179. Asymmetric and *'anti'*-Selective Aldolisations of Acetates and Propionates

Preliminary Communication[1])

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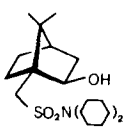
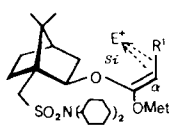
Starting from acetates **1** and propionates **6**, $TiCl_4$-mediated addition of their silylketene acetals **2** and **7** to aldehydes gave aldols **4** and **9**, respectively, with high π-face and *'anti'* differentiation (*Schemes*, and *Tables 1* and *2*). Alternation of the (*E*/*Z*)-enolate geometry led to reversed α- and β-inductions (**7**→**9b**, **8**→**10b**). Non-destructive removal of the auxiliary yielded enantiomerically pure β-hydroxycarboxylic acids **13**.

A rapidly increasing number of studies and applications attest the eminent importance of asymmetric aldol reactions in organic synthesis (*cf.* [1]). Despite these efforts, it is only very recently that enantiomerically pure acetate aldols [2] or *'anti'*-propionate aldols [2b] [3] have been obtained by direct aldolisations[2]).



(–)-X* OH



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We describe here a practical solution to this problem in extension of former work on asymmetric α-alkylations [5], α-acetoxylations [6], and α-halogenation [7] reactions all of which feature the camphor-sulfonamide derivative (–)-X*OH (and its (+)-antipode) as chiral auxiliary[3]) and which are consistent with a preferential C(α)-*Si*-face attack **I**.

Scheme 1 and *Table 1*[4]) summarize our results on π-selective aldolisations of sulfonamide-shielded isobornyl acetate **1**, readily prepared by acetylation of X*OH with AcCl/AgCN [5] (toluene, 70°, 6 h→93%, m.p. 172–174°). Addition of the corresponding lithium enolate **2** (Met = Li) to aldehydes *(Method A, Entries 1–4)* gave aldols **3** and **4** in good overall yields but with low stereodifferentiation in favor of **4** (10–14% d.e. by HPLC).

On the other hand, $TiCl_4$-promoted *Mukaiyama*-type aldolisations [9] of the *O*-silylketene acetal **2** (Met = Si(*t*-Bu)Me_2) with aromatic and aliphatic aldehydes *(Method B,*

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[2]) See [4] for an indirect asymmetric synthesis of acetate and *'anti'*-propionate aldols (*via* oxidative C–Si bond cleavage) using a camphorsultam auxiliary.

[3]) (–)-X*OH and (+)-X*OH, which are commercially available now, have been applied in asymmetric *Diels-Alder* reactions [8] and 1,4-additions of RCu [5].

[4]) All new compounds were characterized by IR, ^{1}H-NMR and MS.

Scheme 1

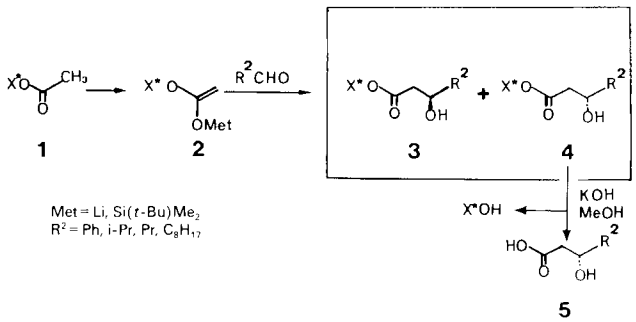


Table 1. *Asymmetric Acetate Aldolisation/Saponification* **1**→**4**(+**3**)→**5**

Entry	Series	R^2	*Method*[a])	Yield [%][b]) **3** + **4**	Ratio **3**/**4** (crude)	Yield [%][b]) of cryst. **4**	Ratio **3**/**4** (cryst.)	Yield [%] **4**→**5**	e.e. [%] **5**
1	**a**	C_6H_5	*A*	83	44:56	–	–	–	–
2	**b**	i-C_3H_7	*A*	85	45:55	–	–	–	–
3	**c**	C_3H_7	*A*	90	43:57	–		–	–
4	**d**	C_8H_{17}	*A*	82	43:57	–	–	–	–
5	**a**	C_6H_5	*B*	56(62)	8:92	45(50)	0.5:99.5	65	99
6	**b**	i-C_6H_7	*B*	47(55)	1:99	45(53)	0.5:99.5	59	98
7	**c**	C_3H_7	*B*	48(57)	8:92	42(49)	0.7:99.3	60	98
8	**d**	C_8H_{17}	*B*	51(63)	8:92	36(44)[c])	3.2:96.8[c])	66	92
9	**a**	C_6H_5	*C*	40(70)	5:95	38(68)	0.5:99.5	–	–
10	**b**	i-C_3H_7	*C*	57(71)	4:96	45(56)	2.5:97.5	–	–

