

Mechanism of the Mukaiyama Aldol Reaction: The First Solid-State Characterization of a Trichlorotitanium Aldolate

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Summary: The reaction of the silyl ketene acetal $\text{Me}_2\text{C}=\text{C}(\text{OMe})\text{OSiMe}_3$ (**1**) with preformed TiCl_4 carbonyl adducts (the monomeric $[\text{PhC}(\text{O})\text{C}(\text{O})\text{PhTiCl}_4]$ (**2**) and the dimeric $\{[\text{MesCHOTi}(\text{Cl})_3]_2(\mu\text{-Cl})\}$ ($\text{Mes} = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$; **3**)) led to the isolation and structural characterization of the corresponding titanium aldolate complexes $\{[(\text{PhCO})\text{PhC}(\text{O})\text{C}(\text{Me}_2)\text{C}(\text{OMe})\text{OTi}(\text{Cl})_2]_2(\mu\text{-Cl})_2\}$ (**4**) and $\{[\text{MesCH}(\text{O})\text{C}(\text{Me}_2)\text{C}(\text{OMe})\text{OTi}(\text{Cl})_2]_2(\mu\text{-Cl})_2\}$ (**5**), in which the aldolate fragment functions as a bidentate ligand in dimeric titanium complexes bridged by two chlorine atoms. Crystallographic details: **4** is monoclinic, space group $P2_1/n$, with $a = 9.029(1)$ Å, $b = 17.468(2)$ Å, $c = 13.165(2)$ Å, $\beta = 98.81(2)^\circ$, $Z = 2$, and $R = 0.53$.

Aldol condensation from the addition of silyl enol ethers and silyl ketene acetals to carbonyl compounds assisted by TiCl_4 , the so-called Mukaiyama reaction,¹ is of major importance in synthetic methodology today.² Furthermore, the almost exclusive use of silyl enol ethers in aldolic reactions catalyzed by Lewis acids should be emphasized.³

The Lewis acid in the Mukaiyama reaction is believed to be enhancing the electrophilicity⁴ of the carbonyl carbon rather than forming titanium enolate.⁵ This assumption is reminiscent of the function of TiCl_4 in the Passerini reaction we elucidated recently.⁶

Although the value of the substrate and reaction conditions greatly affect the reaction pathway,⁷ acyclic

transition states have generally been proposed in the reaction mechanism.⁸ In a recent report Reetz,⁹ though using the fast-inject NMR technique, was unable to observe any intermediate in the reaction between a chiral alkoxy aldehyde and a silyl enol ether.

We propose a reaction pathway for the Mukaiyama reaction based (i) on the use of isolated and well-characterized TiCl_4 -carbonyl adducts, which, in contrast to the reaction carried out *in situ*, make very unprobable the presence in the reaction media of TiCl_4 , which can drive the reaction through a different pathway, and (ii) on the structural characterization of the final TiCl_3 aldolate¹⁰ preceding the normal workup. This is the first example of a structurally characterized TiCl_3 aldolate, showing the aldolate bonding mode to the metal.

Results and Discussion

The silyl ketene acetal **1** was added to the preformed and isolated TiCl_4 -carbonyl adducts **2**⁶ and **3**,¹¹ rather than to a solution of the carbonyl to which TiCl_4 was added. Adducts **2** and **3** have been fully characterized, including a single-crystal X-ray analysis of **2**, and they have been used in the elucidation of Passerini reaction intermediates. They exemplify the structure of monomeric and dimeric TiCl_4 -carbonyl adducts.

Both reactions (Schemes 1 and 2) have been carried out under very similar conditions in toluene at -78°C , and they led to the corresponding titanium aldolate complex in reasonable yield (71%, **4**; 44%, **5**). A plausible self-explanatory pathway is exemplified in Scheme 1, and it is essentially based on the structural characterization of complexes **2** and **4**. The elimination of ClSiMe_3 leaves a vacant coordination site, which is filled by the sharing of a chlorine atom with another titanium in the dimerization process. As opposed to the Passerini intermediates,⁶ the ligand built around titanium is bi- rather than tridentate. We should emphasize how the use of **2**, containing a strongly titanium-bonded bidentate dibenzoyl ligand,⁶

