Lewis Base Effects in the Baylis−Hillman Reaction of Imines with Methyl Vinyl Ketone

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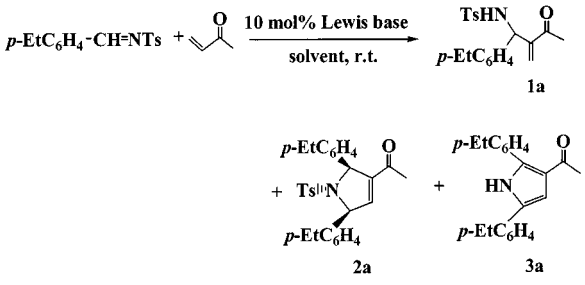
In the Baylis–Hillman reaction of *N*-benzylidene-4-methylbenzenesulfonamide with methyl vinyl ketone (MVK), we found that, in the presence of a catalytic amount of DMAP, PPh_3 or DABCO as Lewis base, the Baylis–Hillman reaction can be greatly accelerated to give the normal Baylis–Hillman adducts **1** in good or very high yields. However, with PBu_3 as a Lewis base, the abnormal Baylis–Hillman adducts **2** and **3** were formed under the same reaction conditions. The effect of the substituents was also examined and a plausible reaction mechanism proposed.

Introduction

The Baylis−Hillman reaction has made great progress[1] — it now includes a catalytic asymmetric version[2] — since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of a strong Lewis base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) in 1972.[3] During our own investigations on this very simple and useful reaction,[4] we found that in the reaction of aryl aldehydes with electron-donating groups such as Et or MeO on the phenyl ring with methyl vinyl ketone (MVK), the reactions were either sluggish or no reactions occurred under traditional Baylis−Hillman reaction conditions. Thus, we decided to use *N*-benzylidene-4-methylbenzenesulfonamides to replace the aryl aldehydes in the traditional Baylis−Hillman reaction with methyl vinyl ketone (MVK) as the C=N double bond of *N*-benzylidene-4-methylbenzenesulfonamides should be more active than the C=O double bond of aryl aldehydes. So far, we have only found one report related to the Baylis−Hillman reaction of MVK with imines generated in situ at 40 °C for 40 h.[5] Herein, we wish to report the results on the reactions of *N*-benzylidene-4-methylbenzenesulfonamides with MVK catalyzed directly by Lewis bases such as DABCO, DMAP, PPh_3, or PBu_3.

Results and Discussion

The promoters for the reaction of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide with MVK were examined systematically (Scheme 1, Table 1). We found that the reaction proceeds very well with 20 mol % of DABCO, DMAP or PPh_3 as a Lewis base, to give the normal Baylis−Hillman adduct **1a** in moderate to good yields (Table 1, entry 1−2, 6). The Lewis base PPh_3 gave the best results, whereas DBU, NEt_3 and SMe_2 showed no activity in this reaction (Table 1, entry 4−5). However, using PBu_3 as a Lewis base gave two unexpected adducts **2a** and **3a** (abnormal Baylis−Hillman adducts) and no formation of the normal Baylis−Hillman adduct **1a** was observed (Scheme 1, Table 1, entry 7). The structures of **2a** and **3a** were established by spectroscopic data and X-ray analyses (Figure 1 and 2).[6,7] The two aryl groups in **2a** are in *syn*-form (Figure 2). The use of 2.0 equiv. of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide and 1.0 equiv. of MVK in the presence of PBu_3 did not improve the yields of **2a** and **3a**.



Scheme 1

Similar results were obtained for other *N*-benzylidene-4-methylbenzenesulfonamides using PPh_3 as a Lewis base under the optimized reaction conditions (Scheme 2). The normal Baylis−Hillman adducts were obtained in good yields. These results are summarized in Table 2.

Abnormal Baylis−Hillman adducts can be obtained exclusively under the same reaction conditions for other *N*-

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Table 1. Baylis−Hillman reactions of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide (1.0 equiv.) with methyl vinyl ketone (1.0 equiv.) in the presence of Lewis base (20 mol %)

Entry	Promoter	Solvent	Time (h)	**1a**[a]	**2a**[a] [b]	**3**[a] [b]
1	DMAP	DMF	48	40	0	0
2	DABCO	DMF	48	36	0	0
3	DMAP	THF	24	40	0	0
4	DBU or NEt_3	THF	48	trace	0	0
5	SMe_2	THF	48	trace	0	0
6	PPh_3	THF	24	80	0	0
7	dppe	THF	9	56	0	0
8	PBu_3	THF	2	trace	60	25

[a] Isolated yield (%). [b] Yield based on imine.

