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# Baylis–Hillman reactions of *N*-arylidenediphenylphosphinamides with methyl vinyl ketone, methyl acrylate, and acrylonitrile

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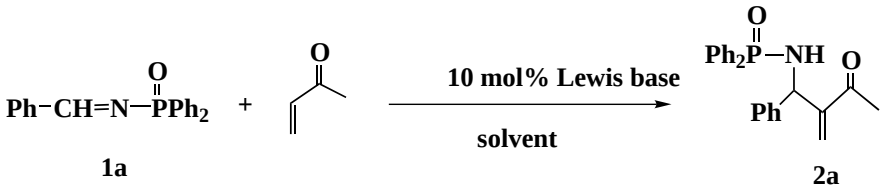
**Abstract**—We have found that in the Baylis–Hillman reactions of *N*-arylidenediphenylphosphinamides **1** with methyl vinyl ketone (MVK), methyl acrylate or acrylonitrile, the Lewis base and solvent can significantly affect the reaction rate. Using $PPh_3$ as Lewis base in the reaction of **1** with MVK in DMF, THF or MeCN, the normal Baylis–Hillman adduct **2** was formed in very high yield. In the Baylis–Hillman reaction of **1** with methyl acrylate, the Lewis base $Ph_2PMe$ must be used in order to get a high yield of the Baylis–Hillman adduct **3**. On the other hand, for the reaction of *N*-arylidenediphenylphosphinamides **1** with acrylonitrile, DABCO is the best Lewis base giving the corresponding Baylis–Hillman adducts **4** in high yields. 

Since Baylis and Hillman first reported the reactions 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,[1] the Baylis–Hillman reaction has made great progress,[1] and now includes a catalytic asymmetric version.[2] However, in this very simple and useful reaction, only aldehydes[1–3] and *N*-benzylidene-4-methylbenzenesulfonamides[4] are in general use as the substrates for reaction with α,β-unsaturated ketones, nitriles or esters. Herein, we wish to report an unprecedented Baylis–Hillman reaction of *N*-arylidenediphenylphosphinamides **1** with methyl vinyl ketone (MVK), methyl acrylate, and acrylonitrile in the presence of various Lewis bases.[5]

The promoters and solvents for the Baylis–Hillman reaction of *N*-arylidenediphenylphosphinamide **1a** with MVK were systematically examined first (Scheme 1, Table 1). We found that the Lewis base and solvent played very important roles in this reaction. For example, using 10 mol% of $PPh_3$ as the Lewis base in DMF or MeCN, the reaction proceeded very well to give the normal Baylis–Hillman adduct **2a** in 81% and 99% yields, respectively (Table 1, entries 2 and 4). Using $Ph_2PMe$ as the Lewis base, **2a** was produced in a relatively low yield (76%) under the same conditions (Table 1, entries 5 and 6). Using $PBu_3$ or $PhPMe_2$ as the Lewis base, only traces of **2a** were produced along with many unidentified products (Table 1, entries 6 and 7). The well established strong Lewis base, DABCO, gave a lower yield of **2a** under the same conditions as those used for $PPh_3$ (Table 1, entries 8–11). In dichloromethane, **2a** was obtained in moderate yield (66%) (Table 1, entry 11). In all these cases, the normal Baylis–Hillman adduct **2a** was formed exclusively.




**Scheme 1.**

*Keywords*: *N*-arylidenediphenylphosphinamide; Lewis base; Baylis–Hillman reaction; methyl vinyl ketone (MVK); methyl acrylate; acrylonitrile.
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**Table 1.** Baylis–Hillman reactions of *N*-benzylidenediphenylphosphinamide **1a** (1.0 equiv.) with MVK (1.0 equiv.) in the presence of a Lewis base (10 mol%) at room temperature

| Entry | Lewis base | Solvent | Time (h) | Yield (%)[a], **2a** |
|---|---|---|---|---|
| 1 | $PPh_3$ | THF | 48 | 52 |
| 2 | $PPh_3$ | DMF | 48 | 81 |
| 3 | $PPh_3$ | $CH_2Cl_2$ | 72 | 27 |
| 4 | $PPh_3$ | MeCN | 48 | 99 |
| 5 | $Ph_2PMe$ | MeCN | 72 | 76 |
| 6 | $PhPMe_2$ | MeCN | 72 | Trace |
| 7 | $PBu_3$ | MeCN | 72 | Trace |
| 8 | DABCO | THF | 144 | 30 |
| 9 | DABCO | DMF | 144 | 37 |
| 10 | DABCO | MeCN | 144 | 35 |
| 11 | DABCO | $CH_2Cl_2$ | 144 | 66 |

[a] Isolated yields.

