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ARTICLE TYPE

Polystyrene resin supported palladium(0) (Pd@PR) nanocomposite catalyzed synthesis of β -aryl and β,β -diaryl unsaturated scaffolds following tandem approaches[†]Arun K. Shil^{a,b} and Pralay Das^{*a,b}⁵ Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

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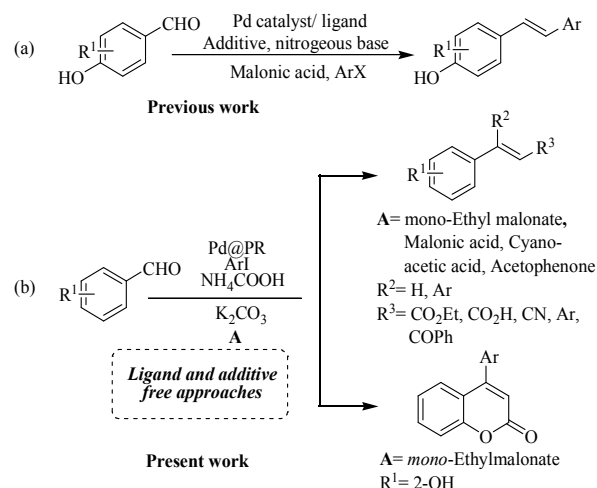
An one pot general tandem procedure is described for β -aryl and β,β -diaryl alkenes synthesis following an alternative to the classical approaches by using aryl aldehyde as one of the starting materials. The developed polystyrene resin supported palladium(0) (Pd@PR) nanocomposite has been applied in an unprecedented sequential condensation-decarboxylation-Heck (CDH) and condensation-Heck (CH) strategies to generate the substituted alkenes ($C_6(C_6)C=C-C$, $C_6-C=C-C_6$, and $C_6(C_6)C=C-CO-C_6$ units) under ligand, and additive free milder basic reaction conditions. The added momentous benefit over the classical methodologies is in terms of its multi-component approach to achieve the desired products without tedious step wise purifications.

1. Introduction

In recent era, β -aryl or β,β -diaryl unsaturated compounds such as cinnamates,¹ stilbenoids,² chalcones³ and neoflavonoids⁴ have attracted huge attention due to their extremely privileged biological profile and natural abundance. The conventional synthetic procedures of these compounds consist of acid or base catalyzed condensation,^{5a,b} Wittig reaction^{5c} and Lewis acid mediated cyclization^{5d} with tedious work up, and step wise purifications. To surmount the limitations, the introduction of tandem or one pot sequential strategy is virtually more beneficial and has been shown significant interest in the area of contemporary organic synthesis especially methodology development^{5e,f} and target oriented synthesis. In recent years, the transition metal catalyzed tandem processes have been highly nourished due to its minimal atom wastage, economic feasibility and efficiency.⁶ In this respect heterogeneous palladium(0) nanocomposite catalyzed domino-Heck approach might be an attractive alternative to furnish the valuable alkene scaffolds. Although the employment of transition metal nanocomposite as heterogeneous catalyst in such reactions is a challenging task mainly due to catalytic stability, reactivity and by-product prone side reactions in a variety of combined substrate/ reagent conditions.⁷

Synthesis of β,β -diarylalkenes through double Heck coupling is much difficult owing to the presence of less reactive β -hydrogen in 1,2-disubstituted olefin. Often palladium-phosphine and carbene complexes have shown good results, but unfortunately

they are expensive, required additives and inert reaction conditions.⁸ Recently, a one pot CDH sequence has been attempted for the synthesis of 4-hydroxy stilbenes under the additive and homogeneous palladium-phosphine complex catalyzed condition.⁹ In this report authors took electro-labile 4-hydroxy aromatic aldehyde as starting material which enabled an easy decarboxylation of the intermediate condensate. The choice of the substrate has greatly restricted the wider scope of this process. Moreover, use of much higher equivalents of active methylene component (14 equiv. malonic acid) and secondary nitrogenous base (15 equiv. piperidine) which might have participated in by-product formation, have limited the outreach of the methodology. But still design based one pot condensative approaches for Pd-catalyzed β -arylation starting from



Scheme 1. a) Previously reported method for the synthesis of 4-hydroxystilbenoids utilizing CDH strategy; b) Present work

arylaldehyde remains untouched. To counteract the existing problems there is an intense urge to develop an efficient and facile single pot strategy for the synthesis of functionalized β -aryl or β,β -diaryl alkenes.

