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Effective Activation of Carbonyl and Related Compounds with Phosphonium Salts. The Aldol and Michael Reactions of Carbonyl Compounds with Silyl Nucleophiles and Alkyl Enol Ethers

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In the presence of a catalytic amount of a phosphonium salt, aldol reaction of silyl enol ethers with aldehydes or acetals and the Michael reaction of silyl enol ethers with α,β-unsaturated ketones or acetals proceed smoothly to afford the corresponding adducts in fairly good yields.

Phosphonium salts are widely employed as useful reagents in synthetic reactions; for example, the Wittig reaction,$^{1)}$ dehydration reactions$^{2)}$ and so on. There have been also reported on the use of a catalytic amount of a phosphnium salt in several carbon-carbon bond forming reactions such as a phase transfer catalyzed reaction.$^{3)}$

In the previous papers, we have shown that, in the presence of a catalytic amount of trityl salts, the aldol reaction of silyl enol ethers with aldehydes$^{4)}$ or acetals,$^{5)}$ and the Michael reaction of silyl enol ethers with α,β-unsaturated ketones$^{6)}$ proceed smoothly to afford the corresponding adducts in high yields. We also found that combined use of a tin(II) compound and a neutral molecule such as trityl chloride,$^{7)}$ trimethylsilyl chloride$^{8)}$ or a Lewis acid$^{9)}$ behaved as an efficient catalyst in several carbon-carbon bond forming reactions with carbonyl compounds. In these reactions, it is also assumed that active cationic species are generated by combination of the above two compounds and the reactions are carried out effectively even by the catalytic use. In the course of our investigations to explore a new type of cationic catalyst, it was expected that phosphonium salts could similarly accept carbonyl compounds to generate positively charged carbonyl carbon, which would be in turn attacked by nucleophiles. Indeed, the aldol reaction of aldehydes or acetals with silyl nucleophiles and the Michael reaction of α,β-unsaturated ketones or acetals with silyl nucleophiles took place smoothly in the presence of a catalytic amount of phosphonium salts.

In the first place, the reaction of p-methoxy benzaldehyde (1) with ketene silyl acetal of methyl acetate (2) was tried by the use of methyltributyl phosphonium perchlorate (3, 30 mol%) in dichloromethane. The reaction proceeded at room temperature and the corresponding aldol adduct was obtained in 50% yield. Then, the effect of the substituents on the phosphonium salts (such as methyltriphenyl, methyltricyclohexyl, tetrabutyl) and that of counter anion such as

$CF_3SO_3^-$ was screened, however, little effect was observed on the reactivity. Finally, it was found that the yield was remarkably improved when diphosphonium salt 4[10)] was employed as a catalyst. (Table 1)

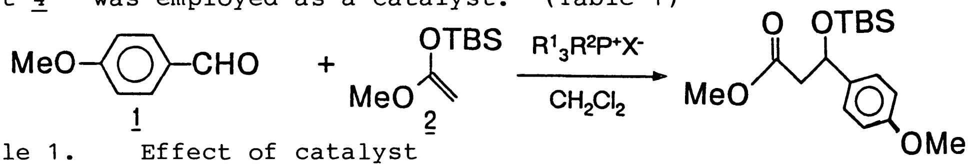
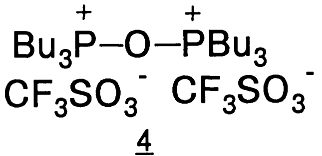


Table 1. Effect of catalyst

Entry	Cat.	mol%	Temp/°C	Yield/%
1	$[Bu_3P^+Me]Br^-$	100	r.t.	0
2	$[Bu_3P^+Me]ClO_4^-$ (3)	30	r.t.	50
3	$[Bu_3P^+CH_2Cl]ClO_4^-$	20	0-r.t.	59
4	$[Bu_3P^+\text{-}O\text{-}P^+Bu_3](CF_3SO_3^-)_2$ (4)	7	-78	66
5	$[Ph_3P^+\text{-}O\text{-}P^+Ph_3](CF_3SO_3^-)_2$ (5)	7	-78	42



$$\overset{+}{Bu_3P}\text{—}O\text{—}\overset{+}{P}Bu_3 \quad CF_3SO_3^- \quad CF_3SO_3^-$$

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Several reactions of aldehydes with silyl enol ethers or ketene silyl acetals in the presence of a catalytic amount of the diphosphonium salt (7 mol%) are demonstrated in Table 2. In all cases, the reactions proceeded smoothly at low temperature and the corresponding aldol adducts were obtained in fairly good yields. The following results are noted as characteristic points of the present reactions; various solvents, such as dichloromethane, toluene, tetrahydrofuran, diethyl ether, acetonitrile, etc., are available, different from the typical acid mediated reactions. And the rate of reactions in polar solvents especially in acetonitrile is faster than in non-polar solvents. The salt is also effective for the reaction of aldehydes containing amino group, such as p-N,N-dimethylaminobenzaldehyde and indole-3-carboxaldehyde (Table 2, entries 6,7).

Next, we examined the reactions of acetals and ortho esters, synthetic equivalents of aldehydes and esters, with silyl nucleophiles in the presence of a catalytic amount of diphosphonium salts 4 and 5. The reaction also proceeded smoothly at -78 °C to afford the corresponding adducts in good yields. Similarly, allyltrimethylsilane and trimethylsilyl cyanide are available as nucleophiles in the above reactions. In addition, alkyl enol ethers also smoothly react with acetals to produce the corresponding adducts in good yields.

