Direct Methods for Stereoselective Polypropionate Synthesis: A Survey

Jun Li,* Dirk Menche**

a Medizinische Chemie, Helmholtz-Zentrum für Infektionsforschung, Inhoffenstr. 7, 38124 Braunschweig, Germany
b Department of Organic Chemistry, University of Heidelberg, INF 270, 69120 Heidelberg, Germany
Fax +49(6221)544205; E-mail: dirk.menche@oci.uni-heidelberg.de

Received 18 March 2009; revised 20 April 2009

Abstract: Polypropionates are key subunits in structurally diverse polyketide natural products and pharmaceuticals, rendering their synthesis an objective of high priority in synthetic organic and medicinal chemistry. A variety of methods have been devised for the direct and enantioselective assembly of the characteristic sequence of alternating methyl- and hydroxy-bearing stereogenic centers. This review presents a survey of well-established and more recently developed methods for the regio- and stereoselective assembly of polypropionates.

1 Introduction

The stereochemical complexity of polyketides presents formidable challenges for organic chemists.1,2 About 25 years after the epochal total synthesis of erythromycin A (1, Figure 1) by Woodward,3 this inherent complexity has captured the imagination of synthetic chemists and the concise assembly of such elaborate systems has been a key driver for the development of new methodologies. A key structural feature in erythromycin and polyketides in general, such as the macrolide antibiotics arachazolid A (2)4a or etnangien (3),4b are the polypropionate segments. They are characterized by sequences of methyl- and hydroxy-bearing stereogenic centers, enabling large numbers of possible stereochemical permutations. Bio-synthetically, these are derived by iterative condensations of propionyl subunits and subsequent reduction of the derived β-keto esters.

Mimicking this biosynthetic pathway, the aldol reaction presents the most important method available for the stereocontrolled formation of propionates and many variants for a regio-, stereo-, and enantioselective carbon–carbon bond formation have been reported. Furthermore, alternative strategies are of increasingly high importance. Within this review, a survey of well-established as well as more recently developed methods for the stereoselective assembly of polypropionates is presented, including propionate aldol reactions, reductive couplings, crotylations, allenylation, sequential radical processes, sequential substitutions, epoxide openings, rearrangements and intramolecular approaches (Scheme 1).

The scope of this overview is limited to methods that are strictly applicable to polypropionate syntheses, namely those that enable access to the characteristic sequences of methyl- and hydroxy-bearing stereogenic centers. Furthermore, only those methods that set these stereogenic centers in a direct fashion, either simultaneously or in a sequential process, are included. Thirdly, only enantioselective procedures are presented. This review aims to provide an overview and is not intended to be an exhaustive coverage of the literature.

Figure 1 Polypropionate fragments in polyketide natural products of propionyl subunits and subsequent reduction of the derived β-keto esters.
2 Propionate Aldol Reaction

The aldol addition reaction continues to be a highly versatile and widely used method for selective polypropionate synthesis.\(^5,6\) The addition reaction involves the condensation of ethyl ketones (4), including esters or amides, with aldehydes (5) to generate the required chiral β-hydroxy carbonyl adducts (6) in a direct fashion (Scheme 2).

The relative configuration of the aldol adduct is usually determined by the geometry of the enolate intermediate, with Z-enolates (7) giving syn products (13) and E-enolates (8) anti products (14). As shown in Scheme 3, this result has been rationalized by Zimmerman–Traxler transition states. Minimization of 1,3-diaxial interactions between \(R_1\) and \(R_2\) in the chair-like transition states 9 versus 10 and 11 versus 12 leads to the observed stereochemical outcome (Scheme 3).\(^7\)

2.1 Auxiliary Control

Evans Aldol Reaction

One of the most widely used methods of auxiliary-controlled diastereoselective aldol reactions employs the class of oxazolidinones (17) (Scheme 4), initially devel-
the aldehyde. For aldehyde addition, the reactive form 22 of enolate 20 has to be considered and two diastereomeric conformations (23 and 24) of the cyclic intermediate have to be taken into account. Due to steric interactions of the ligands on the boron and the chiral auxiliary, transition state 23 is favored, consequently giving rise to ‘Evans syn’ product 25, as opposed to 26.

Scheme 5

One of the first modifications of this procedure was developed by the Heathcock group. They reported a bimetallic system which uses dibutylboron triflate and titanium(IV) chloride to give non-Evans syn-aldol adducts, while the combination of dibutylboron triflate and diethylaluminum chloride provides non-Evans anti-aldol adducts.10

Crimmins has reported the use of acyloxazolidine-thione auxiliaries and titanium(IV) chloride for the preparation of either syn-aldol adduct as a function of the stoichiometry of the amine base and metal.11

Subsequently, Evans reported a variant to access anti-aldol products 28. This procedure uses catalytic amounts of magnesium chloride in the presence of triethylamine and chlorotrimethylsilane and proceeds with high yield and diastereoselectivity.12 As shown in Scheme 6, the stereochemical outcome may be rationalized by chelation-controlled intermediate 27 where the magnesium ion coordinates the aldehyde, the enolate oxygen and the acyloxazolidinone carbonyl (27).

Another extension of this methodology to products with the opposite anti diastereoselectivity, namely ‘Evans anti’ products 31, was likewise reported by the Evans group.13

The yield, diastereomeric ratio and substrate scope are comparable to the magnesium chloride catalyzed anti-aldol reactions. The method uses the thioester analogue 29 and catalytic amounts of magnesium bromide and triethylamine. The stereochemical outcome may be rationalized by intermediate 30.

All enolization procedures with this family of imides to form boron, titanium, lithium, or sodium enolates implicate the intervention of Z-configured metal enolates. Given the assumption that this is the geometry of the in-
tervening enolate, the enolate face selectivity observed for the N-acryloxazolidinone-derived magnesium enolate is fully consistent with chelate-controlled processes, as depicted in 27 and 30. The intervention of a chair Zimmer-
man–Traxler transition state has to be precluded.12,13

A number of structural variants of these chiral N-acrylox-
azolidinones have been developed with modified cleav-
age reactivities or diastereoselectivities. They are shown in Figure 2.14–17

**Figure 2** Variations of chiral acyloxazolidinones

The N-propionylsultams as introduced by Oppolzer may also be regarded as acyloxazolidinone analogues.15,16
They undergo Lewis acid promoted addition of aromatic and aliphatic aldehydes. Particularly reactive are boryl enolates of Yan’s camphor-derived auxiliary17 which allow for highly anti-stereoselective aldol addition reactions. They are promoted by titanium(IV) chloride or tin(IV) chloride as co-catalysts. These high-yielding reactions exhibit remarkable generality with respect to the aldehyde nature.