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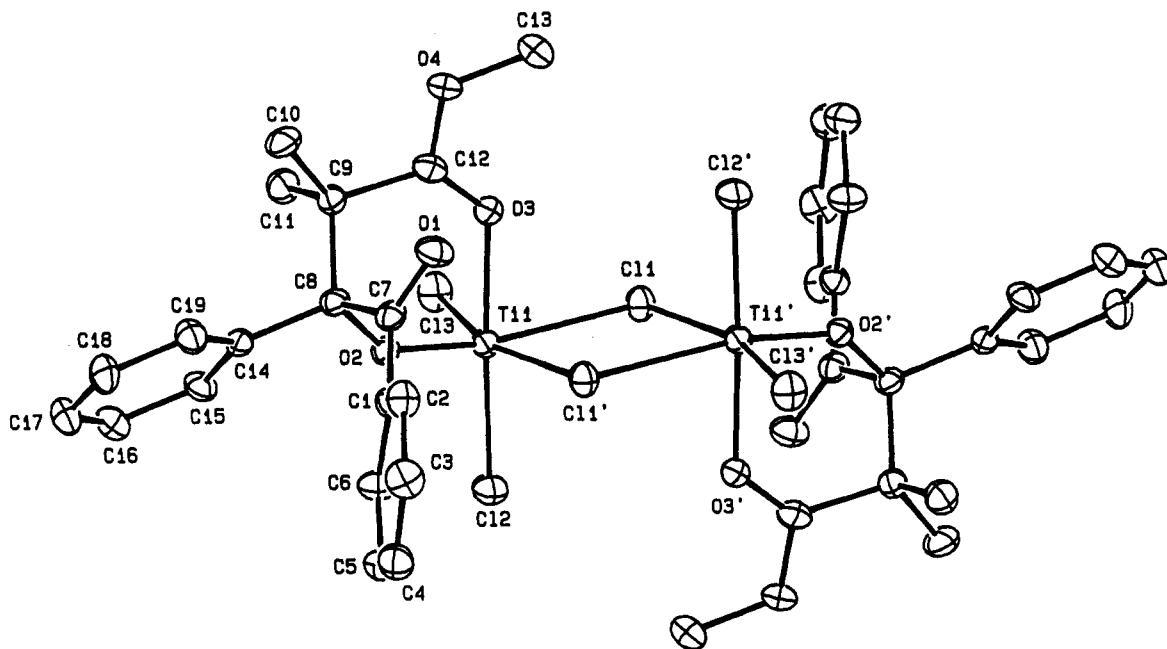
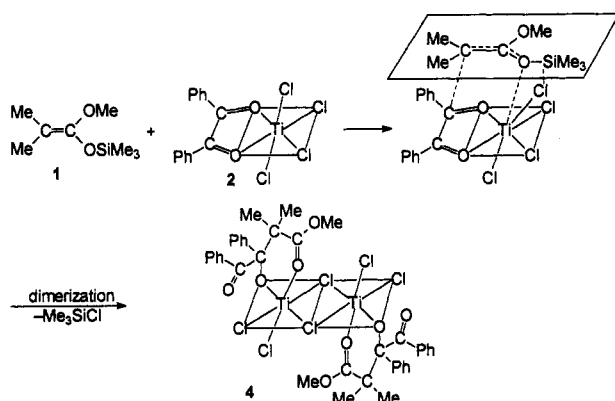
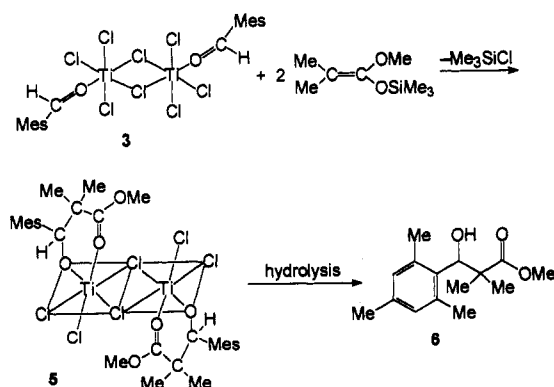


Figure 1. ORTEP view of complex 4 (30% probability ellipsoids).

