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Facile Synthesis of *N*-Tosyl *Aza*-Baylis-Hillman Adducts of Acrylamide *via* a Pd-Catalyzed Hydration of Nitrile to Amide†

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The Baylis-Hillman reaction, which involves the coupling of activated vinyl compounds with electrophiles under the catalytic influence of a tertiary amine, gives rise to adducts, so called Baylis-Hillman adducts, with a new stereocenter and has proven to be a very useful carbon-carbon bond-forming method in the synthesis of highly functionalized molecules.[1] As the activated vinyl compounds, various compounds have been used in the Baylis-Hillman reaction including acrylates, acrylonitrile, vinyl ketones, vinyl sulfones and acrylamides.[1] However, among the activated vinyl compounds acrylamide has not been used much for the synthesis of the corresponding Baylis-Hillman adducts due to its sluggish reactivity.[1-3]

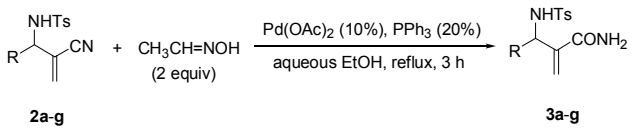
Very recently, we reported an efficient synthetic method of Baylis-Hillman adducts of acrylamide involving a Pd-catalyzed hydration of nitrile to amide with the aid of acetaldoxime.[4] We believe that this method is the best choice for the preparation of the Baylis-Hillman adducts of acrylamide.[4] In these respects, we decided to examine the feasibility for the synthesis of *N*-tosyl *aza*-Baylis-Hillman adducts of acrylamide by using the same strategy. To date, only one example on the synthesis of *N*-tosyl *aza*-Baylis-Hillman adduct of acrylamide was reported involving an enzymatic hydration of nitrile to the corresponding amide.[5,6]

Our synthetic rationale involved a Pd-catalyzed hydration of nitrile group of *N*-tosyl *aza*-Baylis-Hillman adducts of acrylonitrile **2a-g**, as shown in Scheme 1. The preparation of starting material, **2a** as an example, can be carried out in two ways (Scheme 2). One is the synthesis of *N*-tosylimine and DABCO-catalyzed Baylis-Hillman reaction with acrylonitrile.[1,7,8] The other way involved the preparation of the acetate of Baylis-Hillman adduct of acrylonitrile **1a** and the conversion of the acetate group into *N*-tosyl group *via* the corresponding DABCO salt, as reported in the literature.[9] The first approach did not produce desired *N*-tosyl *aza*-Baylis-Hillman adduct **2a** in a pure form due to the partial hydrolysis of *N*-tosylimine to the corresponding aldehyde and tosylamide, thus Baylis-Hillman adduct **1a** was contaminated in a variable amounts depending upon the substrate (Scheme 2).[8,9] To the contrary, the second approach afforded desired starting material **2a** in a very pure state,[9] thus we used this method throughout the whole entries.

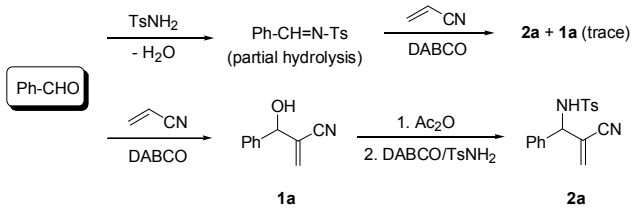
The synthesis of Baylis-Hillman adducts of acrylonitrile and the next acetylation was carried out as already reported.[1,9] Conversions of the acetates into *N*-tosyl *aza*-Baylis-Hillman adducts **2a-i** were performed in moderate yields *via* the corresponding DABCO salts.[9] With these starting materials **2a-i**, we examined a Pd-catalyzed hydration under the influence of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), CH_3CH=NOH (2.0 equiv) in refluxing aqueous EtOH for 3 h,[4] and the results are summarized in Table 1. As shown in Table 1, various kinds of *N*-tosyl *aza*-Baylis-Hillman adducts of acrylamide **3a-g** were synthesized in good yields (83 ~ 91%), as shown in entries 1-7. *N*-Methanesulfonyl derivative **2h** and *N*-phthalyl analog **2i** showed similar reactivity (entries 8 and 9).

