CHEMISTRY LETTERS, pp. 1363-1366, 1985.

IMMOBILIZED CATALYST DIRECTED TO SYNTHETIC CONTROL. CROSS-ALDOL REACTION

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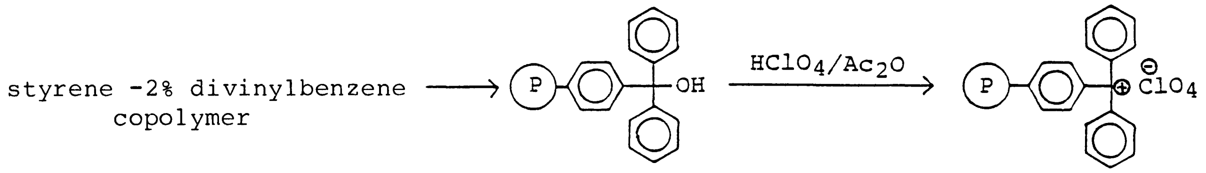
Cross-aldol adducts are stereoselectively formed in good yields by treating acetals or aldehydes and silyl enol ethers in a heterogeneous system with a catalytic amount of polymer-supported trityl perchlorate.

In the previous papers, we have shown that, in the presence of a catalytic amount of trityl perchlorate (1), acetals$^{1)}$ and aldehydes$^{2)}$ react smoothly with silyl enol ethers to give aldol adducts in high yields and good diastereoselectivities. It was revealed that trityl perchlorate behaves as an effective activator for acetals and aldehydes and the characteristic point of trityl perchlorate, compared with other metallic Lewis acids such as $TiCl_4$, BF_3, and $SnCl_4$, is that the aldol reaction can be promoted catalytically. Now, in order to develop a more efficient catalyst with wider applicability directed to synthetic control, the trityl cation was immobilized on the polymer to prepare a polymer-bound trityl perchlorate.

In the first place, polystyrene$^{3)}$-bound trityl alcohol (2) was prepared according to the known method,$^{4)}$ and it was shown there that about 20 out of every 100 styrene unit were transformed to the trityl alcohol. The alcohol 2 was converted to perchlorate 3 on treatment with perchloric acid in acetic anhydride.$^{5)}$ It was found that about 7% of aromatic ring of polystyrene was converted to perchlorate by the quantitative analysis of 3.$^{6)}$



2 3

Then, the aldol-type reaction of silyl enol ethers with acetals was carried out in the presence of polymer-supported trityl perchlorate (3) (*batch system*) and it was found that 3 promoted the reaction effectively to give aldol adducts in high yields with *syn* selectivities (Table 1).

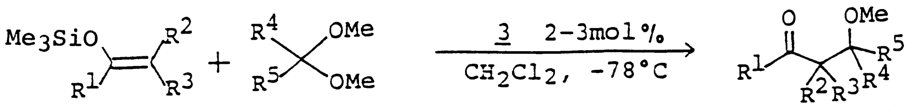
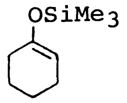
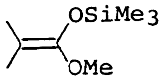
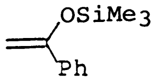


Table 1. The Reaction of Silyl Enol Ethers with Acetals$^{a)}$

Silyl enol ether	Acetal	Yield / %	(*syn* / *anti*)$^{b)}$
	$PhCH(OMe)_2$	86	(88 / 12)
	$PhCH_2CH_2CH(OMe)_2$	80	(73 / 27)
	$HC(OMe)_3$	72	-
	$PhCH(OMe)_2$	89	-
	$Me_2C(OMe)_2$	95	-

a) All products gave satisfactory NMR and IR spectra.
b) Each compound was separated by silica gel TLC.

Next, the same aldol-type reaction was tried in *flow system* with the same immobilized catalyst 3 packed in a glass tube column.[7)] A dichloromethane solution of an acetal and a silyl enol ether was charged from the top of the column and the products were instantly obtained from the bottom (Table 2).

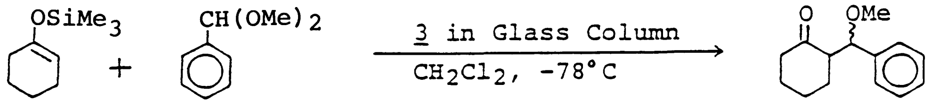


Table 2. The Reaction of Silyl Enol Ether with Acetal in Flow System

Entry	Reaction system	Yield/%	(*syn* / *anti*)	Flow time	3
1	Batch	86	(88 / 12)	1 h	
2	Flow	82	(86 / 14)	40 min	originally prepared
3	Flow	73	(80 / 20)	40 min	2nd use$^{b)}$
4	Flow	72	(79 / 21)	45 min	3rd use$^{b)}$
5	Flow, Recycle$^{a)}$	86	(91 / 9)	4 h	originally prepared
6	Flow, Recycle$^{a)}$	85	(88 / 12)	4 h	regenerated

a) Reaction mixture was recycled several times by using tube pump.
b) Polymer used in entry 2 was re-used without reactivation.

