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Efficient Synthesis of Polysubstituted Olefins Using Stable Palladium Nanocatalyst: Applications in Synthesis of Tamoxifen and Isocombretastatin A4

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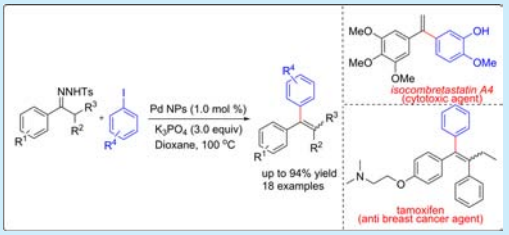
Supporting Information

ABSTRACT: A phosphine-free stable palladium nanocatalyst was used for an efficient synthesis of polysubstituted olefins from *N*-tosylhydrazones and aryl iodides. This methodology was successfully utilized in the synthesis of biologically important tamoxifen and isocombretastatin A4. The nanocatalyst was easily recovered and reused without any apparent loss in size and catalytic activity.



Olefins are one of the versatile functional groups and intermediates in organic synthesis because of their unique reaction properties.[1] In addition, olefins are present in many natural products, biologically active molecules, and fine chemicals. In particular, polysubstituted olefins have widespread applications in natural products, pharmaceuticals, and functional materials synthesis (Figure 1).[2]

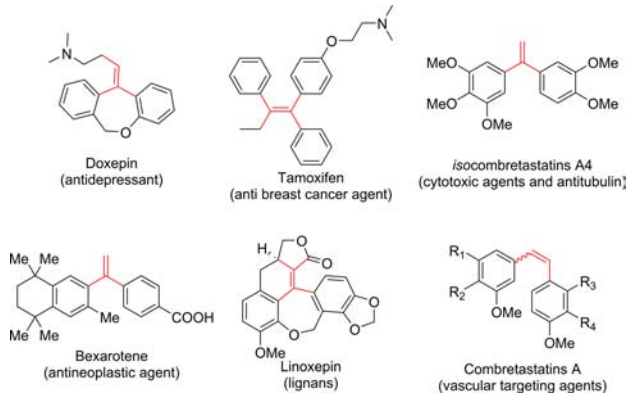


Figure 1. Biologically important polysubstituted olefins.

Although numerous methods exist for the synthesis of simple olefins, synthesis of polysubstituted olefins is a challenging task in synthetic organic chemistry. Among various methods available for the synthesis of polysubstituted olefins, the transition-metal-catalyzed C−C bond-forming cross-coupling reaction is a powerful method.[3] Recently, Barluenga et al. reported a palladium-catalyzed cross-coupling reaction between *N*-tosylhydrazone and aryl halides for the preparation of polysubstituted olefins.[4] Wang et al. and others utilized arylboronic acids as coupling partners for polyolefin synthesis.[5] These methods are highly efficient and use bulky and electron-rich phosphine ligands, which are costly and sensitive to air, and in some cases external co-oxidants are used.[6] From the industrial and economical points of view, large-scale production faces a major challenge in purification of product from expensive catalyst.

In the last few decades, C−C bond-forming cross-coupling reactions catalyzed by transition-metal nanoparticles have emerged as an efficient tool in organic synthesis.[7] In particular, palladium nanoparticles (Pd NP) are one of the most prominent metal nanocatalysts in several C−C bond-forming cross-coupling reactions.[8] The advantages of using Pd NP as catalysts are low catalyst loading, good selectivity, and enhanced reactivity because of their large surface area. In addition, the semi-heterogeneous nature of nanoparticles offers ease of separation and reusability of the catalyst. However, preparation of metal nanoparticles often requires stabilizing agent to prevent agglomerization and precipitation into bulk materials, which are inactive to catalyze the reaction. In the literature, a number of stabilizers such as thiols, phosphines, dendrimers, and polymers are used for the synthesis of nanoparticles.[9] Very recently, we have reported synthesis and application of new type of easily recoverable and reusable stable palladium nanoparticles stabilized by a metal−carbon covalent bond.[10] In this paper, for the first time, we report an efficient phosphine-free synthesis of polysubstituted olefins **3** from *N*-tosylhydrazone **1** and aryl iodides **2** using the stable Pd−$C_{(sp2)}$-stabilized nanoparticle as easily recoverable and reusable catalyst and application of this methodology as key step in the synthesis of biologically important molecules (Scheme 1).

