Control of asymmetry through conjugate addition reactions

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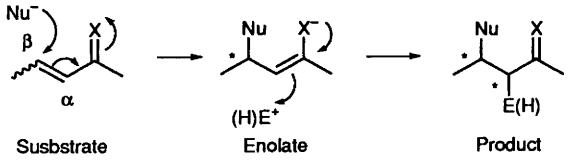
1 Introduction

Nucleophilic conjugate addition reactions, often referred to as Michael additions, comprise some of the most important structure building reactions for organic synthesis. The substrate for the nucleophilic attack is an alkene which can be conjugated to any mesomerically electron-withdrawing group. This group is most commonly a carbonyl (ketone, aldehyde, ester amide, *etc.*), but can be a nitro group, a nitrile, a sulfoxide, a sulfone, an electron-deficient heterocycle, *etc.* (**Scheme 1**).



Scheme 1

When an α,β-unsaturated conjugate addition substrate has prochiral centres at the α and/or β positions there is potential for the creation of new chiral centres. There is also potential for new chiral centres to be formed in the nucleophile, or within the electrophile which reacts with the intermediate enolate ion. The relative and/or absolute stereochemistry generated at these positions can often be controlled efficiently, therefore conjugate addition reactions have gained a prominent role in the synthesis of chiral compounds. A number of recent reviews have covered various aspects of conjugate addition reactions,[1-5] and some have focused specifically on aspects of asymmetric conjugate addition reactions.[1,3(d),4,5] A short review on a subject of this breadth cannot be comprehensive and this review endeavours to provide an overview of where and how stereochemistry can be controlled through conjugate addition reactions.

Sections 2 and 3 of this review will deal with some important aspects of the control of relative stereochemistry through conjugate addition reactions. The rest of the review will be devoted to ways in which the absolute stereochemistry at newly created chiral centres can be controlled. **Figure 1** indicates the four most common sources of chirality which have been exploited for asymmetric induction at the α- and β-positions. Each of these sources of chiral induction will be illustrated in turn in Sections 4–7.

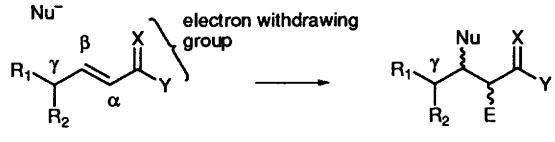
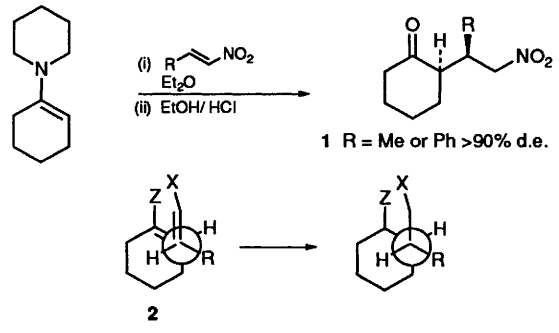


Figure 1

Sources of chirality for control of absolute stereochemisry:
- Chiral centre γ- to the electron withdrawing group
- Chiral centre(s) atached α- to the electron withdrawing group
- Chiral centre(s) at the electron withdrawing group
- Chiral centre(s) covalently bound to nucleophile
- Chiral centre(s) non-covalently bound to nucleophile

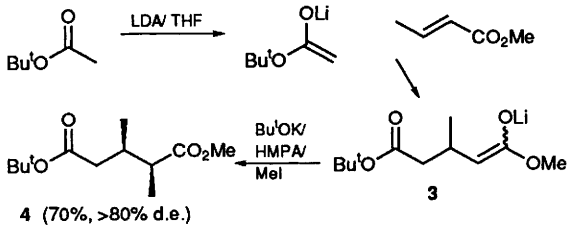
2 Stereoselectivity of enolate additions to acyclic α,β-unsaturated carbonyl compounds

When enolates or enamines react with α,β-unsaturated systems several new chiral centres can be generated and it is very useful to be able to carry out such reactions with good, predictable stereochemical control. It has been known for many years that the stereochemistry generated during these reactions can be highly dependent upon the solvent used.[3(b)] Seebach *et al.* proposed a model to account for the observed stereoselectivity of additions of enamines to α,β-unsaturated systems. An example is shown in **Scheme 2**, where selective production of **1** can be accounted for by a 'closed' transition state model **2**. When chiral enamines, derived from prolinol, were used in such conjugate additions, products with up to 90% e.e. were produced (see Section 6).[6,7]



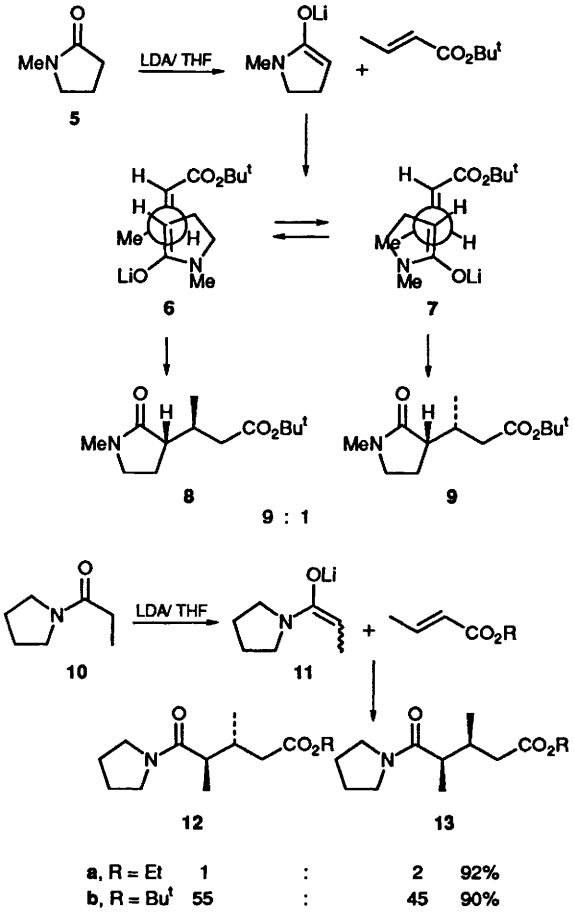
Scheme 2

Heathcock *et al.*[8] and Yamaguchi *et al.*[9,94] investigated the stereochemistry generated when enolates add to α,β-unsaturated ketones and esters. Yamaguchi found that the lithium enolate of t-butyl acetate reacted with methyl crotonate in a conjugate manner, but the intermediate enolate generated **3** could only be alkylated after addition of HMPA and/or Bu^{t}OK. Under such conditions the methylated product **4** was isolated with high *syn* selectivity (**Scheme 3**). Tomioka also found that conjugate addition to *E*-esters followed by methylation gave high *syn* selectivity.[10]



Scheme 3

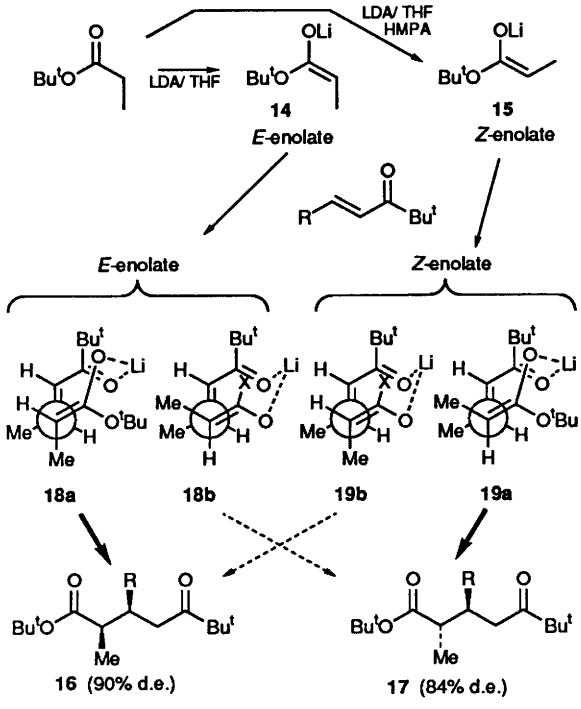
Heathcock *et al.* reacted the enolate of amide **5** with t-butyl crotonate, providing diastereoisomer **8** with high selectivity (**Scheme 4**).[8(a)] This product was not in accord with previously proposed 'closed' transition state models and Heathcock proposed an 'open' transition state model **6** to account for the major stereoisomer. Heathcock *et al.*[8(a)] also reacted the enolate of amide **10** with t-butyl crotonate and Yamaguchi *et al.*[94] reacted the same enolate with ethyl crotonate. Neither reaction was particularly stereoselective and the direction of the selectivity was inconsistent.



Scheme 4

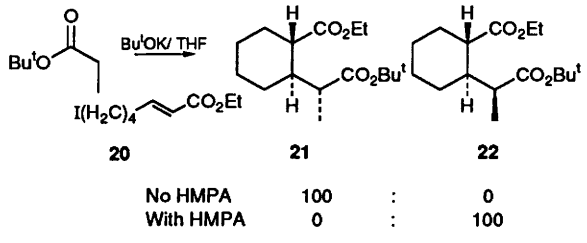
A wide range of ester and ketone enolates have now been reacted with acyclic enones and enoates and the stereochemical outcome of such reactions can be predicted very well. In some of the earliest studies Heathcock *et al.* reacted the enolate of t-butyl propionate with α,β-unsaturated esters or ketones and found that without HMPA in the mixture *syn* diastereoisomer **16** was formed selectively (~ 90% d.e.), but with HMPA present the *anti* isomer **17** was formed selectively (~ 90% d.e.).[8(b)] Yamaguchi carried out similar studies using ethyl propionate and found a similar selectivity pattern.[9(a)] Yamaguchi ascribed the switch of selectivity with HMPA as a solvating effect, but Heathcock has shown from wide ranging studies that the stereoselectivity directly reflects the stereoselective formation of alternative geometrical enolate isomers **14** and **15** under the different reaction conditions. In general, *Z*-enolates such as **15** are formed with HMPA and react to give *anti* addition products, whereas *E*-enolates such as **14** are formed (kinetically) without HMPA and react to give *syn* addition products. Heathcock originally proposed an

'open' transition state model to account for this stereoselectivity,[9(b)] but in a full report of their studies with both ketone and ester enolates they propose chelated transition states.[9(d)] In general, the reactions of both ketone and ester enolates proceed with high stereoselectivity when the substituent on the enolate is large and the enolates are formed with a high degree of geometrical selectivity, as in the examples shown in **Scheme 5**. It was suggested that the *E*-enolate reacts selectively *via* transition state **18a** leading to *syn* product **16** when the enolate substituent is large.



Scheme 5

However, with small substituents (X) the *E*-enolate can react through transition state **18b** to give some *anti* product. Similarly, *Z*-enolates with a bulky substituent will react *via* transition state **19a** to give *anti* product **17** with high selectivity, unless the substituent (X) is small and transition state **19b** becomes viable. Yamaguchi *et al.* have added the enolate of t-butyl propionate to enoate chains bearing a terminal halide. Thus, after initial conjugate addition, the intermediate enolate is trapped by intramolecular alkylation leading to cyclic products (**Scheme 6**). When enoate **20** was the substrate, stereoisomer **21** was the exclusive product without added HMPA, whereas **22** was formed exclusively with HMPA present.[9(b)]



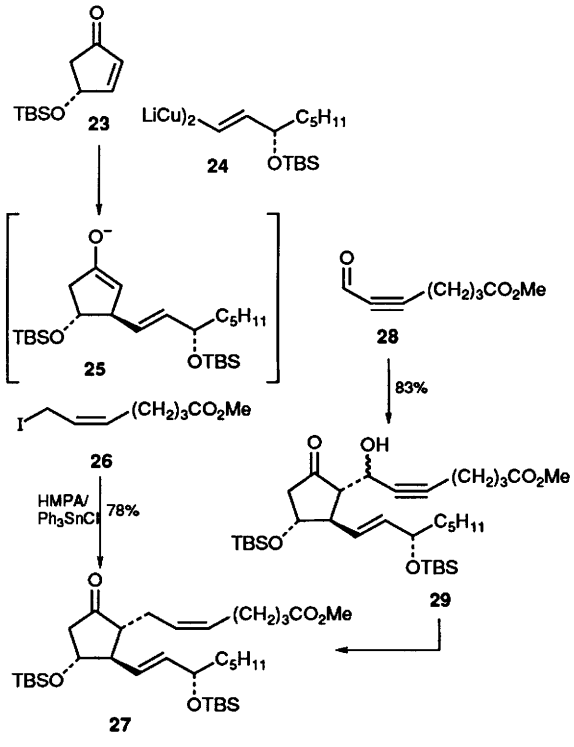
Scheme 6

Lewis acid catalysed Mukaiyama-type conjugate additions, using silyl enol ethers as precursors, also proceed with high stereoselectivity and have been reported by Heathcock *et al.*[9(c)] The mechanism of these reactions is quite different from those using lithium enolates, and the stereoselectivity does not appear to be related to enolate geometry. Bernardi and Scolastico have reported that titanium 'ate' enolates react selectively in conjugate additions, often with enhanced 1,4 *versus* 1,2-selectivity.[11] The control of relative stereochemistry shown in the reactions illustrated in this section is very important and a number of enantioselective procedures have been developed which utilize this diastereoselectivity. Examples of such processes are presented in other sections of this review.

3 Double Michael reactions and other processes in tandem with conjugate additions

3.1 Conjugate addition followed by tandem enolate trapping

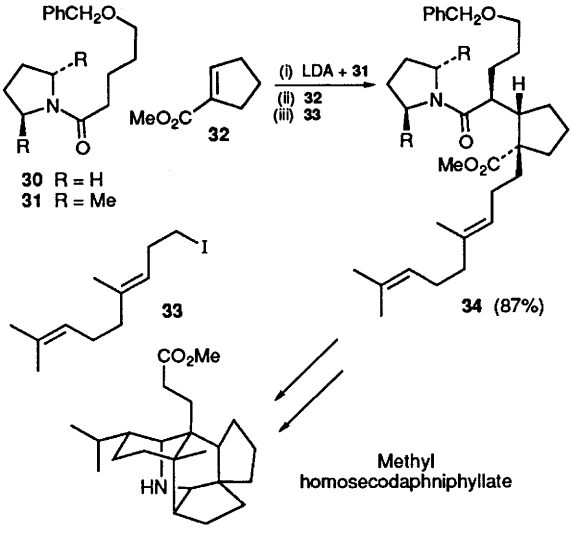
An enolate is generated when an anionic nucleophile is added to an α,β-unsaturated carbonyl compound and this has potential for reaction with an electrophile in a 'one-pot' process. One of the most attractive and convergent strategies for prostaglandin synthesis is stereoselective reaction of a cuprate reagent such as **24** with a chiral enone **23**, followed by stereoselective trapping of enolate **25** with allylic halides **26**. This process would provide the complete prostaglandin framework in one synthetic procedure. The main



Scheme 7

problem is that the copper-lithium enolate **25** is not sufficiently reactive to add to an alkyl halide such as **26**. A number of groups have worked on this problem and there are now several solutions, including two developed by Noyori *et al.* In the first strategy the highly electrophilic aldehyde **28** reacted with the enolate derived from addition of **24** to **23**, providing **29** in 83% yield.[12(a,b)] This was readily converted into intermediate **27** *via* radical deoxygenation. In a later development it was discovered that if enolate intermediate **25** was treated with triphenyltin chloride and HMPA it would react efficiently with alkyl halide **26**, providing **27** directly in 78% yield (**Scheme 7**).[12(c)] Negishi *et al.* also found a solution to the addition of the upper chain which involves a palladium coupling process.[13]

A spectacular example of a 'one-pot' tandem conjugate addition–alkylation process was part of Heathcock's masterful biomimetic study on *daphniphyllum* alkaloids.[14] Compound **34** was produced as a single stereoisomer in 87% yield, when the enolate of amide **30** was reacted with enoate **32** and the intermediate enolate trapped with iodide **33** (**Scheme 8**). Enantiomerically pure compounds were produced when the starting amide **31** was chiral (R = Me).

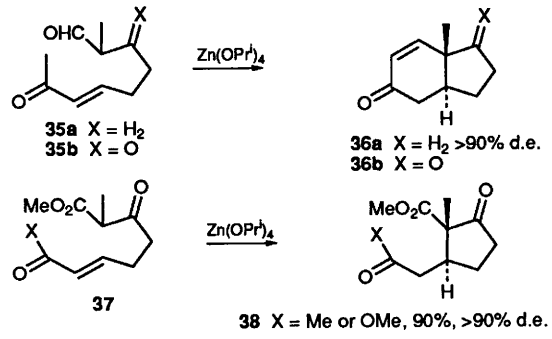


Scheme 8

An intramolecular Michael/aldol strategy has been developed by Stork *et al.*, providing *trans* hydrindenone systems in a highly stereoselective fashion.[15] Various conditions were explored for the cyclization of systems such as **35a** or **35b** and it was found that high yields and stereoselectivities were obtained using zinc isopropoxide (**Scheme 9**). Esters such as **37** could also be cyclized efficiently and a chiral auxiliary could be incorporated to allow control of absolute stereochemistry.[15(c)]

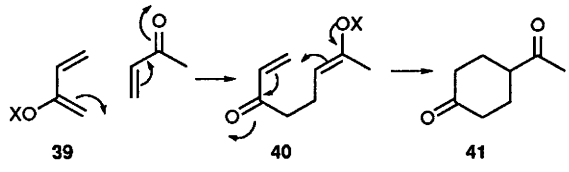
3.2 Double Michael addition reactions

Over recent years the double Michael addition process has been developed as a powerful tool for stereocontrolled synthesis (**Scheme 10**).[16] In this



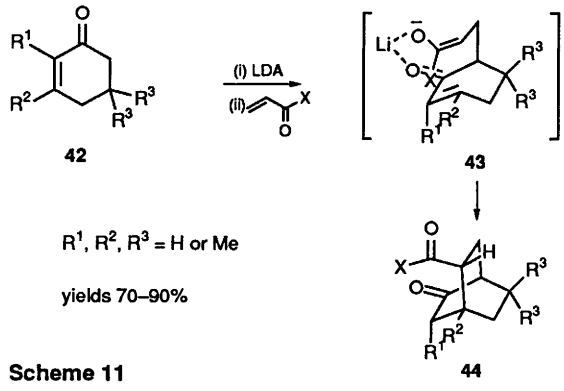
Scheme 9

process a potential Michael acceptor is converted into a Michael donor **39**, usually by enolization. When this reacts as a nucleophile with a second Michael acceptor, it reverts to a Michael acceptor and at the same time converts what had been the acceptor into a nucleophile **40**. Finally, a second Michael addition takes place to complete the cyclization process. The overall process is equivalent to a Diels–Alder reaction and indeed it is often difficult to determine which mechanism is taking place. Although the double Michael reaction comprises two consecutive steps, the new stereocentres are normally formed with a high degree of stereocontrol because the intermediate **40** is a highly ordered entity. Indeed it is sometimes the case that a double Michael process is more stereoselective than the equivalent Diels–Alder reaction.



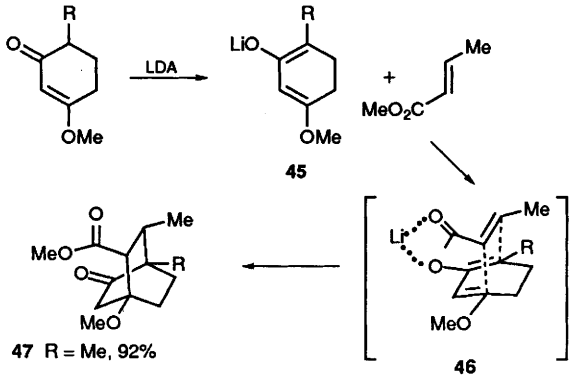
Scheme 10

Bellamy[17] and later Ban[18] reported early double Michael additions and more comprehensive studies were subsequently reported. Important studies were carried out by Lee[19] and White and Reusch[20] into reactions of dienolates, derived from cyclic enones such as **42**, with Michael acceptors such as methyl vinyl ketone and methyl acrylate. Bicyclic products **44** were produced in high yield and with a high degree of stereocontrol, suggesting that a chelated intermediate **43** was involved (**Scheme 11**).



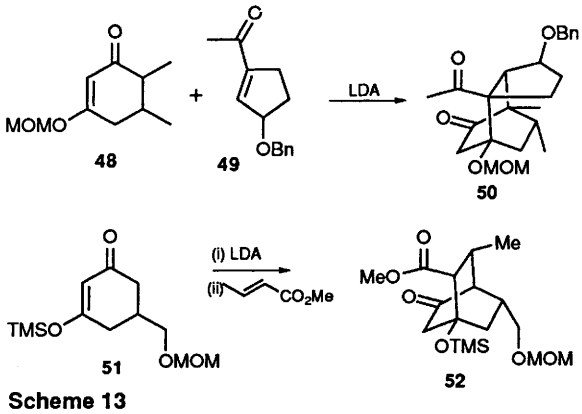
Scheme 11

Several other reports have detailed bicyclo[2.2.2]octane preparations involving double Michael reactions.[21-24] Chelation control has been used to explain the high diastereoselectivity of such reactions, as illustrated by the reaction of dienolate **45** with enoates to give **47**, *via* **46** (**Scheme 12**).[22(b)] In order to achieve control of absolute stereochemistry, Spitzner *et al.* used chiral auxiliaries on the ester of enoate substrates but the best selectivity achieved was 64% d.e.[23(d)] The isolation of uncyclized intermediates from the reactions, which can be cyclized in a second stage, indicates that the double Michael reaction is a stepwise process.[22(a)]



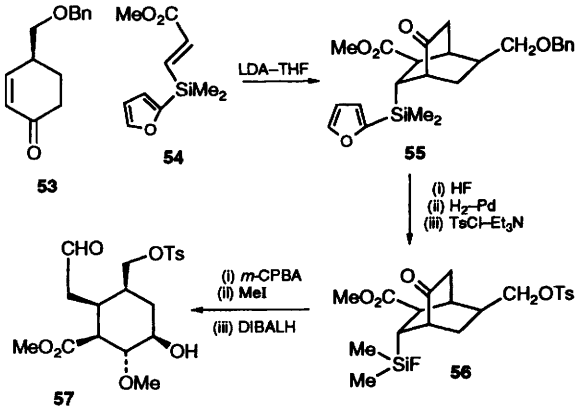
Scheme 12

Where the dienolate substrate already contains stereocentres there is a high degree of asymmetric induction during the reaction (**Scheme 13**).[24-27] For example, reaction of **48** with racemic alkoxyenone **49** gave **50** in which four new chiral centres have been introduced, with good control of stereochemistry relative to the benzyl ether.[25] Similarly, racemic **51** was converted into **52** which was used as an intermediate in a synthesis of (±)-eriolanine.[26]



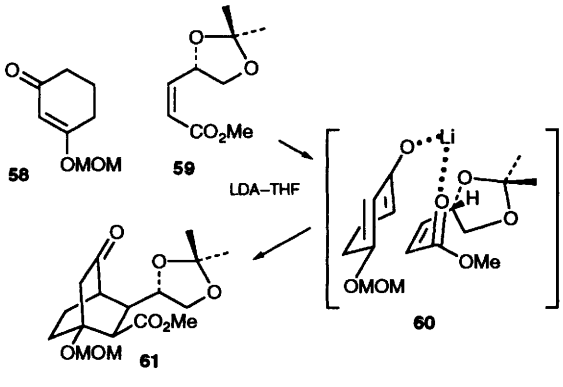
Scheme 13

Perhaps the best illustration of the power of the double Michael strategy is Stork's enantioselective synthesis of reserpine.[27] This is probably the most effective and elegant route to the alkaloid to date (**Scheme 14**). Michael acceptors carrying the required methoxyl group at the C-17 position would not undergo the double Michael cyclization so the silicon reagent **54** was designed for the purpose. It reacted with the enolate of **53** to give **55** as a single stereoisomer in over 80% yield. This has all the stereochemical information required for the key reserpine intermediate **57**. In a very short sequence of steps, involving simultaneous Baeyer–Villiger oxidation of the ketone and stereospecific silane to alcohol interconversion, **55** was converted into **57** *via* **56**.



