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A Rapid Injection NMR Study of the Chelation Controlled Mukaiyama Aldol Addition: $TiCl_4$ Versus $LiClO_4$ as the Lewis Acid

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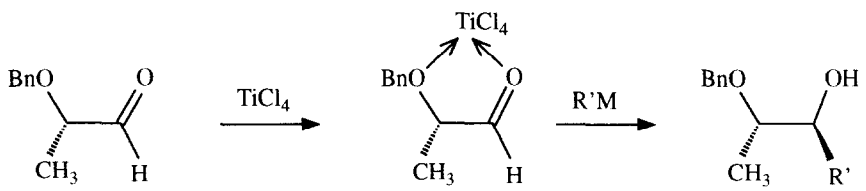
Summary: The concept of chelation controlled addition to chiral alkoxy aldehydes using Lewis acids and mild C-nucleophiles has been extended to include cyclopropylation. The mechanism of the $TiCl_4$-mediated chelation controlled addition of enolsilanes and allylsilanes to chiral α-alkoxy aldehydes has been studied by rapid injection NMR techniques. Accordingly, an acyclic transition state is involved in which the silyl group does not migrate to the carbonyl oxygen atom. In contrast, $LiClO_4$ is an effective Lewis acid (excess or catalytic amounts) which induces chelation controlled group transfer type of aldol additions.

INTRODUCTION

Since Cram's pioneering work on chelation controlled Grignard additions to α-alkoxy ketones[1], several notable extensions to the general concept of stereoselective additions to chiral α- and β-alkoxy carbonyl compounds[2,3] as well as α-amino aldehydes[4] and aldimines[5] have appeared, including mechanistic studies[6,7]. Some time ago we showed that Lewis acidic titanium reagents[8,9] such as CH_3TiCl_3 undergo chelation controlled additions to α-chiral α-alkoxy aldehydes[10], β-chiral α-alkoxy aldehydes[3] and β-chiral β-alkoxy aldehydes[11]. Since the number of reagents of the type $RTiCl_3$ is limited, we were forced to develop an alternative strategy[3,10,11]: α-Alkoxy (or β-alkoxy) aldehydes are first "tied up" by a Lewis acid such as $TiCl_4$, $SnCl_4$ or MgX_2 to form a chelate which is then reacted with an appropriate organometallic reagent such as R_2Zn, Me_3SiCN, enolsilanes or allylsilanes and stannanes, e. g.:



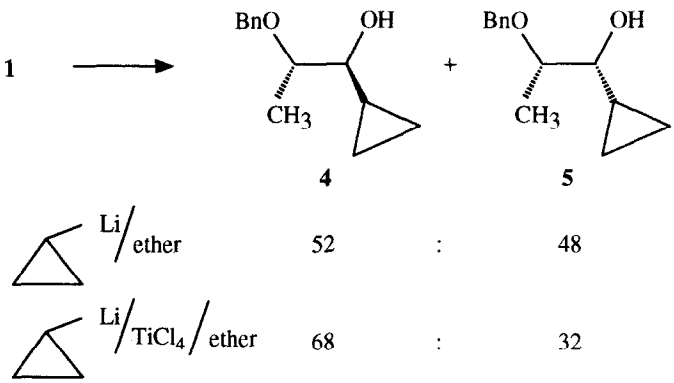
1 (Bn = benzyl) **2** **3**

This concept has turned out to be a general principle in stereoselective C-C bond formation[3,12]. Here we report on three new developments: 1) Chelation controlled cyclopropylation; 2) the mechanism of the

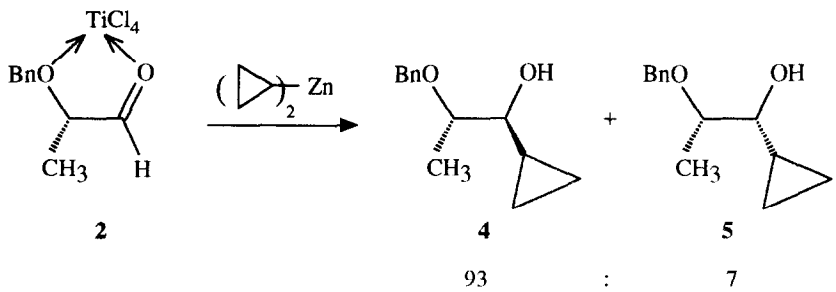
$TiCl_4$-mediated chelation controlled Mukaiyama aldol addition as studied by rapid injection NMR techniques; and 3) $LiClO_4$-mediated chelation controlled addition of enolsilanes using an excess or catalytic amounts of this Lewis acid.

