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Solid supported palladium(0) nano/microparticle: a ligand-free efficient recyclable heterogeneous catalyst for mono- and β , β -double-Heck reaction *

Dharminder Sharma, Sandeep Kumar, Arun K. Shil, Nitul Ranjan Guha, Bandna, Pralay Das*

Natural Plant Products Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur 176061, H.P., India

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ABSTRACT

Solid supported palladium nano/microparticles were found to be active catalysts to perform mono- and β , β -double-Heck reactions. Different β -unsubstituted and substituted alkenes including acrylate, methacrylate, crotonate, styrene, acrylonitrile, and acrylamide were investigated successfully for mono- and β , β -double-Heck reactions with aryl iodide under milder reaction condition. One-pot β , β -double-Heck reaction of aryl iodides with α , β -unsaturated ester, amide, nitrile, and styrene derivatives were also performed under standard reaction conditions. Wide functional group tolerance, easy catalyst recovery, and recyclability up to twelve times without significant loss of catalytic activity added extra importance to the present process.

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Palladium catalyzed Heck reaction of olefin and aryl halide is one of the most fundamental reactions for carbon-carbon bond formation in organic synthesis.¹ Several reports have been published for the Heck reaction of mono- and multi-substituted aryl halides.² β,β-Diarylalkenes synthesized via β,β-double-Heck reaction, are valuable synthetic intermediates for natural products and pharmaceuticals.³ Conventionally Heck reaction of olefin and aryl halide is restricted to mono-Heck reaction due to less active β -proton on the 1,2-disubstituted olefins.⁴ Therefore, β , β -double-Heck has been scarcely reported in the literature with harsh reaction conditions.⁵ The use of non-recyclable homogeneous palladium catalyst,⁶ additives,⁷ moisture sensitive expensive palladium complexes,⁸ longer reaction time, and tedious work-up procedure draw a line of limitation over the previous methods. Recently a greener approach has been developed for β , β -diarylation of acrylate but applicable only in the case of higher alkyl acrylates with longer reaction time (30 h) at 120 °C.⁹ Botella and Najera have established β , β -diarylation of *t*-butyl acrylates using an oximederived palladacycle/Pd(OAc)₂ in water at 120 °C. Especially *t*-butyl acrylate has been used for diarylation to avoid possible hydrolysis of the ester group in the presence of inorganic bases at higher temperature.¹⁰ As per our knowledge there is no ligand-free heterogeneous catalyst available to serve β , β -diarylation product through β , β -double-Heck reaction covering a large number of substrate scopes.

* Corresponding author. Fax: +91 1894 230433.

Recently our group described the synthesis of solid supported palladium(0) and rhodium(0) (SS-Pd and SS-Rh) nano/microparticles as heterogeneous catalyst and their applications in cross coupling, oxidation, and reduction reactions.^{11,13}

As a part of our continuous effort to explore the potential of SS-Pd catalyst, herein we describe a convenient methodology for mono- and β , β -double-Heck reaction of α , β -unsaturated esters, amides, nitriles, and styrenes with different aryl iodides under milder reaction condition.

Initially to search the optimum reaction condition, 4-iodotoluene and ethyl acrylate were taken as test substrates (Table 1). To our delight, a combination of SS-Pd (2 mol % of Pd) and K_2CO_3 (2 mmol) in DMF gave 1 in 93% yield within 6 h and considered as the best condition (Table 1, entry 7). For wider applicability of the present method, 4-iodoanisole with different acrylic ester, acrylonitrile, acrylamide, and styrene afforded good to excellent yields of corresponding cross coupled products with E-isomer (confirmed by ¹H NMR). Different acrylic esters (Me, Et, *n*-Bu, ^{*t*}Bu) were explored in the similar reactions and no significant effect of ester functionalizations was observed (Table 2, entries 1-6). Alongside, positional isomers such as 2-, 3-, and 4- substituted aryl iodides were found to have a negligible impact on reactivity though 4-substitution gave a higher yield of desired cinnamate derivatives (Table 2, entries 2, 5, and 7). Reaction of 4-iodoanisole with different methacrylates produced trisubstituted alkenes which is uncommon in literature¹² (Table 2, entries 8-10). Electron deficient 2- and 4-iodonitro benzenes also afforded the corresponding products in good yields (Table 2, entries 11-13).