Our preliminary investigation for the synthesis of polysubstituted olefin started with coupling of *N*-tosylhydrazone **1a** with 4-iodotoluene **2a** in the presence of Pd NP **4a** (1.0 mol %) and LiO-*t*-Bu base in dioxane at 100 °C. The reaction afforded 75% of 1-methyl-4-(1-phenylvinyl)benzene **3a** in 24 h. It is very

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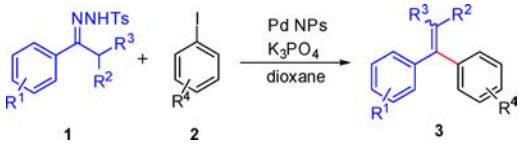
Scheme 1. Stable Pd NP-Catalyzed Polysubstituted Olefin Synthesis



important to mention that this method involves a ligand free protocol for the synthesis of polysubstituted olefins. Encouraged by this initial result, we were curious to investigate the catalytic effect of other aryl derivatives stabilized Pd NP for this polysubstituted olefin synthesis. Thus, simple phenyl **4b**, *p*-decylphenyl **4c**, and *p*-decyloxyphenyl **4d** stabilized Pd NPs were synthesized, characterized (Figure 2), and used as catalyst

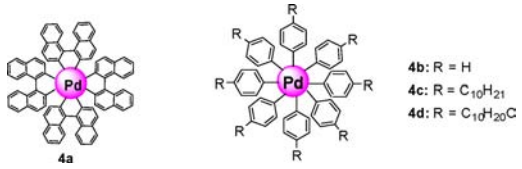


Figure 2. Aryl derivative stabilized Pd NPs.

for the above-mentioned reaction, and the results are summarized in Table 1. The Pd NP **4b** afforded poor yield (30% of **3a**), where **4c** and **4d** gave 62% and 60% yields, respectively (Table 1, entries 1−4).

Table 1. Effect of Solvent and Bases for the Synthesis of Polysubstitued Olefin[a]

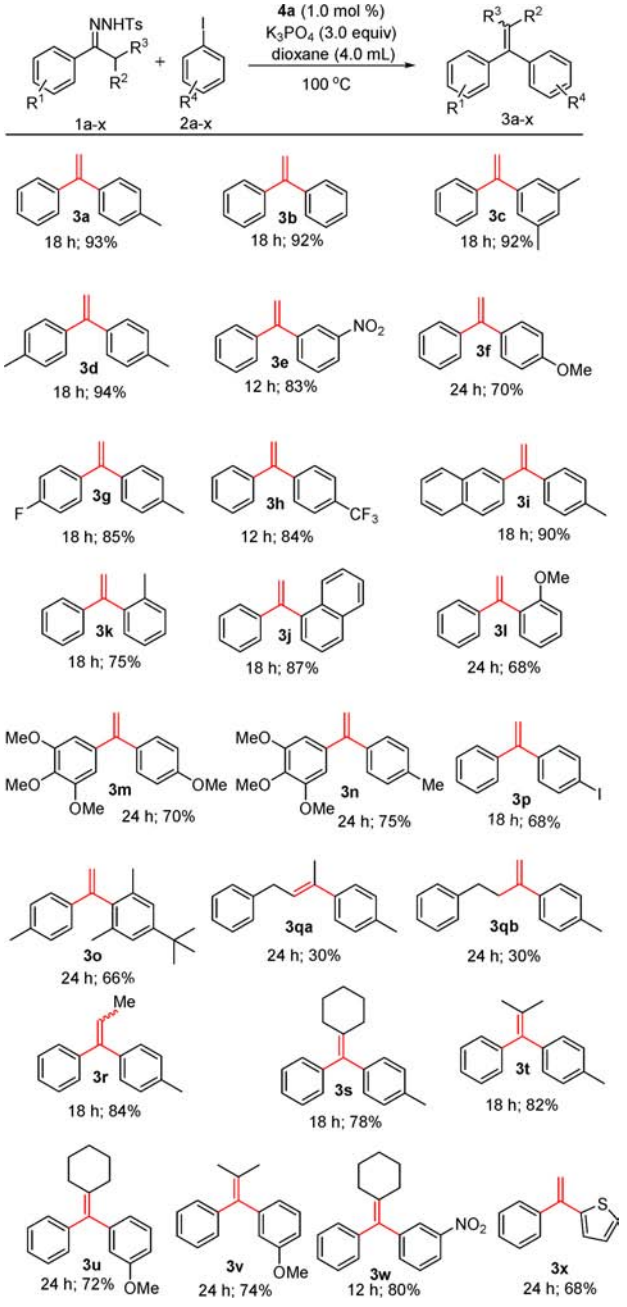
entry	Pd NP	solvent	base	time (h)	yield[b] (%)
1	**4a**	dioxane	LiO-*t*-Bu	18	75
2	**4b**	dioxane	LiO-*t*-Bu	24	30
3	**4c**	dioxane	LiO-*t*-Bu	24	62
4	**4d**	dioxane	LiO-*t*-Bu	24	60
5	**4a**	dioxane	Cs_2CO_3	18	82
6	**4a**	dioxane	K_2CO_3	24	69
7	**4a**	**dioxane**	**K_3PO_4**	**18**	**93**
8	**4a**	dioxane	KOAc	24	10
9	**4a**	THF	K_3PO_4	24	45[c]
10	**4a**	toluene	K_3PO_4	24	42
11	**4a**	EtOH	K_3PO_4	24	trace
12	**4a**	DCE	K_3PO_4	30	38
13	**4a**	DME	K_3PO_4	24	68