Chelation Controlled Cyclopropylation

The cyclopropyl group is of interest in a number of ways, including regioselective hydrogenolysis with formation of isopropyl moieties[13]. We were therefore interested in developing a method to introduce cyclopropyl groups with chelation control. Upon reacting the racemic aldehyde **1** (one enantiomer arbitrarily shown) with cyclopropyllithium in ether, a 1 : 1 mixture of chelation and non-chelation controlled adducts **4** and **5**, respectively, was obtained. Not much improvement resulted by working in the presence of $TiCl_4$.



Presumably, a chelate of the type **2** is broken up by the presence of ether as a donor solvent. Therefore, a cyclopropylmetal reagent had to be employed which can be prepared in an ether-free state. Of such possibilities as zinc[10,14] or lead[15] reagents, we chose the former. Upon reacting **1** with $TiCl_4$ in CH_2Cl_2 and then adding dicyclopropylzinc to the intermediate chelate **2**, a rapid reaction occurred with formation of the adducts **4/5** in a ratio of 93 : 7 (60% isolated yield). The assignment of relative configuration was made on the basis of plausibility and previous experience with the addition of R_2Zn to complexes of the type **2**.

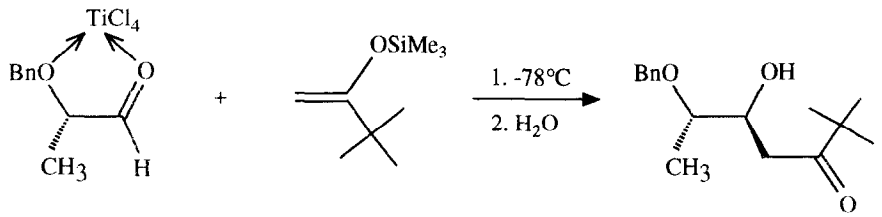


Mechanism of the Chelation Controlled Mukaiyama Aldol Addition

The Mukaiyama aldol addition involving the reaction of enolsilanes with aldehydes in the presence of $TiCl_4$ is a useful C-C bond forming process[16]. Although its mechanism was a question of debate for many

years, it became clear that in most cases $TiCl_4$ does not interact with the enolsilane to produce a trichlorotitanium enolate, since such metal/metal exchange requires longer reaction times[17]. Thus, the role of $TiCl_4$ is to activate the aldehyde, C-C bond formation ensuing from the enol silane. The details of how this process occurs remained obscure until Denmark and coworkers carried out a mechanistic study[18].

Our own interest in the Mukaiyama aldol addition originated from our study of chelation controlled processes[3]. In view of the fact that aldehydes such as **1** react with lithium- and other metal enolates to produce mixtures of aldols[3,19], we had speculated that chelates of the type **2** could react stereoselectively with enolsilanes in CH_2Cl_2. Indeed, this is the first and only effective way to carry out chelation controlled aldol additions to α- and β-alkoxy aldehydes, 1,2- and 1,3-asymmetric induction generally being > 95%[3,10,11,20]. In view of the above mentioned fact that Si/Ti exchange is slow relative to the actual aldol addition, the intermediacy of a trichlorotitanium enolate chelated to the chiral alkoxy aldehyde prior to C-C bond formation could be excluded[3]. However, the details of the chelation controlled Mukaiyama addition remained uncovered. We simply speculated that an "open-chain" mechanism pertains, in which the enolsilane approaches the complexed aldehyde function in such a way that silicon does not interact with the carbonyl function in the transition state[20]. This nicely explains the sense of simple diastereoselectivity which is observed in the case of prochiral enolsilanes (in addition to diastereofacial selectivity due to chelation control)[20]. Nevertheless, these speculations did not include clear statements as to the exact fate of the silyl group. In order to shed some light on this question, we have completed a rapid injection NMR study[21] of the reaction of the chiral chelate **2** with the enolsilane **6** derived from pinacolone. On a synthetic basis this reaction produces essentially a single diastereomer **7**[22]:



2 **6** **7** (ds = 97%)

We and others have previously characterized $TiCl_4$ complexes of chiral α-alkoxy ketones[10] as well as those of chiral α- and β-alkoxy aldehydes by NMR spectroscopy[23,24]. Furthermore, the $SnCl_4$ chelate of a chiral α-alkoxy ketone has been studied by X-ray crystallography[25]. All of the data point to monomeric hexacoordinated MCl_4 complexes having a distorted octahedral geometry.

