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 ³¹P 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 1972² that described the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of 1,4diazabicyclo[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 (PEt₃).^{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 (PPh₃) 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 (PPh₂Me), dimethylphenylphosphine (PPhMe₂), trimethylphosphine (PMe₃) and tributylphosphine (PBu₃) 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, pnitrophenol (p $K_a = 7.2$),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 PPh₃ (0.16 mmol) in THF (2.0 mL).

Using PPh₃ 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 PPh₃ 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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[R ¹		Ph ₃ P, TH add	F, rt, 18 h	R ¹ 3		
Entry	\mathbb{R}^1	Additive	pK _a	Yield of 3 (%) ^{<i>a</i>}		
1 2	H H	F OH	 9.8	25 48		
3	Н	F F F F F	_	32		
4	Н	O2N OH	7.2	52		
5	Н	MeO	10.0	51		
6	Н	ОН	9.9	65		
7 8	p-Cl p-Cl	F OH	 9.8	50 78		
9	p-Cl	F F F F F	_	71		
10	p-Cl	O ₂ N OH	7.2	92		
11	<i>p</i> -Cl	Мео	10.0	72		
12	p-Cl	ОН	9.9	70		
' Isolated yields.						

 Table 1
 Morita-Baylis-Hillman reaction of aryl aldehydes (0.8 mmol) with MVK (2.4 mmol) co-catalyzed by PPh₃ (0.16 mmol) and phenol (0.24 mmol)

 Table 2
 Solvent effects on the Morita–Baylis–Hillman reaction of *p*-chlorobenzaldehyde with MVK co-catalyzed by PPh₃ and *p*-nitrophenol

CI 1b	H + A add	$\frac{Ph_{3}P, rt, 18 h}{\text{litive} = p-nitrophenol} \qquad \qquad$
Entry	Solvent	Yield of 3b (%) ^{<i>a</i>}
1	Et ₂ O	60
2	THF	92
3	DMSO	92
4	DMF	80
5	Ethanol	35
6	Pentanol	21
7	Dichloromethan	e 66
" Isolated yie	elds.	

R ¹	H + H + additive	$_{3}P, rt, 18 h$ = <i>p</i> -nitrophenol R				
Entry	R ¹	Product	Yield of 3 (%) ^{<i>a</i>}			
1 2 3 4 5 6 7 8 9 10 11 12	H p-Cl p-NO ₂ m-NO ₂ o-NO ₂ p-CH ₃ p-CH ₃ O o,p-Cl ₂ p-F m-F p-Br e-H r-	3a 3b 3c 3d 3e 3f 3g 3h 3i 3j 3k 3l	52 92 98 90 98 42 35 95 87 93 83 72			
Isolated yields.						

Table 3 Morita-Baylis-Hillman reaction of aldehydes (0.8 mmol) with

MVK (2.4 mmol) co-catalyzed by PPh3 (0.16 mmol) and phenol

(0.24 mmol)

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 **31** 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 PPh₃ and *p*-nitrophenol-co-catalyzed systems, we carried out ³¹P NMR spectroscopic measurements (in CDCl₃, referenced to 85% H₃PO₄) of the Lewis base PPh₃ in the absence and presence of MVK and *p*-nitrophenol. PPh₃ showed a signal at -4.46 ppm (Fig. 2, ESI†), and PPh₃ 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),^{31,8} but PPh₃ 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 ³¹P NMR of PPh₃ with the addition of MVK is the formation of the new signal at +29.96 ppm. The ratio of the new signal at -4.46 ppm (PPh₃) is 1 : 3 ratio, indicating that the phosphonium enolate formed *in situ* is in equilibrium with free PPh₃.^{31,8} In the case of PPh₃ with the addition of MVK and



Scheme 1 A plausible mechanism for the Morita–Baylis–Hillman reaction of aldehydes with MVK co-catalyzed by PPh₃ and phenol (Brønsted acid).

p-nitrophenol, no signal of the free PPh₃ 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 PPh₃) was added into the solution, we found that a new signal appeared at +24.00 ppm in the ³¹P NMR spectrum (in CDCl₃, referenced to 85% H₃PO₄) 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 ³¹P 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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