In this context herein, we describe ligand free Pd@PR nanocomposite (formerly reported as SS-Pd, prepared from commercially available Amberlite IRA 900 resin (chloride form))¹⁰ catalyzed expeditious one pot sequential CDH and CH approaches using aromatic aldehyde, methylene compound and

aryl halide to cinnamate, stilbene, chalcone and neoflavonoid synthesis.

2. Results and Discussion

The Pd@PR nanocomposite was prepared following our earlier reports (supporting information) through *in situ* reduction-deposition strategy using palladium(II) salt as Pd precursor.^{10a} The heterogeneous Pd@PR nanocomposite was morphologically characterized by transmission electron microscopy (TEM) analysis before its application (Fig. 2). Inspired by our recent results,^{10,11} we applied Pd@PR catalyst for one pot sequential

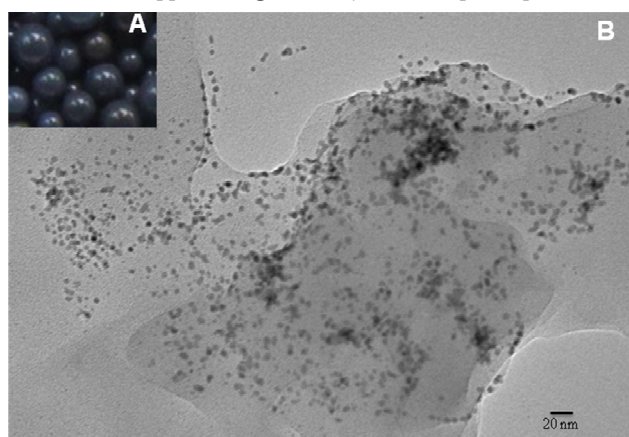
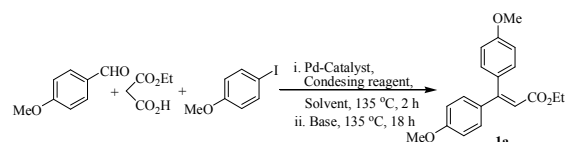


Figure 2. A) Image of Pd@PR catalyst; B) Transmission electron microscopy image of Pd@PR catalyst