Scheme 14

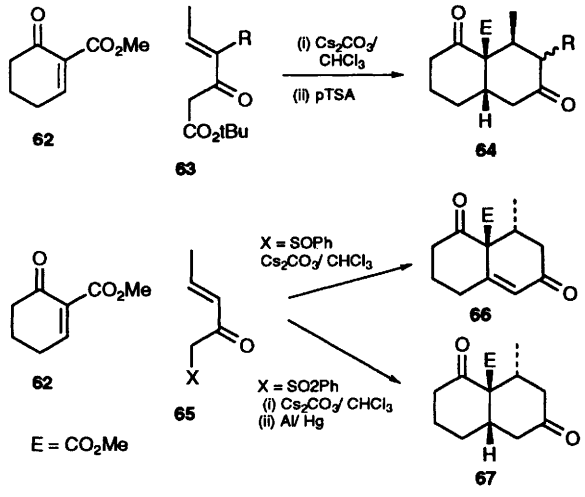
Kobayashi and Yamada have carried out some interesting double Michael studies.[28] When they reacted the *Z* alkoxyenoate **59** with the enolate from **58**, **61** was obtained as a single diastereoisomer and a chelated transition state **60** was proposed to account for this selectivity (**Scheme 15**). The double Michael sequence was much more stereoselective than an equivalent Diels–Alder reaction, carried out on the silyl enol ether of **58**, which gave a 1:1 mixture of diastereoisomers. The *E*-isomer of **59** also reacted much less selectively in double Michael reactions (3.5:1) than the *Z*-isomer. When HMPA was added to the reaction of the *E*-isomer of **59** there was an interesting reversal of the stereoselectivity.[28(b)] The facial selectivity of enoate **59** towards the lithium enolate here is interesting and should be compared to the selectivity observed when other lithium reagents are reacted with this type of enoate (see Section 4).



Scheme 15

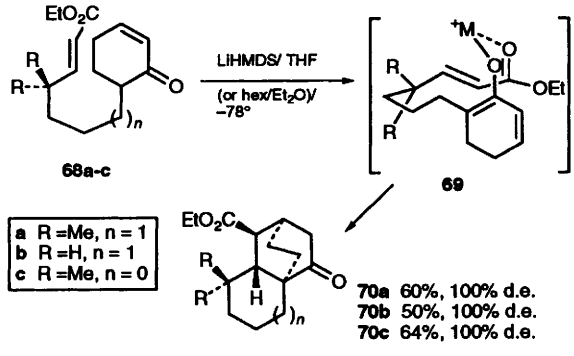
Deslongchamps *et al.* have used stabilized enolates of **63** and **65** in double Michael reactions with activated enone **62** to prepare *cis*-decalins of the type **64**, **66**, and **67**.[29] t-Butyl ester **63** gave **64** (R = H) with

excellent stereoselectivity, but where R is alkyl the stereochemistry at that position was not very well controlled. When sulfones or sulfonates were used the relative stereochemistry of the major product **66** or **67** was reversed (**Scheme 16**).



Scheme 16

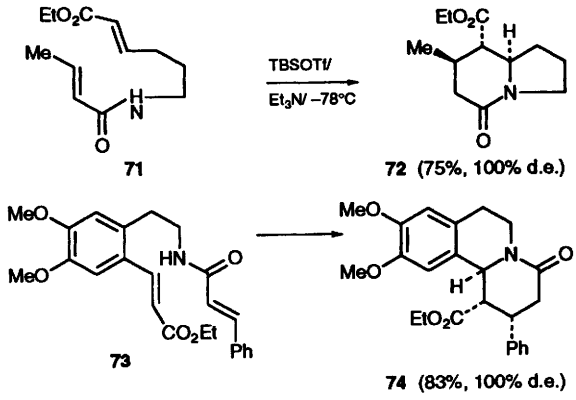
Intramolecular double Michael additions have been investigated extensively by Ihara *et al.*[16] They studied cyclizations of systems such as **68a–c** in some detail and found that lithium amide bases in THF or hexane–Et_2O gave the best results, with high diastereoselectivity for **70a–c**.[30] The absence of cyclization with sodium and potassium bases, and the fact that hexane–Et_2O was the best solvent, led them to suggest that a chelated intermediate **69** is involved. They found that cyclizations under Lewis acid catalysed conditions were less efficient and less stereoselective (**Scheme 17**).



Scheme 17

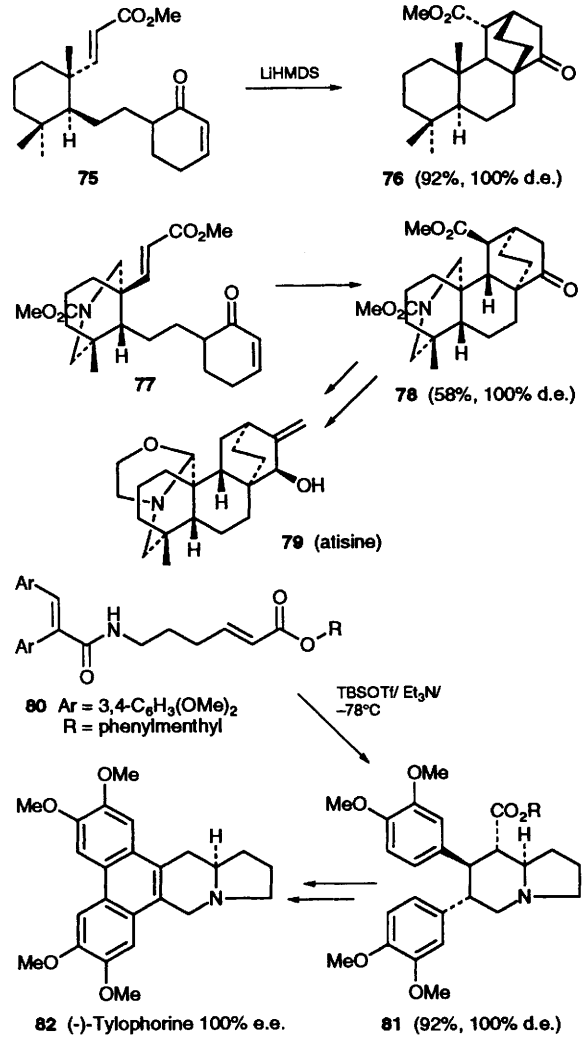
In contrast to the examples above, amides such as **71** and **73** did not cyclize under basic conditions, but were cyclized efficiently, in a highly stereoselective manner, under Lewis acid catalysis at low temperature. Since no intermediate silyl enol ethers could be detected, a double Michael mechanism rather than a Diels–Alder mechanism was suggested (**Scheme 18**).[31]

Ihara *et al.* have also used such intramolecular double Michael reactions in efficient and highly stereoselective approaches to several classes of natural products and some examples are given in **Scheme 19**.



Scheme 18

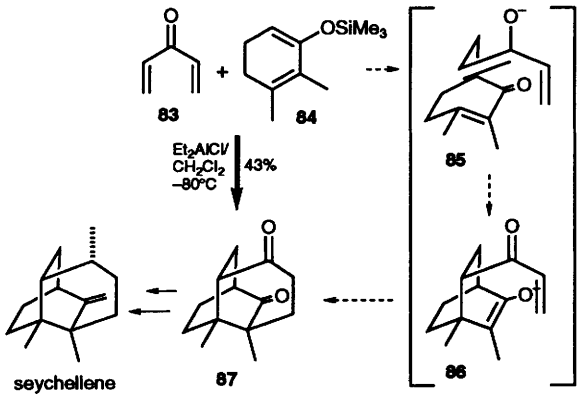
Cyclization of the optically active ester **75** occurred *via* the predicted lithium-chelated intermediate to give **76** which has been converted into the terpene (+)-arisirene.[32] Similarly, a highly stereoselective cyclization of **77** to **78** was the key reaction in an elegant synthesis of the *aconitium* alkaloid atisine.[33] A Lewis acid catalysed double Michael reaction of **80** was used as the key step in a synthesis of tylophorine.



Scheme 19

Using a phenylmenthyl ester as a chiral auxiliary, intermediate **81** was formed as a single stereoisomer and converted into tylophorine **82** in enantiomerically pure form.[34] This group have also used double Michael reactions in approaches to steroids,[35(a,b)] triquinanes,[35(c)] and quinolizidine alkaloids.[31]

A quite spectacular approach to seychellene involved a triple Michael reaction (**Scheme 20**).[36] Hagiwara *et al.* reacted **83** and **84** together under Lewis acid conditions and obtained, in a single step, seychellene precursor **87** in 43% yield. The reaction presumably proceeds *via* intermediates **85** and **86**.

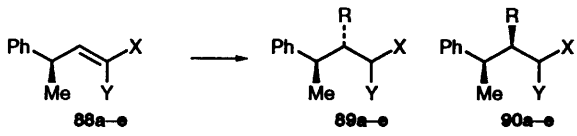


Scheme 20

4 Conjugate addition to acyclic α,β-unsaturated systems bearing a chiral centre at the γ-position

4.1 Reactions with ester and amide chiral auxiliaries

Conjugate additions to cyclic α,β-unsaturated systems bearing a chiral centre at the γ-position are normally very predictable (see Section 3), but that is certainly not the case in acyclic systems, and indeed empirical results are quite confusing.[37-53] Yamamoto *et al.* reported additions of a range of nucleophiles to α,β-unsaturated systems of type **88a–e** (**Scheme 21**).[37] Addition of copper or copper-lithium reagents appeared to favour *anti* products from substrates with an *E*-alkene. Addition of copper-lithium reagents to *Z*-substrates or those with two electron-withdrawing groups generally favoured the *syn* product. Allyl tin reagents generally reacted with the opposite selectivity as did monocopper reagents on *Z*-alkenes. A modified Felkin transition state (**Figure 2a**) with the large phenyl group perpendicular to the alkene and the methyl group on the 'inside' accounts for the formation of the *anti* product from the *E*-alkene. Yamamoto suggested that this mode of reaction was favoured for nucleophilic attack, whereas reagents that react *via* an electron-transfer mechanism would attack predominantly *via* the arrangement in **Figure 2b**, to give the *syn* product as the major isomer. Interestingly, when *p*-dinitrobenzene was added to some of the copper-lithium reactions the stereoselectivity was switched. Heathcock found that TMS-enol ethers react with the *E*-unsaturated methyl ketone **88e**, in the presence of $TiCl_3$, to give *syn* adducts in a highly selective manner.[38]



a X = Y = CN	Bu_2CuLi	68%	9(68)*	:	91(32)*
	BuCu	72%	23(67)*	:	77(33)*
	Bu_3/AIBN/ Bu_3SnH	13%	82	:	18
	$SnBu_3$	52%	71	:	28
b X = Y = CO2Et	Bu_2CuLi	87%	8	:	92
	$BuCu.BF_3$	90%	74	:	26
	$Bu_2CuLi.BF_3$	67%	32	:	68
	$SnBu_3$	93%	96	:	4
c X = CO2Et Y = H	$Bu_2CuLi.BF_3$	90%	70	:	30
	$BuCu.BF_3$	82%	88	:	12
d X = H Y = CO2Et	$Bu_2CuLi.BF_3$	89%	30	:	70
	$BuCu.BF_3$	84%	74	:	26
e X = COMe Y = H	TMSO, R, $TiCl_3$		10	:	90

* Figures in ( ) are for reactions with added *p*-dinitrobenzene

Scheme 21

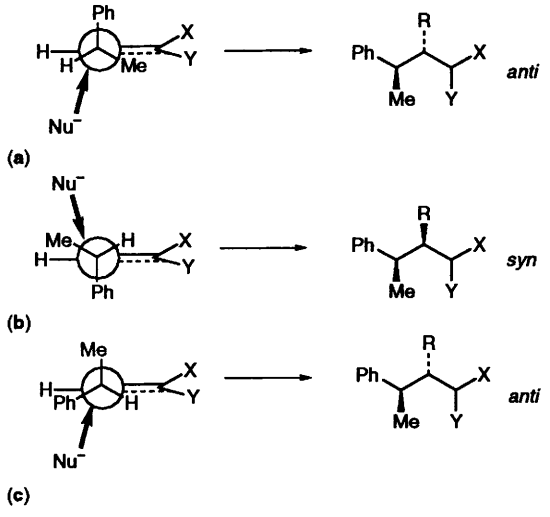
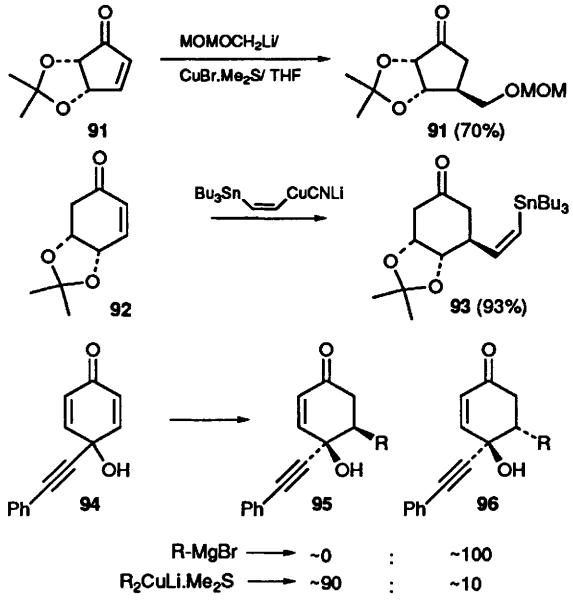


Figure 2 - Modified Felkin model

Morokuma *et al.*[40(a)] and Bernardi *et al.*[40(b)] have carried out molecular mechanics studies to try to account for the observed stereoselectivities of these reactions. They appear to agree that the modified Felkin model (**Figure 2a**) should be preferred for reactions of *E*-alkenes, but both groups have difficulty in accounting for the observed product ratios for the *Z*-alkenes and for the disubstituted alkenes. However, they agree that the 'inside' position of the methyl group is disfavoured and that reaction occurs *via* the arrangement in **Figure 2b** (leading to *syn* product) or that in **Figure 2c** (leading to *anti* product) and that the preference can be dependent upon the reagent, conditions, *etc.*

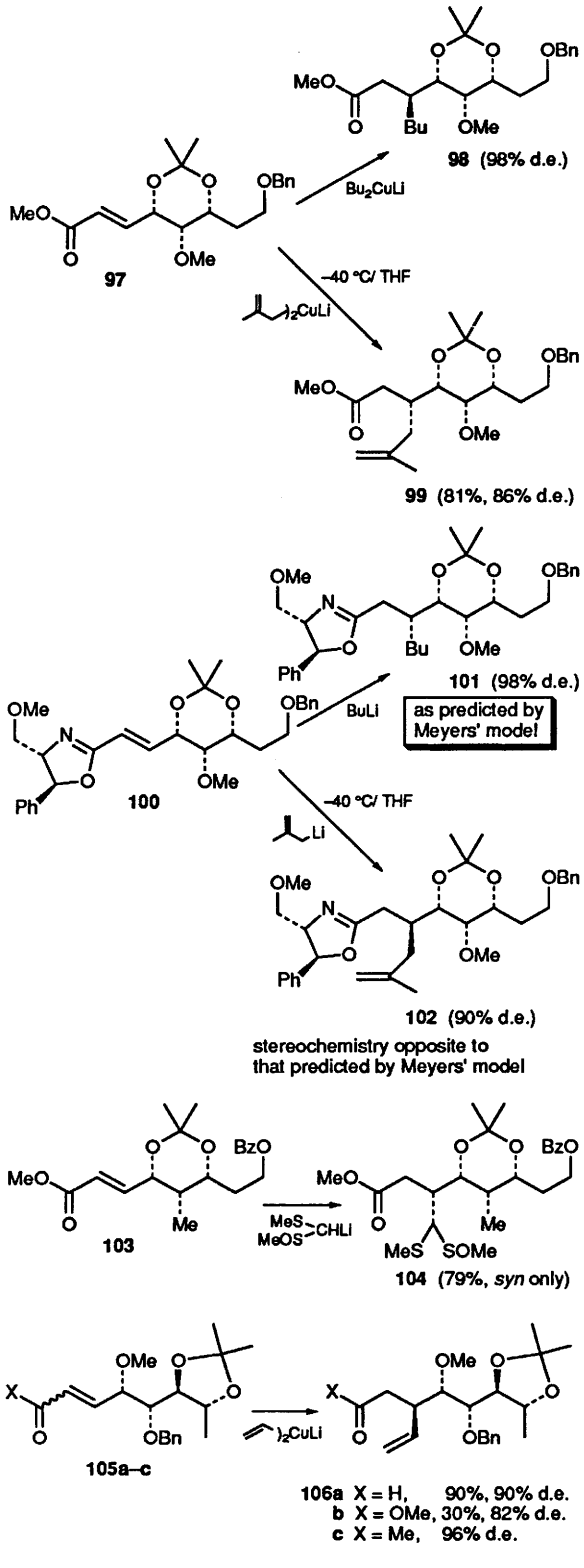
For γ-oxygenated α,β-unsaturated systems, some of the stereoselectivity preferences are even more

difficult to interpret. In contrast, addition of organometallic reagents to cyclic enones bearing an alkoxide at the γ-position is easy to rationalize. For example, cuprate-type reagents add from the opposite face to acetalized diol systems in both five-membered rings (*e.g.* **91**)[41(a)] and six-membered rings (*e.g.* **92**) (**Scheme 22**).[41(b)] In the case of alcohol **94**, chelation of Grignard reagents produced high selectivity for addition *syn* to the hydroxyl, whereas cuprates reacted *anti* to the hydroxyl.[41(c)] The steric preference of cuprates was also illustrated by their selective attack from the same face as oxygen rather than sulfur with a hemithioacetal substitutent in the γ-position.[41(d)]



Scheme 22

Some of the earliest investigations on conjugate additions of organometallic reagents to γ-alkoxy α,β-unsaturated sytems set the pattern that the stereoselectivity of such reactions is very difficult to rationalize (**Scheme 23**). Both Nicolaou[42] and Ziegler[43] investigated conjugate additions to carbohydrate derived ester **97**. They found that most copper-lithium reagents reacted with high selectivity (~ 90% d.e.) in favour of the *anti* addition product (*e.g.* **98**). Roush also found that compounds **105a–c** reacted with similar selectivity.[44] However, it was surprising that allylic cuprates reacted with **97** to give *syn* products (*e.g.* **99**) with high selectivity.[42,43] Unsaturated ester **103** also gave *syn* addition product **104** when reacted with a stabilized sulfoxide lithium reagent.[45] The *E*/*Z* geometry of the alkenes appeared to have little influence over the outcome of these reactions. Roush proposed a modified Felkin transition state to account for the addition of vinyl cuprates to these systems, but suggested that allyl reagents might be an exception.[44(a)] Ziegler *et al.* attempted to clarify the discrepancy by reacting **100** with allyl and butyl-lithium reagents. This substrate bears a chiral oxazoline unit which is also capable of directing an incoming organometallic reagent with predictable face

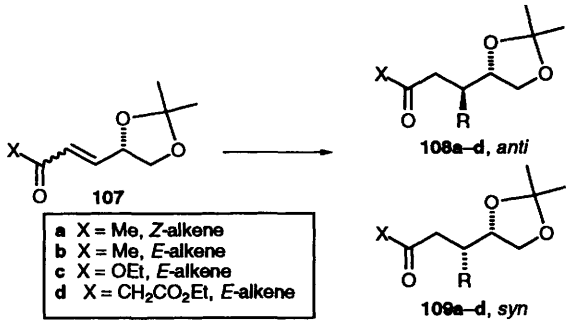


Scheme 23

selectivity (see Section 5 for examples of the use of this auxiliary). They found that butyl-lithium added with higher selectivity from the opposite face than Bu_2CuLi addition to **97**, with the facial selectivity predicted by Meyers' model for such oxazolines. It may have been that the oxazoline was simply overriding the effect of the γ-alkoxide, but unlike cases of very similar simple

oxazolines, allyl-lithium reagents again reacted with the opposite selectivity. Ziegler stated in 1981, 'it is apparent that subtle effects are operative and no simple analysis of reactive transition state conformations of the substrates could have predicted *a priori* the eventual outcome of these reactions'. It is still difficult to rationalize these results and those described below.

