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Acyclic stereocontrol between remote atom centers via intramolecular and intermolecular stereo-communication

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1. Prologue

The practice of organic synthesis is highly dependent on two fundamental operations, the formation of carbon–carbon bonds and the introduction of functional groups. Generally, both of these processes stem from already existing functionality, frequently a carbonyl, and the new bonds are formed at the site of the functionality or at a position proximal to it.[1] To be sure, it is considerably more difficult to functionalize a molecule at a position that is remote from that original location. Breslow discussed this limitation of organic synthesis techniques some years ago and emphasized the importance of developing methodology for remote functionalization.[2] The problem becomes even more acute when stereochemical issues are superimposed. To accomplish the task of controlling stereochemistry at remote locations on a carbon framework, organic chemists have typically resorted to conformationally constrained systems, such as cyclic systems, and especially those comprised of six-membered rings or rigid skeletons. In these situations good stereochemical control is achieved from the structural order in the substrate, arising from strategically placed covalent bonds, biasing substituents,

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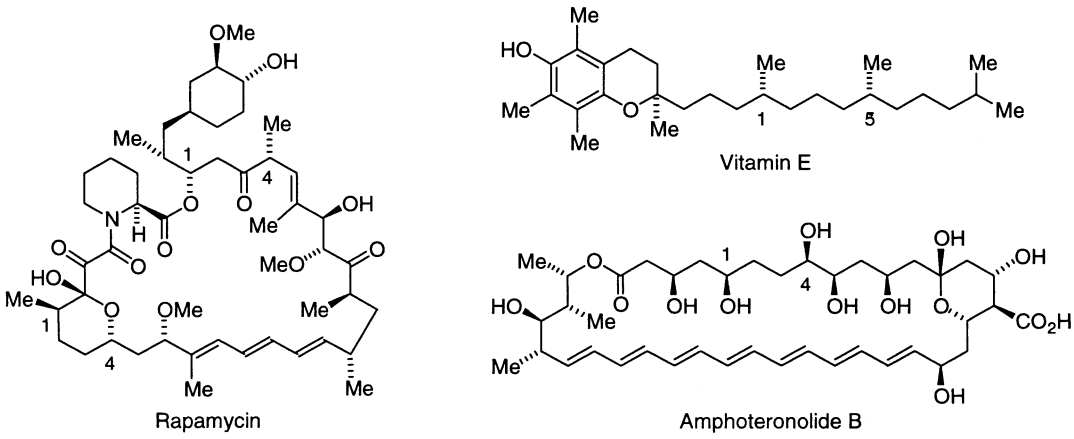


Figure 1.

sp^2 centers, and/or coordinating atoms. For example, medium-sized cyclic compounds with appropriately located sp^2 centers have afforded impressive diastereoselectivities between remote sites at 1,3 and 1,4 locations.[3] By contrast, successful acyclic stereocontrol is much more challenging in that the substrates are intrinsically less ordered conformationally.

In the area of acyclic stereocontrol,[4] there are now many excellent methods, such as those based on aldol reactions, Michael reactions, and nucleophile addition to aldehydes and ketones, to establish proximal sites with 1,2 and 1,3 relationships.[5] This category of reactions will not be addressed in the present report. Rather, we will concentrate on acyclic stereochemical control at more remote sites, i.e. those with 1,>3 relationships, because this is still a comparatively underdeveloped area. As an example, the control of stereochemistry of hydroxyl and methyl groups in 1,4 or 1,5 positions, which is an important arrangement for the synthesis of natural products such as rapamycin, vitamin E, and amphotericins (Fig. 1), could benefit from new and improved synthetic methods.[6] Nevertheless, during the past 10–15 years, the difficult problem of acyclic stereocontrol at remote positions separated by a distance of four or more atoms has yielded to a diversity of notable successes. Many of these cases have relied on some degree of conformational constraint from pre-established covalent bonds, most commonly the presence of a ring structure. In this regard, the substrates involved can not be viewed as 'strictly acyclic'. Other cases have employed sp^2 atom centers, e.g.

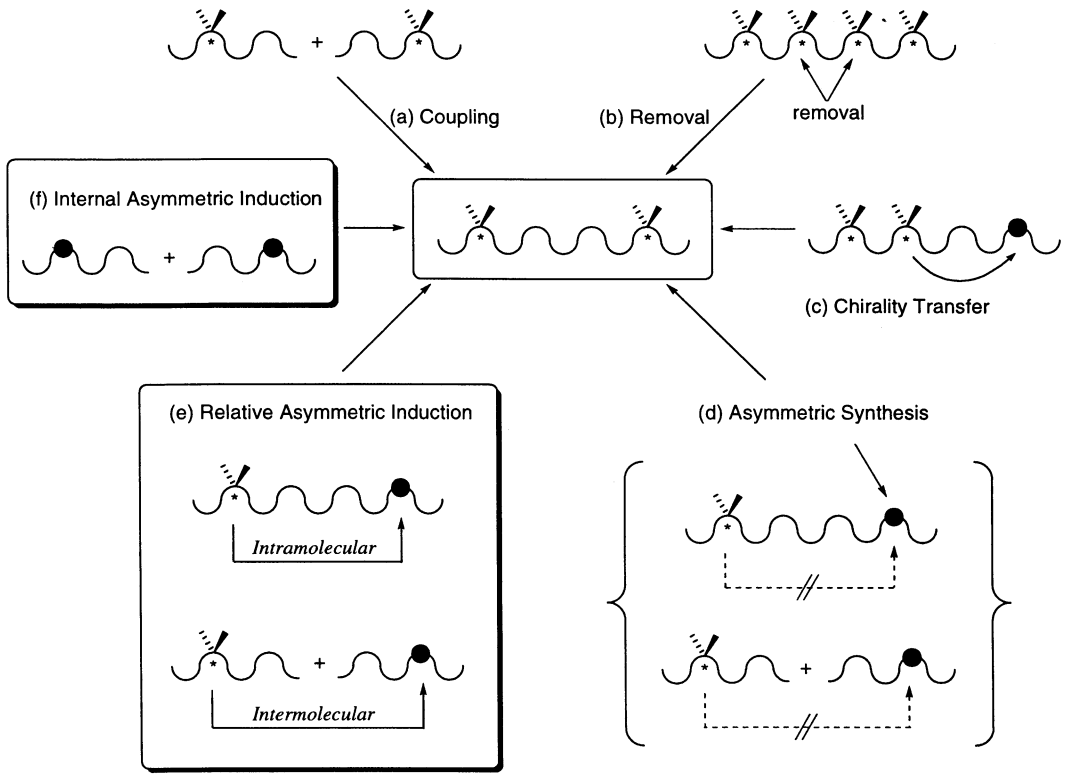


Figure 2.

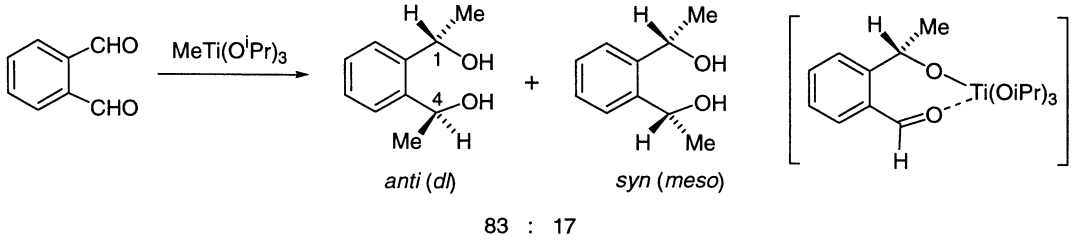


Figure 3.

from alkenes, arenes, or amides, to furnish critical conformational bias. Synthetic methods involving certain ring-constrained chiral auxiliaries, such as oxazolidinones,[7] oxazolines,[8] and camphorsultams,[9] have been widely used to execute 1,4 or 1,5 diastereocontrol. However, remarkable cases exist in which the substrate is devoid of any pre-established structural features for conformational ordering. In these strictly acyclic systems, structural order must be established amidst the reaction itself, basically through a self-assembly process, such as in the spontaneous formation of a conformationally biased, highly ordered metal complex. Indeed, we will present herein some impressive examples that capitalize on such 'supramolecular organization'.

Stereoselectivity in 1,2 and 1,3 asymmetric induction has often been maximized by using chelation control. This method has been very effective since relatively rigid five- and six-membered-ring chelate intermediates, respectively, are involved. It would seem eminently reasonable to extend this approach to 1,4 and 1,5 asymmetric induction, although that would require intrinsically less stable seven- and eight-membered-ring chelate intermediates, respectively. As such, 1,4 and 1,5 chelation control of this kind could mirror the synthesis of medium-size rings, with the expected attendant difficulties. Fortunately, the application of transition metals has proven to be advantageous, probably because of the availability of diverse coordination numbers and geometries at the metal center. The results described in this report will abundantly illustrate the critical role played by chelation control, especially with transition metals, in achieving high levels of remote stereocontrol with acyclic substrates.

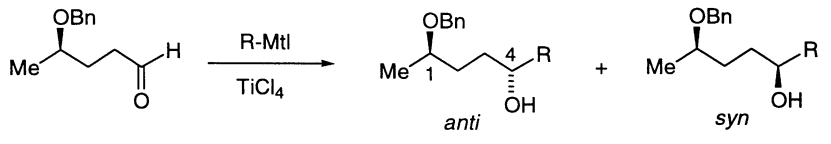
The approaches to remote acyclic stereocontrol can be loosely classified according to the mode of establishing the stereogenic centers (Fig. 2): (a) the 'coupling' of chiral synthons; (b) the 'removal' of stereogenic centers in the middle of a chiral pool with many linked chiral centers, so as to leave the stereogenic centers at the desired remote positions; (c) 'chirality transfer' of an easily introduced proximal stereogenic center to a remote position by sigmatropic rearrangement or stereospecific allylic S_N2' substitution reactions; (d) 'asymmetric synthesis' of remote stereogenic centers that is *independent* of existing stereogenic centers (e.g. regulated by a scalemic, chiral reagent); (e) 'relative asymmetric induction' by control of a remote position through 'stereo-communication' with pre-existing stereogenic centers, either in an in intramolecular or intermolecular mode; and (f) 'internal asymmetric induction' by introducing two (or more) chiral centers simultaneously during the coupling of two segments. In this report, we intend to emphasize the last two approaches, (e) and (f).

Currently, there are numerous examples of high 1,4, 1,5, 1,6, and 1,7 remote asymmetric induction with acyclic substrates. It is particularly promising for the field that positive results have been obtained for diverse synthetic transformations, such as aldol reactions, 1,4 conjugate additions, alkylations, carbonyl additions, epoxidations, cycloadditions, molecular rearrangements, and free radical reactions. The present review will offer a sampling of this body of knowledge, along with mechanistic highlights where pertinent, with a focus on reactions that have a stereochemical bias in excess of 4:1.

2. Intramolecular stereo-communication

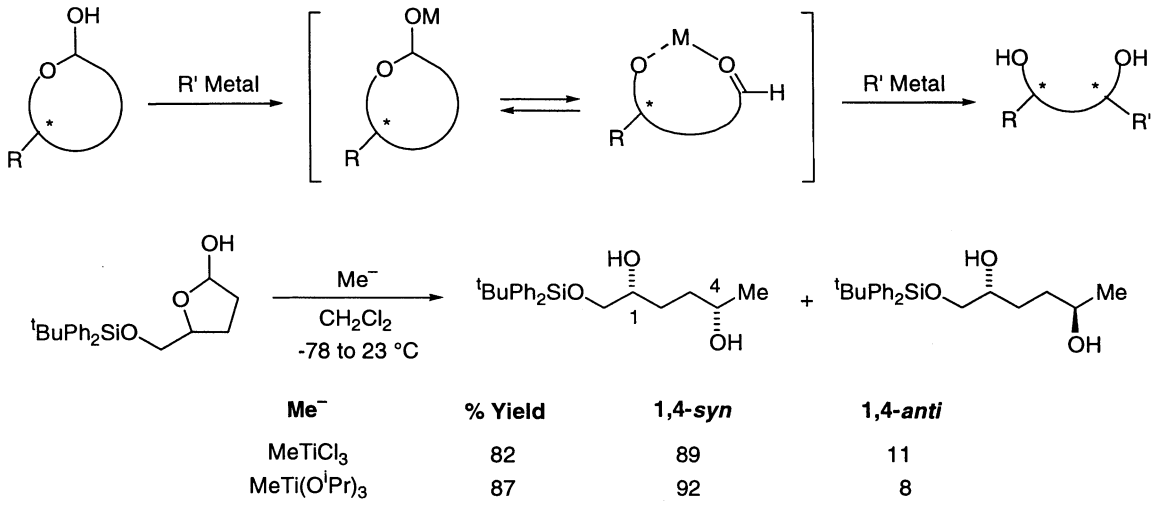
2.1. Addition of nucleophiles to aldehydes and ketones

2.1.1. Strictly acyclic substrates. Reetz and co-workers added MeTi(O-*i*-Pr)$_3$ to phthalaldehyde to obtain 1,4-diol products with a reasonable level of 1,4 asymmetric induction (Fig. 3).[10] It was suggested that titanium forms a seven-membered-ring chelate by coordinating with the alkoxy and



R-MtI	R	1,4-*anti*	1,4-*syn*
Me_2Zn	Me	85	15
CH_2=$CHCH_2SiMe_3$	-CH_2CH=CH_2	75	25
CH_2=$C(^tBu)OSiMe_3$	-$CH_2C(O)^tBu$	76	24

Figure 4.



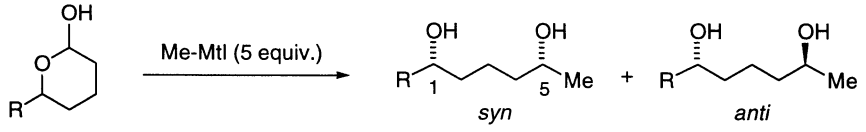
Me⁻	% Yield	1,4-*syn*	1,4-*anti*
$MeTiCl_3$	82	89	11
$MeTi(O^iPr)_3$	87	92	8

Figure 5.

carbonyl groups, as depicted in brackets. The second methyl would then add from the side opposite to the sterically demanding methyl group to favor the *anti* (DL) isomer. Importantly, this approach was extended to 1,4 asymmetric induction by chelation control with a strictly acyclic γ-alkoxy aldehyde to achieve good 1,4-*anti* stereocontrol (Fig. 4).[11] Attainment of this moderate level of stereoselectivity required development of a procedure involving addition of the nucleophilic reagent to a mixture of the γ-benzyloxy aldehyde and $TiCl_4$ at very low temperature (−95°C). Tsuchihashi and co-workers reported a related addition to a lactol cyclic precursor of a γ-alkoxy aldehyde, which resulted in relatively high 1,4-*syn* selectivity (Fig. 5).[12] Curiously, this selectivity contrasts with the *anti* selectivity in Reetz's γ-alkoxy aldehyde reaction. Additionally, Tsuchihashi's group applied this process with moderate success to the corresponding 1,5 remote asymmetric induction (Fig. 6). They proposed that *syn* selectivity predominates here because of peripheral attack on a seven- or eight-membered-ring chelate intermediate (Fig. 7).

Fujisawa et al. reported an interesting example of 1,4 asymmetric induction in organometallic addition to chiral thiomethyl ketones, where either diastereomer of the alcohol product could be obtained by use of the appropriate reagent (Fig. 8).[13] For example, MeLi principally attacked the carbonyl from the *si*-face, while Me_2Zn attacked from the *re*-face. These results might be explained by a difference in coordination ability, especially the coordination number, of the metal center: during addition, the organolithium would adopt a tetracoordinate tetrahedral structure, while the organozinc would adopt a hexacoordinate octahedral structure.

In general, it is difficult to achieve excellent 1,>3 stereocontrol in carbonyl reduction with acyclic substrates devoid



R	Me-MtI	Solvent	Temp.	% Yield	1,5-*syn*	1,5-*anti*
$(CH_2)_2Ph$	$MeTi(O^iPr)_3$	CH_2Cl_2	-78 to 23 °C	75	84	16
$(CH_2)_2Ph$	MeMgBr	THF	23 °C	70	82	18
Me	$MeTi(O^iPr)_3$	CH_2Cl_2	-78 to 23 °C	73	81	19

Figure 6.

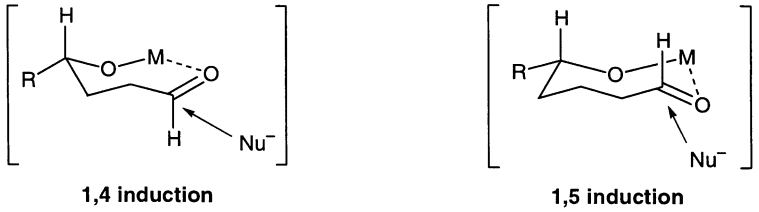
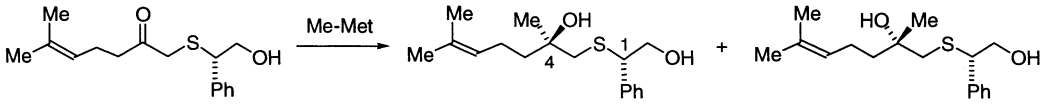


Figure 7.



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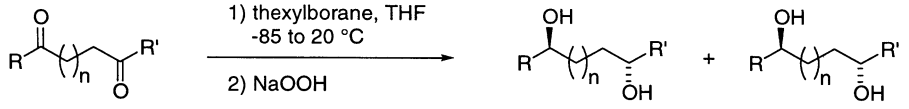


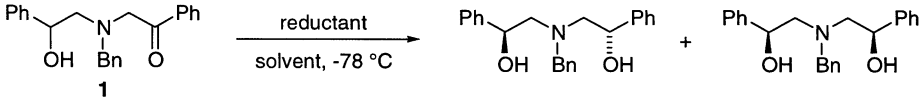
n	R	R'	% Yield	*anti*	*syn*
1	Ph	Ph	59	98	2
1	*i*-Pr	*i*-Pr	78	89	11
1	Me	Me	92	92	8
2	Me	Me	44	50	50

Figure 9.

of *pre-existing* cyclic, configurational, or conformational constraints within the 1,>3 sequence.[6c] A recent, in-depth review on acyclic stereocontrol in carbonyl reductions describes numerous examples of high 1,4 stereoselectivity, mostly for substrates with intervening sp^2 centers or rings in the 1,4 sequence.[6c] Such structural features can exert a strong conformational influence, which results in more favorable outcomes for intramolecular 1,>3 asymmetric induction. However, even with key biasing factors in place, there is a comparative scarcity of examples that illustrate 1,5 stereoselectivity or greater.[6c] This section will cover the few cases of intramolecular 1,>3 asymmetric induction for carbonyl reduction in strictly acyclic substrates.

Harada et al. obtained good *anti* stereocontrol in the double reduction of strictly acyclic 1,4-diketones with thexylborane; however, they could not extend this procedure to the corresponding 1,5 system (Fig. 9).[14] Presumably, after reduction of the first ketone group, the generated boronic ester would deliver hydride to the second ketone intramolecularly, similar to cyclic hydroboration (see Section 2.2.3).