[a]) *A:* 1) **1** + LiN(i-Pr)$_2$ (1.5 equiv.), THF, −78°; 2) R^2CHO, −78°, 1 h; except in *Entry 3* where LiN(i-Pr)-(cyclohexyl) (LICA) was used as the base.
B: 1) **1** + LICA (1.5 equiv.), THF, −78°; 2) Me_2(*t*-Bu)SiCl (2.2 equiv.), HMPA (2 equiv.), −78°→0°; 3) addition to R^2CHO (1.1 equiv.), $TiCl_4$ (1.2 equiv.) in CH_2Cl_2, −78°, 0.5 h.
C: 1) **1** + LiN(i-Pr)$_2$ (1.5 equiv.), THF/HMPA 3:1, −78°, 1 h; 2) Me_2(*t*-Bu)SiTf (2.2 equiv.), −78°→0°; 3) addition of $BF_3 \cdot Et_2O$ (1.2 equiv.) to mixture of crude silylketene acetal + R^2CHO (1.1 equiv.), −78°, 0.5 h.
[b]) Yields in parentheses are based on recovered ester **1**.
[c]) Non-crystalline solid.

Entries 5–8) furnished predominantly aldols **4** in 84 to 89% diastereoisomeric excess (d.e.) and in 47 to 56% yield[5]). All products **4** (except amorphous **4d**) were efficiently purified to 98.5–99% d.e. by subsequent crystallization (pentane or hexane). Nondestructive removal of the auxiliary X*OH (recovered nearly quantitatively) by saponification (1.5N KOH/MeOH, 25°, 2–6 h) gave *β*-hydroxy acids **5** in 58–66% yield. Chiroptic comparison of free acids **5** with published values[6]) and ^{1}H-NMR analyses (Eu(hfc)$_3$) [10d] of their methyl esters (CH_2N_2) revealed the depicted absolute configurations and enantiomeric purities. The sense and extent of induction remained identical when using

[5]) Yields of **3** + **4** were lowered by competitive *C*-silylation in the step **1**→**2**. This side reaction remained unaffected by the silylation conditions of *Method C*.

[6]) Observed $[\alpha]_D$ values (25°, $CHCl_3$, if not mentioned otherwise, *c* [g/100 ml]): **5a**: +14.9° (EtOH, *c* = 1.94), see [2b]. **5b**: +36.9° (*c* = 1.59), see [2b]. **5c**: +25.8° (*c* = 0.53), see [10a]. **5d**: +15.0° (*c* = 1.15), see [10b]. **9a**: −49.0° (*c* = 0.44), see [10c]. **12a** (from *Entry 11*): +20.6° (*c* = 0.46), see [10a]. **9b**: −15.3° (*c* = 0.6), see [10d]. **9c**: −5.0° (*c* = 0.2), see [10d]. **9d**: −5.9° (*c* = 0.44), see [10d]. **10b**: +9.6° (*c* = 0.31), see [10d].

$BF_3 \cdot Et_2O$ (instead of $TiCl_4$) in the absence or presence *(Method C)* of hexamethylphosphoric triamide (HMPA).

We then studied the aldol reactions of propionate **6** as depicted in *Scheme 2* and *Table 2*[4]). Addition of the lithium enolate **7** (Met = Li) to aldehydes *(Method A, Entries 11–14)* afforded mainly the *'anti'*-aldols **9** and **10** together with one minor *'syn'*-product in 84–90% overall yield. The crude product mixtures were directly analyzed by HPLC showing complete separation of the *'anti'*-isomers **9** and **10** in all cases and one peak corresponding to **11** or **12**, except in the series **e** ($R^2 = C_2H_5$) where the minor *'anti'*- and the *'syn'*-isomer(s) were inseparable from each other[7]). The *'syn'*/*'anti'*-configuration of

Scheme 2

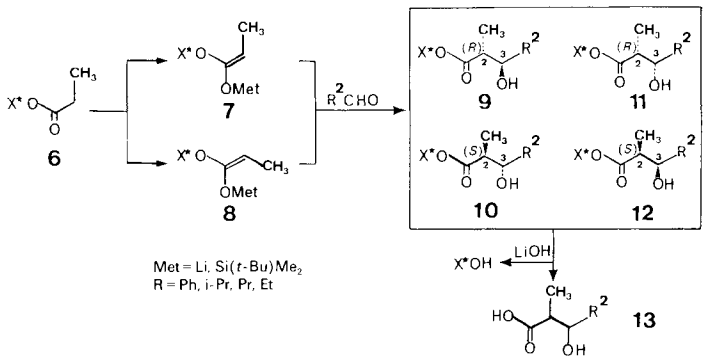


Table 2. *Asymmetric Propionate Aldolisation/Saponification* **6→9** *and* **10→13**

