Diastereoselection in Lewis-Acid-Mediated Aldol Additions

Rainer Mahrwald

Institut für Organische und Bioorganische Chemie der Humboldt-Universität Berlin, Hessische Strasse 1-2, 10115 Berlin, Germany

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Contents

I. Introduction

The aldol addition is one of the most important methods for stereoselective construction of carbon−carbon bonds. New and powerful variants of these classical reactions have been developed in recent years.[1] Two classes were mainly used for asymmetric induction in these reactions: the use of asymmetric modified enolates or electrophiles[2] and the use of chiral Lewis acids.[3]

The chiral enolate or electrophile approach is much more general and gives high stereoselectivities due to the highly ordered nature of transition structures ("closed" transition models). The chiral center has to be removed after the completed aldol addition. To avoid this additional reaction step, a stategy is employed whereby achiral enolates can be reacted with achiral carbonyl compounds in the presence of additional chiral auxiliaries. This method requires the careful use of a chiral auxiliary.[4] Unfortunately, however, stoichiometric amounts of the chiral information are necessary. Up to now and apart from enzymatic transformations, the so-called Mukaiyama reaction has opened an *enantioselective* and *catalytic* approach using chiral Lewis acids.

Rainer Mahrwald obtained his M.S. degree in chemistry from the Martin-Luther-University, Halle, in 1973. In 1975 he joined the Institute "Manfred von Ardenne", Dresden, where he obtained his Ph.D. in 1979 in the field of the synthesis of nuclesides. In 1980 he joined the Academy of Sciences in Berlin. There he worked in the field of total synthesis of prostaglandins. He pursued his formation as a postdoctoral fellow at Philipps-University, Marburg, in the group of Prof. M. T. Reetz (1991). Since 1994 he has been a lecturer at the Humbold-University. His main research interests have been associated with the development of catalytic stereoselective C–C bond formation.

This review covers the evolution of stereoselective Lewis-acid-mediated aldol-type addition up to the recent development of chiral Lewis acids.

Mukaiyama et al. found that silyl enol ether reacts with carbonyl compounds in the presence of Lewis acids to give aldol products (for initial studies, see ref 5). The main advantages in the Mukaiyama approach are the chemoselectivity of the reaction and the possibility of stereoselective execution. Since the mid-1970s, the Mukaiyama reaction has become a useful method for chemo- and regioselective carbon−carbon bond formation.[6] About 10 years later, investigations into stereochemical aspects of these reactions were initiated,[7] and at the end of the 1980s, the development of chiral Lewis acids and thus the development of catalytic, enantioselective versions of the Mukaiyama reaction started.[8]

The reaction mechanism has not been explained yet. The most important fact is that Lewis acid enolates are not involved in this reaction.[7] No transmetalation occurs. In this reaction, the Lewis acids coordinate with the carbonyl function leading to its activation.[9] Two works published by Carreira and Shibasaki suggest the involvement of chiral metal enolates during the aldol addition (for copper enolates, see ref 10; for palladium enolates, see ref 11). Moreover, there is a marked stereochemical differ-

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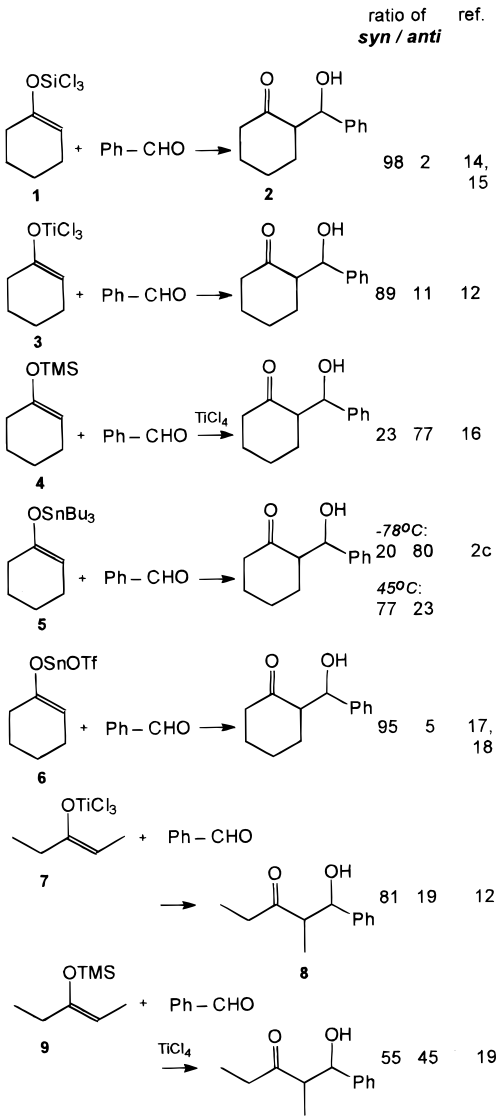
Scheme 1



ence between Lewis-acid-mediated reactions of silyl enol ether and aldol additions of Lewis acid enolates with electrophiles. This fact is illustrated by some examples in Scheme 1. For a comparison of these two types of reactions, see refs 12 and 13. Recently, Denmark et al. described Lewis-base-induced enantioselective aldol additions. By reacting trichlorosilyl enolates with aldehydes in the presence of catalytic amounts of chiral phosphoramides, the *anti*-aldol products were obtained in high enantioselectivities (e.g., **1** in Scheme 1).[14,15]

This difference between these two types of an aldol addition is supported by further experimental evidence (X-ray,[20] NMR-spectroscopy[21]). Nevertheless, there exists a great interest for this reaction because the Mukaiyama reaction opened the way for a real catalytic control of the stereoselectivity during the aldol process.

The subject of this review is to rationalize the various stereochemical results of the Mukaiyama reaction—the Lewis-acid-mediated aldol addition.

II. Additions of Silyl Enol Ethers to Electrophiles

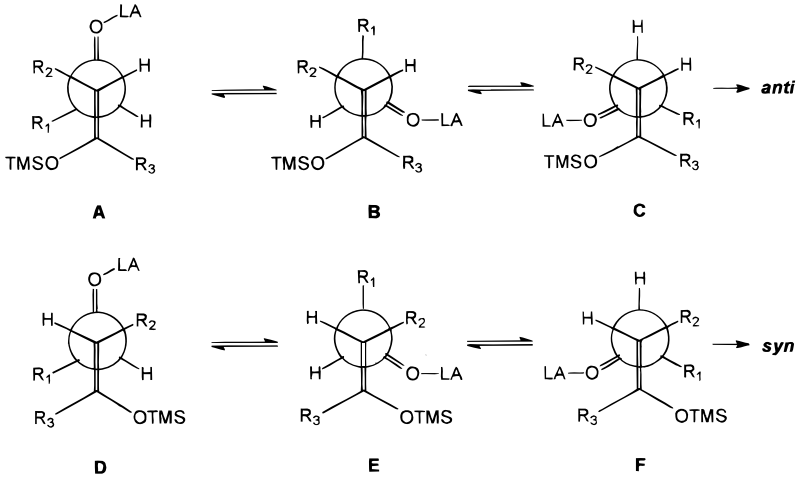
Numerous reactions of aldehydes and enol silanes in the presence of Lewis acids were published to give a diastereomeric pair of aldol products **10** and **11** (Scheme 3). The stereoselectivity obtained by the reaction of two prochiral compounds—the enol silane and the carbonyl compound—is called simple stereoselection.[1d]

Due to the different conditions, various types of enolates and counterions used, a different mechanism in this reaction and, thus, possibly different types of transition-states were proposed. The described different stereochemical outcome of the Mukaiyama reaction and the aldol addition of Lewis acid enolates to carbonyl compounds (Scheme 1) cannot be explained by classical "closed" transition-state models, such as Zimmermann–Traxler models.[22]

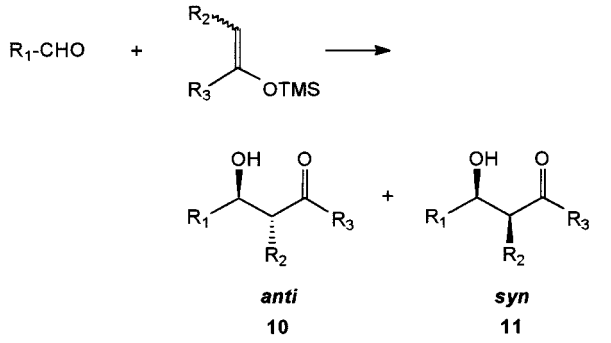
At that time so-called "open" or "extended" transition-state models provided the best agreement of stereochemical results and conceptions about the stereochemistry involved in this aldol-type reaction.[23] Therefore, they have been the best tools so far for explaining and predicting the expected stereoselection (Scheme 2, LA = Lewis acid). For very early discussions of open transition-states, see ref 24.

Initially, no stereochemical advantage has been observed in the reactions of aldehydes with nucleophiles (silyl enol ether, silyl ketene acetals) in the presence of stoichiometric amounts of Lewis acids.

Scheme 2



Scheme 3



entry	R_1	R_2	R_3	*Z* / *E*	Lewis acid	ratio of **10** / **11**	yield[%]	ref.
1	*i*-Pr	Me	OEt	15/85	$TiCl_4$	93/ 7	75	25
2	*i*-Pr	Me	*t*-Bu	100/0	$BF_3{\cdot}OEt_2$	95/ 5	84	26
3	Ph	Me	OEt	25/75	$TiCl_4{\cdot}PPh_3$	91/ 9	79	27
4	Ph	Me	*t*-Bu	100/0	$BF_3{\cdot}OEt_2$	95/ 5	95	28
5	Ph	*t*-Bu	OEt	76/24	$TiCl_4$	8/92	NR	29
6	Ph	*t*-Bu	OEt	5/95	$TiCl_4$	8/92	NR	29
7		Me	Ph	100/0	$TiCl_4$	10/90	NR	30
8		Me	Ph	100/0	$SnCl_4$	5/95	NR	30
9		Me	Ph	100/0	$TiCl_4$	10/90	NR	30
10		Me	Ph	0/100	$TiCl_4$	10/90	NR	30

R_1 in entries 7 and 8: $Ph\text{-}CH_2OCH_2$-
R_1 in entries 9 and 10: $Ph\text{-}CH_2O(CH_2)_2$-

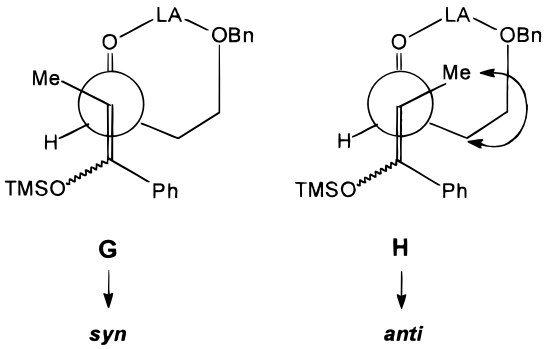
However, by carefully choosing substrates and reaction conditions, a preparatively useful control of the diastereoselectivity of this reaction has been obtained.

The proposed open model assumes that the uncomplexed ionic oxygens are as remote as possible (dipolar repulsion). By "fine tuning", one model is favored in the diastereomeric orientation due to the avoidance of steric repulsive interactions of the substituents. Transition structures **B**, **C**, and **E** are out of the question (**B**, steric interaction between R_3 and LA; **C** and **E**, unfavorable dipole−dipole interaction of the carbon−oxygen bonds) (Scheme 2).

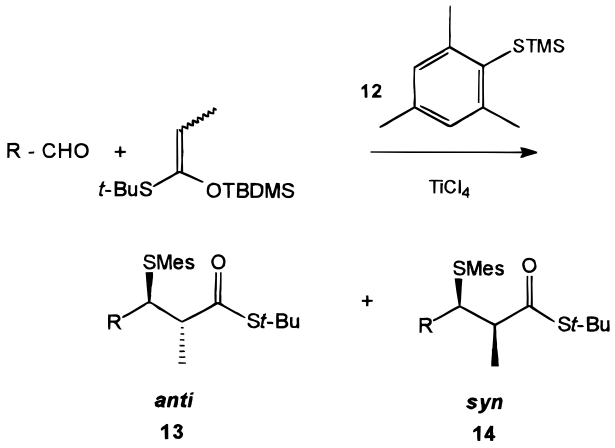
Good *anti*-selectivities were observed independently of the double-bond geometry when R_2 is small and R_3 is a sterically bulky group (entries 1−4, Scheme 3). Transition structures **D** (nonbonded interactions between R_1 and R_3) and **F** (nonbonded interactions between oxygen and R_1) are disfavored compared to **A**. Only a few examples are shown in Scheme 3; for further results, see refs 31a−d, 32, 33, 34. The high simple *anti*-selectivity observed provides a useful complement to the corresponding more *syn*-selective lithium enolates.[35]

In contrast to these results, transition-states **A** and **F** are disfavored compared to **D** (repulsive interactions between R_1 and R_2) when R_2 is replaced by a larger group (entries 5 and 6, Scheme 3). Independent of the geometry of the used silyl enol ether (*Z*- or *E*-silyl enol ether), *syn*-diastereoselection predominates in this stereoconvergent aldol addition.

Scheme 4



Scheme 5



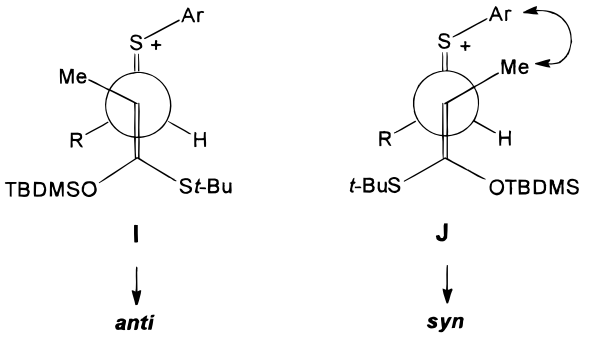
entries	R	*Z* / *E*	ratio of **13** / **14**	yield[%]
1	*n*-Pr	0 / 100	75 / 25	50
2	*i*-Pr	0 / 100	92 / 8	60
3	*i*-Pr	100 / 0	83 / 17	75
4	Ph	0 / 100	94 / 6	91
5	Ph	100 / 0	89 / 11	88

(Mes = 2.4.6-trimethylphenyl)

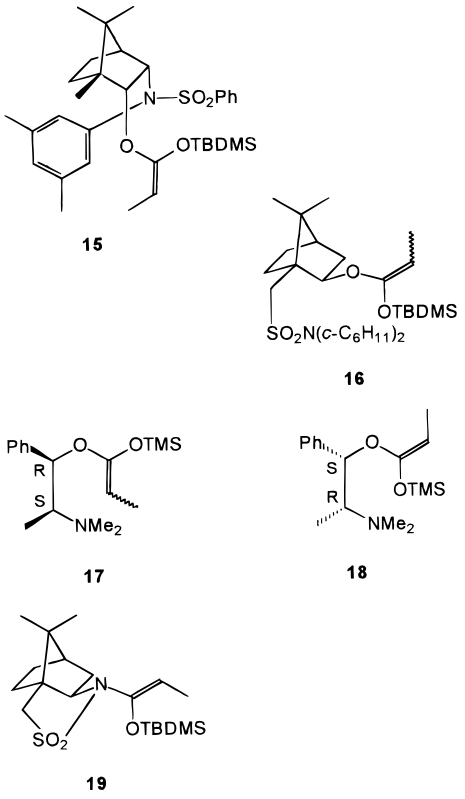
By using aldehydes capable of chelation, a reversal of the high *anti*-selectivity was found and high degrees of simple *syn*-selectivity were observed. This reversal of stereochemical results is due to the chelation influence (entries 7−10, Scheme 3). As a result of chelation and repulsive interactions, the transition-state **H** is disfavored and, independent of the geometry of the enol silanes used, a *syn*-preference is observed (Scheme 4 and entries 9 and 10 in Scheme 3).[30,36,37]

