Pergamon

Tetrahedron Letters 43 (2002) 4459–4461

TETRAHEDRON LETTERS

Insight into the mechanism of direct catalytic aldol addition mediated by ambifunctional titanium complexes

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Received 24 April 2002; accepted 29 April 2002

Abstract—X-Ray structure analysis of a titanium(IV) isopropoxide/mandelic acid complex provides an insight into the mechanism of this novel direct enantioselective aldol addition. The catalytic cycle mediated by the titanium(IV) alkoxide/mandelic acid complex is presented. © 2002 Elsevier Science Ltd. All rights reserved.

The aldol addition is an effective method in organic synthesis for the formation of carbon–carbon bonds. Many efforts have been devoted to control its stereoselectivity. Most require a preconversion of the ketone or ester into an enolate with the consumption of 1 equiv. of reagents.[1] Several groups have reported direct enantio- and diastereoselective aldol additions to overcome this problem.[2,3] We have reported the direct aldol addition of aldehydes to unmodified ketones in the presence of a titanium(IV) alkoxide/α-hydroxy acid reagent, which has provided the corresponding aldol adducts with a high degree of enantioselectivity.[4] In this paper, we communicate the catalytic version of this reaction and propose a mechanism.

In order to confirm and extend earlier yield and stereoselectivity results as well as to develop a catalytic version of this reaction we have investigated this described titanium(IV) alkoxide/α-hydroxy acid system more intensively. As a result we have been able to isolate a crystalline titanium(IV) isopropoxide/mandelic acid complex. In a general procedure, 2 equiv. of titanium(IV) isopropoxide were treated with 1 equiv. of (*R*)-mandelic acid in small amounts of toluene at reflux. Crystals were obtained upon cooling. Structure elucidation of the crystals was not possible based on NMR spectroscopy, as ^{13}C and ^{1}H NMR experiments indicated the existence of at least seven conformers at room temperature. Coalescence of these conformers was found at approximately 50°C in DMSO-d_6.

X-Ray crystallographic analysis of suitable crystals was performed and the sticks picture is shown in Fig. 1.[5]

Two molecules of titanium(IV) isopropoxide are complexed with one molecule of (*R*)-mandelic acid. As a consequence two chemical different titanium atoms were created. We prepared that titanium complex (Scheme 1, **A**) in large quantities (gram scale) without any difficulties. Using this complex, catalysis of aldol additions utilizing aldehydes with unactivated ketones was achieved. 10 mol% of this catalyst is enough for a complete aldol reaction.

High *syn*-selectivities were observed in the aldol adducts. In several experiments, 1 mol% of the catalyst **A** is enough for a complete reaction. However, no enantioselectivities were found in the aldol adducts by utilizing chiral mandelic acid in this titanium(IV)-com-

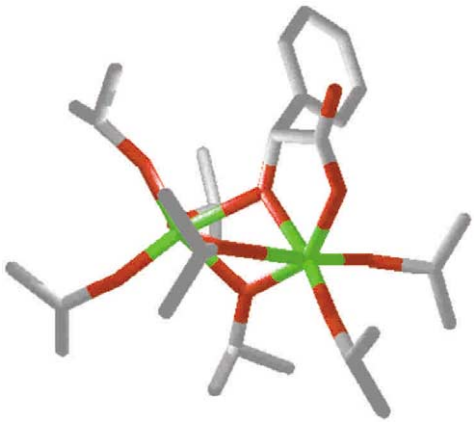

Figure 1.

Keywords: aldol addition; enantioselectivity; catalysis; titanium complexes.

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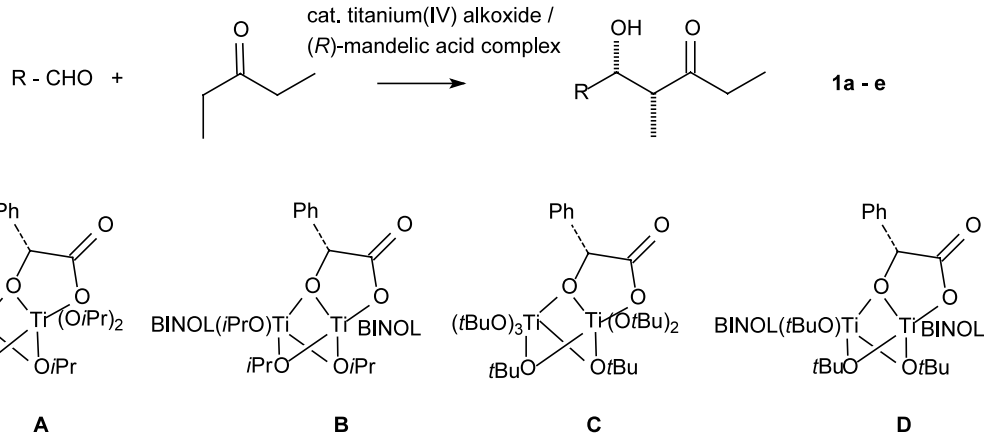
PII: S0040-4039(02)00822-5



