Study on an Aldol Reaction Catalyzed by Ti(IV)/Calix[*n*]arene Complexes

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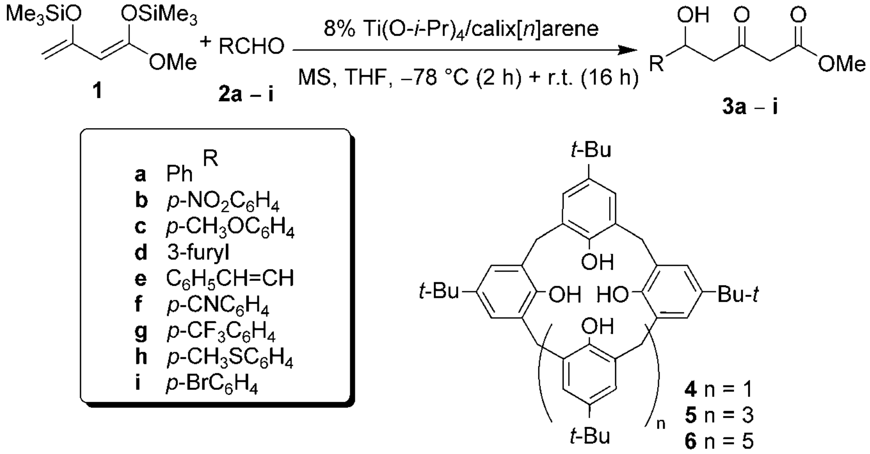
Abstract: Ti(IV)/calixarene complexes, formed *in situ* or previously prepared with standard procedures, can be conveniently used as efficient catalysts in the aldol reaction of Chan's silyloxydiene with a range of aldehydes bearing either activating or deactivating groups, including aromatic, heteroaromatic and α,β-unsaturated ones. The structure of both calixarene ligand and aldehyde, as well as the reaction conditions, strongly influence the efficiency of the reaction. NMR experiments in conjunction with the experimental results suggest that the structure of the catalytic species in the Ti(IV)/calixarene system prepared *in situ* is strongly dependent on the concentration and temperature adopted.

Keywords: aldol condensation; calixarenes; catalysis; Chan's diene; metal-calixarenes complexes

Introduction

In the past two decades calixarene macrocycles have found a wealth of applications in several fields related to supramolecular chemistry,[1] which include, for example, cation,[2] anion,[3] or molecular[4] receptors, chemosensors,[5] self-assembling systems,[6] mechanically interlocked molecules,[7] and nanoporous materials.[8] Among all these applications, their use in catalysis, proposed by Gutsche since his pioneering works,[9] still remains relatively limited and "continues to pose an interesting intellectual and synthetic challenge to organic chemists".[10] In this regard, one of the most promising approaches arises from the association of calixarene scaffolds with single or multiple metal centres.[11] Thus, some interesting biomimetic systems have been proposed,[12] which mainly possess hydrolytic activities,[13] whereas only a very few examples deal with the catalysis of reactions relevant to organic synthesis.[14] These include the enantioselective allylation of aldehydes catalyzed by a zirconium-BINOL catalyst activated by *p-tert*-butylcalix[4]arene,[15] the reductive coupling of alkynes and ketones,[16] the epoxidation of allylic alcohols[17] and alkenes,[18] the Mukaiyama-aldol reaction of aromatic aldehydes with silyl enol ethers,[19] and the cyclotrimerization of alkynes.[20]

Very recently, as a part of our program devoted to efficient approaches to compounds of type **3** (Scheme 1),



Scheme 1. Aldol reaction catalyzed by Ti(IV)/calixarene complexes.

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useful intermediates in the total synthesis of complex molecules,[21] we have found that calix[*n*]arene/Ti(IV) complexes, formed *in situ*, can be used as efficient catalysts in the aldol reaction of Chan's diene **1**[22] with benzaldehyde (**2a**).[23]

It was there evidenced that these complexes act as efficient Lewis acids, enhancing the reactivity of the aldehyde towards the silyloxydiene. In addition, it was found that the catalytic efficiency was affected by the reaction temperature and by the structure of the calixarene ligand **4**–**6**. In particular, three contiguous calixarene phenolic OH groups appeared as a minimal requirement in order to strongly tricoordinate the Ti(IV) cation. In addition, when the macrocycle size was increased to the octameric *p*-*tert*-butylcalix[8]arene (**6**) a decreased yield was observed, probably only limited by solubility factor. As a natural extension of that work, we report here a more detailed study on substrate generality, experimental parameters, and structure of the Ti complex for this aldol reaction.

