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One-pot aza-Baylis–Hillman reactions of arylaldehydes and diphenylphosphinamide with methyl vinyl ketone in the presence of $TiCl_4$, PPh_3, and Et_3N

Min Shi* and Gui-Ling Zhao

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

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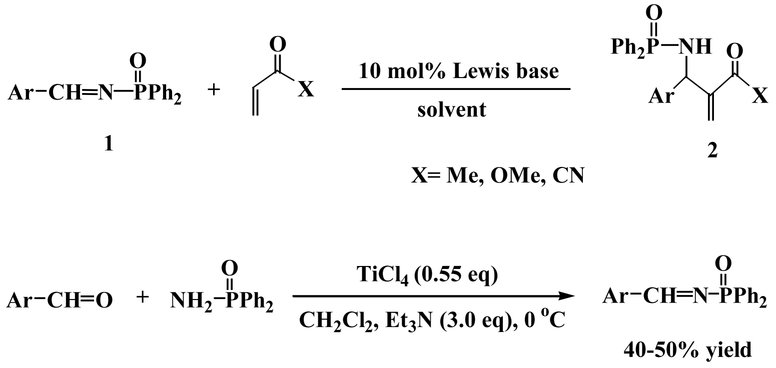
Abstract—We found that one-pot, three-component, aza-Baylis–Hillman reactions of arylaldehydes, diphenylphosphinamide, and methyl vinyl ketone (MVK) can be realized in the presence of $TiCl_4$ (0.8 equiv.), PPh_3 (0.1 equiv.), and Et_3N (12 equiv.) in dichloromethane to give the corresponding aza-Baylis–Hillman adducts **2** in good yields.

Since Baylis and Hillman first reported 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,[2] and now includes a catalytic asymmetric version.[3] However, in this very simple and useful reaction, only aldehydes[1–3] and *N*-benzylidene-4-methylbenzenesulfonamides[4] are generally used as the substrates for reactions with α,β-unsaturated ketones, nitriles or esters. Previously, we reported an unprecedented aza-Baylis–Hillman reaction of *N*-arylidenediphenylphosphinamides **1** with methyl vinyl ketone (MVK), methyl acrylate, and acrylonitrile in the presence of various Lewis bases such as PPh_3, PPh_2Me or DABCO (Scheme 1).[5] In this case, we used *N*-arylidenediphenylphosphinamides **1**, which were prepared in moderate yields from the reaction of diphenylphosphinamide with arylaldehyde in the presence of $TiCl_4$ (0.55 equiv.) and triethylamine (Et_3N, 3.0 equiv.) according to the literature, in this Baylis–Hillman reaction (Scheme 1).[6] Recently, an efficient and selective one-pot, three-component, procedure for the formation of α-methylene-β-amino acid derivatives using the aza-Baylis–Hillman protocol has been disclosed using DABCO (Lewis base) and $La(OTf)_3$ or $Ti(OPr^i)_4$ (Lewis



Scheme 1.

Keywords: diphenylphosphinamide; Lewis base; Baylis–Hillman reactions; methyl vinyl ketone (MVK); titanium(IV) chloride ($TiCl_4$); triethylamine (Et_3N).

* Corresponding author. Fax: 86-21-64166128; e-mail: mshi@pub.sioc.ac.cn

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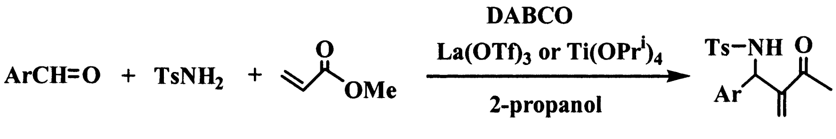
acid) in which methyl acrylate is often utilized as the substrate (Scheme 2).[7] Thus, we attempted to simplify the reaction procedure of the aza-Baylis–Hillman reaction of **1** with MVK in a one-pot manner. Herein, we wish to report an unprecedented one-pot, three component, aza-Baylis–Hillman reaction between arylaldehydes, diphenylphosphinamide, and MVK.

