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A convenient catalytic procedure for the highly enantioselective aldol condensation of *O*-silyldienolates

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Abstract—In the presence of catalytic amount of chiral Ti(O*i*Pr)$_4$/BINOL (0.08 equiv.) the asymmetric aldol condensation of 6-methyl-4*H*-[1,3]-dioxin-4-one-derived silyloxydienes takes place in high yields and enantiomeric excesses with aromatic, heteroaromatic, unsaturated and aliphatic aldehydes. Notable amplification of enantiomeric excesses have been obtained by using enantioenriched catalytic systems.

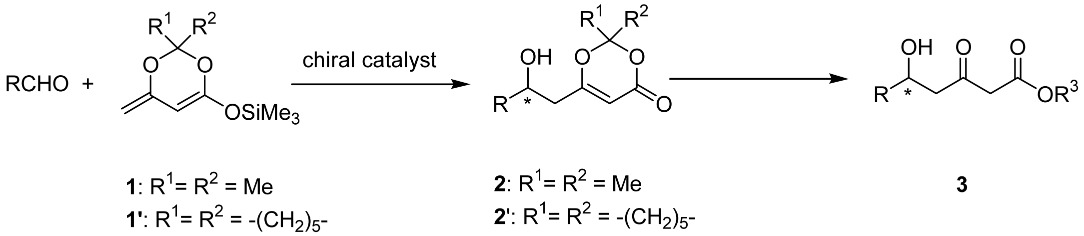
1. Introduction

Chiral δ-hydroxy-β-ketoesters and the derived *syn*- and *anti*-β,δ-diol esters, besides representing the main structural features of bio-active natural products, such as polyene macrolide antibiotics (amphotericin),[1] have been widely used as key-intermediates in the synthesis of pharmaceutically important compounds (manoalide,[2] pestalotin,[3] bryostatins,[4] compactin,[5] streptogramin antibiotics[6]). One typical approach for the synthesis of δ-hydroxy-β-ketoesters of type **3** (Scheme 1) involves the asymmetric aldol-type condensation of the silyldienolate **1**, as synthetic equivalent of the acetoacetate dianion and subsequent deprotection of aldol adduct **2**.[7]

Recently highly enantioselective catalytic procedures have been reported by the Evans and Carreira groups and are based on the use of chiral Cu(II) catalysts, [Cu(S,S)-Ph-pybox] (SbF$_6$)$_2$[8] or (S)-Tol-BINAP/CuF$_2$,[9] or complexes prepared from Ti(OiPr)$_4$ and tridentate ligands derived from 2-amino-2′-hydroxy-1,1′-binaphthyl.[7]

Nevertheless, these procedures suffer from some disadvantages: in fact, the presence of a suitable chelating group, α-situated to the formyl functionality seemed to be a strict pre-requisite in Evan's protocol; furthermore, Carreira's approaches proved to be particularly attractive for aromatic, heteroaromatic and unsaturated aldehydes, while the poor data available for aliphatic aldehydes usually resulted in a modest efficiency (<40% yields) or lower enantioselectivity.

In the course of an investigation devoted to the synthesis of the pharmacophoric pyranofuranone system of



Scheme 1.

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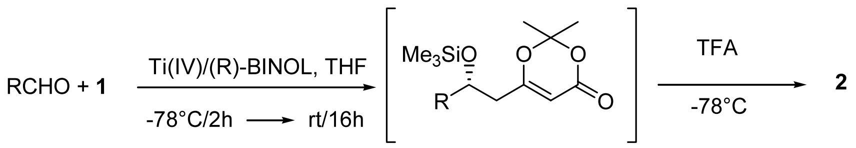


Scheme 2.

manoalide and cacospongionolide B,[10] we have shown that, by a suitable modification of a procedure previously reported by Sato,[11] the formation of the aldols **2** could be achieved in a very satisfactory manner in the presence of a chiral Ti(O*i*Pr)$_4$/BINOL system: however, noticeable amounts of catalyst (0.5–1.0 equiv.) seemed to be necessary to get high levels of efficiency and enantioselectivity. Previous reports have emphasized that optimized chemical and enantiomeric excesses in many Ti(O*i*Pr)$_4$/BINOL catalyzed asymmetric processes are often obtained only within a narrow reaction parameter window and the source of Ti(IV),[12] the method of catalyst preparation,[13] reaction solvent, catalyst and reagent concentration,[13b,d,14] catalyst loading,[13b,c] the presence of hydrated or activated molecular sieves[15] proved to be among the most important factors. Therefore we decided to verify the possibility to achieve an efficient and general catalytic procedure for Ti(IV)/BINOL catalyzed enantioselective condensation of the *O*-silyldienolate **1** (Scheme 2) through an appropriate choice of the experimental conditions.

2. Results and discussion

Because of the scarce availability of data concerning aliphatic aldehydes, decanal (Scheme 2, R = *n*-C_9H_{19}) and **1** were chosen as representative reagents in a set of preliminary experiments. Under the conditions reported in Table 1 and Scheme 2 the formation of the corresponding aldol **2** (R = C_9H_{19}) was found to take place in satisfactory yield and enantiomeric excess (entry 1) in the presence of only 0.08 equiv. of Ti(O*i*Pr)$_4$/(*R*)-BINOL complex.

