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ALDOL REACTIONS OF METHYLKETONES USING CHIRAL BORON REAGENTS: A REVERSAL IN ALDEHYDE ENANTIOFACE SELECTIVITY

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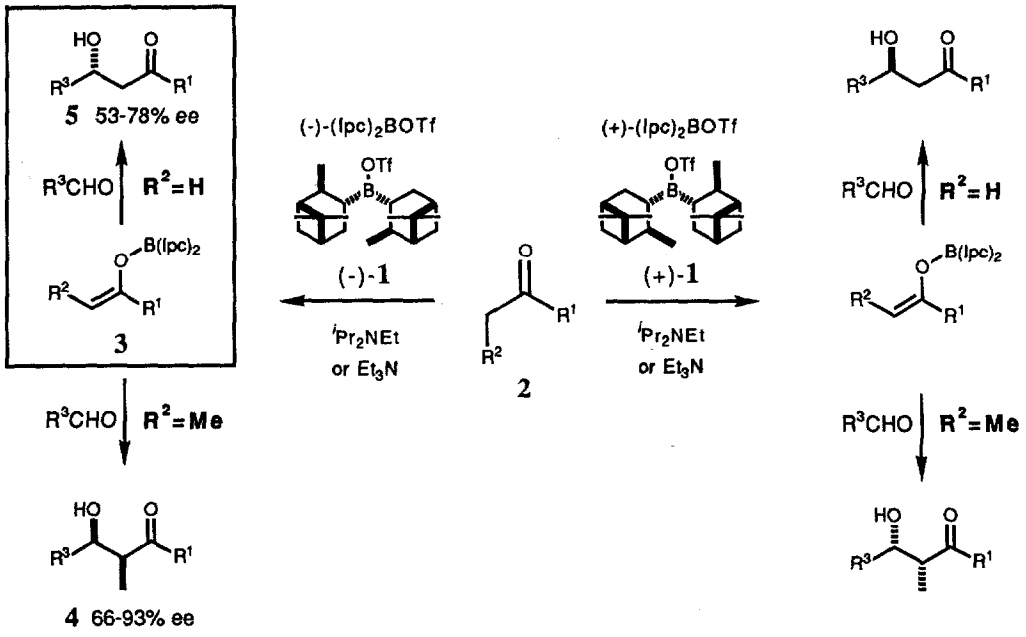
Summary: The enantioselectivity of aldol additions of methylketones to aldehydes using (-)-$(Ipc)_2BOTf$, (-)-**1**, and Pr^i_2NEt is generally lower (53-78% ee) than that for the corresponding ethylketone reaction and occurs with the *opposite* sense of aldehyde enantioface selectivity.

We recently reported a simple method for the enantioselective aldol addition of diethylketone to aldehydes to give *syn*-α-methyl-β-hydroxyketones,[1] which can also lead to useful stereocontrol in the aldol reactions of chiral ethylketones.[2] In this method, the easily prepared chiral boron triflate reagents (-)-**1** and (+)-**1**, in the presence of Pr^i_2NEt or Et_3N, give rise to both high levels of enolisation *Z*-stereoselectivity in the ketone **2** and π-face selectivity in the aldol addition of the derived boron enolate **3**, **Scheme 1**.[1,2] Using (-)-**1** for example, **2** → **4** in up to 90% ee with 90-97% diastereoselectivity for R^1=Et and R^2=Me. This chiral reagent method, therefore, provides a valuable alternative to the use of a chiral auxiliary attached to the boron enolate.[3]

Scheme 1



For some chiral auxiliary based methods, aldol addition reactions which proceed with high stereoselectivity for α-substituted enolates give little or no stereoselectivity if the α-substituent is lacking.[3,4] Therefore, it was important to examine the applicability of our reaction to methylketones.[5] Unexpectedly, we find that the aldehyde enantioface selectivity in addition of the methylketone derived enolate **3** is now *reversed, i.e.* **2** → **5** for R^2=H using (-)-**1**, relative to the ethylketone reaction.[1] The β-hydroxyketone **5** is produced with moderate levels of enantioselectivity, typically 53-78% ee.

