Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5953–6018

TETRAHEDRON

Tetrahedron report number 646

Multiple stereoselectivity and its application in organic synthesis

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Received 29 May 2003

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1. Introduction

Stereoselectivity and stereoselective methods in organic synthesis are a problem of fundamental importance and will be even more important in the future as the drug industry is required to supply 100% optically pure compounds. Much progress in this area has been made in the last few years. A number of new, highly stereoselective reactions and methods have been developed and applied in industry.[1–5] The Nobel Prize in chemistry has been awarded in 2001 to Sharpless, Noyori and Knowles for the development of catalytic asymmetric synthesis, selective processes and chiral catalysts.

One of the methods to increase the stereoselectivity of reactions is multiple stereoselectivity (multiple stereodifferentiation, multiple asymmetric induction), when the stereochemical process proceeds under the control of more than one chiral auxiliary. This kind of chemical transformation occurs in nature because many enzymatic reactions involve the cooperation of several chiral auxiliaries. This type of stereochemical effect, very important from a theoretical and practical standpoint, has not been sufficiently investigated.

In organic chemistry, the earliest attempts to increase the stereoselectivity of a reaction by means of two chiral auxiliaries were described, probably, by Vavon (1950),[6] and Harada and Matsumoto (1966).[7] In 1968, Horeau, Kagan and Vigneron[8] discovered the cumulative effect of two auxiliaries in the reaction of phenyl glyoxalates to mandelate derivatives and named this effect as ‘the double induction’.

Keywords: multiple stereoselectivity; double asymmetric synthesis; chiral catalysts; multiple stereochemical control.

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doi:10.1016/S0040-4020(03)00911-6

In 1977, Izumi[9] has proposed the term 'double stereodifferentiation' which is more exact than the term 'double asymmetric induction'. Articles devoted to the applications of double asymmetric synthesis in different sections of organic chemistry have been published. In 1984, the article of Poulin and Kagan[10] being devoted to asymmetric hydrogenation and the section of Morrison's monograph written by Heathcock reviewing the aldol condensation.[11] The following year, Masamune and co-authors[12] described the application of double stereodifferentiation for four crucial reactions of organic chemistry: aldol condensation, hydrogenation, Sharpless epoxidation and Diels–Alder reactions.

During the past 10–15 years, this field of asymmetric synthesis was advanced and studies which allowed a consideration of the problems of stereodifferentiating reactions more widely and exactly have been performed. Multiple stereoselective reactions have found a use in such fields of organic chemistry as Sharpless dihydroxylation, Michael additions, addition to allylmetals, the Reformatsky reaction, the Mukaiyama reaction, photochemical reactions, alkylation, cycloadditions and the synthesis of heteroatom compounds, etc. New versions of multiple stereoselectivity were developed; the substrates, reagents and catalysts bearing several chiral auxiliaries with an additive effect of stereoselectivities, reacting under control of double asymmetric induction. These outstanding achievements require a generalisation of the existing information on the application of multiple asymmetric induction in organic synthesis and a critical consideration of a number of accumulated theoretical problems.

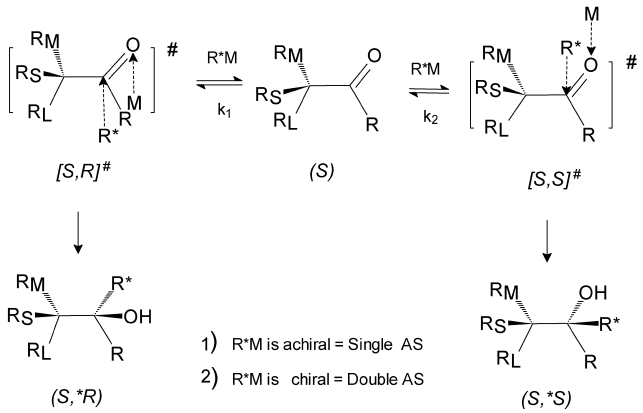
The present review describes the strategy which can be adopted to improve stereoselectivity. The aim of this review is to illustrate the processes to which these principles can be applied and the high degree of stereoselectivity which can be achieved.

The review summarises the progress which has been made and the current state of this field. It consists of two main parts treating the multiple stereodifferentiating reactions. The first part gives a stereochemical analysis of multiple asymmetric induction. The application of multiple stereodifferentiation as a method to increase the stereoselectivity of asymmetric reduction, oxidation, alkylation, addition to multiple bonds, enantioselective cycloaddition and synthesis of chiral heteroatom compounds are discussed in the second part. This part of the review emphasises the practical aspects of organic synthesis using multiple asymmetric induction. The present division of the review focuses on reactions having to demonstrate their potential uses in asymmetric synthesis.

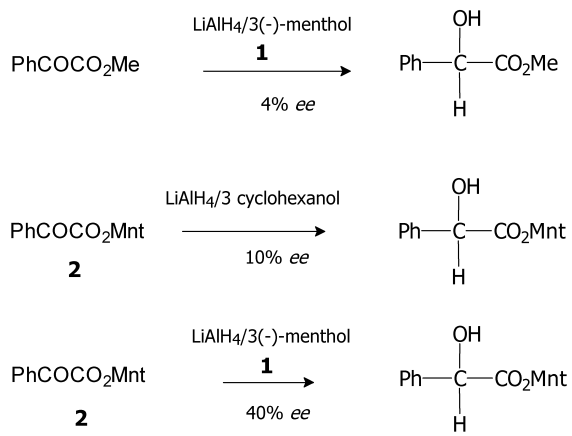
Throughout this review, we employ the following abbreviations: Ac—acetyl, AI—asymmetric induction, All—Allyl, Ar—aryl group, Ar*—aryl group containing an element of chirality, AD—asymmetric dihydroxylation, AE—asymmetric epoxidation, AS—asymmetric synthesis, BINAL-H—lithium (*l*,*r*-binaphthyl-2,2′-dioxy)ethoxy aluminium hydride, BINAP—2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, BPPM—(2*S*,4*S*)-butyl-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)-1-(pyrrolidinecarboxylate), Boc—*t*-BuOCO, Bn—benzyl, Brn—Bornyl, Bz—benzoyl, Cat—catalyst, Cat*—chiral catalyst, CHIRAPHOS—bis(diphenylphosphino)butane, COD—1,5-cyclooctadiene, Cy—cyclohexyl, △—heat, de—diastereomeric excess, ds—diastereoselectivity, dr—diastereomeric ratio, DET—diethyl tartrate, DIBAL—diisobutylaluminium hydride, DIOP—4,5-bis(diphenylphosphinomethyl)-2,2-dimethyldioxolane, DIPAMP—1,4-bis[*O*-methoxyphenyl(phenyl)-phosphino]ethane, DIPHOS—1,2-bis(diphenylphosphino)ethane, DIPT—diisopropyl tartrate, DMSO—dimethylsulphoxide, ee—enantiomeric excess, $Eu(fod)_3$—tris(6,6,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium, $Eu(hfc)_3$—tris(3-heptafluoropropyl)-hydroxymethylene)-D-camphorato]europium, HMPA—hexamethylphosphoric triamide, glc—glucosyl, Ipc—isopinocampheyl, ^{d}Ipc—isopinocampheyl derived from (+)-α-pinene, ^{l}Ipc—isopinocampheyl derived from (−)-α-pinene, KHMDS—potassium hexamethyldisilazide, L—ligand, L*—chiral ligand, LDA—lithium diisopropylamide, LHMDS—lithium hexamethyldisilazide, M—metal, Man—mannosyl, Mes—mesityl, Mnt—menthyl, (+)-Mnt—(1*S*,2*R*,5*S*)-menthyl, (−)-Mnt—(1*R*,2*S*,5*R*)-menthyl, MOM—methoxymethyl, Ms—methanesulphonyl, NaHMDS—sodium hexamethyldisilazide, Phth—phthalyl, R_S, R_M, R_L—small, medium and large groups, R*—alkyl or aryl group containing stereogenic centre or element of chirality, Ra-Ni—Raney nickel, Rha—rhamnosyl, S—substrate (starting material), TBDMS—*t*-butyldimethylsilyl, TBPS—*t*-butyldiphenylsilyl, THP—tetrahydropyran, Tf—trifluorosulphonyl, TMS—trimethylsilyl, THF—tetrahydrofuran, TFA—trifluoroacetic acid, X—group containing heteroatom, X*—chiral auxiliary group.

2. Stereochemical analysis of multiple stereoselectivity

The stereoselectivity can be defined as the preferential formation of one product of several possible products that differ only in their configurations.[1,5] Stereoselectivity can be further subdivided into enantioselectivity and diastereoselectivity. According to Izumi,[9] when the chirality of participating in differentiation occurs in a reagent, the catalyst or the reaction medium, the reaction is classified as an enantiodifferentiating reaction. When the chirality related to the differentiation is present in the substrate, the reaction is classified as a diastereodifferentiating reaction.



Scheme 1. Single and double facial stereoselectivity.



Scheme 2. Substrate–reagent controlled double AS.

Depending on the structure of a substrate, the diastereoselectivity can be facial, topical or isomeric. An example of facial diastereoselectivity is shown in Scheme 1.

The stereoselectivity of reagents can be estimated as a difference of reaction rates or energies of activation leading to two diastereomers.[1,13] The equilibrium concentrations of activated diastereomeric forms are connected with free energy activations of reactions according to the equation.

$$-RT \ln \frac{k_1^{\#}}{k_2^{\#}} = -RT \ln \frac{[S^*R]^{\#}}{[S^*S]^{\#}} = \Delta G_{SR}^{\#} - \Delta G_{SS}^{\#}$$

In order to obtain the highest stereoselectivity, we need to increase the difference between the concentrations of diastereomers. Thus, we can introduce into the reaction system two or several chiral asymmetric centers. In this case, we obtain the double stereoselectivity or multi-stereoselectivity if we have several chiral asymmetric centers taking part in the asymmetric synthesis. In the case of multiple asymmetric induction, the activated diastereomeric forms, $[S,R]^{\#}$ and $[S,S]^{\#}$, leading to the diastereomeric products, differ in energies of formation, that determines a difference in their equilibrium concentration.

In all of the approaches, a chiral substrate or agent is acted upon by another chiral entity. This interaction of two chiral agents gives rise to diastereomeric transition states. The difference in energy between the two transition states ($\Delta\Delta G^{\neq}$) determines the degree of selectivity and the lower energy pathway will provide the major antipode, even if the product is not thermodynamically favoured. It is obvious that every additional chiral auxiliary in a reaction system affects asymmetric induction and changes the difference between the activated diastereomeric forms ($\Delta G_{SR}^{\neq}$ and $\Delta G_{SS}^{\neq}$).[14,15] The individual stereochemical properties of chiral auxiliaries, present in a reacting system, as a rule can reinforce one another (matched asymmetric synthesis), or, on the contrary, counteract each other (mismatched asymmetric synthesis).

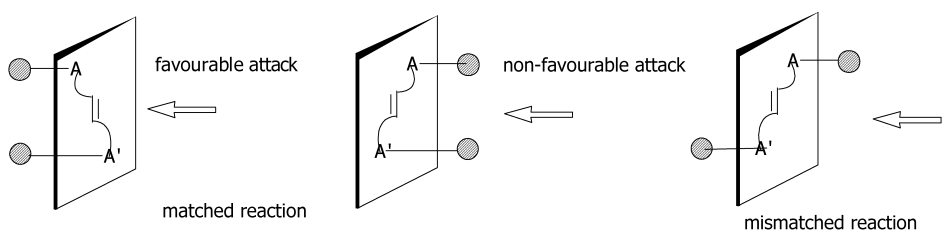
Several versions of multiple stereoselective reactions are known:

- both reagents, a substrate and a reagent, each bear one asymmetric element;
- a single reaction partner, substrate, reagent or catalyst bears two or more asymmetric centers, and the second reaction partner is achiral;
- reaction of the chiral substrate is carried in the presence of an asymmetric catalyst, chiral phase transfer catalyst, chiral crown-ether, etc;
- reaction of a chiral substrate is carried out in a chiral solvent.

In principle, other versions of multiple stereoselectivity are also possible, e.g. the double asymmetric synthesis with a multifunctional chiral catalyst, polarised light and asymmetric catalysis in a chiral solvent.

The first type of multiple stereoselectivity (substrate–reagent controlled asymmetric synthesis) occurs the most frequently. The asymmetric induction of this type can be explained by example of double asymmetric hydrogenations described by Horeau and Kagan.[8] These authors have found an impressive increase in stereoselectivity in the reduction of chiral ethers of phenylglyoxal acids by optically active reductants in comparison with the case when either the ether or the reducing agent were optically active (Scheme 2).[3,5] Chiral groups in the initial compounds **1** and **2** acted in one direction to increase the diastereofacial selectivity of the reagents.

The second version of double stereoselectivity, when a substrate contains two (or more) chiral centers and the reagent is achiral (substrate-controlled asymmetric synthesis), is less studied than the preceding method (Scheme 3). This case is very important for biological systems, usually containing several asymmetric centers controlling the stereo course of highly selective processes in living organisms. The most general, the double asymmetric induction corresponding to this case, is observed in the compounds having a C_2-symmetrical structure.[14] Many chiral auxiliaries involve the cooperation of two or several asymmetric centers affecting the stereochemical properties



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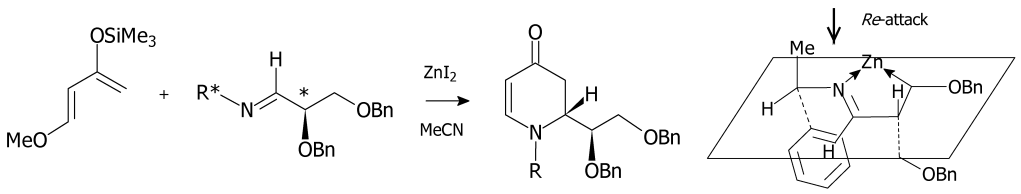
Scheme 3. Matched/mismatched substrate controlled double AS.



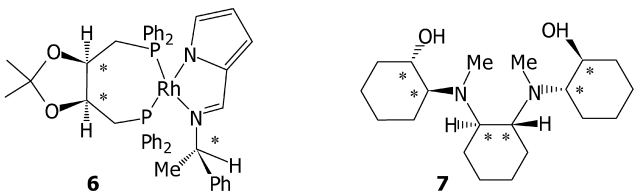
R*	*de* (%)	Double AS
Bn	70	none
(S)-CH(Me)Ph	28	mismatched
(R)-CH(Me)Ph	~100	matched

Scheme 4. Substrate controlled double AS.

of these auxiliaries. The diastereofacial systems **3** containing two chiral elements are more asymmetric then the systems with only one chiral element, and therefore the free energy difference between competitive transition states in a stereoselective reaction increases with the participation of such systems.

The *N*-benzylimines **5**, bearing two chiral centers, underwent a diastereoselective tandem Mannich–Michael reaction with the Danishevsky diene **4** in the presence of Lewis acids.[15] The matched double stereoselective reaction between the achiral diene **4** and the (*S*,*R*)-imine **5** in acetonitrile at −20°C under zinc iodide-catalysed conditions resulted in only a single diastereomer (~100% de), whereas with the (*R*,*R*)-imine a modest asymmetric induction was observed (28% de) (Scheme 4). The diastereoselectivities of these processes reflect the net directing effect of both stereogenic units present in the starting imines, i.e. 1,2-induction from the group at C-2 plus (matched pair) or minus (mismatched pair) 1,3-induction from the respective *N*-α-methylbenzyl moiety. The stereochemistry of this reaction can be explained in terms of a rational model **A** involving a 5-membered compacting chelate with the Zn atom. In the intermediate complex, both the benzyloxymethyl group in the chiral (*R*)-glyceraldehyde moiety and the phenyl group in the chiral amine would effectively block the *Si*-face of the (*E*)-imine complexed with ZnI_2 and the diene would approach the *Re*-face.

The perspective way to increase the stereoselectivity of a reaction is the introduction of additional chiral auxiliaries into the catalyst (catalyst-controlled multiple asymmetric synthesis). For instance, Brunner and Tracht[16a] studied the cooperative effect of the rhodium catalyst **6** bearing an (*R*,*R*)-DIOP ligand and bidentate chiral co-ligands with (*R*)- or (*S*)-configurations on the hydrogenation of diketo derivatives (Scheme 5). The hydrogenation of (*Z*)-α-*N*-acetamidocinnamic acid to *N*-acetylphenylalanine with chiral rhodium catalysts derived from DIOP (or NORPHOS) and ε-1,5-cyclooctadiene rhodium complexes bearing the anions of optically active 1,3-diketones or 1,3-ketoimines proceeded with asymmetric inductions up to 90.7 and 92.3% ee.[16b] In a second example, Cobbe and Marson[16c] introduced new stereogenic centers at the β-amino alcohol **7** used as a catalyst in the addition of Et_2Zn to benzaldehyde and also improved the stereoselectivity of the reaction from 40 to 92% ee (Scheme 5).

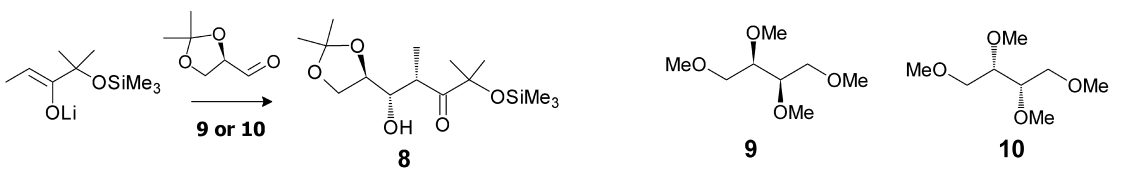


Scheme 5. Catalyst controlled multiple AS.

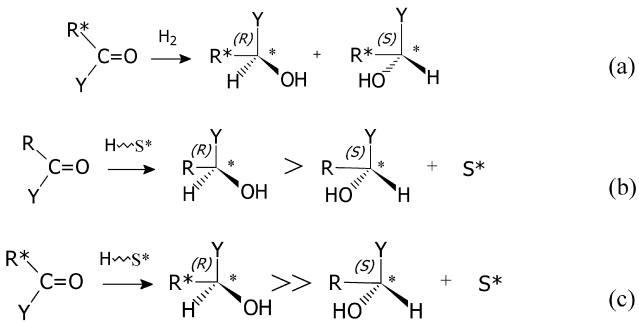
Another way in which mediocre diastereofacial selection might be enhanced is by using a chiral solvent.[9,17] Heathcock[18] has employed the chiral (+)- and (−)-1,2,3,4-tetramethoxybutanes **9** and **10** as chiral solvents in the aldol reaction of the ketone enolate **8** with (*R*)-glyceraldehyde acetonide and observed evident double stereoselectivity (Scheme 6).

The use of chiral phase transfer catalysts and chiral crown ethers as inducers of double stereoselectivity has been described.[19]

Quantitative evaluation of multiple stereoselectivity. Stereoselectivity is a function of many factors (solvation, medium, interaction between groups in molecules of reagents and remote from the reaction centre). Nevertheless, attempts to develop quantitative analysis of diastereofacial selectivity have been undertaken.[20,21] Masamune has suggested a semiquantitative methodology predictive of the results of a double asymmetric induction (Scheme 7).[12] The essence of this method is as follows. There are two identical stereoselective reactions, one of which involves a chiral reagent reacting with an achiral substrate (Eq. (1)), and the other, on the contrary, an achiral reagent reacting with a chiral substrate (Eq. (2)). Therefore, there is a probability that the reaction of the chiral reagent with the



Scheme 6. Example of substrate–solvent controlled double stereoselectivity.



(a)

(b)

(c)

Scheme 7. Masamune's modelling of double asymmetric induction.

chiral substrate will be more stereoselective in the coordinated asymmetric synthesis (Eq. (3)).

This methodology, indeed, provides in many cases good results, but sometimes gives erroneous conclusions. For example, Kagan and co-workers reported[22] that they obtained the highest diastereofacial selectivity in the case of a pair which should be expected to be the 'a priori' mismatched pair, whereas the asymmetric induction is predicted to be opposite. These authors suppose that semiquantitative calculations cannot lead to the production of double asymmetric induction, as pointed out by Masamune.

Izumi has proposed that the degree of asymmetric induction of double stereoselective reactions is expressed as a function of enantioselectivity and diastereoselectivity.[9] Horeau and co-workers[20] have assumed that the selectivity in a double stereoselective reaction should be connected with a difference of free energy activation between the enantioselective and diastereoselective reactions. The Gibbs free energy difference between competitive transition states in a stereoselective reaction can be expressed in energetic terms $\Delta\Delta G_R^{\#}$ and $\Delta\Delta G_S^{\#}$, of the chiral reagent and of the chiral substrate, and the total free energy difference of the double asymmetric reaction in the $\Delta\Delta G_{\mathrm{M}}^{\#}$ or $\Delta\Delta G_{\mathrm{MM}}^{\#}$ terms (matched and mismatched reactions). Some correction terms should be added to compensate for differences (geometric, electronic or otherwise) that may occur in the double asymmetric transition states relative to the single asymmetric models that give rise to the energetic terms.[21] If suitable single asymmetric models are chosen, then the correction terms $\Delta\Delta G_R^{\#}$ and $\Delta\Delta G_S^{\#}$ are small and can be ignored. In this case, the stereoselectivity of the double asymmetric reaction can be expressed as the summary of selectivities of both chiral reaction partners. Addition of Eqs. (1) and (2) gives Eq. (3) which defines the general difference of Gibbs free energy ($\sum\Delta\Delta G^{\#}$=difference in free energy=$\Delta\Delta G_{\mathrm{M}}^{\#}+\Delta\Delta G_{\mathrm{MM}}^{\#}$)

$$\Delta\Delta G_{\mathrm{M}}^{\#} = \Delta\Delta G_R^{\#} + \Delta\Delta G_S^{\#} + \Delta G_{RS}^{\#} + \Delta G'_{RS}\# \tag{1}$$

(matched double stereoselectivity)

$$\Delta\Delta G_{\mathrm{MM}}^{\#} = \Delta\Delta G_R^{\#} - \Delta\Delta G_S^{\#} + \Delta G_{RS}^{\#} + \Delta G'_{RS}\# \tag{2}$$

(mismatched double stereoselectivity)

$$\sum\Delta\Delta G^{\#} = \Delta\Delta G_{\mathrm{M}}^{\#} - \Delta\Delta G_{\mathrm{MM}}^{\#}$$

$$= 2\Delta\Delta G_R^{\#} + \Delta G_{RS}^{\#} + \Delta G_R^{\#} \approx 2\Delta\Delta G_R^{\#} \tag{3}$$

$\sum\Delta\Delta G^{\#}=2\Delta\Delta G_R^{\#}$ if the values ΔG_{RS} and $\Delta G_{RS}^{\#}$ are insignificant and can be ignored and then the average diastereofacial selectivities (a chiral reactant in a pair of double asymmetric experiments) $\Delta\Delta G^{\#}/2=\Delta\Delta G_R^{\#}$. For analytical purposes, it is therefore possible to use the average diastereofacial selectivity, $\Delta\Delta G_R^{\#}$ (av), calculated as a deviation of the experimental determinations $\sum\Delta\Delta G_{\neq}$ divided by two, as shown in Eq. (3). The value of the average diastereofacial selectivity [$\Delta\Delta G_R^{\#}$ (av)] may be compared with the values $\Delta\Delta G_R^{\#}$, determined from the experimental values de of a single asymmetric induction of the chiral reagent with an achiral substrate. These definitions of free energy of a double diastereoselectivity allow a direct comparison to be made of the relative diastereoselectivity of a number of chiral substrates with a given chiral reagent. If good agreement $\Delta G_{RS}^{\#}$ is found, then the $\Delta G_{RS}^{\#}$ and $\Delta G_{RS}^{\#}$ correction terms are, indeed, insignificant and such a chiral reagent/chiral substrate pair can be used for double asymmetric reactions. If the agreement is poor, then the chiral reagent/chiral substrate pair is incorrect.[21] In such cases, the correction terms $\Delta G_{RS}^{\#}$ and $\Delta G_{RS}^{\#}$ cannot be ignored and the achiral substrate chosen for the determination of $\Delta\Delta G_R^{\#}$ values is not suitable.

A number of articles showing good agreement between the calculated and experimental values of average diastereofacial selectivities have been published. At the same time, examples of reactions with an insignificant effect of double stereoselectivity are also known, when introduction of additional asymmetric auxiliaries had a very weak influence on asymmetric induction of both optical antipodes.

Nevertheless, the examples of very effective double asymmetric induction are numerous and can be proposed for the attention of the reader in the following sections of this review.

3. Multiple stereoselectivity as a method of stereocontrol in asymmetric organic synthesis

Multiple stereoselectivity as a method to increase the stereoselectivity has been more and more widely used in organic synthesis in the last few years, in order to find applications in new areas. During the last two decades, a number of powerful double stereoselective reactions have been developed as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Multiple stereoselective reactions provided an especially effective entry to the chiral world due to their economical use of asymmetry-inducing agents. A number of processes have gained wide acceptance, and some of them are even used on an industrial scale. Among the most prominent examples are Sharpless asymmetric epoxidation and dihydroxylation.

3.1. Asymmetric reduction

Double asymmetric induction in asymmetric reduction was

first demonstrated by Horeaux, Kagan and Vigneron,[8] although in 1950 Vavon and Antonini[6] reported that the reduction of phenylglyoxalic acid derivatives proceeds more stereoselectively if it is required to insert an additional chiral center into a reacting system (Scheme 8).

$$PhCOCO_2H + 2Mnt^*OMgBr \longrightarrow PhC^*H(OH)CO_2H \quad (33\ \%)$$

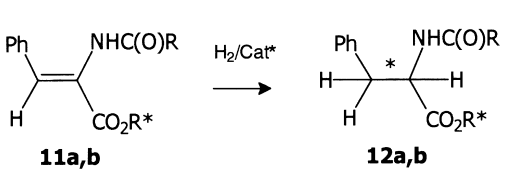
$$PhCOCO_2Mnt^* + 2Mnt^*OMgBr \longrightarrow PhC^*H(OH)CO_2H \quad (41\ \%)$$

Scheme 8. Examples of double AS.

3.1.1. Hydrogenation. Double asymmetric induction has been used with great success for homocatalytic hydrogenation and for the reduction of non-saturated compounds.[23–27]

In 1977, Glazer and co-workers[23] achieved hydrogenation of the chiral menthyl esters **11a** and bornyl esters **12b** (R=Me) in the presence of chiral catalysts [Cat*=[Rh(L*)(COD)][BF_4] (Scheme 9). They discovered that the double asymmetric induction increased the stereoselectivity of the reaction, although the stereoselectivity of hydrogenation was moderate.

Recently, Selke et al.[24] continued these studies with chiral rhodium(I) chelate catalysts containing the ligands **13** and **14**, derived from phenyl 2,3-bis-(*o*-phenylphosphino)-β-D-glucopyranoside in asymmetric hydrogenations of menthyl (*Z*)-2-*N*-benzoylamidocinnamate **11a** (R=Ph) and obtained the amino acid ester **12a** (R=Ph) with high stereoselectivity (Scheme 9 and Table 1). The hydrogenation of the cinnamates **11a** with the rhodium(I) chelate of (Ph-Glup-OH) **13** as a chiral catalyst (L*) in polar solvents proceeded as a matched asymmetric synthesis with a stereoselectivity of >96% leading to the (*S*)-amino acid menthyl esters **12a**. The analogous chelate of (Me-Glup) **14** forms a mismatched pair with the enantiomer (1*R*,2*S*,5*R*)-**11a** to give the (*S*)-



11a,b **12a,b**

Scheme 9. Asymmetric hydrogenation of cinnamic acid derivatives.

Table 1. Hydrogenation of dehydro-α-amino acid **11a** (R=Ph, R*=Mnt) with [Rh(L*)(COD)]BF_4[24]

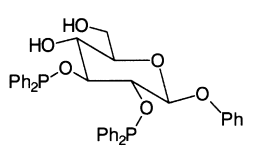
L*	Solvent	R*=(1*R*,2*S*,5*R*)-Mnt		R*=(1*S*,2*R*,5*S*)-Mnt	
		(*S*)	(*R*)	(*S*)	(*R*)
Pd black	Acetone	61%	39%	39%	61%
	Acetone	96.5	3.5	96.0	4.0
13	Methanol	96.3	3.7	97.4	2.6
	Benzene	91	9	79	21
	Acetone	86	14	57	43
14	Methanol	81	19	66	34
	Benzene	75	25	14	86

product **12a** in a low diastereoselectivity, which was inversed in benzene to 86% of the (*R*)-diastereomer, showing that the double diastereoselectivity in asymmetric homolytic hydrogenations reactions depends on the coordinated action of a substrate and catalyst (Table 1).

The asymmetric hydrogenation of dehydropeptides has been extensively studied during the last two decades (Table 2).[22,25–27]

Table 2. Matched/mismatched asymmetric hydrogenation of dehydropeptides **15** with Rh (I)catalysts (Scheme 10)

Entry	Substrate **15**	L*	ds	Ref.
1	Bz-ΔPhe-(*S*)-Phe-OMe	(−)-BPPM	98.7:1.3	27
2	Bz-ΔPhe-(*S*)-Phe-OMe	(+)-BPPM	0.9:99.1	27
3	Ac-ΔPhe-(*R*)-Phe-OMe	(−)-BPPM	99.6:0.4	27
4	Ac-ΔPhe-(*R*)-Phe-OMe	(+)-BPPM	1.5:98.5	27
5	Ac-ΔPhe-(*S*)-Phe-OH	(−)-BPPM	96.2:3.8	27
6	Ac-ΔPhe-(*S*)-Phe-OH	(+)-BPPM	0.6:99.4	27
7	Bz-ΔPhe-(*S*)-Phe-OMe	*p*-BrC_6H_4-CAPP	99.2:0.8	27
8	Bz-ΔPhe-(*S*)-Phe-OMe	DIPAMP	1.4:98.6	27
9	Ac-ΔPhe-(*S*)-Phe-OMe	CBz-(*S*)-Phe-PPM	98.0:2.0	27
10	Ac-ΔPhe-(*R*)-Phe-OMe	CBz-(*S*)-Phe-PPM	99.5:0.5	27
11	Ac-ΔPhe-(*S*)-Phe-OMe	CBz-(*S*)-Pro-PPM	98.1:1.9	27
12	Ac-ΔPhe-(*R*)-Phe-OMe	CBz-(*S*)-Pro-PPM	99.5:0.5	27
13	Ac-ΔPhe-(*S*)-Phe-OMe	CBz-(*S*)-Val-PPM	98.9:1.1	27
14	Ac-ΔPhe-(*R*)-Phe-OMe	CBz-(*S*)-Val-PPM	96.2:3.8	27
15	Ac-Δ(Ac)-Tyr-(*R*)-Ala-OMe	Ph-CAPP	99.8:0.2	27
16	Ac-ΔPhe-(*S*)-Phe-OH	(−)-DIOP	81.8:18.2	27
17	Ac-ΔPhe-(*S*)-Phe-OH	(+)-DIOP	5.9:94.1	27
18	Ac-(*R*)-Phe-ΔPheOMe	(*R*,*R*)-dipamp$^+$	1:22.8	22
19	Ac-(*R*)-Phe-ΔPheOMe	(*S*,*S*)-diopCl	1:2.2	22
20	Ac-(*R*)-Phe-ΔPheOMe	(*R*,*R*)-dipamp$^+$	1:166	22
21	Ac-(*R*)-Phe-ΔPheOMe	(*S*,*S*)-diopCl	4.0:1	22
22	Ac-(*S*)-ΔPhe-AlaOH	**18**	95:5	26
23	Ac-(*S*)-ΔPhe-AlaOH	**19**	>99:1	26
24	Ac-(*S*)-ΔPhe-PheOH	**20**	>99:1	26
25	Ac-(*R*)-ΔPhe-PheOH	**20**	7:93	26
26	Ac-(*S*)-ΔPhe-AlaOH	**18**	*94:6*	26
27	Ac-(*R*)-ΔPhe-AlaOH	**18**	4:96	26
28	Ac-(*S*)-ΔPhe-AlaOH	**20**	98:2	26
29	Ac-(*R*)-ΔPhe-AlaOH	**20**	7:93	26



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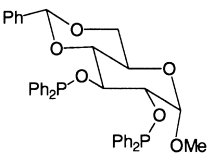
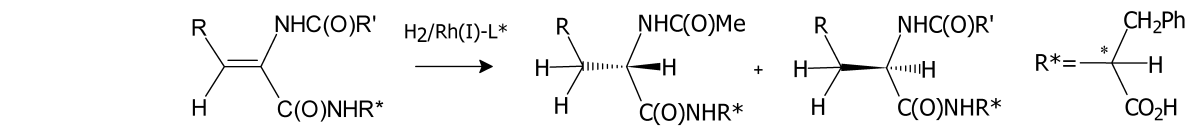


14

Ojima et al.[27] have achieved an extremely high stereoselectivity in the homogeneous asymmetric hydrogenation of the chiral dehydrodipeptides **15** by using chiral rhodium catalysts with a variety of chiral diphosphine ligands such as DIOP, BPPM and DIPAMP (Scheme 10 and Table 2).

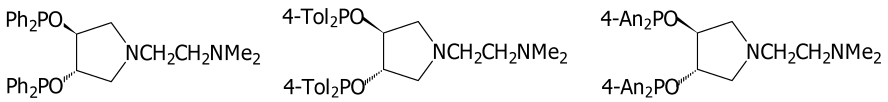
Hydrogenation of the dehydropeptide Ac-ΔPhe-(*S*)-Phe-OH in the presence of achiral rhodium catalysts proceeded with a low stereoselectivity to give a 1.9:1 ratio of the diastereomers *S*,*S*-**16** and *R*,*S*-**17**, whereas, with the chiral rhodium catalyst bearing (+)-BPPM, the matched asymmetric synthesis resulted in a diastereomeric ratio of 161:1 (Table 2, entry 6). With the (−)-BPPM ligand the mismatched asymmetric induction provided a 1:25



15 **16** **17**

R = Me, Ph; R' = Me, OH, OMe

Scheme 10. Double asymmetric synthesis of dipeptides.



18 **19** **20**

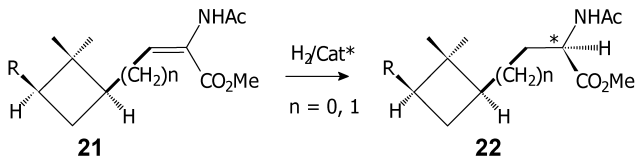
Scheme 11. Chiral diphosphinite (Ar-POP-AE) ligands.

diastereomeric ratio (entry 5).[27] Hydrogenation of Ac-ΔPhe-(*R*)-Phe-OH in the presence of (−)-BPPM afforded the dipeptides **16** in a 249:1 diastereomeric ratio (matched induction, entry 3), whereas the reaction using (+)-BPPM led to the formation of the diastereoisomers **16** and **17** in a ratio of 65.7:1 (mismatched induction, entry 4). Homogeneous hydrogenation of the dehydropeptide Ac-Δ(Ac)-Tyr-(*R*)-Ala-OMe with the rhodium complex containing the Rh-CAPP ligand provided the dipeptide **16** with a 499:1 ratio of (*R*,*R*)/(*S*,*S*)-diastereomers (entry 15).

Kagan and co-workers[22] studied various types of chiral Rh(I) catalysts for asymmetric hydrogenation of dehydropeptides **15**, using L*=DIOP, BPPM or DIPAMP as ligands in the catalysts. They found that BPPM and DIPAMP give rhodium catalysts that were more stereoselective than DIOP in the reduction of various dehydro-peptides. Kagan reported that they obtained the highest stereoselectivity in 'predicted (by Masamune theory) mismatched pair' and lower stereoselectivity in 'predicted matched pair' (Scheme 10 and entries 18–21 in Table 2).

Yamagishi et al.[25,26] developed the chiral diphosphinite ligands **18**–**20**, having diarylphosphinooxy and dimethylamino substituents (Ar-POP-AE catalysts) (Scheme 11). The asymmetric hydrogenation of *N*-(benzoylformyl)amino acids with the Rh catalysts bearing ligands **18**–**20** proceeded with an extremely large double asymmetric induction to give the dipeptides **16** and **17** in stereoselectivities achieving almost 100% de (entries 23 and 24 in Table 2).[26]

Several important findings have been reported during the last few years.[28–36] Ojima and co-workers,[29] and Kagan and co-workers[22] observed the double asymmetric induction during the hydrogenation of chiral benzyl esters of *N*-(*N*-acetyldihydrophenylalanyl)aminoalcohols and also monohydropeptides bearing the dehydroamino acid fragment in the C-terminal or N-terminal position the rhodium complexes containing chiral phosphine ligands. Quite recently, Aguado and co-workers[30] investigated the double stereoselective hydrogenation of optically active cyclobutyl dehydroamino acid derivatives **21** and obtained the amino acid esters **22** employing rhodium catalysts (Cat*) with the chiral (*S*,*S*)-chiraphos and Et-duphos (both enantiomers) ligands (Scheme 12). The use of a chiral catalyst was crucial



21 **22**

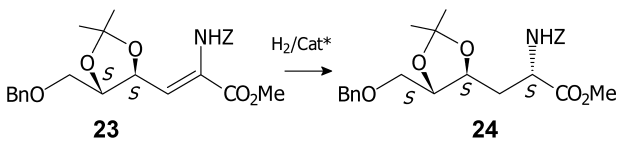
R	Cat*	*n*	Conf.	*dr*
CO_2Me	*a*	0	*R*	75:25
CO_2Me	*b*	0	*R*	95:5
CO_2Me	*c*	0	*R*	85:15
Ac	*b*	1	*R*	> 92:8
Ac	*c*	1	*R*	> 98:2

Cat*=$(Ph_3P)_3RhCl$ (**a**), [Rh(*(S,S)*-chiraphos)]$C1O_4$ (**b**), [(COD)Rh*((R,R)*-Et-duphos)]OTf (**c**)

Scheme 12. Hydrogenation of cyclobutyl dehydroamino acids **21**.

to stereochemical induction in the hydrogenation of enamides **21**, where the stereogenic center is too remote from the double bond to influence the π-facial stereoselection.

Schmidt et al.[36] described the double asymmetric induction in the hydrogenation of optically active didehydroamino acid esters **23** with optically active catalysts [Rh(COD)(DIPAMP)]$^+$ BF_4^- (Scheme 13). When the chiral catalyst (*R*,*R*)-[Rh(COD)(DIPAMP)]$^+BF_4^-$ was used, the protected (2*S*,4*S*,5*S*)-2-amino-4,5,6-trihydroxypentanoic acid **24** was obtained with matched asymmetric induction (de 94.4%). With (*S*,*S*)-[Rh(COD)(DIPAMP)]$^+BF_4^-$, however, these inductions were mismatched to give (2*R*,4*S*,5*S*)-**24** in a de of only 57%.

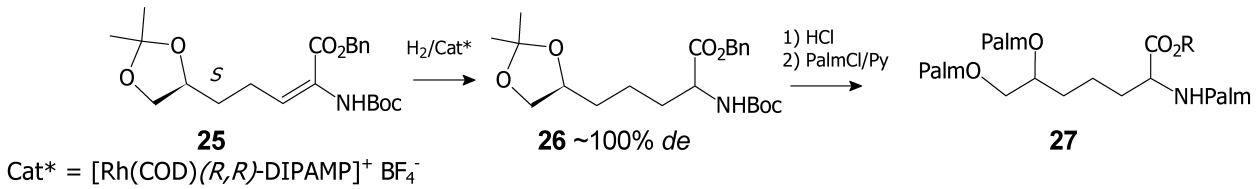


23 **24**

Cat	*de* (%)	Double AI
$[Rh(diphos)]_2^+(BF_4^-)_2$	31.4	none
(R,R) -[Rh(COD)DIPAMP]$^+BF_4^-$	94.4	matched
(S,S)- [Rh(COD) DIPAMP]$^+BF_4^-$	57	mismatched

Scheme 13. Double asymmetric induction in the hydrogenation of didehydroamino acid esters **23**.