Myers has studied the chemistry of cyclic O-silyl ketene N,O-acetals 32 (Figure 3) prepared from optically active (S)-prolinol propionamides and dichlorodimethylsilane.18 They undergo facile and highly diastereoselective carbon–carbon bond-forming reactions with aldehydes to generate syn-aldol products.

Ghosh has reported amino indanol derived chiral esters 33 and their use in titanium enolate aldol reactions with various aldehydes. They enable access to anti-aldol products with high levels of diastereo- and enantioselectivity.19 Both enantiomers of cis-1-aryl sulphonamido-2-indanol are readily prepared from commercially available optically active indanols.

**Abiko–Masamune Aldol Reaction**

Norephedrin-derived chiral auxiliaries 34 for propionate aldol couplings have been introduced by Abiko and Masamune.20 As shown in Scheme 7, they may be selectively transformed into either the Z- or the E-enolate by judicious choice of enolization conditions. Treatment with dicyclohexylboron triflate and triethylamine provides E-enolates, while the combination of dibutyl boron triflate and diisopropylethylamine gives rise to Z-isomers. Both anti- and syn-aldol products 35 are formed with very high degrees of selectivities and yields.21 The proposed conformations of the transition states leading to anti- and syn-aldol products are different.

**Scheme 7**

Abiko–Masamune-type aldol reactions are characterized by a very broad substrate scope and proceed with excellent diastereoselectivities and yields and, consequently, have been widely applied in polypropionate synthesis, in particular for the generation of anti-propionates.22 A drawback of the method is, however, the apparent difficulty in cleaving the chiral auxiliary with nucleophiles.
other than hydride. To circumvent this problem, Hulme’s research group has reported the modified thiol surrogate 37 (Scheme 8). This reaction variant proceeds with comparable diastereoselectivities and yields to give the analogous anti adducts 38. In comparison to the original Abiko–Masamune auxiliary, however, this new thio-analogue promotes facile displacement with a range of nucleophiles.

To further enhance the non-reductive cleavage of the Abiko–Masamune auxiliary, isopropylmagnesium chloride is used for intermediate activation of the aldol product 35. Presumably, it chelates the \( \beta \)-hydroxy ester as shown schematically in 40, leading to ester activation and facilitation of nucleophilic attack.

**Scheme 9**

**Paterson anti-Aldol Reaction**

Lactate-derived ketones of type 42 (Scheme 10) have been developed by Paterson and co-workers. They display high levels of stereoselectivity in boron-mediated anti-aldol reactions and have been widely used in propionate total syntheses. The origin of the high levels of \( \pi \)-face selectivity in these reactions can be traced to the relative steric and electronic contributions of the substituents (H, Me, OBz) of the derived \( E \)-enolate 43. For such (\( E \))-enol borinates, there is a strong preference for the proton to reside in an eclipsed conformation with regard to the double bond in order to minimize 1,3-allylic strain. In the competing transition structures 44 and 45, the benzoate group is directed either inwards (44) or outwards (45) of the chair arrangement. In 45 (\( re \)-face attack on aldehyde), there is likely to be a destabilising lone-pair repulsion between the benzoate and enolate oxygen. Intermediate 45 (\( si \)-face attack on aldehyde), however, may be stabilized due to H-bond interaction between the benzoate oxygen with the aldehyde proton. This analysis accounts for the apparent contrasteric preference of the benzoate to occupy a position above the six-membered ring.

One of the great advantages of this method is the valuable option to readily transform these products into aldehydes, ethyl ketones or even methyl ketones, which in turn may be used for further functionalization or homologation.

**2.2 Substrate Control**

Structurally related to these lactate-based reagents are the Roche ester derived ethyl ketones 48, which were also developed by the Paterson group (Scheme 11). They allow for very high levels of asymmetric induction in purely substrate-controlled aldol reactions, in the sense of 1,4-

\( \text{syn} \) asymmetric inductions. By using either tin(II) \( Z \)-enolates (49) or boron \( E \)-enolates (50), the respective (1,2)-\( \text{syn} \)-(1,4)-\( \text{syn} \) and (1,2)-\( \text{anti} \)-(1,4)-\( \text{syn} \) products 53 and 54 may be obtained in high yields and stereoselectivities. The stereochemical outcome of these reactions may be explained by chelation-controlled cyclic intermediates, as depicted in 51 and 52, whereby intermediate 52 may be proposed in analogy to recent calculations by Goodman on boron-mediated aldol reactions of \( \beta \)-oxygenerated methyl ketones.31
In general, substrate-controlled propionate aldol reactions, where the selectivity relies on the stereoinduction from an existing stereogenic center in the molecule, are particularly attractive and a number of methods have been reported to allow for variable degrees of (1,n)-syn or -anti induction.\textsuperscript{2,5e,6,32–34} To obtain useful levels of stereoselectivity in substrate-controlled aldol couplings, it is usually necessary to impart stereocontrol from the enolate, as the asymmetric induction from the chiral aldehyde alone is usually insufficient to lead to highly stereoselective aldol reactions. Results indicate that the \( \alpha \)-methyl group of ethyl ketones plays a more important role as compared to the \( \beta \)-stereocenter.\textsuperscript{2,5e,6,32–35}

