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C–H Activation of Benzamides Using Biogenically Synthesized Pd@CNTs Catalyst under External Ligand Free Condition: Access to Isoquinolones and A DFT Study of Phytochemicals

Rajeev V. Hegde,[a, d] Rahul Bhondwe,[b] K. A. Sree Raj,[a] Arnab Ghosh,[a, e] Chandra Sekhar Rout,[a] Thrilokraj R.,[a] Siddappa A Patil,[a] Balasubramanian Sridhar,[c] and Ramesh B. Dateer*[a]

Environmentally amiable biogenic strategy for in-situ one-step synthesis of Pd-NPs decorated on carbon nanotubes (CNTs) and its synthetic utility for C–H activation of benzamides to access isoquinolones has been reported for the first time. The phytochemicals present in Gliricidia sepium leaves extract was found to be serve as a reducing agent to reduce Pd (II) to Pd (0) and subsequently acts as a stabilizing agent. The formation of Pd@CNTs was confirmed by *P*-XRD, FE-SEM, EDX and ICP-OES analysis technique with active Pd content 42.82 % w/w. In addition, DFT study of phytochemicals found in Gliricidia sepium leaves extract were conducted. The catalytic activity was showcased for the cost-effective, step and atom economic synthesis of isoquinolones *via* C–H and N–H bond activation without the aid of external ligands. A series of isoquinolone derivatives were synthesized in good to excellent yields under air as a sole oxidant. In addition, catalyst recyclability and mechanistic experiments were deliberated. The Pd@CNTs unveiled superior catalytic activity and high durability towards hydrogen evolution reaction in acidic media. The Pd@CNTs attains the current density of 10 mA/cm2 at an over potential of 127 mV with a small Tafel slope of 41 mV/dec.

Introduction

The nitrogen-containing heterocycles gained significant attention in last decade due to its importance in medicinal chemistry and therefore, it has inspired many researchers to develop new and proficient strategy for their synthesis.[1–2] Indeed, the conventional methods for the synthesis of these molecules involve pre- modification of the coupling partners.[3] Therefore, in recent years direct C–C and C–N bond formation *via* C–H functionalization has arisen as an efficient and alternative route to their synthesis.[4] Additionally, C–H bond functionalization has become one of the most active research studies in recent decades as a result of increasing awareness of atom economy and green chemistry.[5] Under these circumstances, isoquinolone is one of the important cores found in a variety natural compounds and pharmaceutically significant therapeutic prospects (Figure 1). In this context, synthesis of isoquinolones by employing the heterogeneous nanocatalysts found to be more superior alternative in recent years. However, only handful reports for its synthesis using heterogeneous/nanocatalysts has been perceived.[6] Indeed, key benefits of nanocatalysts are high surface area, works without external ligand, easy recovery and reusability.[7]

In this context, new synthetic strategies to design a heterogeneous nanocatalysts and its successful execution for the implementation of value-added compounds are still in requisite. Therefore, as a first part of our investigation herein

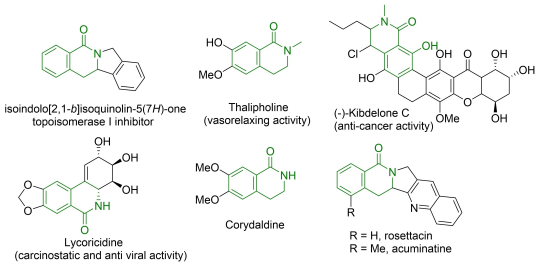

Figure 1. Representative natural products containing isoquinolone framework.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202300673

