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The first successful intermolecular Heck reaction of Baylis–Hillman adducts: synthesis of β-aryl substituted Baylis–Hillman adducts

Jeong Mi Kim [a], Ko Hoon Kim [a], Taek Hyeon Kim [b], Jae Nyoung Kim [a,*]

[a] Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea
[b] Department of Applied Chemistry and Center for Functional Nano Fine Chemicals, College of Engineering, Chonnam National University, Gwangju 500-757, Republic of Korea

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Abstract

The first successful intermolecular Heck reaction between Baylis–Hillman adducts and aryl iodides was achieved under the conditions comprising $Pd(OAc)_2$/*n*-Bu_4NBr/KOAc in CH_3CN.

Keywords: Baylis–Hillman adducts; Heck reaction; $Pd(OAc)_2$

During the last two decades, notable improvements in Baylis–Hillman chemistry have been achieved in view of the reaction rate and synthetic applications of Baylis–Hillman adducts.[1,2] However, the general and efficient synthesis of β-branched Baylis–Hillman adducts has remained unsolved although a few approaches have been reported.[3] Thus, the development of a new method of these compounds would complement other previous by reported methods.[3]

The most simple and convenient method for the preparation of β-aryl substituted Baylis–Hillman adducts could be the palladium-mediated Heck reaction with aryl halides. Actually intermolecular Heck type arylation of Baylis–Hillman adducts has been examined by some research groups.[4] However, the reactions gave benzyl-substituted β-keto ester **4** as the major product instead of β-aryl substituted Baylis–Hillman adduct **3** (Scheme 1).[4] Compound **4** was generated via the *syn*-elimination of H_aPdOAc from the intermediate (**I**) and the following keto–enol tautomerization.[4c,d] This unfavorable result might be the principal reason for the lack of reports on the synthesis of β-aryl substituted Baylis–Hillman adducts via the Heck type arylation strategy.

However, the results of most of the Pd-mediated reactions can be altered by changing the reaction conditions,[5] thus we decided to find a suitable reaction condition for the intermolecular Heck arylation. Although the acidity of H_a must be different from that of H_b/H_c, but while there is only one H_a hydrogen on one side, there are two H_b and H_c hydrogens on the carbon holding palladium. Thus, we imagined that we could control the reaction pathway by using excess amounts of relatively strong base. We examined the reaction of Baylis–Hillman adduct **1a** and iodobenzene (**2a**) under various conditions in Table 1 in these respects, and found an efficient condition comprising $Pd(OAc)_2$ (15 mol %)/TBAB (1.0 equiv)/KOAc (3.0 equiv)/CH_3CN/reflux (Table 1, entry 7). From the experiments, we found that the use of relatively larger amounts of $Pd(OAc)_2$ and KOAc was crucial for the improvement of the yield of Heck product **3**. The use of bromobenzene (**2d**) was less effective (entry 10).

The reaction of **1a** and **2a** under the optimized conditions afforded β-keto ester **4a** (25%) and the desired Heck product **3a** (62%) as cleanly separable *E*/*Z* mixture (26:36, entry 1 in Table 2).[6,7] The reactions between Baylis–Hillman adducts (**1a**–**c**) and aryl iodides (**2a**–**c**) gave

* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.
E-mail address: kimjn@chonnam.ac.kr (J. N. Kim).