Cha and Lewis reported that the addition of Me_2CuLi to a glyceraldehyde derived enone **107a** gave the *anti* product with modest stereoselectivity,[46] but a more extensive study by Leonard *et al.* has again highlighted some anomalies (**Scheme 24**).[47] Both *E*- and *Z*-methyl ketones **107a** and **107b** gave the *anti* product as the major isomer when reacted with isopropenyl copper reagents, but the stereoselectivity was reversed with butyl reagents. It was surprising that both monocopper and most lithium reagents gave high yields of conjugate addition products, with the lithium reagents being highly *syn* selective. Lithium reagents also added in a conjugate manner to ester **107c** and ketoester **107d**, but again the stereoselectivity was puzzling. Most of the reactions were moderately *syn* selective, but



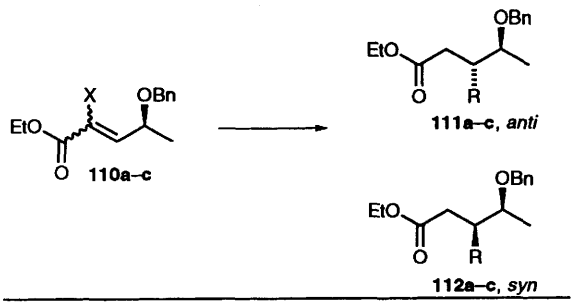
a X = Me, *Z*-alkene
b X = Me, *E*-alkene
c X = OEt, *E*-alkene
d X = CH_2CO_2Et, *E*-alkene

Reagent	1,4:1,2	Yield	*anti*		*syn*
X = Me, *Z*-alkene					
$CH_2(Me)CCu$	1:0	80%	8	:	1
$[CH_2(Me)C]_2CuLi$	1:0	60%	4	:	1
$[CH_2(Me)C]_2CuCNLi_2$	1:0	73%	7	:	1
X = Me, *E*-alkene					
[209]Me_2CuLi	1:0	56%	4	:	1
$CH_2(Me)CCu$	1:0	80%	5		1
$[CH_2(Me)C]_2CuLi$	1:0	60%	3	:	1
Bu^nCu	1:0	70%	1	:	1.5
$Bu^n{}_2CuLi$	1:0	50%	1	:	3
$CH_2(Me)CLi$	19:0	60%	1	:	36
Bu^nLi	2.5:0	76%	1	:	15
PhLi	1:10	76%	2	:	1
X = OEt, *E*-alkene (solvent -Et_2O)					
$CH_2(Me)CLi$	3:1	65%	1	:	5
Bu^nLi	6.5:1	66%	1	:	6
MeLi	6:1	70%	1	:	6
X = CH_2CO_2Et, *E*-alkene (solvent - THF)					
$CH_2(Me)CLi$	25:1	82%	1	:	4
Bu^nLi	3:1	66%	2	:	1
PhLi	1:0	61%	12	:	1

Scheme 24

butyl-lithium added to **107d** with a slight preference for the *anti*-isomer and phenyl-lithium gave high *anti* selectivity. It was intriguing that phenyl-lithium gave only 1,2-addition with **107b** and only conjugate addition with **107d**. Addition of a silicon radical to ester **107c** has recently been reported to take place with 82% d.e. on the *Z*-alkene and 40% d.e. on the *E*-alkene, but the configuration of the major adduct was not determined.[48]

Yamamoto carried out an extensive study of cuprate additions to simple γ-benzyloxy enoates **110a–c** (**Scheme 25**).[49] The *E*-enoate generally reacted with *anti* selectivity, whereas the diester was generally *syn* selective. The selectivity of the *Z*-alkene was variable and the allyl reagent shows some inconsistency with the others, but not the dramatic change noticed for additions to **97**. It was also found that t-butyldimethylsilyl ethers react with almost identical selectivities, indicating that chelation is not an important factor.[49(b)]

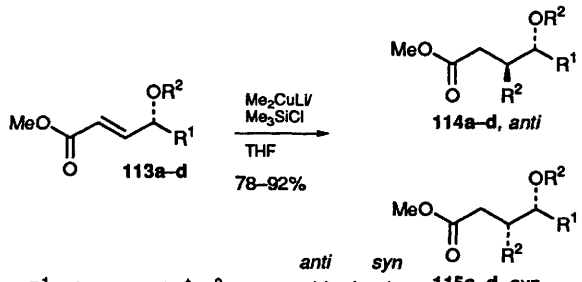


Reagent	Yield	*anti*		*syn*
a X = H, *E*-alkene				
$(CH_2{=}CH)_2CuLi$	99%	72	:	28
$(CH_2{=}CH)_2CuLi.BF_3$	58%	96	:	4
$(CH_2{=}CH)_2CuCNLi_2$	83%	72	:	28
$(CH_2{=}CH)_2CuCNLi_2.BF_3$	66%	95	:	5
$MeCu.BF_3$	60%	69	:	31
$BuCu.BF_3$	64%	92	:	8
$[CH_2{=}CHCH_2]_2CuLi$	99%	42	:	58
b X = H, *Z*-alkene				
$(CH_2{=}CH)_2CuLi$	82%	>99	:	1
$(CH_2{=}CH)_2CuLi.BF_3$	63%	52		48
$(CH_2{=}CH)_2CuCNLi_2$	58%	96	:	4
$(CH_2{=}CH)_2CuCNLi_2.BF_3$	64%	21	:	79
$MeCu.BF_3$	30%	22	:	78
$BuCu.BF_3$	56%	22	:	78
$[CH_2{=}CHCH_2]_2CuLi$	99%	20	:	80
c X = CO_2Et				
$(CH_2{=}CH)_2CuLi$	91%	38	:	62
$(CH_2{=}CH)_2$-$CuLi.BF_3$	91%	39	:	61
$(CH_2{=}CH)_2$-$CuCNLi_2$	94%	29	:	71
$(CH_2{=}CH)_2$-$CuCNLi_2.BF_3$	96%	31	:	69
$MeCu.BF_3$	54%	6	:	94
$BuCu.BF_3$	52%	5	:	95
$[CH_2{=}CHCH_2]_2CuLi$	79%	10	:	90

Scheme 25

Hanessian has shown that γ-alkoxy enoates **113a–d** react with Me_2CuLi/TMS-Cl with consistently high *anti* selectivity (**Scheme 26**). However, the stereoselectivity was reduced slightly when the δ-siloxy group was

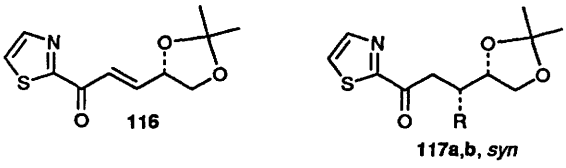
replaced by a methyl group. When the same reaction conditions were applied to enolates bearing a nitrogen group in the γ-position *syn* products were formed selectively.[50]



	anti		syn
a $R^1 = CH_2OSiPhBu^t$, R^2 = BOM	14	:	1
b $R^1 = CH_2OSiPhBu^t$, R^2 = MOM	11	:	1
c $R^1 = CH_2OSiPhBu^t$, R^2 = Me	10	:	1
d $R^1 = CH_3$, R^2 = BOM	2	:	1

Scheme 26

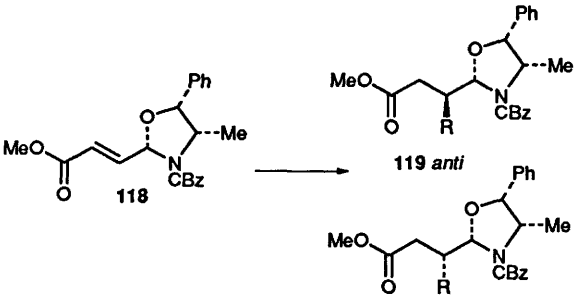
It has also been shown that glyceraldehyde derived systems, for example **116**, react with nitrogen and oxygen nucleophiles with a high degree of *syn* selectivity (**Scheme 27**).[51]



$PhCH_2ONa$ ⟶ 87%, 80% d.e.
$PhCH_2NH_2$ ⟶ 87%, 80% d.e.

Scheme 27

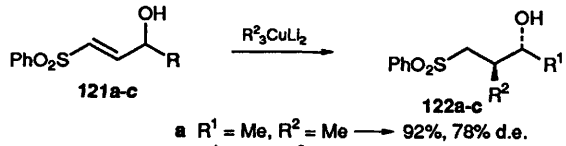
Bernardi and Scolastico have studied a range of conjugate additions on oxazolidine **118**, and found a generally high consistency for *anti* selectivity (with respect to oxygen). The stereochemistry at the γ-position appears to be the controlling factor (**Scheme 28**).[52]



	anti		syn
Me_2CuLi	14	:	1
Bu_2CuLi	11	:	1
$[CH_2{=}CH]_2CuLi$	10	:	1
$[CH_2{=}CH]_2CH_2CuLi$	95	:	5
BnO^-Na^+	95	:	5

Scheme 28

Higher order cuprates (R_3CuLi_2) have also been found to react in a highly stereoselective manner with γ-hydroxy-α,β-unsaturated sulfones **121a–c** (**Scheme 29**). Again the major isomer had an *anti* arrangement between the hydroxyl and the added alkyl group.[53]



a R^1 = Me, R^2 = Me ⟶ 92%, 78% d.e.
b $R^1 = Bu^n$, R^2 = Me ⟶ 90%, 84% d.e.
c $R^1 = Pr^i$, $R^2 = Bu^n$ ⟶ 91%, 82% d.e.

Scheme 29

Roush originally suggested a modified Felkin model,[44(a)] with the small group (H) adopting the 'inside' position (**Figure 3a**), to account for the more common *anti* addition of cuprates to γ-alkoxy-α,β-unsaturated systems. Other workers initially adopted this model and Leonard *et al.* suggested a chelated modification to account for the *syn* selectivity of lithium reagents,[47(a)] although the *syn* addition of allyl cuprates could not be accounted for. Morokuma *et al.*[40(a)] and Bernardi *et al.*[40(b)] have attempted to account for the observed stereoselectivities through molecular mechanics studies, but their conclusions differ.
Bernardi *et al.* suggested that a Felkin-type transition state (**Figure 3b**) accounts for the *syn* selectivity of lithium reagents and alkoxides, and that *anti* addition of certain cuprates may be caused by chelation. However, chelation of cuprates and not lithium reagents would appear to be unlikely, especially in the light of Yamamoto's results with silyl ethers.

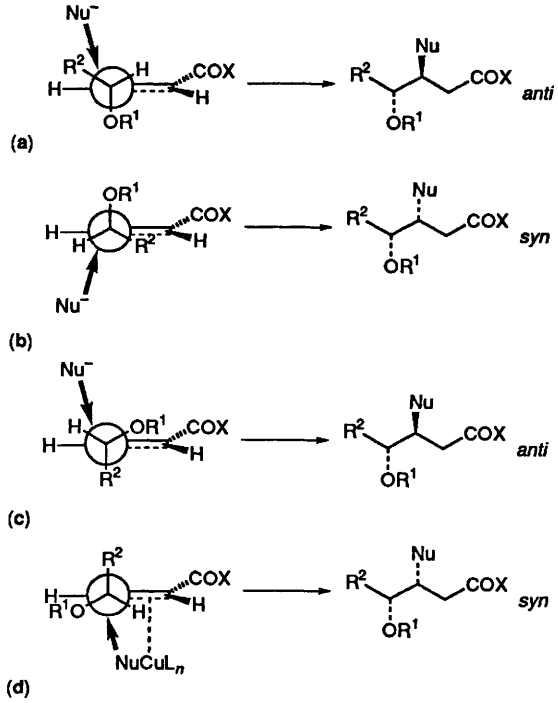
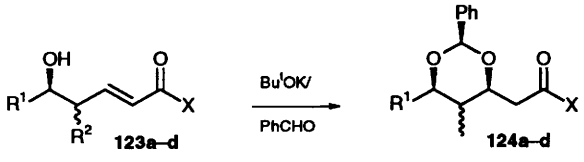


Figure 3

Morokuma *et al.* suggested a transition state with the alkoxide in the inside position (**Figure 3c**) to account for the *anti* attack of most cuprates on *trans*-alkenes. Leonard *et al.* have also proposed a similar arrangement based on the lowest energy ground state conformation of **107a** and again suggest that chelation of lithium reagents could lead to directed *syn* addition.[47(b)] Yamamoto *et al.* suggested several models to account for the results in **Scheme 25**.[49(b)] They concur that the model in **Figure 3c** could account for the *anti* attack of most cuprates on *trans*-alkenes, but suggest that some cuprates react preferentially *via* a π-complex, as in **Figure 3d**, leading to *syn* adducts. Overall, there is no universal model to account for the array of observed selectivities for additions of nucleophiles to γ-alkoxy-α,β-unsaturated systems. There are several unusual anomalies and none of the models proposed so far are really satisfactory.

Although not strictly related to the other reactions in this section, Evans has reported that efficient 1,3-asymmetric induction can occur *via* conjugate addition directed by a hydroxyl at the δ-position on an acyclic chain.[54] Some examples are shown in **Scheme 30**. The reaction process is simple and the structure of substrate **123** appears to be very general. A methyl group of either configuration at position R^2 appears to have little effect on the outcome or stereoselectivity of the reaction and a range of other groups along the chain can also be tolerated.



R^1 = Et, R^2 = H, X = OMe	79%, 90%d.e.
R^1 = Pr^i, R^2 = H, X = OMe	71%, 90%d.e.
R^1 = $PhCH_2CH_2$, R^2 = H, X = OMe	73%, 92%d.e.
R^1 = Pr^i, R^2 = H, X = N(Me)OMe	71%, 90%d.e.

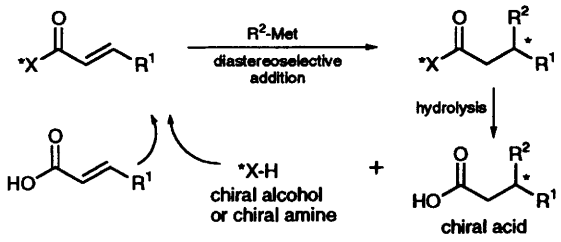
Scheme 30

5 Conjugate additions to α,β-unsaturated systems with chirality in the electron-withdrawing group

5.1 Conjugate additions to α,β-unsaturated esters and amides derived from chiral alcohols and chiral amines

A variety of organometallic reagents add to α,β-unsaturated esters and amides in a conjugate manner. If the alcohol or amide from which the system is derived is a chiral unit there is potential for asymmetric induction. Hydrolysis would then release the original chiral auxiliary group as well as a chiral acid (**Schemes 31 and 32**).

Esters generally have a practical advantage over amides in that they are easier to hydrolyse, and a wide range of chiral alcohols have therefore been investigated as auxiliaries. Addition of organo-copper-lithium reagents to esters is often an inefficient process but Oppolzer *et al.*[56] found that



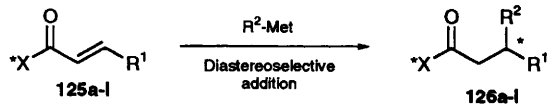
Scheme 31

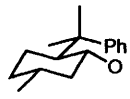
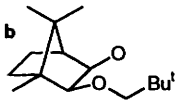
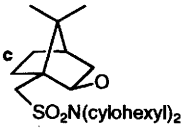
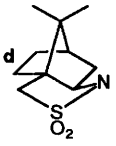
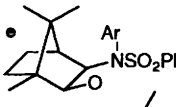
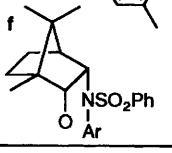
monocopper reagents (RCu) with added $F_3B.OEt_2$ and PBu_3 react with esters of phenylmenthol **125a** in a highly diastereoselective manner. Even when reactions of this sort give high levels of diastereoselectivity it is useful to be able to purify the addition product to a single diastereoisomer before removal of the auxiliary, to provide the final product in enantiomerically pure form. For this reason the use of camphor auxiliaries has been examined because they are generally highly crystalline, allowing the initial addition product to be purified efficiently by simple crystallization.[55] Neopentyloxy esters **125b** reacted with generally good facial selectivity with copper reagents and this auxiliary has been used successfully in several natural product syntheses.[57] Either enantiomer of the auxiliary is available and the mode of attack is indicated in **Scheme 33**, showing how isopropenyl copper reacted with **127** as the key step in a synthesis of California-red-scale pheromone **129**.

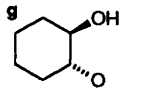
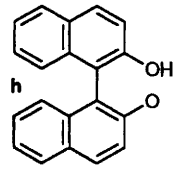
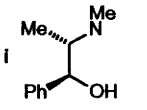
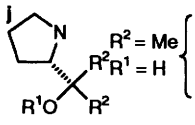
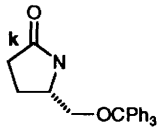
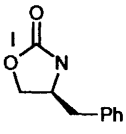
Ester dienolate **130** also reacted with good facial selectivity as a nucleophile in a conjugate addition to cyclopentenone. The enolate generated was reacted *in situ* with allyl bromide to give **131** which was then used as a sesquiterpene precursor (**Scheme 34**).

Sulfonamide esters **125c**, and their enantiomers, also reacted with high diastereoselectivity, but are considered to be more practical than those above because of their ease of preparation and high crystallinity. The mode of reaction of these esters is shown in **Scheme 35**, which illustrates a route to southern corn rootworm pheromone **134**.[58]

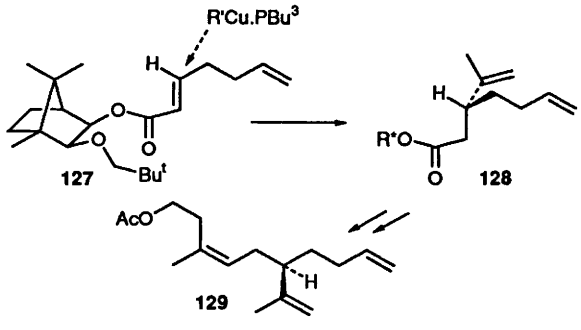
Oppolzer *et al.* also developed the sultam auxiliary **125d** for Diels–Alder reactions initially, but it has proved very useful for conjugate additions.[59] Although an amide bond connects the auxiliary, it is very easily cleaved with LiOH with complete recovery of the auxiliary. The auxiliary is also installed very easily, its derivatives are highly crystalline and hence it is one of the most practical of all the chiral auxiliaries that have been developed, for any purpose, to date. It was discovered that Grignard reagents add very effectively to the sultam enoates and that the stereoselectivity of addition is defined by a chelated transition state (**Scheme 36**). As well as simple conjugate additions, tandem addition–electrophile-trapping reactions have also been achieved with good stereoselectivity at both α- and β-positions. The outcome of the reaction depends on the original substituents present and on whether the intermediate magnesium enolates (*e.g.* **136** or **138**) are protonated or alkylated. Alkylation of **136** leads to **137**, while protonation of **138** leads to **139**. The enoates (*e.g.* **140**) also undergo



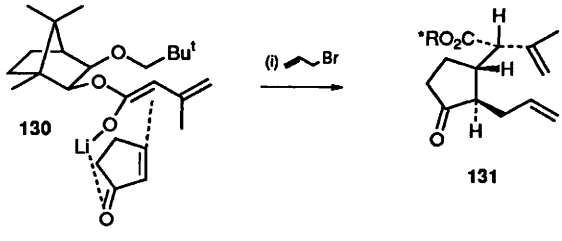
Auxiliary (X*)	R^1	R^2-Met	Yield	d.e.	*R/S*
a 	*trans* Me	$PhCu.BF_3$	76%	>99%	*R*
	trans Me	$Bu^nCu.BF_3$	75%	>99%	*R*
	cis Me	$PhCu.BF_3$	36%	24%	*R*
	trans Bu	$MeCu.BF_3$	96%	87%	*R*
b 	*trans* Bu	$MeCu.BF_3$	82%	94%	*R*
	trans Me	$CH_2{=}CHCu.BF_3$	85%	94%	*R*
	trans Et	$MeCu.BF_3$	85%	92%	*R*
c 	*trans* Me	$Bu^nCu.BF_3$	89%	97%	*S*
	trans Me	$CH_2{=}CHCu.BF_3$	80%	98%	*R*
	trans Bu	$MeCu.BF_3$	93%	97%	*R*
d 	Me_2PhSi	$MeCu.BF_3$	61%	86%	
	Me_2PhSi	$BuCu.BF_3$	61%	92%	
	Me_2PhSi	$PhCu.BF_3$	86%	94%	
	trans Me	EtMgCl	85%	90%	*R*
	trans Me	Bu^nMgCl	82%	84%	*R*
e 	*trans* Me	$EtCu.BF_3$	90%	99%	*R*
	trans Me	$CH_2{=}CHCu.BF_3$	94%	99%	*S*
	trans Me	$PhCu.BF_3$	97%	99%	*S*
f 	*trans* Me	$EtCu.BF_3$	84%	99%	*S*
	trans Me	$CH_2{=}CHCu.BF_3$	81%	99%	*R*
	trans Me	$PhCu.BF_3$	94%	99%	*R*

Auxiliary (X*)	R^1	R^2-Met	Yield	d.e.	*R/S*
g 	*trans* Me	Bu_2CuLi	91%	88%	*R*
	trans Me	Ph_2CuLi	96%	99%	*R*
	trans Ph	Me_2CuLi	71%	84%	*S*
h 	*trans* Ph	Me_2CuLi	84%	87%	*R*
	trans Ph	Bu_2CuLi	71%	58%	
	trans Ph	MeMgBr.CuI	73%	48%	*S*
	trans Ph	EtMgBr.CuI	38%	20%	
i 	*trans* Me	EtMgBr	58%	98%	*S*
	trans Bu	PhMgBr	54%	99%	*R*
	trans Ph	EtMgBr	47%	98%	*R*
j 	*trans* Me	BuMgBr	29%	84%	*S*
	trans Ph	BuMgBr	49%	100%	*S*
	trans Ph	EtMgBr	51%	88%	*S*
k 	*trans* Me	EtMgCl	75%	80%	*R*
	trans Bu	PhMgBr	77%	96%	*S*
	trans Ph	$CH_2{=}CHMgBr$	90%	85%	*S*
l 	*trans* Me	Et_2AlCl		70%	*R*
	trans Ph	Et_2AlCl		78%	*S*
	trans Ph	Me_2AlCl		84%	*S*

Scheme 32



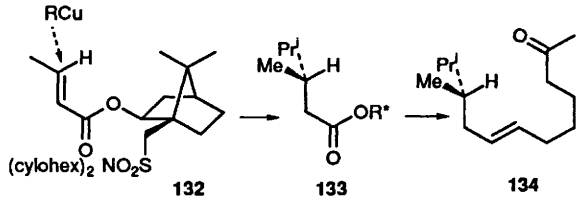
Scheme 33



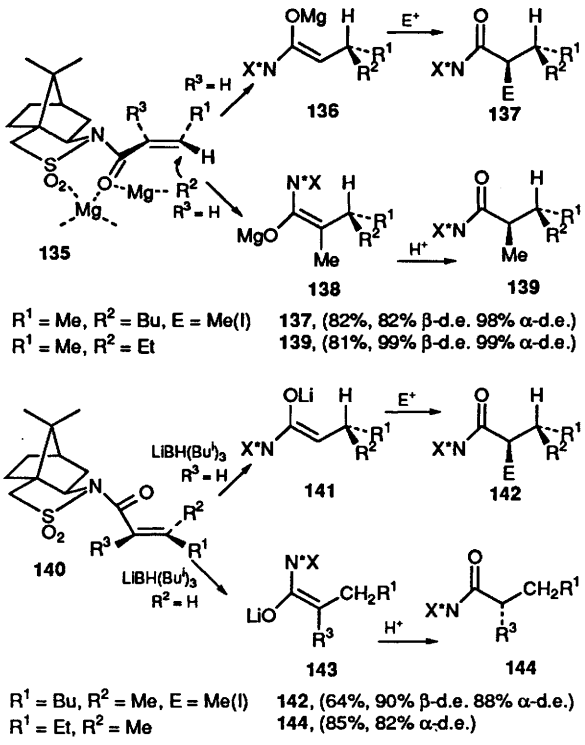
Scheme 34

stereoselective conjugate reduction with lithium tri-s-butylborohydride and again the lithium enolate intermediate **141** or **143** can either be protonated or trapped with electrophiles selectively as shown.