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we pass on a biogenic approach for in-situ one-step synthesis of Pd-NPs decorated on carbon nanotubes (Pd@CNTs). The various analytical and spectroscopic techniques such as UV-VIS, FT-IR, FE-SEM, XRD, BET, TG-DTA and HR-TEM envisage the formation of Pd@CNTs catalyst (See the SI for more details). Based on our recent findings in this direction[8] and with the help of literature precedents[9] it is evident that the phytochemicals present in the aq. extract of Gliricidia sepium leaves reduces the Pd (II) to Pd (0) (See SI for GC-MS chromatogram). Due to its high nutritional content, gliricidia is one of the most important tropical feedstuff plants.[10] Many active constituents, including alkaloids, flavonoids, cardiac glycosides, and steroids, are found in plants. There are proteins, carbohydrates, and tannins can all be present in a plant's various components, including the leaves, flowers, bark, seeds, fruits, and roots. The use of secondary metabolites in illness treatment is advantageous.[10b] Many organic components are frequently employed in human therapy, veterinary care, agriculture, and scientific research, among other uses.[10c]

Results and Discussion

Nevertheless, to get a better insight on role of phytochemicals in the reduction of Pd (II) to Pd (0) Density Functional Theory (DFT) study was carried out (Using Gaussian 09 software) to know different quantum chemical calculations of compounds such as Hydrocoumarine (HCM), coumarin (CM) and Bis(2 propylphenyl) pthalate (BPPP) found in ethyl acetate/DCM extract of Gliricidia sepium leaves. Initially, we have optimized the structures of Hydrocoumarine (HCM), coumarin (CM) and Bis(2 propylphenyl) pthalate (BPPP) (see SI for Figure) using Gaussview06 software and calculations are submitted for DFT with B3LYP method and basis set 6-31G (d) for all the atoms.[11] Results obtained for the parameters such as E_{HOMO}, E_{LUMO}, $\triangle E = E_{HOMO} - E_{LUMO}$, Mulilken charges, dipole moment, hardness, softness, total energy. Molecular electrostatic potential (MEP) was generated by new mapped surfaces for HCM and CM (See SI for tables and Figures).

The properties of FMO, highest occupied molecular orbital (HOMO) and lower unoccupied molecular orbital (LUMO) are calculated by B3LYP/6-31G (d) method for all the compounds under investigation (see SI for more information Table). Highest value for E_{HOMO} suggests its ability to donate electrons equivalent to ionization potential and value E_{LUMO} ability to accept electrons and its value resembles electron affinity, whereas the energy gap between HOMO and LUMO indorse its reactivity. Lowest value of Delta E suggests highest reactivity.[11b] In current study we found that E_{HOMO} values of BPPP, HCM and CM are −7.14 eV, −6.50 eV and −6.56 eV respectively. E_{HOMO} values of HCM and CM are analogous hence they have equal probability of co-ordination with metal while lowest E_{HOMO} value of BPPP makes it least accessible candidate for co-ordination. Considering the HOMO-LUMO energy gap (delta E) CM needs 4.61 eV while HCM need 6.00 eV energy for transferring electrons to LUMO. The smaller HOMO-LUMO gap suggests that CM has higher reactivity slightly better chance of co-ordination and can reduce palladium efficiently than HCM (Figure 2).

Further, on approaching to the synthesis of isoquinolones, the researchers across the globe investigated the diverse routes for their synthesis mainly under homogeneous catalytic condition.[12] (Scheme. 1, eq. 1). Although these catalytic systems are more efficient and afford good yields, the issues such as metal contamination in final product, use of expensive ligands, and catalyst recovery after reaction are still unresolved. In this context, as a second part of our investigation, we have successfully employed biogenically synthesized Pd@CNTs catalyst to access isoquinolones *via* C–H and N–H[13] bonds double activation of N-alkoxy benzamide under external ligand-free condition (Scheme 1, eq. 2).

Our initial examination was commenced by taking N-methoxybenzamide 1a (0.55 mmol) and diarylalkyne 2a (0.6 mmol) as model substrates in reaction with Pd@CNTs catalyst (10 mol%), KI (1.5 equiv.) in DMF at 60 °C. The development of new compound under open air atmosphere was