Didehydroamino acid esters **25** were hydrogenated to give enantiomerically pure substituted amino acid esters **26** (Scheme 14). Acid hydrolysis of the products **26** gave rise to



Scheme 14. The asymmetric synthesis of 2-palmitoylamino-6,7-dipalmitoyloxyheptanoic acids.

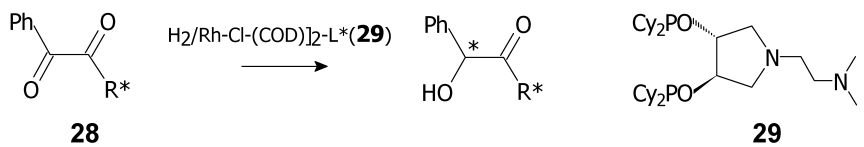
the free benzyl 2-amino-6,7-dihydroxyheptanoates, which were acylated to furnish the tripalmitoyl compounds **27** with complete diastereoselectivity. The synthetic tripalmitoyl derivatives were linked to oligopeptides, conjugated with various antigens and used for the development of a synthetic vaccine against foot-and-mouth disease.[36]

Yamagishi[25,26] observed the double asymmetric induction in the Rh(I)-catalysed asymmetric hydrogenation of α-keto acid derivatives **28** using the chiral diphosphinite ligands **29** containing a pyrrolidine moiety (Cy-POP-AE) (Scheme 15).

Sunjic et al.[31] observed the double asymmetric induction in the hydrogenation of prochiral precursors of (+)-ketoprofen, and (+)-naproxen over a rhodium(I) catalyst containing chiral diphenylphosphine and diphenylphosphinite ligands derived from monosaccharides. The double diastereoselectivity in the hydrogenation of ketones was achieved with rhodium(I) complexes containing optically active peralkyldiphosphine ligands.[32] The differentiation of fluorinated groups in unsaturated ketones with active fermenting yeast and the double asymmetric induction in some perfluoroalkylated ketones have been also reported.[33] Tunglerad[34] and Klabunovskii[35] described the double asymmetric hydrogenation of aminocinnamic acid derivatives with cinchonidine or chiral Pd–polymer catalysts.

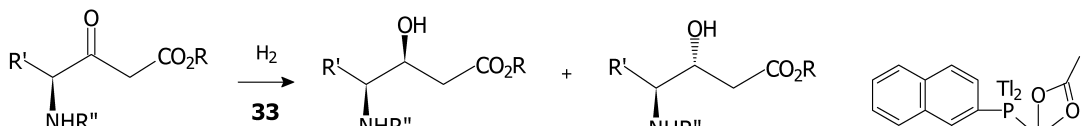
Ruthenium complexes are very effective under double asymmetric hydrogenation conditions.[37–39] The most interesting results were achieved with BINAP–Ru (II) catalysts discovered in 1980 by Noyori and Takaya,[36] and awarded in 2001 by Nobel Prize.[39] Noyori and co-workers[40–44] reported that the diastereoselective hydrogenation of chiral (*S*)-*N*-protected γ-amino-β-ketoesters **30**, in the presence of $RuBr_2$[(*R*)-BINAP)] or Ru–BINAP-complex **33**, furnished the isomer **31** with de >98%, whereas the hydrogenation of achiral β-ketoesters in similar conditions proceeded with low stereoselectivity to give the diastereomeric mixture **31**,**32**. A series of optically pure β-ketoesters was hydrogenated to provide an accessible entry into the statin series (Scheme 16). Both the efficiency of the catalyst–substrate chirality transfer (catalyst control) and intramolecular 1,2-asymmetric induction (substrate control) were observed in the hydrogenation of the *N*-Boc-protected substrate **34**. The reaction in the presence of $RuBr_2$[(*R*)-BiNAP] gave the *threo*-hydrogenation product **35** with (3*S*,4*S*)-configuration almost exclusively, whereas the reaction catalysed by the enantiomeric $RuBr_2$[(*S*)-BINAP] complex afforded a 9:91 mixture of the *threo*- and *erythro*-products **35**:**36**. The *threo*-induction agrees with the Felkin model **B** shown in Scheme 17.

The electronegative Boc-amino group is oriented *anti*-periplanar to the incoming hydride, while the benzyl group avoids non-bonded repulsion with the vicinal ethoxycarbonylmethyl group by occupying the synclinal position to the carbonyl oxygen.



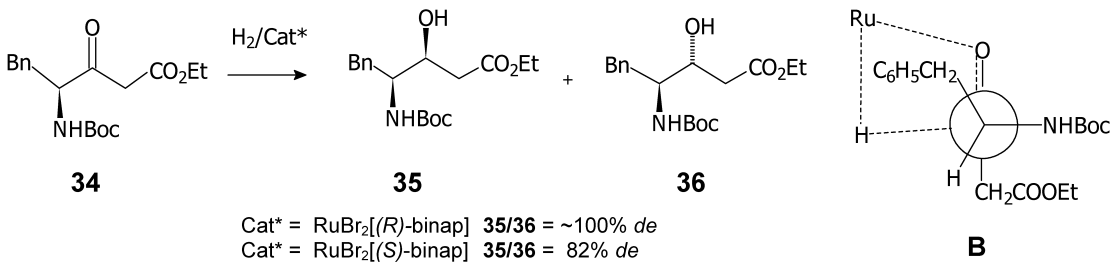
R*	*de* (%)	Double AI
OH	2(*S*)	none
(*R*)-Ala-OH	5(*R*,*R*)	mismatched
(*S*)-Ala-OH	67(R,S)	matched

Scheme 15. Asymmetric hydrogenation of α-keto acid derivatives.



R	R'	R"	Conf	31:32
Et	*i*-Bu	Boc	*R*	> 99:1
Et	Bn	Boc	*R*	> 99: 1
Et	Bn	Boc	*R*	> 99:1
Et	Bn	Boc	*S*	9:91
Me	H	BnOCO	*S*	6:94 (*S*:*R*)

Scheme 16. Asymmetric synthesis of statin analogues.



Scheme 17. Origin of the *threo*-selection in BINAP–Ru-catalysed hydrogenation of **34**.

Enantiomerically pure substrates **37** were employed in the asymmetric catalytic hydrogenation (Scheme 18).[44] Ru complexes bearing both enantiomers of the ligand, i.e. (*R*,*R*)-**40** or (*S*,*S*)-**40**, provided the products **38** and **39**, respectively, with 99% ee to confirm that the catalyst selectivity greatly overrides that of the inherent diastereoselectivity in this process.

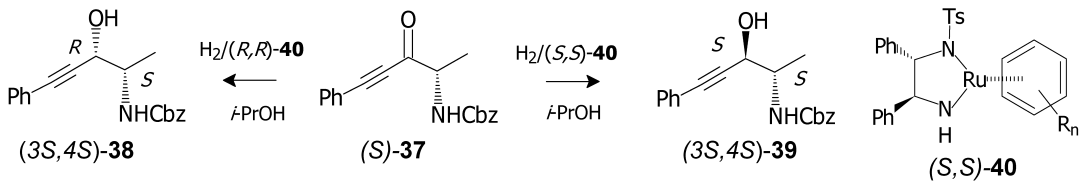
Double stereodifferentiation in BINAP–Ru-catalysed hydrogenation of the enantiomerically pure (*R*)-hydroxyketone with either the (*R*)- or (*S*)-BINAP complex revealed the catalyst control (R^*/S^*) to be 33:1 and the substrate control to be about 6:1.[43] In such a two-step hydrogenation of the diketone **41**, the overall stereochemical outcome was determined by both the efficacy of catalyst/carbonyl chirality transfer (catalyst control) and the structures of the initially created hydroxyketones including the chirality of the stereogenic center (substrate control).[43–46] The high enantiomeric purity of **42** obtained by (*R*)-BINAP–Ru catalysis is a result of double stereodifferentiation in the second step of the hydrogenation: the (*R*,*R*)/(*R*,*S*) ratio in the 1,3-diol **42** was about 900:1, and the minor enantiomer **43** was undetectable by accessible analytical methods (Scheme 19).

The hydrogenation of 1,5-dichloro-2,4-pentanedione has been used for the synthesis of optically pure (2*R*,4*R*)- and (2*S*,4*S*)-1,2:4,5-diepoxypentanes, intermediates of a wide variety of optically active *syn*- and *anti*-1,3-diols that have a symmetrical or unsymmetrical substitution structure.[37] The asymmetric hydrogenation of 3-methyl-2,4-pentanedione, a 2-alkylated 1,3-diketone **44**, viewed formally as triple stereodifferentiation, led to the chiral diol **45** in 99% yield and 99% ee.[43]

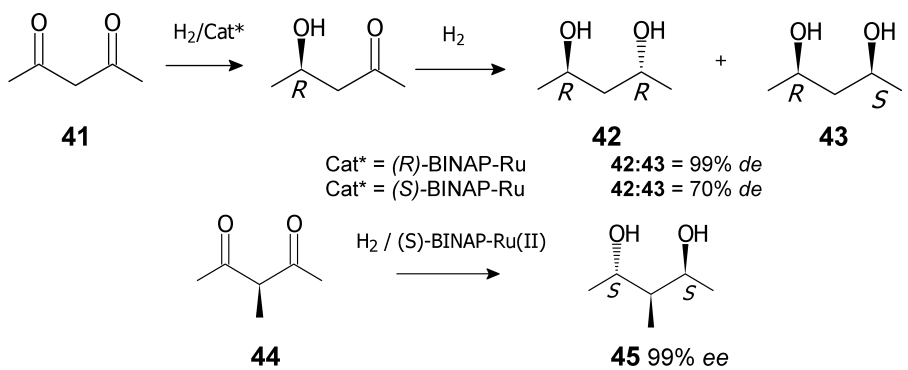
The hydrogenation of chiral (*R*)-α-hydroxyketones **46** with $[NH_2Et_2]^+\{RuCl[(R)\text{-BiNAP}]_2(\mu\text{-}Cl)_3\}^-$ as the catalyst followed by acetonisation produced the corresponding *syn*/*anti*-products **47** with stereoselectivities of 20–64% (mismatched asymmetric induction), whereas the reduction of (*R*)-**46** with the catalyst of the opposite (*S*)-configuration produced the *anti*-diastereomer **48** with 88–90% de (matched induction) (Scheme 20).[45]

Noyori et al.[46] reported the hydrogenation of the chiral substrate **49** with the chiral BINAP–Ru(II) catalyst **33**. The reaction utilising the double asymmetric induction resulted in the formation of a key precursor of 1β-methylcarbapenem antibiotics **50** with a quantitative yield and with extremely high stereoselectivity (ds 1000:1, ~99.99% de!) (Scheme 21).

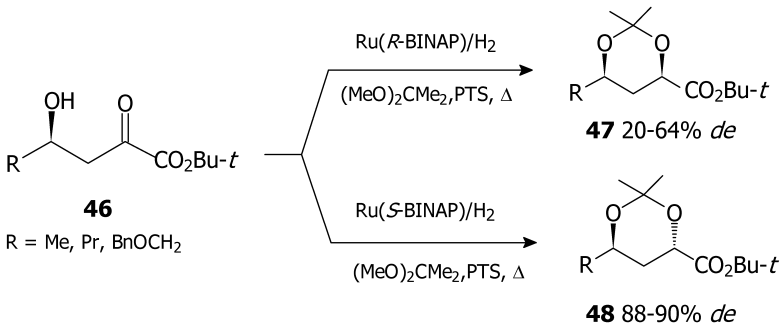
The asymmetric synthesis of the key intermediates **52** and **53** of aspartyl dipeptide sweeteners **54** has been carried out via the hydrogenations of alkenes **51** catalysed by the chiral (*S*)- or (*R*)-BINAP–Ru complexes **33**. The double



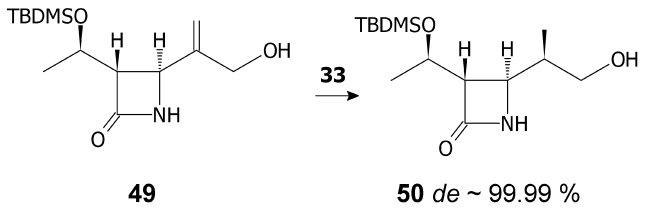
Scheme 18. Asymmetric catalytic hydrogenation of ketones **37**.



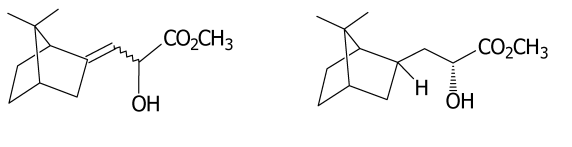
Scheme 19. Double and triple stereodifferentiation in the asymmetric hydrogenation of 1,3-diketones.



Scheme 20. Matched/mismatched catalytic hydrogenation of the chiral (*R*)-β-hydroxyketones **46**.



Scheme 21. BiNAP–Ru(II) catalyzed double asymmetric synthesis of a 1β-methylcarbapenem precursor.



Cat*	Yield (%)	*de* of 52 *(%)*
10% Pt-C	100	50
(S)-BINAP-Ru	100	64
(R)-BINAP-Ru	100	98

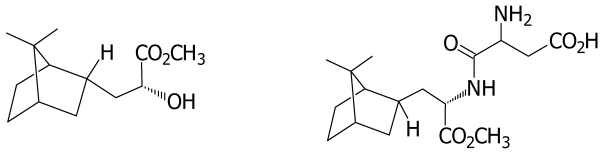
Scheme 22. Asymmetric synthesis of aspartyl dipeptide sweeteners.

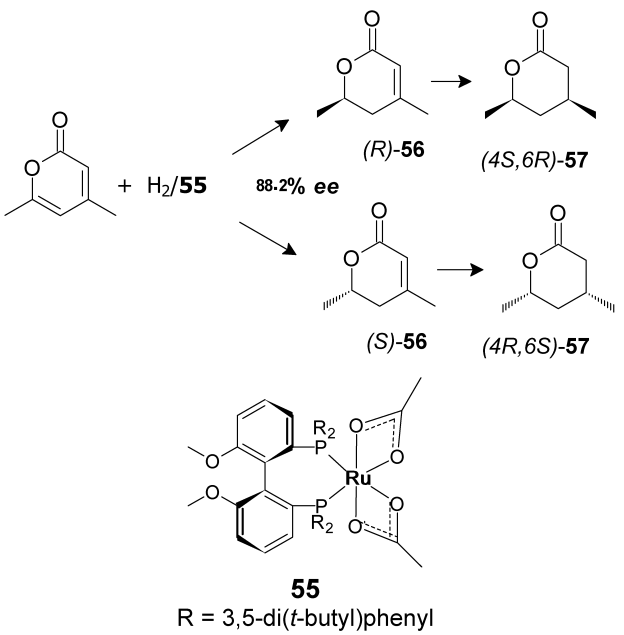
asymmetric induction increased the *exo*-selectivity of the reaction from 75:25 to 99:1. The alcohols **53** were then converted into the amino acid esters **54** (Scheme 22).[47]

Fehr and co-workers[48] have performed the hydrogenation of substituted 2-pyrones using a cationic ruthenium catalyst **55** containing the atropoisomeric (6,6′-dimethoxybiphenyl-2,2′-diyl)-bis[3,5-di(*t*-butyl)phenylphosphine ligands and obtained the corresponding *cis*-5,6-tetrahydropyrones **57** with enantioselectivity up to 97% ee (Scheme 23). The optically active 5,6-dihydro-2-pyrones and δ-lactones possess interesting pharmaceutical properties.[49] The hydrogenation of pyran-2-ones proceeded stepwise with the double asymmetric induction to give at first the 5,6-dihydropyrone **56** (with an insignificant amount of the 3,6-dihydropyrone), which was then converted into the corresponding *cis*-tetrahydropyrones **57**.

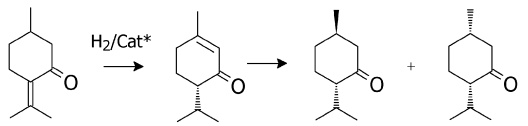
Le Maux[50] reported that the double asymmetric hydrogenation of piperitenone **58** in the presence of chiral ruthenium catalysts $HRuCl(TBPC)_2$, where TBPC is (−)-(*R*,*R*)-*trans*-1,2-bis[(diphenylphosphino)methyl]cyclobutane, leads to the formation of piperitone **58**, menthone **59** and isomenthone **60** with the stereoselectivity from modest (42% ee) to very good (~80% ee) (Scheme 24).

3.1.2. Hydrosilylation and hydroboration. Ojima and co-workers[51,52] studied the asymmetric reduction of α,β,γ-ketoesters via hydrosilylation catalysed by rhodium complexes with chiral phosphines, (+)-BMPP and (+)- or (−)-MOP. The evident double asymmetric induction was observed in the asymmetric hydrosilylation of chiral (−)-menthyl phenylglyoxalate **61a** and pyruvate **61b** with l-NaphPhSiH$_2$ using chiral (+)-DIOP–rhodium complexes as catalysts. The menthyl phenylglyoxalate **61a** was





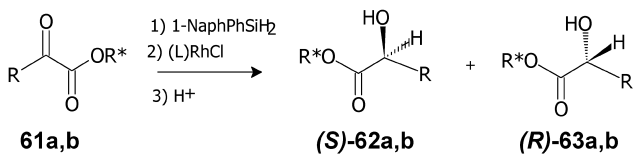
Scheme 23. Asymmetric hydrogenation of 2-pyrones.



Configuration, *ee* (%)			
Cat*	**58**	**59**	**60**
$HRuCl(TBPC)_2$	(+)-*(S)*, 34	(-)-*(S,R)*, 80	(+)-*(R,R)*, 25
$RuCl_2(PPh_3)_3$	(+)-*(S)*, 29	(-)-*(S,R)*, 30	(-)-*(S,S)*, 31.5

Scheme 24. Asymmetric hydrogenation of piperitenone.

transformed into menthyl-(*S*)-mandelate **62a** with 77% ee. The double asymmetric reduction of (−)-menthyl pyruvate **61b** over the chiral catalyst Rh-(+)-DIOP led to the formation of the chiral alcohol **62b** and **63b** with 85.6% de, corresponding to the matched asymmetric reduction of (+)-DIOP–catalyst and (−)-menthyl groups, favourable for the formation of a product with (*S*)-configuration (Scheme 25).[51,52]

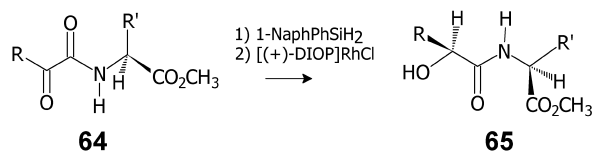


R = Me (a), Ph (b); R* = (*IR,2S,5R*)-Mnt

R	L	*de* (%)
Ph	PPh_3	21
Ph	(+)-DIOP	77*(S)*
Me	(-)-DIOP	82.8*(R)*
Me	(+)-DIOP	85.6*(S)*

Scheme 25. Asymmetric hydrosilylation of ketoesters **61**.

The asymmetric hydrosilylation of α-ketoacylamino esters **64** with $H_2SiPhNaph$ using [(+)-DIOP]–Rh(I) proceeded with stereoselectivity of 42–82% (Scheme 26). The hydrosilylation of (−)-menthone with the same catalyst led to the formation of neomenthol with a higher stereoselectivity than with the (−)-DIOP catalyst (de 82%).[52,53]



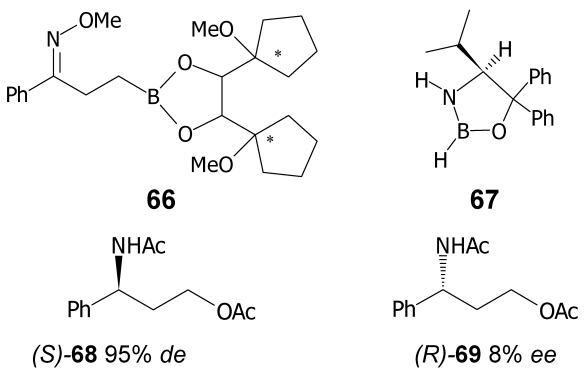
R=Me, Ph; R'=Me, Bz, *i*-Pr,

R	R'	Catalyst	*de*(%)
Me	Pr-i	(+)-DIOP-RhCl	68
		(-)-DIOP-RhCl	72
		$Rh(PPh_3)_3Cl$	42
Ph	Bn	(+)-DIOP-RhCl	82
		(-)-DIOP-RhCl	42
		$Rh(PPh_3)_3Cl$	56

Scheme 26. Matched/mismatched asymmetric hydrosilylation of α-ketoacetylamino esters.

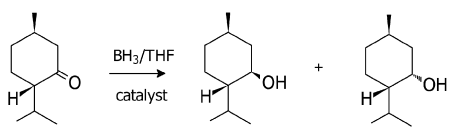
Chiral organoboron reactants were applied for the stereoselective reduction of multiple bonds.[54–59]

Brown and Prasad[59] studied the double asymmetric hydroboration of heterocycles with diisopinocampheylborane (Ipc_2BH). Diisopinocampheylborane of high enantiomeric purity (99.1% ee) has been prepared from borane–methyl sulphide and α-pinene. The reduction of (*S*)- and (*R*)-homochiral ethers of β-boronate oximes **66** with the chiral Izuno oxazaborolidine **67**, obtained in situ from the homochiral α,α-diphenyl-π-aminoalcohol and borane, led to the formation of (*S*)-**68** and (*R*)-**69** diacetyl derivatives (Scheme 27).[60] The reduction of the (4*R*,5*R*)-β-boronate oxime ether **66** resulted in the formation of (*S*)-**68** with matched asymmetric stereoselectivity (ee 95%). In contrast, the reduction of the (4*S*,5*S*)-β-boronate oxime ether **66** afforded the (*R*)-diacetyl derivative **69** with mismatched asymmetric induction (8% ee). This reaction shows that the remote double diastereoselection effect can be 'transmitted' by a suitable choice of a 'partner' molecule.



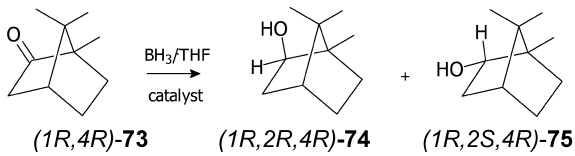
Scheme 27. Double asymmetric hydroboration of homochiral β-boronate oximes.

Martens and co-workers[61] observed the double asymmetric induction in the reduction of enantiomerically pure ketones using oxazaborolidine catalysts with a variety of chiral ligands. The use of borane and catalytic amounts of chiral aminoalcohols with the rigid configuration led to an increased double stereoselectivity. The reduction of (2*S*,5*R*)-menthone **70** and (1*R*,4*R*)-camphor **73** furnished the secondary alcohols **71** and **72** (Scheme 28) and **74** and **75** with stereoselectivity up to 90% de (Scheme 29).



Catalyst	71:72
(S)-1-(1'-amino-1'-phenylmethyl)cyclopentanol	86:14
(R)-1-(1'-amino-1'-phenylmethyl)cyclopentanol	25 :75
(S)-1-(1'-amino-1'-phenylmethyl)cyclohexanol	94:6
(S)-1-pyrrolidin-2-ylcyclopentanol	27:73

Scheme 28. Matched/mismatched asymmetric reduction of (2*S*/5*R*)-menthone.



(1R,4R)-**73** (1R,2R,4R)-**74** (1R,2S,4R)-**75**

Catalyst (10 mol %)	**74:75**
(*S*)-1-pyrrolidin-2-yl-cyclohexanol	> 95:5
(*S*)-2-diphenyl-hydroxymethyl)pyrrolidine	6:94
(*R*)-2-diphenyl-hydroxymethyl)pyrrolidine	90:10
(*S*)-1-(1'amino-1'-phenylmethyl)cyclopentanol	92:8
(*R*)-1-(1'amino-1'-phenylmethyl)cyclopentanol	84:16
(*S*)-2-(diphenyl-hydroxymethyl)pyrrolidine	> 95:5
(*R*)-2-(diphenyl-hydroxymethyl)pyrrolidine	10:90

Scheme 29. Matched/mismatched asymmetric reduction of (1*R*,4*R*)-camphor.

The DIBAL and L-selectride reduction of chiral sulphinyl ketimines was achieved with very high stereoselectivity under ZnX_2 catalysis.[62]

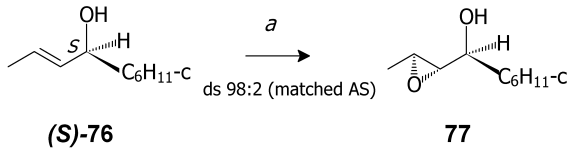
3.2. Asymmetric oxidation

The asymmetric oxidation of carbon–carbon double bonds into a variety of functionalised compounds is undoubtedly one of the most useful transformations in synthetic organic chemistry and efforts have been devoted to the development of efficient methods for asymmetric oxidation.[39,63–78] The most outstanding achievements in this field are enantioselective methods for asymmetric epoxidation (AE) and asymmetric dihydroxylation (AD) of alkenes, developed by Sharpless, who was awarded the Nobel Prize in Chemistry in 2001.[39]

Other major advances in asymmetric oxidation of olefins followed,[63] namely the Jacobsen and Katsuki salen-asymmetric epoxidation,[64,65] and the Sharpless asymmetric aminohydroxylation.[66–69]

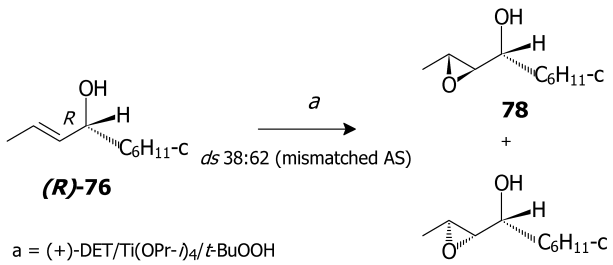
3.2.1. Epoxidation. The asymmetric epoxidation reaction discovered in 1980 by Sharpless[5] and Katsuki[7] is a nice example of the strategy of using a reagent to achieve full stereochemical control. Using titanium(IV) tetraisopropoxide, *t*-butyl hydroperoxide and an enantiomerically pure dialkyl tartrate, the Sharpless reaction accomplishes the epoxidation of allylic alcohols with excellent stereoselectivity. Interest in the Sharpless epoxidation as a tool for industrial organic synthesis increased substantially after Sharpless et al.[39,75] had discovered that the asymmetric epoxidation process can be conducted with catalytic amounts of the enantiomerically pure titanium-tartrate complex simply by adding molecular sieves to the epoxidation reaction mixture. This catalytic variant of the Sharpless reaction was used in industry for the tonne-scale production of (*S*)- and (*R*)-glycidol and (*S*)- and (*R*)-methylglycidol.

The double asymmetric induction allows an increase in the stereoselectivity of the Sharpless epoxidation.[78,79] The epoxidation of the chiral allyl alcohols **76** proceeded with very high enantiofacial selectivity to provide a convenient access to the epoxyalcohols **77** and **78**, if the absolute configurations of allyl alcohol and tartrate acid acted in one direction (Schemes 30 and 31).[76,79–83]



***(S)*-76** **77**

Scheme 30. Matched epoxidation of the chiral allyl alcohol (*S*)-**76**.

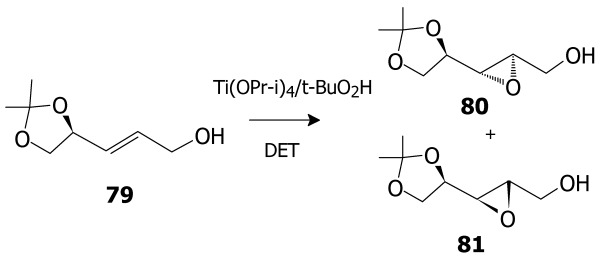


***(R)*-76**

a = (+)-DET/Ti(OPr-*i*)4/*t*-BuOOH

Scheme 31. Epoxidation of the chiral allyl alkohol (*R*)-**76**.

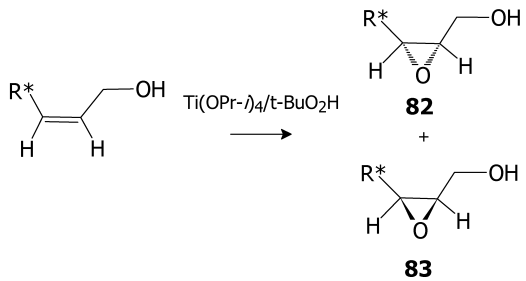
The asymmetric epoxidation of (*E*)-chiral allyl alcohols **79** in the absence of chiral tartaric acid esters afforded a mixture of the epoxyalcohols **80** and **81** in a ratio of 2.3:1. At the same time, the epoxidation of allyl alcohols by a chiral Sharpless oxidant, containing (+)-diethyl tartrate, furnished epoxyalcohols with a higher stereoselectivity than with the oxidant containing (−)-diethyl tartrate (Scheme 32).[12,77,81]



79

DET	**80:81**	**Ref.**
(+)	1:22	12
(-)	90:1	12

Scheme 32. Asymmetric epoxidation of (*E*)-chiral allyl alcohols.



R*	**DET**	**82:83**	**Ref.**
O O	(+)	30:1	58
	(-)	3:2	62
BnO	(+)	5:1	61
	(-)	1:1	61

Scheme 33. Matched/mismatched asymmetric Sharpless epoxidation.

The (+)-diethyl tartrate initiated matched asymmetric oxidation of chiral *Z*-allyl alcohols,[77,84] while the (−)-diethyl tartrate acted as a mismatched auxiliary to give the diastereomeric mixture **82** and **83** (Scheme 33).

Vidari et al.[85] observed an interesting example of double asymmetric induction in the case of asymmetric epoxidation of bis(homoallyl)-*N*-naphthylcarbamates. All four enantiomerically pure tetrahydropyran linalool oxides were synthesised by acid-catalysed cyclisation of the corresponding epoxyalcohol obtained by Sharpless epoxidation of geraniol derivatives.

The double asymmetric Katsuki–Sharpless epoxidation was used for the preparation of bis-epoxides of high optical purity. The bis-enol **84** was converted into the bis-epoxide **85** with high optical purity (99.9% ee). Haye et al.[86,87] have studied cascade reactions of bis-epoxides **85** to form tetrahydrofurans. By adopting an 'inside–out' strategy and double asymmetric induction, the 2,5-linked bis-tetrahydrofurans were stereoselectively prepared. This strategy has been used to synthesise (+)-uvaricin (Scheme 34).

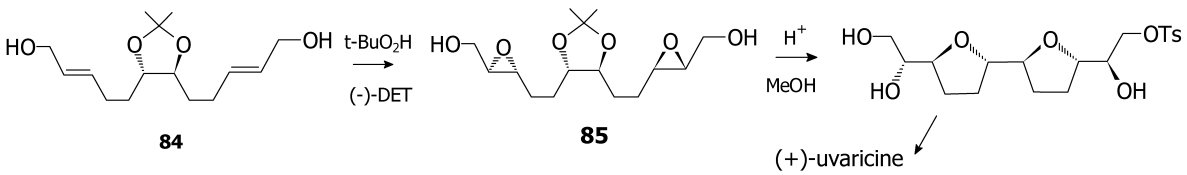
Some other versions of double asymmetric epoxidations, different from Sharpless methodology, have been reported. For example, the oxidation of the α-methylbenzyl-substituted imine by chiral peroxy acids derived from (+)-camphor anhydride afforded only one stereomer **87** of oxazaridine.[88] Polyamino acid-catalysed epoxidation has proved to be useful for the double diastereoselective epoxidation of enones such as **86** (Scheme 35).[72] The use of sodium percarbonate (NaPc) gave a reasonable selectivity for the epoxidation of such substrates in both the matched and mismatched sense.

Detailed information about Katsuki–Sharpless epoxidation can be found in the literature.[72]

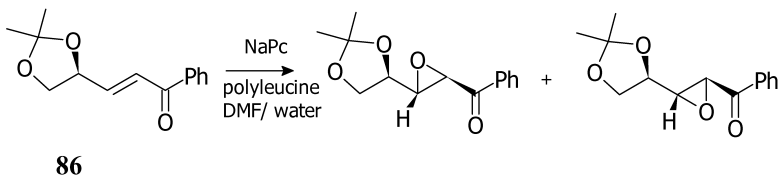
The asymmetric epoxidation possesses great synthetic potential because chiral epoxides can be transformed into various types of compounds (Scheme 36).[76,77] These transformations allow the generation of two chiral hydroxyl groups in the 1,3-positions of a molecule that is widely used in the synthesis of monosaccharides and their analogues, representing an important reaction in fine chemical organic synthesis, i.e. asymmetric hydroxylation.[75]

Scheme 37 shows the synthesis of the 1,3,5-triols **89** and **90** with 99% diastereomeric purity by asymmetric hydroxylation of bis-epoxides **87** and **89**.[84]

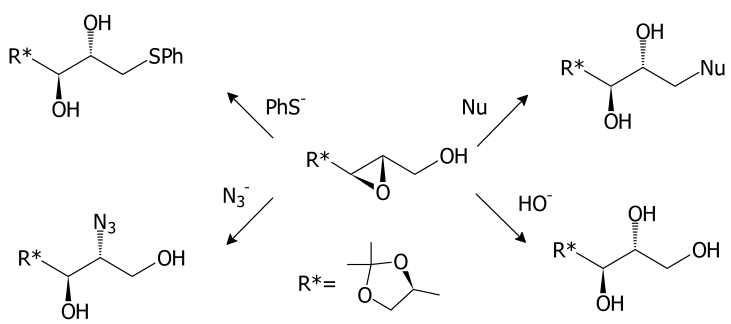
The application of the Sharpless reaction for the synthesis of pentitol, 2-amino-2-deoxy-pentitols,[80] chiral products of palytoxin degradation[89] and plitoxin[90] has been reported. A total synthesis of (−)-swainsonine **91**,[91,92] a trihydroxylated indolizidine alkaloid, has been performed in 21 steps starting from *trans*-1,4-dichloro-2-butene and *N*-benzyl-*p*-toluenesulphonamide according to the Masamune–Sharpless approach to polyhydroxylated natural products (Scheme 38).



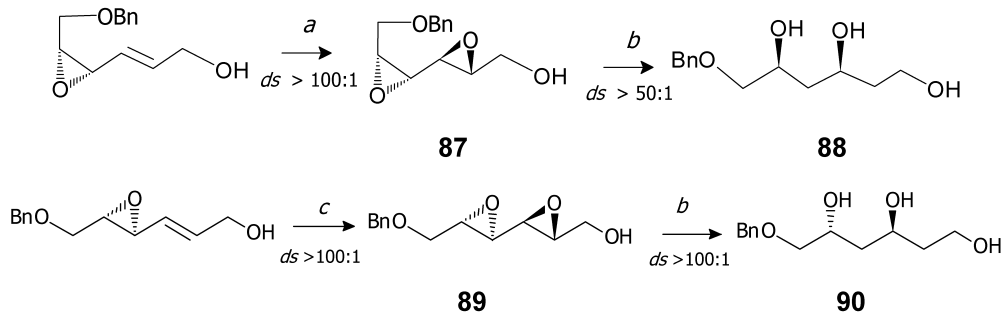
Scheme 34. Asymmetric synthesis of bis-epoxides and stereoselective (+)-uvaricine synthesis.



Scheme 35. Polyamino acid-catalysed epoxidation.

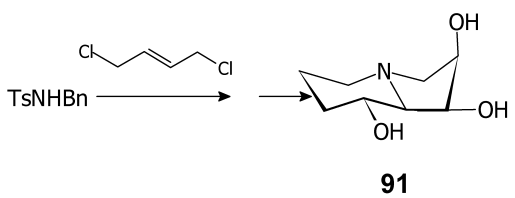


Scheme 36. Asymmetric hydroxylation.



a = Ti(OPr-i)$_4$, *t*-BuO$_2$H, (-)-DET; b = Red-Al, THF; c = Ti(OPr-i)$_4$, (+)-DET, *t*-BuO$_2$H.

Scheme 37. Asymmetric synthesis of 1,3,5-triols.

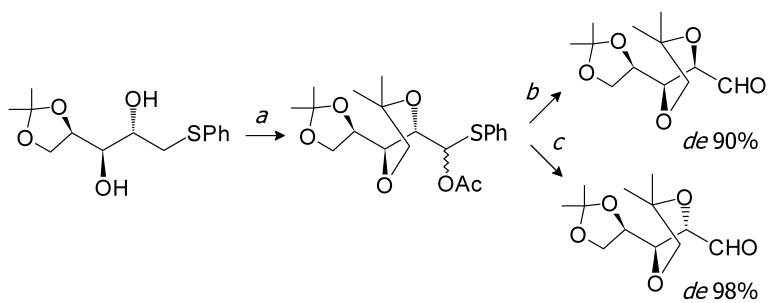


91

Scheme 38. Stereoselective synthesis of (−)-swainsonine.

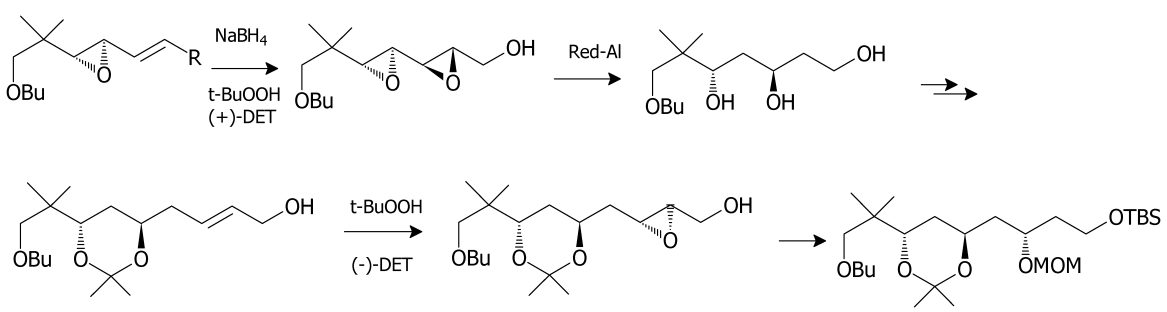
2,4-pentanediol, with *m*-chloroperoxybenzoic acid furnished the 2-hydroxycyclohexanone acetal **93** with 99% de. Oxidation of **92** with *t*-butyl hydroperoxide in the presence of metal catalysts [Ti(OPr-*i*)$_4$, VO(acac)$_2$, MoO$_2$(acac)$_2$] resulted in the product **93** in diastereomeric excesses up to 97% (Scheme 41).[93]

Examples of matched and mismatched double diastereoselection in the asymmetric hydroxylation of chiral olefins



a = 2-methoxypropene, *m*-chloroperoxybenzoic acid, Ac$_2$O; *b* = K$_2$CO$_3$, MeOH; *c* = diisobutylaluminium hydride.

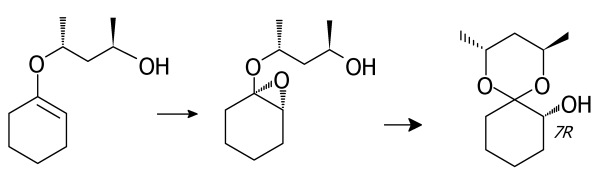
Scheme 39. Asymmetric synthesis of saccharides.



Scheme 40. Chiral substrate and a chiral reactant controlled asymmetric epoxidation.

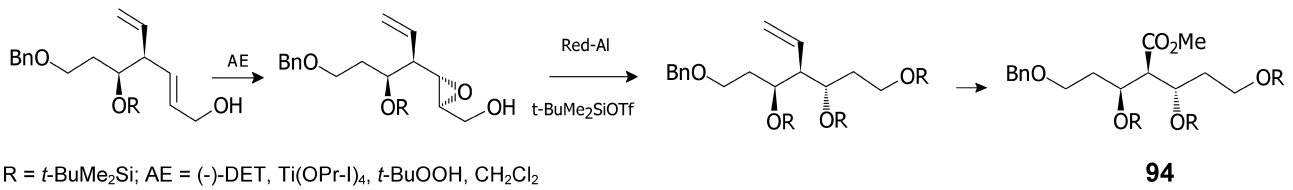
Masamune, Sharpless and co-workers,[81,89] used this route in the synthesis of saccharides, related polyhydroxylated natural products and in the efficient conversion of 2,3-*erythro* aldoses to 2,3-*threo* aldoses (Scheme 39).

