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Novel application of phosphonium salts as co-catalysts for the Baylis–Hillman reaction

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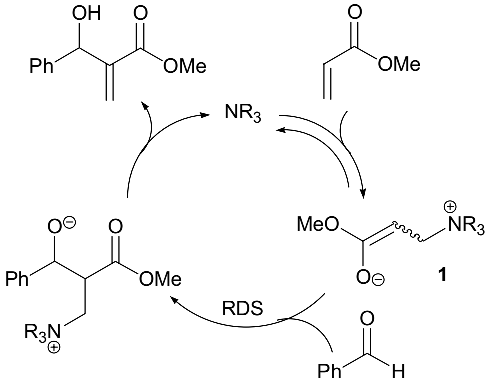
Abstract—Excellent yields have been obtained when the Baylis–Hillman reaction is conducted in the presence of phosphonium salts.

The Baylis–Hillman reaction is an elegant route to multifunctional products. The reaction traditionally involves the coupling of an unsaturated carbonyl compound with aldehydes; it is catalysed by tertiary amines.[1] The key limitation of the reaction is the slow reaction rate, which entails prolonged reaction times. There have been a number of substantial contributions to improving the reaction rates including the use of phosphines as catalysts, addition of Lewis acids, high pressure, ultrasound and microwave irradiation.[2] Modest improvements in reaction rates and yields have been reported in the presence of water (hydrophobic effects); or fluorinated solvents (fluorophobic effects) and the presence of hydrogen bond donors in the reagents used.[2] The increase in the rate in the latter case can be attributed to either stabilisation of intermediate **1** (Scheme 1) or activation of the aldehyde. Recently, imidazolium-based ionic liquids have been used as solvents for the Baylis–Hillman reaction, with moderate success.[3,4] Aggarwal et al. have subsequently shown that these solvents are not inert.[4]

We have found that phosphonium tosylates are effective ionic solvents for hydroformylation reactions,[5] hydrogen transfer reactions[6] and Diels–Alder reactions.[7] This success prompted us to explore the use of phosphonium tosylates as co-catalysts for the Baylis–Hillman reaction. Like the Aggarwal group we believed that their high polarity would provide a higher concentration of the zwitterionic intermediate aza-enolate **1**, therefore facilitating the reaction.



Scheme 1. Reaction of methyl acrylate with benzaldehyde.

The reaction conditions were selected so that meaningful comparisons could be made with literature data. Initial reactions using methyl acrylate, benzaldehyde, DABCO (50 mol%) and ethyltri-*n*-butylphosphonium tosylate, $[Bu_3P^+Et]^-OTs$, (50 mol%) as the co-catalyst showed that the presence of the phosphonium salt caused an increase in the yields; no side products were observed. In refining the method it was discovered that the amount of phosphonium salt could be decreased to 10 mol% without a detrimental effect on the yield of the product and subsequent reactions were performed with this reduced amount.[8] The yield (92%) (Table 1, entry 3) is an improvement over the neat reaction (entry 1) and is superior to that obtained (65%) in the imidazolium ionic liquid, $[bmim][PF_6]$.[3] Next we evaluated the effects of changing the groups on phosphorus and varying the anion. The excellent yields were maintained irrespective of the groups on phosphorus. For example, only a small increase in yield was obtained on changing from the

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Table 1. Baylis–Hillman reactions with phosphonium salts as co-catalysts

Entry	Aldehyde	$[R_3P^+R^1]\ X^-$	Yield (%)
1	Benzaldehyde	Neat	68[a]
2	Benzaldehyde	$[Bmim][PF_6]$	65[a]
3	Benzaldehyde	$[Bu_3P^+Et]^-OTs$	92
4	Benzaldehyde	$[Ph_3P^+Et]^-OTs$	95
5	Benzaldehyde	$[Bu_3P^+Et]^-OMs$	92
6	Benzaldehyde	$[Ph_3P^+Et]^-OMs$	95
7	Benzaldehyde	$[Bu_3P^+Et]Br^-$	97
8	Benzaldehyde	$[Ph_3P^+Et]Br^-$	95
9	Benzaldehyde	$[Bu_3P^+Et]I^-$	95
10	Benzaldehyde	$[Ph_3P^+Et]I^-$	95

Reactions conducted on a 5.0 mmol scale using a ratio of 1:1.1:0.5:0.1 of aldehyde:methyl acrylate:DABCO:phosphonium salt at room temperature for 24 h.

[a] 100% DABCO[3].

tetraalkyl salt, $[Bu_3P^+Et]^-OTs$, to the triarylalkyl salt, $[Ph_3P^+Et]^-OTs$ (entry 4). Changing the anion to the mesylate, bromide or iodide did not affect the yield (entries 5–10).

Lewis acids have been reported to be efficient co-catalysts for the reaction. We selected $Cu(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$ and $LiClO_4$ and found that they had a detrimental effect on the yields. This trend was also observed for the reactions performed in the presence of imidazolium salts.[3,4]

In order to investigate the generality of the DABCO/phosphonium salt catalytic system, a series of aldehydes was investigated. The results are displayed in Table 2. The trend for the methyl-substituted benzaldehydes (entries 1–3) is similar to that observed previously; a poor yield was obtained for 2-methylbenzaldehyde (31%) and moderate yields were obtained for the 3- and 4-methylbenzaldehydes (entries 2–3). Excellent yields were obtained for the 3- and 4-fluoro-, 4-bromo and 4-chlorobenzaldehydes (entries 4–8). Disappointingly, no success was observed for the highly deactivated anisaldehydes (entires 10–11). The aliphatic aldehyde, isobutyraldehyde, gave a yield of 97% (entry 15), which is superior to the yield obtained in the conventional reaction.