High 1,5 and 1,6 diastereoselectivities in the reduction of acyclic hydroxy amino ketones to 1,5- and 1,6-diols were achieved by Maryanoff and co-workers (Figs. 10 and 11).[15] With (*R*)-alpine-hydride or $Zn(BH_4)_2$, they were able to reduce **1** with high 1,5-*anti* diastereoselectivity (Fig. 10).[15a–c] Analogously, (*R*)-alpine-hydride in CH_2Cl_2 reduced **2** to **3/4** with high 1,6-*anti* selectivity (92:8) in 83% yield (Fig. 11).[15b,c] They proposed a chelation-controlled mechanism involving external hydride addition to a bicyclic metal chelate, such as preferential hydride attack from the top face of **5** (Fig. 11). Subsequently, Maryanoff's group reported that **2** can be reduced



Reductant	Solvent	% Yield	*anti* (*dl*)	*syn* (*meso*)
(*R*)-Alpine-Hydride	THF	17	86	14
(*R*)-Alpine-Hydride	CH_2Cl_2	40	91	9
$Zn(BH_4)_2$	CH_2Cl_2	47	93	7
$LiBH_4$	CH_2Cl_2	-	83	17

Figure 10.

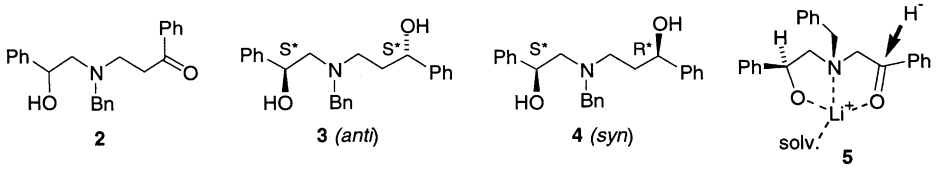


Figure 11.

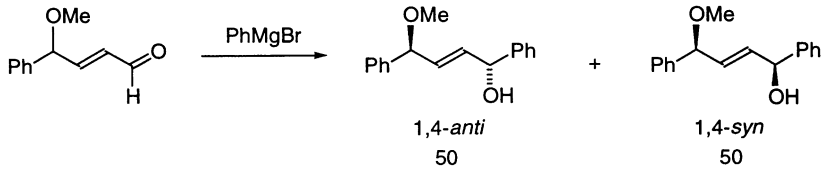
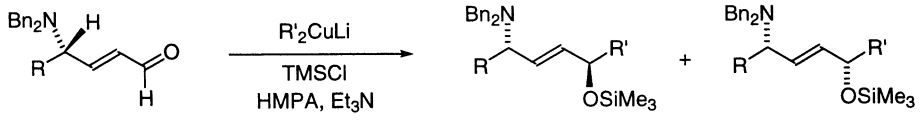


Figure 12.

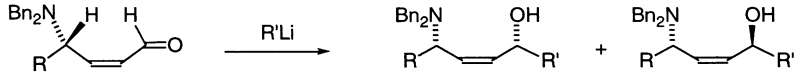


R	R'	% Yield	*anti*	*syn*
Me	Me	83	79	21
Me	Bu	81	82	18
Me_2CHCH_2	Me	77	86	14
Me_2CHCH_2	Bu	79	84	16
Me_2CH	Me	77	89	11

Figure 13.

preferentially to either the *anti* (**3**) or *syn* (**4**) diols with high 1,6 diastereoselectivity by sequential treatment with a Lewis acid and a borohydride reagent, the direction of stereocontrol depending on the Lewis acid complexant.[15d] For example, in the reduction of **2** they realized an amazing *anti*/*syn* ratio of >100:1 with Ti(O-*i*-Pr)$_4$ and K-Selectride, and a 12:88 *anti*/*syn* ratio with Al(OEt)$_3$ and K-Selectride. This reversal of stereochemistry could be associated with a change in coordination number and geometry for the different Lewis acids (e.g. hexacoordinate/octahedral vs tetracoordinate/tetrahedral). Additionally, the use of Al(OEt)$_3$ and K-Selectride enabled the reduction of **1** to diols with a remarkably high 1,5-*syn* diastereoselectivity (*anti*/*syn*=5:95).[15d] For these reactions, it is important to note that the substrate self-assembles by interacting with the metal (and the medium) into an ordered species, which brings the stereogenic element into the sphere of the reacting pro-stereogenic center.

The carbonyl substrates discussed thus far lack constraints



R	R'	% Yield	*syn*	*anti*
Me	Me	78	92	8
Me	CH_2CO_2Ph	67	95	5
Me_2CHCH_2	Bu	82	93	7
Me_2CHCH_2	CMe_2CO_2Me	69	95	5

Figure 14.

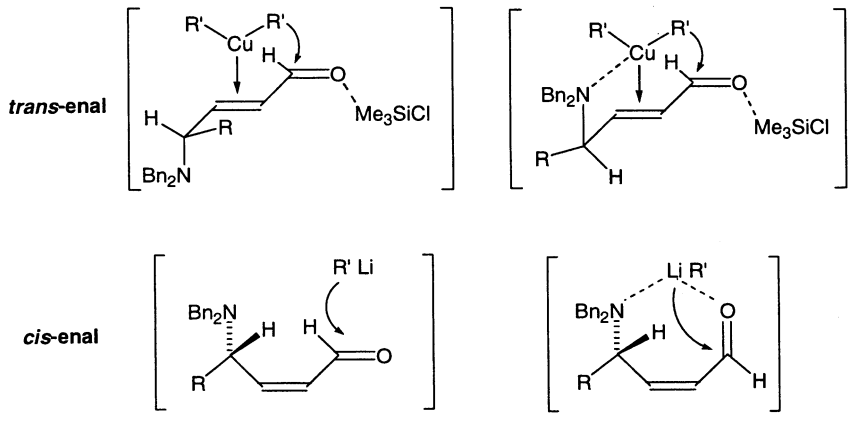
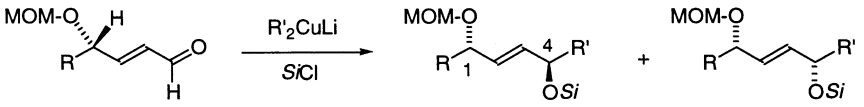


Figure 15.



R	R'	SiCl	% Yield	1,4-*anti*	1,4-*syn*
c-C_6H_{11}	Me	Me_3SiCl	64	78	22
c-C_6H_{11}	Ph	Me_3SiCl	56	75	25
t-Bu	Bu	Me_3SiCl	81	86	14
t-Bu	*t*-Bu	Me_3SiCl	86	40	60
t-Bu	*t*-Bu	*t*-BuMe_2SiCl	90	14	86

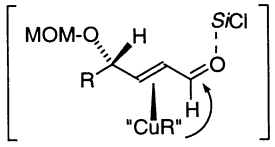
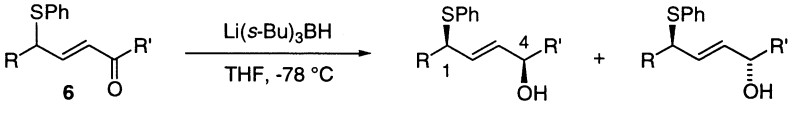


Figure 16.

due to the presence of sp^2 centers between the stereogenic and pro-stereogenic centers. The sp^2 centers of an alkene, a benzene ring, or an amide group, for instance, would introduce significant structural order into the substrate, possibly benefiting stereochemical control. Nevertheless, the reductions of (*E*)-PhC(O)CH=CHC(O)Ph with $LiAlH_4$ or $(i\text{-Bu})_2AlH$ and (*E*)-PhCH(OMe)CH=CHC(O)Ph with $Zn(BH_4)_2$ afforded little or no stereochemical bias in the products.[16] Fleming et al. also obtained poor selectivity for the addition of a Grignard reagent to a related γ-alkoxy enal (Fig. 12).[16] However, Reetz et al. later found that organocuprate reagents add to a (*S*)-*trans*-γ-amino enal with reasonably good 1,4-*anti* stereoselectivity (Fig. 13; TMS=Me_3Si).[17] Intriguingly, much better results were realized for the addition of organolithium reagents to the corresponding (*S*)-*cis*-γ-amino enal (Fig. 14),[16] even though different transition-state models were proposed for the copper- and lithium-based reactions (Fig. 15). On the other hand, Nakamura and co-workers found that organocuprate reagents, in the presence of Me_3SiCl or *t*-$BuMe_2SiCl$, add to an (*S*)-*trans*-γ-alkoxy enal with moderate 1,4-*anti* asymmetric induction (together with 1,2-carbonyl addition) (Fig. 16; MOM=methoxymethyl).[18] They proposed an acyclic transition state, as shown in brackets. Curiously, the sense of selectivity for this addition was reversed with *t*-Bu_2CuLi (Fig. 16).

Reaction of γ-thio-α,β-unsaturated ketone **6** with Li(*s*-$Bu)_3BH$ resulted almost exclusively in hydroxy sulfides with 1,4-*syn* stereochemistry (Fig. 17).[19] This outcome was rationalized by assuming that the nucleophile attacks from the opposite side of the electron-donating phenylthio group via a transition state in which the phenylthio group is oriented perpendicular to the plane of the enone due to a $\sigma-\pi^*$ interaction, and the enone moiety favors the *s-cis* conformation (as shown in brackets).

2.1.2. Substrates with pre-existing rings. The presence of cyclic structures in the substrate can introduce a significant amount of structural order and probably enhance stereochemical control significantly. Thus, systems in which the key stereogenic element is contained within a more-or-less



R	R'	% Yield	*syn*	*anti*
i-Bu	*t*-Bu	91	96	4
Me	*t*-Bu	82	95	5
t-Bu	*i*-Pr	82	94	6
n-C_7H_{15}	*n*-C_5H_{11}	71	93	7

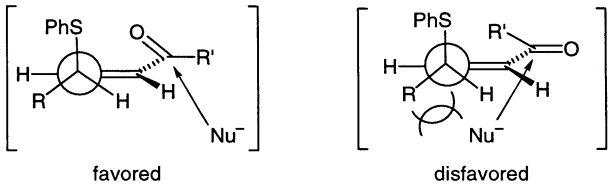
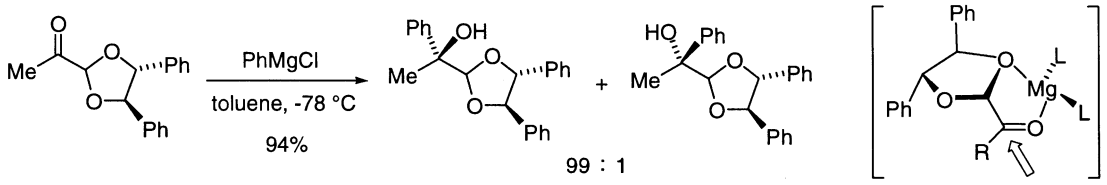


Figure 17.



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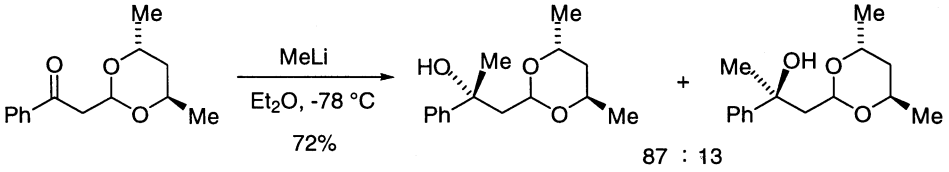


Figure 19.

rigid ring are being considered separately. Akhoon and Myles achieved excellent 1,4 asymmetric induction (≥99:1) in the addition of Grignard reagents to chiral α-keto acetals (Fig. 18).[20] A bicyclic magnesium chelate (shown in brackets) was proposed to be the key reactive species. The alternative chelate, in which magnesium is coordinated to the other dioxolane oxygen, from the same side of the five-membered ring, would be strongly destabilized by steric interactions with the *syn*-facial phenyl substituent. The very high stereocontrol then derives from *exo* addition to the bicyclic chelate shown. There are other examples of high 1,4 diastereocontrol (5:1 or better) for Grignard addition to substrates with this structural motif,[21] as well as examples of high 1,5 diastereocontrol for hydride addition to ketone homologues.[22] A reasonably good result for 1,5 stereoselectivity in organo-lithium addition has been reported (Fig. 19).[23]

Meyers and co-workers obtained moderate to high (up to 90:10) 1,6 asymmetric induction in the addition of Grignard reagents to an acetophenone group by using an intramolecular chiral oxazoline (Fig. 20).[24] This system also benefits from conformational bias from the benzene ring. They proposed a chelation-control model, as indicated in brackets. In a chemically related 1,6 case, phthalaldehyde monoprotected as a chiral 4,5-diphenylimidazolidine auxiliary reacted with lithium dibutylcuprate to give essentially one diastereomer (*S*); however, the corresponding organomanganese reagent afforded the opposite diastereomer (*R*) almost exclusively (Fig. 21).[25] Interestingly, lithium dibutylcuprate addition to a substrate monoprotected as a cyclohexane-fused imidazoline of the same absolute stereochemistry (i.e. by using *N*,*N*′-dimethyl-1,2-diaminocyclohexane) gave the opposite result (*S*/*R* ratio=10:90). This disparate outcome might be associated with certain chelation and conformational factors.[25]

Molander and Bobbitt obtained excellent 1,7 asymmetric induction in the reduction of chiral keto boronates in the preparation of enantiomerically enriched secondary alcohols bearing alkyl substituents that have little steric or electronic differentiation (Fig. 22; ee=enantiomeric excess).[26] They suggested a six-membered-ring transition state involving coordination of the carbonyl to the boron

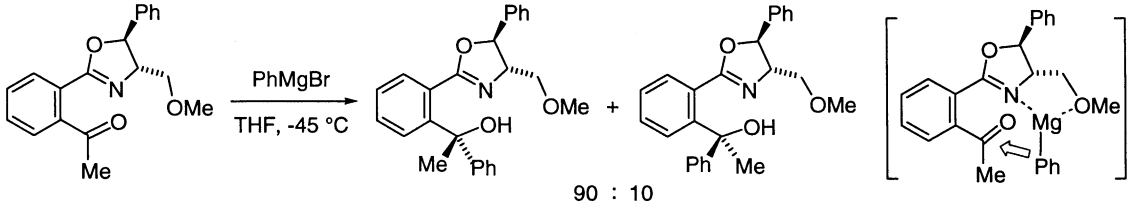


Figure 20.

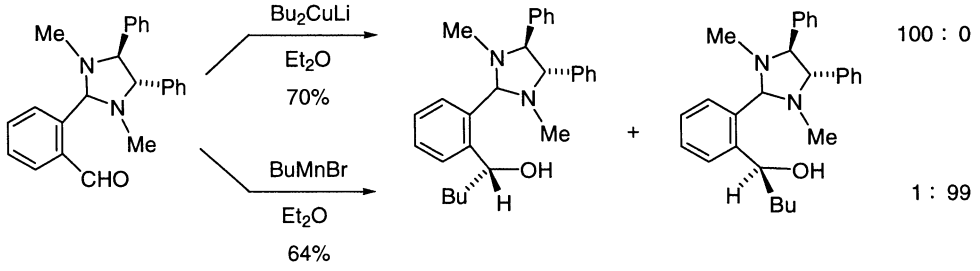


Figure 21.

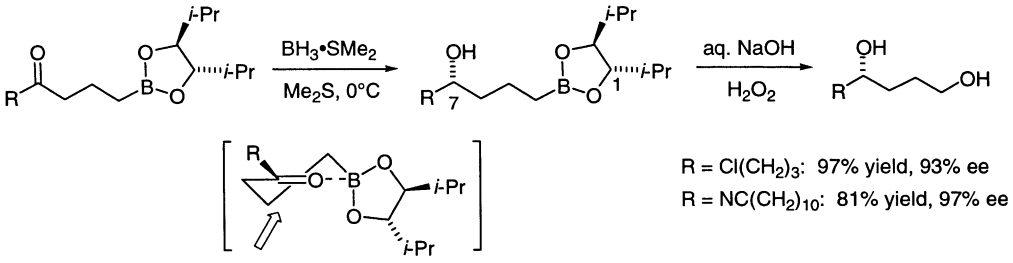


Figure 22.

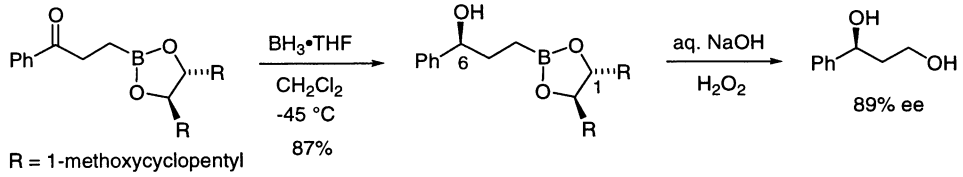


Figure 23.

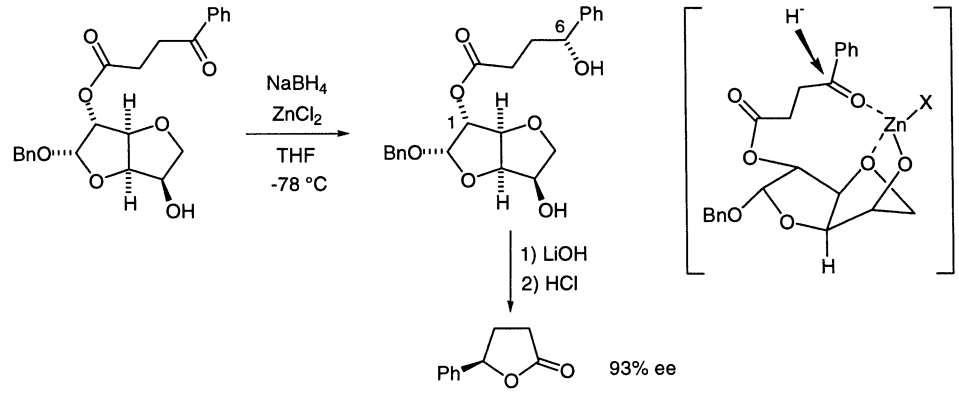


Figure 24.

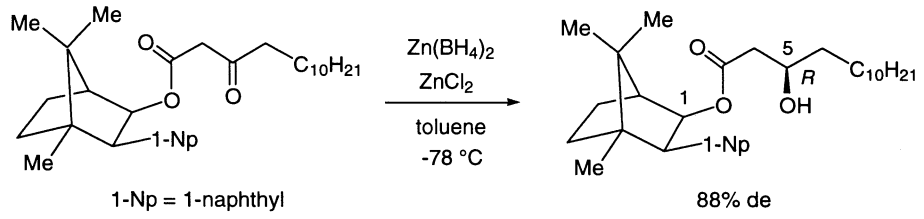


Figure 25.

center to establish a certain preferred conformation (shown in brackets) that strongly favors hydride attack from the direction of the arrow. With a related 1,3,2-dioxaborolidine system, Mears and Whiting obtained high 1,6 stereoselectivity (Fig. 23).[27] To achieve the favorable result shown, they had to employ borane-THF because borane-dimethyl sulfide gave only 55% ee. Whiting and co-workers found that reduction of the corresponding 1,3-dioxolane

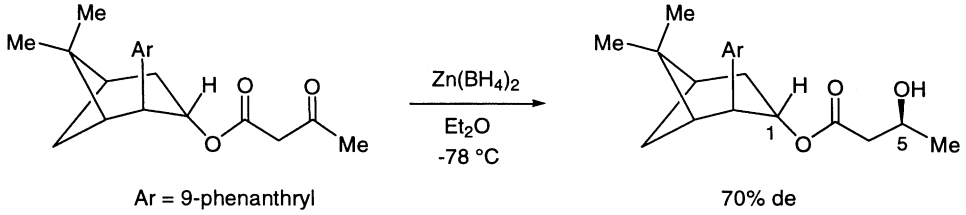


Figure 26.