An instructive example on purely substrate-controlled propionate aldol reactions has recently been devised in a modular synthetic route to the northern fragment of et-nangien.\textsuperscript{35} This approach involves couplings of ketones of type 55 with aldehyde 56. As shown in Scheme 12, all possible 1,2- and 1,4-syn and -anti products 57–59 are accessible, in the sense of a diastereodivergent aldol coupling.\textsuperscript{36} To obtain preparatively useful to excellent stereoselectivity in all cases, careful choice of reaction conditions was critical. Furthermore, the protective group on the \( \beta \)-oxygen was shown to impart a crucial influence on the stereochemical outcome in these reactions. The observed stereoselectivities to access the 1,4-syn products 58A, 58B and 59A may be explained by chelation-controlled intermediates. In analogy to recent calculations by Goodman on boron-mediated aldol reactions of \( \beta \)-oxygenated methyl ketones, albeit without an \( \alpha \)-substituent,\textsuperscript{31} it may be rationalized that a similar hydrogen-bond interaction between the formyl hydrogen of the aldehyde and the \( \beta \)-oxygen substituent, as depicted in 61, may also be present in related reactions of ethyl ketones with an \( \alpha \)-methyl group. Alternatively, the \( \beta \)-oxygen may also coordinate internally to the metal counter-ion, giving intermediate 60. In both cases, the observed diastereoselectivity has been explained by minimization of steric interaction of the \( \alpha \)-methyl group. Conversely, a non-chelation transition model may be used to predict the 1,4-anti
isomers 57A, 57B and 59B.\textsuperscript{37} In order to reduce allylic strain, the respective enolate was expected to reside in a conformation depicted in 63. Diastereofacial attack should then be governed by the relative sizes of the two residues at C-4, the methyl group (small) and the large \( \beta \)-chain (R\textsubscript{\( \beta \)}. Attack of the aldehyde would then proceed to minimize steric interactions, leading to the desired 1,4-\textit{anti} products. Notably, this facial bias also benefits from minimization of \textit{syn}-pentane interactions with the \( \alpha \)-methyl group of the aldehyde.

### 2.3 Organocatalytic Variants

All aldol reactions discussed so far require the regeneration of enolates or enolate equivalents. Recent studies by Barbas,\textsuperscript{38} List,\textsuperscript{39} Shibasaki,\textsuperscript{40} and Trost\textsuperscript{41} have also reported first examples of enantioselective direct aldol reactions, which rely on metal- or proline-catalyzed transformations. In the past decade, considerable progress has been made in the catalysis using small organic molecules and ground-breaking discoveries in which aldol reactions are effectively accelerated by such organocatalysts have been reported, with proline being most prominently used in the Hajos–Parrish–Eder–Sauer–Wiechert reaction.\textsuperscript{42} One of the most fundamental advantages of such approaches is the valuable option to use aldehydes directly as enolate coupling partners.

![Scheme 13](image)

As an extension of these concepts, MacMillan’s research group has recently reported the first direct and enantioselective propionate aldol reaction with two aldehydes.\textsuperscript{43} As shown in Scheme 13, their system uses proline as catalyst and allows for asymmetric coupling of propionaldehyde (64) with \( \alpha \)- or \( \beta \)-branched aldehydes (65) with excellent enantioselectivity and moderate \textit{anti}/\textit{syn} selectivity. Such direct aldol couplings are feasible since enolizations of unsubstituted aldehydes are favored as compared to analogues with additional \( \alpha \)- or \( \beta \)-substituents. In order to avoid direct condensation of the donor component, gradual addition of this partner to the reaction mixture is vital.\textsuperscript{44}\textsuperscript{37} While these results clearly leave room for further improvements, this first example of a direct enantioselective cross-aldolization of aldehydes has to be regarded as a major breakthrough in the field of propionate aldol reactions. Furthermore, the method has proven its usefulness in natural product total synthesis.\textsuperscript{45,46} Extensions of this procedure to aldol–aldol reaction cascades have also been reported.\textsuperscript{37} Subsequently, the MacMillan group also developed the first direct asymmetric propionate aldol reaction catalyzed by an imidazolidinone catalyst (68). It proceeds with \textit{anti}- and enantioselectivities similar to those of the proline catalyst.\textsuperscript{48} An analogous access to the respective \textit{syn}-aldol products was reported by Maruoka and co-workers, who used biaryl catalyst 70.\textsuperscript{49} However, the generation of 71 from 64 and 69 is the only example reported for a propionate-type structure.

### 2.4 Reductive Aldol Reaction

As an alternative entry into enolates, reductive processes have been attracting increasing interest.\textsuperscript{50} As shown in Scheme 14, such aldol couplings are initiated by transition-metal-catalyzed conjugate reductions of \( \alpha,\beta \)-unsaturated carbonyl compounds (72) which are mediated by hydrosilanes or molecular hydrogen as hydride sources, and enable the in situ generation of transition-metal enolates (74), which may then undergo subsequent aldol couplings. These coupling reactions may be assisted by various chiral ligands and auxiliaries, and in recent years, a number of suitable systems have been reported to also access polypropionates with good to high levels of stereo- and enantioselectivity.

The methods by Morken,\textsuperscript{51,52} Nishiyama\textsuperscript{53} and Riant\textsuperscript{54} use silanes as reducing agents and rhodium, copper and iridium catalysts and the chiral ligands 76–79. They proceed with moderate to excellent selectivities and yields. While these methods appear to be limited to unsaturated esters, Krische and co-workers recently reported the first enantioselective reductive aldol coupling of vinyl ketones 80.\textsuperscript{55} The reported system uses hydrogen as reducing agent and catalytic amounts of the TADDOL-type phosphinite ligand 83. The method shows impressive selectivities and yields, but does, however, require an excess of the ketone component.

Complementary to these reductive aldol reactions, diastereoselective hydroformylation of terminal alkenes have also been reported, giving rise to chiral \( \alpha \)-methyl-\( \beta \)-hydroxyaldehydes in a stereoselective fashion.\textsuperscript{56–58}

### 3 Crotylation

Over the last decades, asymmetric crotylation reactions have been studied extensively and used for the stereose-
trolled assembly of polypropionates. These allylmetal–
aldehyde addition reactions have proven to be enormously
successful for the construction of adjacent stereocenters.
The reasons for the success of these methods include high
degrees of enantio- and diastereoinduction, a broad range
of reagent reactivity based on the employed metal, the
ability to access different stereodis and triads and the
inherent versatility of the obtained products towards fur-
ther functionalization.60

One of the most intriguing features of these reactions is
the predictable relationship between the configuration of
the product and the geometry of the starting alkene. Ac-

According to Denmark’s analysis,60 they may be classified
into three mechanistically distinct types. Type I reactions
proceed via a rigid chairlike transition state 84 (Scheme 15) which is characterized by coordination of the
carbonyl to the metal atom. Consequently, the syn/anti
diastereoselectivity of the product 86 reflects the Z/E ratio
of the starting allylic geometry. Boron reagents are the
most prominent representative of this type.61 Type II re-
agents (85), exemplified by trialkysilanes and stannanes,
in contrast, usually proceed via an open transition state
and require Lewis acid activation.62 Type III reactants, not
illustrated in Scheme 15, also proceed via an open transi-
tion state. They provide the same diastereomeric product,
independent of the starting double bond configuration.

