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IMPROVED ENANTIOSELECTIVE SYNTHESIS OF ANTI α-METHYL-β-HYDROXYESTERS THROUGH $TiCl_4$-PPh_3 MEDIATED ALDOL CONDENSATION

Camillo Palazzi, Lino Colombo*, Cesare Gennari*
Dipartimento di Chimica Organica e Industriale, Centro CNR Sost.Org.Nat., Università di Milano, via Venezian 21, 20133 Milan, Italy.

Abstract: The complex between $TiCl_4$ and PPh_3 effectively catalyses the aldol addition of silyl ketene acetals to aldehydes dramatically improving the anti-syn ratios.

The aldol condensation reaction is one of the most straightforward methods for generating C-C bonds and at the same time constructing a framework with 1,3 oxygen functionality. The importance of this reaction in the synthesis of macrolide and ionophore antibiotics has stimulated the search for aldol condensation reactions that are highly diastereoselective and enantioselective.[1]

While a variety of excellent methods have been developed for the enantioselective synthesis of syn-α-methyl-β-hydroxyesters,[1] methods for the enantioselective construction of the anti counterparts have only recently met with reasonable success.[2] We have recently reported an anti-selective, asymmetric aldol reaction using $TiCl_4$ and the silyl ketene acetal derived from 1R,2S-N-methylephedrine-O-propionate. The major drawback of this reaction is that, while the enantiomeric excesses of the anti compounds are always >90%, the anti-syn ratios are in the range 2-5.6 : 1.[2g] This is however a general problem of the $TiCl_4$ mediated silyl ketene acetals addition to aldehydes: the anti-syn ratios are generally poor and strongly dependent on the aldehyde used.[3,4]

Here we report that this problem can be solved using the serendipitous discovery that the complex between $TiCl_4$ and PPh_3 is very effective in promoting high anti-syn ratios and good chemical yields. (Table 1).

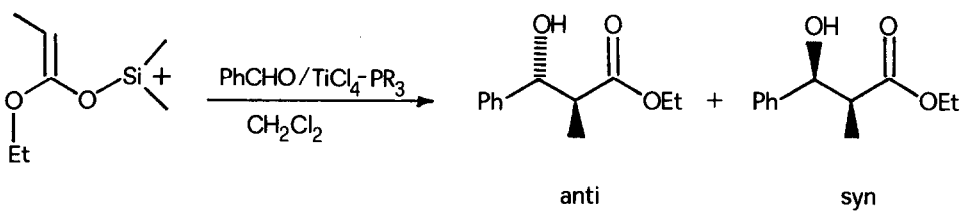


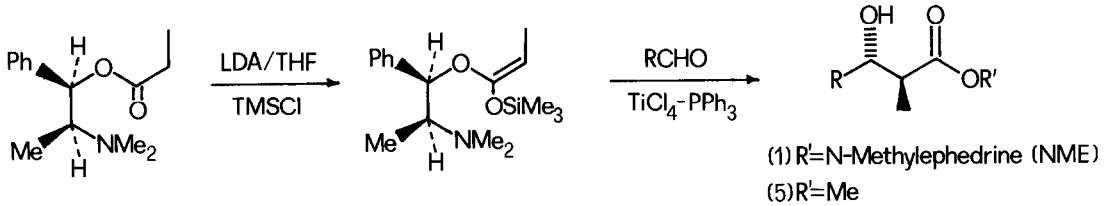
Table 1. (a)

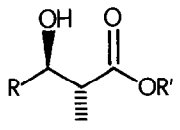
Phosphine added	Anti-syn ratio	% Yield
-	4.0 : 1	80
$n\text{-}Bu_3P$	4.5 : 1	71
$Cyclohexyl_3P$	7.8 : 1	70
$Ph_2P(CH_2)_4PPh_2$	10.0 : 1	70
$Ph_2P(CH_2)_3PPh_2$	10.3 : 1	72
Ph_3P	10.5 : 1	79

(a) The silyl ketene acetal used here was obtained from ethyl propionate by LDA enolization (-78°C/THF) and t-$BuMe_2SiOTf$ trapping (E-Z ratio ca.75:25). A solution of $TiCl_4$ (1 mol.eq.) in CH_2Cl_2 was treated with the phosphine (1 mol.eq.) at RT with stirring. After a few min. the mixture was cooled to -78°C, then the aldehyde was added (1 mol.eq.), followed by the silyl ketene acetal (1 mol.eq.).

