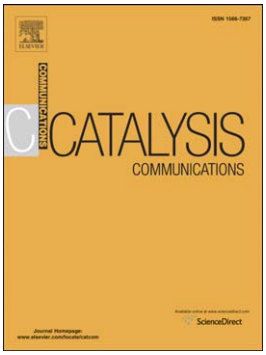

Graphene oxide: An efficient recyclable solid acid for the synthesis of bis(indolyl)methanes from aldehydes and indoles in water

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Graphene oxide: an efficient recyclable solid acid for the synthesis of bis(indolyl)methanes from aldehydes and indoles in water

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Abstract An efficient synthesis of bis(indolyl)methanes from aldehydes with indoles through graphene oxide -catalyzed Friedel-Crafts alkylation is developed. The reaction proceeds in water by using graphene oxide as the single catalyst to provide the desired products in good to excellent yields. Also, this methodology has a broad substrate scope, and is environment friendly and cost economic.

Key words graphene oxide, Bis(indolyl)methanes, Friedel-Crafts reaction, recyclable, water

1. Introduction

Bis(indolyl)methanes (BIMs),which are widely presented in various terrestrial and marine origin bioactive metabolites [1], are important intermediates in synthetic organic and medicinal chemistry [2]. They are finding applications as highly selective colorimetric, fluorescent molecular chemosensors for Cu^{2+} cation [3] and also well known to possess various pharmacological effects such as hypolipidemic [4], antiobesity [5], β-glucuronidase inhibitors [6], anti-microbial [7] and anti-cancer activities [8].

Due to their biological and medicinal activities, great deals of new effective and powerful synthesis routes have been established within the past ten years. Most of synthesis strategies of BIMs are indoles respond to aldehydes or ketones through Friedel-Crafts alkylation reaction route with the presented of Lewis acids [9], brønsted acids [10], solid acids [11], ionic liquids [12] or coordination catalyst [13]. In spite of these catalysts have different structures, all of them have similar reaction mechanism. The reaction process is the acidic ions of catalysts promote the Friedel-Crafts alkylation reaction of indoles with carbonyl compounds to get BIMs. Even if these protocols have proved their efficiency in BIMs synthesis, they also suffered from several drawbacks, such as the toxic metal ions and solvents, high costs, limitations of catalyst recovery and harsh conditions. Consequently, development of milder, convenient, environment friendly method to access BIMs is still highly valuable.

In recent years, high molecular materials are gaining much attention in organic synthesis owe to their easy separation, mild reaction conditions, ease in recovery and low-toxic nature [14]. Among these materials, graphene oxide (GO) interestingly exhibits excellent activity due to its privileged lamellar flexible structure with a wide range of functional groups, such as epoxy (C-O-C), hydroxyl (OH), and carboxyl (COOH) [15]. Because of their high specific surface areas as well as excellent stabilities, GO has become a favorable material to support a wide range of ions or biomolecules, and GO supported catalysts have been applied to many kinds of chemistry reactions [16]. But many literatures ignored that the carboxyl on the surface

of GO played an important role in organic reactions which can be used as solid acids to catalyze Friedel–Crafts reaction. To the best of our knowledge, only very limited ways about using GO as catalyst has been found and the usage of GO served as the single catalyst in the synthesis of BIMs from aldehydes has not been reported before. Apart from that, we decided to explore the viability of using GO as the single catalyst to prepare BIMs.

