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STANNOUS TRIFLATE: A NEW ALDOL REACTION VIA DIVALENT TIN ENOLATES

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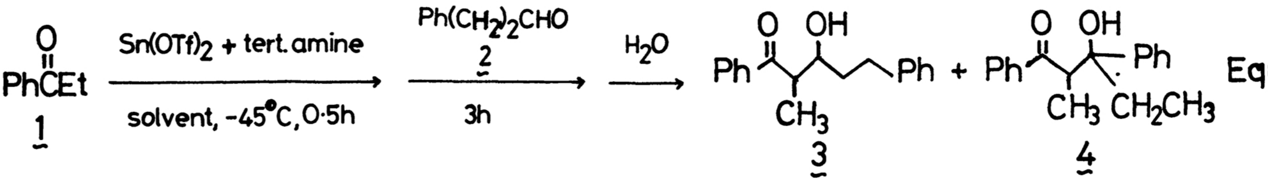
Divalent tin enolates formed from stannous triflate and ketones react with carbonyl compounds under mild conditions to give the corresponding aldol products in good yields. In the case of cross-coupling with aldehydes, good to excellent erythro-selectivity was observed.

Current interest in our laboratory on divalent tin promoted reactions[1)] and the recent focus on diastereoselective aldol reactions[2)] prompted us to investigate the reaction of divalent tin enolates with carbonyl compounds. In this communication we wish to disclose our preliminary observations on a first example of a reaction of a divalent tin enolate with a carbonyl compound. We also report here the good to excellent erythro-selectivity obtained on reaction with aldehydes.

It has been reported in the literature that stannous trifluoromethanesulfonate (triflate)[3)] is readily prepared by heating anhydrous stannous chloride in excess trifluoromethanesulfonic acid, however, no example of its application in organic synthesis has been reported. We therefore, in an analogous procedure to that for the preparation of vinyloxyboranes[4)], attempted to generate divalent tin enolates by treatment of stannous triflate with ketones in the presence of tertiary amines, and then examined the reaction of the enolate with carbonyl compounds.

In the first place, stannous triflate was treated with propiophenone 1 in the presence of triethylamine at -45°C in tetrahydrofuran for 30 min, followed by addition of β-phenylpropanal 2 according to equation 1. Work-up of the reaction mixture clearly showed that the cross-aldol product 3 had been afforded, although only in 15 % yield. Subsequent screening of solvent revealed that dichloromethane is a suitable solvent in which to conduct the present reaction; the cross-aldol product 3 and self-coupled product 4 being obtained in 50% and 15% yield respectively. Results are summarized in Table I.



Equ 1.

Table I. Solvent Effect on Aldol Reaction$^{a)}$

Entry	Solvent	Yield of 3 (%)$^{b)}$	Yield of 4 (%)
1	THF	15	0
2	Et_2O	34	∿ 5
3	CH_2Cl_2	50	15
4	toluene	45	trace
5	n-hexane	0	0

a) Enolization was carried out at -45°C for 30 min employing Et_3N as base, then aldehyde added and reaction run for 3 h. Molar ratio of $Sn(OTf)_2$: Et_3N: propiophenone: β-phenylpropanal = 1.0:1.0:1.0:1.0. b) Isolated yield. 3 gave satisfactory ^1H NMR and IR spectra.