In Fig. 1 the ^1H NMR spectra at -50°C of the uncomplexed aldehyde **1** and the corresponding $TiCl_4$ complex **2** are reproduced[23]. The spectra do not change upon going to -70°C. Complexation results in a single species, in which the positions of the α-protons of the ether moiety are shifted downfield as expected, but the aldehyde proton signal hardly shifts relative to that of the uncomplexed aldehyde **1**. The "non-equivalence" of the diastereotopic benzyl protons increases upon chelation. The spectrum does not allow a decision as to the geometry around the ether function (which has oxonium character). In a non-planar arrangement, the oxygen is chiral and the benzyl group is likely to be trans to the methyl group. However, planarity or near planarity probably pertains, as in the case of a $SnCl_4$ complex of a chiral α-benzyloxy ketone[25].

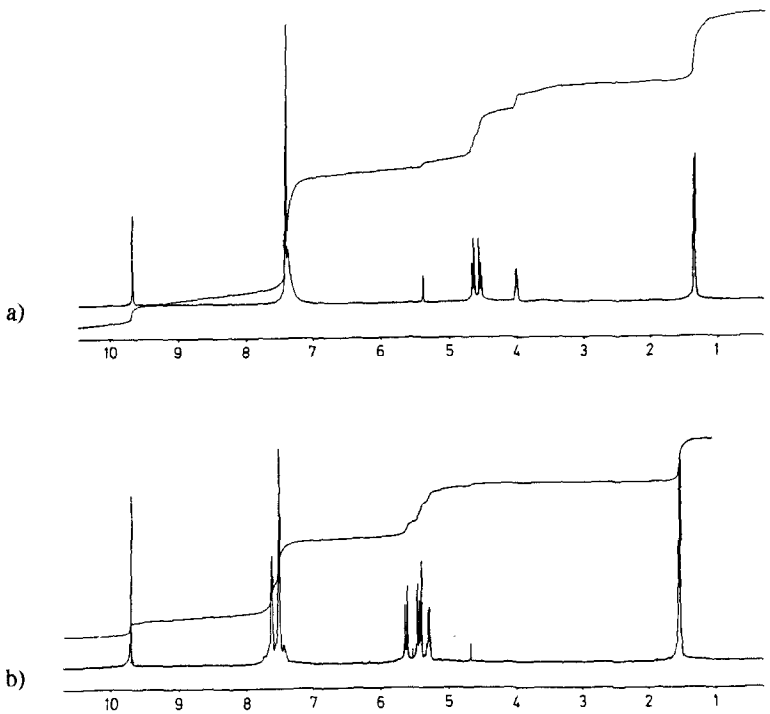


Fig. 1. a) ^{1}H NMR spectrum of **1** (CD_2Cl_2/-50°C; 400 MHz);
b) ^{1}H NMR spectrum of **2** (CD_2Cl_2/-50°C; 400 MHz)

Upon injecting a slight excess of the enolsilane **6** to a CD_2Cl_2 solution of **2** at -70°C and monitoring the changes in the ^{1}H NMR spectrum as a function of time by a rapid injection NMR setup[21], a fairly fast reaction was observed. After 1.42 sec, about two-thirds conversion was observed. After 4.2 sec, only 10% of **2** was left, and after 9.82 sec essentially complete conversion was registered. Fig. 2 shows three interval spectra (5 taken in all). The reaction is surprisingly clean, delivering essentially a single diastereomer. Among other features it is clear that the signal of Me_3SiCl at about 0.5 ppm grows in proportion to the extent of reaction (the Me_3Si peak of the enol silane at 0.22 ppm does not disappear completely due to the excess amount injected).

