h; [e] pre-modified GO with p-toluenesulfonic acid, room temperature.

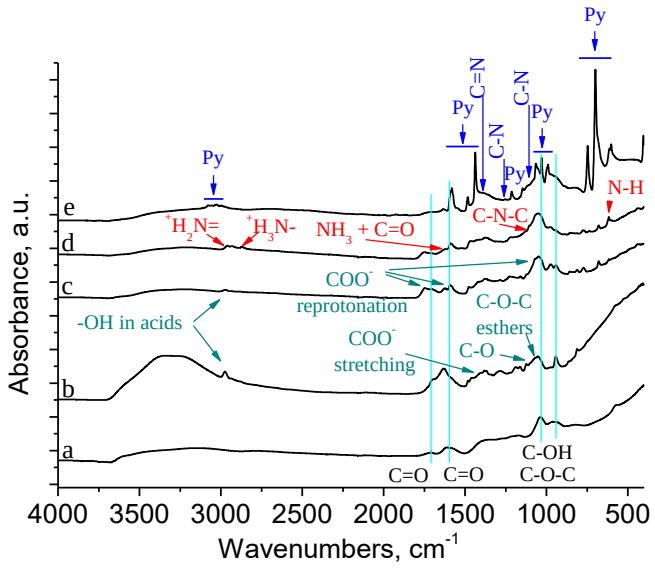


Figure 2. IR spectra of GO (a), and GO after addition of pivalic acid (b), acetic acid (c), butylamine (d), pyridine (e).

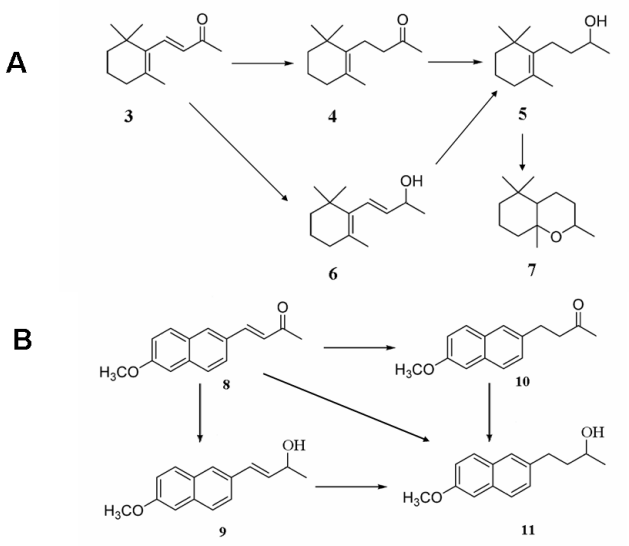
GO exhibits a typical DRIFT spectrum[5, 22] with bands attributed to various oxygen functional groups as hydroxyls (with a broad band at 3200-3500 cm^{-1} and a maximum at 3148 cm^{-1}, a band at 1348 cm^{-1}, and band C-OH at 1038-1175 cm^{-1}), carbonyl (C=O) and carboxyl (COOH) groups (with bands at 1613 cm^{-1} and 1713 cm^{-1}, 3000-3600 cm^{-1} and 1176 cm^{-1}), epoxides (C-O-C) and ethers (C-O) (800-1200 cm^{-1}, intense band at about 1340 cm^{-1}). The band at about 1580 cm^{-1} is attributed to C=C in plane vibrations.[22]

As expected in view of its basic nature chemisorption of butylmine on GO led to a modified DRIFT spectrum in which the most remarkable variations were the decrease in intensity of the 1713 cm^{-1} due to carboxylic acids, accompanied by the appearance of a new band at about 1623 cm^{-1} band attributable to amides formed by reaction of butylamine and carboxylic acid groups.[23] Other peaks ascribed to the presence of C-N and N-H bonds were also observed.[24] In the case of pyridine chemisorption, besides disappearance of the carboxylic acid groups, new bands associated to C=N stretching vibrations were also observed.[25,26]

Chemisorption of acetic acid led to a different pattern. The bands at about 1746, 1623 and 1047 cm^{-1} increased due to the reprotonation of the COO^- groups.[17] Other bands associated to O-CO and CH_2 deformation were also observed**.** Overall FTIR spectroscopy confirms the disappearance and growth of the C=O stretching vibration associated to carboxylic/carboxylate groups depending on the acid/base nature of the additive.

