

Structural, Mechanistic, and Theoretical Aspects of Chelation-Controlled Carbonyl Addition Reactions†

MANFRED T. REETZ

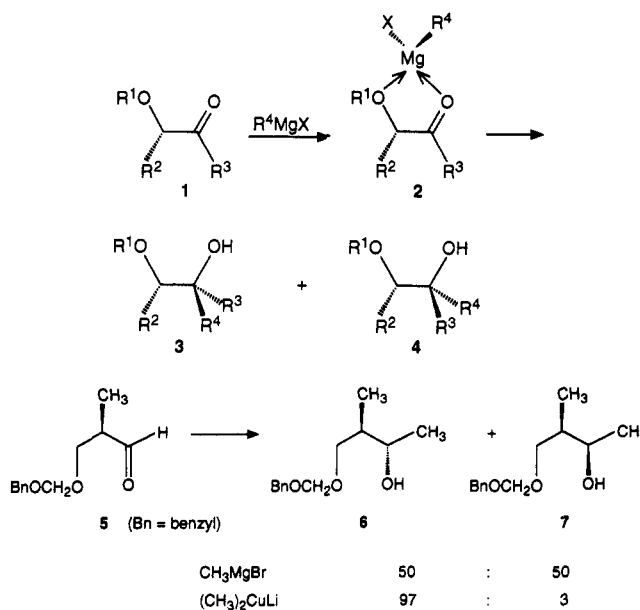
Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany

Received February 16, 1993

The seminal work of Cram in the 1950s concerning Grignard-type addition and reduction reactions of chiral carbonyl compounds is a milestone in organic synthesis because chemists began to think systematically about asymmetric induction.¹ The so-called Cram model provided a means to *predict* the outcome of nucleophilic additions to chiral carbonyl compounds devoid of heteroatoms. Although more refined theories were later proposed, the true origin of stereoselectivity remains uncertain. Due to the large number of different conformers possible, each possessing different or similar energy and reactivity, an all-encompassing theory is likely to be more complicated than the models proposed so far. For example, *ab initio* calculations of 2-phenylpropanal and of its reaction with LiH point to a very complicated situation.² This theoretical challenge goes hand in hand with experimental difficulties in obtaining high levels of Cram selectivity in a general way.³

In the case of chiral α -alkoxy carbonyl compounds, the situation is different. For example, upon reacting chiral α -alkoxy ketones **1** with Grignard reagents RMgX, Cram discovered that the formation of diastereomers **3** is consistently favored.^{4a} On the basis of the stereochemical outcome, intermediate chelates of the type **2** were proposed which were thought to react selectively from the sterically less hindered π -face (Cram's chelation model). The process was later optimized with respect to the choice of solvent and temperature (THF/ -78°C).^{4b} In an elegant application of chelation control Eliel utilized ketones bearing chiral oxathianes to produce α -hydroxy and α -alkoxy aldehydes having high enantiomeric purity.^{4c}

Since the above reaction does not generally extend to the synthetically important chiral α - or β -alkoxy aldehydes, new methods for chelation control had to be developed.⁵ One of the first contributions in this area is due to Still, who showed that β -alkoxy aldehydes of the type **5** react with Gilman reagents to provide the chelation controlled adducts (e.g., **6**) with high levels of stereocontrol.⁶ Unfortunately, cuprates do not usually react stereoselectively with chiral α -alkoxy aldehydes,⁶ and only a few cases are known in which the use of Grignard reagents is successful.⁶ Similar problems arise when attempting aldol additions of



lithium enolates to α -alkoxy aldehydes (1:1 to 1:3 diastereomer mixtures).⁷ On the basis of our early experience with organotitanium reagents RTiL_3 ($\text{L} = \text{Cl}, \text{OR}, \text{NR}_2$),⁸ we speculated that the very Lewis acidic compound CH_3TiCl_3 might react with aldehydes of the type **8** to form Cram-type chelates **9**, which would then lead to chelation-controlled products **10**. Indeed, a 92:8 diastereomer ratio of **10**:**11** was observed.⁹

† Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 60th birthday.

(1) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828-5835. (b) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, 1971.

(2) (a) Köhler, K. F. Dissertation, Universität Marburg, 1993. (b) In contrast, the origin of stereoselectivity in reactions of 2-chloropropanal can be traced to ground-state effects: Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005-9018.

(3) Reetz, M. T.; Stanchev, S.; Haning, H. *Tetrahedron* **1992**, *48*, 6813-6820 and references therein.

(4) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748-2755. (b) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031-1034. (c) Eliel, E. L. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 125.

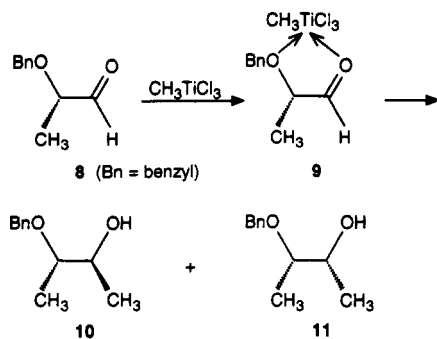
(5) Review of chelation- and non-chelation-controlled additions to chiral alkoxy carbonyl compounds: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556-569.

(6) (a) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035-1038. (b) Exceptions: Lipshutz, B. H. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 107-138.

(7) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 169.

