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First Direct NMR Spectroscopic Observation of a Cram-Chelate Involving a Chiral α-Alkoxy Aldehyde

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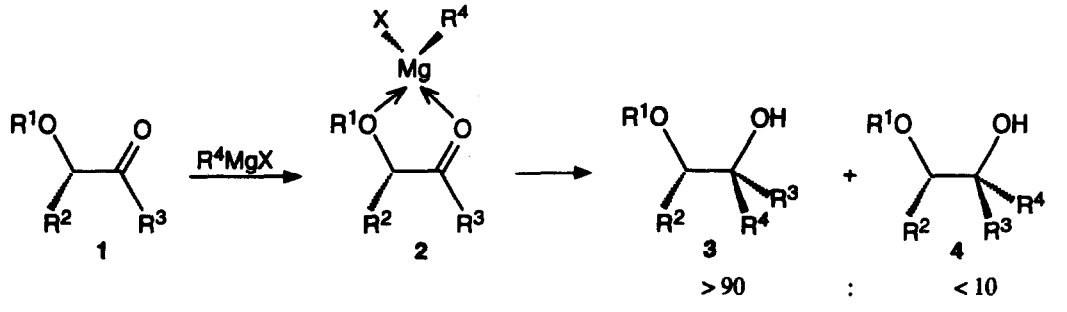
Abstract: The reaction of CH_3TiCl_3 with 2-benzyloxy propanal **10** at low temperatures in CD_2Cl_2 leads to the formation of two diastereomeric Cram-type chelates **13a/13b** which can be observed directly by ^{13}C-NMR spectroscopy. The octahedral chelates undergo C-C bond formation with first order kinetics, suggesting intramolecular 1,3 methyl transfer. Crossover experiments are unsuitable for definitive proof of intramolecularity due to ligand exchange reactions prior to Grignard-type addition.

Introduction

More than 30 years ago Cram postulated intermediate chelates **2** to explain the observed stereoselectivity in the reaction of chiral α-alkoxy ketones **1** with Grignard reagents $RMgX$[1]. Since then the reaction has been used on numerous occasions[2]. For decades the only indication of the existence of such intermediates was the stereochemical outcome (chelation control in favor of diastereomers **3**). Recently, Eliel published a classical series of papers regarding the question of chelates as true intermediates[3]. Using $(CH_3)_2Mg$ as the organometallic reagent and rapid injection ^1H-NMR techniques as described by McGarrity[4], it was unambiguously shown that chelation control correlates with enhanced reaction rates[3]. These kinetic results constitute strong evidence for the intermediacy of chelates. Nevertheless, rapid injection NMR spectroscopy turned out to be too slow for direct observation of reactive chelates.

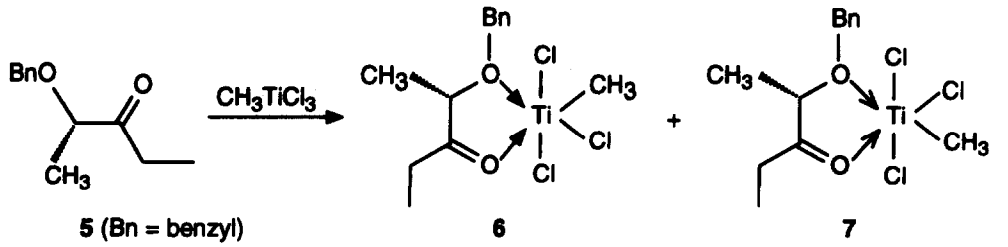


Kauffmann has demonstrated related chelation-induced rate enhancement in reactions involving other organometallics such as chromium reagents[5].