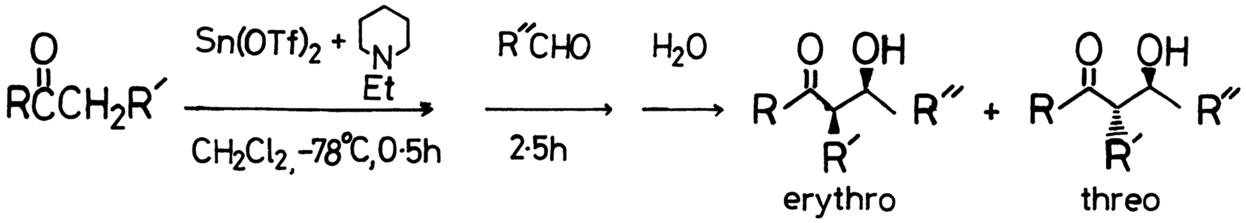
Next, we examined the effect of bases and observed that the present reaction is extremely dependent on the choice of tertiary amine. Whereas bases such as pyridine or 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) which can coordinate strongly to divalent tin failed to promote the reaction at all, use of N-methylmorpholine afforded self-coupled product 4 in 65% yield, while the desired cross-aldol 3 was obtained only in 22% yield. Employing N-ethylpiperidine as base was even more dramatic. In this case the desired cross-aldol 3 was obtained in 80% yield with only a trace of self-coupled product 4 being noted. Results are summarized in Table II.

Table II. Base Effect on Aldol Reaction$^{a)}$

Entry	Base	Yield of 3 (%)$^{b)}$	Yield of 4 (%)
1	pyridine	0	0
2	Et_3N	50	15
3	N-methylmorpholine	22	65
4	N-ethylpiperidine	80	trace
5	DBU	0	0

a) Enolization was carried out in CH_2Cl_2 at -45°C for 30 min, then aldehyde added and reaction run for 3 h. b) Isolated yield.

Realizing that N-ethylpiperidine is an effective base for promotion of the cross-aldol reaction, we next examined the diastereoselectivity which could be achieved between various ketones and aldehydes as illustrated in equation 2. Under the kinetic conditions employed good to excellent erythro-diastereoselectivity was observed in all cases.[5,6] Results are summarized in Table III.



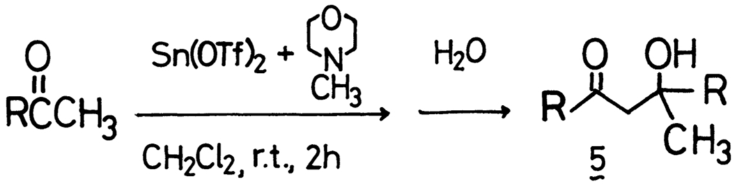
Equ.2.

Table III. Kinetic Cross-Aldol Reactions with Aldehydes a)

Entry	Ketone	Aldehyde	Yield (%) b)	Erythro : Threo c)
1	$C_6H_5COC_2H_5$	C_6H_5-CHO	71	> 95: 5
2	$C_6H_5COC_2H_5$	i-C_3H_7CHO	80	91: 9
3	$C_6H_5COC_2H_5$	n-C_3H_7CHO	79	86:14
4	$C_2H_5COC_2H_5$	C_6H_5-CHO	77	87:13
5	$C_2H_5COC_2H_5$	i-C_3H_7-CHO	73	93: 7
6	$C_2H_5COC_2H_5$	n-C_3H_7-CHO	86	> 91: 9 d)
7	i-$C_3H_7COC_2H_5$	C_6H_5-CHO	72	91: 9
8	cyclohexanone	C_6H_5-CHO	41	> 95: 5

a) Enolization was carried out in CH_2Cl_2 at -78°C for 30 min, then aldehyde added and reaction run for 2.5 h. Molar ratio of $Sn(OTf)_2$: N-ethylpiperidine: ketone: aldehyde = 1.1:1.2:1.0:1.0 (non-enolizable) or 1.3 (enolizable).
b) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.
c) Aldol ratios determined by 90 MHz ^1H NMR or ^{13}C NMR.7)
d) Aldol ratio determined by 270 MHz ^1H NMR.

Since we had observed that use of N-methylmorpholine as base in the reaction of propiophenone 1 and β-phenylpropanal 2 gave a considerable amount of self-coupled product (Table II, entry 3), we examined the self-coupling reaction of various methyl ketones and found that the reaction proceeds smoothly and in good yields to afford β-hydroxy ketones 5 according to equation 3.



Equ.3.

