Stereocontrol in Aldol Addition – Synthesis of *syn* and *anti* 3-Hydroxy Aldehydes

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Abstract: *syn* 3-Hydroxy aldehydes were obtained with a high level of stereoselectivity by aldol addition in the presence of $TiCl_4$. The corresponding *anti* 3-hydroxy aldehydes were obtained by thermodynamic equilibration in the presence of titanium(IV) alkoxides.

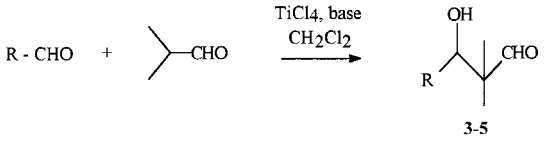
Key words: stereoselective aldol addition, syn 3-hydroxy aldehydes, thermodynamic equilibration, *anti* 3-hydroxy aldehydes

The aldol addition is one of the most important methods for forming carbon–carbon bonds, and is extensively utilized for the construction of 1,3-oxygen functionalities.[1] While the active hydrogen component can consist of either ketones[2] or carboxylic derivatives,[3] very little is known concerning aldol addition of enolized aldehydes to other aldehydes. No method is as yet known for the direct diastereoselective aldol addition of aldehydes.[4] Corey and Enders have published the reaction of metalated *N*,*N*-dimethylhydrazones with carbonyl compounds giving 3-hydroxy aldehydes which were obtained without stereoselectivity.[5] Recently, we have described for the first time both diastereoselective self-addition of aldehydes and a mixed aldol reaction between two different aldehydes in the presence of $TiCl_4$ and base.[6]

Aldehydes form complexes in the presence of Lewis acids,[7] and these complexes resist aldol addition, as is observed upon the reaction of ketones and aldehydes.[8] Lewis acid complexes of aldehydes are stable up to 0°C. However, an aldol addition is observed upon the addition of base. The temperature at which the reaction takes place strongly depends on the substrate and base used. By working with strong bases such as TMEDA or DABCO, the reaction can be executed at –50°C (entry 3, Scheme 1). No aldol addition is observed at –50°C in the presence of triethylamine as base. Complete conversion occurs only at –10°C (entries 1 and 2, Scheme 1). Aldol condensation and acetalization were observed at room temperature.[9,10]

Equimolar amounts of both base and Lewis acid are necessary for complete conversion. This result is in sharp contrast to what has been previously observed upon the reaction of aldehydes and ketones in the presence of Lewis acids. Catalytic amounts of $TiCl_4$ are necessary for this complete stereoselective conversion to their *syn* aldols.[8]

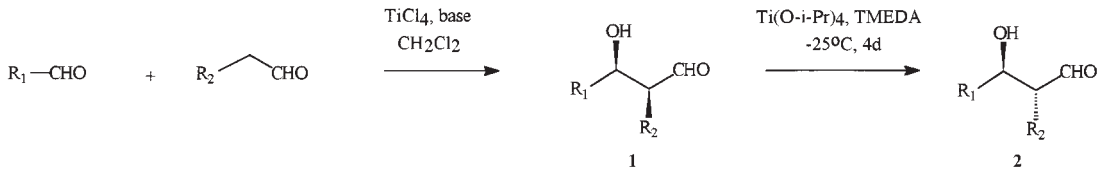
Chemoselectivity was observed in the aldol addition between two different aldehydes. Lieben's rule is followed reacting primary and secondary aldehydes.[11] A complex mixture, with the aldol **1c** as the major product is obtained if one reacts an equimolar mixture of propanal with 2-methylpropanal. One overcomes this problem by reacting an excess (4 equivalents) of pre-$TiCl_4$ complexed active hydrogen primary aldehyde (i.e. propanal) with one equivalent of the carbonyl compound (entry 4, Scheme 1). Tertiary aldehydes (i.e. 2,2-dimethylpropanal) are not reactive enough to give the expected aldols.



3-5

Entry	R	Method/Temp °C	Compound	Yield (%)
1	Et	A/–30	**3**	65
2	i-Pr	A/–25	**4**	72
3	Ph	A/–30	**5**	69