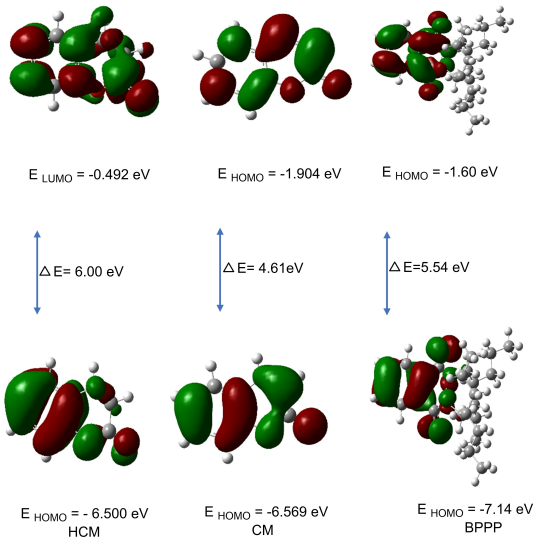
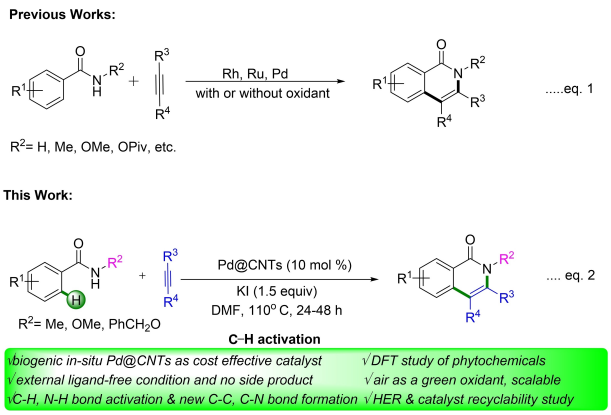


Figure 2. HOMO and LUMO orbital diagram of Phytochemicals extracted from *Gliricidia sepium* leaves.



Scheme 1. Synthesis of isoquinolones from benzamides and alkynes.

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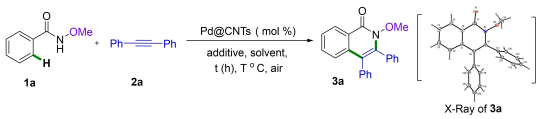
detected (monitored by TLC) and followed by the isolation by column chromatography. The 1H and 13 C-NMR indicates the formation of expected annulation product 3a (in 30% yield with recovery of 45% starting material) occurs mainly through ortho C–H and N–H bond activation of N-methoxy benzamide (Table 1, entry 1). Next, increase in temperature improves the yield (entry 2), While at elevated temperature product 3a obtained in 93% even at shorter reaction time (entry 3). The structure of compound 3a is unambiguously assigned using X-ray crystallographic analysis confirming double C–H and N–H bond activation. Further, increase in temperature resulted in lowering yield might be due to the decomposition of 3a at higher temperature (see SI for more details). The excess of KI (2.0 equiv) gave comparable yield (entry 4) while decreased amount of KI (1.0 equiv) diminish the reaction efficiency (entry 5). Later, use of NaI and KBr as an additive does not improve the yield (entries 6–7). The additives other than KI such as I_2, TBAI, NIS and KF gave lower to no yields (See the SI). While reaction in the absence of KI failed to give desired annulated product 3a indicating role of KI as a reaction promoter (entry 8). Next, change in solvent to THF furnished poor yield (entry 9), while other solvents such as acetonitrile, toluene, DCE, 1,4-dioxane, 2-methyl-THF and PEG are ineffective (See supporting information for details). Following, the reaction using excess of 2a (1.5 equiv) does not improve the yield (entry 10). While, varying a reaction time did not give satisfactory results (See SI for more details). Further, decrease in the catalyst mol% diminish the reaction productivity (entry 11). Whereas reaction outcome is unchanged even at higher catalyst loading (see SI). At last, in the absence of Pd@CNTs reaction failed to give desired annulated product 3a (entry 12) indicating the necessity of palladium catalyst to facilitate C–H and N–H activation/ annulation reaction.