Scheme 1



Scheme 2



rules out an alternative plausible pathway for the Mukaiyama reaction when the reaction is carried out *in situ*. In the latter case, free TiCl_4 can react with the silyl ether to produce the corresponding titanium enolate, driving the reaction through a pathway different from that in Schemes 1 and 2. The structure of the centrosymmetric complex 4 is shown in Figure 1, while selected structural parameters are listed in Table 1. The aldolate ligand, originating from the addition of the nucleophilic silyl ketene acetal to one of the carbonyl groups of the dibenzoyl

Table 1. Relevant Bond Distances (Å) and Angles (deg) for Complex 4

Ti1-C11	2.516(1)	O3-C12	1.224(6)
Ti1-C11' ^a	2.444(2)	O4-C12	1.313(6)
Ti1-C12	2.255(2)	O4-C13	1.453(7)
Ti1-C13	2.260(2)	C1-C7	1.476(7)
Ti1-O2	1.773(4)	C7-C8	1.551(7)
Ti1-O3	2.106(4)	C8-C9	1.566(6)
O1-C7	1.223(7)	C8-C14	1.529(7)
O2-C8	1.433(6)	C9-C12	1.537(7)
O2-Ti1-O3	82.8(2)	C1-C7-C8	121.6(4)
C12-Ti1-O3	175.5(1)	O1-C7-C8	118.2(4)
C12-Ti1-O2	97.6(1)	O2-C8-C7	104.3(3)
C11'-Ti1-C13	162.7(1)	C7-C8-C14	112.4(4)
C11-Ti1-O3	84.0(1)	C7-C8-C9	111.0(4)
C11-Ti1-O2	165.2(1)	O2-C8-C14	109.0(4)
C11-Ti1-C12	95.0(1)	O2-C8-C9	108.6(3)
Ti1-C11-Ti1'	101.6(1)	C9-C8-C14	111.2(4)
Ti1-O2-C8	141.3(3)	C8-C9-C12	107.1(4)
Ti1-O3-C12	129.6(4)	O4-C12-C9	113.1(4)
C12-O4-C13	117.2(4)	O3-C12-C9	125.5(5)
C6-C1-C7	122.5(5)	O3-C12-O4	121.3(5)
C2-C1-C7	117.3(5)	C8-C14-C19	120.1(5)
C2-C1-C6	120.1(5)	C8-C14-C15	120.4(5)
O1-C7-C1	120.2(5)	C15-C14-C19	119.4(5)

^a The prime indicates the symmetry transformation $-x, 1-y, 1-z$.

species, becomes a bidentate ligand, chelating titanium with a concomitant detachment of the other dibenzoyl oxygen. Analogous origin and structural features have been observed in titanium homoenolates¹² and in intermediates of the Passerini reaction.⁶ The six-membered metallacycle is folded along the Ti-C9 line by $29.3(2)^\circ$, the folding being defined by the dihedral angle between the two mean planes of the two moieties Ti₁O₃C₁₂C₉ and Ti₁O₂C₉C₈. The mean plane through the metallacycle is perpendicular to the Ti₂Cl₂ planar core, which is also nearly perpendicular to the best equatorial plane defined by C₁₁, C₁₂, O₂, O₃, the dihedral angle being $92.3(1)^\circ$. Titanium is 0.105(1) Å out of the equatorial plane. The bonding scheme proposed for the aldolate ligand (see Scheme 1) is supported by the structural parameters (see