Helmchen *et al.* have developed **125e** and **125f** as useful camphor derived auxiliaries, which react to give products with opposite configuration at the newly formed centres.[60] Again their enoates react with high

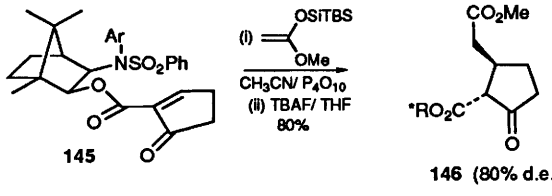


Scheme 35



Scheme 36

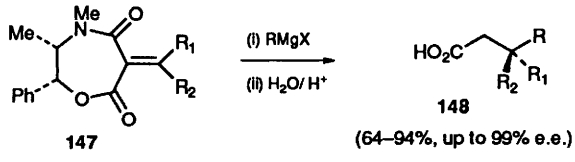
levels of selectivity with copper reagents.[60(a,b)] Recently **145** has been reacted with silylated ester enolates in the presence of a P_4O_{10} catalyst to provide chiral 2,3-disubstituted cyclopentanones **146** in good overall yield (**Scheme 37**).[60(c)]



Scheme 37

Fang *et al.* have reported that enoates, such as **125g**, derived from quite simple diols can give high levels of diastereoselectivity when reacted with copper-lithium reagents.[61] Fuji *et al.* found that both copper-catalysed Grignard reagents and copper-lithium reagents react with reasonable diastereoselectivity with mono-enoates derived from binaphthol **125h**.[62] These two classes of reagent react with opposite face selectivity because of different internal chelation effects. Fleming *et al.* showed that several of the enoates in **Scheme 32** react selectively with phenyldimethylsilyl copper-lithium, allowing the introduction of a chiral centre at silicon.[63(a)] More recently, Polomo *et al.* have shown that higher order silicon cuprates react with sultam derived enoates with a high degree of selectivity.[63(b)] d'Angelo has also shown that amines react with enoates bearing chiral auxiliaries to give addition products with d.e.s. in the range of 75–95%.[64]

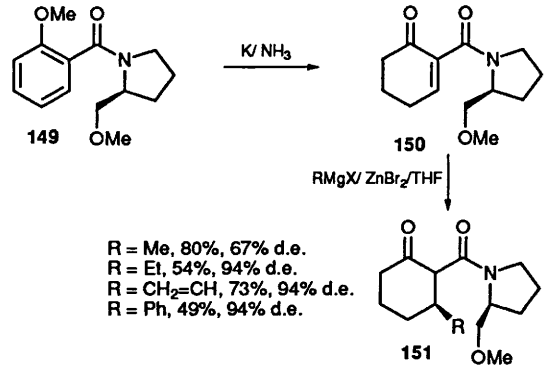
Mukaiyama and Iwasawa found that simple enamides **125i**, derived from ephedrine, add Grignard reagents in a conjugate manner with good diastereoselectivities.[65(a)] A chelated magnesium alkoxide is believed to be responsible for the high levels of stereoselectivity. More recently, Touet *et al.* found that derivatives of the very cheap chiral amine 2-aminobutanol are also very effective auxiliaries.[65(b,c)] Mukaiyama also found that oxazepines **147**, derived from ephedrine, undergo conjugate addition of Grignard reagents with very high facial selectivity, leading to chiral acids with high e.e. on hydrolysis (**Scheme 38**). The drawback with this technique is that the oxazepine is difficult to prepare and is destroyed on the final hydrolysis.[66]



Scheme 38

Soai *et al.* have investigated conjugate additions on several enamides bearing auxiliaries derived from proline and prolinol (*e.g.* **125j**).[67] They achieved fairly good d.e.s. with moderate yields using prolinol derivatives, but the stereoselectivities were not as good using derivatives of proline itself.[67(c)] In either case addition of tertiary amines improved the selectivities. Tomioka *et al.* achieved fairly good diastereoselectivity through conjugate Grignard additions to trityl prolinol derived enamides **125k**.[68]

An interesting use of an *O*-methyl prolinol auxiliary was reported by Schultz and Harrington.[69] A Birch-type reduction of **149** gave enamide **150** which reacted with Grignard reagents, in the presence of $ZnBr_2$, with good facial selectivity (**Scheme 39**).

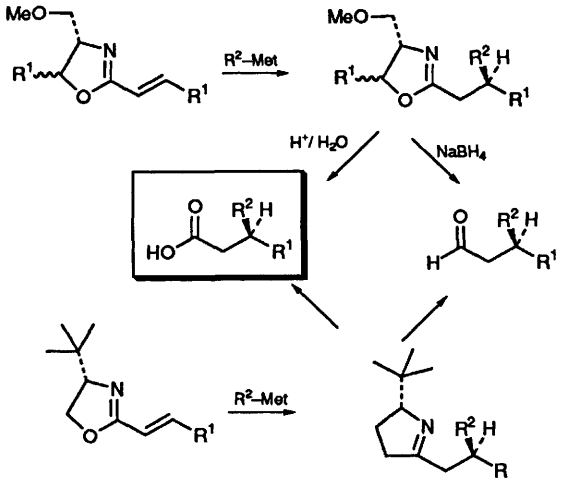


Scheme 39

Oxazolidinone derived enamides **125l** have recently been reacted with alkyl aluminium chlorides with moderate diastereoselectivity,[70] and Cardilo *et al.* have chlorinated similar enamides, although the diastereoselectivity was poor.[71]

5.2 Chiral auxiliaries based on oxazolines and imines

Meyers was one of the pioneers in the use of chiral auxiliaries for creating new chiral centres with high stereoselectivity. In particular, his group were one of the first to develop effective methods for obtaining products with high enantiomeric excess *via* conjugate addition reactions. In order to increase the rigidity of the transition state for the addition they used an oxazoline ring as an equivalent masked form of an acid. The oxazoline ring conveniently holds the chiral auxiliary and, after the conjugate addition, it is released by hydrolysis to unmask the acid unit, or by reduction to provide an aldehyde (**Scheme 40**).[72,73]



Scheme 40

It was discovered that the stereochemistry of the conjugate addition was governed largely by the stereochemistry of the group α-to the nitrogen in the oxazoline. In early studies this was normally a chelating methoxymethyl group. It was found that organometallic reagents react with high selectivity from the face opposite the methoxymethyl group. This was attributed to that face being hindered by chelation, as shown in **Figure 4(a)**.

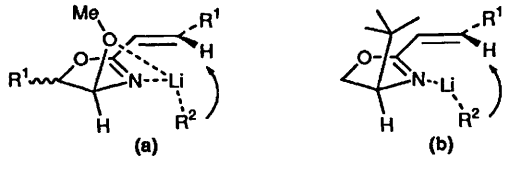
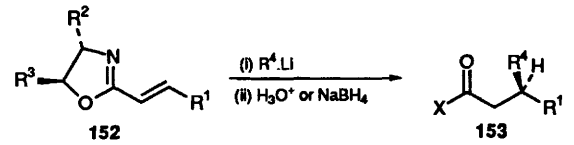


Figure 4

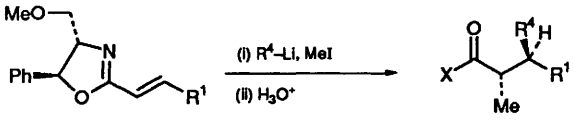
In more recent studies a bulky group in the same position proved to be equally effective in controlling the stereochemistry of addition to the same face (**Figure 4(b)**.[75] Some examples of conjugate additions that have been carried out are shown in **Scheme 41**. The absolute stereochemistry at the new chiral centre can be controlled by reversing the groups attached to the alkene and of the organometallic reagent. The intermediate enolate ion can also be methylated with a high degree of stereoselectivity.[74]

Tomioka *et al.* carried out similar studies to those of Meyers, using imines instead of oxazolines, but the



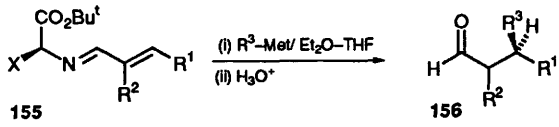
152 153

Auxiliary (X*)	R¹	R⁴–Met	X	Yield	d.e.	R/S
a	Me	EtLi	OH	40%	92%	R
	Me	Bu^{n}Li	OH	38%	91%	R
	Me	PhLi	OH	44%	98%	S
	Cyclohexyl	EtLi	OH	73%	99%	R
	Ph	EtLi	OH	66%	97%	R
b	Bu^n	PhLi	H	53%	97%	S
	Cyclohexyl	PhLi	H	60%	96%	R
	Ph	Bu^{n}Li	H	53%	96%	R



152a 154

Scheme 41



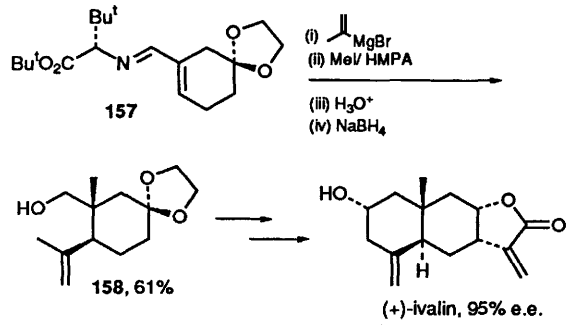
155 156

X	R¹	R²	R³–Met	Yield	d.e.	R/S
Pr^i	Me	H	PhMgBr	49%	65%	R
Bu^t	Me	H	PhMgBr	42%	91%	R
Bu^t	Ph	H	EtMgBr	56%	95%	S
Bu^t	-(CH$_2$)$_3$-		PhLi	82%	82%	
Bu^t	-(CH$_2$)$_3$-		CH$_2$=CHLi	36%	71%	
Bu^t	-(CH$_2$)$_4$-		PhLi	52%	49%	
Bu^t	-(CH$_2$)-		CH$_2$=CHLi	31%	69%	

Scheme 42

e.e.s were generally somewhat lower (**Scheme 42**).[75(c)] Again, a chelated transition state was proposed to account for the high levels of stereoselectivity.

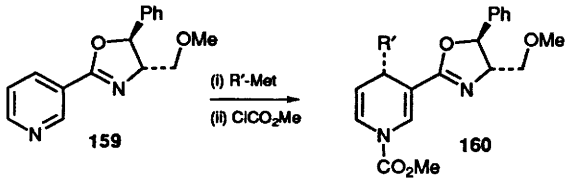
They also found that the intermediate enolates could be alkylated *in situ* with good stereochemical control.[76] An example of one such trapping reaction is shown in **Scheme 43**, which was part of a synthesis of (+)-ivalin.



157 158, 61% (+)-ivalin, 95% e.e.

Scheme 43

Meyers *et al.* found that the chiral oxazoline activated certain aromatic and heteroaromatic rings towards nucleophilic attack and led to induced chirality at the chiral centre formed by the nucleophile.[77] Some examples of nucleophilic additions to 3-substituted pyridines are shown in **Scheme 44**. Alexakis *et al.* have extended this methodology, using an alternative heterocyclic auxiliary and used it in approaches to indole alkaloids.[78]



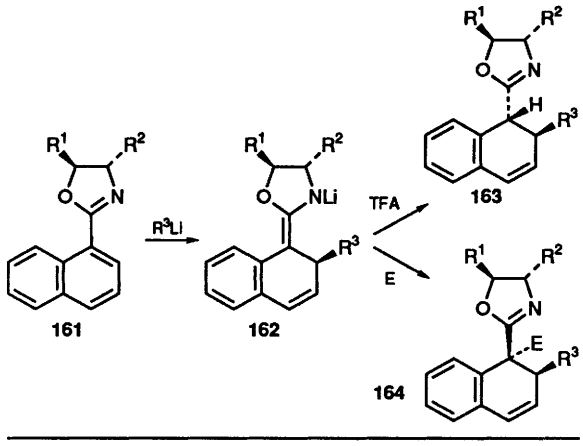
R'-Met	Yield	d.e.	*R/S*
MeLi	79%	88%	*S*
Bu^nMgCl	98%	90%	*S*
PhLi	94%	84%	*S*
PhLi	82%	82%	

Scheme 44

An oxazoline substituent activates naphthalene rings towards nucleophilic addition of lithium reagents, and it was found that such additions can be highly stereoselective with respect to chiral centres in the oxazoline. The anion formed on addition of the lithium reagent is an effective nucleophile and can be trapped by a range of electrophiles. If the intermediate anion is simply protonated the oxazoline ends up *trans* to the nucleophile, whereas trapping with electrophiles leads to a *cis* relationship between the nucleophile and the oxazoline ring. **Scheme 45** shows some representative examples of this type of reaction.[79]

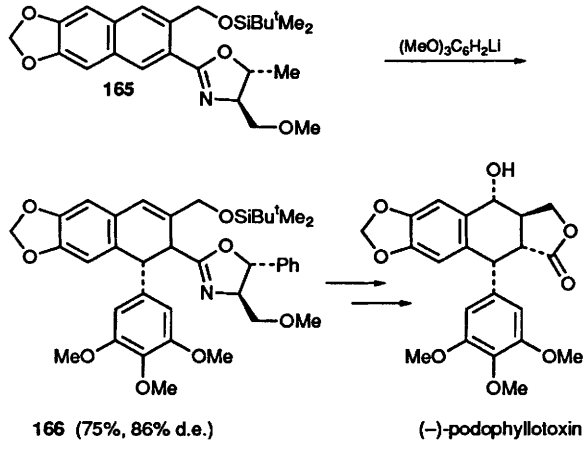
This methodology has been used in several natural product syntheses.[80] A neat example of how it has been exploited is illustrated by the synthesis of podophyllotoxin, as outlined in **Scheme 46**.[80(a)]

It was also found that similar additions to naphthalenes could be carried out using t-butyl substituted imines, rather than oxazolines, as the chiral activating agent.[81] A useful approach to chiral biaryls involves nucleophilic substitution of a methoxyl group *ortho* to an oxazoline ring (**Scheme 47**).[74,82] Diastereoselectivity of the reactions is usually high and is normally governed by the reaction proceeding through the transition state with minimum interaction between the substituents on the nucleophilic ring and the oxazoline substituents. An example is the reaction between Grignard reagent **167** and oxazoline **168** which gives **169** with 87% d.e. An exception to this mode of stereocontrol occurs where there is an alkoxide group on the nucleophilic ring which can chelate with the magnesium in the transition state complex. This results in the opposite stereochemistry at the new chiral centre, as illustrated by the reaction between Grignard reagent **170** and oxazoline **168**.[74] Highly substituted aromatic systems are tolerated in the coupling process and several approaches to natural products have been based on this methodology.[82] An example was the coupling between Grignard reagent



Auxiliary	Naphth.	R^3Li	E	Yield	d.e.	Prod
MeO, Ph (a)	1-	MeLi	H^+	42%	70%	163
	1-	Bu^nLi	H^+	73%	88%	163
	1-	PhLi	H^+	62%	70%	163
	1-	Bu^nLi	Me(I)	97%	88%	164
	1-	Bu^nLi	PhS(SPh)	99%	94%	164
	1-	Bu^nLi	$MeO_2C(Cl)$	42%	70%	164
	1-	CH_2=CHLi	Me(I)	80%	60%	164
	2-	Bu^nLi	Me(I)	85%	96%	164
	2-	PhLi	Me(I)	89%	80%	164
(b)	1-	Bu^nLi	Me(I)	99%	98%	164
	2-	PhLi	Me(I)	81%	90%	164
	1-	CH_2=CHLi	Me(I)	94%	98%	164

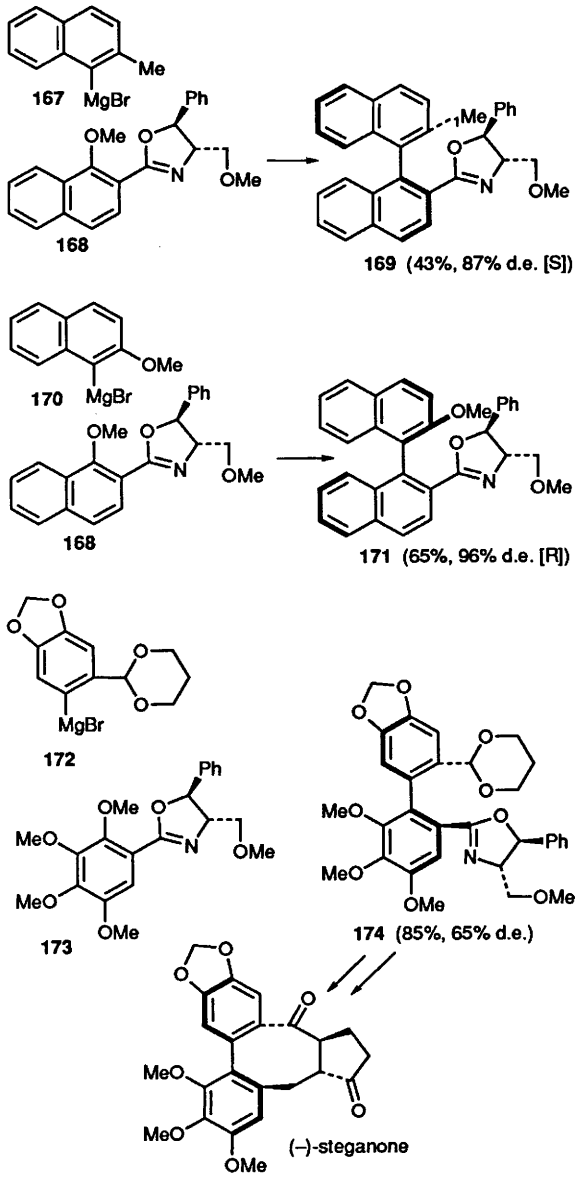
Scheme 45



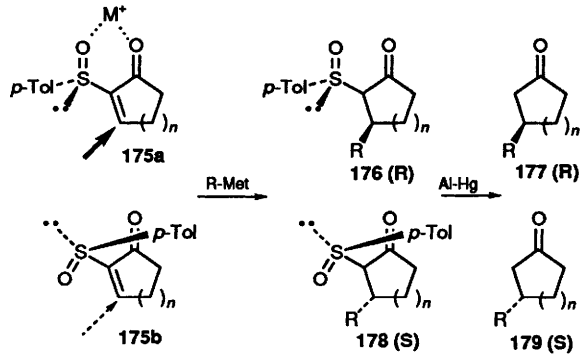
Scheme 46

172 and oxazoline **173** which provided steganone precursor **174** as an 88:12 mixture with its diastereoisomer.[82(b)]

α,β-Unsaturated chiral acetals,[83] and chiral oxazolidines,[84] can be reacted with nucleophiles in conjugate (S_N2') fashion, with induction of chirality at the newly formed chiral centres. These reactions are related to those covered in this section, but will not be described in this review.



Scheme 47



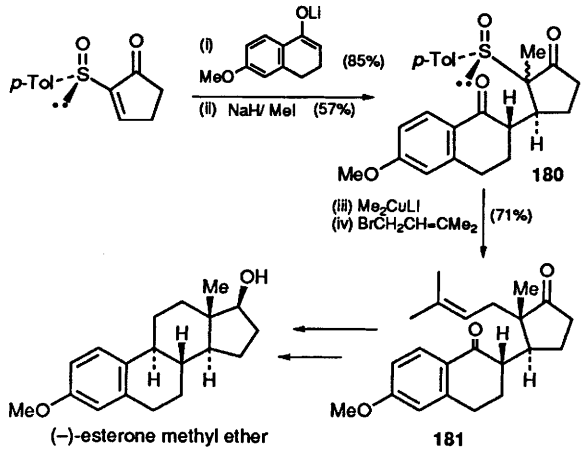
	n	R-Met	Yield	e.e.	R/S
non-chelated	1	Me_2Mg	60%	97%	S
	1	Et_2Mg	81%	81%	S
	1	Ph_2Mg	50%	79%	S
	2	Me_2Mg	50%	79%	S
chelated	1	MeMgCl	91%	98%	R
	1	$EtTi(OPr^i)_3$	67%	98%	R
	1	CH_2=CHMgBr/ $ZnBr_2$	75%	99%	R
	1	PhMgCl/ $ZnBr_2$	70%	92%	R
	2	MeLi/ $TiCl(OPr^i)_3$	83%	96%	R
	2	PhLi/ $TiCl(OPr^i)_3$	58%	93%	R

Scheme 48

$ZnBr_2$, leads to reaction *via* chelated intermediate **175a** which is hindered on the lower face and therefore reacts to provide (*R*)-addition products **176**(*R*) selectively. The sulfoxide unit is easily removed by Al-Hg reduction, providing **177** or **179**.