Table 1. Optimization of reaction condition.[a]



S. N	Additive (equiv)	Solvent	T (°C)/t (h)	Yield **3a** (%)[b]
1	KI (1.5)	DMF	60/30	30
2	KI (1.5)	DMF	80/30	55
3	**KI (1.5)**	**DMF**	**110/24**	**93**
4	KI (2.0)	DMF	110/24	94
5	KI (1.0)	DMF	110/24	78
6	NaI (1.5)	DMF	110/24	55
7	KBr (1.5)	DMF	110/24	35
8[c]	–	DMF	110/24	N.R.
9	KI (1.5)	THF	110/24	trace
10[d]	KI (1.5)	DMF	110/24	90
11[e]	KI (1.5)	DMF	110/24	75
12[f]	KI (1.5)	DMF	110/24	N.R.

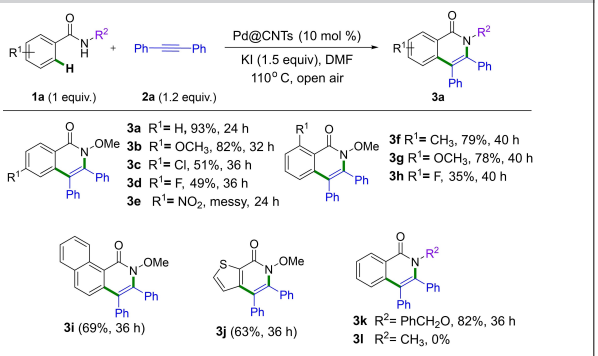
[a] Reaction condition: **1a** (0.5 mmol), **2a** (0.6 to 0.75 mmol), KI (0 to 2 equiv), Pd@CNTs (0–15 mol%, 42.82 w/w%), solvent, at 60–110 °C for 24–30 h, open air. [b] Yields are reported after purification with silica gel column chromatography (average of two runs). [c] Reaction without KI. [d] 1.5 equiv. of **2a** was used. [e] 5 mol% catalyst was used. [f] Reaction without catalyst.

With the optimized reaction condition, we further explored the scope of various substituted benzamides with 2a (Table 2). A series of benzamides bearing electron donating group 4-methoxy and electron withdrawing 4-chloro, 4-fluoro underwent annulations successfully to produce diphenylisoquinolin (2H)-one in good efficiencies (**3b**–**3d**) whereas inseparable mixtures of products obtained with 4-nitro substituted benzamide (**3e**). Nevertheless, benzamides with ortho-substitution on phenyl ring had no adverse effect on reaction outcome and afforded various diphenylisoquinolin (2H)-one in good yields with election donating substituents and comparatively low yield with electron withdrawing substituents albeit of longer reaction time (**3f**–**3h**).

Interestingly, *N*-methoxy-2-naphthamide and *N*-methoxythiophene-3-carboxamide shows promising reactivity delivering desired product **3i** and **3j** respectively in good yield. Delightfully, replacing methoxy group of benzamide to benzyloxy group gives desired product (**3k**) in 82% yield, while methyl substitution unable to furnish desired product presumably due to poor electron donating ability when compared to methoxy group.

Later, the scope of the annulation reaction with various substituted alkynes were tested (Table 3). The symmetrical diary alkynes with electron donating 4-methyl, 4-methoxy and electron withdrawing 4-fluoro, 4-chloro furnished desired product (**3m**–**3p**) in good to excellent yield. In the similar line, electronically biased symmetrical diary alkynes are also tolerated and furnishing desired product in good yields (**3q**). However, reaction of 1-nitro-4-(phenylethynyl)benzene and 1-methyl-4-(phenylethynyl)benzene with **1a**, furnishes regioisomeric mixture (1:1) with combined yield of 90% and 80% for **3r** and **3s** respectively. We have also tested the reactivity of diaryldiacetylene with 1a furnishes a regioisomeric mixture **3t** in 90% yield. Furthermore, replacing the diarylalkynes with diethyl but-2-ynedioate also underwent annulation to form an annulated product surprisingly with the cleavage of methoxy group during the course of reaction (**3u**). At last, we have also made an attempt to access double annulation product (**3v**) by

Table 2. Substrate scope with benzamides.



