Traditional Morita–Baylis–Hillman reaction of aldehydes with methyl vinyl ketone co-catalyzed by triphenylphosphine and nitrophenol†

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In the Morita–Baylis–Hillman reaction of aldehydes with methyl vinyl ketone (MVK), we found that in the presence of a catalytic amount of phenol, the Lewis base triphenylphosphine can effectively promote the reaction to give the corresponding normal Morita–Baylis–Hillman adducts in good yields. The mechanism has been investigated by ^{31}P NMR spectroscopy. The solvent and substituent effects were also examined.

Great progress has been made in the execution of the Morita–Baylis–Hillman reaction,[1] since the seminal report in 1972[2] that described the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO). Recent advances include several catalytic asymmetric versions of the reaction.[3] In the generally accepted mechanism of the Morita–Baylis–Hillman reaction,[1,2] the aldol reaction of the ammonium or phosphonium enolates derived from the nucleophilic promoter DABCO or triphenylphosphine with Michael acceptors with electrophiles has long been believed to be the rate-determining step. However, in a detailed mechanistic investigation into this reaction, it was recently reported that the rate-determining step in the Morita–Baylis–Hillman reaction is the proton transfer rather than the aldol reaction.[4] In addition, Schaus has reported the development of a chiral Brønsted acid-catalyzed asymmetric Morita–Baylis–Hillman reaction of cyclohexenone with aldehyde in the presence of triethylphosphine (PEt_3).[3b] On the basis of all these new findings, we attempted to develop another catalytic system for the traditional Baylis–Hillman reaction of aldehydes with methyl vinyl ketone, which includes a Brønsted acid as proton source and phosphine Lewis base as a promoter. During our ongoing investigation on this very simple and useful reaction, we have so far disclosed several new results on Lewis base and Lewis acid co-catalyzed systems.[5] Moreover, Leitner has recently reported a new bifunctional activation mechanism for the catalytic asymmetric aza-Baylis–Hillman reaction.[5g,6] Herein we wish to report that triphenylphosphine (PPh_3) can promote the traditional Morita–Baylis–Hillman reaction of aldehydes **1** with methyl vinyl ketone (MVK) **2**, in the presence of a catalytic amount of *p*-nitrophenol, to give the corresponding Morita–Baylis–Hillman adducts **3** in good-to-high yields under mild conditions.

In an initial examination, we found that PPh_3 (20 mol%) itself could not efficiently catalyze the Baylis–Hillman reaction of benzaldehyde (0.8 mmol) or *p*-chlorobenzaldehyde (0.8 mmol) with MVK (2.4 mmol) in tetrahydrofuran (THF, 2.0 mL) (Table 1, entries 1 and 7). In addition, the corresponding adducts were always formed along with some impurities (see ESI†). With methyldiphenylphosphine (PPh_2Me), dimethylphenylphosphine ($PPhMe_2$), trimethylphosphine (PMe_3) and tributylphosphine (PBu_3) as catalysts, similar results were also obtained. It is difficult to get the corresponding Morita–Baylis–Hillman reaction product in good yield and high purity with a phosphine Lewis base as a promoter under mild conditions. However, with the addition of various phenols including pentafluorophenol (Table 1, entries 3 and 9) (30 mol%), as a kind of weak Brønsted acid, into this reaction system, we found that the reactions were accelerated (Fig. 1), and that the corresponding adducts could be obtained in good yields and high purities under the same conditions in THF (Table 1, entries 2–6 and 8–12) (see ESI†). The acidity of the phenol also affected the reaction rate, particularly in the case of *p*-chlorobenzaldehyde, which has an electron-withdrawing group on the benzene ring. Among the phenol additives employed, *p*-nitrophenol ($pK_a = 7.2$),[7] which has the highest acidity, gave the best result in THF (Table 1, entries 7–12).

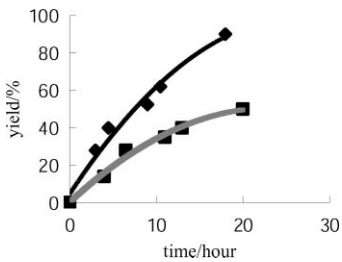

Fig. 1 The effect of an additive (*p*-nitrophenol, 0.24 mmol) on the Morita–Baylis–Hillman reaction of *p*-chlorobenzaldehyde (0.8 mmol) with MVK (2.4 mmol) catalyzed by PPh_3 (0.16 mmol) in THF (2.0 mL).

