



Nonlinear effects and auto-induction in the asymmetric aldol condensation of synthetic equivalents of acetoacetic esters

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Received 26 July 2002; accepted 3 September 2002

Abstract—Positive nonlinear effects, (+)-NLEs, have been detected in the Ti(IV)/BINOL complex-mediated catalytic asymmetric aldol reaction of three different masked acetoacetate esters. The use of a different procedure for the catalyst preparation disclosed the occurrence of aldol condensation of Chan's diene through an auto-inductive process. © 2002 Elsevier Science Ltd. All rights reserved.

In recent years the detection of positive nonlinear effects, (+)-NLE, in asymmetric reactions has represented the main target of several research groups since important preparative results can be achieved in the presence of enantiomerically enriched catalysts and, furthermore, useful information concerning the structure of the effective catalytic species and the mechanism of the reaction, can be obtained.

Consequently, the presence of (+)-NLE has been pointed out in a variety of synthetically useful asymmetric reactions,¹ including the additions of dialkylzinc reagents to aldehydes,² glyoxylate-ene reactions,³ hetero-Diels–Alder reactions,⁴ aldol-type condensations,⁵ sulfide oxidation,⁶ and conjugate addition reactions.⁷

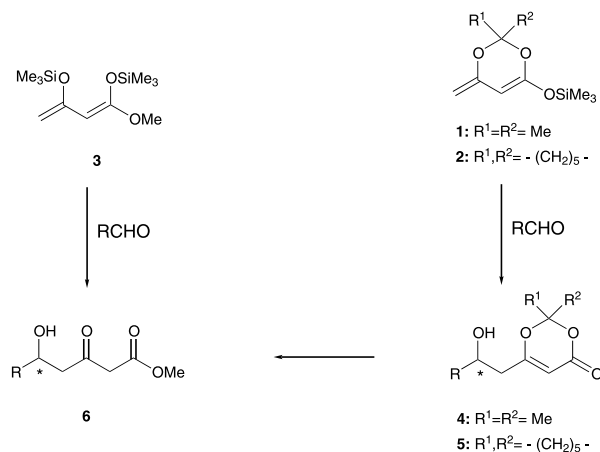
In the course of research devoted to the achievement of efficient and highly enantioselective approaches to compounds of the type **6**, which are key-intermediates in the synthesis of important bio-active compounds, we have found⁸ that the aldol condensation of the synthetic equivalents of acetoacetic ester **1–3** (Scheme 1) can be conveniently performed in the presence of a chiral Ti(O^{*i*}Pr)₄/BINOL complex under stoichiometric and catalytic conditions.

Furthermore, in the case of the silyloxydiene **1**, the occurrence of a process of auto-induction by self-assembly of the chiral ligands was demonstrated.⁹

Since the presence of (+)-NLEs has been pointed out in a variety of asymmetric reactions promoted by different Ti(IV)/BINOL complexes, we decided to investigate the reactivity of compounds **1–3** in the presence of an enantiomerically enriched catalyst.

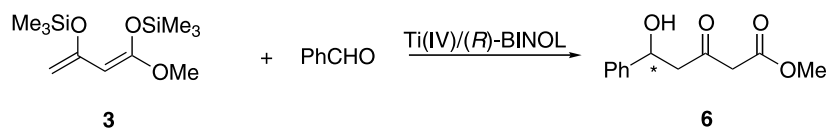
In the first experiments benzaldehyde and Chan's diene **3** (Table 1) were chosen as representative reagents and the reaction was performed under the conditions involved in the previously reported procedure by using Ti(O^{*i*}Pr)₄/(*R*)-BINOL (1:1), prepared in situ from (*R*)-BINOL of varying enantiomeric excess (e.e.).

When the e.e. of the aldol product **6** was plotted against the e.e. of the BINOL, an evident (+)-NLE could be observed as shown in Fig. 1.



Scheme 1.

