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ARTICLE

Supported Palladium Nanoparticles-Catalyzed Decarboxylative Coupling Approaches for Aryl Alkynes, Indoles and Pyrrolines Synthesis

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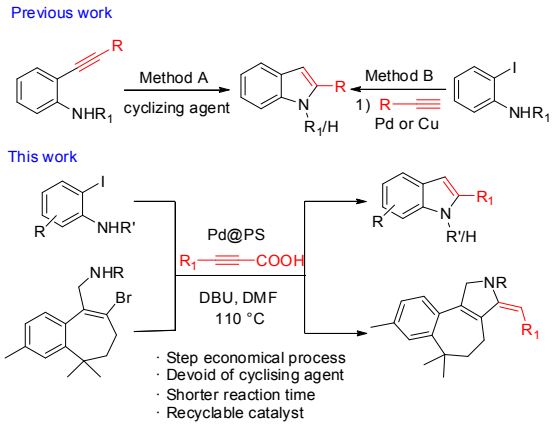
Polystyrene supported palladium (Pd@PS) nanoparticles (NPs) catalyzed decarboxylative coupling (DC) of arylhalides and alkynyl carboxylic acids was developed for diaryl alkynes synthesis. Indole and 3-pyrroline heterocycles were also synthesized from 2-iodo anilines/ amino benzocycloheptene bromide and alkynyl carboxylic acids following a domino decarboxylative coupling-cyclization (DCC) approaches under the same catalytic condition. The combined anchoring and catalytic behaviour of Pd@PS makes the process favourable for the product formation.

Introduction

The decarboxylative couplings of alkynyl carboxylic acids have been identified as a viable tool for C-C, C-heteroatom bond formation processes.[1]Alkynyl carboxylic acids have emerged as coupling partners in Sonogashira type reactions for the synthesis of pharmaceutically potent[2]diaryl motif rather than terminal alkynes due to easy handling, high boiling point, and high stablility.[3] Since the development of first Pd_2dba_3/dppf[4a] catalytic system for decarboxylative coupling of alkynyl carboxylic acids with aryl halides, a number of protocols using palladium complexes[4b-4i] (Pd_2dba_3/dppb, $Pd_2dba_3CHCl_3$/PPh_3 or Xantphos, $Pd(OAc)_2$/XPhos, $Pd(PPh_3)_2Cl_2$/dppb, Palladacycle/Xphos, etc.) and copper[5] (CuI/1,10-Phen, CuI/PPh_3 and CuI/$Fe(acac)_3$) catalyst were developed. The only heterogeneous catalyst reported for decarboxylativeSonogashira coupling is Pd-CNT (carbon nano tube).[4g] Although, decarboxylativeSonogashira coupling reactions under homogeneous catalytic condition are well documented but less attention has been paid to apply the decarboxylative coupling strategy for the synthesis of functionalized indoles and 3-pyrrolines, an important scaffold of natural and pharmaceutical products.[6] Reported protocols to access 2-substituted indoles includes, i) cycloisomerization of 2-alkynyl anilines using transition metal catalysts, lewis acids, and strong bases (Scheme 1, Method A)[7] and ii) domino coupling-cyclization of protected 2-haloanilines and terminal alkynes under copper- and palladium catalyzed conditions (Scheme 1, Method B).[8] Moreover 3-pyrrolines can be afforded by 5-endo cyclization of α-amino allenes prompted by transition metal catalysts and base.[9] In addition few multi-component reactions were also demonstrated by using copper- and organo-catalytic conditions.[9e,9f] Most of the reported methods for the synthesis of indoles and 3-pyrrolines either performed in homogeneous catalytic condition or required additional cyclizing agents. Recently the domino decarboxylative coupling-cyclization has been reported for the synthesis of substituted indoles was performed in CuBr/L-Proline catalytic system which is only applicable for 2-iodotrifluoro acetanilide substates.[10]



Scheme 1. Background of the reaction

Therefore, the development of heterogeneous palladium catalyzed novel and reliable decarboxylative coupling strategy for the synthesis of di-aryl alkynes and five member nitrogen heterocycles under ligand free conditions is highly desirable.