Crotylation reactions may also be classified into stoichio-
meric and catalytic variants. The most widely used sto-
ichiometric crotylation reactions belong to type I reactions,
with Z-crotol reagents giving syn isomers, and E-isomers
the corresponding anti products. This simple stereoselec-
tivity may be readily explained by Zimmermann–Traxler-
type transition states. In this category, excellent results
have been obtained by use of chiral modified allylic bo-
rane and allylic titanium reagents. Recently, the success
of this approach has been extended to include silanes.

B-Crotylation Reaction

Chiral borane reagents have been developed by
Hoffmann, Brown, Roush and others.63 Hoffmann and
Zeiss have shown that the reaction of (E)- or (Z)-crotolbo-
ranes with aldehydes results in the formation of anti- or
syn-β-methyl homoallylic alcohols,64 which may be ex-
plained by chairlike transitions states. Use of crotol(diiso-
-pinochamphey)boranes 87 and 90 was developed by
Brown65 (Scheme 16). Owing to the good performance
and commercial availability of the chiral auxiliary, these
have become the standard method for asymmetric crotyla-
despite certain disadvantages (noncatalytic, reagent
not storable). The high stereospecificity of these reactions
may be explained by closed chair-like transition states 88
and 91, where the boron is coordinated to the carbonyl ox-
xygen. The aldehyde is oriented in such a manner that the
R group is placed in an equatorial position of the chair to
minimize steric interactions between the Ipc group on bo-
rone and the allyl unit. These transition states have been
supported by ab initio calculations that identify a strong
preference for the chair-like arrangement of the two com-
ponents, in close agreement with the experimental re-

results.66

Solvents have a significant effect on the rates of allylbora-
ration reactions.65 Polar solvents, including chloroform,
dichloromethane and diethyl ether, which are either poor-
ly coordinating or non-coordinating, enhance the rate of
allylboration, while solvents capable of stronger coordi-
nation with boron, such as tetrahydrofuran, retard the rate.
Highly substituted aldehydes react significantly more
slowly than less substituted aldehydes.

Other chiral ligands for boron-mediated crotylations have
been reported by Hoffmann,68 Roush,65c,69 Masamune,70
Corey,71 Soderquist72 and Hall73 (Figure 4).

Scheme 14

Scheme 15

---

Duthaler–Hafner Ti-Crotylation Reaction

Chiral crotyltitanium complexes 93 (Scheme 17) have been introduced by Duthaler and Hafner. They may be prepared from readily available nontoxic materials and are available in both enantiomeric forms. In contrast to the crotylboron reagents, these crotyltitanium compounds can be prepared by transmetalation with a variety of crotyl Grignard, crotyllithium and crotylpotassium/lithium compounds and isolation or purification is not necessary. The propensity of these reagents for large-scale conversions is notable.

Scheme 17

The addition reactions of these crotyltitanium compounds 93 with aromatic and aliphatic substrates afford the homoallylic alcohols 92 with high enantio- and diastereoselectivity and excellent yield (Scheme 17). The major product in all cases is the anti diastereomer 92, obtained by addition of the crotyltitanium complex on the si face of the substituted terminus. On the other hand, NMR analyses of crotyl reagents (crotyl Grignard, crotyllithium, and crotylpotassium/lithium) revealed a rapid 1,3-migration of titanium, favoring the E-isomer with titanium 1 bound to the unsubstituted terminus of the crotyl group. This explains the almost exclusive formation of the anti diastereomers, a clear restriction of this method.

Leighton Si-Crotylation Reaction

Chiral cis- and trans-crotylsilane reagents 94 (Scheme 18) have been developed by Leighton. They are storable crystalline solids and may be prepared in bulk amounts, though their synthesis requires a few steps. A survey of the performance of crotylsilane reagents was carried out with a variety of aliphatic, aromatic, and α,β-unsaturated aldehydes. In every case, the cis- and trans-crotylsilane reagents demonstrated their use in highly enantioselective syn- and anti-selective aldehyde crotylation reactions, respectively. The crotylation reactions are experimentally trivial and the chiral diamine may be recovered.
products (\(92\)), independent of the starting allylic geometry. Prominent examples are the asymmetric catalytic variants of Nozaki–Hiyama couplings.\(^\text{86}\) Metallic reductants are required for catalytic turnover. Observed diastereoselectivities are, however, only moderate. The first example was reported by Umani-Ronchi.\(^\text{87}\)

Scheme 20

Additions of crotylic trichlorosilanes (\(97\), Scheme 21) may be catalyzed by chiral Lewis bases. They usually proceed as type I reactions. Catalytic procedures have been reported by Denmark,\(^\text{62a,88a}\) Iseki,\(^\text{88b}\) Nakajima\(^\text{88c}\) and Koovsky.\(^\text{88d}\) Recently, Schaus also reported a chiral diol catalyzed allylboration of ketones.\(^\text{88e}\)

A very interesting novel catalytic variant was recently described by Krische.\(^\text{89}\) This involves the use of a cyclometallated iridium catalyst with chiral phosphine ligand \(99\), \(\alpha\)-methyl allyl acetate (\(98\)) as crotyl equivalent and isopropanol as reductant (Scheme 22). Mechanistically, this reaction proceeds via an intermediate \(\pi\)-crotyl iridium species. The product alcohols \(92\) are obtained with good levels of anti-diastereoselectivity and excellent enantioselectivity.

Scheme 22

### 4 Allenylation

Methodologies for the stereoselective preparation of \(anti\)-configured homopropargylic alcohols \(103\) from enantioenriched propargylic mesylates \(100\) have been developed by Tamaru\(^\text{90}\) and Marshall\(^\text{91}\) (Scheme 23). These mesylates serve as precursors to chiral allenylzinc reagents \(102\) for the coupling to aldehydes. They may be generated in situ through ‘oxidative transmetalation’ of transient allenylpalladium intermediates \(101\).\(^\text{92}\) The homopropargylic alcohol adducts (\(103\)) are obtained with high enantioselectivity and yield.

This reaction has been adapted to various other allenylmetal species, including indium reagents.\(^\text{93}\) These intermediates may also be generated in situ from more readily available chiral silanes \(104\) and diethylzinc or indium(I) iodide in the presence of Pd(OAc)\(_2\)PPh\(_3\) (Scheme 24).\(^\text{94}\) The corresponding aldehyde additions proceed with excellent diastereoselectivity and similar levels of enantioselectivity. Additions of \(\alpha\)-TMS-substituted allenylindium.
reagents afford anti products with enantiomeric ratios of 99:1 or higher and virtually no trace of the syn products.