A range of nucleophiles have been used in these additions and the intermediate α-enolate can be reacted with electrophiles, ether *in situ* or during a subsequent step.[86(b)] The methodology has been used in several neat steroid syntheses, including the route to esterone methyl ether outlined in **Scheme 49**.[86(c)]

Wallace *et al.* synthesized chromones with the tolysulfinyl group in the 3-position and found that copper-lithium reagents add to them, leading to 2-alkyl chroman-4-ones with high e.e.[87]

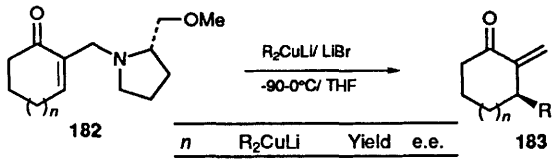


Scheme 49

5.3 Conjugate addition to α,β-unsaturated systems bearing a chiral sulfoxide at the α-position

Although a chiral auxiliary at the α-position can provide effective chiral induction during conjugate additions, removal of the auxiliary might be difficult. α,β-Unsaturated sulfoxides themselves do not react with nucleophiles in a conjugate manner, but Posner *et al.* have shown that the sulfoxide is an excellent chiral auxiliary in the α-position of α,β-unsaturated ketones.[85,86] It was discovered that, depending on reaction conditions, one sulfoxide stereoisomer **175** could direct nucleophiles to either face of cyclic α,β-unsaturated systems. The ground state conformations of the (*S*)-sulfoxides **175** (five and six-membered rings) are similar to **175b** (**Scheme 48**). Nucleophiles will attack this conformation from the lower face and the products will be **178**(*S*). On the other hand, the addition of chelating agents, such as

Another example of a chiral auxiliary in the α-position has recently been reported by Yamamoto *et al.* They found that prolinol methyl ether derivatives, such as **182**, reacted with copper-lithium reagents in a highly diastereoselective manner. The chiral auxiliary was eliminated during the reaction to leave a potentially useful α-methylene group **183** (**Scheme 50**). Acyclic systems reacted with somewhat lower selectivity.[88]

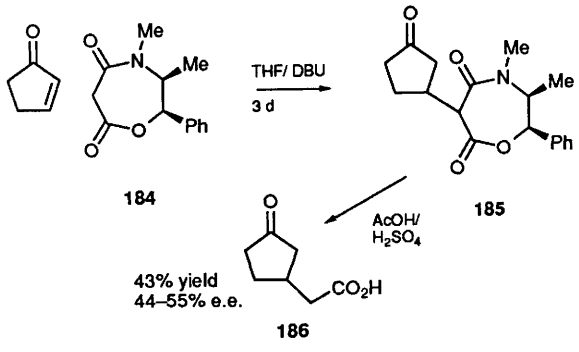


n	R_2CuLi	Yield	e.e.
0	Et_2CuLi	70%	84%
1	Me_2CuLi	81%	95%
1	Bu_2CuLi	81%	95%
2	Me_2CuLi	87%	96%
2	Bu_2CuLi	91%	98%

Scheme 50

6 Conjugate additions where the asymmetry is introduced *via* chiral centres covalently bonded within the nucleophile

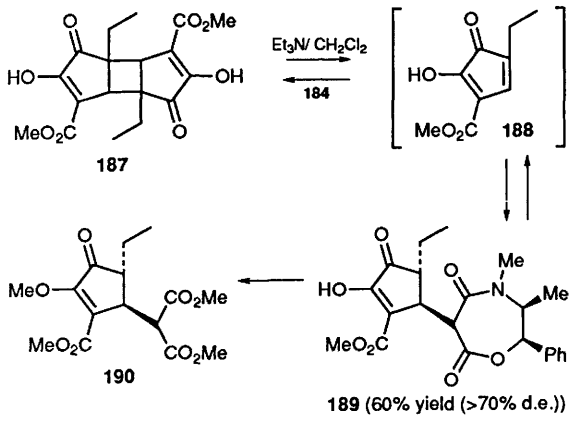
Some time ago Mukaiyama *et al.* developed ephedrine derivative **184** as a chiral malonate analogue. They added it to simple enones such as cyclopentenone, from which they obtained cyclopentanone-3-acetic acid, *via* **185**, with a moderate e.e. (**Scheme 51**).[5(a),89]



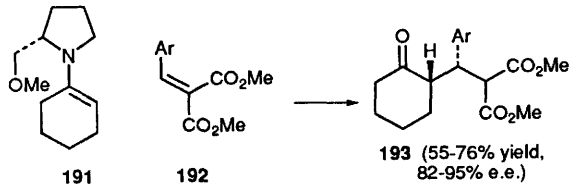
Scheme 51

More recently, Brown *et al.* utilized **184** in an interesting example of a thermodynamically controlled asymmetric Michael addition reaction. Under the reaction conditions cyclopentadienone dimer **187** reacted in its monomeric form, leading to adduct **189** as the dominant product (60% isolated) after equilibration. Enantiomerically pure Michael adduct **189** was then converted into cyclopentenone **190** which was used as a synthon for various monoterpenoids and indole alkaloids (**Scheme 52**).[90]

A number of proline derived nucleophiles have been used successfully to induce chirality during conjugate additions. Seebach *et al.* reacted enamines of prolinol derivatives, such as **191**, with reactive Michael acceptors and obtained products with a high level of diastereoselectivity (**Scheme 53**).[7]



Scheme 52

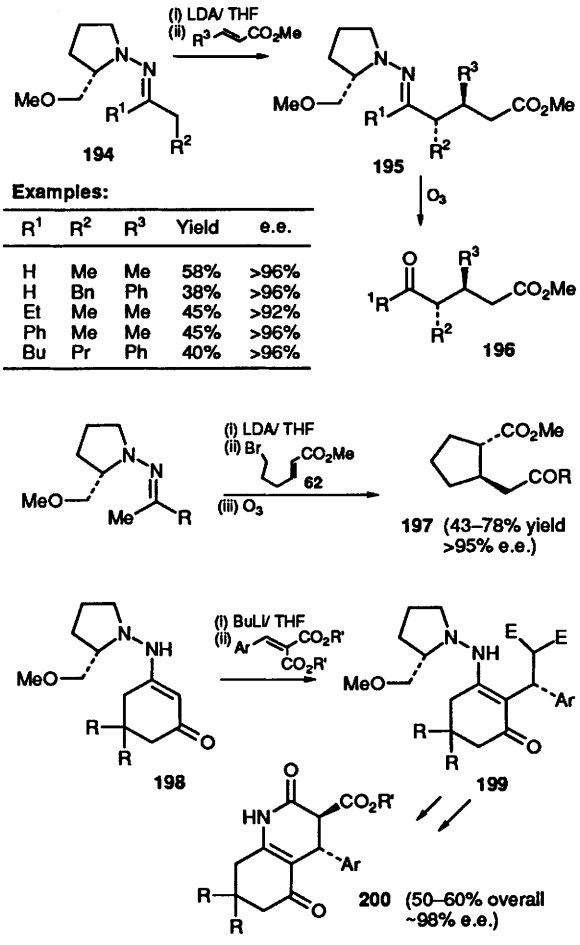


Scheme 53

Enders *et al.* have developed highly diastereoselective conjugate addition reactions using lithium anions of SAMP and RAMP hydrazones (*e.g.* **194**). The hydrazones are usually cleaved by ozonolysis to give the equivalent ketone with high enantiomeric purity.[91] Some examples of simple conjugate addition are shown in **Scheme 54**, together with a more recent example of conjugate addition followed by internal trapping of the initially formed enolate, leading to cyclopentanes **197** of high enantiomeric purity.[91(d)] Similarly, enamines **198** were prepared from 1,3-dicarbonyl compounds and their anions also reacted with high facial selectivity in conjugate additions.[92] This methodology allowed some chiral dihydropyridines and dihydropyridones to be synthesized, and an example is shown in **Scheme 54**.

Enders has also used lithium anions of cyanoamines **201** (derived from aldehydes R_1CHO) as chiral acyl anions equivalents. These reacted with enoates in a conjugate manner with very high diastereoselectivity, and ketones **203** were obtained with high e.e., after hydrolysis of intermediate **202** (**Scheme 55**).[93]

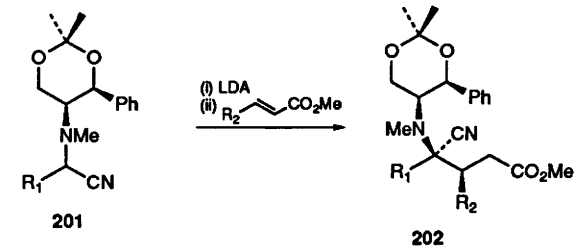
Another example of a proline derived auxiliary was developed by Yamaguchi *et al.* They prepared amides (*e.g.* **204**) from amino alcohols and found that their lithium dianions **205** reacted with enoates. Two new chiral centres are created during the reaction with high selectivity. After hydrolysis of the auxiliary chiral amino alcohol, chiral acids **207** were obtained with high optical purity (~ 80%) and with a high level of diastereoselectivity.[94] When the dianion of prolinol derivative **204** was reacted with diester **208** cyclopentanone **209** was obtained and converted into alcohol **210**. This was then converted into (−)-isodehydroiridodiol with an e.e. of 79% (**Scheme 56**).



Examples:

R^1	R^2	R^3	Yield	e.e.
H	Me	Me	58%	>96%
H	Bn	Ph	38%	>96%
Et	Me	Me	45%	>92%
Ph	Me	Me	45%	>96%
Bu	Pr	Ph	40%	>96%

Scheme 54



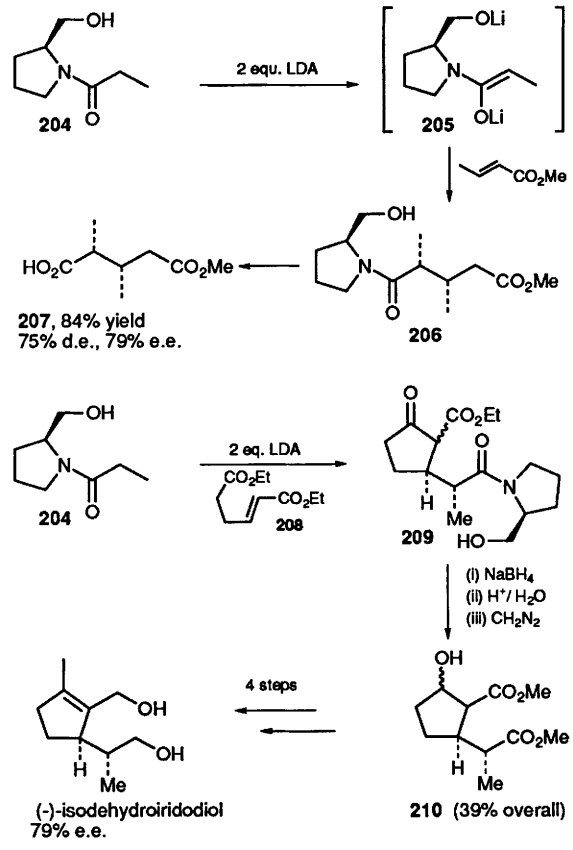
Examples:

R^1	R^2	Yield	e.e.
Me	Me	69%	93%
Et	Bu	47%	>95%
C_6H_4Cl	Me	66%	>95%
furyl	Bu	61%	90%

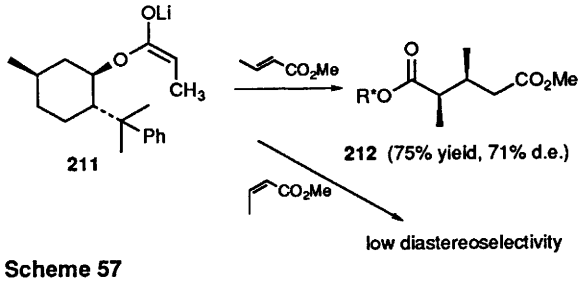
Scheme 55

Corey *et al.*[95] reacted *E*-enolates, such as **211**, derived from phenylmethanol esters with enoates. *E*-Enoates reacted quite selectively, favouring *syn* adduct **212**, whereas *Z*-enoates reacted with very little selectivity (**Scheme 57**).

Haynes *et al.*[96(b)] found that anions from chiral phosphine oxides react in a highly diastereoselective manner with cyclopentenones. For example, the



Scheme 56

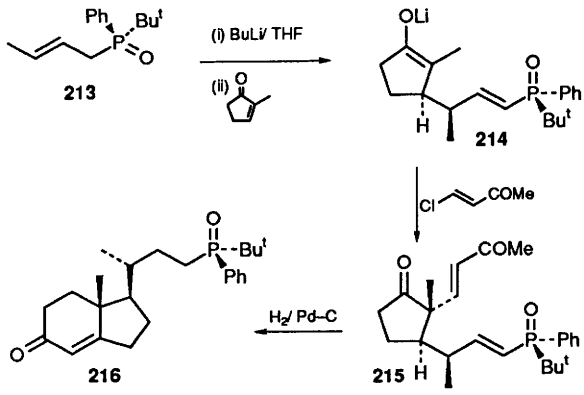


Scheme 57

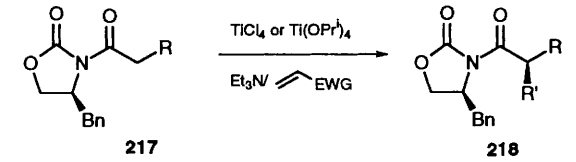
lithium anion of **213** reacted with methyl 2-methylcyclopentenone, and the enolate **214** which was formed was trapped to give **215**. After hydrogenation of the alkene aldol, cyclization gave the hydrindenone **216** (**Scheme 58**). Hua *et al.* carried out similar reactions using phophine oxides derived from ephedrine.[96(b)]

When amides bearing oxazolidinone chiral auxiliaries **217** are converted into titanium 'ate' enolates, they react as nucleophiles in conjugate addition reactions with simple α,β-unsaturated systems giving products **218** with a high degree of stereocontrol (**Scheme 59**). However, Evans *et al.* found that more complex enones, such as cyclohexenone, react with low stereoselectivity.[97]

Conjugate addition reactions of enamines derived from chiral amines have been studied for some time.[6(c),98] For example, Lewis acid catalysed reaction of proline derived enamine **191**, **Scheme 53**. d'Angelo



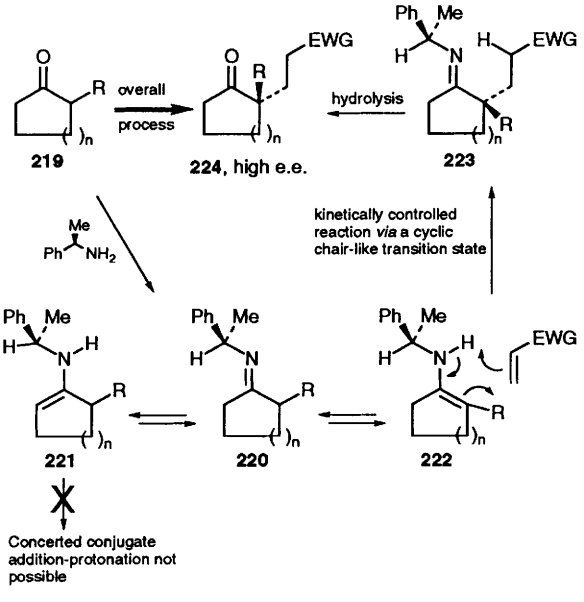
Scheme 58



R	EWG	R'	Yield	d.e.
Me	CH_2=CHCOEt	CH_2CH_2COEt	88%	98%
Me	CH_2=CHCN	CH_2CH_2CN	99%	96%
Me	CH_2=$CHCO_2Me$	$CH_2CH_2CO_2Me$	78%	78%
$CH_2CH_2CO_2Me$	CH_2=CHCN	CH_2CH_2CN	80%	>99%
$CH(Me)_2$	CH_2=CHCN	CH_2CH_2CN	80%	>99%

Scheme 59

and Guingant have developed a powerful series of reaction sequences involving conjugate additions of chiral enamines to achiral Michael acceptors and they have reviewed these recently.[99] In these reactions racemic ketones **219** are converted into chiral Michael adducts **224** *via* chiral imines **220** (**Scheme 60**).



Scheme 60

The outcome of these reactions is highly predictable, in terms of both stereochemistry and regiochemistry. Enamines **221** and **222** can be formed by tautomerism of imine **220** and the conformations shown for **221** and **222** are the ones that are highly favoured over any of the alternatives. In what appears to be a kinetically controlled process enamine **222** reacts with the electrophile selectively and regioisomer **223** is normally produced with high selectivity. It has been demonstrated that the preferred mechanism for this type of reaction is one in which the proton is delivered to the α-position of the Michael acceptor by intramolecular transfer from the enamine nitrogen atom.[100] It is therefore suggested that the process is concerted, involving a cyclic transition state. Clearly, enamine **221** cannot react *via* a concerted cyclic transition state and so its products are disfavoured. A chair-like cyclic transition state is proposed on the basis of molecular modelling studies and an enamine *X*-ray structure and this accounts for the high degree of stereocontrol at the new chiral centre.

d'Angelo *et al.* have found that this type of process is tolerant to a wide variety of enamines and Michael acceptors. They explored the effects of using chiral amines other than α-methyl benzylamine as auxiliaries. Amines without an aromatic substitutent gave much lower enantioselectivity, but the reactions were virtually unaffected by electron-donating, electron-withdrawing, or bulky substituents in the aromatic ring of the auxiliary.[101]

A wide range of Michael acceptors have been used successfully in these reactions and a selection are shown in **Figure 5**. In general, reactants with a substituent at the β-position are quite unreactive.[102–107] Other reagents which did not react successfully were methyl propiolate, nitroethene, and methyl methacrylate.

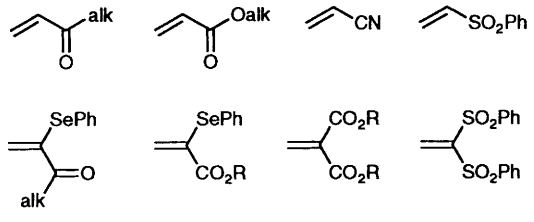
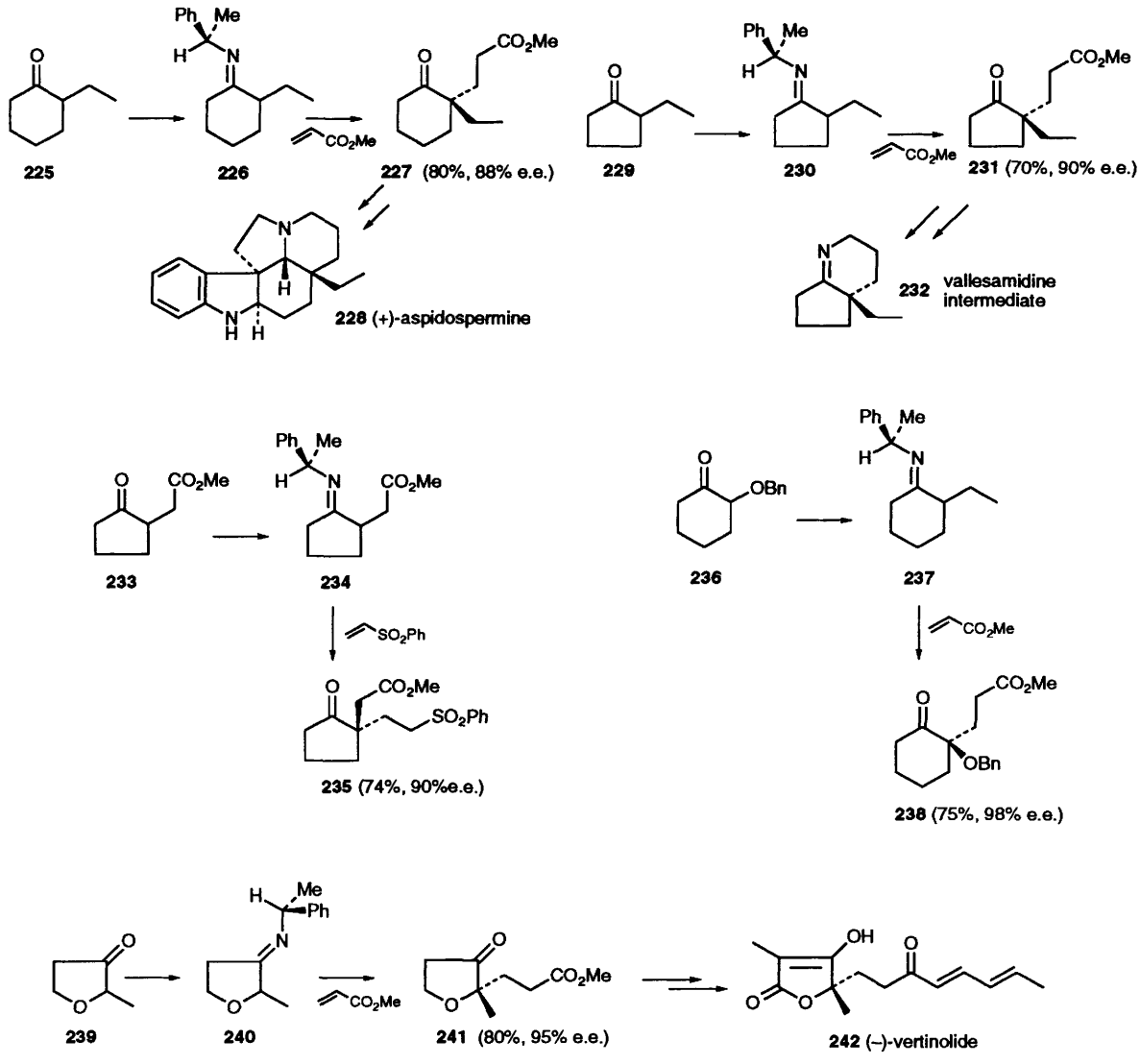


Figure 5

Examples which indicate the scope of these conjugate addition reactions are presented in **Schemes 61 and 62**. Simple cyclic ketones, such as **225** and **229**, bearing an alkyl group at the α-position react with most Michael acceptors, *via* their chiral enamines, to provide adducts such as, **227** and **231** in high yield and with high e.e.[99,102] Ketone **227** has been used in a synthesis of (+)-aspidospermine and ketone **231** has been used to prepare vallesamidine intermediate **232**.[115] The tolerance of the process to other substituents at the α-position of the ketone has been explored. An acetate side chain, as in **233**, does not influence the reaction adversely[106–108] but aromatic substituents reduced the reactivity of the chiral imine. The high