Scheme 40 shows how a combination of a chiral substrate and a chiral reactant influences the stereochemical result of 'matched' and 'mismatched' asymmetric reactions.[11] Diastereofacial differentiation oxidation of chiral enol ethers, e.g. **92**, derived from cyclohexanone and optically active

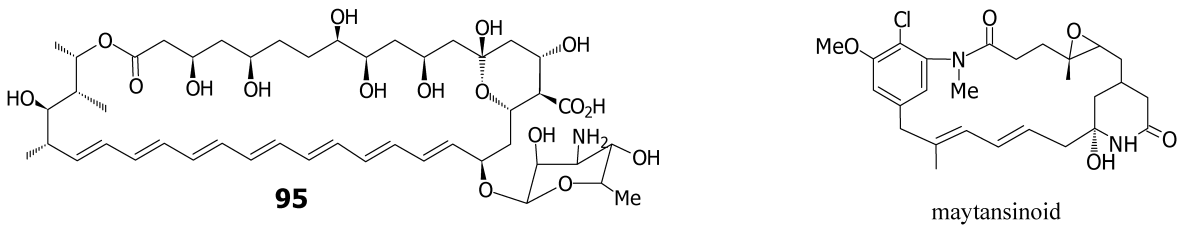


92 **93**

Scheme 41. Diastereofacial differentiating oxidation of the 1-cyclohexenyl ether **92**.



Scheme 42. Double AS of amphotericin B fragment **94**.



Scheme 43. Synthesis of amphotericin **95** and maytansinoid.

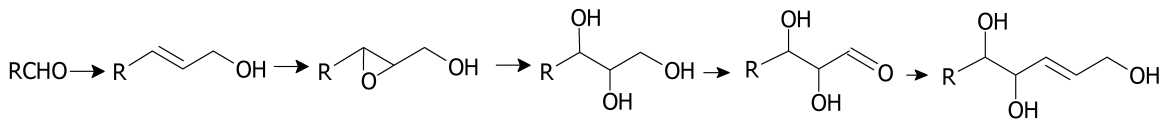
have been described.[94–101] Asymmetric epoxidation[96] and asymmetric dihydroxylation[97] were used in a key step in the industrial synthesis[98] of disparlure, a sexual attractant of gipsy moth. Meyers and Hudspeth,[99] by means of a double diastereoselective Sharpless epoxidation (99% ee), have developed the synthesis of maytansinoids. Chiral 1,3-diols **94** have been obtained by the reduction of epoxyalcohols with Red-Al® (>95% selectivity) (Scheme 42).

Masamune used this method for the transformation of epoxides to diethers, which were then converted into amphotericin B **95** (Scheme 43).[100,101] The route to (+)-maytansinoid was accomplished in 13 steps including several highly stereocontrolled reactions which precluded resolution and separation (Scheme 43).

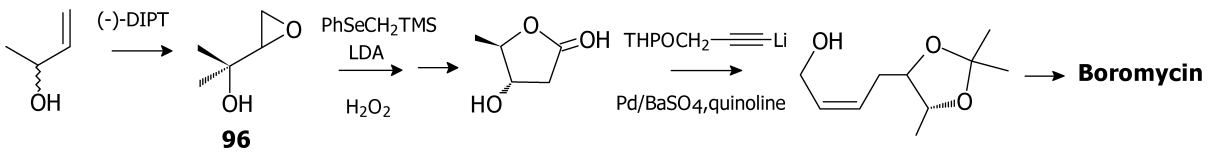
These methods allow the synthesis of compounds possessing several chiral centers. One such sequence was developed by Masamune and Sharpless (Scheme 44).[77,102] This strategy consists of four steps: (1) transformation of an aldehyde to an (*E*)-allylic alcohol, (2) asymmetric epoxidation, (3) treatment of the epoxyalcohol with benzenethiolate anion in a basic medium, and (4) oxidation and Pummerer reaction accompanied by hydrolysis of the acetoxy sulphide without inversion of the asymmetric centre at C-2.[89]

Raush used the double asymmetric Sharpless reaction for the synthesis of 2,6-dideoxyhexoses, verrucarins, roridins and trichoverrins.[103,104] White and co-workers have applied the asymmetric epoxidation to the synthesis of (2*S*,3*R*)-1,2-epoxy-3-butenol **96**, a useful synthon for the preparation of chiral 1,2-diols which was employed in the chiral synthesis of 2,5-dideoxyribose and a segment of the ionophoric antibiotic, boromycin (Scheme 45).[105–107]

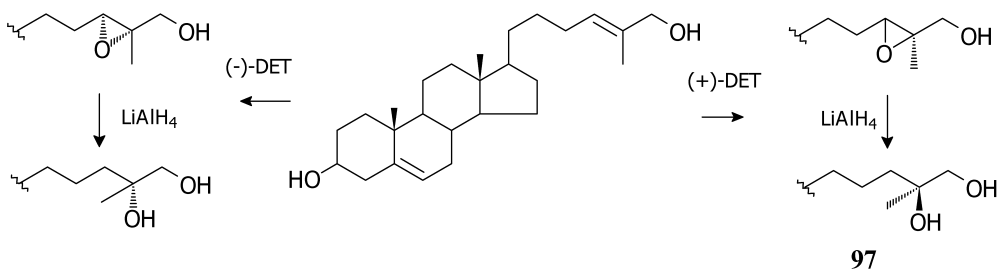
Hydride reactants and heterogeneous hydrogenation have



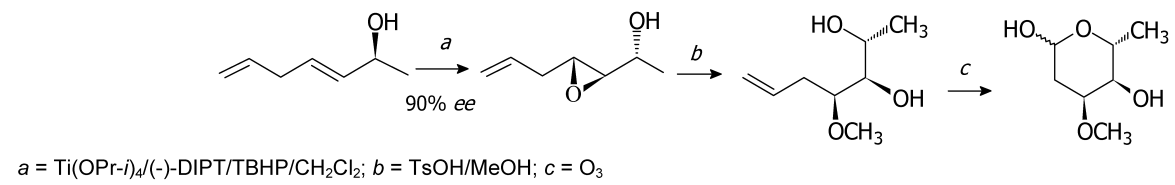
Scheme 44. Asymmetric synthesis of polyols.



Scheme 45. Asymmetric synthesis of boromycin.



Scheme 46. Asymmetric epoxidation of steroids.



a = Ti(OPr-*i*)$_4$/(-)-DIPT/TBHP/CH_2Cl_2; *b* = TsOH/MeOH; *c* = O_3

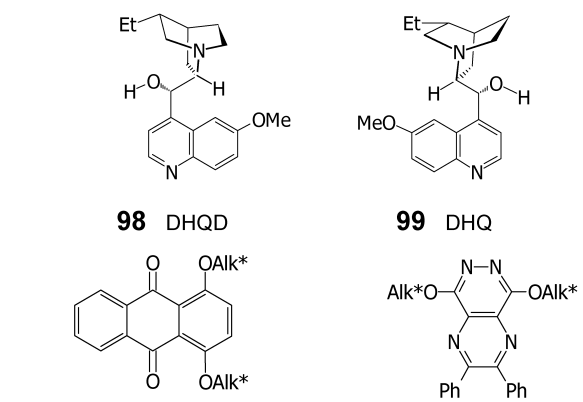
Scheme 47. Asymmetric synthesis of 2,6-dideoxyhexoses.

been used for the selective transformation of epoxides into chiral 1,2-steroid diols **97**, synthesised via asymmetric epoxidation and lithium aluminium hydride reduction (Scheme 46).[106]

Roush and Brown[83] have described a highly diastereoselective synthesis of 2,6-dideoxyhexoses (Scheme 47). These syntheses feature the kinetic resolution–enantioselective epoxidation of allylic alcohols and the highly regioselective ring-opening reactions of *erythro*-epoxy alcohols.

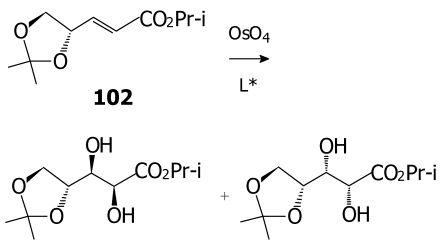
3.2.2. Dihydroxylation. The important approach to asymmetric oxidation of alkenes has been developed by Sharpless on the basis of osmium tetroxide-catalysed asymmetric dihydroxylation.[108] This reagent comprises the osmium tetroxide [OsO_4 or $K_2OsO_2(OH)_4$] containing either dihydroquinidine (DHQD) **98**, or dihydroquinine (DHQ) **99**, as chiral ligands.[92,109,110]

Two cinchonine ligands attached to phthalazine (PHAL)[111] or diphenylpirymidine (PYR)[112] form the asymmetric oxidants $(DHQ)_2$PHAL, $(DHQD)_2$PHAL or $(DHQ)_2$PYR. These chiral oxidants are commercially available as AD-mix-α (0.2% osmium, 1% $(DHQ)_2$PHAL ligand) and AD-mix-β (0.2% osmium, 1% $(DHQD)_2$PHAL ligand). Other ligands, e.g. $(DHQD)_2$AQN **100** or $(DHQD)_2$DPP **101**, which in some cases are more effective than $(DHQD)_2$-PHAL were also proposed (Scheme 48).[108] Co-oxidants, in particular $K_3Fe(CN)_6$ in the presence of K_2CO_3, were also used.[108,112]



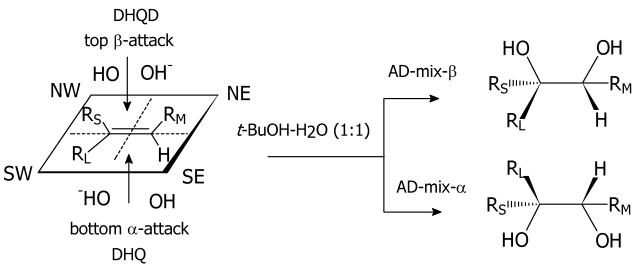
Scheme 48. Dihydroxylation reagents.

Morikawa and Sharpless[110] reported that the double asymmetric dihydroxylation of the olefins such as **102** proceeding with the formation of the diastereomers **103** and **104** is dependent upon the nature of the ligands, as shown in Scheme 49. The effect of these ligands is explained by the model shown in Scheme 50,[108,113] where the plane of the olefin is divided into four quadrants with the substituents placed according to a simple set of rules. The SW quadrant appears to be of particular importance since it must be occupied by the most sterically demanding substituent, especially aromatic groups.



. L*	103:104
quinuclidine	2.6:1
$(DHQD)_2$PHAL	39:1
$(DHQ)_2$PHAL	1:1.3
$(DHQD)_2$PYR	6.9:1
$(DHQ)_2$PYR	1:4.1

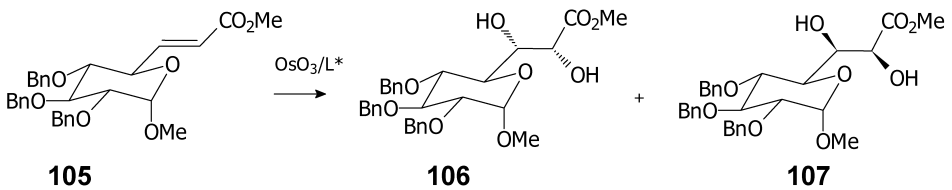
Scheme 49. Sharpless asymmetric dihydroxylation.



Scheme 50. Model for predicting the facial selectivity of the AD.

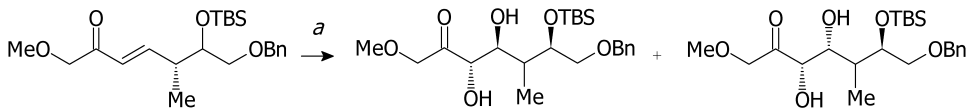
Asymmetric dihydroxylation has been extensively studied under conditions of double stereostereoselectivity.[112–118] The asymmetric dihydroxylation of the carbohydrate-derived olefins **105** using the DHQ–CLB ligand (CLB= chlorobenzoate) is matched since the diastereoselectivity is enhanced relative to the situation without the chiral ligand.[93] The dihydroxylation of **105**, using the DHQD–CLB, proceeded with mismatched stereoselectivity to give a mixture of diastereomers **106** and **107** (Scheme 51).[112]

The AD has proved to be powerful in several important syntheses. The high level of enantioselectivity was reflected in a high level of diastereoselectivity, in the matched or mismatched pairs, where a chiral proximate centre to the double bond was present.[119] It was found that phthalazine ligand $(DHQD)_2$PHAL initiated matched asymmetric



L*	106:107
None	10.3:1
DHQD-CLB	1.3:1
DHQ-CLB	20.5:1

Scheme 51. Doubly diastereoselective dihydroxylation of carbohydrate-derived olefins.



a = OsO_4, NMO (5:1 *ds);* Super AD-mix-β (1:6 *ds)*

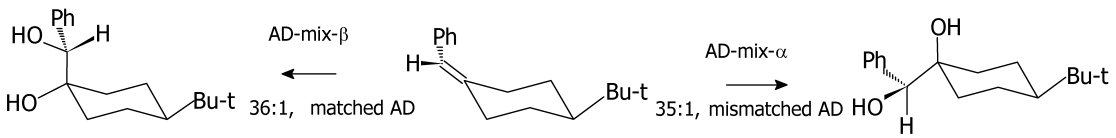
Scheme 52. Reverse selectivity of the double AD.

induction and that $(DHQ)_2PHAL$ initiated mismatched induction.[120] Gurjar et al. have applied the AD to the synthesis of *C*-α-D-glucosyl-α-aminoacids.[118] The influence of allylic or homoallylic alkoxy groups on the diastereoselectivity of the AD has been extensively studied,[121] with interesting observations on the reverse diastereoselectivity in the formation of **108** and **109** with the use of the AD procedure (Scheme 52).[122]

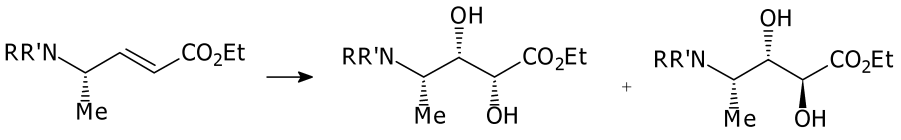
In these experiments, the osmium-catalysed dihydroxylation in the absence of a chiral ligand displays a 6:1 preference for equatorial dihydroxylation. In the double diastereoselective reactions of the enantiomerically pure olefins, the levels of diastereoselectivity in both the matched and mismatched reactions employing the $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ ligands were equal in magnitude and in an opposite direction (Scheme 53).[108]

A study by Reetz[123] has shown that protective group tuning (*N*-Boc- or Bn-protected α,β-unsaturated esters **110**) leads to optimal diastereoselection in the AD of chiral amino derivatives **111** and **112**, with the appropriate choice of the chiral ligand (Scheme 54).

Ward and Procter[114] reported that the stereoselectivity of the dihydroxylation of ether-allylsilanes can be increased using potassium ferricyanide as the stoichiometric oxidant and by double asymmetric induction using dihydroquinidine *p*-chlorobenzoate as a catalyst. They used this methodology in the synthesis of the natural product, baciphelacin. Wade et al.[115] studied the asymmetric dihydroxylation of chiral 3-alkenyl-4,5-dihydroisoxasoles, e.g. **113**, as shown in Scheme 55. The reaction employing the phthalazine class of ligands displayed useful level of matched and mismatched diastereoselectivity. The catalytic asymmetric dihydroxylation of **113** afforded virtually one diastereomer using $(DHQD)_2PHAL$ as the chiral auxiliary (matched pair, 96% de). The other diastereomer predominated with $(DHQ)_2PHAL$ as the chiral auxiliary (mismatched pair, 90% de). The double asymmetric synthesis in the

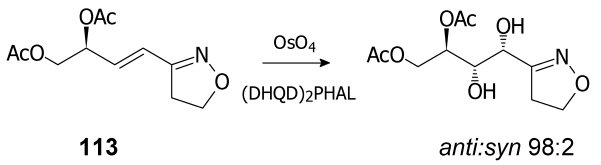


Scheme 53. Matched and mismatched asymmetric dihydroxylation of olefins.



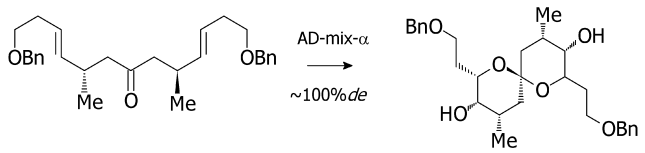
R	R′	AD	111:112
Boc	H	AD-mix-α	97:3
Bn	Bn	AD-mix–α	92:8
Boc	H	AD-mix–β	9:91
Bn	Bn	AD-mix–β	6:94

Scheme 54. Effect of the protective group R and R′ on the AD of the α,β-unsaturated esters **110**.



113 *anti:syn* 98:2

Scheme 55. AD of the chiral 3-alkenyl-4,5-dihydroisoxasoles **113**.

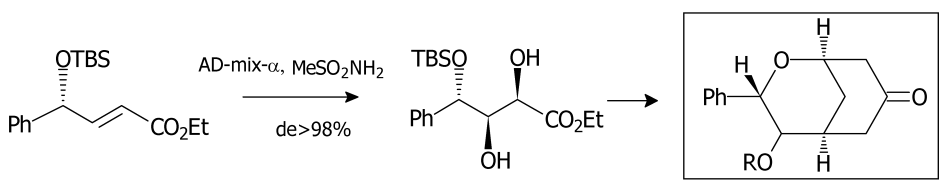


114

Scheme 56. Asymmetric synthesis of the C(38)–C(54) halichondrin B subunit.[124]

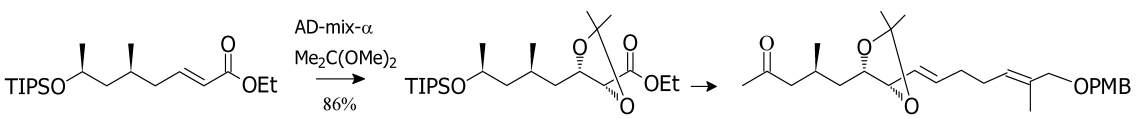
dihydroxylation reaction as well as in the Sharpless epoxidation reaction has found extensive applications in the synthesis of natural products. Some of the more recent investigations are shown in Schemes 56–62.[124–129] In one example, asymmetric dihydroxylation with AD-mix-α afforded the C_2-symmetric tetraol **114**, as a single diastereomer, which was then used in an synthesis of the C(38)–C(54) halichondrin B subunit (Scheme 56).[124] Dihydroxylation of **115** proceeded with a matching double stereoselectivity to give exclusively the diol **116**, which was then converted to (−)-8-*epi*-9-deoxygoniopypyrone (an antitumour styryllactone) **117**, which was identical to the natural compound (Scheme 57).[125]

Takahata and co-workers[130,131] have developed a new method for the synthesis of C_2-symmetric derivatives of *trans*-α,α′-bis(hydroxymethyl)-pyrrolidine and -piperidine starting from the symmetric α,ω-terminal dienes



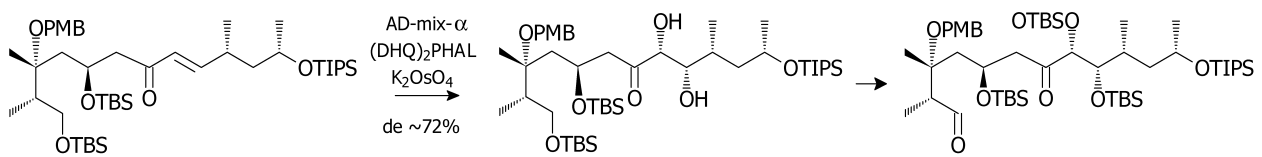
115 **116** **117**

Scheme 57. Asymmetric synthesis of (−)-8-*epi*-9-deoxygoniopypyrone.[125]



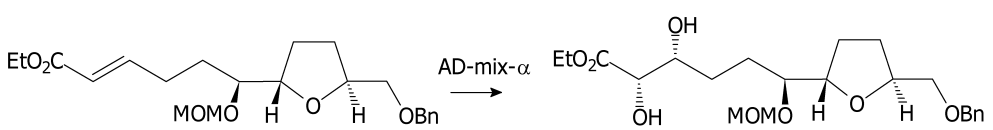
118

Scheme 58. Synthesis of the hydrophobic domain methyl ketone of amphidinolide B1 **118**.[126]

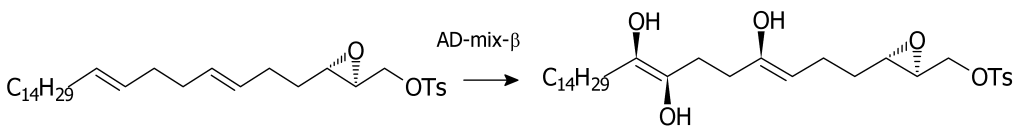


119

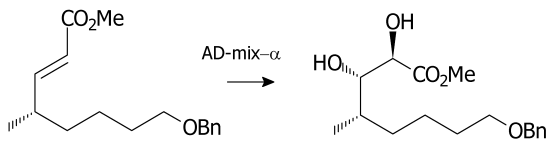
Scheme 59. Synthesis of the fully-functionalised C(14)–C(26) hydrophilic domain of amphidinolide B1 **119**.[126]



Scheme 60. Use of two different AD reactions to establish two 1,2-diol units.[127]



Scheme 61. Asymmetric dihydroxylation of chiral epoxyalkenes.[128]



Scheme 62. Asymmetric dihydroxylation of unsaturated esters.[129]

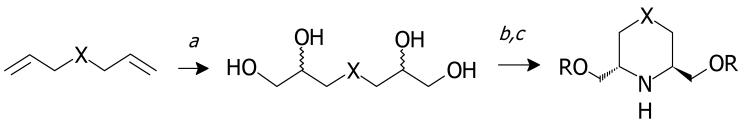
(Scheme 63). The double asymmetric dihydroxylation (*t*-BuOH, water, catalyst 0.2% osmium, and 1% $(DHQ)_2$-PHAL) led to an enantiomeric enhancement of **120** (from 82 to 98% ee).

Sinha and Keinan[116] have described the asymmetric synthesis of the 18-membered macrolide (+)-aspicilin **122** in 14 steps, starting from an achiral, unsaturated triene **121** (Scheme 64). All four stereogenic carbinol centers have been introduced by three asymmetric dihydroxylation reactions.

Hoye and Ye[94] developed an efficient synthesis of the potent antitumour annonaceous acetogenin, (+)-parviflorin **125**, using Sharpless asymmetric epoxidation and asymmetric dihydroxylation with (AD-mix-β) starting from *trans*,*trans*-1,5,9-cyclododecatriene **123** and the 1,4-bis(alkenyloxy) benzene **124** (Scheme 65).

Double AD has been applied to steroid synthesis.[108,132–138] The dihydroxylation of the 5α-ergost-2,22-en-6-one **126** in the absence of chiral ligand furnished the tetrols **127** and **128** in the ratio of 1:1.6.[137] The conversion of **126** to 24-*epi*-brassinolide **127** was accomplished in 80% yield and a 3.4:1 diastereomeric ratio with the DHQD–CLB and NMO co-oxidant system.[132] McMorris and Patil[133] increased the **127**–**128** ratio to 10:1 with a $(DHQD)_2$PHAL and ferricyanide co-oxidant system (Scheme 66).[133]

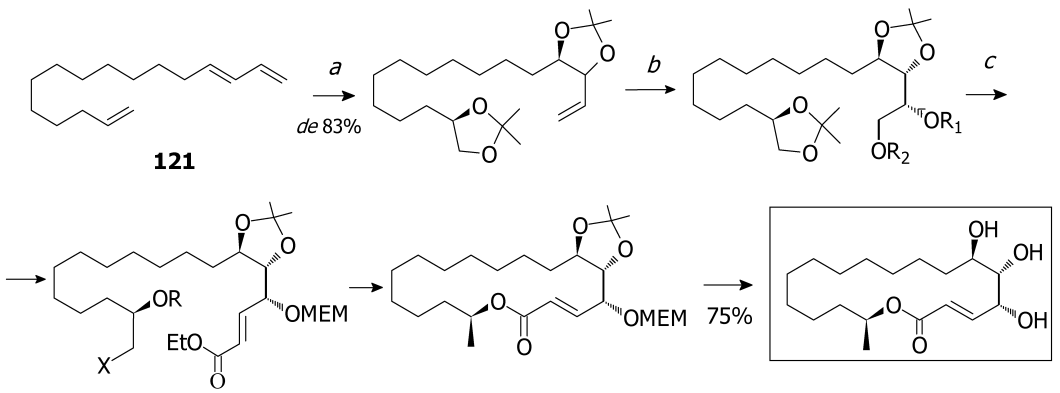
Sharpless asymmetric dihydroxylation of **129** with $(DHQD)_2$PYDZ in 1.5:1 *t*-BuOH–H_2O gave 24(*R*),25-dihydroxycholesterol **130** with 92% de, which was



120

X = O,CH_2; a = AD: $(DHQ)_2$AQN; b = *t*-$BuPh_2SiCl$/imidazole; TsCl/Et_3N; $BnNH_2$; c = $H_2/Pd(OH)_2$

Scheme 63. Double Sharpless asymmetric synthesis of C_2-symmetric *trans*-α,α-bis(hydroxymethyl)piperidine derivatives.

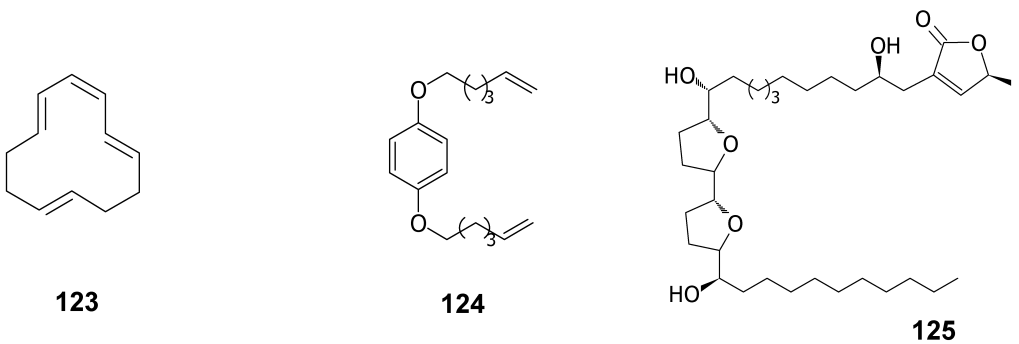


121

a) AD-mix-β; b) AD-mix-α

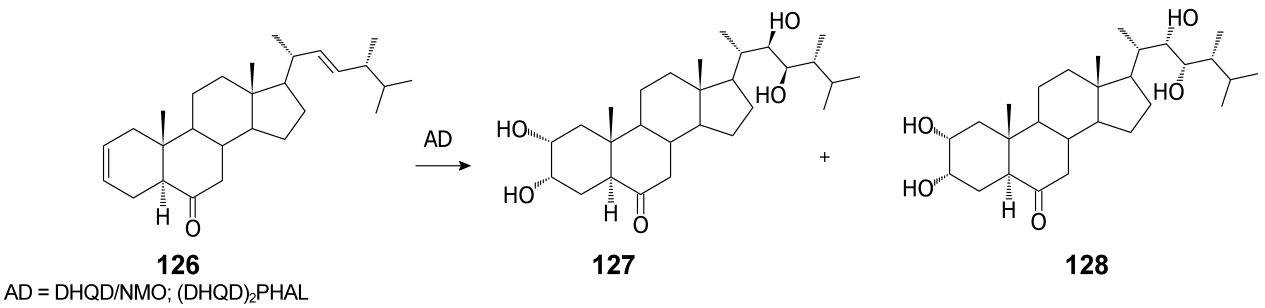
122 (+)–aspicilin

Scheme 64. Asymmetric synthesis of (+)-aspicilin.

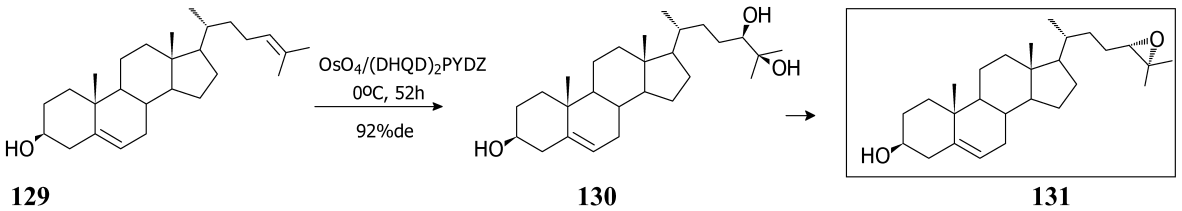


123 **124** **125**

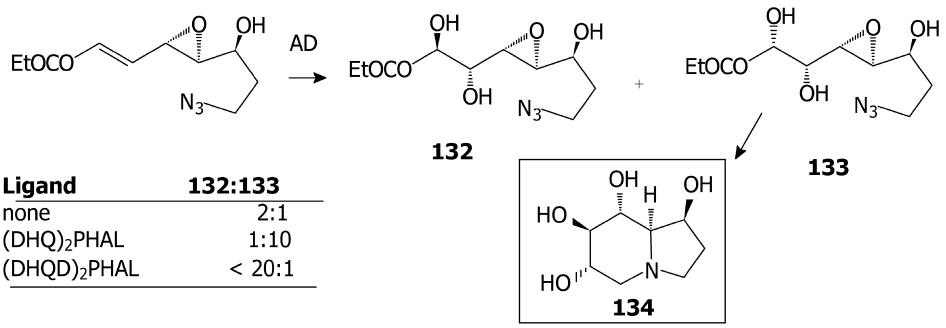
Scheme 65. Synthesis of (+)-parviflorin.



Scheme 66. Asymmetric dihydroxylation of a steroidal unsaturated side chain.



Scheme 67. Stereocontrolled synthesis of 24(*S*),25-epoxycholesterol.



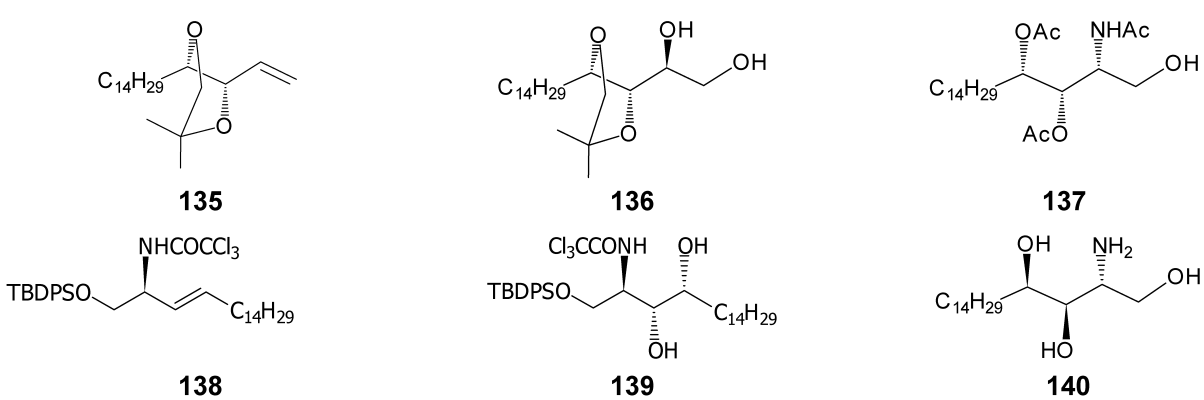
Ligand	132:133
none	2:1
$(DHQ)_2PHAL$	1:10
$(DHQD)_2PHAL$	< 20:1

Scheme 68. Asymmetric synthesis of (+)-castanospermine.

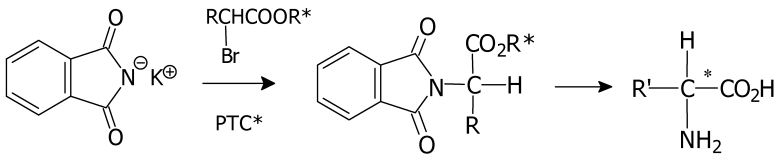
converted to 24(*S*),25-epoxycholesterol **131**: this activator of L_xR_α triggers gene transcription and upregulation of cholesterol 7α-hydroxylase (Scheme 67). Asymmetric dihydroxylation of **129** with OsO_4 and $(DHQ)_2PHAL$ produced 24(*R*),25-dihydroxycholesterol with high stereoselectivity.[138] In the matched asymmetric synthesis they obtained the *anti*-product **132** with >20:1 diastereoselectivity.

Cha and co-workers have applied the double diastereoselective AD to the stereoselective synthesis of the alkaloid, (+)-castanospermine **134** (Scheme 68).[139] The major product **133** from the mismatched reaction was subsequently converted to (+)-castanospermine **134**.

The double stereoselectivity was applied to the asymmetric synthesis of (*R*)-(−)-mevalonolactone, L-xylo-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine[140,141] and L-lyxo-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosine[92] (Scheme 69). The dihydroxylation of the enantiomerically enriched terminal olefin **135** with the

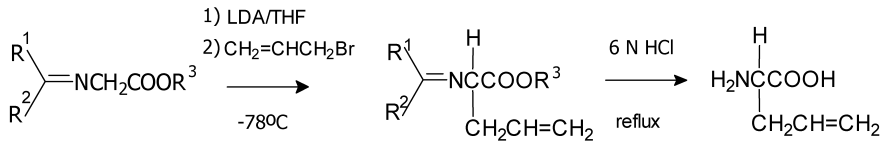


Scheme 69. Asymmetric synthesis of L-xylo-(2*R*,3*S*,4*S*)- and L-lyxo-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosines.



R = Me, Et, Pr, Bu; R' = Et, (-)-*endo*-bornyl
PTC* = TBAB, (+)-*N*-benzylcinchoninium chloride, (-)-*N*-benzylquininium chloride

Scheme 70. Double asymmetric alkylation under S–L phase transfer conditions.



Scheme 71. Asymmetric allylation of the ketimines bearing two chiral auxiliaries **142**.

$(DHQD)_2PHAL$ ligand led to the formation of **136**. The diastereoisomer **136** was then converted into the tetraacetate derivative of L-xylo-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine **137**. Martin and Bloch[92] performed the first synthesis of L-lyxo-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosine **140** using double stereoselectivity. The matched dihydroxylation of the (*S*)-allyl trichloroacetamide **138** by AD-mix-β provided the octadecanediol **139** and then the L-lyxo-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosine **140** with a high diastereoselectivity (de 94%). Asymmetric synthesis of L-xylo-(2*R*,3*S*,4*S*)-C_{18}-phytosphingosine and L-lyxo-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosine. Vidari et al.[85] have synthesised all four enantiomerically pure tetrahydropyran linalool oxides by the acid-catalyzed cyclisation of the corresponding epoxyalcohols prepared by the consecutive asymmetric Sharpless dihydroxylation and epoxidation of geraniol derivatives.

3.3. Asymmetric alkylation

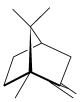
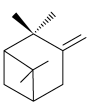
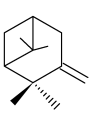
The asymmetric alkylation reaction constitutes one of the most potent methodologies for the stereoselective elaboration of quaternary carbon centers. There are several methods for double asymmetric induction in the alkylation reaction: a chiral substrate reacts with a chiral alkylation agent; a substrate containing two or more chiral auxiliaries reacts with an achiral reagent; deprotonation of a chiral substrate by chiral bases and reaction with an achiral alkylation agent; alkylation of a chiral substrate in the presence of a chiral phase transfer catalyst or chiral crown ether.

Guifa and Lingchong[142] have studied the asymmetric alkylation of carbanions under S–L phase transfer conditions using chiral phase transfer catalysts. The reaction of potassium phthalimide with chiral 2-bromocarboxylates in this case proceeded under the control of double asymmetric induction (Scheme 70).

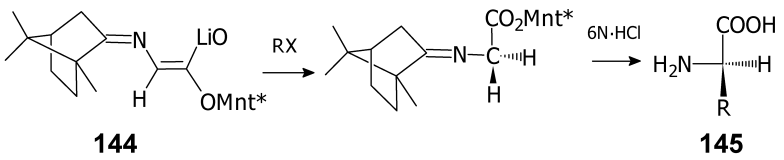
The configurations of the products depended on the chirality of the phase transfer catalysts: the bornyl 2-bromocarboxylates (synthesised from (−)-borneol) and (−)-*N*-benzylquininium chloride afforded predominantly the dextrorotatory L-products **141**, while, with (+)-*N*-benzylcinchoninium chloride, the levorotatory D-products were formed predominantly.[142] The effect of double asymmetric induction of (+)-*N*-benzylcinchoninium chloride was much higher than that of (−)-*N*-benzylquininium chloride.

The best results in the double asymmetric alkylation were achieved with substrates bearing two chiral auxiliaries, which reinforce one another in matched asymmetric induction (Scheme 71). The imines **142**, bearing two chiral auxiliaries, reacted with alkyl halides with a higher stereoselectivity than similar compounds containing only one asymmetric center. Treatment of the imine **142** with lithium diisopropylamide (LDA) at −78°C generated the anion, which reacted with allyl bromide to give allylated intermediate products **143** in good yield. Hydrolysis of the esters **143** with 6N HC1 afforded the α-amino acids in 5–90% optical purity (Table 3).[143]

Table 3. Double asymmetric allylation of ketimines **142** (Scheme 71)

R^1R^2C=	R^3	Yield (%)	ee (%)	Conf.
	(+)-Mnt	81	85	(*R*)
	(−)-Mnt	70	3	(*S*)
	c-C_6H_{11}	70	66	(*R*)
	(+)-Mnt	68	90	(*R*)
	(−)-Mnt	65	74	(*R*)
	c-C_6H_{11}	60	67	(*R*)
	(+)-Mnt	64	78	(*S*)
	(−)-Mnt	52	86	(*S*)
=CPh_2	(+)-Mnt	64	12	(*R*)

Double asymmetric induction was observed during alkylation of the imines **144** obtained from (+)-camphor, and (+)- and (−)-2-hydroxypinan-5-ones with (+)- and (−)-menthyl glycinates (Scheme 72).[144] The diastereoselectivity in the alkylation of the anion of **144** depended on the configuration of the menthyl ester and was controlled by matched induction of two chiral auxiliaries. The (+)-camphor and (+)-menthyl groups in the ketimine, to offer a



144 145

Mnt*	RX	*ee* (%)
(+)-Mnt	BnBr	99
(-)-Mnt	BnBr	7.3
(+)-Mnt	BuBr	84.7
(-)-Mnt	BuBr	26.1
(+)-Mnt	AllBr	85.0
(-)-Mnt	AllBr	3.0

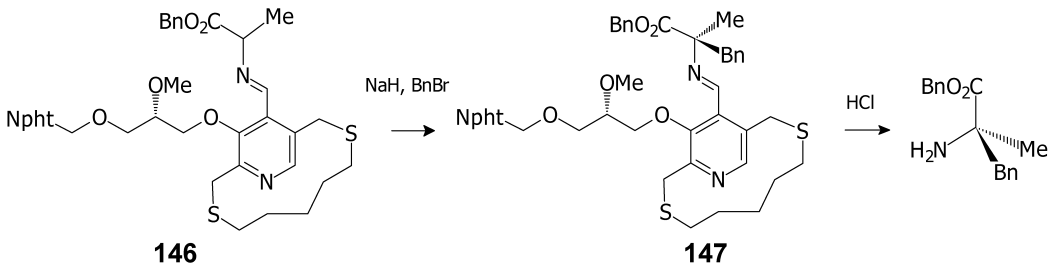
Scheme 72. Double asymmetric synthesis of amino acids.

stereocontrolled method for the synthesis of the (*R*)-α-amino acids **145** (de ~90–99%).[36]

The double asymmetric induction was observed in the alkylation reaction of aldimines, prepared from α-amino acid esters and a pyridoxal, having a chiral *ansa* structure and an ethoxyethoxy group at C-3 of the chiral ionophore side chain (Scheme 73).[145] The combination of the R_{ansa} (S_{ansa})-structures with the *S*(*R*)-chiral side chain is a matched pair, while the S_{ansa} (R_{ansa})-structure with the *S*(*R*)-chiral side chain is a mismatched pair. Benzylation of *S*,S_{ansa}-**146** leading to the formation of **147** therefore proceeded in a very poor stereoselectivity (8% de), while that of *S*,R_{ansa}-**146** gave a good stereoselectivity (96% de) The stereoselective alkylation of the R_{ansa}-isomer was explained by a shielding effect of the terminal ethyl group of the ethoxyethoxy moiety preventing the approach of the electrophile to the other side of the *ansa*-chain, as shown in Scheme 74.