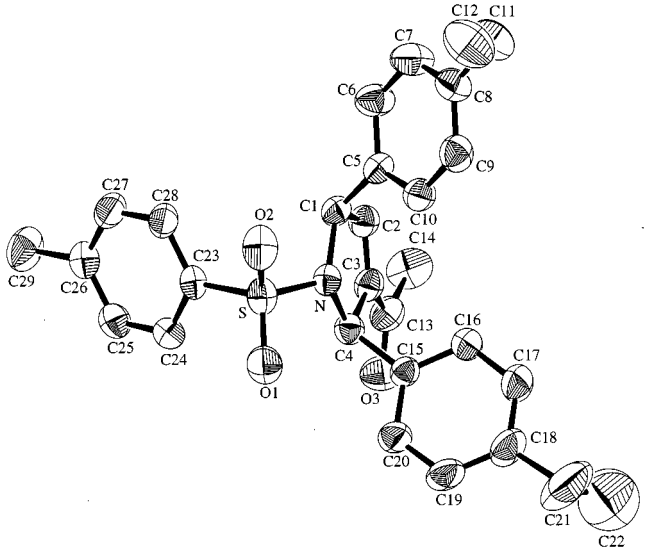


Figure 1. The crystal structure of **2a**

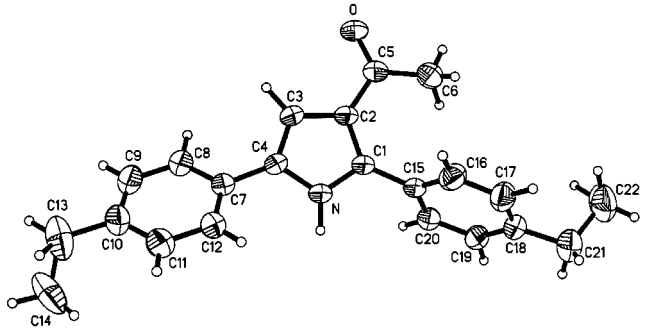
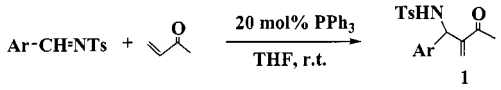


Figure 2. The crystal structure of **3a**

benzylidene-4-methylbenzenesulfonamides with MVK using PBu_3 as a Lewis base in THF (Scheme 3). These results are summarized in Table 3. The total yields of abnormal Baylis−Hillman adducts in general reached 75%. *N*-tosylated imines with electron-donating groups gave **2** as the major product (Table 3, entries 1−3, 8), whereas imines with electron-withdrawing groups gave **3** as the major product (Table 3, entries 4, 5, 7). No reaction occurred with the 2,3-

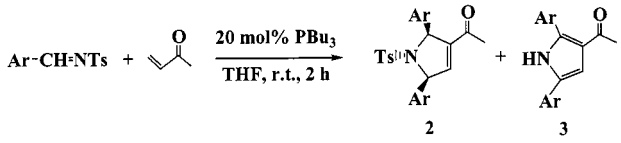


b: Ar = C_6H_5, **c:** Ar = *p*-MeC_6H_4, **d:** Ar = *p*-$MeOC_6H_4$, **e:** Ar = *p*-ClC_6H_4, **f:** Ar = *p*-BrC_6H_4, **g:** Ar = 2,3-$Cl_2C_6H_3$, **h:** Ar = *p*-$NO_2C_6H_4$, **i:** Ar = *m*-FC_6H_4, **j:** Ar = 2-furyl, **k:** Ar = *trans*-C_6H_5-CH=CH

Scheme 2

Table 2. Baylis−Hillman reactions of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide (1.0 equiv.) with methyl vinyl ketone (1.0 equiv.) in the presence of PPh_3 (20 mol %)

Entry	Ar	Yield of **1** (%)
1	C_6H_5	75
2	*p*-MeC_6H_4	92
3	*p*-$MeOC_6H_4$	70
4	*p*-ClC_6H_4	80
5	*p*-BrC_6H_4	80
6	2,3-$Cl_2C_6H_3$	45
7	*p*-$NO_2C_6H_4$	82
8	*m*-FC_6H_4	87
9	2-furyl	78
10	C_6H_4-CH=CH	67



b: Ar = C_6H_5, **c:** Ar = *p*-MeC_6H_4, **d:** Ar = *p*-$MeOC_6H_4$, **e:** Ar = *p*-ClC_6H_4, **f:** Ar = *p*-FC_6H_4, **g:** Ar = 2,3-$Cl_2C_6H_3$, **h:** Ar = *m*-FC_6H_4, **i:** Ar = 2-furyl

Scheme 3

Table 3. Abnormal Baylis−Hillman reactions of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide (1.0 equiv.) with methyl vinyl ketone (2.0 equiv.) in the presence of PBu_3 (20 mol %)

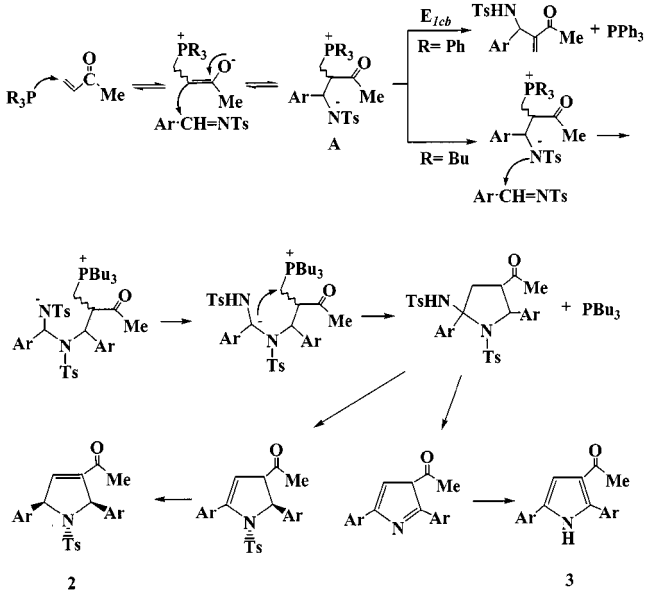
Entry	Ar	Time (h)	Yield of **2** (%)[a]	Yield of **3** (%)
1	C_6H_5	2	31	48
2	*p*-MeC_6H_4	2	48	28
3	*p*-$MeOC_6H_4$	2	65	20
4	*p*-ClC_6H_4	2	29	43
5	*p*-FC_6H_4	2	16	43
6	2,3-$Cl_2C_6H_3$	2	–	–
7	*m*-FC_6H_4	2	18	44
8	2-furyl	2	42	19