Table IV. Self-coupling Reaction of Methyl Ketones a)

Entry	R	Yield of 5 (%) b)
1	$H_2C{=}CH(CH_2)_2$-	84
2	$CH_3(CH_2)_2CH(CH_3)$-	83
3	$CH_3(CH_2)_5$-	82
4	$(CH_3)_2CHCH_2$-	76
5	$Ph(CH_2)_2$-	76

a) Molar ratio of $Sn(OTf)_2$:N-methylmorpholine:methyl ketone = 1.0:1.0:1.0
b) Isolated yield. All samples gave satisfactory ^1H NMR and IR spectra.

In contrast to vinyloxyboranes, the above results suggest that the present divalent tin enolate displays enhanced reactivity towards ketones. Results are summarized in Table IV.

A typical reaction procedure is described for the reaction of 3-pentanone and n-butyraldehyde; to a suspension of stannous triflate (0.458 g, 1.1 mmol) and N-ethylpiperidine (0.138 g, 1.2 mmol) in 2 ml of dichloromethane was added dropwise 3-pentanone (0.086 g, 1.0 mmol) in 2 ml of dichloromethane at -78°C under argon with stirring. At this point the suspension became a solution. After the mixture was stirred for 30 min, n-butyraldehyde (0.093 g, 1.3 mmol) in 2 ml of dichloromethane was added dropwise at this temperature. The reaction mixture was allowed to stand for 2.5 h, then added to a vigorously stirred pH 7 phosphate buffer - dichloromethane mixture at 0°C. After separation of the organic layers, the aqueous layer was extracted with dichloromethane, three times, then the combined organic layers dried over Na_2SO_4. After concentration in vacuo the resultant oil was purified by flash column chromatography (hexane : Et_2O = 4 : 1) to yield 5-hydroxy-4-methyl-3-octanone (0.136 g, 86%).

Thus, the present stannous triflate mediated reaction between ketones and carbonyl compounds - aldehydes and ketones - proceeds under essentially neutral conditions to give aldol in good yields. In the case of the cross-aldol reaction with aldehydes, good to excellent erythro-selectivity was observed. And moreover, the clean self-coupling reaction of methyl ketones demonstrates the enhanced reactivity of divalent tin enolates towards ketones. Further studies directed towards clarification of mechanism as well as application to other reactions utilizing the unique characteristics of divalent tin enolates (for example, cross-aldol reactions between ketones) are currently in progress in our laboratory.

References

1) T. Mukaiyama, T. Harada and S. Shoda, Chem. Lett., 1980, 1507; S. Shoda and T. Mukaiyama, Chem. Lett., 1981, 723.
2) (a) C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn and J. Lampe, J. Org. Chem., 45, 1066 (1980); (b) D.A. Evans, J.V. Nelson, E. Vogel and T.R. Taber, J. Am. Chem. Soc., 103, 3099 (1981), and references cited therein.
3) R.J. Batchelor, J.N.R. Ruddick, J.R. Sams and F. Aubke, Inorg. Chem. 16, 1414 (1977). NOTE: (i) Although the authors reported that the excess trifluoromethanesulfonic acid was removable by evaporation in vacuo, we found that it was necessary to wash the product with minimal dry ether in order to remove the last traces of acid.
(ii) Stannous triflate is an easy to handle white powder that can be prepared in large quantity and stored for many months under an inert atmosphere without observable change in quality.
4) T. Mukaiyama and T. Inoue, Chem. Lett., 1976, 559.
5) The erythro-threo convention used here is as for that discussed in ref. 2(a).
6) Although the present reaction proceeds via a divalent tin enolate, two conflicting results have been reported on the diastereoselective aldol reaction of tetravalent tin enolates with aldehydes. (a) Y. Yamamoto, H. Yatagai and K. Maruyama, J. Chem. Soc., Chem. Commun., 1981, 162; reported moderate erythro-selectivity from tin enolates generated in situ under kinetic control while (b) S. Shenvi and J.K. Stille, private communication, reported threo-selectivity from isolated enolstannanes.
7) See ref. 2(b) and C.H. Heathcock, M.C. Pirrung and J.E. Sohn, J. Org. Chem., 44, 4294 (1979).

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