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Phosphine catalyzed aldol reaction between ketene silyl acetals and aldehydes: nucleophilic O–Si and C–Si bond cleavage by phosphines

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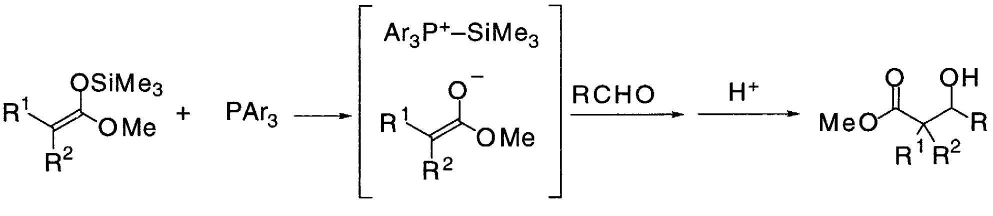
Abstract

A highly nucleophilic phosphine, tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP), catalyzes the aldol reaction between ketene silyl acetals and aldehydes to give the corresponding aldol products in good to high yields. This reaction is considered to proceed through naked enolates produced by nucleophilic O–Si and C–Si bond cleavage.

Keywords: phosphines; aldol reactions; naked enolates.

The aldol reaction has become a fundamental method of carbon–carbon bond forming reactions in modern organic synthesis.[1] One of the most commonly used and best understood is the Mukaiyama aldol reaction (Lewis acid-promoted carbonyl addition of silyl enol ethers).[2] On the other hand, it is well known that the reaction between carbonyl compounds and silyl enol ethers could proceed under various conditions. For example, several efficient activators such as a fluoride ion,[3] trityl salts,[4] water,[5] transition metal salts,[6] HMPA derivatives,[7] high pressure[8] and elevated temperature[9] etc., have been developed to realize high yields and selectivities of this reaction. In this paper, we report the use of phosphines as catalysts[10] in the aldol reaction of ketene silyl acetals through nucleophilic cleavage of the O–Si bond (Scheme 1).



Scheme 1.

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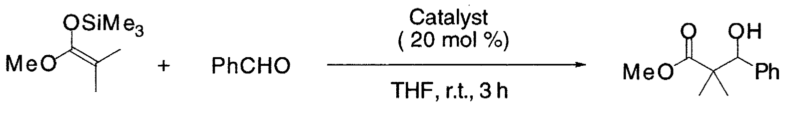
First, we examined the catalytic activity of various phosphines in the reaction of benzaldehyde with a trimethylsilyl enol ether derived from methyl isobutylate. The reaction was carried out by adding the trimethylsilyl enol ether and benzaldehyde to THF containing 20 mol% of phosphine at room temperature. The reaction was monitored by TLC. Careful hydrolytic work-up with 1 M HCl, followed by column chromatography, afforded the desired aldol product. The results are summarized in Table 1. Moderate to good product yields were obtained in the presence of a catalytic amount of the phosphine. Especially, tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP)[11] was found to be quite effective (Table 1,

Table 1



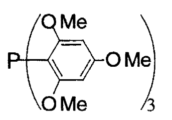
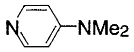
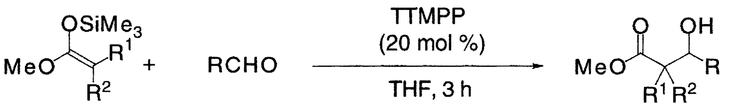
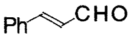
Entry	Catalyst	Yield / %	Entry	Catalyst	Yield / %
1	Ph_3P	70	6		32
2	Cy_3P	59	7	$(Me_2N)_3P=O$	26
3	$^nBu_3P$	34	8	$Ph_3P=O$	8
4	$^tBu_3P$	24	9	$Cy_3P=O$	19
			10	$(PhO)_3P$	–
5	 (TTMPP)	89	11		27
			12	Et_3N	9

