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Phosphine-catalyzed dimerization of activated alkenes under ambient and high pressure conditions

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Abstract

Acrylic compounds dimerize under Morita–Baylis–Hillman conditions in the presence of soluble phosphines. Dimerization of β -substituted analogs may require high pressures. The process is selective and high yielding and affords densely functionalized products.   2000 Elsevier Science Ltd. All rights reserved.

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Morita–Baylis–Hillman (MBH) reactions are currently and intensively reactivated in view of their considerable synthetic interest.¹ The poor yields obtained until these last years are now susceptible to be remarkably increased with the help of new methods: e.g. high pressure^{2,3} or catalysis.⁴ Unhindered acrylic compounds add to benzaldehyde under MBH conditions, affording excellent yields of functionalized acrylic derivatives.⁴ However, if the access to β -reaction centers is hindered, the reaction becomes exceedingly sluggish. As an illustrative example, crotononitrile reacts with benzaldehyde only under pressures in excess of 1200 MPa.⁵ Phosphines were originally the catalysts in the MBH addition of aldehydes to acrylonitrile.⁶ Later, they were replaced by cyclic tertiary amines, mostly DABCO. In the last few years, phosphines emerged again and were used sporadically.^{7–9} Amri et al. could dimerize in this way unhindered acrylates.⁷ However, with this exception, acrylic compounds did not undergo MBH dimerization, especially hindered derivatives, due to the reduced steric accessibility of the β -position in the acrylic compound.

While we were studying nucleophilic addition reactions involving crotononitrile under high pressure, we observed in the slowest reactions a by-product of the expected addition product. It was shown to be a dimer of the acrylic nitrile. The catalyst employed in the reaction was tri-*n*-butylphosphine. Clearly, the reaction afforded dimer **1** formed according to a typical MBH reaction (Eq. (1)). These results prompted us to investigate in more detail the MBH dimerization process of activated alkenes.¹⁰ In the first step, we screened the catalytic ability of several phosphines and cyclic tertiary amines in the dimerization

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of crotononitrile, a hindered acrylic nitrile (Table 1) with comparison to the traditional MBH catalysts (DABCO, 3-quinuclidinol).

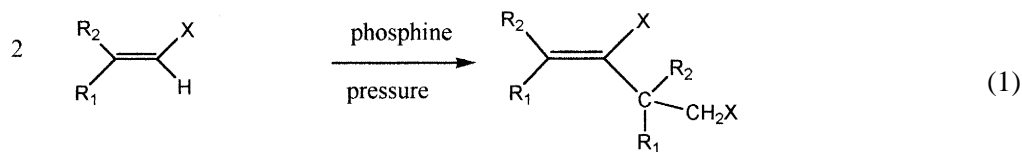


Table 1
MBH dimerization of crotononitrile ($\text{R}_1=\text{CH}_3$, $\text{R}_2=\text{H}$, $\text{X}=\text{CN}$) (bulk, 50°C , 24 h, catalyst-5% molar)

Catalyst	Pressure (MPa)	Yield ^a (%)	<i>trans</i> : <i>cis</i> ^b
DABCO or 3-quinuclidinol	0.1	0	-
	300	0	-
DBU	0.1	3	-
	300	19	65 : 35
DBN	0.1	6	-
	300	54	68 : 32
$\text{P}(\text{nC}_4\text{H}_9)_3$	0.1	7	75 : 25
	300	100	77 : 23
$\text{P}(\text{C}_6\text{H}_{11})_3^c$	300	0	-
$\text{P}(\text{C}_6\text{H}_5)_3^c$	300	0	-
$\text{P}[\text{N}(\text{CH}_3)_2]_3$	0.1	87	71 : 29
Phosphazene ^d	0.1	72 ^d	68 : 32

^a Determined by ^1H NMR

^b Initial ratio in crotononitrile (*trans* : *cis* = 65 : 35)

^c A small amount of dry THF was added to solubilize the phosphine before reaction

^d Phosphazene Base $\text{P}_4\text{-t-Bu}$ solution. Polymeric material was also present

The tertiary amines commonly used for the MBH reaction (DABCO, quinuclidinol) were completely inactive even at 300 MPa. In a former study, it was found that DABCO (10%) was able to catalyze the dimerization of acrylonitrile and methyl acrylate at 300 MPa.³ The interesting point in Table 1 is that phosphines and complex cyclic amines can be efficient. The best was trisdimethylaminophosphine which converted the monomer into the dimer to 87%. Tri-*n*-butylphosphine, DBU and DBN catalyzed the MBH reaction, however it was less efficient. The modest yields obtained in the presence of these catalysts were remarkably increased under pressure, particularly with $\text{P}(\text{nC}_4\text{H}_9)_3$ affording a quantitative yield of **1**. The result is in agreement with the general pressure effect in MBH reactions.^{2,3} The solid phosphines $\text{P}(\text{C}_6\text{H}_{11})_3$ and $\text{P}(\text{C}_6\text{H}_5)_3$ did not catalyze the dimerization reaction.

The effect of pressure on the DABCO-catalyzed *cis:trans* isomerization of crotononitrile was investigated previously. It was found that under neat conditions the formation of the *trans* isomer increased with increasing pressure.⁵ In fact, we observed a higher *trans* concentration in the dimer mixture. This seems mainly due to the phosphine (a slight pressure effect may also be taken into account) since DBN and DBU did not change the isomer ratio of **1** if compared to the *cis:trans* ratio of the starting crotononitrile.

