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Achiral additives dramatically enhance enantioselectivities in the BINOL–Ti(IV) complex catalyzed aldol condensations of aldehydes with Chan's diene

Qinyao Xu[a], Jianghui Yu[a], Fengyan Han[a], Juan Hu[a], Weiping Chen[b,*], Liping Yang[a,*]

[a] *Department of Chemistry, East China Normal University, Shanghai 200062, China*
[b] *Solvias AG, WRO-1055.6.68B, Mattenstrasse 22, Postfach, CH-4002 Basel, Switzerland*

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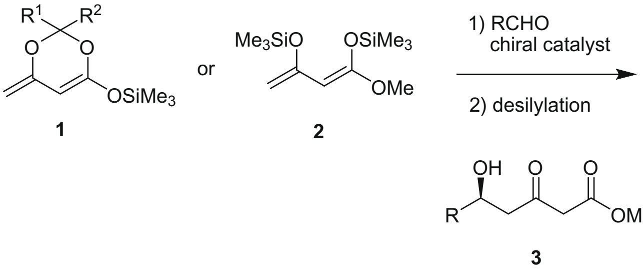
ABSTRACT

Achiral additives can dramatically enhance the enantioselectivities in the BINOL–Ti(IV) complex catalyzed aldol condensations of aldehydes with Chan's diene. The best results were obtained by using 2.0 equiv of LiCl with respect to (*S*)-BINOL/Ti(O*i*-Pr)$_4$ as the additive. In the presence of 4.0 mol % of LiCl and 2.0 mol % of BINOL/Ti(O*i*-Pr)$_4$, all aldehydes tested gave δ-hydroxy-β-ketoesters as almost pure single enantiomers. Moreover, the present catalyst system was highly effective on reducing the catalyst loadings to 0.1 mol %.

1. Introduction

Asymmetric catalysis that provides enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry; a great number of catalytic asymmetric transformations have been developed over the last decade.[1] Although most often enantioselectivities of 90–95% ee. have been achieved for a variety of transformations in the research laboratory, this is usually not sufficient for industrial needs, particularly when it comes to pharmaceutical intermediates and products. Moreover, the catalyst productivity, catalyst activity, catalyst stability, and mild reaction conditions are very important for large-scale practical applications. Chiral Lewis acid-catalyzed enantioselective aldol reactions of aldehydes with *O*-silyldienolates **1** and **2** (Chan's diene) represent some of the most efficient, chemoselective and straightforward methods for the synthesis of enantiomerically enriched δ-hydroxy-β-ketoesters (Scheme 1), versatile intermediates for the synthesis of complex, biologically active compounds, and natural products.[2,3]

Recently, Scettri et al. reported the aldol condensations of aldehydes with Chan's diene **2** catalyzed by a BINOL–Ti(IV) complex.[4] In the presence of molecular sieves and 2–8 mol % of (*R*)-BINOL/Ti(O*i*-Pr)$_4$, the reaction of an aldehyde with Chan's diene **2** for 2 h at −78 °C, then 16 h at room temperature gave product **3** in 48–94% yield and 83–99% ee for aromatic aldehydes, and 31–70% yield and 87–98% ee for aliphatic aldehydes, after desilylation. Over the course of developing a new practical route to anti-obesity agent inhibitor,[5] we found that the reaction of the requisite aldehyde with Chan's diene catalyzed by BINOL–Ti(IV) complex gave very low enantioselectivity in the absence of molecular sieves, but that the enantioselectivities could be dramatically improved upon when a Chan's diene contaminated with lithium chloride was used. Considering the effect of additives on asymmetric catalytic reactions[6] and the use of lithium chloride in the asymmetric nitroaldol reaction[7a] and conjugate addition,[7b] we decided to investigate their influence on this transformation.



Scheme 1.

BINOL–Ti(IV) is one of the most popular chiral Lewis acid catalysts.[8] The effect of achiral additives on asymmetric reactions catalyzed by BINOL–Ti(IV) has been documented previously. For example, molecular sieves have been added to most reactions,[8] hydrated molecular sieves added for ene[9a] and Diels–Alder reactions,[9b] phenols for aldols,[9c,d] alkynylations of aldehydes[9e] and allylations of aldehydes;[9f] water for ene reactions,[9g] ring-opening reactions,[9h] and sulfoxidations;[9i,j] and finally, triphenylphosphine for ring-opening reactions.[9k]

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[*] Corresponding authors. Tel.: +86 (021) 62232487; fax: +86 (021) 62232487 (L.Y.).

