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Ti(IV)/BINOL-catalyzed asymmetric aldol reaction of a masked acetoacetic ester: pronounced influence of catalyst concentration on nonlinear effects☆

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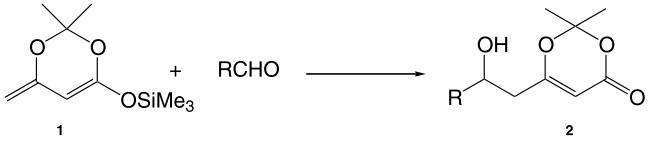
Abstract—Initial concentration of enantioenriched or enantiopure catalysts proved to be an important factor for the achievement of a more pronounced amplification of ee's in the Ti(IV)/BINOL-catalyzed aldol reaction of an *O*-silyldienolate.

In recent years, the presence of nonlinear effects (NLE) has been pointed out in important asymmetric reactions,[1] as addition of organozincs to aldehydes,[2] conjugate additions,[3] glyoxylate-ene reaction,[4] allylation[5] and aldol condensation[6] on aldehydes, asymmetric oxidations,[7] allylic oxidation,[8] Diels–Alder and hetero Diels–Alder reactions,[9] 1,3-dipolar cycloadditions.[10] This increasing interest has allowed us to obtain significant results both from the preparative and mechanistic point of view: in fact, highly enantioselective procedures have been achieved by using non enantiopure catalytic systems and useful information on the structures of the involved catalytic species have been acquired.[11]

In the course of investigations on the reactivity of masked acetoacetic esters,[12] we have found that the asymmetric aldol condensation of silyloxydiene **1** (Scheme 1), catalyzed by the chiral Ti(O*i*Pr)$_4$/BINOL



1 2

Scheme 1.

system, proceeds through an auto-inductive process,[13] involving the incorporation of **2** into the metal complex, to afford the final products in high yield and enantioselectivity.

Furthermore, the presence of positive non linear effects, (+)-NLE, was pointed out by performing the aldol condensation in the presence of enantiomerically enriched Ti(O*i*Pr)$_4$/BINOL complexes. It is noteworthy that, in spite of the wide use of chiral Ti(IV)/BINOL complexes in several important asymmetric processes, high efficiency and enantioselectivity often require a very careful choice of many experimental parameters, as the mode of catalyst preparation[5a,f,9a,14] the catalyst loading,[5a,14b] the solvent, the presence of hydrated or activated molecular sieves,[9b,15] the presence of suitable amounts of water (or other additives)[7b–d] and Ti(IV) compounds/BINOL stoichiometric ratios.[5a,11c]

Since the concentration of the catalyst has proven to be an additional critical factor, so that both the sign and the size of nonlinear effects can be deeply perturbed,[14] we decided to investigate a particular aspect of the influence of the catalyst concentration on nonlinear effects in the aldol condensation of silyloxydiene **1** on benzaldehyde, chosen as representative substrate.

In particular, enantiomerically enriched Ti(O*i*Pr)$_4$/BINOL catalysts were prepared according the procedures depicted in Scheme 2, involving exclusively a difference in the initial concentration of the catalytic systems.

Keywords: asymmetric aldol reaction; titanium complex; binaphthol; nonlinear effects; *O*-silyldienolate.

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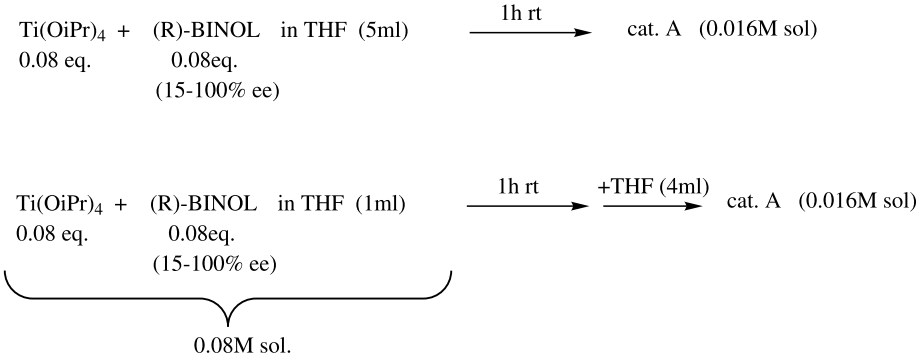
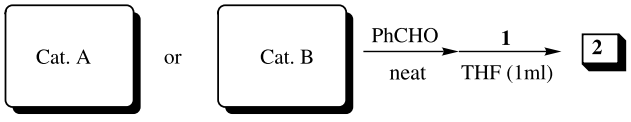


Scheme 2.

Consequently, all the experiments reported in Scheme 3 and Table 1 were carried out under conditions ensuring the same catalyst loading, solvent volume and constant final concentration of Ti(IV), chiral ligand and reagents.