As a next trial, we examined the reaction of 4-chloroaniline derivative **2j** under the same reaction conditions. However, expected product **3j** was not formed at all. Instead, primary compound **5** was isolated as a mixture (*E*/*Z* = 2:1) in 66%, as shown in Scheme 3. The results stated that Pd(0)-catalyzed Tsuji-Trost allylic rearrangement of 4-chloroaniline moiety,[1a,10] from the secondary position to the thermodynamically more stable primary position, occurred prior to the Pd(0)-catalyzed hydration of nitrile moiety, *via* the corresponding π-allylpalladium intermediate (**I**). In the reaction, trace amounts of rearranged nitrile **4** (8%) and 4-chloroaniline (6%) were also isolated, and this is the definitive evidence of the involvement of a Pd(0)-catalyzed Tsuji-Trost allylic rearrangement.[11]

In summary, we developed an efficient palladium-catalyzed two-step protocol for the synthesis of *N*-tosyl *aza*-Baylis-Hillman adducts of acrylamide. The method involved the preparation of the corresponding Baylis-Hillman adducts of acrylo-



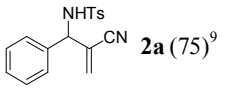
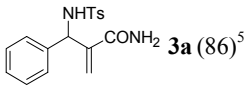
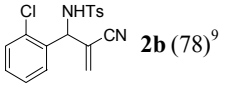
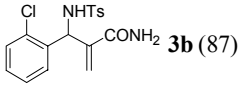
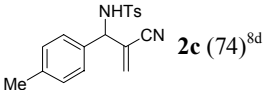
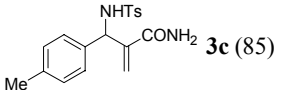
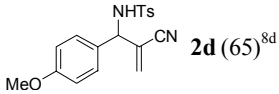
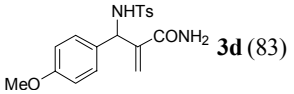
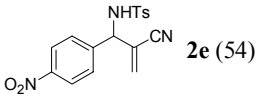
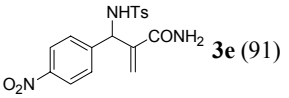
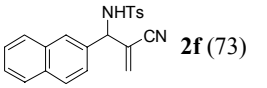
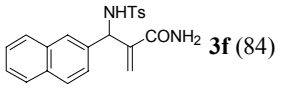
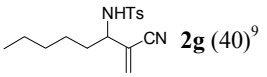
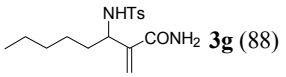
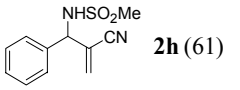
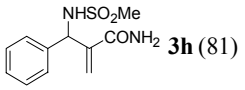
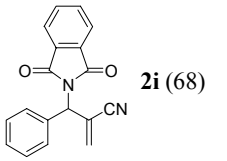
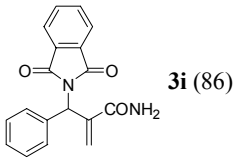
Scheme 1



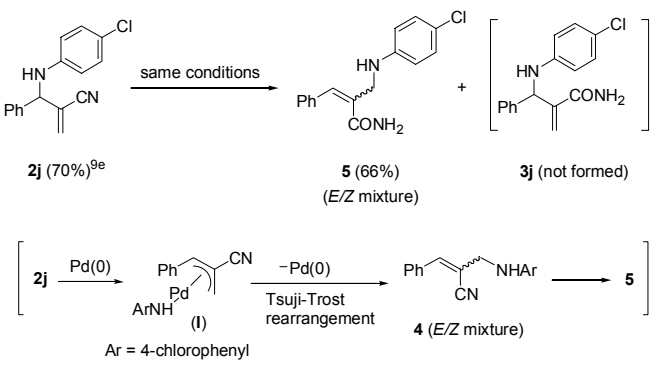
Scheme 2

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.

