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STEREOSELECTIVE ALDOL CONDENSATIONS VIA ENOLBORONATES.

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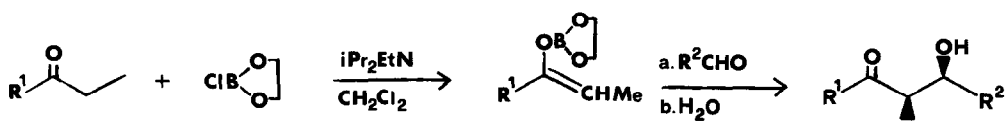
SUMMARY : Enolboronates, new enolates directly accessible from carbonyl compounds, exhibit extraordinary high erythro diastereoselection both with aliphatic and aromatic aldehydes.

Comparing the ^{1}H and ^{13}C NMR data for various enol-derivatives ,[1] enolboronates (2) happen to be very similar to silyl enol ethers. Silyl enol ethers react with aldehydes only at 50-60 deg C, using high pressures (10 Kbar) and long reaction times (days),[2] while enolboronates react smoothly from -78 to -15 deg to give aldol condensation products in good yields.[1] The driving force of this reaction is the high tendency of boron in enolboronates to complete its octet by forming anionic complexes such as (3). It is known, for example, that the tetrahedral monoborate ion forms with ethylene glicol the very stable kelate complex (4).[3] Moreover, the strength (133-189 Kcal/mol) and the short length (1.36-1.47 (Å)) of the B-O bonds could well result in the compression of the cyclic transition state of the kinetically controlled aldol condensation, thereby enhancing those steric parameters which appear to regulate diastereoselection.[4]

This actually proved to be the case: enolboronates afford exceedingly high erythro diastereoselection, and quite good condensation yields (Table 1,2).[6] Erythro diastereoselection remained excellent regardless of any change made to the reaction system, namely varying the steric bulkiness of R^1 (Table 1, entries 1,2,7,10),[7] using both aromatic and aliphatic-enolizable aldehydes (Table 1), using cyclic enolates (Table 2).



(1) (2)

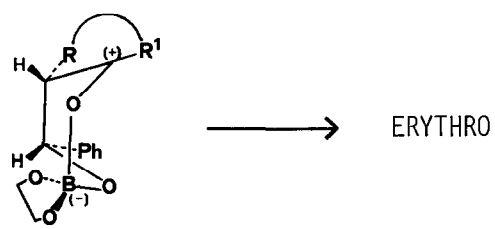
Warming up the enolate (Table 1, entry 8), or using amines with different basicity and steric hindrance (Table 1, entries 3,4) resulted in lower yields but did not alter stereoselection (> 99:1). Warming up the reaction mixtures (Table 1, entries 5,7) allowed higher conversions, but again did not affect the isomer ratios.

A similar erythro-preference, although with lower selectivity, has been reported for tin[8], zirconium[9], titanium[10], and tris(dialkylamino)sulfonium (TAS)[11] enolates to be independent of the enolate geometry. Either an acyclic transition state[8c,9b,11] or a cyclic one[9a,10a] has been considered for explaining the results.

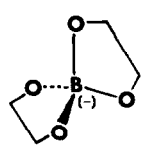
In the case of vinyloxyboranes[12] a good correlation has been observed between the enolate geometry and the product aldol stereochemistry, via a preferred chairlike (Zimmerman)[4] transition state.

For enolboronates a pericyclic boatlike process (e.g. 3) can be hipothesized, giving erythro selectivity from those enolates which have trans geometry (e.g. Table 2, entries 1,2).

The geometry of the enolates derived from acyclic carbonyl compounds as well as the use of chiral, non-racemic 1,2-diols as boron ligands are under current investigation: with these experiments we hope that we shall gain a deeper insight into the transition state and the reaction mechanism.



(3)



(4)

TABLE 1. Stereoselective aldol condensations. Acyclic carbonyl compounds.