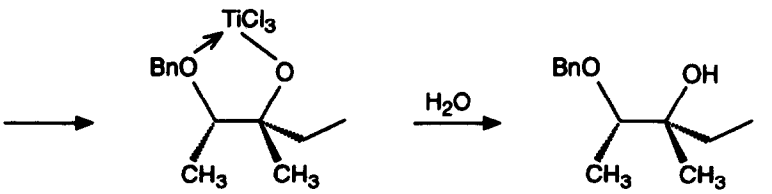
We also observed enhanced rates of Grignard-type additions, particularly in reactions of

$CH_3Ti(OiPr)_3$ with α-alkoxy ketones[6]. However, it was not possible to obtain direct spectroscopic evidence of the postulated intermediate Cram-type chelates.

In contrast, we were able to record ^{13}C-NMR spectra of CH_3TiCl_3 chelates **6**/**7** involving the ketone **5**[*)] and to monitor the formation of the chelation controlled adduct **8** at low temperatures[7]. Two intermediates **6** and **7** of four possible diastereomeric octahedral complexes were identified. The question of how the methyl groups reach the carbonyl C-atoms could not be answered unambiguously. The chelates **6**/**7** do not afford **8** with first order kinetics, which would be required for an intramolecular 1,3 methyl shift. Instead, the data obtained at -15°C speaks more for second order kinetics, although an ideal fit (perfect straight line for the plot of $[1/c\text{-}1/c_0]$ against time) was not observed[7,8]. Thus, a complicated mechanism (probably involving ligand exchange) of this otherwise clean reaction was postulated.

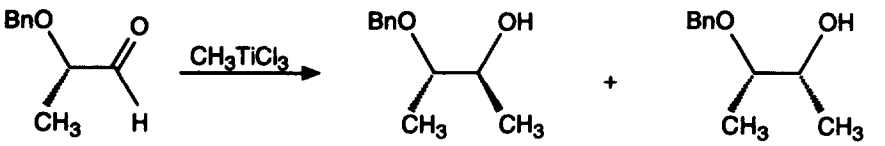


5 (Bn = benzyl) **6** **7**



8 **9**

The present paper describes our efforts to study the mechanism of the chelation controlled addition of CH_3TiCl_3 to the chiral α-alkoxy aldehyde **10**, a process which delivers the products **11**/**12** in a ratio of 92 : 8[9].



10 **11** **12**

*) Here, as in the case of the chiral aldehyde **10**, a racemate was used, although one enantiomeric form is shown arbitrarily.

