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Pronounced asymmetric amplification in the aldol condensation of Chan's diene promoted by a Ti(IV)/BINOL complex

Rosaria Villano, Maria Rosaria Acocella, Margherita De Rosa, Annunziata Soriente and Arrigo Scettri*

Dipartimento di Chimica, Università di Salerno, 84081 Baronissi (Salerno), Italy

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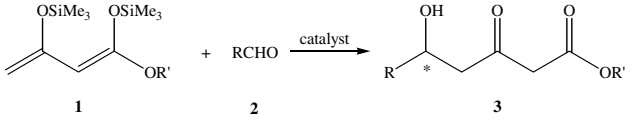
Abstract—A strong enhancement of the enantiomeric excess can be obtained by performing the enantioselective aldol reaction of Chan's diene in the presence of enantiomerically enriched Ti(O-*i*-Pr)$_4$/BINOL catalysts derived from mixing pre-prepared solutions of enantiopure Ti(O-*i*-Pr)$_4$/(*R*)-BINOL and Ti(O-*i*-Pr)$_4$/(*S*)-BINOL at different concentrations.

1. Introduction

1,3-Bis-trimethyl silyloxydienes of type **1** (Scheme 1) represent preparatively useful masked forms of acetoacetate esters, as confirmed by their employment in many important C–C bond forming reactions, such as conjugate additions,[1] oxidative dimerizations,[1] cycloadditions,[2] reactions with 1,2-di-electrophiles,[2b,3] cycloaromatizations with 1,3-dicarbonyl compounds[4] and reactions with 1,4-dicarbonyl compounds.[2b]



1 2 3

Scheme 1.

Furthermore, Chan's diene **1a** (R′ = Me) has been used as the synthetic equivalent of acetoacetate dianion in aldol condensations leading to racemic (catalyst: $TiCl_4$)[1a] or nonracemic polyfunctional aldols **3** (catalysts: chiral B(III),[5] Cu(II)[6] and Ti(IV)[7] complexes).

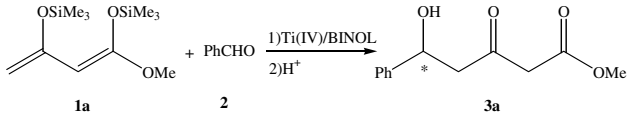
It is noteworthy that compounds **3** can only be obtained in moderate ees by using a chiral borane as catalyst, while the employment of a Cu(II)/pybox complex requires the presence of a chelating group, α-situated to the aldehyde function, to achieve high values of yields and ees.

However, the conversion of **1a** into **3** has been shown to occur with high levels of efficiency and enantioselectivity (up to 99%) with a variety of aromatic, unsaturated, aliphatic aldehydes in the presence of reduced amounts of Ti(O-*i*-Pr)$_4$/BINOL catalytic system (2–8%).[7]

The synthetic importance of the above procedure has been further pointed out by its employment as a key-step in two recent patents[8] for the synthesis of chiral δ-hydroxy-β-ketoesters of type **3**, which are intermediates in the preparation of bioactive compounds used in the treatment of hyperlipidemia and arteriosclerosis.

2. Results and discussion

Further experiments[9] performed on benzaldehyde, chosen as a representative substrate (Scheme 2, Table 1), in the presence of enantioenriched 1/1 Ti(O-*i*-Pr)$_4$/BINOL complexes pointed out the presence of positive nonlinear effects, (+)-NLE (Table 1, entry 2); nevertheless, the mode of preparation of the catalytic system proved to be a critical factor,[10] so that linearity could be



1a 2 3a

Scheme 2.

* Corresponding author. Tel.: +39-089-965374; fax: +39-089-965296; e-mail: scettri@unisa.it

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Table 1. Correlation between the asymmetric amplification and the mode of the preparation of the catalyst

Entry[a]	Catalyst solution (M)	BINOL ee (%)	**3a** Ee (%)[b]	**3a** Yield (%)[c]
1	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL (0.0160)	100 (*R*)	>99	94
2	Ti(O-*i*-Pr)$_4$/(*R*+*S*)-BINOL (0.0160)	15 (*R*)[9]	31 (*R*)	81
3	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL (0.0160) Ti(O-*i*-Pr)$_4$/(*S*)-BINOL (0.0160)	14 (*S*)[9]	14 (*S*)	81
4[d]	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL (0.0077) Ti(O-*i*-Pr)$_4$/(*S*)-BINOL (0.090)	13 (*S*)	29 (*S*)	66
5[d]	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL (0.090) Ti(O-*i*-Pr)$_4$/(*S*)-BINOL (0.0077)	13 (*R*)	41 (*R*)	69