[a] Reaction condition: **1a** (0.5 mmol), **2a** (0.6 mmol), KI (1.5 equiv), Pd@CNTs (10 mol%, 42.82 w/w%), DMF, at 110 °C for 24–40 h open air atmosphere. [b] yields are reported after purification from silica gel column chromatography (average of two runs).

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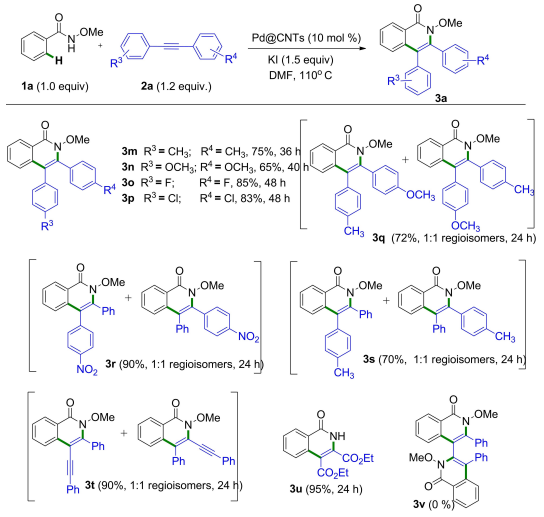
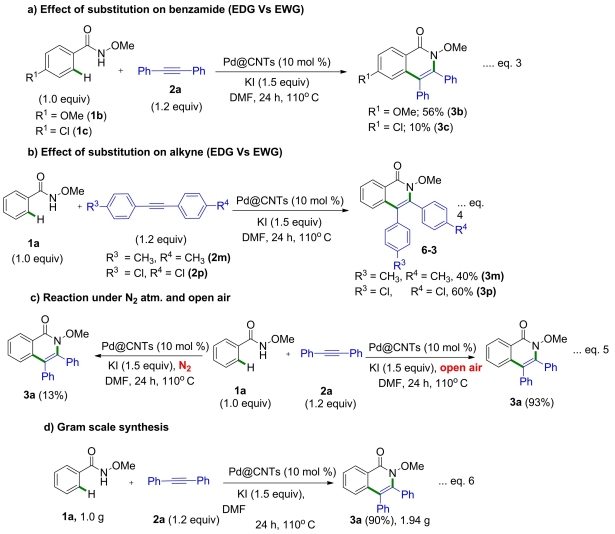
Table 3. Substrate scope with alkynes.



[a] Reaction condition: **1 a** (0.5 mmol), **2 a** (0.6 mmol), KI (1.5 equiv), Pd@CNTs (10 mol%, 42.82 w/w%), DMF, at 110 °C open air, for 24–48 h. [b] yields are reported after purification from silica gel column chromatography (average of two runs).



Scheme 2. Control experiment and gram scale reaction.

subjecting 2a (1.0 equiv) with excess of 1a (2.2 equiv). Unfortunately, desired product not obtained under standard condition mainly due to the possible steric crowding at reaction centre.

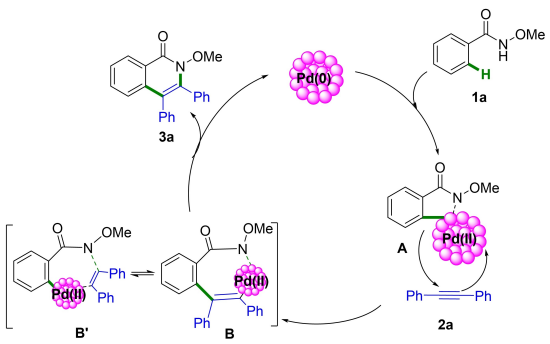
Remarkably, the catalyst recyclability of Pd@CNTs was performed up to five rounds with marginal decrease in the reaction productivity for each following cycles (See SI for graph). Additionally, the hot filtration test was performed under the standard reaction condition indicates that, reaction proceeds only in presence of catalyst and no leaching of Pd@CNTs in reaction mixture was observed (See SI for details). Further, Hg poisoning experiment was performed to confirm the role of Pd@CNTs to accelerate the reaction of *N*-methoxybenzamides and diarylalkynes not by the leached Pd (See SI for details).