Heathcock et al. developed a concept based on the idea that the diastereoselectivity in aldol additions often depends on the size of the activating groups or ligands attached to the carbonyl oxygen. Aldol additions in the presence of the (trimethylthiophenyl)-trimethylsilane **12** gave excellent simple *anti*-diastereoselectivity (Scheme 5).[1j,35,38,39] Thioacetals of the aldehydes used might be intermediates in this reac-

Scheme 6



Scheme 7

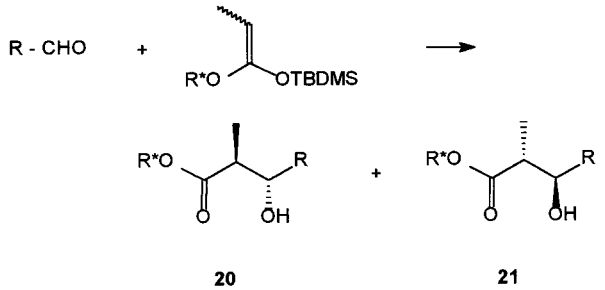


tion, as shown by the authors. Using both the *Z*- and the *E*-trimethylsilyl enol ethers, high selectivity for *anti*-aldols was observed. The authors assumed the methyl/aryl interaction became dominant, and therefore, transition-state **I** was favored (Scheme 6). Reductive removal of sulfur led to an approach to deoxypolypropionates. By reacting *n*-butanal, *iso*-butanal, and benzaldehyde with the silyl enol ether of the Morireagent (2.2-dimethyl-3-pentanone), only the *anti*-isomer of the aldol products was detected.[39]

III. Additions of Chiral Silyl Enol Ethers to Electrophiles

Chiral silyl ketene acetals were introduced for diastereoselective aldol-type addition similar to aldol additions of chiral boron enolates,[2b] titanium enolates,[2d] tin enolates,[2c] and zirconium enolates.[2e] Chiral resources used in the Mukaiyama reaction are shown in Scheme 7 (camphor derivative **15**,[40] camphor derivative **16**,[41] *N*-methylephedrine derivatives **17** and **18**,[42] sultam derived from camphor **19**[43]). Similar

Scheme 8



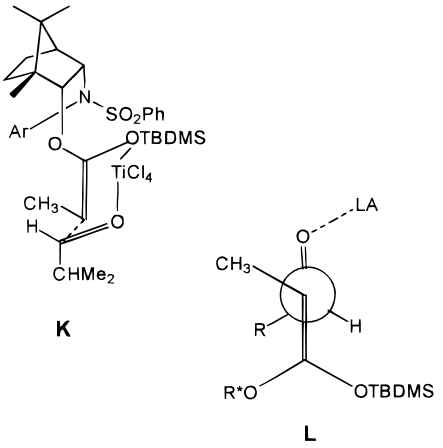
entry	reagent	R	Lewis acid	ratio of *anti* / *syn*	ratio of 20/21	yield [%]	ref.
1	15	*i*-Pr	$TiCl_4$	94/ 6	2/98	66	40
2	E-16	Ph	$TiCl_4$	81/19	5/95	44	41
3	E-16	Et	$TiCl_4$	100/0	6/84	30	41
4	E-16	*n*-Pr	$TiCl_4$	94/ 6	7/93	50	41
5	E-16	*i*-Pr	$TiCl_4$	98/ 2	8/92	60	41
6	E-16	*i*-Pr	$BF_3{\cdot}OEt_2$	73/27	3/97	58	41
7	Z-16	*i*-Pr	$BF_3{\cdot}OEt_2$	94/ 6	94/ 6	57	41
8	E-17	Ph	$TiCl_4$	85/15	97/ 3	80	42
9	E-17	Ph	$TiCl_4{\cdot}PPh_3$	97/ 3	97/ 3	90	27
10	Z-17	Ph	$TiCl_4$	80/20	96/ 4	65	42
11	Z-16	E-Ph-CH=CH	$TiCl_4$	85/15	96/ 4	60	42
12	Z-16	E-Ph-CH=CH	$TiCl_4{\cdot}PPh_3$	94/ 6	93/ 7	50	27
13	Z-16	E-Me-CH=CH	$TiCl_4$	80/20	96/ 4	78	42
14	Z-16	*n*-Pr	$TiCl_4$	80/20	96/ 4	88	42
15	Z-16	n-C_5H_{11}	$TiCl_4$	75/25	97/ 3	60	42
16	Z-19	Ph	$TiCl_4$	99/ 1	>99/<1	70	43
17	Z-19	Me	$TiCl_4$	>99/<1	>99/<1	72	43
18	Z-19	*i*-Pr	$TiCl_4$	>99/<1	>99/<1	76	43
19	Z-19	*i*-Bu	$TiCl_4$	>99/<1	>99/<1	78	43

to the above-described aldol additions, chiral auxiliaries have to be removed from the propionate equivalent after completed aldol addition by saponification or by reduction.

High degrees of simple *anti*-diastereoselectivity were found. Very interesting results were obtained, e.g., the stereochemical outcome of the addition of the chiral enol silanes **15** and *E*-**16** to *iso*-butanal in the presence of $TiCl_4$ (entries 1 and 5, Scheme 8). Though the same relatively simple diastereoselection and absolute configuration were obtained, the authors explained this fact by completely different transition-state models (Scheme 9). Helmchen favored the cyclic transition-state **K**,[40] whereas Oppolzer explained the reaction by the open transition-state **L** (Scheme 9).[41]

Moreover, the aldol additions mediated either by $TiCl_4$ or BF_3 (entries 5 and 6, Scheme 8) gave the same stereochemical results. Chelation control does

Scheme 9



not seem to take place in this reaction. The reversal of the absolute configuration in the *anti* series (entries 6 and 7, 4 and 14, Scheme 8) by changing the double-bond geometry of the chiral auxiliaries derived from camphor (*Z*- and *E*-**16**) is suspicious. On the other hand, by using the ephedrine auxiliaries (*Z*- and *E*-**17**), this phenomenon does not take place. The same relative and absolute configuration is observed by using *Z*- or *E*-configurated enol silanes (entries 8 and 10, Scheme 8).

Nevertheless, these described asymmetric versions helped to solve the longstanding problem of an efficient synthesis of chiral *anti*-aldol products.

Later on, Oppolzer et al. improved the dia- and enantioselectivity by using the cyclic sultam **19** derived from camphor. Very high selectivities were observed (entries 16−19, Scheme 8). The products were obtained in crystalline form.[43]

IV. Additions of Chiral Carbonyl Compounds to Nucleophiles

The two π-faces of the carbonyl function of aldehydes with one or more chiral centers are diastereotopic. For that reason, aldol additions of silyl enol ethers to chiral aldehydes display diastereofacial selectivity in addition to simple diastereoselection.[1d] The stereochemical outcome and the problems arising from the 1,2−1,*n*-asymmetric induction are explained and predicted best by the models of Cram,[44] Felkin,[45] or Anh.[46,47]

Moreover, transition-states may be explained by chelation or nonchelation models in aldol additions of nucleophiles to aldehydes capable of chelation (O-, N-, or *S*-substituted aldehydes).[48] In addition to steric and electronic factors, the trajectory of attack of the incoming nucleophile also determines the stereochemical result of the reaction.[49] For further detailed, theoretical treatment of the aldol addition and trajectory analysis, see ref 50 and references therein.

A more general and theoretical review by O. Reiser dealing with these problems may be found in the same issue of this journal.

Stereochemical results of aldol additions of chiral electrophiles with stereogenic enol silanes should be classified by the kind of asymmetric induction.

A. 1,2-Asymmetric Induction

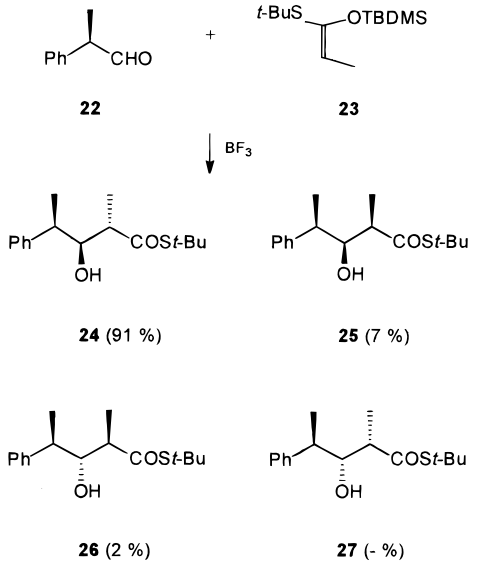
Stereochemical results of the aldol addition of 2-phenylpropanal **22** and the silyl enol ether of the propionic acid-*tert*-butylthioester **23** in the presence of BF_3 demonstrate the most simple case—the problem of simple and facial diastereoselectivity of aldol additions (Scheme 10). High facial *syn*-selectivity and a high degree of simple *anti*-diastereoselectivity were observed in this nonchelation-controlled Mukaiyama reaction. Only one of the four possible diastereomers has been observed.[31a,b]

These results are in accordance with the transition-state **M** shown in Scheme 11. Felkin's rule demands the minimization of nonbonded interactions.[45] The staggered conformation in Scheme 11 is preferred if substituents of different sizes but similar electronic character participate. Generally, one can say in aldol addition the 1,2-asymmetric induction increases with increasing steric demands of the enol silanes. For further and similar stereochemical results, see refs 51 and 52.

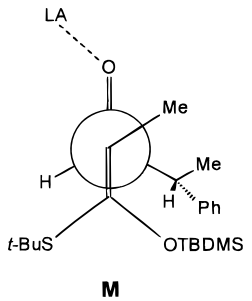
Using the enolborate **28** in the aldol addition instead of the silyl enol ether **23**, a completely different ratio of the isomers was obtained (compare the results in Scheme 10 with the results in Scheme 12).[31a]

A comparison of acetate aldol reactions mediated by BF_3 or by lithium enolates is given in Scheme 13.[52,53] 2-Phenylpropanal shows an exceptional diastereofacial preference in the BF_3-mediated aldol additions.

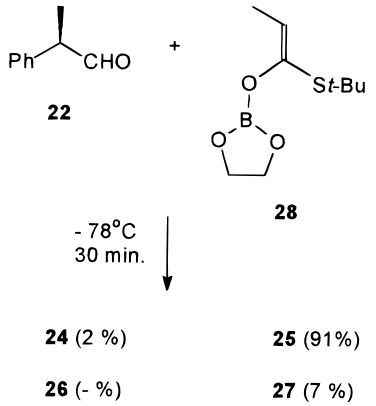
Scheme 10



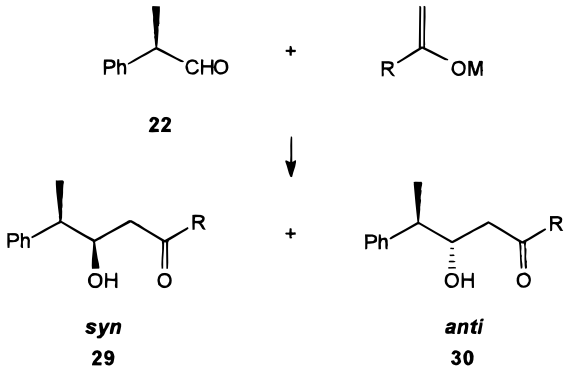
Scheme 11



Scheme 12



Scheme 13

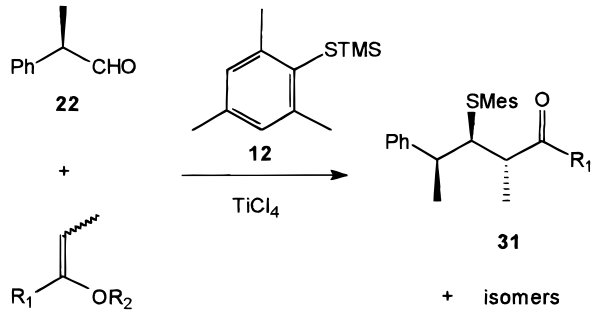


entry	R	M	ratio of **29 / 30**
1	Me	Li	75 / 25
2	*t*-Bu	Li	80 / 20
3	MeO	Li	75 / 25
4	*t*-BuO	Li	80 / 20
5	Me_2N	Li	75 / 25
6	Me	TBDMS	91 / 9
7	*t*-Bu	TBDMS	96 / 4
8	MeO	TBDMS	94 / 6
9	*t*-BuO	TBDMS	97 / 3

By using the Heathcock method (chiral thionium ions[1j]), the same stereochemical patterns were found in high degrees (Scheme 14). High simple *anti* and high facial *syn* selectivities were observed during this process. The silyl enol ether of the so-called Mori reagent was reacted with 2-phenylpropanal **22** in the presence of (trimethylphenyl)thiotrimethylsilane **12** (Mes-STMS) (entry 5, Scheme 14). The bulky *tert*-butyl group in the enol silane (R_1) used in this reaction and the bulky mesitylthio group in the reagent are responsible for these high simple and facial diastereoselectivities. A detailed comparison of the Lewis acids used and facial stereoselection obtained is given in this paper.[39]

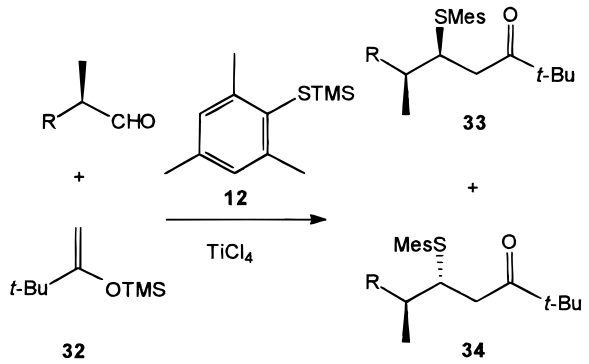
In further experiments, the steric influence of the aldehydes used in this reaction was analyzed. Again,

Scheme 14



entry	R_1	R_2	ratio of *E* / *Z*	ratio of **31** / isomers
1	S*t*-Bu	TBDMS	94 / 6	66 / (16/17)
2	S*t*-Bu	TBDMS	5 / 95	76 / (7/17)
3	S*t*-Bu	TMS	86 / 14	60 / (13/27)
4	S*t*-Bu	TMS	4 / 96	60 / (7/33)
5	CMe_2-CH=CH_2	TMS	98 / 2	97 / (3)
6	*t*-Bu	TMS	98 / 2	97 / (3)

Scheme 15



entry	R	ratio of **33** / **34**
1	Ph	97 / 3
2	*c*-C_6H_{11}	98 / 2
3	$PhCH_2$	97 / 3
4	Et	83 / 17

high degrees of facial *syn*-selectivity were observed by using several chiral aldehydes in the corresponding acetate aldol addition. Even in the reaction of 2-methylbutanal, high *syn*-selectivity was observed (entry 4, Scheme 15). This is the simplest and at the same time the most difficult case; the reagent has to differentiate during the reaction between a methyl and an ethyl group.[39]

In the same year Heathcock et al. described results of Lewis-acid-mediated acetate aldol additions with α-chiral acetals. Again, facial *anti*-selectivity was obtained. Generally, one can say the obtained 1,2-asymmetric induction increases with increasing steric

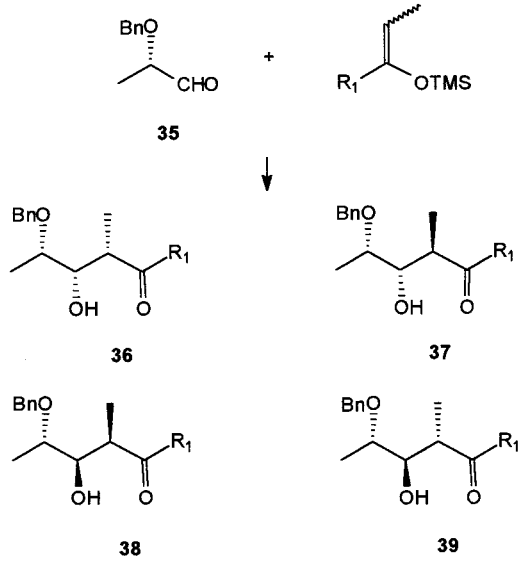
bulk of the used (alkoxy groups) acetals and with increasing polarity of the solvent used. The highest selectivities were observed using the sterically bulky 2-phenylpropanal acetal of pinacol.[54]

B. 1,2-Asymmetric Induction and Chelation Control

Oxygen, nitrogen,[55] or sulfur[56] bearing α-chiral aldehydes are suitable starting products for obtaining appropriate sequences or stereodefined periods of natural products (e.g., polyketide natural products). On one hand, an asymmetric center is introduced into the substrate very easily; on the other hand, an effective transfer of the chiral information of this stereogenetic center to the diastereoface may be achieved by chelation control. Therefore, most of the work in this field was done with oxygen- or nitrogen-heterosubstituted aldehydes or ketones.

