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Application of the retroaldol reaction to asymmetric synthesis: a new concept in organic syntheses

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Abstract

Aldol **5b**, easily obtained from dihydrocarvone **6b**, reacts with organolithium and Grignard reagents leading to enantiomerically enriched alcohols **8** (ee up to 35%). Thus, aldol **5b** is a synthetic equivalent of benzaldehyde with a masked prochiral face.

The retroaldol reaction is very common in organic synthesis and is often a serious limitation during synthetic manipulations.[1] However, reversibility of the aldol reaction, which has been used as a powerful tool in organic synthesis,[2] has not, until now, been exploited in asymmetric synthesis.

In this communication we wish to report on a new approach to enantioselective synthesis of alcohols by a novel use of the retroaldol reaction. Retroaldol cleavage of enantiomerically pure β-hydroxy ketone **1** gives rise to enolate **2** and aldehyde **3** which can undergo further reactions. Following cleavage of the C–C bond in the fragmentation reaction, the two products will be held in close proximity as they are both coordinated to the same metal ion (species **I**). The enolate **2** will thus mask one of the prochiral faces of the newly formed aldehyde **3**. Addition of a second nucleophilic species to the carbonyl group should occur stereoselectively from the unmasked face leading to an enantiomerically enriched carbinol **4** (Scheme 1).

As β-hydroxy ketones with only one stereogenic centre are difficult to obtain enantiomerically pure,[1,3] we decided to prepare aldols **5** from chiral ketones **6** (Table 1). Condensation of lithium enolates of ketones **6** with benzaldehyde led to two diastereoisomeric aldols **5** detected by ^{1}H and ^{13}C NMR.[4] Lithium enolates were obtained using a procedure developed by our group[2d,6] from trimethylsilyl enol ethers[5a] of ketones **6** after cleavage performed with potassium *tert*-butoxide[6] followed by a K–Li exchange.[2d] Aldols **5a** and **5b** were thus obtained with a diastereoisomeric excess greater than 98%

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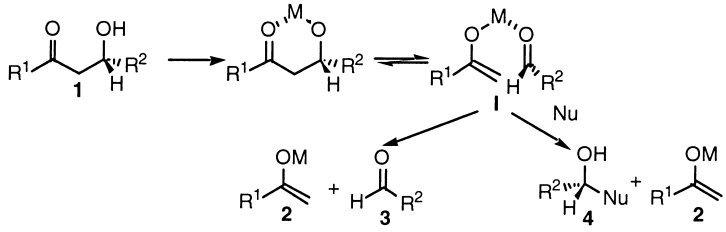
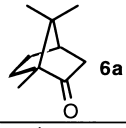
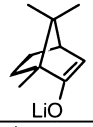
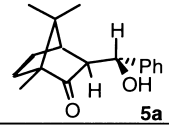
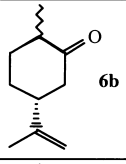
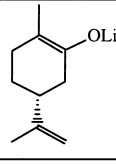
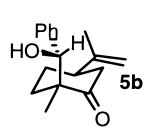
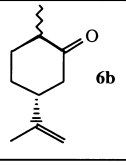
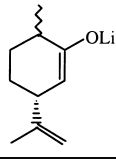
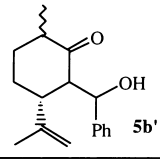


Scheme 1.

after one crystallisation (Table 1). Aldol **5a** was recently reported[7] and configurations of the two new stereogenic centres of **5b** were determined using nOe and X-ray experiments.[8] It is to be noted that when the lithium enolate of dihydrocarvone **6b** was prepared by direct deprotonation with LDA, aldol **5b′**, regioisomer of **5b**, was obtained with a de of 60% (Table 1).[9]

Table 1
Aldols **5** from chiral ketones **6**

Starting material	Lithium enolate	Product	Yield (%)[a]	De (%)[a]
 **6a**	 b	 **5a**	53 (42)	90(>98)
 **6b**	 b	 **5b**	58 (51)	95 (98)
 **6b**	 c	 **5b'**	78	60

a) In brackets, after one crystallisation. b) The lithium enolate was prepared from the potassium enolate obtained from the TMS enol ether of **6**. c) The lithium enolate was prepared from **6** and LDA.

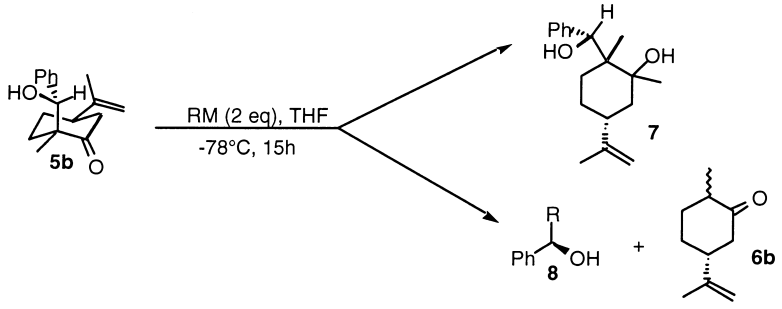
We tested the potential of aldols **5a** and **5b** as synthetic equivalents of benzaldehyde with a masked face, using organolithiums and Grignard reagents as nucleophilic species.