Scheme 2



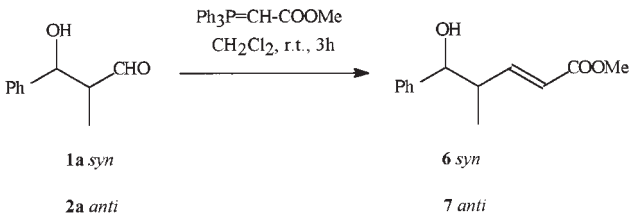
1 **2**

Entry	R_1	R_2	Method/Temp °C	Compound	Yield (%)[a]	Ratio[c] *synlanti*	Compound	Yield (%)[d]	Ratio[c] *synlanti*
1	Ph	Me	B/–10	**1a**	72	97 : 3	**2a**	61	7 : 93
2	Ph	Et	B/–10	**1b**	78	>98 : <2	**2b**	67	5 : 95
3	Et	Me	A/–50	**1c**	84	96 : 4	**2c**	87	11 : 89
4	i-Pr	Me	C/–20	**1d**	49[b]	>98 : <2	**2d**	58	9 : 91

[a] Isolated yields.
[b] Based on the carbonyl componend.
[c] Determined in crude products by ^1H and ^{13}C NMR.
[d] Based on pure *syn* hydroxy aldehyde.

Scheme 1

High *syn* stereoselectivity of the 3-hydroxy aldehydes were observed in all examples [96:4]. The stereoselectivity is observed to be independent of the solvent or base. No equilibration to the thermodynamically more stable *anti* product has been observed under these conditions. The relative *syn* configuration of all products was determined by analysis of coupling constants of the ^{1}H NMR spectra and the data of the ^{13}C NMR spectra. The position and the value of the coupling constants of the aldehyde protons are very characteristic for the relative configuration of the obtained aldols [$\delta_{syn} < \delta_{anti}$ and J_{syn} (0.8–1.0 Hz) < J_{anti} (1.6–2.0 Hz)]. For further identification, the 3-hydroxy aldehydes **1a** and **2a** were reacted with methyl (triphenylphosphoranylidene)acetate to give the expected α,β-unsaturated carboxylic methyl esters **6** and **7**. The physical data (^{1}H and ^{13}C NMR) are in agreement with data reported in the literature (Scheme 3).[12]



Scheme 3

The *anti* 3-hydroxy aldehydes were obtained by equilibration of the corresponding *syn* aldols. Known procedures for this equilibration, i.e. in the presence of $MgBr_2$[13] or titanium ate complexes,[14] were not successful. However, equilibration was achieved by using catalytic amounts of titanium(IV) alkoxides in the presence of base. Best results were obtained by using Ti(O-*i*-Pr)$_4$, a typical Meerwein–Ponndorf catalyst, in the presence of base. By using Ti(O-*t*-Bu)$_4$ or Ti(OEt)$_4$ no equilibration was observed. Complete conversion to the expected *anti* 3-hydroxy aldehydes was carried out by treating *syn* 3-hydroxy aldehydes with 1 mol% titanium(IV) isopropoxide at –20 °C in the presence of TMEDA. The *anti*-configuration was