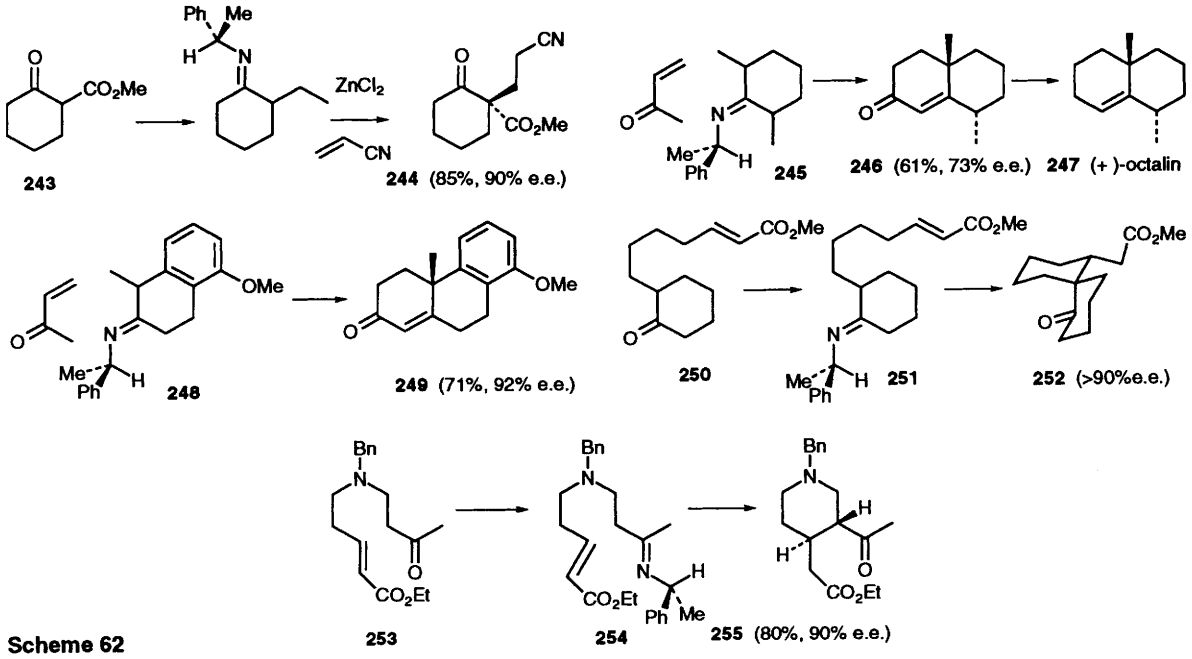


Scheme 61

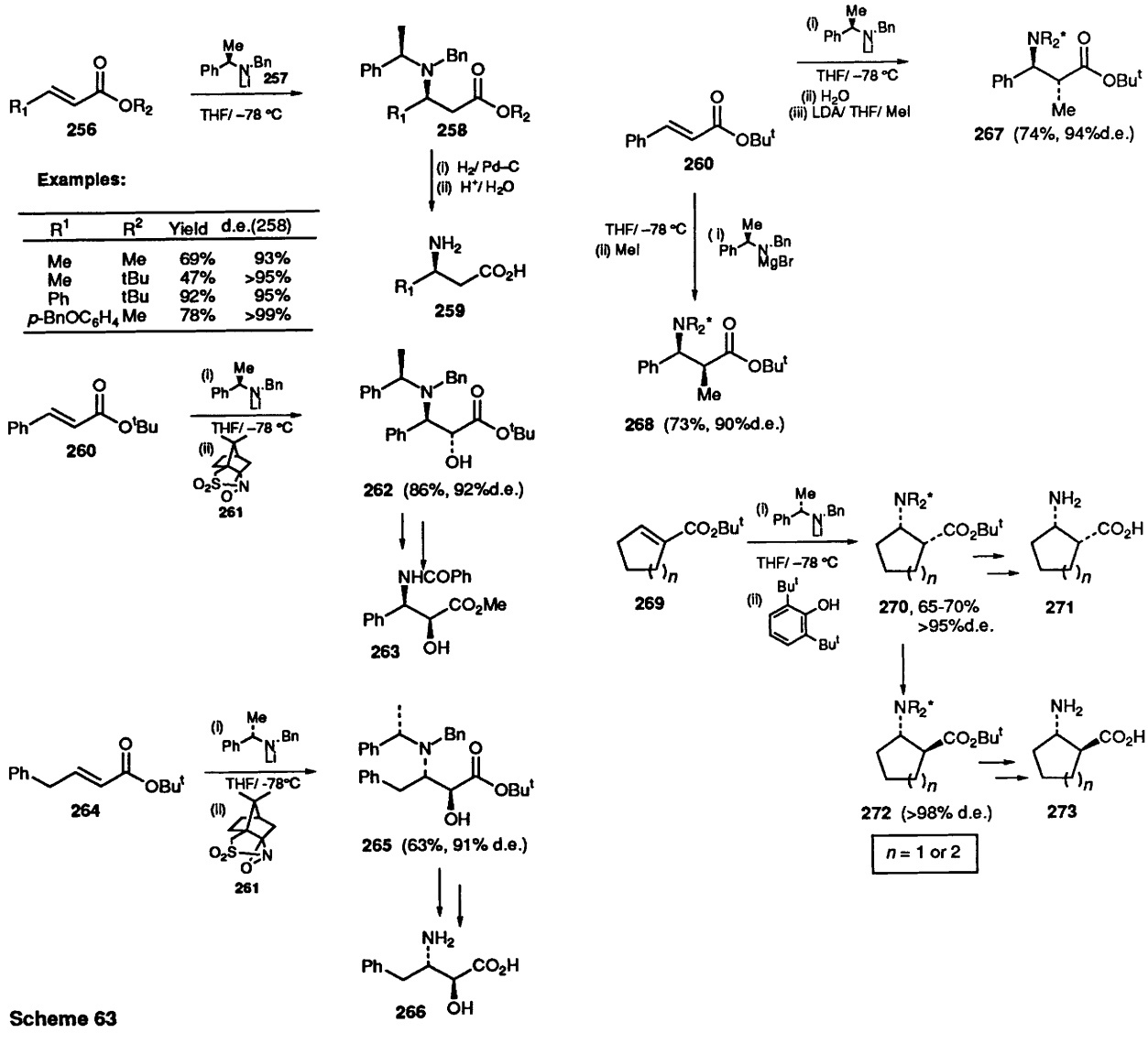
efficiency of the process is retained when an oxygen substituent is attached at the α-position. For example, benzyl ether **238** was obtained with an e.e. of 98% from **236**,[111] and **241** was obtained with an e.e. of 95% from tetrahydrofuranone **239**.[112] Tetrahydrofuranone **241** has been used in the synthesis of several natural products, including the tetronic acid (−)-vertinolide **242**.

Chiral enamines formed from 1,3-dicarbonyl compounds were found to be less reactive towards Michael additions, but reactions were often successful at high pressures or in the presence of a Lewis acid catalyst.[105] For example, nitrile **244** was obtained from **243** in 85% yield (90% e.e.) using $ZnCl_2$ as a catalyst.[116] Some very useful compounds have been synthesized by modified Robinson annulation procedures. The 2,6-dimethyl imine **245** reacted with lower stereoselectivity than normal, providing annulation product **246** with a 73% e.e. However, after three recrystallizations enantiomerically pure material was obtained and converted into (+)-octalin **247**.[103] Robinson annulations with bicyclic imines such as **248** were highly productive, leading to potential steroid/terpenoid precursors, *e.g.* **249** with an e.e. of 92%.[109,110] Intramolecular Michael addition reactions were also successful, provided there are 3–5 atoms between the imine group and the electrophilic alkene.[117] The interesting spiro ketone **252** was formed with an e.e. of > 90%,[113] and Hirai *et al.* have prepared the yohimbine/heteroyohimbine alkaloid precursor **255** with an e.e. of 90%.[114] d'Angelo *et al.* have utilized α-methyl benzylamine as a cheap source of chirality and developed a simple, efficient conjugate addition procedure which is a significant addition to the methodology available for asymmetric synthesis.

Davies *et al.* have developed a simple and effective methodology for introducing chirality at a primary amine centre. They discovered that chiral lithium amides derived from α-methyl benzylamine, for example **257**, react with prochiral enoates with very high diastereoselectivity at the newly generated amine chiral centre (**Scheme 63**). Since both the original



Scheme 62



Scheme 63

groups attached to the nitrogen are benzylic they can easily be removed by simple hydrogenation, and the overall process is therefore equivalent to enantioselective conjugate addition of ammonia to the prochiral enoate.[118-123] Although the chirality of the 'auxiliary' group is destroyed during the process, α-methylbenzylamine is a very cheap reagent which is available in either enantiomeric form. From a practical point of view, the hydrocarbon by-products from the hydrogenolysis are volatile and therefore easily removed. An early application of this procedure was the synthesis of (*S*)-β-tyrosine (**259**, R1 = *p*-OHC_6H_5) from **256** (R^1 = *p*-OHC_6H_5, R^2 = Me).[118] The initial conjugate addition of the lithium amide generates an ester enolate. When the enolate from addition of **257** to enoate **260** was trapped using chiral oxaziridine **261**, aminoalcohol **262** was formed in a highly diastereoselective manner. The enantiomer of the taxol side chain **263** was then prepared from **262** *via* a few simple steps, including Mitsunobu inversion of the hydroxyl group.[119] When the homologous enoate **264** was subjected to the same addition–oxidation sequence as **260**, the selectivity between *anti* and *anti* hydroxylamine isomers was very poor, caused by an enantiomeric mismatch of reagents. Thus, when the opposite enantiomer of the lithium amide was incorporated into the sequence, *anti* aminoalcohol **265** was obtained with 91% diastereoselectivity.[120] When the intermediate lithium enolates formed after conjugate addition were alkylated with methyl iodide, the *syn*:*anti* relative stereochemistry was disappointing (about 30% d.e.). However, when the reaction was quenched with water and the product re-enolized with LDA, then alkylated amine **267** was obtained with high *anti* selectivity.[121] Interestingly, it was later found that the enolates from magnesium amide addition were alkylated with high selectivity, but in that case *syn* amine **268** was obtained from **260**.[122]
Lithium amides added to cyclic enoates **269** (n = 1 or 2) in a highly stereocontrolled manner. The initial product, after conjugate addition and enolate quenching with a bulky proton source, had the amine and ester groups *cis* to one another and this allowed the antifungal antibiotic *cis*-peritacin **271** (n = 1) to be prepared efficiently. However, the ester group in **270** could be inverted by treatment with base giving access to the *trans* compound **272**.[123]

7 Conjugate additions of achiral nucleophiles to achiral α,β-unsaturated systems in the presence of chiral ligands or other chiral mediators

Enantioselective reactions of achiral substrates in the presence of chiral additives is a very attractive prospect, especially if the chiral additive can be used as a catalyst. This is an area of study that has attracted a good deal of attention in recent years. Many of the studies carried out so far have been quite similar and enantioselectivities have often been quite low. Recent reviews[1,3(c)] have covered the literature up to 1992 in some detail and this review will therefore highlight processes that proceed with high enantioselectivity and novel methods that have been reported recently. Certain processes of the type covered in this section proceed with very high enantioselectivity, but they are normally substrate specific, rather than general processes.

7.1 Modification of cuprate and magnesium reagents

An array of chiral alcohols and amines have been incorporated with cuprate reagents as non-transferable ligands. The most common substrates used to test such reagents have been chalcone-type enones and simple carbocyclic enones. **Scheme 64** shows selected examples these reactions. Most of the early studies gave low e.e.s.,[124] but Mukaiyama achieved an e.e. of 66%,[125] which was later improved to 88% by Leyendecker[126] for $Me_2MgCuBr$ addition to chalcone in the presence of *N*-methyl prolinol **276**. Leyendecker also found that other proline derivatives, such as **277** were good chiral mediators for cuprate additions to chalcone.[126(c)]

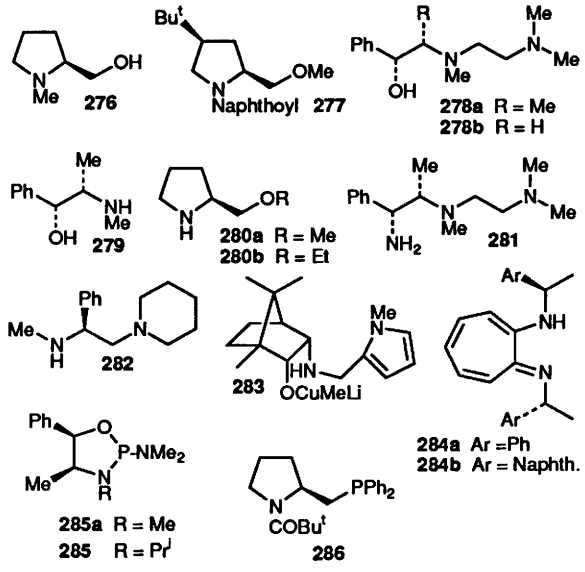
One of the main breakthroughs was made by Corey,[127] using amino alcohols **278a** and **278b** to achieve reasonable levels of e.e. for cuprate additions to cyclic enones. It also became clear that the purity of the lithium reagent used and all other experimental variables, such as counter-ions, solvent, temperature, *etc.*, were critical for achieving high enantioselectivity.[127,128,129(b)] Corey suggested the transition state model shown in **Figure 6** to account for the observed enantioselectivity.

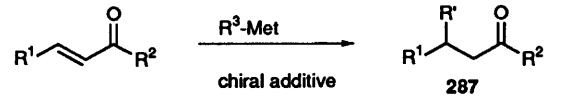
Rossiter *et al.* screened a range of chiral amine ligands for cuprate additions to cycloalkenones and found that **282** (*S*-MAPP) was particularly effective.[131] The products from reactions of cycloheptenone had the highest e.e. and asymmetric amplification was recognized in the process.[131(c)] A study of the amplification led to the suggestion that the reactive form of the reagent is a dimer and that the *meso* form of the reagent does not react. Tanaka *et al.* screened a range of camphor-derived aminoalcohols as chiral ligands for methyl cuprate addition to enone **289**. They found that **283** was the best reagent and only 0.33 equivalents were used with CuI and MeLi to give a 76% yield of muscone **290** with 96% e.e. (**Scheme 65**),[132] Lippard *et al.* found that the Cu^I complex of **284** acts as a chiral catalyst for Grignard additions to cyclohexenone. The e.e. was dependent on reaction conditions and they found that the addition of HMPA and trialkylsiyl chlorides was advantageous, with a highest e.e. of 78%.[133]

Alexakis *et al.* have achieved high e.e. levels using ligands **285a** and **285b** to mediate alkyl copper additions to cyclohexenone.[134] They found that addition of several equivalents of LiBr to the reactions led to improved e.e.s.

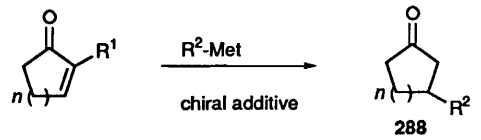
Quite recently, Tomioka *et al.* have evaluated a range of proline derived diphenylphosphines in enantioselective conjugate additions of copper reagents to chalcone and cyclohexenones.[135] t-Butyl ester **286** was the most effective ligand investigated

Examples of chiral additives used with cuprate reagents





Ref.	Additive	R^1	R^2	R^3-Met	Yield	e.e.	*R/S*
125	**276**	Ph	Ph	$Me_2CuMgBr$	88%	68%	*S*
126b	**276**	Ph	Ph	$Me_2CuMgBr$	80%	88%	*S*
126c	**277**	Me	Me	Bu_2CuLi	37%	68%	*R*
128	**279**	Ph	Ph	$MeCu.BF_3$	96%	87%	*R*
135	**286**	Ph	Ph	MeCuLi	79%	84%	*S*



Ref.	Additive	n	R^1	R^2-Met	Yield	e.e.	*R/S*
127	**278a**	1	H	Et_2CuLi	68%	77%	*R*
127	**278a**	1	H	Bu_2CuLi	60%	72%	*R*
127	**278a**	2	H	Et_2CuLi	90%	92%	*R*
127	**278a**	2	H	Bu_2CuLi	90%	89%	*R*
127	**278b**	2	H	Me_2CuLi	60%	90%	*R*
128	**279**	1	H	Ph_2CuLi	90%	50%	*R*
129	**280a**	1	H	Me_2CuLi	45%	77%	*S*
129a	**280a**	2	H	Me_2CuLi	77%	41%	*S*
129b	**281**	2	H	Bu_2CuLi	63%	63%	*R*
130	**280b**	1	Me	$(CH_2{=}CHMe)_2CuLi$	88%	88%	*R*
131	**282**	1	H	Me_2CuLi	40%	32%	*R*
131	**282**	1	H	Bu_2CuLi	51%	45%	*S*
131	**282**	2	H	Me_2CuLi	57%	58%	*S*
131	**282**	2	H	Bu_2CuLi	92%	83%	*S*
131	**282**	3	H	Me_2CuLi	60%	97%	*S*
131	**282**	3	H	Bu_2CuLi	63%	96%	*S*
131	**282**	4	H	Me_2CuLi	48%	67%	
131	**282**	4	H	Bu_2CuLi	50%	86%	
133	**284a**	2	H	Bu_2MgCl/CuI	97%	78%	*S*
134	**285b**	2	H	MeCu	75%	26%	*R*
134	**285b**	2	H	EtCu	81%	95%	*R*
134	**285b**	3	H	BuCu	82%	95%	*R*
134	**286**	1	H	EtCu	90%	94%	*R*
134	**286**	1	H	BuCu	99%	95%	*R*
134	**286**	2	H	MeCu	66%	92%	*R*
134	**286**	2	H	EtCu	89%	91%	*R*
134	**286**	2	H	BuCu	97%	90%	*R*

Scheme 64

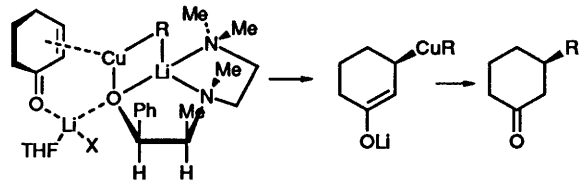
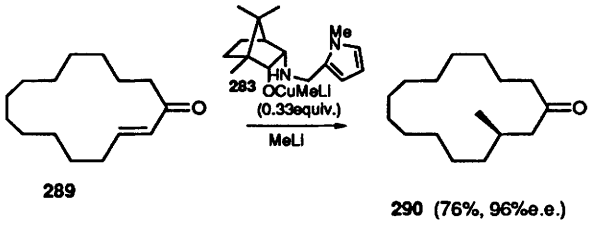


Figure 6



Scheme 65

and induced high levels of enantioselectivity, although reaction conditions were critical and three equivalents of the ligand were normally required.

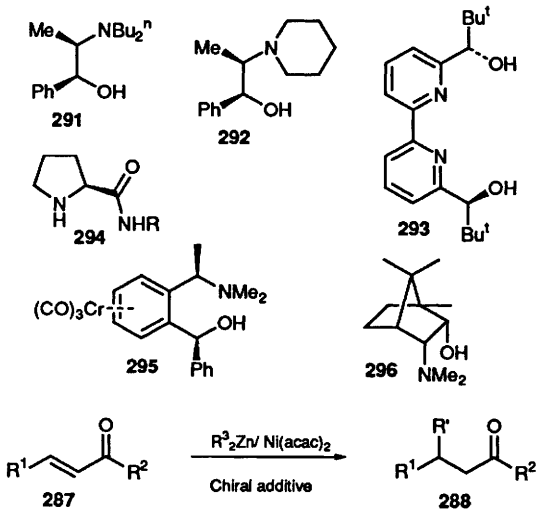
7.2 Modification of organozinc reagents

Jansen and Feringa carried out conjugate additions using chiral zinc complexes in conjunction with Grignard reagents, but the enantioselectivities of such reactions were generally very low.[136] The same workers, and several other groups,[137–141] have used dialkyl zinc reagents, with catalytic quantities of ligands **291–296**, together with $Ni(acac)_2$. High enantioselectivities have been achieved with these reagents (**Scheme 66**), but the reactions conditions are quite critical and it was found that certain achiral amine additives (*e.g.* 2,2′-bipyridine) led to enhanced enantioselectivity.

7.3 Modification of 1,3-dicarbonyls and other activated nucleophiles

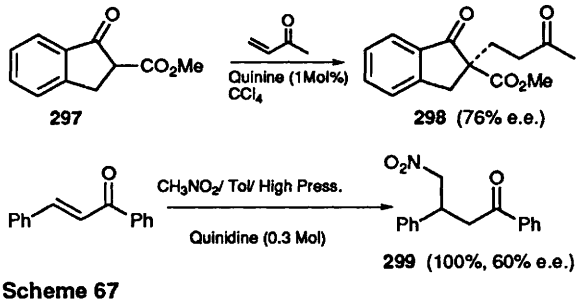
Some time ago Wynberg showed that cinchona alkaloids act as chiral catalysts for conjugate additions of certain activated nucleophiles, for example **297** was reacted with MVK in the presence of 1% quinine to give **298** in 99% yield with 76% e.e. (**Scheme 67**).[142] It was also found that quaternary ammonium salts derived from cinchona alkaloids can act as chiral phase transfer catalysts in similar processes.[142,143] This

Examples of chiral additives used with organozinc reagents



Ref.	Additive	R^1	R^2	Mol%(cat)	R^3-Met	Yield	e.e.	*R/S*
137a	291	Ph	Ph	0.5	Et_2Zn	75%	45%	*R*
137c	291	Ph	Ph	0.5	Et_2Zn	63%	82%	*R*
137d	292	Ph	CPh_3	0.25	Et_2Zn	81%	80%	
137d	292	Ph	CPh_3	1	Et_2Zn	96%	94%	
137d	292	Ph	Bu^t	0.25	Et_2Zn	82%	72%	
137d	292	Me	Ph	1	Et_2Zn	34%	82%	
138a	293	Ph	Ph	20%	Et_2Zn	75%	72%	*R*
138a	293	Ph	Me	20%	Et_2Zn	76%	2%	*R*
139	294	Ph	Ph		Et_2Zn	80%	91%	*R*
137d	292	Ph	Me		Et_2Zn	74%	95%	*R*
140	295	Ph	Ph	10	Et_2Zn	90%	62%	*R*
141	296	Ph	Ph	7	Et_2Zn	75%	85%	*R*

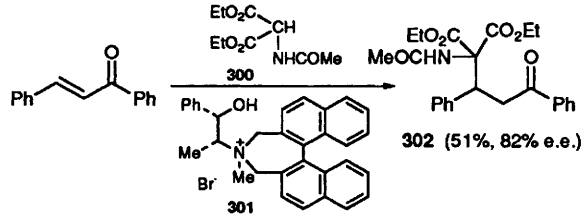
Scheme 66



Scheme 67

particular process appears to be unusually well suited to this type of catalysis and chiral cobalt complexes have also proved to be effective.[144] Moderate enantioselectivities (~ 60%) have also been achieved for additions of thiols to cyclic enones and for addition of cyclic α-nitroketones to methyl vinyl ketone.[145] The catalysts can be polymer supported and Sera *et al.* found that although enantioselectivities generally fall when the reactions are carried out at high pressure, addition of nitromethane to chalcone was only possible at high pressure and proceeded to give **299** with 61% e.e.[146]

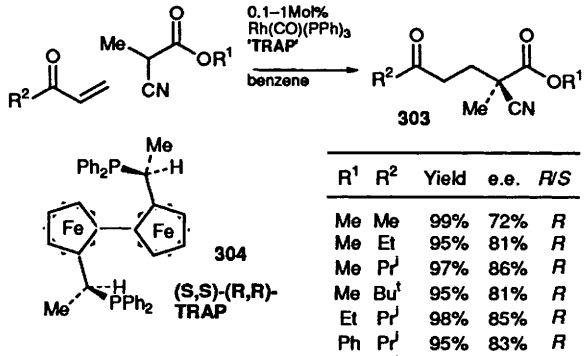
Loupy and Zaparucha found that various quaternary ammonium salts catalysed the enantioselective conjugate addition of diester **300** to



Scheme 68

chalcone.[147] The best catalyst was **301** which led to **302** with 82% e.e. (**Scheme 68**).