Results and Discussion

Experimental Parameters and Substrate Generality

The first step in the extension of our previous work was to widen the applicability of the Ti(IV)/calix[*n*]arene catalysis to aldol reactions of Chan's diene with other aldehydes (Scheme 1) besides benzaldehyde, previously used as a test compound. *p*-*tert*-Butylcalix[6]arene (**5**) was chosen as ligand of the Ti(IV) catalytic complex because it gave the best results when benzaldehyde was the substrate.[23]

The catalyst was prepared *in situ* by stirring, for 1 h at room temperature, a 0.02 M solution of the ligand **5** in anhydrous tetrahydrofuran and Ti(O-*i*-Pr)$_4$, in a molar ratio of 1:1. The catalyst solution was then cooled at −78 °C and the aldehyde was added, followed after 30 minutes by the Chan's diene **1**. The resulting solution was stirred under an inert gas atmosphere at −78 °C for 2 h. After warming at room temperature the mixture was stirred for additional 16 h. Then, a desilylation treatment with trifluoroacetic acid afforded the aldol **3** and eventual unreacted materials with no evidence of side products. The results are summarized in Table 1.

Table 1. Aldol reaction catalyzed by 8% mol of Ti(IV)/**5** [catalyst 0.02 M, −78 °C (2 h) → rt (16 h)].

Entry	Aldehyde	Product	Yield [%]
1	**2a**	**3a**	99
2	**2b**	**3b**	40
3	**2c**	**3c**	24
4	**2d**	**3d**	nd
5	**2e**	**3e**	20

According to the results shown in Table 1, the Ti(IV)/*p*-*tert*-butylcalix[6]arene complex gave products in low yields with all tested substrates with the exception of benzaldehyde (entry 1, Table 1). Clearly, the complex still shows some catalytic activity, but the reaction conditions seem to be inappropriate both for the *p*-substituted benzaldehydes (entries 2 and 3, Table 1), as well as for heteroaromatic (entry 4, Table 1) and α,β-unsaturated aldehydes (entry 5, Table 1). Therefore, we decided to verify the possibility to improve the efficiency of the procedure through appropriate changes of the experimental conditions.

In particular, our previous studies on the analogous Ti(IV)/BINOL catalytic system[24] suggested that the catalyst concentration, the substrate concentration, and the temperature represented the most significant parameters of the reaction.[25] Therefore, we decided to test the effect produced by changes in the concentration of the complex and using *p*-nitrobenzaldehyde (**2b**) as substrate (Table 2).

When the reaction was carried out in a more concentrated solution of the catalyst (0.04 M) (entry 2, Table 2) a significant improvement in efficiency was observed (84% yield). In addition, it was observed that by performing the reaction simply at room temperature for 16 h the aldol adduct was formed in 92% yield (entry 3, Table 2).

This result induced us to extend these last catalytic conditions to other aldehydes (Table 3).

A comparison of the experimental results (entries 2–4 and entries 5 and 6, Table 3) revealed a strong influence of the *p*-substitution of the aromatic aldehyde on the efficiency of the reaction. In particular, electron-withdrawing *para*-substituents (entries 2–4, Table 3) had a positive effect on the yield (84–92%), whereas electron-donating groups (entries 5 and 6, Table 3) decreased the yield of aldol adduct (10–50%). As expected, with *p*-bromobenzaldehyde (**2i**) as substrate (entry 7, Table 3) the yield (39%) was of intermediate value

Table 2. Effects of the catalyst concentration and of the temperature on the aldol reaction of **2b** catalyzed by the complex Ti(IV)/**5**.

Entry	Catalyst Concentration [M]	Temperature (time)	Yield of **3b** [%]
1	0.02	−78 °C (2 h) + rt (16 h)	40
2	0.04	−78 °C (2 h) + rt (16 h)	84
3	0.04	rt (16 h)	92

with respect to the two groups of aldehydes. In addition, these new reaction conditions seemed to be better than the previous ones also for heteroaromatic aldehyde 3-furfural (**2d**) (entry 8, Table 3) and for α,β-unsaturated cinnamaldehyde (**2e**) (entry 9, Table 3).

p-tert-Butylcalix[4]arene (**4**) was also examined as ligand of the Ti(IV) catalytic complex, because in the previous work it showed a good yield (77%)[23] of adduct in the aldol reaction of benzaldehyde with Chan's diene (**1**). However, its screening with several aldehydes generally gave low chemical yields (Table 4), the best result (56%) being with *p*-nitrobenzaldehyde (entry 1, Table 4).

In analogy with the Ti(IV)/*p-tert*-butylcalix[6]arene complex, changes of reaction conditions were also examined using *p*-nitrobenzaldehyde (**2b**) as substrate and the results are listed in Table 5. A more concentrated catalyst solution gave no difference in efficiency (entry 2, Table 5), while no aldol adduct was observed when the reaction was performed at room temperature (entry 3, Table 5).

In order to obtain a more complete picture of the catalytic properties of the Ti(IV)/*p-tert*-butylcalix[4]arene system the reaction conditions of entry 2, Table 5 were also extended to different substrates and the results are summarized in Table 6.