Table 1 Optimization of the reaction condition for CDH reaction

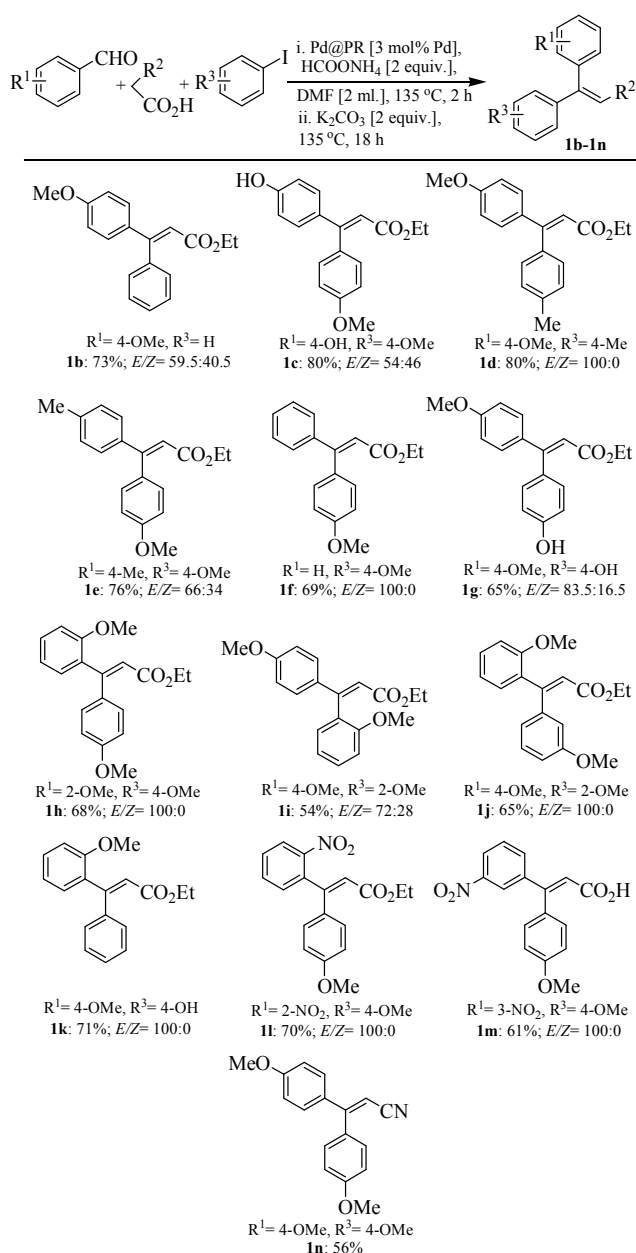


Entry	Condensing reagent [equiv.]	Pd Catalyst [mol% of Pd]	Base [equiv.]	Solvent	1a % Yield ^a
1	NH ₄ OAc [2]	Pd@PR [3]	K ₂ CO ₃ [2]	DMF	47
2	NH ₄ OOCH [1]	Pd@PR [3]	K ₂ CO ₃ [2]	DMF	66
3 ^c	NH ₄ OOCH [1]	Pd@PR [3]	K ₂ CO ₃ [2]	DMF	trace, 39 ^b
4	NH ₄ OOCH [1]	Pd@PR [4]	K ₂ CO ₃ [3]	DMF	68
5	K ₂ CO ₃ [3]	Pd@PR [3]	—	DMF	trace, 42 ^b
6	KOOCH [2]	Pd@PR [3]	K ₂ CO ₃ [2]	DMF	trace, 31 ^b
7	Et ₃ N [2]	Pd@PR [2]	K ₂ CO ₃ [2]	DMF	trace, 37 ^b
8	NH ₄ OOCH [2]	Pd@PR [2]	K ₂ CO ₃ [2]	DMF	60
9	NH ₄ OOCH [2]	Pd@PR [3]	K ₂ CO ₃ [2]	DMF	72
10	NH ₄ OOCH [2]	Pd@PR [3]	K ₂ CO ₃ [2]	Dioxane	52
11	NH ₄ OOCH [2]	Pd@PR [3]	K ₂ CO ₃ [2]	Toluene	53
12	NH ₄ OOCH [2]	Pd@PR [4]	K ₂ CO ₃ [2]	PEG-400	46
13	NH ₄ OOCH [2]	Pd(OAc) ₂ [3]	K ₂ CO ₃ [2]	DMF	30
14	NH ₄ OOCH [2]	Pd(allyl) ₂ Cl ₂ [3]	K ₂ CO ₃ [2]	DMF	37
15	NH ₄ OOCH [2]	Pd ₂ dba ₃ [3]	K ₂ CO ₃ [2]	DMF	41

^a Yields of isolated products; Reaction condition: A mixture of substrates (4-methoxybenzaldehyde (150 mg), monoethyl malonate (1.2 equiv.) and 4-iodoanisole (1.2 equiv.)) and palladium catalyst were magnetically stirred at 135 °C in presence of condensing agent for 2 hours and then base was added into the reaction mixture; ^b Yield of isolated by-product, 4,4'-dimethoxybiphenyl; ^c Both NH₄OOCH (1 equiv.) and K₂CO₃ (2 equiv.) were added simultaneously into the reaction mixture.

three component reactions for the synthesis of diaryl substituted olefin scaffolds following CDH and CH strategies. To select the best reagents and condition several optimization studies were performed to achieve the highest yield of the products (Table 1). 4-Methoxybenzaldehyde (150 mg), monoethyl malonate (1.2 equiv.), 4-iodoanisole (1.2 equiv.), Pd@PR (3 mol% Pd), and NH₄OOCH (1 equiv.) followed by K₂CO₃ (2 equiv.) in DMF at 135 °C was found to be the optimum condition to give **1a** in 72% yield (Table 1, entry 9). Considering other reagents

Table 2 Pd@PR nanocomposite catalyzed tandem synthesis of β,β -diarylacryl derivatives^a

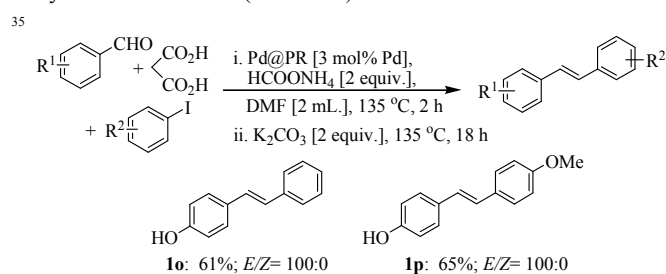


^a All are isolated yields; Reaction conditions: Aryl aldehyde (150 mg), active methylene carboxylic acid (1.2 equiv.), aryl iodide (1.2 eq.), Pd@PR (3 mol% Pd), NH₄OOCH (2 equiv.), K₂CO₃ (2 equiv.), DMF (2 ml), 135 °C, the reaction was continued for 2 h before addition of K₂CO₃ followed by 18 h; E/Z ratio was determined by ¹H NMR spectra.