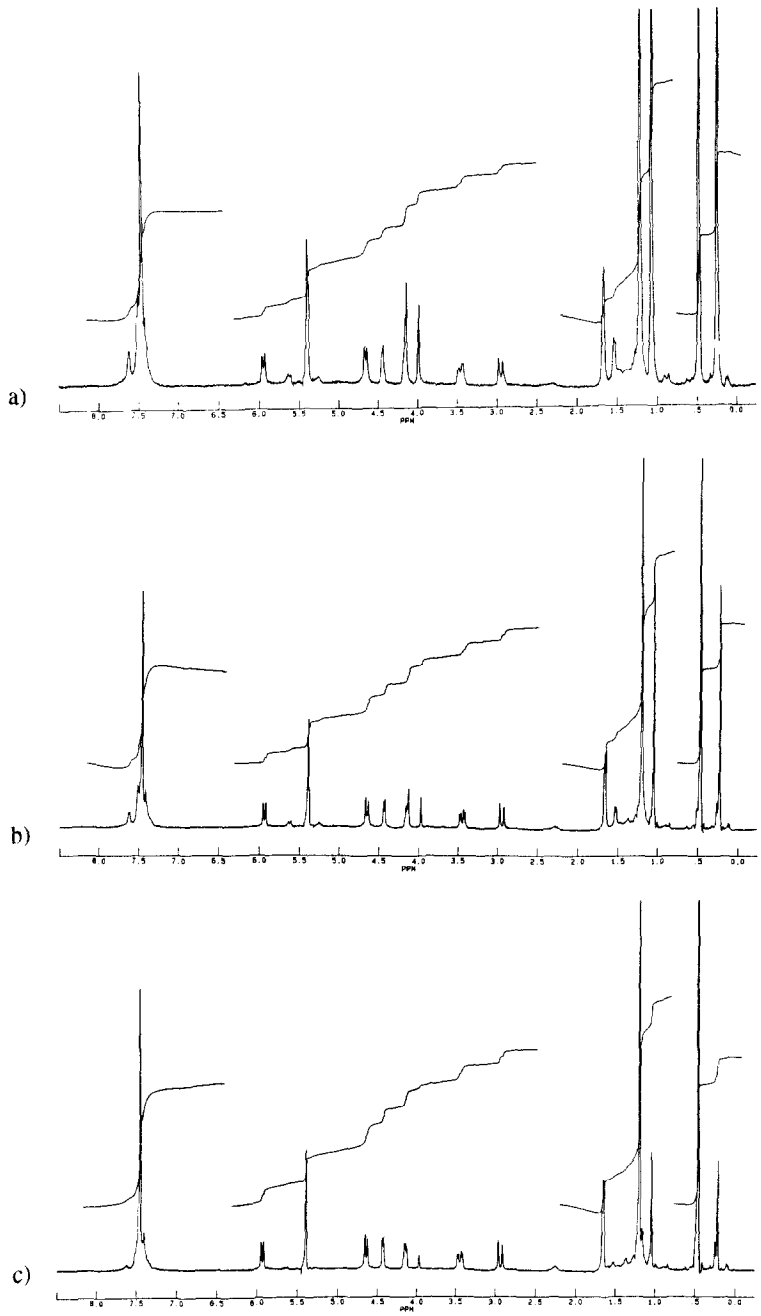


Fig. 2. Rapid injection ^1H NMR spectra of the reaction of **2** with **6** at -70°C in CD_2Cl_2 (400 MHz): a) after 1.42 sec; b) after 4.2 sec; c) after 9.82 sec.

The final spectrum (Fig. 2c) is that of the trichlorotitanium aldolate **9**. Although the initial product is expected to be the aldolate **8**, it was not possible to identify it under the conditions used, i. e., it rapidly rearranges to **9**. That this is so, becomes particularly clear when examining the ^{13}C NMR spectrum (Fig. 3). Among other features, the carbonyl signal at 225.6 ppm clearly indicates carbonylmetal complexation. The carbonyl signal of the aldol product **7** occurs at 216.5 ppm and that of the silylated aldol product **11** (see below) at 214.4 ppm. Furthermore, the signal of the benzylic C-atom of **9** appears at 72.9 ppm. For comparison, this C-atom appears at 71.5 ppm in the uncomplexed aldehyde **1**, at 80.2 ppm in the $TiCl_4$ complex **2**, at 70.2 ppm in the aldol **7** and at 75.7 ppm in the silylated aldol **11**.

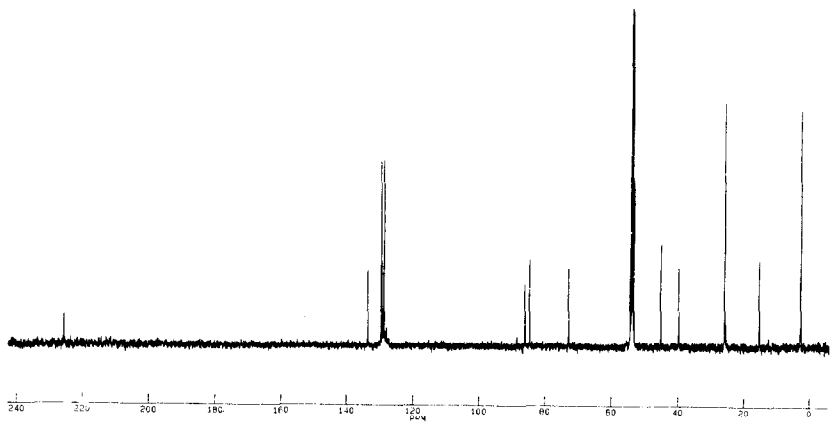
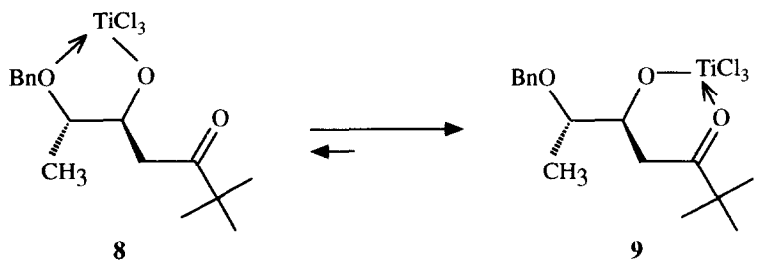
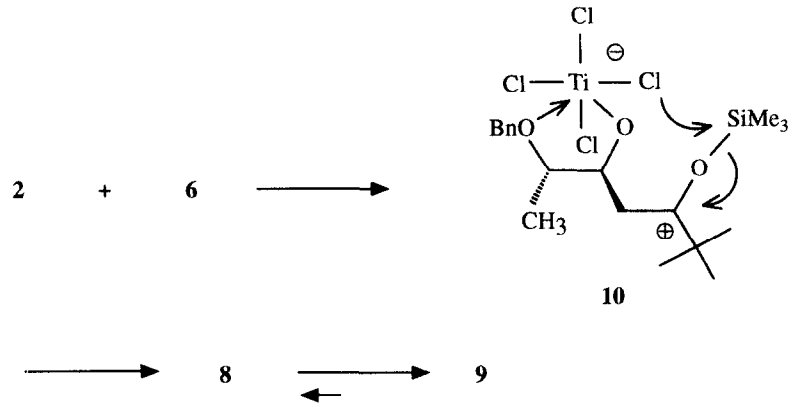


