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A Superior Chiral Auxiliary in Aldol Condensations: Camphor-Based Oxazolidone

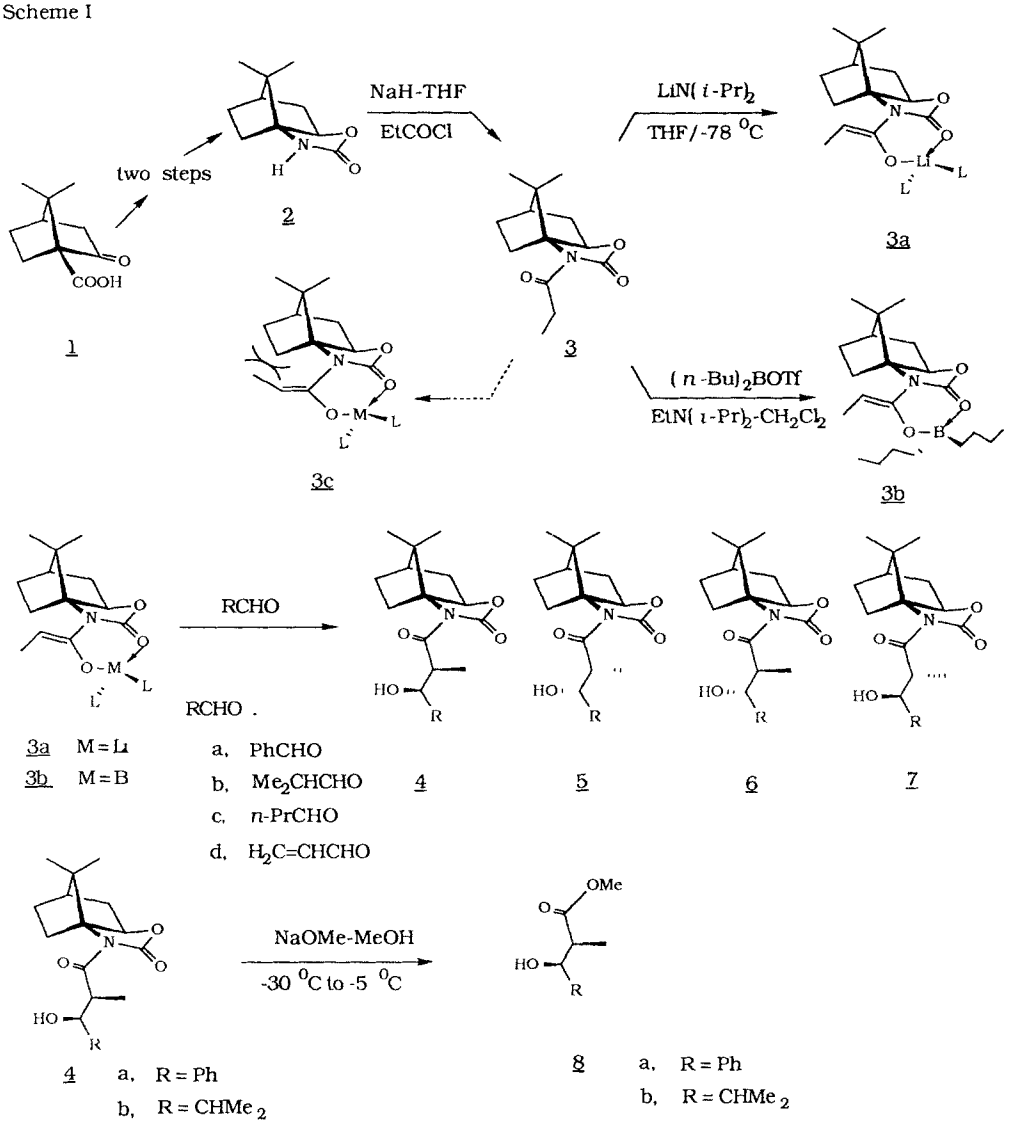
Tu-Hsin Yan,* Vir-Vir Chu, Ta-Chin Lin, Woei-Hung Tseng, and Tun-Wen Cheng
Department of Chemistry, National Chung-Hsing University
Taichung, Taiwan 40227, Republic of China

Abstract: The aldol reactions from boron enolate derived from camphor-based *N*-propionyloxazolidone exhibit exceptionally high stereoselection. The initial aldol adducts from lithium mediated reactions equilibrate to furnish erythro isomers. Erythro selection is controlled by the choice of the enolate counterion.