Several important new organometallic catalysts for conjugate additions have been reported recently. Ito *et al.* found that the ferrocene compound **304** ('TRAP') catalysed the enantioselective addition of α-cyanoesters to enones, leading to 1,5-dicarbonyls **303** with high e.e.s (**Scheme 69**).[148]

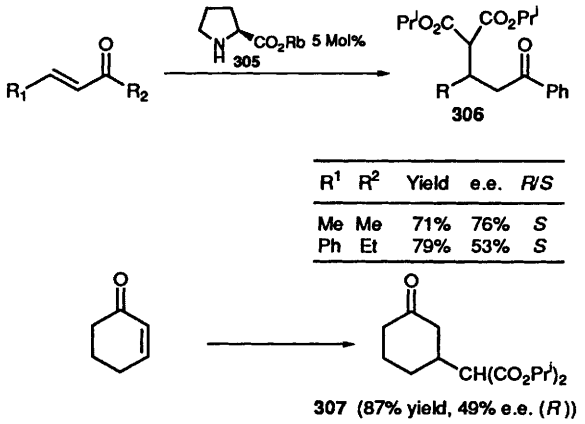


R^1	R^2	Yield	e.e.	*R/S*
Me	Me	99%	72%	*R*
Me	Et	95%	81%	*R*
Me	Pr^i	97%	86%	*R*
Me	Bu^t	95%	81%	*R*
Et	Pr^i	98%	85%	*R*
Ph	Pr^i	95%	83%	*R*
H	Pr^i	88%	87%	*R*

Scheme 69

Yamaguchi *et al.* explored the use of simple proline salts as catalysts for malonate-type additions and found that rubidium salt **305** was very effective. They found that cyclic enones reacted preferentially from the *Re* face, whereas acyclic enones reacted from the *Si* face, with enantioselectivities of up to 77% e.e. (**Scheme 70**).[149]

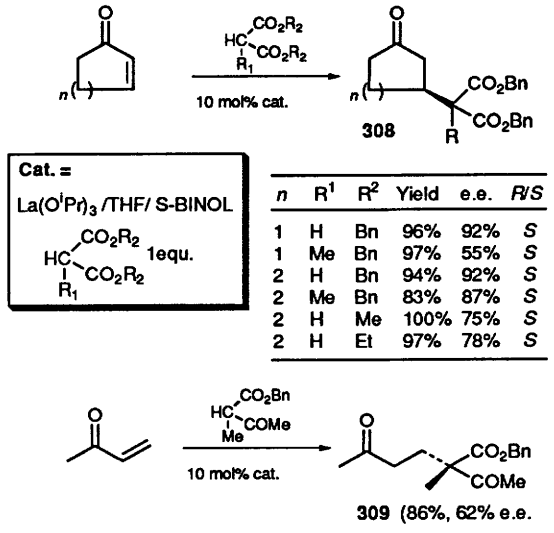
Very high enantioselectivities for a range of reactions were reported by Sasai *et al.* using



R^1	R^2	Yield	e.e.	*R/S*
Me	Me	71%	76%	*S*
Ph	Et	79%	53%	*S*

Scheme 70

BINO-rare earth bimetallic complexes as catalysts.[150] Several catalyst systems were investigated and the best of them gave uniformly high e.e.s over a range of reactions, as shown in **Scheme 71**. This appears to be the most effective generally applicable catalyst for enantioselective malonate additions reported to date.

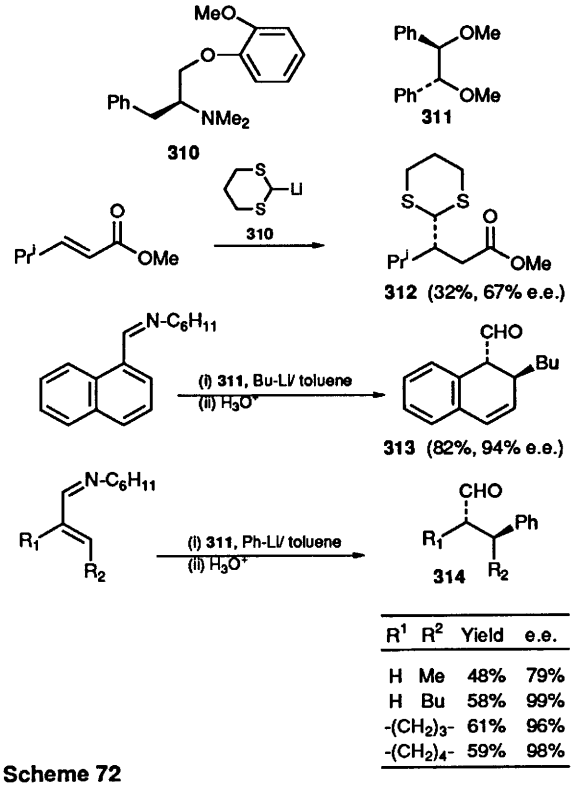


n	R^1	R^2	Yield	e.e.	*R/S*
1	H	Bn	96%	92%	*S*
1	Me	Bn	97%	55%	*S*
2	H	Bn	94%	92%	*S*
2	Me	Bn	83%	87%	*S*
2	H	Me	100%	75%	*S*
2	H	Et	97%	78%	*S*

Scheme 71

7.4 Other miscellaneous reactions

Tomioka *et al.* investigated conjugate addition reactions of simple lithium reagents mediated by chiral ethers **310** and **311** (**Scheme 72**). Thioacetal **312** was prepared from the lithium dithiane anion with an e.e. of 67% using **310**,[151(a)] Using diether **311**, simple

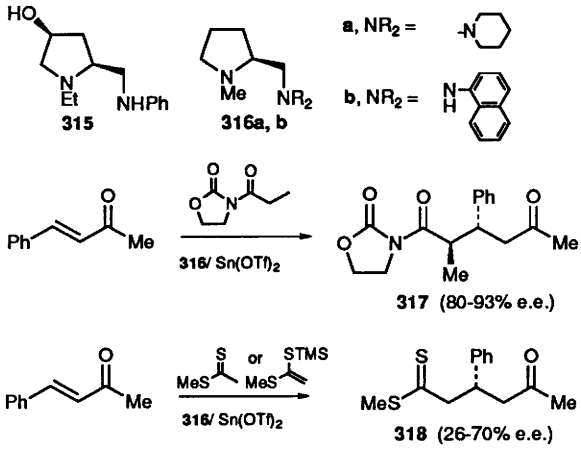


R^1	R^2	Yield	e.e.
H	Me	48%	79%
H	Bu	58%	99%
-$(CH_2)_3$-		61%	96%
-$(CH_2)_4$-		59%	98%

Scheme 72

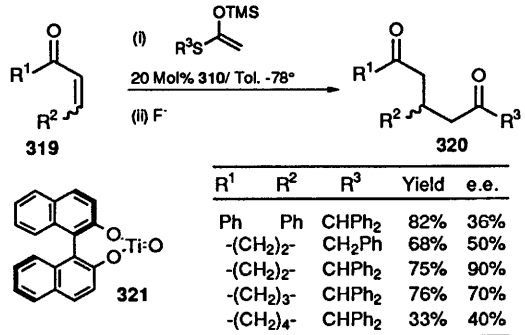
lithium reagents reacted with conjugated imines, leading to **313** and **314** with very high e.e.s.

Yura and Mukaiyama *et al.* used proline derived diamines as catalysts in a number of enantioselective processes (**Scheme 73**). Addition of aryl thiols to cyclohexenone proceeded with enantioselectivities of up to 88% e.e. in the presence of 2 mol% **315**.[152(a)] The more simple bidentate bases **316a** and **316b** catalysed enolate and enethiolate conjugated additions, leading to **317** with an e.e. of up to 93%, and **318** with an e.e. of up to 70%.[152(b,c)]



Scheme 73

Kobayashi *et al.* used binaphthol derivative **321** to catalyse the addition of thioester enolates to **319** leading to products **320** with up to 90% e.e. (**Scheme 74**).[153]



R^1	R^2	R^3	Yield	e.e.
Ph	Ph	$CHPh_2$	82%	36%
-$(CH_2)_2$-		CH_2Ph	68%	50%
-$(CH_2)_2$-		$CHPh_2$	75%	90%
-$(CH_2)_3$-		$CHPh_2$	76%	70%
-$(CH_2)_4$-		$CHPh_2$	33%	40%

Scheme 74

8 Conclusion

There is now a great wealth of knowledge of how to control absolute and relative stereochemistry during conjugate addition reactions and they are therefore some of the most powerful structure building reactions available for organic synthesis. Synthetic methods whereby chiral reagents mediate in reactions between achiral substrates and give products with high enantiomeric purity are particularly important. There are now several such methods available for specific reactions, and developing reagents with general applicability is one of the major challenges for the future.

9 References

1 B.E. Rossiter and N.M. Swingle, *Chem. Rev.*, 1992, **92**, 771.

2 P. Perlmutter, 'Conjugate Addition Reactions in Organic Synthesis', Tetrahedron Organic Chemistry Series, No. 9; Pergamon Press, Oxford, 1992.

3 (a) M.E. Jung in 'Comprehensive Organic Synthesis', ed. B.M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, Vol. 4, chapter 1.1, p. 1; (b) V.J. Lee, *ibid.*, chapter 1.2, p. 66; (c) V.J. Lee, *ibid.*, chapter 1.3, p. 139; (d) J.A. Kozlowski, *ibid.*, chapter 1.4, p. 169; (d) H.-G. Schmalz *ibid.*, chapter 1.5, p. 199.

4 D.A. Oare and C.H. Heathcock, *Top. Stereochem.*, 1989, **19**, 227.

5 (a) K. Tomioka and K. Koga, in 'Asymmetric Synthesis', ed. J.D. Morrison, Academic Press, 1983, Vol. 2, chapter 7, p. 201; (b) G.H. Posner, *ibid.*, chapter 8, Vol. 2, p. 239; (c) A.I. Meyers, *ibid.*, Vol. 3, chapter 3, p. 213.

6 (a) D. Seebach and J. Golinski, *Helv. Chim. Acta*, 1981, **64**, 1413; (b) R. Häner, T. Laube, and D. Seebach, *Chimia*, 1984, **38**, 255.

7 S.J. Blarer and D. Seebach, *Chem. Ber.*, 1983, **116**, 2250.

8 (a) C.H. Heathcock, M.A. Henderson, D.A. Oare, and M.A. Sunner, *J. Org. Chem.*, 1985, **50**, 3019; (b) C.H. Heathcock and D.A. Oare, *J. Org. Chem.*, 1985, **50**, 3022; (c) C.H. Heathcock, M.H. Norman, and D.E. Uehling, *J. Am. Chem. Soc.*, 1985, **107**, 2797; (d) D.A. Oare and C.H. Heathcock, *J. Org. Chem.*, 1990, **55**, 157.

9 (a) M. Yamaguchi, M. Tsukamoto, S. Tanaka, and I. Hirao, *Tetrahedron Lett.*, 1984, **25**, 5661; (b) M. Yamaguchi, M. Tsukamoto, and I. Hirao, *Tetrahedron Lett.*, 1985, **26**, 1723; (c) M. Yamaguchi, K. Hasebe, S. Tanaka, and T. Minami, *Tetrahedron Lett.*, 1987, **28**, 1785.

10 K. Tomioka, *Tetrahedron Lett.*, 1985, **26**, 3031.

11 A. Bernardi, P. Dotti, G. Poli, and C. Scolastico, *Tetrahedron*, 1992, **48**, 5597.

12 (a) M. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, 1982, **23**, 5563; (b) R. Noyori and M. Suzuki, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 847; (c) M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, 1985, **107**, 3348.

13 E. Negishi and F. T. Luo, *Tetrahedron Lett.*, 1985, **23**, 2177.

14 (a) C.H. Heathcock, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 665; (b) C.H. Heathcock, M.M. Hansen, R.B. Ruggeri, J.A. Ragan, and J.C. Kath, *J. Org. Chem.*, 1992, **57**, 2544; (c) C.H. Heathcock and J.A. Stafford, *J. Org. Chem.*, 1992, **57**, 2566.

15 (a) G. Stork, C.S. Shiner, and J.D. Winkler, *J. Am. Chem. Soc.*, 1982, **104**, 316; (b) G. Stork, J.D. Winkler, and N.A. Saccomano, *Tetrahedron Lett.*, 1983, **24**, 465; (c) G. Stork and N.A. Saccomano, *Nouv. J. Chim.*, 1986, **10**, 677.

16 M. Ihara and K. Fukumoto, *Angew. Chem., Int. Ed. Engl.*, 1993, **33**, 1010.

17 A.J. Bellamy, *J. Chem. Soc. (B)*, 1969, 449.

18 T. Ohnuma, T. Oishi, and Y. Ban, *J. Chem. Soc., Chem. Commun.*, 1973, 301

19 R.A. Lee, *Tetrahedron Lett.*, 1975, **14**, 2439.

20 L.B. White and W. Reusch, *Tetrahedron*, 1978, **24**, 2439.

21 H. Hagiwara, K. Nakayama, and H. Uda, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 3769.

22 (a) D. Schinzer, M. Kalesse, and J. Kabbarra, *Tetrahedron Lett.*, 1988, **29**, 5241; (b) D. Schinzer and M. Kalesse, *Tetrahedron Lett.*, 1991, **32**, 4691.

23 (a) D. Spitzner, *Tetrahedron Lett.*, 1978, **19**, 3349; (b) W. Weber, D. Spitzner and W. Kraus, *J. Chem. Soc., Chem. Commun.*, 1980, 1212; (c) D. Spitzner, *Angew. Chem. Int., Ed. Engl.*, 1982, **21**, 636; (d) D. Spitzner, P. Wagner, A. Simon, and K. Peters, *Tetrahedron Lett.*, 1989, **30**, 547.

24 R.-B. Zao, Y. Zhao, G.-Q. Song, and Y.-L. Wu, *Tetrahedron Lett.*, 1990, **31**, 3559.

25 E. G. Gibbons, *J. Org. Chem.*, 1980, **45**, 1540, and *J. Am. Chem. Soc.*, 1982, **104**, 1767.

26 (a) M.R. Roberts and R.H. Schlessinger, *J. Am. Chem. Soc.*, 1981, **103**, 724; (b) M.L. Quesada, R.H. Schlessinger, and W.H. Parsons, *J. Org. Chem.*, 1978, **43**, 3968.

27 G. Stork, *Pure Appl. Chem.*, 1989, **61**, 439. See also 'The Chemistry of Natural Products', ed. R.H. Thomson, chapter 6, 'Alkaloids', p. 218, Chapman and Hall, 1993.

28 (a) H. Nagaoka, K. Ohsawa, T. Takata, and Y. Yamada, *Tetrahedron Lett.*, 1984, **25**, 5389; (b) H. Nagaoka, K. Kobayashi, T. Matsui, and Y. Yamada, *Tetrahedron Lett.*, 1987, **28**, 2021; (c) H. Nagaoka, K. Kobayashi, T. Okamura, and Y. Yamada, *Tetrahedron Lett.*, 1987, **28**, 6641; (d) H. Nagaoka, K. Kobayashi, and Y. Yamada, *Tetrahedron Lett.*, 1988, **29**, 5945; (e) M. Iwashima, H. Nagaoka, K. Kobayashi, and Y. Yamada, *Tetrahedron Lett.*, 1992, **33**, 81.

29 (a) J.-F. Lavallée and P. Deslongchamps, *Tetrahedron Lett.*, 1988, **29**, 5117; (b) J.-C. Spino and P. Deslongchamps, *Tetrahedron Lett.*, 1990, **31**, 3969; (c) J.-F. Lavallée, C. Spino, R. Ruel, K.T. Hogan, and P. Deslongchamps, *Can. J. Chem.*, 1992, **70**, 1406.

30 (a) M. Ihara, M. Toyota, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 2167; (b) M. Ihara, M. Toyota, M. Abe, Y. Ishida, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1543; (c) M. Ihara, Y. Ishida, M. Abe, M. Toyota, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1155; M. Ihara, Y. Ishida, K. Fukumoto, and T. Kametani, *Chem. Pharm. Bull.*, 1985, **33**, 4102.

31 (a) M. Ihara, T. Kirihara, K. Fukumoto, and T. Kametani, *Heterocycles*, 1985, **23**, 1097; (b) M. Ihara, T. Kirihara, A. Kawaguchi, M. Tsuruta, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1719; (c) M. Ihara, T. Kirihara, A. Kawaguchi, M. Tsuruta, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 4541.

32 (a) M. Ihara, M. Toyoto, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1985, **26**, 1537; (b) M. Ihara, M. Toyota, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2151.

33 (a) M. Ihara, S. Suzuki, K. Fukumoto, T. Kametani, and C. Kabuto, *J. Am. Chem. Soc.*, 1988, **110**, 1963; (b) M. Ihara, S. Suzuki, K. Fukumoto, and C. Kabuto, *J. Am. Chem. Soc.*, 1990, **112**, 1164; (c) M. Ihara, S. Suzuki, and K. Fukumoto, *Heterocycles*, 1990, **30**, 381; (d) M. Ihara, A. Hirabayashi, N. Taniguchi, and K. Fukumoto, *Heterocycles*, 1992, **32**, 851; (e) M. Ihara, A. Hirabayashi, N. Taniguchi, and K. Fukumoto, *Tetrahedron*, 1992, **48**, 5089.

34 (a) M. Ihara, M. Tsuruta, K. Fukumoto, and T. Kametani, *J. Chem. Soc. Chem., Commun.*, 1985, 1159; (b) M. Ihara, Y. Takino, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1988, **29**, 4135; (c) M. Ihara, Y. Takino, K. Fukumoto, and T. Kametani, *Heterocycles*, 1989, **28**, 63; (d) M. Ihara, Y. Takino, M. Tomotake, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2287.

35 (a) M. Ihara, S. Suzuki, N. Taniguchi, K. Fukumoto, and C. Kabuto, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2527; (b) M. Ihara, T. Takahashi, N. Shimizu, Y. Ishida, I. Sudow, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1985, 529; (c) M. Ihara, A. Kawaguchi, H. Ueda, M. Cihiro, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1331.
36 H. Hagiwara, A. Okano, and H. Uda, *J. Chem. Soc., Chem. Commun.*, 1985, 1047.
37 (a) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, 1987, 1572; (b) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Am. Chem. Soc.*, 1988, **110**, 617.
38 C. H. Heathcock and D.E. Uehling, *J. Org. Chem.*, 1986, **51**, 279.
39 (a) Y. Honda, S.M. Hirai, and G. Tsuchiashi, *Chem. Lett.*, 1989, 255; (b) D. Kruger, A.E. Sopchik, and C.A. Kingsbury, *J. Org. Chem.*, 1984, **49**, 778.
40 (a) A.E. Dorigo and K. Morokuma, *J. Am. Chem. Soc.*, 1989, **111**, 6524; (b) A. Bernardi, A.M. Capelli, C. Gennari, and C. Scolastico, *Tetrahedron: Asymmetry*, 1990, **1**, 21.
41 (a) C.R. Johnson and J.R. Medich, *J. Org. Chem.*, 1988, **53**, 4131; (b) J.P. Mariano, M.V.M. Emonds, P.J. Stengel, A.R.M. Oliveira, F. Simonelli, and J.T.B. Ferreira, *Tetrahedron Lett.*, 1992, **33**, 49; (c) K.A. Swiss, W. Hinkley, C.A. Maryanoff, and D.C. Liotta, *Synthesis*, 1992, 127; (d) S. Sonda, H. Honchigai, M. Asaoka, and H. Takei, *Tetrahedron Lett.*, 1992, **33**, 3145.
42 (a) K.C. Nicolaou, M.R. Pavia, and S.P. Seitz, *J. Am. Chem. Soc.*, 1981, **103**, 1224; (b) K.C. Nicolaou, M.R. Pavia, and S.P. Seitz, *J. Am. Chem. Soc.*, 1982, **104**, 2027; (c) K.C. Nicolaou, M.R. Pavia, and S.P. Seitz, *Tetrahedron Lett.*, 1979, **20**, 2327.
43 F.E. Ziegler and P.J. Gilligan, *J. Org. Chem.*, 1981, **46**, 3874.
44 (a) W.R. Roush and B.M. Lesur, *Tetrahedron Lett.*, 1983, **24**, 2231; (b) W.R. Roush, M.R. Michaelides, D.F. Tai, and W.K. Chong, *J. Am. Chem. Soc.*, 1987, **109**, 7575; (c) W.R. Roush, M.R. Michaelides, D.F. Tai, B.M. Lesur, W.K. Chong, and D.J. Harris, *J. Am. Chem. Soc.*, 1989, **111**, 2984.
45 K. Tatsuta, Y. Amemiya, Y. Kanemura, and M. Kinoshita, *Tetrahedron Lett.*, 1981, **22**, 3997.
46 J.K. Cha and S.C. Lewis, *Tetrahedron Lett.*, 1984, **25**, 5263.
47 (a) J. Leonard and G. Ryan, *Tetrahedron Lett.*, 1987, **28**, 2525; (b) J. Leonard, G. Ryan, and P.A. Swain, *Synlett*, 1990, 613; (c) J. Leonard, S. Mohialdin, D. Reed, and M.F. Jones, *Synlett*, 1992, 741; (d) J. Leonard, S. Mohialdin, G. Ryan, D. Reed, and M.F. Jones, *J. Chem. Soc., Chem. Commun.*, 1993, 23.
48 W. Smadja, M. Zahouily, M. Journet, and M. Malacria, *Tetrahedron Lett.*, 1991, **32**, 3683.
49 (a) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, 1987, 464; (b) Y. Yamamoto, Y. Chounan, S. Nishii, T. Ibuka, and H. Kitahara, *J. Am. Chem. Soc.*, 1992, **114**, 7652.
50 S. Hanessian and K. Sumi, *Synthesis*, 1991, 1083.
51 (a) A. Dondoni, P. Merino, and J. Orduna, *Tetrahedron Lett.*, 1991, **32**, 3247; (b) A. Dondoni, A. Boscarato, and A. Marra, *Synlett*, 1993, 256.
52 (a) A. Bernardi, S. Cardani, G. Poli, and C. Scolastico, *J. Org. Chem.*, 1986, **51**, 5041; (b) A. Bernardi, S. Cardani, G. Poli, and C. Scolastico, *J. Org. Chem.*, 1988, **53**, 1600; (c) A. Bernardi, S. Cardani, C. Scolastico, and R. Villa, *Tetrahedron.*, 1990, **46**, 1987.
53 E. Dominguez and J.C. Carretero, *Tetrahedron Lett.*, 1993, **34**, 5803.
54 D.A. Evans and J.A. Gauchet-Prunet, *J. Org. Chem.*, 1993, **58**, 2446.
55 W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969.
56 W. Oppolzer and H.J. Löher, *Helv. Chim. Acta*, 1981, **64**, 2808.
57 (a) W. Oppolzer, R. Moretti, T. Godel, A. Meunier, and H. Löher, *Tetrahedron Lett.*, 1983, **24**, 4971; (b) W. Oppolzer, and T. Stevenson, *Tetrahedron Lett.*, 1986, **26**, 1139.
58 (a) W. Oppolzer, P. Dudfield, T. Stevenson, and T. Godel, *Helv. Chim. Acta*, 1985, **68**, 212; (b) W. Oppolzer, R. Moretti and G. Bernardinelli, *Tetrahedron Lett.*, 1986, **27**, 4713.
59 (a) W. Oppolzer, C. Chapuis, and G. Bernardinelli, *Helv. Chim. Acta*, 1984, **67**, 1397; (b) W. Oppolzer and G. Poli, *Tetrahedron Lett.*, 1986, **27**, 4717; (c) W. Oppolzer, G. Poli, A.J. Kingma, C. Starkemann, and G. Bernardinelli, *Helv. Chim. Acta*, 1987, **70**, 2201; (d) W. Oppolzer, R.J. Mills, W. Pachinger, and T. Stevenson, *Helv. Chim. Acta*, 1986, **69**, 1542; (e) W. Oppolzer and A.J. Kingma, *Helv. Chim. Acta*, 1989, **72**, 1337; (f) W. Oppolzer and A.J. Kingma, *Tetrahedron*, 1989, **45**, 479; (g) W. Oppolzer and P. Schneider, *Helv. Chim. Acta*, 1986, **69**, 1817.
60 (a) G. Helmchen and G. Wegner, *Tetrahedron Lett.*, 1985, **26**, 6051; (b) G. Helmchen, *Tetrahedron Lett.*, 1985, **26**, 6047; (c) V. Berl, G. Helmchen, and S. Preston, *Tetrahedron Lett.*, 1994, **35**, 233.
61 (a) C. Fang, H. Suemune, and K. Sakai, *Tetrahedron Lett.*, 1990, **31**, 4751; (b) C. Fang, T. Ogawa, H. Suemune, and K. Sakai, *Tetrahedron: Asymmetry*, 1991, **2**, 389; (c) C. Fang, H. Suemune, and K. Sakai, *J. Org. Chem.*, 1992, **57**, 4300.
62 K. Fuji, K. Tanaka, M. Mizuchi, and S. Hosoi, *Tetrahedron Lett.*, 1991, **32**, 7277.
63 (a) I. Fleming and N.D. Kindon, *J. Chem. Soc., Chem. Commun.*, 1987, 1177; (b) C. Polomo, J.M. Aizpurua, M. Iturburu, and R. Urchegui, *J. Org. Chem.*, 1994, **59**, 241.
64 J. d'Angelo and J. Maddaluno, *J. Am. Chem. Soc.*, 1986, **108**, 8112.
65 (a) T. Mukaiyama and N. Iwasawa, *Chem. Lett.*, 1981, 913; (b) J. Touet, S. Baudouin, and E. Brown, *Tetrahedron: Asymmetry*, 1993, **4**, 587; (c) J. Touet, C. LeGrumelee, F. Huet, and E. Brown, *Tetrahedron: Asymmetry*, 1993, **4**, 1469.
66 (a) T. Mukaiyama, T. Takeda, and M. Osaki, *Chem. Lett.*, 1977, 1165; (b) T. Mukaiyama, T. Takeda, and K. Fujimoto, *Bull. Chem. Soc. Jpn*, 1978, **51**, 3368; (c) T. Mukaiyama, K. Fujimoto, and T. Takeda, *Chem. Lett.*, 1979, 1207; (d) T. Mukaiyama, K. Fujimoto, T. Hirose, and T. Takeda, *Chem. Lett.*, 1980, 635.
67 (a) K. Soai and A. Ookawa, *J. Chem. Soc., Chem. Commun.*, 1985, 469; (b) K. Soai, H. Machida, and N. Yokota, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1909; (c) K. Soai, H. Machida, and N. Yokota, *J. Chem. Soc., Perkin Trans. 1*, 1986, 759.
68 K. Tomioka, T. Suenaga, and K. Koga, *Tetrahedron Lett.*, 1986, **27**, 369.
69 A. G. Schultz and R.E. Harrington, *J. Am. Chem. Soc.*, 1991, **113**, 4926.
70 K. Rück and H. Kunz, *Synthesis*, 1993, 1018.
71 G. Cardilo, A. DeSimone, L. Gentilucci, and C. Tomasini, *J. Chem. Soc., Chem. Commun.*, 1994, 735.
72 (a) A.I. Meyers and C.E. Whitten, *J. Am. Chem. Soc.*, 1975, **97**, 6266; (b) A.I. Meyers and C.E. Whitten, *Heterocycles*, 1976, **4**, 1687; (c) A.I. Meyers and R.K. Smith, *Tetrahedron Lett.*, 1979, **20**, 2749; (d) A.I. Meyers, R.K. Smith, and C.E. Whitten, *J. Org. Chem.*, 1979, **44**, 2250.