Fig. 3. ^{13}C NMR spectrum of **9** at -70°C (CD_2Cl_2)

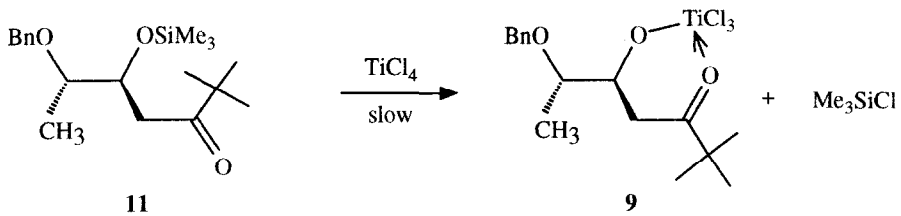


8 **9**

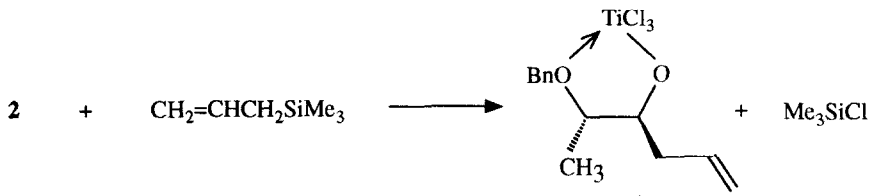
It is thus tempting to postulate a mechanism in which the enolsilane approaches the chelate via an acyclic transition state[20], and that the silyl group never reaches the oxygen of the aldehyde carbonyl function:



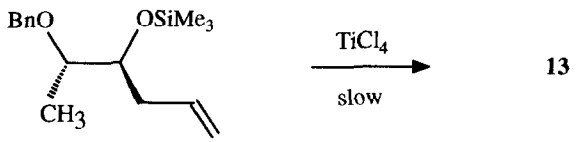
In order to test this hypothesis, we performed a control experiment in which the silylated aldol **11** was subjected to treatment with $TiCl_4$ at -70°C in CD_2Cl_2. The ^1H NMR spectra taken during the first 10 minutes were poorly resolved. After 12 minutes, about 15% of the Si/Ti-exchanged product, i. e., the trichlorotitanium aldolate **9** could be detected. Even after 40 minutes only about 33% of **9** had formed. Upon warming to 0°C over 15 minutes, a clean spectrum of **9** was obtained. The fact that this reaction is slow relative to the formation of **9** in the actual aldol addition disproves a two-step mechanism of the Mukaiyama addition in which the silyl group first migrates to the carbonyl oxygen followed by Si/Ti exchange. A similar conclusion regarding the $TiCl_4$-mediated Mukaiyama aldol addition to simple aldehydes has been made by Denmark[18].



Finally, we have also carried out similar rapid injection NMR studies of the chelation controlled Hosomi-Sakurai reaction[26] of the aldehyde **1**[10,27]. The $TiCl_4$-chelate **2** reacts with allyltrimethylsilane **12** within 10 seconds at -75°C in CD_2Cl_2 to form adduct **13** prior to aqueous workup. It is interesting to note that the same reaction involving the analogous tin chelate **1**/$SnCl_4$ requires about 10 minutes for completion[27]. A control experiment involving the reaction of the silylated adduct **14** with $TiCl_4$ showed that Si/Ti-exchange is slow compared to the actual Hosomi-Sakurai reaction of **2**. After 15 minutes only a trace of **13** had formed[27]. Therefore, we conclude that the mechanism of the Hosomi-Sakurai reaction is similar to that of the Mukaiyama aldol addition.



