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TETRAHEDRON: *ASYMMETRY*

Enantioselective aldol condensation of 1,3-bis-(trimethylsilyloxy)-1-methoxy-buta-1,3-diene promoted by chiral Ti(IV)/BINOL complex

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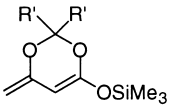
Abstract

Enantiomerically enriched δ-hydroxy-β-ketoesters are easily available by aldol condensation of 1,3-bis-(trimethylsilyloxy)-1-methoxy-buta-1,3-diene in the presence of Ti(O-*i*Pr)$_4$/(*S*)-(–)-BINOL system. All reaction mixtures were separated by column chromatography and mostly isolated in moderate to good yields and all in high enantiomeric excesses.

Aldol condensation of synthetic equivalents of acetoacetic esters represents an important preparative reaction that allows the formation of a polyfunctional C_5 fragment and the corresponding aldols have proven to be versatile key-intermediates in the synthesis of complex, biologically active natural products such as manoalide,[1] compactin and (+)-dihydrocompactin,[2] (–)-pestalotin,[3] mevinolin analogues,[4] lepicidin,[5] bryostatin **2**.[6]



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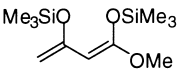

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Compounds **1** and **2** can be considered among the most popular masked acetoacetic esters and recently the silyl dienolate **1** (R′ = Me), deriving from commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, has been used in a variety of aldol reactions, based on the employment of Ti(IV),[7–9] or Cu(II),[10–12] chiral complexes, taking place with high efficiency and enantioselectivity.

On the contrary, the highly oxygenated diene **2**[13] (Chan's diene) has been essentially used in the synthesis of racemic aldols by $TiCl_4$ catalysis[14] while the presence of a chelating substituent α- or β-situated seemed to be a strict structural requirement for attaining high levels of diastereo- and enantioselectivity.[15]

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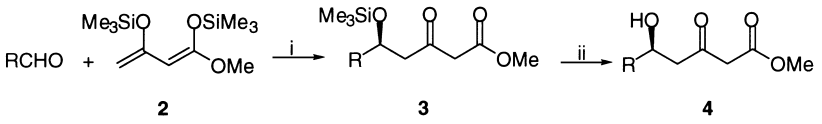
Now we report the first application of Chan's diene **2** in asymmetric aldol reactions, promoted by a Ti(O-*i*Pr)$_4$/(*S*)-(–)-1,1′-bi-2-naphthol (BINOL) complex in the presence of activated molecular sieves.

Under the conditions reported in Scheme 1 and Table 1, with the exception of entry b, silylated aldols **3** proved to be the only reaction products, as confirmed by ^{1}H NMR analysis (400 MHz) on crude reaction mixture.



2 **3** **4**

Scheme 1. Synthesis of δ-hydroxy-β-ketoesters **4**; reagents: (i) Ti(O-*i*-Pr)$_4$, THF, *S*-(–)-BINOL, CH_2Cl_2, –78°C, m.s.; (ii) H^+/THF, 0°C

Table 1
Asymmetric aldol reaction promoted by Ti(IV)/(*S*)-(–)-BINOL complex

Entry	R	Product	Yield(%)[a]	Ee(%)[b]	$[\alpha]_D$
a	3-Furyl	4a	48	83	-36
b	C_6H_5	4b[c]	19	99	-46
		4b[d]	33	95	-45
c	*p*-NO_2 C_6H_4	4c	86	90	-39
d	*p*-$CH_3OC_6H_4$	4d	54	93	-45
e	n-C_9H_{19}	4e	50	87	-22

a)All the yields refer to isolated chromatographically pure compounds, whose structure were confirmed by ^{1}H-NMR and ^{13}C analysis.[16]
b) E.e.s have been determined by HPLC analysis.
c) Yield refers to pure aldol **4b** isolated directly after aldol reaction.
d) Yield refers to pure aldol **4b** isolated after desilylation procedure.

Although the experimental conditions have not been optimized, satisfactory results in terms of enantioselectivity have been obtained by using catalytic amounts of chiral complex (8% molar) while no significant improvement was observed by performing the reaction in the presence of increasing amounts of catalyst (up to 30%).

Removal of the -$SiMe_3$ group required controlled conditions: in fact, almost complete retro-aldol reaction resulted from *n*-$Bu_4N^+F^-$ treatment, while the occurrence of this undesired side-reaction was considerably limited by acidic work-up of crude silylated **3** according to Carreira's procedure.[7b]

However it is noteworthy that in entry b the usual conditions for aldol condensation afforded both products **3b** and **4b** (99% ee). Desilylation of **3b** afforded aldol **4b** for which a 95% ee was determined, indicating racemization in the course of the deprotection procedure could be responsible for a slight lowering of ee.