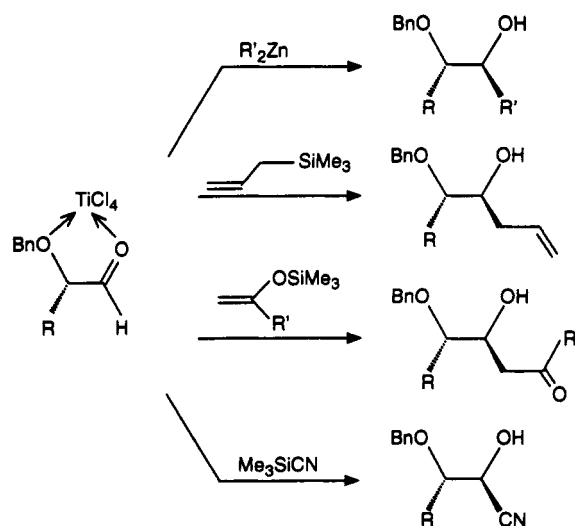
(8) (a) Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 900-901. (b) Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 901-902. (c) Reetz, M. T.; Wenderoth, B.; Peter, R.; Steinbach, R.; Westermann, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1202-1204.

Manfred T. Reetz was born in Hirschberg, Germany, in 1943 and obtained his doctorate under the direction of U. Schöllkopf at the Universität Göttingen in 1969. After a postdoctorate in Marburg with R. W. Hoffmann he habilitated there in 1974. From 1978 to 1980 he was Professor in Bonn and moved to the Universität Marburg in 1980. Since the summer of 1991 he has been Director at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr. His research priorities lie in the development of new methods in synthetic organic chemistry, in particular the search for selective organometallic reagents. His other fields of interest are peptide chemistry, molecular recognition, and polymer chemistry.



Since the number of reagents RTiCl_3 is limited,¹⁰ the need for a more general method of chelation control became apparent. In searching for a solution to this problem, we made use of the known Lewis acid-induced activation of carbonyl compounds toward nucleophilic attack by such reagents as enolsilanes (Mukaiyama aldol addition),¹¹ allylsilanes (Hosomi-Sakurai reaction),¹² cyanotrimethylsilane,¹³ dienes (hetero Diels-Alder reaction),¹⁴ olefins (ene reactions),¹⁵ and dialkylzinc.^{10a} Accordingly, the alkoxy aldehyde is "tied up" with a Lewis acid capable of bis-ligation (e.g., TiCl_4 , SnCl_4 , or MgX_2), and the intermediate chelate is then reacted with such carbon nucleophiles as R_2Zn , allylsilanes, enolsilanes, or Me_3SiCN . As illustrated in Scheme I, this simple idea has turned out to be a general principle in stereoselective C-C bond formation, 1,2-asymmetric induction usually being 90–100%.^{5,9,10a,c,16,17} The concept has been extended to β -alkoxy aldehydes having a stereogenic center at the α - or β -position (1,2- and 1,3-asymmetric induction, respectively).^{18,19} It also works well for the reaction of the corresponding chiral acid nitriles, processes that lead to tertiary cyanohydrins.²⁰ Finally, chelation-controlled hetero Diels-Alder²¹ and ene reactions²² of chiral alkoxy aldehydes as well as a variety of reactions involving α -amino aldehydes²³ are possible along similar lines.

Scheme I. Chelation-Controlled Nucleophilic Addition Reactions



Recently, we showed that in the Mukaiyama aldol addition TiCl_4 ^{5,11} can be replaced by LiClO_4 as a 5 M ether solution.²⁴ In the case of chiral α -alkoxy aldehydes (e.g., **8**), chelation control is 95%.²⁴ The reaction also proceeds with a catalytic amount of LiClO_4 , albeit at a lower rate.²⁴ In an independent study Grieco demonstrated that 5 M LiClO_4 in ether induces the addition of allylstannanes to chiral α -alkoxy aldehydes with excellent degrees of chelation control.²⁵ A disadvantage of these methods has to do with the environmental implication associated with the disposal of the excess perchlorate. The discovery that a suspension of 3 mol % of LiClO_4 in dichloromethane is a much *more reactive catalytic* system is therefore of considerable synthetic interest.²⁶ Importantly, catalytic amounts of LiClO_4 induce chelation control, as shown by the addition of the enolsilane **12** to the alkoxy aldehyde **8**.²⁶ Similarly, complete chelation control is possible in the hetero Diels-Alder reaction of **15** with **8**.²⁷ On the basis of the stereochemical outcome, it is likely that some kind of a lithium chelate is involved.^{24,26} The hetero Diels-Alder reaction of **15** with **8** had previously been shown by Danishefsky to occur in the presence of stoichiometric amounts of MgBr_2 .²¹

Chelation control in carbonyl addition reactions thus occurs under a variety of properly chosen conditions, but studies relating to structural, mechanistic, and theoretical aspects have lagged behind. In this Account current knowledge concerning these points is summarized.

Spectroscopic and X-ray Structural Evidence for Chelates as Intermediates

The first direct evidence for chelates of chiral alkoxy carbonyl compounds was obtained by recording the ^1H -

(9) (a) Reetz, M. T.; Kessler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989–990; *Angew. Chem. Suppl.* **1983**, 1511–1526. (b) Recent use of CH_3TiCl_3 in chelation-controlled addition: Baldwin, S. W.; McIver, J. M. *Tetrahedron Lett.* **1991**, *32*, 1937–1940.

(10) (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986. (b) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (c) Reetz, M. T. *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: New York, 1993. (d) Ferreri, C.; Palumbo, G.; Caputo, R. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139–172.

(11) Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331.

(12) (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295–1298. (b) Fleming, I. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 563–593.

(13) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer: Berlin, 1983.

(14) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.

(15) Snider, B. *Acc. Chem. Res.* **1980**, *13*, 426–432.

