

Decarboxylative Heck Reaction of Aryl Iodide with Baylis-Hillman Adduct Using Pd/C as a Catalyst in Aqueous Media

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Alkyl aryl ketones are of much importance as useful intermediates in a variety of fields, such as the pharmaceutical, fragrance, dye and agrochemical industries.¹

These compounds are synthesized traditionally by Friedel-Crafts acylation, which needs dangerous reagents and fails with electron-deficient arenes.² In recent years, alternative methods have been developed, using transition metal catalysts and allowing easy-to-handle substrates. Other examples include hydroacylation of olefins³ using $(\text{Ph}_3\text{P})_3\text{RhCl}$ as a catalyst although these reactions generally require chelate ligands. Another transition metal catalyzed approach is acylation of aryl iodide with *N*-*tert*-butylhydrazones *via* palladium-catalyzed reaction using a protocol of $\text{Pd}_2(\text{dba})_3$ and DPEphos followed by hydrolysis to give alkyl aryl ketones.⁴ In related studies, efficient protocols were also recently reported for the direct palladium catalyzed acylation of aryl halides⁵ including aryl chlorides,⁶ allowing a variety of alkyl aryl ketones to be synthesized. The other different type approaches are the conjugate reductions of α,β -unsaturated ketones with HSiCl_3 ⁷ or a protocol of trichlorosilyl triflate and tertiary amine as a hydride donor.⁸

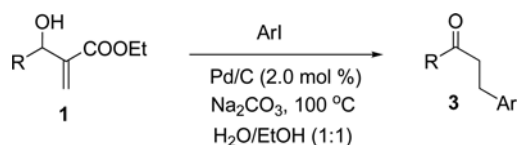
The Baylis-Hillman reaction⁹ is an useful pathway for C-C bond formation and Baylis-Hillman (BH) adducts **1** have been used as versatile building blocks to generate heterocyclic compounds, synthetic intermediates and natural products. Heck reactions are one of the most important and attractive reactions among transition metal catalyzed C-C bond formation methods, due to their applications to a variety of unprotected functional group resulting from mild reaction conditions.¹⁰ One approach to appeal green chemistry¹¹ is to conduct palladium catalyzed cross coupling reactions under heterogeneous conditions¹² including commercially available Pd/C¹³ that has found increasing popularity in the Heck reactions¹⁴ because the use of Pd/C avoids contamination of the product with palladium and expedites recovery of the metal, and therefore the reactions are practical and cost-effective for large scale reaction.

As a result of continuous researches on Baylis-Hillman adducts,¹⁵ we report the simple and efficient decarboxylative Heck reaction of Baylis-Hillman adducts with iodobenzenes in aqueous solution using Pd/C [STREM, 46-1900] as a catalyst to provide the corresponding decarboxylative Heck products. This protocol might be a nice alternative way to recently reported two methods: 1) Rh or Pd catalyzed coupl-

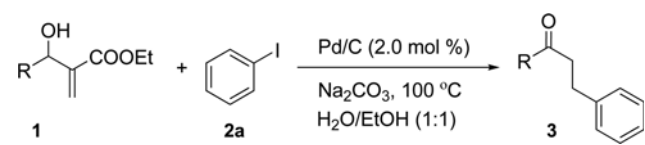
ing reaction of aryl halides with alkenes or aldehydes which might be limited by availability of aryl halide and alkenes or aldehydes and 2) the α,β -conjugate reduction of unsaturated ketones with air sensitive reagent such as HSiCl_3 ⁷ or a system of trichlorosilyl triflate

Optimum reaction condition was investigated using ethyl acrylate **1a** and iodobenzene **2a**, commercially available Pd/C [STREM, 46-1900] as a catalyst and a variety of inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate and cesium carbonate in a various ratio solution of water and ethanol. As a result, the choice of the base and the reaction time were found to be sodium carbonate and 6 h. The optimum amount of iodobenzene, sodium carbonate and Pd/C was turned out to be 1 eq, 2.4 eq and 2.0 mol % respectively and the reaction temperature was found to be 100 °C. The reaction of ethyl 2-(hydroxy(phenyl)methyl)acrylate **1a** (0.48 mmol), iodobenzene **2a** (0.40 mmol), sodium carbonate (0.96 mmol) and 10 % Pd/C (2.0 mol %) at 100 °C for 6 h gave a decarboxylated Heck product **3a** in 86% isolated yield (Table 1, entry 1). To examine the limitation, the reaction of iodobenzene with other various Baylis-Hillman adducts with electron-withdrawing (**1b** and **1c**) or electron-donating group (**1d**, **1e** and **1f**) at phenyl ring were conducted under the optimized condition to give the corresponding β -arylated ketones **3** in high to excellent isolated yields, and the results are listed in Table 1. Baylis-Hillman adducts with other heterocyclic ring system such as furan **1g** and thiophene **1h** and with alkyl group **1i** reacted with iodobenzene nicely under the reaction condition to afford the corresponding coupling products in high to excellent isolated yields.

