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Multinuclear enantiopure titanium self-assembly complexes—synthesis, characterization and application to organic synthesis

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Hexa- and nonanuclear titanium complexes were obtained by self-assembly of titanium(IV)-*tert*-butoxide and D-mandelic acid. Suitable single crystals of these complexes were characterized by X-ray structure analysis. When used with these complexes, aldol adducts were isolated with a high degree of regioselectivity in direct aldol additions of aromatic and aliphatic aldehydes to functionalized unsymmetrical ketones. High *syn*-diastereoselectivities were obtained in aldol additions of enolizable aldehydes with hydroxyacetone and methoxyacetone. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: chiral titanium complexes; direct aldol addition; carbonyl-ene reaction

INTRODUCTION

The use of titanium(IV)-alkoxides in organic carbanion chemistry is well established.[1–4] Since direct and catalytic aldol additions are of increasing importance for organic synthesis,[5,6] several attempts have been made to synthesize chiral catalytic active titanium complexes, especially by ligand exchange of titanium(IV)-alkoxides.[7,8] Often these catalysts are produced *in situ*, making reproduceable reaction conditions as well as mechanistic studies difficult to achieve.[9–15] For that reason, we carried out a systematic study of the preparation of mononuclear titanium(IV) complexes by ligand exchange of titanium(IV)-isopropoxide with several mono- and bidentate ligands.[16] The synthesis as well as the application of defined mononuclear titanium(IV) complexes in C–C bond formation processes are well documented in several comprehensive reviews and book chapters.[17–33]

In contrast to that, little is known about the synthesis, characterization and application of multinuclear titanium complexes in C–C bond formation processes. So far, titanium–BINOL complexes have been investigated intensively.[34–37] First examples of the characterization and application of multinuclear complexes in organic syntheses have been reported.[38] Mikami *et al.* described the synthesis and characterization of a tetranuclear titanium(IV)–BINOL complex as well as its application in carbonyl-ene reactions.[39,40] Recently, we described the use of a tetranuclear titanium-BINOL complex in direct aldol additions.[41] Exceptionally high regioselectivities were observed when reacting unsymmetrical ketones with enolizable aldehydes using this tetranuclear titanium–BINOL complex in direct aldol additions. Only a low catalyst loading was necessary for a full conversion (0.02 mol%). A remarkable feature of this tetranuclear titanium complex is its extreme stability against air and moisture. The results of these experiments encouraged us to transfer this concept of multinuclear complexes to other bidentate ligands. Higher functionalized ligands might be able to interact with the substrate in a more sophisticated way to achieve higher regio- or stereoselectivities. Therefore, we focused our attention on the ligand exchange of titanium(IV)-*tert*-butoxide and D-mandelic acid. When used with this ligand system, the best results in the direct catalytic enantioselective aldol addition were obtained (Fig. 1).[42,43] There are only a few further examples of synthesis and application of titanium(IV)–mandelic acid complexes. For the use of a titanium(IV)–mandelic acid complex in asymmetric oxidation of sulfides see Matsugi *et al.*[44,45] For syntheses and characterization of a mandelic acid-salen-titanium complex see Carroll *et al.*[46] In our ongoing studies we were able to isolate the highly catalytic active titanium(IV)–mandelic acid complexes **2** and **3** (Figs 2 and 3).

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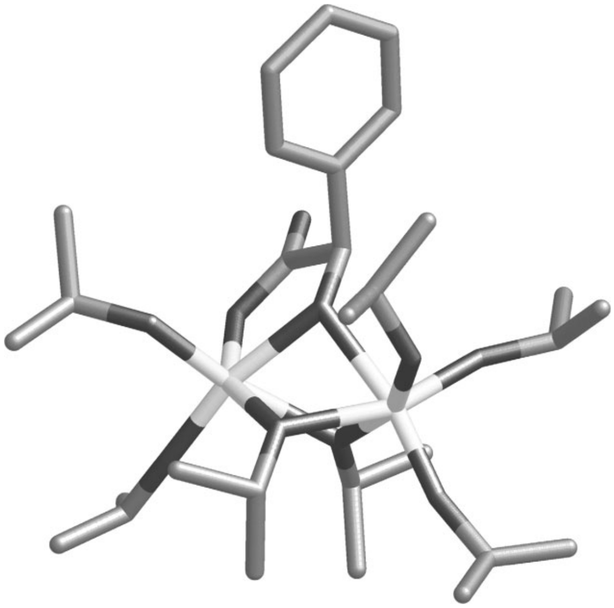

Figure 1. Chiral self-assembly binuclear titanium(IV) complex **1** obtained from titanium(IV)-isopropoxide and D-mandelic acid.[42,43] For clarity hydrogens have been omitted.