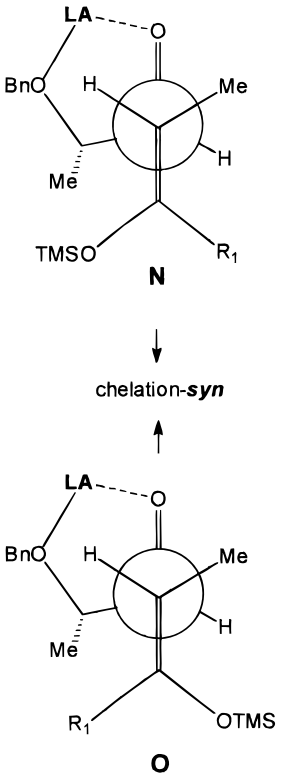
Some of the results of aldol additions of α-alkoxy aldehydes with enol silyl ether are given in Scheme 16. Only the most exciting results are shown. For

Scheme 16

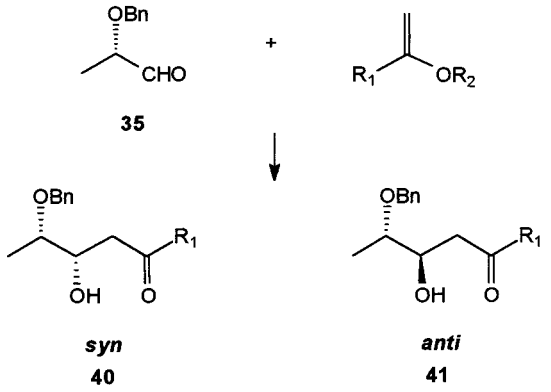


entry	R_1	*E* / *Z*	Lewis acid	36	37	38	39	ref.
1	*i*-Pr	0 / 100	$TiCl_4$	50	50	0	0	16,28
2	*i*-Pr	100 / 0	$TiCl_4$	88	12	0	0	16,28
3	Ph	0 / 100	$TiCl_4$	95	5	0	0	16,28,57
4	Ph	100 / 0	$TiCl_4$	85	15	0	0	16,28,30
5	S*t*-Bu	93 / 7	$SnCl_4$	95	5	0	0	31a,31b,58
6	S*t*-Bu	10 / 90	$SnCl_4$	85	15	0	0	31a,31b,58
7	S*t*-Bu	93 / 7	$TiCl_4$	94	6	0	0	31a,31b
8	S*t*-Bu	10 / 90	$TiCl_4$	83	17	0	0	31a,31b
9	S*t*-Bu	93 / 7	$BF_3{\cdot}Et_2O$	6	22	12	60	31a,31b
10	S*t*-Bu	93 / 7	TBAF	16	3	73	8	31a,31b,58
11	S*t*-Bu	10 / 90	TBAF	13	3	72	12	31a,31b,58

Scheme 17



Scheme 18

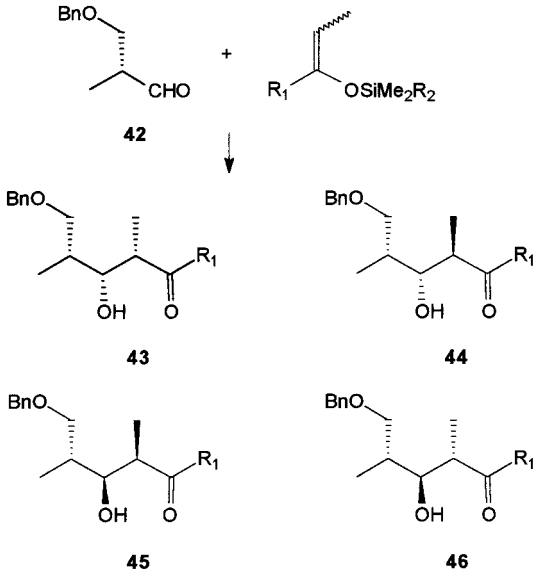


entry	R_1	R_2	Lewis acid	ratio of 40 / 41	yield [%]	ref.
1	OMe	TBDMS	$BF_3{\cdot}Et_2O$	60 / 40	48	26,28
2	O*t*-Bu	TBDMS	$SnCl_4$	65 / 35	65	26,28
3	S*t*-Bu	TBDMS	$SnCl_4$	98 / 2	50	65
4	*t*-Bu	TMS	BF_3 (gas)	10 / 90	85	59
5	*t*-Bu	TMS	$SnCl_4$ or $TiCl_4$	99 / 1	86	26,28,66
6	*t*-Bu	TMS	$BF_3{\cdot}Et_2O$	50 / 50		67
7	Ph	TMS	$SnCl_4$ or $TiCl_4$	99 / 1	70	26,28,57

further examples, see refs 28, 30, 36, 26, 57, 59.

By using suitable Lewis acids, chelation-controlled aldol additions may occur. The careful choice of Lewis acids is important in these reactions. The best results of chelation control were obtained by using $SnCl_4$ or

Scheme 19



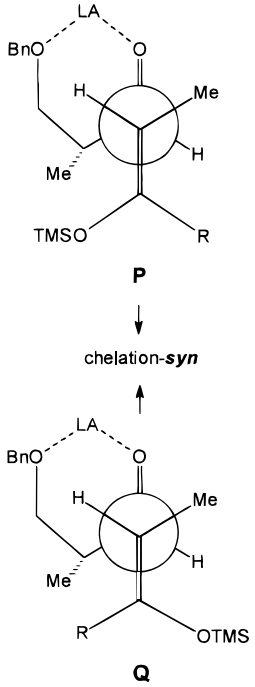
entry	R_1	R_2	*E*/*Z*	Lewis acid	43	44	45	46	ref.
1	Ph	Me	0/100	$TiCl_4$	91	9	0	0	48
2	Et	Me	0/100	$TiCl_4$	50	50	0	0	48
3	S*t*-Bu	*t*-Bu	95/5	$TiCl_4$	99	1	0	0	68
4	S*t*-Bu	*t*-Bu	5/95	$TiCl_4$	99	1	0	0	31a,31b,68
5	S*t*-Bu	Me	93/7	$SnCl_4$	97	3	0	0	31a,31b
6	S*t*-Bu	Me	10/90	$SnCl_4$	46	3	0	51	31a,31b
7	S*t*-Bu	*t*-Bu	95/5	$BF_3{\cdot}Et_2O$	0	9	14	77	31a,31b,68
8	S*t*-Bu	*t*-Bu	5/95	$BF_3{\cdot}Et_2O$	0	7	16	77	31a,31b,68

$TiCl_4$. Independent of the geometry of the silyl enol ether, mainly the chelation syn products were obtained by using $SnCl_4$ or $TiCl_4$ as Lewis acids. The *syn*-preference increases with the increase of sterically bulky substituents (R_1) in the silyl enol ether (Scheme 16). The application of BF_3 (entry 9, Scheme 16) as a Lewis acid or flouride ions (entries 10 and 11, Scheme 16) afforded nonchelation products, since it is known that these reagents are not capable of chelation due to their monodentate nature.[59] For comparing 1,2-asymmetric induction of $TiCl_4$- and BF_3-mediated aldol additions of thio-substituted aldehydes, see ref 60.

In general, chelation control results in a complete reversal of the simple diastereoselectivity if one compares the corresponding results of chelation (simple *syn*-selectivity, Scheme 16) and nonchelation aldol addditions (simple *anti*-selectivity, Scheme 10). A plausible explanation for this phenomenon is given by the transition-states **N** and **O** in Scheme 17. These transition-states are the result of several considerations: beside steric interactions between the ligands, one has to justify unfavorable dipole−dipole interactions.[26]

When reacting heterosubstituted enol silanes with α-alkoxypropanal in the presence of Lewis acids, the same stereochemical tendencies were observed. For detailed results, see the following references (instead of Me, the following substituents were used $-OCH_2Ph$;[61] $-N(CH_2Ph)$;[62] $-CH_2SMe$, $-CH_2OCH_2Ph$;[63] and $-SMe$[64]).

Scheme 20



In the corresponding acetate aldol additions (reactions of substituted silyloxyethenes) with α-alkoxypropanal, only the facial diastereoselectivity is observed.

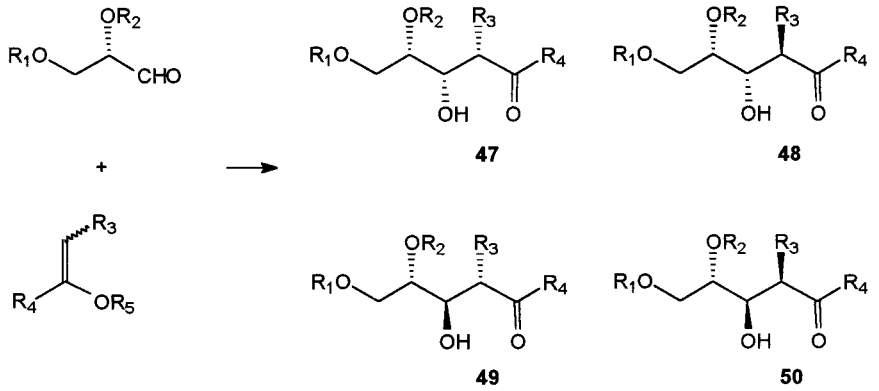
By using chelating agents ($TiCl_4$ or $SnCl_4$), high degrees of *syn*-selectivity were obtained. Applying BF_3 as a Lewis acid led to a reversal of the facial diastereoselectivity due to its inability to chelate (Scheme 18). When BF_3 is used as a gas in this reaction, an increase in the *anti*-preference was observed (compare entries 4 and 6 in Scheme 18).

Independent of the distance of the alkoxy group to the carbonyl function, chelation control also occurs in the aldol addition of *β*-alkoxy-α-chiral aldehydes. The use of these electrophiles led to chelation control in these reactions. High degrees of simple *syn*-selectivity and chelation-controlled diastereofacial selectivity were obtained (Scheme 19). A six-membered chelated structure is proposed as a possible transition-state (Scheme 20). By using BF_3 as the Lewis acid, the expected nonchelation selectivity has been observed (compare enries 7 and 8, Scheme 19).

Aldol additions of α,*β*-dialkoxy aldehydes gave more differentiated results. The possibility of chelating the α- or *β*-position or both of them and the different roles of Lewis acids play an important role for the stereochemical outcome of this aldol-type reaction (Scheme 21).

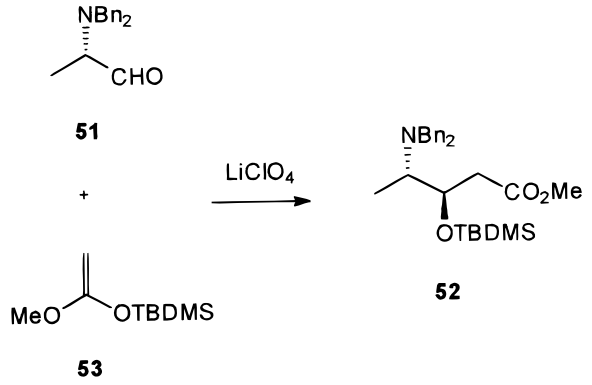
An exceptional behavior was observed in the Mukaiyama aldol addition using *N*,*N*-dibenzylaminoaldehyde **51** and the enol silane **53** (Scheme 22). High degrees of *anti*-aldol products **52** were obtained in the presence of catalytic amounts of $MgCl_2$,[55] $EtAlCl_2$,[71] or $LiClO_4$.[72] *N*,*N*-Dibenzylaminoaldehydes show a

Scheme 21



entry	R_1	R_2	R_3	R_4	R_5	*E*/*Z*	Lewis acid	**47**	**48**	**49**	**50**	ref.
1		-CMe_2-	Me	OMe	TMS	100 / 0	ZnI_2	(12)		64	24	69
2		-CMe_2-	Me	OMe	TBDMS	0 / 100	ZnI_2	(10)		76	14	69
3		-CMe_2-	Et	OMe	TBDMS	100 / 0	ZnI	(6)		84	10	69
4		-CMe_2-	Et	OMe	TBDMS	0 / 100	ZnI_2	(8)		83	9	69
5	TBDMS	$PhCH_2$	Me	Ph	TMS	0 / 100	$SnCl_4$	94	0	0	6	70
6	$PhCH_2$	$PhCH_2$	Me	S*t*-Bu	TBDMS	95 / 5	$SnCl_4$	95	5	0	0	31a,31b
7	$PhCH_2$	$PhCH_2$	$MeSCH_2$	OMe	TMS	-	$MgBr_2$	(98)		(2)		63

Scheme 22



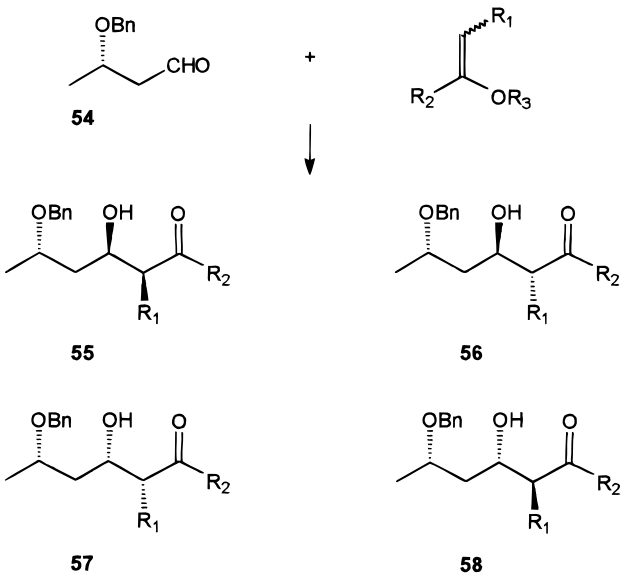
high propensity for nonchelation control in a variety of nucleophilic addition reactions.[55]

C. 1,3 Asymmetric Induction

Good levels of anti 1,3-induction and high degrees of simple *syn*-selectivity may be realized in the Lewis-acid-promoted addition of *β*-alkoxyaldehydes with enol silanes (Scheme 23).[73]