The competition experiments[6] are performed to test the reactivity of benzamides bearing 4-methoxy and 4-chloro substituent with **2 a** under standard condition. The formation of **3 b** (56%) and **3 c** (10%) indicates that, annulation reaction proceeds faster with benzamides bearing electron donating substituent than electron withdrawing substituent (Scheme 2a, eq. 3). Similarly, reactivity of diarylalkynes bearing electronically biased substituents were tested wherein electron withdrawing 4-chloro substituent is more reactive than analogous 4-methyl substituent (Scheme 2b, eq. 4). Next, reaction of benzamides with diarylalkynes under N_2 atmosphere produces only 13% desired product [Scheme 2c, (eq. 5 left)] while under open air condition [Scheme 2c, (eq. 5 right)] produces 93% yield indicates involvement of air as an external oxidant source. Nevertheless, our protocol for synthesis of isoquinolones was effectively scaled up and final product is obtained simply by washing with solvent without affecting the chemical yield [Scheme 2d, (eq. 6)].

On the basis of literature precedents,[6b,14,15] a plausible mechanism is proposed in Scheme 3. At first, Pd (0) mediated ortho C–H[14] bond and N–H[13] bond cleavage occurs to form a five-membered palladacycle A followed by co-ordination of diarylalkynes leading to formation of seven membered palladacycle B/B′. Finally, the reductive elimination furnishes the 3a with the regeneration of active Pd (0) for the next catalytic cycle.

Electrocatalytic Hydrogen Evolution Reaction of Pd@CNTs

To demonstrate the multi-functional nature of Pd@CNTs catalyst we performed hydrogen evolution reaction (HER) in 0.5 M H_2SO_4 electrolyte at room temperature using a conventional three electrode set up. Linear sweep voltammetry (LSV) was implemented to study the water splitting reaction of the Pd@CNTs catalyst. The LSV polarization curves of current density *vs* applied potential for Pd@CNTs catalyst along with a comparison of HER activity of CNTs, functionalized CNTs and Pd nanoparticles is shown in Figure 3a. The functionalized CNTs and pristine CNTs exhibits low activity towards water splitting



Scheme 3. Plausible mechanism.

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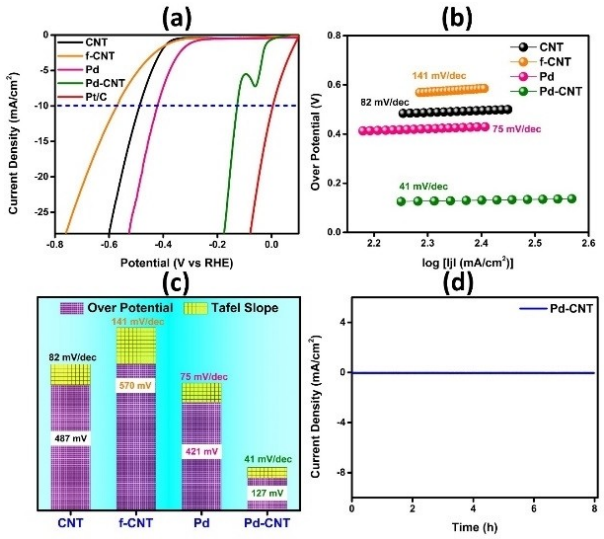

Figure 3. (a) LSV polarization curves at a scan rate of 5 mV/s, (b) Tafel plot, (c) comparative over potential and Tafel slopes and (d) Stability of the Pd@CNTs catalyst at a constant over potential

while the Pd@CNTs catalyst exhibits excellent HER activity. Apparently, the noble metal-based Pt/C electrode shows the highest HER activity with an over potential (η) very close to zero. For practical applications we are calculating the over potential of all the electrodes at current density of 10 mA/cm^2. The Pd@CNTs catalyst showed an over potential of 127 mV at 10 mA/cm^2 which is lower than all the other samples presented in this study. The Tafel slope is an important parameter to understand the kinetics of water splitting reactions of any electrode. The Tafel slope can be obtained by resolving the Tafel equation (eq. 7),

$$\eta = a + b \; X \log (J) \tag{7}$$

where η is the over potential, j is the current density, b is the Tafel slope and a is the constant. Tafel plot of Pd@CNTs catalyst along with other samples are provided in Figure 3b.