In conclusion, these first results seem to broaden the synthetic validity of Chan's diene whose main applications in asymmetric processes concerned essentially the well-known hetero-Diels–Alder reactions with aldehydes in the presence of chiral Lewis acids;[17] only recently a paper about catalytic asymmetric allylation reactions using (*S*)-BINOL/Ti(O-*i*Pr)$_4$ and the Chan's diene

reported that, in all cases studied, either the chemical yields or the enantiomeric execess were unacceptably low using reasonable amounts of catalyst.[18]

In a typical experimental procedure, a mixture of Ti(O-*i*-Pr)$_4$ (0.08 mmol) and (*S*)-(–)-BINOL (0.08) in 1 ml THF and molecular sieves (375 mg) was stirred at rt for 1 h. After cooling the mixture to –78°C the aldehyde (1 mmol) was added dropwise followed, after 20 min, by silyloxy-diene **2** (2 mmol). The resulting solution was stirred in an inert gas atmosphere at –78°C for 3 h; after warming at rt the mixture was stirred overnight. The progress of reaction was monitored by TLC. Upon completion a saturated aqueous solution of $NaHCO_3$ (2 ml) was added until the evolution of gas ceased (20 min); the reaction mixture was diluted with ether and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo affording a yellow oil. The residue, diluted in THF, after cooling to 0°C, was treated with 10% TFA in water. After desilylation was complete, the solution was warmed to rt and partitioned between Et_2O and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and then dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography on silica gel using 8:2 $CHCl_3$:Et_2O afforded the aldol adduct **4**. The enantiomeric excess of the aldol-products were determined by HPLC analyses with a Chiralpak AD column using a racemic sample as reference.

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16. 5-(*S*)-[Furan-3-yl]-5-hydroxy-3-oxo-pentanoic acid methyl ester **4a**. Pale yellow oil. R_f 0.3 (Et_2O:$CHCl_3$, 2:8); ν_{max} (liquid film) 3480, 1740, 1713 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34 (s, 1H), 7.32 (d, *J* 1.5 Hz, 1H), 6.33 (s, 1H), 5.09 (dd, *J* 8.7, 3.6 Hz, 1H), 3.66 (s, 3H), 3.46 (s, 2H), 2.96 (dd, *J* 17.2, 8.7 Hz, 1H), 2.85 (dd, *J* 17.2, 3.6 Hz, 1H); δ_C (62.89 MHz, $CDCl_3$) 202.5, 167.2, 143.4, 139.0, 127.2, 108.3, 62.8, 52.5, 50.2, 49.5; *m*/*z* (EIMS) 212 (M^+). $[\alpha]_D = -36$

($c=1$, $CHCl_3$), 83% ee (*S*). HPLC analysis (hexanes:isopropanol:trifluoroacetic acid, 6:4:0.01), 0.5 mL/min; (*R*) enantiomer $t_R=15.59$ min; (*S*) enantiomer $t_R=16.84$ min. 5-(*S*)-*p*-Nitrophenyl-5-hydroxy-3-oxo-pentanoic acid methyl ester **4c**. Pale yellow oil. R_f 0.2 (Et_2O:$CHCl_3$, 2:8); ν_{max} (liquid film) 3510, 2987, 2950, 1740, 1646, 1314, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.12 (d, $J=8.6$ Hz, 2H), 7.50 (d, $J=8.6$ Hz, 2H), 5.26 (dd, *J* 7.3, 4.3 Hz, 1H), 3.69 (s, 3H), 3.50 (s, 2H), 2.93 (m, 2H); δ_C (62.89 MHz, $CDCl_3$) 208.2, 169.0, 145.5, 145.6, 129.2, 123.4, 68.4, 50.1, 44.4; *m*/*z* (EIMS) 267 (M^+). $[\alpha]_D=-45$ ($c=1$, $CHCl_3$), 90% ee (*S*). HPLC analysis (hexanes:isopropanol:trifluoroacetic acid, 6:4:0.01), 0.5 mL/min; (*R*) enantiomer $t_R=15.25$ min; (*S*) enantiomer $t_R=14.36$ min. 5-(*S*)-*p*-Methoxyphenyl-5-hydroxy-3-oxo-pentanoic acid methyl ester **4d**. Pale yellow oil. R_f 0.3 (Et_2O:$CHCl_3$, 2:8); ν_{max} (liquid film) 3500, 2988, 2940, 1740, 1616, 1514, 1378, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.27 (d, $J=8.3$ Hz, 2H), 6.86 (d, $J=8.3$ Hz, 2H), 5.12 (dd, *J* 9.1, 3.2 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.50 (s, 2H), 2.98 (dd, *J* 17.0, 9.2 Hz, 1H), 2.86 (dd, *J* 17.0, 3.2 Hz, 1H); δ_C (62.89 MHz, $CDCl_3$) 208.2, 169.0, 159.2, 131.7, 129.3, 113.9, 68.4, 50.2, 50.1, 44.4; *m*/*z* (EIMS) 252 (M^+). $[\alpha]_D=-45$ ($c=1$, $CHCl_3$), 93% ee (*S*). HPLC analysis (hexanes:isopropanol:trifluoroacetic acid, 6:4:0.01), 0.5 mL/min; (*R*) enantiomer $t_R=10.49$ min; (*S*) enantiomer $t_R=12.07$ min. 5-(*R*)-5-Hydroxy-3-oxo-tetradecanoic acid methyl ester **4e**. Pale yellow oil. R_f 0.5 (Et_2O:$CHCl_3$, 2:8); ν_{max} (liquid film) 1740, 1616, 1514, 1378, 1106 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.06 (s, 1H), 3.77 (s, 3H), 3.46 (s, 2H), 2.75–2.64 (m, 2H), 1.51–1.25 (m, 16H), 0.87 (t, 2H). δ_C (62.89 MHz, $CDCl_3$) 208.2, 169.0, 65.2, 50.1, 44.4, 37.4,32.5, 30.6, 30.3, 30.0, 23.8, 23.1, 14.0; *m*/*z* (EIMS) 252 (M^+). $[\alpha]_D=-22$ ($c=1$, $CHCl_3$), 87% ee (*S*). HPLC analysis (hexanes:isopropanol, 9:1:), 0.3 mL/min; (*S*) enantiomer $t_R=17.78$ min; (*R*) enantiomer $t_R=19.24$ min.

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