However, catalyst loading and concentration proved to be important factors: in fact, no beneficial effect was obtained by using greater amounts of catalyst (entry 2). Furthermore, when the reaction was carried out in more concentrated solution both of catalyst (0.08 equiv.) and reagents, a significant drop in efficiency and enantioselectivity was observed (entry 3). On the contrary, a not negligible improvement of yield and e.e. were obtained by doubling the reaction times (entry 4).

The presence of additives in Ti(IV)/BINOL-catalyzed asymmetric processes has been sometimes exploited to achieve an enhancement of the level of efficiency and/or enantioselectivity. The experiments of entries 5 and 6 showed that the aldol **2** (R = C_9H_{19}) could be isolated in the highest e.e., albeit in poor yield, by performing the preparation of the catalyst in the presence of 1 equiv. of *i*-PrOH.

Table 1. Enantioselective aldol condensation of **1** to decanal (R = *n*-C_9H_{19})[a]

Entry	Additive	Yield (%)[b]	E.e. (%)[c]
1	–	79	89
2[d]	–	73	84
3[e]	–	62	76
4[f]	–	85	92
5	*i*-PrOH (0.2 equiv.)	73	91
6	*i*-PrOH (1.0 equiv.)	35	>99

[a] **1**/RCHO/Ti(O*i*Pr)$_4$/(*R*)-BINOL 2/1/0.08/0.08 molar ratios were used.

[b] The yields refer to isolated chromatographically pure compounds, obtained as predominantly (*S*)-enantiomers.

[c] E.e.s were determined by HPLC analysis using a CHIRALPAK AD column.

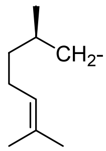
[d] In this entry 0.2 equiv. of Ti(IV)/BINOL were used.

[e] The reaction was performed in 1 ml THF.

[f] Reaction time 32 h.

The generality of the procedure was then checked by submitting a series of aldehydes to the conditions used in entry 1, Table 1. As reported in Table 2, the best e.e.s were obtained with aromatic, heteroaromatic and unsaturated aldehydes (entries 5–8); however, aliphatic aldehydes afforded the corresponding aldols **2** in very good efficiency and enantioselectivity (entries 1–3).

Table 2. Enantioselective aldol condensation of **1** to RCHO[a]

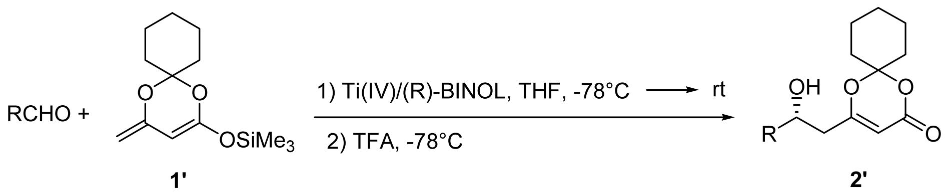
Entry	R	Product	Yield (%)[b]	E.e. (%)[c]
1	*n*-C_9H_{19}	**2a**	79	89 (*S*)
2	*n*-C_7H_{15}	**2b**	90	92 (*S*)
3	Ph-CH_2CH_2-	**2c**	85	89 (*S*)
4		**2d**	29	88/12[d]
5	Ph	**2e**	84	>99 (*R*)
6	3-Furyl	**2f**	75	>99 (*R*)
7	Ph-CH=CH-	**2g**	92	99 (*R*)
8	*p*-MeO-C_6H_4	**2h**	66	97 (*R*)

[a] **1**/RCHO/Ti(O*i*Pr)$_4$/(*R*)-BINOL 2/1/0.08/0.08 molar ratios were used.

[b] The yields refer to isolated chromatographically pure compounds.

[c] E.e.s were determined by HPLC analysis using a CHIRALPAK AD column.

[d] Diastereomeric ratio.



Scheme 3.

Steric factors seemed to exert a strong influence on the efficiency of the reaction: In fact, 2-phenyl propionaldehyde was recovered almost completely unchanged after prolonged reaction times (48 h). Furthermore, a lower reactivity was observed for (*R*)-(+)-citronellal, bearing a methyl group β-situated to the formyl group, so that the corresponding aldol **2d** was isolated in only 29% yield but with a good diastereoselectivity.

The ready availability of silyloxydiene **1**′, starting from *t*-butyl acetoacetate,[16] suggested the possibility to extend the above catalytic procedure to a different masked acetoacetate ester. In fact, again under the usual conditions of catalyst loading, catalyst and reagents concentration (Scheme 3 and Table 3) the formation of aldols **2**′ was generally shown to take place with high yields and e.e.s, although a lower efficiency was observed for aliphatic aldehydes.