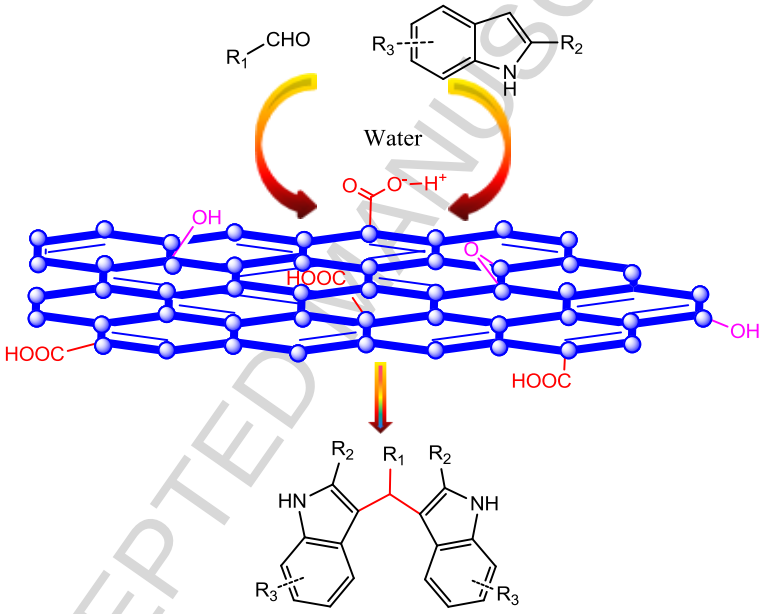


Figure 1. The synthesis of BIMs catalyed by Go

In this paper, we report GO, which can be used as solid acids to promote Friedel-Crafts reaction. Compared with the traditionally applications, we developed a new area of GO which is not only a support material, but also a powerful catalyst in the synthesis of BIMs (as shown in **Figure 1**).

2. Experimental

2.1 Synthesis of GO

Graphene oxide (GO) used in this work was synthesized from graphite according to the modified Hummers method as reported [17]. To begin, 3.0 g of graphite and 1.5 g of $NaNO_3$ were placed in a 500 ml beaker. After adding 69 ml of 98% sulfuric acid, the mixture was stirred until cooled to 0 ^oC in an ice-water bath. $KMnO_4$ (9.0 g, 99%) was gradually added to the mixture and control the temperature below 20 ^oC. After complete the adding, the ice-bath was exchanged for an oil-bath and the mixture was heat up to 35 ^oC and maintain this temperature for 30 min. Then, 138 ml deionized water was added gradually to the reaction and the resulting mixture was heated at 98 ^oC for 15 min. As the reaction progressed, the reaction mixture was cooled to room temperature and diluted with 420 ml deionized water and 3 ml H_2O_2 (30%) was also added to the reaction. The suspension was filtered and washed with 200 ml of 5% hydrochloric acid solution. Next, the suspension was washed with deionized water three times until the pH turn nature. The final precipitated GO was dried on vacuum at 60 ^oC for 24 hours for further use.

2.2 General experiment for the synthesis of bis(indolyl)methanes (3a as an example)

A mixture of benzaldehyde **1a** (0.5 mmol), indole **2a** (1.5 mmol) and GO 150 mg were added in 10 mL water with a condenser and then stirred under air at 40 ^oC for 3h. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica to afford pure 3,3'-(phenylmethylene)bis(1H-indole) **3a** as a pink solid (92% yield).

3. Results and discussion

3.1 Catalyst characterization

Fourier transform infrared (FTIR) spectra were recorded using a Nicolet 6700 FI-IR spectrometer (Nicolet). The GO powder was mixed with potassium bromide to form the pellets in order to scan the FTIR spectra.

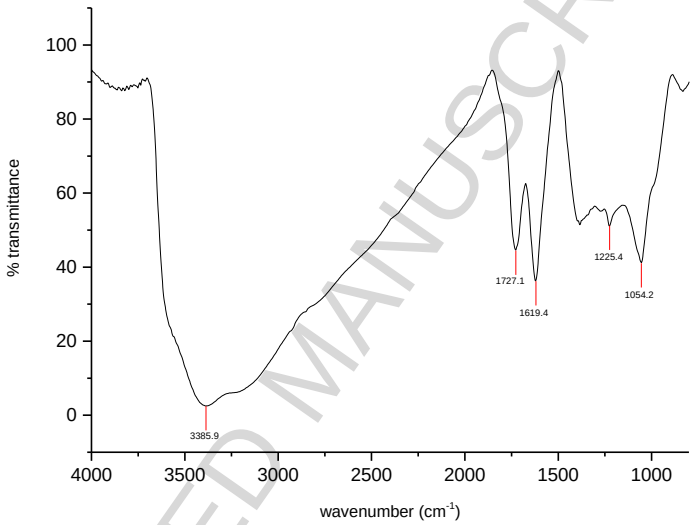


Fig 2. FTIR spectra of GO

The FTIR spectra of GO was shown in **Fig 2**. The wide peak at 3385.9 cm^{-1} in the GO is attributed to the stretching mode of the O–H bond. Stretching vibration of the C=O bond of carboxy on the surface of GO was observed as the band present at 1727.1 cm^{-1}. The other intense band at 1619.4, 1225.4, 1054.2 cm^{-1} are attributed to the *v* (C=C) of skeletal vibrations from unoxidized graphitic domains, C–OH and C–O (epoxy) groups in the GO respectively [18].