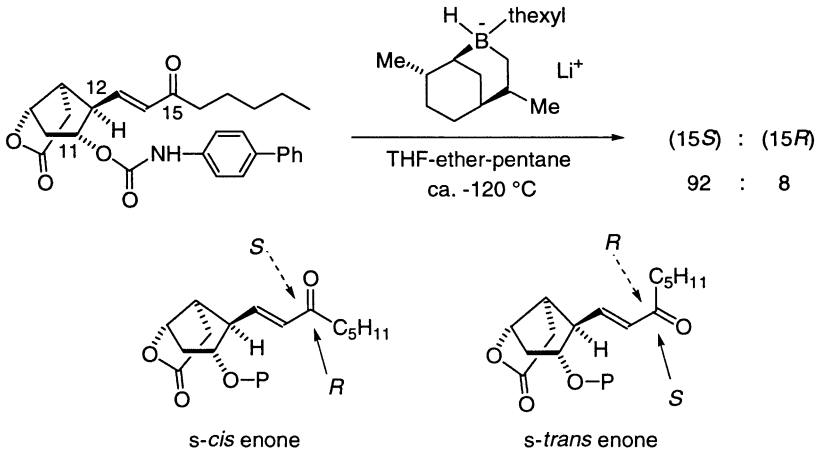
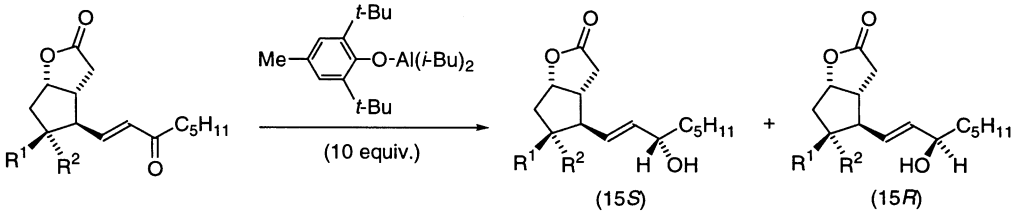


Figure 27.

substrate did not give any stereoselection, indicating that a cyclic boron-carbonyl complex is crucial for robust stereocontrol.[27b]

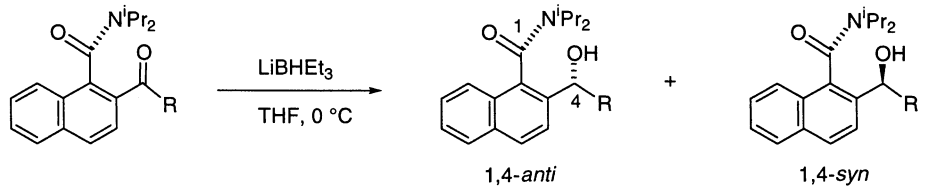
Keto esters derivatized with bulky, cyclic chiral auxiliaries have been reduced to hydroxy esters with high 1,5 and 1,6 asymmetric induction.[28–30] Nair and co-workers reported high 1,6 stereoselectivity in the reduction of a γ-keto ester of an anhydrofuranoside chiral auxiliary (Fig. 24).[28] A zinc chelate with a caged structure, such as that shown in brackets, may have been responsible for the stereochemical outcome. Bicyclic chiral auxiliaries have been used in a similar manner with β-keto esters to effect good 1,5 stereocontrol (Figs. 25 and 26; de=diastereomeric excess).[29,30]

Stereochemical control via remote asymmetric induction can be crucial in the synthesis of natural products, and a particularly relevant example is the stereoselective reduction of the ketone at the prostaglandin 15-position (Fig. 27). Effective control of this 1,4 stereoselective reduction depended on the conformation (*s-cis* vs *s-trans*) of the enone and the direction of attack of the reducing agent. Corey and co-workers achieved high 15*S* selectivity by choosing an appropriate protecting group for the hydroxyl



Enone	% Yield	(15*S*)	(15*R*)
R^1 = H, R^2 = OH	95	92	8
R^1 = OH, R^2 = H	94	85	15
R^1 = H, R^2 = OTHP	98	66	34
R^1 = OTHP, R^2 = H	92	79	21

Figure 28.



R =	Me	Et	*n*-C_5H_{11}	*i*-Pr	Ph
anti*:*syn =	93:7	93:7	98:2	92:8	99:1

Figure 29.

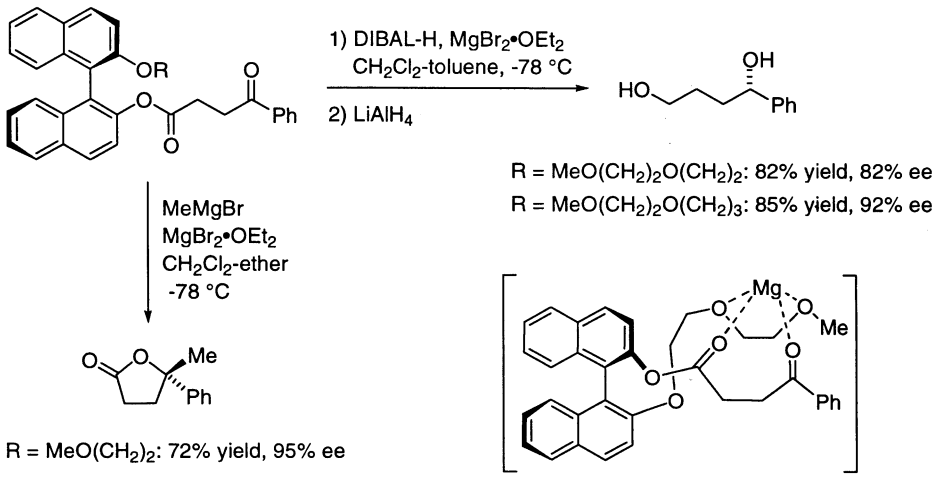


Figure 30.

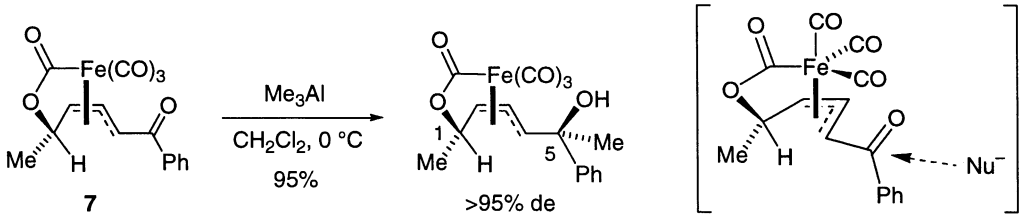
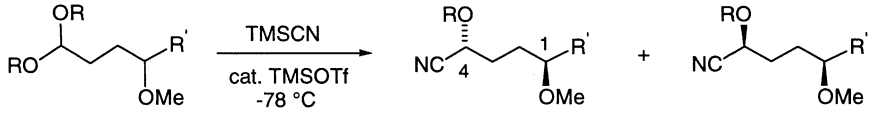


Figure 31.

at the 11-position, thereby biasing the conformation of the enone to *s-cis* and allowing the reduction to proceed preferentially from the β-face (Fig. 27).[31] On the other hand, Yamamoto and co-workers achieved high 15*S* selectivity without 11-hydroxyl protection by using a bulky aluminum-based reducing agent (Fig. 28; THP=2-tetrahydropyranyl).[32] In this case, the aluminum reagent was thought to play two roles, as a Meerwein–Pondorf–Verley reducing agent and a hydroxyl protecting group.

2.1.3. Substrates with axial chirality. Axial chirality from atropisomerism has been used to achieve remote asymmetric induction. Reduction of a 2-acyl-1-naphthoic amide with $LiBHEt_3$ proceeded with high 1,4-*anti* selectivity (Fig. 29).[33] The excellent stereochemical bias can be explained by a transition state similar to the ground state conformation, with the reducing agent attacking the ketone carbonyl from the opposite side of the bulky amide group (Fig. 29).

Tamai and co-workers reported high 1,7 asymmetric induction for the addition of hydride and Grignard reagents to γ-keto esters of binaphthalene diols bearing an oligoether group (Fig. 30).[34] Reduction of two keto ester variants with *i*-Bu_2AlH in the presence of excess $MgBr_2$·OEt_2 yielded,



R	R'	% Yield	1,4-*anti*	1,4-*syn*
i-Pr	Bu	95	83	17
i-Pr	*t*-Bu	95	86	14
i-Pr	*i*-Pr	97	94	6
i-Pr	C_6H_{11}	100	91	9
Bn	*i*-Pr	94	89	11

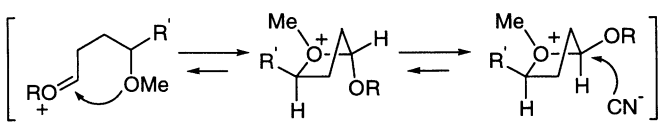
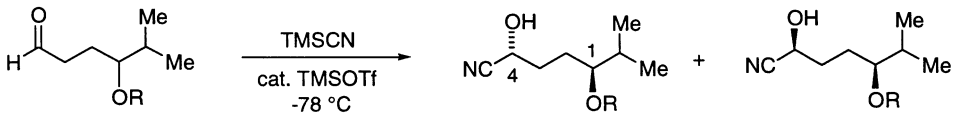


Figure 32.



R	% Yield	1,4-*anti*	1,4-*syn*
Ac	80	50	50
t-BuMe$_2$Si	80	50	50
H$_2$C=CHCH$_2$	70	88	12
Bn	50	88	12
Me	92	91	9

Figure 33.

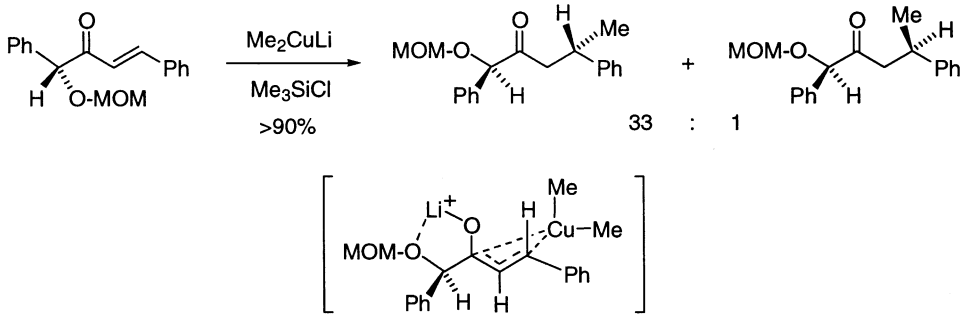


Figure 34.

after further reduction of the resulting hydroxy esters, 1,4-diols with 82 and 92% ee. Additionally, treatment of the keto esters with Grignard reagents gave butyrolactones with up to 99% ee. A transition state involving a pseudo-macrocyclic magnesium complex was proposed, as shown in brackets (Fig. 30). In a similar manner, 1,8 to 1,12 asymmetric induction was achieved in the addition of Grignard reagents to ω-keto esters.[35]

A high level of 1,5 asymmetric induction occurred in the addition of organoaluminum reagents to the keto group in iron tricarbonyl complex **7** (Fig. 31).[36] However, this is not a rigorous example of 1,5 stereocontrol because the η^3-allyl iron complex defines a more proximal stereogenic element.

2.1.4. Neighboring group participation. Molander and Haar realized high 1,4 asymmetric induction in the cyanation of a γ-alkoxy acetal or a γ-alkoxy aldehyde by a process involving neighboring group participation of the ether oxygen in an oxonium intermediate (Figs. 32 and 33, respectively; TMS=Me$_3$Si).[37] Interestingly, although high selectivities were obtained when using a methyl or benzyl protecting group, rather low selectivities were obtained when using a silyl or acetyl protecting group, suggesting that the neighboring group is indispensable for this remote asymmetric induction.

2.2. Reactions of alkenes

2.2.1. Addition of nucleophiles. Corey et al. reported very high 1,4-*anti* asymmetric induction (13:1–33:1) in the conjugate addition of methyl cuprates to acyclic α,β-enones

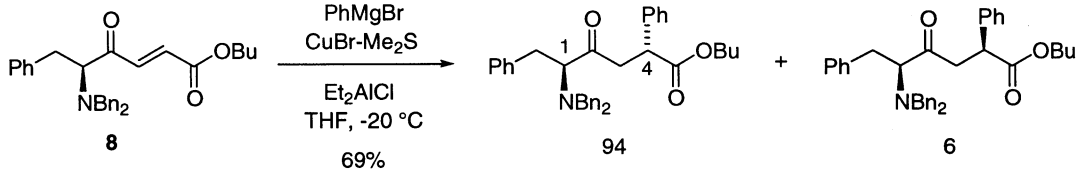


Figure 35.

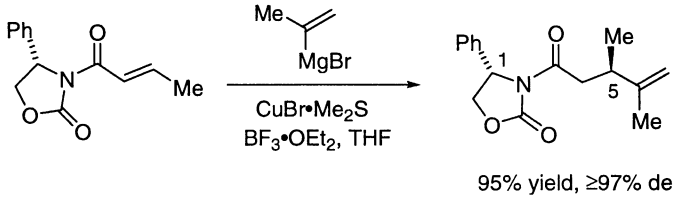


Figure 36.

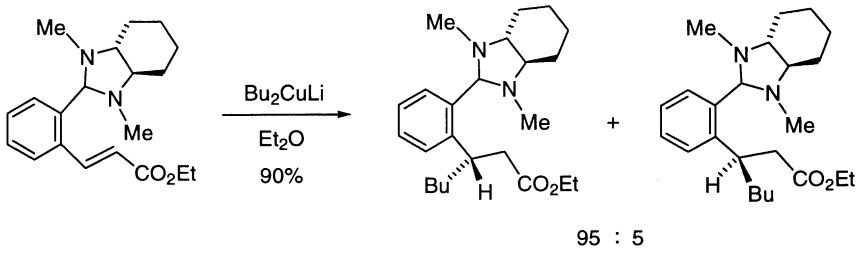


Figure 37.

containing a chiral group α to the carbonyl (Fig. 34).[38] Their results could be explained by formation of an intermediate in which the enone is activated by bidentate coordination of the α′-alkoxy carbonyl subunit to lithium ion and d,π*-complexation of the π-allyl type with Me_2Cu would occur selectively at one face of the π-system because of steric screening by the phenyl substituent on the five-membered chelate ring (shown in brackets). Similarly, an amino group facilitated 1,4-*anti* asymmetric induction in an enone conjugate addition by reaction of higher-order organocopper reagents with 3-ketoacrylate **8** (Fig. 35).[39]

The conjugate addition of reagents to α,β-unsaturated *N*-acyloxazolidinones resulted in excellent 1,5 stereocontrol (Fig. 36).[40] Interestingly, diastereofacial selectivity was reversed for 4-phenyl and 4-benzyl substitution on the oxazolidinone ring (same configuration). Alkenylcopper reagents demonstrated superior 1,5-*anti* stereoselectivity in addition to the 4-phenyloazolidinone auxiliary. High 1,5 stereocontrol was also obtained in the conjugate addition of alkyl copper·BF_3 reagents to enoates containing chiral method or camphor auxiliaries.[41]

Conjugate addition of various organocuprates to a cinnamate system occurred with high 1,6 diastereoselectivity, as illustrated for lithium dibutylcuprate in Fig. 37.[42] Related oxazolidine substrates derived from ephedrine or pseudoephedrine were able to deliver high 1,4 stereocontrol (presence of a new stereogenic center) for this type of reaction, but the levels of diastereoselectivity were less consistent.

η^4-Diene iron tricarbonyl complex **9** afforded 1,6 asymmetric induction in the conjugate addition of a vinyl Grignard reagent (Fig. 38), as part of a formal total synthesis of ikarugamycin.[43] The bulky $Fe(CO)_3$ group, which represents an axial stereogenic element, is principally responsible for the virtually exclusive α-face addition of the vinyl group, with the magnesio alkoxide group playing a minimal role as a stereodeterminant.

High levels of 1,5 remote stereocontrol have been achieved in the 1,4-addition of carbon nucleophiles to the carbon–carbon double bond of chiral ethylene acetals, in a type of S_N2' reaction.[44] Yamamoto's group found that trialkylaluminum reagents would add to α,β-unsaturated aldehyde tartramide acetals to give (*E*)-vinyl ethers with excellent diastereoselectivity (Fig. 39).[44a] Intriguingly, a strong

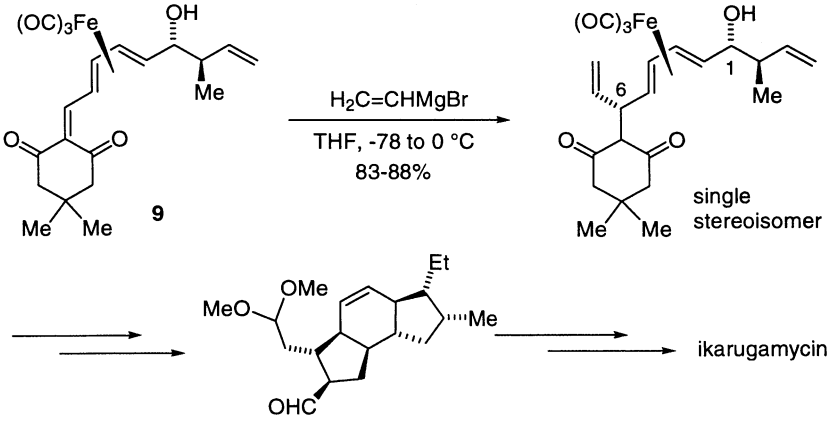


Figure 38.

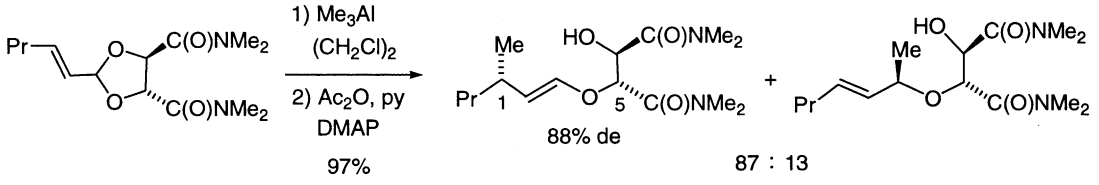


Figure 39.

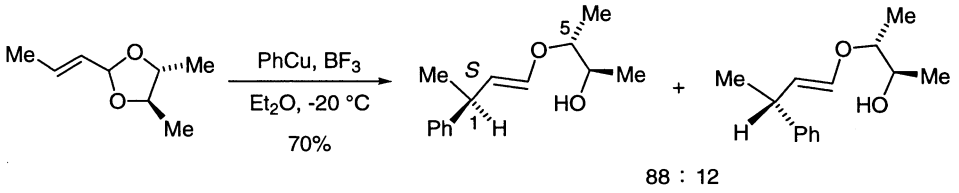


Figure 40.