[a] In entries 1–5 the catalytic species were prepared in order to have a final volume of THF of 5 mL. All reactions were performed in the presence of a constant amount of molecular sieves (350 mg).
[b] Ees have been determined by HPLC analysis.
[c] Yield refers to chromatographically pure compounds.
[d] The catalytic systems were obtained by mixing Ti(O-*i*-Pr)$_4$/(*R*)-BINOL and Ti(O-*i*-Pr)$_4$/(*S*)-BINOL solutions at different concentrations.

observed by using an enantioenriched complex derived from mixing pre-prepared equimolar solutions of Ti-(O-*i*-Pr)$_4$/(*R*)-BINOL and Ti(O-*i*-Pr)$_4$/(*S*)-BINOL (entry 3).

As has been shown by Keck and Krishnamurthy,[11] the catalytic properties of Ti(IV)/BINOL complexes are very often found to depend strongly on the experimental conditions (source of Ti(IV), presence of suitable amounts of water,[12] stoichiometric ratios,[13] temperature, solvent). High levels of efficiency and enantioselectivity can only be attained in a narrow window of concentration values, for both the catalyst and the reagents.

Over the course of a recent research we have shown[14] that a significant increase in size of the asymmetric amplification could be observed by performing the vinylogous aldol condensation of (2,2-dimethyl-6-methylene-6*H*-[1,3]dioxin-4-yloxy)-trimethyl-silane in the presence of enantioenriched Ti(O-*i*-Pr)$_4$/BINOL complexes, previously prepared in more concentrated solutions.

Keeping in mind this unprecedented result, the experiment of entry 3 (Table 1) was repeated (entries 4 and 5) using catalytic systems obtained from mixing Ti-(O-*i*-Pr)$_4$/(*R*)-BINOL and Ti(O-*i*-Pr)$_4$/(*S*)-BINOL solutions at different concentrations.

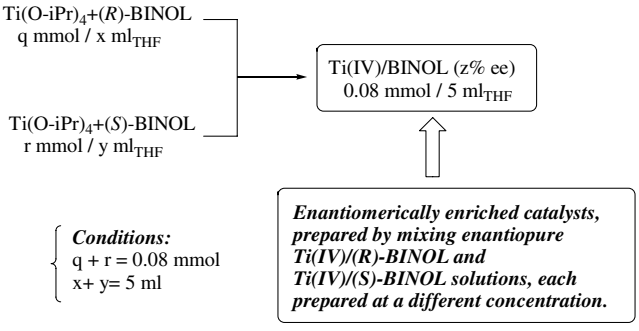
It is notable that, although the experiments of entries 3–5 were carried out under the same conditions as with regards to the solvent volume, catalyst loading and final Ti(IV), chiral ligand and reagent concentration, deviations from linearity were detected in both entries 4 and 5.

The presence of (+)-NLE in entries 4 and 5 can be tentatively explained by assuming that the formation of structurally different Ti(IV)/BINOL systems takes place in the separate solutions of enantiopure catalysts at different concentrations and, after mixing, the aldol reaction proceeds to a greater extent through a pathway involving the catalyst prepared in a more concentrated solution.

In fact, in dilute solution, on the basis of previous reports,[15] the formation of homochiral monomeric species was to be expected. ^{1}H NMR analysis (400 MHz) in solution at rt of titanium complexes prepared in more concentrated solutions showed a complex pattern of NMR peaks, very similar to that reported by Mikami and co-workers[16] and attributed to highly enantioselective Ti/BINOL catalysts. Mikami et al. reported that the active species corresponding to this spectrum was a high nuclearity cluster.[16]

The aggregates prepared according to the procedures of entries 4 and 5 showed a negligible tendency to dissociate by increasing, after their synthesis, the solvent volume since no appreciable change in the ^{1}H NMR spectrum was observed after dilution up to 0.016 M concentration value. Moreover, after mixing, the combined solutions were again submitted to ^{1}H NMR analysis showing signal patterns corresponding to both the cluster and the complex prepared in dilute solution.

This strong dependence of the enantioselectivity from the initial concentrations was confirmed by performing a set of experiments in the presence of Ti(O-*i*-Pr)$_4$/BINOL complexes at different ees, prepared according to the procedure depicted in Scheme 3 and under conditions



Scheme 3. Mode of catalyst preparation.