For Baylis–Hillman reactions of other *N*-arylidenediphenylphosphinamides **1** with MVK using $PPh_3$ as Lewis base under the optimized reaction conditions, the Baylis–Hillman adducts **2** were obtained in good to excellent yields (Scheme 2). The results are summarized in Table 2. For *N*-arylidenediphenylphosphinamides **1** having an electron-donating group on the phenyl ring, the corresponding Baylis–Hillman adducts **2b** and **2c** were obtained in low yields in DMF (Table 2, entries 1 and 2),[6] but in MeCN or THF, **2b** and **2c** were formed in 77 and 80% yields (Table 2, entries 8 and 10) or 90 and 70% yields (Table 2, entries 9 and 11), respectively.[7] For *N*-arylidenediphenylphosphinamides **1** having an electron-withdrawing group on the phenyl ring, the Baylis–Hillman adducts **2d–h** were produced in good yields (Table 2, entries 3–7, 12–15). In some cases, the reactions proceeded quantitatively.

We also examined the Baylis–Hillman reactions of *N*-arylidenediphenylphosphinamides **1** with methyl acrylate in the presence of various Lewis bases (Scheme 3). Using $PPh_3$ or DABCO as the Lewis base, the reaction was very sluggish (Table 3, entries 1–7), but we were pleased to find that using $Ph_2PMe$ as the Lewis base in dichloromethane gave the corresponding Baylis–Hillman adduct **3a** in 71% yield (Table 3, entry 10).[8] It should be emphasized that when using $PBu_3$ or $PhPMe_2$ as the Lewis base, **3a** was obtained only in traces along with many unidentified products (Table 3, entries 8 and 9).

**Table 2.** Baylis–Hillman reactions of *N*-arylidenediphenylphosphinamide (1.0 equiv.) with MVK in the presence of $PPh_3$ (10 mol%)

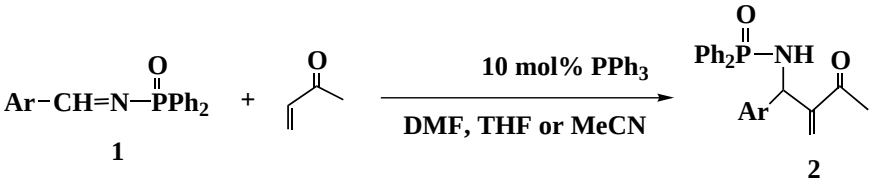
| Entry | Ar | Solvent | Time (h) | Yield (%)[a], **2** |
|---|---|---|---|---|
| 1 | *p*-$EtC_6H_4$ | DMF | 48 | 20 |
| 2 | *p*-$MeOC_6H_4$ | DMF | 72 | 19 |
| 3 | *p*-$FC_6H_4$ | DMF | 48 | 76 |
| 4 | *p*-$ClC_6H_4$ | DMF | 48 | 67 |
| 5 | *p*-$BrC_6H_4$ | DMF | 48 | 99 |
| 6 | *p*-$NO_2C_6H_4$ | DMF | 4 | 60 |
| 7 | $C_6H_5CH{=}CH$ | DMF | 72 | 67 |
| 8 | *p*-$EtC_6H_4$ | MeCN | 48 | 77 |
| 9 | *p*-$EtC_6H_4$ | THF | 48 | 90 |
| 10 | *p*-$MeOC_6H_4$ | MeCN | 48 | 80 |
| 11 | *p*-$MeOC_6H_4$ | THF | 48 | 70 |
| 12 | *p*-$FC_6H_4$ | MeCN | 36 | 99 |
| 13 | *p*-$ClC_6H_4$ | MeCN | 48 | 87 |
| 14 | *p*-$BrC_6H_4$ | MeCN | 24 | 99 |
| 15 | *p*-$NO_2C_6H_4$ | MeCN | 48 | 99 |

[a] Isolated yields.

For the Baylis–Hillman reactions of other *N*-arylidenediphenylphosphinamides **1** with methyl acrylate using $Ph_2PMe$ as the Lewis base under the optimized reaction conditions, the Baylis–Hillman adducts **3** were obtained in good to excellent yields (Scheme 4). The results are summarized in Table 4. The aliphatic Baylis–Hillman adduct **3h** was formed in moderate yield (Table 4, entry 7).

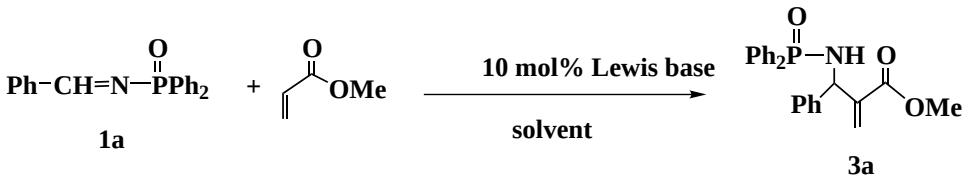
On the other hand, for the reaction of *N*-arylidenediphenylphosphinamides **1** with acrylonitrile, we examined many Lewis bases in the same manner as described above, but we found that only DABCO can effectively catalyze this reaction to give the corresponding Baylis–Hillman adduct **4** in high yield (Scheme 5, Table 5). Using $Ph_2PMe$, $PhPMe_2$ or $PBu_3$ as the Lewis base, the reaction solution immediately became dark in color giving **4** in lower yields along with many unidentified products.