As a part of our continuous research on the development of supported transition metal nanoparticles as a catalyst and its applications in various organic transformations,[11] herein

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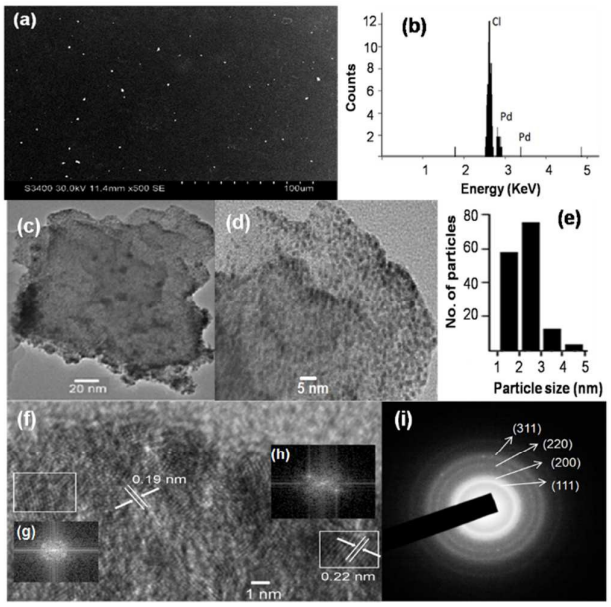


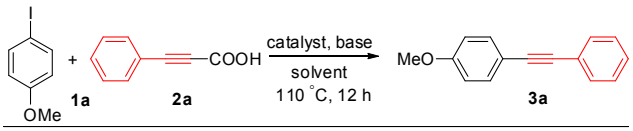
Fig 1. (a) SEM, (b) EDS, (c) TEM at 20 nm scale, (d) TEM at 5 nm scale, (e) Particle size distribution histrogram as calculated from (d), (f) HRTEM image showing lattice fringe spacing, (g), (h) FFT of selected region showing icosahydral and cubic structure of planes, (i) SAED diffraction pattern.

we present Pd@PS NPs catalyzed decarboxylative coupling for the synthesis of di-aryl alkynes and domino DCC to synthesize functionalized indoles. Further structurally similar antidepressant molecules,[12] amino benzocycloheptene vinyl bromides were also converted to corresponding new class of 3-pyrrolines by domino decarboxylative coupling-5-*exo* cyclization reaction with phenylpropiolic acid under the same catalytic conditions.

The Pd@PS NPs were prepared by following our earlier reported reduction deposition method (Electronic Supplementary Information ESI). The developed Pd@PS catalyst was further analyzed for its morphology and crystalline structure by scanning electron microscopy (SEM), transmission electron microscopy (TEM) and selected area electron diffraction (SAED) studies. The particles at surface were analyzed by SEM and SEM-EDS (energy dispersive spectra) that revealed the presence of palladium NPs at the surface of PS (Fig. 1a, 1b). The low field TEM image of Pd@PS further confirmed the impregnation of palladium NPs of size in between 1-5 nm with largest average number in range 1-3 nm (Fig. 1c-e). The high resolution TEM (HRTEM) image of Pd@PS showed interplanar distance of 0.22 nm corresponding to (111) plane and 0.19 nm corresponding to (200) planes of face centered cubic arrangement of palladium (Fig. 1f). The heterogeneity of Pd@PS catalyst was further confirmed by Hg(0) poisoning and hot filtration tests (Fig. 3) that revealed the catalysis took place in a truly heterogeneous manner as the negligible leaching of palladium was detected by ICP-AES analysis after the fifth reaction cycle (Fig. 2).