Table 1. Synthesis of *aza*-Baylis-Hillman adducts of acrylamide

entry	substrate **2** (%)[a]	product **3** (%)[b]
1	 **2a** (75)[9]	 **3a** (86)[5]
2	 **2b** (78)[9]	 **3b** (87)
3	 **2c** (74)[8d]	 **3c** (85)
4	 **2d** (65)[8d]	 **3d** (83)
5	 **2e** (54)	 **3e** (91)
6	 **2f** (73)	 **3f** (84)
7	 **2g** (40)[9]	 **3g** (88)
8	 **2h** (61)	 **3h** (81)
9	 **2i** (68)	 **3i** (86)

[a]Compounds **2a-i** were prepared from Baylis-Hillman acetates *via* the DABCO salt.[9,8d] [b]Conditions: $CH_3CH{=}NOH$ (2 equiv), $Pd(OAc)_2$ (10%), PPh_3 (20%), aqueous EtOH, reflux, 3 h.



Scheme 3

nitrile and the following Pd-catalyzed hydration of nitrile with acetaldoxime.

Experimental Section

Typical procedure for the synthesis of *N*-tosyl *aza*-Baylis-Hillman adduct of acrylamide 2a.[9a] To a stirred mixture of the Baylis-Hillman acetate **1a** (402 mg, 2.0 mmol) in aqueous THF (1:1, 10 mL) was added DABCO (270 mg, 2.4 mmol) at room temperature and stirred for 10 min. To the reaction mixture *p*-toluenesulfonamide (345 mg, 2.0 mmol) was added and the whole mixture was stirred at 60 ~ 70 °C for 2 days. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 4:1), **2a** was obtained as a white solid, 468 mg (75%). Other starting materials **2b-j** were prepared similarly from the corresponding Baylis-Hillman acetates and appropriate nitrogen nucleophiles ($TsNH_2$, $MeSO_2NH_2$, phthalimide, and *p*-chloroaniline), and the spectroscopic data of unknown compounds (**2e**, **2f**, **2g**,[9a] **2h**, and **2i**) are as follows. Compounds **2a**,[5,9a-c] **2b**,[8d,9a] **2c**,[8d] and **2d**[8d] were known.

Compound 2e: 54%; white solid, mp 137 ~ 139 °C; IR (KBr) 3257, 2227, 1528, 1351 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 5.21 (d, J = 8.1 Hz, 1H), 5.91 (d, J = 8.1 Hz, 1H), 6.01 (s, 1H), 6.04 (s, 1H), 7.25 (d, J = 6.6 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 6.6 Hz, 2H), 8.12 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.53, 59.10, 115.90, 122.17, 124.22, 127.15, 128.03, 129.87, 133.04, 136.47, 142.81, 144.56, 148.01; ESIMS *m*/*z* 358 (M^++1).

Compound 2f: 73%; white solid, mp 163 ~ 164 °C; IR (KBr) 3234, 2231, 1593, 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 5.20 (d, J = 7.8 Hz, 1H), 5.73 (d, J = 7.8 Hz, 1H), 5.99 (s, 1H), 6.06 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.12-7.16 (m, 1H), 7.42-7.51 (m, 3H), 7.63 (d, J = 8.4 Hz, 2H), 7.66-7.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.36, 59.78, 116.61, 123.21, 123.85, 126.50, 126.62, 126.77, 127.15, 127.57, 128.03, 129.23, 129.57, 131.98, 132.93, 133.05, 133.09, 136.69, 143.89; ESIMS *m*/*z* 363 (M^++1).