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), Pd NPs **4a** (1 mol %), base (1.5 mmol), solvent (4 mL). [b]Isolated yield. [c]Pressure tube was used.

To improve the yield of this olefin synthesis, several bases were screened and K_3PO_4 gave the best result with 93% of isolated yield within 18 h (Table 1, entries 5−8). To increase the efficiency of the reaction, the effect of solvents and temperature were studied and in all the cases, the olefin **3a** was obtained comparatively in poor yield (Table 1, entries 9−13). The optimization results are summarized in Table 1.

Having optimized reaction conditions in hand (Table 1, entry 7), several polysubstituted olefins were synthesized to show the substrate scope, and the results are summarized in Scheme 2. The coupling of various substituted *N*-tosylhydrazone and aryl iodides smoothly proceeded with good to

Scheme 2. Pd−$C_{(binaphthyl)}$ NP 4a Catalyzed Synthesis of Polysubstituted Olefins[a]



[a]Reaction conditions: **1a−x**(0.5 mmol), **2a−x** (0.5 mmol), Pd NPs **4a** (1 mol %), K_3PO_4 (1.5 mmol), in dioxane (4 mL). [b]Mixture of isomers from same starting material. All are isolated yields.

excellent yield to produce polysubstituted olefins. Both electron-withdrawing and electron-donating groups in the coupling partners have efficiently worked in this synthesis. In particular, *N*-tosylhydrazone substituted with three methoxy groups coupled with 4-methoxybenzene efficiently to form highly electron-rich olefin (**3m**). In addition, it is worthy to note that even sterically hindered aryl iodides afforded good yields (**3k,l,o**). 1,4-Diiodobenzene reacted with acetophenon-derived hydrazone and gave iodoolefin (**3p**) with 68% yield. The hydrazone derived from linear ketone such as propiophenone reacted with 4-iodotoluene and gave a 1:1mixture of *E*/*Z* isomers. Similarly, the hydrazone derived

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from 4-phenylbutan-2-one gave a mixture of regioisomers **3qa** and **3qb**. Interestingly, α-disubstituted hydrazones are efficiently coupled with aryl iodides (Schemes 2, **3s–x**). The hydrazone derived from 2-methyl-1-phenylpropan-1-one gave tetrasubstituted olefins **3t** and **3v** with 82 and 74% yield, respectively. Heteroaromatic iodide also coupled, and the reaction afforded 68% of **3x**. When the reaction was carried out with 4-bromotoluene in the presence 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) 12% of **3a** was isolated. However, the yield was not increased by changing the ligands and the reaction conditions.

Then we investigated the recyclability nature of catalyst **4a**, and catalyst **4a** was successfully recovered by centrifugation and reused for four cycles without any appreciable loss in the catalytic efficiency (Figure 3). This is in agreement with HRTEM analysis as the **4a** showed same particle size without any obvious agglomerization before and after the catalytic cycles (Figure 4).

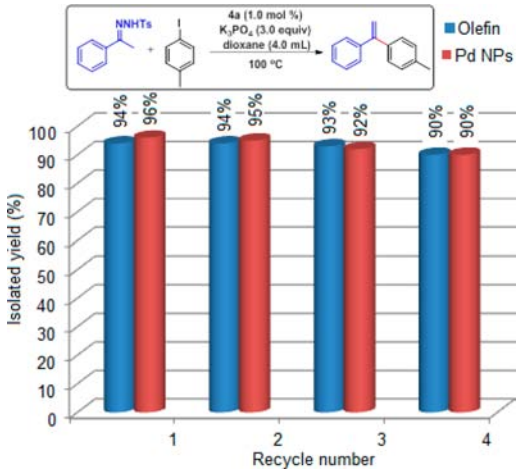


Figure 3. Catalytic recycles for the synthesis of polysubstituted olefins.

