Pd-Mediated Cross-Coupling Reactions between the Bromide of Baylis-Hillman Adduct and Organostannanes

Saravanan Gowrisankar, Sung Hwan Kim, and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
**E-mail: kimjn@chonnam.ac.kr*
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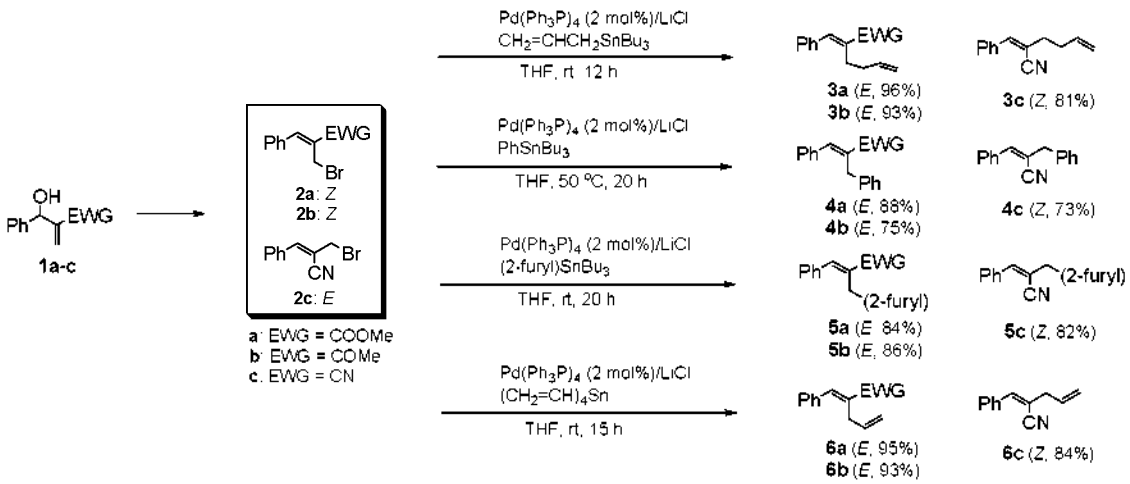
Recently numerous chemical transformations of Baylis-Hillman adducts have been published involving the synthesis of cyclic and acyclic compounds.[1] Among the reactions introduction of allyl,[2] vinyl[3] and aryl[4,5] moiety at the primary position of the Baylis-Hillman adducts can be regarded as an important transformation due to the usefulness of the compounds thereof as synthetic intermediates.[2-5]

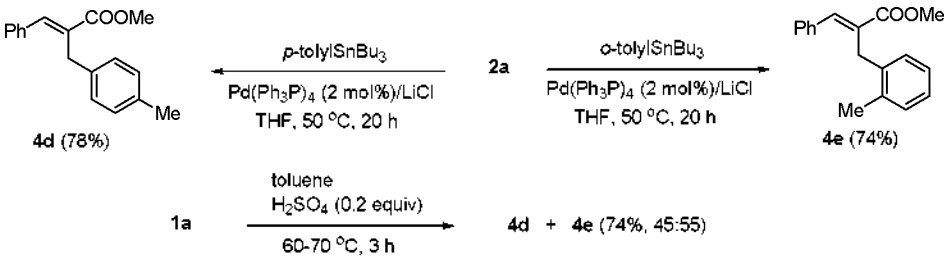
Introduction of allyl group at the primary position of Baylis-Hillman adduct was studied by Yadav and coworkers.[2a,b] They reported the synthesis of 1,5-diene derivatives involving the use of *in-situ* generated allylzinc reagent and Baylis-Hillman acetates.[2a] Later, they reported another method, the reaction of allyltrimethylsilane and Baylis-Hillman alcohol in the presence of BF_3 etherate.[2b] Introduction of alkenyl moiety at the primary position of Baylis-Hillman adduct has not been reported much.[3] Isobutenyl and isopentenyl groups were introduced using the corresponding Grignard reagents and used for the synthesis of dihydronaphthalenes.[3a] Very recently Ranu and coworkers published an elegant method, a Pd-mediated introduction of aryl and vinyl moiety to Baylis-Hillman acetate, using triorganoindium reagents.[3b] Introduction of aryl group at the primary position of the Baylis-Hillman adduct has been studied relatively well and carried out by using Friedel-Crafts type reaction under various acidic conditions.[4] However, regioselectivity is the principle problem in this case.[4c,d] As an example, Friedel-Crafts reaction with toluene produced a mixture of *ortho*- and *para*-isomers (*vide infra*, Scheme 2). In addition, various Pd- and Rh-catalyzed introduction of aryl moiety has been studied.[5] Kabalka group reported a Pd-catalyzed cross-coupling of Baylis-Hillman acetate and organosilane[5a] or potassium organotrifluoroborate.[5b] Genet and coworkers examined a Rh-catalyzed arylation with arylboronic acid[5c] or potassium aryltrifluoroborate.[5d]

