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Stereocontrol in One-Pot Syntheses of 1,3-Diols

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Abstract: Titanium mediated aldol addition reduction sequence is described for the synthesis of stereodefined 1,3-diols. Diastereochemical control is surprisingly achieved through the careful selection of starting materials used.
Keywords: aldol reaction, reduction, stereocontrol, diols.

INTRODUCTION

Stereogenic carbon-carbon bond formation processes are of great interest in stereoselective synthesis. Sequences of adjacent stereogenic centers are of particular interest, because they are important precursors in polyketide natural product synthesis. Several methods have been developed to obtain such stereodefined sequences and stereoselectivities in high yields and in a suitable manner.[1] Most of the previously described methods are multistep transformations.[2] Recent work has been published dealing with the tandem-aldol Tishchenko reaction. High stereoselectivities were reported; lithium enolates give the 1,2-*syn*-1,3-*anti* diols[3], samarium promoted reactions yield the 1,2-*anti*-1,3-*anti* diols (by utilization of acyclic ketones)[4] and titanium catalyzed reactions yield the corresponding 1,2-*anti*-1,3-*anti* diols.[5] However, with access to only one possible isomer and with the loss of one equivalent of the starting aldehyde, this method is not a flexible stereo-selective reaction. Examples of boron-mediated one-pot aldol-reduction sequences have also been published for the synthesis of typical polyketide fragments. However, the approach to only one of the possible isomers was described.[6]

RESULTS AND DISCUSSION

We describe herein a very simple and flexible titanium-mediated approach to defined stereotriades. The starting point is based on the strategy of a Lewis-acid-mediated aldol addition of unactivated carbonyl compounds. We have recently demonstrated the applicability of this transformation with several examples.[7]

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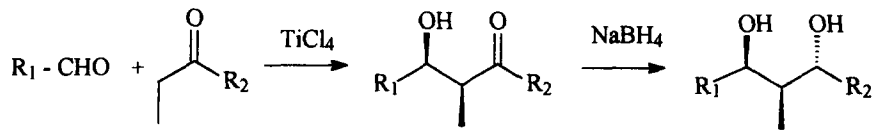
Aldehydes react with ketones in the presence of substochoimetric amounts of titanium(IV) chloride to give the aldol products **1a** (R^1 = Ph, R^2 = Et) and **1b** (R^1 = R^2= Me) in high yields and high degree of *syn*-stereoselectivity (Scheme 1).

Subsequent one-pot reduction of the crude reaction mixture with $LiAlH_4$, DIBAlH or CaH_2 is unsuccessful. This is in contrast to what is observed with reductions of $TiCl_4$ -complexed ß-dicarbonyl compounds[8] and is perhaps due to the reducing agents not „recognizing" the keto group as a carbonyl function under these reaction conditions.



1 **2**

Scheme 1

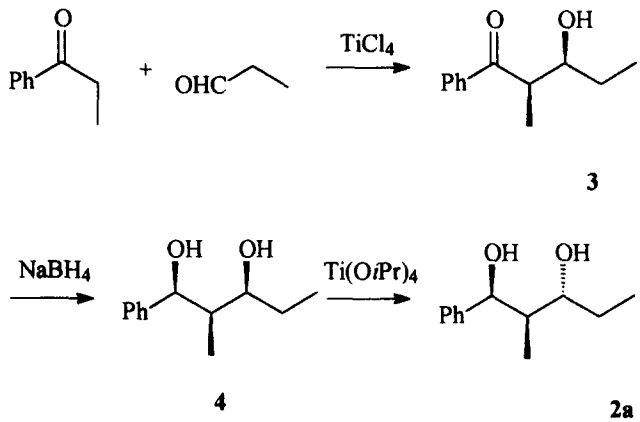
Furthermore, use of a large excess of reducing agents does not lead to a product arising from a reduction process. 1,2-diols of the starting aldehydes were isolated, indicating a McMurry-like carbonyl-coupling process.[9] However, sodium borohydride reduction of the crude aldol addition mixture did in fact lead to the desired diols with a high degree of stereoselectivity. It is assumed that $TiCl_4$ reacts with $NaBH_4$ to give borane - which is the active reducing agent.[10] Similiar results have been obtained in reduction processes of carboxylic acids derivatives using the $TiCl_4$ / $NaBH_4$- or BF_3 / $NaBH_4$-system.[11] Thus, one obtains with this one-pot sequence the 1,2-*syn*-1,3-*anti* diol **2a** and even with the aliphatic series the diol **2b** in high stereoselectivity (Scheme 1). It is necessary to work at least with 50 mol% of $TiCl_4$ to obtain the diols in high yields. Catalytic versions with substoichiometric amounts of $TiCl_4$ didn't lead to the yields shown in Table 1.

