Phosphazene base-catalyzed condensation of trimethylsilylacetate with carbonyl compounds†

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The *t*-Bu-P4 base was found to be an excellent catalyst for the condensation of trimethylsilylacetate or trimethylacetonitrile with carbonyl compounds to form functionalized alkenes and β-enaminoesters were also synthesized by the condensation with formanilides.

Condensation of α-silylalkyl compounds with carbonyl compounds to form alkenes has been known as the Peterson olefination reaction.[1] Usually an α-silanyl carbanion generated *in situ* using a stoichiometric metallic base such as LDA or an alkyllithium has been utilized for the reaction. The reaction has been widely employed as an important method for alkene synthesis, because of simpler workup and purification procedure than the Wittig reaction. This condensation reaction will be more valuable if the transformation can be accomplished with a catalytic base.

Phosphazene bases[2] developed by Schwesinger and proazaphosphatranes[3] developed by Verkade are known as strong non-metallic organic superbases (Fig. 1). Among them, *t*-Bu-P4 base shows extremely high basicity and has been used for various selective deprotonative transformations.[4] The strong affinity of *t*-Bu-P4 base to protons is regarded as synthetically useful, however the ability of *t*-Bu-P4 base to activate α-silylalkyl compounds has not been reported. In connection with our recent interest on the catalytic activation of organosilicon compounds using *t*-Bu-P4 base,[5] we investigated catalytic condensation reactions of α-silylalkyl compounds with carbonyl compounds in the presence of the catalytic *t*-Bu-P4 base.
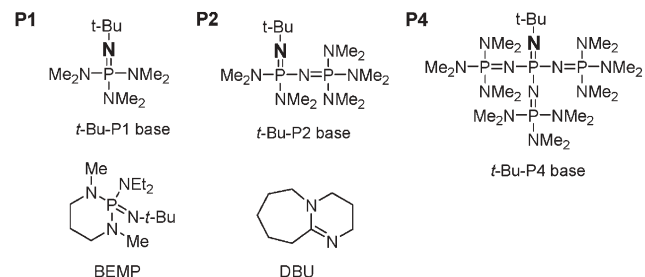

Fig. 1   Organic strong bases.

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In our initial investigation for the condensation reaction, we chose the reaction of ethyl trimethylsilylacetate with benzophenone (**1**). When the reaction of **1** and ethyl trimethylsilylacetate in THF in the presence of 10 mol% *t*-Bu-P4 base was carried out at −78 °C, the condensation reaction proceeded smoothly and the unsaturated ester (**2**) was isolated in 94% yield (Table 1, entry 1). Other phosphazene bases with weaker basicity such as *t*-Bu-P2 base and BEMP showed no effect on the condensation under the same reaction conditions (Table 1, entries 2 and 3). DBU also showed no catalytic effect on the condensation (Table 1, entry 4). When tetrabutylammonium fluoride (TBAF) was used for the reaction, the 1,2-adduct was isolated in 38%, but no formation of alkene was observed (Table 1, entry 5).

Table 1

Entry	Base	Time/h	Yield (%)
1	*t*-Bu-P4 base	6	94
2	*t*-Bu-P2 base	24	0
3	BEMP	24	0
4	DBU	24	0
5	TBAF	6	0 (38)[a]

[a] β-Trimethylsilyloxy ester was obtained in 38% yield.

As shown in Table 1, it was found that *t*-Bu-P4 base is an excellent catalyst for the condensation, and in order to examine further scope and limitations, reactions using other substrates were investigated. As another trimethylsilylalkyl substrate, *N,N*-diethyl-trimethylsilylacetamide was reacted with **1** to give the unsaturated amide **4a** in 87% yield (Table 2, entry 1) and the reaction of trimethylsilylacetonitrile with **1** was also successful to give **4b** in 78% yield (Table 2, entry 2). Benzaldehyde (**3a**) was then used as a carbonyl compound and ethyl cinnamate (**4c**) was obtained in 89% yield using ethyl trimethylsilylacetate (Table 2, entry 3). Condensation of other arylaldehydes (**3b,c,d**) with ethyl trimethylsilylacetate proceeded smoothly and the corresponding arylacrylates (**4d,e,f**) were obtained in good yields (Table 2, entries 4,5,6). The double bonds of the products from arylaldehydes were *E* geometry. When acetophenone (**3e**) was used as a carbonyl compound, the reaction with trimethylsilylacetonitrile proceeded smoothly to give the alkene (**4h**) in 63% yield as an *E,Z* mixture (*E* : *Z* = 89 : 11) (Table 2, entry 8), however the reaction with ethyl trimethylacetate gave the β-trimethylsilyloxy ester (**4g**) in 29% yield