Compound 2g:[9a] 40%; colorless oil; IR (film) 3278, 2956, 2930, 2860, 2223, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 6.9 Hz, 3H), 1.16-1.23 (m, 6H), 1.53-1.66 (m, 2H), 2.43 (s, 3H), 3.89 (q, J = 7.2 Hz, 1H), 5.40-5.46 (m, 1H), 5.78 (s, 1H), 5.80 (s, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H); ESIMS *m*/*z* 307 (M^++1).

Compound 2h: 61%; colorless oil; IR (film) 3271, 2227, 1326 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.87 (s, 3H), 5.27 (d, J = 8.1 Hz, 1H), 5.71 (d, J = 8.1 Hz, 1H), 6.05 (s, 1H), 6.10 (s, 1H), 7.33-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.07, 59.66, 116.63, 123.96, 126.89, 129.19, 129.37, 132.19, 136.29; ESIMS *m*/*z* 237 (M^++1).

Compound 2i: 68%; yellow solid, mp 105 ~ 107 °C; IR (KBr) 2227, 1766, 1720, 1381 cm^{-1}; ^1HNMR ($CDCl_3$, 300 MHz) δ 5.76 (s, 1H), 6.11 (s, 1H), 6.24 (s, 1H), 7.32-7.42 (m, 3H), 7.48-7.56 (m, 2H), 7.70-7.75 (m, 2H), 7.82-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.81, 116.95, 121.50, 123.62, 128.94, 129.02 (2C), 131.36, 133.42, 134.37, 134.43, 167.16; ESIMS *m*/*z* 289 (M^++1).

Typical procedure for the Pd-catalyzed conversion of 2a to 3a. A mixture of Baylis-Hillman adduct **2a** (312 mg, 1.0 mmol),

acetaldoxime (118 mg, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 10 mol %), PPh_3 (52.5 mg, 20 mmol %) in aqueous EtOH (H_2O/EtOH, 1:4, 5 mL) was heated to reflux for 3 h under nitrogen atmosphere. The reaction mixture was diluted with EtOH (5 mL) and filtered through a Celite pad and washed with EtOH and CH_2Cl_2. After removal of solvent and column chromatographic purification process (hexanes/EtOAc/$CHCl_3$, 1:1:1), compound **3a** was obtained as a white solid, 284 mg (86%). Other compounds were synthesized similarly and the representative spectroscopic data of **3a-i** are as follows.

Compound 3a:[5] 86%; white solid, mp 201 ~ 203 °C; IR (KBr) 3442, 3349, 3215, 1665, 1637, 1600 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.33 (s, 3H), 5.45 (d, J = 9.6 Hz, 1H), 5.57 (s, 1H), 5.73 (s, 1H), 6.95 (br s, 1H), 7.06-7.21 (m, 5H), 7.26 (d, J = 7.8 Hz, 2H), 7.49 (br s, 1H), 7.56 (d, J = 7.8 Hz, 2H), 8.32 (d, J = 9.6 Hz, 1H); ESIMS m/z 331 (M^++1). Anal. Calcd. For $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.97; H, 5.83; N, 8.22.

Compound 3b: 87%; white solid, mp 211 ~ 213 °C; IR (KBr) 3468, 3352, 3269, 1666, 1633, 1596 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.31 (s, 3H), 5.31 (s, 1H), 5.82 (s, 1H), 5.89 (d, J = 5.7 Hz, 1H), 7.00 (br s, 1H), 7.14-7.30 (m, 6H), 7.48 (br s, 1H), 7.54 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 5.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.92, 53.81, 119.78, 126.41, 126.74, 128.85, 129.06, 129.14, 129.20, 132.50, 136.95, 138.77, 142.18, 143.23, 167.79; ESIMS m/z 366 (M^++1). Anal. Calcd. For $C_{17}H_{17}ClN_2O_3S$: C, 55.96; H, 4.70; N, 7.68. Found: C, 56.14; H, 4.91; N, 7.56.