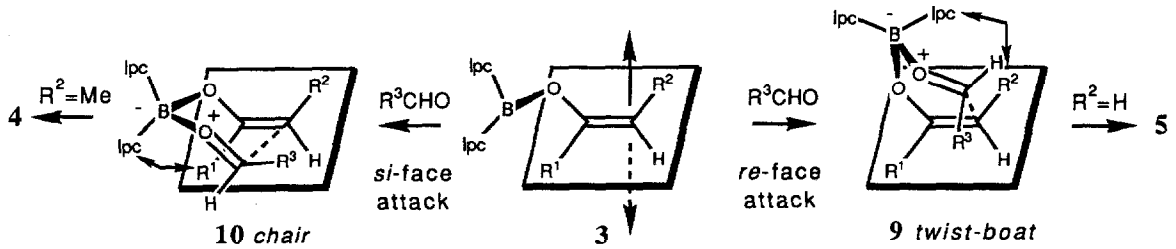
Table 1. Enantioselective aldol reactions of acetone using (-)-**1**[1,2b] and Pr^i_2NEt.

entry	aldehyde	solvent [a]	product[8]	% ee[b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	% yield[c]
1		hexane		65		34
2	CHO	CH_2Cl_2	HO O	68		61
3		PhMe		67		20
4		CH_2Cl_2[d]	**6**	73	+48.9° (3.8)	59
5	^{n}PrCHO	CH_2Cl_2	HO O **7**[e]	78	+39.1° (6.3)	68
6	PhCHO	CH_2Cl_2	HO O Ph **8**[f]	57	+40.9° (10.3)	78

[a] Enolisation at -78 → 0°C (2-5 h) followed by addition of aldehyde at -78°C and warming to 0°C (2 h); experimental conditions as previously described in ref. 1. [b] Determined by ^{1}H-NMR spectroscopy using Eu(hfc)$_3$. [c] Isolated yield after chromatography. [d] Enolisation and aldol addition performed at -78°C. [e] Configuration assigned from ref. 7a. [f] Configuration assigned from ref. 7b.

The aldol addition of acetone to simple aldehydes was first examined. Enolisation of acetone with (-)-**1**/Pr^i_2NEt was carried out in a range of solvents (dichloromethane, hexane and toluene) at -78°C, followed by addition of methacrolein, then warming to 0°C and working up the reaction in the usual way.[1] The results are shown in **Table 1**. The dichloromethane run (entry 2) gave the best result in terms of both ee and yield of the adduct **6**, such that these conditions[6] were adopted as the standard; although reasonably similar ee values were obtained in the other two solvents. When the reaction in dichloromethane was repeated at different reaction temperatures (-110°C, -78°C, and 20°C), only small changes were obtained in the product enantiomeric excess. Enolisation and aldol addition at -78°C (without warming to 0°C) gave (+)-**6** with a slightly improved 73% ee. In comparison, the corresponding reaction of diethylketone with methacrolein, mediated by (-)-**1**, gives **4** (R^1=Et, R^3=*iso*-propenyl) in 90% ee.[1] The acetone aldol was repeated using (-)-**1** with *n*-butanal to give (+)-**7** in 78% ee (entry 5), while addition to benzaldehyde gave (+)-**8** in 57% ee (entry 6). In these two cases the absolute configuration of the adduct was assigned as shown from literature data.[7,8] This means that the sense of asymmetric induction in addition to the aldehyde carbonyl group is opposite for methylketones to that obtained in the ethylketone reaction, *cf* **Scheme 1**.