As shown in Table 6, the Ti(IV)/*p-tert*-butylcalix[4]arene system gave slightly higher yields of adduct with deactivated (entries 5 and 6 Table 6) and α,β-unsaturated aldehydes (entry 8, Table 6) with respect to activated ones (entries 2–4, Table 6), showing a different trend with respect to the calix[6]arene-based complex.

At this point it can be concluded that with an appropriate choice of the calix[*n*]arene ligand and reaction parameters the aldol reaction catalyzed by the Ti(IV)/calixarene system could very likely be applied to a wide range of aldehyde substrates.

Structure of the Ti(IV)/Calixarene Catalyst. NMR Experiments

An interesting question that can be posed at this point concerns the structure of the "catalytically active species" formed *in situ* in the preparation of the Ti(IV)/calixarene catalytic system.

In order to clarify this aspect, NMR experiments were performed under conditions similar to those adopted in the aldol reaction. Thus, a 0.04 M solution of the catalytic system was prepared by adding 1 equiv. of *p-tert*-butylcalix[4]arene to 1 equiv. of Ti(O-*i*-Pr)$_4$ in THF-d_8, and ^{1}H NMR spectra were measured at room temperature (Figure 1). As illustrated in Figure 1a, a complex methylene region of the spectrum was observed, with a large number of AX systems of ArCH$_2$Ar groups, indicating that several species are under equilibrium in solution and whose characterization proves to be impracticable. An analogous experiment on a 0.02 M catalyst solution

Table 3. Aldol reaction catalyzed by 8% mol of Ti(IV)/**5** [catalyst 0.04 M, rt (16 h)].

Entry	Aldehyde	Product	Yield [%]
1	**2a**	**3a**	56
2	**2b**	**3b**	92
3	**2f**	**3f**	84
4	**2g**	**3g**	90
5	**2c**	**3c**	10
6	**2h**	**3h**	50
7	**2i**	**3i**	39
8	**2d**	**3d**	13
9	**2e**	**3e**	46

Table 4. Aldol reaction catalyzed by 8% mol of Ti(IV)/**4**[catalyst 0.02 M, −78 °C (2 h) → rt (16 h)].

Entry	Aldehyde	Product	Yield [%]
1	**2b**	**3b**	56
2	**2c**	**3c**	10
3	**2d**	**3d**	Nd
4	**2e**	**3e**	27

Table 6. Aldol reaction catalyzed by 8% mol of Ti(IV)/**4** [catalyst 0.04 M, −78 °C (2 h) → rt (16 h)].

Entry	Aldehyde	Product	Yield [%]
1	**2a**	**3a**	50
2	**2b**	**3b**	56
3	**2f**	**3f**	68
4	**2g**	**3g**	50
5	**2c**	**3c**	74
6	**2h**	**3h**	65
7	**2i**	**3i**	55
8	**2e**	**3e**	70
9	**2d**	**3d**	34

Table 5. Effects of catalyst concentration and of the temperature on the aldol reaction of **2b** catalyzed by the complex Ti(IV)/**4**.

Entry	Catalyst Concentration [M]	Temperature (time)	Yield of **3b** [%]
1	0.02	−78 °C (2 h) + rt (16 h)	56
2	0.04	−78 °C (2 h) + rt (16 h)	56
3	0.04	rt (16 h)	nd