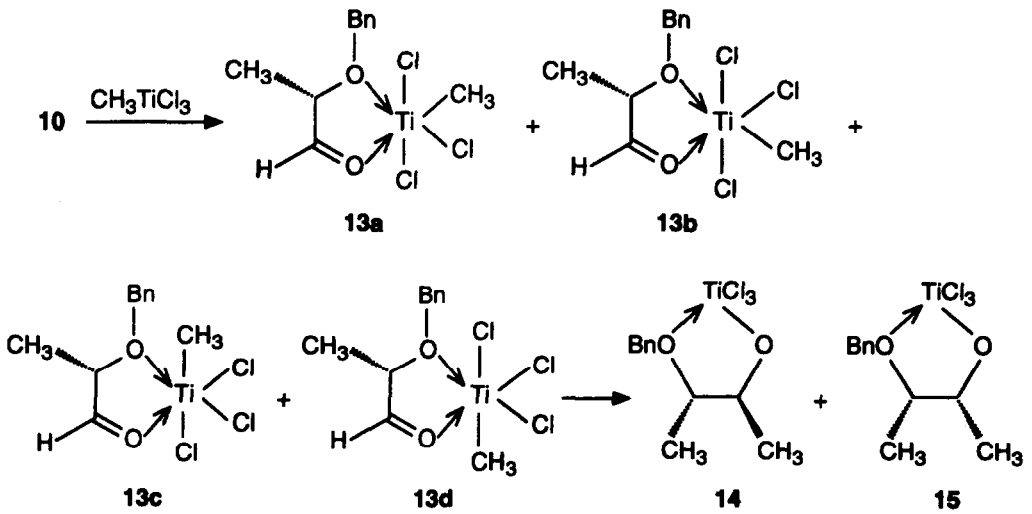
Results and Discussion

Upon injecting a CH_2Cl_2 solution of CH_3TiCl_3 into a CH_2Cl_2 solution of aldehyde **10** at -60°C the ^{13}C-NMR spectrum was immediately recorded using a modified[10] rapid injection NMR setup[4]. The spectrum shows a double set of signals in a ratio of about 93 : 7 (Table 1). We tentatively assign structures **13a** and **13b** to the two discrete species. It is particularly revealing that the signal of the carbonyl C-atom of uncomplexed aldehyde **10** shifts downfield from 203.2 to 210.9 and 211.2 ppm upon complex formation. The signal of the methyl C-atom in umcomplexed CH_3TiCl_3 shifts upfield from 117 to 112 ppm upon complexation. The two other diastereomers **13c/13d** are not directly observed (see discussion below).

Table 1. ^{13}C-NMR data (ppm) of the Cram-type chelates **13a** (major) and **13b** (minor) at -60°C and of the uncomplexed components CH_3TiCl_3 and aldehyde **10**

Signal of	$\underline{C}H_3TiCl_3$	$\underline{C}HO$	$PhCH_2$-O-$\underline{C}H$-		$\underline{C}H_3$-
13a	112.3	210.9	81.7	74.6	11.5
13b	112.3	211.2	87.9	80.5	12.5
CH_3TiCl_3 (uncomplexed)	117	—	—	—	—
10 (uncomplexed)	—	203.2	79.3	71.8	15.5

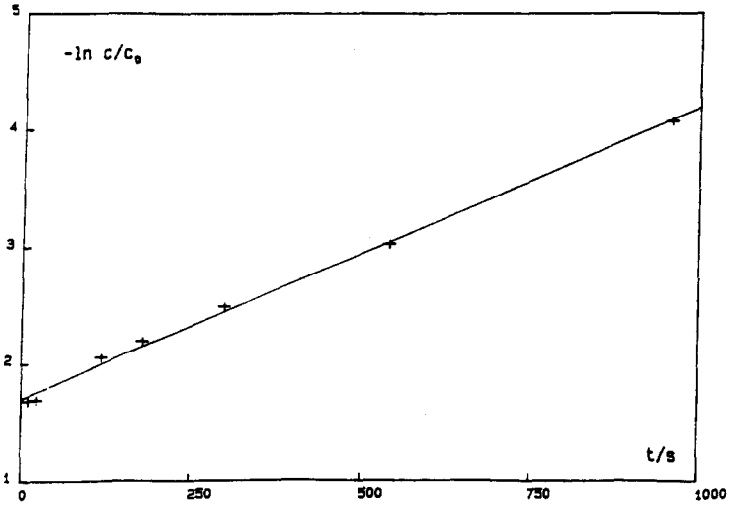
This is only the second case of direct spectroscopic observation of a Cram chelate, and the first involving an alkoxy aldehyde. There is no C-C bond forming reaction at -60°C for at least one hour. At longer reaction times or higher temperatures smooth Grignard-type reaction sets in to form two adducts **14/15** in a ratio of about 92 : 8, which correspond to the final products **11/12** following aqueous workup.



It should be stressed that in all cases distilled CH_3TiCl_3 was used, prepared by the reaction of $(CH_3)_2Zn$ with $TiCl_4$ in dry dichloromethane[8,9,10]. If the crude products of transmetalation (CH_3TiCl_3 + $ZnCl_2$) are added to the aldehyde **10**, C-C bond formation is faster than in the case of the reaction involving pure CH_3TiCl_3. Thus, the presence of $ZnCl_2$ speeds up the reaction, although stereoselectivity is practically the same[9].