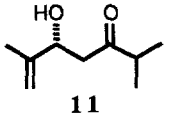
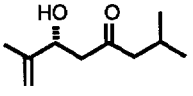
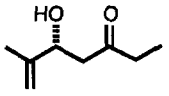
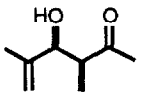
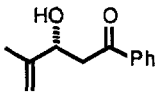
Scheme 2



The change in the aldehyde enantioface selectivity for methylketones *vs* ethylketones suggests that the mechanism of this aldol reaction cannot easily be rationalised by considering a common Zimmerman-Traxler chair model.[9,10] One possibility, as shown in **Scheme 2**, is that with the methylketone derived enolate, R^2=H, the *twist-boat* arrangement **9** is favoured[4,5a,9] in the aldol reaction as it avoids steric interactions between R^1 and a bulky Ipc group in the *chair* structure

10. The ethylketone reaction, however, favours the *chair* form **10** avoiding the more serious interaction between R^2=Me and an Ipc group in the *twist-boat* structure **9**. This then leads to opposite enantioface selectivity in the aldehyde for attack on the same π-face (top face attack=solid arrow) of the enolate **3**, which prefers to have the $(Ipc)_2B$ group tilted up out of the plane.[11] Recent *ab initio* calculations[12] on simple boron enolate aldol transition structures suggest that a twist-boat is easily accessible if there is no *Z*-substituent in the enolate, *i.e.* R^2=H in **9**. However, a more extensive theoretical analysis is still needed to appreciate the subtle controlling factors in these chiral enolate aldol reactions.[11,13]

Table 2. Enantioselective aldol reactions of methylketones with methacrolein using (-)-**1**.

entry	ketone	conditions[a]	major product[8]	regiosel.[b]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	% ee[c]	% yield[d]
1	^{i}PrCOMe	*A*	 **11**	12:1	+35.9° (3.2)	65	56
2	^{i}PrCH$_2$COMe	*B*	 **12**	>30:1	+39.0° (1.2)	53	62
3	EtCOMe	*B*	 **13**	1.8:1	+24.6° (6.8)	62	71
4	EtCOMe	*C*	 **14**[e]	4.5:1	-45.7° (4.3)	93	42
5	PhCOMe	*B*	 **15**	—	+57.9° (2.3)	61	48

[a] *A*: reaction in PhMe at -78°C using Pr^i_2NEt. *B*: reaction in CH_2Cl_2 at -78 → 0°C using Pr^i_2NEt. *C*: reaction in CH_2Cl_2 at 20°C using Et_3N. [b] Enolisation towards underlined group; isomer ratios determined by weighing isolated components after chromatographic separation. [c] Determined by ^{1}H-NMR spectroscopy using Eu(hfc)$_3$. [d] Combined yield after chromatographic isolation. [e] Syn:anti > 30:1.

We next looked at the regioselectivity of the reaction with unsymmetrical methylketones (**Table 2**). Under the standard conditions, >90% regioselectivity for reaction at the methyl position was obtained with methyl *iso*-propyl ketone and methyl *iso*-butyl ketone (entries 1 and 2). The major aldol adducts **11** and **12** were obtained in 65 and 53% ee, respectively. Methyl ethyl ketone (entry 3) gave poorer regioselectivity, despite attempts to improve the kinetic discrimination in deprotonation using more hindered amine bases. The regioselectivity could be reversed to 1:4.5 (entry 4) by using thermodynamic conditions, enolising at room temperature in CH_2Cl_2 using Et_3N, to give **14** as the major aldol product in 93% ee.

In summary, while our method gives lower levels of enantioselectivity with prochiral methylketones *vs* ethylketones, it is still comparable to other methods available[5b-c,7,14] and is easy to carry out. It also has potential value for achieving useful diastereoselectivity in the aldol reactions of chiral methylketones.[15] The change in the aldehyde enantioface selectivity for methylketones *vs* ethylketones means that the mechanistic details of this aldol process are not intuitively obvious.

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