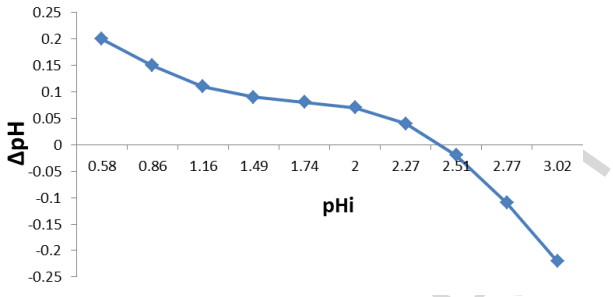


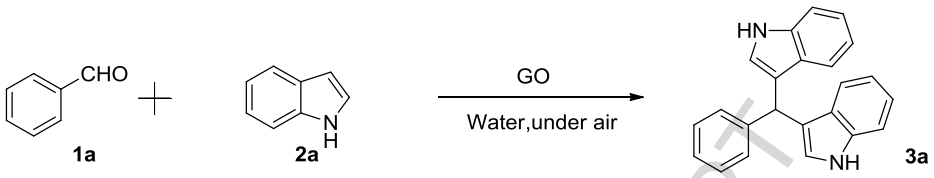
Figure 3. Point of zero charge of GO using 0.1 M KNO_3.

The pH_{pzc} (point of zero charge) of GO was determined by plotting Δ pH against initial pH (**Figure 3**). GO was added to 50 ml of 0.1 M of KNO_3 solutions at various solution pH (0.58–3.02) as per solid addition method. The curve crosses the horizontal line at pH 2.32, suggesting that the surface charge is zero at pH 2.32. If pH < pH_{pzc}, the surface of the adsorbent becomes more positively charged. In contrast, when pH > pH_{pzc}, it is negatively charged.

3.2. Catalyst reaction activity

At the beginning of our investigation to synthesize BIMs, experiments were carried out using benzaldehyde **1a** and indole **2a** as prototypical substrate.

Table 1 Optimization of the reaction conditions[a]



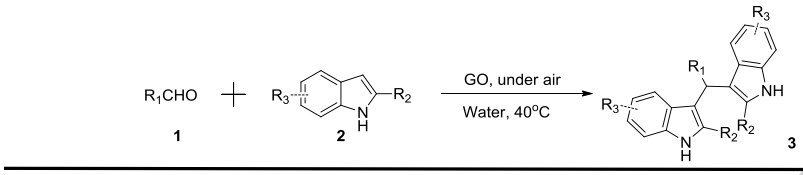
Entry	GO(mg)	Solvent	Temp.(^{o}C)	1a : 2a	Yield[b] (%)
1	100	DCM	r.t	1:3	5
2	100	EA	r.t	1:3	68
3	100	CH_3CN	r.t	1:3	50
4	100	EtOH	r.t	1:3	80
5	100	THF	r.t	1:3	66
6	100	H_2O	r.t	1:3	82
7	50	H_2O	r.t	1:3	77
8	150	H_2O	r.t	1:3	85
9	200	H_2O	r.t	1:3	85
10	0	H_2O	r.t	1:3	0
11	150	H_2O	40	1:3	92
12	150	H_2O	60	1:3	80
13	150	H_2O	80	1:3	75
14[c]	150	H_2O	40	1:2	76
15[d]	150	H_2O	40	1:4	91

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst (as indicated), solvent (10mL) for 3h under air. [b] Isolated yield. [c] **1a** (0.5 mmol), **2a** (1.0 mmol), [d] **1a** (0.5 mmol), **2a** (2.0 mmol).