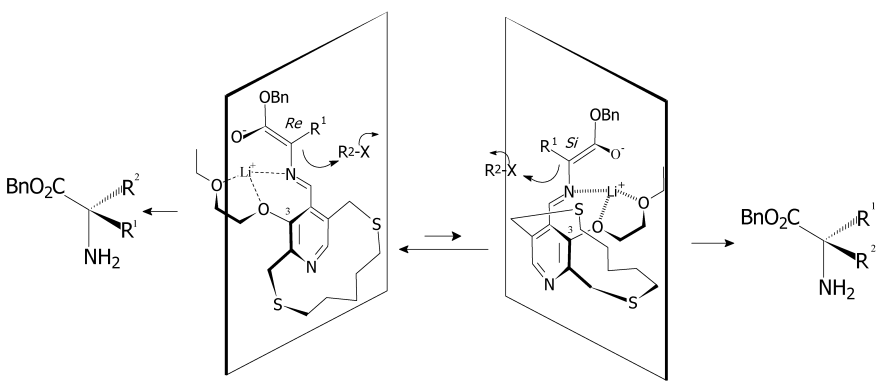
Tripathy and Matteson[146] developed the asymmetric synthesis of 4-methyl-3-heptanol derivatives **154** which are known to be components of insect aggregation pheromones (*Scolytus multistriatus* and *Leptogenus diminuta*).[147] The double stereoselective reaction of (*S*,*S*)-diisopropylethane diol boronic esters **148** bearing two chiral centers with achiral chloromethyl lithium yielded the chain-extended (α*R*)-(α-chloroalkyl)boronic esters in ≥98% diastereoisomeric excess (Scheme 75). The major (α*R*)-isomer with Grignard reagents provided the products of displacement of chloride by alkyl **149**. The utility of this methodology has been demonstrated with the asymmetric synthesis of each of the four stereoisomers of 4-methyl-3-heptanol **150a–d** in very high chiral purity (ds 350:1–1000:1 per chiral center).

Genet et al.[148] described the double stereodifferentiation in the allylation of chiral Schiff bases **151**, derived from glycine bearing a chiral ester group (R*=Mnt, PhMnt,

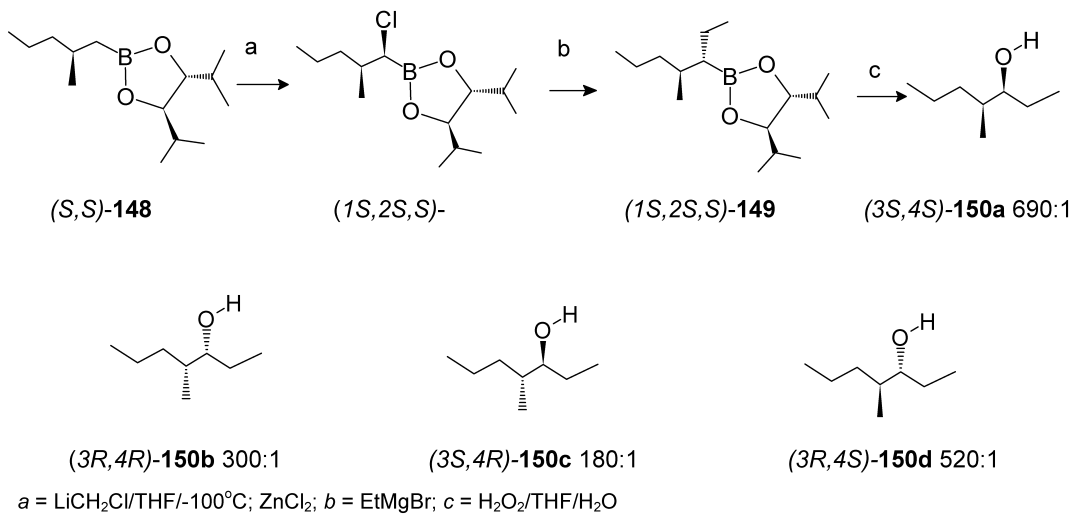


146 147

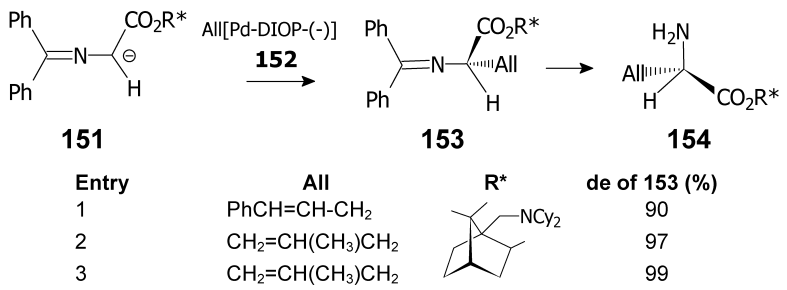
Scheme 73. Double asymmetric induction in the alkylation reaction of aldimines **146**.



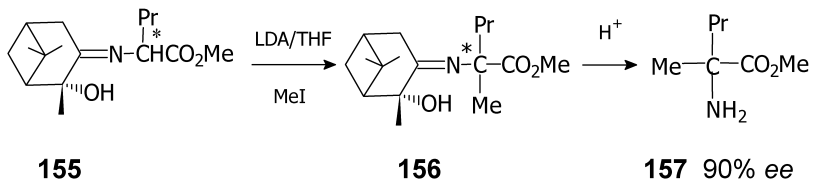
Scheme 74. Shielding effect of the ethoxyethoxy group in the alkylation of aldimines **146**.



Scheme 75. Asymmetric synthesis of 4-methyl-3-heptanol derivatives.



Scheme 76. Double stereodifferentiation in the allylation of chiral Schiff bases **151**.



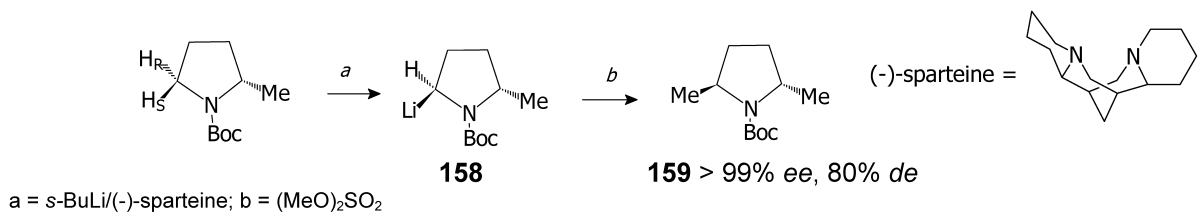
Scheme 77. Asymmetric synthesis of α,α-disubstituted amino acids.

N,*N*-dicyclohexylsulphamoylisobornyl, *N*,*N*-diethylsulphamoylisobornyl) with the chiral allylic palladium complexes **152**. When the two chiral components (+)-DIOP and alkoxyl R*=*N*,*N*-dicyclohexylsulphamoylisobornyl are acting in concert, the highest matched asymmetric induction (90–99% de) was observed to give the amino acid esters **154** of good optical purity (Scheme 76).

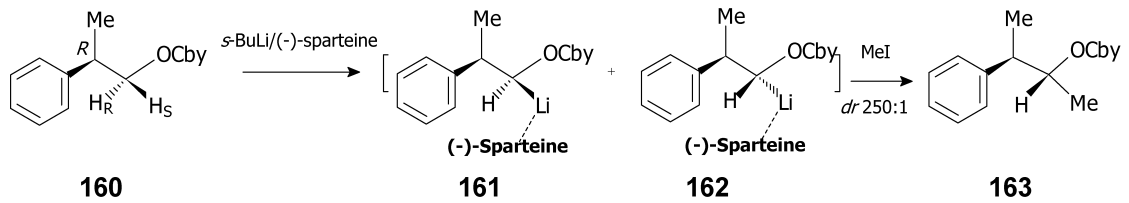
α,α-Disubstituted amino acids such as **157** were additionally prepared with good stereoselectivity by enantioselective alkylation using the Schiff base **155** derived from α-monosubstituted amino acids and (*S*,*S*,*S*)- or (*R*,*R*,*R*)-2-hydroxypinan-3-one as chiral reagents (Scheme 77).[149] Their configurations were dependent on the shielding effect of the aliphatic chain in the intermediary dianion of the Shiff base. α,α-Dialkylamino acids, e.g. **157**, are interesting as biologically and pharmacologically active compounds.

In the last few years, asymmetric deprotonation reactions and their asymmetric substitutions have found applications in asymmetric synthesis.[150] Asymmetric deprotonation of prochiral methylene group with an *s*-BuLi/(−)-sparteine chiral complex provided the dipole-stabilised carbanion with retention of configuration to give enantio-enriched products. Chiral organolithium derivatives such as **158** are configurationally stable owing to their reactions with electrophiles being stereoselective.[150–152] The alkylation of **158** with dimethyl sulphate provided (*S*,*S*)-**159** in an enantiomeric excess of >99% (Scheme 78).[151]

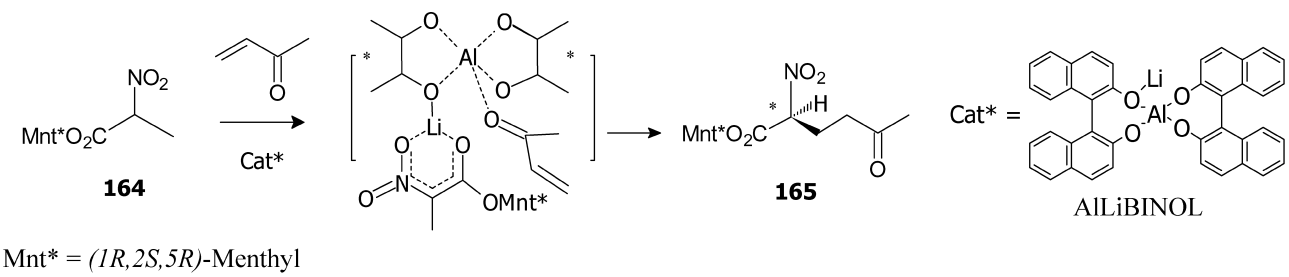
Hoppe reported that the asymmetric deprotonation of chiral alkyl carbamates, e.g. **160**, with *s*-butyl lithium/(−)-sparteine generates the diastereomeric intermediates **161** and **162**, which undergo double stereoselective reactions.[151] One of these chiral intermediate forms is a matched diastereomer in which both chiral inductors act in one direction and the other is a mismatched diastereomer (Scheme 78). The subsequent carbonylation or methylation of the diastereomeric intermediates proceeded under kinetically controlled differentiation between diastereotopic



Scheme 78. Asymmetric alkylation of the chiral carbanion **158**.



Scheme 79. Stereoselective methylation of the diastereomeric intermediates **161** and **162**.



Scheme 80. AlLiBINOL-catalysed double stereoselective Michael addition.

methylene protons to give the alkylated product **163** in a ratio of 250:1, whereas the similar mismatched pair combination using (*S*)-**160** for the reaction gave a 1:3.5 diastereoisomeric ratio (Scheme 79).

3.4. Asymmetric addition reactions

Addition reactions of nucleophiles to unsaturated compounds is one of the most important bond-forming strategies available to the synthetic organic chemist.[153] This is mainly due to the broad spectrum of donor and acceptors that can be employed in these reactions.

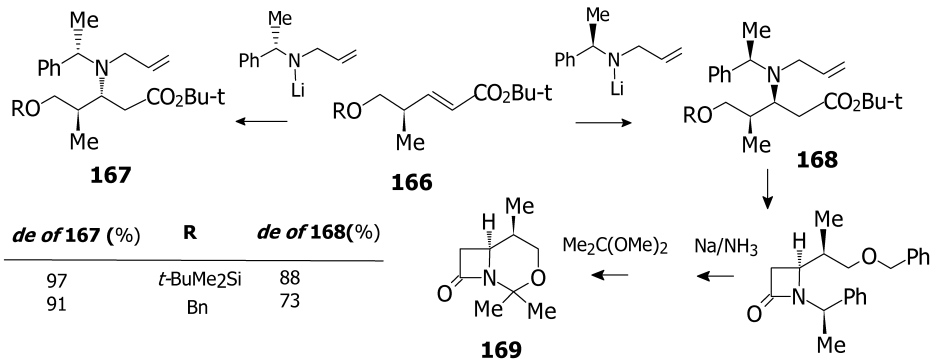
The biggest success in the application of the multiple asymmetric induction to increase the stereoselectivity of addition reactions was achieved in the asymmetric conjugate additions, including the Michael reaction, and also in aldol-type reactions, i.e. carbonyl addition reactions to enolates, including zinc enolates (the Reformatsky reaction) and silyl enolates (the Mukaiyama reaction) or to allylmetals.

3.4.1. Conjugate addition reactions. Asymmetric conjugate addition reactions are among the most widely used methods for the carbon-bond formation in organic synthesis.[153–155] During the last few years, examples of double asymmetric induction in conjugate addition have been reported.[155–160]

The addition of chiral anions complexed with chiral catalysts was used in the reaction of α-nitroesters such as **164** with α,β-unsaturated ketones in the presence of a chiral AlLiBINOL complex, prepared in situ from $LiAlH_4$ and (*R*,*R*)-BINOL (Scheme 80).[155] The reaction of the α-nitroester **164** with the AlLiBINOL complex gave the corresponding lithium enolate which then reacted with the enone to generate the desired Michael adduct **165**, the AlLiBINOL complex being regenerated to react in the following catalytic cycle. The reaction furnished the Michael adduct **165** with a diastereoselectivity which was extremely temperature dependent: de=7% at room temperature and 72% at −23°C. The stereoselectivity was also dependent on the solvent: THF gave a selectivity of ≤80% ee, whereas in CH_2Cl_2 the selectivity was only 25% ee.

Davies and co-workers[158] have reported the conjugate addition of lithium *N*-allyl-*N*-α-methylbenzylamide to chiral α,β-unsaturated esters **166** proceeding as matched asymmetric synthesis with the formation of **167** in the case of (*R*)-methylbenzylamides and as mismatched AS in the case of (*S*)-methylbenzylamides (Scheme 81). The product **168** of the mismatched reaction was used as a key intermediate for the synthesis of 1β-methylcarbapenem **169**.

Tran Huu Dau et al.[157] investigated asymmetric Michael reactions using chiral imines/secondary enamines with the help of AM_1 calculations. They came to the conclusion that steric factors control the π-facial discrimination in the Michael addition. For minimising steric effects, the phenyl



Scheme 81. Synthesis of a key intermediate of 1β-methylcarbapenem.

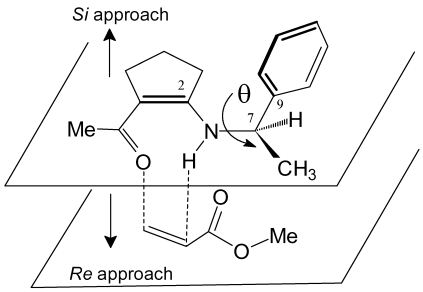
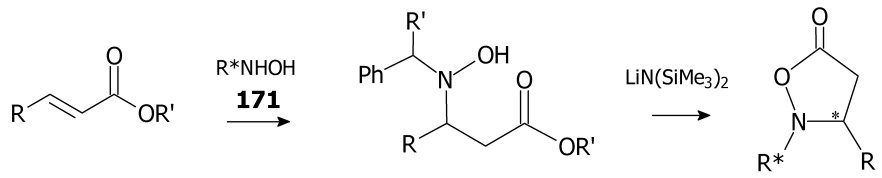


Figure 1. Steric control of the π-facial discrimination in asymmetric Michael reactions.

group should be pushed away from its most stable position (Fig. 1).

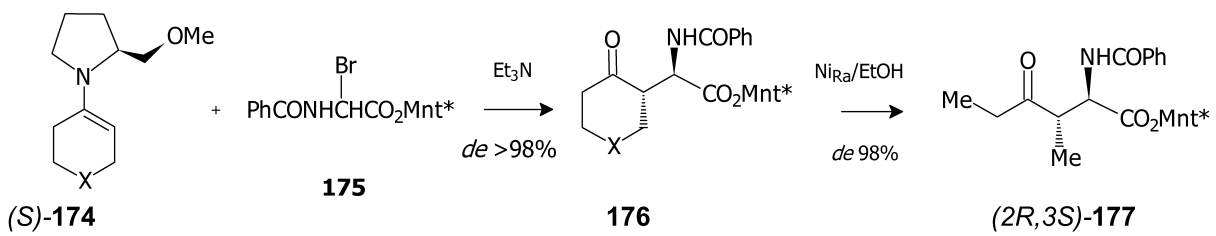
Takasu et al.[159] used the stereoselective intramolecular double Michael addition for the synthesis of culmorine and longiborneol possessing antifungal activity. An example of the addition of a chiral anion to chiral Michael acceptors has been described by Saito et al. (Scheme 82).[160] The asymmetric synthesis of isoxazolidinones **173** was developed by double asymmetric Michael addition of chiral hydroxylamines (MBHA) **171** with chiral α,β-unsaturated esters **170** and a cyclisation process involving intramolecular trans-esterification. The reaction between the ester **170** and the (*S*)-MBHA **171** provided the products **172** and then **173** with matched asymmetric induction (80–84% de), whereas the reaction employing the (*R*)-MBHA occurred as a mismatched asymmetric synthesis.

The matched asymmetric induction was observed in the reaction of enamines (*S*)-**174** with the (+)-menthyl ester of the acylimino acetate **175**, resulting in the diastereoisomerically pure products (1*S*,2*R*)-**176** (de=98–99.99%). The (−)-menthyl esters **175** reacted with the enamines



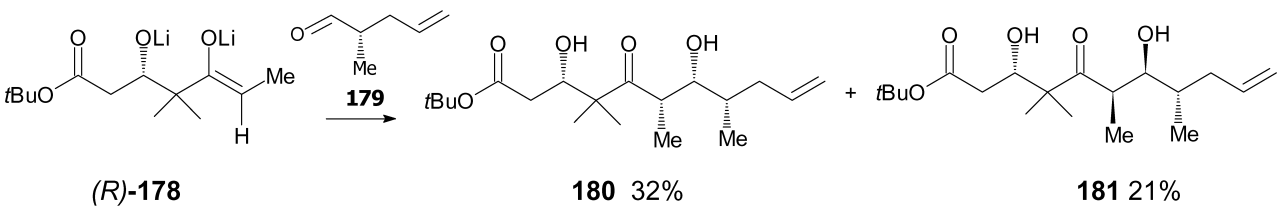
R	R'	R*	Conf	*de* (%)	Double AI
Me	Me	Bn	-	10	none
Me	Me	*(S)*-CH(Me)Ph	*S*	70	matched
Me	Me	*(R)*-CH(Me)Ph	*R*	63	mismatched
Ph	Me	*(S)*-CH(Me)Ph	*S*	80	matched
Ph	Me	*(R)*-CH(Me)Ph	*R*	75	mismatched
Ph	*i*-Pr	*(S)*-CH(Me)Ph	*S*	84	matched

Scheme 82. Double asymmetric synthesis of substituted isoxazolidinones **173**.



X = CH_2, S; Mnt* = *(1R,2S,5R)*-(-)-Menthyl, *(1S,2R,5S)*-(+)-menthyl, *(1R,2S,5R)*-8-phenylmenthyl.

Scheme 83. Substrate–reagent controlled diastereoselective synthesis of amino acid esters **177**.



Scheme 84. Asymmetric aldol reaction of the chiral lithium enolate **178** with the chiral aldehyde **179**.

(*S*)-**174** with mismatched asymmetric induction and lower diastereoselectivity. The desulphurisation of the sulphur-bearing cyclic products **176** with a Raney nickel catalyst provided the optically pure acyclic amino acid derivatives **177** (Scheme 83).[156]

3.4.2. Condensations of the aldol type. The aldol condensation is the most important carbon–carbon bond-forming reaction in the field of organic synthesis and natural product chemistry.[161,162]

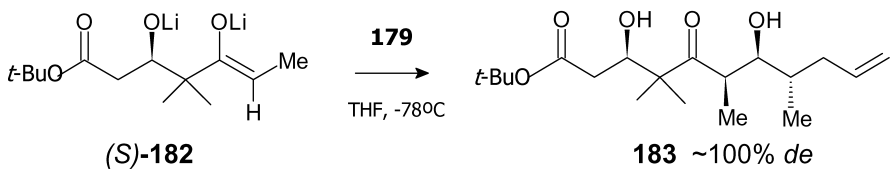
Double stereoselectivity in the aldol reaction can be achieved in a number of ways: addition of a chiral enolate to a chiral aldehyde or ketone; addition of a chiral enolate to an achiral aldehyde in the presence of a chiral catalyst; addition of a chiral enolate bearing two (or more) chiral asymmetric centres to an achiral aldehyde or ketone (and vice versa).

The double stereoselectivity (double stereodifferentiation) was extensively used in the aldol reaction to give very high levels of diastereoselectivity.[11,161–194] The stereochemistry of the aldol reaction depends strongly on the nature of the cation in the enolate, affecting the structure of the transition state complex.[163–167]

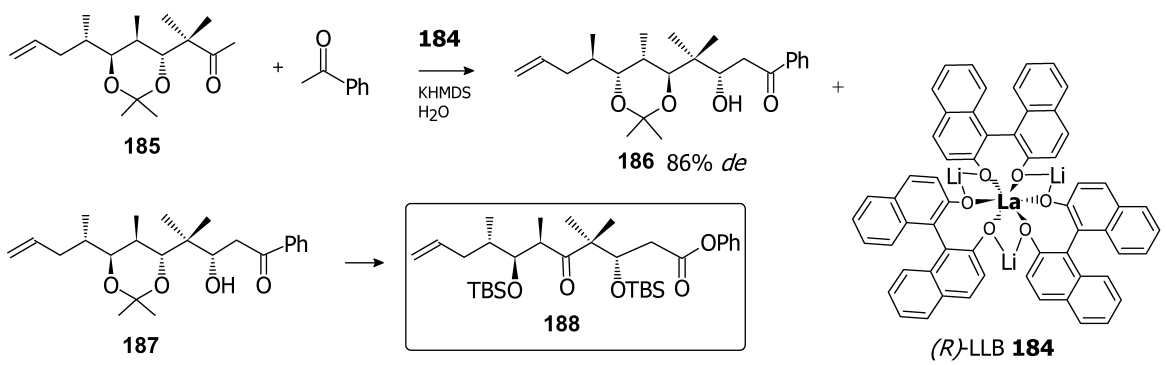
Lithium enolates. Lithium enolates are the most important among the enolates of the alkali metals because they can be easily generated by the action of organolithium compounds on ketones and can be easily transformed into the enolates of other metals. The stereochemistry of lithium enolates in the aldol condensation depends on the solvation and coordination of the metal in the coordination sphere of the transition state complex.[164] Lithium enolates form complexes with chiral ligands and the solvent to produce a 'supramolecule', using the definition of Juaristi and Seebach.[155] Lithium enolates in the aldol reaction form a well-ordered activated complex, in which the lithium ion is chelated with oxygen atoms belonging to the enol and aldehyde moieties. Introduction of additional auxiliaries or chiral additives into the sphere of this complex therefore usually strongly affects the double stereoselectivity of the aldol reaction.

The corresponding selection of chiral auxiliaries and their configurations allows the stereoselectivity of the aldol reaction to be influenced and impressing results to be achieved. In one example, the mismatched asymmetric aldol reaction of the chiral enolate (*R*)-**178** with the optically pure aldehyde **179** afforded a mixture of the compounds **180** and **181** in a ratio of 3:2 (Scheme 84), while the matched reaction of the enolate (*S*)-**178** with the aldehyde **179** provided the single aldol product **183** (Scheme 85). Remote stereochemical control in the matched aldol condensation through five bonds was observed.[168] Danishefski and co-workers[168a] used this methodology in the total synthesis of epothilone B, representing a very promising antitumour agent.

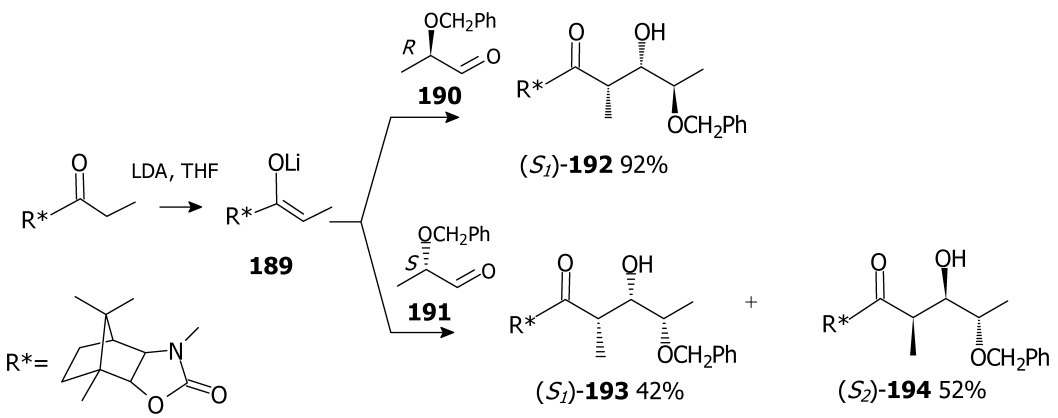
Shibazaki[169] proposed the multifunctional Li–La–BINOL



Scheme 85. Synthesis of the C(6)–C(7) stereogenic fragment of epothilone B.

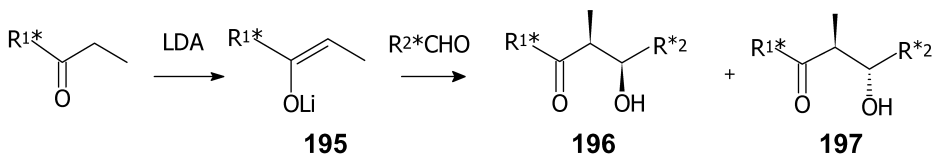


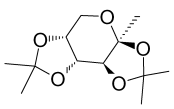
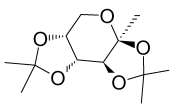
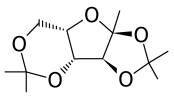
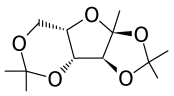
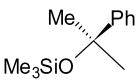
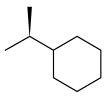
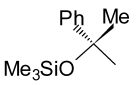
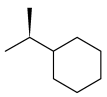
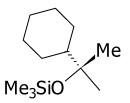
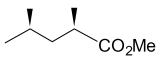
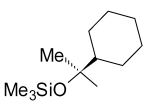
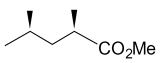
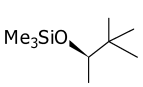
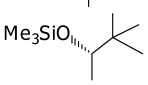
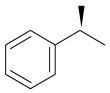
Scheme 86. Synthesis of the C(1)–C(11) fragment of epothilone A.



Scheme 87. Matched/mismatched asymmetric aldol addition.

Table 4. Matched and mismatched stereoselective aldol condensations



Entry	Compound	R^{1*} (in **195**)	Compound	R^{2*}(CHO)	dr (%)	Ref.
1	**198**		**199**		62:28:10 (*syn*-, *anti*- and *threo*-isomers)	18
2	**198**		**200**		98.5:1.5	18
3	**201**		**199**		66:34	18
4	**201**		**200**		97:3	18
5	**202**		**203**		11:89	172
6	**204**		**203**		60:40	172
7	**205**		**206**		9:91	172
8	**207**		**206**		94:6	172
9	**208**		**199**		~100	173
10	**209**		**210**		~100	173

complex **184** (LLB catalyst) for the aldol reaction (Scheme 86). The double asymmetric aldol reaction of **185** with acetophenone and (*R*)-**184** as the catalyst provided the aldol products **186** and **187** with 86% de, which were converted into the C(1)–C(11) fragment of epothilone A **188** with 88% ee.

Bonner and Thornton[170] applied conformationally rigid camphor-derived *N*-propionyl-oxazolidinones as a chiral auxiliary and achieved a very good level of double diastereoselectivity in the aldol reaction (Scheme 87). The lithium enolate **189** reacted with (*R*)-2-(benzyloxy)propanal **190** with matched asymmetric induction to afford the *syn*-product **192** having an (*S*)-absolute configuration in 92% de. The reaction of the lithium enolate **189** with (*S*)-2-(benzyloxy)propanal **191** occurred as a mismatched addition to afford a 42:52 mixture of the products **193** and **194** with low stereoselectivity.

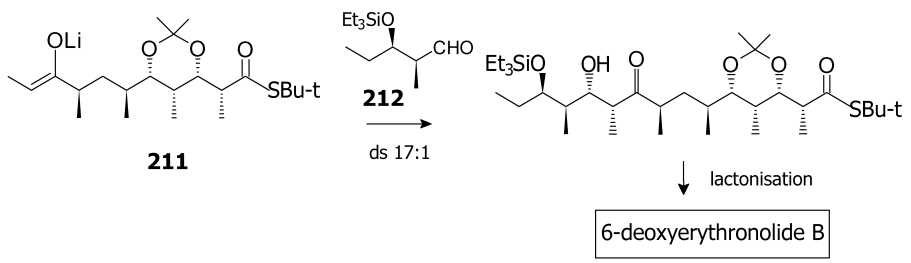
Examples of matched and mismatched asymmetric aldol condensations of chiral ketones **195** with chiral aldehydes leading to the formation of *syn*- and *anti*-aldols **196** and **197** are shown in Table 4.[18,162,172,173]

The chiral glyceraldehyde acetonides have proved to be the most useful building blocks in aldol methodology (entries 1–5). The mismatched asymmetric reaction of the chiral lithium enolate **198** with the acetonide of (*R*)-glyceraldehyde **199** furnished a mixture of three aldols in a 6.2:2.8:1 ratio (entry 1). At the same time, the matched asymmetric reaction of the enol **198** with the (*S*)-glyceraldehyde **200** acetonide resulted in the formation of only one (*R*,*R*)-diastereomer of *syn*-aldol (ds ~100%, entry 2). The reaction of the enolate **201** with (*R*)-glyceraldehyde acetonide **199** furnished the aldol with a diastereoisomeric excess of ~94%,[173] whereas the reaction of the enolate **201** with the acetonide **199** furnished a diastereomer of *erythro*-aldehyde in a ~2:1 ratio. The chiral lithium enolates **202**,**204**,**205** and **207** bearing silyloxy-group showed significant differences in matched and mismatched asymmetric aldol reactions with chiral aldehydes **203** and **206** (entries 5–8). The reaction of the sterically hindered enolates **208** and **209** bearing *t*-butyl and Me_3SiO-groups with the chiral aldehydes **199** and **210** resulted in only one diastereomer of aldol with matched stereoselectivity (entries 9 and 10).[173]

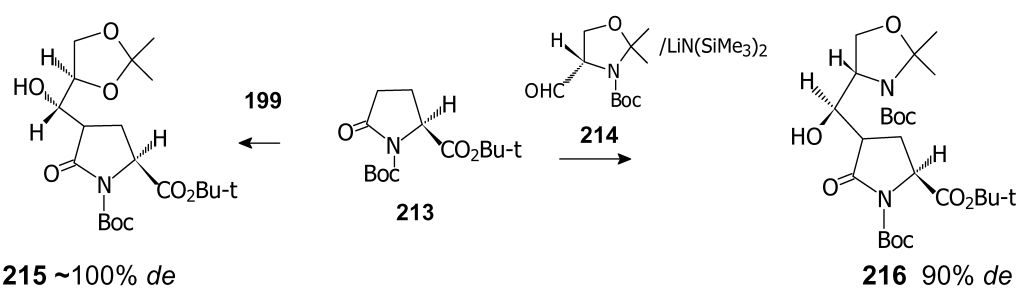
Masamune[171,172] studied the aldol condensation of the silylated aldehyde **212** with the lithium enolate **211** which resulted in the formation of the aldol with 94% de (Scheme 88). The good stereoselectivity was explained by the formation of a chelate complex between the lithium cation and the oxygens of the aldehyde and the R_3SiO group owing to the *Re* side of the aldehyde being less shielded than the *Si* side. This reaction was applied to the total synthesis of 6-deoxyerythronolide B.

Hitchcock[174] observed the double asymmetric induction in the aldol condensation of the lithium enolate of the (2*S*)-pyroglutamate ester urethane **213** with (*R*)-glyceraldehyde acetonide **199** (Scheme 89). The matched pairs of (*S*)-**213**–(*R*)-**199** resulted in the formation of a single diastereomer of the aldol **215**. The reaction of the pyroglutamate **213** with (*S*)-Garner aldehyde **214** also proceeded with a high diastereoselectivity to give the adduct **216** with 19:1 ds. At the same time, the mismatched reaction of the pyroglutamate **213** with both the (*S*)-glyceraldehyde and (*R*)-Garner aldehyde afforded the aldol adducts with low stereoselectivity.

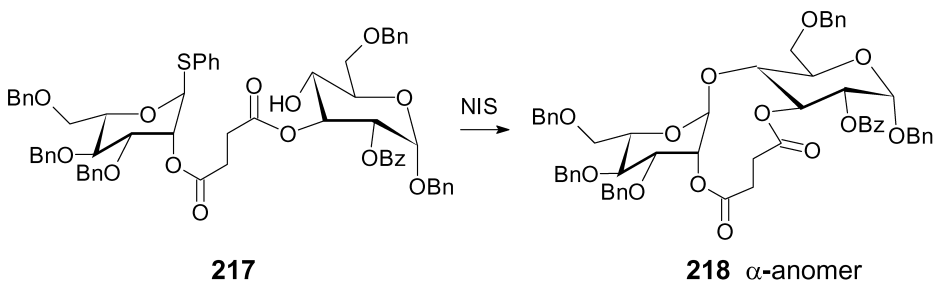
A significant effect of double stereodifferentiation was observed in the intramolecular glycosylation of the prearranged glycosides **217** and **219** under *N*-iodosuccinimide activation (Schemes 90 and 91).[175] The derivatives of mannose initiated the matched double asymmetric induction of intramolecular glycosylation. For the succinyl-bridged glycosides **219**, derivatives of rhamnose, however, the asymmetric induction of intramolecular glycosylation was rather weak to result in the diastereomeric mixture **220** and



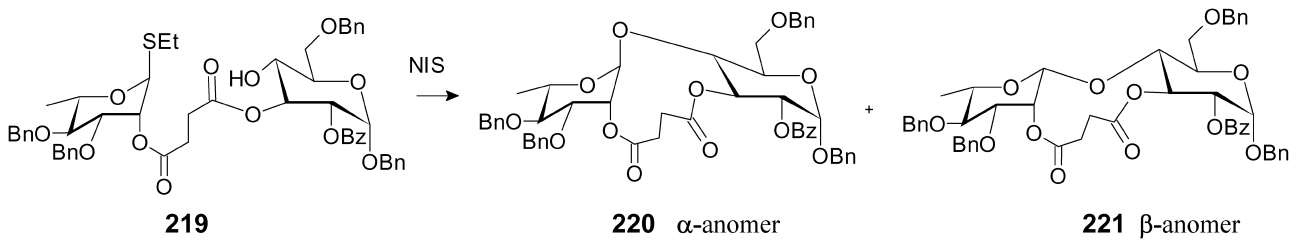
Scheme 88. Double AS in the total synthesis of 6-deoxyerythronolide B.



Scheme 89. Double asymmetric induction in the aldol condensation of the lithium enolate **213** with (*R*)-glyceraldehyde acetonide **199**.



Scheme 90. Double stereodifferentiation in the intramolecular glycosylation of the glycosides **217**.

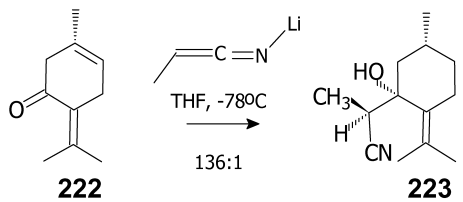


Configuration of glycoside	α/β ratio of products	Double AS
L-Man/L-Glc	100:0	matched
D-Man/D-Glc	100:0	matched
L-Rha/D-Glc	18:82	mismatched

Scheme 91. Double asymmetric intramolecular glycosylation.

221. The diastereoselectivity of intramolecular glycosylation was independent on the topographic properties of the prearranged glycosides **217** and **219** (the α-anomers **218** predominate for L-Man/L-Glc and D-Man/D-Glc), but depended on the geometric properties (Scheme 91).

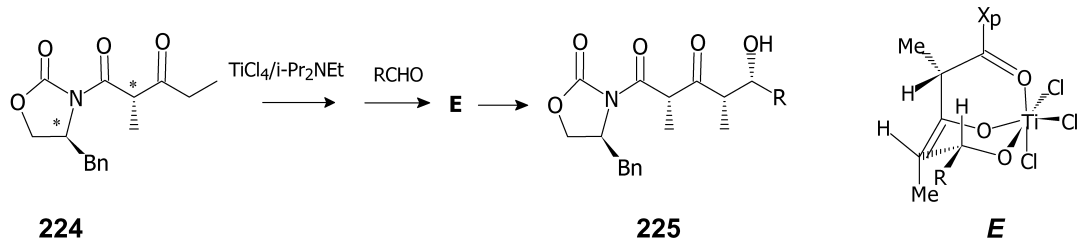
Trost and co-workers[176] studied double diastereoselectivity in the addition of metallated propionitriles to enones (fulegone, carvone and others). The reaction of fulegone with a metallated propionitrile afforded the aldol adduct **223**



Scheme 92. Double stereoselective addition of a metallated propionitrile to enones.

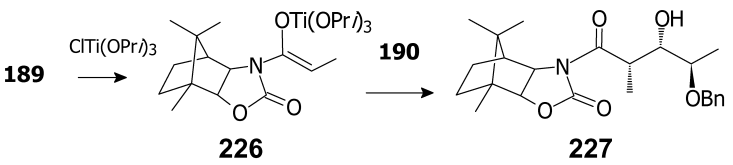
with a high diastereoselectivity (136:1), whereas the cyclohexenones reacted with sterically smaller metallated acetonitriles with a low stereoselectivity (Scheme 92).