Scheme 1. Catalytic aldol addition.

plex **A**. As we discussed earlier, the use of BINOL as a ligand in this titanium(IV) alkoxide/(*R*)-mandelic acid system is necessary for obtaining enantioselectivities in these aldol additions.[4] The simple exchange of isopropoxyligands to BINOL-ligands was achieved by known procedures.[6] And indeed, high enantioselectivities were found in aldol additions using this catalyst system (Scheme 1, **B**; Table 1, reaction conditions[c]).[7] Catalyst **B** (Scheme 1) is postulated from the X-ray analysis of complex **A**. Catalyst **B** was used as a raw material in this reaction. So far we were not able to obtained compound **B** as crystalline material.

In order to prevent side reactions (reduction of the starting aldehydes, Tishchenko-reaction etc.—in particular when using isobutyraldehyde) the $Ti_2(OtBu)_7$/(*R*)-mandelic acid system was used (Scheme 1, **C**). Based on an even reaction mechanism, 2 equiv. of titanium(IV) tertbutoxide were treated with 1 equiv. of (*R*)-mandelic acid. Nearly the same yield and simple stereoselectivity was observed using this titanium catalyst for aldol additions. No side reactions were observed. Structure **C** (Scheme 1) is postulated. To date we are not able to isolate this titanium(IV) tertbutoxide/(*R*)-mandelic acid complex **C** in crystalline form. Enantioselective, catalytic aldol addition was achieved by using catalyst **D**. The exchange of the tertbutoxyligands to BINOL was performed out by the methode described above.[6] The *syn*-aldol adducts were observed with a high degree of enantioselectivity (Table 1, entries 1–5, reaction conditions[d]).

Based on the X-ray analysis of this titanium(IV) isopropoxide/(*R*)-mandelic acid complex **A** and on the absolute configuration found in the aldol products (Table 1, entries 1, 4, 5), we propose the following reaction mechanism (Scheme 2).

Structure **B** represents the titanium complex **B**. A weakening of the carboxylic bond strength to the titanium is assumed by complexation of aldehyde and ketone (Scheme 2, **E**). Thus, carboxylic functionality is able to act as a base. As a consequence a proton is abstracted from the ketone and a new C–C-bond is formed (Scheme 2, **F**). An isopropoxyligand abstracts this proton and the resulting aldol is released from the catalyst by isopropanol (Scheme 2, **G**). The titanium complex **B** is regenerated. The configurative arrangement in **E** is determined by BINOL-ligands and the (*R*)-configuration of the mandelic acid as suggested by molecular modeling of complex **B** (geometry optimization). The abstraction of a proton from diethylketone in structure **E** is in accordance with the 4(*R*)-configuration obtained in the aldol products (Table 1, entries 1, 4, 5).

Investigations for applying this direct catalytic aldol addition to other substrates are ongoing.