Firstly, a series of solvents, such as DCM, EA, CH_3CN, EtOH, THF and H_2O were screened for this reaction under air. The results showed that H_2O was the best solvent for the ambient temperature employed (**Table 1**, entries 1-6), presumably due to its favorable dispersion ability to GO. Next, we varied the amount of catalyst and found that 150 mg of GO gave the best result (Table 1, entries 6-9), and no products were detected without the presence of GO (Table 1, entry 10). In order to get even higher yield, the reaction was performed at different temperatures. At 40 ^{o}C, the highest yield of **3a** (92%) was obtained and when the temperature was carried out at 60 ^{o}C and 80 ^{o}C only led to a decrease in the yield (Table 1, entries 11-13). Finally, we searched the optimal ratio of the reaction substrate in this reaction and 1:3

equivalent weights of **1a** and **2a** was the superlative proportion to prepare BIMs (Table 1, entries 14-15). Consequently, the optimal reaction conditions to get BIMs tend to be: benzaldehyde **1a** (0.5 mmol), indole **2a** (1.5 mmol) and GO 150 mg in water at 40 ^{o}C for 3h.

With the optimal reaction condition in hand, a range of reactions was carried out to expand the scope of substituted indoles and aldehydes, the yields and reaction time were shown in **Figure 4**. Firstly, when electron-withdrawing and electron-donating groups were employed as the substituent on benzaldehyde, BIMs were obtained in good to excellent yields (Figure 3, 3a-3l) and the results showed that substrates with electron-withdrawing groups were more reactive. Additionally, other aromatic aldehydes such as furan, thiophene, pyridine, pyrrole as well as naphthalene were well tolerated in this reaction (Figure 3, 3m-3q) and this condition can also applied to aliphatic aldehyde (Figure 3, 3r). Different substituted indoles were investigated too. The results showed that methyl, halogen and cyano substituted indoles are compatible and good yields were obtained (Figure 3, 3s-3w).