73 A.I. Meyers and M.J. Shipman, *J. Org. Chem.*, 1991, **56**, 7098.
74 A.I. Meyers and K.A. Lutomski, *J. Am. Chem. Soc.*, 1982, **104**, 879.
75 (a) S. Hashimoto, S. Yamada, and K. Koga, *J. Am. Chem. Soc.*, 1976, **98**, 7450; (b) S. Hashimoto, S. Yamada, and K. Koga, *Chem. Pharm. Bull.*, 1979, **27**, 771; (c) S. Hashimoto, H. Kogen, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, 1979, **20**, 3009.
76 (a) K. Tomioka, F. Masumi, T. Yamashita, and K. Koga, *Tetrahedron Lett.*, 1984, **25**, 333; (b) H. Kogen, K. Tomioka, S. Hashimoto, and K. Koga, *Tetrahedron Lett.*, 1980, **21**, 4005; (c) H. Kogen, K. Tomioka, S. Hashimoto, and K. Koga, *Tetrahedron*, 1981, **37**, 3951.
77 (a) A.I. Meyers, N.R. Natale, D.G. Wettlaufer, S. Rafii, and J. Clardy, *Tetrahedron Lett.*, 1981, **22**, 5123; (b) A.I. Meyers and N.R. Natale, *Heterocycles*, 1982, **18**, 13.
78 (a) R. Gosmini, P. Mangeney, A. Alexakis, M. Commercon, and J.F. Normant, *Synlett*, 1991, **111**; (b) P. Mangeney, R. Gosmini, and A. Alexakis, *Tetrahedron Lett.*, 1991, **32**, 3981.
79 (a) B.A. Barner and A.I. Meyers, *J. Am. Chem. Soc.*, 1984, **106**, 1865; (b) A.I. Meyers and D. Hoyer, *Tetrahedron Lett.*, 1984, **25**, 66; (c) A.I. Meyers and B.A. Barner, *J. Org. Chem.*, 1986, **51**, 120; (d) A.I. Meyers, G.P. Roth, D. Hoyer, B.A. Barner, and D. Laucher, *J. Am. Chem. Soc.*, 1988, **110**, 4611; (e) D.J. Rawson and A.I. Meyers, *J. Org. Chem.*, 1991, **56**, 2292.
80 (a) R.C. Andrews, S.J. Teague, and A.I. Meyers, *J. Am. Chem. Soc.*, 1988, **110**, 7854; (b) A.I. Meyers and K.J. Higashiyama, *J. Org. Chem.*, 1987, **52**, 4592; (c) G.P. Roth, C.D. Rithner, and A.I. Meyers, *Tetrahedron*, 1989, **45**, 6949; (d) A.J. Robichaud and A.I. Meyers, *J. Org. Chem.*, 1991, **56**, 2607; (e) A.I. Meyers and G. Licini, *Tetrahedron Lett.*, 1989, **30**, 4049.
81 A.I. Meyers, J.D. Brown, and D. Laucher, *Tetrahedron Lett.*, 1987, **28**, 5283.
82 (a) A.I. Meyers and R.J. Himmelsbach, *J. Am. Chem. Soc.*, 1985, **107**, 682; (b) A.I. Meyers, R. J. Flisak, and R.A. Aitken, *J. Am. Chem. Soc.*, 1987, **109**, 5446; (c) A.M. Warshawsky and A.I. Meyers, *J. Am. Chem. Soc.*, 1990, **112**, 8090.
83 A. Alexakis and P. Mangeney, *Tetrahedron: Asymmetry*, 1990, **1**, 477 (review).
84 (a) J. Aubouet, G. Pourcelot, and J. Berlan, *Tetrahedron Lett.*, 1983, **24**, 585; (b) J. Berlan, Y. Besace, G. Pourcelot, and P. Cresson, *Tetrahedron*, 1986, **42**, 4751; (c) J. Berlan and Y. Besace, *Tetrahedron*, 1986, **42**, 4767; (d) P. Mangeney, A. Alexakis, and J.F. Normant, *Tetrahedron Lett.*, 1993, **24**, 585; (e) P. Mangeney, A. Alexakis, and J.F. Normant, *Tetrahedron*, 1994, **40**, 1803.
85 G.H. Posner, *Acc. Chem. Res.*, 1987, **20**, 72.
86 (a) G.H. Posner, L.L. Frye, and M. Hulce, *Tetrahedron*, 1984, **40**, 1401; (b) G.H. Posner and E. Asirvatham, *J. Org. Chem.*, 1985, **50**, 2589; (c) G.H. Posner and C. Switzer, *J. Am. Chem. Soc.*, 1986, **108**, 1239.
87 S.T. Saengchantara and T.W. Wallace, *Tetrahedron*, 1990, **46**, 6553.
88 R. Tamura, K. Watabe, N. Ono, and Y. Yamamoto, *J. Org. Chem.*, 1992, **57**, 4895.
89 T. Mukaiyama, Y. Hirako, and T. Takeda, *Chem. Lett.*, 1978, 461.
90 R.T. Brown and M.J. Ford, *Tetrahedron Lett.*, 1990, **31**, 2029.
91 (a) D. Enders and K. Papadopoulus, *Tetrahedron Lett.*, 1983, **24**, 4967; (b) D. Enders and K. Papadopoulus, *Tetrahedron Lett.*, 1983, **27**, 3491; (c) D. Enders and B.E.M. Rendenback, *Tetrahedron*, 1986, **42**, 2235; (d) D. Enders, H.J. Scherer, and G. Rabbe, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1664.
92 (a) D. Enders and A.S. Demir, *Tetrahedron Lett.*, 1987, **28**, 3797; (b) D. Enders and B.E.M. Rendenback, *Chem. Ber.*, 1987, **120**, 1223; (c) D. Enders, A.S. Demir, and B.E.M. Rendenback, *Chem. Ber.*, 1987, **120**, 1731; (d) D. Enders, S. Müller, and A.S. Demir, *Tetrahedron Lett.*, 1988, **29**, 6437.
93 (a) D. Enders, P. Gerdes, and H. Kipphardt, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 179; (b) D. Enders, D. Mannes, and G. Rabbe, *Synlett*, 1992, 837; (c) D. Enders and W. Karl, *Synlett*, 1992, 895.
94 M. Yamaguchi, K. Hasebe, S. Tanaka, and T. Minami, *Tetrahedron Lett.*, 1986, **27**, 959.
95 E.J. Corey and R.T. Paterson, *Tetrahedron Lett.*, 1985, **26**, 5025.
96 (a) R.K. Haynes, J.P. Stokes, and T.W. Hambley, *J. Chem. Soc., Chem. Commun.*, 1991, 58; (b) D.H. Hua, R. Chan-Yu-King, J.A. McMie, and L. Myer, *J. Am. Chem. Soc.*, 1987, **109**, 5026.
97 D.A. Evans, M.T. Bilodeau, T.C. Somers, D. Cherry, and Y. Kato, *J. Org. Chem.*, 1991, **56**, 5750.
98 (a) S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Lett.*, 1969, **10**, 4233; (b) B. DeJeso and J.C. Pommier, *Tetrahedron Lett.*, 1980, **21**, 4511; (c) Y. Ito, M. Sawamura, K. Kominami, and T. Saegusa, *Tetrahedron Lett.*, 1985, **26**, 5303; (d) K. Tomioka, W. Seo, K. Ando, and K. Koga, *Tetrahedron Lett.*, 1987, **28**, 6637; (e) K. Tomioka, K. Yasuda, and K. Koga, *Tetrahedron Lett.*, 1986, **27**, 4611; (f) K. Tomioka, K. Yasuda, and K. Koga, *J. Chem. Soc., Chem. Commun.*, 1987, 1345.
99 J. d'Angelo, D. Desmaële, F. Dumas, and A. Guingant, *Tetrahedron: Asymmetry*, 1992, **3**, 459.
100 B. DeJeso and J.C. Pommier, *J. Chem. Soc., Chem. Commun.*, 1977, 565.
101 J. d'Angelo, G. Revial, A. Guingant, C. Riche, and A. Chiaroni, *Tetrahedron Lett.*, 1989, **30**, 2645.
102 M. Pfau, G. Revial, A. Guingant, and J. d'Angelo, *J. Am. Chem. Soc.*, 1985, **107**, 273.
103 G. Revial, *Tetrahedron Lett.*, 1989, **30**, 4121.
104 A. Guingant, *Tetrahedron: Asymmetry*, 1991, **2**, 415.
105 A. Guingant and H. Hammami, *Tetrahedron: Asymmetry*, 1991, **2**, 411.
106 J. d'Angelo, G. Revial, P.R.R. Costa, R.N. Castro, and O.A.C. Antunes, *Tetrahedron: Asymmetry*, 1991, **2**, 199.
107 J. d'Angelo, A. Guingant, C. Riche, and A. Chiaroni, *Tetrahedron Lett.*, 1988, **29**, 2667.
108 S. Pinheiro, A. Guingant, D. Desmaële, and d'Angelo, *Tetrahedron: Asymmetry*, 1992, **3**, 1003.
109 J. d'Angelo, G. Revial, T. Volpe, and M. Pfau, *Tetrahedron Lett.*, 1988, **29**, 4427.
110 T. Volpe, G. Revial, M. Pfau, and J. d'Angelo, *Tetrahedron Lett.*, 1987, **28**, 2367.
111 D. Desmaële and J. d'Angelo, *Tetrahedron Lett.*, 1989, **30**, 345.
112 D. Desmaële, J. d'Angelo, and C. Bois, *Tetrahedron: Asymmetry*, 1990, **1**, 759.
113 J. d'Angelo and C. Riche, *Tetrahedron Lett.*, 1989, **30**, 6511.
114 (a) Y. Hirai, T. Terada, and T. Yamazaki, *J. Am. Chem. Soc.*, 1988, **110**, 958; (b) Y. Hirai, T. Terada, Y. Okaji, T. Yamazaki, and T. Momose, *Tetrahedron Lett.*, 1990, **31**, 4755.
115 P.R.R. Costa, R.N. Castro, F.M.C. Farius, O.A.C. Antunes, and L. Bergter, *Tetrahedron: Asymmetry*, 1993, **4**, 1499.
116 A. Guingant and H. Hammami, *Tetrahedron: Asymmetry*, 1993, **4**, 25.
117 F. Dumas and J. d'Angelo, *Tetrahedron: Asymmetry*, 1990, **1**, 167.

118 S.G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183.
119 M.E. Bunnage, S.G. Davies, and C.J. Goodwin, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1375.
120 M.E. Bunnage, S.G. Davies, and C.J. Goodwin, *Synlett*, 1993, 731.
121 S.G. Davies, N.M. Garrido, O. Ichihara, and I.A.S. Walters, *J. Chem. Soc., Chem. Commun.*, 1993, 1153.
122 M.E. Bunnage, S.G. Davies, C.J. Goodwin, and I.A.S. Walters, *Tetrahedron: Asymmetry*, 1994, **5**, 35.
123 S.G. Davies and O. Ichihara, and I.A.S. Walters, *Synlett*, 1993, 461.
124 For examples of early studies see: (a) R.A. Kretchmer, *J. Org. Chem.*, 1972, **37**, 2744; (b) J.S. Zweig, J.-L. Luche, E. Barreiro, and P. Crabbé, *Tetrahedron Lett.*, 1975, **16**, 2355; (c) B. Gustafsson, G. Hallnemo, and C. Ullenius, *Acta Chem. Scand., Ser. B*, 1980, **34**, 443; (d) A. Takeda, T. Sakai, S. Shinohara, and S. Tsuboi, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1133; (e) F. Ghozland, J.-L. Luche, and P. Crabbé, *Bull. Soc. Chem. Belg.*, 1978, **87**, 369; (f) M. Huché, J. Berlan, G. Pourcelot, and P. Cresson, *Tetrahedron Lett.*, 1981, **22**, 1329.
125 T. Imamoto and T. Mukaiyama, *Chem. Lett.*, 1980, 45.
126 (a) F. Leyendecker, F. Jesser, and B. Ruhland, *Tetrahedron Lett.*, 1981, **22**, 3601; (b) F. Leyendecker, F. Jesser, and D. Laucher, *Tetrahedron Lett.*, 1983, **24**, 3513; (c) F. Leyendecker and D. Laucher, *Tetrahedron Lett.*, 1983, **24**, 3517.
127 E. J. Corey, R. Naef, and F. J. Hannon, *J. Am. Chem. Soc.*, 1986, **108**, 7114.
128 S.H. Bertz, G. Dabbagh, and G. Sundararajan, *J. Org. Chem.*, 1986, **51**, 4953.
129 (a) R.K. Dieter and M. Tokles, *J. Am. Chem. Soc.*, 1987, **109**, 2040; (b) R.K. Dieter, B. Lagu, N. Deo, and J.W. Dieter, *Tetrahedron Lett.*, 1990, **31**, 4105.
130 G. Quinkert, T. Muller, A. Königer, O. Schultheis, B. Sickenberger, and G. Dürner, *Tetrahedron Lett.*, 1992, **33**, 3469.
131 (a) B.E. Rossiter and M. Eguchi, *Tetrahedron Lett.*, 1990, **31**, 965; (b) B.E. Rossiter, M. Eguchi, A.E. Herández, and D. Vickers, *Tetrahedron Lett.*, 1991, **32**, 3973; (c) B.E. Rossiter, G. Miao, N.M. Swingle, M. Eguchi, A.E. Herández, and R.G. Patterson, *Tetrahedron: Asymmetry*, 1992, **3**, 231.
132 (a) K. Tanaka, H. Ushio, and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1990, 795; (b) K. Tanaka and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1991, 101; (c) K. Tanaka, J. Mutsui, H. Suzuki, and A. Watanabe, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1193.
133 (a) G.M. Villacorta, C.P. Rao, and S.J. Lippard, *J. Am. Chem. Soc.*, 1988, **110**, 3175; (b) K.-H. Ahn, R.B. Klassen, and S.J. Lippard, *Organometallics*, 1990, **9**, 3178; (c) S.G. Bott, K.-H. Ahn, and S.J. Lippard, *J. Acta Crystallogr., Sect. C*, 1989, **45**, 1738.
134 (a) A. Alexakis, S. Mutti, and J.F. Normant, *J. Am. Chem. Soc.*, 1991, **113**, 6332; (b) A. Alexakis, J. Frutos, and P. Mangeney, *Tetrahedron: Asymmetry*, 1993, **4**, 2427.
135 (a) M. Kanai, K. Koga, and K. Tomioka, *Tetrahedron Lett.*, 1992, **33**, 7193; (b) M. Kanai and K. Tomioka, *Tetrahedron Lett.*, 1994, **35**, 895.
136 (a) J.F.G.A. Jansen and B.L. Feringa, *J. Chem. Soc., Chem. Commun.*, 1989, 741; (b) J.F.G.A. Jansen and B.L. Feringa, *J. Org. Chem.*, 1990, **55**, 4168.
137 (a) K. Soai, S. Yokoyama, T. Hayasaka, and K. Ebihara, *J. Org. Chem.*, 1988, **53**, 4148; (b) K. Soai, S. Ugajin, and S. Yokoyama, *Chem. Lett.*, 1988, 1571; (c) K. Soai, T. Hayasaka, and S. Ugajin, *J. Chem. Soc., Chem. Commun.*, 1989, 516; (d) K. Soai, M. Okudo, and M. Okamoto, *Tetrahedron Lett.*, 1991, **32**, 95.
138 (a) C. Bolm and M. Ewald, *Tetrahedron Lett.*, 1990, **30**, 5011; (b) C. Bolm, *Tetrahedron: Asymmetry*, 1991, **2** 701; (c) C. Bolm, M. Felder, and J. Müller, *Synlett.*, 1992, 439.
139 A. Corma, M. Igesius, M.V. Martin, J. Rubio, and F. Sanchez, *Tetrahedron: Asymmetry*, 1992, **3**, 845.
140 (a) M. Uemura, K. Kazao, K. Nakayama, and Y. Hayashi, *Tetrahedron: Asymmetry*, 1992, **3**, 713; (b) M. Uemura, R. Miyake, K. Nakayama, M. Shiro, and Y. Hayashi, *J. Org. Chem.*, 1993, **58**, 1238.
141 J.F.G.A. Jansen and B.L. Feringa, *Tetrahedron: Asymmetry*, 1992, **3**, 581.
142 (a) H. Wynberg and R. Helder, *Tetrahedron Lett.*, 1975, **16**, 4057; (b) H. Wynberg and B. Greijdanus, *J. Chem. Soc., Chem. Commun.*, 1978, 427; (c) K. Hermann and H. Wynberg, *J. Org. Chem.*, 1979, **44**, 2238; (d) S. Colonna, A. Re, and H. Wynberg, *J. Chem. Soc., Perkin Trans. 1*, 1981, 547.
143 (a) R.S.E. Conn, A.V. Lovell, S. Karady, and L.M. Weinstock, *J. Org. Chem.*, 1986, **51**, 4710; (b) A. Battacharya, U.-H. Dolling, E.J.J. Garbowski, S. Karady, K.M. Ryan, and L.M. Weinstock, *Angew. Chem.*, 1986, **98**, 442.
144 H. Brunner and B. Hammer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 312.
145 A. Latvala, S. Stanchez, A. Linden, and M. Hesse, *Tetrahedron: Asymmetry*, 1993, **4**, 173.
146 A. Sera, K. Takagi, H. Katayama, and H. Yamada, *J. Org. Chem.*, 1988, **53**, 1157.
147 A. Loupy and A. Zaparucha, *Tetrahedron Lett.*, 1993, **34**, 473.
148 M. Sawamura, H. Hamashima, and Y. Ito, *J. Am. Chem. Soc.*, 1992, **114**, 8295.
149 (a) M. Yamaguchi, N. Yokota, and T. Minami, *J. Chem. Soc., Chem. Commun.*, 1991, 1088; (b) M. Yamaguchi, T. Shiraishi, and M. Hirama, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1176.
150 H. Sasai, T. Arai, and M. Shibasaki, *J. Am. Chem. Soc.*, 1994, **116**, 1571.
151 (a) K. Tomioka, M. Sudani, Y. Shinmi, and K. Koga, *Chem. Lett.*, 1985, 329; (b) K. Tomioka, M. Shindo, and K. Koga, *J. Am. Chem. Soc.*, 1989, **111**, 8266.
152 (a) T. Mukaiyama, A. Ikegawa, and K. Suzuki, *Chem. Lett.*, 1981, 165; (b) T. Yura, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, 1988, 1021; (c) T. Yura, N. Iwasawa, N. Narasaka, and T. Mukaiyama, *Chem. Lett.*, 1988, 1025.
153 S. Kobayashi, S. Suda, M. Yamada, and T. Mukaiyama, *Chem. Lett.*, 1994, 97.