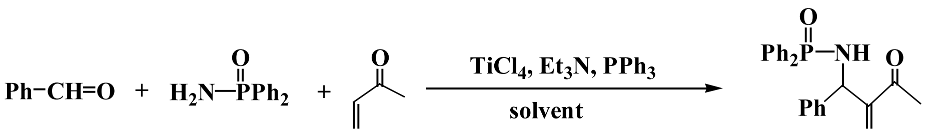
First of all, we examined this one-pot reaction using the reported methods shown in Scheme 2. However, we found that no reactions occurred under these conditions. We selected $TiCl_4$ as the Lewis acid and PPh_3 as the Lewis base to examine this one-pot reaction of an arylaldehyde (2.0 equiv.), diphenylphosphinamide (1.0 equiv.), and MVK (2.0 equiv.) because *N*-arylidenediphenylphosphinamides **1** have been synthesized in the presence of $TiCl_4$ (Scheme 1) and PPh_3 is the best Lewis base for promoting the Baylis–Hillman reaction of arylaldehydes with **1**.[5] As a result, it was found that when the reaction was carried out in the presence of $TiCl_4$ (0.55 equiv.), PPh_3 (1.0 equiv.) and triethylamine (Et_3N) (9.0 equiv.) in dichloromethane, the corresponding aza-Baylis–Hillman adduct **2a** was formed in 58% yield (Table 1, entry 3). Triethylamine (Et_3N) itself cannot promote the Baylis–Hillman reaction of **1** with MVK, but it was employed to quench the HCl formed during the reaction. $TiCl_4$ acted as a Lewis acid in the condensation of an arylaldehyde with diphenylphosphinamide to produce **1** in situ; we were able to observe the formation of **1** on a TLC plate during the reaction. The amount of Et_3N is crucial for this one-pot reaction because 3 or 20 equiv. of Et_3N can completely stop the reaction under the same conditions (Table 1, entries 1, 2 and 4). Dichloromethane is the best solvent for this reaction (Table 1, entries 3 and 5–7). During further optimizing the reaction conditions, we found that the best reaction conditions for this one-pot aza-Baylis–Hillman reaction involve using PPh_3 (0.1 equiv.) as the Lewis base and $TiCl_4$ (0.8 equiv.) as the Lewis acid in the presence of Et_3N (12 equiv.) (Table 1, entry 8).[8] The results are summarized in Table 1. The presence of 4 Å molecular sieves did not improve the yield of **2a** (Table 1, entry 10).

Under the optimized reaction conditions, we next carried out this novel one-pot reaction using various arylaldehydes as the substrates (Table 2). In general, the corresponding Baylis–Hillman adducts were obtained in 40–86% yields. The results are summarized in Table 2. For the arylaldehydes having strongly electron-withdrawing substituents such as *p*-nitrobenzaldehyde and *p*-fluorobenzaldehyde (active arylaldehydes), we found that some by-products were formed and the yields of **2** decreased. This is because these active arylaldehydes can undergo a $TiCl_4$ and amine promoted Baylis–Hillman reaction to give the chlorinated adducts and rearranged *Z*-olefins in addition to the normal Baylis–Hillman products.[2t–y] Therefore, in these cases (Table 2, entries 4, 6 and 7), 1.0 equiv. of arylaldehyde was employed and the corresponding aza-Baylis–Hillman adducts were obtained in moderate yields.



Scheme 2.

Table 1. One-pot three component aza-Baylis–Hillman reaction of benzaldehyde (2.0 equiv.), diphenylphosphinamide (1.0 equiv.), with MVK (2.0 equiv.) in the presence of $TiCl_4$, Et_3N and PPh_3 at room temperature



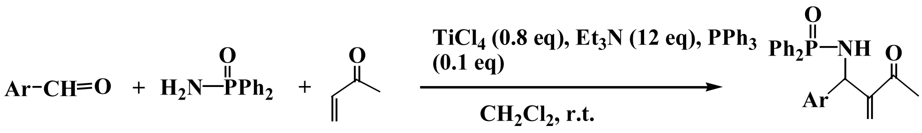
2a

Entry	$TiCl_4$ (equiv.)	Et_3N (equiv.)	Lewis base PPh_3 (equiv.)	Solvent	Time (h)	Yield (%)[a] **2a**
1	0.55	3.0	0.2	CH_2Cl_2	72	No reaction
2	0.55	3.0	1.0	CH_2Cl_2	72	No reaction
3	0.55	9.0	1.0	CH_2Cl_2	72	58
4	0.55	20.0	1.0	CH_2Cl_2	72	Trace
5	0.55	9.0	1.0	THF	72	11
6	0.55	9.0	1.0	DMF	72	Trace
7	0.55	9.0	0.1	CH_2Cl_2	72	57
8	0.8	12.0	0.1	CH_2Cl_2	72	64
9	1.0	15.0	0.1	CH_2Cl_2	72	34
10[b]	0.55	9.0	0.1	CH_2Cl_2	72	30

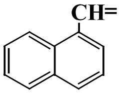
[a] Isolated yields.