To expand the scope of this reaction, a Baylis-Hillman adduct **1a** was reacted with a variety of electron deficient phenyl iodides (**2b**, **2c** and **2d**) and electron sufficient phenyl iodides (**2e-2j**) under the condition to give the corresponding β -arylated ketones products in high to excellent isolated

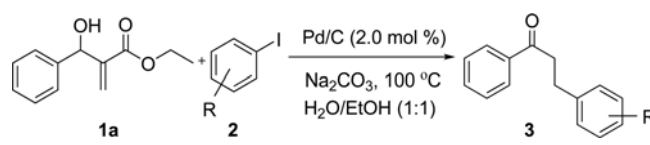


Scheme 1

Table 1. Decarboxylative Heck reaction^a of various Baylis-Hillman adducts with iodobenzene


Entry	Substrate	Product ^b	Yield (%) ^c
1	1a: R = Phenyl	3a	86
2	1b: R = 4-NO ₂ -Ph	3b	76
3	1c: R = 4-Cl-Ph	3c	90
4	1d: R = 4-Me-Ph	3d	92
5	1e: R = 4-MeO-Ph	3e	86
6	1f: R = Piperonyl	3f	84
7	1g: R = 2-Furanyl	3g	71
8	1h: R = 2-Thiophenyl	3h	77
9	1i: R = Ethyl	3i	94

^aCondition: ethyl acrylate **1** (1.2 eq), iodobenzene **2a** (0.40 mmol), Na₂CO₃ (2.4 eq), 10% Pd/C (2.0 mol %) at 100 °C for 6 h. ^bAll products are known¹⁶ and their spectral data are consistent with the reported ones. ^cIsolated yields.

Table 2. Decarboxylative Heck reaction^a of a Baylis-Hillman adduct **1a** with various iodobenzenes


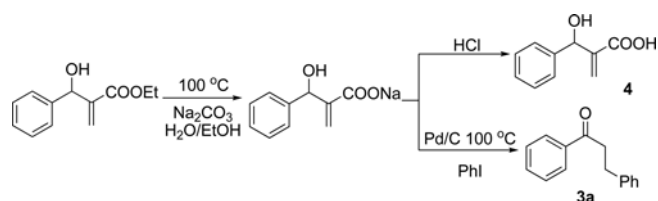
Entry	Iodobenzene	Product ^b	Yield (%) ^c
1	2b: R = <i>p</i> -NO ₂	3j	75
2	2c: R = <i>p</i> -Br	3k	87
3	2d: R = <i>p</i> -Cl	3l	84
4	2e: R = <i>p</i> -Me	3m	82
5	2f: R = <i>m</i> -Me	3n	93
6	2g: R = <i>o</i> -Me	3o	86
7	2h: R = <i>p</i> -OMe	3p	85
8	2i: R = <i>m</i> -OMe	3q	81
9	2j: R = <i>o</i> -OMe	3r	86

^aCondition: ethyl acrylate **1a** (1.2 eq), iodobenzene **2** (0.40 mmol), Na₂CO₃ (2.4 eq), 10% Pd/C (2.0 mol %) at 100 °C for 6 h. ^bAll products are known¹⁶ and their spectral data are consistent with the reported ones. ^cIsolated yields.

yields and the results are shown in Table 2.