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Table 1. (+)-NLE in the aldol reaction of **3**

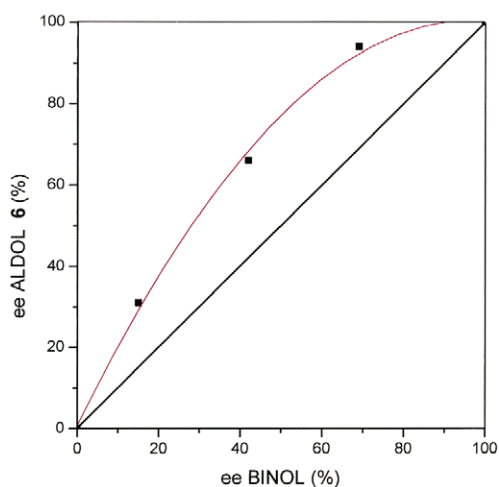
Entry	(<i>R</i>)-BINOL e.e. (%)	6 e.e. (%) ^a	Yield (%) ^b
1	0	0	74
2	15	31 ^c	82
3	42	66 ^c	78
4	69	94 ^c	72
5	100	>99 ^c	94

3/PhCHO/Ti(O^{*i*}Pr)₄/*R*-BINOL 2/1/0.08/0.08 molar ratios were used.

^a E.e.s were determined by HPLC analysis using a CHIRALPAK AD column.

^b Yields refer to isolated chromatographically pure compounds.

^c The *R* enantiomer was predominant.

**Figure 1.**

Rather interestingly, the mode of preparation of the enantiomerically enriched catalyst was found to exert a marked influence on the nonlinear effects: in fact, mixing enantiopure Ti(IV)/(*S*)-BINOL and Ti(IV)/(*R*)-BINOL in order to obtain the specific e.e.s reported in Table 2, led to linearity (Fig. 2).

These results can be reasonably explained by the fact that the complexes consist of stable homochiral

Table 2. Aldol reaction of **3** in the presence of Ti(IV)/(*S*)-BINOL + Ti(IV)/(*R*)-BINOL catalyst

Entry	(<i>S</i>)-BINOL e.e. (%)	6 e.e. (%) ^a	Yield (%) ^b
1	14	14 (<i>S</i>)	81
2	52	52 (<i>S</i>)	82
3	70	74 (<i>S</i>)	54
4	100	>99 (<i>S</i>)	52

3/PhCHO/[Ti(O^{*i*}Pr)₄/*R*-BINOL]+[Ti(O^{*i*}Pr)₄/*S*-BINOL] 2/1/0.08 molar ratios were used.

^a E.e.s were determined by HPLC analysis using a CHIRALPAK AD column.

^b Yields refer to isolated chromatographically pure compounds.

oligomers: the absence of ligand exchange prevents trapping of the less abundant chiral auxiliary in ineffective heterochiral oligomers, thereby leading to the observed linearity.

It is noteworthy that a similar dependence on the mode of preparation of a catalyst^{1a} has been observed previously in other important processes, such as the asymmetric Diels–Alder reaction,¹⁰ allylation of aldehydes with allylstannanes,¹¹ and in the oxidation of sulfides.¹²

Conveniently, this finding can be exploited to obtain information about the active species involved in the catalytic cycle.

In the course of research related to a previous investigation on the addition of Et₂Zn to benzaldehyde, promoted by Ti(O^{*i*}Pr)₄/BINOL complexes, Walsh¹³ reported three different solid state structures for titanium BINOLate complexes obtained by reaction of Ti(O^{*i*}Pr)₄ and BINOL under carefully chosen stoichiometric ratios. In particular, the combination of equimolar amounts of BINOL and titanium tetraisopropoxide, followed by crystallization at –30°C, afforded crystals characterized by a trimeric [(BINOLate)Ti(O^{*i*}Pr)₂]₃ structure and the involvement of this trimer in the asymmetric addition of Et₂Zn was considered unlike on the ground of the absence of NLE under the reported conditions.

The detection of a (+)-NLE in the addition of Chan's diene in the presence of the chiral catalyst prepared in situ from equimolar amounts of Ti(O^{*i*}Pr)₄ and enantiomerically enriched BINOL suggests that the observed deviation from linearity could be attributed to a concomitant auto-inductive process,^{1,9,14} i.e. the incorporation of the aldol **6** produced in the original catalytic species by ligand exchange to give a more enantioselective multi-component Ti complex.