Titanium enolates. Titanium enolates have been proposed in addition to lithium enolates to control the stereoselection of the aldol reaction (vide supra).[161,177,178] Evans et al.[178a] have described the diastereoselective aldol reactions of titanium(IV) enolates. The consecutive treatment of the β-ketoimide **224** with $TiCl_4$, *i*-Pr_2NEt and an aldehyde provided the aldol adducts **225** with <1:99–4:96 diastereoselectivity (Scheme 93). The stereochemical outcome was determined by matched asymmetric induction of two chiral auxiliaries in the β-ketoimide **224** (substrate-controlled AS). The reaction probably proceeded via a diastereomeric transition state **E**. Fringuelli et al.[163] studied the aldol reaction of titanium(IV) enolates of a conformationally rigid camphor-derived *N*-propionyloxazolidinone **226** with (*R*)-(2-benzyloxy)propanal **190**. The

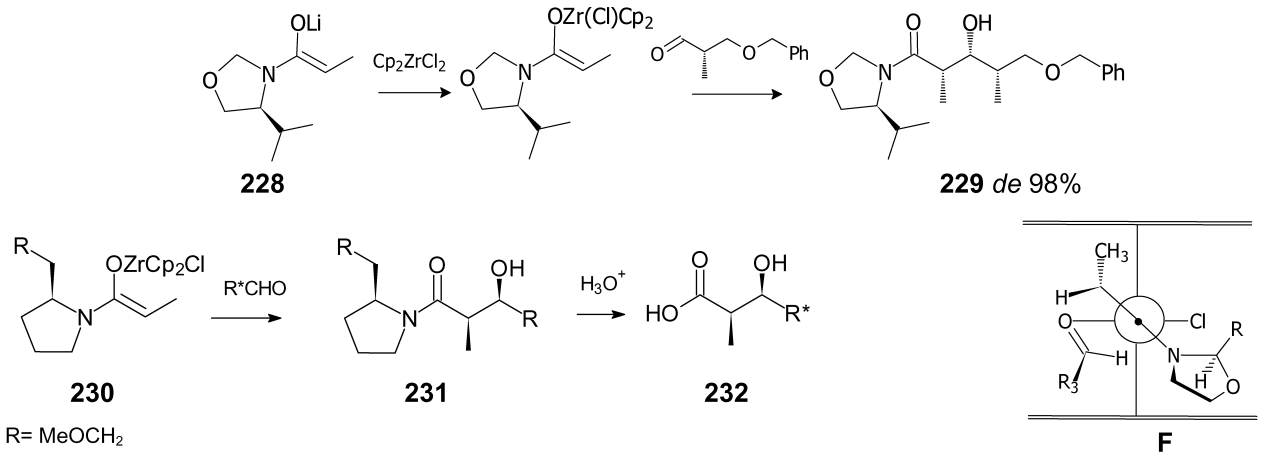


R	Yield (%)	*ds* (%)
i-Pr	86	< 1:99
$MeC{=}CH_2$	64	2:98
Et	86	< 1:99
Ph	81	4:96

Scheme 93. Titanium enolate-controlled double AS.



Scheme 94. Double stereoselectivity in the reaction of a camphor-derived *N*-propionyloxazolidinone with (*R*)-2-(benzyloxy)propanal.

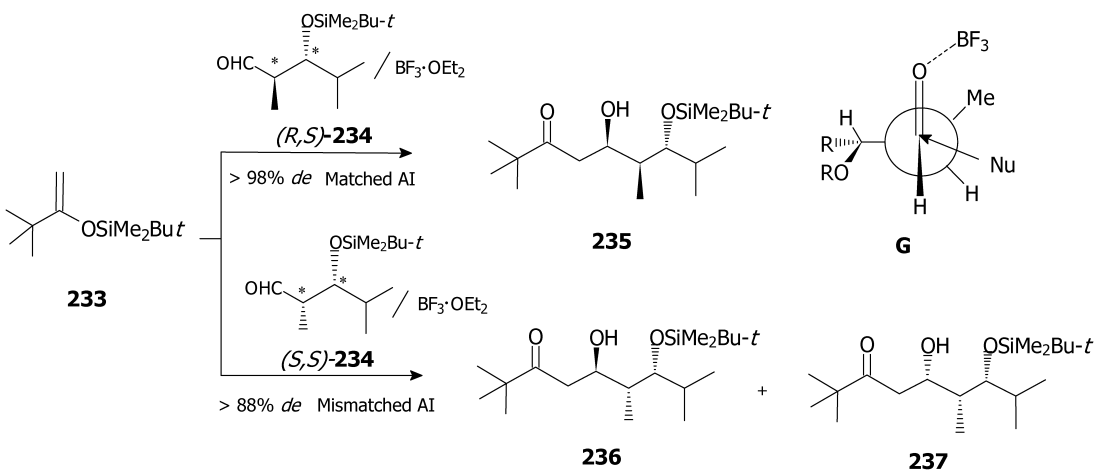


Scheme 95. Aldol reaction of the zirconium enolate of a propionamide with chiral aldehydes.

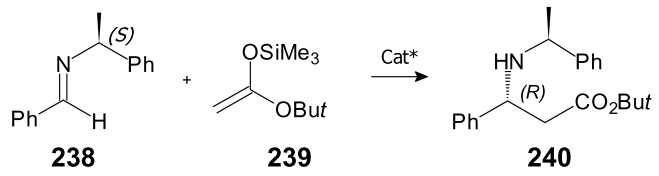
reaction proceeded with the matched asymmetric induction to yield the *syn*-aldol **227**, having an (S_1)-configuration. The authors explained the double diastereoselectivity by a *Z*-geometry of the titanium enolate and by intramolecular chelation between the metal and the oxazolidinone carbonyl oxygen in the transition state (Scheme 94).

Zirconium enolates. In some cases, the exchange of lithium for zirconium in enolates improves the stereoselectivity of the aldol reaction. For example, the zirconium enolate of a chiral propionamide **228** reacted with the enantiomers of 3-benzyloxy-2-methylpropanal to afford the *syn*-aldol **229** with a diastereomeric excess of >98% (Scheme 95).[178] The reactions of the chiral zirconium enolate **230** with a number of chiral aldehydes proceeded with high double *erythro*-diastereofacial selectivity (dr 50:1–200:1) to furnish the *syn*-aldols **231**, which were converted into the enantiopure carboxylic acids **232** (Scheme 95). The *erythro* specificity of the zirconium enolates **230** is probably due to steric interactions in the transition state **F** between the substituents on the enolate and the bulky cyclopentadienyl ligands of the metal.

Silyl enolates (*Mukaiyama reaction*). Mukaiyama et al.[179] have discovered that silyl enol ethers react with carbonyl compounds to afford aldol-type products in the presence of a Lewis acid catalyst ($TiCl_4$, $SnCl_4$, $ZnCl_2$, boron derivatives etc.) or fluoride ions derived from tetrabutylammonium fluoride in THF.[180,181] The main advantage of this reaction is its high stereoselectivity.[162,179–186] The Mukaiyama reaction provides interesting effects in the double diastereoselective aldol condensation that is determined by a specific coupling of the oxygen atom of R_3SiO group with metal ions. In one example, condensation of the silyl derivative **233** with the chiral aldehyde (*R*,*S*)-**234** bearing two chiral auxiliaries with a matched configuration was



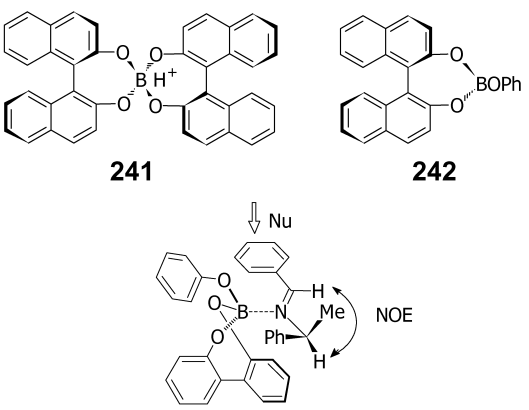
Scheme 96. Double asymmetric induction in the Mukaiyama reaction.



238 239 240

Cat* = (*S*)-**241**/(*S*)-**238**/PhOH or (*S*)-**241**

Catalyst	*de* of 240 (%)	Config of 240	Double AI
(*S*)-**241**	62	*R*	mismatched
(*R*)-**241**	> 99	*R*	matched
(*S*)-**242**	74	*R*	mismatched
(*R*)-**242**	92	*R*	matched
$B(OPh)_3$	78	*R*	none



241 **242**

H

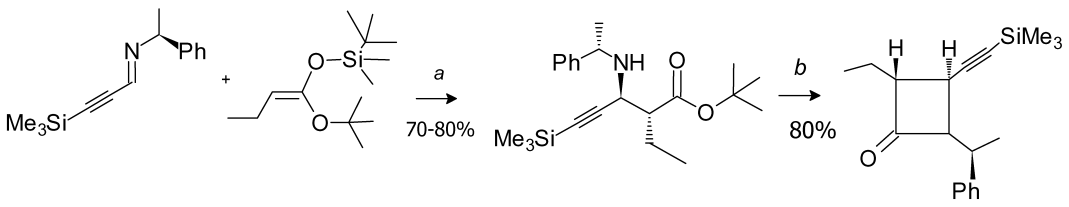
transition state complex of (*S*)-**238**/(*R*)-**242**

Scheme 97. BLA-induced double asymmetric aldol-type reaction.

more stereoselective (only one diastereomer **235**) than the condensation of the enolate **233** with the chiral aldehyde (*S*,*S*)-**234** resulting in the formation of the diastreomers **236** and **237**. The relative diastereoselectivity (high degree of 1,2-*syn*- and 1,3-*anti*-asymmetric inductions) observed in this reaction is a result of an *anti* relationship between the α-methyl and the β-alkoxy group in the Felkin–Anh model **G** (Scheme 96).[162]

Hattori and Yamamoto[183] developed very effective chiral organoboron catalysts **241** and **242** as chiral BLA promoters (Brønsted acid-assisted chiral Lewis acid) for the asymmetric aldol-type reactions. For example, the reaction of the *N*-benzhydrylimine **238** with the trimethylsilyl ketene acetal **239** mediated by the chiral BLA catalyst (*R*)-**241** afforded the β-amino acid esters **240** with a diastereoselectivity of >99% (Scheme 97). The absolute configuration of the adducts agrees with predictions based on the transition state complex **H**: the nucleophile would approach the *Re* face of the (*E*)-imine (*S*)-**238**–(*R*)-**242** complex. This reaction was used in the development of a highly stereoselective synthesis of the carbapenem antibiotic (+)-PS-5 **243**, active against Gram-positive and Gram-negative bacteria (Scheme 98).[183]

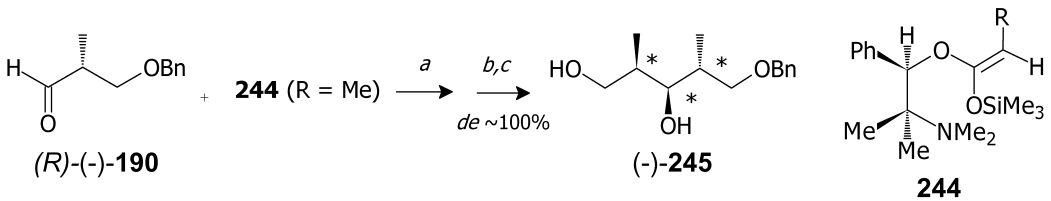
Gennari and co-workers,[184–186] studied the $TiCl_4$-mediated Mukaiyama aldol reaction between silyl acetals derived from *N*-methylephedrine **244** (R=Me) and the (*R*)- and (*S*)-enantiomeric aldehydes **190**. The reaction of the chiral aldehyde (*R*)-(−)-**190** with the ephedrine derivative **244**



a = (*R*)-**241**, CH_2Cl_2, -78°C; *b* = CF_3CO_2H, $PPh_3(PyS)_2$

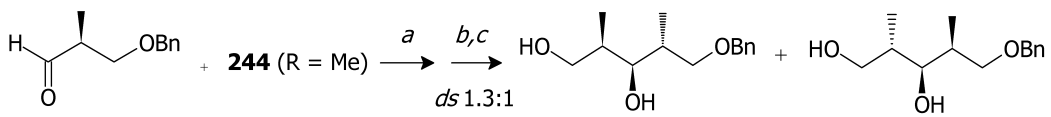
243

Scheme 98. Synthesis of carbapenem antibiotic (+)-PS-5 **243**.



(*R*)-(-)-**190** (-)-**245** **244**

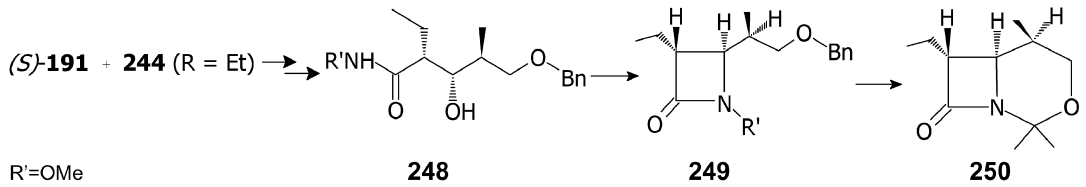
Scheme 99. Matched AI in the $TiCl_4$-mediated Mukaiyama reaction.



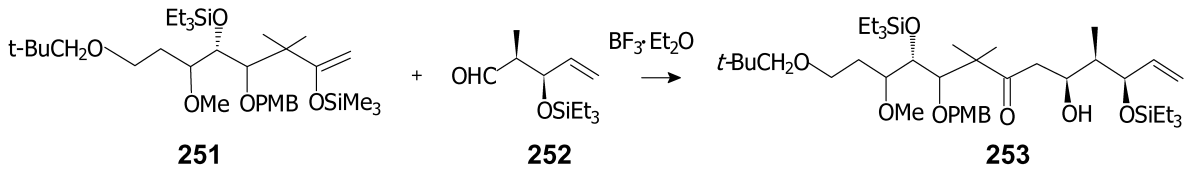
(*S*)-(+)-**191** (+)-**246** (+)-**247**

a = $TiCl_4/CH_2Cl_2$; b) Raney Ni, H_2, MeOH; c) $LiAlH_4/Et_2O$.

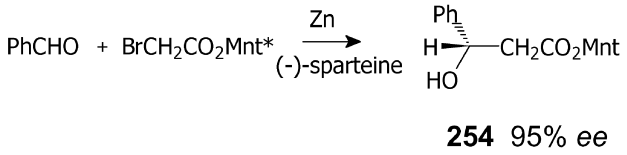
Scheme 100. $TiCl_4$-mediated asymmetric Mukaiyama reaction.



Scheme 101. Synthesis of carbapenem antibiotic 1β-methyl-PS-5 **250**.



Scheme 102. Synthesis of the C(1)–C(25) spiroketal fragment of calyculin A.



Scheme 103. Asymmetric Reformatsky reaction.

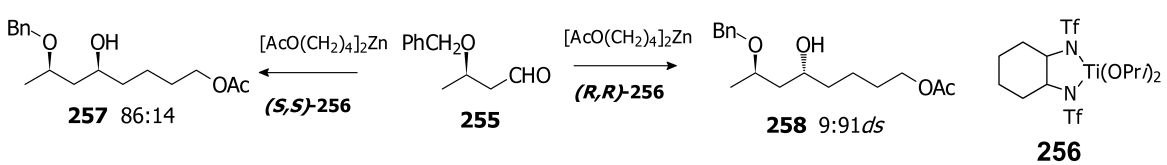
afforded a single diastereomer of the aldol **245** (matched asymmetric induction) (Scheme 99), while the mismatched asymmetric reaction of the aldehyde (*S*)-(+)-**191** with **244** afforded a 1.3:1 diastereomeric mixture **246**–**247** (Scheme 100). In the matched pair case, three contiguous stereocentres were established with complete selectivity.[184] The product **248** was converted into the key intermediate **249** for the preparation of the carbapenem antibiotic 1β-methyl-PS-5 **250** (ee >99%) (Scheme 101).[185]

Evans and co-workers[187,188] developed a total synthesis of the tumour protector calyculin A using the Mukaiyama reaction, catalysed by boron trifluoride etherate. The *syn*-aldehyde **252** reacted with the chiral enol-silane **251** to give the aldol product **253** with de ~90% (Scheme 102).

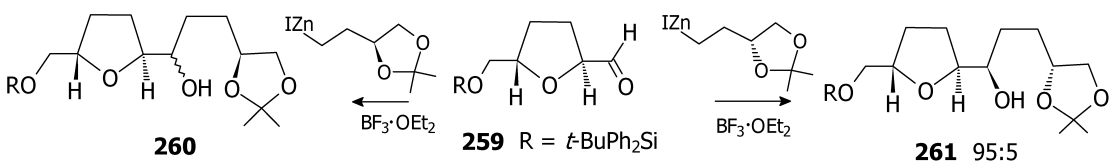
Ley et al.[189] reported the double diastereoselectivity in the Mukaiyama aldol reaction of trimethylsilyl enol ether-substituted allyltricarbonyl–iron lactone complexes with chiral aldehydes under $BF_3{\cdot}OEt_2$ activation. The reaction proceeded with high levels of substrate control (1,7-induction) overriding 1,2-induction from the aldehyde stereogenic centre. Enantiomerically pure homoallyl alcohols and ethers were obtained with a high stereoselectivity (de ~98%) by the reaction of aldehydes with trimethylsilyl ethers of *N*-trifluoroacetylnorpseudoephedrine in the presence of catalytic amounts of TMS triflate or TMS boron triflate, but the difference between matched and mismatched pairs was low, because of a strong reagent control overriding the substrate control.[182b]

Zinc enolates and the Reformatsky reaction. The Reformatsky reaction is closely related to the aldol reaction.[195–198] The double asymmetric induction was observed when chiral ligands matched with optically active substrates were used.[199] The double asymmetric Reformatsky reaction between benzaldehyde and an α-bromoester in the presence of zinc and (−)-sparteine afforded predominantly a 95% optical yield of **254** (Scheme 103).

The asymmetric Reformatsky reaction of benzaldehyde with optically active menthyl bromoacetate in the presence of a copper–zinc couple and (1*R*,2*S*)- or (1*S*,2*R*)-*N*,*N*-dimethyl-2-amino-1,2-diphenyl-ethanol as the chiral ligand provided the *t*-butyl hydroxyesters with enantioselectivities of up to 60.2%. A number of functionalised organometallics reacted with excellent stereoselectivity with aromatic and aliphatic aldehydes such as **255** in the presence of catalytic amounts of the chiral titanium derivatives **256**: the pair (*R*)-**255**–(*R*,*R*)-**256** was matched and the pair (*R*)-**255**/–(*S*,*S*)-**256** was mismatched (Scheme 104).[195]



Scheme 104. Substrate–catalyst controlled asymmetric Reformatsky reaction.



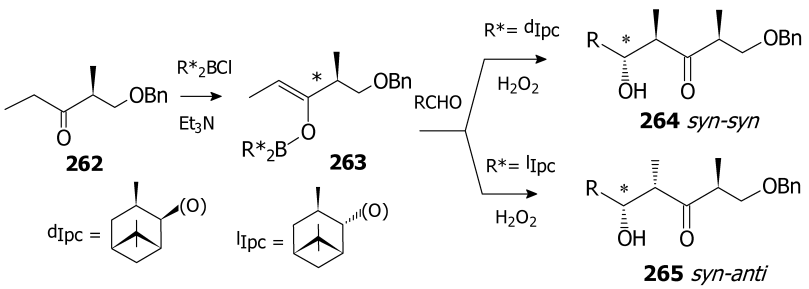
Scheme 105. Asymmetric synthesis of oligo(tetrahydrofuran)s.

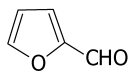
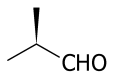
The addition of enantiomerically pure organozinc reagents to the chiral THF–aldehyde **259** in the presence of $BF_3{\cdot}OEt_2$, resulted in the non-chelation-controlled addition products **261** and **260** corresponding to matched or mismatched asymmetric induction (the stereoselectivities were 95:5 and 73:27, respectively) (Scheme 105).[196,197] Two directing effects determined the stereochemical outcome of this reaction: the stereocentre in the organozinc reagent and the stereocentres in the α-alkoxyaldehyde. The influence of two aldehyde stereocentres in **259** dominates the influence of the single organozinc stereocentre.

Boron and aluminium enolates. Boron enolates have been used most extensively to control the stereochemistry of the aldol condensation. In general, the aldol reaction of boron enolates is more stereoselective than the reaction of lithium enolates or any other enolates. The B–O bond is shorter than the Li–O bond and therefore the transition state containing the boron atom is more compact and steric factors have a greater influence on increasing the stereoselectivity of the aldol reaction. The substituent R of the BR_2 group in a boron enolate can be achiral or chiral. The most interesting reagents for the aldol reactions are enols of the chiral ketones **262**, bearing additional chiral $^{d}Ipc_2B$ or $^{l}Ipc_2B$ groups increasing the diastereoselectivity of the aldol reaction (Scheme 106).[200–204] The enols **263**, bearing two chiral inductors, reacted with aldehydes under multiple asymmetric substrate control (matched or mismatched AS) to afford the aldol adducts **264** and **265** with excellent stereoselectivity (up to >99% ee and 93% de).[181]

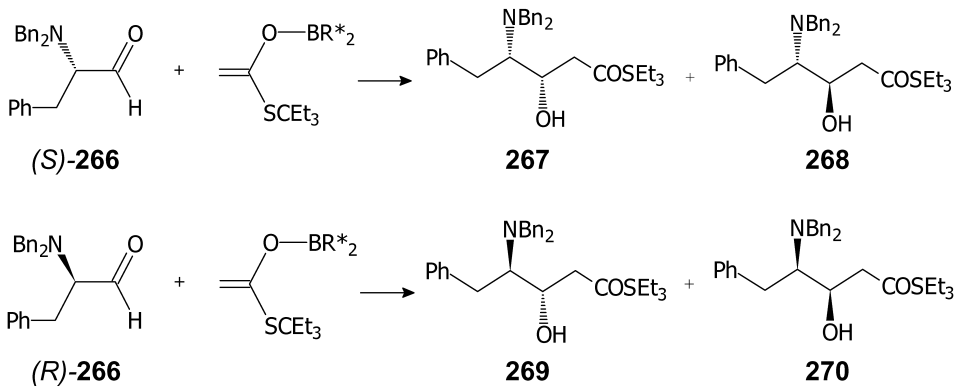
The reaction of a chiral boron enolate with the enantiomers of the aldehyde (*S*)-**266** and (*R*)-**266** resulting in the aldols **267**–**270** proceeded under reagent control, mediated by chiral substituents on boron, in spite of the proximity of the chiral centre in the substrate to the nascent chiral centre (Scheme 107).[205] As indicated above, boron can coordinate to only two oxygen atoms during the reaction, but the facial selectivity is still high and control of the enolate geometry can be exercised and allows access to either the *syncat* or *ancat* products.

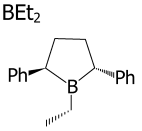
Masamune et al.[101,171] used boron enolates of the (*S*)- and (*R*)-ketones **271** in the synthesis of 6-deoxyerythronolide B,



R*	RCHO	Syn-Syn:Syn-Anti	RCHO	Syn-Syn:Syn-Anti	Double AS
Bu		1:1		1:1.2	none
^{d}ipc		1:9		1:2.6	mismatched
^{l}ipc		11:1		13:1	matched

Scheme 106. Substrate-controlled double asymmetric aldol condensation.



BR_2	Aldehyde	*dr* (%)	Double AS
BEt_2	*S*-**266**	1:1	none
	*S*-**266**	28:1	matched
	R-**266**	1:15	mismatched

Scheme 107. Chiral organoboron reagent controlled aldol condensation.

a biosynthetic precursor of erythromycin. They obtained in this reaction the aldol **272** in 97.6% diastereoselectivity (Scheme 108). Masamune used these routes also for the synthesis of the C(13)–C(19) fragment of amphotericin B and the C(11)–C(17) fragment of tylonolide.[101]

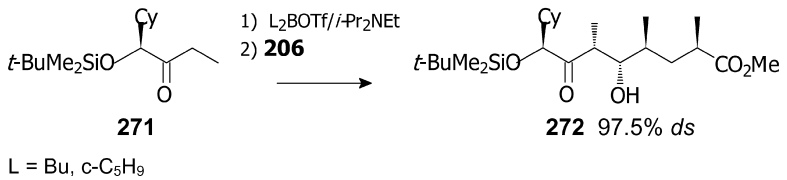
The aldol reaction of a chiral enolate derived from (*S*)-**273** with the chiral aldehyde (*S*)-(−)-**274** proceeded with matched asymmetric induction to give the diastereomer **275** in >98% de. The reaction of the aldehyde (−)-**206** with the enolate (*R*)-**276** furnished the compound **277** in 93% de (Scheme 109).[12] The reaction of the compound **278** with the chiral aldehyde (*S*)-**274** led to the formation of the adduct **279** with a very high level of asymmetric induction (dr 660:1). The aldol **279** was then converted to the acid **280** (Scheme 110).[12]

Davies et al.[198] studied the highly stereoselective aldol reaction between the diethyl-aluminium enolate derived from the (*S*)- or (*R*)-iron acetyl complex **281** and homochiral 2,3-*O*-isopropylidene-D-glyceraldehyde **199** (Scheme 111).

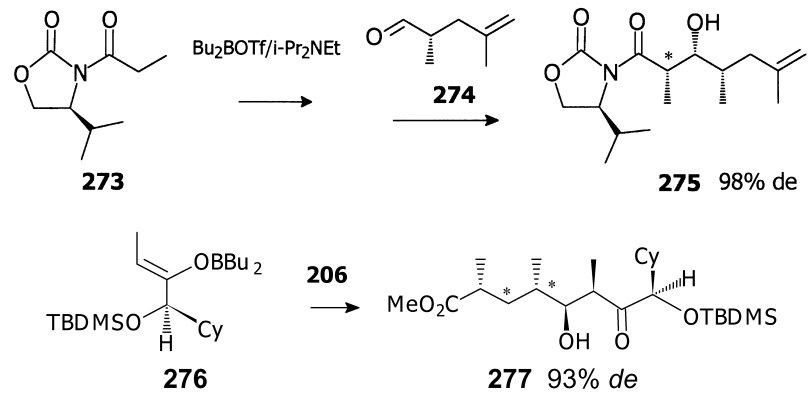
The matched double asymmetric induction increased the stereoselectivity of adduct **282** formation up to 99% de. Analogous tin(II) enolates also reacted with high diastereoselectivity to give (*R*,*S*,*R*)-**282**.

Both the 2(*R*)- and 2(*S*)-stereoisomers of *o*-hydroxylacetates **284** and **285** have been prepared from phenols such as **283** and pyruvic acid esters bearing a chiral (L)-menthyl group. The double asymmetric induction increased the diastereomeric purity of the *o*-hydroxylactates **285** from 13–46% to 36–88% de (Scheme 112).[199]

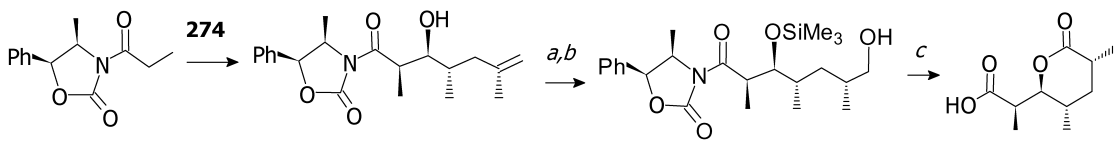
3.4.3. Addition of allylmetallic reagents. The reaction of allylic organometallic reagents with aldehydes is



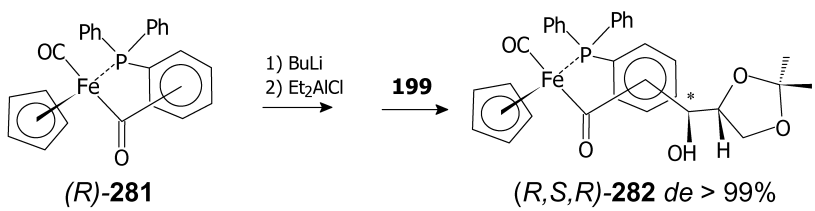
Scheme 108. Double asymmetric synthesis of 6-deoxyerythronolide B.



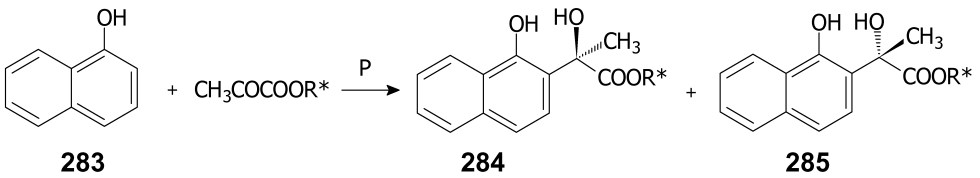
Scheme 109. Substrate–reagent-controlled double asymmetric aldol condensation.



Scheme 110. Stereoselective synthesis of the Prelog–Djerassi lactone.

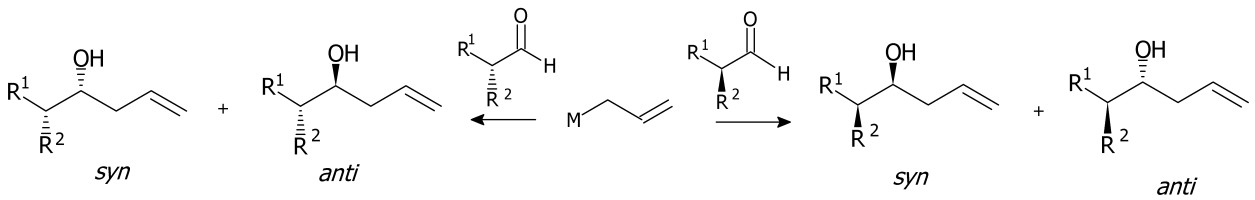


Scheme 111. Stereoselective aldol reaction of the diethyl-aluminium enolate **282**.



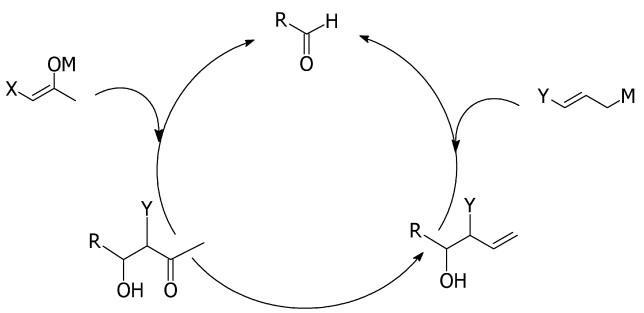
R*	P = Promoter	*dr*	Conf
(-)-Mnt	(-)-Mnt-$OTiCl_3$	6:94	*R*
(+)-Mnt	(+)-Mnt-$OTiCl_3$	93:7	*S*

Scheme 112. Double asymmetric synthesis of the *o*-hydroxylactates **284** and **285**.



Scheme 113. Asymmetric reaction of allylic organometallic reagents with aldehydes.

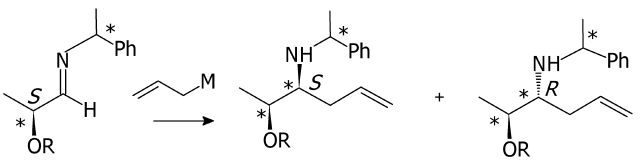
synthetically analogous to the aldol addition of metal enolates, since the resulting homoallylic alcohol can be easily converted to the aldol (Scheme 113).[206–209] Like enolates, allylmetallic reagents reacted with chiral aldehydes to furnish diastereomeric mixtures of *syn*- and *anti*-alcohols. Allylmetal additions have significant advantageous over aldol condensations since alkenes may undergo a facile one-carbon homologation to δ-lactones via hydroformylation or may be selectively epoxidised to introduce a third chiral centre. Moreover, the newly-formed alkenes may be easily transformed into aldehydes and the operation repeated (Scheme 114).[209,210]



Scheme 114. Reaction of allylic organometallic reagents with aldehydes.

Numerous examples of highly stereoselective additions of allylmetallic reagents to carbonyl compounds and imines reinforced by double asymmetric induction have been described in the last few years.[211–235]

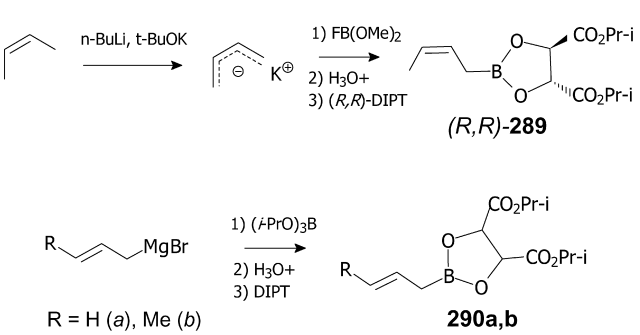
The double asymmetric induction is possible when both reactants, the aldehyde (or imine) and the allylmetallic reagent, are chiral or the substrate contains two (or more) chiral auxiliaries and the reagent is achiral. Many allylmetallic reagents, Allyl-M, where M=B, Sn, Si etc, react smoothly with carbonyl compounds to yield the corresponding homoallylic alcohols. The stereochemistry of such reactions depends on the nature of the metal. For example, the diastereoselective 1,2- and 1,3-asymmetric induction of α- and β-alkoxyimines **286** was realised via a combination of metal tuning and double asymmetric induction with 90% de. The 1,2-asymmetric induction is determined by the chirality of the carbon atom and the nature of metal and does not depend on the chirality of the substituent at the nitrogen atom (Scheme 115).[211,212]



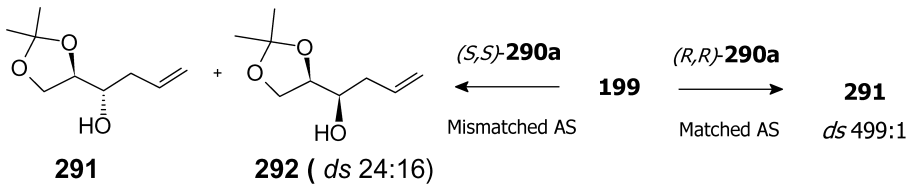
M	*Ds* of **287/288**		
	S	*S*/*R*	*R*
9-BBN	3:97	> 99:1	> 99:1
$B(OMe)_2$	10:90	7:93	10:90
$AlEt_3MgCl$	89:11	93:7	95: 5
ZnBr	76:24	78:22	92: 8
MgCl	70:30	79:21	86:14
$Ti(OPr\text{-}i)_3$	6:94	23:77	20:80

Scheme 115. Double asymmetric induction in addition of allylmetallic reagents to imines.

Allyllboranes are the most highly diastereoselective and appear ideally suited for use in synthetic organic chemistry



Scheme 116. Synthesis of the (*R*,*R*) and (*S*,*S*)-tartrate allylboronates **289** and **290**.



Scheme 117. Matched/mismatched asymmetric reaction of the tartrate allylboronates **290** with the glyceraldehyde acetonide **199**.

as enolate equivalents. Highly effective types of chiral allylboron reagents bearing chiral boron ligands have been developed. In one example, Roush[21,214,215] developed the (*R*,*R*) and (*S*,*S*)-tartrate allylboronates **289** and **290** which were prepared from cheap starting reagents (Scheme 116).

The stereoselective reaction of the tartrate allylboronates **290** with chiral aldehydes, depending on the chirality of the starting reagents, can proceed as a matched or mismatched asymmetric synthesis to give the adducts **291** or **292** as major products (Scheme 117).[21] The double stereoselectivity of this reaction was sensitive to the reaction temperature (−78°C was the best), solvent (toluene was the best for aliphatic aldehydes and THF was preferred for aromatic aldehydes), moisture (the use of molecular sieves was recommended).[21,23,214]

Examples of matched and mismatched asymmetric aldol reactions of chiral allylboronates with chiral aldehydes are collected in Table 5.[215–227] The examples demonstrating significant differences of diastereomeric ratios are shown in entries 1–20 of this table. For instance, the (*S*,*S*)-tartrate crotylboronates showed excellent stereoselectivity in entries 4, 12, 14 and 18, but are much less selective in entries 3, 11, 13 and 17. The chiral (*R*,*R*)-crotylboronates in matched asymmetric reactions with the chiral aldehydes also provided a high selectivity (entries 1, 19, 33 and 37). Their reaction with chiral aldehydes provided an effective enantioselective method for the preparation of *syn*- and *anti*-1,2-diols.[225] The matched double asymmetric allylborations of chiral 2,3-epoxyaldehydes using tartrate allylboronates provide *erythro*-epoxy alcohols with excellent diastereoselectivity (>97% de) and enantioselectivity (>96% ee) (entries 13–20). The glyceraldehyde acetonide gives a 499:1 (entry 1) diastereoselectivity, whereas the corresponding (*S*,*S*)-crotylboronate gives a ratio of 5.25:1 (mismatched reaction, entry 2). The matched asymmetric reaction of chiral (*S*,*S*)-crotylboronate with the chiral cyclohexylidene glyceraldehyde in entry 16 produces a 300:1 ratio of product diastereomers, whereas the corresponding (*R*,*R*)-crotylboronate in the mismatched allylboration gives a ratio of 1:2.7 (entry 11). The silyl-substituted allylboronates bearing a tartrate auxiliary reacted with mismatched asymmetric induction to give diastereomeric *threo*-epoxy alcohols with low (ca. 75:25) selectivity (entries 23–30).[222] The TBDMS-protected aldehydes are the optimal substrates for the matched double asymmetric reaction with allylboron tartrates (entries 25,26 and 29–36).[215]

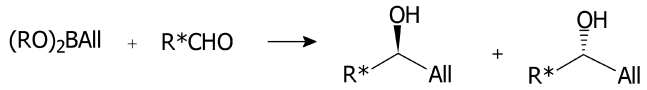
In addition to tartrate allylboronates, Roush developed allylboronates of *N*,*N*′-dibenzyl-*N*,*N*′-ethylenetartramide **294** and **295**, which exhibited substantially improved stereoselection relative to other tartrate allylboronates (Scheme 118).[215,228] The best result achieved in the reaction of allylboronates with glyceraldehyde acetonide was 300:1 in the matched double asymmetric reaction (entries 1 and 3) and 50:1 selectivity in the mismatched allylboration (entries 2 and 4). These results suggest a mechanism of asymmetric induction with tartrate allylboronates, namely that n/n electronic interactions between electron pairs on the aldehydic oxygen atom and an ester carbonyl disfavour the transition state **H**.

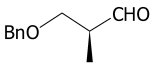
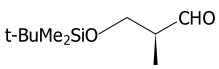
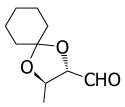
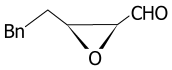
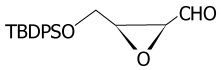
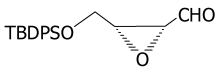
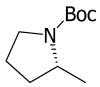
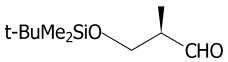
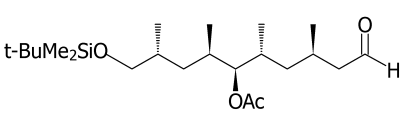
Roush et al.[21] have analysed the average diastereofacial selectivity of chiral (*Z*)- and (*E*)-allylboronates **296** in pairs of double asymmetric reactions with chiral alkoxyaldehydes on the basis of an estimation of the free energy difference between competitive transition states $\Delta\Delta G^{\#}$. The $\sum\Delta\Delta G^{\#}$, values have been obtained by the addition of $\Delta\Delta G^{\#}_{M}$, and $\Delta\Delta G^{\#}_{MM}$ values, defined as the total free energy swing for the pair of matched and mismatched double asymmetric reactions (Schemes 119 and 120). Roush came to the conclusion that the observed trends in stereoselection are not steric in origin, but rather that unfavourable lone pair/lone pair interactions occur between the tartrate ester carbonyl and alkoxy substituents that result in a diminished reaction stereoselections.