[a] Based on imine.

dichloro-substituted imine (Table 3, entry 6). We confirmed that **2a** and **3a** were formed independently during the reaction as **2a** cannot be transformed into **3a** under the reaction conditions. *N*-tosylated imines can react with methyl acryl-

ate or acrylonitrile under the same conditions, but the corresponding **2** and **3** were obtained in very low yields.

In Scheme 4, we tentatively propose a reaction mechanism for the formation of **2** and **3**. We believe that the difference of nucleophilicity between triphenylphosphane (PPh_3) and tributylphosphane (PBu_3) is the key factor for the different reaction products shown in Scheme 2 and 3. Using PPh_3 as the Lewis base (a weaker Lewis base), the corresponding Baylis−Hillman reaction intermediate **A**, which immediately gives the normal Baylis−Hillman adduct **1** by an E_{1cb} mechanism, is relatively difficult to form and thus requires a longer reaction time (24 h). With PBu_3 as the Lewis base (a stronger Lewis base), the easily formed corresponding intermediate **A** can attack the next imine to give the cyclized products (the reactions are generally complete within 2 h). This plausible reaction mechanism is supported by a known phosphane-catalyzed [3+2] cycloaddition of methyl 2,3-butadienoate and *N*-tosylimines.[8]



Scheme 4

In conclusion, we have found that in the Baylis−Hillman reaction of *N*-benzylidene-4-methylbenzenesulfonamides with MVK, the Lewis bases play a very important role. Normal Baylis−Hillman adducts were obtained using DMAP, DABCO or PPh_3 (20 mol %) as the Lewis base, whereas abnormal Baylis−Hillman adducts were formed exclusively using PBu_3 (20 mol %) as the Lewis base. Efforts are underway to elucidate the mechanistic details of this reaction and to determine the scope and limitations of this reaction.

Experimental Section

General Remarks: Unless otherwise stated, all reactions were carried out under an argon atmosphere. All solvents were purified by distillation. Methyl vinyl ketone and tributylphosphane were obtained from Tokyo Chemical Industry (Tokyo Kasei Co. Ltd.) and used without purification. All *N*-tosyl imines were prepared according to the literature. Infrared spectra were measured on a Perkin−Elmer 983 spectrometer. ^1H NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard. Mass spectra were recorded with an HP-5989 instrument and the HRMS were measured on a Finnigan MA+ mass spectrometer. Satisfactory CHN microanalyses were obtained with a Carlo−Erba 1106 analyzer. Melting points were obtained with a micro melting point apparatus and are uncorrected.

Typical Reaction Procedure for Triphenylphosphane-Catalyzed Baylis−Hillman Reaction of Methyl Vinyl Ketone and an *N*-(4-Ethylbenzylidene)-4-methylbenzenesulfonamide. Synthesis of 1a: Methyl vinyl ketone (41 μl, 0.5 mmol) was added to a solution of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide (144 mg, 0.5 mmol) and triphenylphosphane (26 mg, 0.1 mmol) in THF (1.0 mL) at room temperature. After stirring for 24 h at room temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, EtOAc/petroleum ether, 1:5) to yield **1a** (142 mg, 80%) as a colorless solid which was recrystallized from acetone and *n*-hexane. M.p. 126−128 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1674 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 1.23 (t, *J* = 7.6 Hz, 3 H, Me), 2.15 (s, 3 H, Me), 2.39 (s, 3 H, Me), 2.54 (q, *J* = 7.6 Hz, 2 H, CH_2), 5.20 (d, *J* = 6.1 Hz, 1 H, NH), 5.51 (d, *J* = 8.4 Hz, 1 H, CH), 6.09 (s, 2 H), 6.97 (d, *J* = 6.1 Hz, 2 H, Ar), 6.98 (2 H, *J* = 6.1 Hz, Ar), 7.21 (d, *J* = 8.4 Hz, 2 H, Ar), 7.63 (d, *J* = 8.4 Hz, 2 H). MS (EI): *m/z* (%) = 358 (0.5) [M^+ − 1], 288 (5.6) [M^+ − 69], 202 (100) [M^+ − 155] . $C_{20}H_{23}NO_3S$ (357.5): calcd. C 67.2, H 6.49, N 3.92; found C 67.04, H 6.42, N 3.74.

1b: Isolated as a colorless solid from the reaction of MVK with *N*-benzylidene-4-methylbenzenesulfonamide; m.p. 113−114 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1667 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.16 (s, 3 H, Me), 2.42 (s, 3 H, Me), 5.26 (d, *J* = 8.6 Hz, 1 H), 5.61 (d, *J* = 8.6 Hz, 1 H), 6.10 (s, 1 H), 6.11 (s, 1 H), 7.11 (m, 2 H, Ar), 7.20−7.27 (m, 5 H, Ar), 7.66 (d, *J* = 8.1 Hz, 2 H, Ar). MS (EI): *m/z* (%) = 260 (14.09) [M^+ − 69], 174 (100) [M^+ − 155], 155 (29.60) [$MePhSO_2^+$]. $C_{18}H_{19}NO_3S$ (329.4): calcd. C 65.63, H 5.81, N 4.25; found C 65.64, H 5.74, N 4.14.