Therefore in a set of experiments the catalytic species was prepared by mixing, under the same conditions involved in Table 2, pre-prepared solutions of Ti(IV)/(*S*)-BINOL, Ti(IV)/(*R*)-BINOL and (*R*)-aldol **6**.¹⁶

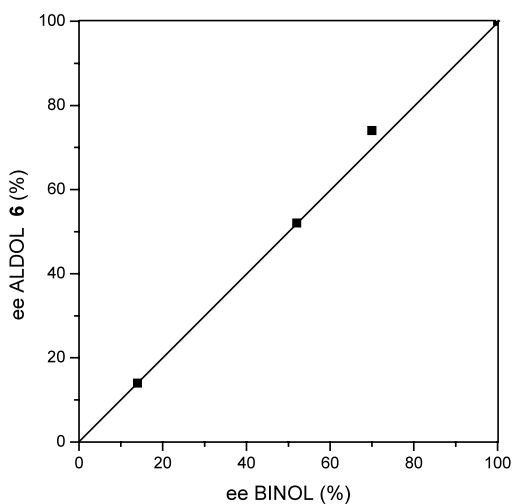


Figure 2.

The results, reported in Table 3 (compared with those in Table 2), confirm that a significant amplification of the e.e. can be obtained by favouring a process of self-organization of the chiral ligands (i.e. BINOL and the chiral aldol (*R*)-**6**) in the preliminary phase of synthesis of the catalyst.

The critical influence exerted by the mode of preparation of the catalyst was further confirmed by carrying out the aldol condensation in the presence of $\text{Ti}(\text{O}^i\text{Pr})_4/(\pm)\text{-BINOL}/(\text{R})\text{-6}$: in this case completely racemic aldol **6** was isolated in 71% yield. Furthermore, when the experiment of entry 2, Table 3, was repeated using the opposite combination $\text{Ti}(\text{IV})/(\text{R})\text{-BINOL}+\text{Ti}(\text{IV})/(\text{S})\text{-BINOL}$ and (*R*)-**6**, in order to get a resulting 11% e.e. of (*R*)-BINOL, amplification of e.e. was again observed since **6** was obtained with 28% e.e. (yield=88%) and the chiral induction was shown to be controlled by the chiral auxiliary (BINOL) since in this case **6** was obtained with the *R* enantiomer predominant.

Finally, the behaviour of silyloxydienes **1** and **2** was examined in aldol condensations carried out on benzaldehyde, as a representative substrate, in the presence of the usual 1/1 $\text{Ti}(\text{O}^i\text{Pr})_4/(\text{R})\text{-BINOL}$ complex, pre-

Table 3. (+)-NLE by $[\text{Ti}(\text{IV})/(\text{S})\text{-BINOL}+\text{Ti}(\text{IV})/(\text{R})\text{-BINOL}+(\text{R})\text{-6}]$ system

Entry	S-BINOL e.e. (%)	6 e.e. (%) ^a	6 e.e. (%) ^b	6 Yield (%) ^c
1	0	1 (<i>R</i>)	10 (<i>S</i>)	74
2	11 (<i>S</i>)	14 (<i>S</i>)	24 (<i>S</i>)	90
3	49 (<i>S</i>)	67 (<i>S</i>)	82 (<i>S</i>)	88

3/PhCHO/ $[\text{Ti}(\text{O}^i\text{Pr})_4/(\text{R})\text{-BINOL}]+[\text{Ti}(\text{O}^i\text{Pr})_4/(\text{S})\text{-BINOL}]/(\text{R})\text{-6}$ 2/1/0.08/0.08 molar ratios were used.

^a E.e.s were determined by HPLC analysis using a CHIRALPAK AD column.

^b E.e.s of newly formed aldol **6** calculated according to Ref. 15.

^c All yields refer to isolated chromatographically pure compounds correct by the amount of added **6**.

pared directly in situ from enantiomerically enriched (*R*)-BINOL.¹⁷

Rather interestingly, in both cases, (+)-NLE could be observed (Fig. 3) although a more complex curve was obtained on plotting the e.e. of aldol **5** against the e.e. of BINOL.