Reaction of aldol **5b** with methyllithium and methylmagnesium bromide led to diol **7** (one diastereomer) by a classical addition on the carbonyl group, but with bigger organometallics we were pleased to obtain enantiomerically enriched alcohols **8**, involving a retroaldolisation for the first reaction step (Table 2, Scheme 2).[10,11]

Table 2
Alcohols (*R*)-**8** by reaction of organometallics with **5b**

RM	tBuLi	nBuLi	tBuMgBr	nBuMgBr	nPrMgBr	EtMgBr
Ee %[a,b]	/	6	/	18	24	35
Yd %[a]	6	61	5	71	62	57

a) After chromatography on silicagel. b) Determined by HPLC using Daicel Chiralcel OD (see ref [10,11]).



Scheme 2.

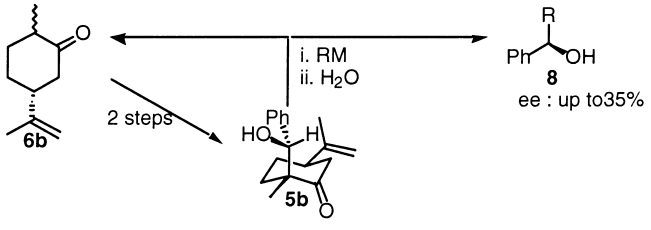
Their (*R*)-absolute configuration agrees with the predicted model Ib where the *si*-face of benzaldehyde is masked (Fig. 1). The higher ee (up to 35%), obtained using Grignard reagents, can be explained by considering the greater propensity of the magnesium atom to tether the aldehyde and enolate together.

Figure 1.

Starting from aldol **5b′** (de=60%), regioisomer of **5b**, the reaction with organometallics does not lead to the alcohols **8**, thus ruling out the intermediary of this species in the formation of **8** from **5b**.

Under the same conditions, reaction of aldol **5a** with butyllithium does not give alcohol **8** (R=Bu) but enone **9** (Fig. 1).

In conclusion, we have demonstrated that starting from dihydrocarvone **6b** we could synthesise enantiomerically enriched alcohols **8** by a novel use of the retroaldol reaction. The recovered ketone **6b** can be reused (Scheme 3).



Scheme 3.

Although the reported ees are modest, these promising preliminary results unambiguously show for the first time that enantiomerically pure aldols can be considered as a new class of carbonyl compounds with a masked face.

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4. To the silyl enol ether (5 mmol) obtained from **6a** or **6b**[5a] in THF (3 ml) was added potassium *tert*-butoxide (0.56 g, 5 mmol) in THF (2 ml) at −20°C. After 1 h, lithium bromide (1.74 g, 20 mmol) in THF (3 ml) was added and the reaction was stirred for 15 min. The mixture was cooled to −78°C and benzaldehyde (0.53 g, 5 mmol) in THF (3 ml) was added. After 5 h, water was added and the residue was purified by chromatography on silica gel leading to aldols **5a** and **5b** with a de >98% after one crystallisation from petroleum ether.
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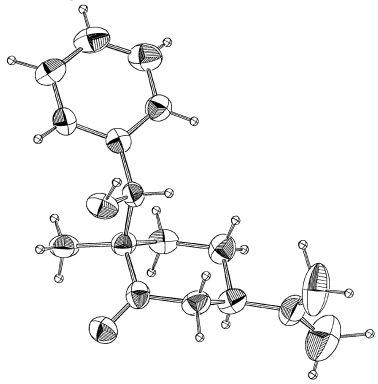
8. **5b**: Crude: Yield 58% de=95%. After crystallisation from petroleum ether: de >98%; mp: 76–77°C. $[\alpha]_D^{25}$=8.9 (*c* 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.91 (3H, s), 1.13 (2H, dt, J=4.4, 8.8), 1.73 (1H, ddt, J=4.4, 7.0, 14.8), 1.79 (3H, s), 1.81 (1H, dq, J=4.4, 8.8), 2.46 (1H, m), 2.58 (2H, dq, J=8.8, 14.8), 3.35 (OH, d, J=3), 4.71–4.82 (2H, 2s), 4.99 (1H, d, J=3), 7.21–7.27 ($5H_{arom}$, s). ^{13}C NMR ($CDCl_3$): 16.5, 21.2, 25.1, 34.2, 43.2, 45.0, 52.4, 76.0, 110.7, 127.6, 139.5, 147.8, 216.1. IR: 3438, 2934, 1686, 1644, 1598. Microanalysis for $C_{17}H_{22}O_2$: Calcd C, 79.03; H, 8.59; found: C, 78.44; H, 8.81.



X-ray analysis of **5b**

9. Two diastereomers were detected by NMR. Their absolute configurations were not determined.
10. Aldol **5b** (1.12g, 5 mmol) was dissolved in THF (5 ml) and cooled to −78°C. Then the organometallic compound (2 equiv.) was added dropwise under an argon atmosphere over 30 min. After 15 h, the mixture was hydrolysed (5 ml of water) at −78°C and the crude mixture was extracted with diethylether (4×10 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The alcohols **8** were purified by flash column chromatography on silica gel (using petroleum ether:ether, 93:7, as eluent). The ees were determined by HPLC according to Ref. 11. The ee of **8** (R=Et) was confirmed by polarimetry; found: $[\alpha]_D^{21}$=15.8 (*c* 2.12, hexane); for the (*R*)-isomer $[\alpha]_D^{11.2}$=47.0 (*c* 2.2, hexane) see: (a) Pickard, R. A.; Fenyon, J. *J. Chem. Soc*. **1914**, 1115. (b) Niwa, S.; Soai, K. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717.
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