(16) (a) Reetz, M. T.; Kessler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729–732. (b) Reetz, M. T. *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; NATO ASI Series; Kluwer Academic Publishers: Dordrecht, 1989; pp 107–125.

(17) Reetz, M. T.; Kessler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327–4336.

(18) Reetz, M. T.; Kessler, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1079–1080.

(19) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833–4835.

(20) Reetz, M. T.; Kessler, K.; Jung, A. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 989–991.

(21) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456–2458.

(22) (a) Mikami, K.; Loh, T. P.; Nakai, T. *Tetrahedron: Asymmetry* **1990**, *1*, 13–16. (b) Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 477–480.

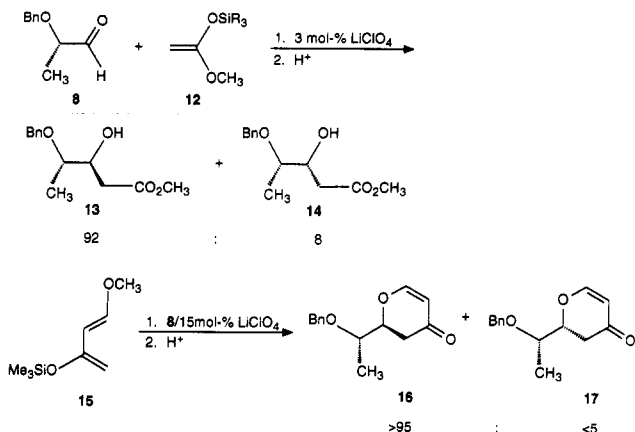
(23) Reviews of chelation- and non-chelation-controlled additions to chiral α -amino aldehydes: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531–1546. (b) Reetz, M. T. *Pure Appl. Chem.* **1992**, *64*, 351–359. (c) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164.

(24) Reetz, M. T.; Raguse, B.; Marth, C. F.; Hügel, H. M.; Bach, T.; Fox, D. N. A. *Tetrahedron* **1992**, *48*, 5731–5742.

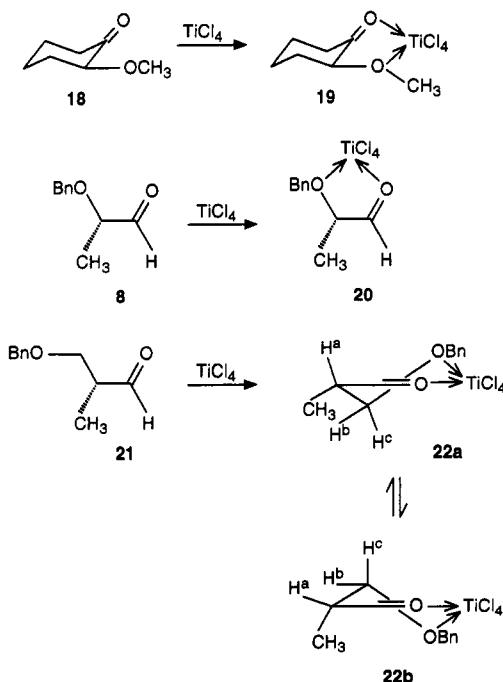
(25) Henry, K. J.; Grieco, P. A.; Jagoe, C. T. *Tetrahedron Lett.* **1992**, *33*, 1817–1820.

(26) Reetz, M. T.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119–1122.

(27) Reetz, M. T.; Gansäuer, A. *Tetrahedron*, in press.



and ¹³C-NMR spectra of the TiCl₄ complex **19**.^{9a} Later, NMR spectra of TiCl₄ adducts of the chiral aldehydes **8** and **21** were shown to be in line with the structures **20** and **22a**, respectively.^{10a,28,29} It should be noted that charge-induced downfield shifts in the ¹³C-NMR spectra may be (partially) compensated by upfield shifts arising from steric compression. In the case of the complexation of aldehyde **21**, two (idealized) chair conformers **22a** and **22b** are possible. The observed coupling constants $J_{a-c} = 9.5$ Hz and $J_{a-b} = 4.0$ Hz show that the geometry indicated in **22a** describes reality more closely than that in **22b**.^{10a,28} However, in both cases the methyl group occupies an equatorial (or pseudo-equatorial) position, and in both cases stereoselective attack is expected to proceed from the top face of the chelate. Indeed, such reagents as allylsilanes, allylstannanes, and enolsilanes follow this trajectory.⁵ In an independent NMR study of **22** and of the corresponding SnCl₄ and MgBr₂ chelates, Keck has reached similar conclusions.²⁹



It was not clear whether the geometry around the ether oxygen in such complexes as **20** is planar or tetrahedral. In the latter case, oxygen would constitute a *second* chiral center in the molecule which could also contribute to the origin of stereoselectivity. Precise

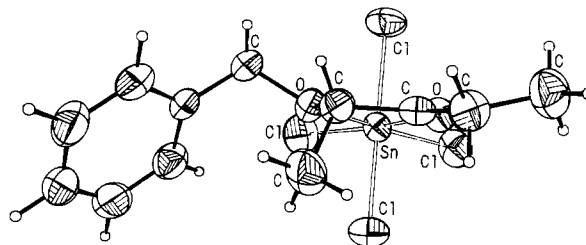
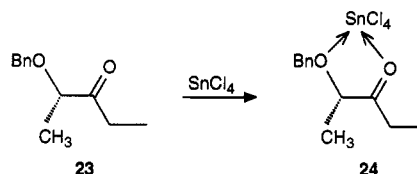


Figure 1. Crystal structure of adduct **24**.

data regarding such structural details should be accessible via X-ray structural analysis. Although it was not possible to obtain suitable crystals of **20** or **22**, we were successful in the case of a related SnCl₄ complex **24**.