E-mail address: lpyang@chem.ecnu.edu.cn (L. Yang).

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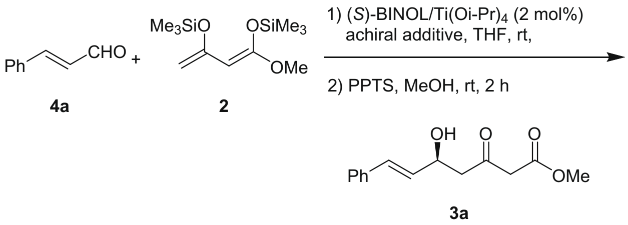
2. Results and discussion

Initially in this study, the effect of various achiral additives on the aldol reaction of cinnamaldehyde with Chan's diene **2** was examined. Thus, in the presence of (*S*)-BINOL/Ti(O*i*-Pr)$_4$(0.1 mmol) and an achiral additive in the desired amount, cinnamaldehyde **4a** (5 mmol) was reacted with Chan's diene (10 mmol) in THF at room temperature, followed by desilylation, to give the product (*S*)-**3a** (Table 1). In the absence of additives, the reaction gave very low enantioselectivity (4% ee, entry 1). Many achiral additives, of different properties, could significantly enhance the enantioselectivity. The most outstanding results were achieved using LiCl as the additive (entry 18–20), giving products in up to 97% ee. Best results were obtained using 2.0 equiv of LiCl with respect to (*S*)-BINOL/Ti(O*i*-Pr)$_4$ (entry 19). However, only a marginal effect on the enantioselectivity was observed on reducing LiCl to 1.0 equiv or increasing it to 4.0 equiv (entries 18 and 20).

Table 1
Asymmetric aldol condensation of cinnamaldehyde with Chan's diene catalyzed by BINOL/Ti(O*i*-Pr)$_4$in the presence of achiral additives[a]



Entry	Additive	Equivalent (based on cat.)	Time (h)	Yield[b] (%)	ee[c] (%)
1			2	90	4
2	Water	2.0	2	89	6
3	4 Å MS		12	91	23
4[d]	4 Å MS		12	90	89
5	EtOH	2.0	30	80	73
6	Pyridine	2.0	12	90	29
7	Et_3N	2.0	12	93	74
8	*i*-$PrNH_2$	2.0	12	93	52
9	TMEDA	1.0	30	85	92
10	PhOH	2.0	12	88	56
11	$PhCO_2H$	2.0	54	75	69
12	AcOH	2.0	12	92	36
13	$ZnCl_2$	2.0	12	93	12
14	$MgCl_2$	2.0	54	75	85
15	LiBr	2.0	12	90	73
16	KCl	2.0	12	90	38
17	NaCl	2.0	12	90	28
18	LiCl	1.0	12	92	95
19	LiCl	2.0	12	95	97
20	LiCl	4.0	12	91	95

[a] Reaction conditions: (1) cinnamaldehyde (5.0 mmol), (*S*)-BINOL (0.1 mmol), Ti(O*i*-Pr)$_4$ (0.1 mmol), additives in the specified amount, Chan's diene (10.0 mmol), THF (16 mL), room temperature, 12 h; (2) PPTS (1 mmol), MeOH (10 mL), room temperature, 2 h.

[b] All the yields refer to isolated, chromatographically pure compounds.

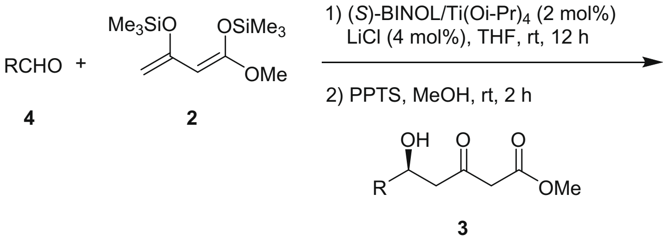
[c] Determined by HPLC with an AD-H column.

[d] The reaction was performed according to Scettri's procedure at −78 °C.