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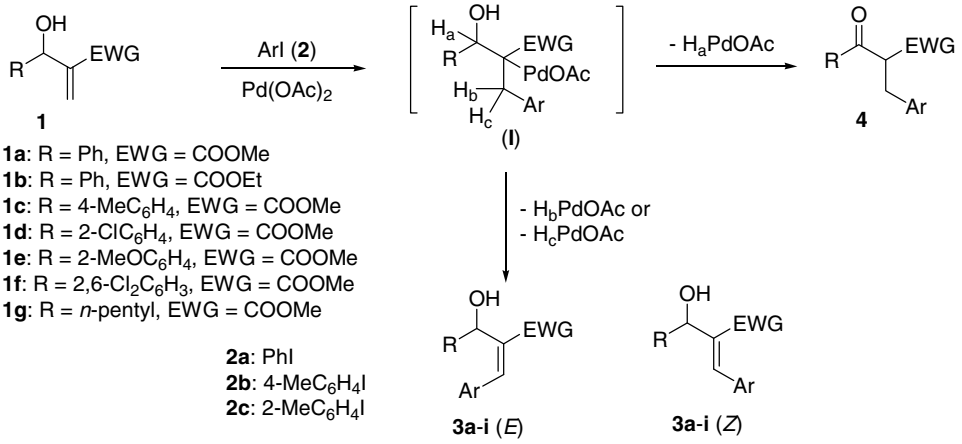
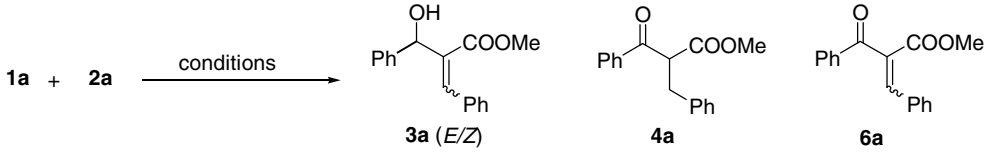


Scheme 1.

Table 1
The reaction of **1a** and iodobenzene (**2a**) under various conditions



Entry	Conditions[a]	Products[b] (%)
1	$Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %)/TBAB (1.0 equiv)/KOAc (3.0 equiv)/CH_3CN/reflux/24 h	**1a** (5)/**3a** (45)/**4a** (42)
2	$Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %)/KOAc (3.0 equiv)/CH_3CN/reflux/7 h	**1a** (30)*/**3a** (15)/**4a** (50)*
3	$Pd(OAc)_2$ (5 mol %)/TBAB (1.0 equiv)/KOAc (3.0 equiv)/CH_3CN/reflux/12 h	**1a** (14)/**3a** (50)/**4a** (30)
4	$Pd(OAc)_2$ (5 mol %)/TBAB (1.0 equiv)/K_2CO_3 (3.0 equiv)/CH_3CN/reflux/4 h	No **1a**/**3a** (36)/**4a** (34)/**6a** (18)
5	$Pd(OAc)_2$ (10 mol %)/TBAB (1.0 equiv)/Et_3N (3.0 equiv)/CH_3CN/reflux/1 h	**1a** (20)*/**3a** (15)*/**4a** (60)*
6	$Pd(OAc)_2$ (10 mol %)/TBAB (2.0 equiv)/KOAc (3.0 equiv)/CH_3CN/reflux/24 h	No **1a**/**3a** (50)*/**4a** (15)*/**6a** (15)*
7	$Pd(OAc)_2$ (15 mol %)/TBAB (1.0 equiv)/KOAc (3.0 equiv)/CH_3CN/reflux/24 h	no **1a**/**3a** (62)/**4a** (25)
8	$Pd(OAc)_2$ (15 mol %)/TBAB (1.0 equiv)/KOAc (0.3 equiv)/CH_3CN/reflux/24 h	**1a** (21)/**3a** (42)/**4a** (24)
9	$Pd(OAc)_2$ (15 mol %)/TBAB (1.0 equiv)/KOAc (3.0 equiv)/DMF/80 °C/24 h	No **1a**/**3a** (50)*/**4a** (25)*
10	$Pd(OAc)_2$ (15 mol %)/TBAB (1.0 equiv)/KOAc (3.0 equiv)/CH_3CN/reflux/24 h	**1a** (30)*/**3a** (35)*/**4a** (10)*

[a] **1a** (1.0 mmol) and **2a** (2.0 mmol) were used and bromobenzene (**2d**) was used in entry 10.
[b] Isolated yield and the yield marked with asterisk were estimated on TLC and decarboxylated compound **5a** (Table 3) was observed in some cases in trace amounts.