In order to study the mechanism of methyl transfer in the chelates **13a/13b**, the kinetics of the formation of **14/15** was measured at -20°C in CD_2Cl_2 using rapid injection ^{1}H-NMR spectroscopy[4]. The data gives rise to first order kinetics, i. e., a plot of -ln c/c_0 versus time results in a straight line (Fig. 1). Accordingly, the rate constant is $k = 2.49 \cdot 10^{-3} l \cdot mol^{-1} \cdot s^{-1}$ and $t_{1/2}$ = 150 s at this temperature. It is presently unclear why the chelates **6/7** and **13a/13b** behave differently.

Fig. 1. Kinetics of the formation of adducts **14/15** at -20°C in CD_2Cl_2

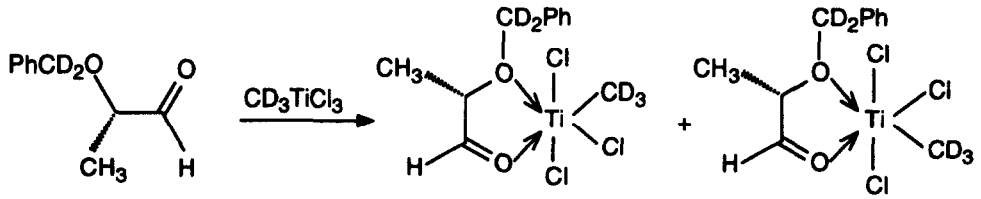


The present results are interesting because they suggest (but do not rigorously prove) that the methyl groups in **13a/13b** undergo an intramolecular 1,3 shift from titanium to the carbonyl moiety, possibly via the diastereomer **13c** which may well be in equilibrium with **13a/13b**. The possibility of an equilibrium **13a** ⇌ **13b** ⇌ **13c** ⇌ **13d** is supported in part by experimental observations and by recent theoretical calculations[11]. Concerning the former, an important observation was made during the NMR experiments: The original 93 : 7 ratio of diastereomeric Cram chelates **13a/13b** changes to ~70 : 30 as C-C bond formation occurs. Thus, the original 93 : 7 ratio of Cram chelates is kinetically controlled, and complete thermodynamic equilibration is not possible because under these conditions irreversible C-C bond formation sets in simultaneously. The configurational assignment of **13a/13b**, i. e., the postulate that major complex is **13a** and the minor **13b**, is plausible. On the basis of NMR and X-ray structural data, it is known that CH_3TiCl_3 forms octahedral complexes with bidentate ligands such as glycol ethers[12], ethylene diamines[12] and diphosphines[13], and that in such compounds the methyl group always occupies the equatorial position

(CH_3 trans to donor ligands). In particular, the X-ray structural analysis of a disphosphine adduct of CH_3TiCl_3 reported by Green[13] unambiguously proves this structural feature. Thus, it is likely that the two complexes observed in the present case are those in which the methyl groups are trans to the oxygen-containing donors as in **13a** and **13b** (and not as in the two alternative diastereomers **13c** and **13d**). Quantum mechanical calculations of octahedral complexes involving CH_3TiCl_3 and a variety of bidentate donor molecules clearly show that the thermodynamically most stable adducts are those in which the methyl group is, indeed, trans to the donor ligands[11]. Using 2-hydroxypropanal as a model for 2-benzyloxypropanal (**10**), all four diastereomeric adducts were calculated (models for **13a**, **13b**, **13c** and **13d**). It turned out that the most stable diastereomer is the one with the methyl group trans to the hydroxy moiety. In the (real) case of the alkoxy aldehyde **10**, the situation is expected to be similar. Thus, it is likely that initial octahedral complex formation is kinetically controlled, and that partial equilibration from **13a** to the thermodynamically more stable chelate **13b** occurs simultaneously with the actual C-C bond formation.