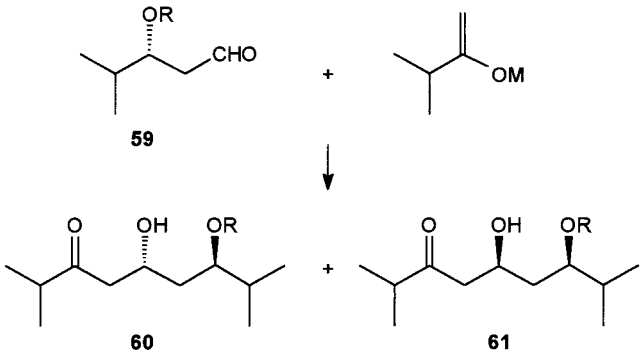
In contrast to these results, no control of 1,3-asymmetric induction has been observed in similar aldol additions using analogous borinate nucleophiles.[74,75] This is an advantage of the Lewis-acid-mediated aldol addition over established enolate aldol additions.[2] A comparison of the different stereochemical outcome in the acetate aldol addition with different metal enolates is given in Scheme 24.[75]

Scheme 23



entry	R_1	R_2	R_3	*E*/*Z*	Lewis acid	**55**	**56**	**57**	**58**	ref.
1	H	Ph	TMS		$TiCl_4$	92	-	8	-	73
2	Me	Ph	TMS	0/100	$TiCl_4$	92		(8)		30,73
3	H	Ph	TMS		$BF_{3\,(gas)}$	85	-	15	-	66
4	Me	Ph	TMS	0/100	$BF_{3\,(gas)}$	55	27	12	6	66

Scheme 24



entry	M	R	ratio of 60	61
1	TMS / $BF_3{\cdot}Et_2O$	PMB	92	8
2	Li	PMB	71	29
3	$TiCl_n$	PMB	60	40
4	9-BBN	PMB	42	58
5	TMS / $BF_3{\cdot}Et_2O$	TBDMS	80	20
6	Li	TBDMS	76	24
7	$TiCl_n$	TBDMS	58	42
8	9-BBN	TBDMS	52	48

(PMB = p-methoxybenzyl)

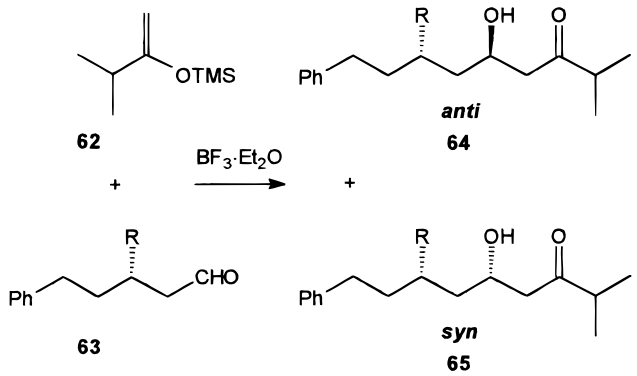
Similar results were found in the total synthesis of Swinholide A. By using the vinylogous Mukaiyama reaction for C−C bond formation, high degrees of *anti*-facial selectivity were obtained under non-chelated reaction control.[76,77]

No significant differences in the direction of the obtained 1,3-asymmetric induction were observed using BF_3 or $TiCl_4$ as Lewis acids. A general *anti*-preference can be stated. This is in contrast to the results obtained in 1,2-asymmetric inductions (compare the results of 1,2-asymmetric induction in Schemes 16 and 19 with the results of 1,3-asymmetric induction in Schemes 23 and 24). The BF_3-mediated aldol addition simulates a chelation-controlled reaction, or in other words, the chelating ability of $TiCl_4$ is not relevant to the stereochemical outcome of this reaction.

A possible explanation for this phenomenon is given by the results published recently by Evans et al.[75] They investigated the stereochemical outcome of 1,2- and 1,3-asymmetric induction in acetate aldol additions. To preclude chelation control, BF_3 was used as the Lewis acid in all these experiments (monodentate nature of boron Lewis acid[59]).

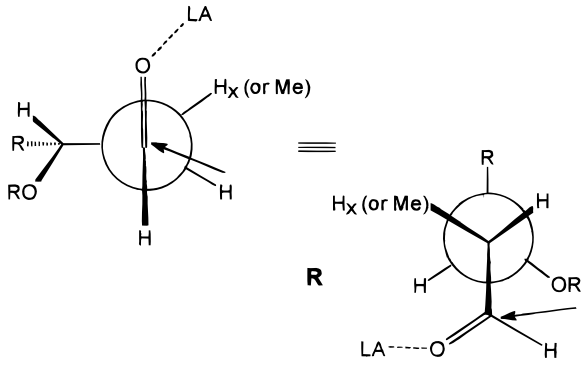
To analyze the electrostatic and steric effects in 1,3-asymmetric induction, the β-chiral aldehydes **63** were reacted with the enol silane **62** (Scheme 25). The highest levels of diastereoselection were obtained by reacting aldehydes with polar β-heteroatom substit-

Scheme 25



entry	R	ratio of 64	65
1	OPMB	81	19
2	OTBDMS	73	27
3	OAc	43	57
4	Cl	83	17

Scheme 26

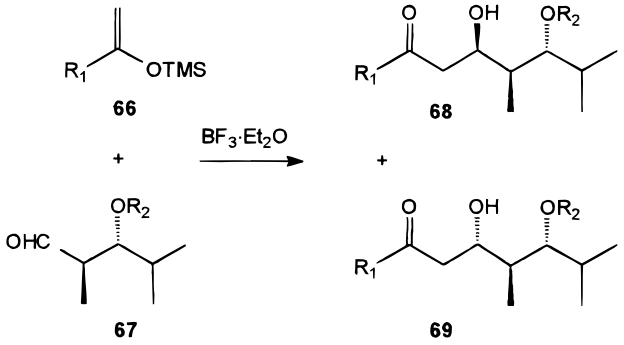


uents (R−Cl), whereas the lowest levels of selectivity were observed by reacting chiral β-alkyl aldehydes with enol silanes. In reactions of enol silane **62** with the aldehyde $CH_2{=}CH{-}CMe_2{-}CHMe{-}CH_2{-}CHO$ (R-alkyl) in the presence of BF_3, a ratio of 58:42 was observed. A comparison of these experimental data obtained with conformational analysis (semiempirical calculations AM1) shows a preference for the conformation of the aldehyde **63** (transition-state **R** in Scheme 26). This transition-state presents the minimization of destabilizing dipolar and steric interactions. The 1,3-*anti*-product results from this transition-state.

The next step was to compare the 1,2- and 1,3-asymmetric induction. The authors did not observe differences in the stereochemical outcome by reacting *anti*-substituted α-methyl-β-alkoxy aldehydes with differently substituted enol silanes. Independent of the steric bulk of the substituent R_1, high degrees of 1,2-*syn*-1,3-*anti*-diastereoselectivity (Felkin) were observed (Scheme 27).

A possible transition structure is generated if you replace the H_x atom with a methyl group in Scheme 26. This replacement results in a substrate bearing an *anti*-relationship between the α-methyl and the β-alkoxy group in the Felkin−Anh model (Scheme

Scheme 27



entry	R_1	R_2	ratio of 68	69
1	*t*-Bu	PMB	99	1
2	*i*-Pr	PMB	98	2
3	Me	PMB	97	3
4	*t*-Bu	TBDMS	99	1
5	*i*-Pr	TBDMS	95	5
6	Me	TBDMS	71	29

26). This relative configuration supports the nucleophilic trajectory shown in Scheme 26.

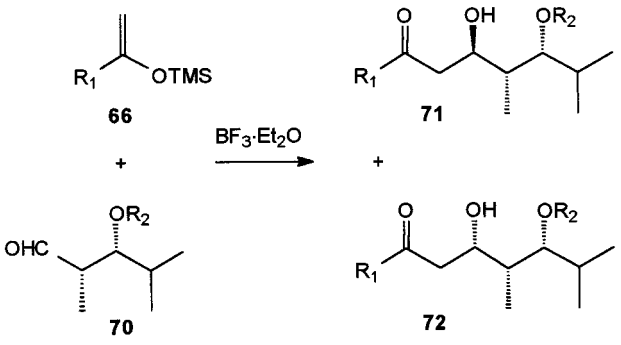
A different situation arises from reacting the corresponding *syn*-substituted α-methyl-*β*-alkoxy aldehydes **70** with enol silanes **66** (Scheme 28). In contrast to the reaction of anti-α,*β*-substituted aldehydes, different stereochemical results were obtained depending on the steric size of the substituents R_1 of the enol silanes **66** used. By reactions with *tert*-butyl-substituted enol silanes, the all-*syn*-products **72** (Felkin) were obtained. The *antiperiplanar* transition-state **V** is preferred due to the steric repulsive interaction (Scheme 29).

By continuously decreasing the steric bulk of R_1, an increasing formation of the 1,2-*anti*-1,3-*anti* products has been observed. In high degrees of stereoselectivity the 1,2-*anti*-1,3-*anti*-aldols **71** (*anti*-Felkin) were found in aldol additions with methyl-substituted enol silanes **66** (entries 5 and 6, Scheme 28) (*synclinal* transition-state **S** is favored, Scheme 29).

In the aldol additions of *syn*-aldehydes **70**, the α-stereogenic center becomes more and more the element of control.

These considerations were supported by several further observations. By increasing the size of the Lewis acids used in these aldol additions, the same phenomenon was observed. The sterically bulky Lewis acid trityl perchlorate produces a reversal of the 1,3-asymmetric induction in acetone aldol additions with the *syn*-aldehyde **70** (Scheme 30) so that the Felkin product **72** was obtained. Due to nonbonded interactions (trityl and enol silane), the transition-states **S** and **U** are disfavored and the *antiperiplanar* transition-state **V** is preferred (Scheme 29, see also results in ref 78).

Scheme 28



entry	R_1	R_2	solvent	ratio of 72	71
1	*t*-Bu	PMB	CH_2Cl_2	96	4
2	*t*-Bu	PMB	toluene	88	12
3	*i*-Pr	PMB	CH_2Cl_2	56	44
4	*i*-Pr	PMB	toluene	32	68
5	Me	PMB	CH_2Cl_2	17	83
6	Me	PMB	toluene	6	94
7	*t*-Bu	TBDMS	CH_2Cl_2	96	4
8	*t*-Bu	TBDMS	toluene	94	6
9	*i*-Pr	TBDMS	CH_2Cl_2	87	13
10	*i*-Pr	TBDMS	toluene	75	25
11	Me	TBDMS	CH_2Cl_2	58	42
12	Me	TBDMS	toluene	40	60

These data have supported the transition-states and experimental results in 1,3-asymmetric induction.[75,79,80]

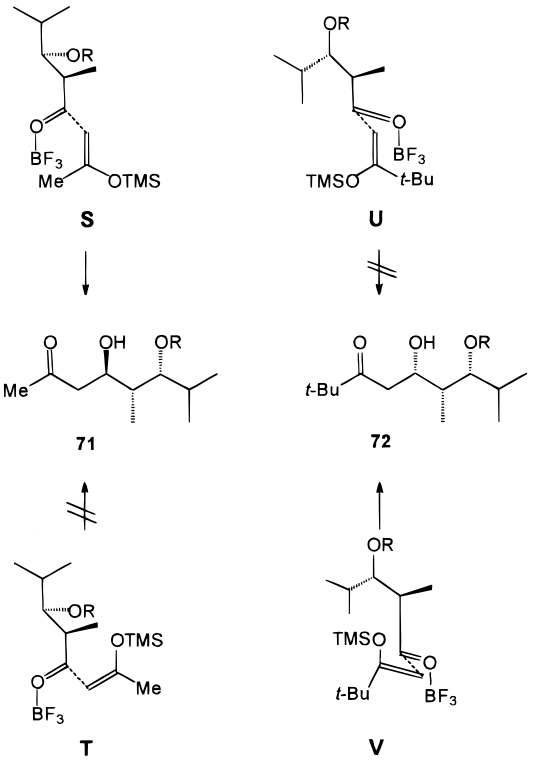
A very instructive example for these considerations was found in the total synthesis of 6-deoxyerythronolide B (Scheme 31). The combination of the C_1-C_7 subunit (an *anti*-aldehyde) **74** with the C_8-C_{15} subunit **75** was achieved by a Mukaiyama aldol addition in the presence of $BF_3{\cdot}Et_2O$. The relative diastereoselectivity (Felkin/1,3-*anti*) observed in this reaction is identical with those already shown in Scheme 27.[81]

Further examples of 1,3-asymmetric induction in polyketide synthesis support the calculations made by Evans et al.

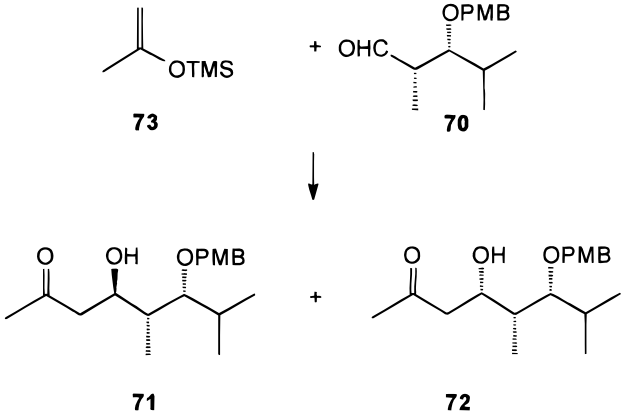
In the total synthesis of the C_1-C_{25} spiroketal fragment of Calyculin A, Evans et al. used the *syn*-α,*β*-chiral aldehyde **86** as an electrophile in a Mukaiyama reaction (Scheme 35). The high all-*syn*-diastereoselectivity obtained in the $C_{15}-C_{23}$ subunit is in agreement with the results and conclusions of Scheme 28.[82]

A similar case is described by Paterson et al. During the total synthesis of Swinholide A, an *anti*-aldehyde similar to **74** is used in a Mukaiyama reaction. The same high 1,2-*syn*, 1,3-*anti* (Felkin/1,3-*anti*) diastereoselectivity is obtained (ds = 97%) in the $C_{15}-C_{23}$ subunit.[83,84]

Scheme 29



Scheme 30



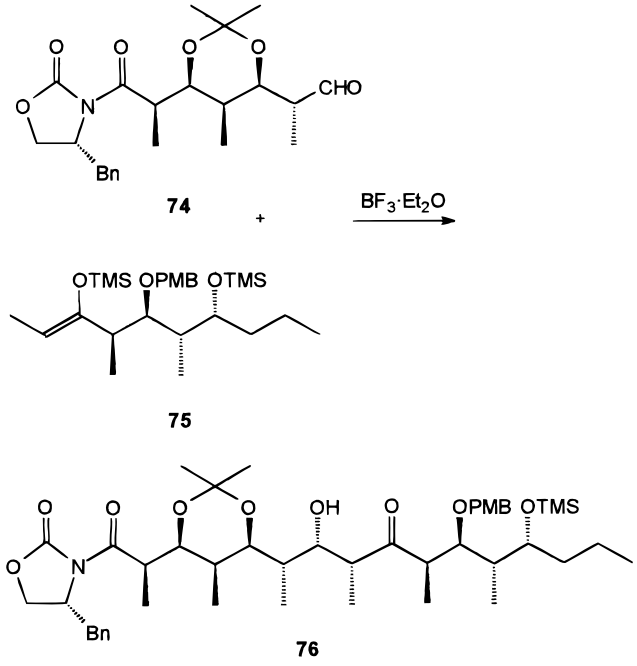
	ratio of **71**	**72**
$BF_3{\cdot}Et_2O$ / toluene	94	6
trityl perchlorate / CH_2Cl_2	11	89

In the synthesis of Concanamycin A, the same authors described a Mukaiyama reaction with an *anti*-α,*β*-chiral aldehyde. And again, the Felkin/1,3-*anti* aldol product was obtained in high degrees (ds > 97%).[85]