The Pd@CNTs catalyst has showed the lowest Tafel slope of 41 mV/dec in the bunch. The reduced Tafel slope signifies the enhanced hydrogen evolution rate of the catalyst. The comparative over potential and Tafel slope values of CNTs, functionalized CNTs, Pd nanoparticles and Pd@CNTs are provided in Figure 3c (See SI for Plausible HER reactions). Further, to understand the kinetics of the HER activity electrochemical impedance spectroscopy was implemented. The diameter of the semi-circular region in the Nyquist plot represents the charge transfer resistance (R_{ct}) of the electrode which signifies the reaction kinetics at the electrode/electrolyte interface (for Nyquist plots of CNTs, functionalized CNTs, Pd nanoparticles and Pd@CNTs See SI). The R_{ct} values for CNTs, functionalized CNTs, Pd nanoparticles and Pd-CNTs are 8.8 Ω, 10 Ω, 4.2 Ω and 2.9 Ω respectively. The small R_{ct} value underlines the excellent electrocatalytic activity of Pd@CNTs catalyst. The electrochemical durability of the catalyst is an important parameter for practical applications. Figure 3d represents the stability plot of the Pd@CNTs catalyst at a constant over potential for 8 h. The catalyst showed excellent durability and the long-term stability study. The superior electrocatalytic performance of our catalyst is compared with recent literature (See the SI).

The Pd@CNTs catalyst has more active sites for electrochemical reactions than that of other samples studied here. The highly conductive CNTs provides fast channels for ionic/electronic transfer. The high surface area of CNTs can accommodate more metal nano particles on its surface. The Pd nanoparticles decorated on these CNTs have comparable HER activity by itself. In the Pd@CNTs hybrid the grafted Pd nanoparticles on highly conductive CNTs provide interconnected networks of Pd@CNTs all over the sample which creates rich active sites for the catalytic activity.[16] On the top the CNTs support also reduces the aggregation of Pd nanoparticles.[17] The presence of CNTs reduces the volume expansion of the nanoparticles which could help catalyst for its durability. Consequently, the hybrid system has the advantage of both CNTs and the Pd nanoparticles. The synergy of their individual properties constitutes the excellent HER activity of the Pd@CNTs catalyst. With excellent values in all electrochemical parameters implemented here, the Pd@CNTs is a promising candidate for HER catalytic study.

Conclusions

In summary, we have successfully established a biogenic synthesis route using *Gliricidia sepium* leaves extract for in-situ preparation of palladium nanoparticles decorated on carbon nanotubes (Pd@CNTs) and characterised by various spectroscopic techniques. The phytochemicals present in *Gliricidia sepium* leaves extract were analysed through GC-MS analysis and subsequently studied by DFT analysis. Further, catalytic potential of Pd@CNTs was investigated by developing an external ligand-free synthesis of isoquinolones *via* directing group assisted C–H and N–H activation under open air condition. The gram scale reaction and catalyst recyclability study were depicted. The HER study was performed wherein, Pd@CNTs catalyst showed excellent activity in acidic media showcasing the multi-functional performance of catalyst. Nevertheless, catalyst required only a potential of 127 mV to attain the current density of 10 mA/cm^2 with a Tafel slope of 41 mV/dec. The synergistic effect of both CNTs and the Pd nanoparticles produces a promising HER catalyst in Pd@CNTs. Further application of catalyst in terms of material and synthetic chemistry perspectives are still ongoing in our laboratory.

Experimental Section

Materials, instrumentation and characterization of catalyst (Pd@CNTs) are included in supporting information in detail.