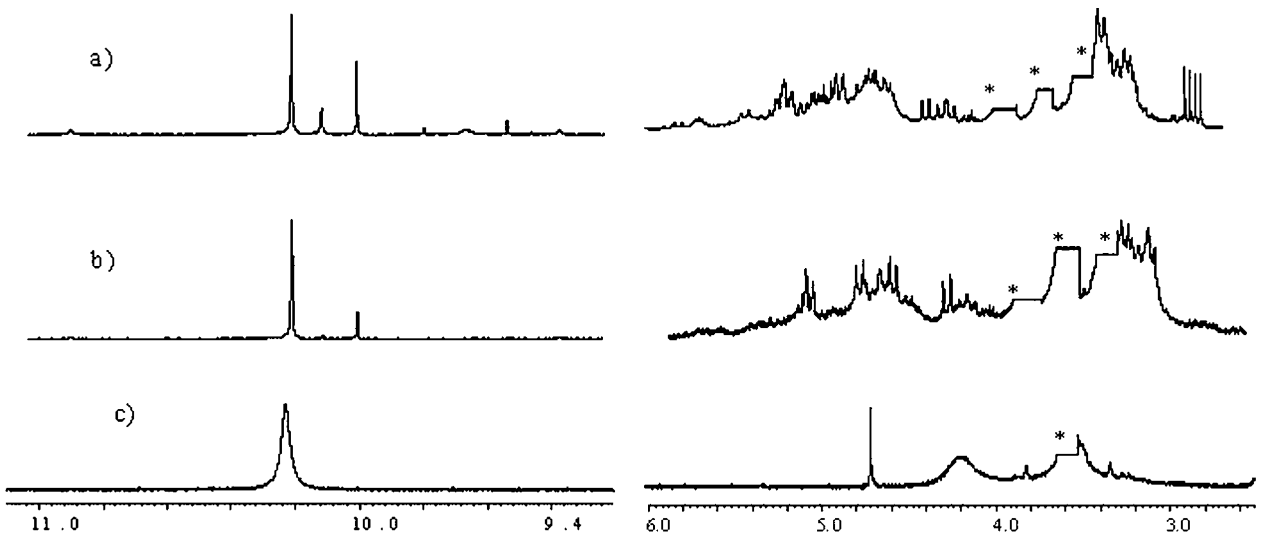

Figure 1. Comparison of methylene and OH regions of the ^{1}H NMR spectra of Ti(IV)/*p-tert*-butylcalix[4]arene system in THF-d_8: a) 0.04 M catalyst solution; b) 0.02 M catalyst solution; c) free ligand **4** (asterisks denote peaks of residual solvents).

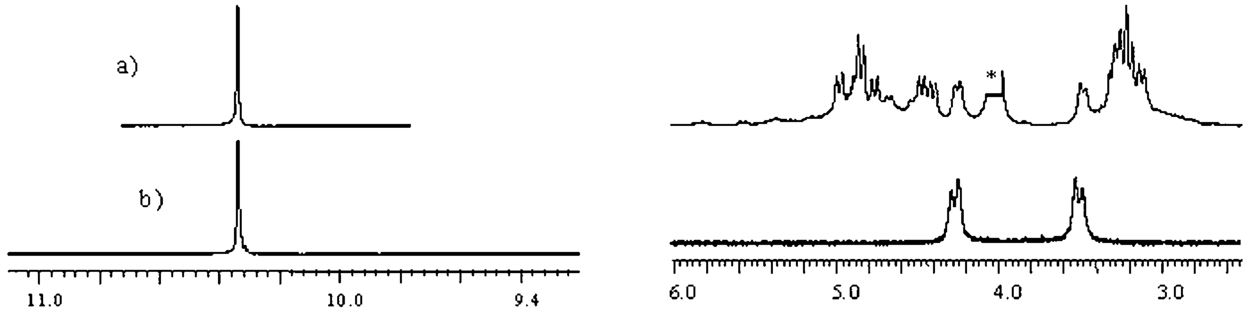

Figure 2. Comparison of methylene and OH regions of the ^{1}H NMR spectra of Ti(IV)/*p-tert*-butylcalix[4]arene system in $CDCl_3$: a) 0.04 M catalyst solution; b) free ligand **4** (the asterisk denotes a peak of a residual solvent).

showed a modified pattern of $ArCH_2Ar$ AX systems (Figure 1b) suggesting that concentration-dependent oligomeric complexes could also be present, besides unreacted calix[4]arene **4** (Figure 1c).

A similar behaviour was also observed for an NMR experiment on a 0.04 M catalyst solution in $CDCl_3$ (Figure 2) where sharper signals for several $ArCH_2Ar$ AX systems were observed (Figure 2a), besides those of unreacted calix[4]arene (Figure 2b), indicating the formation of more than one species. Considering the structural diversity and complexity observed for the catalytic system, no further attempts were made towards its complete characterization.

Structure of the Ti(IV)/Calixarene Catalyst. Use of Preformed, Structurally Characterized Ti(IV)/Calixarene Complexes

Useful information concerning the structure of the Ti(IV)/calixarene catalyst could be alternatively gained by the study of the catalytic activity of preformed and structurally well-characterized Ti(IV)/calixarene complexes. Among the several examples of such complexes characterized by X-ray analysis and reported in the literature,[26] we first examined the Ti(IV)/*p-tert*-butylcalix[4]arene complex **7** reported by Clegg et al. (Figure 3).[27] The X-ray crystal structure of **7** evidenced a centrosymmetric *p-tert*-butylcalix[4]arene dimer containing a tetranuclear Ti(IV) core, whose metal centres exhibit a distorted trigonal bipyramidal geometry.

The crystalline complex **7** was prepared and fully characterized in agreement with literature data.[27] Its catalytic activity in the aldol reaction of **1** with various aldehydes was evaluated at room temperature using a 0.02 M catalyst solution in THF stirred at room temperature for 1 h before use (Table 7).