1c: Isolated as a colorless solid from the reaction of MVK with *N*-(4-methylbenzylidene)-4-methylbenzenesulfonamide; m.p. 118−119 °C. IR (KBr): $\tilde{\nu}$ = 1664 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.16 (s, 3 H, Me), 2.27 (s, 3 H, Me), 2.42 (s, 3 H, Me), 5.23 (d, *J* = 8.4 Hz, 1 H), 5.56 (d, *J* = 8.4 Hz, 1 H), 6.10 (s, 2 H), 6.95 (d, *J* = 8.2 Hz, 2 H, Ar), 7.00 (d, *J* = 8.2 Hz, 2 H, Ar), 7.24 (d, *J* = 8.2 Hz, 2 H, Ar), 7.65 (d, *J* = 8.2 Hz, 2 H, Ar). MS (EI): *m/z* (%) = 274 (4.44) [M^+ − 69], 188 (100) [M^+ − 155], 91 (50.98) [$PhMe^+$]. $C_{19}H_{21}NO_3S$ (343.4): calcd. C 66.47, H 6.12, N 4.08; found C 66.74, H 6.47, N 3.89.

1d: Isolated as a colorless solid from the reaction of MVK with *N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide; m.p. 136−137 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1675 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.17 (s, 3 H, Me), 2.41 (s, 3 H, Me), 3.74 (s, 3 H, Me), 5.21 (d, *J* = 8.3 Hz, 1 H, NH), 5.49 (d, *J* = 8.3 Hz, 1 H, CH), 6.10 (s, 2 H), 6.73 (d, *J* = 6.8 Hz, 2 H, Ar), 6.99 (d, *J* = 6.8 Hz, 2 H, Ar), 7.25 (d, *J* = 9.3 Hz, 2 H, Ar), 7.65 (d, *J* = 9.3 Hz, 2 H, Ar). MS (EI): *m/z* (%) = 359 (0.30) [M^+], 290 (9.61) [M^+ − 69], 204 (100) [M^+ − 155], 91 (45.58) [$PhMe^+$]. $C_{19}H_{21}NO_4S$ (359.4): calcd. C 63.49, H 5.89, N 3.90; found C 63.24, H 5.81, N 3.73.

1e: Isolated as a colorless solid from the reaction of MVK with *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide; m.p.112−113

°C. IR ($CHCl_3$): $\tilde{\nu}$ = 1674 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.11 (s, 3 H, Me), 2.38 (s, 3 H, Me), 5.24 (d, *J* = 9.1 Hz, 1 H, NH), 5.99 (d, *J* = 9.1 Hz, 1 H, CH), 6.03 (s, 1 H), 6.06 (s, 1 H,), 7.01(d, *J* = 8.6 Hz, 2 H, Ar), 7.12 (d, *J* = 8.6 Hz, 2 H, Ar), 7.19 (d, *J* = 8.1 Hz, 2 H, Ar), 7.59 (d, *J* = 8.1 Hz, 2 H, Ar). MS (EI): *m*/*z* (%) = 294 (2.36) [M^+ − 69], 208 (100) [M^+ − 155], 91 (39.81) [$PhMe^+$]. $C_{18}H_{18}ClNO_3S$ (363.9): calcd. C 59.42, H 4.99, N 3.85; found C 59.43, H 4.94, N 3.78.

1f: Isolated as a colorless solid from the reaction of MVK with *N*-(4-bromobenzylidene)-4-methylbenzenesulfonamide; m.p. 115−116 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1674 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.16 (s, 3 H, Me), 2.42 (s, 3 H, Me), 5.20 (d, *J* = 8.9 Hz, 1 H), 5.71 (d, *J* = 8.9 Hz, 1 H), 6.06 (s, 1 H), 6.10 (s, 1 H), 6.99 (d, *J* = 6.7 Hz, 2 H, Ar), 7.24 (d, *J* = 8.4 Hz, 2 H, Ar), 7.32 (d, *J* = 6.7 Hz, 2 H, Ar), 7.63 (d, *J* = 8.4 Hz, 2 H, Ar). MS (EI): *m*/*z* (%) = 252 (92.12) [M^+ − 155], 254 (85.18) [M^+ − 153], 130 (100) [M^+ − 277], 91 (73.41) [$PhMe^+$]. $C_{18}H_{18}BrNO_3S$ (408.3): calcd. C 52.94, H 4.41, N 3.43; found C 52.96, H 4.46, N 3.42.

1g: Isolated as a colorless solid from the reaction of MVK with *N*-(2,3-dichlorobenzylidene)-4-methylbenzenesulfonamide; m.p. 96−98 °C. IR (KBr): $\tilde{\nu}$ = 1672 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.22 (s, 3 H, Me), 2.38 (s, 3 H, Me), 5.69 (d, *J* = 8.6 Hz, 1 H), 5.79 (d, *J* = 8.6 Hz, 1 H), 6.12 (s, 1 H), 6.17 (s, 1 H), 7.05 (dd, *J* = 8.0, 7.8 Hz, 1 H, Ar), 7.18 (d, *J* = 8.2 Hz, 2 H, Ar), 7.28 (m, 2 H, Ar), 7.62 (d, *J* = 8.2 Hz, 2 H, Ar). MS (EI): *m*/*z* (%) = 242 (5.00) [M^+ − 155], 171 (65.36) [M^+ − 226], 91 (100) [$PhMe^+$]. $C_{18}H_{17}Cl_2NO_3S \cdot 1/6C_6H_{14} \cdot 1/6C_3H_6O$ (422.3): calcd. C 55.50, H 4.82, N 3.32; found C 56.09, H 5.30, N 3.03.