Table 2. Fractional Atomic Coordinates ($\times 10^4$) for Complex 4

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
Ti1	1338.6(9)	5656.2(5)	4398.0(7)
Cl1	779.7(13)	4264.2(6)	4652.0(11)
Cl2	-225.5(15)	5766.2(7)	2896.2(11)
Cl3	3259.0(14)	5208.3(7)	3650.9(12)
O1	1453(4)	6966(2)	6893(3)
O2	1800(3)	6639(2)	4569(3)
O3	2649(3)	5558(2)	5860(3)
O4	4169(4)	5877(2)	7278(3)
C1	-122(5)	7730(3)	5727(4)
C2	-765(6)	8085(3)	6494(4)
C3	-2066(6)	8512(3)	6245(6)
C4	-2743(6)	8566(3)	5228(6)
C5	-2097(6)	8217(3)	4460(5)
C6	-771(6)	7807(3)	4701(5)
C7	1242(5)	7271(3)	6047(4)
C8	2452(5)	7171(2)	5339(4)
C9	3914(5)	6808(3)	5941(4)
C10	4642(6)	7326(3)	6829(5)
C11	5084(5)	6643(3)	5225(5)
C12	3477(5)	6028(3)	6348(4)
C13	3827(6)	5152(3)	7731(5)
C14	2791(5)	7919(3)	4817(4)
C15	3055(6)	7919(3)	3806(4)
C16	3372(7)	8603(3)	3323(5)
C17	3405(6)	9280(3)	3868(6)
C18	3127(7)	9282(3)	4868(6)
C19	2829(6)	8600(3)	5347(4)

Table 1). For Ti-O and Ti-Cl bond distances a significant comparison can be made with recently reported analogous complexes. Given the atomic coordinates in Table 2, the asymmetric C8 atom assumes an *R* conformation. Since the dimeric complex is centrosymmetric, Figure 1 refers to the *R,S* enantiomorph, and since the space group is centrosymmetric, the *S,R* enantiomorph is present in the unit cell.

A sequence analogous to that in Scheme 1 can be proposed for the reaction between the mesityl aldehyde-TiCl₄ adduct **3** and the silyl ketene acetal **1** (Scheme 2). The characterization of **5** is hampered by its rather high insolubility. Indirect proof of its structure comes from the hydrolysis product (see Experimental Section), from the IR spectrum, which is consistent with the binding of the carbonyl group (1618 cm⁻¹), and from the usual propensity of titanium to achieve hexacoordination in such compounds.

Experimental Section

All operations were carried out under an atmosphere of purified nitrogen. All solvents were purified by standard methods and freshly distilled prior to use. NMR spectra were recorded on a Bruker 200-AC instrument.

Preparation of Complex 4. To a suspension of the TiCl₄ dibenzoyl complex **2** (2.32 g, 5.95 mmol) in toluene (50 mL) was added 1-methoxy-2-methyl-1-trimethylsilyloxypropene (1.2 mL, 5.93 mmol) at -78 °C. The mixture was warmed to room temperature overnight and stirred for another day. The yellow precipitate was collected, washed with CH₂Cl₂ (10 mL), and recrystallized by extraction with CH₂Cl₂ (50 mL). The crystalline product, **4**, was filtered and collected (1.92 g, 71%). Crystals suitable for X-ray analysis were obtained by recrystallization from hot CH₂Cl₂. Anal. Calcd for C₁₉H₁₉Cl₃O₄Ti: C, 49.01; H, 4.11. Found: C, 49.54; H, 4.63. ¹H NMR (CD₂Cl₂, 200 MHz): δ 7.7-7.3 (m, 10 H, Ph), 4.04 (s, 3 H, O-CH₃), 1.73 (s, 3 H, CH₃), 1.57 (s, 3 H, CH₃).

Preparation of Complex 5. To a suspension of **3** (2.098 g, 6.22 mmol) in toluene (50 mL) was added 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (1.3 mL, 6.22 mmol) at -78 °C. The