Table 1. Stereoselectivity of the One-Pot Aldol-Addition-Reduction Reaction

entry	compound	R^1	R^2	yield (%)	ds (%)[a]
1	**2a**[3]	Ph	Et	72	83
2	**2b**[16]	Me	Me	58	84
3	**4**			62	91

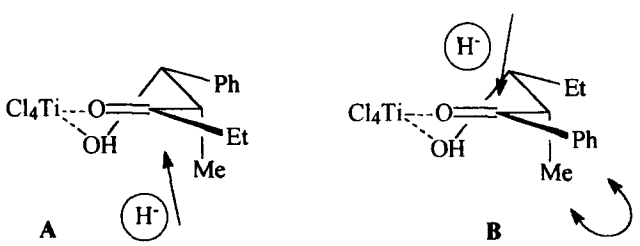
[a]ratios were determined by ^{1}H NMR of the unpurified reaction mixtures. Confirmation of the assigned stereochemistry of all the diols was achieved by ^{1}H- and ^{13}C NMR analysis and by comparison with the corresponding data in the literature.

For comparative reasons, another pathway to the 1,3-diols was performed. Propiophenone was reacted with propionaldehyde in the presence of $TiCl_4$ to give the expected aldol product **3** in high yields with a high degree of *syn*-selectivity. Surprisingly, subsequent one-pot reduction with $NaBH_4$ yielded the 1,2-*syn*-1,3-*syn* diol **4** (Scheme 2).



Scheme 2

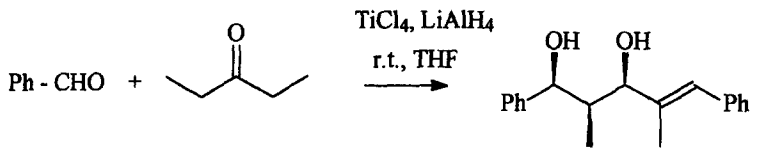
The different stereochemical outcome of the in-situ reduction of ß-hydroxy ketones **1a** (Scheme 1) and **3** (Scheme 2) can at best be explained by considering the transition states shown in Scheme 3. In order to avoid interactions of the methyl and the phenyl group,[12] we propose conformer **B** to be the favoured transition state during the reduction of compound **3** to give the *syn*-diol **4**. These results are in accordance with those obtained by DiMare et al. in reductions of **isolated**, BCl_3- and $TiCl_4$-precomplexed ß-hydroxy ketones.[13] In contrast, other stereochemical results were obtained by in-situ reductions of the ß-hydroxy ketones **1a** and **1b** (Scheme 1). Conformer **A** seems to be responsible for the formation of the 1,2-*syn*-1,3-*anti* sequence of the diol **2a**.



Scheme 3

In order to prove the configuration of the diol **4**, thermodynamical equilibration using $Ti(OiPr)_4$ was accomplished. This in-situ method yields the 1,2-*syn*-1,3-*anti* diol **2a**.[14] The obtained purified diol **2a** is identical to diol **2a** obtained in the approach of Scheme 1. The equilibration takes place only at the carbon atom of the former aldehyde function. No equilibration was observed at the former keto carbon atom. This is consistent with the known chemoselectivity of titanium-reagents.[15]

This one-pot procedure is very solvent-sensitive. Both the yields and stereoselectivity are increased by working in dichloromethane as opposed to toluene. Reactions in oxygen-containing solvents (reduction with $LiAlH_4$), in particular THF, result in a tandem aldol-addition / reduction / aldol-condensation process. The 1,2-*syn*-1,3-*syn* diol **5** is isolated in high yield and high degree of stereoselectivity.



5

Scheme 4

The structure of diol **5** was confirmed by X-ray crystallography (Figure 1).[18]

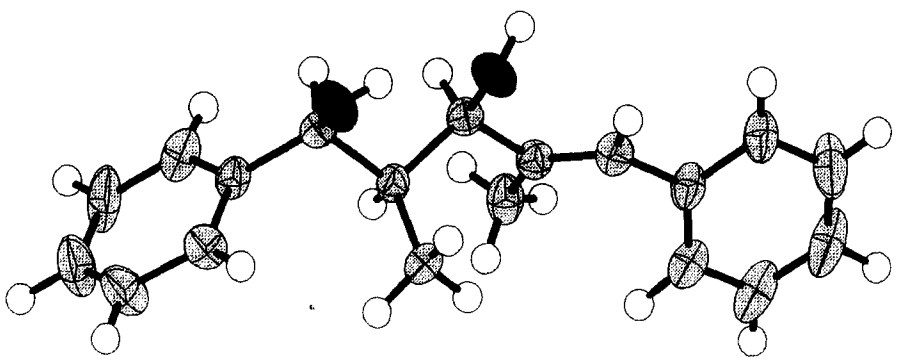


Figure 1

These experiments demonstrate that the simple one-pot aldol-reduction sequence can be used for the synthesis of defined stereotriades. The stereochemical outcome of this reaction is determined by the careful choice of reactants and reaction conditions.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively using a AC-300 spectrometer. Mass spectra were aquired on a HP 5995 (Hewlett Packard) spectrometer (70 eV).