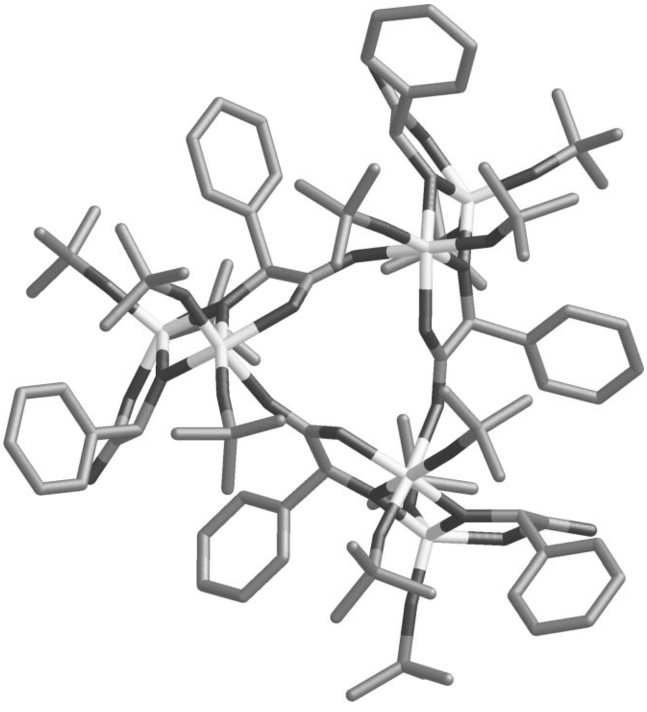

Figure 2. Hexanuclear titanium complex **2** with a chiral cave obtained from titanium(IV)-*tert*-butoxide and D-mandelic acid. For clarity hydrogens have been omitted.

The results of these investigations of the catalytic activity of complexes **2** and **3** in direct aldol addition as well as in glyoxylate-ene reation will be dicussed here.

RESULTS AND DISCUSSION

Owing to the results that we had obtained in enantioselective aldol addition of aldehydes to ketones in the presence of the titanium(IV)-isopropoxide–mandelic acid complex **1**,[42,43] we decided to synthesize and characterize the corresponding complexes of titanium(IV)-*tert*-butoxide and D-mandelic acid. First, we reacted titanium(IV)-*tert*-butoxide with equimolar amounts of D-mandelic acid in small amounts of toluene by heating the reaction mixture (method A). A homogeneous clear or slightly opaque solution of high viscosity was obtained. This solution showed a highly catalytic activity in direct aldol additions, but the reproducibility was not satisfactory. Moreover, the storability of these catalyst solutions was poor as well. After several days, the solution became more and more yellow and even brown, and its activity dramatically decreased. From several carefully heated reaction mixtures, clear colorless crystals could be obtained, which were analyzed by X-ray diffraction. The crystal structure of this titanium(IV)-*tert*-butoxide mandelic acid complex **2** is depicted in Fig. 2.

Six titanium atoms form a complex with a chiral cave. Three titanium atoms are coordinated 5-fold, and the other three 6-fold. Since the conditions that lead to this complex **2** were difficult to reproduce, further experiments with other, easier controllable reaction conditions were carried out. Mixing equimolar amounts of titanium(IV)-*tert*-butoxide and D-mandelic acid at room temperature in large amounts of toluene resulted in clear, pale yellow colored solutions (method B). Overnight, colorless crystals of a nonanuclear titanium–mandelic acid complex **3** were formed, which were then also analyzed by X-ray diffraction. The structure of this complex is depicted in Fig. 3.

This complex possesses a C_2-symmetry. The titanium atom Ti^1 is situated on the twofold axis, dividing the complex into two identical chiral parts. Each of those two parts is bearing five molecules of D-mandelic acid and six *tert*-butyl groups. Further, a direct conjunction of two titanium atoms by a sole oxygen atom (Ti–O–Ti) appears in each part of this complex. The origin of this oxygen is not completely clear at the moment. Traces of water in the commercially purchased D-mandelic acid might be responsible. Certain amounts of water proved to be essential for the formation of several titanium complexes.[47–49] The complex is stable enough against air and moisture for handling without any special care. Storage for several weeks does not incur any significant changes in its activity, but it has to be pointed out that its stability is significantly inferior to that of the tetranuclear BINOL–titanium complex that we have examined before.[41]

The obtained crystalline nonanuclear titanium complex **3** was found to be able to promote aldol processes. The catalytical activity of this complex was examined in direct aldol additions as well as in the glyoxylat-ene reaction. In both cases, the catalyst was found to be mildly active, providing the desired reaction products with low catalyst loadings in moderate yields. The complex was even