Table 2

Entry	Substrate	R	R'	EWG[d]	Time/h	4	Yield (%)
1	**1**	Ph	Ph	$CONEt_2$	12	**4a**	87[a]
2	**1**	Ph	Ph	CN	6	**4b**	78
3	**3a**	Ph	H	COOEt	6	**4c**	89
4	**3b**	$4\text{-}MeC_6H_4$	H	COOEt	6	**4d**	91
5	**3c**	$4\text{-}MeOC_6H_4$	H	COOEt	6	**4e**	69
6	**3d**	2-furyl	H	COOEt	6	**4f**	85
7	**3e**	Ph	Me	COOEt	6	**4g**[b]	(29)[b]
8	**3e**	Ph	Me	CN	13	**4h**	63[c]
9	**3f**	Ph	CH=CHPh(E)	COOEt	6	**4i**	81
10	**3f**	Ph	CH=CHPh(E)	CN	13	**4j**	80[c]
11	**3g**	*n*-Pentyl	H	COOEt	6	**4k**	35

[a] The reaction was carried out at room temperature followed by 50 °C. [b] The 1,2-adduct, β-trimethylsilyloxy ester (**4g**) was isolated in 29% yield. [c] The reaction was carried out at −78 °C followed by 50 °C. [d] EWG = electron withdrawing group.

(Table 2, entry 7). The reaction of chalcone (**3f**) with trimethylsilylacetate gave the diene (**4i**) in 81% yield (*E* : *Z* = 100 : 0) (Table 2, entry 9). Similarly, the condensation of **3f** with trimethylsilylacetonitrile also gave the corresponding diene (**4j**) in 80% yield (*E* : *Z* = 50 : 50) (Table 2, entry 10). As an example of aliphatic aldehyde, *n*-hexanal **3g** was used as a substrate and the desired unsaturated ester **4k** was obtained in 35% yield (Table 2, entry 11). Enolizable substrates seem unfavorable for this condensation.

Our next interest was focused on the condensation of formanilides with α-trimethylsilylalkyl compounds because the examples of enamine synthesis using the Peterson reaction are few.[6] No precedent example for the condensation of formamides with α-trimethylsilylalkyl compounds have appeared to the best of our knowledge.[7]

Table 3

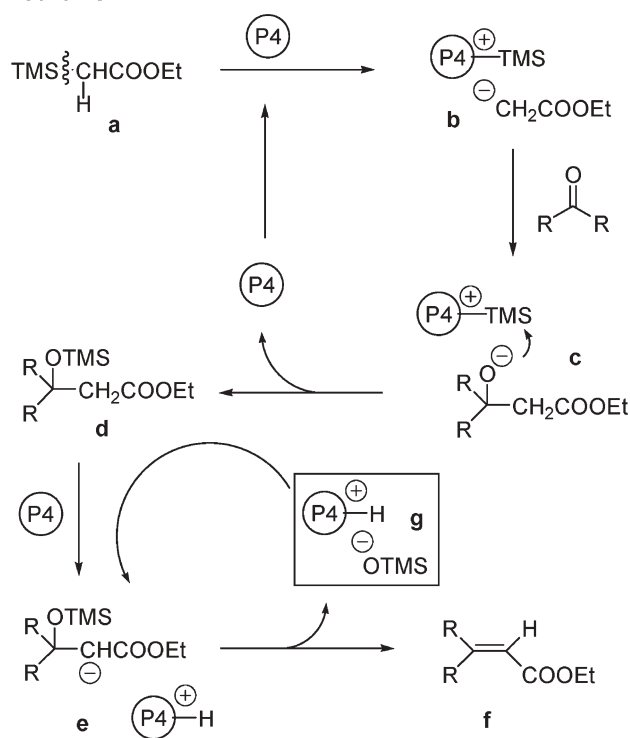| Entry	Substrate	X	R	EWG	Time/h	6	Yield (%)
1	**5a**	H	Me	COOEt	24	**6a**	90
2	**5a**	H	Me	COOEt	24	**6a**	92[a]
3	**5a**	H	Me	CN	24	**6b**	78[a]
4	**5b**	Me	Me	COOEt	48	**6c**	74
5	**5c**	OMe	Me	COOEt	48	**6d**	47
6	**5d**	COOEt	Me	COOEt	24	**6e**	85
7	**5d**	COOEt	Me	CN	48	**6f**	87
8	**5e**	CN	Me	COOEt	20	**6g**	80
9	**5e**	CN	Me	CN	48	**6h**	80
10	**5f**	H	$CH_2CH=CH_2$	COOEt	24	**6i**	83[a]
11	**5f**	H	$CH_2CH=CH_2$	CN	24	**6j**	42[a]
12	**5g**	H	CH_2Ph	COOEt	24	**6k**	99[a]
13	**5g**	H	CH_2Ph	CN	24	**6l**	88[a]

[a] Solvent free reaction.