As can be seen from the experimental results reported in Table 7, Clegg's complex **7** generally shows an improved catalytic efficiency with respect to the Ti(IV)/calix[4]arene system prepared *in situ* (for comparison see Tables **4** and **6**). This result could be partially ex-

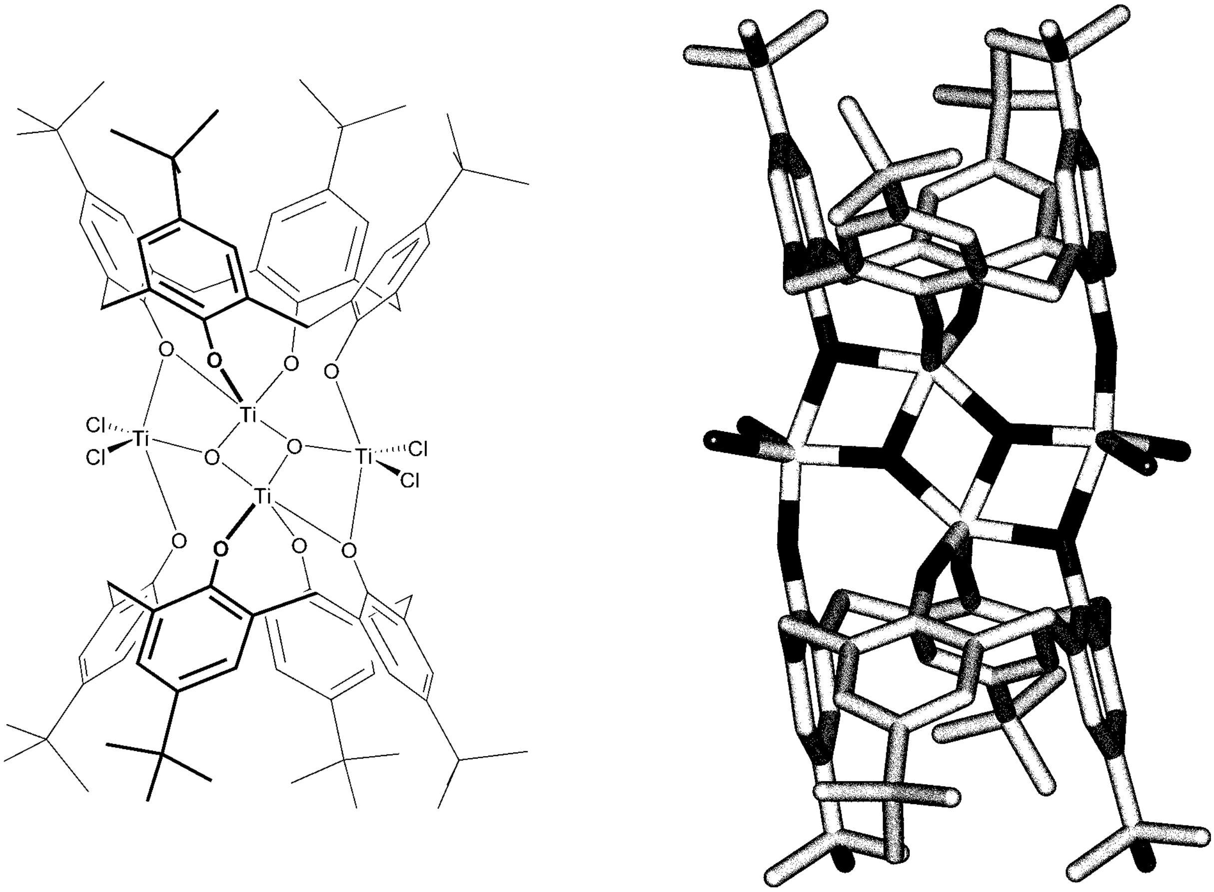

Figure 3. Structure drawing (*left*) and X-ray crystal structure (*right*, CCDC reference number 186/1091) of Clegg's complex **7**.

Table 7. Aldol reaction catalyzed by 8% mol of the complex **7** [catalyst 0.02 M, rt (16 h)].

Entry	Aldehyde	Product	Yield [%]
1	**2a**	**3a**	74
2	**2b**	**3b**	93
3	**2f**	**3f**	80
4	**2g**	**3g**	89
5	**2c**	**3c**	50
6	**2d**	**3d**	91
7	**2e**	**3e**	66

plained by the high nuclearity of the complex and by the enhanced Lewis acidity of chlorine-bearing titanium(IV) metal centres.

In order to verify the influence of the nuclearity, the Ti(IV)/*p-tert*-butylcalix[4]arene complex **8** reported by Floriani and co-workers[28] (Figure 4) was also examined.

In this instance the X-ray crystal structure evidenced a mononuclear Ti(IV) complex with a single calix[4]arene ligand and with the metal centre linked to a single chlorine atom. The experimental results of the examination of the catalytic activity of complex **8** are reported in Table 8.

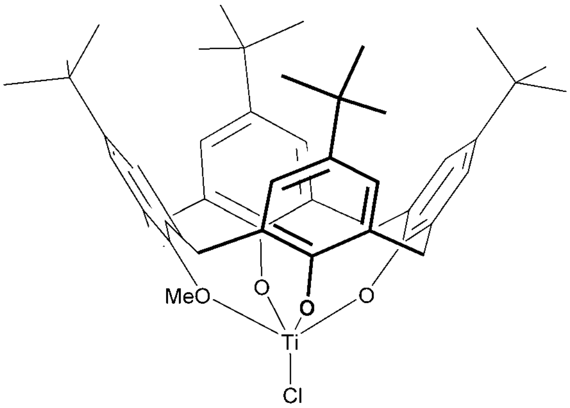

Figure 4. Structure drawing of complex **8**.