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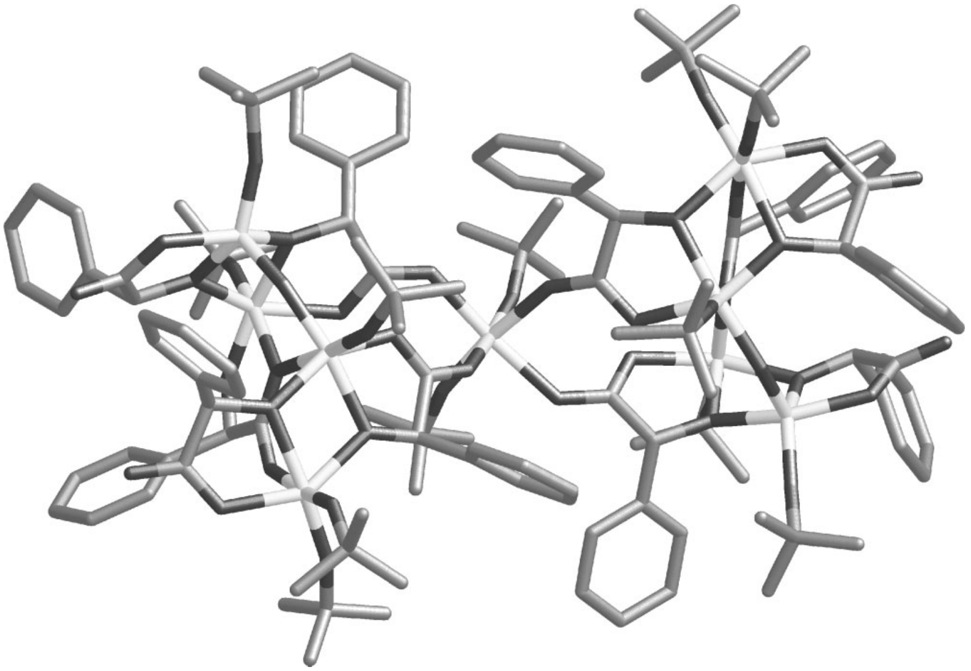
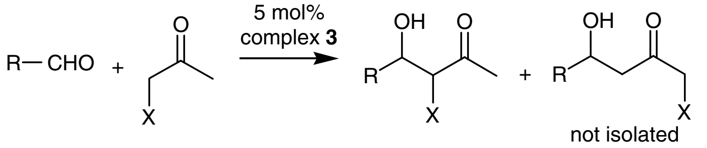


Figure 3. Nonanuclear self-assembly titanium complex **3** obtained from titanium(IV)-*tert*-butoxide and D-mandelic acid in toluene. For clarity hydrogens have been omitted.



Scheme 1. The regioselectivity in aldol additions with unsymmetrical ketones (X = Me, OH, OMe).

found to catalyze aldol additions with higher functionalized enolate components. High regioselectivities were detected when unsymmetrical enolate components were used like hydroxyacetone, methoxyacetone or methylethylketone (Scheme 1). Aldol addition was strongly preferred at the sterically more encumbered α-side of the ketones. In all experiments only one regioisomer could be detected (Scheme 1).

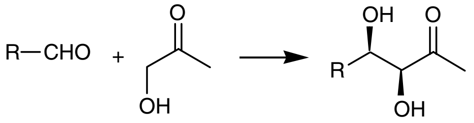
The results obtained concerning to yields as well to stereoselectivity with aldehydes **4**–**12** and hydroxyacetone **7** are summarized in Table 1. The outcome of the reaction was surprising. So far, we had isolated 'protected' aldols only with the tetranuclear BINOL–titanium complex that we have examined earlier.[41] In contrast to that, with this mandelic acid titanium complex **3** we were able to isolate the 'unprotected' aldols **14**–**22**. In a reaction with aromatic aldehydes no diastereoselectivities were observed (entries 1–3, Table 1). By reacting aromatic aldehydes with electron withdrawing groups, a slight increasing of yields and favoring of the formation of *anti*-configurated aldols was observed (entry 2, Table 1).

Aliphatic and olefinic aldehydes **7**–**12** reacted in a similar way. High regioselectivities and high diastereoselectivities were obtained. The kinetic controlled *syn*-configured products **17**–**22** were generally favored (entries 4–8, Table 1). So far, aldol adducts of hydroxyacetone were only accessible by proline-catalysis. They were isolated with a high degree of *anti*-diastereoselectivity.[49,50,54] These results demonstrate the feasibility of a metallorganic approach to aldol adducts of hydroxaycetone. Moreover, the obtained *syn*-configured aldol adducts make this method to a valuable addition to the well-established *anti*-selective proline-catalysis.[49,50,55]

Methoxyacetone is also a suitable substrate for this approach. When used with methoxyacetone **23** the observed *syn*-preference was intensified (Scheme 2). The *syn*-diastereoselectivity was significantly increased. Only one regioisomer was isolated with a high degree of *syn*-diastereoselectivity (compare entry 1 in Table 1 with Scheme 2).

Nonfunctionalized, unsymmetrical ketones reacted exclusively at the more sterical encumbered side. Only one regioisomer could be detected. In reactions of ethylmethylketone **26** with the non-enolizable aldehydes **4, 6** and **25** a slight

Table 1. Reaction of hydroxyacetone with aldehydes



Entry no.	R	Product	Yield (%)[a]	*Syn*/*anti* ratio
1	Ph	**14**	18	57 : 43
2	4-Cl–C_6H_4	**15**	22	38 : 62
3	3-MeO–C_6H_4	**16**	7 (25)[b]	66 : 34
4	Et	**17**	13	65 : 35
5	*i*Pr	**18**	8	89 : 11
6	*t*Bu	**19**	9	94 : 6
7	Cy	**20**	11	80 : 20
8	Ph–CH_2–CH_2	**21**	24	61 : 39
9	Ph–CH=CH	**22**	33	65 : 35

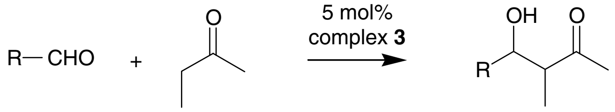
[a] Yields obtained by extraction with saturated aqueous NH_4Cl solution.