Table. Spectral Data of Compounds **1–5**

Product	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (CI) *m/z* (%)
1a	1.08 (d, 3 H, *J* = 7.3), 2.69 (ddq, 1 H, *J* = 1.1, 3.9, 7.3), 5.25 (d, 1 H, *J* = 3.8), 7.23 (m, 5 H arom.), 9.79 (d, 1 H, *J* = 1.1)	7.4, 53.0, 72.4, 125.8, 127.7, 128.4, 140.9, 204.44	182 (28), 164 (100), 147 (41)
1b	0.83 (tr, 3 H, *J* = 7.7), 1.4–1.8 (m, 2 H), 2.57 (ddtr, 1 H, *J* = 2.0, 4.5, 5.1), 5.05 (d, 1 H, *J* = 5.1), 7.35–7.35 (m, 5 H arom), 9.69 (d, 1 H, *J* = 2.0)	12.0, 17.6, 60.1, 73.0, 126.6, 127.6, 128.6, 140.9, 205.0	196 (40), 178 (100), 161 (41)
1c	1.07 (tr, 3 H, *J* = 7.3), 1.23 (d, 3 H, *J* = 7.3), 1.53 (dq, 2 H, *J* = 3.2, 7.3), 2.48 (ddq, 1 H, *J* = 0.8, 5.5, 7.3), 4.01 (ddq, 1 H, *J* = 3.3, 5.3, 7.9), 9.71 (d, 1 H, 0.8)	8.9, 10.3, 27.2, 50.8, 71.6, 205.7	232 (59), 215 (35), 134 (100), 116 (4)
1d	0.89 (d, 3 H, *J* = 6.7), 0.94 (d, 3 H, *J* = 6.7), 1.02 (d, 3 H, *J* = 7.3), 1.72 (dsp, 1 H, *J* = 6.7, 8.5), 2.59 (ddq, 1 H, *J* = 0.8, 3.2, 7.3), 3.76 (dd, 1 H, *J* = 3.2, 8.5), 9.73 (d, 1 H, *J* = 0.8)	8.3, 18.6, 19.9, 29.7, 50.5, 76.6, 205.3	
2a	0.93 (d, 3 H, *J* = 7.3), 2.77 (ddq, 1 H, *J* = 2.0, 8.6, 7.3), 4.81 (d, 1 H, *J* = 8.6), 7.23 (m, 5 H arom.), 9.84 (d, 1 H, *J* = 2.0)	11.0, 53.2, 75.5, 126.6, 128.3, 128.6, 141.5, 204.9	
2b	0.83 (tr, 3 H, *J* = 7.4), 2.58 (ddtr, 1 H, *J* = 2.9, 4.5, 8.5), 4.84 (d, 1 H, *J* =8.5), 7.33 (m, 5 H arom.), 9.78 (d, 1 H, *J* = 2.9)	11.3, 19.6, 60.3, 74.1, 127.0, 128.2, 128.5, 141.7, 205.1	
2c	1.10 (tr, 3 H, *J* = 7.5), 1.22 (d, 3 H, *J* = 7.3), 1.67 (dq, 2 H, *J* = 3.5, 7.3), 2.37 (ddq, 1 H, *J* = 1.6, 7.7, 8.7), 3.75 (ddq, 1 H, *J* = 3.7, 7,3, 8.1), 9.76 (d, 1 H, *J* = 1.5)	9.3, 13.2, 27.7, 51.4, 73.5, 205.9	
2d	0.90 (d, 3 H, *J* = 6.7), 0.95 (d, 3 H, *J* = 6.7), 1.12 (d, 3 H, *J* = 7.3), 1.69 (dsp, 1 H, *J* = 2.0, 6.7), 2.57 (ddq, 1 H, *J* = 2.0, 7.3, 9.1), 3.43 (dd, 1 H, *J* = 2.0, 9.1), 9.77 (d, 1 H, *J* = 2.0)	12.8, 18.7, 19.9, 30.1, 50.6, 79.7, 205.8	
3	1.03 (tr, 3 H, *J* = 7.3), 1.05 (s, 3 H), 1.09 (s, 3 H), 1.33 (ddq 1 H, *J* =3.5, 7.5, 10.7), 1.51 (ddq, 1 H, *J* = 2.2, 3.5, 7.4), 3.62 (dd, 1 H, *J* = 2.1, 10.6), 9.53 (s, 1 H)	11.0, 16.5, 19.0, 24.2, 50.5, 76.6, 206.8	
4	0.9 (d, 3 H, *J* = 6.9), 0.97 (d, 3 H, *J* = 6.9), 1.88 (dsp, 1 H, *J* = 4.1, 6.9), 3.55 (d, 1 H, *J* = 4.1), 9.63 (s, 1 H)	17.2, 18.6, 19.9, 21.7, 29.9, 50.5, 80.3, 206.8	
5	0.93 (s, 3 H), 1.09 (s, 3 H), 4.82 (d, 1 H, *J* = 0.8), 7.3 (m, 5 H arom.), 9.63 (d, 1 H, *J* = 0.8)	15.8, 19.9, 50.6, 77.4, 127.5, 127.9, 128.5, 139.8, 206.6	196 (100), 178 (8)

established by the described analysis of coupling constants of ^{1}H NMR with the characteristic shifts of the signals in the ^{13}C NMR spectrum.

^{1}H NMR spectra were recorded on a Bruker WP 200 SY and Varian Unity 500; the ^{13}C NMR spectra were obtained at 75 MHz on a Varian GEMINI 300 instrument in $CDCl_3$ (unless otherwise stated); chemical shifts are related to TMS. Low-resolution impact mass spectra: GC-MS Datensystem HP 5985 B. Microanalyses: Carlo Erba autoanalyzer 1106.
Stereochemical assignments of all products were determined by analysis of ^{1}H NMR coupling constants, via homodecoupling techniques.

(2*RS*,3*RS*)-3-Hydroxy-2-methylpentanal (1c);[15] Method A:
Propanal (0.72 mL, 10.0 mmol) was dissolved in CH_2Cl_2 (20 mL) with TMEDA (3.02 mL, 20.0 mmol). This mixture was cooled to –78 °C. $TiCl_4$ (2.19 mL, 20.0 mmol) was carefully added at this temperature under inert conditions. The resulting yellow-brown mixture was stirred for further 3 h at –40°C, after which water was added (30 mL) and the resulting emulsion extracted with Et_2O (100 mL) and water (30 mL) until neutral. The organic layer was separated, dried (Na_2SO_4), filtered and evaporated in vacuo. The pure 3-hydroxy aldehyde **1c** was separated by flash chromatography using hexane/EtOAc (90:10) as eluent (Table).