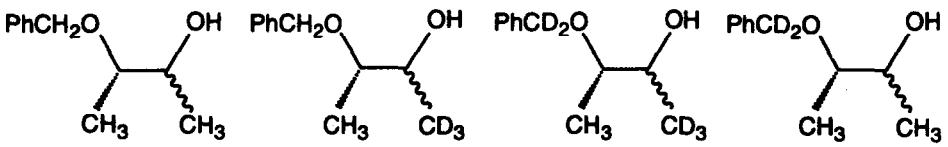
If C-C bond formation occurs via intramolecular 1,3 methyl shifts, diastereomers **13a/13b** cannot be involved directly due to obvious stereoelectronic reasons. Rather, equilibration **13a** ⇌ **13b** ⇌ **13c** ⇌ **13d** must be postulated. Diastereomer **13c** could then undergo the 1,3 methyl shift to produce the major diastereomeric product **14**. Indeed, the above cited quantum mechanical calculations show that in the case of CH_3TiCl_3/2-hydroxypropanal, the complex with the methyl in the axial position (corresponding to **13c**) lies only 2.1 kcal/mol higher in energy than the complex with the methyl in the equatorial position (corresponding to **13b**)[11].

In order to experimentally prove the anticipated intramolecularity of C-C bond formation, a crossover experiment involving the non-labeled adduct(s) **13a/13b** and the separately prepared labeled analog(s) **17a/17b** was carried out[8]. The non-labeled and labeled adducts were prepared at -78°C (at which no C-C bond formation occurs), and mixed at this temperature in a ratio of 1 : 1.



16 (Ph = phenyl) **17a** **17b**

The mixture consisting of **13a/13b** and **17a/17b** was allowed to reach -15°C and kept there for one hour before being worked up. Following aqueous workup, the crude product was studied by mass spectroscopy. A statistical 1 : 1 : 1 : 1 mixture of products **11/12**, **18**, **19** and **20** was found.



11/12 **18** **19** **20**

Unfortunately, the results cannot be interpreted on an unambiguous basis. They do not disprove the assumed intramolecular 1,3 methyl shift because rapid ligand exchange reactions prior to C-C bond formation may be occurring, just like in the previously described case of CH_3TiCl_3/**5**[7,8]. Indeed, rapid ligand exchange could be made spectroscopically visible upon adding a small amount of aldehyde **10** to the complex **13a/13b**. The otherwise sharp lines of uncomplexed **10** and of **13a/13b** became broad, even at -60°C.

Summary

It is possible to observe by ^{13}C NMR spectroscopy Cram-type chelates **13a/13b** in the reaction of CH_3TiCl_3 with the chiral benzyloxy aldehyde **10**. The kinetics of the disappearance of **13a/13b** (i. e., of the formation of Grignard-type products **14/15**) follows a first order rate law. Thus, it is likely that an intramolecular 1,3 methyl transfer defines C-C bond formation. However, it is not possible to prove this latter detail by crossover experiments because ligand exchange of labeled and non-labeled complexes may occur prior to C-C bond formation.

The present postulates and observations regarding the mechanism of reaction are in line with recent quantum mechanical calculations[11]. It remains to be seen whether the isolation of such Cram-type chelates as **6/7**, **13** or RMgCl analogs at low temperatures for X-ray crystallographic analyses will be possible.

Acknowledgement

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Experimental Section

General remarks: All synthetic manipulations were carried out under an inert atmosphere of dry argon or nitrogen. CH_2Cl_2 and CD_2Cl_2 were stored over P_2O_5 for several hours an distilled under dry nitrogen prior to use. ^1H- and ^{13}C-NMR spectra were recorded on a Bruker WH 400 instrument. Mass spectra were recorded on a Varian CH 7 A instrument.