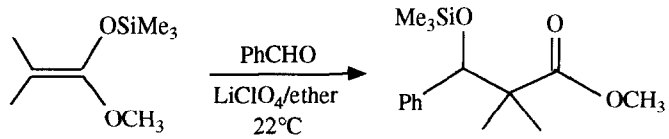
12 13



14

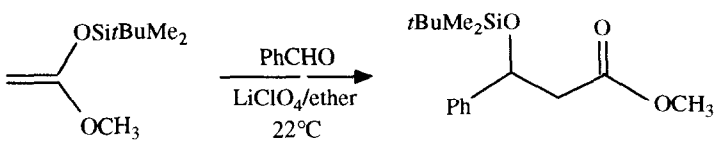
Lithium Perchlorate Induced Aldol Additions of Enolsilanes

Obviously, the above mechanistic conclusions are restricted to reactions involving $TiCl_4$ as the Lewis acid. Milder Lewis acids of the type LiX, MgX_2 or ZnX_2 may be expected to induce group transfer type of aldol additions of enolsilanes with formation of silylated aldols[28]. Indeed, some time ago we discovered that excess $LiClO_4$/ether[29] induces the aldol addition of enolsilane **15** to benzaldehyde[30], the yield of this non-optimized reaction being 56%. The crude product following aqueous workup contained mainly the silylated aldol **16** (15% desilylation, probably during workup).



15 16

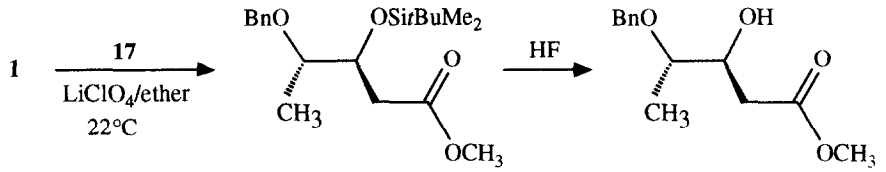
In order to explore the synthetic potential of this interesting reaction, the *O*-silyl ketene ketal **17** derived from acetic acid methyl ester was reacted with benzaldehyde at room temperature in ether containing an excess of $LiClO_4$ (5 M solution). A clean reaction set in within 1 h with the sole formation of the silylated aldol **18**. Since the Lewis acid $LiClO_4$ is not consumed during the above reaction, we reasoned that catalytic amounts should suffice. Indeed, the use of catalytic amounts of $LiClO_4$ (3 mol-%) required a reaction time of 5 d for 86% conversion to **18**.



17 18

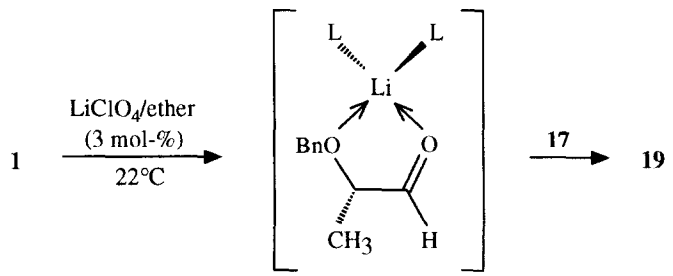
Finally, we were intruiged by the possibility of $LiClO_4$-induced chelation controlled aldol addition to chiral α-alkoxy aldehydes. To this end, the aldehyde **1** was first reacted with the enolsilane **17** in the

traditional $LiClO_4$/ether solution (5 M). Conversion to **19** turned out to be complete within 1 h. In order to assign the relative configuration, the crude product was subjected to desilylation (40% aq. HF/MeCN) with formation of the aldol **20** previously obtained by $TiCl_4$-mediated chelation controlled Mukaiyama aldol addition[12,31]. The crude product of desilylation was very clean, containing essentially only the chelation controlled adduct **20** (ds > 96%).



19 **20**

The use of 3 mol-% of $LiClO_4$ in ether resulted in complete conversion to **19** (22°C/20 h), diastereoselectivity being > 96%. Desilylation afforded aldol **20**, which was isolated in 67% overall yield based on aldehyde **1**. The higher reaction rate of **1** compared to that of benzaldehyde may be attributed to chelation. The above results clearly show that the chelation controlled aldol addition of an enolsilane and an α-alkoxy aldehyde is possible using catalytic amounts of a Lewis acid. Mechanistically, intermediate chelates of the type **21** are likely which - in contrast to the $TiCl_4$-analog **2** - undergo group transfer aldol addition. At present we do not know whether perchlorate is a ligand at lithium, or whether the chelate is ionic in nature.