Table 3. Enantioselective aldol condensation of silyloxydiene **1**′ to RCHO[a]

Entry	R	Product	Yield (%)[b]	E.e. (%)[c]
1	Ph	**2′a**	81	96 (*R*)
2	3-Furyl	**2′b**	89	97 (*R*)
3	Ph-CH=CH-	**2′c**	82	84 (*R*)
4	*n*-C_9H_{19}	**2′d**	60	>99 (*S*)
5	*n*-$C_{11}H_{23}$	**2′e**	48	>99 (*S*)

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

[b] The yields refer to isolated chromatographically pure compounds.

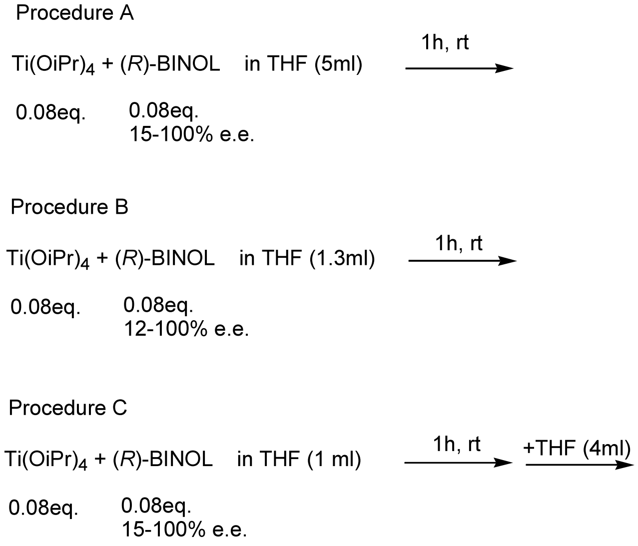
[c] E.e.s were determined by HPLC analysis using a CHIRALPAK AD column.

Rather surprisingly, a strong substrate dependence was found in the case of octanal since the corresponding aldol was obtained in >99% e.e. but only in 23% yield.

2.1. Detection of positive nonlinear effects [(+)-NLE]

In these last years an ever increasing interest has been devoted to asymmetric amplifications obtained by the suitable exploitation of (+)-NLE,[17] which have been detected in several asymmetric reactions involving the use of BINOL-derived /Ti(IV) catalysts.

Therefore, in order to verify the possibility to achieve high levels of enantioselectivity in the presence of partially resolved BINOL, an initial set of experiments were performed on benzaldehyde and *O*-silyloxydiene **1**, chosen as representative reagents, under the typical experimental conditions (Proc. A, Scheme 4), by using Ti(O*i*Pr)$_4$/(*R*)-BINOL catalytic systems prepared in situ from (*R*)-BINOL of varying e.e.s.



Scheme 4.

When the e.e. of the aldol **2e** was plotted against the e.e. of the BINOL (Fig. 1) a convex deviation [(+)-NLE] was clearly observed (curve A). A comparable size of amplification was obtained by performing the reaction in a more concentrated solution (Proc. B), both as regards the catalytic systems and the reagents. On the contrary, an intriguing result was afforded by Proc. C, involving, with respect to Proc. A, only a different initial concentration of the catalytic systems, while the same catalyst loading, solvent volume and constant final concentration of Ti(IV), chiral ligand and reagent were ensured. In fact, a notable enhancement of e.e. was observed in all the reported experiments (Curve C).

This unprecedented dependence on the catalyst concentration and mode of preparation further confirm the determining influence exerted by the experimental parameters on the occurrence, the sign and the size of NLE.

In conclusion, this investigation has allowed the achievement of two catalytic procedures for the highly efficient and enantioselective aldol reaction of masked acetoacetates; very satisfactory results have been obtained with aliphatic aldehydes and, finally, chiral aldols can be prepared in good yields and e.e.s by using enantioenriched Ti/BINOL catalysts.

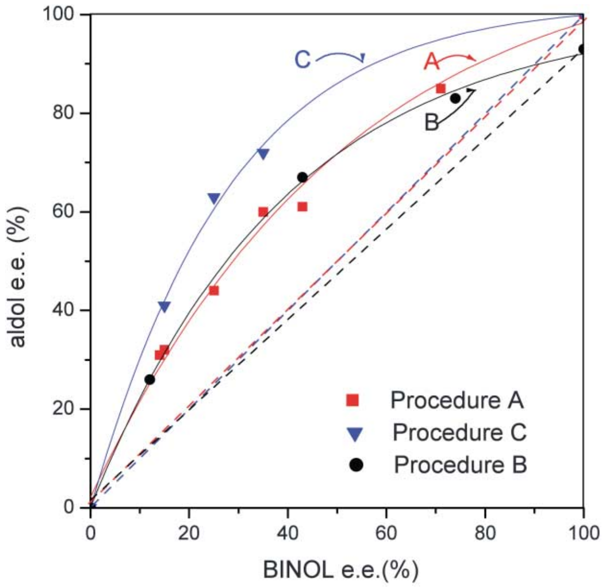


Figure 1. Influence of the mode of the preparation of the catalyst on NLE.

Acknowledgements

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