According to Marshall’s analysis, the stereochemical outcome may be explained by two competing cyclic transition states 106 and 107 as shown in Figure 5. In the unfavored syn pathway, the methyl group is placed in a nearly eclipsed conformation with the R substituent of the aldehyde, whereas these groups are at some distance in the anti array. Such an eclipsed transition state has also been discussed for the analogous allenylzinc additions on the basis of ab initio calculations.  

**Figure 5** Proposed transition states for additions of allenylmetal reagents to aldehydes

### 5 Epoxide Opening

Stereoselective epoxide-opening reactions have been recognized as an important transformation in organic synthesis and are widely used as key steps in natural product syntheses. Nucleophilic substitution reactions of trans- or cis-configured epoxy-ols 108 and 113 with organometallic reagents, including organocuprates and organoaluminum complexes, provide an efficient method for the stereoselective construction of propionate frameworks.  

Regioselective openings with lithium dimethyl cuprate or trimethylaluminum and butyllithium preferentially lead to 2-methyl-1,3-diols 109 and 112, while trimethylaluminum reacts at C3 to give the 3-methyl-1,2-diols 109 and 111 (Scheme 25). Miyashita has developed the stereo- and regiospecific methylation of γ,δ-epoxy acrylates 114 and 116 by trimethylaluminum in the presence of water. As shown in Scheme 26, methylation occurs diastereospecifically following an S_N2 process. The anti compounds 115 are obtained from (E)-epoxy acrylates 114, while the syn congeners 117 are derived from (Z)-epoxy acrylates 116. The method can also be applied iteratively.  

**Scheme 25**

The results reported by Miyashita demonstrate that the use of bidentate aluminum catalysts from the trimethylaluminum/water system strongly enhance the reactivity of the epoxy oxygen toward alkyl transfer via double electrophilic activation (118) as shown in Scheme 27. Key intermediates in this system at low temperature are thought to involve partial generation of hypothetical bidentate reagents of type 121 or 122. Presumably, the epoxide moiety will be activated and alkylated via a highly coordinated aluminum species (119).
Stereospecific methylation of epoxy sulfides 123 and 126 with trimethylaluminum was developed by Saigo 103 and Miyashita 104 (Scheme 28). The reaction proceeds via episulfonium ions 124 and 127 with double inversion of the configuration to syn- and anti-alcohols 125 and 128. A variety of optically active epoxy sulfides are readily available from the corresponding epoxy alcohols. Furthermore, the phenylthio groups at the terminal position of the products can be easily transformed into the corresponding aldehydes. Miyashita has used this method for the total synthesis of scytophycin C 101c and premisakinolide A. 105 Optically active epoxy alcohols (130) are readily available from allylic alcohols (129) following the Sharpless protocol, which adds to the significance of the methods discussed within this section. 106 Treatment of these epoxy alcohols with Lewis acids (TBSOTf, TESOTf or BF3) provides syn-aldol products enantiospecifically in high yield. The mechanism of this transformation, as proposed by Jung, 107 involves Lewis acid activation of the epoxide, followed by intramolecular hydride transfer as shown in transition state 134 to generate the new stereocenter at the methyl-substituted carbon in 133. Desilylation then gives the final product 132 (Scheme 29). As shown, (E)-allylic alcohols give the syn products, while (Z)-allylic alcohols afford the anti analogues. An application of this methodology in natural product total synthesis has been reported. 108

Following a similar strategy, Bode developed a catalytic method for the generation of anti-propionates 137 from epoxyaldehydes 135. 109 These reactions are catalyzed with the NHC catalyst 136 and proceed in the presence of base and with good yield and diastereoselectivity. Presumably, the reaction follows the mechanism shown in Scheme 30. Of particular importance is the epoxide-opening step, which has been postulated to occur via intermediates 140 and 141. Notably, this concerted mechanism is different from the Favorskii-type hydride shift, as discussed above. Possibly, the observed anti-diastereoselectivity in the protonation step (141→139) is governed by the minimization of 1,3-allylic strain.

A selective palladium-catalyzed hydrogenolysis of alkenyloxiranes 142 and 144 has been reported by Shimizu and Tsuji (Scheme 31). The reaction is performed with tris(dibenzyldieneacetone)dipalladium chloroform complex [Pd(dba)2·CHCl3] in the presence of tri(n-butylyphosphine, formic acid and triethylamine, and affords alcohols 143 and 145 stereoselectively. 110

Hydrogenolysis occurs with inversion of stereochemistry. This has been explained by the pathway shown in Scheme 32. At first, the palladium(0)–phosphine complex coordinates to the olefin 142 and opens the epoxide with inversion to form π-allylpalladium complex 148. Then, formic acid adds to this complex, giving formate 147, which then undergoes decarboxylation to π-allylpalladium hydride 146. Finally, regioselective reductive elimination by internal attack of the hydride to the more distant double bond then provides the desired anti-propionate 145.

Scheme 28

Scheme 29

Scheme 30

Scheme 31
substituted carbon of this complex liberates the homoallylic alcohol 143 and regenerates palladium(0). An application of this method in natural product total synthesis has been reported.111

Scheme 32

6 [2,3]-Wittig Rearrangement

[2,3]-Sigmatropic rearrangements constitute a versatile type of bond reorganization with many applications in organic synthesis. This reaction may be generalized as shown in Scheme 33 for structures 149 and 150. It is defined as a thermal isomerization that proceeds through a six-electron, five-membered cyclic transition state.112

Scheme 33

Mikami and Nakai have studied the diastereoselectivity of a broad range of [2,3]-Wittig rearrangements and proposed transition states 152, 153, 156 and 157 to explain the results (Scheme 34). In general, E-configured substrates (151) give anti products (154) while the Z-congeners (158) give syn isomers (155). This may be explained in terms of pseudo-1,3-diaxial interactions of R with Hβ in 153 and 156. Accordingly, 157 should be sterically favored, thus leading to syn-selectivity. The order of selectivity is correlated with an increase in 1,3-repulsion. A marked dependence of the anti-selectivity on the size of the substituent R is best explained by additional steric gauche interactions between R and Me in the preferred transition state 152, hence the anti selectivity decreases with an increase of this gauche interaction.112a