In the next step we extended the study to the MBH dimerization of acrylic nitriles, esters, ketones (Table 2).

- (i) Acrylonitrile dimerized spontaneously at ambient pressure using $P(C_4H_9)_3$ as catalyst (entry 1). In a former study it was found that DABCO was also able to catalyze the dimerization of this nitrile, however, only under 300 MPa.³ *cis*-2-Pentenenitrile could be dimerized to **2** in nearly quantitative yield at 300 MPa (entries 3 and 4) whereas cinnamionitrile was unreactive even at very high pressures (900 MPa) (entry 5).

Table 2
Phosphine-catalyzed dimerization of activated alkenes (bulk, 50°C, 24 h) (Eq. (1))

Entry	R ¹	R ²	R ³	Catalyst concentration (molar)	Yields %		Product
					0.1 MPa	300 MPa	
1	H	H	CN	$P(C_4H_9)_3$ (5 %)	98 ^a	no run	dimer
2	CH ₃	"	"	$P[N(CH_3)_2]$ (5 %)	87	no run	1
3	C ₂ H ₅	"	"	$P(C_4H_9)_3$ (5 %)	0	86	2
4	"	"	"	$P[N(CH_3)_2]$ (5 %)	8	96	2
5	C ₆ H ₅	"	"	" (15 %)	0	0	
6	H	"	CO ₂ CH ₃	$P(C_4H_9)_3$ (5 %)	59	no run	dimer
7	CH ₃	"	"	" (10 %)	0	0	
8	"	"	"	$P[N(CH_3)_2]$ (10 %)	0	38	3
9	"	"	"	" (30 %)	0	88	3
10	"	"	CO ₂ C ₂ H ₅	" (30 %)	0	45	4
11	"	CH ₃	CO ₂ CH ₃	" (30 %)	0	1	
12	1-cyclohexen-3-one			$P(C_4H_9)_3$ (5 %)	100	no run	5 ^[12]

^a A solvent was necessary to prevent the rapid polymerization reaction

- (ii) Methyl acrylate was converted to 2-methylene glutaric methyl ester with $P(C_4H_9)_3$ at ambient pressure (entry 6)¹¹ (51% yield with DABCO at 300 MPa³). Crotonates, however, did not react under normal conditions. Dimerization of methyl and ethyl crotonate occurred under 300 MPa with $P[N(CH_3)_2]$ as catalyst (entries 8–10). Other phosphines as well as DBU and DBN were unable to catalyze the reaction. The highly crowded methyl 3,3-dimethyl acrylate was practically unreactive even under elevated pressure (entry 12) affording only a trace of the supposed dimer.
- (iii) The enone examined dimerized easily at 0.1 MPa with phosphine catalysts (entry 12). The dimer **5** was previously obtained in 85% yield in the presence of DBU at 185°C in imidazolinedione as solvent.¹²

In summary, activated alkenes can undergo dimerization under MBH conditions in the presence of peculiar trialkylphosphines.¹³ Whereas unhindered compounds dimerize in high yields at ambient pressure, substituted acrylic compounds generally require high pressures (300 MPa and above). The process affords selectively densely functionalized ethylenic derivatives.

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10. A PTFE tube was filled up with hydroquinone (polymerization inhibitor), standard (trimethoxybenzene or bibenzyl according to run), phosphine and completed with the acrylic compound. After reaction the content was poured into a 4N HCl solution to remove the phosphine. Usual work-up yielded the residue which was directly analyzed by ¹H NMR (CDCl₃, 200 MHz, δ ppm): **1 trans**: 6.48 (q, 1H, CH-C), 2.69 (m, 1H, CH-C=C), 2.44 (d, 2H, CH₂), 1.96 (d, 3H, CH₃), 1.24 (d, 3H, CH₃); **1 cis**: 6.55 (q, 1H, CH-C), 3.12 (m, 1H, CH-C=C), 2.51 (d, 2H, CH₂), 1.97 (d, 3H, CH₃), 1.33 (d, 3H, CH₃); **2**: 6.31 (t, 1H, CH=C), 2.81 (m, 1H, CH-C=C), 2.35–2.46 (br, 4H, CH₂), 1.56 (br, 2H, CH₂), 1.04 (m, 3H, CH₃), 0.90 (t, 3H, CH₃); **3**: 6.74 (q, 1H, CH=C), 3.63 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 3.26 (m, 1H, CH-C=C), 2.44–2.72 (dd, 2H, CH₂), 1.78 (d, 3H, CH₃), 1.14 (d, 3H, CH₃); **4**: 6.74 (q, 1H, CH=C), 4.16 (t, 4H, OCH₂), 3.32 (m, 1H, CH-C=C), 2.50–2.78 (dd, 2H, CH₂), 1.76 (d, 3H, CH₃), 1.18 (br, 6H, CH₃).
11. 2-Methylene glutaro-nitrile and methyl ester could be synthesized via transition metal catalyzed dimerization of acrylonitrile and methyl acrylate, respectively. However, the reactions were not selective (other dimers were also produced) and needed prolonged reaction times. Crotonic derivatives did not react under such conditions. Watanabe, Y.; Takeda, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 883–887.
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13. In contrast with the excellent yields reported in the DBU catalyzed MBH reaction (Ref. 4), the phosphines used in the present work did not catalyze the MBH addition of benzaldehyde to acrylic compounds.