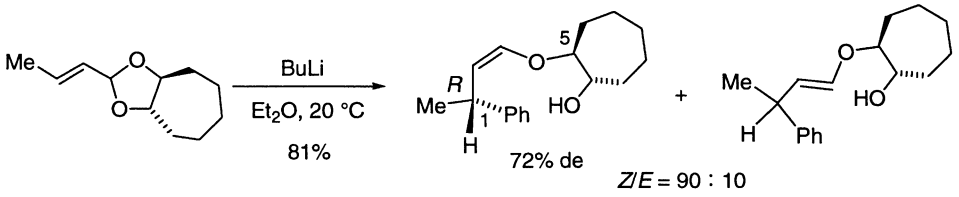


Figure 41.

preference for the 1,2-adduct was observed with chloroform as the solvent. The Lewis acid-catalyzed addition of organocopper reagents to such allylic substrates resulted in exclusive 1,4-addition with *E* alkene geometry, and good diastereoselectivities (Fig. 40).[44b–d] Alexis et al. also realized favorable results for the addition of organolithium reagents to analogous ethylene acetals (Fig. 41).[44e] In an exciting extension of the organocopper reaction, it was found that phenylcopper/BF_3·Et_2O can undergo 1,6-addition to chiral diene acetals with respectable 1,7 stereocontrol (Fig. 42),[44d] although the stereochemistry of addition for this S_N2'' reaction (*syn*) is opposite to that for the related S_N2' reaction (*anti*) (e.g. Fig. 40).[44d]

2.2.2. Epoxidation and cyclopropanation. Excellent remote asymmetric induction has been obtained in alkene electrophilic addition reactions, such as epoxidation, cyclopropanation and hydroboration (discussed in Section 2.2.3), via some form of *cyclic* transition state. Kishi and co-workers reported high 1,4-*anti* asymmetric induction in the epoxidation of bishomoallylic alcohols with $VO(acac)_2$ and *t*-BuOOH (TBHP), followed by cyclization to produce tetrahydrofurans (Fig. 43).[45] They proposed cyclic transition states in which the zig-zag conformation in the ground state of the substrate is reflected, and explained the stereoselectivity by the presence of steric repulsion between the ethyl group and the substituent R^3 (Fig. 44). Later, Wuts et al. studied a similar epoxidation reaction and proposed a boat-like transition-state model (Figs. 43 and 44).[46]

Shirahama and co-workers[47] and Hanessian et al.[48] independently produced 2,5-*cis*-tetrahydrofuran rings stereo-

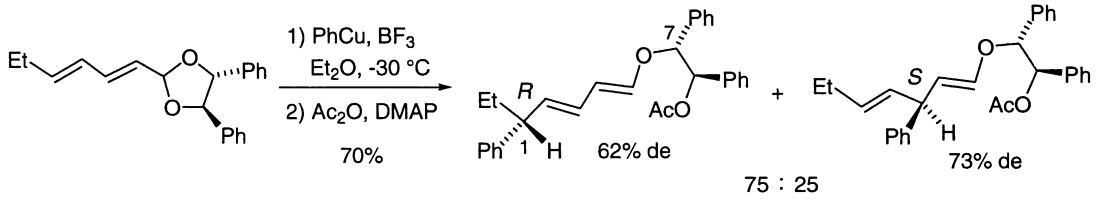


Figure 42.

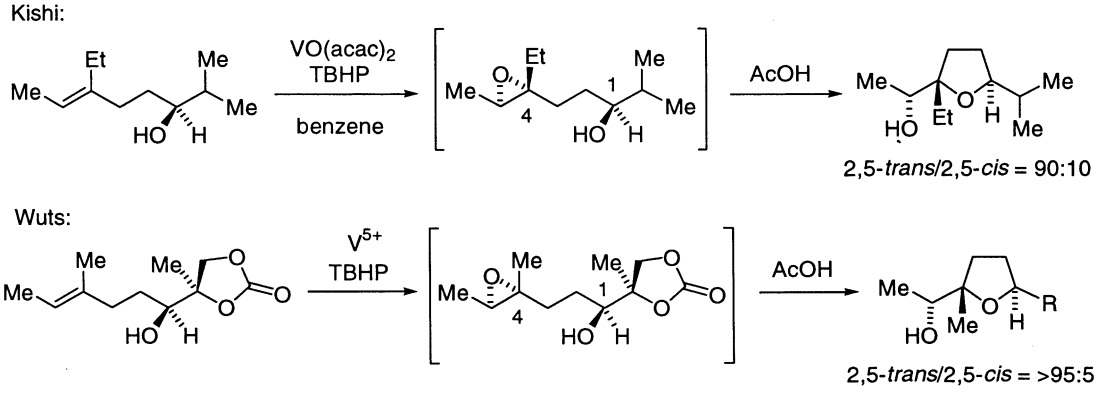


Figure 43.

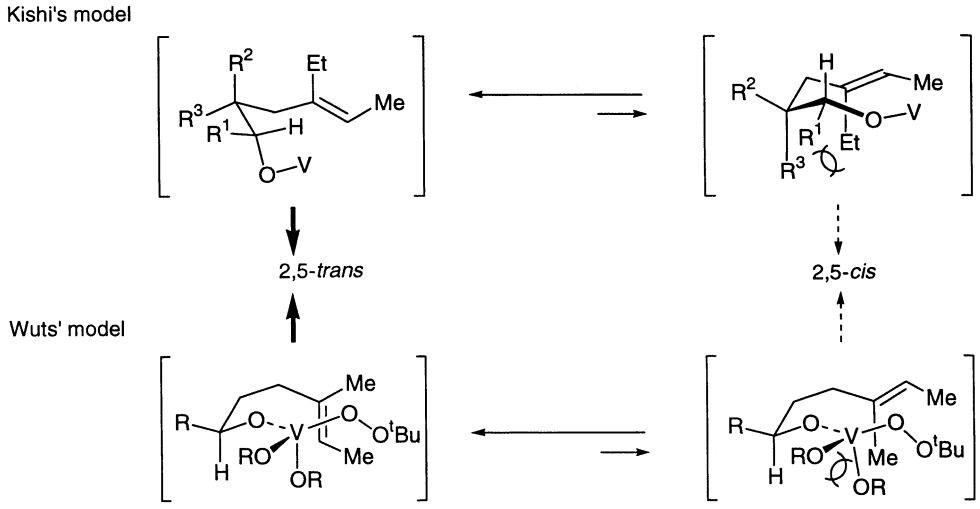


Figure 44.

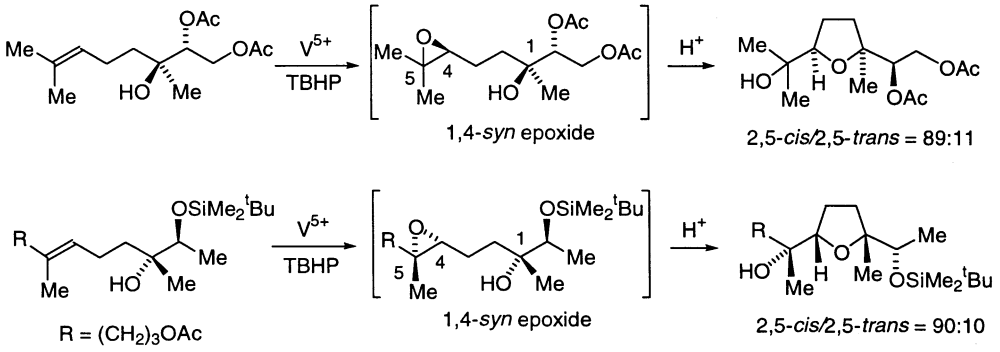
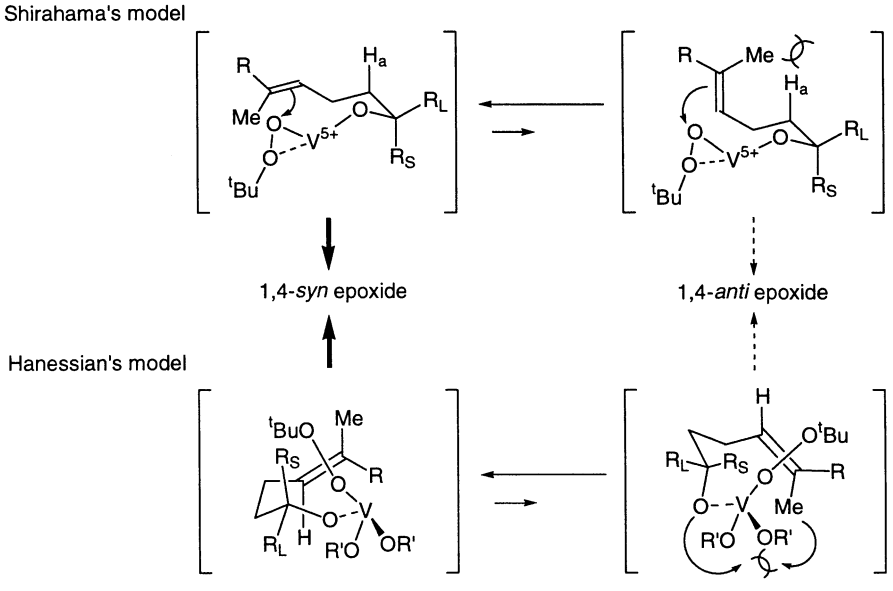


Figure 45.

selectively via 1,4-*syn* epoxides, in the epoxidation-cyclization of *trans*-bishomoallylic alcohols containing a methyl group at the 5-position (Fig. 45). This 1,4-*syn* selectivity is in sharp contrast to the above-mentioned 1,4-*anti* examples. Although they proposed different transition state models, both groups explained the high *syn* selectivity on the basis of steric repulsion from the methyl group at the 5-position (Fig. 46). Corey's total synthesis of venustatriol involved a



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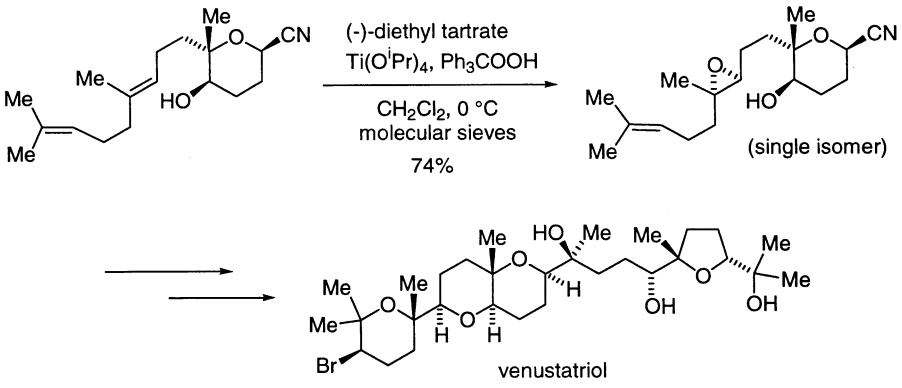


Figure 47.

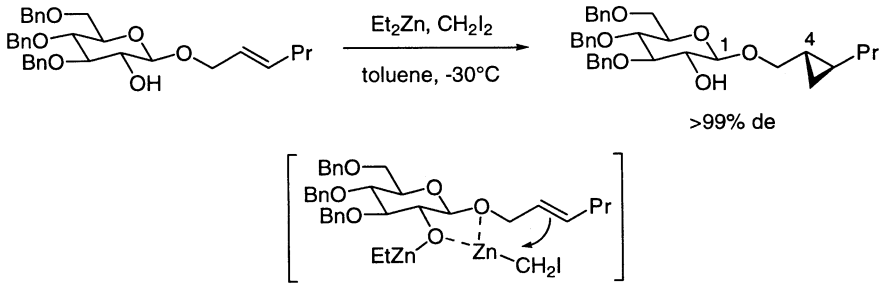


Figure 48.

key, highly stereoselective epoxidation of a trishomoallylic alcohol by using the conditions of the enantioselective Katsuki–Sharpless epoxidation (Fig. 47).[49] However, to realize success the epoxidation had to be conducted with trityl hydroperoxide, rather than *tert*-butyl hydroperoxide, and with carefully selected conditions.

Good results for 1,4 stereocontrol have been obtained in the asymmetric cyclopropanation of allylic ethers through the use of a variety of chiral auxiliaries.[50] Carbohydrate-based chiral auxiliaries have proven to be particularly advantageous.[50] For example, treatment of a glucose-based allylic ether with diethylzinc (10 equiv.) and diiodomethane afforded the corresponding cyclopropane with >99% diastereoselectivity (Fig. 48).[51] A cyclic zinc-chelated transition state, as shown in brackets, was proposed.

Tartrate-based chiral auxiliaries have also been useful in asymmetric cyclopropanation.[49,52] For example, cyclopropanation of the α,β-unsaturated acetals derived from a

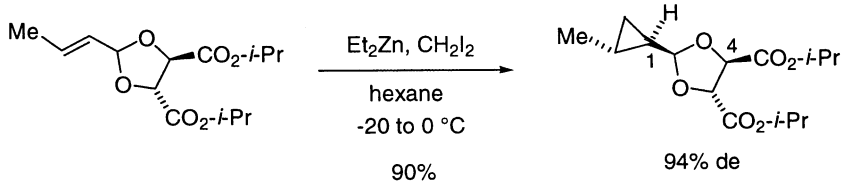


Figure 49.

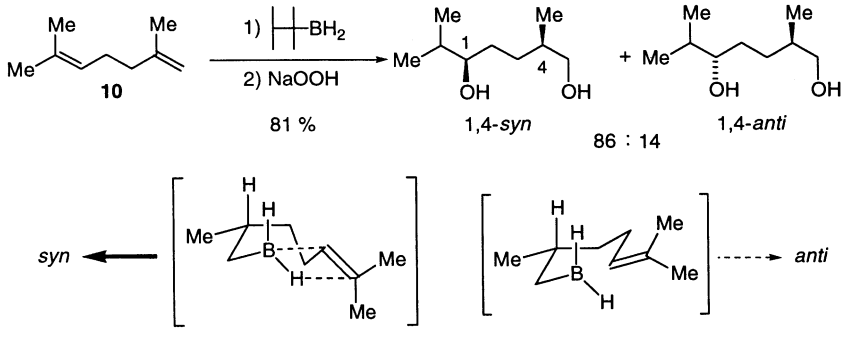


Figure 50.

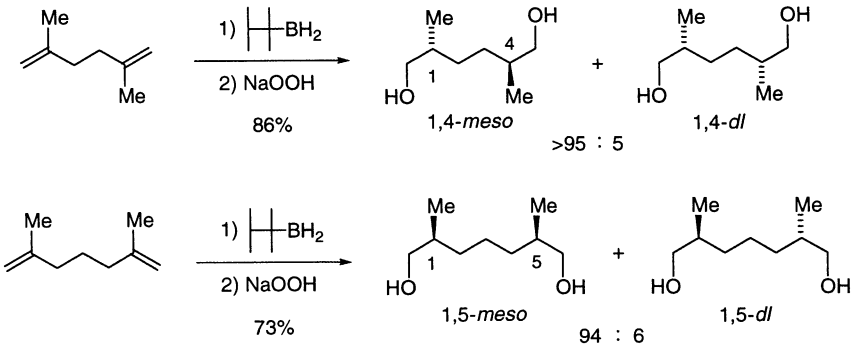
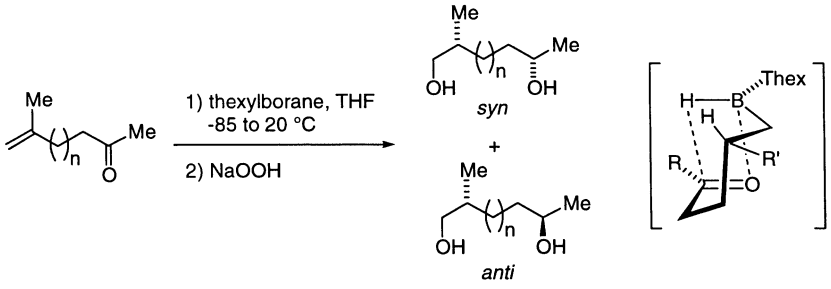


Figure 51.

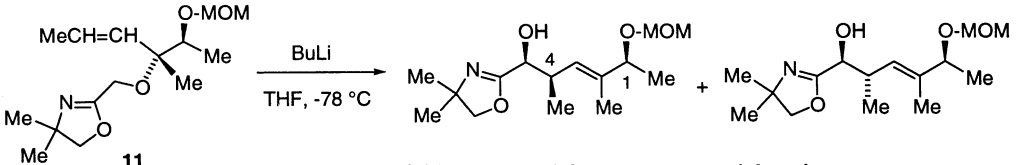


n = 1: *syn*/*anti* = 94:6 (84%); n = 2: *syn*/*anti* = 87:13 (86%); n = 3: *syn*/*anti* = 55:45

Figure 52.

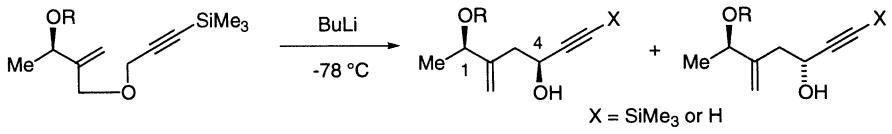
chiral dialkyl tartrate with Et_2Zn/CH_2I_2 gave cyclopropanes with high 1,4 diastereoselectivity (85–94% de) (e.g. Fig. 49).[52a]

2.2.3. Cyclic hydroboration. The cyclic hydroboration developed by Still and Darst is one of milestones in remote asymmetric induction (Figs. 50 and 51).[53] For example, 1,5-diene **10** was converted to a predominance of the *syn* 1,4-diol (Fig. 50). This reaction proceeds by virtually exclusive hydroboration of the terminal alkene in **10** followed by loss of the thexyl group to generate an intermediate RBH_2 species (shown), which undergoes cyclic hydroboration via the expected four-centered transition state. The preferred *syn* pathway, which involves a boat-like conformation in the transition-state structure, is less strained. High 1,4 and 1,5 asymmetric induction was also achieved with other dienes (e.g. Fig. 51), and in these cases the thexyl group was retained in the cyclic hydroboration.[53] This methodology provided straightforward access to a vitamin E side chain. In related chemistry, thexylborane was used to effect the hydroboration-reduction of keto alkenes, which yielded good *syn* stereocontrol for 1,4 and 1,5 positions,



	% Yield	1,4-*syn*	1,4-*anti*
E-**11**	87	99	1
Z-**11**	91	>1	>99

Figure 53.



R	Solvent	% Yield	1,4-*syn*	1,4-*anti*
Si^iPr_3	THF	88	85	15
Li	THF-DMPU	86	11	89

Figure 54.

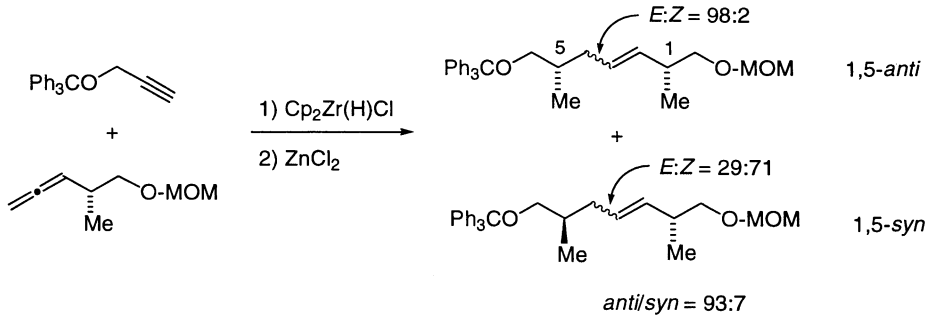
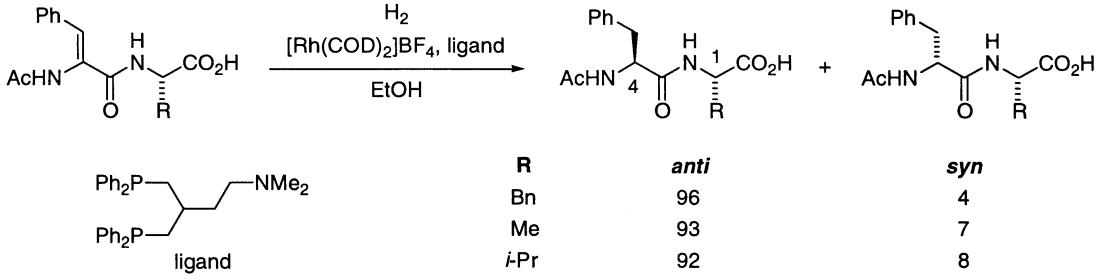


Figure 55.