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E-mail addresses: pdas@ihbt.res.in, pdas_nbu@yahoo.com (P. Das).

Table 1

3

4

5

6

Optimization of reaction condition for mono-Heck reaction



^a Isolated yields, reaction condition: 4-iodotoluene (1 equiv), ethyl acrylate (2 equiv), base (2 equiv), catalyst (2 mol %).¹⁴

Та SS

ble 2
-Pd catalyzed mono-Heck reaction of substituted aryliodides and
$$\alpha,\beta$$
-unsaturated compounds

$$R^{1} \stackrel{f}{\amalg} \stackrel{f}{\downarrow} \stackrel{f}{\downarrow} \stackrel{f}{\downarrow} \stackrel{f}{=} \stackrel{f}{\underset{R^{2}}{\overset{R^{3}}{\overset{SS-Pd, K_{2}CO_{3}}{DMF, 6h, 110 °C}}} R^{1} \stackrel{f}{\amalg} \stackrel{f}{\underset{R^{2}}{\overset{R^{3}}}{\overset{R^{3}}{\overset{R^{3}}{\overset{R^{3}}{\overset{R^{3}}{\overset{R^{$$

$$\begin{array}{c} & & & & & & & & \\ & & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\$$

Under this milder condition, active functional groups such as OH, CN, and CHO were found to be tolerated and gave products 15-17 in considerable yields (Table 2, entries 14–16). 4-Iodobenzoic acid and 4-iodoaniline also participated in Heck reaction with ethyl acrylate to give corresponding E-cinnamates which otherwise were rare to accomplish in previous reports. (Table 2, entries 17 and 18). 4-Bromoiodo benzene is selectively converted into 4-bromoethylcinnamate 21 with excellent yield (Table 2, entry 20). Acrylonitrile, acrylamide, and styrene derivatives were similarly found to be tolerated and gave good conversions with different aryliodides (Table 2, entries 21-26). 1,2- and 1,3-diiodobenzene gave 1, 2- and 1,3-diacrylobenzenes in excellent yields (Table 2, entries 27 and 28). After the completion of reaction, the catalyst was recovered by filtration, washed with water and acetone, dried under reduced pressure and used for the next cycle. The catalyst could be recycled up to twelve runs successfully without significant loss of activity (Fig. 1).

Synthesized cinnamate, cinnamonitrile, and stilbene derivatives were further used for second Heck reaction to prepare corresponding β , β -diarylalkenes.

Monoarylated alkenes **3** and **6** were applied for β -arylation to produce β , β -diaryl substituted alkenes **30** and **31** in satisfactory yield. When both electron rich and deficient cinnamates were treated with different functionalized aryliodides, β,β-double-Heck products 32-38 were formed with satisfactory yields (Table 3, entries 3-9). Tetrasubstituted olefines 39 were synthesized from the

-OMe

90

93

95

92^b

Table 2 (continued)

Entry	Aryl iodides	Olefins	Products	Yield ^a (%)
7	MeO	∕ ^{CO₂Et}	CO ₂ Et	95
8	MeO	=	MeO 8 CO ₂ Me	93
9	MeO	= CO₂-n-Bu	CO ₂ -n-Bu MeO	91
10	MeO	=< CO₂′Bu	CO ₂ ^t Bu MeO	92
11	O ₂ N	^{CO2Et}	CO ₂ Et	86 ^b
12	O ₂ N	/ ^{CO} 2 ^{-n-Bu}	CO ₂ -n-Bu	80
13	NO ₂	/ ^{CO2Et}		82
14	HO	^{CO} 2 ^{Et}		88
15	NC	^{CO} 2Et	CO ₂ Et	89
16	OHC	CO2Et		88
17	HO ₂ C	/ ^{CO2} Et		81
18	H ₂ N	CO2Et	HO ₂ C CO ₂ Et H ₂ N	75





^a Isolated yields, reaction conditions: aryliodide (1 equiv), ethyl acrylate (2 equiv), K₂CO₃ (2 equiv), and SS-Pd (2 mol %), only the *E*-isomers were isolated in all the cases. b Reaction was carried out by using 5 g of substrate.