We started our investigation using 4-iodo anisole and phenyl propiolic acid as model substrates. Among different bases (Table 1, entries 1-6) and solvents (Table 1, entries 7-13) screened, DBU as base and DMF as solvent gave the best result. Gratifyingly, the Pd@PS catalyst was found more active than the commercially available Pd/C (Table 1, entries 14). The optimum condition was found to be: Pd@PS (3 mol%), DBU (3 equiv) in DMF at 110 °C for 12 h giving 78% of desired product. Under the optimized condition phenyl acetylene was found to be less active for the coupling reaction (Table 1, entry 15) therefore, oxidative adduct (Ar-Pd-halide) may be responsible for the decarboxylation of palladium carboxylate to form aryl alkynyl palladium and further reductive elimination gave the desired product.

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	base	solvent	yield (%)[b]
1	Pd@PS (3)	K_2CO_3	DMF	22
2	Pd@PS (3)	Et_3N	DMF	nr
3	Pd@PS (3)	K_3PO_4	DMF	14
4	Pd@PS (3)	DABCO	DMF	16
5	Pd@PS (3)	KOtBu	DMF	37
6	Pd@PS (2)	DBU	DMF	65
7	Pd@PS (3)	DBU	DMF	89 (78)
8[c]	Pd@PS (3)	DBU	DMF	45
9	Pd@PS (3)	DBU	1,4-dioxane	6
10	Pd@PS (3)	DBU	toluene	nr
11	Pd@PS (3)	DBU	CH_3CN	10
12	Pd@PS (3)	DBU	DMA	20
13	Pd@PS (3)	DBU	DMSO	56
14	Pd/C (3)	DBU	DMF	10
15[d]	Pd@PS (3)	DBU	DMF	34

[a]Reaction conditions: **1a** (0.42 mmol), **2a** (0.51 mmol), base (3 equiv), catalyst (3 mol %) and DMF (2 mL) at 110 ºC. [b] GC-MS yield; isolated yield in parenthesis. [c] At 90 °C.[d] 2a = phenyl acetylene.

The scope of DC reaction was investigated by using different aryl iodides and aryl bromides with alkynyl carboxylic acids under the optimized reaction conditions (Scheme 2). Electron-rich and neutral aryl iodides successfully coupled with phenylpropiolic acid in good yields (70 and 66%) of **3b** and **3c**. Moreover base sensitive and electron withdrawing groups (e.g, CO_2CH_3, $COCH_3$, CHO, CN, CF_3 and Cl) were well tolerated under the reaction conditions and furnished the corresponding internal alkynes **3d**-**3i** in 58-96% yields. In addition, ortho substituted aryl iodides such as 2-iodoaniline, 2-iodo acetanilide smoothly yielded desired products **3j** and **3k** in 74% and 76% respectively. Alcohol substituted aryl halide such as 3-iodobenzylalcohol was allowed to react with phenylpropiolic acid under the optimized reaction conditions, di-aryl alkyne **3l** was formed in 86% yield. Heterocyclic halide such as 2-iodothiophene also found to be compatible with the employed

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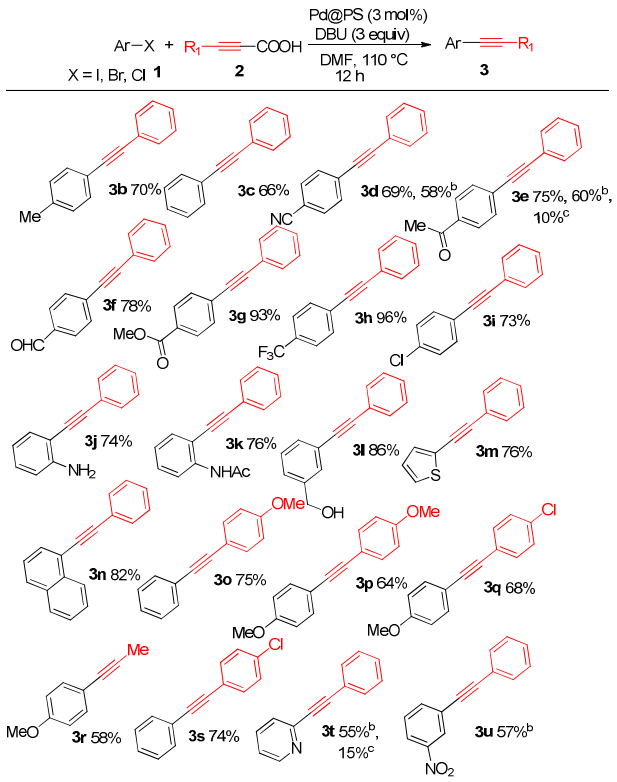
Scheme 2. Substrate Scope of Pd@PS Catalyzed Decarboxylative Coupling[a]

