A stereoselective and novel approach to the synthesis of 1,3-diols: simple control of diastereoselectivity

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Complete control of simple diastereoselectivity in the synthesis of 1,3-diols was realized through the use of a one-pot aldol addition and reduction process.

The diastereoselective synthesis of *syn* and *anti* 1,3-diols is currently of considerable interest, as these synthons are frequently found in a variety of polyketide natural products. Those diols with two chemically distinct hydroxy groups are of particular interest, as they are suitable building blocks for further stereoselective transformations. Multistep and more particular syntheses were found in the literature (hydrosilylation[1] or alkylmagnesation[2] of suitable alkenes, oxidative cleavage of double bonds,[3] reductive rearrangement of alkenyl acetals[4]). Moreover there are only a few examples of procedures for synthesising *anti* diols.[5]

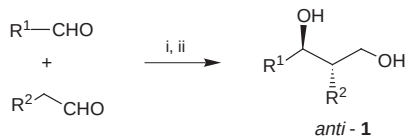
Herein, we describe a simple and more general one-pot procedure for the synthesis of both *syn* and *anti* 1,3-diols by the utilization of titanium Lewis acids. Our studies on diastereoselective aldol additions in the presence of titanium Lewis acids have outlined a new series of highly regio-[6] and stereoselective reactions.[6,7] Very recently, we described the stereoselective aldol addition of aldehydes with enolizable aldehydes in the presence of titanium(IV) chloride.[7] The reactions were accomplished with the aid of an amine base. Surprisingly, substituting a titanium(IV) alkoxide as a base resulted in complete reduction of the intermediate β-hydroxy aldehydes when used in a one-pot procedure (Scheme 1).

Importantly, equimolar amounts of titanium(IV) alkoxides were added to a mixture of each starting aldehyde and 1 equiv. titanium(IV) chloride. When using a chloroisopropoxytitanium agent [*i.e.* $ClTi(OPr^i)_3$, $Cl_2Ti(OPr^i)_2$ or $Cl_3Ti(OPr^i)$] in place of both titanium(IV) chloride and the titanium(IV) alkoxide no reactions occurs; neither aldol additions nor reduction processes are observed.‡

Reactions were carried out in toluene or CH_2Cl_2; when using oxygen-containing solvents (Et_2O, THF) this described aldol addition-reduction sequence failed to occur.

The reaction mechanism is thus likely to be very similiar to a Meerwein–Ponndorf reduction. No reduction was observed by using tertiary titanium(IV) alkoxides [*e.g.* titanium(IV) alkoxides derived from from Bu^tOH or BINOL]. Thermodynamic equilibration occurs during the reduction process. The isolated 1,3-diols were formed with a high degree of *anti* selectivity (entries 1–4, Table 1). Similar observations were made in catalytic equilibration processes of hydroxy aldehydes.[7]

Utilizating the $TiCl_4/Ti(OPr^i)_4$ system at low temperature (−78 °C) only equilibration of the formed 3-hydroxy aldehydes is observed, whereas at higher temperatures (0–10 °C) an additional reduction process to the corresponding diols takes place.

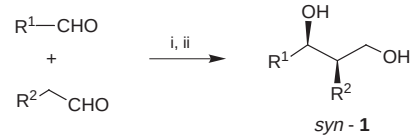


Scheme 1 *Reagents and conditions*: i, $TiCl_4$, CH_2Cl_2, 5 °C; ii, $Ti(OPr^i)_4$

Table 1 Diastereoselective synthesis of 1,3-diols

Entry	R^1	R^2	Method	Compound	Yield[a] (%)	Ratio[b] *syn*/*anti*
1	Ph	Me	A	**1a**[c]	73	9/91
2	Ph	Et	A	**1b**[d]	68	12/88
3	Et	Me	A	**1c**[e]	81	13/87
4	Pr^i	Me	A	**1d**[f]	48	15/85
5	Ph	Me	B	**1a**[c]	81	92/8
6	Ph	Et	B	**1b**[d]	72	90/10
7	Et	Me	B	**1c**[g]	71	86/14
8	Pr^i	Me	B	**1d**[h]	43	92/8

[a] Isolated yields. [b] Determined for the crude products by ^1H and ^{13}C NMR spectroscopy. Method A: $Ti(OPr^i)_4$ was added to a mixture of 1 equiv. of $TiCl_4$ and 1 equiv. of the corresponding starting aldehyde (ref. 5). (Scheme 1). Method B: the β-hydroxy aldehydes were synthesized by a literature procedure (ref. 7). After 16 h, 1 equiv. of $LiAlH_4$ was added to the crude reaction mixture (Scheme 2). [c] Ref. 8. [d] Ref. 2. [e] Ref. 1 and 12. [f] Ref. 11. [g] Ref. 1 and 9. [h] Ref. 10.



Scheme 2 *Reagents and conditions*: i, $TiCl_4$, base, −78 °C; ii, $LiAlH_4$

Reversal and thus complete control of the simple diastereoselectivity using this one-pot aldol addition-reduction sequence was realized through the synthesis of the corresponding *syn* 1,3-diols. This was achieved by reduction of the crude aldol reaction mixture[7] with $LiAlH_4$. The 1,3-diols thus obtained were isolated with a high degree of *syn* selectivity (see entries 5–8, Table 1 and Scheme 2).

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Notes and References

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‡ *General procedure* for **1a**: propanal (0.72 ml, 10.0 mmol) and benzaldehyde (1.02 ml, 10.0 mmol) were dissolved in CH_2Cl_2 (20 ml) under inert conditions. $TiCl_4$ (1.1 ml, 10.0 mmol) was added and the solution was cooled to −10 °C. After 30 min at this temperature, $Ti(OPr^i)_4$ (1.5 ml, 5.0 mmol) was carefully added and the solution was stirred for further 16 h at 5 °C, after which water was added (30 ml) and the resulting emulsion filtrated through silica gel–sand. The filtrate was extracted with Et_2O (100 ml) and brine (30 ml) until neutral. The organic layer was separated, dried (Na_2SO_4), fitrated and evaporated *in vacuo*. The pure *anti* 1,3-diol **1a** was separated by flash chromatography using hexane–EtOAc (80:20) as eluent.

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