According to this pattern, *i*-propanol will undergo different reactivity pattern with the GO surface depending on the nature of the groups. Also, the C=O group of the substrate **1** will have a different interaction with the surface modified by the organic acid or base. In addition, the π-π stacking[24] and other types of interactions with contribution of electrostatics, dispersion forces, and direct interactions to the substituent effects should not be disregarded.[27-31]

In order to expand the scope of the new catalytic system two more α,β-unsaturated ketone structures were hydrogenated, namely, β-ionone (**3**) and 4-(6-methoxy-2-naphtyl)-3-buten-2-one (**8**) (Schemes 4A and 4B). 4-(6-Methoxy-2-naphtyl)-2-butanone (**10**) with the trade name Nabumetone, is a non-acidic broad-spectrum anti-inflammatory, analgesic and antipyretic agent for which several synthetic strategies have already been reported.[32]



Scheme 4. Hydrogenation of β-ionone (**3, A**) and 4-(6-methoxy-2-naphtyl)-3-buten-2-one (**8, B**)

In line with the hydrogenation of enone **1**, the hydrogenation of the isolated double bond in β-ionone (**3**) is only a minor reaction, and a selectivity of 81% for the allylic alcohol (*ie*, β-ionol **6**) was obtained at a high conversion (> 90%). However, by association with pyridine, the GO catalyst also allow the selective hydrogenation of β-ionone **3** to dihydro-β-ionone **4** (89% yield), but with a very low reaction rate (reaction time of 48h). The role of the Brønsted acidity in this reaction has been demonstrated from the reactions carried out in the presence of carboxylic acids (*ie*, acetic or pivalic acid). Under these conditions the reaction took place with a high conversion (>95%) to tetrahydroedulane (**7,** Scheme 4A). The extra Brønsted acidity brought by these molecules allowed both the hydrogenation of β-ionone (**3**) to saturated alcohol (**5**) and the nucleophilic attack of the OH to the C=C double bond.

The GO catalyst also resulted a convenient catalyst for the hydrogenation of 4-(6-methoxy-2-naphtyl)-3-buten-2-one (**8**) to the saturated alcohol (**11**) in the absence of any additive. Differently to the enone **1** (Scheme 1) or β-ionone (**3**), in the present case, the π-π stacking interactions may orientate the chemisorption of the substrate molecule in a parallel position to the GO surface favoring the one-pot hydrogenation of both the C=O and C=C bonds.

Conclusions

The present study has shown that GO exhibits catalytic activity for the hydrogen transfer from *i*-propanol to enones with high conversions and selectivities to the corresponding allylic alcohols with prostaglandin structure. For low conversions, GO behaves as a distereoselective hydrogen transfer catalyst with an acceptable d.e. value of 77.8 % towards the *epi* isomer. The modification of GO by organic molecules changes the electronic properties of the graphene tuning the catalytic activity, affecting the selectivity to allyl alcohol and diastereoselectivity to the resulted product. Among the various acid and base additives, pyridine produced remarkable positive effects in the hydrogen transfer reaction of the investigated enone providing high activity, selectivity to allylic alcohols and diastereoselectivity in the synthesis of an important prostaglandin product. Also, pivalic acid swap the diastereoselectivity the natural diastereoisomer with a total d.e. Also, GO is able to hydrogenate α,β-unsaturated ketones such as β-ionone or 4-(6-methoxy-2-naphtyl)-2-butanone to the corresponding allylic or saturated alcohols with excellent yields. This behavior has been associated to the chemisorption modes of the substrates. Noteworthy, the system does not contain metals and is recyclable.

Acknowledgements

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Notes and references

‡ GO has been obtained starting from graphite by conventional Hummers oxidation to graphite oxide, followed by exfoliation by ultrasounds.[33] In brief, graphite flakes (3 g) were suspended in a mixture of concentrated H_2SO_4/H_3PO_4 (360:40 ml). To this mixture, $KMnO_4$ (18 g) was added by producing an exothermic reaction raising the temperature to 35–40 °C. This reaction mixture was then heated to 50 °C under stirring for 12 h. The reaction was cooled to room temperature and poured into 400 g of ice containing 30 % H_2O_2 (3 ml). After allowing the suspension to cool at the air, the mixture was filtered, washed with 1:10 HCl (37%) solution and then further washed with additional water. The remaining solid was sonicated in 400 ml of water for 30 min and centrifuged at 4,000 r.p.m. for 4 h. The supernatant was again centrifuged at 15,000 r.p.m. for 1 h. The solid obtained, after centrifugation at 15,000 r.p.m., was dried at 60 °C.

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