Compound 3c: 85%; pale yellow solid, mp 209 ~ 211 °C; IR (KBr) 3467, 3370, 3203, 1663, 1638, 1603 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.21 (s, 3H), 2.34 (s, 3H), 5.37 (d, J = 9.3 Hz, 1H), 5.54 (s, 1H), 5.69 (s, 1H), 6.91-6.99 (m, 5H), 7.26 (d, J = 8.1 Hz, 2H), 7.46 (br s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 8.23 (d, J = 9.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.57, 20.93, 56.58, 118.01, 126.44, 127.18, 128.52, 129.22, 136.23, 136.89, 138.70, 142.22, 144.03, 168.22; ESIMS m/z 345 (M^++1). Anal. Calcd. For $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.84; H, 5.67; N, 8.01.

Compound 3d: 83%; white solid, mp 194 ~ 195 °C; IR (KBr) 3499, 3391, 3180, 1670, 1636 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.34 (s, 3H), 3.68 (s, 3H), 5.37 (d, J = 9.0 Hz, 1H), 5.55 (s, 1H), 5.70 (s, 1H), 6.73 (d, J = 8.7 Hz, 2H), 6.94 (br s, 1H), 6.96 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.46 (br s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 8.23 (d, J = 9.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.98, 55.08, 56.36, 113.41, 117.82, 126.49, 128.53, 129.27, 131.84, 138.74, 142.24, 144.22, 158.34, 168.30; ESIMS m/z 361 (M^++1). Anal. Calcd. For $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 60.23; H, 5.87; N, 7.52.

Compound 3e: 91%; white solid, mp 180 ~ 182 °C; IR (KBr) 3479, 3376, 3134, 1659, 1634, 1596 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.31 (s, 3H), 5.53 (br s, 1H), 5.65 (s, 1H), 5.85 (s, 1H), 7.05 (br s, 1H), 7.23 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.57 (br s, 1H), 8.04 (d, J = 9.0 Hz, 2H), 8.53 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.86, 56.37, 119.60, 123.19, 126.46, 128.44, 129.31, 138.19, 142.56, 142.88, 146.40, 147.47, 167.57; ESIMS m/z 376 (M^++1). Anal. Calcd. For $C_{17}H_{17}N_3O_5S$: C, 54.39; H, 4.56; N, 11.19. Found: C, 54.73; H, 4.88; N, 10.97.

Compound 3f: 84%; white solid, mp 239 ~ 241 °C; IR (KBr) 3461, 3365, 3198, 1664, 1636, 1601 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.23 (s, 3H), 5.59 (d, J = 9.6 Hz, 1H), 5.66 (s, 1H), 5.81 (s, 1H), 6.97 (br s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.43-7.51 (m, 2H), 7.54 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.69-7.84 (m, 3H), 8.40 (d, J = 9.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.85, 57.00, 118.53, 125.50, 125.94 (2C), 126.13, 126.48, 127.37, 127.66, 127.68, 129.19, 132.07, 132.45, 137.08, 138.55, 142.29, 143.84, 168.21; ESIMS m/z 381 (M^++1). Anal. Calcd. For $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36. Found: C, 66.33; H, 5.63; N, 7.23.

Compound 3g: 88%; white solid, mp 126 ~ 128 °C; IR (KBr) 3469, 3367, 3200, 2929, 1663, 1635 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 0.76 (t, J = 6.9 Hz, 3H), 1.00-1.11 (m, 6H), 1.16-1.24 (m, 1H), 1.30-1.37 (m, 1H), 2.35 (s, 3H), 4.11-4.13 (m, 1H), 5.37 (s, 1H), 5.57 (s, 1H), 6.98 (br s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.45 (br s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 13.78, 20.97, 21.96, 24.91, 30.65, 35.02, 53.47, 117.57, 126.47, 129.35, 138.92, 142.25, 145.10, 168.76; ESIMS m/z 325 (M^++1). Anal. Calcd. For $C_{16}H_{24}N_2O_3S$: C, 59.23; H, 7.46; N, 8.63. Found: C, 59.56; H, 7.44; N, 8.45.