[b] In the presence of 4 Å molecular sieves.

Table 2. One-pot three component aza-Baylis–Hillman reaction of arylaldehydes (2.0 equiv.), diphenylphosphinamide (1.0 equiv.), with MVK (2.0 equiv.) in the presence of $\mathrm{TiCl_4}$, $\mathrm{Et_3N}$ and $\mathrm{PPh_3}$ at room temperature



2

Entry	Ar	Product	Time (h)	Yield (%)[a] **2**
1	*p*-$\mathrm{MeC_6H_4}$	**2b**	120	51
2	*p*-$\mathrm{EtC_6H_4}$	**2c**	120	86
3	*p*-$\mathrm{MeOC_6H_4}$	**2d**	120	52
4[b]	*p*-$\mathrm{ClC_6H_4}$	**2e**	72	56
5	*p*-$\mathrm{BrC_6H_4}$	**2f**	72	60
6[b]	*p*-$\mathrm{FC_6H_4}$	**2g**	48	40
7[b]	*p*-$\mathrm{NO_2C_6H_4}$	**2h**	12	48
8	$\mathrm{C_6H_5CH{=}CH}$	**2i**	120	42
9		**2j**	120	70
10	*m*-$\mathrm{C_6H_5OC_6H_4}$	**2k**	120	52

[a] Isolated yields.

[b] 1.0 equiv. of arylaldehyde was employed.

It should be emphasized here that when methyl acrylate or acrylonitrile is used as the Michael acceptor under the above, one-pot, reaction conditions, no reaction takes place.

In conclusion, we have found that a novel one-pot three component aza-Baylis–Hillman reaction of arylaldehydes, diphenylphosphinamide, and MVK can be achieved using $\mathrm{TiCl_4}$ (0.8 equiv.) and $\mathrm{PPh_3}$ (0.1 equiv.) in dichloromethane in the presence of $\mathrm{Et_3N}$ (12 equiv.). The reaction proceeds via the reaction of **1** formed in situ with MVK promoted by the Lewis base $\mathrm{PPh_3}$. Efforts are underway to elucidate the mechanistic details of this reaction and the key properties required of the Lewis bases for the different substrates in this novel, one-pot, aza-Baylis–Hillman reaction. Work along these lines is currently in progress.

Acknowledgements

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8. Typical reaction procedure for the one-pot aza-Baylis–Hillman reaction of *p*-chlorobenzaldehyde, diphenylphosphinamide, methyl vinyl ketone (MVK): To a Schlenk tube with *p*-chlorobenzaldehyde (70 mg, 0.50 mmol), diphenylphosphinamide (113.5 mg, 0.5 mmol), and triphenylphosphine (13.1 mg, 0.050 mmol) in CH_2Cl_2 (2.0 mL) was added methyl vinyl ketone (MVK) (70 mg, 81 μL, 1.0 mmol) under an argon atmosphere and the reaction mixture was stirred for 72 h at room temperature (20°C). The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography (eluent: EtOAc/petroleum = 1/1) to give **2e** (117 mg, 56%) as a colorless solid.

The spectral data of **2e**: mp 161–164°C; IR (KBr) ν 1674 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.28 (3H, s, CH_3), 3.37 (1H, dd, $J_{CH\text{-}NH} = 11.1$ Hz, $J_{P\text{-}N\text{-}H} = 8.4$ Hz, NH), 4.87 (1H, t, $J_{CH\text{-}NH} = 11.1$ Hz, $J_{P\text{-}N\text{-}CH} = 11.1$ 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. $C_{23}H_{21}NClO_2P$ requires C, 67.40; H, 5.17; N, 3.42%].