The X-ray structural analysis (Figure 1) shows that the adduct is indeed monomeric, with tin being hexacoordinate in a distorted octahedral environment.³⁰ The two chlorine ligands above and below the 5-membered stannacycle form an angle of 166.91(5)° with the metal. The carbonyl oxygen-tin bond [2.184(3) Å] is 0.075 Å shorter than the ether oxygen-tin bond. It is interesting to compare the former value with the oxygen-titanium bond lengths of the achiral TiCl₄ complex of 3,3-dimethyl-2,4-pentanedione [2.077(3) and 2.086(3) Å], reported by Maier.³¹ Importantly, the geometry about the ether oxygen in **24** is almost planar. The benzyl CH₂ group points only slightly away from the methyl group attached to the stereogenic center. Puckering in the stannacycle due to tin leaning *toward* the methyl group at the stereogenic center amounts to 10°. It is clear that the bottom face of the carbonyl function is sterically shielded by the methyl group. The source of asymmetric induction in reactions in **24** and related aldehyde complexes thus relates directly to this effect; i.e., it is not greatly influenced by a possible second center of chirality at the ether oxygen, nor by effects due to possible dimeric forms of chelates. Puckering enhances the shielding effect, although this may be due to crystal packing. In solution, complex **24** is also a discrete species, as shown by ¹H-, ¹³C-, and ¹¹⁹Sn-NMR spectroscopy.³⁰

The above evidence for the intermediacy of chelates reveals nothing about the mechanism of reactions with C nucleophiles such as allyl- and enolsilanes. In a rapid injection NMR³² study of the chelation-controlled Mukaiyama aldol addition, we were able to demonstrate an acyclic approach of the enolsilane **25** to the chelate

(28) Kessler, K. Dissertation, Universität Marburg, 1986.

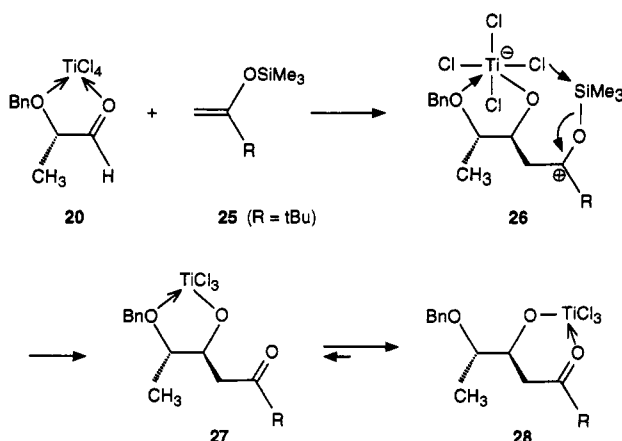
(29) (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847-3849. (b) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281-284. (c) Keck, G. E.; Castellino, S.; Andrus, M. B. *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; NATO ASI Series; Kluwer Academic Publishers: Dordrecht, 1989; pp 73-105.

(30) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881-5884.

(31) Maier, G.; Seipp, U.; Boese, R. *Tetrahedron Lett.* **1987**, *28*, 4515-4516.

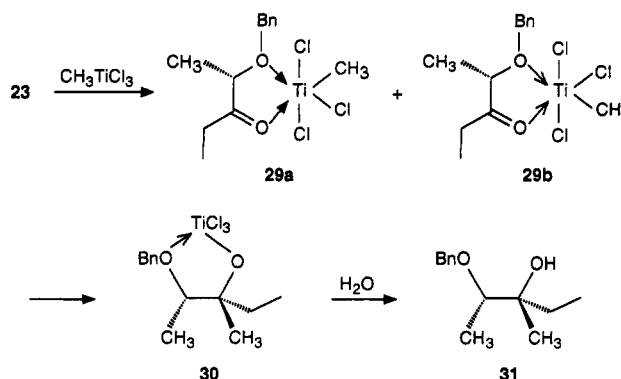
(32) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985**, *107*, 1810-1815.

20.²⁴ Upon injecting **25** into a CD₂Cl₂ solution of **20** at -70 °C, ¹H-NMR spectra were recorded at 400-ms intervals. After 1.4 s, about two-thirds conversion was observed. The reaction was complete within 9 s, delivering a single species **28** formed by rearrangement of the primary adduct **27**. The silyl group never reaches the carbonyl O atom, as shown by control experiments involving treatment of the separately synthesized silylated aldol adduct with TiCl₄ (no reaction to **28** under comparable reaction conditions). Thus, **25** approaches the chelate **20** in an acyclic manner, probably first forming intermediate **26**. Such an acyclic mechanism nicely explains the original observation that many prochiral enolsilanes react with chelates of the type **20** via a synclinal approach to deliver primarily one of four possible diastereomers, simple diastereoselectivity being syn.^{5,9a,17} This added feature is of obvious synthetic importance and has been exploited in a number of other cases^{5,19,33} involving prochiral enolsilanes, siloxydienes, allylstannanes, and silylated allenes.