All reactions were carried out under an argon atmosphere in glassware which had been flame-dried under a stream of argon. Solvents were dried and distillled prior to use.

General Procedure for the One-Pot Aldol-Reduction Reaction: The ketone (20.0 mmol) was added to a solution of titanium(IV) chloride (1.1 mL, 10 mmol) in 20 mL of anhydrous dichloromethane. To the resulting brown-orange mixture the aldehyde (20.0 mmol) was carefully added at 0°C and the mixture was stirred for further 10 h at r.t. After that time sodium borohydride (760 mg, 20.1 mmol) was added and the reaction mixture was stirred for further 5-7 h at r.t. (TLC-control). The reaction mixture was then quenched carefully with 20 mL of saturated aq $NaHCO_3$ and 5 mL of aq H_2O_2 -solution and stirred for further 30 min at r.t. The mixture was then extracted several times with EtOAc; the organic layers were separated, dried (Na_2SO_4) and concentrated i. vac. Purification by flash chromatography (8:2 hexane: EtOAc) provided the diol as a colorless oil.

(1*SR*, 2*RS*, 3*RS*)-1-Phenyl-2-methyl-1,3-pentanediol (2a)[3]

^{1}H NMR(300 MHz, $CDCl_3$) δ 0.83 ppm (d, 3H, J= 7.15 Hz), 1.02 (tr, 3H, J=7.54 Hz), 1.66 (ddq, 2H, J=5.28, 7.54, 10.58 Hz), 1.88 (ddq, 1H, J=2.63, 5.27, 7.16 Hz), 3.59 (ddd, 1H, J=5.28, 7.54, 10.55 Hz), 5.15 (d, 1H, J= 2.64 Hz), 7.36-7.2 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.37, 128.43, 127.28, 126.33, 77.18, 74.73, 43.62, 28.51, 11.5, 10.4.

(2*RS*, 4*RS*)-2-Methyl-1,3-pentanediol (2b)[16]

^{1}H NMR(300 MHz, $CDCl_3$) δ 0.81 (d, 3H, J=7.1 Hz), 1.13 (d, 3H, J=6.4 Hz), 1.17 (d, 3H, J=6.4 Hz), 1.57 (dqq, 1H, J=6.78, 2.64 Hz), 3.83 (dq, 1H, J=6.78, 6.41 Hz), 4.06 (dq, 1H, J=6.4, 2.64 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 70.8, 70.5, 44.4, 12.5, 13.4.

(3*SR*, 2*RS*)-1-Phenyl-2-methyl-3-hydroxy-pentan-1-one (*syn*-3)

The aldol adduct **3** was described by several authors.[17] No full characterizations of the *syn*- and *anti*-isomers of compound **3** were given. Therefore we describe herein the two isomers.

Propiophenone (2.7 mL, 20.0 mmol) was added to a solution of titanium(IV) chloride (1.1 mL, 10 mmol) in 20 mL of anhydrous dichloromethane. To the resulting brown-orange mixture propionaldehyde (1.4 mL, 20.0 mmol) was carefully added at 0°C and the mixture was stirred for further 10 h at r.t. The reaction mixture was

then quenched carefully with 20 mL of saturated aq $NaHCO_3$ and extracted several times with EtOAc; the organic layers were separated, dried (Na_2SO_4) and concentrated i.vac. Purification by flash chromatography (8:2 - hexane : EtOAc) provided the *syn*-ß-hydroxyketone **3** as a colourless oil.

Yield: 2.7 g, 70.3 %. ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (tr, 3H, J=7.54 Hz), 1.26 (d, 3H, J=7.16 Hz), 1.50 (dq, 1H, J=5.28, 7.54 Hz), 1.62 (dq, 1H, J=7.53, 7.93 Hz), 3.50 (dq, 1H, J=3.02, 7.16 Hz), 3.95 (ddd, 1H, J=3.02, 5.28, 7.92 Hz), 7.59 - 7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.84, 135.94, 133.41, 128.75, 128.37, 72.89, 44.12, 27.20, 11.05, 10.49.