Midland has reported [2,3]-Wittig rearrangements of optically active (Z)-allylic ethers 159 to provide allylic alcohols 160 with complete control of olefin geometry and chirality transfer and high degrees of diastereoselectivity (Scheme 35).113 The rearrangement of (E)-allylic ether 161 provides allylic alcohol 162 with high anti stereoselectivity. High selectivities were observed with R being an alkylnyl substituent, which can be explained by a decrease of the gauche interactions, as discussed above. Midland used this reaction for synthesis of the (+)-Prelog–Djerassi lactone.114

Recently, the application of the [2,3]-Wittig rearrangement reactions of (Z)-allylic ether 163, a cyclohexanecarboxaldehyde-derived intermediate for the synthesis of syn stereodiad 164, was described by Parker (Scheme 36).115 This product was converted into (syn, anti)-polypropionate building blocks.115

Scheme 35

Parker has also reported the Wittig rearrangement of propargyl ether 165 for the synthesis of anti stereodiad 166,116 which can be further transformed into (anti,anti)-polypropionates (Scheme 37). The highly selective depyro-
tonation at one of the four allylic positions of 165 is noteworthy.

\[
\begin{align*}
\text{BuLi, } & \text{BuOK} \\
\text{THF} & \text{–78 to 0 °C} \\
\end{align*}
\]

\[
\text{83%, } \text{dr} > 20:1
\]

\text{Scheme 37}

### 7 Sequential Substitution

The archetypal cases of stereoselective nucleophilic substitution reactions for propionate synthesis based on substrate control were described by Fräter in 1979\(^{117}\) and Seebach in 1980,\(^{118}\) namely, the stereoselective alkylation of chiral β-hydroxy esters.

A sequential approach allowing for the asymmetric construction of both the methyl and the hydroxy-bearing stereogenic center by a sequential process has been reported by Hanessian,\(^{119}\) A shown in Scheme 38, it first involves the addition of a lithium dimethylcuprate to acyclic α,β-unsaturated esters 167, containing a γ-alkoxy substituent (BOM, MOM, etc.) leading to a high preponderance of the anti-configured methylated product.\(^{120}\) Subsequently, nucleophilic addition of the enolate of 168 to Davis oxaziridine reagent generates the propionate triad 169 with high levels of stereoselectivity.

\[
\begin{align*}
\text{BuLi, THF} & \text{–78 to 0 °C} \\
\text{Me}_2\text{CuLi} & \text{TMSCl} \\
\end{align*}
\]

\text{Scheme 38}

The anti stereoselectivity in the conjugate methyl addition may be explained by conformation 170, which is stabilized by a favorable interaction of the alkoxy group (OR\(^2\)) with the π-system through a two-electron (p) and a four-electron (π) interaction in the ground state. In addition, the high-lying σ (RCH\(_2\)-C) orbital can interact with the low-lying π* orbital, thus stabilizing the α,β-unsaturated fragment and increasing the Lewis basicity of the carbonyl for chelation. The anti orientation of the RCH\(_2\) group may also stabilize the incipient σ*(C-Cu) orbital in the d,π*-complex-β-cuprido(III) adduct, through σ-bond donation. Furthermore, conformation 170 is free of 1,2-allylic strain.\(^{120}\)

A plausible mechanistic rationale for the observed syn-selectivity in the hydroxylation of the enolate of 168 is depicted in structure 171. According to Felkin’s argument,\(^{121}\) refined by Anh\(^{122}\) and Houk,\(^{123}\) the preferred conformation 171 has the small substituent (H) eclipsing (or partially eclipsing) the double bond, and the electrophile attacking from within the double bond on the less-hindered side. Consequently, attack by ‘O+’ takes place anti to the R group to produce the α,β-syn product. Alternatively, a chelate model may also explain the observed selectivity.\(^{119,124}\)

Hanessian also explored the possibility of iterating this process, which involves the chain extension via Wittig olefination, thus generating a new γ-alkoxy-α,β-unsaturated ester motif, which may again be submitted to the same procedure.\(^{125}\) This strategy was used for the stereocontrolled construction of polypropionate stereotriads in natural product total synthesis.\(^{126}\)

Recently, Hanson and co-workers reported a strategy for selective S\(_\text{N}2\)’ substitution which employs phosphate tethers. As shown in Scheme 39, they serve a dual role, as tether for the coupling of two allylic alcohols (172) via ring-closing metathesis (RCM), and as a leaving group in selective anti-S\(_\text{N}2\)’ displacement reactions of derived pseudo-C\(_2\)-symmetric cyclic intermediate 173 with organocuprates to give 175 (Scheme 39). Reductive removal of the auxiliary gives syn-homoallylic alcohols 174 in high yield and diastereoselectivity.\(^{127}\)

\[
\begin{align*}
\text{BuLi, } & \text{THF} \\
\text{Me}_2\text{Zn} & \text{CuCN} \\
\end{align*}
\]

\text{Scheme 39}

As highlighted in Figure 6, the remarkable selectivity for this transformation can be rationalized using Corey’s proposed model for a concerted, asynchronous mechanism for cuprate additions.\(^{128}\) According to this model, the reacting cuprate simultaneously coordinates both the π* orbital of the olefin and the π* orbital of the phosphate ester leaving group. The asynchronous nature of the transformation predicts a transition state in which substantial bond lengthening occurs with respect to the σ* bonding orbital.
8  Radical Processes