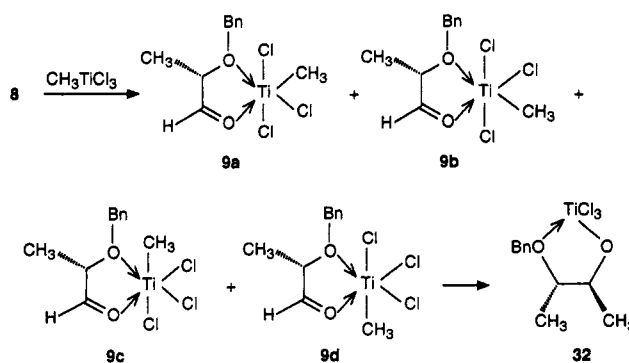


Attempts to characterize real Cram chelates **2** by NMR spectroscopy or X-ray structural analysis have failed so far due to spontaneous C-C bond formation.³⁴ However, some time ago we reported the first direct observation of a Cram-type chelate involving CH₃TiCl₃ and the ketone **23**.³⁵ Two adducts **29a** and **29b** (of four possible diastereomeric octahedral complexes) were identified by low-temperature ¹³C-NMR spectroscopy, and it was possible to monitor their reaction to the (single) adduct **30**. The question as to how the methyl group reaches the carbonyl C atom could not be answered unambiguously. The chelates **29a/29b** do not afford **30** with first-order kinetics, which would indicate an intramolecular 1,3 methyl shift. The data obtained at -15 °C speak more for second-order kinetics, although an ideal fit [perfect straight line for the plot of (1/c -

1/c₀) against time] was not observed.^{35,36} Thus, a complicated mechanism, perhaps involving fast ligand exchange reactions, seems to be operating for this synthetically clean reaction.



In a recent ¹³C-NMR study involving the analogous reaction of the aldehyde **8**, two chelates in a ratio of 93:7 were observed at -60 °C, probably **9a/9b**.³⁶ The two alternative diastereomers **9c** and **9d** are expected to be of higher energy (see theoretical discussion below). Upon raising the temperature to -30 °C, partial equilibration **9a** ⇌ **9b** as well as reaction to the adduct **32** occurs. In a kinetic study, data were obtained at -20 °C, which is in line with clean first-order kinetics. This speaks for an intramolecular 1,3 methyl shift, probably via the higher energy species **9c**, which is expected to be in equilibrium with **9a/9b** (see below). In order to gain support for this conclusion, crossover experiments were performed. Unfortunately, they turned out to be inconclusive due to fast complexation/decomplexation (scrambling of labeled species) prior to C-C bond formation.³⁶ The difference in behavior between **9a/9b** and **29a/29b** is presently unclear.



Kinetic Evidence for Chelates as True Intermediates

In a series of classical papers regarding the question of Cram chelates as true intermediates in Grignard additions, Eliel pointed out that if chelates are in fact reactive intermediates, enhanced rates must result.³⁴ In the case of chiral substrates, higher rates should correlate with higher degrees of stereoselectivity. Dimethylmagnesium was chosen as the reagent because it is a well-characterized single, monomeric species in THF, which simplifies the interpretation of the kinetic results obtained by rapid-injection NMR techniques.³²

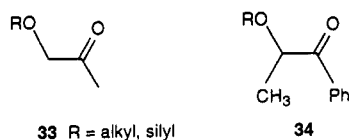
(33) Typical examples: (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* 1984, 25, 1879-1882. (b) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* 1984, 25, 1883-1886. (c) Danishefsky, S. J.; Pearson, W. H.; Harvey, D.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* 1985, 107, 1256-1268. (d) Heathcock, C. H.; Montgomery, S. H. *Tetrahedron Lett.* 1985, 26, 1001-1004. (e) Uenishi, J.; Tomozane, H.; Yamato, M. *Tetrahedron Lett.* 1985, 26, 3467-3470. (f) Shirai, F.; Nakai, T. *Chem. Lett.* 1989, 445-448. (g) Bernardi, A.; Cardani, S.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron Lett.* 1985, 26, 6509-6512. (h) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* 1983, 39, 935-947. (i) Marshall, J. A.; Wang, X. *J. Org. Chem.* 1990, 55, 6246-6248. (j) Gennari, C. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 629-660.

(34) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* 1992, 114, 1778-1784 and references therein.

(35) Reetz, M. T.; Hüllmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* 1987, 26, 477-479.

(36) Reetz, M. T.; Raguse, B.; Hüllmann, M.; Seitz, T. *Tetrahedron*, submitted.

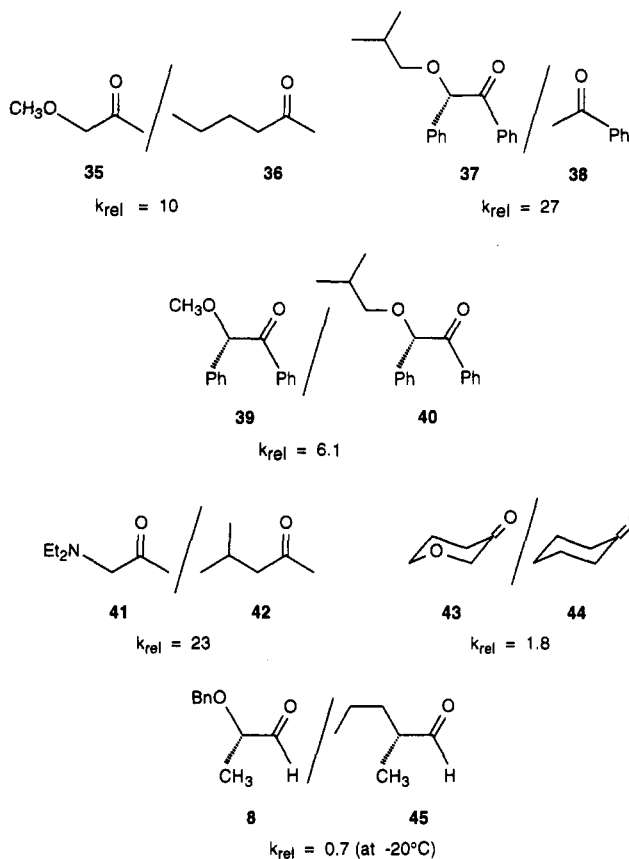
By using alkoxy and silyloxy ketones **33** and **34**, it was unambiguously shown that the above conjectures are correct.³⁴ Accordingly, alkoxy ketones **33** and **34** react much more rapidly than the silyloxy analogs. In stereochemically relevant cases (**34**) the alkoxy ketones provide chelation-controlled adducts, whereas silyloxy derivatives react with low or no stereoselectivity. Breslow has drawn an analogy between these observations and an enzyme-mediated stereoselective transformation.³⁷