[b] Owing to the high oxophilicity of the titanium(IV) complex **3** it was not possible to extract the whole amount of products using saturated aqueous NH_4Cl solution. Extraction with diluted, aqueous acids (tartaric acid, etc.) or with acidic buffer solutions yielded incomplete dehydratization to form the corresponding β-enol ketones. However high yields were detected by extraction with saturated aqueous solution of potassium sodium tartrate over a period of 5–8 h at room temperature. We optimized this work-up procedure for compound **16** and obtained a yield of 25% (7% with NH_4Cl solution, entry 3).

syn-preference in the isolated aldol adducts were observed (Table 2).

The glyoxalat-ene reaction was also investigated. Methylstyrene **30** was reacted with ethyl glyoxalate **31** in the presence of 5 mol% of complex **3**. Surprisingly, besides the expected olefin **32** (26% yield) the γ-lactone **33** (35% yield) was isolated with a high degree of diastereoselectivity (Scheme 3). Only one diastereomer could be detected.

Table 2. Reaction of aromatic aldehydes with ethylmethylketone

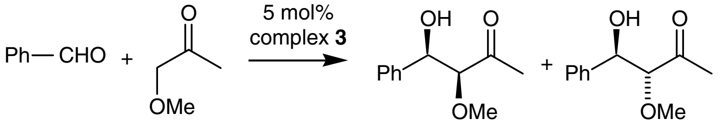


4, **6**, **25** **26** **27**-**29**

Entry	R	Product	Yield (%)	*Syn*/*anti*
1	Ph	**27**	34	82 : 18
2	3-MeO–C_6H_4	**28**	14	56 : 35
3	Ph–C≡C	**29**	5	67 : 33

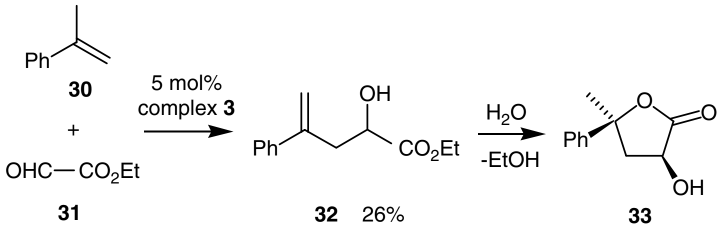
EXPERIMENTAL

Titanium-(IV)-*tert*-butoxide was synthesized from commercial titanium(IV)-isopropoxide by ligand exchange with *tert*-butanol and removal of isopropanol by evaporation. This procedure was repeated until no more traces of titanium(IV)-isopropoxide were detectable by ^1H NMR spectroscopy. This rough material was distilled *in vacuo* to obtain the pure colorless titanium-(IV)-*tert*-butoxide. Silica gel 60 was used for CC. TLC was carried out on Merck silica gel 60 F_{254} plates. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer as solutions in $CDCl_3$. Mass spectra were recorded with a MSI Concept H-spectrometer. Single crystal X-ray data sets were collected on a STOE IPDS2 image plate diffractometer using MoK_α-radiation. The structures were solved by direct methods and refined by full matrix least squares on F^2 using SHELX 97.[51] All non-hydrogen atoms were refined anisotropically to give the final *R* values. The hydrogen atoms were placed in idealized locations and refined by riding on their carbon atoms.



4 **23** *syn*-**24** *anti*-**24**

Scheme 2. Aldol addition with methoxyacetone (*syn*/*anti*, 95/5).



Scheme 3. Glyoxalate-ene reaction in the presence of titanium(IV) complex **3**.

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Preparation of the catalytic active complexes

Method A

Aliquots of 2 g D-mandelic acid and 2 ml titanium(IV)-*tert*-butoxide were mixed with 2 ml toluene and heated under stirring until a clear solution was obtained. Cooling down resulted in slightly yellowish colored viscoseous clear or slightly opaqueous liquids. Within several days colorless crystals were formed in several cases. Washing with toluene and hexane gave the pure product. Nevertheless, the reaction conditions were too difficult to obtain reproducible results, and sometimes the reaction mixtures did not crystallize at all, or the mixtures turned solid without the formation of macroscopic crystals.

Method B

Aliquots of 5 g D-mandelic acid and 5.5 ml titanium(IV)-*tert*-butoxide were dissolved in 80 ml toluene. When a clear solution was obtained and all the mandelic acid was dissolved, the reaction mixtures were kept at a calm place. Overnight colorless crystals were formed. These were filtered off and washed twice with toluene and hexane.

Crystallography

Suitable crystals were selected and sealed together with mother liquor in glass capillaries (diameter 0.7 mm). This procedure was found to be mandatory, since drying of the crystals immediately turned them useless for X-ray analysis. This structural change was proved to be not the result of a chemical decomposition, as it was possible to grow new and intact crystals from those that had lost their crystallographic order by drying. This phenomenon was also observed when crystallography was executed on the tetranuclear BINOL–titanium complex,[41] although this effect was not as strong in these cases. In the meantime, we synthesized several other multinuclear titanium species, and drying seemed to be a general problem for crystallographic studies. It has to be pointed out that neither inert oils nor cooling down with nitrogen could avoid crystallographic changes of those sensible crystals, and in fact in several cases these inert shielding liquids accelerated the changing process significantly. Sealed together with mother liquor, the crystals were storable for several days without any changes in their diffraction pattern.