Although various methods have been reported and most of the methods provided moderate yields of products.[2-5] development of an efficient and general method for the introduction of carbon nucleophile at the primary position of Baylis-Hillman adduct is still highly required, especially in a stereoselective manner. Thus we decided to examine the cross-coupling reactions between the bromide of Baylis-Hillman adduct and allyl-, aryl-, and vinylstannane (Scheme 1) as a continuous work on our recent Pd-mediated reactions with Baylis-Hillman adducts.[6] Although cross-couplings involving the use of allyl bromides and organostannanes have been studied extensively,[7] this is the first trial in the Baylis-Hillman chemistry to the best of our knowledge. Fortunately we obtained good results and wish to report herein the results. The results are summarized in Scheme 1.

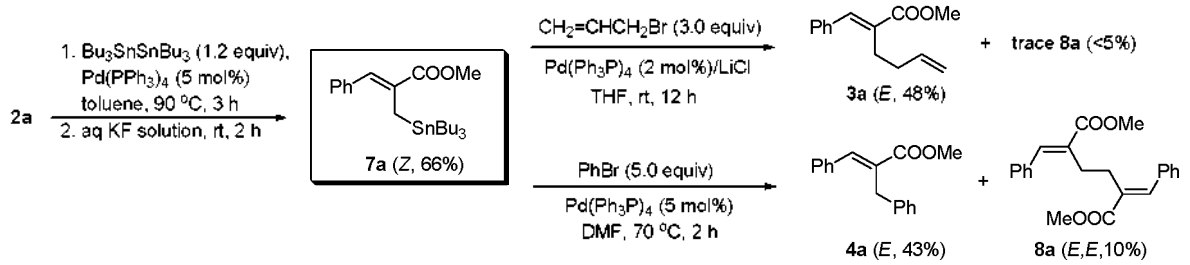
We decided to use the bromides of Baylis-Hillman adducts and chose three representative Baylis-Hillman adducts, **2a-c**.[8] The starting materials **2a-c** were prepared in pure form (*Z* for **2a** and **2b**, *E* for **2c**) as shown in Scheme 1.[9,10] The reaction of cinnamyl bromide **2a** and allyltributylstannane (1.2 equiv) in the presence of $Pd(Ph_3P)_4$/LiCl (0.5 equiv) in THF afforded desired product **3a** in 96% yield.[2a,5d,11] As a palladium catalyst, $Pd(Ph_3P)_4$ was superior than $Pd(OAc)_2$ and only 2



Scheme 1



Scheme 2



Scheme 3

mol% of catalyst was sufficient. The reaction time can be shortened by raising the reaction temperature with 5 mol% of Pd(0) catalyst. Similarly, **3b** and **3c** were prepared in high yields also (81-93%). The arylation and vinylation of **2a-c** were examined with phenyltributylstannane, 2-(tributylstannyl)furan, and tetravinylstannane. The corresponding products **4a-c**, **5a-c**, and **6a-c** were obtained in good yields (73-95%). The yields of nitrile-containing compounds were comparatively lower than those of the ester- or acetyl-containing compounds. The reaction of phenyltributylstannane required elevated temperature (50 °C).

Tolyl-substituted products **4d** and **4e** were synthesized in good yields (74-78%) similarly by the reactions of **2a** and *ortho*-tolyltributylstannane and *para*-tolyltributylstannane which were prepared from Pd-mediated reactions between *n*-tributyltin hydride and 2-iodo- and 4-iodotoluene, respectively,[12] while the traditional Friedel-Crafts reaction of Baylis-Hillman adduct **1a** and toluene under the influence of H_2SO_4 (0.2 equiv) afforded *ortho*:*para* mixture in 74% yield (55:45 ratio in ^{1}H NMR) as in Scheme 2.

As a next trial we prepared tributylstannyl derivative **7a** by the Pd-mediated reaction of **2a** and hexabutylditin in the presence of Pd(0) in 66% yield as in Scheme 3.[13,14] The reaction of **7a** and allyl bromide under the influence of $Pd(Ph_3P)_4$/LiCl produced **3a** in low yield (48%). Similarly the reaction of **7a** and bromobenzene afforded **4a** in low yield (43%) also together with some self-coupling product **8a** (10%).[15]

In summary, we disclosed an efficient synthetic method of allyl-, aryl- and vinyl-attached Baylis-Hillman adducts *via* the Pd-mediated cross-coupling reactions between the bromide of Baylis-Hillman adduct and the corresponding organostannane compounds.