Over the past few years, the utilization of camphor as a source of chirality for the preparation of various enantiomerically enriched compounds has been illustrated by Eliel,[1] Hoffman,[2] Taber,[3] Oppolzer,[4] Davis,[5] and others.[6] Driven by the rapidly growing demand for highly enantiomerically pure β-hydroxy carbonyl containing compounds, the development of superior metal-chelated enolates, which can achieve exceptionally high diastereoselectivity, has evidently become both desirable and challenging.[7] In the preceding communications[8] we have shown that (+)-camphor-based imide enolate can display excellent π-topological differentiation on alkylation reactions. The ready availability of optically pure 2-oxazolidone 2 from ketopinic acid 1[8] made consideration of it very attractive for use as chiral auxiliary in aldol condensations Herein we describe in detail the development of enantioselective aldol condensations via the lithium- and boron-chelated enolates derived from the imide 3

The lithium-chelated (*Z*)-enolate of 3 was generated under kinetic conditions ($LiN(i\text{-}C_3H_7)_2$, -78 °C, THF) The boron-chelated (*Z*)-enolate 3b was prepared under mild conditions from chiral imide 3 and di-*n*-butylboryl trifluoromethanesulfonate.[7d,8,9,10] As the new metal-chelated enolates, 3a and 3b, possess a relatively rigid camphor ring which serves as a sterically demanding group to retard the formation of chelated (*E*)-enolates 3c (Scheme I), we hoped to achieve greater diastereoselectivities on aldol condensations. Indeed the aldol products from di-*n*-butylboryl trifuoromethanesulfonate mediated aldol condensations always consisted of a single erythro diastereomer within 400-MHz ^1H NMR detection limits. The illustrated aldol condensations of enolates, 3a and 3b, with representative aldehydes summarized in Table I were carried out according to the following general procedure Aldehyde was added to the solution containing the lithium enolate 3a (~0.2M) at -78 °C. The resulting solution was stirred at -78 °C for 30 min, quenched with 20% aqueous THF solution, and worked up In the process of conducting erythro/threo equilibration studies, the resulting mixture was quenched at -78 °C and stirred at -5 °C for 30 min before the usual workup In the condensations of the boron enolate 3b with aldehydes, the reaction mixture was stirred at -78 °C for 1 hr and then at room temperature for 2 hr. The resultant solution was cooled to 0 °C and quenched with a mixture of methanol and pH 7 phosphate buffer (2.1). The resulting borate was oxidized by 30% H_2O_2 for 1 hr at 0 °C In all cases studied, the aldol condensations from boron enolate 3b exhibited complete erythro stereoselection and absolute stereochemical control. In fact, none of the other three diastereoisomeric aldol adducts could be detected by 400-MHz ^1H NMR Our assignment of the syn configuration is based on the consideration of the carbinol resonances in the ^1H NMR spectra of the crude aldol product, using the well-established fact that

Scheme I



1 2 3 3a 3b 3c

3a M = Li
3b M = B

4 5 6 7

4 a, R = Ph
b, R = CHMe2

8 a, R = Ph
b, R = CHMe2

J_{threo} (7~9Hz) > $J_{erythro}$ (3~6Hz) [11] The absolute stereochemical assignments were made in two cases Nondestructive removal of the chiral auxiliary 2 via methanolysis (NaOMe, 0 °C) of 4a and 4b afforded the corresponding known colorless optically active methyl esters 8a ($[\alpha]^{20}_D$ = - 22 5 (c 4 8, $CHCl_3$)) and 8b ($[\alpha]^{20}_D$ = -