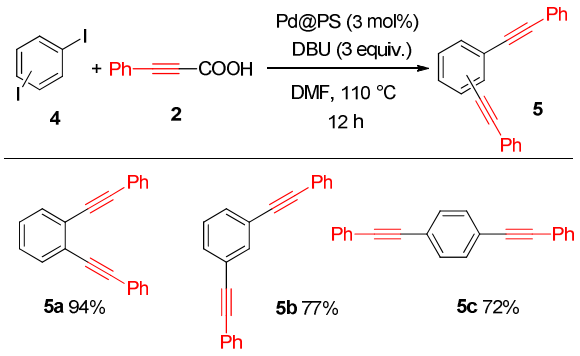


[a]Reaction conditions: aryl halide 1 (1 equiv.), alkynyl carboxylic acid 2 (1.2 equiv.), DBU (3 equiv.), Pd@PS (3 mol%), DMF (2 mL), at 110 ºC for 12 h; all are isolated yields. [b]Reactions of aryl bromide.[c]Reactions of aryl chlorides

reaction conditions, producing **3m** in 76% yield. Poly substituted aromatic iodide also reacted smoothly and produced **3n** in 82% yield. It is gratifying to say that the reaction conditions were compatible to a variety of propiolic acids bearing electron donating and withdrawing functionalities in the coupling reaction with different aryl iodides and gave the coupled products **3o-p** and **3s** in high yields. To our surprise the reaction of 4-iodoanisole with 2-butynoic acid gave the corresponding internal alkyne **3r** in 58% yield. In addition the decarboxylative coupling of arylbromides were also studied under the same catalytic conditions and the corresponding products **3d, 3e, 3t** and **3u** were attained in moderate yields. Finally the decarboxylative coupling of aryl chlorides with phenyl propiolic acid were also attained to get the coupled products **3e** and **3t** in lower isolated yields and the major quantity of starting material was recovered.

The reactions of diiodobenzenes with phenylpropiolic acid were also carried out under the aforementioned reaction conditions (Scheme 3). Intriguingly, the reaction of 1,2-diiodobenzene with phenylpropiolic acid gave the corresponding bis-coupled product **5a** in 94% yield. Similarly the coupling reaction of 1,3- and 1,4-diiodobenzenes with phenylpropiolic acid afforded the desired bis coupled products **5b** and **5c** in 77% and 72% yields respectively which indicates that the present protocol may have a broad potential for constructing extended π-electron systems.

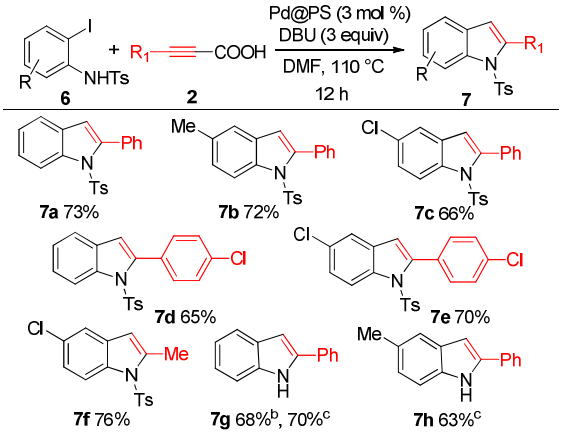
Scheme 3. Pd@PS Catalyzed Decarboxylative Coupling of Diiodoarenes[a]



[a]Reaction conditions: 4 (1 equiv.), 2 (1.2 equiv.), DBU (3 equiv.), Pd@PS (3 mol%), DMF (2 mL), at 110 ºC for 12 h; all are isolated yields.