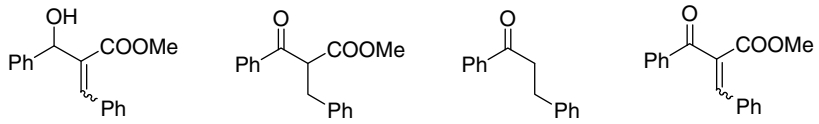
Table 2
Heck reaction of Baylis–Hillman adducts to prepare β-aryl Baylis–Hillman adducts[a]

Entry	Substrates	Products (%)		
1	**1a** + **2a**	**3a**-*E* (26)	**3a**-*Z* (36)	**4a** (25)[4a]
2	**1a** + **2b**	**3b**-*E* (28)	**3b**-*Z* (38)	**4b** (24)[4a]
3	**1a** + **2c**	**3c**-*E* (35)	**3c**-*Z* (33)	**4c** (21)
4	**1b** + **2a**	**3d**-*E* (23)	**3d**-*Z* (38)[3a]	**4d** (24)
5	**1c** + **2a**	**3e**-*E* (24)	**3e**-*Z* (38)	**4e** (27)[4a]
6	**1d** + **2a**	**3f**-*E* (10)[b]	**3f**-*Z* (72)	**4f** (not)
7	**1e** + **2a**	**3g**-*E* (19)	**3g**-*Z* (43)	**4g** (15)[4a]
8	**1f** + **2a**	3h-*E* (3)[c]	**3h**-*Z* (76)	**4h** (not)
9	**1g** + **2a**	**3i**-*E* (30)	**3i**-*Z* (24)	**4i** (not)

[a] Conditions: compound **1** (1.0 equiv), compound **2** (2.0 equiv), $Pd(OAc)_2$ (15 mol %), TBAB (1.0 equiv), KOAc (3.0 equiv), CH_3CN, reflux, 24 h.
[b] Contaminated with some **3f**-*Z*.
[c] Contaminated wih some **1f**.

similar results (entries 1–5). In all the cases, desired Heck products **3a**–**e** were isolated in 61–68% yields and β-keto esters **4a**–**e** in 21–27% yields. It is interesting to note that the reaction of **1d** and **2a** under the same conditions produced **3f** in 82% yield (entry 6). We could not observe the formation of the corresponding β-keto ester **4f**. The results could be explained well by the increased steric hindrance around the proton H_a during the last elimination stage in intermediate (**I**) to increase the formation of Heck product. Similar tendency was observed in 2-methoxy and 2,6-dichloro derivatives (entries 7 and 8). Moreover, *Z*-isomer was the predominant one (43–76:3–19) for the Baylis–Hillman adducts having *ortho*-substitutent, presumably due to the steric hindrance between the two aryl moieties. In addition, we obtained Heck product **3i** as the sole product in 54% yield when we use the Baylis–Hillman adduct **1g**

Table 3
The reaction of **1a** and iodobenzene (**2a**)/bromobenzene (**2d**) under reported conditions



3a (*E*/*Z*) **4a** **5a** **6a**

Entry	Conditions	Products[a] (%)
1	**1a**/**2d** (2.0 equiv)/$Pd(OAc)_2$ (2 mol %)/TBAB (1.0 equiv)/$NaHCO_3$ (2.5 equiv)/THF/reflux/7 h	**4a** (81)[4a]
1′	**1a**/**2d** (2.0 equiv)/$Pd(OAc)_2$ (2 mol %)/TBAB (1.0 equiv)/$NaHCO_3$ (2.5 equiv)/THF/reflux/17 h	**1a** (15)*/**3a** (5)*/**4a** (65)
2	**1a**/**2d** (not mentioned)/$Pd(OAc)_2$ (1 mol %)/PPh_3 (2 mol %)/Et_3N (1.25 equiv)/sealed tube/100 °C/20 h	**4a** (48)/**5a** (28)[4b]
2′	**1a**/**2d** (2.0 equiv)/$Pd(OAc)_2$ (1 mol %)/PPh_3 (2 mol %)/Et_3N (1.25 equiv)/sealed tube/100 °C/20 h	**1a** (5)*/**3a** (5)*/**4a** (28)/**5a** (6)
3	**1a**/**2a** (2.0 equiv)/$Pd(OAc)_2$ (2.5 mol %)/TBAB (0.5 equiv)/KOAc (0.3 equiv)/DMF/70 °C/3 h	**4a** (79)[4c]
3′	**1a**/**2a** (2.0 equiv)/$Pd(OAc)_2$ (2.5 mol %)/TBAB (0.5 equiv)/KOAc (0.3 equiv)/DMF/70 °C/24 h	**1a** (50)*/**4a** (22)
3″	**1a**/**2a** (2.0 equiv)/$Pd(OAc)_2$ (10 mol %)/TBAB (0.5 equiv)/KOAc (0.3 equiv)/DMF/70 °C/24 h	**1a** (28)/**3a** (39)/no **4a**/no **5a**/**6a** (13)

[a] Isolated yield and the yield marked with asterisk are estimated yield on TLC.

derived from hexanal. The results might be due to relatively lower acidity of the corresponding H_a to make the elimination of H_aPdOAc difficult to form β-keto ester **4i**. The reaction of methyl (2-hydroxymethyl)cinnamate (**1h**) and **2a** was not effective and we obtained small amounts of the corresponding acetate (8%), and **1h** was recovered in 54% yield.

From the whole results we could draw some trends for the Heck reaction of Baylis–Hillman adducts: (i) the yield of Heck product was increased when we use relatively larger amounts of $Pd(OAc)_2$, (ii) larger R (Scheme 1) made the elimination of H_aPdOAc difficult and increase the Heck product, (iii) excess amounts of KOAc made the reaction more effective, and (iv) Heck product could be the sole product for the substrate having less acidic H_a.

At the earliest stage of this study, we examined the reported conditions on the Pd-mediated reaction of Baylis–Hillman adduct and aryl bromide/iodide.[4a–c] The following three conditions were repeated in some cases without much problem in our hands, but showed much discrepancy to the reported results in some cases. The results are summarized in Table 3.

(i) PhBr/$Pd(OAc)_2$ (2 mol %)/TBAB (1.0 equiv)/$NaHCO_3$ (2.5 equiv)/THF/reflux.[4a]
(ii) PhBr/$Pd(OAc)_2$ (1 mol %)/PPh_3 (2 mol %)/Et_3N (1.25 equiv)/sealed tube/100 °C.[4b]
(iii) PhI/$Pd(OAc)_2$ (2.5 mol %)/TBAB (0.5 equiv)/KOAc (0.3 equiv)/DMF/70 °C.[4c]

When we carried out the reaction of **1a** and **2a** under the first condition (entry 1),[4a] almost similar results were observed (entry 1′). However, the reaction was not completed even after 17 h and we recovered the remaining **1a** (15%) and observed the formation of small amounts of Heck product **3a** (5%). When we used the second condition (entry 2),[4b] we observed the formation of β-keto ester **4a** (28%), decarboxylated product **5a** (6%),[4b] remaining **1a** (ca. 5%), and Heck product **3a** (ca. 5%) (entry 2′). However, when we repeated the third condition (entry 3),[4c] we observed somewhat different results. Under the exactly same conditions (entry 3′), we obtained β-keto ester **4a** in only 22% and **1a** was remained in about 50% yield. When we increased the amount of $Pd(OAc)_2$ to 10 mol % (entry 3″), we observed the formation of Heck product **3a** (20%) and an oxidized compound **6a** (20%), and we could not observe the formation of β-keto ester **4a** at all.

In summary, we prepared some β-aryl Baylis–Hillman adducts via the Heck type reaction of Baylis–Hillman adduct and aryl iodide under the influence of $Pd(OAc)_2$ (15 mol %)/TBAB (1.0 equiv)/KOAc (3.0 equiv) in refluxing CH_3CN in a moderate yield as a cleanly separable *E*/*Z* mixture.

Acknowledgments

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6. *Typical procedure for the synthesis of* **3a**: A stirred solution of **1a** (192 mg, 1.0 mmol), **2a** (408 mg, 2.0 mmol), $Pd(OAc)_2$ (34 mg, 15 mol %), TBAB (322 mg, 1.0 mmol), KOAc (294 mg, 3.0 mmol) in CH_3CN (3 mL) as heated to reflux for 24 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 7:1), we obtained compounds **3a**-*Z* (97 mg, 36%), **3a**-*E* (70 mg, 26%), and **4a** (67 mg, 25%) as colorless oils. Other compounds were synthesized similarly and the structures were identified by their spectroscopic data. Representative spectroscopic data of prepared compounds **3a**-*Z*, **3a**-*E*, **3i**-*Z*, and **3i**-*E* are as follows.

   Compound **3a**-*Z*: 36%; colorless oil; IR (film) 3469, 3028, 1728, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.00 (d, $J = 5.7$ Hz, 1H), 3.54 (s, 3H), 5.60 (d, $J = 5.7$ Hz, 1H), 6.92 (s, 1H), 7.24–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.67, 75.60, 126.56, 127.98, 128.16, 128.34, 128.38, 128.50, 135.16, 135.26, 135.41, 140.92, 169.08; ESIMS *m*/*z* 269 (M^++H). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.38; H, 6.27.

   Compound **3a**-*E*: 26%; colorless oil; IR (film) 3515, 2953, 1713, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3H), 4.06 (d, $J = 11.4$ Hz, 1H), 5.88 (d, $J = 11.4$ Hz, 1H), 7.24–7.43 (m, 10H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.07, 69.72, 125.43, 127.26, 128.41, 128.68, 129.10, 129.22, 132.37, 134.19, 141.84, 142.66, 168.01; ESIMS *m*/*z* 269 (M^++H). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.31; H, 6.39.

   Compound **3i**-*Z*: 24%; colorless oil; IR (film) 3446, 2931, 1716, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, $J = 6.9$ Hz, 3H), 1.26–1.52 (m, 6H), 1.67–1.74 (m, 2H), 2.36 (d, $J = 6.3$ Hz, 1H), 3.67 (s, 3H), 4.40 (d, $J = 6.3$ Hz, 1H), 6.84 (s, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.99, 22.53, 25.39, 31.59, 36.16, 51.75, 74.62, 128.20 (2C), 128.24, 133.27, 135.35, 136.40, 169.44; ESIMS *m*/*z* 263 (M^++H). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.33; H, 8.72.

   Compound **3i**-*E*: 30%; white solid, mp 57–58 °C; IR (film) 3527, 2954, 1697, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, $J = 6.9$ Hz, 3H),1.16–1.49 (m, 6H), 1.60–1.72 (m, 1H), 1.85–1.96 (m, 1H), 3.32 (d, $J = 11.4$ Hz, 1H), 3.85 (s, 3H), 4.63–4.71 (m, 1H), 7.26–7.42 (m, 5H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.96, 22.55, 25.73, 31.52, 36.76, 51.94, 68.94, 128.49, 128.71, 129.06, 134.15, 134.63, 140.23, 168.33; ESIMS *m*/*z* 263 (M^++H). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.56; H, 8.42.
7. *E* and *Z* isomers could be separated cleanly without loss in most cases, and the chemical shifts of the vinyl protons of *E* isomers appeared at 7.69–7.99 ppm and *Z* isomers at 6.57–7.11 ppm, which are the characteristic chemical shifts ranges of this type compounds.[1–3]