Compared to ketones or aldehydes, the reactivities of formamides to nucleophiles were considered to be lower and the investigation was started with the reaction at room temperature. When *N*-methylformanilide (**5a**) was reacted with ethyl trimethylsilylacetate in THF at room temperature, the condensation proceeded smoothly and the enaminoester (**6a**) was obtained in 90% yield (Table 3, entry 1). The same condensation was also carried out under solvent free conditions and **6a** was obtained in 92% yield (Table 3, entry 2). Similarly trimethylsilylacetonitrile was condensed with **5a** to give the enaminonitrile (**6b**) in 78% (Table 3, entry 3). Various substituents on the aromatic ring of the formanilides were compatible with this condensation (Table 3, entries 4–9) and the tolerance of alkoxycarbonyl group and cyano group during the condensation is considered to be synthetically important. *N*-Allyl and *N*-benzyl formanilides were also reacted with trimethylsilylalkyl compounds to give the corresponding enamines (**6i–l**) (Table 3, entries 10–13).
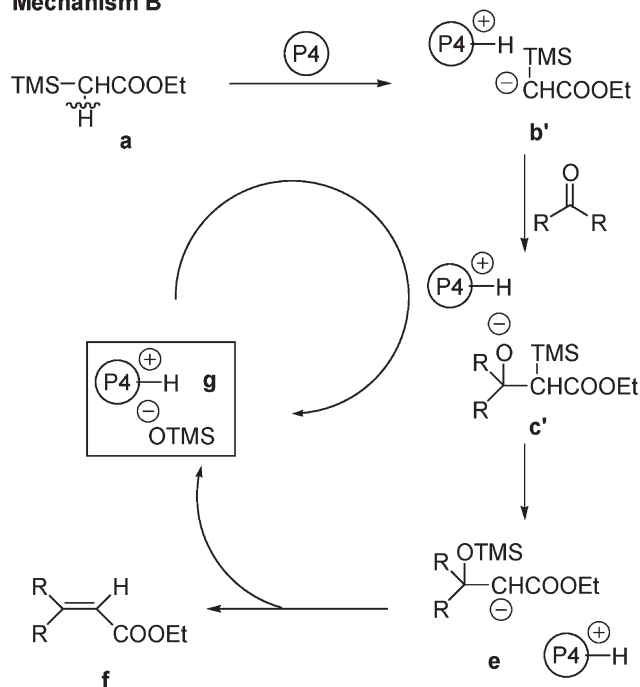
On the mechanism of the condensation, two different types of the initial activation of trimethylsilylalkyl compounds can be speculated. One is the deprotonative activation of the carbon–hydrogen bond and the other is direct carbon–silicon bond activation. Mechanism A is based on the activation of the carbon–silicon bond by *t*-Bu-P4 base and ethyl trimethylsilylacetate (**a**) is reacted with *t*-Bu-P4 base to form the reactive anion **b**. 1,2-Addition of **b** gives **c** and the oxy anion of the adduct **c** is silylated to form the silyl ether **d**. The deprotonation of **d** with *t*-Bu-P4 base gives the carbanion **e**, which eliminates trimethylsilyloxy anion to form the desired alkene **f**. Here the formation of phosphazenium silanoxide **g** is important and **g** is considered to catalyze the elimination reaction of **d** to give **f** as well as the P4 base. This mechanism is different from the pathway of conventional Peterson olefination and from our other examples on the activation of the carbon–silicon bond using *t*-Bu-P4 base,[5] mechanism A seems to be acceptable as a candidate. In this mechanism, *t*-Bu-P4 base catalyzes the initial 1,2-addition and in the elimination both *t*-Bu-P4 base and phosphazenium silanoxide **g** act as catalysts.

Mechanism B is based on the initial deprotonation of ethyl trimethylsilylacetate (**a**) and the carbanion **b′** is first formed. The 1,2 addition of **b′** gives the alkoxide **c′** which TMS rearranges to oxygen to give the carbanion **e**. The elimination reaction of **e** gives the alkene **f**. The phosphazenium silanoxide **g** is also used in the deprotonation of **a** in the following catalytic cycles. In

Mechanism A

Mechanism B

both mechanisms, the role of the phosphazenium silanoxide **g** is important and **g** has the highly delocalized, large cation and the counter anion is considered to show highly ionic character which is favorable for deprotonation. The formation of the reactive phophazenium intermediates is considered to be the big difference from the situation using conventional ionic bases. At this point we do not have experimental evidence to determine which mechanism is operating in the reaction, and the NMR analysis of the reaction of trimethylsilylalkyl compounds with *t*-Bu-P4 base has not given us any suggestive evidence.

In summary, *t*-Bu-P4 base was found to be an effective catalyst for the condensation of functionalized trimethylsilylalkanes with carbonyl compounds, and the selective alkene formation was accomplished. Further investigations on the scope and limitation of the *t*-Bu-P4 base promoted condensation are in progress and the mechanistic studies on this olefination are also underway.

Notes and references

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