Hexanuclear titanium complex **2**: $[\alpha]_D^{25} = +80°$ (c = 1 g/100 ml, CH_2Cl_2); IR(KBr) ν_{max}: 2973, 2929, 1450, 1361, 1301, 1235; ^{1}H NMR: δ 1.04 (s, 9H), 1.28 (s, 18H), 1.48 (s, 9H), 5.93 (s, 2H), 7.17–7.57 (m, 10H); ^{13}C NMR: δ 30.6, 31.2, 31.6, 69.1, 89.4, 90.0, 90.9, 125.5, 128.6, 128.8, 135.8.

Nonanuclear titanium complex **3**: $[\alpha]_D^{25} = +140°$ (c = 1 g/100 ml, CH_2Cl_2); IR(KBr) ν_{max}: 2973, 1493, 1451, 1362, 1252, 1237, 1188, 1086, 1026; ^{1}H NMR: δ 0.83 (s, 3H), 0.95 (s, 3H), 0.97 (s, 3H), 1.05 (s, 6H), 1.22 (s, 3H), 5.06 (s, 1H), 5.71 (d, J = 3.8 Hz, 1H), 5.94 (s, 1H), 6.81–6.90 (m, 1H), 7.10–7.60 (m, 6H), 7,73 (d, J = 7.5 Hz, 1H) 7.85 (d, J = 8.1 Hz, 1H); ^{13}C NMR: δ 29.7, 30.5, 30.8, 30.96, 30.99, 31.3, 86.4, 86.7, 87.5, 89.1, 89.5, 89.7, 89.8, 90.3, 90.5, 92.3, 92.7, 126.4, 126.6, 126.9, 127.9, 128.0, 128.29, 128.34, 128.6, 128.8, 128.9, 129.2, 129.6, 136.1, 138.6, 139.0, 139.6, 140.8, 175.6, 177.0, 180.0, 181.8, 183.4.

Catalytical investigations[52]

Standard reaction mixtures contained a mixture of each 1 equiv. ketone or α-methylstyrene and 1 equiv. aldehyde. To each of these mixtures 0.05 equiv. complex **3** was added and stirred at room temperature. The advance of the reaction was monitored by TLC. The reaction mixture was then diluted with the 100-fold amount of Et_2O, quenched with aqueous NH_4Cl, the aqueous layer and the white residue were separated and the organic phase was dried over $MgSO_4$. Purification was carried out by flash-CC using petrol ether-EtOAc-mixtures.

3,4-Dihydroxy-4-phenylbutanon **14**.[53] *syn*-**14**: ^{1}H NMR: δ 2.21 (s, 3H, CH_3), 3.16 (s, 1H), 3.78 (s, 1H), 4.35 (d, J = 3.08 Hz, 1H), 4.98 (s, 1H), 7.31–7.39 (m, 5H, ar). ^{13}C NMR: δ 26.3, 73.9, 80.6, 128.1, 128.3, 128.5, 139.9, 208.1. *anti*-**14**: ^{1}H NMR: δ 1.94 (s, 3H, CH_3), 3.27 (s, 1H), 3.78 (s, 1H), 4.45 (d, J = 4.20 Hz, 1H), 4.99 (s, 1H), 7.30–7.39 (m, 5H, ar). ^{13}C NMR: δ 27.6, 74.8, 81.0, 126.1, 126.2, 126.5, 139.0, 208.2.

3,4-Dihydroxy-4-(4-chlorophenyl)-butan-2-one **15**.[54] *syn*-**15**: ^{1}H NMR: δ 2.24 (s, 3H, CH_3), 2.76 (d, J = 6.91 Hz, 1H), 3.68 (d, J = 4.93 Hz, 1H), 4.32 (dd, J_1 = 1.54 Hz, J_2 = 3.18 Hz, 1H), 4.98 (dd, J_1 = 2.84 Hz, J_2 = 3.41 Hz, 1H), 7.33 (s, 2H, ar), 7.34 (s, 2H, ar). ^{13}C NMR: δ 26.2, 73.3, 80.3, 127.6, 127.7, 134.0, 138.5, 207.4. *anti*-**15**: ^{1}H NMR: δ 1.97 (s, 3H, CH_3), 2.91 (d, J = 3.44 Hz, 1H), 3.63 (d, J = 5.02 Hz, 1H), 4.40 (dd, $J_1 = J_2$ = 4.68 Hz, 1H), 4.94 (dd, $J_1 = J_2$ = 3.63 Hz, 1H), 7.33 (s, 2H, ar), 7.34 (s, 2H, ar). ^{13}C NMR: δ 27.7, 74.4, 80.8, 128.8, 134.1, 137.5, 207.4.

3,4-Dihydroxy-4-(3-methoxyphenyl)butan-2-one **16**. Pale yellow oil, R_f = 0.34 (petrolether–EtOAc = 7 : 3). HRMS: (m/z) calcd for $C_{11}H_{14}O_4$: 210.0892; found, 210.0892. *syn*-**16**: ^{1}H NMR: δ 2.21 (s, 3H, CH_3), 3.36 (s, 2H), 3.79 (s, 3H, OCH_3), 4.32 (d, J = 3.26 Hz, 1H), 4.95 (d, J = 3.09 Hz, 1H), 6.82–7.27 (m, 4H, ar). ^{13}C NMR: δ 26.3, 55.1, 73.8, 80.7, 111.9, 113.4, 118.4, 129.5, 141.6, 159.6, 208.3. *anti*-**16**: ^{1}H NMR: δ 1.94 (s, 3H, CH_3), 3.36 (s, 2H), 3.79 (s, 3H, OCH_3), 4.42 (d, J = 4.34 Hz, 1H), 4.94 (d, J = 3.96 Hz, 1H), 6.82–7.30 (m, 4H, ar). ^{13}C NMR: δ 27.6, 55.4, 74.7, 81.0, 113.3, 121.5, 129.5, 129.9, 140.7, 160.0, 208.4.

