Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1529–1531

TETRAHEDRON: *ASYMMETRY*

Asymmetric auto-inductive aldol reaction by self-assembly of chiral ligands

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Received 30 May 2001; accepted 6 June 2001

Abstract—The Ti(IV)/(*R*)-BINOL catalyzed aldol condensation of trimethylsilyloxydiene, deriving from 2,2,6-trimethyl-4H-[1,3]-dioxin-4-one, is shown to proceed through an auto-inductive process with amplification of enantiomeric excess (e.e.).

1. Introduction

Asymmetric catalysis plays a pivotal role in modern preparative organic chemistry. In recent years an ever increasing interest has stimulated the elaboration of efficient enantioselective procedures involving the exploitation of positive non-linear effects[1] of non-racemic catalysts, the asymmetric activation and deactivation of racemic catalysts[2] and the use of chirally flexible ligands.[2b] Furthermore, intriguing results have been obtained in aldol condensation processes with 2-trimethylsilyloxyfuran,[3] glyoxylate-ene reactions,[1c] and cyanohydrin formation by self-assembly of chiral ligands.[4]

2. Results and discussion

We have recently reported[5] an improved procedure for the enantioselective aldol condensation of *O*-silyl dienolates of type **2** that allowed an easy and convenient approach to chiral δ-hydroxy-β-ketoesters **3**, which are well-known key-intermediates in the synthesis of many important bioactive natural products.[6] However, in our opinion, the main disadvantage of this procedure was the need for high levels of the Ti(O*i*-Pr)$_4$/(*R*)-BINOL chiral catalyst (0.2–0.5 equiv.) to obtain satisfactory levels of efficiency and enantioselectivity.

Therefore, silyloxydiene **2** and benzaldehyde **1** were chosen as representative reagents and a set of experiments was designed to improve the above procedure, particularly with respect to the catalyst loading and the enantioselectivity of the process (Scheme 1).

Under the previously reported conditions,[5] 0.5 equiv. of the chiral Ti(O*i*-Pr)$_4$/(*R*)-BINOL complex was used and the corresponding aldol **4** was formed in 63% yield with e.e. of 92% (Table 1, entry a).

A promising initial result was obtained when the aldol reaction was completed in the presence of only 8 mol% of the Ti(O*i*-Pr)$_4$/(*R*)-BINOL catalyst, prepared in more dilute THF solution with respect to entry a. After stirring for 2 h at −78°C and a further 16 h at rt, the formation of a mixture of the silylated and free aldols **3** and **4** was observed. After in situ desilylation according to Carreira's procedure,[8] **4** was isolated with 82% e.e. in 79% yield (entry b).

The information was obtained when reactions were stopped after stirring for either 1 or 2 h at −78°C, (entries c and d, respectively). Markedly lower yields and enantioselectivies were seen in both cases, clearly showing that the aldol condensation occurs essentially at room temperature with amplification of the e.e. (92% c.f. 85%, entries a and c, respectively; 82% c.f. 61%, entries b and d, respectively).

As is known, many asymmetric reactions are based on a suitable combination of metal compounds and chiral ligands: normally the catalyst remains unaffected by the newly formed products so that a constant stereoselectivity is observed. On the contrary, the results from our study suggested that an auto-inductive process of aldol condensation[2c,3] could have been involved; therefore, the

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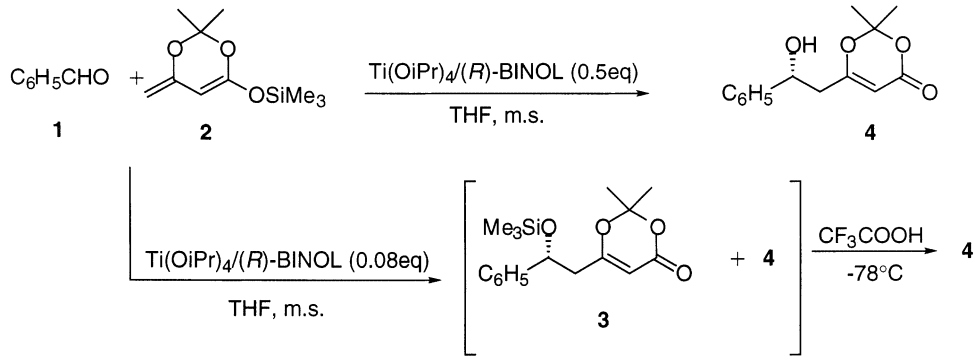
0957-4166/01/$ - see front matter
PII: S0957-4166(01)00261-0



Scheme 1.

Table 1. Enantioselective aldol condensation of **2** with aldehyde **1**

Entry	Time/temp.	Ti(IV)/(*R*)-BINOL	Yield (%)[a]	E.e. (%)[b]	E.e. (%)[c]
a	1 h/−78°C+16 h/rt	0.5 equiv.	63	92	–
b	1 h/−78°C+16 h/rt	0.08 equiv.	79	82	–
c	1 h/−78°C	0.5 equiv.	22	85	–
d	2 h/−78°C	0.08 equiv.	2	61	–
e	2 h/−78°C+16 h/rt	0.08 equiv.+(*R*)-**4** (82% e.e.)	79[d]	92	93
f	2 h/−78°C+16 h./rt	0.08 equiv.+(*S*)-**4** (80% e.e.)	82[d]	89	>99
g	2 h/rt	0.08 equiv.	53	76	–

[a] All the yields refer to isolated, chromatographically pure compounds. 2/1/0.08/0.08 *O*-silyl dienolate/benzaldehyde/Ti(O*i*-Pr)$_4$/(*R*)-BINOL molar ratios were used with the exception of entries a and c where 0.5 equiv. of Ti(IV) and 0.5 equiv. of (*R*)-BINOL were used.