Table 2. Reactions of methyl acrylate with aldehydes

Entry	Aldehyde	$Additive^-$	Yield (%)
1	2-Methylbenzaldehyde	$[Bu_3P^+Et]^-OTs$	31
2	3-Methylbenzaldehyde	$[Bu_3P^+Et]^-OTs$	64
3	4-Methylbenzaldehyde	$[Bu_3P^+Et]^-OTs$	56
4	3-Fluorobenzaldehyde	$[Bu_3P^+Et]^-OTs$	99
5	4-Fluorobenzaldehyde	$[Bu_3P^+Et]^-OTs$	86
6	2-Chlorobenzaldehyde	$[Bu_3P^+Et]^-OTs$	99
7	4-Chlorobenzaldehyde	$[Bu_3P^+Et]^-OTs$	96
8	4-Bromobenzaldehyde	$[Bu_3P^+Et]^-OTs$	96
9	4-Nitrobenzaldehyde	$[Bu_3P^+Et]^-OTs$	96
10	2-Anisaldehyde	$[Bu_3P^+Et]^-OTs$	<1
11	4-Anisaldehyde	$[Bu_3P^+Et]^-OTs$	2
12	*trans*-Cinnamaldehyde	$[Bu_3P^+Et]^-OTs$	58
13	4-Pyridinecarboxaldehyde	$[Bu_3P^+Et]^-OTs$	95
14	2-Furaldehyde	$[Bu_3P^+Et]^-OTs$	95
15	Cyclohexanecarboxaldehyde	$[Bu_3P^+Et]^-OTs$	20
15	Butylaldehyde	$[Bu_3P^+Et]^-OTs$	97
16	Isobutyraldehyde	$[Bu_3P^+Et]^-OTs$	58

Reactions conducted on a 5.0 mmol scale using a ratio of 1:1.1:0.5:0.1 of aldehyde:methyl acrylate:DABCO:phosphonium salt at room temperature for 24 h.

In view of the results obtained with the phosphonium salt/DABCO system, we explored the utility of the reaction with the other activated alkenes traditionally used in this reaction. The conventional reaction with acrylate esters requires lengthy reaction times, for example, the reaction of ethyl acrylate and benzaldehyde requires seven days to produce a reasonable yield of the Baylis–Hillman adduct, and the same reaction with *t*-butyl acrylate affords 65% yield after 28 days.[9] Excellent yields were obtained using our reaction conditions with acrylate esters (Table 3, entries 1–3) and a 35% yield (entry 4) was obtained for the *t*-butyl analogue after 24 h. Acrylonitrile gave a quantitative yield; surprisingly, however, a low yield was obtained with methyl vinyl ketone (entry 5). The yields for the reactions with *t*-butyl acrylate and methyl vinyl ketone improve when the reactions are continued for a longer time. No product was isolated for the reactions with phenyl vinyl sulfone and diethyl vinyl phosphonate (entries 6–7).

The phosphonium salt could perform a number of roles in the reaction; it can be involved in activating the alkene, activating the aldehyde and in stabilising the zwitterionic intermediate **1**.[10] Also, it is puzzling that the combination of DABCO/phosphonium salt/Lewis acid additive has a detrimental effect on the reaction.

There are some limitations in the use of the phosphonium salt/DABCO catalytic system, for example, poor yields with the anisaldehydes, and we are currently conducting further experiments that could address these problems and explain the mechanism of the reaction.

In conclusion, this study demonstrates the use of an attractive (readily available, stable and cheap) alternative co-catalyst for the Baylis–Hillman reaction. In addition, the practical procedure for the phosphonium salt/DABCO catalysed reaction is straightforward; there is no need for special precautions such as an inert atmosphere or dry reagents.

Table 3. Reactions of benzaldehydes with activated alkenes

Entry	Alkene	Additive	Yield (%)
1	Methyl acrylate	$[Bu_3P^+Et]^-OTs$	88
2	Ethyl acrylate	$[Bu_3P^+Et]^-OTs$	90
3	*n*-Butyl acrylate	$[Bu_3P^+Et]^-OTs$	80
4	*t*-Butyl acrylate	$[Bu_3P^+Et]^-OTs$	35
5	Acrylonitrile	$[Bu_3P^+Et]^-OTs$	100
6	Methyl vinyl ketone	$[Bu_3P^+Et]^-OTs$	35
7	Phenyl vinyl sulfone	$[Bu_3P^+Et]^-OTs$	0[a]
8	Diethyl vinyl phosphonate	$[Bu_3P^+Et]^-OTs$	0[a]

Reactions conducted on a 5.0 mmol scale using a ratio of 1:1.1:0.5:0.1 of aldehyde:acrylate:DABCO:phosphonium salt at room temperature for 24 h.

[a] Only unreacted starting materials were isolated.

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8. Illustrative procedure: benzaldehyde (5 mmol) and methyl acrylate (5.5 mmol) were added to a round-bottomed flask containing the phosphonium salt (0.5 mmol) and DABCO (2.5 mmol). The flask was stoppered and the mixture was stirred at room temperature for 24 h. The mixture was diluted with dichloromethane (10 cm^3) and washed successively with aq HCl (2 M), NaOH, (2 M) and water. The organic phase was dried and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane, 1:3) to give methyl 3-hydroxy-2-methylidene-3-phenylpropionate. The spectra for all the compounds were compared with the literature data.
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