(specially NH_4OAc), NH_4OOCH was found to be performing dual roles for facile condensation-decarboxylation reaction and as a reducing agent to facilitate conversion of $\text{Pd}(\text{II})$ to $\text{Pd}(0)$, and *in situ* repairing/ regeneration of Pd@PR catalyst which further confirmed by ICP-AES analysis (overall Pd leaching 0.14 ppm after three cycles, supporting information).

The optimized condition was further applied to investigate the broader substrates scope as outlined in Table 2. Under the standard reaction condition, both aryl aldehydes and aryl iodides containing electron releasing substituents ($-\text{OMe}$, $-\text{OH}$ and $-\text{Me}$) participated in CDH sequence to afford corresponding β -aryl ethylcinnamates ($\text{C}_6(\text{C}_6)\text{C}=\text{C}-\text{C}$ unit) (**1b-g**) in good to moderate yields. No significant effect of steric hindrance was observed for 2-OMe substituted aryl aldehydes or iodides for the same reaction and gave corresponding CDH products **1h-1k** in good yields. More challenging electron withdrawing 2- NO_2 and 3- NO_2 substituted benzaldehydes were smoothly reacted with both mono ethyl malonate and malonic acid respectively in combination with 4-iodoanisole to furnish **1l** and **1m** in moderate yields. Similarly, 3,3-bis(4-methoxyphenyl)acrylonitrile **1n** was obtained in 56% when 4-anisaldehyde was treated with cyanoacetic acid and 4-iodoanisole under the same reaction condition. Most of the products in Table 2 were found to be 100% *E* configuration (confirmed by NMR studies and the reason might be the *E*-configured dehydro-decarboxylation (**I**) as described in mechanism section).

In continuation, we applied the set tandem protocol for the synthesis of hydroxystilbenes which are among the most privileged scaffolds owing to their diversified biological and unrivalled physicochemical activities. The cascade Knoevenagel condensation-double decarboxylation-Heck process resulted hydroxy stilbene derivatives (**1o** and **1p**) in 61% and 65% yields (*E/Z* = 100:0) respectively through the formation of corresponding styrene intermediates (Scheme 2).

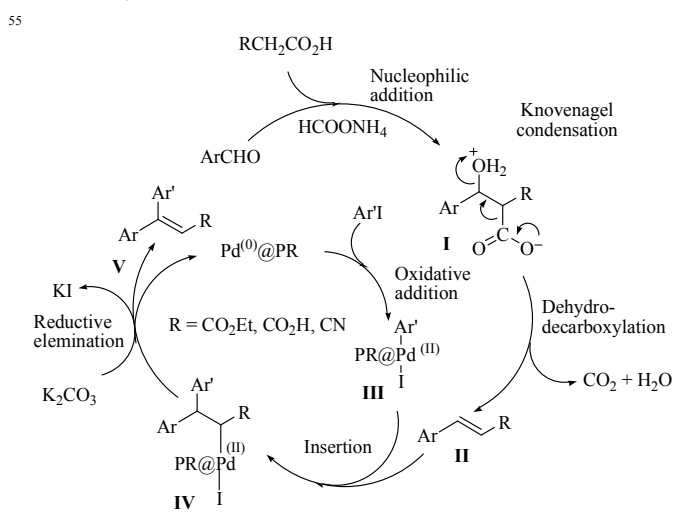


Scheme 2. Pd@PR nanocomposite catalyzed tandem synthesis of hydroxy stilbenoids (*E/Z* ratio determined by ^1H NMR spectra)

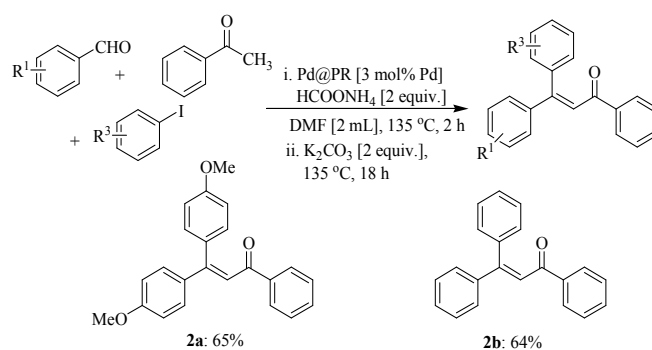
Mechanistically it was presumed that the aromatic aldehyde first undergoes Knoevenagel condensation with α -carboxy active methylene component leading to the formation of most favourable *E*-configuration of the cinnamyl intermediate (**II**) after dehydro-decarboxylation of (**I**). The intermediate (**II**) is then coupled with aryl iodide in presence of Pd@PR catalyst through the oxidative addition, insertion and reductive elimination steps, to afford the desired β,β -diaryl alkene (**V**) (Scheme 3).