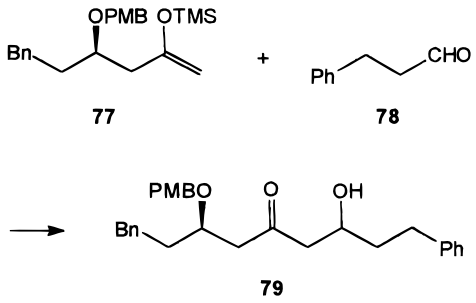
The reactions of the Danishefsky diene with aldehydes are probably Mukaiyama reactions too.[87] The additions of *syn*-configurated aldehydes **70** to the Danishefsky diene system gave high degrees of *anti*-Felkin products.[86−88]

Examples of 1,4-induction are very rare.[48] Very recently Evans et al. have published examples of 1,5 induction in Lewis-acid-mediated aldol addition. No asymmetric induction was observed in these reactions using several Lewis acids (BF_3, $TiCl_4$, $SnCl_4$, $ZnCl_2$, $TrCl/SnCl_2$, $TrClO_4$) (Scheme 32). This is in sharp contrast to what happens in similar aldol additions with dialkylboron enolates where high *anti*-1,5-induction was reported by the authors.[89]

Scheme 31



Scheme 32

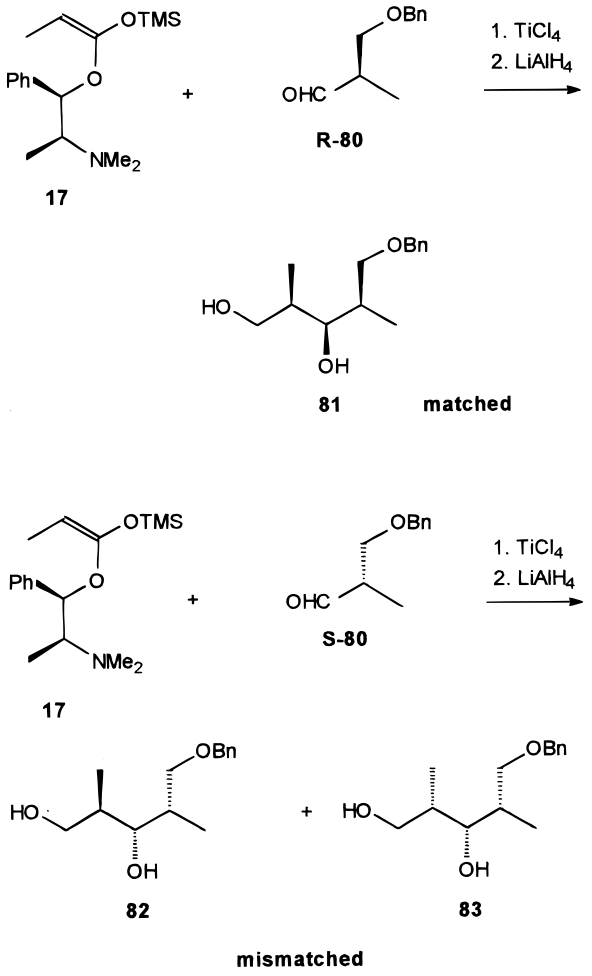


V. Additions of Chiral Nucleophiles to Chiral Electrophiles

On the basis of the problems described in the preceding chapters (chelation control, 1,2- and 1,3-asymmetric addition), one can imagine the difficulties arising from the double stereodifferentiation. Predictions of the stereochemical outcome in Mukaiyama reactions of chiral aldehydes with chiral silyl enol ether are very difficult. The verbal expression for the inability of general prediction and theoretical understanding results in the "matched" (the reactants cooperate to realize the same stereochemical outcome[1f]) and "mismatched" pairs (the diastereofacial preferences of the reactants oppose one another[1f]) of the diastereomers formed. Therefore only illustrative examples will be discussed in this section.

A very instructive example shown by Gennari et al. is given in Scheme 33.[42b,90] Both *R*-**80** and *S*-**80** were reacted with the enantiomerically pure ephedrine derivative **17**. Only isomer **81** is observed in

Scheme 33



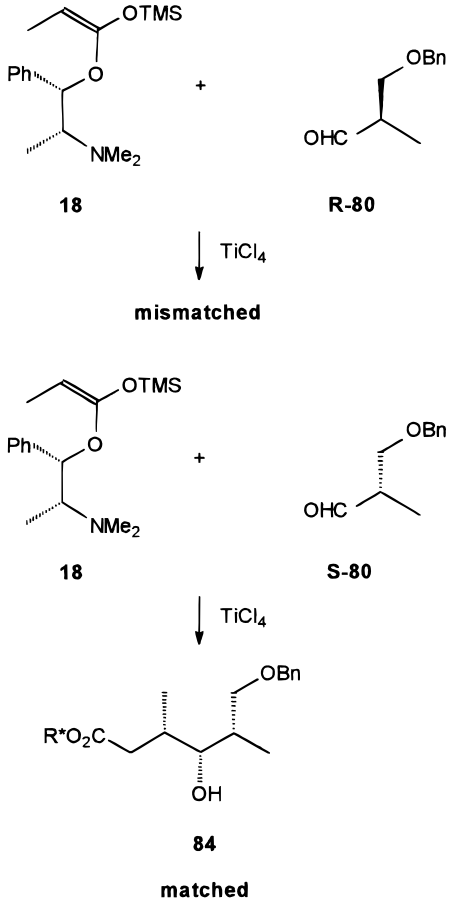
the matched case. The selectivity inherent in the chiral aldehyde is higher than in the corresponding additions to lithium or magnesium enolates.[91] The same relative diastereoselectivity was observed in Scheme 19. In the mismatched pair, isomers **82** and **83** were found in a ratio of about 1,3:1 (Scheme 33).

The next scheme demonstrates the Mukaiyama reaction of *S*-**80** and *R*-**80** with the other enantiomer of the silyl ketene acetal **18** derived from (1*S*,2*R*)-*N*-methylephedrine (Scheme 34). Only one (compound **84**) of the four possible isomers was afforded in 70% yield. The stereoselectivity obtained is a matched one. By applying the corresponding *R*-**80** to the described method, no reaction occurs. Moreover, in mixtures of *R*- and *S*-configurated aldehydes **80**, only the *S*-**80** reacts with silyl ketene acetal **18** in the sense of the desired Mukaiyama reaction.

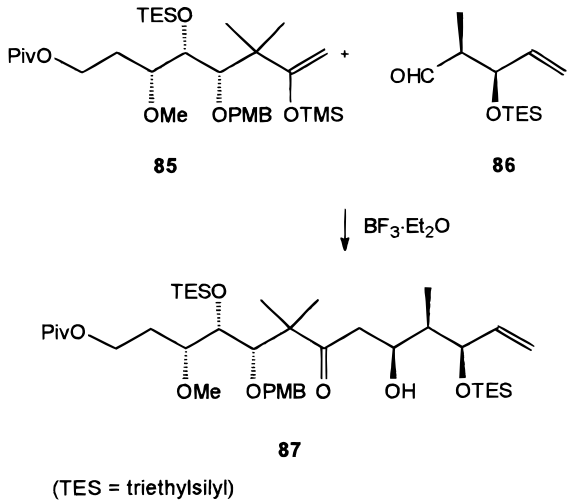
Evans et al. decribed a matched case of BF_3-mediated Mukaiyama reaction in the total synthesis of Calyculin A.[82] In early studies the authors observed the opposite sense of asymmetric induction by using the corresponding lithium enolate for analogous aldol additions.[53]

The *syn*-aldehyde **86** was reacted with the chiral enol silane **85** to give the aldol product **87** in a d.r. of about 95:5 (Scheme 35). The high all-*syn*-selectivity is in agreement with that found in the corresponding reactions of α,β-chiral aldehyde with enol silanes in Scheme 28 (Felkin control).

Scheme 34



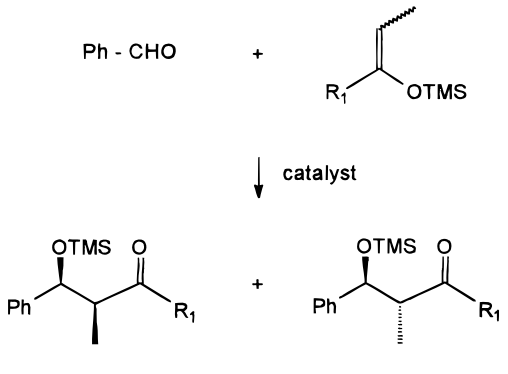
Scheme 35



VI. Catalytic Versions of the Mukaiyama Reaction

Many results have been published dealing with a really catalytic execution of the Mukaiyama reaction. Since the first reports, a variety of Lewis acids have been used as catalysts in these versions of the Mukaiyama reaction (for a compilation, see ref 92). For recently published mechanistic studies of the catalytic version of the Mukaiyama aldol addition, see ref 93. Kinetic and stereochemical studies were done by Denmark et al. They could demonstrate the catalytic activity of triarylcarbenium ions in the Mukaiyama reaction.[93b] Recently an enantioselective

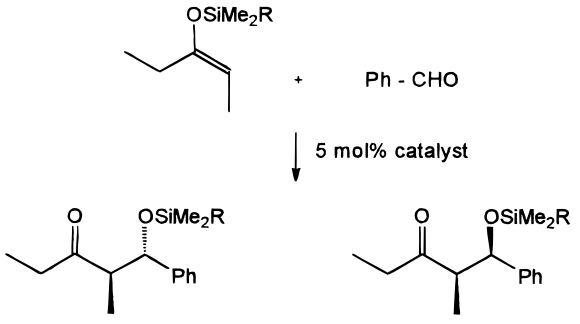
Scheme 36



syn **88** ***anti*** **89**

entry	R_1	*E* / *Z*	catalyst	ratio of **88** / **89**	ref.
1	OTMS		TBAF	79 / 21	97
2	S*t*-Bu	93 / 7	TBAF	95 / 5	31a, 31b
3	S*t*-Bu	10 / 90	TBAF	57 / 43	31a, 31b
4	Et	0 / 100	$TASTMSF_2$	86 / 14	99,100
5	Et	70 / 30	$TASTMSF_2$	63 / 37	99,100
6	Ph	1 / 99	$TASTMSF_2$	95 / 5	99,100
7	Ph	9 / 91	$TASTMSF_2$	94 / 6	99,100

Scheme 37



anti **91** ***syn*** **92**

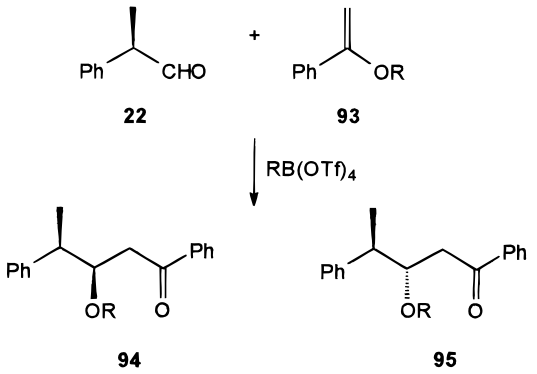
		ratio **91** / **92**
catalyst: $TrClO_4$	R = *t*-Bu	84 / 16
catalyst: TrOTf	R = Ph	29 / 71

application of this triarylcarbenium ion approach was published by Chen et al.[94]

Detailed theoretical investigations of the nature of Lewis acids used for the Mukaiyama reaction were carried through by Reetz et al.[95]

Fluoride ions catalyze the reaction of silyl enol ethers with aldehydes.[96,97] Independent of the enolate geometry used in this aldol-type reaction, high *syn*-selectivity is obtained by using 10 mol % tris-(dimethylamino)sulfonium (TAS)−difluorotrimethylsiliconate ($TMSF_2$) as the fluoride ion source. For chiral tetraalkylammonium fluorides, see ref 98. The

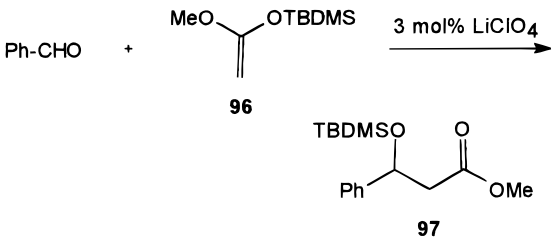
Scheme 38



94 **95**

entry	R	ratio of **94** / **95**
1	TMS	89 / 11
2	TES	95 / 5
3	TBMS	96 / 4
4	TIPS	99 / 1

Scheme 39



	time	yield
diethylether	5 days	86 %
dichloromethane	15 min	100 %

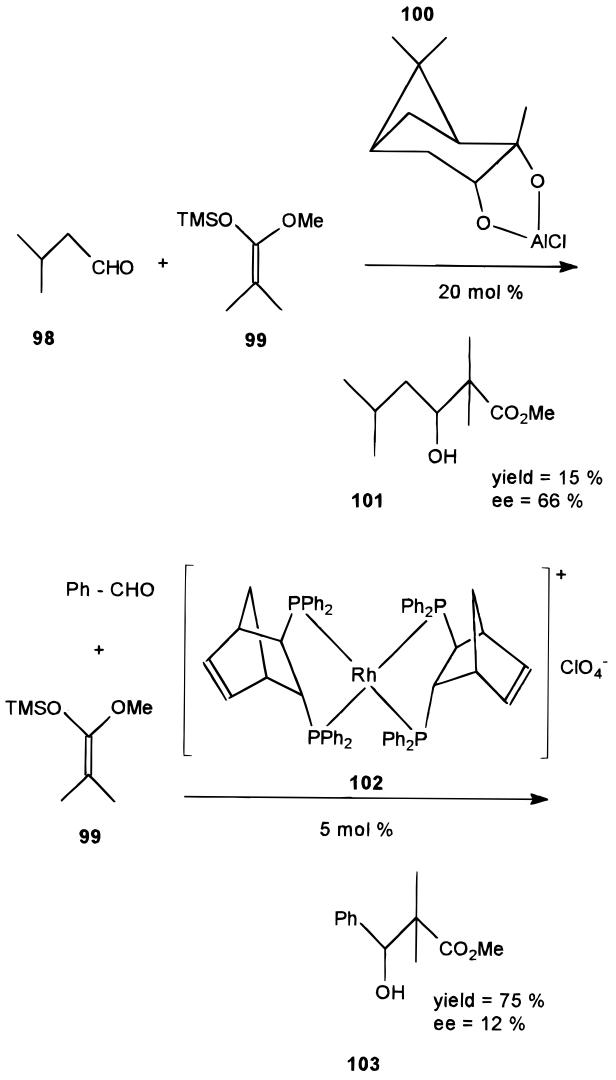
Mukaiyama group showed that trityl salts are efficient catalysts in this reaction.[101]

While the original Mukaiyama reaction required stoichiometric amounts of Lewis acids, 5−10 mol % of trityl salts were sufficient for a complete reaction. The most interesting feature is the occurrence of trans-silylation in this reaction—the migration of the silyl group from the enolate to the former electrophile in the product. The choice of the size of the counterions of these trityl salts is very important for the stereochemical outcome. A preference for *syn*- and *anti*-aldols is observed by the suitable choice of the trityl salts and of the substituents at silicon of the enolates (Scheme 37).[102]

Davies et al. described aldol additions in the presence of catalytic amounts of so-called "supersilylating agents"—a mixture of $B(OTf)_3$ and R_3SiOTf.[78] In acetate aldol additions with 2-phenylpropanal, they observed the same stereochemical tendencies as those found by Heathcock[52] and Evans[53] (Scheme 38). By using sterically bulky silyl groups, an increase in the facial *syn*-diastereoselectivity was obtained (see 1,2-Asymmetric Induction).