Guindon has reported a strategy that employs a Mukaiyama reaction in tandem with a free-radical-based hydrogen-transfer reaction for the elaboration of propionate motifs.\textsuperscript{139} The general strategy is illustrated in Scheme 40. It first involves a Mukaiyama aldol reaction between aldehyde 176 and tetrasubstituted enoxysilane 177, which bears a functionality that may be subsequently removed through a free-radical process (e.g., I, Br, or SePh). Bidentate Lewis acid (e.g., MgBr\textsubscript{2}·OEt\textsubscript{2}) mediated activation of β-alkoxy-α-methyl aldehyde 176 favor the 3,4-anti adduct 180 via a Cram chelate transition state (178), while monodentate Lewis acids such as boron trifluoride–diethyl ether complex lead to the 3,4-syn product (181/182) through a Felkin–Anh-type pathway (179). In this strategy, the E/Z stereochemistry of the enoxysilane 177 does not need to be controlled. Indeed, the stereochemistry at C-2 of the Mukaiyama adducts is not important in the approach, as this site is transformed into a carbon-centered free radical in the next step. The hydrogen-transfer step can give either 2,3-syn or 2,3-anti relative stereochemistry. Minimization of 1,3-allylic strain and intramolecular dipole–dipole interactions is at the origin of the anti selectivity in these π-delocalized radicals. This anti preference can be enhanced by taking advantage of the exocyclic effect, as shown in Scheme 40. Formation of a six-membered ring adjacent to the carbon-centered radical is discussed and bidentate Lewis acids have been shown to generate such a temporary ring by chelating the C-3 and C-5 hydroxy groups (transition states 183, 184). Hydrogen transfer then leads selectively to 2,3-anti propionate products 186 and 187. On the other hand, the 2,3-syn relative stereochemistry in 188 can be induced in the hydrogen-transfer reaction by taking advantage of an endocyclic effect. In this case, the carbon-centered free radical, now embedded within the Lewis acid induced ring of 185, will give 2,3-syn propionate product 188.

This usefulness of this consecutive strategy has been demonstrated in the stereoselective synthesis of extended propionate units.\textsuperscript{130}

Kiyooka recently developed a related methodology, which first involves enantio- and diastereoselective aldol reactions of enolate 190 with aldehyde 189, followed by diastereoselective radical debromination (Bu\textsubscript{3}SnH, Et\textsubscript{3}B, MgBr\textsubscript{2}) (Scheme 41). The bromo substituent in 190 has two roles: the first is to provide a suitable steric bulk of the silyl nucleophile leading to very high enantioselectivity in the aldol condensation process, and the second is to serve as a group which can be readily eliminated from the resulting intermediate 192 in a subsequent selective radical reduction process, giving the desired products 193 and 194 with very good selectivity.\textsuperscript{131}

In the case of these chiral oxazaborolidinone-promoted asymmetric aldol reactions, the predominance of the catalyst (promoter) control over substrate control has been explained by the intermediate depicted in Figure 7.

A strategy toward the quite effective enantioselective synthesis of versatile stereotriads has been designed in a sequence of an oxazaborolidinone-promoted asymmetric aldol reactions of racemic aldehyde 199 with silylketene acetal 200 and an ensuing radical debromination reaction. The enantioselective synthesis of all stereotriads of ethyl 5-(tert-butylphenyloxy)-2,4-dimethyl-3-hydroxypentanoates (195, 196, 203–206) may be achieved by using this sequence (Scheme 42).\textsuperscript{132}

Figure 6  Corey’s model for the stereoselective cuprate $S_{N}2^{\prime}$ displacement reactions

Scheme 40
The methoxymethyl moiety is expected to play a key role for enhanced steric assistance in both dipole and chelation modes, as shown in Figure 8.  

Sibi reported the first example of an intermolecular radical addition to \( \alpha,\beta \)-disubstituted substrates 211 followed by hydrogen atom transfer, which proceeds with high diastereoselectivity in the presence of chiral ligand 213 (Scheme 43). The method has been applied to the preparation of \( \text{anti} \)-propionate aldol products 212 with very good selectivities.  

The stereochemical outcome of these reactions can be explained by using model 214 in which initial addition to the \( \beta \)-carbon occurs from the top face, opposite to the aryl group of the ligand. Subsequent hydrogen transfer to the
α-carbon is apparently controlled not by the chiral ligand (which might be expected to block the bottom face resulting in syn addition) but by the newly formed β-stereocenter, with the radical R group shielding the top face.134

9 Intramolecularization

All methods discussed so far rely on acyclic stereocontrol. To overcome the inherent entropy problem and to allow for high degrees of asymmetric induction, the concept of intramolecularization has become an increasingly important principle in polypropionate method development in recent years.

9.1 [2+2] Cycloaddition

Asymmetric acyl halide–aldehyde cyclocondensation (AAC) reactions that deliver highly enantiomerically enriched oxetanones (218, Scheme 44) from commercially available starting materials have been developed by Nelson and co-workers. Optically active aluminum(III)–triamine complexes of type 216 catalyze the cyclocondensation of propionyl bromide (215) and a variety of aldehydes (217) to afford β-lactone adducts with uniformly high enantioselection (90–98% ee), diastereoselection (74–98% de), and chemical yields (71–90%). Subsequent lactone-ring opening reveals that the enantiomerically enriched β-lactones act as surrogates for syn propionate aldol adduct 219.135

These aluminum(III)-catalyzed AAC reactions are postulated to proceed via amine-mediated ketene generation (216) with ensuing Lewis acid catalyzed [2+2] cycloaddition to afford the desired β-lactone adducts 218,136 in agreement with experimental results.137

Later, Nelson reported asymmetric cinchona alkaloid (222 or 223)-catalyzed AAC reactions, which are applicable to a range of structurally diverse aldehydes,138 and their use in the catalytic asymmetric synthesis of extended propionate networks (225–227)139 (Scheme 45). These reactions are characterized by high enantio- and diastereoselection and operational simplicity, the use of readily available reaction catalysts, and in situ ketene generation. Mechanistically, it has been proposed that nucleophilic addition of alkaloid additives (222 and 223) to ketenes generates an acylammonium enolate (228) that will be activated by a metallic Lewis acid cocatalyst (M). Such metal-stabilized ammonium enolates (229) would then add to the aldehyde through metal-templated, closed transition states 230, 231, providing both enthalpic and entropic activation to the ensuing enolate–aldehyde addition, leading to 224 (Scheme 46).138

The group of Calter developed a biomimetic, catalytic, asymmetric variant of this reaction that may produce any stereoisomer of a general dipropionate synthon from commercially available materials without isolation of intermediates (Scheme 47). The reaction sequence is based on the opening of methylketene dimer 236, generated in situ from α-bromopropionyl bromide (235) via the ketene intermediate (216). Trapping of this dimer with a secondary amine (e.g., N,O-dimethylhydroxylamide), followed by reduction of the derived amide 234 under the appropriate conditions [e.g., KB(HEt3), or Zn(OTf)2 with NaBH4], affords either the anti or the syn diastereomer 232 or 233.140
Furthermore, opening of the dimer 236 with the lithium amide of \(N,O\)-dimethylhydroxylamine generates, in situ, the lithium enolate 238, which may react with a variety of aldehydes to yield (\(\text{syn, syn}\))-aldol adducts 237.\(^{141}\) These ketene dimerization–opening–aldol reaction sequences provide a convenient and diastereoselective method for a one-step construction of polypropionate segments. They have demonstrated their usefulness in the total synthesis of natural products such as siphonarienal,\(^{142}\) siphonarienedione and siphonarienolone\(^{143}\) and the C21–C34 segment of the aplyronines.\(^{144}\)