Entry	Series	R^2	*Method*[a])	Yield [%][b]) **9** to **12**	Ratio[c]) **9**/**10**/(**11** + **12**)	Major-product Yield [%][b]) (cryst.)	Yield [%] **13**	Config. **13**	e.e. [%] **13**
11	**a**	C_6H_5	*A*	87	41.5:33:25.5		–	–	–
12	**b**	i-C_3H_7	*A*	87	45.6:42.7:11	–	–	–	–
13	**c**	C_3H_7	*A*	90	36:39:25	–	–	–	–
14	**e**	C_2H_5	*A*	84(91)	37.3:62.7	–	–	–	–
15	**a**	C_6H_5	*B*	44(71)	77:4:19	30(53)	83	(2*R*,3*S*)	99
16	**b**	i-C_3H_7	*B*	60(84)	90.9:7.3:1.8	–	–	–	–
17	**c**	C_3H_7	*B*	50(90)	87.4:6.6:6	42(75)	83	(2*R*,3*R*)	99
18	**e**	C_2H_5	*B*	30(75)	84:16	30(75)	90	(2*R*,3*R*)	99
19	**b**	i-C_3H_7	*C*	58(85)	71:2:27	–	–	–	–
20	**b**	i-C_3H_7	*D*	57(81)	6:87.5:6.5	49(70)	80	(2*S*,3*S*)	99

[a]) *A:* 1) **6** + $LiN(i\text{-}Pr)_2$ (1.1 equiv.), THF, −78°; 2) R^2CHO, −78°, 0.5 h.
B: 1) **6** + LICA (1.5 equiv.), THF, −78°; 2) $Me_2(t\text{-}Bu)SiCl$ (2.2 equiv.), HMPA (2 equiv.), −78°→0°; 3) addition to R^2CHO (1.1 equiv.), $TiCl_4$ (1.2 equiv.) in CH_2Cl_2, −78°, 0.5 h.
C: Analogous to *A* but using $BF_3 \cdot Et_2O$ instead of $TiCl_4$.
D: 1) **6** + $LiN(i\text{-}Pr)_2$ (1.5 equiv.), THF/HMPA 3:1, −78°, 1 h; 2) $Me_2(t\text{-}Bu)SiTf$ (2.2 equiv.), −78°→0°; 3) addition of $BF_3 \cdot Et_2O$ (1.2 equiv.) to mixture of crude silylketene acetal + R^2CHO (1.1 equiv.), −78°, 0.5 h.

[b]) Yields in parentheses are based on recovered ester **6**.

[c]) Usually, only one *'syn'*-product was isolated which was either identified as **12a**, **11b**, or not assigned (series **c**); product **9e** was inseparable from its *'syn'*-isomer(s).

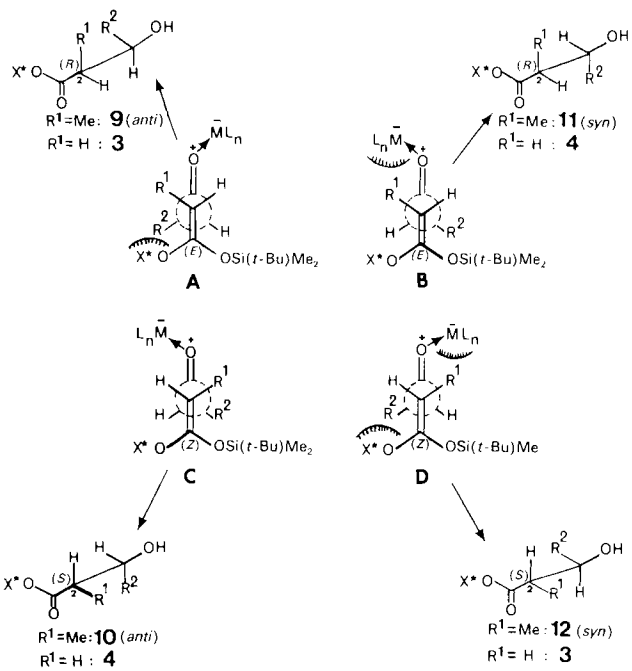
[7]) In *Entry 11*, a fourth, unidentified product was formed in 0.6% yield.

the isolated (flash chromatography) diastereoisomers was readily assigned on examination of the H–C(2) signal in ^{1}H-NMR [1b] (2.45–2.80 ppm) which shows a vicinal coupling constant $J(2,3) = 7.0$–7.5 Hz for the *'anti'*-products **9b**, **10b**, **9c**, **10c**, and **9e** *vs.* a coupling constant $J(2,3) = 2.5$–3.0 Hz for the *'syn'*-products **12a** and **11b**.