Further, the Michael reaction of α,β-unsaturated ketones or acetals with silyl or alkyl enol ethers took place at -78 °C by the use of a catalytic amount of the diphosphonium salt and the corresponding Michael adducts are obtained in good yields. (Table 3)

A typical procedure for the reaction of trimethylsilyl enol ether of propiophenone with benzaldehyde is as follows; a mixture of benzaldehyde (0.4 mmol), trimethylsilyl enol ether of propiophenone (0.4 mmol) and the diphosphonium salt 5 (7 mol%, 0.03 mmol) in dichloromethane (3 ml) was stirred at -78 °C for 2 h. After the reaction was completed (checked by TLC), aqueous sodium hydrogen carbonate was added. Then, the aqueous layer was extracted with dichloromethane and the combined organic layer was dried. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel to yield the

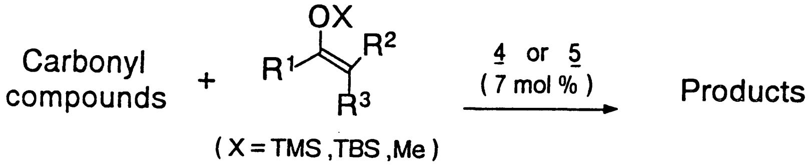
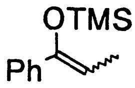
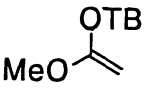
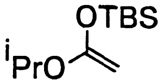
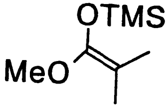
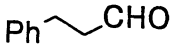
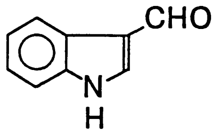
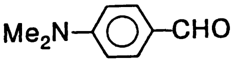
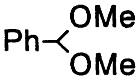
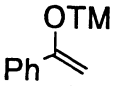
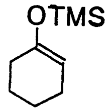
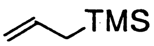
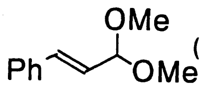
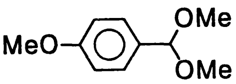
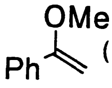


Table 2. The reaction of carbonyl compounds with silyl nucleophiles or alkyl enol ethers a)

Entry	Carbonyl compound	Nucleophile	Cat.	Solv.	Temp/°C	Yield/%	(syn:anti) b)
1	PhCHO (6)	 (9)	4	CH_2Cl_2	-78	83	(78:22)
			5	CH_2Cl_2	-78	98	(71:29)
2	6	 (10)	4	CH_2Cl_2	-78	76	
			4	toluene	-78	66	
			4	THF	-78	73	
			4	CH_3CN	-23	70	
3	6		4	CH_2Cl_2	-78	67	
4	6		4	CH_2Cl_2	-78	54	
5		10	4	CH_2Cl_2	0	53	
6		10	4	THF	-78	71	
7		10	5	CH_2Cl_2	-78	70	
8	 (7)	 (11)	4	CH_2Cl_2	-78	90	
9	7		4	CH_2Cl_2	-78	70	(90:10)
10	7		4	CH_2Cl_2	-78-0	67	
11	 (8)	11	4	CH_2Cl_2	-78	80	
12	8	TMSCN	4	CH_2Cl_2	-23	60	
13	$(EtO)_3CH$	11	4	CH_2Cl_2	-78	86	
14		 (12)	4	CH_2Cl_2	-78	83	

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a) All products gave satisfactory ^{1}H NMR and IR spectral data.
b) Determined by ^{1}H NMR.

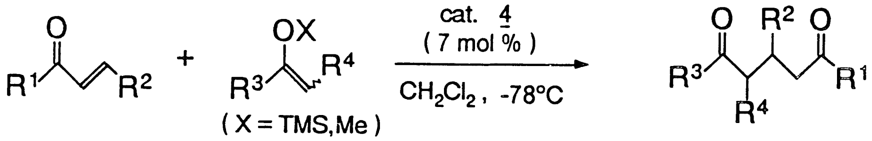
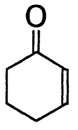
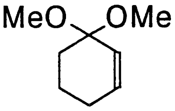
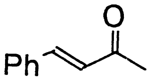


Table 3. The reaction of α,β-unsaturated ketones or an acetal with silyl or alkyl enol ethers[a)]

Entry	Ketone or acetal	Nucleophile	Yield/%	(syn:anti)[b)]
1		9	52	(74:26)
2		11	58	
3		11	61	
4		12	51	
5		11	61	

a) All products gave satisfactory ^{1}H NMR and IR spectral data.
b) Determined by GC.

corresponding aldol adduct in 98% yield. (syn:anti=71:29)

Thus, the diphospohonium salt is shown to be an effective catalyst in various carbon-carbon bond forming reactions of carbonyl compounds with silyl carbon nucleophiles. It should be noted that, different from the similar reactions mediated by a typical acid catalyst, the present reactions proceed smoothly under mild conditions by employing various solvents such as dichloromethane, toluene, tetrahydrofuran, diethyl ether, acetonitrile, etc.

We are currently investigating further new possibilities of this diphosphonium salt in synthetic reactions.

References

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2) J. B. Hendrickson and S. M. Schwartzman, Tetrahedron Lett., 4, 277 (1975); and references cited therein.
3) G. Märkl and A. Merz, Synthesis, 1973, 295; and references cited therein.
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5) T. Mukaiyama, S. Kobayashi, and M. Murakami, Chem. Lett., 1984, 1759.
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7) T. Mukaiyama, S. Kobayashi, M. Tamura, and Y. Sagawa, Chem. Lett., 1987, 491.
8) N. Iwasawa and T. Mukaiyama, Chem. Lett., 1987, 463.
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10) This diphosphonium salt was prepared according to the literature; D. Crich and H. Dyker, Tetrahedron Lett., 30, 475 (1989); 4 : ^{31}P NMR (CH_2Cl_2) δ:84.74.

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