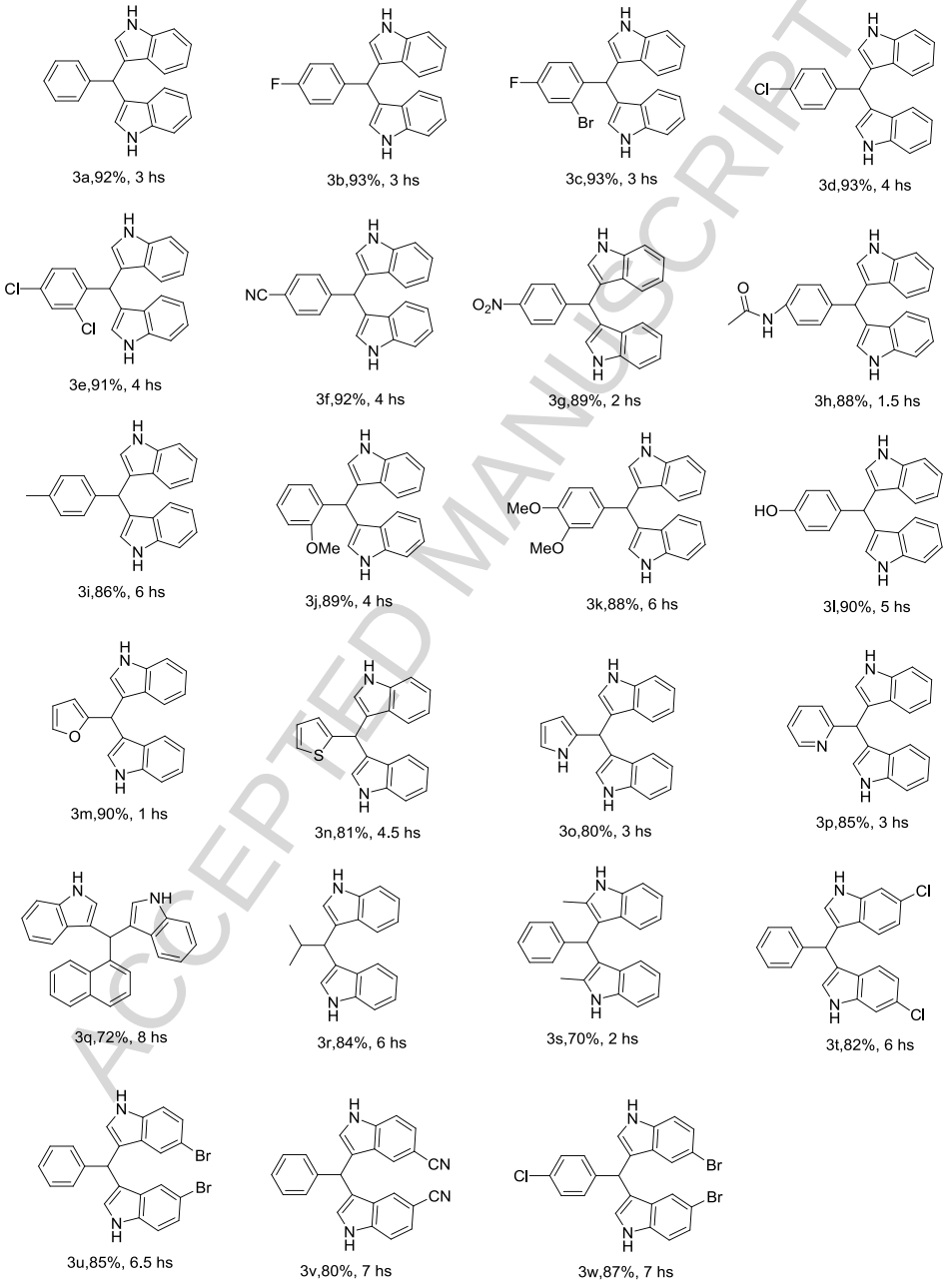


Figure 4. The synthesis of BIMs (**3**) from aldehydes (**1**) and indoles (**2**).

Reaction conditions: aldehydes (**1**, 0.5 mmol), indoles (**2**, 1.5 mmol), GO (150 mg) in water (10 mL) at 40 ^{o}C for indicated time.[a] Isolated yield.

The further studying to check the recovering and reusing of GO was also performed (**Figure 5**). After completion of the reaction, GO was separated by filtration, and wash with ethyl acetate until all the organic residuals were completely removed. The catalysis was recovered directly in the new reaction, and almost no loss of activity occurs even after being reused ten times.

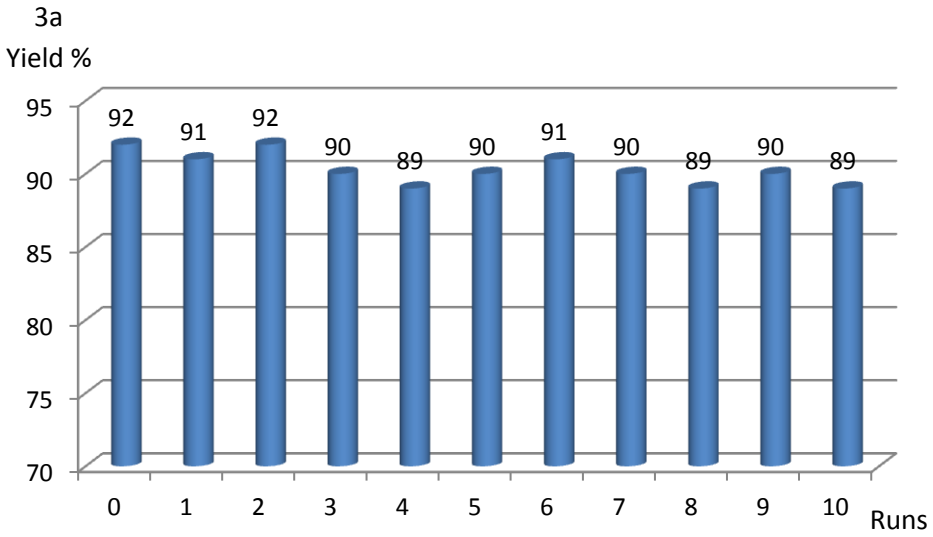
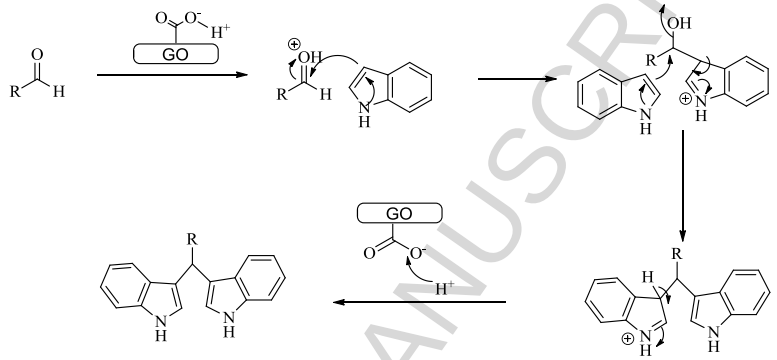