It is clearly evident that, under similar conditions, this complex exhibited a lower catalytic efficiency with respect to **7**, lending support to the above nuclearity argument.

A further preformed Ti(IV)/*p-tert*-butylcalix[4]arene complex **9**, also reported by Floriani and co-workers,[28] was examined in this study (Figure 5).

The structure of **9** is very similar to that of **8**, with the exception that two chlorine atoms are here linked to the

Table 8. Aldol reaction catalyzed by 8% mol of the complex **8** [catalyst 0.02 M, rt (16 h)].

Entry	Aldehyde	Product	Yield [%]
1	**2a**	**3a**	27
2	**2b**	**3b**	91
3	**2f**	**3f**	45
4	**2g**	**3g**	31
5	**2c**	**3c**	10
6	**2d**	**3d**	nd
7	**2e**	**3e**	10

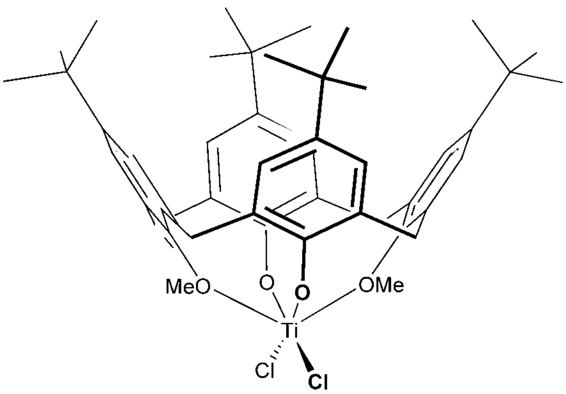

Figure 5. Structure drawing of complex **9**.

Table 9. Aldol reaction catalyzed by 8% mol of the complex **9** [catalyst 0.02 M, rt (16 h)].

Entry	Aldehyde **2**	Product **3**	Yield [%]
1	**2a**	**3a**	17
2	**2b**	**3b**	83
3	**2f**	**3f**	70
4	**2g**	**3g**	52
5	**2c**	**3c**	0
6	**2d**	**3d**	nd
7	**2e**	**3e**	0

Ti(IV) atom. This offers the opportunity to test the influence of an additional chloride ligand in **9** with respect to **8**.

The results shown in Table 9 indicate that complex **9** was catalytically less efficient in comparison to **8** under similar conditions. Therefore, in contrast to what was supposed to explain the higher efficiency of **7**, it seems that the presence of one more chloride ligand negatively affects the catalytic activity.

A comparison of the data reported in Tables 7–9 suggests that even slight changes in the structure of the complex are determinant with respect to its catalytic activity (*cf.* **9** with **8**), but, on the other hand, no clear structural conclusions can be inferred on the basis of the observed efficiency.

Conclusion

This study has evidenced that Ti(IV)/calixarene complexes, formed *in situ* or previously prepared by a standard procedure, can be conveniently used as efficient catalysts in aldol reaction of Chan's silyloxydiene with a range of aldehydes bearing either activating or deactivating groups. High yields of aldol adduct can be obtained by a proper choice of the calix[*n*]arene ligand and reaction conditions (mainly catalyst concentration and temperature). The use of preformed and well-characterized complexes has evidenced that the structure strongly affects the catalytic efficiency.

NMR experiments in conjunction with the experimental results suggest that the actual structure of the catalytic species in the Ti(IV)/calixarene system prepared *in situ* is strongly dependent on the concentration and temperature adopted. Therefore, upon changing the experimental conditions the catalyst could be either a monomeric/mononuclear species as well as a di- or polymeric/polynuclear one. Clearly, these structural changes imply a different catalytic efficiency which is testified by the quite different results obtained under diverse conditions.

In accordance with previous reports,[29] the above results suggest a catalytic mechanism in which the aldehyde is activated upon coordination to a Lewis acid. The electrophilic complex is then attacked by the silyloxydiene to produce an intermediate which undergoes a silyl group transfer to aldolate oxygen and thus regenerates the catalyst and provides the silylated aldol product.

The extension to an enantioselective version of this aldol reaction, which would require the use of properly designed chiral calixarene ligands, is currently under study in our laboratory. In addition, the results of this work strongly encourage further studies on the catalytic activity of metal/calixarene complexes in other reactions useful in organic synthesis.