Table 1. Enantioselective aldol addition

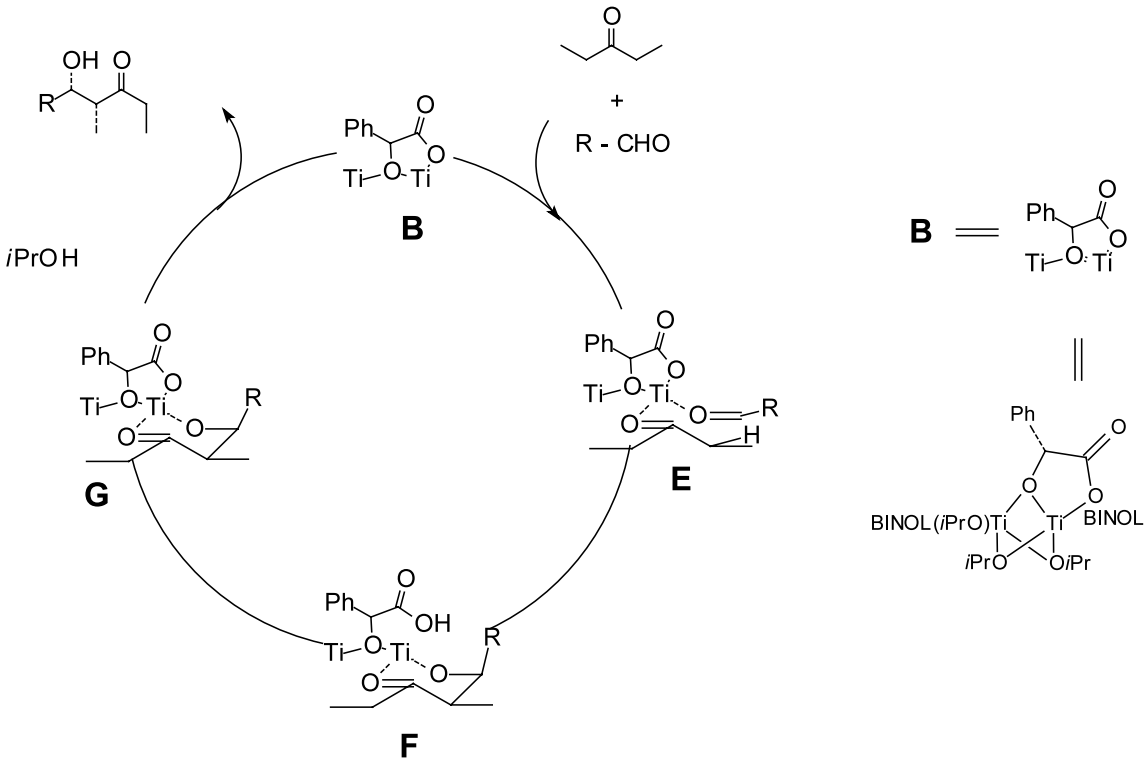
Entry	R	Product	*syn*/*anti* ratio[a]	ee [%] (configuration)[b]	Yield (%)
1	Ph	**1a**	91/9[c]; (85/15)[d]	91 (4*R*)[c,8]; 88 (4*R*)[d,8]	85[c]; 68[d]
2	*t*Bu	**1b**	88/12[c]; (81/19)[d]	93 (n.d.)[c]; 86 (n.d.)[d]	71[c]; 70[d]
3	Ph≡	**1c**	73/27[c]; (75/25)[d]	78 (n.d.)[c]; 81 (n.d.)[d]	68[c]; 71[d]
4	*i*Pr	**1d**	79/21[c]; (71/29)[d]	71 (4*R*)[c,9]; 74 (4*R*)[d,9]	43[c]; 39[d]
5	Et	**1e**	72/28[c]; (76/24)[d]	74 (4*R*)[c,10]; 76 (4*R*)[d,10]	78[c]; 75[d]

[a] *syn*/*anti* ratio was determined by ^1H and ^{13}C NMR spectroscopy.

[b] The enantiomeric excess and the configuration of the aldol products were determined by the corresponding MTPA ester. The signals in the ^1H and ^{13}C NMR spectra were compared with those obtained by reference substances. The values correspond to the *syn*-diastereoisomer.

[c] Reaction conditions: *rac*$BINOL_2$–$Ti_2(OiPr)_3$/(*R*)-mandelic acid **B** (1 mmol), aldehyde (15 mmol), 3-pentanone (10 mmol), rt.

[d] Reaction conditions: *rac*$BINOL_2$–$Ti_2(OtBu)_3$/(*R*)-mandelic acid **D** (1 mmol), aldehyde (15 mmol), 3-pentanone (10 mmol), rt.



Scheme 2. Assumed catalytic cycle of the aldol addition.

Acknowledgements

This research was supported by the Deutsche Forschungsgemeinschaft. The authors thank Mrs. P. Neubauer for technical assistance.

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7. **General experimental procedure**: *rac*$BINOL_2$–$Ti_2(OPr)_3$/mandelic acid complex **B** (100 mg, 0.1 mmol) were dissolved in freshly distilled propionaldehyde (110 μl, 1.5 mmol) at room temperature. 3-Pentanone (106 μl, 1.0 mmol) were added after 10 min. The reaction was monitored by thin-layer chromatography (dichloromethane/acetone: 99/1). At the end of the reaction, the mixture was diluted with diethylether and quenched successively with aq. saturated $NaHCO_3$ and NH_4Cl. The organic layer was separated, dried (Na_2SO_4), filtered, and finally concentrated in vacuo. Purification by column chromatography (hexane/ethylacetate) afforded *syn*-5-hydroxy-4-methyl-3-heptanone (**1e**, 113 mg) in 78% yield.
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