Recently Reetz et al. described a catalytic version of the Mukaiyama reaction by reacting silyl ketene acetals with benzaldehyde in the presence of 3 mol

Scheme 40



% of lithium perchlorate. The reaction time strongly depends on the solvent used (see Scheme 39). A 3 mol % amount of lithium perchlorate in diethyl ether requires 5 days for a complete conversion. The same results were obtained by a suspension of 3 mol % of lithium perchlorate in dichloromethane within a period of 15 min. The authors suggested a heterogeneous catalysis. The catalyst can be recycled by simple manipulation.[72,103]

VII. Chiral Lewis Acids

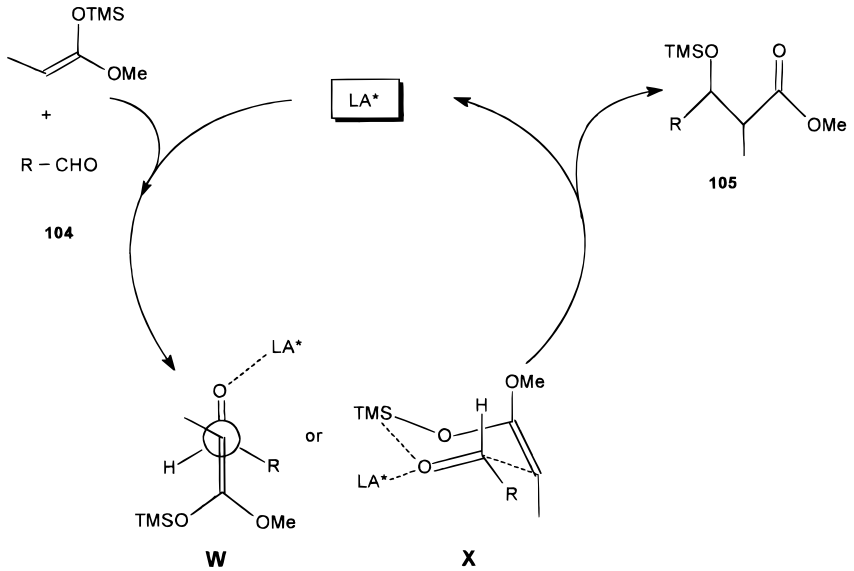
Reetz was one of the first to publish results of a catalytic asymmetric Mukaiyama reaction using Lewis acids derived from aluminum **100**[104b] and rhodium **102.**[104a] However, the ee obtained were not high enough for a general application (Scheme 40). Two reviews covering the development of catalytic aldol additions were published during the preparation of this manuscript. [105,106]

The requirements for a real and, therefore, efficient catalytic way in this reaction are stringent:[107,108] First of all, dissociation between X and LA* (Scheme 41) has to take place to generate the Lewis acid catalyst. Second, any irreversible binding of the catalyst with the product, substrate, or any component in this reaction should be avoided. In that undesired case, stoichiometric or substoichiometric amounts of Lewis acids are necessary for quantitative yields. Third, the catalyst has to hinder any approach to one side of the prochiral carbonyl compounds in order to afford an efficient side differentiation, which is a necessary prerequisite for achieving high enantiomeric excess.

The catalytic cycle for the Mukaiyama reaction including these requirements is shown in Scheme 41. The proposed transition-states discussed in the literature are listed as an acyclic **W** or a cyclic **X**. Several publications exist dealing with the mechanism of this reaction.[103,109]

At the beginning of this development most of the published methods described aldol products obtained with a high degree of ee. However, large amounts of Lewis acids were used (up to 40 mol %!). The problem of a catalytic procedure was of minor importance. The amounts of Lewis acids used have been diminished subsequently in this development. In summary, examples for a real and general *asymmetric* and

Scheme 41



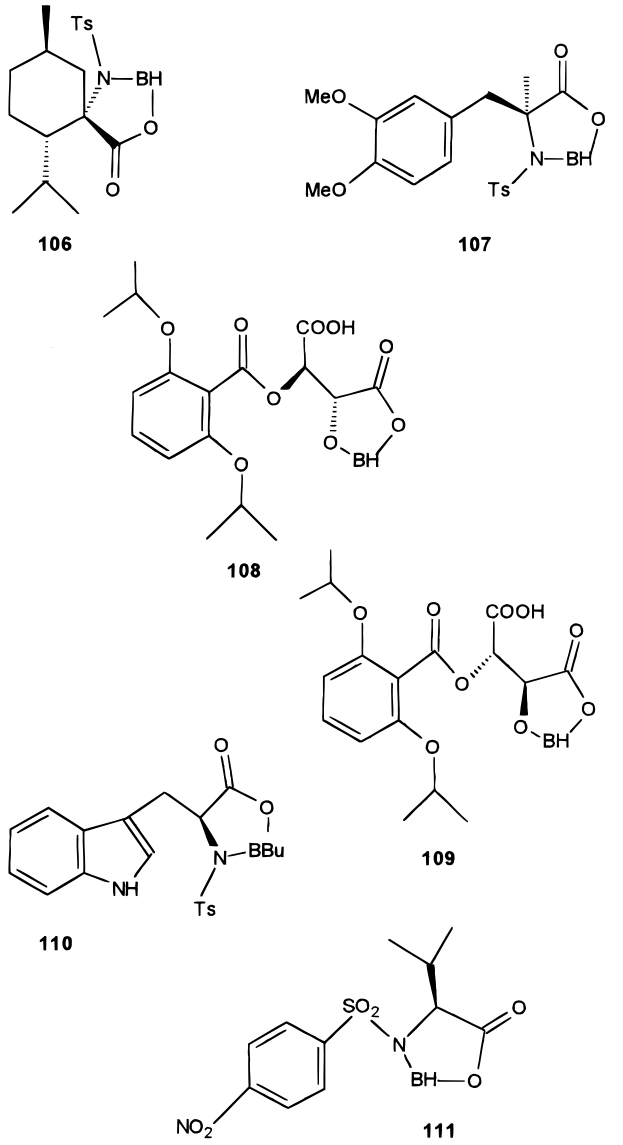
catalytic Mukaiyama reaction are still rare whereas satisfactory results were observed either by Lewis-acid-promoted catalytic aldol additions[110−112] or by asymmetric aldol additions using stoichiometric amounts of Lewis acids.[8,113]

Excellent enantioselectivities were obtained by using only 1 mol % of a chiral ferrocenylphosphine-gold(I) catalyst in aldol additions. However, it seems that these conditions are limited to aldol additions of isocyanoacetates with aldehydes. Moreover, the authors suggest the formation of enolates during the reaction.[110a] The chiral Lewis acids described in this chapter are classified by the metal used.

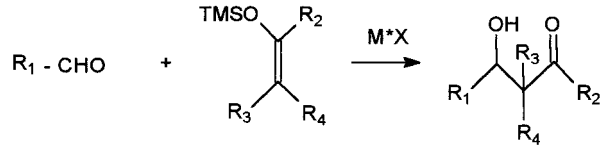
A. Boron Lewis Acids

A lot of work has been devoted to the application of boron Lewis acids in the Mukaiyama reaction. Two comprehensive reviews have been published dealing with this research development.[114] The first methods using stoichiometric amounts of chiral boron Lewis acids[115] were followed by experiments using substoichiometric amounts of Lewis acids. Kiyooka showed that changing the solvent (from CH_2Cl_2 to $MeNO_2$)

Scheme 42



Scheme 43



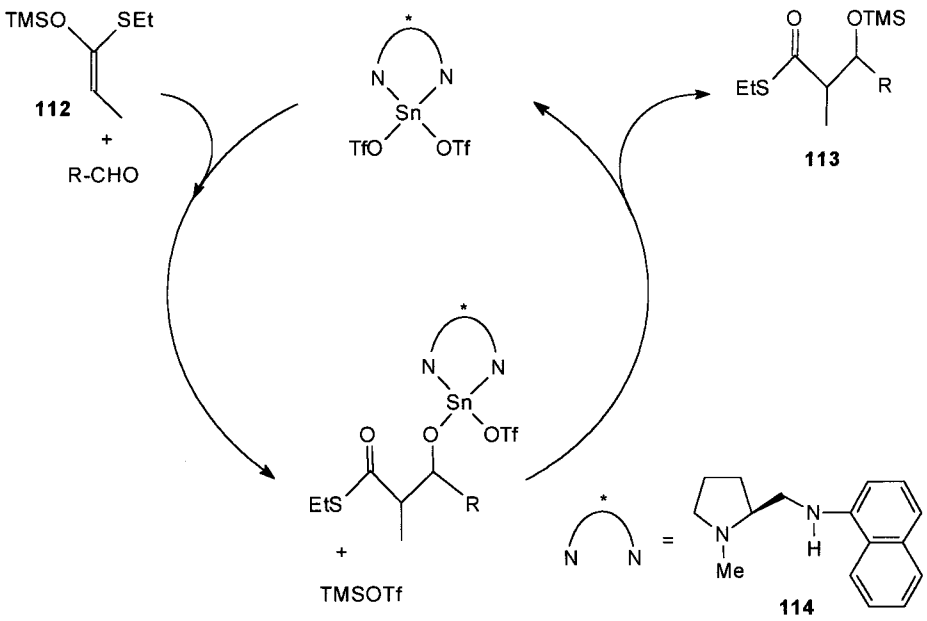
entry	R_1	R_2	R_3	R_4	M*X (20 mol%)	yield [%]	ratio of *syn*/*anti*	ee [%]
1	Ph	OEt	Me	Me	**106**	83		91(R)
2	C_6H_{11}	OEt	Me	Me	**106**	59		96(R)
3	Pr	OEt	Me	Me	**106**	82		> 98
4	Ph	OEt	Me	Me	**107**	80		84(R)
5	C_6H_{11}	OEt	Me	Me	**107**	68		91(R)
6	Pr	OEt	Me	Me	**107**	81		> 98
7	Ph	S*t*-Bu	H	H	**106**	86		87(S)
8	C_6H_{11}	S*t*-Bu	H	H	**106**	75		81(S)
9	Pr	S*t*-Bu	H	H	**106**	91		92(R)
10	Ph	SEt	H	Me	**106**	89	13/87	80(R,S)/4(S,S)
11	Pr	SEt	H	Me	**107**	81	12/88	70(R,R)/81
12	Ph	Bu	H	H	**108**	81		85
13	Ph	Ph	H	H	**108**	98		85(R)
14	Ph	Ph	Me	H	**108**	86	95/5	95
15	Pr	Ph	Me	H	**108**	62	88/12	80
16	Ph	OEt	H	Me	**108**	51	50/50	61/47
17	Ph	OPh	H	Me	**108**	83	79/21	92(R)/6(R)
18	Ph	OPh	H	Me	**109**	73	79/21	92(S)/3(R)
19	Pr	OPh	H	Me	**108**	57	65/35	88/71
20	Ph	Et	H	Me	**108**	96	94/6	96(R)
21	Ph	Et	H	Me	**109**	99	94/6	96(S)
22	Ph	Ph	H	H	**110**	82		89(R)
23	C_6H_{11}	Ph	H	H	**110**	67		93(R)
24	Pr	Ph	H	H	**110**	94		89(S)
25	Ph	Bu	H	H	**110**	100		90(R)
26	C_6H_{11}	Bu	H	H	**110**	56		86(R)
27	Ph	OEt	Me	Me	**111**	92		90(R)
28	Ph	OPh	H	Me	**111**	91	24/76	90(2S,3S)/ 66(2R,3S)
29	Pr	OPh	H	Me	**111**	60	40/60	91(2S,3R)/ 60(2R,3R)

"...resulted in a completely catalytic cycle...".[116] In this work, the Lewis acid **111** (Scheme 42) was used in substoichiometric amounts of 20 mol % (Scheme 43).

The design of ligands for the boron Lewis acid catalysts included bidentate chelates derived from optically active amino acids, tartrates, or sulfonamides (Scheme 42). Corey et al. used Lewis acid **110** derived from *S*-tryptophan.[117] By using 20 mol % of this oxazaborolidine, quantitative yields were obtained (Scheme 43). Silyl ketene acetals do not seem to react with high enantioselectivity under these standard conditions for catalysis by oxazaborolidine **110**.

Yamamoto reported the reactions of silyl enol ether with aldehydes using Lewis acids with ligands de-

Scheme 44



entry	R	addition time [h]	yield [%]	ratio of *syn* / *anti*	ee[%][a]
1	Ph	3	77	92 / 8	90
2	p-ClC_6H_4	4.5	83	87 / 13	90
3	p-MeC_6H_4	3	75	98 / 11	91
4	*n*-Hept	4.5	80	100 / 0	> 98
5	*c*-C_6H_{11}	3	71	100 / 0	> 98
6	*E*-Me-CH=CH	3	76	96 / 4	93
7	*E*-Me-$(CH_2)_2$-CH=CH	3	73	97 / 3	93

[a] values correspond to the major diastereomer

rived from tartrates (**108** and **109**, Scheme 42).[118] The aldol products obtained are mostly *syn*-configurated. The observed high *syn*-selectivity is independent of the geometry of silyl ethers in these reactions. This fact is in agreement with TMS−triflate-catalyzed aldol additions of acetals and may reflect the acyclic *antiperiplanar* transition-state mechanism (**W** in Scheme 41).[110d] Predominant *re*-face attack of enol ethers at the aldehyde carbonyl carbon was confirmed in cases where a natural tartaric acid derivative was used as the ligand (**108**, Scheme 42; entries 17 and 20, Scheme 43). The application of unnatural tartaric acid as a ligand for the used Lewis acid afforded the other enantiomer (**109**, Scheme 42; entries 18 and 21, Scheme 43).[118b]

Masamune and co-worker used a chiral ligand derived from the sulfonamide of α-amino acids (**106** and **107**, Scheme 42). Application of 20 mol % of these Lewis acids in the Mukaiyama reaction gave good results (entries 1−11, Scheme 43).[119]

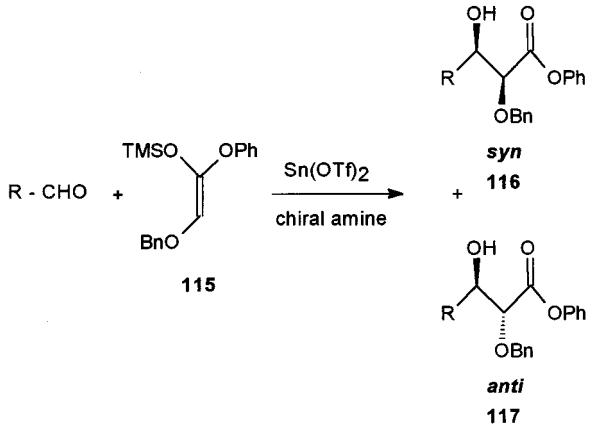
In contrast to the described independence of the stereochemistry of obtained aldols of the geometry of the used silyl enol ether,[118b] Masamune described the reaction of silyl ketene thioacetals to give the *anti*-aldol adducts in moderate to good optical purity (entries 10 and 11, Scheme 43).[119] This led for the very first time to an enantioselective approach of *anti*-products in the Mukaiyama reaction.

For further applications of chiral oxazaborolidinone in asymmetric Mukaiyama reactions, see ref 120.