Hoffmann et al.[229–232] developed highly stereoselective chiral α-chloro- and α-methoxy-(*E*)-crotylboronates **302** and **304** (Scheme 121). Addition of the (*S*)-α-chloro-(*E*)-crotylboronate **302** to chiral aldehydes **301** proceeded with predominant formation of the isomer **303** and was controlled by double stereoselectivity. The matched asymmetric induction was observed when the (*S*)-α-chloro-(*E*)-crotylboronate **302** reacted with (*S*)-(+)-methyl-ethylketone to yield the product **303** with >98:2 diastereoselectivity. The (*S*)-**302** reacted with (*S*)-(+)-methyl-ethylketone with 90:10 diastereoselectivity (mismatched AS).[230] Addition of (*S*)-(+)-α-methylbutyraldehyde to α-methoxy-(*Z*)-crotylboronate **304** resulted in the formation of Cram- and *anti*-Cram diastereomers **305**. Their ratio (95:5–77:23) depended on the chirality of the organoboron component.[231] Hoffmann[230] reported that the allylboronates **306**–**308** derived from (−)- and (+)-camphor react with chiral aldehydes with matched and mismatches asymmetric induction. These reagents were used for the stereoselective synthesis of the Prelog–Djerassi lactone **280** (Scheme 122).[229,232]

Asymmetric addition of allyl and related groups can be carried out with an even higher enantioselectivity by using allylboranes with ligands other than tartrate, in particular the isopinocampheyl (Ipc) group as shown in Scheme 123.[233–236] These ligands are easily attached to the boron by hydroboration of (+)- or (−)-α-pinene.[210] Both enantiomers ($^{d}Ipc_2B$-Allyl and $^{l}Ipc_2B$-Allyl) are available

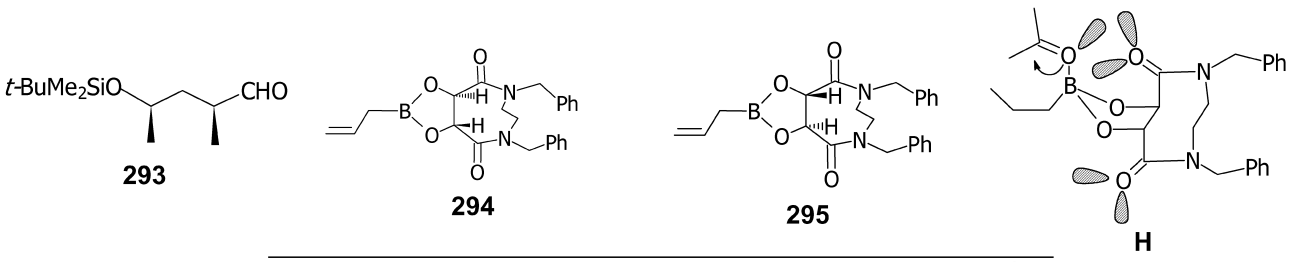
Table 5. Matched and mismatched pairs in the reaction of $(RO)_2$B-All with chiral aldehydes



Entry	$(RO)_2$	All	R*CHO	dr	Ref.
1	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_3$-(*Z*)	**199**	99.8:0.2	21
2	(*S*,*S*)-DIPT			84:16	21
3	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_3$-(*E*)	**199**	91:9	21
4	(*S*,*S*)-DIPT			2:98	21,216
5	(*R*,*R*)-DIPT	$CH_2CH{=}CH_2$	**199**	98:2	21,213
6	(*S*,*S*)-DIPT			7:93	21,213
7	(*R*,*R*)-DIPT	$CH_2CH{=}CH_2$		89:11	21,216
8	(*S*,*S*)-DIPT			19:81	21,217
9	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_2$-(*E*)		97:3	217
10	(*S*,*S*)-DIPT			81:19	217
11	(*R*,*R*)-DIPT	$CH_2CH{=}CH_2$		27:73	21
12	(*S*,*S*)-DIPT			99.67:0.3	21
13	(*R*,*R*)-DET	$CH_2CH{=}CH_2$		13:87	21
14	(*S*,*S*)-DET			98:2	21
15	(*R*,*R*)-DET	$CH_2CH{=}CH_2$		96:4	21
16	(*S*,*S*)-DET			16:84	21
17	(*R*,*R*)-DET	$CH_2CH{=}CH_2$		25:75	222
18	(*S*,*S*)-DET			99:1	222
19	(*R*,*R*)-DET	$CH_2CH{=}CH_2$		97:3	222
20	(*S*,*S*)-DET			23:77	222
21	(*R*,*R*)-DET	$CH_2CH{=}CHCH_3$-(*Z*)		87:13	223
22	(*S*,*S*)-DET			96:4	223
23	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_2SiMe_2(OC_6H_{11})$-(*E*)	**199**	85:15	224
24	(*S*,*S*)-DIPT			95:5	224
25	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_2SiMe_2(OC_6H_{11})$-(*E*)		64.3:35.7	224
26	(*S*,*S*)-DIPT			95:5	224
27	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_2SiMe_2Ph$-(*E*)	**199**	95.8:4.2	226
28	(*S*,*S*)-DIPT			95:5	225
29	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_2SiMe_2Ph$-(*E*)	**293**	>95:5	225
30	(*S*,*S*)-DIPT			60:40	225
31	(*R*,*R*)-DIPT	$CH_2CH{=}CH_2$	**293**	92:8	215
32	(*S*,*S*)-DIPT			13:87	215
33	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_3$-(*Z*)	**293**	78:16	215
34	(*S*,*S*)-DIPT			6:94	215
35	(*R*,*R*)-DIPT	$CH_2CH{=}CHCH_3$-(*E*)	**293**	98:2	215
36	(*S*,*S*)-DIPT			16:84	215
37	(*R*,*R*)-DIPT	$CH_2CH{=}CH_2CH_3$-(*E*)		−100	226
					227

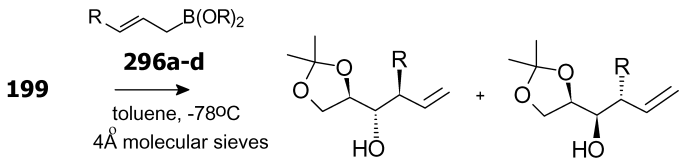
by this route. Brown reported that the β-allyldiisopino-campheylboranes of the type **309** are the most highly diastereoselective allylboranes.

The high effectiveness of allyldiisopino-campheylboranes is displayed in the Table 6. The allyldiisopinocampheyl-boranes add chiral aldehydes with very high diastereofacial selectivity (ds 98:2 in entry 1). In the reaction of the antipodal reagent with the aldehyde, the facial selectivity was completely reversed (5:95 in entry 2). The asymmetric



Entry	Allyl borane	Aldehyde	*ds*	Double AS
1	**294**	**293**	97:3	matched
2	**295**	**293**	93:7	mismatched
3	**294**	**200**	99.7:0.3	matched
4	**295**	**200**	2:98	mismatched

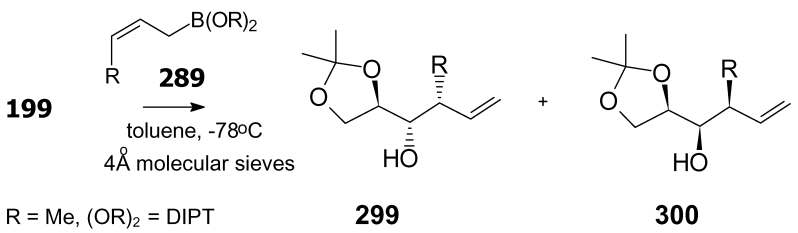
Scheme 118. Highly stereoselective addition of boronates **294** and **295** to aldehydes **200**, **293**.



R = H, $(OR)_2$ = DIPT (**296a**); R = Me, $(OR)_2$ = DIPT (**296b**); pinacol silylboronate (**296c**); pinacol *(E)*-crotylboronate (**296d**);

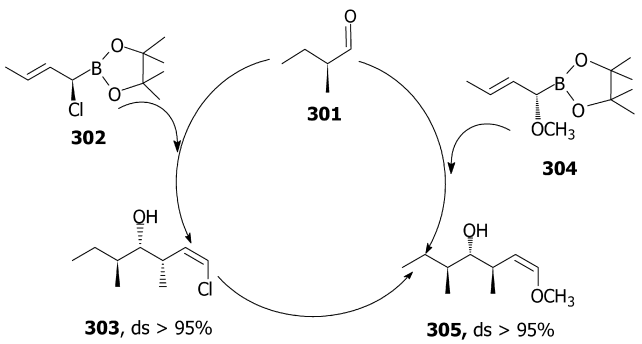
Entry	Reagent	297:298	$\Delta\Delta G^{\neq}_{reaction,}$ (kcal/mol)	$\Delta\Delta G^{\neq}_{reagents}$(kcal/mol)
1	*(R,R)*-**296a**	98:2	1.50	
2	**296c**	80:20	0.54	0.96
3	*(S,S)*-**296a**	7:93	1.00	1.54
4	*(S,S)*-**296b**	91:9	0.88	0.80
5	**296d**	55:45	0.08	
6	*(S,S)*-**296b**	2:98	1.50	1.58

Scheme 119. Diastereofacial selectivity in the reaction of (*E*)-allylboronates with glyceraldehyde.



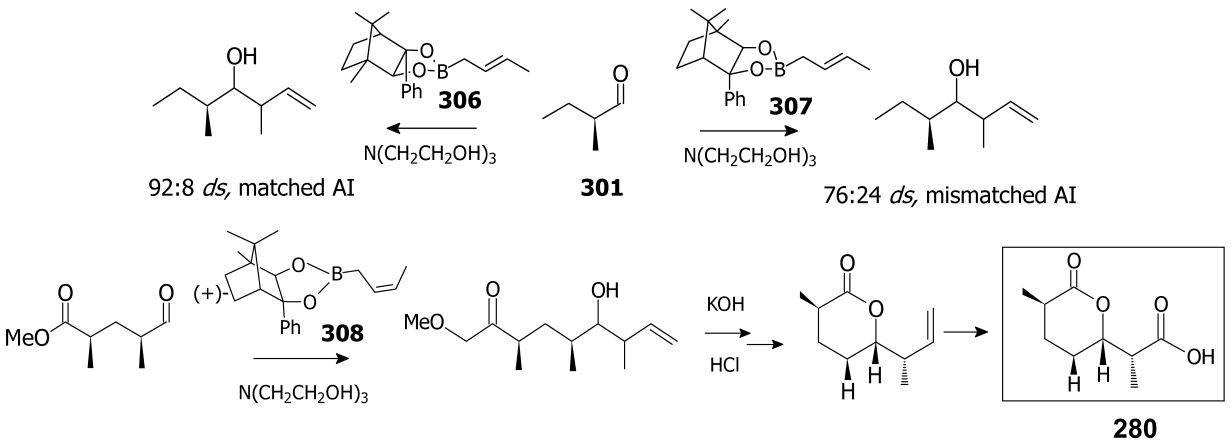
Entry	Reagent	299:300	$\Delta\Delta G^{\neq}_{reaction}$(kcal/mol)	$\Delta\Delta G^{\neq}_{reagent}$(kcal/mol)
1	*(R,R)*-**289**	> 99.8:0.2	> 2.40	0
2	Pinacol *(Z)*-crotylboronate	97:3	1.34	1.06
3	*(S,S)*-**289**	84:16	0.64	70

Scheme 120. Diastereofacial selectivity in the reaction of (*Z*)-allylboronates with glyceraldehyde.

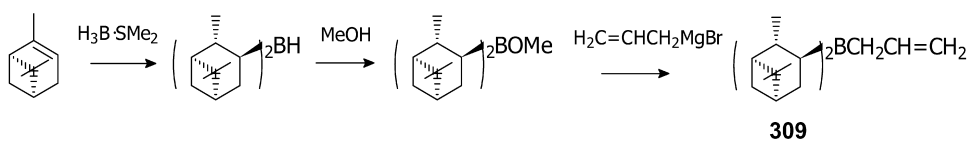


Scheme 121. Double asymmetric induction in addition of chiral crotylboronates to chiral aldehydes.

version of the reaction and a number of highly stereoselective chiral allylmetallic reagents have been developed.[207–210] Allylboranes[237] react with α-chiral aldehydes and, in all cases, the stereochemistry of the addition is controlled by the chirality of the boranes (entries 1–18). The reaction of (*S*)-α-(benzyloxy)propanal with $(Ipc)_2$B-Allyl reagents provides excellent diastereoselectivity: the (+)-allylborane gives a 97:3 mixture of *syn*- and *anti*-diastereomers (entry 6).[210] It is surprising that even a simple chiral aldehyde such as 2-methylbutanal produces a very high diastereoselectivity (entries 9–14) and the reactions of $(Ipc)_2$B-Crotyl with chiral α-methylaldehydes consistently give excellent results (entries 9 and 12). It is remarkable that



Scheme 122. Prelog–Djerassi lactone synthesis.



Scheme 123. Synthesis of enantiomerically pure (−)-β-allyldiisopinocampheylboranes.

a single enantiomeric reagent ($^{d}Ipc_2B$-Allyl or $^{l}Ipc_2B$-Allyl) introduces two new stereocentres with high de and ee and determines the absolute stereochemistry at five preexisting stereo centres (entries 21 and 22).[235]

The stereochemistry of the reaction of crotyldiisopinocampheylboranes with α-chiral aldehydes is controlled by the chirality of the boranes.[238] A serine aldehyde was smoothly homologated, without racemisation, using diisopinocampheylborane to produce a key intermediate in the stereocontrolled synthesis of the C(26)–C(37) amide-oxazole unit of calyculin A.[239] The effect of the leaving group in dialkylboron chlorides and triflates in controlling the stereospecific conversion of ketones into either (*E*)- or (*Z*)-enol borinates has been investigated.[240]

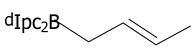
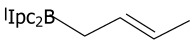
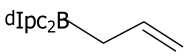
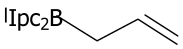
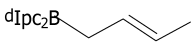
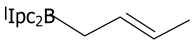
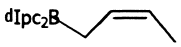
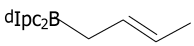
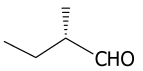
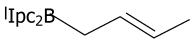
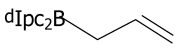
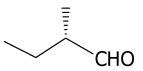
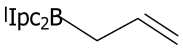
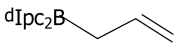
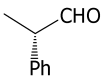
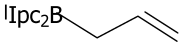
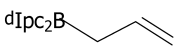
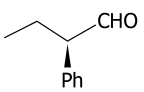
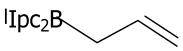
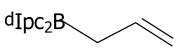
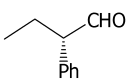
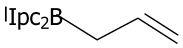
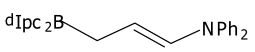
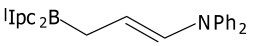
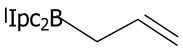
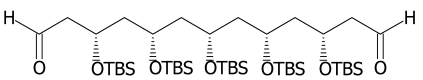
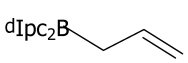
Niel et al.[223] reported that the double asymmetric addition reactions of the $(^{l}Ipc)_2B$-(*Z*)-crotylborane **311** to the aldehyde **310c** produced quasi-exclusively the *anti*-Cram compound **312** (Scheme 124, entry 5), whereas the $(^{d}Ipc)_2B$-(*Z*)-crotylborane afforded a diastereomeric mixture **312**–**315** containing predominantly Cram product **313** (21:79 ratio of **312**–**313**) (entry 6). The γ-amino-β-hydroxy-α-methyl acid dolaproine **316**, present in the antiproliferative dolastatin 10, has been prepared by the reaction of *N*-(*t*-butoxycarbonyl) prolinal **310c** with (*E*)-allylboronate **311**.

The double asymmetric reactions of the (*E*)- and (*Z*)-crotyldimethylborolanes **317**, **318**, **321** and **322** with (*R*)-*O*-isopropylidenglyceraldehyde **200** provided the homoallylic alcohols **319** and **320** with excellent diastereoselectivity (Scheme 125).[241,242] A high selectivity was observed in the reaction of (D)-glyceraldehyde with the crotyl-*trans*-2,5-dimethylboranes. The (*S*,*S*)-(*Z*)- and -(*E*)-crotylboronates **317** and **321** derived from pinacol derivatives produced a very high diastereoselectivity, whereas the corresponding (*E*)- and (*Z*)-(*R*,*R*)-boronates **318** and **322** gave a low selectivity. Besides the allylboronates, high levels of stereoselectivity[243] have been achieved in the addition of aldehydes to chiral allylstannanes. The addition of allylsilanes and allylstannanes to aldehydes is promoted by Lewis acids and can often lead to high levels of diastereoselectivity.[209,210,244]

Marshall and Luke[245a] reported that the γ-alkoxyallylstannane (*S*)-**323** reacted with the aldehyde (*S*)-**191** in the presence of boron trifluoride etherate to give a 67:33 ratio of the products **324** and **325** (mismatched induction), whereas the (*R*)-enantiomer of **323** afforded a 92:8 mixture of alcohols **326** and **327** (matched induction) (Scheme 126). Interestingly, if the reaction was catalysed by magnesium bromide instead of boron trifluoride, the matched and mismatched pairs were reversed. The major diastereomer **326** obtained in the matched pair (*R*)-**324**–**191** was, probably, formed under the influence of the chelate aldehyde attacked in the transition state **J** in which the C═O and C═C assume an antiperiplanar relationship, as shown in Scheme 127.

Marshall and Wang[182] studied the BF_3 and $MgBr_2$-promoted addition of chiral (*S*)- and (*R*)-allenylstannanes **328** and **329** to (*S*)-2-(benzyloxy)propanal **191** (Scheme 128). In the presence of boron trifluoride, the addition of the (*S*)-allenyl-stannane **328** to the aldehyde (*S*)-**191** afforded a 68:32 mixture of the diastereomeric alcohols **330** and **331**, whereas the (*R*)-allenylstannane **329** with (*S*)-**191** yielded a 30:1 mixture of the *syn*- and *anti*-alcohols **332** and **333**, i.e. the (*S*)/(*R*) pair was matched and (*S*)/(*S*) pair was mismatched. The stereoselectivity of the reaction was reversed under $MgBr_2$ catalysis: (*S*)-**328** with (*S*)-**191** afforded the adduct **334** as a single diastereomer and the

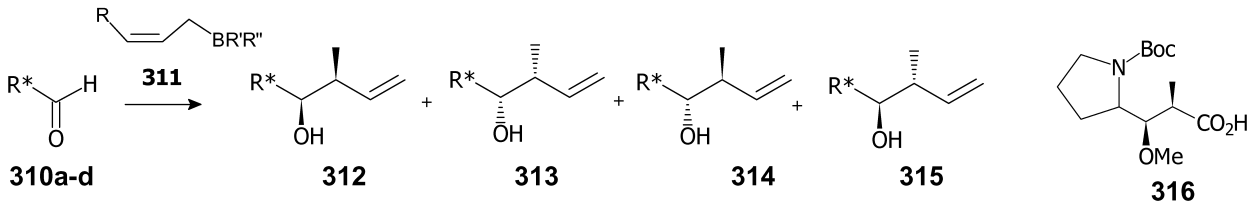
Table 6. Matched/mismatched pairs in the addition of isopincampheylboranes with chiral aldehydes

Entry	Allyl borane	Substrate	dr	Ref.
1		**190**	98:2	210
2			5:95	210
3		**191**	96:4	210,237
4			2:99	210,237
5		**191**	95:5	238
6			3:97	238
7		**191**	73:27	238
8			1:99	238
9			96:4	238
10			9:91	238
11			96:4	237
12			5:95	237
13			97:3	210
14			28:74	210
15			67:33	237
16			2:98	237
17			97:3	237
18			26:74	237
19		**200**	21:79	238
20			100:0	238
21			>94:6 (>98% ee)	235
22			<4:96	235

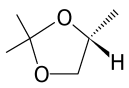
(*R*)-allenylstannane yielded a 1:92 mixture favouring the anti adduct **332** via the transition state **334** shown in Scheme 129. Note that the allene **328** is chiral, although it lacks a chiral centre (Scheme 129).[182] Double stereodifferentiation in the Lewis acid *C*-glycosidation of activated glycals with chiral (*E*)-crotylsilanes has been reported.[244] The BF_3-promoted cyclisation of the chiral α-alkoxyallylstannane **335** shown in Scheme 130 proceeded with high stereoselectivity to give optically pure adduct **336**.

Even though a chelated cyclic transition state is not involved in the reaction, the BF_3-promoted reaction showed efficient chiral transfer.

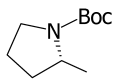
3.4.4. Application of aldol condensation in the synthesis of natural compounds. Double stereoselective aldol condensation was extensively used in the asymmetric synthesis of natural compounds.[245–258] In particular, it was applied for the synthesis of such antibiotics as venturicidine A (a 20-membered macrolide antibiotic



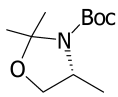
R* =



a



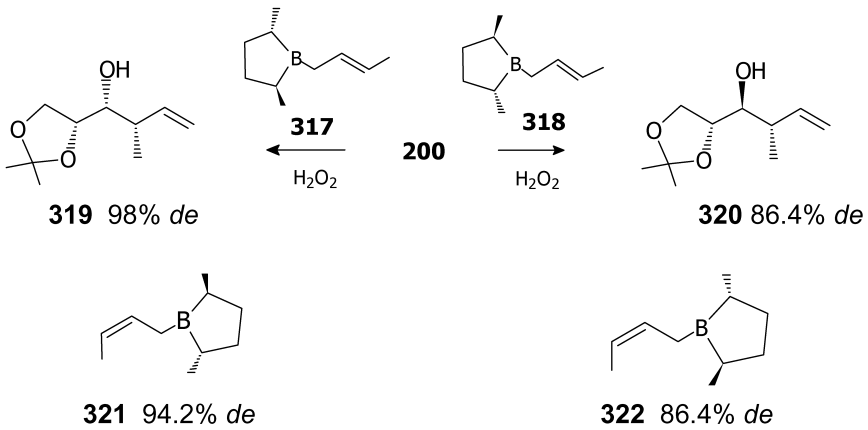
b



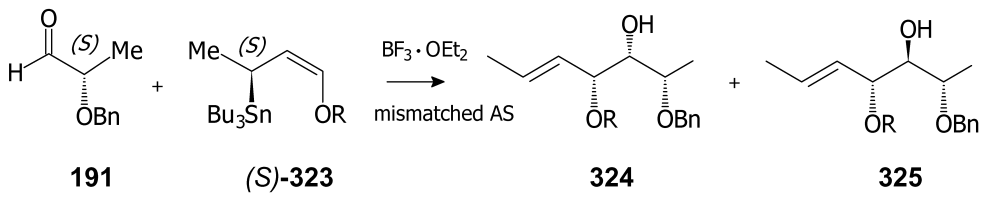
c

Entry	311	R	R'R"	R*	*dr*
1	*(Z)*	$SiMe_2NPr\text{-}i_2$	^{l}Ipc	***c***	67:33
2	*(Z)*	$SiMe_2NPr\text{-}i_2$	^{d}Ipc	***c***	98:2
3	*(Z)*	Me	^{l}Ipc	***b***	99:1
4	*(Z)*	Me	^{d}Ipc	***b***	80:20
5	*(E)*	NPh_2	^{l}Ipc	***a***	100:0
6	*(E)*	NPh_2	^{d}Ipc	***b***	21:79

Scheme 124. Addition of chiral crotylboranes to aldehydes.



Scheme 125. Addition of the (*E*)- and (*Z*)-crotyldimethylborolanes to the glyceraldehyde acetonide **200**.

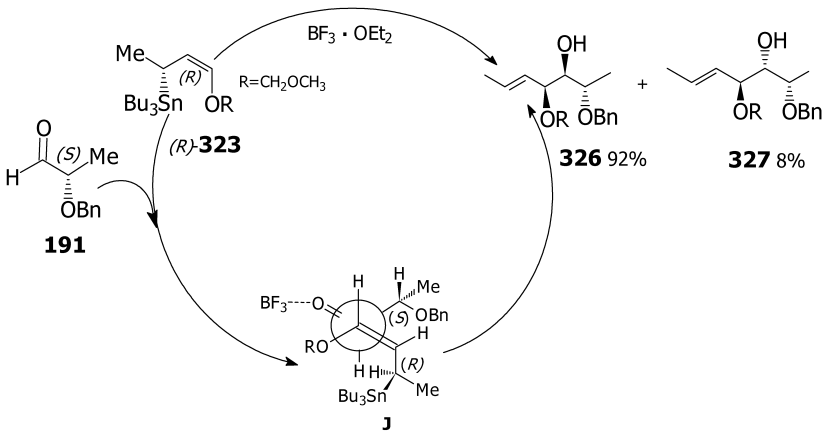


Scheme 126. Double asymmetric induction in addition of chiral allylstannanes with the chiral aldehyde **191**.

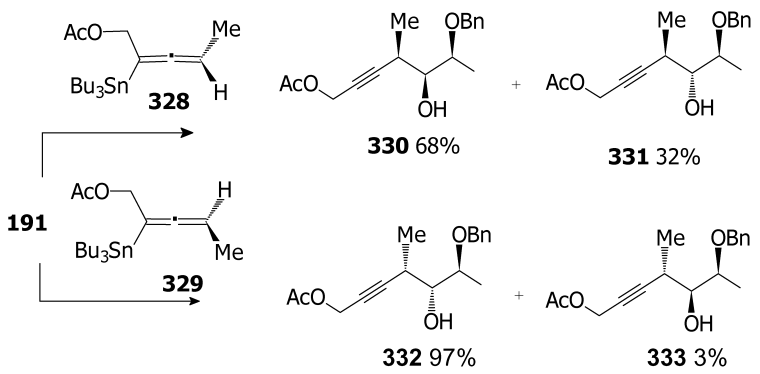
isolated from streptomyces),[245] and 6-deoxyerythronolide B **337** produced by blocked mutants B of *Streptomyces erythreus*.[101,171] The methodology utilising chiral boron enolates and the aldol strategy was applied successfully for the synthesis of cembranolide precursors. The connection of the two chiral fragments of **337** was realised by means of a double stereoselective aldol condensation (Scheme 131).[169] The remote double stereodifferentiation in the macrocyclisation of α-alkoxyallylstannanes **338** has been described by Marshall and co-workers.[246] This methodology was applied for the synthesis of epoxy cembranolides **339**, isolated from species of the genus *Efflatounaria* (Scheme 131).

Danishevsky and co-workers used the double diastereoselective aldol reaction in the semipractical total synthesis of epothilone B **340**, representing a very promising class of antitumour agents (Scheme 132).[168a–d]

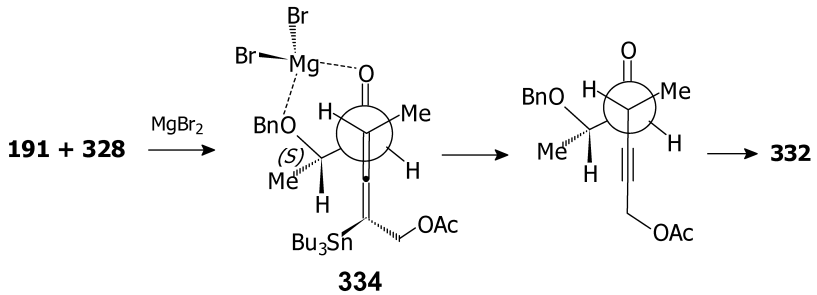
The aldol reaction was used in the synthesis of lasalocid A, a naturally occurring ionophore which is a polyether antibiotic. Lasalocid A has ten chiral centres on the carbon



Scheme 127. Matched asymmetric addittion of allylstannanes with the aldehyde **191**.

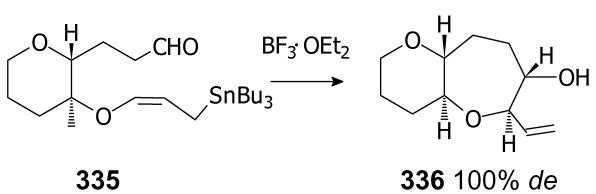


Scheme 128. Double asymmetric addition of chiral allenylstannanes **328** and **329** to the (*S*)-2-(benzyloxy)propanal **191**.



Scheme 129. Matched/mismatched asymmetric reaction of chiral allenes with chiral aldehydes.

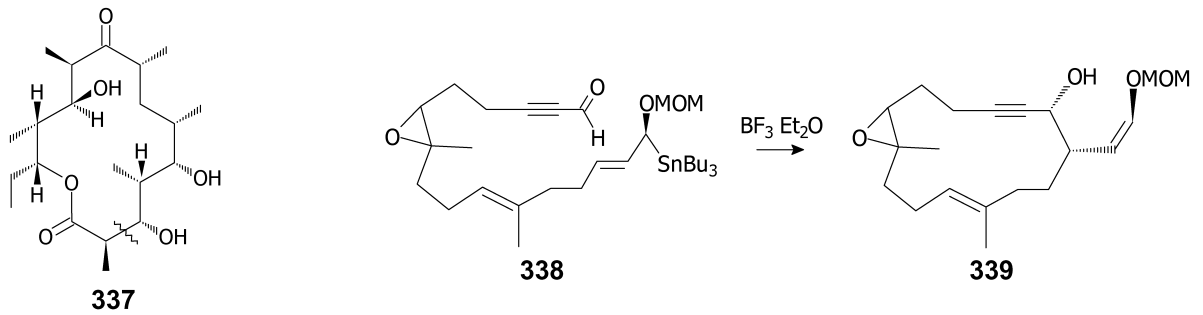
backbone. The reaction of the ethylketone **341** with the aldehydes **342** led to the formation of a mixture of four possible diastereomeric aldols **343** in the ratio 40:10:7:3, which were separated by silica gel preparative TLC (Scheme 133).[247]



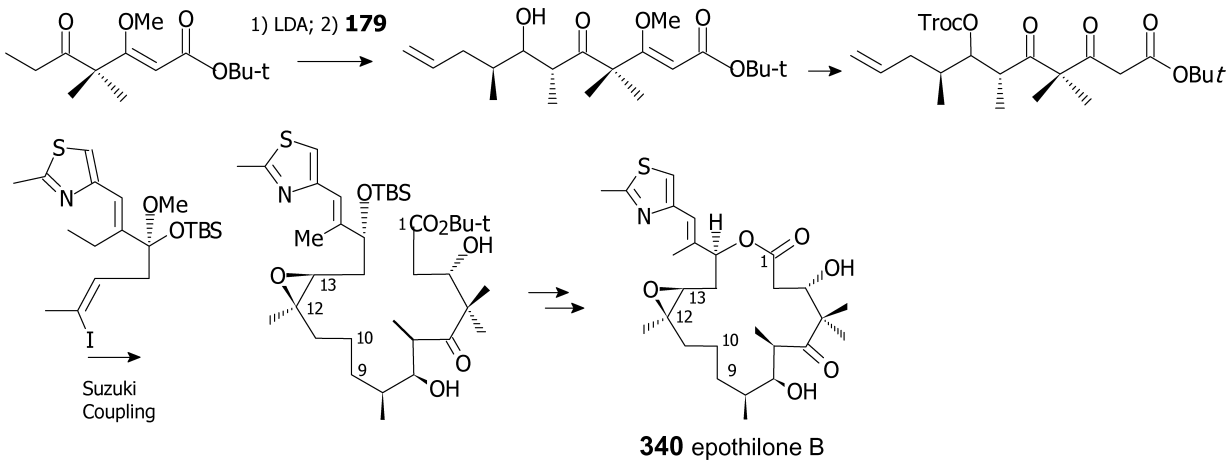
Scheme 130. Cyclisation of the chiral α-alkoxyallylstannane **335**.

Aldol connection of two chiral fragments as a key step in the total synthesis of monensin was realised by Kishi. The condensation was performed by the addition of excess diisopropylamide magnesium bromide to a mixture of the ketone **344** and the aldehyde **345**. Monensin was isolated by preparative TLC in 53% overall yield (Scheme 134).[248] It is interesting that the β-hydroxyketone **346** was formed as a 1:1 diastereomeric mixture if the condensation was carried out at 0°C, but the stereoselectivity rose up to >89:11 if the condensation was performed at −78°C.

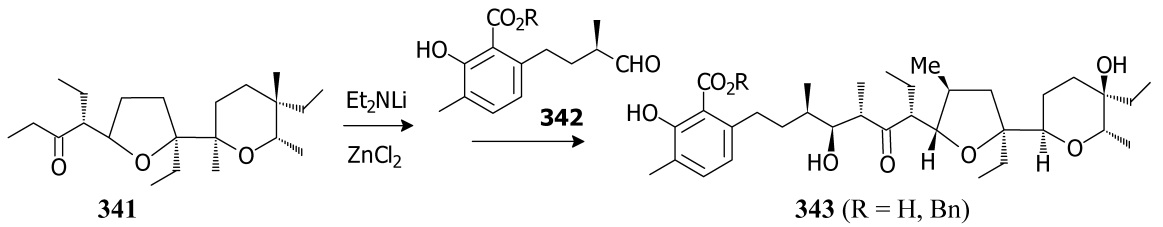
Chiral catalysts were used for the initiation of an asymmetric aldol reaction developed for the synthesis of



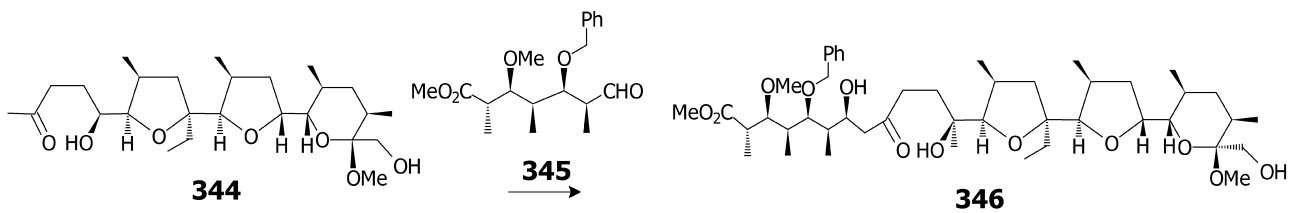
Scheme 131. Synthesis of 6-deoxyerythronolide B **337** and epoxy cembranolides **339**.



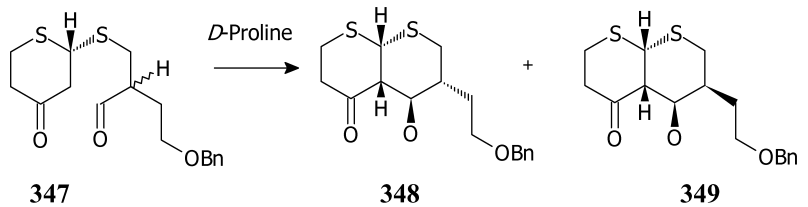
Scheme 132. Total synthesis of epothilone B.



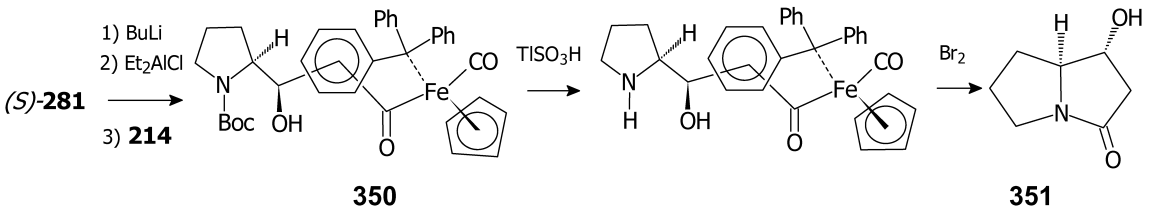
Scheme 133. Total synthesis of lasalocid A.



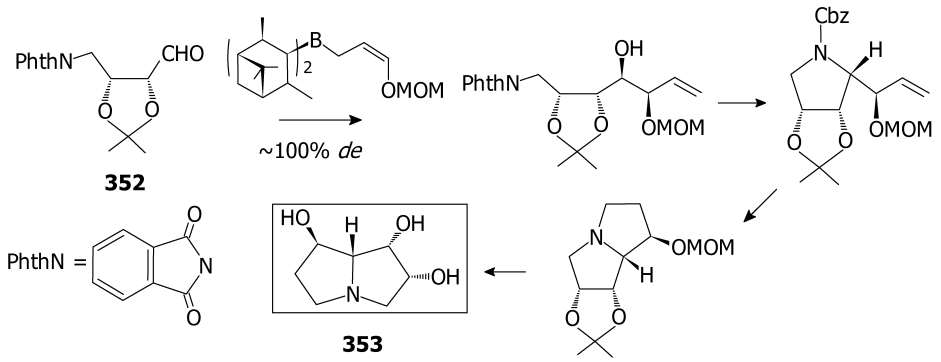
Scheme 134. Total synthesis of monensin.



Scheme 135. Asymmetric synthesis of erythromycin.



Scheme 136. Asymmetric synthesis of (1*R*,8*S*)-1-hydroxypyrrolizidin-3-one.



Scheme 137. Asymmetric synthesis of swainsonine and castanospermine analogues **353**.

erythromycin. The reaction initiated by L-proline gave only the racemic products, whereas the reaction with D-proline proceeded with a high double asymmetric induction (Scheme 135).[171,172]

The 1,4-remote stereocontrol was carried out through the double asymmetric induction in asymmetric catalytic carbonyl-ene reactions of homoallyl ethers and a binaphthol–titanium catalyst in the asymmetric synthesis of (11*R*,14*S*)-*anti*- and (31*R*,34*S*)-*syn*-segments of the immunosuppressant, rapamycin.[249]

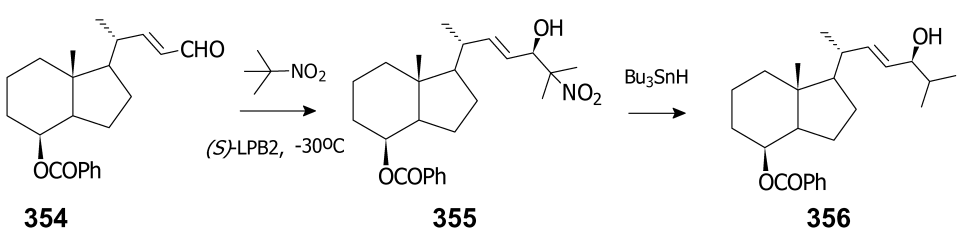
The double asymmetric induction has been extensively used in the synthesis of pyrrolizidine alkaloids, possessing important pharmacological properties as antitumour agents. In one example, the double asymmetric synthesis of (1*R*,8*S*)- and (1*S*,8*S*)-1-hydroxypyrrolizidin-3-ones **351** has been achieved with excellent stereocontrol (~99% de) via the aldol reaction between *N*-Boc-(*S*)-prolinal and chiral acetate enolate equivalents **350** derived from the (*S*)- or (*R*)-iron acetyl complex **281** [η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$] (Scheme 136).[250]

The (1*S*,2*R*,7*R*,7α*R*)-1,2,7-trihydroxypyrrolizidine **353** was prepared via a double asymmetric allylation reaction of **352** proceeding with exceptionally high stereocontrol (de ~100%) (Scheme 137).[251,252] Subsequent steps in this synthesis centred around ring closures and manipulation of the protecting groups led to the formation of the swainsonine derivative **353**.

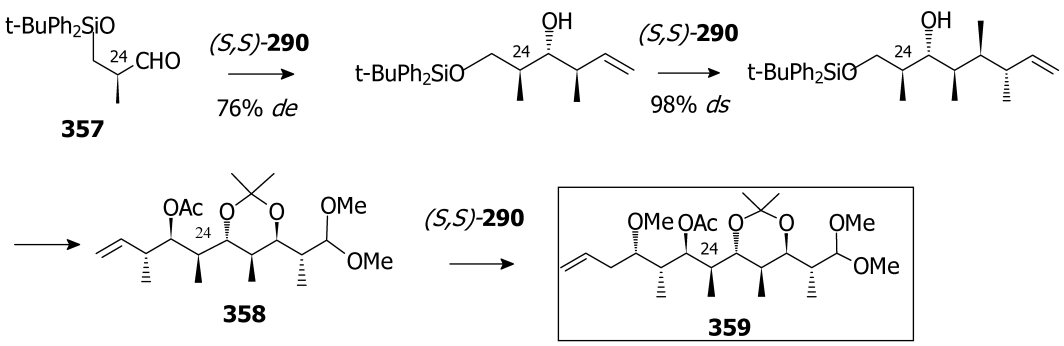
The synthetic utility of the heterobimetallic catalysts has been illustrated extensively by Okamoto and co-workers.[253] They prepared an intermediate **356** towards the total synthesis of qd,24(*R*)-dihydroxyvitamin D_3 (Scheme 138). Henry reaction of α-nitropropane with the aldehyde **354** catalysed by LaK_3tris[(*S*)-6,6′-bis(triethylsilyl)ethynyl]-BINOL gave the desired alcohol **355** in 70% yield and 88% ee. Radical denitration with tributyltin hydride furnished the intermediate **356**.