R	*anti*	*syn*
Bn	96	4
Me	93	7
i-Pr	92	8

Figure 56.

but not for 1,6 positions (Fig. 52).[14] Since borane-THF gave relatively poor stereocontrol, Harada et al. proposed an intramolecular mechanism involving a transition state with a boat-like conformation (Fig. 52, shown in brackets). This method was extended to the double reduction of 1,4-diketones, which resulted in good *anti* stereocontrol. (Fig. 9; see Section 2.1.1).[14]

2.2.4. Sigmatropy. The transfer of chirality from a hydroxyl-bearing center of an allylic alcohol, constructed perhaps by a Cram-style carbonyl addition, an aldol reaction, or a [2,3]-Wittig sigmatropic rearrangement, can be effected by a [3,3]-sigmatropic rearrangement. This process can be used for 1,4 remote asymmetric induction via sequential 1,2 asymmetric induction and sigmatropic O→C chirality transfer. The [2,3]-Wittig rearrangement would thus afford 1,4 or 1,5 stereochemical control. For example, in the rearrangement of tertiary allylic ethers, (*E*)- and (*Z*)-ethers **11** afforded exclusively 1,4-*syn* and 1,4-*anti* isomers, respectively (Fig. 53).[54] Without the olefinic methyl group, a reasonably high level of 1,4 remote asymmetric induction via [2,3]-Wittig rearrangement was obtained, either *syn* or *anti*, by having the proper combination of alkoxy group and solvent (Fig. 54; DMPU=*N*,*N*′-dimethylpropylene urea).[55]

A zinc-mediated Claisen rearrangement[56] can be effective for 1,5 remote stereocontrol between methyl groups, which

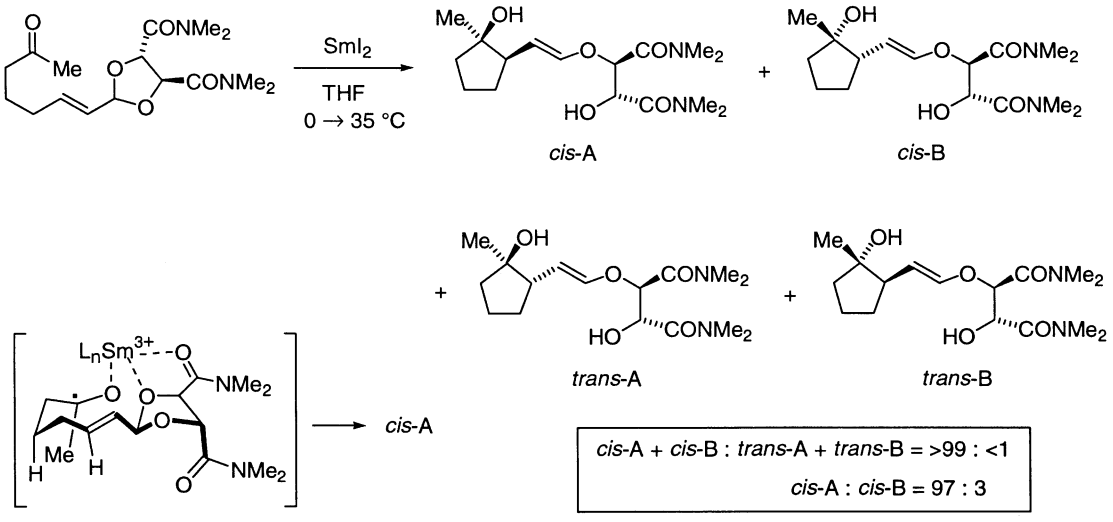


Figure 57.

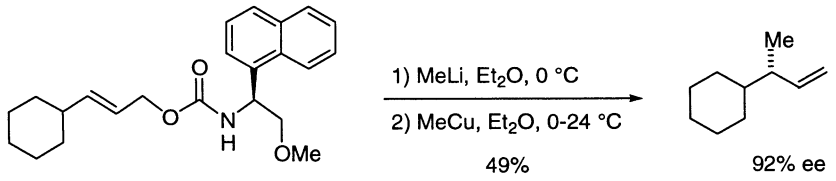


Figure 58.

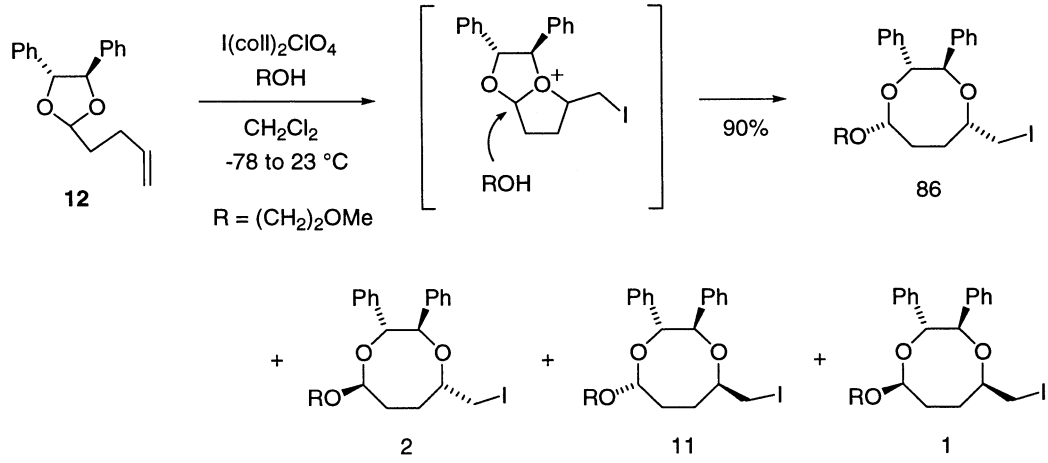
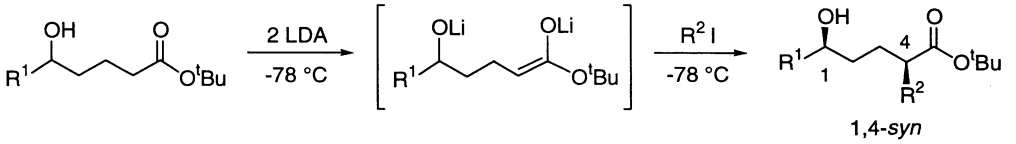


Figure 59.

is important *inter alia* for synthesis of the vitamin E side chain (Fig. 55; MOM=methoxymethyl, Cp=η^5-cyclopentadienyl).[57]

2.2.5. Other reactions. In rhodium-catalyzed homogeneous hydrogenation, an efficient level of 1,4 asymmetric induction was realized through a reliance on electronic interactions between the ligand and dehydrodipeptide substrate (Fig. 56).[58]

Molander et al. obtained high levels of remote asymmetric induction in a radical addition reaction, guided by a chelating metal (Fig. 57).[59] The SmI_2-promoted ketyl-olefin cyclization of tartramide-derived keto allylic acetals proceeded with good stereocontrol at both new stereocenters (1,5 and 1,6). Asymmetric induction may arise from a highly ordered, tridentate transition structure in which the ketyl oxygen, an ether oxygen, and one of the amide carbonyl groups are bound to the samarium atom (shown in brackets).



R^1	R^2	Solvent	1,4-*syn*	1,4-*anti*
Me	Me	THF	56	44
Me	Me	THF-HMPA	86	14
Bu	Bu	THF	52	48
Bu	Bu	THF-HMPA	88	12

Figure 60.

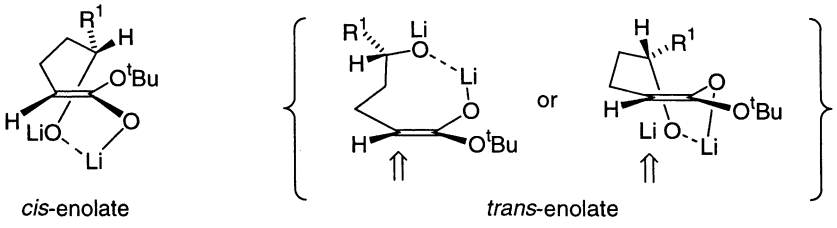
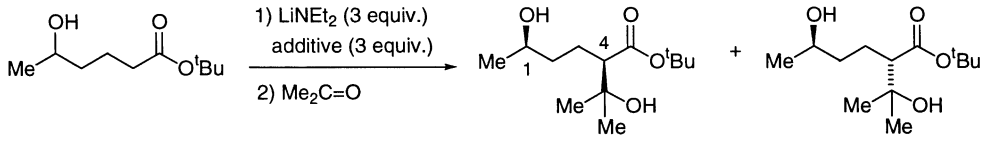


Figure 61.



Additive	% Yield	1,4-*syn*	1,4-*anti*
none	53	86	14
LiI	79	88	12
LiOTf	92	91	9

Figure 62.

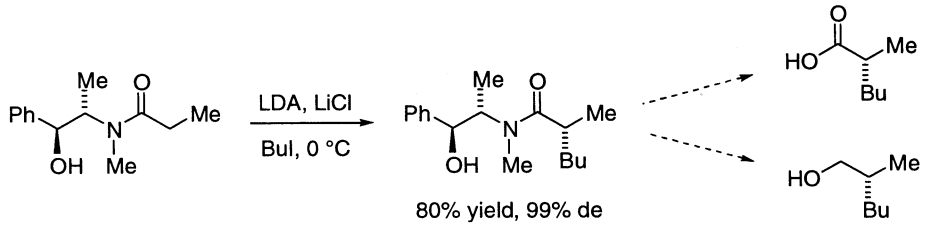


Figure 63.

A high level of 1,7 asymmetric induction (up to 95%) was reported by Denmark and Marble in the S_N2' displacement of chiral carbamates derived from an achiral allylic alcohol with copper reagents (Fig. 58).[60] In this reaction the chiral auxiliary is expected to be coordinated to the metal in the transition state for alkene addition, but it then departs as a nucleofuge.

A nice route to chiral 1,4-diols involved remote asymmetric induction by neighboring group participation during electrophilic addition to a terminal alkene (Fig. 59; coll=2,4,6-collidine).[61] During iodonium ion addition to ene acetal **12**, an acetal oxygen atom participates to form a intermediate oxonium species, which is cleaved by the alcohol to yield a series of 1,4-dioxacines highly enriched in one of four possible products. In a sense, this example is not truly representative of acyclic stereocontrol because of the covalent dioxabicyclo[3.3.0]octane intermediate.

2.3. Alkylation of carbanions and carbon radicals

Narasaka and co-workers achieved high 1,4 stereocontrol in the alkylation of enolates generated from δ-hydroxy esters, based on chelation control of the enolate nucleophile (Fig. 60).[62] High *syn* selectivities resulted by changing the solvent from THF to THF-HMPA (HMPA=hexamethylphosphoric

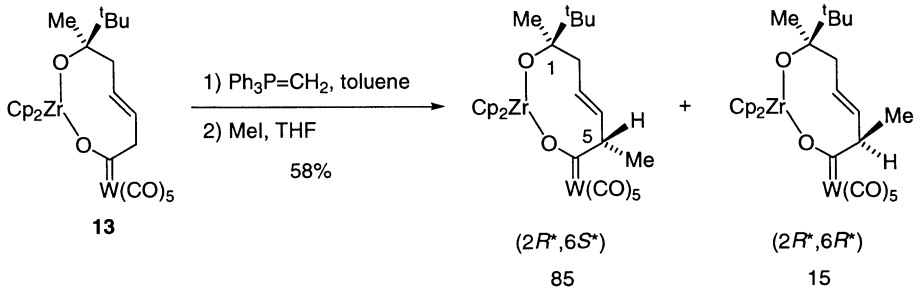


Figure 64.

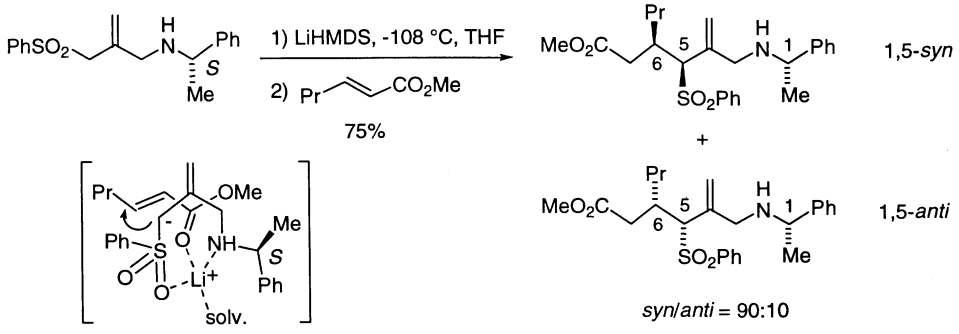


Figure 65.

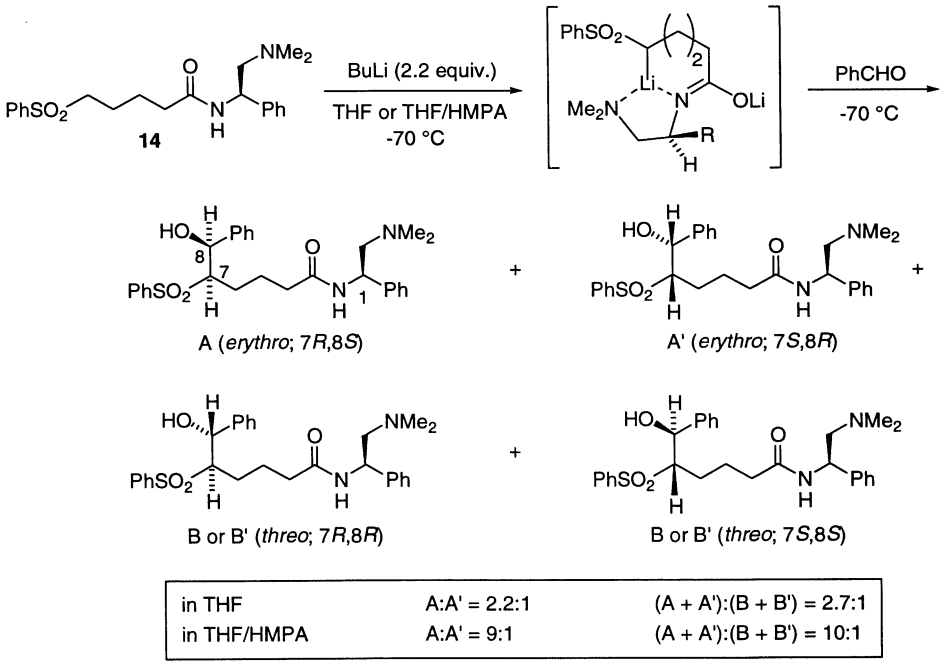


Figure 66.

triamide), presumably reflecting a biasing of the enolate geometry. It was proposed that the *cis*-enolate forms mainly in THF and that it cannot adopt an eight-membered-ring chelate structure for steric reasons, whereas the *trans*-enolate forms mainly in THF-HMPA and it can adopt an eight-membered-ring chelate structure (Fig. 61). This kind of 1,4 asymmetric induction methodology is effective in aldol reactions, as well, although the addition of a lithium salt is needed then to attain high selectivities and yields (Fig. 62).

Pseudoephedrine has been successfully employed to direct 1,4 or 1,5 diastereoselective alkylations and aminations.[63] For example, Myers and co-workers developed an efficient synthesis of highly enantiomerically enriched carboxylic acids, alcohols, aldehydes, and ketones by means of 1,4 diastereoselective alkylation of pseudoephedrine amides in the presence of lithium chloride (e.g. Fig. 63).[63a] An improved procedure for preparing highly enantiomerically enriched α-amino acids involves the direct alkylation of pseudoephedrine glycinamide hydrate.[63b]

Interestingly, the coupling of $W(CO)_6$, butadiene, and pinacolone on a Cp_2Zr template provided a nine-membered-ring chelate **13**, containing a *trans* double bond (Fig. 64; Cp=η^5-cyclopentadienyl).[64] This cyclic zirconium species served as an unusual substrate for 1,5 remote asymmetric induction via the deprotonation and alkylation sequence shown.

Carbanions derived from allylic sulfones containing a chiral amine underwent Michael addition with conjugated esters to give aminosulfones with good 1,5 diastereoselectivity in favor of the 1,5-*syn* isomer (Fig. 65; HMDS=hexamethyldisilazide).[65] The relative stereochemistry at the vicinal carbons (positions 5 and 6) was *syn* in both products. The stereochemical preference in this reaction can be rationalized by a Li-chelate transition-state model (shown in brackets).

The alkylation of α-lithio sulfones containing a co-metalated chiral group was taken to a remarkable level by Magnus and co-workers, who were able to convey molecular asymmetry over very remote distances.[66] An example of their interesting studies on sulfonyl carbanions is the reaction of **14** with benzaldehyde (Fig. 66).[66a] The lithiated species of **14** (in brackets) combined with benzaldehyde in THF/HMPA to give a preponderance of *anti* alkylation at position 7 (A/A′=9:1), as well as a strong preference for the vicinal hydroxyl at position 8 to be *erythro* (*syn*) to position 7 (A+A′/B+B′=10:1). This 1,7 stereoselectivity presumably involves self-assembly into lithium chelate of the lithio amide, a bicyclic metal chelate, as shown. Omission of the 2.2 equiv. of HMPA caused a sharp reduction in the stereoselectivity. Under the THF/HMPA conditions, the stereoselectivity suffered with the corresponding trimethylene and pentamethylene homologues, but was 5:1 for the hexamethylene substrate. A similar reaction of chiral amino sulfone carboxamide **15** (*n*=4) with

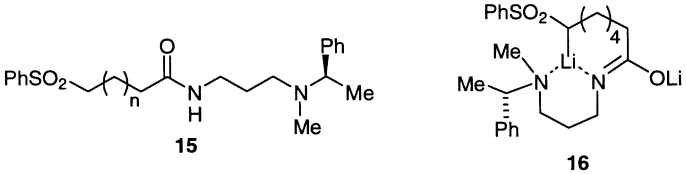
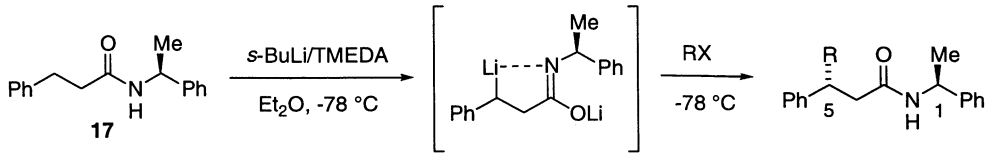


Figure 67.



R	Yield (%)	1,5-*anti*	1,5-*syn*
Me	50	91	9
Bn	55	90	10
Bu	55	88	12
$SiMe_3$	46	94	6

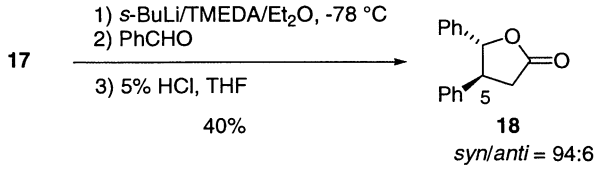


Figure 68.