1h: Isolated as a pale-yellow solid from the reaction of MVK with *N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide; m.p. 140−142 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1674 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.15 (s, 3 H, Me), 2.44 (s, 3 H, Me), 5.32 (d, *J* = 9.4 Hz, 1 H), 5.94 (d, *J* = 9.4 Hz, 1 H), 6.08 (s, 1 H), 6.14 (s, 1 H), 7.25 (d, *J* = 8.3 Hz, 2 H, Ar), 7.34 (d, *J* = 8.7 Hz, 2 H, Ar), 7.65 (d, *J* = 8.3 Hz, 2 H, Ar), 8.07 (d, *J* = 8.7 Hz, 2 H). MS (EI): *m*/*z* (%) = 305 (3.77) [M^+ − 69], 219 (100) [M^+ − 155], 155 (29.96) [$MePhSO_2^+$]. $C_{18}H_{18}N_2O_5S$ (374.4): calcd. C 57.74, H 4.85, N 7.48; found C 57.62, H 4.84, N 7.39.

1i: Isolated as a colorless solid from the reaction of MVK with *N*-(3-fluorobenzylidene)-4-methylbenzenesulfonamide; m.p. 98−99 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1673 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.16 (s, 3 H, Me), 2.41 (s, 3 H, Me), 5.24 (d, *J* = 9.2 Hz, 1 H, NH), 5.78 (d, *J* = 9.2 Hz, 1 H), 6.06 (s, 1 H), 6.11 (s, 1 H), 6.79−6.92 (m, 3 H, Ar), 7.14−7.23 (m, 3 H, Ar), 7.65 (d, *J* = 8.6 Hz, 2 H, Ar). MS (EI): *m*/*z* (%) = 278 (7.84) [M^+ − 69], 192 (100) [M^+ − 155], 155 (44.33) [$MePhSO_2^+$]. $C_{18}H_{18}FNO_3S$ (347.4): calcd. C 62.23, H 5.22, N 4.03; found C 62.38, H 5.34, N 3.82.

1j: Isolated as a colorless solid from the reaction of MVK with *N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide; m.p. 114−115 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1673 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.21 (s, 3 H, Me), 2.41 (s, 3 H, Me), 5.35 (d, *J* = 9.2 Hz, 1 H, NH), 5.70 (d, *J* = 9.2 Hz, 1 H), 6.00 (d, *J* = 3.2 Hz, 1 H, Ar), 6.08 (s, 1 H), 6.11 (s, 1 H), 6.19 (dd, *J* = 3.2, 1.8 Hz, 1 H, Ar), 7.18 (d, *J* = 1.8 Hz, 1 H, Ar), 7.26 (d, *J* = 8.6 Hz, 2 H), 7.68 (d, *J* = 8.6 Hz, 2 H, Ar). MS (EI): *m*/*z* (%) = 250 (2.77) [M^+ − 69], 164 (52.53) [M^+ − 155], 155 (40.56) [$MePhSO_2^+$]. $C_{16}H_{17}NO_4S$ (319.4): calcd. C 60.17, H 5.37, N 4.39; found C 60.23, H 5.33, N 4.19.

1k: Isolated as a pale-yellow solid from the reaction of MVK with 4-methyl-*N*-(3-phenylallylidene)benzenesulfonamide; m.p. 129−130 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1667 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.19 (s, 3 H, Me), 2.33 (s, 3 H, Me), 4.77 (dd, *J* = 8.8, 7.3 Hz, 1 H, CH), 5.62 (d, *J* = 8.8 Hz, 1 H, NH), 6.00 (m, 3 H), 6.25 (d, *J* = 15.9 Hz, 1 H), 7.14−7.26 (m, 7 H, Ar), 7.66 (d, *J* = 7.9 Hz, 2 H, Ar). MS (EI): *m*/*z* (%) = 286 (3.08) [M^+ − 69], 200 (100) [M^+ − 155], 157 (34.73) [M^+ − 198]. $C_{20}H_{21}NO_3S$ (355.5): calcd. C 67.58, H 5.95, N 3.94; found C 67.41, H 6.06, N 3.68.

Typical Reaction Procedure for the Tributylphosphane-Catalyzed Baylis−Hillman Reaction of Methyl Vinyl Ketone and an *N*-(4-Ethylbenzylidene)-4-methylbenzenesulfonamide. Synthesis of 2a and 3a: Methyl vinyl ketone (41 µl, 0.5 mmol) was added to a solution of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide (144 mg, 0.5 mmol) and tributylphosphane (25 µl) in THF (1.0 mL) at room temperature. The reaction was monitored by TLC. After stirring for 2 h the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/petroleum ether, 1:10−1:5) to yield **2a** (71 mg, 60%) and **3a** (20 mg, 25%) as solids that were recrystallized from acetone and *n*-hexane, respectively.