As reported in Table 1, aldol condensations showed to proceed with rather variable efficiency, but, more interestingly, an appreciable enhancement of enantioselectivity was observed by using a catalyst initially prepared in more concentrated solutions (compare entries 1, 3, 5, 7, respectively, with entries 2, 4, 6, 8).

This stereochemical outcome can be considered rather surprising on the ground of previous reports pointing out the monomeric nature of the active catalytic species and, consequently, the employment of dilute catalyst solutions seemed to be a strict pre-requisite to avoid pronounced drops of enantioselectivity deriving from the formation of poorly enantioselective titanium multi-aggregates.[11c,14b]



Scheme 3.

Table 1. Influence of initial catalyst concentration on (+)-NLE

Entry	Catalyst	(*R*)-BINOL	Aldol **2**	
		Ee (%)	Ee (%)[a]	Yield (%)[b]
1	A	15	32	69
2	B	15	41	78
3	A	25	44	90
4	B	25	63	73
5	A	35	60	86
6	B	35	72	72
7	A	100	98	86
8	B	100	>99	91

[a] The enantiomeric excess was determined by HPLC analysis using a CHIRALPAK AD column.

[b] The yields are referred to chromatographically pure compounds.

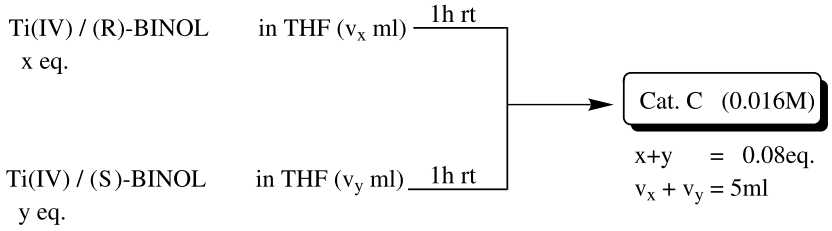
The beneficial influence on the size of (+)-NLE exerted by the use of a Ti(O*i*Pr)$_4$/BINOL complex, prepared in initially more concentrated solution, was further confirmed by performing the aldol reaction of **1** on benzaldehyde through a modified procedure. Therefore, Ti(O*i*Pr)$_4$/BINOL complexes at different ee's (*R* predominant enantiomer) were prepared by mixing equimolar solutions of enantiopure Ti(IV)/(*R*)-BINOL and Ti(IV)/(*S*)-BINOL solutions and, alternatively, concentrated Ti(IV)/(*R*)-BINOL and dilute Ti(IV)/(*S*)-BINOL solutions, according to the procedure depicted in Scheme 4.

The aldol condensations of **1** on benzaldehyde were carried out in the presence of so formed enantioenriched Ti(IV)/(*R*)-BINOL complexes and the experimental conditions again ensured the same catalyst loading, final solvent volume and concentration of Ti(IV), chiral ligand and reagents, as in all entries of Table 1.

As reported in Table 2, in the procedure involving mixing of equimolar solutions (entries 1–3), the use of the chiral ligand at increasing ee resulted in a decrease of the size of (+)-NLE, while the opposite result, that is a notable amplification of ee's, could be obtained through an appropriate choice of the relative concentration values of the separate Ti/(*R*)-BINOL and Ti/(*S*)-BINOL solutions (entries 4–6).

Furthermore, comparable results have been obtained by carrying out the aldol reaction in the presence of enantioenriched Ti(O*i*Pr)$_4$/(*S*)-BINOL complex: in fact, for example, (*S*)-**2** was isolated in 81% yield and 84% ee by using Ti(IV)/(*S*)-BINOL catalyst prepared in 35% ee according the procedure reported in Scheme 4.

In conclusion, the disclosure of a new peculiar aspect of the influence of a Ti(IV)/BINOL concentration on NLE has allowed to obtain a further amplification of ee's in the asymmetric aldol condensation of the silyloxydiene **1**.



Scheme 4.

Table 2. Influence of the mode of the preparation of the catalyst on NLE

Entry	Ti(IV)/(*R*)-BINOL	Ti(IV)/(*S*)-BINOL	(*R*)-BINOL	Aldol **2**	
	conc. (M)	conc. (M)	Ee (%)	Ee (%)[a]	Yield (%)[b]
1	0.016	0.016	15	44	92
2	0.016	0.016	25	31	89
3	0.016	0.016	35	43	90
4	0.090	0.0075	15	32	80
5	0.100	0.0067	25	61	60
6	0.108	0.0058	35	90	64

[a] The enantiomeric excess was determined by HPLC analysis of the aldol product using a CHIRALPAK AD column.
[b] The yields are referred to chromatographically pure compounds

Acknowledgements

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