21 (L = ligand)

CONCLUSIONS

The idea[10,11] of "tying up" chiral α- and β-alkoxy aldehydes using Lewis acids capable of bis-ligation followed by the addition of mild C-nucleophiles such as R_2Zn, allylsilanes, allylstannanes, enolsilanes and Me_3SiCN is a useful principle in stereoselective C-C bond formation[3,12]. In this paper we have extended this concept to include chelation controlled cyclopropylation. Rapid injection NMR studies of the $TiCl_4$-promoted chelation controlled Mukaiyama aldol addition and Sakurai reaction show that an acyclic transition state must be involved in which the silyl groups never reach the carbonyl oxygen atom. In the case of $LiClO_4$-mediated enolsilane additions, a different mechanism pertains, namely group transfer aldol reactions. The fact that chelation control can be induced by catalytic amounts of $LiClO_4$ opens up new avenues for stereoselective C-C bond formation, particularly in view of the mildness of the reaction conditions.

ACKNOWLEDGEMENT

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EXPERIMENTAL

General Information. ^1H and ^{13}C NMR spectra were recorded on a Bruker WH 300 or 400 instrument. Mass spectra were recorded on a Varian MAT CH 711 instrument. GC studies were performed on a Perkin-Elmer EM 960 using capillary columns/carbowax. Combustion analyses were performed by the Analytical Department of the Fachbereich Chemie (Universität Marburg). All synthetic reactions were carried out in flame-dried flasks under an atmosphere of argon. Syringes were dried and flushed with argon gas prior to use. Diethyl ether was dried by distillation over NaH. Dichloromethane was dried by distilling from P_2O_5 and then CaH_2. $TiCl_4$ was distilled under argon. In all reactions racemic 2-benzyloxypropanal (**1**) was used.

Chelation controlled cyclopropylation. Preparation of (1SR,2SR)-2-benzyloxy-1-cyclopropyl-propanol-1 (4). To a stirred solution of (SR)-2-benzyloxypropanal (**1**) (410 mg, 2.5 mmol) in CH_2Cl_2 (20 ml) is added at -78°C $TiCl_4$ (470 mg, 2.5 mmol). After 15 min dicyclopropylzinc (360 mg, 2.5 mmol) is added dropwise. The reddish-brown solution is allowed to warm to -30°C and stirred for 3 h before being quenched with 20 ml of H_2O. The aqueous layer is extracted with ether (3 x 30 ml), the combined organic phases are successively washed with sat. $NaHCO_3$ (2 x 50 ml) and sat. NaCl (1 x 50 ml) and then dried over $MgSO_4$. After GC analysis (93 : 7 diastereomer ratio of **4** : **5**; conversion > 95%) the solution is filtered and concentrated on a rotary evaporator. Flash chromatography over SiO_2 (pet. ether/ether 5 : 1) affords 309 mg (60%) of a 93 : 7 mixture of **4/5**. ^1H NMR of major isomer **4** (300 MHz; $CDCl_3$): δ = 0.23-0.32 (m, 1H), 0.35-0.44 (m, 1H), 0.46-0.58 (m, 2H), 0.76-0.94 (m, 1H), 1.21-1.31 (d, 3H, J = 6.3 Hz), 2.6-2.8 (br, 1H), 2.68-2.82 (q, 1H, J = 6.3 Hz), 4.40-4.74 (q, 2H), 7.24-7.40 (m, 5H). FD-MS (mixture **4/5**): M/Z 135 (55%), 205 (m^+-1, 100%), 206 (m^+, 15%); anal. calcd. for $C_{13}H_{18}O_2$ (206.27): C 75.69; H 8.79; found: C 75.66; H 8.88.

Rapid injection NMR studies. A slightly modified version of McGarrity's apparatus[21] was built at the University of Marburg (Fachbereich Chemie, NMR Department led by Prof. S. Berger) and an improved computer program (KIN4.BOC) written (W. Bock, Dissertation, Universität Marburg 1990). A 1.0 M standard solution of $TiCl_4$ in dry CD_2Cl_2 was prepared as follows. $TiCl_4$ was freshly distilled from copper wire into a dry tared round bottom flask under argon. The amount of $TiCl_4$ was determined by weight, then enough CD_2Cl_2 (dried and distilled over CaH_2) was added to make a 1.0 M solution, which was stored at -20°C under argon. Aliquots were transferred by cannula into NMR tubes as needed. The solution volume was measured by the height of the liquid column in the NMR tube. For the Mukaiyama aldol reaction, the 1.0 M $TiCl_4$ solution (0.05-0.1 ml) was placed in a rapid injection NMR tube, and CD_2Cl_2 was added to make 0.5 ml of solution (0.1 or 0.2 M). The NMR tube was cooled to -70°C and the equivalent amount of racemic aldehyde **1** was added. The NMR monitor showed only the complex **2** as previously published[23] and shown again in Fig. 1b. The enolsilane **6** (slightly more than the equivalent amount) was rapidly injected. The first ^1H NMR spectrum was recorded 0.02 seconds after injection, at which point only 5% of conversion had occurred. The reaction is essentially over within 10 seconds.