Using PPh_3 as a Lewis base promoter and *p*-nitrophenol as additive, the solvent effect was examined. The results are summarized in Table 2. As can be seen from Table 2, THF and dimethylsulfoxide (DMSO) are the best solvents for this reaction (Table 2, entries 1–7). Therefore, the best reaction conditions are to carry out this reaction with PPh_3 as a Lewis base promoter in the presence of *p*-nitrophenol in THF or DMSO.

Under these optimized conditions, we next examined a variety of aldehydes. The results are shown in Table 3. For aryl aldehydes having an electron-withdrawing group on the aromatic ring, such as *p*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, *o*-nitrobenzaldehyde, *p*-bromo- or *p*-chlorobenzaldehyde, *p*-fluoro- or *m*-fluorobenzaldehyde, and pyridylaldehyde, the corresponding Morita–Baylis–Hillman adducts **3** were obtained in good-to-high

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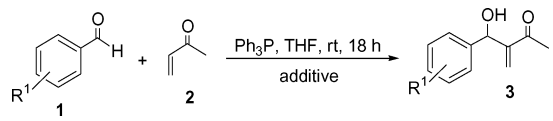
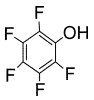
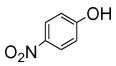
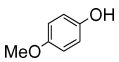
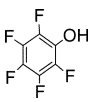
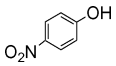
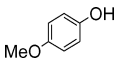
† Electronic supplementary information (ESI) available: Spectroscopic data, Figs. 2–5 and detailed description of experimental procedures. See DOI: 10.1039/b600854b

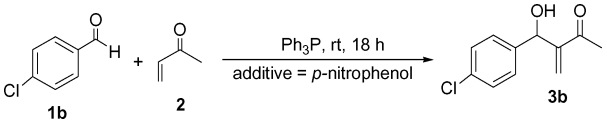
Table 1 Morita–Baylis–Hillman reaction of aryl aldehydes (0.8 mmol) with MVK (2.4 mmol) co-catalyzed by PPh_3 (0.16 mmol) and phenol (0.24 mmol)



Entry	R^1	Additive	pK_a	Yield of **3** (%)[a]
1	H	—	—	25
2	H		9.8	48
3	H		—	32
4	H		7.2	52
5	H		10.0	51
6	H		9.9	65
7	*p*-Cl	—	—	50
8	*p*-Cl		9.8	78
9	*p*-Cl		—	71
10	*p*-Cl		7.2	92
11	*p*-Cl		10.0	72
12	*p*-Cl		9.9	70

[a] Isolated yields.

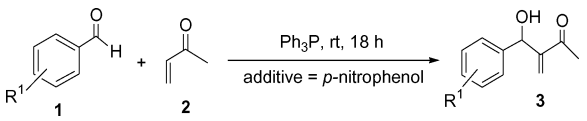
Table 2 Solvent effects on the Morita–Baylis–Hillman reaction of *p*-chlorobenzaldehyde with MVK co-catalyzed by PPh_3 and *p*-nitrophenol

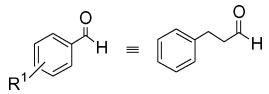
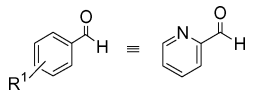


Entry	Solvent	Yield of **3b** (%)[a]
1	Et_2O	60
2	THF	92
3	DMSO	92
4	DMF	80
5	Ethanol	35
6	Pentanol	21
7	Dichloromethane	66

[a] Isolated yields.

Table 3 Morita–Baylis–Hillman reaction of aldehydes (0.8 mmol) with MVK (2.4 mmol) co-catalyzed by PPh_3 (0.16 mmol) and phenol (0.24 mmol)



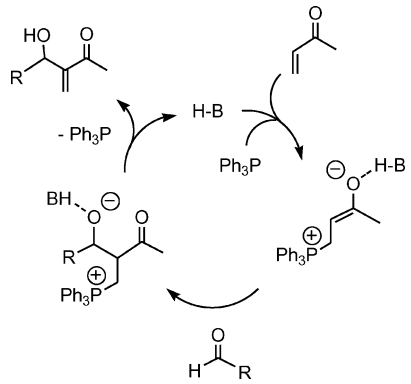
Entry	R^1	Product	Yield of **3** (%)[a]
1	H	**3a**	52
2	*p*-Cl	**3b**	92
3	*p*-NO_2	**3c**	98
4	*m*-NO_2	**3d**	90
5	*o*-NO_2	**3e**	98
6	*p*-CH_3	**3f**	42
7	*p*-CH_3O	**3g**	35
8	*o*,*p*-Cl_2	**3h**	95
9	*p*-F	**3i**	87
10	*m*-F	**3j**	93
11	*p*-Br	**3k**	83
12		**3l**	72
13		**3m**	80