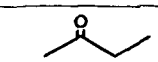
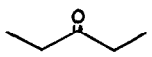
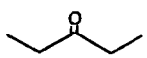
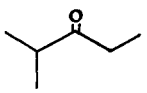
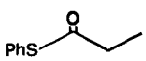
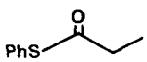
Entry	$R^1COCH_2CH_3$	R^2CHO	Enolization	Reaction	Erythro-threo[a]	Yield%[b]
1		PhCHO	-78°,30 MIN	-78°, 1H	>99:1	85[c]
2		PhCHO	-78°,30 MIN	-78°, 1H	>99:1	82
3			-78°,30 min[d]	-78°, 1h	>99:1	42[d]
4			-78°,30 min[e]	-78°, 1h	>99:1	9[e]
5		$n\text{-}C_5H_{11}CHO$	-78°,30 MIN	-78°,30 MIN -15°, 1 H	97:3[f]	88
6			-78°,30 min	-78°,30 min -40°,30 min	97:3[f]	41
7		PhCHO	-78°,30 MIN	-78°,30 MIN -30°,30 MIN	>99:1	71
8			-50°,30 min	-78°, 1 h	>99:1	40
9			-78°,30 min	-78°, 1 h	>99:1	52
10		PhCHO	0°,45 MIN	-78°,30 MIN -20°, 3 H	95:5[g]	63
11		$n\text{-}C_5H_{11}CHO$	0°,45 MIN	-78°,30 MIN -20°, 3 H	92:8[g]	55

TABLE 2. Stereoselective aldol condensations. Cyclic ketones.

Entry	Ketone	Aldehyde	Enolization	Reaction	Erythro-threo[a]	Yield%[b]
1.		PhCHO	-78°,30 MIN	-78°, 1 H	96:4	90
2.		PhCHO	[h]	-78°, 1 H -30°, 1 H	81:19	41

[a] Isomer ratios were measured by integration of well-resolved signals in the ^1H NMR spectrum. Authentic mixtures were synthesized for comparison using lithium enolates (ref.5). [b] Isolated yields. [c] Linear-branched ca 58:42 (ref.1). [d] 2,6-Lutidine was used as base instead of DPEA. [e] Triethylamine was used as base instead of DPEA. [f] Determined by ^1H-NMR and by capillary VPC analyses. [g] Determined by ^1H-NMR and by HPLC analyses. [h] The enolate from cyclohexanone tends to decompose or selfcondense under the enolization conditions (-78°, 30 min). A modified procedure was thus followed: to the mixture of cyclohexanone, benzaldehyde (2 eq.), and DPEA in methylene chloride at -78°, the solution of (1) in methylene chloride was slowly added.

NOTES AND REFERENCES :

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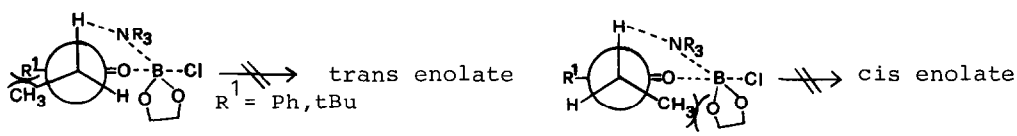
6. GENERAL PROCEDURE FOR THE ALDOL CONDENSATION: to a stirred solution of (1) (1.1 mmol) and iPr_2EtN (1.15 mmol) in methylene chloride (2.5 ml), at -78 deg C, under nitrogen, the carbonyl compound (1.0 mmol) was added dropwise. The mixture was stirred at the temperature and for the time stated (enolization), then the aldehyde (1.0 mmol non-enolizable; 1.2 mmol enolizable) was added at -78°. The reaction was then stirred at the temperature and for the time stated (reaction), and quenched at that temperature by adding pH 7-phosphate buffer. The product was extracted into methylene chloride, the extracts were dried (Na_2SO_4) and evaporated. The crude product was analyzed by ^{1}H-NMR spectroscopy and, whenever possible, by HPLC and capillary VPC for determining ratios. The compound was then isolated by flash chromatography (W.C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923 (1978)) for determining yields.

7. Propiophenone and 2,2-dimethyl-3-pentanone gave negligible yields under a variety of conditions, probably because they cannot be enolized. A possible explanation is shown below.



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   (b) T. Mukaiyama, R.W. Stevens, N. Iwasawa, Chem. Letters, 353 (1982);
   (c) Y. Yamamoto, H. Yatagai, K. Maruyama, J.C.S. Chem. Commun.,162 (1981).

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