2a: Colorless solid; m.p. 151−152 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1676 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 1.21 (t, *J* = 7.6 Hz, 3 H, Me), 1.24 (t, *J* = 7.6 Hz, 3 H, Me), 2.17 (s, 3 H, Me), 2.30 (s, 3 H, Me), 2.60 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.65 (q, *J* = 7.6 Hz, 2 H, CH_2), 5.84 (t, *J* = 2.6 Hz, 1 H, CH), 5.93 (dd, *J* = 2.6, 2.1 Hz, 1 H), 6.62 (t, *J* = 2.1 Hz, 1 H, CH), 6.99 (d, *J* = 8.2 Hz, 2 H, Ar), 7.08 (d, *J* = 8.2 Hz, 2 H, Ar), 7.16 (d, *J* = 6.4 Hz, 2 H, Ar), 7.19 (d, *J* = 6.4 Hz, 2 H, Ar), 7.25 (d, *J* = 8.1 Hz, 2 H, Ar), 7.28 (d, *J* = 8.1 Hz, 2 H, Ar). MS (EI): *m*/*z* (%) = 473 (3.9) [M^+], 318 (100) [M^+ − 155], 276 (98) [M^+ − 197]. $C_{29}H_{31}NO_3S$ (473.6): calcd. C 73.54, H 6.60, N 2.96; found C 73.60, H 6.61, N 2.78.

3a: Yellow solid; m.p. 163−165 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1645 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 1.26 (t, *J* = 7.5 Hz, 3 H, Me), 1.28 (t, *J* = 7.5 Hz, 3 H, Me), 2.34 (s, 3 H, Me), 2.65 (q, *J* = 7.5 Hz, 2 H, CH_2), 2.68 (q, *J* = 7.5 Hz, 2 H, CH_2), 6.92(1 H,d, *J* = 2.9 Hz), 7.25 (d, *J* = 8.2 Hz, 2 H, Ar), 7.29 (d, *J* = 8.2 Hz, 2 H, Ar), 7.41 (d, *J* = 8.2 Hz, 2 H, Ar), 7.53 (d, *J* = 8.2 Hz, 2 H, Ar), 8.42 (1 H, br, s, NH). MS (EI): *m*/*z* (%) = 317 (90.7) [M^+], 302 (100) [M^+ − 15]. $C_{22}H_{23}NO$ (317.4): calcd. C 83.24, H 7.43, N 4.41; found C 83.00, H 7.30, N 4.22.

2b: Isolated as a colorless solid from the reaction of MVK with *N*-benzylidene-4-methylbenzenesulfonamide; m.p. 79−81 °C. IR (KBr): $\tilde{\nu}$ = 1674 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.19 (s, 3 H, Me), 2.31 (s, 3 H, Me), 5.90 (t, *J* = 2.6 Hz, 1 H), 5.97 (dd, *J* = 2.6, 1.8 Hz, 1 H), 6.65 (dd, *J* = 2.6, 1.8 Hz, 1 H), 7.02 (d, *J* = 8.1 Hz, 2 H, Ar), 7.21−7.28 (m, 6 H, Ar), 7.31−7.36 (m, 6 H, Ar). MS (EI): *m*/*z* (%) = 417 (7.07) [M^+], 262 (94.74) [M^+ − 155], 220 (100) [M^+ − 197]. $C_{25}H_{23}NO_3S$ (417.5): calcd. C 72.27, H 5.09, N 3.37; found C 72.01, H 5.29, N 3.32.

3b: Isolated as a yellow solid from the reaction of MVK with *N*-benzylidene-4-methylbenzenesulfonamide; m.p. 192−193 °C. IR (KBr): $\tilde{\nu}$ = 1627 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.35 (s, 3 H, Me), 6.96(t, *J* = 2.8 Hz, 1 H), 7.29 (d, *J* = 6.2 Hz, 1 H, Ar), 7.39−7.54 (m, 5 H, Ar), 7.53 (d, *J* = 8.9 Hz, 2 H, Ar), 7.62 (d, *J* = 6.2 Hz, 2 H, Ar), 8.60 (1 H, br, s, NH). MS (EI): *m*/*z* (%) = 261 (66.60) [M^+], 246 (100) [M^+ − 15]. $C_{18}H_{15}NO$ (261.3): calcd. C 82.73, H 5.79, N 5.36; found C 82.72, H 5.48, N 5.17.

2c: Isolated as a colorless solid from the reaction of MVK with *N*-(4-methylbenzylidene)-4-methylbenzenesulfonamide; m.p. 132−133 °C. IR (KBr): $\tilde{\nu}$ = 1675 cm^{-1} (C=O). ^1H NMR ($CDCl_3$, TMS,

300 MHz): δ = 2.17 (s, 3 H, Me), 2.30 (s, 3 H, Me), 2.32 (s, 3 H, Me), 2.34 (s, 3 H, Me), 5.80 (t, *J* = 2.5 Hz, 1 H), 5.88 (dd, *J* = 2.5, 1.9 Hz, 1 H), 6.60 (dd, *J* = 2.5, 1.9 Hz, 1 H), 7.03−7.12 (m, 6 H), 7.23−7.30 (m, 6 H). MS (EI): *m*/*z* (%) = 445 (7.89) [M$^+$], 290 (100) [M$^+$ − 155], 274 (67.94) [M$^+$ − 171]. $C_{27}H_{27}NO_3S$ (445.6): calcd. C 72.81, H 6.07, N 3.15; found C 73.01, H 6.30, N 2.98.