^c Aryliodide (1 equiv), ethyl acrylate (4 equiv), K₂CO₃ (4 equiv), and SS-Pd (2 mol %), reaction time 10 h.

reaction of 11 with 4-iodoanisole in 80% yield (Table 3, entry 10). Interestingly, when 4-methoxy cinnamate 3 was treated with comparably bulky aryl halide (such as 1-iodonaphthalen) the reaction followed both cis and trans approach at intermediate steps and produced 40 with E/Z: 52/48 (Table 3, entry 11). Although, when naphthyl substituted acrylate 20 was treated with 4-iodoanisole the reaction followed the major trans orientation to form a stable intermediate and gave 40 in comparable yield with E/Z: 90/10 (Table 3, entry 12). 1,2-Bis(4-methoxyphenyl)ethane 24 coupled efficiently with 4-iodoanisole to afford 41 in 72% yield. 3-(4-Methoxyphenyl)acrylonitrile 22 was also found to be a suitable

substrate for β , β -double-Heck reaction and gave corresponding homodiarylated alkene product 42 (Table 3, entry 14). Interestingly, highly conjugated β,β-double-Heck product 43 was prepared by the reaction of 29 with 4-iodoanisole following the same reaction condition (Table 3, entry 15). Methyl and ethyl crotonates were also tested with 4-iodoanisole for the same reaction to give **44** and **45** in excellent yields regardless of β -methyl substitution (Table 3, entries 16 and 17).

β,β-Double-Heck reactions of alkenes were further investigated in one-pot. Addition of 2.4 equiv of aryl iodide at a time increases the formation of homocoupled diaryls and decreases the yield of



Figure 1. Recyclability studies of SS-Pd catalyst for compound 3.

corresponding β , β -double-Heck products. To overcome this problem, a one pot sequential strategy was adopted. Desired β , β -double-Heck product was produced in one-pot on addition of another 1.2 equiv of aryl iodide after 6 hours of reaction (Table 4). The reaction of ethyl and *n*-butyl acrylates with methyl and methoxy substituted aryl iodides under similar condition afforded the corresponding β , β -double-Heck products in good yields (Table 4, entries 1–4). 4-Methoxystyrene also participated in the same reaction to give **41** in satisfactory yield (Table 4, entry 5). Interestingly, acryl amides and acrylonitriles also participated in the same reaction with different aryl iodides to produce **42**, **48**, **49**, and **50** in good yields (Table 4, entries 6–9).

In summary, a ligand-free heterogeneous palladium catalyst SS-Pd was used for mono- and β , β -double-Heck reactions of different

Table 3

Heck reaction of β -substituted α , β -unsaturated compounds using SS-Pd





7049

Table 3 (continued)

Entry	Olefins	Aryl iodide	Products	Yield ^a (%)/E/Z ratio
6	1	MeO	CO ₂ Et 35 MeO	77 E Z::77 23
7	12	MeO		75 <i>E</i> /2::86/14
8	14	MeO	MeO MeO CO ₂ Et	72 E/Z::72/28
9	12		CO ₂ Et	68 <i>E</i> /Z::82/18
10	11	MeO	O ₂ N MeO CO ₂ 'Bu 39 MeO	80
11	3		MeO CO ₂ Et	66 <i>E</i> /Z::52/48
12	20		40	70 <i>E</i> / <i>Z</i> ::90/10
13	24	MeO MeO	OMe MeO 41 OMe	72

(continued on next page)

Table 3	(continued)
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^a Isolated yields; Reaction conditions: aryliodide (1 equiv), β-substituted acrylic ester/nitrile (1 equiv), K₂CO₃ (2 equiv), and SS-Pd (2 mol %). *E/Z* ratio was determined by ¹H NMR (300 MHz).¹⁵

Table 4

One pot β , β -double-Heck reaction of aryliodide and α , β -unsaturated compounds



_					
	Entry	R′	R	Product	Yield ^a (%)
	1	<i>m</i> -OMe	CO ₂ Et	46	72
	2	p-OMe	CO ₂ Et	30	70
	3	o-OMe	CO ₂ Et	31	86
	4	p-Me	CO ₂ nBu	47	66
	5	p-OMe	p-OMe-Ph	41	55
	6	p-OMe	CONH ₂	48	72
	7	o-OMe	CONH ₂	49	70
	8	p-OMe	CN	42	88
	9	o-OMe	CN	50	84

^a Isolated yields; reaction conditions: aryliodide [(1.2 equiv) \times 2], ethyl acrylate (1 equiv), K₂CO₃ (4 equiv), and SS-Pd (3 mol %).

aryl iodides with olefins. Different sensitive functional groups attached to the aryl iodides were observed to be compatible with a range of olefins such as acrylate, methacrylate, crotonate, styrene, acrylonitrile, and acrylamide for mono- and β , β -double-Heck reactions. Subsequently one pot sequential β , β -double-Heck reactions were investigated successfully. The catalyst was recovered only by filtration and recycled up to twelve runs without significant loss of catalytic activity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 10.062.