We also observed higher reaction rates as a consequence of chelation, particularly in reactions of $\text{CH}_3\text{-Ti}(\text{OiPr})_3$ with alkoxy and amino ketones (at +22 °C).³⁸ This reagent is much less Lewis acidic than CH_3TiCl_3 , but complete chelation control is nevertheless observed (cf. **37**, **39**).^{38,39} The relative rates of Grignard-type addition summarized below clearly support the Eliel theory. For example, ketone **37** reacts 27 times faster than acetophenone **38**, the sole product being the chelation-controlled adduct. It should be mentioned that the bulky reagent $\text{CH}_3\text{Ti}(\text{OiPr})_3$ is quite sensitive to steric factors,^{10,38,39} but in competition reactions such as **35/36**, **37/38**, and **41/42** chelation is the overriding factor. Field or inductive effects as postulated by Thornton in certain lithium enolate additions to alkoxy ketones⁴⁰ appear not to be important (cf. **43** vs **44**). In contrast to alkoxy ketones, the analogous aldehydes (e.g., **8**) do not chelate with $\text{CH}_3\text{Ti}(\text{OiPr})_3$ and rate enhancement is not observed³⁸ (cf. **8** vs **45**) in a process which in fact leads to the non-chelation-controlled product **11** with 90% stereoselectivity!⁹ The question of the origin of non-chelation control has been treated elsewhere.^{5,9,18,23}

Kauffmann has demonstrated similar chelation-induced rate enhancement in reactions involving other organometallics such as chromium reagents.⁴¹ All of these observations suggest that high degrees of chemoselectivity in reactions of polyfunctional compounds should be possible. Several other rate data also speak for enhanced reactivity as a result of chelation. For example, CH_3TiCl_3 undergoes C–C bond formation with the α -alkoxy ketone **23** faster than with the desoxy analog 3-pentanone ($t_{1/2} = 310$ s and $t_{1/2} = 2200$ s, respectively, at –15 °C in CH_2Cl_2).⁴²

Finally, the relationship between chelation, enhanced rate, and stereoselectivity was also observed in the LiClO_4 -catalyzed aldol addition of enolsilane **12** to aldehydes in ether²⁴ and in CH_2Cl_2 .²⁶ The reaction with 2-methylpropanal requires 18 h at room temperature for completion, whereas the alkoxy aldehyde **8** reacts



within 20 min to yield the chelation-controlled adduct **13**. In ether the effects are just as dramatic.²⁴ To our knowledge, these are the first examples of enhanced rate of carbonyl addition due to chelation in a catalytic process.^{24,26} The Breslow analogy³⁷ is of particular interest in this system because it involves catalysis. The LiClO_4 -catalyzed hetero Diels–Alder reaction of **15** also occurs much faster with alkoxy aldehydes than with normal aldehydes.²⁷ For example, in a 1:1:1 competition experiment involving the diene **15**, the alkoxy aldehyde **8**, and 2-methylpropanal, the sole product turned out to be the adduct derived from **8**. Relevant is the important observation of Nakai that in $\text{Eu}(\text{fod})_3$ -catalyzed enolsilane additions the benzyl-protected aldehyde **8** reacts somewhat faster than the $\text{tBu}(\text{Me})_2\text{Si}$ -protected analog, diastereoselectivity being determined by chelation and non-chelation control, respectively.⁴³

Theoretical Studies

Quantum chemistry has made great strides in the last two decades, particularly in the area of calculating the structures and properties of organic molecules composed of first and second row atoms of the periodic table.⁴⁴ The development of theoretical methods in transition metal chemistry has lagged behind because the quantitative wave functions are much more complicated. Two different theoretical models appear to be on the verge of a breakthrough in this area: the pseudopotential method⁴⁵ based on effective core potentials (ECP) or on model potentials (MP), which

(43) Terada, M.; Gu, J. H.; Deka, D. C.; Mikami, K.; Nakai, T. *Chem. Lett.* 1992, 29–32.

(44) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(45) Szasz, L. *Pseudopotential Theory of Atoms and Molecules*; Wiley: New York, 1985.

(37) Quoted in footnote 21 of ref 34.

(38) (a) Reetz, M. T.; Maus, S. *Tetrahedron* 1987, 43, 101–108. (b) Reetz, M. T. *Top. Curr. Chem.* 1982, 106, 1–54 (specifically p 18).

(39) Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* 1986, 1600–1602.

(40) (a) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* 1990, 112, 5360–5362. (b) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* 1993, 115, 1302–1312.

(41) Kauffmann, T.; Möller, T.; Rennefeld, H.; Welke, S.; Wieschollek, R. *Angew. Chem., Int. Ed. Engl.* 1985, 24, 348.