3,4-Dihydroxyhexan-2-one **17**. Colorless oil, R_f = 0.42 (petrolether–EtOAc = 1 : 1). HRMS: (m/z) calcd for $C_6H_{12}O_3Na$: 155.0684; found, 155.0682. *syn*-**17**: ^{1}H NMR: δ 1.03 (t, J = 7.78 Hz, 3H), 1.31–1.43 (m, 1H), 1,44–1.61 (m, 1H), 2.84 (s, 3H), 3.72 (s, 1H), 3.90 (ddd, J_1 = 1.32 Hz, J_2 = 1.44 Hz, J_3 = 6.92 Hz, 1H), 4.11 (s, 1H), 4.26 (d, J = 3.56 Hz, 1H); ^{13}C NMR: δ 10.3, 25.2, 27.4, 73.3, 78.8, 208.2. *anti*-**17**: ^{1}H NMR: δ 0.98 (t, J = 7.42 Hz, 3H), 1.30–1.42 (m, 1H), 1.44–1.60 (m, 1H), 2.61 (s, 3H), 3.53 (s, 1H), 3.79 (ddd, J_1 = 1.64 Hz, J_2 = 3.83 Hz, J_3 = 5.53 Hz, 1H), 4.10 (s, 1H), 4.27 (d, 1H, J = 4.06 Hz); ^{13}C NMR: δ 10.1, 24.9, 26.9, 74.2, 80.3, 208.1.

3,4-Dihydroxy-5-methylhexan-2-one **18**.[55] Colorless oil, *syn*-**18**: ^{1}H NMR: δ 0.97 (d, J = 7.76 Hz, 3H), 1.03 (d, J = 6.69 Hz, 3H), 1.82–1.99 (m, 1H), 2.28 (s, 3H), 3.77 (d, J = 1.34 Hz, 1H), 4.01 (J = 1.34 Hz, 1H). ^{13}C NMR: δ 19.1, 19.2, 25.0, 31.7,

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77.3, 77.6, 208.7. *anti*-**18**: ^{1}H NMR: δ 0.97 (d, $J = 6.69$ Hz, 3H), 1.03 (m, $J = 6.69$ Hz, 1H), 1.81–1.98 (m, 1H), 2.23 (s, 3H), 3.77 (d, $J = 1.32$ Hz, 1H), 4.22 (d, $J = 0.56$ Hz, 1H). ^{13}C NMR: δ 16.8, 19.5, 27.6, 29.9, 77.9, 78.5, 210.0.

3,4-Dihydroxy-5,5-dimethylhexan-2-one **19**. Colorless oil, $R_f = 0.51$ (petrolether–EtOAc = 1 : 1). HRMS: (m/z) calcd for $C_8H_{16}O_3Na$: 183.0997; found, 183.0992.*syn*-**19** ^{1}H NMR: δ 1.00 (s, 9H), 2.25 (s, 3H), 3.54 (s, 1H), 3.77 (d, $J = 3.79$ Hz, 1H), 4.28 (d, $J = 1.32$ Hz, 1H), ^{13}C NMR: δ 24.9, 26.3, 35.7, 76.6, 77.5, 208.9. *anti*-**19** ^{1}H NMR: δ 1.00 (s, 9H), 2.28 (s, 3H), 3.55 (s, 1H), 3.79 (d, $J = 1.42$ Hz, 1H), 4.28 (s, 1H). ^{13}C NMR: δ 24.2, 26.3, 35.7. 76.7, 79.9, 208.9

4-Cyclohexyl-3,4-dihydroxybutan-2-one **20**.[55] *syn*-**20**: ^{1}H NMR: δ 0.99–1.19 (m, 4H), 1.42–1.67 (m, 6H), 1.93 (d, $J = 13.05$ Hz, 1H), 2.11 (s, 3H), 2.64 (d, $J = 9.18$ Hz, 1H), 3,46 (dd, $J_1 = J_2 = 8.73$ Hz, 3.82 (d, $J = 4.66$ Hz, 1H), 4.11 (dd, $J_1 = 1.31$ Hz, $J_2 = 4.46$ Hz, 1H). ^{13}C NMR: δ 25.0, 25.5, 25.6, 26.0, 28.9, 29.3, 40.2, 76.0, 77.2, 209.2. *anti*-**20**: ^{1}H NMR: δ 1.27–1.32 (m, 4H), 1.58–1.64 (m, 6H), 1.98–2.09 (m, 1H), 2.36 (s, 3H), 3,59 (dd, $J_1 = 1.36$ Hz, $J_2 = 8.96$ Hz), 4.09 (d, $J = 7.15$ Hz, 1H), 4.23 (s, 1H). ^{13}C NMR: δ 25.0, 25.7, 26.2, 29.1, 29.5, 40.7, 76.2, 77.2, 208.9.