Further investigation will be devoted to verify if a process of auto-induction is involved in the asymmetric aldol condensation of silyloxydiene **2** and to ascertain whether the linear relationship observed in the area of BINOL e.e.=40% is a consequence of a loss of efficiency of the above process.

In conclusion these results represent further confirmation of the involvement of Ti/BINOL complexes in enantioselective processes characterized by the presence of (+)-NLE. In particular, in the case of Chan's diene **3**, a different mode of preparation of the catalyst was shown to determine the presence or the absence of (+)-NLE. Furthermore, the occurrence of a concomitant auto-inductive process in the aldol reaction of **3** was pointed out.

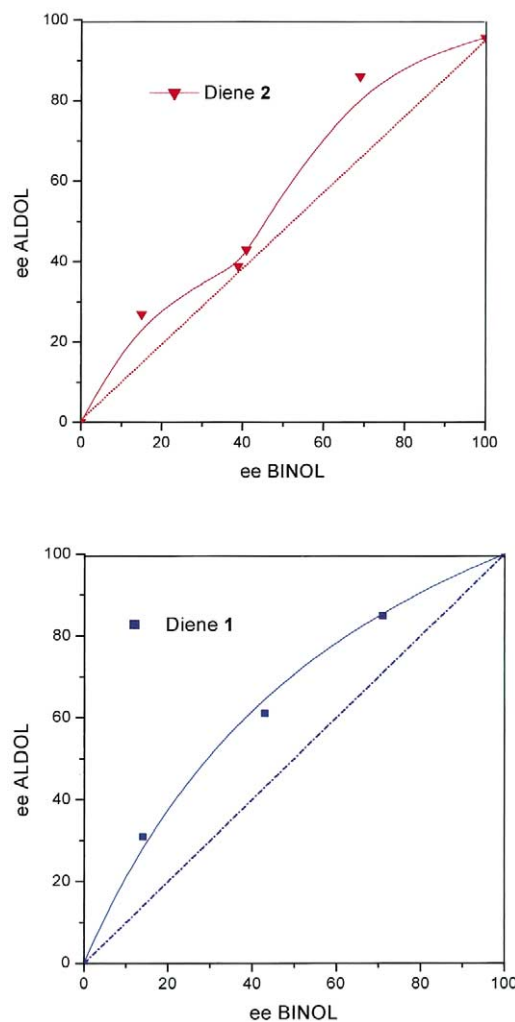


Figure 3.

Acknowledgements

We thank MIUR for financial support.

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16. Typical experimental procedure for asymmetric aldol reaction in the presence of (*R*)-aldol **6** (entry 2, Table 3): Two mixtures of (*S*)-1,1'-bi-2-naphthol (0.0445 mmol), Ti(OⁱPr)₄ (0.0445 mmol) and 4 Å molecular sieves (195 mg) in THF (2.78 ml) and (*R*)-1,1'-bi-2-naphthol (0.0355 mmol), Ti(OⁱPr)₄ (0.0335 mmol) and 4 Å molecular sieves (155 mg) in THF (2.22 ml) were separately stirred at rt for 1 h under argon atmosphere. After mixing the two suspensions together, (*R*)-**6** (0.08 mmol) was added and the mixture was stirred at rt for 0.5 h. The mixture was cooled to –78°C and the aldehyde (1 mmol) was added followed, after 30 min, by a solution of silyloxydiene **3** (2 mmol) in THF (1 ml). The mixture was stirred at –78°C for 2 h and then at rt overnight. After cooling the mixture at –78°C, TFA (0.4 ml) was added and the solution was warmed to rt. After stirring at rt for 1 h desilylation was complete and the reaction mixture was diluted with ether and saturated aqueous NaHCO₃ solution (3 ml) was added dropwise. The pure product **6** was obtained by usual work-up and purification procedures^{8c} (90% yield, 24% e.e.).
17. It is noteworthy that in the experiments performed with silyloxydienes **1** and **2** in the presence of Ti(IV)/(*R*)-BINOL (100% e.e.) complex, the corresponding aldols (*R*)-**4** and (*R*)-**5** were respectively obtained in 93% yield (>99% e.e.) and 81% yield (96% e.e.).