[a] Isolated yields.

yields (Table 3, entries 2–5, 8–11 and 13). But for benzaldehyde, *p*-methyl- and *p*-methoxybenzaldehyde, the corresponding adducts **3** were obtained in moderate yields under similar conditions (Table 3, entries 1, 6 and 7). For an aliphatic aldehyde, the corresponding Morita–Baylis–Hillman adduct **3l** was obtained in good yield under the standard conditions (Table 3, entry 12). For 2-pyridine carboxaldehyde, the reaction also proceeded smoothly to give the corresponding Morita–Baylis–Hillman adduct **3m** in good yield under the standard conditions (Table 3, entry 13).

According to the generally accepted mechanism of the Morita–Baylis–Hillman reaction,[1,2] we believe that *p*-nitrophenol (a weak Brønsted acid) in the co-catalyzed systems can stabilize the enolate intermediate in the conjugate addition step through its hydrogen-bonding with the enolate, driving the reaction forward and accelerating the reaction rate (Scheme 1).

In order to get more mechanistic insight into these PPh_3- and *p*-nitrophenol-co-catalyzed systems, we carried out ^{31}P NMR spectroscopic measurements (in $CDCl_3$, referenced to 85% H_3PO_4) of the Lewis base PPh_3 in the absence and presence of MVK and *p*-nitrophenol. PPh_3 showed a signal at −4.46 ppm (Fig. 2, ESI†), and PPh_3 with MVK (molar ratio = 1 : 5) showed an additional signal at +29.96 ppm, which is believed to correspond to the phosphonium enolate (Fig. 3, ESI),[3l,8] but PPh_3 with MVK and *p*-nitrophenol (molar ratio = 1 : 5 : 1) only showed a signal at +29.96 ppm (Fig. 4, ESI). A significant feature in the ^{31}P NMR of PPh_3 with the addition of MVK is the formation of the new signal at +29.96 ppm. The ratio of the new signal and the signal at −4.46 ppm (PPh_3) is 1 : 3 ratio, indicating that the phosphonium enolate formed *in situ* is in equilibrium with free PPh_3.[3l,8] In the case of PPh_3 with the addition of MVK and



Scheme 1 A plausible mechanism for the Morita–Baylis–Hillman reaction of aldehydes with MVK co-catalyzed by PPh_3 and phenol (Brønsted acid).

p-nitrophenol, no signal of the free PPh_3 was observed, indicating that the interaction of phenolic hydroxy groups with oxygen atom of MVK (hydrogen bonding) does indeed exist, which strongly stabilizes the phosphonium enolate and drives the equilibrium largely in this direction. This is the key reason why the co-catalyzed system of phosphine Lewis bases and *p*-nitrophenol was more effective. When the phosphonium enolate was formed *in situ*, and *p*-chlorobenzaldehyde (molar ratio 5 : 1 to PPh_3) was added into the solution, we found that a new signal appeared at +24.00 ppm in the ^{31}P NMR spectrum (in $CDCl_3$, referenced to 85% H_3PO_4) of the mixture, along with the signal at +29.96 ppm, in a 1 : 8 ratio (Fig. 5, ESI). According to the generally accepted mechanism, this new signal might be the second phosphonium intermediate resulting from the aldol reaction, which did not decompose too quickly.

In conclusion, we have found that the Lewis base promoter triphenylphosphine can promote the traditional Morita–Baylis–Hillman reaction of aldehydes with methyl vinyl ketone (MVK), in the presence of a catalytic amount of *p*-nitrophenol. The phenolic hydroxy group in *p*-nitrophenol played a key role in achieving high yields in this reaction. The co-catalyzed mechanism has been investigated by ^{31}P NMR spectroscopy. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose the scope and limitations of this reaction.

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References

1 For reviews, see: (*a*) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001–8062; (*b*) S. E. Drewes and G. H. P. Roos, *Tetrahedron*, 1988, **44**, 4653–4670; (*c*) E. Ciganek, *Org. React. (N. Y.)*, 1997, **51**, 201–350; (*d*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811–892; (*e*) Y. Iwabuchi and S. Hatakeyama, *J. Synth. Org. Chem., Jpn.*, 2002, **60**, 2–14; (*f*) J.-X. Cai, Z.-H. Zhou and C.-C. Tang, *Huaxue Yanjiu*, 2001, **12**, 54–64.