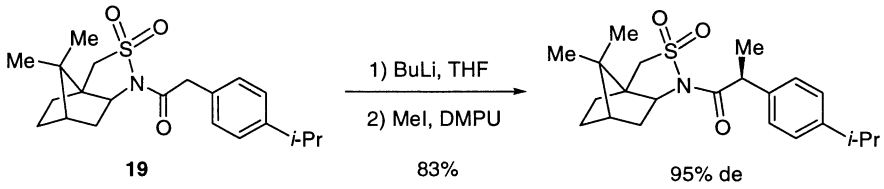
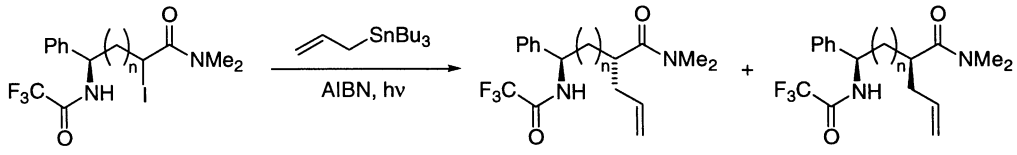


Figure 69.



n	% Yield	*anti*	*syn*
2	79	86	14
3	72	26	74

Figure 70.

benzaldehyde, presumably via bicyclic chelate **16**, resulted in amazingly high 1,13 asymmetric induction with the formation of just one *threo* and one *erythro* diastereomer (both with unknown absolute stereochemistry; Fig. 67).[66b] In fact, cases of **15** with n=1–3 also gave rise to one *erythro* and one *threo* diastereomer. However, the stereoselectivity was dissipated by the presence of LiCl or HMPA.

Complex-induced proximity effects in chiral amides have been applied to remote 1,5 stereocontrol by Beak and co-workers (Fig. 68; TMEDA=*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine).[67] It is noteworthy that, compared to the alkylation-type reaction, the carbonyl addition reaction, viz. **17→18**, gave an opposite sense of relative configuration at the newly formed stereogenic center.

Camphor-based sultams have been widely used to direct 1,4 or 1,5 asymmetric induction.[9a–c,68] For example, alkylation of the chiral lithium enolate derived from **19** with methyl

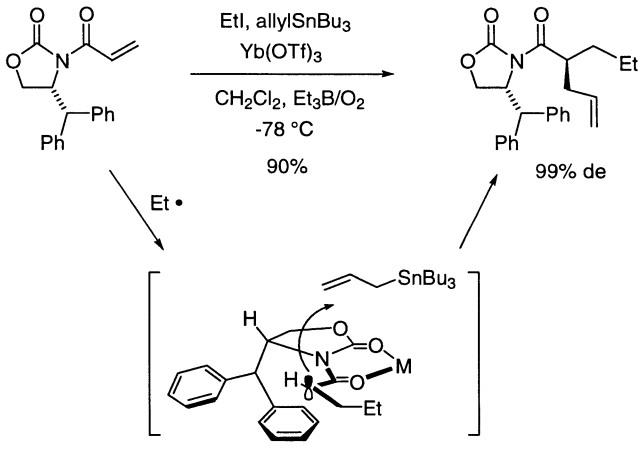
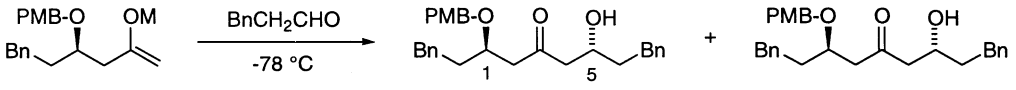


Figure 71.



M	Solvent	% Yield	1,5-*anti*	1,5-*syn*
Li	THF	79	40	60
$SiMe_3/BF_3{\bullet}OEt_2$	CH_2Cl_2	85	50	50
$(c\text{-}C_6H_{11})_2B$	CH_2Cl_2	85	82	18
Bu_2B	CH_2Cl_2	80	87	13
Bu_2B	Et_2O	83	94	6

Figure 72.

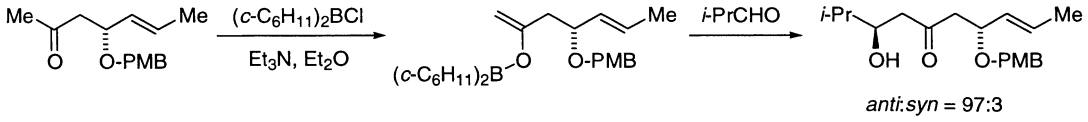
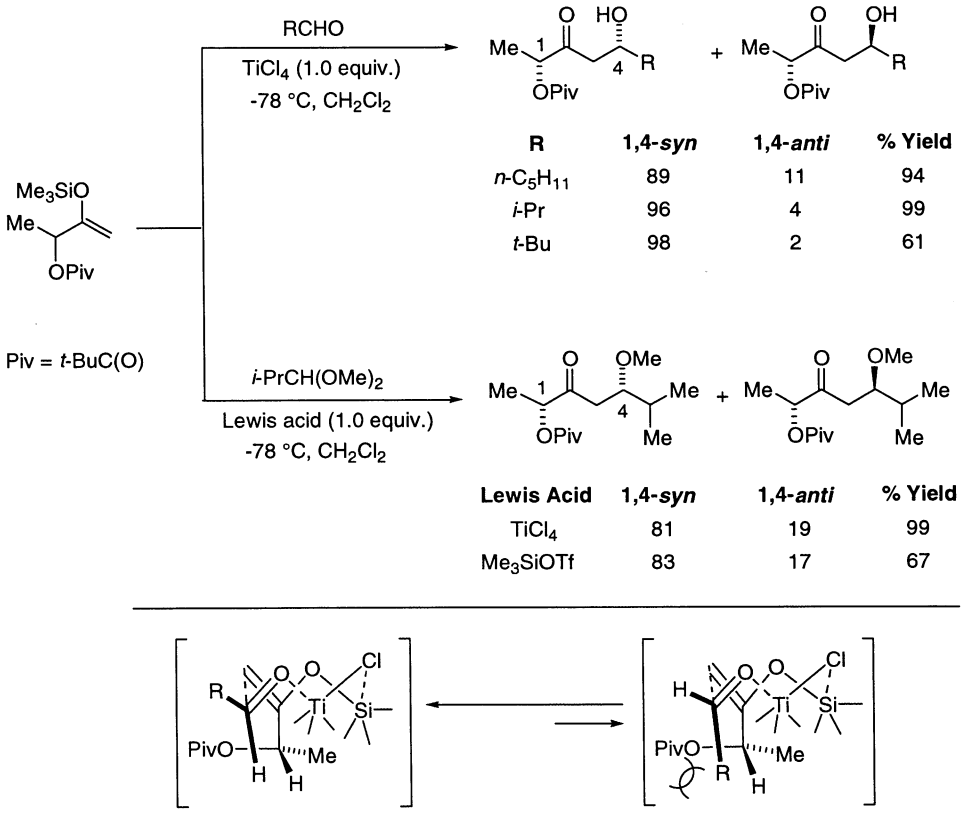


Figure 73.

iodide provided the alkylated product with a diastereomeric excess of 95% (Fig. 69; DMPU=*N*,*N*′-dimethylpropyleneurea).[9c]

Relatively high levels of 1,4-*anti* and 1,5-*syn* stereochemistry were observed in free-radical C-allylation reactions of γ- and δ-trifluoroacetamido radicals (Fig. 70; AIBN=2,2′-azobisisobutyronitrile).[69] Hydrogen bonding probably played an important role in controlling stereochemistry of carbon–carbon bond formation.

Oxazolidinone auxiliaries have been applied to directing 1,4 asymmetric induction in radical reactions.[70] For example, Lewis acid-mediated conjugate radical addition/allylation of *N*-propenoyloxazolidinone proceeds in 50–93% chemical yield and high 1,4 diastereoselectivity (>50:1 de) (Fig. 71).[70a] The results can be explained in terms of a metal chelate where the Lewis acid coordinates with the two carbonyl groups of the *N*-enoyloxazolidinone (shown in brackets). With the two carbonyls locked in a *syn* configuration, the radical site also adopts a *syn* configuration for steric reasons. Allylstannane addition would then take place from the face opposite to the bulky oxazolidinone 4-substituent.



R	1,4-*syn*	1,4-*anti*	% Yield
$n\text{-}C_5H_{11}$	89	11	94
i-Pr	96	4	99
t-Bu	98	2	61

Lewis Acid	1,4-*syn*	1,4-*anti*	% Yield
$TiCl_4$	81	19	99
Me_3SiOTf	83	17	67

Figure 74.

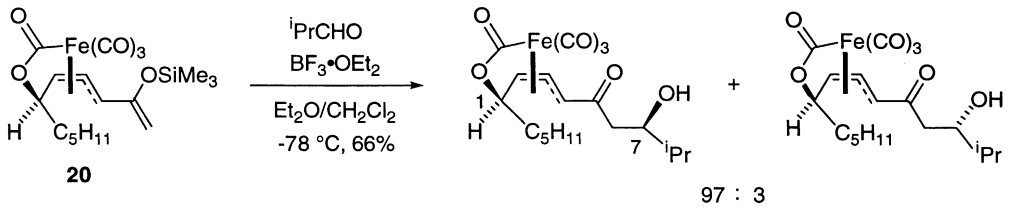
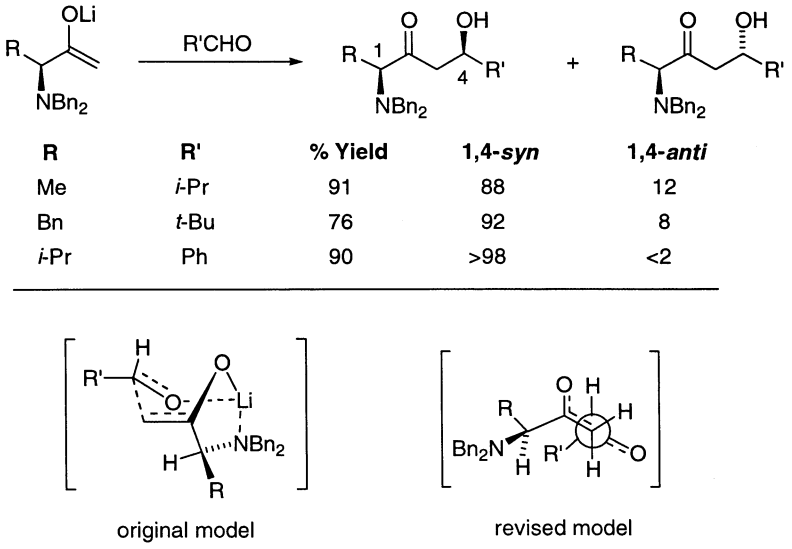


Figure 75.



R	R'	% Yield	1,4-*syn*	1,4-*anti*
Me	*i*-Pr	91	88	12
Bn	*t*-Bu	76	92	8
i-Pr	Ph	90	>98	<2

Figure 76.

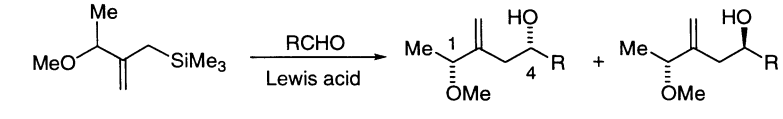
3. Intermolecular stereo-communication

3.1. Reaction of chiral enolates and enol derivatives

Stereochemical information in chiral enolates can be transferred to a prochiral aldehyde with high 1,5-*anti* selectivity by an appropriate combination of metal catalyst and solvent (Fig. 72; PMB=4-methoxybenzyl).[71]

Similarly, high levels of 1,5-*anti* stereoselectivity were obtained in boron-mediated aldol reactions of β-oxygenated methyl ketones with achiral aldehydes (Fig. 73).[72] The π-facial selectivity was found to be critically dependent on the nature of the β-alkoxy group and the ligands on boron.

Trost and Urabe realized a robust 1,4 asymmetric induction with a prochiral aldehyde and a chiral silyl enol ether; they proposed a crown-type, eight-membered-ring transition state (Fig. 74).[73]



R	Lewis Acid	% Yield	1,4-*syn*	1,4-*anti*
o-$NO_2C_6H_4$	$TiCl_4/Et_2O$	93	100	0
n-C_7H_{15}	$TiCl_4/Et_2O$	94	100	0
o-$NO_2C_6H_4$	$BF_3•OEt_2$	91	13	87
n-C_7H_{15}	$BF_3•OEt_2$	28	29	71

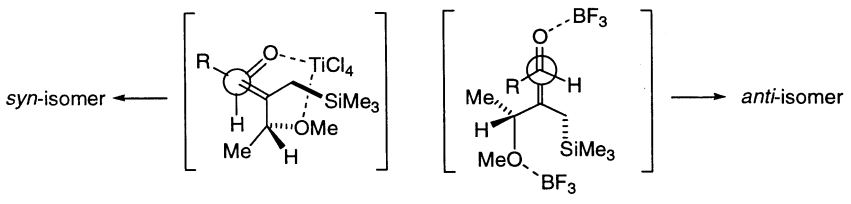


Figure 77.

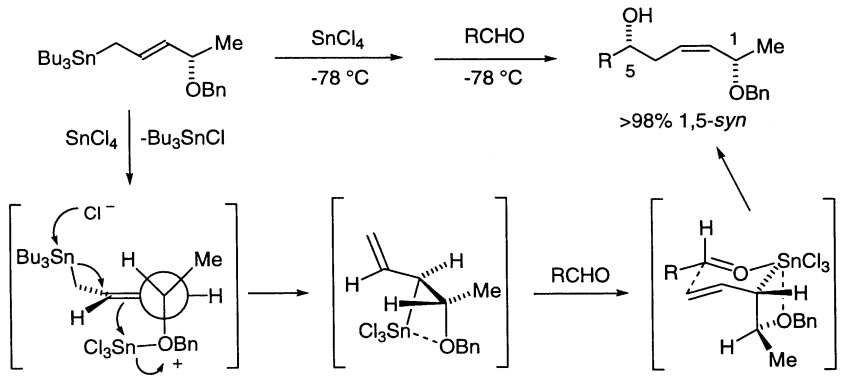


Figure 78.

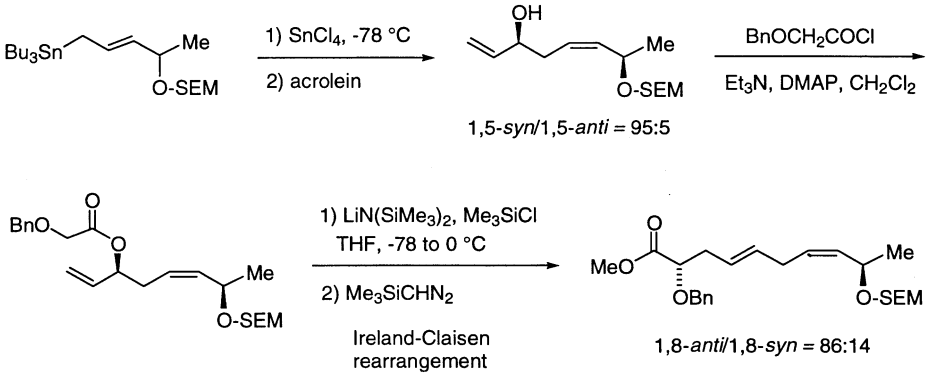


Figure 79.

Ley and co-workers achieved impressively high 1,7 stereocontrol in the Lewis acid-catalyzed aldol reaction of related iron tricarbonyl complex **20** (Fig. 75).[74] This example is not a pure 1,7 system, however, because the η^3-allyl iron complex has introduced another stereogenic element.

Liotta and co-workers obtained high 1,4 asymmetric induction in the aldol reaction of chiral lithium enolates of α-(*N*,*N*-dibenzylamino)alkyl methyl ketones, in the absence of additives or adduct formation (Fig. 76).[75] To rationalize the results, they first proposed a bicyclic transition state model, but later revised that model to one involving an acyclic, non-chelated transition state.

3.2. Reaction of chiral allyl organometallics

Remote asymmetric induction was reported in the allylation of aldehydes with a chiral allylsilane (Fig. 77).[76] Through the proper choice of Lewis acid, *syn* and *anti* isomers are formed selectively, with chelation and non-chelation transition-state models being proposed, respectively.

Thomas and co-workers have generated a collection of exciting results in the area of remote acyclic stereocontrol.[77] They reported high levels of 1,5, 1,6, and 1,7 asymmetric induction in the addition reactions of chiral allylic tin reagents to aldehydes or imines in the presence of tin tetrachloride.[77a–c] These results can be explained by assuming that 'homometallic' transmetalation occurs first between the allylic tin and tin tetrachloride (i.e. $Bu_3Sn \rightarrow Cl_3Sn$) to produce the allyltin trichloride, which contains a four-membered-ring tin chelate for the case of 1,5 asymmetric induction (Fig. 78), and a related five- or six-membered-ring chelate for the cases of 1,6 or 1,7 asymmetric induction, respectively. This cyclic species then reacts with an aldehyde via a bicyclic, chair-like transition state involving chelation with the alkoxy functionality to derive the 1,5-*syn* product (Fig. 78). By combining this methodology with the Ireland–Claisen or [2,3]-Wittig rearrangements, Thomas' group was able to control the stereochemical relationship for stereocenters separated by eight or nine atoms (1,8 or 1,9 stereoselectivity) (Fig. 79).[77d–f] Nishigaichi et al. used the transmetalation protocol with a chiral δ-alkoxyallylstannane and $SnCl_4$ to obtain good 1,4 stereocontrol between methyl and hydroxy groups (Fig. 80; MOM=methoxymethyl).[78] The Thomas protocol for remote

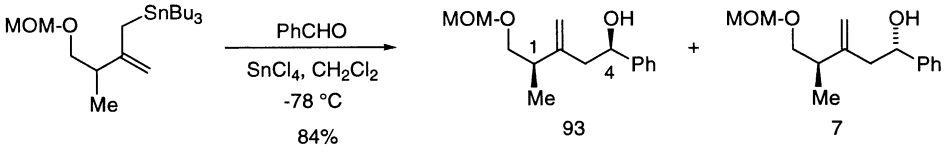
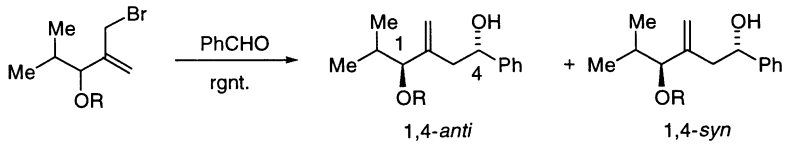


Figure 80.



Reagent/conditions	% Yield	*anti*/*syn*
$CrCl_3/LiAlH_4$, THF, 0 to 23 °C	60	95:5
In, H_2O, 25 °C	76	97:3

Figure 81.

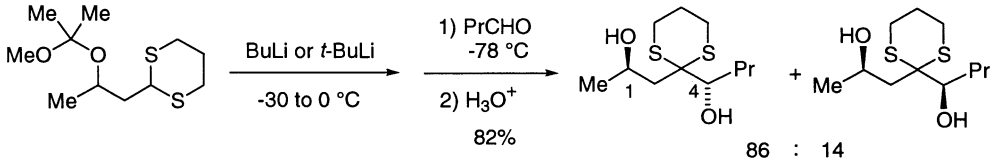


Figure 82.

acyclic stereocontrol appears to have a considerable degree of generality.[77a,g]

Coupling reactions of chiral allylic bromides with aldehydes, mediated by either chromium (Nozaki–Hiyama reaction)[79] or indium,[80] proceeded with very high 1,4-*anti* stereoselectivity (Fig. 81).