We next attempted the Pd@PS catalyzed decarboxylative coupling of 2-iodo-*N*-tosylanilines with various alkynyl carboxylic acids (Scheme 4). We were delighted to observe the synthesis of *N*-tosylated indoles without any need of external cyclizing agent. The mechanistic investigation reveals that palladium catalyst as well as DBU assisted the cyclization reaction (ESI). The various substituents on 2-iodo-*N*-tosylanilines had no effect as all reacted smoothly with phenylpropiolic acid to give approximately same yield of corresponding products **7a**-**7c**. Similarly, 3-(4-chlorophenyl)propiolic acid and but-2-ynoic acid were also found effective coupling partners yielding the desired products **7d**-**7f** in good yields. Surprisingly, *N*-(2-iodophenyl)methane sulfonamide, 2-iodotriflouroacetanilide, 2,2,2-trifluoro-1-(2-iodo-4-methylphenyl)ethanone reacts with phenylpropiolic acid gave indole **7g** and **7h** in one pot coupling cyclization and deprotection approaches.

Scheme 4. Pd@PS Catalyzed One-pot Decarboxylative Coupling-Cyclization to access Functionalized Indoles[a]



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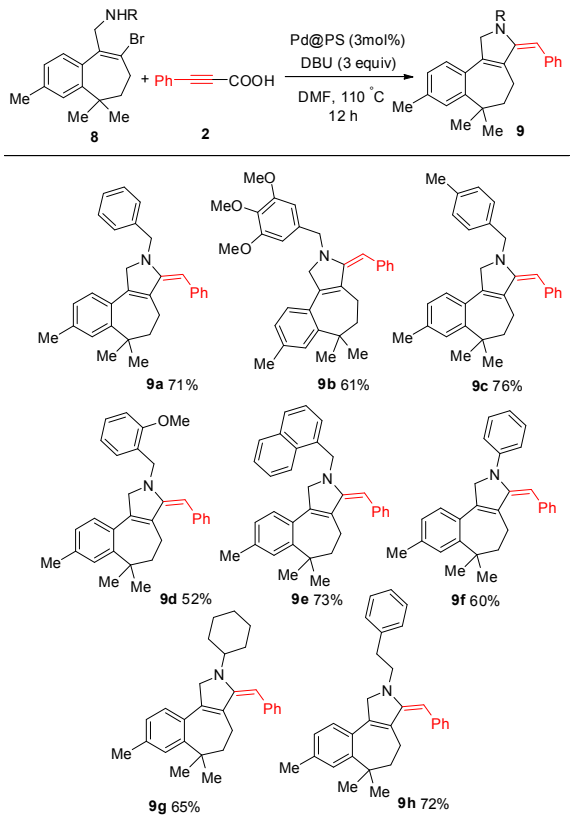
[a]Reaction conditions: **6** (1 equiv.), **2** (1.2 equiv.), DBU (3 equiv.), Pd@PS (3 mol%), DMF (2 mL), at 110 °C for 12 h; all are isolated yields. [b]reaction with *N*-(2-iodophenyl)methanesulfonamide. [c]reaction when Ts replace by $COCF_3$

The methodology was further extended for the synthesis of bioactive, 3-pyrroline derivatives by tandem decarboxylativecoupling-5-exo cyclization of amino benzocycloheptene bromides with phenylpropiolic acid (Scheme 5).[12] Different Benzyl substituted amino benzocycloheptene bromides were easily coupled and cyclized to furnish new class of 3-pyrroline compounds **9a**-**9d** in 71-52 % yields. Naphthyl-methyl substituted amino benzocycloheptenebromide also coupled to get the desired pyrroline **9e** in 73%. Interestingly, aryl substituted amino benzocycloheptene bromide also participated in the similar reaction with phenyl propiolic acid to produce corresponding 3-pyroline product **9f** in considerably good yield 60%. Alkyl amine substituted amino benzocycloheptene bromides were also found to be reactive and gave the corresponding products **9g** and **9h** in good yields.