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- 13. The solution of 100 mg of $NaBH_4$ in 30 ml of water was added to 4 g of Amberlite IRA 900 resin (chloride form) (Across, BE) in a 100 ml flask. The mixture was stirred for 4 h at room temperature. Then the resin was washed with water till pH became neutral and then with acetone to remove water from

the solid surface. The resin beads (borohydride exchanged) were dried under reduced pressure. Borohydride exchanged resin beads (solid surface) (1 g) were added to a solution of palladium(II) acetate (10 mg) in DMF (2 ml) and then the mixture was stirred at room temperature to 100 °C for 1 h or till the brown color of the solution changed into colorless and simultaneously white solid beads turned into black. After cooling, the beads were filtered through a cotton bed, washed with water and acetone, and dried under reduced pressure.

- 14. (*E*)-Ethyl 3-p-tolylacrylate 1 (Table 1, entry 7): a mixture of 4-iodotoluces (5 g. 22.93 mmol), ethyl acrylate (4.587 g, 45.87 mmol), and potassium carbonate (6.330 g, 45.87 mmol) was taken in DMF (15 ml) and then added SS-Pd (10.27 g, 2 mol % Pd). The reaction mixture was heated at 110 °C for 6 h under nitrogen atmosphere. After completion, the reaction mixture was treated with water (15 ml) and extracted with ethyl acetate (3 × 15 ml). The combined organic layer was finally washed with brine and dried over anhydrous Na₂SQ₄. The crude mixture was purified by column chromatography (EtOAc/Hexane, 1:99), which afforded (*E*)-ethyl 3-*p*-tolylacrylate 1 as a colorless liquid (4.051 g, 93% yield); ¹HNMR (300 MHz, CDCl₃) δ 1.30–1.39 (m, 3H), (s, 3H), 4.24–4.33 (m, 2H), 6.41 (d, *J* = 15.9 Hz, 1H), 7.19–7.20 (m, 2H), 7.41–7.44 (m, 2H), 7.69 (d, *J* = 16.00 Hz, 1H); ¹³CNMR (75 MHz, CDCl₃) δ 14.76, 21.81, 60.75, 117.14, 128.73, 130.01, 132.20, 140.96, 144.96, 167.50; HREIMS data: *m/z* Calcd for [M+H]* C₁₂H₁₅O₂ 191.2463, obsd 191.2460.
- 15. Ethyl 3,3-bis(4-methoxyphenyl)acrylate 30 (Table 3, entry 1): A mixture of (E)ethyl-3-(4-methoxyphenyl)acrylate (100 mg, 0.48 mmol), iodoanisole (114 mg, 0.48 mmol), and potassium carbonate (132 mg, 0.96 mmol) was taken in DMF (0.5 ml) and then added SS-Pd (216 mg, 2 mol % Pd). The reaction mixture was heated at 110 °C for 6 h under nitrogen atmosphere. After completion, the reaction mixture was treated with water (1 ml) and extracted with ethyl acetate $(3 \times 5 \text{ ml})$. The organic layer was finally washed with brine and dried over anhydrous Na₂SO₄. The crude mixture was purified by column chromatography (EtOAc/Hexane, 3:97), which afforded ethyl 3,3-bis(4methoxyphenyl)acrylate 25 as a light yellow gummy liquid (135 mg, 90% yield) ¹H NMR (300 MHz, CDCl₃) δ 1.15−1.20 (t, J = 7.1, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.05–4.13 (m, 2H), 6.25 (s, 1H), 6.84–6.94 (m, 4H), 7.16–7.28 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) & 14.96, 56.04, 56.15, 60.76, 114.04, 114.52, 115.78, 130.80, 131.67, 131.12, 134.67, 157.15, 160.50, 161.57, 167.26; HREIMS data: m/z Calcd. for [M+H]+ C19H21O4 313.3676 obsd. 313.3643.