In conclusion, we have found that in the Baylis–Hillman reaction of *N*-arylidenediphenylphosphinamides **1** with MVK, methyl acrylate or acrylonitrile, the Lewis base and solvent can significantly affect the reaction. Using $PPh_3$ as the Lewis base in the reaction of **1** with MVK in DMF, THF or MeCN, the normal Baylis–Hillman adduct **2** was formed in very high yields. In the




**b: Ar= *p*-$EtC_6H_4$, c: Ar= *p*-$MeOC_6H_4$, d: Ar= *p*-$FC_6H_4$, e: Ar= *p*-$ClC_6H_4$, f: Ar= *p*-$BrC_6H_4$, g: Ar= *p*-$NO_2C_6H_4$, h: Ar= $C_6H_5$-CH=CH.**

**Scheme 2.**




1a 3a

**Scheme 3.**

**Table 3.** Baylis–Hillman reactions of *N*-benzylidenediphenylphosphinamide **1a** (1.0 equiv.) with methyl acrylate (1.0 equiv.) in the presence of a Lewis base (10 mol%) at room temperature

| Entry | Lewis base | Solvent | Time (h) | Yield (%)[a], **3a** |
|---|---|---|---|---|
| 1 | $PPh_3$ | DMF | 48 | Trace |
| 2 | $PPh_3$ | $CH_2Cl_2$ | 480 (20 days) | 12 |
| 3 | DABCO | THF | 120 | 12 |
| 4 | DABCO | DMF | 120 | 12 |
| 5 | DABCO | $CH_2Cl_2$ | 120 | Trace |
| 6 | DABCO | MeCN | 120 | 26 |
| 7 | DABCO | MeCN[b] | 120 | 58 |
| 8 | $PhPMe_2$ | MeCN | 72 | Trace |
| 9 | $PBu_3$ | $CH_2Cl_2$ | 72 | Trace |
| 10 | $Ph_2PMe$ | $CH_2Cl_2$ | 42 | 71 |
| 11 | $Ph_2PMe$ | THF | 42 | 39 |
| 12 | $Ph_2PMe$ | MeCN | 42 | 36 |
| 13 | $Ph_2PMe$ | DMF | 42 | 30 |

[a] Isolated yields.
[b] The reaction was carried out at 60°C.

**Table 4.** Baylis–Hillman reactions of *N*-arylidenediphenylphosphinamide (1.0 equiv.) with methyl acrylate in the presence of $Ph_2PMe$ (10 mol%)

| Entry | Ar | Time (h) | Yield (%)[a], **3** |
|---|---|---|---|
| 1 | *p*-$EtC_6H_4$ | 96 | 50 |
| 2 | *p*-$MeOC_6H_4$ | 96 | 78 |
| 3 | *p*-$FC_6H_4$ | 42 | 92 |
| 4 | *p*-$ClC_6H_4$ | 48 | 50 |
| 5 | *p*-$BrC_6H_4$ | 48 | 60 |
| 6 | *p*-$NO_2C_6H_4$ | 4 | 63 |
| 7 | $C_6H_5CH$=CH | 42 | 40 |

[a] Isolated yields.

Baylis–Hillman reaction of **1** with methyl acrylate, the Lewis base $Ph_2PMe$ must be used in order to give **3** in high yields. On the other hand, for the reaction of *N*-arylidenediphenylphosphinamides **1** with acrylonitrile, DABCO is the best Lewis base giving the corresponding Baylis–Hillman adduct **4** as the sole product in high yield. Efforts are underway to elucidate mechanistic details of this reaction and the key factors required from the Lewis base for the different substrates for the Baylis–Hillman reactions. Work along these lines is currently in progress.