3,4-Dihydroxy-6-phenylhexan-2-one **21**.[54] *syn*-**21**: ^{1}H NMR: δ 1.88–2.08 (m, 4H), 2.22 (s, 3H), 2.72–2.84 (m, 1H), 3.75 (s, 1H), 3.98 (dd, $J_1 = 0.87$ Hz, $J_2 = 5.71$ Hz, 1H), 4.07 (s, 1H), 7.17–7.32 (m, 5H, ar). ^{13}C NMR: δ 25.2, 32.0, 35.8, 71.0, 79.2, 126.0, 128.4, 128.5, 141.2, 208.0. *anti*-**21**: ^{1}H NMR: δ 1.47–1.58 (m, 1H), 1.78–1.90 (m, 1H), 2.09 (s, 3H), 2.60–2.71 (m, 1H), 2.82–2.91 (m, 1H), 3.11 (d, $J = 7.13$ Hz, 1H), 3.86 (ddd, $J_1 = 3.03$ Hz, $J_2 = 3.47$ Hz, $J_3 = 6.76$ Hz, 1H), 3.93 (d, $J = 5.22$ Hz, 1H), 4.26 (dd, $J_1 = 0.86$ Hz, $J_2 = 3.96$ Hz), 7.16–7.19 (m, 3H, ar), 7.24–7.29 (m, 2H, ar). ^{13}C NMR: δ 26.7, 31.6, 33.2, 71.5, 80.6, 125.9, 128.3 (two signals), 141.6, 208.4.

3,4-Dihydroxy-6-phenylhex-5-en-2-on **22**. Orange oil. HRMS: (m/z) calcd for $C_{12}H_{14}O_3$: 206.0943; found, 206.0943. *syn*-**22**: $R_f = 0.50$ (petrolether–EtOAc = 6 : 4). ^{1}H NMR: δ 2.32 (s, 3H), 3.77 (d, $J = 4.19$ Hz, 1H), 4.24 (s, 1H), 4.66 (d, $J = 4.94$, 1H), 6.34 (dd, $J_1 = 6.41$ Hz, $J_2 = 9.53$ Hz, 1H), 6.70 (dd, $J_1 = 0.47$ Hz, $J_2 = 15.95$ Hz, 1H), 7.25–7.34 (m, 3H, ar), 7.37–7.41 (m, 2H, ar). ^{13}C NMR: δ 25.9, 73.0, 79.8, 126.7, 127.5, 128.1, 128.6, 132.6, 136.0, 207.5. *anti*-**22**: $R_f = 0.49$ (petrolether–EtOAc = 6 : 4). ^{1}H NMR: δ 2.24 (s, 3H), 3.77 (s, 1H) 4.39 (d, $J = 3.62$ Hz, 1H), 4.62 (ddd, $J_1 = 1.00$ Hz, $J_2 = 1.44$ Hz, $J_3 = 3.87$ Hz, 1H), 6.19 (dd, $J_1 = 6.36$ Hz, $J_2 = 15.97$ Hz, 1H), 6.70 (dd, $J_1 = 1.34$ Hz, $J_2 = 15.95$ Hz, 1H), 7.22–7.38 (m, 5H, ar). ^{13}C NMR: δ 27.2, 73.7, 80.3, 125.7, 126.6, 128.1, 128.6, 132.9, 135.9, 207.2.

4-Hydroxy-3-methoxy-4-phenylbutan-2-one **24**.[56] *syn*-**24**: ^{1}H NMR: δ 2.06 (s, 3H), 3.25 (d, $J = 4.15$ Hz, 1H), 3.29 (s, 3H), 3.76 (d, $J = 6.23$ Hz, 1H), 4.88 (dd, $J_1 = 2.27$ Hz, $J_2 = 3.78$ Hz, 1H), 7.28–7.40 (m, 5H, ar). ^{13}C NMR: δ 27.1, 59.0, 74.0, 90.2, 126.6, 128.0, 128.2, 139.6, 210.0. *anti*-**24**: ^{1}H NMR: δ 1.99 (s, 3H), 3.17 (s, 3H), 3.66 (d, $J = 4.35$ Hz, 1H), 3.76 (d, $J = 5.66$ Hz, 1H), 4.80 (dd, $J_1 = 4.72$ Hz, $J_2 = 5.10$ Hz, 1H), 7.20–7.29 (m, 5H, ar). ^{13}C NMR: δ 27.6, 59.2, 74.1, 91.0, 126.4, 127.9, 128.3, 140.0, 210.3.

4-Hydroxy-3-methyl-4-phenylbutan-2-one **27**.[57] *syn*-**27**: ^{1}H NMR: δ 1.09 (d, $J = 7.21$ Hz, 3H), 2.13 (s, 3H), 2.83 (dq, $J_1 = 4.03$ Hz, $J_2 = 7.18$ Hz, 1H), 3.19 (d, $J = 2.62$ Hz, 1H), 5.08 (dd, $J_1 = 1.38$ Hz, $J_2 = 3.72$ Hz, 1H), 7.22–7.35 (m, 5H, ar). ^{13}C NMR: δ 10.1, 29.3, 53.2, 73.0, 125.9, 127.3, 128.2, 141.7, 213.4. *anti*-**27**: ^{1}H NMR: δ 0.91 (d, $J = 7.20$ Hz, 3H), 2.03 (s, 3H), 2.78–2.89 (m, 1H), 3.11 (s, 1H), 4.63 (d, $J = 8.59$ Hz, 1H), 7.19–7.25 (m, 5H, ar). ^{13}C NMR: δ 13.9, 29.9, 53.6, 76.4, 126.5, 127.8, 128.3, 141.9, 213.3.