Table 3. Experimental Data for the X-ray Diffraction Study

compd	4
formula	C ₃₈ H ₃₈ Cl ₆ O ₈ Ti ₂
cryst color and habit	yellow prismatic fragment
<i>M_r</i>	931.2
cryst syst	monoclinic
space group	<i>P</i> 2 ₁ / <i>n</i>
cell params at 295 K ^a	
<i>a</i> , Å	9.029(1)
<i>b</i> , Å	17.468(2)
<i>c</i> , Å	13.165(2)
α and γ , deg	90
β , deg	98.81(2)
<i>V</i> , Å ³	2051.9(5)
<i>Z</i>	2
<i>D</i> _{calcd} , g cm ⁻³	1.507
cryst dimens, mm	0.18 × 0.20 × 0.22
linear abs coeff, cm ⁻¹	73.21
diffractometer	Siemens AED
radiation	graphite-monochromated Cu K α (λ = 1.541 78 Å)
scan type	$\theta/2\theta$
scan width, deg	$(\theta - 0.6) - [\theta + (0.6 + \Delta\theta)]$; $\Delta\theta = [(\lambda_{\alpha_2} - \lambda_{\alpha_1})/\lambda] \tan \theta$
scan speed deg min ⁻¹	3.1-9.4
data collcn range of 2θ , deg	6-140
total no. of unique data	3876
criterion for observn	$I > 2\sigma(I)$
no. of unique obsd data	2032
no. of params refined	244
$R = \sum \Delta F / \sum F_o $	0.045
$R_w = [\sum w^{1/2} \Delta F] / \sum F_o $	0.054
GOF = $[\sum w \Delta F ^2 / (\text{NO} - \text{NV})]^{1/2}$	1.044
largest shift/esd, final cycle	<0.1
largest peak, e/Å ³	0.53

^a Unit cell parameters were obtained by least-squares analysis of the setting angles of 25 carefully centered reflections chosen from diverse regions of reciprocal space.

suspension was warmed to room temperature overnight; then the solvent was evaporated and the yellow solid extracted with CH₂Cl₂. The methylene chloride was removed under reduced pressure, and Et₂O (50 mL) was added. The resulting pale yellow solid, **5**, was collected, washed with Et₂O (50 mL), and dried under vacuum (1.1 g, 44%). The solid was insoluble in noncoordinating solvents after treatment with Et₂O. Anal. Calcd for C₁₅H₂₁Cl₃O₃Ti: C, 44.64; H, 5.24. Found: C, 44.42; H, 5.56. IR (Nujol): 1618 cm⁻¹.

Hydrolysis of Complex 5. Complex **5** (0.678 g, 1.681 mmol) was suspended in CH₂Cl₂ (25 mL) at -60 °C, and then a saturated solution of NaHCO₃ was added. The mixture was warmed to room temperature and filtered through a sintered-glass septum. The septum was washed with NaHCO₃ (10 mL) and CH₂Cl₂ (10 mL). The aqueous phase was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were washed with brine, dried, and evaporated in vacuo. The crude product was purified by flash chromatography (6:4 hexane/Et₂O) to give **6** (330 mg, 78%). ¹H NMR (CD₂Cl₂, 200 MHz): δ 6.81 (s, 2H, Mes), 5.51 (s, 1H, CH-OH), 3.70 (s, 3H, MeO), 2.7-2.6 (br, 1H, OH), 2.48 (br s, 3H, Me Mes), 2.32 (br s, 3H, Me Mes), 2.22 (s, 3H, Me Mes), 1.20 (s, 3H, Me), 1.10 (s, 3H, Me).

Crystallography. Intensity data were collected at room temperature on a single-crystal four-circle diffractometer. Crystal data and refinement details for complex **4** are given in Table 3. The reduced cells were obtained with use of TRACER.¹³ For intensities and background individual reflection profiles were analyzed.¹⁴ Intensity data were corrected for Lorentz and polarization effects and for absorption.¹⁵ The function minimized

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during the full-matrix least-squares refinement was $\Delta w|\Delta F|^2$ using a weighting scheme based on counting statistics. Anomalous scattering corrections were included in all structure factor calculations.^{16b} Scattering factors for neutral atoms were taken from ref 16a for non-hydrogen atoms and from ref 17 for H. Among the low-angle reflections, no correction for secondary extinction was deemed necessary.

The structure was solved by the heavy-atom method (Patterson and Fourier syntheses). Refinement was first done isotropically for all the non-H atoms. The H atoms were located in a ΔF map and introduced in the refinement as fixed contributors with

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isotropic U values fixed at 0.08 Å². The final difference map showed no unusual features, with no significant peak above the general background. Final atomic coordinates of the non-hydrogen atoms are given in Table 2.

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Supplementary Material Available: Anisotropic thermal parameters, atom coordinates for hydrogen atoms, and additional bond distances and angles (Tables SI–SIII) for complex 4 (3 pages). Ordering information is given on any current masthead page.

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