B. Tin Lewis Acids

At the beginning of the 1990s, Mukaiyama himself succeeded in the enantioselective execution of this aldol reaction.[121] Chiral tin(II) Lewis acids (20 mol %) consisting of tin(II) triflate and the chiral diamine **114** derived from proline (Scheme 44) were used in this reaction. The group showed through several experiments that the coexisting undesired TMSOTf-promoted aldol addition[122] (affording the achiral aldol-type adduct) could be suppressed. This was achieved by slowly adding the substrates to a solution of the catalyst, thus keeping the TMSOTf concentration as low as possible. Polar solvents were used to accelerate the metal exchange step (metal exchange

Scheme 45



entry	R	chiral diamine	yield [%]	ratio of *syn* / *anti*	ee [%][a]
1	Ph	118	85	95 / 5	91
2	Me-CH=CH	118	89	> 99 / 1	98
3	Ph-CH=CH	118	89	> 99 / 1	98
4	2-furyl	118	88	> 99 / 1	94
5	Ph	119	80	9 / 91	90
6	C_5H_{11}	120	88	8 / 92	92
7	Me-CH=CH	119	51	7 / 93	92
9	Ph-CH=CH	119	63	12 / 88	94
9	2-furyl	120	77	12 / 88	91

[a] enantiomeric excesses of the major isomer

between tin(II) and silicon). By applying propionitrile as the solvent, good results in terms of both yields and selectivity were obtained (Scheme 44). The observation that the catalytic cycle could be accelerated by using polar solvents is fully consistent with Kiyooka's results of aldol addition in nitromethane.[116] Note the complete reversal of diastereoselectivity by this method compared with the results of Masamune[119a] (compare entry 1 in Scheme 44 with entries 10 and 11 in Scheme 43).

Later Kobayashi et al. reported the diastereo- and enantioselective Mukaiyama reaction using stoichiometric amounts of tin(II) Lewis acids.[123] Several chiral diamines, all of them derived from proline, were used as ligands in the tin(II) Lewis acids (**118**, **119**, **120,** Scheme 45). A complete reversal of the diastereoselectivity was observed when different chiral diamines were used as ligands in this reaction (compare entries 1 and 6, 2 and 7, Scheme 45). These results were explained by a possible coordination of the alkoxy oxygen of the aldehydes to the tin(II).

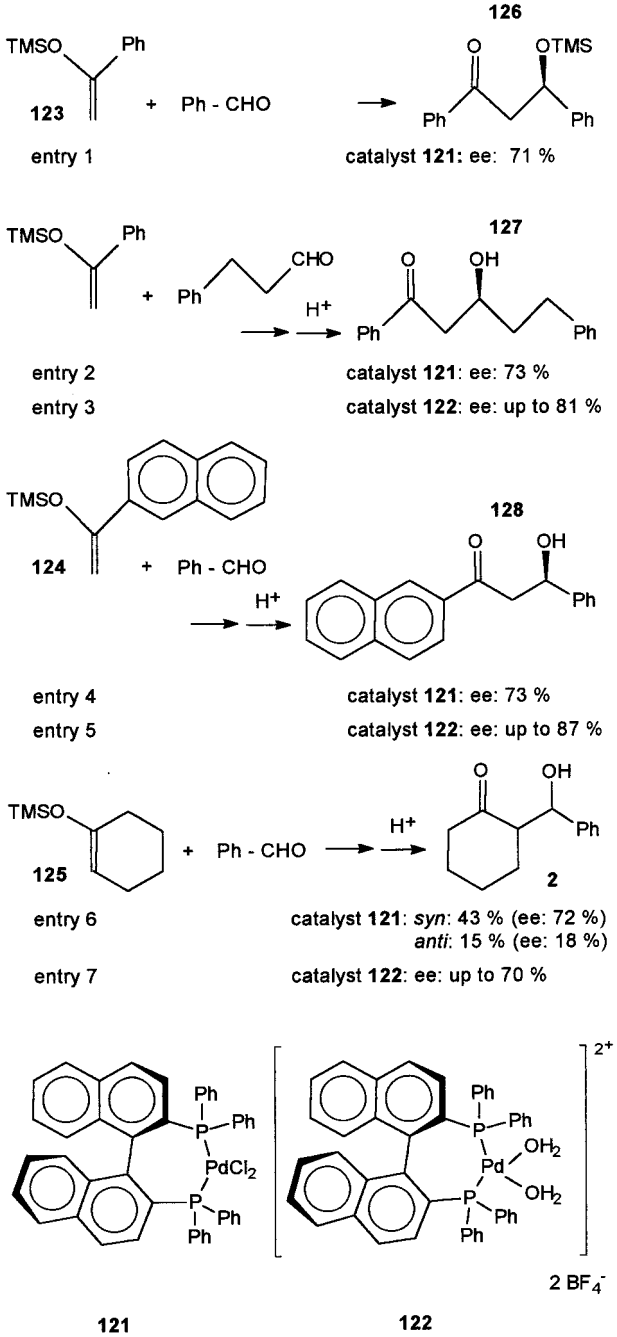
Recently, the Evans group described the use of stannous triflates of chiral bisoxazoline complexes (10 mol %) in aldol additions of thioester-derived silyl ketene acetals to glyoxylate and pyruvate esters. High enantioselectivities of *anti*-aldols were obtained[124] (cf. Copper Lewis Acids).

C. Palladium Lewis Acids

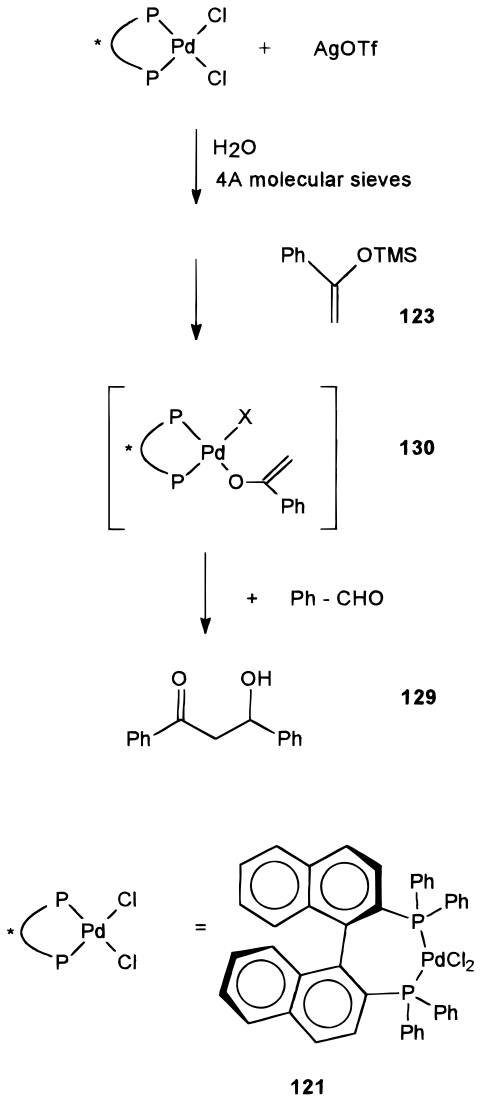
In the cases described so far, Lewis-acid-coordinated aldehydes react with activated carbonyl compounds (e.g., silyl enol ether). Shibasaki et al. showed that one can also work in another direction—the reaction of Lewis-acid-coordinated enolates with aldehydes.

In these cases, chiral palladium enolates react with aldehydes in the sense of a catalytic Mukaiyama

Scheme 46



Scheme 47



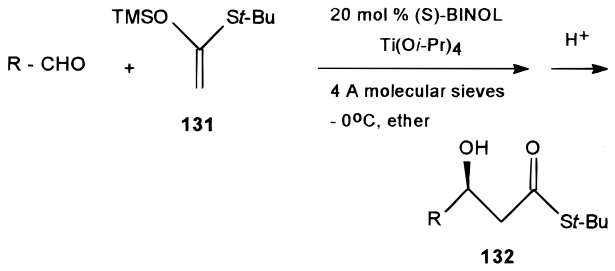
reaction (Scheme 47).[11] In the presence of 5 mol % of a palladium(II)−BINAP complex, the silyl enolates react with aldehydes in good yields to give the expected aldols in good to moderate optical purity (Scheme 46). The palladium(II)−BINAP complex **121** has to be activated by AgOTf. Furthermore, small amounts of water and molecular sieves are necessary for this reaction. The authors determined by several NMR experiments, that this reaction is mechanistically different from the other Lewis-acid-mediated processes. Palladium catalyst **121** reacts with the enolate **123**, and the resulting complex **130** attacks the carbonyl compound (Scheme 47). NMR studies suggested that X in complex **130** might be some oxygen ligand such as OH, H_2O, or Me_3SiOH.[125]

In a very recent work, the same group isolated modified stable diaquapalladium(II) complexes and used them in the Mukaiyama reaction (1−5 mol % of the catalyst **122** in Scheme 46).[125] The ee obtained do not differ significantly from those obtained by using catalyst **121** (Scheme 46).

D. Titanium Lewis Acids

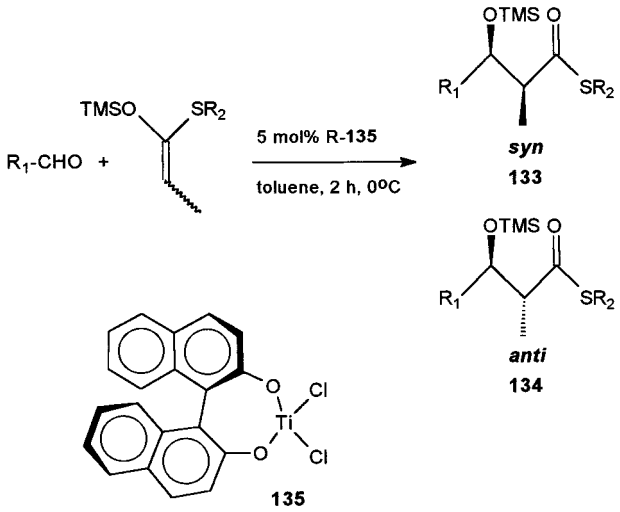
There is a range of publications dealing with the application of titanium(IV) Lewis acids to the Mukaiyama reaction. Though titanium is believed to be a hard metal and "...since these metals (titanium and aluminum) strongly coordinate to oxygen, the smooth exchange between the metal and silicon would hardly take place...",[8] the best results were obtained by

Scheme 48



entry	R	yield [%]	ee [%]
1	Ph	90	97
2	$PhCH_2CH_2$	80	97
3	n-C_8H_{17}	74	98
4	furyl	88	> 98
5	c-C_6H_{11}	70	89
6	PhCH=CH	76	89
7	$PhCH_2OCH_2$	82	> 98

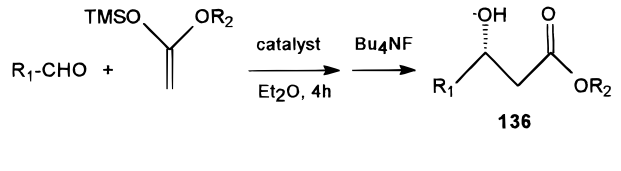
Scheme 49

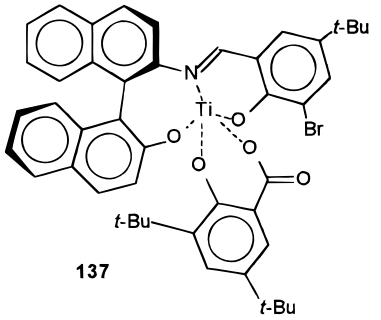


entry	R_1	R_2	E/Z	yield [%]	ratio of **133 / 134**	ee [%][a] (config.)
1	BnO-CH_2	Et	77 / 23	85	72 / 28	90 (R)
2	n-BuO_2C	Et		64	92 / 8	98 (R)
3	n-BuO_2C	t-Bu	95 / 5	57	57 / 43	88 (R)
4	BnO-CH_2	Et	5 / 95	80	48 / 52	86 (R)
5	BnO-CH_2	t-Bu	7 / 93	72	8 /92	90 (R)
6	n-BuO_2C	t-Bu		81	20 / 80	86 (R)

[a]values correspond to the major diastereomer

Scheme 50





entry	R_1	ee [%]: R_2 = Et (5 mol% cat.)	ee [%]: R_2 = Me (2 mol% cat.)
1	*E*-MeCH=CH	92	97
2	$MeCH_2CH_2$	88	95
3	*E*-PhCH=CH	93	97
4	$PhCH_2CH_2$	89	94
5	*c*-C_6H_{11}	94	95
6	Ph	93	96

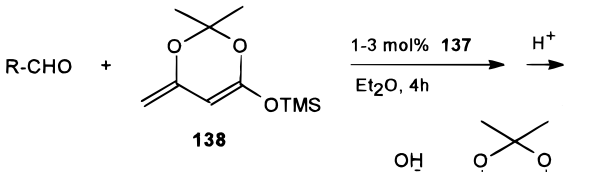
performing a catalytic and enantioselective cycle using titanium(IV) Lewis acids.

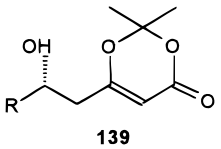
Recently Keck et al. presented a catalytic way toward the enantioselective Mukaiyama reaction.[126] They used the proven BINOL as a source of enantioselectivity (Scheme 48). In these experiments surprisingly large and unexpected solvent effects on both yields and enantioselectivity were observed. Optimal conditions were established using ether as the solvent. However, 20 mol % of the catalyst system is required for sufficient yield and enantioselectivity. Moreover, the authors pointed out that both the structure of the catalysts and the mechanism in this reaction remain unknown.

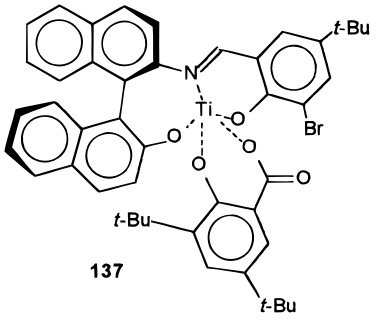
At the same time, Mikami et al. published the application of chiral titanium dichloride in the Mukaiyama reaction (Scheme 49).[127] Fortunately, only 5 mol % of the developed catalyst is necessary for this reaction. The geometry of the silyl ketene acetals used influences the syn/anti ratio of the aldols obtained. The *syn*-isomer was formed mainly from the *E*-silyl ketene acetals, whereas the *anti*-isomer was obtained by using *Z*-silyl ketene acetals (compare entries 3 and 5, Scheme 49). These results are inconsistent with the acyclic transition-state structure **W** in Scheme 41. The Zimmermann−Traxler transition-state is much more likely, i.e., the *E*- to *syn*- and *Z*- to *anti*-isomer. The diastereoselectivity can be explained by the cyclic transition-state **X** in Scheme 41.

The best results using catalytic amounts of titanium Lewis acids were reported by Carreira et al.[128] This group developed a catalyst consisting of a

Scheme 51







entry	R	yield [%]	ee [%]
1	TIPS-C≡C	86	91
2	*Z*-TBDMS-OCH2CH=CH	97	94
3	*E*-PhCH=CH	88	92
4	*E,E*-MeCH=CHCH=CH	95	92
5	Ph	83	84
6	$PhCH_2CH_2$	97	80
7	*E*-Bu_3SnCH=CH	79	92

tridentate ligand, Ti(Oi-Pr)$_4$ and di-*tert*-butylsalicylic acid. A 0.5 mol % amount of the catalyst gave satisfactory results (Scheme 50). Although the preparation of the catalyst system is described, the structure of the active catalyst has not been determined yet (ref 11 in ref 128). The illustrated structure of the catalyst is intended to be a composition model only. As described by Keck,[126] very complex ligand exchanges and multimeric structures of the titanium complexes were observed.

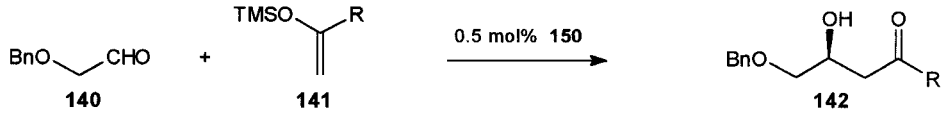
Later, Carreira et al. used this catalyst system in aldol additions of silyl dienolates (Scheme 51).[129] The addition of *O*-silyl dienolates to aldehydes is catalyzed by 1−3 mol % of the chiral titanium complex and affords the aldol adducts in both good yields and enantioselectivity. The carbinol adducts obtained serve as a versatile precursor for the preparation of optically active δ-hydroxy-β-ketoester, amides, or lactones.