Next, the scope of aforementioned reaction was extended by using a number of aromatic and aliphatic aldehydes in the presence of 2.0 equiv of LiCl with respect to (*S*)-BINOL/Ti(O*i*-Pr)$_4$(Table 2). It was found that the novel system was highly efficient for the reactions of a variety of aldehydes, including aromatic, olefinic, and aliphatic derivatives. In all cases, full conversion of the aldehydes was obtained within 12 h at room temperature, giving products with almost perfect enantioselectivities.

To further evaluate the catalytic efficiency of the present system, the effect of the catalyst loading on the aldol reaction of cinnamaldehyde with Chan's diene **2** was examined. As shown in Table 3, the reaction with reduced catalyst loadings as low as 0.1 mol % was highly effective, affording the product in 79% yield and with 95% ee. The reaction using 0.05% catalyst was still effective (entry 5) but further reduction of catalyst loadings gave significantly lower enantioselectivities (entry 6–7).

Table 2
Asymmetric aldol condensations of Chan's diene with different aldehydes catalyzed by BINOL/Ti(O*i*-Pr)$_4$ in the presence of lithium chloride[a]



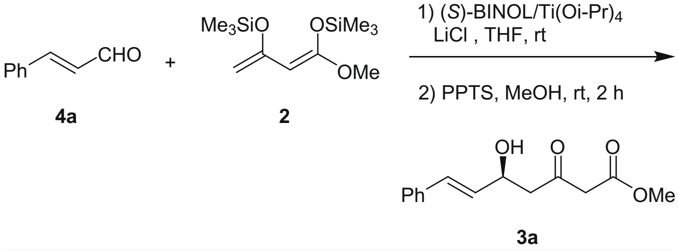
Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	$C_6H_5CH{=}CH–$	**3a**	95	97
2	$C_6H_5–$	**3b**	93	99
3	4-CH_3O–C_6H_4–	**3c**	90	99
4	4-NO_2–C_6H_4–	**3d**	75	95
5	3-NO_2–C_6H_4–	**3e**	75	99
6	*n*-C_2H_5–	**3f**	45	96
7	*n*-$C_{11}H_{23}$–	**3g**	55	99

[a] Reaction conditions: (1) cinnamaldehyde (5.0 mmol), (*S*)-BINOL (0.1 mmol), Ti(O*i*-Pr)$_4$(0.1 mmol), LiCl (0.2 mmol), Chan's diene (10.0 mmol),THF (16 mL), room temperature, 12 h; (2) PPTS (1 mmol), MeOH (10 mL), room temperature, 2 h.

[b] All the yields refer to isolated, chromatographically pure compounds.

[c] Determined by HPLC with AD-H column.

Table 3
Asymmetric aldol condensation of cinnamaldehyde with Chan's diene catalyzed by BINOL/Ti(O*i*-Pr)$_4$[a]



Entry	Catalyst (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	2.0	12	95	97
2	1.0	12	95	96
3	0.5	24	89	96
4	0.1	60	79	95
5	0.05	84	70	88
6	0.01	108	40	35
7	0.005	108	30	12

[a] Reaction conditions: (1) cinnamaldehyde (5 mmol), (*S*)-BINOL and Ti(O*i*-Pr)$_4$ in the desired amount, LiCl (2 equiv to catalyst), Chan's diene (10.0 mmol), THF (16 mL), room temperature; (2) PPTS (1 mmol), MeOH (10 mL), room temperature, 2 h.

[b] Isolated yield.

[c] Determined by HPLC with an AD-H column.

3. Conclusion

In conclusion, achiral additives can dramatically enhance the enantioselectivities in the BINOL–Ti(IV) complex-catalyzed aldol condensations of aldehydes with Chan's diene. The best results were obtained by using 2.0 equiv of LiCl with respect to (*S*)-BI-

NOL/Ti(O*i*-Pr)$_4$ as the additive. In the presence of 4.0 mol % of LiCl and 2.0 mol % of BINOL/Ti(O*i*-Pr)$_4$, all the aldehydes tested gave δ-hydroxy-β-ketoesters as almost pure single enantiomers . Moreover, the present catalyst system was highly effective in reducing the catalyst loadings to 0.1 mol %. This new methodology has been successfully used in the practical synthesis of the anti-obesity agent Orlistat.[10] Mechanistic studies and the application of the present catalyst system in other reactions are currently in progress.

Acknowledgments

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