(42) Reetz, M. T., et al. Unpublished results.

replaces the core electrons and treats only the valence electrons in the Hartree–Fock (HF) procedure, and the density functional theory (DFT).⁴⁶ The relative merits of the two approaches have been summarized by Frenking.⁴⁷ Although a number of ECPs for transition metals are known in the literature, the major problem is the lack of systematic investigations of the accuracy of the results using different ECPs, valence basis sets, and correlation energies. The situation is similar to that of ab initio methods in organic chemistry 15–20 years ago, at which the time groups such as those of Schleyer began systematic studies directed toward defining the best basis set for a given organic class of compounds or reactive species.⁴⁴

In collaboration with our group, Frenking has initiated an extensive investigation of the performance of various ECP models in organometallic chemistry. We began by studying the titanium reagents TiCl_4 , CH_3TiCl_3 , $(\text{CH}_3)_2\text{TiCl}_2$, $(\text{CH}_3)_3\text{TiCl}$, and $(\text{CH}_3)_4\text{Ti}$, particularly their geometries and energies of reactions.⁴⁷ The best overall agreement with experimental geometries and energies resulted when using the $(n-1)s^2(n-1)p^6(n-1)d^a(n)s^b$ ECP developed by Hay and Wadt⁴⁸ combined with the 3-21G* basis set⁴⁴ for the ligands at titanium. Improved total energies were calculated using the less contracted ECP valence basis set (3311/2111/311) for titanium and the 6-31G(d) basis set for the other atoms.

The same conclusion regarding the choice of ECPs and basis sets became apparent when calculating 16 different octahedral complexes of TiCl_4 and CH_3TiCl_3 involving various bidentate ligands.⁴⁹ In all cases geometry optimization showed that the axial ligands tilt toward the bidentate ligand, resulting in a distorted octahedral arrangement. Excellent agreement with X-ray data of the TiCl_4 complexes of acetic acid anhydride⁵⁰ and 3,3-dimethyl-2,4-pentanedione³¹ was found. Interestingly, the SnCl_4 adduct **24** shows a similar distortion from ideal octahedral geometry³⁰ (Figure 1). Although ECP calculations of Si, Sn, and Pb compounds have been carried out,⁵¹ octahedral complexes remain to be studied. In the case of $\text{TiCl}_4/2$ -hydroxypropanal (as a model for complex **20**), distortion again becomes apparent (Figure 2).⁴⁹ The five-membered ring is nearly planar, and the calculated Ti–O bond lengths are 2.146 (Ti–O¹) and 2.125 (Ti–O²).

The results of the calculations of $\text{CH}_3\text{TiCl}_3/2$ -hydroxypropanal (as a model for **9a–d**) are intriguing.⁴⁹ Figure 3 shows the calculated geometries and relative energies of the four possible diastereomers.

The adducts in which the methyl group occupies the axial positions are of higher energy. The same trend is observed in calculations of CH_3TiCl_3 adducts of glycol and ethylenediamine.⁴⁹ Experimentally, glycol ether⁵² and diamine⁵² adducts of CH_3TiCl_3 all have the methyl group in the equatorial position, as shown by NMR

(46) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1988.

(47) Jonas, V.; Frenking, G.; Reetz, M. T. *J. Comput. Chem.* **1992**, *13*, 919–934.

(48) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270, 284, and 299.

(49) Jonas, V.; Frenking, G.; Reetz, M. T. *Organometallics* **1993**, *12*, 2111–2120.

(50) Viard, B.; Poulain, M.; Grandjean, D.; Amaudrut, J. *J. Chem. Res.* (S) **1983**, 84–85.

(51) Jonas, V.; Frenking, G.; Reetz, M. T. *J. Comput. Chem.* **1992**, *13*, 935–943.

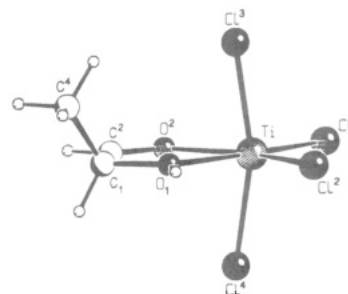


Figure 2. Optimized geometry of $\text{TiCl}_4/2$ -hydroxypropanal.

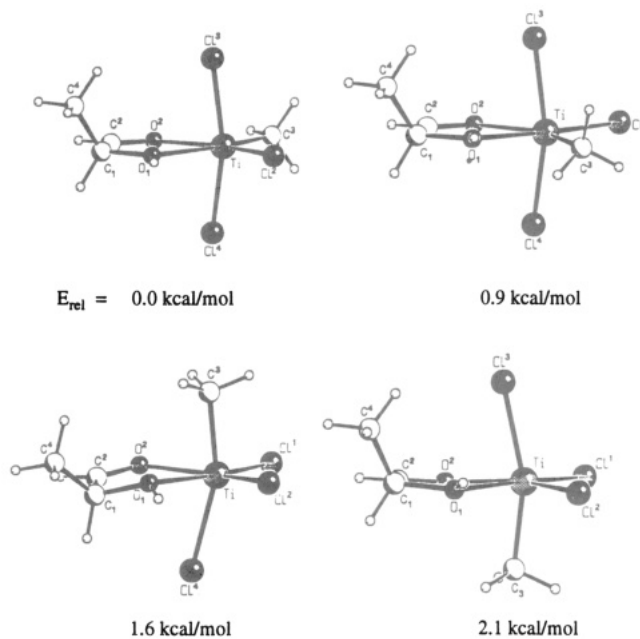


Figure 3. Optimized geometries of $\text{CH}_3\text{TiCl}_3/2$ -hydroxypropanal.