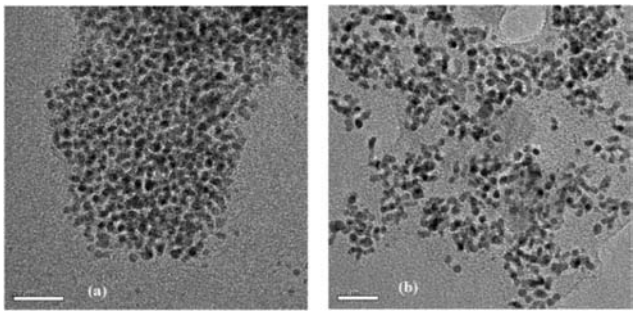
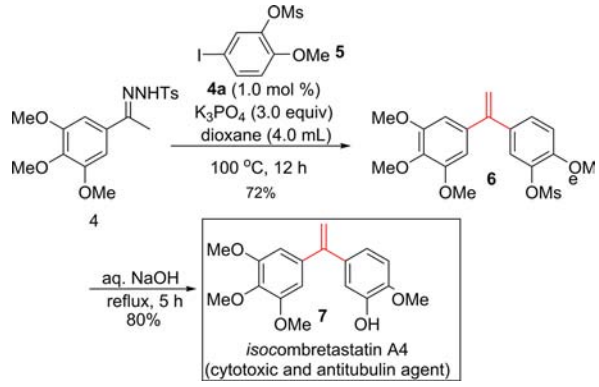


Figure 4. HRTEM images of Pd NPs **4a** before catalytic (a) and after the catalytic cycles (b).

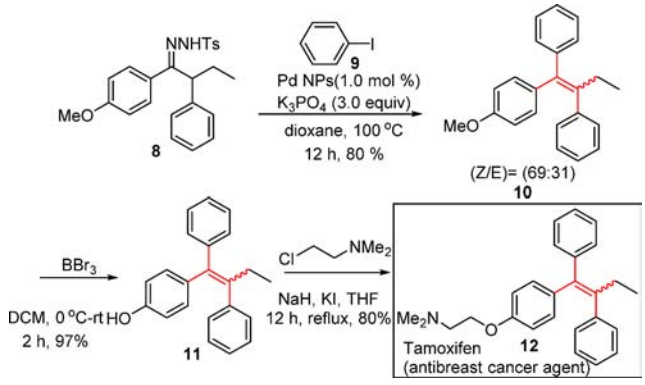
To know the application of this methodology, it was used as key step for the synthesis of biologically important molecules such as isocombretastatin A4 and tamoxifen. The synthesis of cytotoxic agent isocombretastatins[11] **7** was accomplished by the coupling of *N*-tosylhydrazone **4** derived from 1-(3,4,5-trimethoxyphenyl)ethanone with iodo derivative **5** in the presence of **4a** under optimized reaction conditions with 72% yield. The hydrolysis of **6** afforded isocombretastatin A4 **7** with 80% isolated yield (Scheme 3).

Tamoxifen is currently used as a potential antagonistic prodrug for the treatment of all stages of estrogen-receptor-positive breast cancer.[12] This molecule was successfully synthesized by coupling of iodobenzene **9** with the aryl hydrazone **8** to afford the precursor of tamoxifen **10** as a mixture of *Z*/*E* isomer (69:31 ratios) with 80% of isolated yield.[13] Later, the intermediate **10** was successfully converted to tamoxifen in two steps (Scheme 4).

Scheme 3. Synthesis of Cytotoxic Agent Isocomberstatin A4



Scheme 4. Synthesis of Anticancer Agent Tamoxifen



We have developed an efficient methodology for the synthesis of polysubstituted olefins using stable, easily recoverable, and reusable Pd NP as catalyst from tosylhydrazone and aryl iodides. This methodology was successfully utilized as a key step for the synthesis of very important anticancer agents, isocombretastatins, and tamoxifen in good yields. The application of this methodology in the synthesis of other biologically important molecules and the mechanistic studies are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and procedures, compound characterization data, and copies of ^{1}H and ^{13}C spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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