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Tandem Catalysis of Amines Using Porous Graphene Oxide

Chenliang Su[†], Rika Tandiana[†], Janardhan Balapanuru[†], Wei Tang[†], Kapil Pareek[†], Chang Tai Nai[†], Tamio Hayashi[†, ‖] and Kian Ping Loh*[,†]

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KEYWORDS: Graphene Oxide, Carbocatalysis, Heterogeneous Catalysis, Tandem Reaction.

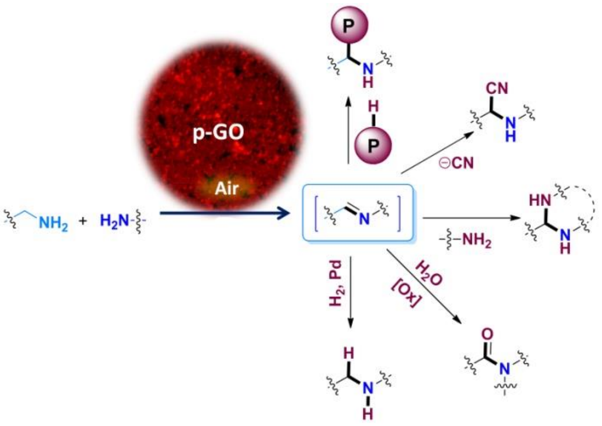
ABSTRACT: Porous graphene oxide can be used as a metal free catalyst in the presence of air for the oxidative coupling of primary amines. Herein, we explore GO-catalysed carbon−carbon or/and carbon−heteroatom bond formation strategy to functionalize primary amines in tandem to produce a series of valuable products, i. e. α-aminophosphonates, α-aminonitriles and polycyclic hetero compounds. Furthermore, when decorated with nano-Pd, the Pd-coated porous graphene oxide can be used as a bifunctional catalyst for tandem oxidation and hydrogenation reactions in the *N*-alkylation of primary amines, achieving good to excellent yields under mild conditions.

Introduction

Owing to the natural abundance of carbon, the development of carbon materials as environmentally benign catalysts is currently an active area of research.[1] Graphene oxide (GO),[2-4] a water-soluble derivate of graphene, has emerged as a new class of carbon catalyst for a wide range of synthetic transformations.[5-10] However, because GO only has moderate catalytic efficiency when used as a substitute for metal catalysts, a high weight loading of GO relative to the substrate is usually required.[8] Recently, we reported a sequential base and acid treatment of GO that dramatically improves its catalytic efficiency due to the generation of porosity by the base treatment and the acidification of its functional groups.[9] To broaden the classes of reactions catalysed by the porous, acidic GO, we consider the concept of tandem catalysis whereby distinct multi-step reactions can be catalysed to generate the desired product. In addition, the aromatic scaffold in GO provides an anchoring site for a second catalyst, which allows the rational design of a tandem catalytic system in which sequential oxidation and hydrogenation reactions can take place.

Functionalised secondary amines are important for chemical, biological and pharmaceutical applications because these valuable amines are widely used as pharmacophores in many bioactive compounds and agrochemicals.[11-13] Although the common synthetic route for secondary amines is the coupling of amines with alkyl halides in the presence of stoichiometric amounts of bases, this approach often suffers from over-alkylation.[12] The toxic nature of the numerous alkyl halides and the production of large quantities of undesired waste create an undesirable environmental footprint. To address these problems, a wide variety of alternative environmentally benign approaches have been developed including the *N*-alkylation of amines with alcohols/amines via the hydrogen-borrowing process,[14-16] tandem oxidation/coupling of amines followed by the hydrogenation/addition process[17, 18] and so on. Along this line, the discovery of a recyclable bifunctional catalytic system that uses ambient air as the terminal oxidant is highly desirable. It is also highly promising to allow the chemistry of C-H bond functionalization to be extended to the α-position of primary amines under mild conditions,[19] which can be achieved via the tandem modification strategy described here.

Scheme 1. The use of p-GO for the tandem functionalisation of primary amines *via* carbon−carbon or/and carbon−heteroatom bond formation.



Herein, we present a systematic study to explore the carbocatalysed carbon−carbon or/and carbon−heteroatom bond formation strategy to functionalize primary amines in tandem to produce a series of valuable products in good to excellent yields, i. e. α-aminophosphonates, α-aminonitriles and potential bioactive polycyclic hetero compounds. The carbocatalyzed active imine intermediates formation is the key step and the concept is illustrated in Scheme 1. Interestingly, this tandem strategy can also be applied for the production of classes of potential biologically active heterocyclic compounds, i.e., the analogue of Tröger's base, and isoindolo-benzodiazepine derivative, in moderate to good yields. Highly porous GO (p-

GO) contains a higher density of catalytically active defect sites[9] and shows a higher catalytic activity compared to as-made GO. When hybridised with a nano-Pd catalyst, the composite becomes a bifunctional catalyst for tandem oxidation (open air) and hydrogenation (H_2, 1 atm) in the *N*-alkylation of primary amines. In terms of turn over number (TON), the catalytic activity of this bifunctional catalyst is almost 10 times higher than that of other reported bifunctional catalysts (Figure S1).[17, 18] The latter require harsh conditions such as high pressure of oxygen (>5 atms) and hydrogen (>5 atms).

Experiment Section

Catalysts Preparation. Synthesis of porous graphene oxide (p-GO). The as-produced GO was dispersed in 1000 ml DI water at a concentration of 1.5 mg/mL^{-1}. 10 g of NaOH plate was added into GO solution. The mixture was refluxed in a round bottom flask under constant magnetic stirring for 1 hour. Subsequently, the NaOH treated GO were separated by centrifuging at 13000 rpm and dispersing in 1000 ml DI water. Then, 25 ml HCl (37%) was added into the solution slowly. The mixture was refluxed for another 1 hour. The base treatment reduced the GO and introduced porosity, while the subsequent acid treatment ensured that the carboxylic functionalities remained acidic.[9] The final p-GO obtained were filtered and washed by DI water and acetone. The synthesized p-GO was kept in vacuum desiccators.

Synthesis of Pd@porous graphene oxide (p-GO). 300 mg of p-GO was added to 40 mL ethylene glycol (EG) and 20 mL dimethyl formamide (DMF) and the mixture was sonicated for 12 h. Subsequently, a mixture of 6 mg $Pd(OAc)_2$ in 10 mL EG and 5 mL DMF was sonicated for 1 h. At the same time, a separate mixture containing 40 mg sodium ascorbate in 10 mL EG and 5 mL DMF was also sonicated for 1 h. While still under sonication, the $Pd(OAc)_2$ solution was added to the p-GO solution. Next, the sodium ascorbate solution was introduced dropwise into the resulting mixture under sonication before leaving it to stir overnight. The mixture was then centrifuged at 13,500 rpm to remove the supernatant and the Pd@p-GO obtained was washed with acetone and ethanol before drying in the oven.

Results and Discussion

We first consider the use of p-GO in the phosphonation of primary amines using an oxidative cross coupling strategies[20-22], which are very attractive as they provide efficient access to valuable α-aminophosphonates and their derivatives.[23, 24] The carbocatalysed oxidative cross coupling reaction of benzylamine with diethyl phosphonate is investigated in detail here by screening various heterogeneous carbons. Our results show that p-GO yields the best results (88% of NMR yield) among all the tested carbocatalysts, including as-made GO, reduced-GO, carbon black and CNT (Table S1 and Figure 1a). Figure 1b shows that the conversion of the starting material reaches 100% in the first hour, giving 48% imine intermediate along with 39% α-aminophosphonate **3a**; the NMR yield of **3a** reaches 88% along with a few byproducts after 8 h.

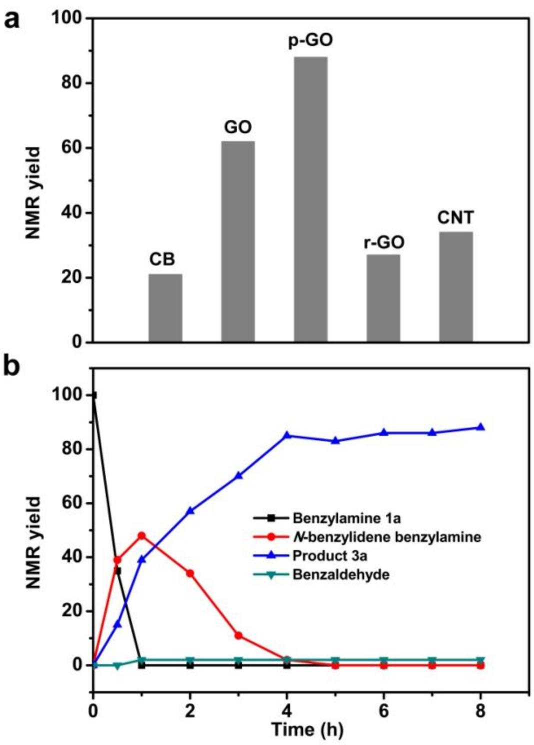


Figure 1. (a) Comparing the catalytic reactivity with various carbocatalysts. (b) Time conversion plots showing the temporal evolution of substrates, intermediates and products using p-GO as the catalyst.

Defect sites, especially in the form of pores or vacancies, are usually catalytically active[9], therefore the porosity of p-GO is carefully examined by AFM, STM and BET analysis. Due to the limited resolution of our AFM, only large holes (>10 nm) can be imaged on the surface of p-GO. The area of large-size holes can be quantified as 1.57% (Figure 2a-b). STM was applied to image nanosized pores on p-GO. As shown in Figure 2c-d, p-GO has very high density of pores and the total holes area of p-GO can be quantified as 5.74% by pore area analysis of STM images. The size of the pores in p-GO as observed by STM is also consistent with BJH Adsorption (average diameter: 2.16 nm). BET analysis further support that p-GO has high micro-pore area (331.28 m^2/g, see Table S2).

Different substrates are screened and the results are summarized in Table 1. Regardless of the nature of the functional groups in benzylamine derivatives, the corresponding α-aminophosphonates can be obtained in good isolated yields (62-84%). Long alkyl chain substituted phosphonate can be used as a substrate (Table 1, entry 11). In comparison to as-made GO, p-GO has much less oxygen-functionalities and exhibits higher thermal stability. These properties afford the good stability (Figure S2) and recyclability of this carbocatalyst in subsequent multi-run experiments (Table 1, entries 1-3).

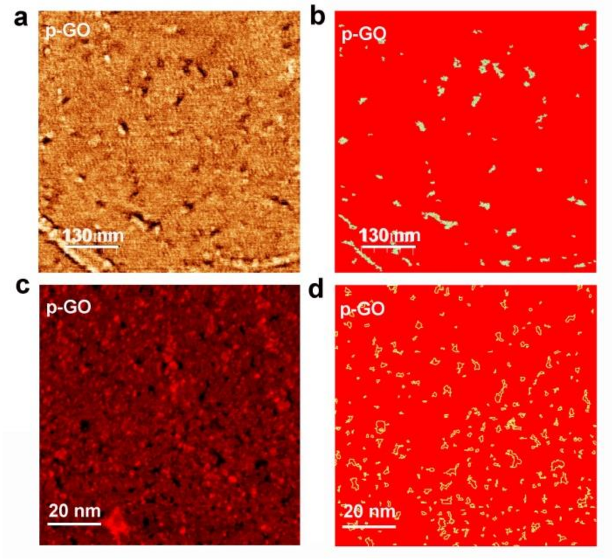
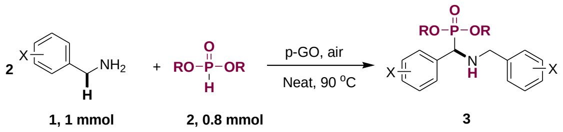
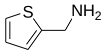


Figure 2. STM and AFM topography images of p-GO. a) AFM topography image of p-GO (scale bar, 100 nm). Large holes (10-20 nm) can be seen on the surface of p-GO. b) Hole analysis of AFM topography image of p-GO (scale bar, 100 nm). c) STM topography image of p-GO (scale bar, 20 nm). d) Hole area analysis of STM topography image of p-GO (scale bar, 20 nm).

Table 1. α-position functionalisation of primary amines via tandem reaction of primary amines with nucleophiles.

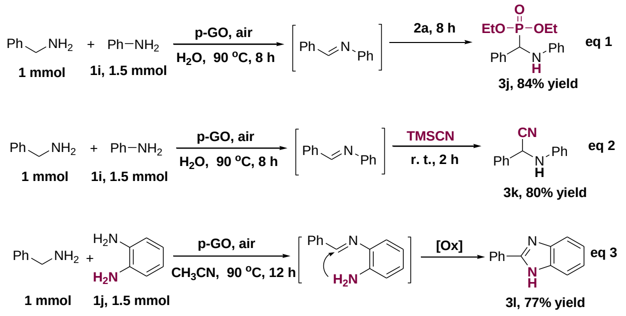


Entry	*X (1)*	*R (2)*	*T (h)*	*Yield*[b]
1	H (1a)	Et (2a)	8	84 (88[c])
2	H (1a)	Et (2a)	8	74[c] (Run 4)[d]
3	H (1a)	Et (2a)	8	79[c] (Run 5)
4	4-Cl (1b)	2a	8	74
5	4-Me (1c)	2a	12	80
6	3-Me (1d)	2a	12	82
7	2-Me (1e)	2a	12	83 (86[c])
8	4-OMe (1f)	2a	12	78 (87[c])
9	4-CF_3 (1g)	2a	11	62
10	 (1h)	2a	12	64 (72[c])
11	1a	*n*-Bu (2b)	11	70 (75[c])

[a] Unless otherwise specified, nucleophiles (0.8 mmol) was added very slowly (over 3 hours) into the reaction mixture of primary amines (1.0 mmol) and p-GO (30 mg) at 90 °C under open air and neat conditions; [b] Isolated yield. [c] NMR yield; The conversion is 100% and trace amount of aldehyde and few unidentified mixtures can be observed. [d] The catalyst was recovered by simple filtration and further washed by CH_3CN for 3 times and then dried in oven at 60 °C before reuse.

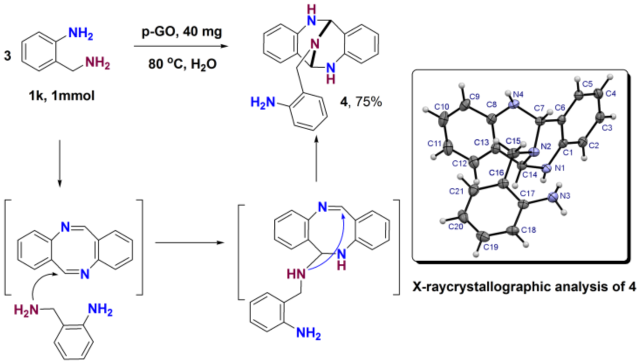
The three component reaction of aniline, benzylamine and diethyl phosphate successfully furnishes the corresponding products **3j** in 84% isolated yield and extremely high selectivity (Scheme 2, eq 1). Cyanide anion can be employed as a nucleophile in such a three component reaction giving rise to the α-amino nitrile product in good yield (Scheme 2, eq 2). It is also attractive to apply carbocatalysts in the synthesis of heterocyclic compounds via multi-step oxidation and nucleophilic addition reactions. A simple example is the one-pot synthesis of benzimidazole, in which the initial imines generated from the oxidative coupling reaction undergo intramolecular addition by amine group and subsequent oxidation to the target compound (Scheme 2, eq 3).

Scheme 2. p-GO catalysed tandem reactions of benzylamine with different nucleophiles.



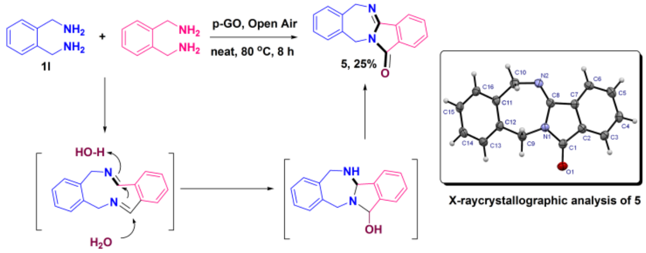
Following the lines of the above results, introducing an amino group into the primary amine should be suitable for the construction of heterocyclic compounds using the tandem reaction strategy. Therefore, the carbocatalysed tandem reaction of 2-amino-benzylamine **1k** is explored. Surprisingly, an unexpected trimer product **4** is obtained in 75% yield, probably via the formation of the dibenzo[b,f][1,5]diazocine intermediate followed by tandem nucleophilic addition by another equivalent of primary amine. The structure of **4** is established as 13-(2-amino-benzyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo-[b,f][1,5]diazocine through X-ray analysis of its single crystal (Scheme 3). As the analogous scaffold of Tröger's base,[25] these epiminodibenzo[b,f]-[1,5]diazocine derivatives not only possess most of the applications of Tröger's base but are also potentially useful in molecular recognition.[26, 27] Here, we have identified a novel methodology for the convenient synthesis of **4** via the tandem reaction of 2-aminobenzylamine using a carbocatalyst.

Scheme 3. p-GO catalysed tandem reactions of 2-aminobenzylamine for the construction of the analogues of Tröger's base. The ORTEP representation of product 4 is inserted.



When o-xylylenediamine **1l**, a derivative compound of 2-aminobenzylamine, is used as the substrate, isoindolo-benzodiazepine derivative is obtained in 25% yield along with a few unidentified mixtures (Scheme 4). The structure is further confirmed by NOESY spectrum and X-ray crystallographic analysis. Due to their potential biological properties, these isoindolo-benzodiazepine derivatives are the targets of many synthetic efforts.[28-30] The carbocatalysed tandem reaction strategy provides unprecedented straightforward access to these useful heterocyclic compounds.

Scheme 4. p-GO catalysed tandem reactions of *o*-xylylenediamine for the construction of heterocyclic compounds. The ORTEP representation of isoindolo[2,1-*b*][2,4]benzodiazepine product 5 is inserted.



X-raycrystallographic analysis of 5

p-GO alone does not catalyse the *N*-alkylation of primary amines to produce secondary amines. However, we can exploit the aromatic scaffold in p-GO to anchor a second catalyst, which allows the carbocatalysed oxidative coupling of primary amines followed by sequential metal-catalysed hydrogenation to proceed. To develop this bifunctional catalytic system in which the advantages of the graphene material as a support and catalyst can be combined, metal-nanoparticles (i. e. Pd, Au and Pt) are loaded onto p-GO for sequential catalytic activation of hydrogen. Here, the extensive screening of metals and carbon materials is used to identify the strongest cooperative effect between the Pd nanoparticles and p-GO, which gives 100% conversion along with 91% isolated yield (Table S3, entry 2). Control experiments using either bare p-GO or Pd nanoparticles loaded on other carbon supports (i.e. carbon black or as-synthesised GO) show very poor performance in these reactions, which indicates that the tandem nature of the catalysed reaction requires two types of catalytic sites to be present for concerted action.

The presence of Pd nanoparticles attached to the surface of p-GO is confirmed by ICP and the initial loading value of Pd is determined to be 4.4 wt%. TEM is also applied to investigate the morphology, composition and crystal structure of the bi-functional catalyst. From the TEM images in Figures 3a and 3b, we can see the presence of Pd nanoparticles on Pd@p-GO, and the particle size mostly ranges 4 nm to 8 nm. Figure 3c shows Pd (111) lattice planes with spacing d(111) = 0.222 nm, which corresponds to the literature value for nanocrystalline Pd.[31] The active Pd surface area, dispersion (the ratio between surface and total metal atoms) as well as particle size was further evaluated by means of CO chemisorption test. Assuming the adsorption ratio of CO to Pd = 1[32, 33], the fraction of available surface Pd atoms can be calculated. The dispersion of our Pd-loaded p-GO is 0.18 and the calculated average particle size is 6.5 nm, which agrees well with the TEM results (See Table S4). The Pd 3*d* XPS spectra in Figure 3d consists of two spin-orbit coupled peaks with chemically shifted components, which can be fitted using two doublets. The peaks around 335.5 and 340.7 eV are attributed to metallic Pd^0, while those around 338.1 and 343.4eV correspond to Pd^{2+} species. Remarkably, a loading of Pd as low as 0.52wt% on Pd@p-GO shows an isolated yield of 92% with a reasonably high TON value (459). In comparison to reported bifunctional catalysts (e.g. $Au@TiO_2$) that require high pressure of oxygen (> 5 atms) and hydrogen (> 5 atms), our Pd@p-GO bifunctional catalyst exhibits almost 10 times higher catalytic reactivity under very mild reaction conditions (Air and 1 atm H_2) (Figure S1).[17, 18]

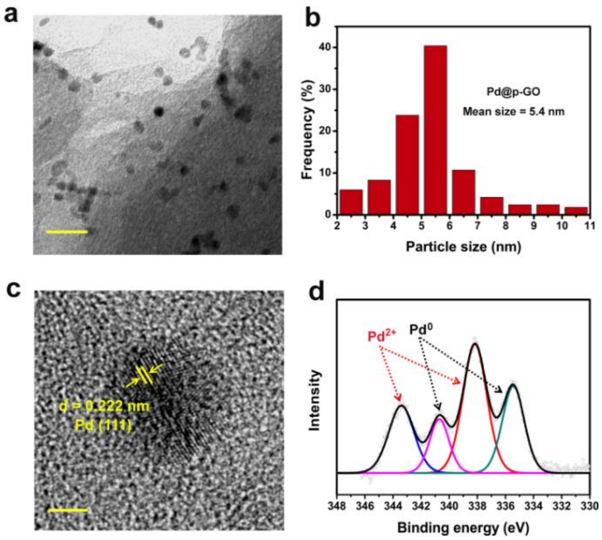
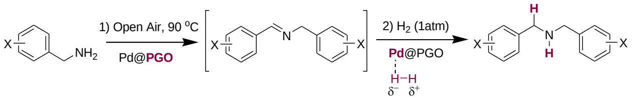
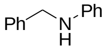


Figure 3. (a) TEM images of Pd@p-GO (4.4wt%), scale bar 10 nm; (b) Pd particle size distribution; (c) HRTEM image of Pd@p-GO, scale bar 3 nm; (d) XPS spectrum of Pd@p-GO.

Table 2. Bifunctional catalysed *N*-alkylation of primary amines to secondary amines.[a]



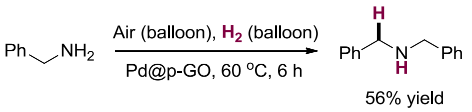
Entry	*X (6)*	*T (h)*	*Yield*[b]
1	H (6a)	5, 5	90
2	H (6a)	5, 5	84 (Run 4)
3	4-Me (6b)	5, 4	93
4	3-Me (6c)	5, 5	93
5	2-Me (6d)	5, 4	92
6	4-OMe (6e)	5, 5.5	88
7	$4-CF_3$ (6f)	5, 5	91
8[c]	 (6g)	13, 5	70

[a] The reaction was carried out by using 40 mg of catalyst with 2 mmol of substrate in 0.2 mL CH_3CN at 90 °C under open air conditions followed by introducing hydrogen (balloon) at 90 °C. [b] Isolated yield. [c] The reaction was carried out by using 40 mg of catalyst with 1 mmol of benzylamine and 1.5 mmol of aniline in 0.1 mL H_2O at 90 °C under open air conditions followed by introducing hydrogen (balloon) at 90 °C.