Polniaszek and Bell[254] used the double diastereodifferentiation for the synthesis of eudistomin and eudistomidin alkaloids. Depezay and Dureault[255] have carried out the synthesis of branched-chain sugar derivatives. The use of double asymmetric induction increased the diastereoselectivity of the hydroxyalkylation of (L)-alanine by glyceraldehyde. The total synthesis of bicyclomycin was achieved in 19 steps from diketopiperazine by applying a stereospecific aldol condensation of the aldehyde and the carbanion on the bridge-head position of the bicyclic [4.2.4]-ring.

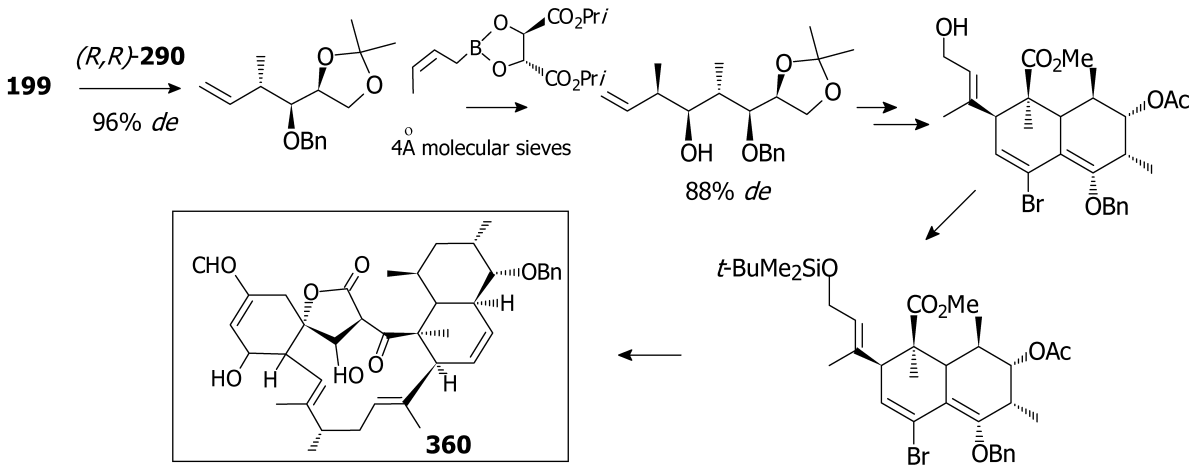
Asymmetric synthesis by the addition of DIPT allyl or crotyl units **290** can be iterative, simply by protection of the hydroxyl group followed by alkene cleavage to the



Scheme 138. Catalyst controlled asymmetric Henry reaction.



Scheme 139. Highly stereoselective synthesis of the C(19)–C(29) segment **359** of rifamycin S.



Scheme 140. Stereoselective synthesis of the hydronaphthalene subunit of kijanolide and tetronolide.

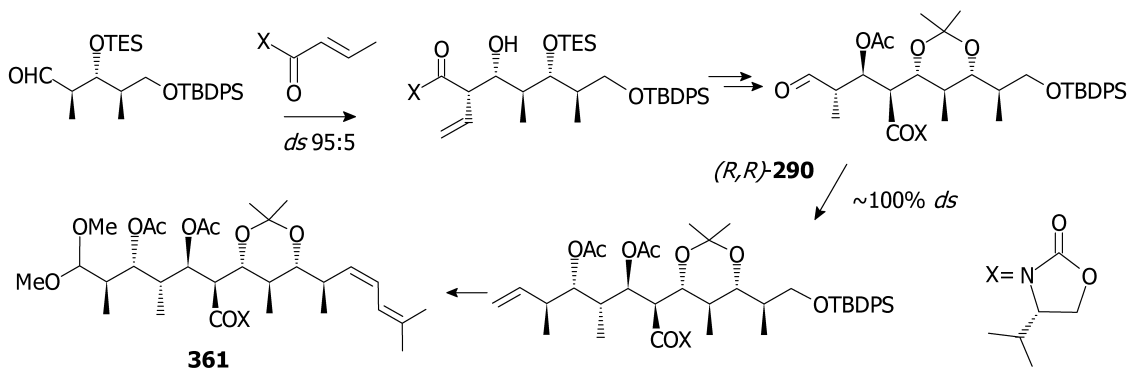
protected aldehyde **357**. This aldehyde then serves as the substrate for the next allylation or crotylation. This approach is illustrated in Scheme 139 and has been used in the total synthesis of **359**, which represents the 'ansa' chain of the natural antibiotic, rifamycin S.[213,215,256]

Roush used the same strategy for the development of a highly stereoselective synthesis of the octahydronaphthalene subunit of kijanolide **360**[219–221] and tetronolide,[219] which are novel antitumour agents and antibiotics (Scheme 140).

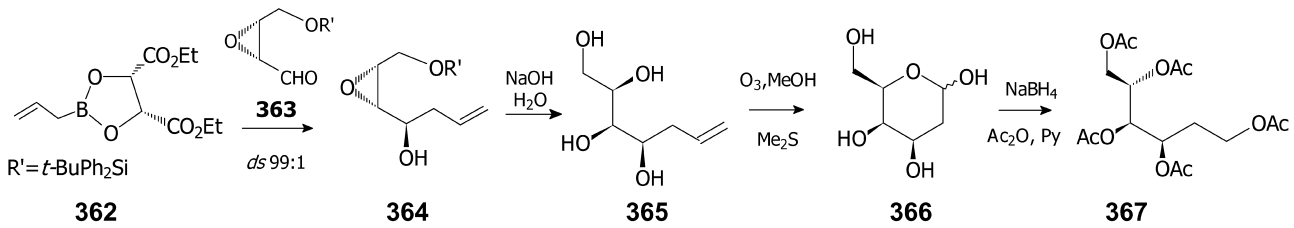
Roush and Palkowitz[227] have developed a highly stereoselective synthesis of the C(1)–C(15) segment of streptovaricin D **361** (a biologically active ansamycin antibiotic) using the matched asymmetric synthesis of the boron enolate and the (*R*,*R*)-tartrate (*E*)-crotylboronate in two key steps of this synthesis (Scheme 141).

The matched double asymmetric allylborations of chiral epoxyaldehydes **363** using the (*S*,*S*)-tartrate allylboronate **362** provided the *erythro*-epoxyalcohols **364** with a very good diastereoselectivity (dr ~99:1) and enantioselectivity (>98% ee). The mismatched double asymmetric reactions of the (*R*,*R*)-tartrate allylboronate **362** with the aldehydes **363** provided the diastereomeric *threo*-epoxyalcohols only with 70:30 stereoselectivity (Scheme 142).[222]

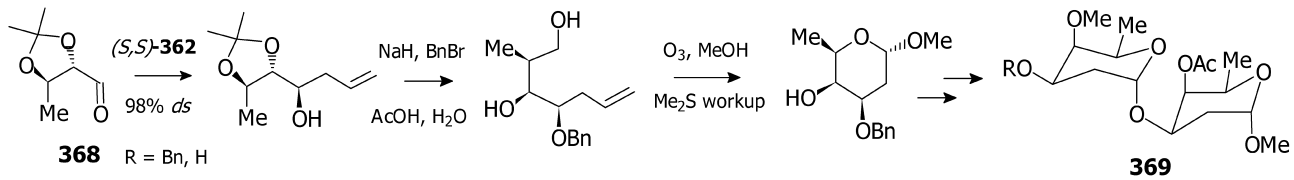
Roush and co-workers[222a] developed this method as a stereochemically general strategy for the synthesis of



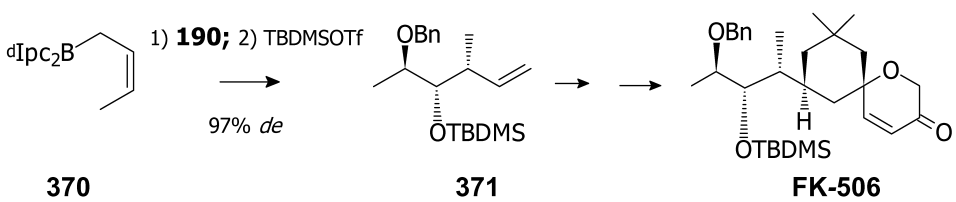
Scheme 141. Highly stereoselective synthesis of the C(1)–C(15) segment of streptovaricin D.



Scheme 142. Stereochemically general synthesis of 2-deoxyhexoses.

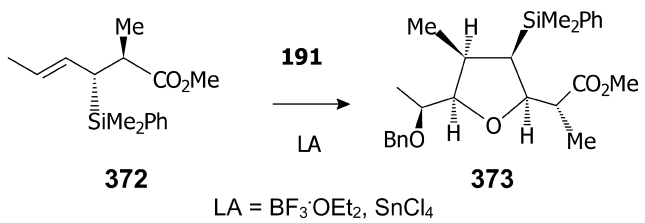


Scheme 143. Highly stereoselective synthesis of the AB disaccharide unit of olivomycin A.



Scheme 144. Asymmetric synthesis of the right-side portion of FK-506.

2-deoxyhexoses **365** via the double asymmetric induction. For example, the epoxyalcohol **364** were converted with excellent selectivity to the D-arabino-tetrol **365**. The D-arabino-tetrol **365** was converted to the 2-deoxy-D-galactose **366** and 2-deoxy-D-galactitol pentaacetate **367**.

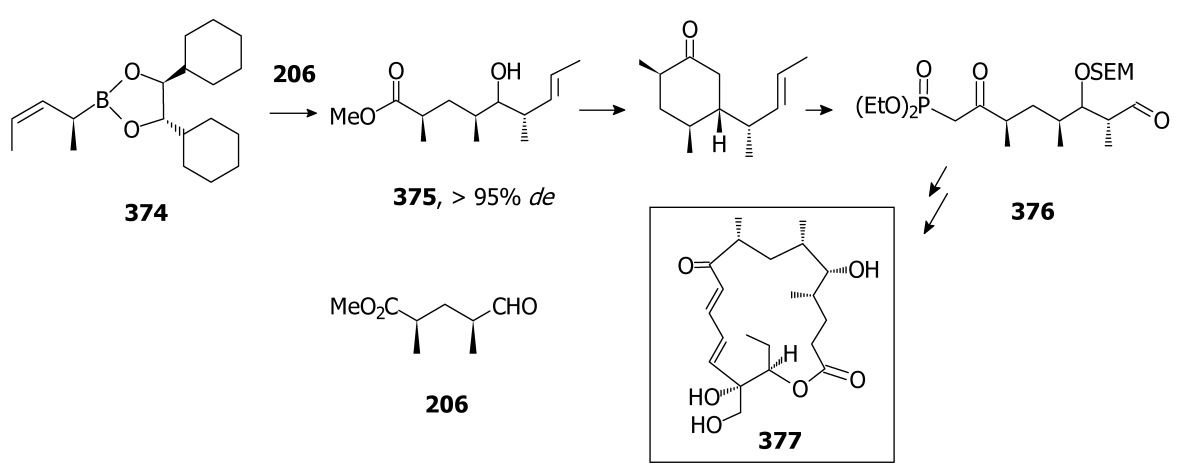


Scheme 145. Asymmetric synthesis of *cis*-2,5-disubstituted tetrahydrofurans **373**.

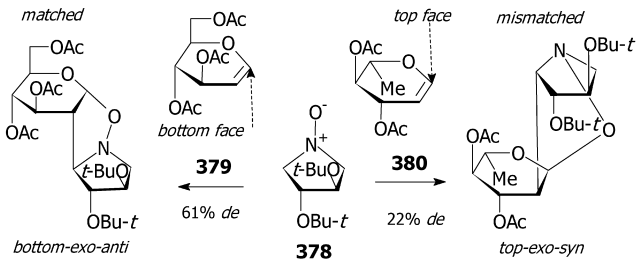
Roush[222b] used the double asymmetric allylboration of the α,β-dialkoxyaldehyde **367** with the (*S*,*S*)-tartrate allylboronate **362** for the development of a highly stereoselective synthesis (98% de) of the AB disaccharide unit of olivomycin A **368**, a clinically active member of the aureolic acid family of anticancer agents (Scheme 143).

The isopinocampheylborane **370** was used in the stereoselective synthesis of a key intermediate of the immunosuppressant, FK-506 **371** (Scheme 144).[257]

Panek and Beresis[258] developed a stereoselective method for the asymmetric synthesis of *cis*-2,5-disubstituted tetrahydrofurans **373**. The addition of chiral (*E*)-crotylsilanes **372** under BF_3 catalysis to (*S*)-2-(benzyloxy)propanal **191**



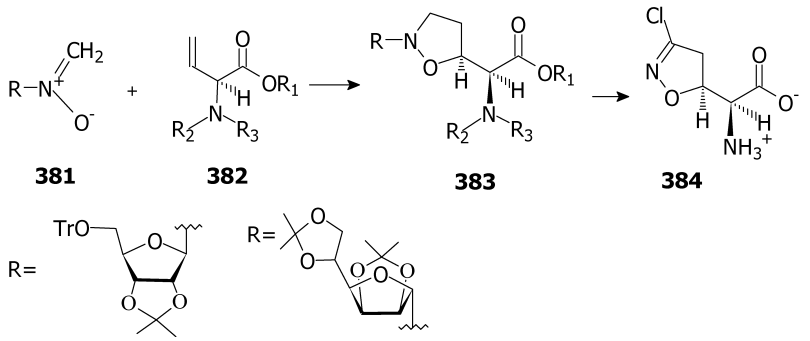
Scheme 146. Total synthesis of mycinolide V.



Scheme 147. Double asymmetric induction of nitrone addition.

compounds.[260] New and powerful variants of asymmetric cycloadditions based on the double asymmetric induction have been developed in recent years. The carbo-Diels–Alder and hetero-Diels–Alder dipolar cycloaddition reactions have been the subject of intensive research activity in this field.

3.5.1. Dipolar cycloadditions. Excellent examples of asymmetric 1,3-dipolar cycloaddition have been reported in the past several years and these studies have impacted on synthetic organic chemistry. As an example, the double



Scheme 148. Asymmetric synthesis of acivicin (AT-125).

initiated a silicon migration and subsequent heterocyclisation (Scheme 145).

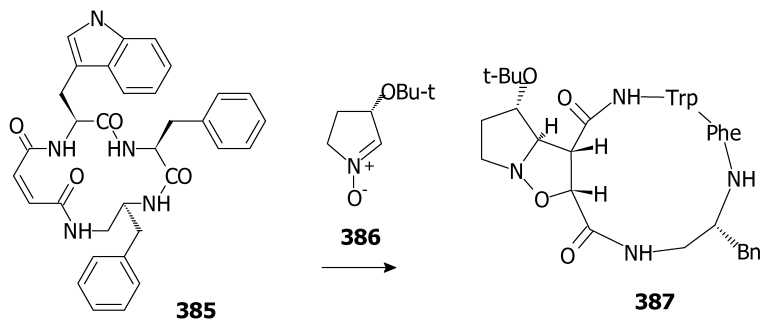
The reaction produced nearly diastereoisomerically pure *cis*-2,5-tetrahydrofurans **373**.[258] The formation of the *cis*-2,5- or *trans*-2,5-disubstituted tetrahydrofuran products **373** was shown to be dependent on the type of Lewis acid and the absolute stereochemistry of the silane reagent. Under $BF_3{\cdot}OEt_2$ catalysis (non-chelation-controlled conditions), a *cis*-2,5-disubstituted tetrahydrofuran **373** was produced. In contrast, the use of $SnCl_4$ (chelation-controlled conditions) resulted in the formation of the *trans*-2,5-disubstituted tetrahydrofuran.[258] Hoffmann et al.[259] used the diastereomerically pure allylboronate **374** in the total synthesis of the antibiotic mycinolide V **377**. The reaction of **374** with the chiral aldehyde **206** provides the hydroxyester **375** with 95% de. The intermediate product **375** was converted into the phosphonic aldehyde **376** and then into mycinolide V **377** (Scheme 146).

3.5. Asymmetric cycloaddition reactions

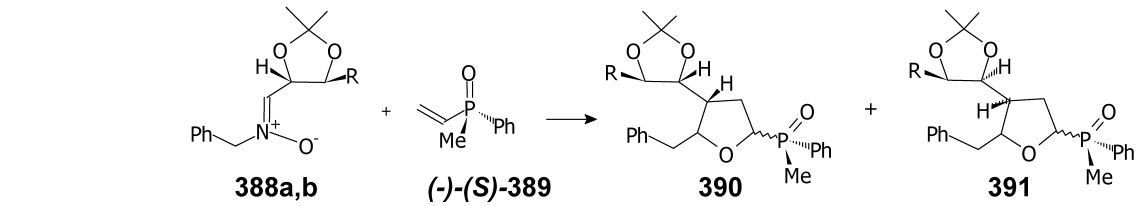
Asymmetric cycloaddition reactions provide a very important route to optically active carbocyclic and heterocyclic

asymmetric induction increasing the stereoselectivity of the cycloaddition of nitrones to olefins has been extensively studied.[261–268] Brandi, Goti and co-workers[261] have reported that the cycloaddition of chiral hydroxylated pyrroline *N*-oxides **378** to chiral 1,2-glycals **379** and **380** displayed a high double asymmetric induction. The stereoselectivity of the reaction was controlled by the pseudo-equatorial group on the C-3 atom of the glycals. The mismatched addition occurred when the *exo* approach, i.e. *anti*- to the C-3 group of (L)-rhamnal **380**, forced the nitrone to react *syn*- with respect to the vicinal *O*-*t*-butyl group. Vice versa, the enantiomorphic nitrones **378**, derived from α-tartaric acid, reacted with L-rhamnal **379** to afford the 'matched' top-*anti*-cycloadducts in high yield (Scheme 147). These researches have been applied to the synthesis of important biologically active and natural compounds.[261–264] For example, the cycloaddition reaction of sugar nitrones with nitro-olefins led to 4,5-*trans*-4-nitroisoxazolidines with complete stereospecificity.[262] The best π-diastereofacial selectivity was observed when both the substrate and reagent were chiral sugar derivatives.

The total synthesis of acivicin (AT-125) **384**, isolated from



Scheme 149. Synthesis of a tachykinin NK-2 receptor ligand.



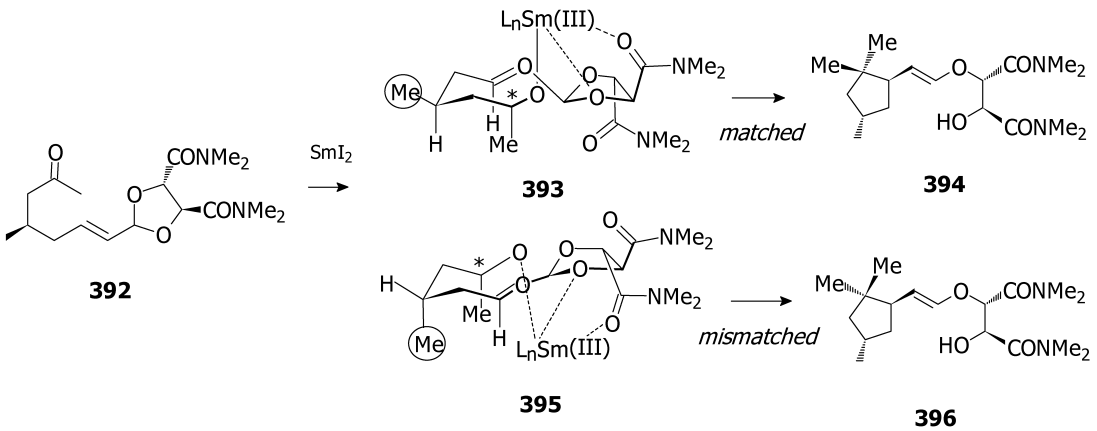
Scheme 150. 1,3-Dipolar cycloadditions of chiral nitrones to chiral vinyl-phosphine oxides.

fermentation broths of the soil bacterium *Streptomyces sviceus*, was developed by this methodology (Scheme 148).[264] The reaction of the chiral *N*-glycosyl nitrone **381**, derived from D-ribose, with the chiral (2*S*)-vinylglycine derivative **382** led stereoselectively, through double asymmetric induction (ds=19:1), to the required diastereomer **383**. The diastereomer **383** was then converted into the acivicin **384**.

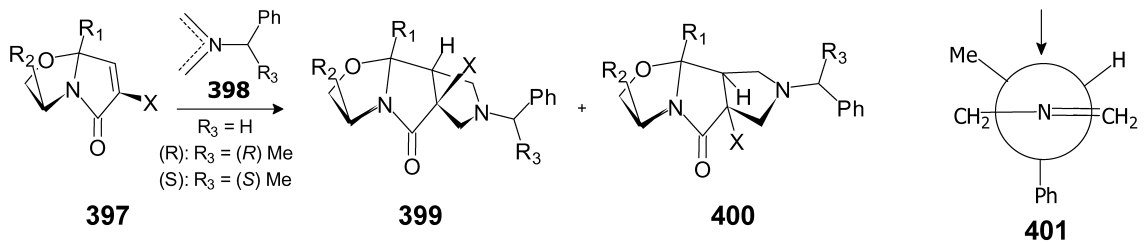
Brandi et al.[263] used the double asymmetric induction in the synthesis of a new class of potent human tachykinin NK-2 receptor ligands **387** (Scheme 149). They carried out the cycloaddition of chiral nitrones such as **386** to an unsymmetrically substituted chiral amide **385**. The highest stereoselectivity (26:1) was observed when the nitrone substituent on the pseudopeptidic tether initiated the double asymmetric induction.[264]

Brandi, Goti et al.[265] also studied the 1,3-dipolar cycloadditions of chiral nitrones with chiral vinyl-phosphine oxides, sulphides and selenides. The cycloaddition of the nitrones **388** to enantiomerically pure (−)-*S*-methylphenylvinylphosphine oxide **389** proceeded as a matched double asymmetric synthesis to afford a ca. ~40:1 diastereomeric ratio of the compounds **390** and **391** (Scheme 150).[266,267]

The tartaric acid amide **392** underwent a stereoselective ketyl–olefin radical cyclisation initiated with samarium(II) iodide.[269] The remote diastereoselection in this reaction was achieved in a radical process via the formation of the tricyclic transition state structures **393** and **395** containing tridentate chelation between the ketyl intermediate and the samarium counterion (Scheme 151). The preparation of enantiomerically enriched cyclopentanediols and lactols was achieved by this method. Cyclisation of the substrate



Scheme 151. Double stereoselective ketyl–olefin radical cyclisation.



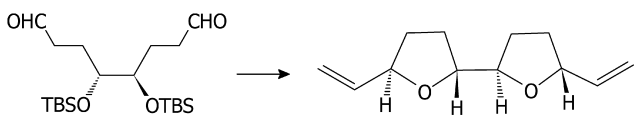
Entry	R^2	R^1	X	*(R)*-399:400	*(S)*-399:400
1	*i*-Pr	Me	H	94:6	91:9
2	Ph	Me	H	91:9	92:8
3	*i*-Pr	Me	CO_2Me	87:13	59:41
4	*i*-Pr	Me	CO_2Bu-t	92:8	51:49

Scheme 152. Double asymmetric induction in a dipolar cycloaddition of azomethyne ylides **398** to the lactams **397**.

392 yielded the diastereomers **394** and **396** with a diastereoselectivity of 99:1 (matched induction) and 88:12 (mismatched induction).[269]

Fray and Meyers[270] studied the double stereodifferentiation in a dipolar cycloaddition reaction of the chiral azomethyne ylides **398** with the chiral unsaturated bicyclic lactams **397** resulting in the diastereomers **399** and **400** (Scheme 152).

In cases where the α-substituent, X, was hydrogen it was observed that the π-facial selectivities were insensitive to the configuration at the benzylic carbon of the dipole (entries 1 and 2). In contrast, where X was larger than hydrogen, a significantly enhanced selectivity was observed for cycloaddition with the dipole (*R*)-**398**, compared to the ratios provided by the achiral and chiral dipole (*S*)-**398** (entries 3 and 4). This is the result of the preferential approach of the dipole to the 'top' or β-face of the unsaturated lactams **397**. The observed trends in diastereoselection were best rationalised using the Felkin–Ahn model of the transition state **401**. In this model, approach of the dipolarophile occurs antiperiplanar to the phenyl that is oriented perpendicular to the π-system of the dipole.



402 **403**

Scheme 153. Synthesis of the C_2-symmetric bis-tetrahydrofuran core of acetogenins.

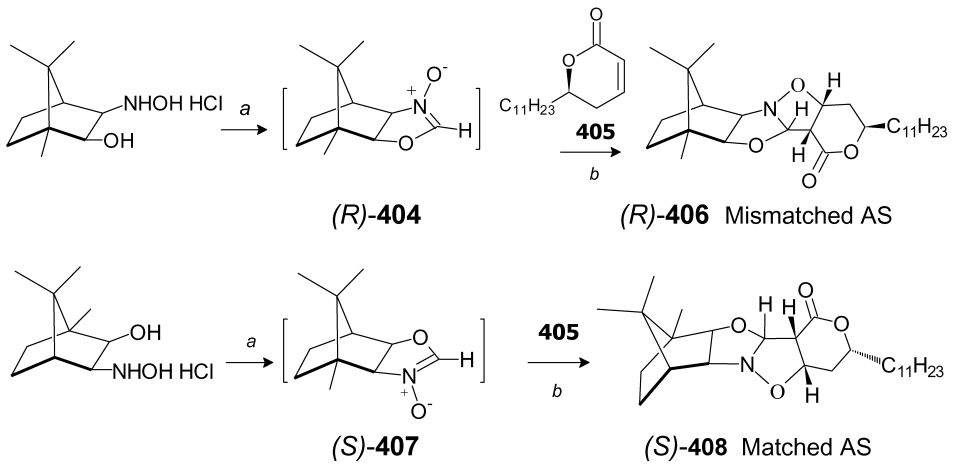
The C_2-symmetric bis-tetrahydrofuran core of the acetogenins **403** has been prepared via a double intramolecular S'_n *O*-cyclisation of **402**.[270] The acetogenins, isolated from the plants *Annonacea*, exhibit very important biological activity including antitumor, immunosuppressive and pesticidal properties (Scheme 153)

Recently, Dirat et al.[271] have reported the asymmetric [2+3]-cycloaddition reaction between chiral oxazoline *N*-oxides and α,β-unsaturated chiral lactones. The oxazoline *N*-oxide (1*R*)-**404** and the α,β-unsaturated (*R*)-lactone **405** formed a mismatched pair, resulting in the lactone (*R*)-**406** with 70% ee, whereas the enantiomeric (1*S*)-oxazoline *N*-oxide (*S*)-**407** and **405** formed a matched pair, resulting in only the cycloadduct (*S*)-**408** (Scheme 154).

The use of acyclic stereodifferentiation in the selective construction of tetrahydropyran/oxepane via intramolecular nitrone–alkene cycloaddition (INAC) of acyclic 3-D-allylmonosaccharides has been reported.[268]

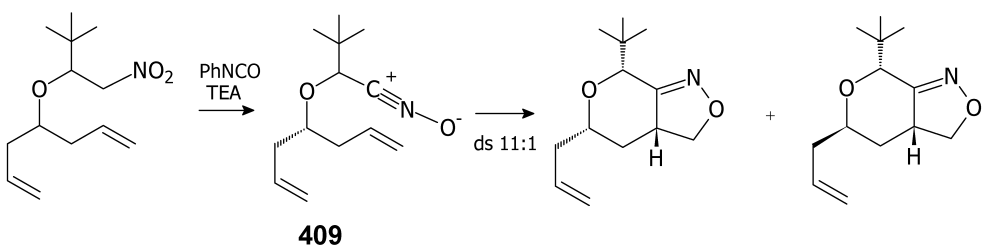
Double diastereoselectivity was observed in the intramolecular nitrile oxide–olefin cycloaddition (^{dd}INOC reaction).[272] Subsequent dehydration and 1,3-dipolar cycloaddition of the substrate **409** proceeded with complete facial selectivity (Scheme 155).

The double asymmetric induction in the dipolar cycloaddition reactions of diazoalkanes has been extensively studied. In one example, the C–C bond formation has been achieved with tetrakis[*N*-phthaloyl-(*R*)- or (*S*)-phenylalaninates] as chiral catalysts in the intramolecular CH-insertion of the α-diazo-β–ketoester **410** (Scheme 156).

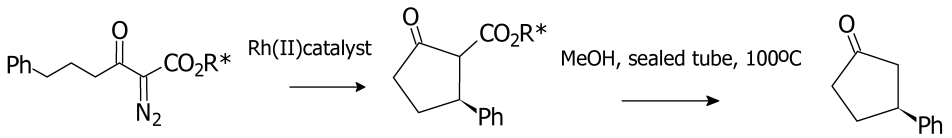


.a: $HC(OMe)_3$. $CaCO_3$, PhMe, 45°C. 4 h; b: 80°C, 12 h

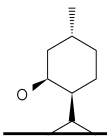
Scheme 154. Asymmetric [2+3]-cycloaddition of the chiral oxazoline *N*-oxides **407** to α,β-unsaturated chiral lactones **405**.



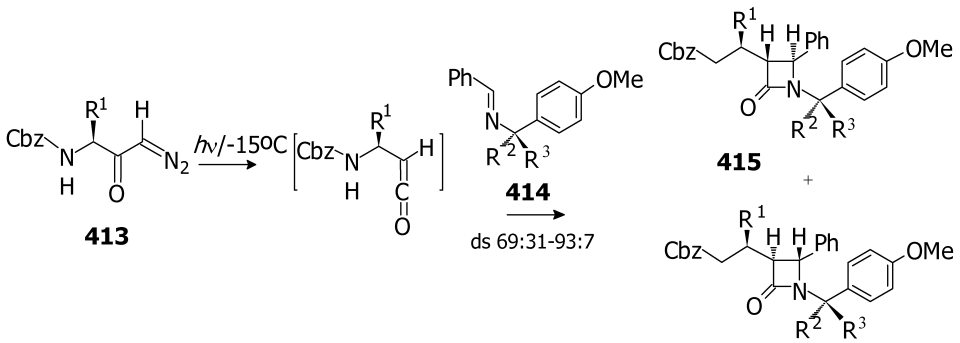
Scheme 155. Double asymmetric ^{dd}INOC reaction.



410 411 412

R*	Rh(n) catalyst	Yield of 412 (%)	*ee* (%)	Conf.	Double AI
	$Rh_2(OAc)_4$	85	23	*S*	none
	Rh_2[(*S*)-PTPA)$_4$]	88	53	*R*	matched
	Rh_2[(*R*)-PTPA)$_4$]	90	80	*S*	mismatched

Scheme 156. Double asymmetric CH insertion reaction of the chiral α-diazo-β-ketoester **410** catalysed by chiral Rh_2(PTPA).

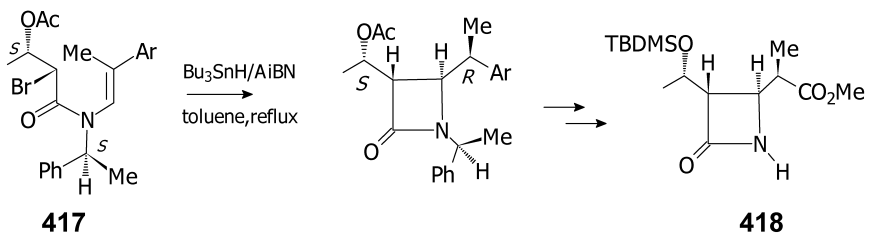


413 414 415 + 416

ds 69:31-93:7

R^1 = Me, *i*-Pr, *t*-Bu; R^2 = H, Me; R^3 = H, Me

Scheme 157. Double stereoselective synthesis of β-lactams.



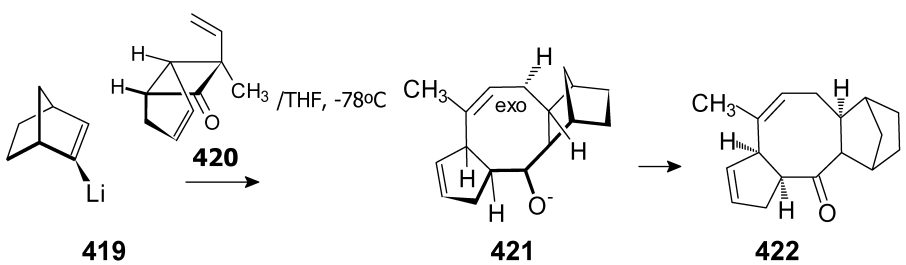
417 418

AiBN = azo-*bis*(isobutyronitrile).

Scheme 158. Asymmetric synthesis of 1β-methylcarbapenems.

The matched combination of the (+)-neomenthyl esters and Rh_2[(*R*)-PTPA)$_4$] derived from (*R*)-phenylalanine produced **411** and, after a removal of the ester group, the optically active 3-substituted cyclopentanones **412** of up to 80% ee.[273] The chirality of the dirhodium(II) catalyst rather than that of the substrate determined the stereochemical course of the double asymmetric C–H insertion reactions of the chiral α-diazo β-ketoesters **410**. The stereoselective cycloaddition of diazoalkanes to chiral 1,5-dioxan-4-ones has been described by Liebscher and co-workers.[274]

Podlech and Steurer[275] reported the photochemical-induced rearrangement of the diazoketones **413** in the presence of the PMPE-substituted imines **414**, leading to the formation of the corresponding β-lactams **415** (Scheme 157). The stereoselectivity decreased with the (*R*)-configured imine



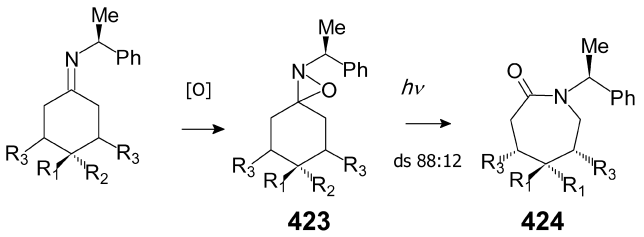
419 420 421 422

Scheme 159. Stereoselective addition of the norbornenone **420** to the cyclopentenyl lithium derivatives **419**.

416 (ds ~69:31), whereas, with the (*S*)-imine, an improvement in the product ratio was observed (ds up to 93:7). The reaction was catalysed by a chiral bis-oxazoline copper(I) complex. The double asymmetric reaction was used in the synthesis of both enantiomers of the vitamin D_3.[276]

The chiral 1β-methylcarbapenems **418** were prepared using an asymmetric radical cyclisation of the *N*-vinylic α-bromoamides **417**, bearing a matched pair of asymmetric auxiliaries (Scheme 158).[277]

Paquette and co-workers have studied the diastereoselective reactions of the norbornenone **420** with cyclopentenyllithium reagents such as **419** (dr=16:1) (Scheme 159).[278] Due to ring strain, the alkoxides **421** that are formed undergo an anionic oxy-Cope rearrangement, resulting in the production of **422**.

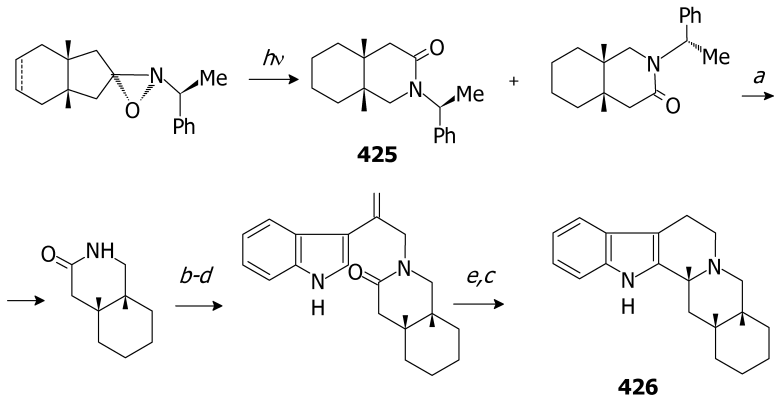


Scheme 160. Photochemical rearrangement of the chiral oxaziridines **423**.

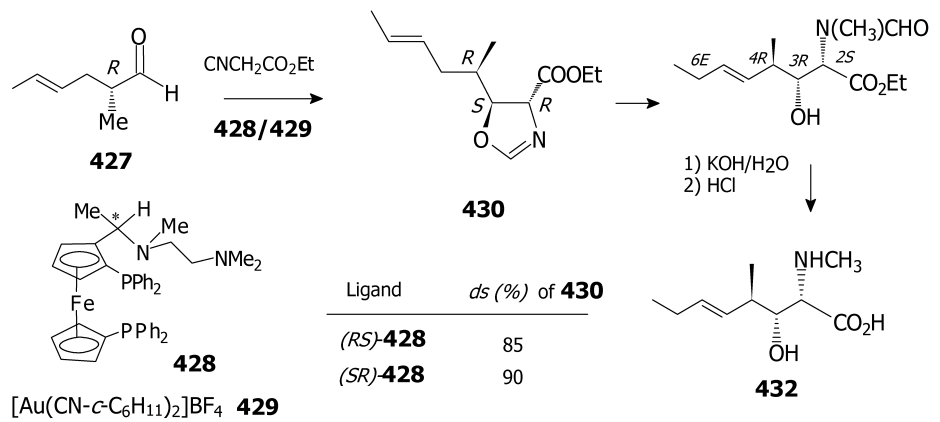
Aube et al.[88] described the stereoelectronically controlled photochemical rearrangement of the chiral axially- dissymmetric oxaziridines **423** to the corresponding lactams **424** with good stereoselectivity (Scheme 160). The direction of stereoselectivity for the rearrangement reaction was found to depend only on the axial chirality of the substrate oxaziridine **423** and not on the stereo-chemical or conformational factors. This methodology was applied to the synthesis of key intermediates in the total synthesis of (−)-alloyohimbane (Scheme 161).

Addition of the optically pure aldehyde **427** to ethyl isocyanoacetate in the presence of the chiral organometallic complexes **428** and **429** as catalysts was accompanied by double diastereodifferentiation, resulting in the formation of the dihydrooxazole **430** in 90% diastereoselectivity (matched asymmetric induction). The optically active 3-hydroxy-4-methyl-2-(methylamino)oct-6-enoic acid **432** was prepared from **430** in three steps and in 13% general yield (Scheme 162).[279,280]

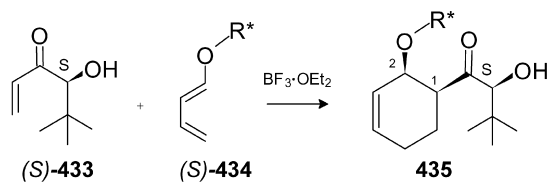
3.5.2. Diels–Alder reactions. The Diels–Alder reaction comprises one of the most powerful methods in organic chemistry. The high regio- and stereoselectivity typically displayed by this cycloaddition, the ease of its execution and the feature that, during its course, up to four new stereocentres may be created simultaneously have resulted in innumerable applications.[281,282,283] Although successful examples of diastereoselective approaches using chiral



Scheme 161. The total synthesis of (−)-alloyohimbane **426**.



Scheme 162. Asymmetric synthesis of the dihydrooxazole **430** and 3-hydroxy-4-methyl-2-(methylamino)oct-6-enoic acid **432**.



Scheme 163. Matched asymmetric Diels–Alder reaction.

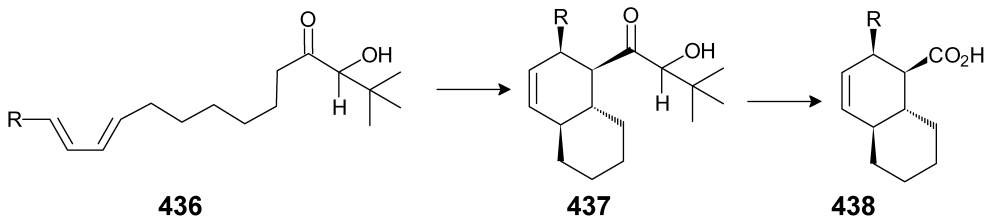
auxiliaries have been reported, there have been few reports on the double stereoselective carbon Diels–Alder reaction.[3,12] Scheme 163 shows the Diels–Alder reaction in which both the diene and dienophile each contain a chiral centre and both of these chiral centres are retained in the product. The dienophile (*S*)-**433** reacted with the diene (*S*)-**434** with the formation of a diastereoisomeric mixture **435** in a ratio of >130:1, while the reaction between the dienes (*R*)-**433** and (*S*)-**434** afforded the adduct **435** with a diastereoisomeric ratio of 35:1 that corresponded to the matched and mismatched pairs. The stereochemistry of this reaction was controlled only by the (*R*)- or (*S*)-configuration of the dienophile **433**.