2 (*a*) A. B. Baylis, M. E. D. Hillman, *Ger. Pat.* 2,155,113, 1972 (*Chem. Abstr.*, 1972, **77**, 34174q); M. E. D. Hillman and A. B. Baylis, *US Pat.* 3,743,669, 1973; (*b*) K. Morita, Z. Suzuki and H. Hirose, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2815.

3 (*a*) A. G. M. Barrett, A. S. Cook and A. Kamimura, *Chem. Commun.*, 1998, 2533–2534; (*b*) N. T. McDougal and S. E. Schaus, *J. Am. Chem. Soc.*, 2003, **125**, 12094–12095; (*c*) Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219–10220; (*d*) K.-S. Yang, W.-D. Lee, J.-F. Pan and K.-M. Chen, *J. Org. Chem.*, 2003, **68**, 915–919; (*e*) J. E. Imbriglio, M. M. Vasbinder and S. J. Miller, *Org. Lett.*, 2003, **5**, 3741–3743; J. E. Imbriglio, M. M. Vasbinder and S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601–610; (*f*) For others, see: P. Langer, *Angew. Chem., Int. Ed.*, 2000, **39**, 3049–3051; (*g*) S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi and S. Hatakeyama, *Org. Lett.*, 2003, **5**, 3103–3105; (*h*) P. R. Krishna, V. Kannan and P. V. N. Reddy, *Adv. Synth. Catal.*, 2004, **346**, 603–606; (*i*) Y. Sohtome, A. Tanatani, Y. Hashimoto and K. Nagasawa, *Tetrahedron Lett.*, 2004, **45**, 5589–5592; (*j*) K.-S. Yang and K.-M. Chen, *Org. Lett.*, 2000, **2**, 729–731; (*k*) M. Shi and L. H. Chen, *Chem. Commun.*, 2003, 1310–1311; (*l*) M. Shi, L. H. Chen and C.-Q. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3790–3800; (*m*) S. Luo, X. Mi, H. Xu, P. G. Wang and J.-P. Cheng, *J. Org. Chem.*, 2004, **69**, 8413–8422; (*n*) S. Luo, P. G. Wang and J.-P. Cheng, *J. Org. Chem.*, 2004, **69**, 555–558; (*o*) X. Mi, S. Luo and J.-P. Cheng, *J. Org. Chem.*, 2005, **70**, 2338–2341; (*p*) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.*, 2005, **127**, 3680–3681; (*q*) D. Balan and H. Adolfsson, *Tetrahedron Lett.*, 2003, **44**, 2521–2524.

4 (*a*) K. E. Price, S. J. Broadwater, H. M. Jung and D. T. McQuade, *Org. Lett.*, 2005, **7**, 147–150; (*b*) V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2005, **44**, 1706–1708; (*c*) B. Lesch, J. Toräng, S. Vanderheiden and S. Bräse, *Adv. Synth. Catal.*, 2005, **347**, 555–562; (*d*) K. E. Price, S. J. Broadwater, B. J. Walker and D. T. McQuade, *J. Org. Chem.*, 2005, **70**, 3980–3987.

5 (*a*) M. Shi, J.-K. Jiang and Y.-S. Feng, *Org. Lett.*, 2000, **2**, 2397–2400; (*b*) M. Shi and Y.-S. Feng, *J. Org. Chem.*, 2001, **66**, 406–411; (*c*) M. Shi, J.-K. Jiang, S.-C. Cui and Y.-S. Feng, *J. Chem. Soc., Perkin Trans. 1.*, 2001, 390–393; (*d*) M. Shi and J.-K. Jiang, *Tetrahedron*, 2000, **56**, 4793–4797; (*e*) M. Shi, C.-Q. Li and J.-K. Jiang, *Chem. Commun.*, 2001, 833–834; (*f*) M. Shi, J.-K. Jiang and C.-Q. Li, *Tetrahedron Lett.*, 2002, **43**, 127–130; (*g*) M. Shi and W. Zhang, *Tetrahedron*, 2005, **61**, 11887–11894.

6 P. Buskens, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2005, **127**, 16762–16763.

7 *Lange's handbook of chemistry* (15th edn, version II), ed. J. A. Demn, McGraw-Hill, New York, vol. V, 1973, pp. 13–39.

8 The ^{31}P NMR signal of alkyl(triphenyl)phosphonium ions is in the range +20 to +30 ppm, see: (*a*) M. M. Kayser, K. L. Hatt and D. L. Hopper, *Can. J. Chem.*, 1991, **69**, 1929–1939; (*b*) *CRC Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*, ed. J. C. Tebby, CRC Press Inc., Boca Raton, Florida, 1990, pp. 215–217.