With these optimised conditions, the effectiveness of Pd@p-GO for the tandem catalytic system is assessed (Table 2). The electronic effects of the substituents on the phenyl ring have little effect on the efficiency of the coupling process under mild reaction conditions (Table 2, entries 3-7). Catalytic cross coupling of benzylamine with aniline can be successfully achieved by Pd@p-GO with 70% yield of the corresponding product and excellent selectivity (Table 2, entry 8).

To date, no studies have reported applying one catalytic material for catalytic oxidation and hydrogenation without compromising the catalytic reactivity of either. It is interesting to see whether such "incompatible" reactions can be first achieved by using graphene bifunctional catalyst. Because it is not safe to perform the reaction under a mixture gas of hydrogen and oxygen (air) at high temperature, this reaction is carried out under low temperature and it successfully furnishes the desired product in 56% yield (scheme 5).[34]

Scheme 5. Simultaneous activation of molecular oxygen and hydrogen.



A plausible mechanism for the tandem catalysis by Pd@p-GO is as follows: first, primary amine undergoes an oxidative coupling reaction on the active defect sites[9] to produce imine intermediates and H_2O_2. The imine intermediates react with the nucleophiles to furnish the corresponding α-position functionalised secondary amines. In the presence of the Pd nanocatalyst, molecular hydrogen is activated and imine intermediates are then transferred to secondary amine products via tandem hydrogenation, as shown in Figure 4.

Figure 4. Proposed mechanism for the Pd@p-GO bifunctional catalytic system.

Conclusion

In conclusion, we have identified several classes of multi-step reactions involving amines that can be catalysed by p-GO with high yields. p-GO has been successfully applied as a carbocatalyst in the tandem reaction of primary amines to produce polycyclic *N*-containing heterocyclic compounds via multi-step oxidative coupling and intramolecular additions. When p-GO is hybridised with a co-catalyst such as Pd nanoparticles, the composite works well as a synergistic catalytic system for the sequential oxidation of amine and the hydrogenation of imine intermediates to furnish secondary amines as the coupling products. Our work suggests that appropriately treated GO and its composites can be a powerful synthetic tool in tandem reactions.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data and NMR spectrua. This material is available free of charge via the Internet at http://pubs.acs.org.

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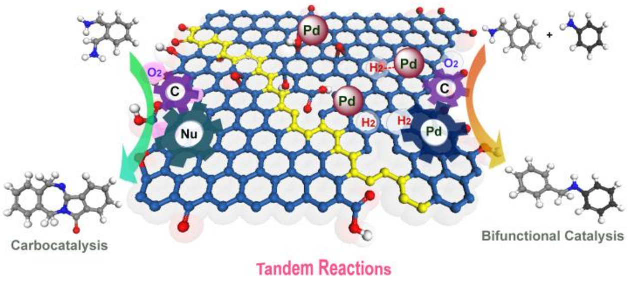
(34) Caution!!!: The reaction is potentially explosive. Only a small spark is needed to trigger an explosive reaction of hydrogen with oxygen. Sufficient precautions must be taken while carrying out this reaction. **Detailed experimental description of the simultaneous activation of oxygen and hydrogen by Pd@p-GO.** The reaction should be carried out in a fumehood with an anti-explosion shield: the obtained Pd@p-GO (40 mg), benzylamine (2.0 mmol) and CH3CN (0.2 mL) was added to a three necked round bottom flask with water-cooling system. 1 atm air (balloon) and 1 atm hydrogen (balloon) was introduced into the reaction. The reaction temperature was slowly increased to 60 oC and stirred for 6 hours (Caution: the temperature should be precisely controlled; take note of explosion risk using higher temperature and pure oxygen gas instead of air balloon; any spark source and organic solvent should be removed; the reaction should be carried out under fully open-system to allow pressure release). After that, the solution was cooled to RT. After filtration, washing by CH3CN and evaporation afforded 6a in 56% yield.

TOC


Pd
Pd
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C
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Carbocatalysis
Bifunctional Catalysis
Tandem Reactions