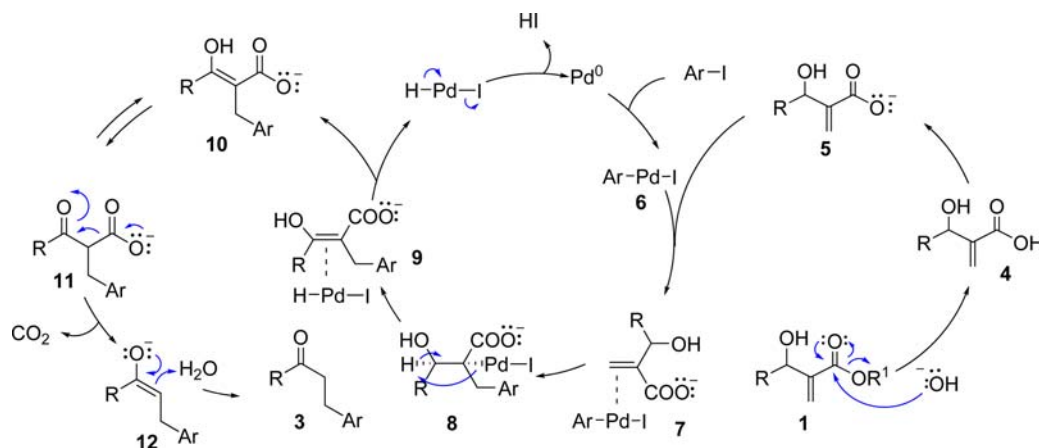
The reaction seemed to proceed *via* hydrolysis of ester group of Baylis-Hillman adduct at first followed by Heck reaction with iodobenzene and decarboxylation. During the reaction, Heck cross-coupling product of BHA **1a** with iodobenzene and decarboxylated BHA were not detected in the reaction mixture. To investigate the substrate for Heck reaction, a solution of BHA and sodium carbonate in a solution of water and ethanol (1:1) in the absence of iodobenzene and Pd/C was heated at 100 °C for 2 h. And then, half of the reaction mixture was neutralized with 1 N HCl and followed by common work-up to give a carboxylic acid **4** as a sole product. The other half of the reaction mixture was treated with Pd/C (2.0 mol %) and iodobenzene (1 eq), heated at 100 °C for 3 h, and followed by usual work-up to give a decarboxylated Heck coupling product **3a** as a sole product as shown in Scheme 2.

The plausible mechanism on the basis of the above experimental result is as follows. The first step of the reaction

**Scheme 2**

mechanism is the hydrolysis of ester **1** followed by ligand exchange of aryl palladium iodide **6** which is generated by oxidative addition of palladium into aryl iodide to afford η²-complex **7**. Intermediate **8** formed *via* the *syn* insertion of aryl palladium iodide **6** into C=C bond undergo *syn* β-elimination to give η²-complex **9** followed by dissociation from palladium iodide, tautomerization, decarboxylation and protonation of an enolate **12** to give decarboxylated Heck product **3**.

In conclusion, a synthetic protocol for the decarboxylative Heck reaction of a various Baylis-Hillman adduct with aryl

**Scheme 3.** Proposed mechanism of the Heck reaction of Baylis-Hillman adduct.

iodides was developed using commercially available Pd/C as a catalyst and sodium carbonate as a base at 100 °C for 6 h. The protocol is very efficient and essentially quantitative yields for crude product were observed.

Representative Experimental Procedure. To a mixture of 2-(hydroxy(phenyl)methyl)acrylate (**1a**) (100 mg, 0.48 mmol, 1.2 eq), iodobenzene (**2a**) (82.5 mg, 0.045 mL, 0.40 mmol), and a sodium carbonate (103 mg, 0.97 mmol, 2.4 eq.) in a solution of water and ethanol (3 mL, 1:1) in 5 mL v-vial was added 10% Pd/C (8.5 mg, 2.0 mol %). After the resulting mixture was heated 100 °C at 6 h, the reaction mixture was cooled, extracted with an solution (2 mL × 5) of ethyl acetate and hexane (1:2). The extracts was concentrated and chromatographed on silica gel column using a solution of ethyl acetate and hexane (1:4) to give a decarboxylative coupling product **3a**, 1,3-Diphenylpropan-1-one, in 86% isolated yield (Table 1. entry 1): ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, *J* = 7.5 Hz, 2H); 7.55 (t, *J* = 7.5 Hz, 1H); 7.45 (t, *J* = 7.5 Hz, 2H); 7.20-7.33 (m, 5H); 3.31 (t, *J* = 7.4 Hz, 2H); 3.07 (t, *J* = 7.4 Hz, 2H).

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