3.3. Reaction of chiral carbanions

Chikashita et al. reported high 1,4 remote asymmetric induction in the addition of a chiral 2-lithio dithiane to an aldehyde (Fig. 82).[81] They proposed a chelated intermediate in which the ether oxygen at the β position and the carbonyl oxygen of the aldehyde are coordinated to a lithium cation

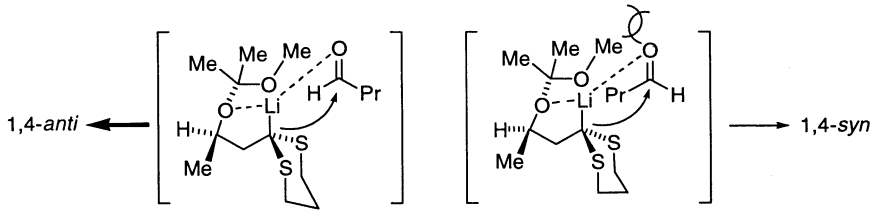
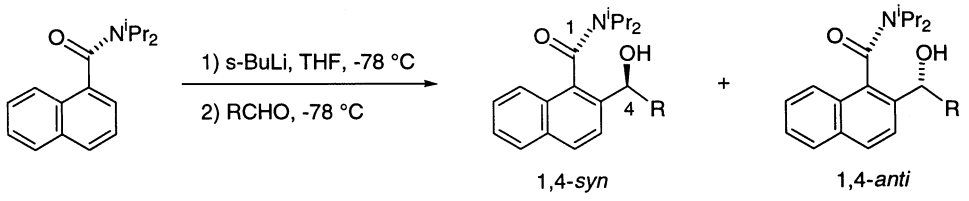


Figure 83.



R =	Me	Et	*n*-C_5H_{11}	*i*-Pr	Ph
***syn*:*anti* =**	85:15	90:10	82:18	77:23	72:28

Figure 84.

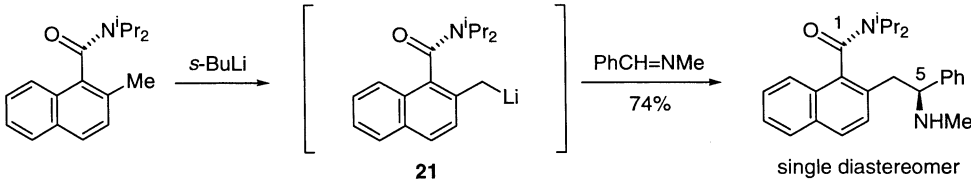


Figure 85.

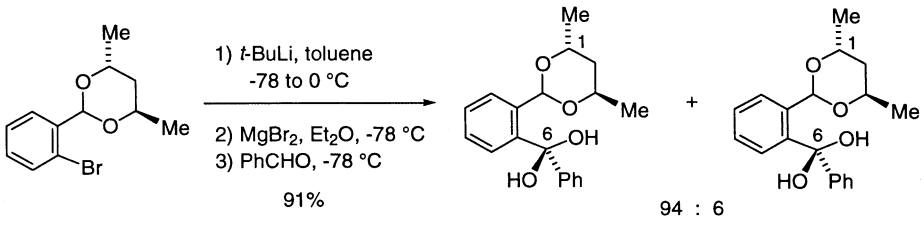


Figure 86.

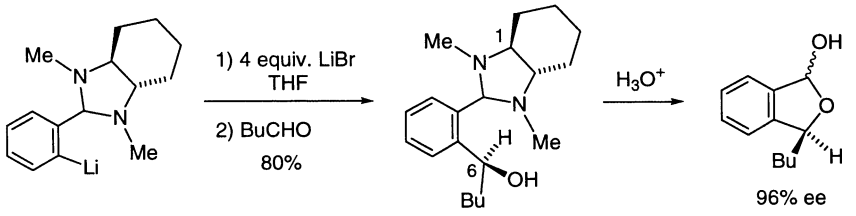


Figure 87.

(Fig. 83). This reaction may proceed with *anti* selectivity to avoid the steric repulsion between the β-methyl substituent and the propyl group of the condensing aldehyde. Similar 1,5 asymmetric induction was reported for the reaction of a chelated lithio dithiane with an aldehyde.[82]

A high level of 1,4 asymmetric induction occurred in the addition of *ortho*-lithiated 1-naphthoic amide to aldehydes (Fig. 84)[83] and 1,5 in the reaction of lithiated 2-alkyl-naphthoic amide **21** with an imine (Fig. 85).[84]

High levels of 1,6 asymmetric induction have been achieved in the addition of chiral arylmetal reagents to aldehydes. With aryl Grignard reagents Yamamoto and co-workers were able to attain 88% de with chiral ketals (e.g. Fig. 86),[85] and with aryl lithium reagents Alexakis and co-workers were able to attain 98% de with chiral ketals (e.g. Fig. 87).[86]

A (η^6-arene)chromium complex was used to effect 1,4 asymmetric induction; with the bulky $Cr(CO)_3$ group contributing a second stereogenic element (Fig. 88).[87]

SAMP/RAMP hydrazone derivatives have delivered

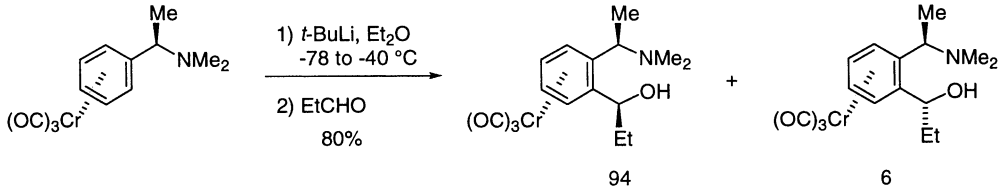


Figure 88.

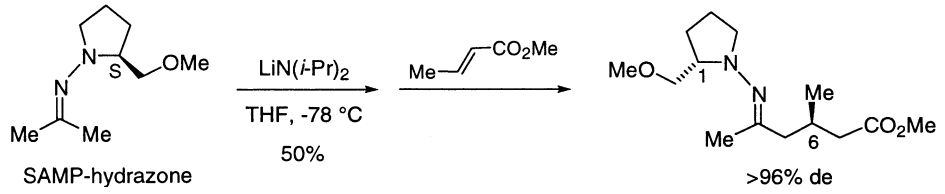


Figure 89.

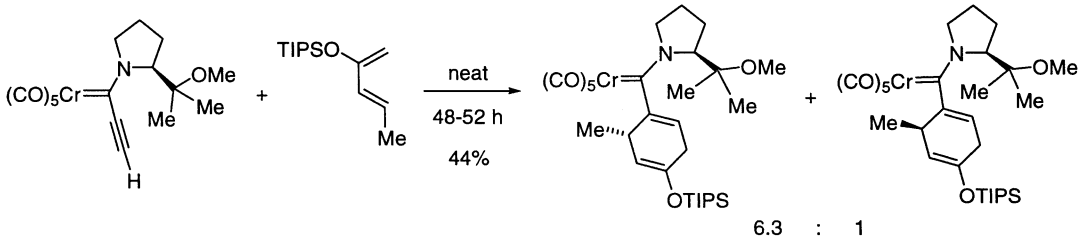


Figure 90.

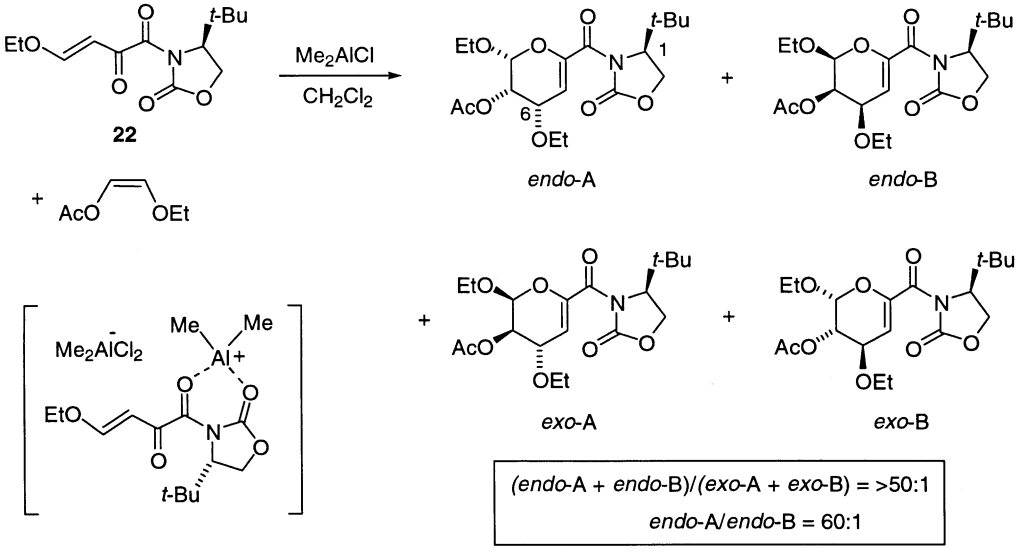


Figure 91.

excellent remote diastereoselectivity for a variety of reactions.[88] Here, we point out the remarkably high 1,6-*anti*[89] or 1,5-*syn* stereocontrol[90] found for the 1,4 addition of lithiated SAMP/RAMP hydrazones to α,β-unsaturated esters (e.g. Fig. 89[89]).

3.4. Cycloaddition reactions

A useful level of 1,5 asymmetric induction (73% de) was achieved in the Diels–Alder reactions of acetylenic carbene complexes with 2-triisopropylsiloxy-1,3-pentadiene (Fig. 90; TIPS=triisopropylsilyl).[91] Acetylenic Fischer carbene complexes with chiral pyrrolidines as the heteroatom-stabilizing substituent were suggested to block three of the four possible approaches of a diene and lead to selective asymmetric cycloadditions.

A high level of 1,6 asymmetric induction (60:1) was reported in the Lewis acid-catalyzed hetero-Diels–Alder reaction of an activated α,β-unsaturated ene dione bearing an oxazolidine chiral auxiliary (**22**; Fig. 91).[92] The aluminum is believed to complex the substrate to attain order, as shown, and a metal-chelated transition state would then account for the remarkable outcome.

Chiral sulfoxides have been used to direct remote asymmetric induction in various reactions.[93] For example, high 1,5 stereocontrol (98% de) was obtained in the Lewis acid-mediated Diels–Alder reaction of sulfinyl-pyrrole enone **23** with cyclopentadiene (Fig. 92).[93b] A seven-membered cyclic transition-state model, with participation by the Lewis acid, was proposed.

3.5. Ene reactions

Mikami and Shimizu obtained high 1,4 and 1,5 asymmetric induction in the glyoxylate-ene reaction of bishomoallylic silyl ethers (Fig. 93).[94] These results are thought to stem from the orbital interaction between the lone pair electrons of the ether oxygen and the π^* orbital of the olefin. This interaction was very small with methyl and benzyl protecting groups; high asymmetric induction could only be seen when a bulky silyl group was used. This n–π^* orbital interaction appears to promote the reaction, and the reactivity of a silyl ether is as about twice that of an olefin with no siloxy

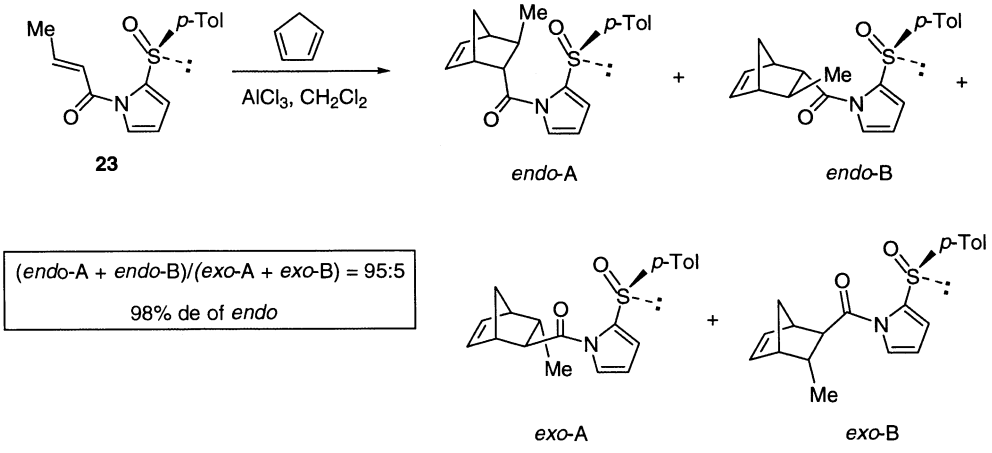


Figure 92.

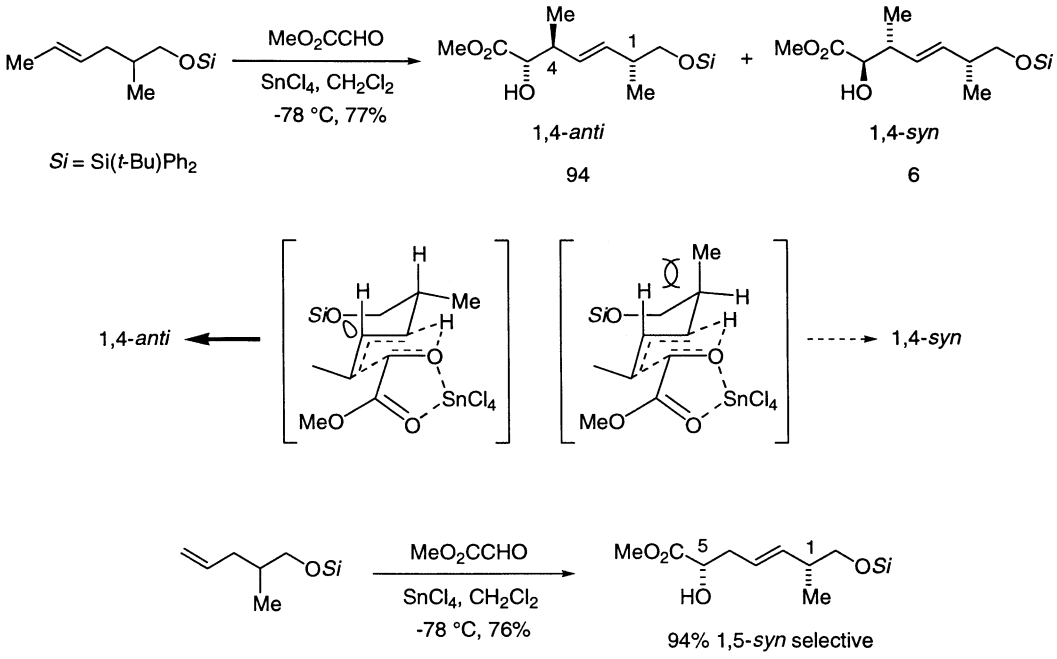
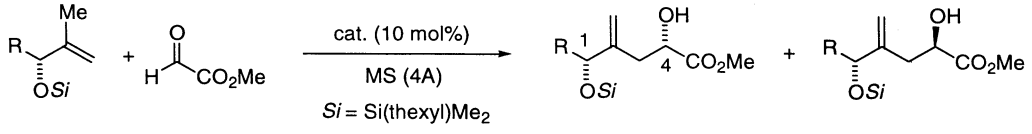


Figure 93.



R	Catalyst	% Yield	1,4-*syn*	1,4-*anti*
i-Pr	(*S*)-BINOL/(*i*-PrO)$_2$TiCl	96	>99	<1
Me	(*S*)-BINOL/(*i*-PrO)$_2$TiCl	71	>99	<1
Me	(*R*)-BINOL/(*i*-PrO)$_2$TiCl	33	50	50

Figure 94.

groups presumably because of a 'through space β-silyl effect'. Furthermore, Mikami et al. showed that extremely high 1,4-*syn* asymmetric induction would take place when a chiral titanium complex based on binaphthol is used as a chiral Lewis acid catalyst in the glyoxylate-ene reaction of a chiral allylic ether (Fig. 94; BINOL=2,2′-dihydroxybinaphthyl, MS=molecular sieves).[95] Match/mismatch in the orbital interaction between the allylic ether and glyoxylate/(*S*)-BINOL–Ti complex was determined by the configuration of the stereogenic center at the allylic position, and high 1,4 asymmetric induction was achieved by double asymmetric induction of the matched catalyst system. This successful double asymmetric induction suggests that the kinetic optical resolution of a racemic allylic ether could be achieved efficiently. In fact, when the reaction was carried out with a racemic ether with (*R*)-BINOL/(*i*-PrO)TiCl$_2$, the 1,4-*syn* isomer was obtained with a diastereoselectivity of more than 99% and in extremely

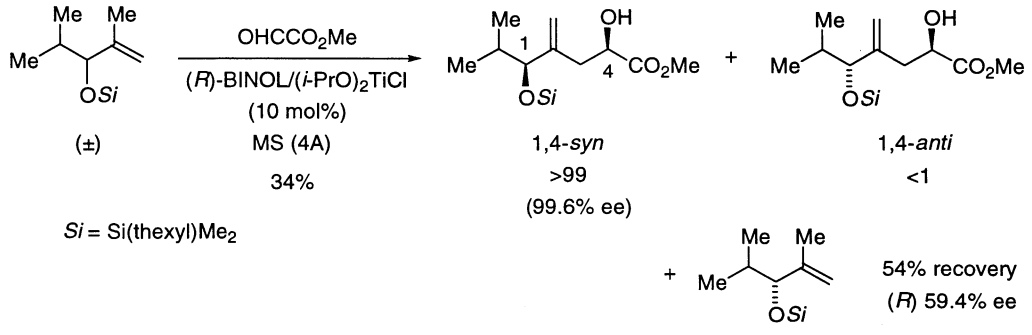


Figure 95.

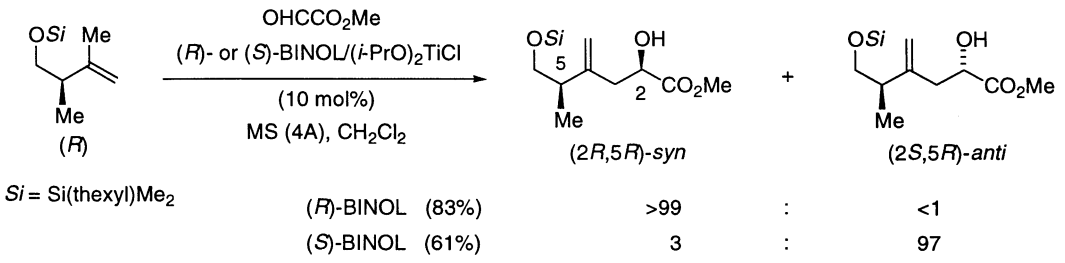


Figure 96.

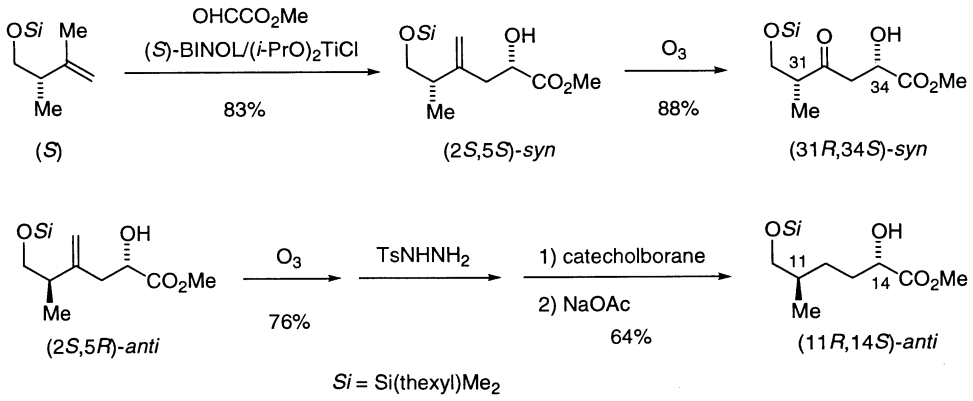


Figure 97.

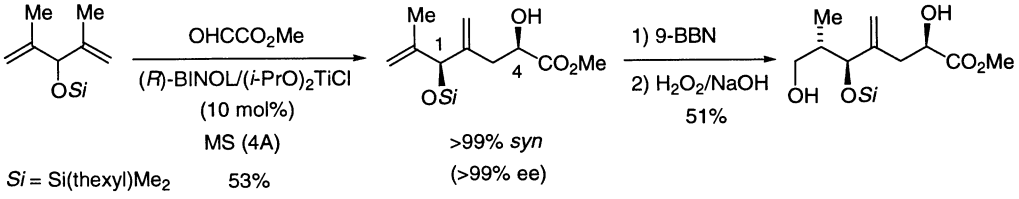


Figure 98.

high optical purity of 99.6% ee (Fig. 95). In addition, the starting allylic ether was recovered in a purity of 59.4% ee, as the (*R*) form, and the ratio of reaction rate for allylic ethers was calculated to reach as high as 700, (*S*)/(*R*).