8 1 (c 3.1, $CHCl_3$)) for comparison of optical purity.[7d,12] The aldol reactions from lithium enolate 3a afforded erythro and threo products. In all cases examined, however, the initial kinetic mixture of erythro and threo aldols can be equilibrated to thermodynamic erythro adducts by quenching the reaction mixture with aqueous THF and stirring the resulting solution at -5 °C for 0.5 h. The two erythro aldol stereoisomers, 4 and 5, in all cases reported could be conveniently purified to high optical purity by a single recrystallization or column chromatography The assignment of stereochemistry of 6 is based on the above equilibration studies of the initial kinetic aldols (e.g., compare entries 2 vs. 3 and 5 vs. 6) The diastereoselectivity of the aldol reaction with lithium enolates 3a was generally moderate. The origin of the lower level of the stereoselection could be largely due to the long Li-O bond length as compared to B-O bond length [7e, 10c] Of particular note is the opposite sense of chirality transfer with lithium as compared to boron enolates (e.g , compare entries 1 vs. 2, 4 vs. 5, and 7 vs 8). This behavior has also been observed by Abdel-Magid et al.[7e] The origin of this marked difference in enantioselection may lie in the difference in the coordination numbers of boron and lithium.[13]

Table I Aldol Condensations of Metal Enolates 3a and 3b with Representative Aldehydes

entry	electrophile	enolates	erythro/threo[a] (4+5 : 6+7)	enantioselection[a] 4,5	6,7	yield[d] (%)	$[\alpha]^{20}_D$ deg	(c, CH_2Cl_2)[f]	mp °C
1	PhCHO	B(*n*-Bu)$_2$	> 99 1	> 99 1	b	91	+9 4	(12 6)	121-122
2	PhCHO	Li(-78 °C)	1 1	1.4	> 99 1	75	-	-	-
3	PhCHO	Li(equilibration)	>99 1	1·9	c	61	+50 5[e]	(3 7)	43-44
4	Me_2CHCHO	B(*n*-Bu)$_2$	> 99 1	> 99 1	b	92	+84 6	(8 8)	91-92
5	Me_2CHCHO	Li(-78 °C)	13·6	1:12	> 99 1	82	-	-	-
6	Me_2CHCHO	Li(equilibration)	>99 1	1 18	c	65	+49 0[e]	(4 0)	100-101
7	*n*-PrCHO	B(*n*-Bu)$_2$	> 99 1	> 99 1	b	92	+81 0	(10 1)	51-52
8	*n*-PrCHO	Li(-78 °C)	> 99 1	1 6	c	85	-	-	-
9	*n*-PrCHO	Li(equilibration)	> 99 1	1·6	c	85	+57 5[e]	(5 0)	56-57
10	H_2C=CHCHO	B(*n*-Bu)$_2$	> 99 1	> 99 1	b	92	+105 7	(7 4)	103-104

[a]Ratios determined by 400-MHz ^{1}H NMR. [b]The erythro-isomer 4 was the only detected product by 400-MHz ^{1}H NMR. [c]None of the threo-isomers could be detected by ^{1}H NMR [d]Satisfactory spectral data (NMR and IR) and analytical data obtained for all new compounds [e]Optical rotation of purified erythro-isomer 5 [f]Concentration in methylene chloride (c = g/100ml)

This work provides a practical asymmetric synthesis of β-hydroxy carbonyl containing compounds both enantiomers of erythro aldols can be prepared easily via metal and temperature modifications The remarkable ease of the preparation of both antipodes of 2 and the exceptional quality of stereocontrol exhibited by the camphor-based boron enolate 3b highlight the synthetic utility of the auxiliary 2.

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12 The absolute stereochemical configuration of 8a has also been studied by C H Heathcock and D A Evans The optical rotations reported by Heathcock and Evans are $[\alpha]^{20}_D$ -19 30 (*c* 1 74, $CHCl_3$) and $[\alpha]^{25}_D$ -23 1 (*c* 3 2, $CHCl_3$), respectively Our reported optical rotation for 8b also show good agreement as to the highest literature value ($[\alpha]^{25}_D$ -7 9 (*c* 5 7, $CHCl_3$)) reported for this ester [7d] This information permitted a tentative assignment of absolute stereochemical configuration to the erythro aldols 4c and 4d

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