spectroscopy. Furthermore, Green has published the results of an X-ray structural analysis of a diphosphine adduct of CH_3TiCl_3 , which again shows that the methyl group occupies the equatorial position.⁵³ We initially thought that we could explain this structural generality by invoking differences in donor–acceptor interactions between the ligands. This turned out to be difficult and is still being studied. However, we were able to trace the geometric preference to differences in deformation of the CH_3TiCl_3 “fragment” in the complexes.⁴⁹ Following geometry optimization of the two $\text{CH}_3\text{TiCl}_3/\text{glycol}$ adducts, the bidentate ligands were “removed” and the energies of the two distorted CH_3TiCl_3 recalculated. The results turned out to be revealing, the relative energies being 0, 31.0, and 41.1 kcal/mol for CH_3TiCl_3 in the ground state, for distorted CH_3TiCl_3 derived from the complex with an equatorial methyl, and for distorted CH_3TiCl_3 derived from the complex with an axial methyl, respectively (Figure 4). These and other calculations suggest that it is the difference in deformation of the CH_3TiCl_3 fragments which determines the preferred geometry.⁴⁹ It remains to be seen whether the inclusion of effects due to possible agostic hydrogen interaction^{53,54} will modify this important conclusion.⁵⁵

(52) (a) Clark, R. J. H.; McAlees, A. J. *J. Chem. Soc. A* **1970**, 2026–2033. (b) Clark, R. J. H.; McAlees, A. J. *Inorg. Chem.* **1972**, *11*, 342–348.

(53) Dawoodi, Z.; Green, M. L. H.; Mtetwa, V. S. B.; Prout, K.; Schultz, A. J.; Williams, J. M.; Koetzle, T. F. *J. Chem. Soc., Dalton Trans.* **1986**, 1629–1637.

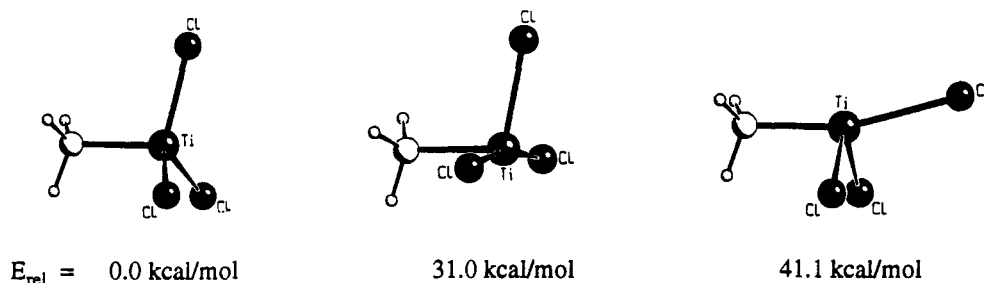


Figure 4. Distorted forms of CH_3TiCl_3 (see text).

Of the two complexes in Figure 3 having equatorial methyl groups, the one with methyl trans to the hydroxy group is thermodynamically more stable.⁴⁹ It is likely that an alkoxy group would lead to a similar preference. Thus, in a thermodynamically controlled reaction with aldehydes of the type 8, mainly diastereomeric **9b** is expected to be formed. Experimentally, under kinetic conditions a 93:7 mixture of diastereomeric complexes is observed which reacts to the final products 10/11 before complete equilibration $\mathbf{9a} \rightleftharpoons \mathbf{9b}$ occurs. These observations in conjunction with the calculations allow for a fairly certain configurational assignment. The initially formed major diastereomer is **9a** which (partially) isomerizes to the thermodynamically more stable form **9b** prior to C–C bond formation. If an intramolecular 1,3 methyl shift defines the mechanism of C–C bond formation,³⁶ we expect equilibration $\mathbf{9a}/\mathbf{9b} \rightleftharpoons \mathbf{9c}$ to be operating and the latter species to be the intermediate which undergoes C–C bond formation.

Conclusions

Chelation control in a variety of C–C bond forming reactions of chiral alkoxy carbonyl compounds is possible if the proper reagents or catalysts are chosen.

(54) Weiss, H.; Haase, S. H.; Ahlrichs, R. *Chem. Phys. Lett.* **1992**, *194*, 492–496.

(55) Jonas, V.; Frenking, G.; Reetz, M. T. Work in progress.

(56) Ab initio calculations of the transition state of LiH addition to 2-methoxypropanal show chelation in the transition state: Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron*, in press.

The stereochemical outcome is no longer the sole indication of the intermediacy of chelates. In all cases in which kinetic experiments were carried out, rate enhancement due to chelation was observed. This in itself is a powerful indication that chelates are true intermediates. NMR and X-ray studies of TiCl_4 , SnCl_4 , and MgBr_2 chelates of chiral alkoxy carbonyl compounds show that discrete monomeric species are usually involved. Their geometries reveal the source of stereoselectivity in reactions with R_2Zn , enol- and allylsilanes, Me_3SiCN , olefins (ene reactions), and dienes (hetero Diels–Alder reactions). Cram-type chelates of CH_3TiCl_3 and α -alkoxy ketones and aldehydes can be observed directly by rapid-injection NMR spectroscopy. A challenge for the future is the X-ray structural analysis of such reactive intermediates.

Concerning theory, effective core potentials (ECPs) within the Hartree–Fock level provide a good basis for calculating octahedral chelates of TiCl_4 and CH_3TiCl_3 . It remains to be seen whether ab initio methods can be applied successfully to SnCl_4 chelates⁵⁵ and to LiClO_4 -catalyzed reactions.⁵⁶ Finally, the density functional theory (DFT)⁴⁶ needs to be tested in chelation-controlled reactions and systematically in the general area of organometallic chemistry as well.

Sincere thanks are due to my co-workers whose names are listed in the references, and to the Deutsche Forschungsgemeinschaft (SFB 260 and Leibniz-Program) for support.