Recently chiral diethertitanium(IV) complexes and their application in the acetate Mukaiyama reaction have been described, but the obtained enantioselectivities were low to moderate.[130]

E. Copper Lewis Acids

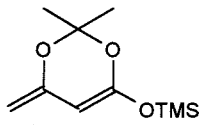
Evans et al. applied bis(oxazolinyl)pyridine copper(II) complexes to the aldol reaction of α-(benzyloxy)-acetaldehyde[131] and pyruvate esters[132] with a wide

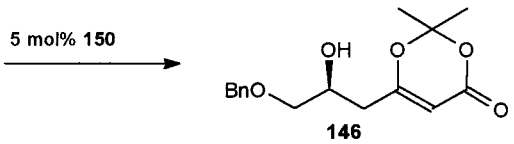
Scheme 52



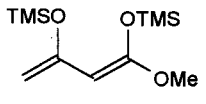
entry	R	yield [%]	ee [%]
1	S*t*-Bu	100	99
2	SEt	95	98
3	OEt	99	98

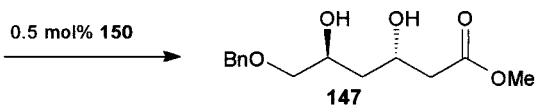
silyl ketene acetals



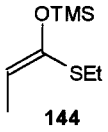


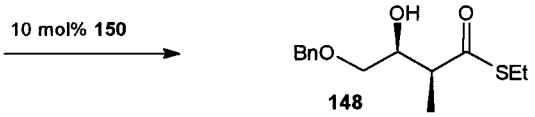
4 94 92





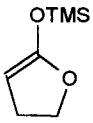
5 *syn* / *anti* = 1 / 15 98[b] 97[a]





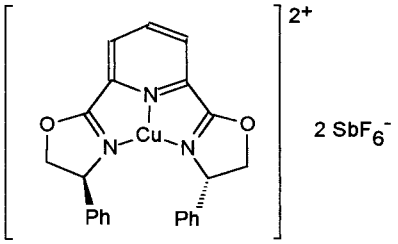
6 Z / E = 95 / 5 *syn* / *anti* = 97 / 3 90 97[a]

7 Z / E = 1 / 99 *syn* / *anti* = 86 / 14 48 85



8 *syn* / *anti* = 96 / 4 95 95[a]

[a]values refer to the major diastereomer; [b]reduction of the aldol product with $Me_4NBH(OAc)_3$



150

variety of silyl ketene acetals (Scheme 52). A 5 mol % amount of the copper catalyst was used. These activated electrophiles were chosen in order to produce an effective catalyst−substrate organization through bidentate chelation. And, indeed, aldol additions of benzaldehyde or dihydrocinnamaldehyde with silyl ketene acetals were nonselective. Interestingly, β-(benzyloxy)propionaldehyde gave racemic products. This indicates a rigid requirement for a five-membered catalyst−aldehyde chelate. The geometry of the applied ketene thioacetals influences the yields of the aldols formed decisively (compare entries 6 and 7 in Scheme 52). Similar asymmetric ligands were used by the same authors in tin(II)−triflate-catalyzed aldol additions (see Tin Lewis Acids).[124]

F. Rare Earth Lewis Acids

Triflates of several rare earth metals (La, Eu,[88] Yb[133]) were complexed with the chiral bidentate ligand 1,2-diphenylethylenediamine. The thus prepared catalysts were employed to the Mukaiyama reaction.[134] Aromatic aldehydes and hydrocinnamaldehyde were reacted with silyl ketene acetals in the presence of 20 mol % of the described lanthanide Lewis acids; however, only poor to moderate enan-

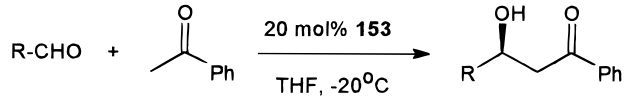
tioselectivities were reported. Recently, Kobayashi et al. described the results of Mukaiyama reactions in the presence of scandium(III) triflates. The reactions were carried out in aqueous media. Unfortunately, only poor stereoselectivities were observed in these transformations.[135,136]

VIII. Related Reactions

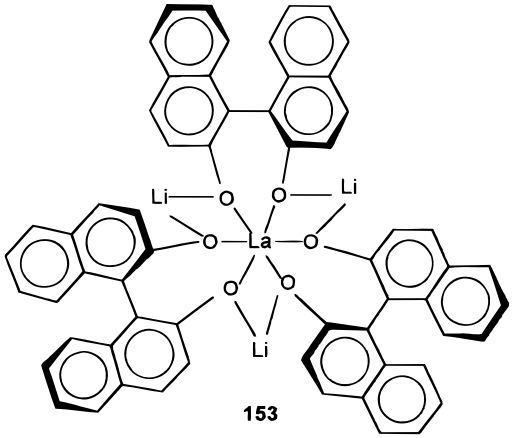
Recently Shibasaki et al. described the direct asymmetric aldol addition with a heterodinuclear catalyst (Scheme 53) (for a review, see refs 105 and 137). The catalyst **153** (20 mol %) seems to imitate the double function of enzymes such as DAHP−aldolases (cocatalysis with a Zn^+ ion and a basic functional group at the active side of the enzyme). The lithium alkoxides act as bases, whereas the central lanthanum ion works as a Lewis acid. Unlike in the described Mukaiyama reaction using activated ketones (e.g., silyl enol ether), Shibasaki et al. applied unmodified ketones directly to this type of aldol addition. The lithium alkoxides convert the ketones into their enolates and the central lanthanum ion acts as a Lewis acid and fixes the aldehydes in an asymmetric environment. Results of this research are compiled in Scheme 53.

Even masked carbonyl compounds such as acetals **154** undergo aldol additions. They react in the presence of catalytic amounts of Lewis acids with silyl enol ethers to give the expected "protected" aldol products (Scheme 54).[59,138−144] For a detailed mechanistic study, see the results of Heathcock et al.[54] For further application in natural product synthesis, in particular the use of sugar-derived acetals, see ref 136 and references therein.

Scheme 53



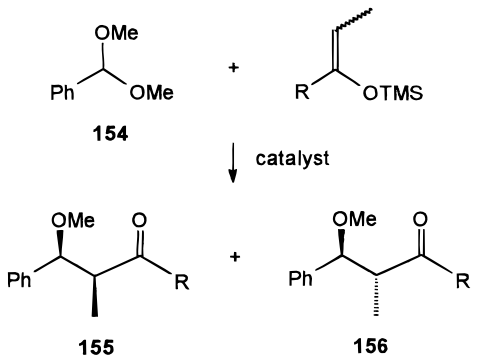
151 152



153

entry	R	yield [%]	ee [%]
1	*t*-Bu	43	89
2	$PhCH_2C(CH_3)_2$	90	69
3	*c*-C_6H_{11}	72	44
4	*i*-Pr	59	54
5	$Ph(CH_2)_2$	71	94

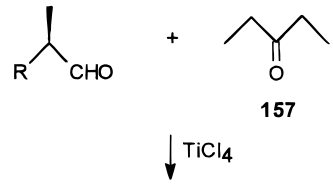
Scheme 54



154 155 156

entry	R	*Z* / *E*	catalyst	ratio of **155** / **156**	ref.
1	Ph	0 / 100	TMSOTf	71 / 29	146
2	Ph	100 / 0	TMSOTf	84 / 16	146
3	t-Bu	100 / 0	TMSOTf	95 / 5	146
4	S*t*-Bu	0 / 100	TMSOTf	78 / 22	146
5	OMe	0 / 100	TMSOTf	50 / 50	146
6	Et	79 / 21	TMSI	57 / 43	147

Scheme 55



157

158 **159**

R = Ph 12 % 60 %

R = OAc 72 % -

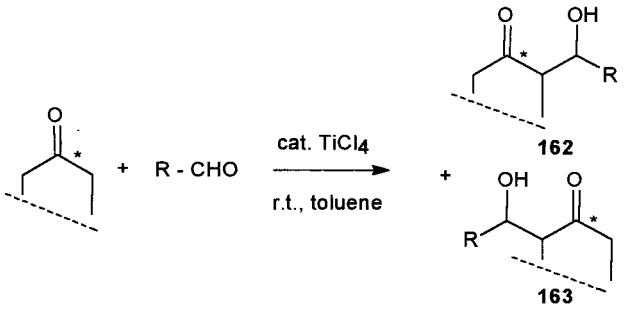
160 **161**

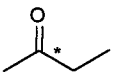
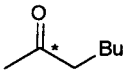
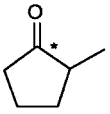
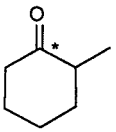
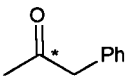
R = Ph 21 % 7 %

R = OAc 28 % -

Carbonyl compounds also react without activation (formation of the corresponding silyl enol ether) in the sense of an aldol addition. A variety of aldehydes and ketones react in the presence of substoichiometric amounts of $TiCl_4$ and in the absence of bases to give the expected aldols. The aldols were isolated in a high degree of simple *syn*-selectivity.[111] In reactions of ketones with 2-phenylpropanal, simple *syn*-selec-

Scheme 56



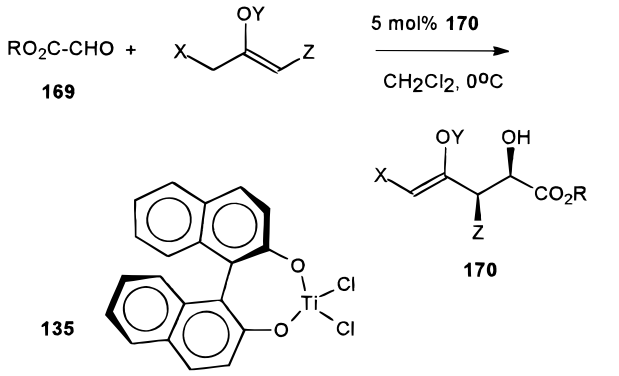
entry	ketone	aldehyde	yield [%]	ratio of 162 / 163
1		Ph - CHO	83	97 / 3
2		*i*-Pr - CHO	72	91 / 9
3	**164**	Pr - CHO	68	89 / 11
4	 **165**	Ph-CHO	87	89 / 11
5		Ph-CHO	88	99 / 1
6		*i*-Pr - CHO	81	95 / 5
7	**166**	Ph-CHO	67	89 / 11
8		*i*-Pr - CHO	71	88 / 12
9	**167**	Pr-CHO	62	86 / 14
10		Ph-CHO	91	> 99 / 1
11		*i*-Pr - CHO	89	96 / 4
12	**168**	Pr-CHO	82	94 / 6

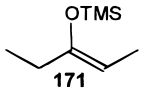
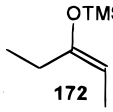
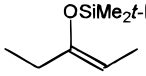
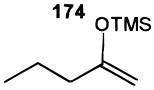
tivity was observed. This is in contrast to results found in 1,2-asymmetric induction of the Mukaiyama reaction (compare R = Ph in Scheme 55 with the results of Scheme 10). In aldol additions of α-acetoxypropanal with diethyl ketone the same stereochemical tendency was found as that observed in the Mukaiyama reaction (compare R = OAc in Scheme 55 with Scheme 16).[112]

In addition to the high *syn*-selectivity, a high regioselectivity was observed in aldol additions of aldehydes with unsymmetrical ketones. Only the more encumbered α-side of the unsymmetrical ketones was attacked by the aldehydes used. This is formally a result of thermodynamical control; on the other hand, the high *syn*-selectivity observed is a result of kinetic control (Scheme 56).[148]

A synthetic equivalent to the described Mukaiyama reaction is represented by the ene-type reaction. An aldehyde is reacted with an enol ether containing an allylic hydrogen atom. The transfer of the silyloxy group, a characteristic feature of the Mukaiyama reaction, could not be found in ene-type reactions.[149]

Scheme 57



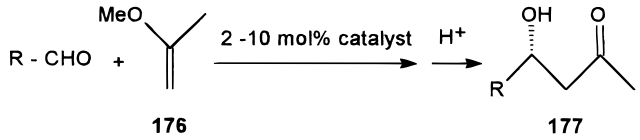
entry	silyl ether	R	*Z* / *E*	yield [%]	ratio of *syn* / *anti*	ee [%] (config.)
1	 **171**	Bu	99 / 1	63	99 / 1	99(R)
2		Me	94 / 6	58	98 / 2	99(R)
3	 **172**	Me	96 / 4	54	98 / 2	99(R)
4	 **173**	Me	84 / 16	73	73 / 27	77(R)
5	 **174**	Me		71		> 99(R)
6		Bu		73		> 99(R)
7	 **175**	Bu	95 / 5	67		> 99(R)

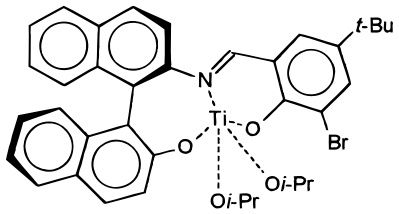
The ene-type reactions were carried out in the presence of Lewis acids.[150] The obtained β-hydroxy enol ethers are useful intermediates for further transformations. Designing chiral Lewis acids did not only influence the Mukaiyama reaction or the Diels–Alder reaction, but also the development of the ene-type reaction. With these new Lewis acids, some progress has been made: chiral titanium(IV) dibromides derived from optically active BINOL were used as catalysts in the ene-type reaction of trisubstituted olefins with aldehydes, [151] 0.5 mol % of this chiral Lewis acid was used as a catalyst in this reaction between vinyl sulfides and glyoxylates.[152]

Recently, the group of Mikami has developed the enantioselective catalytic ene-type reaction. Mikami used the BINOL–titanium(IV) dichloride catalyst for this reaction.[149a] The optically active BINOL ligand was responsible for the high enantioselectivity observed in this reaction (Scheme 57). Activated aldehydes (glyoxylates) reacted with silyl enol ether in the presence of 5 mol % of the catalyst **135**. By using trisubstituted olefins, the geometry of the double bond is not significant for the obtained syn/anti ratios of the silyl enol ether (compare entries 2 and 3, Scheme 57). High *syn*-selectivity is observed in a stereoconvergent way.

Carreira et al. used catalyst **178** in the ene-type reaction.[153] A 2–10 mol % amount of **178** is necessary

Scheme 58





178

entry	R	yield [%]	ee [%]
1	$PhCH_2CH_2CH_2$-C≡C	99	98
2	$TBSOCH_2$-C≡C	85	93
3	Ph-C≡C	99	91
4	$PhCH_2CH_2$	98	90
5	Ph	83	60
6	*c*-C_6H_{11}	79	75

for both complete conversion and high enantioselectivity. Methoxypropene served as the enecomponent and was used as the solvent at the same time. A variety of aldehydes were tested to be used as substrates in this addition reaction, which yielded the vinyl ether products in the absence of an acidic workup (Scheme 58). The latter can be used for further synthetic transformations.

IX. Concluding Remarks

The catalytic enantioselective aldol addition which is arguably one of the most important C−C bond formation reactions constitutes a great challenge. However, as one can see in this review, examples for a real and general **asymmetric** and **catalytic** aldol addition are still rare. Moreover, these few examples are limited in scope. On the other hand, the application of aldolases as synthetic catalysts has yielded a lot of efficient syntheses of stereochemically complex molecules.[154] High turnover rates and enantioselectivities were observed in these processes, but the use of enzymes has limitations too. The development of these two approaches and their relative influence are expected to contribute to the solution of this problem of organic chemistry. A promising example is presented by the works of the Shibasaki group.[134,137]

X. References

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