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Synthesis of Pd@CNTs using Gliricidia sepium leaf (GSL) extract

Preparation of (Gliricidia sepium leaf) GSL extract

Gliricidia sepium Leaves were accumulated from the resident area of Sirsi, Uttara Kannada, India and washed thoroughly using deionised water, air dried and chopped with the help of scissor. After that, 10 g of dried leaves were added to a 250 mL conical flask with 150 mL of solvent (H_2O). To extract the phytochemicals present in the mixture, the mixture was heated to 80 °C for one hour (Figure 4). *Gliricidia sepium* leaves and then was cooled, followed by centrifugation, filtered and kept at 4 °C for further use.

Preparation of Pd@CNTs using GSL extract

1 g of Multiwall Carbon Nanotubes (MWCNTs) is added directly to 100 mL of GSL extract in a 250 mL round bottom flask. In a separate 100 mL round bottom flask, 0.5 g of Pd(OAc)2 is added to 50 mL of DI water. Both flasks were sonicated for 10 minutes. Further, the solution of $Pd(OAc)_2$ is added to the flask containing MWCNTs in *GSL* extract under constant stirring at 80 °C. The heating is continued overnight (16 h) in order to get Pd-NPs decorated MWCNTs i.e. Pd@CNTs. By examining the reaction mixture's UV-visible spectral data, which showed the synthesis of Pd@CNTs, it was determined that Pd(II) had been completely reduced. The reaction n mixture at this point cooled to ambient temperature, and afresh generated Pd@CNTs was accumulated by centrifugation at 3000 rpm for 10 min. Followed by washing with acetone and deionised water, it is then dried out at 80 °C for eight hours and examined using different spectroscopic methods (Figure 5). (Note: MWCNTs are treated with conc. HNO_3 in reflux (140 °C) condition for 16 h in order to functionalize and break the long CNTs).

General experimental procedure for synthesis of isoquinolones

In an dried, sealed 15 mL tube with compounds 1a (0.5 mmol, 1 equiv.), and 2a (0–1.5 equiv), the Pd@CNTs (0-15 mol%, Pd content: 42.82 w/w%) was added. The additive (0–2.0 equiv) and solvent (1–2 mL) were then added to the tube in an environment of air. The mixture was stirred at 60–110 °C for 18–40 h, After completion of starting material (monitored by TLC), the mixture was quenched with brine solution and the organic layer was separated with EtOAc (10×3) the collective organic layer was dried over anhydrous Na_2SO_4 followed by solvent evaporation by vacuum and crude mixture was isolated by column chromatography (eluent: 5–25 % EA/Hexane) to obtain the product **3 a**. The repeatability of reaction was determined twice and product was isolated to quantify the yield (by average of two runs).

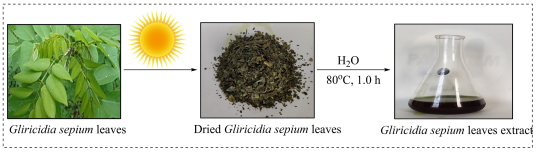

Figure 4. Preparation of *Gliricidia sepium* leaf extract.

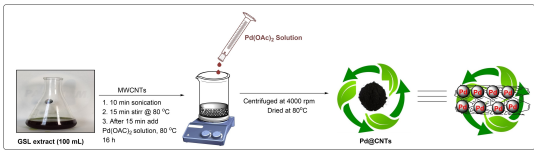

Figure 5. Preparation of Pd@CNTs using *Gliricidia sepium* leaves extract.

X-Ray Crystallographic data

Deposition Number 2193455 (for **3 a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Supporting Information Summary

The supporting information includes all the characterization of both synthesised catalyst and all the substrates (**3 a**–**3 v**) and crystallographic data of compound **3 a**.

Acknowledgements

Author thanks to, DST-SERB, Government of India, for the financial support through the research grant: File Nos. SB/S2/RJN-042/2017 and ECR/2017/002207. Author also thanks to Jain University, India, for financial support. Author also thanks to Jain University Minor Research Project Grant (Ref. JU/MRP/CNMS/17/2022), for financial support.

Conflict of Interests

"There are no conflicts to declare".

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Benzamides · Biogenic synthesis · C–H Activation · DFT Study · HER study

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Submitted: February 21, 2023
Accepted: May 30, 2023

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