In the glyoxylate-ene reaction of a chiral homoallylic ether, match/mismatch systems afforded almost the same level of high diastereoselectivity (Fig. 96).[96] The present approach to 1,4 remote stereocontrol was applied to the asymmetric synthesis of the (11*R*,14*S*)-*anti* and (31*R*,34*S*)-*syn* fragments of rapamycin, with the 1,4 relationship between Me and OH groups being established by simple transformations (Fig. 97).

In the absence of pre-existing stereogenic centers, it is not possible to control two (or more) stereogenic centers at remote positions by *internal asymmetric induction* with prochiral substrates. However, Mikami et al. accomplished such 1,4 remote acyclic stereocontrol during their study of chiral catalytic asymmetric desymmetrization of a symmetrical bis-allylic silyl ether in the glyoxylate-ene reaction.[94] Not only was the relative configuration of two remote stereogenic centers established, but also their absolute configuration was controlled to a high degree. This technique can be extended to an efficient asymmetric synthesis of macrolide segments by judicious combination of diastereoselective reactions, for example, via hydroboration (Fig. 98; 9-BBN=9-borabicyclo[3.3.1]nonane).

4. Epilogue

As mentioned earlier, although tremendous progress has been made in the area of acyclic stereocontrol at carbon centers with 1,2 and 1,3 relationships, the regulation of stereochemistry at centers with 1,>3 relationships is much less developed. There are a limited number of effective methodologies for stereochemical control over remote sites (1,>3-positions), especially in strictly acyclic substrates. Furthermore, the highly successful cases are often not generally applicable, as the realization of excellent results is very dependent on the nature of the substrate, reagents, and reaction conditions. Nevertheless, the past 15 years have witnessed significant advances in this area of remote acyclic stereocontrol, with the more notable successes having emanated from reactions involving 1,4 and 1,5 asymmetric induction.

A basic principle for developing effective methodology for remote acyclic stereocontrol is the achievement of a high

degree of structural organization in the substrate or transition state of the asymmetric reaction. The use of coordination complexes involving metals has proven to be a effective strategy for establishing such order. Hopefully, the broad sampling of methodologies for remote stereocontrol presented in this report will provide an inspiration to researchers and a valuable foundation for future developments in the field.

References

1. (a) Ireland, R. E. *Organic Synthesis*; Prentice-Hall: Englewood Cliffs, NJ, 1969. (b) Warren, S. *Organic Synthesis: The Disconnection Approach*; Wiley: New York, 1982. (c) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.
2. (a) Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553. (b) Breslow, R. *Acc. Chem. Soc.* **1980**, *13*, 170.
3. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981–3996.
4. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2–72.
5. (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. (c) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1991**, *20*, 87–170.
6. (a) Mikami, K.; Shimizu, M. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 3–13. (b) Thomas, E. J. *Chemtracts-Org. Chem.* **1994**, *7*, 207–234. (c) Sailes, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1785–1805.
7. (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23–32. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3–12. (d) Davies, S. G.; Sanganese, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 671–674. (e) Han, Y.; Hruby, V. J. *Tetrahedron Lett.* **1997**, *38*, 7317–7320. Also, for imidazolin-2-ones, see: (f) Abdel-Aziz, A. A.-M.; Okuno, J.; Tanaka, S.; Ishizuka, T.; Matsunaga, H.; Kunieda, T. *Tetrahedron Lett.* **2000**, *41*, 8533–8537. (g) Guillena, G.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 7310–7322.
8. (a) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375–381. (b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297–2360. (c) Maryanoff, B. E. *Chem. Heterocycl. Compd.* **1986**, *45*, 963–1017.
9. (a) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241–1250. (b) Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479–488. (c) Oppolzer, W.; Rosset, S.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 1539–1542.
10. (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem. Suppl.* **1982**, 257–268. See, also: (c) Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704–721.
11. (a) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989–990. (b) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem. Suppl.* **1983**, 1511–1526.
12. Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6335–6338.
13. Fujisawa, T.; Takemura, I.; Ukaji, Y. *Tetrahedron Lett.* **1990**, *31*, 5479–5482.
14. Harada, T.; Matsuda, Y.; Imanaka, S.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1641–1643.
15. (a) Zhang, H.-C.; Costanzo, M. J.; Maryanoff, B. E. *Tetrahedron Lett.* **1994**, *35*, 4891–4894. (b) Zhang, H.-C.; Harris, B. D.; Maryanoff, C. A.; Maryanoff, B. E. *Tetrahedron Lett.* **1996**, *37*, 7897–7900. (c) Zhang, H.-C.; Harris, B. D.; Costanzo, M. J.; Lawson, E. C.; Maryanoff, C. A.; Maryanoff, B. E. *J. Org. Chem.* **1998**, *63*, 7964–7981. (d) Lawson, E. C.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron Lett.* **1999**, *40*, 593–596.
16. Fleming, I.; Kuhne, H.; Takaki, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 725–728.
17. Reetz, M. T.; Wang, F.; Harms, K. *J. Chem. Soc., Chem. Commun.* **1991**, 1309–1311.
18. Arai, M.; Nemoto, T.; Ohashi, Y.; Nakamura, E. *Synlett* **1992**, 309–310.
19. Sato, T.; Kido, M.; Otera, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2254–2256.
20. Akhoon, K. M.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6041–6045.
21. (a) Heitz, M. P.; Gellibert, F.; Mioskowski, C. *Tetrahedron Lett.* **1986**, *27*, 3859–3862. (b) Tamura, Y.; Ko, T.; Kondo, H.; Annoura, H. *Tetrahedron Lett.* **1986**, *27*, 2117–2120. (c) Tamura, Y.; Annoura, H.; Fugi, M.; Yoshida, T.; Takenchi, R.; Fujioka, H. *Chem. Pharm. Bull.* **1987**, *35*, 4736–4746.
22. (a) Hasegawa, K.; Matsuda, F.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 1671–1674. (b) Matsumoto, T.; Matsuda, F.; Hasegawa, K.; Yanagiya, M. *Tetrahedron* **1984**, *40*, 2337–2343.
23. Hosokawa, T.; Yagi, T.; Ataka, Y.; Murahashi, S. I. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3380–3382.
24. Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991–1999.
25. Alexakis, A.; Sedrani, R.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 283–286.
26. Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 7517–7518.
27. (a) Mears, R. J.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 8155–8156. (b) Conole, G.; Mears, R. J.; De Silva, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1825–1836.
28. (a) Nair, V.; Prabhakaran, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 593–594. (b) Nair, V.; Prabhakaran, J.; George, T. G. *Tetrahedron* **1997**, *53*, 15,061–15,068.
29. Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488–7494.
30. (a) Vasconcellos, M. L.; D'Angelo, J.; Desmaele, D.; Costa, P. R. R.; Potin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 353–356. (b) Alencar, K. G.; Filho, U. F. L.; Vasconcellos, M. L. A. A.; Costa, P. R. R. *Synth. Commun.* **2000**, *30*, 455–468.
31. (a) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491–1493. (b) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616–8618.
32. (a) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363–1364. (b) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3033–3041.
33. Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1996**, *37*, 5577–5580.
34. (a) Tamai, Y.; Koike, S.; Ogura, A.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1991**, 799–800. (b) Tamai, Y.; Hattori, T.; Date, M.; Koike, S.; Kamikubo, Y.; Akiyama, M.; Seino, K.;

Takayama, H.; Oyama, T.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1685–1694.
35. Tamai, Y.; Hattori, T.; Date, M.; Takayama, H.; Kamikubo, Y.; Minato, Y.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1141–1142.
36. (a) Ley, S. V.; Cox, L. R.; Meek, G.; Metten, K.-H.; Pique, C.; Worrall, J. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3299–3313. (b) Ley, S. V.; Cox, L. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3315–3325. (c) Ley, S. V.; Burckhardt, S.; Cox, L. R.; Meek, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3327–3337.
37. (a) Molander, G. A.; Haar, Jr., J. P. *J. Am. Chem. Soc.* **1991**, *113*, 3608–3610. (b) Molander, G. A.; Haar, Jr., J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40–49.
38. Corey, E. J.; Hannon, F. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545–555.
39. Captain, L. F.; Xia, X.; Liotta, D. C. *Tetrahedron Lett.* **1996**, *37*, 4293–4296.
40. Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett.* **1998**, *39*, 8593–8596.
41. (a) Oppolzer, W.; Löher, H. *Helv. Chem. Acta* **1980**, *64*, 2808–2811. (b) Oppolzer, W.; Moretti, R.; Godel, T.; Meunier, A.; Löher, H. *Tetrahedron Lett.* **1983**, *24*, 4971–4974.
42. Alexakis, A.; Sedrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 4411–4414.
43. Roush, W. R.; Wada, C. K. *J. Am. Chem. Soc.* **1994**, *116*, 2151–2152.
44. (a) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004–5005. (b) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477–511. (c) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 3143–3146. (d) Rakotoarisoa, H.; Perez, R. G.; Mangeney, P.; Alexakis, A. *Organometallics* **1996**, *15*, 1957–1959. (e) Alexakis, A.; Mhmadi, F.; Lagasse, F.; Mangeney, P. *Tetrahedron: Asymmetry* **1996**, *7*, 3343–3346.
45. (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933–2935. (b) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741–2744.
46. Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582–2588.
47. Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299–2311.
48. Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276–5290.
49. Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171–3174.
50. Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 1197–1207.
51. Charette, A. B.; Cote, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166–8167.
52. (a) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254–8256. (b) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986–4988.
53. Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385–7387.
54. (a) Wittman, M. D.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 4631–4633. (b) Balestra, M.; Kallmerten, J. *Tetrahedron Lett.* **1988**, *29*, 6901–6904.
55. Tomooka, K.; Keong, P.-H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 2789–2792. Also: Mikami, K.; Kawamoto, K.; Nakai, I. 56th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1988, Abstr. 3XIIA32.
56. (a) Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241–3267. (b) Brasseur, D.; Marek, I.; Normant, J.-F. *Tetrahedron* **1996**, *52*, 7235–7250.
57. Suzuki, K.; Imai, T.; Yamanoi, S.; Chino, M.; Matsumoto, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2469–2471.
58. (a) Yamagishi, T.; Ikeda, S.; Yatagai, M.; Yamaguchi, M.; Hida, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1787–1790. (b) Ikeda, S.; Yamagishi, T.; Yamaguchi, M.; Hida, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3508–3512.
59. Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265–1276.
60. Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984–1986.
61. Fujioka, H.; Kitagawa, H.; Matsunaga, N.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **1996**, *37*, 2245–2248.
62. (a) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, 81–84. (b) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Chem. Lett.* **1986**, 1755–1758. (c) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1457–1464.
63. (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511. (b) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322–3327.
64. Erker, G.; Sosna, F.; Betz, P.; Werner, S.; Kruger, C. *J. Am. Chem. Soc.* **1991**, *113*, 564–573.
65. Ghera, E.; Kleiman, V.; Hassner, A. *J. Org. Chem.* **1999**, *64*, 8–9.
66. (a) Linnane, P.; Magnus, N.; Magnus, P. *Nature* **1997**, *385*, 799–801. (b) Magnus, N.; Magnus, P. *Tetrahedron Lett.* **1997**, *38*, 3491–3494.
67. Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2–3.
68. (a) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772. (b) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2280.
69. Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507–2508.
70. (a) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090–6091. (b) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190–192.
71. Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem.* **1997**, *62*, 788–789.
72. Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585–8588.
73. Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982–3983.
74. Ley, S. V.; Cox, L. R.; Middleton, B.; Worrall, J. M. *Tetrahedron* **1999**, *55*, 3515–3530.
75. (a) Lagu, B. R.; Crane, H. M.; Liotta, D. C. *J. Org. Chem.* **1993**, *58*, 4191–4193. (b) Goh, J. B.; Lagu, B. R.; Wurster, J.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 6029–6032.
76. Nishigaichi, Y.; Takuwa, A.; Jodai, A. *Tetrahedron Lett.* **1991**, *32*, 2383–2386.
77. (a) Thomas, E. J. *Chem. Commun.* **1997**, 411–418. (b) Hobson, L. A.; Vincent, M. A.; Thomas, E. J. *Chem. Commun.* **1998**, 899–900. (c) Taylor, N. H.; Thomas, E. J. *Tetrahedron* **1999**, *55*, 8757–8768. (d) Moffatt, E.-M.; Thomas, E. J. *Tetrahedron* **1999**, *55*, 3723–3734. (e) Dorling, E. K.; Thomas, E. J. *Tetrahedron Lett.* **1999**, *40*, 471–474. (f) Dorling, E. K.; Thomas, A. P.; Thomas, E. J. *Tetrahedron Lett.* **1999**, *40*, 475–476. (g) Ley, S. V.; Innes, J. E. *Chemtracts-Org. Chem.* **1996**, *9*, 204–210.
78. (a) Nishigaichi, Y.; Yoshikawa, M.; Takigawa, Y.; Takuwa, A. *Chem. Lett.* **1996**, 961–962. See, also: (b) Nishigaichi, Y.;

Kuramoto, H.; Takuwa, A. *Tetrahedron Lett.* **1995**, *36*, 3353–3356.
79. Maguire, R. J.; Mulzer, J.; Bats, J. W. *J. Org. Chem.* **1996**, *61*, 6936–6940.
80. Paquette, L. A.; Bennett, G. D.; Chhatriwalla, A.; Isaac, M. B. *J. Org. Chem.* **1997**, *62*, 3370–3374.
81. Chikashita, H.; Yasuda, H.; Kimura, Y.; Itoh, K. *Chem. Lett.* **1992**, 195–198.
82. Jenkins, P. R.; Selim, M. M. R. *J. Chem. Res., Synop.* **1992**, 85.
83. Bowles, P.; Clayden, J.; Tomkinson, M. *Tetrahedron Lett.* **1995**, *36*, 9219–9222.
84. Clayden, J.; Darbyshire, M.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1997**, *38*, 8587–8590.
85. Kaino, M.; Ishihara, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3736–3738.
86. Commercon, M.; Mangeney, P.; Tejero, T.; Alexakis, A. *Tetrahedron: Asymmetry* **1990**, *1*, 287–290.
87. Uemura, M.; Miyake, R.; Shiro, M.; Hayashi, Y. *Tetrahedron Lett.* **1991**, *32*, 4569–4572.
88. Enders, D.; Bettray, W. *Pure Appl. Chem.* **1996**, *68*, 569–580.
89. Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967–4970.
90. Enders, D.; Papadopoulos, K.; Rendenbach, B. E. M.; Appel, R.; Knoch, F. *Tetrahedron Lett.* **1986**, *27*, 3491–3494.
91. Rahm, A.; Rheingold, A. L.; Wulff, W. D. *Tetrahedron* **2000**, *56*, 4951–4965.
92. Tietze, L. F.; Schneider, C.; Montenbruck, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 980–982.
93. (a) Arai, Y. *Rev. Heteroatom Chem.* **1999**, *21*, 65–71. (b) Arai, Y.; Masuda, T.; Masaki, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2165–2170.
94. Shimizu, M.; Mikami, K. *J. Org. Chem.* **1992**, *57*, 6105–6106.
95. Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566–6568.
96. Mikami, K.; Yoshida, A. *Tetrahedron Lett.* **1994**, *35*, 7793–7796.

Biographical sketch

Koichi Mikami was born in 1953 in Bousou, Chiba, Japan. He received his PhD degree in 1982 under the supervision of Professors Takeshi Nakai and Nobuo Ishikawa and became an Assistant Professor at Tokyo Institute of Technology. He advanced to Associate Professor in 1987. In 1982–1983, he was a postdoctoral fellow at Yale University with Professor Frederick Ziegler. He has received a Tejima Award on stereocontrol based on [2,3]-sigmatropic rearrangements, a Chemical Society of Japan Award (Shinpo-Sho) on asymmetric transmission and asymmetric synthesis based on the [2,3]-Wittig rearrangements, a Society of Synthetic Organic Chemistry Japan Award (Asahi-Kasei Award) on asymmetric synthesis based on carbonyl-ene reactions, and an IBM Award on highly efficient asymmetric catalysis. Prof. Mikami was a Bristol-Myers-Squibb Lecturer (Colorado State University) and has held Visiting Professorships at the Université Paris-Sud and in Taiwan.

Masaki Shimizu was born in 1965 in Tokyo, Japan. He received his PhD degree from Tokyo Institute of Technology in 1994 under the supervision of Associate Professor Koichi Mikami and Professor Takeshi Nakai. He received the Inoue Award for his PhD thesis. After working at Mitsubishi Chemical as a research associate for 14 months, he joined Research Laboratory of Resources Utilization, Tokyo Institute of Technology as a research associate in 1995 under the supervision of Prof. Tamejiro Hiyama. In 1998, he moved to Kyoto University as an instructor working with Prof. Hiyama. He spent one year at the Massachusetts Institute of Technology as a postdoctoral fellow with Prof. Stephen Buchwald (1999–2000). His research interests are synthesis of silicon-containing cage compounds, synthesis of organofluorine compounds, and molecular material science.

Han-Cheng Zhang was born on 13 June 1959 in People's Republic of China. He earned BS and MS degrees in chemistry from Xiamen University and a PhD degree in organic chemistry from Rensselaer Polytechnic Institute in 1992 working with Prof. Doyle Daves. He joined the R. W. Johnson Pharmaceutical Research Institute first as a Postdoctoral Scientist with Dr Bruce Maryanoff and, after one year, as a Scientist. Since then, he has worked in medicinal chemistry to discover new drug candidates and has advanced ranks to Principal Scientist. Dr Zhang recently led a research effort that identified the first potent, selective antagonists for the thrombin receptor, protease-activated receptor 1 (PAR-1). His scientific interests involve the design and synthesis of novel therapeutic agents, stereoselective reactions, organometallic chemistry, solid-phase organic synthesis, and heterocyclic synthesis.

Bruce E. Maryanoff was born on 26 February 1947 in Philadelphia, Pennsylvania. He earned a BS degree in chemistry from Drexel University (1969) and a PhD degree at Drexel (1972) with Prof. Robert O. Hutchins. After postdoctoral studies at Princeton University with Prof. Kurt Mislow, Dr Maryanoff joined McNeil Laboratories, a Johnson & Johnson Company, in 1974. Working as medicinal chemist, he advanced through the ranks to Distinguished Research Fellow, the highest scientific-ladder position in the company. He became part of the R. W. Johnson Pharmaceutical Research Institute in 1990, following the merger of divisions from McNeil and Ortho Pharmaceutical. For 15 years, his drug discovery efforts were focused mainly on therapeutic agents for central nervous system disorders. During this time, he discovered TOPAMAX® topiramate, a sugar sulfamate drug that is marketed worldwide for the treatment of epilepsy. In 1992, he moved into cardiovascular research and has directed drug discovery efforts as Co-Leader of the Vascular Research Team. Dr Maryanoff is an author on over 170 scientific papers and an inventor on 45 US patents (issued or pending). He was editor of *Advances in Medicinal Chemistry* for 10 years, and has presented 100 invited lectures worldwide. He recently received a Heroes of Chemistry 2000 Award from the American Chemical Society. Some of his chemical interests have been stereochemistry and conformational analysis, the mechanism of the Wittig olefination reaction, solid-phase organic synthesis, and the synthesis of heterocycles.