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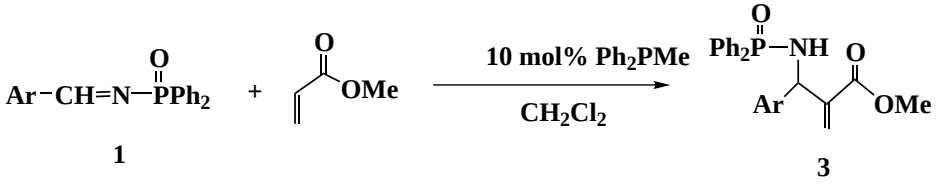
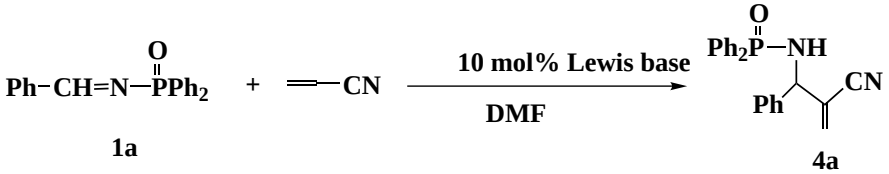



1 3

**b: Ar= *p*-$EtC_6H_4$, c: Ar= *p*-$MeOC_6H_4$, d: Ar= *p*-$FC_6H_4$, e: Ar= *p*-$ClC_6H_4$, f: Ar= *p*-$BrC_6H_4$, g: Ar= *p*-$NO_2C_6H_4$, h: Ar= $C_6H_5$-CH=CH.**

**Scheme 4.**




1a 4a

**Scheme 5.**

**Table 5.** Baylis–Hillman reactions of *N*-benzylidenediphenylphosphinamide **1a** (1.0 equiv.) with acrylonitrile (1.0 equiv.) in the presence of a Lewis base (10 mol%) at room temperature

| Entry | Lewis base | Time (h) | Yield (%)[a], **4a** |
|---|---|---|---|
| 1 | $PPh_3$ | 24 | Trace |
| 2 | DABCO | 24 | 80 |
| 3 | $PhPMe_2$ | 24 | 24 |
| 4 | $PBu_3$ | 10 | 60 |
| 5 | $Ph_2PMe$ | 24 | 50 |

[a] Isolated yields.

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5. *N*-Arylidenediphenylphosphinamide **1** was prepared according to the literature: (a) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561; (b) Yamada, K.; Harwood, S. J.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, 3504.
6. Typical reaction procedure for the Baylis–Hillman reaction of **1a** with MVK: To a Schlenk tube with **1a** (76 mg, 0.25 mmol) and triphenylphosphine (13.1 mg, 0.050 mmol) in DMF (0.5 mL) was added MVK (25.8 mg, 24 μL, 0.30 mmol) under an argon atmosphere and the reaction mixture was stirred for 48 h at room temperature (20°C). The reaction mixture was washed with water (3×10 mL) and extracted with dichloromethane (2×10 mL). The organic layer was dried over anhydrous $Na_2SO_4$, the solvent removed under reduced pressure and the residue purified by silica gel column chromatography (eluent: EtOAc/petroleum = 1/4) to give **2a** (72 mg, 81%) as a colorless solid.
7. The spectral data of **2e**: mp 161–164°C; IR (KBr) $\nu$ 1674 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$, 300 MHz, TMS) $\delta$ 2.28 (3H, s, $CH_3$), 3.37 (1H, dd, $J_{CH-NH}$ = 11.1 Hz, $J_{P-N-H}$ = 8.4 Hz, NH), 4.87 (1H, t, $J_{CH-NH}$ = 11.1 Hz, $J_{P-N-CH}$ = 11.1 Hz, CH), 6.11 (1H, s, =CH), 6.21 (1H, s, =CH), 7.20–7.31 (4H, m, Ar), 7.37–7.56 (6H, m, Ar), 7.80–7.90 (4H, m, Ar); MS (EI) *m/e* 409 ($M^+$, 4.82), 340 ($M^+$–69, 12.31), 208 ($M^+$–201, 100); [found: C, 67.44; H, 5.36; N, 3.38%. $C_{23}H_{21}ClNO_2P$ requires: C, 67.40; H, 5.17; N, 3.42%].
8. The spectral data of **3e**: mp 173–175°C; IR (KBr) $\nu$ 1719 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$, 300 MHz, TMS) $\delta$ 3.65 (3H, s, $OCH_3$), 4.33 (1H, dd, $J_{CH-NH}$ = 11.4 Hz, $J_{P-N-H}$ = 8.4 Hz, NH), 5.04 (1H, t, $J_{CH-NH}$ = 11.4 Hz, $J_{P-N-CH}$ = 11.4 Hz, CH), 5.86 (1H, s, =CH), 6.34 (1H, s, =CH), 7.20–7.31 (4H, m, Ar), 7.37–7.56 (6H, m, Ar), 7.80–7.95 (4H, m, Ar); MS (EI) *m/e* 425 ($M^+$, 9.54), 356 ($M^+$–69, 18.65), 224 ($M^+$–201, 100); [found: C, 64.67; H, 5.00; N, 3.16%. $C_{23}H_{21}ClNO_3P$ requires: C, 64.87; H, 4.97; N, 3.29%].