3c: Isolated as a yellow solid from the reaction of MVK with *N*-(4-methylbenzylidene)-4-methylbenzenesulfonamide; m.p. 206−207 °C. IR (KBr): $\tilde{\nu}$ = 1627 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.32 (s, 3 H, Me), 2.36 (s, 3 H, Me), 2.40 (s, 3 H, Me), 6.90(d, *J* = 2.9 Hz, 1 H), 7.19 (d, *J* = 8.1 Hz, 2 H, Ar), 7.25 (d, *J* = 8.1 Hz, 2 H, Ar), 7.40 (d, *J* = 8.1 Hz, 2 H, Ar), 7.48 (d, *J* = 8.1 Hz, 2 H, Ar), 8.53 (br. s, 1 H, NH). MS (EI): *m*/*z* (%) = 289 (87.84) [M$^+$], 274 (100) [M$^+$ − 15]. $C_{20}H_{19}NO$ (289.4): calcd. C 83.04, H 6.57, N 4.84; found C 82.99, H 6.49, N 4.57.

2d: Isolated as a colorless solid from the reaction of MVK with *N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide; m.p. 116−117 °C. IR (KBr): $\tilde{\nu}$ = 1675 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.19 (s, 3 H, Me), 2.33 (s, 3 H, Me), 3.77 (s, 3 H, Me), 3.80 (s, 3 H, Me), 5.80 (t, *J* = 2.4 Hz, 1 H, CH), 5.89 (dd, *J* = 2.4, 1.8 Hz, 1 H, CH), 6.62 (dd, *J* = 2.4, 1.8 Hz, 1 H), 6.76−6.87 (m, 4 H, Ar), 7.05 (d, *J* = 7.9 Hz, 2 H), 7.22 (m, 6 H, Ar). MS (EI): *m*/*z* (%) = 477 (21.60) [M$^+$], 322 (96.31) [M$^+$ − 155], 306 (100) [M$^+$ − 197]. HRMS calcd. for $C_{27}H_{27}NO_5S$ requires 477.1610 [M$^+$]; found 477.1584.

3d: Isolated as a yellow solid from the reaction of MVK with *N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide; m.p. 186−188 °C. IR (KBr): $\tilde{\nu}$ = 1627 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.41 (s, 3 H, Me), 3.85 (s, 3 H, Me), 3.87 (s, 3 H, Me), 6.85 (m, 1 H), 6.94 (d, *J* = 6.7 Hz, 2 H, Ar), 6.97 (d, *J* = 6.7 Hz, 2 H, Ar), 7.44 (d, *J* = 8.0 Hz, 2 H, Ar), 7.53 (d, *J* = 8.0 Hz, 2 H, Ar), 8.57 (br. s, 1 H, NH). MS (EI): *m*/*z* (%) = 321 (100) [M$^+$], 306 (78.84) [M$^+$ − 155]. HRMS calcd. for $C_{20}H_{19}NO_3$ requires 321.1365 [M$^+$]; found 321.1325.

2e: Isolated as a colorless solid from the reaction of MVK with *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide; m.p. 135−137 °C. IR (KBr): $\tilde{\nu}$ = 1648 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.21 (s, 3 H, Me), 2.37 (s, 3 H, Me), 5.88 (t, *J* = 2.4 Hz, 1 H), 5.90 (dd, *J* = 2.4, 1.8 Hz, 1 H), 6.62 (dd, *J* = 2.4, 1.8 Hz, 1 H), 7.09 (d, *J* = 8.2 Hz, 2 H, Ar), 7.23−7.32 (m, 10 H, Ar). MS (EI): *m*/*z* (%) = 485 (6.55) [M$^+$], 330 (100) [M$^+$ − 155], 288 (64.31) [M$^+$ − 197]. $C_{25}H_{21}Cl_2NO_3S$ (486.4): calcd. C 59.42, H 4.99, N 3.88; found C 59.68, H 4.84, N 3.72.

3e: Isolated as a yellow solid from the reaction of MVK with *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide; m.p. 231−232 °C. IR (KBr): $\tilde{\nu}$ = 1635 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.39 (s, 3 H, Me), 6.92(d, *J* = 3.1 Hz, 1 H), 7.37−7.48 (m, 6 H, Ar), 7.52−7.56 (m, 2 H, Ar), 8.63 (br. s, 1 H, NH). MS (EI): *m*/*z* (%) = 329 (84.23) [M$^+$], 314 (100) [M$^+$ − 15]. HRMS calcd. for $C_{18}H_{13}Cl_2NO$ requires 329.0374 [M$^+$]; found 329.0401.

2f: Isolated as a colorless solid from the reaction of MVK with *N*-(4-fluorobenzylidene)-4-methylbenzenesulfonamide; m.p. 127−128 °C. IR (KBr): $\tilde{\nu}$ = 1648 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.24 (s, 2 H, Me), 2.33 (s, 2 H, Me), 5.86 (t, *J* = 2.4 Hz, 1 H, CH), 5.93 (t, *J* = 2.0 Hz, 1 H, CH), 6.62 (t, *J* = 2.0 Hz, 1 H), 6.91−7.07 (m, 6 H, Ar), 7.22−7.35 (m, 6 H, Ar). MS (EI): *m*/*z* (%) = 453 (5.13) [M$^+$], 298 (100) [M$^+$ − 155]. HRMS calcd. for $C_{25}H_{21}F_2NO_3S$ requires 453.1210 [M$^+$]; found 453.1187.