Preparation of CH_3TiCl_3: In a dry flask equipped with a nitrogen inlet and a serum cap is placed 15.2 ml (80 mmol) of $TiCl_4$ in 50 ml of dry CH_2Cl_2. After cooling to -78°C, 10 ml (40 mmol) of a 4 M solution of $(CH_3)_2Zn$[14] in CH_2Cl_2 are slowly added with rapid stirring. The color changes from orange to black-violet. After stirring at -78°C for 1 h, the product (CH_3TiCl_3) is distilled together with the solvent in vacuum (oil pump) into a cooled flask (-78°C). Multiple integrations and averaging of the ^1H-NMR peaks (signals of CH_3TiCl_3 at 2.9 ppm and of CH_2Cl_2) allows the determination of the concentration[8]. Typically, 1.1 g (6.3 mmol) of CH_3TiCl_3 in 10 g of solution. The color of such CH_3TiCl_3 solutions is red-orange. An analogous procedure on a smaller scale in CD_2Cl_2 is used to prepare solutions of CH_3TiCl_3 in this solvent.

Preparation of CD_3TiCl_3: A similar procedure as above using $(CD_3)_2Zn$[15] results in solutions of CD_3TiCl_3 in CH_2Cl_2. The concentration of $(CD_3)_2Zn$ is determined by reaction with cumyl chloride, which forms D_3-tert-butyl benzene quantitatively[8]. The concentration of CD_3TiCl_3 was determined by reaction

with aldehyde **10** and GC analysis of conversion to products **18**[8].

Preparation of 2-benzyloxypropanal (**10**) and of 2-[2D]-benzyloxypropanal (**16**)[8]: Using the procedure of Heathcock[16] racemic aldehyde **10** is prepared from (R,S)-2-hydroxy-propionic acid ethyl ester (benzylation employing benzyl bromide and NaH followed by reduction employing diisobutylaluminium hydride). Racemic labeled aldehyde **16** is prepared analogously using $PhCD_2Br$[17].

^{13}C-NMR spectroscopic study of chelates **13b/13b** and their reaction to **14/15**: Using a modified[10] rapid injection NMR (RI NMR) apparatus[4], CH_3TiCl_3/CH_2Cl_2 is injected into a spinning NMR tube containing the equivalent amount of racemic aldehyde **10** in CH_2Cl_2. Sealing the NMR tube is not necessary[4,10] because of the helium atmosphere. Note: The RI NMR apparatus is really not needed for this experiment because the reaction is slow that it can be monitored by ^{13}C-NMR spectroscopy; it was used here nevertheless due to convenience. At a given temperature and time ^{13}C-NMR spectra were recorded (Table 1).

Kinetic studies: Using the RI NMR apparatus described above, a CH_3TiCl_3/CD_2Cl_2 solution was injected into a solution of the racemic aldehyde **10** in CD_2Cl_2 at -20°C. The reaction of the octahedral complexes to form the products **14/15** was monitored by ^{1}H-NMR integration and evaluated (Fig. 1).

Crossover experiments: A dry flask equipped with a Ar-inlet and a serum cap is charged with 1.4 mmol of CH_3TiCl_3 in dry CH_2Cl_2 (0.467 mmol reagent/g of solution). At -78°C racemic aldehyde **10** (232 mg, 1.4 mmol) is added. In a second flask a similar solution involving CD_3TiCl_3 (1.4 mmol) and the D_2-labeled aldehyde **16** is prepared at -78°C. The contents of the two flasks are mixed at -78°C, and the solution is allowed to reach -15°C. After additional hour of stirring, the mixture is poured on ice water. The aqueous phase is extracted with ether and the combined organic phases are washed several times with $NaHCO_3$ and NaCl solutions. The organic phase is dried over $MgSO_4$, the solvent removed and the crude product (0.5 g, 99%) studied by mass spectroscopy[8]. Following correction due to the natural abundance of ^{13}C isotopic proportion, the following distribution of products **11/12** (d_0), **20** (d_2), **18** (d_3) and **19** (d_5) is observed:

d_0 (m/e = 180): 6.96% d_2 (m/e = 182): 4.87% d_3 (m/e = 183): 8.40% d_5 (m/e = 185): 4.46%

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