[b] E.e.s were determined by HPLC analysis of the aldol adduct using a Chiralpack AD column. In all the reported entries (*R*)-**4** was isolated as predominant enantiomer.

[c] E.e.s of newly formed aldol **3**, calculated according to Ref. 7.

[d] The yields refer to pure compounds corrected by the amount of additive.

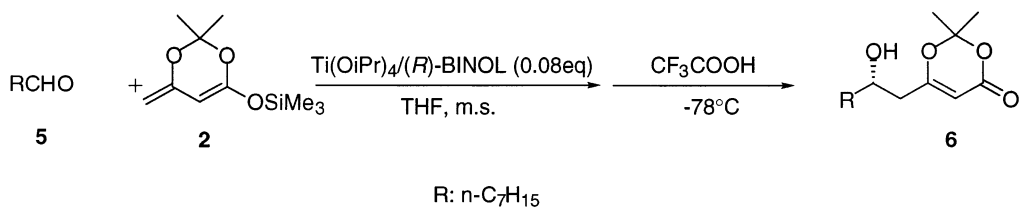
possibility of self-organization of the chiral ligands (i.e. (*R*)-BINOL and the newly formed chiral aldol **4**) to give a multi-component Ti(IV) catalyst was proposed.

This hypothesis was confirmed by carrying out the reaction in the presence of 0.05 equivalents of enantiomerically enriched aldol (*R*)-**4** (entry e) or (*S*)-**4** (entry f). In both cases, (after the desilylation reaction)[8] the newly formed aldols **4** were obtained in comparable yields and significantly higher e.e.s than that observed in entry b (e.e.=93 and >99% c.f. 82% from entry b). Furthermore, these results proved that the observed chiral induction in the system was controlled by (*R*)-BINOL since in both entries e and f (*R*)-**4** was the predominant enantiomer. Moreover, a further experiment (entry g) showed that performing the asymmetric aldol condensation at room temperature gave good efficiency and promising levels of enantioselectivity.

The presence of an auto-inductive process was also supported by experiments carried out with an aliphatic aldehyde substrate.

When octanal **5** was submitted to the usual treatment in the presence of 0.08 equivalents of Ti(IV)/(*R*)-BINOL complex the corresponding aldol (*S*)-**6** was obtained in 51% yield and 85% e.e. (Scheme 2 and Table 2, entry a).

In spite of the slightly lower efficiency, amplification of e.e. was again observed when the Ti(O*i*-Pr)$_4$/(*R*)-BINOL complex was prepared in the presence of enantiomerically enriched (*R*)-aldol which gave product with e.e. of 89% c.f. 85% from the reaction with no aldol additive (entries b and a, respectively) and (*S*)-aldol which gave product with e.e. of 94% c.f. 85% e.e. (entries c and a, respectively).



Scheme 2.

Table 2. Enantioselective aldol condensation of **2** with octanal

Entry	Time/temp.	Additive (5% mol)	Yield (%)[a]	E.e. (%)[b]	E.e. (%)[c]
a	2 h/−78°C+16 h/rt	–	51	85	–
b	2 h/−78°C+16 h/rt	(*S*)-**6** (85.5% e.e.)	44[d]	88	89
c	2 h/−78°C+16 h/rt	(*R*)-**6** (89.2% e.e.)	42[d]	75	95

[a] All the yields refer to isolated, chromatographically pure compounds. 2/1/0.08/0.08 O-silyl dienolate/octanal/Ti(O*i*-Pr)$_4$/(*R*)-BINOL molar ratios were used.

[b] E.e.s were determined by HPLC analysis of the aldol adduct using a Chiralpack AD column. In all the reported entries (*S*)-**6** was isolated as predominant enantiomer.

[c] E.e.s of newly formed aldol **6**, calculated according to Ref. 7.

[d] The yields refer to pure compounds corrected by the amount of additive.

3. Conclusion

In conclusion, these results are of high synthetic value since the occurrence of an auto-inductive process allows a convenient approach to polyfunctional C_5 key-intermediates with high efficiency and enantioselectivity.

4. Experimental

4.1. Typical experimental procedure

(*R*)-1,1′-Bi-2-naphthol (23 mg, 0.08 mmol), Ti(O*i*-Pr)$_4$ (24 μL, 0.08 mmol) and 4 Å MS (310 mg) were stirred in THF (1.3 mL) at rt for 1 h under an Ar atmosphere. The mixture was cooled to −78°C and the aldehyde (1 mmol) was added. After stirring the mixture for 20 min, a solution of **2** (2 mmol) in THF (1 mL) was added. The reaction mixture was stirred for 2 h at −78°C and then at room temperature overnight. After cooling to −78°C, trifluoroacetic acid (0.3 mL) was added. The solution was allowed to warm to rt, and stirring was continued for 1 h. The mixture was diluted with ether and saturated aqueous $NaHCO_3$ solution was added dropwise until the evolution of gas ceased. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude by chromatography on silica gel ($CHCl_3$:Et_2O 9:1) afforded the aldol adduct.

Acknowledgements

We are grateful to Ministero dell'Università e Ricerca Scientifica e tecnologica (MURST) and Italian CNR for financial support.

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