(2*RS*,3*SR*)-3-Hydroxy-3-phenyl-2-methylpropanal (1a); Method B:
Propanal (0.72 mL, 10.0 mmol) was dissolved with Et_3N (2.78 mL, 20.0 mmol) in CH_2Cl_2 (20 mL); the solution was cooled to –78 °C. $TiCl_4$ (2. 19 mL, 20.0 mmol) was carefully added at this temperature under inert conditions. Benzaldehyde (1.02 mL, 10.0 mmol) was added at –78 °C and the temperature was raised to –10°C. The yellow-brown emulsion was stirred for a further 2 h at this temperature. Workup is as described in Method A (Table).

(2*RS*, 3*SR*)-3-Hydroxy-2,4-dimethylpentanal (1d);[16] Method C:
Propanal (2.88 mL, 40.0 mmol) was dissolved with TMEDA (6.04 mL, 40.0 mmol) in CH_2Cl_2 (40 mL). The solution was cooled to –78 °C and $TiCl_4$ (4.37 mL, 40.0 mmol) was carefully added under inert conditions. The resulting brown solution was stirred for a further 30 min at this temperature and 2-methylpropanal (0.91 mL, 10.0 mmol) was added. The temperature was raised to –20°C and the dark brown solution was stirred for further 12 h at this temperature. Workup as described in Method A (Table).

(2*SR*,3*SR*)-3-Hydroxy-3-phenylpropanal (2a); Typical Procedure for Equilibration:
syn 3-Hydroxy aldehyde **1a** (328 mg, 2.0 mmol) was dissolved in CH_2Cl_2 (20 mL) and then TMEDA (0.30 mL, 2.0 mmol) was added. The solution was cooled to –60°C and Ti(O-*i*-Pr)$_4$ (6 μL, 0.02 mmol) was added. The temperature was raised to –20°C and the light-yellow solution was allowed to stand at this temperature for 4 d. The *anti* 3-hydroxy aldehyde **2a** was isolated by flash chromatography using hexane/EtOAc (9:10) as eluent (Table).

Methyl (*E*)-(4*RS*,5*SR*)-5-Hydroxy-4-methyl-5-phenylpent-2-enoate (6):[12]
The *syn* 3-hydroxy aldehyde **1a** (493 mg, 3.0 mmol) was dissolved in CH_2Cl_2 (20 mL). Methyl (triphenylphosphoranylidene)acetate (2.00 g, 6.0 mmol) was added. No aldehyde **1a** could be detected after stirring for 3 h at r.t. The resulting pentenoate **6** was purified by flash chromatography using hexane/*i*-PrOH (95:5) as eluent; colorless oil; yield: 0.48 g (73%).

$C_{13}H_{16}O_3$	calcd	C	70.89	H	7.32
(220.27)	found		71.13		6.89

^{1}H NMR (300 MHz): δ = 1.08 (d, J = 6.8 Hz, 3 H), 1.90 (d, J = 3.1 Hz, 1 H), 2.72 (ddq, J = 1.2, 5.7, 6.9 Hz, 1 H), 3.71(s, 3 H), 4.67 (dd, J = 2.8, 5.5 Hz, 1 H), 5.77 (dd, J = 1.2, 15.8 Hz, 1 H), 6.44 (dd, J = 7.5, 15.8 Hz, 1 H), 7.2–7.4 (m, 5 H, arom.).
^{13}C NMR (76 MHz): δ = 13.9, 43.6, 51.4, 76.7, 121.2, 126.3, 127.9, 128.2, 142.0, 150.7, 166.9.

Methyl (*E*)-(4*SR*,5*SR*)-5-Hydroxy-4-methyl-5-phenylpent-2-enoate (7):[12]
The *anti* product **7** was obtained by the same procedure described above, using the corresponding *anti* 3-hydroxy aldehyde **2a** as starting material.

$C_{13}H_{16}O_3$	calcd	C	70.89	H	7.32
(220.27)	found		70.62		6.92.

^{1}H NMR (300 MHz): δ = 0.93 (d, J = 6.9 Hz, 3 H), 1.96 (d, J = 3.0 Hz, 1 H), 2.68 (ddq, J = 1.0, 6.9, 7.3 Hz, 1 H), 3.74 (s, 3 H), 4.52 (dd, J = 3.0, 7.5 Hz, 1 H), 5.90 (dd, J = 1.0, 15.8 Hz, 1 H), 7.09 (dd, J = 8.1, 15.8 Hz, 1 H), 7.2–7.4 (5 H arom.).
^{13}C NMR (76 MHz): δ = 16.1, 44.4, 51.5, 77.9, 121.8, 126.6, 127.8, 128.4, 142.2, 150.8, 166.9.

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