Table 2

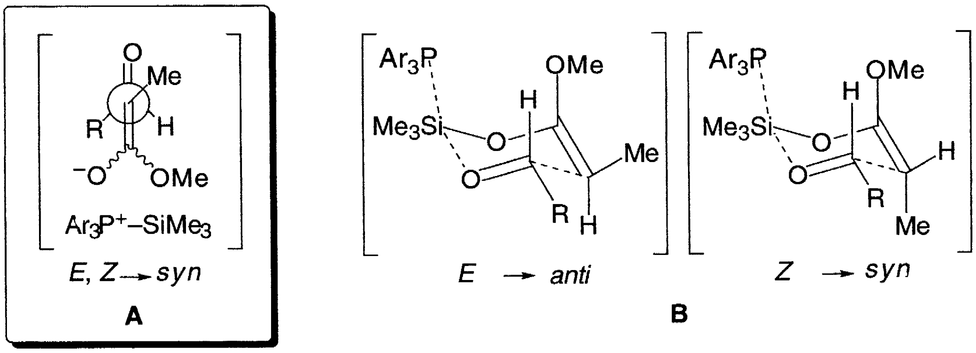


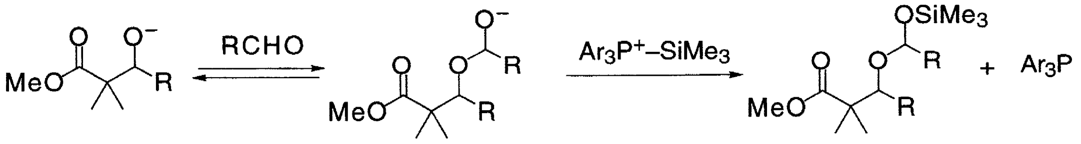
Entry	Aldehyde	R^1	R^2	Temperature	*Syn* : *Anti*[a]	Yield / %
1	PhCHO	Me	Me	r.t.	–	89
2[b]	PhCHO	Me	Me	r.t.	–	93
3	*p*-$MeOC_6H_4CHO$	Me	Me	r.t.	–	89
4	*p*-MeC_6H_4CHO	Me	Me	r.t.	–	82
5	*p*-ClC_6H_4CHO	Me	Me	r.t.	–	68
6	$C_8H_{17}CHO$	Me	Me	r.t.	–	50
7	*c*-$C_6H_{11}CHO$	Me	Me	r.t.	–	48
8		Me	Me	r.t.	–	59
9[c]	PhCHO	Me	H	0 °C	67 : 33	67
10[c]	PhCHO	Me	H	−78 °C → −40 °C	65 : 35	58
11[d]	PhCHO	H	Me	0 °C	67 : 33	60

[a] Diastereoselectivity was determined by ^1H NMR spectroscopy (400 MHz).
[b] Water (10 mol %) was added. [c] The starting material consists of 81% *E* and 19% *Z*. [d] The starting material consists of 22% *E* and 78% *Z*.

entry 5). TTMPP is a highly nucleophilic and basic phosphine and, thus, it is likely to have played an important role in this reaction. A bidentate phosphine, 1,2-bis(diphenylphosphino)ethane, did not catalyze this reaction (Table 1, entry 6). Phosphine oxides, phosphate, HMPA and amines were also used as catalysts. Although this reaction proceeded under these conditions, chemical yields were low (Table 1, entries 7–12). Thus, only phosphine among these activators effectively catalyzed this aldol reaction.

In order to clarify the scope of this phosphine catalyzed reaction, several aldehydes were examined in the presence of 20 mol% of TTMPP (Table 2). Good results were obtained for both aromatic and aliphatic aldehydes. In some cases, the addition of a small amount of water increased the chemical yield (entries 1 versus 2), but the role of water is not clear. Small amounts of acetal products were produced in all cases, particularly when aliphatic aldehydes were used. These acetal products were easily converted to normal aldol product by treatment with 1 M HCl. Furthermore, moderate *syn*-diastereoselectivity was observed irrespective of the geometry of the silyl enol ether derived from methyl propionate.

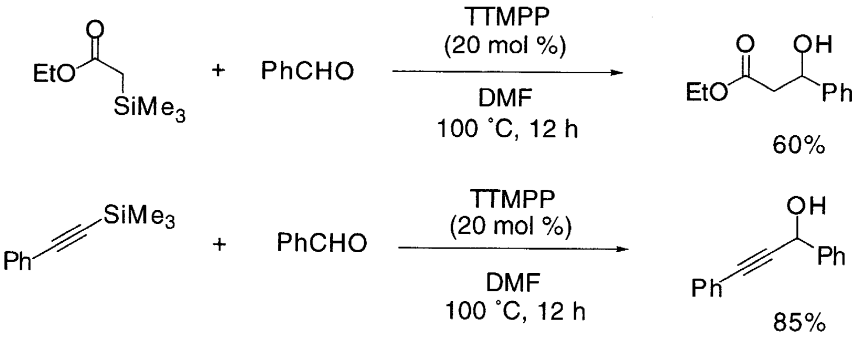




The observed diastereoselectivity can be reasonably explained by considering an extended transition state **A**[12] rather than a cyclic transition state **B**,[13] because it is well recognized that, via the cyclic transition state, (*E*)-enolate affords *anti*-diastereomer and (*Z*)-enolate leads to *syn*-diastereomer. On the other hand, *syn*-diastereomer is formed via transition state **A** irrespective of the geometry of silyl enol ether. In addition, acetal products are produced in this reaction. It is well known that acetal products are obtained in the fluoride ion-catalyzed aldol reaction.[3d] These facts suggest that naked enolates are generated through a nucleophilic O–Si cleavage by phosphines, similar to a fluoride ion-catalyzed reaction.

The reaction of α-silyl ester with benzaldehyde in the presence of TTMPP (20 mol%) was also examined. The reaction proceeded to give the corresponding product in 60% yield. Reaction of phenyltrimethylsilyl acetylene with benzaldehyde also took place under similar conditions. These reactions are considered to proceed through a pathway in which TTMPP attacks the silyl atom and the generated carbanion[14] reacts with aldehyde (Scheme 2).

In summary, phosphines catalyze the aldol reaction through a nucleophilic O–Si and C–Si bond cleavage. Further studies along these lines, including asymmetric reactions are now underway in our laboratory.



Scheme 2.

Acknowledgements

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