3f: Isolated as a yellow solid from the reaction of MVK with *N*-(4-fluorobenzylidene)-4-methylbenzenesulfonamide: m.p. 205−206 °C. IR (KBr): $\tilde{\nu}$ = 1634 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.37 (s, 3 H, Me), 6.87 (d, *J* = 3.0 Hz, 1 H), 7.12 (d, *J* = 6.8 Hz, 2 H, Ar), 7.16 (d, *J* = 6.8 Hz, 2 H, Ar), 7.48 (m, 2 H, Ar), 7.60 (m, 2 H, Ar), 8.48 (br. s, 1 H, NH). MS (EI): *m*/*z* (%) = 297 (69.19) [M$^+$], 282 (100) [M$^+$ − 15]. $C_{18}H_{13}F_2NO$ (297.3): calcd. C 72.72, H 4.41, N 4.71; found C 72.53, H 4.28, N 4.33.

2h: Isolated as a colorless solid from the reaction of MVK with *N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide: m.p. 126−127 °C. IR (KBr): $\tilde{\nu}$ = 1673 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.29 (s, 2 H, Me), 2.47 (s, 2 H, Me), 5.88 (t, *J* = 2.5 Hz, 1 H, CH), 5.92 (dd, *J* = 2.5, 1.2 Hz, 1 H, CH), 6.65 (dd, *J* = 2.5, 1.2 Hz, 1 H), 6.94−7.36 (m, 12 H, Ar). MS (EI): *m*/*z* (%) = 453 (18.93) [M$^+$], 298 (100) [M$^+$ − 155]. $C_{25}H_{21}F_2NO_3S$ (453.5): calcd. C 66.21, H 4.67, N 3.09; found C 66.44, H 4.88, N 2.91.

3h: Isolated as a yellow solid from the reaction of MVK with *N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide: m.p. 205−206 °C. IR (KBr): $\tilde{\nu}$ = 1622 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.40 (s, 3 H, Me), 6.95 (d, *J* = 3.0 Hz, 1 H), 7.01−7.44 (m, 8 H, Ar). MS (EI): *m*/*z* (%) = 297 (72.04) [M$^+$], 282 (100) [M$^+$ − 15]. $C_{18}H_{13}F_2NO$ (297.3): calcd. C 72.72, H 4.41, N 4.71; found C72.80, H 4.23, N 4.48.

2i: Isolated as a black viscous oil from the reaction of MVK with *N*-(3-fluorobenzylidene)-4-methylbenzenesulfonamide. IR (KBr): $\tilde{\nu}$ = 1648 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.30 (s, 2 H, Me), 2.37 (s, 2 H, Me), 5.97 (t, *J* = 2.5 Hz, 1 H, CH), 6.10 (dd, *J* = 2.5, 1.8 Hz, 1 H, CH), 6.23−6.35 (m, 4 H, Ar), 6.62 (dd, *J* = 2.5, 1.8 Hz, 1 H), 7.03 (d, *J* = 8.6 Hz, 2 H, Ar), 7.17−7.34 (m, 4 H, Ar). MS (EI): *m*/*z* (%) = 330 (27.28) [M$^+$ − 67], 242 (100) [M$^+$ − 155]. HRMS calcd. for $C_{21}H_{19}NO_5S$ requires 397.0984 [M$^+$]; found 397.0967.

3i: Isolated as a black viscous oil from the reaction of MVK with *N*-(3-fluorobenzylidene)-4-methylbenzenesulfonamide. IR (KBr): $\tilde{\nu}$ = 1627 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.57 (s, 3 H, Me), 6.50 (m, 3 H, Ar), 6.80 (d, *J* = 3.1 Hz, 1 H), 7.40 (dd, *J* = 7.3, 1.9 Hz, 2 H, Ar), 7.77 (d, *J* = 3.1 Hz, 1 H, Ar). MS (EI): *m*/*z* (%) = 241 (100) [M$^+$], 226 (48.57) [M$^+$ − Me]. HRMS calcd. for $C_{20}H_{19}NO_3$ requires 241.0739 [M$^+$]; found 241.07298.

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[6] **Crystal data of 2a:** Empirical formula $C_{29}H_{31}O_3NS$; molecular mass: 473.63; crystal color, habit: colorless, prismatic; crystal dimensions: 0.20 × 0.20 × 0.30 mm; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 12.066(2) Å, b = 11.913(2) Å, c = 18.406(3) Å, β = 100.91(1)°, V = 2597.8(7) Å^3; space group: $P2_1/n$ (no. 14); Z = 4; $D_{calcd.}$ = 1.211 g/cm^3; F_{000}= 1008.00; μ(Mo-K_α) = 1.54 cm^{-1}; diffractometer: Rigaku AFC7R; R = 0.059, Rw = 0.070. **Crystal data of 3a:** Empirical formula $C_{22}H_{23}NO$; molecular mass: 317.41; crystal color, habit: colorless, prismatic; crystal dimensions: 0.20 × 0.20 × 0.30 mm; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 7.2847(6) Å, b = 16.3050(14) Å, c = 16.3928(14) Å, V = 1904.1(3) Å^3; Space group: $P2_1/n$; Z = 4; $D_{calcd.}$ = 1.107 g/cm^3; F_{000}= 680.00; R = 0.057, Rw = 0.15. CCDC-165307 (**2a**) and -165308 (**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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