To our great interest, the set reaction condition was further extended for one pot tandem approach synthesis of β -arylchalconoids ($\text{C}_6(\text{C}_6)-\text{C}=\text{C}-\text{CO}-\text{C}_6$ unit) (Scheme 4) and neoflavonoids ($\text{C}_6(\text{C}_6)-\text{C}=\text{C}-\text{C}$ unit) (Scheme 5). The sequential

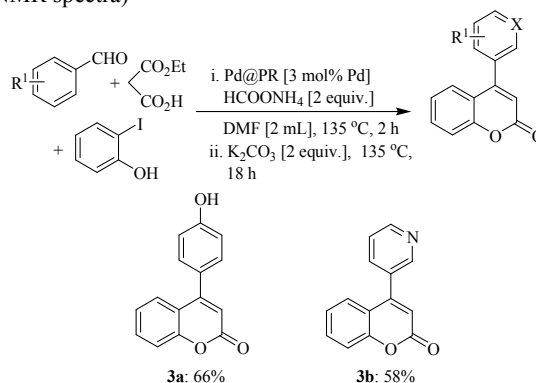
Aldol condensation of acetophenone with aromatic aldehydes and Heck reaction afforded the desired β -aryl chalcones **2a** and **2b** in moderate yields (Scheme 4).



Scheme 3. Plausible mechanistic pathway for the one pot synthesis of β,β -diaryl alkenes



Scheme 4. Pd@PR nanocomposite catalyzed tandem synthesis of β -aryl chalcones following CH approach (*E/Z* ratio determined by ^1H NMR spectra)



Scheme 5. Pd@PR nanocomposite catalyzed tandem synthesis of neoflavonoids following CDH approach

Whereas, the palladium catalyzed Heck arylation at β -position of *in situ* produced ethyl cinnamate intermediate with 2-iodophenol followed by cyclization gave neoflavonoids **3a** and **3b** in comparable yields (Scheme 5).

3. Conclusions

In summary, we have developed Pd@PR nanocomposite catalyzed proficient multicomponent strategies for the synthesis of β -aryl cinnamates, stilbenes, chalcones and neoflavonoids. The additive free one pot sequential process for the synthesis of β -aryl substituted alkene derivatives employing combined substrate/reagent compatible heterogeneous palladium nanocatalyst have imparted its potential future practical utility. In addition, we have explored the dual roles of NH_4OOCH which governs the efficiency of condensation and stabilization of palladium(0) nanoparticles over the solid surface. Overall, the developed methodology comprises of the application of heterogeneous transition metal catalyst in multicomponent reactions, additive and ligand free process, and catalyst recyclability.

4. Experimental Section

General experimental procedure for one pot sequential condensation-decarboxylation-Heck (CDH) approach: To a mixture of arylaldehyde (150 mg), aryl iodide (1.2 equiv.), active methylene carboxylic acid (1.2 equiv.), ammonium formate (1.5 equiv.) and Pd@PR (3 mol% Pd) in 40 mL reaction vial was added 2 mL of dry DMF. The reaction mixture was stirred in preheated silicone oil bath at 135 °C for 2 hours and then K_2CO_3 (2 equiv.) was added into it. After addition of K_2CO_3 the reaction was again continued at the same temperature. The progress of the reaction was monitored by TLC. On completion, the cooled reaction mixture was extracted with ethyl acetate (3×5 mL) by addition of 2 mL of water and dried over anhydrous Na_2SO_4 . Evaporation of the combined organic layer followed by column chromatography (Hexane and ethyl acetate gradient) over silica gel (mesh 60-200) afforded the desired products (**1a-1p**).

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† Electronic Supplementary Information (ESI) available: [Typical experimental procedures, recyclability experiment, Hg poisoning experiment, spectral data and copies of ^1H , ^{13}C NMR and ESIMS spectra of synthesised products]. See DOI: 10.1039/b000000x/
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