9.2 Silicon Tether

Reactions of Silacyclopropanes

Silacyclopropanes such as 241 are strained silanes that undergo carbon–carbon bond-forming reactions with various carbonyl compounds.\(^{145}\) Carbonyl insertions proceed with high stereo-, regio-, and chemoselectivity to afford oxasilacyclopentane adducts (244) under mild, metal-catalyzed conditions (Scheme 48).\(^{146}\)

Woerpel has developed a silver-catalyzed silylene transfer as a mild and efficient method for the synthesis of silacyclopropanes 241;\(^{146–148}\) the process uses a stereospecific silylene transfer from cyclohexene silacyclopropane 240 to alkene 239 (Scheme 48). Treatment of intermediate 241 in situ with \(N\)-methyl-\(N\)-benzylformamide and catalytic amounts of copper iodide resulted in an \(N,O\) acetal, which may be hydrolyzed and acetylated to provide oxasilacyclopentane 244 in high yield. Nucleophilic substitution with silyl enol ether 243 produced ketone 242 in high yield and diastereoselectivity. Wittig methylation followed by carbon–silicon bond oxidation afforded diol 245, a key fragment for the synthesis of \(1\)-\(\text{epi}\)-stegobinone (246).\(^{149}\)

Scheme 48

Enyne Methathesis

Titanium(II)-mediated cyclization of (silyloxy)enyynes (247, Scheme 49) have been studied by Phillips.\(^{150}\) They may be obtained by silylation of alcohol 249 with bromodisopropylpropynylsilane. For cyclization, they are treated with (\(\text{2-propene}\))titanium diisopropoxide \([\text{Ti}((i-\text{Pr})\text{O})_2]\\) , generated in situ from chlorotitanium(IV) triisopropoxide \([\text{ClTi}(i-\text{PrO})_3]\\) and isopropylmagnesium chloride. Desilylation of the derived 248 gives rise to the corresponding propionates 250, which are obtained exclusively as the \(\text{anti}\) diastereoisomers. This reaction proceeds by an enyne mechanism. The titanium(II)-mediated cyclization of (silyloxy)enyynes has also been applied to the synthesis of \(\text{(syn,anti)}\) - and \(\text{(anti,anti)}\)-stereotriads and utilized in complex natural products syntheses.\(^{150,151}\)

Scheme 49

10 Conclusions

The development of practica methods for the synthesis of propionates remains a vibrant area of methodology development in organic chemistry. Approximately 25 years af-
ter Woodward’s epochal erythromycin synthesis, a variety of procedures for the regio- and stereoselective assembly of the characteristic sequences of methyl- and hydroxy-bearing stereogenic centers have been established. Most importantly, a large number of reliable and predictable methods for acyclic stereocontrol have been devised based on aldol reactions. Despite this predominance, a wide variety of alternative synthetic approaches have also been developed, involving crotylations, allenylations, stereoselective substitutions, cycloadditions, rearrangements, and even stereoselective radical reactions. Often, they enable access to certain stereochemical permutations with high stereoselectivity and yield.

With these methods in hand, even complex propionates may now be assembled in impressively short time frames. Nevertheless, the structural and stereochemical complexity of the products still often require adaptations of existing methods. Furthermore, for true applicability, these methods have to be robust enough to allow for scalable approaches, in order to exploit the full biological potential of polypropionates. While the first examples of impressive large-scale approaches to propionates have recently been reported, both in academia and industry, there continues to be a demand for the development of practical, stereochemically predictable and reliable methods for propionate synthesis. These will be crucial in order to exploit the full biological and medicinal potential of propionates and polyketides in general. Along these lines, direct methods as well as sequential approaches will be particularly attractive. Furthermore, concepts that proceed without extensive protective group strategies and/or are selective enough to proceed without protective groups at all are highly desirable.

References
According to the (1,n)-nomenclature, 1 denotes the newly formed stereogenic center, while n stands for the pre-existing chiral center.


(28) According to the (1,n)-nomenclature, 1 denotes the newly formed stereogenic center, while n stands for the pre-existing chiral center.


(37) (a) This non-cyclic transition state is in agreement with that proposed by Evans for a boron-mediated aldol reaction: see Ref. 36c. (b) For titanium-mediated aldol couplings, a different non-cyclic model has been discussed: see Ref. 32b.


Recent results by Denmark suggest that crotylchlorosilanes may also react diastereoselectively, possibly via a Type I transition state: (a) Denmark, S. E.; Almstead, N. G.; In Recent results by Denmark suggest that crotylchlorosilanes may also react diastereoselectively, possibly via a Type I transition state: (a) Denmark, S. E.; Almstead, N. G.; In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 11. (c) Denmark, S. E.; Almstead, N. G. In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 10.


Recent results by Denmark suggest that crotylchlorosilanes may also react diastereoselectively, possibly via a Type I transition state: (a) Denmark, S. E.; Almstead, N. G.; In Recent results by Denmark suggest that crotylchlorosilanes may also react diastereoselectively, possibly via a Type I transition state: (a) Denmark, S. E.; Almstead, N. G.; In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 11. (c) Denmark, S. E.; Almstead, N. G. In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 10.


Recent results by Denmark suggest that crotylchlorosilanes may also react diastereoselectively, possibly via a Type I transition state: (a) Denmark, S. E.; Almstead, N. G.; In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 11. (c) Denmark, S. E.; Almstead, N. G. In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 10.


Recent results by Denmark suggest that crotylchlorosilanes may also react diastereoselectively, possibly via a Type I transition state: (a) Denmark, S. E.; Almstead, N. G.; In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 11. (c) Denmark, S. E.; Almstead, N. G. In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 10.


Recent results by Denmark suggest that crotylchlorosilanes may also react diastereoselectively, possibly via a Type I transition state: (a) Denmark, S. E.; Almstead, N. G.; In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 11. (c) Denmark, S. E.; Almstead, N. G. In Modern Carbonyl Chemistry: Otera, J., Ed.; Wiley-VCH: Weinheim, 2000, Chap. 10.