$LiClO_4$-induced aldol additions

Reaction of enol silane **15**: A 5 molar solution of $LiClO_4$ in ether was prepared by stirring dry $LiClO_4$ (5.32 g, 50 mmol) in dry ether (10 ml) for 1 h at room temperature. Benzaldehyde (212 mg, 2 mmol) and the enol silane **15** (383 mg, 2.2 mmol) were added and after stirring for 12 h at room temperature, the mixture was poured into water (20 ml). The aqueous phase was extracted with ether (5 x 20 ml), the combined organic phases were washed with sat. $NaHCO_3$ (30 ml) and sat. NaCl (30 ml) dried over $MgSO_4$ and the solvent was carefully removed. Conversion and ratio of silylated product **16** to desilylated aldol was determined by ^1H NMR spectroscopy (6 : 1; 56% yield). ^1H NMR (300 MHz; $CDCl_3$): δ = -0.05 (s, 9H), 0.98 (s, 3H), 1.11 (s, 3H), 3.67 (s, 3H), 4.96 (s, 1H), 7.25 (s, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 0.0, 19.2, 21.7, 49.1, 51.6, 79.2, 127.4, 127.5, 127.9, 140.9, 177.3.

Reaction of enol silane **17**: To a 5 molar solution of $LiClO_4$ in ether (12 ml) was added benzaldehyde (106 mg, 1 mmol) followed by **17** (216 mg, 1.1 mmol) and the solution was allowed to stir at room temperature for 1 h. Work-up was carried out as described above to provide the product **18** as a colorless oil (287 mg, 98% yield). ^1H NMR (300 MHz; $CDCl_3$): δ = -0.19 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 2.54 (dd, 1H, J = 14.5, 3.9 Hz), 2.72 (dd, 1H, J = 14.5, 9.4 Hz), 3.67 (s, 3H), 5.13 (dd, 1H, J = 9.4, 3.9 Hz), 7.22-7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = -5.3, -4.7, 18.0, 25.6, 46.3, 51.5, 72.2, 125.8, 127.5, 128.3, 144.1, 171.6.

Chelation controlled addition of **17** *(excess $LiClO_4$)*: To a 5 molar solution of $LiClO_4$ in ether (10 ml) was added the aldehyde **1** (164 mg, 1 mmol) and **17** (216 mg, 1.1 mmol) and the reaction was allowed to stir at room temperature for 1 h. Work-up as before provided **19** in essentially quantitative yield. Subsequent desilylation was effected by addition of aqueous HF (40%, 2 ml) to a solution of **19** in acetonitrile (20 ml) and stirring at room temperature for 2 h. The reaction mixture was then neutralised with sat. $NaHCO_3$ and extracted with ether (2 x 30 ml). The combined organic layers were washed with water (20 ml) and sat. NaCl (20 ml), dried over $MgSO_4$ and evaporated. ^1H and ^{13}C NMR of the resulting product **20** indicated essentially quantitative conversion to a single diastereomer. This could be isolated in 46% overall yield by silica gel chromatography (pentane/ether 5:1)[31]. ^{13}C NMR (100.6 MHz, $CDCl_3$): *(Shift of appropriate signals corresponding to the non-chelation controlled product given in parentheses)* δ = 14.7 *(14.9)*, 37.6 *(36.9)*, 51.6, 70.8, 70.9, 76.4 *(76.2)*, 127.6, 127.8, 128.3, 138.0 *(138.1)*, 172.5 *(172.7)*.

Chelation controlled addition of **17** *(catalytic $LiClO_4$)*: To a solution of $LiClO_4$ (3 mg, 0.028 mmol) in dry ether (10 ml) was added **1** (164 mg, 1 mmol) and the enol silane **17** (216 mg, 1.1 mmol) and the reaction was stirred at room temperature. Complete conversion to **19** occurred within 20 h, as evidenced by thin layer chromatography and subsequently by ^1H and ^{13}C NMR of the product following the standard work-up. Direct desilylation of **19** as described above allowed clean conversion to **20** as the sole product (159 mg, 67% overall yield).

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