Similar to the *batch type* reaction, aldol adducts were also successfully obtained in good yields by the *flow type* reaction. This method makes it possible to separate the aldol adducts from reaction system by simple procedure and the catalyst can be re-used although the activity is slightly decreased(entries 3,4).

When the catalyst loses the activity, it is easily reactivated by flowing acetic anhydride solution of perchloric acid, followed by successive washing with acetic anhydride and dichloromethane. Reactivated catalyst has the same activity compared with the catalyst originally prepared from polymer-bound trityl alcohol (2) (entry 6).

Polymer-supported trityl perchlorate (3) was also applied to the reaction of aldehyde and silyl enol ethers and, in this case, *anti* isomers were predominantly obtained in good yields by using *t*-butyldimethylsilyl enol ethers (entries 5,6), as summarized in Table 3.

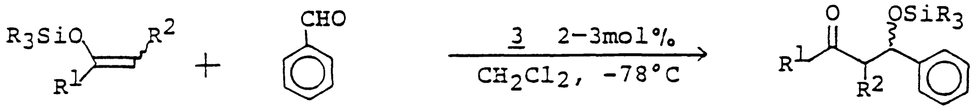
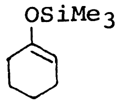
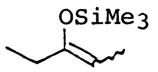
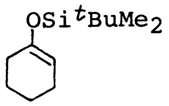
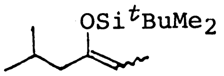


Table 3. The Reaction of Silyl Enol Ethers with Benzaldehyde

Entry	Silyl enol ether		Yields / %	(*syn* / *anti*)
1			72	(45 / 55)a)
2			79b)g)	(46 / 54)a)
3			76c)g)	(47 / 53)a)
4		(E/Z=37/63)	87	(49 / 51)d)
5			96	(25 / 75)d)
6		(E/Z=82/18)	79e)	(≈20 / 80)f)

a) Each compound was separated by silica gel TLC.

b) Polymer supported p-methoxy trityl perchlorate was used as a catalyst.

c) Toluene was used as a solvent.

d) Determined by ^{1}H NMR.

e) Reaction was carried out with 11 mol% of 3 at -78 °C for 18 h.

f) Determined by ^{13}C NMR.

g) Reaction was carried out at -78 °C for 18 h.

Desired diastereomer (*syn* or *anti*) could be obtained by the appropriate choice of both carbonyl acceptor and the substituent of silyl group in analogy with the similar reaction carried out in homogeneous solution.2)

It was found that less active polymer-supported p-methoxy trityl perchlorate, prepared similarly to 3,4) can also promote the reaction (entry 2), and toluene can be successfully used as a solvent (entry 3).

A typical procedure for the *batch type* reaction of a silyl enol ether with an acetal or an aldehyde is as follows; the suspended mixture of a silyl enol ether (0.6 mmol), an acetal or an aldehyde (0.5 mmol) and polymer-supported trityl perchlorate (3) (0.01-0.015 mmol) in CH_2Cl_2 (3 ml) was stirred at -78 °C for 1-2 h. Aqueous sodium hydrogencarbonate was added and extracted with CH_2Cl_2. The organic layer was dried and the solvent was removed under reduced pressure. The residue was separated by silica gel TLC to give the corresponding aldols.

The practical advantages of carrying out this heterogeneous reaction using the immobilized catalyst are the readiness in the separation of the product from the catalyst i.e. only by filtration and the possibility to re-use the catalyst effectively. It was also found that both yields and the diastereoselectivities of the produced aldols are quite similar in the cases of using trityl perchlorate (1).

Further investigation to add more evidence directed to synthetic control by using the immobilized catalyst is now in progress.

References

1) T. Mukaiyama, S. Kobayashi, and M. Murakami, Chem. Lett., 1984, 1759.
2) T. Mukaiyama, S. Kobayashi, and M. Murakami, Chem. Lett., 1985, 447.
3) Commercially available macroporous styrene -2% divinylbenzene copolymer (DIAION HP-50) was used as base resin.
4) H. Hayatsu and H. G. Khorana, J. Am. Chem. Soc., 88, 3182 (1966); 89, 3880 (1967); F. Cramer, R. Helbing, H. Hettler, K. H. Scheit, and H. Seliger, Angew. Chem., 78, 640 (1966).
5) To prepare the reagent 3, a solution of 70% perchloric acid (4 g) in acetic anhydride (20 ml) was slowly passed through a column filled with 2 (0.5 g), previously washed with the same solvent, followed by successive washing with acetic anhydride and dichloromethane, and dried under reduced pressure.
6) The trityl perchlorate content in 3 was estimated by two methods. a) 0.45 mmol per gram resin was obtained by titration (0.01 mol dm^{-3}-NaOH, phenolphthalein as an indicator); b) 0.56 mmol per gram resin was obtained by elemental analysis of Cl.
7) The polymer 3 packed in the column was prepared *in situ*; the polymer 2 (60 mg) with chopped glass fiber (300 mg) was packed in 2-3 mmϕ glass column, and was converted to 3 according to Ref. 5.

(Received June 24, 1985)