Experimental Section

General Remarks

All reactions were carried out under an atmosphere of argon using oven-dried glassware with freshly distilled solvents. THF was distilled from CaH_2 and then from $LiAlH_4$; toluene and *n*-hexane were distilled from CaH_2. Molecular sieves (4 Å) were oven dried at 250 °C overnight and stored under an atmosphere of nitrogen. Thin-layer chromatography was performed on Merck Kiesegel 60 (0.25 mm) eluting with the solvents indicated, visualized by a 254 nm UV lamp or aqueous ceric sulfate solution followed by heating. Column chromatography was carried out using silica gel 60 (70–230 mesh, Merck). NMR spectra were recorded on a Bruker DRX 400 (400.13 MHz for ^1H and 100.03 for ^{13}C), chemical shifts are given in ppm (δ) scale; for the spectra in $CDCl_3$, the $CHCl_3$ signal was used as internal standard ($\delta = 7.26$ for ^{1}H, $\delta = 77.0$ for ^{13}C). The mass spectra were recorded on a VG TRIO 2000 spectrometer. *p-tert*-Butylcalix[4]arene (4),[30] *p-tert*-butylcalix[6]-arene (5),[31] complexes **7**,[27] **8**,[28] and **9**[28] were prepared as reported. The aldol adducts **3a–e** were previously described.[24]

General Procedure for Aldol Reactions Catalyzed by Ti(IV)/*p-tert*-Butylcalix[*n*]arene Prepared *in situ* [0.02 M Catalyst Concentration, −78 °C (2 h) → rt (16 h)]

A mixture of Ti(O-*i*-Pr)$_4$ (0.08 mmol), *p-tert*-butylcalix[*n*]arene (0.08 mmol), and molecular sieves (340 mg) in THF (4 mL) was stirred at room temperature for 1 h. After cooling the mixture to −78 °C, the aldehyde **2** (1 mmol) was added dropwise followed, after 30 min, by silyloxydiene **1** (2 mmol) in THF (1 mL). The resulting solution was stirred under an argon atmosphere at −78 °C for 2 h. After warming at room temperature, the mixture was stirred overnight (16 h). The mixture was cooled to −78 °C and TFA (0.4 mL) was added. The solution was warmed to room temperature and stirred for 1 h until the desilylation was complete. The reaction mixture was diluted with ether and a saturated aqueous solution of NaHCO$_3$ (2 mL) was added dropwise. The mixture was stirred until the evolution of gas ceased (30 min), then the organic layer was separated and washed with brine, dried over MgSO$_4$ and concentrated under vacuum. Purification by chromatography on silica gel, using CHCl$_3$/MeOH (98:2, *v/v*) as the eluent, afforded the aldol adduct **3**.

Procedure for Aldol Reactions Catalyzed by Ti(IV)/*p-tert*-Butylcalix[6]arene Prepared *in situ* [0.04 M Catalyst Concentration, rt (16 h)]

A mixture of Ti(O-*i*-Pr)$_4$ (0.08 mmol), *p-tert*-butylcalix[6]arene (0.08 mmol), and molecular sieves (340 mg) in THF (2 mL) was stirred at room temperature for 1 h. The mixture was cooled to −78 °C and then THF (2 mL) and the aldehyde **2** (1 mmol) were added. After 30 min, silyloxydiene **1** (2 mmol) with THF (1 mL) were added in a similar way and the mixture was stirred overnight (16 h). The mixture was cooled to −78 °C and TFA (0.4 mL) was added. Then the solution was warmed to room temperature and stirred for 1 h after which desilylation was complete. The reaction mixture was treated as described above.

Procedure for Aldol Reactions Catalyzed by Ti(IV)/*p-tert*-Butylcalix[4]arene Prepared *in situ* [0.04 M Catalyst Concentration, −78 °C (2 h) → rt (16 h)]

A mixture of Ti(O-*i*-Pr)$_4$ (0.08 mmol), *p-tert*-butylcalix[4]arene (0.08 mmol), and molecular sieves (340 mg) in THF (2 mL) was stirred at room temperature for 1 h. The mixture was cooled to −78 °C and then THF (2 mL) and aldehyde **2** (1 mmol) were added. After 30 min, silyloxydiene **1** (2 mmol) with THF (1 mL) were added in a similar way. The resulting solution was stirred under an argon atmosphere at −78 °C for 2 h. After warming at room temperature the mixture was stirred overnight (16 h). The mixture was cooled to −78 °C and TFA (0.4 mL) was added. Then the solution was warmed to room temperature and stirred for 1 h after which desilylation was complete. The reaction mixture was treated as described above.

Procedure for Aldol Reactions Catalyzed by Preformed Ti(IV)/Calixarene Complexes 7, 8, and 9 [0.02 M Catalyst Concentration, rt (16 h)]

A mixture of the complex (0.02 mmol), and molecular sieves (100 mg) in THF (0.5 mL) was stirred at room temperature for 1 h. Then THF (1.5 mL) and aldehyde **2** (0.25 mmol) were added. After 15 min, silyloxydiene **1** (0.5 mmol) with THF (0.5 mL) were added in a similar way and the mixture was stirred overnight (16 h). The mixture was cooled to −78 °C and TFA (0.1 mL) was added. The solution was warmed to 0 °C and stirred for 1 h, then further warmed to room temperature and stirred for 1 h after which desilylation was complete. The reaction mixture was treated as described above.