Figure 5. Reuse of GO in the synthesis of 3a.

A plausible mechanism for this reaction is shown in **Scheme 1**. Promoted by carboxylic acid in the surface of GO, the electrophilicity of the carbonyl carbon increased and which in turn facilitates the reactivity of indole molecules. After the Friedel-Crafts reaction, aldehydes and indoles were successful transformed into BIMs.



Scheme 1. Plausible mechanism for this reaction.

4. Conclusion

In summary, we have successfully developed a highly efficient, environment friendly and metal-free synthesis of BIMs. This green synthesis offers the corresponding products with good yields and excellent functional group tolerance. In addition, compared with the traditionally applications, we found that GO is not only a support material, but also a powerful catalyst to synthesis BIMs. Further applications of this method to other substrates are in progress.

Acknowledgment

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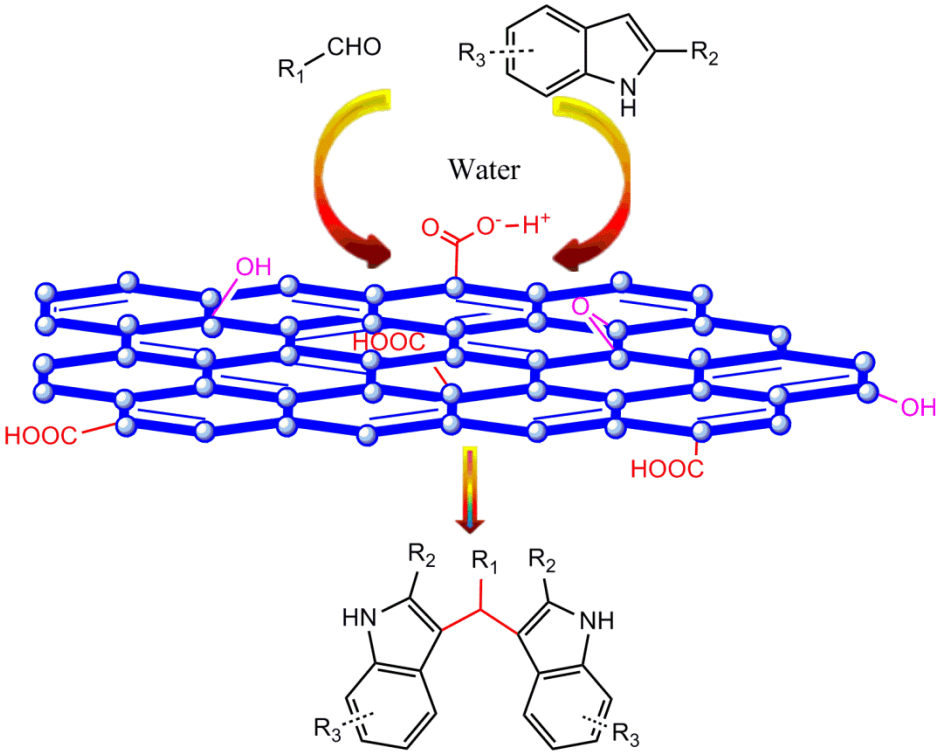
Graphical abstract



23 examples
up to 93% yield

R_1 = alkyl, aryl

R_2 = methyl, hydrogen

R_3 = cyan, halogen

Highlights

The synthesis of bis(indolyl)methanes catalyzed by graphene oxide is developed.
Graphene oxide could be used as solid acids to catalyze Friedel–Crafts reaction
The reaction was performing in water and the catalyst could be reused ten times.
This methodology has a broad substrate scope and good to excellent yields.