Experimental Section

Typical experimental procedure for the preparation of 3a. To a stirred mixture of **2a**[10] (128 mg, 0.5 mmol) and allyltributylstannane (200 mg, 0.6 mmol) in dry THF (2 mL) was added $Pd(PPh_3)_4$ (12 mg, 2 mol%) and LiCl (11 mg, 0.25 mmol) and the reaction mixture was stirred at room temperature for 12 h. After removal of solvent and column chromatographic purification process (hexanes/EtOAc, 95:5) analytically pure product **3a** was obtained as colorless oil.[2a] 104 mg (96%). Other compounds were synthesized similarly and the known compounds, **3a**,[2a] **4a**,[5b] **4b**,[5a] **4c**,[5e] **4d**,[5b] **4e**,[5b] **6a**,[3b] **6c**[16] and **8a**[15] were identified by comparison with their ^{1}H NMR and IR spectroscopic data with the reported. The spectroscopic data of unknown compounds, **3b**, **3c**, **5a**, **5b**, **5c**, **6b** and **7a**, are as follows.

Compound **3b**: 93%; colorless oil; IR (film) 3077, 2927, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20-2.24 (m, 2H), 2.45 (s, 3H), 2.60-2.63 (m, 2H), 4.95-5.05 (m, 2H), 5.78-5.87 (m, 1H), 7.34-7.43 (m, 5H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.61, 26.07, 33.00, 114.77, 128.56, 128.60, 129.20, 135.57, 137.88, 140.02, 142.06, 200.06.

Compound **3c**: 81%; colorless oil; IR (film) 3080, 2924, 2209 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37-2.54 (m, 4H), 5.04-5.16 (m, 2H), 5.75-5.88 (m, 1H), 6.94 (s, 1H), 7.26-7.44 (m, 3H), 7.69-7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.27, 35.64, 110.66, 116.45, 118.65, 128.55, 128.78, 129.93, 133.67, 136.04, 143.84.

Compound **5a**: 84%; yellow oil; IR (film) 2951, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.80 (s, 3H), 3.88 (s, 2H), 6.06-6.08 (m, 1H), 6.30-6.31 (m, 1H), 7.33-7.47 (m, 6H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.89, 52.15, 106.00, 110.39, 129.23, 128.55, 128.89, 129.33, 134.99, 141.23, 141.30, 152.96, 168.22.

Compound **5b**: 86%; yellow oil; IR (film) 2957, 2924, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46 (s, 3H), 3.87 (s, 2H), 6.00-6.02 (m, 1H), 6.27-6.29 (m, 1H), 7.32-7.49 (m, 6H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.78, 26.05, 106.01, 110.37, 128.60, 129.04, 129.36, 134.99, 137.45, 141.14, 141.45, 153.04, 199.13.

Compound **5c**: 82%; yellow oil; IR (film) 2913, 2212 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.73 (s, 2H), 6.26-6.27 (m, 1H), 6.35-6.36 (m, 1H), 6.99 (s, 1H), 7.38-7.43 (m, 5H), 7.72-7.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.58, 107.60, 108.00, 110.63, 118.33, 128.73, 128.80, 130.28, 133.34, 142.46, 144.84, 149.82.

Compound **6b**: 93%; colorless oil; IR (film) 3079, 2978, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.47 (s, 3H), 3.26-3.29 (m, 2H), 4.99-5.11 (m, 2H), 5.91-6.03 (m, 1H), 7.32-7.46 (m, 5H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.05, 30.57, 115.51, 128.48, 128.82, 129.28, 135.34, 135.73, 139.20, 141.03, 199.54.

Compound **7a**: 66%; colorless oil; IR (film) 2956, 2925, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84-0.94 (m, 15H), 1.23-1.31 (m, 6H), 1.37-1.46 (m, 6H), 2.29 (s, 2H), 3.80 (s, 3H), 7.35-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.22, 11.80, 13.67, 27.33, 28.95, 51.98, 127.47, 128.30, 129.25, 131.78, 133.89, 136.88, 169.46; ESIMS *m/z* 465 (M^++1). Anal. Calcd for $C_{23}H_{38}O_2Sn$: C, 59.37; H, 8.23. Found: C, 59.02; H, 8.44.

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