Examples of the intramolecular double asymmetric Diels–Alder reaction which has been used for the synthesis of natural compounds with significant success have been described.[284] The substituent, which functioned as a chiral auxiliary group, can be a part of substrate **436** to provide the stereoselective formation of the adducts **437** and **438** (Scheme 164).

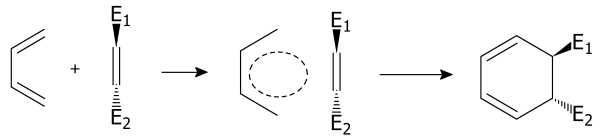
Tolbert and Ali[285] studied the uncatalysed and Lewis acid-catalysed double asymmetric Diels–Alder reaction using kinetic measurements (Scheme 165). They showed that the Diels–Alder reaction exhibits cooperativity in asymmetric induction. The reaction of di-*l*-bornyl fumarate or di-*l*-menthyl fumarate with 1,3-diphenylisobenzofuran proceeds with cooperativity in asymmetric induction.

Some additional data concerning the double asymmetric induction in the case of the carbon Diels–Alder reaction can be found in the following references.[4,12]

During the last few years, the double diastereoselective hetero Diels–Alder reaction has been studied the most extensively. The asymmetric hetero Diels–Alder reaction

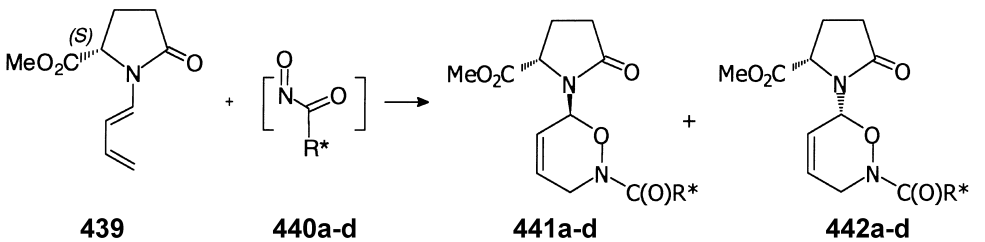


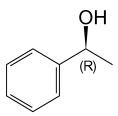
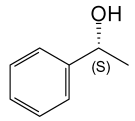
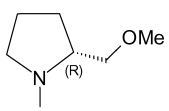
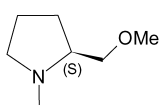
Scheme 164. Intramolecular double asymmetric Diels–Alder reaction.



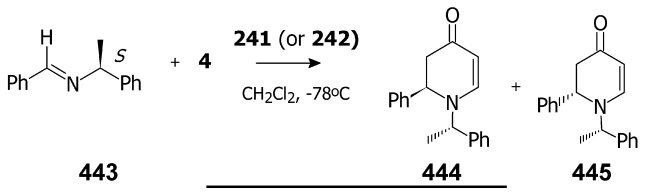
E_1, E_2 = (*L*)-(-)-menthyl or (*L*)-(-)-bornyl.

Scheme 165. Double asymmetric Diels–Alder reaction.



R*=				
	a	***b***	***c***	***d***
de (%)	46	10	96	4

Scheme 166. Double asymmetric induction of aza-Diels–Alder reactions.



Boron mediator	*de* (%)
(R)-**241**	> 99
(S)-**241**	84
(R)-**242**	86
(S)-**242**	92

Scheme 167. Double asymmetric induction in the aza-Diels–Alder reaction catalysed by chiral BLA complex.

provides a useful route to optically active heterocyclic compounds[282] which are versatile building blocks in the preparation of biologically important compounds.

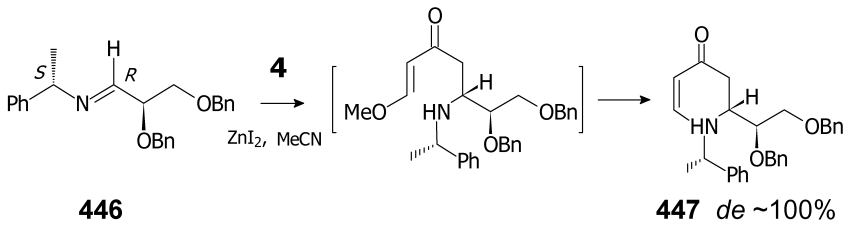
Defoin and co-workers[283] observed the matched diastereoselectivity (de 96%) in the reaction of the chiral diene (*S*)-**439** with the chiral (*R*)-prolinol dienophile **440** (Scheme 166). The mismatched asymmetric cycloaddition of the enantiomer (*S*)-**439** with the diene (*R*)-**440d** gave only poor stereoselectivity (de 4%). The same conditions controlled the Diels–Alder reaction of mandelic acid derivatives. The reagents **439**–**440a** (de 46%) functioned as the matched pair, and the reagents **439**–**440b** as the mismatched pair (de 10%) upon double asymmetric induction.

Hattori and Yamamoto[286] reported the double asymmetric induction of the aza-Diels–Alder reaction mediated by the chiral BLA catalysts **241** and **242**. The matched aza-Diels–Alder reaction of prochiral benzylidene benzylamines (*S*)-**443** with the Danishevsky diene **4** in the presence of the chiral BLA complex (*R*)-**241** provided the cycloadduct **444** with 99% stereoselectivity (matched pair) (Scheme 167). The imine (*S*)-**443** reacted with the diene **4** and the catalyst (*S*)-**241** with mismatched asymmetric induction to give diastereomeric mixture **444**,**445**. The reaction was applied to the efficient synthesis of anabasine and coniine.

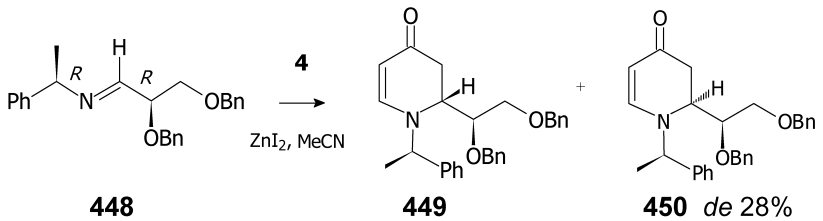
The (*S*,*R*)-*N*-benzylimine **446**, containing two matched chiral auxiliaries, reacted with the Danishevski diene **4** in the presence of zinc iodide (substrate-controlled double asymmetric induction) to give the adduct **447** with excellent stereoselectivity (Scheme 168). The reaction of the (*R*,*R*)-imine **448** with **4** proceeded as a mismatched asymmetric synthesis to give a 64:36 diastereomeric mixture of **449** and **450** (Scheme 169).[286,287]

A highly stereoselective aza-Diels–Alder reaction was observed in the cycloaddition reactions of the chiral *N*-acylimines **451**, containing two asymmetric inductors R^* and R^{**}, with cyclopentadienes and with 1,3-butadienes in the presence of trifluoroacetic acid to provide the adduct **452** (Scheme 170)[288]

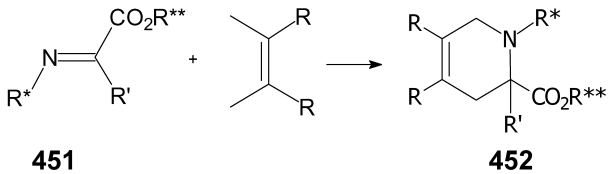
Bednarski and Danishevski[289–292] reported that $Eu(fod)_3$ and $Eu(hfc)_3$ catalysed the cycloaddition of aldehydes to the



Scheme 168. Substrate-controlled matched double asymmetric aza Diels–Alder reaction.



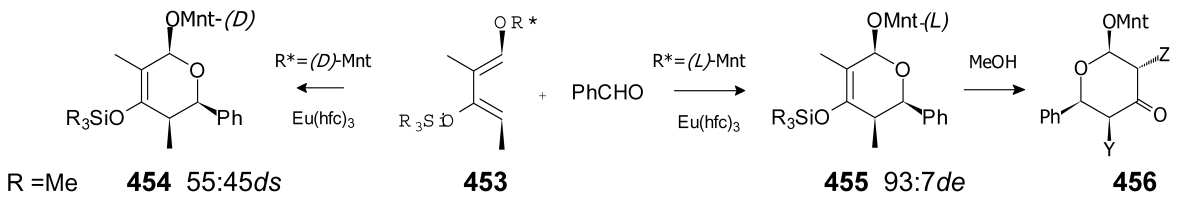
Scheme 169. Mismatched aza-Diels–Alder reaction.



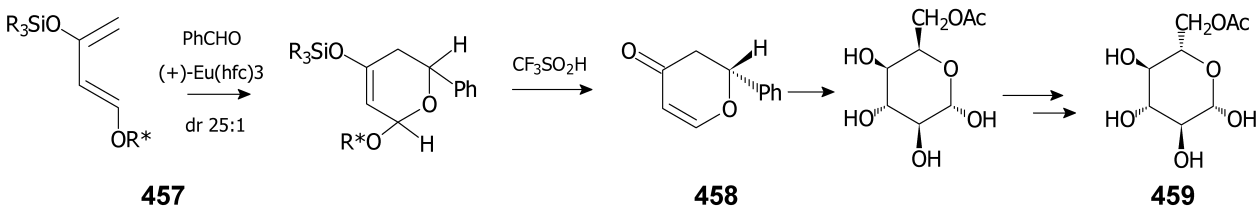
R*= Ph(Me)CHNH, R**= 8-phenylmenthyl;

R*= *(R)*, R**= *(RR)*, *de* 95% (matched AI);
R*= *(S)*, R**= *(RR)*, *de* 38-61% (mismatched AI)

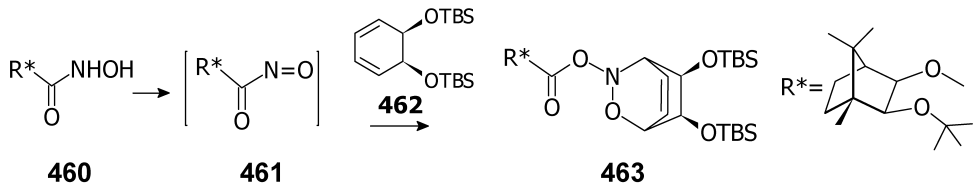
Scheme 170. Aza-Diels–Alder reaction of the chiral *N*-acylimines 451 with dienes.



Scheme 171. Eu(fod)$_3$ and Eu(hfc)$_3$ catalysed the cycloaddition of the benzaldehydes to the oxygenated butadienes **453**.



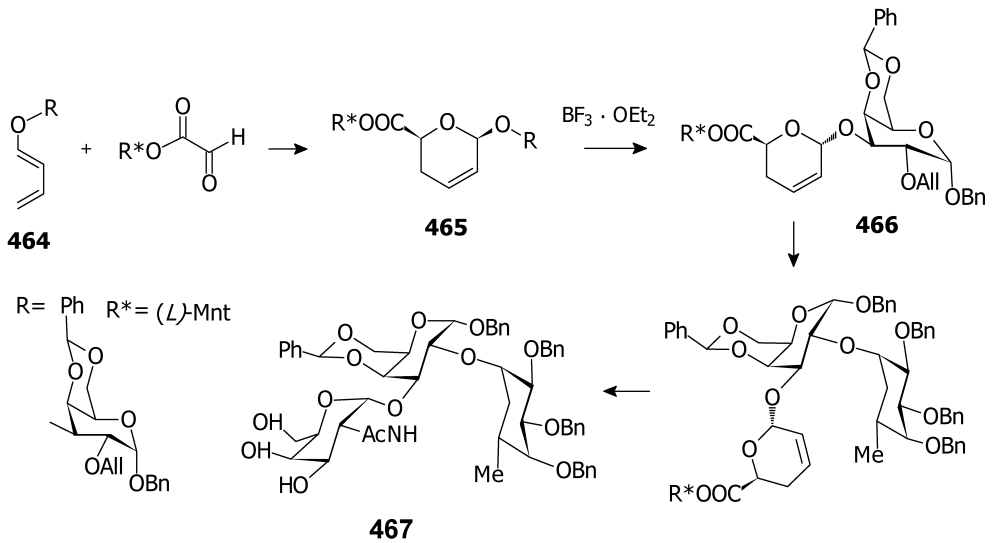
Scheme 172. Double asymmetric synthesis of (*R*)-dihydropyrone and (L)-glucose.



Scheme 173. Asymmetric aza-Diels–Alder reaction of the acylnitrososultam **461** with the cyclohexadiene **462**.

oxygenated butadienes **453**. With achiral dienes, (+)-Eu(hfc)$_3$ shows only modest enantiofacial selectivities. Similarly, modest selectivities were observed in the reactions of chiral dienes with aldehydes in the presence of the achiral Eu(fod)$_3$. A combination of the chiral dienes with the chiral (+)-Eu(hfc)$_3$, however, exhibited double diastereoselectivity. Matched stereoselectivity (93:7) was observed with (+)-Eu(hfc)$_3$ and (L)-**453**, resulting the formation of optically pure **455** and **456**, while the chiral catalyst (+)-Eu(hfc)$_3$ and (D)-**453** did not influence the stereoselectivity to give the diastereomeric mixture **454** (Scheme 171).[291,292]

Bednarski and Danishefsky[257] used the diastereoselective reaction of the chiral dienes **457** with benzaldehyde in the presence of (+)-Eu(hfc)$_3$ for the synthesis of artificial (L)-glucose **459**, glycolipids, and substituted pyrans as shown in Scheme 172. A matched combination of chiral dienes with the chiral (+)-Eu(hfc)$_3$ catalyst resulted in diastereofacial excesses of 95%. This asymmetric hetero Diels–Alder process has formed the basis of a new and flexible route to various types of natural products in an enantiomerically pure form, e.g. the synthesis of optically pure substituted (*R*)-dihydropyrone **458** and (L)-glucose **459**.[292]



Scheme 174. Stereoselective synthesis of the *N*-acetylgalactosamine unit.

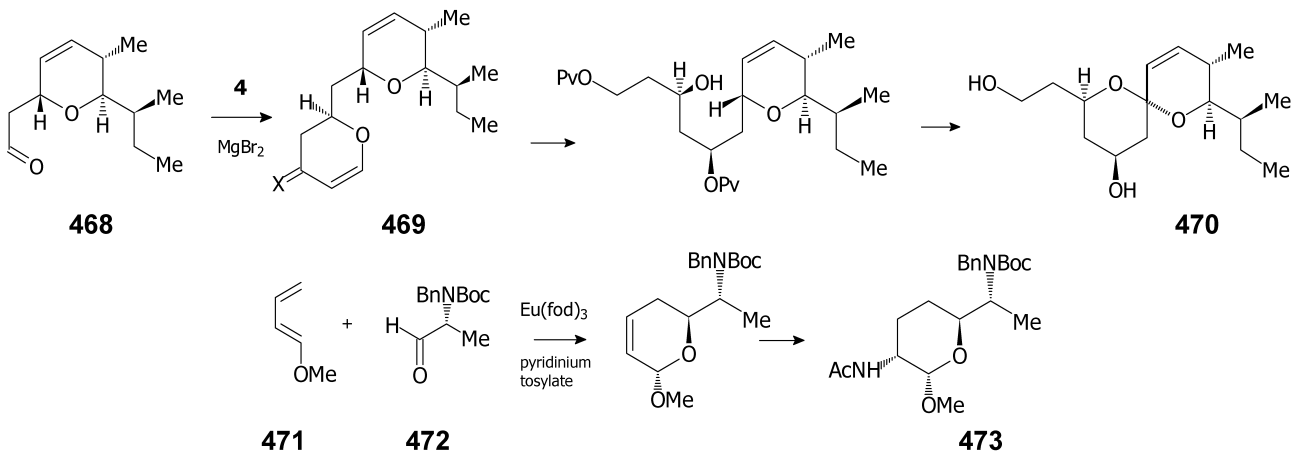
N-Acyl- and α-chloro nitroso compounds are very reactive heterodienophiles which, at low temperatures, undergo hetero Diels–Alder reactions. In one example, the reaction of the acylnitrososultam **461** with the cyclohexadiene **462** led to the formation of the cycloadducts **463** with matched diastereoselectivity (>98% de) (Scheme 173).[293,294] The acylnitroso intermediates **461** were generated at low temperature by treatment of the respective hydroxamic acid **460** with the Moffat reagent. They reacted with chiral dienes to give cycloadducts with matched diastereoselectivity.[295]

The hetero Diels–Alder reactions have opened up an route to the synthesis of oligosaccharides,[296–298] as shown in Scheme 174, where the trisaccharide **467** of the human blood group A antigenic determinant was synthesised.[299] The galactose-derived diene **464** was subjected to cycloaddition with (−)-menthyl glyoxylate to give a mixture of the diastereoisomers **465**, which was subsequently equilibrated to the *trans*-dihydropyrone by treatment with $BF_3{\cdot}OEt_2$. After removal of the allyl protecting group at O-2 of **466**, a fucose unit was attached. Finally, the dihydro-pyrone moiety formed in the cycloaddition was elaborated to an *N*-acetylgalactosamine unit. The two chiral auxiliaries reinforce each other, i.e. they represent a matched pair.

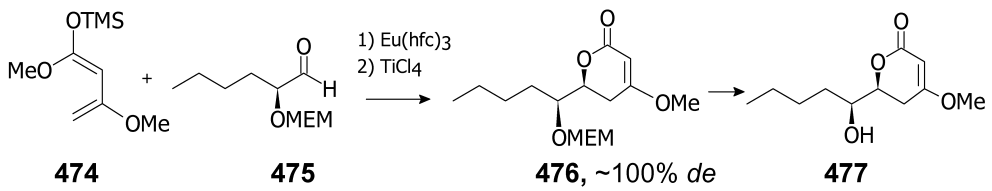
The asymmetric hetero Diels–Alder cycloadditions have been applied to the synthesis of natural products in an enantiomerically pure form.[289,300–302] Danishevsky has developed a total synthesis of the aglycon of avermectin A_{1a} **470** using in the key step cycloaddition of the aldehyde **468** with the Danishevsky diene **4** which afforded the pyrone–pyran product **469** with good stereoselectivity. The 6-amino-6-deoxycarbohydrate D-purpurosamine B **473** has been prepared from the D-alanine-derived aldehyde **470** and aminoaldehyde **471**.[302] D-Purpurosamine B **473** is a sugar component of the aminoglycosidic antibiotic, gentamycin C2 (Scheme 175).

1,3-Dimethoxy-1(trimethylsiloxy)butadiene (Brassard's diene) **474** reacted with the chiral aldehyde **475** in the presence of $Eu(hfc)_3$, to give the desired *threo*-cycloadduct **476** as a single product, which was then deprotected to afford the fungal metabolite (−)-pestalotin **477** in 50% overall yield (Scheme 176).[303]

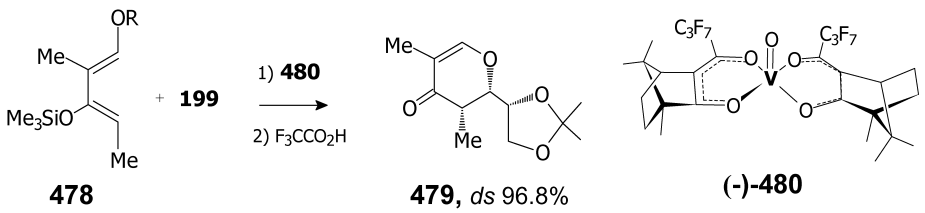
Optically active oxovanadium complexes, bearing camphor-derived 1,3-diketonato ligands, were employed as effective catalysts of the hetero Diels–Alder reaction.[304] If a chiral aldehyde was used as the heterodienophile, a pronounced double diastereoselection was observed. In one example, the matched combination of the chiral



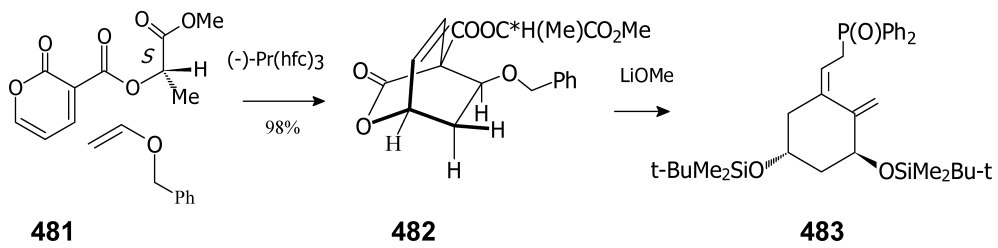
Scheme 175. Synthesis of the aglycon of avermectin A_{1a} **470** and of D-purpurosamine B **473**.



Scheme 176. Synthesis of the fungal metabolite (−)-pestalotin.



Scheme 177. Oxovanadium complexe **480** catalysed the hetero Diels–Alder reaction.



Scheme 178. Asymmetric synthesis of an A-ring precursor of 1α-hydroxyvitamin D_3 steroids.

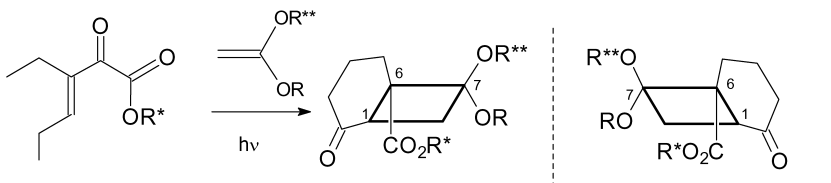
oxovanadium complex (−)-**480** with (*R*)-glyceraldehyde acetonide **199** gave the pyrone products **479** in 96.8% de (94% ee), whereas the mismatched combination of (+)-**480** and (*S*)-glyceraldehyde **200** afforded **478** only, with 43% de (Scheme 177).

The [2+4]-cycloaddition leading to the bicyclic lactone **482** proceeded with double stereodifferentiation in which the absolute stereochemistry of the chiral diene and of the chiral Lewis acid were mutually compatible. The highly-stereocontrolled Diels–Alder reaction involving the stereochemically-matched pyrone (*S*)-lactate **481** and Lewis acids such as (−)-Pr(hfc)$_3$ produced the bicyclic lactone *endo*-**482** via a double stereodifferentiation process.[305] The bicyclic lactone **482** was then converted in high yield into the phosphine oxide (−)-**483**, an important A-ring precursor to various physiologically active 1α-hydroxyvitamin D_3 steroids (Scheme 178).

3.5.3. [2+2]-Photocycloadditions. Stereoselective [2+2]-photocycloadditions of alkenes are a powerful tool for the synthesis of cyclobutanes.[305,306] In diastereoselective reactions, however, cyclic enones have been examined with moderate success.[306]

Herzog et al. have applied double asymmetric induction to increase the stereoselectivity of the bimolecular photoreaction of the chiral cyclenone-3-carboxylates **484** with optically active ketene acetals (Scheme 179).[306]

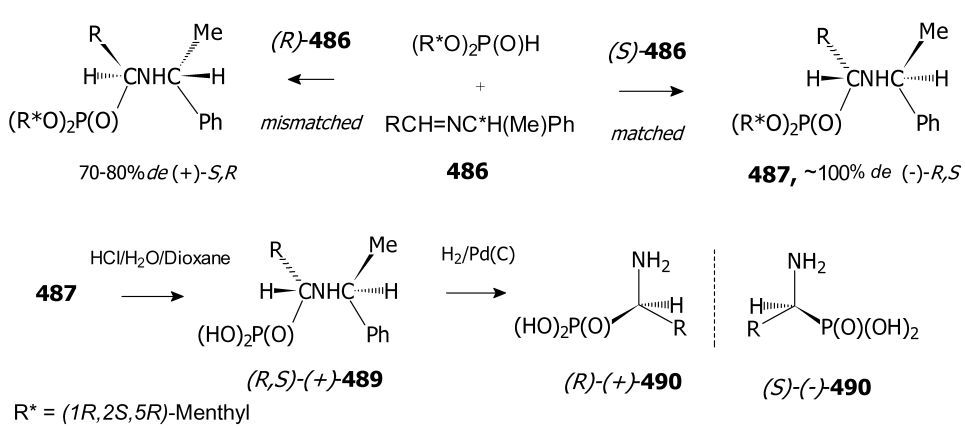
The single asymmetric induction of the reaction of chiral enone esters with achiral keteneacetals and achiral



R*	*de* (%)	Config
(-)-Mnt	45	*1S,6R,(7R)*
(+)-Mnt	17	*1S,6R,(7R)*
(-)-PM	72	*1S,6R,(7R)*
(+)-IPM	22	*1R,6S,(7S)*

R** = (-)-Mnt; PM = 8-Phenyl-3-menthyl; IPM = *ent-iso*-8-phenyl-3-menthyl

Scheme 179. Double asymmetric induction in [2+2]-photocycloadditions.



Scheme 180. Double asymmetric synthesis of aminophosphonic acids.

enone–esters with chiral keteneacetals proceeded with a low diastereoselectivity (~27% de). The reaction of optically active (−)-3-menthyl-3-oxo-l-cyclohexen-1-carboxylate with achiral 1,1-diethoxyethylene afforded the (1*S*,6*R*)-cyclobutane derivatives **484** and **485** only with 14% de. At the same time, the reaction of chiral cyclohexenone carboxylates with chiral (−)-3-menthyl keteneacetals proceeded with essentially higher matched double asymmetric induction (74% de).[307]

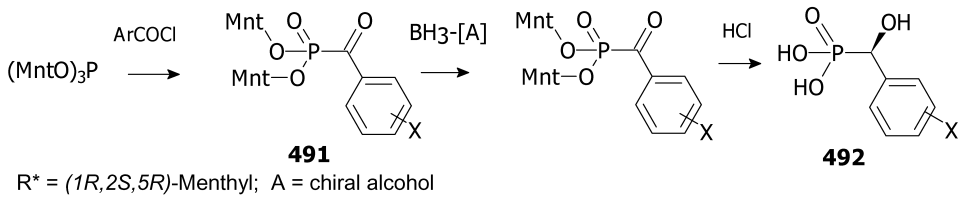
3.6. Asymmetric synthesis of heteroatom compounds

In the last few years, optically active heteroatom compounds have found a wide application in asymmetric synthesis. Examples of double asymmetric synthesis with participation of chiral heteroatom auxiliaries have been described.[5,309] The chiral heteroatom group that induces optical activity can be easily removed from the molecule, thus presenting an additional advantage in the asymmetric synthesis of chiral compounds. The double stereodifferentiation has been used for the synthesis of optically active phosphorus and organosulphur compounds. Chiral phosphoric acid esters add chiral aldimines with a high asymmetric induction. A matched addition was observed in the case of the addition of dimenthylphosphite to the aldimine derivative (*S*)-2-methylbenzylamine, furnishing practically a single diastereomer of the aminophosphonic acid esters. In the case of the aldimine derivative of (*R*)-2-methylbenzylamine, the mismatched asymmetric induction, with a lower diastereomeric ratio, was observed (Scheme 180).[308–311]

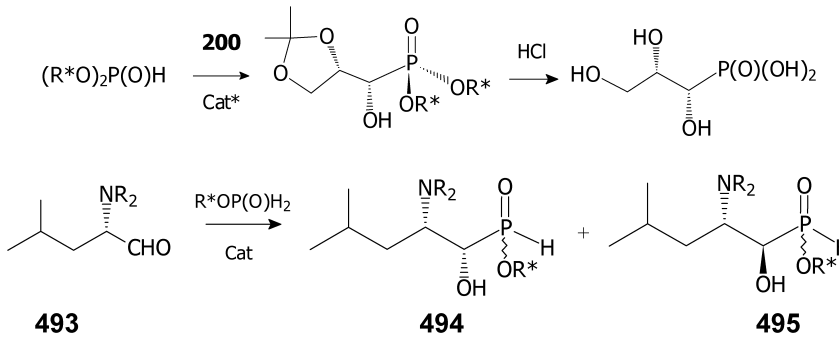
Hydrolysis and catalytic debenzylation provided the enantiomerically pure (*R*)- and (*S*)-aminophosphonic acids **490**. Reduction of dimenthyl acylphosphonates with $NaBH_4$ afforded a mixture of chiral (*R*)- and (*S*)-diastereomers in the ratio of 4:1, whilst catalytic hydrogenation of the acylphosphonates by complexes of sodium borohydrate with chiral alcohols and aminoalcohols furnishes predominantly one diastereomer of the 1-hydroxybenzylphosphonic acids (Scheme 181).[310]

The diastereoface selectivity was explained by shielding effect of menthyl groups of the compound which closes one of the sides of carbonyl group in such a manner that *Si*-side of ketone is shielded more than *Re*-party and boronhydrate attacks predominantly this side. A stereodivergent synthesis of the β-amino-α-hydroxy-H-phosphinates **494** and **495** was achieved by ALB-catalysed hydrophosphonylation of the *N*,*N*-dibenzyl-α-amino-aldehydes **493**, tuning the chirality of the catalysts (Scheme 182).[312–314]

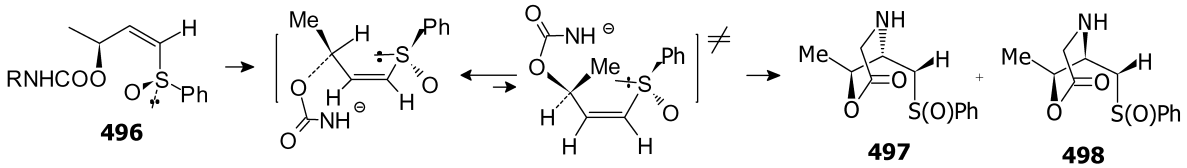
Heteroolefins **496** containing an *N*-trichloroacetyl-carbamoyloxy group underwent the cyclisation reaction under conditions of low-alkaline hydrolysis to convert into the 2,3-*syn*- and 2,3-*anti*-compounds **497** and **498** (dr 110:1, matched AS). The stereochemical behaviour of the sulphoxides **496** is a result of the 'intramolecular' double



Scheme 181. Asymmetric catalytic hydrogenation of the acylphosphonates.

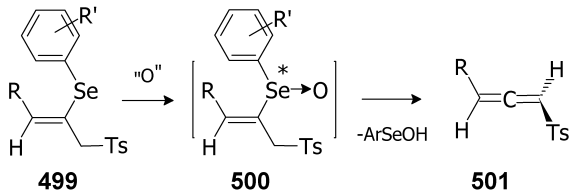


Scheme 182. Asymmetric Abramov reaction.



Scheme 183. Asymmetric cyclization of chiral sulfoxides **497** and **498**.

asymmetric induction, determined by two stereogenic centres at the allylic carbon and sulphur atoms. While the carbon centre stimulates a 1,2-asymmetric induction, the additional chirality of the sulphoxide has an effect on 1,3-asymmetric induction through steric interaction between a suitable nucleophile and the phenyl group on the sulphur or electronic interaction between a nucleophile and a free pair of electrons in a transition state (Scheme 183).[315] The double asymmetric induction increased the stereoselectivity of asymmetric oxidation of the arylvinylselenides **499** with a chiral modified Sharpless or David oxidant.[316] The reaction proceeded with the formation of chiral selenoxides **500**. Asymmetric elimination of the selenoxide resulted in the formation of the chiral allene sulphones **501**. The highest enantiomeric excess of the allenes has been obtained in the case of selenides containing an R=*o*-nitrophenyl group (Scheme 184).



Scheme 184. Asymmetric oxidation of the arylvinylselenides **500**.

Ruano et al.[318] reported the additions of lithium anions derived from (*R*)- and (*S*)-methyl and -ethyl *p*-tolyl sulphoxides to (*S*)-*N*-benzylidene-*p*-toluenesulphinamide, resulting in the formation of enantiomerically pure β-(*N*-sulphinyl)amino sulphoxides. The highest stereoselectivity was achieved when the configurations at the sulphur atoms of the two reagents were opposite (matched pair), thus resulting in only one diastereomer, even for the case in which two new chiral centres are created.

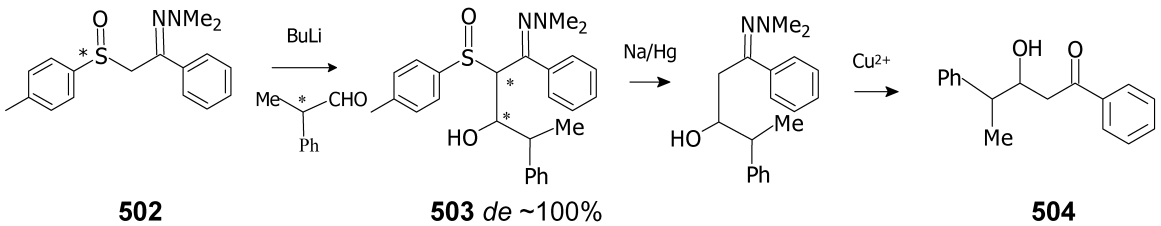
The optically active γ-methyl-β-hydroxy- and γ-alkoxy-β-hydroxy ketones **504** have been obtained by condensing chiral aldehydes with chiral α-sulphinyl hydrazones **502**. Good to very good enantioselectivity and diastereoselectivity (up to 88% ee), both strongly dependent on the nature of the substrates and the reaction conditions, were achieved. The double stereodifferentiation was complete in the reaction of (−)-(*R*)-**502** with 2-phenylpropanal, resulting in the formation of only one of the four possible stereoisomers **503** (Scheme 185).[319,320]

This methodology was used for the synthesis of manicone **506**, one of the alarm pheromones of *Manica mutica* and *M. bradleyi*, starting from the sulfoxide (*R*)-**505** (Scheme 186).[320]

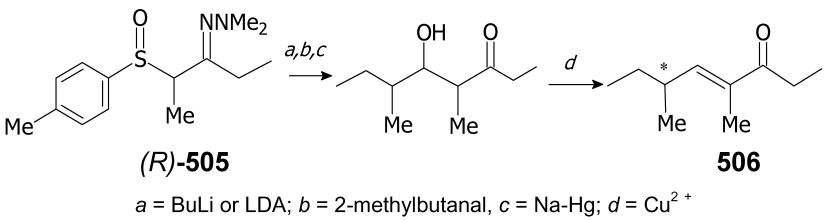
Chiral reagents containing two asymmetric auxiliaries in one molecule increasing asymmetric induction are especially interesting. In one example, the lithium derivative of a Schiff base formed from (*R*)-camphor and aminomethanephosphonates was allowed to react with alkyl and benzyl halides to yield the corresponding esters of (*S*)-α-aminoalkanephosphonic acids **507** (Scheme 187).[310,321,322]

3.7. Miscellaneous

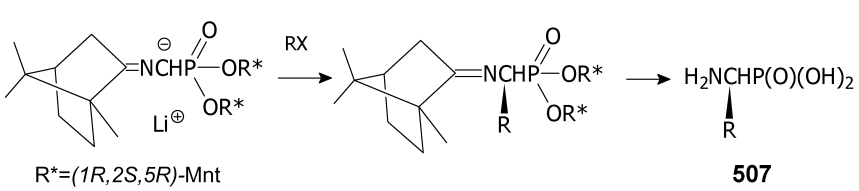
Condensation of chiral 2-silyloxypyrroles with achiral and



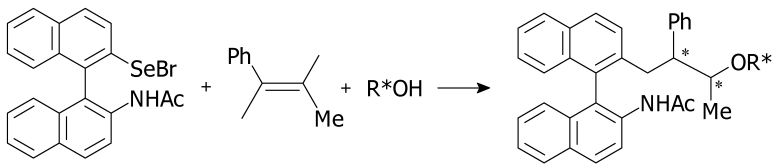
Scheme 185. Astmmetric synthesis of the γ-methyl-β-hydroxy- and γ-alkoxy-β-hydroxy ketones **504**.



Scheme 186. Asymmetric synthesis of manicone.

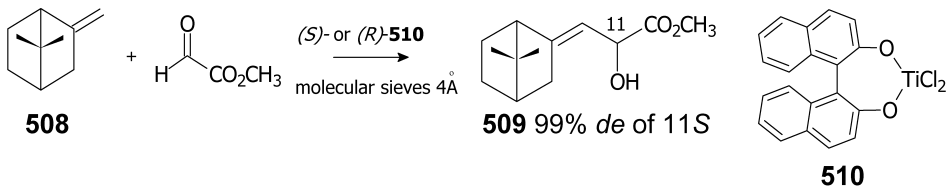


Scheme 187. Asymmetric synthesis of the (*S*)-α-aminoalkanephosphonic acid esters **507**.



R*OH	*de*, %	Double AS
D-Menthol	80	matched
L-Menthol	12	mismatched
MeOH	54	none

Scheme 188. Double asymmetric oxyselenylation of olefins.



Scheme 189. Double asymmetric induction in the carbonyl-ene reaction of the glyoxalate **508** with the (+)-α-fenchene.

chiral formyl derivatives afforded pyroglutamic aldehydes and prolinal systems, with the stereocontrol from good to excellent. Considering that the chiral auxiliary residing on the pyrrole system shows a good level of diastereofacial selectivity in C-5, the joint use of 2-methoxy-3-tosyl-oxazolidine as a chiral formylating reagent has enabled a full stereocontrol of the condensation to be carried out.[323,324]

Trost and Mallart reported the double diastereo-differentiation in the hydroxylative Knovenagel condensation.[325]

Tomoda et al.[317] used the double asymmetric induction in the oxyselenylation of olefins. The diastereoisomeric excess was essentially increased in the case of a coordinated asymmetric interaction between (*R*)-binaphthyl derivative **509** and (D)-menthol and decreased in the case of the mismatched interaction between (*R*)-binaphthyl derivative **509** and (L)-menthol (Scheme 188).

The double asymmetric induction was observed in the carbonyl-ene reaction of the glyoxalate with the chiral ene components, (−)-β-pinene or (+)-α-fenchene, catalysed by a chiral titanium complex **510** derived from optically pure binaphthol and $(i\text{-PrO})_2TiCl_2$. A reaction of the Friedel–Crafts type with (+)-α-fenchene and (*S*)- or (*R*)-BINOL–$TiCl_2$ as catalyst provided mainly the allylic alcohol products **511** in extremely high levels of 11*S* and 11*R* selectivity, 98.8 and 97.4% de, respectively (Scheme 189).[49,249]

4. Conclusion and perspective of application

I hope that this review of multiple stereodifferentiating reactions and their application in organic synthesis will be useful to chemists interested in various aspects of chemistry and stereochemistry. The facts and problems discussed provide numerous possibilities for the study of additional stereochemical phenomena of stereoselective reactions and stereoselectivity.

Looking to the future, it may be said that the multiple asymmetric synthesis will be and should be the subject of future studies. Opportunities lie in the development of the application of reagents and catalysts containing several chiral auxiliaries, studies of the mechanisms and stereochemistry of reactions and studies dedicated to the diastereodifferentiating reactions in biochemical processes. Today, synthetic organic chemists have several possibilities for the multiple asymmetric induction on an achiral molecule. The broad spectrum of possibilities offered by the developed methodologies therefore covers all types of different substrates. In addition, the manipulation of the introduced functional groups has reached a high level of sophistication in terms of stereo-, regio- and chemoselectivity. The level of manipulation of the various functional groups can allow the same final compounds to be obtained by different routes and starting from different precursors.[326] The newly introduced methodologies allow shorter synthetic sequences and higher yields in many instances, with respect to the originally developed methodologies. A careful analysis of all the methodologies is still required, however, in planning a synthesis that implies an asymmetric reaction for the introduction of the correct absolute configuration.

Further development will involve studies of the stereochemistry of chiral multifunctional catalysts. In spite of the successes in the area of basic research on chiral catalysts bearing several matched asymmetric centres, their application in asymmetric synthesis is obviously deficient at present. Finally, wider applications of multiple stereodifferentiating reactions in asymmetric organic synthesis are expected to appear.

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