4-Hydroxy-4-(3-methoxyphenyl)-3-methylbutan-2-one **28**. pale yellow oil. HRMS: (m/z) calcd for $C_{12}H_{16}O_3$: 208.1099; found, 206.208.1099. *syn*-**28**: $R_f = 0.38$ (petrolether–EtOAc = 8 : 2) ^{1}H NMR: δ 1.04 (d, $J = 7.18$ Hz, 3H), 2.06 (s, 3H), 2.78 (m, 1H), 3.47 (d, $J = 2.83$ Hz, 1H), 3.74 (s, 3H), 4.97 (dd, $J_1 = 2.14$ Hz, $J_2 = 3.70$ Hz, 1H), 6.73–6.96 (m, 4H, ar). ^{13}C NMR: δ 10.1, 29.1, 53.2, 54.9, 72.9, 111.3, 112.5, 118.0, 129.0, 143.6, 159.3, 213.0. *anti*-**28**: $R_f = 0.37$ (petrolether–EtOAc = 8 : 2) ^{1}H NMR: δ 0.90 (d, $J = 7.22$ Hz, 3H), 2.03 (s, 3H), 2.84–2.94 (m, 1H), 3.16 (s, 1H), 3.79 (s, 3H), 4.67 (dd, $J_1 = 3.56$ Hz, $J_2 = 5.08$ Hz, 1H), 6.80–8.89 (m, 4H, ar). ^{13}C NMR: δ 14.0, 29.9, 53.5, 55.1, 76.3, 112.0, 113.3, 118.9, 129.3, 143.6, 159.6, 213.3.

4-Hydroxy-3-methyl-6-phenylhex-5-in-2-one **29**.[41] *syn*-**29**: ^{1}H NMR: δ 1.37 (d, $J = 7.27$ Hz, 3H), 2.25 (s, 3H), 2.87 (dq, $J_1 = 2.83$ Hz, $J_2 = 7.28$ Hz, 1H), 3.35 (s, 1H), 4.90 (dd, $J_1 = 4.35$ Hz, $J_2 = 4.53$ Hz, 1H), 7.30–7.32 (m, 3H, ar), 7.41–7.42 (m, 3H, ar). ^{13}C NMR: δ 11.6, 29.0, 52.0, 63.4, 85.5, 87,7, 122.2, 128.2, 128.4, 131.6, 211.5. *anti*-**29**: ^{1}H NMR: δ 1.27 (d, $J = 7.24$ Hz, 3H), 2.25 (s, 3H), 2.96 (m, 1H), 3.34 (s, 1H), 4.76 (dd, $J_1 = 2.57$ Hz, $J_2 = 5.00$ Hz, 1H), 7.27–7.29 (m, 3H, ar), 7.43–7.44 (m, 3H, ar). ^{13}C NMR: δ 13.6, 29.7, 52.6, 64.5, 85.8, 88.0, 122.2, 128.2, 128.4, 131.6, 211.7.

3α-Hydroxy-5β-methy-5-phenyl-dihydrofuran-2-one **33**.[58] ^{1}H NMR: δ 1.75 (s, 3H), 2.36 (dd, $J_1 = 1.70$ Hz, $J_2 = 10.76$ Hz, 1H), 2.99 (dd, $J_1 = 4.53$ Hz, $J_2 = 8.12$ Hz, 1H), 3.10 (d, $J = 3.40$ Hz), 4.82–4.36 (m, 1H), 7.28–7.36 (m, 5H, ar.). ^{13}C NMR: δ 30.7, 44.1, 68.2, 84.5, 124.0, 127.9, 128.8, 143.1, 177.0.

SUMMARY

To sum it up, we were able to obtain a deep insight into the formation of catalytically active multinuclear titanium complexes with mandelic acid as chiral ligand. The formation of titanium(IV)–alkoxide–mandelic acid complexes is very sensitive to the reaction conditions. Under uncontrolled reaction conditions several multinuclear titanium species are formed simultaneously. This might be the reason for the great difficulties, which occurred in the sufficient characterization of those titanium species. When used with these complexes adducts of direct aldol additions with hydroxylated ketones were observed with a high degree of regio- as well as diastereoselectivity. The achieved enantioslectivities were moderate so far, and much more research has to be carried out on the correlation between regio-, diastereo- and enantioselectivity and structure of the multinuclear complexes used.

In the meantime, we have been able to produce titanium catalysts with a higher catalytic activity using other chiral ligands, and future work will aim at the full characterization of these titanium species. On the other hand, we will explore the catalytic properties of the complexes described herein for more organic purposes as alkylations, cyanhydrin syntheses, asymmetric epoxidations and Diels–Alder reactions.

Supporting information

Crystallographic data has been deposited at the Cambridge Crystal Data Centre (CCDC 628487 and 628488). This material can be obtained upon request to CCDC, 12 Union Road, Cambridge, 1EZ, UK (http://www.ccdc.cam.ac.uk; email: deposit@ccdc.cam.ac.uk).

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