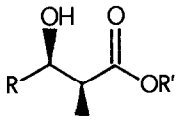
Using the $TiCl_4$-PPh_3 complex in our asymmetric aldol reaction with the E silyl ketene acetal derived from 1R,2S-N-methylephedrine-O-propionate,[5] the anti-syn ratios are increased dramatically. (Table 2). In the lucky case of benzaldehyde and cinnamaldehyde (entries 1,2) essentially only one compound (1) is formed out of the possible four stereoisomers (1-4). With butenal and hexenal (entries 3,4) the disappearance of the syn isomer (3) is unfortunately balanced by the appearance of some anti (2), and therefore the e.e. are lowered. The $TiCl_4$-PPh_3 modification is limited to aromatic and α,β -unsaturated aldehydes: non-conjugated aldehydes react very sluggishly or do not react at all. The reasons for this intriguing behaviour and the mechanism of the asymmetric aldol reaction are under active investigation and will be discussed in a full paper. A typical procedure is reported below.

To a solution of LDA (1.2 mol.eq.) in THF (0.5 M) at -78°C 1R,2S-N-methylephedrine-O-propionate (1.0 mol.eq.) in THF (0.5 M) was added dropwise. After 1 hr at -78°C, Me_3SiCl (1.2 mol.eq.) was added dropwise. After 0.5 hr the mixture was slowly warmed-up to RT (during 2 hr). The mixture was then evaporated in vacuo and the residue (THF free !) was taken-up in CH_2Cl_2 (1 M solution) A solution of $TiCl_4$ (1 mol.eq.) in CH_2Cl_2 (1 M) was treated with a solution of PPh_3 (1 mol.eq.) in CH_2Cl_2 (0.33 M) at 0°C with stirring. After 10 min. at RT, the mixture was cooled to -78°C, and the aldehyde (1 mol.eq.) was added. After 10 min. the silyl ketene acetal (1 mol.eq.) in CH_2Cl_2 (1 M) was slowly added dropwise. The mixture was warmed up to -60°C and stirred for 2 hr. Then the mixture was quenched with saturated $NaHCO_3$-1 N NaOH (1:1), filtered through celite, extracted with CH_2Cl_2.
The crude compound (after 200 MHz ^1H NMR analysis) was treated with NaOH (5 mol.eq.) in MeOH-H_2O (8:2, 0.1 M) at RT for 15 hr. After usual work-up and CH_2N_2 treatment the methylesters were isolated by flash-chromatography (n-hexane-EtOAc 80:20).

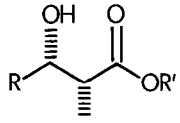




(2) R'=NME



(3) R'=NME



(4) R'=NME

Table 2

Entry	RCHO	anti-syn[a]	anti1-anti2[a]	%Yield[b]	Methylester(5) %Yield	%e.e.[c]
1	Ph-	≥30:1[g] (5.6:1)[d]	≥30:1	90	70	94[e] (94)[d]
2	(E)Ph-CH=CH-	≥15:1[h] (5.6:1)[d]	f	50	70	86[e] (91)[d]
3	(E)CH_3-CH=CH-	≥20:1[i] (4.0:1)[d]	f	60	65	67[e] (91)[d]
4	(E)$CH_3(CH_2)_2$CH=CH-	≥10:1[k] (3.5:1)[d]	f	50	68	66[e] (91)[d]

a) Ratio determined by 200 MHz-^{1}H NMR spectroscopy.

b) Overall yield of silylation and aldol condensation.

c) The enantiomeric excess was assessed by optical rotation comparison (see ref. 2a,b,g), and by ^{1}H NMR spectroscopy ($CDCl_3$) in the presence of Eu(hfc)$_3$: the OMe singlet was seen as separate signals, and the ratio was obtained by peak area.

d) Values in brackets refer to the reaction without PPh_3 added (see ref.2g).

e) The methylester with 100% e.e. was easily obtained starting from the isolated major stereoisomer anti (1), obtained by flash-chromatography.

f) Not detectable by ^{1}H-NMR spectroscopy.

g) δ 4.80 (anti, C<u>H</u>OH,d, J=9.4 Hz), 5.15 (syn,C<u>H</u>OH,d, J=3.1 Hz).

h) δ 4.42 (anti, C<u>H</u>OH,dd, J=8.5, 6.8 Hz), 4.68 (syn, C<u>H</u>OH,dd, J=4.0, 6.8 Hz).

i) δ 4.15 (anti, C<u>H</u>OH,dd, J=8.7, 6.7 Hz), 4.38 (syn, C<u>H</u>OH,m).

k) δ 4.18 (anti, C<u>H</u>OH,dd, J=8.7, 6.7 Hz), 4.40 (syn, C<u>H</u>OH,m).

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4) For a solution of the anti-syn problem using thiolester silyl ketene acetals and BF_3-OEt_2, see: Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. Tetrahedron Letters 1985, 797.

5) Both enantiomers of N-methylephedrine are commercially available (Fluka).

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