(3*SR*, 2*SR*)-1-Phenyl-2-methyl-3-hydroxy-pentan-1-one (*anti*-3)[17]

The *anti*-isomer **3** was obtained by thermodynamical equilibration of the *syn*-isomer **3** in the presence of 20 mol% $Ti(OiPr)_4$ in toluene.[14] After 24 h at r.t. the reaction mixture was quenched with saturated aq NH_4Cl and extraxted several times by ethyl acetate. The organic layers were separated, dried (Na_2SO_4) and concentra-ted i. vac. Purification by flash chromatography (8:2 - hexane : EtOAc) provided the *anti*-ß-hydroxyketone **3** as a colourless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (tr, 3H, J=7.54), 1.26 (d, 3H, J=7.16), 1.53 (dq, 1H, J=4.14, 7.54), 1.61 (dq, 1H, J=7.54, 8.66), 3.58 (dq, 1H, J=6.02, 7.16), 3.80 (ddd, 1H, J=4.14, 6.01, 8.66), 7.6 - 7.5 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 135.9, 133.3, 128.7, 128.36, 75.36, 45.3, 27.69, 15.46, 10.15. MS: *m/z* (relative intensity) 193 (0.5, [M+1]), 177 (0.7), 174 (3), 163 (2), 159(1), 145 (4), 133(25), 105 (100).

(1*SR*, 2*RS*, 3*SR*)-1-Phenyl-2-methyl-1,3-pentanediol (4)

Propiophenone (2.55 mL, 20.0 mmol) was added to a solution of titanium(IV) chloride (1.1 mL, 10 mmol) in 20 mL of anhydrous dichloromethane. To the resulting brown-orange mixture propionaldehyde (1.44 mL, 20.0 mmol) was carefully added at 0°C. The mixture was stirred for further 10 h at r.t. After that time sodium borohydride (760 mg, 20.1 mmol) was added and the reaction mixture was stirred for further 5-7 h at r.t. The mixture was then quenched carefully with 20 mL of saturated aqu. $NaHCO_3$ and 5 mL of aqu. H_2O_2 -solution and stirred for further 30 min at r.t. The resulting emulsion was then extracted several times with EtOAc; the organic layers were separated, dried (Na_2SO_4) and concentrated i. vac. Purification by flash chromatography (8:2 hexane: EtOAc) provided the diol **4** as a colorless oil.

Yield: 2.4 g (62%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, 3H, J=7.16 Hz), 0.89 (tr, 3H, J=7.53 Hz) 1.44 (dq, 1H, J=6.03, 7.54 Hz), 1.52 (dq, 1H, J=7.54, 7.92 Hz), 1.75 (ddq, 1H, J=1.89, 2.64, 7.16 Hz), 3.82 (ddd, 1H, J= 1.89, 6.03, 7.92 Hz), 4.94 (d, 1H, J=2.64 Hz), 7.25-7.19 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 127.9, 127.4, 126.1, 79.01, 78.42, 43.3, 28.54, 10.85, 4.62. Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.22; H, 9.28. Found: C, 74.46; H, 9.10.

(1*SR*, 2*RS*, 3*RS*)-1,5-Diphenyl-2,4-dimethyl-pent-4-ene-1,3-diol (5)

3-Pentanone (2.0 mL, 20.0 mmol) was added to a solution of titanium(IV) chloride (1.1 mL, 10 mmol) in 20 mL of anhydrous tetrahydrofuran. To the resulting yellow mixture benzaldehyde (2.0 mL, 20.0 mmol) was carefully added at 0°C and the mixture was stirred for further 10 h at r.t. After that time lithium aluminium hydride (760 mg, 20.0 mmol) was carefully added and the reaction mixture was stirred for further 5-7 h at r.t. (TLC-control). The reaction mixture was then carefully quenched with 20 mL of saturated aq $NaHCO_3$, stirred for further 30 min at r.t. and extracted several times with EtOAc. The organic layers were separated, dried (Na_2SO_4) and concentrated i. vac. Purification by flash chromatography (8:2 hexane: EtOAc) provided the diol **5** as a colorless oil. Recrystallization from hexane afforded the crystalline diol **5.**

Yield: 1.3 g; 46.1 % (related to benzaldehyde). mp.: 153 - 154°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, 3H, J = 7.15 Hz), 1.83 (d, 3H, J = 0.76 Hz), 2.05 (ddq, 1H, J = 1.88, 2.64, 7.15 Hz), 2.71 (d, 1H, J = 2.64 Hz), 3.07 (d, 1H, J = 1.88 Hz), 4.45 (s, 1H), 5.09 (s, 1H), 6.64 (s, 1H), 7.2-7.4 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) 143,79, 138.84, 138.10, 129.38, 128.55, 128.52, 127.57, 126.74, 126.08, 125.00, 80.41, 78.33, 42.72, 16.03, 5.23. Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.18; H, 8.16.

Acknowledgements

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