Scheme 5. Pd@PS Catalyzed One-pot Decarboxylative Coupling-5-exo Cyclization to access new class of 3-Pyrrolines[a]



[a]Reaction conditions: 8 (1 equiv.), 2 (1.2 equiv.), DBU (3 equiv.), Pd@PS (3 mol%), DMF (2 mL), at 110 °C for 12 h; all are isolated yields.

Recyclability experiments

The recyclability of Pd@PS catalyst was investigated in the decarboxylative coupling of 4-iodoanisole with phenylpropiolic acid under standard reaction condition. After completion of the reaction the catalyst was recovered by simple filtration and washed with water, acetone and dried over reduced pressure and reused. It was found that the catalyst was recycled upto 5 times without significant loss of activity (Fig. 2). ICP-AES analysis was used to detect the palladium leaching into the resulting reaction solution and only <1 ppm of palladium was detected (ESI).

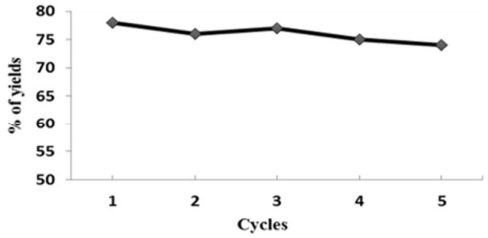


Fig. 2 Recyclability experiment of Pd@PS catalyst

Mercury test

Mercury drop test was operated to evaluate the heterogeneity of the catalyst as well as catalytically active species under the reaction condition. The addition of Hg(0) to the heterogeneously catalysed reactions is known to inhibit the activity of the catalyst due to amalgam formation on the catalytic surface. In contrast, Hg(0) does not inhibit the catalytic activity of homogeneous palladium catalysts. When a drop of mercury was added to the reaction mixture of 4-iodoanisole and phenylpropiolic acid under optimized reaction conditions traces of product was observed, whereas mercury free experiment give highest yield of the desired product indicating that the mercury leads to amalgamation of the catalytic surface of the heterogeneous catalyst (Pd@PS) which further confirms that the catalytic active species under the reaction condition are Pd(0) and the reaction occurred in a truly heterogeneous manner.

Hot filtration test

The reaction of 4-iodoanisole with phenylpropiolic acid was carried out under the standard reaction condition, after 2h (the yield of the product was 30%) the solid catalyst was filtered out and the reaction continued for 12h no further increase in the yield of the product was observed indicating the absence of palladium (II) species in the solution and the decarboxylation reaction was truly heterogeneous (Fig. 3).

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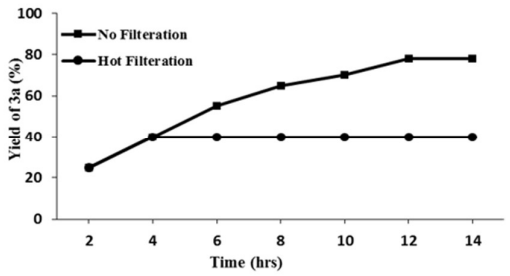

Fig. 3 Hot filtration test for decarboxylative coupling reaction

Conclusions

In conclusion, Pd@PS NPs was found to be highly active catalyst for the decarboxylative coupling of arylhalides and alkynyl carboxylic acids to produce diaryl alkynes. The ability of the catalyst has also been exploited in domino decarboxylative coupling-cyclization (DCC) reaction for indoles and new classes of pyrrolines synthesis. The benefits of this process such as simple operation, recyclability, vast selectivity profile and milder reaction conditions produce an alternative decarboxylative coupling strategy in comparison with the existing procedures.

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Graphical Abstract: