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An expedient aralkylation of Baylis–Hillman adduct via the Pd-catalyzed decarboxylative protonation strategy

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ABSTRACT

An expedient protocol of aralkylation of Baylis–Hillman adducts has been developed. This method used Pd-catalyzed decarboxylative protonation strategy to the allyl ester precursor that was made from the Baylis–Hillman adduct and allyl phenylacetate.

Introduction of aryl group at the primary position of the Baylis–Hillman adduct has been carried out in a variety of ways.[1–3] Friedel–Crafts reaction of Baylis–Hillman alcohol, acetate, and *aza*-Baylis–Hillman adduct with arenes has been used most frequently.[2] Recently, Pd-catalyzed cross-coupling protocol was reported.[3] However, an efficient method for the introduction of arylmethyl group at the Baylis–Hillman adducts has not been reported although the product α-substituted acrylate ester has been used extensively in organic synthesis.[4] Very recently, Roy and co-workers reported on the preparation of these compounds via Cp_2TiCl-mediated radical-induced addition protocol.[4]

After Tsuji's brilliant contributions, Pd-mediated decarboxylative protonation and allylation have been used widely in organic synthesis.[5–8] Recently, we also reported on Pd-catalyzed decarboxylative protonation protocol for the synthesis of 1,5-dicarbonyl compounds from Baylis–Hillman adducts.[7] During the project we imagined that we could introduce arylmethyl moiety at the primary position of the Baylis–Hillman adduct and could prepare homologous series of the Friedel–Crafts products by using the Pd-catalyzed decarboxylative protonation strategy as in Scheme 1.

As is often the case, the corresponding π-allylpalladium carboxylate intermediate cannot lose carbon dioxide without an electron-accommodating group.[5–8] Many functional groups have been reported as the electron-accommodating moieties including ester, nitrile, and acetyl groups.[5–8] Recently, Waetzig and Tunge used electron-deficient aryl and heterocyclic moieties as the electron-accommodating group in their Pd-assisted decarboxylative allylation.[9] Thus, we selected *para*-nitro derivative **3a** as the model substrate and examined the whole process: introduction of allyl *p*-nitrophenylacetate (**2a**) at the primary position of the bromide of Baylis–Hillman adduct **1a** to make **3a,** and the following Pd-catalyzed decarboxylative protonation to desired compound **4a** (Table 1). The plausible mechanism for the Pd-catalyzed decarboxylative protonation is depicted in Scheme 1 (vide supra).

Introduction of **2a** was carried out using K_2CO_3/CH_3CN at room temperature in good yield (88%).[10] With compound **3a** we examined the conditions of decarboxylative protonation as shown in Table 1. The formation of compounds **5a** and **6a** was also observed during the reaction besides that of **4a**.[10] As shown, variable ratios of compounds **4a**–**6a** were observed, and were dependent on the ratio/amounts of Et_3N/HCOOH and reaction temperature. Best result was observed with 1.1 equiv of Et_3N and 1.1 equiv of HCOOH conditions in refluxing CH_3CN (entry 1). The reaction at room temperature produced carboxylic acid **6a** as the major compound (entry 4), and excess amounts of Et_3N/HCOOH increased the amounts of amino compound **5a** (entries 2 and 3). The use of ammonium formate showed similar results (entry 5).

Encouraged by the successful results, we prepared various starting materials **3a**–**g** by the reaction of allyl arylacetates **2a**–**d** and the bromide of Baylis–Hillman adducts **1a**–**c** in good yields (52–91%). In some cases when the use of K_2CO_3 is less effective, we used Cs_2CO_3 or TBAF (*n*-tetrabutylammonium fluoride, THF solution) as in entries 5–7. The next Pd-catalyzed decarboxylative protonation reactions were carried out under the optimized conditions (entry 1

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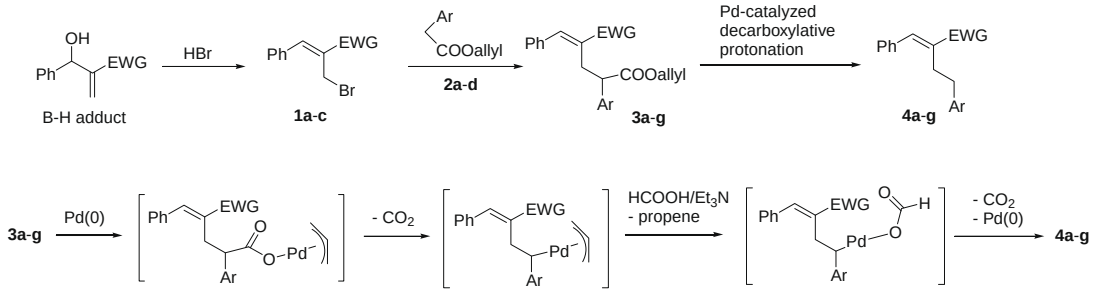
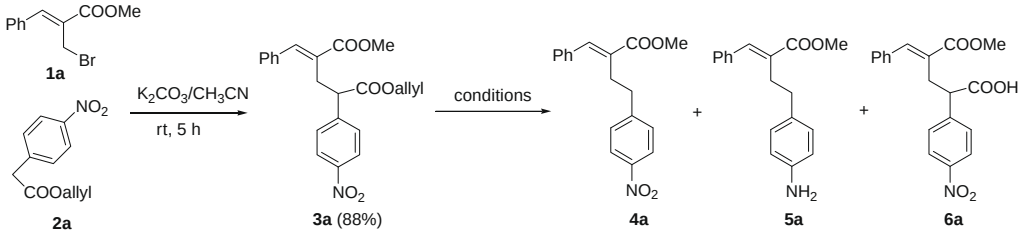


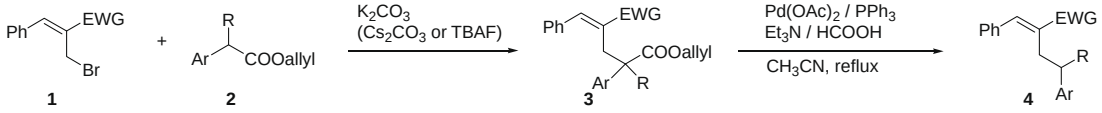
Scheme 1.

Table 1
Optimization of reaction conditions with **3a**



Entry	Conditions	Products (%)
1	$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (1.1 equiv), HCOOH (1.1 equiv), CH_3CN, reflux, 2 h	**4a** (90), no **5a**
2	$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (2.4 equiv), HCOOH (2.4 equiv), CH_3CN, reflux, 3 h	**4a** (68), **5a** (18)
3	$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (3.0 equiv), HCOOH (6.0 equiv), CH_3CN, reflux, 24 h	**4a** (13), **5a** (51)
4	$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (2.0 equiv), HCOOH (2.0 equiv), CH_3CN, rt, 5 h	**4a** (12), **6a** (82)
5	$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), $HCOONH_4$ (1.1 equiv), CH_3CN, reflux, 4 h	**4a** (79), **5a** (5)

Table 2
Aralkylation of Baylis–Hillman adducts at the primary position



1a: EWG = COOMe
1b: EWG = COMe
1c: EWG = CN

2a: Ar = 4-$NO_2C_6H_4$, R = H
2b: Ar = 4-$NO_2C_6H_4$, R = Me
2c: Ar = 2-$NO_2C_6H_4$, R = H
2d: Ar = 4-$MeSO_2C_6H_4$, R = H

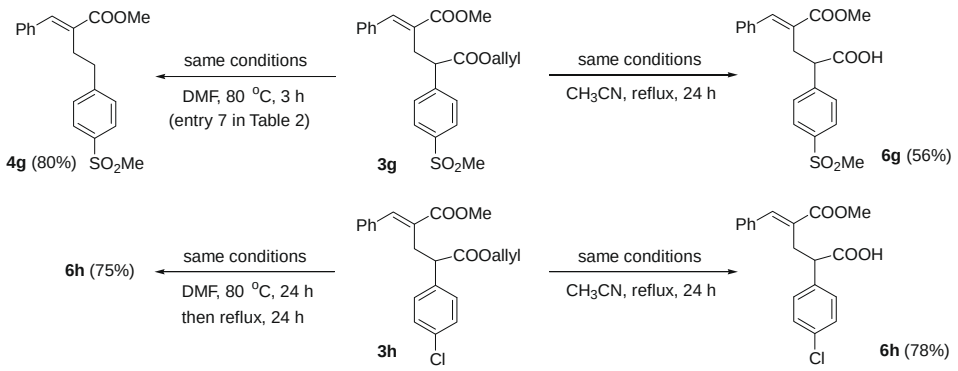
For compounds **3** and **4**
a: EWG = COOMe, Ar = 4-$NO_2C_6H_4$, R = H
b: EWG = COOMe, Ar = 4-$NO_2C_6H_4$, R = Me
c: EWG = COOMe, Ar = 2-$NO_2C_6H_4$, R = H
d: EWG = COMe, Ar = 4-$NO_2C_6H_4$, R = H
e: EWG = COMe, Ar = 2-$NO_2C_6H_4$, R = H
f: EWG = CN, Ar = 4-$NO_2C_6H_4$, R = H
g: EWG = COOMe, Ar = 4-$MeSO_2C_6H_4$, R = H

Entry	Conditions	Compound **3** (%)	Conditions[a] (h)	Compound **4** (%)
1	K_2CO_3 (1.5 equiv), CH_3CN, rt, 5 h	**3a** (88)	2	**4a** (90)
2	K_2CO_3 (1.5 equiv), CH_3CN, 50 °C, 24 h	**3b** (62)	2	**4b** (88)
3	K_2CO_3 (1.5 equiv), CH_3CN, rt, 12 h	**3c** (91)	12	**4c** (96)
4	K_2CO_3 (1.5 equiv), CH_3CN, rt, 7 h	**3d** (60)	3	**4d** (94)
5	Cs_2CO_3 (2.0 equiv), CH_3CN, rt, 4 h	**3e** (74)	4	**4e** (96)
6	TBAF (2.0 equiv), THF, rt, 30 min	**3f** (52)[b,c]	2	**4f** (88)[c]
7	Cs_2CO_3 (2.0 equiv), CH_3CN, rt, 12 h	**3g** (74)	3[d]	**4g** (80)

[a] Conditions: $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (1.1 equiv), HCOOH (1.1 equiv), CH_3CN, reflux.
[b] Appreciable amounts of 1:2 adduct of **2** and **1** were formed (40%) as a side product.
[c] The stereochemistry is *Z*.
[d] DMF was used as solvent (80 °C).

in Table 1). Good to excellent yields of products **4a–g** were obtained, and the results are summarized in Table 2.

The reaction of methanesulfonyl derivative **3g** did not produce **4g** under the same conditions in CH_3CN (24 h, reflux). Instead of **4g**, we isolated acid compound **6g** in 56% (Scheme 2). However, we could prepare **4g** in good yield (80%) by exchanging the solvent CH_3CN to DMF (entry 7 in Table 2 and Scheme 2). Due to the relatively weak electron-accommodating ability of methanesulfonyl group than the nitro group of compounds **3a–f**, the reaction was sluggish in CH_3CN. However, decarboxylation was effective in



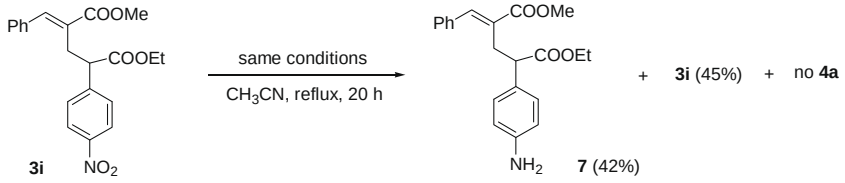
Scheme 2.

more polar solvent DMF, fortunately. The reaction of *p*-chloro derivative **3h** produced the corresponding carboxylic acid compound **6h** (78%). In this case, decarboxylation was impossible due to lack of π-electron-accommodating substituent even in DMF solvent under very harsh conditions (reflux, 24 h) as shown in Scheme 2. As expected, the reaction of ethyl ester **3i** did not produce any trace amounts of product **4a** under the same conditions (Scheme 3). We isolated amino compound **7** in 42% after 20 h.

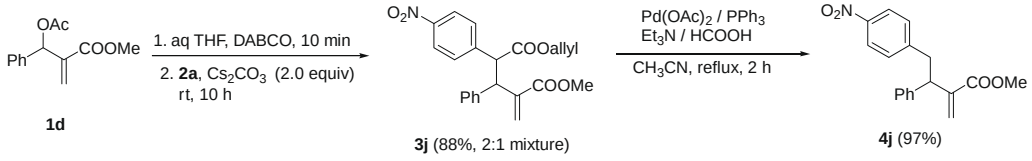
As a next entry, we examined the feasibility for the introduction of arylmethyl moiety at the secondary position of the Baylis–Hillman adduct as shown in Scheme 4. Required starting material **3j** was synthesized using DABCO salt concept[11] from the acetate **1d** in 88% yield as a diastereomeric mixture (2:1). The next Pd-mediated decarboxylative protonation was carried out under the same conditions and we obtained **4j** in excellent yield (97%). However, during the preparation of compound **3k** from the reaction of **1a** and **2e**, inseparable mixture of primary **3k** and secondary **3l** was obtained (88%, 1:1 mixture) as shown in Scheme 5. Thus, we used the mixture without separation in the next decarboxylative protonation reaction and obtained compounds **4k** (38%) and **4l** (39%).

As the last manipulation, we examined Pd-catalyzed decarboxylative allylation with compound **3a** as shown in Scheme 6 under the conditions of $Pd(OAc)_2/PPh_3$ in dry toluene,[5,8,9] and obtained product **8** (75%) as the major compound together with small amounts of **4a** (19%). The compound **8** could also be prepared from the Pd-catalyzed decarboxylative protonation reaction of compound **9** that was synthesized by the allylation of **3a** with allyl bromide.

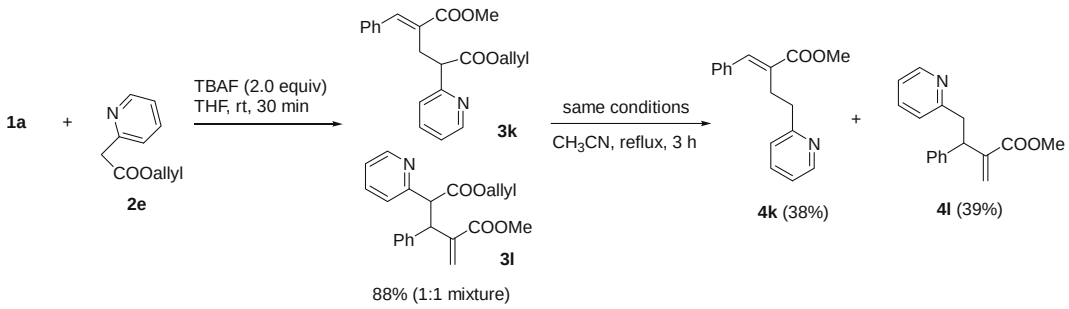
In summary, we disclosed an efficient aralkylation protocol at either primary or secondary position of the Baylis–Hillman adducts



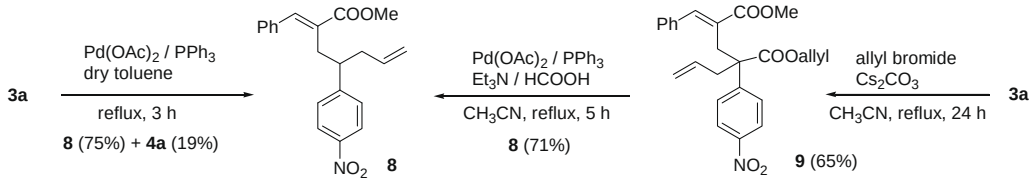
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

via the novel Pd-mediated decarboxylative protonation protocol as the key step.

Acknowledgments

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10. *Typical procedure for the synthesis of* **3a** *and* **4a**: A mixture of **1a** (306 mg, 1.2 mmol), **2a** (221 mg, 1.0 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (3 mL) was stirred at room temperature for 5 h. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 10:1:1), compound **3a** was isolated as a white solid, 348 mg (88%). A stirred mixture of **3a** (198 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 5 mol %), PPh_3 (13 mg, 10 mol %), HCOOH (25 mg, 0.55 mmol), and Et_3N (56 mg, 0.55 mmol) in CH_3CN (3 mL) was heated to reflux for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 9:1), compound **4a** was isolated as a white solid, 140 mg (90%). Selected spectroscopic data of prepared compounds, **3a**, **4a**, **4j,** and **8** are as follows.
Compound **3a**: 88%; white solid, mp 56–58 °C; IR (film) 2951, 1736, 1712, 1522, 1348, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.20–3.34 (m, 2H), 3.80 (s, 3H), 4.07 (dd, J = 9.3 and 6.6 Hz, 1H), 4.45–4.49 (m, 2H), 5.14–5.21 (m, 2H), 5.72–5.85 (m, 1H), 7.07–7.10 (m, 2H), 7.20 (d, J = 9.0 Hz, 2H), 7.29–7.33 (m, 3H), 7.67 (s, 1H), 7.98 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.5, 49.9, 52.2, 65.8, 118.5, 123.4, 128.5, 128.6, 128.7, 128.8, 129.2, 131.5, 134.9, 142.3, 145.1, 147.1, 168.0, 171.8; ESIMS m/z 396 (M^++1).
Compound **4a**: 90%; white solid, mp 77–79 °C; IR (film) 2955, 1706, 1509, 1349, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.83–2.97 (m, 4H), 3.84 (s, 3H), 7.22–7.40 (m, 7H), 7.74 (s, 1H), 8.09 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.8, 35.0, 52.1, 123.6, 128.5, 128.6, 128.8, 129.2, 131.5, 135.4, 140.6, 146.5, 149.2, 168.4; ESIMS m/z 312 (M^++1). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.58; H, 5.37; N, 4.42.
Compound **4f**: 88%; pale yellow solid, mp 142–144 °C; IR (film) 2928, 2208, 1511, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.72–2.78 (m, 2H), 3.07–3.12 (m, 2H), 6.84 (s, 1H), 7.34–7.42 (m, 5H), 7.63–7.68 (m, 2H), 8.17 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.3, 37.5, 109.3, 118.3, 123.9, 128.6, 128.9, 129.4, 130.3, 133.2, 144.8, 146.8, 147.4; ESIMS m/z 279 (M^++1). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.59; H, 5.34; N, 9.86.
Compound **4j**: 97%; pale yellow oil; IR (film) 2951, 1720, 1519, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.14 (dd, J = 13.5 and 9.3 Hz, 1H), 3.33 (dd, J = 13.5 and 6.3 Hz, 1H), 3.66 (s, 3H), 4.20 (dd, J = 9.3 and 6.3 Hz, 1H), 5.71 (s, 1H), 6.34 (s, 1H), 7.10–7.25 (m, 7H), 8.02 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.4, 47.7, 51.9, 123.2, 124.9, 126.8, 128.0, 128.3, 129.7, 140.5, 142.6, 146.3, 147.6, 166.8.
Compound **8**: 75%; pale yellow oil; IR (film) 2949, 1712, 1519, 1346, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26–2.47 (m, 2H), 2.85–3.09 (m, 3H), 3.76 (s, 3H), 4.90–4.97 (m, 2H), 5.49–5.61 (m, 1H), 7.01–7.07 (m, 4H), 7.28–7.33 (m, 3H), 7.61 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.2, 40.0, 44.9, 52.0, 117.0, 123.2, 128.3, 128.4, 128.6, 128.7, 130.8, 135.4, 135.5, 141.0, 146.4, 151.6, 168.4; ESIMS m/z 352 (M^++1). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.45; H, 6.23; N, 3.67..
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