Procedure for Preparation of Ti(IV)/*p-tert*-Butylcalix[4]arene Complex for NMR Studies

A mixture of Ti(O-*i*-Pr)$_4$ (0.08 or 0.02 mmol), *p-tert*-butylcalix[4]arene (0.08 or 0.02 mmol), and molecular sieves (340 mg) in THF-d_8 (or CDCl$_3$) (2 or 1 mL) was stirred at room temperature for 1 h. Then the ^{1}H NMR spectra were measured at room temperature.

Characterization of Products 3

***5-(*p*-Cyanophenyl)-5-hydroxy-3-oxo-pentanoic acid methyl ester* (3f):** Pale yellow oil. $R_f = 0.25$ (MeOH/CHCl$_3$, 1/9 v/v); IR (liquid film): $\nu_{max} = 3508$, 2985, 2940, 2230, 1740, 1646, 1314, 1106 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.65$ (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 5.24 (dd, $J = 8.0$, 6.0 Hz, 1H), 3.80 (s, 3H), 3.49 (s, 2H), 2.94 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (62.89 MHz, CDCl$_3$): $\delta = 202.2$, 167.4, 148.2, 132.4, 126.5, 118.8, 69.0, 52.6, 51.3, 49.6; EI-MS: $m/z = 249$ (M$^+$); anal. calcd. for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, N 5.67; found: C 63.24, H 5.20, N 5.82.

***5-(*p*-Trifluoromethylphenyl)-5-hydroxy-3-oxo-pentanoic acid methyl ester* (3g):** Pale yellow oil. $R_f = 0.2$ (MeOH/CHCl$_3$, 1/9 v/v); IR (liquid film): $\nu_{max} = 3500$, 2988, 2950, 1740, 1640, 1358, 1106 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.62$ (d, $J = 8.1$ Hz, 2H), 7.49 (d, $J = 8.1$ Hz, 2H), 5.27 (dd, $J = 8.2$, 4.2 Hz, 1H), 3.73 (s, 3H), 3.52 (s, 2H), 2.95 (m, 2H); ^{13}C NMR (62.89 MHz, CDCl$_3$): $\delta = 202.4$, 167.2, 146.5, 125.9, 125.5, 123.0, 69.1, 52.5, 51.3, 49.5; EI-MS: $m/z = 292$ (M$^+$); anal. calcd. for $C_{13}H_{13}F_3O_4$: C 53.80, H 4.51, F 19.64; found: C 53.71, H 4.41, F 19.73.

***5-(*p*-Methylthiophenyl)-5-hydroxy-3-oxo-pentanoic acid methyl ester* (3 h):** Pale yellow oil. $R_f = 0.36$ (MeOH/CHCl$_3$, 1/9 v/v); IR (liquid film): $\nu_{max} = 3504$, 2988, 2940, 1740, 1616,1378, 1106 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.24$ (m, 4H), 5.11 (dd, $J = 9.0$, 3.2 Hz, 1H), 3.71 (s, 3H), 3.48 (s, 2H), 2.96 (dd, $J = 17.2$, 9.0 Hz, 1H), 2.85 (dd, $J = 17.2$, 3.2 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (62.89 MHz, CDCl$_3$): $\delta = 202.5$, 167.3, 139.4, 137.9, 126.7, 69.4, 52.4, 51.2, 49.6, 15.8; EI-MS: *m/z* = 280 (M^+); anal. calcd. for $C_{13}H_{16}O_4S$: C 58.19, H 6.01, S 11.95; found: C 58.06, H 6.09, S 11.87.

***5-(p-Bromophenyl)-5-hydroxy-3-oxo-pentanoic acid methyl ester* (3i):** Pale yellow oil. R_f = 0.28 (MeOH/CHCl$_3$, 1/9 v/v); IR (liquid film): ν_{max} = 3508, 2978, 2950, 1740, 1616, 1316, 1106, 1070 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.15 (dd, *J* = 8.1, 3.5 Hz, 1H), 3.74 (s, 3H), 3.49 (s, 2H), 2.96 (dd, *J* = 17.5, 8.1 Hz, 1H), 2.89 (dd, *J* = 17.5, 3.6 Hz, 1H); ^{13}C NMR (62.89 MHz, CDCl$_3$): δ = 202.7, 169.0, 141.4, 131.6, 127.6, 113.0, 69.1, 52.4, 49.5, 31.3; EI-MS: *m/z* = 302 (M^+); anal. calcd for $C_{12}H_{13}BrO_4$: C 47.86, H 4.35, Br 26.53; found: C 47.91, H 4.43, Br 26.41.

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