Kinetically controlled deprotonation [11] of propionate **6** with LiN(i-Pr)(cyclohexyl) followed by enolate *O*-silylation gave a (*tert*-butyl)dimethylsilylketene acetal to which we assign the (*E*)-configuration **7**. Treatment of **7** with aldehyde/$TiCl_4$ *(Method B, Entries 15–18)* furnished the corresponding aldols with greatly improved *'anti'*/*'syn'* ratios (4:1 to 55:1) and (2*R*)-*'anti'*/(2*S*)-*'anti'* ratios (13:1). The major *'anti'*-aldols **9** were readily purified to 99% d.e. by flash chromatography and crystallization. Nondestructive cleavage of the auxiliary from the aldol was accomplished without α-epimerization by reduction with $LiAlH_4$ (*e.g.* **11b**→(2*S*,3*S*)-2,4-dimethyl-1,3-pentadiol) or, more interestingly, by mild hydrolysis with 1.6 N LiOH (40 equiv. in THF/H_2O 1:1.2, r.t., 9–14 days) to give β-hydroxy acids **13** in 83–90% yield). The tabulated absolute configurations of **13** follow from chiroptic comparison with published values[6]). Acids **13** were shown to be ⩾ 99% enantiomerically pure by measuring the MeO signals of their methyl esters in the ^{1}H-NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ [10d].

Two further trends are evident from the data in *Table 2*. First, the use of $BF_3 \cdot Et_2O$ *(Entry 19)* leads to a decrease of the *'anti'*/*'syn'* ratio as compared to that of $TiCl_4$ *(Entry 16)*. Second, the (*Z*)-ketene acetal **8** was obtained by deprotonation of **6** under thermodynamic control [11]; **8** furnished aldol **10b** with excellent *'anti'* selection even under the influence of $BF_3 \cdot Et_2O$ *(Method D, Entry 20)*. Accordingly, each of the enantiomeric

Scheme 3



(2*R*,3*R*)- or (2*S*,3*S*)-hydroxy acids **13** may be prepared in 99% e.e. from the same precursor depending on the (*E*)/(*Z*)-geometry of the enolate intermediate.

The observed stereoselectivities may be rationalized on inspection of the following 'open' transition state topologies [3a] **A**–**D** *(Scheme 3)*. In analogy to former C(α)-*Si*-face-selective electrophilic attack to (*E*)-'enolates' **I** (Met = Li or Si Me_3) [5–7], we assume a synperiplanar disposition of the C–OMet/(O)C–H bonds and an aldehyde approach from the less shielded olefinic back face. In line with previous suggestions, we assume a *Lewis*-acid coordination with the aldehyde O-atom *'cis'* to its H-atom [3a] which, due to ML_n/R^1 repulsion, destabilizes transition states **B** and **D**. In the propionate series ($R^1 = CH_3$), we suppose this nonbonding interaction to override that between R^2 and OX* which disfavors transition states **A** and **D**. Thus, the preferences **A** > **B** and **C** > **D** seem to govern the *'anti'*-selective formation of aldols **9** or **10** from the (*E*)- or (*Z*)-ketene acetals **7** or **8** (Met = Si(*t*-Bu)Me_2), respectively. For the acetate aldolisations (R^1 = H), the R^1/ML_n repulsion becomes irrelevant, and it is the *gauche* interaction R^2/OX* which disfavors **A** = **D** over **B** = **C**. Accordingly, aldols **4** appear to be formed *via* the latter transition state. In agreement with this postulate, acetate aldolisations **1**→**2**→**4** display similar inductions with $BF_3 \cdot Et_2O$ or $TiCl_4$, whereas the nature of the *Lewis* acid is critical in the propionate series **6b**→**7b**→**9b** (*Entries 16* and *19*). On comparing the aldolisation of the (*E*)- (**7**→**9b**) *vs.* that of the (*Z*)-ketene acetal (**8**→**10b**), the latter reveals a higher *anti* selection consistent with the preferences **A** > **B** and **C** ≫ **D** (*Entries 19* and *20*).

In practical terms we believe that the above aldolisations compare favorably with alternative [2] [3] or less direct[2]) approaches to enantiomerically pure acetate aldols and *'anti'*-propionate aldols. This work highlights once more the versatility of simple camphorsulfonic-acid-derived auxiliaries in asymmetric synthesis [5–7].

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