Compound 3h: 81%; white solid, mp 153 ~ 155 °C; IR (KBr) 3415, 3278, 3195, 1663, 1629 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.74 (s, 3H), 5.49 (d, J = 9.9 Hz, 1H), 5.69 (s, 1H), 5.92 (s, 1H), 7.08 (br s, 1H), 7.23-7.36 (m, 5H), 7.63 (br s, 1H), 7.91 (d, J = 9.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 41.28, 56.74, 118.85, 127.31, 127.37, 128.29, 140.51, 144.67, 168.44; ESIMS m/z 255 (M^++1). Anal. Calcd. For $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02. Found: C, 52.27; H, 5.48; N, 10.86.

Compound 3i: 86%; white solid, mp 203 ~ 205 °C; IR (KBr) 3450, 1764, 1704, 1687, 1600 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 5.20 (s, 1H), 6.02 (s, 1H), 6.36 (s, 1H), 7.11 (br s, 1H), 7.30-7.37 (m, 5H), 7.80 (br s, 1H), 7.83-7.88 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 54.22, 120.94, 123.30, 127.76, 128.43, 128.45, 131.16, 134.78, 137.45, 141.92, 167.48, 168.31; ESIMS m/z 307 (M^++1). Anal. Calcd. For $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.50; H, 4.92; N, 8.89.

Synthesis of compound 2j and the Pd(0)-catalyzed hydration reaction. Compound **2j** was prepared as reported,[9e] and the Pd(0)-catalyzed hydration was carried out under the same conditions (*vide supra*). In the reaction, we isolated **4** (8%), **5** (66%), and 4-chloroaniline (6%), and the spectroscopic data of compounds **4** and **5** are as follows.

Compound 4: 8% (major/minor = 6:1); yellow oil; IR (film) 3404, 2211, 1599, 1502 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.09 (d, J = 5.1 Hz, major, 2H), 4.12 (d, J = 5.7 Hz, minor, 2H), 4.22 (br s, major+minor, 1H), 6.37 (d, J = 9.0 Hz, minor, 2H), 6.57 (d, J = 9.0 Hz, major, 2H), 7.07 (d, J = 9.0 Hz, minor, 2H), 7.14 (d, J = 9.0 Hz, major, 2H), 7.13-7.75 (m, major+minor, 6H); ESIMS m/z 270 (M^++1).

Compound 5: 66% (major/minor = 2:1); yellow solid; IR (KBr) 3337, 3181, 1664, 1599, 1497 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.90 (d, J = 4.8 Hz, major, 2H), 3.91 (d, J = 6.0 Hz, minor, 2H), 5.91 (t, J = 4.8 Hz, major, 1H), 6.25 (t, J = 6.0 Hz, minor, 1H), 6.32 (s, minor, 1H), 6.55 (d, J = 9.0 Hz, major, 2H), 6.65 (d, J = 9.0 Hz, minor, 2H), 7.05 (d, J = 9.0 Hz, major, 2H), 7.09 (d, J = 9.0 Hz, minor, 2H), 7.20 (br s, minor, 2H), 7.21-

7.42 (m, major+minor, 5H), 7.48 (s, major, 1H), 7.57 (br s, major, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 47.17, 47.23, 113.62, 113.69, 119.18, 119.22, 124.41, 127.35, 128.07, 128.26, 128.39, 128.41, 128.51, 128.55, 129.09, 133.49, 135.31, 135.46, 136.03, 136.88, 147.39, 147.46, 169.45, 171.20; ESIMS *m/z* 288 (M^++1).

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