Table 2. Influence of the initial concentration of the catalyst on NLEs

Entry[a]	Concentration of solutions (M)		BINOL ee (%)	**3a** Ee (%)[b]	**3a** Yield (%)[c]
	Ti(IV)/(*R*)-BINOL	Ti(IV)/(*S*)-BINOL			
1	0.016	—	100 (*R*)	>99 (*R*)	94
2	0.013	0.040	50 (*R*)	41 (*R*)	74
3	0.010	0.070	12 (*R*)	3 (*S*)	89
4	0.090	0.0078	13 (*R*)	41 (*R*)	69
5	0.100	0.0067	25 (*R*)	82 (*R*)	82
6	0.106	0.0060	32 (*R*)	77 (*R*)	61
7	0.100	0.016	25 (*R*)	53 (*R*)	98

[a] All the reactions were performed in the presence of a constant amount of molecular sieves (350 mg).
[b] Ees have been determined by HPLC analysis.
[c] Yield refers to chromatographically pure compounds.

ensuring the usual catalyst loading (0.08 equiv) and constant final concentration of Ti(IV), chiral ligand and reagents. The experimental results are reported in Table 2.

In entries 2 and 3 slightly negative deviations from linearity, (−)-NLE, were observed. These results can be reasonably attributed to the greater enantioselectivity of the Ti(IV)/(*S*)-BINOL complex, generated in the more concentrated solution.

This hypothesis was confirmed by carrying out the aldol reaction in the presence of catalytic species obtained by mixing enantiopure Ti(IV)/(*R*)-BINOL solutions at ever increasing concentrations and enantiopure Ti(IV)/(*S*)-BINOL solutions at ever decreasing concentrations. A pronounced amplification of the ee was observed in entries 4–6 confirming the more enhanced level of enantioselectivity of the catalyst prepared at higher concentrations. The observed amplification of ees could be considered the overall result of two opposite effects, that is, the initial concentration of one Ti(IV)/BINOL complex and the initial dilution of the other one. In fact, when the experiment of entry 7 was carried out under the same conditions as entry 5, with the exception of the use of a Ti(IV)/(*S*)-BINOL catalyst prepared at higher concentration, the reaction was shown to take place with a noticeable drop of enantioselectivity. Furthermore, the replacement in entry 5 of Ti(IV)/(*S*)-BINOL (0.030/4.5) solution with Ti(IV)/(*rac*)-BINOL (0.030/4.5) did not cause any significant variation in terms of both efficiency and enantioselectivity since aldol **3a** was isolated in 84% yield and 77% ee. Finally, the stereochemical outcome of entry 6, where a slightly lower value of ee (77%) was obtained in comparison with entry 5 (82% ee) in spite of the use of a more enantiomerically enriched catalyst, seemed to indicate that the most favourable combination of concentration and dilution of the separate catalyst solutions was obtained in entry 5.

3. Conclusion

In conclusion, these first results confirm that the efficiency and enantioselectivity of asymmetric Ti(IV)/BINOL-catalyzed reactions is deeply influenced by the experimental parameters and, in particular, as regards the aldol condensation of Chan's diene, by the mode of preparation of the catalyst. More interestingly, the disclosure of the unprecedented dependence of NLE on the starting concentration in the separate catalyst solutions has been conveniently exploited for the achievement of a process characterized by pronounced amplification of ees.

4. Typical experimental procedure for asymmetric aldol reaction in the presence of Ti(O-*i*-Pr)$_4$/(*R*)-BINOL+ Ti(O-*i*-Pr)$_4$/(*S*)-BINOL (Table 2, entry 5)

Two mixtures of (*S*)-1,1′-bi-2-naphthol (0.030 mmol), Ti(O-*i*-Pr)$_4$ (0.030 mmol) and 3 Å molecular sieves (131 mg) in THF (4.5 mL) and (*R*)-1,1′-bi-2-naphthol (0.050 mmol), Ti(O-*i*-Pr)$_4$ (0.050 mmol) and 3 Å molecular sieves (219 mg) in THF (0.5 mL) were separately stirred at rt for 1 h under an argon atmosphere. The (*R*)- and (*S*)-catalyst were then mixed and the mixture cooled to −78 °C. Benzaldehyde **2** (1 mmol) was then added followed, after 30 min, by a solution of silyloxydiene **1a** (2 mmol) in THF (1 mL). This mixture was stirred at −78 °C for 2 h and then at rt overnight. Then, after cooling the mixture at −78 °C, TFA (0.4 mL) was added and the solution warmed to rt. After stirring at rt for 1 h, desilylation was complete and the reaction mixture diluted with ether and a saturated aqueous $NaHCO_3$ solution (3 mL) was added dropwise. The pure product (*R*)-**3a** was obtained by the usual work-up and purification procedures.[7b] (82% yield, 82% ee).

(5*R*)-5-Hydroxy-3-oxo-5-phenyl-pentanoic acid methyl ester. The physical and spectroscopic data of compound **3a** match those described.[7b]

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